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Textbook of Clinical Pediatrics

Springer

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Textbook of Clinical Pediatrics

Second Edition

With 990 Figures and 812 Tables

Springer

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Preface to the Second Edition

I am pleased to present the second edition of the *Textbook of Clinical Pediatrics*. The first edition of this textbook (published in 2001) proved to be both a scientific and a clinical success. Scholarly reviews recommended the book as a primary textbook for residents and medical students and an excellent resource for practicing pediatricians as well as other pediatric health care providers.

The primary goal of the editor of any clinically oriented textbook is to make sure that the text is comprehensive, with updated knowledge, and draws together best practices in practical clinical management. This can be achieved only by utilizing the expertise of those colleagues who have special knowledge and talent in the discipline of pediatrics as a whole and in its various sub-specialties. It is with great pleasure that I welcome along with Harb Harfi and Hisham Nazer, the new co-editors—Dr. Bruder Stapleton (University of Washington School of Medicine), Dr. William Oh (Brown University School of Medicine) and Dr. Richard Whitley (University of Alabama School of Medicine) who have brought in their deep knowledge and practical expertise to harness the best available knowledge in pediatrics. All of us together are also delighted to welcome our very eminent panel of outstanding leaders who performed the role of editing various topical sections on pediatric sub-specialties strengthening them with their specialized knowledge, authority, and experience. The second edition includes an expanded team of 17 new section editors who contribute to a wider coverage and scope of this new edition. We are pleased to welcome our 389 expert contributors from leading medical schools and medical centers around the world who contributed chapters.

This second edition constitutes a major revision, update, and reorganization of the textbook based on systematic reviews of advances in pediatric science and clinical application while retaining the reader- and practitioner-friendly features of the first edition. It is designed to cover contemporary pediatrics totally in logical sequence and with maximum authority. All pediatric sub-specialties are covered and discussed. The textbook's size and number of illustrations have been increased significantly. The scope of this text is wider than most other textbooks of pediatrics—this is deliberate and reflects the growth of knowledge in the field as well as the changing trends in medical practice and education. The contents have therefore been redeveloped to serve as a substantial and comprehensive pediatric text, balanced scientifically and clinically to be a problem- and evidence-based global reference for clinicians.

To this end, many fields have been extensively rewritten, including—genetic disorders, neonatology, infectious diseases, blood diseases, endocrine disorders, cardiology, pediatric oncology, developmental, learning and behavioral disorders, allergic disorders, primary immunodeficiency disorders, respiratory disorders, neurology, kidney and urinary tract disorders, disturbances in acid-base and electrolyte disorders, critical care, rheumatology, pediatric orthopedics, and disorders of the skin. Three new sections have been added on pediatric surgery (intended to help practitioners to benefit from the knowledge and clinical management experience of medically important pediatric surgery problems through the eyes of expert pediatric surgeons), on adolescent medicine (an important new area of knowledge related to the practice of pediatrics), and on drug dosing in pediatrics (providing important reference information to busy practitioners on dosage and value).

A total of 155 new chapters have been added including—principles of genetic testing, treatment of genetic disorders, surfactant replacement therapy, ECMO, neonatal neurology, common procedures in neonatology, ethics and decision making in neonatology, autism spectrum disorders, children in disaster, nutritional modulation of intestinal gene expression, animal and human bites, infection associated with medical devices, Chlamydial infections, Listeria monocytoenes, Mycoplasma infection, Actinomycosis, influenza, 2009 H1N1, rotaviruses and noro-and caliciviruses, innate immune defect, immune dysregulation, cutaneous disorders of neonate, pediatric surgical dermatology, skin barrier management and topical treatment in pediatric dermatology, pain amplification syndromes, autoinflammatory diseases, post-infectious arthritis and related conditions, probiotics in gastrointestinal disorders, capsule endoscopy in childhood, intestinal transplantation in children, mitochondrial hepatopathies and Reye's syndrome, pulmonary complications of the immunocompromised patients, cardiovascular genetics, sudden cardiac

death and pre-participation sports screening, secondary cardiac morbidities, noninvasive cardiovascular imaging, interventional cardiology, cardiomyopathies and heart transplantation, acute respiratory failure, mechanical ventilation, and infections in PICU.

In addition there are chapters on the management of snake bites and spider bites, clinical disorders associated with altered potassium metabolism, care of the child refusing blood products, thrombosis, sleep and its disorders in childhood, stroke in children, headache and head pain, pediatric neurorehabilitation and many others.

The textbook places special emphasis on the clinical aspects of various practical pediatric problems. Actual prototype case histories, intended to reinforce the basic principles in clinical management, are presented in sections where it contributes to an enhanced understanding of the subject, such as genetic disorders, inborn errors of metabolism and immunology.

Sections also have been enriched with chapters on clinical scenarios that form the basis for discussion of the relevant clinical problem and are commonly encountered by practitioners and residents, such as anemia, child with recurrent infections, failure to thrive, cough, chest pain, abdominal pain, diarrhea, vomiting, abdominal masses, limping child, heart murmur, metabolic acidosis, metabolic alkalosis, proteinuria, hematuria, and enlarged lymph nodes. These chapters provide an overview of the background for these clinical problems as well as an approach for managing the problem.

Wherever possible, the textbook has based its contents on the best available evidence. The level of evidence preferred is the systematic review of randomized control trials. It is the editors' earnest hope that these efforts provide for a significant enhancement of the management and care for sick children around the world.

On a personal note, I would also like to add for those interested, a short history of the development of this work. It was several years ago in Benghazi (Libya), my home town, where I thought to edit a textbook that would cover new ground clinically and yet be of global relevance. Dr. Hassan Majeed was the first person who accepted the idea and gave his guidance and support. Dr. Ahmad Teebi contributed to the first edition as section editor for genetic disorders. Both were inspiring teachers with unique clinical competence (Majeed syndrome, Teebi syndrome). It is sad that both these giants of clinical pediatrics passed away in 2010. Majeed and Teebi will not be forgotten and will be missed by all who were inspired by them to work with children.

The editors and I also thank the staff at Springer who did a great job to ensure the best major reference work possible. Particularly, Sandra Fabiani, Anil Chandy, and Sunali Mull from Springer's major reference work division as well as Marion Kraemer and Sverre Klempe from the Clinical Medicine editorial division.

For this new edition, I also appreciate and acknowledge the support of the Faculty of Medicine, Umm Al-Qura University.

The editors and I like to dedicate this textbook to our contributors and section editors. It is their book and it is their work that has given our textbook its strength and authority.

September 2011

Abdelaziz Y. Elzouki
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Preface to the First Edition

It is with great pleasure, that we launch the first edition of the *Textbook of Clinical Pediatrics*. The textbook went through several stages of ideas, development, design, writing, revision, editing and extensive critical review by authorities in their field before it was submitted for publication. All the above stages demanded a great amount of effort. The aim was to produce a textbook that has both a global appeal and interest and would help practicing pediatricians, pediatric residents and family practitioners to manage sick children in a practical way, but on a sound scientific basis. The textbook is also intended to help pediatricians in training who are preparing for board or membership examinations and to function as a desk reference with updated information for practicing physicians and pediatricians. Our aim was also to develop a textbook that covers in some detail prevalent childhood diseases. In doing so, we are privileged to acknowledge the contribution of over 100 distinguished pediatricians and scientists from 34 well-known medical schools, major hospitals and health centers from five continents. Therefore, this textbook is enriched with international experience in childhood health care.

Almost all pediatric subspecialties are well covered in this textbook, including blood diseases, neoplastic disorders, infectious diseases, respiratory disorders, allergic disorders, immunodeficiency disorders, inborn metabolic disorders, rheumatic disorders, cardiovascular disorders, diseases of the kidney and urinary tract, nutritional disorders, neonatology, endocrinology, oral and craniofacial disorders, gastrointestinal and liver disorders, neurological disorders, skin diseases, orthopedic, otolaryngology, ophthalmological disorders, pediatric poisoning, critical care, burns, acid base and electrolytes disturbance. The textbook puts special emphasis on the clinical aspects of various practical pediatric problems. Prototype actual case histories, to enforce the basic principles in clinical management, are presented in sections where we think it will make the subject more understandable, such as in inborn errors of metabolism and immunology. Some sections also have been enriched with a chapter on a clinical scenario that forms the basis for discussion of relevant clinical problems. For example, in the hematology section, there is a chapter on approach to a child with anemia; in the kidney and urinary tract disorders section there is a chapter on clinical approach to a child with urinary tract obstruction; in the section on malignant and neoplastic disorders, there is a chapter on clinical approach to a child with abdominal mass, and lymph node enlargement; in the immunology section, there is a chapter on approach to a child with recurrent infection; and in the genetic section, there is a chapter on approach to the child with dyamorphic features.

We would like to dedicate this textbook to all those who contributed to it either directly, such as our contributors, section leaders and supportive staff, or indirectly by being supportive and patient during the preparation, writing and editing of this text, including our families and colleagues. Special appreciation is due to the staff of Lippincott Williams & Wilkins who took a keen interest and labored to ensure the best book possible. We particularly thank Ellen DiFrancesco and James D. Ryan, Vice President of Lippincott Williams & Wilkins.

We wish to give a special mention and acknowledgment to King Khalid Foundation, Saudi Arabia for their generous contribution and support.

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Genetic Disorders

Bruce R. Korf

1 Genetics in Pediatric Medicine

Bruce R. Korf

Introduction

Genetics has long been recognized as playing an integral role in pediatric medicine, given that many genetic disorders are congenital or have their onset in childhood. Medical genetics came of age as a discipline in the 1950s, with the discovery of the chromosomal basis of disorders such as Down syndrome and the advent of treatment for inborn errors of metabolism and newborn screening in the 1960s. Over the ensuing years, great progress has been made in both diagnosis and management of genetic disorders, congenital anomalies, and chromosomal abnormalities. Nevertheless, through most of the past 50 years, two notions have been associated with medical genetics. First, it was perceived that medical genetics focused on rare, if not obscure, conditions – conditions that were important to the individuals and families that are touched by them, but having an impact on only a small slice of medicine. The second notion was that, with the exception of some inborn errors of metabolism, most genetic disorders were untreatable, and that geneticists were far better at diagnosing and counseling than at managing their patients' problems. In recent years, both of these notions are being dispelled. Although it has long been recognized that genetic factors predispose to both rare and common disorders, it is only recently that the tools of genomics have made it possible to identify these genes and thereby develop predictive tests and understand pathophysiology. Moreover, insights into basic mechanisms of disease are revealing approaches to treatment that were previously out of reach. The scope of genetics in pediatric practice therefore has expanded to include both rare and common disorders, and to encompass the full spectrum of care, from prevention through diagnosis and treatment. This chapter will provide an overview of medical genetics in pediatric medicine, exploring this spectrum of activity and laying the groundwork for the more detailed chapters that follow.

The Scope of Genetics in Pediatrics

It has been estimated that 71% of children admitted to the hospital are there due to complications of a genetic disorder or a congenital anomaly. These include a wide range of conditions, including chromosomal abnormalities, mutations in single genes, inborn errors of metabolism, and congenital anomaly syndromes. More common multifactorial conditions such as asthma are not counted in this tally; if all disorders with a genetic contribution were included, then virtually all children with non-traumatic illnesses in the hospital would be there by virtue of a genetic predisposition. In this section the major classes of genetic contributions to ill health will be considered.

Chromosomal Disorders

Chromosomal abnormalities were among the first genetic disorders to be amenable to laboratory testing. In 1959, shortly after techniques that permit the study of mitotic chromosomes were introduced, trisomy 21 was found to be the basis for Down syndrome. In the years that followed, several other disorders associated with abnormalities of chromosome number were described – trisomies 13 and 18, and sex chromosome aneuploidies such as Turner syndrome and Klinefelter syndrome. Initial approaches permitted only gross changes of chromosome number, or extreme gains or losses of material or rearrangements to be identified. Another wave of discovery ensued when in the late 1960s chromosome banding techniques were developed, along with approaches to high-resolution analysis. This yielded a much larger number of disorders associated with more subtle chromosomal rearrangements. A third technological advance that revealed the basis for additional genetic disorders was the advent of fluorescence in situ hybridization (FISH). This began the era of molecular cytogenetics, in which purified fragments of DNA were labeled with fluorescent dyes and hybridized to homologous sequences on the chromosomes, marking the chromosomal loci corresponding to the DNA fragments. This permitted the detection of regions of gain or loss of material that were too small to visualize with the microscope. Several disorders were attributed to changes in gene dosage, and by the mid-1990s, FISH had become a standard and critical tool in clinical cytogenetics. Currently, a fourth wave of

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discovery is underway that is dramatically changing the diagnostic approach. This employs molecular cytogenetic analysis, including array comparative genomic hybridization or SNP arrays, collectively referred to as "cytogenomic arrays." In array comparative genomic hybridization, DNA from a patient and reference "normal" DNA are labeled with different fluorescent dyes and allowed to compete for hybridization to thousands of DNA fragments attached to a glass "chip." Gains or losses of material in the patient sample can be visualized by unequal hybridization to a specific fragment. This approach offers much higher resolution than is possible with FISH, which relies on hybridization to fixed whole chromosomes. It also permits a rapid scan of the entire genome for gain or loss of material, with no need to specify in advance a region of interest. Cytogenomic arrays are revealing rearrangements that could not have been detected with cytological means, often in children with relatively nondescript phenotypes characterized mainly by developmental impairment or autism spectrum disorders.

The phenotype associated with chromosome abnormalities occurs due to genetic imbalance, that is, gain or loss of genetic information. Most trisomies and all monosomies involving non-sex chromosomes are lethal in early development; only trisomies 13, 18, 21, X, and Y are compatible with live birth, and trisomies 13 and 18 usually are lethal early in life. Each chromosome contains hundreds to thousands of genes, many of which are highly regulated, so that having a missing or an extra copy has profound effects on development. Gains or losses of smaller regions of a chromosome are more likely to result in live birth, but still have significant phenotypic effects. It is becoming clear that some small rearrangements are not associated with recognizable phenotypic consequences, and probably are common benign variants (polymorphisms). Others may be phenotypically important, causing problems such as developmental delay or autism.

To the pediatrician, the typical "signature" of a chromosomal abnormality was a defined constellation of congenital abnormalities constituting a syndrome, such as Down syndrome. Usually these are recognized at birth or in early childhood, although sex chromosome abnormalities such as Turner syndrome or Klinefelter syndrome might not be suspected until later on. In most cases, the child would be the only affected member of the family, except in the rare case of translocation, in which balanced carriers could have children with unbalanced karyotypes.

The microdeletion and microduplication syndromes also have well-defined phenotypes, although their number is sufficiently large that the pediatrician may not be familiar with all of the disorders. Although usually sporadic, there are instances where the condition is transmitted as a dominant, since an affected parent may be able to reproduce and can pass the chromosome with the deletion or duplication on to a child. The very subtle gains or losses now being found with array comparative genomic hybridization may produce complex malformation syndromes, or more selective effects on a single developmental system. Both sporadic and inherited versions may occur.

Inborn Errors of Metabolism

The term "inborn errors of metabolism" was coined by the British physician Archibald Garrod, working in the first decade of the twentieth century. He recognized a set of inherited conditions in which there was an apparent block in some essential metabolic pathway. The paradigm was further developed later in the century with the discovery that phenylketonuria, at the time a common cause of several developmental impairment, was due to accumulation of toxic metabolites of phenylalanine due to the lack of activity of the enzyme phenylalanine hydroxylase.

Inborn errors of metabolism represent breakdowns of biochemical pathways due to genetic mutations that interfere with the function or production of a specific enzyme or coenzyme. The phenotypes are the result of some combination of accumulation of substrate and/or deficiency of product. In some cases, such as phenylketonuria, the substrate is soluble and circulates throughout the body, causing toxicity. In other cases, the substrate may be an intracellular component, leading to engorgement of cells and consequent tissue or organ damage. The latter is the case for lysosomal storage disorders.

Inborn errors of metabolism have been among the first of genetic disorders to be amenable to treatment. Disorders such as phenylketonuria are treated by restriction of dietary intake of the offending substance, phenylalanine in this case. In some cases, residual enzyme activity can be stimulated using coenzymes or other pharmaceuticals, or biochemical approaches can be used to remove toxic substrates. Lysosomal storage disorders are now increasingly treatable by infusing purified enzyme, modified chemically so that it is taken up into cells to replace missing enzyme. Eventually, approaches of gene replacement may be possible to effect true "cures" of some inborn errors.

Most inborn errors of metabolism are inherited as recessives, in that both alleles that encode an enzyme must be altered by mutation to produce the phenotype. This results from the catalytic properties of enzymes; heterozygotes with half the normal amount of enzyme

activity still produce sufficient activity to avoid a phenotype. Because of this, most couples at risk do not know that they are carriers until an affected child is born. In some cases, where a disorder is common in a specific population, individuals may be screened before childbearing to identify carriers. This is the case, for example with Tay–Sachs disease, a lysosomal storage disorder that is more common in individuals of Ashkenazi Jewish or French Canadian background. Advances in genetic testing now make it possible to offer screening for a large number of recessive disorders, both rare and common, regardless of ancestry. This approach raises questions of clinical utility, however, that remain unanswered.

Inborn errors of metabolism tend to be progressive disorders. In most cases, this is due to gradual accumulation of toxic substrates. Those associated with soluble factors usually do not present until after birth, since the toxic material crosses the placenta and is cleared by the mother in utero. These disorders present in infancy or childhood, but by the time symptoms are recognized irreversible damage may be done. This has led to newborn screening programs to enable presymptomatic detection and prompt institution of treatment. Newborn screening is practiced throughout the developed world; the scope of testing is rapidly expanding due to new technologies, most notably tandem mass spectrometry used for detection of a large array of metabolites. The pediatrician is usually the first responder to an abnormal newborn screen, and needs to be familiar with the immediate care and availability of specialists in biochemical genetics.

Single Gene Disorders

This term is used to describe disorders associated with mutation of specific individual genes. Inborn errors of metabolism are a special case of single gene disorders, as discussed earlier. In fact, no condition is truly due solely to mutation in a single gene. All genes function in a complex physiological environment in which there are multiple interactions between genes and gene products. To some extent, this complexity may explain differences in phenotype between two individuals with the same disorder. Nevertheless, although no disorder is totally determined by the effects of a single gene, there are many examples where mutations in specific genes lead to dramatic phenotypes.

The first single gene disorder to be characterized at the molecular level was sickle cell anemia, a recessive trait due to mutation of a single nucleotide in the beta globin gene. It is found primarily in individuals with ancestry traced to sub-Saharan Africa, where being a carrier conveyed relative resistance to malaria. The single base change alters the chemical properties of beta globin so as to alter the structure of the red cell, which interferes with its traverse through small vessels, leading to pleiotropic effects on many systems of the body.

Several thousand single gene disorders have been defined, cataloged in Mendelian Inheritance in Man, initially a book and now an online database (www.ncbi.nlm.nih.gov/omim/). These include both exceedingly rare and surprisingly common disorders with all possible modes of inheritance: recessive and dominant, autosomal, sex-linked, and maternal (mitochondrial). Some, such as cystic fibrosis or Marfan syndrome, are likely to be familiar to pediatricians. Others are so-called private syndromes that have only been seen once, in a specific individual family. Many have onset in childhood, whereas others, such as Huntington disease, usually have onset in adulthood.

The major advance in the field of single gene disorders in recent years has been the advent of molecular diagnostic testing. There has been an exponential increase in the number of disorders that have been associated with mutation in specific genes in recent years, and once the gene is identified, molecular genetic testing becomes possible for diagnostic purposes. Testing is offered for many of these in both commercial and academic laboratories, and databases are available to guide the clinician to laboratories where testing is offered (e.g., www.genetests.org). Tests for very rare disorders may be available on a clinical basis in a limited number of laboratories, or on a research basis in some. The increasing availability of genetic testing makes it easier to provide a definitive diagnosis and offer anticipatory guidance and counseling regarding risk of recurrence.

As the genes associated with specific conditions are identified, the pathophysiology of these disorders can be brought to light. This is revealing fundamental mechanisms of the control of critical cellular processes, and is opening avenues of possible treatment. Treatments may include the use of pharmacological agents that modulate these pathways, or, eventually, perhaps the substitution of cells or genes to overcome the defect. Although many of these disorders are well established by the time of birth, there is a possibility that progressive symptoms may be prevented and even established symptoms ameliorated.

Multifactorial Disorders

It has long been recognized that some disorders tend to cluster in families, yet do not segregate according to

Mendel's laws as single gene conditions. This includes rare congenital anomalies, such as spina bifida, and more common conditions such as asthma. Aside from familial clustering, these conditions tend to be concordant in identical twins more often than in sibs, yet even identical twins are not always concordant with respect to disease. This has led to the model of multifactorial inheritance, in which liability to a disease phenotype is due to a combination of genetic and nongenetic factors; the latter includes environmental factors and others, such as chance.

Until recently, the genetic approach to multifactorial disorders was limited to empirical recurrence risk counseling, using population data to estimate risk. Since the introduction of genomic approaches, however, it has become possible to identify the genes that predispose to both rare and common disease. Much of this work has been based on genetic association, that is, finding genetic variants that are seen more often in those with a condition than in unaffected controls. Variants are now known throughout the genome, and advances in genotyping technology have made it possible to do whole-genome scanning for association in large case-control cohort studies. This has led to a flood of discovery of genes associated with disease, though in most cases the contribution of any specific genetic factor is small.

The clinical impact of identification of genes associated with multifactorial disorders is just beginning to be felt. Predictive testing to identify individuals at risk may be possible if specific genetic variants are strongly associated with disease. These associations, however, are not the equivalent of diagnostic tests, and relative risks may be very modest. An additional benefit of identification of genetic factors in multifactorial disease may be the discovery of cellular mechanisms of disease, leading to new approaches to prevention or treatment.

Cancer Genetics

Several lines of evidence have implicated genetic changes as contributing to cancer. This includes the occasional instance of familial segregation of cancer, the occurrence of chromosomal abnormalities in cancer cells, the fact that mutagens are also usually carcinogens, and the observation that DNA repair disorders are associated with increased risk of cancer. In recent years, it has become clear that genetic changes are at the heart of the process of cellular transformation to malignancy and malignant progression. Two major types of genes, referred to as oncogenes and tumor suppressor genes, have been identified that underlie these processes.

Oncogenes behave in a dominant manner; mutation leads to activation of the genes, which in turn cause the cell to escape from normal controls that limit cell division. Tumor suppressor genes behave in a recessive manner in the cell, so that mutation of both alleles is found in tumor cells. Most oncogene mutations are acquired somatically. Mutation of the two alleles of a tumor suppressor gene may be somatic events, but in some cases the first mutant allele is inherited. This leads to cancer predisposition syndromes, in that individuals who inherit a mutant allele are at vastly increased risk of cancer if the other allele is mutated in a somatic cell. These syndromes are typically inherited as dominants, since it is the first of the two mutations that constitutes the inherited trait. Although most of these disorders, such as breast and ovarian cancer syndrome, are of adult onset, some, such as familial adenomatous polyposis or familial medullary thyroid carcinoma can have onset in childhood.

Recognition of genetic contributions to malignancy is changing clinical practice at many levels. Familial cancer predisposition syndromes may be amenable to genetic testing to identify individuals at risk, so that surveillance or management strategies can be instituted. Understanding the genetic pathophysiology of cancer is leading to new insights into possible avenues of treatment, and the development of a new set of pharmacological agents that target the aberrant cellular pathways.

The Genetic Approach

The pediatrician will usually be the first to recognize the possibility of a genetic disorder in a child, or will be the first to hear of an inborn error of metabolism identified by newborn screening. Early diagnosis can be important for many reasons. In some cases, treatment can be started before irreversible damage is done; this is the basis for newborn screening, as has been noted. Prompt diagnosis can also provide a basis for recurrence risk counseling; some couples only learn that they are at risk of having a child with a genetic disorder after their *second* affected child is born. Finally, establishing a diagnosis can help a family understand the basis for their child's problem, providing a basis for predicting future problems and avoiding an odyssey of fruitless medical testing.

Family History

The family history is the most powerful and least expensive of genetic tests. Patterns of inheritance will be covered

in a later chapter, but the pediatrician should be familiar with the basic Mendelian modes of recessive and dominant inheritance, as well as the difference between autosomal and sex-linked inheritance. Recent discoveries have expanded the concept of inheritance to encompass maternal transmission of traits encoded in the mitochondrial DNA and complex patterns of inheritance due to the phenomenon of genomic imprinting.

Ideally, a three-generation family history would be obtained at the time when a child is first seen, and updated at subsequent visits. Standard pedigree symbols used in assembling the family history are shown in *Fig. 1.1*. It is important to ask about miscarriages and early childhood deaths, as some individuals will not remember to include this important information when asked about the family. Complex family relationships, including adoption, should also be noted.

Obtaining and documenting a family history is time-consuming, and may be difficult in the course of a routine pediatric visit. The family can be encouraged to assemble the basic information outside the visit, using family get-togethers as an opportunity to gather information about relatives. There are tools available to assist in this process, such as the US Surgeon General's "My Family Health Portrait" (https://familyhistory.hhs.gov/fhh-web/home.action).

Clues to Genetic Disorders

Given the diversity of genetic disorders, there is no single "red flag" that will invariably identify all children at risk. As noted, newborn screening will identify some children early in life. The specific targets of the screening program vary regionally; the pediatrician should

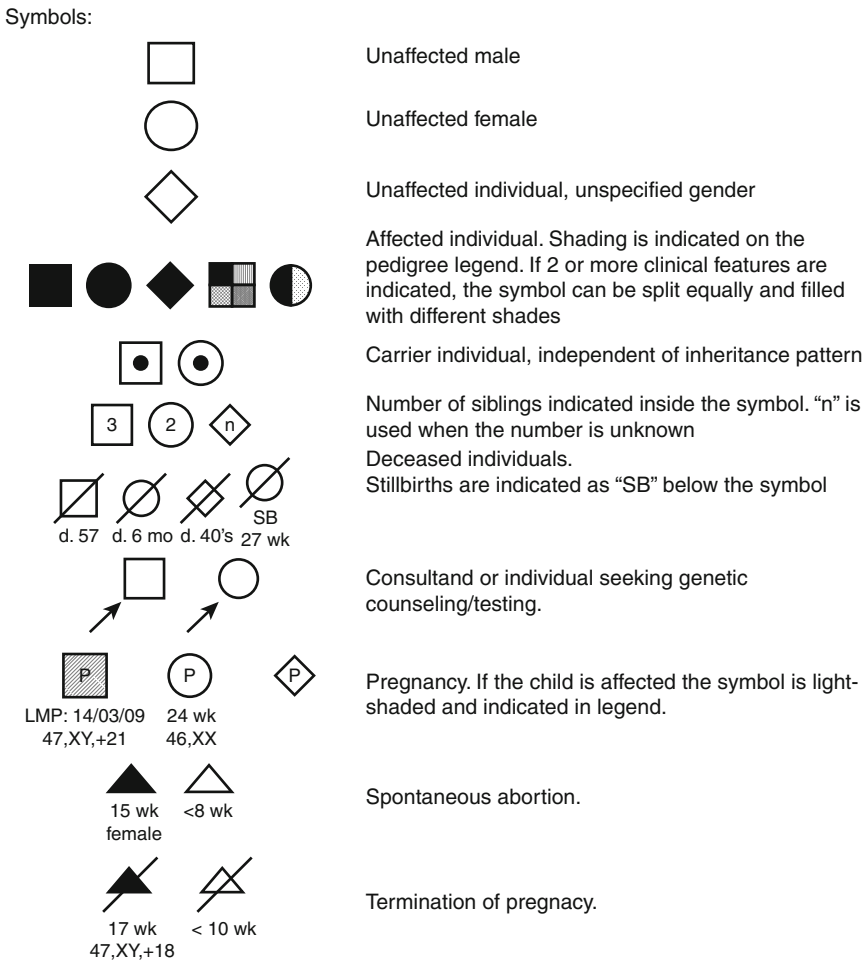

Figure 1.1
(Continued)

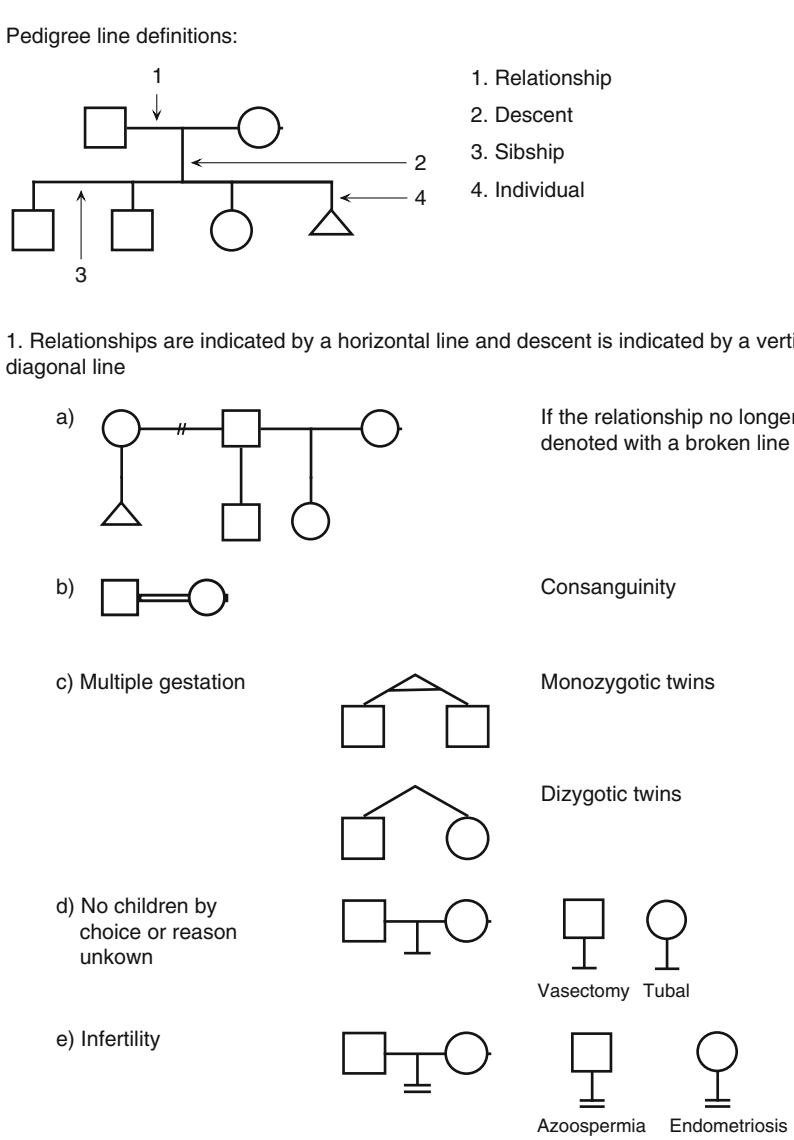

Figure 1.1
Standardized symbols used in the construction of a pedigree (Courtesy of Dr. Gabriela Repetto)

become familiar with the disorders subject to newborn screening in the local community. In the absence of newborn screening, there are some clues that may be helpful.

The value of family history has already been noted. It is important to recognize, however, that many children with genetic disorders are the first to be affected in their families. This is common with recessive disorders, in which both parents are carriers, but neither parent, and probably no close relative, is affected. Chromosomal disorders are usually sporadic, but a family history of others with congenital anomalies or developmental delay, or recurrent spontaneous abortion, may be a clue to a familial chromosome rearrangement. Dominant disorders can be passed from generation to generation, but the phenotype may be variable, and some affected parents are unaware of their diagnosis prior to the birth of an affected child. Also, some dominant disorders arise spontaneously due to new mutation in a child. In some cases, one of the parents may have additional mutated sperm or egg cells (germline mosaicism), and therefore may be at risk to have additional affected children.

Many congenital anomalies are associated with a genetic etiology, either single gene, chromosomal, or multifactorial. A specific constellation of anomalies may suggest a defined syndrome, but many of these are rare and difficult to recognize. The presence of two or more congenital anomalies in a child may suggest a genetic etiology and should prompt referral to a geneticist for further investigation. There are common variants, referred to as "minor anomalies," such as a single transverse palmar crease, that convey less significance. This topic is discussed in the chapter on congenital anomalies.

Specific single gene disorders are highly varied, so it is difficult to state a rule that will insure their recognition. The pediatrician should be alert to clues such as failure to thrive, especially in a child with intrauterine growth retardation, unusual body habitus, macro- or microcephaly, disproportionate limb to body size, developmental delay or regression, autism spectrum disorder, and distinctive skin pigmentation as clues. Specific syndromes may only become clear with the passage of time, and may require a trained eye to be recognized. Increasingly, genetic testing is available to confirm a suspected diagnosis, and array comparative genomic hybridization may reveal an otherwise unsuspected gain or loss of genetic material.

Genetic Testing

The possibility of chromosomal analysis, FISH, array comparative genomic hybridization, and molecular genetic testing has already been mentioned; these are covered in greater detail in later chapters. The pediatrician will likely work together with genetic professionals in ordering and interpreting these tests, but should be familiar with basic principles that govern genetic testing.

Genetic tests can be assessed in terms of analytic validity, clinical validity, clinical utility, and the ethical implications of testing. Analytical validity relates to the degree to which the test result correctly identifies the presence or absence of a particular mutation. For the most part, genetic tests tend to have a high degree of analytic validity, barring the possibility of human error such as sample mix-up. It should be remembered, though, that genetic tests are unlikely to be repeated once done, unlike most other medical tests. Therefore, if an error is made, it may be difficult to detect.

Clinical validity refers to the degree to which the test diagnoses or excludes a particular disorder. Many genetic variants are nonpathogenic; although some are common and are easily dismissed as being clinically significant, some benign variants are rare and may be unique to a particular family. Sometimes, a mutation will have obvious effects on the function of the gene. For example, a mutation that causes premature termination of translation of a gene product has a high likelihood of being clinically significant. Other times, it may be more difficult to know whether a variant is significant. The laboratory should report both the nature of the mutation and the evidence that supports pathogenicity.

The phenomena of non-penetrance and genetic heterogeneity may further complicate interpretation of clinical validity. Some mutations are pathogenic, but the phenotype is not invariably seen, or may only be seen after a long period of time. Such disorders are said to be non-penetrant or to exhibit age-dependent penetrance. Finding a mutation therefore does not guarantee that a disease phenotype will occur, or say when it will occur. Genetic heterogeneity means that multiple different mutations in one or several genes can lead to the same phenotype. A negative genetic test may not exclude a specific diagnosis if some of these mutations are not included in the test.

Clinical utility refers to the degree to which the test informs clinical management. Some tests can diagnose disorders that are already evident clinically. Unless the test reveals prognosis or severity, it may add little to the care of the individual, though it could still be useful as a basis for genetic counseling. Also, some tests may reveal risk of disease for which there is no intervention. Whether it is worth ordering an expensive test that may also cause anxiety if there is no intervention to alter the outcome is a matter of debate and, to some extent, personal choice.

Finally, the ethical implications of testing need to be considered. Individuals with a positive genetic test may be subject to anxiety, stigmatization, and discrimination. In some regions, federal or regional laws may offer some degree of protection from some of these risks. There are also questions about whether genetic tests should be done in children. The consensus in the medical genetics community is that testing is justified in children if the child will immediately benefit from the results of testing. This is the case, for example, in diagnostic tests for a child with symptoms of a genetic disorder. On the other hand, tests that predict predisposition to adult-onset disease where there is no intervention that can be offered to the child are best left to adulthood, when the child is old enough to understand the implications of testing and provide informed consent.

Management of Genetic Disorders

Diagnosis of a genetic disorder should be a prelude to management strategies to help the child and family deal

with the disorder. Management usually begins with explanation of the diagnosis, the underlying genetic mechanisms, natural history of the disorder, and available interventions. This will often be done by a genetic professional working in partnership with the pediatrician. Even if there is no treatment, the family may benefit from a discussion of the likely course of the disorder and interventions that may ameliorate the effects. Genetic counseling can explain the risks of recurrence to the parents or other family members, and the availability of interventions such as prenatal or preimplantation diagnostic testing. Many parents will feel guilt at the birth of a child with a genetic disorder and wonder if they in some way "caused" the condition. Genetic counseling can help parents understand what is known about etiology and may help assuage feelings of guilt.

As noted earlier in the chapter, genetic disorders are increasingly becoming amenable to treatment. Outcomes range from essential elimination of the phenotype to improvement in quality of life and comfort for the patient and family. Most currently available treatments focus on dietary manipulation, coenzyme supplementation, enzyme replacement, or substrate reduction for inborn errors of metabolism. Surgical correction of congenital anomalies such as congenital heart defects can be lifesaving. Other disorders may benefit from therapeutic interventions to reduce the burden of disease. Examples include use of antibiotics and pancreatic enzymes in cystic fibrosis or use of steroids in Duchenne muscular dystrophy. Individuals with cancer predisposition syndromes can be offered surveillance such as colonoscopy in familial adenomatous polyposis, or risk-reduction strategies, including surgery.

The success of therapy in recent decades has significantly improved life expectancy in many individuals with genetic disorders. This is dramatically exemplified by Down syndrome and cystic fibrosis, where survival into adulthood is now more the rule than the exception. This is creating challenges of transition from pediatric to adult care, given that physicians who care for adults may have little experience in management of these disorders previously thought of as "pediatric."

Insights into pathogenesis of disease are increasingly offering the hope of new targeted approaches to treatment. These may include drugs that affect the specific cellular pathway involved in disease, as well as the prospect of gene replacement or cellular therapies involving stem cell approaches. The ability to treat genetic disorders is a rapidly moving area of research; it is important, therefore, that physicians who manage children with genetic disorders have access to current information on available treatments and clinical trials for new treatments.

Medical Genetic Professionals

Although the pediatrician will likely be the first to recognize the possibility of a genetic disorder in a child, diagnosis and management may benefit from referral to a genetic specialist. Medical genetics is a recognized specialty for physicians in many parts of the world, with defined courses of training and specialty certification. In addition, genetic counselors are health professionals with specific training in genetic counseling. Physician geneticists are skilled at establishing a diagnosis and providing a plan for management. Genetic counselors are trained to review family history for risk of genetic disorder, provide counseling regarding options to manage risk, including prenatal diagnosis, and working with a physician to provide long-term management.

Pediatrics in the Genomic Era

Since the introduction of tools of molecular genetics in the mid-1970s, there has been a gradual advance in the ability to diagnose and manage genetic disorders. The pace of discovery and translation to clinical application accelerated considerably, however, beginning in the mid-1990s with the initiation of the human genome project. The completion of the sequencing of the human genome has ushered a new era in the study of rare and common disorders, and offers to significantly change the landscape of medical practice.

The Structure and Function of the Human Genome

It is now estimated that there are approximately 20,000 genes comprising the human genome, significantly fewer than had been estimated prior to the Human Genome Project. It has become apparent, however, that there is a surprising degree of complexity in the genome that goes far beyond the diversity of coding sequences represented by these 20,000 genes. Indeed, the entire set of protein-encoding gene comprises only a very small proportion of the coding capacity of the genome (*Fig. 1.2*).

Aside from protein-encoding genes, there is a wealth of both expressed and non-expressed sequences. There are blocks of highly repeated DNA sequences located at the centromeres and near the ends (telomeres) of each of the chromosomes; these do not encode proteins but probably play a role in maintaining the structural integrity of the chromosome. Many of the sequences that are transcribed encode RNAs that are not translated into protein. These

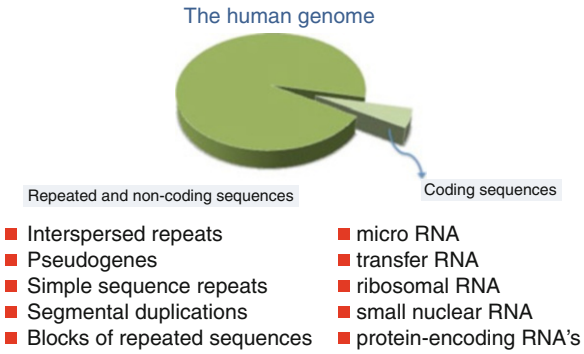

Figure 1.2
Composition of the human genome. Only a small portion encodes protein or RNA that is transcribed but not translated into protein

include transfer and ribosomal RNAs, small nuclear RNAs involved in RNA splicing, and micro RNAs that play a role in gene regulation. There are also a very large number of sequences that are repeated thousands of times in the genome. These include sequences called transposable genetic elements, which can move from place to place in the genome using enzymes that copy RNA into DNA (reverse transcriptase) and that promote recombination of extrachromosomal DNA sequences with chromosomal DNA. These elements comprise a remarkable proportion of the genome and have been major drivers of genome rearrangement and, hence, of evolution.

The full range of types of DNA sequences, their function, and regulation are just beginning to come to light. Recent studies suggest that a very large proportion of sequences may be transcribed, even though only a small proportion encodes protein. Moreover, the boundaries that comprise a protein-encoded gene are not always clear; examples have been found of separate adjacent genes that are transcribed as a single RNA.

Genomic Testing

Traditional approaches to molecular genetic testing have focused on analysis of individual genes, one at a time. This requires prior knowledge of the appropriate target for testing, and may be limited if the gene is very large or the diversity of mutations is great. In a sense, whole genome testing has a longer history, if one considers cytogenetic analysis as a whole genome "scan." The resolution of such a study, however, is very low, so only the grossest of changes can be detected. As discussed above, cytogenomic arrays afford a much higher resolution screen for changes in gene copy number without a need to select a specific region for analysis.

Other genomic approaches are permitting wide scale analysis both of DNA sequence variation and patterns of gene expression. These "high-throughput" approaches are based on an increasing variety of technological advances. Hundreds of thousands of single nucleotide polymorphisms can now be genotyped for a few hundred dollars. Sequencing of the entire coding region of the genome can be done for a few thousand, and whole genome sequencing, now costing a few tens of thousands of dollars, is expected to cost under $1,000 within the next few years. Already, genome analysis has become the approach of choice to identify the gene underlying a rare genetic disorder. It is likely to become a mainstream approach to genetic testing within the next decade.

Genomic Medicine

The ability to study the human genome at extremely high resolution will vastly alter the approach to medical care in all areas of specialty. This will include advances in genetic testing as well as new insights into pathogenesis that will guide treatment. It is likely that medical decisions will increasingly be informed by genetic and genomic tests, although the clinician may not always be aware that this is happening in the background. The volume of genomic information is likely to be so large that it will only be useful if coupled with electronic health records and computational approaches to guide medical decision-making.

Genomic testing may also permit disease stratification and selection of an appropriate mode of therapy. It is likely that common diseases such as hypertension are really symptom complexes that reflect a variety of underlying pathophysiological mechanisms. If genetic factors that underlie these different mechanisms can be identified, it may become possible to select a pharmacological therapy based on the specific genetic profile of a given individual. This approach is sometimes referred to as "personalized medicine." The hope is that it will lead to more effective treatments and fewer side effects.

Genetic testing can also be used to customize drug dosage to the physiology of an individual. Many aspects of the way drugs are absorbed, metabolized, and excreted, as well as how they interact with cellular targets, are under genetic control. In some cases, common genetic variants explain why drug doses that are nontoxic in some individuals lead to side effects in others, or conversely why doses that are effective in some are insufficient in others. Such pharmacogenetic tests will likely be another component of

the personalized medicine paradigm, and are already being used to a limited extent to titrate drug dosage to the needs of a specific individual.

Genetic diagnosis has already been revolutionized in the genomic era, but is likely to undergo further evolution in the years to come. If whole genome sequencing is done on a wide scale, it may be the case that all possible genetic tests will already have been done on a child before he or she presents with symptoms of disease. Genetic testing may become more a matter of querying the DNA sequence database than ordering any particular test. The challenge is likely to be sorting out clinically significant from nonsignificant variants. Moreover, the definition of "clinically significant" will need to be carefully considered. Some of the genetic changes found will be associated with a phenotype, but not necessarily one that would be classified as "disease." Even variants that predispose to disease may have a double role – increasing risk of one condition while decreasing risk of another, perhaps.

Conclusion

Genetics has played an important role in pediatrics for at least the last half century, and most pediatricians are aware of the need to understand the basic principles of genetics. The notion that medical genetics deals exclusively with rare, untreatable disorders is rapidly being dispelled. Genetic and genomic approaches can greatly improve diagnostic efficacy for rare disorders, and increasing knowledge of disease mechanisms will allow interventions to improve health and quality of life for many. Most importantly, the scope of genetic medicine is undergoing a vast expansion, to the point where it will touch all areas of medicine, and people at all ages. In the coming generation, genetics and genomics will increasingly be incorporated into the basic fabric of all medical practice.

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2 Approach to Single-Gene Disorders

Taosheng Huang · Steven Keiles

Single-gene disorders have a straightforward inheritance pattern, and the genetic causes can be traced to changes in specific individual genes. A particular disorder could be rare; however, as a group, single-gene disorders are responsible for a significant percentage of pediatric diseases. Autosomes refer to the numbered chromosomes (chromosome 1–22), as opposed to the sex chromosomes, X and Y. Every individual carries two copies of each autosome and, therefore, also has two copies of every gene carried on those chromosomes, one inherited from each parent. Based on the location of the relevant genes, single-gene traits can be divided into autosomal inheritance and sex-linked. Autosomal inheritance, depending on whether one or two mutant alleles are required to cause a phenotype, can be divided into autosomal dominant or autosomal recessive. Based on Mendel's laws, the two alleles segregate and pass to different offspring, as shown in ❯ *Fig. 2.1*; A and A' will pass to different individuals, as will a and a'.

Terminology

- *Allele*: Specific version of a gene.
- *Mutation*: Nucleotide change in a gene. This may result in a recognizable phenotype, including a genetic disorder.
- *Phenotype*: Observable physical manifestations of a genotype.
- *Genotype*: Genetic constitution of an individual.
- *Homozygote*: Genotype consisting of identical alleles of a particular gene.
- *Heterozygote*: Genotype consisting of different alleles for the same gene.
- *Compound heterozygote*: Genotype consisting of two different mutations at each allele.
- *Penetrance*: Proportion of individuals carrying a mutation who exhibit a specific phenotype.
- *Expressivity*: Variations of a phenotype in individuals carrying a particular genotype.
- *Pleiotropy*: A single-gene mutation that can affect several traits.
- *Age-dependent penetrance*: A phenomenon in which a phenotype is increasingly expressed with age. For example, in Huntington disease, a majority of individuals with the mutation will not express a clinical phenotype until late age (❯ *Fig. 2.2a*).
- *Anticipation*: A phenomenon in which clinical symptoms become apparent at an earlier age and are more severe as a gene is passed from generation to generation. For example, in myotonic dystrophy, as the mutated gene is passed on, the severity of muscle weakness can become more severe and the age of onset earlier (❯ *Fig. 2.2b*).
- *Genetic heterogeneity*: The occurrence of similar phenotypes resulting either from distinct mutations in the same gene (allelic heterogeneity) or mutations in different genes (locus heterogeneity).
- *Germline mosaicism* or *gonadal mosaicism*: A situation in which precursor cells of the ova and the spermatozoa are a mixture of wild type and mutant cells (❯ *Fig. 2.3*).
- *Sex-influenced phenotype*: Preferential expression of a trait in a particular sex. For example, alopecia is more common in males, and in contrast, breast cancer is more common in females. Although the disease genes are found on the autosomes, in these situations, the phenotypes are influenced by the sex.

Autosomal Dominant Inheritance

Autosomal dominant inheritance is the most common form of inheritance. Here, mutation on one allele is sufficient to cause an individual to express the phenotype. A review of the family history will typically demonstrate affected individuals in every generation. The risks for all members who carry a genetic mutation would be 50% for each offspring to be affected (see ❯ *Fig. 2.4a* and ❯ *b*). In some families, however, a dominant trait may appear to skip an individual or a generation. This could be the result of someone who has not exhibited symptoms yet (incomplete penetrance) or who has not been diagnosed because of being mildly affected (variable expression). Some of the

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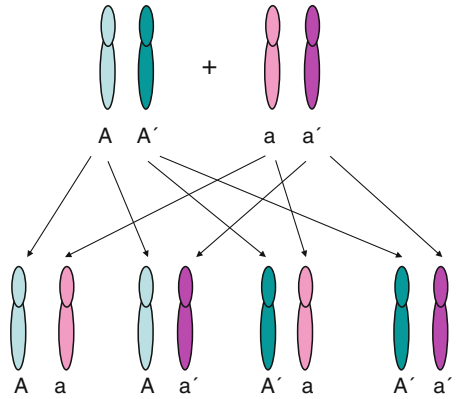

Figure 2.1
Mendel's law of segregation. The father (*left*) is heterozygous for A and A'; the mother (*right*) for a and a'. Offspring can receive either of the father's alleles and either of the mother's alleles, giving four possible combinations, shown at the bottom

more common dominantly inherited conditions include Marfan syndrome (*Fig. 2.5*), Huntington disease, tuberous sclerosis complex, and neurofibromatosis (*Table 2.1*).

Case Presentation

Mr. Williams is a 22-year-old man who was previously healthy. He presents to a primary care physician with a 2-day history of chest pain. A physical examination shows that Mr. Williams' weight is 150 lbs and his height 6′8″. He has long fingers, severe scoliosis, and near-sightedness. The rest of his physical exam is unremarkable. Mr. Williams is referred to a cardiologist to rule out coronary arterial disease. The cardiologist tests him on the treadmill. After the treadmill exercise, Mr. Williams' echocardiogram shows dilated aorta and aortic aneurysm. He is admitted to hospital for emergency surgery. It is found that he has a nearly dissected aorta, with leaking of the blood into the chest. He recovers well after emergency surgery. He is referred to a genetics clinic to rule out Marfan syndrome. His clinical features meet the diagnostic criteria of Marfan syndrome, and molecular tests confirm the diagnosis. He has three children, two girls and one boy. All look healthy and their physical examinations are unremarkable. Diagnostic molecular test results reveal that the two girls carry the same mutation in the fibrillin gene. Therefore, a diagnosis of familial Marfan syndrome is established.

The severity and clinical presentation of Marfan syndrome can vary greatly. Another factor that can increase the difficulty in making a diagnosis is that up to 50% of cases are the result of spontaneous mutations in the affected child and, therefore, will not be associated with a positive family history. It is also possible for a parent to be so mildly affected that a diagnosis is not made previous to having a more severely affected child. Advances in molecular diagnosis and the ability to sequence the *FBN1* gene, which encodes the protein fibrillin and is the site of mutations in individuals with Marfan syndrome, have allowed more families to obtain an accurate diagnosis. It is also important to confirm the presence of a mutation in affected children to allow for identification of additional at-risk individuals in the family. Once a mutation has been identified in an affected child, it becomes easy to cost-effectively screen other family members.

The Features of Autosomal Dominant Inheritance

- One mutated allele at a locus is sufficient to cause a phenotype
- Inherited from parent to child
- Fifty percent risk to each offspring of an affected individual
- Those who do not inherit the gene cannot transmit it
- Males and females equally likely to be affected

Autosomal Recessive Inheritance

Autosomal recessive inheritance means that both copies of a particular gene must carry a mutation in order for the phenotype to be expressed. If only one copy is inherited, that person is referred to as a carrier, and, in general, will not express the phenotype (see *Fig. 2.6*). Some common autosomal recessive conditions are illustrated in *Table 2.1*. Most commonly, a child is affected with a recessive condition if both parents are carriers and each transmits a mutated gene to the child. The likelihood of this occurring when both parents are carriers would be 25% (see *Fig. 2.6*, aa). Some of the more common diseases inherited in this fashion include cystic fibrosis and sickle-cell anemia, which are also routinely included in most state newborn screening programs in the United States.

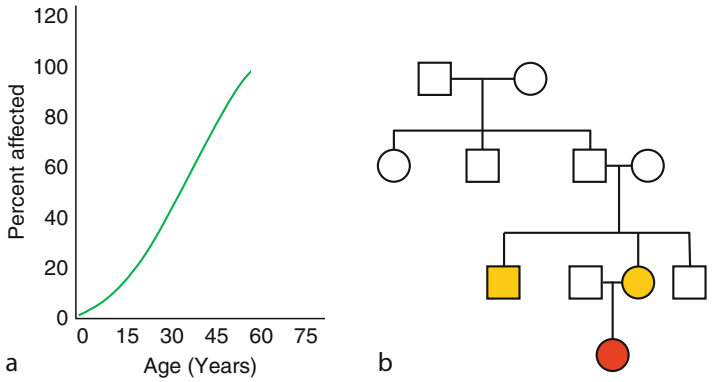

Figure 2.2
Age-dependent penetrance (a), a phenotype is increasingly expressed with age; and anticipation (b), clinical symptoms become apparent at an earlier age and are more severe as a gene is passed from generation to generation

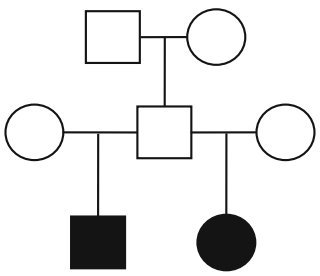

Figure 2.3
Germline mosaicism. The spermatozoa are a mixture of wild type and mutant cells

The Features of Autosomal Recessive Inheritance

- Both alleles must be mutated to produce a phenotype (homozygous), one from each parent (who are heterozygous carriers)
- "Horizontal inheritance" – siblings affected, generally not parents or children
- Males and females equally likely to be affected

Case Presentation

A 6-month-old male infant presents in the clinic with a chronic cough. Review of the history reveals that he was treated for an upper respiratory infection on two other occasions at 2 and 4 months, respectively. At birth he was 75th percentile in both height and weight but he has trended downward since then and is currently in the 50th percentile of height and only 10th percentile in weight. The remainder of the physical exam is unremarkable and he appears to be meeting all milestones of development. He is treated for another respiratory infection, and it is recommended that he return to clinic in 2 months to assess his growth. He returned to the clinic in 3 weeks, however, with the same chronic cough and inability to clear mucus from the lungs. A review of the chart indicates that he had a negative newborn screening test for cystic fibrosis. Given the symptoms, a fecal elastase and sweat test are ordered. The fecal elastase is normal and the sweat test comes back in the borderline range. A *CFTR* DNA mutation panel is ordered and also comes back negative. Based on these findings, cystic fibrosis is no longer considered by his physician. The parents seek another opinion since there is still a persistent chronic cough. At this visit a deep throat culture is obtained and the patient is confirmed to be growing *Pseudomonas aeruginosa* and is treated with tobramycin. In addition, a comprehensive CFTR sequence analysis is ordered which reveals two known cystic-fibrosis-disease-causing mutations. The parents are then tested and each is found to carry one of these mutations, thereby confirming the diagnosis of cystic fibrosis.

Sex-Linked Traits

Sex-linked traits are associated with mutations in genes that are located on the sex chromosomes. Males have a Y-chromosome and only one X-chromosome, whereas females have two X-chromosomes without a Y; therefore,

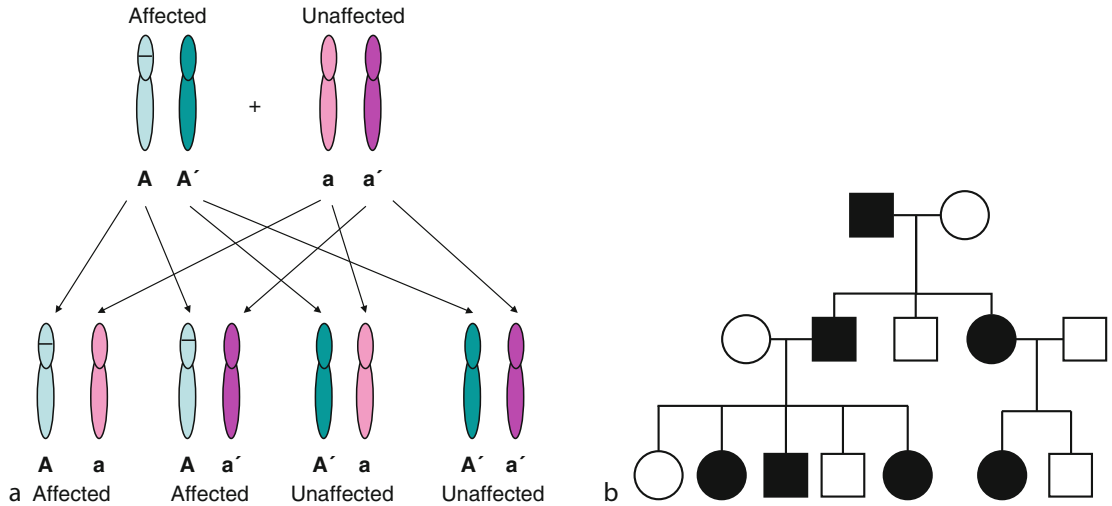

Figure 2.4
(a) Autosomal dominant trait. The risks for all members who carry a genetic mutation would be 50% for each offspring to be affected. (b) Autosomal dominant pedigree. Affected individuals in every generation

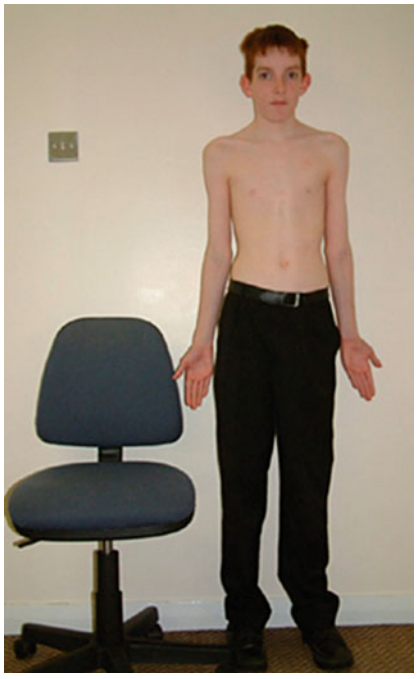

Figure 2.5
Boy with Marfan syndrome at age 12 with tall stature and joint hypermobility

the inheritance pattern for this group of traits is quite different from those that are due to mutation in genes on the autosomes. If the mutant gene is located on the X-chromosome and the father is affected, he will transmit this mutant allele to all of his daughters but none of his sons. In contrast, if the mutated gene is located on the Y-chromosome it will be passed to all of his sons. In females, the mutated gene will be transmitted to both sons and daughters 50% of the time (*Fig. 2.7*). Some common X-linked conditions are illustrated in *Table 2.1*.

X-Inactivation

Since males have only one X-chromosome and the Y-chromosome is much smaller and has far fewer genes than the X-chromosome, it seems that males and females are genetically imbalanced. This dosage difference is compensated for by X-inactivation. X-inactivation, also known as Lyonization, is a process in which one of the two copies of the X-chromosome in females is inactivated early in development. As shown in *Fig. 2.8*, for an individual cell, which of the two copies of the X-chromosome is inactivated is random. Once an X-chromosome is inactivated, however, it will remain inactive. If an individual cell has more than two X-chromosomes, still only one will be active. X-inactivation is controlled by the X-inactivation center (XIC), which is necessary and sufficient to cause X-chromosome inactivation. The inactivated X-chromosome is packed into a high density of heterochromatin and can be seen in the nucleus as a "Barr body." A small number of genes on the inactivated X-chromosome are expressed. The ends of the X and Y contain homologous genes that escape inactivation on

Table 2.1
Common conditions of Mendelian Inheritance

Inheritance pattern	Disease	Gene	Clinical features
AD	Marfan's syndrome	FBN1	Displacement of lens
		TGFBR2	Bone overgrowth
			Joint laxity
			Scoliosis
			Dilation of aorta
	Huntington's disease	HD	Progressive motor, cognitive, and psychiatric disturbance
			Chorea voluntary movement
			Cognitive decline
			Change in personality and/or depression
	Neurofibromatosis	NF1	Multiple café au lait spots
			Axillary and inguinal freckling
			Cutanis neurofibroma
			Iris lisch nodules
	Achondroplasia	FGF-R3	Short stature
			Disproportionately short arms and legs
			Large head
			Frontal bossing
			Middle-face hypoplasia
			Delayed motor skills
			Normal intellect and lifespan
	Familiar hypocholestrolemia	LDLR	Elevated cholesterol levels in blood
			Premature cardiovascular disease
AR	Cystic fibrosis	CFTR	Chronic lung infection
			Pancreatic insufficiency
			Meconium illium
			Infertility in males
	Sickle-cell disease	HBB	Anemia
			Acute and chronic pain resulting from ischemia secondary to vaso-occlusive events
			Bacterial infection
			Splenic sequestration
	Phenylketonuria	PAH	Mental retardation in untreated patients resulting from accumulation of phenylalanine
X-L D	Rett syndrome	PECP2	Repetitive hand movements in females
			Deceleration of head growth
			Seizure disorder
			No verbal skills
			Constipation
			Growth failure

Table 2.1 (Continued)

Inheritance pattern	Disease	Gene	Clinical features
	Incontinentia Pigmenti	HPEX	Skin lesions variable in different stages
			Blistering at birth
			Linear hypopigmentation
			Alopecia
			Hypodontia
X-L R	Duchenne muscular dystrophy	DMD	Progressive muscular degeneration
			Psuedo-hypertrophia
	Hemophilia A	F8	Bleeding secondary to factor-A deficiency
	Fragile-X Syndrome	FMR1	Mental retardation
			Macrocephaly
			Prominent ears

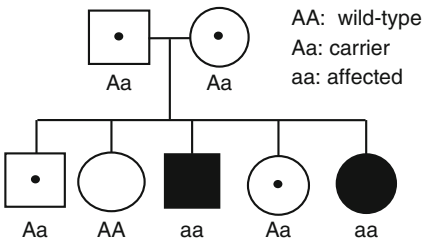

Figure 2.6
Autosomal recessive inheritance. "Horizontal inheritance" – siblings affected, generally not parents or children; males and females equally likely to be affected

the X. These regions are referred to as pseudo-autosomal. Both sexes will have two copies of every gene from the pseudo-autosomal region.

X-linked conditions can be classified into X-linked dominant or X-linked recessive. A classic example of an X-linked recessive disorder is Duchenne muscular dystrophy (DMD) (*Table 2.1*). DMD is characterized by progressive muscle degeneration and weakness. Symptoms typically manifest in a male at an early age. Muscle weakness progresses from proximal to distal. Psuedo-hypertrophy of the calves is often seen early in the course. As the disease progresses, muscle loss occurs and myocytes are eventually replaced by fat and fibrotic tissue. Before reaching the teenage years, the majority of patients have difficulty walking. Most become wheelchair bound by early adolescence. Skeletal deformities can occur secondary to muscle weakness. Some patients with DMD also develop cardiomyopathy; some will have intellectual impairment. DMD is caused by a mutation of the dystrophin gene on the X-chromosome. Dystrophin is a component of the protein-complex in skeletal muscle (*Fig. 2.9*). Loss of dystrophin results in an increased calcium release in the sarcolemma, and then cell death.

DMD and Becker muscular dystrophy, or BMD, are allelic disorders. DMD is mainly caused by a deletion or frameshift or stop mutation in the dystrophin gene. In contrast, the milder phenotype of BMD is due to mutations that maintain the dystrophin reading frame. Females who are heterozygous carriers of a mutation in the dystrophin gene are usually asymptomatic, though some may experience mild weakness.

X-Linked Recessive Traits

- The clinical phenotypes are always expressed in males, but are usually not expressed or only mildly expressed in females. Therefore, mutated genes may be transmitted through a series of unaffected females (*Fig. 2.8*).
- All daughters of affected males are unaffected. Female carriers will transmit the mutant gene to 50% of her sons who will be affected, and to 50% of her daughters, who will be carriers.
- New mutations could occur, especially if the mutations are genetically lethal (i.e., not compatible with reproduction). Those mutations will be replaced by novel mutations.

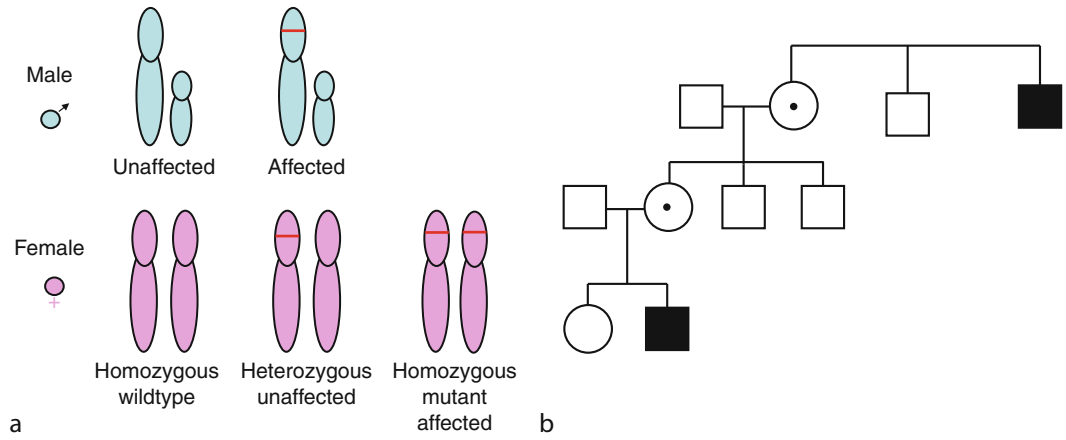

Figure 2.7

(a) X-linked recessive traits. The clinical phenotypes are always expressed in males, but are usually not expressed or only mildly expressed in females unless homozygous and compound heterozygous mutations occur. (b) Pedigree demonstrating X-linked recessive traits skipping generations through unaffected, carrier women

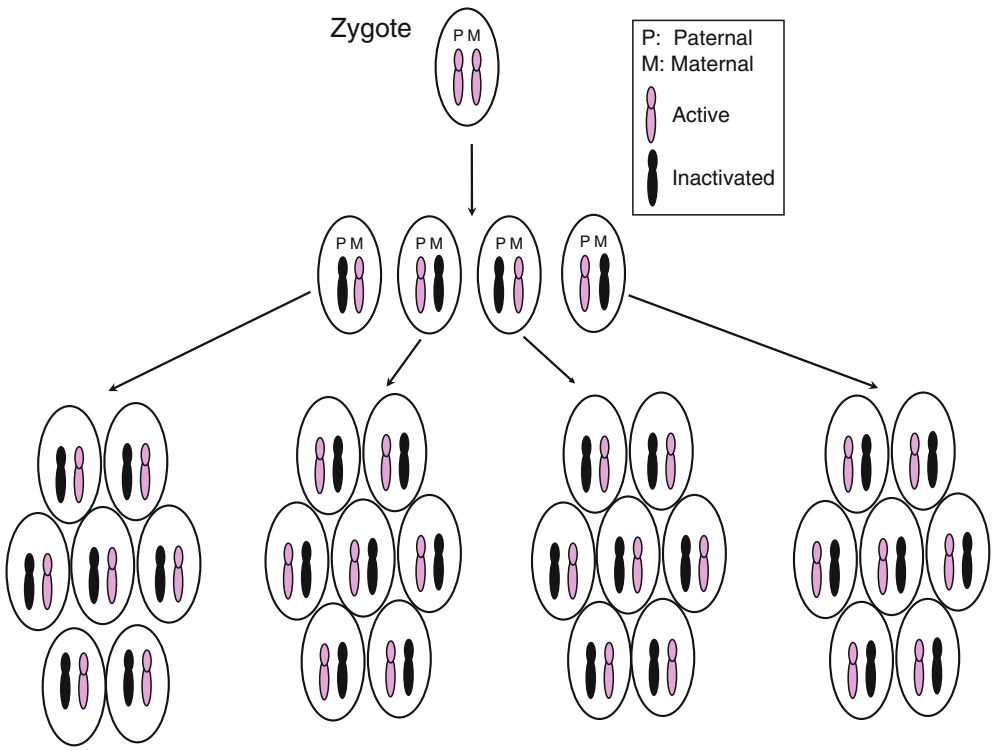

Figure 2.8

X-chromosome inactivation. In females, one of the two copies of the X-chromosome is inactivated randomly. Once an X-chromosome is inactivated, however, it will remain inactive. X-inactivation is controlled by the X-inactivation center (XIC), which is necessary and sufficient to cause X-chromosome inactivation

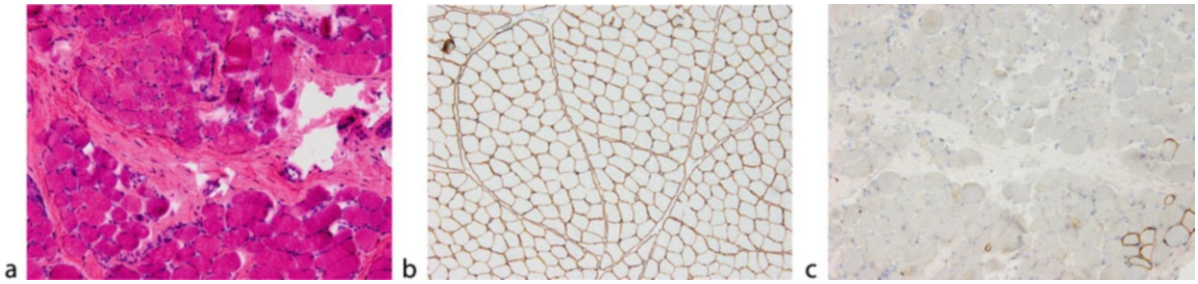

Figure 2.9
Dystrophin staining of skeletal muscle from a DMD patient. (Courtesy of Hart G.W. Lidov M.D., Ph.D. Department of Pathology, Children's Hospital Boston, Boston, MA) (a) H&E stained frozen section of skeletal muscle from a 6-year-old boy with Duchenne dystrophy. Fibers are slightly more rounded than usual for age, the diameter of fibers is more variable than normal, there is increased connective tissue between fibers (endomysial fibrosis) and scattered basophilic fibers (regenerating fibers) are present. Degenerating or necrotic fibers and inflammatory cells are sometimes seen in this condition, but are not prominent in this image. (b) A muscle biopsy from a child, without neuromuscular disease, immunostained for dystrophin. The brown reaction product, indicating the location of dystrophin, is found as a layer along the plasma membrane of all muscle fibers, a subsarcolemmal location. (c) Immunoperoxidase staining for dystrophin, in the same patient as above. Dystrophin is completely absent in most fibers, although a small cluster of dystrophin positive fibers are seen in the lower right, so-called revertant fibers

X-Linked Dominant Traits

For X-linked dominant conditions, the phenotypes in females are generally milder than in males. Therefore, daughters and sons of affected females are at 50% risk of being affected. All daughters but no sons of affected males will be affected. An example of an X-linked dominant condition is Rett syndrome (*Fig. 2.10*, *Table 2.1*). In a female, classical Rett syndrome is a progressive neurodevelopmental disorder. Clinical features include normal psychomotor development during the first 6–18 months of life followed by a period of developmental stagnation, then rapid regression in language and motor skills. During the progressive period, the typical clinical signs are repetitive stereotypic hand movements. Other clinical features include screaming, inconsolable crying, and autistic tendencies. Head growth may begin decelerating as early as 3 months of age. Brain size may be smaller than normal, but microcephaly is not an invariant feature of Rett syndrome. Seizures occur in 90% of affected females. Generalized tonic-clonic seizures and partial complex seizures are common. Failure to thrive is also often seen in affected females. It is possible that this may be associated with oropharyngeal and gastroesophageal incoordination, which cause poor feeding. In classical Rett syndrome, the female can survive into adulthood. Most males with Rett syndrome do not survive pregnancy, but some affected males present with severe neonatal encephalopathy, which usually results in death before age two.

Figure 2.10
Five-year-old girl with Rett syndrome. She had normal developmental milestones until 18 months of age and then lost most speech capability at 2½ years

Case Presentation

A 3-year-old girl born of non-consanguineous parents presented to the clinic with aggressive behavior since 1 year of age. She had normal developmental milestones until 18 months of age. However, she seemed to plateau in development and then lost most speech capability at 2½ years. There was no history of seizures or hyperventilation. On examination she had hypotonia, unusual hand movements, and autistic behavior. There was no ataxia. Her systemic examination was normal. She was diagnosed as being autistic. At age 5 years, she was reevaluated at a genetics clinic in an effort to determine an underlying cause for her delay. A review of her history confirmed that there had been no developmental progression beyond the 2-year level despite several years of intensive intervention. The history and exam revealed moderate dementia, partial apraxia, and microcephaly. She also had constant wringing movements of hands, patting, clapping, was easily annoyed, and could utter only two to three meaningless words. Based on the clinical findings and history, a diagnosis of Rett syndrome was made and a DNA blood test was sent for confirmation. Results indicated a known mutation in the *MECP2* gene, thereby confirming the diagnosis of Rett syndrome.

Rett syndrome is caused by mutations of methyl CpG binding protein 2 (*MECP2*). This protein plays an important role in the function of neuronal cells. The protein binds to methylated DNA, interacting with other proteins to form a complex that leads to inhibition of gene expression. Methylation occurs in CpG islands, which are frequently found near the promoter region of a gene. Once MECP2 binds to DNA, the DNA will condense and become inactive. Recent studies show that MECP2 forms a complex with histone deactylase (hDac), which catalyzes the removal of an acetyl group on the histone, therefore blocking the transcription of the gene. Rett syndrome is often misdiagnosed as autism, cerebral palsy, or nonspecific developmental delay, and can be a frequent cause of delayed development in girls. Diagnosis is mainly clinical, after excluding neurodegenerative disorders and other causes of delayed development. Confirmatory DNA testing is available in several specialty labs. The treatment is mainly speech therapy and counseling.

Y-Linked Disorders

Disorders associated with Y-linked inheritance are relatively few. In this case, the disease-causing gene is on the Y-chromosome. Only males are affected and every son of an affected male is affected. Most Y-linked disorders involved male-sex determination, particularly due to mutation in genes controlling sperm quality and quantity. They are most commonly diagnosed in men who seek evaluation for infertility.

Maternal Inheritance

The mitochondrion is the site in the cell where the majority of the ATP is produced. Each mitochondrion contains multiple copies of a circular double-stranded DNA molecule that encodes 13 protein subunits of the respiratory chain. The vast majority of mitochondria are maternally inherited. Mitochondrial genome mutations can lead to failure of energy metabolism and follow a pattern of maternal inheritance. It should be noted, however, that most mitochondrial proteins are encoded by genes in the nucleus, and mutations display typical Mendelian inheritance (usually autosomal recessive). As shown in *Fig. 2.11*, a mutation at the A3243G position of the mitochondrial genome causes maternal inheritance of

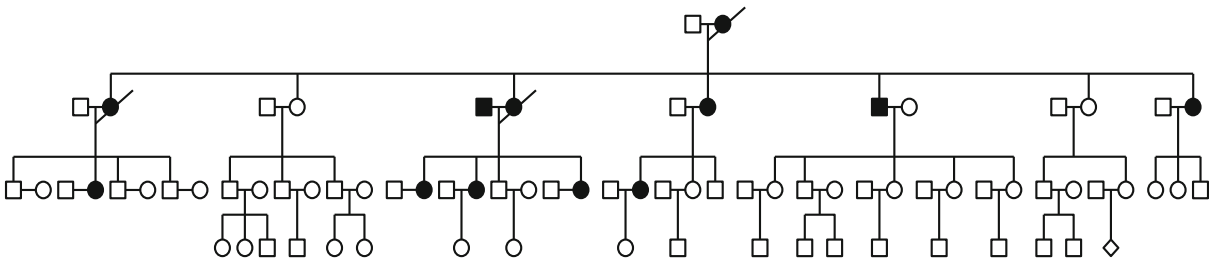

Figure 2.11
Maternal inheritance in mitochondrial diseases. The mutation in the mitochondrial genome is passed to offspring exclusively through women

diabetes. All affected individuals inherit the mutant mitochondrial genome from their mothers. No affected males pass the mutated genome to their offspring. Since each cell contains hundreds to thousands of mitochondria, each mitochondrion also contains multiple copies of the mitochondrial genomes. Therefore, the mutant and wild type mitochondrial genome can coexist, which is known as heteroplasmy. The degree of heteroplasmy can affect the clinical expression of the mutation.

Genomic Imprinting

For a majority of autosomal genes, the paternal and maternal alleles are both expressed. However, a small portion of genes are expressed in a parent-of-origin-specific manner. For example, gene *H19* on Chromosome 11 is only expressed from the maternal allele. In contrast, *IGF2* on the same chromosome is only expressed from the paternal allele. This phenomenon is referred to as genomic imprinting.

Prader–Willi syndrome is a typical example of a disorder of genomic imprinting. Prader–Willi syndrome is characterized by hypotonia, short stature, polyphagia, obesity, and small hands and feet. Hypogonadism and mental retardation also occur. The disorder results from lack of expression of a gene on chromosome 15 that is normally expressed from the paternal copy. A variety of types of mutation can lead to Prader–Willi syndrome. The most common is deletion of the region on 15q11.2. An alternative mechanism is uniparental disomy, in which both copies of 15 are derived from the mother. This can occur as shown in *Fig. 2.12*. Deletion of the maternal copy, or paternal uniparental disomy results in a different disorder – Angelman syndrome, characterized by seizures, developmental delay, and poorly coordinated body movements.

In summary, Mendelian disorders comprise an important component of pediatric genetic disorders. The most critical diagnostic tool is the family history. Being able to accurately analyze the pattern of inheritance can help making a diagnosis and identifying any at-risk family members. To analyze a pedigree, it is very important to know if transmission is vertical and to examine for male–male transmission (X-linked disorders will not have male-to-male transmission).

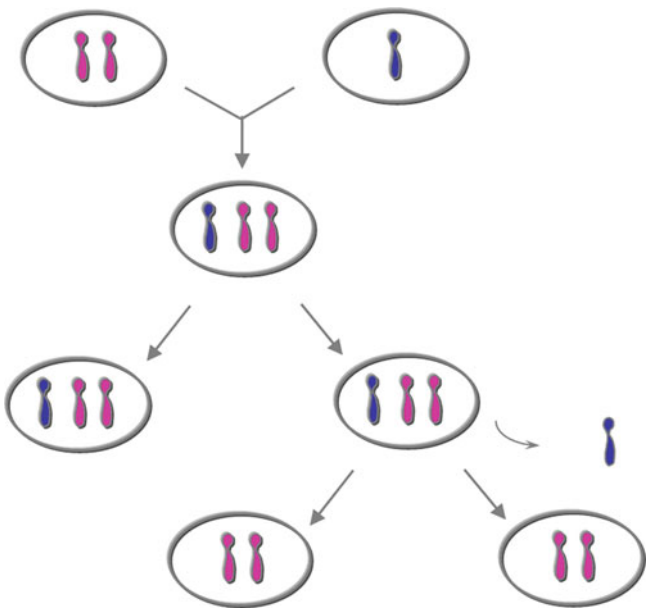

Figure 2.12

Genomic imprinting of Prader–Willi syndrome. A normal sperm is fertilized with an egg with two copies of chromosome 15, and this will result in trisomy 15. Since trisomy 15 is lethal, the cell will often find a way to remove one copy of chromosome 15. If the paternal chromosome 15 is eliminated, the remaining two copies of chromosome 15 will be both from the mother and result in maternal uniparental disomy. Since some genes are only expressed in paternal alleles and when two copies of gene are the maternal alleles, some of the genes normally expressed from the paternal allele are missing. In this case, this would result in Prader–Willi syndrome

In addition, it is also very helpful to examine the pedigree to determine if all the daughters of an affected father are affected. This could be an evidence of sex-linked-dominant mode of transmission. Does the trait skip a generation, indicative of non-penetrance? If the pedigree is large enough, determination of the segregation ratio is important (expect half of the offspring of affected individuals to be affected for a dominant trait).

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3 Congenital Malformation Syndromes

Gabriela M. Repetto

The birth of a child with single or multiple congenital anomalies is a source of stress for the family and the healthcare team, even in the presence of a known family history of the condition or of prenatal diagnosis. Identifying the correct etiology is relevant to plan for appropriate interventions, to search for possible associated abnormalities, to establish a prognosis, and to predict recurrence risk. This chapter summarizes the clinical evaluation of the child with congenital anomalies in the context of a syndrome, defined as a *recognizable pattern of abnormalities that share a common underlying etiology.* Approaches to common clinical problems with a brief depiction of some relatively frequent syndromes are included. Several thousand syndromes have been recognized and their individual description is beyond the scope of this section. References to specialized textbooks or databases have been incorporated for further reading.

Definitions/Classifications

Dysmorphology is the term used to describe the study of congenital anomalies. It is estimated that 2–3% of newborns have *major congenital abnormalities*, that is, those that are present at birth and require surgical or medical treatment because of functional or cosmetic consequences. Most newborns with major congenital anomalies have isolated ones, but it has been estimated that about a third to a half of those with congenital abnormalities, or 0.7–1% of all newborns, have multiple anomalies.

Recognizable patterns of anomalies are usually categorized as syndromes, sequences, and associations. As mentioned above, a *syndrome* is a recognizable pattern of anomalies with a common underlying etiology. For example, individuals with Down syndrome have identifiable facial features, developmental delay and mental retardation, central hypotonia, risk of congenital heart disease, hearing and visual impairment, among others; these manifestations are due to the presence of additional material from chromosome 21. Marfan syndrome is characterized by tall stature with long extremities, pectus carinatum or excavatum, lens dislocation, aortic root dilatation, and other features (*Fig. 3.1*) that are the result of mutations in the *FBN1* gene encoding for fibrillin, an extracellular matrix protein. A *sequence* is defined as a group of anomalies resulting as a cascade from a single initial defect in morphogenesis. Robin sequence, for example, refers to the association of microretrognathia (small and receding chin), glossoptosis and respiratory distress with or without cleft palate. It is presumed that microretrognathia in early development is the initial defect, causing a displacement of the tongue backwards and upward to a position that interferes with palatal closure. Potter sequence is characterized by flat facial features, abnormal positioning of the extremities, and pulmonary hypoplasia – findings that are secondary to oligohydramnios – and this is due to renal agenesis. An *association* refers to a group of congenital anomalies that occur together with higher frequency than expected by chance, but without a known common etiology. For instance, VACTERL (or VATER) association includes vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal and limb defects. Though there is no agreement on how many of these anomalies are sufficient to establish the diagnosis of VACTERL (authors suggest anomalies in at least three different anatomic regions), it is relevant to be aware of this association, as the presence of one of the defects should prompt the clinician to carefully search for the others. MURCS association includes Mullerian duct (upper vagina and uterus) hypoplasia, renal and cervical vertebra defects, also of so far unknown etiology.

With the increasing knowledge on the pathogenesis and availability of molecular tests, some conditions previously categorized as associations are now classified as syndromes. One example is CHARGE syndrome (coloboma, heart disease, choanal atresia, renal anomalies, growth and mental retardation, genital hypoplasia, and ear anomalies): microdeletions and mutations in the *CHD7* gene have recently been identified as the cause of the multiple and apparently unrelated anomalies. *CHD7* is a member of the chromodomain helicase DNA-binding (*CHD*) genes that encode for a class of proteins that are thought to have pivotal roles in regulating chromatin structure and gene expression in early embryonic development.

Clinical series and large epidemiologic studies have shown that syndromes may be recognized in the neonatal

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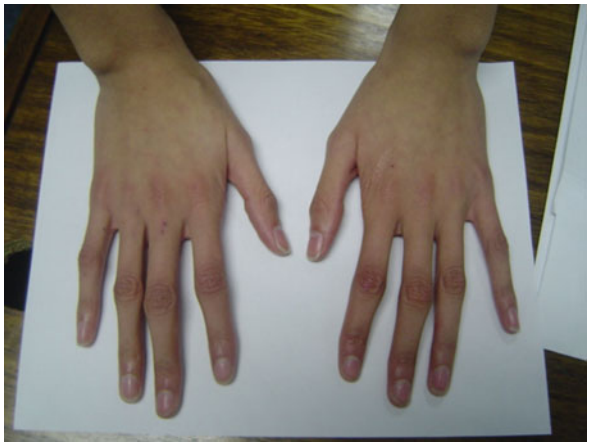


Figure 3.1
Arachnodactyly in a girl with Marfan syndrome

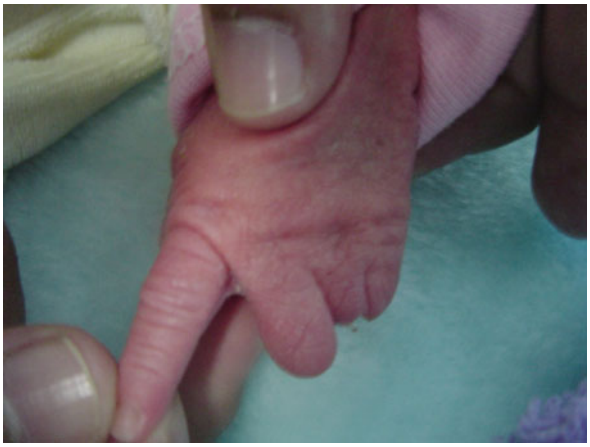


Figure 3.2
Third to fifth digit amputations due to amniotic bands

period in about 25% of newborns evaluated for congenital anomalies. A substantial portion of syndromes are recognized later in life, especially since several cardinal manifestations, such as developmental or growth delays can present in an age-dependant manner. This has practical implications for the clinician and the family, since arriving to a correct diagnosis may require long-term follow up and re-evaluation.

Several thousand syndromes have been delineated and many are described and catalogued in textbooks, such as Smith's Recognizable Patterns of Malformations and Syndromes of the Head and Neck, or computer or web-based clinical databases, such as the Baraitser-Winter Dysmorphology database (formerly London Dysmorphology database) and Pictures of Standardized Syndromes and Undiagnosed Malformations (POSSUM).

Etiology

On a pathogenic basis, congenital anomalies are classified as *malformations* (abnormal organ or tissue formation, as seen in congenital heart defects or spina bifida), *dysplasias* (abnormal organization of cells, such as skeletal dysplasias and lysosomal storage diseases), *deformations* (effect of extrinsic forces acting on an otherwise normal fetus or embryo, for example, intrauterine constraints leading to club foot), and *disruptions* (destruction of normal tissue, for example, by amniotic bands (*Fig. 3.2*), infections or hypoxia). Though there may be overlap within these categories, the classification has practical implications in terms of prognosis and recurrence risks. Patients with deformations tend to have relatively good therapeutic prognosis and low recurrence risks unless the underlying cause persists (such as uterine myomata or bicornuate uterus). Dysplasias are usually of genetic origin with recurrence risks that depend on the pattern of inheritance, and there is, in general, a paucity of curative therapies.

The term "congenital" (present at birth) does not in itself imply a specific etiology and is not synonymous with genetic cause. It has been estimated that chromosome abnormalities or rearrangements account for 5–10% of cases of major congenital anomalies, single gene defects for 10–15%, environmental (non genetic) causes such as infections or teratogens in 10%, polygenic/multifactorial (i.e., the result of an interaction between genetic and nongenetic factors) in 30–40%, and unknown cause in 30–50%.

Epidemiology

Birth defects surveillance systems have been implemented in different countries or regions to monitor the occurrence of congenital anomalies and conduct research geared towards understanding the causes, decreasing their consequences, and elaborating preventive strategies. The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) (http://www.icbdsr.org) collects information from over 40 programs around the world, a strategy that has been useful in understanding the causes that underlie several defects.

Based on data provided by these monitoring systems, it has been estimated, as described above, that about 2–3% of newborns have major congenital abnormalities.

In addition, other relevant anomalies, such as growth failure, developmental delays, mental retardation, hearing or vision loss, may be evident later, so that, by age 5 years, approximately 7% of children may have major anomalies that warrant the search for an underlying etiology.

Major congenital anomalies were estimated to account for half a million deaths worldwide in 1997 and constitute a substantial cause of neonatal and infant mortality in both developed and developing countries. As infant mortality rates have decreased worldwide in the past 50 years, the relative contribution of congenital anomalies to infant mortality has increased. Major congenital anomalies are also one of the most frequent causes of pediatric hospitalization, accounting for a third to one half of admissions to tertiary care hospitals.

Common types of major anomalies include, among many others, congenital heart disease, cleft lip and/or palate, and neural tube defects (including anencephaly and spina bifida) that have average incidences of 8/1,000, 1.6/1,000, and 1.1/1,000 live births, respectively. There is evidence of geographic or ethnic differences in frequencies of several birth defects. For example, the incidence of neural tube defects was highest, almost 19/1,000, in the Netherlands and 5/1,000 in France in the early 1990s, before folic acid supplementation was widely implemented in these countries. Regional differences have also been observed in the incidence of cleft lip.

Clinical Manifestations and Diagnosis: The Clinical Evaluation of the Child with Congenital Anomalies

Finding the correct diagnosis for a patient with single or multiple congenital anomalies has several implications: existing knowledge of the natural history of the condition will allow planning for additional evaluations and necessary care, available information on the particular syndrome will serve as a prognostic guideline, and knowledge of the cause of the syndrome will be necessary to estimate risk of recurrence and to consider and implement available preventative measures. Nevertheless, it is estimated that a definitive diagnosis is reached in only approximately 20–50% of children with multiple anomalies.

A genetic evaluation of an infant or child with congenital anomalies should be considered in the presence of two or more major anomalies (including mental retardation and short stature), one major and multiple minor anomalies, or a major anomaly and/or multiple minor ones and a family history of congenital anomalies, recurrent miscarriages (>2), neonatal death, parental consanguinity and infants with congenital anomalies and a history of potential teratogen exposure (◉ *Table 3.1*).

Table 3.1
Common reasons for referral to pediatric genetics evaluation

Two or more major anomalies
One major and multiple minor anomalies
One or more major and/or multiple minor anomalies and family history of congenital anomalies, parental consanguinity, recurrent miscarriages or teratogen exposure
Known genetic syndrome
Neonatal death

As in every area of medicine, achieving a correct syndrome diagnosis starts with a detailed clinical history and physical examination. The clinical evaluation of a child with congenital anomalies requires thoroughness. Relevant elements of the clinical history include the pregnancy history (pregnancy planning, parental age, occupation and health status, exposure to drugs, medications, alcohol, evidence of maternal infectious diseases and chronic illness, fetal movements, oligo- or polyhydramnios, ultrasound or other antenatal screening results), delivery (gestational age, presentation and mode of delivery, birth weight, length and head circumference and their relationship to gestational age), as well as neonatal adaptation and behavior, including evidence of asphyxia, neurological and biochemical abnormalities, such as hypoglycemia or hypocalcemia. If the child is older, information on growth and development as well as the interval medical history may also provide important diagnostic clues.

The family history is also relevant to diagnosis, since there may be other relatives with similar or related findings, including more subtle ones, or it may reveal other individuals at risk of developing the disease or of transmitting it to their offspring. Information is gathered as a minimum of three-generation pedigree and should include affected individuals, miscarriages, and consanguinity. A useful way of summarizing the family history is the drawing of a pedigree using standardized symbols (◉ *Fig. 3.1*).

The physical examination of the affected child, and other family members if necessary, constitutes another crucial diagnostic element. Growth and proportions should be documented and compared to age-appropriate percentiles. The basic parts of the general and segmental physical exam are performed, but special attention should be given to findings that may constitute major or minor

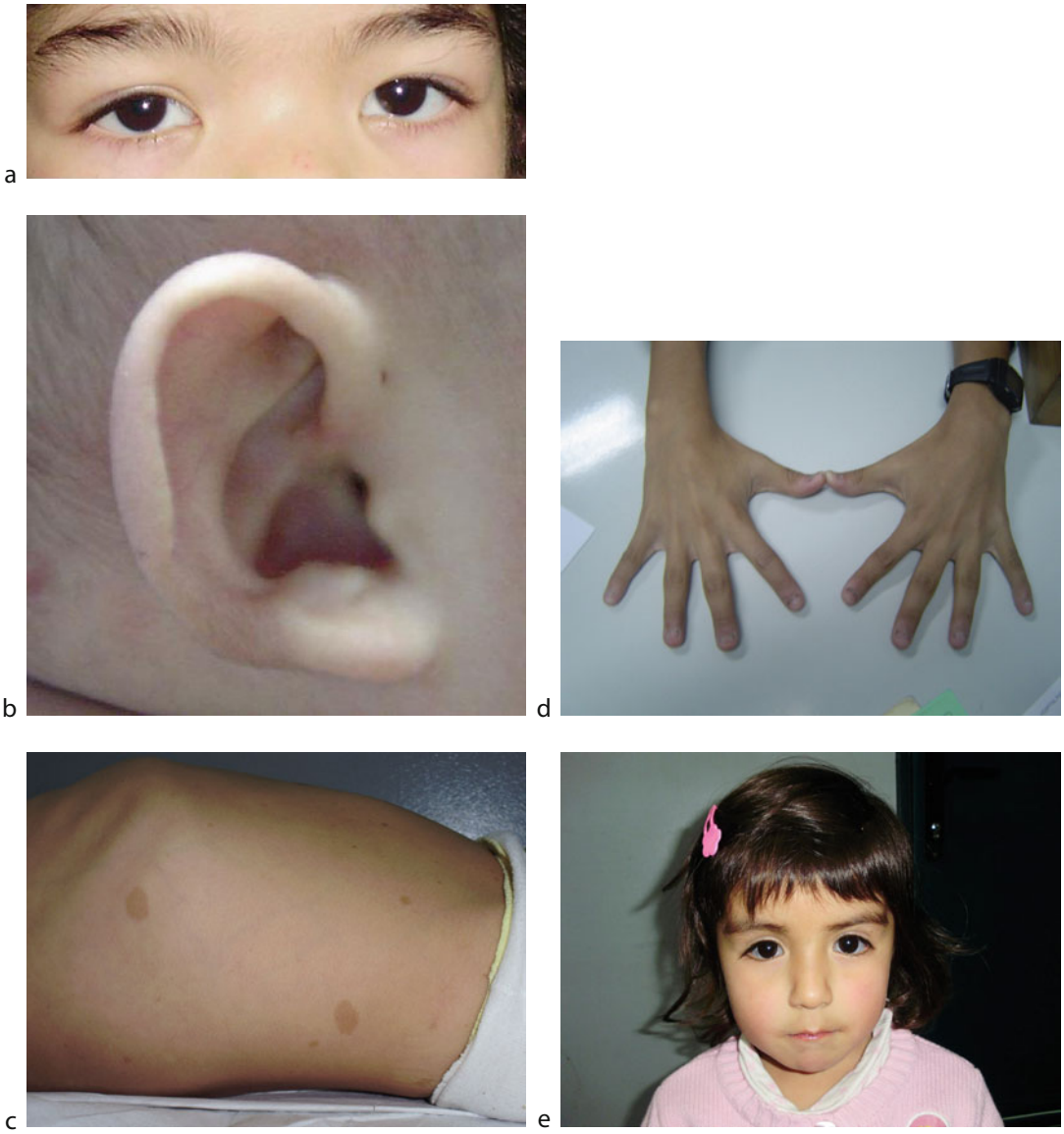


Figure 3.3
Examples of minor anomalies. (a) Inner epicanthal folds and depressed nasal bridge, (b) preauricular pit, (c) multiple café au lait spots, (d) interdigital webbing, (e) blue sclerae

anomalies, as well as the distinction of the latter from normal variants. *Minor anomalies* are those that constitute morphologic abnormalities that are of no serious medical or cosmetic consequence, and are present in 4% or less of the population. They tend to be more frequent in areas of complex formation, such as the face, ears, and hands. Examples include epicanthal folds, preauricular tags or pits, hypo-or hyperpigmented maculae, etc. (*Fig. 3.3*). The identification of these minor anomalies is relevant since they may provide diagnostic clues in the evaluation of a child with major anomalies. Additionally, it has been shown that the presence of three or more minor anomalies may be associated with the presence of major ones in 20–90% of infants. Therefore, it has been recommended to search for major anomalies in newborns with multiple minor anomalies. It can be challenging for the clinician to distinguish these minor anomalies from *normal variants*, defined as structural variations without

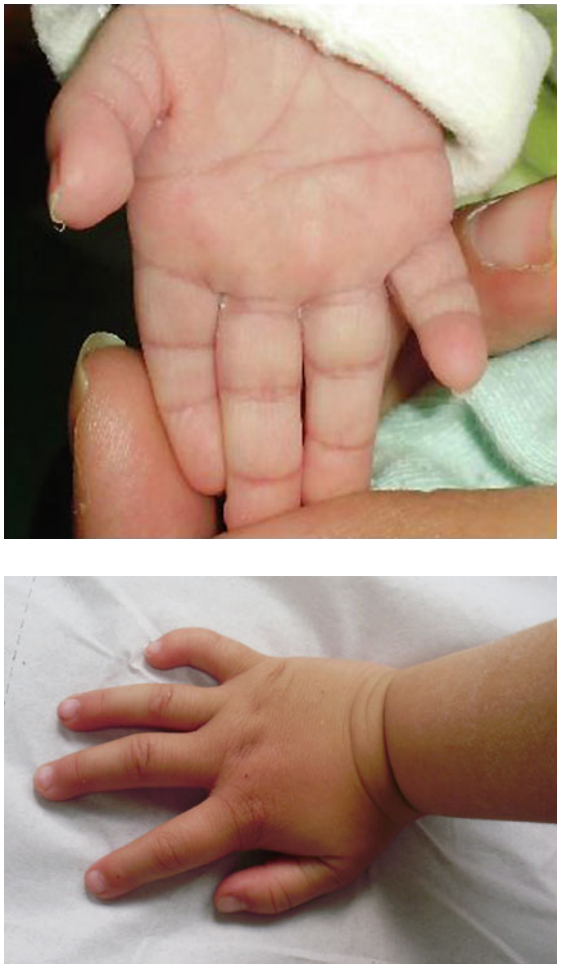


Figure 3.4
Examples of normal variants. (a) (Incomplete) transverse palmar crease, (b) fifth finger clinodactyly

medical consequences that are common in a population, occurring with a frequency of 4% or greater, such as transverse palmar creases, fifth finger clinodactyly, etc. (*Fig. 3.4*). The clinician should be aware of ethnic differences in frequencies of these minor findings; for example, epicanthal folds are common in Asian individuals and would thus be considered a normal variant in these populations, but they are infrequent in Caucasian individuals and therefore, would be catalogued as a minor anomaly in them.

It is useful to obtain objective measurements and to compare them with available standards. These standards have been constructed predominantly with data from Caucasian individuals; therefore, comparisons may also need to be interpreted with caution when used for patients of other ethnic origins. Photographs obtained with informed consent are useful to document the condition and age-related changes as well as to facilitate consultation with pertinent specialists. Several sites have implemented telemedicine services to facilitate evaluation of patients in remote locations, and this type of service is likely to continue growing in the future, allowing for access to specialist consultation.

Useful laboratory tests to further assess the phenotypic features include imaging studies to search for malformations not evident on surface exam, hearing and vision evaluations, formal developmental assessments, and biochemical tests, for example mucopolysaccharides when a lysosomal storage disease affecting these metabolites is suspected, or cholesterol levels in the case of Smith-Lemli-Opitz syndrome – a severe defect in cholesterol biosynthesis that causes microcephaly, a distinctive facies, congenital heart disease, genital abnormalities, Y-shaped syndactyly between the second and third toes, high prenatal and neonatal mortality, and mental retardation in the survivors.

Once all this clinical information has been gathered, the next step is to consider possible differential diagnoses. The clinician needs to keep in mind that no single sign is pathognomonic of a syndrome, minor anomalies are seen in otherwise healthy children, and there can be crucial diagnostic signs and symptoms that may appear later in life.

For the experienced clinician, a diagnosis may be achieved through what is known as the "gestalt" or pattern recognition approach. Since most syndromes are individually infrequent, it is unlikely that all of them would have been seen or recognized by a physician. As mentioned above, there are useful textbooks and computer databases that may aid in the identification of a diagnosis. It must be emphasized that the accuracy of such diagnosis relies fundamentally in the adequate recognition, description and prioritization of signs and symptoms by the clinician. As expressed by Hunter, these databases should be considered "systems for experts" rather than "expert systems."

If possible, once a diagnostic hypothesis has been proposed, laboratory confirmatory tests should be performed. Specific genetic tests are not available for all recognizable syndromes. In some cases, the underlying genetic etiology is unknown; in others, cost or accessibility issues may make testing not feasible. These limitations should not preclude the implementation of adequate care measures and education of the patient and his or her family.

The most commonly used genetic test is the karyotype, and it should be considered in the presence of a known recognizable chromosome abnormality syndrome, or in children with multiple major congenital anomalies or minor anomalies, mental retardation, or short stature.

If a specific microdeletion or microduplication is suspected based on the clinical findings, fluorescence in situ hybridization (FISH) testing with specific probes is a necessary additional form of testing. Higher resolution testing for genomic imbalances, such as array comparative genomic hybridization (array-CGH), has been shown to increase the rate of detectable chromosome abnormalities from 5–10% to an average of 17–20%. If a specific monogenic disorder is recognized, molecular testing to identify the causative mutation will be useful for confirmation and, if indicated, to offer testing to other relatives at risk. The detection rate of molecular testing for most monogenic disorders is less than 100% and it is necessary to begin testing with the affected individual if available. Once a mutation has been found, testing can be offered to affected or at-risk relatives. Web-based databases of laboratories that perform genetic clinical and research tests and descriptions of their uses are listed in *Table 3.2*, along with other useful sources of genetics information.

Some inborn errors of metabolism can be a cause of congenital anomalies, and biochemical tests may also be useful as diagnostic tools. Smith-Lemli-Opitz syndrome, described above, is an example. Defects in mitochondrial energy production may cause central nervous system malformations and patients may have abnormalities in lactate and pyruvate levels and in urine organic acids that aid in orienting to a specific diagnosis.

It is estimated that in about 50% or more of the evaluated patients no diagnosis will be made, even after a complete evaluation. The family should be reassured that the lack of a specific diagnosis will not impede access to therapies and that an incorrect diagnosis may be more harmful than no diagnosis. It is relevant, in these cases, to reevaluate the child with certain periodicity, since new and/or more specific signs or symptoms may appear in the patient with age, and new diagnosis or diagnostic tests may have been described or developed. A summary of the approach is presented in *Fig. 3.5*.

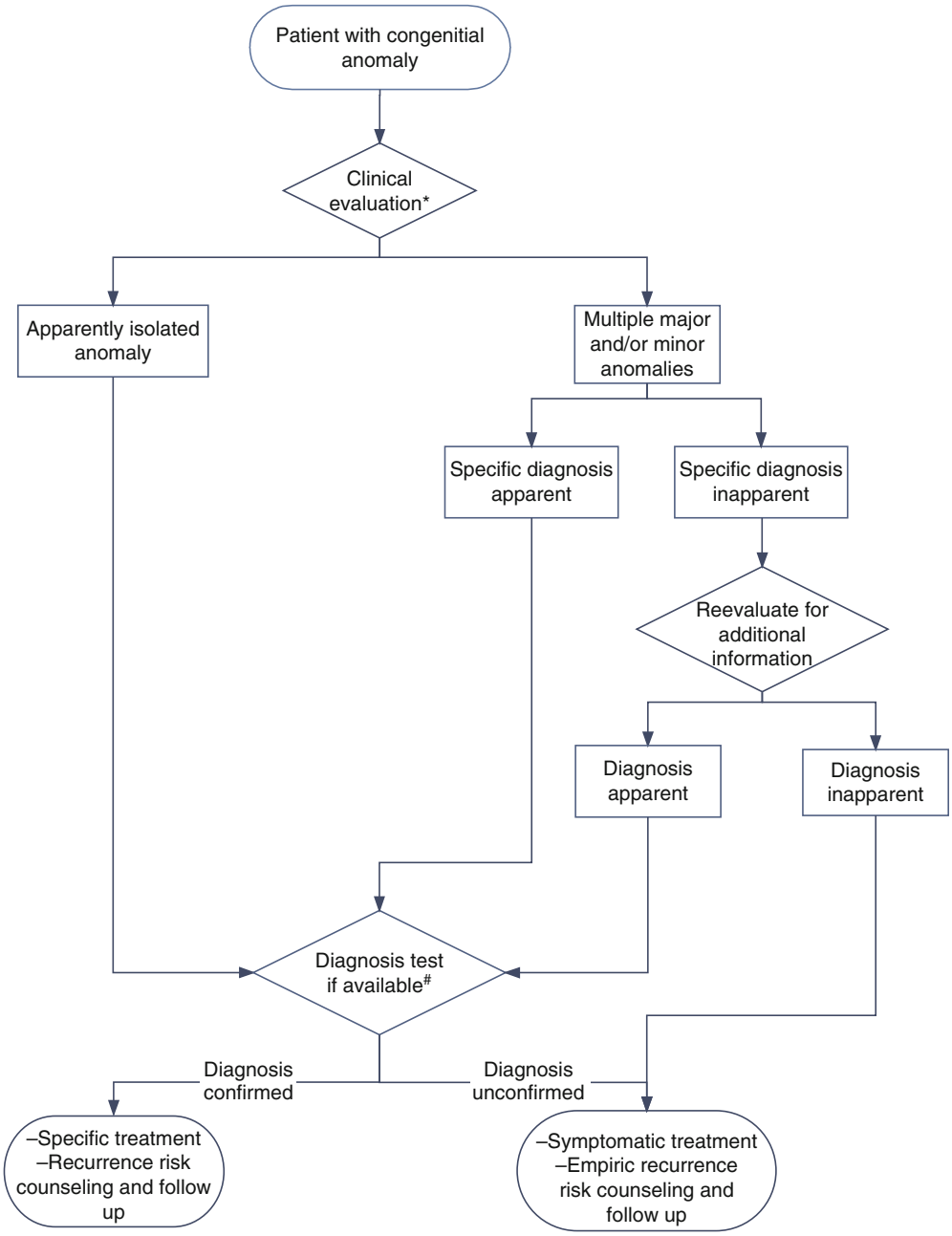
Management of the Child with a Congenital Malformation Syndrome

Because syndromes can be so different in manifestations and consequences, it is not possible to describe specific recommendations in this chapter. Nevertheless, there are some common relevant points: Medical care, psychological support and education of the family are all integral parts of the care of infants and children with congenital malformation syndromes. Information given to the family regarding prognosis and available therapies should be realistic. Referral to support groups is usually beneficial and appreciated by the parents. Some useful resources for parents are listed in *Table 3.3*.

Anticipatory care guidelines for several common genetic syndromes have been published by the Committee on Genetics of the American Academy of Pediatrics. They include recommendations for the care of children and adults with achondroplasia, Down, fragile X, Marfan, neurofibromatosis type 1, Turner, and Williams syndromes. These are useful sources for the clinician involved in the care of these patients, and place emphasis on the early detection and management of the manifestations of these conditions. Some of these guidelines also include

Table 3.2
Useful resources for information on diagnosis and management of children with congenital malformation syndromes

Website	Description	URL
Eurogentest	Information on genetic testing and clinics available in Europe	www.eurogentest.org
Genetests	Expert-authored reviews on genetic diseases, and listings of laboratories offering research and clinical genetic testing	www.ncbi.nlm.nih.gov/sites/GeneTests/ or www.genetests.org
Kansas University Medical Center Genetics Education Center	Listings of genetics websites and educational resources	www.kumc.edu/gec/
Online Mendelian Inheritance in Man (OMIM)	Updated information on human genes and Mendelian phenotypes	www.ncbi.nlm.nih.gov/omim
Orphanet	European resource for information on rare disorders and orphan drugs	www.orpha.net



* Patient and family history, physical examination, imaging studies, etc.
# Karyotype, molecular, and/or metabolic testing

Figure 3.5
Summary of clinical evaluation of the child with congenital anomalies, based on American College of Medical Genetics Guidelines

diagnosis-specific growth charts and expected development. Other useful sources of clinical information can be found in the sites listed in *Table 3.2*.

Recurrence risks are estimated based on the specific diagnosis and its cause. In the case of monogenic disorders, estimates can be made based on Mendelian proportions if the type of inheritance of the syndrome is known. For autosomal recessive conditions, the risk of having an affected child is 25% for each pregnancy if both parents are carriers. In the case of autosomal dominant disorders, the risk to an affected parent to have an affected child is 50%. In some cases, new mutations give rise to autosomal dominant disorders, implying low recurrence risks, but this information needs to be taken with caution, because of the phenomena of incomplete penetrance (a parent has the mutation but shows no phenotypic consequence, but still has a 50% chance of inheriting it to his/her offspring) and gonadal mosaicism, that is, the presence of other gametes with the mutation, leading to the possibility of recurrence. For X-linked recessive disorders, carrier mothers have a 50% chance of having an affected son and a 50% chance of having a carrier daughter for each pregnancy if the father is unaffected. In the case of fathers affected with X-linked disorders, every daughter will be an obligate carrier and sons will be unaffected, since they will inherit a Y chromosome from their father. In X-linked dominant disorders, both males and females are affected, though phenotypes may be more severe (or even lethal) in males. All daughters and no sons of an affected father are affected; the risk to sons and daughters of an affected woman is 50%.

Most of the isolated anomalies described at the beginning of the chapter have a complex or multifactorial cause, with contributing genetic and nongenetic factors. Their risk of recurrence is usually estimated based on empirical data. Recurrence risks for a selection of common isolated congenital anomalies are summarized in *Table 3.4*.

Empiric figures are also used for recurrence risk estimation of common aneuplodies or other chromosome abnormalities, which take into account the type of abnormality, the mode of ascertainment (e.g., through the birth of a child with anomalies, or through recurrent miscarriages), parental karyotype, and parental age.

The prognosis will depend on the underlying diagnosis, the manifestations in the particular child, and the

Table 3.3
Useful resources for parents (this table lists a limited number of resources, more can be found in the specific disease description in the Genetests or Orphanet websites)

Little People of America	www.lpaonline.org
National Down Syndrome Society	www.ndss.org
National Organization for Rare Disorders	www.raredisorders.org
Support Organization for Trisomy 18 and 13 (SOFT)	www.trisomy.org
Velocardiofacial Syndrome Educational Foundation	www.vcfsef.org

Table 3.4
Empiric average occurrence and recurrence risk for some relatively common, isolated, congenital anomalies (From Harper 2004)

Condition	Baseline population occurrence risk in Caucasians (%)	Recurrence risk for first-degree relatives if one person affected (%)	Recurrence risk for first-degree relatives if two persons affected (%)
Congenital heart disease	0.8	2–3	10
Cleft lip, with or without cleft palate	0.1	4	10
Cleft palate	0.04	1.8	8
Anencephaly/spina bifida[a]	0.16	3	10
Moderate to severe mental retardation	0.3	2.8	25

[a]Without periconceptional folic acid supplementation

availability and access to care. Particular issues arise in the presence of a diagnosis associated with poor survival in the neonatal or early infancy periods. Examples include trisomy 13, trisomy 18, or lethal skeletal dysplasias. In these cases, diagnostic confirmation allows to plan for appropriate and proportionate care and support of the child and family.

Approaches to Some Common Clinical Problems and Anomalies

A significant proportion of pediatric patients are referred to genetics evaluation due to a categorical problem or a specific major anomaly. As expressed above, the identification of the underlying cause may aid in the care, prognosis, and recurrence risk estimation. A brief description of key elements in the genetic evaluation of children with suspected syndromic causes of short stature, congenital heart disease, or cleft lip/palate is given below.

Syndromes Associated with Short Stature

Short stature, whether of prenatal or postnatal onset, is a relatively common medical problem, and a frequent reason for genetics evaluation. There are a wide number of causes, including normal variation as well as nutritional, gastrointestinal, renal, endocrine, and social causes that interfere with growth, among others. Nevertheless, short stature is also frequent in syndromes; therefore, genetic causes may need to be evaluated in a substantial portion of infants and children manifesting growth problems. As described above, the clinical evaluation is crucial, and should include a thorough pregnancy history in search for prenatal onset of growth deficiency, maternal illness, exposure to teratogens, etc., medical history in search for other illnesses and evaluation of growth velocity. Family history is important to assess the growth pattern, final height, age at puberty, and presence of hereditary diseases. The physical examination, in addition to the growth parameters, should include a search for major or minor anomalies that might provide clues to the underlying diagnosis. A helpful tool is the measurement of body segments to evaluate body proportions, in addition to height or length. These measurements include arm span (measured from the tip of one middle finger of one hand to the other with the arms fully extended in the horizontal plane) that normally is similar to total height or length. Measurements of lower and upper segments and of limb segments are also useful to assess body proportions. Standards have been published for these more specific dimensions, but should be used with caution since they have been obtained from North American individuals.

The presence of disproportion suggests a skeletal dysplasia. These are abnormalities in growth and development of bone and cartilage and usually affect bones or parts of bones differently, resulting in disproportion. If a skeletal dysplasia is suspected, the laboratory evaluation requires a radiologic skeletal survey, including anteroposterior (AP) and lateral (L) views of the skull, full spine and knees, and AP views of the thorax, pelvis, upper and lower extremities, hands, and feet. On occasion, and due to the age-dependant process of bone ossification, some abnormalities will not be evident in X-rays of infants and small children and therefore clinical and radiologic reevaluation will be required. One of the most common types of skeletal dysplasia is achondroplasia, due to mutations in the *FGRF3* gene that encodes for fibroblast growth factor receptor 3. Patients have short stature with short spine and limbs, macrocephaly, and normal intellectual abilities (*Fig. 3.6*).

Many other conditions show short stature without (or with more subtle) disproportion. Some examples are Williams syndrome, with features that include supravalvular aortic stenosis, hypercalcemia, developmental delays, and recognizable facial features; Russell-Silver syndrome, with relative macrocephaly, limb asymmetry, café-au-lait macules and clinodactyly of the fifth fingers; or Seckel syndrome, with severe pre- and post-natal growth failure, microcephaly that can be more pronounced than the short stature, prominent nose, micrognathia, and varying degree of mental retardation (*Fig. 3.7*).

Karyotype should be included in the evaluation of children with short stature. Several studies have shown that about 20% of girls with pathologic short stature have Turner syndrome. This is characterized by congenital heart disease in 30–40%, puffy hands, and feet at birth due to lymphedema (*Fig. 3.8*) webbed neck, widely spaced nipples, and ovarian dysgenesis, among other features. Molecular diagnosis is available for a constantly increasing number of conditions associated with syndromic and non-syndromic short stature.

Syndromes Associated with Congenital Heart Disease

Congenital heart disease (CHD) is one of the most common major congenital anomalies; with an estimated incidence of 8/1,000 live births. Genetic causes are being

Figure 3.6
A boy with achondroplasia, with a height of 115 cm at age 10 years

Figure 3.7
A girl with Seckel syndrome, with a length of 65 cm at age 2 years

increasingly identified not only for syndromic CHD, but also for nonsyndromic or isolated defects, thereby improving the understanding of the etiology of these anomalies. Several chromosomal syndromes include CHDs: 40–50% of newborns with Down syndrome have CHD and it is recommended that a cardiac evaluation, including an echocardiogram, be performed at the time of diagnosis. Frequent defects include common atrioventricular canal, ventricular septal defects (VSD), and atrial septal defects (ASD). CHD is also frequent in girls with Turner syndrome, with anomalies such as coarctation of the aorta, bicuspid aortic valve, valvular aortic stenosis, and risk of aortic dissection in adulthood. Some chromosome microdeletion syndromes also lead to an increased risk of CHD. About 60–75% of patients with chromosome 22q11 or velocardiofacial syndrome have defects in the cardiac outflow tract, such as tetralogy of Fallot, interrupted aortic arch and VSD, along with developmental delays, cleft palate or velopharyngeal insufficiency, among other features (*Fig. 3.9*). Patients with Williams syndrome, due to a microdeletion at chromosome region 7q11, frequently have supravalvular aortic stenosis, peripheral pulmonary

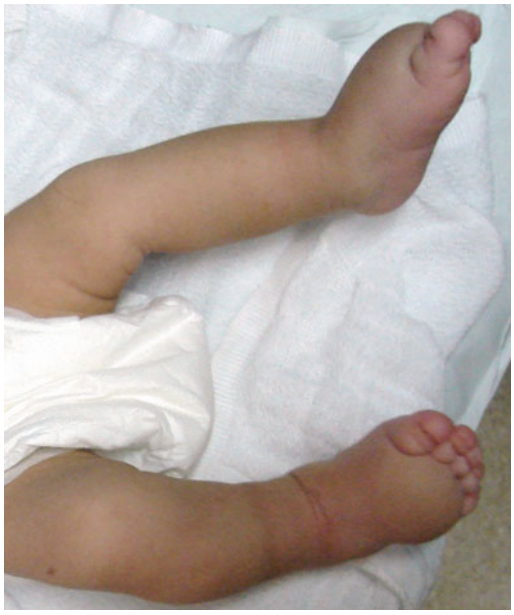


Figure 3.8
Lymphedema in a girl with Turner syndrome (Photograph courtesy of G. Lay-Son, MD)

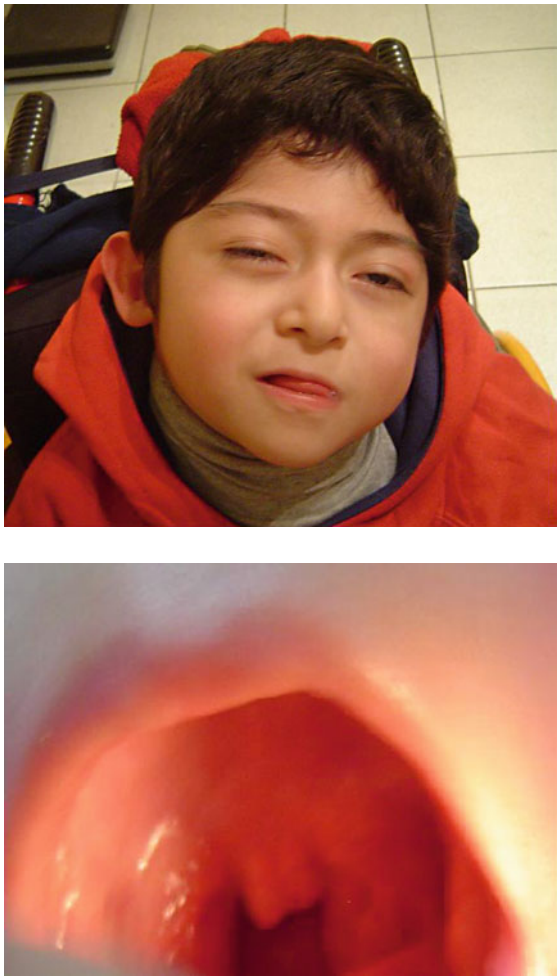


Figure 3.9
A boy with velocardiofacial syndrome (22q11 deletion). (a) facial features, including bulbous or round nasal tip and minor ear anomalies, (b) bifid uvula

artery stenosis or pulmonic valve stenosis associated with short stature, hypercalcemia, and hypertension.

CHD is also a relevant feature of several monogenic syndromes. The majority of patients with Noonan syndrome have CHD; characteristic types include dysplastic pulmonary valve leading to stenosis, and/or hypertrophic cardiomyopathy. Other syndromes, such as Costello and cardio-facial-cutaneous, share similar features (CHD, short stature, developmental delays, and characteristic facial features) and are due to mutations in *PTPN11*, *SOS*, and *KRAS* genes that are part of a common signaling pathway.

CHD can also be a part of syndromes due to teratogenic exposure. Examples include maternal phenylketonuria and maternal diabetes, fetal alcohol syndrome, and retinoic acid embryopathy. In addition, some teratogens can mimic the effect of genetic abnormalities, a phenomenon known as phenocopy. For example, DiGeorge sequence (abnormalities in the embryonic development of the third and fourth branchial arches and pouches leading to cardiac outflow tract defects, thymic and parathyroid aplasia or hypoplasia, resulting in immune deficiency and hypocalcemia respectively) can be caused by prenatal exposure to retinoids or by chromosome 22q11 microdeletion (*Fig. 3.9*).

Cardiovascular disease can also present later in several syndromes, so early awareness of the diagnosis can help in planning for appropriate screening and prevention. As mentioned above, girls with Turner syndrome can develop aortic dissection in adulthood and it is recommended for them to have regular cardiological evaluation in adulthood even if the person did not have CHD. Individuals with Marfan syndrome can have dilatation and dissection of the aorta, a life-threatening complication that can be partly reduced in rate with the use of beta-blockers or angiotensin II-receptor blockers.

Syndromes Associated with Cleft Lip or Cleft Palate

Orofacial clefts are relatively frequent major anomalies, and are second in frequency to congenital heart defects. As has been described for cardiac defects, most cases of orofacial clefts are isolated, that is, without other anomalies (but still may have a genetic etiology) and a proportion of individuals have syndromic clefts. From a pathogenic point of view, cleft lip with or without cleft palate (CL±P) is considered distinct from cleft palate (CP), they occur separately in families, and the former is more frequent than the latter (1–2/1,000 and 1/500 live births, respectively). CL±P is more commonly associated with other anomalies than CP alone.

Several common syndromes are associated with orofacial clefts: CL±P is frequent in trisomy 13 and 18, and CP, whether in overt or submucous forms, is seen in 70–80% of patients with chromosome 22q11 deletion or velocardiofacial syndrome. Monogenic syndromes that may manifest clefts include Stickler (CP with myopia, hearing loss, and arthropathy) (*Fig. 3.10*), Larsen syndrome (CP with flat facial profile and multiple joint dislocations), and van der Woude syndrome (one of the few conditions in which affected family members can have either CL±P or CP, associated with lip pits).

Teratogens can also be a cause of clefting. CL±P is seen in patients with fetal alcohol syndrome (with growth

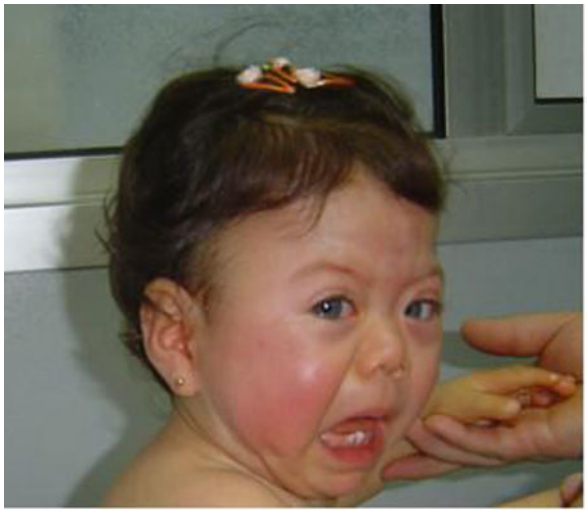


Figure 3.10
A girl with Stickler syndrome, with flat facial profile and relatively prominent eyes

deficiency, variable mental retardation, microcephaly, short palpebral fissures, and flat philtrum), fetal hydantoin syndrome (short stature, mental retardation, hypoplasia of distal phalanges and small nails), and fetal valproate syndrome (with congenital heart disease and spina bifida).

Prevention

As neonatal and infant mortality from infections and complications of prematurity have decreased worldwide, there has been a relative increase in morbidity and mortality from congenital anomalies, both in an isolated manner and in the context of syndromes. Most cases of congenital malformation syndromes will arise in families without a previous history, making the identification of couples at risk difficult. Most common chromosome abnormalities are sporadic, as is the case of the majority of instances of Down and Turner syndromes. With respect to monogenic disorders, de novo or new mutations occur for a large proportion of autosomal dominant (as in achondroplasia and neurofibromatosis type 1, among others) or X chromosome-linked conditions (e.g., Rett syndrome and Goltz syndrome), and most individuals with autosomal recessive conditions have healthy heterozygous carrier parents (as in Smith-Lemli-Opitz syndrome or Seckel syndromes).

Nevertheless, a proportion of these seemingly unexpected conditions have known, identifiable risk factors, such as advanced maternal age for chromosome aneuploidies, advanced paternal age for de novo dominant mutations, parental consanguinity for autosomal recessive syndromes, teratogen exposures, such as fetal alcohol syndrome and chronic uncontrolled maternal illnesses, such as diabetes mellitus or phenylketonuria. Hence, the Latin American Collaborative Study of Congenital Malformations (ECLAMC, for Estudio Colaborativo Latinomericano de Malformaciones Congénitas) has proposed a "Decalogue for Prevention of Congenital Anomalies" focused on the avoidance of known risk factors such as unintended pregnancy, advanced maternal age, deficient prenatal controls, rubella, self-medication, alcohol, smoking, malnutrition, occupational risks, and poor health care.

In addition to these preconceptional preventative measures, options are available for antenatal screening or diagnosis of several syndromes. First and second trimester screening for common aneuploidies such as trisomies 21 and 18 is usually performed by a combination of maternal age, ultrasound markers (most commonly nuchal translucency), and/or biochemical markers. Screening has incidentally been found to be useful to identify fetuses at risk for other conditions such as Smith-Lemli-Opitz syndrome as well as adverse perinatal outcomes. Fetal ultrasound is also useful to identify structural anomalies that may suggest the existence of a syndrome. These screening procedures are useful to select pregnancies that warrant further studies, such as invasive karyotype or molecular testing (by chorionic villous sampling, amniocentesis or chordocentesis) or additional studies such as fetal magnetic resonance imaging.

Education is also a crucial part of prevention. This can be accomplished through genetic counseling, defined as "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease" (National Society of Genetic Counselors, www.nsgc.org). This process includes, in the case of congenital malformation syndromes, providing information to the patient and/or family about the specific diagnosis, mode of inheritance, occurrence or recurrence risks, and the available therapeutic and preventative alternatives.

Case Histories

Case 1

You are called to evaluate a term adequate-for-gestational-age (AGA) newborn with feeding difficulties and respiratory distress. On physical examination you note that the

newborn shows mild tachypnea with mild intercostal retractions but normal pulse oxymetry in the supine position. You find that she has microretrognatia and a cleft of the soft palate, without other evident anomalies. You position her on her side and the respiratory rate and pattern normalize. The pregnancy history is unremarkable. The mother has high myopia and a history of chronic joint pain, and has been given the diagnosis of arthritis of unknown etiology; the rest of the family history is noncontributory. Given the association of microretrognathia, cleft palate, and respiratory difficulties, you consider that she has Robin sequence. This malformation could be "non-syndromic," of unknown cause, or perhaps due to fetal crowding or decreased intrauterine mobility. You also learn that about 40–50% of cases can be caused by syndromes, the most common ones being 22q11 microdeletion (or velo-cardio-facial) syndrome (◉ *Fig. 3.9*) and Stickler syndrome (◉ *Fig. 3.10*), a connective tissue disorder due to mutations in *COL2A1*, *COL1A1*, *COL9A1*, or *COL11A1*, genes encoding for collagen chains. Karyotype and FISH 22 studies are normal in your patient, and you request an ophthalmologic evaluation that shows that the newborn has high myopia, like her mother. Stickler syndrome is characterized by arthropathy, flat vertebrae, myopia with risk of retinal detachment, Robin sequence, and deafness. You review the maternal X-rays, and they are consistent with this diagnosis. You conclude that the newborn and her mother have Stickler syndrome, and in addition to managing her airway and feeding problems, you make a plan to continue to follow the baby's and mother's vision and hearing, as well as future musculo-skeletal manifestations. The family is counseled that Stickler syndrome is inherited as an autosomal dominant condition and that the probabilities of recurrence are 50% for each subsequent pregnancy. Molecular analysis of the *COL2A1* gene identifies the causative mutation, information that may be used for prenatal diagnosis or other at-risk relatives.

Case 2

A term AGA, 5-day old newborn boy has hypotonia and feeding difficulties, with loss of 12% of his birth weight. On physical examination, he is noted to have a narrow forehead, small hands and feet, small male genitalia, and cryptorchidism. He has moderate hypotonia, poor Moro and suck reflexes, and normal deep tendon reflexes. He is also noted to have hypopigmentation of his skin, hair, and irides compared with his family. He is diagnosed with central hypotonia. Brain imaging studies are normal. Given his findings, the diagnosis of Prader-Willi syndrome (PWS) is considered. Confirmatory genetic studies show a normal karyotype, absent paternal contribution on chromosome 15 methylation analysis, and a microdeletion in the proximal part of chromosome 15 (15q11q13), consistent with the suspected diagnosis. PWS is a genetic disorder due to the absence of the paternal genes in chromosome region 15q11q13. In this case, it was due to a small deletion in the region. PWS is characterized by neonatal central hypotonia with transient feeding difficulties and failure to thrive in the first year or two of life. Children subsequently develop hyperphagia and obesity, short stature, hypogonadism, developmental delays, and mild to moderate mental retardation. Given the transient nature of the infantile feeding difficulties, nasogastric tube feedings were started on the patient, and referral was made to an Early Intervention Program, as well as follow up by an endocrinologist. PWS due to 15q11q13 microdeletion is usually a sporadic condition, and the parents were informed that the risk of recurrence in future pregnancies is probably low (≈1% or less).

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4 Cytogenetic Testing and Chromosomal Disorders

Joris Robert Vermeesch · Karen Buysse

Cytogenetic Testing

It took until 1956 before the correct number of human chromosomes of 46/cell was determined by Tjio and Levan. The discovery of the correct number of human chromosomes lead to the subsequent discovery that trisomy 21 is the cause of Down syndrome. Soon thereafter, a series of associations of different birth defects with specific chromosomal imbalances became apparent. First, the chromosomes 13 trisomy (Patau syndrome), trisomy 18 (Edwards syndrome), and monosomy and trisomy X syndromes were identified. Subsequently, smaller segmental chromosomal imbalances such as 5p- and 4p- were proven to cause birth defects. These associations launched cytogenetic genetic testing as a routine diagnostic tool and resulted in systematic screening for children with birth defects. These screenings, in turn, resulted in the identification of thousands of chromosomal imbalances associated with specific syndromic features.

Initially, chromosome studies were performed using simple staining techniques that only allowed the detection of entire groups of chromosomes. The degree of precision was increased in the 1970s with the introduction of chromosome banding techniques. These techniques enabled the detection of individual chromosomes and segments (bands) within chromosomes. Although chromosomal karyotyping allows a genome-wide detection of large chromosomal abnormalities and translocations, it has a number of inherent limitations: (1) it takes 4–10 days to culture the cells, visualize the chromosomes and perform the analysis; (2) the resolution is limited to 5–10 Mb depending on (a) the location in the genome, (b) the quality of the chromosome preparation, and (c) the skill and experience of the cytogeneticist; (3) it requires skilled technicians to perform a Giemsa-banded karyotype analysis, which increases employment costs and can lead to organizational difficulties in small laboratories.

With the introduction of fluorescence in situ hybridization (FISH), the detection of submicroscopic chromosomal imbalances (imbalances not visible by conventional karyotyping because they are too small) became possible. In FISH, labeled DNA probes are hybridized to nuclei or metaphase chromosomes to detect the presence, number, and location of small (submicroscopic) regions of chromosomes. FISH is routinely applied to confirm the clinical suspicion of known microdeletion syndromes. Some common examples are the detection of the velocardiofacial (VCFS, 22q11 deletion, OMIM 192430), William's (7q11.23 deletion, OMIM 194050) and Prader-Willi (15q11.2–13 deletion, OMIM 176270) syndromes. FISH also detects deletions in the gene-rich subtelomeres, which are involved in mental retardation and a number of syndromes, such as the Wolf–Hirschhorn (deletion 4p, OMIM 194190) and chromosome 1p36 deletion (OMIM 607872) syndromes.

Unfortunately, FISH can only detect individual DNA targets rather than the entire genome. To overcome this problem, multicolor FISH–based karyotyping (SKY, MFISH, and COBRA FISH) was developed, which enables simultaneous detection of all chromosomes. Another technology allowing the genome-wide detection of copy number aberrations was introduced in 1992 and termed comparative genomic hybridization (CGH). In CGH, test and reference genomic DNAs are differentially labeled with fluorochromes and then co-hybridized onto normal metaphase chromosomes. Following hybridization, the chromosomes are scanned to measure the fluorescence intensities along the length of the normal chromosomes to detect intensity ratio differences that subsequently pinpoint to genomic imbalances. Overall, the resolution at which copy number changes can be detected using these techniques are only slightly higher as compared to conventional karyotyping (>3 Mb) and experiments are labor intensive and time consuming.

By replacing metaphase chromosomes with mapped DNA sequences or oligonucleotides arrayed onto glass slides as individual hybridization targets, the resolution could be tremendously increased. Following hybridization of differentially labeled test and reference genomic DNAs to the target sequences on the microarray, the slide is scanned to measure the fluorescence intensities at each

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target on the array. The normalized fluorescent ratio for the test and reference DNAs is then plotted against the position of the sequence along the chromosomes. Gains or losses across the genome are identified by values increased or decreased from a 1:1 ratio ($\log_2$ value of 0), and now the detection resolution only depends on the size and the number of targets on an array and the position of these targets (their distribution) on the genome. A schematic overview of the technique is provided in *Fig. 4.1*. This methodology was first described in 1997 and is termed "matrix CGH" or "array CGH". Array CGH has initially been employed to analyze copy number changes in tumors with the aim to identify genes involved in the pathogenesis of cancers. More recently however, this methodology has been optimized and applied to detect unbalanced constitutional human rearrangements. With improved protocols, it rapidly became clear that not only larger insert BAC clones were appropriate targets for array CGH, but also smaller-sized cDNA fragments, PCR products, and oligonucleotides. In addition to comparative hybridization using two differentially labeled DNA samples, single sample hybridization can also be compared versus different reference arrays. This approach is the basis of the so-called SNP arrays.

Genome-wide array CGH has been called molecular karyotyping in analogy with conventional karyotyping. Because many cytogeneticists object to this term, most recently, the term "cytogenomic array" has been put forward to refer to high-resolution array-based whole genome testing for genomic copy number (recommendation of the consortium of International Standards on Cytogenomic Arrays (ISCA), https://isca.genetics.emory.

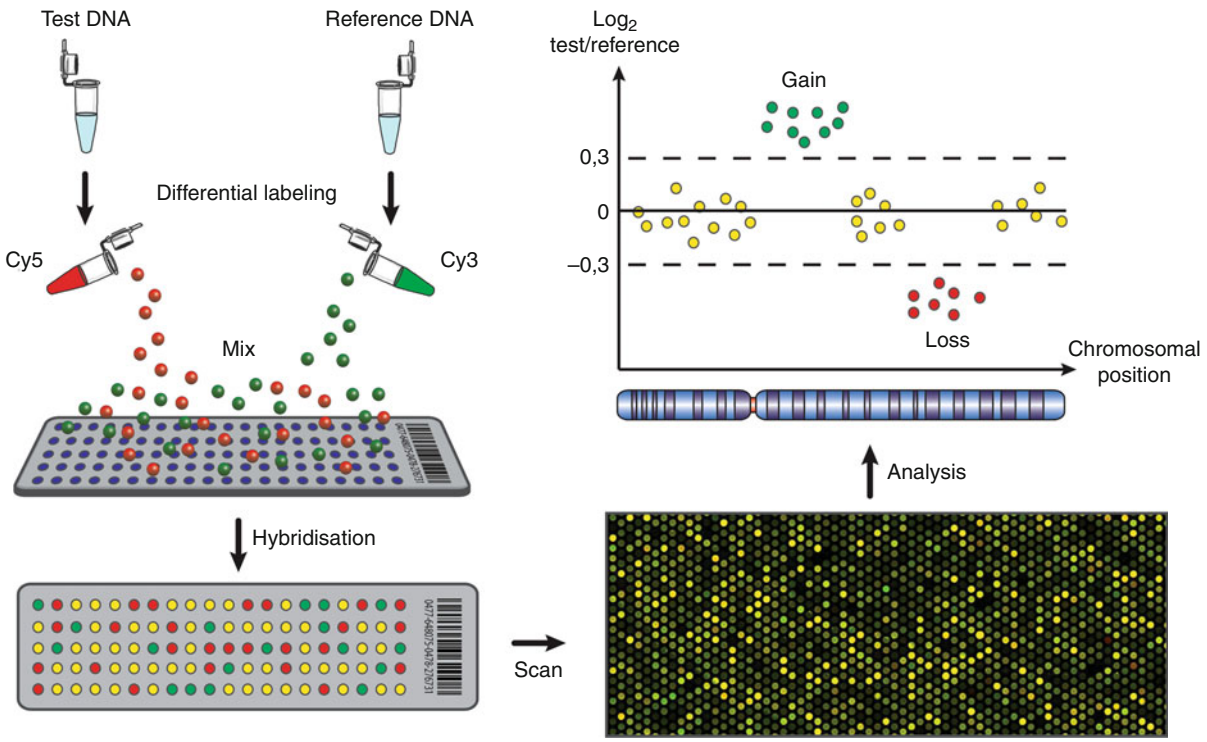

Figure 4.1

Principle of array CGH. Equal amounts of test and reference DNA are differentially labeled with fluorochromes (e.g., Cy5 and Cy3), mixed and when necessary supplemented with Cot-1 DNA to block repetitive sequences. This mixture is denatured and hybridized on a microarray slide on which DNA probes (e.g., BACs or oligonucleotides) are immobilized. Slides are scanned and fluorescent intensities quantified from the image. Signal intensity ratios are plotted corresponding to the genomic position of the DNA probe and represent the relative DNA copy number of the test DNA in comparison with the reference DNA

edu/iscaBrowser/learnabout.jsp). The implementation of genome-wide arrays as a tool to screen children with developmental anomalies has increased the diagnostic yield significantly. A series of early studies showed diagnostic yields between 9% and 25%. A meta-analysis of patients with congenital and mental anomalies on 13,926 subjects reported an overall diagnostic rate of 10% for causal anomalies and a retrospective analysis of 36,325 patients revealed abnormalities in about 19% of the patients. While conventional G-banding has a diagnostic yield of about 3% in similar patient populations, it can be concluded that molecular karyotyping is outperforming conventional karyotyping for the detection of causative chromosomal imbalances in patients with birth defects. Therefore, the technology is currently complementing traditional cytogenetic testing and is recommended as a first-tier diagnostic test for children with developmental disorders.

Types and Incidences of Chromosomal Abnormalities

Microscopically Visible Chromosomal Imbalances

All chromosomal imbalances that can be detected by conventional karyotyping are microscopically visible. These aberrations are either numerical (abnormal chromosome number) or structural (altered structure).

Numerical Chromosome Aberrations

Normal humans are diploid, meaning they have 22 pairs of autosomes and one pair of sex chromosomes. The presence of three sets (triploidy) or four sets (tetraploidy) can occasionally occur; however, these are not viable.

Numerical aberrations result from the loss (monosomy) or gain (trisomy) of an individual chromosome. Autosomal monosomies are inviable, while the absence of one X chromosome may result in a liveborn girl with Turner syndrome (45,X). A few autosomal trisomies are compatible with life. Fetuses with trisomy 13 (Patau syndrome) and trisomy 18 (Edwards syndrome) can survive to term but usually die shortly after birth due to severe congenital anomalies. Individuals with trisomy 21 (Down syndrome) can stay alive longer, with an average life span reaching up to 55 years. In addition, sex chromosomal trisomies and tetrasomies are often encountered; the best known is Klinefelter syndrome (47,XXY).

Structural Chromosome Aberrations

Structural chromosomal aberrations result from double-strand breaks and inappropriate DNA repair leading to translocations, deletions, duplications, inversions, isochromosomes, and ring chromosomes (*Fig. 4.2*). They may involve single or multiple chromosomes. One can distinguish rearrangements without and with loss or gain of chromosomal segments. The former are most often not associated with an abnormal phenotype, while the latter most often cause developmental disorders. Carriers of apparently balanced rearrangements, however, are at risk for having children with chromosomal imbalances.

In translocations, chromosomal segments between two or more chromosomes are exchanged. Robertsonian translocations are translocations between two acrocentric chromosomes (chromosomes 13, 14, 15, 21, and 22). There is no loss of euchromatin and the carriers are normal. In reciprocal translocations, segments between two chromosomes are exchanged. The translocation is termed balanced if no chromosomal material has been lost or gained. Inversions represent a special type of apparently balanced rearrangement. In an inversion, the rearrangements occur intrachromosomally and a chromosomal segment is inverted. If the inversion occurs within one chromosomal arm it is called "paracentric" (not including the centromere); if it occurs in two chromosomal arms it is termed "pericentric" (spanning the centromere). Carriers of balanced translocations and inversions are usually normal, but developmental anomalies are detected in 6% of de novo translocation carriers. The presence of a developmental disorder can be due to (1) the breakage of a gene resulting in a dominant disorder or in a recessive disorder if the second allele is also mutated, (2) a position effect on a gene flanking the breakpoint, or (3) the gain of function via the creation of a fusion gene. Recently, it was shown that 40% of the apparently balanced translocation carriers with developmental disorders have submicroscopic imbalances at the breakpoints or elsewhere in the genome that may be disease causing.

If genetic material is gained or lost, the abnormality is called unbalanced. If there is loss of a chromosomal segment it is called a deletion, or if there is a gain, a duplication. The presence of both a large deletion and duplication suggests the presence of an unbalanced translocation. Those usually result from the transmission of the unbalanced products during the meiosis of a balanced translocation-carrying parent. Occasionally unbalanced

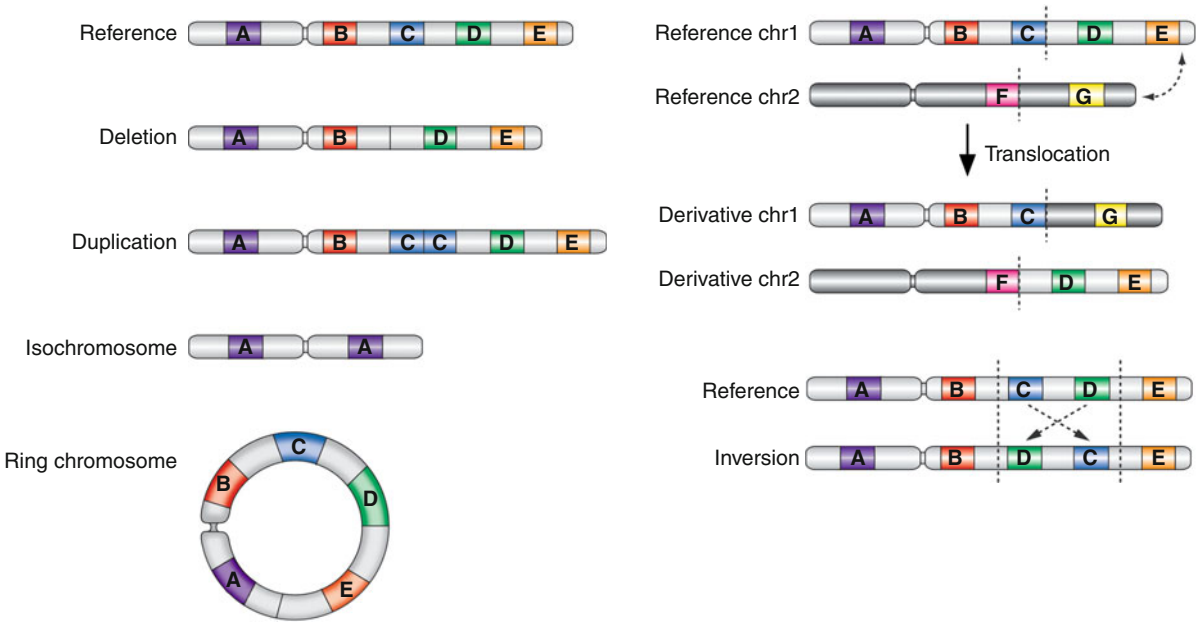

Figure 4.2

Schematic overview of structural chromosomal rearrangements. A deletion results in the loss of chromosomal material (segment C), while there is a gain of material (two copies of part C) in a duplication. Duplication of one arm and deletion of the other arm gives rise to an isochromosome, while fusion of the short and long arms of a chromosome leads to a ring chromosome. In a translocation, part of one chromosome is transferred to another chromosome. In this example, there is an exchange between segments D and E of chromosome 1 and segment G of chromosome 2. An inversion results in a reversed orientation of genetic material (inversion of segments C and D)

translocations arise de novo. The deletion or duplication of one or more dosage-sensitive genes usually results in developmental disorders.

Incidence of Chromosomal Abnormalities

Studies performed in the late 1960s and early 1970s (i.e., before the widespread use of prenatal diagnosis and pregnancy intervention) provide estimates for the frequencies of chromosomal abnormalities at birth. A combined survey of 68,159 livebirths and of 34,910 liveborns found that 0.65–0.84% of newborns or 1 in 119–154 livebirths had a major chromosomal abnormality (*Table 4.1*). Trisomy 21 (Down syndrome) was shown to be the most frequent chromosomal anomaly, with an incidence of 1.2–1.7/1,000 liveborns. Sex chromosome aneuploidies were the next most common, with approximately one XYY and one XXY in every 900–1,000 male and one XXX in every 900–1,000 female livebirths. Structural balanced rearrangements had a frequency of approximately 2/1,000 livebirths.

Structural rearrangements can occur de novo or be the consequence of the unbalanced transmission of a parent carrying a chromosomal rearrangement. However, all arose de novo at one point. It is estimated that de novo balanced reciprocal translocations arise at birth with a frequency of 1.6×10^{-4} and unbalanced rearrangements with a frequency of 2.9×10^{-4}.

Submicroscopic Imbalances

The first methodology to enable the visualization of imbalances below the resolution of regular light microscopes was FISH. Recurrent syndromes were proven to be caused by recurrent submicroscopic imbalances. Once the imbalance was characterized, metaphase spreads or interphase nuclei of patients with similar phenotypes could be screened with locus specific probes for the loss or gain of a specific locus. This methodology requires careful clinical examinations in order to instigate appropriate genetic testing.

Table 4.1
Incidence of chromosomal abnormalities in newborns

Type of abnormality	Rate per 1,000 Benn and Hsu (2004)	Rate per 1,000 Nielsen and Wohlert (1991)
Autosomal trisomies		
+13	0.04	0.09
+18	0.13	0.29
+21	1.2	1.69
Sex chromosomes males		
47,XYY	1.03	1.18
47,XXY	1.03	1.57
Other	0.73	0.17
Sex chromosomes females		
45,X	0.24	0.53
47,XXX	1.09	1.06
Other	0.36	0.06
Structural balanced		
Robertsonian	0.9	1.23
Reciprocal and insertional	1.21	1.74
Structural unbalanced		
Deletions & duplications	0.4	0.34
Marker chromosomes	0.2	0.66
Total	6.24	8.42

With the advent of cytogenomic arrays, a true revolution in the analysis of genomes in general and especially the analysis of the genomes of patients with mental retardation and developmental anomalies is taking place for two reasons: (1) It has now become possible to screen the genome at very high resolution for copy number changes and (2) no *a priori* clinical identification is required to enable correct cytogenetic testing. In the last 5 years, more pathogenic copy number changes have been linked to developmental disorders than in the 50 years before.

Recurrent Submicroscopic Rearrangements

Recurrent imbalances often result from nonallelic homologous recombination (NAHR) between low-copy repeats (LCRs) flanking the commonly deleted or duplicated region (see Recurrent Submicroscopic Imbalances). Many of such recurrent imbalances, also known as *genomic disorders*, were identified before the array era and were often known as clinically well-delineated syndromes and are typically screened for by FISH. The first recurrent imbalance identified was the imbalance at 17p12 associated with Charcot-Marie-Tooth disease type 1A (CMT1A, OMIM 118220). A list of well-known recurrent submicroscopic imbalance syndromes is shown in *Table 4.2*. With the advent of molecular karyotyping, a series of novel recurrent imbalances causal for or associated with MR/MCA (mental retardation/multiple congenital anomalies) have been identified and these are listed in *Table 4.3*.

Nonrecurrent Submicroscopic Rearrangements

For several genomic regions, overlapping rearrangements have been identified that show variable breakpoints in each patient. Despite the different sizes, these nonrecurrent imbalances share a shortest region of overlap (SRO) for which a copy number change may lead to similar phenotypes in different patients. Two pertinent examples are the *MECP2* gene duplications at Xq28 and the 12q14 microdeletion syndrome.

Table 4.2

Microdeletion/duplication syndromes associated with developmental disorders identified before the advent of array CGH

Syndrome	Chromosome location	Deletion incidence	Parental origin	Deletion size (Mb)	Gene (incidence)
Sotos	5q35	ND	Paternal (90%)	2.2	*NSD1* (10%)
Williams	7q11.23	1/20,000–1/50,000	Equal	1.6	CGS
8p deletion	8p23.1	ND	Maternal	5	CGS
Prader–Willi	15q11.2–13	1/20,000	Paternal	3.5	CGS
Angelman	15q11.2–13	1/20,000	Maternal	3.5	*UBE3A* (10–15%)
Smith–Magenis	17p11.2	1/25,000	Equal	4	*RAI1* (ND)
Neurofibromatosis 1	17q11.2	1/40,000–1/80,000	Maternal	1.5	*NF1* (90–95%)
Velocardiofacial	22q11.2	1/4,000	Equal	3 (1.5)	CGS

CGS contiguous gen syndrome, *ND* not determined

Table 4.3

Newly recognized interstitial microdeletion/duplication syndromes identified by array CGH and associated with developmental disorders

Name	Size (Mb)	OMIM	Clinical features	Reference
1q21 microdeletion (TAR syndrome)	0.5	27400	Hypomegakaryocytic thrombocytopenia and bilateral radial aplasia	(Klopocki et al. 2007)
1q21 microdeletion & microduplication	1.35	612474 and 612475	Asymptomatic to severe developmental delay and multiple congenital anomalies, susceptibility locus for neuropsychiatric disorders	(Brunetti-Pierri et al. 2008; Mefford et al. 2008)
3q29 microdeletion	1.6	609425	MR, mild FD including high nasal bridge and short philtrum	(Ballif et al. 2008; Willatt et al. 2005)
3q29 microduplication	1.6	611936	Mild/moderate MR, MC, obesity	(Ballif et al. 2008; Lisi et al. 2008)
7q11.23 microduplication	1.5	609757	MR, speech and language delay, autism spectrum disorders	(Somerville et al. 2005)
15q13.3 microdeletion	1.5	612001	MR, epilepsy, FD, digital dysmorphisms	(Sharp et al. 2008)
15q24 microdeletion	1.7		MR, growth retardation, MC, digital abnormalities, genital abnormalities	(Sharp et al. 2007)
16p13.11 microdeletion	1.7		MR, MC, seizures	(Hannes et al. 2009; Ullmann et al. 2007)
17p11.2 microduplication	3.7	610883	MR, infantile hypotonia, autistic features	(Potocki et al. 2007)
17q21.31 microdeletion	0.5	610443	MR, hypotonia, typical face	(Koolen et al. 2006; Sharp et al. 2006; Shaw-Smith et al. 2006)
22q11.2 distal microdeletion	1.4–2.1	611867	MR, growth delay, mild skeletal abnormalities, FD.	(Ben-Shachar et al. 2008)

FD facial dysmorphism, *MC* microcephaly, *MR* mental retardation

Mechanisms Causing Genomic Disorders

Mutations causing chromosomal rearrangements can occur during both meiosis and mitosis. Classically, meiosis has been considered the main period during which chromosomal rearrangements occur. Chromosomes are very active during meiosis, because the homologues pair, synapse, and crossover. During this process, multiple DNA nicks are generated and it is likely that some of the rearrangements originate as a result of these processes. The recent discovery of large-scale chromosomal rearrangements in the cleavage stage embryo makes it likely that many chromosomal rearrangements originate at this time. How the chromosomal breaks originate remains unclear.

Aneuploidies

The majority of aneuploidies arise via meiotic nondisjunction events, though mitotic nondisjunction events are also a frequent cause of constitutional aneuploidies. Nondisjunction is defined as the failure of homologous chromosomes to segregate symmetrically at cell division. If the pair of homologues comprising a bivalent at meiosis I fail to separate, one daughter cell will have two of the chromosomes while the other will have none (*Fig. 4.3a*). Nondisjunction may also occur in meiosis II when the chromatids fail to separate (*Fig. 4.3b*). In both meiotic errors, the conception ends up trisomic or monosomic. The majority of the nondisjunction events appear to occur at meiosis I. An alternative mechanism for nondisjunction is premature separation of the chromatids. First, homologues fail to pair during meiosis I. These univalents are prone to predivide, that is, separation of the two chromatids, and subsequently these chromatids segregate independently (*Fig. 4.3c*). Since the frequency of meiotic errors increases with advanced maternal age, not surprisingly the overwhelming majority of aneuploidies are of maternal origin.

Recurrent Submicroscopic Imbalances

Recurrent rearrangements are often flanked by low-copy repeats (LCRs). LCRs or segmental duplications (SDs) are segments of DNA that map to two or more genomic locations, are >1 kb in size and share a sequence identity of at least 90%. Segmental duplications account for about 5% of the human genome. Due to their high degree of sequence homology, these segmental duplications provide substrates for nonallelic homologous recombination (NAHR) in which crossing over occurs between two similar sequences at nonallelic positions that erroneously align in mitosis or meiosis (*Fig. 4.4*). Depending on their location and orientation, they give rise to various types of rearrangements. Misalignment and subsequent recombination between two LCRs that are in direct orientation on the same chromosome cause deletions and duplications, while inversions are driven by LCRs that are in

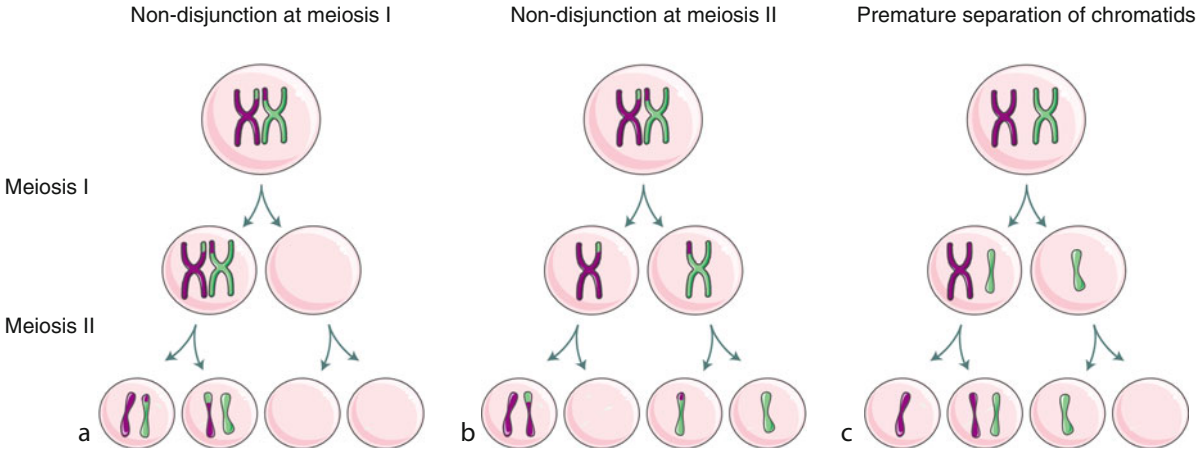

Figure 4.3

Different possibilities for nondisjunction during meiosis leading to trisomic or monosomic conceptions. (a) Nondisjunction at meiosis I; (b) nondisjunction at meiosis II; (c) premature separation of the chromatids of one of the homologous chromosomes at meiosis I and subsequent random migration of the chromatid to either pole at meiosis II

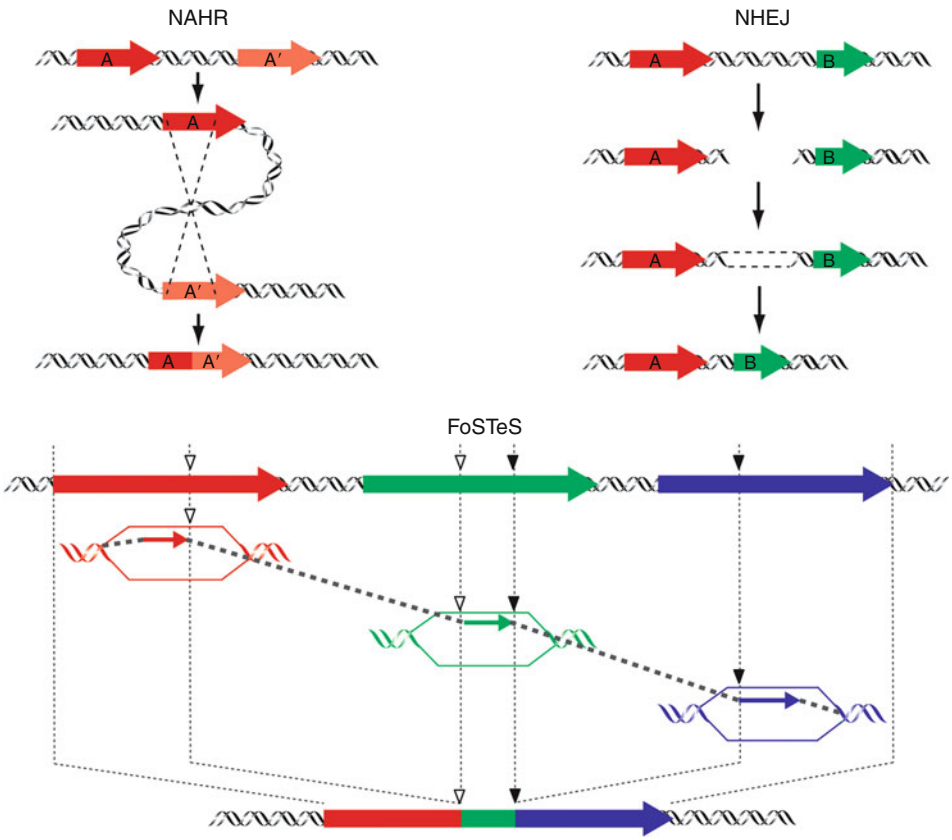

Figure 4.4

Schematic representation of nonallelic homologous recombination (NAHR), nonhomologous end-joining (NHEJ), and Fork Stalling and Template Switching (FoSTeS) mechanisms that lead to chromosomal rearrangements. The examples shown here lead to genomic deletion. *Upper left panel*: an intrachromatid NAHR event. The arrows A and A′ depict two highly homologous low-copy repeats (LCRs) that are in direct orientation. The LCRs align at nonallelic positions and subsequent recombination results in deletion of part of the two LCRs and the segment in between them. *Upper right panel*: a NHEJ event. Double-strand breaks (DSB) occur between two sequences that share no homology, represented as differently sized arrows (A and B). The NHEJ system modifies and rejoins the two ends, resulting in the deletion of the segment between the two DSBs. *Lower panel*: a FoSTeS × 2 event. The arrows depict three substrate sequences that do not share extensive homology. However, the small open and filled triangles depict a site of microhomology between the respective sequences. The leading strand of the first fork invades the second fork via the site of microhomology and primes its own further synthesis using the second fork as template. This event happens again between the second and third fork, leading to the deletion of the two fragments flanked by each pair of microhomology sites. This results in the juxtaposition of genomic sequences from multiple distinct regions yielding a complex deletion (Adapted from Gu W, Zhang F, Lupski JR (2008) Mechanisms for human genomic rearrangements. Pathogenetics 1:4)

opposite orientation on the same chromosome. NAHR between LCRs on different (nonhomologous) chromosomes leads to translocations. Recombination may occur between LCRs on the same chromatid (intrachromatid), on sister chromatids (intrachromosomal or interchromatid) or on homologous chromosomes (interchromosomal). The efficiency of NAHR is influenced by the distance, size, and degree of homology between two LCRs. Larger genomic rearrangements tend to correlate with larger LCRs and most genomic disorders result from NAHR between LCRs that are 10–400 kb in length and have >96% sequence identity.

NAHR can also be mediated by highly homologous repetitive sequences such as *Alu*'s (a class of SINEs, short interspersed nuclear elements) and LINEs (long interspersed nuclear elements) or LTRs (long terminal repeats), thus accounting for some of the nonrecurrent rearrangements.

The incidence of those recurrent genomic disorders varies and their estimated incidence for well-established recurrent disorders is indicated in *Table 4.2*.

Nonrecurrent Submicroscopic Imbalances

Nonhomologous End-Joining (NHEJ)

NHEJ is one of the two major repair mechanisms (the other being homologous recombination) for double-strand breaks (DSB) in mammals. After detection of the DSB and molecular bridging of the broken DNA ends, modifications are made to the ends to make them compatible for the final ligation step (*Fig. 4.4*). This process implies two important characteristics of NHEJ: it does not require sequence homology at the breakpoints and it leaves an "information scar" at the rejoining site due to the addition or deletion of several nucleotides. Interestingly, breakpoints of nonrecurrent rearrangements that are apparently caused by NHEJ are often located within LCRs or repetitive elements such as LTR, LINE, *Alu,* and MER2 DNA elements. This indicates that NHEJ may be stimulated and regulated by specific genomic features.

Fork Stalling and Template Switching (FoSTeS)

By breakpoint sequence analysis of nonrecurrent *PLP1* duplications associated with Pelizaeus-Merzbacher disease, Lee et al. discovered an unexpected complexity that is inconsistent with a simple recombination model. Within the duplicated sequence, they found interspersed stretches of DNA that were triplicated or of normal copy number and additional sequence complexity at the junctions. They proposed a model of replication Fork Stalling and Template Switching to explain these complex duplication and deletion rearrangements. During DNA replication, the replication fork stalls or pauses at a DNA lesion and the leading or the lagging strand disengages and switches to another replication fork where it anneals on the invaded site by virtue of microhomology and restarts DNA synthesis (*Fig. 4.4*). The replication forks are in physical proximity, but may be separated by sizeable linear distances, even megabases away. This procedure of disengaging, invading/annealing and synthesis/extension could occur multiple times in series (that is FoSTeS × 2, FoSTeS × 3 and so on), causing the observed complex rearrangements. Depending on whether the invaded fork is located downstream or upstream, this will result in a deletion or a duplication event, respectively.

Interestingly, the genomic positions at which FoSTeS occurs show a very complex genomic architecture including multiple LCRs, cruciforms, and palindromes that may stimulate and facilitate the FoSTeS mechanism. As opposed to NAHR and NHEJ, a single-strand DNA lesion is the initiating damage rather than a double-strand break.

Microhomology-Mediated Break-Induced Replication (MMBIR)

As an alternative to FoSTeS, the MMBIR model has been proposed in which the rearrangement is initiated by a single-end double-strand DNA break resulting from a collapsed replication fork. This model is based on the break-induced replication model observed in yeast. The single-strand 3′ tails from the broken replication fork will anneal with microhomology on any single-stranded DNA nearby, where it forms a new replication fork. The replication in this new fork is of low processivity and the extended end will dissociate and invade different templates. Multiple template switches generate complex rearrangements until there is reestablishment of processive replication (*Fig. 4.5*). Again, complex genomic architecture may play a role in this process by generating secondary DNA structures such as cruciforms and hairpin loops that expose single-stranded sequence.

Molecular Mechanisms Leading to Phenotypes

There are several ways in which chromosomal rearrangements can lead to a clinical phenotype. The most obvious mechanism is altering the copy number of dosage-sensitive genes that are encompassed within the rearrangement (*Fig. 4.6a*). When the breakpoint is located within a gene, it will be disrupted, leading to loss-of-function. The disruption can occur either through deletion (*Fig. 4.6b*), duplication, or translocation, as well as inversion (*Fig. 4.6c*). Alternatively, new transcripts can be created at the breakpoint through gene fusion (*Fig. 4.6d*) or exon shuffling. This leads to gain-of-function mutations, a mechanism that is

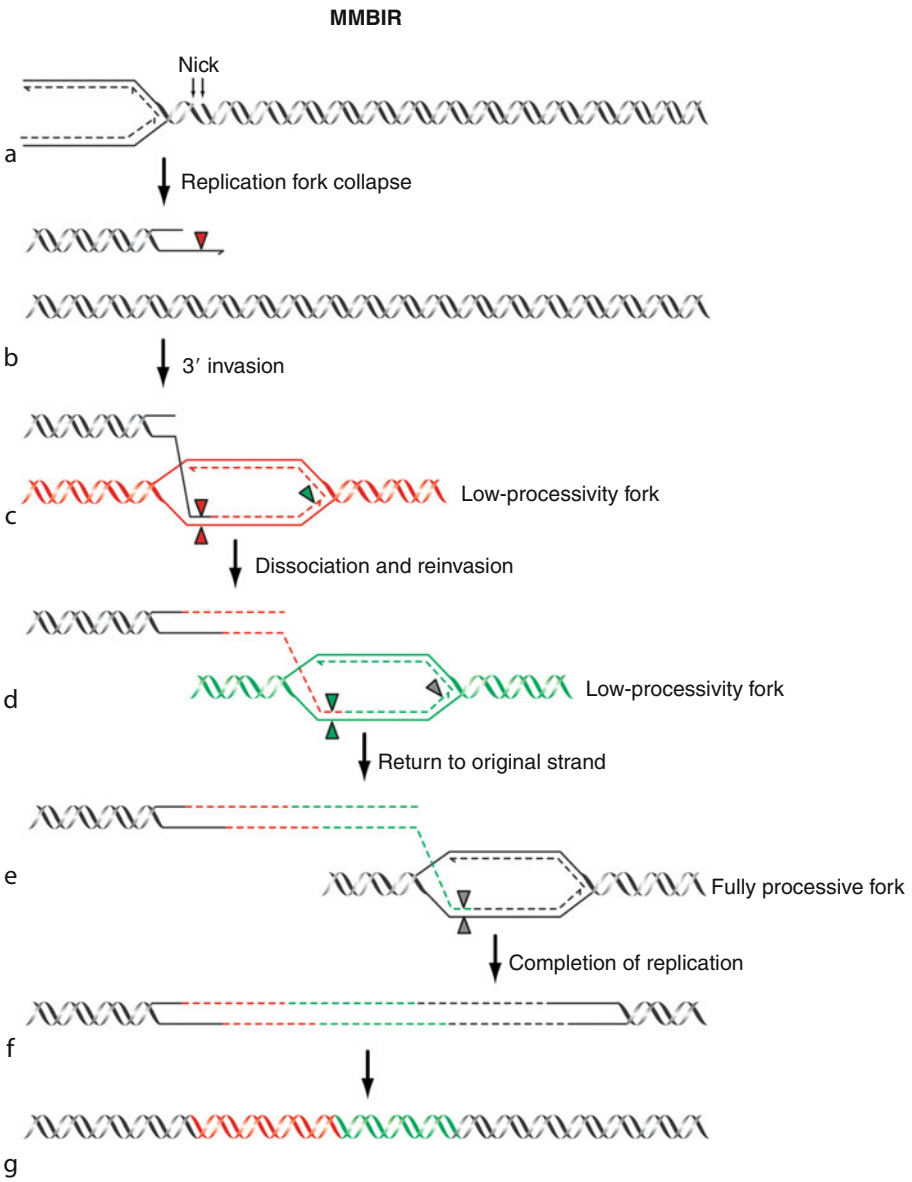

Figure 4.5

Schematic representation of microhomology-mediated break-induced replication (MMBIR). Successive switches to different genomic positions forming microhomology junctions (filled triangles) are shown. When a replication fork encounters a nick in a template strand (a), one arm of the fork breaks off, producing a collapsed fork (b). The single-stranded 3′ end will invade a site of microhomology (filled triangle) and form a new low-processivity fork (c). The extended end will dissociate repeatedly and reform the fork on different templates, using sites of microhomology (d). When the switch returns to the original sister chromatid (e) it will form a processive replication fork that completes replication (f). The final product contains sequences from different regions (g). Whether the return to the sister chromatid occurs in front of or behind the position of the original collapse determines if there is a deletion or duplication (Adapted from Hastings PJ, Ira G, Lupski JR (2009) A microhomology-mediated break-induced replication model for the origin of human copy number variation. PLoS Genet 5:e1000327)

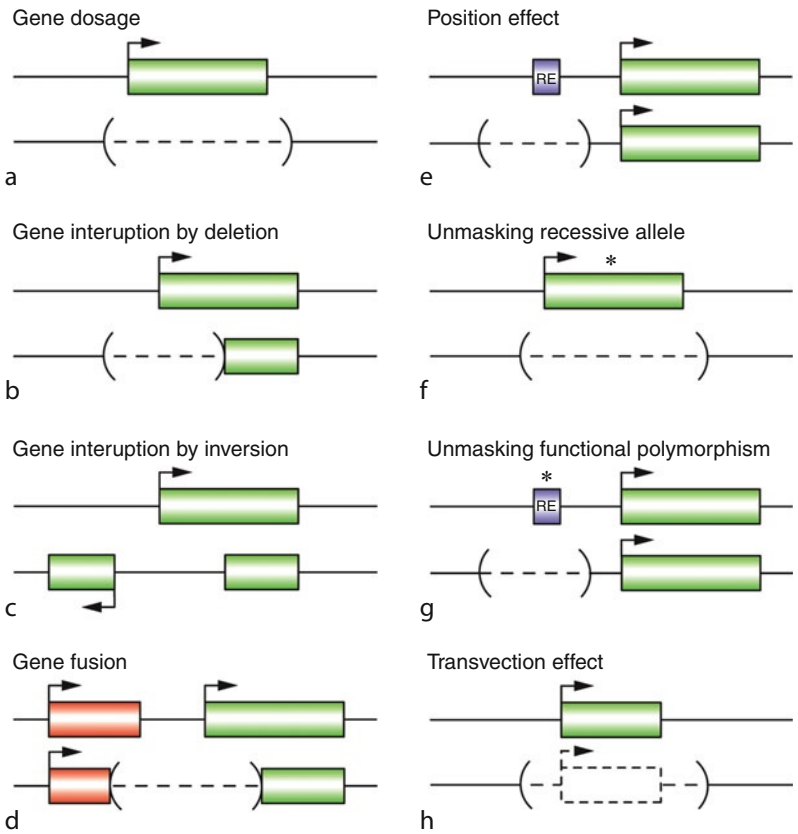

Figure 4.6

Molecular mechanisms by which chromosomal rearrangements can influence phenotypes. The rearrangement can encompass a dosage-sensitive gene that causes disease (a); disrupt a dosage sensitive gene through deletion (b); duplication, translocation or inversion (c); create a fusion gene (d); exert a position effect by affecting a regulatory element (e); unmask a recessive allele (f) or functional polymorphism (g) on the homologous chromosome; and interrupt effects of transvection (h) where the deletion of a gene affects communication between alleles. Genes are depicted as rectangles, regulatory elements as RE and an asterisk (*) indicates a point mutation (Adapted from Lupski JR, Stankiewicz P (2005) Genomic disorders: molecular mechanisms for rearrangements and conveyed phenotypes. PLoS Genet 1:e49 and Feuk L, Carson AR, Scherer SW (2006) Structural variation in the human genome. Nat Rev Genet 7:85–97)

prominent amongst cancers associated with specific chromosomal translocations. The rearrangement can also influence the regulation of a nearby gene by position effects (*Fig. 4.6e*). Deletion, duplication, or translocation of important regulatory elements may alter gene expression at distances as far as ~1 Mb from the target gene. Dosage-insensitive genes can also cause disease if a deletion of the gene unmasks a recessive mutation or a hypomorphic allele on the homologous chromosome (*Fig. 4.6f*) or when the deletion unmasks a functional polymorphism in a regulatory element of the remaining allele (*Fig. 4.6g*). Another way in which deletions can convey a phenotype is by interrupting transvection, where communication and interaction between two alleles on homologous chromosomes is disturbed (*Fig. 4.6h*).

Indications for Cytogenetic Testing

Indications in Children

Intellectual disability and developmental disorders affect up to 3% of the population and remains to this day an enormous etiological challenge. The finding of the cause is of great importance not only to the individual, his or her parents, and family but also to the treating physician. For

the individual, it adds to the identification of appropriate medical and related therapies, indicates medical interventions/referrals, presymptomatic screening for associated complications, educational planning, and elimination of further unnecessary evaluations. For the family, it forms a step toward the acceptance of the disability and the basis to understanding the cause, the reason and the recurrence risks. Carrier testing and reproductive options become a reality. It also allows social support and contact with other similarly affected families. The ongoing etiological evaluation in a bid to attain a diagnosis does thus have a significant role to play in the all-round care of the intellectually disabled individual and the family.

The etiology of intellectual disability is extensive and ranges from acquired/environmental (sequelae of prematurity, pre- and postinfections, trauma, and neurotoxicity – alcohol, metals), to chromosomal (aneuploidy, genomic imbalances – microdeletions and duplications), and to monogenic disorders. The rate of etiological diagnosis is influenced by the level of the intellectual disability – the more severe, the higher the diagnostic success. A systematic literature review of the usefulness of classical karyotyping, subtelomere screening, and molecular genetics investigations in institutionalized individuals with mental retardation indicated 0% etiological detection in borderline to mildly retarded individuals as opposed to 6.5% (range 0.8–13.0%) in those moderately to severely/profoundly retarded. Also, the differences in setting, the patient selection criteria, study protocols, technological advances, definition of a positive diagnosis, method of classification, and expertise of the clinician have been factors resulting in the varying rate of diagnosis.

In a systematic etiological study of 471 institutionalized individuals with mild to profound intellectual disability, 92.6% of which were males, Van Buggenhout et al. reported 49.5% without known cause. Chromosomal anomalies accounted for 21.2% (87 or 18.5% of the 471 individuals had Down syndrome), monogenic disorders 13%, and acquired causes 14.6%.

This was, however, before the era of array comparative genomic hybridization (array CGH). The initial studies using this new technology on selected cohorts of individuals with an intellectual disability and dysmorphism made use of around 3,500 BAC clones, resulting in an average resolution of 1 Mb. The rate of genomic imbalance detection was between 9% and 25%. The few studies at higher, 100 kb resolution, have also detected about 10% of pathogenic submicroscopic aberrations. The chromosome imbalances occur throughout the genome. Once the validity of the technique to detect chromosomal constitutional imbalances was demonstrated it was rapidly introduced into the genetic diagnostic laboratories as a routine technique in the genetic diagnostic workup of patients with learning disabilities and/or multiple congenital anomalies.

In addition to the identification of pathogenic imbalances in patients with intellectual disabilities, several studies have proven associations of copy number variants (CNVs) with several other conditions or specific patient groups: Lu et al. reported an incidence of 17.1% imbalances in neonates with various birth defects. Thienpont et al. report a frequency of 17% causal imbalances in patients with heart diseases. Finally, CNVs are now believed to be an important cause of neuropsychiatric conditions such as autism spectrum disorders and psychiatric diseases such as schizophrenia. Hence, also for these indications it is or will be warranted to perform cytogenetic testing.

Indications in Parents

Balanced translocations are relatively common in the population. The translocation heterozygote (carrier) may have a risk to have a child with developmental disorders because of a segmental aneusomy. Typically, the imbalance in the child is due to a segment of one of the participating chromosomes being duplicated, and a segment of the other chromosome being deleted. This confers a partial trisomy and a concomitant partial monosomy. In families where more than one child is born with developmental disorders and/or families with recurrent miscarriages, a chromosomal investigation is warranted.

In addition, when an imbalance is identified in a child, it is common practise to determine whether or not the imbalance is derived de novo or was inherited. When terminal imbalances are identified, the presence of a balanced translocation in one of the parents should be investigated. In addition, for submicroscopic interstitial imbalances, the presence of a balanced insertional translocation in one of the parents can be present.

Interpretation Issues

Chromosomal Polymorphisms

Chromosomal polymorphisms or heteromorphisms are structural chromosome variants that are widespread in human populations and have no effect on the phenotype. These variants are most often found at the centromeric regions of chromosomes 1, 9, and 16, the distal part of the long arm of the Y chromosome and the short arms of the

acrocentric chromosomes. In addition to these recurrent imbalances, many more cytogenetically visible but apparently benign imbalances have been described. An excellent overview on this topic is provided in the article by Barber , *Directly Transmitted Unbalanced Chromosome Abnormalities and Euchromatic Variants*, and the collected data is online available at the "Chromosome Anomaly Collection" at http://www.ngrl.org.uk/Wessex/collection.

Submicroscopic Chromosomal Polymorphisms (The Blurred Boundary Between Benign and Pathogenic CNVs)

Besides the identification of disease-associated CNVs, molecular karyotyping has also uncovered large numbers of copy number variants between normal individuals. Thus far, single-nucleotide polymorphisms have been considered the main source of genetic variation; hence the discovery of an unexpected large number (12% of the genome) of apparently benign copy number variants, regions of 1–1,000 kb that are present in different copy numbers in different individuals, was rightly called the discovery of the year 2007, according to *Science* magazine.

A number of array CGH studies had demonstrated the presence of polymorphic copy number variants. In a first large systematic study, Redon et al. mapped all CNVs using both array CGH and single nucleotide polymorphism (SNP) genotyping arrays on the 270 individuals of the HapMap collection from ancestry in Europe, Africa, and Asia. In the human genome, 1,447 submicroscopic copy variable regions were uncovered. This involves about 12% of the genome and includes hundreds of genes in deletions, duplications, insertions and complex multisite variants. These nonpathogenic variations are scattered throughout the human genome and contain also 12% of the genes, including a large number of genes known to be involved in genetic disorders and registered in OMIM. Recent fine mapping studies have revealed that those CNVs can result in intragenic variation resulting in different splice variants, the use of different exons and even new gene products. The most comprehensive population-based CNV map so far consists of 11,700 CNVs and is estimated to include about 80–90% of common CNVs greater than 1 kb in length. Although the authors indicate that those common CNVs are highly unlikely to account for much of the missing heritability for complex traits, they suggest that CNVs might contribute appreciably to rare variants involved in common and rare diseases.

The consequence of the detection of large numbers of benign CNVs is that, at present, the clinical significance of a novel CNV remains often unclear. The traditional rules of thumb used when analyzing genomes by conventional karyotyping are not applicable anymore. The identification of a large de novo cytogenetically visible imbalance was usually sufficient to confidently associate it with the disease phenotype. However, it is obvious that smaller imbalances carrying few or no genes may not at all be associated with a disease phenotype. Equally, it is becoming clear that de novo copy number variation arises frequently. Van Ommen estimated that copy number changes arise every one in eight births. Hence, not all de novo copy number changes would be pathogenic.

To determine which, if any, CNVs might be associated with the disease phenotype, the collection of large numbers of patient genotypes and phenotypes is required. Several efforts are currently ongoing to collect both large numbers of phenotypes and genotypes. These efforts will eventually allow pinpointing highly penetrant CNVs, revealing which imbalances are causal and which imbalances are spurious. The best-known open source examples are the DatabasE of Chromosomal Imbalances and Phenotype in Humans using Ensembl Resources with acronym DECIPHER which is organized at the Sanger institute (https://decipher.sanger.ac.uk/) and the European Cytogenetics Association Register of Unbalanced Chromosome Aberrations, ECARUCA, a register with a basis in Nijmegen, The Netherlands (http://www.ecaruca.net).

In addition, several large-scale collaborative efforts are underway to map population-embedded, apparently benign CNVs. These data are collected in the database of genomic variants (DGV, http://projects.tcag.ca/variation/). To fine map those imbalances, increasingly higher resolution arrays are being used. Those efforts aim to identify CNVs with likely minor or no developmental consequences.

While the mapping of apparently benign and pathogenic CNVs is an important endeavor, it is not sufficient to predict whether an imbalance will cause an abnormal phenotype. Apparently benign CNVs can cause autosomal recessive, autosomal dominant, and X-linked disorders, and imprinted regions may only cause disease dependent on the parental origin. In addition, variable expressivity and penetrance may obscure the pathogenic relevance of CNVs. It is not only becoming clear that interindividual phenotypic variation is caused by benign copy number variations, but more and more it is realized that even well-known disease-causing copy number variations may occasionally be tolerated and be part of the normal human phenotypic spectrum. For example, the 22q11 deletion as well as the duplication can cause both heart anomalies and midline defects such as cleft palate. However, both the

familial inherited 22q11 deletion and duplication have now recurrently been reported. The parent carrying the 22q11 duplication is phenotypically normal. Similarly, subtelomeric imbalances are known to be a major cause of birth defects and mental retardation. In contrast to the view that these imbalances are always causal and result in phenotypic anomalies, several reports indicate that several subtelomeric imbalances, up to 10 Mb in size, may not result in obvious phenotypic anomalies.

More recently identified recurrent imbalances with variable penetrance are the 16p13.1 region and the 1q21 region. During the screening of patients with mental handicap and developmental anomalies, reciprocal deletions, and duplications of the 16p13.1 region were recurrently observed. This 1.65 Mb rearrangement involves 15 genes. At first, it was unclear whether these imbalances were causing the developmental problems in patients because of two reasons: First, the imbalance, be it deletion or duplication, was often observed to be inherited from an apparently normal parent. Second, the phenotypes associated with either the deletion or duplication are quite variable. An association study showed that the deletion is a risk factor for mental handicap while the duplication is more likely to be a benign variant. Interestingly, Law et al. reported the prenatal diagnosis of a de novo 16p13.11 microdeletion by array CGH. Because of the unclear clinical significance, the pregnancy was not terminated and an apparently healthy baby was born. Chromosome 1q21 harbors two flanking regions, where, recently, recurrent reciprocal rearrangements were detected in patients with MR/MCA. The deletions and duplications are mediated by nonallelic homologous recombination of flanking low-copy repeats. All 30 investigated patients with thrombocytopenia absent radius (TAR) syndrome carry a 200 kb deletion on chromosome 1q21.1. Analysis of the parents revealed that this deletion occurred de novo in 25% of affected individuals. Intriguingly, inheritance of the deletion along the maternal line as well as the paternal line was observed in the other patients. The absence of this deletion in a cohort of control individuals argues for a specific role played by the microdeletion in the pathogenesis of TAR syndrome. It is hypothesized that TAR syndrome is associated with a deletion on chromosome 1q21.1 but that the phenotype develops only in the presence of an additional as-yet-unknown modifier (mTAR). Recently, the first prenatal diagnosis of TAR by array CGH was reported.

Mefford and colleagues identified 20 individuals with a recurrent 1.35 Mb deletion distal from the TAR region from a screen of about 5,000 patients ascertained with mental retardation and/or associated congenital anomalies (MR/MCA). The microdeletions arose de novo in six patients, were inherited from a mildly affected parent in three patients, and were inherited from an apparently unaffected parent in five patients. The absence of the deletion in about 5,000 control individuals represents a significant association with disease. In addition, the reciprocal duplication was also enriched in children with mental retardation or autism spectrum disorder although very few cases have been observed to conclude statistical significance.

It seems likely that those recurrent rearrangements with variable penetrance and expressivity are only the tip of an iceberg of a large number of structural variants with diverse and complex phenotypes that will elude both traditional syndromic classifications as well as evade traditional Mendelian inheritance patterns. The elucidation of their association with disease will require genotyping and phenotyping large numbers of patients and controls. These imbalances pose challenges to the clinician upon interpreting array CGH data. It seems likely that, in the future, the interpretation will be aided by computerized expert systems to aid the interpretation of a genomic profile.

Technical Issues in Array CGH

Quality Parameters

In a clinical setting, it is of utmost importance to detect all chromosomal abnormalities (i.e., to avoid false negatives) without calling false positives. In other words, both the sensitivity, which is the ability to detect a true positive result, and the specificity, which is the correct assessment of true negatives, should be as high as possible. This is dependent on the resolution of the platform, but also on the quality of the hybridization experiment. Therefore, strict quality parameters such as a maximum allowable standard deviation, appropriate thresholds, and algorithms for CNV calling and a minimum number of flagged reporters (i.e., those that are excluded from analysis due to technical artifacts) need to be maintained.

Chromosomal Rearrangements Missed by Array CGH

Array CGH is often touted to be able to replace conventional karyotyping in a diagnostic analysis of pediatric disorders. However, it should be realized that some chromosomal anomalies would be missed.

Inherent to the technique, balanced chromosomal rearrangements (inversions and balanced translocations) are not detected. When balanced rearrangements are detected prenatally on karyotypes, parents are usually tested and if a "normal" parent carries the same rearrangement, the translocation is considered benign. If the rearrangement is de novo, counseling is very difficult and the risk for developmental defects is estimated to be 6%. Array CGH analysis of patients with developmental anomalies and de novo translocations has revealed that about 45% of these are actually imbalanced. Considering that de novo translocations occur in about 1/1,000 births with 6% pathogenic and half of these detectable by array CGH, this would leave 0.003% pathogenic translocations undetected if no karyotype is performed.

Also neither triploidies, 69,XXX and 69,XXY, nor tetraploidies are readily detected. The use of DNA from a patient with Klinefelter (47,XXY) as a control does result in aberrant X and Y chromosome ratios, enabling the detection of XXX triploidies and all tetraploidies.

It should also be borne in mind that array CGH results represent the additive and not the allele-specific copy number. In this way, the true inheritance pattern can be masked and what looks like a de novo event may actually be the inheritance of a copy number variant in one of the parents. Carelle-Calmels and colleagues have recently reported a striking example. FISH analysis of the parents of a girl carrying a deletion at 22q11.2 revealed an unexpected rearrangement of both 22q11.2 regions in the phenotypically normal father. He carried a 22q11.2 deletion on one copy of chromosome 22 and the reciprocal duplication on the other copy of chromosome 22. Quantitative expression analysis of the genes located in the critical DiGeorge/VCFS region showed genomic compensation, consistent with the normal phenotype of the father. As the total copy number in the father equals the reference copy number, this would not have been detected by array CGH and the rearrangement would have been classified as de novo. The finding of the mirror rearrangement in the father has tremendous clinical consequences for genetic counseling, as there is a 100% risk of an unbalanced outcome.

Technical Standards for Cytogenetic Laboratories

A broad range of platforms including BAC, oligonucleotide, and SNP arrays has become commercially available, greatly facilitating the introduction of molecular karyotyping in the diagnostic setting. For the clinical implementation of array CGH in cytogenetic laboratories, the following technical standards should be achieved. The chosen methodology has to be validated with known aberrations, the performance of the arrays evaluated by internal and external quality controls, standard protocols have to be established, and the effective resolution of the platform has to be determined, as this differs from the theoretical resolution of the array as provided by the manufacturer. When reporting array CGH results, referral should be made to the platform, effective resolution, procedures, and quality parameters used. The detected aberrations should be defined according to the ISCN 2009 nomenclature with reference to the appropriate genome build in order to guide standardization across different cytogenetic laboratories.

Mosaicism

Chromosomal mosaicism can be defined as the coexistence, within one conceptus, of two or more distinct cell lines that are genetically identical except for the chromosomal difference between them, these cell lines having been established by the time that embryonic development is complete (the point at which the embryo becomes a fetus). Thus, the different cell lines are fixed in the individual and are a part of his or her chromosome constitution.

The phenotype associated with any particular type of mosaicism can be expected to be highly variable, reflecting the differences in the proportions of normal and abnormal cells. Mosaicism has been detected for all different chromosome abnormalities described in the section Types and Incidences of Chromosomal Abnormalities. Mosaicism is especially common for (small) marker chromosomes. Clinically, mosaicism can be suspected when a patient shows nonsymmetrical features, pigmentation lines, or specific syndromic features known to be associated with certain forms of mosaicism.

In order to detect mosaicism, sufficiently many cells must be analyzed. In most cytogenetic laboratories, 15–20 karyotypes are analyzed. This will allow the detection of a chromosomal abnormality with a certainty of 95% when present in 22–28% of the cells. With arrays it is equally possible to detect low-grade mosaicism. With the BAC arrays mosaicism as low as 7% could be detected. The degree of mosaicism that can be detected depends on the standard deviation of the array as well as on the size of the imbalance. In general, mosaicism down to 30% should readily be detected.

Current State of the Art and Future of Cytogenetic Testing

Current State of the Art

Any cytogenetic laboratory should be skilled in all conventional and molecular cytogenetic techniques. These include G-banded karyotyping, fluorescent in situ hybridizations, and array CGH. G-banded karyotyping has been available for more than 40 years and has the advantage that there is a widely accepted and uniform technique with an international system of cytogenetic nomenclature (ISCN). By contrast, cytogenomic arrays are much newer. Because of this novelty, there is still discussion about the best platforms to use, there is not yet a comprehensive knowledge base about the clinical consequences of all CNVs, the language to describe CNVs is still evolving. Currently, some recommendations are provided by the International Standard Cytogenomic Array (ISCA) Consortium:

- Cytogenomic array testing standards should not be specific to a particular array platform. Arrays based on BAC, oligonucleotide, or SNP probes can achieve the recommended coverage and level of resolution.
- In order to perform the same intended purpose as a karyotype, cytogenomic arrays must have uniform coverage to detect all areas of imbalance greater than or equal to 400 kb throughout the genome.
- Cytogenomic array testing can be prioritized over G-banded karyotyping. Cytogenomic arrays will detect many more submicroscopic genomic CNVs than the number of balanced rearrangements it would miss.
- G-banded karyotyping should always be available to patients with a family history of a rearrangement or a history of multiple miscarriages. In addition, G-banded karyotyping should still be offered in settings where both tests will be covered by insurance.

Decision Tree(s) for Array CGH Interpretation

Cytogenomic arrays have moved from bench to bedside for the genetic screening of patients with mental retardation and/or congenital anomalies. The advent of commercially available microarrays has facilitated the implementation of this technique in clinical diagnostic laboratories. As described earlier, the incomplete understanding of structural polymorphism and the appreciation that many disorders show a high degree of clinical variation and incomplete penetrance is blurring clear-cut genotype–phenotype correlations. As a consequence, the causality of many smaller CNVs often remains to be elucidated and the clinical interpretation of the detected CNVs has become a major challenge for diagnostic laboratories. To aid in the assessment of the clinical significance of a CNV, several decision trees that can be used as a guideline have been proposed. These decision trees all include three major steps as outlined in *Fig. 4.7*. The first step is to identify known causal CNVs, which include: (1) CNVs that overlap with well-established as well as recently recognized microdeletion and microduplication syndromes, (2) CNVs that overlap with pathogenic CNVs detected by other (microarray) studies in patients with similar phenotypes, and (3) CNVs that encompass known OMIM genes that have been associated with the phenotype observed in the affected patient. In this way, the pitfall of unintentionally disregarding a causal CNV as a benign variant is avoided because the fact is that some CNVs have been described as benign variants but reside in regions that are known to be associated with disease or are at recessive loci that are only pathogenic in the homozygous state. The second step is to remove normal benign variants (also known as common CNVs) that have been detected in healthy individuals and are thus less likely to account for the patient's phenotype. The third step is to determine the inheritance for the remaining CNVs. Aberrations that occur de novo in the patient are more likely to be pathogenic, especially when they are relatively large and/or contain several genes. For inherited CNVs and CNVs of unknown inheritance, the clinical interpretation is more complicated and these CNVs are currently classified as of unknown clinical significance. However, as international efforts are underway to map both pathogenic and benign CNVs (see Submicroscopic Chromosomal Polymorphisms (The Blurred Boundary Between Benign and Pathogenic CNVs)), it can be expected that a significant proportion of these CNVs will turn out to be causal, thus increasing the diagnostic yield in patients with mental retardation and/or congenital anomalies.

Future

Conventional and molecular cytogenetic testing will remain important since it provides information about the location of the abnormality. With the advent of arrays, the connection between the visible localization of the abnormality is somewhat lost. This trend is likely to

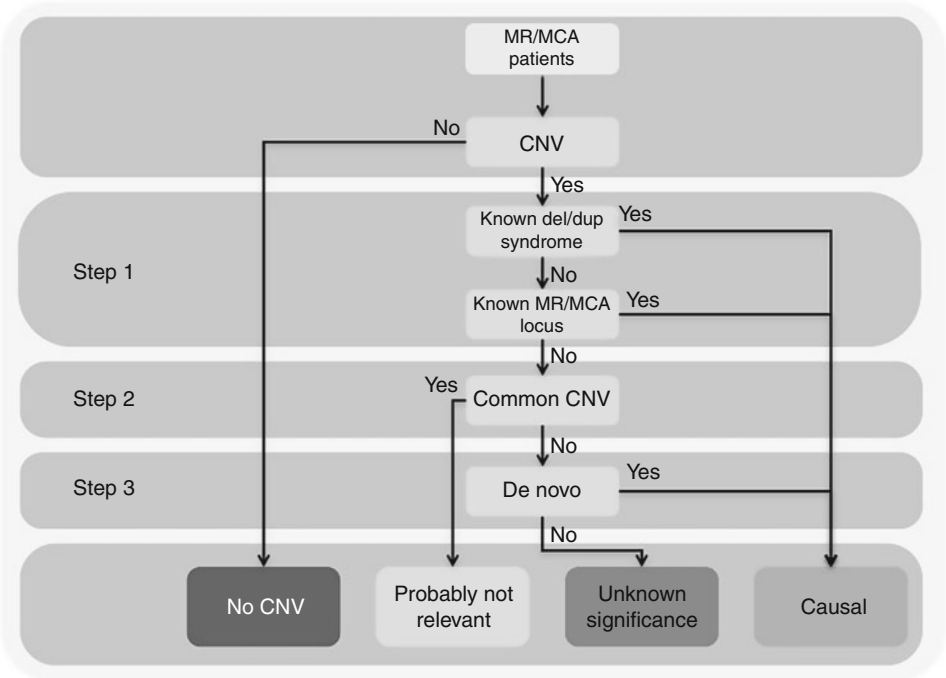

Figure 4.7
Decision tree for the assessment of clinical relevance for a particular CNV. Step 1: Identify known causal CNVs. Step 2: Discard common CNVs. Step 3: Determine the inheritance. Details are described in the text (Adapted from Buysse K, Delle Chiaie B, Van Coster R et al. (2009a) Challenges for CNV interpretation in clinical molecular karyotyping: lessons learned from a 1001 sample experience. Eur J Med Genet 52:398–403)

continue with the advent of full genome sequencing techniques. The latest technical revolution in human genetics is next-generation sequencing (NGS). Its strength lies in the ability to process millions of sequence reads in parallel rather than 96 at a time. Several platforms using different techniques are commercially available (Roche's 454 sequencing, Illumina's Solexa Genome Analyzer technology, and the SOLiD platform from Applied Biosystems), but they all rely on cyclic-array sequencing, which involves the sequencing of thousands to millions of immobilized DNA features by iterative cycles of enzymatic manipulation and imaging-based data acquisition. Depending on the platform, NGS generates hundreds of megabases to gigabases of nucleotide-sequence output in a single instrument run.

It is expected that costs will drop and that genome sequencing of individuals will be commonplace in the foreseeable future. If it will become feasible to assemble complete genomes as well as accurately determine copy numbers, full genome sequencing may ultimately replace cytogenetic as well as molecular genetic testing.

Concluding Remarks

In this chapter, the aim was to touch upon the important aspects of cytogenetic testing and provide a basic text on the topic for pediatricians new to the field. Considering that several books and numerous articles have been written about this topic, it is realized that the resume presented here is incomplete and biased. For those interested, a number of excellent books on the topics touched upon here are referred to. To help pediatricians in the interpretation of cytogenetic results and counseling of those results with patients, the books "Chromosome abnormalities and genetic counselling" as well as "The principles of clinical cytogenetics" are recommended. Phenotypic information about chromosomal imbalances has been collected by Schinzel in "Catalogue of unbalanced chromosome aberrations in man". Clinicians closely interacting with obstetricians and involved in prenatal diagnosis can consult "Genetic disorders and the fetus". Those interested to know more about the mechanisms underpinning genomic disorders

are referred to "Genomic disorders: the genomic basis of disease".

Over the last 50 years, cytogenetics has become a cornerstone of genetic testing of children with birth defects and developmental anomalies. Conventional karyotyping is rapidly replaced or at least complemented by array screening. In the future possibly full genome sequencing will enable both mutation and copy number detection in all individuals with developmental disorders. Certainly, knowledge about the organization and location of chromosomal aberrations is important for counseling and family planning, and therefore cytogenetics is here to stay, perhaps under a new name – "cytogenomics?"

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5 Principles of Genetic Testing

Margaret A. Chen

An Introduction to Clinical Molecular Genetics

There is a general misperception that heritable genetic disorders are rarely encountered in clinical pediatrics. At least 2% of live born infants have a genetic disease, and genetic disorders are responsible for more than 30% of pediatric hospital admissions. Moreover, congenital anomalies, many of which are caused in part by genetic factors, are the leading cause of infant mortality. It is therefore of utmost importance for the general pediatrician to recognize when a patient may have a genetic condition and to be able to order the appropriate test(s).

The Human Genome Project was completed in 2003, and with its completion it was determined that the human genome contains 20,000–25,000 genes. By 2008, more than 2,000 single-gene disorders were catalogued in Online Mendelian Inheritance in Man (OMIM). The identification of the genes responsible for these disorders has been the result of a technological revolution in molecular genetics.

Today, genetic testing is becoming increasingly important in medical practice. Such testing can be used to confirm a clinically based diagnosis and may be especially helpful when disorders show clinical and/or radiographic overlap. Moreover, genetic testing is performed for purposes other than diagnosis. For example, genetic testing can identify individuals harboring a deleterious mutation or mutations prior to onset of symptoms, as well as asymptomatic carriers of autosomal recessive traits. Genetic testing is playing an increasingly important role in diagnosis, medical management, and family planning. Because the results of genetic testing may have implications for individuals besides the individual being tested, genetic counseling is always recommended and most clinical molecular diagnostic laboratories require informed consent prior to testing.

Indications for Molecular Testing

The vast majority of genetic testing performed in the pediatric population is diagnostic in nature. There are a number of situations where molecular genetic testing is warranted. Clinical indications include multiple congenital anomalies, dysmorphic features, developmental delay (in either speech or motor milestones), intellectual impairment of unknown etiology, growth abnormalities, ambiguous genitalia, failure to develop secondary sexual characteristics, congenital heart defects, solid tumors or hematological malignancies, and a positive newborn screen. Genetic testing may also be performed in asymptomatic children if there is a family history for a single-gene disorder of childhood onset that has been confirmed by laboratory diagnostics and such testing contributes to medical management and/or relieves parental anxiety.

Through careful examination of a family pedigree, it may be possible to ascertain mode of inheritance, and this may provide a clue to diagnosis. Although most physicians are familiar with basic Mendelian inheritance, there are several pitfalls in pedigree analysis. Variable expressivity can affect the ability of the physician to diagnose a genetic disorder. For example, there may be variation among family members in visible features, disease severity, age of onset, and/or rate of disease progression. Disease penetrance is another factor that can affect the pediatrician's ability to diagnose a genetic disorder. Penetrance refers to the expression of the mutant phenotype and is expressed as the percentage of individuals who have the mutant allele and are actually affected. Most genetic disorders show incomplete penetrance, meaning that not all individuals who have the disease genotype manifest symptoms. Nonpenetrance refers to the situation in which the mutant allele is inherited but is not expressed. Other factors that might complicate pedigree analysis and impede accurate diagnosis include the occurrence of new mutations, mosaicism, and phenocopies. New mutation can lead to a child being affected without family history. Mosaicism due to post-zygotic mutation can cause a parent to display few or no signs of a disorder. A phenocopy mimics the clinical picture that is usually produced by a specific genotype and may be caused by an environmental factor. Finally, there are multifactorial disorders that result from a combination of both genetic and environmental factors; they often recur in families but do not show the characteristic

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transmission typically seen with single-gene disorders. Multifactorial traits can be common, and include neural tube defects, non-syndromic cleft lip with or without cleft palate, congenital heart defects, and diabetes. A non-Mendelian inheritance pattern may also be seen with genetic disorders that arise from mutations in the mitochondrial genome. Disorders that result from mutations in mitochondrial DNA are only passed through maternal cell lineage; as a result, while both males and females can be affected, only females can pass the gene mutation to their offspring. Finally, mutations in imprinted gene regions may also show non-Mendelian inheritance; this topic will be discussed in further detail later in this chapter.

Genetic testing is performed for more than diagnosis of affected individuals. For example, carrier testing is possible. Heterozygous carriers of autosomal recessive and X-linked recessive disorders can be identified via direct DNA analysis. (While carrier testing is also performed to detect individuals with balanced chromosomal rearrangements, such testing needs to be performed using traditional cytogenetic techniques rather than molecular diagnostics.) Prenatal diagnosis is also feasible if a familial mutation (or mutations) has been identified. Traditionally, fetal samples are obtained via chorionic villus sampling at 10–12 weeks gestation or amniocentesis at 15–20 weeks gestation. Because both methods are invasive and pose some risk to the fetus, attempts are currently being made to study free fetal DNA found in the maternal circulation. This type of analysis is only being performed in a research setting, but early reports suggest it is possible to identify trisomies and paternally inherited mutations using this method.

Presymptomatic testing can likewise be performed, including predictive testing and predispositional testing. Predictive testing and predispositional testing are different, because a positive test result is interpreted differently for each. Predictive testing is performed for late-onset conditions such as Huntington disease, and a positive result implies that the individual will eventually develop the disorder with certainty. In contrast, a positive result for predispositional testing implies that the person is at increased risk for disease development, but such testing cannot firmly establish future disease. Predispositional testing may include *ApoE* genotyping for Alzheimer's disease (where presence of the ε4 allele confers increased disease risk), and *CAPN10* and *TCF7L2* genotyping for increased risk to develop type 2 diabetes. Because such risk factors are neither necessary nor sufficient for disease development and may not lead to effective risk reduction strategies, many experts advise against genetic testing for susceptibility alleles.

There are situations in which presymptomatic testing is justified. Presymptomatic testing is often performed for familial cancers, where test results play a critical role in medical management. Sequencing of *BRCA1* and/or *BRCA2* genes can provide information regarding risk to develop breast and/or ovarian cancer; results influence decisions regarding surveillance, Tamoxifen treatment, or prophylactic mastectomy and oophorectomy. Similarly, mutation testing of the *APC* gene can provide information regarding risk to develop colon cancer. Mutations resulting in a truncated APC protein are associated with familial adenomatous polyposis, a highly penetrant disorder where mutation carriers have a near 100% risk of developing colon cancer if left untreated. Identification of a mutation allows other at-risk family members to be tested. Unlike many other cases of presymptomatic testing in children, testing for a familial *APC* mutation has clear medical benefit. Children who are at 50% risk for familial adenomatous polyposis (i.e., children of a mutation carrier) normally must undergo annual sigmoidoscopy surveillance beginning at 10 years of age. A negative genetic test result would allow the child to avoid the sedation and discomfort associated with this medical procedure.

With a few noted exceptions, such as the one described above, genetic testing of minors in the absence of clinical presentation remains controversial. Numerous articles and position statements have been written on this subject. In 1995, the board of directors of both the American College of Medical Genetics and the American Society of Human Genetics issued a joint report regarding the ethical, legal, and psychosocial implications of genetic testing in children and adolescents. The primary justification for genetic testing in minors is that the testing should provide timely medical benefit. In addition, testing may also be justified when there is substantial psychosocial benefit to the competent adolescent (e.g., to help with decision-making regarding reproduction, education, and career). Genetic testing for adult-onset disorders or to determine carrier status should generally be deferred until the individual is old enough to make this decision voluntarily. Of course, it has been argued that prohibiting genetic testing in minors deprives the individual and the family of potentially important health information that might be used to make important lifestyle decisions, including limiting environmental exposures and risk behaviors. ❯ *Table 5.1* summarizes the benefits and risks of genetic testing in children.

Table 5.1
Benefits and risks of genetic testing in children

Category	Benefits	Risks
Medical issues	Clarify diagnosis	Ineffective or potentially harmful preventive or therapeutic interventions
	Improve prognosis through early therapeutic or preventive intervention	
	Increase surveillance	
	Avoid costly and/or risky unnecessary surveillance	
	Limit environmental exposures	
	Reduce risk behaviors	
Psychosocial issues	Reduce uncertainty and anxiety	Loss of autonomy
	Gradual adjustment by child to diagnosis	Increased anxiety and/or guilt
	Financial planning	Altered self-image/Diminished self-esteem
	Informed decision-making regarding education, employment, insurance, and personal relationships	Parents' changed perception of child
		Altered expectations regarding education, career, marriage, and life activities
	Alert other family members regarding their own risk	Stigmatization
		Employment and/or insurance discrimination
		Incidental determination of other family members' genetic status

Ordering a Diagnostic Genetic Test

Almost all clinical molecular diagnostic laboratories examine genomic DNA derived from lymphocytes. Blood samples are simple to collect and such testing may obviate the need for tissue-specific biochemical testing requiring invasive biopsy. Another advantage to DNA testing is that heterozygous carriers of autosomal recessive disorders can be definitively diagnosed, whereas carrier testing using an enzymatic assay might provide an ambiguous result (e.g., the result may overlap with those from either normal individuals or affected homozygotes).

DNA may be extracted from tissues and fluids besides peripheral blood. A number of diagnostic laboratories will accept mucosal cells from buccal swabs and saliva collections. Furthermore, genomic DNA may be extracted from cultured fibroblasts, especially when mosaicism is suspected. Prenatal testing of fetal cells from amniotic fluid and chorionic villi is routinely performed. In laboratories performing cancer diagnostics, DNA extracted from a solid tumor may be compared to DNA derived from lymphocytes; such examination may reveal either a loss of heterozygosity or a novel oncogene in the tumor sample. A number of laboratories in the United States perform mitochondrial DNA testing in addition to genomic DNA testing. Finally, a few clinical laboratories examine cDNA derived from messenger RNA (mRNA); such testing is performed to confirm a suspected splicing error.

Molecular genetic testing is categorized as non-waived, high-complexity testing. Although the Food and Drug Administration (FDA) does not currently regulate genetic testing in the United States, this may occur in the future. Presently, all diagnostic laboratories that report patient results must comply with the Clinical Laboratory Improvement Amendments (CLIA) that were legislated by Congress in 1988. As part of CLIA'88, regulations have been established by the Department of Health and Human Services (HHS) to ensure the quality and reliability of diagnostic testing performed on human specimens for disease diagnosis, prevention, or treatment. In addition, the Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) have been working with other federal agencies and professional organizations since 1997 to promote the quality of genetic testing and appropriate use of genetic tests in health care. In order to maintain CLIA certification, clinical labs must undergo inspections, usually every 2 years. CLIA-certified laboratories follow good laboratory practice and provide information to ordering

physicians regarding the selection of appropriate tests, intended use of the test, indications for testing, testing methodology and limitations, plus cost.

In 1997, the Department of Energy Task Force on Genetic Testing proposed three criteria for the evaluation of genetic tests, including analytic validity, clinical validity, and clinical utility. Analytic validity refers to how well the test predicts the presence or absence of a particular gene or genetic change. Analytic validity includes both analytic sensitivity and analytic specificity. Molecular genetic testing may consider analytic sensitivity to be the proportion of samples that have a positive test result or known mutation and that are correctly classified as positive. In contrast, analytic specificity in molecular testing is the ability of a test method to differentiate target sequences, alleles, or mutations from other sequences (e.g., homologous genes). A general definition of clinical validity is the accuracy with which a test identifies or predicts a patient's clinical status. Clinical validity takes into account clinical sensitivity and specificity, as well as positive and negative predictive values. Clinical sensitivity is the clinical detection rate, while clinical specificity is the proportion of individuals who do not have the clinical phenotype and test negative. The positive predictive value of a test is indicated by the proportion of individuals with a positive test result who have, or will develop, disease; in contrast, the negative predictive value of a test is equal to the proportion of individuals with a negative test result who do not have, and will not develop, disease. Finally, the clinical utility of a test takes into account the risks and benefits resulting from test use. Clinical utility refers to whether the test can provide information about diagnosis, treatment, medical management, or disease prevention.

In March 2010, the National Institutes of Health announced that it is creating a public database that can be used to search for information about the availability, validity, and utility of genetic tests. Until the NIH Genetic Testing Registry (GTR) is operational, the GeneTests Web site (www.genetests.org) can be used to obtain information about molecular genetic tests currently offered by CLIA-certified laboratories.

Types of Changes Associated with Heritable Disorders

Disease-associated genetic changes can occur anywhere in the genome, from the level of a chromosome down to the level of a single nucleotide. Although most changes may involve aberrations in gene dosage or gene sequence, epigenetic modifications can also lead to a disease phenotype. Cytogenetic testing, including the application of microarrays, is covered in Chap. 4 "Cytogenetic Testing and Chromosomal Disorders". In this section, the focus is on molecular diagnosis at the level of individual genes.

In the early days of molecular testing before the availability of direct mutation analysis, linkage studies were performed to follow a gene mutation through a family. In linkage studies, a genetic marker in close proximity to the gene of interest is tracked through the family to follow inheritance of the disorder. Because linkage analysis requires samples from multiple family members and not just the proband, such studies can be difficult to perform. Furthermore, linkage testing is not always informative for a particular family. Another limitation of linkage analysis is that the results always involve some uncertainty, because recombination may occur between the marker locus and the disease locus. Nevertheless, a number of clinical molecular laboratories continue to offer linkage analysis, especially when the disease gene is large and mutations are difficult to identify.

Most molecular testing performed today involves direct mutation analysis. With the completion of the Human Genome Project in 2003, molecular analysis is now possible for a very large number of single-gene disorders. The technique used for mutation detection is specific for the gene being tested and the type of mutation most likely to be found. For example, congenital myotonic dystrophy is the result of a large CTG trinucleotide expansion in the *DMPK* gene; this type of large expansion can only be confirmed with Southern Blot. Multiplex ligation-dependent probe amplification (MLPA) was first described in 2002 as a novel method to detect copy number variants, including small-scale exon deletions and duplications. Because this method is simple, cost-effective, and high-throughput, MLPA is used to detect deletions associated with many different disorders, including Duchenne or Becker muscular dystrophies (both caused by deletions within the *DMD* gene encoding dystrophin) and Type I spinal muscular atrophy (SMA) (Werdnig–Hoffmann disease, usually caused by homozygous deletion of exon 7 in the *SMN1* gene). Quantitative PCR is yet another method used to detect gene deletions or duplications at the level of a single exon within a gene of interest.

Gene sequencing is currently the gold standard used for mutation detection when variations at the single nucleotide level are the main cause of disease pathogenesis. Dideoxy terminator-based sequencing (i.e., Sanger sequencing) has been in use for at least 30 years and continues to be used by most clinical laboratories because it is amenable to automation. Identifiable DNA alterations

include frameshift mutations (due to small insertions and deletions) and base pair substitutions (point mutations). Although nucleotide changes may occur anywhere in the genome, clinical diagnostic laboratories often limit analysis to exons (i.e., protein coding regions) plus approximately 20 base pairs of flanking noncoding intronic DNA.

A few different types of sequence variants are easy to classify as pathogenic. Examples include nonsense mutations that lead to the production of a termination codon and alterations at invariant GT-AG sequences at splice donor and splice acceptor sites. In most other cases, interpretation of sequence variants is complex. Many genes are large and highly polymorphic (meaning more than one form of DNA sequence may exist at a particular site). Some variations are specific for particular ethnic groups and are not associated with a disease phenotype. Base pair substitutions may be synonymous or non-synonymous in nature. Synonymous changes (i.e., silent mutations) are those that lead to no foreseeable protein alteration. Such variants can be associated with disease, however, as they may lie in an important regulatory element and affect gene expression. In contrast, non-synonymous substitutions (i.e., missense mutations) are those that lead to a change in the encoded protein. Such changes may be deleterious or non-deleterious. To confidently classify a missense mutation as pathogenic, several factors must be taken into account, including the following: (1) Has the variant been previously reported in the literature or in a public database? (2) Does the variant co-segregate with the disease? (3) Are other mutations found in *cis* (i.e., on the same chromosome)? (4) Does the mutation fall in a conserved protein domain? (5) Is there evolutionary conservation of the encoded amino acid in other animal species? (6) Does the amino acid change affect the function of the protein?

Limitations of DNA Sequencing

As with other genetic testing techniques, DNA sequencing has limitations. First, and most important, sequencing of DNA requires an initial suspected clinical diagnosis. Even when a specific diagnosis is entertained, the genetic factor(s) responsible for the disorder may not be known or completely understood. Many genetic disorders are heterogeneous, meaning that a mutation in one of several genes may lead to the disease phenotype. Genetic heterogeneity can lead to a false-negative test result if the wrong gene is examined.

A false-negative test result can also occur because DNA sequencing cannot detect all possible variants. Although small microdeletions and microduplications several nucleotides in length can be detected, sequencing will not detect larger-sized copy number changes. Also, sequencing will not detect positional rearrangements of genetic material, including gene inversions, translocations, and inversions of larger chromosomal segments. Furthermore, because most clinical laboratories only sequence coding regions that give rise to protein, changes in nucleotide sequence within a promoter region or deep within an intron may go undetected.

In contrast to false-negative results, false-positive results can occur when variants of unknown significance are incorrectly classified as being associated with disease. As previously mentioned, variants of unknown significance can be difficult to classify as benign or pathogenic; often, parental studies are necessary to interpret an affected child's result.

Another limitation to direct DNA sequencing is this test technique will not detect epigenetic modifications. Such modifications are described in greater detail below.

Epigenetics

Epigenetic changes play an important role in pathogenesis of some disorders. Epigenetic factors affect the expression of genes without altering the genotype. Improper epigenetic programming can lead to consequences similar to the effects of a genetic mutation. Aberrant epigenetic programming can lead to inactivation of a gene that is normally expressed, or activation of a gene that is normally silenced.

Epigenetics is a normal cellular phenomenon that involves heritable transmission of information from one generation of cells to the next; this information is transferred through DNA and chromatin modifications, rather than specific alterations in the DNA sequence. Methylation of cytosines at CpG dinucleotides in promoter regions constitutes one form of epigenetic modification; the addition of phosphate, acetyl, and ubiquitin groups to histone proteins constitute other forms of epigenetic modification. Two important cellular processes, X inactivation and genomic imprinting, are examples of normal epigenetic mechanisms that can be associated with disease.

Although females normally have two X chromosomes and males have one, the quantity of X-linked gene product is usually the same in males and females due to the dosage compensation that occurs due to X inactivation (Lyonization). As a consequence, X chromosome aneuploidy usually has a milder clinical presentation than aneuploidy involving an autosome (chromosomes 1–22),

and therefore monosomy for the X chromosome (Turner syndrome) and trisomy X are relatively common. There are other important clinical implications of X inactivation. A woman who carries an X-linked recessive mutation on one of her two X chromosomes may express the mutant phenotype if most of her cells happen to have inactivated the X chromosome carrying the normal gene. Female expression of X-linked recessive disorders such as Fragile X syndrome and hemophilia has been reported.

Genomic imprinting is a developmental mechanism that occurs during gametogenesis and early development in a subset of genes. Imprinting mediates differential expression of a gene depending on whether it is inherited from the mother or the father (otherwise known as a "parent-of-origin" effect). To achieve allele-specific expression, special control elements known as imprinting control regions (ICRs) are regulated at imprinted loci via epigenetic modifications such as methylation of CpG dinucleotides and histone modifiers normally associated with transcriptional repression.

Several genetic disorders result from consequences of genomic imprinting (❯ *Table 5.2*). Diseases associated with small deletions may occur due to lack of expression of essential imprinted gene(s) on the intact homologue; likewise, diseases associated with uniparental disomy (where two copies of a chromosome are inherited from one parent and no copies are inherited from the other parent) may also result from failure to express essential imprinted genes. Prader–Willi syndrome and Angelman syndrome are two pediatric genetic disorders that are associated with imprinting. Prader–Willi syndrome, characterized by infantile hypotonia, developmental delay, childhood obesity, and hypogonadism, can result from either a deletion of the paternally inherited chromosomal segment 15q11-13 or from maternal uniparental disomy for chromosome 15. In both cases, the affected child fails to express crucial gene products because multiple maternally inherited genes in this chromosome region are imprinted and therefore are not expressed. Angelman syndrome, a clinically distinct condition characterized by severe intellectual impairment, seizures, ataxia, and apraxia, results from differential expression of other genes at 15q11-q13; however, Angelman syndrome is associated with a deletion of the maternal copy of chromosome 15q11-13 or paternal uniparental disomy. DNA sequencing studies have shown that approximately 10% of patients with Angelman syndrome have mutations in the maternally expressed copy of the *UBE3A* gene.

Silver–Russell syndrome (SRS) and Beckwith–Wiedemann syndrome (BWS) are two other genetic disorders that are associated with genomic imprinting. SRS is characterized by prenatal and postnatal growth retardation, relative macrocephaly, and a triangular-shaped face. In contrast, individuals with BWS display an overgrowth phenotype, abdominal wall defects, and a predisposition to develop certain malignancies, including Wilms' tumor. The first evidence that Silver–Russell syndrome is a disorder related to genetic imprinting came from Kotzot et al. in 1995. This group was the first to report maternal uniparental disomy of chromosome 7 in affected patients. Other researchers later reported a link between Silver–Russell syndrome and epigenetic changes in a specific region on the short arm of chromosome 11 at 11p15. Interestingly, Beckwith–Wiedemann syndrome is also associated with methylation defects in this same region. This specific area of chromosome 11p15 can be divided into two distinct imprinted domains, where the imprinting centers ICR1 and ICR2 play a critical role in regulating allele-specific expression of at least five different genes, including *H19*, *Insulin-Like Growth Factor II* (*IGF II*), *CDKN1C*, *KCNQ1*, and *KCNQ1OT1* (*LIT1*). Imprinting center 1 (ICR1) controls the expression of two genes, *H19* and *Insulin-Like Growth Factor II* (*IGF II*), in an opposite manner. ICR1 normally ensures that IGF II, a fetal growth factor, is expressed only from the paternal allele, and ensures H19, a noncoding RNA, is expressed only from the maternal allele. Loss of ICR1 methylation (so-called ICR1 "hypomethylation") has been found in approximately 30% of patients with Silver–Russell syndrome. Conversely, "hypermethylation" of ICR1 can be found in 2–7% of patients with Beckwith–Wiedemann syndrome. In these BWS patients, methylation of ICR1 on both parental chromosomes leads to biallelic silencing of *H19* and biallelic activation of *IGF II*. Nevertheless, most patients with Beckwith–Wiedemann syndrome have epigenetic changes in the ICR2-controlled imprinting domain as opposed to the ICR1-controlled imprinting domain. ICR2 is normally methylated only on the maternal allele. This imprinting control region regulates the allele-specific expression of the cyclin-dependent kinase inhibitor *CDKN1C*, the potassium voltage-gated channel *KCNQ1*, and the noncoding RNA *KCNQ1OT1* (*LIT1*). Approximately 50% of patients with Beckwith–Wiedemann syndrome show hypomethylation of ICR2.

Cancer Genetics in the Pediatric Population

There are a number of malignancies predominantly found in children. As previously mentioned, Wilms' tumor, a nephrogenic malignancy, may be found in association

Table 5.2
Genetic disorders associated with imprinting defects

Genetic disorder	OMIM#	Estimated incidence	Chromosome	Gene(s)	Imprinted (inactivated) parental allele	Protein	Clinical features
Prader–Willi syndrome	176270	1 in 10,000	15q11-13	*SNRPN* plus others (including *MKRN3* and *NDN*)	Maternal	Small nuclear ribonuclear protein polypeptide N	Infantile hypotonia, developmental delay, childhood obesity, hypogonadism
Angelman syndrome	105830	1 in 20,000	15q11-13	*UBE3A*	Paternal	Ubiquitin-protein ligase E3A	Severe mental retardation, apraxia, ataxia, seizures
Beckwith–Wiedemann syndrome	130650	1 in 14,000	11p15.5	*H19*	Paternal	(Untranslated mRNA)	Overgrowth, hemihypertrophy, macroglossia, omphalocele, neonatal hypoglycemia, predisposition to tumorigenesis (especially Wilms tumor)
				IGFII	Maternal	Insulin-like growth factor II	
				CDKNIC	Paternal	Cyclin-dependent kinase inhibitor 1 C	
				KCNQ1	Paternal	Voltage-gated potassium channel	
				KCNQ1OT1(LIT1)	Maternal	(Untranslated mRNA)	
Silver–Russell syndrome	180860	Wide variation in reports	11p15.5	*H19*	Paternal	(Untranslated mRNA)	Intrauterine and postnatal growth retardation, relative macrocephaly, triangular-shaped facies
			7p11.2-p13	*GRB10* (Candidate locus)	Maternal	Growth factor receptor-bound protein-10	

with Beckwith–Wiedemann syndrome. However, this tumor can also be found in isolation, or in association with another inherited syndrome called WAGR (an acronym for Wilms' Tumor/Aniridia/Genitorurinary anomalies/mental Retardation). WAGR is a contiguous gene syndrome associated with a deletion of several genes on chromosome 11p13.

Retinoblastoma is a solid tumor of the eye that is usually not associated with a syndrome. There is a form of retinoblastoma that is familial and presents bilaterally; it is the result of an inherited mutation in the tumor suppressor gene *RB1*. Children who have inherited an *RB1* mutation on chromosome 13 tend to present at a very early age and are six times more likely to develop other types of cancer later in life.

Specific gain-of-function mutations in the *RET* proto-oncogene on chromosome 10q11.2 are associated with multiple endocrine neoplasia, types 2A and 2B (MEN 2A and MEN 2B). Individuals with MEN Type 2 are at risk to develop medullary thyroid carcinoma, pheochromocytoma, and benign parathyroid tumors. It is recommended that prophylactic thyroidectomy be performed before the age of 6 years in children with MEN2A and before the age of 3 years in children with MEN2B.

In contrast to the solid tumors just described, there are several types of hematological malignancies predominantly found in infants and young children. One form of leukemia with a poor prognosis is acute lymphocytic leukemia (ALL) resulting from a defined translocation of chromosomes 4 and 11. Normally, chromosome 4

encodes AFF1, an ATP/GTP binding transcription factor, and chromosome 11 encodes MLL, a histone methyltransferase that acts as a global regulator of gene transcription. The t(4;11)(q21;q23) translocation leads to the production of an MLL-AFF1 fusion product whose role in leukemogenesis is not completely understood.

Pharmacogenetics in Pediatrics

Pharmacogenetics is the study of heritable variation to help determine drug metabolism and response to therapeutic agents. The goal is to minimize adverse drug events and maximize efficacy. Pharmacogenetics is currently being used in the areas of psychiatry, anesthesiology, hematology, and oncology to prevent adverse events and design optimal treatment regimens.

Genetic testing of the *TPMT* gene in children with acute lymphocytic leukemia (ALL) has been shown to be cost-effective. Chemotherapy for ALL typically includes treatment with several different thiopurines, including 6-mercaptopurine (6-MP) and 6-thioguanine (6-TG). Decreased levels of TPMT are associated with particular polymorphisms; these weak alleles lead to decreased thiopurine clearance and fatal toxicity in a small percentage of treated children. In contrast, individuals with high TPMT activity are fast metabolizers who show decreased therapeutic effect; these individuals may need a higher drug dose for sufficient response.

Population-Based Genetic Screening

Genetic screening consists of genetic testing at the population level. Carrier screening is available for people who have no personal or family history of a condition, but who may have a greater than average chance of carrying a particular gene mutation due to ancestry. A negative carrier screening test significantly lowers, but does not completely eliminate, the risk of being a disease carrier. This is because carrier screening detects specific mutant alleles, and less common mutations may go undetected. The goal of carrier screening is to help identify couples who are at risk for having an affected child to allow them to make informed reproductive decisions. For a screening program to be successful, the disorder should be clinically severe, there should be a relatively high frequency of carriers in a population, a reliable genetic test must exist, and there must be access to genetic counseling.

Population-based carrier screening for Tay–Sachs disease has been performed in individuals of Ashkenazi Jewish heritage since 1969. The scope of carrier screening in the United States broadened in 2001 when the American College of Obstetricians and Gynecologists and the American College of Medical Genetics recommended that cystic fibrosis (CF) carrier screening be offered to all couples planning a pregnancy or seeking prenatal care following review by an NIH Consensus Development Panel. The frequency of cystic fibrosis varies by ethnicity, and includes an estimated disease incidence of 1 in 3,300 Caucasians. Therefore, approximately 1 in 28 individuals of Northern European descent carries a mutation in the *CFTR* gene. The American College of Medical Genetics and the American College of Obstetricians and Gynecologists currently recommend population CF carrier screening for 23 specific *CFTR* mutant alleles.

In November 2008, the American College of Medical Genetics published an SMA carrier screening practice guideline recommending that SMA carrier testing be offered to all expectant couples regardless of race or ethnicity. Spinal muscular atrophy (SMA) is the most common inherited cause of early childhood mortality, and the second most common fatal autosomal recessive disorder after cystic fibrosis. The estimated incidence of SMA is 1 in 10,000 live births, and the estimated carrier frequency ranges from 1 in 40 to 1 in 60 individuals, depending on heritage.

Newborn screening is another example of population-based genetic testing. Newborn screening is a widely accepted public health program that integrates sample collection, laboratory testing, follow-up, diagnosis, treatment of identified disease, and tracking of long-term outcomes. Although the majority of conditions examined are numerous inborn errors of metabolism, other conditions include hemoglobinopathies, endocrine disorders, and cystic fibrosis. The main goal of newborn screening is to detect disorders that are threatening to long-term health before patients become symptomatic, since early treatment may significantly reduce mortality and morbidity.

Newborn screening began in the 1960s when Robert Guthrie developed a system for collecting small blood samples on filter paper (known as a Guthrie card). Guthrie developed an initial screening test for phenylketonuria (PKU) using a bacterial inhibition assay. This assay was later used to detect a number of additional amino acidopathies. By the end of the twentieth century, newborn screening programs had rapidly expanded. Because newborn screening programs have traditionally been state-mandated programs, there has been inconsistency regarding the number and types of diseases that are screened from state to state. In order for a disorder to be considered for newborn screening, the testing must be

relatively cost-effective, and some early intervention must exist that will reduce morbidity and mortality. In addition, the screening test must be sensitive, specific, and ideally have a high positive predictive value. Screening programs choose quantitative cutoffs that minimize both false-positive and false-negative test results. In 2005, the American College of Medical Genetics Newborn Screening Expert Group recommended a universal panel of metabolic disorders that should be included in every newborn screening program in the United States.

All patients who have an initial positive newborn screen require more definitive confirmatory testing. The American College of Medical Genetics publishes ACTion (ACT) sheets on its Web site that provide management guidelines for infants who screen positive; in many cases, the guidelines include DNA studies. In addition, there are several genetic disorders covered by newborn screening programs where molecular testing is part of the screening process. Many states screen neonates for cystic fibrosis using a combination of first-tier immunoreactive trypsinogen testing and second-tier DNA mutation analysis. Pilot programs in Wisconsin and Massachusetts have been initiated to screen for severe combined immunodeficiency syndromes (SCIDs). These programs use quantitative PCR to examine T-cell receptor excision circles (TRECs) produced during normal T-cell development. Abnormally low levels of TRECs may be indicative of an immunodeficiency syndrome and therefore require appropriate follow-up. Because the Wisconsin pilot program was able to successfully identify a newborn with SCID shortly after program implementation, it is expected that other state newborn screening programs will develop similar testing in the near future.

Looking Ahead: The Future of Molecular Genetic Testing

This chapter provides a brief overview of molecular genetic testing, including its current uses and limitations. Development of novel testing methodologies has greatly advanced this subspecialty of clinical laboratory-based genetics, and it is now possible to test for a very large number of single-gene disorders. Many patients who have previously tested negative for a genetic condition may benefit from retesting, since methods have changed substantially over the past decade. In instances where genetic testing remains uninformative, DNA can be isolated and stored (i.e., "banked") for future analysis.

It is expected that the field of molecular genetics will continue to rapidly evolve, and the technological limitations present today will be overcome tomorrow. Indeed, it is now possible to sequence the entire human genome of a single individual. This has become possible with the development of non-Sanger-based sequencing (so-called next-generation sequencing) that is based on a sequencing-by-synthesis technology first reported in 2005. This approach is extremely powerful and is capable of greatly outperforming automated Sanger sequencing at a fraction of the cost.

Technological advances are expected to improve the state of human health, but they also raise complex ethical and legal issues. To help address some of these concerns, the National Human Genome Research Institute (NHGRI) and the Department of Energy (DOE) set up the ELSI research program to study the ethical, legal, and social implications (ELSI) of genetic research. Information gathered from ELSI has been used to examine questions regarding genetic privacy and genetic discrimination. In 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law by President Bush. GINA protects Americans against health insurance and employment discrimination based on an individual's genetic information. The passage of GINA was a milestone that now paves the way for people to take advantage of personalized medicine with reduced fear of discrimination.

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Online Resources

National Human Genome Research Institute at the National Institutes of Health. www.genome.gov

Genetics Home Reference, National Library of Medicine. www.ghr.nlm.nih.gov

Centre for Genetics Education, Australia. www.genetics.edu.au

GeneTests. www.genetests.org

American College of Medical Genetics. www.acmg.net

Centers for Disease Control and Prevention. www.cdc.gov/genomics

The American Medical Association's Council on Ethical and Judicial Affairs. www.ama-assn.org/go/policyfinder

6 Principles of Therapeutics

Maria Descartes · Edward J. Lose

The medical treatment of genetic disease is now at the stage that the field of infectious disease was at after Koch's postulates were formulated. The causes of disease and malformations due to changes in the genetic sequence or outside of the genetic code (epigenetic modification) have been rapidly catalogued over the last few decades. Treatment of genetic disease has been so far mainly palliative in nature and generally addresses the pleiotropic manifestations. The complications of many genetic disorders are increasingly amenable to some form of medical or surgical treatment. Accomplishing a more disease-specific treatment of genetic disorders has remained an elusive goal, yet the growing number of therapeutic responses shows that progress has been made in controlling and reducing associated symptoms. The foundation of future-directed therapy for genetic disorders is based on the understanding of genetic disease at the molecular level.

Systemic Therapy

Many genetic syndromes exhibit organ or multisystem malformations. The surgical and medical treatment of these complications is long established, and results in prolonged survival with improved quality of life. These treatments include congenital heart disease repair, orthopedic surgery for skeletal malformations, neurosurgery for hydrocephalus, and many more. Although successful, these interventions are not unique to genetic disease and do not specifically address the underlying pathology (*Fig. 6.1*).

Organ Transplantation

Organ transplantation involves replacing the malfunctioning organ along with the relevant somatic stem cells and differentiated cells. Liver transplantation is used for a number of metabolic disorders, including urea cycle disorders, organic acidurias, homozygous familial hypercholesterolemia, and severe forms of glycogen storage disease. The liver disease associated with cystic fibrosis and α-1-antitrypsin deficiency may also be treated with liver transplantation. Somatic stem cells are capable of self-renewal and differentiation into different cell types, making them excellent candidates for cellular therapy. Liver repopulation by transplanted hepatocytes is a promising approach.

Hematopoietic Cell Transplantation

Transplantation of hematopoietic (multipotent) stem cells from bone marrow (HCT) has been used for the past 2 decades in immunodeficiency, lysosomal, and peroxisomal disorders. The rationale of this treatment is based on providing the missing enzyme through donor cells within and outside the blood compartment. The great majority of transplants have been performed in patients with Hurler syndrome (MPSI), Hunter syndrome (MPSII), Sanfilippo syndrome (MPSIII), Maroteaux–Lamy syndrome (MPSVI), X-linked adrenoleukodystrophy, metachromatic leukodystrophy, globoic-ceroid leukodystrophy (including Krabbe disease), and others (Pelizaeus–Merzbacher, Zellweger syndrome, and vanishing white matter disease).

Allogenic hematopoietic cell transplantation (HCT) is the only treatment with curative potential for sickle cell disease and beta-thalassemia. Successful treatment relies on a permanently viable engraftment as opposed to a transient engraftment. Availability of matched donor, graft failure, and transplantation-related mortality remain limiting factors.

Unrelated cord blood (UCB) transplantation is the utilization of umbilical cord blood as a stem cell source. The use of cord blood has several advantages over bone marrow as a source of stem cells. The recipients are more tolerant of histoincompatible blood than other donor cells. Placental cord blood is widely available and transplantation from unrelated donors appears to be as effective as from a matched donor, at least for Hurler syndrome and neonatal Krabbe disease. Still investigational is the use of mesenchymal stem cells (MSCs) infusions. Mesenchymal stem cells are pluripotent cells that have the potential of differentiating into various cells of meshencymal origin: osteoblast, chondrocytes, adipocytes, and astrocytes.

In mice, inducible pluripotent stem cells (iPS cells) have been created from skin fibroblasts and effectively transformed into hepatocytes. In the model utilized, the

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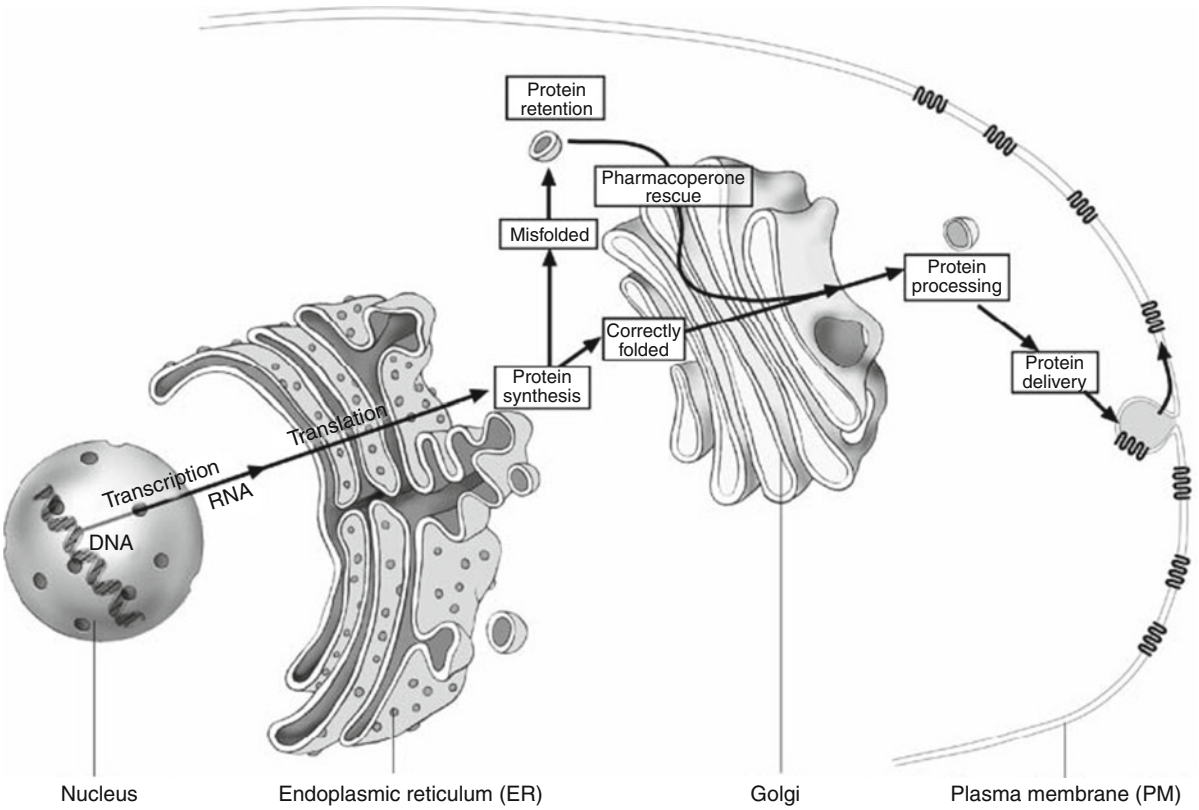


Figure 6.1
Various levels of treatment for genetic diseases (Pharmacol Rev 2007 59:225–250

subject mice were homozygous for fumarylacetoacetate hydrolase deficiency (hereditary tyrosinemia). The FAH -/- cells died and the iPS cells effectively replaced the entire liver. Human iPS cells have been generated and considerations for trials include the following conditions: α-1-antitrypsin deficiency, familial hypercholesterolemia, glycogen storage disease type 1 (von Gierke disease), hereditary tyrosinemia, and Crigler–Najjar syndrome.

Therapy at the Extracellular Level

Metabolic Pathway Modification

Inborn errors of metabolism are the archetype of genetic disorders. Newborn screening programs are the most widespread genetic tests performed. These programs are effective in modifying or preventing complications because early therapy is often easily implemented. Treatment is targeted at restricting dietary intake of the substrates early in the metabolic pathway, increasing excretion of toxic metabolites, replacing deficient substances, and altering the primary metabolic rate. To achieve metabolic balance and stabilization of symptoms, these strategies are used individually or in combination.

Dietary therapy is a long-established and effective method of managing genetic disorders (*Table 6.1*). Dietary modification has been used successfully in aminoacidopathies, urea cycle disorders, and diseases of carbohydrate metabolism. Dietary restriction is usually a lifetime commitment and can be imposing to the family and the patient. Total protein restriction is necessary and sometimes severe for disorders of amino acid catabolism and the urea cycle. This must be balanced by supplying essential substrates and cofactors to allow for growth and development. Sugar restriction for disorders of carbohydrate metabolism can be as simple as limiting lactose consumption in galactosemia or as difficult as limiting total glucose consumption in pyruvate dehydrogenase deficiency. Patients with fatty acid oxidation defects usually require acute management only and are otherwise allowed a relatively unrestricted diet.

Table 6.1
Disorders that respond to dietary therapy

Disorder	Restriction	Supplementation
Aminoacidopathies		
Phenylketonuria	Phenylalanine	Tetrahydrobiopterin for responsive patients
	Total protein	
Tyrosinemia Tyrosenemia I? or tyrosemia I and II? Tyrosemia I is usually responsive with NTBC (nitisinone) also known as: 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3 cyclohexanedione	Phenylalanine	
	Tyrosine	
Homocystinuria	Methionine	Pyridoxine for responsive types, betaine, folate, hydroxycobalamin
	Total protein	
Carbohydrate metabolism defects		
Pyruvate carboxylase deficiency	High carbohydrate and high protein diet to avoid activation of gluconeogenesis	Citrate supplementation, biotin, aspartic acid, triheptanoin
		Thiamine, carnitine, lipoic acid
Pyruvate dehydrogenase deficiency	Glucose/Carbohydrates	Fat intake
	Branched chain amino acids	Thiamine, lipoic acid
		Cornstarch
		Protein
Hereditary fructose intolerance	Fructose, sucrose	
	Sorbitol	
Galactosemia	Galactose, lactose	
Fatty acid oxidation defects		
Short chain acyldehydrogenase deficiency	None	Carnitine
Medium chain acyldehydrogenase deficiency	None	Carnitine
Long chain acyldehydrogenase deficiency	None	MCT oil and low fat diet
Trifunctional protein deficiency	Long chain fats	MCT oil, carnitine, DHA
Organic acidemias		
Branched chain organic acidurias		
Maple syrup urine disease	Isoleucine, leucine, valine	
Isovaleric acidemia	Leucine	Levocarnitine and glycine
Propionic acidemia	Isoleucine, valine, methionine, threonine	Levocarnitine and biotin
Methylmalonic acidemia	Isoleucine, valine, methionine, threonine	Folate, betaine, and levocarnitine Cyanocobalamin for cobalamin responsive patients
Glutaric Acidemia Type 1	Lysine, hydroxylysine, tryptophan	Levocarnitine, riboflavin
	Tryptophan	
Urea cycle defects		
In general	Total protein	
N-Acetylglutamate synthetase deficiency		Carbamylglutamate

Table 6.1 (Continued)

Disorder	Restriction	Supplementation
Carbamoylphosphate synthetase deficiency		
Ornithine transcarbamylase deficiency		Arginine, citrulline
		Sodium benzoate
		Sodium phenylacetate
Citrullinemia		Arginine
Arginosuccinic aciduria		Arginine
Arginase deficiency		

Limited understanding of the metabolic pathway and interactions involved in disease progression still poses a barrier to effective treatment. Despite a reduction in the occurrence of cataracts and mental retardation with the institution of lactose restriction in galactosemia patients, 81% of females with this disorder experience premature ovarian failure and 56% of males and females have delayed vocabulary and articulation milestones. Additionally, intercurrent illness and stress may provoke a crisis in otherwise stable patients. Rapid response with dietary modifications and intravenous therapy can avert deterioration in many cases.

In a number of metabolic disorders, the efficiency of the defective enzyme or an alternative pathway can be enhanced by the administration of large amounts of the vitamin cofactor. The administration of cofactor may overcome reduced affinity of the mutant enzyme for the cofactor or stabilize the enzyme. Nonresponsive patients generally have a mutation that result no residual enzyme activity.

Phenylketonuria (PKU) is the first genetic disorder for which a screening process was introduced in the 1960s. PKU is traditionally treated with a phenylalanine-restricted diet. Tetrahydrobiopterin is a cofactor that binds to the affected enzyme, phenylalanine hydroxylase. A tetrahydrobiopterin analog, Sapropterin, is the first non-dietary treatment for patients with phenylketonuria (PKU). Sapropterin dihydrochloride (Kuvan®) is a synthetic formulation of the active 6R-isomer of tetrahydrobiopterin, a naturally occurring cofactor of phenylalanine hydroxylase. The mechanism of action appears to be related to its effect in augmenting and stabilizing abnormal phenylalanine hydroxylase molecules, thus increasing the clearance of phenylalanine from the body. It is approved to treat hyperphenylalaninemia in patients ages 4 or more years with tetrahydrobiopterin-responsive phenylketonuria.

For disorders characterized by accumulation of toxic metabolites, excretion of the offending substance is the preferred therapeutic method. Additionally, the offending substance can be reduced by activation of alternative pathways, inhibition of normal feedback inhibition, and pharmacologic agents used to promote elimination.

Nitrogen scavengers such as sodium benzoate, phenylbutyrate, or phenylacetate are utilized in patients with urea cycle disorders. They promote nitrogen elimination and avoid toxic accumulation of the ammonium ion. Adjunct clearance mechanisms are used in disorders characterized by failure of normal metabolic clearance to excrete excess amounts of substrate. Chelation therapy with penicillamine and trienetine are used to increase copper excretion in Wilson disease. Serial phlebotomy is the treatment of choice in hemochromatosis to remove the excess iron.

Hereditary tyrosinemia type I is due to a deficiency of fumarylacetoacetase, which leads to the accumulation of fumarylacetoacetate and maleylacetoacetate. Both chemicals are then metabolized via an alternative pathway to succinylacetone – the metabolite responsible for many of the neurological symptoms of this disorder. In addition to dietary restriction of tyrosine and phenylalanine, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) is used to divert the tyrosine catabolism pathway upstream of homogentisic acid toward a normally dormant urinary excretion pathway. This reduces the levels of fumarylacetoacetate, maleylacetoacetate, and succinylacetone, thus reducing or averting the hepatic complications of the syndrome such as cirrhosis and hepatocellular carcinoma. Allopurinol has been used similarly in disorders leading to hyperuricemia like Lesch–Nyhan syndrome, and hematin is used in acute intermittent porphyria to decrease the activity of δ-aminolevulinic acid synthetase, thereby reducing porphyrin production.

Replacement of a deficient substrate can also be an effective treatment. Smith–Lemli–Opitz syndrome is a disorder of cholesterol biosynthesis. Cholesterol supplementation has provided some benefit to patients with this

disorder. Large doses of carnitine are effective in carnitine transport defects.

Protein Replacement Therapies

Protein replacement therapy refers to production, purification, and administration of the missing protein to the patient. This therapy is used in several hereditary disorders, including cystic fibrosis, hereditary angioedema, coagulation disorders, α-1-antitrypsin deficiency, immunoglobulin deficiencies, endocrine disorders, and lysosomal storage diseases (Table 6.2).

Enzyme replacement therapy is effective in the nonneurological symptoms of mucopolysaccharidosis types I, II, IV, and VI, Pompe, and Niemann–Pick B (not approved), but has not yet proven to be beneficial in storage diseases that primarily affect the central nervous system, since the replacement enzymes do not efficiently cross the blood–brain barrier.

Metabolic inhibition

Another approach to the therapy of lysosomal storage disorders due to defects in enzymes involved in glycosphingolipid degradation (including Gaucher disease types 1, 2, and 3, Fabry disease, Tay–Sachs disease, Sandhoff disease, and G_{M1} gangliosidosis) is substrate reduction therapy (SRT). SRT is a biochemical approach that makes use of substrates that inhibit and therefore reduce the rate of macromolecule synthesis. Miglustat (*N*-butyl-deoxynojirimycin/NB-DNJ) inhibits the initial committed step in glycosphingolipid synthesis, therefore reducing the substrate of the missing enzyme. For example, children with Tay–Sachs disease accumulate high levels of G_{M2} ganglioside in brain cells, which causes cell death. Decreasing the synthesis of G_{M2} would presumably decrease cell death and moderate the course of the disease. Miglustat has been approved in Europe and the United States for the treatment of the mild form of Gaucher type 1 and in Europe for the treatment of Neiman–Pick type C. Miglustat is in clinical trials in adults and children with juvenile G_{M2}, Tay–Sachs, and Sandhoff disease, and in young children under the age of 2 with Tay–Sachs and Sandhoff disease. Some affected individuals or parents of those affected do explore with their physicians the option of using this treatment on an "off-label" basis.

Treatment of the Molecular Mechanism

Marfan syndrome affects 1 in 5,000 individuals and is a systemic connective tissue disorder caused by mutations in the gene for fibrillin-1. It was originally thought that the clinical manifestations of Marfan syndrome were solely

Table 6.2
Protein replacement therapy

Disease	Protein	Trade name
Cystic fibrosis	Digestive enzymes	Multiple
Hereditary angioedema	C1 inhibitor	Cinryze
Coagulation disorders		
For example, Hemophilia A	Factor VIII	
α-1-Antitrypsin deficiency	α-1-Antitrypsin	Prolastin
Immunoglobulin deficiencies	Intravenous immunoglobulin	IVIG
Gaucher disease	Glucosidase	Imiglucerase (Cerezyme), velalglucerase (VPIV)
Fabry disease	α-Galactosidase	Agalsidase-beta (Fabrazyme, Replagal)
Type 1 Hurler, Scheie, Hurler-Scheie	α-L-Iduronidase	Aldurazyme
Type 2 Hunter	Iduronate-2-sulfatase	Idurulfase (Elaprase)
Type 4 Morquio		
A	Galactosamine-6-sulfatase	
B	α-Galactosidase	
Type 6 Maroteaux–Lamy	*N*-Acetylhexosamine-4-sulfatase	Galsulfase (Naglazyme)
Pompe	Acid α-glucosidase	Alglucosidase alfa (Myozyme, Lumizyme)

the result of the production of abnormal fibrillin-1, resulting in changes in the structural integrity of the affected organs. Recent molecular and animal studies have shown that it is a developmental abnormality due to altered transforming growth factor-beta signaling. In the mouse model of Marfan syndrome, the use of an antagonist (Losartan) of the transforming growth factor beta-angiotensin II signaling pathway has been shown to prevent and reverse manifestations of the disease, including aortic root dilation. Losartan is currently undergoing clinical trials.

Therapy at the Intracellular Level

Protein Enhancement Therapy: Chaperones

Inherited mutations can disrupt native protein folding, thereby producing proteins with an abnormal three-dimensional conformation. These misfolded proteins, which may otherwise be sufficiently active, are consequently retained and degraded in the endoplasmic reticulum-associated degradation pathways. The most widely known of these is the ΔF508 mutation in the cystic fibrosis transmembrane conductance regulator.

Among the newest therapeutic modalities is the utilization of low-molecular-weight compounds known as chaperones to stabilize the functional form or three-dimensional shape of a mutated protein in the endoplasmic reticulum. The binding of the chaperone molecule allows the protein to fold into its correct three-dimensional conformation and be properly trafficked through the endoplasmic reticulum. The protein then resumes its proper path to the correct site in the cell. Pharmacological chaperone therapy is in early stage clinical trials for lysosomal storage diseases: Fabry disease utilizing 1-deoxygalactonojirimycin which is a potent inhibitor of α-galactosidase. The inhibitor is given in low quantities which paradoxically enhances the intracellular activity of the residual enzyme.

Transcriptional Therapy

Increasing knowledge of gene expression will allow another potential tool for therapy, transcriptional therapy. Transcriptional therapy is aimed at modulating, modifying, or reactivating genes. These types of modifications of the genome include: reducing the expression of a dominant mutant gene product by RNA interference (RNAi), increasing the expression of a gene that can compensate for the effect of the mutation at another locus, and increasing the amount of messenger RNA (mRNA) of silent or poorly expressed genes.

Hereditary angioedema (AD inheritance) is a potentially fatal disorder due to a mutation in complement 1 (C1) esterase inhibitor. Affected individuals have unpredictable episodes of submucosal and subcutaneous edema. If the upper respiratory tract is involved, this disease can be fatal. Danazol, an attenuated androgen, is used in the long-term prophylactic treatment of this condition, by increasing the abundance of C1 inhibitor mRNA. Current treatment for sickle cell disease includes hydroxyurea, which results in an increased production of fetal hemoglobin. A promising strategy in the treatment of hemoglobinopathies such as sickle cell disease and β-thalassemia is the use of drugs that induce DNA hypomethylation. These drugs increase the abundance of fetal hemoglobin (HbF, $\alpha 2\gamma 2$). HbF is normally underexpressed in adults (<1% of total hemoglobin) as a result of normal globin switching in infancy. The underexpression of the HbF is in part due to methylation of the promoter of the γ-globin gene. This methylation can be inhibited by cytidine analogs, such as decitabine (5-aza-2′deoxycytidine).

Conditions that are the result of pathologically silenced (hypermethylated) genes could theoretically be treated with drugs that cause DNA demethylation, thereby reactivating normal transcription. Fragile X syndrome is the result of pathological silencing of the FMR1 gene (Xq27.3) due to an abnormal trinucleotide repeat (CGG) expansion near the FMR1 promoter. The nucleotide analog 5-azadeoxycytidine (5-azadC) is an irreversible inhibitor of DNA methyltransferases, which predominantly methylate CpG dinucleotides in the human genome. In vitro treatment of fragile X cells with 5-azadC lead to reactivation of FMR1 transcription. Drugs that target other forms of gene inactivation are also being investigated (e.g., histone acetylation). Other candidates are conditions that result from deletion or uniparental disomy of an imprinted gene.

Pathological changes can result from the production of a gene product that is toxic to the cell, as in Huntington disease. Additionally, an abnormal collagen chain produces a structurally weakened collagen triple helix in osteogenesis imperfecta. Diminishing the amount of the mutant protein without altering the production of the normal allele may ameliorate the phenotype. This goal might be reached by creating double-stranded RNA molecules that are degraded prior to translation. RNA interference (RNAi) technology utilizes RNAi directed against the mutant mRNA, which inactivates the specific mRNA transcribed

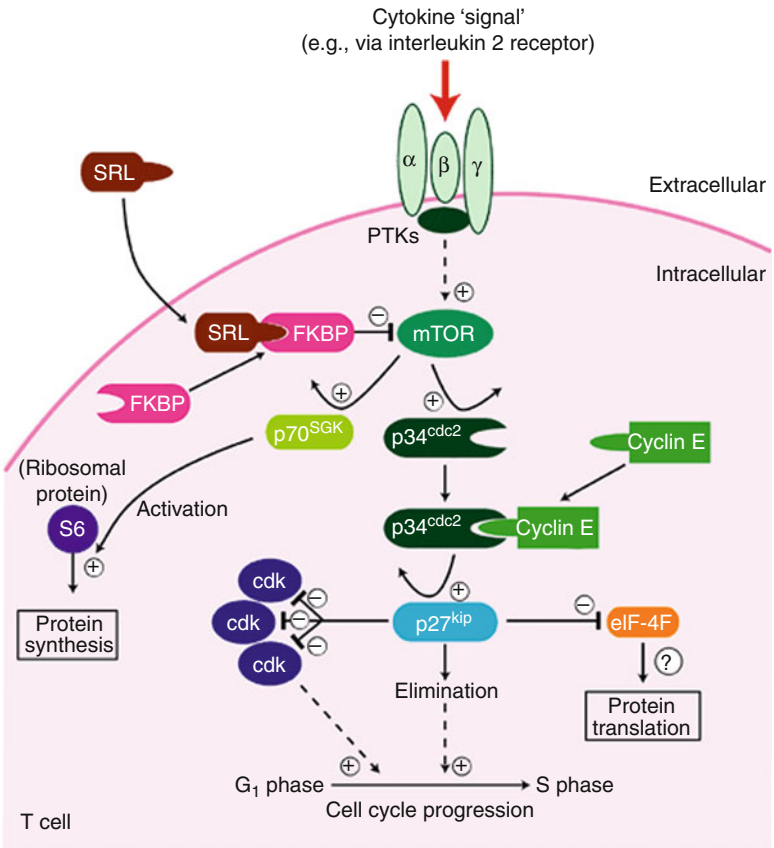
by the mutant allele while not binding and inactivating the mRNA transcribed by the normal allele.

Translational Therapy: Stop-Codon Read-Through Drugs

One-third of inherited diseases are the result of mutations that create premature termination codons. These include cystic fibrosis, muscular dystrophy, hemophilia, familial hypercholesterolemia, lysosomal storage disorders, and several types of cancer. Aminoglycosides (gentamicin) can suppress premature translational termination induced by nonsense mutations and prompt ribosomes to generate full-length proteins. In preclinical and pilot clinical studies, this therapeutic approach shows promise in reducing or eliminating the phenotype by promoting protein synthesis. The challenge ahead is to maximize efficacy and minimize side effects.

Pathway Modification

Several genetic syndromes are the result of mutations in known pathways that control transcription. Sirolimus (rapamycin) is an immunosuppressant medication with activity in the mTOR pathway (see *Fig. 6.2*). This results in blocking of cytokine-initiated signaling. The mTOR pathway is affected in several syndromes such as tuberous sclerosis complex (TSC) and the Ras pathway syndromes – neurofibromatosis, Noonan syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and LEOPARD syndrome. These syndromes are marked by the constituitive activation of ras-signaling the mTOR



Mechanism of action of sirolimus (rapamycin)
Expert Reviews in Molecular Medicine © 2000 Cambridge University Press

Figure 6.2
Mechanism of action of sirolimus (rapamycin) (Expert Reviews in Molecular Medicine ©2000 Cambridge University Press)

pathway. Rapamycin and other mTOR inhibitors are currently in clinical trials to gauge effectiveness in preventing the formation and growth of neurofibromas in NF1 and various manifestations of TSC.

Cell Replacement Therapy

The isolation and utilization of pluripotent and totipotent embryonic stem cells has previously been restricted to the creation of recombinant animal models of human disease. Recently, these stem cells have been stimulated to follow known differentiation pathways which yield specific cell types. These manufactured cells might then correct human disease resulting from the lack of secreted products, or urged to differentiate in situ to replace the diseased cells. There are currently multiple entries in ClinicalTrials.gov regarding stem cell research. Some examples of diseases are listed in *Table 6.3*.

Gene Therapy

In principle, this approach seems straightforward. It is possible now to create mutant animal phenotypes and to correct them utilizing recombinant technology. The application to humans is problematic. One cannot reverse the embryologic development of a human fetus; therefore, altering a structural defect is not currently possible. The diseases considered for gene therapy are thus restricted to those associated with continuously replicating cells such as hematopoietic cells and epithelial cells, or enzyme defects in accessible cells. The mechanism of molecular modification utilizes both random insertion of a correct genetic sequence into the genome and homologous recombination to correct the specific mutation. For each specific combination of vector, transgene and target tissue one or two of the following problems predominate: gene silencing, insertional mutagenesis, phenotoxycity, immunotoxicity, horizontal transmission of the donated DNA, vertical transmission (Mingozazi F, High KA. Therapeutic in vivo gene transfer for genetic disease using AAV: progress and challenges).

The vectors utilized to deliver the DNA therapy must be taken up by mammalian cells and ultimately the DNA must travel to the nucleus and become incorporated either by insertion or homologous recombination. Eukaryotic viruses such as adeno-associated viruses (AAV) have been most commonly utilized. The mammalian cells are efficient in the uptake of AAV, and the therapeutic DNA sequence is effectively delivered to the nucleus where recombination or insertion takes place.

Table 6.3
Conditions amenable to stem cell therapy

Disease	Organ	Therapy	Phase	Sponsor
Multiple sclerosis	Brain	PBSCT	3	Northwestern University
Myasthenia gravis	Brain	Hematopoietic stem cells	1	Northwestern University
Pressure sores	Skin	Hematopoietic stem cells	1	University Hospital Basel, Switzerland
Coronary artery disease	Heart	Cardiac stem cells	1	University of Louisville
Congestive heart failure	Heart	Hematopoietic stem cells	3	Johann Wolfgang Goethe University Hospitals
Brachial plexus denervation	Arm	Hematopoietic stem cells	3	Leiden University Medical Center

Table 6.4
Conditions amenable to DNA therapy

Disease	Organ	Therapy	Phase	Sponsor
Leber congenital amaurosis	Eye	rAAV2-hRPE65	1	Hadassah Medical Organization
Chronic granulomatous disease	Hematopoietic	Retroviral	0	NAIAD
Advanced malignant thyroid tumors	Thyroid	rAd-p53	4	Shenzhen SiBiono Genetech
Malignant glioma	Brain	ADV-TK	2	Huazhong University

If the desired effect is to suppress gene expression, then small inhibitory RNA strands (siRNA) can be used. The siRNA binds selectively to mRNA strands and the resulting double-stranded RNA is degraded by the cell prior to translation. The delivery systems for siRNA are numerous and summarized in a table. The siRNA incorporation is transient and does not yield a long-term solution.

Children with cystic fibrosis have temporarily incorporated exogenous DNA in their lungs utilizing an adenovirus vector, but the underlying stem cells were not transfected and the effect was transient. Another setback occurred with the death of a patient with OTC deficiency. It is believed that an immune response to the vector was the cause of death. The same results have occurred with a child who was being treated for severe combined immunodeficiency disorder (SCID). These issues have been addressed and therapies have been formulated for many disease states.

Newer trials are being undertaken with the hope of correcting mutations in target organs. There are currently many trials utilizing gene therapy. A few examples are listed in *Table 6.4*.

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Neonatology

Martin Keszler

7 The Field of Neonatology

William Oh

During the eighteenth century, the care of sick infants was extremely primitive resulting in an extremely high infant mortality rate: 290/1,000 live birth or a whopping 29%. In the next century, persistently high infant mortality rate raised concerns of depopulation and potential lack of military enrollees which prompted the European governments' initiatives to improve maternal and child health. The late nineteenth century witnessed the beginning of some attempts to improve neonatal care with the advent of primitive but effective warming devices. This simple intervention resulted in improvement of infant mortality rate. In the United States the reduction of infant mortality was dramatic dropping from 100/1,000 to approximately 35/ 1,000 live birth from 1915 through 1940s (*Fig. 7.1*). This reduction was in part a result of the decline in neonatal mortality rate from 44 to 25/1,000 live births.

In the nineteenth century, attempts to provide better care of the high risk infants were done by midwives and obstetricians. Ironically, pediatricians were not involved. A French obstetrician Stephane Tarnier was credited for developing the incubator, which markedly reduced the mortality rate of infants under 2,000 g from 66% to 38%. Pierre Budin another French obstetrician was generally considered as one of the pioneers in improving neonatal care by extending the works of Tarnier and introducing the principles and methods of neonatal care. Martin Couney, a physician who championed the cause of premature care immigrated to the United States and brought the idea of improving premature care by the use of incubators. He was a clinician as well as a showman. He took the advantage of novelty of the care of premature infants with incubator and brought it to the public by showing them in various venues including fairs in cities such as Buffalo, New York, and Chicago. One vignette regarding the Chicago exhibition is that Dr. Couney presented the premature babies in the incubators to the public charging fees and made quite a bit of profit. Unfortunately, many of the infants developed diarrhea ending in death to some that prompted the closure of the show.

At about the same time, the first premature nursery was established at Sarah Morris Hospital of Michael Reese Hospital in Chicago in 1934. The nursery was directed by Dr. Julius Hess with the assistance of a very dedicated nurse, Evelyn Lundeen. This probably marked the beginning of modern Neonatology because in addition to being an excellent and dedicated clinician for this nursery, Dr. Hess started to engage in research for new knowledge to improve the care of the premature infants. The two pioneers also published textbook devoted to the principles and methods of premature care, many of which are still valid today. Other publications that enhanced the knowledge in the care of newborn soon followed and a new science was born. This era also marked the gradual introduction of pediatricians into the care of the newborns both in the delivery room and in the nursery.

At the end of World War II, several advances were responsible for the marked improvement of neonatal care. In addition to continued use of the incubator as a warming device for premature and other high risk infants, the discovery of blood type, introduction of blood transfusion, use of oxygen, fluid therapy, and antibiotics markedly improved the outcomes of the high risk infants. Advances in knowledge through clinical investigation such as establishing the diagnosis of congenital rubella syndrome, and identification of the cause of Rh erythroblastosis continued to improve the progress of the field. Some notable technological advances included the use of tiny needles (butterfly needles) designed by Dr. Robert Usher that allowed for intravenous fluid infusion as well as provision of sodium bicarbonate that improved outcomes of infants with respiratory distress syndrome. The technique of exchange transfusion was extremely valuable for the treatment of severe Rh erythroblastosis.

Some of the interventions were made without solid evidence of efficacy or freedom from potential harms. An example of this phenomenon was clearly illustrated with the oxygen treatment story. Liberal use of oxygen became commonplace in the 1950s not only to treat respiratory distress, but also more benign conditions, such as periodic breathing. While oxygen was responsible for saving many infants by reducing death or morbidity form hypoxia, ignorance of its potential adverse effects led to the tragic epidemic of retrolental fibroplasia (now known as retinopathy of prematurity) that blinded thousands.

During the past 5 to 6 decades, the emergence of the vibrant and productive subspecialty of Neonatology within Pediatrics has been witnessed; the evolution of the

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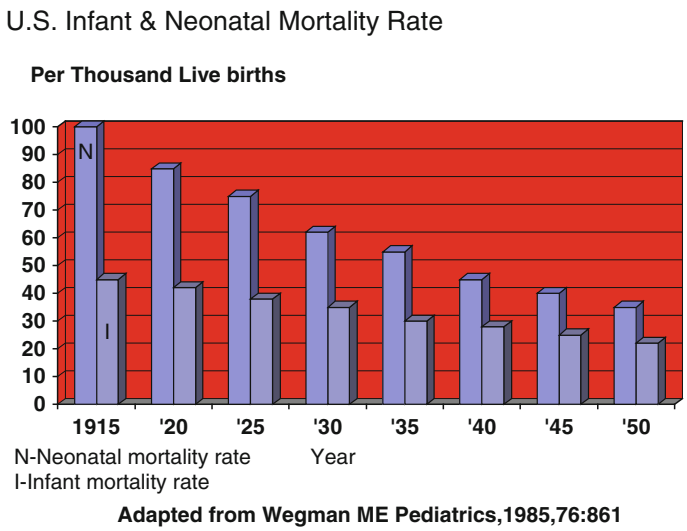

Figure 7.1
US infant and neonatal mortality rate per thousand live births

specialty was very nicely documented by Alistair Philip. It is not entirely clear when and how the term Neonatology came about, although it is most likely that the term was introduced by Alexander Shaffer who used the term in his textbook in 1960. The emergence of this subspecialty along with tremendous advances in medical care for the high risk infants have resulted in marked improvement in neonatal mortality rate in industrialized countries. Lee et al have shown that from 1950 to 1975, the US neonatal mortality rates have fallen significantly from 20 to 11.5/1,000 live births. This fall was not associated with any change in important demographic variables such as birth weight and gestational age that might affect neonatal mortality rates, clearly suggesting that the improvement is a result of improved medical care provided by the clinicians in this specialty. In 2005, the US neonatal mortality rate has fallen further to a low of 4.54/1,000 live births. This remarkable change in statistics was associated with the lowering of gestational age range for viability. In the 1950s and 1960s, only the very preterm infants (32 plus weeks of gestation) had a realistic chances of survival. In fact, in those days, in many countries, the neonatal survival statistics only list those who are 28 weeks in gestation or above. Today, the threshold of viability in the developed countries is close to 24–25 weeks. Unfortunately, the improvement in survival rate in the most immature infants has not been associated with improved outcomes of these infants at 2 years corrected age and in resource-limited circumstance, provision of intensive care to these infants may not be appropriate. The lowering of the threshold of viability also sparks intense debate among neonatologists, ethicists, and many concerned parties as to how far is too far in saving these tiny babies. The debate is also a result of very high morbidity rates among survivors of the extremely low birth weight and preterm infants. Most parties in this debate consider 22–23 weeks gestation as futile while the center of intense disagreement is for infants in the 24–25 weeks gestation because of increasing chances of survivors but the rate of poor neurodevelopmental abnormality remains high. Substantial differences exist even between industrialized countries with the Dutch drawing the line for intensive care at 25 weeks and the Japanese attempting to save infants as immature as 22 weeks. These difficult issues are further addressed in the chapter on Chap. 37, "Ethics and Decision Making in Neonatology" elsewhere in this section.

The improvement in neonatal mortality rates during the past half century is a result of many advances derived from plethora of accomplishments in basic science, translational and clinical research, and the implementation of these research findings into clinical practice by the neonatologists as the core clinician leaders working with obstetricians, medical and surgical subspecialists, along with a cadre of multidisciplinary personnel who are involved in

neonatal care. These advances include, among others, the use of antenatal steroids for acceleration of fetal maturation, surfactant for the treatment of hyaline membrane diseases, antibiotics for neonatal sepsis, inhaled nitric oxide for persistent pulmonary hypertension, and hypothermia for infants with hypoxic ischemic encephalopathy just to name a few. A more detailed list of these advances is presented in *Table 7.1*. These therapies are also described in detailed in various chapters of this section.

Historically, in the 1950s and 1960s the venue for the care of sick neonates was primarily located in a number of premature nurseries around the country which were associated with obstetrical wards and were designed primarily for the care of premature babies. The high risk term infants were generally cared for in the pediatric wards. The responsibility for the care of these infants was generally assumed by pediatricians who were interested and dedicated to this particular group of high risk infants. These clinicians were ably supported by dedicated and experience nurses. As more sophisticated and useful medical advances such as mechanical ventilation, were introduced to the field, there was a transition of the venue from premature nurseries to neonatal intensive care units (NICUs). The high risk term infants were integrated into the neonatal intensive care units. The clinicians who were responsible for the delivery of care in these units gradually organized themselves into a distinct group of physicians and over time, the specialty of Neonatology became a reality.

At around the mid-1960s an important event occurred that was in part responsible for improved neonatal outcomes: the implementation of perinatal regionalization. The concept emerged from the clear demonstration in a Canadian study that neonatal mortality rate was markedly lower when the high risk infants were cared for in institutions with neonatal intensive care units. At about the same time, there was strong interest in regionalizing medical programs which include cardiac care and others; the neonatal regionalization program was benefitted by the endorsement of the American Medical Association which strengthened its implementation. The strategy was further enhanced by the publication by March of Dimes and supported by key medical organizations including American Academy of Pediatrics (AAP) and American College of Obstetricians and Gynecology (ACOG) of a document entitled "Toward Improving the Outcomes of Pregnancy." The Program called for the designation of various levels of obstetric and neonatal facilities in a region in accordance with their capabilities to care for infants with graded levels of risk. The Program established the core infrastructure nationwide of having the Tertiary Care Center in a region serving as the leader in providing care to the high risk

Table 7.1
Introduction of perinatal therapies that improved neonatal care and outcome during the past six decades

Decades	Therapy
1950s	First-generation antibiotics
	Blood transfusion; exchange transfusion
	Incubators: Armstrong, Hess bed
1960s	Assisted ventilation: Intermittent positive pressure ventilation
	Incubator: Air shields isolette
	Negative pressure ventilator
	Usher's butterfly needles; umbilical vessel catheterization
	Newborn screening (PKU and Hypothyroidism)
1970s	Assisted ventilation: Continuous positive airway pressure
	Antenatal steroids
	Tocolysis for preterm labor
	Phototherapy for hyperbilirubinemia
	Central line placement/parenteral nutrition
	Rhogam for prevention of Rh disease
	Cyclooxygenase inhibitors for patent ductus arteriosus
	Noninvasive diagnostic technology (echocardiography, cranial ultrasound, other advanced imaging techniques)
1980s	Assisted ventilation: High-frequency ventilation; extracorporeal membrane oxygenation
	Cardiac surgery for congenital heart disease
	Extracorporeal oxygenation for cardiac surgery and cardiorespiratory failure
1990s	Surfactant therapy for hyaline membrane disease
	Inhaled nitric oxide for pulmonary hypertension
	Indomethacin prophylaxis for intraventricular hemorrhage
	Intraparatum antibiotic prophylaxis for neonatal group B Streptococcus sepsis
	Fetal surgery
	Laser therapy for severe retinopathy of prematurity
	Assessment of neurodevelopmental outcomes of high risk infants
2000s	Hypothermia for term infants with hypoxic ischemic encephalopathy
	Gentle ventilation to prevent bronchopulmonary dysplasia
	Probiotics for prevention of necrotizing enterocolitis

mothers and infants. Each tertiary care center is associated with several Level I and II facilities with appropriate transfer and retrotransfer guidelines for the high risk mothers and infants. The AAP and ACOG published specific guidelines that defined the various levels of perinatal care facilities that serve as the blue print for local implementation.

To support the medical staffing of these facilities, the American Board of Pediatrics have approved a 3-year Fellowship Program for Neonatal Perinatal Medicine to train a cadre of neonatologists to deliver high-quality clinical care. The 2007 statistics showed that there are approximately 5,000 + board certified or eligible neonatologists in North America who served this function. Because of unabated high preterm birth in the United States, it appears that there will be continuing need for this workforce to staff the neonatal intensive care units. Many of the trainees came from various parts of the world. Most of them returned to their home countries and set up neonatal programs to deliver intensive care for the high risk newborns. The establishment of these programs in part account for the improvement of the neonatal mortality rates worldwide, particularly in the developing countries.

The Future

Clinicians and scientists in the field of Neonatology have come a long way in achieving improved outcomes of the high risk newborns worldwide. There are many challenges ahead that may positively or negatively impact continuing efforts to achieve the goal of improving the outcomes of pregnancy. The list below in by no means all inclusive but deserves consideration.

- Preterm birth – Over the past decades, there have been significant monetary investment and efforts by many scientists to uncover the cause of preterm birth with the goal of reducing its incidence. Unfortunately, to date, the etiology of preterm labor is still incompletely understood and during the past several years, the incidence of preterm birth has inched up, in part due to an increase in the birth of late preterm infants. This group of infants has higher neonatal morbidity rate than term infants and has required NICU admission. The reduction of late preterm birth from planned cesarean section by quality improvement approach would be an appropriate and likely an effective approach.
- Congenital anomalies, which occur in approximately 3% of live birth, represent an important risk factors for admission to the NICU. Both syndromic and nonsyndromic congenital anomalies account for a significant portion of admissions to the NICU, taxing medical and surgical resources in their care. To date, very little is known in regard to the causes of various significant anomalies. Research in this area should be of high priority.
- Treatment-related Injury – This is another area that deserves high priority in basic science and clinical investigation. Our attempts to increase survival involve therapies that often produce iatrogenic consequences. Prime examples are bronchopulmonary dysplasia from treatment of neonatal respiratory failure in very low birth weight infants, retinopathy of prematurity in extremely low birth weight infants due to oxygen toxicity, and short bowel syndrome in very low birth weight infants with surgical necrotizing enterocolitis. Strategies that will prevent the occurrence of these posttreatment complications are urgently needed, because these conditions produce long-lasting disability, often with poor neurodevelopmental outcomes. Adoption of lower oxygen saturation targets may be one effective intervention, because virtually all complications of prematurity are meditated to some degree by oxygen radical injury.
- Technology evaluation – Delivery of care to high risk infants often requires sophisticated technology. The intervention may produce harms if its safety is not fully evaluated. The use of the technology should be evidence based and fully evaluated for safety and potential adverse effects. Drugs used in newborns should undergo similar rigorous evaluation for safety and efficacy.
- The impact of noxious environmental stimuli on the neurodevelopmental outcome of critically ill newborns is being increasingly recognized. Attention to these environmental factors and on pain control along with developmentally supportive care hold promise for improving functional outcomes in extremely preterm survivors of neonatal intensive care.
- Behavioral research – As the survival of high risk infants (particularly the extremely low birth weight infants) increases there is a need to evaluate the neurodevelopmental and behavioral outcomes of the survivors. The goal is to identify potential deficits and formulate appropriate neuroprotective and other behavioral interventions to improve outcomes.
- Family Center Care – Involvement of families in the care of high risk infants has been shown to benefit both patients and their families. Future model of care in neonatal intensive care unit needs to incorporate the family center concept in its construction and design to allow for operational implementation of this important concept.

While the history of neonatology is a story of triumph over life-threatening conditions and enormous improvements in survival of extremely premature infants it has been punctuated by a multitude of serious missteps and errors that led to unnecessary morbidity and mortality in thousands of infants. Sadly, the well-publicized retrolental fibroplasia epidemic is but one example of the consequences of uncritical acceptance of new therapies. Other examples include such apparently benign interventions as routine use of Sulfa drug prophylaxis in all preterm infants, which led to a sixfold increase in kernicterus and a doubling of mortality affecting thousands of infants and empiric treatment with large doses of Chloramphenicol, which led to the Gray baby syndrome and numerous unnecessary deaths in the 1950s. Hexachlorophene baths for prevention of staphylococcal infection led to neurotoxicity and permanent brain damage in thousands of infants in the 1960s. More recent examples from the 1990s and beyond indicate that modern neonatology is not immune from serious errors in judgment. Hyperventilation/hyperoxia was widely used to treat persistent pulmonary hypertension without ever being subjected to prospective clinical trials and resulted in increased rates of chronic lung disease, periventricular leukomalacia, and sensorineural hearing loss in large number of term infants. Liberal use of dexamethasone for treatment/prevention of bronchopulmonary dysplasia was a universally accepted therapy for more than a decade before a significant increase in cerebral palsy was recognized.

The urgent nature of our work makes it tempting to embrace new promising therapies without waiting for adequate evidence of safety and efficacy. The examples cited above should serve as a cautionary note for neonatologists around the world to remember the first dictum of medicine: "Primum non nocere" (first, do no harm).

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8 Intrauterine Development/Pregnancy

Hector Mendez-Figueroa · Edward Chien

General Introduction

Knowledge of obstetrical complications and its impact on the condition of the newborn is of valuable interest to the Pediatrician. Complications can occur in normal pregnancies that can be associated with neonatal depression. High-risk pregnancies are associated with increased risk of preterm birth and intrauterine growth restriction. These complications are associated with both increased infant morbidity and mortality. The condition of the newborn maybe impacted by both antepartum and intrapartum events. Understanding terminology and common obstetrical complications will allow for more directed management and improved communication between Obstetricians and Pediatricians.

The complete assessment of the neonate should include knowledge of the antenatal course. Maternal-fetal interactions can impact overall fetal well-being. For example, maternal nutrition and exposure to tobacco affects fetal birth weight. Socioeconomic, education, and employment status affect pregnancy outcomes indirectly. Chronic medical conditions such as hypertension, diabetes, and autoimmune diseases are associated with adverse perinatal outcomes, including a direct impact on birth weight (*Table 8.1*). Even methods of conception can have implications for the newborn (e.g., assisted reproductive techniques and imprinting errors). All these factors highlight the importance and the need for Pediatricians to understand and appreciate maternal status and its implications. This chapter focuses on common obstetric conditions and practices that will assist a Pediatrician in evaluation of the newborn.

Antepartum Fetal Assessment

The health of the fetus is assessed multiple times throughout pregnancy using a variety of different tools. These assessments often begin prior to conception and continue through pregnancy up to delivery. A variety of tests are used to define risk or identify fetal anomalies. Tests performed in the third trimester are often used to assess fetal well-being. The overall basic principles, indications, and implications for each test will be reviewed.

Prenatal Diagnosis

One of the greatest advances in modern perinatal medicine is the evolution of prenatal diagnosis. The major factors contributing to these advances include the wide use and development of ultrasound technology and understanding of genetic basis of human diseases. These advances have allowed for earlier diagnosis and earlier intervention. Earlier diagnosis has allowed parents more time for preparation and adjustment to the special needs of their future children. Prenatal identification of congenital malformations allows the neonatal team to prepare for interventions immediately at delivery.

Noninvasive Prenatal Diagnosis

Ultrasound

In the past three decades, ultrasound has become the one of the most common obstetrical procedures performed prenatally. In developed countries, the use of ultrasound is almost universal. The increase in power outputs has provided better resolution and sensitivity, allowing identification of smaller lesions at earlier gestational ages. The introduction of three-dimensional (3-D) and four-dimensional (4-D) ultrasound in the past decade is likely to further advance prenatal diagnostic accuracy. Ultrasound has not been shown to produce any adverse outcomes to the fetus, although the increase in power output limits can have biological effects. Because of these potential effects, the American College of Obstetrics and Gynecology (ACOG) continues to recommend its use only for specific medical indications.

Gestational-age determination/confirmation is one of the most valuable pieces of information obtained as well as one of the most common indications for first trimester ultrasounds. This diagnostic tool provides the most accurate method for confirming or establishing

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Table 8.1
Chronic maternal medical conditions associated with low birth weight

Chronic maternal medical conditions associated with low birth weight	
Chronic hypertension	Pregestational diabetes mellitus
Systemic lupus erythematous	Antiphospholipid syndrome
Other collagen vascular disease	Hemoglobinopathies
Chronic pancreatitis	Inflammatory bowel disease
Malabsorption disorders	Cyanotic heart disease
Chronic respiratory disease	Chronic kidney disease

Various medical conditions can affect birth weight directly and should be taken into consideration when treating low birth weight neonates

gestational age. Studies have demonstrated that biologic variability from LMP varies from 4 to 7 days, depending on if the examination is performed early or late during the first trimester. Examinations performed during the second trimester vary from 10 to 14 days, while those during the third trimester can be as great as 21 days. The use of ultrasound to confirm or determine gestational age has narrowed the gestational length distribution so that only 3% of pregnancies progress past 42 weeks compared to 10% prior to the wide use of ultrasound. Ultrasound confirmation is widely used to assist in delivery timing.

Ultrasound is also widely used to detect fetal malformations (birth defects). First trimester ultrasound is becoming more widely used to assess risk for aneuploidy and identify congenital malformations. Ultrasound examinations performed during the second trimester are performed routinely to evaluate fetal anatomy. In the United States, these exams are performed by individuals with diverse training and background (radiologists, obstetricians, and maternal-fetal medicine subspecialists). Examinations are often categorized as screening or targeted examinations. The ACOG and the American Institute of Ultrasound in Medicine (AIUM) provide a standard list of items to be evaluated in each type of examination (*Table 8.2*). The screening exam (aka, fetal survey, level 1, anatomic survey) is the most widely ordered evaluation and is commonly performed by obstetricians and radiologists. Targeted exams (aka Level 2 and higher, detailed, genetic sonogram) are performed for an identified risk factor such as advanced maternal age,

Table 8.2
Standard list of items to be evaluated during obstetrical ultrasound after first trimester

Level I ultrasound Anatomic survey[a]	Level II ultrasound Detailed exam
Anatomy in addition to level I anatomy	
Maternal adnexa and cervix	
Fetal number	
Fetal presentation	
Amniotic fluid volume	
Placental location	Umbilical cord insertion into placenta
Cardiac activity	
Fetal biometry Biparietal diameter Head circumference Abdominal circumference Femur length	Long bone biometry if indicated
Head, face, and neck Cerebellum Choroid plexus Cisterna magna Lateral cerebral ventricles Midline falx Cavum septi pellucidi Upper lip	Measurements of Nuchal fold when appropriate Atrium of lateral ventricle Cerebellum Cisterna magna Hard palate Nasal bone
Chest 4-Chamber view of the fetal heart	Left outflow Right outflow Three vessel view
Abdomen Stomach (presence, size, and situs) Kidneys (presence) Bladder (presence) Umbilical cord insertion site Umbilical cord vessel number	Echogenicity of bowel Renal collecting system
Spine Cervical Spine Thoracic Spine Lumbar Spine Sacral Spine	
Extremities (presence or absence)	Identification of 12 long bones Hands Feet
Sex (when indicated)	

From AIUM practice guidelines for obstetrical ultrasound October 2007 and the ACOG practice bulletin on ultrasound in pregnancy February 2009

suspected congenital malformation, exposure to teratogens, or family history of a congenital malformation. These exams are commonly performed by individuals with advanced training in prenatal diagnosis (Maternal-Fetal Medicine or Radiologists with advanced training in ultrasound). Ultrasound is routinely used late in pregnancy to clarify a specific characteristic such as fetal presentation, placental location, and fetal size.

Another important aspect evaluated by ultrasound is fetal growth. Patterns of growth are impacted by various factors including race, age, fetal gender, maternal health status, cigarette smoking, and presence of congenital anomalies. The original nomograms for fetal size and weight were established in individuals residing around Denver, Colorado. It has been shown that altitude above sea level can impact fetal size. Various groups and investigators have developed nomograms from other populations that are specific for multiple gestations, fetal gender, maternal ethnicity, and geographical location. Definitions for growth abnormality are often regionally dependent. Two common terms that are often used interchangeably are small for gestational age (SGA) and intrauterine growth restriction (IUGR) but can imply different clinical meaning. SGA is most commonly used when referring to a fetus with an estimated fetal weight (EFW) less than the 10% but growing parallel to growth curve lines; this is often referred to as constitutionally small. IUGR, on the other hand, is a term used to infer a pathologic cause as the source for small size or decelerating growth.

Serum Screening

Much interest and resources have been invested in detecting abnormal fetuses by evaluating analytes of fetal and placental origin in maternal serum. Maternal serum alpha-fetoprotein (MSAFP), one of the original analytes found to have clinical utility, identified individuals at higher risk for neural tube defects. The association of low MSAFP values in women carrying a fetus with Down syndrome (trisomy 21) began the search to develop additional methods for screening low- and high-risk pregnancies. The majority of methodologies have been geared toward the identification of Down syndrome (*Table 8.3*), mainly focusing on combinations between first and/or second trimester analytes with and without ultrasound. These methods assess risk but are not diagnostic.

Screening has also expanded into single gene disorders by identifying carrier status for many conditions based on family history or other risk factors. These disorders include recessive metabolic disorders common to specific populations or disorders that have higher frequencies in the general population (i.e., cystic fibrosis, spinal muscular atrophy, etc.). The advances in human genetics has allowed for prenatal diagnosis in situations where single nucleotide abnormalities are known. ACOG and the American Society of Human Genetics (ASHG) continue to modify and expand recommendations for screening of inheritable disorders. These screening techniques identify a fetus at risk for specific disorders but are generally not diagnostic. Currently, positive screens will often require an invasive test for confirmation. Newer, less-invasive techniques are in development that will allow for both screening and diagnosis. These methods are based on detection of fetal DNA/RNA in maternal serum.

Table 8.3
Different strategies for detecting fetuses with chromosome abnormalities

Different strategies for detecting fetuses with chromosome abnormalities	
Measurement of nuchal translucency alone	Measurement occurs between 10 3/7 weeks and 13 6/7 weeks
First trimester serum screen	Measurement of serum PAPP-A and free βhCG
First trimester combined	Nuchal translucency measurement with first trimester serum screen
Triple screen	Measurement of second trimester alpha-fetoprotein, total hCG, and unconjugated estriol
Quad screen	Measurement of second trimester alpha-fetoprotein, total hCG, unconjugated estriol, and inhibin A
Full integrated screen	First trimester PAPP-A levels and nuchal translucency measured, as well as Quad screening during second trimester

Various strategies with different sensitivity and specificity have been developed over the years. *PAPP-A* pregnancy-associated plasma protein A, *fβhCG* free beta subunit human chorionic gonadotropin, *hCG* human chorionic gonadotropin

Cell-Free Fetal DNA

In 1997, the isolation of fetal DNA in maternal serum paved the way for new methods in prenatal diagnosis. Since this discovery, methods for isolating fetal DNA and RNA have improved. Disease processes that can be identified by DNA analysis have grown with sequencing of the human genome. Private corporations have now started to

offer diagnostic kits capable of diagnosing fetal sex and RhD genotype. As our knowledge increases and technology advances, these newer methods will expand and replace current procedures.

Invasive Prenatal Diagnosis

Screening techniques are widely used to identify subsets of the population at greater risk for specific conditions. Invasive diagnostic techniques are still required to identify affected individuals. This section describes the various techniques available to confirm a suspected diagnosis. Each of these techniques can be associated with increased pregnancy loss and, therefore, decisions to proceed must be weighed against the benefit from the information obtained.

Chorionic Villous Sampling

Chorionic villous sampling (CVS) entails obtaining a small amount of developing placental tissue during early gestation. First described in the early 1950s, it can be done at an earlier gestational age than other techniques. CVS is usually done between 10 and 12 weeks and can be done transcervically or transabdominally. The sample obtained contains both maternal and fetal cells that must be separated, making maternal contamination a concern. The risk of this procedure is pregnancy loss. A recent meta-analysis reported an average increase in pregnancy-loss rates of 0.7% within the first 14 days. CVS is not generally performed prior to 10 weeks gestation due to reports describing an increase in oromandibular-limb hypogenesis in procedures performed at earlier gestational ages. This procedure is referred to as a placental biopsy when performed in the second or third trimester and is associated with higher complication rates.

Amniocentesis

The removal of amniotic fluid through needle aspiration done under ultrasound guidance for years was considered the "gold standard" for prenatal diagnosis. This procedure is more commonly done in the second trimester after 15 weeks of gestation. There is a lower risk for maternal cell contamination. Cells recovered from the amniotic fluid are of fetal origin. Pregnancy-loss rates are generally lower than those reported for CVS. Recent studies have suggested loss rates as low as 0.2% within 14 days of the procedure. Amniotic fluid can be found to leak transiently in 1–2% of cases. Early amniocentesis is performed in some center prior to 15 weeks, but earlier procedures are associated with higher failure and loss rates. Amniocentesis can be used to assess fetal lung maturity during the third trimester in at risk pregnancies.

Percutaneous Umbilical Blood Sampling

Generally considered a more invasive procedure with increased morbidity, PUBS allows direct access to the fetal circulation. Under ultrasound guidance, a needle is introduced into the umbilical cord to obtain fetal blood. This allows for both diagnostic testing and therapeutic interventions. The main concern with PUBS is the higher risk of fetal loss when compared to other invasive procedures. The reported procedure related loss at institutions with expertise is approximately 2.3%. Indications and use of this procedure have decreased in recent years. The most common indication is hemolytic disease. In recent years, the incidence of this disease has dropped with the use of anti-D immunoglobulin. As techniques for isolating cell-free fetal DNA advance, the use of PUBS will become even more uncommon. PUBS has also been used as a method to administer medications directly to the fetus in a variety of disorders.

Prenatal Diagnosis of Congenital Malformations

The detection of congenital anomalies has increased in the past three decades. The development of microprocessors has revolutionized ultrasound technology and prenatal diagnosis. Preparation for the delivery of a newborn with a congenital abnormality is an obvious advantage provided by prenatal diagnosis. It is now possible to detect both lethal and nonlethal malformations during the prenatal period. The breadth of congenital malformations that can be detected prenatally has become too extensive to be covered in this format. More details can be obtained for specific disorders in other sources. ❯ *Table 8.4* provides a list of disorders that are commonly detected using antenatal ultrasound.

Central Nervous System

Central nervous system (CNS) malformations are one of the most common anomalies found antenatally with an incidence of approximately 1–2 cases per 1,000 births. The examination of the fetal brain and spine consists of identification of the falx cerebri, thalami, lateral cerebral ventricles, cistern magna, cerebellum, cavum septum pellucidum, and the bony structures enclosing the CNS. The structures evaluated during routine second trimester examination allow for detection of many major structural abnormalities. Neural tube defects such as anencephaly are routinely identified from visualization of the calvarium

Table 8.4
Commonly detected fetal disorders detected during antenatal ultrasound

Commonly detected fetal disorders
Multiple gestations
Monozygosity
Conjoined
Twin reverse arterial perfusion (TRAP) syndrome
Twin-to-twin transfusion syndrome
Monoamniotic multiple gestations
Central nervous system
Hydrocephalus
Dandy–Walker malformation
Anencephaly
Encephalocele
Microcephaly
Holoprosencephaly
Hydranencephaly
Porencephaly
Agenesis of corpus callosum
Arachnoid cyst
Choroid plexus cyst
Spina bifida
Face
Proboscis
Cleft lip
Cleft palate
Micrognathia
Macroglossia
Neck
Goiter
Cystic hygroma
Cardiovascular system
Tetrology of Fallot
Atrial septal defect primum
Ventricular septal defect
Endocardial cushion defect
Ebstein's anomaly
Transposition of the great vessels
Pulmonic stenosis
Aortic stenosis
Anomalous pulmonary venous return
Truncus arteriosus
Double outlet right ventricle
Arrythmias
Ectopia cordis
Rhabdomyomas
Pulmonary system
Congenital cystic adenomatous malformation (CCAM)
Broncho pulmonary sequestration (BPS)
Congenital diaphragmatic hernia
Chylothorax

Table 8.4 (Continued)

Commonly detected fetal disorders
Abdominal wall
Gastroschisis
Omphalocele
Bladder exstrophy
Gastrointestinal system
Esophageal atresia
Duodenal atresia
Intestinal atresia
Intestinal malrotation
Meconium peritonitis
Anal atresia
Splenomegaly
Hepatomegaly
Enteric duplication
Megacolon
Genitourinary anomalies
Renal agenesis
Hydronephrosis
Duplication of collecting system
Ureteropelvic junction obstruction
Infantile polycystic kidney disease
Renal dysplasia
Posterior urethral valves
Prune belly syndrome
Congenital mesoblastic nephroma
Neuroblastoma
Hydrocele
Ambiguous genitalia
Ovarian cysts
Musculoskeletal system
Arthrogryposis
Achondrogenesis
Thanatophoric dysplasia
Campomelic dysplasia
Osteogenesis imperfecta
Hypophosphatasia
Achondroplasia
Mesomelic dysplasia
Syndactaly
Polydactaly
Club feet
Rocker-bottom feet
Placenta
Previa
Abruption
Accreta
Vasa previa
Chorioangioma
Umbilical cord cysts
Amniotic band syndrome

Ultrasound evaluation of the fetus have allowed for more disorders to be diagnosed prenatally

above the level of the orbits typical of anencephaly as early as the latter half of the first trimester (Fig. 8.1). Spina bifida is commonly associated with an abnormally shaped cerebellum (banana sign), calvarium (lemon sign), and enlarged ventricles (hydrocephalus/ventriculomegaly) (Fig. 8.2). High-resolution ultrasound examinations have led to a decline in the use of amniocentesis for detection of open neural tube defects. Although ultrasound provides high specificity and sensitivity, the detection of amniotic fluid acetyl cholinesterase remains the gold standard. Evaluation of the falx and ventricular atrium allows for identification of hydrocephaly, porencephalic cysts, holoprosencephaly, and other cystic abnormalities of the brain. Other imaging modalities such as fetal MRI can often assist in diagnosis but require special expertise.

Our current understanding of structural abnormalities and their implications is far from complete. Part of the limitation is secondary to imaging limitations and in part from understanding the progressive development of the fetal brain. Our ability to differentiate outcomes based on ultrasound findings is still limited. The advance in three-dimensional imaging may improve our ability to diagnose abnormalities.

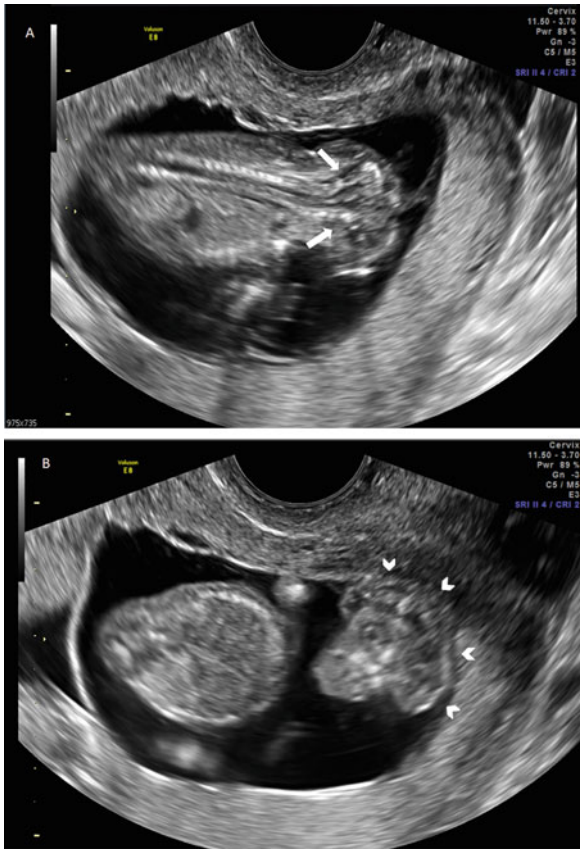

Figure 8.1
Transvaginal ultrasound done at 12 weeks gestation, revealing a fetus with anencephaly. (a) Coronal view of the fetal spine reveals an abrupt interruption in the caudal area (white *arrows*). (b) Coronal view of the fetal skull reveals exposed neuronal tissue with no calvarium (white *arrows*)

Cardiovascular System

Congenital heart disease is the most common group of severe congenital anomalies. The overall incidence is approximately 8–9 per 1,000 live births. Certain maternal conditions/exposures increase the incidence of these anomalies, e.g., poorly controlled pregestational diabetes, lithium therapy for bipolar disorder, and valproic acid for seizure disorders. More recently, commonly used medications have been associated with anomalies in the fetal heart; although, this relationship still needs to be confirmed. The standard examination of the fetal heart consists of evaluation of relative heart to thorax size, orientation of the heart, chamber size and number, and sometimes evaluation of outflow orientation. These views allow for detection of congenital heart defects such as hypoplastic left or right heart, significant stenotic valvular lesions, tetralogy of Fallot, and endocardial cushion defects that often distort the standard views. Conotruncal anomalies, septal defects, and lesions that are not associated with flow disturbance through the heart are less commonly detected because the standard views are often not distorted. The majority of septal defects are not associated with significant hemodynamic instability at birth and may not be appreciated during the fetal period (Fig. 8.3). Prenatal diagnosis provides the opportunity to deliver within a facility that is able to manage neonatal circulatory changes after birth.

Respiratory System

The normal fetal pulmonary system is characterized by homogeneous echogenicity. Abnormalities in development are identified based on relative proportion of thoracic and cardiac silhouettes, nonhomogeneous echo density, or the absence of amniotic fluid. Congenital thoracic lesions are being detected with increased frequency in recent years. Improvement in ultrasound technology

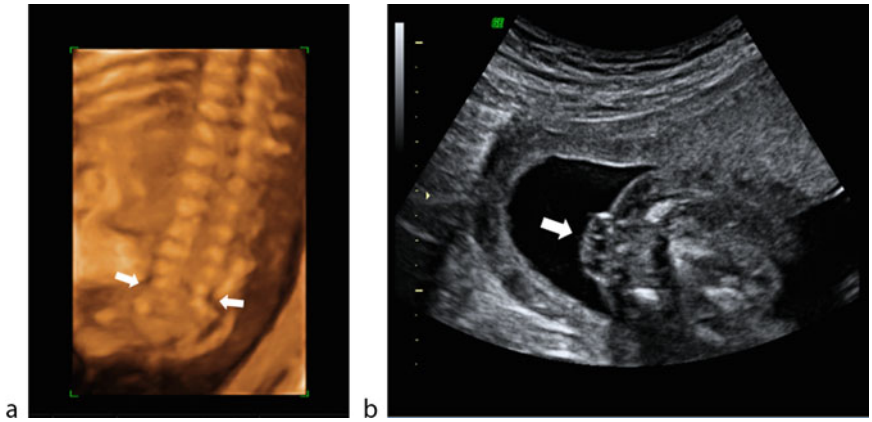

Figure 8.2
Ultrasound images of myelomeningocele diagnosed at 22 weeks. (a) 3-D skeletal reconstruction of fetal spine. Note the abnormal formation of the third sacral vertebra at the level of the defect (white *arrows*). (b) Transverse view of the fetal spine demonstrating the myelomeningocele sac (white *arrow*)

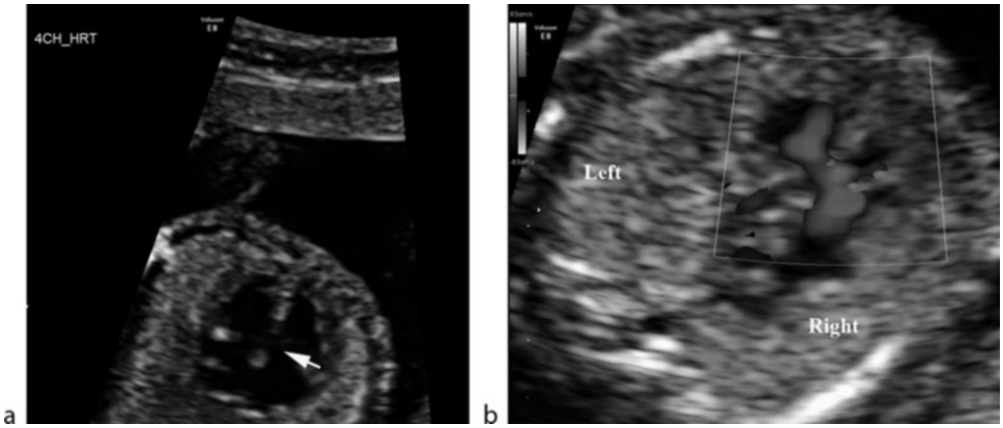

Figure 8.3
Ultrasound images of an atrioventricular canal defect. A ventricular septal defect detected at 21 weeks gestation. (a) Four-chamber cardiac view reveals the central defect and a single atrioventricular (AV) valve (white arrow). (b) Color Doppler confirming the presence of a defect in the interventricular septum. Right to left shunting is seen through the defect

and recognition are probably contributing factors. The two most common masses, bronchopulmonary sequestration (BPS) and congenital cystic adenomatoid malformation (CCAM), present as hyperechogenic lesions in or near the thoracic cavity (*Fig. 8.4*). They are often difficult to differentiate from each other. Both of these space occupying lesions can be associated with severe pulmonary hypoplasia by preventing normal growth and development of normal fetal pulmonary tissue.

Congenital diaphragmatic hernia (CDH) is another malformation that is frequently detected antenatally and can impact intrapartum management. It is defined as a defect in the embryologic development of the diaphragm, allowing herniation of abdominal organs into the thoracic cavity. Its overall incidence is approximately 1/2,500 to 1/5,000 live births. They are typically recognized due to a cystic chest lesion (stomach/intestine herniation) but can also present as a solid homogenous lesion (liver herniation). The compression effect of the abdominal organs in the thoracic cavity cause both pulmonary hypoplasia and pulmonary hypertension, leading to an overall mortality rate as high as 50%. Additional findings

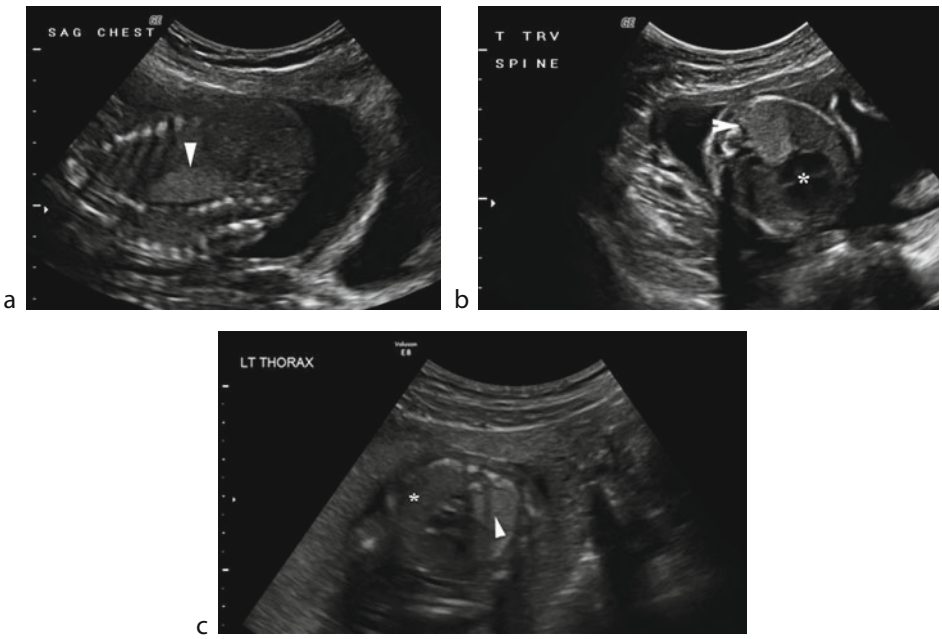

Figure 8.4
Congenital cystic adenomatous malformation (CCAM). (a) Parasagittal view through the fetal chest revealing the presence of hyperechogenic lung tissue suggestive of a CCAM (white *arrow*). (b) Transverse view of the chest at the level of the fetal heart (white asterisk). Note the presence of a hyperechoic tissue posterior to the heart (white *arrow*). (C). Another view of the CCAM revealing the difference in echogenicity characteristics between CCAM (white *arrow*) and normal lung tissue (white asterisk)

on ultrasound include deviation of the heart in the thoracic cavity. Prenatal detection may lead to improved outcomes by allowing for delivery in specialized neonatal centers.

Other structural abnormalities and complications can impact pulmonary development. Compression of the lungs by pleural effusions or absence of amniotic fluid during the midtrimester from renal anomalies can prevent normal lung development, leading to pulmonary hypoplasia. Skeletal dysplasias associated with restricted development of the thoracic cage can have similar effects. Unfortunately, current ultrasound technology prevents definitive determination of lung maturation or adequacy of pulmonary tissue.

Abdominal Malformations

The majority of antenatally detected abdominal lesions do not impact management in the delivery room but often require evaluation and/or intervention postnatally. Renal tract anomalies are detected in approximately 5/1,000 births. Obstructive renal lesions preventing normal egress of urine into the amniotic space, absence of kidneys or bilateral multicystic dysplastic kidneys can lead to pulmonary hypoplasia and impact delivery-room management. Intestinal atresias as a group are inconsistently identified antenatally. Proximal lesions can present with polyhydramnios or cystic abdominal lesions due to distention of the hollow viscous as in duodenal atresia (double bubble sign). Distal lesions are less frequently recognized. They more frequently present as echodense areas within the abdominal cavity rather than cystic lesions due to the lack of fluid from intestinal reabsorption.

Defects in the abdominal wall are the most common lesions of the abdominal cavity impacting delivery-room care. Gastroschisis is characterized by a right-sided periumbilical defect in the anterior abdominal wall (*Fig. 8.5*). Isolated gastroschisis is rarely associated with chromosomal abnormalities. Omphalocele, also a defect of the anterior abdominal wall, differs from gastroschisis in that the defect is covered by a peritoneal sac and is associated with abnormal development of anterior abdominal muscles, fascia, and skin. The incidence of

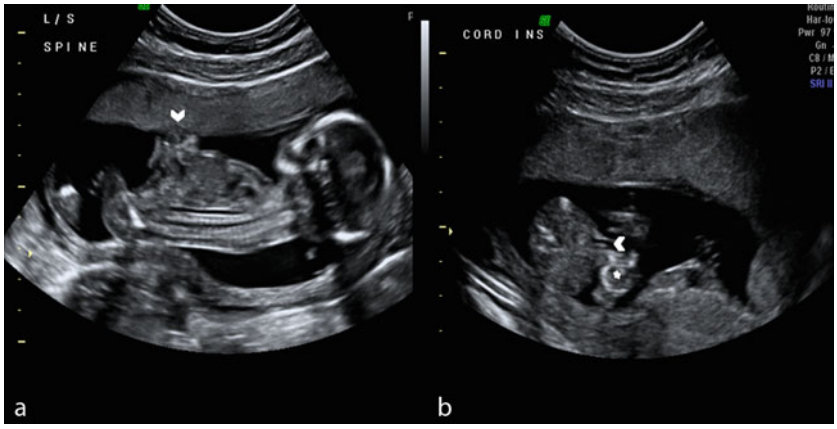

Figure 8.5
Fetal gastroschisis detected at 13 weeks gestations. (a) Sagittal view of fetal spine, note the interruption on the abdominal wall with protrusion of abdominal organs into amniotic sac (white *arrow*). (b) Cord insertion noted (white *arrow*) with intestines protruding from the right of cord insertion (white star)

this defect ranges between 1.5 and 3 per 10,000 births. Contrary to gastroschisis, omphaloceles are associated with a high rate of aneuploidy. Upon delivery of the affected neonate with an abdominal wall defect, the intestines and involved organs are draped in sterile wrapping to avoid loss of fluid and heat.

Tests of Fetal Well-being

A number of tests have been developed to assess the status of the fetus while in utero. These tests are based on recognition of normally developing fetal physiological processes or responses. The clinical context is important when interpreting these tests. *Table 8.5* shows the different antenatal fetal testing modalities available.

Fetal Movement Assessment

Maternal assessment of fetal movements has historically been used as a screening tool for detecting fetal compromise. Although it is widely used, the ideal protocol and interpretation remains controversial. Structured fetal movement monitoring is performed while the mother is sedentary so that she can focus on fetal movements. The goal is to perceive ten distinct movements in a 1–2 h period. Given the inexpensive nature of this method, most obstetricians recommend daily fetal movement assessment during the third trimester. The presence of fetal movement is considered a reassuring sign of fetal health.

Nonstress Testing

Nonstress testing (NST) is one of the most commonly used tests in obstetrics (*Fig. 8.6*). The basic principle governing this method of testing is the presence of fetal heart rate accelerations associated with fetal movement. The fetal baseline heart rate is assessed along with variability. Fetal heart rate variability indicates an intact autonomic regulatory system. Loss of this mechanism in the heart can result from depression of the central nervous system. Decreased variability is most commonly seen during normal fetal sleep cycles but can also result from pathological states that are associated with fetal acidosis occurring during anaerobic metabolism.

An NST is cataloged as reactive or nonreactive. The standard definition is an increase in fetal heart rate of 15 beats/min (bpm) from the baseline, lasting 15 s, occurring two or more times during a 20 or 30 min period in conjunction with fetal movement. The degree of heart rate acceleration is gestational age dependent with 15 bpm commonly seen at gestational ages of 32 weeks and above. At gestational ages less than 32 weeks, reactivity has been defined using an increase of only 10 bpm from baseline. The NST is considered reactive if there are two or more fetal heart rate accelerations within a 20–30 min period. An NST is considered nonreactive if it lacks a sufficient number of fetal heart rate accelerations. Testing is commonly extended for up to 40 min since fetal sleep cycles typically last less than 40 min. The NST is associated with a high false positive rate and is generally not recommended to be used in isolation for the assessment of fetal well-being when nonreactive.

Table 8.5

Tests used to assess fetal status

Name	Normal	Equivocal	Abnormal	Frequency
Fetal movement	>10 Movements in 1 h	1–9 Movements in 1 h	No movements	Daily
Nonstress test (NST)	Reactive	–	Nonreactive	2×/week
Contraction stress test (CST)	Negative	Equivocal	Positive	1–2×/week
Biophysical profile (BPP)	8–10/10	6/10	0–4/10	1–2×/week
Umbilical artery Doppler (systolic/diastolic ratio)	Gestational age dependent	–	Absent or reverse end-diastolic flow	1–2×/week
Middle cerebral artery peak velocity (MCA)	<1.5 MOM for gestational age	–	>1.5 MOM for gestational age	1×/week

Fetal status can be evaluated with multiple testing modalities

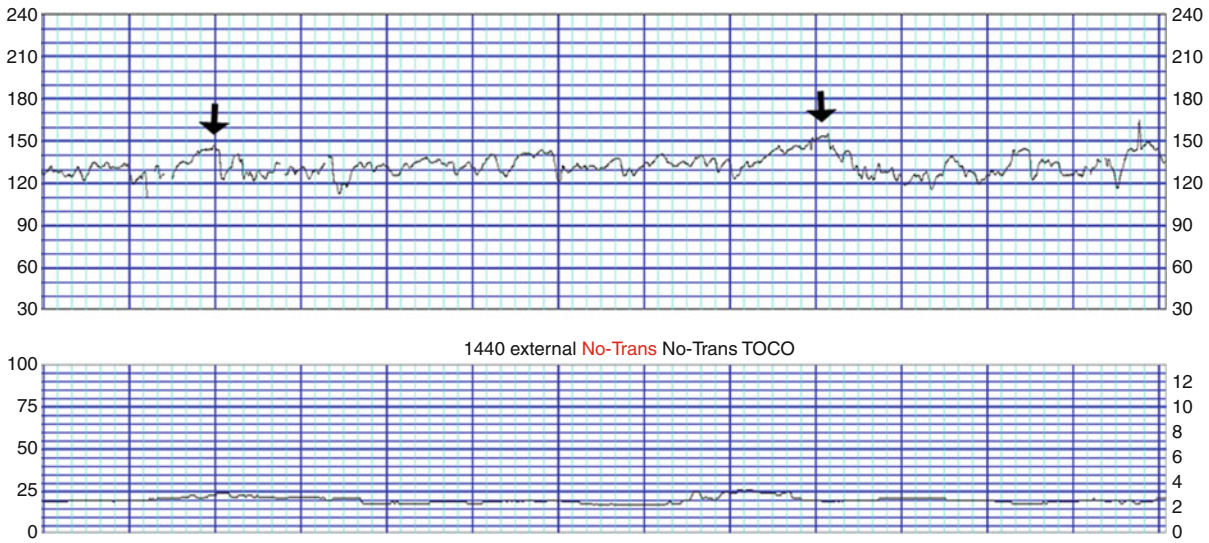

Figure 8.6

Nonstress fetal testing revealing two fetal heart rate accelerations in a 20-min period (Black *arrows*). Note the absence of contractions on the tocometer

Amniotic Fluid Index

In certain circumstances, ultrasound measurement of the amniotic fluid index (AFI) provides reliable information on fetal status. During the second half of the pregnancy, fetal urine is the major source of amniotic fluid. Similar to adults, the fetal circulatory system can redirect flow to maintain perfusion to vital organs. A decrease in placental perfusion can cause the fetus to redirect flow and decrease renal perfusion, leading to a decrease in urine/amniotic fluid production. The most widely used method of amniotic fluid assessment is the amniotic fluid index. This is performed by dividing the uterus into four quadrants and measuring the largest vertical amniotic fluid pocket in each quadrant. The sum of these four measurements is the AFI. During the third trimester, the AFI generally is between 8 and 25 cm. Oligohydramnios is generally defined as an AFI less than 5 cm and polyhydramnios

greater than 25 cm. Both abnormal measurements are associated with increased incidence of adverse perinatal outcomes. Oligohydramnios is associated with an increase in cesarean section rate for fetal distress and an increased risk of low Apgar score. Polyhydramnios has been associated with an increase in perinatal mortality rates, fetal anomalies, and an increased cesarean section rate. Oligohydramnios with intact membranes are often a reflection of a chronic condition impacting fetal well-being.

Biophysical Profile

Biophysical profile (BPP) is a more comprehensive test used to evaluate fetal status. The test is based on the principle that fetal well-being is associated with adequate oxygen delivery. With inadequate oxygen delivery, the fetus attempts to decrease oxygen consumption to preserve oxygen delivery to vital systems such as the CNS. These conservation efforts manifest itself in decreased fetal activity that can be evaluated by ultrasound.

The BPP consists of five components, an NST, and four parameters evaluated by ultrasound: fetal movement, fetal breathing, fetal tone, and amniotic fluid volume. The presence of each component is scored with a value of 2 if present or zero if not identified to be adequate. Scores range from 10 to 0. An inverse relationship has been observed between BPP scores and perinatal mortality. Scores have also been related to cord pH values obtained at cordocentesis, rates of admission to NICU, and low 5-min Apgar scores. Reassuring BPP scores are 8 and 10, while lower scores are followed by additional evaluation or delivery. The BPP is often used when a nonreactive NST is obtained.

Contraction Stress Test

The basis for this test is to assess placental functional reserve. The test is based on the principle that during contractions maternal blood flow to the placenta is interrupted, decreasing oxygen delivery to the fetus (*Fig. 8.7*). This transient reduction will be tolerated in a fetus with adequate reserves. In a fetus with inadequate placental reserve, the contractions will increase anaerobic metabolism producing fetal acidosis. The acidosis causes flattening of the fetal heart rate baseline. Hypoxia can also contribute to decreased myocardial function that is associated with late decelerations. A negative contraction stress test (CST) (normal/reassuring test) is defined as the absence of late decelerations; whereas a positive CST is one that has late decelerations in 50% or more of the contractions. Since its

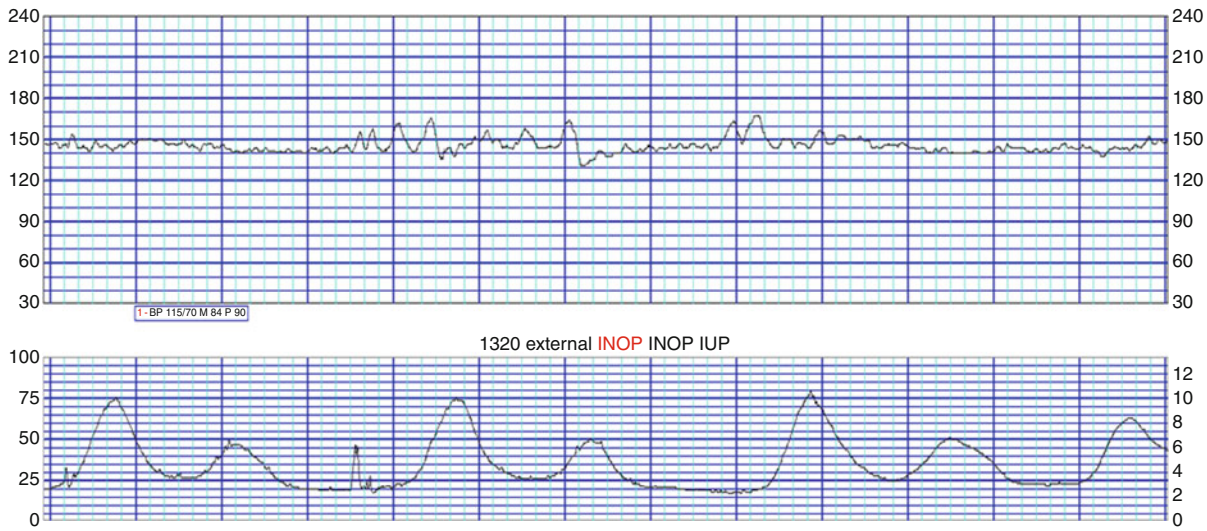

Figure 8.7

Contraction stress test done on a mother with pregestational diabetes at 34 weeks. Note the presence of more than three contractions (lower panel) in a 10-min period and the absence of late decelerations seen on the fetal heart rate (upper panel)

introduction into clinical practice, the use of CST in high-risk pregnancies has led to a reduction of stillbirth and unnecessary fetal interventions. It is most commonly used in pregnancies complicated by chronic maternal medical conditions.

Umbilical Artery Doppler Evaluation

During the past two decades, research assessing fetal status has focused on patterns of blood flow in the fetal circulation. The vessels with blood flow patterns having the greatest clinical utility are the middle cerebral artery and the umbilical artery. Peak velocities in the middle cerebral artery have been used to monitor for fetal anemia due to hemolytic disease but has found utility with other complications. The umbilical artery Doppler is most commonly used to evaluate pregnancies suspected of IUGR. The umbilical circulation is associated with declining resistance as pregnancy progresses. In pregnancies complicated by IUGR, the presence of increased vascular resistance suggests decreasing placental reserve (*Fig. 8.8*). This increase in resistance is reflected by an increase in the systolic to diastolic (S/D) ratio measured in the umbilical artery. The loss of continuous forward flow in the third trimester is associated with increased perinatal mortality in IUGR pregnancies and is often an indication for delivery to avoid stillbirth. Research into other arterial and venous fetal vessels have shown significant promise for assessing fetal status and may have additional clinical utility in the future.

Intrapartum Fetal Monitoring

Monitoring of the fetal heart rate by auscultation or with electronic monitors during labor has become universal in most developed countries. Although auscultation is still considered acceptable, most labor and delivery units have switched to electronic monitoring for a variety of reasons, including lower staffing requirements and improved documentation. Although the major goal of this obstetrical intervention is to detect fetal hypoxia and prevent subsequent injury, its implementation into clinical practice has not lead to a decrease in the rates of cerebral palsy. Other methods have been tested and have not been found to improve outcome (fetal pulse oximetry). New methods are undergoing clinical trials with initial studies suggesting some promise (STAN-ST-segment analysis).

Electronic Fetal Monitoring

Electronic fetal monitoring (EFM) is generally performed using an external Doppler device mounted on the anterior abdomen (*Fig. 8.9*). A Doppler signal is used to calculate the fetal heart rate. Internal fetal monitoring, using a fetal electrode attached to the fetal skin, is used in a similar fashion but measures the fetal heart rate by detecting fetal cardiac electrical activity. Technological advances have resulted in nearly identical patterns when comparing external and internal monitoring. Monitoring has been associated with high interobserver and intraobserver variability. In an effort to standardize interpretation, the National Institute of Child Health and Human Development in association with other medical professionals and experts developed a classification system aimed at standardizing fetal heart tracing analysis by all health care workers. Many of the obstetrical decisions, including route and timing of delivery, are based on individual interpretations of the fetal heart rate.

Fetal Pulse Oximeter

Fetal pulse oximeter (FOX) has been studied in an attempt to identify fetuses with diminished oxygen delivery to tissues. The technology consisted of a specialized sensor placed against the fetal face inserted through a dilated cervix after membrane rupture. The device measured fetal oxygen saturation through changes in light absorbance and emission of oxyhemoglobin. A large randomized controlled trial supported by the NICHD revealed fetal pulse oximetry monitoring did not lead to a reduction in the rate of cesarean sections nor did it result in improved newborn outcomes. A recent Cochrane review examining published trials of intrapartum pulse oximetry concluded that its use was not associated with a decrease in the overall cesarean section rate for non-reassuring fetal status.

ST-Segment Analysis

Recently, a new testing modality was introduced to evaluate fetal function and perfusion. ST-segment analysis is based on changes in repolarization of cardiac muscle associated with acid-base status and metabolism. The principle behind this technology was first observed in animal models; anaerobic myocardial metabolism was shown to be associated with changes in fetal ST waveforms. Small trials have reported mixed results with the introduction of this new device. Information from several large

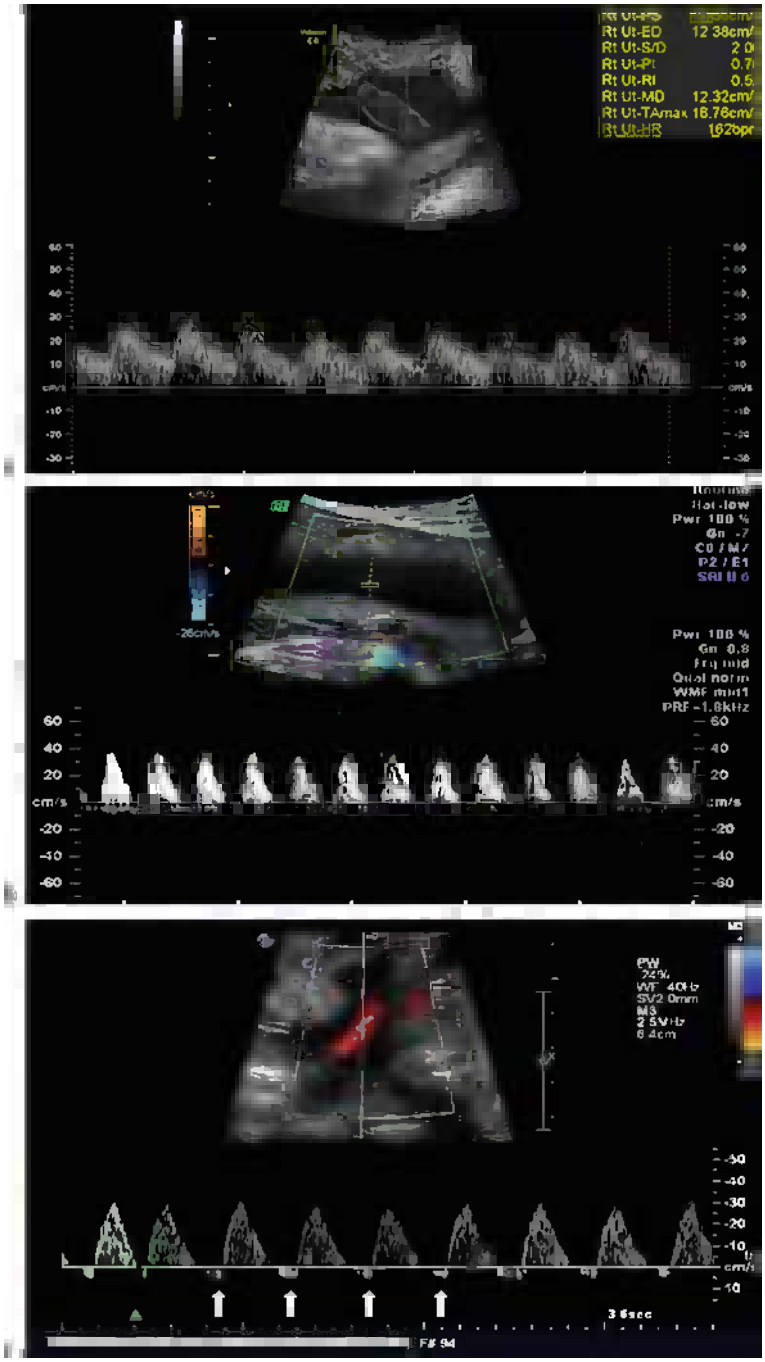

Figure 8.8

Umbilical Doppler velocimetry. Three different waveform patterns in umbilical artery Dopplers. (a) Normal umbilical artery blood flow as seen with a forward flow in diastole and a normal S/D ratio. (b) Absent end-diastolic flow. Note the forward flow during systole and the absence of flow during diastole. (c) Reverse end-diastolic flow. Flow is seen during systole, but there is retrograde flow during diastole (white *arrows*)

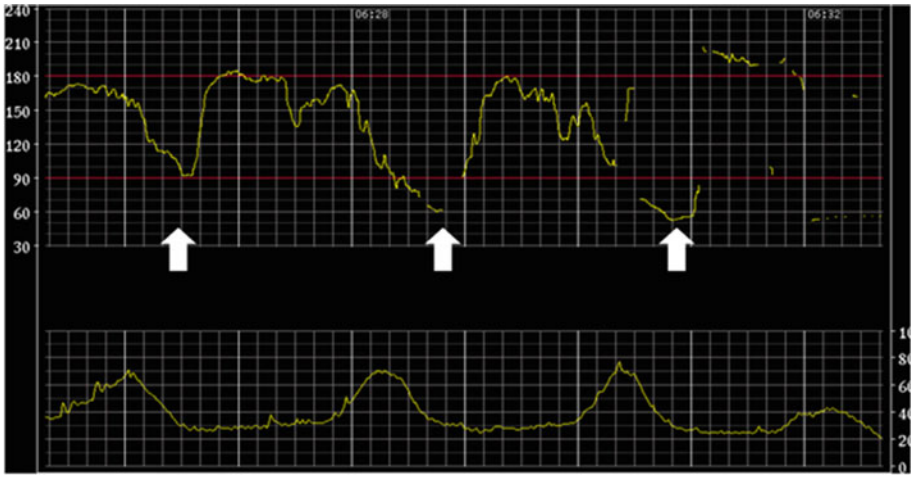

Figure 8.9
Illustration showing a case of late deceleration in the fetal heart rate. Notice the nadir of the heart rate occurs after resolution of the uterine contraction (white *arrows*). The fetal heart rate is also noted to have tachycardia after recovery suggestive of acidosis. The patient was taken to the operating room for an emergent cesarean section

randomized controlled trials currently underway will hopefully provide data that could allow its generalized clinical use.

Common Obstetrical Complications

Complications developing during or prior to pregnancy can have a negative impact on the fetus and neonate. The main factor outside of congenital malformations impacting neonatal outcome is prematurity. Preterm birth can result in chronic health problems and increased economic burden. Preterm birth is commonly divided into three major groups: spontaneous preterm birth, PPROM, and indicated preterm birth (*Fig. 8.10*). Conditions specific to pregnancy such as preeclampsia and gestational diabetes can impact neonatal condition. In addition, chronic health conditions such as essential hypertension and pregestational diabetes mellitus also can adversely impact neonatal health. Basic knowledge of these complications can allow for a more directed and tailored approach by the neonatal team.

Preterm Labor

No other subject in obstetrics has received more attention than preterm birth. The incidence of preterm birth has risen in the past two decades with current estimates of 12.7% in the United States, a 20% rise since 1990. Late preterm delivery, defined as the delivery between 34 and

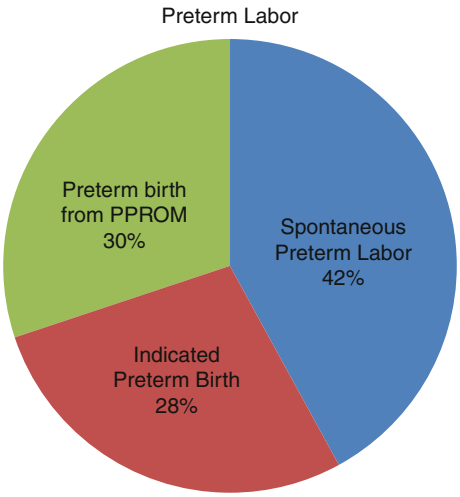

Figure 8.10
Pie chart distribution of preterm birth causes. Note that the most common cause of preterm birth is spontaneous

37 weeks, has seen the greatest increase. The rate of preterm birth is unequal across socioeconomic, ethnic, and racial groups. Non-Hispanic whites have seen the greatest increase in number of cases, although blacks still have the highest incidence overall.

Various factors have been linked to the increased rate of preterm birth. One factor believed to contribute significantly in the past decade is multiple gestations largely secondary to the increased use of assisted reproductive

Table 8.6
Risk factors for preterm delivery

Risk factors
Multiple gestation
Cervical instrumentation/surgery
Low socioeconomic status
Race
Smoking
Use of alcohol
Low maternal body mass index
Short interval between pregnancies
Advances maternal age
Previous preterm birth
Periodontal disease

Various risk factors have been associated with developing preterm labor

Table 8.7
Singleton preterm-birth risk factors

Risk factor	Relative risk SPB <37 weeks	95% CI
Short cervical length < 25 mm	3.5	(2.7–4.6)
Fetal fibronectin positive	3.3	(2.5–4.2)
Previous spontaneous preterm birth	2.7	(2.1–3.5)
Low body mass index	2.5	(1.8–3.5)
Uterine contractions	1.8	(1.4–2.3)
Vaginal bleeding	1.5	(1.1–2.1)
Black race	1.5	(1.2–1.9)
Pelvic infection	1.3	(1.0–1.6)
Bacterial vaginosis	1.3	(0.98–1.6)

A short cervix (<25 mm) and a positive FFN have shown to have the highest relative risk for preterm birth

technology. In singleton pregnancies, a variety of risk factors are associated with an increase rate of preterm birth (*Table 8.6*). Both cervical length and fetal fibronectin (FFN) have been used as screening tests. A short cervix less than 25 mm and a positive FFN have shown to have the highest relative risk for preterm birth (*Table 8.7*). Prematurity is a major cause for increased perinatal morbidity. The complications of prematurity can affect all organ systems; it is the primary contributor to three of the most significant neonatal complications: respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), and intraventricular hemorrhage (IVH). The frequency of these complications is directly related to gestational age (*Table 8.8*). The incidence of major neurological morbidity, such as cerebral palsy (CP), is also inversely proportional to gestational age.

Because of the detrimental effects on fetal health caused by prematurity, much interest has been placed on prevention and management strategies. Antenatal steroids have been one of the most successful therapies introduced into modern obstetrics to decrease both morbidity and mortality. The American Congress of Obstetrics and Gynecology (ACOG) has endorsed the use of corticosteroids between 24 and 34 weeks with impending preterm birth to improve fetal lung maturity. Antibiotic prophylaxis for group B streptococcus is also a common strategy implemented when the carrier status has not yet been assessed. Tocolytic agents are widely prescribed with limited evidence of long-term benefit. The current indications for tocolytic use rests on delaying delivery to allow for administration of antenatal steroids or to transfer to a tertiary care center. Recently, magnesium sulfate has shown promise as a neuroprotective agent to prevent cerebral palsy. These limited therapies have been shown to have the greatest effect on improving neonatal outcomes. To date, therapies designed to treat preterm labor have been disappointing.

Prevention trials have shown some promise in reducing preterm birth. The treatments found to have the greatest effect in the past decade has involved the use of progesterone or its analogs. Two large randomized placebo-controlled trials have shown a benefit from weekly administration of intramuscular 17 alpha-hydroxyprogesterone caproate or daily administration of intravaginal progesterone in women at high risk for preterm birth. Other therapies, including bed rest, antioxidant vitamins, and fish oil, have not been shown to reduce preterm birth. Interventions such as smoking cessation can reduce a woman's overall risk for preterm birth. Surgical techniques such as cerclage placement have also been explored in an attempt to reduce preterm birth. Historically, cervical cerclages have been employed to decrease fetal loss and preterm labor in women with cervical insufficiency. Studies suggest some limited benefit in specific situations. The rate of preterm birth has paradoxically increased despite the use of different approaches, indicating the need for more research.

Preterm Premature Rupture of Membranes

Fetal membranes are composed of two layers: chorion and amnion, which become fused by the 14th week of gestation. They serve as a physical barrier, preventing bacteria

Table 8.8
Frequency of complications by gestational age at birth

	Gestational Age				
Complication	<24 weeks	24–28 weeks	28–32 weeks	33–36 weeks	>37 weeks
RDS (%)	95–98	90–97	86	15–30	>5
IVH (%)	9–30	5–13	10	7–10	2–5
NEC (%)	5–15	9–13	8	8–10	1–4
PDA (%)	54–60	42–55	32	15–19	>1
ROP (%)	88–96	49–79	32	11–18	1–4
Abnormal neurological exam at age 2 (%)	75–85	43–60	21–35	5–9	–

Common medical complications found in preterm infants. The overall frequency is expressed in percentages

from entering the amniotic cavity at the same time serving as a "container" for amniotic fluid. *Preterm* premature rupture of membranes (PPROM) is a significant contributor to prematurity. A growing body of evidence has linked intraamniotic infections with local weakening and subsequent membrane rupture. Polyhydramnios, because of increased pressure on the membranes, can also lead to PPROM. Other risk factors have been identified that predispose women to PPROM (*Table 8.9*). They including: low socioeconomic status, multiple gestations, cigarette smoking, history of prior PROM and cervical conization. Labor is more likely to ensue after membrane rupture. Ninety-five percent of women that develop PROM will deliver within 22 h of rupture. If rupture of membranes occurs at less than 37 weeks, 75% of these cases will deliver within 1 week.

Table 8.9
Risk factors for premature rupture of membranes

Risk Factors
Intrauterine infection
Polyhydramnios
Low socioeconomic status
Multiple gestations
Cigarette smoking
h/o prior premature rupture of membranes
Cervical conization

Various risk factors have been associated with developing premature rupture of membranes

The diagnosis of fetal membrane rupture is based on history, examination, and confirmatory tests. Each of these tests has a high sensitivity and specificity but do not have 100% positive predictive value. To improve test performance, multiple tests are often combined to improve specificity and predictive value. Pooling, the visualization of fluid in the posterior vaginal fornix, can be amniotic fluid or urine. The nitrazine test is an assessment of pH. Amniotic fluid is neutral, typically above 6.0, and turns nitrazine to a deep blue color but can also turn blue from small amounts of blood. Ferning, allowing a sample of fluid to dry on a microscope slide, is the visualization of salt crystallization pattern that has similarity to the appearance of fern leaves. A variety of additional tests have also been introduced that detect specific proteins found at high levels in the amniotic fluid but absent or at low levels elsewhere (e.g., Amniosure).

Management of PPROM has focused on balancing the risk for infection and prematurity. The loss of the protective barrier function increases the risk for chorioamnionitis with reported incidence as high as 24%. The loss of amniotic fluid can also lead to pulmonary hypoplasia (when occurring in the second trimester), umbilical cord compression and contraction deformities secondary to prolonged compression. These risks are balanced against the known risks of prematurity.

Once rupture of membranes has been confirmed, the management often depends on gestational age. If PROM occurs at term or after 34 weeks, labor induction is generally recommended. For rupture of membranes occurring prior to 34 weeks, conservative management is considered. When rupture occurs between 32 and 34 weeks gestation, assessment of fetal lung maturity is advocated and delivery induced if mature; since prolonging latency would increase the potential risk of intrauterine infection with diminishing benefit to the fetus. For rupture less than 32 weeks, prolonging pregnancy with the administration of corticosteroids in the absence of intrauterine infection is recommended. Antibiotic prophylaxis in the setting of PPROM has been shown to improve outcome by

increasing the latency period from rupture to labor onset. A variety of antibiotic combinations have been evaluated that generally involve providing broad spectrum coverage of known perinatal pathogens. The most common combination involves ampicillin and erythromycin. Prophylaxis is commonly administered for a specified duration, typically 7 days. Patients are typically monitored as an inpatient with frequent assessments for infection. PPROM prior to 24 weeks is managed on a case by case basis due to the high morbidity and mortality.

Placental Complications

Abnormalities of placental location, function, and development are common contributing factors leading to a depressed neonate at birth. The two most common disorders associated with obstetric hemorrhage are discussed in this section.

Placental Abruption

Placental abruption is defined as the separation of a normally implanted placenta prior to birth. The overall incidence has been reported at 6.5 per 1,000 births. A variety of factors have been associated with higher rates (*Table 8.10*). Abruptions have been shown to present with varying severity from minor separation with limited symptoms (majority of cases) to complete separation associated with both maternal and neonatal morbidity/mortality. Abruption involving more than 50% of the placenta has been associated with fetal demise. The classical signs of abruption include third trimester vaginal bleeding with painful uterine contractions. Bleeding associated with placental abruption is typically maternal in origin, although fetomaternal hemorrhage can occur from disruption of the maternal-fetal interface. The separation can impact uteroplacental perfusion and fetal hypovolemia if fetomaternal hemorrhage occurs producing a depressed neonate. The majority of the observed infant morbidity is secondary to preterm delivery.

The diagnosis of abruption is clinical. A retroplacental collection of blood is seen in only 20% of cases. This high, false, negative rate for ultrasound has made this of limited value in diagnosis. Fetomaternal hemorrhage can be detected using the Kleihauer-Betke (KB) test. Fetal blood can be identified using the Apt test. Since the majority of bleeding is maternal in origin, this test is often negative. Vaginal bleeding is the presenting symptom in the majority of cases. Preterm contractions and uterine tenderness are also reported. Fetal compromise may be the only clinical finding in the absence of visible bleeding.

The management of abruption will depend on multiple factors, including gestational age, degree of bleeding, and overall fetal status. If abruption is suspected prior to 34 weeks but not severe enough to require immediate delivery, administration of corticosteroids is considered. The decision for delivery is individualized and dependent on the maternal and fetal status. Rapid progression of an abruption can lead to a precipitous delivery or an

Table 8.10
Risk factors for placental abruption

Risk factors
Chronic hypertension
Mild/severe preeclampsia
Cocaine use during pregnancy
Multiparity
Cigarette smoking
h/o prior premature rupture of membranes
Multiple gestations
Chorioamnionitis
Premature rupture of membranes

Various risk factors have been associated with developing placental abruption

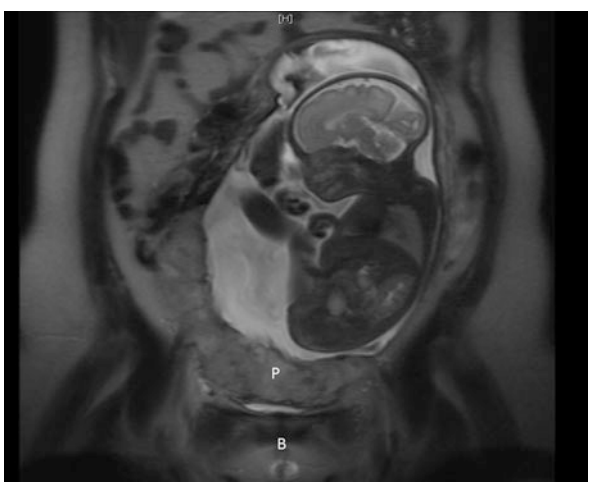

Figure 8.11
MRI image at 32 weeks in a pregnancy, complicated by placenta previa. Notice the location of the placenta over the bladder and cervical os. *P* placenta, *B* bladder

emergent cesarean section. Neonatal anemia is a consideration at delivery in a depressed newborn. Abruptions can present as a chronic disorder that may be associated with intrauterine growth restriction and oligohydramnios.

Placenta Previa

The implantation of the placenta over the cervix is referred to as placenta previa (*Fig. 8.11*). The placenta can cover the cervix either completely or partially, commonly classified descriptively (complete, marginal/partial, low lying). Studies suggest that implantation of the placental edge within 2 cm of the internal cervical os is associated with significant hemorrhage, frequently leading to operative delivery in labor. This has led to the use of 2 cm as defining normal versus a low-lying implantation. Hemorrhage is the principal complication of a previa. The bleeding is mainly of maternal origin similar to an abruption. The incidence of placenta previa has been reported to be approximately 0.55% of all deliveries and is associated with a variety of risk factors (*Table 8.11*).

The presenting symptom in most cases of placenta previa is painless vaginal bleeding. The diagnosis of placenta previa is based on a clinical suspicion that is confirmed by ultrasound examination. It is important to note that placentas are found close to or on the cervix commonly during ultrasound examinations performed during the second trimester. Reevaluation in the third trimester is generally recommended for confirmation. The management of placenta previa depends on both the maternal and fetal status similar to abruptions. The goal is to try to reach a gestational age close to term. Because labor can increase the risk of bleeding, conservative management past 38 weeks is not typically advocated. The decision to manage these patients in an outpatient setting versus in-house observation is individualized. If delivery is anticipated at less than 34 weeks, corticosteroids for fetal lung maturity are often administered. Cesarean section is the recommended mode of delivery. In the presence of acute hemorrhage, neonatal depression can occur due to diminished uteroplacental perfusion. Fetal hypovolemia or anemia secondary to hemorrhage can occur and can lead to a depressed neonate, but this is far less common.

Table 8.11
Risk factors for placenta previa

Risk factors
Prior cesarean deliveries
Prior suction curettage
Uterine surgery
Age
Multiparity
Cocaine use
h/o Prior placenta previa

Various risk factors have been associated with developing placenta previa

Placenta Accreta

Placenta accreta is the abnormal invasion of the placenta through the decidua into the myometrium. In recent years, an upward trend in overall incidence has been observed due to the increased rate of cesarean section. With each cesarean section, the risk of developing a placenta accreta and placenta previa increases. Studies have found that the risk of previa with an associated accreta can range from 11% to 24% in women with history of one prior cesarean delivery. Placenta accreta can be associated with abnormal fetal growth due to abnormal placentation but is more of a problem for the mother with a high risk of severe hemorrhage, more so the deeper the abnormal invasion of the placental tissue into the myometrium (increta) or even beyond the uterus (percreta).

Vasa Previa

The presence of fetal vessels traversing within the fetal membranes in the vicinity of the cervix is defined as a vasa previa. These vessels can occur from insertion of the umbilical cord away from the placenta (velamontous insertion) or from vessels traversing between accessory (succinturate) lobes of the placenta. The exposure and lack of protection of these vessels makes them vulnerable to injury with the associated risk of severe fetal hemorrhage. Disruption of the vessels can lead to fetal exsanguination in a few minutes. The associated mortality with a ruptured vasa previa is close to 60%. The incidence is approximately 1 in 2,500 deliveries. The use of high-resolution and color Doppler ultrasound has increased the antenatal detection rate allowing for planned delivery. The timing of delivery is an area of much controversy, with some authors suggesting delivery at 35–36 weeks without assessment of fetal lung maturity.

Intrauterine Growth Restriction

One of the main methods of assessing fetal health is by the evaluation of fetal growth. Prior to the development of fetal ultrasound, growth was assessed by measurement of uterine size/fundal height. Since the development of ultrasound in the early 1980s, a combination of fetal measurements have served as the basis for determining fetal weight and growth. Today a variety of terms are used interchangeably to describe a fetus that is at risk for adverse outcome due to size or growth rate, including SGA (small for gestational age), FGR (fetal growth restriction), and IUGR (intrauterine growth restriction). Fetal growth is known to be influenced by gender, race, nutrition, and geographic location. It is recognized that fetal size at less than the 10% is associated with increased adverse outcome, but the majority of fetuses are normal. Differentiating a constitutional small fetus (SGA) from a pathologically small fetus (IUGR) is difficult by size alone. In addition, IUGR can be defined as a fetus that has not reached its growth potential, given that some pathological conditions in the mother will affect fetal growth without causing the weight to be below the 10% percentile. Differentiation is important because it can impact management decisions. A variety of different fetal growth curves have been developed that can be specific for a given population. Determining the cause of IUGR can be a daunting task. IUGR is often divided into fetal causes, maternal causes, and placental factors. IUGR occurs more commonly in the presence of fetal anomalies, aneuploidy, and congenital infections (*Table 8.12*).

Antenatal testing is generally prescribed after the diagnosis of IUGR has been made. Protocols for monitoring vary between institutions but generally involve a combination of monitoring of fetal movement, NST, amniotic fluid volume, ultrasound biometry, and vascular Doppler measurements. Doppler interrogation of the umbilical artery has been shown to aid in the evaluation of IUGR fetuses. Doppler studies that fail to show forward flow (absent or reverse flow) during diastole in the umbilical artery are at significant risk for stillbirth and is also associated with increased morbidity and mortality in the newborn period. Decision for delivery is dependent on antenatal testing results, progressive fetal growth, and gestational age.

Table 8.12
Common causes of intrauterine growth restriction

Common causes of IUGR		
Maternal	**Fetal**	**Placental**
Maternal hypertension (chronic hypertension, preeclampsia)	Chromosome abnormalities	Confined placental mosaic
Renal disease	Anomalies (congenital diaphragmatic hernia, congenital heart disease)	Placenta previa/accreta
Autoimmune disorders	Multiple gestation	Placental abruption
Cyanotic heart diseases	Fetal infection (cytomegalovirus, toxoplasmosis, malaria, rubella)	Placental infarction
Hemoglobinopathies		Circumvallate placenta
Severe lung disease		Large hemangiomas
Malnutrition		Velamentous cord insertion
Drugs (alcohol, cocaine, medications)		

Intrauterine growth restriction can have a maternal, placental, or fetal cause

Multiple Gestations

The incidence of multiple gestations has been on the rise in the past decade mainly due to assisted reproductive technology. Although multiple gestations account for less than 3% of all live births, they disproportionately contribute to perinatal morbidity and mortality. When compared to singletons, multiple gestations have an increased risk of low birth weight (relative risk [RR] of 8.6) and neonatal death (RR of 7.06). Preterm birth occurs in over 50% of twin gestations and even greater with higher-order multiples. The incidence of congenital abnormalities is also increased in multiples, occurring more than twice as often than singleton gestations.

Zygosity and placentation are important factors that can be used to assess risk. In twin gestations, birth outcomes and complications are related to type of placentation. Monozygotic twins have significantly greater morbidity and mortality than dizygotic twins. In monozygotic twinning, the timing of division determines the type of placentation (*Fig. 8.12*). Other pregnancy complications are also increased in individuals having multiple gestations, including a 2.62 RR for preeclampsia

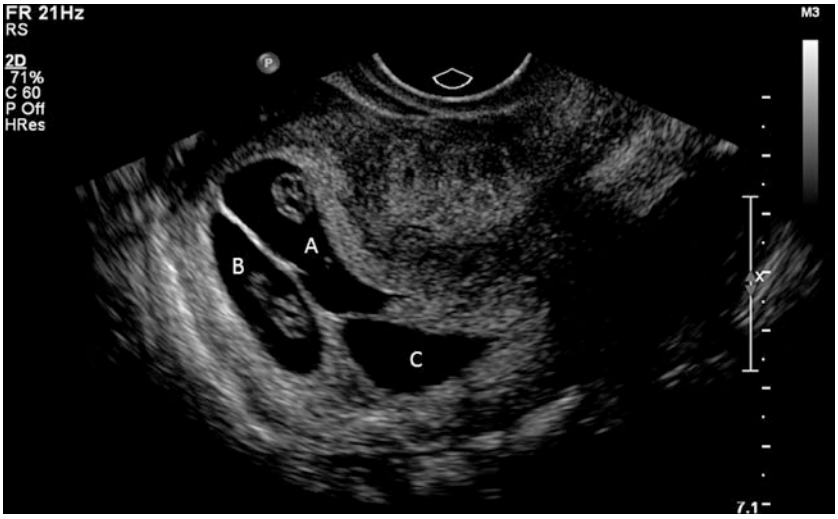

Figure 8.12
Triplet gestation. Intrauterine pregnancies seen at 9 weeks. Note the presence of three separate gestational sacs. The membranes separating each sac appears thick, consistent with a triamniotic-trichorionic placentation

and a 1.8 RR for gestational diabetes that can impact newborn health. IUGR is also more common with multiple gestations.

Management of multiple gestations involves monitoring for these complications often with more frequent antepartum visits, testing, and ultrasounds. Twin-to-twin transfusion syndrome (TTTS) is a complication unique to monozygotic twins. This syndrome is characterized by unequal shunting of blood amongst twins through placental vascular communications. Interventions such as laser ablation of communicating vessels and reduction of amniotic fluid have been shown to improve outcomes. Monochorionic monoamniotic (mono-mono) pregnancies are at greater risk of morbidity and mortality than monochorionic diamniotic twins. Mono-mono twins are at high risk of cord entanglement in up to 71% of cases with a reported mortality rates of 50%. The timing of delivery in these cases should balance the risk of prematurity versus the risk of fetal death.

Maternal Medical Complications

Maternal medical complications frequently impact newborn outcomes. Some of these complications are specific to pregnancy such as gestational diabetes and preeclampsia, while other disorders are unrelated. As technology improves, individuals with chronic diseases often choose to bear children. It has become more important for physicians to understand potential implications of chronic diseases on pregnancy. Medical therapies can increase the risk for malformations and impact fetal development. Maternal medical diseases such as autoimmune diseases can cause neonatal effects such as neonatal lupus or neonatal Graves disease which are generally self-limited until clearance of the offending antibody. Optimal treatment of maternal medical diseases such as Type 1 diabetes mellitus or phenylketonuria (PKU) can decrease the risk of malformations. In this section, we will discuss two of the more common medical complications impacting newborn health.

Diabetes in Pregnancy

Diabetes mellitus is a common maternal condition, complicating 1–14% of all pregnancies. It is often classified based on time of diagnosis: during pregnancy (Gestational Diabetes) and prior to pregnancy (Type 1 and 2). Gestational diabetes and pregestational diabetes are generally associated with different risks to mother and fetus. Diabetes mellitus diagnosed during pregnancy may be preexisting but not diagnosed prior to pregnancy, which can occur in individuals for a variety of reasons. Management is based on the implicit risk in pregnancy.

Gestational Diabetes

Gestational diabetes (GDM) is the most common form of diabetes occurring during pregnancy. This disorder is

typically characterized by insulin resistance similar to type-2 diabetes mellitus. The main risks to gestational diabetes on pregnancy outcome are related to fetal and neonatal complications, although it is associated with higher incidence of cesarean section. A number of large multicentered studies evaluating the implications of mild gestational diabetes support routine screening in order to initiate therapy. These studies demonstrated that pregnancies complicated by mild gestational diabetes were at increased risk for fetal macrosomia and cesarean section. Pregnancy outcomes were associated with degree of hyperglycemia. In addition to increased birth weight, poorly controlled GDM has been associated with increased rates of respiratory insufficiency, neonatal hypoglycemia, polycythemia, hyperbilirubinemia, myocardial hypertrophy, and electrolyte abnormalities.

The associated neonatal morbidities can be directly associated with degree of maternal hyperglycemia, resulting in fetal hyperglycemia. Fetal hyperglycemia is associated with increased fetal pancreatic production of insulin that is believed to contribute to excessive fetal growth and neonatal hypoglycemia. In addition, the increased circulating glucose requires an increase in metabolic demand, resulting in increased oxygen consumption. This increased metabolic demand can lead to fetal acidosis and even fetal demise. Fetal acidosis can inhibit surfactant production that increases the need for respiratory support after birth. Increased oxygen consumption is likely to be the cause of increased red cell production, resulting in polycythemia and hyperbilirubinemia. In well-controlled GDM, the incidence of neonatal complications approaches that of the general population supporting the benefit of monitoring and medical interventions.

Pregestational Diabetes

In addition to the complications of GDM, pregnancies complicated by either Type-1 or -2 diabetes mellitus are at increased risk for additional complications. These complications are also related to the degree of hyperglycemia occurring during the first trimester. The main fetal risk is due to the increased risk of congenital malformations. Although malformations can occur in any organ system, the two most frequently affected by hyperglycemia in the first trimester are the cardiovascular system and the central nervous system. Congenital heart defects and neural tube defects are more frequently seen in fetuses of mothers with hyperglycemia during the first trimester. Glycosylated hemoglobin level obtained during the first trimester is used commonly to assess the degree of hyperglycemia affecting the fetus during the period of organogenesis. Patients identified at increased risk are often screened with targeted ultrasound examinations to evaluate for these complications as well as serum analytes like alpha-fetoprotein.

Fetal malformations are not the only factors contributing to the increased morbidity and mortality in pregnancies of women with pregestational diabetes. These pregnancies are at increased risk for indicated preterm birth from a variety of causes. Preeclampsia (PE) occurs more frequently and more often at earlier gestational ages. The duration of preexisting diabetes mellitus and the degree of end-organ disease can be associated with the risk for poor pregnancy outcome and frequency of early delivery. This is reflected in the commonly used White's Classification for diabetes in pregnancy (*Table 8.13*). Although large for gestational age, infants are commonly associated with diabetes in pregnancy, growth-restricted fetuses occur more commonly with White's class D and higher.

Preeclampsia

Hypertension frequently complicates pregnancy leading to premature birth. Preeclampsia similar to GDM is a pregnancy specific disorder that resolves after delivery

Table 8.13
White's classification for diabetes during pregnancy

Class	Definition
A	Diagnosed during pregnancy
A1	Diet-controlled
A2	Diabetes controlled with medication
B	Duration of disease <10 years or age of onset ≥20 years
C	Duration of disease between 10 and 19 years or age of onset between age 10 and 19
D	Duration of disease ≥20 years or age of onset prior to 10 years age
F	Nephropathy (>500 mg/day proteinuria)
H	Atherosclerotic heart disease
R	Proliferative retinopathy or vitreous hemorrhage
T	After renal transplant

Classification used to stratify diabetes during pregnancy

of the fetus. In contrast to GDM, therapeutic interventions to control blood pressure have shown limited benefit on neonatal outcomes. Women with preexisting hypertension are also choosing to become pregnant more frequently. The increase can be attributed to the delay in reproduction in many developed countries. Although most hypertensive women have successful pregnancy outcomes, these pregnancies are associated with increased maternal and neonatal morbidity and mortality. Preeclampsia superimposed onto chronic hypertension can occur at higher rates as well as higher incidence of growth restriction and stillbirth. Antihypertensive therapy can also affect pregnancy outcome. Angiotensin converting enzyme inhibitors, a commonly used class of antihypertensive therapy, are associated with significant adverse pregnancy outcomes and are proscribed during pregnancy.

Preeclampsia is a disease occurring during the second half of pregnancy. Although the cause for this disorder remains unknown, research over the past two decades has demonstrated that factors associated with angiogenesis and placental growth are involved. Similar to preterm birth, a variety of conditions can predispose to this complication including preexisting hypertension, nulliparity, renal disease, diabetes mellitus, and autoimmune diseases. The characteristic maternal findings associated with PE include hypertension and proteinuria but is not limited to the cardiovascular and renal systems. Although edema is no longer used as one of the defining characteristics, third spacing of fluid also contributes to significant morbidities. PE can affect any organ system in the body. Central nervous system vasoconstriction can lead to cerebral edema that may manifest as seizure activity (eclampsia) or in cortical blindness (amaurosis fugax). Hepatic vasoconstriction can lead to subcapsular bleeding and elevated transaminases. Microvascular angiopathy is a finding associated with PE that can be associated with increased platelet consumption and red blood cell fragility. PE manifesting as a combination of hemolysis, thrombocytopenia, and elevated hepatic transaminases is referred to as HELLP syndrome. Increased capillary leak can lead to pulmonary edema. Third spacing of fluid can lead to decreased intravascular volume that affects both renal and uterine perfusion. These serious complications often necessitate preterm delivery in order to prevent further deterioration of the maternal condition.

The neonate can also be affected directly by PE. Because PE is associated with abnormal placentation and increased vascular resistance, fetal growth restriction may be discovered at the onset of clinical symptoms. Decreased perfusion can result in fetal acidosis and a depressed neonate. Thrombocytopenia is commonly observed in the neonate born to mothers with severe forms of preeclampsia, probably due to increased platelet activation and consumption in the neonate similar to the mother. Neutropenia is also commonly seen in the infant. Delivery is generally prescribed when PE develops at term. Delivery is generally delayed when mild forms of PE develop prior to term. Delivery is expedited when individuals develop severe forms of PE, although in some cases delivery is delayed to allow for the administration of corticosteroids.

Summary

Effective communication between the obstetrician and pediatrician can positively affect the transition of the neonate after birth. Prenatal care has evolved over the past five decades from mainly monitoring maternal health to include assessing fetal health. The field of prenatal diagnosis has grown exponentially, allowing for the health care team to anticipate neonatal needs at birth and during the neonatal period. Obstetric care has also evolved with greater understanding of the effects of various therapeutic interventions on fetal health. Selection of medical therapy is often based on balancing the potential adverse effects on the fetus with the therapeutic benefit on the mother. This chapter summarizes the many different assessments and interventions used during pregnancy to monitor and improve pregnancy outcome. Although the timing of delivery may not always be to the benefit of the neonate, the obstetrician's decisions are an attempt to balance the needs of the mother and the fetus.

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9 Transition to Extrauterine Life

Anton H. van Kaam

Introduction

The transition from intrauterine to extrauterine life is a complex process involving virtually every organ system in the body. The most dramatic changes are seen in the lung and the cardiovascular system, resulting in the transition from placental to pulmonary gas exchange. Failure to adequately make this transition can be life-threatening and these infants often require supportive care. In order to select the optimal intervention, it is essential to understand the normal physiology of respiratory and cardiovascular transition. It is important to realize that most data on neonatal transition are obtained from animal studies, because of the limitations in studying human fetuses and newborn infants at this critical time.

Respiratory Transition

The Fetal Lung

During intrauterine development the fetal lungs are filled with fluid, receive little blood flow, and take no part in gas exchange. Experimental studies in fetal sheep have shown that lung fluid is produced by the pulmonary epithelium as the net result of active chloride secretion via Cl^- channels and relatively low reabsorption activity of Na^+ channels. There is some efflux of liquid from the lung via the trachea, but this process is restricted by the fetal upper airway (mainly the glottis), thereby promoting the retention of fluid and causing a continuous distending pressure within the fetal lungs, which is critical to normal lung growth and development. Besides lung fluid, fetal breathing movements, which start as early as 10 weeks' gestation, also play an important role in maintaining fetal lung distension. During fetal breathing movements rhythmic contractions of the diaphragm seem to oppose the pulmonary recoil pressure, thereby preventing lung deflation. Although never directly measured in humans, animal studies indicate that the fetal lung volume is probably at or above functional residual capacity (FRC), i.e., the volume that remains inside the lung after a normal expiration. Fetal lung distension and the associated lung tissue stretch is an essential stimulus for normal lung growth and structural development. Studies in fetal lambs have shown that a reduction (lung liquid drainage, absent fetal breathing) or an increase (tracheal occlusion) in lung expansion causes, respectively, a decrease or an increase in lung growth.

As the fetal lung slowly matures to an organ capable of extrauterine gas exchange, it undergoes enormous structural and biochemical changes. Structurally, the lung passes through four developmental stages: the pseudoglandular (5–17 weeks), the canalicular (16–26 weeks), the saccular (24–38 weeks), and finally the alveolar stage (36 weeks 2 years). The most important hallmark of the biochemical maturation is the formation of pulmonary surfactant. Lamellar bodies – containing pulmonary surfactant – in the type II pneumocytes appear between 20 and 24 weeks' gestation, but actual secretion is delayed until 30 weeks' gestation. Besides playing a role in host defense, the most important function of pulmonary surfactant is stabilization of the alveoli after birth when air has entered the lung and the alveolar surface tension has greatly increased by the creation of an air–liquid interface.

As the fetal lung grows and matures, intrauterine gas exchange is governed by the placenta. It is important to realize that, compared to extrauterine life, the fetus lives in a relatively hypoxemic environment with arterial oxygen saturation of approximately 60%.

Clearance of Lung Fluid at Birth

In order to make the transition from placental to pulmonary gas exchange successful, fluid need to be cleared rapidly from the newborn lung. Although the precise mechanisms are still unclear, animal and a few human studies have provided some of the answers.

With the onset of labor, there is a dramatic change in the transepithelial ion and fluid movement in the fetal lung. The pulmonary epithelial cells stop secreting and start reabsorbing lung liquid by activating the so far dormant epithelial sodium channels. This shift from fluid

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excretion to absorption seems to be mediated by epinephrine, which is secreted in large amounts by the fetus at the onset of labor. Maternal thyroid hormone and glucocorticoids also play an important role by augmenting the absorptive response to epinephrine.

During labor, intrauterine pressures can increase up to 75 cmH_2O and these pressures are transmitted to the fetus causing changes in fetal posture and chest wall configuration. As a result, the intra-abdominal and intrathoracic pressures increase leading to an efflux of lung fluid. As the infant passes through the distal part of the birth channel, the pressure on the thorax may increase to as much as 200 cmH_2O, causing further egress of lung fluid (vaginal squeeze).

Despite these prenatal mechanisms promoting lung liquid clearance, the lungs and airways are still filled with fluid prior to the first breath after birth. Studies in rabbit pups using phase contrast imaging have shown that the entry of air into the airways is an essential part for completing the process of liquid clearance. As air enters the airways, fluid is pushed distally and moves into the interstitial compartment where it is gradually cleared via the pulmonary circulation and lymphatics.

Aeration of the Lungs After Birth

The basic goal of lung aeration after birth is to replace lung liquid by air and to build up a normal FRC of about 30 ml/kg of body weight. Although many theories such as thoracic recoil, frog breathing, and pulmonary capillary erection have been postulated to explain the start of lung aeration in spontaneously breathing newborn infants, it is now believed that the most important mechanism for air entry is the generation of a negative transpulmonary pressure via an inspiratory effort of the infant. Studies in newborn infants have shown that this inspiratory effort during the first breath consists of a diaphragmatic contraction and results in mean subatmospheric intrathoracic pressure of 52 cmH_2O (range 28–105 cmH_2O) producing a mean tidal volume of 38 ml (range 6–69 ml). Immediately after the first inspiration, expiration is postponed by closure of the upper airways (glottis), which prevents the inspired air to escape. This process, also called expiratory breaking, generates a high positive intrathoracic pressure (mean 71 cmH_2O, range 18–115 cmH_2O) during expiration, which facilitates the distribution of air within the lung and promotes lung liquid clearance. Following this first breath, almost half of the inspired tidal volume is maintained in the lung. It usually takes several hours to achieve a normal FRC.

The moment air enters the lung, it creates an air–liquid interface at the alveolar level, which greatly increases the surface tension and thereby the elastic recoil force of the lung. This increased recoil force tends to collapse the lungs as it encounters little resistance from the relatively compliant newborn chest wall. Pulmonary surfactant which lines the alveolar surface helps to counteract this tendency by reducing the surface tension. Normally surfactant is already present in the lung during the transition at birth, as it is secreted in the lung liquid from 30 weeks' gestation. Alveolar stretch during tidal breathing after birth results in the secretion of large quantities of surfactant from the type II pneumoctyes in the alveolar space. The newborn infant also maintains end-expiratory lung volume by extending the process of expiratory breaking beyond the first breath after birth. Studies in term newborn infants have shown that 90% of the breaths in the first minutes after birth contain some form of expiratory breaking, such as crying and grunting.

As mentioned previously, the placental gas exchange provides a hypoxemic fetal environment compared to the postnatal conditions. Studies in healthy vigorous term newborn infants have shown that oxygen saturation measured by pulse oximetry gradually increases from a median saturation of 65–70% at 1 min to 85–92% at 5 min and do not reach 95% until 7–10 min of life. However, many normal healthy term newborns do not reach saturation of 90% until after 10 min of life. Data on carbon dioxide (PCO_2) changes after birth in term newborn infants are limited, but seem to indicate that PCO_2 remains stable at approximately 50 mmHg during the first 5 min of life, after which there is a steady decline toward 40 mmHg at 30 min after birth.

Respiratory Transition in Preterm Infants

There are several reasons why preterm infants have an increased risk for failing to achieve normal respiratory transition at birth. First, studies in fetal sheep have indicated that the epinephrine-induced reabsorption of fetal lung liquid during labor is compromised during preterm delivery. Studies in preterm infants with respiratory distress syndrome also showed a reduced sodium transport capacity in the nasal epithelial cells. This less efficient prenatal clearance of lung liquid may hinder aeration of the preterm lung at birth. The fact that many preterm newborn infants are born by cesarean delivery contributes to these problems (see below).

Second, the preterm infants' muscle strength is often insufficient to create the high inspiratory pressures

needed to aerate the lungs during the first breaths. The highly compliant chest wall deforms during diaphragmatic contraction, thereby limiting the inspired tidal volume. Due to the deficit of pulmonary surfactant and the high chest wall compliance, preterm infants are unable to effectively counteract the high recoil forces of the lung, which reduces the lung gas volumes at the end of expiration (FRC). This is probably the reason why preterm infants frequently continue to use expiratory breaking during spontaneous breathing (manifested as grunting).

Finally, the preterm lung is structurally immature with the lungs of most infants still being in the saccular stage. This will reduce lung surface area and thus compromise gas exchange.

Today, most preterm infants receive antenatal steroids, which stimulate both the structural and biochemical (surfactant) maturation of the lung and the prenatal clearance of lung liquid in response to epinephrine. This way many preterm infants are now able to successfully aerate their lungs at birth and create a stable FRC with only nasal continuous positive airway pressure.

Due to the above mentioned differences in respiratory transition between preterm and term infants, most preterm infants will take a longer time to reach a preductal oxygen saturation of 90% (preterm 6.5 min vs term 4.7 min). In contrast to term infants who often do not need supplemental oxygen during their transition, greater proportion of the preterm infants less than 30 weeks' gestation need supplemental oxygen at some point during their transition.

Most preterm infants will need some supportive care during their respiratory transition after birth. Studies in preterm rabbit pups have shown that supporting the first breath with positive pressure at the airway opening using prolonged inspiration time (sustained inflation) and a positive end-expiratory pressure (PEEP) facilitates lung aeration. Applying this strategy in preterm infants significantly reduces the need for intubation in the delivery room and within 72 h of age. It is, however, important to realize that this support needs to be accurately tailored to the needs of each individual infant because inappropriate ventilator support (high tidal volumes, insufficient PEEP) during the first minutes after birth can cause irreversible lung injury which increases the risk for bronchopulmonary dysplasia (BPD).

Several randomized controlled trials have shown that restoring the surfactant function in preterm infants by administration exogenous surfactant soon after birth (prophylactic use) improves lung function and reduces mortality.

Respiratory Transition After Cesarean Section

Several studies have documented the high incidence of respiratory distress and neonatal intensive care admission in infants born by Cesarean section (CS) before the onset of spontaneous labor (elective CS). There are strong indications that this increased risk for pulmonary morbidity is caused by an abnormal respiratory transition.

As mentioned previously, lung liquid clearance starts before birth in response to the epinephrine surge at the onset of labor. Studies in fetal rabbits have shown that absence of labor and thus epinephrine results in excessive retention of lung fluids. Studies in infants with transient tachypnea of the newborn are consistent with this finding showing an immaturity of the transepithelial sodium transport.

Lung liquid clearance is facilitated by the intrauterine contractions prior to delivery and the vaginal squeeze as the infants passes through the birth canal. During elective CS, intrauterine contractions are absent and a study in newborn infants showed that the delivery pressures are halved compared with vaginal delivery. In addition, significantly fewer infants born by CS retained air at the end of their first breath. This probably explains the slower increase in postnatal oxygen saturation in newborn infants delivered by CS.

Cardiovascular Transition

The Fetal Circulation

The fetal circulation differs considerably from the extrauterine circulation because the placenta and not the lung provides intrauterine gas exchange. Placental oxygenated blood needs to be directed to the left side of the heart as efficiently as possible and poorly oxygenated blood returning to the right side of the heart needs to be directed to the placenta without passing through the liquid-filled lungs. This is accomplished by the presence of central shunts via the foramen ovale and the ductus arteriosus. After passing through the umbilical vein and the ductus venosus, oxygenated blood returning from the placenta enters the right atrium via the medial aspect of the inferior vena cava. The latter facilitates oxygenated blood to cross the foramen ovale into the left atrium. The left ventricle delivers the majority of its output to the heart, brain, and upper body for optimal oxygen use. Poorly saturated blood returning from the upper body via the superior vena cava and the lower body via the lateral aspect of the

inferior vena cava predominantly crosses the tricuspid valve. Most of the right ventricular output passes through the patent ductus arteriosus into the distal aorta and reaches the placenta via the umbilical arteries. Studies in fetal lambs have shown that only 8–10% of the right ventricular output passes through the lung. In human fetuses, this percentage increases from 13% at 20 weeks to approximately 20–25% in the third trimester. The main reason for the right ventricular output to bypass the lungs via the ductus arteriosus is the relatively high pulmonary vascular resistance compared with the low systemic vascular resistance. It has been suggested that the high pulmonary vascular resistance is caused by compression of small pulmonary arteries by the liquid filling the alveolar space, but hypoxic pulmonary vasoconstriction mediated through several vasoactive substances is the most important mechanism. The placenta is the biggest contributor to the low systemic vascular resistance.

Transitional Changes at Birth

For a successful transition from placental to pulmonary gas exchange at the time of birth, lung liquid clearance and aeration needs to be accompanied by a rapid increase in pulmonary perfusion. This means that the intrauterine central right-to-left shunts must close or reverse, a process triggered by a fall in pulmonary vascular resistance and an increase in systemic vascular resistance.

The fall in pulmonary vascular resistance, resulting in an eight- to tenfold increase in pulmonary blood flow at birth, is caused by physical changes at lung expansion and the concomitant increase in oxygenation. Studies in fetal lambs have shown that lung expansion decreases PVR by unkinking of small pulmonary arteries and by exerting a direct dilating effect on these same vessels via the increased alveolar surface tension at the air–liquid interface. In addition, pulmonary vascular resistance is decreased by the stretch-induced release of prostaglandins (PGI_2, PGD_2).

Oxygenation causes pulmonary vasodilatation via the synthesis of nitric oxide (NO), although the exact stimuli for NO production are not yet fully defined.

The systemic vascular resistance increases as soon as the umbilical cord is clamped and the low-resistance placental circulation is cut off. This will further decrease the ratio between the pulmonary and systemic vascular resistance and increase pulmonary perfusion.

Studies in newborn infants have also shown a rapid decrease in the ratio between pulmonary and systemic arterial pressure during the first 12–24 h after birth. This was accompanied by a decrease in ductal right-to-left shunt and an increase in left-to-right shunt. In most term infants, the ductus arteriosus will close within 48 h after birth. As soon as pulmonary blood flow increases, the left atrial filling pressure becomes higher than the right atrial filling pressure, causing the foramen ovale to close functionally; anatomical closure occurs days to weeks later.

Cardiovascular transition also results in a significant increase in cardiac output. Although the precise mechanisms responsible for this increased output are not fully understood, several explanations have been suggested. First, studies in fetal lambs have shown a thyroid hormone mediated increase beta-adrenoreceptor responsiveness during the last weeks of pregnancy, which potentiates the ability of the heart to increase its output in response to the catecholamine surge that occurs at birth. Second, the decrease in right ventricular afterload after birth probably reduces the constraining effect of the right ventricle on the left ventricle, allowing the latter to contract more efficiently in response to the large increase in preload at birth. Finally, cardiac output is probably stimulated by the increased cardiorespiratory and thermoregulatory work after birth.

Animal studies and human data clearly demonstrate that the process of labor is also important for cardiovascular transition. Labor results in key changes in the hormonal milieu of the fetus and impacts on the key mechanisms responsible for postnatal fall in pulmonary vascular resistance. Slower fall in pulmonary vascular resistance and increased incidence of persistent pulmonary hypertension have been documented in infants born by elective Cesarean delivery without labor, compared to infants born vaginally.

It is clear from the above that cardiovascular transition is a complex process consisting of several physical and biochemical changes. Failure of just one of these changes can jeopardize normal cardiovascular transition and lead to severe disease states such as persistent pulmonary hypertension of the newborn (see Chap. 15, "Respiratory System").

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10 Delivery Room Management of the Newly Born Infant

Maximo Vento

Definition/Concept

According to WHO estimates, between 0.5% and 3% of approximately 120 million infants born every year suffer birth asphyxia requiring resuscitation, and some 900,000 of these newborns die each year, and a similar number will develop motor and/or neurocognitive dysfunctions. The incidence of birth asphyxia is higher in developing countries because of a higher prevalence of risk factors, namely, women are in poor health when they become pregnant; the incidence of pregnancy and delivery complications in these women is high; care during labor and delivery is often inadequate or nonexistent. Delivery room stabilization of the newborn is the most frequent intervention in the neonatal period; however, many newborns do not receive adequate care in the delivery room (DR) because birth attendants have not been adequately trained, necessary equipment is lacking, international guidelines are not put into practice and certain traditional practices are not only ineffective but may be also harmful.

In this chapter, the pathophysiology of asphyxia and resuscitation procedures will be described based on ILCOR 2010 guidelines and evidence-based information published in recent years.

Pathophysiology of Asphyxia

Cardiocirculatory Changes During Fetal to Neonatal Transition

Life in utero occurs in a low oxygen atmosphere. The fetus is persistently hypoxemic compared to the adult, and whereas human maternal arterial and venous pO_2 is ~12 kPa (90 mmHg) and 5.3 kPa (40 mmHg), respectively, the highest arterial or venous pO_2 in the late gestation fetus rarely exceeds 4 kPa (30 mmHg) .The pCO_2 of the fetus is slightly higher than adult levels with an umbilical venous pCO_2 from 35 to 45 mmHg (4.6–6 kPa).

During labor, the fetus experiences brief periods of ischemia and hypoxemia because with each uterine contraction, flow to the placenta (and the fetus if there is cord compression) decreases transiently, impairing placental gas exchange. However, the fetus is able to recover between each contraction and blood gases performed in the umbilical cord immediately after birth are within a "normal" range. Overstimulation of the uterus with oxytocin may lead to excessively frequent contractions with limited recovery time and thereby compromise fetal well-being.

To achieve successful transition to extrauterine life, the infant must accomplish dramatic cardiorespiratory changes. In the first minutes after cord clamping, with the initiation of breathing, lungs must be expanded and fluid inside the alveoli and airways must be rapidly absorbed. Pulmonary blood flow must increase dramatically, and intracardiac and extracardiac shunts initially reverse direction and subsequently close. The first breaths of a normal-term neonate exert negative pressures that may reach pressures as high as -80 cmH_2O. Expansion of the lungs and the increase in alveolar oxygen tension both mediate the fall in pulmonary vascular resistance and increase in pulmonary blood flow after birth. Premature infants and infants born by cesarean section, without the effect of labor, do not clear the lung fluid and expand their alveoli as easily as term babies born by vaginal delivery.

Pathophysiologic Changes During Asphyxia

Dawes et al. performed experiments with rhesus monkeys asphyxiated by sealing their heads in a bag containing saline immediately after delivered by cesarean section (*Fig. 10.1*). Respiratory rate increased for a few breaths and then stopped (primary apnea). However, after 1 or 2 min, gasping was re-initiated with vigor and higher frequency and was accompanied by thrashing movements of the extremities. In this period, spontaneous ventilation could be still induced by appropriate sensory stimuli. Simultaneously, HR dropped from 200 to 100 bpm. Respiratory efforts gradually decreased and completely ceased at around 8 min. Cardiac activity continued until

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_10,

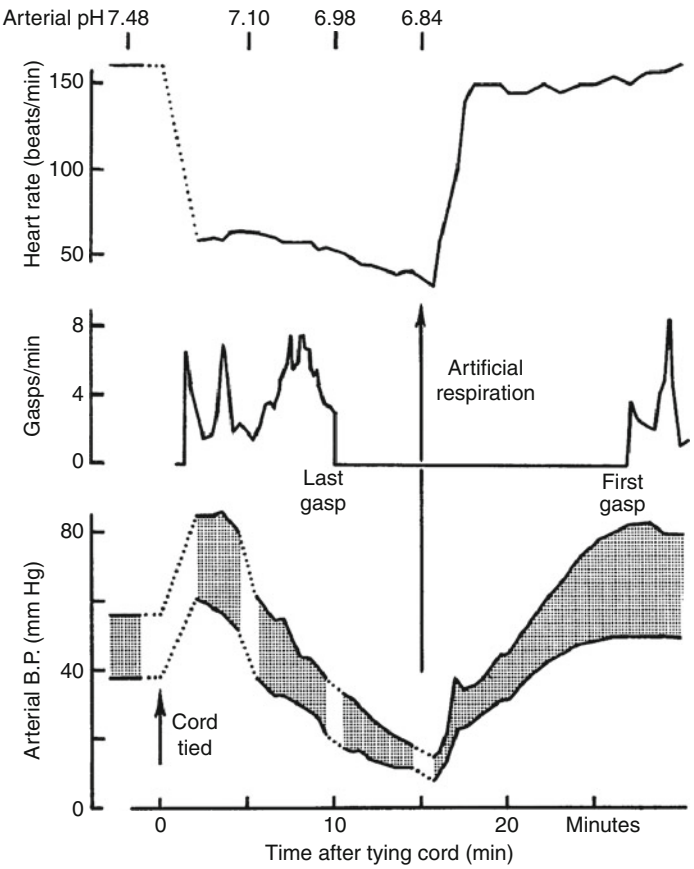


Figure 10.1

Time course of vital signs and acid base balance in an animal model of acute total asphyxia. The time course of partial and/or intermittent asphyxia may differ. Note the rapid response in HR following initiation of positive pressure ventilation (*Source*: Dawes GS, Jacobson HN, Mott JC et al (1963) The treatment of asphyxiated, mature foetal lambs and rhesus monkeys with intravenous glucose and sodium bicarbonate. J Physiol 169:167–184)

approximately 10 min. The period between the last gasp and cardiac arrest is known as secondary or terminal apnea. The time gap between secondary apnea and initiation of resuscitation correlates directly with the success of resuscitation.

Metabolic Changes in Asphyxia

Asphyxia is characterized by periods of hypoxia and ischemia. During hypoxia, limited oxygen availability decreases oxidative phosphorylation, resulting in a failure to resynthesize energy-rich phosphates, especially ATP, leading to alterations in cellular ion flux leading to cell cytotoxic edema. If an excess oxygen is given during reoxygenation, a burst of oxygen free radicals will be formed, further increasing cellular damage and inducing cell apoptosis, thus amplifying the initial damage caused by hypoxia/ischemia. Thus, limiting the oxygen amount given during resuscitation of the asphyxiated neonate is essential to prevent further increase in damage upon resuscitation.

Initial Actions

Anticipating the Need for Resuscitation

Personnel

Caregivers responsible for attending births in the DR should have an adequate training in basic neonatal resuscitation skills, which include evaluation of clinical status of the

newborn (HR, respiratory efforts, color, and tone), bag and mask ventilation, and cardiac compressions. One person should be always available for the care of each infant. In addition, a skilled caregiver trained in advanced neonatal resuscitation (intubation, ventilation, IV cannulation, use of drugs and fluids) should be available for second call for low-risk deliveries and present for all deliveries at high risk, where he or she should take the leadership of the procedure.

Equipment

Ideally, basic DR installations should be based on the DRICU concept (Delivery Room Intensive Care Unit) which means that technology used in the intensive care unit should be available in the delivery room to adequately provide care immediately after birth. Equipment should be applicable to any gestational age (23–44 weeks of gestation), and it should be regularly checked to ensure it is complete and operational (detailed description in *Table 10.1*).

Communication with the Obstetric Team and Identification of Newborn at Risk

Caregivers in charge of the neonate should request information from the obstetric eam regarding maternal medical condition, medication, and fetal status (*Table 10.2*).

Environment

Temperature

Neonates, and especially preterm infants, have a tendency toward hypothermia because of their diminished capability of generating heat (inability to shiver) and an increased ability to lose it (increased surface area to body-weight ratio, thin stratum corneum and extremely thin insulator of subcutaneous tissue). Therefore, if measures are not promptly initiated to counteract this negative heat balance, body temperature will fall, independently of the environment temperature, during the first 12 h of life. For the full-term newborn, both standard thermal care (removing wet blankets, promptly drying, and wrapping the infant in a warm blanket) and placing the dried infant under a radiant heater in a draft-free room at minimum 25°C are effective in maintaining normal body temperature. For preterm infants <28 weeks gestation, randomized controlled trials have shown that covering infants up to the neck in a transparent heat-resistant

Table 10.1
Equipment and drugs in the delivery room

Equipment
– Resuscitator with overhead warmer and light, and firm, padded, and heated mattress
– Two sources of medical oxygen
– Two sources of medical air
– Two blenders (air/oxygen)
– Clock with timer in seconds
– Warmed towels or other covering
– Polyethylene bag, or wrap, big enough for a baby less than 1,500 g birth weight.
– Stethoscope, neonatal size
– Suction catheters (6 F, 8 F, 10 F, 12 F)
– Oxygen/Air admixture supply (flow rate up to 10 L) with flow meter and tubing
– Face masks (various sizes)
– Oropharyngeal airways (sizes 0 and 00)
– Positive pressure ventilation (Two in case of twin deliveries):
• T-piece device
• Self-inflating bag with an oxygen reservoir and a manometer if available
• Flow-inflating bag with a pressure safety valve and manometer
– Laryngoscopes with straight blade (00, 0, 1), spare bulbs, and batteries
– Endotracheal tubes (sizes 2.5, 3, 3.5, and 4 mm ID)
– Endotracheal stylet or introducer
– Magill forceps, neonatal size
– Supplies for fixing endotracheal tubes and IVs (e.g., scissors, tape)
– End-tidal carbon dioxide detector (to confirm intubation)
• Chemical detector (e.g., Pedicap®)
• End-tidal CO_2 monitor
– Meconium suction device (to apply suction directly to endotracheal tube)
– Feeding tubes for gastric decompression
– Umbilical vein catheterization set and umbilical catheters (5 F) with suitable skin prep solution
– Syringes with needles (assorted sizes)
– Intravenous cannulae (assorted sizes)
– Pulse oximeter with sensors adequate for different gestational ages

Table 10.1 (Continued)

Drugs
– Adrenaline: 1:10 000 concentration (0.1 mg/mL)
– Volume expanders: Normal saline, O Rh –ve blood needs to be readily available for a profoundly anemic baby
– Sodium bicarbonate: 0.5 mmol/mL solution (4.2% concentration, or diluted 8.4%)
– Naloxone hydrochloride: 400 μg/mL solution
– Sterile water for injection

plastic (polyethylene/polyurethane wrapping) without previous drying results in a higher body temperature at admission (*Fig. 10.2*). Only the head is dried and covered with a cap. All resuscitation interventions can be performed with the plastic cover in place. Currently, there is no direct evidence that this procedure improves mortality or long-term outcome. Monitoring of body temperature should be considered, especially when resuscitation is prolonged, to avoid the small risk for inducing hyperthermia. When resuscitation is not required, the mother's body can keep the infant warm by using her as a heat source, placing the infant skin-to-skin on the mother's chest or abdomen and putting a blanket or warm wrap on top.

Avoidance of Hyperthermia

Of note is that babies born to febrile mothers (>38°C) have an increased risk of death, perinatal respiratory depression, neonatal seizures, and cerebral palsy. Therefore, normothermia (36.5–37.2°C) should be the target body temperature for newly born infants and iatrogenic hyperthermia must be avoided.

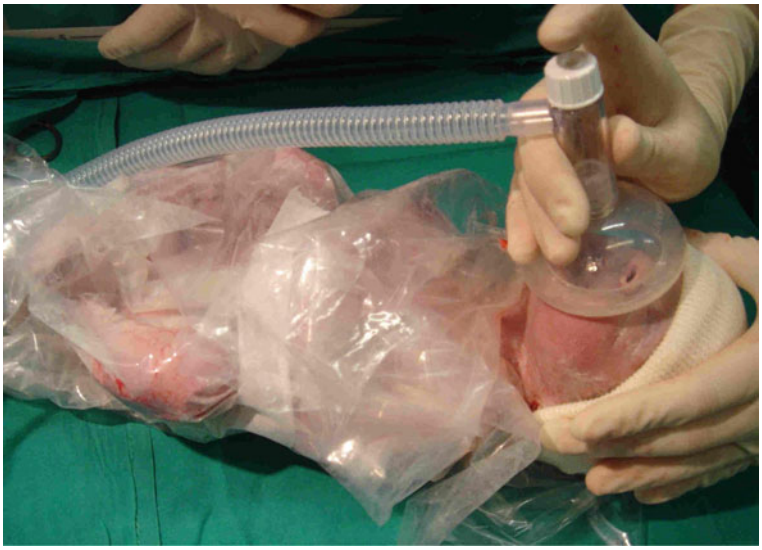
Evaluation of the Newly Born Infant

The assessment of the newborn's postnatal adaptation in the DR is usually done using the Apgar score, which evaluates five clinical signs: heart rate, respiratory effort, color, tone, and response to stimuli at 1 and 5 min (*Table 10.3*). To avoid interobserver variability, caregivers should be trained in assessing the different parameters of the Apgar score in a uniform manner, and objective means of evaluation should be pursued (e.g., pulse oximetry). Thus, an apneic infant should score "0", even if the infant is ventilated and inadequate respiratory efforts should score "1", also if the infant is ventilated. The premature infant that is hypotonic scores "1" for muscle tone, even though this may be physiologic for the gestational age.

Table 10.2
Identification of the newborn at risk

Maternal risk factors
• Prolonged rupture of membranes (>24 h)
• Bleeding in second or third trimester
• Severe pregnancy-induced hypertension
• Chronic hypertension
• Substance abuse
• Drug therapy (e.g., lithium, magnesium, adrenergic blocking agents, narcotics)
• Diabetes mellitus
• Chronic illness (e.g., anemia, cyanotic congenital heart disease)
• Maternal infection
• Chorioamnionitis
• Heavy sedation
• Previous fetal or neonatal death
• No prenatal care
Fetal risk factors
• Twins or triplets
• Preterm gestation (especially <35 weeks)
• Post-term gestation (>41 weeks)
• Large for dates
• Fetal growth restriction
• Rhesus, or other types of isoimmunisation, especially those causing hydrops fetalis
• Polyhydramnios and oligohydramnios
• Reduced fetal movement before onset of labor
• Congenital abnormalities which may affect breathing
• Intrauterine infection
Intrapartum risk factors
• Non-reassuring fetal heart rate patterns on CTG
• Abnormal presentation
• Prolapsed cord
• Prolonged labor (or prolonged second stage of labor)
• Precipitate labor
• Antepartum hemorrhage
• Thick meconium in the amniotic fluid
• Narcotic administration to mother within 4 h of delivery
• Forceps delivery
• Cesarean section under general anesthesia

Heart rate (HR) is the most relevant clinical sign indicating adequate postnatal adaptation and/or response to resuscitation. In addition, HR in the first minutes of life has prognostic value regarding mortality in the early



Newly born infant wrapped in poly-ethylene bag

Figure 10.2
Preterm newborn infant wrapped in polyethylene bag

Table 10.3
The Apgar score for evaluation of adaptation of the newborn infant after birth (32)

Sign	0	1	2
Heart rate	Absent	<100 bpm	>100 bpm
Respiratory effort	Absent	Slow, irregular	Good, crying
Muscle tone	Flaccid	Some flexion extremities	Active motion
Reflex irritability	No respond	Grimace	Vigorous cry
Color	Pale	Cyanotic	Completely pink

neonatal period. HR may be assessed by palpation of umbilical cord pulsations or direct auscultation of the *precordium*; however, randomized studies have shown that both of these methods could delay or underestimate the heart rate, compared to electrocardiography. Therefore, it is advised to use pulse oximetry for monitoring HR, especially in case of an extended resuscitation. Healthy newborn achieve a HR around 130 bpm (110–160 bpm) within the first minute of life; importantly, it should be consistently above 100 bpm within a minute after birth. Hence, if HR is persistently below 100 bpm, resuscitation should be initiated.

Assessment of the color also shows high interobserver variability, especially in preterm infants. This can be avoided with the use of pulse oximetry. It is important to understand that healthy-term newborns do not reach *preductal* oxygen saturations greater than 85–90% until 5 min and preterm infants not until 10–15 min after birth.

After initial breathing efforts, the newborn should then establish a regular pattern of respiration sufficient to maintain the HR >100 bpm. If a newborn exhibits an irregular respiratory pattern but is able to maintain an adequate HR, he/she should be closely observed but not given respiratory aid. However, if irregular breathing movements are unable to sustain HR >100 bpm, positive pressure ventilation (PPV) should be immediately applied. Importantly, in the presence of suprasternal, intercostal, and subcostal retractions, distending airway pressure should be immediately applied to help establish functional residual capacity. Finally, the absence of respiratory movements with persistent apnea generally associated with hypotonia non-responsive to stimuli, and bradycardia (HR <100 bpm) requires immediate PPV.

Newborns moving their extremities soon after birth do not require any assistance. However, if these responses are absent or weak, stimulation by rubbing the back with a dry soft towel should suffice. Other methods such as slapping, foot flicking, shaking, spanking, or holding the baby upside down are potentially dangerous and should not be used. If the infant does not respond promptly, PPV should be started.

An infant with good tone (moving the limbs and with a flexed posture) is unlikely to be severely compromised, whereas a floppy infant (not moving and extended posture) is likely to need active resuscitation. However, as indicated above, special attention should be paid especially to very premature infants for whom a hypotonic state is physiologic.

Airway and Breathing

Positioning

The newborn that needs PPV should be positioned on his/her back with the head in a neutral or slightly extended position (sniffing position) (*Fig. 10.3*).

Airway Suctioning

Routine oropharyngeal suction is not recommended; a normal newborn clears its airways effectively. However, if secretions are obstructing the airway, it should be suctioned with a special catheter with an adequate size (French gauge 10–12) and pressure not surpassing 133 cmH_2O (13 kPa). Suction should be brief (10 s) and performed carefully (not further than 5 cm from the lips) because it may cause laryngeal spasm, bradycardia, and/or delay the onset of spontaneous respiration.

Meconium-Stained Liquor

If meconium is passed into the amniotic fluid, it may be inhaled before or during delivery and lead to inflammation of the lung and airway obstruction. Complications of meconium aspiration are more likely in infants small for their gestational age, those born after term, and especially those with significant perinatal compromise.

In the presence of meconium-stained amniotic fluid, 2–9% of the neonates will develop meconium aspiration syndrome (MAS). Intrapartum oronasopharyngeal suctioning of meconium before delivery of the shoulders is no longer recommended. However, if meconium is thick, the baby is hypotonic and respiration is shallow or absent; the mouth, pharynx, and trachea should be suctioned under direct vision with the laryngoscope. If the infant is vigorous, endotracheal suction is not recommended because it may cause harm and does not improve the outcome.

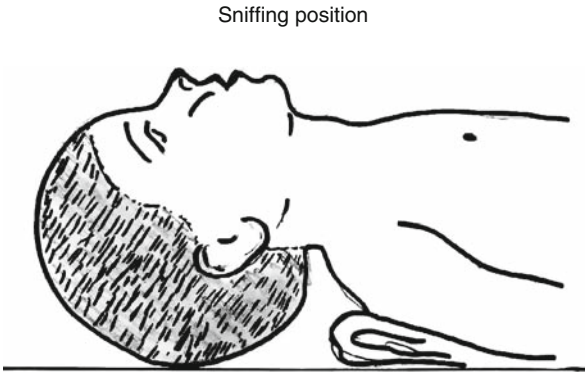


Figure 10.3
Infant in the "sniffing" position. Because of the prominent occiput of infants, positioning is facilitated by a rolled blanket placed under the shoulders (not under the neck!)

Ventilation Strategies: Initial Breaths

The establishment of adequate gas exchange by performing effective PPV at a rate of 30–60/min is without any doubt the single most effective maneuver to overcome bradycardia and hypoxemia. If HR does not improve and no thoracic expansion is observed, positioning of the face mask should be corrected to avoid leakage, which causes ventilation to be ineffective. Ensuring that the head position is correct (sniffing position described above) is essential to maintaining airway patency. In term infants, initial inflations, either spontaneous or assisted, create a functional residual capacity (FRC). The optimum pressure, inflation time, and flow required to establish an effective FRC have not been determined. However, peak inflating pressures of 30–40 cmH_2O have been shown to be effective to ventilate unresponsive term infants. Importantly, sustained inflation pressure of 30 cmH_2O for 5 s for the first breath seems to be more effective in achieving FRC than lower pressures for shorter periods of time. Once the newborn has achieved an adequate FRC, lower pressures in the range of 15–25 cmH_2O and a pace of 30–60/min seem to be adequate. However, the ILCOR 2010 guidelines state that optimal ventilation rates and pressures should be individualized according to each infant's response. The goal is to achieve a visible, but not excessive, chest rise and audible breath sounds. Excessively large tidal volume can lead to lung injury in less than a minute; therefore, careful attention to the pressure being applied is essential.

Assisted Positive Pressure Ventilation Devices

Three different devices have been successfully employed to ventilate newborn infants: self-inflating bag, flow-inflating

(anesthesia) bag, and T-piece mechanical device designed to regulate pressure.

Self inflating bags (Fig. 10.4a) are devices consisting of an elastic bag that re-expands due to its intrinsic recoil and does not depend on a gas source for inflation (although a gas source may be attached for administering gas admixture). It is simple and portable, allowing its use outside the hospital. It has a pressure limited pop-off valve that usually triggers at 40 cmH_2O, although these valves activate at a wide range of pressures, and therefore it is difficult to adjust to desired target values. Self-inflating bags do not administer PEEP effectively, even with a PEEP valve, are not capable of providing CPAP for infants with adequate respiratory effort but needing help to establish FRC, and do not permit adjustment of inspiratory times, therefore unable to deliver sustained inflation. Inspiratory fraction of oxygen cannot be precisely adjusted, and only with an additional reservoir administration of close to 100% oxygen may be achieved. The preferred size in neonatology is of 240 mL because it covers tidal volume needs of newborn infants (5–8 mL/kg).

Flow-inflating (anesthesia) bag (Fig. 10.4b) must be connected to a compressed gas source, which provides the gas admixture to inflate the bag when in use. If the face mask is not perfectly adjusted (leaks) or the flow is too low, the bag will collapse and ventilation will be rendered impossible. Special attention should be paid to the inspiratory pressure since these devices can reach very high pressures

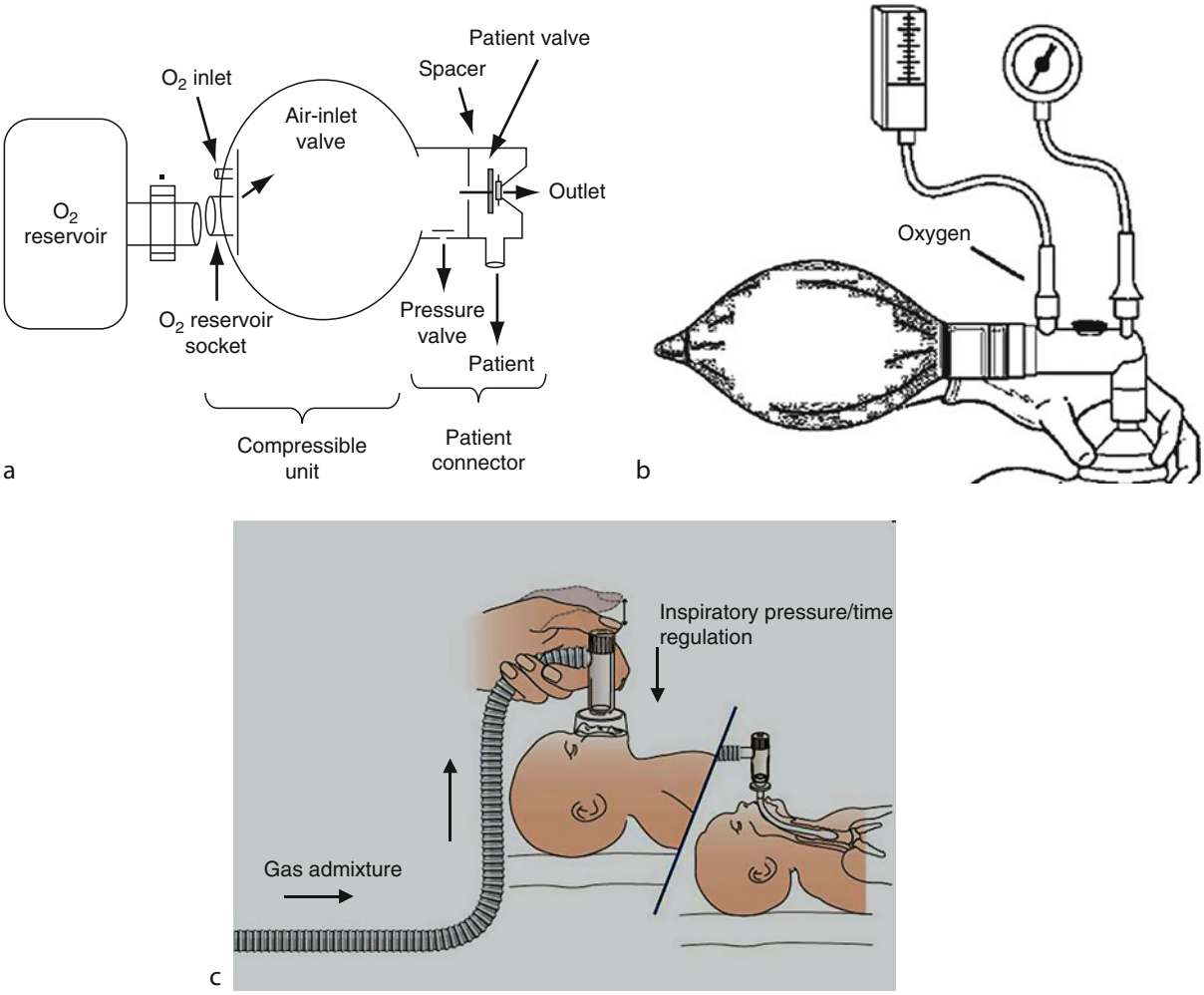


Figure 10.4

Devices for administering positive pressure in the delivery room (a) Self-inflating bag with reservoir and pop-off valve (b) Flow-inflating bag with oxygen supply and pressure manometer (c) T-piece resuscitator with gas admixture supply, inspiratory pressure/time regulation

which could cause pulmonary leaks. To avoid this, incorporating a pressure gauge and blow-off valve in the circuit is mandatory. Expiratory pressure (CPAP or PEEP) can be provided by controlling the pressure in the bag by adjusting the flow of gas into the bag and the rate of gas escape from the bag at the outlet valve. Flow-inflating bags can be used to deliver sustained inflations. However, these bags require substantially more skill and training than self-inflating bags and are generally limited to hospital settings.

The T-piece device (*Fig. 10.4c*) consists of an inlet arm to the patient through which the gas flows into a facemask or endotracheal tube (ETT). Positive inspiratory pressure (PIP) is achieved by interrupting the escape of gas through an outlet hole using a thumb or finger, so that the pressure rises and is displayed by a manometer. PIP is controlled by adjusting the release valve. The inflation time is voluntarily regulated by the caregiver by varying the duration of occlusion of the outlet hole; therefore, sustained inflation is easily administered. CPAP or PEEP is delivered automatically and the pressure varied by adjusting the outlet valve. This controls the rate of escape of gas when the outlet is not occluded (i.e. in expiration) and generates a set level of PEEP or CPAP. The level of PEEP or CPAP can also be adjusted by altering the gas flow in the system. T-piece resuscitator has been shown to deliver PIP and tidal volume that was closer to target values and more consistent than self-inflating bags. However, the preferred system may be that with which the caregivers are most acquainted and self-confident.

Interfaces for Administration of Respiratory Support

Noninvasive ventilation is generally performed with face mask (FM), although nasal prongs may also be used, and invasive intubation is performed using an endotracheal tube (ETT). Indications, advantages, and disadvantages of each interface will depend on the severity, gestational age, and/or experience of the caregiver. As a rule, FM is the first choice for moderately depressed neonates, while endotracheal intubation (ETI) is preferred for more severe conditions or as second choice when FM fails to adequately recover the newborn's HR.

FM is more gentle to the airway, easier to use and maintain expertise because it is frequently used in the DR. It is important that the FM is of the appropriate diameter according to the infant's birth weight and preferably with cushioned rims to avoid leakage. Available masks have diameters ranging from 35 to 72 mm that will provide adequate seal in newborns from 24 to 40 weeks gestation (*Fig. 10.5*). Adequate application of the mask is essential, and adequate training significantly reduces air leakage (*Fig. 10.6*). Controlled studies comparing FM versus intubation have shown that although inflation pressures were similar, inflation volumes, especially expiratory volumes, were difficult to assess with mask ventilation because of frequent leakage even with higher inflation pressures. FM ventilation seems to induce breathing by Head's paradoxical reflex, and therefore successful resuscitation is dependent to a substantial degree on the baby's spontaneous respiration. In severely asphyxiated babies, a brief trial with FM should be performed, but if after 30 s there is no improvement in HR (persistently <100/m) or the infant does not make effective respiratory effort or is profoundly bradycardic (<60 bpm), intubation should be considered, if a skilled person is available. Intubation is potentially the most injurious invasive procedure performed during neonatal resuscitation. Every effort should be made to stabilize an infant before attempting intubation to mitigate occurrence of bradycardia/hypoxia. Surfactant administration should be delayed until the baby has recovered. It's important to be gentle to avoid damaging the anatomical structures (oral route is easier for the non-experienced resuscitator), use an appropriate laryngoscope blade size – 0 or 00 (7.5 cm) for preterm babies, 1 (10 cm) for term infants, and ETT size, and depth of insertion (*Table 10.4*). Location of the ETT should always be clinically verified. The tip of the laryngoscope should be advanced over the tongue to the vallecula or on top of the epiglottis and elevated gently to reveal the vocal cords (*Fig. 10.7a*). Cricoid pressure may be helpful

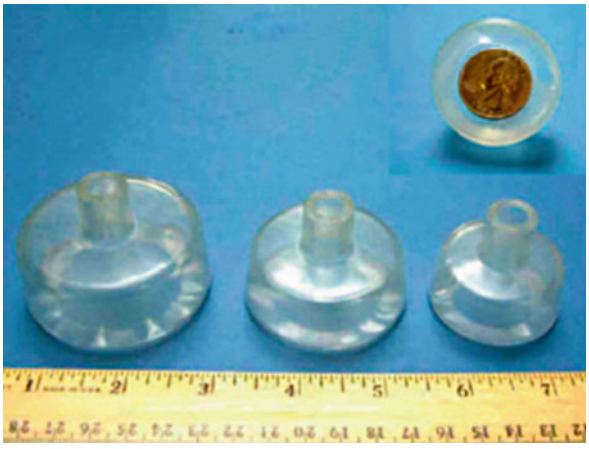


Figure 10.5
Different size masks for use in term and preterm infants. Choice of correct size is critical to achieve good seal

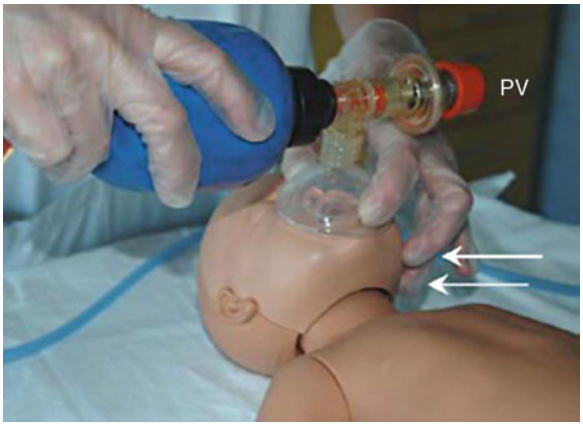


Figure 10.6
Correct technique for holding a face mask. Note the position of the fingers under the chin and the way they are able to position the infant's head while firmly holding the mask against the face. The mask should not press on the eyes, which could trigger a vagal reflex bradycardia

Table 10.4
Endotracheal tube sizes and depth of insertion from the lips

Weight (g)	Gestation (weeks)	Tube size (mm)	Depth of insertion from lip (cm)
< 1,000	< 28	2.5	6.5–7
1,000–2,000	28–34	3.0	7–8
2,000–3,000	34–38	3.0/3.5	8–9
> 3,000	> 38	3.5/4.0	> 9

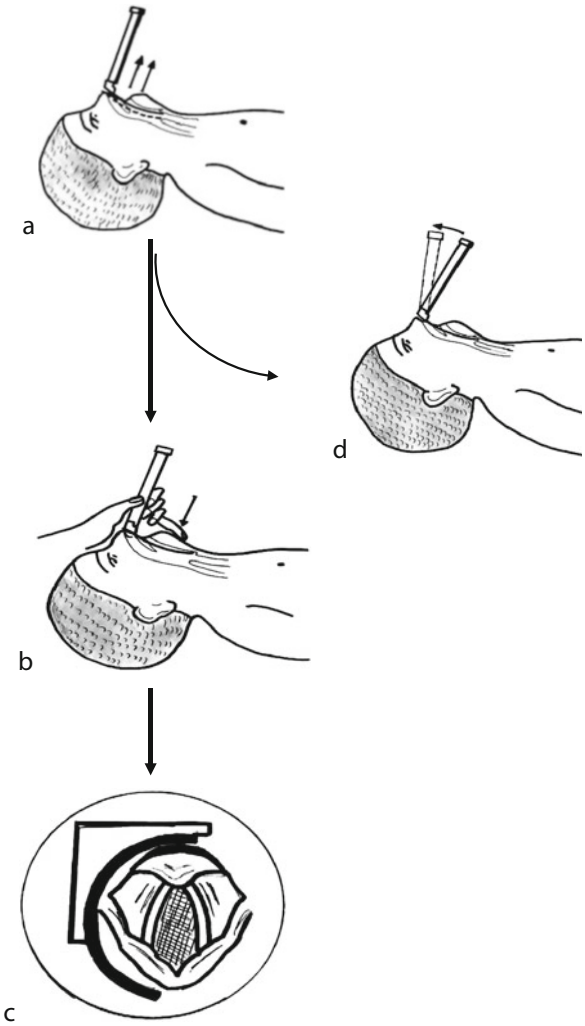


Figure 10.7
Technique of endotracheal intubation. Please see the text for explanation

(*Fig. 10.7b*). ETT should be inserted through the vocal cords to a depth indicated by marks on the tube, which should be annotated, and safely secured to avoid extubation or bronchial intubation (*Fig. 10.7c*). Common problems experienced during neonatal intubation:

- If the laryngoscope is advanced too far, the larynx will not be seen (*Fig. 10.7d*).
- If the blade does not support the tongue, it will obscure the view of the larynx.
- If the laryngoscope is not held slightly toward the left side, the larynx will not been seen.
- If the neck is flexed or overextended the larynx may not be seen.

The use of a stylet inside the ETT should be done with care to prevent damaging the trachea.

Most of the caregivers are successful in intubating in 30 s, and saturation and HR will not differ from those intubated in <20 s. Once the tube is secured, the position of the tip should be verified as soon as possible to avoid hypoxia/hypercapnia. Air entering both lungs and absence of sounds in the stomach can be detected by auscultation; however, in preterm infants, in special situations such as diaphragmatic hernia, or pneumothorax, this may be difficult. End-tidal carbon dioxide ($ETCO_2$) detectors or colorimetric CO_2 detectors may be used to rapidly verify if the ETT tip is in a correct position. Remarkably, colorimetric CO_2 detectors have been shown to be effective in confirming ET intubation or detecting a misplaced ETT within six inflations even in babies of less than 400 g. When CO_2 is detected, the color changes from purple to

yellow. If there is no color change, the likely causes are: the ETT is not in the trachea, the PIP is inadequate, or no CO_2 is being excreted because of absent lung perfusion due to cardiac arrest. If a colorimetric detector indicates the presence of CO_2, the operator can be certain that the airway is patent and fresh gas is being delivered into the lungs. Interestingly, the CO_2-detector has been shown to indicate the return of circulating rhythm during chest compressions, an observation recently confirmed in an animal model of neonatal resuscitation.

Special Circumstances: The Very Preterm Neonate

Postnatal adaptation of preterm infants <29 weeks requires almost always some respiratory support to establish functional residual capacity (FRC). Frequently, the infant has adequate respiratory effort, but is retracting. In that situation, provision of CPAP via a T-piece resuscitator, anesthesia bag, or ventilator is indicated to help the infant establish FRC, a task made more difficult for the preterm infant because of relative surfactant deficiency and very compliant chest wall. If atelectasis is allowed to develop, the marginal surfactant pool will be further reduced by surfactant inactivation, leading to respiratory failure. The benefits of sustained inflation to rapidly recruit lung volume and achieve homogeneous lung inflation remain unproven, but the maneuver is physiologically attractive. The dilemma between early intubation and surfactant administration or noninvasive CPAP is still under debate; however, the trend is toward noninvasive support in the DR. Observational studies have suggested that using early CPAP in very preterm infants may reduce intubation rate, need for oxygen, and incidence of BPD without increasing morbidity. The COIN trial, which compared early CPAP in spontaneously breathing infants born at 25–28 weeks with intubation showed no difference in mortality between both groups. Interestingly, at 28 days, the CPAP group had a significantly lower incidence of death or oxygen requirement, although by 36 weeks' gestation the differences disappeared. However, the CPAP group had significantly fewer days on ventilation. There were no significant differences in any complications of prematurity, except for an increased rate of pneumothorax in the CPAP group. Thus, preterm infants 25–29 weeks breathing spontaneously at birth should be initially supported with CPAP, titrating pressures and FIO_2 to meet HR and saturation targets. In case of respiratory failure, intubation and positive pressure with PEEP should be administered.

Laryngeal Mask

Laryngeal masks (LMA) are rarely used in newborn resuscitation. They only come in full-term size, although they have been successfully employed even in preterm newborns but not below 1,500 g. With increasing use of noninvasive ventilation in the DR and in the NICU, intubation skills might be increasingly difficult to maintain. Therefore, LMA insertion should be considered a valid alternative for problematic intubations and included in every resuscitation training program.

Oxygen Use in Resuscitation

Term Infants

The ILCOR 2005 statement concluded that there was insufficient evidence to specify the FIO_2 for initiation of resuscitation in the DR. Recently, a new meta-analysis was published including ten studies under which six randomized controlled trials in European countries fulfilled strict methodological criteria. A subgroup analysis of these European studies showed a reduction in mortality with RA resuscitation from 3.9% to 1.1% with a number needed to harm by use of 100% of 36. These recent data question the decision of the ILCOR 2005 guidelines and open the door to start resuscitation of full-term infants with room air and to adjust FIO_2 according to the infant's response, keeping in mind the normal course of SPO_2 in the first 10 min of life. Hence, in the ILCOR 2010 guidelines, air has been recommended as the preferred gas admixture to initiate ventilation of the depressed term or near term neonate. Nevertheless, a subgroup of newborn infants will benefit from the additional supply of oxygen (e.g., persistent pulmonary hypertension). At present, no scientific guidelines are available for the use of oxygen in newborns not responding to the initial steps of newborn resuscitation. Therefore, it seems reasonable to start supplying additional oxygen whenever a newborn is not responding despite adequate ventilation with room air. The focus for assessing response should be HR, keeping in mind that even normal newborn infants do not become pink (reach O_2 saturation >85%) until after 5 min. Importantly, it must be always emphasized that lung inflation/ventilation should be the priority. Once adequate ventilation is established, if HR remains low, there is no evidence to support or refute a change in the oxygen concentration that was used initially. Monitoring of SpO_2 by pulse oximetry makes it possible to adjust FIO_2 to achieve physiologic levels of oxygen saturation.

Preterm Infants

More limited information is available for resuscitation of preterm infants, in whom normal lung function cannot be assumed. Recently a series of studies reported that very preterm infants especially <27 weeks gestation will need additional oxygen in most cases, typically in the range of 30–40%. Therefore, for preterm infants, a higher initial FIO_2 may be appropriate, although evidence is currently not sufficient to recommend an optimal initial oxygen fraction.

Recommendations for therapeutic use of oxygen during and after resuscitation: (1) Positive pressure ventilation should be initiated with 21% oxygen in term infants. (2) Supplemental oxygen should be used if the baby remains deeply cyanotic or the heart rate is <100 bpm at 90 s of age. (3) Blended gases should be available in the DR and during transport to the NICU. (4) To avoid hyperoxemia, pulse oximetry should be available in DR were babies <32 weeks are delivered. It seems reasonable to avoid saturations >95% when supplemental oxygen is used, especially in preterm infants and those who suffered perinatal depression and thus are uniquely susceptible to oxygen free radical injury.

Circulation

In the newborn, cardiac output correlates with HR and rates <100 bpm will not support optimal tissue oxygenation. If HR is absent or intense bradycardia (<60 bpm) non-responsive to adequate ventilation is present ≥30 s, chest compressions (CC) should be initiated at a rate of approximately 100/min. The main goal of CC is to achieve/sustain sufficient diastolic blood pressure to assure coronary perfusion and restore effective myocardial function. The two-thumb method, which is generally considered more effective than the two-finger method, is performed by placing both thumbs on the lower third of the sternum, gripping the chest with the hands and supporting the back with the fingers, depressing the sternum about 1/3 of the anterior–posterior diameter of the chest or about 5 cm in term infants (*Fig. 10.8*). The official recommendation (although not evidence-based) is that CC should be coordinated with ventilation at a ratio of 3:1 and a rate of 120 "events" per minute to achieve approximately 90 compressions and 30 breaths per minute. However, there is good experimental evidence that adequate diastolic pressure is only achieved after several compressions and each interruption causes the diastolic pressure to fall back to 0, putting in question the appropriateness of frequent interruption of CC. Compressions are only effective if the lungs have first been successfully aerated, making the quality of the breaths and compressions more important than the rate. Cardiac compressions *do not* substitute for lack of adequate ventilation in the newborn infant; therefore, CC should not be allowed to interfere with the establishment of an airway and adequate ventilation.

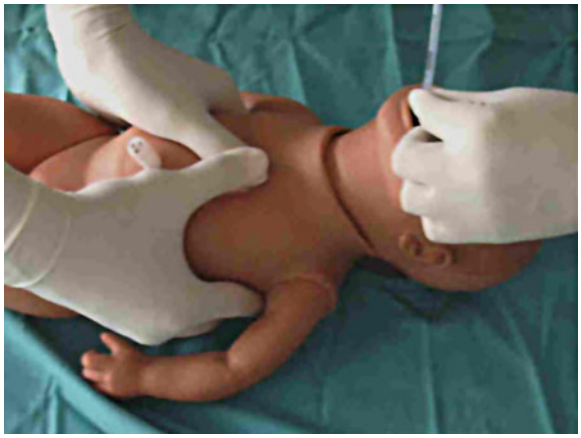


Figure 10.8
The preferred two-thumb technique for cardiac compressions

Medication and Fluids

Epinephrine

Medications and fluids are rarely needed for resuscitation of newborn infants if the ABCs of resuscitation are carried out effectively. Bradycardia is usually caused by hypoxia and inadequate ventilation, and apnea is due to insufficient oxygenation of the brainstem. Both can be readily reversed in most newborns with adequate ventilation of the lungs and brief cardiac compressions, if indicated. However, if the infant remains bradycardic (<60 bpm) despite adequate ventilation and chest compressions for 1–2 min, drugs may be needed to improve cardiac contractility. Epinephrine is a sympathetic monoamine produced by the adrenal gland. It exerts its effects through the α_1-adrenoreceptors, causing peripheral vasoconstriction, and the β_1-adrenoreceptors, increasing HR, output, and cerebral blood flow. Importantly, cardiac effects are obtained by epinephrine's direct action on the myocardial fibers, and therefore it is essential to administer it as close to the heart as possible.

Umbilical vein is the most accessible and recommended site for administering drugs and fluids. Umbilical artery is not recommended because of serious side effects of vasoactive or hypertonic solutions administered into an artery. Access to peripheral veins in a shocky newborn is extremely difficult, and only very expert caregivers can access this route rapidly enough. Intraosseous lines are not commonly used in neonates because of the fragility of small bones and the small intraosseous space, particularly in the preterm infant. The intratracheal route should exclusively be used for epinephrine when umbilical venous access is not immediately available.

Epinephrine is recommended via the intravenous route (preferably via the umbilical venous catheter), and the dosage should be 0.01–0.03 mg/kg. The dosage can be repeated every 1–3 min. Intratracheal route may be used at higher dose (100 mcg/kg). Canadian guidelines recommend the use of the intratracheal route first flushed with 5 mL of saline while preparing for insertion of the umbilical catheter. Subsequent doses, if necessary, should be administered by the umbilical vein.

A flow diagram of newborn resuscitation is represented in *Fig. 10.9*.

Volume Expanding Fluids

Intravascular fluids should be considered when there is suspected blood loss and/or the infant appears to be in shock (pale, poor perfusion, weak pulse) and has not responded adequately to other resuscitative measures. The clinical assessment of shock is difficult in a hypovolemic neonate, and shock may not be evident at first in the asphyxial process. Early, there may be peripheral vasoconstriction, which helps maintaining an adequate perfusion of the vital organs (myocardium and brain). If resuscitation is effective, clinical signs of shock may become more evident and the clinician will be able to asses indication for fluid expanders with greater acuity. Most infants with mild to moderate depression are not hypovolemic, and their peripheral perfusion will improve spontaneously without the need for volume expansion.

In the absence of suitable blood for neonatal transfusion (preferably O-negative blood cross-matched against the mother's blood), isotonic crystalloid (normal saline) should be used. The initial dose is 10 mL/kg given by quick IV push. This dose may be repeated after observation of the response. In preterm infants, rapid push of intravascular fluids should be avoided because of increased risk of intraventricular hemorrhage. When needed, volume expansion should be given more slowly over 10 min, unless frank hemorrhage is present.

Sodium Bicarbonate

Routine use of Sodium bicarbonate is no longer recommended during newborn resuscitation. Mounting evidence indicates that it may not only lack benefit but may potentially make the situation worse by lowering intracellular pH, especially when adequate ventilation cannot be assured.

General Supportive Management

Glucose

Glucose administration is essential for adequate brain and cardiac metabolism, and it should not be delayed. Anaerobic metabolism is inefficient and increases glucose depletion. Low blood glucose at admission to the NICU after resuscitation was associated with poorer neurological outcome. A glucose rate of 8 mg/kg/min will assure brain metabolic needs and myocardial glycogen restoration. Administration of intravenous glucose should be started in the DR only after adequate oxygenation has been achieved because anaerobic metabolism of carbohydrates leads to the formation of additional lactic acid, worsening the acidosis.

Fluids

The urine output of any baby who has gone through an asphyctic episode should be closely monitored since a certain degree of renal insufficiency is always present in moderate to severe asphyxia. Thus, the possibility of fluid overload and electrolyte disturbance is present.

Feeding

Human studies have reported intestinal injury occurring in 6–29% of severely asphyxiated neonates, and newborn animal models of intestinal hypoxia-reoxygenation and ischemia-reperfusion have clearly demonstrated characteristic histopathologic lesions similar to those seen in necrotizing enterocolitis. Therefore feeding should be cautiously initiated, preferably with human milk, only after a period of clinical observation. There are no definitive clinical studies to inform the decision about how soon after an asphyxial insult it is safe to initiate feedings.

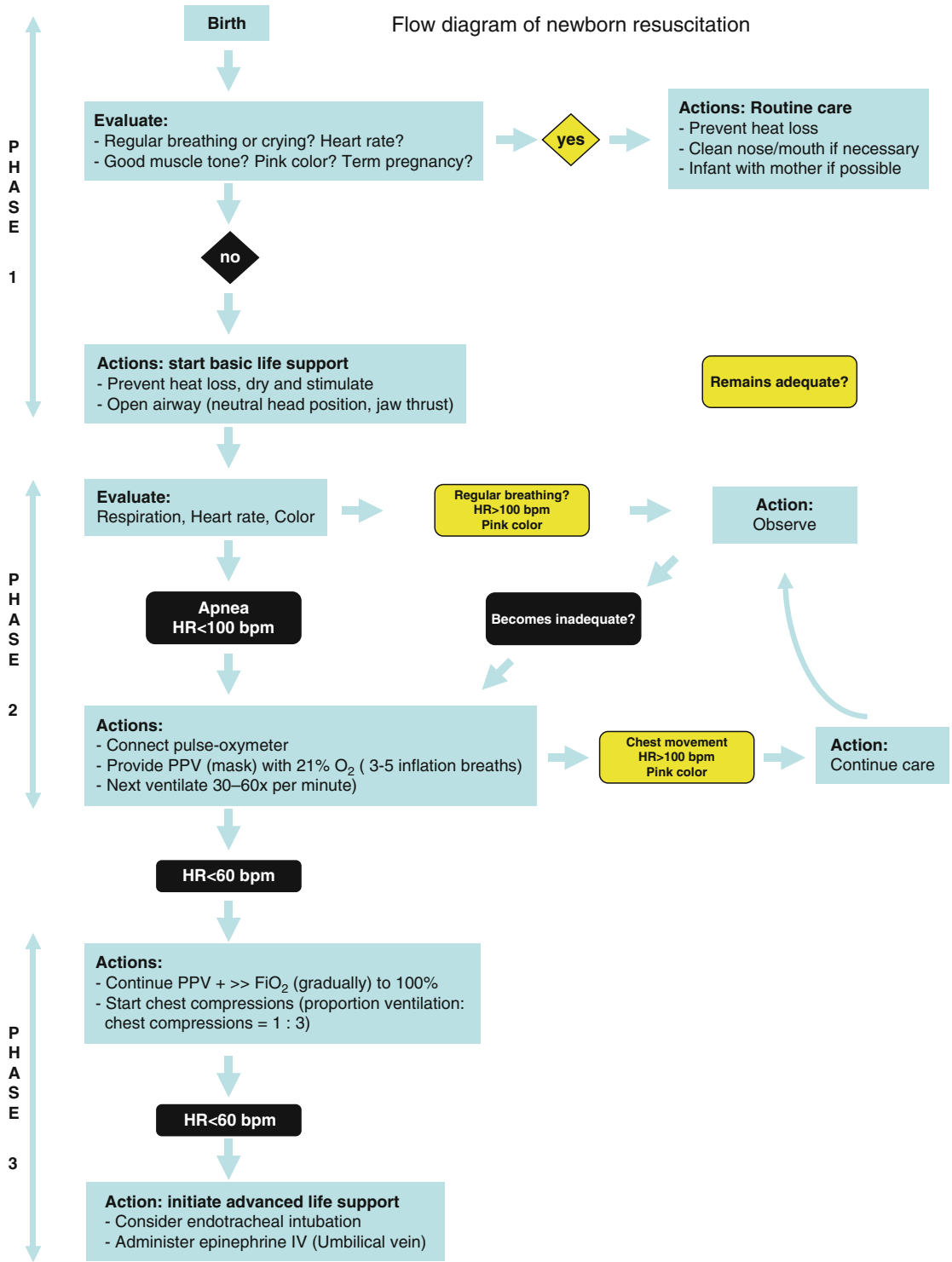


Figure 10.9
Flow diagram of newborn resuscitation

Ethical Issues

Initiating Resuscitation

Mortality and morbidity in the neonatal period is different according to the region and availability of resources. Caregivers should be aware of it before initiating or withholding resuscitation of a newborn with a specific gestational age or clinical condition. Increasingly, parents especially in highly developed countries want to take part in the decision of starting and continuing life support in severely compromised newborns. Religious beliefs and cultural traditions are also factors that should be taken into account.

Initial resuscitation does not mandate continued support. Therefore, not starting resuscitation and discontinuation of life-sustaining treatment during or after resuscitation are ethically equivalent and clinicians should not be hesitant to withdraw support when it becomes clear that functional survival is highly unlikely. If there is doubt whether to initiate or withhold resuscitation, it is best to start and later withdraw treatment when the situation has been clarified and discussed with the family and other experts. As a general rule, the following guidelines should be interpreted according to local vital statistics and societal principles or belief:

- When gestation, birth weight, or congenital anomalies are associated with almost certain early death and an unacceptably high morbidity is likely among the rare survivors, resuscitation is not indicated. Examples from the published literature from developed countries include:
  - Extreme prematurity (gestation of <23 weeks or birth weight <400 g).
  - Anomalies such as anencephaly and confirmed trisomy 13 or 18.
  - In conditions associated with a high rate of survival and acceptable morbidity, resuscitation is nearly always indicated.
  - In conditions associated with uncertain prognosis when there is borderline survival and a relatively high rate of morbidity and where the burden to the child is high, the parents' views on starting resuscitation should be supported.

Discontinuing Resuscitation

It is reasonable to consider discontinuing resuscitation if an infant that has not responded with any measurable HR after 10 min of *effective* resuscitation. In a systematic review, it was shown that 94% of newborns without any sign of life during the first 10 min after birth died or had severe neurological handicaps, and only 2% had moderate or minor handicaps. Data for infants of very low birth weight also suggest that survival is negligible if there is no heart beat after 10 min of appropriate cardiopulmonary resuscitation. Before resuscitation is stopped a second opinion should be sought if immediately available and wherever possible by agreement with parent(s). Local discussions are recommended to formulate guidelines consistent with local resources and outcome data.

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11 General Care of the Newborn

Marcia Wenner VanVleet

Care of the Newborn

Whoever says "all newborns look alike" has not been in a nursery for more than a few minutes. Each newborn has their unique physical features and personalities from day 1. A few things are common to newborns of all types, shapes, and sizes but there are a lot of natural variations and findings of interest. This chapter will attempt to serve as a guide in the general medical care of these young patients.

Newborn History

Care of the newborn starts in the form of a complete history and physical. However, the newborn's history is really one of the mother's and the pregnancy. Even in the developed world, obtaining this accurate history can be complicated by the inconsistent transmission of data from the chart of one patient (the mother) in the outpatient setting to that of another (the newborn) in the inpatient setting. But due diligence is necessary to fully assess the newborn and to provide effective preventative care.

Maternal History

Although covered elsewhere in this textbook, it is important to emphasize that there are many preexisting maternal conditions that may affect the fetus as well as the health and subsequent management of the newborn. Some notable maternal conditions that the pediatrician should be aware of are breast disease (including any interventions that might interrupt lactogenesis), congenital heart disease, diabetes mellitus, developmental hip dysplasia (DDH – increases risk of DDH in newborn), fatty liver disease (associated with long-chain acyl-CoA dehydrogenase deficiency (LCAD) in newborns), genetic/heritable disorders, hypertension, infections (such as malaria and tuberculosis), mental health, polycystic ovary syndrome, autoimmune diseases (i.e., systemic lupus erythematosus where the newborn should be screened with and EKG for heart block), substance use (including tobacco and caffeine), social concerns, and thyroid disease (both hyper- and hypothyroidism).

A detailed history of the pregnancy is necessary for caring for the newborn. Key elements include: (1) medications, tobacco, alcohol, and illicit drug use during pregnancy, (2) medical conditions during the pregnancy including diabetes mellitus, pregnancy-induced hypertension or preeclampsia, (3) duration of the rupture of fetal membranes, (4) analgesics or anesthetics administered during labor, (5) infections or illnesses (keeping in mind geographically specific risks such as malaria), (6) mental health, especially anxiety and depression, and (7) compliance with care. The history of previous pregnancies, including miscarriages, previous child with congenital heart disease or neonatal illness, such as group B strep (GBS) sepsis or severe jaundice, also provides important clues. The pediatric care provider needs to obtain the results of maternal screening obtained during the pregnancy as recommended by organizations such as the American College of Obstetrics and Gynecology (ACOG). Key elements that should be obtained and clearly documented in the newborn's, record for every pregnancy include the items listed in *Table 11.1*.

The results from any prenatal ultrasonography should be obtained as these help in confirming gestational age, assessing the risk for conditions such as Trisomy 21, spinal dysraphisms, and with some notable exceptions, congenital heart disease. One ultrasound finding worth discussing in detail is that of fetal renal hydronephrosis. Many cases of fetal hydronephrosis will spontaneously resolve during the pregnancy. There is some small uncertainty in the exact measurement that should raise pediatric concern but 15 mm is concerning for blockage and most would agree that those with a diameter >8 mm warrant follow-up. Certainly, any cases with associated oligohydramnios should be evaluated. Additionally, males with bilateral involvement warrant postnatal renal ultrasonography in the birth hospital stay to rule out vesicoureteral reflux or posterior urethral valves. However, due to the relative dehydration of newborns, even negative postnatal screening should be repeated at 3–4 weeks. Antibiotic prophylaxis is indicated for those with evidence of bilateral involvement in utero, abnormal renal

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Table 11.1
Maternal screening

Blood type and antibody screening	Rubella
Syphilis (RPR repeated in third trimester based on epidemiological prevalence)	Hepatitis B surface antigen
HIV (1 & 2)	TB (PPD)
Diabetes screening	GC and CT for high risk pregnancy
Urinalysis (especially if GBS positive)	GBS (rectovaginal screening within the last 5 weeks)
Domestic violence	Serum lead level (if high-risk category)

architecture, collecting system dilatation, documented reflux, or hydronephrosis on postnatal ultrasound. Due to the high concentration of the drug and general susceptibility patterns, prophylaxis with Amoxicillin suspension (20–25 mg/kg, PO, once a day) is effective and well tolerated. Surgical consultation with a pediatric urologist should also be obtained to help coordinate ongoing assessment. Antibiotic prophylaxis should continue until repeat imagining is obtained at 3–4 weeks, including a VCUG when indicated.

Maternal medications and the consumption of other substances need to be reviewed by the pediatric provider as some may cause problems in the newborn. Antihypertensive medications may cause hypoglycemia in the newborn. Serotonin uptake inhibitors, tobacco, caffeine, and opiate containing narcotics either prescribed or otherwise, may cause toxicity or withdrawal symptoms in the newborn (which is discussed in detail in Chap. 34, "Miscellaneous Disorders").

Gestational Age

The physical examination of the newborn starts with the assessment of gestational age and in utero growth. In industrialized countries, most pregnancies currently have accurate dating through confirmation of gestational age with prenatal ultrasound. As a general rule, determinations from the first trimester are accurate to within ±1 week, those in the second trimester within 2 weeks, and third trimester within 3 weeks. However, second and third trimester dating by ultrasound may substantially underestimate true gestational age in the presence of abnormal fetal growth. Additionally, prenatal gestational age estimates can be confirmed with the use of the New Ballard score (see Web site listed in the Resources). With the trained examiner, this scale has been shown to have good reliability and validity. With the best estimate of gestational age, the clinician can then plot the birth weight, the head circumference, and the length on a standardized graph to evaluate fetal growth.

Growth Assessment

In September 2010, the Center for Disease Control and Prevention (CDC) published a recommendation that from birth to 24-month age groups, all clinicians should use the 2006 World Health Organization (WHO) graphs. The WHO charts were designed as a reference (goal) growth curves within breastfeeding populations from a sampling of countries (Brazil, Ghana, India, Oman, and the USA). The clinician, when interpreting the growth of infants who are formula fed should be aware that breastfed babies do gain more weight in the first 2–3 months, and then stabilize or slow down thereafter. These graphs are available on the organization's Web site with links in the reference section. Although the WHO is an international reference, clinicians may choose to use normative graphs developed within their own country, as there may be ethnic and demographic differences – though these were surprisingly small in the diverse population included in the WHO study. Preterm and late preterm infants (those with completed gestational age of 34^{+0}–36^{+6} weeks) are best plotted on the Fenton graph, until 50 weeks of corrected age. There are also condition-specific growth charts for infants with diagnoses such as Trisomy 21 and Turner's syndrome.

Newborns are categorized as either appropriate for gestational age (AGA), small for gestational age (SGA), or large for gestational age (LGA) based on their percentiles. Classically defined, SGA is below the 10th and LGA as above the 90th percentiles. However, more recent cutoffs are using either the 5th/95th or 3rd/97th percentiles as these approach the two standard deviations used to define abnormal versus normal distributions, or those constitutionally small or large. Some have also suggested that customizable birth weight centiles would help to distinguish between those whose weight is constitutional from those at risk from pathologic SGA or LGA. Traditionally, SGA infants were also divided based on whether the growth restriction has been symmetric or asymmetric with sparing of the head circumference. In an attempt to better understand the significance of being SGA, researches looked at the mortality and morbidity rates in

a large US population-based sample for those SGA at preterm versus term birth. They found higher rates of mortality and morbidity for all preterm births and a greater adjusted relative risk in relation to SGA at term than preterm. However, they also found that the adjusted excess mortality risk from SGA declined until term with a plateau after 37 weeks. Both SGA and LGA status has inherent risks that need to be addressed and are fully discussed in a subsequent chapter (see Chap. 13, "The High-Risk Infant").

Newborn Physical Examination

For all newborns, the examination should start with a general observation of the state (sleeping, awake and quiet, awake and stirring, or crying), color (pink, acrocyanosis, perioral cyanosis, or central cyanosis), and pattern or work of breathing (e.g., grunting, flaring, retractions). From there, generally the best approach to examining the newborn is to keep them warm and let them lead the sequence of the exam. This means that if they are quiet, one starts with auscultation of the heart and lungs and palpation of the femoral pulses (crying makes these small pulses a moving target). But if they are crying or unsettled, then it is best to start with other parts and work on consoling them. But wherever one starts, it is best to continue the examination in your set sequence so not to miss critical parts when you are interrupted with crying or regular newborn care. Included in *Table 11.2* is a description of an approach to complete examination of the newborn. The next section of this chapter will highlight normal findings or variants found in newborns.

Skin

Through the course of sequentially unwrapping part of the newborn, the examiner will eventually get to visualize the entire skin surface of the newborn for rashes and other lesions. Common skin findings unique to the newborn are discussed below:

Erythema toxicum: This very common rash occurs in almost 50% of newborns. These transient flesh-colored to whitish papules on erythematous macules that appear over the first few days (with about two thirds occurring between 24 and 48 h of life) spread with individual lesions that come and go, and then resolve spontaneously. These can appear in any distribution and commonly coalesce on the face, abdomen, and back. These papules have no known cause but are very common and contain

Table 11.2
Key elements of newborn exam

General	*Abdomen*
• Wash hands prior to examining infant • Keep infant warm when examining (under warmer, blankets) • Support head/neck when moving infant • Assess maturity appropriately (term, preterm) • Assess intrauterine growth appropriately (AGA, SGA, LGA)	• Palpate for liver, spleen, kidneys, masses • Examine umbilicus visually; palpate for umbilical hernia
Order of exam	*GU*
• Auscultate heart and lungs while infant calm	• Boy: Examine penis for hypospadias; Palpate testes (undescended, hernia, hydrocele) • Girl: Examine hymen visually, labia
General appearance	*Anus*
• Note general appearance, distress, color, tone, spontaneous motor activity	• Visual check for patency • Visual assessment of placement of anus, measure if concerns
Skin	*Back*
• Examine skin; note birthmarks, jaundice, rashes if present	• Look for scoliosis, sacral dimple, or sinus tract
HEENT	*Extremities*
• Palpate fontanel (anterior, posterior), sutures, measure if concerns • Examine for cephalohematoma, caput • Check red-reflex • Examine pinnae: position, preauricular pits or tags • Check for septal dislocation or choanal atresia • Check for cleft palate (visually back to uvula and palpation)	• Palpate for femoral pulses • Examine hands/feet (creases, symmetrical size) • Examine gluteal and thigh folds for symmetry • Barlow/Ortolani tests
Chest	*Neuro*
• Palpate clavicles smoothness and symmetry • Auscultate heart • Auscultate lungs, work of breathing	• Root, suck, palmar grasp, cry • Examine for symmetric Moro

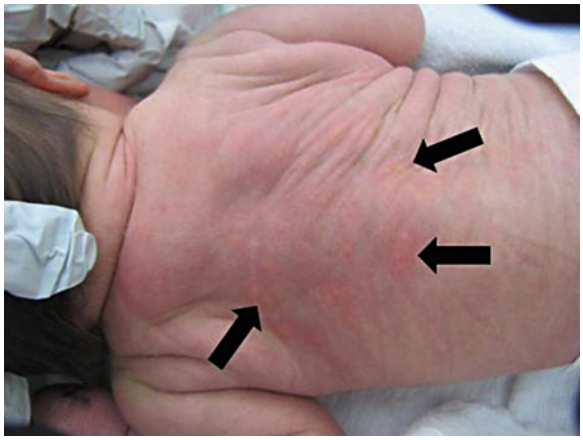

Figure 11.1
Erythema toxicum coalescing on the back of a 2-day-old newborn infant (Photograph by Cindy Klipfel, MD)

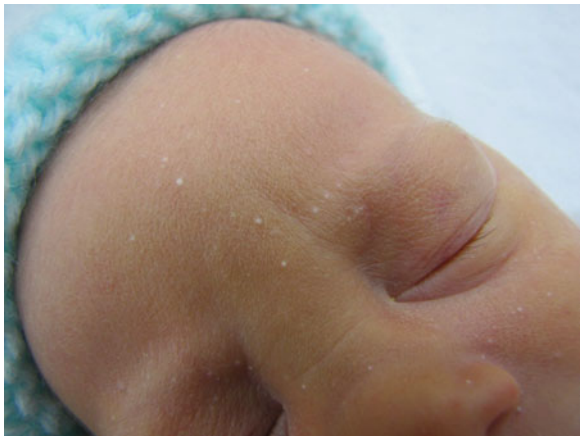

Figure 11.2
Classic scattered milia on a 2-day-old newborn (Photograph by Marcia W. Van Vleet, MD, MPH)

eosinophils, which suggest the involvement of a histamine pathway and as such might be a response to the general stress of delivery. The only rare potential complication of erythema toxicum is secondary infection (Fig. 11.1).

Harlequin change: This distinctive and well-demarcated color change is only seen in newborns and is a transient hemi color change with erythema on one half of the body and pallor on the other. It presents in the first few 2–5 days of life in approximately 10% of healthy newborns (although some have linked it to low birth weight, hypoxia, intracranial injury, prematurity, or use of prostaglandins). It may persist for 30 s to 20 min and has no long-term sequelae.

Milia: These are present at birth as white papules without erythema commonly occur on the face of up to 50% of newborns. They are inclusion cysts of sebaceous material with similar etiology to the Epstein pearls on the palate, Bohn nodules on the gingival ridge, and other inclusion cysts on any other midline structure including the foreskin of the penis. Milia can be seen on newborns born in any season but might have a slightly increased prevalence in the warmer months (summer in the northern hemisphere). Parent should be advised that these are not pimples and should not be squeezed but left alone. Of note, there are smaller sebaceous inclusion cysts that occur more frequently usually on the nose that are commonly although perhaps mistakenly called "milia" as well. Both "milia" lesions are self-limited and are reabsorbed by the body by 3 months of age (Fig. 11.2).

Neonatal acne: This is a relatively common transient form of the common teenage affliction that occurs in about 20% of infants and usually appears about 3 weeks after birth, although it rarely can be present at birth. It usually appears on the face, mainly on the cheeks, forehead, and chin as erythematous papules and pustules, or as white closed comedones. It is thought to be caused by transplacental passage of the mother's hormones and the newborn's own androgens. Male babies are more prone than females and spontaneous resolution is the rule. There is another form of acne that occurs after 3 months of age which is usually called infantile acne and seems to have a different etiology and is likely multifactorial, similar to the adolescent form.

Sucking blister: Occurring as the result of the fetus sucking in utero, these are apparent at birth. As such, their oval to circular shape and distribution on the dorsum of the hands, wrists, and forearms is characteristic. They may be fluctuant bullae that can be fairly large (up to 1.5 cm) which then quickly evolve to reveal a superficial erosion. There is a notable lack of other blisters, vesicles, or marked erythema that would otherwise suggest other etiologies. The residual hyperpigmentation or scaring heals on its own relatively quickly (Fig. 11.3).

Transient neonatal pustular melanosis (TNPM): These are small superficial white pustules on a non-erythematous base that easily unroof to reveal superficial, well-circumscribed scales and subsequent melanotic macules. Frequently, the pustules will be unroofed in utero or in bathing so only scales and freckling is observed on the initial exam. These can be frequently observed on the face, neck, abdomen, and lower back/sacrum. They also occur more frequently in those with darker skin coloring including Asian and African infants, with an overall incidence of

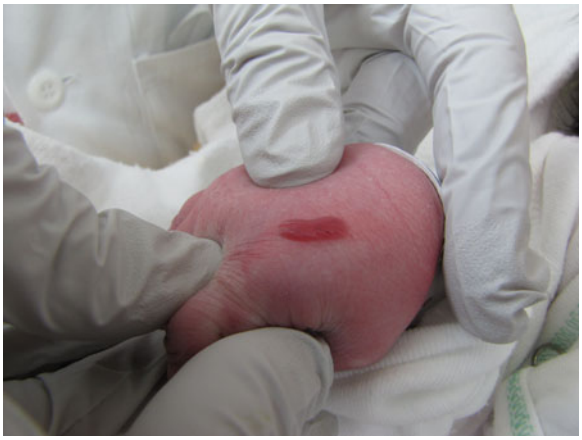

Figure 11.3
Characteristic appearance, shape, and distribution of a sucking blister seen on a newborn's initial examination (Photograph by Cindy Klipfel, MD)

0.2–4.4%. To confirm the diagnosis, it is best to observe lesions in all three forms (pustule, scale, freckle), but if gram stain were to be obtained, it would demonstrate neutrophils. Differential diagnosis of TNPM includes staphylococcal infection (usually erythematous and yellowish pustules), and herpes simplex virus (multiple forms classically with an erythematous base and clear vesicles that may cluster). It is very important in newborns to keep HSV in the differential diagnosis for any unknown rash as there are serious consequences if not treated immediately (discussed in detail in Chap. 27, "Neonatal infections").

Jaundice: This yellowish appearance to the skin and sclerae is very common in newborns and represents hyperbilirubinema, primarily due to physiologic increase in hematocrit of the newborn with shorter lifespan of neonatal erythrocytes and the slower/delayed conjugation in the newborn's liver. Most newborns, up to 60% of full term and 80% of preterm, will develop some degree of visible jaundice with most peaking in the first 3–4 days. For those born prematurely and those with extensive bruising or cephalohematomas, the maximal intensity may occur closer to 5–7 days of life. Although many newborns develop jaundice, its appearance in the first 24 h of life is pathological in nearly all cases. Jaundice generally moves from a cephalad to caudal progression and has historically been correlated to serum bilirubin levels with the loose rule of "Head= 5 mg/dL, chest =10 mg/dL, umbilicus=15 mg/dL" adapted from Kramer. Multiple studies have subsequently demonstrated; (1) a lack of agreement between examiners (at every level of training) and serum bilirubin levels, and (2) a very good negative predictive value for visual inspection (meaning no visual jaundice is predictive of not developing significant hyperbilirubinemia). Keren et al. recently found a negative predictive value of 98.6% for the complete absence of jaundice and the subsequent development of significant hyperbilirubinemia, defined as within 1 mg/dL of requiring phototherapy by the American Academy of Pediatrics (AAP) recommendations.

Birth marks: These should be described in quality and distribution in the newborn's documentation. Most are beyond the scope of this chapter/text but a few with unique characteristics in the newborn will be discussed.

Capillary hemangiomas: Although these are easy to diagnose later in infancy when they develop thickening, they can either not be apparent or have a subtle appearance that is difficult to diagnose in the newborn. When they are present in the newborn they can appear as a nondescript, slightly erythematous blanching macule or a spider like telangiectasia with irregular boarder and can frequently have a surrounding "halo" or blanching. Clinical course is sufficient for the diagnosis and management of most of these lesions. However, those over key organs such as the liver, spleen or spine, and when three or more appear on a patient warrant ultrasound investigation, as they may have deeper vascular connections. Capillary hemangiomas will progress over the first 6–12 months of life, and then will regress with 50% resolving by 5, and 90% by 9 years of age. Most need no intervention; however some will depending on location, such as if they interfere with binocular vision, obstruct airway or breathing, or lie over the liver, spleen or spine. Although a rare occurrence those lesions over the liver or spleen with vascular connections can become significant reservoirs potentially causing fluid shifts, and clinical instability. The development of large lesions can also rarely cause a Kasabach–Merritt syndrome with rapid platelet consumption and DIC (*Fig. 11.4*).

Nevus flammeus (aka Nevus Simplex, salmon patch): These erythematous macules with irregular boarders occur on the forehead, eyelids, glabella, nose ("Angel Kisses"), and most commonly on the nape of the neck ("Stork Bite"). They cross the midline and blanche, but otherwise can be difficult at times to differentiate in the newborn from more serious lesions such port wine stains which are usually unilateral. Those lesions that occur unilateral in the distribution of trigeminal nerve first branch (cranial nerve V1) covering the lateral canthus of the eye should be evaluated by ophthalmology and MRI imaging at 6 months of age to evaluate for the potential

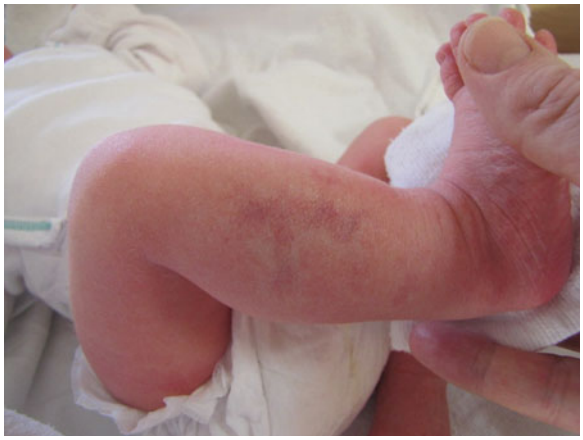

Figure 11.4
Although most are not apparent on the newborn, this capillary hemangioma found at birth on a newborn's leg is characteristic for its blanching central purplish macule or telangiectasia with surrounding hypopigmentation or halo. Upon questioning, the mother also had a capillary hemangioma that spontaneously resolved by 5 years of age (Photograph by Cindy Klipfel, MD)

Figure 11.5
Nevus flammeus or simplex in the classic "Angel Kiss" distribution in the midline of the forehead. Although slightly less visible on this photograph, the patient also had one just under the nose on the upper lip (Photograph by Cindy Klipfel, MD)

for Sturge Weber syndrome. Clinical course of nevus flammeus or simplex is equally distributed in three groups: those that essentially remain the same, those that lighten, and those that totally disappear (*Fig. 11.5*).

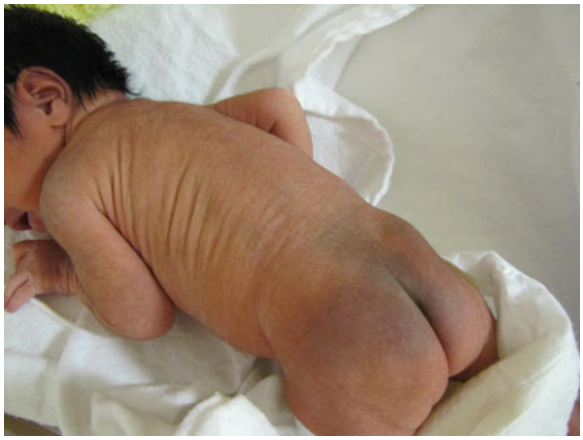

Figure 11.6
Newborn with characteristic distribution of a dermal melanocytosis over the lower back and sacrum, as well as one on the left shoulder (Photograph by Marcia W. Van Vleet, MD, MPH)

Dermal melanosis: These melanotic lesions commonly with irregular borders and pigmentation that can vary from brown, blue-gray, to blue-black. Previously called "Mongolian spots" these can occur in any location they are commonly found on the back, sacrum, arms and legs. They can be found on any newborn but occur more commonly in those with more melanin or darker skin (up to 80% of African and Asian newborns). They can even appear even slightly more bluish in parts and might be confused with a blue nevus. Many will fade in adulthood but some may not totally disappear. There is otherwise no specific management or treatment necessary for these benign lesions except to monitor for changes (*Fig. 11.6*).

Head and Neck

Careful inspection of the head and neck of the newborn includes observation for shape and palpation of normal structures such as the sutures, anterior and posterior fontanels, as well as any abnormal bony prominences. Molding and overriding sutures are common, but should be documented to help interpret changes in head circumference. Molding, which generally resolves in 3–5 days is the result of compression of the head in utero either from being engaged in the pelvis or from passage through the birth canal. Overriding sutures are also due to similar causes and should resolve in 2–3 weeks with the expansion of normal growth of the brain. Palpation of the

sutures can also reveal craniotabes or a sensation of a "ping-pong" which is usually a normal variant in the newborn especially those born at lower gestational ages. These usually resolve with the natural ossification of bones, but if delayed should raise suspicion for alterations in ossification.

Fontanels and suture lines: These should be palpated and their size assessed (see *Fig. 11.7*). Sagittal sutures can be open with a normal gap of up to ½ cm. Midway along the sagittal suture a third fontanel exists in 6.3% of newborns, with a higher percentage found in those with Trisomy 21 or congenital rubella. The normal metopic suture also can be open, however when extremely large or deep can be suggestive of delayed ossification, including hypothyroidism. The anterior fontanel should be palpated for firmness, bulging, or depression with the newborn's head elevated to 30°. The fontanels can be measured by finding the mean of the distances of the axis, as shown in *Fig. 11.7*. This measurement may increase slightly in the newborn period as the molding and overriding sutures resolve. In the USA, the average size of the anterior fontanel at birth is 2.1 cm (range 0.6–3.6 cm). This statistic varies in ethnic groups with African Americans reported as slightly larger with average 3.6 cm (range 1.4–4.7 cm) and a reported mean in a sample from India of 3.37 cm (range 2.2–4.5 cm). Posterior fontanel averages 0.5 cm in size but also has ethnic differences (Black/African American reported average also slightly larger at 0.7 cm). These differences may either be related to constitutional differences or may be an effect of nutritional status. The fontanels then close over the course of the next 1½–2 years with the posterior closing first (average of 2 months) and the anterior closing at an average of 13.8 months (reported as 9–24 months), with the study from India finding that 50% had closed sometime between the 12 and 15 month exams (91.3% closed at 2 years).

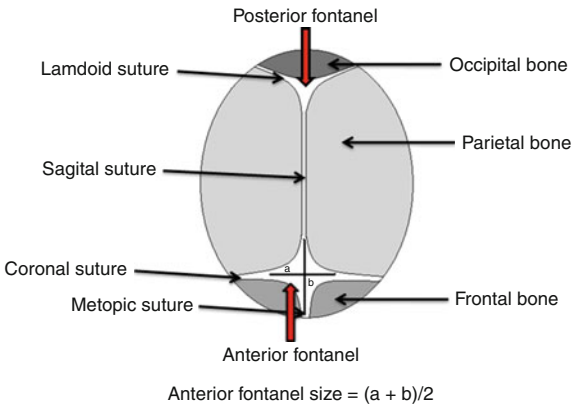

Figure 11.7
Schematic of newborn skull facing examiner (as seen from above). Note the demonstration of how to measure fontanel size as the average of the anterior–posterior and transverse diameters (Drawn by Marcia W. Van Vleet, MD, MPH [Adapted from Kiesler])

Ears: Complete examination of the newborn's ears includes visual inspection of the position, size, and external structures. With an otoscope internally visualize for the presence of a gray-white tympanic membrane. It will not be possible (due to small anatomy and likely obstruction by vernix) to distinguish the internal landmarks, but visualization is just to confirm the existence of the canal.

Eyes: The placement, position, spacing of the eyes, and size of the opening of the eyelids should be inspected visually. Normal palpebral fissure length in the newborn is over 5 mm. Rarely, the intercanthal distance may appear wide on the newborn due to a dacryocystocele. Although it might not be apparent on the first few days of life, the dacryocystocele classically presents with a bluish nodule palpable between the nose and inner canthus. Commonly, inspection of the eyes during the first few days is obscured by eyelid edema. Ideally, the eyes would be observed simultaneously for pupil symmetry and the red reflex. However, this is usually not possible in the newborn. The red reflex should be observed for any defects as well as white appearance suggestive of congenital glaucoma or retinal masses. In darker skinned newborns, the red reflex might be difficult to appreciate but should be visible in a dark room and may appear silvery in color. Visualization of the retinal vessels may be helpful in determining the presence of a red reflex. The eyes should be inspected for signs of infection (erythema, swelling, conjunctival injection, and purulent discharge). Please refer to the section below on the management of eye discharge.

Nose: The nose should be inspected for general symmetry or dislocation of the septum. Patency could be confirmed with movement of a thin tissue or cotton ball wisp under each nare while the contralateral nare is obstructed and newborn is sucking.

Mouth: It is important to visualize the newborn's mouth including the gums, the frenulum (both lingual and labial), the soft and hard palates and all the way back to the uvula. Having the newborn suck on the examiner's finger helps in assessing the pattern of tongue movements (milking front to back) and for how far the newborn is able to extend the tongue. Minimally, this would be past the gums, but ideally past the lips for optimal breastfeeding. Additionally, the hard and soft palate should be palpated to detect any submucosal clefts which

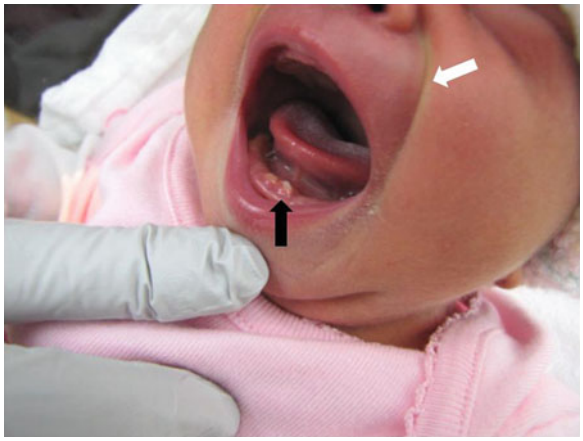

Figure 11.8
Newborn with two natal teeth found on the discharge exam. Note also the jaundice visible in the nasolabial folds when crying (Photograph by Cindy Klipfel, MD)

would not be detected on direct visualization alone. Absence of the uvula or a bifid uvula would also suggest a palate cleft. Common findings in the mouth include Epstein pearls (midline on hard palate), Bohn nodules (on gingivae), epulis, ranula, and neonatal teeth (*Fig. 11.8*).

Neck: The neck of the newborn should be inspected and palpated for tracheal deviation, and any masses (it is common to feel hyoid bone on newborns). Depending on their exact location, midline masses may represent thyromegaly or thyroglossal duct cysts, and those just anterior to the sternocleidomastoid muscle being brachial cleft (I, II, III) cysts or nodules.

Thorax

Examination of the thorax starts with auscultation of the heart and lungs. This can be done underneath the shirt so as to limit disruption of the calm newborn. Murmurs are very common in the first 24 h of life (up to 80%) and are discussed later in the chapter. Palpation of the point of maximal impulse is also important to help in the diagnosis of dextrocardia and hyperdynamic states (common during transitioning). Inspect the breathing pattern, shape (barrel, pectus, etc.), and symmetry of the chest. Palpate clavicles from sternal notch to acromion for continuity, smoothness, tenderness, and especially symmetry between to two sides. In the newborn period, the most sensitive presenting sign of a clavicular fracture is asymmetry and not the classic step off or crepitus (please refer to the Chap. 12, "Birth-Related Injury" for more details). Both males and females can have gynecomastia and possibly even milk discharge (a.k.a. "witches milk") from exposure to maternal estrogen in utero. Stimulation from palpation should be limited; however, other masses and mastitis can rarely occur.

Abdomen

Again examination starts with auscultation, this time for the presence of bowel sounds. Next, palpate for the size and texture of the liver, spleen, kidneys, and for the existence of any other masses. Visually inspect the umbilical cord for number of vessels, any erythema, swelling, or discharge. Variants to the umbilical cord include Wharton's jelly/umbilical hematoma (which can be fatal in utero but is of little significance in an otherwise stable newborn). Examination of the umbilical cord also includes palpation for abdominal contents and the base for any defects or bulging through the fascia consistent with an omphalocele or umbilical hernia.

Extremities

Examination of the lower extremities includes simultaneous palpation of the femoral pulses. The absence or asymmetry of the pulses would require immediate evaluation for coarctation of the aorta. However, in the newborn period, the pulses may exist even with a coarctation during the period of cardiovascular transition while the ductus arteriosus is open. Assess for symmetry of the major folds, knee height, leg length, and size of feet. Serial examinations of the newborn's hips are essential. Specifically, the Barlow (dislocation/subluxation) and Ortolani (reduction) tests should be performed to assess for hip stability. Commonly in the newborn, clicks or ligamentous laxity is felt without subluxation of the joint. Any actual movement of the hip greater than 5 mm or joint subluxation should be referred to orthopedics for placement in a Pavlik harness. Imaging in the newborn period is not necessary, but ultrasounds at 4–6 weeks of life may help to further assess those at increased risk (such as breech females and breech males with a family history) or the inconclusive exam. Orthopedics will follow serial hip ultrasounds to assess the progress of treatment. After about 6 months of age, MRI becomes the image of choice. Subluxation of other joints should also be referred to orthopedics for treatment and may be associated with certain syndromes. Grasp of all four

Figure 11.9
Newborn with postaxial polydactyly, on a thin pedicle with a nail (Photograph by Cindy Klipfel, MD)

extremities is important to assess both for neurological changes but also for general strength. Digits should be counted on both hands and feet. Although linked with many syndromes, syndactyly of the feet and polydactyly of the fingers, commonly occur in normal families. Thin-stalked supernumerary digits could be tied off by the pediatrician. When performed correctly (sufficiently tight and flush with the adjacent skin), the digit will drop off in several days, leaving no remnant. Creases of the hands and feet are important to assess as these may reflect in utero movements or conditions such as Trisomy 21 (non-pathognomonic single transverse palmar creases and prominent vertical crease on the foot) and fetal alcohol syndrome (hockey stick palmar crease) (*Fig. 11.9*).

Genitourinary (GU) System

External inspection of the female and male genitourinary system is important. For the female, this would include the clitoral hood, labia majora/minora, and the hymen. Frequently a newborn female will have milky white vaginal discharge, hymenal/vaginal tags, and possibly even serosanguinous vaginal discharge, all believed to be due to exposure to the mother's hormones (estrogen effects). Examination of male genitalia includes palpation of the testes. At least one of the testicles should be palpable in the scrotal sac. The absence of both should be investigated as soon as possible with ultrasonography. The penis should be examined for length (normal greater than 2 cm stretched on the full-term newborn), for chordee (curvature when erect), for penoscrotal web (a common form of chordee), for the course of the raphae, and for the location of the meatus. The raphae may be tortuous but should end near the 6 o'clock position. Raphae that do not should raise the examiner's diligence in looking for other GU findings as these rarely can be associated with hypospadias and torsion of the glans. The meatus should be midline central on the glans and no more than 5 mm in length. Longer length is suggestive of megameatus. Minor variations in the position of the meatus is normal; however, any that approach the edge of the glans or with other GU findings should be referred for urologic evaluation before circumcision. Frank hypospadias or epispadias are definite contraindications for circumcision. Ambiguous genitalia appear as a spectrum best summarized by Prader staging. However, the newborn physician should be aware that ambiguity of the genitalia has large social ramifications for the families.

Anus

Visual inspection of the anus and its position is important. Roughly, the anus should be about halfway between the scrotum or vaginal opening and the coccyx. The normal position of the anus has been described as the anal position index (API), or the ratio of the distance from anus to fourchette/scrotum to the total distance from the coccyx to fourchette/scrotum. In male newborns, this is a mean of 0.54 (95% CI 0.53–0.55) and in females it might be slightly anterior to this at about 0.45 (95% CI 0.44–0.46). Ratios less than the 95% CI warrant further investigation. Internal exam of the anus/rectum is not routinely necessary. Current recommendations that newborn screening temperatures be taken in the axilla (during the birth hospital stay) means that the physician needs to do careful inspection of the anus as the nurses may not detect cases of imperforate anus they would have with rectal temperatures (*Fig. 11.10*).

Back/spine

It is imperative to visually inspect a newborn's spine from head to sacrum for dimples, curvature (scoliosis), or masses. Simple dimples (<5 mm and superficial with visible base) in the intergluteal fold are very common. In the case of normal lower extremity tone and neurological exam, these do not warrant imaging. However, dimples that occur outside of the gluteal crease (more than 2.5 cm from the anus), or have any associated skin changes including tufts of hair, should be evaluated with an ultrasound in the first few weeks of life to rule out a tethered

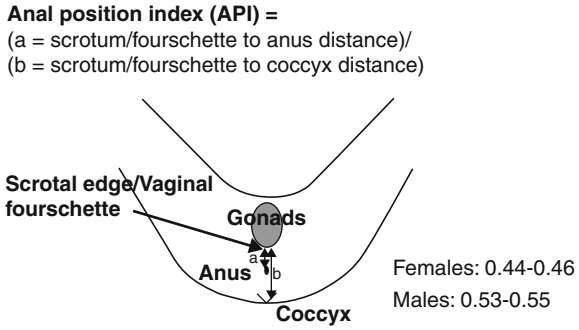

Figure 11.10
Schematic of how to measure the anal position index (API) (Drawn by Marcia W. Van Vleet, MD, MPH [Adapted from Davari])

cord. Any open spinal defects or neurological changes warrant immediate evaluation.

Neurobehavioral

The examination of the newborn needs to include a careful assessment of the general state, tone, posture, and reflexes. All newborns should have certain innate reflexes independent of gestational age. These reflexes include suck, moro, root, grasp of hands and feet, stepping, gallant, fencing, and deep tendon reflexes. At rest, the late preterm infant will have some flexion of their extremities, while full-term infants are more relaxed and extended when calm. Tone should be examined when the newborn is at rest, upright, and prone over the examiner's palm. The newborn when prone should not be either "stiff as a board, nor as floppy as a scarf." Preterm and even those late preterm infants will have subtle differences in their tone and magnitude of reaction to stimuli. But again, hypotonia and the absence of reactions to stimuli are abnormal at any gestational age. Newborns should show good state variability, by being able to go from sleep, to awake with cry, and back to calm during the exam. Poor state variability and "shutting down" are signs that the newborn is stressed. These stressed infants, as well as any found not to have intact reflexes, require immediate full evaluation including laboratory assessment looking for the existence of sepsis/meningitis and imaging of the central nervous system.

Newborn Screening

Primary screening in the newborn is very important to detect disease before irreversible damage or mortality. Some of these recommended screens are disease- or condition-specific (e.g., glucose screening for those SGA, LGA, or infants of diabetic mothers), and others are universal (e.g., hearing screening and metabolic newborn screening panels).

Glucose: It is recommended that newborns with risk factors for hypoglycemia such as those SGA, LGA, infants of diabetic mothers (IDM), IUGR, premature, evidence of perinatal stress or failure to adapt, and any with symptoms of hypoglycemia undergo routine glucose screening. Symptoms associated with hypoglycemia in the newborn include change in mental status (irritability, lethargy, stupor), poor feeding especially after feeding well, jitteriness or tremors, hypothermia, cyanotic spells or apnea, hypotonia, seizures, or coma. Screening can be done quickly and easily at the bedside with an appropriate whole blood point of care testing device. Not all such devices correlate well at lower glucose levels (some even at or below 55 mg/dL). Levels determined to require intervention should be confirmed by serum glucose analysis before but without delaying the first intervention. Variation in nursery protocols for the frequency of testing and the interpretation of results exist, as the evidence is not universally clear on the definition of hypoglycemia in the newborn. As summarized by Cornblath, the classic diagnosis of hypoglycemia in a newborn needs to meet Whipple's triad of (1) presence of characteristic clinical manifestations, (2) coincident with low plasma glucose level, and (3) resolution of the clinical symptoms once normoglycemia is established. However, it is probably that otherwise well, asymptomatic full-term newborns may tolerate glucose levels much lower than adults, questionably lower than preterm newborns, and perhaps below those previously suggested without adverse outcomes. What can be universally accepted is that newborns: (1) with hypoglycemia may present with a wide variety of nondescript symptoms or may be totally asymptomatic, (2) that any newborn with symptoms consistent with hypoglycemia should be treated more aggressively than those without, (3) that really low levels (less than $<$20–25 mg/dL (1.1–1.4 mmol/L)) require immediate correction with IV dextrose (please refer to Chap. for the IV management of hypoglycemia), (4) that prolonged hypoglycemia is probably worse than isolated events, and lastly (5) once hypoglycemia requiring intervention (cutoff is debatable but Cornblath suggests $<$36 mg/dL (2.0 mmol/L)) is documented, it is important to intervene, test to make sure that your intervention has worked ($>$45 mg/dL or 2.5 mmol/L), and then repeat testing prior to subsequent feedings (every 2–3 h) to make sure the newborn does not become hypoglycemic

again. Most newborns when feeding well will stabilize their glucose levels by 18–24 h of age, so primary screening in asymptomatic newborns after this time period is not necessary. Newborns that develop or continue with hypoglycemia warrant investigation for causes including sepsis and metabolic conditions including hyperinsulinemia.

Hearing: Universal hearing screening is recommended during the birth hospital stay as permanent hearing loss has been reported in up to 2.2 per 1,000 live births. Additional screenings to detect delayed onset hearing loss or deficits are based on risk factors (such as hyperbilirubinemia, exposure to ototoxic medications, cranial facial anomalies and associated syndromes, in utero infections like CMV, and family history) (see *Table 11.3*). Generally hearing screening in the newborn nursery in absence of the aforementioned risk factors can occur with otoacoustic emission testing (OAE). Those with risk factors, or failure of the OAE should undergo screening with the auditory brain stem response (ABR) testing. Early universal hearing screening has been demonstrated to be effective in detecting disease, in providing amplification when necessary at an earlier age, and in preventing long-term speech and developmental delays (including better performance on measures of social development, gross motor skills, quality of life, and overall scores). The Joint Committee on Infant Hearing in the USA has set forth the following goals for hearing screening programs: (1) that all infants

Table 11.3
Risk factors or markers associated with hearing deficits

In utero/familial factors	Neonatal/perinatal factors	Postnatal factors
In utero infections: • CMV (5–61%) • Rubella (50–76%) • Syphilis • HSV • Toxoplasmosis	Birth weight: • <1,500 g (2–10%) • <800 g (20%)	Prolonged NICU stay >5 days Seizures or apnea spells
Maternal exposure to aminoglycosides	Low APGAR scores: • 1 min: 0–5 • 5 min: 0–6	Respiratory markers: • Mechanical ventilation • ECMO • Persistent pulmonary hypertension
Family history of hearing loss during childhood	Syndromes: • Alport • Branchio-Oto-Renal • Cornelia de Lange • Jervell/Lange-Nielsen • Pierre Robin • Treacher–Collins • Trisomy 21 • Usher • Waardenburg (white forelock)	Hyperbilirubinemia • Requiring exchange • >22 mg/dL in BW >2,000 g • >17 mg/dL in BW <2,000 g
	Cranial facial abnormalities • Cleft lip/palate	Bacterial infections: • Meningitis (up to 30%) • Sepsis
	Neurodegenerative disorders • Charcot–Marie–Tooth • Friedreich ataxia • Hunter syndrome • Neurofibromatosis type I	Exposure to ototoxic medications: • Gentamicin (>2 days) • Tobramycin • Furosemide (Lasix) • Chemotherapy
		Birth-related or postnatal injury • Facial nerve • Head

should be screened by 1 month of age, (2) infants who do not pass should undergo additional hearing testing by 3 months of age, and (3) that infants diagnosed with hearing loss or deafness should start early intervention as soon as possible but no later than 6 months of age.

Hyperbilirubinemia: The most recent recommendations from the AAP in 2004 include the development of systematic screening processes that include universal risk assessments, parental education, early bilirubin level determinations that can be initiated by nursing staff based on clinical appearance, encourage and support of breastfeeding, and close follow-up for reassessment in the 48–72 h after hospital discharge based on the preceding determinations. Many, including the Canadian Pediatric Society and other opinion statements from experts, have recommended that each newborn have a determination of their bilirubin level prior to discharge from the birth hospital. Multiple studies have investigated universal screening with either a serum or transcutaneous bilirubin level in conjunction with hour-specific levels or nomograms and have found them to be effective in preventing excessive levels of hyperbilirubinemia. However, it is difficult to document the effectiveness of these universal screening methods in reducing the rate of kernicterus, because of its low incidence. Transcutaneous levels (TcB) should be confirmed with a serum level (TSB). Maisels et al. suggest obtaining a TSB level when the TcB is 70% of the TSB level for phototherapy, is greater than the Bhutani nomogram's 75th percentile (discussed below), >95% on a TcB specific nomogram, or when the TcB is >13 mg/dL after discharge.

In order to interpret the serum result obtained, we need to know if the newborn has any risk factors for hyperbilirubinemia. The effectiveness of all screening programs depends on close clinical follow-up and awareness that up to 10% of newborns do not follow the course predicted by these nomograms (primarily the late preterm infants and those with hemolysis of any cause). One of the most important of these factors is gestational age (preterm at largest risk, but those less than 38 weeks are also at increased risk), because the preterm infant is more likely to have both delayed hepatic clearance as well as inadequate intake. Other risk factors to consider in interpreting a bilirubin level are conditions that would cause increased hemolysis. Note, however, that all causes of hemolysis in a newborn do not cause the DAT to be positive (in 8%), and that some with a positive DAT may not have clinically significant hemolysis. Also it is important to determine how well the newborn is feeding, as poor breastfeeding (and hence decreased stooling) will increase the newborn's risk of hyperbilirubinemia. Additional risk factors are found in *Table 11.4*.

Table 11.4
Risk factors for the development of severe hyperbilirubinemia

Major risk factors	Minor risk factors
• Predischarge TcB or TSB in high-risk zone[a]	• Predischarge TcB or TSB in intermediate risk zone
• Gestational age 34–35 weeks[a]	• Gestational age 36–37 weeks
• DAT+ or other known hemolysis[a]	
• Jaundiced before 24 h	• Jaundiced before discharge
• Exclusive breastfeeding (especially if not well or with excessive [8–10%] weight loss)	
• Sibling received phototherapy	• Sibling with jaundice
• Cephalohematoma or excessive bruising	• Macrosomic IDM
	• Maternal age ≥25 years old
• East Asian race	• Male gender[b]

Adapted from the AAP 2004 Guideline
[a]More recent studies have consistently shown predischarge TcB or TSB and GA are most significant predictors. In general these studies have not included patients with known hemolysis
[b]Unsure clinical significance, and not included in more recent studies

Once these risk factors or the lack thereof have been determined, it is best to interpret the level based on an hour-specific nomogram. Lease and Whalen have a very thorough assessment of the current limitations and need for further studies in the interpretation of both TCB and TSB levels. The nomogram supported by the AAP's 2004 policy was developed by Vinod Bhutani in 1999. The clinician utilizing the Bhutani nomogram should be aware of its limitations: (1) it was developed with a discrete population of newborns (2,840 newborns at an urban hospital in the USA, none with a positive DAT, and none requiring phototherapy before 60 h or NICU level care), (2) most of the newborns did not have a bilirubin obtained before 18 h or after 132 h. The latest 2004 policy statement of the AAP on hyperbilirubinemia for newborns ≥35 weeks, extrapolated from this nomogram to make suggestions on when to start phototherapy and when to consider an exchange transfusion. These are very helpful tools in making decisions, but each case needs to be evaluated individually. The use of electronic versions of these tools has been shown to

help in the management, including a free Web-based program (www.Bilitool.org).

Patients who do not clearly fall in the group requiring phototherapy or in the low-risk group need a repeat level to establish a trend or ensure that dangerous level is not reached. The timing of this repeat level is again dependent on the risk factors, including gestational age and feeding, social situations, the family's ability to assess and act upon the potential signs and symptoms of worsening hyperbilirubinemia, and the risk category of the initial level with most requiring repeated testing within 1–3 days. If multiple levels have been obtained, then the rate of rise can be used in addition to all of the other clinical indicators, keeping in mind the levels of some infants will not track as predicted.

The specific management of hyperbilirubinemia will be discussed in ❯ Chap. "Neonatal Hyperbilirubinemia".

Metabolic/newborn screening: The goal of newborn screening programs is to utilize reliable testing methods to detect disease prior to the onset of symptoms, when the early detection and treatment has proven to be effective in preventing the complications of the disease. Traditionally these screening programs began as the Guthrie blood spot for phenylketonuria (PKU) testing in newborns. Subsequently, other disorders were added, including congenital hypothyroidism, hemoglobinopathies (sickle cell), biotinidase deficiency, congenital adrenal hyperplasia (21 hydroxylase deficiency), maple syrup urine disease, and classic galactosemia. In May 2006, an expert panel of the American College of Medical Genetics (ACMG) published an executive summary of their process for developing their recommended core panel of 29 different disorders and 25 secondary targets for universal newborn screening. The main criteria used in their recommendations were divided into three main categories: (1) clinical characteristics including incidence, burden of disease, and presentation in the newborn, (2) analytic characteristics of the screening test, and (3) the diagnosis, treatment, and management of the disease including the availability of health professionals with experience with the disease. Their panel is summarized in ❯ *Table 11.5*. Since these 2006 recommendations, others have put forward the addition of severe combined immunodeficiency (SCID) to the universal newborn screening panel.

Maternal/Caretaker Aspects of Care

Much of what occurs after birth during the hospital stay is teaching or anticipatory guidance for the mother and family members who will be primary caregivers. The care and education is meant to optimize the health of the newborn and well-being of the expanding family during this time of transition. The following sections are key teaching points for the general care of newborns in the hospital stay and anticipatory guidance for the first few days at home. Teaching in the birth hospital stay occurs through many different methods, one of these is in modeling the care the staff/nurses provide to the newborn.

Skin to Skin/Rooming-In

One of the earliest and most important interventions in the first few hours of life is to provide skin-to-skin (STS) contact between mother and newborn. As the newborn is most alert for the first 2 h of life, STS can occur as quickly after birth (once stabilized if resuscitation is necessary) and for as long as possible. When initiated within ½ h of life and maintained for at least 1 h, STS has been demonstrated to improve the newborn's regulation of temperature and glucose, as well as neurobehavioral benefits (less crying, more flexed movements). The STS benefits for mothers include increased demonstration of affection, more parental confidence, less breast engorgement pain, and less anxiety. Breastfeeding dyads with STS achieve effective breastfeeding twice as fast as controls, increased rates of breastfeeding at time of discharge, and longer duration of breastfeeding. Additional benefits for the dyad were found in Russia with the implementation of the World Health Organization's (WHO) Ten Steps to Successful Breastfeeding. Here, they showed that the benefits went beyond breastfeeding and found a reduced rate of infant abandonment. Step 7 of Ten Steps is to practice "rooming-in," where mother and infant are allowed to remain together 24 h a day. Studies have demonstrated that rooming-in increases milk volumes by day 4 and in some studies increased breastfeeding duration by 4 months. This early contact is theorized to better introduce the dyad to each other's cues and encourage on-demand feeding.

Feeding

Mothers should be encouraged to feed their newborns on demand. Ideally, this would mean feeding with those first early cues of hunger which include rooting, sucking on hands or lips, starting to wake and stir, before the newborn escalates to crying. It is not always possible to do this, but feedings are more successful when the infant is in a calm

Table 11.5
ACMG newborn screening panel

	Core panel (29)	Secondary targets (25)
Organic acid metabolism	Isovaleric academia (IVA) Glutaric academia type 1 (GA 1) 3-Hydroxy-3-methyglutaric aciduria (HMG) Multiple carboxylase deficiency (MCD) Methylmalonic academia (MUT) 3-Methylcrotonyl-CoA carboxylase (3MCC) Methylmalonic academia (Cbl A,B) Propionic academia (PROP) Beta-Ketothiolase deficiency (BKT)	Methylmalonic academia (Cbl C,D) Malonic academia (MAL) Isobutyryl-CoA dehydrogenase (IBG) 2-Methyl-3-hydroxybutyric (2M3HBA) 2-Methylbutyryl-CoA (2MBG) 3-Methylglutaconic aciduria (3MGA)
Fatty acid metabolism	Medium-chain acyl-CoA (MCAD) Very long-chain acyl-CoA (VLCAD) Long-chain L3 hydroxyacyl- (LCHAD) Trifunctional protein deficiency (TFP) Carnitine uptake deficiency (CUD)	Short-chain acyl-CoA (SCAD) Glutaric academia type II (GA2) Medium/short-chain l-3hydroxyacyl-CoA (M/SCHAD) Medium-chain ketoacyl-CoA thiolase deficiency (MCKAT) Carnitine palmitoyltransferase II (CPTII) Carnitine/acylcarnitine translocase deficiency (CACT) Carnitine palmitoyltransferase I deficiency (liver) (CPT IA) Dienoyl-CoA reductase deficiency (DE RED)
Amino acid metabolism	Phenylketonuria (PKU) Maple syrup urine disease (MSUD) Homocystinuria (HCY) Citrullinemia (CIT) Argininosuccinic acidemia (ASA) Tyrosinemia type I (TYR I)	Benign hyperphenylalaninemia (H-PHE) Tyrosinemia type II (TYR II) Defects of biopterin cofactor biosynthesis (BIOPT-BS) Argininemia (ARG) Tyrosinemia type III (TYR III) Defects of biopterin cofactor regeneration (BIOPT-REG) Hypermethioninemia (MET) Citrullinemia type II (CIT II)
Hemoglobin-opathies	Sickle cell (Hb SS) Hemoglobin S Beta Thal (Hb S/Beta Th) Hemoglobin S/C (Hb S/C)	Variant including Hgb E (Var Hb)
Other	Congenital hypothyroidism (CH) Biotinidase (BIOT) Congenital adrenal hyperplasia (CAH) Galactosemia (GALT) Hearing screening (HEAR) Cystic fibrosis (CF)	Galactokinase deficiency (GALK) Galactose epimerase deficiency (GALE)

Source: Adapted from Watson (2006) and the ACMG

alert state. It is very common for newborns to sleep for long periods of time in the first day and can continue to do so for a few weeks. During this time, there may be times when the mother needs to wake the newborn to feed. A healthy satisfied newborn will wake easily (or with the gentle to direct encouragement such as undressing or a diaper change), and then they will feed actively, only to quickly fall back to sleep when the feeding is complete. In general, the goal for breastfeeding would be 8–12 feedings a day, which averages out to be a rough goal of every 2–3 h. For newborns taking formula, which is not as easily digested, the feedings might be spread out longer to every 3–4 h, but then the diaper changes might not be as pleasant. The newborn's stomach is smaller than their fist (which is an estimated volume of 5–7 mL), it expands to a little less than an ounce by day 3 and to 2–3 oz by 10 days of life. Ameda has a Belly Balls Lactation Education Tool, which visually demonstrates this for mothers (volumes correspond to

marble, ping-pong ball, and extra large chicken egg). Another helpful way to help parents gauge volumes (which is more applicable for bottle feeding) is to expect up to ½ oz per feeding on day 1, and then increase feeding volume by ½ oz each day until they reach 2–3 oz each feeding by day 3–4, which many continue for the first couple of weeks.

Elimination and Weight

The adequacy of feeding can be determined by the adequacy of elimination (specifically stooling) and with daily weights. The number of wet diapers (urination) does not correlate as well with hydration or the adequacy of elimination as newborns do not concentrate their urine well. Diapers can also be weighed to strictly quantify elimination; however, this is not necessary with the otherwise well newborn. A rough rule of thumb to help evaluate the adequacy of urination would be for one wet diaper each day for every day old (e.g., one on day 1, two on day 2, three on day 3, etc. until they get to seven to eight wet diapers by a week of age). Less than that would be suggestive of dehydration, which in the newborn is usually due to inadequate intake. Most full-term newborns will pass meconium in the first 24 h (late preterm by 36 h). Those who have not should have their feeding reviewed and have careful examination of their abdomen and anus. Findings consistent with obstruction such as abdominal distention or feeding intolerance should be urgently evaluated with the concurrent initiation of intravenous fluids while the newborn is being evaluated and remains NPO. Those without evidence of obstruction can be examined and gently stimulated with a small gloved digit (inserted no more than 2 cm). If there is still no passage of meconium, then the newborn should be evaluated with an AP abdominal radiograph to evaluate for the possibility of meconium plug, meconium ileus (associated with cystic fibrosis), Hirschsprung's disease, or other lower abdominal obstruction (imperforate anus).

Normal stooling pattern is at least one good size stool a day (size of a quarter), with stool transitioning from meconium by day of life 3–4. Ideally, the newborn who is breastfeeding well will have at least three, and up to eight to ten stools a day (the gastrocolic reflex can produce stool with every feeding). Breastfeeding newborns should have this frequent stooling, but may at about 1 month of age develop their own stooling pattern which can even be less than once a day. Until that time, breastfeeding newborns should be evaluated for dehydration in the presence of decreased stooling. Newborns will make funny faces while stooling (including bearing down and getting red), which is normal as long as the stools are soft and not hard little pellets. The breastfeeding newborn's stool will transition from meconium to yellow seedy. The formula feeding newborn's stool may transition from meconium earlier (perhaps day 1–3) but the resulting texture and color is not as predictable. Weighing newborns daily in the birth hospital setting is an additional tool to evaluate the adequacy of feedings. The average breastfeeding newborn will lose about 2–3% of their birth weight each day with an expected total average loss of 6–8%. Those who lose more than 3% in a day, or who are between 8% and 9% below birth weight should have their latch and feeding history reviewed. This is a good time to make any necessary interventions, including getting lactation services involved to help with the development of a feeding plan. This could also include more frequent weights to help assess whether the feeding plan/interventions are helping. Ten percent or more weight loss would currently be considered excessive weight loss in the USA, and one would want to make sure the mother is supplementing, ideally with expressed breastmilk (EBM), and depending on the clinical scenario, possibly formula if EBM is not available. Newborns with more than 10% weight loss should have their hydration status evaluated with a clinical exam. And those clearly above 10% weight loss and not improving (especially with other findings like those readmitted with hyperbilirubinemia) should have their electrolytes (especially sodium) evaluated for hypernatremic dehydration. Prior to discharge from the birth hospital, it would be best to prove that this plan can stabilize the weight loss, if not demonstrating minimal weight gain. These dyads will need careful follow-up to make sure the feeding and weight is improving. The late preterm infant (LPTI) is even more susceptible to these feeding challenges.

Umbilical Cord Care

Topical care of the umbilical cord has many cultural or traditional variations. Some of these may have some benefit (perhaps olive oil) and others (coal, spices, cow dung, ash, machine oil, turmeric, mustard oil, and dried banana) may be harmful. It is theorized that the earlier the cord stump separation the better to reduce the risk of introducing microorganisms as the necrotic tissue of the stump is an excellent medium for bacterial growth. In addition to best cord care practices in preventing omphalitis, it is important to provide Tetanus toxoid

immunization to pregnant women, clean birthing surfaces, clean cord tying and cutting devices, thermal regulation (with skin-to-skin contact and a hat), and employ hand washing during the delivery and newborn care. Hand washing by the birth assistant and before cord care has been shown to be the most effective in preventing omphalitis in developing countries. Many have suggested that in otherwise clean conditions with good hand washing, that serial inspections or "dry" cord care is viable option. Recent literature reviews have not found a difference between topical agents (triple dye, alcohol, chlorhexidine, etc.), and most have favored dry cord care in developed countries.

The WHO has developed and is now distributing clean delivery kits (CDKs). Their program also promotes keeping the cord clean and dry. However, the feasibility and effectiveness of using topical antimicrobials in developing countries with perhaps less clean conditions or where traditional cord care methods might be harmful is currently being investigated. There is preliminary evidence from the Projahnmo Study in Nepal that cord cleansing with 4.0% chlorhexidine in the first 24 h of life could reduce neonatal infection by 87% and mortality by 34%. More data are needed to promote this as a worldwide initiative, but the preliminary results are encouraging.

Safe Sleep Environment

Newborns can spend up to 20 h a day sleeping in the first few days of life and continue to need lots of sleep each day for the first few months. Therefore, sleep positioning and the sleep environment are very important to the newborn's health. Public health interventions with the "Back to sleep" program have demonstrated a dramatic decline in the rate of sudden infant death syndrome (SIDS) in the USA. However, the uptake of this message has been variable in different ethnic and cultural groups with a variety of barriers identified. Additionally, worldwide there are a variety of cultural practices related to newborn sleep environment. Many cultures practice bed sharing between the newborn and mother without evidence of effect on infant mortality or rates of SIDS. However, these may be confounded by the fact that these mothers may be breastfeeding more with its likely protective effects against SIDS. In the USA, there is strong epidemiologic evidence that bed sharing with adults raises the risk of SIDS. This is especially so when co-sleeping in waterbeds or soft surfaces like couches or chairs, as well as when the co-sleeping adult has ingested substances that alter alertness (like alcohol, as well as prescribed, over the counter or illicit drugs). Expansion of the safe sleep educational program includes parental education about the risks of co-sleeping, smoking cessation, and modeling of the safe sleep environment of the child. It has been demonstrated that when nursery staff practice placing newborns supine in a safe sleep environment, there is better adoption of these recommendations. The safe sleep environment for a newborn should be located as close to the mother as possible to promote breastfeeding while being separate from the adult bed. The safe sleep environment should be free of loose bedding, fabric near the head, stuffed animals or pillows, bumpers, and fluffy blankets or comforters.

Injury Prevention/Shaken Baby Syndrome Awareness

Shaken baby syndrome (SBS) is a devastating condition of brain injury due to violent shaking of a newborn or young child. Symptoms of SBS include apparent life-threatening events (ALTEs), retinal hemorrhage, subdural hemorrhage, permanent brain injury, and a mortality rate of close to 40%. Identified risk factors include male infant, firstborn, twin or other multiple, prematurity, low birth weight, difficult temperament/difficult to console, in utero exposure to substances causing withdrawal, drug or alcohol use, history of domestic violence, young unmarried mother with less than a high school education, and living with nonrelated adult. Some hospital-based programs are showing promising results with educational interventions that discuss the dangers of SBS, give information about child development, and provide suggestions toward nonviolent behavior management. These management plans need to help the parent or care provider recognize their own limitations, acknowledge their stress, and develop a plan in advance of when these situations arise.

Discharge and Post Hospital Follow-Up

The pediatric care provider should make sure that the mother and family have a good understanding of the care of their newborn. This would include discussion of both issues of safety and general care of their newborn. Ideally, this is done over more than one visit in the birth hospital, as research has demonstrated that postpartum mothers do not retain as much information as other patients. It is important to tailor these instructions to

match the infant's clinical scenario and to meet the parents' educational needs. At a minimum, the following safety issue should be covered in each discussion: how and when to contact the pediatric care provider after discharge, the signs and symptoms of jaundice, omphalitis, respiratory distress, sepsis, and how to take a temperature. Additional care topics that should also be reviewed include feeding, elimination, cord care, safe sleep positioning, and if applicable car seats and circumcision care. *Table 11.6* contains a sample list of topics discussed as discharge anticipatory guidance.

The AAP recommends that every newborn gets seen by a trained professional 2–3 days after discharge from the birth hospital to minimize the risk of excessive bilirubin levels and to encourage optimal breastfeeding. This can be done either by a physician or by a physician extender/nurse specialist experienced in newborn care. This and subsequent scheduled follow-up is likely more important in preventing hyperbilirubinemia and its consequences than many other interventions. This visit establishes the medical home as an outpatient and allows the physician to assess the newborn when it is at the most risk for hyperbilirubinemia. For those newborns with additional concerns such as risk factors for hyperbilirubinemia, difficulty breastfeeding, excessive weight loss, those discharged prior to 48 h of life, the LPTI, or with concerns about either the social situation or about maternal adjustment should be seen in 24–48 h after discharge. While there are many things to assess about the physical health of the newborn at this visit, it is also great time to reinforce the strengths of the dyad as the first few nights at home may leave parents with more questions than answers.

Table 11.6
Sample topics for discharge anticipatory guidance

Safety issues:
• How to call pediatrician and first appointment in 2–3 days (time/date)
• How to take rectal temperature, availability of thermometer, temperatures to notify PMD [if <97.5°F (36.4°C) or >100.4°F (38.0°C) rectally]
• How to evaluate for jaundice, to call PMD if approaches umbilicus or symptoms of hyperbilirubinemia develop
• Safe sleep environment
• Back to sleep, safe bedding, SIDS prevention
• Car seat (backward for at least the first 2 years and minimum 20 lbs, backseat in middle), where to get checked
• Smoke detectors (check each month)
• Temperature of hot water heater (<120°F)
• Injury prevention/SBS (shaken baby syndrome)
Care issues:
• Care for umbilicus, signs of infection, and when it should fall off
• Bathing
• Feeding: breast, bottle
• Urination and defecation (expected numbers and consistency)
• Dressing
• Sibling rivalry/adjustment
Parent concerns:
• As directed by discussion, give ample time and encourage the parents to ask questions

Management of Common Newborn Problems

There are many problems that occur in otherwise well newborns. A few that occur very commonly are discussed below.

Eye Discharge

Erythema, swelling, discharge, and conjunctival injection is consistent with conjunctivitis. In the newborn, this can be due to chemical conjunctivitis or infection. Factors to consider when evaluating neonatal conjunctivitis include organisms in the maternal birth canal, identification and treatment of maternal infections during pregnancy, adequacy of ocular prophylaxis, and potential trauma to the eye. Chemical conjunctivitis occurs soon after birth, lasts between 24 and 36 h, and is a reaction to the administration of ocular prophylaxis. There may be a linear erythema of the eyelids continuing onto the face or temples due to irritation of the surrounding skin. Incidence of chemical conjunctivitis is slightly higher with silver nitrate than erythromycin ointments. The presence of purulent discharge suggests an infectious etiology with Chlamydia trachomatis, the most common cause, followed by Neisseria gonorrhoeae, and then other bacterial and viral causes. Distinguishing between chlamydial and neisserial causes can usually be made based on timing and clinical appearance. Gonococcal conjunctivitis occurs earlier usually beginning within 24–48 h of life and is marked by profuse purulent discharge and eyelid edema. Chlamydial conjunctivitis appears later, most between 5 and 7 days (but can present up to 21 days)

with discharge that is initially watery progressing to mucopurulent. Although chlamydial conjunctivitis may be self-limited, it is important to test for nasopharyngeal colonization as treatment is necessary to prevent the development of pneumonitis. Diagnosis of bacterial conjunctivitis should include bacterial cultures and direct immunofluorescent antibody testing versus chlamydia. Treatment of chlamydial conjunctivitis requires oral antibiotics. Use of oral erythromycin has been associated with infantile hypertrophic pyloric stenosis but is still recommended by the AAP for treatment of chlamydial conjunctivitis after appropriate risk counseling with the parents. Treatment of gonococcal conjunctivitis requires systemic antibiotics, and with full evaluation for systemic disease in an intensive care unit. Additionally treatment of disseminated gonococcal disease requires treatment for 7 days and one should consider Cefotaxime instead of Ceftriaxone in newborns with significant hyperbilirubinemia (*Fig. 11.11*).

Viruses specifically herpes simplex virus (most commonly Type 2 but also Type 1) can cause neonatal conjunctivitis with serous to serosanguineous discharge. These may or may not appear with characteristic vesicles surrounding the eye. Prompt evaluation for CNS and disseminated HSV disease is prerequisite for determining length of treatment. Lastly commonly occurring clear watery to slightly yellowish discharge or tearing without conjunctival injection is consistent with dacryostenosis or lacrimal duct stenosis. Treatment includes warm compress or massage from outer to inner canthal folds to "milk the duct." Occasionally, these can become secondarily infected and would need topical antibiotics. A summary of the presentation and treatment of the major causes of neonatal conjunctivitis appears in *Table 11.7*.

Jitteriness

The newborn that is jittery or has an exaggerated Moro reflex should be evaluated for hypoglycemia or, less commonly, electrolyte abnormalities. With normal serum levels, the examiner should obtain a detailed obstetrical history to include risk factors for infection and potential exposures to medications (including SSRI's, opiates, etc.), illicit drugs, tobacco, and caffeine. The newborn should have a careful exam for signs and symptoms of infection and a complete neurological exam. Newborns with specific risk factors for infection (i.e., GBS positive mother, history of HSV or concurrent infection, maternal fever, prolonged rupture of membranes, chorioamnionitis, etc.) should be evaluated for infection and those with clinical manifestations of infection should be started on systemic antibiotic therapy. In the absence of risk factors or clinical manifestations, serial examinations should occur. Those with increasing jitteriness, additional neurological findings, or change in mental status including poor feeding should be evaluated for both CNS infection as well as neuroimaging to evaluate for a potential bleed or lesion. Once the other more worrisome etiologies have been eliminated as causes, and based on exposure history, one can start to think of neonatal withdrawal as the possible cause. In the case of opiates, this is described as neonatal abstinence syndrome (NAS) but has also been associated with other more commonly occurring substances such as SSRI, tobacco, and caffeine (see Chap. 34, "Miscellaneous Disorders" for a more detailed description). Lastly, there is a small subset of newborns who are neurobehaviorally more immature, but otherwise normal. These newborns and their families benefit from a complete evaluation with an occupational therapist performing a Neonatal Network Neurobehavioral Score (NNNS), with

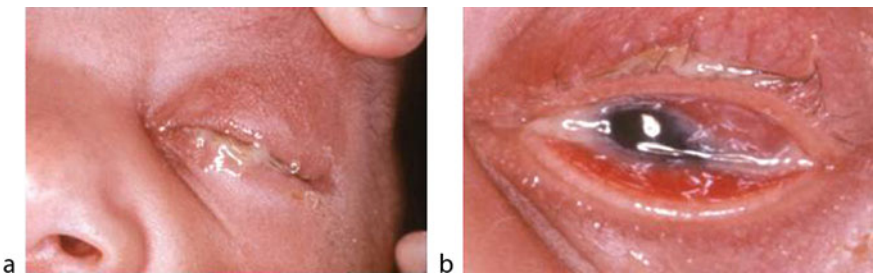

Figure 11.11
Newborn with conjunctivitis cause by Neisseria *gonorrhoeae*. (b) is a close up of the same patient in (a). In (b), note the collection of purulent eye discharge in the inner canthal region right after wiping the eye (Photograph from the patient files of James F. Padbury, MD)

Table 11.7
Summary of characteristics of common causes of neonatal conjunctivitis

Type of conjunctivitis	Agent/organism	Typical onset of symptoms	Description of discharge	Treatment
Chemical	Silver nitrate, or erythromycin prophylaxis	Birth to 1 day	Watery	Self-limited, warm compress
Bacterial	Chlamydia trachomatis	4–10 days (up to 21 days)	Watery then mucopurulent	Erythromycin PO (50 mg/kg/day in four divided doses per day for 14 days)
	Neisseria gonorrhoeae	1–4 days (up to 21 days)	Purulent and profuse, "hyper purulent"	Ceftriaxone IV or IM (25–50 mg/kg not to exceed 125 mg, once) and saline eye irrigation until resolution of discharge
	Gram positive including S. aureus, Streptococcal species, etc.	4–7 days (may be 2–21 days)	Mucopurulent (moderate)	Erythromycin 0.5% ointment topically to eyes four times a day for 3–7 days
	Gram negative including Haemophilus species, E. *coli*, etc.	5–10 days (may be 2–21 days)	Mucopurulent	Trimethoprim-polymyxin B or Gentamicin eye drops
Viral	Herpes Simplex Virus (Type 2 more common then Type 1)	6–14 days (may be up to 6 weeks of age)	Serous to serosanguineous	Acyclovir IV, (60 mg/kg in 3 divided doses per day for 14 days) and 1% trifluridine or 3% vidarabine topically to eyes

demonstration of modifications to care that would benefit their newborn. These newborn warrant close follow-up and prompt referral to early intervention services with any ongoing concerns.

Heart Murmur

Murmurs are very common in newborns, and most will resolve spontaneously. Roughly 80% of infants will have a transient murmur related to closing PDA in the first 24 h of age. The risk for pathologic murmurs/congenital heart disease (CHD) is higher in newborns with other anomalies, newborns with first-degree relatives with CHD, certain in utero exposures, and in infants of diabetic mothers (IDMs). Up to 30% of IDM newborns will have some form of CHD. Once a murmur is detected, subsequent action depends on its nature and a determination of whether it is a cause for concern. "Transitional murmurs" are common, have no clear structural basis and resolve spontaneously. Grade I–II, ejection (crescendo–decrescendo) murmurs, musical or vibratory in quality that are best heard on the left sternal border in an otherwise well newborn with normal femoral pulses, color, and capillary refill (<3 s) are usually benign. More worrisome murmurs are those associated with clinical signs or other anomalies, are harsh or blowing, holosystolic, obscure S1 or are diastolic, and grade III or higher. Transitional murmurs may start off being loud at a Grade III but then will generally decrease in intensity, sometimes even disappearing over the first 24 h. In contrast, pathological murmurs remain loud, intensify, or may develop later. In the first few days of life, murmurs may be very dynamic, due to changes in pulmonary vascular resistance.

For any worrisome murmur, or one that persists beyond 24–48 h, additional information should be obtained. The first step (when available) is to obtain a pre- and postductal pulse oximetry. The postductal SPO_2 in a full-term newborn after 4–6 h of age should be >95% on room air. Some authorities are proposing that a postductal saturation should become the fifth vital sign, or part of universal newborn screening. In general, the pulse oximetry has a good positive predictive value, and will detect about 98% of major congenital heart defects in the newborn period. However, the negative predictive value is not as good, because not all significant heart defects present with right to left shunting. The second step in evaluating the newborn's heart murmur is to obtain upper and lower extremity blood pressures. Presence of good femoral pulses does not rule out coarctation or interrupted arch, because flow across an open PDA may provide adequate systemic blood flow initially. The systolic pressures of the lower extremity should be higher than in the upper extremities (think higher pressure

downstream unless there is a dam blocking flow). Systolic pressure in the upper extremity that are ≥9–12 mmHg higher than the lower is worrisome. Blood pressure is highly state-related in the newborn, so abnormal blood pressures should generally be repeated and proper cuff sizes confirmed. If the screening SPO_2 and blood pressures are not reassuring, the newborn should be referred for cardiology evaluation and an echocardiogram. If the screening SPO_2 and blood pressures are reassuring, the newborn with a non-worrisome murmur and an otherwise normal exam can be followed with serial exams. In areas without access to cardiology or echocardiograms, additional information can be obtained from an EKG, looking primarily for right-axis deviation greater than expected for age (in the LUQ), as well as a PA and lateral chest radiograph to evaluate the cardiac silhouette for size (watch the thymus shadow which is best distinguished on the lateral), location (dextrocardia), shape (i.e., that classic "egg on a string" from transposition of the great arteries (TGA) and "boot shape" of tetralogy of Fallot (TOF)). The lung fields are assessed for pulmonary vascular markings (decreased in right-sided obstructive lesions or increased in mixing lesions with increased pulmonary blood flow). (For additional information on pediatric cardiology refer to ❯ Chap. "Pediatric Cardiology").

Omphalitis

Omphalitis or infection of the newborn's umbilical cord presents as discharge or oozing (4%), spreading erythema (6%), swelling, warmth, and tenderness (7%) of the cord stump. Redness extending more than 2 cm from the cord is generally consistent with infection. Mean time to presentation is about 2.5 days with a range from 1 to greater than 8 days. Estimates of omphalitis range from 1% to 16% of newborns depending on the criteria used in defining the diagnosis. The etiology of omphalitis traditionally includes *Staphylococcus (*both *aureus* and *epidermidis*), *Streptococcal* (group A), *Klebsiella pneumoniae*, *Escherichia coli*, *Proteus mirabilis*, and anaerobic *Bacteroides and Prevotella organisms*. With the implementation of antistaphylococcal cord care techniques such as triple dye, hexachlorophene, and alcohol, the incidence of gram-negative organisms have been increasing, although this may not be the case in developing countries. In most cases, omphalitis remains a localized infection, but complications can include neonatal sepsis and meningitis. Additionally, there can be rapid progression of the infection to the abdominal wall causing cellulitis and necrotizing fasciitis, which have a high risk of mortality. Treatment of omphalitis includes prolonged parenteral antibiotics.

Conclusion

Care of the newborn demands an attention to details, both in obtaining the maternal history and in completing the early exams as many subtle differences would be indications for adjustments in care to promote the well-being of the family and the newborn's development over time. This includes screening both in the primary or universal sense of all newborns (such as hearing and NBS programs) but also secondary screening for specific diseases (such as infection, for hypoglycemia in the IDM, and cardiac workup or screening with a murmur). Public health both nationally and internationally has its roots in maternal child care, and as such has had great impact in reducing infant mortality. Much of the care currently provided in nurseries is evidenced based only in that it has stood the test of time, and little of what is done has ever been scientifically evaluated. At present, newborn care is far from proven best practices. But we are moving toward that direction as exemplified by the work to determine the best systematic methods for screening for hyperbilirubinemia to prevent chronic bilirubin encephalopathy (kernicterus), and in evaluation of cord care techniques in real practice and developing countries. Until these and many other answers are obtained, one should continue to work toward providing the best of what is known so far, and in encouraging families to embrace the care of their newborns.

Resources

New Ballard Score: http://www.ballardscore.com/

World Health Organization:

(a) Evidence for the ten steps to successful breastfeeding: http://whqlibdoc.who.int/publications/2004/9241591544_eng.pdf

(b) Growth Curves: http://www.who.int/childgrowth/standards/en/

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12 Birth-Related Injury

Marcia Wenner VanVleet

Birth-related injury is broadly defined as a physical injury sustained by a newborn during the process of birth. This definition places no blame or fault, but recognizes that in many cases, such injuries are unpredictable and perhaps have unavoidable outcomes. Estimates from the USA are that approximately 2.6% of births will end with some kind of injury. The severity of birth-related injury varies greatly from the minor and temporary, such as ecchymosis, swelling, or superficial lacerations, to the more serious longer lasting conditions such as brachial plexus injury, and even a fatal outcome. This chapter will describe those conditions that are most likely the result of mechanical forces on the newborn through the birth process.

Incidence

In many countries, the rate of birth-related injury has markedly decreased due to improved prenatal care, greater use of imaging, and presence of skilled attendants at deliveries with the tools necessary for intervention (both obstetrical and neonatal), including cesarean sections, fetal monitoring, and newborn resuscitation. In the USA, an estimate of overall birth-related injury indicated a rate of 37.0 per 1,000 in 1989–1990 and 29.2 per 1,000 in 1999–2000. However, birth-related injury continues to occur with the most sophisticated prenatal diagnosis, the best obstetrical practices, and even in the absence of any identifiable risk factors, occurring at times in utero. It has been suggested that despite optimal care, the birth-related injury rate will never be zero and that perhaps its low might be closer to 18 per 1,000 births as seen in normal, uncomplicated in-hospital births. This should not be surprising, as the process of birth requires the fetus to squeeze through the narrow confines of the maternal bony pelvis, propelled by the powerful contractions of the uterine myometrium and using the presenting part as a battering ram to dilate the soft tissues. However, these considerations should not prevent us from seeking to decrease birth injury as close as possible to this irreducible minimum. It should be noted that while cesarean delivery is associated with lower rates of birth trauma, it does not eliminate it.

In the USA, the reduction of infant death and injury during delivery has gained much attention including a Sentinel Event Alert from the Joint Commission in July of 2004. In an attempt to reduce the preventable injuries, the Agency for Healthcare Research and Quality (AHRQ) in the USA has developed, through expert consensus, a group of Patient Safety Indicators (PSI's) which includes seven types of birth-related injury. These include (1) subdural and cerebral hemorrhage, (2) epicranial subaponeurotic hemorrhage, (3) other injuries to skeleton, (4) injury to spine and spinal cord, (5) other cranial and peripheral nerve injuries, (6) other specified birth trauma, and (7) birth trauma unspecified. Using hospital discharge data from a 2004–2005 USA sample, Moczygemba et al. found a PSI rate of 2.45 per 1,000 and an overall birth trauma rate of 25.85 per 1,000 (*Table 12.1*). Reported rates of birth-related injury vary greatly based on the year of publication, study population (hospital-based versus larger population-based samples), the specific conditions included in the study, and geographical location. In the USA, estimates for overall birth trauma rates vary widely from 0.2 to 37 per 1,000 births. A recent robust estimate comes from a cross-sectional study using in-hospital birth discharge diagnosis codes from 2003. In this study, Sauber-Schatz found a raw data estimate of 50 per 1,000 births which, when weighted by hospital characteristics, yielded an estimate of national rate of birth-related injury of approximately 29 per 1,000 births.

International estimates of overall birth-related injury rates vary greatly based on the country and the year. Estimates from developed countries range from Salonen's multiyear estimate in Finland publish in 1990 with 31.6 per 1,000 to that of Awari's et al. in 2003 with a rate in Saudi Arabia of 6.7 per 1,000. These differences might reflect time-related changes as Zeck et al. looked at similar time periods in Austria and found a drop in incidence or birth-related injury of any sort from 24.6% (246 per 1,000 births) in 1989 to 13.2% (132 per 1,000 births) in 2000. The reduction in injury rate was not explained fully by the change in cesarean section rate. International rates for birth-related injury as defined by the AHRQ PSI from 2004 to 2006 ranged between 0.151% and 1.448%

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Table 12.1
Birth-related injury statistics

Type of trauma	Moczygemba ('04–05 Data)		Sauber-Schatz ('03 Data) (890,582 Total births)		USA	International
	USA rate* for Cesarean section	USA rate* for vaginal delivery	Un-weighted *number*	Weighted rate*	Rates* or percentages reported in literature	Rates* or percentages reported in literature
Eye					0.2–12%	
Nasal septal dislocation					0.6–1.9%	3.4–17%
Cranial or peripheral nerve	N/A	0.04	124	0.05		
Facial nerve injury	0.24	0.22	661	0.26	0.8–7.5	0.03%
Torticollis					0.3–3.9%	
Other injury to scalp	13.15	23.17	22,764	20.06		
Cephalohematomas					1.0–2.5%	
Subgaleal hemorrhage					0.4–0.8	
Epicranial subaponeurotic	0.15	0.11				
Subdural and cerebral hemorrhage	0.23	0.19	1,064	0.41	0.29–2.9	
Subarachnoid hemorrhage					0.13–1.07	
IVH due to birth trauma					4%	
Brachial plexus injury	0.17	1.49	3,302	1.28	0.13–3.6	0.42–4.17
Clavicle fracture	0.25	3.29	6,353	2.43	2–29	0.4–18.7
Injuries to skeleton	0.33	0.34	9,525	3.70	0.04–0.2	
Spine or spinal cord			10	0.00	0.014	
Other specified birth trauma	2.61	1.23	3,994	1.56		
Other unspecified birth trauma	0.17	0.15	218	0.09		
AHRQ PSI birth trauma	3.46	2.03				0.13–1.45%
Birth trauma-All	17.07	29.53	44,658	28.56	1.1–7%	8–24.6%
Death					0.075**–0.642***	

*Rates per 1,000 births unless stated as %, ** 1985 Data, *** 1970 Data
Table compiled from data from multiple sources, most notably Moczygemba (2010) and Sauber-Schatz (2010)

(1.51–14.48 per 1,000 births) in the seven countries participating in the Organization for Economic Co-operation and Development (Austria, Canada, Germany, Spain, Sweden, UK and USA). However, the study noted that the PSI birth-related injury indicator might be unreliable for international comparison.

Sule and Onayade's review of literature from the World Health Organization (WHO), Save-the-Children,

United Nations Children's Fund (UNICEF), and other scientific sources reports that 99% of neonatal deaths occur in developing countries with a 30-fold disparity between those countries with the highest (found in sub-Saharan Africa) and lowest neonatal mortality rates. Within developing countries, estimates based on the deaths of four million newborns indicate that birth injuries at 11% was the second most common cause, behind infection, which accounted for 42%. Two hospital-based studies of birth-related injury from the country of Iran point to regional differences even within a single country and underscore the impact of sampling (denominator). Borna's study limited to singleton vaginal deliveries in 2002–2005 found incidence of 41.16 per 1,000, where Mosavat's study of all live births in 2004–2005 in Rafsanjan (south Iran) found 0.8% (or 8 per 1,000) with a relatively high cesarean delivery rate.

Overall Birth-Related Injury Risk Factors

Risk factors can be broken into three groups: those related to mother, to baby, and to delivery characteristics.

Maternal factors include: maternal obesity (BMI > 40 kg/m^2), preexisting or gestational diabetes, large weight gain, previous history of macrosomic infant, small maternal stature, and the presence of maternal pelvic anomalies.

Newborn factors include: macrosomia, prolongation of pregnancy (>42 weeks or 298 days), and abnormal (other than vertex, occiput anterior) presentation.

Delivery factors include: induction of labor, epidural analgesia, shoulder dystocia, and operative or instrumented vaginal delivery.

Specific Types of Birth-Related Injury

Skin/Soft Tissue

Superficial injury to the skin is the most common birth-related injury. Bruising, petechiae, abrasions, and even lacerations can occur on the scalp or on any other presenting part during passage through the bony pelvis, from the dilating cervix, or from instruments (including vacuum, forceps, and hands) used in delivering the newborn. Extensive bruising may predispose a newborn to jaundice peaking a little later at 5–7 days of life as reabsorption occurs. Abrasions seldom need treatment with antibiotics but should be monitored for signs and symptoms of infection (including edema, erythema, induration, warmth, or tenderness). Mild symptoms of infection can be treated topically but careful observation is necessary as cellulitis requires treatment with systemic intravenous antibiotics. Abrasions that are near the eye should prompt a careful eye examination, and any that cross the edge of the orbit should be referred to an ophthalmologist for assessment. Superficial lacerations are also rarely prone to infection, but topical antibiotics and sterile strips may aid healing. Those lacerations that are full thickness (through the epidermis) or in key anatomical locations such as the face, near the eye, or in an area with traction (over a joint) should be cleaned and then referred to a plastic surgeon (if available) for suturing in the nursery. Long-term prognoses for these superficial injuries are excellent and generally heal very quickly in the newborn.

Deeper injury to the skin and subcutaneous fat tissue leading to fat necrosis can occur rarely in any area of trauma. These usually appear on the back, buttocks, or extremities of full term infants during the first several days to weeks of life as firm, indurated and erythematous (either red to purplish-blue but occasionally fleshy colored) nodules and plaques that lack warmth but potentially may be tender. It is unclear exactly what causes fat necrosis but theories include (1) some type of mechanical trauma or pressure which induces ischemia, (2) possibly defect in fat composition with a stressful event, or (3) cold- or hypothermia-induced saturated fatty acid crystallization. After the solidification and necrosis of the fat, a granulomatous infiltrate forms increasing the extrarenal absorption of calcium. Histological examination of the tissue reveals increased levels of 25-hydroxyvitamin D3-1alpha-hydroxylase (AKA 1alpha-hydroxylase) which activates vitamin D. Subcutaneous fat necrosis is a self-limited condition resolving in about 6–8 weeks of life with some subcutaneous atrophy, but these infants can have serious alterations in their calcium levels (*Fig. 12.1*). Hypercalcemia has been reported up to 6 months after initial presentation and can rarely lead to seizures, coma, and death. Symptomatic hypercalcemia (presenting as irritability, poor feeding, etc.) should be treated in the hospital with hydration, calcium wasting diuretics, furosemide, and corticosteroids. It is recommended to check calcium levels periodically in all infants with subcutaneous fat necrosis for several months, and dietary changes would be advised in those with documented asymptomatic hypercalcemia. Thrombocytopenia, anemia, hypertriglyceridemia, and hypoglycemia have also been reported. Although presentation and history are likely enough to make the diagnosis, fine needle aspiration and punch biopsy are definitive in confirming the diagnosis. Differential diagnosis includes cellulitis, erysipelas, sclerema neonatorum, deep hemangioma, or other tumors.

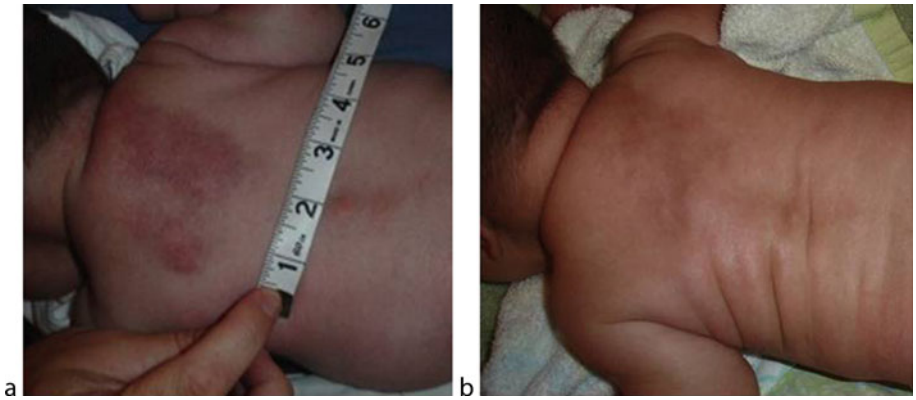

Figure 12.1
Subcutaneous fat necrosis. This large-for-gestational-age (*LGA*) newborn was born by vaginal delivery with documented shoulder dystocia. (a) Initial concern for possible midline hemangioma on day of life (DOL) 4. Note the purplish red lesions above and below the tape measure. (b) Infant referred to Dermatology at one month of life, diagnosed as subcutaneous fat necrosis (Photograph from the patient files of Tricia L. Groff, MD)

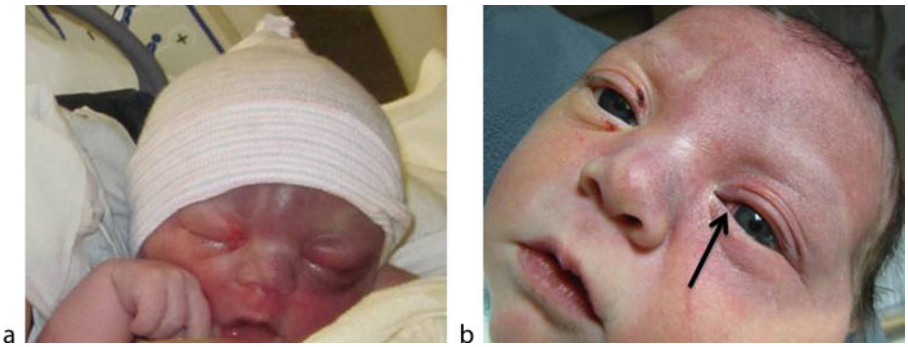

Figure 12.2
Subconjunctival hemorrhage in a newborn. (a) Taken very shortly after birth of a full-term newborn delivered by uncomplicated vaginal delivery in the occiput posterior position with no instrumentation to a gravida 2 para now 2 mother. Note the significant swelling of bilateral eyelids, and ecchymosis over most of the forehead. (b) Taken on day of life (DOL) two at the time of discharge, the swelling was nearly resolved and subconjunctival hemorrhages were now visible on the medial aspect of the left eye (Photograph by Marcia W. VanVleet, MD, MPH)

Face and Neck Injuries

Ocular Injuries

Ocular injuries can occur in up to 12% of newborns as they pass through the birth canal or with instrumentation, especially with forceps. The most common eye injury is the subconjunctival hemorrhage that appears as red bands around the iris (*Fig. 12.2*). It is usually present at birth but may not be apparent until the normal eyelid swelling/edema subsides revealing the conjunctiva over the white sclera. As with other microvascular bleeds or ecchymosis, these might appear to change color during the healing process, but usually heal spontaneously in 10–15 days. Subconjunctival hemorrhages occur as the result of elevated venous pressure in the head and neck from the increased intrathoracic pressure from passage through the birth canal. However, as they are also seen in cesarean section deliveries, it is likely that compression of the thorax/abdomen by uterine contractions, or a tight nuchal cord may have the same consequences. Other injuries to eye are more frequent when there has been

instrumentation with forceps. These can include hyphema (bleed into the anterior chamber of the eye), corneal abrasions (or vertical tears in Descemet's membrane), or orbital injuries (including fractures, and damage to the optic or oculomotor nerves). These should be referred to an ophthalmologist promptly.

Nasal Septal Dislocation

Dislocation of the nasal septum can occur in passage through the birth canal. Reports suggest that some type of usually transient nasal deformity may occur in up to 58% of births. However, the rates for nasal septal dislocation vary based on the method of diagnosis. Those relying on external exam and rhinoscopy find rates near 1.2–3.4%, whereas those that actually try to pass 2 mm struts through the nasal cavity find rates up to 14.5–25%. Reported risk factors include primiparity, breech presentation, prolonged second stage of labor, vaginal delivery, and large head circumference. Nasal septal dislocation has a clinical range of presentation based on degree of involvement, but usually presents with symptoms of airway obstruction (difficulty when feeding and mild respiratory distress). Clinical exam can include bruising and edema, but more commonly these present with just deviation of the septum or asymmetry of the nares with flattening of the affected side (Metzenbaum's sign). Further diagnostic refinement can be made 85% of the time by pressing on the tip of the nose which will, in the case of septal dislocation, worsen the deviation and flatten the nostril (Jeppesen and Windfeld test). These cases should be referred within the first 3 days of life to an ENT specialist who will confirm the diagnosis with rhinoscopy and manually reduce the dislocation. Prompt intervention is necessary to prevent long-term cosmetic deformity and potential outcomes of epistaxis, Eustachian tube dysfunction, abnormal development of the maxilla, and repeat sinusitis.

Neck/Torticollis

Torticollis defined as limitation of the lateral flexion of the neck can be the result of birth-related injury in about 10% of cases, but the majority are likely due to in utero positioning in the restricted intrauterine environment (postural asymmetry without muscular tightness). Torticollis has been associated with a maternal report of the fetus being "stuck" for more than 6 weeks prior to delivery. Many cases of torticollis (up to 40%) are due to congenital spindle-shaped mass or tumor in the midportion of the sternocleidomastoid muscle. Torticollis can be apparent at birth, but generally presents between 1 and 4 weeks of age, most commonly at 3 weeks. Careful examination of the neck includes measurements of the range of motion comparing sides and palpation of the sternocleidomastoid muscles for masses. Diagnosis is usually by clinical exam, in consultation with the occupational (OT) or physical therapist (PT). However, radiographs of the spine and ultrasonography may be helpful in confirming the diagnosis. Parents should be instructed to perform range of motion exercises, provide regularly observed prone "tummy time," and encourage the infant to look toward the non-preferred direction with the use of mirrors, pictures, etc. Most do well with stretching, but prognosis can be related to the degree of limitation. Of the cases whose range of motion is limited by more than 10°, 5% will go on to need surgical intervention. Indication for surgery includes lack of improvement in 6 months, continuation of greater than 15° of limitation, or ongoing head tilt. If left untreated, asymmetry or positional preference (either awake or asleep) strongly correlates with deformational posterior plagiocephaly at 7 weeks of age.

Head Injuries

Injuries to the head can be divided into three categories based on their anatomical location: (1) extracranial injury, (2) cranial or skull fractures, or (3) intracranial hemorrhage (*Fig. 12.3*). Although any of these injuries can occur in deliveries without instrumentation, all are more common with vacuum and forceps delivery. Any newborns with serious or massive extracranial or any intracranial hemorrhages should undergo a hematological evaluation that includes PT/PTT, fibrinogen, platelet count, and confirmation that Vitamin K has been administered.

Extracranial Injuries

Extracranial injuries are the most common type of birth-related head injury, and include caput succedaneum, cephalohematomas, or subgaleal hemorrhages.

Caput Succedaneum (or "second head" in Latin) appears first after delivery and is purely a severe form of diffuse soft tissue swelling of the scalp. Caput is thought to be the result of squeezing of the head in the birth canal or by the constriction of the cervix. They may or may not have overlying ecchymosis. These serosanguineous fluid

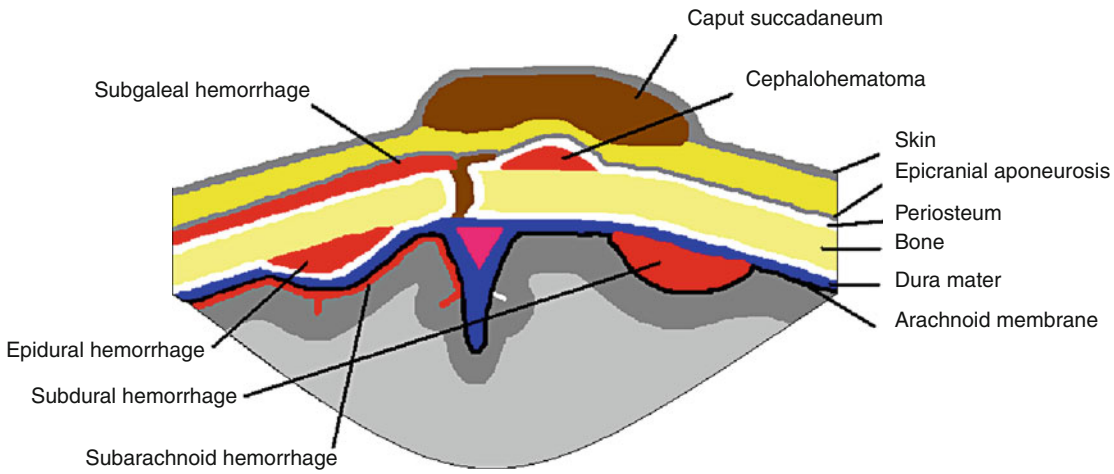

Figure 12.3
Schematic of cranial birth injuries. Diagram of location of cranial birth injuries drawn by Victoria A. VanVleet (Adapted from multiple sources including Sheikh, McKee-Garrett, Volpe)

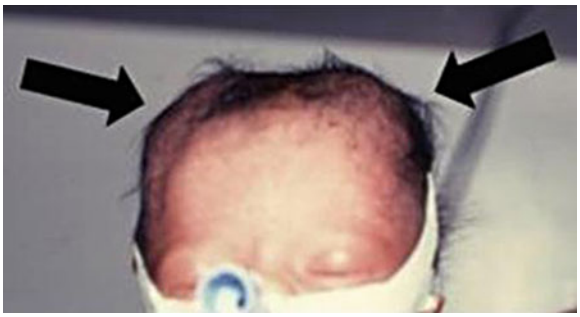

Figure 12.4
Bilateral parietal cephalohematomas. *Arrows* point to bilateral swelling of scalp in a near-term infant nasally intubated for other reasons (Photograph from the patient files of James F. Padbury, MD)

collections occur in the plane between the skin and the epicranial aponeurosis and therefore have ill-defined margins not limited by bony landmarks. A caput can occasionally be fairly large but starts to regress quickly and usually resolves within a few days. It can mask molding or a cephalohematoma that may become more apparent as the caput resolves.

Cephalohematomas are subperiosteal collections of blood just under the outer surface of the bone (*Fig. 12.4*). They are the result of shearing friction to the bone that ruptures the bridging vessels, leading to slow bleeding. As such, they may not be apparent at the time of birth but slowly increase over the next few days. The lesions tend to become firm masses but occasionally fluctuant with distinct borders as they are limited to the edges of the bones and do not cross suture lines. This is a key distinguishing characteristic between cephalohematoma and caput. Initially, it might be difficult to distinguish between a caput and a cephalohematoma when they coexist, but over the first few days, the caput should regress and potentially reveal a cephalohematoma (or two as trauma may not be limited to just one bone of the skull). Cephalohematomas will slowly be reabsorbed over 2–3 weeks (up to 3 months) depending on size, potentially leading to increased hyperbilirubinemia as well as calcified masses. Occasionally, these create bony protuberances which can appear for many years on X-rays as cyst-like defects. Cephalohematomas may be associated with skull fractures in 5–25% of cases. Cases of infection and osteomyelitis have been reported in cephalohematomas. Cephalohematomas rarely need treatment, but often can lead to exaggerated and prolonged hyperbilirubinemia, which may require phototherapy later then physiologic jaundice.

Subgaleal hemorrhages represent the third and potentially most serious form of extracranial injuries. These rare bleeds (estimated overall at 0.8 per 1,000, and 6.4 per 1,000 of vacuum-assisted deliveries) occur between the epicranial aponeurosis and the outer periosteum of the skull bones. As such, they are not limited by bone edge and can accumulate large volumes of blood into this potential space, and even into the soft tissue of the neck. These usually result from rupture of the emissary veins, or less frequently fracture of a bone, but occasionally can be the

result of hereditary coagulopathy such as hemophilia. These can be fluctuant masses that steadily grow in size extending from the edge of the orbital ridges to the nape of the neck and to the ear and may lead to an impression of dysmorphology. The large amount of blood accumulation can cause anemia, hypovolemic shock (pallor, tachypnea, tachycardia, and hypotension), consumptive coagulopathy, and death in 12–22%. Early recognition and effective treatment is the key to a good outcome. Serial assessment of blood pressure, hemoglobin/hematocrit, and head circumference are warranted. It has been documented that an increase in head circumference of 1 cm can represent 38 mL of blood, and that subgaleal bleeds can collect 31–58% of the newborn's blood volume. Prognosis is worse for those with 25% decrease in hematocrit, shock, or evidence of asphyxia. Testing should include assessment for coagulopathy, which has been found in 30% of cases. Serial bilirubin levels should be assessed over the next few weeks of life as the hemorrhage is reabsorbed. Prognosis is good for survivors.

Cranial Injuries/Skull Fractures

Cranial Injuries/Skull fractures can occur from pressure against the maternal pubic symphysis, sacral promontory or ischial spines in vaginal deliveries, or from forceps, similar to the causes of facial nerve palsy. Most are linear fractures and are asymptomatic, requiring no treatment. The exception to this is the rare occurrence of an occipital bone fracture in a breech delivery that may be fatal due to bleeds associated with the underlying vascular sinuses. Depressed fractures (like a ping pong) are typically also asymptomatic unless there is underlying intracranial hemorrhage. Depressed fractures require brain imaging and neurosurgical evaluation.

Intracranial Injuries/Hemorrhage

Intracranial hemorrhages can occur in the epidural, subdural, subarachnoid, intraparenchymal, or intraventricular spaces.

Epidural hemorrhages (EDH) are extremely rare bleeds in newborns. They occur between the dura and the skull, often associated with a parietotemporal skull fracture. Additionally EDH may occur in association with cephalohematomas. These are arterial in source, usually from the middle meningeal artery, and can progress rapidly. Newborns with EDH present with nonspecific neurological findings (such as change in mental status or hypotonia), seizures, or symptoms of increased intracranial pressure (ICP). Diagnosis is made with CT or MRI, and serial images may need to be obtained to assess progression. Neurosurgical involvement is indicated with signs of increased ICP, and also potentially when the bleed is large, or when there is a depressed skull fracture, hydrocephalus, or a significant mass effect.

(See Resources for link to Web site with a CT Scan of a Newborn with a Cephalohematoma and Epidermal Hematoma.)

Subdural hematoma (SDH) is also a rare occurrence but is the most common intracranial hemorrhage attributed to birth-related injury. These bleeds occur between the dura mater and the subarachnoid membrane usually in the tentorial or intrahemispheric location. Some newborns remain asymptomatic, but if the volume of blood grows, they usually present in the first 24–48 h of life with apnea, respiratory distress, and/or seizure. Some may present with mental status changes such as irritability or depressed activity. The newborn skull is pliable with open sutures and fontanels; therefore, it can expand in response to the accumulated blood before the ICP rises. Rarely, when there is increased ICP, the infant can progress to increasing head circumference, tense or bulging anterior fontanel and if left untreated, progress to apnea, bradycardia, coma, and possibly death. Management of subdural hemorrhages depends on the location and symptomatology. Due to the potential for large blood loss, serial hematocrits and volume support is recommended as indicated; those with larger blood loss should be evaluated for coagulopathy. The few with increased ICP or those with bleeds located in the posterior fossa potentially causing rapid brainstem compression immediately need neurosurgical intervention/evacuation of the hematoma for decompression. The others can be conservatively managed after a period of observation.

Subarachnoid hemorrhages (SAH) result from small tears in the leptomeningeal arteries or the bridging veins and are generally asymptomatic. Usually there is no history of difficult or instrumented delivery and SAH may be more common in newborns born prematurely or with evidence of asphyxia than due to birth-related injury. Some infants develop seizures on the second day of life, and lumbar puncture may reveal red blood cells in the cerebrospinal fluid. SAH is one of the more benign etiologies of neonatal seizures and typically resolves without intervention. Rarely SAH presents with more severe neurological findings with arteriovenous malformations, and when associated with catastrophic bleeds can lead to fatality. Diagnosis is based on CT or MRI findings. Long-term course can rarely be complicated by hydrocephalus.

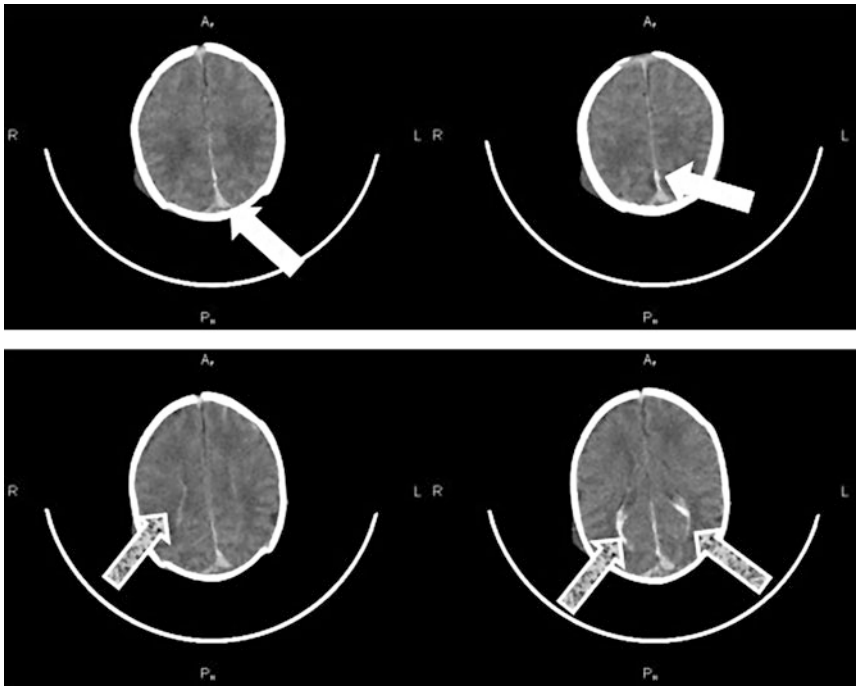

Figure 12.5
CT Scan of newborn with subtle subdural, subarachnoid, and intraventricular hemorrhages. Newborn who presented with significant soft tissue swelling on the lest (evident on CT scan) and a question of depressed skull fracture. CT scan demonstrated: A) subdural blood in the tentorium extending into the interhemispheric fissure posteriorly (white arrows), B) small amount of subarachnoid hemorrhage in the right posterior parietal region (not apparent on these images), and C) blood in the occipital horns into the lateral ventricles consistent with intraventricular hemorrhage (patterned arrows). (Image from the patient files of Marcia W. VnVleet, MD, MPH)

Intraventricular hemorrhages (IVH) can rarely occur during birth process of full-term newborn but much more commonly associated with preterm births (*Fig. 12.5*). Risk for IVH is inversely related to gestational age and birth weight. Occurrence in full-term newborns indicates a need for hematological evaluations. Otherwise, IVH is discussed elsewhere in the text (see Chap. 360, "Neonatal Neurological Disorders").

Nerve Injuries

Nerve injuries from birth-related injury can affect cranial or peripheral nerves and can be divided into three degrees of severity: (1) neuropraxia (Sunderland's class I, nerve intact but conduction blocked), (2) axonotmesis (Sunderland's class II-IV, axon not continuous but nerve is intact with increasing scarring), and (3) neurotmesis (Sunderland's class V, complete rupture of the nerve). Sunderland's five classes go from least to most severe, with the most severe cases (V) requiring surgical intervention.

Facial Nerve Injury (VII Cranial Nerve)

Facial nerve palsy has been reported to occur at a rate anywhere from 0.8 to 7.5 per 1,000 deliveries and up to 8.8 per 1,000 in deliveries with forceps. Most studies support the association with forceps-assisted deliveries; however, a recent study from Saudi Arabia spanning the years 1994–2005 found that 25% were delivered by cesarean section and the remaining 75% by vaginal delivery without forceps. Facial nerve palsy is most often caused by swelling resulting in compression due to the superficial course of the nerve as it exits the stylomastoid foramen or passes over the ramus of the mandible. This compression may be from intrauterine posture of the shoulder pushing the jaw and region in front of the ear, intrapartum compression against the maternal

boney prominences (e.g., pubic rami, ischial spines, sacral prominence) or by forceps. Clinical presentation usually involved the lower portion of the facial nerve noticeably with asymmetric cry and nasolabial folds. If there is involvement of the upper portion of the nerve, then the eye will also be involved with incomplete closure (or persistently opened) on the affected side. Differential diagnosis includes; congenital absence of the depressor anguli oris muscle (aka CULLP with isolated asymmetry with just the cry but spares the nasolabial folds), congenital facial palsy, and associated syndromes such as 22q11.2 deletion syndrome (DiGeorge or velocardiofacial with isolated asymmetric cry possibly with heart murmur), CHARGE syndrome (Coloboma, heart disease, atresia of choanae, retarded growth, genital hypoplasia, and ear anomalies within 68% are associated with cranial nerve involvement including VII), trisomy 13 or 18, Moebius (bilateral facial and abducens nerve palsy), and rarely Poland's (absence of pectoralis major muscle), or Goldenhar's. Diagnosis is generally clinical; however, imaging should be considered in cases with other paralysis suggestive of infarct or central lesions. All should be tested for hearing loss. Those newborns with associated findings should undergo chromosomal analysis, especially those with complete facial nerve palsy suggestive of 22q11 deletion.

Multiple studies report that approximately 90% of facial nerve palsies will have spontaneous recovery in 1–2 months. The House–Brackman scale has been utilized to assess the severity of facial nerve involvement. In newborns, facial injuries are usually classified on the House–Brackman scale as either mild (II with about 80% function) or moderate (III with 60% function). Treatment is generally to protect the cornea with taping, artificial tears and lubrication for those with persistently opened eyelids. Poor prognosis is associated with complete unilateral paralysis present at birth, hemotympanum, displaced temporal bone fracture, absence of movement of all facial nerve muscles by 3–5 days, or lack of improvement by 5 weeks. Treatment with corticosteroids, and especially with surgery, is controversial. Timing of surgical intervention is not uniform and some wait for a full year, but any infant with the poor prognostic factors listed should be referred at 5 weeks of age to a neurosurgeon for consultation.

Laryngeal Nerve Injury

Laryngeal nerve injury from the stretching associated with birth, usually associated with shoulder dystocia, represents 5–26% of vocal cord paralysis cases apparent at birth. Again found more commonly with forceps deliveries, laryngeal nerve injuries occur unilaterally more on the left than the right due to the longer course of the nerve on the left. Symptoms of unilateral vocal cord paralysis include hoarse, faint, or weak cry, as well as mild respiratory distress, dysphagia, aspiration, and stridor. Bilateral involvement presents sooner with more severe symptoms of respiratory distress possibly requiring intubation and tracheostomy. The differential diagnosis of bilateral paralysis includes congenital syphilis, and central nervous causes including asphyxia, hemorrhage, hydrocephalus, meningomyelocele, bulbar injury, and Arnold–Chiari malformation. For those presenting primarily with stridor, the differential diagnosis in newborns includes choanal atresia, laryngeal web, and vascular ring. Diagnosis of vocal cord paralysis is made on direct laryngoscopy. Evaluation in cases without documented birth trauma and in bilateral involvement should include imaging of the CNS and brainstem for possible etiologies. Most cases of unilateral vocal cord paralysis due to birth-related injury resolve spontaneously.

Spinal Cord Injury

Spinal cord injury is a rare but very serious form of birth-related injury, which frequently goes undiagnosed due to the critical status of the newborn. Laxity of the ligaments, muscle weakness, and incomplete mineralization of the vertebrae allow the spine to stretch to the point of pulling on the actual spinal cord. Perinatal depression with poor muscle tone probably contributes to the susceptibility to stretch injury. Higher cervical lesions are most common and associated with forceps use, while lower cervical and thoracic lesions occur during breech vaginal deliveries. Spinal injury has been reported with cesarean deliveries, especially with breech presentation. Symptoms present immediately in the labor room include decreased movements, hypotonia, areflexia, and apnea. Diagnosis can be made with MRI or bedside ultrasonography. Survival is dependent on the anatomic level and severity of the injury, but mortality rates are high (70–87%). Prognosis is poor for those requiring mechanical ventilation after 24 h of life, and long-term disabilities are common even among survivors. Surgical intervention for lower cord injuries is possible but less likely to be beneficial due to the observed delay in making this difficult diagnosis after which there is irreversible damage.

Upper Extremity Injury and Associated Conditions

There is great overlap in the etiology, pathophysiology, diagnosis, and treatment of injuries to the upper extremity including clavicular and humeral fractures, and the

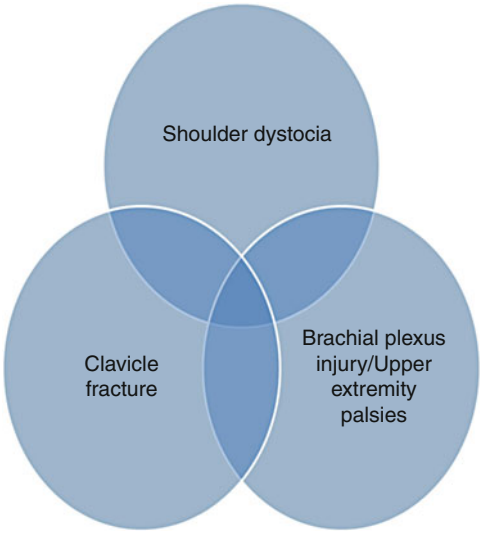

Figure 12.6
Venn diagram demonstrating relationship between shoulder dystocia, clavicle fractures, and brachial plexus injuries (Diagram by Marcia W. VanVleet, MD, MPH)

brachial plexus; therefore, these will be discussed together. There is an interrelationship between shoulder dystocia, clavicle fractures, and brachial plexus injuries that is best represented by a Venn diagram (*Fig. 12.6*).

Clavicle fractures are the most common fractures in newborn infants. Rates vary greatly partly based on study design and timing of assessment from 0.2% to 3.5% of births. Risk factors for clavicular fractures are similar to those for any birth trauma including higher gestational age, larger birth weight, and shoulder dystocia. The clinical presentation of clavicle fractures is varied as well, with up to 50% going undetected until callus formation is noted 2 weeks later. Infants often present with irritability, asymmetric arm movement, and asymmetric Moro reflex. Cases of breastfeeding difficulty only on the affected side have also been reported. The most sensitive clinical sign in the birth hospital stay is that of asymmetry of the clavicles, or difficulty palpating the margins of the fractured clavicle when compared to the normal side. Clavicle factures can be associated with injury to the brachial plexus or with a pneumothorax based on the proximity of fracture to the nerves and the apex of the lung. No active treatment is needed for a simple clavicular fracture, as the bone is quickly stabilized with callus formation and remodels without sequelae even in the presence of considerable displacement. However, the implementation of precautions is advisable to prevent injury to the brachial plexus during the healing process.

Humeral fractures is the second most common fracture in the newborn and the most common long bone fracture. It should be suspected in any newborn with asymmetric movement of the upper extremity, especially in the presence of any ecchymosis, tenderness, or swelling. It should also be actively ruled out with plain films of the arm for any infant who is not symmetrically moving the upper extremity after hospital discharge. The healing process is quick and usually does not need intervention except for wrapping the arm with a bandage to help with comfort and handling. But as with clavicle fractures mentioned above, the primary reason for intervention is to prevent secondary or recurrent trauma to the nerves that pass near the bone.

Brachial Plexus Injury (BPI) can occur alone or in conjunction with clavicular fractures. These injuries traditionally have been theorized to be the result of downward traction on the head in an effort to dislodge the anterior shoulder from under the maternal symphysis pubis and stretching of the brachial plexus roots as they emerge from the spinal cord. However, in as many as 40% of the cases, the injury occurs in the absence of shoulder dystocia and may occur even in infants delivered by cesarean section. Though BPI is one of the most common causes of malpractice allegations, its occurrence is unpredictable and not necessarily preventable. Various studies have shown links between macrosomia (>4.5 kg), shoulder dystocia, and BPI. Lispcomb reported in 1995 that out of 157 vaginal deliveries of macrosomic newborns, there were 29 cases (18.5%) of shoulder dystocia which were associated with 7 Erb's palsies, 7 clavicle fractures, and 1 humeral fractures. Gilbert in 1994–1995 found a local BPI rate of 0.15% with the following risk factors listed in order by decreasing odds ratios: Shoulder dystocia (OR 76.1), Forceps (OR 3.4), Vacuum (OR 2.7), and Gestational Diabetes Mellitus (OR 1.9), with a protective effect from prematurity and fetal growth restriction. However, the connection between shoulder dystocia and BPI is neither direct, nor constant across all birth weights. For patients with BPI weighing between 2.5 and 3.5 kg, only 22% had shoulder dystocia. While for those with BPI weighing >4.5 kg, the rate of shoulder dystocia increased to 74%. This suggests that there are different mechanisms of action for brachial plexus injury for those with lower birth weights. Additionally, as with spinal cord injuries, the depressed infant with reduced muscle tone to protect the shoulder joint may be more susceptible to stretch injury.

Brachial plexus injury will present as muscular weakness or paralysis to the affected upper extremity. In the nursery, this can be subtle with just an asymmetric Moro or grasp reflex or unequal spontaneous movements so that the affected hand does not extend above the height of the

shoulder. The exact presentation of brachial plexus injury is related to the nerve roots involved.

Erb's palsy (also called Erb-Duchenne's) presents with involvement of C5 and C6 as the arm hanging at the side, with the forearm internally rotated, extended, and pronated (*Fig. 12.7*). If C7 is involved, the wrist and fingers lose extension and are flexed/curled into the classic "waiters tip" positioning. Frequently, the hand movements and grasp will start to show improvement within hours of birth and is a good prognostic indicator; however, careful follow-up for all of these infants is imperative.

Klumpke's palsy presents with involvement of C8-T1 with weakness in the triceps, in pronation of the forearm, and in wrist flexors with the "claw-like" paralyzed hand but preserved functioning at the shoulder and elbow. Isolated injury to C8-T1 is rare and most infants present with some combination of signs of Klumpke's along with some features of Erb's palsy. A summary of these injuries can be seen in *Table 12.2* with the Narakas classification.

Careful examination would include investigating for sympathetic cervical nerve involvement with the loss of sensation on the affected side of the face, constricted pupil, and ptosis of the eyelid or "Horner's syndrome." (See Resources for link to Web site with picture of Horner's syndrome in an infant.)

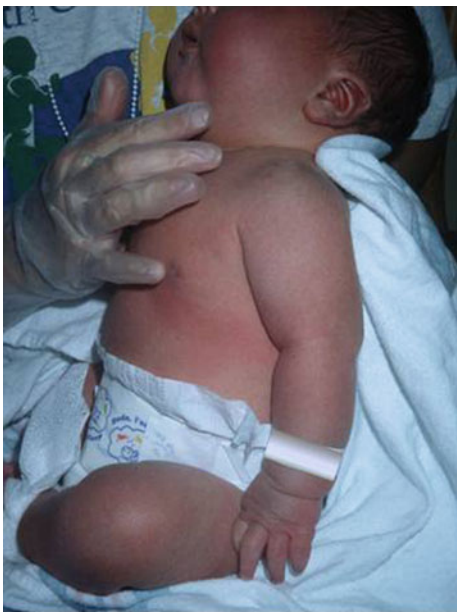

Figure 12.7
Newborn with brachial plexus injury to C5-C6: Erb's Palsy: Large-for-gestational-age (*LGA*) newborn with brachial plexus injury, with absence of arm movement at the shoulder, elbow, and forearm supination. The hand lies at the side of the infant without the classic waiter's tip, thus suggesting a C5-C6 injury (Photograph from the patient files of Rebecca L. Collins, MD)

Treatment of Upper Extremity Injury

As soon as an upper extremity deficit is suspected by the nurse or any other examiner, it is important to intervene to reduce the risk of further damage. The affected side should be place on "precautions" with care taken in the handling of the newborn to protect the nerves involved. This includes making sure the arm does not dangle but is supported in all care including dressing (affected arm in shirt first and out last), and that positions for both sleep and feeding do not place additional weight or stress on the plexus. Additionally, the examiner should be careful not to elicit the Moro reflex before assessing for the presence of associated clavicular or humeral fractures.

Exam of the newborn with suspected upper extremity paralysis should include careful inspection for other injuries including symmetry of the face (facial nerve palsy), eye (Horner's syndrome with drooping eyelid, constricted pupil and sunken eye), neck for movement and masses, cry (laryngeal nerve palsy), respiratory pattern (phrenic nerve involvement), and skin for bruising, swelling, or tenderness suggestive of other muscle or bone involvement (humeral or clavicular fracture). As mentioned above, the Moro reflex should not be elicited. Instead the examiner should carefully observe the newborn's spontaneous movements including: (1) whether there is flexion of the fingers, wrist, elbow, and shoulder, (2) how far is the newborn able to spontaneously lift the hand against gravity (with a goal of symmetric above shoulder height), (3) assessment of grip strength comparing sides for symmetry, and (4) gently stroke the forearm looking for grimace and movement to assess sensory involvement.

Definitive diagnosis of a fracture of the clavicle or the humerus is based on plain radiographs (*Fig. 12.8*). For the clavicle, it is best to get two views, which will include the AP and lordotic views as the natural curvature of the clavicle sometimes obscures the site of the fracture when only seen from one view. Newborn X-rays with clavicle fractures should be also carefully examined for the presence of associated pneumothoraces, elevated hemidiaphragm, and midline posterior rib fractures.

The short-term treatment for newborns with upper extremity injury has recently changed. If there is a clavicle fracture, the current treatment is to place the arm at the newborn's side in a neutral position with a diaper or small

Table 12.2
Summary of brachial plexus injuries including Narakas classification and Sunderland lesions

Cranial nerves	Brachial plexus	Narakas group (at 3 weeks)	Percentage and newborn clinical presentation	Evidence-based recovery (S. Foad)				Probable lesion with Sunderland degree
				Biceps recovery		Complete recovery		
				@3 months	@6 months	@ 3 months	@ 6 months	
C4	Phrenic nerve	N/A	Diaphragm paralysis with paroxysmal breathing pattern	N/A	N/A	N/A	N/A	N/A
C5-C6 (Erb's/ Duchene's)	Upper	1	46%: Paralysis of shoulder and biceps Absence of abduction, external rotation, elbow flexion, forearm supination	64%	68%	59%	65%	Upper trunk: I and II degree
C5-C7	Middle	2	30%: Paralysis of shoulder, biceps, and forearm extenders Group 1 with weaker wrist extension = waiter's tip					Upper trunk: II and III C7: I and II
C 8, T1 (Klumpke's)	Lower		2%: Intact shoulder and elbow but floppy hand with claw-like deformity	N/A	N/A	N/A	N/A	
C5-T1	Complete	3	20%: Complete paralysis of the entire limb Flail shoulder, absence of elbow flexion, weak extension, flexed wrist, closed fist	9%	38%	0%	14%	Upper trunk: IV and V C7: III and IV
C5-T1 with sympathetic involvement (Horner's)		4	Complete paralysis of limb with Horner's Flail extremity, half-open hand, little finger movement and constricted pupil and ptosis					Upper, middle and lower trunks: II-VI varies

Source: Adapted from Foad (2008, 2009), Narakas (1986), and Sunderland (1990)

cloth folded under the axilla to help with positioning. It is no longer recommended that the arm be pinned to the shirt to prevent movement as this places additional strain on the fracture and may lead to iatrogenic shoulder dislocations. In the case of clavicle or other bone fractures, it is important to keep the patient comfortable during care, which may include the use of oral analgesia for the first few days. After discharge from the hospital, non-pharmacological care measures should be adequate.

Prior to discharge from the hospital, the parents should be instructed by an occupational (OT) or physical (PT) therapist on how to support the upper extremity during care. And with a goal of preventing contractures and improving range of motion (ROM), the therapist will also instruct the parents on how to perform gentle ROM exercises with each diaper change (as tolerated by the newborn). Those with clavicle fractures should be advised that the bone will heal with the formation of a callus, and so a visible bump is to be expected as a sign of healing. Those with an isolated clavicle fracture should also be advised to follow up with the PT or OT specialist as an outpatient if the infant is not moving both upper extremities symmetrically above the shoulder or if there is any loss of movement. The vast majority of patients with isolated clavicle fractures do well with no long-term sequelae.

Patients with nerve involvement should be seen by the PT or OT specialist prior to discharge and then again at about 2 weeks of age to evaluate the progress, to carefully

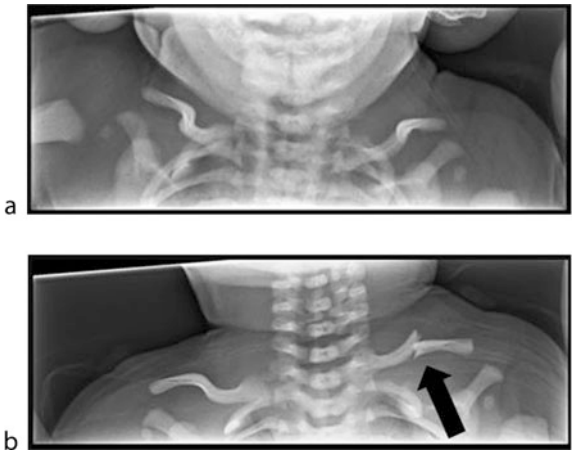

Figure 12.8
Radiograph with clavicle fracture: Patient with crepitus over the left clavicle and an otherwise normal upper extremity exam. (a) AP view without distinct fracture. (b) Lordotic view with clear mid left clavicle fracture with minimal displacement (Image from the patient files of Marcia W. VanVleet, MD, MPH)

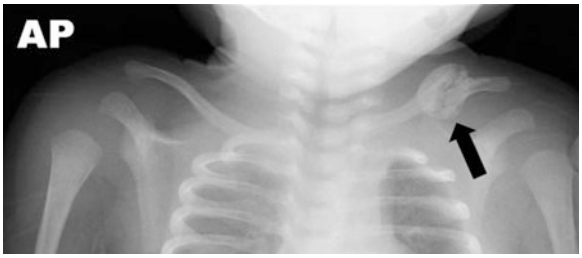

Figure 12.9
Radiograph of newborn at 3 weeks with Callus over left healing clavicle fracture. This patient was in hospital for prolonged newborn stay as a border baby. *Arrow* points to callus which was discovered when the patient was 21 days old during the discharge examination by the attending physician. There was a palpable bump, the contour of which is visible above the *arrow*. The patient otherwise had a normal upper extremity exam (Image from the patient files of Marcia W. VanVleet, MD, MPH)

document physical movement, and to provide ongoing education to the parents. Many (originally thought to be 80–90%, but more recent statistics reveal less at 60–70%) of patients with brachial plexus injury spontaneously recover by 3 months, with the majority of those doing so in the first 3 weeks of age (*Fig. 12.9*). Those with a lack of improvement by 2–3 weeks should be investigated by exam and radiographically for the presence of a coexisting humeral fracture. If there has not been full recovery of function at one month of age, the infant should be referred to a pediatric neurologist or brachial plexus injury center. Recovery should be progressive; however, a key time point is at about 2 months when the return of biceps function is anticipated. By 2 months of time those who are not able to flex at the elbow, and sooner for those with additional nerve involvement such as phrenic or Horner's, should be confirmed that they have connected with a brachial plexus injury center or neurosurgeon specializing in brachial plexus injury treatment and repair.

Surgical treatment of BPI is evolving. At present, approximately 10% of infants with BPI will require some form of surgical intervention, either primary nerve grafting or secondary reconstruction. Key criteria for surgical intervention vary by center, but most decisions are based on biceps functioning at 3 months of age. Those with natural recovery of function before 3 months or surgical repair between 3 and 6 months do better in terms of long-term functioning than those who are delayed until after 6 months. Most of the evidence for surgical repair is from case reports and offers a 60–80% improvement in function postoperatively. After 12–18 months, most would agree that there is little benefit to primary neurosurgical intervention. At that point, surgery is indicated to reduce contractures or deformities. Also these patients will need to be screened for the development of posterior shoulder dislocation that can occur in up to 7.3%. It cannot be stressed more, how critical careful follow-up and early intervention is in effectively minimizing long-term disabilities for these newborns.

Phrenic Nerve Palsy

Phrenic nerve paralysis often coexists with brachial plexus injury and is believed to arise by similar mechanisms. Injury to the upper root of C4 which innervates the phrenic nerve (recall the mnemonic: "3, 4, 5, keeps the diaphragm alive") can present as paroxysmal breathing patterns, increased work of breathing, asymmetric chest movement or the "dancing" umbilicus, cyanosis or tachypnea due to the diaphragm paralysis. Injury to C4 should be considered with careful auscultation of the breath sounds at the bases for symmetry in any infant with Erb's palsy. Phrenic paralysis can be related to trauma but the differential diagnosis in cases of bilateral involvement also includes genetic disorders such as muscular atrophy (Werdnig–Hoffmann) and acid maltase deficiency.

Phrenic nerve involvement can be diagnosed by plain films with elevation of the affected hemidiaphragm (*Fig. 12.10*); however, ultrasonography is preferred to

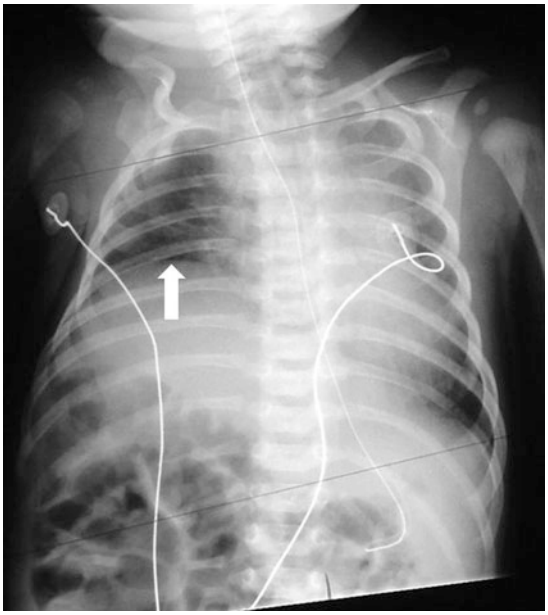

Figure 12.10
Radiograph with elevated right hemidiaphragm from phrenic nerve palsy. *Arrow* points to the elevated right diaphragm. This is a preoperative image before plication of the diaphragm on a patient admitted for feeding difficulties/failure to thrive (Image from the patient files of Joseph Bliss, MD, PHD)

analyze the pattern of movement with respirations. These newborns should be observed carefully for respiratory distress especially during their feedings as some may need additional mechanical support of respiration. Mechanical ventilation may obscure the diagnosis. Infants requiring prolonged ventilatory support need surgical evaluation as some may require plication of the affected diaphragm to correct the paradoxical diaphragmatic motion. Phrenic nerve involvement does not help in determining the prognosis of the motor recovery of the upper extremity palsy.

Lower Extremity Injury

Injury to the lower extremities from birth trauma is rare and includes femoral fracture, epiphyseal separation, joint dislocations primarily of knee and hip. Injury to the lower extremities presents as decreased movement, swelling, pain, and crepitus. Femoral fractures occur in approximately 0.13 per 1,000 births. Fracture of the femur is diagnosed by plain X-rays, but epiphyseal injury in the newborn requires ultrasonography as they are not yet ossified at birth. Long bone fractures heal well but may need to be splinted and immobilized for comfort. Proximal fractures of the femur may need spica casting or Pavlik harness to assist in immobilization. Pavlik harnesses needs to be applied carefully as an inappropriate fit may cause femoral nerve palsy and avascular necrosis. Orthopedics consult is appropriate for fractures of the femur especially with displaced fractures as these may need closed reduction and casting. Similar to other newborn fractures like the clavicle, a callus forms at the site of fracture with bone reorganization in 7–10 days.

Congenital hip dislocation is usually not a result of birth trauma but from developmental hip dysplasia, with increased incidence in newborns born breech or in breech positioning in utero late in pregnancy (estimated 35 weeks or later), female gender, and those with a family history of developmental hip dysplasia. Treatment of the subluxable hip is the same regardless of cause and includes continuous placement in the Pavlik harness and monitoring with serial ultrasound measurements of hip angles. Dislocation of the knee or hip should be referred to orthopedic surgeons for ongoing management. The subluxable or dislocated knee can be associated with other syndromes. Prognosis for these conditions is generally good.

Intra-abdominal Injury

Intra-abdominal injury from birth trauma is rare but can involve the liver, spleen, and adrenal glands. Injury is more common with prematurity, coagulation disorders, asphyxia and with hepatosplenomegaly or other organ enlargement such as of the adrenals in Beckwith–Wiedemann syndrome. Abdominal organs are relatively protected, but mechanisms of injury include direct trauma, damage from rib edges to the liver or spleen, or from chest compressions tearing ligamentous insertions into the liver or spleen. Bleeding from trauma to these organs can either be insidious, collecting in subcapsular hematomas or fulminant from frank rupture that leads to rapid clinical deterioration with shock. Postmortem examinations of early neonatal deaths reveal that 15% have some type of liver hemorrhage. The most common abdominal injury is subscapular hematoma of the liver. These can increase slowly until reaching a critical size of 4–5 cm before rupture. Splenic hemorrhage occurs one-fifth as commonly as those to the liver. Diagnosis should be suspected in any newborn with history of difficult delivery, or who presents with unexplained anemia, abdominal distention, hypovolemia, or hemorrhagic shock. Rupture of either the liver or spleen can cause scrotal swelling or discoloration as blood passes through

the patent processus vaginalis. Adrenal injury occurs in 1.9 per 1,000 births due to the larger size of the adrenal glands in the newborn. Adrenal injury can present with subtle symptoms like poor feeding, lethargy, jaundice, or irritability or may present symptoms similar to those found with injury to the liver and spleen. Palpable masses in the flank may be present. In adrenal rupture, scrotal swelling and discoloration can occur through the aforementioned mechanism with liver or spleen injuries, or directly through retroperitoneal extension. Diagnosis of abdominal injury can be made by CT but many infants are too unstable and the diagnosis will be made by ultrasonography at the bedside. For all cases, treatment starts with supportive care with special attention to volume support and fluid resuscitation as necessary. Early surgical consult is important as there can be rapid deterioration. Surgical intervention is indicated to stabilize the newborn, or stop uncontrollable bleeding. In terms of adrenal hemorrhage, damage or removal of one (or both) of the glands can result in adrenal insufficiency requiring replacement to treat hypoglycemia, hypotension, and hypernatremia. Hypertension can be a late complication of adrenal injury. As mentioned previously, the diagnosis of abdominal injury, especially to the liver or spleen, is often discovered postmortem. Prognosis is dependent on early recognition, active management of blood loss, and the ability to control the bleeding. For those who survive with preservation of the organs, the prognosis is generally good.

Conclusion

Birth-related injury is a very common occurrence that in many cases may not be avoidable. Even so, as we seek to improve medical care around the world, it is important to keep searching for methods to decrease as many of these injuries and their sequelae as possible. Fortunately, most birth injuries are superficial and self-limited. For the rare more serious injuries, it is imperative that the practicing pediatric provider recognize the risk factors and signs of these conditions, and then take action to appropriately manage them both in the short and long term.

Resources

1. Stanford University Newborn Nursery Photo Gallery: A great site for pictures of many newborn findings, compiled by Janelle Aby, MD. http://newborns.stanford.edu/PhotoGallery/
2. Springer Images: http://www.springerimages.com/. A warehouse for various pictures found in previous Springer Publications including examples of rarer findings, such as:

(a) CT Scan of Newborn with Cephalohematoma and Epidural Hematoma found at SpringerImages:

On CT scan, a concomitant depressed fracture is present together with an EDH and cephalohematoma. **a** Axial view; **b** coronal view.

With kind permission from Springer Science+ Business Media (Child's Nervous System, 2010, Motomi Noguchi, Figure 2, Copyright 2010 by Springer).

(b) Infant with Congenital Horner's Syndrome found at SpringerImages:

Congenital Horner syndrome. Note right upper lid ptosis, right miosis, and mild heterochromia. Right lower lid shows mild reverse ptosis, covering more of cornea than its left counterpart.

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13 The High-Risk Infant

Tonse N. K. Raju

Definitions

A "high-risk infant" is broadly defined as one who requires more than the standard monitoring and care offered to a healthy term newborn infant. Thus, infants born pre- or post-term, those with inappropriate growth for gestational age, those with manifest signs and symptoms of systemic illnesses, metabolic abnormalities, or congenital malformations requiring early evaluation and treatment are considered "high-risk infants." An important determinant of risk categorization is the overall condition of the infant, which often requires continuous monitoring, and specialized tests and treatments. Common conditions considered "high risk" in the modern neonatal intensive care unit (NICU) are listed in *Table 13.1*.

Levels of Care

The clinical condition of the infant should also determine the appropriate level of monitoring and care available in the healthcare facility. The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) Policy Statement recommends three major levels of newborn care with specific criteria outlined for each designation. The policy stems from the recognition that maternal and neonatal care should be based on matching the complexity of the illness with the availability of resources. In the mid-1970s, this concept spearheaded a nationwide movement in the USA, leading to regionalized perinatal care system in many states. Similar progress occurred in other industrialized nations, too. The regionalized perinatal system helps provide care that matches the needs of the high-risk infant, and when local resources are limited, for a timely referral to other facilities. A revised AAP policy on the levels of neonatal care is expected to be published in 2011.

Gestation Age and Postnatal Age Terminologies

Using consistent definitions to describe the duration of gestation, postnatal age, and fetal growth parameters are helpful for effective communication. Poster-size pictures of *Fig. 13.1* and *Table 13.2* in newborn units may help the staff to use consistent terminology and avoid confusion in designating gestational and postnatal age categories. For reporting purposes, a "gestational week" is assigned only after the completion of full 7 days, as explained below.

Gestational Age Terminology

Gestational age in completed weeks is the time elapsed between the first day of the last menstrual period and the day of delivery. If pregnancy was achieved using assisted reproductive technology, gestational age is calculated by adding 2 weeks to the conceptional age.

Term births are those that occur between 260th day through the 294th day, or $37^{0/4}$ through $41^{6/7}$ weeks of gestation. Because of their increased risk for morbidity and mortality (see below) some authors further categorized the first 2 weeks of term gestation (for those born between 260th through 274th day, or $37^{0/7}$ through $38^{6/7}$ weeks of gestation) as "early term" (*Fig. 13.1*).

The World Health Organization (WHO) defines "preterm birth" as delivery occurring before 37 completed weeks of gestation, or on or before the 259th day (*Fig. 13.1*). The week of the gestational age is rounded off to the nearest completed week of gestation. Thus, infants born 5 days after 35 weeks of gestation will be 35, not 36 weeks of gestation. The superscript may be used to reflect the number of days lapsed since the completed week, as $35^{5/7}$ in the above example.

The National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention (CDC) also provides data on three subcategories of preterm births. Late preterm births are those that occur between $34^{0/7}$ and $36^{6/7}$ weeks of gestation (239–259 days), moderately preterm births are those that occur between 32 and 33 weeks of gestation, and very preterm births are those that occur before 32 weeks of gestation.

"Post-term births" are those that occur on or after the 295th days, or the 42nd week of pregnancy (*Fig. 13.1*).

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_13,

Table 13.1
Conditions that determine "high-risk infant" designation

Time	Condition/diagnosis and comments
Immediate peripartum period, either in the delivery room, or in the stabilization area, usually obvious at birth, or within 10–20 min after birth	Pre- or post-term birth
	Requiring resuscitation in the delivery room
	Perinatal asphyxia
	Congenital infections (e.g., syphilis, CMV, toxoplasmosis, herpes simplex)
	Cardiopulmonary distress
	Drug withdrawal syndrome requiring monitoring
	Suspected or proven congenital malformation requiring immediate evaluation and/or treatment
	For example, congenital heart disease
	Omphalocele, gastroschisis; prune belly syndrome
	Meningomyelocele, hydrocephalus, etc
	Ambiguous genitalia
	Chromosomal anomalies, especially those with manifest distress
	Multiple congenital anomalies
Early neonatal period (The first day)	Small or large for gestational age
	Cardiorespiratory distress
	Drug withdrawal syndrome requiring monitoring
	Suspected/proven neonatal sepsis
	Seizures
	Metabolic abnormalities (e.g., hypoglycemia; hypocalcemia); anemia
First week and beyond	Jaundice requiring exchange transfusions
	Sepsis
	Necrotizing enterocolitis
	Other surgical conditions
	Bleeding diathesis and other hematological conditions

Postnatal Age Terminology

The AAP recommends precise postnatal age terminology. These concepts are explained in *Table 13.2*. Chronological age, in days, weeks, months, or years is the time elapsed from birth; postmenstrual age in weeks is gestational age plus the chronological age; corrected age in weeks or months is chronological age reduced by the number of weeks born before 40 weeks of gestation. The later term should be used only for children up to 3 years of age who were born preterm.

During the perinatal period and neonatal hospital stay, the term "postmenstrual age" is preferred to describe the age of preterm infants. After the perinatal period, "corrected age" is the preferred term. According to the AAP, one should avoid using such terms as "conceptional age," "postconceptional age," "conceptual age," and "postconceptual age," and scientific publications reporting on fetal and neonatal outcomes should clearly describe the methods used to determine gestational age.

Variations in Intrauterine Fetal Growth

With the gestational age information and anthropometric measurements (see below), infants are classified according to the appropriateness of growth for gestational ages. This is particularly important for high-risk infants, since such categorization helps identify specific risks factors.

Appropriate, Small, and Large for Gestational Age and Intrauterine Growth Restriction

Infants with a birth weight between the 10th and the 90th percentile for gestation are referred to as appropriate for gestational age (AGA). The term "average" for gestational age should be avoided, as an infant who is at the 80th percentile is appropriate for gestational age, but is well above average. Those with a birth weight below the 10th percentile are referred to as small for gestational age (SGA), and those above the 90th percentile are referred to as large for gestational age (LGA). Some experts recommend considering those with a birth weight below two standard deviations from the mean birth weight for the gestation as SGA, and those with more than two standard deviations above the mean birth weight for gestation as LGA. The latter definitions lead to considering SGA as those below the 3rd percentile and LGA as those above the 97th percentile birth weight for gestational age,

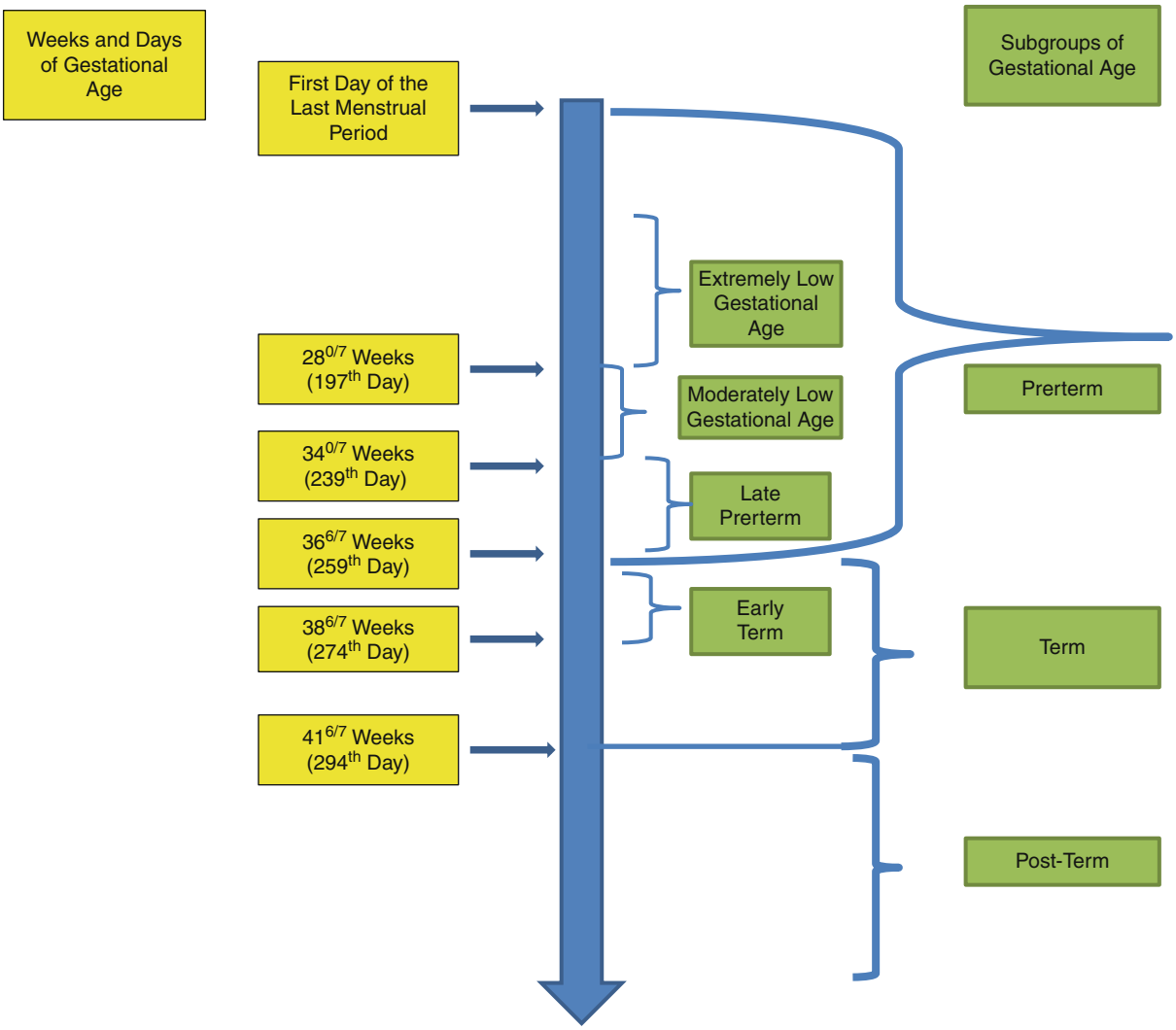

Figure 13.1
Gestational age terminology (Note: The phrase "Early term" is not universally accepted. The remainder is modified from the reporting practice of the National Center for Health Statistics, of the Centers for Disease Control and Prevention, USA. CDC web site is publicly accessible: www.http.cdc.gov)

respectively. Furthermore, such "conservative" estimates of deviations from anticipated fetal growth helps identify the subsets of SGA and LGA infants with the highest risk for neonatal mortality and morbidity.

IUGR and SGA Distinction

The terms SGA and intrauterine growth restriction (IUGR) are often used interchangeably, which is not correct. While most (not all), IUGR infants are likely to be SGA, not all SGA infants are IUGR. IUGR is due to the processes, mostly pathological, that affect the growth potential of the fetus, whereas small size for gestation is a reflection of birth weight being less than a set threshold, or "norm," based on the population distribution of birth weights. Therefore, a healthy SGA infant may be constitutionally small without any pathology.

When assessing the appropriateness of intrauterine growth, the ponderal index (weight divided by length cubed) and relative proportions of other body measurements (e.g., head circumference to weight, or femur length-to-abdominal circumference ratios) may be more useful than birth weight in distinguishing IUGR from

Table 13.2
Age terminology during the neonatal period

1.	Gestational age: (a) Days elapsed between the first day of the last regular menstrual period and the day of delivery of fetus, or fetuses (b) Count only completed weeks; any fraction thereof be shown with a superscript as described in the text
2.	Chronological age: (a) Infant's age counting from the day of birth, expressed in days, weeks, months, or years (b) Typically rounded off the completed month (e.g., 1 year and 5 months, or 17 months of age)
3.	Corrected age: (a) Chronological age minus the number of weeks or months born before 40 weeks of gestation (e.g., a preterm infant born at 28 weeks of gestation at one year of age will be of 9 months of corrected age) (b) For infants born preterm, the correction is applied only up to 3 years of age
4.	Postmenstrual age: (a) Chronological age plus the gestational age expressed in weeks (b) Usually used during the first months of hospitalization for preterm infants; or in research studies for all infants for consistency

SGA. IUGR infants tend not to gain weight to a greater extent than failure to gain in length or head circumference. Thus, their relatively large head sometimes has been referred to as "head sparing." The time course of intrauterine pathology also differentially influences growth rates of organ systems. Placental pathology early in pregnancy causes more uniform reduction in all of the growth variables (symmetric growth restriction) as opposed to pathology later in pregnancy that tends to affect weight to a greater extent than length and head size.

For further discussions on the deviations from normal fetal growth and the obstetric aspects of SGA, IUGR, and LGA, please consult other chapters in this section (Chap. 8, "Pregnancy: Intrauterine Development and Assessment").

Physical Examination and Gestational Age Assessment of the High-Risk Infant

Infants are assessed and given Apgar scores at 1 and 5 min of age (Delivery Room Stabilization). If the scores remain low, assessment is continued at 5-min intervals until the score reaches 7 or more, and the time to reach this threshold is recorded in the medical records. The infant is also assessed for general well-being, and when stable, a complete physical examination is performed as described elsewhere (Care of the Normal Newborn). For high-risk infants, when clinical conditions require, plans need to be made for continued monitoring during their hospital stay.

Routine body measurements to be obtained are birth weight, crown-heel length, and head and abdominal circumferences, which are plotted on intrauterine growth curves to facilitate infant classification. One should also calculate the ponderal index to assess growth asymmetry.

Gestational age calculated using maternal menstrual history is very helpful, especially if supported by fetal ultrasound studies done at or before 20 weeks of gestation. These estimates are accurate to ± 1 or 2 weeks. For clinical assessment of gestational age, one of several published scoring methods can be used. In the USA, the New Ballard scale is the most frequently used method. Other methods are also available, all of which provide reasonably accurate estimates of the gestational age. It is more important to develop proficiency in one method to ensure accuracy and consistency of assessment.

Two sets of clinical features are included the New Ballard scoring system. One set of physical features include, the skin texture; distribution of lanugo; the extent of the plantar crease; the thickness of the breast tissue nodule; the stiffness of the ear pinna; and the maturity of the external genitals. In male infants, the extent of the descent of the testes is assessed, and in females, the appearance and the size of the clitoris and the labia are assessed. The second set of neuromuscular features include the posture; the "square window" (the extent infant's hand can be flexed toward the wrist); arm recoil; popliteal angle; the "scarf" sign; and the heel-to-ear maneuver. The total score is then used to assign the gestational age in weeks.

The New Ballard score provides an estimation of gestational age to within 1–2 weeks accuracy. The neurological features are more stable and less variable among healthy infants. Decreased neuromuscular tone may be encountered in sick infants, affecting the neurological score. If the discrepancy between the obstetric estimate and clinical assessment exceeds 2 weeks, one needs to ascertain the accuracy of obstetric history, and reassess the gestational age, if possible by a different examiner after a period of 24 h. In preterm infants, the New Ballard score has been shown to be reliable up to 7 postnatal days.

Common Clinical Problems Associated with High-Risk Infants

Thermoregulation

High-risk infants should be cared for in a neutral thermal environment, defined as the ambient temperature and humidity settings at which the oxygen consumption required to maintain the internal body heat is at its lowest. When exposed to a cold environment, newborn infants rely upon non-shivering mechanism to generate internal heat, enhancing oxygen consumption. However, since oxygen consumption is not routinely measured, a common practice to determine the optimal ambient thermal environment is to base it on the previously developed charts and graphs, keeping in mind, the general principles of thermogenesis in high-risk infants. The hypothalamus in mature infants exposed to cold releases norepinephrine, which leads to a breakdown of brown adipose tissue to fatty acids and the oxidation of the latter generates internal heat. However, preterm, SGA, and IUGR infants are deficient in brown fat, and their neural responses to cold may be inadequate. Thus, the smaller and more immature an infant, the narrower is the required ambient neutral thermal environment.

In most modern neonatal units, sick newborn infants are cared for inside double-walled incubators or under overhead-warming intensive care beds, which are equipped with servo-controlled systems for maintaining the infant's skin temperature at 98.5 ± 0.5° F. This topic is covered in more detail in Chap. 14, "Thermoregulation/Environment".

Abnormalities of Glucose Homeostasis

The mammalian fetus relies upon placental transport of glucose and other nutrients for growth and development. Termination of this supply at birth leads to an immediate demand for maintenance of glucose homeostasis through the initiation of glucose production in the newborn. Such transitions occur smoothly in most newborn infants; but in SGA, IUGR, and LGA infants, the transition may not be smooth, leading to low plasma glucose concentrations, with or without manifest signs and symptoms.

However, since the "natural history" of the glucose changes following birth in healthy infants has not been studied using continuous, noninvasive methods, "postnatal euglycemia" remains undefined. Therefore, at present there is no universally accepted definition of clinically significant, transient neonatal hypoglycemia. An NIH expert panel concluded that, "there is neither a rational basis nor sufficient evidence to identify a specific value or a range of plasma glucose concentrations that would define hypoglycemia as a pathological entity." The complexity of postnatal homeostasis has also been discussed in other excellent reviews. Some experts recommend that plasma glucose concentrations <40–45 mg/dL after birth (which occurs in ~5–15% of normal newborn infants), may be deemed as operational threshold for supplementing glucose or additional feeding. The AAP Clinical Report on this topic is currently in print; this will provide additional guidelines on monitoring and treating altered neonatal glucose homeostasis in term and late preterm infants.

Compared to term infants, the incidence of low concentration of plasma glucose after birth (persisting for several hours, and rarely for a few days) is higher among SGA and IUGR infants. This is due to low hepatic concentrations of glycogen stores, immature hepatic enzymes (glucose-6-phosphatase), decreased ketogenesis, and increased brain-to-body mass ratio with increase in relative brain consumption of glucose in these infants. On the other hand, in LGA infants, especially those born of diabetic mothers, hyperinsulinemia is considered a major cause for drops in plasma glucose concentration after birth.

For infants at risk for hypoglycemia, early initiation of breastfeeding is an important first step. If the infant is feeding well and has no clinical symptoms, some experts recommend bedside check of glucose *after the feeds* between 1 and 4 h of age. Such tests are done immediately, when symptoms suggestive of hypoglycemia, for example, jitteriness seizures occur. If plasma glucose levels are below 35 mg/dL in asymptomatic infants, some experts recommend additional feeds or oral glucose supplements with a goal to raise the plasma glucose concentrations above 40 mg/dL.

However, repeated additional feeding (especially commercial formula or glucose solutions) may impede success rates for breastfeeding. Therefore, the WHO recommends that in asymptomatic LGA infants with no maternal history of diabetes, bedside glucose checks should be avoided during the first 4 h or longer, to prevent unnecessary interference with the normal process of breastfeeding. This is an advice especially valuable in resources-limited parts of the world. Additional details concerning hypoglycemia and its management are discussed elsewhere (Chap. 29, "Disorders of Glucose Homeostasis in the Newborn"), and a new Clinical Report from the AAP on the management of altered glucose homeostasis in term and late preterm infants is under review for publication in 2011.

Feeding and Nutritional Issues

Due to the immature sucking and swallowing reflexes, even otherwise healthy preterm infants may feed poorly. Nasogastic tube feedings may be considered using mother's expressed breast milk, or where resources permit, banked human breast milk. Human milk is to be preferred to commercial infant formula. If oral feedings are not possible because of illness, intravenous alimentation should be begun, usually within the first 24 h. Fluid and nutritional support and other medical conditions of high-risk infants are discussed elsewhere in this Section.

Late Preterm Infants: A Special Category of High-Risk Infants

Since the publication of the executive summary of a workshop on late preterm births sponsored by the NIH, and a Clinical Report on the same topic by the AAP, there has been a greater awareness that late preterm infants are indeed "high-risk." In fact, recent studies have shown that compared to those born at 39 or 40 weeks, even early term infants born at 37 or 38 weeks of gestational age are at risk for higher risks for neonatal morbidity and mortality, underscoring the dictum that maturation is a continuous process, and no single calendar date can be considered to provide assurance that all organ systems are completely mature. This is in part true because individual infants have different rates of maturation, resulting in substantial differences in physiologic maturity in infants of the same gestational age.

The NIH and AAP reports also recommended discontinuation of the phrase "near-term," because the latter implies that such infants are "almost term," requiring no special monitoring or care. Because of their growing importance and high prevalence, the section that follows provides a detailed, albeit brief, discussion on the epidemiology and clinical issues in late preterm infants.

The US preterm birth rate increased each year since 1992, reaching an all-time high of 12.8% in 2006. The rates have dropped slightly in 2007 and 2008; yet, each year more than 375,000 late preterm births (8.8% of all live births) occur in the USA. Since 75% of all preterm births are late preterm gestations, even a slight increase in the risk of illness in this group has a major impact on healthcare resources.

Possible contributing factors for increasing rates of preterm births include: increasing maternal age at first pregnancy, higher proportion of pregnancies conceived through artificial reproductive technologies (with higher risks for multi-fetal pregnancies), and increased rates of labor-inductions and cesarean births at all gestations. A recent study found that the average gestational age at term births dropped about 0.33–0.42 weeks over a 15-year period in the USA (◉ *Fig. 13.2*). The authors hypothesized that higher levels of stress or environmental pollutants may be the unmeasured causes for shortened pregnancy durations across the population. Some nonmedical reasons for increasing preterm births include parental requests, the convenience and logistical reasons of the healthcare team, and errors in estimating gestational age. However, the relative proportions of the causes leading to increased preterm birth rates have not been studied.

About 60% of preterm births are due to spontaneous onset of preterm labor, with or without rupture of the fetal membranes prior to the onset of labor, and the remainder are "indicated" preterm births due to interventions carried out because of specific medical, surgical, or obstetric conditions in the mother or the fetus (◉ *Fig. 13.3*).

A recent study found that in about 20% birth certificates of late preterm births, no specific medical, obstetrical, or fetal condition was documented as the cause for preterm birth (◉ *Fig. 13.4*). The authors implied that these might be due to nonmedical indications. Sociodemographic factors also have been etiologically linked to spontaneous onset of preterm labor, which include black race/ethnicity, maternal age <17 years or >35 years, smoking, substance abuse, and poor socioeconomic status. Note that many of these factors are interrelated and may coexist along with medical or obstetric pathological conditions.

Outcome Data for Late Preterm Infants

The neonatal and infant mortality rates, as well as cause-specific mortality rates, are much higher in late preterm infants than in term infants. Among the late preterm infants with a maternal history of hypertensive disorders of pregnancy, antepartum hemorrhage, diabetes, infections, or chronic renal, lung, or cardiac disease, the morbidity risks were 10- to 14-fold higher compared to term infants with similar history. The morbidity rates also doubled for each gestational week earlier than 38 weeks, implying an independent effect of low gestational age on morbidity. Some specific conditions leading to poor outcome in late preterm are described below.

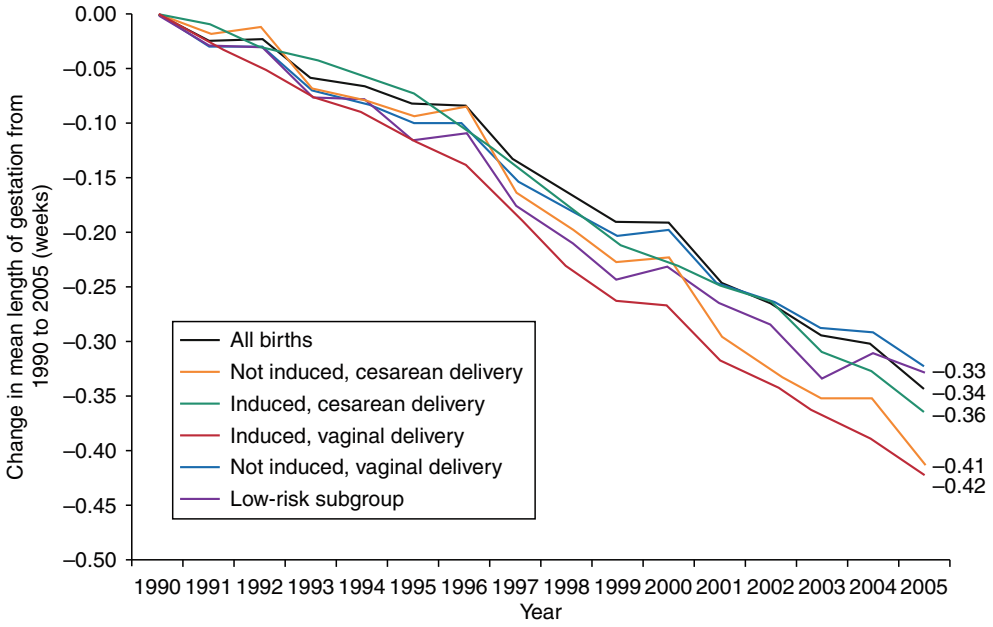

Figure 13.2

Trends in length of gestation from 1990 to 2005, according to induction of labor status and route of delivery, among 36,827,828 singletons born at 37–41 completed weeks of gestation, and among a low-risk subgroup of 502,716 singleton neonates born to mothers aged 25–29 years, of non-Hispanic white race/ethnicity, with 13 or more years of education, of married status, who received prenatal care in the first trimester, were nonsmokers, had no pregnancy complications, delivered vaginally, did not have labor induced, had a prenatal ultrasound examination, and gained 26–35 lb during pregnancy (Reproduced from Donahue SM, Kleinman KP, Gillman MW, Oken E (2010) Trends in birth weight and gestational length among singleton term births in the United States: 1990–2005. Obstet Gynecol 115 (2 Pt 1):357–364. With permission)

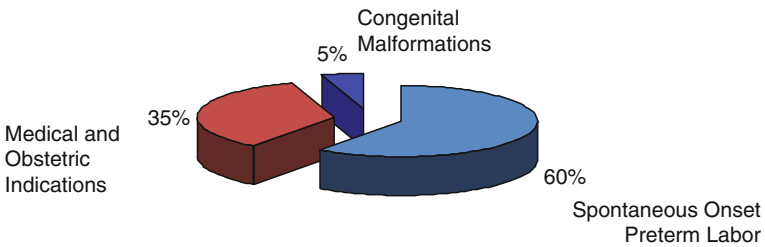

Figure 13.3

Possible causes of preterm births (Redrawn based on compilation of statistics from various publications)

Rehospitalization

For late preterm infants, the rates for readmissions to the nursery within 4 weeks of initial discharge was between 5.3% and 9.6%, compared to 3.6–4.4% for term infants, with the risk increasing threefold if the initial hospital discharge occurred at <96 h of age. Common reasons for readmission were jaundice, feeding difficulties, poor weight gain, dehydration, and apnea with apparent life-threatening events.

The risk for hospital admission is higher for late preterm infants compared to term infants throughout the

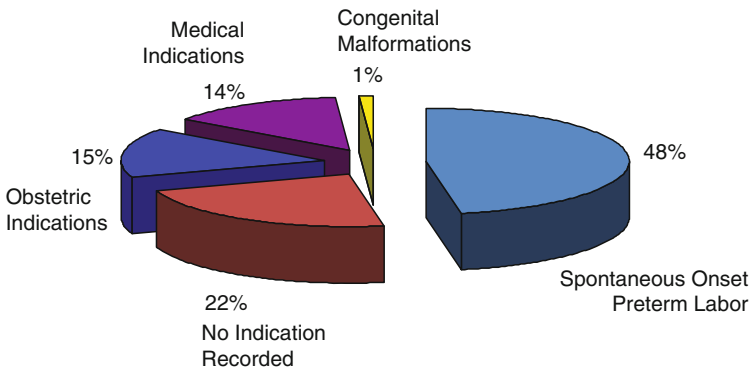

Figure 13.4
Delivery indications for late preterm births compiled using various published data sources

first year of age. A California study found that 13% of infants born at 35 weeks were readmitted at least once during the first year of age, adding $80 million to the healthcare cost.

Specific Morbidities Associated with Late Preterm Births

Hypothermia and hypoglycemia: Late preterm infants develop hypothermia and hypoglycemia far more quickly and more often than term infants. Since they generally appear normal at birth, they are likely to be left in the delivery room with their mothers or to be "rooming-in" with minimal monitoring. Of the 196 infants consecutively admitted to a newborn nursery, 48.8% were hypothermic (core temperature <36°C). Over half of the hypothermic infants were late preterm, who became hypothermic while in the delivery room. Neonatal hypoglycemia is nearly threefold higher in late preterm compared to term infants (14% vs 5.3%), because of some of the reasons noted above.

Respiratory distress: About 1–4% of late preterm infants develop some form of respiratory distress, including the classical respiratory distress syndrome (RDS). The risk for RDS is higher when there is no exposure to antenatal steroids. A failure of fetal pulmonary surfactant surge that usually occurs at 34 weeks may be one reason for RDS in late preterm infants. Maternal diabetes or planned cesarean delivery in the absence of labor increases the risk for RDS due to lack of labor-related biochemical changes that enhance fetal lung maturation and facilitate pulmonary fluid clearance. Transient tachypnea of the newborn, absorption atelectasis, and persistent pulmonary hypertension are also other causes of respiratory distress in late preterm infants.

Hyperbilirubinemia: Because of immaturity and delay in the development of hepatic bilirubin conjugation pathways, late preterm infants are more likely than term infants to develop physiological jaundice, to have higher serum bilirubin concentrations, and to have longer duration of jaundice. In addition, feeding difficulties lead to delay in the resolution of enterohepatic recirculation of bilirubin and cause an increase in the systemic bilirubin load. Immaturity of the bilirubin blood–brain barrier functions, lower circulating albumin concentrations for bilirubin-binding, and concurrent illnesses increase the risk for bilirubin-induced brain injury and kernicterus in late preterm infants.

The AAP has recommended steps to treat neonatal jaundice based on hour-specific bilirubin values in high-risk as well as term infants.

Feeding and apnea: Oro-buccal coordination and swallowing mechanisms remain immature in most late preterm infants, leading to considerable difficulty in establishing successful feeding, especially breastfeeding. Late preterm infants also have a higher frequency of gastroesophageal reflux, further reducing food intake and affecting weight gain. In some cases, this chain of events leads to dehydration and hypernatremia during the first few weeks of life and may lead to severe hyperbilirubinemia, which in turn makes feeding difficulties worse. This interruption of adequate protein and caloric intake at a critical part in brain growth and development may have significant adverse effects (discussed further below). Both obstructive and mixed apneas occur at higher frequencies in late preterm than in term infants.

Brain maturation and development: Recent imaging and pathological studies have shown that the brain remains significantly immature in late preterm relative to term infants. The external surface at 34 weeks of gestation shows fewer sulci, and the brain weight is only 65% of full-term infant's brain weight. Between 35 and 40 weeks gestation, there is also a marked increase in synaptogenesis, neuronal connectivity, and dendritic arborization. Using advanced neuroimaging studies at 9 years of age in 192 infants who were born between 32 weeks gestation and term, a recent study noted a significant reduction in cerebellar volumes in relation to earlier gestations, independent of birth weight, sex, and intracranial volume. Cerebellar injury has been recognized as an important contributor to adverse motor, language, and social–behavioral outcomes.

Taken together, the above anatomical changes, and higher prevalence of morbidities may be the underpinnings of brain injury in late preterm infants, which might explain the reasons for the reported cognitive deficits documented in late preterm infants during school age (see below).

Learning disabilities and scholastic problems and adult age outcomes: Several recent reports have raised concerns about the long-term neurological and psychological outcomes for late preterm infants. In a cohort of 970 preterm and 13,671 term infants from a longitudinal study, late preterm infants on average performed worse on reading and math tests from kindergarten through fifth grades. The requirement for special education at early grades was also higher for the late preterm group compared to the term counterpart (odds ratio, 1.4:2.1). A Norwegian study based on a national cohort found that in nearly 33,000 adults born at late preterm gestations, most psychosocial measures were 50–200% worse compared to those born at term.

Thus, the burden of short- and long-term morbidities should be a matter of great concern for those caring for late preterm infants. The AAP has made the following recommendations for the care of late preterm infants.

Prevention of non-indicated preterm births: In the absence of medical or obstetric indications, no planned, induced vaginal or planned cesarean delivery is to be conducted prior to 39 weeks of gestation.

Clinical assessment and transitional care: All infants need accurate assessment of gestational age and comprehensive clinical examination within the first hours of birth. Close monitoring of temperature and feeding patterns during the transitional period is needed to avoid delayed recognition of feeding problems, jaundice, and hypoglycemia.

Feeding adequacy and stability of vital signs: Irrespective of the method of feeding, late preterm infants should be monitored for the adequacy of feeding, age-appropriate changes in weight and well-being. An infant who is losing >3% of body weight in a single day, or a total weight loss of >7% at any time needs further evaluation for dehydration and feeding status.

Hyperbilirubinemia: Early assessment, monitoring, and implementation of treatment should be based on the AAP guidelines.

Timing and preparation for discharge: Individualized timing of discharge should be based on overall stability, feeding status, and clinical well-being. Prior to discharge, a successful pattern of breastfeeding needs to be demonstrated for at least 24 h, and that the infant must have had normal passage of at least one stool. Other predischarge requirements are those that are recommended by the AAP for all high-risk infants (see below).

Follow-up: When the infant is discharged prior to 48 h, a repeat visit needs to be planned 24–48 h after discharge. During this visit, one needs to assess the overall well-being, nutritional status, and the status of jaundice. Additional visits may be needed based on clinical course. Late preterm infants also need thorough evaluation of neurological status during all their subsequent clinic visits.

Education: Healthcare providers caring for late preterm infants throughout the pediatric age group need to be educated about the vulnerability of this cohort of infants and a need for close surveillance and comprehensive follow-up. Parents and family members should be educated about the special needs of late preterm infants during the first months of life.

Hospital Discharge Planning for All High-Risk Infants

As per the AAP Policy Statement, special attention should be given during discharge planning for all high-risk infants, since for many, medical care may be needed even after discharge. The group of infants qualifying for special consideration include all preterm infants; infants with special health care needs or dependence on technology; infants at risk because of family issues; and infants with anticipated early death. The plan should be individualized to ascertain that the infant is physiologically stable; the parents are involved and are ready for the care of their infant at home; arrangements have been made for healthcare after discharge by a physician, or other healthcare professionals with experience in the

care of high-risk infants; and an organized program for tracking and surveillance to monitor growth and development.

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14 Thermoregulation/Environment

Andrew James Lyon

Children and adults maintain a constant deep body temperature over a wide range of ambient thermal conditions (homeothermic). This is achieved by physiological and behavioral responses that control the rate at which heat is produced and lost. The newborn infant is also homeothermic but control of body temperature can only be achieved over a narrower range of ambient conditions. The preterm infant has even greater difficulty in body temperature control, and the most immature infants behave at times as if they are poikilothermic – their body temperature tending to drift up and down with the ambient temperature. The aim in neonatal care is to provide a thermal environment which keeps body temperature in the normal range, and which does not stress the infant to produce or lose large amounts of heat.

The importance of thermoregulation in the newborn has been recognized for a long time. In late nineteenth century Paris, Tarnier, and Budin reduced by half the mortality of infants, under 2,000 g birthweight, by nursing them in a warming chamber they designed from an incubator used for rearing poultry. In a series of randomized controlled trials in the 1950s, William Silverman showed that keeping babies warm resulted in a 25% absolute reduction in mortality in all birthweight groups, including those under 1,000 g. Subsequent studies in the 1960s showed a significant reduction in death rate among low birthweight infants when their abdominal skin temperature was maintained at 36°C (relative risk 0.72–95% CI 0.54, 0.97). This effect was even greater among the very low birthweight infants.

Despite the lessons from these studies, there is evidence that newborn babies today are still being allowed to get cold and hypothermia, especially in the preterm infant, remains independently associated with increased mortality.

Heat Balance

Heat is produced as a by-product of cell metabolism. The basal metabolic rate is the lowest obligatory rate of heat production which occurs when an individual is starved, quiet, and resting. In the newborn, this is usually taken as the minimal rate of oxygen consumption in an infant who is lying still and asleep, at least 1 h after a feed in a neutral thermal environment. Values depend on gestation and postnatal age. Heat production must be balanced by that lost from convection, radiation, evaporation, and conduction.

The more immature the infant, the greater the difficulty in temperature control. Heat loss is related to surface area, which is relatively high in the smaller babies. There is reduced insulation due to lack of subcutaneous tissue and the poorly developed stratum corneum results in high transepidermal water loss (TEWL) and evaporative heat loss. TEWL is related to both gestational age and postnatal age. The ability to conserve heat by vasoconstriction is limited, and heat production, which is related to mass, is low. This poor response to relatively high heat losses means that hypothermia is a common problem in the immature baby.

Response to Thermal Stress

The thermoneutral environment is a range of environmental temperature over which an infant has a minimum rate of heat production and is not sweating. Within this range, small adjustments to thermal control can be made by alterations in posture, activity, and skin blood flow with deep body temperature remaining constant. The thermoneutral range is wide if the infant is mature and well insulated by clothes and bedding, but narrow in the small and naked baby. As environmental temperature falls below the lower end of the thermoneutral range, the newborn baby is unable to shiver but increases metabolic heat production. This is mainly the result of oxidation of brown adipose tissue which is distributed in the neck, between the scapulae and along the aorta. The metabolism of brown fat to produce heat is controlled by catecholamine release (non-shivering thermogenesis). A term newborn infant can double his resting heat production in this way without any increase in activity. As environmental temperature continues to decline, heat production reaches a maximum and below this point the body temperature falls. If environmental temperature rises above the upper end of the thermoneutral range, sweating occurs

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until a point is reached when the heat lost by sweating is insufficient and body temperature starts to rise.

In all infants, heat production is delayed during adaptation to extrauterine life, especially if there is asphyxia, hypoxia, or maternal sedative administration. Heat production per unit area is lower in preterm infants, particularly below 28 weeks' gestation, and the immature infant has a more prolonged impairment of non-shivering thermogenesis.

Sweating occurs from birth in infants above 36 weeks' gestation but is delayed by 2–3 weeks in the most immature infants. This is a result of neurological rather than glandular immaturity. Sweating is a relatively poor defense against overheating in the newborn because the production of sweat per unit area of skin is low compared with a child or adult. The term newborn can alter skin blood flow effectively, and hence the amount of heat lost by convection and radiation, but this is impaired in the very immature infant. Change of posture to increase or decrease the surface area available for heat loss by convection and radiation is important in thermoregulation. It occurs in the healthy term infant and to some extent in the preterm infant but not in the presence of illness.

Body Temperature and Its Measurement

The only practical method in day-to-day care for assessing the effects of the thermal environment on the baby is to measure body temperature. This is crude because it tells us nothing about the amount of energy the baby may be using to maintain its body temperature. An infant can be exposed to very significant thermal stress and still maintain a normal deep body temperature. The corollary of this is that just because a baby has a normal deep body temperature does not necessarily mean that it is in a neutral thermal environment.

In clinical practice, we need an easily measured temperature that is at least close to, and follows changes in, deep body temperature. There is, however, no such thing as a single deep body temperature. The temperature of a tissue will depend on its metabolic rate, with the brain being the highest. The temperature in mid esophagus is often used to represent deep body temperature as this measures the temperature of the blood in the great veins returning to the heart from all the tissues. However, this is invasive and difficult to use in routine care.

Rectal temperature should no longer be used routinely in infants and children as there is a significant risk of damage to the mucosa. Temperature in the rectum is an unreliable measure as it is affected by the depth of insertion of the thermometer, whether the baby has just passed a stool and by the temperature of the blood returning from the lower limbs. It is very difficult to retain rectal probes in the same position if continuous temperature monitoring is being used. The one exception is for babies who are being cooled for management of hypoxic ischemic encephalopathy when rectal probes are a reasonable alternative to continuous esophageal temperature monitoring of deep body temperature.

Tympanic temperature closely correlates with that of the brain and is commonly used for intermittent recording in children but is less practical in the newborn infant.

Axillary temperature is a reasonable guide to deep body temperature. The bulb of the thermometer should be held in the roof of the axilla with the infant's arm pressed against the side of the chest until a stable reading is obtained, usually by 3 min. The normal range is 36.3–37.0°C.

Skin temperature reflects tissue insulation and environmental conditions as well as deep body temperature. In the preterm baby, the temperature of the skin over the liver can be used to monitor trends in deep body temperature. If the infant lies on a temperature probe which is insulated on the outside, the skin under the probe cannot lose heat and so equilibrates with the deep body temperature. This is the zero heat flux temperature and is a practical method for continuous monitoring of a central temperature.

A single temperature, measured intermittently, gives limited information on the thermal state of the baby. Particularly in the sick or unstable baby, more information can be obtained from the continuous measurement and display of a central (abdominal, axillary, or zero heat flux) and a peripheral (foot) temperature. Changes in peripheral temperature can detect cold stress before the central temperature falls. The preterm baby, who appears to be comfortable in its environment, will have a central temperature, measured from a skin probe, of 36.8–37.3°C and a central-peripheral temperature difference of 0.5–1°C. An increasing central-peripheral temperature difference, particularly above 2°C, is commonly due to cold stress and occurs before any fall in central temperature. Hypovolemic babies will vasoconstrict their peripheral circulation in an attempt to maintain blood pressure. This results in a rise in central-peripheral temperature difference but, in such cases, there are other signs of hypovolemia, such as a rising heart rate and falling blood pressure. A raised and unstable central temperature, along with a wide central peripheral gap, is seen in septic babies.

Management of the Thermal Environment

At Delivery

Delivery rooms should be warm, with a minimum temperature of 25°C, and well insulated against drafts to reduce radiative and convective heat losses. Evaporation of amniotic fluid from the skin is the greatest source of heat loss following delivery. The term newborn infant should be dried at delivery, wrapped in a warm dry blanket, and given to the mother. Skin to skin contact with the mother is an effective way of maintaining body warmth but it is important to cover the baby to prevent heat loss from exposed skin on the back.

In the preterm infant, low temperature on admission to the neonatal unit has been shown to be independently associated with increased mortality. The use of heated mattresses has been shown to prevent hypothermia and in well infants skin to skin contact is effective. Evaporation is the major source of heat loss, particularly in the very immature infant, and this can be significantly reduced using occlusive dressings. Plastic wraps or bags are effective in reducing heat losses in infants <28 but were not more effective than standard care in those between 28 and 31 weeks' gestation. Clear plastic bags are easy to use and prevent hypothermia immediately after delivery. The baby can be slid into the bag, up to the neck, whilst still wet. The head is dried and covered with a hat. No blankets are used, allowing radiant heat to warm the infant through the bag. Clinical inspection and auscultation during resuscitation can be done through the bag and if vascular access is needed a small hole can be cut in the plastic. The infant can be transported while still in the bag, which is only removed once the baby is in a humidified environment.

Nursing

The healthy term newborn will maintain a normal temperature if nursed fully dressed in a cot in a warm room. Most healthy preterm babies can be managed in the same way, although comparative data between cot and incubator care are limited. Some very small infants may need to be nursed clothed in an incubator to provide a sufficiently warm ambient temperature.

- Over 2 kg: nurse clothed, with bedding in a cot, in a room temperature of about 24°C.
- 1.5–2 kg: nurse clothed with a hat and bedding in a cot, in a room temperature of about 26°C.
- Below 1.5 kg: nurse clothed with a hat, in an incubator temperature of 30–32°C.

Heated Cot

A water-filled mattress, heated to a set temperature between 35°C and 38°C, can be used to provide conductive heat to a preterm infant nursed in a cot. This can be as effective as an incubator for keeping small babies warm, resulting in similar rates of resting metabolism and growth. It is cheap, simple, and does not depend on a constant unbroken supply of electricity (because of its stored heat), so that it is particularly useful in developing countries. It is only of use if the infants are healthy and do not need to be nursed naked for observation and access. It has been effectively used as a method of rewarming cold preterm infants. Gel-filled heated mattresses are also available but are more expensive.

Incubator

The incubator provides a warm, humid environment suitable for nursing small or sick infants, particularly if they need to be naked for observation and access. Air within the canopy is warmed by a heater and circulated by a fan. The heater output can be controlled in two ways. In air mode, the incubator air temperature is set to a point between 30°C and 37°C, and the heater is thermostatically controlled to reach and maintain this temperature. In servo mode, a thermistor probe is taped to the infant's abdominal skin and the desired skin temperature is set – the heater output varies to provide an air temperature which maintains the set skin temperature. In practice, air mode control is simpler to use, safer, and results in a very constant ambient air temperature regardless of the condition of the infant and the amount of care being receiving. Servo control results in wide fluctuations in air temperature, particularly during handling, and in the preterm baby this has been associated with an increase in apnea and possibly a poorer outcome. The probe can become detached or wet, and the infant's own attempts at thermoregulation are overridden so that a fever may be disguised. For these reasons, air temperature control is preferred in most circumstances.

Suggested air temperature (*Table 14.1*) and skin temperature settings (*Table 14.2*) for the two modes of control are shown.

These are a guide only and there will be variation in individual requirements. In particular, dressed babies will need lower incubator temperatures. Monitoring of body temperature is essential to allow appropriate changes in environmental settings.

Table 14.1
Average incubator air temperatures needed to provide a suitable environment for naked, healthy infants (From Rutter N (2005) Temperature control and its disorders. In: Rennie JM (ed) Roberton's textbook of neonatology, 4th edn. Churchill Livingstone, Edinburgh)

	Environmental temperature					
Birthweight (kg)	37°C	36°C	35°C	34°C	33°C	32°C
Less than 1.0	For 1 day	After 1 day	After 2 weeks	After 3 weeks	After 4 weeks	After 6 weeks
1.0–1.49			For 10 days	After 10 days	After 3 weeks	After 5 weeks
1.5–1.99				For 10 days	After 10 days	After 4 weeks
2.0–2.5				For 2 days	After 2 days	After 3 weeks
More than 2.5					For 2 days	After 2 days

Table 14.2
Suggested abdominal skin temperature settings for infants nursed in servo-mode incubators or under radiant warmers (From Rutter N (2005) Temperature control and its disorders. In: Rennie JM (ed) Roberton's textbook of neonatology, 4th edn. Churchill Livingstone, Edinburgh)

Weight (kg)	Abdominal skin temperature (°C)
Less than 1.0	36.9
1.0–1.49	36.7
1.5–1.99	36.5
2.0–2.5	36.3
More than 2.5	36.0

The naked infant will lose heat by radiation to the cooler walls of the incubator. This loss can be reduced by raising the temperature of the nursery, and therefore of the incubator wall, raising the incubator air temperature, using a radiant heat shield within the incubator which warms to the air temperature and shields the infant from the canopy, or by using a double-walled incubator. Although radiative heat losses can be minimized, there are no data available that show an impact on outcome in low birthweight infants.

In infants below 30 weeks' gestation, especially if weighing less than 1 kg, evaporative water and heat loss is high during the first days of life and may exceed the infant's own heat production. Raising the humidity of the air around the body will reduce evaporative losses so that a normal body temperature can be achieved and fluid losses minimized. Beyond 1 week of age, the immature infant's skin has matured to such an extent that evaporative water and heat losses are less important and added humidity is rarely required. Incubators using a sealed system do not need to be run dry for part of the day and there does not appear to be any increased risk of infection when humidity is used. Evaporative heat losses can also be reduced by covering the baby with a plastic sheet. This reduces visibility and when removed to handle the baby there are high evaporative losses. The use of semipermeable nonadhesive skin dressings lowers TEWL and reduces the number of bacteria in the covered skin. Emollients have also been used to cover the skin and reduce fluid loss. They are safe and reduce excessive drying, skin cracking, and fissuring. However, the effect of these products wears off after about 3 h, necessitating repeated application.

There are few data available to help in deciding the optimum time to make the transition from incubator to cot. Traditionally, this is based on weight, with most babies able to maintain their temperature in a cot, and continue to gain weight, when they are between 1,700 and 1,800 g.

Radiant Warmer

With the use of radiant warmers, the infant lies naked on a platform with a radiant heat source above. The output of the heater is controlled by a temperature sensor in contact with the infant's skin, set to the desired temperature. The sensor should be taped to the abdomen or chest rather than a limb and must be shielded from the heat source. The normal range of abdominal skin temperature under neutral thermal conditions for infants of different size is shown in *Table 14.2*.

Heat losses by convection and radiation are high when radiant warmers are used. Evaporative water loss is also

very high even in term infants, with a mean of about 23 ml/kg/day, due to the low relative humidity in the surrounding air. These losses are all balanced by a large radiant heat gain from the heater. Wide fluctuations in heater output occur, producing a very uneven, asymmetrical thermal environment compared with an incubator. In the more immature infants, increased evaporative water loss may lead to hypernatremia and dehydration. The wide fluctuations in thermal environment and high evaporative water losses can be reduced by placing a small clear plastic canopy over the infant – radiant heat can still reach the infant but heat losses by convection, radiation, and evaporation are greatly reduced.

Overheating can occur and regular measurement of the infant's body temperature by an independent method is essential. It is important to be sure that the skin temperature probe is securely attached to the baby. If the heater is switched off, moved to one side or if something is interposed between the infant and the heat source, the infant's heat losses are very great and rapid cooling occurs. Their advantage is that they allow access to the infant for practical procedures while keeping the infant warm.

Babies nursed with similar skin temperatures have a higher basal metabolic rate when managed under radiant heaters compared with incubators. However, no study has shown any significant difference in outcome for babies nursed using either device.

Transport

The newborn, and in particular the preterm infant, is at high risk of cold stress during transport. High radiative heat losses, especially in cold weather, can be reduced by covering the incubator and using blankets around the baby. Evaporative heat loss can be reduced by placing the baby in a plastic bag. If ventilator gases are not heated and humidified, there will be high evaporative heat losses from the respiratory tract. Heated gel mattresses that can be used during transport are available, with the baby gaining heat by conduction. All units transporting babies should collect data on temperature control during transfer and use this to audit the quality of care during the transport process, because, as previously stated, admission temperature is an important predictor of outcome.

Surgery

There is a major risk of cold stress during surgery. The baby is starved and anesthetized, reducing the normal metabolic response to cold. The operating theatre is often cool and the baby may have had to travel some distance from the nursery. Exposure of the skin and moist organs increases heat loss significantly. Heat losses can be minimized by increasing the environmental temperature to 28–30°C, exposing only the minimum area during surgery and adding a supplementary heat source such as an electric heating pad or radiant heater. Careful intraoperative temperature monitoring is advisable.

Disorders of Body Temperature in the Newborn

A Low Body Temperature (Below 36°C)

Mild hypothermia (central temperature 34 –36°C) is not uncommon. In hospitals, it is most often seen following resuscitation or when infants are exposed to a cool delivery room or theatre. This is easily preventable by paying careful attention to keeping infants warm after delivery. Moderate (30–34°C) or severe (below 30°C) hypothermia due to cold exposure occur most often when infants are born outside hospital, either unexpectedly or after a concealed delivery – if the infant is small, born into a toilet, abandoned, or inadvertently exposed to cold, severe hypothermia may result.

Accidental hypothermia also occurs later in the newborn period or early infancy because of inadvertent cold exposure due to inadequate clothing or cold thermal environments. Infants with bacterial sepsis or with respiratory syncytial virus (RSV) infection are prone to mild hypothermia – so too are infants in severe heart failure or with marked cyanosis. Malnutrition predisposes to hypothermia because of poor tissue insulation and an impaired metabolic response to cold. Hypothyroidism also results in an impaired metabolic response to cold. Drugs given to the mother which cross the placenta have a similar effect on the newborn infant, particularly the long-acting sedatives such as diazepam.

Intentional hypothermia is used as an adjunct to cardiopulmonary bypass – the body temperature being lowered to about 28°C to reduce the metabolic demands of the brain. The infants tolerate this brief, acute severe hypothermia well.

Whole body or preferential head cooling with mild systemic hypothermia appear to be effective in reducing brain damage in asphyxiated animals, and trials have shown improved survival and neurodevelopmental outcome in term newborn infants following birth asphyxia.

Cooling to around 33.5°C is now a common part of the management of hypoxic ischemic encephalopathy with remarkably few adverse effects. The safety and effectiveness of therapeutic hypothermia in preterm infants has not been established.

Hypothermic infants develop symptoms when their deep body temperature falls below 34°C. They become lethargic, feed poorly, have a weak cry and reduced movements. The heart rate falls in proportion to the degree of hypothermia. If exposure to cold has been persistent, there may be peripheral oedema, sclerema, and marked facial erythema in the presence of a strikingly cold skin – these are the features of neonatal cold injury. In very severe hypothermia, there is profound bradycardia with slow, shallow respiration and the infant may appear to be dead. There are anecdotal reports of such infants being left for dead yet eventually making a full recovery. The diagnosis of hypothermia is made by recording a low rectal temperature – it is important that a low reading thermometer is used, not the standard clinical thermometer with a minimum reading of 35°C.

The treatment of accidental hypothermia is rewarming – if there is an underlying cause, this obviously needs to be treated too. There is limited information about the correct rate for rewarming cold infants but in cases of mild hypothermia this can take place fairly rapidly. In moderate or severe cases, there is concern that rapid rewarming of the infant's surface causes peripheral vasodilatation, diversion of blood from the core, and therefore hypotension. There is no evidence for the routine use of plasma expanders in these cases. Following acute accidental hypothermia, it appears to be safe to restore deep body temperature to normal over a few hours. This can be achieved using a radiant warmer, an incubator, or a heated cot. Rapid rewarming in preterm infants has been associated with increased apnea of prematurity.

Hypoglycemia may occur during rewarming and should be anticipated and prevented with an intravenous infusion of 10% dextrose. Care should be taken in interpreting blood gas results – a metabolic acidosis at 37°C is less severe at 30°C and should not be overenthusiastically treated. Abdominal distention is common as a result of ileus and feeding should not be started until a normal body temperature is achieved. NEC and hemorrhagic pulmonary edema have been described. The reported mortality rate in severe hypothermia is 25–50% but this includes infants with overwhelming sepsis or congenital abnormalities that predisposed them to cold. Most survivors develop normally.

A High Body Temperature (Above 38°C)

Most commonly an infant with a high body temperature is being overheated iatrogenically. It is important, however, to be sure that the baby is not truly febrile due to an underlying disease. An intrinsically febrile infant has a high set point temperature and behaves as if cold. He makes physiological and behavioral responses which reduce heat loss, increase heat production, and therefore raise body temperature. Although he has a raised central temperature, his central-peripheral temperature difference will be high (above 2°C).

In contrast, an overheated infant makes physiological and behavioral responses in an effort to increase heat loss and therefore lower body temperature. In this case, the central temperature will be high but the central peripheral temperature gap will be small (below 1°C). Overheated infants simply need a cooler environment, not a series of painful investigations to find a cause for the "fever."

The newborn infant may develop a raised body temperature in the presence of infection but this is usually not marked. It is not known why serious infection in a newborn seems to elicit such a mild febrile response when mild infection in a toddler is often associated with a very high body temperature. Infection is not the only cause of a raised set point temperature in the newborn; it is also caused by a severe cerebral abnormality, either congenital (holoprosencephaly, hydranencephaly, encephalocele) or acquired (birth asphyxia). Such infants have hypothalamic dysfunction leading to poor temperature control.

Overheating is less common than accidental hypothermia in the newborn. Mild degrees occur when active, large infants are overwrapped and left in a warm room, or when small infants are overheated by an incubator or radiant warmer. Severe overheating occurs when there is electrical or mechanical failure of a warming device, or when an incubator is exposed to direct sunlight (this turns it into a greenhouse). It can also occur if infants are left in closed cars exposed to direct sunlight.

Mild overheating has been suggested as a predisposing factor in apnea of prematurity but otherwise seems not to be dangerous. Severe overheating leading to hyperpyrexia (rectal temperature above 41°C) has caused sudden death in the newborn without prior symptoms.

Recent data from the therapeutic hypothermia trials indicate that overheating should be carefully avoided in infants with perinatal asphyxia, because asphyxiated infants who became hyperthermic had significantly worse neurodevelopmental outcome than similar infants who remained normothermic.

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15 Respiratory System

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Lung Development

The tracheobronchial airway system develops as a ventral outpouching of the primitive foregut, which leads to the formation of the embryonic lung bud. The lung bud subsequently divides and branches, penetrating the mesenchyma and progressing toward the periphery. Lung development is divided into five phases (*Table 15.1*). A variety of physical, hormonal, and other factors affect the pace of lung development and maturation. Normal lung growth and development requires adequate distending pressure of fetal lung fluid and normal fetal breathing movements – their absence leads to pulmonary hypoplasia. Lack of saccular development and surface area for gas exchange are the limiting factors for survival of infants born in the late cannalicular phase before 24 weeks of gestation.

Respiratory Physiology/Lung Mechanics/ Gas Exchange

Although basic principles of lung mechanics and gas exchange are similar to those of older children and adults, newborn infants present the clinician with a number of special challenges that are the consequence of their unique physiology and pathophysiology. This is especially true when they are born prematurely. The reader is referred to any of the major texts on respiratory physiology for in-depth coverage of the subject. The key concepts are briefly reviewed below.

Lung Mechanics

The lungs of preterm infants are relatively noncompliant (stiff), while the chest wall lacks rigidity. As a result of this disturbed balance between the tendency of the lungs to collapse due to elastic recoil and the rigidity of the chest wall that maintains lung expansion, the lungs come to rest at a lower functional residual capacity and the airways tend to close near the end of exhalation. Therefore, special attention needs to be paid to maintaining adequate lung volume during respiratory support of newborn infants. Differences between the shape of an adult versus newborn infant's chest put the infant at a mechanical disadvantage. The infant's thorax is more cylindrical than ellipsoid and the ribs are more horizontal, rather than oblique. Because of these anatomic differences, the intercostal muscles in infants have a shorter course and provide less mechanical advantage for elevating the ribs and increasing intrathoracic volume during inspiration. Because the insertion of the infant's diaphragm is more horizontal than in the adult, the lower ribs tend to move inward rather than upward during inspiration. The compliant chest wall exacerbates this inward deflection with inspiration. This results in inefficient respiratory effort, which may be manifested clinically by intercostal and substernal retractions associated with abdominal breathing, especially when lung compliance is decreased. Additionally, infants have low muscle mass and a low percentage of type 1 (slow twitch) muscle fibers compared to adults, making infants with respiratory distress prone to respiratory muscle fatigue and respiratory failure.

During expiration the main driving force is elastic recoil, which depends on the surface tension produced by the air–liquid interface, the elastic elements of lung tissue, and the bony development of the rib cage. Expiration is largely passive. Because the chest wall of premature infants is compliant, it offers little resistance against expansion upon inspiration and little opposition against collapse upon expiration.

The airways of the preterm infants are very small, resulting in relatively high airway resistance, especially as airway epithelium becomes injured during mechanical ventilation. Additionally, the small size of the trachea necessitates the use of narrow endotracheal tubes that add substantially to the airway resistance (recall that resistance to flow is inversely proportional to the fourth power of the radius). All of these factors confer a significant mechanical disadvantage to the respiratory mechanics of newborn and especially preterm infants, making them more vulnerable to fatigue and respiratory failure.

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Table 15.1
The phases of lung development. There is some overlap between the phases

Embryonic phase (weeks 3–6)	Development of proximal airways. The lung bud arises from the foregut 21–26 days after fertilization
Pseudoglandular phase (weeks 6–16)	Development of the first 20 generations of conducting airways. The first eight generations (the bronchi) ultimately acquire cartilaginous walls. Generations 9–20 are the nonrespiratory bronchioles. Lymph vessels and bronchial capillaries follow the airways as they grow and develop
Canalicular phase (weeks 16–26)	Respiratory bronchioles (generations 21–23) develop. The proportion of parenchymal connective tissue diminishes. Pulmonary capillaries develop
Terminal sac phase (weeks 26–36)	Rudimentary primary saccules subdivide by formation of secondary crests into smaller saccules and alveoli, greatly increasing the surface area for gas exchange. The interstitium continues to thin out, decreasing the distance for diffusion. Capillary invasion leads to an increase in alveolar–blood barrier surface area. The surfactant system develops and matures
Alveolar phase (week 36–3 years)	Saccules become alveoli due to thinning of the acinar walls and invagination of alveoli by pulmonary capillaries with secondary crest formation. The alveoli attain a polyhedral shape

Oxygenation

As in older patients, oxygenation is a function of the fraction of inspired oxygen and optimal ventilation/perfusion (V/Q) matching. Optimal V/Q ratio occurs at normal lung volume. Atelectasis results in intrapulmonary right-to-left shunting and V/Q mismatch with resulting hypoxemia. The condition can be corrected by increasing mean airway pressure (best accomplished by raising positive end-expiratory pressure = PEEP), until oxygenation improves. Overexpansion of the lungs also results in V/Q mismatch and additionally may increase pulmonary vascular resistance by compressing pulmonary capillaries and result in extrapulmonary right-to-left shunt. Both over- and under-expansion contribute to lung injury and should be avoided. Chest radiographs, though not a direct measure of lung volume, are helpful in assessing the appropriateness of lung expansion. It is important to recognize that several factors influence mean airway pressure (MAP), including positive end-expiratory pressure (PEEP), peak inspiratory pressure (PIP), inspiratory:expiratory ratio, and, finally, the slope of the inspiratory waveform, which determines how rapidly the pressure limit is reached. Alteration of any of these variables will affect MAP and thus may alter lung expansion. Because, in addition to the effects of their excessively compliant chest wall, newborn infants commonly are surfactant deficient, special attention must be directed toward maintaining adequate lung expansion.

CO_2 Elimination

CO_2 elimination (ventilation) is relatively independent of oxygenation and requires a flux of fresh gas in and out of terminal respiratory units. With conventional respiratory rates, the gas moves by bulk flow or convection in the large and small airways with diffusion accounting for gas movement in the respiratory bronchioles and terminal air sacs. Bulk flow of gas is greatly influenced by the mechanical properties of the lungs: compliance, airway resistance, and time constants. Understanding the concept of time constants is important for optimal selection of respiratory rate, specifically inspiratory and expiratory time. Conceptually, time constants describe the length of time required for gas to get in and out of the lungs when a change in pressure is applied at the airway opening (three time constants are required to reach 95% equilibration of pressure). Mathematically, the following equation describes the phenomenon of time constants:

$$\text{Time constant(s)} = \text{airway resistance}\left(\text{cmH}_2\text{O} \times \text{L}^{-1} \times \text{s}\right) \times \text{lung compliance}\left(\text{L/cmH}_2\text{O}\right)$$

Because total compliance, not compliance/kg is used, time constants are also a function of subject size – as is intuitively obvious, the larger the lung is the longer it takes to get gas in and out.

The practical consequence of this relationship is that small infants with respiratory distress syndrome (i.e., low compliance, low resistance) have very short time constants and normally have rapid respiratory rates with little danger of air trapping, while larger infants with meconium aspiration or bronchopulmonary dysplasia (high airway

resistance) need slower respiratory rates and are more prone to air trapping, thus require longer expiratory times. Inspiratory times are normally shorter than expiratory times, because expiratory airway resistance is always higher, but should also be adjusted according to patient size and pathology. Typically, inspiratory to expiratory ratio of 1:2 is used, as this approximates normal breathing.

CO_2 elimination is determined by how effectively fresh gas is moved in and out of the terminal gas exchanging units. Total minute ventilation is the product of respiratory rate and tidal volume (V_T). Tidal volume is principally determined by lung compliance and pressure amplitude or ΔP (peak pressure – PEEP). In newborn respiratory support, pressure-limited ventilation has traditionally been used. In this mode, V_T is not set directly, but is a derived variable, which is indirectly controlled by adjusting ΔP and is affected by changes in lung compliance. An additional consideration is the fact that exhaled alveolar gas occupies the upper airway, endotracheal tube, and any additional apparatus such as a flow sensor at the end of each exhalation. Thus, with the next breath, at least a portion of this dead space gas flows back into the lungs, followed by fresh gas. Traditional physiology teaches that:

$$\text{Alveolar minute ventilation} = (\text{VT} - \text{dead space volume}) \times \text{respiratory rate}.$$

In practice, at the high flow rates seen in small infants with very short time constants, there appears to be considerable mixing of gases in the dead space volume, resulting in partial bypass of the anatomical and instrumental dead space.

Regulation of Respiration

Regulation of breathing is accomplished by a complex process involving the respiratory control center, peripheral and central sensors, and respiratory muscles. The respiratory control center consists of a group of neurons in the brainstem that receive and integrate the afferent information from the sensors and in turn send motor impulses to the respiratory muscles to regulate respiratory activity. The respiratory regulatory mechanism undergoes a significant maturation process during the neonatal period. The preterm infant's respiratory control center is immature, resulting in irregular respiratory pattern, periodic breathing, and apnea. Sleep states have the potential for profound influences on the control of respiration. In the older, awake individual, respiratory activity is under a significant degree of voluntary control. The degree to which this is true in the immediate neonatal period is unclear, but an infant's activity and emotional state clearly do influence the respiratory pattern.

A group of 150–200 neurons, known as the *pre-Botzinger complex* (PBC), located in the medullary region of the brainstem functions as the pacemaker for automatic respiratory activity. PBC neuron activity is modulated by afferent input from neurons located in the lower pons called the *apneustic center* (stimulatory effect) and inhibited by neurons in the upper pons, known as the *pneumotaxic center.* Thus, damage to various parts of the brain often manifests with abnormal respiratory pattern.

Central and peripheral chemoreceptors and a variety of mechanoreceptors provide feedback to the central respiratory controller. Central chemoreceptors located over a large area of the brain are bathed by the cerebrospinal fluid (CSF) and respond to changes in the H^+ concentration, i.e., pH. A decrease in pH concentration stimulates ventilatory activity, while an increase inhibits it. The CSF is separated from the blood by the blood-brain barrier, which is relatively impermeable to H^+ and HCO_3^- ions, but readily permeable to CO_2. A rise in $PaCO_2$ is quickly reflected in a similar rise in the CSF, resulting in a fall in CSF pH and stimulation of ventilation. It is important to understand that changes in $PaCO_2$ exert their influence on ventilation through changes in CSF pH. The CSF has much less CO_2 buffering capacity than blood because of a much lower protein concentration. This amplifies the response to CO_2, because the same change $PaCO_2$ in blood leads to a larger change in CSF pH. With a persistent elevation in $PaCO_2$, the pH of the CSF gradually normalizes as HCO_3^- equilibrates across the blood-brain barrier. Thus compensated respiratory acidosis is associated with a relatively normal CSF pH and therefore these infants do not increase their ventilatory response in response to these high levels of $PaCO_2$.

Peripheral chemoreceptors, located in carotid bodies just above the bifurcation of the common carotid arteries, and in the aortic bodies in the aortic arch primarily respond to changes in PaO_2 with hypoxia stimulating ventilation and hyperoxia having an inhibitory effect. Exposure to unnecessarily high FiO_2 may thus depress the respiratory response to CO_2, another of the many reasons to avoid hyperoxia. The carotid bodies also respond to pH irrespective of whether the acidosis is respiratory or metabolic. The effect of hypoxia and acidosis is synergistic, leading to a greater degree of stimulation by their combination than either one alone. Hypoxia is a more potent stimulus than alkalosis; therefore hypoxic respiratory drive usually leads to some degree of hyperventilation when hypoxemia persists.

Mechanical receptors provide additional input to the respiratory control center. *Stretch receptors* located within the airway smooth muscle are stimulated by lung inflation, decreasing the respiratory rate by inhibition of inspiratory muscle activity and an increase in expiratory time. This reflex is called the Hering–Breuer inflation reflex. Hering–Breuer deflation reflex stimulates inspiratory muscle activity in response to deflation of the lung. *Irritant receptors* in the airway mucous membranes are stimulated by particulate matter and other noxious stimuli, including cold air. So-called J receptors or juxta-capillary receptors located in the alveolar walls close to the pulmonary capillaries respond to pulmonary capillary engorgement, interstitial and alveolar wall edema by inducing shallow and rapid respirations and a sensation of dyspnea. *Muscle receptors* in the diaphragm and the intercostal muscles sense the degree of stretch of the muscle and control the strength of contraction. Activation of muscle receptors by excessive chest wall distortion occasioned by the very compliant rib cage may be partially responsible for the cessation of inspiration and apnea seen with airway obstruction in preterm infants. Important afferent input also originates in the upper airway and especially the laryngeal area. Superior laryngeal nerve afferents are connected to cardiac vagal neurons in nucleus ambiguus, or terminate in the nucleus of the solitary tract with inhibitory connections to phrenic motor neurons. Inhibition of phrenic and cardiac motor neurons with laryngeal stimulation is likely the mechanism of apnea and bradycardia associated with gastroesophageal reflux.

The response of the respiratory control center to chemoreceptor and mechanoreceptor input and the efficiency of the respiratory muscles are markedly altered in the preterm newborn infant, compared to older subjects. Unlike adults who have an immediate and sustained response to hypoxemia characterized by hyperventilation, the newborn exhibits a biphasic response. After an initial brief period of hyperventilation, the newborn exhibits hypoventilation and apnea in the face of sustained hypoxemia. The more premature the infant is, the more pronounced and earlier is the apneic response to hypoxemia. Neonates also have a decreased CO_2 responsiveness as measured by an increase in minute ventilation for a given increase in $PaCO_2$. This decreased chemoreceptor responsiveness and the paradoxical response to hypoxia is a key difference between the newborn and older subjects and a major contributor to their susceptibility to various forms of respiratory depression and apnea. Additionally, the inhibitory stimuli from the larynx of newborn infants appears to be more active than in older subjects and appears to play an important role in the genesis of neonatal apnea/bradycardia.

Sleep has a profound effect on respiratory control, decreasing central responsiveness to CO_2. Rapid eye movement (REM) sleep, the predominant sleep pattern in premature babies that accounts for more than 60% of the total, leads to suppression of postural muscle tone and lack of spontaneous movements. The depression of muscle tone during REM sleep has two important effects. Increased compliance of the chest wall leads to less efficient respiration and may lead to loss of lung volume (microatelectasis) with resulting hypoxemia. Relaxation of upper airway muscles cause airway obstruction and contribute to obstructive apnea.

Apnea of Prematurity

A striking feature of the resting breathing pattern of the premature newborn is its irregularity, characterized by large breath-to-breath variability accompanied by long stretches of periodic breathing and brief apnea. Clinically important apnea of prematurity is almost always associated with periodic breathing. Although the mechanisms have not been fully elucidated, it is likely that the periods of hyperpnea or hyperventilation decrease the $PaCO_2$ thus reducing the stimulus to breathe, resulting in apnea; the resulting hypoxemia may then further depress the respiratory center.

Apnea of prematurity (AOP) can be thought of as a developmental disorder that reflects physiological immaturity of respiratory control. AOP occurs in up to 85% of infants of less than 34 weeks' gestational age. AOP increases in frequency with decreasing maturity and resolves with increasing maturity. In $>$90% of infants, AOP resolves by 37 weeks postmenstrual age, but occasionally it may last until 40 weeks or beyond, especially in infants born at 24–26 weeks or those with chronic lung disease.

Clinically significant apnea is defined as cessation of breathing that lasts for at least 20 s. Shorter apneas, if associated with significant bradycardia or oxyhemoglobin desaturation, may also be considered clinically significant. Lack of airflow may occur despite continued respiratory effort in the presence of airway obstruction and may be the reason for the shorter "apneas" being associated with bradycardia and desaturation.

Brief episodes of bradycardia are common and typically not associated with desaturation.

Apnea is traditionally classified as central, obstructive, or mixed, based on the primary mechanism involved. These mechanisms can be distinguished by simultaneous measurement of chest wall movement by electrical

impedance, airflow by nasal thermistor, and heart rate by EKG. Central apnea is, as the name implies central in origin, characterized by cessation of respiratory effort and airflow and is related to immaturity of the respiratory control center. Obstructive apnea is characterized by cessation of airflow despite continued respiratory movement and is believed to be related to poor pharyngeal muscle tone, especially during REM sleep. The majority of apneas are mixed with central apnea preceded or followed by obstructive apnea. These events represent a continuum and are the result of a complex interaction of airway obstruction and central respiratory depression: central apnea leading to hypoxemia results in relaxation of the pharyngeal muscles and the resulting airway obstruction will prolong the duration of apnea. Airway obstruction in turn produces desaturation with resulting depression of central respiratory control. Most such events are self-limited and terminated eventually by arousal, but in some infants, active intervention is required when the normal arousal mechanisms fail and the infant enters a state of severe bradycardia and hypoxemia.

Treatment of apnea should be guided by an assessment of the predominant nature of the apneic events. Methylxanthines are a mainstay of therapy for central apnea. Caffeine has now been shown to be safe and in fact was associated with improved neurodevelopment and lower incidence of BPD. Adjunctive treatments include continuous positive airway pressure (CPAP), which helps maintain lung volume and counteract the REM sleep-related chest wall distortion issues, as well as reduce airway obstruction by providing distending pressure that helps maintain pharyngeal patency. Nasal cannula flow may serve the same function, though perhaps less effectively. Avoidance of hypoxemia is important in reducing central apnea, but possible benefit of higher oxygen saturation targets must be weighed against adverse consequences of oxygen exposure. Lower environmental temperature has been shown to reduce apnea in preterm infants. Although acid reflux is capable of triggering reflex apnea and bradycardia, there are no studies that have established a causative relationship between gastroesophageal reflux and apnea/bradycardia in the preterm infant and no studies that have demonstrated benefit of anti-reflux drugs.

Controversy persists regarding the question of whether the episodes of apnea/bradycardia/desaturation are associated with neurodevelopmental sequelae. Clearly, since most preterm infants experience a substantial number of such events, harm, if any, is minimal with the commonly seen brief episodes. However, alterations in cerebral oxygenation have been documented and there is substantial concern that more prolonged and profound episodes are likely to lead to some degree of cumulative harm. It is unclear whether the improved neurodevelopmental outcome seen in the caffeine-treated infants in the CAP trial reflects a decrease in such episodes or is due to the lower incidence of BPD; the frequency of apnea was not documented in that study.

Persistent apnea is often the last remaining condition that delays discharge. There is no uniform approach to judging an infant's readiness for discharge. Most clinicians rely on an apnea-free interval of 5–7 days as indicative of a safe discharge to home care without the need for home monitors. However, it has been demonstrated that only 33–50% of apnea or bradycardia events recorded by bedside pneumograms are documented by nursing staff, raising a question about the reliability of this approach. The alternative is to perform screening pneumogram recordings on all infants with history of apnea. This approach is also controversial, as most infants will continue to have some events well past the stage when clinical symptoms are apparent and these recordings have not been shown to have good predictive value. Because most apnea resolves prior to 37 weeks postmenstrual age, it is customary to discontinue methylxanthines when an infant reaches 34–36 weeks and observe. It must be understood that these are long-acting drugs that require several days to drop below therapeutic levels. If symptoms recur, pharmacotherapy is restarted and if effective, the infant may be discharged home with outpatient follow-up.

The Infant with Respiratory Distress

Respiratory distress is a common presenting sign in newborn infants with potentially life-threatening implications. In considering the approach to such infants, it is important to recognize that the underlying cause may not be limited to the respiratory tract. Respiratory distress may be a nonspecific manifestation of neurologic, cardiovascular, metabolic, hematologic, or neuromuscular disorders, as well as reflection of sepsis, drug withdrawal, and other conditions such as severe anemia (*Table 15.2*).

The diagnostic approach begins with obtaining a good medical history focusing on potential risk factors for any of the possible etiologies. Is the infant term, preterm or postmature? Was there any difficulty at birth? What was the route of delivery? When did the signs begin? Was the amniotic fluid stained with meconium or blood? Was it foul smelling? Maternal history may offer important clues to possible infection, maternal medical conditions, intrauterine medication exposure, or family history of heritable disorders. A thorough physical examination needs to focus

Table 15.2
Differential diagnosis of respiratory distress in newborn infants

Major category	Subcategory	Examples
Pulmonary	Airway	Laryngeal web, tracheomalacia, TE fistula, vascular ring
	Congenital	Hypoplasia, CDH, CCAM, sequestration, lobar emphysema
	Developmental	RDS, TTN, pulmonary insufficiency of prematurity
	Aspiration	Meconium, blood, amniotic fluid
	Miscellaneous	Pneumothorax, pulmonary hemorrhage, pleural effusion
Cardiac	Structural heart disease	Transposition, anomalous venous return, coarctation
	Pulmonary hypertension	Primary, secondary
	Myocardial dysfunction	Myocardiopathy, myocarditis, asphyxia
	Hypovolemia/shock	Hemorrhage, capillary leak, sepsis
	Congestive failure	PDA, VSD, A-V malformation, severe anemia
Infectious	Sepsis	Group B strep, *E. coli*
	Congenital pneumonia	Bacterial, viral, chlamydia
Metabolic	Hypoglycemia	Infant of a diabetic mother
	Severe acidosis	Lactic acidosis, inborn errors
	Polycythemia	
Neuromuscular	CNS depression	Anesthetic, narcotic analgesics, asphyxia
	Nerve injury	Phrenic nerve, laryngeal nerve
	Muscle weakness	Muscular dystrophy, MgSO4
	Anterior motor neuron	Werdnig Hoffman, spinal muscular atrophy
Skeletal	Asphyxiating thoracic dystrophy	Thanatophoric dwarfism
		Camptomelic dwarfism
	Rib fractures	Severe osteogenesis imperfecta

not only on the evaluation of breath sounds, but also the general appearance and activity of the infant, the nature of respiratory efforts, adequacy of the circulatory status, and coexisting physical findings in other organ systems. The history and physical exam will then guide the next steps in the evaluation, which will likely include a chest radiograph, evaluation for possible infection, a basic chemistry panel including glucose, plus additional studies based on clues from the H&P. Cardiology consultation may be appropriate if there is suspicion of cardiac anomaly based on clinical findings of a murmur, congestive failure, abnormal pulses, cyanosis out of proportion to the degree of distress, or abnormal cardiac shape on chest radiograph. Pulse oximetry now provides a quick assessment of the oxygenation status of the infant and will also detect a pre- and post-ductal saturation gradient that may be indicative of heart disease or persistent pulmonary hypertension.

While general supportive measures, including provision of supplemental oxygen when needed, thermal support, and provision of adequate fluid and calories, are common to all infants with respiratory distress, specific intervention depends on accurate diagnosis. In the majority of infants, the respiratory illness will be self-limited with full recovery, but management and outcome depend heavily on the underlying cause. The pulmonary causes of respiratory distress will be reviewed in the following paragraphs.

Specific Respiratory Disorders

Transient Tachypnea/Delayed Transition

Definition: Transient tachypnea of the newborn (TTN) is a usually benign condition associated with delayed clearance of lung fluid after birth.

Etiology/Pathogenesis: TTN typically occurs in term or late preterm infants and is greatly increased in infants born

by elective cesarean delivery. The process of lung fluid reabsorption normally begins prior to the onset of spontaneous labor and is greatly accelerated during labor. Infants who do not benefit from this normal process are at a distinct disadvantage and require a longer time to achieve adequate fluid clearance, because they have a substantially larger volume of fluid to clear and have not initiated this process in utero. The exact mechanism responsible for changing the lung epithelium from a Cl-secretory to a Na-reabsorption mode is the subject of intense study. Postnatally, lung fluid is taken up by the lung lymphatics and capillaries by a process mediated by the epithelial Na channels (ENaC). These mechanisms are less effective in the preterm infant and also vary among full-term infants, explaining the variation in the presence and extent of delayed fluid clearance.

Epidemiology: The true incidence of TTN is unknown as milder forms are often unreported. TTN account for a substantial number of admissions to NICUs, especially where the rate of cesarean section and late preterm delivery is high.

Clinical Manifestations: TTN presents with tachypnea, occasionally grunting respirations, and minimal retractions. The oxygen requirement, if any, is usually no more than 30%. The onset is shortly after birth and the signs resolve within a few hours to 2–3 days. Occasionally, TTN may be accompanied by persistent pulmonary hypertension (PPHN) with a high oxygen requirement out of proportion to the degree of lung disease and this can become a life-threatening illness, discussed further under PPHN.

Diagnosis: The presence of a compatible history, absence of infection, and a benign clinical course may be sufficient to establish the diagnosis. The chest radiograph may show hazy lung fields, but good lung expansion (as opposed to the loss of lung volume in respiratory distress syndrome), but more classically reveals streaky increased perihilar lung markings due to engorged lymphatics. The lung volume is normal or increased. Blood cultures, leukocyte counts, and other tests to rule out infection may be indicated.

Differential Diagnosis: TTN must be distinguished from respiratory distress syndrome (RDS), pneumonia, aspiration syndromes, and all the other common causes of respiratory distress.

Treatment: Treatment is supportive with provision of supplemental oxygen if hypoxemia is present, maintenance of temperature and provision of fluids/nutrition if the distress is severe enough to preclude oral feeding. There is no contraindication to breastfeeding of the tachypneic infant, as long as the distress is mild and the infant is not exhibiting desaturation during feeding. Nasogastric tube feeding is usually well tolerated. Continuous positive airway pressure is often used in these infants, but this practice is not evidence-based or physiologically sound, since the etiology of TTN is not specifically addressed by increased distending airway pressure. Antibiotics may be appropriate until infection has been ruled out.

Prognosis: The clinical course is usually benign and the signs resolve quickly. Duration and severity greater than described above should prompt a reevaluation of the diagnosis.

Prevention: Avoidance of elective cesarean delivery without labor would reduce the incidence dramatically. There are no other known prevention strategies.

Respiratory Distress Syndrome (RDS)

Definition: RDS is a specific disorder that occurs almost exclusively in preterm infants and is due to deficiency, inactivation, or dysfunction of pulmonary surfactant. It is not to be confused with "respiratory distress," which is merely a clinical sign. RDS is synonymous with the older term "hyaline membrane disease" (HMD).

Etiology: RDS results from functional deficiency of pulmonary surfactant, the surface tension lowering substance produced in type II pneumocytes.

Epidemiology: The incidence of RDS is inversely proportional to gestational age and is higher in male infants, those born by cesarean section, and in infants of mothers with diabetes. RDS is rare, but can occur in early-term infants and becomes progressively more common in late preterm, preterm and extremely preterm infants. Reported rates of RDS range from 80% in infants $<$26 weeks to 50% at 26–28 weeks, and under 30% at 30–32 weeks. RDS is the most common cause of respiratory failure in preterm infants. It is estimated that approximately 25,000 cases of RDS occur in the United States alone and it is known to occur in all races and regions of the world, though precise statistics are unavailable. Genetic variations underlying individual variation in susceptibility to RDS for individuals of the same gestational age are the subject of intense study.

Pathogenesis: Surfactant is a complex mixture of phospholipids and four types of surfactant-associated proteins. Surfactant lines the terminal air sacs and reversibly lowers the surface tension at the air–liquid interface, allowing alveoli of different sizes to coexist. In the absence of sufficient amount of functional surfactant, smaller alveoli, which require greater pressure to remain

open, will empty into larger alveoli, leading to diffuse microatelectasis. Atelectasis results in further surfactant inactivation, worsening lung compliance, increased pulmonary vascular resistance, increased ventilation/perfusion mismatch, and hypoxemia. Anatomical immaturity of the lung coexists with RDS in the very preterm infants and contributes to their respiratory insufficiency. Surfactant-associated protein B (SP-B) and to a lesser degree surfactant-associated protein C (SP-C) are necessary for adequate surfactant function. Rare mutations in SP-B and SP-C and ATP-binding cassette transporter *A3* (*ABCA3*) genes lead to severe, often fatal cases of RDS in term infants.

Clinical Manifestations: Infants with RDS present with tachypnea, cyanosis, grunting, subcostal and intercostal retractions, and nasal flaring. Oliguria with mild generalized edema may be present. Oxygen requirement may increase rapidly and is typically higher than that seen in infants with TTN. The natural course of the disease is worsening in the first 24 h, followed by stabilization and recovery by 72–96 h, usually heralded by spontaneous diuresis. In the modern era, this course is modified by therapeutic interventions.

Diagnosis: Typical clinical signs coupled with a characteristic appearance on chest radiograph of "ground glass" parenchymal opacification, air bronchograms, and decreased lung volume are sufficient to establish the diagnosis.

Differential Diagnosis: RDS must be distinguished from TTN, spontaneous pneumothorax, sepsis, and pneumonia. The clinical and radiographic presentation of RDS and group B streptococcus pneumonia are often indistinguishable. Other, less common etiologies listed previously should be considered when the clinical picture is atypical.

Treatment: Mild cases only require supplemental oxygen and supportive treatment as described above. Continuous positive airway pressure (CPAP) is helpful in preventing or reversing the diffuse microatelectasis and maintaining FRC. Surfactant replacement therapy has become standard of care in industrialized countries for infants who require mechanical ventilation and for those deemed at very high risk of RDS, namely, those below 27 weeks GA. More recently, it has been demonstrated that even very premature babies can be effectively treated with CPAP without surfactant replacement with similar results to those treated with mechanical ventilation and surfactant. This is particularly encouraging news for practitioners in resource-limited settings, as bubble CPAP can be delivered with very simple equipment. Surfactant replacement therapy, noninvasive respiratory support, and mechanical ventilation are covered in greater detail elsewhere in this Section.

Prognosis: Prognosis depends on gestational age and the presence of complications, many of which are a function of prematurity, rather than directly related to RDS, but all tend to occur more frequently in infants with RDS. Complete recovery is the rule in infants >30 weeks gestation with uncomplicated disease. In contrast, extremely preterm infants of 26 weeks or below often progress to bronchopulmonary dysplasia, discussed in more detail below. Mortality directly attributable to RDS is relatively low even in extremely low birth weight infants – more commonly, these infants succumb to sepsis, intraventricular hemorrhage, or pulmonary hemorrhage.

Prevention: Antenatal administration of betamethasone or dexamethasone at least 48 h prior to preterm birth dramatically lowers mortality and morbidity from RDS, as well as other complications of prematurity. Early application of CPAP in the delivery room and avoidance of excessive tidal volume with positive pressure ventilation can prevent inactivation of the marginal surfactant pool present in preterm newborns.

Meconium Aspiration Syndrome (MAS)

Definition: MAS refers to a clinical syndrome of respiratory distress associated with aspiration of meconium into the lungs before, during, or immediately after delivery.

Etiology: Fetal hypoxemia associated with placental insufficiency or limited fetal reserve leads to passage of meconium into the amniotic fluid prior to delivery. Subsequent gasping inspiratory effort caused by continued fetal distress leads to aspiration of meconium in utero. Rarely, aspiration of meconium present in the upper airway may occur after delivery. This only occurs in depressed infants, because vigorous infants are able to protect their airway against aspiration.

Epidemiology: Approximately 10–15% of all term deliveries have meconium stained amniotic fluid (MSAF). Passage of meconium is rare in preterm infants but occurs in as many as 33% of deliveries beyond 42 weeks gestation. Only about 5% of infants born through MSAF will have aspirated the material into their lungs and develop symptoms of MAS. A recent study from Australia and New Zealand reported an overall rate of MAS requiring mechanical ventilation of 0.43 per 1,000 live births.

Pathogenesis: Particulate meconium leads to partial or complete obstruction of the airways. Partial obstruction often results in hyperinflation, as air passes beyond the obstruction during inspiration when the airway dilates,

but it is trapped behind the obstruction on exhalation when the airway collapses around the obstruction, causing a ball-valve effect. Complete obstruction results in distal reabsorption and atelectasis. These events result in the typical radiographic picture of patchy atelectasis with areas of overexpansion. More dilute meconium that reaches the distal air spaces inactivates surfactant and leads to a picture similar to RDS with diffuse haziness and decreased lung volumes. Subsequently, the inflammatory response to the various components of meconium mediated by release of cytokines leads to alveolar and airway edema with release of protein-rich edema fluid further inactivating surfactant. Ventilator-induced lung injury may worsen the condition further, especially when aggressive hyperventilation is applied to treat PPHN, a practice no longer recommended.

Clinical Manifestations: Infants often appear dysmature with loose, peeling skin, greenish-yellow staining of the umbilical cord, nails, and skin. They present with tachypnea, nasal flaring, retractions, cyanosis, coarse rales, and rhonchi. There may be a barrel-shaped appearance of the chest related to air trapping or pneumomediastinum. Perinatal depression and PPHN often coexist as do complications of IUGR.

Diagnosis: The diagnosis is made in the presence of history of MSAF, respiratory distress, and radiographic changes. The radiographic appearance may be highly variable and changes over time. In the acute phase of MAS with particulate meconium, there is a typical patchy infiltrate with air trapping and increased lung volume, often accompanied by airleak. Where surfactant inactivation is the predominant pathophysiologic mechanism and in later stages of chemical pneumonitis, the chest radiograph may show homogeneous opacification with normal or low lung volume. Recovery of meconium from the trachea with suctioning confirms the diagnosis, but is not always present.

Differential Diagnosis: Because MSAF occurs in 10% of all deliveries, infants with other causes of respiratory distress may well have a history of MSAF. Most commonly, the dilemma is between MAS and TTN. The chest radiograph of an infant with TTN may be very suggestive of MAS; the differentiation rests on rapid clearance of the "infiltrate" in the infant with TTN, whereas meconium pneumonitis persists radiographically for many days. Other etiologies of respiratory distress, including infection, structural abnormalities of the lungs or airways, need to be considered.

Treatment: Supplemental oxygen, CPAP and mechanical ventilation may be required in that sequence if the severity of the illness is sufficient to require these steps. Avoidance of hypoxemia is important because of the propensity of these infants to develop PPHN. Hyperoxia does not offer any benefit over normoxia (PaO_2 50–70 mmHg); it may increase pulmonary artery vasoreactivity and blunt the response to inhaled nitric oxide if PPHN develops. Suctioning of the airway should be done judiciously, because each time the infant is suctioned, lung volume recruitment is lost. Saline lavage of the airways is ineffective and is not recommended. Surfactant replacement therapy is warranted because of the surfactant inactivation caused by meconium. Larger doses and repeated application may be necessary. Surfactant preparations that are more resistant to degradation by meconium may be preferred. Lung lavage with dilute surfactant may be effective, but is difficult to perform and not always well tolerated by the infant. Steroids may be effective in supressing the inflammatory and may reduce the severity of the disease process. However, their safety in this context has not been established. Antibiotics are indicated, typically for a 5–7-day course, because the aspirated material may have bacterial contamination and meconium may enhance bacterial growth. When mechanical ventilation is required, care must be taken to set an adequate inspiratory and expiratory time because infants with MAS have increased airway resistance and are thus prone to air trapping; therefore, rapid respiratory rates are to be avoided. Moderate PEEP of 4–7 cmH_2O is appropriate, despite evidence of overexpansion. This is because the distending expiratory pressure helps maintain airway diameter during expiration and decreases the ball-valve effect. When surfactant inactivation predominates and diffuse atelectasis is present, even higher PEEP of up to eight or more cmH_2O may be needed. High-frequency ventilation is widely used in infants with MAS with some objective evidence of benefit, but care must be taken to use lower frequencies to avoid air trapping. With very severe disease, especially when complicated by PPHN, rescue with extracorporeal life support (ECMO) may be required, where available – see Chap. 22, "ECMO".

Prognosis: With modern newborn intensive care, MAS is now rarely fatal, though it is occasionally associated with chronic lung disease. In a resource-limited setting MAS remains an important cause of morbidity and mortality. Associated PPHN increases mortality substantially.

Prevention: Avoidance of postmaturity is effective in reducing the number of infants at risk. Routine suctioning of the trachea after delivery is no longer recommended for vigorous infants, but remains an important preventive measure in depressed infants. Amnioinfusion has not been shown to reduce incidence or severity of MAS.

Persistent Pulmonary Hypertension of the Newborn (PPHN)

Definition: Persistent pulmonary hypertension of the newborn is a clinical syndrome, peculiar to the early neonatal period, characterized by severe arterial hypoxemia caused by increased pulmonary vascular resistance (PVR) with resultant right-to-left shunting of deoxygenated blood through fetal channels.

Etiology: Pulmonary hypertension of the newborn may be a primary disorder in infants with no associated lung disease, or secondary to a variety of disease conditions. Some of these are associated with hypoplasia of the lung parenchyma and decreased number of pulmonary arteries (i.e., pulmonary hypoplasia or CDH). Most commonly it occurs in infants with normal lung parenchyma and pulmonary vasculature because of a failure to make the normal transition at birth to decrease PVR (maladaptation). This may occur in intrapartum asphyxia, meconium aspiration syndrome, infection, and RDS. Cesarean delivery substantially increases the risk of PPHN due to maladaptation. Chronic intrauterine hypoxia causes pulmonary smooth muscle remodeling with increase in resistance across the vessels (maldevelopment). Severe polycythemia with sludging of blood in the pulmonary vessels can increase PVR. Recent evidence suggests that exposure to selective serotonin reuptake inhibitors (SSRIs) during late gestation is associated with a sixfold increase in the prevalence of PPHN. Pulmonary hypertension associated with severe bronchopulmonary dysplasia is a separate entity, but shares some of the same clinical features.

Epidemiology: Severe persistent pulmonary hypertension of the newborn affects approximately 1–2 infants per 1,000 live births, but some degree of transient pulmonary hypertension complicates the course of >10% of all neonates with respiratory failure. PPHN is typically seen in term infants with MAS, respiratory distress syndrome, sepsis, and congenital diaphragmatic hernia. Idiopathic pulmonary hypertension is responsible for only 10–20% of all infants with PPHN. Thought less common, PPHN may occur in preterm infants, especially in the presence of pulmonary hypoplasia due to prolonged preterm rupture of the membranes with prolonged oligohydramnios, CDH, or with sepsis.

Pathogenesis: High pulmonary vascular resistance (PVR) is the normal condition in utero. With the clamping of the umbilical cord at delivery, systemic vascular resistance increases and PVR begins to fall in response to alveolar expansion, clearance of lung liquid, decreasing carbon dioxide tension, and increasing oxygen tension. These changes are mediated by nitric oxide and prostacyclin pathways that cause pulmonary vascular smooth muscle relaxation. This reverses the fetal shunts and allows increasing blood flow to the lungs. The failure to achieve this normal circulatory transition is the fundamental problem in infants with PPHN.

Pulmonary hypoplasia is associated with a decrease in the number and cross-sectional area of pulmonary blood vessels with increased muscularization of pulmonary arterioles and increased vasoreactivity. Chronic fetal hypoxia induces vascular remodeling with increased smooth muscle proliferation resulting in thickening of the media and increased PVR. Premature closure of the ductus arteriosus from exposure to non-steroidal anti-inflammatory agents in the third trimester causes structural remodeling of the peripheral pulmonary vascular bed, resulting in PPHN. Maladaptation or failure to establish adequate vasorelaxation at birth from intrapartum asphyxia, meconium aspiration syndrome, and respiratory distress syndrome or release of vasoactive mediators that may contribute to pulmonary vasoconstriction as a result of infection leads to sustained high PVR and severe hypoxemia. Elective cesarean delivery without labor is associated with a slower fall in pulmonary vascular resistance and increased incidence of PPHN, because the normal process of labor leads to changes in the elaboration of mediators of vascular tone and prepares the fetus for successful transition to extrauterine life.

Clinical Manifestations: Severe hypoxemia out of proportion to the degree of lung disease is the hallmark of PPHN, often presenting as cyanosis and respiratory distress within a few hours of birth in a term or late preterm infant. Classically, there is great lability of oxygen saturation with frequent desaturation with any stimulation or stress and there may be a history of MSAF, fetal distress during labor, or antenatal ultrasound findings of CDH.

Diagnosis: The diagnosis of PPHN is suggested by the presence of cyanosis/labile hypoxemia and respiratory distress out of proportion to any lung disease that may be present. Examination of the heart sounds may reveal a harsh systolic murmur with a loud S2 secondary to tricuspid regurgitation. Pulse oximetry will demonstrate the severity of the hypoxemia. Simultaneous monitoring of pre-ductal (in the right hand) and a post-ductal (in any lower extremity) oxygen saturation may show significantly lower post-ductal saturation. This is a reflection of right-to-left shunting across the PDA, a finding also seen in neonates with a duct-dependent cyanotic heart lesion, coarctation of the aorta, or interrupted aortic arch. Consequently, pulse oximetry does not reliably differentiate PPHN from cyanotic heart disease. Additionally, if the ductus arteriosus is closed, no gradient will be seen,

because the shunting may be at the atrial level. CXR may show evidence of MAS, pneumonia, diaphragmatic hernia, or the pulmonary hypoplasia. In primary PPHN, the lung fields look clear and oligemic, similar to cyanotic heart disease with decreased pulmonary blood flow. Definitive diagnosis is made by echocardiography. This will help rule out cyanotic heart disease and identify signs of pulmonary hypertension. Echocardiogram typically shows right-to-left or bidirectional shunting across the PDA and PFO, tricuspid regurgitation, and flattening of the interventricular septum as a result of increased right ventricular pressure. By using peak velocity of the tricuspid regurgitant flow, it is possible to estimate pulmonary artery pressure. Echocardiogram is also vital in evaluating ventricular filling and ejection as sudden decompensation in neonates with PPHN can often be caused by poor myocardial function and right heart failure. Because in most infants the PVR is quite labile, the evidence of pulmonary hypertension may not be clear if the echocardiogram is done at a time the infant is responding to treatment and oxygenating well.

Differential Diagnosis: PPHN must be distinguished from cyanotic heart disease and severe parenchymal lung disease. When PPHN and severe lung disease coexist, it may be difficult to determine the relative contribution of pulmonary hypertension, in part because hypoxia and atelectasis itself increases pulmonary vascular resistance. Clinically, this may be done with the hyperoxia test. Briefly increasing the FiO2 to 1.0 will have no effect on oxygen saturation in an infant with a fixed intracardiac right-to-left shunt caused by cyanotic heart disease. A modest improvement in oxygenation is seen in infants with parenchymal lung disease and a dramatic improvement is often (but not always) seen when PPHN is the predominant cause of hypoxemia. Echocardiography will usually establish the diagnosis, but partial anomalous pulmonary venous drainage, which presents clinically with very similar findings, may be difficult to diagnose by echocardiography.

Treatment: Treatment of PPHN is focused on lowering pulmonary vascular resistance, supporting systemic blood pressure to keep it above pulmonary pressure, and providing gentle respiratory support in order to avoid complications, as the elevated PVR will eventually fall in most patients. Systemic blood pressure support can be achieved by judicious use of crystalloids (e.g., normal saline) in boluses of 10–20 mL/kg to improve circulating blood volume. This and the appropriate use of inotropic agents improve cardiac output and systemic blood pressure. Excessive use of saline can lead to volume and sodium overload. With adequate preload, the inotropic agents dopamine and dobutamine improve cardiac contractility and output. The use of epinephrine and higher doses of dopamine increase peripheral vascular tone and raise systemic blood pressure. Care should be exercised in the use of these agents, as they can be associated with tachycardia, arrhythmia, increased afterload, myocardial ischemia, and may increase PVR. Milrinone is a useful agent in PPHN, because it provides positive inotropic effect, does not cause systemic vasoconstriction, and achieves pulmonary vasodilatation because it inhibits phosphodiesterase 3, the enzyme that breaks down cyclic AMP.

Respiratory stabilization may require intubation and mechanical ventilation with the goal of providing sufficient mean airway pressure to achieve optimal lung volume, improve ventilation/perfusion matching, and lower pulmonary vascular resistance. Adequate oxygenation and avoidance of hypoxemia minimize pulmonary vascular resistance but supraphysiologic arterial oxygen tension should be avoided. Pulmonary vascular resistance only increases with PaO2 below 50 torr and no further fall in PVR is seen at PaO2 above 70 torr. Exposure to hyperoxia even for short periods of time increases oxidative stress and actually increases vasoreactivity of the pulmonary vessels and blunts response to inhaled nitric oxide (iNO). Target PaO2 therefore should be in the range of 60–80 torr. Acidosis increases PVR and should generally be avoided in patients with PPHN. Slightly alkaline arterial blood pH between 7.4 and 7.5 may be needed in some patients whose pulmonary hypertension fails to improve with more conservative ventilation and other appropriate therapies, including iNO. However, the practice of hyperventilation to achieve significant respiratory alkalosis is associated with increased likelihood of hemodynamic impairment, lung injury, chronic lung disease, and neurologic sequelae and is no longer recommended. The goal should be to maintain physiologic PCO2 between 35 and 45 torr. The use of alkali infusion (sodium bicarbonate) to increase blood pH has been used to reduce the need for respiratory alkalosis, but was associated with increased need for ECMO rescue in a large retrospective study. The choice of conventional ventilation or high-frequency ventilation (HFV) depends on availability and the underlying disease condition. HFV may offer advantages in patients with pulmonary hypoplasia, congenital diaphragmatic hernia, and airleak syndromes, and may be useful in achieving optimal lung inflation. Intravenous vasodilators have been used in the past, but lack specificity for the pulmonary circulation and generally have been ineffective. There is no sound evidence to support the widespread use of MgSO4 to treat pulmonary hypertension. Inhaled nitric oxide (iNO) has been studied extensively and is currently

the only specific pulmonary vasodilator approved for treatment of PPHN. Nitric oxide (NO) is generated by NO synthase from L-arginine. NO then activates guanyl cyclase leading to the production of cyclic GMP, which causes relaxation of the vascular smooth muscle by decreasing cytosolic calcium concentration. The use of iNO in doses of up to 20 PPM improves oxygenation and decreases the risk of death or need for ECMO by up to 50%, except in neonates with congenital diaphragmatic hernia in whom no significant benefit was demonstrated. Doses of iNO greater than 20 PPM do not result in greater efficacy but are associated with higher toxicity. iNO is most effective when the circulatory status and pH have been optimized and adequate lung expansion has been achieved. iNO in combination with HFV may be more effective than iNO used with conventional ventilation in infants with significant lung disease. Traditionally, iNO is started at oxygenation index (OI) levels of 25 or above; ($OI = [(F_IO_2 \times Paw)/PaO_2] \times 100$), where Paw is mean airway pressure and F_IO_2 is the fraction of inspired oxygen. However, when PPHN persists despite optimized ventilatory and hemodynamic support, iNO use at lower OI appears justified. Response to iNO should be evident within a short period of time when pH and perfusion have been optimized first. Treatment should be weaned as soon as possible after the FiO_2 has decreased to 70% or less by decrements of 5 PPM, down to 5 PPM, and more slowly thereafter with the goal of weaning from iNO by 3–4 days. Prolonged exposure to iNO will suppress endogenous nitric oxide production and make it more difficult to discontinue the drug. Although iNO has been shown to be safe and effective in the treatment of PPHN, it is expensive and not readily available everywhere. Sildenafil, a phosphodiesterase five inhibitor improves oxygenation in patients with PPHN. Sildenafil decreases the degradation of cyclic GMP resulting in higher concentrations of cyclic GMP locally, which in turn leads to relaxation of pulmonary vascular smooth muscles. Its lower cost and greater availability has made sildenafil very attractive to clinicians with no access to iNO. Despite the absence of definitive studies to determine the safest effective dose and to evaluate its safety profile in neonates, this drug is widely used in less affluent countries.

The general care of infants with PPHN is crucial to optimizing outcome. Correction of acidosis, glucose and other electrolyte derangements, aggressive treatment of sepsis, circulatory support, correction of coagulopathy, and institution of appropriate supportive treatments for perinatal asphyxia are vital determinants of response to treatment and survival. Minimal handling and use of adequate sedation/analgesia to avoid agitation are very important. Although routine use of paralytic agents is not recommended, at times they may be necessary to control agitation. Up to 40% of patients with PPHN and most infants with CDH do not respond to iNO. In these patients, ECMO is the ultimate rescue treatment and should be instituted while the infant has some degree of stability. It is vital for clinicians to recognize early those patients who are nonresponders to iNO and anticipate the need for ECMO where available. Institutions that do not have ECMO as a treatment option readily available should perhaps consider how nitric oxide is used and be prepared for early transfer of nonresponders to an ECMO center.

Prognosis: Prognosis in PPHN depends on the underlying diagnosis, response to treatment, and availability of rescue therapies. Mortality has been reduced to $<5\%$ with more optimal ventilatory support, iNO, and ECMO, but remains high where these advanced therapies are not available. An early and sustained response to inhaled nitric oxide is associated with clinical improvement and better outcomes. Patients with perinatal asphyxia, pulmonary hypoplasia, and CDH often have the worst prognosis. Residual chronic lung disease and/or sensorineural hearing loss have been reported to correlate with duration of hyperventilation.

Prevention: Many infants that develop PPHN exhibit signs of respiratory distress early in their course. Progression of respiratory disease with failure to establish adequate oxygenation and ventilation will impair the normal newborn transition and lead to the persistence of high PVR leading to PPHN. Recognition of infants with early respiratory disease and acting quickly to provide adequate respiratory support to maintain good oxygenation may reduce the progression to hypoxemic respiratory failure and PPHN. Many infants that develop PPHN were born late preterm via elective C-section who then exhibit signs of surfactant deficiency or retained lung fluid that can progress to PPHN. Avoiding elective delivery before 38 weeks of completed gestation will significantly reduce respiratory morbidity in this subgroup of patients. Prenatal ultrasounds are now able to readily identify infants with oligohydramnios and CDH so that delivery can occur in a tertiary center where optimal treatments can be instituted early.

Airleak Syndrome

Definition: Pulmonary airleak is defined as accumulation of air outside of the airway and alveolar space. Depending on the location of the air it may be described as a pneumothorax, pneumomediastinum, pulmonary

interstitial emphysema (PIE), pneumopericardium, or subcutaneous emphysema.

Etiology: Airleaks are caused by over-distension of alveoli or terminal bronchioles with resultant rupture and escape of air into the interstitium. Spontaneous pneumothorax can occur soon after birth due to the high pressures generated by the baby taking their first breaths. High positive airway pressure used during resuscitation may also cause airleak. Most airleaks are associated with lung diseases such as RDS, meconium aspiration syndrome, pneumonia, pulmonary hypoplasia, and congenital diaphragmatic hernia. The majority of airleaks are associated with mechanical ventilation, particularly with the use of inappropriately high inspiratory pressure or tidal volume, use of unsynchronized ventilation. Direct injury to the trachea or airway can occasionally result from suctioning through the endotracheal tube (ETT), use of introducers through the ETT for their placement, or central venous catheter placement.

Epidemiology: The overall incidence of airleaks in term infants is about 1%, although only about 10% of these are symptomatic. The incidence of airleak is significantly higher in preterm infants requiring mechanical ventilation and was reported to occur in 3–13% of infants less than 28 weeks gestation born between 2003 and 2007 from the NICHD Neonatal Research Network centers. PIE is predominantly seen in the extremely low birth weight infant with RDS on mechanical ventilation with a reported incidence of 3–5%.

Pathogenesis: The development of airleak starts with over-distension of alveoli or terminal bronchioles with subsequent rupture and escape of air into the interstitial tissue. This free air then tracks along the bronchial and vascular sheaths to the hilum of the lung. The air can escape into the mediastinum producing a pneumomediastinum or dissect through the visceral pleura producing a pneumothorax. A pneumopericardium may develop when the air dissects into the pericardial sac usually in association with a pneumothorax in ventilated infants. Free air in the mediastinal space can track into the subcutaneous tissues of the neck or chest wall as subcutaneous emphysema or into the abdomen causing a pneumoperitoneum. In ELBW infants with pulmonary interstitial emphysema, the lung connective tissue is more abundant and less dissectible, therefore the air remains in the bronchovascular sheaths splinting the alveoli in a state of inflation causing significant ventilation perfusion mismatch by impeding alveolar emptying and pulmonary blood flow.

Clinical Manifestations: The clinical presentation of airleak syndromes is varied from the asymptomatic to sudden acute decompensation depending on the amount of air that has collected and whether it is under tension compressing the lung and other intrathoracic structures. Most cases of pneumomediastinum are not associated with significant clinical symptoms because the air is usually not under tension. Subcutaneous emphysema can be recognized by a "crackly feeling" on palpation of the anterior chest wall or over the neck. Pneumoperitoneum may present with abdominal distension or rarely enlargement of the scrotum in boys. A small pneumothorax in an infant with little or no lung disease can be asymptomatic. This is typical with a spontaneous pneumothorax. Tension pneumothorax presents with respiratory distress, hypoxia, acute respiratory acidosis, and rapid deterioration. Clinical examination will show subcostal retractions, cyanosis, decrease or absence of breath sounds on the ipsilateral side, shift of heart sounds to the contralateral side due to mediastinal shift, and abdominal distention due to downward displacement of the diaphragm. There may be associated hypotension and bradycardia because of impaired cardiac output from impeded venous return. Pneumopericardium may be asymptomatic, but usually presents acute circulatory decompensation due to cardiac tamponade with distant heart sounds on auscultation. PIE is usually encountered in the ELBW infant on mechanical ventilation who has progressive worsening of respiratory status without localizing signs, unless it is unilateral.

Diagnosis: The diagnosis of airleak syndrome should be suspected in any infant with sudden respiratory deterioration particularly those with underlying lung disease on mechanical ventilation or CPAP. A pneumothorax can be diagnosed by the use of a high-intensity fiberoptic light placed firmly against the skin in the midaxillary line or anteriorly in a darkened room. Free air in the pleural space lights up the affected hemithorax. In an emergency when there is clinical suspicion of a pneumothorax thoracocentesis by aspiration of air with a syringe attached to a 23- or 25-gauge butterfly needle or an 20–22 gauge angiocatheter can be both diagnostic and therapeutic. Definitive diagnosis of all airleaks is made by chest x-ray. (Please see the paragraph on airleak in Chap. 21, "Complications of Mechanical Ventilation" for further description).

Differential Diagnosis: Pulmonary airleaks are easily recognizable on CXR although they may be confused with or coexist with other pulmonary diseases like congenital diaphragmatic hernia, cystic adenomatoid malformation, congenital lobar emphysema, and pulmonary abscess. Diminished breath sounds and mediastinal shift to the opposite side may be due to a large pleural effusion,

while diminished breath sounds with shift to the ipsilateral side may be due to atelectasis. In the delivery room, the scenario of a distressed, cyanotic infant with diminished breath sounds on one side and shift of the heart sounds to the other most often is due to a pneumothorax, but a congenital chylothorax or diaphragmatic hernia can have a similar presentation. The key difference is that with tension pneumothorax and pleural effusion the abdomen should be distended, whereas it is flat or scaphoid with diaphragmatic hernia.

Treatment: Most cases of pneumomediastinum, subcutaneous emphysema, and non-tension pneumothoraces cause few symptoms and resolve spontaneously. The patient should be observed for any sudden deterioration in clinical status suggesting worsening accumulation of air. Nitrogen washout with 100% oxygen is not recommended as the toxicity caused by high amounts of oxygen likely outweighs the problems caused by a non-tension pneumothorax. A tension pneumothorax represents a medical emergency and should be treated promptly. Immediate relief can be achieved by thoracocentesis with aspiration of air with a syringe attached to a 23- or 25-gauge scalp vein needle or an 18–22-gauge angiocatheter. Definitive treatment is by insertion of a chest tube into the anterior pleural space attached to underwater seal with continuous suction at 15–20 cm H2O. For infants on mechanical ventilation, the level of support should be evaluated to correct atelectasis by optimizing adequate but not excessive PEEP and reduce PIP/VT to the lowest value consistent with adequate CO2 elimination. High-frequency ventilation has advantages over conventional ventilation in the presence of airleak because adequate MAP can be provided with lower tidal volume and still remove CO2 efficiently. HFJV has unique benefits in the treatment of airleak, specifically PIE and bronchopleural fistula. When HFV is not available, rapid rate and short inspiratory times are preferable. Lateral decubitus positioning of the infant with unilateral PIE, placing the affected lung in a dependent position improves gas exchange and reduces mediastinal shift with faster resolution of PIE. Selective main-stem bronchus intubation is not always well tolerated, but is an effective way of resolving unilateral PIE.

Prognosis: Spontaneous resolution occurs in most infants with pneumomediastinum and pneumothoraces even when they require drainage. Tension pneumothorax is a known risk factor for intraventricular hemorrhage in preterm infants. Failure to recognize and quickly treat the acute hemodynamic compromise caused by tension pneumothorax and pneumopericardium can lead to sudden death. ELBW infants who develop PIE have substantially increased mortality and are at increased risk of developing BPD.

Prevention: Early provision of distending airway pressure in infants with respiratory distress to recruit and maintain optimal lung volume and avoidance of excessive tidal volume are the two steps most helpful in reducing the risk of airleak. Surfactant replacement therapy also reduces airleak. The infant with respiratory distress and progressive atelectasis that is not treated early is more likely to develop an airleak when subsequently placed on positive pressure support because most of the distending pressure will now be delivered to the compliant parts of the lung making them more prone to over-distension and airleak. Therefore early administration of surfactant in preterm infants with RDS and subsequent support with CPAP or mechanical ventilation as appropriate will maintain more uniform lung volume and reduce alveolar injury. Avoidance of hyperventilation with inappropriately high tidal volumes and peak airway pressure will lessen the likelihood of developing airleak. Although PEEP is generally lung protective and helps to achieve more uniform lung inflation, the optimal pressure required to maintain good lung volume should be reassessed frequently by checking lung expansion on CXR and lowering PEEP if the FiO2 is close to room air, as inappropriately high lung volumes can lead to alveolar rupture at peak inspiration and produce airleak. It is not clear that avoidance of mechanical ventilation with the use of noninvasive modes of ventilation reduces airleak; increased rate of airleak was reported in the CPAP arm of the COIN trial. Both volume-targeted ventilation and high-frequency ventilation have been shown to reduce airleak.

Pulmonary Hemorrhage

Definition: Pulmonary hemorrhage is assumed to be present when there is appearance of bloody fluid from the upper respiratory tract or the endotracheal tube (ETT).

Etiology: What is commonly referred to as pulmonary hemorrhage may be true hemorrhage originating in the lung parenchyma or the airways, but much more commonly is actually hemorrhagic pulmonary edema. Risk factors for the development of pulmonary hemorrhage include: extreme prematurity, surfactant treatment of RDS, left to right shunt through a patent ductus arteriosus (PDA), fluid overload, intrauterine growth restriction, hypoxic insults, and generalized coagulopathy.

Epidemiology: The overall incidence of pulmonary hemorrhage is reported to be 1/1,000 live births, but in ELBW infants with RDS it is as high as 4–7%.

Pathogenesis: True hemorrhage may result from trauma or coagulopathy. The more common hemorrhagic pulmonary edema occurs as a result of acute left ventricular decompensation leading to increased pulmonary capillary pressure. Many factors may contribute to acute decompensation, but most commonly this results from increased pulmonary blood flow caused by left to right shunting through a PDA. The association with surfactant therapy is thought to be due to rapid improvement of lung compliance and fall in pulmonary vascular resistance, allowing greater left to right shunt. The preterm myocardium has limited reserve and does not cope effectively with a large volume overload. Hypoxia and acidosis may also lead to decreased left ventricular function with resultant acute increase in pulmonary capillary pressure. Because of this increase in pressure, capillary ultrafiltrate leaks into the pulmonary interstitial space. The fluid is initially drained via the lymphatics, but as these get overwhelmed the fluid ruptures through the alveolar epithelial walls. As the leak worsens red cells and plasma escape into the alveolar space leading to hemorrhagic pulmonary edema. The fluid initially has a frothy bloody appearance and a hematocrit of about 10% but may progress to frank hemorrhage into the lungs. Coagulopathy is usually not present with hemorrhagic pulmonary edema, but does play a part in frank pulmonary hemorrhage in term infants.

Clinical Manifestations: The clinical presentation of pulmonary hemorrhage is usually sudden and catastrophic. Patients are usually ELBW infants on mechanical ventilation for RDS following surfactant therapy and usually have an underlying large left to right shunt via a PDA. Symptoms most commonly appear around the second or third day of life with sudden deterioration in the infant's condition manifested as acute fall in oxygen saturation, loss of chest wall excursion, respiratory acidosis, hypotension, and bradycardia. The appearance of bloody fluid in the ETT may accompany the sudden deterioration, but sometimes is only evident upon suctioning.

Diagnosis: The diagnosis of pulmonary hemorrhage is usually obvious from the clinical presentation and sudden appearance of bloody fluid in the ETT. Chest radiograph will typically show diffuse opacification or a complete "white out." The presence of the usual predisposing factors supports the diagnosis. Air bronchogram may not be seen, however, since the airways may be filled with hemorrhagic fluid.

Differential Diagnosis: Hemorrhagic pulmonary edema must be differentiated from local bleeding due to mucosal trauma. In this instance, the volume of blood is usually small, it does not appear frothy, and is typically not associated with the sudden deterioration seen in hemorrhagic pulmonary edema. The distinction is of critical importance, because the treatment is very different. True pulmonary hemorrhage is much less frequent, but may present with a large amount of almost pure blood in the trachea in the setting of coagulopathy or very high ventilator settings in a larger infant. Obtaining a hematocrit may help differentiate the two conditions, but is usually not necessary.

Treatment: Treatment of hemorrhagic pulmonary edema requires aggressive resuscitation starting with maintenance of adequate gas exchange. The urge to continuously suction blood from the ETT should be resisted, as any loss of distending airway pressure would worsen the hemorrhage. The fluid has low viscosity and will not clot in the airways. The use of PEEP as high as 10–12 cmH2O is the most effective means of stabilizing the patient and reversing the outflow of hemorrhagic fluid. This approach mitigates the left to right shunt through a PDA, promotes uptake of fluid into the pulmonary lymphatics and capillaries, clears the fluid from the airways, and improves lung compliance. Peak pressure adequate to achieve desired tidal volume or chest wall movement should be selected. High-frequency ventilation is often used, because clinicians are more comfortable using higher mean airway pressure with high-frequency devices. However, because of the acute nature of the crisis, changing ventilators may not be optimal; sufficient PEEP will achieve similar results with conventional ventilation. Inotropic support may be beneficial to optimize myocardial contractility, but aggressive volume expansion is contraindicated, because the infant is usually *not* hypovolemic and excessive volume administration may worsen the ventricular failure. Appropriate ventilator management limits intravascular volume loss and the need for replacement. An echocardiogram should be obtained if available and a significant PDA should be treated. Coagulopathy is usually not an issue, but, if present, should be corrected with the use of fresh frozen plasma and/or cryoprecipitate to supply clotting factors as needed. After stabilization, infants may benefit from surfactant replacement, as the hemorrhagic alveolar edema inevitably leads to inactivation of surfactant and secondary surfactant deficiency.

Mucosal bleeding usually subsides spontaneously with avoidance of further trauma. If persistent, coagulopathy/thrombocytopenia should be sought and corrected. Local administration of epinephrine via the endotracheal tube and lavage with iced saline are traditional therapies, although their value is unproven. These measures have *no place* in the treatment of hemorrhagic pulmonary edema.

Prognosis: Pulmonary hemorrhage has traditionally been associated with high mortality of up to 80%. With better understanding of the underlying pathophysiology and more appropriate therapy, the mortality rate has declined to <50%. However, these infants are usually the smallest and sickest, and are at high risk for long-term pulmonary morbidity (chronic lung disease) between 60% and 80% and an increased risk of developing intraventricular hemorrhage and retinopathy of prematurity.

Prevention: The use of prenatal steroids before preterm delivery has reduced pulmonary morbidity significantly including pulmonary hemorrhage. Timely recognition and treatment of a significant PDA will reduce the likelihood of hemorrhagic pulmonary edema, particularly in infants with history of hypoxia and poor left ventricular function.

Pulmonary Hypoplasia

Definition: Pulmonary hypoplasia refers to impaired growth and development of lung tissue and the pulmonary vascular bed.

Etiology: Pulmonary hypoplasia can result from (1) lack of adequate space for the lung to grow either from intrathoracic space occupying lesion, longstanding pleural effusion, or extrathoracic compression (asphyxiating thoracic dystrophies); (2) reduction in fetal breathing movements; and (3) decreased amniotic fluid volume. Rarely, pulmonary hypoplasia may be associated with Trisomy 21 due to reduced numbers of alveoli and a smaller alveolar surface area.

Epidemiology: The true incidence of pulmonary hypoplasia is unknown because many infants with severe pulmonary hypoplasia die in utero, during labor or at birth. The frequency of pulmonary hypoplasia is related to the incidence of underlying causes. In cases of premature rupture of membranes at 15–28 weeks gestation, the reported incidence of pulmonary hypoplasia ranges from 9% to 28%. The occurrence of congenital diaphragmatic hernia (CDH) is estimated at 1/2,500–3,000 live births and cystic adenomatoid malformation (CCAM) 1 per 25,000–35,000 pregnancies. Adding to the difficulty in estimating the frequency is the wide spectrum of severity and presentation.

Pathogenesis: Lung development starts with the ventral outpouching of the primitive foregut to form the lung bud which then subsequently divides and branches through several phases to form the airways and lung parenchyma. Pulmonary vasculature develops in parallel with lung parenchyma. Any physical limitation to the space available for lung growth may impair lung development. This may result from intrathoracic compression (CDH, CCAM, large pleural effusion secondary to hydrops or congenital chylothorax) or extrathoracic compression secondary to skeletal abnormalities (asphyxiating thoracic dystrophy). Fetal lung growth is also dependent on adequate distension of the lung by fetal lung fluid and on fetal breathing movements, which are impaired or absent in conditions such as fetal akinesia syndromes, congenital myopathies, and phrenic nerve agenesis. The fetal kidney produces proline which together with several growth factors found in amniotic fluid aid in lung collagen and mesenchyme formation. As fetal lung liquid pressure is slightly higher than amniotic fluid pressure any decrease in amniotic fluid volume will be associated with loss of lung liquid and a decrease in the distending pressure to the developing lung. Fetal urine is an important component of amniotic fluid and renal agenesis/dysplasia or complete urinary tract obstruction (e.g., posterior urethral valves) is associated with oligohydramnios leading to pulmonary hypoplasia. The severity of lung hypoplasia depends on the timing of the insult in relation to the stages of lung development. The earlier the insult in gestation, the more severe the degree of lung hypoplasia. Physical and histological examination of the hypoplastic lung will show reduced lung weight, fewer generations of airways, decreased number of alveoli with delayed epithelialization, as well as paucity and maldevelopment of the corresponding pulmonary arteries.

Clinical Manifestations: The clinical presentation of infants with pulmonary hypoplasia depends on severity of disease and the underlying cause. In the severe forms, respiratory distress, hypercapnia, and hypoxemia are universal together with signs and symptoms of associated conditions. Infants with CDH may have a scaphoid abdomen and decreased breath sounds on the affected side. Infants with severe oligohydramnios may present with a small chest, contraction deformities such as arthrogryposis, and "Potters facies." Severe hypotonia with a small chest compared to the rest of the body may indicate an underlying central nervous system abnormality. Pulmonary hypertension commonly accompanies pulmonary hypoplasia.

Diagnosis: Most conditions associated with pulmonary hypoplasia can be identified through antenatal ultrasound and magnetic resonance imaging (MRI). The presence of pulmonary hypoplasia should be expected with any of the underlying associated conditions. Chest x-ray after birth will show an underdeveloped "bell shaped" rib cage with decreased lung expansion in patients with history of oligohydramnios or underlying neurologic disease.

Conditions where there is restriction of lung growth from external compression are often unilateral and can be identified on x-ray with the ipsilateral lung affected more than the contralateral lung. Definitive diagnosis of pulmonary hypoplasia requires pathologic examination of the lung to determine lung weight, perform radial alveolar counts, and measure the total lung DNA. Hypoplastic lungs have a decreased number of airway generations, with fewer and smaller peripheral airspaces and decrease in the number and cross-sectional area of pulmonary vessels.

Differential Diagnosis: The degree of pulmonary hypoplasia, if any, may be difficult to determine in milder cases and also when associated with other conditions. Severe RDS with poor lung expansion in a premature infant is difficult to differentiate from pulmonary hypoplasia radiographically. If the lung fields are relatively clear but with very low lung volume, hypoplasia is more likely.

Treatment: Recognition of conditions associated with pulmonary hypoplasia and instituting appropriate resuscitative measures are key to early management. Infants with CDH require immediate intubation with avoidance of facemask ventilation and rapid decompression of the stomach (see ❯ section on CDH). Infants with pulmonary hypoplasia have severely decreased lung compliance requiring higher airway pressure to achieve adequate gas exchange. This, together with the underdeveloped lung parenchyma, places these patients at increased risk of developing an airleak syndrome. Pulmonary hypertension from decreased pulmonary vascular development requires specific therapy as discussed in the section on PPHN. It should be noted that excessive expansion of the hypoplastic lungs will worsen PPHN due to compression of the pulmonary capillaries. Distending pressure should therefore be used with caution. High-frequency ventilation can provide better support with its ability to remove CO2 more efficiently and to treat or mitigate airleak syndromes better than conventional ventilation. In most patients with pulmonary hypoplasia, surfactant replacement therapy has not been shown to be beneficial unless the infant is also premature. Inhaled nitric oxide therapy may only show a transient improvement. Caution should be exercised in considering patients with severe pulmonary hypoplasia as candidates for ECMO, as the degree of lung hypoplasia and pulmonary vascular underdevelopment may not be reversible.

Prognosis: The outcome of infants with pulmonary hypoplasia is dependent on the degree of lung underdevelopment and the nature of the underlying disease. Conditions that hinder lung development early in gestation are associated with more severe hypoplasia and have the worst prognosis. Most infants with severe pulmonary hypoplasia die in utero, during labor, or soon after birth. Associated conditions with poor prognosis include: renal dysplasia, asphyxiating thoracic dystrophy, congenital myopathies, and other neurologic conditions. Surviving patients may go on to develop chronic pulmonary insufficiency requiring long-term care.

Prevention: There are no proven methods of prevention for most of the conditions leading to pulmonary hypoplasia. Animal and human studies have shown that tracheal occlusion in utero will reverse pulmonary hypoplasia but because of the high incidence of preterm deliveries related to this intervention, it has not been widely accepted and remains experimental. In utero placement of pleuroperitoneal shunt to treat pleural effusion and vesicoperitoneal shunt to relieve bladder outlet obstruction has met with mixed success as well.

Congenital Diaphragmatic Hernia (CDH)

Definition: CDH refers to herniation of abdominal contents into the chest through a defect in the diaphragm and the associated pulmonary hypoplasia present at birth.

Etiology: CDH is a developmental abnormality of the diaphragm resulting in a defect with resulting herniation of abdominal viscera into the chest. The diaphragmatic defect occurs when some of the structures making up the fetal diaphragm fail to develop adequately or to fuse by the eighth week post conception. Abnormalities in the retinoic acid signaling pathway may be important in the maldevelopment of the diaphragm early in gestation and may independently contribute to pulmonary hypoplasia.

Epidemiology: CDH occurs in 1/2,500–3,000 live births with a slight preponderance of males (1.5:1 male to female ratio). Recurrence risk for future pregnancies is approximately 2%. Worldwide incidence appears to be the same as that in the United States: 85–90% occur on the left side, 10% and a small number are bilateral. There are two types of diaphragmatic hernias: the posterior Bochdalek hernia accounting for about 95% of the total and the anterior Morgagni hernia for the remaining 5%.

Pathogenesis: In the fetus with CDH, the bowel, sometimes stomach, spleen, or liver herniate into the chest impairing lung development. Lung hypoplasia is thought to be secondary to the in utero compression of the fetal lung. Both the ipsilateral and contralateral lungs are involved, because the herniated abdominal contents cause mediastinal shift. The degree of hypoplasia is often severe on the ipsilateral side with only a minute lung seen in the apex of the chest at surgery. The severity of pulmonary hypoplasia roughly correlates with the size of the

defect, which may range from a small posterior opening to complete agenesis of the hemidiaphragm. Lung hypoplasia involves not just a decrease in lung parenchyma, but a dramatic decrease in the number and cross-sectional area of the pulmonary blood vessels. Additionally, there is abnormal muscularization of the pulmonary arterioles and increased vasoreactivity, which often leads to associated refractory PPHN.

Clinical Manifestations: The severity of respiratory distress is highly variable. Most infants present in the delivery room with cyanosis, retractions, and tachypnea. Breath sounds are decreased on the affected side with shift of the breath sounds to the opposite side – all signs consistent also with the more common problem of spontaneous tension pneumothorax. The key differentiating factor is that the abdomen is distended in the presence of pneumothorax, while it is flat or scaphoid with CDH. Bowel sounds are rarely heard in the chest, but this sign is diagnostic, if present. Some infants have minimal signs initially and may not be recognized for some time. The clinical status often remains reasonably stable for the first 12–24 hours, a period referred to as the "honeymoon," followed by development of severe pulmonary hypertension.

Diagnosis: In industrialized countries, the majority of cases are diagnosed by antenatal ultrasound. Postnatal diagnosis is based on clinical presentation and radiographic confirmation. Initial chest films may not show the classical bowel pattern in the chest, if air has not yet filled the bowel, but may instead just show a water density mass with mediastinal shift.

Differential Diagnosis: CDH must be distinguished from eventration of the diaphragm, pulmonary sequestration, pleural effusion, or cystic adenomatoid malformation involving the lower lobes of the lung. Acutely, it must be distinguished from tension pneumothorax.

Treatment: Immediate intubation with avoidance of facemask ventilation is critical to avoid filling the bowel with air and causing further lung compression. A naso- or oro-gastric tube is rapidly placed for gastric decompression. Muscle relaxation is advocated by some to prevent the infant from swallowing air, but this is not usually needed when effective gastric decompression. Nasal CPAP or high-flow nasal cannula are to be avoided. Pulmonary hypertension is triggered or aggravated by pulmonary overexpansion; therefore distending airway pressure is applied cautiously. Gentle ventilation with either conventional or high-frequency ventilators, allowing moderate permissive hypercapnia and accepting just adequate oxygenation, appears to improve outcome, compared to the more aggressive traditional treatment, even when PPHN is present. Exogenous surfactant does not appear to be beneficial (unless the infant is premature) and was associated with worse outcomes in a large retrospective study. Infants with CDH and PPHN do not usually respond well to inhaled NO, but many show a modest transient improvement.

CDH is no longer considered a surgical emergency, since it is now well recognized that the fundamental problem is the pulmonary and pulmonary vascular hypoplasia, which is not reversed by removing the herniated contents from the chest. In fact it is now clear that early surgery at the time of greatest physiologic instability and highest pulmonary vascular resistance often makes matters worse. The surgical approach now is to await improvement in pulmonary status and delay surgery for 3–7 days or until the infant is on low ventilator settings and FiO_2. In unstable patients ECMO, where available, is offered prior to surgical repair. ECMO remains the treatment of last resort, but survival remains only about 50% in infants sick enough to require this rescue therapy.

Prognosis: Prognosis depends on the presence or absence of other anomalies, severity of the defect, and availability of state of the art treatment. Associated anomalies, especially chromosomal, portend a poor prognosis. Polyhydramnios, presence of liver in the chest, and low lung-to-head ratio (LHR) are poor prognostic factors. The LHR, is a ratio of the visible lung on the contralateral side to fetal head. MRI volumetry has been proposed as a better tool, but requires validation. Echocardiography is utilized to detect associated fetal cardiac anomalies. Various estimates of left ventricular mass and pulmonary artery diameters appear to be good indicators of pulmonary hypoplasia. Survival depends on the denominator used in the calculation. Many CDH pregnancies end in elective termination, spontaneous abortion, or stillbirth, especially when associated anomalies are found. A substantial number of live born infants succumb in the delivery room. Therefore, reported survival statistics from tertiary centers include only a selected group of infants who reached the center alive. This "hidden mortality" not seen at the tertiary center accounts for large differences in reported survival. When all CDH pregnancies are counted, survival may be as low as 25%. Infants reaching tertiary centers have a 60–80% survival with the most advanced care, but continue to have long-term sequelae, including growth failure, severe gastroesophageal reflux, and developmental delays. Late death may occur after apparently successful treatment from recurrent pulmonary hypertension.

Prevention: There is no known prevention for CDH, but in utero fetal therapy has been a subject of intense study. It has been shown that the lung hypoplasia can be reversed by fetal tracheal occlusion, but improved survival

has been difficult to demonstrate, in part due to high rate of preterm delivery associated with this procedure. The treatment remains experimental.

Bronchopulmonary Dysplasia (BPD)

Definition: Bronchopulmonary dysplasia is defined as lung injury in preterm infants resulting from oxygen and mechanical ventilation. Various definitions have been used since its initial description in 1967. Oxygen requirement at 36 weeks postmenstrual age has been the most widely used definition. Current definition has been modified to define severity of BPD and differentiate between infants of different gestational age. This definition, based on the NIH consensus conference in 2001, is shown in *Table 15.3*.

Etiology: BPD is believed to result from the combination of oxygen-mediated injury and exposure to mechanical ventilation in immature lungs with limited antioxidant defenses.

Oxygen exposure impairs secondary crest formation and alveolar septation, leading to a "simplified lung," which lacks adequate surface area and sufficient pulmonary capillaries in close proximity to the saccules. Mechanical ventilation results in disruption of cellular structures, release of inflammatory mediators, chemokines, and influx of activated neutrophils, beginning a sequence of injury, inflammation, and repair that eventually results in the clinical picture of BPD.

Epidemiology: The Neonatal Research Network study of 1,598 inborn survivors 501–1,249 g born between 2000 and 2002 showed that 31% received oxygen or ventilatory assistance at 36 weeks. Prematurity is the single most important predisposing factor for BPD; in one study, the incidence of BPD using the 36 weeks postmenstrual age definition was 42% for infants weighing 501–750 g, 25% for 751–1,000 g, and 11% for infants 1,001–1,250 g. Data from the Israeli National VLBW database showed that 19% of 3,689 VLBW infants met the definition of BPD. BPD is the most common form of chronic lung disease in infants in the United States with an estimated 7,000–10,000 new cases occurring each year.

Pathogenesis: Tissue stretch associated with mechanical ventilation results in disruption of airway epithelial and alveolar cells with early interstitial and alveolar edema which progresses to persistent structural changes, persistent inflammation, and fibrosis in the lung that ultimately result in significant effects on lung mechanics, gas exchange, and pulmonary vasculature. It is a heterogeneous condition and its manifestations vary. In some infants it is characterized primarily by arrest of normal lung development, resulting in a "simplified lung," which has decreased number of larger alveoli, paucity of pulmonary capillaries in close proximity to the saccules, and decreased total surface area for gas exchange (the "new BPD"). Various degrees of interstitial fibrosis and elastin deposition in alveolar walls may be associated with the more severe forms of BPD, as a result of the complex sequence of lung injury, inflammation, and remodeling. These infants typically have significant airway disease as part of their clinical picture with increased airway resistance, mucosal thickening, ongoing inflammation, increased mucus production, and varying degrees of airway smooth muscle hyperplasia.

The pathogenesis of PBD is complex and multifactorial. The role of inflammation is increasingly recognized with both prenatal and postnatal infection contributing substantially to the development of BPD. It has been shown that the rate of histologic chorioamnionitis is

Table 15.3
Diagnostic criteria for BPD

Gestational Age	<32 weeks	≥32 weeks
Time of assessment	36 weeks PMA or discharge, whichever comes first	28–56 days postnatal age or discharge, whichever comes first
	Treatment with oxygen >21% for at least 28 days, *plus*	Treatment with oxygen >21% for at least 28 days, *plus*
Mild BPD	Breathing room air at 36 weeks PMA or discharge, whichever comes first	Breathing room air by 56 days
		PMA or discharge, whichever
Moderate BPD	Need[a] for <30% oxygen at 36 weeks PMA or discharge, whichever comes first	Need[a] for <30% oxygen at 56 days of age or at discharge, whichever comes first
Severe BPD	Need[a] for <30% oxygen and/or positive pressure (PPV or NCPAP) at 36 weeks PMA or discharge, whichever comes first	Need[a] for ≥30% oxygen and/or positive pressure (PPV or NCPAP) at 56 days of age or discharge, whichever comes first

PMA postmenstrual age, PPV positive pressure ventilation, NCPAP nasal continuous positive pressure ventilation

[a]Need should ideally be defined by physiologic criteria, e.g., need to maintain SPO2 >90%. The optimal SPO2 targets are not yet well defined

inversely proportional to gestational age. Other contributing factors include excessive fluid intake, presence of patent ductus arteriosus, and exposure to high FiO2 and large tidal volume ventilation. Infection with Ureaplasma Urealyticum is associated with a high incidence of BPD, but its postnatal eradication does not appear to improve outcome. There is considerable variation in susceptibility to BPD and the underlying mechanisms for the genetic basis of this are under intense investigation.

Clinical Manifestations: BPD evolves insidiously when the initial RDS fails to resolve. The infant will have persistent or increasing oxygen requirement, tachypnea, and retractions with increased secretions noted in intubated infants. Some VLBW infants may have little or no RDS initially, but then gradually develop increasing oxygen requirement and classical features of BPD. Chest radiographs initially show diffusely hazy lungs with good lung expansion and this may progress to the more patchy, hyperinflated lung fields associated with classical BPD. The increased airway resistance is in part due to the poorly supported small airways with tendency to airway collapse at low lung volume. There is airway mucosal edema with increased secretions, but usually there is no active bronchoconstriction in the first few weeks of life. In later stages of BPD, reactive airway disease may develop. Severe cases of BPD may be associated with pulmonary hypertension and this is occasionally fatal.

Diagnosis: There is no single diagnostic test. The condition evolves over time, beginning within days of birth, but the formal diagnosis is based on oxygen or positive pressure ventilation requirement at 28 days or beyond. Radiographic changes are no longer a requirement for the diagnosis, but are typically present.

Differential Diagnosis: The main distinction is between BPD and chronic pulmonary insufficiency of prematurity (CPIP), related to insufficient rigidity of the chest wall leading to diffuse microatelectasis and consequent oxygen requirement. The differentiation is best made on chest radiographs. In both instances, there is increased opacification of the lung fields, but the lung expansion is normal or increased in BPD and reduced with CPIP. When respiratory status is deteriorating during the second or third week of life in a ventilated preterm infant, evolving BPD needs to be differentiated from ventilator associated pneumonia. This is not always easy, as endotracheal tube cultures and gram stains only indicate colonization, not necessarily infection. The chest x-ray may not be helpful, as diffuse pulmonary opacities are seen in both conditions. Acute deterioration is more likely to represent infection. Presence of leukocytes on gram stain of ET secretions and changes in peripheral white count support the diagnosis of infection. Recurrent aspiration pneumonia may contribute to or mimic BPD – evidence of gastroesophageal reflux should be sought in infants whose BPD is worsening over time.

Treatment: Treatment is primarily supportive with optimization of ventilator support and aggressive nutritional support. The ventilator settings need to reflect the longer time constants resulting from increased airway resistance. Therefore, inspiratory and expiratory time need to be sufficiently long. Overexpansion and air trapping are often seen in these infants. The common response to this is lowering of the PEEP setting, which is actually counterproductive. Air trapping typically results from airway closure at low lung volume and is made worse at low PEEP. This can be seen on the flow-volume loop with pulmonary function testing. Increasing the PEEP setting until the flow limitation at low lung volume resolves is helpful. Optimal oxygenation targets remain the subject of intense study. Higher targets appear to increase lung injury in the majority of infants. However, lower oxygen tension may over time lead to increased pulmonary vascular resistance and increase the risk of serious pulmonary hypertension. Current practice is to limit oxygen exposure until PMA of about 34–35 weeks by targeting SPO2 of 85–93% and to use somewhat higher targets beyond that period. In infants with documented pulmonary hypertension, SPO2 should be maintained in mid to high 90 s. The role of diuretics remains controversial. There is good evidence of short-term benefit in lung mechanics, but the diuretics often lead to electrolyte imbalance and their impact on ultimate outcome is unproven. Thiazides and spironolactone are most widely used for treatment of BPD. Furosemide is associated with more severe adverse effects, including osteopenia, rib fractures, and renal calculi. Bronchodilators are commonly used without evidence of long-term benefit. The elevated airway resistance in early BPD is not due to bronchoconstriction, therefore unlikely to be affected by bronchodilators. Later on, there may be a place for bronchodilators in selected infants, but lack of tools to measure airway resistance in non-intubated infants hampers rational use of these drugs. Methylxanthines are widely used and probably beneficial, although this may be more related to increased CO2 responsiveness and increased diaphragmatic contractility than bronchodilation.

Postnatal steroids were once used liberally and at high doses lasting up to 6 weeks. This practice was later recognized as increasing the incidence of abnormal neurologic outcome especially when started in the first week of life. Steroids are now used much more. Short courses Dexamethasone at doses of 0.15 mg/kg/d, divided q12 h appear to be effective and is thought to be safer than the much

higher cumulative doses used previously. Inhaled corticosteroids are widely used, but evidence of benefit is scant. No sound evidence exists to guide the treatment of pulmonary hypertension when it develops. The use of iNO has become widespread and it has at least transient benefits in most infants. Transition to an oral agent such as sildenafil, a phosphodiesterase 5 inhibitor appears warranted. Higher oxygen saturation targets and avoidance of hypercapnia are thought to be beneficial.

Prognosis: A small proportion of infants fail to wean from mechanical ventilation and go on to worsening lung disease with progressive pulmonary hypertension and death. Most infants ultimately outgrow the disease and become symptom free by early childhood. However, they remain at increased risk of lower respiratory tract infections, especially with respiratory syncytial virus, require more frequent rehospitalization, and are more likely to develop asthma. These infants may fail to thrive and are at risk of significant post-discharge morbidity and mortality. Careful pulmonary function testing at school age and beyond shows continued subtle abnormalities, but these are generally not functionally limiting. Infants with BPD have worse neurodevelopmental outcome compared to infants of similar gestational age without BPD.

Prevention: Prevention of BPD is the ultimate goal of care, but an elusive one. Antenatal corticosteroids, avoidance of injurious ventilation, use of noninvasive respiratory support, and surfactant administration are all important in limiting lung injury. Recent trials of HFV have failed to show clear benefit over lung-protective conventional ventilation. Vitamin A has been shown to reduce BPD, but requires frequent intramuscular injection. Early and continued treatment with caffeine reduces the risk of BPD by a similar amount and is much less onerous. Avoidance of excessive fluid intake is advisable. It is unclear whether early treatment of PDA reduces the incidence of BPD. Prophylactic use of iNO may be an effective strategy for BPD prevention when initiated at 1–2 weeks of life and administered for several weeks, but despite very strong laboratory evidence of efficacy, the clinical data are conflicting. Prevention of prematurity is the only definitive way of preventing BPD.

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16 Oxygen Therapy

Maximo Vento

Introduction

Aerobic Metabolism

Highly energized electrons liberated in the mitochondrial tri-carboxylic cycle are transported to the electron transport chain, and finally captured by oxygen. In this process known as oxidative phosphorylation, ADP is transformed into ATP and ground molecular di-oxygen is reduced by four electrons, and combining with protons intruded through the ATP synthase pump forms water. Remarkably, aerobic metabolism (i.e., with the concourse of oxygen) is 20 times more efficient than anaerobic metabolism thus providing sufficient energy for cell growth, development, and reproduction (e.g., 1 molecule of glucose forms 34 molecules of ATP through the aerobic pathway and 4 through the anaerobic). Of note is that specific cells such as neurons are unable to accumulate energy and are only able to survive for few minutes under hypoxic conditions rendering oxygen indispensable for central nervous system survival.

Each oxygen molecule has two unpaired electrons in its outer shell that prevent it from forming new chemical bonds. Partial reduction of oxygen with just one electron at a time will lead to the formation of reactive oxygen species (ROS) such as anion superoxide (O_2^-), hydroxyl radical (OH●), and hydrogen peroxide (H_2O_2). Some of these chemicals will be highly reactive species known as free radicals. Free radicals are atomic or molecular species capable of independent existence that contain one or more unpaired electrons in their molecular orbits. They are able, therefore, to oxidize cellular membranes, structural proteins, enzymes, and nucleic acids.

Oxygen Free Radicals

In the presence of nitric oxide, these oxygen free radicals will react forming reactive nitrogen species (RNS) such as peroxynitrite (ONOO–) (*Fig 16.1*). ROS and RNS are potent oxidizing and reducing agents with an extremely short half-life that will damage any nearby cellular structure.

Antioxidant Defenses

Biologic systems using aerobic metabolism have been able to survive the deleterious effects of free radicals because a large number of enzymatic and non-enzymatic antioxidants has evolved. The antioxidant enzymes are represented by the family of superoxide dismutases (SOD) formed by Cu-Zn SOD or soluble SOD1 located in the cytosol, Mn-SOD or SOD2 located in the mitochondria, and extracellular or SOD3. In addition, catalase, glutathione peroxidases, and glucose 6-phosphate dehydrogenase altogether constitute the most relevant enzymatic defense against free radicals. The major non-enzymatic intracellular antioxidant is glutathione (GSH), a ubiquitous tri-peptide formed by γ-glutamine, L-cysteine, and glycine. GSH is able to reduce free radicals by establishing a di-sulfur bond with another GSH molecule forming oxidized glutathione (GS=SG) and thus providing one electron. Oxidized glutathione is reduced again to its reduced form (GSH) by the action of glutathione reductase (GSH-reductase) with the electrons provided by NADPH. Other relevant non-enzymatic antioxidants are proteins that bind transition metals such as transferrin and ceruloplasmin, or molecules that quench free radicals such as uric acid and bilirubin.

Oxidative Stress

This concept refers to the imbalance between the formation of free radicals and the capability of the biologic system to neutralize them. In order to evaluate oxidative stress different biomarkers have been used. They may directly reflect a pro-or-antioxidant status such as GSH/GSSG quotients, one of the most reliable and employed oxidative stress markers. Other biomarkers may reflect direct damage to the cell structures. Hence, for lipid peroxidation, malondialdehyde or *n*-aldehydes (e.g., 4-hydroxy-nonenal) have been widely employed. Nucleic acid damage is generally reflected by guanosine base oxidation products such as 8-oxo-dyhydro-guanosine. Isoprostanes and isofurans have evolved as one of the most reliable markers of oxidative stress and reflect

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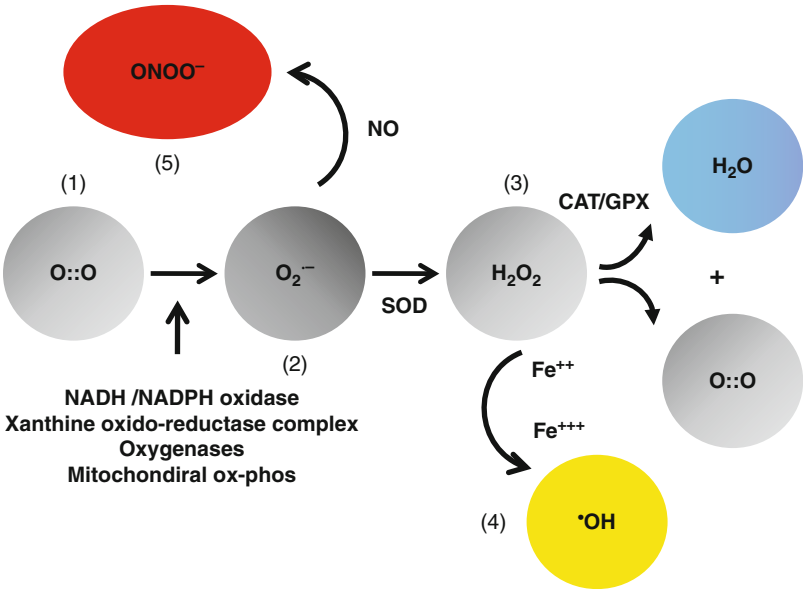

Figure 16.1

Oxygen (1) is partially reduced by the action of a series of enzymatic complexes to anion superoxide (2). Anion superoxide is dismutated by superoxide dismutases (*SOD*) to hydrogen peroxide (3), which in turn is transformed into water and oxygen by the action of catalases (*CAT*) and glutathione peroxidase (*GPX*). In the presence of transition metals (e.g., iron, copper), hydrogen peroxide can be transformed into hydroxyl radical (4). Moreover, in the presence of nitric oxide (*NO*), anion superoxide can also be transformed into peroxynitrite (5)

non-cyclo-oxygenase peroxidation of polyunsaturated fatty acids (PUFA) and intriguingly have important vaso-active properties. Oxidation of proteins can be measured by the action of free radicals on specific amino acids such as phenylalanine. As a consequence of the attack by hydroxyl radicals, phenylalanine is converted into orto-tyrosine (o-tyr). Other markers of protein oxidation are known as carbonyl compounds (C=O), which have been closely correlated when found in the lung alveolar lavage fluid with development of chronic lung disease.

In addition to causing oxidative damage to cell structures, ROS and RNS are capable of triggering inflammatory response in the cells triggering the transformation of I-κB into NF-κB, a transcription factor for multiple inflammation related genes. ROS and RNS are also capable of activating the tumor necrosis factor alpha (TNFα) essential in the inflammatory response as well as in the activation of apoptosis.

Fetal to Neonatal Transition

Fetal life develops in an environment that is relatively hypoxemic as compared to the extra uterine; hence, arterial partial pressure of oxygen (P_aO_2) in utero is of 25–35 mmHg. Immediately after birth, with the initiation of spontaneous respiration and alveolar-capillary gas exchange P_aO_2 rises to 50–70 mmHg in the first 5–10 min of life. This abrupt change causes a physiologic oxidative stress necessary to trigger the expression of a number of significant genes necessary for postnatal adaptation. The first studies of fetal pulse oximetry (SpO_2) during labor revealed that normal values were approximately 58 ± 10%. Studies performed in term newborn infants have shown that SpO_2 does not reach stable values ≥85% until 5 min after birth have elapsed, and some normal newborn infants need even more time especially if they are born by cesarean section. In addition, preterm infants especially extremely low birth weight infants will not reach an SpO_2 of ≥85% at least after 10–15 min after birth.

Arterial Oxygen Saturation Nomogram

In a large prospective observational study a total of 468 newly born infants covering gestational ages from 25 through 42 weeks of gestation and who did not need

resuscitation maneuvers in the delivery room were recruited (Fig. 16.2). SpO_2 using advanced technology with maximum sensitivity was measured in the right wrist thus representing pre-ductal oxygen saturation during the first 10 min after birth. Two graphs have been developed from the data set for babies between 32 and 36, and between 37 and 42 weeks gestation, respectively. It took a median of 7.9 (interquartile range (IQR): 5.0–10.0) min to reach $SpO_2 > 90\%$, and preterm infants needed significantly more time to reach this saturation.

Oxygen Administration in the Delivery Room

In experimental and clinical studies, it has been shown that the use of room air (21% oxygen) offers substantial advantages over the use of 100% oxygen as had been traditionally recommended in the resuscitation of depressed newborn infants. Meta-analysis of the published evidence has concluded that the use of room air significantly reduces mortality in term neonates. Moreover, air-resuscitation also shortens the time needed to initiate spontaneous respiration, improves Apgar score, and

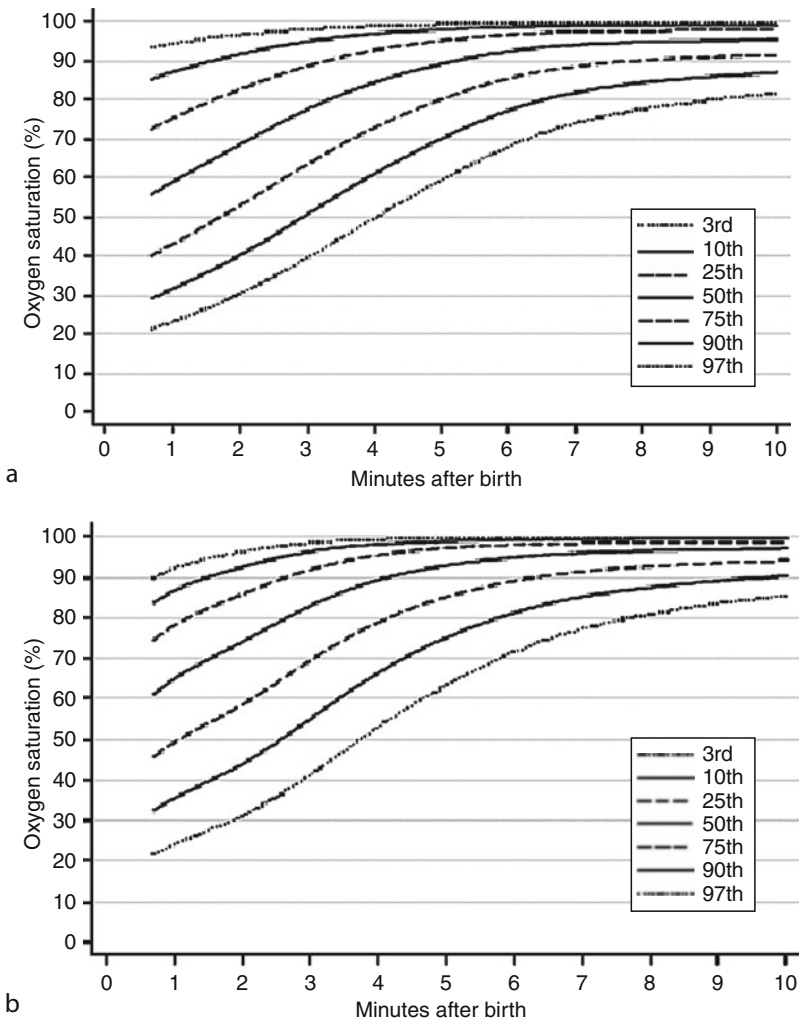

Figure 16.2

Panel a: Third, 10th, 25th, 50th, 75th, 90th, and 97th SpO_2 percentiles for preterm infants at 32–36 weeks of gestation with no medical intervention after birth. Panel b: Third, 10th, 25th, 50th, 75th, 90th, and 97th SpO_2 percentiles for infants at <32 weeks of gestation with no medical intervention at birth (From Dawson JA et al (2010) Pediatrics 125:e1340–e1347. With permission)

reduces oxidative stress and oxidative damage to vital organs such as myocardium and kidneys. As a consequence, 2010 international guidelines recommend the use of air as the initial gas admixture for the depressed neonate. Moreover, both pulse oximetry monitoring of SpO_2 and titration of the inspiratory fraction of oxygen (FIO_2) to avoid hyper-or-hypoxic damage are also encouraged.

Preterm babies do not frequently suffer from birth asphyxia; however, they experience difficulties in adapting to extra uterine due to lung and thoracic cage immaturity. Hence, a significant proportion of preterm infants will need proactive interventions in the delivery room. Positive pressure ventilation is the cornerstone of preterm resuscitation. Initial ventilation is performed in spontaneous breathing neonates with continuous positive pressure ventilation (CPAP) applying 4–8 cmH_2O. Available studies have shown that it is feasible to start resuscitation even in the most preterm infants using an initial FIO_2 of 21–30%. Regardless of whether high or low oxygen concentration was used initially, on average, the infants were on similar FiO_2 of 30–40% within 5–10 min of life with no difference in SPO_2, heart rate, Apgar scores, or acid–base status. While more studies are needed, many clinicians now opt to initiate resuscitation with 30% oxygen in preterm infants in whom normal lung function cannot be assumed. Immediately after birth, pulse oximeter probe should be adjusted to the right wrist. Reliable pre-ductal readings will be obtained in 60–90 s. Once readings are available FIO_2 should be titrated against SpO_2 readings in the pulse oximeter adjusting the air/oxygen blender to keep SpO_2 within saturation nomogram (*Fig. 16.2*). Changes should be performed every 30–60 s allowing infant's response in the form of increase/decrease in SpO_2. Abrupt changes in heart rate or saturation may be a consequence of mask leakage or incorrect endotracheal tube position. End tidal CO_2 detectors are useful in these circumstances. Once the baby is stable and maintains an adequate heart rate and SpO_2, he/she can be transferred to the NICU. Using lower oxygen load in the resuscitation process it has been shown that oxidative stress biomarkers are significantly reduced and there is less need for oxygen supplementation, and less tendency toward developing chronic lung disease.

Oxygen During Neonatal Care in Premature Infants

The conundrum regarding the establishment of upper and lower limits of oxygen saturation especially in extremely low birth weight (ELBW) infants is still open (*Fig. 16.3*). ELBW infants are very sensitive to both hyperoxia, which may lead especially to lung and retinal damage, and to hypoxia, which may cause white matter injury. Studies that have compared different limits for SpO_2 have concluded that neonatal units maintaining ELBW infants within low saturation limits (85–92%) have significantly lower incidence (~50%) of retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) than those units allowing SpO_2 within higher limits (>95%). This has been confirmed in the SUPPORT trial, the only randomized study published to date. Although some concerns have been raised in relation to a small

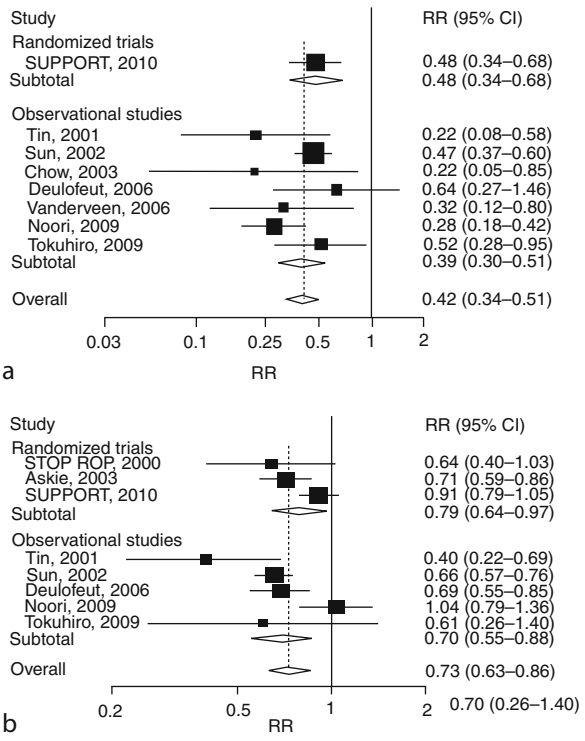

Figure 16.3

Panel a: Relative Risk (*RR*) and 95% Confidence Interval (*CI*) for randomized studies and observational studies as well as overall estimate in eight studies examining the effect on ROP of high versus low SpO_2 in preterm infants. A RR < 1 favors low SpO_2. Panel b: RR and 95% CI for randomized studies and observational studies as well as overall in eight studies examining the effect on BPD and/or lung problems of high versus low SpO_2 in preterm infants. An RR < 1 favors low SpO_2 (From Saugstad OD et al (2011) Neonatology 100:1–8. With permission)

increase in mortality in the low saturation group, there is no conclusive evidence and 85% as lower saturation limit seems to be safe. Several other clinical trials are underway with close monitoring of the mortality rate by their data safety monitoring boards. Until these studies are published, definitive recommendations are difficult. However, majority of NICUs in the USA and Europe appear to have adopted the range of 85–92% in preterm infants, and anecdotal evidence supports the decreased incidence of ROP.

Of note, studies have suggested the establishment of two different periods with different oxygen saturation targets. Preterm infants below 32 weeks postmenstrual age would benefit from lower SpO_2 limits (e.g., 85–95%). In a phase of rapid vascular growth and extreme tissue sensitivity to oxygen due to an immature antioxidant defense system, the use of higher oxygen limits would lead to oxidative stress and inflammation in the lung, intestine, or brain leading to BPD, necrotizing enterocolitis (NEC), or intra-periventricular hemorrhage (IPVH). However, older neonates (>32 weeks postmenstrual age) with a more mature antioxidant system and a tendency toward hyper-proliferation of the vascular bed of the retina due to a relative hypoxia of the retinal tissue might benefit from higher SpO_2 ranges (98–99%). This latter approach is intended for infants with pre-threshold ROP, but its benefit has not been conclusively established. Further, the potential benefit on the retina must be weighed against the apparent adverse effects on the lungs as suggested by the STOP ROP study. Perhaps, in addition to pulse oximeter monitoring levels of growth factors such as insulin-like growth factor (IGF), vascular endothelial growth factors (VEGF) and others should be closely monitored aiming to advert the initiation of ROP 2 phase that would prompt the use of higher oxygen saturation limits to avoid retinal vessel overgrowth.

Oxygen Therapy in the Term Infant

Term infants with meconium aspiration syndrome, pneumonia, or other conditions may have pulmonary hypertension and often also require respiratory support. Traditionally, clinicians were less concerned about hyperoxia in view of their more mature antioxidant defenses and often used high FiO_2 in infants with or at risk for pulmonary hypertension (PPHN). More recently, it has become clear that hyperoxia and exposure to high FiO_2 is not only unnecessary in terms of treating PPHN, but actually increases pulmonary vasoreactivity to hypoxia and decreases response to inhaled nitric oxide. Many infants with meconium aspiration and/or PPHN have a history of perinatal asphyxia and are uniquely vulnerable to oxygen radical injury to the brain. Additionally, prolonged exposure to high FiO_2 will cause lung injury even in term infants. Therefore, the current recommendations are to target normoxia (PaO_2 60–80 s) and avoid PaO_2 over 90 mmHg. The upper limit of SPO_2 should be set no higher than 99%, because when SPO_2 is >99%, the PaO_2 may well be over 100 mmHg.

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17 Noninvasive Respiratory Support

Peter Davis

Neonatal Respiratory Support in the Modern Era

Assisted ventilation of infants was first reported in the modern era in 1953 by Donald and Lord. Initially, this was provided in the form of intermittent positive pressure ventilation via an endotracheal tube. Adult techniques and equipment were adapted with disappointing results. Survival rates did not improve and adverse effects such as air leak appeared more frequent. In response to the high mortality rates, particularly of newly born very low birth weight infants, Gregory developed a technique of continuous positive airway pressure (CPAP).

Initially CPAP was delivered via an endotracheal tube, but soon after, other interfaces were developed to avoid the complications associated with endotracheal intubation. Ahlström used a face chamber to deliver up to 15 cm of water pressure. Using a tight-fitting face mask, Rhodes showed that CPAP enhanced survival compared to conventional therapy with warmed humidified oxygen. Pressure effects from these devices, as well as problems accessing the mouth and nose for suctioning and feeding, led to the development of nasal interfaces.

Noninvasive ventilation grew in popularity because of the perception that it reduced the risks of trauma to the larynx and trachea, infection, and chronic lung disease. The debate over the specific roles of endotracheal intubation and noninvasive methods of support continues, but there is general agreement that the duration of endotracheal intubation, when required, should be as brief as possible.

Problems Associated with Noninvasive Ventilation

Although portrayed as simpler and easier to administer than ventilation via an endotracheal tube, noninvasive ventilation is not without its own difficulties. Nasal prongs rarely fit tightly into the nostrils. Gas can leak around the prongs or from the mouth, leading to a variable reduction of pressure delivered to the pharynx. The nasal septum and alae nasi are frequently damaged by nasal prongs and injuries including inflammation and laceration are reported. Graham described an association between NCPAP and late-onset gram-negative sepsis. Others have described a similar association between nasal trauma and coagulase negative staphyloccal infection. Airleak was found to be more prevalent in the earliest randomized trials of CPAP. An increased rate of pneumothorax was also described in preterm infants managed with CPAP compared with endotracheal intubation and surfactant. The success of noninvasive ventilation depends on the expertise of the nursing staff. Attention to detail, gentleness, and careful monitoring are as important for care of infants on CPAP as they are for those managed with an endotracheal tube.

The Physiology of Continuous Positive Airway Pressure

Surfactant deficiency, muscle hypotonia, delayed clearance of lung fluid, and a compliant chest wall combine to make it difficult for a preterm infant to establish and maintain adequate lung volumes. By assisting expansion of the lungs and preventing lung collapse at the end of expiration, CPAP helps maintain aeration. In addition, CPAP reduces the protein leak associated with atelectasis and reexpansion, thereby conserving surfactant. CPAP also helps splint the upper airway, which is very compliant and prone to collapse. In doing so, it reduces obstruction and apnea.

Types of Interfaces

There are a variety of interfaces for delivering CPAP. Endotracheal tubes are no longer recommended because they have a high resistance and increase the work of breathing. Gregory developed a head chamber with a tight seal and a pressure release valve. Subsequently face chambers and face masks were tried. Problems establishing a good seal without causing damage to the head led to the development of nasal prongs. These had the additional advantage of allowing easier access to the infant's nose and mouth.

There are at least four types of nasal CPAP device. A long nasopharyngeal tube, passed through one nostril

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with its tip lying just above the epiglottis is an inexpensive, readily available interface. However, these tubes have a high resistance and therefore a large reduction in delivered pressure and high work of breathing. A single, short nasal prong fashioned by cutting down an endotracheal tube is simple and easy to use. The problems with this interface are the leak of gas through the other nostril and the high resistance of the tube relative to double nasal prongs. Short bi-nasal prongs provide a low resistance to gas flow and good delivery of pressure to the airway. Double prongs are more effective in managing infants after extubation than single prongs. Nasal masks have been developed in an attempt to reduce the nasal trauma seen with prongs. There is little published information on their effectiveness compared to nasal prongs, and studies addressing the issue of trauma report similar rates of nasal damage, albeit at different sites.

Types of Pressure Generators

Bubbly bottle: Bubble CPAP is a simple, inexpensive technique, whereby pressure is generated by placing the distal limb of the circuit under a known depth of water. Continuous underwater bubbling occurs once sufficient flow is delivered and correct prong position with minimal leak is achieved. Operators are alerted to prong displacement by disappearance of the bubbling. It has been suggested that oscillations produced in the circuit by the bubbling may enhance gas exchange. In a preterm lamb model, Pillow et al. found that bubbling appeared to improve blood gases compared to CPAP delivered from a conventional ventilator. However, a short-term crossover human study comparing fast bubbling with minimal bubbling found no difference in blood gases.

Ventilator: CPAP may be generated using the PEEP valve of a conventional ventilator. This is a reliable way of delivering CPAP, as the pressure generated is independent of flow until the leak at the nose is large. For some, the use of a neonatal ventilator for the simple task of generating CPAP represents an unacceptable cost when alternative methods are available.

Variable flow devices (including Infant Flow Driver): These devices have an integrated nasal interface and pressure generator. Pressure is determined by altering the gas flow through the circuit. The nasal interface delivers a jet of gas into the nose, which responds to the infant's respiratory efforts. Claimed advantages include enhanced stability of pressure and decreased work of breathing. Studies of this technique have produced conflicting results. In a randomized trial, Mazzela reported that infants managed with the Infant Flow Driver (IFD) had better oxygenation and lower respiratory rates than those managed with a single nasopharyngeal prong. This result may be due, at least in part, to the high resistance of the single nasopharyngeal tube as discussed above. In a recent randomized trial, Gupta et al. showed that the underwater bubbling system was at least as effective as the IFD for the post-extubation management of preterm infants. In the subgroup of infants ventilated for less than 14 days, infants randomized to bubble CPAP were more likely to be successfully extubated than those managed on the IFD.

Nasal Intermittent Positive Airway Pressure (NIPPV)

NIPPV is a form of respiratory support characterized by the provision of CPAP augmented by mechanical inflations, and delivered in neonates using nasal prongs. The operator sets a peak inspiratory pressure, an end expiratory pressure, a rate, and an inspiratory time. The technique was used with success in adults and applied to neonates in the 1980s. A survey of neonatal units in the UK in 2006 found that 48% of regional nurseries were using NIPPV. Proposed mechanism of action of NIPPV include induction of Head's paradoxical reflex, increased mean airway pressure, increased alveolar recruitment, pharyngeal dilation, and increased pharyngeal pressure.

NIPPV has been used in a number of clinical settings: post-extubation care, primary therapy for respiratory distress syndrome, and treatment of apnea. Its use in post-extubation care is the most thoroughly evaluated. Meta-analysis of three studies comparing NIPPV with NCPAP showed that infants managed with NIPPV were more likely to be successfully extubated than those receiving NCPAP. There are small studies that suggest NIPPV may have a role in initial management of respiratory distress syndrome, but more evidence is required before NIPPV is used routinely in this patient group. Evidence for the use of NIPPV for apnea is limited, but it is now commonly used in this group of patients when NCPAP fails.

The RCTs evaluating NIPPV in the post-extubation setting all used a ventilator capable of synchronizing ventilator inflations with the infants own breathing efforts. These used an abdominal sensor. Synchronized NIPPV is now less widely available, and many units now use ventilators that do not attempt to provide synchronized inflations. Recently, Moretti et al. have described the use of a promising device for delivering NIPPV which used a flow sensor to trigger ventilator inflations synchronized with the infant's own breaths. It appears that NIPPV has

an important role to play in neonatal respiratory support. More research is required to determine the best devices and settings when using this technique.

High-Flow Subnasal Oxygen (High-Flow Nasal Cannula)

Although proven to be effective, NCPAP and NIPPV have important problems. Infants managed with nasal prongs often appear uncomfortable, and nasal trauma is an ongoing concern. Nasal cannulae have increased in popularity in the past decade as clinicians seek for a system that is easier to use and more comfortable for babies. These cannulae are used in conjunction with humidified high gas flow, and studies have shown that the technique improves lung compliance and reduces work of breathing. The mechanism of action of high-flow subnasal oxygen is unclear. Locke measured oesophageal pressure in infants treated with 2 L/min of flow through 0.3 cm prongs and showed that this device produced a mean-positive end-distending pressure of 9.8 cmH_2O. They and others have warned that delivered pressures are variable and potentially higher than commonly used CPAP levels. Pressures depend not only on the flow through the cannulae but also on the leak from the nose. This may vary considerably depending on nasal secretions. Trials are currently underway testing the safety and efficacy of high-flow nasal cannulae in this patient group. Widespread application should wait until the results of these trials are known.

Indications for Noninvasive Ventilation

Post-extubation care: Infants are intubated and ventilated for respiratory failure due to conditions, including hyaline membrane disease, sepsis, and apnea. By extubating as soon as possible, clinicians seek to avoid the complications associated with an endotracheal tube. Atelectasis, respiratory failure, and apnea are frequent, and re-intubation may be required. Noninvasive ventilation is often used in an attempt to maintain lung volumes and enhance stability. A systematic review comparing CPAP with supplemental oxygen for post-extubation care identified nine randomized trials addressing this question. Infants treated with CPAP had a reduction in the need for increased respiratory support [Relative risk (RR) 0.62 (0.51, 0.76)] with a number needed to treat of six to prevent one extubation failure. This review suggested that if resources were limited, CPAP could be reserved for use in infants who were failing supplemental oxygen. A subgroup analysis of trials in this review according to the CPAP pressure used showed no benefit in trials using <5 cmH_2O and a significant benefit for infants treated with > 5 cmH_2O CPAP.

Respiratory distress syndrome: In the presurfactant era, a series of randomized trials compared noninvasive ventilation in the form of facemask CPAP and negative pressure ventilators with headbox oxygen. Although now largely of historical interest only, meta-analysis of the trials showed continuous distending pressure (CDP) reduced the overall rate of mortality and the rate of the combined outcome of death or need for assisted ventilation [RR 0.52 (0.32, 0.87)]. However, the rate of pneumothorax was increased in infants managed with CDP [RR 2.36 (1.25, 5.54)]. A more recent trial by Buckmaster showed that the use of CPAP reduced the need for transfer of babies with respiratory distress to intensive care units.

CPAP vs *intubation in the Delivery Room*: Standard treatment of very preterm infants over the past three decades has included intubation and ventilation in the delivery room. Similarly, early administration of exogenous surfactant has become routine treatment. A small number of units reported that use of CPAP instead of an endotracheal tube was associated with reduced rates of bronchopulmonary dysplasia without increasing mortality or other morbidities. Morley et al. conducted a RCT comparing early intubation with CPAP from 5 min of life. They found that although there was no difference in the primary outcome, death or the need for supplemental oxygen at 36-week corrected age [odds ratio 0.80 (0.58, 1.12)], babies commenced on CPAP spent fewer days on an endotracheal tube. Pneumothorax rate was however increased in the CPAP group. The authors concluded that CPAP is an effective alternative to endotracheal intubation in the delivery room.

Optimum Settings

The choice of the best CPAP pressure is based more on expert opinion than evidence. Traditionally, a pressure of 5 cmH_2O has been used. Some units use this level for all infants, irrespective of disease severity and claim good results. Others have argued for allowing higher pressures. As noted above, the use of CPAP levels of 5 cmH_2O and above appears to be more effective than pressures of less than 5 cmH_2O for post-extubation care. Elgellab et al. reported that a pressure of 8 cmH_2O was associated with higher end-expiratory lung volumes, greater tidal volumes, and lower respiratory rates. Probyn et al., in an animal model, found that alveolar–arterial gradients fell

with increasing PEEP up to 8 cmH_2O. Importantly, no evidence of cardiovascular compromise was found at higher pressure levels. It seems logical that infants with hyaline membrane disease and non-compliant lungs which are prone to collapse may need higher levels of pressure than infants with normal or mildly effected lungs. Assessment of respiratory distress and oxygen requirement may help clinicians "titrate" the CPAP pressure to match the infant's requirements.

Weaning

Deciding when an infant should have CPAP pressures reduced or CPAP stopped is similarly more an art than a science. Several strategies have been tried. Gradually increasing periods of time spent off CPAP (or cycling) has not been shown to be more effective than stopping CPAP and recommencing if symptoms of apnea or respiratory failure occur. In a randomized trial, weaning pressure rather than increasing time spent off CPAP led to a shorter duration of weaning. Reducing CPAP pressure to 5 cmH_2O and discontinuing when the oxygen requirement falls below 30% appears to be a reasonable strategy with recommencement if oxygen requirements or frequency of apneas increase.

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18 Surfactant Replacement Therapy

Richard Plavka

Surfactant therapy has changed neonatal respiratory care over the past two decades and dramatically improved neonatal outcome. Pulmonary surfactant is a complex mixture of phospholipids and proteins that reduce surface tension at the air–liquid interface of alveoli. The origin of its name is a collocation of the capitals from the compound lexeme "SURFace ACTive AgeNT".

In 1929, Kurt von Neergard suggested the presence of pulmonary surfactant in newborn lungs to be followed almost 25 years later by the contributions of R. Pattle, J. Clements and C. Macklin to our understanding of the physiology of pulmonary surfactant. In 1959, M.E. Avery and J. Mead reported that preterm neonates *dying from hyaline membrane disease* had surfactant deficiency. First successful use of bovine surfactant in preterm newborns with respiratory distress syndrome (RDS) was published by T. Fujiwara in 1980. Since then, a number of randomized trials of different natural and synthetic surfactants clearly demonstrated *reduction in neonatal mortality and air-leak syndrome.*

Composition

The basic composition of human surfactant is shown in Fig. 18.1. Surfactant contains about 85% phospholipids, 5% neutral lipids and 10% proteins. The main phospholipid component is phosphatidyl choline (PC, 70%), further 7% is phosphatidyl glycerol (PG), and 8% other phospholipids like phosphatidyl inositol (PI), phosphatidyl serine (PS), and phosphatidyl ethanolamine (PE). Saturated PC containing two palmitic acids is called *dipalmitoil phosphatidil choline (DPPC).* DPPC is hydrophobic and is oriented to the gas phase; the unsaturated PC is hydrophilic and is in contact with the liquid phase. It is able to generate a monolayer, thereby *lowering surface tension* in the alveolar space. DPPC is a principal surface-active component of surfactant and is responsible for the low surface tension at end-expiration. Surfactant-associated *proteins A, B, C, and D* (SP-A, SP-B, SP-C, and SP-D) are the most important protein components of surfactant. The two hydrophobic surfactant proteins, SP-B and SP-C, are important for the adsorbtion and spreading of surfactant in a monolayer film at the air–liquid interface, therefore responsible for the biophysical properties of the lungs. The hydrophilic SP-A and SP-D play an important role in innate immunity and immunomodualtion of the lungs.

Metabolism, Turnover and Quantity

Surfactant is synthesized in type II pneumocytes, where it is also transported and secreted into the alveolus. The cell pool of potentially active surfactant is collected in lamellar bodies (large aggregates) which are able to release the final active form by exocytosis; this form is called tubular myelin that creates finally a monolayer in the alveoli and effectively lowers surface tension. The inactive and damaged surfactant (small aggregate) can be recycled and reused for new synthesis. This cycle of surfactant metabolism requires adequate maturation and is insufficient in preterm and especially in extremely preterm infants. Defective pulmonary surfactant metabolism results in RDS with its attendant mortality and morbidity.

Surfactant amount in alveoli differs in preterm and term newborns. The preterm newborn has a lesser amount and different composition of surfactant, which leads to inefficient function, such that more surfactant is needed to effectively lower surface tension. The conversion from active to inactive forms is more rapid in preterm infants and the sensitivity to inhibition caused by lung injury is high. Term newborns have about 100 mg/kg and preterm infants only about 10 mg/kg of phospholipid. Physiologically, surfactant is under the ontogenetic maturation process. The less mature the infant, the more common and severe RDS can be anticipated. The acute biophysical effects of surfactant on lung function and gas exchange result in *better functional residual capacity* as well as increase in total lung capacity and are accompanied by improved oxygenation, better compliance and decreased work of breathing.

Balance Between Synthesis and Inactivation

End-expiratory stability resulting from the intraalveolar surfactant monolayer is the result of a balance between

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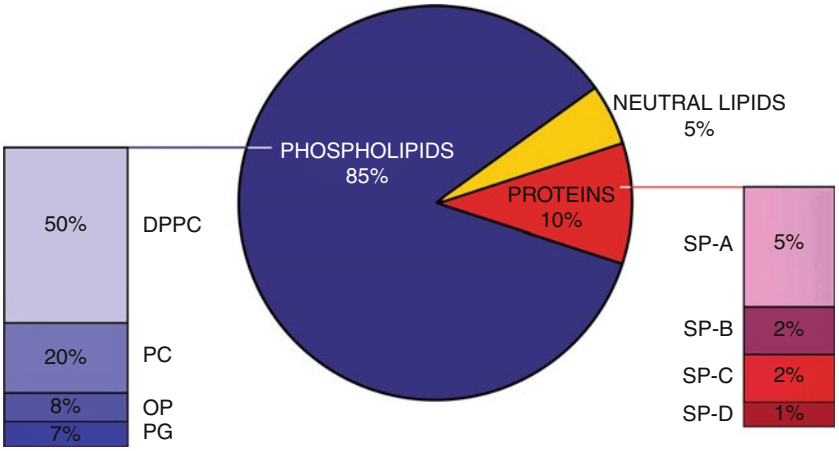

Figure 18.1
The composition of human surfactant legend: DPPC, dipalmitoil phosphatidil choline; PC, phosphatidil choline; OP, other phospholipids; PG, phosphatidil glycerol. SP-A, B, C, D, surfactant proteins A, B, C, D

the synthesis/release and inactivation or inhibition of surfactant. The main promoters of synthesis are antenatal steroids, thyroid hormones, beta adrenergic agents, and estrogens. On the other hand, inhibitors such as proteins, meconium, blood and neutrophils with inflammatory enzymes inactivate surfactant. Ventilatory strategies during mechanical ventilation, which do not minimize alveolar collapse (atelectrauma) and use high volumes (volutrauma) cause protein influx into the alveoli with inactivation of surfactant. If the balance shifts in favor of inactivation and inhibition and the respiratory properties of lungs worsen, exogenous surfactant instillation should be considered by the clinician. It should be kept in mind that factors that inactivate endogenous surfactant also inactivate exogenous surfactant. Therefore, steps must be taken to avoid injurious ventilation strategies, in addition to surfactant replacement therapy (*Fig. 18.2*).

Surfactant Preparations

The available surfactants can be divided into three main groups according to their composition: (1) old synthetic and protein free, (2) natural surfactants (animal derived or human amnionic fluid extract, (3) new synthetic surfactant with protein analogues (*Table 18.1*).

A systematic review of ten randomized trials comparing the effects of old protein-free synthetic and natural surfactants confirmed that treatment with natural surfactants results in a further decrease of air-leaks and mortality and that natural surfactants have a more rapid onset of action. Both old protein-free surfactant preparations have largely disappeared from clinical use, one having been withdrawn completely. In contrast, the new, SP-B mimic containing synthetic surfactant Surfaxin appears to be as safe and effective as the most widely used animal-derived natural surfactant and superior to synthetic, protein-free surfactant. However, as of this writing, it is not yet approved for clinical use. Venticute, the recombinant SP-C-based synthetic surfactant, has not been studied in infants. Studies in ARDS failed to show improved outcome.

Indications for Surfactant Therapy and Recommended Doses

The main indication for surfactant replacement therapy (SRT) with proven long-term benefit is RDS in premature newborns. Administration of surfactant leads to rapid improvement of oxygenation accompanied by an increase of functional residual capacity and lung compliance. Because of this, there is a risk of inadvertent hyperventilation when peak inspiratory pressure is not reduced quickly enough when using pressure limited ventilation, and hyperoxia may result if FiO_2 is not adjusted appropriately. Pulmonary blood flow improves as the ventilation–perfusion mismatch decreases and oxygenation improves. Both prophylactic SRT in preterm infants at high risk for developing RDS and early rescue within 2 h of birth in symptomatic infants decreases mortality and air leaks significantly (*Table 18.2*).

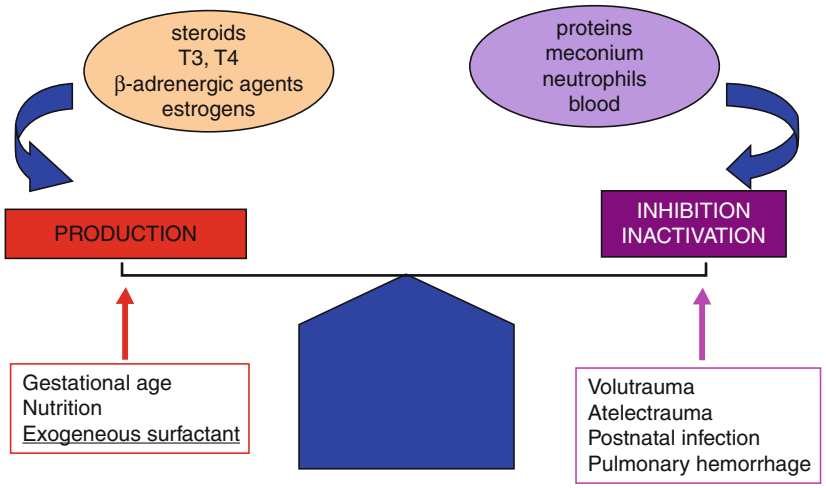

Figure 18.2
The pathological and therapeutic factors influencing the balance between synthesis and inactivation of surfactant

Table 18.1
Surfactant groups and key characteristics of clinically used surfactants

Preparation group	Surfactant	Phospholipid concentration (mg/ml)	Surfactant proteins	dose (ml/kg)
Synthetic, protein free	Exosurf (colfosceril)	13.5	No	5
	Pumactant (ALEC)	40	No	1.2
Natural, animal derived	Survanta (beractant – bovine)[a]	25	SP-B and SP-C (low)	4
	Curosurf (poractant – porcine)[a]	80	SP-B and SP-C	1.25–2.5
	Infasurf (calfactant – bovine)[b]	35	SP-B and SP-C	3
	Alveofact (bovactant – bovine)[b]	40	SP-B and SP-C	1.2
Synthetic protein analogues	Surfaxin (lucinactant)	30	KL4 peptide as SP-B	5.8
	Venticute (lusupultide)	50	rSP–C	1

[a]Minced lung extract
[b]Lung lavage extract; a fourth group is human surfactant derived from amniotic group

Other potential indications and recommended doses for SRT are listed in *Table 18.2*. In these indications, the short-term effect on gas exchange has been dominant, without demonstrated long-term benefits. Despite lack of definitive evidence of long-term benefit, surfactant is widely used in infants with these diagnoses.

Repeated administration of surfactant is generally accepted in clinical practice despite the modest evidence that subsequent doses improve long-term outcomes. Persistent or worsening signs of RDS are the usual criteria for surfactant retreatment. The balance between synthesis and inactivation of surfactant may be shifted in favor of inactivation, even in late preterm or term infants and therefore SRT is indicated when signs of RDS are present. The newer animal-derived surfactants have higher SP-B content and appear to require retreatment less frequently, compared to Survanta. Re-treatment is usually considered if the infant still requires mechanical ventilation with $FiO_2 > 0.30$.

Technique and Method of Surfactant Administration

Initial attempts at surfactant replacement were via aerosol administration, but were unsuccessful. Therefore, surfactant is administered as a liquid instillate, relying on its

Table 18.2
Proven and potential indications for surfactant replacement therapy

Indication	RDS	MAS	ARDS	Pneumonia/BPD	Pulmonary hemorrhage
Short-term effect	Better gas exchange	Better gas exchange	Better gas exchange	Better gas exchange	Better gas exchange
	↑ FRC	↓ ECMO			
	↑ Compliance				
Recommended dose of phospholipid (mg/kg)	100–200	200–400 repeatedly	200	100–200	200–400
Improvement of long-term outcome	↓ Mortality	Unproven	Unproven	Unproven	Unproven
	↓ Air-leak				

RDS, respiratory distress syndrome; *MAS*, meconium aspiration syndrome; *ARDS*, acute respiratory distress syndrome; *ECMO*, extracorporeal membrane oxygenation; ↑, the increase, ↓, the decrease

unique properties to spread relatively uniformly throughout the lungs. There are 250,000 binary airway branch points leading to 500,000 distal airways ending in terminal saccules. There is inevitably some degree of maldistribution, more so if the lungs are atelectatic prior to administration. The maldistribution is to some degree mitigated by the large (sometimes supraphysiologic) dose given. The distribution of instilled is influenced by the physical variables, such as volume and speed of instillation, gravity depending on position of lungs, fluid content in lungs and by surfactant properties like adsorption and spreading. Available data suggest that surfactant should be instilled as rapidly as tolerated, because slow administration results in greater maldistribution.

Timing of Surfactant Administration

Both early rescue treatment (within a few hours after delivery) of RDS or prophylactic use (within minutes) have been shown to decrease mortality, air-leaks and possibly even the incidence of bronchopulmonary dysplasia in preterm infants requiring mechanical ventilation.

There is no clear evidence that prophylactic administration is superior to early rescue treatment in spontaneously breathing very preterm infants on nasal CPAP. The criteria for selection of very preterm infants who might benefit from prophylactic administration have not been established. Surfactant should be administered as soon as practical in extremely premature infants who need to be intubated in the delivery room and artificially ventilated. There is no advantage to administering surfactant before the first breath, therefore resuscitation efforts should never be delayed for the sake of surfactant administration.

Adverse Effects of Surfactant Instillation

Transient hypoxemia and bradycardia are common during surfactant administration and are caused by obstruction of the small airways or the endotracheal tube. Transiently, higher inspiratory pressures may be needed to overcome the added resistance. Transient hypercapnia commonly develops following surfactant administration and may be later followed by hypocapnia as airway obstruction clears and compliance improves. The use of volume-targeted ventilation techniques, such as volume guarantee may be effective in reducing these adverse effects. A transient decrease in blood pressure is described immediately after administration and usually recovers within a few minutes. Decreased cerebral blood flow velocities, oxyhemoglobin concentration and depression of amplitude-integrated encephalographic record are also reported in several papers. The relationship of surfactant treatment and cerebral ischemia or intraventricular hemorrhage has not been confirmed in systematic reviews. Increased incidence of "pulmonary hemorrhage" has been associated with surfactant administration. This entity is actually hemorrhagic pulmonary edema that results from left ventricular volume overload due to rapid fall in pulmonary vascular resistance and increased left to right shunting through the ductus arteriosus.

Practical Issues

Surfactant should be administered rapidly, using the recommended volume/dose with the infant in the supine position or in equal aliquots in the right and left lateral position. Prior to administration, care must be taken to

ensure that the endotracheal tube is not in one of the mainstem bronchi. Different manufacturers have various recommendations regarding positioning of the infant during administration, based on how the drug was delivered during the pivotal trials. These methods were not evidence based; rather, they were consensus decisions of investigators planning the various clinical trials. Nonetheless, deviation from the recommended method of administration could theoretically alter the effectiveness of the drug. In practice, it appears that surfactant spreads remarkably effectively, regardless of the infant's position. The most common method is to administer one half of the dose with the infant in right lateral position and the other half in the left lateral position, but administering the entire dose in the supine position is also quite acceptable. Brief gentle positive pressure ventilation with adequate levels of PEEP and PIP following quick intratracheal instillation may aid distribution and clear the substance from the ETT and the large airways. Administration via a sideport adapter or dual lumen endotracheal tube rather than feeding tube inserted into the endotracheal tube, which requires disconnecting from the ventilator appears to lead to fewer dosing problems. Close continuous monitoring of heart rate, oxygen saturation, and pattern of breathing with extent of chest movement are essential for adjustment of ventilatory parameters appropriately. Hyperoxygenation and volutrauma should be avoided scrupulously as well as hypoxia and atelectasis.

Combination of Nasal CPAP with Surfactant

Widespread use of antenatal steroids, antibiotic treatment of mothers with chorioamnionitis, and less-invasive stabilization and resuscitation approach in the DR with controlled positive pressure, provision of early CPAP, and controlled FiO_2 have improved the clinical status of preterm infants. Majority of even extremely preterm infants 24–28 weeks' gestation can breathe spontaneously and even cry after delivery. Despite lack of definitive evidence from controlled trials, it is generally accepted that reduction of intubation and mechanical ventilation can improve the long-term outcome of these infants.

To reduce the duration of endotracheal intubation and mechanical ventilation, less-invasive techniques have been introduced into clinical practice. Brief intubation to administer surfactant followed by extubation as soon as possible to nasal CPAP called INSURE (INtubation-SURfactant-Extubation) technique is now widely used. Other even less-invasive techniques, such as surfactant administration with a fine thin gastric tube or nebulization in spontaneously breathing infants are under investigation with the goal of avoiding intubation and positive pressure ventilation completely. The author's criteria for surfactant administration to reduce need for intubation and duration of mechanical ventilation are summarized in *Table 18.3*.

Inherited Surfactant Disorders

Life-threatening or lethal surfactant deficiency may result from rare inherited disorders. There are three single-gene lung diseases that exhibit Mendelian inheritance and cause SP-B, SP-C and ABCA3 surfactant protein deficiency. In the early stages, it may be difficult to distinguish genetic causes of surfactant deficiency from transient neonatal surfactant deficiency. Infants with hereditary SP-B deficiency are typically full term and present with classic signs of severe RDS. The respiratory failure is usually severe and they respond to SRT with only a modest, transient

Table 18.3
Criteria for surfactant administration in combination with CPAP in preterm newborns at First Faculty of Medicine, Charles University, Prague

	Selective prophylaxis	Very early rescue treatment	Early rescue treatment
Gestational age (weeks)	24–27		≥28
Level of NCPAP (cm H_2O)	Intubation needed in DR	5–6	6–7
FiO_2		>0.30	>0.40*
Dose (mg/kg)	100–200		100
	INSURE		

* FiO_2 0.3–0.4, when increasing work of breathing is present; º intubation-surfactant administration –extubation; DR, delivery room

improvement followed by return to severe RDS. There is no effective treatment and the disease is ultimately fatal. Lung transplantation has been used for some of these infants, but 5-year survival is only about 30%. Expression of hereditary SP-C deficiency is much more variable and symptoms resemble the picture of interstitial chronic pneumonitis. ABCA3 deficiency is the most recently recognized genetic defect associated with surfactant production. The clinical phenotype resembles that of SP-B deficiency with a fatal outcome within 3 months of life.

Polygenic Surfactant Variations

RDS of prematurity is a complex of disease with multiple factors influencing susceptibility and outcome. A greater degree of prematurity, white ethnicity, male gender, and monozygotic twins are some of the risk factors for more sever RDS. A number of polymorphisms have been identified in the various surfactant genes associated with RDS of prematurity.

Conclusion

Surfactant replacement therapy is an effective intervention in newborn infants with surfactant deficiency or dysfunction. SRT substantially improves survival and decreases complication in infants with RDS. The indications for SRT continue to expand as our understanding of the role of surfactant inhibition in a variety of conditions other than RDS of prematurity increases. The development of effective synthetic surfactants may eventually substantially reduce the current high cost of treatment and expand indications for its use.

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19 Conventional Mechanical Ventilation

Martin Keszler · Colin J. Morley

Introduction

Despite a shift to noninvasive respiratory support, mechanical ventilation remains an essential tool in the care of critically ill neonates. In industrialized countries, respiratory support has improved to the point where few infants now die of acute respiratory failure; early mortality is now predominantly from other complications of extreme prematurity, such as infection and hemorrhage or to congenital anomalies. While improving survival remains a challenge in less developed countries, the focus in industrialized countries has shifted from simply improving survival to reducing the incidence of chronic lung disease and neurodevelopmental sequelae, which remain high in extremely premature survivors. Preterm infants are more vulnerable to respiratory failure because of unfavorable chest wall mechanics and limited muscle mass and endurance. Ventilatory support of preterm infants is made more difficult by their small size, rapid respiratory rates with short inspiratory times, high resistance of small endotracheal tubes (ETT), and variable leak of gas around uncuffed ETT. Immature respiratory control, problems associated with the transitional circulation, and patency of the ductus arteriosus add to the challenges. These are the reasons why "universal" ventilators designed primarily for adult patients do not perform optimally in preterm newborn infants.

Indications for Mechanical Ventilation

Mechanical ventilation should be reserved for infants who are exhibiting signs of respiratory failure or have inadequate spontaneous respiratory effort. There is no weight limit below which premature infants should be automatically intubated and mechanically ventilated. However, the most immature infants are more likely to fail trials of continuous positive airway pressure (CPAP) often because of intractable apnea not responsive to caffeine and require mechanical ventilation. In some NICUs, infants below a certain gestational age (typically 26–27 weeks) are routinely intubated for the purpose of surfactant replacement therapy, followed by some period of ventilation. Mechanical ventilation may also be needed after a surgery or because of congenital anomalies. The diagnosis of respiratory failure in the preterm infant is somewhat subjective. In general, severe respiratory acidosis with pH <7.20 is considered an indication for mechanical ventilation. High work of breathing and excessive oxygen requirement despite optimization of CPAP therapy is generally viewed as an indication for intubation and surfactant administration with some period of mechanical ventilation. The FiO_2 at which this decision is made varies, but there is evidence that earlier intervention at FiO_2 of ≥ 0.40 may be associated with fewer complications. Infants with persistent pulmonary hypertension may benefit from mechanical ventilation even when their pH is otherwise acceptable, because even modest degree of acidosis may contribute to elevated pulmonary vascular resistance.

Synchronized Mechanical Ventilation

The most basic form of mechanical ventilation is intermittent mandatory ventilation (IMV). This is a time-cycled, pressure-limited mode that provides a set number of "mandatory" mechanical breaths. The patient breathes spontaneously between mechanical breaths, using the fresh gas flow in the ventilator circuit that also provides positive end-expiratory pressure (PEEP). With simple IMV, the random respiratory rate of the baby frequently leads to asynchrony between the infant and the ventilator, resulting in high airway pressures, poor oxygenation, and large fluctuations in intracranial pressures. Heavy sedation and muscle paralysis are needed to prevent the baby from "fighting the ventilator," resulting in more dependence on respiratory support, lack of respiratory muscle training, generalized edema, and inability to assess the neurologic status. The advantages of synchronizing the infant's own effort with the ventilator instead of using muscle relaxants are obvious and include better oxygenation and ventilation and easier weaning from ventilatory support (*Table 19.1*). Synchronization can be achieved by a variety of ways, each with its own advantages and disadvantages. The ideal trigger device will have rapid response time, high sensitivity, and be immune from

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autotriggering caused by leak artifact. Table 19.2 lists available trigger systems and their characteristics. Currently, flow triggering is the standard trigger mode; the susceptibility to autotriggering has been overcome by the use of effective leak compensation in some devices. The terminology used to describe various modes of respiratory support can be quite confusing. Device manufacturers often use different terms to describe essentially identical modes. In basic terms, ventilator breaths can be time- or flow-cycled (onset of inspiration and expiration), pressure or volume-limited. Breath initiation can occur at a fixed rate (controlled ventilation) set by user or variable rate determined by the patient (assisted ventilation). The basic modes that are primarily used in newborn infants with their definitions, advantages, and limitations are described in Table 19.3.

Table 19.1
Documented and generally accepted benefits of synchronized mechanical ventilation

Eliminates asynchrony
Avoids muscle paralysis
Decreases need for sedation/analgesia
Reduces airway pressures
Decreases risk of volutrauma
Decreases risk of IVH
Allows respiratory muscle training
Facilitates weaning

Table 19.2
Comparison of triggering methods

Method	Advantages	Disadvantages
Pressure	No added dead space	Poor sensitivity
	Unaffected by leak	Long trigger delay
		High WOB
Airflow	Good sensitivity	Added dead space
	Rapid response	Leak sensitive
Surface capsule	Rapid response	Positioning is critical
	No added dead space	May trigger out of phase
	Unaffected by leak	Not currently available
EADi	Very good sensitivity	Limited availability
	Very rapid response	Expensive probe
	No added dead space	Careful positioning needed
	Unaffected by leak	Invasive

WOB work of breathing, *EADi* electrical activity of the diaphragm

Volume-Controlled Versus Pressure-Limited Ventilation

Pressure-limited ventilation has been the standard mode in newborn respiratory support, because early attempts to use traditional volume-controlled (VC) ventilation showed it to be impractical in small preterm infants. With VC ventilation, volume is the primary control variable with pressure in the system rising passively in inverse proportion to lung compliance and the breath is terminated when the set volume is delivered. VC delivers a set tidal volume (V_T) into the ventilator circuit, but in small infants with uncuffed endotracheal tubes, there is a large and unpredictable loss of V_T to gas compression in the circuit, stretching of the tubing and variable ETT leak. Pressure-limited ventilation remains the primary mode of ventilation in newborns because of its relative simplicity, ability to ventilate effectively despite large ETT leak, improved intrapulmonary gas distribution due to the decelerating gas flow pattern, and the presumed benefit of directly controlling PIP as the primary control variable. The disadvantage is that the V_T is a dependent variable and can change rapidly with changes in lung compliance. The availability of independent flow and volume monitoring makes it possible to manually adjust the set V_T of VC ventilation to target an appropriate exhaled V_T at the airway opening, but this is cumbersome, time consuming, and difficult with variable ETT leak. A more practical alternative is pressure-limited ventilation with volume-targeting, described later in this chapter.

Choice of Synchronized Ventilation Modes

No clear consensus exists regarding the relative merits of assist/control (AC) and synchronized intermittent mandatory ventilation (SIMV), the two most common types of synchronized ventilation. Short-term clinical trials have demonstrated smaller and less variable V_T, less tachypnea, more rapid weaning from mechanical ventilation, and smaller fluctuations in blood pressure with AC, when compared to SIMV. In very premature infants with small

Table 19.3
Available modes of synchronized mechanical ventilation with their key features and limitations

	Key features	Set variables	Advantages	Limitations
SIMV	Time-cycled, pressure-limited mode. Set number of breaths are supported	IMV rate, PIP, PEEP, T_I, FiO_2 rise time/ flow rate	Familiar, simple to understand	High WOB, high deadspace: V_T ratio Larger mechanical V_T
AC	Time-cycled, pressure-limited mode. Every breath is supported	Backup rate, PIP, PEEP, T_I, FiO_2, rise time/flow rate	Lower WOB, faster weaning, smaller V_T, smaller BP fluctuations	Lack of control of RR, autocycling can cause excessive RR
PSV as stand-alone	Flow-cycled, pressure-limited mode. Every breath is supported	Backup rate, PIP, PEEP, T_I limit, FiO_2, rise time/flow rate	Lower WOB, faster weaning, smaller V_T, smaller BP fluctuations, better synchrony	Lack of control of RR, autocycling can cause excessive RR
PSV + SIMV	Flow-cycled, pressure-limited mode. Every breath beyond SIMV rate is supported	As in SIMV plus positive pressure above PEEP	Avoids most problems of SIMV alone, faster weaning	More complex, not available on all ventilators

SIMV synchronized intermittent mandatory ventilation, *AC* assist/control, *PSV* pressure support ventilation

endotracheal tubes, the high airway resistance for unsupported spontaneous breaths results in ineffective rapid shallow breathing, high work of breathing, and exhaustion. Nonetheless, many clinicians still prefer SIMV, especially for weaning from mechanical ventilation based on the flawed assumption that weaning of ventilatory rate is necessary prior to extubation. However, experience with high-frequency ventilation demonstrates that lowering pressure amplitude and leaving the rate unchanged is an effective way of reducing ventilator support to the point of extubation. It has been clearly demonstrated that lung injury is most directly caused by excessive V_T, irrespective of the pressure required to generate that V_T. Because the mechanical breaths of SIMV must compensate for the ineffective spontaneous breaths in small infants, significantly larger tidal volume is needed to maintain adequate alveolar minute ventilation. Thus, it would be reasonable to accept that a larger number of smaller breaths with AC is probably less injurious. Many also believe that supporting every breath results in lack of respiratory muscle training. This concern stems from a failure to recognize that during synchronized ventilation the delivered tidal volume is the result of the combined negative inspiratory pressure of the patient and the positive pressure generated by the ventilator. This combined effort (the baby "pulling" and the ventilator "pushing") results in the transpulmonary pressure, which determines the V_T delivered at a given compliance of the respiratory system. Thus, as ventilator pressure is decreased during weaning, the infant gradually assumes a greater proportion of the work of breathing and in the process achieves training of the respiratory muscles. Ultimately, the ventilator pressure is decreased to the point of merely overcoming the added resistance of the ETT and circuit, at which point the infant is achieving a normal level of work of breathing and is ready for extubation. The limitations of SIMV can be mitigated by provision of pressure support for the spontaneous breath, when this mode is available. Pressure support ventilation (PSV) can also be used as a stand-alone mode (without SIMV), when it is very similar to AC (including a backup apnea rate on the specialty neonatal ventilators), with the difference being that PSV is flow-cycled, rather than time-cycled.

Volume-Targeted Ventilation

Recognition that volume, not pressure, is the critical determinant of ventilator-induced lung injury, along with clear evidence that hypocarbia is associated with neonatal brain and lung injury has made direct control of V_T more desirable. Modifications of time-cycled, pressure-limited ventilation have evolved that are designed to target a target tidal volume by microprocessor-directed adjustments of peak pressure or inspiratory time. Each of the available modes has advantages and disadvantages. The most widely available modes of volume-targeted ventilation (VTV) are briefly described in *Table 19.4*. All forms of volume-targeted ventilation depend on accurate measurement of V_T and are adversely affected by large leak around uncuffed endotracheal tubes. Volume guarantee (VG) is the most extensively studied form of volume-targeted ventilation. It is an option available on the Draeger Babylog 8000-plus and the newer

Table 19.4
Various forms of volume-targeted ventilation (VTV)

	Controls	Adjusts	Based on
PRVC (Servo 300, Servo i)	V_T to circuit	Inspiratory pressure	Exhaled V_T
VAPS (VIP Gold, Avea)	V_T to circuit	Inspiratory time/flow	Inspiratory V_T
VL (Bear Cub 750, Avea)	V_T to circuit	Inspiratory time	Inspiratory V_T
TTV (SLE 5000)	V_T to circuit	Inspiratory time	Inspiratory V_T
VV+ (Puritan Bennett 840)	V_T to circuit	Inspiratory time/flow	Inspiratory V_T
VG (Babylog 8000, VN500)	V_T to patient	Inspiratory pressure	Exhaled V_T

PRVC pressure-regulated volume control, *VAPS* volume-assured pressure support, *VL* volume limit, *TTV* targeted tidal volume (essentially same as VL), *VV* volume ventilation+, *VG* volume guarantee. V_T to circuit = control of V_T is based on volume measurement at the ventilator end of the circuit (affected by circuit compliance), V_T to patient = control of V_T is based on proximal (accurate) V_T measurement. Exhaled V_T = V_T is controlled based on previous breath

VN500 (Dräger, Lübeck, Germany) that may be combined with any of the basic ventilator modes (AC, SIMV, and PSV). The user chooses a target V_T and a pressure limit up to which the inspiratory pressure (the working pressure) may be adjusted. The microprocessor compares the V_T of the previous breath, using exhaled V_T to minimize possible artifact due to airleak, and adjusts the working pressure of the next breath up or down to achieve the target V_T. The PIP increase from breath to breath is limited in order to avoid over-correction leading to excessive V_T. This means that with rapid changes in compliance or patient inspiratory effort, several breaths are needed to reach target V_T. A volume limit function based on inspiratory tidal volume is a secondary safety feature to minimize the risk of excessively large V_T. The microprocessor opens the expiratory valve, terminating inspiration if the delivered V_T exceeds 130% of the previous breath. The servoregulation of inspiratory pressure makes VG a self-weaning mode. Because weaning occurs in real-time, rather than intermittently in response to blood gases, VG has the potential to achieve faster weaning from mechanical ventilation. The documented benefits of volume guarantee are listed in *Table 19.5*.

Table 19.5
Documented benefits of volume guarantee ventilation in comparison to traditional pressure-limited ventilation

Same or lower PIP	Cheema 2001, Abubakar 2001, Herrera 2002
More stable V_T	Cheema 2001, Abubakar 2001, Keszler 2004
Less hypocapnia	Keszler 2004, Dawson 2005, Cheema 2007
Pro-inflammatory cytokines lower @ 5 ml/kg	Lista 2004, 2008
Faster weaning from mechanical ventilation	Lista 2004
Fewer blood gas measurements needed	Nafday 2005

Novel Modes of Respiratory Support

Proportional assist ventilation has been available on the Stephanie ventilator (Stephan GmbH Medizintechnik, Gackenbach Germany) for a number of years. It is a modality that modulates inspiratory pressure in proportion to tidal volume and inspiratory flow, providing elastic and resistive unloading. It is a form of positive feedback delivering support in proportion to patient effort and as such, it assumes mature respiratory control. It therefore may not be suitable for premature infants. The common problem of periodic breathing would be accentuated by the ventilator, with less support being generated with hypopnea and excessively high level of assist provided when the infant becomes agitated. Also, because the system responds to inspiratory flow and volume, a large leak around the ETT would be interpreted as a large inspiration and supported by correspondingly large inspiratory pressure, potentially leading to dangerously large V_T.

Neurally Adjusted Ventilator Assist (NAVA) is an interesting approach that uses the patient's own respiratory control to drive the ventilator. Bipolar electrodes mounted on a nasogastric tube and positioned at the level of the diaphragm sense the diaphragm's electrical activity to trigger and adjust the level of support in proportion to the inspiratory effort. NAVA is still

experimental in newborn infants. As a trigger, the concept is attractive, because it is not affected by leak around endotracheal tubes. However, like PAV, it utilizes a positive feedback scheme and assumes that the respiratory control center is mature, an assumption that is clearly not valid in the preterm infant.

Clinical Application

As discussed above, the choice of SIMV or AC is, to some extent, a matter of personal preference and practice style. In reality, there is little difference between the two in the acute phase of respiratory failure, especially when the infant has little or no respiratory effort of their own. Under these circumstances, simple IMV is provided, regardless of the ventilator mode selection. However, the differences between SIMV and AC/PSV become more pronounced during weaning and are especially important in the smallest infants with narrow endotracheal tubes. Prolonged ventilation with low SIMV rates without pressure support should be avoided in these infants, as it imposes an undesirably high work of breathing.

Standard Synchronized Ventilation Modes

As with all pressure-limited, time-cycled ventilators, the operator must chose inspiratory and end-expiratory pressure (PIP and PEEP), inspiratory time, ventilator rate (either directly or by separately adjusting inspiratory and expiratory time), inspiratory flow rate or rise time, and FiO_2. The initial steps are common to all forms of synchronized ventilation.

Initial Settings

The starting **PIP** is selected based on severity of lung disease and adequacy of chest rise and should then be adjusted to achieve an appropriate V_T, typically 4–7 ml/kg, measured at the airway opening. Contrary to widely held beliefs and numerous published tables, the requirement for PIP is *not* related to the baby's size, but to severity of illness. The misconception arose from the fact that larger babies cope with poorly compliant lungs more effectively because of their greater strength and endurance. Consequently, respiratory failure occurs at lesser degrees of illness severity in the smaller infant. However, even small preemies may have very stiff lungs and may, at times, require fairly high pressures. On the other hand, the term infant with normal lungs who is ventilated for non-respiratory reasons will only need PIP of 12–14 cmH_2O to achieve a normal V_T. Beware of rapid improvement in compliance following surfactant administration or lung volume recruitment! When tidal volume measurement is not available, the clinician must rely on assessment of chest rise, air entry on auscultation, and blood gas determination.

The use of adequate **PEEP** to achieve a well-aerated "open lung," along with avoidance of excessive V_T, is central to the prevention of ventilator-associated lung injury. PEEP should be set in proportion to the oxygen requirement, because, except when extrapulmonary right-to-left shunting is present, hypoxemia is a reflection of ventilation/perfusion imbalance and intrapulmonary right-to-left shunting, a reflection of atelectasis and low lung volume. With few exceptions, high oxygen requirement can be corrected by adequate PIP to open atelectatic alveoli, and sufficient PEEP to maintain lung volume. PEEP of 5 cm H_2O is usually adequate if the FiO_2 is 0.25–0.35, PEEP should be increased to 6 cm H_2O with oxygen requirement between 0.35 and 0.50 and 7–10 cm H_2O if FiO_2 remains >0.60. Selection of the level of PEEP can additionally be guided by lung expansion on chest X-ray.

Selection of **inspiratory time** ($\mathbf{T_i}$) should reflect the infant's time constants, a measure of how rapidly gas can get in and out of the lungs; mathematically the product of resistance and compliance. Small preterm infants with respiratory distress syndrome (low compliance, low resistance) have very short time constants and should be ventilated with Ti of 0.3 s or less. Large infants or those with increased airway resistance (e.g., chronic lung disease, meconium aspiration) have longer time constants and require longer Ti, up to 0.5 s, occasionally more. Prolonged Ti as a means of improving oxygenation is now rarely used, because it is associated with greater risk of airleak.

Ventilator rate should reflect the severity of illness and the infant spontaneous respiratory effort. Infants with severe lung disease and little or no respiratory effort need a fairly rapid rate of 50–60 breaths/min. Spontaneously breathing infants with less severe disease can be supported with rate of around 40 breaths/min, allowing them to trigger the ventilator. It is important to keep in mind the need to allow sufficient expiratory time to avoid air-trapping due to incomplete exhalation. Therefore, rates >60/min in larger infants or those with increased airway resistance and >80 in small preemies should be avoided. Adequacy of inspiratory and expiratory time can be verified by observing the flow waveform and making sure that flow returns to zero (baseline) before each expiration and inspiration begins.

Some ventilators have continuous flow through the circuit that remains constant throughout the breath cycle; others have demand flow that provides additional gas flow over a low baseline available for spontaneous breathing. Continuous flow devices need the user to choose **inspiratory flow rate** (usually 4–10 l/min, depending on patient size). Demand flow devices require the user to select a **"rise time"** which is a reflection of how rapidly the circuit is pressurized. Currently, there is little evidence available to guide the setting of optimal rise time, but most clinicians elect to use 50–75% rise time.

Subsequent Adjustments

When the infant begins to generate spontaneous respiratory effort, ventilator rate should be lowered to just below the normal breathing rate, to allow the infant to take over some of the work of breathing; an excessively rapid rate will override the infant's own effort and defeat the purpose of synchronized ventilation, i.e., the infant and the ventilator working together. Similarly, low $PaCO_2$ will suppress the infant's respiratory drive and is equally undesirable.

It is important to understand clearly how different ventilator variables affect gas exchange and how they interact with the underlying pathophysiology. ***Oxygenation*** is controlled by adjustments in FiO_2 and mean airway pressure, as discussed above. The goal should be to optimize lung volume and ventilation/perfusion matching and lower FiO_2 to <0.35 ("open the lung and keep it open"). PEEP is the most important determinant of mean airway pressure (Paw) with PIP, inspiratory time and rise time (how quickly plateau pressure is reached) being the other factors. ***Ventilation*** (CO_2 elimination) is controlled by adjusting ventilatory rate and V_T. In standard pressure-limited ventilation, V_T, is determined by lung compliance and the ΔP or pressure amplitude (difference between PIP and PEEP). Thus, increasing PIP will improve ventilation as well as oxygenation, through its effect on V_T and Paw. Increasing PEEP and/or lowering PIP will decrease V_T, if all other factors remain equal. However, if the increased PEEP results in recruitment (normalization) of lung volume, this will lead to better lung compliance and may actually improve ventilation, sometimes quite dramatically and lead to inadvertent hyperventilation (this can be avoided by the use of volume-targeted ventilation). Excessively high PEEP will cause overexpansion of the lungs with resultant hemodynamic compromise and incomplete exhalation (lower V_T), resulting in hypercapnia. Lowering PEEP in such situations will improve ventilation. It is important to recognize that as the patient's lung disease evolves major changes in compliance and resistance will occur. Therefore, the appropriateness of all settings needs to be reevaluated frequently. For example, PEEP of 6 or 7 cm H_2O, which would be quite appropriate early in the course of RDS when the lungs are stiff will become excessive as compliance and lung volume improve. Oxygen requirement is the best bedside tool to assess adequacy of lung volume. If FiO_2 is <0.25, PEEP should be no higher than 4–5 cm H_2O.

Weaning

With SIMV, weaning is accomplished by reducing PIP as well as ventilator rate. In general, rate should not be reduced substantially until PIP is down to relatively low values ($<$16–20 cm H_2O) that signify improved lung compliance. Weaning the rate while the lungs are still quite stiff would impose a high work of breathing and may require excessively large V_T for the machine breaths to compensate for ineffective spontaneous breaths that may do little more than rebreathe the anatomical dead space. The rate should not be reduced to $<$10 breaths/min, especially in small infants, because of the high work of breathing associated with small ETT. As a rule, infants who are able to generate adequate V_T and gas exchange with PIP of 15–18 cm H_2O and rate of 10 breaths/min are ready for extubation. Tachypnea and retractions suggest that the infant is not tolerating the weaning and needs a higher level of support.

With AC and PSV, the infant controls the ventilator rate, therefore there is little impact of lowering the set rate, which only acts as backup in case of apnea. Weaning is accomplished by lowering the PIP, thereby decreasing the amount of support for each breath and transferring gradually the work of breathing to the infant. The infant should be extubated when PIP is reduced to 10–14 cm H_2O in small preemies and 15–20 cm H_2O in larger infants and there is a sustained spontaneous effort without excessive work of breathing. In very premature infants, the backup rate should be reduced to 15–20 breaths/min for a few hours prior to extubation to uncover inconsistent respiratory effort/periodic breathing that may be masked by a higher backup rate.

Volume-Targeted Ventilation

VTV is best implemented soon after initiation of mechanical ventilation, as this is the time when most rapid changes in lung mechanics are likely to occur. Success

with volume-targeted ventilation (VTV) depends on the appropriate choice of target V_T. Exhaled V_T of 4–5 ml/kg during the acute phase of the illness in term and preterm infants with homogeneous lung disease is appropriate. Infants with heterogeneous lung disease and/or lung overinflation have increased physiologic dead space and need larger V_T (as much as 6–8 ml/kg). When changing from simple pressure-limited mode, the easiest approach is to start with a V_T similar to what was generated on the pressure-limited mode, assuming the $PaCO_2$ was normal. Appropriate pressure limit should be selected to minimize the potential for excessive V_T delivery. The unique characteristics of each VTV mode must be considered when selecting specific settings. The site of V_T measurement is critical – accurate measurement can only be obtained by a flow sensor at the airway opening. The "open lung concept" is central to optimizing the impact of volume-targeted ventilation: Its benefits cannot be realized without ensuring that this tidal volume is distributed evenly throughout the optimally aerated lungs. With improving lung compliance and patient respiratory effort, the ventilator pressure will come down with volume guarantee, referred to as self-weaning. However, with the volume limit type of VTV, the effective inspiratory time is what is reduced if the set PIP is kept unchanged, resulting in an abnormally short Ti with the airways being exposed to high PIP. Therefore, with volume limit modes, the PIP needs to be lowered manually to generate a V_T close to the target volume. Regardless of VTV mode, the target V_T should not be lowered below a normal physiologic value of about 4 ml/kg – doing so would only impose an excessive workload on the infant and impair weaning.

Conclusion

Avoidance of mechanical ventilation by means of early CPAP with or without surfactant administration may be the most effective way to reduce the risk of chronic lung disease, but the smallest and sickest infants continue to require mechanical ventilation. A host of new modalities and techniques have been made available for the treatment of respiratory failure. The understanding of how to optimally use these devices, while improving constantly, remains somewhat behind the pace of technological innovation. Each ventilator functions differently and it is critical that the user becomes familiar with the specific features of their device. The reader is referred to user manuals of their respective devices for further guidance. A ventilator is only a tool in the hands of the clinician; a tool that can be used well, or not.

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20 Mechanical Ventilation: HFV

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Basic Principles

Like with any other mode of mechanical ventilation, the basic goal of high-frequency ventilation (HFV) is to deliver oxygen to and clear carbon dioxide from the blood, while minimizing ventilator-induced lung injury (VILI) as much as possible. In order to achieve this goal, a constant pressure, often referred to as mean airway pressure or continuous distending pressure (CDP), is applied to the lungs. This CDP stabilizes airways and alveoli/saccules. Superimposed on this CDP are small pressure swings, usually at a frequency of 6–15 Hz or 240–900 cycles/min, resulting in small volume changes of approximately 1–3 ml/kg. Despite the fact that these volume changes are sometimes smaller than the anatomical dead space, HFV is very efficient in clearing carbon dioxide from the lungs. Some of the mechanisms responsible for adequate gas exchange during HFV are coaxial flow, asymmetric velocity profiles, the pendelluft effect and molecular diffusion.

High-Frequency Modalities

There are three types of HFV available for clinical use. Although similar in the basic principles of ventilation, each HFV modality has its own unique characteristics. During *high-frequency oscillatory ventilation (HFOV)*, gas within the airways is moved in and out (oscillated) by an in-line piston or diaphragm (so-called piston oscillators) or an intermittent expiratory venturi jet (non-piston oscillators). The key feature of HFOV is that at 1:1 inspiratory: expiratory ratio, the negative pressure deflection is equal to the positive deflection, therefore both the inspiration and expiration phases are active. Examples of piston oscillators are the Sensormedics 3100A & 3100B, the Humming V, the Flowline Dragonfly, the Leoni plus, and the Stephan SHF 3000. Contemporary non-piston oscillators include the SLE 5000, the Drager Babylog 8000+, and the Babylog VN 500.

High-frequency jet ventilation (HFJV) delivers short pulses of pressurized gas directly into the upper airway via a special endotracheal tube containing a HFJV injector port. In contrast to HFOV, exhalation is passive, resulting in somewhat lower optimal operating frequencies. The mean airway pressure is primarily generated by applying positive end-expiratory pressure via a conventional ventilator used in tandem, sometimes combined with very low-rate conventional mechanical ventilation to provide periodic sigh as a means of lung volume recruitment.

High-frequency flow interruption (HFFI), also known as *high-frequency percussive ventilation,* is usually delivered by hybrid ventilators, also capable of delivering conventional mechanical ventilation. These devices generate short bursts of gas delivered directly into the ventilatory circuit without the narrow injector cannula used in HFJV. For many years, the Infant Star 950 ventilator was widely used in the USA, Europe, and elsewhere. It is no longer manufactured, but remains in use in many parts of the world. In this device, a venturi system on the exhalation valve assists the return of pressures to expiratory baseline and results in a modest negative deflection, facilitating expiration. However, the negative deflection is much smaller than the positive deflection leading to air trapping and increased risk of air leak. The Bronchotron, a pneumatically powered high-frequency flow interrupter developed in the 1980s, is gaining popularity as a neonatal transport ventilator because of its light weight, low gas consumption, and ability to function as both conventional and high-frequency ventilator. The Volumetric Diffusive Respirator – VDR 4 – is a time-cycled, pressure-limited, pneumatically driven high-frequency flow interrupter device similar to the Bronchotron, but more complex and designed for hospital use.

Animal studies have shown that mechanical ventilation can lead to VILI and identified alveolar overdistension (volutrauma) and collapse (atelectrauma) as important risk factors. As previously mentioned, by design, HFV uses very small tidal volumes, which can potentially reduce VILI (less volutrauma) during mechanical ventilation. Animal studies comparing HFV to conventional mechanical ventilation have indeed shown that HFV attenuates lung injury but only when combined with an optimal lung volume or open-lung ventilation strategy (less atelectrauma).

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High-Frequency Ventilation: The Open Lung Strategy

The primary goal of the open-lung strategy is to avoid both alveolar overdistension and collapse. To achieve the latter, collapsed alveoli need to be actively recruited and thereafter stabilized with sufficient airway pressure (CDP). *Figure 20.1* shows the pressure-volume (P/V) relationship of a single alveolus. After a critical opening pressure is reached, the collapsed alveolus pops open, immediately resulting in a large volume increase. As follows by the law of LaPlace, which states that the pressure (P) necessary to keep a spherical structure opened is two times the surface tension (γ) divided by the radius (r), the critical closing pressure of the alveolus will be lower than the opening pressure (increased radius). The P/V curve of the entire lung reflects the cumulative volume changes of all alveoli during incremental (inflation limb) and decremental (deflation limb) airway pressure steps (*Fig. 20.2*). Comparable to the behavior of a single alveolus, the lung volume gained during incremental pressure steps can be maintained at a lower airway pressures, a phenomenon called *lung hysteresis*. Placing HFV on the deflation limb of the P/V curve will optimize lung volume and compliance at the lowest possible airway pressure.

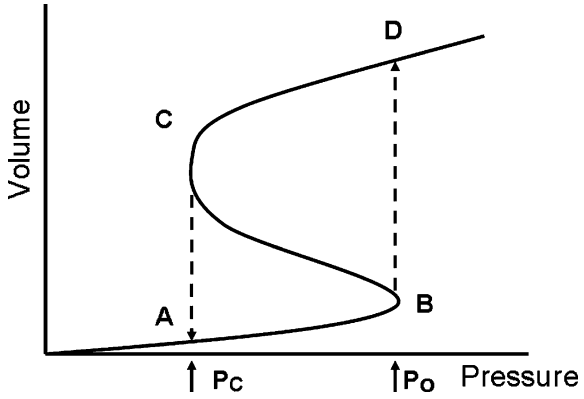

Figure 20.1
Schematic drawing of the pressure-volume relationship of a single alveolus during inspiration and expiration (solid line). At the start of the inspiration, (A) the alveolus is collapsed. At point B, the pressure increase has reached the critical opening pressure (Po), leading to an immediate volume increase (dashed line) as the alveolus is recruited (D). As the pressure is slowly decreased, there is little volume loss until the critical closing pressure (Pc) is reached at point C. The alveolus immediately collapses to point A. Note that Pc is lower than Po due to the law of LaPlace

Although the importance of an open lung strategy during HFV is well recognized, there is currently no validated, easy to use, bedside tool to measure changes in lung volume in newborn infants. Most clinicians have therefore adopted oxygenation as an indirect tool to measure changes in lung volume. Increases in airway pressure that result in alveolar recruitment will reduce intrapulmonary shunt and improve oxygenation. In theory, optimal recruitment will reduce intrapulmonary shunt to <10%, allowing for adequate oxygenation without supplemental oxygen. However, most clinicians use a target fraction of inspired oxygen (FiO_2) ≤ 0.30 to define optimal recruitment. *Figure 20.3* shows a schematic overview of the recruitment procedure. First, the CDP is stepwise increased over time until oxygenation no longer improves or the $FiO_2 \leq 0.30$, whichever comes first (opening pressure). Next, the CDP is stepwise reduced until oxygenation deteriorates (closing pressure). Finally, the CDP is briefly increased to the opening pressure in order to recruit the collapsed alveoli and is then set 2 cmH_2O above the closing pressure (optimal pressure). A recent study in preterm infants with respiratory distress syndrome (RDS) showed that this approach resulted in an optimal recruitment ($FiO_2 \leq 0.30$) in 96% of the included infants. The association between lung volume and oxygenation can be compromised by extrapulmonary right-to-left shunting (congenital heart defect, persistent pulmonary hypertension) and reduced pulmonary diffusion capacity (pneumonia, aspiration syndromes).

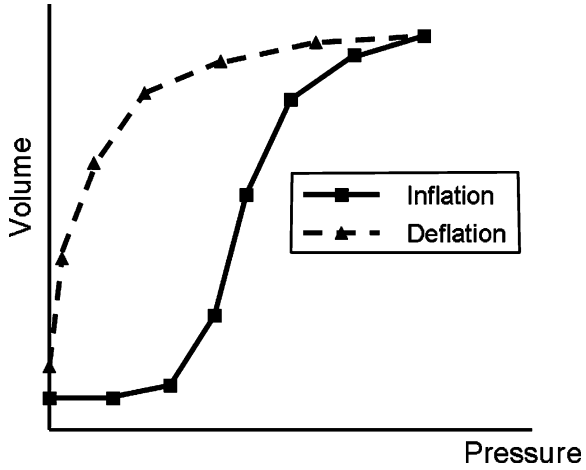

Figure 20.2
Pressure–volume relationship of the lung showing the inflation (solid line) and the deflation limb (dashed line). Note the clear difference in lung volume between both limbs at identical pressures (*hysteresis*)

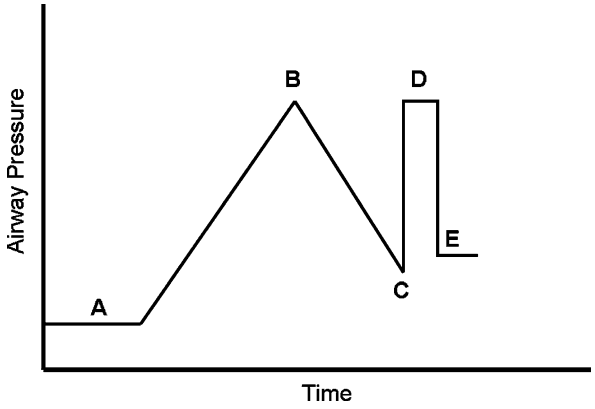

Figure 20.3

Schematic presentation using oxygenation to optimize lung volume in preterm infants with RDS. At the start, (A) airway pressures is low and FiO_2 is high, indicating a high degree of atelectasis and intrapulmonary shunt. Over time, airway pressures are stepwise increased, resulting in alveolar recruitment, a reduction in intrapulmonary shunt, and an improvement in oxygenation. The latter will allow a stepwise reduction in FiO_2, thus preventing hyperoxia. Airway pressures are increased until FiO_2 is below 30% or oxygenation no longer improves (B). The pressure level at point B is called the opening pressure. Airway pressures are stepwise reduced until FiO_2 starts to increase, indicating alveolar derecruitment (C). This pressure level is called the closing pressure. After reopening collapsed alveoli (D), airway pressure is set to 2 cmH_2O above closing pressure to ensure a stabilization of lung volume (E)

Based on the encouraging results from experimental reports, showing less VILI compared to conventional mechanical ventilation, HFV was also investigated in newborn infants. Most of these studies were conducted in preterm infants with RDS, and only a few studies explored the use of HFV in other causes of neonatal respiratory failure.

HFV in RDS

Starting in 1989, to date, 17 randomized controlled trials have compared HFV to conventional positive pressure ventilation as a primary treatment in preterm infants with RDS. Most of these trials used mortality and/or bronchopulmonary dysplasia (BPD) as the primary outcome parameters. Meta-analysis of the trial results showed, at most, a modest but inconsistent reduction in the incidence of BPD in favor of HFV. Some of the suggested reasons for this disappointing effect of HFV on the incidence of BPD are changes over time of the conventional ventilation strategy (more lung protective), and the fact that in the majority of trials that intended to apply an open-lung strategy during HFV were probably not successful. Primary HFV may be beneficial in a subgroup of preterm infants with RDS but only when combined with an open-lung strategy. HFV is used most often in infants with RDS as an early rescue rather than as a primary modality. Infants are transitioned to HFV if they are showing early signs of air leak, or if they are judged to be at high risk of complications, because they are requiring relatively high inspiratory pressure to achieve adequate gas exchange. Most clinicians experienced in the use of HFV will begin HFV if infants with birth weight $<$1,000 g are requiring PIP of 25 cmH_2O and slightly higher in larger infants. The greatest benefit of HFV may be the relative ease with which lung volume recruitment can be achieved. Animal studies have suggested that the same benefits as with HFV can be achieved when conventional ventilation is used with the open lung strategy.

HFV in Other Causes of Respiratory Failure

Animal studies have shown that when combined with an open-lung strategy, HFV improves gas exchange and attenuated VILI compared to conventional mechanical ventilation in a model of *meconium aspiration syndrome* (MAS). Two randomized controlled trials in infants with MAS suggested that both HFOV and HFJV improve gas exchange, compared to conventional ventilation, and may reduce the need for more invasive therapies. However, there were no differences in mortality and long-term morbidity. Because of the longer time constants in term infants in general and those with airway obstruction due to MAS in particular, lower frequencies should be used with both HFJV and HFOV. Similar results were also reported for other aspiration syndromes and in *pneumonia*.

HFV has also been investigated in infants with *air leak syndrome (ALS)*. One cohort study reported a successful resolution of the ALS during HFOV. A larger, prospective randomized trial showed higher success rate and faster resolution of *pulmonary interstitial emphysema* with HFJV. When crossover was taken into account, HFJV improved survival. No long-term effects were reported. It appears that HFJV is uniquely suited for the treatment of air leak because of its extremely short inspiratory time and the nature of the compact streaming of gas down the center of the larger airways. HFJV has been shown also to be effective in the treatment of *bronchopleural* and *tracheoesophageal fistulae.*

The use of HFV in patients with *congenital diaphragmatic hernia* (CDH) and *lung hypoplasia* have mainly been reported in case reports and series. Compared to historical controls, most of these reports showed an improved survival after adopting HFV in the management of CDH/lung hypoplasia. To date, no randomized controlled trials have explored effect of HFV on long-term outcome parameters.

In summary, HFV can potentially improve gas exchange and mortality in other causes of neonatal respiratory failure, but the randomized evidence on these outcomes is limited and the effect on long-term morbidity needs to be established.

Recommended initial settings and subsequent adjustments are briefly outlined in ❯ *Table 20.1*.

High-Frequency Ventilation: Complications

HFV has been associated with several adverse effects. Some of the earlier trials on HFV reported an increased risk for severe intraventricular hemorrhage and

Table 20.1
Suggested initial settings and subsequent adjustments for HFOV and HFJV in infants with various diagnoses

Diagnosis	HFOV	HFJV
RDS		
Initial settings	Freq 10–15 Hz, MAP 8–10 cmH_2O (or 2 cmH_2O > than on CV), power/amplitude sufficient to cause adequate chest vibration. 1:2 I:E ratio, if available.	Rate 400–450, PIP sufficient to cause adequate chest movement (or same as on CV), PEEP 6–8 cmH_2O. Ti 0.02 s.
Subsequent adjustment	Increase Paw in increments of 1–2 cmH_2O if FiO_2 > 0.30. Once oxygenation improves, decrease Paw to find point just above critical closing pressure. Adjust amplitude in response to $PaCO_2$, changes in chest vibration. Adjust Paw in response to SPO_2, PaO_2.	Increase PEEP in increments of 1–2 cmH_2O if FiO_2 > 0.30. Once oxygenation improves, decrease PEEP to find point just above critical closing pressure. Adjust PIP in response to $PaCO_2$, changes in chest vibration. Adjust PEEP in response to SPO_2, PaO_2.
Air leak		
Initial settings	Freq 10–12 Hz, MAP 8–10 cmH_2O (or 2 cmH_2O > than on CV), power/amplitude sufficient to cause just adequate chest vibration. Accept moderate hypercapnia, higher FiO_2, avoid aggressive recruitment.	HFJV is preferred, if available. Rate 380–420, PIP sufficient to cause just adequate chest movement (or 2 cm <CV), PEEP 6–7 cmH_2O. Accept moderate hypercapnia, higher FiO_2, but avoid atelectasis by using enough PEEP.
Subsequent adjustment	Adjust amplitude in response to $PaCO_2$, changes in chest vibration. Adjust Paw in response to SPO_2, PaO_2.	Adjust PIP in response to $PaCO_2$, changes in chest vibration. Adjust PEEP in response to SPO_2, PaO_2.
MAS		
Initial settings	Freq 6–8 Hz, MAP 10–14 cmH_2O (or 2 cmH_2O > than on CV), power/amplitude sufficient to cause adequate chest vibration. Accept mild hypercapnia, higher FiO_2.	Rate 280–360, PIP sufficient to cause adequate chest movement (or same as CV), PEEP 7–10 cmH_2O. Accept mild hypercapnia, higher FiO_2. Avoid atelectasis and air trapping by using enough PEEP.
Subsequent adjustment	Adjust amplitude in response to $PaCO_2$, changes in chest vibration. Adjust Paw in response to SPO_2, PaO_2. If PPHN is present, iNO may be indicated.	Adjust PIP in response to $PaCO_2$, changes in chest vibration. Adjust PEEP in response to SPO_2, PaO_2. If PPHN is present, iNO may be indicated.
CDH		
Initial settings	Freq 10–12 Hz, MAP 8–10 cmH_2O (or 1 cmH_2O > than on CV), power/amplitude sufficient to cause just adequate chest vibration. Accept mild hypercapnia, higher FiO_2, avoid aggressive recruitment.	Rate 360–420, PIP sufficient to cause adequate chest movement (or same as CV), PEEP 6–8 cmH_2O. Accept mild hypercapnia, higher FiO_2.
Subsequent adjustment	Adjust amplitude in response to $PaCO_2$, changes in chest vibration. Adjust Paw in response to SPO_2, PaO_2. Avoid lung overexpansion.	Adjust PIP in response to $PaCO_2$, changes in chest vibration. Adjust PEEP in response to SPO_2, PaO_2. Avoid lung overexpansion.

periventricular leucomalacia. It has been suggested that these adverse effects were caused by the use of a low volume HFV strategy and/or these trials were not successful in avoiding hypocapnia. More recent studies in extremely preterm infants did not report an increased risk of the aforementioned adverse effects. Studies with the Infant Star HFFI in aggregate showed increased incidence of air leak. There have been concerns that the relatively high airway pressures applied during open-lung HFV can compromise the hemodynamic status. However, two recent cohort studies showed that open-lung HFV when applied correctly did not compromise heart, blood pressure, and systemic blood flows. It must be understood that once lung-volume recruitment is achieved, the lungs become more compliant, and mean airway pressure must be reduced to a point just above the critical closing pressure in order to avoid hemodynamic compromise. Finally, several early animal studies reported increased inflammation of the tracheal and bronchial mucosa (necrotizing tracheobronchitis) after HFV, which can cause airway and endotracheal tube obstruction. However, this problem is not unique to HFV and appears to have been caused by high airway pressure with systemic hypotension with HFOV and inadequate humidification of inspired gases with early prototype HFJV devices. The clinical relevance of these studies today appears limited.

Conclusion

High-frequency ventilation is a valuable, often life-saving treatment modality in infants who are not responding well to conventional ventilation. Its role as a primary treatment modality in infants with uncomplicated RDS remains controversial, although it is used with considerable success in select NICUs. The benefits of HFV as a primary mode have become more difficult to demonstrate more recently as the nature and severity of RDS have evolved due to greater use of antenatal steroids, effective, rapidly acting surfactants and more sophisticated, gentler, conventional ventilation modes have become available. Knowledge of the unique characteristics of each HFV (or conventional) device is critical to optimal use. Careful attention to accurate assessment of the underlying disease process and tailoring the ventilation strategy to address the predominant pathophysiology are vital to achieving the best results. The recognition of the importance of the open-lung approach is probably the single most important development in mechanical ventilation.

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21 Complications of Mechanical Ventilation

Kabir M. Abubakar

Even though mechanical ventilation provides lifesaving support for infants with respiratory failure, it can be associated with a variety of complications. Adverse effects associated with mechanical ventilation range from events related to endotracheal intubation, airway and tracheal injury, air-leak syndromes, volutrauma/bronchopulmonary dysplasia, hemodynamic compromise, and neurologic injury.

Complications of Endotracheal Intubation

The process of introducing a laryngoscope to visualize the larynx and vocal cords and insertion of the endotracheal tube (ETT) produces significant stress to the infant, very often leading to periods of bradycardia and oxygen desaturation. Premedication with several pharmacologic agents either alone or in combination including atropine, fentanyl, muscle relaxants, benzodiazepines, and other agents has been shown to facilitate the procedure (fewer attempts and shorter times), reducing potentially harmful physiological fluctuations and pain. Tracheal injury can lead to tracheal perforation, which is associated with significant mortality. Subglottic stenosis, although now rare (1–2%), can occur in intubated neonates (sometimes in association with subglottic cysts) primarily as a result of friction injury from the endotracheal tube. Palatal deformities can develop with resultant grooves and a high-arched palate that can lead to significant feeding and speech problems. The presence of the ETT is an important portal for infection leading to ventilator-associated pneumonia (VAP). The frequency of VAP is directly related to duration of mechanical ventilation and can be minimized by prompt extubation as soon as possible.

Mechanical complications associated with endotracheal intubation can be minimized by a skillful technique, premedication for elective intubation, use of appropriate size endotracheal tubes, and avoidance of intubation by using less invasive modes of respiratory support where possible.

Air-Leak Syndromes

Pulmonary air-leak syndromes are a cause of significant mortality and morbidity in ventilated neonates, particularly extremely low birth weight infants. Air-leak syndromes can present as *pneumothorax* (Fig. 21.1), *pneumomediastinum*, or *pulmonary interstitial emphysema* (PIE). Occasionally they may present as a *pneumopericardium* and *subcutaneous emphysema.*

Air-leak complications generally occur in infants with significant lung disease undergoing mechanical ventilation, but can occur spontaneously or in infants receiving continuous positive airway pressure (CPAP). In general, their incidence parallels the severity of lung disease, but inappropriate ventilator settings can cause air leak even in infants who are less ill. Poor lung compliance and extensive atelectasis increase the risk of alveolar rupture. Prolonged inspiratory time, high peak inspiratory pressure, excessive tidal volume, and air-trapping due to insufficient expiratory time all increase the risk of airleak during mechanical ventilation. All air leaks start with overdistension of alveoli or terminal bronchioles with resultant rupture and escape of air into the interstitium. The air then tracks along the peribronchovascular sheaths to the hilum and into the mediastinum producing a pneumomediastinum or dissects through the visceral pleura producing a pneumothorax. With pulmonary interstitial emphysema, the air remains in the interstitial space.

Pulmonary interstitial emphysema is predominantly seen in the extremely low birth weight infant with RDS on mechanical ventilation with a reported incidence of 3–5% in that category of infants. The lung connective tissue in these infants is more abundant and less dissectible; therefore, the air remains at this site and splints the alveoli in a state of inflation by impeding alveolar emptying in the distal alveoli while causing compression atelectasis of adjacent alveoli. Because of the perivascular location of this air, it also impedes pulmonary blood flow causing significant ventilation perfusion mismatch.

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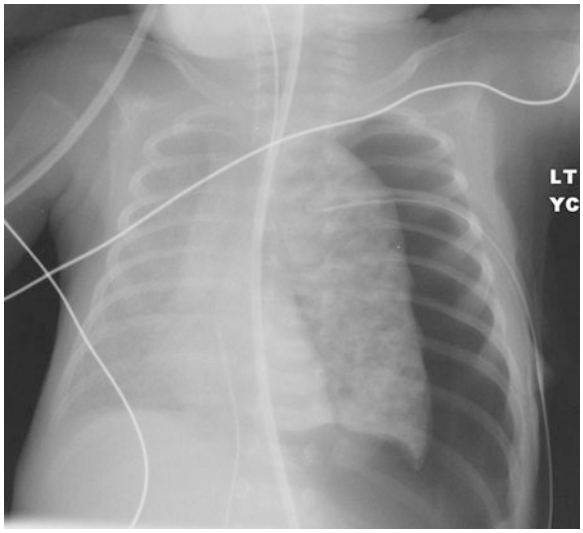

Figure 21.1
Left-sided tension pneumothorax with chest tube in place. Note how the left lung is compressed by pleural air, the mediastinal structures are shifted to the right and both lungs have become atelectatic

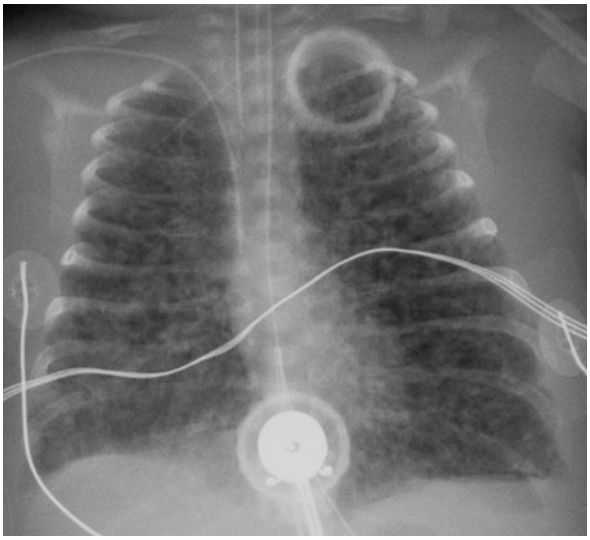

Figure 21.2
Bilateral pulmonary interstitial emphysema. Note the heart has been squeezed in the middle of the thorax by the over-expanded lung fields. The circular shadows at the top and bottom of the image are made by transcutaneous carbon dioxide sensors placed on the baby's skin

On x-ray, this appears as overexpanded lung fields with small round or branching lucencies of air interspersed with areas of atelectasis. The branching pattern may cause it to be confused with air bronchograms. PIE, unlike a pneumothorax, is not amenable to external drainage (*Fig. 21.2*). Management of an infant with PIE can present a special challenge and it is important to remember that in spite of the air leak, adequate MAP/PEEP is required to keep the unaffected alveoli open and maintain oxygenation. To this end, high-frequency ventilation has been shown to be better than conventional ventilation in these infants because adequate MAP can be provided with a lower lung volume and still remove CO_2 more efficiently. High-frequency jet ventilation has been shown to lead to faster and more frequent resolution of PIE in a multicenter randomized clinical trial. Oscillatory ventilation is also used with apparent success, though evidence for its benefit is anecdotal. PIE is often unilateral making management even more difficult. In those situations, use of selective main stem bronchial intubation/occlusion has been reported with varying success. Lateral decubitus positioning of the infant with the affected lung in a dependent position has been reported to be beneficial in unilateral PIE possibly because it causes plugging of dependent airways and improves oxygenation of the nondependent lung.

Pneumomediastinum is rarely associated with significant clinical symptoms because the air is usually not under tension and causes little respiratory compromise. Radiological appearance of pneumomediastinum can be varied but an area of hyperlucency in the superior retrosternal space can usually be seen and often the air elevates the lobes of the thymus producing the classic "sail sign." When large amounts of air are present, the thymus can be pushed to the apex of the lung, a finding often confused with atelectasis, or it can overlie the heart to be confused with a pneumopericardium. Pneumomediastinum is classically seen in infants with meconium aspiration syndrome because of the ball valve effect of particulate meconium. Because the air is usually not under tension, external drainage of a pneumomediastinum is usually not required. Air from a pneumomediastinum can track into the subcutaneous tissues of the neck and anterior chest wall producing subcutaneous emphysema or into the abdomen causing a *pneumoperitoneum.*

A pneumothorax is commonly associated with respiratory distress syndrome, meconium aspiration syndrome, and pulmonary hypoplasia, although it can occur spontaneously in nonventilated infants particularly term or late preterm infants with retained lung fluid born after elective cesarean section. Pneumothorax is seen more frequently

in immature infants requiring mechanical ventilation and was reported to occur in 3–13% of infants less than 28 week gestation born between 2003 and 2007 from the NICHD Neonatal Research Network centers.

Pneumothorax appears on chest x-ray as an area of hyperlucency lateral to the lung with no lung markings beyond the demarcation line. It can be unilateral or bilateral. On an anteroposterior film, the air may layer anteriorly and the noncompliant RDS lung may not collapse, making diagnosis more difficult. Greater lucency of one lung field with a very sharp heart border may be the only clue to the presence of an anterior pneumothorax. Lateral decubitus film is helpful in clarifying the diagnosis. Smaller collections of pleural air in a pneumothorax can be only mildly symptomatic and require observation/conservative management. The practice of nitrogen washout with 100% oxygen is strongly discouraged as the toxicity caused by hyperoxia likely outweighs the benefit of a slightly more rapid resolution of a non-tension pneumothorax. When a large amount of air collects in the pleural space under pressure it causes a "tension pneumothorax" leading to alveolar collapse and shift of the mediastinum to the contralateral side, compromising gas exchange as well as cardiac output. This presents acutely with a sudden decrease in oxygen saturation, hypotension, and bradycardia and represents a medical emergency requiring rapid evacuation of the air to allow lung reexpansion, adequate ventilation, and restoration of venous return/cardiac output. Bedside detection can be aided by use of a focused bright light to "transilluminate" the air in the pleural space. Rapid evacuation of the air can be achieved quickly with a 22–25 gauge needle inserted over the superior aspect of the rib in the midclavicular line and attached to a three-way stop cock and a syringe. Definitive evacuation of a pneumothorax may require chest tube drainage. Tension pneumothorax increases the risk of intracranial hemorrhage, likely by several mechanisms. The increased intrathoracic pressure from tension pneumothorax impairs venous return and at the same time reduces cardiac output, reducing cerebral perfusion and increasing venous back pressure. Following resolution, there may be a surge in cerebral blood flow as cardiac output is restored and enters the cerebral circulation rendered pressure-passive by hypoxia induced loss of autoregulation.

Pneumopericardium develops when there is dissection of air into the pericardial sac and is seen almost excusively in ventilated infants and is commonly in association with a pneumothorax. Some cases are asymptomatic, but if sufficient air accumulates, it will cause cardiac tamponade requiring urgent drainage. The infant presents with acute circulatory collapse, decreased pulse volume, and inaudible or distant heart sounds. The diagnosis is confirmed by lucency all the way around the heart on x-ray (*Fig. 21.3*) or by recovery of air and immediate improvement in the patient's condition after pericardiocentesis. This complication is now uncommon, but is still associated with a high mortality if immediate drainage is not accomplished.

Hemodynamic Compromise

Normal respiration generates negative pressure in the thorax, which facilitates venous return from the superior and inferior vena cavae. Mechanical ventilation by its nature delivers positive pressure to the lungs during all phases of respiration. This increase in intrathoracic pressure impedes venous return and therefore decreases ventricular filling, cardiac output, and pulmonary and systemic blood flow.

Systemic venous return depends on a pressure gradient between the peripheral veins and intrathoracic or right atrial pressure. This gradient is increased by spontaneous respiration because it generates a negative intrathoracic

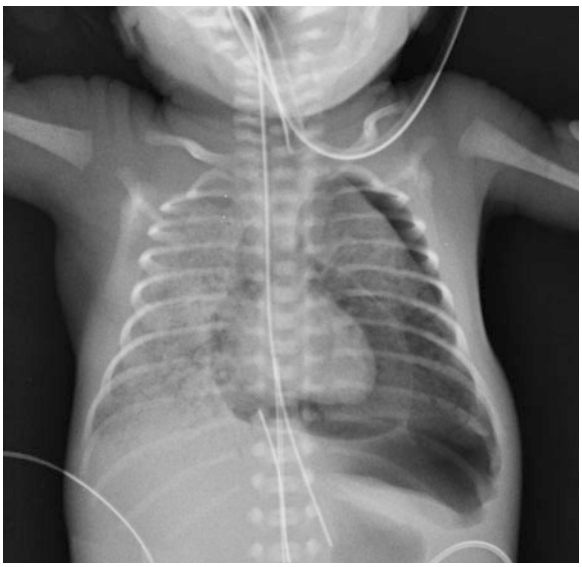

Figure 21.3
Pnemopericardium with tension pneumothorax. Note that the air completely surrounds the heart, including the infracardiac space. This clearly distinguishes this as pneumopericardium, rather than bilateral pneumomediastinum

pressure, therefore right ventricular filling and stroke volume will both increase during spontaneous inspiration. Positive pressure ventilation on the other hand increases both intrathoracic and right atrial pressures reducing right ventricular filling and preload. The use of PEEP prevents the intrathoracic pressure from returning to atmospheric levels, and the positive intrapleural pressure throughout the respiratory cycle leads to some degree of circulatory compromise with all forms of positive pressure ventilation. The transmission of airway pressure to the mediastinum is limited when the lungs are poorly compliant and increases when the airway pressure is excessive relative to lung compliance and leads to overexpansion of the lungs (*Fig. 21.4*). These effects are exaggerated in the presence of hypovolemia and decreased peripheral vascular tone as seen in patients with septic shock. In addition, the relative compliance of the chest wall and the lungs determines the amount of pressure transmitted to the pleural space. The relationship is described by the following equation:

$$\mathbf{P_{PL} = AWP \times (C_L/C_L + C_{CW})},$$

where P_{PL} is pleural pressure, AWP is mean airway pressure, C_L is compliance of the lungs, and C_{CW} is compliance of the chest wall. It can be seen that in situations of good lung compliance but poor chest wall compliance, transmission of pressure to the pleural space and hemodynamic compromise are increased. This is often seen in cases of increased intraabdominal pressure impairing diaphragmatic motion, or with massive chest wall edema.

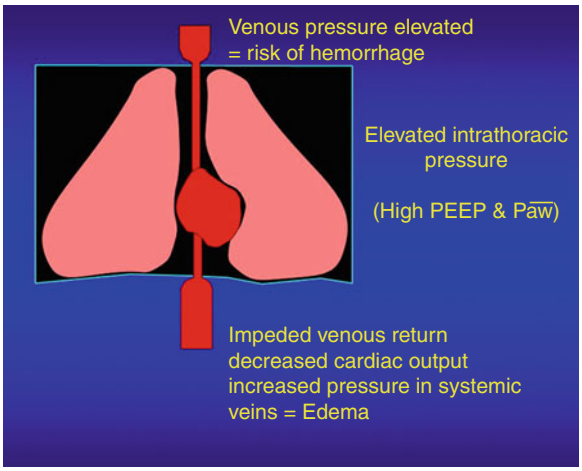

Figure 21.4
Schematic representation of impairment of venous return in the presence of excessive intrathoracic pressure

Changes in lung volume also affect pulmonary vascular resistance and right ventricular afterload. At excessive lung volumes, the alveolar vessels become directly compressed as a result of alveolar overdistension. Low lung volumes with atelectasis leads to collapse of intrapulmonary veins and hypoxic vasoconstriction, both leading to increased pulmonary vascular resistance. Aiming to maintain optimal lung volume at near FRC is essential to minimize the hemodynamic consequences of mechanical ventilation.

Bronchopulmonary Dysplasia

The use of both high inflating pressures and high tidal volumes has been shown to cause lung injury. But it has now become clear that large tidal volumes are the primary cause of lung injury regardless of pressure used (volutrauma). Excessive alveolar stretch causes epithelial injury, influx of inflammatory cells and protein leakage into the alveolar space, hyaline membrane formation, changes in lymphatic flow, and disruption of surfactant activity. Even very few large breaths immediately after birth can alter lung compliance and surfactant function. Although excessive tidal volume can lead to alveolar injury, suboptimal lung inflation and alveolar collapse with inadequate use of PEEP has been shown to have deleterious effect on the lungs (atelectotrauma) and should be avoided.

The use of mechanical ventilation is associated with the development of bronchopulmonary dysplasia since it was first described by Northway in preterm infants who were mechanically ventilated for RDS. Ample studies have demonstrated the association of BPD and mechanical ventilation, but avoidance of mechanical ventilation by using noninvasive modes of respiratory support such as CPAP have not clearly reduced the risk of BPD. The most important determinant of the risk of BPD remains gestational age. In those infants who still require mechanical ventilation, several lung protective strategies have been suggested to decrease BPD including the use of volume-targeted ventilation to avoid excessive tidal volumes, adequate PEEP to maintain lung volume and minimize atelectotrauma, permissive hypercapnia, and the judicious use of supplemental oxygen to minimize oxygen toxicity. The use of antioxidants, such as vitamin A, appears to offer some benefit. Because the etiology of BPD is multifactorial, none of these strategies by themselves may show demonstrable decrease in BPD. The ideal mode of respiratory support should maintain adequate lung volume at minimal pressures and reduce work of breathing.

Neurologic Injury

Although it may not be immediately obvious, the use of mechanical ventilation can be associated with significant neurologic morbidity. Cerebral blood flow in the preterm infant is poorly regulated due to the relatively narrow window of effective autoregulation of immature cerebral vessels. Therefore, changes in systemic blood flow are easily reflected in the cerebral vascular system. Systemic hypotension caused by decreased cardiac output as a result of increased intrathoracic pressure can lead to decreased cerebral blood flow and cerebral ischemia particularly in the periventricular regions of the immature brain. Subsequent return of normal or increased blood pressure can then lead to a reperfusion injury that can contribute to intracranial hemorrhage. By the same token, impedance of venous return from the superior vena cava as seen with tension pneumothorax can lead to venous congestion in the brain possibly contributing to intracranial hemorrhage.

Several events during mechanical ventilation can result in rapid changes in cerebral circulation. Endotracheal intubation and suction are painful procedures associated with surges in blood pressure followed by periods of bradycardia and oxygen desaturation that can affect cerebral blood flow. Patient ventilator asynchrony between spontaneous and mechanically delivered breaths is associated with a "valsalvar-like maneuver" during which excessive intrathoracic pressures can be generated. This used to require administration of sedative and paralytic agents to prevent the patient from "fighting the ventilator." Now this can be mitigated by the use of synchronized ventilation, which allows the machine to breathe with the baby thereby avoiding asynchrony and obviating the need for paralysis and excessive sedation. The use of synchronized ventilation is associated with more stable blood pressures, stable cerebral perfusion, and a lower incidence of intracranial hemorrhage.

The development of air-leak syndromes such as pneumothorax can very quickly increase intrathoracic pressure impeding venous return and decreasing blood pressure. Rapid evacuation of the pneumothorax with return of systemic and cerebral blood flow has been implicated in the development of intraventricular hemorrhage (IVH). In the same way, lung overdistention either as a result of inappropriately high tidal volume, high mean airway pressure, or PEEP will decrease venous return and impair cerebral blood flow.

Arterial blood pH, carbon dioxide concentration, and oxygen levels all have significant effects on neonatal cerebral blood flow. Hypocapnia decreases cerebral blood flow whereas hypercapnia causes cerebral vasodilation, increases CBF in premature infants, and may contribute to the development of IVH. Several studies report a strong association between PaCO2 levels less than 25–30 mm Hg and an increased incidence of cystic periventricular leukomalacia (PVL) IVH and cerebral palsy in preterm infants. Prolonged exposure to PaCO2 values less than 25–30 mm Hg is also associated with hearing loss in term and near-term infants. Inadvertent hyperventilation and the previous practice of hyperventilation in patients with PPHN to achieve pulmonary vasodilatation is strongly discouraged. Earlier concerns about the association of high-frequency ventilation with increased incidence of IVH and PVL appears to be related to inadvertent hyperventilation in those patients. Permissive hypercapnia, even though promoted within reasonable limits to minimize the development of BPD should be used with caution as rapid increases in CO_2 are associated with loss of cerebral autoregulation in very low birth weight infants. Exposure to high $PaCO_2$ during the first few days of life in preterm infants has been associated with increased risk of severe intraventricular hemorrhage.

Mechanical ventilation is an important lifesaving tool in our hands. Like all tools, it can be used optimally or not and have more or fewer adverse effects, depending on how well that tool is used. Awareness of the possible deleterious effects related to mechanical ventilation will help the clinician in adopting ventilation strategies to minimize these complications and the ability to recognize them promptly when they do occur. Some complications are inherent to mechanical ventilation, but careful attention to all aspects of neonatal care particularly the effects of positive pressure ventilation and the physiologic derangements associated with it can help improve outcomes.

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22 ECMO (Extracorporeal Membrane Oxygenation)

Martin Keszler

Introduction

Extracorporeal membrane oxygenation (ECMO) is an effective, but costly and invasive rescue therapy for term and late preterm infants with reversible heart and/or lung failure unresponsive to maximal conventional therapies. These include less invasive newer technologies, such as, high-frequency ventilation, surfactant replacement therapy, and inhaled nitric oxide (iNO). ECMO is the application of modified extracorporeal bypass technology for a period of days to weeks to provide temporary life support allowing the injured lungs and/or heart to recover. The first successful clinical application in infants was reported by Bartlett in 1976 and the treatment began to be adopted widely in the mid to late 1980s. ECMO has been shown to significantly improve mortality in a randomized controlled trial and has been the standard of care in industrialized countries for over 20 years. Availability in less-developed countries is limited due to its high expense, need for sophisticated equipment and training, and limited patient volume (relatively low cost-effectiveness in resource-limited countries). ECMO utilization peaked in the 1990s and has steadily declined over the past 10–12 years with the availability of iNO and adoption of less-aggressive ventilation strategies.

Indications

The most common conditions requiring ECMO support are meconium aspiration syndrome, congenital diaphragmatic hernia, sepsis/pneumonia, severe RDS or airleak syndrome. Typically, these are complicated by persistent pulmonary hypertension of the newborn (PPHN). Severe airleak syndrome may also necessitate ECMO to allow lung rest and resolution of the lung injury. Less commonly, PPHN of the primary or idiopathic variety may lead to ECMO (*Table 22.1*). Transient causes of myocardial failure, such as perinatal asphyxia or viral myocarditis can also be effectively supported with ECMO. Oxygenation index > 40 despite optimal respiratory support remains the most widely used indication of poor likelihood of survival and the need for ECMO. However, some infants require ECMO for impending cardiac failure without reaching the traditional ECMO criteria. Because of improvements in mechanical ventilation techniques and the effectiveness of iNO, fewer infants now require ECMO, but those who do are more often suffering from multiorgan dysfunction, sepsis, and circulatory failure. As a result, traditional ECMO criteria are no longer adequate as a sole basis for the decision to initiate ECMO and more attention needs to be given to assessing the adequacy of myocardial function.

Technique

ECMO differs from cardiopulmonary bypass as performed in the operating room (OR) in three important ways: (1) ECMO is partial, not complete bypass; some amount of blood continues to flow through the heart and lungs. Unlike OR bypass, diversion of blood into the extracorporeal circuit begins and ends gradually, not all at once. (2) Because ECMO is only partial bypass, the patient's arterial oxygen saturation reflects not only the values in the ECMO circuit, but primarily the proportion of oxygenated blood returning from the oxygenator vs. that of the desaturated blood that shunted through the patient's nonfunctioning lungs. (3) ECMO is performed for much longer periods; therefore, anticoagulation must be carefully titrated to avoid serious bleeding complications.

Traditional venoarterial ECMO utilizes a 10–14Fr. cannula placed in the external jugular vein for drainage and an 8–12Fr. cannula inserted into the common carotid artery and advanced just to the junction with the arch of the aorta. The venous cannula has many side holes in the final 5 cm of its length to improve drainage and is advanced into the body of the right atrium. Blood is drained from the right atrium by gravity, is pumped through an artificial lung where gas exchange takes place, rewarmed to body temperature in a heat exchanger and returned into the aorta. Most centers use a bubble detector between the oxygenator and heat exchanger to minimize the risk of air embolism.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_22,

Table 22.1
Survival rates and primary diagnoses of Neonatal ECMO cases according to the Extracorporeal Life Support Organization Registry, Jan 2010

Primary diagnosis	Number of cases	Survival (%)
Meconium aspiration syndrome	7584	94
Congenital diaphragmatic hernia	5929	51
Persistent pulmonary hypertension	3870	78
Sepsis	2617	75
Respiratory distress syndrome	1484	84
Other	2383	63

Patients with adequate cardiac function can be supported with veno-venous ECMO, utilizing a double-lumen cannula inserted into the right atrium via the internal jugular vein. Adequate gas exchange can be maintained with this approach, although oxygen delivery is less efficient due to recirculation of blood in the right atrium and a longer period is required to stabilize the patient.

The effectiveness of ECMO depends on the ability to drain a sufficient volume of blood to meet the oxygen demand of the infant. Typically, this requires bypassing about 70–85% of the available venous return, or about 100 ml/kg/min. Oxygenation is controlled by adjusting ECMO pump flow while CO_2 elimination is regulated by adjusting the composition and flow rate of gases ventilating the oxygenator. The standard silicone rubber membrane oxygenator remains the most widely used device, but newer hollow fiber oxygenators have improved resistance to plasma leak and are increasingly finding their way into long-term bypass with ECMO.

Once on bypass, the ventilator settings are rapidly reduced to achieve lung rest. Originally, this was done by reducing ventilator rate, inspiratory pressure, and end-expiratory pressure to very low values. However, this approach leads to severe atelectasis, which increases patient dependence on bypass and prolongs the duration of ECMO. Many centers now employ a lung rest strategy with high end-expiratory pressure that has been shown to shorten duration of ECMO and minimize deterioration of lung function.

Inotropic support can be weaned rapidly once on VA bypass, since cardiac support is provided, but is continued with VV bypass. Deterioration of cardiac function known as myocardial stun is sometimes seen with VA ECMO, but is always transient. Management of circulating blood volume is often complicated by capillary leak, renal insufficiency, and volume shifts between infant and circuit.

Table 22.2
ECMO mechanical complications (Adapted from the Extracorporeal Life Support Organization Registry, Jan 2010)

Complication	Incidence	Associated survival
Oxygenator failure	5.9%	53%
Circuit disruption	0.9%	67%
Pump malfunction	1.7%	66%
Clots: oxygenator	17.5%	65%
Clots: bridge	10.2%	67%
Clots: bladder	15.4%	68%
Clots: other	8.7%	54%
Air in circuit	4.9%	70%
Cannula problems	11.5%	68%

Anticoagulation must be carefully monitored and frequent adjustments made to the rate of heparin infusion to minimize the risk of clotting and bleeding. Activated clotting time is a rapid bedside tool utilized by most ECMO programs and is usually maintained at about 1.5–2 times normal values (160–220 s). Platelets counts are monitored closely and are kept >100,000 by means of transfusion as needed.

Optimal nutritional support is important for recovery and is usually provided by parenteral nutrition. Enteral feeding is feasible, but used infrequently in these critically ill infants. Electrolyte shifts and oliguria are common and edema is always present, in part due to capillary leak. Hemofiltration is widely used to aid fluid management, but overly aggressive fluid removal will lead to hypovolemia and jeopardize renal recovery. Diuretics are often needed in order to help mobilize fluid. Resolution of the severe edema often seen in ECMO patients is a prerequisite for successfully coming off ECMO.

Once cannulation is completed, the patient is allowed to be awake and moving. Spontaneous respiration is encouraged. Careful neurologic assessment is performed frequently to detect significant change that might signal intracranial bleeding. Seizures are fairly common in infants with history of perinatal asphyxia. Cranial ultrasound is done daily at least initially for early detection of intracranial hemorrhage, which would necessitate discontinuation of ECMO.

Complications

The majority of ECMO patients do not experience serious complications, but the potential for catastrophic events is ever present, because patients are, for a period of time,

Table 22.3
ECMO patient complications (Adapted from the Extracorporeal Life Support Organization Registry, Jan 2010)

Complication	Incidence	Survival
Cannulation site bleeding	6.9%	65%
Surgical site bleeding	6.3%	44%
Central nervous system hemorrhage	6.8%	45%
Pulmonary hemorrhage	4.5%	44%
Gastrointestinal hemorrhage	1.7%	45%
Hemolysis	1.0%	65%
Disseminated intravascular coagulation	2.4%	40%
Seizures	10.8%	60%
CNS infarction	7.7%	54%
Hemofiltration/Dialysis required	19.7%	51%
CPR required	2.3%	43%
Myocardial stun	5.1%	59%
Cardiac arrhythmia	4.0%	53%
Hypertension requiring vasodilators	12.5%	72%
Cardiac tamponade	0.7%	36%
Pneumothorax requiring treatment	6.0%	59%
Culture proven infection	6.1%	53%
Hyperbilirubinemia (> 2 direct or > 15 total)	7.5%	65%

completely dependent on extracorporeal support with significant potential for life-threatening complications and mechanical failure. Minimizing such problems requires meticulous attention to detail, careful maintenance of the equipment, close monitoring of the patient and circuit, and continuous staff training. Mechanical or electrical failure, air embolization, thrombus formation with embolization, and massive hemorrhage from circuit disruption are the main circuit-related complications (*Table 22.2*). The most serious patient complication of ECMO is internal hemorrhage, especially intracranial hemorrhage. Renal insufficiency, edema, hypertension, conjugated hyperbilirubinemia, and metabolic disturbances are common, but typically are transient (*Table 22.3*). Neurologic manifestations usually reflect pre-ECMO events, such as perinatal asphyxia or severe hypoxemia, rather than being caused by the procedure.

Outcomes

Survival depends on underlying diagnosis, patient condition at the start of the procedure and on occurrence of complications, if any. Patients with congenital diaphragmatic hernia have the lowest survival (51%), whereas those with meconium aspiration syndrome have survival >90% (*Table 22.1*). Overall survival rates have been declining since they peaked at 82% in the late 1980s, because only the more severely ill patients now require ECMO and because the patient mix is shifting to diagnoses with lower survival rates. In the past few years, survival has dropped to around 65%. Neurodevelopmental outcome in infants treated with ECMO is similar to those who were comparably ill but did not require ECMO. Severe neurodevelopmental impairment is present in only about 10% of survivors.

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23 Cardiovascular System

Afif El-Khuffash · Patrick J. McNamara

Preamble

The management of the hemodynamic status of neonates, particularly premature infants, poses many challenges. There is currently a lack of clarity on the subject of whether therapeutic intervention should be based on arterial pressure or systemic blood flow. What is clear, however, is that the subject of neonatal hemodynamics is highly complex and influenced by developmental, transitional, and pathological factors. The approach to therapeutic intervention does not lend itself toward any directive or strict protocol, but must be individualized based on maturity, disease, and response to intervention. It is likely that a composite approach based on blood flow and arterial pressure is required, with careful consideration of the influence of preload, afterload, and myocardial performance in the context of individual patient. Serial echocardiography may better facilitate this decision-making process. This chapter will deal with these issues and provide a comprehensive assessment and management pathway for infants with hemodynamic instability.

Abbreviations: *cAMP*, Adenosine monophosphate; *SaO_2*, Aortic oxygen saturation; *AET*, Atrial ectopic tachycardia; *AT*, Atrial tachycardia; *AVRT*, Atrioventricular reentry tachycardia; *AVNRT*, AV nodal reentry tachycardia; *BP*, Blood pressure; *BNP*, B-type natriuretic peptide; *cTnTCHB*, Cardiac troponin T; *CAF*, Celiac artery flow; *CLD*, Chronic lung disease; *CHB*, Congenital heart block; *CHD*, Congenital heart disease; *cGMP*, Cyclic guanosine monophosphate; *COX*, Cyclo-oxygenase; *DA*, Ductus arteriosus; *E/A*, E wave to A wave ratio; *ECG*, Electrocardiogram; *HCM*, Hypertrophic cardiomyopathy; *IDM*, Infant of a diabetic mother; *IVC*, Inferior vena cava; *IVH*, Intraventricular hemorrhage; *IVRT*, Isovolemic relaxation time; *LA:Ao*, Left atrial to aortic ratio; *LV*, Left ventricle; *LVO*, Left ventricular output; *LCOS*, Low cardiac output syndrome; *$SmVO_2$*, Mixed venous oxygen saturation; *NEC*, Necrotizing enterocolitis; *NO*, Nitric oxide; *NOS*, Nitric oxide synthase; *NSAIDS*, Nonsteroidal anti-inflammatory drugs; *NTpBNP*, N-terminal-pro-BNP; *PDA*, Parent ductus arteriosus; *PFO*, Patent foramen ovale; *PVL*, Periventricular leukomalacia; *PPHN*, Persistent pulmonary hypertension of the newborn; *Kv*, Potassium voltage channels; *$SpAO_2$*, Pulmonary arterial oxygen saturation; *PVR*, Pulmonary vascular resistance; *$SpVO_2$*, Pulmonary venous oxygen saturation; *RV*, Right ventricle; *SVC*, Superior vena cava; *SVT*, Supraventricular tachycardia; *SLE*, Systemic lupus erythematosus; *SVR*, Systemic vascular resistance; *TnECHO*, Targeted neonatal echocardiography; *Qp: Qs*, The ratio of pulmonary to systemic blood flow; *TNF*, Tumor necrosis factor; *WPW*, Wolff–Parkinson–White

Hemodynamic Compromise in the Neonate

Introduction

The adaptive process for the preterm circulation, particularly those less than 30 weeks gestation, may be complex and if abnormal may result in compromise to vulnerable organs such as the brain, bowel, and kidneys. Persistence of the ductus arteriosus, delay in the normal postnatal fall in pulmonary artery pressure, and failure to increase cardiac output all contribute to the delay in the normal postnatal transition. The reasons for this maladaptation are unclear. The potential determinants of cardiovascular compromise may include immaturity of the myocardium and blood vessels, poor tolerance of afterload, hypovolemia, high volume shunts through the ductus arteriosus or foramen ovale, adverse consequence of positive pressure ventilation, or other treatments with cardiovascular consequences. These factors may all play a role in reducing systemic blood flow and oxygen delivery to vital organs potentially leading to irreversible damage.

Fetal Physiology of the Cardiovascular System

Fetal cardiac output rises from 50 ml/kg/min at 18 weeks gestation to 120 ml/kg/min at term reflecting the growing

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demand on the myocardium to supply vital organs in the developing fetus. Cardiac function is dependent on a variety of factors: *Preload* (amount of blood present in the ventricle at end diastole) which is dependent on the intravascular volume status of the infant and diastolic compliance of the ventricle. *Afterload* (resistance against which the ventricle muscle must contract) which depends on vascular resistance, blood viscosity, and ventricular outflow tract obstructions. *Myocardial performance* (the intrinsic ability of the myocardium to contract) and *heart rate* are the other two determinants. The fetal heart is usually subjected to a low afterload due to the low-pressure system of the placenta; therefore, the myocardium is subjected to very little wall stress antenatally. This low-pressure system suits the immature myocardium as it is unable to adapt when subjected to additional stresses.

Transitional Changes in the Premature Neonate

In the early postnatal period, the patent ductus arteriosus (PDA) and the patent foramen ovale (PFO) play a vital role in determining cardiac output and systemic perfusion. The PDA in premature neonates is unpredictable and poses different hemodynamic influences depending on whether it is persistent, closed, or initially constricted followed by patency. Contrary to previous belief, the shunt across a PDA is predominantly left to right. Similarly, an atrial shunt is usually present and is left to right in direction. These early shunts dramatically increase pulmonary blood flow and reduce systemic blood flow due to short-circuiting of blood in the lungs. This may lead to increased ventilator dependence, pulmonary edema and hemorrhage, and poor end organ perfusion leading to ischemia, anaerobic metabolism, and loss of function.

Myocardial Function

The problem of low systemic blood flow in the early transitional period is further compounded by the universally poor myocardial function in preterm neonates. In mature myocardium, surface L-type calcium channels cause a small amount of interstitial calcium molecules to enter the myocytes following depolarization; these in turn lead to more intracellular calcium release from intrinsic stores called the sarcoplasmic reticulum leading to effective myofibril shortening and muscle contraction. Conversely, the preterm heart muscle relies on L-type calcium channels as a source of calcium contraction. Furthermore, the immature myocytes have a higher surface area-to-volume ratio to compensate for the lack of the T-tubule system necessary for effective calcium entry into the cell. These developmental differences drastically reduce the functional reserve of the premature heart in the face of postnatal stresses (◉ *Fig. 23.1*). The neonatal myocardium is poorly tolerant of increased afterload compared to older children. Furthermore, the immature myocardium contains a higher proportion of noncontractile collagen and an inefficient process of calcium extrusion from the myocytes. This leads to impaired relaxation and ventricular filling during diastole and contributes to diastolic dysfunction. The immediate postnatal period following the loss of the low-pressure system of the placenta and postoperative period following PDA ligation represent two clinical situations in which the neonatal myocardium is subjected to afterload stress. The net effect is impaired myocardial systolic performance and consequential poor systemic blood flow due to low cardiac output, oftentimes despite a normal systemic blood pressure. This problem is further compounded by any potential stressors such as hypoxia, anemia, and mechanical ventilation, which reduces venous return and causes pressure on the myocardium preventing effective contraction.

Ventricular Afterload

As mentioned earlier, the sudden increase in systemic vascular resistance immediately after birth poses a major afterload challenge to the preterm infant, which may limit its ability to support cardiac output with resultant compromise to organ blood flow. After the transitional period, vascular tone may fall in certain clinical circumstances such as sepsis. Vascular smooth tone muscle is controlled by a balance between vasoconstrictors, for example, thromboxane, vasopressin, and vasodilators, for example, nitric oxide and prostaglandins. Immaturity of the central nervous system may also impact on transitional vascular changes. The clinical situation of systemic hypotension but normal or high cardiac output is oftentimes missed as these patients may appear pink and well perused. Targeted neonatal echocardiography is likely to be useful in this situation to guide choice of cardiovascular intervention.

Nitric oxide (NO) is produced by actions of nitric oxide synthase (NOS), present in abundance in smooth muscle tissue and acts via cyclic guanosine monophosphate (cGMP) on calcium-sensitive potassium channels and myosin light-chain phosphatases to cause smooth muscle relaxation. Endotoxins and cytokines such as tumor necrosis factor alpha (TNF-α) and a variety of

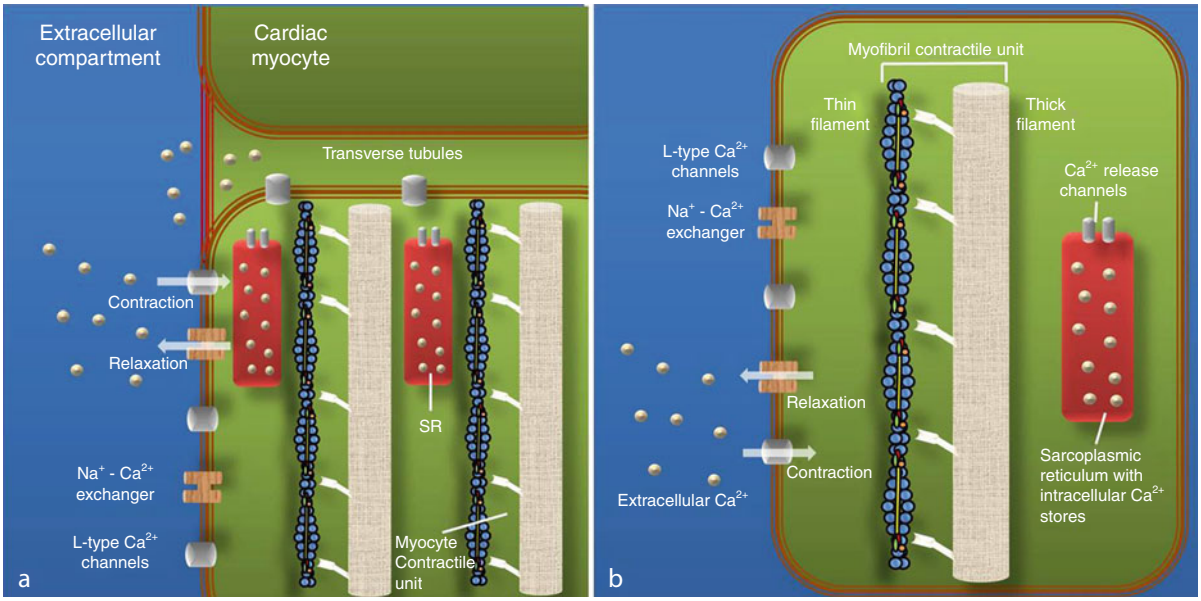


Figure 23.1

Diagram of a myocyte in the adult (a) and preterm infants (b). **In normal adult myocytes, extra cellular calcium (*white circles*) enters the cell via L-type calcium channels. This in turn activates the release of large amounts intracellular calcium stored in the sarcoplasmic reticulum (SR) into the cytosol. This results in contraction of the myofilament. This whole process is facilitated by the proximity of the SR to the L-type Ca channels and by the presence of transverse tubules, which are invaginations of the myocyte cell wall into the cytosol. Relaxation is a result of active reuptake of cytosolic calcium into the SR. The small amount of calcium that entered the cell via L-type calcium channels is transported back to the extracellular compartment via Na^+-Ca^{2+} exchanger. In preterm infants, the SR is physically separated from L-type Ca channels (diagram b), the transverse tubules are absent, and the myocyte has a greater surface area to volume ratio. Consequently, contraction is dependent on extracellular calcium influx into the cells**

interleukins can induce NOS and NO synthesis leading to profound dilatation and a reduced systemic blood flow in the presence of sepsis. In addition, excess NO leads to formation of free oxygen radicals leading to vascular wall damage.

Vasopressin plays an important role in regulating vascular tone postnatally. It increases vascular tone via vasopressin (V1) receptors in many organs, excluding the lung, brain, and heart, which in turn increase calcium release from the sarcoplasmic reticulum, upregulate adrenaline receptors on smooth muscle walls, and reduce NO synthesis. Its implication in shock has been studied in adults. Initially, vasopressin levels increase in response to shock to maintain vascular tone; however, as shock progresses, vasopressin stores are depleted and vascular tone is therefore compromised.

Prostaglandins are eicosanoids derived from cell membrane arachidonic acid by the actions of cyclooxygenase enzymes and play an important role of regulation of vascular tone. Prostaglandin E2, a vasodilator, and Thromboxane A2, a vasoconstrictor are both implicated in the early regulation of vascular tone and may have a role in the pathogenesis of hypovolemia associated with shock.

Adrenal Insufficiency

Low-birth-weight infants have an immature hypothalamic–pituitary–adrenal axis. This immaturity was highlighted by Ng et al. who showed an exaggerated pituitary response with cortisol deficiency in the presence of severe hypotension. Corticosteroids regulate vascular tone by upregulating adrenergic receptors on vascular smooth muscle wall. Sick preterm neonates cannot increase glucocorticoid production in response to stress; this may be due to the lack or immaturity of enzymes necessary for synthesis. This may explain the poor cardiopulmonary status in sick newborns. Furthermore, inotrope-resistant preterm neonates have low cortisol levels.

Arterial Pressure and Systemic Blood Flow

The thresholds for consideration of a stable or compromised circulation pose to be an ongoing challenge for neonatologists. Systemic low blood flow states in neonates have been associated with mortality. In addition, hypotension has been associated with the development of intraventricular hemorrhage, periventricular leukomalacia, and adverse neurodevelopmental outcome. The goal of therapy is to counteract or minimize the evolution of these morbidities. The prevalence of systemic hypotension in preterm infants is around 40%. There are no data to show that correction of low arterial pressure leads to a reduction in adverse neurodevelopmental outcomes. Studies investigating the association between hypotension and acute brain compromise or injury have documented both an association and a lack of an association. The study by Martens et al. sheds important light on the topic. In a cohort of over 200 babies, they found an association between hypotension and adverse neurological outcome; however, when they controlled for postnatal steroids and intrauterine growth retardation, the association no longer existed suggesting that hypotension was merely a marker of potential neurological compromise but this was not a cause-and-effect relationship.

A common misconception among clinicians is that arterial pressure is a reliable surrogate and correlates well with systemic blood flow implying that a normal mean arterial pressure confirms the adequacy of blood flow to essential organs. This conceptual framework fails to consider the third determinant of blood pressure and flow, which is peripheral vascular resistance. Several studies have confirmed that the relationship between arterial pressure and cardiac output was found to be loose at best. As arterial pressure is a product of systemic blood flow and peripheral vascular resistance, it follows that blood pressure is partly determined by resistance. A normal mean arterial pressure in the setting of a high-resistance systemic circulation can only be explained by reduced systemic blood flow. This, in part, explains why premature neonates suffer from low systemic blood flow in the first 24 h of life. Conversely, a low blood pressure in the setting of low peripheral vascular resistance may imply normal or high systemic flow. In addition to vasoactive hormones and maturity of the sympathoadrenal system, core body temperature, arterial carbon dioxide, sepsis, and a patent ductus arteriosus (which exposes the left ventricle to combined systemic and pulmonary resistance) all impact on systemic blood flow.

There is emerging evidence to support the influence of systemic vascular resistance on cardiac output. Some groups have demonstrated reciprocal relationships between cardiac output and systemic vascular resistance in preterm neonates. The relationship between cardiac output, blood pressure, and systemic blood flow needs to be examined beyond the first few days of life. In the preterm infant, further problems arise. The presence of a PDA, with systemic to pulmonary shunting, will lead to an elevated left ventricular output not translated to improved flow. The presence of a PFO, with left-to-right flow, will falsely elevate right ventricular output. Reliance on arterial pressure and ventricular output alone will not provide a complete representation of the adequacy of systemic blood flow and organ perfusion. Nevertheless, serial evaluation of cardiac output and arterial pressure in tandem may provide more insights regarding need for intervention, therapeutic agents of choice, and long-term consequences.

Superior Vena Caval (SVC) Flow

SVC flow measurement as a marker of systemic perfusion has recently come to light. Blood returning from the SVC reflects blood supply to the brain (80%) and the upper body (20%) and is not influenced by the presence of a PDA or atrial shunting. Doppler volumetric measurements of SVC flow are feasible and have been described and validated with normal ranges established. Low SVC flow is defined as a value less than 30 ml/kg/min at 6 h or a value less than 46 ml/kg/min at 48 h. Low systemic blood flow was found to be common in preterm infants, with over a third having at least one measurement below the established thresholds. Low SVC flow was commonly associated with low gestational age, high systemic vascular resistance, PDA, mechanical ventilation, and a high mean airway pressure. The limitation of blood pressure as a measure of systemic blood flow are further emphasized by the weak correlation between mean blood pressure (BP) and SVC flow. Furthermore, low systemic blood flow assessed by SVC flow is independently associated with late intraventricular hemorrhage (IVH) which occurs as flow improves. This may be explained by fragility of cerebral blood vessels upon exposure to prolonged periods of ischemia with loss of cerebral autoregulation and secondary reperfusion intracranial hemorrhage. Neurodevelopmental outcome at 3 years has also shown to be adversely influenced by early low SVC flow states. This method has been superior to middle cerebral artery flow velocity measurements in predicting neurological outcome.

Although SVC flow measurement is useful, caution should be exercised regarding its everyday applicability to neonatal intensive care. SVC venous return reflects blood supply to the brain and upper body and therefore no information regarding blood supply to the liver,

kidney, and gut can be derived. SVC return may not be reflective of inferior vena cava (IVC) return especially when a PDA is present as the carotid arteries arise preductally and are therefore not subjected to diastolic steal in the presence of a large left-to-right shunt. Secondly, cerebral blood flow is subjected to intrinsic autoregulatory mechanisms (see below) that may directly alter SVC flow, independent of myocardial performance. Thirdly, SVC flow estimation relies on measurement of the diameter of the vessel as it enters the right atrium. The latter is subject to a high degree of operator-dependent variability, particularly in the setting of lung hyperinflation, which may compromise its reliability.

Cerebral Blood Flow and Autoregulation

Cerebral blood flow is important in determining oxygen delivery to the brain. It is determined by perfusion pressure, systemic blood flow, and resistance in the cerebral circulation. Cerebral autoregulation is an intrinsic mechanism which ensures constant cerebral blood flow in the setting of varying blood pressure, flow, and resistance. Unfortunately, studies examining the relationship between cerebral blood flow and mean blood pressure are conflicting. Cerebral autoregulation appears functional in normotensive preterm infants with mean BP above 30 mmH with a suggestion that sick neonates (particularly neonates with IVH) lose the autoregulation mechanism resulting in passive circulation independent of pressure and resistance making brain tissue more vulnerable to fluctuations in blood pressure and hypotension. On the contrary, there is alternative evidence documenting a lack of change in cerebral perfusion across a wide range of mean blood pressures (23–40 mmHg). This is further complicated by the observation that cerebral fractional oxygen excretion is unaffected by hypotension but inversely proportional to left ventricular output. This supports the concept of left ventricular output being the major determinant of cerebral blood flow.

Clinical Assessment of the Adequacy of the Preterm Circulation

The determination of an adequate circulation cannot be made on the basis of any one variable. It is a composite appraisal of clinical indices such as arterial pressure, heart rate, urinary output, laboratory parameters such as arterial pH, lactate and plasma troponin, and echocardiography markers such as cardiac output or SVC flow, which reflect the adequacy of tissue oxygenation. The value of these parameters is likely to be best when used in combination and longitudinally to document trends or response to therapeutic intervention. Therapeutic decisions should not be made on the basis of any one parameter. In addition, the decision to intervene is likely to depend on the underlying disease process.

Arterial Pressure Measurement

There are no set criteria to define true hypotension in neonates. Studies correlating blood pressure with tissue perfusion are lacking. Furthermore, as explained earlier, systemic resistance is an important determinant of systemic blood flow. Therefore, treatment remains a dilemma with many physicians still relying on blood pressure alone to guide management as it is the most readily available measure of cardiovascular performance. In general, there are two definitions of hypotension in widespread use. The first is based on data stating that a mean BP < 30 mmHg is associated with cerebral injury (with white matter damage and IVH) and a reduction in cerebral blood flow measured by spectroscopy. The second definition uses the gestational age as a guide for the cutoff for treatment. Little attention is paid to blood pressure components such as the systolic and diastolic arterial pressures, when adjudicating circulatory stability or selecting a cardiovascular intervention. Normative population-based data for systolic arterial pressure are available, but rarely used in practice. Systolic arterial pressure is a useful surrogate of the adequacy of cardiac output whereas diastolic arterial pressure reflects preload and systemic vascular resistance. The nature of low mean arterial pressure, whether it reflects systolic or diastolic pressure compromise, is likely to be helpful in better selection of cardiovascular treatments.

Heart Rate

A heart rate greater than 160 can be a physiological response to hypovolemia. However, there are several other causes of tachycardia in the neonate. This includes pain, sepsis and fever, hyperthyroidism, catecholamine excess, drugs (caffeine), hypoglycaemia, anemia, and neonatal arrhythmias.

Capillary Refill Time

A capillary refill of >5 s correlates weakly with low flow states. In addition, cool extremities, acrocyanosis, and pallor are all early signs of peripheral vasoconstriction and redirecting of blood to vital organs.

Laboratory Markers

Surrogate markers of poor systemic perfusion in neonates include a rising lactate, reduced urine output, and a rising urea and creatinine.

Cardiac Output Measurement

In pediatric and adult intensive care units, catheter-derived measurements of cardiac output give a quick and continuous monitoring of systemic blood flow. In neonatal intensive care, pulmonary artery catheterization of preterm infants is not feasible. Doppler-derived measurements of cardiac output are possible and have been validated. The normal range for preterm neonates, as reported in the literature, is between 150 and 300 ml/kg/min per ventricle. Evaluation of cardiac output requires comprehensive echocardiography skills but these may be acquired by the neonatologist after a period of sufficient training. It should be recognized that these calculations may be inaccurate in the presence of intra- and extracardiac shunts.

Causes of Hypotension in the Newborn

There are many causes of neonatal hypotension and shock. Therapy must be specifically directed at the underlying cause. It should be noted that hypovolemia is not a common cause of hypotension and shock in the preterm neonate soon after birth, but more common later:

1. Cardiogenic shock
   (a) Asphyxia
   (b) Arrhythmia
   (c) Congenital heart disease
   (d) Cardiomyopathy and myocarditis
2. Impedance of venous return
   (a) Pneumothorax
   (b) High intrathoracic pressure secondary to positive pressure ventilation
3. Sepsis and septic shock
4. Hemodynamically significant patent ductus arteriosus
5. Large systemic A-V malformation
6. Drug induced: opiates, vasodilator drugs, for example, milrinone
7. Adrenal insufficiency
   (a) Extreme prematurity
   (b) Adrenogenital syndromes
   (c) Adrenal hemorrhage
8. Hypovolemia
   (a) Placental blood loss
   (b) Feto-maternal hemorrhage
   (c) Twin–twin transfusion
   (d) Birth trauma
   (e) Ruptures spleen/liver
   (f) Disseminated intravascular coagulation

Treatment of Preterm Circulatory Compromise

Despite the high prevalence of hypoperfusion states, the treatment remains controversial. Treatment of low blood pressure does not necessarily translate into an improvement in systemic blood flow as many cardiotropic agents, for example, high-dose dopamine act by increasing systemic vascular resistance but at the expense of cardiac output which falls. The use of regimented protocols, which usually recommend the use of volume administration followed by dopamine, dobutamine, and epinephrine, should be avoided. This approach does not take into account the maturity of the infant, the underlying cause, the presumed physiology or other potential iatrogenic influences on systemic blood flow including other medication, mechanical ventilation in the presence of a PDA. There is limited evidence supporting the use of current therapeutic agents. However, understanding the mechanisms of action of the various available agents will aid in their selection to address the various situations. The ultimate goal of treatment is to maintain adequate oxygen delivery and tissue oxygenation to ensure normal cellular metabolism. Other factors influencing the adequacy of cellular oxygen delivery include hemoglobin, oxygen saturation, as well as factors influencing myocardial performance. Oxygen consumption should also be minimized by ensuring adequate sedation if necessary, pain control, and normothermia (*Fig. 23.2*).

Volume Expansion

The benefit of using crystalloids or colloids to treat hypotension has not been established. In hypotensive normovolemic neonates, volume expanders generally do not improve arterial pressure. They do however increase left ventricular output in the short term. There are no studies examining whether this rise is maintained beyond the immediate period. Liberal administration of fluid is not recommended as there are no data to suggest benefit. Indeed, some data suggest a detrimental effect in preterm

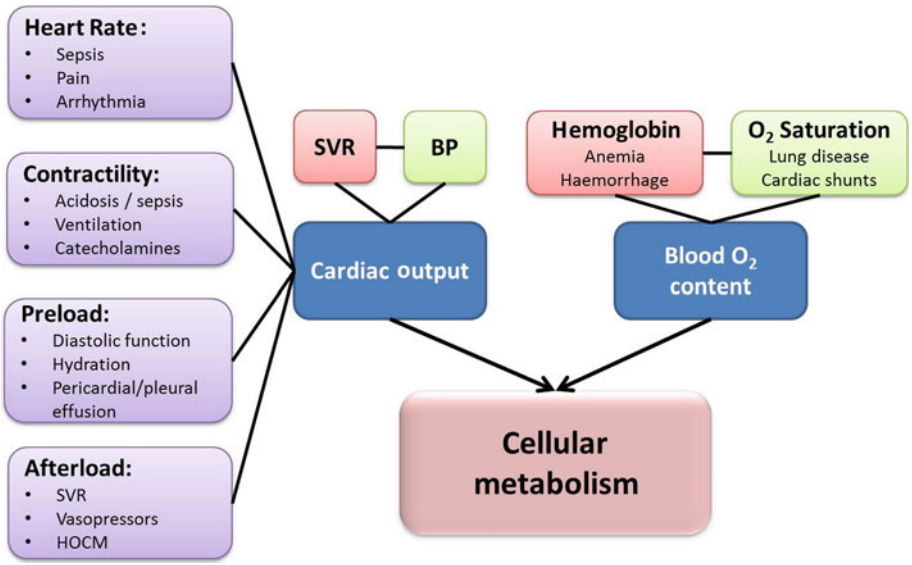


Figure 23.2
***Factors affecting cellular metabolism, cardiac output and blood oxygen content*. See text for details**

neonates with a higher incidence of PDA, necrotizing enterocolitis (NEC) and death. This may be due to the inability of the premature myocardium to cope with the extra preload, which may lead to increased heart rate. In addition, volume loading of asphyxiated babies with a damaged myocardium may cause ventricular wall stress and circulatory compromise. The use of volume expanders in hypovolemic neonates may be beneficial as it restores intravascular volume; however, this has not been adequately studied. The subpopulation of neonates with high insensible losses or transepithelial losses such as gastroschisis, malabsorptive syndromes are likely to benefit from increased fluid administration. The presence of sepsis, capillary leak, or unrecognized perinatal blood loss must however be considered as potential causes of hypovolemia. Clinical assessment of intravascular volume status is difficult. Targeted neonatal echocardiography can be helpful in assessing ventricular filling when doubt exists regarding intravascular volume status.

Hypotension and Inotropes

Arterial pressure thresholds, which commonly form the basis for treatment, are not based on systemic blood flow. As highlighted earlier, the assumption that pressure and flow are proportionate is not true. Future studies need to examine the effect of inotropes on systemic blood flow. A Cochrane review of literature on dopamine versus dobutamine showed that dopamine was more reliable in increasing arterial pressure. *Dopamine* is a synthetic amine and is the most commonly used vasoactive agent. It has mixed β1 and α-adrenergic effects depending on the dose. There is some evidence of improved left ventricular performance at levels of 2.5 μg/kg/min. Vasoconstricting effects can occur at levels as low as 6 μg/kg/min leading to increased systemic vascular resistance (SVR) and potentially reducing cardiac output and organ perfusion. *Epinephrine* is an endogenous catecholamine with β1 effects at low doses and α-adrenergic effects at levels of 0.3 μg/kg/min. It is an effective vasopressor and is usually reserved as a rescue agent but may be beneficial in cases of septic shock and NEC. Prolonged treatment may be associated with myocardial ischemia and dysfunction. Epinephrine is equally effective as dopamine in increasing arterial pressure but no data exist regarding its effects on systemic blood flow, intraventricular hemorrhage, or neurodevelopmental outcome. *Dobutamine* acts by improving left ventricular output and systemic blood flow with a marginal increase in arterial pressure; it may in fact reduce systemic vascular resistance. It has predominant β1 effect with marginal effects on systemic vascular resistance. High doses, however, may lead to hypotension through its action on vascular β receptors. *Milrinone* is a phosphodiesterase III inhibitor that acts through increasing the bioavailability of cyclic adenosine monophosphate (cAMP). It is a systemic and pulmonary vasodilator with positive inotropic and lusitropic

properties. It is used in infants following cardiac surgery to prevent low cardiac output syndrome and reduce mortality. There is also evidence of benefit in neonates with pulmonary hypertension. In addition, it has been used in preterm infants following PDA ligation to prevent low cardiac output states and subsequent clinical and respiratory deterioration. *Vasopressin* use in preterm and term infants with refractory hypotension is gaining interest. It is a nine-amino acid structure synthesized in the pituitary, commonly known as the antidiuretic hormone. Its acts via V1 receptors leading to systemic vasoconstriction through phospholipid-mediated calcium release and pulmonary vasodilatation through modulation of nitric oxide release. It may be beneficial in infants not responding to conventional inotropes and/or hydrocortisone, or in infants with pulmonary hypertension. It must be used with caution, however, as evidence of safety is lacking; in some patients it may cause oliguria and renal failure or liver necrosis secondary to compromised splanchnic perfusion. Infants with septic shock, high cardiac output, and low diastolic arterial pressure are likely to benefit from a vasopressor, for example, dopamine, vasopressin. Conversely, infants with cardiogenic shock, low cardiac output, and low systolic arterial pressure may benefit from and inodilator agent, for example, milrinone (◉ *Table 23.1*).

Corticosteroids

A small proportion of preterm neonates may suffer from a relative adrenal insufficiency leading to a poor response to stress, which may manifest as refractive hypotension. Steroid administration to these neonates can improve arterial pressure and reduce the need for inotropes. Their use has been associated with NEC and intestinal perforation, especially when combined with indomethacin. Prophylactic administration of hydrocortisone cannot be recommended in the first days of life due to the potential harmful side effects.

Role of Targeted Neonatal Echocardiography (TnECHO) in Guiding Therapy

The lack of a reliable measure of systemic blood flow as highlighted in this section is one example of a clinical situation which has prompted neonatologists to perform echocardiographic examinations. Clinical signs such as heart rate, blood pressure, and capillary refill time, which traditionally physicians have relied upon, provide limited insight into the adequacy of systemic blood flow and organ perfusion. Targeted neonatal echocardiography (TnECHO) is increasingly used by neonatologists in the intensive care setting to support clinical decisions. It provides hemodynamic information, which may provide novel insights regarding actual physiology and nature of cardiovascular disease. The technology may be applied to evaluation of cardiac output and systemic blood flow. The provision of real-time information on cardiovascular performance and systemic hemodynamics, the noninvasive nature of the technique, the rapidity of data acquisition, and ability to perform longitudinal functional assessments have all contributed to the increased utilization of functional echocardiography by neonatologists in the neonatal intensive care.

Summary

Premature infants, in the immediate transitional period, are at increased risk of cardiovascular compromise manifested as low systemic blood flow or hypotension, which relates to afterload stressors; therefore, dobutamine may be the best first line option as it reduces SVR and improves cardiac output. Dopamine or epinephrine in high doses should be avoided as these vasoactive agents act by increasing SVR which imposes an additional afterload stress on the preterm myocardium leading to reduced blood flow. Measures of blood flow, in addition to blood pressure, should be used to assess treatment success. If mean or diastolic arterial pressure is very low (there are no definitive cutoffs), then dopamine or adrenaline may be used. A hemodynamically significant ductus arteriosus should also be considered in early hypotension, as vasoactive agents may increase the volume of the ductal shunt. Volume expansion is indicated when there is clear evidence of hypovolemia, for example, hemorrhage, capillary leak, gastroschisis, and dehydration. Functional hypovolemia induced by high intrathoracic pressure requires volume expansion to allow adequate ventricular filling. There is no evidence that routine volume augments cardiac output. Crystalloid fluid is as effective as colloid in volume expansion, but hypotonic fluids, such as dextrose solutions, should not be used for volume expansion.

In persistent pulmonary hypertension of the newborn, inhaled nitric oxide reduces right ventricular (RV) afterload leading to enhanced right ventricular performance, improves ventilation–perfusion matching, and increases left heart preload. The net effect is improved systemic blood flow. Dopamine is not recommended in

Table 23.1
Drug used in the cardiovascular support of the neonate

Agent	Dose	Mechanism of action	Indications	Clinical considerations
Inodilator agents				
Dobutamine	5–20 [μ]g/kg/min	β: Increased myocardial contractility and SBF. Higher doses lead to a fall in SVR and PVR	Low CO states including early preterm transitional period, asphyxia, PPHN, and in low SBF stated such as PDA	Dobutamine is effective at improving SBF. BP may not improve. Monitor response clinically (blood gas, urine output, etc.) and TnECHO
Milrinone	0.75 [μ]g/kg/min loading dose over 30 min 0.33–0.99 [μ]g/kg/min maintenance dose	Phosphodiesterase III inhibitor. Increases availability of cAMP. Leads to improved contractility, and a fall in SVR/PVR. Net effect is increased SBF	Low CO states in early transitional period, infants with PPHN, post PDA Ligation to reduce the risk of post ligation low cardiac output syndrome	May result in a fall in BP. Volume support could be used in conjunction with milrinone. No long term data available
Vasopressor agents				
Dopamine	2–10 [μ]g/kg/min	β: Increases contractility at low doses (2.5 [μ]g/kg/min) α: At doses of >6 [μ]g/kg/min leading to increased SVR/PVR. Vasoconstircting effects have been reported at doses <6 [μ]g/kg/min	Septic shock, refractory hypotension in the setting of adequate myocardial performance. Can be used in conjunction with dobutamine in low CO/low BP states	Higher doses have a negative effect on systemic blood flow and may compromise contractility due to increased afterload. Should be avoided in infants with PPHN and after PDA ligation. Dopaminergic effects on renal blood flow have not been established in neonates
Epinephrine	0.05–0.5 [μ]g/kg/min	β: Increases contractility at low doses (<0.3 [μ]g/kg/min). Will have α effects as well. May improve SBF α: At doses of >0.3 [μ]g/kg/min leading to increased SVR/PVR with a negative effect on SBF	Consider as a rescue therapy or in cases of septic shock. Can be used in conjunction with dobutamine in low CO/low BP states	High doses may lead to myocardial ischemia due to increased oxygen demand. May lead to profound increase in systemic and pulmonary vascular resistance. Should be avoided in PPHN
Vasopressin	0.0001–0.002 units/kg/min	V1: Increase SVR and decrease PVR. No effect on contractility. May reduce splanchnic circulation	Refractory hypotension. PPHN no responding to NO (experimental). Cardiovascular copromise secondary to ventricular hypertrophy states, e.g., infant of diabetic mother, cardiomyopathy	Use not established in clinical practise but promising observational data in neonates with PPHN

SBF systemic blood flow, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance, *BP* blood pressure, *CO* cardiac output, α alpha adrenergic receptors, β beta adrenergic receptors, *PPHN* persistent pulmonary hypertension of the newborn, *TnECHO* targeted neonatal echocardiography

persistent pulmonary hypertension of the newborn (PPHN) due to its potent vasoconstricting effects, particularly in the setting of a hypoxic inflammatory environment. Dobutamine is a more desirable agent in this setting due its vasodilator properties and ability to enhance right ventricular performance. Epinephrine has been shown to increase pulmonary vascular resistance (PVR) and SVR equally, in both animal and human studies. In inotropes-refractory cases, intravenous steroids should be considered.

Patent Ductus Arteriosus in the Preterm Infant

Introduction

The diagnosis and management of a patent ductus arteriosus (PDA) in preterm neonates poses a major challenge. It is the most common cardiovascular abnormality of prematurity occurring in about a third of infants below 30 weeks gestation and up to 60% of infants less than 28 weeks. There is little consensus to guide management, and treatment policies vary among centers depending on the expertise, presence of on-site echocardiography, and ease of access to a surgical center. Timing of treatment remains controversial as there is no clear long-term benefit to prophylactic and early treatment based on clinical and conventional echocardiographic parameters.

Physiology and Pathophysiology of the Ductus Arteriosus

The ductus arteriosus (DA) connects the main pulmonary artery to the descending aorta and is necessary for fetal survival. In the fetus, the left ventricle delivers oxygenated blood returning from the placenta and shunting through the foramen ovale to vital organs. The right ventricle delivers deoxygenated blood returning from the SVC via the ductus arteriosus to the placenta as the lungs are bypassed. Following birth, as the lungs expand and become the oxygen-exchange organ, the DA is no longer needed and it normally closes.

Ductus arteriosus patency and closure is influenced by a multitude of factors. In utero, low systemic oxygen tension and elevated circulating prostaglandins are important in maintaining ductal patency. Functional closure of the ductus arteriosus begins within a few hours after birth and is usually complete by a week of age in preterm infants. This is partly due to the increase in oxygen tension and the falling prostaglandin levels postnatally. Anatomical closure is achieved due to hypoxia-ischemia in ductal tissue resulting in cell apoptosis leading to the transformation of ductal tissue to a non-contractile element.

Prostaglandin E_2 is the most important factor in the regulation of DA tone during fetal development. It is generated through the actions of cyclo-oxygenase 1 and 2 (COX 1 and 2) on arachidonic acid. Animal models demonstrate that COX-2 expression plays a major role in maintaining fetal DA but the emphasis is switched to COX-1 after birth. The inhibition of COX-1 leads to reduced PGE_2 levels and ductal constriction. The low oxygen tension in the fetus is important to maintain ductal patency. After birth, increased oxygen tension leads to ductal closure. This oxygen-mediated constriction is facilitated by a mechanism intrinsic to the DA. Potassium voltage channels (Kv Channels) present on the ductal smooth muscle cells function to keep the cells in a hyperpolarized state. The presence of oxygen leads to depolarization which in turn activates L-type calcium channels allowing an influx of calcium into the smooth muscle cells causing constriction. Levels of inflammatory mediators, namely, TNF-α and prostaglandins, are elevated in the presence of infection associated with late ductal opening. Therefore, late-onset sepsis may be an important contributing factor to ductal reopening, especially when anatomical closure is not achieved in preterm infants. Once functional DA closure is achieved, the smooth muscle cells migrate from the media to the subendothelial layer. This results in an interruption of the vasa vasorum blood supply to the innermost layer resulting in hypoxia and cell death. In term infants, the DA wall thickness exceeds the distance which allows nutrients to travel by passive diffusion (500 μm). In premature infants, tissue hypoxia may not occur as the inner layers may effectively be supplied by blood flow through the ductal lumen rendering these cells resistant to local hypoxia thereby delaying anatomical ductal closure and predisposing the duct to reopening.

Hemodynamic and Clinical Effects of a PDA

Pulmonary Effects of a PDA

Left-to-right shunting across the PDA leads to important hemodynamic changes. As pulmonary arterial resistance falls, the degree of shunting across the duct becomes more significant leading to increased pulmonary blood flow and compromised systemic blood flow. The nature of the volume of the transductal shunt is dependent on the size of the vessel and transductal pressure differential. A ductal diameter greater than 1.6 mm is associated with high pulmonary blood flow and increased incidence of pulmonary hemorrhage (hemorrhagic pulmonary edema). Increased pulmonary flow may contribute to increased oxygen dependency and pulmonary edema. The presence of a PDA has been shown to be a risk factor for chronic lung disease (CLD) due to altered pulmonary mechanics and arrested alveolar development. Pulmonary vasculature overload may also lead to pulmonary hemorrhage and eventually the development pulmonary vascular disease.

Cardiovascular and Systemic Effects of PDA

One of the consequences of a high order of magnitude left-right transducal shunt is increased left ventricular output (LVO) secondary to increased pulmonary venous return and augmented left ventricular (LV) systolic performance. This increase in cardiac output does not translate into improved systemic perfusion, as the left-to-right shunt continues to short-circuit blood flow back into the lungs. The net effect is higher LVO, increased pulmonary blood flow, but lower systemic blood flow. In addition, increased left heart preload leads to left atrial dilatation, stretching of the foramen ovale, increased left-right trans-atrial flow, and increased left ventricular diameter reflecting volume loading of the heart.

Shunting from the systemic to the pulmonary circulations is referred to as ductal steal and results in systemic hypoperfusion (*Fig. 23.3*). The clinical consequences include hypotension, oliguria, abdominal distension, and metabolic acidosis. Although systolic, diastolic, and mean arterial pressure may fall in the most immature patients, systolic pressure may be maintained in older or more mature patients through augmentation of cardiac output. A hemodynamically significant PDA is associated with lower blood flow volumes in the abdominal aorta with retrograde flow in diastole reflecting a severe shunt leading to diastolic steal. In addition, compromised arterial flow, predominantly during diastole, to the celiac, superior mesenteric, renal, and cerebral arteries despite a rising LVO may indicate a decompensated state. These biological effects support the association between PDA and NEC, renal dysfunction, and IVH.

Diagnosis of a PDA

Clinical Diagnosis

Prior to the advent of routine echocardiography, the diagnosis of a PDA was reliant on the evolution of clinical signs including: a pansystolic, or a continuous systolic/diastolic (machinery-like) murmur, increased precordial activity, and bounding peripheral pulses. In some patients, a difference of greater than 20 mmHg between the systolic and diastolic arterial pressure may also occur, as described earlier. Bounding pulses and a murmur

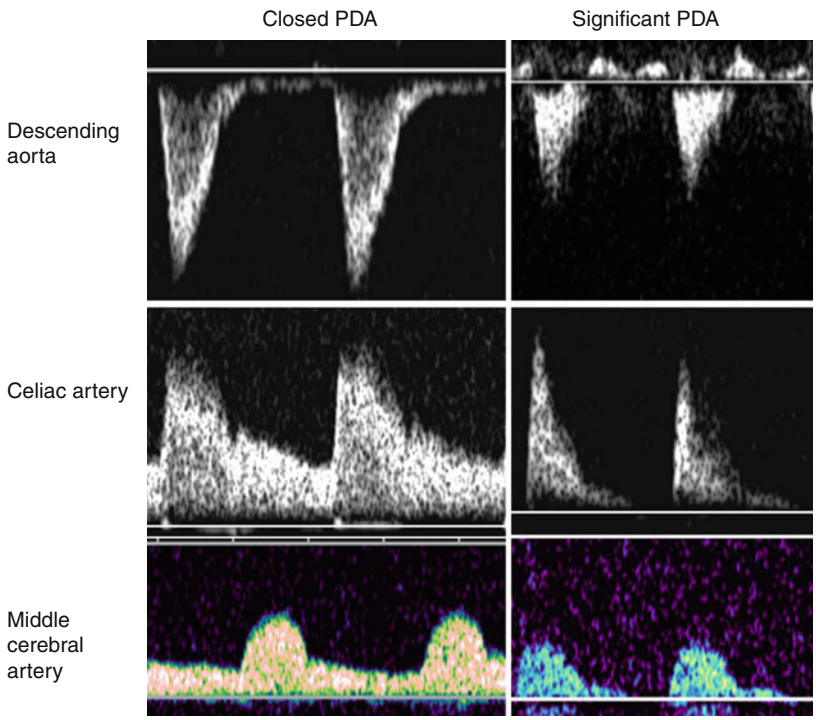


Figure 23.3
***The effect of a significant PDA on systemic blood flow*. Note the reduced systolic velocity and absent or reversed diastolic flow in all three blood vessels**

may be absent in up to 20% of infants with a PDA. Chest radiograph finding include increased pulmonary vascular markings, pulmonary edema, a large cardiac silhouette, and a splayed carina due to a large left atrium moving the left main bronchus superiorly. The development of a significant PDA by echocardiography precedes the development of clinical signs by a mean of 2 days. Correlation between physical signs and the presence of a PDA by echo in the first week of life is poor. Therefore, Doppler echocardiography remains the gold standard for PDA diagnosis.

Echocardiographic Assessment of PDA

In most centers, the adjudication of hemodynamic significance is made on the basis of a 2D or color Doppler measurement of the internal ductal diameter (*Fig. 23.4*). The rationale is that a diameter greater than 1.5 mm is predictive of persistence of the ductus arteriosus. The value of a single point estimate of transductal diameter is questionable as it does not consider architectural variability of the ductus arteriosus, temporal changes in ductal size, or provide any information about the magnitude of the ductal shunt. The traditional focus on transductal diameter has contributed to consideration of the ductus arteriosus as a binary variable or "all or none phenomenon." The determinants of transductal flow are the size of the vessel and the transductal pressure differential. Although the volume of the transductal shunt may not be quantified by conventional echocardiography, the physiologic or hemodynamic effects on pulmonary and systemic blood flow caused by left-to-right shunting can be demonstrated by various echocardiographic measures (*Table 23.2*). Left atrial to aortic ratio (LA:Ao) uses the fixed diameter of the aorta to assess the degree of left atrial volume loading. LA:Ao ratio correlates significantly with increased pulmonary flow due to a duct, and optimal cutoff point is $\geq$1.4 to predict a significant PDA. Furthermore, diastolic blood flow velocity in the left pulmonary artery is also a useful indicator of ductal significance with a high-end diastolic velocity representing a large left-to-right shunt and increased pulmonary perfusion. Turbulent pulmonary arterial flow at the level of the pulmonary valve also implies a more significant shunt. Left ventricular output usually rises in the presence of a patent ductus. Transmitral Doppler flow measurement may be a useful marker of left atrial pressure/volume loading. A phenomenon referred to as pseudo-normalization of the Doppler pattern is seen in infants with a significant PDA.

A hemodynamically significant PDA is associated with lower blood flow volumes in the abdominal aorta and lower mean blood flow velocities in the celiac, superior mesenteric, and renal arteries despite a rising LVO. Superior vena cava (SVC) flow measurement has been recently described and advocated as a marker of systemic blood flow. The effect of a PDA on the systemic circulation may be quantified by comparing LVO to superior vena caval flow (LVO: SVC). Infants without a PDA have an LVO: SVC of 2.4 (SVC return account for 40% of LVO). In the presence of a significant PDA, LVO: SVC increases to 4.5 (SVC return accounts for 22% of LVO) indicating a compromised upper body circulation. Low SVC return is associated with an increased incidence of late IVH and may be one factor in the causal pathway of impaired preterm neurodevelopmental outcome. Comparing celiac artery blood flow to LVO may give an accurate quantitative measure of the degree of ductal steal and lower systemic body flow. Volumetric analysis of celiac artery flow (CAF) shows that it receives approximately 20% of LVO at 12 h of life regardless of the presence of a PDA. In other words, the ratio of celiac artery blood flow to left ventricular output (CAF: LVO) is 0.2. The lack of influence of a PDA and its diameter on the flow parameters and CAF: LVO at the 12 h may demonstrate the lack of a significant pressure gradient between the systemic and pulmonary circulations during the early transitional period. Flow across the PDA at this stage may not be hemodynamically significant. At 48 h, the pulmonary artery pressure drops and shunting across

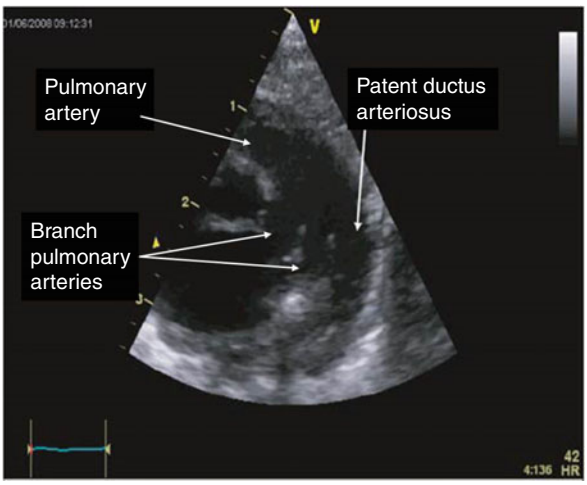


Figure 23.4
Echocardiographic image of the PDA

Table 23.2
Echocardiographic markers of ductal significance

Measurement	Modality and sample gate	Moderate PDA	Large PDA
Ductus arteriosus			
Diameter (mm)	High parasternal ductal view	1.5–3.0	>3.0
Ductal velocity (m/s)	PWD at ductal view (PA)	1.5–2.0	<1.5
PA diastolic flow (m/s)	PWD at left PA	0.3–0.5	>0.5
Pulmonary overcirculation			
LA: Ao ratio	M-mode: long axis view	1.5–1.8	>1.8
E wave to A wave ratio	Doppler: transmitral view	0.8–1.2	>1.2
IVRT (ms)	PWD between MV and AV	35–45	<35
Systemic hypoperfusion			
Left ventricular output (ml/kg/min)	PWD at LV outflow tract	300–400	>400
Diastolic descending Ao flow (%)	PWD at beyond PDA	30–50	>50
LVO/SVC ratio	PWD of flow at SVC	<2.4	>2.4
Celiac artery flow: LVO ratio	PWD at celiac artery	0.10–0.15	<0.10
Celiac, renal or middle cerebral diastolic flow		Absent	Reversed

See text for abbreviations and details

the PDA increases. As a result, the celiac artery receives proportionately less of the LVO in infants with a PDA compared to infants with spontaneous ductal closure at 48 h (11% vs 19%) showing a reduction in systemic perfusion.

The Use of Biomarkers in the Diagnosis of PDA

B-type natriuretic peptide (BNP) is a 32-amino acid ring structure. The ventricles of the heart are the main site of BNP synthesis and release in response to volume loading, pressure loading, and ventricular stress. BNP causes diuresis, natriuresis, arterial and venous vasodilatation, and antagonizes the renin-angiotensin system. The net effect is a reduction of intravascular volume, ventricular preload, and afterload. N-terminal-Pro-BNP (NTpBNP) is the inactive by-product of BNP resulting from the cleavage of the parent peptide Pro-BNP. In the presence of a PDA, BNP and NTpBNP levels rise significantly and fall following treatment. They may be used as screening tools for the presence of a PDA and in monitoring treatment response, though their value and reliability is not yet clearly established.

Cardiac troponin T (cTnT) is another useful marker of DA significance and associated myocardial ischemia secondary to diastolic steal. cTnT is significantly higher in infants with hemodynamically significant PDA compared to controls in a study of 80 preterm infants. cTnT levels also correlated significantly with echocardiographic markers of PDA significance. Following successful treatment of the PDA group, cTnT fell significantly to levels comparable to the control group. McNamara et al. have proposed that ductal steal due to left-to-right shunting may also affect coronary arteries leading to myocardial ischemia and a resultant rise in cTnT. cTnT may identify infants at risk of PDA-associated myocardial ischemia and therefore warrant PDA treatment. The associated fall in cTnT levels following successful PDA closure may reflect the resolution of ductal steal from the coronary arteries.

Targeted Treatment of PDA: The Use of Echocardiography and Biochemical Markers

Conventional echocardiographic markers such as ductal diameter and left atrial to aortic ratio (LA:Ao) applied at 48 h of life do not predict outcome associated with a PDA. In addition, treatment based on these parameters has not led to improved neurodevelopmental outcome at 2 years in preterm infants. Biochemical markers may prove to be a useful adjunct to a recent clinical and echocardiographic

PDA staging system proposed by McNamara et al. Medical therapy for PDA has well-recognized adverse effects and neither prophylaxis nor treatment on the basis of clinical and echocardiographic signs has been shown to improve long-term outcomes. Accurately identifying infants with PDA who are at highest risk of poor outcome using biomarkers may allow more successful trials of targeted medical therapy of PDA.

Management of the Preterm PDA

Once a PDA is diagnosed, the clinician faces multiple management challenges including whether or not to treat, and the timing and method of treatment. Nonsteroidal anti-inflammatory drugs are the first-line medical treatment. Indomethacin and more recently ibuprofen are used in prophylactic and early treatment of a PDA. Ibuprofen does not appear to confer a net benefit over indomethacin for the effective treatment of a PDA. However, ibuprofen reduces the risk of oliguria but may increase the risk for CLD and pulmonary hypertension. Surgical ligation of a PDA is usually only undertaken following failure of medical treatment as there is no evidence it confers any benefit over medical treatment when used as first-line therapy.

Conservative Management of a PDA

Most centers implement systematic treatment of a PDA using medical therapy. However, controversy still exists about the optimal timing for starting treatment. The ductus arteriosus will close in 40–60% of preterm infants spontaneously by 48 h of life. Conservative PDA management has been advocated as an alternative or an interim measure. In addition, there is concern in infants with NEC or severe IVH, that instituting medical therapy with nonsteroidal anti-inflammatory drugs (NSAIDS) may exacerbate the preexisting conditions due to their antiplatelet and vasoconstrictive properties. Little attention has been paid to strategies that may modulate transductal flow by controlling pulmonary or systemic vascular resistance. These include permissive hypercapnia, judicious use of oxygen, and avoidance of high arterial PaO_2, increasing the positive end-expiratory pressure (PEEP) on the ventilator, and avoidance of vasopressor drugs, for example, dopamine which may increase systemic vascular resistance (*Fig. 23.5*). Cardiotropic agents such as dobutamine are preferable in the setting of circulatory compromise by nature of its ability to augment cardiac output with negligible effects on vascular resistance. Severe fluid restriction and diuretic use are not

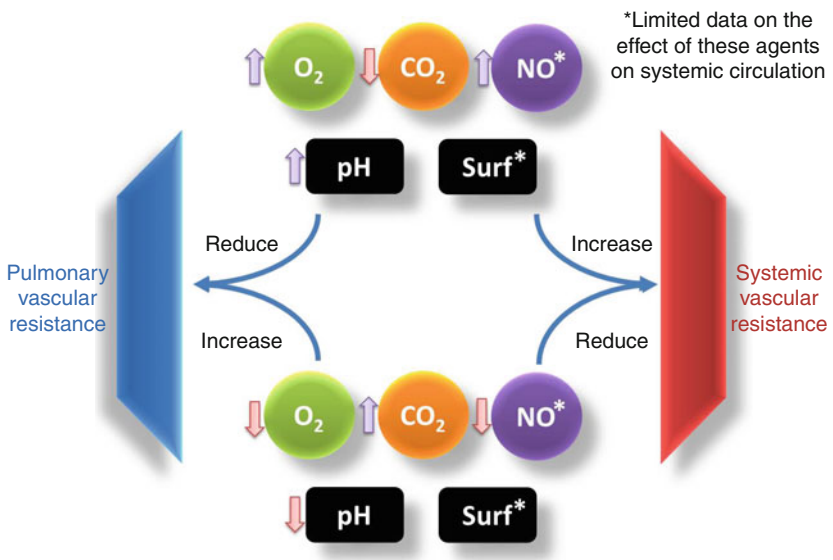


Figure 23.5

***Biological effects of vasoactive mediators on the systemic and pulmonary circulations*. O_2: oxygen; CO_2: carbon dioxide; NO: nitric oxide, Surf: surfactant**

recommended as they may lead to further compromise of systemic blood flow, electrolyte derangement, and impaired growth. In addition, the promoting effect of frusemide (furosemide) on renal prostaglandin production is counterintuitive.

Medical Treatment of a PDA

Indomethacin has been the mainstay of medical PDA treatment to date and successfully closes around 90% of PDAs. Indomethacin is a nonspecific prostaglandin inhibitor and therefore causes ductal closure by reducing prostaglandin levels. This effect, however, is also responsible for the range of well-recognized side effects including oliguria, hyponatraemia, reduction in systemic blood flow, gastrointestinal bleeding, and decreased splanchnic perfusion potentially leading to NEC and perforation. Ibuprofen is another NSAID with similar antiprostaglandin properties to indomethacin and has recently emerged as an alternative agent. It is a nonselective COX inhibitor which causes a reduction in circulating prostaglandin levels. Compared to indomethacin, ibuprofen does not significantly reduce mesenteric and renal blood flow velocity in a study of 17 preterm infants. It also causes less cerebral blood flow disturbances.

Prophylactic Treatment of a PDA

The optimal timing of PDA treatment remains controversial. The Trial of Indomethacin Prophylaxis in Preterms (TIPP) randomized 1202 ELBW infants to receive either placebo or prophylactic indomethacin soon after birth. There was no difference in death, or a composite of death and cognitive delay, cerebral palsy, blindness, or hearing impairment between the treatment and placebo group. The prophylactic use of indomethacin reduced the incidence of grades III/IV IVH (from 13% to 9%, $p = 0.02$), the incidence of PDA (from 50% to 24%, $p < 0.001$), the need for later closure with indomethacin (from 46% to 17%, $p < 0.001$), and the need for surgical ligation (from 12% to 7%, $p = 0.001$). There was no difference in the incidence of NEC or pulmonary hemorrhages between the groups. In addition, outcome at 2 years was not affected by prophylactic treatment. Further review of the TIPP data shows that prophylactic indomethacin increased oxygen dependency in the first 7 days of life and increased the incidence of CLD among infants who did not develop a PDA but received indomethacin (43% vs 30%, $p = 0.015$) . It was postulated that this was a result of the drug's oliguric properties leading to pulmonary edema. Adult studies show that indomethacin augments lung inflammation and fibrosis by increasing elastase activity and fibronectin concentration.

A recent Cochrane review of four trials comparing prophylactic ibuprofen to placebo found it effective in reducing the incidence of PDA on day 3, reducing the need for rescue treatment and the need for surgical ligation. There was no difference in ventilator dependence, urine output, IVH of any grade, periventricular leukomalacia (PVL), CLD, NEC, or other gastrointestinal complications, or duration of hospital stay. There are no trials comparing prophylactic ibuprofen versus indomethacin. There is some evidence suggesting that prophylactic use of ibuprofen may precipitate pulmonary hypertension. Giving ibuprofen early probably prevented the natural decrease of pulmonary vascular resistance as prostaglandins play a role in regulating pulmonary vasculature in the first hours of life. Secondly, micro-emboli due to ibuprofen precipitation may have explained this phenomenon. The preparation used by this group was ibuprofen–tromethamine but most other groups use L-lysine ibuprofen. Recently, a case report of severe pulmonary hypertension following administration of L-lysine ibuprofen on day 3 of life to a premature infant of 32 weeks gestation was reported.

Early Treatment of PDA

There is no difference in mortality or other outcomes such as NEC or CLD when an echo-patent duct was treated at day 3 of life, although there was less need for later PDA treatment. This possibly indicates that treatment on day 3 may be too late. These studies however are limited by the early introduction of backup treatment soon after initial randomization, and therefore conservative versus active treatment was not adequately tested. In the TIPP trial, all PDAs were either medically or surgically treated by day 5. The lack of changes on outcome may relate to the homogenization of the problem and lack of consideration of variability of ductal effect. Attribution of hemodynamic significance based on a single-point estimate of ductal diameter, without consideration of its systemic and pulmonary effects, is a hemodynamic oversimplification which may lead to incorrect treatment choices. A better definition of significance as highlighted earlier will lead to more streamlining of patients according to illness severity, and a better identification of infants responding to treatment.

Surgical Treatment of PDA

Surgical ligation of a PDA is influenced by availability and ease of access to a pediatric cardiothoracic center. In addition, in some centers, surgery may be considered the

first-line treatment in infants with NEC, severe IVH, and pulmonary hemorrhage, in view of the potential adverse effects associated with NSAIDs. There is currently no evidence in the literature supporting surgical over medical treatment as a first-line approach. Perioperative complications include pneumothorax, accidental ligation of the thoracic duct leading to chylothorax, intraoperative bleeding, and hemodynamic instability. There is substantial late mortality and a high incidence of morbidity in the survivors. Low cardiac output syndrome (LCOS) is now a recognized postoperative complication with potentially harmful effects. After PDA ligation, there is an initial acute deterioration followed by an improvement in global cardiac function. Recently, PDA ligation has been associated with poorer neurosensory outcomes compared with medical treatment alone.

The postoperative course after PDA ligation is variable and unpredictable, with about 30% of infants requiring initiation of inotropes for hypotension. Recent publications have demonstrated echocardiographic evidence of poor myocardial contractility and low cardiac output which precedes the development of hypotension and respiratory failure. The impact of postoperative cardiorespiratory instability and poor systemic blood flow is the subject of recent debate due to the reported association of surgical ligation and adverse neurodevelopmental outcome. Whether the latter relates to prematurity, magnitude of ductal illness, or is a complication of surgical ligation remains unknown. In addition, an association between surgical ligation and the development of chronic lung disease, independent of immaturity or/and ductus arteriosus–related variables, has been reported. These findings add to the growing uncertainty about the benefits and risks of surgical ligation during the neonatal period.

Conclusion

The management of a patent ductus arteriosus has become a subject of much controversy and debate. The current definition of a hemodynamically significant PDA is probably too simplistic as it considers the problem to be a binary variable requiring a dichotomous approach to therapeutic intervention. It is not surprising that all trials to date have failed to demonstrate a benefit of therapeutic intervention due to such homogenization of the patient population. In addition, the focus to date has been on ductal size, rather than the volume or magnitude of the ductal shunt. Echocardiography may facilitate a better understanding of the hemodynamic effects of a PDA and the magnitude of the shunt. A more comprehensive appraisal of echocardiography markers may optimize the definition of hemodynamic significance, enhance selection of patients who may benefit from therapeutic intervention, and facilitate longitudinal monitoring of response to therapeutic intervention. The association between cTnT and NTpBNP with severe IVH and death in infants with a PDA suggests that it may also facilitate stratification of neonates with a PDA into high-and low-risk groups allowing more focused early targeted treatment. Future randomized trials of targeted PDA treatment require an enhanced definition of hemodynamic significance and should stratify patients according to echocardiography markers, and biomarkers such as cTnT and NTpBNP. This may allow identification of those patients who may benefit from therapeutic intervention.

The Approach to an Infant with Suspected Congenital Heart Disease

Introduction

Congenital heart disease (CHD) occurs in 8 per 1,000 live births and is a major cause of morbidity and mortality in the neonatal population. Fifteen percent infants with CHD have potentially life-threatening lesions. Up to 35% on infants with congenital heart disease have low birth weight (<2,500 g). The incidence in the preterm population is around 12 per 1,000. The preterm population are at an increased risk of adverse outcome due to composite and additive effects of morbidities attributable to prematurity and the specific cardiac defect, or their treatment. Therefore, premature infants with CHD represent a highly vulnerable population who constitute a major challenge to daily management. This section will review the approach to the management of neonates with congenital heart disease. Detail of specific lesions is covered elsewhere.

Clinical Features and Assessment of CHD in Neonates

Antenatal diagnosis of most major cardiac lesions is now possible with the improvement in fetal ultrasound technique and the increasing expertise. Detection rates vary widely however, depending on operator experience, the gestational age of infants, fetal position, and the type of defect. A thorough history is important in identifying maternal conditions that increase the risk of CHD.

Maternal diabetes is associated with transient hypertrophic cardiomyopathy, transposition of the great arteries, and ventricular septal defects. Mothers with connective tissue disease (see later) are at an increased risk of congenital heart block. Congenital infection and maternal intake of certain drugs will also predispose to CHD. Examples include pulmonary or aortic stenosis in fetal hydantoin syndrome, Epstein's anomaly with lithium treatment, and septal wall defects with fetal alcohol syndrome. A family history of CHD also leads to a slight increase in CHD presence in the fetus. Clinical assessment of the neonate and certainly the preterm infant for symptoms of CHD is difficult, and many findings may be lacking before discharge. Early diagnosis of even major cardiac defects may be challenging as the typical clinical features, for example, hypotension, hypoxemia, and metabolic acidosis may be attributed to prematurity.

The physician should be extra vigilant in looking for the following symptoms: poor or slow feeding, frequent vomiting, tachypnea at rest or with feeds, cyanosis or pallor, persistent couch or unexplained wheeze, sweating, lethargy, irritability, decreased activity, and poor weight gain. These symptoms may be absent in up to 75% of infants in the early newborn period and are, unfortunately quite nonspecific. Cyanosis is an important sign of CHD but may be very difficult to assess in the first 24–48 h of life, particularly in dark pigmented infants. As a result, pulse oximetry screening has recently been advocated in all infants prior to discharge from hospital. Postductal oxygen saturations below 95% have a sensitivity and specificity of 75% and 88% for the detection of congenital heart disease, respectively.

The hyperoxia test is useful in distinguishing cardiac and pulmonary causes of cyanosis. In this test, arterial oxygen tension is measured in the right radial artery (preductal) and in a lower extremity artery while the patient breathes 100% oxygen (postductal). In clinical practice, a preductal blood gas will suffice, particularly in premature infants where sampling is more challenging. A transcutaneous oxygen monitor can be used to assess whether arterial oxygen tension rises in response to the increased inspired oxygen concentration, thereby avoiding arterial puncture for blood sampling but is generally not recommended if an arterial sample may be obtained. Lung disease is more likely than CHD in cyanotic patients whose postductal arterial PaO_2 increases to >150 mmHg in a hyperoxia test. Patients with cyanotic lesions such as TGA or severe pulmonary outflow obstruction typically have $PaO_2 < 50$–60 mmHg during hyperoxia. In lesions with intracardiac mixing and increased pulmonary blood flow such as trunks arteriosus, PaO_2 may increase to 75–150 mmHg.

Approach to Management

Early identification of CHD, and in particular a duct-dependant lesion, allows the opportunity for focused cardiac interventions, which may ultimately improve patient outcomes. The yield from clinical assessment in preterm infants is low but the possibility of a CHD should be entertained in all neonates who present with cyanosis, systemic hypoperfusion, pulmonary congestion, or heart failure. Occasionally, CHD is suspected after abnormal findings on a chest x-ray or electrocardiogram (ECG). The clinical course is often altered by comorbid pathophysiologic processes normally associated with prematurity, for example, respiratory distress syndrome. The gold standard for diagnosis is two-dimensional echocardiography. The approach to management of a preterm infant with CHD is dependent on two important physiological considerations: *first*, whether the lesion is duct dependent, and *second*, whether there is single ventricle type physiology. In the latter situation, the DA controls blood supply to both the pulmonary and systemic circulation. Hypoplastic left-heart syndrome and pulmonary atresia with a hypoplastic right ventricle are two examples of duct-dependant lesions with single ventricle physiology. The term single ventricle type physiology (SVP) refers to the anatomic anomalies that result in a single ventricle supporting both pulmonary and systemic circulations. In these lesions, there is complete mixing of both systemic and pulmonary venous return; and as a result, the pulmonary arterial saturation equals systemic arterial saturation.

Echocardiography and Preterm CHD

The role of echocardiography in the care of preterm neonates is twofold: First, to establish the anatomical diagnosis and second to monitor patency of the DA, myocardial performance, and pulmonary arterial pressures. Serial echocardiography is often necessary prior to surgical intervention to monitor cardiovascular health and the effects of the CHD on pulmonary arterial pressures.

Management of the Preterm Neonate with a CHD

The care of the preterm neonate with a CHD should take into account the morbidities specific to this population as well as those related to the particular CHD. The approach in the initial postnatal period is often predominantly medical.

Surgical interventions or other invasive procedures are usually delayed until the neonate reaches a maturity and weight at which the risks of an expectant approach outweigh the risks of the specific intervention. Management of the premature infant with a CHD requires expertise to ensure both focused cardiovascular and neonatal care, neither of which is mutually exclusive. It is only by ensuring excellence in each that outcomes will be improved.

Focused Cardiovascular Care: Medical Management

Prostaglandin Treatment

Neonates with a duct-dependant CHD require continuous intravenous prostaglandin E_1 therapy to sustain patency of the DA. In the early stabilization phase, the dose required may range from 0.01 to 0.2 μg/kg/min. For neonates with an antenatal diagnosis, the lowest dose should be prescribed immediately after birth since this is usually sufficient to maintain ductal patency; however, in those presenting with acute hypoxemia or circulatory collapse, high doses are often required. Once clinical and hemodynamic stability has been achieved, the intravenous prostaglandin E_1 dose is usually weaned to the lowest effective dose in order to avoid excessive pulmonary vasodilatation. This is particularly relevant for neonates with SVP where a profound or sustained fall in PVR leads to excessive pulmonary blood flow at the expense of systemic perfusion. In many cases, prostaglandin therapy is required for several weeks or months while awaiting surgical intervention. This increases the risks of complications related to prostaglandin administration including apnea, hyperthermia, hypotension, gastric outlet obstruction secondary to gastric foveolar hyperplasia, and cortical hyperostosis.

Cardiovascular Monitoring

This is particularly relevant in premature infants with single ventricle type physiology because acute physiologic changes in arterial oxygen or carbon dioxide content or common neonatal treatments, for example, increased ambient oxygen, surfactant replacement therapy, or inhaled nitric oxide may affect pulmonary and/or systemic vascular resistance (Fig. 23.5). The consequences may include altered ventricular afterload, transductal, pulmonary, or systemic blood flow. As pulmonary vascular resistance falls in the immediate postnatal period, increased pulmonary blood flow may occur at the expense of systemic perfusion thereby leading to end-organ compromise and suboptimal tissue oxygenation. Arterial $PaCO_2$, pH, and FiO_2 should be carefully monitored and controlled therefore to prevent excessive pulmonary vasodilatation and consequential overcirculation

Hemodynamic stability and the adequacy of either pulmonary or systemic blood flow may be evaluated both clinically and biochemically. Signs of circulatory compromise include tachycardia, hypotension, and decreased urinary output. Biochemical markers of the efficacy of oxygen delivery include: plasma lactate, arterial pH, base deficit, and mixed venous oxygen saturation. Lactic acidosis, metabolic acidosis, or falling mixed venous oxygen saturation are suggestive of suboptimal systemic perfusion and tissue oxygenation. Arterial access is an essential prerequisite of the care of these patients, particularly in the first 1–2 weeks of life, when major changes in transductal vascular resistance are most likely. The ratio of pulmonary to systemic blood flow (Qp: Qs) is another useful tool to evaluate the adequacy of systemic oxygen delivery. The Qp: Qs ratio is calculated as follows: SaO_2–$SmVO_2$/$SpVO_2$–$SpAO_2$ (where SaO_2 aortic oxygen saturation, $SmVO_2$ mixed venous oxygen saturation, $SpVO_2$ pulmonary venous oxygen saturation, and $SpAO_2$ pulmonary arterial oxygen saturation). In patients with single ventricle physiology, $SpAO_2$ can be assumed to be equal to SaO_2 since blood supply to both great vessels is from the same ventricle. $SpVO_2$ can be assumed to be 100% in the absence of lung parenchymal disease. $SmVO_2$ is obtained from a central venous catheter placed in the SVC. A normal SaO_2/$SmVO_2$ difference is 25–30%. Using these assumptions, the optimal Qp: Qs ratio is thought to be 0.5–1. Both circulations are balanced and the aortic arterial saturation tends to range from 75% to 85%. An aortic arterial saturation of 95% is therefore indicative of pulmonary blood flow five times that systemic.

Cardiotropic Support

There is a paucity of data describing physiologic norms for blood pressure and indices of systemic perfusion in the premature population. The goal of treatment is to ensure that blood pressure is maintained within a range that sustains adequate systemic perfusion. As indicated earlier, monitoring heart rate, urinary output, arterial pH, and lactate are essential components of the stabilization and ongoing care of neonates with CHD. Treatments options should be selected based on the underlying pathophysiology and the likelihood of the intervention to correct the abnormal physiologic state. Therapeutic options include volume

expansion with crystalloids, the use of inodilators like dobutamine and milrinone, and in special circumstances pressor agents, for example, dopamine, epinephrine, and vasopressin. Volume expansion is useful in neonates with abnormal right ventricular performance to support pulmonary blood flow. Milrinone has been shown to reduce both mortality and low cardiac output syndrome in postoperative cardiac patients. In many centers, milrinone is routinely administered to all neonates after complex cardiovascular surgery as the first-line cardiotropic agent. High-dose dopamine and epinephrine are rarely recommended in premature infants because of their adverse effects on both myocardial performance and vascular resistance.

Catheterization Procedures

Cardiac catheterization is occasionally performed in preterm infants. There are some reports in the literature of successful balloon dilation of the pulmonary valve in neonates at a weight of less than 750 g. Balloon atrial septostomy can be performed in neonates with Transposition of the Great Arteries or other conditions dependant on a transatrial shunt. Surgical intervention in premature neonates with single ventricle physiology is challenging. To avoid the risks of cardiopulmonary bypass and the need for chronic prostaglandin administration in this highly vulnerable population, a new technique called the "Hybrid procedure" has been developed to replace the first stage of the Norwood procedure. The procedure is performed in the cardiac catheterization laboratory and involves the placement of a stent in the DA to ensure both pulmonary and systemic blood flow. Pulmonary arterial bands are placed to reduce excessive pulmonary blood flow. This procedure has been performed on a number of premature neonates and early results are encouraging; however, long-term data are not yet available. The age and weight thresholds for performing these procedures are likely to vary significantly between neonatal cardiac centers.

Surgical Procedures

Determining the optimal time for surgical intervention in the preterm population has proven to be a challenge because of technical issues related to both low birth weight and the comorbidities inherent within this population. Typically, an expectant approach has been employed with a view to intervention at a higher weight, although this is oftentimes a moving target with little consistency between centers and cardiovascular surgeons. Delaying surgery until a predetermined weight is achieved is not without risks which include:

1. Prolonged exposure to abnormal physiology and hypoxia
2. Failure to thrive
3. Prolonged need for central venous access and total parenteral nutrition administration and the attendant risks of infection, thrombosis, and cholestasis
4. Prolonged volume overload and its possible contribution to the development of pulmonary hypertension and the progression of chronic lung disease

Corrective Surgery

Total anatomic correction is possible in neonates with transposition and anomalous pulmonary venous drainage or coarctation of the aorta. Several studies have demonstrated a more favorable outcome in patients greater than 1,500 g at the time of surgical intervention. For this reason a weight $\geq$1,800 g has been widely accepted as the target weight for intervention; particularly in light of the challenges of cardiopulmonary bypass, the potential need for postoperative extracorporeal life support and the risks to the developing organs especially the brain. In most centers, the average weight at surgery is between 2,000 and 2,500 g, although with modified techniques of cardiopulmonary bypass surgical intervention is attempted at less than 1,800 g.

Palliative Surgery

Palliative surgical interventions refer to procedures where total anatomic correction is not possible and blood flow is controlled by natural or artificial shunts and a single ventricle. Neonates with hypoplastic left heart syndrome, pulmonary atresia, or tricuspid atresia undergo a three-stage surgical repair called the "Norwood or single ventricle" track. These patients will have lower oxygen saturation than normal, limited exercise capacity and significant periods of hospitalization during this time period. The final step in this staged approach results in the complete separation of pulmonary and systemic circulations by the fashioning of a Fontan circulation whereby inferior and superior venous blood flow is directed to the pulmonary artery while the single ventricle supplies the systemic circulation. Mortality rates associated with these procedures have improved over the past 10 years; however, significant acute and long-term morbidity remains a reality.

Focused Preterm Care

Preterm neonates with congenital heart disease should ideally be cared for in tertiary neonatal intensive care units with a critical mass of preterm neonates with CHD and in close proximity to pediatric cardiology services. There are no published data or guidelines on best practice for the management of preterm neonates with congenital cardiovascular malformations. Most of the current practices extrapolate from evidence for the care of term neonates with CHD. Close collaboration between neonatology and pediatric cardiology is recommended to optimize the quality of care delivered to these patients, which ensures the needs of prematurity and cardiovascular care are met.

Assisted Mechanical Ventilation

Routine intubation of all neonates when prostaglandin E_1 is administered is not necessary. Intubation is recommended in the presence of respiratory failure, clinical signs of cardiogenic shock, the need for cardiotropic support, profound metabolic or lactic acidosis, gestational age less than 28 weeks, and an associated airway disorder. In general, patients should be ventilated to maintain a $PaCO_2$ of 40–50 mmHg and an arterial pH of 7.25–7.35 to avoid excessive pulmonary blood flow in those patients with single ventricle type physiology. The provision of optimal positive end-expiratory pressure may have the additional benefit of limiting left-to-right shunting across a patent ductus arteriosus and may therefore be useful in controlling transductal flow. One of the most challenging aspects of management is supporting those neonates with evolving chronic lung disease and pulmonary hypertension secondary to pulmonary vascular remodeling. Episodic apnea and/or hypoxemia occur frequently in these patients necessitating therapeutic intervention. Oxygen therapy is normally administered to preterm neonates when the oxygen saturation falls below 88% although the optimal saturation for preterm neonates remains controversial. An oxygen saturation range of 75–85% is normally targeted in neonates with duct-dependant CHD, particularly if single ventricle type physiology exists. This range has been chosen to minimize an excessive decline in pulmonary vascular resistance in an attempt to maintain satisfactory systemic perfusion. At the same time, the risk of tissue hypoxia and adverse neurodevelopmental outcome must be taken into consideration and judicious oxygen administration may be required. Neuroimaging studies of neonates report a high incidence (>50%) of periventricular leucomalacia after cardiac surgery. Arterial $PaO_2 < 40$ mmHg and diastolic hypotension were two of the most important risk factors associated with the evolution of brain injury. There are limited studies addressing the relationship of CHD or oxygen saturations to abnormal respiratory outcomes in premature infants and the mechanism of lung injury.

Other Respiratory Interventions

The administration of prophylactic surfactant to preterm neonates with an antenatal diagnosis of a duct-dependant systemic circulation may result in an excessive fall in PVR leading to excessive pulmonary blood flow at the expense of systemic perfusion. A recent prospective evaluation of delivery room surfactant demonstrated increased transductal diameter, decreased cardiac output, and increased Qp:Qs. This may be particularly hazardous for neonates with hypoplastic left heart syndrome in whom the systemic circulation tends to be extremely tenuous. The radiological confirmation of a diagnosis of respiratory distress syndrome is recommended for these neonates before surfactant administration.

Neurological Care

The risk of an adverse neurological event is significantly increased in neonates with a CHD requiring cardiopulmonary bypass or postoperative extracorporeal life support due to the fragility of the developing brain, particularly in premature infants. Intracranial hemorrhage and non-hemorrhagic infarction are the most common adverse events in the immediate postoperative period. There is, however, increasing evidence that neurological damage may occur preoperatively and perhaps in utero. Neonates with congenital heart disease have an increased incidence of structural central nervous system and neurobehavioral abnormalities. The incidence of microcephaly was 24–36% in one series. Infants with hypoplastic heart disease have also been reported to have an increased incidence of holoprosencephaly, agenesis of the corpus callosum, and abnormalities of the operculum in other series. Magnetic resonance image evaluation preoperatively in newborns with congenital heart defects has revealed periventricular leukomalacia in 16–28% . It has been reported that more than 50% of infants with congenital heart disease have poor state regulation and abnormalities of tone preoperatively. There is a strong correlation between these findings and preoperative

arterial PaO_2 and blood pressure. Preoperative neurological abnormalities portend a poor neurodevelopmental outcome. In addition, the presence of perioperative hyperthermia or seizures, coexisting genetic abnormalities, or associated organ defects also increase the risk of neurological morbidity. The preterm neonate is even more vulnerable to the effects of chronic hypoxaemia and intermittent periods of systemic hypoperfusion on the developing brain because of poor cerebral autoregulation. There are limited published data on the neurodevelopmental outcome of premature infants with CHD.

Nutritional Support

The risk of necrotizing enterocolitis is significantly increased in neonates with a CHD. This is most likely to be related to intestinal hypoperfusion and/or chronic hypoxaemia. Extreme immaturity, higher doses of prostaglandin treatment, and episodic low cardiac output syndrome are also strong predictive factors. These newborns required a focused approach to nutrition that balances the risks of prematurity within the context of a fragile circulation. Wherever possible, guidelines should be developed that focus on the unique needs of preterm neonates with cardiac disease. While growth is paramount to achieve target surgical weights, these newborns should be fed cautiously. Expressed breast milk is recommended, and feeds should be increased slower compared to their gestational age counterparts, although there are few supporting data for the latter in currently published literature.

Miscellaneous

The risk of anemia is likely to be increased in this population due to more frequent blood sampling. Although the threshold for transfusion in preterm neonates remains unclear, it is probably advisable to implement a lower more liberal transfusion policy for transfusion to maintain oxygen-carrying capacity. This is particularly relevant for neonates with single ventricle type physiology who are at greater risk of tissue hypoxia. Plasma hemoglobin should probably be maintained > 100 g/dl but during periods of instability the level should be maintained > 120 g/dl.

The risk of infection is higher in preterm neonates with CHD; for this reason vigilance is required and that possibility entertained in the presence of hemodynamic instability.

Due to the challenges of clinical assessment of preterm neonates for dysmorphism or genetic abnormalities, routine karyotype analysis as well as screening for 22q microdeletion is recommended.

Outcome

Mortality rates for preterm infants with CHD of 10–43% have been reported by various studies. Few of these studies however take into account the heterogeneity of the cardiovascular malformations. With advances in antenatal diagnosis and postnatal management, there has been a trend toward improved survival in patients with CHD. As a result, the focus has shifted toward evaluating the long-term neurodevelopmental outcome of these infants. Annette Majnemer et al. examined the neurodevelopmental outcome of 131 term neonates with CHD who underwent surgical intervention at Montreal's Children's Hospital between 1994 and 1998. Evaluation of the patients at 12–18 months revealed global delays in 25%; delays in speech and hearing in 34%; locomotor 26%; hand-eye coordination 24%; personal/social 17%; and abnormal neurological exam in 41%. Dittrich et al. investigated the neurodevelopmental outcome at 1 year of age of 90 infants who had surgical repair of various congenital heart defects. Mean developmental quotient was statistically significantly lower in test subjects than controls (who were infants with minor or no congenital heart defect). Thirty-two percent of the index patients had neurological abnormalities compared with 5% of the controls. In each of these scenarios, outcome was worse for those patients offered palliative surgery compared with patients who underwent corrective surgery. There is a paucity of data on long-term outcome in the premature population, however. Additionally, outcome data for specific lesions are lacking. This makes accurate counseling of the parents of affected newborns a challenge.

Summary

With an improvement in the survival rates for neonates with CHD over the past 10–15 years, the high incidence of cognitive and neurodevelopmental impairment have become a cause for concern. The care of the preterm neonate with a CHD poses a significant challenge for neonatal intensivists attempting to stabilize a vulnerable circulation within the context of organ immaturity. A multidisciplinary approach with collaboration between neonatal intensivists and cardiologists with careful

attention to the issues peculiar to this population is of paramount importance. Prospective research evaluating the physiological and hemodynamic impact of acute therapeutic and surgical interventions on morbidity, mortality, and neurodevelopmental outcome are urgently required to further guide and shape the optimal approach to management.

Common Neonatal Arrhythmias

Introduction

The incidence of serious neonatal arrhythmias is not well defined as the problem is relatively rare. Benign arrhythmias, such as premature atrial beats, are common and often cause concern when frequent, leading to "irregular heartbeat." Tachyarrhythmias represent the most common form of dysrrhythmias, of which supraventricular tachycardia (SVT) occurs most frequently. Ventricular arrhythmias are usually a complication of metabolic disturbances, illness severity. Bradyarrhythmias may also occur and range from relatively benign sinus bradycardia to complete heart block most commonly associated with maternal systemic lupus erythematosus (SLE). The majority of neonatal arrhythmias occur in a structurally normal heart. However, infants with congenital heart disease, particularly in the postoperative period, are at a higher risk of developing arrhythmias. This chapter will review the two commonest pathological neonatal arrhythmias, namely, SVT and complete heart block.

Supraventricular Tachycardia

Introduction

SVT can be defined as an abnormally fast regular heart rhythm originating above the ventricle with a narrow QRS complex. The heart rate usually ranges from 230 to 250 beats per minute (and up to 300) during an SVT episode. It is characterized by a sudden onset of a regular fast rhythm with no beat-to-beat variability and a narrow QRS complex. The p wave is often absent but may be seen after the QRS wave. These features distinguish SVT from sinus tachycardia, which is characterized by a gradual onset with beat-to-beat variability and rate between 180 and 240. The incidence was previously quoted at 1 in 25,000 infants. However, with increased index of suspicion and improved detection modalities, the incidence has increased to 1 in 250.

Pathophysiology and ECG Features

The normal cardiac impulse originates from the sinoatrial (SA) node in the right atrium and travels through the atria to the atrioventricular (AV) node. The impulse is then delayed to accommodate the completion of atrial contraction. Further impulse propagation occurs through the AV node and spreads to the right and left ventricles through the bundle of His. Normal conduction from atria to ventricles only occurs though the AV node (Fig. 23.6).

Atrioventricular reentry tachycardia (AVRT): This is the commonest form of SVT in neonates and accounts for about 70% of cases. Mechanistically, the AV node usually acts as the antegrade pathway (from atria to ventricles) and an accessory pathway acts as a retrograde pathway leading to impulse reentry into the atria. This is referred to as orthodromic AV reciprocating tachycardia and results in a circular pathway of the impulse leading to a tachycardia. Occasionally, the accessory pathway serves as the antegrade and AV node serving as the retrograde course of conduction. This is called antidromic AV reciprocating tachycardia. The ECG is characterized by a narrow complex QRS, an inverted P wave that may be seen following a QRS complex, and a PR longer than an RP interval. In 10–50% of the cases, ventricular preexcitation may occur resulting in the formation of a short PR interval and a delta wave. This is caused by early antegrade propagation of the impulse through the accessory pathway leading to early depolarization followed by delayed antegrade impulse conduction through the AV node completing the depolarization of the ventricles. This is referred to as Wolff–Parkinson–White (WPW) syndrome.

AV nodal reentry tachycardia (AVNRT): This is the second most common form of SVT and accounts for about 15% of cases. There are two pathways within or adjacent to the AV node. Typically, the impulse is conducted slowly through one pathway to the ventricles with a rapid retrograde conduction back to the atria (slow-fast AVNRT). The ECG is characterized by a narrow QRS, with the P wave often not visible (within the ORS). Atypical AVNRT is characterized by fast antegrade flow and slow retrograde flow (fast-slow). The ECG may show a P wave after the QRS with a PR shorter than the RP interval.

Atrial Tachycardia (AT): This is the third most common form of SVT in neonates (15%). AT includes atrial

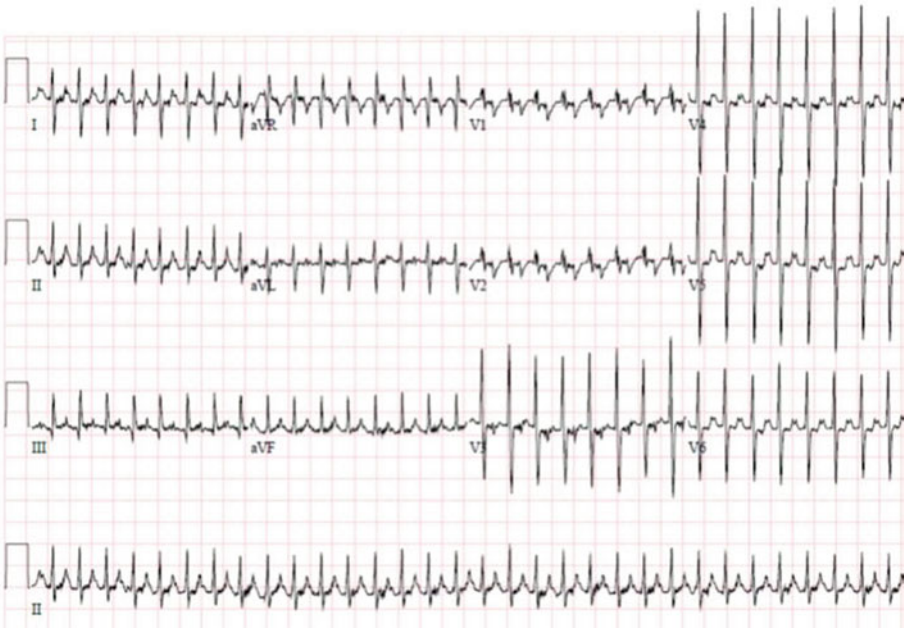


Figure 23.6
***SVT* (Courtesy of Dr. Gil J. Gross)**

flutter and atrial ectopic tachycardia (AET). Atrial flutter occurs due to accessory pathways within the atrial muscle leading to atrial rates of up to 600 beats per minute. The ECG shows flutter waves and varying ratios of conduction via the AV node. AET results from ectopic foci within the atria with automaticity with a rate of firing higher than the SA node. There is a period of gradual heart rate escalation preceding AET. The ECG shows abnormal P wave morphology, a short PR interval, and varying degrees of conduction to the ventricles via the AV node. AV node is not a part of this arrhythmia.

Clinical Features

Fetal SVT may be identified in utero upon routine ultrasound examination of the heart beat and may lead to hydrops fetalis. SVT in neonates is usually paroxysmal in nature with a sudden onset and resolution. Episodes usually occur at rest and may last from minutes to hours. They may go undetected in neonates. Hemodynamic instability is relatively rare. Infants with sustained SVT lasting greater than 24 h may present with signs and symptoms of heart failure, such as poor feeding, respiratory distress, sweating, lethargy, irritability, and restlessness. Syncope and ventricular fibrillation is rare in neonates. Sudden death is very uncommon in neonates. Chronic tachycardia will lead to ventricular dilatation. This cardiomyopathy may be reversible if the arrhythmia is terminated. However, cardiac injury from untreated SVT may be permanent leading to myocardial dysfunction and ventricular arrhythmias.

Management of SVT

Infants presenting with SVT need a comprehensive evaluation aiming to identify the cause and the type of SVT. Electrolytes associated with the development of SVT should be checked including sodium, calcium, potassium, and magnesium. The presence of peripherally inserted central catheters (PICC) or umbilical catheters should be noted as they may act as a trigger if the tip is in the right atrium. A 12-lead ECG with a rhythm strip is essential to assess the heart rate and identify the type of arrhythmia. An echocardiogram should be done to assess cardiac anatomy once the infant is stable. *Adenosine* can be used to both terminate and help diagnose the type of arrhythmia. Adenosine acts directly on the AV node to terminate conduction; therefore, it will terminate AVRT and AVNRT but not AET as the latter has the arrythmogenic

focus in the atria. Consultation with the cardiology service is essential in providing ongoing management.

In a stable infant, a graded approach is utilized. Vagal maneuvers such as applying an ice pack on the face and nose for 10–20 s will trigger the diving reflex (peripheral vasoconstriction and a vagal discharge). This maneuver is successful in around 60% of cases. Eyeball pressure, carotid message, and immersion in water *are not recommended* in the neonatal population.

Adenosine may be used if vagal maneuvers are unsuccessful. A rapid intravenous bolus of 0.05 up to 0.3 mg/kg may be used followed by a saline flush with continuous ECG monitoring. It can terminate SVT in up to 90% of cases. Adenosine has a very short half-life of 15 s, and repeat administration may be used for resistant SVTs. Side effects include bronchospasm, and premature atrial and ventricular contractions. It may also cause varying degrees of AV block.

Esmolol is a beta blocker with class II antiarrhythmic properties. It has a very short half-life and may be used in resistant SVTs, including AETs to achieve ventricular rate control. It acts by increasing the refractory period of the AV node and interrupting the reentry circuit. It is administered as a continuous infusion of 50 to 100 μg/kg/min following a bolus of 100–500 μg/kg/min. It may cause profound hypotension and bradycardia, and therefore, its use should be guided by a pediatric cardiologist. Further, heart rate control and management should be done in consultation with the cardiology services and the choice of drug will be dependent on local experience and preference. Amiodarone, flecanaide, and procainamide are alternative agents that are sometimes used, although amidorone is now contraindicated in the newborn period. Digoxin should be avoided in WPW syndrome as it only slows conduction on the AV node and not the accessory pathway.

If the infant shows signs of cardiovascular compromise, immediate *synchronized* cardioversion is needed. The starting dose is 0.5 J/kg increasing to 1 J/kg if no response. Cardioversion will only restore (and not maintain) cardiac rhythm and therefore, pharmacological therapy is needed to maintain sinus rhythm. Intravenous (IV) access should be instituted as soon as the infant is stable, preferably in a vein in close proximity to the heart such as the right or left antecubital fossa.

Prognosis

The majority of infants (50–70%) with a normal heart will be free of SVT by 1 year of age, and up to 85% are SVT-free by 5 years of age. Infants with early persistent SVTs, infants requiring multiple drug therapy, and those with structural heart defects are at greater risk of developing recurrence particularly during the teenage years. These infants may need radiofrequency ablation of the accessory pathways.

Congenital Heart Block

Incidence and Etiology

Congenital heart block (CHB) is defined as a neonatal bradycardia of 40–80 beats per minute. It occurs in around 1 in 20,000 live-born infants. The majority of cases are secondary to maternal SLE antibodies that cross the placenta and cross-react with the AV node, accounting for up to 90%. The remainder are caused by myocarditis, congenital heart disease (particularly AV and VA discordance), some hereditary disorders, and polysplenia.

Pathophysiology

In neonatal lupus, maternal anti-Ro/SSA and anti-La/SSB antibodies cross the placenta and bind to fetal cardiac tissue, particularly the AV node; a site is rich in La/SSA and Ro/SSB antigen. This antibody–antigen interaction leads to AV nodal fibrosis and inhibition of calcium channel activation thereby preventing impulse propagation from the SA node to the ventricles. Occasionally, the SA node may be involved as well. CHB occurs in 2% of women with these antibodies.

Clinical Features and Prognosis

CHB usually presents in utero by ultrasonic detection of fetal bradycardia usually at 18–24 weeks gestation. Fetal echocardiography can estimate the PR interval and assess the anatomy of the heart. The degree of heart block is variable and can start as second-degree heart block later progressing to third-degree heart block. Ninety-five percent of cases detected in utero are due to maternal antibodies. Hydrops fetalis, endocardial fibroelastosis, pericardial effusion, and fetal demise may all arise. Death can occur in 5–20% of cases. Early mortality is high with CHB with up to 25% of affected infants dying in the first 3 months of life. Infants born with first- or second-degree heart block can also progress to complete heart block.

The cardinal sign in neonates is the detection of a slow heart rate soon after birth. Infants usually tolerate the low

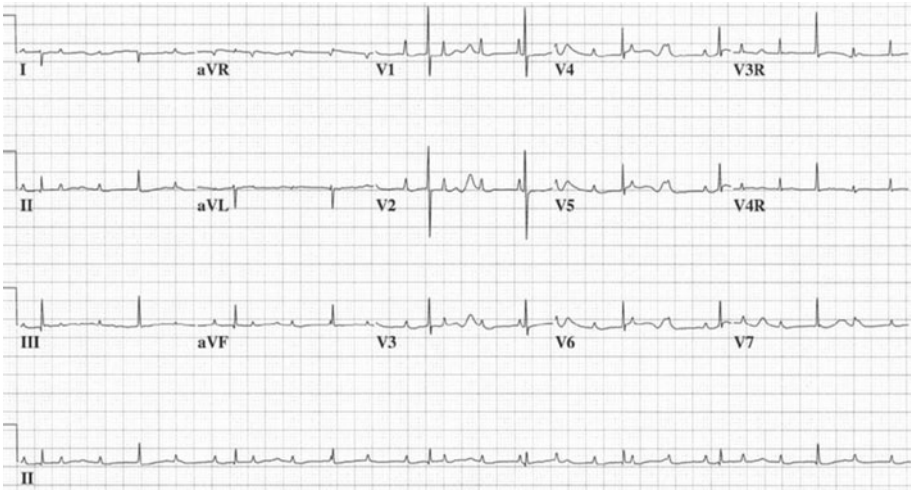


Figure 23.7
Congenital heart block **(Courtesy of Dr. Gil J. Gross)**

heart rate well in the initial period. Heart failure will develop in untreated infants. Other signs include canon waves in the neck, and a first heart sound varying in intensity. The ECG shows a narrow QRS due to the junctional or AV origin of the escape rhythm (*Fig. 23.7*), and complete p wave dissociation.

Management

Antenatal management includes steroid administration in an attempt to arrest the progression to complete heart block. The mainstay of treatment is pacemaker insertion either soon after birth or when symptoms arise. The indications for pacemaker insertion include the following: symptomatic bradycardia, ventricular dysfunction, wide QRS escape rhythm, ventricular rates <55, and complex ventricular ectopic beats.

Neonatal Cardiomyopathies

Introduction

Cardiomyopathy is an intrinsic myocardial disease. These rarely present in neonates, with the exception of asphyxia cardiomyopathy. Primary cardiomyopathies are disorders confined to the heart and have no systemic disease. Secondary cardiomyopathies are associated with other disease states. A detailed description of the various disease states is outlined elsewhere.

Etiology

The following are causes of cardiomyopathies that may present in the neonatal period. This is not an exhaustive list:

- Primary Causes
  - Endocardial fibroelastosis
  - Familial hypertrophic/dilated cardiomyopathies
  - Noncompaction of the left ventricle
- Secondary Causes:
  - Neonatal asphyxia
  - Cor pulmonale: following chronic lung disease
  - Genetic syndromes: Beckwith–Wiedemann, Noonan, neurofibromatosis I
  - Infectious myocarditis: congenital viral infections, syphilis
  - Inflammatory: SLE, peripartum myocarditis
  - Myocardial insufficiency: tachyarrythmias, anomalous left coronary artery origin
  - Metabolic: infants of diabetic mothers, inherited disorders of metabolism (e.g., glycogen storage disease), pheochromocytoma, thyroid disease, mitochondrial disease
  - Toxic: alcoholic myopathy, cocaine use, cyclophosphamides

Clinical Approach to Neonates with Suspected Cardiomyopathies

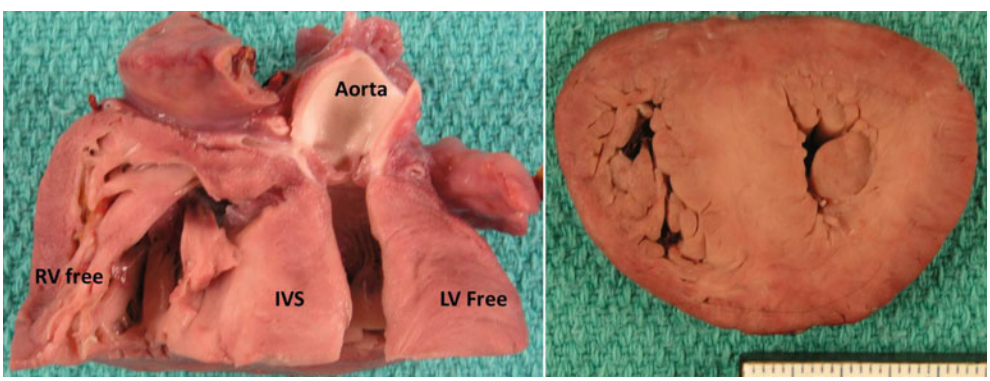
As the causes of neonatal cardiomyopathies are many, a focused history, physical examination in addition to laboratory and imaging modalities may narrow down the diagnosis. A history of stillbirths or cardiomyopathies in the family or siblings may be indicative of a familial cause; in addition, a maternal history of diabetes or autoimmune disease (such as SLE) may provide further clues. A history of antenatal and postnatal events needs to be completed. Clinical examination of the cardiovascular status looking for signs of heart failure or a low cardiac output state is necessary. In addition, dysmorphic features often give clues toward a diagnosis. Hypotonia and encephalopathy may lead to a diagnosis of mitochondrial disease. Chest radiographs and echocardiogram will provide supporting evidence of heart failure and distinguish hypertrophic from dilated types. Laboratory investigations will be exhaustive and include basic tests such as full blood counts, electrolytes, and basic metabolic screens. Further testing will depend on initial investigations and advice from other consultative services. Prognosis is varied and depends on the underlying pathology.

Infants of Diabetic Mothers

Infants of diabetic mothers (IDM) are at an increased risk of developing transient hypertrophic cardiomyopathy (HCM). It occurs in around 5% of infants with mothers with gestational diabetes. The incidence is higher in mothers with type 1 and 2 diabetes where 25–50% of infants are at risk of developing HCM (◉ *Fig. 23.8*). Hypertrophy of the cardiac myocytes develops as a result of fetal hyperinsulinemia secondary to impaired glucose metabolism in the mother. This leads to increased synthesis and deposition of fat and glycogen in the myocardial cells. It is more common in mothers with poor glycemic control, but can occur in mothers with diabetes and good glycemic control throughout pregnancy. The condition may be identified on antenatal scans. Severe cases could be associated with third trimester polyhydramnious, severe ventricular hypertrophy, and pericardial effusion.

The majority of infants are asymptomatic at birth. About 10% of infants are symptomatic with signs of respiratory distress and poor cardiac output. Heart failure could also develop. The heart will appear large on chest radiographs. Echocardiography is the gold standard for diagnosis. The heart usually appears hypertrophied, with prominent thickening of the interventricular septum. The ventricular chambers are usually small in size and may be associated with left ventricular outflow tract obstruction. This may be aggravated by anterior systolic motion of the mitral valve.

HCM is usually transient and resolves as insulin levels fall. Symptomatic infants, however, may need cardiovascular support. This includes administration of intravenous fluids and the judicious use of propranolol. Inotropes are generally contraindicated as they may further increase afterload, decrease ventricular size, and further obstruct outflow. Intravenous vasopressin should be



◉ **Figure 23.8**
***Pathology specimen of an infant with hypertrophic cardiomyopathy*. Note the thickened left ventricular free wall and the intraventricular septum. There is also evidence of left ventricular outflow tract obstruction**

considered as it will increase myocardial preload with negligible direct effects on myocardial performance. Diuretics are absolutely contraindicated, as a reduction of preload will be detrimental to ventricular filing and systemic blood flow.

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24 Fluids, Electrolytes, Renal Function and Acid-Base Balance

Neena Modi

General Principles

This chapter aims to inform the reader of the underlying principles that guide the day-to-day assessment and management of fluid and electrolyte therapy in newborn infants. A good history, consideration of the clinical context, careful examination of the baby, and review of charts are essential and should precede laboratory or other investigations. Case histories and common clinical scenarios are described to illustrate the application of these principles.

Changes in Body Water During Normal Postnatal Adaptation

All newborn infants lose around 10% of total body water after birth. This is from the extracellular compartment and includes pulmonary interstitial fluid. Loss of extracellular fluid is a component of normal postnatal adaptation to a gaseous environment. The size of the extracellular compartment reduces with increasing gestational age. At birth, it is around 65% of body weight at 26 weeks gestation and has fallen to 40% by full term. Loss of extracellular fluid is marked clinically by postnatal weight loss, the extent of which is variable and reflects the loss of body water as well as the balance of loss and gain of body solids that is in turn a reflection of nutritional support provided. It is therefore unhelpful to suggest a specific target for postnatal weight loss, but in the majority of newborn babies provided with adequate nutritional support, this should not exceed 10% of birth weight. Delay in the loss of body water, marked clinically by delayed postnatal weight loss, is associated with increased respiratory morbidity in all babies, regardless of gestational age. This is because postnatal extracellular fluid loss appears triggered by a rise in circulating atrial natriuretic peptide, induced by the fall in pulmonary vascular resistance, rise in pulmonary blood flow, and increase in left atrial venous return and atrial distension, resulting in an acute natriuresis and accompanying loss of body water. Sodium and water balance during this period of postnatal adaptation will consequently be negative. Antenatal steroids and postnatal surfactant have altered the natural history of classical respiratory distress syndrome, and delayed postnatal loss of extracellular fluid does not pose the major problem it did previously. Nonetheless, it is important to recognize that clinical management must be directed at avoiding interventions that adversely affect postnatal extracellular fluid loss; in particular, the administration of sodium in maintenance intravenous fluids should be delayed until postnatal weight loss is underway. This is especially relevant in preterm babies that have not received antenatal steroid therapy to promote pulmonary maturation, and in term babies with respiratory problems.

Case history: *An infant is delivered at 37 weeks gestation by elective Cesarean section. The baby weighs 3.500 kg and is in good condition at birth, but he rapidly develops signs of respiratory distress with grunting, tachypnea, and intercostal recession. He is admitted to the neonatal unit and placed on CPAP. Baseline blood biochemistry results are serum sodium 134 mmol/l, potassium 4.5 mmol/l, and creatinine 64micromol/l. What fluids would you prescribe?*

This baby most likely has transient tachypnea of the newborn characteristic of delivery without exposure to labor. However, at this stage, the precise diagnosis and the time scale of resolution are unknown. The differential diagnosis includes respiratory distress syndrome, and Group B streptococcal infection. Loss of extracellular fluid will be delayed until there is improvement in respiratory status. Hence, only glucose-containing fluid should be prescribed; no intravenous sodium is necessary. Glucose 10% at 60 ml/kg/day is prescribed.

At 4 h of age, chest x-ray shows an air bronchogram and a ground-glass appearance. Serial arterial blood gas measurements show worsening respiratory acidosis; by 7 h, the oxygen requirement has risen to 60%. The baby is intubated and positive pressure ventilation commenced. Surfactant is administered. The oxygen requirement falls to 30%, but at the age of 12 h, the baby suddenly desaturates. Examination suggests a tension pneumothorax, confirmed on chest x-ray. A chest drain is inserted. At 24 h of age, repeat blood biochemistry values are serum sodium 129 mmol/l,

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potassium 4.3 mmol/l, and creatinine 76 micomol/l. Blood glucose measurements have been normal and stable. Urine output has not been monitored, but his weight has risen to 3.540 kg. What would your day 2 fluid prescription be?

By this stage, a small quality of fresh maternal colostrum should be available and may be administered by nasogastric tube. Transepidermal water loss will be no more than 15 ml/kg/day, and glucose 10% at 60 ml/kg/day is sufficient to maintain hydration. However, the baby has not lost weight, indicating positive water balance and the serum sodium has fallen; urine output is unknown.

Examination reveals good peripheral perfusion, a core–peripheral temperature gap of 1°C, and a capillary-refill time of 1.5 s. No bladder is palpable. Mean arterial blood pressure is 45 mmHg. The baby's respiratory requirements have not reduced.

The likely diagnosis is mild dilutional hyponatremia (see section below). Monitoring of urine output is begun and the intravenous infusion rate reduced to 40 ml/kg/day with no added sodium.

Over the next 4 h, the baby's urine output increases from 1.2 ml/kg/h to 3 ml/kg/h. Respiratory requirements fall. Ventilator settings are weaned and he is extubated at 48 h of age. The next set of blood biochemistry results are serum sodium 132 mmol/l, potassium 3.8 mmol/l, and creatinine 70 micomol/l. What would your fluid prescription be for day 3?

Following extubation, he is placed at the breast, and over the next 12 h, suckling progressively improves while he continues to receive nasogastric milk feeds. The intravenous infusion of 10% glucose is discontinued. By day 4, he has shown a 2% weight loss. He is discharged on day 5, exclusively breastfeeding.

Renal Function

Fetal urine production begins at around 8–10 weeks gestation. Nephrogenesis proceeds centrifugally with the deep cortical juxtamedullary zone developing first, and those in the superficial cortex, last. Nephrogenesis continues through most of the third trimester and is completed by a gestational age of around 34–36 weeks. The increase in renal mass during infancy and childhood is due to tubular growth as nephrons that die are not replaced. Renal function in healthy preterm and term newborn babies should be regarded as immature, not abnormal. Although often described as "low" or "reduced" in the newborn, the glomerular function rate (GFR) is adequate for need.

Tubular function is immature, and the preterm baby has a narrower capacity to conserve and excrete sodium than the term infant; hence, preterm newborns are highly susceptible to both sodium depletion and sodium overload. Many tubular functions are upregulated by antenatal glucocorticoid therapy. In newborns, in comparison with older subjects, a smaller proportion of filtered sodium is absorbed in the proximal tubule and a larger proportion delivered distally where sodium reabsorption is regulated by the renin-angiotensin-aldosterone-system (RAAS). The retention of approximately 1 mmol/kg per day of sodium is necessary for growth in preterm and term neonates. Healthy, mature breast-fed neonates achieve this by excreting virtually sodium-free urine; limited sodium conservation in preterm babies of less than 32 weeks gestation requires that they receive an intake of at least 4 mmol/kg per day. Intestinal absorption is an important route for sodium conservation but is also reduced.

Babies receive nutrition only in liquid form and must therefore be able to sustain a high urine flow rate to maintain water balance. This is achieved by reduced proximal tubular reabsorption of filtered water, with a correspondingly greater fraction delivered to the distal nephron. Here water moves across the tubular membrane following an arginine vasopressin (AVP)-dependent increase in water permeability brought about through the insertion of water channels, principally acquaporin 2 (AQP2), from intracellular vesicular reservoirs into the apical membranes of cells of the collecting ducts. The capacity of the healthy term and preterm baby to dilute urine matches that of adults in that a minimum urine osmolality of 50 mOsmol/kg H_2O is achievable. The clinical implication is that impaired water excretion should not be attributed to limited diluting ability.

Urinary concentrating capacity increases with postnatal age. In adults, maximum urine concentration is around 1200–1400 mOsmol/kg water. The capacity to concentrate urine in neonates is lower at around 600–800 mOsm/kg because of the low urea concentration and low tonicity of the medullary interstitium of the anabolic, rapidly growing infant, and reduced expression of AQP2. Antenatal glucocorticoid therapy enhances concentrating ability as does high protein feeding leading to an increased urea production rate. In the first postnatal days, very immature babies with extremely limited concentrating ability may become dehydrated while continuing to pass dilute urine.

Nonrenal Influences on Fluid Balance

The skin is an important organ of water balance particularly in extremely preterm babies. Although keratinization of the stratum corneum commences at around 18 weeks

gestation, the epidermis remains very thin until the third trimester. Water loss through the skin, transepidermal water loss, may be considerable, even exceeding urine volume. Excessive transepidermal water loss is the cause of hypernatremic dehydration in extremely preterm babies, as sodium is not lost through the skin. The evaporation of each milliliter of water from the skin also results in the loss of 560 cal of heat. This is the rationale for placing extremely preterm babies in plastic bags at delivery, and for maintaining a high-humidity environment around them in the neonatal unit. Unlike nephrogenesis, which proceeds along a predetermined and fixed time scale, skin maturation is accelerated by birth. Hence, transepidermal water loss at birth is dependent on gestational age; thereafter, it falls exponentially with postnatal age. After 32 weeks gestation, water loss through the skin in an ambient humidity of 50%, falls to around 12 ml/kg/day. The extent to which transepidermal loss can be reduced is an index of the quality of nursing and medical care. Insensible water loss can be reduced to less than 40 ml/kg/day even in infants weighing less than 1000 g if ambient humidity is maintained above 90%. Babies must be protected from draughts, and care taken to maintain skin integrity and reduce excoriations using nonabrasive tape. Concern about increased infection and difficulty in fixing electrodes has limited the use of water-impermeable barrier ointments and soft paraffin to reduce transepidermal water loss. As radiant heat increases transepidermal water loss considerably, humified incubator care is preferable for the most immature infants. An effective, low cost option is to use a plastic sheet or a humidified body box to achieve a high-humidity microenvironment immediately around the baby.

The Principles of Constructing an Intravenous Fluid Prescription

As neonates receive nutrition only in fluid form, fluid balance and nutritional support are closely interrelated. The clinician must be careful to distinguish the demands of fluid balance and hydration, from those of nutrition. The volume required for nutritional support is determined by the energy density and composition of the fluid used. Put simply, 150 ml/kg of 10% glucose will deliver 60 kcal/kg purely as carbohydrate; this volume of parenteral nutrition could be constituted to deliver around 120 kcal/kg as a balanced intake of carbohydrate, protein, and lipid. The volume required to maintain hydration is determined by insensible water loss, urine output, and any other sources of substantial loss such as stoma output. In preterm babies, the fluid requirement to maintain hydration *falls* with postnatal age, as transepidermal water loss decreases. Hence, a stepwise daily *increase* in intravenous intake is illogical. Each neonatal service should establish guidelines for immediate fluid administration to preterm babies based on their ability to provide a high-humidity environment. Given present day care and ability to provide an ambient humidity in excess of 50%, this equates to around 80–100 ml/kg/day for babies below 32 weeks gestation. The higher the humidity, the lower the volume required to maintain hydration. It may be helpful to prescribe a higher volume during the few initial hours of stabilization when arterial and intravenous lines are being inserted when it can be difficult to maintain a high-humidity environment around the baby. This is particularly helpful in the most immature babies, below 26 weeks gestation. Once a stable high-humidity environment is established, the intravenous flow rate may be reduced. It is important to realize that the initial fluid prescription is a "best estimate," based upon a judgment regarding likely transepidermal water loss, renal function, and rate of postnatal adaptation. The adequacy of this estimate must be assessed within 6–8 h. Traditionally, glucose 10% has been used as the initial intravenous fluid, but with recognition of the importance of good immediate nutritional support, many centers now commence with an amino acid/glucose solution. If glucose tolerance is unstable, as is not uncommon in extremely immature babies, the use of 5% and 50% glucose solutions delivered through a Y connection allows the glucose delivery and fluid volume to be altered independently. After the period of postnatal adaptation, the volume of fluid administered should be based on the volume required to deliver the desired nutritional intake. If parenteral nutrition is delivered by central venous line, a concentrated solution can be used. Administration by peripheral line requires an isotonic solution and hence a larger volume. Milk feed volume is determined by enteral tolerance. The justification for "restricting" fluid intake must be considered very carefully as this will compromise nutrition. Meta-analysis of studies suggesting that "high" fluid intake leads to increased ductal patency and necrotizing enterocolitis have not taken into account the failure to control sodium intake, so that an increase in total fluid volume was in fact an increase in both sodium and water. Preterm babies with intact renal function tolerate abrupt changes in intravenous volume from 95 to 200 ml/kg/day without adverse effect, if sodium intake remains constant. Delaying maintenance intravenous sodium administration until postnatal weight loss is underway is associated with reduced respiratory

1	Estimate insensible water loss	Based on gestational age, postnatal age and humidification
2	Assess gastrointestinal and respiratory fluid losses	Unless there is gastrointestinal pathology, or stoma losses, these will be minimal; respiratory losses will also be minimal if inspired gases are adequately humidified
3	Assess urine output	If the baby has just been born, estimate this as 40ml/kg.day
4	The sum of steps 1, 2, and 3 above represents the volume of fluid required to maintain hydration (H)	
5	Determine what nutrition you wish to provide and by what route	Are you providing fluid enterally, or by central or peripheral intravenous line?
6	The energy density of this fluid will determine the volume required to deliver the required amount of nutrition (N)	
7	If transepidermal water loss, or other fluid losses are high, H may exceed N; if there is need to restrict fluid intake (e.g. in renal or heart failure), H is likely to be less than N	Healthy preterm and term neonates can safely tolerate up to 200ml/kg.day intravenously after the period of postnatal adaptation is over, as long as sodium intake does not exceed maintenance requirements (Coulthard and Hey 1985)

Figure 24.1
Key steps in developing a fluid prescription

morbidity. Key steps in developing a fluid prescription are set out in *Fig. 24.1*.

Case History

A 25-week gestation infant weighing 620 g was delivered following spontaneous preterm labor. Her mother had received a full course of treatment with antenatal steroids. The baby was in good condition at birth and was immediately placed in a plastic bag. She became apneic at 1 min, was intubated, and received surfactant prior to transfer to the neonatal unit. A peripheral intravenous line was sited and 10% glucose at 120 ml/kg/day commenced. Umbilical venous and arterial lines were inserted and chest x-ray and cranial ultrasound scan performed. At 4 h of age, the initial glucose infusion was replaced with Vamin-glucose (an amino acid–containing solution) at 90 ml/kg/day. By the second day, her weight had fallen to 605 g and ventilator requirements were minimal. The Vamin-glucose infusion rate was increased to 120 ml/kg/day with the addition of lipid, delivering approximately 100 kcal/kg/day. Trophic feeds of expressed breast milk at 15 ml/kg/day were commenced. By day 12, she was tolerating 150 ml/kg/day of expressed breast milk. Parenteral nutrition was discontinued, and next milk feeds gradually increased over the following week to 200 ml/kg/day.

Monitoring Renal Function

Formal measurement of GFR is not usually made in the newborn though the plasma or serum creatinine (SCr) is widely used as a proxy. Serial measurement of SCr is recommended over blood urea for assessment of renal function as the latter is influenced by many nonrenal factors. Sequestered blood in the gastrointestinal tract as well as an excessive protein intake will result in a rise in blood urea despite unaltered renal function. The SCr at birth reflects the maternal value. SCr falls with postnatal age at a rate influenced initially by the magnitude of the maternally derived load and subsequently, as creatinine is derived from the turnover of phosphocreatine in muscle, the balance between creatinine production, dependent on muscle mass and clearance, dependent on GFR. Hence in the newborn, failure to observe the expected postnatal fall

in SCr, or a sustained rise, is indicative of reduced GFR and impaired renal function. In term newborns, the SCr at birth is around 70–90 micromol/l (about 1 mg/dl), falling to about 30 micromol/l (0.3 mg/dl), range of 15–40 micromol/l (0.17–0.45 mg/dl), by 1 week and remaining at this level up to the end of the first month.

The urine flow rate is important clinical index. Urine can be collected into adhesive urine bags, or into pre-weighed nappies. Catheterization is practicable even in very small babies and is preferable in critical care situations. Healthy breast-fed infants usually excrete urine approximately isotonic to plasma at a rate of about 3 ml/kg/h. A urine osmolality that lies between 200 and 400 mOsm/kg suggests that fluid intake is satisfactory. The minimum acceptable urine flow rate, beyond which solute retention would occur, is widely accepted as around 1 ml/kg/h. This value is based on a maximal urine concentration of 600 mOsm/kg, and the need to achieve a urine flow rate of 25 ml/kg.24 h (1 ml/kg/h) in order to excrete a renal solute load of approximately 15 mOsm/kg/day. The maximal urine flow rate achievable by babies below 30 weeks gestation is around 7 ml/kg/h, rising to around 12 ml/kg/h in mature infants.

Fluid balance monitoring is the responsibility of both medical and nursing staff. The aim of monitoring is to detect problems early, in particular to avoid a potentially reversible situation such as prerenal failure becoming irreversible. At a minimum, fluid balance monitoring for babies receiving intensive care requires that serum sodium, potassium, creatinine, and body weight are measured daily; urine output should also be monitored. A useful adjunctive measure particularly in babies that are very ill or unstable, and in the postoperative period, is continuous monitoring of core–peripheral temperature gap. Satisfactory management is marked by a urine flow rate of at least 0.5–1 ml/kg/h on the first day, rising to 2–3 ml/kg/h thereafter, daily weight loss of the order of 1–2%, followed by weight gain once a balanced energy intake greater than 100 kcal/kg/day has been achieved, a progressive fall in serum creatinine, and Na and K concentrations within the normal range.

Oligo-anuria

Around 7% of healthy term neonates do not pass urine in the first 24 h. In babies receiving intensive care, a fall in urine output below 1 ml/kg.h should lead to prompt assessment and investigation of possible acute renal impairment. The spectrum extends from a reversible reduction in glomerular filtration, mild tubular dysfunction to tubular or cortical necrosis and established glomerular injury. Recovery may be complete or partial, or failure may be irreversible. The clinical history and context are as important as the clinical examination and investigations. The immediate goal is to establish if the cause is due to impaired renal perfusion (prerenal), established renal failure (renal), or obstruction to urine flow (postrenal).

Maternal antenatal treatment with ACE inhibitors, angiotensin receptor blockers, and cyclo-oxygenase (COX) inhibitors may present as renal impairment in the newborn. Impaired renal perfusion accompanies dehydration, hypovolemia, shock and as a consequence of high dose administration of the vasoconstricting inotropes dopamine and epinephrine. The nonselective COX inhibitors, indometacin and ibuprofen, used to promote closure of the ductus arteriosus, reduce GFR and may also reduce urine flow rate through stimulation of the AVP V2-receptor. The COX inhibitors inhibit prostaglandin synthetase, and the effect on glomerular filtration is believed to reflect the dependence of the preterm infant on renal prostaglandins to maintain renal blood flow in the face of high RAAS activity. Ensure the baby is not dehydrated at the start of treatment with indometacin or ibuprofen as this will potentiate renal toxicity. On starting treatment, reduce fluid intake by a third, and monitor daily weight, serum sodium, and urine output. If the baby gains weight, serum sodium falls, or urine output declines acutely, reduce intake volume further. If oliguria persists, it may be necessary to miss a dose until renal function has recovered. The response to COX inhibitors is variable and cannot be predicted with certainly.

Established renal injury may result from failure to recognize and treat preexisting prerenal impairment. Other well-recognized antecedents are perinatal hypoxic-ischemic injury, acute blood loss as in major feto-maternal hemorrhage, systemic sepsis, and hypovolemia arising during surgery. There can be major loss of fluid into the intestinal tract in necrotizing enterocolitis, volvulus, and other intestinal emergencies. Causes of acute renal impairment are shown in *Table 24.1*.

Failure to void in an otherwise healthy newborn baby boy should give rise to suspicion of a diagnosis of posterior urethral valves though this diagnosis is usually now made at antenatal screening. Acute urinary retention is not uncommon in the immediate postoperative period.

Oliguria of antenatal origin, and hence oligohydramnios, is associated with Potter's syndrome (pulmonary hypoplasia and respiratory insufficiency, talipes and joint contractures, low-set ears and flattened nasal bridge). Clinical examination should include abdominal palpation for presence of renal masses and evidence of

Table 24.1
Renal impairment: causes and common clinical situations

Prerenal (*if untreated may progress to established renal failure*)
Dehydration (e.g., high transepidermal losses; unreplaced intraoperative losses; gastrointestinal losses)
Hypovolemia (feto-maternal or other hemorrhage)
Decreased effective intravascular volume (heart failure, lung over-inflation during high-frequency oscillatory ventilation, systemic sepsis)
Cyclo-oxygenase inhibitors (indometacin, ibuprofen)
Intrinsic Renal Disease
Acute tubular necrosis (hypoxic-ischemic insult, aminoglycoside induced, hemoglobinuria, rhabdomyolysis)
Acute cortical necrosis (hypoxic-ischemic insult)
Renal artery/venous thrombosis)
Intrauterine exposure to angiotensin-converting enzyme inhibitors
Congenital renal disorders (cystic dysplasia, autosomal dominant/autosomal recessive polycystic renal disease, congenital nephritic syndrome, renal hypoplasia)
Pyelonephritis
Postrenal obstruction
Unilateral or bilateral uteteral obstruction
Posterior urethral valves
Drug induced (spinal anesthesia)

a distended bladder, assessment of perfusion, measuring capillary-refill time, toe-core temperature gap, and blood pressure. In mature infants, reduced skin turgor, a sunken anterior fontanelle, and excessive weight loss are indicative of dehydration. Poor perfusion is indicated by a core–peripheral temperature gap exceeding 2°C and a capillary-refill time exceeding 2 s. Clinical signs are less reliable with increasing immaturity. Renal function in the neonate is not at steady state, but alters with gestational and postnatal age. Therefore, unlike other age groups, there can be no fixed definition for ARF in the newborn. Renal impairment should be considered if the SCr does not decline with postnatal age or remains above 1.5 mg/dl (about 130 micromol/l). Renal artery or venous thrombosis, and cortical necrosis should be considered when oliguria is accompanied by thrombocytopenia, macroscopic or microscopic hematuria, and hypertension.

In prerenal failure, the avid stimulus to retain sodium and water results in urine with high osmolality (greater than 350 mOm/l), high urea and creatinine, and low sodium concentration (less than 30 mmol/l). This is the basis for attempting to distinguish prerenal from established renal failure from the fractional excretion of sodium (Fe_{Na}), calculated as:

$$FE_{Na}(\%) = \frac{U_{Na} * S_{Cr}}{S_{Na} * U_{Cr}} \times 100$$

where U_{Na} = urine sodium, S_{Na} = serum sodium, U_{Cr} = urine creatinine, and S_{Cr} = serum creatinine. With intact tubular function, sodium reabsorption continues, the Fe_{Na} will be less than 2.5% in mature infants. However, the Fe_{Na} and other similar indices such as the renal failure index ($U_{Na} * S_{Cr} / U_{Cr}$) are unreliable in extremely preterm babies.

Ultrasound examination of the renal tract will identify congenital abnormalities, obstructive lesions, bladder distension and the large, swollen kidneys of renal venous thrombosis. Radionuclide studies are unhelpful in acute renal failure in the newborn.

Prompt recognition is crucial for restoration of renal perfusion and avoidance of progression to overt renal failure. Equally, recognition of established renal failure is essential for optimal management of fluid balance. If prerenal impairment is suspected, administer an initial intravenous volume of 0.9% NaCl, 15–30 ml/kg, over 30–60 min, followed by a single intravenous dose of 2 mg/kg furosemide. As the scant pharmacokinetic information available indicates that the half-life of furosemide is prolonged, exceeding 24 h in healthy preterm infants below 32 weeks gestation, avoid repeated doses as this will result in accumulation and progressive risk of ototoxicity. If restoration of intravascular volume does not result in an increase in urine flow rate, a diagnosis of established renal failure must be made.

Clinical Management of Established Renal Failure

The principles of immediate management are to maintain stable fluid and electrolyte balance, avoid catabolism, support growth, and await recovery. Fluid requirements are calculated as the sum of estimated transepidermal water loss, and measured urine and gastrointestinal losses. In term babies, fluid intake should be restricted to 30 ml/kg/day plus gastrointestinal losses. Central venous access is recommended for the infusion of hypertonic glucose or parenteral nutrition. Intravenous sodium and potassium should be avoided. The intravascular compartment should be supported with infusions of 0.9% NaCl administered as necessary as a bolus over 1 h. Red cell transfusions may be required to maintain an

adequate hemoglobin concentration. Milk feeds are recommended if the baby's condition permits but parenteral nutrition is often required. An energy intake adequate to avoid catabolism and hence hyperkalemia, hyperphosphatemia, and acidosis is desirable. Dietary sodium should not exceed 1 mmol/kg/day and may be given as sodium bicarbonate if metabolic acidosis is present. Hyperphosphatemia is managed by the addition of oral calcium carbonate to feeds. This binds phosphate, rendering it insoluble, thereby reducing intestinal absorption.

Unproven therapies include furosemide by infusion (0.1 mg/kg/h), low-dose dopamine (2–5 μg/kg/min), and low-dose theophylline (8 mg/kg per dose). Dopamine has several effects that potentially affect renal function. Inotropic actions may improve renal perfusion, though vasoconstrictor effects may be detrimental. Dopamine is also a proximal tubular diuretic, increasing the presentation and reabsorption of chloride by the ascending limb of the loop of Henlé, an effect that may increase medullary oxygen consumption and exacerbate medullary ischemia. The direct renal actions of dopamine include inhibition of renal Na^1/K^1-ATPase and Na^1H^1 exchange and attenuation of aldosterone and AVP. In critically ill adult patients, low-dose dopamine does not protect against renal dysfunction.

Except in situations such as overwhelming sepsis and multiorgan failure, the majority of babies in acute renal failure can be maintained in stable condition for several days and even weeks. Elevation in serum creatinine is not an indication for dialysis. Dialysis is indicated when there is inability to meet the baby's nutritional needs because of limitation in the amount of fluid that can be given, intractable metabolic acidosis, volume overload, and severe electrolyte disturbance. A discussion of dialysis techniques is beyond the scope of this chapter. The prognosis of acute renal failure depends on the underlying etiology. Acute cortical necrosis has a poorer prognosis than acute tubular necrosis. Mortality is highest when renal failure is part of a spectrum of multiorgan failure.

Case History

A baby boy weighing 3.0 kg is delivered by emergency Cesarean section following placental abruption at 37 weeks gestation. His heart rate is 40/min, he has no respiratory effort, and he is pale and limp. He receives full cardiopulmonary resuscitation, infusion of 20 ml/kg 0.9% NaCl, and is transferred ventilated to the neonatal unit. The first arterial blood gas at 20 min age shows a profound metabolic acidosis; the pH is 6.95 and the blood lactate 16.9 mmol/l. His mean arterial blood pressure is 32 mmHg. What fluid would you prescribe?

This infant has had a profound hypoxic-ischemic insult. He is shocked and a further infusion of 20 ml/kg 0.9% NaCl is indicated in view of the low blood pressure, aiming to restore renal perfusion. As he is a full-term baby, transepidermal water loss will be less than 15 ml/kg/day. He is at high risk of acute tubular necrosis and fluid overload. A urinary catheter is inserted. Glucose 10% at 30 ml/kg/day is prescribed. However, this will deliver a glucose infusion rate of only 2 mg/kg/min. Careful monitoring of blood glucose is indicated.

Umbilical and venous and arterial catheters are inserted. At 4 h of age, the blood glucose is noted to be 1.9 mmol/l. He receives a glucose bolus.

To increase the glucose delivery to 5 mg/kg/min using 10% glucose would require an increase in infusion volume to 70 ml/kg/day. The fluid prescription is changed to glucose 5% (2.2 ml/h) with glucose 50% (1.6 ml/h) administered through a Y connection by umbilical venous catheter. This delivers a glucose infusion rate of 5 mg/kg/min in a total volume of 30 ml/kg/day. Further infusion of 0.9% NaCl is required, with dobutamine, for blood pressure support.

Over the first 24 h, the urine flow rate averages 0.6 ml/kg/h. By day 2, the baby's weight has risen to 3.2 kg. The SCr has risen from 75 microl/l to 110 micromol/l; serum sodium and potassium are within normal limits. The gain in weight is predictable as total fluid intake over the first 24 h has been 90 ml/kg (270 ml); urine output has been 42 ml. Assuming an insensible water loss of 12 ml/kg/day (36 ml), this would leave him in positive balance of 192 ml. Over the second 24 h, urine output gradually increases.

Trophic milk feeds are commenced at 15 ml/kg/day. His general condition improves. By day 3, his weight has fallen to birth weight. Urine output continues to improve. Milk feeds are increased, blood glucose values stabilize, and the glucose delivery rate is reduced maintaining total intravenous infusion volume at 30 ml/kg/day.

Electrolyte Disturbances

Hypernatremia and Hyponatremia

Sodium is the principal electrolyte of extracellular fluid, and disorders of sodium balance are common in the newborn. It is important to recognize that changes in the serum sodium concentration primarily reflect changes in water balance. In both hypernatremia and hyponatremia, total body sodium may be increased,

decreased, or unchanged. Hypernatremia (serum sodium >145 mmol/l) is an indication that there is an absolute or relative deficit of water in relation to body sodium. Conversely, in hyponatremia (serum sodium <135 mmol/l), there is relative or absolute excess of body water.

When confronted with hyponatremia or hypernatremia, consider the clinical history and assess the change in body weight. Hypernatremia with weight loss suggests dehydration; hyponatremia with weight loss or inadequate weight gain suggests sodium depletion. Hyponatremia in a sick neonate is usually accompanied by water excess; the diagnostic challenge is to establish if whole body sodium is depleted, normal, or increased. In otherwise healthy, stable preterm babies receiving feeds of expressed breast milk, whole body sodium depletion should be suspected if there is poor weight gain despite an intake of 180–200 ml/kg/day. The serum sodium concentration will initially be normal, but the urinary sodium concentration will be less than 20 mmol/l. Chronic sodium depletion is associated with poorer long-term neurodevelopmental outcome.

Appropriate and Inappropriate ADH Secretion

A rise in serum osmolality triggers the release of ADH (AVP) from the posterior pituitary increasing the reabsorption of water. ADH also has vasoconstrictor effects relevant to blood pressure regulation. Hypovolemia and hypotension stimulate baroceptors in the heart and great vessels leading to a rise in circulating ADH. Under experimental conditions, a rise in ADH occurs when intravascular volume falls by about 10%. Pain is known to provoke an antidiuresis, and this may contribute to impaired free water excretion in the sick newborn baby. The syndrome of inappropriate ADH secretion (SIADH) is rare in the newborn baby and should only be made when hyponatremia exists with normovolemia, normal blood pressure, normal renal and cardiac functions, evidence of continuing sodium excretion, and urine that is not maximally dilute. In the newborn, SIADH has been described in acute brain injury and central nervous system infection and following maternal substance abuse. Elevated ADH and hyponatremia are common in acutely ill infants, but this is most likely attributable to reduced intravascular volume that is all too often unrecognized. In the face of hypotonicity and intravascular volume depletion, defense of the latter will take precedence. This effect, namely an ADH response *appropriate* to intravascular volume status, probably underlies the impaired water excretion seen in ill infants. The assessment of adequacy of intravascular volume in babies is not easy. Precipitate cord clamping at birth can result in a reduction in blood volume by as much as 50% when compared with late clamping. The normal range for blood pressure is wide. Blood pressure correlates poorly with blood volume and cannot be relied upon to detect hypovolemia. The core–peripheral temperature difference correlates with circulating AVP; this is useful simple, low cost index ideal for longitudinal monitoring in neonatal intensive care.

Common Clinical Scenarios Leading to Hypovolemia-Induced ADH Secretion

Unrecognized postoperative hypovolemia is a common cause of ADH-driven impairment in free water excretion. Thoracic air trapping in severe chronic lung disease, pneumothorax, and overdistension of the lungs during high-frequency oscillatory ventilation may compromise central venous return with similar effect. Use glucose in 0.9% NaCl, not glucose 5% or 10% alone for intraoperative and postoperative fluid support.

Central Nervous System Effects of Hypernatremia and Hyponatremia

The regulation of cell volume in response to changes in extracellular tonicity is effected through the accumulation or loss of inorganic ions and organic solutes. Acute alterations in tonicity result in cell swelling or shrinkage. Compensation is initially brought about by the movement of electrolytes out of or into the cell. With a hypertonic stimulus, there is cell shrinkage, followed by rapid movement of electrolytes and accompanying water, into the cell, restoring cell volume. If the hypertonic stimulus persists, the concentration of intracellular organic osmolytes rises. With correction of the hypertonic state, loss of organic osmolytes occurs more slowly than movement of electrolytes out of the cell. The persisting intracellular hypertonicity, in the face of falling extracellular tonicity, results in continuous movement of water into the cell, cell swelling, cerebral edema, occlusion of blood flow, and cell death. Conversely, an acute fall in serum sodium concentration and extracellular hypotonicity will lead to intracellular influx of water, edema, and brain swelling. Over a period of time, the intracellular osmolyte concentration decreases to favor the movement of water out of the cell. If extracellular hypotonicity is corrected rapidly after these slow

compensatory changes have occurred, the continuous movement of water out of the cell will result in acute brain shrinkage.

Common Clinical Scenarios

Hypernatremia in the extremely preterm baby is almost always due to excessive transepidermal water loss. Hypernatremia in an otherwise healthy, breast-fed, full-term neonate is well described. It results from inadequate lactation and the baby is dehydrated and sodium depleted. The classic picture is that of an exhausted mother and a hungry baby. Rarer causes of hypernatremia are excessive, injudicious, or accidental administration of sodium bicarbonate or hypertonic sodium chloride. Hypernatremia due to salt poisoning is distinguished by a high fractional excretion of sodium and absence of weight loss.

Treatment

Hypernatremia

Mild hypernatremic dehydration in a mature baby may be corrected with milk feeding. If intravenous rehydration is necessary, the initial fluid should be 0.9% NaCl with glucose 5% or 10%, followed by 0.45% saline with glucose 5% or 10%. Do not use hypo-osmolar salt-poor fluid. Milk feeds should be continued except where a specific contraindication exists. The intravenous infusion rate (ml/h) may be calculated as:

$$[M + D/T]/24$$

where: M = Daily maintenance volume (ml); D = total Deficit (ml); T = Time over which to correct deficit (days).

Serum electrolytes and blood glucose must be monitored closely. If the serum sodium falls at a rate exceeding 0.5 mmol/l/h, reduce the rate of infusion. Though the exact time scale over which the neonatal brain adapts to alterations in tonicity is unclear, correction must be tailored to the duration of the imbalance. If hypernatremia develops over a period of hours, as with excessive transepidermal water loss, reducing the serum sodium by 1 mmol/l/h is believed to be safe. In all other circumstances, the rate of reduction should not exceed 0.5 mmol/l/h. Too rapid correction can cause cerebral edema, convulsions, and permanent brain injury. Extremely severe hypernatremia (serum sodium >200 mmol/l) requires correction by peritoneal dialysis.

Hyponatremia

Restriction of water intake to correct dilutional hyponatremia should not obviate the need to treat the underlying cause. Acute severe hyponatremia (serum sodium <120 mmol/l) is rare in neonatal medicine. If associated with neurological signs, the intravenous infusion of 3% sodium chloride (sodium content approximately 0.5 mmol/ml) is justified but should never exceed 1 ml/kg/h and should be stopped before the serum sodium has normalized. A sodium deficit requires correction, but once body stores have been replenished, intake must be reduced to maintenance requirements. Sodium depletion in babies fed exclusively with expressed breast milk is likely to require an oral sodium supplement of 2–4 mmol/kg/day until a postmenstrual age of 32 weeks is reached.

Potassium Balance

Potassium is the principal electrolyte of intracellular fluid. The normal serum potassium concentration is 3.5–5 mmol/l. The kidney is the primary regulator of potassium balance. More than 60% of filtered potassium is reabsorbed in the proximal tubule; reabsorption continues along the thick ascending limb of the loop of Henlé so that only around 10% is delivered to the distal tubule and collecting ducts. Here potassium is exchanged for sodium driven by Na+K+ATPase. Aldosterone and acute respiratory and metabolic alkalosis stimulate potassium excretion. In children and adults, the major component of dietary potassium is reabsorbed in the small intestine, with fine-tuning in the colon.

Hypokalemia

Common causes of hypokalemia in the neonate are insufficient intake, metabolic or respiratory acidosis, and treatment with loop diuretics. Preterm neonates fed intravenously require a potassium intake of 2 mmol/kg/day, commencing within 48 h of birth if urine output and renal function are normal.

Hyperkalemia

Spurious hyperkalemia is common in neonatal intensive care when blood sampling is difficult and samples are hemolysed. True hyperkalemia results from renal failure and is a medical emergency when severe, with the risk of

death from ventricular fibrillation. The classical ECG changes of peaked T-waves, PR prolongation, of P-wave flattening, and QRS widening are not usually evident in extremely preterm babies until the serum potassium exceeds 8 mmol/l. Values exceeding 6 mmol/l should be checked in a free-flowing blood sample. If confirmed, immediate measures that promote a shift in potassium from the extracellular to intracellular compartment are indicated. These include administration of intravenous (4 mcg/kg over 5 min) or nebulized (2.5–5 mg) salbutamol (albuterol), intravenous glucose and insulin by infusion (12 units soluble insulin in 100 ml 25% glucose; 5 ml/kg given over 30 min), intravenous sodium bicarbonate 1 mmol/kg (2 ml/kg 4.2%) and 10% calcium gluconate (0.1 ml/kg) by intravenous injection over 10 min. The blood glucose should be monitored closely. Sodium bicarbonate is effective even if the baby is not acidotic but should not be administered through the same line as calcium gluconate because of the risk of precipitation. Oral/rectal cation exchange resins (calcium polystyrene sulfate) remove potassium. To reduce the risk of bowel obstruction, administer rectally and remove prior to the next dose by gentle saline lavage.

Acid-Base Disturbances

Acidosis (or acidemia) is defined as an arterial pH below 7.35 and alkalosis as a pH exceeding 7.45. This normal pH range for extracellular fluid corresponds to an H^+ concentration of 35–45 mEq/l. Acidosis and alkalosis may be metabolic, respiratory, or mixed in origin. Regulatory responses to acid-base disturbances involve immediate buffering, respiratory and renal compensation, in order of speed of onset. Bicarbonate is the most important buffer, illustrated by the classic equation, $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ where CO_2 clearance is regulated by respiratory function, and HCO_3^- regeneration by the kidneys. In the face of an acid challenge, the equation is pushed to the left. In healthy individuals, respiratory rate increases, carbon dioxide is eliminated, and equilibrium is restored. Renal compensation involves the formation of carbonic acid from carbon dioxide and water. This dissociates into H^+ and HCO_3^- in the proximal tubular cells. H^+ is actively pumped into the renal tubular lumen to combine with filtered bicarbonate to form carbonic acid, which dissociates into water and CO_2. The CO_2 diffuses back into the tubular cell to repeat the cycle, regenerating one bicarbonate ion for each hydrogen ion excreted. In adults, bicarbonate is regenerated so as to maintain a plasma concentration of about 25 mmol/l. Preterm babies have a lower threshold. Hydrogen ions are excreted along the nephron and combine with other base-buffers, chiefly phosphate, sulfate, and ammonia in the tubular fluid, when bicarbonate reabsorption is complete. Newborn infants can acidify urine to the same extent as healthy adults.

Interpretation of Blood Gas Results

In an otherwise normal subject, a fall in pH will stimulate hyperventilation, shift the carbonic acid equation to the left, and increase CO_2 elimination. The features of acute metabolic acidosis are a low bicarbonate, normal PCO_2, and low pH; the features of compensated metabolic acidosis are a low bicarbonate, low PCO_2, and normal pH. Infants with both respiratory disease and a metabolic acidosis will show a mixed picture, with a high PCO_2, low bicarbonate, and low pH. In a ventilated infant, acute respiratory acidosis is managed by increasing the tidal volume or respiratory rate to lower the PCO_2. Once compensatory changes have taken place, lowering the PCO_2 will lead to a respiratory alkalosis, hence the importance of recognizing if compensation has taken place and in this case, targeting ventilation management upon achieving a normal pH, and not a normal PCO_2. The best measure of metabolic acidosis is the Standard Base Excess (SBE) as this is independent of PCO_2. Changes in arterial blood in acid-base disturbances are shown in *Table 24.2*.

Table 24.2
Changes in arterial blood in acid-base disturbances

	pH	PaCO2	$HCO3^-$
Metabolic acidosis, acute	↓	→	↓
Metabolic acidosis, compensated by increased ventilation	→	↓	↓
Respiratory acidosis, acute	↓	↑	→
Respiratory acidosis, compensated by increased renal $HCO3^-$ retention	→	↑	↑
Metabolic alkalosis, acute	↓	→	↑
Metabolic alkalosis, compensated by decreased ventilation	→	↑	↑
Respiratory alkalosis, acute	↓	↓	→
Respiratory alkalosis, compensated by increased renal $HCO3^-$ excretion	→	↓	↓

Metabolic Acidosis

Renal excretion is the only route for the elimination of acids generated by oxidative metabolism. Metabolic acidosis arises from increased production (or administration) of acids, decreased excretion, or reduced bicarbonate regeneration. Acid gain may arise from respiratory or metabolic disorders. The commonest causes in neonatal intensive care are tissue hypoxia and renal failure. Parenteral nutrition amino acid intolerance and inborn errors of metabolism are well recognized but rare causes. Proximal and distal renal tubular acidosis are rare disorders that usually present beyond the neonatal period. Hypovolemic situations are characterized by lactic acidosis. If the cause of a metabolic acidosis is unclear, measurement of the anion gap (AG) may be helpful. This is the difference between the sum of the serum sodium and potassium concentrations and the sum of chloride and bicarbonate, $AG = (Na^+ + K^+) - (Cl^- + HCO_3^-)$. In practice, the K is often ignored and the simplified formula $AG = Na^+ - (Cl^- + HCO_3^-)$ may be used. The normal AG is 12–20 mmol/l and reflects unmeasured anions, albumin, phosphate, and small amounts of lactate and other organic anions. Modern blood gas analyzers provide a measure of lactate. A wide AG should raise suspicion of the possibility of an inborn error of metabolism. Management should be directed toward restoring tissue perfusion; as this improves, the acid load is eliminated. Treatment with base, as sodium bicarbonate or THAM, is probably employed far more often than is necessary. If treatment with base is considered, bear in mind that commonly used formulae to calculate the "dose" to be administered are imprecise. The widely used formula "0.3 × body weight × base deficit" to estimate the full correction requirement is based on adult extracellular volume (20% of body weight) increasing the factor 0.2 – 0.3 as administered base equilibrates in part with the intracellular compartment. The extracellular compartment is larger in the neonate, and in most neonatal intensive care situations, the rate of acid accumulation is uncertain. Recent evidence does not support any benefit for acute correction of base deficit. Acute administration of base may actually exacerbate intracellular acidosis; care should be directed toward addressing the underlying cause of the acidosis.

Respiratory Acidosis

This arises in respiratory failure, when carbon dioxide elimination is impaired, pushing the equation $CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^-$ to the right. As a result, the $PaCO_2$ and blood HCO_3 rise and pH falls. The renal response involves increased H^+ excretion and bicarbonate regeneration, leading to gradual compensation over many days.

Metabolic Alkalosis

A metabolic alkalosis is caused by gain of base, as in the injudicious use of sodium bicarbonate or from loss of acid. A common cause is loss of gastric acid and chloride in high intestinal obstruction, vomiting or failure to replace gastric aspirates. In the distal tubule and collecting duct, sodium is reabsorbed in exchange for either potassium or hydrogen ions, under the influence of aldosterone. If intracellular H^+ is low, potassium is preferentially lost and vice versa, explaining the association between alkalosis and hypokalemia. Hypokalemia is both a cause and a consequence of metabolic alkalosis. Chronic diuretic therapy results in metabolic alkalosis through multiple mechanisms and is commonly seen in infants with chronic lung disease who are receiving diuretics. Other causes of metabolic alkalosis are Bartter's syndrome, a tubulopathy caused by mutations in membrane transporters in the thick segment of the ascending limb of the loop of Henlé that result in failure of reabsorption of sodium, potassium, and chloride, increased salt delivery to the distal nephron, and salt loss, volume depletion, hyperaldosteronism, hypokalemia, and metabolic alkalosis. Polyuria may be evident antenatally. Similar biochemical findings can occur due to transcutaneous electrolyte loss in cystic fibrosis and intestinal loss in congenital chloride-losing diarrhea. Treatment consists of potassium supplements and indometacin (up to 3 mg/kg/day in divided doses). Sodium supplementation may also be required.

Respiratory Alkalosis

This results from hyperventilation; the PCO2 will be low. The commonest cause in the neonatal unit is iatrogenic and occurs during assisted ventilation, particularly high-frequency oscillatory ventilation. This is dangerous because of the consequent reduction in cerebral blood flow. Spontaneous hyperventilation may be a feature of neurologically damaged infants.

Long-Term Renal Sequelae of Extremely Preterm Birth

Preterm birth is emerging as a risk factor for higher blood pressure and hypertension in adult life, though whether this is renal or vascular in origin is unclear. Plausible contributors to impaired third trimester nephrogenesis are nephrotoxic medications, ischaemic injury and poor nutrition. The concern is that nephron deficit may lead to compensatory hyperfiltration, glomerulosclerosis, deteriorating renal function, and elevated blood pressure in adult life. To-date assessment of renal function in preterm cohorts has not identified consistent alteration in renal function. As the earliest of these cohorts are still in early adulthood, continued follow-up is essential.

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25 Gastrointestinal System and Neonatal Nutrition

Christopher Young · Maka Mshvildadze · Josef Neu

Introduction

The intestine is one of the most active and complex organ systems in the body. As an example of its complexity, it is notable that the system contains neural tissue equivalent to the entire spinal cord. The intestine is involved in important endocrine and exocrine roles and also serves as the largest and most active immune organ of the body. In addition to the intestine itself, the luminal microbiota and its interactions with the intestinal mucosa and submucosa are becoming increasingly recognized as critical in postnatal development and lifelong health and disease. In addition to these seemingly newfound GI tract functions, its classic role in digestion and absorption of nutrients remains of utmost importance in health and needs to be understood in order to optimize nutrition during these highly critical windows of development.

Dramatic events in gastrointestinal (GI) system development begin in the 3rd week of fetal development. Gastrulation, organ formation, growth, herniation, rotation, and retraction complete the major anatomic features of normal fetal GI system development over the first 12 weeks. During this time, a complex mixture of neurologic, vascular, endocrine, exocrine, and immune tissue development also occurs, which will postnatally provide not only nutritive, but also immune, barrier, endocrine, and other critical functions. The goal of this chapter is to provide an overview of some of the salient features of physiology and development of the GI tract and how it relates to neonatal nutrition and other aspects of neonatal and subsequent health.

Gastrointestinal System Development

Beginning around the 3rd week of gestation, gastrulation begins the complex process of GI system development. By the end of the first week of gastrulation, the newly formed gut tube is nearly closed and development of the liver, gallbladder, and pancreas has begun as evaginations from the endoderm. At about 4 weeks of gestation, the human esophagus can be identified as a distinct structure. The fetal stomach begins to develop at 13 weeks and characteristic anatomical features can be identified by the 14th week. This is important in that failure to identify the fetal stomach by ultrasound in the second trimester indicates the possibility of esophageal atresia, and an enlarged stomach may herald the presence of duodenal atresia or a gastric outlet obstruction. The liver begins its development as a diverticulum which emerges from the caudal foregut, distal to the stomach, at about the 4th week of gestation. Morphogenesis of the pancreas begins at about 30 days of gestation, and at around 20 weeks of gestation, enzyme activity is detectable. By the 13th week, organogenesis of the human intestine is complete (*Table 25.1*).

The three major arteries supplying the GI system, the celiac, and superior and inferior mesenteric arteries, have also begun to form and help establish further growth and development. With establishment of the vascular system, growth proceeds rapidly with the continued expansion and rotation of the primordial GI tract. By the 5th week, growth has produced herniation of the gut tube into the umbilical cord. Beginning at week 7, rotation of the intestine begins and continues until about the 11th week, at which time retraction occurs, and the process is completed by the 12th week with the establishment of neural innervations. The fetus starts to swallow amniotic fluid at 16 weeks, which plays an important role in intestinal growth and differentiation.

The fetal GI lumen is bathed in the nutrient rich milieu of amniotic fluid and extracellular matrix. Unless there is an intra-amniotic infection or other major insult, the fetal GI system remains primarily in growth mode, preparing for the extrauterine environment. Once birth occurs, the GI system's functions accelerate in its roles as a nutritional, endocrine, and immunologic organ. It is also almost immediately exposed to external microbes, most of which are incorporated into a symbiotic relationship. It takes over the conduit role of the mother and the umbilical cord for food digestion, absorption, and assimilation. Most of the required GI physiologic mechanisms to achieve this nutritive function are mature at term birth;

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Table 25.1
GI tract developmental milestones

Event	Timing
Gastrulation begins	Week 3
Liver and pancreatic buds develop, esophagus established	Week 4
Organogenesis complete	Week 13
Stomach has identifiable anatomic features	Week 14
Fetus begins to swallow amniotic fluid	Week 16
Pancreatic enzyme secretion detectable	Month 5

however some, such as bilirubin conjugation and hepatic drug metabolism, only mature in the postnatal period. Other mechanisms, such as esophageal motility and sphincter function, gastric acid and bile salt synthesis and secretion, glucose absorption, and bile salt absorption continue to develop well after birth. One notable example is that pancreatic exocrine function is only completely developed after 6 months postnatal age. The normal growth, development, and subsequent maturation of this complex organ system establish one of the most important systems of the body.

Gastrointestinal System Function

Barrier Function

The GI system performs many physiologic functions, as mentioned previously. As the largest surface area of the body that is exposed to trillions of microbes and a large mass of food antigens, the intestine requires a barrier mechanism that provides for selective entry of luminal constituents. There is only a single cell layer, the intestinal luminal epithelial surface, covered by a thin layer of mucus, which separates the extremely sensitive immunoreactive submucosa from potentially immunogenic substances in the lumen. This epithelial layer comprises a large surface area in the adult, encompassing approximately 200 m^2, through the formation of crypts, villi, and microvilli throughout the length of the small intestine. The epithelial surface has a rapid turnover: it is completely replaced every 2–5 days as cells migrate from the crypts to the tips of the villi, eventually dying, and being sloughed into the intestinal lumen. About 20–50 million cells per minute are shed in the small intestine, and 2–5 million cells per minute are shed in the colon. These cells are continuously replaced by dividing multipotent stem cells, which replace each cell lost with cells of the same lineage.

Much like the epithelial lining of the skin, the luminal epithelial layer of the GI system provides an important boundary with the external environment. This single-cell layer has many defense mechanisms, however, to help ward off invasion from offending exogenous agents. Tight junctions located intercellularly form complexes that regulate molecular transport both into and out of the intestinal lumen. This also adds a protective feature to the GI system, being the apparatus by which the intestine can secrete large amounts of chloride and water to flush exogenous toxins and pathogens. This layer also contains specialized mucin-producing goblet cells that provide a thick protective mucous layer to protect and lubricate the cells of the intestinal epithelium. Other cell types, such as Paneth cells, secrete defensive antimicrobial peptides into the lumen of the GI system to help modulate pathogenic bacterial content. Breakdown of this barrier has been related to several pathologic processes including neonatal sepsis and subsequent autoimmune and allergic diseases. It is becoming increasingly recognized that commensal bacteria play an integral role in the process of epithelial repair and barrier integrity, and that disruption of these microbes could have deleterious consequences.

Digestive–Absorptive Function

The process of digestion starts in the mouth and continues throughout the GI system (*Fig. 25.1*). It is important to note that this complex process is more involved than the purpose of this chapter, so a physiology text would be best for full details. Here, the salient features are summarized for clinical application.

Starting with the mouth, mechanical and chemical breakdown are initiated; mechanically through the process of mastication, and chemically with the presence of primary reducing enzymes in the saliva. For neonates and infants, the initial steps in the process are obviously dependent on the type of feeding the baby is receiving. The simpler the starting food source, the easier the process of digestion will be.

In the mouth, enzymes, such as amylase, begin the process of digesting relatively complex carbohydrates into simple sugars for subsequent absorption (*Table 25.2*). Mastication allows the food to be mechanically broken apart and provides more surface area for the action of these digestive enzymes.

As the food passes to the stomach, acids are released from the parietal lining which further the process of breakdown in addition to the mechanical action of the stomach with churning and mixing. Lipases derived from

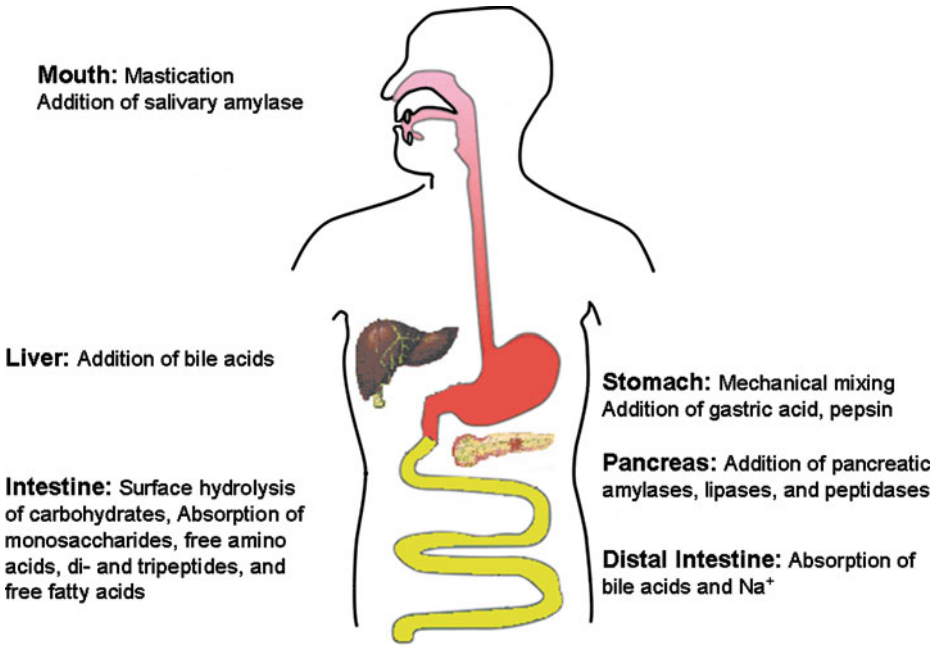

Figure 25.1
Overview of digestion and absorption

Table 25.2
Digestive enzymes and functions

Location	Digestive enzyme	Function
Mouth	Amylase	Breaks down simple sugars
Stomach	Stomach acids	Mechanical action of the stomach and addition of acids aids in digestion
Small intestine	Lipases, pancreatic enzymes, bile, pepsin, proteases	Continues the process of digestion as the food passes through to the colon

breast milk and from lingual, gastric, and pancreatic origins are added to the mixture and digestion proceeds as the food passes from the stomach into the small intestine. Pancreatic enzymes, bile, pepsin, proteases, and many other digestive enzymes continue the process of digestion as the food passes through the small intestine.

As food passes through the digestive system and is broken down, absorption of the nutrients occurs at the level of the microvillus (brush border) membrane. Among the several cell types that comprise the intestinal mucosa, the differentiated villus enterocyte, at the mid villus to the tip regions, are the most specialized for absorptive purposes.

Neonatal Nutrition

In order to understand the intricacies of neonatal nutrition, it is vitally important to understand the processes through which the different nutritional components are digested and absorbed. By understanding these key processes and combining them with an understanding of fetal and neonatal growth, it is easier to understand the nutritional requirements and feeding methods used for neonates. The following sections will describe these processes and how they relate to neonatal nutrition.

Carbohydrate Digestion and Absorption

The simplest process involves the breakdown of simple and complex carbohydrates. For complex carbohydrates, they must first be broken down into their main components, the oligosaccharides, by digestion via salivary amylase in the mouth and stomach, and pancreatic enzymes added in the upper small intestine (*Table 25.3*). For absorption, the oligosaccharides must be hydrolyzed into

Table 25.3
Carbohydrate digestion and absorption

Location	Digestive entity	Function
Digestion of carbohydrates		
Mouth	Amylases derived from the saliva (and colostrum)	Hydrolyze starches and complex carbohydrates into oligosaccharides
Small Intestine	Pancreatic amylases	Hydrolyze carbohydrates into oligo- and monosaccharides
Distal intestine	Bacteria	Hydrolysis of undigested sugars into short-chain fatty acids
Absorption of carbohydrates (oligosaccharides must be hydrolyzed into monosaccharides)		
Intestinal epithelial brush border	Maltase	Cleaves maltose into two molecules of glucose
	Lactase	Cleaves lactose into glucose and galactose
	Sucrase	Cleaves sucrose into glucose and fructose

monosaccharides, a process which occurs primarily at the intestinal epithelial brush border by hydrolytic enzymes such as lactase, sucrase, and maltase (*Table 25.3*). Dietary lactose, sucrose, and maltose come in contact with the surface of absorptive epithelial cells covering the villi where they engage with brush-border hydrolases performing the following functions:

- Maltase cleaves maltose into two molecules of glucose
- Lactase cleaves lactose into a glucose and a galactose
- Sucrase cleaves sucrose into a glucose and a fructose

The process of absorption of each of these monosaccharides is different. Glucose and galactose are taken into luminal enterocytes by a transport mechanism involving sodium cotransport. Fructose, on the other hand, is taken up by enterocytes by facilitated diffusion (passive transport) (*Fig. 25.2*).

For the purposes of neonatal nutrition, this process is vitally important. Depending on the starting carbohydrate composition of the infant's primary food source, the process of carbohydrate digestion can be affected by many factors, including the maturity of the infant's pancreatic function, the presence and functionality of the intestinal hydrolytic enzymes, and whether or not the infant is breast-fed.

Breast-feeding, for the purposes of carbohydrate metabolism, is important in that the breastmilk of mothers with babies born preterm actually contains an enzyme, α-amylase, that aids in oligosaccharide digestion. This is important, because even in babies born at term, there are lower levels of amylase from both salivary and pancreatic sources than at adulthood. As the baby matures, these enzymes increase in quantity, but their low levels in the neonatal period are important to remember when administering any complex carbohydrates to these infants.

For these reasons, most preterm and some term formulas contain partially hydrolyzed carbohydrates. This helps aid in digestion by providing a simpler and easily accessible source of sugars, but also increases the osmolality of the formula. It has not yet been established whether the hydrolyzed starch formulas have any advantage over those containing lactose or other disaccharides. Whether lack of salivary or pancreatic amylase plays a significant role in premature infants is questionable, since the major carbohydrate in human milk is lactose. Also, many premature babies are fed by tube in neonatal intensive care units; thus the food partially bypasses the action of the salivary amylase and appears to be digested without problem in healthy infants.

The majority of the carbohydrate contained in standard cow's milk formulas and in human milk is lactose. Lactase activity is relatively low in preterm infants but increases with maturity. This concept has led to many formulas being produced that contain carbohydrates other than lactose. However, bacteria in the lumen of the intestine have the ability to ferment lactose into short-chain fatty acids, which can then be salvaged via absorption into the distal intestine and utilized for energy production and other important roles. Thus, the use of lactose-containing formulas or human milk feedings in preterm infants is not contraindicated, especially since feedings in these infants are advanced slowly and do not exceed the theoretical thresholds for enzymatic capability.

Protein Digestion and Absorption

The protein composition of feedings provided to neonates is largely dependent on either the composition of the

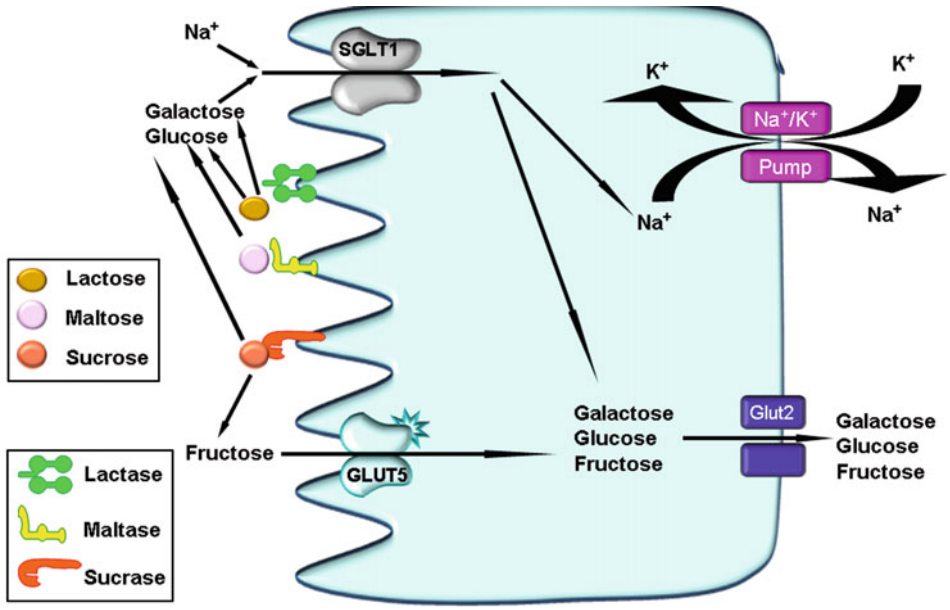

Figure 25.2
Digestion and absorption of carbohydrates

maternal breastmilk or that of the infant formula chosen for the baby. Understanding the process of protein digestion and absorption should help with the choice of feeding provided to infants.

The process of protein digestion begins in the stomach as the food enters the acidic environment (*Table 25.4*). The mechanical forces of the stomach ensure mixture of the food with gastric acid and the proteolytic enzymes that begin the digestive process. As the food enters the intestine, pancreatic enzymes, including proteases and peptidases, are added and the digestive process continues. It is important to note that, in most instances, the proteins must be digested into their amino acid components, or at least into smaller peptides, to be absorbed by the intestinal enterocyte.

Proteolysis occurs through the actions of pepsinogen, which is converted in the stomach by the acidic environment into pepsin, and the other pancreatic peptidases, including trypsin. Through the action of these enzymes, the proteins are broken down into shorter oligopeptides (di- or tripeptides). These oligopeptides can then generally be absorbed into the cells. This occurs through a cotransport mechanism with hydrogen ions (*Fig. 25.3*).

Once the oligopeptides have entered the cell, they are then further hydrolyzed by intracellular peptidases into their individual amino acids, which can then be assimilated into the bloodstream. Only a few of the oligopeptides enter the blood without having been hydrolyzed into individual amino acids.

An important aspect of the neonatal absorptive process is that early in the newborn period, some proteins are allowed to pass into the cells from the intestinal lumen without being broken down. This is important in the passing of maternal antibodies (passive immunity) to the infant. This ability is rapidly lost, so feedings with colostrum in infants whose mothers intend to breast-feed should be initiated as soon as possible after birth. This also, in part, describes why it may be important to limit the intake of certain highly antigenic proteins (such as peanuts, eggs, and shellfish) during this hyper-permeable period.

Just as with the hydrolytic enzymes needed for carbohydrate digestion, the proteolytic enzymes are present in much lower concentrations in neonates than in adults. This is especially true in the premature infant. Peptic activity is low and is in proportion to the degree of maturity. As was true of the formulas containing hydrolyzed carbohydrates, some formulas also contain hydrolyzed proteins as well as different proportions of casein and whey. The use of these formulas is still an area of much debate.

For clinical correlation, it is important to note that there is a large amount of protein present in the amniotic

Table 25.4
Protein digestion and absorption

Location	Enzyme	Function
Digestion of proteins		
Stomach	Stomach acid	Food is mixed well with the stomach acid and proteolytic enzymes
	Pepsinogen – converted to pepsin by the acidic environment	Proteolysis – proteins are broken down into shorter oligopeptides
Intestine	Pancreatic enzymes – proteases, peptidases, trypsin	Proteolysis continues
Absorption		
Enterocytes	Hydrogen ions	Amino acids are taken into the cell by a cotransport mechanism
	Intracellular peptidases	Hydrolyzed into their amino acid building blocks, they can then enter the bloodstream

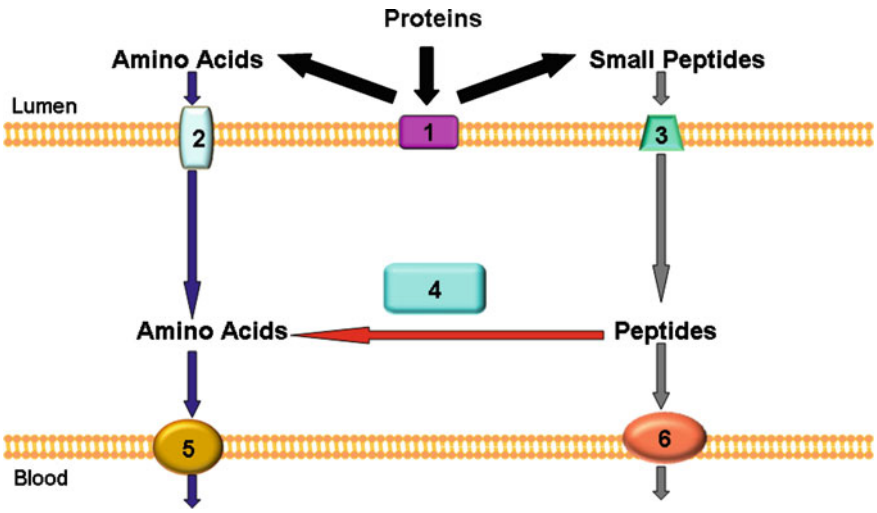

Figure 25.3
Protein absorptionProtein absorption in the small intestine: *1* brush-border membrane peptidases; *2* brush-border membrane amino acid transporters; *3* brush-border membrane di- and tripeptide transporters; *4* intracellular peptidases; *5* basolateral membrane amino acid carriers; *6* basolateral membrane di- and tripeptide carriers

fluid. Each day, approximately 50% of the amniotic fluid volume is swallowed by the fetus. Thus, the fetus at or near term ingests about one fifth of its daily protein from the amniotic fluid alone. Once the amniotic membranes rupture or if the baby is born prematurely, this important source of protein is removed. In the fluid, a fairly wide spectrum of proteins are obtained which include human serum albumin, immunoglobulin (Ig) G, IgA, chorionic gonadotropin, and growth hormone. It is important to note that the protein requirements for preterm infants are significantly higher than in those infants delivered at term.

Another clinical consideration should be that there is lower acid secretion in the stomach of the premature infants. Studies suggest that critically ill premature infants treated with H_2 blockers have a higher incidence of nosocomial infections and necrotizing enterocolitis. It is speculated that with the already limited hydrogen ion production in the stomach of the preterm infant, additional reduction further diminishes the acid barrier and

allows for a higher load of potentially pathogenic bacteria to reach the more distal regions of the intestine.

Lipid Digestion and Absorption

There are many different types of lipid molecules that comprise the food that we eat. Most of them are neutral lipids or triglycerides, but they are also made up of phospholipids, sterols, and fat-soluble vitamins. An understanding of their digestion and absorption is vital in order to optimize infant nutrition.

The process of lipid digestion occurs in two major steps and requires bile acids and lipases (*Table 25.5*). The first step involves the breakdown of large globules of lipid into smaller particles via micellar emulsification. This is a process that allows for greater fat-mucosal interaction at the absorptive surface and allows for more efficient absorption. Bile acids, through their amphipathic properties, form a micelle, which is a circular structure with a hydrophilic exterior and hydrophobic interior that leads to emulsification of the larger lipid globules. The triglycerides in the emulsified micellar particles are then de-esterified into their main components, 2-monoglyceride and free fatty acids, via the action of lipases and are then are transported into the enterocyte (*Fig. 25.4*). Most of the primary lipases are derived from the pancreas but there are several other lipases that are thought to be important, including human milk–derived bile salt stimulated lipase, lingual lipase, gastric lipase, and intestinal epithelial cell–derived lipases.

Once inside the enterocyte, the process takes different pathways depending on the chain length of the free fatty acid. Longer chain fatty acids and 2-monoglycerides are transported to the Golgi apparatus where they are resynthesized into triglycerides and packaged into chylomicrons. The chylomicrons are packaged into vesicles which are exocytosed into the lymphatic system, which

Table 25.5
Lipid digestion and absorption

Steps	Enzyme/structure	Function
Digestion of lipids		
Micellar emulsification of fat globules	Bile acids	Formation of micelles – provide a larger charge-specific surface area for the enterocytes to uptake the fatty acids and monoglycerides
Triglyceride hydrolysis	Lipases	Formation of absorbable 2-monoglycerides and free fatty acids
Transport into the enterocytes	Poorly understood transport processes	Transport of the 2-monoglycerides and free fatty acids into the intestinal epithelial cell
Absorption		
Golgi apparatus processing	Golgi apparatus	Monoglycerides resynthesized into triglycerides and packaged into chylomicrons
Lymphatic system	Chylomicrons	Chylomicrons are packaged into vesicles, exocytosed into the lymphatics, and rapidly enter the blood

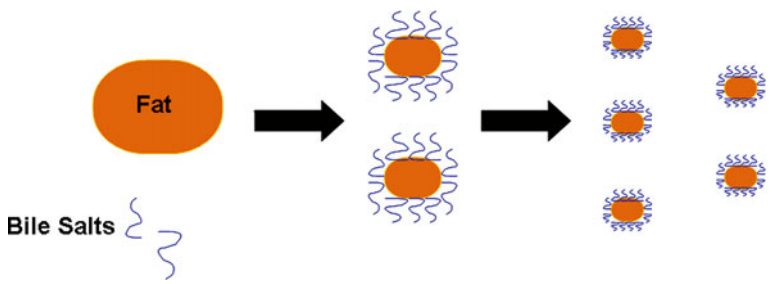

Figure 25.4
Digestion of lipids-micellar emulsification

rapidly flows into the blood. The blood carries these chylomicrons throughout the body where they are broken down and used for energy or stored.

Medium-chain fatty acids are processed differently. Once they enter the enterocyte, instead of being reprocessed, they are able to directly enter the portal venous system. This process is important to understand for instances where the lymphatics are obstructed or severed, such as in a chylothorax. Feeding those infants with long-chain fatty acid rich formulas is not recommended, but using a formula with medium-chain fatty acids would be helpful.

Another developmentally important aspect of lipid digestion and absorption is that in the preterm neonate, bile acid formation and reabsorption are limited, so the use of large amounts of fat in their formulas could lead to undigested and unabsorbed fat passing through the intestines. The use of medium-chain triglyceride lipids that do not undergo such complex processes of digestion and absorption should lead to better growth. However, comparative benefits of routinely using the medium- versus long-chain triglycerides in the nutrition of premature infants have not been firmly established.

Fat absorption from breast milk increases slightly during the first month in infants born at term. In total, this increase results in absorption values reaching close to 90%. Surprisingly, the absorption of fat in premature infants is close to that of full-term infants. This is due to the fact that although long-chain fatty acid absorption is lower during the first 6 weeks of life, medium- and short-chain fatty acids are absorbed quite efficiently in premature infants soon after birth.

The long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexaenoic acid (DHA), are critical in the formation of the structural components of the central nervous system. They are found in relatively high concentrations in human milk, especially in mothers who live in marine coastal areas who also eat a diet rich in fish. These have recently been added to many commercial formulas, but are not present in routinely used intravenous lipid solutions. Whether the addition of these LCPUFAs to formulas results in improved neurodevelopment remains the subject of current intense investigation.

Other Aspects of the Infant GI System

As mentioned in the introduction to this chapter, the gastrointestinal system is one of the most complex and integral organ systems in the body. It is considered to be one of the largest immune structures in the body. The luminal surface is constantly being exposed to bacteria and other antigens, essentially the external environment. The infant GI system is responsible for protecting the infant against pathogens, establishing a healthy relationship with commensal organisms, and preventing the development of autoimmunity, among other important tasks.

The development of this system is vitally important to set the infant up for a life of health and proper nutrition. One important aspect of the development of the GI tract is the colonization by bacteria. The steps that initiate this process begin almost immediately as the gut tube is formed early in gastrulation. It has previously been held as convention that the amniotic fluid that the fetus swallows in utero is sterile. However, recent studies have found, using non-culture-based techniques, that there are bacteria present in the amniotic fluid that may not have been detected by standard culture-based techniques. There has also been research performed that shows the fetal GI tract can produce a systemic inflammatory response. Further studies have shown a link between these bacteria and an inflammatory response that may lead to preterm labor. Postnatally, in premature infants, an inflammatory process likely related to aberrant intestinal microecology has also been shown to be important in the pathogenesis of necrotizing enterocolitis, and there is currently a great deal of research being performed to help diagnose this devastating condition.

The colonization of the infant with commensal, or "good," bacteria however helps to establish the GI tract as a healthy, protective system. Studies show that if kept in a sterile environment, animals had an increased susceptibility to infections, decreased digestive enzyme activity, decreased smooth muscle thickness, and reduced vascularity when compared with animals that had a normally developed intestinal microbiota.

Therefore, the composition of the intestinal flora has been determined to be important in both health and disease states. In this context, it can be seen that excessive use of antibiotics is likely to have adverse consequences on the bowel intestinal microbiota. Further, it is important to keep this delicate balance in mind when considering the use of nutritional adjuncts such as pre- or probiotics. There has been a recent trend toward the addition of these supplements to infant formulas and in the treatment of infants; however, there is still not enough data to promote their regular use in the neonatal population. By altering the delicate balance of the intestinal flora, the use of these and other supplements could alter the natural state of immune tolerance in the GI tract and potentially lead to autoimmunity, atopy, serious infections, or other disease states.

Summary

The theme presented throughout this chapter is that developmental stages of intestinal development relate to our capabilities to provide different nutrients. Colonization of the intestine by microbes is also important for the infant in establishing a life of good nutrition and health. When this process is disrupted, disease states can easily follow. For this reason, there is currently intense investigation ongoing in the areas of the neonatal intestinal microbiota and neonatal nutrition. As research emerges, optimization of feeding guidelines, composition of both enteral and parenteral formulations for premature infants, and many other aspects of neonatal and infant care will be in flux. As evidence arises, this should be used to provide a strong foundation upon which to help neonates and infants develop a healthy GI system which will set them up for a lifetime of health.

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26 Hyperbilirubinemia

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Jaundice is the most common condition leading to medical evaluation, treatment, and follow-up in otherwise healthy newborns. Average neonatal bilirubin levels are 6–8 mg/dL (100–135 micromol/L) in term infants, predominantly unconjugated or indirect-reacting, and slightly higher in breast-fed than in formula-fed infants. Peak bilirubin levels in the blood are usually found at about 3–5 days of postnatal age, although a minority of cases peak later or last longer.

Unconjugated bilirubin is poorly soluble in water. Water solubility and biliary excretion are facilitated by glucuronide conjugation in a two-step process, followed by apical excretion of conjugated bilirubin into the biliary system and proximal G.I. tract. In fetal life, these steps are bypassed in favor of placental return of fetal unconjugated bilirubin to the maternal circulation. For several days after birth, neonatal bilirubin conjugation (and sometimes biliary excretion) remain somewhat downregulated, with a modest elevation of unconjugated bilirubin (and occasionally of conjugated bilirubin as well) to levels that are "physiologic" for the newborn, but which would be considered abnormal at any other age. Developmental implications of this postnatal delay may include (1) an antioxidant function for bilirubin during neonatal adaptation to an oxygen-rich environment, and (2) avoidance of a dead-end pathway for bilirubin in the bowel prior to the onset of feeding.

Bilirubin levels may be exaggerated in the newborn period by overproduction of bilirubin due to hemolysis, inefficient conjugation/excretion of bilirubin due to underlying genetic or metabolic disorders, or hepatic injury, e.g., due to infection, ischemia, or intoxication.

Premature infants may have any or all of the above, leading to exaggerated levels or longer duration of jaundice.

This writer prefers the term "neonatal jaundice" for the expected mild, generally short-lived, and benign elevation of plasma bilirubin noted in most if not all newborns, with the term "hyperbilirubinemia" reserved for cases in which jaundice appears earlier, lasts longer, reaches higher levels than expected for age, or has a recognized pathologic cause.

Hemolytic Jaundice

Overproduction of bilirubin can occur with immunologically mediated maternal-fetal blood group incompatibility, sepsis with hemolysis, G6PD deficiency with an oxidative triggering event, resolving bruises or hematomas, or red cell structural defects such as hereditary spherocytosis.

Common features of neonatal hemolytic disorders include early onset of jaundice, sometimes present even at birth; often, an abrupt unexpected increase in plasma bilirubin level; and an overall rate of increase more rapid than expected for age, often several times greater than the usual upper limit of hour-specific increase at 0.2–0.25 mg/dL/h. A rate of increase in plasma bilirubin equal to or greater than 1 mg/dL/h is nearly always indicative of hemolytic jaundice, although milder cases of hemolysis may show slower rates of increase than that. Hepatosplenomegaly may or may not be present.

The most common presentation of neonatal hemolytic jaundice is with maternal-fetal ABO blood group incompatibility. Group O mothers have preformed anti-A and anti-B immunoglobulins capable of crossing the placenta and attaching to fetal A or B cellular antigens. Although 20–25% of pregnancies are ABO incompatible, only 10% of potentially exposed infants show clinical evidence of hemolytic disease (therefore, the overall risk of ABO hemolytic disease in newborns is about 2–3%). The anemia associated with this disorder is usually mild. Jaundice appears early, and some infants have splenomegaly. Many cases self-resolve in 3–5 days. Some show jaundice appearing early enough or progressing rapidly enough to require early treatment, usually phototherapy. "False positive" anti-A or anti-B antibody tests may be found in 75–80% of infants with no clinical evidence of hemolytic disease.

Fifteen to thirty percent of Caucasian mothers and, approximately, 2–10% of mothers in "other" ethnic groups lack the "Rh D" antigen on their red cells and are, thereby, classified as "Rh negative" Since "race" is often not a reliable genetic or medical classification, all pregnant women should be screened for their major (ABO) and minor blood types.

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Parturition for an Rh positive baby by an Rh negative mother is often accompanied by maternal trans-uterine exposure to Rh positive cells, with a maternal antibody response which is recalled and exaggerated in subsequent Rh positive pregnancies. The exposed fetuses and infants can have a severe, prolonged reaction to the maternal antibodies, with jaundice and profound anemia at or even before birth, a rapid postnatal increase in plasma bilirubin, and a prolonged course of anemia and jaundice if treatment is not early and adequate.

Rh negative mothers should be screened for anti-Rh antibodies as well as major and minor (Rh) blood groups, past history of transfusions, and personal and family history of newborns requiring transfusions or treatment for jaundice. During pregnancy, the mother has serial testing for presence and titer of anti-Rh antibodies. Prophylactic Rh immune antiglobulin is given in midpregnancy (27–28 weeks) and at delivery.

Neonatal treatment of Rh hemolytic disease is presented later in this chapter.

The X-linked gene for G6PD deficiency is associated with an increased risk of hyperbilirubinemia in two apparently different ways. First is the rare but potentially severe event of an acute hemolytic crisis in a male infant exposed to an oxidant agent such as fava beans or naphthalene. The patient may be well at birth and may not be noticeably jaundiced until exposure. Post exposure, which may not occur until after discharge, there is an abrupt decrease in hematocrit and an abrupt increase in bilirubin, sometimes to potentially hazardous levels. As the oldest red cells are preferentially hemolyzed, the underlying enzyme deficiency may be masked during recovery by near – normal enzyme levels in a new population of red cells. Despite carrier rates for G6PD deficiency of 10% or more in some minority populations, hemolytic crises are uncommon in the newborn period and, often, unexpected and difficult to diagnose when they do occur.

A second pattern of jaundice associated with the gene mutation for G6PD deficiency is an increase in average neonatal bilirubin levels and in clinically apparent hyperbilirubinemia without evidence of hemolytic disease. This pattern shows itself even in hemizygous female infants, who have a normal gene for G6PD production and are not at apparent risk for hemolytic crises. The single gene defect for G6PD deficiency in this otherwise asymptomatic group of infants appears to act in concert with heterozygous mutations or polymorphisms in the gene for bilirubin glucuronyl transferase. The most common of these gene variants is an odd, rather than an even number of TATA repeats in the promoter region for glucuronyl transferase. Perhaps this group of patients combines a slight but subclinical increase in bilirubin production from red cells with an inefficient production or function of the conjugating enzyme in the newborn period.

Sepsis may contribute to neonatal jaundice by accelerating red cell breakdown with increased bilirubin production or by endotoxin-mediated hepatocellular toxicity.

Structural defects in red cell membranes, such as hereditary spherocytosis or elliptocytosis, may be associated with increased bilirubin production. Splenomegaly is common with red cell membrane defects, and may be an early clue to the need for a detailed hematologic evaluation.

Hemoglobinopathies, such as classic sickle cell disease and Beta-thalassemia, may not present with neonatal jaundice because of the predominance of fetal hemoglobin in the perinatal period. Some variants of alpha thalassemia may be associated with neonatal hyperbilirubinemia, but homozygous alpha thalassemia usually presents with profound anemia and hydrops before the clinical onset of jaundice.

Defects in Bilirubin Conjugation/ Excretion

As noted above, bilirubin glucuronyl transferase is relatively downregulated and not fully functional in newborns until several days or even several weeks after birth. In addition to perinatal "physiologic" downregulation of the enzyme, more than 50 polymorphisms in the gene for glucuronyl transferase have been described, some with significant negative effects on production or function of the enzyme. Briefly, several classes of deleterious mutations can be described:

1. An odd number of TATA repeats in the promoter region of the gene, rather than the usual number of 6. The efficiency of enzyme synthesis is limited by these mutations, with exaggerated or persistent jaundice in the newborn period followed by recurrent mild indirect hyperbilirubinemia (often termed Gilbert's Disease) in later childhood and adult life. The associated neonatal jaundice is often severe enough to require treatment, and in adult life, mild jaundice is prone to recur during acute illness or with metabolic stress, such as prolonged fasting.
2. Single amino acid substitutions in the enzyme protein are relatively common and vary from almost negligible to moderately severe in their clinical effects. These substitutions may alter rates of enzyme

synthesis and protein stability, binding and stereospecificity of the enzyme, or both. Hyperbilirubinemia may be limited to the newborn period or may persist into adulthood. Clinical phenotypes may be described as Crigler–Najjar Type 2 Syndrome or as a variant of Gilbert's Disease, with considerable overlap between the two clinical syndromes.

3. A nonsense or "stop" mutation may inhibit synthesis of the enzyme or severely truncate its carboxy terminal so that no functioning enzyme is produced. This condition, clinically known as Crigler–Najjar Syndrome Type 1, is associated with severe lifelong unconjugated hyperbilirubinemia, and with eventual development of signs of bilirubin encephalopathy in most cases.

Although specific genetic tests are seldom indicated for neonatal jaundice which is time-limited and responsive to treatment, mutations and polymorphisms in glucuronyl transferase with mild or minor clinical consequences may explain many instances of family histories with recurrent cases of neonatal jaundice, some cases of "breast milk" jaundice, and some individual cases of severe or prolonged nonhemolytic jaundice in newborns.

Certain metabolic disorders and dysmorphology syndromes are associated with nonhemolytic neonatal hyperbilirubinemia. Infants of diabetic mothers, infants with congenital hypothyroidism, and those with galactosemia are at increased risk for hyperbilirubinemia. The pediatric and medical literature describe an increased frequency of conjugated or direct hyperbilirubinemia with galactosemia or hypothyroidism, but affected infants may first present with indirect hyperbilirubinemia as newborns.

The most common form of toxic hyperbilirubinemia in newborns at present is probably that associated with prolonged parenteral nutrition. Infants at particular risk are very low-birth-weight infants receiving total or partial parenteral nutritional support, and surgical patients receiving total parenteral nutrition (TPN) for long periods of bowel rest. Most such infants have a mixed presentation of elevated conjugated as well as unconjugated hyperbilirubinemia, often with the conjugated fraction predominating. The exact etiology of this TPN-related cholestasis is unknown with both fat and protein components variously believed to be responsible. The condition is usually self-limited and resolves with resumption of enteral feeds.

Conjugated hyperbilirubinemia secondary to intracellular liver disease or extracellular hepatobiliary obstruction usually presents later or persists longer than the newborn period, and is beyond the scope of this chapter. The author, however, has seen numerous cases of neonatal indirect hyperbilirubinemia with concomitant mild elevations of their direct-reacting fractions, both resolving simultaneously with treatment. This appears to be the result of increased bilirubin load that is progressively more effectively conjugated by the hepatocytes with the active transport of conjugated bilirubin into the hepatic canaliculi becoming the rate-limiting step and leading to some accumulation of conjugated bilirubin.

Breast-Feeding Jaundice

The cause of increased unconjugated bilirubin levels in breast-fed newborns is not clearly known. Some breast-fed infants may have exaggerated physiologic jaundice in their first few days because of low milk intake, mild dehydration, lack of stooling, and hemoconcentration. Others appear to have decreased rates of bilirubin conjugation, increased enteric reabsorption of bilirubin from the proximal small bowel, or both. Family histories of breast-feeding jaundice are possibly associated with mutations in the gene for glucuronyl transferase, as noted above. Most elevations of plasma bilirubin in breast-fed infants are within or only slightly above the physiologic range (but above average levels compared to formula-fed infants). Most cases of breast-feeding jaundice are benign and eventually self-correcting, although a minority of cases are severe or persistent enough to require diagnostic intervention and treatment. Withholding of breast milk is not indicated, but if dehydration is significant, supplementation may be necessary. Severe unconjugated hyperbilirubinemia may occur in the late preterm infant who is exclusively breast-feeding and not able to achieve adequate intake. This, in combination to their more immature liver function, is associated with increased risk of hospital readmission and, in rare instances, has led to kernicterus.

Assessment and Diagnostic Evaluation of Hyperbilirubinemia

The appearance of cutaneous or scleral jaundice in newborn infants should be documented with the nursing assessment of skin color as part of the infants' daily vital signs. The observations should be made under adequate light and preferably against a neutral color background. Although visual assessment does not always correlate well with actual plasma bilirubin levels, visual recognition of jaundice should be taught and learned as a simple initial screening tool, and in some settings, the only tool

immediately available. The observations may be structured in several ways:

1. By intensity – Is the jaundice barely discernible, faint but obvious, or intensely orange-yellow?
2. By location – Is the jaundice facial only, does it include the face and trunk, or does it also reach the extremities? For this assessment, scleral jaundice is part of facial jaundice, and not by itself a good sign of intensity or severity.
3. By age – visible jaundice on Day 1 should never be considered normal. The earlier jaundice appears, the more likely it is to be a sign of hemolysis or significant hepatic dysfunction. Widely disseminated or very intense cutaneous jaundice at any age is probably above the average levels for age, requiring further assessment.

Semiquantitative or quantitative screens can be accomplished by skin photometry, or by age-specific serum bilirubin measurement at the time of metabolic screening or on the day of discharge. The numerical results obtained by either method can be plotted against postnatal age in hours and compared to reference data graphed by percentile or risk assessment for age. Many of these numerical screens, whether based on bedside colorimetry or laboratory measurement, require a subsequent age-specific follow-up measurement by the same technique or by laboratory measurement if the instrumental measurement of skin color is above the average range. Transcutaneous screening should incorporate a threshold for laboratory determination if the transcutaneous value is above the expected normal range for age.

Screening for jaundice in many nurseries also incorporates a nurse-generated order to the laboratory for serum bilirubin measurement if certain threshold criteria are met (e.g., jaundice on the first day or a transcutaneous value in a high percentile for the patient's age). This strategy can generate an early warning for subsequent evaluation and treatment, can give the pediatrician useful information at the time of daily assessment, and can facilitate the timing of discharge and scheduled follow-up if the laboratory value is normal.

Bilirubin level may still be rising at the time of an "early" discharge (<48 h).

Therefore, reassessment for jaundice (and overall state of health) by a trained provider is recommended within two working days of discharge for normal vaginally delivered newborns, and within three working days for those delivered by cesarean section. If clinic or office hours or other limits on provider availability (e.g., multiple sites for one provider) preclude follow-up at the exact recommended intervals, a follow-up visit should be arranged for as soon as possible thereafter.

Early jaundice should be assessed for hemolysis, including:

- Assessment for anemia – RBC dysmorphology, reticulocytes, nucleated RBC count, Hemoglobin, hematocrit, RBC indices
- Comparison of maternal and neonatal blood types and antibody screens
- Examination for hepatosplenomegaly
- Family history
- A plan for age-specific periodic reassessment if treatment is not required immediately

Persistent or later jaundice should be assessed in the context of family history, feeding, adequacy of hydration, any laboratory findings known at the time or later requested, and follow-up bilirubin measurements based on age, rate of increase, and need for treatment. Some cases of mild persistent jaundice readily responsive to phototherapy or self-resolving may be followed only with repeat bilirubin measurements at intervals suitable to verify that the problem is correcting itself. This is especially so for otherwise well breast-fed infants without evidence of blood group incompatibility or other significant risk indicators.

Treatment

The major goal of treatment is to control plasma bilirubin concentration in order to keep accumulated bilirubin from reaching potentially neurotoxic levels. Concomitant treatment for associated conditions such as sepsis or anemia from severe hemolysis may also be part of the treatment of neonatal jaundice.

Cases of congenital hemolytic disease of the newborn or occasional hemolytic crises may require prompt or even prospective intervention with tranfusion and/or cardiorespiratory support. Most cases of hyperbilirubinemia evolve within a postnatal time frame, allowing for observation, evaluation, and non-emergent treatment. For these as well as for hemolytic disorders which are not life-threatening, phototherapy is the first line of treatment.

Intravenous immunoglobulin (IVIG), when used as early as possible in cases of severe alloimmune hemolytic jaundice has been shown to significantly decrease the need for exchange transfusion, as well as significantly reduce the length of phototherapy and hospitalization. The exact mechanism of action is unknown, but it is thought to inhibit hemolysis by blocking antibody receptors on red blood cells.

How Phototherapy Works

Bilirubin is a slightly asymmetric tetrapyrrole, rendered largely nonpolar by internal hydrogen bonding. Blue light excites a central carbon bond between two paired sets of pyrrole groups, breaking the hydrogen bonds to form bilirubin isomers of identical molecular weight and primary structure, but with their polar groups now exposed.

"Photobilirubin" is more water soluble than the parent compound, Bilirubin IX – alpha, and therefore more readily excretable into the biliary tract. The photochemical reaction occurs in the skin and subjacent capillaries, and its effectiveness is proportional to the light intensity in the blue spectral region and the area of skin exposed. Isomerization takes place within the first hour of light exposure, and the subsequent excretory phase is probably rate-limiting if the dose of light is adequate. Once excreted, the isomers gradually revert to the parent structure if they are retained in the biliary tree and proximal small bowel. This reversion and reabsorption of bilirubin partly explains the "rebound" in plasma bilirubin concentration after phototherapy.

Indications for Phototherapy

The 2004 recommendations of an American Academy of Pediatrics expert committee for evaluation, treatment, and follow-up of neonatal hyperbilirubinemia have largely been adopted in pediatric primary care, with some individual and local variations based on resource availability, community or institutional past experience, and the presence of certain high-risk groups in the population. These guidelines apply to term (equal to or greater than 38 weeks) and late preterm (35–37 weeks) infants. Guidelines for newborns less than 35 weeks are less uniformly established and more likely to reflect individual or institutional preferences.

The AAP guidelines for treatment are based on stratification of risk according to hour-specific percentile rankings for serum bilirubin levels and comorbidities such as prematurity or blood group incompatibility. The hour-specific rate of physiologic increase up to the 95th percentile of bilirubin concentration for age is generally within 0. 2–0.25 mg/dL/h. Approximate 95th percentile values are 8 mg/dL at 24 h, 13 mg/dL at 48 h, and 17–18 mg/dL at 72–96 h. Percentile value for age is not by itself considered a strict indication for treatment, for several reasons:

- Early-appearing jaundice in the absence of severe hemolysis may begin to self-resolve as early as the second or third hospital day. In these cases, a rapid initial rate of increase will be seen to slow itself with subsequent bilirubin measurements.
- Transient plasma bilirubin levels <20–22 mg/dL do not have a high risk of neurotoxicity for otherwise well infants. Plateau values of 15–18 mg/dL at 3–5 days may be observed for self-resolution if they do not continue to rise.
- Disruption of breast-feeding by treatment at 15–18 mg/dL or lower may not be in the best interests of the mother–baby pair.
- The early age-specific percentiles are partial predictors of continued and potentially progressive hyperbilirubinemia, rather than reliable predictors for risk of kernicterus.

Practical Guidelines for Phototherapy

Hospitals should invest in the best affordable blue-light phototherapy equipment to gain maximal therapeutic effectiveness and reduce hospital length of stay.

Undress the baby except for a small mask over the eyes and, if desired, a small bikini-style diaper (such as a surgical mask).

Measure light intensity at the bed surface. An intensity of at least 30 μWatts/cm^2 is recommended.

Expose a maximum area of skin for an optimal rate of photoconversion. Multidirectional light sources, "top and bottom" LED sources, reflecting devices, and turning the baby periodically may all be helpful. Partially dressed babies do not gain full advantage.

Set a goal, including a clinically meaningful decrease in bilirubin within 6–12 h and an overall decrease to 50–60% of the starting bilirubin value, or less.

Ignore small rebounds of <2 mg/dL. These are to be expected after the lights are off.

Arrange a follow-up appointment, with or without a scheduled bilirubin measurement, for 1–3 days after hospital discharge.

Exchange Transfusion

Exchange transfusion is now an uncommon procedure, generally performed by experienced operators in specialty centers. Phototherapy is usually performed as a preliminary or concomitant treatment, and should

always be continued while preparations for the exchange transfusion are underway. Each center should develop a locally applicable set of policies/procedures for exchange transfusion.

The principal indications are:

Hemolytic disease with early or perinatal anemia and/or a rate of bilirubin increase of 0.5–1.0 mg/dL/h or greater.

Potentially toxic bilirubin levels not promptly responsive to intensive phototherapy.

The approximate levels of risk for CNS toxicity are 25–30 mg/dL for previously "well" term infants, 20–25 mg/dL for term infants with hemolytic disease, and approximately15–20 mg/dL for premature infants of 33–34 weeks gestation or less. The last of these "threshold" values, for preterm infants, are based more on historical and customary practices than on current evidence. An exchange transfusion threshold based on birth weight in kilograms × 10 is widely used but lacks sound scientific basis.

The procedure usually requires reconstitution of irradiated packed RBC's with compatible plasma. The target volume for exchange of 85–90% of the infant's blood is 2× the estimated neonatal blood volume of 80 mL/kg, or 160 mL/kg of exchange blood.

For a one-vessel technique (usually the umbilical vein), the "push–pull" volumes per exchange can approximate 5 mL/kg, withdrawn and replaced in a 1 min cycle.

A two-vessel technique of simultaneous withdrawal and infusion can be accomplished in 30–45 min, depending on catheter diameter, pump capacity, and patient condition.

Bilirubin, hematocrit, glucose, and electrolytes should be monitored at beginning and end of the procedure. The bilirubin level may fall by more than half the initial value, but return of extravascular bilirubin from the tissues to the blood may create a substantial post transfusion rebound. Transient hypocalcemia occurs during the procedure in nearly half of the infants if blood anticoagulated with citrate phosphate dextrose (CPD) is used for the exchange transfusion. Metabolic acidosis and thrombocytopenia are seen in 25–30% of infants following exchange transfusion. The infant should be made NPO for the procedure because necrotizing enterocolitis has been associated with exchange transfusion. The reported incidence of serious complications was nearly 24% in a recent review. Careful monitoring of vital signs and of blood volume withdrawn and infused are essential safety precautions.

The Small Premature Infant

For premature infants of very low birth weight, the evidence base for risk assessment, early treatment, and the relative contribution of bilirubin to adverse outcomes is not well established. There is no known safe bilirubin level in very preterm infants. This is largely because the blood brain barrier, which keeps albumin-bound bilirubin from entering the CNS, is frequently rendered open by hypoxia, acidosis, and other events commonly seen in critically ill extremely low-birth-weight infants. Most tertiary centers have adopted strategies to control bilirubin concentrations within low levels in these infants. This strategy may be counterproductive based on the following concerns:

1. A possible contribution of prophylactic or very early phototherapy to excess mortality in the lowest-birth-weight group of infants in a large randomized trial.
2. Blue light applied to thin non-jaundiced skin may predispose to excessive insensible water loss or to photochemical injury in the absence of bilirubin to absorb most of the photons from the light exposure. Intuitively, a firm indication for early phototherapy should entail that at least some cutaneous jaundice is present as a "target" for treatment.
3. Bilirubin is also an important antioxidant and a transient rise in bilirubin during a period of increased oxidative stress may be an important defense mechanism, with which early phototherapy may interfere.

Levels of 13–15 mg/dL or greater in VLBW prematures may be associated with increased risk of hearing loss and motor delay, but without the characteristic findings of subsequent choreoathetosis and cranial nerve motor damage associated with "classic" kernicterus in older newborns.

Prudent current advice for VLBW and ELBW infants would seem to be to avoid gratuitous prophylactic phototherapy but to use phototherapy early enough in most such infants to constrain bilirubin concentrations in the range of 5–10 mg/dL. Additional clinical trials of treatment and follow-up appear necessary to clarify the indications and contraindications for phototherapy in VLBW infants.

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27 Infections of the Fetus and Newborn

Joseph M. Bliss

The far-reaching impact of microbes on the human condition cannot be overestimated. The microbial species are vast, diverse, and present in virtually every ecosystem on earth. A single gram of human feces, for example, is estimated to contain 10^{11} bacteria, which is equivalent to 10–50% of all the human cells in the body, and is nearly two orders of magnitude higher than the total number of people on the planet. Humans have therefore evolved elaborate and elegant defense mechanisms to maintain health in a microbe-rich environment. Nowhere are these mechanisms more important for the overall health of the species than in pregnancy and childbirth, and in the vast majority of cases, host defense mechanisms provide for healthy infants. A very small subset of microbes have developed ways to subvert host defense and cause infections in pregnancy or the perinatal period that are damaging to the fetus and/or infant, and these infections cause substantial morbidity and mortality throughout the world. These microbes and the diseases that they cause are the focus of this chapter.

The clinical manifestations of infection during gestation or surrounding birth vary depending on the properties of the infectious agent, the timing of the infection, and the extent of inflammation resulting from the host's response to the infection. The microorganisms that cause disease in this period include viruses, bacteria, protozoa, and fungi. They can be further divided into agents that are acquired during pregnancy and lead to symptomatic infection in the fetus prior to birth (congenital infection), and those acquired in the perinatal period, either during or shortly after delivery. Although useful from a conceptual point of view, this classification is somewhat artificial, as considerable overlap exists between these groups. This chapter will focus on those microorganisms that are well recognized to lead to disease in the fetal and neonatal period and have serious impact in terms of prevalence and severity of symptoms. An exhaustive review of all possible infections in the neonatal period is beyond the scope of this chapter, and readers are referred to specialty texts devoted exclusively to neonatal infections that provide additional breadth and depth.

Congenital Infections

Exposure to infectious agents during pregnancy is unavoidable, and the majority of infections in pregnant women lead to self-limited respiratory or gastrointestinal illnesses that resolve without specific intervention or with antimicrobial therapy. However, a subset of infectious agents is capable of infecting the placenta and fetus with potential adverse consequences. Risk of infection in the fetus and newborn varies with each infectious agent and depends on timing of maternal exposure in pregnancy (summarized in *Table 27.1*). Prompt and accurate diagnosis of these infections in the fetus and newborn is complicated by the fact that maternal infections with many of these agents are asymptomatic or cause minor, nonspecific symptoms.

The classic pneumonic for microbes that lead to congenital infections is "ToRCH", referring to *Toxoplasma gondii*, rubella, cytomegalovirus (CMV), and herpes simplex virus (HSV). However, equally important causes of congenital infection are not reflected in this acronym, including syphilis, parvovirus, varicella-zoster virus (VZV), and human immunodeficiency virus (HIV), which seriously limits its utility. Further, the clinical features, diagnostic studies, and sequelae related to these infections differ depending on the unique aspects of each disease. Thus, the concept of a "ToRCH workup" in the setting of a fetus or neonate with signs that may be related to congenital infection is an oversimplification that should be avoided. This section will focus on the clinical aspects that are characteristic of infection with each of these agents.

Toxoplasmosis

Etiology

Toxoplasmosis is caused by infection with the protozoan parasite, *Toxoplasma gondii*. The life cycle of this organism is relevant to understanding its transmission, and has three stages: tachyzoite, bradyzoite, and sporozoite. Domestic and feral cats are the definitive host for the sexual stage of

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Table 27.1
Disease manifestations of congenital infections based on timing of maternal exposure

Infectious disease	Timing of maternal infection/fetal exposure	Disease manifestations*
Toxoplasmosis	First Trimester – 10–25% transmission	More severe
	Third Trimester – 60–90% transmission	Less severe
Rubella	First trimester – 85% transmission	Congenital rubella syndrome
	Second trimester – 25% transmission	
Cytomegalovirus	First trimester	More likely severe
Herpes Simplex	In utero – rare	CNS damage
	Primary infection close to delivery	SEM, CNS, or disseminated disease
Syphilis	14 weeks through term	Congenital syphilis
Parvovirus B19	First half of pregnancy (13–20 weeks)	Highest risk of hydrops
Varicella	First half of pregnancy (13–20 weeks)	Congenital varicella syndrome (rare)
	5 days prior to 2 days after delivery	Perinatal varicella
Hepatitis B	In utero – rare	Fulminant or chronic HBV
	At delivery	
HIV	In utero – less than half of cases	Congenital HIV
	At delivery – most common	
	Breast feeding – well documented	

*See text for additional details

the organism, and generally acquire the infection by feeding on infected animals such as mice or from uncooked meats. The sexual stage occurs at the intestinal mucosa and results in unsporulated, and therefore noninfectious, oocysts that are excreted in the feces. The oocysts then sporulate (sporozoites) and become infectious within one day to several weeks, depending on climate. Infectious oocysts are then ingested by humans or other animals and become tachyzoites in the acute stage of infection where they can invade the heart, muscles, liver, spleen, and central nervous system. In immunocompetent hosts, the acute infection is controlled and latent infection is established, characterized by bradyzoites in tissue cysts. In humans, ingestion of oocytes can occur through contact with cat litter, contaminated soil encountered through gardening or unwashed vegetables, or contaminated water supplies. Humans can also become infected by the ingestion of undercooked infected meat or uncooked foods that have come into contact with raw meat. Finally, reactivation of latent infection can occur in the setting of immune compromise from HIV, chemotherapy, or organ transplantation. Infection of the fetus occurs by transplacental transmission in the setting of acute maternal infection during pregnancy. The fetus is also at risk in the setting of reactivation due to maternal immunosuppression during pregnancy. Infection of the fetus in most likely when maternal infection occurs during the third trimester (60–90% transmission vs. 10–25% in the first trimester), but the consequences of infection are more severe when it occurs early in gestation.

Epidemiology

Infection with *T. gondii* is common and is estimated to be present in up to one-third of the world's population. It has its highest prevalence in tropical areas and prevalence decreases with distance from the equator. In Europe, for example, seroprevalence is 54% in Southern European countries but only 5–10% in northern Scandinavian countries. *T. gondii* infection is common in South America and Africa, while seroprevalence is lower in most Asian countries. In the United States, approximately 11% of women of childbearing age are seropositive and congenital infection is estimated to occur at a rate of 1 in 1,000 to 1 in 10,000 live births.

Clinical Manifestations

Infection during pregnancy is most often asymptomatic for the mother. Infants who were congenitally infected are also asymptomatic 70–90% of the time. However, the majority of these infants (up to 80%) will go on to develop manifestations of infection such as learning disabilities or impaired

vision months to years later. In infants who are symptomatic at birth, signs of congenital infection include hepatomegaly, splenomegaly, thrombocytopenia, generalized lymphadenopathy, and a maculopapular rash. Infection of the central nervous system and the accompanying inflammation account for the most severe consequences of intrauterine infection, both in the short and long term. These include the classic triad of congenital toxoplasmosis: chorioretinitis, microcephaly, and intracranial calcifications. Other signs of CNS infection include meningoencephalitis, hydrocephalus, seizures, and deafness. Indeed, CNS calcifications, microcephaly, and/or hydrocephalus on prenatal ultrasound can be the first clues of infection in the developing fetus. Manifestations of toxoplasmosis in the premature infant can include CNS and ocular disease in the first 3 months of life, while infants born at term tend to have milder disease with hepatosplenomegaly and lymphadenopathy in the first 2 months of life.

Diagnosis

Diagnosis of acute infection with *T. gondii* during pregnancy is based on specific antibody detection in the maternal serum, but the interpretation of these tests can be difficult. IgG and IgM levels are detectable within 1–2 weeks of infection. Detection of IgG alone documents past infection with the organism, but cannot distinguish between recent infection and infection sometime prior to pregnancy. Since the risk to the fetus is associated with acute, active infection, this distinction is paramount. The presence or absence of IgM is helpful in this regard. The lack of *T. gondii*-specific IgM in the presence of IgG is indicative of infection more than 6 months prior to obtaining the test. However, the fact that IgM antibody can persist up to 18 months following infection and false positives are also known to occur complicates the interpretation of positive IgM serology. Therefore, consultation with a reference laboratory is recommended in cases where acute infection is likely and IgM is positive. Additional testing available through reference laboratories includes IgG avidity testing and tests for *T. gondii*-specific IgA and IgE which can help to determine timing of infection and risk to the fetus. If acute infection is likely, fetal infection can be assessed by PCR-based techniques on sampled amniotic fluid or fetal blood as well as serial by serial ultrasound examinations.

Treatment

Treatment for pregnant women with a confirmed case of acute *T. gondii* infection is recommended with spiramicin. The goal of treatment is to prevent transmission to the fetus. However, fetal transmission is thought to occur quickly after maternal infection and institution of maternal treatment probably needs to occur within 2 weeks of infection. As such, there is little evidence that treatment in pregnancy impacts maternal-fetal transmission, and spiramicin does not treat the fetus in utero. If fetal infection is confirmed or maternal infection is documented in the third trimester, the combination of pyrimethamine and sulfadiazine should be considered, but only after the 17th–18th week of gestation due to toxicities of these agents. Additionally, folinic acid should be given to offset the bone marrow toxicity associated with pyrimethamine. There is some evidence that maternal treatment may decrease the severity of manifestations of fetal infection. Combined therapy with pyrimethamine and sulfadiazine is recommended for treatment of both symptomatic and asymptomatic congenital infection, generally for the entire first year.

Prevention

Education relating to the risks of exposure and infection with *T. gondii* during pregnancy is the mainstay of prevention and should focus on avoiding contamination from contact with meat, soil, and cats. Pregnant women should avoid raw or undercooked meats and ensure that meat is cooked to a safe temperature prior to consumption. Fruits and vegetables should be thoroughly washed or peeled before eating. Hands and utensils that come into contact with meat or unwashed vegetables during their preparation should be carefully cleaned. Gloves should be worn in gardening. Cat owners should be encouraged to keep their cats inside and cats should be fed commercially canned or dried cat foods, avoiding raw meats. Pregnant women should avoid contact with cat feces or litter boxes or wear gloves when handling them. Clearly, avoiding infection during pregnancy is by far the best way to reduce morbidity and mortality related to congenital infection.

Rubella

Etiology/Epidemiology

Also known as "German measles," rubella is caused by infection with rubella virus. It is found only in humans and is transmitted through either direct or droplet contact with the nasopharyngeal secretions of an infected person. Prior to widespread vaccination programs, rubella was endemic worldwide and occurred in 6–9 year cycles with children infected most commonly. With the approval and

widespread usage of rubella vaccine, the virus is no longer endemic in the United States, and the virus has essentially been eliminated from some industrialized countries. Cases in these countries have become exceedingly rare and occur primarily among women born in areas with poor vaccine coverage. In developing countries with limited vaccination, 15–20% of women of childbearing age are susceptible to rubella, with higher rates in rural areas and in island communities. In 2003,>100,000 infants were estimated to be affected by congenital rubella syndrome worldwide. Attention from the World Health Organization has improved vaccination rates, such that as of 2005, 117 of 214 countries and territories have included rubella in national vaccine programs.

Clinical Manifestations

Symptoms of rubella infection tend to be milder in children than in adults. Infections are subclinical in 20–50% of cases, depending on the population. After an incubation period of 14–23 days, symptoms include a characteristic erythematous maculopapular rash that starts on the face and then becomes generalized, lymphadenopathy that may precede the rash, low-grade fever, headache, sore throat, cough, and conjunctivitis. Polyarthritis and polyarthralgia are uncommon in children, but more common in adolescents and adults, particularly in females. Encephalitis and thrombocytopenia are rare complications. Congenital rubella syndrome (CRS) occurs when a susceptible pregnant woman is infected, with early gestation being the most critical time period. CRS results in 85% of cases in which infection occurred before 12 weeks gestation, and multiple defects are most likely before 8 weeks. Spontaneous abortion occurs in 20% of fetuses affected in this time period. The risk to the fetus declines rapidly after 12 weeks, with estimates of 54% during 13–16 weeks and 25% during the second trimester. The most common manifestations of CRS are summarized in ❯ *Table 27.2*.

Table 27.2
Clinical manifestations of congenital rubella syndrome (CRS)

Organ System	Signs
Ophthalmologic	*Cataracts (33%, 50% bilateral)
	Pigmentary retinopathy
	Microophthalmos
	Glaucoma
Cardiac	*Patent ductus arteriosus (30%)
	Pulmonary artery stenosis/hypoplasia
Auditory	*Sensorineural or central auditory deafness
Neurologic	Microcephaly
	Meningoencephalitis
	Mental retardation
	Psychomotor retardation
	Language delay
Other	Low birth weight, Growth restriction, Failure to thrive
	Hepatosplenomegaly
	Interstitial pneumonitis
	Thrombocytopenia
	Radiolucent bone disease
	Dermal erythropoiesis (Purpura; "Blueberry Muffin" lesions)

*Classic abnormalities

Diagnosis

Congenital rubella can be diagnosed by the presence of rubella-specific IgM in serum or oral fluid of an infected infant. The test is most reliable when it is obtained before 3 months of age and reliable detection of IgM decreases thereafter (85% of symptomatic infants between 3 and 6 months; > 30% at 6–12 months). Stable or increasing titer of rubella-specific IgG after 6 months of age also supports the diagnosis. Culture of rubella virus from throat or nasopharyngeal swabs is also useful to establish a diagnosis, and PCR-based tests on throat swabs or urine specimens are available as well. A diagnostic evaluation of pregnant women with symptoms of rubella (fever, rash, joint pain) should also be undertaken. A positive rubella IgM is strongly suggestive, but subsequent samples should be drawn to confirm the result and document a rising IgG titer. False positives are common with this testing, particularly in areas with low disease incidence, and referral to reference laboratories for supplemental testing is useful before decisions regarding possible pregnancy termination are made.

Treatment and Prevention

There are no antiviral chemotherapeutic agents available to treat CRS or deter transmission to the fetus. Human immune globulin may reduce clinically apparent

infection, viral shedding, and viremia in exposed, susceptible women and may theoretically reduce transmission to the fetus. Its use can be considered in susceptible women who are rubella exposed early in pregnancy, but its efficacy is not well understood. Vaccination is therefore the mainstay of prevention, and has been remarkably safe and effective. The vaccine is generally administered in combination with measles vaccine (MR), measles and mumps vaccine (MMR), or measles, mumps, and varicella vaccines (MMRV). In many countries, rubella immune status is screened during pregnancy, and women who are not immune are offered vaccination in the immediate postnatal period. Because it is a live vaccine, vaccination during pregnancy is contraindicated due to the theoretical risk of harm to the fetus. However, in studies of women who inadvertently received the vaccine during pregnancy, only a small percentage of their infants had evidence of infection, and none had congenital defects.

Cytomegalovirus

Etiology/Epidemiology

Cytomegalovirus (CMV) is a ubiquitous DNA virus and is a member of the herpesvirus group. Numerous strains have been identified and, like other herpes viruses, primary infection is followed by life-long latency in infected hosts. Reactivation and viral shedding can occur years after primary infection. The virus is shed in secretions, including saliva, semen, cervical secretions, breast milk, and urine, and is transmitted by close person-to-person contact. Transmission has no seasonal variation and can also occur through blood transfusion and organ transplantation. Infection is common during childhood and well documented to occur at child care centers. Rates of seroprevalence vary significantly based on varied living conditions, hygiene practices, breast feeding rates, and socioeconomic factors and range from 35% to 95%. Infection among children in the first years of life is therefore less common in industrialized countries and high socioeconomic groups, resulting in higher rates of susceptibility among women in childbearing years in these populations.

Clinical Manifestations

Primary infection with CMV is most frequently asymptomatic, although a mononucleosis-like syndrome with malaise, fever, and mild hepatitis can occur in a small number of adolescents and adults. Approximately 1% of all live born infants are infected with CMV and shed virus at birth, making this infection the most common congenital viral infection. However, manifestations of the infection and subsequent sequelae vary dramatically depending on timing of infection. Transmission of CMV to a fetus or infant can occur in three settings. The fetus can be infected in utero by passage of virus from the mother across the placenta, by contact with cervical secretions or maternal blood during delivery, or from breast milk after delivery. Transmission can occur in the setting of primary infection or with reactivated disease, but transmission is much more common in primary infection. Approximately 1–4% of seronegative women acquire primary CMV infection during pregnancy and the risk of transmission is estimated at 30–40%, while reactivation occurs in 10–30% of seropositive women during pregnancy with a transmission risk of 1–3%.

Among the 1% of infants who are infected with CMV at birth, approximately 10% are symptomatic. Manifestations of symptomatic congenital CMV include growth restriction, microcephaly, intracerebral calcifications, retinitis, hepatosplenomegaly, jaundice, and purpura. These infants have a mortality rate of approximately 30%, generally secondary to liver failure, and the survivors are at the highest risk for neurodevelopmental sequelae. Severe consequences of CMV infection are most likely to occur when primary infection occurs in the mother in early pregnancy. The central nervous system is particularly susceptible to these insults. Infection early in pregnancy can alter neural migrational patterns in the brain and lead to polymicrogyria and microcephaly. Later in pregnancy, effects on the cortex are less pronounced while the white matter remains susceptible. Sensorineural hearing loss is the most common later manifestation of congenital CMV infection, making CMV the most common nongenetic cause of hearing loss in children. Hearing loss is more common and more severe in symptomatic than in asymptomatic congenitally infected infants, but asymptomatic infants still carry a 10% risk of progressive hearing loss. Further, hearing loss may not be apparent in the first months of life. Therefore, infants known to have congenital CMV should have careful audiologic follow-up throughout their early childhood as hearing loss can fluctuate and be progressive.

Infection from cervical secretions or blood during birth or from breast milk after birth is most commonly asymptomatic, although interstitial pneumonia has been reported in this setting. Preterm infants, however, are at higher risk for symptomatic infection than full term infants as well as neurodevelopmental sequelae.

Diagnosis

The most common method used to diagnose congenital CMV is through detection of the virus in urine samples using tissue culture techniques. PCR-based assays are also available, particularly for cerebrospinal fluid. Detection of CMV-specific IgM in the newborn can also support a diagnosis, but can only be detected in 70% of infected infants at birth. Diagnosis of primary infection in a pregnant woman is more difficult because of frequent reactivation of the virus, infection of a seropositive woman with a different strain, and the tendency for development of an IgM response with reactivation. Seroconversion of CMV-specific IgG between paired samples when available is the most reliable means to identify primary infection in pregnancy. Fetal infection can be evaluated in these cases by viral culture and PCR of an amniotic fluid sample. The sensitivity of amniotic fluid testing is highest when it is obtained after 21 weeks gestation and at least 5 weeks after the onset of infection. Still, the risk of neurodevelopmental consequences in an individual infected fetus is difficult to predict.

Treatment

Ganciclovir is used to treat CMV in the setting of retinitis or other end-organ manifestations in immunocompromised patients and prophylactically in organ transplant recipients. Data concerning the use of this drug in neonates are limited. However, in symptomatic congenitally infected infants with CNS disease, 6 weeks of intravenous ganciclovir therapy may protect against hearing deterioration and improve developmental outcomes at 1–2 years of age. Its use is limited by toxicity and the high rate of neutropenia in infants on this regimen. Preterm infants with symptomatic disease and evidence of end-organ damage have also been treated empirically, but ganciclovir has not been studied in this population.

Prevention

Because of the ubiquitous nature of this virus and the absence of a vaccine, prevention is centered on education, particularly in industrialized countries with high rates of seronegative women of childbearing age. Because reactivation of infection with viral shedding is commonplace, avoiding contact with the virus is difficult. However, daycare and child care centers, particularly with children under 2 years of age, are very frequent sources of exposure. Women in these settings should focus on frequent hand washing to reduce exposure, particularly after contact with saliva or changing diapers.

Herpes

Etiology/Epidemiology

Two species of herpes simplex virus infect humans. Infection with type 1 (HSV-1) generally involves the face and skin above the waist while infection with type 2 (HSV-2) generally involves the genitals and skin below the waist. However, either virus can lead to genital infection. Approximately 75% of neonatal infections are caused by HSV-2. Like other herpes virus infections, infection with HSV is characterized by latency after primary infection with intermittent reactivation and viral shedding. Current estimates in the United States are that 25–60% of pregnant women are infected. Infants born to mothers with genital HSV infection are at risk of acquiring the infection either before birth or after delivery, but the majority of neonatal HSV is acquired at delivery from active viral shedding in cervical secretions. Infection prior to delivery is rare. Postnatal acquisition of HSV can come from health-care workers or family members as well as the mother and is almost always due to HSV-1. Depending on the population studied, estimates of incidence of neonatal HSV range from 1 in 12,500 to 1 in 1,700 live births. Because of the severe morbidity and mortality associated with neonatal infection, these rates represent a substantial disease burden that is as high as or substantially higher than that associated with other congenital infections. Primary genital HSV infection in women is very commonly asymptomatic and therefore frequently undiagnosed. The risk to the infant is substantially higher in the setting of primary infection during pregnancy (25–60% incidence) than in reactivated disease with viral shedding (1–2% incidence), likely due to the absence of protective maternal antibodies in the former. As a result the majority of neonatal HSV infections (50–80%) occur in babies born to women who acquired primary HSV-1 or HSV-2 genital infection close to term and are unaware of their HSV status.

Clinical Manifestations

In the rare cases of in utero acquisition of HSV, the central nervous system is susceptible to damage leading to microcephaly and hydrocephalus. Chorioretinitis can also be seen. The much more common acquisition through

exposure at delivery can manifest in one of three ways: skin, eye, mouth disease (SEM), central nervous system disease (CNS), or disseminated disease. Each type of infection has distinct clinical features, response to therapy, and prognosis. Evidence of HSV infection typically presents within the first month. Infants with SEM and disseminated disease present somewhat earlier, in the first 1–2 weeks, while those with CNS disease typically develop symptoms between 2 and 3 weeks.

SEM disease accounts for approximately 45% of neonatal HSV infection. These infants develop vesicular lesions of the skin, eyes, and/or mucus membranes without involvement of the CNS or other organ systems. There is little to no mortality in this category and with treatment, neurodevelopmental outcomes are normal. However, skin lesions commonly recur, and those that do frequently in the first 6 months can be associated with CNS sequelae. Infection of the CNS occurs in approximately 30% of cases. Skin and mucosal lesions may or may not be present. Infants with CNS disease may present with poor feeding, lethargy, and seizures. Timely initiation of therapy improves the outcomes of these infections and reduces later sequelae, but because the signs are nonspecific, diagnosis can be delayed. Antiviral therapy improves mortality from 50% to 6%, but sequelae such as epilepsy, blindness, and developmental delay remain common, particularly with HSV-2. More than half of these children have moderate to severe neurodevelopmental problems. Disseminated disease occurs in approximately 25% of cases and involves other organ systems in addition to the CNS, particularly liver and lungs. The presentation of these infants is identical to bacterial sepsis and skin lesions are absent in approximately 40% of cases. Thus, diagnosis requires a high index of suspicion for timely initiation of therapy, and HSV should be considered in any infant with culture negative sepsis and severe hepatic dysfunction. Mortality occurs in approximately 30% of patients, even with treatment. Survivors have a somewhat better neurodevelopmental prognosis than in CNS disease.

Diagnosis

Available diagnostic tests for HSV include culture, direct fluorescent antibody (DFA) staining, and PCR. Cell culture methods are sensitive and specific, and can be positive in as little as 1–3 days. DFA is much more rapid, but slightly less sensitive. PCR to detect viral DNA is quite sensitive, and is particularly useful for neonatal CSF specimens where culture is usually negative. Any infant with signs of possible HSV infection or with suspicious skin lesions should be evaluated. Swabs of the mouth, nasopharynx, conjunctivae, and rectum, and specimens of blood, CSF, and any skin vesicles should be obtained for culture. Any positive culture from these sites obtained more than 12–24 h after delivery is highly suspicious for neonatal infection. PCR should also be obtained on CSF. DFA or enzyme immunoassays can be useful for rapid confirmation on scrapings from skin lesions. Although not useful in neonates, serologic testing is available for adults and can distinguish between antibodies to HSV-1 and HSV-2. These antibodies develop between 2 and 12 weeks after primary infection and persist indefinitely. Serologic testing can therefore be useful in distinguishing recent from past infection and in identification of discordance among sexual partners of uninfected women. Such testing can therefore be useful to inform the risk of infection in an individual infant.

Treatment

Treatment of infants infected with HSV with IV acyclovir (20 mg/kg every 8 h) has dramatically reduced mortality from these infections. Because infants with SEM disease can have progression to the CNS, any infant diagnosed with HSV should be treated with IV acyclovir. Treatment is recommended for 14 days for SEM disease and 21 days for disseminated and CNS disease. Longer-term suppressive therapy and treatment of recurrent disease are the subject of current investigation. Management of the exposed infant who is asymptomatic is controversial. Because of the high rates of perinatal infection, some experts recommend treatment for 14 days in asymptomatic infants born vaginally to mothers who acquire primary HSV late in pregnancy. However, distinction between primary infection and reactivation can be difficult. Others recommend cultures of mouth, nasopharynx, conjunctivae, and rectum between 12 and 24 h after birth, with either empiric therapy initiated after cultures are obtained or awaiting culture results with completion of the evaluation (hepatic transaminase measurement, CSF PCR) and therapy if positive.

Prevention

A number of strategies to reduce the risk of neonatal HSV have been discussed, including serologic testing of women and their partners to identify those at risk of acquisition during pregnancy, counseling of pregnant women to avoid unprotected intercourse or oral-genital contact in late

pregnancy, and rapid testing for HSV shedding in mothers at delivery. The effectiveness of such strategies is currently unknown. During labor, all women should be asked about recent or current signs or symptoms of herpes infection and should be examined for lesions. Current guidelines recommend cesarean delivery for any woman with genital herpes lesions and this approach decreases the risk to the neonate. The use of antiviral agents for suppression of viral shedding in infected women late in pregnancy has also been suggested and may reduce the rates of cesarean delivery, but the safety of this approach and whether such treatment reduces neonatal infection is unknown. In most cases, this approach targets recurrent disease which is much less commonly the source of neonatal infection. In any case, HSV infection of the neonate remains a prevalent and severe problem with considerable need for research to identify effective preventive strategies and the optimal identification and management of the exposed newborn.

Syphilis

Etiology/Epidemiology

Syphilis is caused by the bacterial spirochete, *Treponema pallidum*. Features of this organism, such as having humans as its only natural host and its inability to be cultured on artificial media, have limited progress in understanding its biology for decades. It has a worldwide distribution, and its incidence varies dramatically based primarily on the local resources available for screening and treatment. Screening programs in industrialized countries have made congenital syphilis a rare disease, although resurgence has been detected in recent years. In the United States, for example, the rate of congenital syphilis increased by 23% from 2005 to 2008. Current estimates of the rate of congenital syphilis in the United States and in Europe range from 1.9 to 10.1 cases per 100,000 live births. Rates are much higher and potentially underappreciated in developing countries where limited resources make screening programs difficult to achieve. Rates of syphilis in pregnant women are estimated to be below 5% in Asia, 5–10% in the Caribbean and Latin America, and as high as 17% in sub-Saharan Africa. Estimates from the World Health Organization indicate that approximately 1,000,000 pregnancies are affected by syphilis annually worldwide, resulting in 460,000 infants who are stillborn or die in the perinatal period; 270,000 infants born preterm or with low birth weight, and 270,000 infants with stigmata of congenital syphilis.

Clinical Manifestations

The stages of acquired syphilis in adults are well known and have been extensively discussed elsewhere. In the setting of maternal syphilis, the fetus can acquire the infection transplacentally from about 14 weeks of gestation, with increasing rates of infection as pregnancy progresses. The potential short- and long-term impacts of fetal infection are numerous and profound, and recognition and treatment of syphilis early in pregnancy makes these manifestations almost entirely preventable. The chance of fetal transmission from an untreated pregnant woman is approximately 70%, and about 40% of pregnancies in untreated women result in stillbirth, hydrops fetalis, and/or perinatal death. Infected infants who are live born may be entirely asymptomatic (about two-thirds) or may be born prematurely or with low birth weight. Manifestations of congenital syphilis may occur early or later in life, regardless of symptoms at birth, and are summarized in *Table 27.3*. Treatment of early infection prevents the development of late manifestations.

Diagnosis

In the absence of the capacity to culture the organism, diagnosis of syphilis infection relies primarily on serologic testing. Microscopy can be used for secretions and tissues,

Table 27.3
Clinical manifestations of congenital syphilis

Early ($\leq$ 2 years)	Late ($>$ 2 years)
Nasal discharge ("snuffles")	*Interstitial keratitis (5–20 years)
Maculopapular rash	*8th cranial nerve deafness (10–40 years)
Hepatosplenomegaly	*Hutchinson teeth (peg-shaped, notched central incisors)
Lymphadenopathy	Mulberry molars
Edema	Saber shins (anterior tibial bowing)
Pneumonia	Frontal bossing
Osteochondritis with pseudoparalysis	Saddle nose
Hemolytic Anemia	Clutton joints (painless swelling of knees)
Thrombocytopenia	Rhagades (linear scars around mouth/nose)

*Hutchinson's triad

but requires darkfield examination or *T. pallidum*-specific fluorescent antibody staining. Serologic tests can be classified as nontreponemal and treponemal, and both are necessary to establish a diagnosis with the least ambiguity. Nontreponemal tests can yield false positive results in the setting of some viral and autoimmune conditions, and treponemal tests remain positive long after effective treatment is instituted and can be positive with other spirochete infections. The commonly used nontreponemal tests are the rapid plasma reagin (RPR) and the Venereal Disease Research Laboratory (VDRL) slide test. They have the advantage of being inexpensive and easy to perform, and they provide quantitative results that can be used to measure disease activity and response to therapy. Positive nontreponemal tests should be confirmed with treponemal tests to exclude a false positive result. Treponemal tests include fluorescent treponemal antibody absorption (FTA-ABS) and *T. pallidum* particle agglutination (TP-PA) tests. All pregnant women presenting for prenatal care should receive a nontreponemal screening test early in pregnancy. Although the utility of additional screening varies based on prevalence, in women at high risk or in areas with high prevalence of syphilis, the test should be repeated at 28–32 weeks gestation and at delivery. Additionally, any woman that delivers a stillborn infant after 20 weeks gestation should be screened for syphilis. In the setting of a positive screen, a treponemal test should be done to confirm the diagnosis and treatment initiated. Infants born to mothers who are seropositive should also receive a quantitative nontreponemal test, preferably of the same type that the mother received and ideally at the same laboratory, as relative titers can inform the likelihood of infection versus passive transfer of maternal antibody only.

Treatment

Definitive diagnosis in the neonate born to a seropositive mother is challenging because many infants are asymptomatic at birth and there is no diagnostic test that yields an unambiguous result in this setting. In spite of this difficulty, identifying infected infants is paramount, because early treatment is effective and prevents much of the severe sequelae that can present later in life. As such, algorithms have been developed that utilize conservative strategies to identify and treat infants who have either proven or suspected disease, while excluding as many infants as possible who are uninfected and therefore will not benefit from treatment. One such algorithm endorsed by the American Academy of Pediatrics is depicted in *Fig. 27.1*. Follow up of treated infants is important to ensure that therapy was effective. Positive syphilis serology generally clears by 6 months of age with effective treatment. Testing serologic titers with a nontreponemal test at 1, 3, 6, 12, and 24 months following treatment should document a fourfold decrease by 6 months post therapy and should be nonreactive by 12 and 24 months. Titers that increase or fail to fall are concerning for treatment failure or reinfection and these infants should be reevaluated and treated. Infants that had congenital neurosyphilis on the basis of a positive CSF VDRL or abnormal CSF parameters should undergo repeat lumbar puncture every 6 months until it normalizes. Abnormal CSF parameters or a continued positive VDRL is an indication for further treatment.

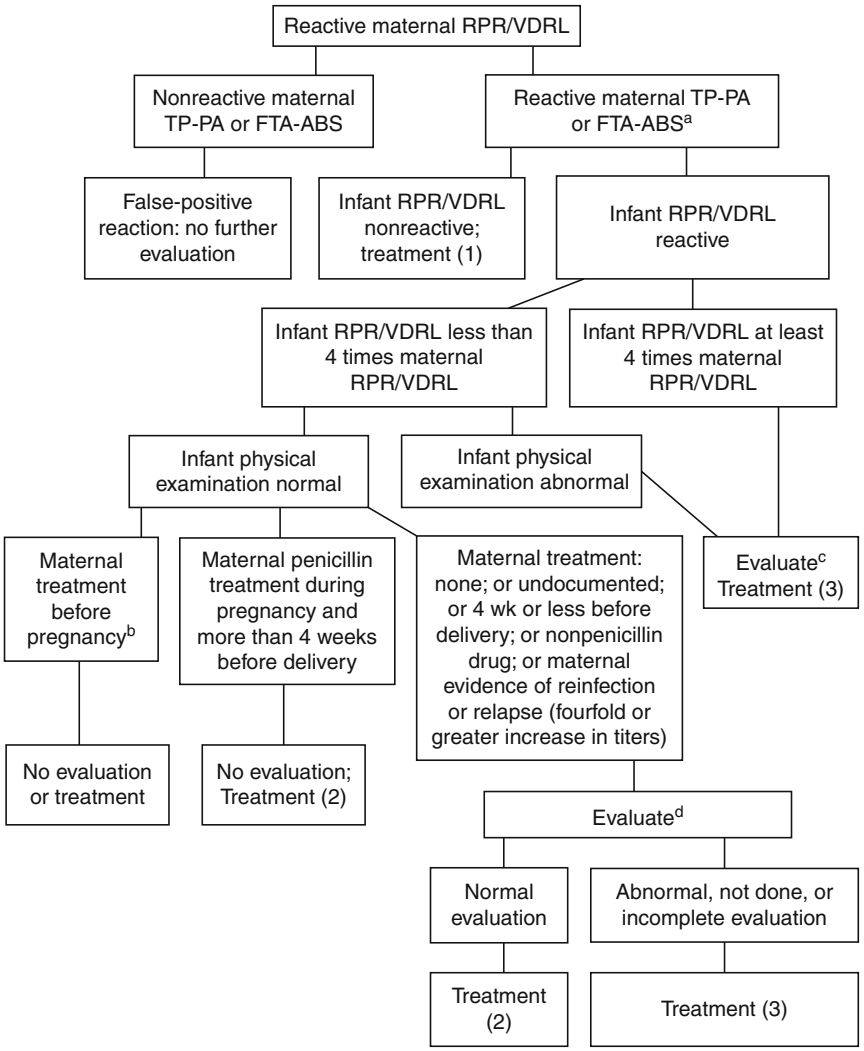
Prevention

The complications of untreated congenital syphilis can be avoided by optimal identification and treatment of patients at risk. Education regarding the benefits of syphilis screening and treatment and the importance of early prenatal care is important, as well as education about avoidance of high-risk sexual behaviors and the benefits of condom use. Case reporting to local public health agencies with investigation, testing, and treatment of all sexual contacts is important and effective at limiting spread of the disease. Confirmation of maternal serologic screening should be documented on all newborn infants before discharge from the hospital. With due diligence and appropriate resources, the significant burden of congenital syphilis could be drastically reduced.

Parvovirus B19

Etiology/Epidemiology

Parvovirus B19 has worldwide distribution and humans are its only known host. It replicates exclusively in erythroid precursors through recognition of its receptor, the P-antigen. Infections peak in late winter/early spring and epidemics tend to occur every 4 years. It is transmitted by contact with infected respiratory secretions or through blood products. Seroprevalence increases with increasing age; ranging from 2% to 15% in children under age 5, 15–60% at ages 6–19, 30–60% in adults and>90% among the elderly. Women of childbearing age are seronegative about 40% of the time. When infection occurs during pregnancy,



RPR indicates rapid plasma reagin (test); VDRL, Venereal Disease Research Laboratory (test); TP-PA, *Treponema pallidum* particle agglutination (test); FTA-ABS, fluorescent treponema antibody absorption (test).

[a]Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment.

[b]Women who maintain a VDRL titer 1:2 or less (RPR 1:4 or less) beyond 1 year after successful treatment are considered serofast.

[c]Evaluation consists of complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL. Other tests as clinically indicated; long-bone and chest radiographs, neuroimaging, auditory brainstem response, eye examination, liver function tests.

[d]CBC, platelet count; CSF examination for cell count, protein, and quantitative VDRL; long-bone radiography.

TREATMENT:

(1) If the mother has had no treatment, undocumented treatment, treatment 4 weeks or less before delivery or evidence of reinfection or relapse (fourfold or greater increase in titers) AND the infant's physical examination is normal, THEN treat infant with a single intramuscular (IM) injection of benzathine penicillin (50 000 U/kg). If these criteria are not met, no treatment is required. In both scenarios, no additional evaluation is needed.

(2) Benzathine penicillin G, 50 000 U/kg, IM 1 dose.

(3) Aqueous penicillin G, 50 000 U/kg, IV, every 12 hours (1 week of age or younger), every 8 hours (older than 1 week), or procaine penicillin G, 50 000 U/kg, IM, single daily dose, 10 days.

Figure 27.1

Algorithm for evaluation and treatment of infants born to mothers with reactive serologic tests for syphilis. From Red book: report of the Committee on Infectious Diseases by American Academy of Pediatrics. Copyright 2009 by American Academy Of Pediatrics - Books. Reproduced with permission of American Academy Of Pediatrics - Books in the format Textbook via Copyright Clearance Center

transmission to the fetus occurs in one-third to one-half of cases, and estimates of adverse fetal outcome are 10%.

Clinical Manifestations

Infection with parvovirus B19 can be asymptomatic but classically causes "Fifth Disease" or erythema infectiosum, characterized by mild malaise with or without fever and a subsequent facial rash with a "slapped cheek" appearance and circumoral pallor. A diffuse maculopapular, pruritic rash may also occur. Arthralgia and arthritis occur uncommonly in children but are much more common in adults and especially women. Infection during pregnancy places the fetus at risk for infection, with the greatest risk associated with the first half of pregnancy. The overall risk of hydrops is 4% in the setting of maternal infection during pregnancy. The maximum risk is when infection occurs between 13 and 20 weeks gestation and is estimated to be 7%. Infection of the fetus can result in a lytic infection of fetal erythrocyte precursors that leads to anemia. When anemia is severe, high output cardiac failure can occur, leading to nonimmune hydrops fetalis and ultimately intrauterine fetal death. Infection of the fetus has not been associated with specific congenital anomalies. In the setting of fetal hydrops, a maternal condition termed "mirror syndrome" can also develop that is similar to preeclampsia and manifests with hypertension, proteinuria, edema, and anemia.

Diagnosis

In the setting of exposure to parvovirus B19 in a pregnant woman, serologic testing is a sensitive and specific means to diagnose new infection. Parvovirus B19-specific IgM can be detected 7–10 days after infection and rapidly decreases by 2–3 months after infection. IgG antibodies are detected later and rise more slowly. When IgM titers exceed that of IgG, recent infection is likely and the fetus should be closely monitored for signs of anemia. Because of the delay in detectable IgM, if the contact is too recent diagnosis can be missed. Likewise, because of the delay between maternal infection and the development of hydrops, a negative or low IgM does not exclude parvovirus infection as the etiology. Serological testing of fetal or infant blood is much less reliable, and confirmation of infection should be confirmed by PCR based methods. Cell culture methods for parvovirus B19 are not currently available. When a fetus is determined to be at risk for congenital infection, regular ultrasound examination should be undertaken to look for signs of fetal anemia and hydrops. Because of the low viscosity and high cardiac output that accompanies anemia, changes in middle cerebral artery peak systolic velocity are detectable by Doppler examination and provide a sensitive method to diagnose fetal anemia. Hydrops can be detected by abnormal fluid accumulation in two or more fetal body compartments. In the setting of anemia, the first changes notable are ascites and thickening of the fetal heart. Pericardial effusion, skin edema, and placental edema will ensue if untreated.

Treatment

Intrauterine fetal transfusion is the mainstay of therapy in the setting of severe fetal anemia and hydrops. Unlike immune-mediated hemolytic anemia, a single transfusion is usually sufficient for fetal recovery. The precise indication and timing for intervention is somewhat controversial, based in part on reports of spontaneous resolution of symptoms in the setting of fetal anemia and even hydrops. Most clinicians use the results of hemoglobin level on percutaneous umbilical blood sampling to guide their decision regarding transfusion. The prognosis for infants surviving fetal anemia and or hydrops after intrauterine transfusion is generally quite favorable.

Prevention

Avoiding exposure to parvovirus B19 is complicated by the fact that many cases are asymptomatic, and among those that develop symptoms, infectivity precedes the development of symptoms attributable to the virus. Women who are exposed to children at home or at work are at increased risk of exposure, but community outbreaks generally coincide with these exposures and further complicate measures to avoid infection. Pregnant women who are known to be seronegative can be educated about the risk of infection and general means to decrease that risk through frequent hand washing and avoidance of sick contacts, but these measures may have limited efficacy for this particular virus. Pregnant women with known exposure can be counseled about the relatively low potential risk of infection and serologic testing offered with ultrasound monitoring as indicated. Candidate vaccines have also been described, but the relative infrequency of severe intrauterine infection casts doubt on the cost-effectiveness of immunization strategies on a population basis.

Varicella

Etiology/Epidemiology

Varicella zoster virus (VZV) is a member of the herpesvirus group and is present throughout the world. Like other herpes viruses, primary infection is followed by latent infection that can reactivate at a later time. Primary infection with VZV is recognized clinically as varicella (chicken pox), and reactivation leads to herpes zoster. The virus is transmitted through respiratory droplets or direct contact with skin lesions. Because the virus is highly infectious, childhood acquisition is common and most individuals acquire immunity by adulthood. An effective vaccine against VZV has been available since 1995, and has dramatically reduced rates of natural infection with this virus while maintaining high levels of immunity in areas with effective vaccination programs. There is considerable geographic variation in VZV incidence. In temperate climates, infections peak in winter and spring and >90% of children become infected by age 15. In tropical climates, the infections tend to occur less frequently and therefore at an older age. The majority of infections lead to benign, self-limited illness, but pregnant women and newborn infants are at considerably higher risk for complications from this disease. Because rates of immunity are very high among adults in most populations, infection during pregnancy is fortunately uncommon.

Clinical Manifestations

Primary infection with VZV generally manifests with prodromal flu-like symptoms in approximately 50% of older children and adults and less frequently in young children. The prodrome is followed by a characteristic vesicular rash ("dew drops on a rose petal") that can be diffuse and is intensely pruritic. Complications of varicella are more common in adults than children and pregnant women are at higher risk. Varicella pneumonia is the complication that leads to the majority of morbidity and mortality. Mortality rates of 20–45% have been reported, but these rates have been significantly reduced with current respiratory care and antiviral agents. Infection during pregnancy can also lead to infection of the fetus, and like many infections, the timing during pregnancy determines the likelihood of adverse outcomes for the infant. Spontaneous abortion, intrauterine fetal demise, and premature birth have all been reported in the setting of varicella in pregnancy, but these complications are rare. Likewise, the majority of infants born to mothers with varicella during pregnancy are healthy, although some have been reported to have zoster in infancy. Congenital varicella syndrome (CVS) is an uncommon complication that occurs primarily in infants whose mothers had varicella in the first half of pregnancy, with the highest risk between 13 and 20 weeks gestation, but the overall incidence is approximately 1%. The primary manifestations of CVS involve the central nervous system (CNS) including the eye, the musculoskeletal system, and the skin. CNS manifestations include microcephaly, cortical atrophy, seizures, and cognitive impairment. Autonomic dysfunction is also seen, leading to esophageal dilation, severe reflux and aspiration pneumonia. Horner syndrome, neurogenic bladder and hydroureter are other autonomic manifestations. Cataracts, chorioretinitis, ptosis, microophthalmia, and nystagmus are typical eye findings. Hypoplasia of limbs, muscle, and digits can occur and cicatricial lesions or cutaneous defects are skin findings. The prognosis of CVS is poor.

A more common severe manifestation of varicella exposure during pregnancy results from acquisition in the perinatal period. The highest risk period for the infant is when maternal infection occurs within 5 days prior to delivery to 2 days after delivery. The basis for severity in this window is that there is insufficient time for protective maternal IgG to be generated and transferred to the fetus. Estimated rates of perinatal infection range from 17% to 30% with a risk of mortality of up to 30% in those infected. The availability of varicella zoster immune globulin (VZIG) has improved these outcomes (see Treatment). Infants with perinatal varicella are generally well appearing at birth and subsequently develop the characteristic rash. Because of their impaired immune status and the absence of maternal protective antibody, disseminated viral infection can occur with significant end-organ damage. Pneumonia, hepatitis with coagulopathy and liver failure, encephalitis, and thrombocytopenia are typical.

Diagnosis

The diagnosis of varicella infection during pregnancy can often be made on clinical grounds with a history of exposure and development of the characteristic rash. Laboratory tests are also available for confirmation when necessary. Vesicles contain abundant virus, which can be unroofed and scraped for culture or direct staining. Antibodies are available for direct fluorescent antigen staining of scrapings from lesions which has high sensitivity and specificity. VZV PCR tests are also available and offer even

higher sensitivity. Culture is highly specific but less sensitive and requires more time for results. Unlike many of the other infections in pregnancy, there is very little role for serologic testing in varicella. Serial ultrasound examination of the fetus after maternal varicella can be used to detect evidence of CVS. Amniotic fluid testing is of limited value, because detection of VZV DNA by PCR in amniotic fluid is not indicative of whether active fetal infection has occurred and has a poor predictive value for fetal disease or disease severity.

Treatment

Acyclovir and valacyclovir are antiviral agents with activity against varicella and other herpes viruses. The United States Food and Drug Administration has designated acyclovir as a category B drug in pregnancy. In the setting of uncomplicated varicella in pregnancy, some experts recommend oral acyclovir treatment, particularly in the second and third trimester when the risk of the drug to the fetus is likely to be low but the risk of maternal complications is higher. IV therapy is recommended should any signs of pneumonia develop. Acyclovir should also be given to any infant with signs of perinatal varicella infection, and must be given IV secondary to poor oral bioavailability.

Passive immunization with immune globulin preparations is also an effective strategy for prevention of severe sequelae. VariZIG is an immunoglobulin preparation with high titers of varicella-specific antibody and can be administered IM. IV immune globulin (IVIG) preparations also contain varicella-specific antibody and are an acceptable substitute, but must be administered IV. If a varicella-susceptible pregnant woman has close contact with an infected person, prophylaxis should be administered within 72–96 h of exposure. Infants born to women who develop varicella infection in the perinatal period should also receive passive immunization with VariZIG or IVIG if VariZIG is unavailable. They should also be monitored closely for any signs of varicella infection and treated with IV acyclovir promptly if signs are detected.

Prevention

The availability of a VZV vaccine has significantly altered the epidemiology of these infections. Ideally, the immune status of women should be determined before pregnancy. A history of disease or receiving two doses of varicella vaccine is indicative of immunity. If neither is present, VZV IgG testing can be performed and vaccination offered if negative. Because it is a live vaccine, immunization during pregnancy is contraindicated because of the theoretical risk of adverse effects on the fetus. However, there have been no reports of congenital varicella in infants whose mothers were inadvertently exposed to vaccine during or immediately prior to pregnancy. Vaccination is safe in the immediate postpartum period and breast feeding is not a contraindication.

Hepatitis B

Etiology/Epidemiology

The hepatitis B virus (HBV) is distributed worldwide and can lead to acute hepatitis that is sometimes fulminant, chronic hepatitis, liver cirrhosis, or liver cancer. It is transmitted efficiently through blood and body fluids, and exposure to infected maternal blood during delivery is a highly efficient route of transmission. Those with chronic HBV infection are the primary source of new infections, and the prevalence varies dramatically by region. Prevalence is as high as 10–20% in Asia, Africa, and Southern Europe, while North America and Northern Europe have a prevalence of approximately 0.1%. In areas where prevalence is high, the majority of new infections occur in infancy, whereas in places with lower prevalence, transmission occurs primarily in adolescents and adults through high risk sexual or drug abuse behaviors or among health-care workers. Implementation of vaccination programs has successfully reduced the transmission rates, particularly in the perinatal period, and therefore prevalence is decreasing.

Clinical Manifestations

Acute infection with HBV can be symptomatic or asymptomatic. Asymptomatic infection is more common in younger people, but even in older children and adults acute infection is accompanied by symptoms only 30–50% of the time. Symptoms can be nonspecific and mild such as anorexia and malaise, but can also include clinically apparent hepatitis and jaundice or fulminant hepatitis. The risk of developing chronic HBV infection, marked by the persistence of hepatitis B surface antigen (HBsAg), varies markedly based on the age of acquisition. When infants are infected perinatally, more than 90% will develop chronic infection. Children infected between 1 and 5 years of age progress to chronic infection 25–50% of the time, whereas the rate

is 2–6% in older children and adults. Hepatitis B e antigen (HBeAg) is a marker for active viral replication, and patients who are HBeAg-positive generally have high levels of HBV DNA is their serum. These patients are more likely to transmit infection. In fact, in the absence of prophylaxis, the risk of perinatal transmission in a mother who is HBsAg and HBeAg positive is estimated at 70–90%, whereas the risk in a mother who is positive for only HBsAg is 5–20%. Intrauterine transmission has also been documented to occur, but is fairly uncommon. The majority of perinatally acquired HBV remains asymptomatic, however infants can develop fulminant hepatitis between 6 weeks and 6 months of age. This clinical course occurs most commonly in infants infected from HBsAg-positive, HBeAg-negative mothers, and the mortality is high in this setting (approximately 67%). Among infants and children that acquire chronic infection with HBV, an estimated 25% will develop hepatocellular carcinoma or cirrhosis later in life.

Diagnosis

Tests for HBV-specific antigens and antibodies are commercially available, including HBsAg, HBeAg, anti-HBs, anti-HBe, and anti-hepatitis B core antigen (anti-HBc). Molecular methods are also available to detect HBV DNA. HBsAg is detectable in acute and chronic infection, and is also the antigen used in HBV vaccine. Anti-HBs is seen in both resolved infection and in vaccine recipients. Anti-HBc is present in acute, chronic, and resolved infections, but not in vaccine recipients. Detection of HBeAg is indicative of a higher risk of transmitting the virus, whereas presence of anti-HBe is associated with lower risk. Tests for HBeAg and HBV DNA can guide the use of antiviral therapy and monitor response to treatment.

Treatment

Agents that are used to treat HBV include interferon-α and the nucleoside analogue, lamivudine. Treatment is not recommended in infants during the neonatal period or in children with chronic infection and normal transaminase levels.

Prevention

Immunization is a safe and very effective strategy for preventing HBV infection and has been an area of focus for the World Health Organization. HBV immunization had been integrated into the Expanded Program of Immunization in 155 countries by 2005, leading to a current coverage rate of approximately 50% of newborn infants worldwide. Infection rates are low and continue to decrease in countries where implementation of vaccination programs has led to near universal coverage. Immunoprophylaxis at birth achieves the primary goal of decreasing prevalence of chronic HBV-infection and related chronic liver disease as well as decreasing acute HBV infection. HBV immune globulin (HBIG) provides passive immunity for 3–6 months, while HBV vaccine can prevent perinatal infection in many and provides lifelong immunity. There are several strategies for prophylaxis that are used throughout the world, depending on the incidence and resources available. In Taiwan, where prevalence is historically high, pregnant women are screened for HBsAg and HBeAg. Infants born to mothers positive for both receive HBIG, while all infants receive the HBV vaccine series initiated shortly after birth. In the USA, a similar strategy is employed, except that screening for HBsAg only is performed during pregnancy, and HBIG is given regardless of HBeAg status. Finally, some countries with fewer resources and/or low prevalence have no maternal screening program and use the vaccine series starting at birth only. The vaccine should be administered within 12 h of birth for maximum efficacy. The combination of HBV vaccine and HBIG in exposed infants is highly effective at preventing transmission. Efficacy for vaccine only without HBIG has also been demonstrated, albeit to a more modest degree.

Human Immunodeficiency Virus (HIV)

Etiology/Epidemiology

Two types of human immunodeficiency virus (HIV), HIV-1 and HIV-2, cause disease in humans. These RNA-containing retroviruses undergo reverse transcription of their genome to double-stranded DNA followed by incorporation into the host genome where it persists as a provirus. Persistent virus has been detected in peripheral blood mononuclear cells, as well as in the brain, bone marrow, and genital tract. Transmission of infection has been documented through exposure to blood, semen, cervicovaginal secretions, and breast milk. Of all the infectious agents discussed in this chapter, vertical transmission of HIV to newborn infants is by far the most common neonatal infection with severe consequences worldwide. In 2008, an estimated 1,200 children became infected with HIV daily. Children account for 14% of new infections with HIV globally and nearly 20% of annual

deaths from AIDS. The tragedy in these data is that vertical transmission of HIV is almost entirely preventable with current prophylactic strategies. In countries with adequate resources, the rate of new HIV infections in children continues to decline, with an estimated 300 cases in Western and Central Europe in 2005. Likewise, the estimated number of perinatally acquired infections in the United States is 141 in 2008, among the 37 states with HIV reporting.

Clinical Manifestations

Transmission of HIV from mother to infant can occur in utero, at delivery, or postnatally through breast feeding. Estimated rates of transmission from an HIV-positive mother to her infant in the absence of preventive measures range from 12% to 40%. Less than half of the transmission is believed to occur in utero, and may occur through infection of the placenta or exposure to virus in amniotic fluid. Infection in the perinatal period is the most common and can occur through exposure to maternal blood during labor and delivery or ascending infection from the genital tract to the amniotic fluid surrounding membrane rupture. The most relevant predictor of risk for perinatal transmission is maternal viral load. Primary HIV acquisition during the third trimester of pregnancy is particularly high risk, because viral load is high in this setting with insufficient time to generate an immune response that could protect the fetus. Other risk factors for transmission include prolonged membrane rupture, vaginal delivery, cervicovaginal viral load, low maternal $CD4^+$ T-lymphocyte count, advanced maternal disease, chorioamnionitis, prolonged labor, and prematurity. Postnatal transmission through breast feeding is also well documented and is estimated to account for 30–50% of transmission to infants worldwide.

In the absence of treatment, manifestations of perinatally acquired HIV infection generally occur within 12–18 months of age, but the distribution is bimodal with both rapid and slow progression. Approximately 20% of infants develop symptoms early and die before the age of 4 with a medium age of death at 11 months. The remainder have much slower disease progression, remaining asymptomatic for 5 years or more. Early manifestations can be nonspecific and include fever, lymphadenopathy, hepatosplenomegaly, hepatitis, recurrent diarrhea, failure to thrive, parotitis, or recurrent invasive or opportunistic infections. Multiple infectious agents and malignancies have been described. The natural history of the disease has been substantially modified by current therapeutic strategies.

Diagnosis

Serologic and nucleic acid detection based tests are available for the diagnosis of HIV infection. Because infants born to seropositive mothers will acquire maternal antibody, serological tests are not useful in the newborn period and are generally not recommended until after 18 months of age. The HIV-1 DNA PCR test is widely used in infancy and has excellent sensitivity and specificity. A positive result before 48 h of age occurs in 30–40% of infected infants and generally signifies in utero transmission. By 2 weeks of age, 93% of infected infants are positive and by 1 month of age, 95% are positive. Diagnostic testing is recommended in infants born to HIV-positive mothers at 14–21 days of age, and if negative, repeated at 1–2 months and again at 4–6 months. Some experts recommend testing within the first 48 h as well. An infant is considered infected in the setting of two separate positive tests. In non-breast-feeding infants less than 18 months of age, infection is considered to be excluded with (1) at least two negative nucleic acid tests obtained after 1 month of age with at least one obtained after 4 months of age, (2) at least two negative HIV antibody tests obtained at 6 months of age and older, and (3) no other laboratory or clinical evidence of HIV infection.

Enzyme immunoassays (EIA) are the most widely used tests for HIV antibody testing. They have high sensitivity and specificity, but confirmation of a positive test by Western blot is required. Rapid tests that can provide results within 20 min are also available and are used primarily to screen mothers of unknown HIV status when in labor. Confirmation is still required. Because identification and prophylactic treatment of HIV-positive women is so effective at reducing perinatal transmission, some areas have implemented universal screening algorithms for pregnant women. In these scenarios, HIV testing is routinely recommended to pregnant women when they present for prenatal care on an "opt-out" basis. In the setting of presentation in labor in the absence of prenatal care, rapid testing is performed on the mother at presentation. Should maternal testing be declined, universal testing of the infant at delivery is then performed. In areas where this strategy has been implemented, screening rates during pregnancy have risen dramatically, with the expected drop in perinatal transmission rates.

Treatment

Treatment of patients infected with HIV is an area of active investigation and as such is rapidly evolving. Involvement

of experts in pediatric HIV disease is strongly recommended to ensure that patients receive the maximum benefit from treatment. Current US treatment recommendations are available online at http://aidsinfo.nih.gov. The use of highly active antiretroviral therapy (HAART) began in 1996 and has been associated with marked improvement in survival and quality of life in patients infected with HIV. Multiple categories of drugs are available that target various aspects of the viral infectious cycle. The categories include Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Fusion Inhibitors, Entry Inhibitors, and HIV Integrase Strand Transfer Inhibitors. The goals of therapy are to suppress viral replication, preserve immune function, reduce morbidity and mortality, maintain normal growth and development, and improve quality of life, while minimizing drug toxicity. Although indications for antiretroviral (ARV) therapy vary based on clinical status in older children, HIV-infected neonates should receive therapy regardless of symptoms or status, because of the risk of rapid disease progression in these patients. In general, at least three drugs are included when ARV therapy is initiated, most often including two NRTIs plus either a PI or a NNRTI. Viral genotyping can be used to assess resistance to ARV agents and guide therapy.

Prevention

As mentioned above, screening for HIV infection during pregnancy with application of prophylactic measures and modified obstetrical practices has dramatically reduced the rates of perinatal HIV transmission in resource-rich countries. This reduction has come about primarily through optimizing ARV therapy during pregnancy, complete avoidance of breast feeding, and planned cesarean section prior to onset of labor and membrane rupture. The first documentation of the success of ARV therapy in prevention of perinatal transmission came from a study in which zidovudine (AZT) was given to HIV-positive pregnant women beginning at 14–34 weeks' gestation and continued for the remainder of pregnancy, given IV during labor until delivery, and then given orally to the infant for the first 6 weeks. Perinatal transmission was reduced by two-thirds in this study. Currently in the United States, most HIV-positive pregnant women receive combination ART, as there is some suggestion that this approach is more effective than AZT alone. Many questions related to the optimal type, timing, and duration of HAART in pregnancy, the potential for toxicity to exposed infants, as well as the best prophylaxis strategies for these infants remain and are the target of ongoing investigation. AZT is then given with the ART drugs during labor and delivery, and the infants receive 6 weeks of therapy. From an obstetrical standpoint, any procedure that is likely to increase exposure of the infant to maternal blood or secretions (instrumented delivery, scalp electrodes, episiotomy, etc.) should be avoided. Delivery by cesarean section prior to labor or rupture of membranes is recommended for women with plasma viral loads greater than 1,000 copies/ml or those with unknown viral loads at term. The baby should be bathed promptly and postnatal prophylaxis should begin within 12 h. Breast feeding is associated with approximately double the risk of HIV transmission, and the risk persists as long as breast feeding continues. These findings are the basis for the recommendation that breast feeding is contraindicated in countries where alternative feeding methods are available that are safe, affordable, and culturally acceptable. In countries where alternatives are not available that meet these criteria, exclusive breast feeding is recommended for 6 months, with introduction of supplemental food sources after 6 months. Given the dramatic potential to reduce perinatal transmission and therefore overall disease burden using preventive strategies, successful implementation of these strategies in resource-poor countries would have a profound impact on world health.

Neonatal Sepsis

Etiology/Epidemiology

Current estimates indicate that infections cause approximately a third of the four million neonatal deaths each year worldwide. Although the most robust epidemiologic data have come from studies in industrialized countries, by far the highest burden of neonatal sepsis is in the developing world, particularly in South Asia and sub-Saharan Africa. Precise knowledge of the true disease burden in these regions is very difficult to quantify on a population basis because many deliveries occur outside of health-care facilities and reporting is limited. Irrespective of these difficulties in epidemiological assessments, however, the global burden of neonatal sepsis is tremendous and strategies to reduce its impact are clearly needed.

Neonatal sepsis is conceptually divided into two categories based on timing of infection after birth, but the definitions are somewhat varied in the literature. Early-onset disease generally occurs within the first 72 h after birth, although the first 7 days has been used as a cutoff in

some studies, particularly with Group B *Streptococcus* (GBS). Late-onset disease is therefore defined as sepsis occurring after day 4 or day 8, through day 28. Infections after day 28 are sometimes also considered late-onset neonatal sepsis, particularly in neonatal intensive care units caring for premature infants who have not yet attained a post-menstrual age of 44 weeks. The distinction between early-onset and late-onset sepsis is useful because it reflects differences in acquisition and risk factors. Early-onset sepsis is generally caused by pathogens to which the infant is exposed during delivery and is associated with maternal risk factors, while late-onset disease is generally from a hospital or community acquired pathogen.

The organisms associated with early-onset neonatal sepsis vary over time and also by region. *Streptococcus pneumoniae* and Group A *Streptococcus* were prevalent in the United States in the 1930s and 1940s. These have sharply declined in incidence, being largely replaced in recent years by GBS and *Escherichia coli*. Sepsis caused by *Listeria monocytogenes* is considerably less common, but is also unique to the neonatal period and seems to be predominant in developed countries. This is primarily an early-onset pathogen, but is also less commonly associated with late-onset sepsis and/or meningitis. Although data on etiologic agents in developing countries are more limited because of challenges in methodology, GBS sepsis seems to be less prevalent in these areas for reasons that are not well understood, whereas *Klebsiella* species and *Staphylococcus aureus* appear to be more common. Late-onset sepsis is associated with many of the same organisms, but coagulase-negative *Staphylococcus* becomes increasingly prevalent in this setting, particularly in premature infants. Generally speaking, infections with Gram-positive organisms are most common in premature infants and are not associated with increased mortality. Gram-negative infections are less frequent than Gram-positive infections in this population, but fulminant infections with high mortality are considerably more common with these organisms. Infections with *Pseudomonas* sp. are well known to have a frequently fulminant course with high mortality.

Premature infants are also uniquely susceptible to disseminated fungal infection. The vast majority of these are with *Candida* species. These infections are the second most common cause of infection-related death in extremely low birth weight infants and are associated with high rates of neurodevelopmental impairment among survivors. The susceptibility of these patients to *Candida* infections relates to their immature immune system as well as to well-described risk factors including the use of third-generation cephalosporins and foreign bodies such as central venous catheters and endotracheal tubes. Rates of invasive candidiasis differ dramatically among centers throughout the world. Centers with high incidence have successfully reduced their rates of invasive disease by instituting prophylaxis of at-risk infants with fluconazole. Widespread application of this strategy, particularly where rates of disease are low, is controversial secondary to concerns of increased drug resistance.

Other infectious complications rarely seen in resource-rich settings are also problematic in developing nations. Neonatal tetanus occurs in areas where maternal tetanus vaccination is not universal and hygienic practices surrounding labor and delivery are suboptimal. Estimates from the WHO indicate that 180,000 neonatal deaths were attributable to tetanus in 2002. Infections of the umbilical cord (omphalitis) can lead to peritonitis and bacteremia, but these infections are also uncommon in settings with clean cord care and hygienic birth practices. Estimates of rates of omphalitis in resource-poor settings range from 55 to 197 cases per 1,000 live births where cord care is not optimal, such as the common use of unsterile instruments to cut or tie the cord. Mortality from omphalitis has been reported as high as 15%.

Clinical Manifestations

The term "sepsis" as applied to neonates is essentially a set of nonspecific clinical features characteristic of disseminated bacterial infections, including temperature instability (fever or hypothermia), lethargy, irritability, poor feeding, apnea, respiratory distress, vomiting, and jaundice. These features overlap with other conditions such as encephalopathy from noninfectious causes and prematurity, making accurate estimates of sepsis rates due to bacterial infection difficult, particularly in areas that lack sophisticated microbiology laboratories. The strictest definition of sepsis includes the presence of blood culture documented bacteremia. These infections may also be accompanied by pneumonia, meningitis, and urinary tract infections. Because positive cultures of cerebrospinal fluid have been well documented in the setting of negative blood cultures, including a lumbar puncture in the evaluation for presumed sepsis is encouraged. However, since meningitis is more common with late-onset disease, a lumbar puncture is sometimes not included in sepsis evaluations performed shortly after birth, although this practice is controversial and subject to ongoing debate. Similarly, urine cultures are often omitted in early sepsis evaluations. Pneumonia should be considered in infants with respiratory symptoms such as grunting, tachypnea, nasal flaring, retractions, and hypoxemia. However, many

of these signs are also present in the setting of sepsis, and radiographic findings are likewise nonspecific.

Factors that increase the risk for sepsis in neonates are well established. For early-onset disease, many of these risk factors are maternal, including chorioamnionitis, maternal fever, prolonged rupture of membranes, and bacteriuria during pregnancy. Prematurity and low birth weight also increase risk. For late-onset disease, low birth weight, prematurity, mechanical ventilation, use of central venous catheters and total parenteral nutrition all increase risk. Rates of late-onset sepsis increase dramatically as birth weight decreases below 1000 g. These factors should be considered in the evaluation of symptoms potentially attributable to sepsis.

Diagnosis

Although a positive blood culture is considered the gold standard for diagnosis, even where laboratories are available blood cultures are relatively insensitive. Maternal treatment with antibiotics likely reduces the utility of blood cultures, and the amount of blood that can be sampled in neonates further limits sensitivity of the test. As mentioned above, cultures of cerebrospinal fluid are quite useful and should be obtained. Urine cultures are also recommended, but should be obtained in a sterile fashion; either by clean catheterization or suprapubic aspiration from the bladder. Adjunctive laboratory tests are also frequently obtained to aid in the diagnosis of sepsis in a symptomatic infant or when maternal risk factors are present. These include complete blood count, platelet count, absolute neutrophil count, calculation of the immature to total neutrophil ratio, C-reactive protein, and erythrocyte sedimentation rate. Although routinely obtained, these tests lack positive predictive value. The negative predictive value of normal results is considerably better and can be reassuring. In the absence of laboratory tests that are completely sensitive and reliable in distinguishing symptoms attributable to sepsis from other etiologies, many infants are treated with extended courses of antibiotics in the absence of positive cultures. Although this practice results in antibiotic use that may not be needed, the clinician must weigh the risk of therapy against the risk of a poor outcome due to an undetected and untreated infection.

Treatment

Because of the nonspecific symptoms and potential difficulties in establishing a diagnosis, recognition and treatment of neonatal sepsis requires a high index of suspicion. Empiric treatment is frequently indicated in the setting of risk factors and/or signs of infection. However, antibiotic use is far more prevalent than culture-proven neonatal sepsis due to this same combination of factors. The most common choice for empiric therapy is ampicillin and an aminoglycoside. This combination is efficacious against both Gram-positive and Gram-negative organisms and covers the most common etiologic agents. In late-onset disease, substitution of an agent with better staphylococcal activity for ampicillin such as oxacillin or vancomycin is recommended by some. However, such recommendations are controversial from an antibiotic stewardship point of view as resistance continues to emerge and become increasingly problematic worldwide. When candidiasis is suspected or confirmed, amphotericin B is recommended as first line therapy in the neonate. In any case, empiric antibiotic therapy should be based on the local epidemiology of common causative organisms and appropriately tailored to the organism involved when positive blood cultures are available to guide therapy.

Prevention

Strategies to prevent neonatal sepsis begin in the prenatal period and extend through labor, delivery, and postpartum care of the infant. Routine prenatal care is common in developed countries and can have a positive impact on infections in the newborn. Screening for and treatment of maternal sexually transmitted infections, urinary tract infections or asymptomatic bacteriuria, and administration of tetanus vaccine can mitigate risk of infection in the newborn. Delivery in a setting that allows a skilled attendant to be present and provide hygienic birth practices further reduces risk. Antibiotic treatment for preterm prolonged rupture of membranes as well as for maternal chorioamnionitis may reduce neonatal sepsis by as much as a third. In the postnatal period, the benefits of exclusive breast feeding in preventing infection are well established. The inexpensive and practical intervention of increasing breast feeding rates could provide an extremely cost-effective and far-reaching impact on neonatal infection rates. Ensuring good hand hygiene and the availability of clean water with sanitary disposal of waste are additional interventions that reduce disease burden. For preterm infants, many of these same strategies are important. Strict adherence to routine hand washing procedures is well documented to effectively reduce late-onset sepsis in premature infants. Additionally, utilization of best practices for placement and maintenance of central venous catheters while minimizing their use as much as possible is an important means to reduce one of the most important risk factors

for sepsis. Early introduction of enteral feedings and provision of breast milk are also well-established interventions that reduce infection rates. Evidence is also accumulating that provision of "kangaroo care," including frequent if not exclusive skin-to-skin contact with the mother and frequent breast feeding has a number of benefits for the preterm infant including lower infection risk.

Early-onset GBS sepsis is the best example demonstrating the potential for well-designed preventive strategies to decrease rates of neonatal sepsis. In the United States, GBS emerged as the leading cause of early-onset sepsis in the 1970s. Approximately 10–30% of women are colonized with GBS in the vagina or rectum, and in the absence of intervention, 1–2% of infants born to these mothers will develop early-onset GBS infection. Consensus guidelines were developed by the Centers for Disease Control and Prevention, the American College of Obstetricians and Gynecologists, and the American Academy of Pediatrics in 1996 with revisions in 2002 and 2010. Current recommendations include universal screening for GBS colonization by recto-vaginal culture of all pregnant women at 35–37 weeks gestation. Colonized women should receive intrapartum antibiotic prophylaxis with penicillin or ampicillin. Women who have GBS bacteriuria at any point during pregnancy or those with a previous infant with invasive GBS disease should also receive intrapartum prophylaxis. Because GBS colonization occurs rarely in the absence of labor with intact membranes, prophylaxis is not recommended for those women who undergo cesarean section before onset of labor when membranes are intact. When GBS colonization status is uncertain, prophylaxis is recommended for those at highest risk, including prematurity (gestational age less than 37 weeks), rupture of membranes for 18 or more hours, or maternal temperature during labor greater than 38°C. Before preventive strategies were implemented, the early-onset GBS sepsis rate was estimated at 1.7 per 1,000 live births. In recent years, the rate has dropped 80% to 0.34 per 1,000 live births. Ongoing study and surveillance is utilized to identify barriers to compliance with guidelines, strategies to further reduce infection rates, and the potential emergence of other pathogens or altered resistance patterns in the era of widespread prophylaxis.

Conclusion

The human newborn is uniquely susceptible to a host of infectious pathogens that have a substantial impact on morbidity and mortality worldwide. Their risk is impacted by innumerable factors including the immaturity of their immune mechanisms; the general health and exposures of their mothers; the prenatal, intrapartum, and postnatal health-care practices where they are born; and the local economic resources available for treatment and prevention. Tremendous progress has been made in decreasing the impact of these infections, but a tremendous need for improvement remains on a global scale. Extending the best practices available to the regions with the least resources remains a major challenge of this century.

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28 Common Endocrine Problems in Neonatology

Jose Bernardo Quintos

Congenital Adrenal Hyperplasia

Definition/classification: Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of adrenal steroidogenesis characterized by impaired cortisol synthesis. CAH results from a deficiency of one of the enzymes necessary for normal steroid synthesis (Fig. 28.1). Ninety five percent of all CAH cases are caused by 21 hydroxylase deficiency. There are two forms of 21 hydroxylase deficiency: classic and nonclassic CAH (late onset). Classic CAH includes the salt-wasting form (cortisol deficiency and aldosterone deficiency) and simple virilizing form (cortisol deficiency without aldosterone deficiency). Patients with the classic form have severe enzyme deficiency and prenatal onset virilization while the nonclassic form patients have mild enzyme deficiency and postnatal hyperandrogenism and are not virilized at birth.

Etiology: The most common form of CAH is caused by mutations in CYP21A2, the gene encoding the adrenal steroid 21-hydroxylase enzyme (P450c21). The steroid 21-hydroxylase enzyme converts 17-hyrdroxyprogesterone (17-OHP) to 11-deoxycortisol and progesterone to deoxycorticosterone, which are precursors of cortisol and aldosterone, respectively. In 21-hyroxylase deficiency, there is deficient cortisol synthesis impairing cortisol-mediated negative feedback of ACTH secretion leading to accumulation of cortisol precursors that are shunted to the sex hormone (androgen) pathway.

Epidemiology: The incidence of CAH in the general population, as shown by newborn screening, ranges from 1 in 5,000 live births in Saudi Arabia to as low as 1 in 21,270 live births in New Zealand. The newborn screening incidence in the United States and Canada is 1 in 14,203 live births, Brazil 1 in 1,863 live births, Japan 1 in 18,827. A high frequency of CAH exists among Yupik Eskimos from western Alaska at 1 in 282 live births.

Clinical Manifestations: The cardinal feature of classic CAH in newborn females is ambiguous genitalia (Fig. 28.2).

Neonates with classic salt-wasting CAH exhibit salt-wasting crisis during the first 1–3 weeks of life but it may occur as late as few months of age. This manifests as poor feeding, vomiting, loose stools, weak cry, failure to thrive, dehydration, and lethargy. The biochemical hallmark of salt-wasting crisis is hyponatremia, hyperkalemia, metabolic acidosis, and hypoglycemia. Without treatment, circulatory collapse, arrhythmias from hyperkalemia, and death may occur within days or weeks. In females with classic CAH, genital ambiguity ranging from clitoromegaly to complete virilization occurs while internal genitalia (uterus and fallopian tubes) are normal (Fig. 28.3). Boys with classic CAH do not manifest ambiguity at birth but can have subtle scrotal hyperpigmentation because of ACTH hypersecretion or phallic enlargement because of excessive adrenal androgens in utero. Postnatally in untreated boys and girls, excessive adrenal androgen secretion leads to rapid growth, bone age advancement, progressive penile or clitoral enlargement, and premature appearance of pubic hair, axillary or facial hair, and acne. Without treatment, early epiphyseal closure occurs and result in short adult height.

Diagnosis: CAH is the most common cause of ambiguous genitalia in the newborn period. The physician is obliged to make timely diagnosis to prevent sex misassignment and initiate immediate treatment to prevent salt-wasting crisis in the salt-wasting form of CAH. Karyotype will identify chromosomal sex and pelvic ultrasonography will help identify mullerian structures (ovaries and uterus). Consultation with an endocrinologist should be sought. Adrenal steroids should be measured by blood sample on day 2–3 of life. A markedly elevated level of 17-OHP in a virilized 46, XX female with nonpalpable gonads is most likely due to CAH. In affected females, androstenedione and testosterone levels are high. In males, testosterone is usually elevated because of minipuberty in the first 6 months of life and is thus not helpful. ACTH levels are high but are not needed for diagnosis. In salt-wasting CAH, plasma renin is elevated and serum aldosterone is inappropriately low for the renin level. Diagnosis of 21 hydroxylase deficiency

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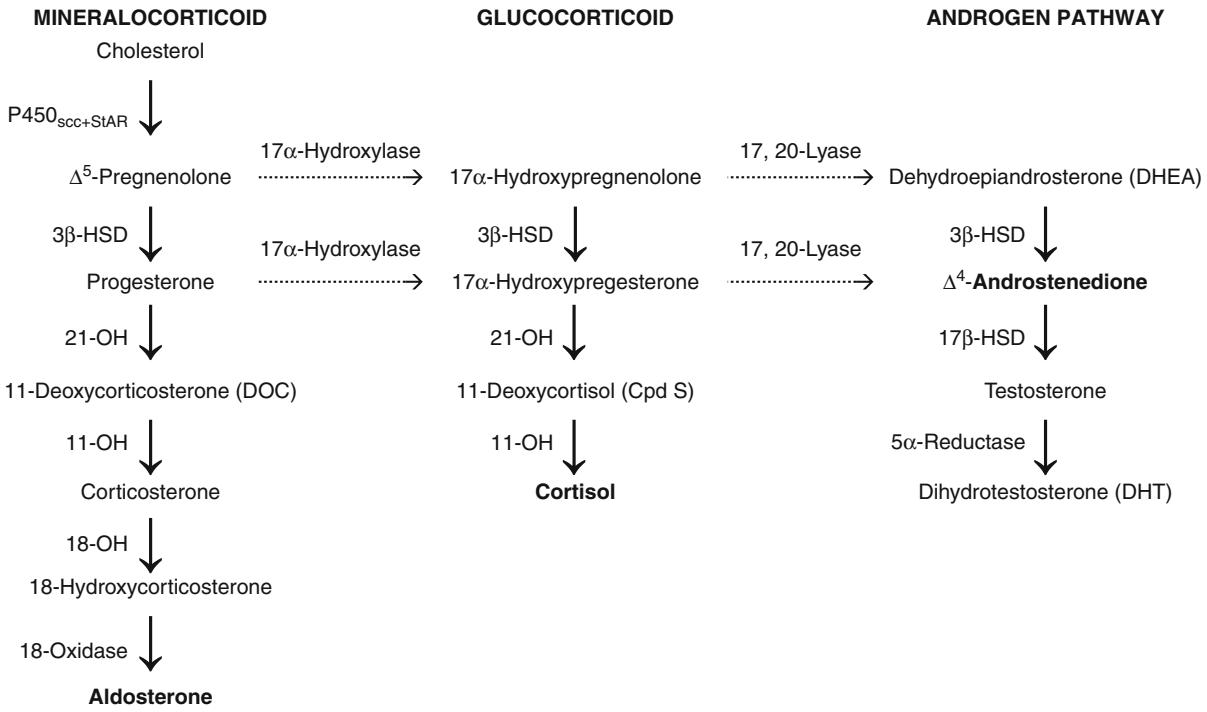

Figure 28.1
Adrenal hormone synthesis. P450 scc: cholesterol side chain cleavage; 3β-HSD: 3β-Hydroxysteroid Dehydrogenase; 11-OH: 11β-Hydroxylase; 17β-HSD: 17β-Hydroxysteroid Dehydrogenase; 18-OH: 18-Hydroxylase; 21-OH: 21α-Hydroxylase; StAR: Steroidogenic acute regulatory protein

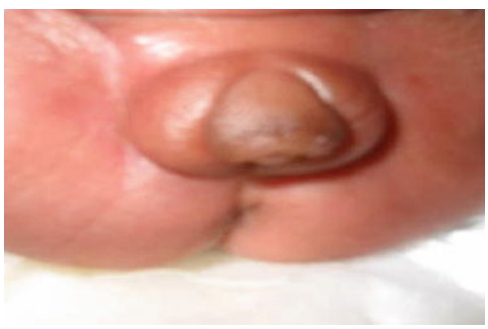

Figure 28.2
Newborn female with clitoromegaly with non-palpable gonads

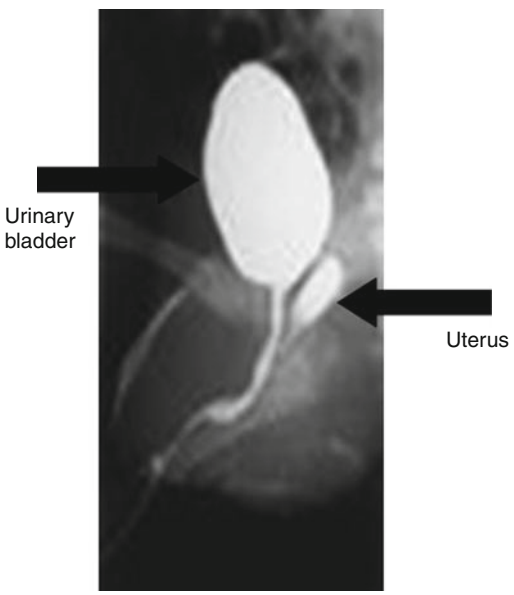

Figure 28.3
Urogenitogram showing urogenital sinus

is most accurately established by measuring 17-hydroxyprogesterone before and 30 or 60 min after intravenous injection of 0.25 mg of Cosyntropin (ACTH1-24). Basal and 60 min 17-OHP are plotted on a nomogram and distinguish normal and patients with nonclassical and classical CAH.

Differential Diagnosis: The result of physical exam, karyotype, and adrenal steroids will narrow differential diagnosis into four categories: (1) chromosomal or gonadal disorders (e.g., 45X/46 XY), (2) 46, XX patients with adrenal insufficiency, (3) 46, XY patients with adrenal insufficiency, and (4) 46, XY patients without adrenal insufficiency with testosterone biosynthesis defect or action.

Treatment: Cortisol deficiency is treated with glucocorticoids. Glucocorticoid treatment also suppresses excessive adrenal androgens preventing rapid somatic growth and early epiphyseal fusion. Hydrocortisone tablets at a dose of 10–15 mg/m^2/day in 2–3 divided doses is the preferred treatment. Infants with CAH require higher doses 50 mg/m^2/day during the first few weeks of life to suppress ACTH hypersecretion. Patients with salt-wasting CAH require mineral corticoid replacement with Fludrocortisone 0.05–0.3 mg daily in 1–2 divided doses and Na CL supplementation 1–3 g/day. NaCL tablets are available and one tablet is equivalent to 17 meq of NaCL. Stress dosing (2-3X maintenance dose) is needed in febrile illness (>38.5°C), gastroenteritis with dehydration, surgery accompanied by general anesthesia, and major trauma. For infants, parenteral dose of Solucortef (Hydrocortisone sodium succinate) 25 mg IM or IV could be given for severe vomiting, diarrhea, surgical stress, or severe trauma. Surgery for significantly virilized females (urogenital sinus and severe clitoromegaly) is usually done between 2 and 6 months of age and performed by an experienced surgeon. The need for clitoral recession for severe clitoromegaly should be individualized and discussed with family.

Prognosis: Untreated salt-wasting CAH can lead to circulatory collapse, arrhythmia, and death. Untreated nonclassical and simple virilizing CAH can lead to excessive adrenal androgen secretion and cause rapid bone age advancement and ultimate short adult stature.

Prevention: Since CAH is common and potentially fatal, it is a disease that is ideal for newborn screening. As of 2009, all 50 states in the United States and 12 other countries screen for CAH. Early recognition and treatment can prevent morbidity and mortality. CAH is an autosomal recessive condition. If a mother has a previously affected child with CAH and is pregnant with the same father, the fetus has a one in four chance of having CAH. Prenatal treatment of 21 hydroxylase deficiency with dexamethasone has been used since 1984 to prevent virilization should the fetus be an affected female. Dexamethasone is preferred because it is not bound to cortisol binding globulin in the maternal blood, and the placenta which has 11β-hydroxysteroid dehydrogenase enzyme cannot metabolize dexamethasone the way it metabolizes hydrocortisone. Dexamethasone crosses the placenta from the mother to the fetus and suppresses ACTH secretion. Dexamethasone at a dose of 20 mcg/kg/day in three divided doses is administered to pregnant mother before 10 weeks gestation. Prenatal therapy is considered experimental and should be pursued through protocols approved by Institutional Review Boards at specialized centers.

Adrenal Insufficiency

Definition/classification: Adrenal insufficiency is divided into congenital forms or acquired. Congenital adrenal insufficiency consists of group of disorders including (1) defects of adrenal development; (2) hypothalamic or pituitary dysfunction leading to ACTH deficiency and adrenocortical insufficiency; (3) inborn defects of steroidogenesis; and (4) degenerative, metabolic, or immune disorders affecting the adrenal glands (which are rare conditions in the neonatal period).

Etiology

1. *Defects of adrenal development*: Cytomegalic Adrenal hypoplasia congenita. (SF-1 and DAX1 deficiency).
   (a) SF-1 Deficiency: Steroidogenic Factor-1 (SF-1, NR5A1) belong to the family of nuclear hormone receptor. SF-1 is a transcription factor required for adrenal and gonadal development. The classic phenotype of SF-1 loss of function gene mutation is 46 XY sex reversal (female internal and external genitalia, complete gonadal dysgenesis (streak gonads), and primary adrenal failure). Given that SF-1 is a key regulator of adrenal and reproductive development and function, other phenotype of SF1 mutation include 46 XX primary adrenal failure, 46 XY Disorder of Sex Development (DSD), hypospadias, anorchia, male factor infertility, and primary ovarian insufficiency in women.
   (b) DAX 1 deficiency: DAX1 (NROB1) Human mutation of DAX-1 (dosage sensitive sex reversal adrenal hypoplasia congenital (AHC), critical region on the X chromosome), causes the

cytomegalic form of AHC, the most common variant of congenital adrenal insufficiency. Male 46 XY patients with DAX1 mutations typically present with hypogonadotropic hypogonadism and adrenal insufficiency.

2. *Abnormal hypothalamic-pituitary development*: ACTH deficiency may be isolated or may be a part of multiple pituitary hormone deficiency (MPHD).
   (a) Isolated ACTH insufficiency due to TPIT mutations: Tpit is a T box transcription factor important for terminal differentiation of pituitary propiomelanocortin-expressing cells. Patients with loss of function Tpit mutations present with low cortisol with undetectable or inappropriately low ACTH level, neonatal hypoglycemia associated with seizures in half of the cases, cholestatic jaundice, and occasionally hepatomegaly. Symptoms of adrenal insufficiency as well as cholestatic jaundice disappear after hydrocortisone treatment.
   (b) Multiple pituitary hormone deficiency (MPHD): ACTH deficiency may be part of multiple pituitary hormone deficiency caused by abnormal hypothalamic-pituitary development caused by mutations in transcription factors HESX1, LHX4, SOX3, PROP1, and OTX2.

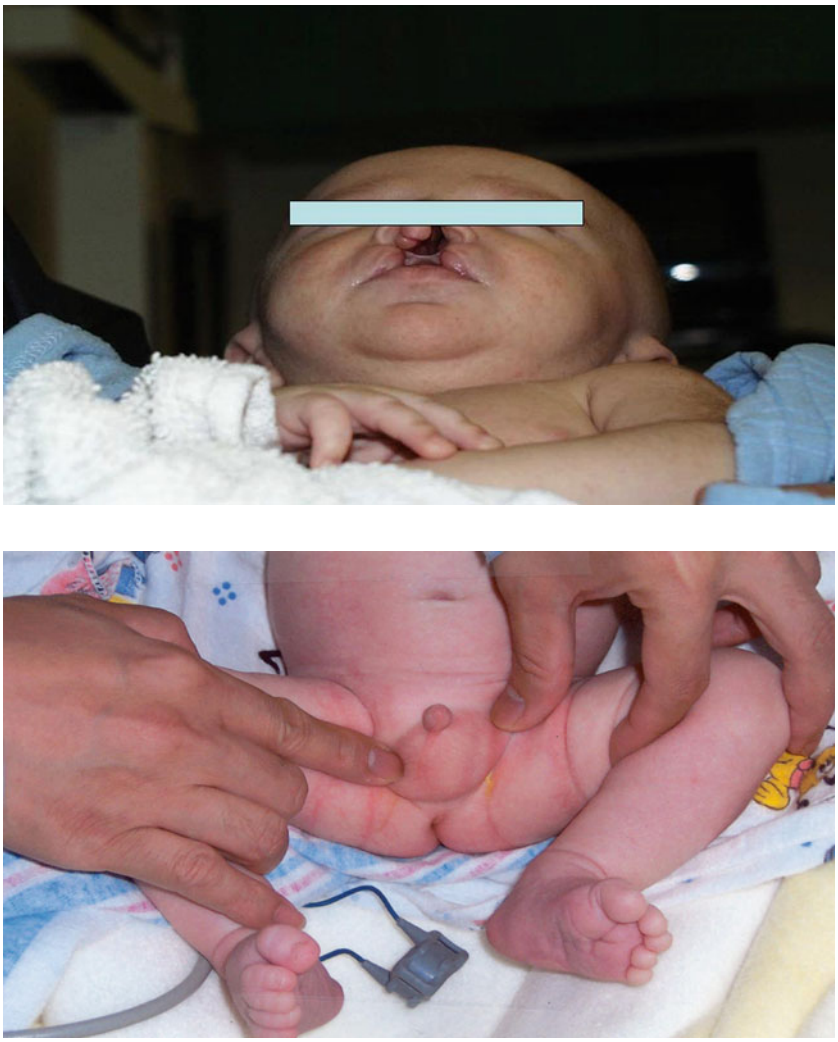

Figure 28.4
Baby boy with (a) cleft lip and palate associated with hypopituitarism; (b) micropenis associated with hypopituitarism

3. *Inborn defects of steroidogenesis*: The most common cause of adrenocortical insufficiency in infancy is the salt-wasting form of 21 hydroxylase deficiency. Almost 75% of 21 hydroxylase deficiency is due to salt losing form. Congenital lipoid adrenal hyperplasia (StAR deficiency) in newborns, a rare disorder due to mutations in steroidogenic acute regulatory protein (StAR) which is required for cholesterol delivery to the mitochondria, leads to inability to convert cholesterol to pregnenolone, preventing synthesis of all steroids (cortisol, aldosterone, and androgens). Genetic males present with normal female genitalia, signs and symptoms of adrenal insufficiency, and salt loss. Infants with deficiency of 3β-hydroxysteroid dehydrogenase manifest salt losing symptoms in the newborn period.
4. *Adrenoleukodystrophy*: Neonatal ALD is a rare autosomal recessive disorder associated with neonatal seizures, psychomotor retardation, developmental regression, and impaired adrenocortical function.

Clinical Manifestations: Clinical signs and symptoms of hypopituitarism in neonates include hypoglycemia, poor feeding, apnea, jitteriness, temperature instability, recurrent sepsis, prolonged jaundice, conjugated hyperbilirubinemia, lethargy, and electrolyte abnormalities (hyponatremia without hyperkalemia). Physical exam findings suggestive of hypopituitarism include micropenis, bilateral undescended testes, cleft lip and palate (◉ *Fig. 28.4*), nystagmus, anophthalmia, and microphthalmia.

Diagnosis: Patients with primary or secondary adrenal insufficiency present with signs and symptoms of hypoglycemia in the newborn associated with low cortisol level with undetectable or inappropriately low or normal ACTH level in ACTH deficiency (secondary adrenal insufficiency) or low cortisol with high ACTH level in primary adrenal insufficiency.

Treatment: Treatment with hydrocortisone, NaCL, fludrocortisone is needed for inborn errors of steroidogenesis. Hydrocortisone alone is needed for patients with isolated ACTH deficiency. Hydrocortisone, Levothyroxine, growth hormone, and DDAVP is needed in neonates with panhypopituitarism.

Prognosis: Hypoglycemia should be treated aggressively to prevent adverse neurocognitive sequela. Growth and development should be monitored closely.

Prevention: Genetic counseling to families of affected patients is needed to discuss risk of having another affected child in future pregnancies.

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29 Disorders of Glucose Homeostasis in the Newborn

William Oh

Normal glucose homeostasis in the newborn is maintained by adequate intake of glucose or glucose-producing substrates and appropriate balance of hormones that regulate glucose production and utilization. Insulin is the primary hormone while glucagon, glucocorticoid, epinephrine, and growth hormones are the counter-regulatory hormones. Inadequate or excessive intake of glucose or improper balance of insulin and the counter-regulatory hormones will produce abnormally low or high blood glucose values resulting in hypoglycemia and hyperglycemia respectively. Both conditions can cause clinical signs that require prompt management to avoid undesirable short- and long-term outcomes.

Neonatal Hypoglycemia

Definition

The definition of neonatal hypoglycemia is based on the normative blood glucose values and the 95th% confidence intervals. Hypoglycemia is defined as blood glucose falling below the 95th percentile of the normal values. The normative value is gestational and postnatal age dependent. Based on the data published by Srinivasan and Cornblath (*Figs. 29.1* and *29.2*), blood glucose values of <30 mg/dL is considered hypoglycemic for term infants during the first 24–48 h of life. In preterm infants, a value of <20 mg/dL is considered hypoglycemic during the same postnatal age period. There are several reasons for the lower values in preterm infants: (1) they have lower glycogen reserve, (2) less efficient gluconeogenesis, and (3) they are more likely to have lower enteral intake. The latter is often modified by early parenteral nutrition which is a common practice in the care of these infants. During the third day through the first week of life, hypoglycemia is defined as blood glucose <40 and 30 mg/dL for term and preterm infants respectively. Beyond the first week, <50 and <40 mg/dL are considered hypoglycemic for term and preterm infants respectively. It should be noted that the normative data for preterm infants were collected in the 1960s when very preterm and extremely preterm infants did not survive and the normative data are primarily obtained in the larger preterm infants. Thus, it is quite likely that the definition we use may "over-diagnose" the condition among very or extremely preterm infants. Nevertheless, while there are considerable debates and controversies on the precise values for the definition of this disorder, most clinicians consider the definition clinically acceptable.

A common clinical practice in the management of hypoglycemia is to screen for this condition at the point of care using heel stick to obtain a small amount of blood for glucose determination using a reflectance meter. The procedure has the advantages of being simple, requiring a small amount of blood and having a quick turn-around time for the result. The distinct disadvantage is that there is a relatively poor correlation between the values obtained by this technique when compared with those obtained by standard laboratory measurements. This phenomenon is particularly true in the high and low range of the blood glucose values. Because of this limitation, it is important that when a screening value suggests the possibility of hypoglycemia, the diagnosis should be confirmed with a standard laboratory determination.

Infants at Risk for Neonatal Hypoglycemia

The following are the conditions that put an infant at risk for hypoglycemia:

- Infants of diabetic mothers
- Intrauterine growth restriction
- Perinatal asphyxia
- Extreme prematurity
- Beckwith–Wiedemann Syndrome
- Severe Rh erythroblastosis
- Inborn error of metabolism
- Glycogen storage disease

Infants of diabetic mothers are at risk because of fetal hyperinsulinemia resulting from exposure to episodic

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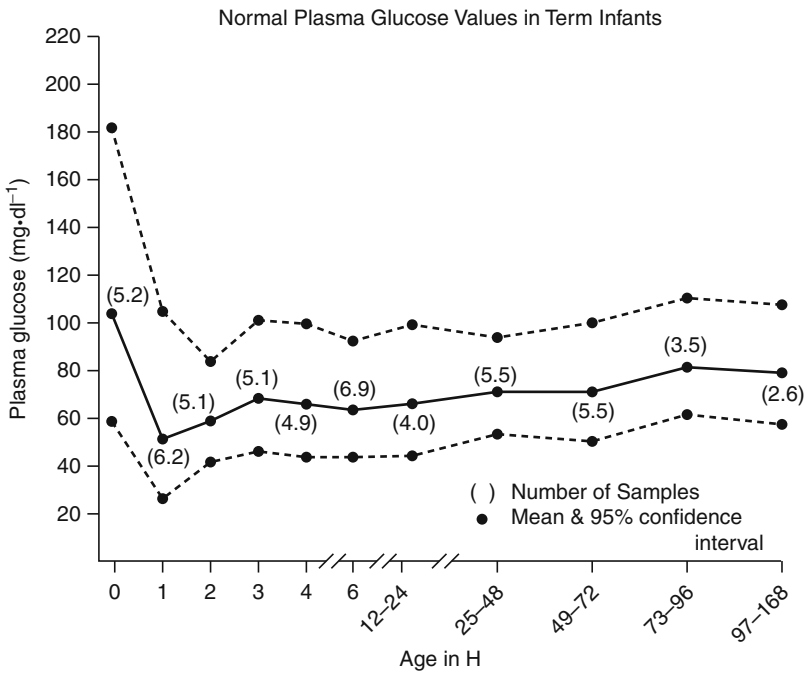
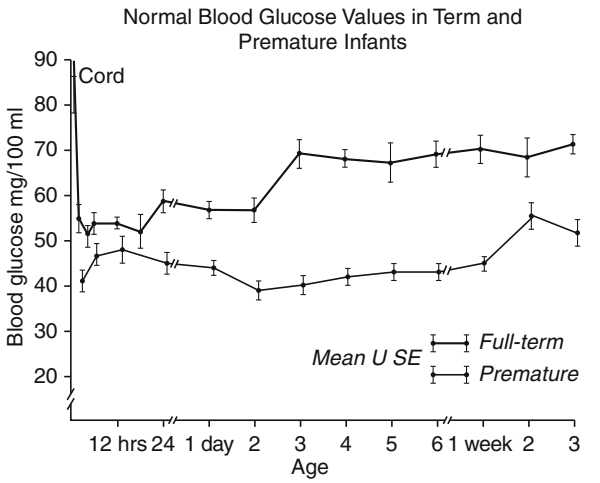


Srinivasan, G. et al J Pediatr. 109:114.1986

Figure 29.1

Normal plasma glucose values in term infants (From Srinivasan G, Pildes RS, Cattamanchi G, et al (1986) Plasma glucose values in normal neonates: a new look. J Pediatr 109:114–117)



From Cornblath, M and Reisner, SH: New Engl J Med 273:378, 1965

Figure 29.2

Normal blood glucose values in term and premature infants (From Cornblath M, Reisner SH (1965) Blood glucose in the neonate and its clinical significance. N Engl J Med 273:378–381)

maternal hyperglycemia in a poorly controlled diabetic state. The episodic fetal hyperglycemia stimulates the pancreatic islet cells and produces an increased amount of insulin. Hypoglycemia occurs during the first few hours of life when the placental glucose supply is terminated by birth due to the sustained effect of hyperinsulinemia. Intrauterine growth restriction (IUGR) is associated with increased incidence of neonatal hypoglycemia because of decreased glycogen reserve and impaired gluconeogenesis. The association is particularly common in IUGR due to placental insufficiency as in the cases of maternal preeclampsia and/or pregnancy-induced hypertension. Perinatal asphyxia is associated with increased risk of hypoglycemia because of increased metabolic demand when the infant is ill from ischemic hypoxia. Extreme prematurity is associated with decreased glycogen reserve since fetal glycogen storage occurs in late gestation. The prematurely born infants are deprived of the glycogen accretion leading to reduced glucose production during early neonatal life. Beckwith–Wiedemann syndrome, a relatively uncommon condition characterized by macrosomia, macroglossia, and umbilical hernia, is prone to hypoglycemia because of pancreatic beta cell hyperplasia and hyperinsulinemia.

Although rare nowadays because of successful prevention by administration of Rhogam (anti Rh antibodies), severe Rh erythroblastosis has been shown to have an increase incidence of hypoglycemia because of inhibitory effect of glutathione, a by-product of hemolysis.

Clinical Signs and Manifestations

During the first 24–48 h of life, the infant with hypoglycemia is often asymptomatic despite the fact that glucose is the main source of energy for brain metabolism. This is due to the fact that a newborn infant has an abundance of alternative substrate in the brain that can provide the energy for metabolism in the presence of low glucose supply. If the condition is undetected or untreated, the infant will eventually exhaust the alternative substrates and become symptomatic. This is the reason that hypoglycemia needs to be treated promptly despite the absence of clinical signs. The signs relate primarily to the central nervous system with jitteriness, tremor, apnea, bradycardia, and, in the worst scenario, seizure. Seizure is the worst sign because it signals severe brain cell dysfunction and has been shown to result in poor developmental outcomes at a later age.

Management

When diagnosis of hypoglycemia is established, the condition should be treated promptly even if the infant is asymptomatic. Intravenous glucose infusion at a rate of 4–5 mg/kg/min will approximate the fetal glucose intake and will maintain adequate glucose concentration and delivery to the brain. Concentrated glucose bolus infusion should be avoided in infants whose hypoglycemia is a result of hyperinsulinemia because such infusion may result in rebound hypoglycemia that may lead to persistent hypoglycemia.

Early enteral feeding is encouraged to promote early onset of gluconeogenesis. Feeding can be in the form of breast milk or infant formula. If infant is stable at the time of birth, breast feeding soon after birth in the delivery room is encouraged. This practice has been shown to improve glucose homeostasis and reduce the incidence of hypoglycemia.

Neonatal Hyperglycemia

Definition

Neonatal hyperglycemia occurs primarily in very and extremely low birth weight infants. The lack of normative data in this population makes it difficult to provide a blood glucose value for such definition. In the absence of a universally accepted definition, most clinicians consider blood glucose values of >125 mg/dL or plasma glucose >150 mg/dL as hyperglycemic.

Risk Factors and Mechanism

There are several risk factors for neonatal hyperglycemia: low gestational age, intrauterine growth restriction, excessive glucose and lipids intakes, sepsis, and use of glucocorticoids. It is well known that neonatal hyperglycemia is very common among extremely low birth weight infants. There is good evidence that insulin resistance in the peripheral tissues is the main reason for elevation of blood glucose values. Moreover, these infants often received a large amount of parenteral glucose and lipids in an attempt to meet their nutritional requirements. The combination of large substrate intakes and diminished ability to utilize the glucose because of insulin resistance results in the elevation of blood glucose. *Figure 29.3* shows the direct relationship between glucose infusion load and plasma glucose levels for infants at two birth weight groups. The smaller infants (birth weight 500 g) have a higher plasma glucose value at a similar glucose load than infants with higher birth weight (900 g). The data illustrate the interaction between maturity and glucose load, which is an important concept in understanding the inverse relationship in gestation and degree of insulin resistance and the effect of large glucose load in considering the strategy of management. The increased risk of IUGR infants for hyperglycemia has been well documented. However, the mechanism for such association is poorly understood. Sepsis is a risk factor primarily because of stress produced by such conditions. Similarly, the administration of glucocorticoid for clinical indication (such as blood pressure support or bronchopulmonary dysplasia) results in enhanced glucose production and elevation of blood glucose value if utilization is impaired by insulin resistance.

Clinical Manifestations and Complications

Hyperglycemia per se does not usually produce any symptom. However, when the degree of hyperglycemia is severe (e.g., >300 mg/dL of blood or plasma glucose levels), osmotic diuresis occurs because the blood/plasma glucose levels exceed the renal glucose threshold. Marked water loss and potential development of dehydration often occur

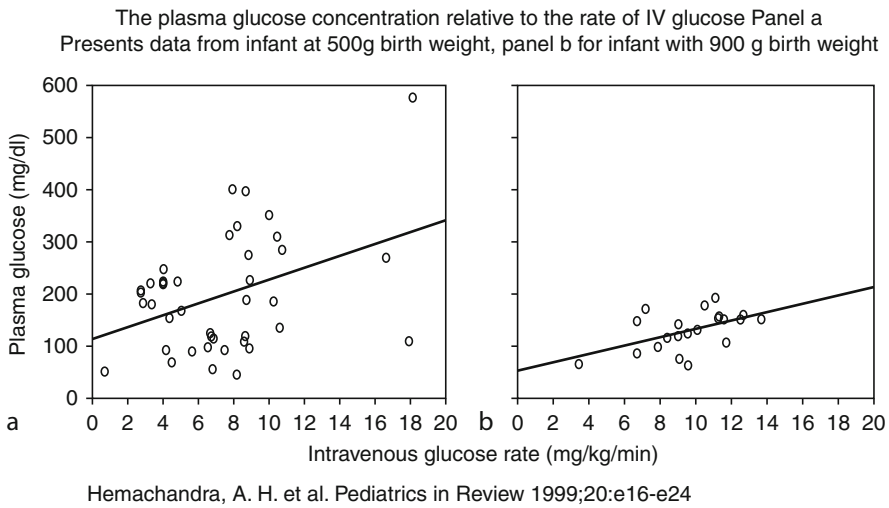


Figure 29.3

The plasma glucose concentration relative to the rate of IV glucose. Panel a presents data from infant at 500 g birth weight, Panel b for infant with 900 g birth weight (From Hemachandra AH et al (1999) Pediatr Rev 20:e16–e24)

if fluid balance is not maintained. A very high plasma osmotic level can also result in water shift in the brain increasing the risk of CNS injury including intracranial hemorrhage. Thus, it is important that the condition is treated to avoid these complications.

Management

The first step in the management of infant with hyperglycemia is to consider the cause. If the condition is due to administration of medication such as glucocorticoid, consideration should be made to discontinue the treatment, balancing the risk of such approach against the harm of not continuing the medication. Because the adverse effect of glucocorticoids is dose related, lowering the dose may reduce the hyperglycemia. If the infant has signs of sepsis, use of appropriate antibiotics to treat the sepsis will usually result in amelioration of hyperglycemia. If immaturity and large doses of glucose and lipids are the causes of hyperglycemia, the glucose and intravenous lipid doses should be reduced to meet the minimum nutritional requirement. The usual approach is to reduce the glucose infusion rate at 1 mg/kg/min and intravenous lipid at 1 g/kg/24 h while monitoring the blood glucose at the point of care. The approach should be balanced with the maintenance of adequate nutrient intakes providing at least 60 kCal/kg/day to maintain a protein sparing state and minimal metabolic requirement.

If the above procedures do not result in abatement of hyperglycemia, continuous low-dose insulin infusion will often produce the desirable outcomes. The usual dose of insulin is 0.02–0.05 U/kg/h. Since the response may be rapid with potential development of hypoglycemia, point of care monitoring of blood glucose at 4–6 h interval is essential.

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30 Infant of Diabetic Mother

William Oh

Basic science and clinical research during the past several decades have significantly enhanced our understanding of the various perinatal morbidities and childhood problems relating to infants of diabetic mother (IDM). These morbidities include congenital anomalies, hypoglycemia, respiratory distress syndrome, macrosomia, fetal distress, neonatal depression and asphyxia, polycythemia/hyperviscosity, hyperbilirubinemia, shoulder dystocia, birth injury, hypocalcemia, childhood obesity, and metabolic syndrome. With the exception of congenital anomalies, the etiology of which is still unknown, the pathophysiology of these morbidities are accounted for by various events that stem from poor maternal diabetic control. The pathophysiologic basis of these morbidities are for the most part evidence based (*Fig. 30.1*) and discussed below.

When the maternal diabetes is poorly controlled, episodic hyperglycemia occurs. Since there is a constant gradient (maternal blood glucose level is 10% higher than the fetal), episodic fetal hyperglycemia ensues, which results in fetal hyperinsulinemia. The latter accounts for the higher risk of neonatal hypoglycemia and respiratory distress syndrome (RDS). In vitro studies have shown that insulin is a potent inhibitor of surfactant synthesis in fetal pulmonary type II cell explaining the increase risk of RDS in IDM. Enhanced fetal growth is a result of abundance of substrate and hyperinsulinemia since insulin is a significant fetal growth factor. Enhanced fetal growth will in some cases result in fetal macrosomia, which increases the risk of shoulder dystocia and birth injury. There is also good evidence that macrosomia is associated with increased risk of childhood obesity and metabolic syndrome. Increased fetal growth will require an increase fetal metabolic demand. If placental oxygen transfer does not meet the increased demand, a relative fetal hypoxemia ensues leading to fetal hypoxia/distress and neonatal depression/asphyxia. Fetal hypoxia will stimulate the synthesis of erythropoietin, which is a hormone that promotes erythropoiesis. This accounts for the increased risk of neonatal polycythemia and hyperviscosity as well as hyperbilirubinemia. It is apparent that if maternal diabetes is well controlled, these morbidities would likely not occur. Unfortunately, there are multiple reasons why we still see these problems in the clinical setting, including lack of adequate prenatal care and lack of patient compliance. In some cases, the severity of the diabetes is so high that it defies optimal control during gestation.

Congenital Malformation

Infants of a diabetic mother have significantly higher incidence of congenital malformation than normal newborn population. The incidence is estimated to be between 5% and 10% for major malformations in contrast to the usual 1–2% among normal newborn population. The prevalence rate appears to be related to types, severity, and level of control of diabetes particularly with reference to hyperglycemia. The incidence is higher among infants of type I diabetes than those born to mothers with gestational diabetes, probably because the onset of insulin-resistant glucose intolerance occurs around 24–28 weeks of gestation which is well past the period of embryogenesis (first 12 weeks of gestation). The anomalies usually affect cardiovascular and gastrointestinal systems, although other organ systems are not spared. The more common anomalies are listed in *Table 30.1*.

The pathogenesis of congenital malformations in IDM is not known. However, based on indirect evidence that tight control of blood glucose level during preconception and early embryogenesis periods results in marked reduction in its incidence, it is likely that hyperglycemia may well be the main culprit for the malformations.

Neonatal Hypoglycemia

Neonatal hypoglycemia is the most common metabolic disorder in the newborn and IDMs are at higher risk. Because glucose is transported from the mother to the fetus by facilitated diffusion, episodic maternal hyperglycemia (reflected by high hemoglobin A_1C) in poorly controlled diabetic state will result in episodic fetal hyperglycemia. The latter will stimulate the beta cells of the fetal pancreatic islet cell with release of insulin resulting in fetal hyperinsulinemia.

When the infant is delivered and the maternal placental supply of glucose is interrupted, the fetal

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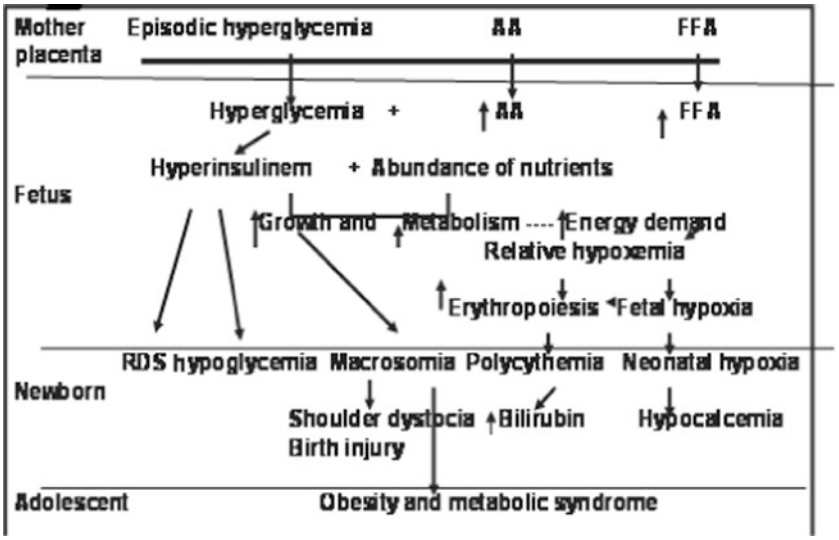

Figure 30.1
Pathophysiology of perinatal and childhood morbidity in IDM

Table 30.1
Common congenital malformations in infant of diabetic mother

Organ system	Anomaly
CNS	Caudal regression syndrome
	Neural tube defect
	Microcephaly
Cardiac	Ventricular septal defect
	Atrial septal defect
	Coartation of the aorta
	Transposition of the great vessels
Gastrointestinal	Duodenal atresia
	Micro colon (descending colon)
	Anorectal atresia
Renal	Renal agenesis
	Multicystic kidney
	Hydronephrosis
	Ureteral anomalies

hyperinsulinemia will precipitate a rapid fall in blood glucose during the first hours of life. In contrast to the full-term newborn of the nondiabetic mothers, the fall in blood glucose value and duration of low blood glucose are exaggerated in IDM because of the hyperinsulinemic state which may last beyond the first few hours of life. The latter suppresses endogenous production of glucose by gluconeogenesis and glycogenolysis accounting for a delay in recovery of blood glucose value during the immediate postnatal period. It is a common practice that bedside or point of care determination of blood glucose values are done using reflectance meter because of ease in performing the measure and immediate availability of results. The screening is generally done every 30–60 min during the first 2 h to evaluate the trend and the rate of fall in blood glucose. When the level is in the hypoglycemic range, the infant is managed accordingly. Since reflectance meter for screening is not precise, it is advisable to obtain a blood glucose measurement by regular laboratory technique to confirm the diagnosis. If the blood glucose screening showed a normal range during the first 2–3 h, or if treatment results in normal values, the frequency of screening can be extended to every 3–6 h during the first 24 h and every 12 h in the second and third day of life.

There is considerable controversy on the biochemical definition of hypoglycemia and current number used by clinicians is arbitrary. Most clinicians consider values <30 mg/dL for term and 20 mg/dL for preterm infants as diagnostic of this condition. When the blood glucose reached normal levels (generally considered as 50 mg/dL or higher), hypoglycemia is considered resolved.

Newborn infant's brain uses glucose as the main substrate for metabolism. However, there is evidence that the developing brain is capable of using alternative substrates for metabolism. This may explain why most infants with hypoglycemia in the first hours of life are asymptomatic. If the hypoglycemia is not corrected, the infant may

eventually become symptomatic when alternative substrate is exhausted. Thus, it is important that the hypoglycemia be treated even in the absence of clinical manifestations. The signs are usually nonspecific and may include jitteriness, tremor, apnea, feeding intolerance, and seizures.

If the infant is stable and without respiratory distress, early enteral feeding (first 6 h of life) is recommended for IDM to minimize the risk of hypoglycemia. The initial feeding can be in the form of 10% glucose solution or formula. If the mother intends to breast-feed, breast-feeding should commence in the delivery room when the infant is stable. It has been shown that delivery room breast-feeding improves glucose homeostasis in gestational IDM with lower incidence of hypoglycemia than those who were not nursed. Intravenous glucose infusion should be initiated if the infant is hypoglycemic. Intravenous glucose infusion at a rate of 4–5 mg/kg/min in the form of 10% glucose at a dose of 60–70 mL/kg/day will often maintain euglycemia. Concentrated glucose bolus infusion should be avoided because it tends to provide a very high dose of glucose over a short period of time which may trigger an abrupt rise in serum insulin level followed by a rebound fall in blood glucose values. The rebound hypoglycemia may require further bolus infusion, which may result in persistent hypoglycemia that may require other forms of treatment, such as the use of glucocorticoid.

Respiratory Distress Syndrome

In 1974, Smith et al. showed that insulin inhibits the production of lecithin in rat type II cell fibroblasts. Robert et al. subsequently showed that at matched gestational age, the IDM has a higher incidence of RDS than their non-IDM counterparts (*Fig. 30.2*). Subsequent studies showed that the insulin inhibitory effects involved other classes of phospholipids in the surfactant specifically the phosphotidyl glycerol (PG) resulting in part from the delay in structural development of fetal lung type II cells. Another measure that has been proven useful in predicting fetal lung maturity is the TDx-FLM assay. This is a technique that measures total lamellar body counts in the amniotic fluid. The presence of more than 70 mg/dL is an assurance of lung maturity with none of cases with such number has respiratory distress syndrome. Close monitoring of fetal well-being by noninvasive means and maintaining the pregnancy to as close to term as possible is probably the best approach in avoiding the complication of neonatal disorders in this population. Although there are no data in the use of antenatal steroids to accelerate fetal lung maturation and surfactant synthesis for IDM who develops respiratory distress syndrome, it is probably safe to state that such usage is likely to be effective.

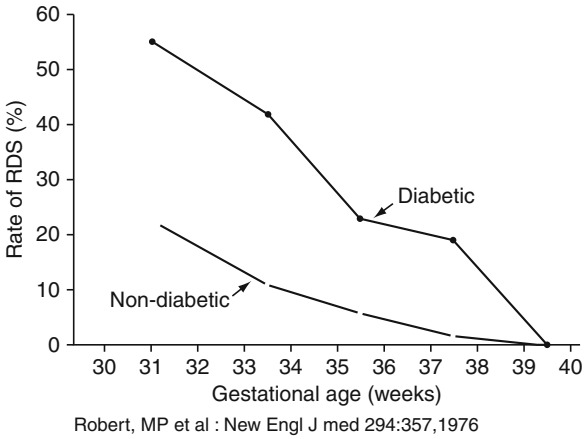

Figure 30.2
Incidence of respiratory distress syndrome in infants of diabetic mothers (From Robert MR, Neff RK, Hubbell, JF et al (1976) Association between maternal diabetes and the respiratory-distress syndrome in the newborn. N Engl J Med 294:357–360)

Macrosomia

Macrosomia or large for gestational age is defined as birth weight exceeding the 95th percentile of the intrauterine growth curve. A birth weight of >4.5 kg at term or close to term will likely fall under this category. The enhanced fetal growth in IDM is due to a combination of fetal hyperinsulinemia and the presence of abundance of substrate. The acceleration in fetal growth usually occurs at around 32–33 weeks of gestation reaching its peak at term. However, it should be noted that macrosomia is not all due to maternal diabetes; other factors can cause macrosomia, including maternal obesity without diabetes and constitutional statures of the parents.

The morbidity rate of macrosomia in IDM is similar to macrosomic infants without a history of maternal diabetes. Thus, surveillance for potential problems related to macrosomia should disregard the diabetic status of the mothers.

Prenatal diagnosis of macrosomia is feasible by fetal ultrasound conducted during the accelerated fetal growth phase at around 32–33 weeks of gestation. Such serial assessment is an important part of the management of diabetic pregnancy because early identification of

macromia will allow for serial assessment of fetal well-being. Macrosomia has been shown to increase the risk of fetal hypoxia and related neonatal morbidities including low 5-min Apgar score, seizure, hypoglycemia, polycythemia and, meconium aspiration syndrome. The reason for the association is that macrosomia is associated with increased metabolic rate that results in an increase in fetal oxygen consumption. If the placenta cannot accommodate this increased demand, relative fetal hypoxia can occur leading to fetal distress and all the subsequent adverse fetal and neonatal events.

Other perinatal complications related to macrosmia include shoulder dystocia resulting in difficult labor and delivery and often requires cesarean delivery, birth injury including fracture of clavicles, Erb's palsy, and paralysis of the diaphragm due to phrenic nerve injury. In an observational cohort study comparing the neonatal mortality rate of marosomic infants with reference to mode of delivery, Boulet et al. showed that the hazard ratio (demonstrating advantage of cesarean delivery) was 1.4, 1.3, and 0.8 for infants weighing 4.0–4.5 kg, 4.5–5.0 kg, and >5 kg, respectively, suggesting that cesarean delivery is most beneficial for extremely large infants (>5.0 kg) but debatable among infants weighing between 4.0 and 5.0 kg.

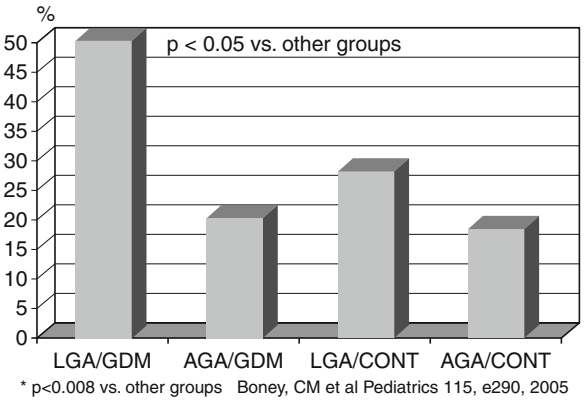

Figure 30.3
Prevalence of metabolic syndrome in macrosomic infant of gestational diabetes (From Boney CM, Verma A, Tucker R et al (2005) Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. Pediatrics 115:e290–e296)

Childhood Obesity and Metabolic Syndrome

There is evidence that macrosomic infants, particularly those born to mothers with gestational diabetes, are at increased risk of childhood obesity and metabolic syndrome. In a long-term follow-up program of 207 gestational diabetic mothers, Boney et al. showed that the macrosomic (LGA) infants of gestational diabetes have a 50% prevalence of metabolic syndrome during late childhood. The metabolic syndrome was defined as having two or more of the following conditions: obesity (BMI > 85th percentile), hypertension (systolic or diastolic BP > 95th percentile), high triglyceride (>95th percentile for age), and low HDL (<5th percentile for age). The LGA (macrosomic) infants of nondiabetic (control) mothers also have a higher prevalence of metabolic syndrome but not as high as the LGA infants of gestational diabetic mothers (*Fig. 30.3*). The data are consistent with those found in animal models in which the macrosomic pups of streptozotocin-induced diabetic pregnant rats remain macrosomic at later age with development of glucose intolerance. The data emphasize the importance of anticipatory guidance in regard to diet and exercise for children who were macrosomic infants born to gestational diabetic mothers, to minimize the risk of metabolic complications and obesity that may lead to cardiovascular and other metabolic syndrome-related diseases during adulthood.

Polycythemia and Hyperviscosity

Polycythemia is defined as venous hematocrit value exceeding 65%. The condition is of clinical significance because this level of hematocrit may result in hyperviscosity. The latter may cause circulatory sludging, which may in turn result in dysfunction of the organs supported by the circulation. Complete blood counts are often obtained by heel puncture providing hematocrit values of the capillary blood. In interpreting the hematocrit values in making the diagnosis of polycythemia, it is important to keep in mind that the capillary hematocrits are 10% higher than the simultaneously obtained venous hematocrits. If the capillary hematocrit is high (>65%) and polycythemia is suspected, a venous hematocrit should be obtained to confirm the diagnosis.

In IDM, polycythemia is a result of hypoxia-induced erythrocytosis. In fetal monkey model, Susa et al. showed that hyperinsulinemia induced by fetal implantation of an insulin pump resulted in marked increase in erythropoietin levels and histologic evidence of increased hepatic erythropoietic activities. In human IDM, Widness et al. provided evidence of increased erythropoiesis with higher cord serum erythropoietin levels than in non-IDM. Other

than a ruddy appearance, most infants with polycythemia are asymptomatic. When symptomatic, the signs are nonspecific and may involve various organ systems including CNS and gastrointestinal and respiratory systems. Tachypnea, feeding intolerance, and jitteriness are common signs. These signs are indistinguishable from such conditions as sepsis and metabolic problems such as hypoglycemia. Management is by performing a partial exchange transfusion in which the infant's blood is removed to achieve a normal hematocrit level. The formula used for calculation of blood to be removed and replaced with normal saline or equivalent is as follows:

Blood to be removed and replaced with saline = infant's current hematocrit (%) − desired hematorit (55%) × 80 (infant's estimated blood volume) × body weight ÷ infant's current hematocrit.

The indication of doing the partial exchange transfusion is somewhat controversial because of lack of evidence that such treatment will assure good outcome. The empiric approach is to perform the procedure if the infant is symptomatic and the hematocrit is greater than 70%. If the infant is asymptomatic, the indication of such procedure is less definite, unless the hematocrit is exceedingly high (e.g., 75% or higher).

Hyperbilirubinemia

In IDM, this condition is often associated with polycythemia. The reason is that excess red cell volume results in increased break down of red blood cells and bilirubin production. If the infant's bilirubin conjugating and elimination capacity are immature, bilirubin accumulation will occur leading to hyperbilirubinemia. The degree of bilirubin elevation is often modest and the infant will respond promptly to phototherapy. Exchange transfusion is rarely required.

Hypocalcemia

This is another common metabolic problem in newborn and the IDM is at higher risk than non-IDM. The reason for an increased risk is not entirely clear. One hypothesis is that in the presence of fetal or neonatal hypoxia, the calcitonin level may be elevated. The latter is a hormone that can act in opposite direction as parathyroid hormone accounting for the fall in serum calcium levels.

The diagnosis of hypocalcemia is based on serum calcium level of < 7 mg/dL in term and 6 mg/dL in preterm infants. It should be noted that data for this definition were derived from the studies conducted in the era when the very low or extremely low birth weight infants were not surviving and thus not included in the survey for normative values. Since serum calcium levels have been shown to directly correlate with gestational age, it is likely that lower cutoff level for serum calcium levels in very low and extremely low birth weight infants are lower than the 6 mg/dL. Clinical signs of hypocalcemia are nonspecific and similar to those listed for hypoglycemia. The most serious sign is seizure. Hypocalcemia can be treated readily with parenteral calcium administration given as constant infusion. The prognosis for this condition is good.

In summary, infants of diabetic mother are at risk for various fetal, neonatal, and childhood morbidity due to maternal episodic hyperglycemia and concomitant fetal hyperglycemia and hyperinsulinemia. It is apparent that good control of maternal diabetes will markedly reduce the risk of the infants' morbidities with benign neonatal course and at lower risk for late childhood obesity and metabolic syndrome.

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31 Neonatal Hematology

Eric Werner

Introduction

From fetal life to infancy, through childhood and adolescence, the cellular and plasma components of the blood undergo dramatic change. This is especially true in the first few months of life as the infant transitions from the protected, hypoxic intrauterine environment to extrauterine life. In this chapter, many aberrations of the blood in the neonatal period are briefly discussed. There are several textbooks that cover the topic of neonatal hematology to which the reader can refer for more in-depth discussion of these disorders.

Red Cell

The site of erythropoiesis migrates in the fetus from the yolk sac to the liver to the marrow. During this time, the predominant hemoglobin also changes from the early embryonic hemoglobins Gower 1 (ε_4 or $\zeta_2\varepsilon_2$) and Gower 2 ($\alpha_2\varepsilon_2$) to Hb Portland ($\zeta_2\gamma_2$). By the beginning of the second trimester, Hb F ($\alpha_2\gamma_2$) is the predominant Hb, while Hb A ($\alpha_2\beta_2$) synthesis begins in utero and increases in the third trimester. At birth, the median Hb F fraction for the term and preterm infant is 68% and 75% Hb F, respectively. By 6 months of age, these decrease to a median of 5% for the term and 9% for the preterm infant. The mean Hb of cord blood is 16.5 g/dL, higher than at any other time in life, but quickly decreases to 11.2 g/dL by 2 months of age. From that point on, the hemoglobin increases to a mean value of ~12.6 g/dL at 6–12 months. The reference range for Hb concentration for the term and preterm infant are shown in ❯ *Table 31.1*.

Anemia, usually defined as a hemoglobin or hematocrit level more than two standard deviations below the mean for age, can be due to blood loss, accelerated red blood cell destruction (hemolysis), or decreased erythrocyte production. Hemolysis typically presents with an elevated reticulocyte count and may have elevated indirect bilirubin, aminoaspartate transferase, and lactate dehydrogenase levels. Serum haptoglobin levels are generally low but are unhelpful in the neonatal period. Hypoplastic anemias usually have a low reticulocyte count. Occasionally, hemolytic disorders will present with a low reticulocyte count due to bone marrow suppression as occurs with parvovirus B19-induced aplastic crises.

Site and Timing of Collection

The hematocrit value is usually higher from capillary blood specimens such as those obtained by heelstick as compared with venous specimens in the first several weeks of life. Hematocrit values increase with delayed clamping of the umbilical cord at birth. There is also a slight increase in hematocrit in the first few hours of age, but by 24 h of age, the values are similar to cord blood levels.

Red blood cell production dramatically decreases at the end of the first week of life. Over the first few months of age, as the neonate adapts to the extrauterine environment, the hemoglobin decreases with a trough level of approximately 11 g/dL at 2 months of age. This is commonly called the physiologic anemia of infancy. As discussed below, this effect is more exaggerated in the preterm infant, where symptomatic anemia can result.

Neonatal Anemia

Blood Loss

Placental Blood Loss

Blood loss from the fetal side of the placental circulation can occur leading to anemia in the newborn. The most common causes are placental bleeding as occurs in placenta previa, placental abruption or rupture of the umbilical cord, feto-maternal bleeding, and twin–twin transfusion syndrome.

While the majority of the blood loss with placental bleeding is maternal, the risk of neonatal anemia increases with the severity of the maternal bleeding. The Apt test can be used to test vaginal blood for fetal hemoglobin. Umbilical cord rupture may occur with traumatic delivery or the presence of placental/cord anomalies such as a velamentous cord insertion. Surgical laceration of the

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_31,

Table 31.1
Red cell values in the first year of life (Adapted from Simpkin PS, Hinchliffe RF (2006) Reference values. In: Arceci RJ, Hann IM, Smith OP (eds) Pediatric hematology. Blackwell, Malden, pp 792–810)

Value	0.5 month	1 month	2 months	4 months	6 months	9 months	12 months
Hemoglobin (g/dL)	16.6	13.9	11.2	12.2	12.6	12.7	12.7
−2SD	13.4	107	9.4	10.3	11.1	11.4	11.3
Hematocrit (%)	53	44	35	38	36	36	37
−2SD	41	33	28	32	31	32	33
MCV (fL.)	105	101	95	87	76	78	78
−2SD	88	91	84	76	68	70	71
MCH (pg.)	33.6	32.5	30.4	28.6	26.8	27.3	26.8
−2SD	30	29	27	25	24	25	24

placenta may occur with C-section or rarely with traumatic amniocentesis or cordocentesis.

Feto-maternal Blood Loss

While a small amount of fetal blood crosses into the maternal circulation with most deliveries, in 0.1–0.3% of pregnancies, this volume can exceed 20–30 mL and can lead to significant or even fatal neonatal blood loss. On occasion, chronic feto-maternal bleeding can lead to hydrops fetalis. The diagnosis of feto-maternal hemorrhage is made by examining maternal blood for fetal erythrocytes using the Kleihauer-Betke stain or flow cytometry. Disorders where there is a high percentage of Hb F in maternal erythrocytes such as hereditary persistence of fetal hemoglobin can lead to false positive results.

The infant who has suffered acute hemorrhage can present with signs of hypovolemia such as hypotension, pallor, and tachycardia. The hemoglobin measurement obtained at birth may not accurately demonstrate the amount of blood loss as equilibration has not yet occurred. In addition, capillary hemoglobin values are especially higher than those obtained centrally in the acidotic newborn. Treatment usually begins with volume expanders and red cell transfusion may be indicated.

Twin–Twin Transfusion

Twin–twin transfusion syndrome (TTTS) occurs when there is unbalanced blood flow between diamniotic, monochorionic, monozygotic twins via placental vascular anastomoses. The donor twin becomes hypovolemic with oliguria, while the recipient twin has polyhydramnios. The older criteria of a >5 g/dL difference in neonatal Hb concentration and a >20% difference in birth weight are no longer used. Fetal diagnosis currently is based on sonographic criteria. Obstetric management may include serial amnioreduction or laser ablation of the anastomoses. There may be multiple complications for survivors of TTTS, including cardiac hypertrophy, hyperviscosity, and vascular occlusion in the recipient, and renal failure, severe anemia, neutropenia, and cutaneous erythropoiesis in the donor twin.

Hypoplastic Anemia

Anemia of Prematurity

Physiologic Anemia of Infancy

Adaptations to intrauterine life include the increased oxygen affinity of fetal hemoglobin due to the decreased sensitivity of Hb F to the ability for 2–3 DPG to modulate the oxygen sensitivity and the relatively high hemoglobin of the fetus. After delivery and exposure to extrauterine oxygen content, red cell production in the neonate decreases for several weeks, demonstrated by a low reticulocyte count at the end of the first week of life and a gradual decrease in Hb concentration from a mean of 16.6 g/dL at birth to 11.2 g/dL at 8–9 weeks of age. As Hb A becomes the predominant Hb, red cell production again increases gradually, and the Hb increases to a mean of ∼12.6 g/dL at 6–12 months of age. This expected decline in red cell production during the first 3 months of age is referred to as physiologic anemia of infancy.

Several factors make this phenomenon more pronounced in the premature infant. The premature infant has a smaller red blood cell mass at birth, often requires iatrogenic blood loss for monitoring in the hospital, and there is a relative insensitivity of the erythropoietin response. Hb concentrations can fall below 8 g/dL and cause clinical symptoms including poor growth in these infants. Erythropoietin treatment has generally not been shown to be effective in the prevention of this anemia of prematurity.

Nutritional

Iron

While iron deficiency remains the most common form of anemia in children worldwide, it is rarely seen in the newborn because the fetus is particularly good at extracting iron from the mother. Iron deficiency at birth is usually caused by chronic fetal blood loss.

The peak age for iron deficiency begins in late infancy with some evidence that the risk for severe iron deficiency is highest in the second year of life after the use of iron fortified formulas is discontinued. Other risk factors in this age group include prematurity, blood loss, use of non-iron fortified formulas, and lead intoxication. Exclusively human-milk-fed infants usually receive adequate iron intake in the first 6 months of age, but then may become iron deficient if additional sources of iron are not supplied.

Clinical manifestations: Typically, iron deficiency or iron deficiency anemia is discovered by screening studies. More severe cases may present with pallor, decreased activity, and tachycardia. Often, a sallow appearance is appreciated. Pica is often described in children who are mobile. In the developing child, there is concern that iron deficiency can lead to permanent neurodevelopmental effects.

Diagnosis: There are a number of laboratory tests which can indicate the presence of iron deficiency, including the hemoglobin concentration, red cell distribution of width (RDW), iron saturation ratio (serum iron/total iron binding capacity), serum ferritin, serum transferrin receptor level, and reticulocyte hemoglobin content. None of these tests in and of themselves are pathognomonic for iron deficiency as false positives and false negatives may occur. Thrombocytosis is common in iron deficiency anemia, while thrombocytopenia may be seen especially with severe cases. Iron deficiency can be present in the absence of anemia. Most recommendations for replenishing iron stores apply to either the presence of iron deficiency or iron deficiency anemia.

Treatment: The best approach is prevention. Formula-fed infants should receive iron-supplemented formulas, and iron supplementation should begin in infants fed human milk by 6 months of age, earlier for high-risk infants such as premature infants. Screening for iron deficiency is now recommended at the end of the first year of life and again at 18 months of age. For children with iron deficiency or iron deficiency anemia with intact intestinal systems, oral treatment with iron preparations containing the ferrous form of iron is appropriate. The usual dose is 3–6 mg/kg/day of elemental iron/day. Failure to respond to oral iron therapy may be due to noncompliance, the presence of *Helicobacter pylori* infection, ongoing blood loss, or inability to absorb iron. Parenteral iron sucrose infusions have been used in children with a high degree of safety.

Folate and Cobalamin

Folate is found in both animal products and leafy vegetables, but can be destroyed with heat. The addition of mandated folate supplementation of cereal-grain products in the USA and Canada has increased the American daily folate to over 400 μg/day.

Cobalamin is found in only animal products. Cobalamin has a slow turnover, so deficiency tends to take months to develop upon removal of cobalamin from the diet. The adequate vitamin B12 intake for infants <6 months of age is 0.4 μg/day and for those 6–12 months of age is 0.6 μg/day.

Folate deficiency is common in undeveloped countries but is relatively rarely seen in developed countries. It is very uncommon in the neonatal population. In addition to poor diet, a number of disorders can lead to folate deficiency. Goat's milk has very low folate content and infants fed with goat's milk are prone to deficiency. Intestinal disorders such as celiac disease, tropical sprue, and jejunal resection are causes. Disorders with increased cell turnover such as hemolytic anemias can lead to an increased folate requirement. Anticonvulsants and other medications may cause folate deficiency.

Cobalamin deficiency in infants is rare and usually due to these infants receiving exclusive human milk nutrition from cobalamin-deficient mothers as a result of a vegan diet, gastric bypass, pernicious anemia, or other disorders. As it takes many months to deplete cobalamin stores, deficiency is rarely recognized in infants who are born with adequate amounts of this vitamin. Cobalamin

deficiency can be caused by short-gut syndrome or removal of the distal ileum as can occur as a complication of necrotizing enterocolitis. Long-term use of antacids or H2 blockers has also been associated with cobalamin deficiency. Two rare congenital disorders, intrinsic factor deficiency and Imerslund–Gräsbeck syndrome, a defect in the ability of enterocytes to absorb the cobalamin-intrinsic factor complex, can lead to severe cobalamin deficiency early in childhood.

In addition to inadequate folate or cobalamin levels due to dietary or absorptive problems, there are several metabolic derangements in folate and cobalamin metabolism that can have profound neurodevelopmental effects. Not all of these cause anemia and some may be found newborn screening.

Hematologically, patients with cobalamin or folate deficiency may present with the typical signs of anemia such as pallor and fatigue. Ineffective erythropoiesis may lead to an elevated bilirubin and mild clinical jaundice. Neutrophil function defects have been described in cobalamin deficiency.

Neuropathy is seen in children with severe cobalamin deficiency as well as defects in cobalamin metabolism. Folate treatment may mask some of the features of cobalamin deficiency but will not treat the neurologic manifestations. Hence, proper diagnosis is necessary to prevent permanent neurologic damage.

Diagnosis: The classic hematologic feature of folate or cobalamin deficiency is anemia with an elevated mean cell volume (MCV). This may be accompanied by neutropenia and/or thrombocytopenia. The peripheral blood film can show macrocytes, misshapen red blood cells, and often hypersegmented neutrophils defined as >5% of neutrophils with five clearly distinct lobes or the presence of any neutrophils with six clear lobes. When performed, bone marrow findings include dyserythropoiesis, giant bands, and metamyelocytes. There is also a relative decrease in the late hematopoietic precursors due to ineffective hematopoeisis. As previously noted, serum bilirubin and lactate dehydrogenase can be elevated.

Diagnosis of folate deficiency is usually confirmed by demonstrating low levels of either serum or red blood cell folate levels. Cobalamin levels are useful, but there is often overlap between clinical deficiency and the documented reference range due to the effect of holotranscobalamin I, which is metabolically inactive. In such instances, levels of methylmalonic acid and homocysteine, which are elevated in cobalamin deficiency, can be helpful. In addition, these may be increased and lead to a diagnosis in the rare disorders of cobalamin metabolism. Reference ranges for neonates have been published.

Treatment of folate deficiency is initiated by giving large doses of folic acid for 4 months. Continued folate supplementation is continued if the underlying condition causing folate deficiency cannot be reversed. Annual check of serum cobalamin levels is advisable to avoid masking of unsuspected cobalamin deficiency. Prophylactic folic acid is often given to children with severe hemolytic anemias, e.g., sickle cell anemia, thalassemia major or intermedia, and severe autoimmune hemolytic anemia. When they are old enough to practically receive the medication.

Cobalamin deficiency treatment is usually initiated with a series of intramuscular or subcutaneous injections of hydroxocobalamin, at least until it is clear that the absorptive mechanisms are intact. Prophylactic cobalamin therapy is given to patients with an ileal resection or total gastrectomy. The management of children with metabolic derangements of folate or cobalamin is beyond the scope of this chapter. Where possible such children should be referred to centers with the requisite expertise.

Vitamin E Deficiency

Vitamin E is a natural antioxidant with an important protective effect from lipid peroxidation of the erythrocyte membrane. Unsupplemented premature infants are at risk for vitamin E deficiency in the first few months of age. The anemia of vitamin E deficiency is hemolytic and disappears rapidly with treatment. Most at-risk infants currently receive supplementation of this vitamin in the nursery.

Other Nutrient Deficiencies

Deficiencies of other vitamins, minerals, and nutrients may also result in anemia. The clinician should consider in these instances whether multiple deficiencies coexist. Riboflavin and pyridoxine deficiency can cause anemia.

Copper deficiency can cause anemia and neutropenia and may be due to decreased intake, especially in infants and children on total parenteral nutrition.

Bone Marrow Infiltration

Malignant disorders that involve the bone marrow inhibit erythropoiesis leading to anemia. Two of the most common malignancies in infants, neuroblastoma, and leukemia can involve the marrow. Following diagnosis, usually confirmed by a bone marrow aspirate and/or biopsy,

the treatment includes management of the underlying malignancy. Often red blood cell transfusion will be a component of therapy. Irradiated and CMV safe blood products should be used in the setting of immunosuppressive therapy.

Inherited Bone Marrow Failure Syndromes

There are many inherited syndromes associated with bone marrow failure. Some, such as Fanconi Anemia cause pancytopenia, while others such as Diamond–Blackfan Anemia (DBA) are usually restricted to a single cell line. The reader is referred to reviews of this topic for detailed information, and this chapter will only briefly discuss Fanconi Anemia (FA) and DBA in this section, Thrombocytopenia with Absent Radii in the platelet section, and Severe Congenital Neutropenia in the white blood cell section.

Fanconi Anemia

The underlying defect in Fanconi Anemia (FA) is in the ability to repair breaks in double stranded DNA. Causative mutations have been identified in >13 genes. Over 2,000 cases of FA have been described in the medical literature and a registry of patients (http://www.rockefeller.edu/labheads/auerbach/clinresearch.php) has provided information regarding recognized patients. FA often presents with aplastic anemia in childhood but can be identified in adults, some of whom are asymptomatic. While the median age at diagnosis is 6.5 years, the disorder can be identified in neonates, especially those with consistent physical stigmata of the disorder. Physical abnormalities are present in approximately 60% of individuals reported in the literature, especially short stature, café-au-lait spots, and hyper- and hypopigmented areas. Abnormalities of the thumbs with or without radial ray anomalies are seen in 35% and 20–25% have microcephaly, micropthalmia, structural renal anomalies, or hypogonadism. In addition to aplastic anemia, there is a markedly elevated risk for malignancy, both hematologic and solid tumors.

Diagnosis: FA should be considered in anyone with aplastic anemia, especially a young person. The diagnosis is confirmed by an assay of chromosomal breakage using peripheral blood T cells exposed to a DNA cross-linking agent such as diexpoxybutane or mitomycin C. A few specialized laboratories perform this assay. Testing of asymptomatic family members should be entertained, especially when they are being considered as possible stem cell donors for transplantation.

Management: Comprehensive management for FA requires a multispecialty group of health care professionals to address the many physical, hematologic, and health maintenance needs for these children. Guidelines for management are available online at http://www.fanconi.org/index.php/publications/guidelines_for_diagnosis_and_management.

Diamond–Blackfan Anemia

Diamond–Blackfan Anemia (DBA) or congenital pure red cell anemia is a rare inherited disease caused by a defect in ribosome biosynthesis that causes the erythroid precursor to be prone to early apoptosis. Over 90% present in the first year of life. Congenital anomalies such as short stature, low birth weight, microcephaly, cardiac, genitourinary, and thumb abnormalities are common but not universal.

Hematologic findings usually demonstrate a macrocytic anemia with an elevated Hb F. These may overlap with the relatively high MCV and Hb F levels of the newborn in the first months of life. The diagnosis is usually made by bone marrow examination, which demonstrates normal cellularity with an absence of red blood cell precursors. In most patients, the red blood cell adenosine deaminase levels are elevated. Ribosomal gene mutations have been identified in approximately 50% of patients and can be used for diagnosis in asymptomatic family members. A registry for DBA patients is located at http://www.dbar.org/.

Management of infants and children with DBA is not fully defined and should be done, where possible, in a center with expertise in the disorder. The anemia often responds to corticosteroid treatment, and some patients who respond achieve complete remissions with the ability to discontinue the medication, although relapses can occur. Transfusion therapy is indicated for those who do not respond and possibly as an alternative to corticosteroids in infants, but long-term transfusion therapy causes iron overload. Individuals with DBA have a lifelong increased risk for malignancy.

Hemolytic Disorders of Infancy

Hemolysis, by definition, is a shortened red blood cell life span. The life span of the neonatal erythrocyte is about 80 days, slightly shorter than the 120 day survival seen later in childhood and in adults. It is even shorter in premature infant. Causes of hemolytic anemia include

disorders of the erythrocyte membrane, hemoglobin, enzyme pathways, and extra-erythrocytic disorders such as infection or antibody formation.

Immune

Maternal sensitization, from exposure to fetal blood passed transplacentally in a prior pregnancy or possibly other blood product exposure, can lead to alloantibody formation. During pregnancy, maternal IgG crosses transplacentally to the fetus and can attach to antigens on the fetal erythrocyte leading to hemolysis. In the past, the Rh antigen was the most common cause of severe hemolytic disease of the newborn, but in one of the great medical triumphs of the last century, this is now a quite uncommon disorder. ABO incompatibility occurs more commonly, but the severity of hemolysis is generally less than for Rh disease. There are several other antigens, referred to as minor group antigens such as c, C, e, E, Kell, and others, which can occasionally lead to significant hemolytic disease in the neonate. Of note, previously transfused women account for 50% of the mothers of infants with non-Rh antibody hemolytic disease of the newborn.

Severe fetal hemolytic disorders can present with hydrops fetalis identified by the obstetrician. Screening of maternal blood can identify the causative antibody and intrauterine transfusion may be necessary. The pediatric service should be consulted prenatally in cases of identified maternal sensitization. In the newborn, hemolysis often presents with early-onset hyperbilirubinemia. Cord blood is routinely screened for blood type and antibody on the neonatal erythrocyte via the direct antiglobulin test also called the direct Coomb's test. Due to the low density of many antigens on the neonatal erythrocyte, on occasion, it is necessary to use the indirect antiglobulin test that looks for unattached antibody in plasma to identify antibody.

Management includes treating the hyperbilirubinemia with phototherapy and, when indicated, exchange transfusion and treating the anemia with transfusion if necessary. In some cases, additional modalities such as intravenous gammaglobulin are indicated. Parents of children with neonatal alloimmune hemolysis should be counseled about the potential for future affected infants. Infants with Rh disease who receive intrauterine transfusion may have a prolonged effect and require red cell transfusion postnatally until the antibody levels decline.

T-Antigen Activation

The T antigen is a usually hidden galactosyl residue present on the erythrocyte membrane and exposed by cleavage of sialic acid residues by neuramidase during major bacterial infections, especially *Clostridium perfringens* and *Streptococcus pneumoniae*. Most adults have IgM antibodies against the T-antigen. Infected infants may develop severe hemolysis upon exposure to adult plasma. Neonates with necrotizing enterocolitis appear to be especially at risk for T-activation hemolysis. Its presence should be suspected when marked hemolysis is present after transfusion and often spherocytes are seen on the peripheral blood smear. It can be confirmed in the blood bank by the demonstration of agglutination in vitro when donor serum and patient red blood cells are mixed. If further transfusion is necessary, washed blood products to eliminate the antibody can be used.

Hemoglobinopathy and Thalassemia Syndromes in the Newborn

Hemoglobin molecules all consist of four globin chains connected to a heme moiety. The globin chains vary to create the different hemoglobin forms, while the heme moiety remains the same. Hb A contains 2 α and 2 β chains, while Hb F consists of 2 α and 2 γ chains. The common genetic hemoglobin abnormalities are either decreased production of normal hemoglobin molecules, known as thalassemia syndromes, or the production of abnormal hemoglobins that are called hemoglobinopathies. There are hundreds of identified hemoglobin abnormalities that affect the α, β, or γ chains. In the heterozygous state, most are asymptomatic and identified usually by newborn screening. However, in the homozygous or double heterozygous state, they may produce a wide variety of problems, including hemolysis, sickling, altered oxygen affinity, and methemoglobinemia. The interested reader is referred to multiple resources on this topic.

Thalassemia

The thalassemia syndromes are named for the affected hemoglobin chain, alpha, beta, gamma, or a combination of two or three (e.g., gamma-beta-delta). Thalassemias present with a hypochromic, microcytic anemia of variable severity as described below. In addition

to specific management, genetic counseling is appropriate with all of the identified thalassemia syndromes. There are four alpha chain genes located on the short arm of chromosome 16 and four gamma chain genes, two delta chain genes and two beta chain genes on chromosome 11.

Gamma-Beta-Delta Thalassemia

Rare, large deletions within the β globin gene cluster may affect the γ, β, and δ genes, leading to gamma-beta-delta thalassemia. In the newborn, this may present with a moderate, hypochromic, microcytic anemia that usually evolves into a phenotype consistent with β thalassemia trait with the exception that the Hb A_2 is not elevated. In the homozygous state, these gene deletions would be fatal.

Alpha Thalassemia

Most alpha gene abnormalities are gene deletions, and alpha thalassemia is very common worldwide, particularly in Africa, Asia, and the Mediterranean. The four alpha thalassemia syndromes are defined by the number of functioning genes. With each nonfunctional alpha gene, there is a greater imbalance in the ratio of beta or gamma to alpha chains within the erythrocyte. These excess beta or gamma chains form abnormal hemoglobins, Hb H (β_4) or Hb Barts (γ_4) which are unstable, precipitate out in the cytoplasm, to cause hemolysis. Many of these abnormal erythrocytes do not leave the bone marrow (ineffective erythropoiesis). There are four alpha thalassemia syndromes and other multiply heterozygous conditions that may present similarly such as Hb Constant Spring described below.

Silent Carrier (–α/αα). When one alpha gene is defective, there are minimal or no hematologic consequences. In the neonate, small amounts of Hb Barts may be identified.

Alpha Thalassemia Trait. (−α/−α) or (–/αα). With two defective alpha genes, there is usually a mild anemia. In the neonate, this also usually presents with 3–10% Hb Barts and an MCV <100 fL. In older children, anemia is generally quite mild with a low MCV. Of note, the genotype of individuals with alpha thalassemia trait can be with the deletions occurring in the cis position, i.e., on the same chromosome (–/αα) or in the trans position on the opposite chromosome (−α/−α). While phenotypically these appear identical, genetically there are significant differences as only the cis abnormalities that are found commonly in the Southeastern Asian population will lead to the more severe alpha thalassemia syndromes described below. The trans deletions are common in the African-American population.

Hb H disease (–/−α). Loss of three alpha genes causes a moderately severe anemia with excessive Hb Barts in the neonatal period and Hb H after that. Splenomegaly may develop and hemolysis may be accentuated by infection or exposure to oxidative agents as described for G6PD deficiency. Intermittent transfusion may be indicated and occasionally splenectomy is indicated. Treatment includes folic acid supplementation and counseling of the parents regarding signs/symptoms of anemia.

Hydrops Fetalis (–/–) Deletion of all four alpha genes prevents the formation of both Hb A and Hb F and is generally not compatible with extrauterine life. Some fetuses can survive in utero perhaps due to the presence of the embryonic Hb Portland, but the infants are prone to multiple problems and pregnancy complications such as toxemia appear to be increased. Intrauterine transfusions may be helpful for fetuses diagnosed prenatally. Postnatally, chronic transfusion therapy and/or stem cell transplantation are possible for the surviving infants.

Hb Constant Spring. Hb CS is caused by a mutation that prevents the normal termination of the alpha chain leading to an elongated variant. While this is actually a hemoglobinopathy, Hb CS is produced at a very low rate and functionally produces a thalassemia phenotype. For unclear reasons, Hb CS only occurs in conjunction with a normal alpha gene on the same chromosome. Heterozygous Hb CS ($\alpha^{CS}\alpha/\alpha\alpha$) may be asymptomatic or have an alpha thalassemia trait phenotype. Homozygous Hb CS ($\alpha^{CS}\alpha/\alpha^{CS}\alpha$) or double heterozygous Hb CS/alpha thalassemia trait ($\alpha^{CS}\alpha/-$) would have more of a Hb H phenotype. Homozygous Hb CS typically has a mild anemia, splenomegaly, a normal MCV, marked basophilic stippling and continues to produce Hb Barts after infancy.

Beta Thalassemia

Unlike the alpha chain, there are only two beta genes. Hence, the two potential phenotypes are beta thalassemia minor (heterozygous) and beta thalassemia major (homozygous). In addition, beta thalassemia genes can lead to the production of no beta chains (β^0) or a variably decreased rate of beta chain production (β^+) with significantly different phenotypes. Of note, since beta chain

production does not become the predominant non-alpha chain until after the neonatal period, usually beta gene abnormalities are not symptomatic until that point. Major abnormalities may be identified on newborn hemoglobin screening, however. In addition, co-inheritance of a beta thalassemia gene with an abnormal hemoglobin gene on the other chromosome can lead to a symptomatic hemoglobin disorder.

Beta thalassemia minor. Affected children have a mild hypochromic, microcytic anemia, and no clinical symptoms. Often, these children are diagnosed with iron deficiency and repeatedly treated with therapeutic doses of iron. As iron absorption can be increased in these children, iron overload can result. Therefore, in addition to genetic counseling, affected children and their parents should be advised that iron therapy is only indicated if iron studies have demonstrated a deficiency. Diagnosis is usually made by exclusion of iron deficiency and documentation of an elevation in Hb A_2 ($\alpha_2\delta_2$). As Hb A_2 does not reach adult levels until toward the end of the first year of life, testing can be deferred until that point.

Beta thalassemia major (Cooley's Anemia). Homozygous β^0 thalassemia presents in infancy with marked anemia, signs of extramedullary hematopoiesis such as hepatomegaly and splenomegaly, and markedly abnormal erythrocytes on the peripheral smear with numerous normoblasts. In the past, this disorder was managed with lifelong transfusion therapy and the complications of iron overload were often fatal. Recently, the availability of iron chelation therapy and stem cell transplantation has dramatically improved the outcome for affected individuals. Homozygous β^+ thalassemia usually has a milder phenotype with moderately severe anemia and may not be transfusion dependent. Co-inheritance of Hb E (β 26 Glu $\rightarrow$ Lys), the second most common hemoglobinopathy, with β^0 thalassemia leads to a more severe phenotype that may be as severe as homozygous β^0 thalassemia.

Hemoglobinopathies

Because Hb A only accounts for a minority of the hemoglobin at birth, disorders of the β chain, such as sickle cell, rarely present clinical problems in the newborn but can be identified by newborn screening techniques. More recent techniques such as isoelectric focusing or HPLC have been very good at identifying abnormal hemoglobin molecules. It should be remembered that cellulose acetate hemoglobin electrophoresis (pH 8.6) does not separate Hb A from Hb F well making it hard to distinguish sickle trait from sickle cell disease. In the newborn, often citrate agar electrophoresis is used in addition to cellulose acetate to better separate these hemoglobins.

In the newborn, gamma chain disorders can cause significant hemolysis. However, because of their rapid disappearance, they are infrequently identified. For example, Hb F Poole is an unstable hemoglobin due to a mutation in the gamma gene. Alpha chain disorders can and do occasionally cause neonatal hemolytic anemia. For example, Hb Hasharon is an unstable hemoglobin due to a mutation in the alpha chain gene. Unstable hemoglobins precipitate within the erythrocyte causing hemolysis. They are usually identified by unstable hemoglobin preparations using techniques such as isopropyl alcohol or heat sensitivity that can identify these abnormal erythrocytes with subsequent hemoglobin identification in specialized laboratories. The number of laboratories with expertise in these techniques is small, and use of reference laboratories may be necessary.

Sickle Cell

Sickle hemoglobin (β 6 Glu $\rightarrow$ Val) is the most common hemoglobin variant with a worldwide distribution. As the heterozygous state is believed to offer protection from malaria, it is very common in central Africa, the Near East, Mediterranean, and parts of India. While numerous variants are described, in practice, the most common sickle syndromes are homozygous Hb SS and heterozygous Hb SC and Hb $SB^{thalassemia}$. Sickle trait (Hb AS) is generally asymptomatic, and other than parental counseling, no specific intervention is indicated in infancy. After the transition from Hb F to Hb A occurs in infancy, examination of the peripheral blood smear can demonstrate sickle cells in Hb SS and Hb $SB^{thalassemia}$. The smears from patients with Hb SC disease show large numbers of target cells with an occasional sickle form. Diagnosis can be proven by any of the hemoglobin analysis techniques currently available, including hemoglobin electrophoresis, isoelectric focusing, high-performance liquid chromatography, immunologic techniques, or DNA analysis. Hemoglobin solubility tests are of limited use as false negative tests occur, and they do not distinguish Hb AS from Hb SS or other clinically significant sickle cell syndromes. False normal tests are especially common in the presence of Hb F. Genetic counseling is indicated for parents of identified children and for the affected individuals themselves when they reach childbearing age.

Sickle cell disease syndromes develop over the first year of life. A discussion of the complications of the disorder and

their management is beyond the scope of this chapter, the reader is referred to some excellent discussions of the topic. Guidelines have also been developed and are available online (http://www.nhlbi.nih.gov/health/prof/blood/sickle/sc_mngt.pdf). Two complications, bacterial sepsis and splenic sequestration are especially problematic in infancy, and the parents should be counseled on the importance of immediate medical attention with fever, pallor, splenomegaly, pain, or ill appearance.

Membrane Defects

The red cell membrane consists of a lipid bilayer, an underlying protein cytoskeleton, and many integrated proteins that serve as transportation channels and other functions. Disorders of this red cell membrane, especially the cytoskeleton, cause morphologic changes to the erythrocyte that generally lead to decreased deformability and a decreased life span.

Spherocytosis

Hereditary spherocytosis is one of the more common membrane disorders with a frequency of 1 in 2,500–4,000 in Northern European populations. Inheritance is autosomal dominant in 67–75% of cases and recessive in the rest. Defects in the cytoskeleton proteins Band 3, α spectrin, β spectrin, ankyrin, and palladin have been identified as causing HS. The degree of hemolysis can vary quite widely, from minimal hemolysis indicated by a mild elevation in reticulocyte count to severe, transfusion-dependent anemia. Red cell destruction takes place in the relative hypoxic splenic environment. In most instances, splenectomy normalizes or nearly normalizes the red cell life span.

The diagnosis is often suspected by a positive family history. In the author's experience, sometimes the affected parent is unaware of their diagnosis but is aware that she/he had splenectomy in childhood. In addition to the usual features of hemolysis, the peripheral blood film demonstrates an increased number of small, dense spherocytes. The MCHC is usually elevated. A hemolytic anemia with the classic morphology in the presence of a history of the disorder in the parent can be sufficient for diagnosis, especially if immune hemolysis is excluded. The standard confirmatory diagnostic test is an osmotic fragility that demonstrates the increased sensitivity of the spherocyte to hypotonic conditions. In the neonate, controls must also come from newborns, so this may be harder to accomplish. Red cell membrane cytoskeleton protein analysis can be formed in some highly specialized laboratories.

Management: Most children with HS do well with minimal intervention. However, anemia may be more pronounced in the first few months of life, and red cell transfusion may be necessary in this time. Such infants should be followed relatively closely until the severity of their anemia becomes clear. Folate supplementation can be used to prevent deficiency, especially with severe hemolysis. Parents should be counseled regarding signs and symptoms of anemia as may occur with parvovirus B19 infection-induced aplastic crisis, where the transient decrease in erythropoiesis induced by this virus can cause a severe decrease in hemoglobin concentration due to the shortened red cell life span. Spleen size should be monitored and counseling to avoid splenic trauma is appropriate. Splenectomy may resolve the hemolysis, but the decision whether to proceed with this surgery needs to be individualized as there are significant short and long-term complications. Immunization, especially against encapsulated organisms, should be done. Unless absolutely necessary, splenectomy should be delayed until after 5 years of age to decrease the risk of fatal bacterial sepsis, especially due to *Streptococcus pneumoniae*.

Elliptocytosis

Abnormalities of several cytoskeletal protein abnormalities, including protein 4.1, α spectrin, β spectrin, Band 3, and glycophorin, give rise to the hereditary elliptocytosis (HE) phenotype. There is an increased prevalence noted in malarial areas of Africa and SE Asia. The inheritance of the common HE is usually autosomal dominant. Hemolysis is generally mild, with morphologic changes showing elongated red blood cells on the peripheral blood smear. For most patients with HE, treatment is unnecessary. As noted below, in the neonatal period and occasionally with infection, more severe hemolysis may occur transiently.

Hereditary Pyropoikilocytosis

HPP is a rare, recessively inherited hemolytic disorder with severe hemolysis and distinctive morphology. It is now recognized that HPP is a variant of HE, where often both parents have HE. Alternatively, one parent may be

a silent carrier for HE or carry another mutation that contributes to the phenotype.

Patients with HPP generally have a lifelong moderate hemolytic anemia. Splenomegaly may develop. The diagnosis can be made by review of the peripheral blood smear. Osmotic fragility may be increased. Red cell cytoskeleton protein analysis may be useful to confirm the diagnosis, and DNA mutation analysis may be used for prenatal diagnosis. Treatment is much the same as outlined for HS.

HE can present with more severe hemolysis in the neonatal period. This infantile pyropoikilocytosis may require transfusion or even exchange transfusion and red cell morphology identical to HPP. Over the first 3–12 months of life, the rate of hemolysis lessens and the red cell morphology transitions to that of HE. As it is not possible to distinguish infantile pyropoikilocytosis from HPP in the first few months of life, these infants should be observed closely.

Enzymopathy

The red blood cell utilizes glucose to produce ATP via the Embden–Myerhoff pathway and to a lesser degree to create NADPH, which is involved with the protection of the erythrocyte from oxidative damage. While disorders of the glycolytic pathway are well described, with the exception of glucose-6-phosphate dehydrogenase (G6PD) deficiency, which is the gateway into the hexosemonophosphate shunt, they are all quite rare.

Glucose-6-Phosphate Dehydrogenase Deficiency

The red blood cell is protected from oxidative damage by the glutathione system that requires NADPH to regenerate reduced glutathione. G6PD deficiency can lead to a defect in this pathway, allowing for hemolysis especially at times of infection or exposure to potential oxidants.

The gene for G6PD is located on the X-chromosome. Hundreds of variant enzymes have been described with varying degrees of clinical manifestations. Over 400 million people are affected worldwide. Hemizygous males with G6PD deficiency account for the majority of symptomatic individuals, but females can also be affected if they have homozygous or double heterozygous gene defects or via the Lyon hypothesis, where the normal gene is inactivated in an imbalanced manner. Over 400 variants of the G6PD enzyme have been described, and a classification system has been developed based on the severity of the deficiency. Class I, the most severe G6PD variants can cause a chronic hemolytic anemia and can affect leukocyte function. Class II variants, such as the common $G6PD^{Mediterranean}$, has $<10\%$ residual activity but typically presents with hemolysis, which while intermittent can be quite severe. Class III variants, such as the $G6PD^{A-}$, seen in 10–15% of the African-American population causes hemolysis upon exposure to infection or drugs. In this variant, the erythrocyte G6PD activity falls off more quickly than normal as the red cell ages.

Clinical manifestations of G6PD deficiency are typical for acute hemolysis, usually upon exposure to infection or oxidants. Broad or fava beans and naphthalene are common offending agents. Patients develop pallor, jaundice, and dark urine. The peripheral blood smear often shows "bite cells" and polychromasia. The diagnosis can be confirmed with a quantitative G6PD enzyme test, but this test can miss the diagnosis if there are a large number of reticulocytes, especially with the $G6PD^{A-}$ variant.

Neonatal hyperbilirubinemia, including severe hyperbilirubinemia, has been well described with G6PD deficiency and is more common with the $G6PD^{Mediterranean}$ than the $G6PD^{A-}$ variant, and may be caused by oxidant exposure in the nursery and/or maternal fava bean ingestion. Despite the hemolysis and hyperbilirubinemia, anemia is not always present.

Management begins with counseling the family on the signs/symptoms of anemia and medications and foods to avoid. The handling of a particular episode of hemolysis depends upon the severity of the anemia. Exposure to the offending agent should be removed if possible, bacterial infection treated, and transfusion may be indicated. If transfusion is given prior to testing, the quantitative G6PD assay should be deferred until the transfused red cells are gone – usually approximately 3 months. Hyperbilirubinemia should be managed as per established guidelines.

Other Hemolytic Diseases in the Neonate

Infantile Pyknocytosis

Infantile pyknocytosis is a rarely recognized hemolytic disorder identified in infancy. The pyknocyte morphologically appears as an irregularly contracted, dense cell with irregular projections. The etiology is unknown, but as transfused cells can acquire the pyknocytic morphology, it is presumably caused by an extra-erythrocytic factor.

Clinical features are similar to other hemolytic disorders: hyperbilirubinemia, pallor, and, occasionally, hepatomegaly and splenomegaly. The laboratory features are also typical of hemolytic disease, including an elevated reticulocyte count, elevated indirect bilirubin, and elevations in the aspartate aminotransferase and lactate dehydrogenase enzymes. Diagnosis is usually made by examination of the peripheral blood smear and exclusion of other disorders that can occasionally have a similar appearance such as G6PD deficiency, pyruvate kinase deficiency, vitamin E deficiency, and other Heinz body producing anemias. Infantile pyknocytosis is usually a transient disorder with resolution in the first few months of life, but other disorders that may have a similar appearance may be lifelong. Management involves treatment of hyperbilirubinemia as necessary and occasional red blood cell transfusion for severe anemia.

Microangiopathic Disorders

While thrombocytopenia and coagulopathy are the more often clinically relevant problems with microangiopathic disorders such as DIC, red cell destruction with prominent schistocytes on the peripheral blood film is common. Mechanical hemolysis can occur with congenital heart disease, ECMO, and cavernous hemangiomas. In addition to a schistocytic hemolytic anemia, hemoglobinuria is often present and may lead to the diagnosis. Management is dependent upon the severity of the anemia but should include the recognition that chronic mechanical hemolysis can lead to iron deficiency.

Infection

Congenital infections often can cause hemolysis. This includes intrauterine infections such as TORCH and enterovirus, as well as postnatal infections with cytomegalovirus.

Methemoglobinemia

Methemoglobin is formed when the iron in the heme moiety is oxidized from the usual ferrous (Fe^{2+}) to the ferric (Fe^{3+}) state. Methemoglobin is unable to carry oxygen and high levels interfere with oxygen delivery to the tissues. The erythrocyte enzyme NADH-methemoglobin reductase acts to keep methemoglobin levels below 1%, and another enzyme, NADPH-methemoglobin reductase, can function under certain conditions in this activity. Exposure to oxidizing agents such as nitrites, aniline dyes, nitrous oxide among others can trigger methemoglobinemia. Intrinsic factors such as the presence of M hemoglobins that are particularly susceptible to oxidation or deficiency of NADH-methemoglobin reductase increase the risk of the disorder and cause chronic methemoglobinemia.

There are several reasons that the neonate is particularly susceptible to methemoglobinemia. Hb F is more prone to oxidation, and neonatal levels of NADH-methemoglobin reductase are lower than adult levels. Sick neonates may be exposed to nitric oxide that is known to trigger methemoglobinemia.

The principal clinical manifestation of methemoglobinemia is cyanosis. A screening test is done with a drop of blood on filter paper waved in the air. With methemoglobin, the color of the blood does not change upon exposure to air as it should when cyanosis is due to deoxyhemoglobin. Cyanosis is apparent with methemoglobin levels about 10% (1.5 g/dL). Diagnosis can be confirmed via use of a co-oximeter. Symptoms caused by interference with oxygen delivery usually do not appear until the methemoglobin level is in excess of 30%. Asymptomatic individuals with chronic methemoglobinemia do not usually need treatment, especially if the level is $<30\%$. Treatment begins with removal from exposure to any offending agent. Methylene blue can reverse methemoglobinemia in individuals who do not have M hemoglobins but requires a functioning NADPH-methemoglobin reductase system, so it will not be effective in individuals with G6PD deficiency.

Thrombocytopenia

The reference range for platelet counts in the newborn is considered to be the same as for adults, 150,000–450,000/μL. While neonatal thrombocytopenia is defined as a platelet count $<150/000/\mu L$, platelet counts of 100,000–150,000/μL are more common in the newborn than in the adult and, do not necessarily indicate a disease state. Neonatal thrombocytopenia occurs in 22–35% of infants admitted to neonatal intensive care units with the higher frequencies occurring in the more premature infants.

While there are a large number of potential etiologies for neonatal thrombocytopenia, important clues can be determined from the perinatal history, the physical appearance of the infant, the timing, and the

severity of the thrombocytopenia. The more common causes of neonatal thrombocytopenia are shown in *Table 31.2*.

Table 31.2
Causes of neonatal thrombocytopenia

Feto-maternal unit
Pregnancy-induced hypertension
Maternal diabetes mellitus
Immune thrombocytopenia
Maternal autoimmune
Neonatal alloimmune
Infection
Neonatal sepsis
Intrauterine infection
Neonatal illness
Disseminated intravascular coagulation
Necrotizing enterocolitis
Thrombosis
Inherited thrombocytopenia syndromes
Thrombocytopenia with absent radii
Thrombocytopenia with radiosynostosis
Congenital amegakaryocytic thrombocytopenia
Macrothrombocytopenias
Bernard–Soulier syndrome
Grey platelet syndrome
Paris-Trousseau-Jacobsen syndrome
Montreal platelet/type 2b von Willebrand disease
MYH9-related Thrombocytopenia
May–Hegglin anomaly
Epstein syndrome
Fechtner syndrome
Sebastian syndrome
Other bone marrow failure syndromes
Fanconi anemia
Dyskeratosis congenita
Chromosomal anomalies
Trisomy 13
Trisomy 18
Trisomy 21
Others
Noonan syndrome
Bloom syndrome
Turner syndrome
Gaucher type 1

Infection

Neonatal sepsis needs to be considered in any infant with thrombocytopenia, whether this occurs in the first few days of life or later. Such infants usually appear quite ill with respiratory symptoms and/or hemodynamic instability.

Disorders of the Fetal-Maternal Unit

The most frequent cause is chronic fetal hypoxia as is seen in infants with intrauterine growth delay, maternal diabetes, or maternal hypertension. The platelet count is usually not severely depressed (e.g., >50,000/μL) and usually recovers to normal levels within 10 days. This thrombocytopenia appears to be due to decreased production and is often accompanied by neutropenia and increased numbers of nucleated red blood cells. Some causes of this problem include:

Maternal Hypertension

Maternal hypertension is one of the more common causes of thrombocytopenia in the neonate, especially in the neonatal intensive care unit. The platelet count in these children is usually just moderately reduced to 50,000–100,000/μL. As discussed in the below section, neutropenia may coexist in these infants. The mechanism of this thrombocytopenia appears to be decreased production. In most instances, the platelet count returns to normal within 7–10 days of birth.

Maternal Diabetes

Infants of mothers with gestational diabetes may have low platelet counts at birth. The platelet count may decrease over the first few days of life. As with maternal hypertension, the thrombocytopenia tends to be mild to moderate. The etiology is unclear as well but may be similar to that of maternal hypertension and other placental insufficiency syndromes. Thrombosis, especially renal vein thrombosis, has also been seen in these infants and should be considered strongly in any child born to a diabetic mother who has a flank mass or hematuria. In most instances, this thrombocytopenia is short lived and recovers within the first 2 weeks of age.

Maternal Medications

In the unusual case of a mother who receives chemotherapy during pregnancy, myelosuppression may affect the newborn. Infants of such mothers should have an initial CBC, and if thrombocytopenia is present, be monitored until it has recovered. Rarely, other medications administered to mothers may suppress platelet production. Maternal medications, such as aspirin, may decrease platelet function without affecting platelet count. When necessary, platelet transfusion may be given to manage bleeding complications or severe thrombocytopenia.

Intrauterine Infection

Several intrauterine infections including the TORCH (Toxoplamosis, Other, Rubella, Cytomegalovirus, and Herpes Simplex) infections, enterovirus, and HIV may result in neonatal thrombocytopenia. The mechanisms involved may differ between these infections but may include viral suppression of platelet production, splenic sequestration, maternal medications, antiplatelet antibody (as with maternal HIV infection), and consumptive coagulopathy as may occur with perinatal enterovirus infection. Cytomegalovirus infection when it occurs early in gestation may cause intrauterine growth restriction, multiple congenital anomalies, and extramedullary hematopoiesis, presenting as a blueberry muffin rash. In contrast, perinatal CMV infection may be less clinically obvious but can present with thrombocytopenia.

The management of infected children depends upon the underlying infection and is beyond the scope of this chapter. The reader should refer to sections on these specific infections.

Immune Thrombocytopenia

Immune thrombocytopenia usually presents with the well-appearing child with the exception of petechiae and/or purpura. A careful maternal history is very important to determine the cause in such infants.

Maternal Autoimmune Thrombocytopenia

Mothers with autoimmune thrombocytopenia generally have a low platelet count at the time of delivery, although on occasion the mother has undergone splenectomy for the disorder, and while she still has circulating antiplatelet antibody, she may no longer be thrombocytopenic. The incidence of thrombocytopenia in pregnancy is 7–8% and in addition to maternal ITP, can have a number of causes, including pregnancy-induced hypertension, DIC, HELLP, TTP/HUS, and medications, although the most common cause is gestational thrombocytopenia. The history of thrombocytopenia predating pregnancy, other autoimmune disorders such as systemic lupus erythematosis or earlier treatment for ITP can lead to the correct diagnosis for the neonate.

The IgG antiplatelet antibody can cross the placenta and affect the fetus. Fortunately, 85–90% of infants born to mothers with ITP have a platelet count $>50{,}000/\mu L$ and <1–5% have a platelet count $<20{,}000/\mu L$. No reliable predictors of severe fetal thrombocytopenia have been identified; however, the history of maternal splenectomy, severe thrombocytopenia, or a prior pregnancy with a severely affected newborn has been associated with lower platelet counts with this child. Prenatal or fetal scalp platelet counts are not generally recommended during the pregnancy; however, a cord blood platelet count should be obtained after delivery.

The platelet count can decrease from cord blood levels over the first few days of life. Few infants will need intervention other than monitoring of the platelet count over this period of time. Infants with severe thrombocytopenia or hemorrhage should be managed as described for neonatal alloimmune thrombocytopenia.

Neonatal Alloimmune Thrombocytopenia (NAIT)

With a mechanism analogous to Rh disease for red blood cells, a mother can be sensitized to platelet antigens that do not occur on her own platelets. Genetic polymorphisms in the major platelet surface glycoproteins account for the antigenic differences are defined serologically and given a designation as human platelet antigen (HPA) number. The most common antigens to cause NAIT are HPA (human platelet antigen) 1 and 5, except in women of Asian descent, where it is HPA-4. There is a recommendation to screen HPA 1, 3, and 5 (and HPA-4 in women of Asian descent) in cases of NAIT. In most cases, maternal serum, and if available, both parents' platelets are sent for analysis. It is important to utilize a laboratory with expertise in studying women for NAIT.

Despite the analogy with Rh disease, there are significant differences between NAIT and red cell

alloimmunization. These include the finding that the first pregnancy can be affected, pregnancies are not screened for NAIT (except in Norway or in the presence of a prior history), only a small percentage of women with platelet antigen mismatch become sensitized and when the disorder is diagnosed, treatment is often given to the mother prenatally. Obviously, the bleeding manifestations of NAIT, including intrauterine intracranial hemorrhage, are very different than the anemia and hyperbilirubinemia caused by Rh incompatibility.

NAIT usually presents with a platelet count $<50{,}000/\mu L$. While helpful if present, only a minority of cases have a history of a prior affected pregnancy. Hemorrhage may occur in utero, at delivery, or postpartum. Intracranial hemorrhage occurs in 11–21% of clinically recognized cases of NAIT and may be higher in infants whose mother had a prior severely affected pregnancy.

The management of pregnancies known to be at risk or affected should be done by obstetricians familiar with the disorder and is beyond the scope of this chapter. It is important to monitor the affected neonate's platelet count over the first few days as it often falls from cord blood levels. Treatment depends upon the presence of bleeding and the platelet count. An urgent head ultrasound should be obtained. Platelet transfusion has been recommended if the asymptomatic term infant's platelet count is $\leq 30{,}000/\mu L$, although some have recommended transfusion for platelets $\leq 50{,}000$ for all cases of NAIT, especially those with HPA-5b incompatability. A threshold of $50{,}000/\mu L$ may be appropriate in the presence of prematurity, birth asphyxia, or other factors predisposing to ICH, and $100{,}000/\mu L$ if ICH or other significant bleeding is present. Of note, recent studies have demonstrated that random donor platelet transfusions are often effective in infants with NAIT. IVIg, 1 g/kg daily for 1–2 days can be given if the initial platelet count is low, especially in the first day of life, or in conjunction with platelet transfusion. Corticosteroids have also been used, preferably for a very short course due to the risk of infection. For infants who do not responds to random donor platelets, HPA 1 and 5 negative platelets (HPA-4 for mothers of Asian descent) can be tried if available. Maternal platelets were previously recommended but are problematic, in that immediately postpartum women are not ideal platelet donors, they have high levels of antiplatelet antibody, and platelet washing damages the platelets. If maternal platelets are used, they should be volume-reduced to decrease the amount of antibody infused and irradiated to prevent graft-versus-host disease.

In most instances, NAIT resolves completely within 2 weeks of birth. Infants should be followed until it has resolved, and if thrombocytopenia persists, evaluation should be done for alternative diagnoses.

Congenital Disorders

Trisomy 13, 18, and 21 can all be associated with early-onset thrombocytopenia. Infants with Down's syndrome can develop transient myeloproliferative disorder, also called transient abnormal myelopoiesis, that presents with leukocytosis, peripheral blasts, hepatosplenomegaly, and, occasionally, pulmonary or pericardial effusions. While this usually resolves spontaneously, some infants do require treatment for hepatic, renal, pulmonary, or cardiac insufficiency. Of note, about 20–30% of these infants develop acute myelogenous leukemia in the first few years of life.

Bone Marrow Failure Syndromes

As discussed above, thrombocytopenia may be the presenting finding for Fanconi Anemia and other marrow failure syndromes. Two syndromes in particular can present in the newborn with isolated thrombocytopenia.

Thrombocytopenia with Absent Radii (TAR)

Infants with TAR are identified either by prenatal ultrasonography or at birth by their radial defects. Of note, the thumbs are present in children with TAR. In addition to the radial ray anomalies and thrombocytopenia, which is present at birth, other anomalies may be present, including other skeletal defects (ulnar, humeral, knees, hips), microcephaly, capillary hemangiomata, cardiac defects, and short stature. Radial ray defects are not specific for TAR as other syndromes may present with this skeletal defect.

The etiology of TAR is not completely understood. Thrombocytopenia is hypoproductive with bone marrow examination documenting decreased and abnormal megakaryocytes. Serum levels of thrombopoietin are elevated, consistent with decreased megakaryopoiesis. Inheritance appears to be autosomal recessive in most cases with autosomal-dominant inheritance described as well. Recently, abnormalities in chromosome 1q21.1 have been identified in patients with TAR and unaffected family members, suggesting that this gene defect is contributory

but not sufficient to cause TAR. In addition to the thrombocytopenia, some evidence for platelet functional abnormalities in TAR has also been described.

The platelet count usually increases in the first year of life, and while mild to moderate thrombocytopenia may persist, the risk of bleeding decreases at that time. In addition to the thrombocytopenia, other issues for children with TAR exist. There appears to be an increased incidence of lactose intolerance and GI bleeding may be problematic, especially in infancy. Bleeding may in turn lead to anemia for which iron supplementation is indicated. Orthopedic anomalies need long-term attention. Procedures to address the radial ray and functional hand defects are currently available. Other limb defects such as genu varum need to be monitored and managed. Children with TAR have an increased incidence of leukemia and long-term follow-up is necessary. However, aplastic anemia does not appear to occur in TAR.

Management for TAR consists of platelet transfusion support. As noted, usually the need for platelet transfusion decreases after the first year of life, occasional platelet transfusion may still be necessary if the platelet count falls with infection or a higher platelet threshold is necessary for surgical procedures. Long-term follow-up is also indicated to look for the development of leukemia.

Congenital Amegakaryocytic Thrombocytopenia (CAMT)

CAMT may also present with bruising, petechiae, and thrombocytopenia in the newborn. Unlike the radial ray abnormalities of TAR, there are no diagnostic physical anomalies in children with CAMT, but anomalies are present in about half the cases, including skull, cardiac, renal, optic nerve, and other skeletal defects. GI and other mucous membrane bleeding can occur as can more severe internal and CNS hemorrhage. CAMT may progress to myelodysplastic syndrome and aplastic anemia. Additional long-term complications include the cardiac, renal, skeletal abnormalities, and some who have psychomotor retardation.

Like TAR, the thrombocytopenia of CAMT is hypoproductive with elevated TPO levels and decreased bone marrow megakaryocytes. Defects in the thrombopoietin receptor gene c-MPL have been identified and are causative in most cases. An additional form of CAMT with radioulnar synostosis due to defects in the HOX-A11 gene has been described.

Management in the immediate newborn period is supportive, but long-term management is best done with hematopoietic stem cell transplantation. There is a high frequency of aplastic anemia and leukemia development long-term.

Wiscott–Aldrich Syndrome (WAS)

WAS is an X-linked disorder that affects more than platelets. The classic triad includes thrombocytopenia, immunodeficiency, and eczema. The defect lies in the Wiscott–Aldrich associated protein (WASp), the responsible gene for which is located on Xp11.23. A more complete description of this disorder and its immunologic complications is reviewed in Chap. _____.

Infants with WAS often present with perinatal bleeding. A striking feature of the thrombocytopenia is the small platelet size. These small, misshapen platelets may be sequestered in the spleen. Splenectomy may improve the platelet count in most patients, but this may be problematic due to the immune deficiency in these children. While corticosteroids have increased the platelet count in some children with WAS, intravenous gammaglobulin therapy does not appear to be helpful for the thrombocytopenia. Platelet transfusion may be necessary. The long-term management of WAS is hematopoietic stem cell transplantation where available. This addresses the immune deficiency as well as the thrombocytopenia.

X-linked thrombocytopenia is disorder related to WAS. These patients also present with thrombocytopenia and small platelets and may have eczema. The degree of immunodeficiency is less than that in WAS, but immunologic disturbances may increase over time.

Qualitative Platelet Disorders

In addition to thrombocytopenia, platelet function disorders can and do present in the neonatal period. The most common are probably disorders caused by medications that inhibit platelet function such as cyclo-oxygenase inhibitors. These are rarely diagnosed. Rare but severe platelet function disorders such as Glanzmann's thrombocythemia and Bernard–Soulier syndrome may present in the neonatal period. Infants treated with extracorporal membrane oxygenation (ECMO) may have both thrombocytopenia and acquired platelet function abnormalities.

Late-Onset Thrombocytopenia

Consumptive Coagulopathy and Thrombosis

Disseminated intravascular coagulation (DIC) appears to occur fairly commonly in sick neonates. DIC can be triggered by sepsis, necrotizing enterocolitis, hypotension, hypoxia, congenital enterovirus infection, and other causes. While bleeding symptoms are usually apparent to the clinician, intravascular thrombosis is the underlying pathology and thrombotic complications of DIC can occur. The most important component of management is to treat the underlying cause. Blood product support, such as platelets or fresh frozen plasma, may be necessary to manage bleeding episodes. DIC is discussed more completely in the hemostasis chapter.

Infection

Late-onset sepsis can cause thrombocytopenia in the newborn and should be strongly considered in an infant who develops this finding.

Thrombosis

Thrombocytopenia can also be caused by thrombosis within the infant; therefore a search for a blood clot can be revealing, especially in the older infant with unexplained thrombocytopenia. In infants with central venous catheters, Doppler ultrasound studies may demonstrate the clot. Neonatal thrombosis is discussed in the hemostasis chapter.

Neutropenia

Several factors can affect the reference range for neutrophil counts in the neonate. Manroe et al. first published a reference range for neonates in 1979 when survival of very low birth-weight infants was rare. In 1994, Mouzinho et al. published neutrophil counts from VLBW infants demonstrating a lower limit below that of Manroe. Infants born at high altitude have higher absolute neutrophil counts. Schmutz et al. published data on neutrophil counts from >30,000 infants born at high altitude. These three studies have had somewhat different results. For infants >36 weeks gestational age at delivery, the reference range lower limits were 3500/microliter (Schmutz) or 1800/microliter (Manroe) while these levels were 2700/microliter and 3000/microliter respectively at hours 72-240. For infants 28-36 weeks gestational age, the lower limits of the reference range at delivery were 1000/microliter (Schmutz) and 2100/microliter (Mouzinho) and these values were 800/microliter and 1100/microliter respectively at 72-240 hours of age. Finally, for infants <28 weeks gestational age at delivery the lower limit of neutrophil counts were 500/microliter (Schmutz) and 2100/microliter (Mouzinho). These authors had similar lower neutrophil counts at 72-240 hours of 1100-1300/microliter. While these reference ranges show a lower limit that may be as high as 8,200/μL, it is not clear that infants whose absolute neutrophil count (ANC) is above 1,000/μL are at increased risk for infection. Hence, mild neutropenia, where the ANC remains above 1,000/μL, may not need extensive evaluation. In addition, preanalytic specimen degradation can affect the neutrophil count, so it is often wise to repeat the CBC in a well-appearing child who is found to have unexpected neutropenia.

The evaluation of the infant with neutropenia can be directed by the timing and the severity of the neutropenia, the clinical picture the infant presents with and other findings on the CBC and peripheral blood smear. The presence of a left shift with metamyelocytes and band forms on the peripheral blood smear suggests that there is intact neutrophil production. A bone marrow test is occasionally indicated in the work-up of such infants but is not commonly performed in the infant and usually requires an individual with expertise with the procedure.

In this section, some of the more common causes of neutropenia are discussed (*Table 31.3*). There are several excellent discussions available on the topic for additional information.

Infection

Infection is probably the most common cause of neonatal neutropenia. Such infection can be bacterial, viral, fungal, or other, and severe neutropenia can be a sign of overwhelming septicemia. There may be an increased percentage of immature granulocytes such that the ratio of bands to segmented neutrophils is elevated (increased I/T ratio). Examination of the peripheral blood smear may also demonstrate toxic granulation, vacuoles, and Döhle bodies within the neutrophils.

Usually, the infant with infection-induced neutropenia is clinically ill. The work-up should be directed at identifying the underlying cause of the neutropenia. Management is focused on treating the underlying cause, usually with empiric antimicrobial therapy.

Table 31.3
Causes of neutropenia in newborns

Infection
Necrotizing enterocolitis
Medication induced
Maternal fetal unit
Pregnancy-induced hypertension
Rh incompatibility
Twin–twin transfusion
Maternal medications
Immune
Maternal autoimmune neutropenia
Neonatal alloimmune neutropenia
Inherited disorders
Severe congenital neutropenia
Schwachman–Diamond syndrome
Glycogen storage type 1b
Reticular dysgenesis
Osteopetrosis
Cartilage-hair hypoplasia
Cyclic neutropenia
X-linked agammaglobulinemia
Bone marrow failure syndromes, e.g., Fanconi anemia
Chronic benign neutropenia

Transient Neonatal Neutropenia

Infants of Hypertensive Mothers

Neutropenia is commonly found in infants of hypertensive mothers. While the ANC can be quite low, studies of infection rates in these infants have yielded conflicting results, and it is unclear if such infants have an increased risk for serious infection. The neutropenia is hypoproductive but usually lasts only a few days postdelivery. Management can be supportive with little evidence to date that in the absence of clinical symptoms, these infants require either empiric antibiotics or the use of growth factors such as filgrastim.

As with infants of mothers with pregnancy-induced hypertension, infants with Rh incompatability or survivors of twin–twin transfusion may be born with a transient neutropenia. In most cases, the neutropenia is self-limited, and the clinical approach to these infants may be similar to that for pregnancy-induced hypertension.

Immune Neutropenia

As for red cells and platelets, alloimmune and isoimmune neutropenia may occur. The neutropenia in such infants is present at birth and may last for several weeks depending upon the maternal titers of anti-neutrophil antibody.

In isoimmune neutropenia, the mother has autoimmune antibody formation and may have a low ANC herself. In alloimmune neutropenia, the mother is sensitized against antigens on the neonate's neutrophils that she does not carry.

The diagnostic work-up usually begins with the maternal history and examination of her CBC results. The history of a previously affected sibling is very helpful but may not be present. The diagnosis can be confirmed by sending anti-neutrophil antibody studies to a specialized reference laboratory with expertise in this area.

Management of immune neutropenia depends upon clinical symptoms, degree of neutropenia, and cause. For severe, persistent neutropenia, infants should be monitored closely for the development of infection. Recombinant granulocyte stimulating factor has been demonstrated to be effective in increasing the ANC and is often used in these infants; however, the long-term effects are unknown, and there are no controlled trials to demonstrate improved outcomes. Other therapies, such as corticosteroids, have not been demonstrated to be beneficial. The long-term outlook is good and the neutropenia should resolve within several weeks without recurrence.

Congenital Neutropenia Disorders

Severe Congenital Neutropenia (SCN)

SCN is a rare, inherited disorder characterized by persistent, severe neutropenia (ANC $< 500/\mu L$), and recurrent severe infections. Infants usually present within the first few months of age with infection. Monocytosis and eosinophilia often accompany the neutropenia. The diagnosis can be confirmed by bone marrow examination which typically demonstrates an arrest of myeloid differentiation at the promyelocyte/myelocyte stage. Abnormal, vacuolated promyelocytes can be seen.

Inheritance can be autosomal dominant, autosomal recessive, or X-linked. A slight majority is caused by mutations in the neutrophil elastase gene ELA2 and demonstrates autosomal dominant inheritance. Interestingly, defects in this same gene are thought to be responsible for cyclic neutropenia. Another form of SCN, caused by mutations in the mitochondrial protein gene HAX1, has an autosomal recessive inheritance. Defects in the glucose

6 phosphate dehydrogenase catalytic subunit three gene have recently been shown to cause autosomal recessive SCN. X-linked SCN can be caused by mutations in the WASP protein also associated with Wiscott–Aldrich Syndrome. Barth Syndrome is an X-linked recessive neutropenia due to defects in the tafazzin gene. There are other forms of SCN caused by other identified and as yet unidentified gene defects.

The immediate management of infections in infants with severe neutropenia includes a search for the etiology of the infection and empiric broad spectrum antibiotics. Additional management of fever and neutropenia and fever in infants is discussed in Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism".

The development of an SCN registry (http://depts.washington.edu/registry) has provided a good deal of information regarding the management and long-term complications for SCN. Most children with SCN respond to G-CSF therapy with the dosage adjusted to maintain the absolute neutrophil count above 1,000/μL. The dose can vary widely, but an analysis of the SCN registry showed the median dose to be approximately 5 μg/kg/day and that most children could be effectively maintained at this level with doses <25 μg/kg/day. For children whose neutrophil count does not respond to G-CSF treatment, hematopoietic stem cell transplantation is recommended.

Children with SCN have an increased risk of development of myelodysplastic syndrome or leukemia with a cumulative incidence of 21% at 10 years. Children who require higher doses of G-CSF may be more at risk for leukemic development. Neurologic abnormalities have been identified in children with HAX1 defects, cardiac and urogenital defects in children with glucose 6 phosphate dehydrogenase catalytic subunit 3 gene, and organic aciduria, dilated cardiomyopathy, and distal muscle weakness in Barth Syndrome.

Other Inherited Neutropenia

Many other congenital syndromes may be associated with neutropenia, including glycogen storage disease type 1, Schwachman–Diamond syndrome, reticular dysgenesis, X-linked agammaglobulinemia, cartilage-hair hypoplasia, and others.

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32 Neonatal Neurology

Matthias Keller · Elke Griesmaier

Introduction

In neonatology the physicians are faced with numerous challenges in the field of neonatal neurology. In this chapter the most prominent and challenging conditions are discussed complementary to the section of Neonatal Neurology in the Pediatric Neurology chapter.

Most important to note is that the brain of term infants is not the same as of preterm infants and even within preterm born infants there is a clear difference depending on gestational age. Therefore, insults like hypoxia and ischemia will have a different effect depending on the stage of brain development. This has also consequences for treatment. Treatments shown to be protective in term newborns are not necessarily protective in preterm infants.

In order to understand these particularities, it is mandatory to know the key aspects of brain development. It can be separated into structural and functional. Structural brain development is characterized by the proliferation of neural cells in the subventricular zone and migration of glia and neuronal cells to the cortex. Functional brain development is characterized by organizational events, which occur over a time period spanning from the fifth month of gestation to several years after birth. Key features of functional brain development include attainment of proper alignment, orientation and layering of cortical neurons, elaboration of dendritic and axonal ramifications, establishment of synaptic contacts, and cell death as well as selective neuronal/synaptic elimination. Development of the functional neuronal network depends mainly on the establishment of afferent input and synaptic activity. The timing and spacing of an adequate level of stimulation is thereby essential for normal brain development. This phase is reflected by a tremendous growth of the brain from 70 g at 24–350 g at 40 weeks of gestation (term). During this period up to 40,000 synapses per second are established. Furthermore this phase is characterized by a high level of neurotransmitter receptor expression which surpasses levels in adults. In addition the function of neurotransmitter receptors is developmentally regulated. The GABA receptor known to act inhibitory in adults acts excitatory in the developing brain. The development of functional neural networks is susceptible to changes in neurotransmitter signaling. It has been shown that inhibition of activating receptors causes neuronal cell death and impacts on brain development. In summary, it is important to note that (1) the preterm brain is not comparable to the adult brain and not even to the mature newborn brain, (2) that any factor which modifies neurotransmitter signaling might potentially disturb brain development, and (3) that drugs shown to have beneficial effects in the adult brain might have other, potentially negative effects in the developing brain.

Developmental Brain Injury in the Preterm Infant

Premature birth itself affects brain development at a very early stage of neuronal network development, leading to lifelong sequelae. Depending on the gestational age and birth weight there is an increased risk of lifelong disabilities such as cerebral palsy and cognitive disorders. This poses a serious burden to the children, their families and to the healthcare system and therefore to society in general. Besides severe impairments such as cerebral palsy, it has been shown that several cognitive dysfunctions have a higher incidence in formerly preterm children. Even in premature infants without severe neurodevelopmental impairments, the risk of attention deficit hyperactivity disorder (ADHD) is increased 2.6–4.0 times in early childhood. Some of these difficulties persist into adolescence and early adulthood. Magnetic resonance imaging (MRI) studies of ex-premature infants less than 32 weeks of gestation revealed reduced brain volumes and cortical folding, delayed maturation, and disturbed myelination, all of which result in an impaired neurological development. It is important to take into account that also the so-called "late preterm infants," born at a gestational age >32 weeks of gestation, are at a higher risk of cerebral palsy and connectivity disorders such as ADHD and psychiatric disorders in childhood and even adulthood.

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From Periventricular Leukomalacia via White Matter Disease to Encephalopathy of Prematurity

Within the last 10 years major progress has been made in understanding the pathophysiology of perinatal brain injury in preterm infants. The classic description of developmental brain injury in preterm newborns is periventricular leukomalacia (PVL). The term periventricular leukomalacia describes injury of the white matter around the lateral ventricles, which mainly involves fibers that come from or lead to the cerebral cortex. Therefore, the corticospinal tract, associating fibers and the optic and acoustic radiation are mainly affected. Infants who suffer from PVL often develop motor disabilities, cognitive, visual, or acoustic impairment.

A condition called "Little´s disease" was described by Little in 1853. He related this condition with its prominent features – limb contractures, diplegia, and mental retardation – to preterm birth and asphyxia at birth. In 1867 a disease called "congenital encephalomyelitis" was first described by Virchow. As many of the children´s mothers suffered from smallpox or syphilis, he related the disease to acute infection. Examination of the brains post mortem showed pale softened zones within the periventricular white matter, glial hyperplasia, and evidence of necrosis. In this context, infarction and hemorrhage was connected by Parrot, proposing that white matter damage was the result of nutritional and circulatory disturbances during development. In 1962 Banker and Larroche first introduced the term "periventricular leukomalacia," describing cardiopulmonary diseases or abnormalities, placental abnormalities, or a severe anoxic period prior to or shortly after birth as risk factors for PVL.

The histopathology of PVL is characterized by a chronological sequence of astrocytosis, microglial reactivity, and swollen axons to astrocytic proliferation and capillary hyperplasia, followed by microglial proliferation and accumulation of lipid-laden cells within 7 days after the insult. Cavitation emerges within 3–4 weeks. According to the histopathological distribution, three types of PVL are distinguished: focal, diffuse, and widespread. The focal type is located deep in the cerebral white matter and characterized by localized necrosis of all cellular elements and progression to cyst formation. The diffuse type mainly affects oligodendrocyte precursors and thus seemed to be cell specific. The prognosis for the diffuse is better than for the focal type. In the last decade the incidence of the cystic form of PVL is declining, presumably because of improvement of perinatal and neonatal care.

Pathophysiology of Developmental Brain Injury

The pathogenesis of PVL is complex and not yet completely understood. One major factor is hypoxia-ischemia. The preterm brain is prone to low oxygen delivery, due to the immature vascularization resulting in so-called watershed areas in which perfusion is marginal and to the lack of proper autoregulation of cerebral blood flow in preterm infants. Furthermore, precursor cells of the white matter in these periventricular regions are particularly sensitive to hypoxia. In addition to hypoxia-ischemia, inflammation plays a major role in the pathophysiology of developmental brain damage. Inflammation *per se* causes injury not only to the white but also to the cortical gray matter. Inflammation sensitizes the developing brain toward hypoxia-ischemia, causing an aggravation of brain injury. Although inflammation and hypoxia-ischemia are seen as major factors for brain injury, it has been shown that also so-called environmental factors like premature exposure to high levels of oxygen (hyperoxia), pain, and drugs contribute to disturbances of brain development. *Figure 32.1* summarizes the current knowledge about the pathophysiology of PVL.

Recent MRI studies of infants with very low birth weight (VLBW) have revealed that not only white matter injury occurs but that also cortical gray matter volume is affected and reduced. Consequently, in the last decade the term PVL has been modified and expanded to "white matter disease" and "encephalopathy of prematurity" or "developmental brain injury of the preterm infant."

Diagnostic Approach

An early diagnostic test to detect developmental brain injury is not yet available. Cysts and enlargement of the lateral ventricles as a consequence of white matter loss occur around 3–4 weeks after the damaging insult. Current state-of-the-art diagnostic approaches are cranial ultrasound and MRI as described in the section Neonatal Neurology in the Pediatric Neurology chapter. Especially in very high-risk infants, cranial ultrasound should be performed at regular intervals, e.g., 24, 72 h, and 7 days after birth and subsequently weekly. In resource-limited settings cranial ultrasound can be obtained at the end of the first week looking for early hyperemic changes in the periventricular region and again at 4–6 weeks, at which time cystic changes would be detectable, if present.

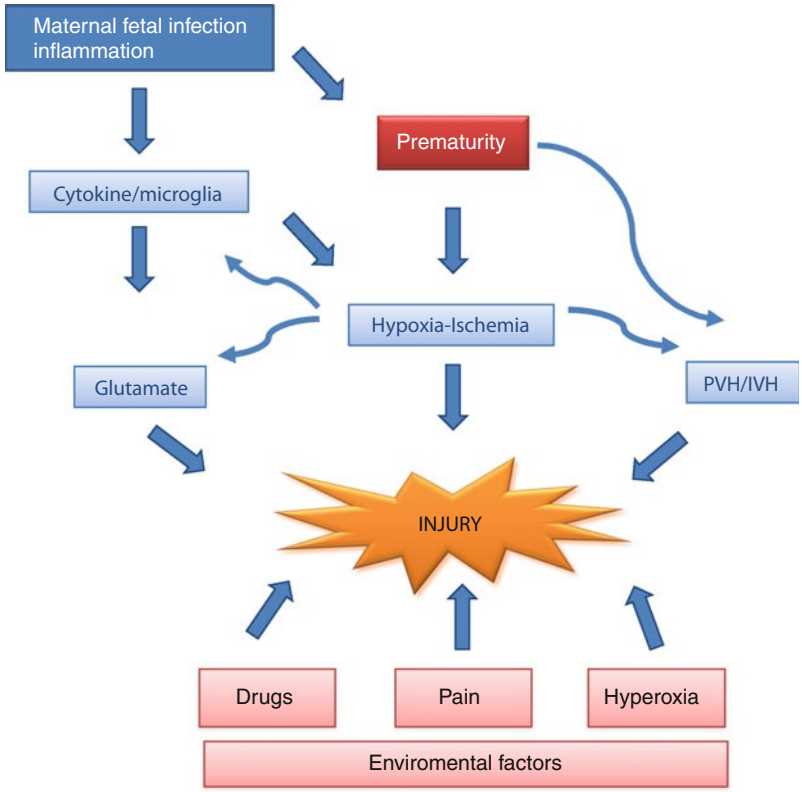

Figure 32.1

Inflammation is a major cause of preterm birth. Preterm birth per se is associated with a greater risk for hypoxia-ischemia and can also result in intraventricular hemorrhage, causing an increase in oxidative stress and excitotoxic cell death by increased levels of glutamate. In addition inflammation per se triggers microglial cell activation, sensitizes to hypoxia-ischemia and also contributes directly to cell death. In addition to hypoxia-ischemia environmental factors like hyperoxia, drugs and pain can cause cell death and can induce developmental brain injury

Therapeutic Strategies

Several therapeutic interventions have been evaluated, but up to now no treatment is available for clinical application. Promising strategies are, e.g., postnatal administration of high-dose erythropoietin or melatonin. The neuroprotective effects of these drugs are currently being investigated in controlled-randomized clinical trials. However, at present the best neuroprotective strategy is excellent peri- and neonatal care. In particular, factors such as hypocapnia and hypotension that are known to be associated with increased risk of PVL should be avoided. The overall principle is "do not harm the infant" by reducing pain and stress and by avoiding any potential harmful interventions, drugs, and unnecessary negatively impacting environmental factors.

Intraventricular Hemorrhage

One important factor contributing to neonatal neurological morbidity and often also mortality in preterm infants is intraventricular/periventricular hemorrhage (IVH/PVH). As described in *Fig. 32.1* intraventricular/periventricular hemorrhage is a major contributing factor to PVL. A detailed description of the classification as well as the pathophysiology is given in the section Neonatal Neurology in the Pediatric Neurology chapter.

Most hemorrhages occur when the preterm newborn is younger than 72 h, with 50% occurring on the first day of life. However IVH/PVH can also occur when the individual is older than 3 days, especially as a result of a significant life-threatening disease. Clinical symptoms of IVH/PVH are often subtle. They can include a sudden

drop in hematocrit by more than 10%, metabolic acidosis, glucose instability, apnea, hypotonia, and sometimes seizure activity. Because these symptoms are often nonspecific, cranial ultrasound screenings for IVH/PVH should be performed on a regular basis within the first 7 days in very high-risk infants (e.g., day 1, 3, 7 of life). Early cranial ultrasound may be helpful in decisions regarding limitation of care in the most immature infants. Otherwise, it may be sufficient to obtain a study at 3 and 7 days, since there is no active intervention available. If significant hemorrhage is found, subsequent studies are needed to monitor for possible development of ventriculomegaly. The major risk factor for IVH/PVH is prematurity itself. However, the incidence of severe IVH/PVH is declining despite constant or even increasing numbers of preterm infants, presumably due to the increased knowledge of the risk factors and subsequent improvement of perinatal and neonatal care. Major risk factors described so far are the use of catecholamines, occurrence of hypertension, bradycardia, hypocapnia, rapid volume expansion, and infusion of hypertonic solutions like sodium bicarbonate. Additional risk factors are pneumothorax, hypoxic-ischemic insults, but also improper care-giving such as tracheal suctioning and frequent handling causing stress and pain. Severe hypercapnia in the first few days of life and large swings in $PaCO_2$ have also been linked to increased risk of severe IVH. Since no effective treatment of IVH/PVH is yet available, the most effective neuroprotection remains excellent, gentle, and least aggressive neonatal care. Beside the impact of IVH/PVH on the development of encephalopathy of prematurity, IVH/PVH can lead to the development of posthemorrhagic hydrocephalus by a decreased absorption of CSF secondary to obstruction of the arachnoid villi by blood and debris or the development of obliterative arachnoiditis or as a consequence of the obstruction of the CSF circulation. In some cases subsequent interventions like regular tapping of cerebrospinal fluid (CSF) or the insertion of an intraventricular reservoir, which can be tapped, or ventriculo-peritoneal shunt are needed.

Pain in the Neonate

Newborns admitted to the neonatal intensive care unit (NICU) may experience prolonged pain and repeated painful procedures as part of their medical treatment. Several hundreds of invasive procedures may be performed in extremely preterm infants during their stay in neonatal intensive care units, particularly during the first weeks after birth. The most frequent procedures include heel sticks for blood sampling, endotracheal suctioning during mechanical ventilation, and intravenous line insertion. As described above, pain is one negative environmental factor which contributes to developmental brain injury. Repeated or prolonged pain in the newborn period causes adverse neurological cognitive outcome, adverse behavioral and neuroendocrine responses, and alterations in somatosensory perception (both hypo- and hypersensitivity). Pain may also lead to an increase in blood pressure and fluctuations in the cerebral blood flow, which can lead to the development of intracranial hemorrhage in the preterm infant. Therefore, regular pain assessment, prevention of pain, and adequate treatment is mandatory.

Pain Assessment

Clinical signs of pain in preterm and term born infants include behavioral and physical responses, like an increase in the heart rate and drop in oxygen saturation. Behavioral responses in healthy full-term infants include vigorous facial behavior and crying responses to procedural pain such as blood collection. Pain scales based on these observations have been established and adopted to prematurely born infants. Currently used pain scores are the "Premature Infant Pain Profile" (PIPP) and "Neonatal Infant Pain Scale" (NIPS). In addition "Behavioral Indicators of Infant Pain" (BIIP) have been developed particularly for use in preterm infants.

Pain Treatment

The American Academy of Pediatrics and the Canadian Pediatric Society recommend that each health care facility that treats neonates establishes a neonatal pain control program. These recommendations include (1) the routine assessment for the detection of pain, (2) to reduce the number of painful procedures, (3) to prevent/reduce acute pain from invasive procedures performed at the bedside, (4) to anticipate and treat postoperative pain following surgery, and (5) to avoid chronic pain/stress during neonatal intensive care.

The overall principle is to reduce the number of painful interventions. Preemptive analgesia before and during elective painful procedures should be provided to all neonates. Analgesia should be performed in a stepwise manner with increasing analgesia as the degree of anticipated procedural pain increases and by the use of a combination of non-pharmacologic and pharmacologic techniques.

Non-pharmacologic interventions can effectively reduce pain arising from minor procedures in neonates. These include pacifier use (non-nutritive sucking), breastfeeding, administration of sucrose or glucose solutions, skin to skin contact (kangarooing), swaddling, facilitated tucking, etc. These approaches are more effective when used in combination, depending on the extent of pain induced. They may eliminate the need for pharmacologic use or at least reduce the drug dosage or the frequency of doses required, and thus the risk of pharmacologic side effects. Anesthetics being infiltrated or applied topically can reduce procedural pain in neonates. Systemic pharmacologic agents that have been used in neonates to reduce pain and stress include nonsteroidal anti-inflammatory agents, non-opioid analgesics, and opioid analgesics. Opioids are the most effective therapy for moderate to severe pain in patients of all ages. They provide both analgesia and sedation, have a wide therapeutic window, and attenuate physiologic stress responses. Morphine and fentanyl are the most commonly used opioids in neonates, including preterm infants.

Perinatal Asphyxia and Hypoxic-Ischemic Encephalopathy

Perinatal asphyxia is a worldwide problem and a leading cause of morbidity as well as mortality in the neonatal period, causing around one million deaths each year. Approximately 5–10% of newborns require some kind of assistance to start breathing after birth, and approximately 1% need more extensive interventions. Despite declining incidence of hypoxic-ischemic encephalopathy (HIE) following asphyxia, still approximately one per 1,000 newborns, and in developing countries as many as 5–10 per 1,000, suffer from moderate or severe HIE, with at least a 25% risk of permanent neurological impairment. Perinatal asphyxia and its long-lasting consequences are a huge burden to the child, family, and produce a worldwide burden of disability.

Pathophysiology of HIE

Hypoxia-ischemia is associated with two phases – primary and secondary energy failure – that culminate in brain injury. Perinatal hypoxia-ischemia can cause primary neuronal injury and cell necrosis as a response to low cerebral blood flow, low energy substrates (adenosine triphosphate, phosphocreatine) which is termed primary energy failure (◉ *Fig. 32.2*).

Impaired mitochondrial function and energy failure are followed by an impairment of ion pump activity, hypopolarization of cell membranes, and ensuing opening of voltage-dependent ion channels. This in turn sensitizes neurons toward glutamate stimulation by releasing the magnesium sulfate blockade of the NMDA receptor. NMDA receptor activation leads to a massive influx of calcium, followed by activation of the neuronal nitric oxide synthase (nNOS), translocation of proapoptotic genes to the mitochondria, mitochondrial dysfunction, release of cytochrome *C* into the cytosol, activation of caspases, and subsequent cell death. After recovery from primary energy failure and a short period of normal energy and cell status a second interval of energy failure occurs timely remote from the initial injury. This second wave process of cell destruction can continue over several days and weeks. The hypoxic-ischemic insult as well as reperfusion elicit an inflammatory response with increased levels of pro-inflammatory cytokines and delayed brain injury. The continued generation of free radicals is contributing to the ongoing cell destruction. The short interval between primary and secondary energy failure, called "therapeutic time window," offers the possibility for therapeutic interventions to protect the neonatal brain from further injury. The beginning of treatment during this latent phase has been shown to be successful in several animal models in reducing the injury. The exact duration of this therapeutic time window in humans is still unknown, but it has been shown to be about 6 h in animal studies using near-term fetal sheep.

Treatment: Induced Hypothermia as Standard of Care

Until recently, therapy has been limited to preventive approaches and supportive strategies such as avoidance of hypocapnia, hypotension, metabolic disturbances (acidosis, electrolyte imbalance, hypoglycemia), and treatment of seizure activity, if present. The first established neuroprotective strategy to reduce HIE in full-term infants is induced hypothermia by either total body cooling or selective head cooling. Both methods of induced hypothermia minimize the continuation of neuronal injury, improve mortality, and reduce subsequent neurodevelopmental disability at 18 months of age. Immediate identification of affected infants after delivery, initiation of cooling as soon as possible, and, equally important, no active re-warming and subsequent transfer to a center that provides hypothermia therapy is necessary

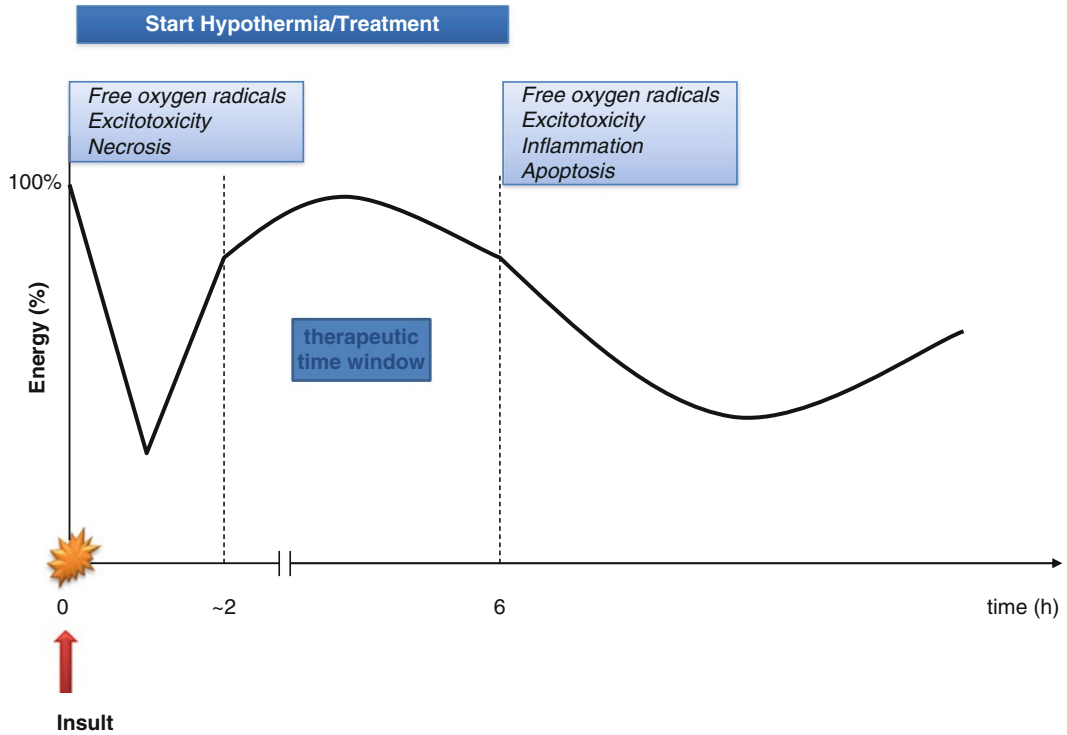

Figure 32.2
Pathophysiology of HIE

to maximize the potential of this therapeutic intervention. A delay of more than 6 h in initiating hypothermia reduces the neuroprotective potential. On the other hand, the earlier the therapy is initiated, the higher the protective effect. In regions where infants must be transported over long distances, initiating cooling during transport has been shown to be feasible and relatively safe. Standard whole body cooling protocol involves cooling to 33.5 degrees Centigrade for 72 h with gradual re-warming over 6 h. Studies are under way to determine if longer period of cooling or cooling to a lower temperature improves therapeutic efficacy. Co-treatment with other potentially neuroprotective agents, such as erythropoietin, is also being investigated.

Diagnosis

The diagnostic criteria for hypoxic-ischemic encephalopathy in term newborn infants require (1) signs of perinatal or postnatal asphyxia: obstetrical causes of hypoxia-ischemia, as well as clinical condition at birth such as low Apgar score, large base deficit, elevated blood lactate values, low cord pH, and the need for resuscitation, and (2) signs of encephalopathy characterized by abnormal neurological scores (Sarnat or Thompson score) and presence of seizure activity. When available, electroencephalographic evidence of abnormal cerebral function by means of the amplitude-integrated or ten-lead standard EEG is helpful in establishing the diagnosis (◉ *Fig. 32.3*). However currently used diagnostic procedures still require refinements. A combination of neurological scores (in particular the Thompson score), continuous electroencephalographic assessment by aEEG and neuroimaging methods (MRI) are providing the most accurate predictive power regarding neurological outcomes.

Seizures in the Neonate

Neonatal seizures occur in 2–4 per 1,000 live births in full-term newborns, with an even higher incidence in preterm infants, most of them occurring in the first days of life.

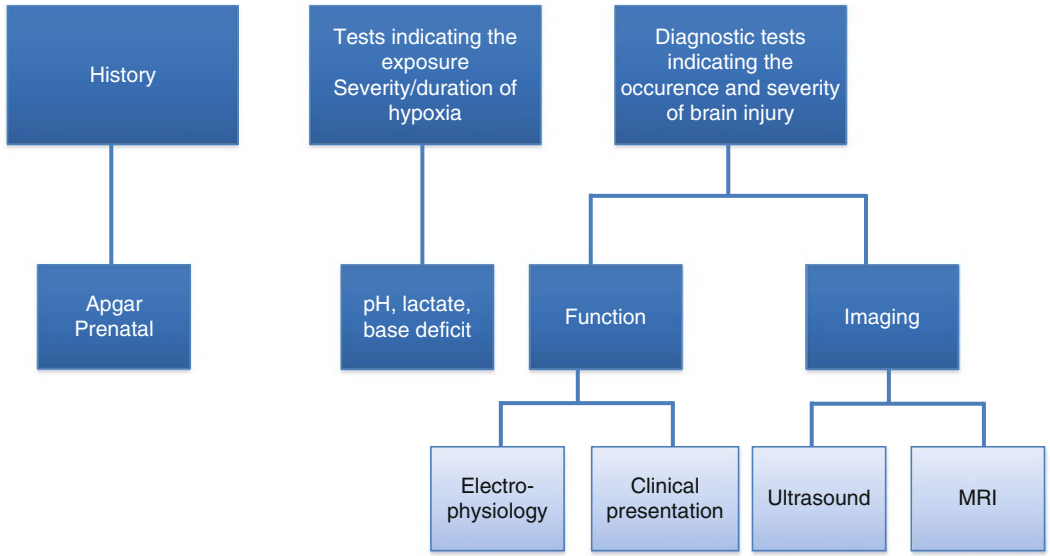

Figure 32.3
Diagnosis of HIE

Table 32.1
Challenges in neonatal seizures

• Seizures in term versus preterm infants
• Electrographic versus clinical seizures
• Impact of seizures on neurological outcome
• Potential harmful effects of anticonvulsants for the developing brain
• Uncoupling by anticonvulsant treatments

Table 32.2
Key messages of neonatal seizures

• Monitor infants at risk
• Ensure diagnosis using EEG and/or CFM before initiation of treatment
• Ensure proper electrolytes, ventilation, and blood glucose before anticonvulsant therapy
• Avoid combinations of anticonvulsants
• Before adding an additional drug, ask yourself whether you have the right diagnosis
• Monitor the "treated" brain

Diagnosis and treatment of neonatal seizures are one of the most challenging issues in neonatology. *Table 32.1* summarizes the major challenges. They include the differentiation between seizures occurring in term versus preterm born infants, the difference between clinical and electrographic seizures, and the challenge of uncoupling by anticonvulsant treatments. An additional important challenge is that currently used anticonvulsants like phenobarbital (PB), benzodiazepines, and phenytoin potentially cause brain injury because of their interference with neurotransmitter signaling impacting brain development.

Causes of Seizures in the Neonate

Seizures in the newborn always indicate some form of brain injury, as they occur with hypoxic-ischemic injury (HIE), stroke, intracranial infection, hypoglycemia, inborn errors of metabolism, and brain malformations (see also *Table 32.2*). A long debate has been ongoing whether seizures per se damage the brain since the answer would determine whether seizures in the newborn should be treated or not. However, currently evidence is emerging that neonatal seizures occurring as manifestation of existing brain injury are a very bad prognostic sign and per se harmful. The consequences of seizures at different stages of brain development differ substantially. Seizures can cause neuronal cell death in term infants. Seizures in the immature brain may in addition alter neuronal circuitry, resulting in impaired learning and memory and enhanced susceptibility to further seizures.

Diagnosis

The diagnosis of neonatal seizures is challenging, since the clinical manifestation of ongoing seizure activity might be very mild and subtle and in many cases is even absent. In addition some normal physiological movement patterns in the neonate mimic seizure activity. Even for experienced neonatologists and trained neonatal staff it might be difficult to identify the patient suffering from seizures. Therefore adequate diagnosis using standard EEG and/or amplitude-integrated EEG (CFM) with or without display of raw EEG is important to avoid overtreatment of patients on one hand and missing patients with seizures on the other hand. A particular challenge in diagnosis is "electric uncoupling," as anticonvulsant treatment might reduce clinical seizures while electrographic seizures are ongoing, warranting continuous monitoring of cortical activity by CFM, also after clinical seizure activity ceased due to treatment. Besides the diagnosis of seizures per se, it is of uttermost importance to diagnose the underlying cause of seizure activity. ❯ *Figure 32.4* summarizes causes of neonatal seizures according to their classical day of presentation.

Clinical Management

Clinical management of seizures in the newborn has remained unchanged in spite of almost 10 years of evidence that medications commonly used in newborns are not very effective and potentially neurotoxic by inducing apoptotic neurodegeneration in the developing brain. International surveys indicate that phenobarbital (PB) is by far the most commonly used first line antiepileptic agent in neonatology. PB is the oldest antiepileptic drug available and is widely used for treatment of seizures in preterm and full-term born infants during the neonatal period. However, it has been shown that PB induces apoptotic neurodegeneration in the developing brain and causes decrements in spatial learning tasks, increases aggression and locomotor activity. Therefore, other medicaments are increasingly used, such as Lorazepam, Levetiracetam, and Bumetanide. In case of ongoing continuous seizures activity the use of Lidocaine seems to be particularly effective. Clinical trials investigating anticonvulsant treatment regimens against neonatal seizures are ongoing and hopefully new knowledge about the best treatment will be gained. In addition to controlling seizure activity, it is of utmost importance to treat the underlying cause of seizure activity if treatment is available. The length of treatment with anticonvulsants is another area of controversy. Many newborns without identifiable brain lesions on imaging studies will not have recurrent seizures, but many are sent home on prolonged anticonvulsant medications that may have profound detrimental effects.

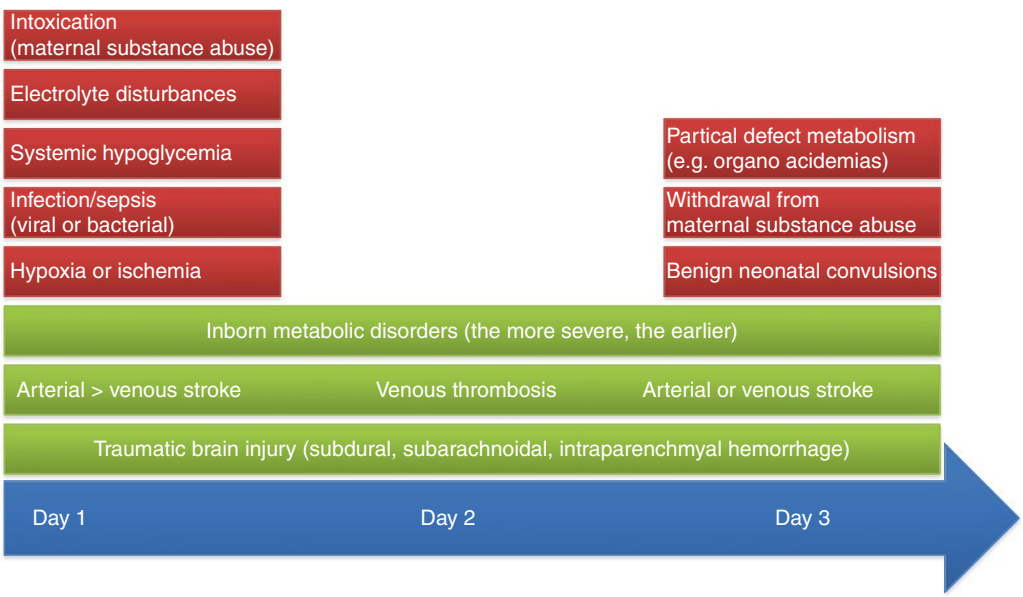

Figure 32.4
Causes of neonatal seizures

The Floppy Newborn: The Neonatal Workup

The "floppy newborn" represents a diagnostic challenge for the neonatologist. Frequently the term "floppy infant" is used to describe a condition caused by neurological or neuromuscular disorders. However this does not cover the entire spectrum of disorders that present as floppy newborn infant. Newborns can present with hypotonia due to central or peripheral nervous system abnormalities, myopathies but also because of genetic disorders, endocrinopathies, metabolic diseases, and acute illness like sepsis and hypoxic-ischemic encephalopathy. *Table 32.3* provides an overview of the differential diagnosis of the floppy newborn. Central causes are sepsis, hypoxic-ischemic encephalopathy, chromosomal disorders, congenital syndromes, inborn errors of metabolism, and neurometabolic diseases. Peripheral disorders include abnormalities in the motor unit (e.g., spinal muscular atrophy), peripheral nerve (e.g., myasthenia), neuromuscular junction, and the muscle. As highlighted in *Table 32.3* the central causes in particular HIE account for the majority of floppy newborns. The most common neuromuscular causes, although still rare, are congenital myopathies, congenital myotonic dystrophy, and spinal muscular atrophy.

Diagnostic Approach

The diagnostic approach in the newborn is based on thorough medical history and physical examination. Particular attention should be paid to the maternal and family history with assessment of pre-existing disease(s) of the mother as well as in the family, such as genetic disorders and inborn errors of metabolism; e.g., transient maternally acquired myasthenia gravis can be diagnosed by the maternal history. The prenatal history should include information on reduced or absent movements of the fetus, the existence of poly- or oligohydramnion, as well as maternal exposure to toxins, drugs, or infections. An examination of the mother might also bring new information in the case of heritable diseases, e.g., the diagnosis of myotonic dystrophy in a floppy newborn is suggested by a history of uterine dystonia as well as by examination of the handshake of the mother, who demonstrates an inability to relax her hand. The perinatal history includes the mode of delivery, since breech delivery or brow presentation is associated with cervical spinal cord trauma. Perinatal depression with low Apgar scores might be due to HIE; however, a respiratory insufficiency is also often seen in myotonic dystrophy. An infant who was born initially healthy and becomes hypotonic the first days of life should be considered septic until proven otherwise. In addition an inborn error of metabolism should be considered.

Physical Examination

The physical examination of the newborn should focus on the cardiovascular status, need for ventilation despite of good pulmonary function (compliance and oxygenation normal), signs and symptoms of sepsis and HIE, and evidence of malformations, dysmorphic features, or organomegaly. Since many heritable disorders are associated with hypotonia, the more common syndromes should be considered with the initial evaluation. Pertinent clinical features (e.g., the presence of fixed deformities) need a comprehensive neurologic evaluation. The neurological clinical examination is summarized in the neonatal neurology section in the Pediatric Neurology Chapter. Key clinical features of central hypotonia are abnormal depressed level of consciousness or seizures. Newborns with central hypotonia do not track visually and appear lethargic. They instead show abnormal eye movements in addition to apnea or exaggerated irregular breathing patterns. Dysmorphic features and malformations of other organs are also frequently present. The degree of muscle weakness is usually mild and the tendon reflexes are normal or hyperactive.

Causes of peripheral hypotonia are usually not associated with malformations of other organs, except deformities of bones or joints. In contrast to central hypotonic newborns, peripheral hypotonic newborns are alert, have a normal level of consciousness, respond appropriately to surroundings, and show normal sleep-wake patterns. Muscle weakness and hyporeflexia or areflexia are usually present, in addition to muscle atrophy.

Investigations

After assessing the history and the clinical examination a targeted approach toward a rational diagnostic should be chosen according to the clinical presentation of the infant. The initial laboratory evaluation of the hypotonic newborn is directed at ruling out systemic disorders. This includes an evaluation for sepsis with complete blood count, C-reactive protein, IT-ratio, blood culture, urine, and cerebrospinal fluid culture. In addition, measurement of serum electrolytes, glucose, parameters of liver functions, and creatinine should be taken as primary workup.

Table 32.3
Causes of a floppy newborn

Differential diagnosis of the floppy newborn		Prevalence	Central/peripheral hypotonia
Anterior horn cell disorders	Acute infantile spinal muscular atrophy		Peripher
	Traumatic myelopathy		
	Neurogenic arthrogryposis		
	Infantile neuronal degeneration		
Congenital neuropathy	Hypomyelinating neuropathy, congenital or non-congenital	1.4%	Peripher
	Charcot-Marie-Tooth disease		
	Dejerine-Sottas disease		
	Hereditary sensory and autonomic neuropathy		
Neuromuscular junction disorders	Transient acquired neonatal myasthenia	0.4%	Peripher
	Congenital myasthenia		
	Magnesium toxicity		
	Aminoglycoside toxicity		
	Infantile botulism		
Congenital myopathy	Nemaline myopathy	5%	Peripher
	Central core disease		
	Myotubular myopathy		
	Congenital fiber type disproportion myopathy		
	Multicore myopathy		
Muscular dystrophy	Dystrophinopathy	2%	Peripher
	Congenital muscular dystrophy (with or without merosin deficiency, with brain malformations)		
	Walker-Marburg disease		
	Muscle-eye-brain disease		
	Fukuyama disease		
	Congenital muscular dystrophy with cerebellar atrophy/ hypoplasia, with occipital agyria		
	Early infantile facioscapulohumeral dystrophy		
	Congenital myotonic dystrophy		
Metabolic and multisystem disease	Disorders of glycogen metabolism	3%	Central
	Glycogen storage disease Typ II (Pompe)		
	Acid maltase deficiency		
	Severe neonatal phosphofructokinase or phosphorylase deficiency		
	Debrancher deficiency		
	Primary carnitine defect		
	Peroxismal disorders		
	Neonatal adrenoleukodystrophy		
	Cerebrohepatorenal syndrome		
	Disorders of creatine metabolism		
	Mitochondrial myopathies		
	Cytochrome-c oxidase deficiency		

Table 32.3 (Continued)

Differential diagnosis of the floppy newborn		Prevalence	Central/peripheral hypotonia
Genetic/chromosomal syndromes	Down syndrome	31%	Central
	Prader-Willi-Syndrome		
	Fragile X syndrome		
	Trisomy 18		
	Trisomy 13		
	22q11.2 deletion syndrome		
	Cri-du-Chat syndrome		
	Wolf-Hirschhorn syndrome		
	Sotos syndrome		
Others	Hypoxic-ischemic encephalopathy	19%	Central
	Teratogens	1%	
	Brain tumors	0.4%	
	Sepsis		

Primary investigations for inborn errors of metabolism should be performed by determination of serum lactate, ammonia, and blood gases in particular pH, base deficit and urine analyses for ketone bodies. Particularly in intrauterine growth retarded newborns, a urine drug screen should be performed, since up to 4% of pregnant women in the United States use illicit drugs (marijuana, cocaine, ecstasy, amphetamines, and heroin). If the hypotonia is considered and dysmorphic features are present, analyses of the karyotype as a detailed molecular genetic testing might be indicated.

In case of any evidence of intrauterine infection like intracranial calcifications, thrombocytopenia and hepatosplenomegaly, titers for toxoplasmosis, rubella, cytomegalovirus infection (CMV), and herpesvirus should be determined and urine analyses for CMV (culture, PCR) should be performed. Thyroid function tests should be considered if the newborn suffers also from other signs of hypothyroxinemia. Determination of serum creatinine kinase (CK) should also be performed in suspicion of neuromuscular disease. However, at an early stage soon after birth this might not add new information, since increased levels of CK can be observed several hours to days after birth in normal infants. Imaging of the brain using cranial ultrasound and MRI is also a valuable tool for further diagnostics to detect nervous system analyses and metabolic diseases and can be easily performed in newborns. After these initial assessments additional tests like nerve conduction studies, electromyography, and muscle or sural nerve biopsy might be necessary.

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33 Eye Disorders of the Newborn

Rosemary D. Higgins

There are multiple eye disorders that can present in the neonatal period, with which the pediatrician should be familiar. Some are isolated to the eye; others have systemic manifestations. The primary care pediatrician must recognize the signs of serious eye disorders, which if undetected and untreated can lead to blindness in the case of cataracts and to death in the case of retinoblastoma. A thorough eye examination with, at a minimum, visual inspection of the external eye structures plus elicitation of a red reflex is essential. Eye findings may also provide clues to a number of genetic disorders where these findings are peripheral to the overall condition. This chapter covers the common eye observations and diseases seen in the neonatal period, including an abnormal red reflex, cataracts, infections, retinopathy of prematurity (ROP), and retinoblastoma.

Abnormal Red Reflex

An uncommon but urgent finding in newborns is an absent or decreased red reflex. This is usually a sign of serious eye or possibly systemic disease. Proper workup involves a slit lamp examination. If normal, evaluation of the fundus for retinoblastoma, infection, or coloboma is warranted.

The most common cause of absent or diminished red reflex in newborn infants is congenital cataract. Cataracts can occur unilaterally or bilaterally. It is critical to properly diagnose congenital cataracts because failure to treat could result in amblyopia (central loss of vision from disuse).

Cataracts

The incidence is about 2–5/10,000 births in the Western world and substantially higher in the developing world. About half are unilateral. The evaluation of congenital cataracts requires a thorough history and physical examination. There are multiple causes of congenital cataract, listed in *Table 33.1*. Bilateral cataracts are more likely to be associated with systemic disease or infection. If the examination, other than presence of congenital cataract, is normal workup may be limited, but an urgent referral for ophthalmologic evaluation is essential to preserve vision. Treatment usually involves surgical removal of the cataracts. If there are systemic findings, detailed further assessment is warranted and may include a search for evidence of infection, neuroimaging, and genetic and metabolic workup.

Infection

Chlamydia

Chlamydia conjunctivitis can present in the newborn period. It is characterized by ocular discharge, edema, and congestion. Chlamydia conjunctivitis typically presents a few days to several weeks after birth and lasts 1–2 weeks. The causative agent is *Chlamydia trachomatis* and it is acquired via vertical transmission from the genital tract of infected mothers to the infant. The conjunctivitis can occur in conjunction with *Chlamydia pneumonia*.

Diagnosis of Chlamydia conjunctivitis can be made by isolation of the organism in tissue culture and by nucleic acid amplification (NAA). Treatment of Chlamydia conjunctivitis is with oral erythromycin base or ethyl succinate for 14 days. Topical treatment is ineffective. Efficacy of oral treatment is 80% and a second course may be needed; so a follow-up is recommended for infected infants.

Infants born to untreated mothers with Chlamydia infection are at high risk for infection. Efficacy of prophylaxis is unknown, therefore not indicated. Newborn infants should be monitored clinically and treated if they develop signs of Chlamydia infection.

Gonorrhea Ophthalmitis

Gonorrhea ophthalmitis is caused by *Neisseria gonorrhoeae*, a gram-negative diplococcus. Eye involvement (ophthalmia neonatorum) is the typical infection in newborn infants with gonococcal infection. Infants can have concurrent scalp abscess (associated with internal fetal monitoring) or disseminated infection. Diagnosis is

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_33,

Table 33.1
Causes of congenital cataracts. There are many others besides the examples given

General classification	Example
Genetic – single gene disorders	Oculocerebrorenal syndrome, many others
Genetic – aneuploidy	Trisomy 21, Trisomy 18, Trisomy 13
Congenital infection	Rubella, toxoplasmosis, CMV, herpes
Metabolic	Galactosemia
Idiopathic	No identifiable cause

made by culture of the appropriate bodily fluid including eye discharge, blood, and sites to include cerebrospinal and joint fluid. The organism requires antibiotic testing to determine sensitivity due to the prevalence of penicillin and tetracycline resistant strains. Other sexually transmitted diseases should be tested for as well as hepatitis B in the mother and her partner(s).

Control measure for routine prophylaxis includes 1% solution of silver nitrate, 1% tetracycline ointment, or 1% erythromycin ointment into each eye within an hour following birth. For infants born to mothers with known gonococcal infection, a single dose of ceftriaxone (1 mg IV or IM for term infants, 25–50 mg/kg for preterm and low birth weight infants) is recommended to avoid gonococcal ophthalmitis and disseminated disease.

TORCH Infections

Some of the TORCH (toxoplasmosis, "other," rubella, cytomegalovirus, and herpes) can have ophthalmologic manifestations as part of their clinical presentation and diagnosis. If a diagnosis of toxoplasmosis, rubella, or cytomegalovirus is being considered, ophthalmologic consultation can be helpful.

The ocular finding in toxoplasmosis is chorioretinitis. *Toxoplasma gondii*-specific IgG or IgM antibodies should be looked for in the serum to confirm the diagnosis.

Congenital rubella syndrome can have several ocular manifestations including cataracts, pigmentary retinopathy, microophthalmos, congenital glaucoma, and chorioretinitis. Rubella-specific IgM or increasing serum concentrations of rubella-specific IgG over several months are confirmatory for the diagnosis.

Cytomegalovirus can be transmitted to infants by in utero transplacental passage of maternal virus, vertically at birth through the genital tract, or postnatally by ingestion of CMV-positive breast milk. Diagnosis can be made by serology or direct virus culture. Ocular manifestations include retinitis.

Retinopathy of Prematurity

ROP is a serious vasoproliferative disorder affecting preterm infants who have immature retinal vasculature. Normal development of the retinal vasculature in utero occurs at a lower oxygen tension than the prematurely delivered infant is exposed to as a result of preterm birth. Immediately following preterm birth, the retina is exposed to a higher oxygen tension resulting in a delay in the maturation of retinal blood vessels. This is also known as the vaso-obliterative phase of ROP. Over time, the retina grows in thickness and the distance for diffusion of oxygen and nutrients increases and retinal hypoxia ensues. Hypoxia at the tissue level in the retina results in an increase in hypoxia-inducible factor 1 (HIF-1) and vascular endothelial growth factor (VEGF); both growth factors result in retinal vasoproliferation and the development of ROP. ROP can lead to visual impairment, blindness, amblyopia and strabismus.

Risk factors for ROP include low birth weight, gestational age, and oxygen exposure. Infants born at less than 25 weeks have an 18–28% rate of severe ROP. Retinal screening on infants with a birth weight $<$1,500 g or gestational age $\leq$32 weeks is recommended, as well as selected infants with birth weight 1,500–2,000 g or gestational age $>$32 weeks with an unstable clinical course including those requiring cardiorespiratory support.

Diagnosis of ROP is made by retinal screening examination following pupillary dilation with indirect ophthalmoscopy and described using the international classification of ROP. The examination has several components including location of the disease, extent (clock hours) of disease, stage, and presence or absence of plus or pre-plus disease. The location of ROP is described by zone 1–3. Zone 1 is the innermost zone, which extends from the optic disc to twice the distance from the center of the optic disc to the macula. Zone I disease carries the greatest risk of visual impairment. Zone II is the area of the retina extending from the edge of zone I to the nasal ora serrata. Zone III is the remaining crescent of retina anterior to zone II. The extent of ROP, if present, is quantified in clock hours, or 30° segments.

Severity of ROP can be classified as one of five stages. Stage 1 is a demarcation line, which is a visible line of abnormally branching blood vessels at the vascular and

avascular border. Stage 2 is characterized by a ridge at the junction of the vascular and avascular retina. Stage 3 refers to extraretinal neovascularization extending from the ridge into the vitreous. Stage 4 is divided into extrafoveal (stage 4a) and foveal (stage 4b) of partial retinal detachments. Stage 5 refers to total retinal detachment and results in complete loss of vision.

ROP is also characterized by presence or absence of pre-plus and plus disease. Pre-plus disease refers to posterior pole arterial tortuosity and venous dilatation, not yet severe enough to be classified as plus disease. Plus disease is defined as venous dilatation and arteriolar tortuosity of posterior retinal vessels. There may be vascular engorgement, poor pupillary dilatation, and vitreous haze. Presence of plus disease denotes a more severe form of ROP and is considered an indication for laser therapy.

If the retinal vasculature is mature at the initial exam, there is no need for further evaluation. If the retinal vasculature is immature or there is evidence of ROP, the follow-up examination is warranted depending on the presence or absence of ROP, stage, zone, and presence or absence of plus disease. Follow-up guidelines are published by the American Academy of Pediatrics, American Academy of Ophthalmology, and the America Association for Pediatric Ophthalmology and Strabismus (ICROP).

Treatment of ROP was nonexistent until the advent of cryotherapy, validated by the CRYO-ROP study. Currently, laser surgery is used for ROP. Treatment involves retinal ablation to destroy tissues (hypoxic tissue) that is the source of growth factors. Treatment should generally be performed within 72 h of reaching treatment criteria (zone 1 ROP, any stage with plus disease; zone 1 ROP, stage 3; zone II or III ROP with plus disease) to minimize the risk of retinal detachment.

Infants who have a history of ROP, unresolved ROP prior to hospital discharge, immature retinal vasculature prior to hospital discharge, or ablative treatment or other procedures including vitrectomy, scleral buckle, or other ophthalmologic intervention should have appropriate ophthalmologic follow-up. Children with ROP are at risk for strabismus, amblyopia, cataract, and late retinal detachment.

Retinoblastoma

Retinoblastoma is the most common eye tumor in children, occurring in 1/15,000 live births and usually presents with leukocoria (absent red reflex). It can also present with strabismus or hyphema. Retinoblastoma can occur unilaterally or bilaterally and can be inherited in an autosomal-dominant pattern. The hereditary form is usually bilateral and multifocal, whereas the nonhereditary form is generally unilateral and unifocal. For small tumors, local therapy of thermal ablation or irradiation can be performed. For larger tumors, enucleation of the eye may be required. Investigation of metastatic disease including spinal tap and bone marrow aspiration are indicated. The prognosis for infants with retinoblastoma depends on the size and extent of the tumor. When confined to the eye, treatment is usually curative. The prognosis for survival is poor when the tumor has extended into the orbit or along the optic nerve.

Benign Conditions Affecting the Newborn Eye

Conjunctival hemorrhages are readily apparent and frequently occur during birth. No treatment is necessary, as they are resorbed spontaneously without consequence. Less commonly, a collection of blood is seen in the anterior chamber of the eye (*Hyphema*) and is usually associated with the rigors of passage through the birth canal, although rarely can be associated with retinoblastoma. No intervention is typically required. Parental reassurance is all that is necessary. Remnants of the *pupillary membrane* (anterior vascular capsule) are sometimes seen with the ophthalmoscope, appearing as cobweb-like lines crossing the pupil, especially in preterm infants. Superficial *retinal hemorrhages* are occasionally found in newborn infants soon after birth. These are usually absorbed promptly and normally do not have any permanent effect. The majority of birth-related retinal hemorrhages resolve within 2 weeks. *Lacrimal duct stenosis* (dacryostenosis) is a common finding that presents with crusting of the eyelids in newborn infants. It is distinguished from conjunctivitis by the absence of associated redness of the conjunctiva. Warm compress and gentle massage are the recommended treatment of this self-limited disorder. Occasionally, superimposed infection develops and requires treatment.

In summary, there are several eye disorders that can present in the newborn and early infancy period. Most eye problems can be diagnosed by ophthalmology referral. Prompt diagnosis and treatment can preserve visual function.

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34 Miscellaneous Chapter

Mara G. Coyle

This chapter deals with those issues not well ascribed to a particular organ system or single diagnosis. The first section will focus on nonimmune hydrops, a nonspecific finding occurring as a common final pathway due to a multitude of reasons, many of which carry a grave prognosis, the minority of which are amenable to therapeutic intervention. The second section will focus on the effect of maternal substance use on the fetus and newborn. Both licit and illicit drug use will be described as both have implications for fetal and newborn well-being.

Hydrops Fetalis

Hydrops fetalis was first described by Ballantyne over 110 years ago, and over 60 years later by Potter, who described nonimmune hydrops. Hydrops is defined by the presence of fluid accumulation in the fetal extravascular space and body cavities. It is characterized by greater than 5 mm of generalized skin thickening, with associated pericardial or pleural effusions, ascites, or placental enlargement. While in the 1970s over 80% of cases were due to maternal isoimmunization against rhesus or other red cell antigens, these immune hydrops cases today are extremely rare, due to improved antenatal interventions. Today, 85–90% of hydrops cases are nonimmune-mediated. As such, the remainder of this discussion will focus on nonimmune hydrops.

The incidence of nonimmune hydrops ranges from 1:1,500 to 1:3,800 births, although this may represent an underestimation, as a majority of fetuses die in utero or are electively terminated, and are not always included in analysis. Given improved ultrasound capabilities, the diagnosis is usually made prior to delivery. In a series of 82 cases limited to fetuses after 20 weeks, all were diagnosed by ultrasound before delivery. Despite improved diagnostic capabilities, the perinatal mortality remains high, particularly if the diagnosis is made before 24 weeks gestation. In a series by McCoy, the overall mortality was 86.6%. Fetuses diagnosed prior to 24 weeks had a perinatal morality of 95% with nearly one-third having an abnormal karyotype. In some case series, survival is notably greater (69%) when only those cases felt to be amenable to intrauterine therapies are included.

Hydrops is not a diagnosis but rather a nonspecific finding, which occurs as the final common pathway for a multitude of disorders of the fetus, umbilical cord, and placenta, which lead to deranged fluid homeostasis. The underlying pathophysiology for hydrops is not clearly understood, although the majority of cases are felt to be due to one or more of the following mechanisms, all of which lead to generalized edema.

High Central Venous Pressure

The pathway through which cardiac failure is responsible for edema is high right atrial pressure or volume overload, which leads to increased central venous pressure and heart failure. Alternatively, obstruction of venous or arterial flow or inadequate diastolic filling as seen in rhythm disturbances, intrathoracic masses, or cardiomyopathies will lead to increased central venous pressure and edema. It should be noted that while there is a large list of cardiac disorders associated with nonimmune hydrops (*Table 34.1*), they are not all necessarily causal. The hematologic disorders known to cause hydrops all lead to anemia, resulting in high-output cardiac failure, increased umbilical venous pressure, and extramedullary hematopoesis. Portal hypertension can develop in severely affected fetuses, which leads to liver dysfunction. Resultant hypoxia and acidosis will ultimately predispose the fetus to capillary epithelial damage, which will foster loss of fluid into the extravascular space. Rapidly occurring anemia is often fatal whereas chronic blood loss can lead to hydrops.

Reduced Plasma Oncotic Pressure

Those disorders that lead to compromised liver function and reduced protein synthesis, or disorders leading to excessive protein loss will result in a reduction of intravascular oncotic pressure and interstitial edema. Congenital nephrotic syndrome, for example, will lead to excess protein loss whereas high-output failure will lead to hepatic congestion, decreased function, and

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Table 34.1
Associations with non-immune Hydrops

Cardiovascular
Structural:
Left heart hypoplasia
Right heart hypoplasia
Atrioventricular canal defect
Truncus arteriosus
Tetralogy of Fallot
Premature closure of foramen ovale
Ebstein's anomaly
Single ventricle
Ventricular/atrial septal defect
Transposition of the great arteries
Premature closure of ductus arteriosus
Aortic or pulmonary stenosis
Valvular insufficiency
Arrhythmia:
Supraventricular tachycardia
Atrial flutter
Paroxysmal atrial tachycardia
Wolff–Parkinson–White
Heart block
Prolonged QT
High-Output Failure:
Chorangioma
Sacrococcygeal teratoma
Neuroblastoma
Hemangioma
Aneurysm
Arteriovenous malformation
Other:
Cardiac tumors
Myocarditis
Asplenia syndrome
Arterial calcification
Genetic
Chromosomal:
45X (Turner's syndrome)
Trisomy 21,18,13,12
Tetraploidy
Triploidy
Nonchromosomal:
Arthrogryposis multiplex congenita
Congenital myotonic dystrophy
Pena Shokeir syndrome
Neu Laxova syndrome
Multiple pterygium syndrome
Noonan syndrome
Familial nuchal bleb
Elejalde syndrome
Lymphedema distichiasis syndrome

Table 34.1 (Continued)

Skeletal dysplasias:
Short rib polydactyly syndromes
Camptomelic dysplasia
Lethal chondrodysplasia
Thanatophoric dysplasia
Homozygous achondrodysplasia
Hypophosphatasia
Osteogenesis imperfecta
Asphyxiating thoracic dystrophy
Achondogenesis
Saldino–Noonan dwarfism
Metabolic Storage Diseases:
Gaucher's disease
Hurler syndrome
Sialidosis
GM1 gangliosidosis
Mucopolysaccharide (MPS) IVA
Galactosialidosis
Mucolipidosis type I+II
Anatomic disorders
Gastrointestinal:
Jejunal atresia
Biliary atresia
Midgut volvulus
Duplication of intestinal tract
Meconium peritonitis
Malrotation
Hepatic fibrosis
Liver tumors
Hepatic vascular malformations
Hepatitis
Cholestasis
Polycystic disease of the liver
Familial cirrhosis with portal hypertension
Genitourinary:
Congenital nephrotic syndrome
Urethral obstruction and renal dysplasia
Polycystic kidneys
Renal vein obstruction
Posterior urethral valves
Prune belly syndrome
Thoracic:
Congenital cystic adenomatoid malformation
Diaphragmatic hernia
Chylothorax
Airway obstruction
Intrathoracic mass
Hamartoma
Tracheo-esophageal fistula
Pulmonary lymphangiectasia
Pulmonary neoplasia
Bronchogenic cyst
Cystic hygroma

Table 34.1 (Continued)

Hematologic
Twin to twin transfusion syndrome
Feto-maternal hemorrhage
Homozygous alpha thalassemia
Glucose-6-phosphate dehydrogenase deficiency
Red cell enzyme deficiencies
Red cell aplasia
Pyruvate kinase deficiency
Fetal anemia
Myeloproliferative disorders
Thombosis of major vessel
Infection
Parvovirus B19 (Fifth's disease)
Cytomegalovirus
Toxoplasmosis
Syphilis
Herpes
Coxsackie
Rubella
Leptospirosis
Trypanosoma cruzi
Placenta/umbilical cord
True knot in cord
Umbilical vein thrombosis
Chorangioma of placenta
Aneurysm of umbilical artery

hypoalbuminemia. Inborn errors of metabolism, hematologic disorders, infections, and certain cardiac disturbances can all lead to hepatic congestion, dysfunction, and hypoproteinemia.

Reduced Lymph Flow

Lymphatic vessel dysplasia can lead to fluid imbalance with resultant hydrops due to the low output failure of the lymphatic system. In addition to lymphatic dysplasia, those disorders that lead to severe loss of fluid into the interstitial compartment due to low osmotic pressure that can only partially be reabsorbed by the lymphatic system will exacerbate intravascular fluid loss and lead to hydrops.

Diagnoses Associated with Hydrops

While most categories of diagnoses (*Table 34.1*) can be explained by one or more of the above pathophysiologic mechanisms, in a large cohort of 5,437 hydropic cases, 15.8% were felt to be idiopathic, and not easily assigned to a specific cause. In addition, the ability to assign a patient into a category may not guarantee that the cause of the hydrops is well understood. This is particularly true of the syndromic/chromosomally anomalous patient, which comprised 17.8% of the aforementioned cohort. For example, while Trisomy 21 patients can be born with hydrops, the cause may not be the congenital heart malformation, but rather isolated lymphangiectasia. As such, as many as 33.6% of cases from this cohort were not easily assigned to one of the pathophysiologic mechanisms. While the list of diagnoses associated with nonimmune hydrops is extensive, the following categories represent the more common diagnoses. Attempts to establish an etiology are essential, as several diagnoses are amenable to intrauterine therapies.

Genetic Disorders

Hydrops diagnosed prior to 24 weeks gestation is usually associated with aneupliody, which, as the most common genetic etiology of hydrops, represents 10% of all cases. The most common chromosomal abnormality linked to hydrops is monosomy X (i.e., Turners syndrome), which accounts for 42–67% of aneuploid cases. Trisomy 21, 13, 18, and 12 as well as tetraploidy, triploidy, and rare deletions and duplications have also been seen. While the mechanism behind hydrops in these cases is not always clear, explanations include congenital heart disease, and incomplete formation or obstruction of the lymphatic system leading to lymphatic dysplasia. A mechanism for hydrops associated with other genetic nonchromosomal disorders is fetal akinesia, as is seen with arthrogryposis multiplex congenital, congenital myotonic dystrophy, and Pena Shokeir and Neu Laxova syndromes. Skeletal dysplasias that present with thoracic involvement can result in hydrops due to insufficient venous return and cardiac tamponade. Examples would include short rib polydactyly syndromes, camptomelic dysplasia, lethal chondrodysplasia, thanatophoric dysplasia, and homozygous achondrodysplasia. Prognosis is usually poor when hydrops is present in association with these genetic lesions.

Autosomal recessive metabolic storage diseases account for 1–10% of nonimmune hydrops cases. These disorders usually occur because of an enzyme defect leading to an accumulation of metabolic products in the lysosome, which leads to cell death, and organ dysfunction, particularly of the liver, heart, brain, and kidneys. While death is common, making a diagnosis is important given the recurrence risk as high as 25% with future pregnancies.

Cardiovascular Disorders

Disorders of the heart are responsible for up to 40% of cases of nonimmune hydrops. These include arrhythmias, structural defects, and vascular anomalies.

Cardiac arrhythmias, felt to be suitable to fetal intervention, represent 25–50% of treatable hydrops cases in several series. Both tachyarrhythmias and bradyarrhythmias can lead to hydrops. Many of the bradyarrhythmias are associated with structural abnormalities, particularly at the AV node. Others are due to damage to the fetal bundle of His and Purkinje fibers by maternal IgG antibodies related to maternal autoimmune disease.

Blood flow velocity in the descending aorta drops significantly at cardiac rates of 230–250 beats per minute, with the development of pericardial effusions within 24 h. Treatment for tachyarrhythmias, the most common of which is SVT, includes maternal administration of antiarrhythmic agents, which pass to the fetus via the placenta. Transplacental drug therapies include digoxin, verapamil, amiadarone, and flecanide, the latter of which has been demonstrated to be superior to the other antiarrhythmic agents. While effective, these agents are less successful in achieving cardioversion and cardiac recompensation when hydrops has already occurred, due to poor placental passage of the drug. Maternal side effects may also preclude this approach to therapy. Alternative treatment modalities include administration of antiarrhythmic agents into the fetal intravascular, intraperitoneal, or intramuscular space. Careful monitoring of both the fetus and mother is essential.

The common structural heart lesions associated with hydrops include hypoplastic left and right heart, atrioventricular canal defects, and less commonly tetralogy of Fallot and premature closure of the ductus arteriosus. When hydrops develops in the context of these disorders, the prognosis is poor, with mortality reaching 100%. High-output failure from arteriovenous shunting can result from vascular abnormalities, including arteriovenous malformations (most commonly seen in the brain and liver), large (>4 cm) placental chorioangiomas, sacrococcygeal teratomas, neuroblastomas, hemangiomas, and large aneurysms. Fetal endoscopic laser coagulation therapy has been reported, but carries risks of bleeding, exsanguination, and death.

Anatomic Abnormalities

Chylothorax accounts for half of the thoracic lesions associated with nonimmune hydrops. Other lesions in order of frequency include congenital cystic adenomatoid malformation, diaphragmatic hernia, pulmonary sequestration, bronchogenic cyst, and least commonly, the aforementioned skeletal dysplasias. The mechanism for the hydrops is obstruction of venous return due to increased intrathoracic pressure, which leads to peripheral venous congestion. The overall prognosis depends upon the timing of the development of pleural effusions as well as whether the effusions are isolated, or in conjunction with hydrops. Accumulation prior to 20 weeks is associated with a poor prognosis due to associated pulmonary hypoplasia, the extent of which cannot be well ascertained by fetal ultrasound. When pleural effusions develop as part of hydrops, the outcome is usually worse.

Fetal management of pleural effusions includes the placement of a pleuro-amniotic shunt to decrease intrathoracic pressure and promote lung growth. In a systematic review of the literature including 99 cases of primary chylothorax complicated by hydrops, the survival rate was 66% with shunting versus <25% with expectant management. The main complication of this procedure was preterm rupture of membranes and premature delivery. The outcome is generally worse when the pleural effusions are due to something other than a chylothorax. In addition, the literature is limited mostly to case series, and to date, no randomized trials have been performed. Needle aspiration of pleural effusions is usually limited to diagnostic testing, as fluid generally re-accumulates within 48 h. Ex utero intrapartum treatment (EXIT) with thoracentesis as an alternative to fetal shunting has been reported, but this therapy is not available in all treatment centers.

Urinary tract and gastrointestinal anomalies rarely cause nonimmune hydrops. Posterior urethral valves associated with prune belly syndrome or urethral atresia likely cause hydrops by obstructing venous return or mechanical tamponade. Congenital nephrosis leads to hydrops because of hypoproteinemia, which can also be seen with hepatic tumors, volvulus, and meconium peritonitis. Isolated abdominal wall defects causing lymphatic obstruction can also lead to hydrops.

Lymphatic Disorders

Primary congenital pulmonary lymphangiectasia is an abnormality of lymphatic development leading to thoracic duct obstruction. Secondary forms of this disease occur due to thoracic duct obstruction by masses, total anomalous pulmonary venous return, or as a component of a discrete syndrome. The resultant chylothorax can be treated with mid gestation pleuro-amniotic shunting to avoid resultant pulmonary hypoplasia. Generalized lymphangiectasia occurs because of systemic lymphatic vessel ecstasies. In addition to chylothorax, these patients develop subcutaneous edema and hepatic, pancreatic, and

renal lymph edema. These disorders can occur spontaneously or by autosomal recessive inheritance.

Anemia

Fetal anemia, accounting for 10–27% of hydrops can result from a variety of causes including abnormal hemoglobin formation, red blood cell destruction or defective production, and hemorrhage. Regardless of the cause, anemia can result in high-output failure and hydrops. Unlike in the Caucasian population, the major cause of hydrops in Southeastern Asia is homozygous alpha-thalassemia-1 or Bart's hemoglobin. This gamma-4 tetramer, while having a high affinity for oxygen, is unable to release it to the tissues, resulting in anemia, profound hypoxia, acidosis, hydrops, and fetal death.

Feta-maternal hemorrhage, which can be diagnosed by the Kleihauer-Betke test, can present as hydrops if the anemia is chronic. Monochorionic twins are at increased risk of anemia due to twin–twin transfusion. The anemia seen in Parvovirus B-19, (see below) can be transient, as erythroid bone marrow aplasia can resolve in 7–10 days. In these cases, spontaneous resolution of the hydrops can be seen. If severe anemia persists, intrauterine transfusions are performed. Aggressive management is suggested, as the general outcome for these fetuses is good, particularly if the diagnosis is made after the first trimester.

Infectious Diseases

There are multiple infectious organisms responsible for nonimmune hydrops, of which parvovirus B-19 (Fifth Disease) is the most common. Other associated organisms include the TORCH pathogens (toxoplasmosis, cytomegalovirus, rubella, and herpes) as well as varicella, syphilis, and coxsackie. Unlike with other infectious agents where the mechanism of hydrops is not well understood, fetal anemia, hepatitis, and myocarditis can develop with parvovirus B-19, because the virus affects the bone marrow, hepatic, and myocardial tissues. As the disease is self-limited, the prognosis is good if the fetus receives red cell transfusions until the anemia resolves. The presentation of the TORCH and other organisms is one of multisystem organ failure, as the infection affects the myocardium, bone marrow, and vascular endothelium, leading to heart failure, fetal sepsis, anemia, and hypoalbuminemia with resultant anoxia, endothelial damage, increased capillary permeability, and hydrops. Interventional therapy, if the diagnosis is made prenatally, can include hyperimmune globulin for the mother and fetus in the case of CMV, or Gancyclovir for the newborn if the diagnosis of CMV is made after birth (see chapter on infectious diseases).

Maternal Presentation

While hydrops is a fetal condition, maternal morbidities can complicate the presentation. Hydrops occurs more commonly in mothers who have had a previous stillbirth or hydropic infant or twin pregnancies, particularly monochorionic twins. Additional maternal complications such as polyhydramnios/oligohydramnios, preeclampsia, preterm labor/delivery, and anemia have all been described. In an attempt to compensate for fetal hypoxia, the placenta enlarges and can penetrate deeper into the myometrium. As such, additional complications can arise after birth including retained placenta and postpartum hemorrhage.

Mirror syndrome, first described by John Ballantyne in 1892 (Ballantyne's syndrome), refers to a maternal condition of generalized edema that mirrors the edema of the hydropic fetus and placenta. This "triple edema" syndrome (mother, fetus, and placenta) can present with both immune and nonimmune-mediated hydrops. While the pathogenesis is unknown, postulated hypotheses include a systemic inflammatory response from increased shedding of trophoblastic debris into the maternal blood. A proposed mediator of this response is soluble fms-like tyrosine kinase, which has been associated with the development of preeclampsia. Mirror syndrome can present similarly to severe preeclampsia, although, unlike with preeclampsia, the maternal hematocrit is usually low, amniotic fluid volume is usually high, and the fetus is always hydropic. Delivery will usually reduce maternal symptoms, although persistence of symptoms into the postpartum period can occur. If the cause of the fetal hydrops is reversed, reversal of maternal symptoms can be seen. Additionally, if the fetal hydrops resolves spontaneously, or if the fetus dies, spontaneous resolution of maternal symptoms can occur.

Diagnosis

The diagnosis of hydrops is established with prenatal ultrasound. It is defined by the presence of fluid accumulation in the fetal extravascular space and body cavities. Polyhydramnios, defined as an amniotic fluid volume (AFI) of greater than 24 cm or a vertical pocket greater than 8 cm, is present in 40–75% of pregnancies complicated by nonimmune hydrops. An early sign of ascites is the outlining of the intraabdominal organs by a thin rim of fluid. It is important to distinguish this from pseudoascites, in which the abdominal wall muscles appear as a hypoechoic band. As ascites worsens, the bowel may appear compressed, with its walls accentuated due to the excess fluid allowing for increased ultrasound transmission. Significant pleural effusions that develop

prior to 20 weeks gestation, can prohibit normal lung growth and development, and result in pulmonary hypoplasia, a cause of death in many hydropic infants. The fetal heart should carefully be visualized for congenital defects as well as for the presence of pericardial fluid, with the knowledge that the presence of a small amount of fluid in the pericardial sac may be physiologic. Venous Doppler sonography can be a useful tool in the evaluation of the hydropic fetus as changes in velocimetry have corresponded to alterations in cardiac function.

Skin edema is a late sign of fetal hydrops. It is considered pathologic if the subcutaneous tissue on the chest or scalp measures greater than 5 mm. Attention should be paid to avoid including fat in this measurement. Placentomegaly, defined as a thickness of greater than 4 and 6 cm, may occur due to intravillous edema. However, if the polyhydramnios is profound, the placenta may be compressed.

The first site to demonstrate excess fluid can vary depending on the cause of the hydrops. In a series of 100 hydropic patients, those with a chromosomal disorder developed soft tissue swelling around the head and chest, with minimal limb swelling. Those patients with anemia or cardiovascular disease tended to have more evenly distributed fluid throughout multiple sites.

As hydrops is the final common pathway for multiple disease states, understanding the etiology can be difficult. A careful evaluation to assess for diagnoses amenable to treatment should be pursued. A detailed evaluation for structural anomalies as well as fluid assessment, placental thickness, and Doppler blood flow studies are considered part of the initial evaluation. Measurement of the fetal middle cerebral artery peak systolic velocity is a noninvasive tool for predicting fetal anemia. A careful personal and family history should be obtained to look for ethnic, genetic, or heritable disorders associated with hydrops. Alpha-thalassemia is the most common cause of nonimmune hydrops in Southern China and Thailand. Knowledge of recent exposure to infectious agents, as well as noting the time of year, may help identify parvovirus, the most common infectious etiology of hydrops. Suggested maternal laboratory testing includes a complete cell blood count with red blood cell indices, blood type, serologies, and the Kleihauer-Betke test.

Based on the initial evaluation, it may be appropriate to undertake further invasive testing in order to arrive at a fetal diagnosis. Amniocentesis or cordocentesis can be performed for karyotype although cordocentesis has the advantage that results are generally available sooner, and fetal hemoglobin and blood grouping can be obtained as well. Either fetal blood or amniotic fluid should be tested for TORCH pathogens specifically CMV, toxoplasmosis, and parvovirus B19. Amniotic fluid can be saved for additional testing should baseline studies be unrevealing and rare metabolic disorders considered.

Management

Despite improved diagnostic techniques, mortality for nonimmune hydrops remains high. The management depends on timing of diagnosis and etiology. Those cases diagnosed prior to 20 weeks, are often aneuploid and will be complicated by pulmonary hypoplasia, both poor prognostic signs. The temptation to deliver a sick fetus before term should be avoided given the added complications anticipated from the prematurity. Options for the family include termination of the pregnancy, therapeutic intervention in specific instances, and close monitoring of the mother and her fetus. Amniocentesis or aspiration of pleural or ascitic fluid before delivery can make the delivery less traumatic, and can facilitate resuscitation. There is not evidence that mode of delivery has a marked effect on outcome, although most fetuses are delivered by cesarean section, many because of dystocia and nonreassuring heart rate patterns. Antenatal consultation with appropriate neonatal and pediatric subspecialty teams, as well as planned delivery at a tertiary care center is recommended.

Antenatal diagnosis can allow for delivery to occur in a controlled setting. The neonatal team should ensure the availability of O negative blood cross matched against the mother, full monitoring capability and availability of equipment to perform an exchange transfusion. Initial resuscitation may be difficult for three main reasons. Pulmonary hypoplasia can complicate a majority of cases due to lung compression by pleural fluid, gross abdominal ascites, or a mass. Intrapartum asphyxia may complicate the delivery, and endotracheal intubation may be challenging due to the hydrops and laryngeal edema. The infant may require high positive pressure as well as thoracentesis and/or abdominal paracentesis before adequate gas exchange can be ensured. As peripheral venous access will be difficult due to skin edema, there should be a low threshold for the placement of an umbilical catheter. If associated anomalies are identified or, if despite these interventions the infant is unable to maintain a stable heart rate and ability to oxygenate/ventilate, this may be an appropriate time to discuss with the family the discontinuation of support.

If the infant is stillborn or dies in the immediate newborn period, continued evaluation should be considered including the consent for an autopsy in order to assist in counseling of the family with regard to future

pregnancies. If the parents do not wish for an autopsy to be performed, consent for a skin or liver biopsy as well as full radiographs and photographs should be made. The placenta should be sent fresh and not fixed in formalin, to be evaluated by a perinatal pathologist.

Substance Use in Pregnancy

Substance use during pregnancy presents a complex issue of challenges for the mother and her fetus and is a growing international concern. Illicit drug use is the ninth leading cause of death in the United States. The number of pregnant women reported using illicit drugs during pregnancy in the United States has increased from 2.8% during 1996–1998 to 4% in 2006. The prevalence was highest among women aged 18–30 years, unmarried and with less than a high school education. The Annual report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), estimates that there are as many as 30,000 pregnant women using opioids in Europe with a speculation that use of other drugs is equally high. Since 1996, the nonmedical use of analgesics has increased for pregnant women, with self-reported use increasing from 51,900 in 1993, to an average of 109,000 in 2002 to 2004. As these data are generated from self-report, they likely represent substantial underestimates. In addition to illicit drugs and nonmedically used analgesics, 35% of pregnant women are now using psychotropic medications to treat disorders such as anxiety and depression. These medications, although felt to be safe when used during pregnancy, have the potential of affecting the fetus and newborn.

Drug use during pregnancy is a public health concern not only because of the direct effect of the drug on the mother, but because of the associated morbidities encountered for the pregnant patient with respect to infectious diseases, social and personal stressors, comorbid mental illness either with or without concomitant illicit drug use, and risk to the fetus and neonate who require prolonged hospitalizations. Issues that deserve particular attention when considering a substance using pregnant woman and her fetus are discussed below. The effects of particular substances on the fetus and neonate are discussed under each particular drug.

Infectious Diseases

Infectious diseases including HIV, hepatitis B (HBV), and C (HCV), and other sexually transmitted diseases such as syphilis, chlamydia, and gonorrhea are more prevalent in the drug using pregnant population. Early identification of these illnesses can ensure a reduction in the risk of vertical transmission. As of September 2006, the US Centers for Disease Control (CDC) recommended universal screening for HIV in all pregnant women regardless of risk. Current practice in the United States reflects state law. Given the reduction of the risk of vertical transmission to under 2% with treatment, practitioners are strongly encouraged to offer testing. Without treatment, HIV perinatal transmission rates range from 25% to 30%.

Ten to 20% of women seropositive for HBsAg transmit the virus to their neonates in the absence of immunoprophylaxis. In women who are both positive for HBsAg and HBeAg, vertical transmission is approximately 90%. In patients with acute hepatitis B, the likelihood of transmission is greater if infection develops in the third trimester. Hepatitis B testing in pregnancy is recommended by the CDC and the World Health Organization (WHO). With appropriate hepatitis B immunoprophylaxis, breastfeeding poses no increased risk for transmission to the neonate.

The prevalence of hepatitis C in a healthy pregnant woman is 3.44%. Injecting drug use accounts for 60% of HCV transmission in the United States, and is the leading cause of transmission in the UK. The risk of vertical transmission is related to the level of viremia in the mother and not her mode of delivery. Neither the CDC, the American Academy of Pediatrics (AAP), or the American College of Obstetrics and Gynecology (ACOG) recommend operative birth for mothers with hepatitis C. Approximately 7–8% of hepatitis C-positive women can transmit hepatitis C to their offspring, with a higher rate of transmission seen in women co-infected with HIV. While routine screening is not recommended in the general pregnant population, women who have ever injected illegal drugs, including those who injected once or a few times many years ago and do not consider themselves drug users should be screened. Breastfeeding does not increase the risk of transmission to the neonate.

Societal Stressors

Compounding the expected stress of pregnancy and substance use are issues of homelessness, unemployment, legal complications, fractured relationships, and physical and emotional abuse. Infant neurodevelopmental outcome has as much to do with fetal exposures as it does with the environment. Determining developmental risk for fetal drug exposure is often complicated by the confounding environment in which many of these

children reside. Prenatal clinics and drug treatment centers should offer multidisciplinary coordinated services to address the many needs of this population and ensure adequate intervention.

Psychiatric Comorbidity

Up to 70% of pregnant women experience depressive symptoms and 9–14% of all pregnant women will display signs of depression or fulfill criteria for the diagnosis of depression. For bipolar disease and severe chronic depression, pregnancy and the postpartum period present an especially greater risk period. Untreated depression is associated with significant morbidities including inadequate self-care, hypertension, spontaneous abortion, preeclampsia, fetal growth restriction, and substance abuse. Furthermore, patients should understand that stopping antidepressant medications during pregnancy because of a concern about exposing the fetus, can led to a maternal discontinuation syndrome, as well as a significantly greater risk of relapse when compared to the treated patient.

The selective serotonin uptake inhibitors (SSRI), first introduced in 1988, are the treatment of choice for mood disorders during pregnancy. These medications, which readily cross the placenta, expose the fetus to increased serotonin levels. Epidemiologic studies have demonstrated that first trimester exposure to Paroxetine (Paxil) has been associated with an increased risk of cardiac malformations. As a result, in 2005, the US Food and Drug Administration (FDA) issued an advisory reclassifying Paroxetine as category D and warned against its use in pregnancy.

There is evidence to support the notion that infants exposed to SSRI medications, particularly in the last trimester can exhibit either a discontinuation syndrome or serotonin toxicity, manifest by irritability, crying, tremulousness, hypertonia, feeding and sleeping difficulties, and rarely seizures. The symptoms can develop in a few hours up to a few days, and are typically short-lived, but can last for up to a month. Most infants are managed with supportive care, and rarely require medication intervention. Phenobarbital is generally the drug of choice in those situations where environmental intervention is not sufficient. Additional complications for the neonate born to a mother using an SSRI include prematurity, admission to a special care nursery, poor neonatal adaptation, and in rare cases pulmonary hypertension. As SSRIs are relatively new, inquiries regarding the long-term neurobehavioral effects of these drugs on the newborn and developing child are ongoing.

The decision to treat a pregnant woman with psychotropic medications during pregnancy should be made with the following considerations. Each patient should be treated individually using the lowest possible medication dose and avoiding multiple medications. The practitioner should be aware of the particular side effects when these medications are used, and the patient should be educated as to the risks/benefits and uncertainties of pharmacotherapy as well as the risk of not treating significant mental illness. These conversations should be documented in the medical record. Collaboration with mental health professionals regarding alternative therapies including cognitive, behavioral, interpersonal, and electroshock therapy should be considered.

Drugs Used During Pregnancy

Licit Drugs

Nicotine Pregnant women who use drugs also frequently drink alcohol and smoke cigarettes. While neither substance is illegal, both have known adverse effects for the mother, her fetus, and her neonate. Cigarette smoke is a complex mixture of chemicals with approximately 4,000 compounds including those that cross the placenta and may affect the fetus. Prenatal nicotine exposure, described as the most widespread prenatal drug insult in the world, is also one of the known preventable causes of low birth weight, prematurity, placental abruption, and miscarriage. Neonates born to mothers who smoke weigh an average of 150–250 g less than infants born to unexposed women. Neurotoxic effects of prenatal tobacco exposure on newborn neurobehavior have been noted 48 h after birth, with poorer self-regulation, and an increased need for external intervention as late as 27 days of age. Smoking in pregnancy is decreasing in high-income countries, increasing in low- to middle-income countries and is strongly associated with poverty, low educational attainment, poor social support, and psychological illness.

Those women who start smoking by 15 years of age are less likely to stop and report higher levels of nicotine dependence when compared to women who initiate smoking later in life. Furthermore, offspring of mothers who smoked a pack or more of cigarettes during pregnancy are at increased risk of developing nicotine dependence as an adult. Smoking cessation programs during pregnancy can reduce the proportion of women who continue to smoke in late pregnancy and reduce the incidence of low birth weight and preterm birth, stressing the value of early education on minimizing these untoward outcomes.

Alcohol Fetal alcohol spectrum disorder (FASD) is used as an umbrella term to describe the range of outcomes associated with all levels of prenatal alcohol exposure. Risk drinking during pregnancy (enough to potentially damage the fetus) has been defined as an average of more than one drink (0.5 oz) daily, or less if massed (binges of >5 drinks per episode). Adverse childhood behavioral outcomes have been noted after these exposures, leading the AAP and ACOG to recommend abstaining from alcohol during preconception and pregnancy. Testing for alcohol exposure is imprecise, and most clinicians rely on maternal history where underreporting is common. While there is no standard neonatal screen for alcohol exposure, identifying stable biologic markers of ethanol, such as fatty acid ethyl esters is being explored as a potential screening tool.

Infants with FASD have a characteristic facial dysmorphology (midface hypoplasia, long smooth philtrum, thin upper lip, small hyperteloric eyes, and inner epicanthal folds). They can be growth restricted and have relative microcephaly, ophthalmologic involvement, and over time neurodevelopmental, cognitive, and behavioral abnormalities. Making a diagnosis in the newborn period can be difficult, as features can be subtle, and often an accurate history is not obtained. Exposure to alcohol during pregnancy has been implicated as the most common cause of mental retardation and the leading preventable cause of birth defects in the United States, accounting for significant educational and public health expenditures. Substantially higher rates of FASD have been demonstrated among low socioeconomic and minority groups, with African American children more than five times as likely and American Indian/Alaskan Native children 16 times more likely than white children to exhibit FAS. Additionally, up to 50% of women of childbearing age consume alcohol and 15–20% acknowledge continuing to drink during pregnancy. Up to 1% of pregnant women drink at levels considered heavy, with such consumption more common among women 30 years or older, unmarried, and with low incomes. Routine use of a screening tool for alcohol consumption during pregnancy should be a part of every prenatal assessment.

Illicit Drugs

Toxicology Screening

Screening for illicit substance use begins with assessing the maternal history. The Committee on Substance Abuse of the AAP recommends obtaining a comprehensive medical and psychological history that includes specific information regarding maternal drug use. As this information is not always reliable, providers should develop a nonjudgmental set of criteria for when screening should be performed. Establishing substance exposure risk might include inadequate prenatal care, clinical concerns such as inappropriate behavior, disorientation, somnolence, or physical signs of substance use or withdrawal. If there is a known history within the past year of substance use, substance screening should be considered. Urine screening for the mother and urine and meconium screening for the infant are the typical specimens provided. While urine testing demonstrates recent exposure to drugs, meconium testing can ascertain remote exposure, as early as 12–13 weeks of gestation, when fetal swallowing begins. Because drugs can accumulate in the meconium from the second trimester until delivery, meconium testing affords a greater window of detection. Maternal and neonatal hair testing can detect prenatal drug exposure, as drugs of abuse are incorporated into the hair shaft at the time of formation of the follicle and can be subject to analysis. Hair sampling can be problematic given inadequate hair to sample in some infants, the fact that coarse black hair incorporates more of the drug than brown or blonde hair, requiring a differential scaling for hair color, and that parents may object to shaving the infant's hair. Testing of umbilical cord tissue with ELISA-based screening has been shown to detect fetal exposure to methamphetamine, opiates, cocaine, and cannabinoids. Unlike meconium sampling which can take days to collect, umbilical cord tissue is available immediately after delivery. It is important to know which substances are tested in the substance screen ordered, as this can vary from one screen to another. Furthermore some substances, such as buprenorphine, are not routinely identified in the standard screen, and require a separate order. Relying solely on the results of a toxicology screen to dictate care may underserve the neonate, as false negative results can occur if the exposure was early in pregnancy, or the urine sample was not obtained right after birth, or laboratory variability is not sensitive enough to pick up small amounts of drug. Each physician should also be familiar with local laws regarding screening, consenting, and reporting of prenatal substance exposure.

Opiates

In 2008, the United Nations Office of Drugs and Crime (UNODC) estimated that between 12.8 and 21.9 million people worldwide abused opioids, with the prevalence ranging between 0.3% and 0.5% of the global population aged 15–64. In a US prevalence survey of prenatal drug

exposure, 53,400 used heroin or nonprescribed opioid medications annually. There are two approaches to the opioid-dependent pregnant woman, namely, detoxification and maintenance therapy. While detoxification has been reported to be safe in select populations, the dropout rate can be as high as 50% with a relapse rate approaching 70%. Furthermore, the stabilization of the pattern of use of one drug may be associated with the misuse of other drugs. Because opioid withdrawal has been associated with morbidities including preterm labor, poor fetal growth, and fetal death, and because decades of research has demonstrated methadone's safety and effect on improving the outcome for both the mother and her fetus, many countries including the United States and Australia currently recommend methadone maintenance as the treatment of choice throughout pregnancy. To date, however, neither methadone nor buprenorphine are approved for use in pregnancy by the FDA, and remain listed as category C medications.

Methadone

Methadone, a full mu opioid receptor agonist, has been the most frequently studied medication during pregnancy, and has been available in the United States as an opioid maintenance medication since the 1970s. Interestingly, methadone treatment in Russia is illegal, as health officials are not convinced of the treatment's efficacy. Instead, doctors encourage immediate abstinence from drug use, rather than the gradual process of substitution therapy.

Methadone maintenance during pregnancy has both direct and indirect effects on the fetus. Pregnant women stabilized on methadone are more likely to seek prenatal care, and less likely to engage in injection related risk-taking and illicit behaviors. As the metabolism of methadone is increased with pregnancy resulting in a shortened half-life, particularly during the third trimester, women will frequently require an increase in maintenance dosing. This information should be made known to the pregnant women, as often, there is great resistance to dose adjustment.

Buprenorphine

Buprenorphine, a partial opioid agonist has been available in France since 1996, and approved for use in the United States in the nonpregnant adult population since 2002, and in the European Union since 2006. Unlike methadone, buprenorphine has a high affinity at the mu receptor, but a low activity. As such, when taken, it displaces the full opioid agonist from the receptor, but has limited activity, leading to a "ceiling effect" where if more drug is taken, no more opioid effect is realized. Given this difference in maximal opioid effect between full and partial opioid agonists, buprenorphine is not a replacement for all methadone clients, as, with higher methadone dosing requirements, replacing with buprenorphine could precipitate withdrawal. Buprenorphine is available as Subutex (buprenorphine alone) and Suboxone (buprenorphine + naloxone). Suboxone was developed in an effort to limit its appeal as a substance of abuse, as, if it is crushed and injected (normal route of administration is sublingual), the buprenorphine component will remain inactive and the naloxone activated, precipitating acute withdrawal. Subutex is the form of buprenorphine preferred in pregnancy so as to limit the fetus to naloxone exposure.

Abrupt cessation of buprenorphine has resulted in a milder withdrawal in the adult population when compared to methadone. Until recently comparative effects of methadone vs. buprenorphine during pregnancy and effects on the neonate were limited to case series and short studies, most of which had methodological flaws such as lack of blinding, small sample size, and concomitant additional drug use.

Neonatal Withdrawal

Between 55% and 94% of neonates born to women on maintenance, opioid therapy will experience neonatal abstinence syndrome (NAS). There are conflicting data regarding the effect of maternal dosing on the degree of neonatal withdrawal. Most studies do not support a clear relationship, and if the mother is taking other prescribed medications or using other illicit drugs, estimations about degree of neonatal withdrawal become speculative at best. While maternal dose of opioid may not clearly parallel degree of neonatal withdrawal, the type of opioid used during pregnancy may affect the neonatal course. Results from the MOTHER (Maternal Opioid Treatment: Human Experimental Research) trial, a double blind double dummy prospective randomized clinical trial, demonstrated that while the number of infants who required neonatal morphine did not differ between the methadone- and buprenorphine-exposed infants, the buprenorphine cohort required significantly less morphine to treat NAS and had a significantly shorter duration of hospitalization. These results suggest that for select patients, buprenorphine might be the optimal medication given its amelioration of NAS in the newborn when compared to the methadone exposed neonate.

NAS is characterized by central and autonomic nervous system irritability, gastrointestinal dysfunction, and some component of respiratory distress. Management often requires prolonged hospitalization due to pharmacologic intervention. Assessment of NAS is performed using a standardized scoring tool to allow for objective

data to guide care. The most frequently used scoring tool, developed by Finnegan, is a 31 item scale administered every 4 h. Alternative tools used include the Lipsitz Score, the Ostrea tool, the Neonatal Withdrawal Inventory, and the Neonatal Narcotic Index. Most centers utilize the Finnegan score or its variations, given its comprehensive nature and recommended treatment schedule. A limitation of the tool is that it was developed for the full-term infant during the neonatal period, and as such does not fully address the needs of the preterm neonate, nor the infant who requires hospitalization beyond the neonatal period.

Multiple medications have been described to treat neonatal withdrawal including morphine, diluted tincture of opium (DTO), methadone, phenobarbital, clonidine, diazepam, clorpromazine, and buprenorphine. Paregoric, a camphorated tincture of opium that contains many potentially toxic substances, such as anise oil, benzoic acid, camphor, and alcohol is no longer recommended. Opioid medications are felt to be the most effective agents in the treatment of neonatal opioid withdrawal, although a recent Cochrane review failed to find one opioid superior to another. Phenobarbital and clonidine have both been studied as adjuncts to DTO in the treatment of NAS, and found to be superior when compared to treatment with DTO alone. Infants who require medication should remain hospitalized given the fact that opioid medications are prescribed in very small doses and inadvertent administration of a larger dose could lead to serious respiratory depression. Furthermore, allowing a mother who has opioid dependency to take home a prescribed opiate medication could be a trigger for relapse which could place the infant at risk. Finally, infants undergoing withdrawal exhibit a spectrum of symptoms the management of which can change frequently and require repeated intervention, which cannot easily be provided in the home setting.

Medications to treat withdrawal are generally begun when environmental intervention alone is insufficient to relieve symptoms. The dose of the opiate is increased until scores are stabilized (less than 8 for the Finnegan scale) at which point the dose is maintained for 48 h before weaning is begun. Opiate weaning is usually offered once daily, or up to twice daily if the scores demonstrate minimal withdrawal (i.e., <4 on the Finnegan scale). The nature of withdrawal is such that some infants will require a reescalation of opiate medication once weaning has begun. Generally, reescalation doses are less than the initial escalating dose. Once the opioid medication is discontinued, an observation period for 24–48 h occurs to ensure that the infant remains comfortable without medication, at which point discharge can occur. If an additional medication has been used, such as phenobarbital, it is continued at the time of discharge, and weaned as an outpatient.

In addition to medication intervention, following adequate growth and nutrition is vital, as some infants will continue to lose weight despite adequate caloric intake, or fail to gain weight because of poor feeding. Intervention strategies include higher calorie formula or nasogastric feedings. Breast-feeding is compatible with opiate exposure, although care should be taken if breast-feeding is erratic or acutely stopped as withdrawal signs can worsen.

Long-term outcome for infants exposed to opiates in utero is compounded by the environmental stressors frequently encountered in this population. In addition, some studies compare the opiate-exposed newborn to a healthy control without similar environmental stressors. When controlling for confounding factors, Messinger et al. found no significant differences between opiate-exposed and non-drug-exposed infants at 1, 2 and 3 years of age.

Cocaine

According to the National Survey of Drug Use and Health (NSDUH), of the 3.3% of women who used illicit drugs during pregnancy, 10% used cocaine. From the mid-1980s into the early 1990s, observations were made describing fetal teratogenic and toxic effects of cocaine. The maternal lifestyle study (MLS), a large multisite, prospective, randomized investigation was conducted to confirm or negate the hypothesis that fetal cocaine exposure during pregnancy has no impact on maternal and infant outcomes. Unlike previous studies that noted an increased risk of congenital anomalies, this was not supported by the MLS. While human studies conflict in terms of an association between cocaine exposure and cardiovascular changes, animal studies demonstrate that fetal cocaine exposure results in changes on the cellular and genetic level that may not manifest as neonatal gross cardiac problems, but result in an increase risk of heart disease over time. The possibility that fetal cocaine exposure could affect cardiac programming warrants continued investigation as this exposed population ages.

Growth restriction, prematurity, and increased central and autonomic nervous system dysfunction have been noted with cocaine exposure. In the MLS study, the cocaine-exposed infants were more tremulous, had a higher pitched cry, irritability, excessive suck, and hyperalertness during the first days of life. Because the neurobehavioral symptoms can occur before the half-life of the drug, there is reason to believe that these symptoms

are a reflection of cocaine toxicity rather than withdrawal. While these symptoms warrant close observation, rarely do they require pharmacologic management. At 1 month of age, subtle effects of cocaine persist and may be dependent on degree of exposure. Higher excitability has been seen in heavy cocaine exposure, while lower arousal scores are noted in neonates exposed to lesser amounts of cocaine, suggesting that there may be a dichotomous presentation based on degree of exposure. Similarly, long-term developmental outcomes, often confounded by multiple exposures and environmental risk, appear to be related to degree of cocaine exposure. When controlling for confounding factors, it appears that deficits in language, cognition, and motor skills parallel the degree of cocaine exposure, namely, the greater the exposure, the greater the deficit.

Methamphetamines

Methamphetamine is a highly addictive central nervous system stimulant, and the most potent member of the amphetamine group of synthetic drugs. Since 1992, methamphetamine use in pregnant US teenagers has more than quadrupled. While it was the primary substance of abuse in 4.3% of treated pregnant teens in 1992, by 2007 that number had risen to 18.8%. In New Zealand, referrals for methamphetamine use to the Alcohol Drug and Pregnancy Team (ADAPT) program increased from 10% of total referrals in 2001 to 59% in 2003.

While the pharmacologic properties of methamphetamines are similar to cocaine, methamphetamine has a longer half-life and greater sympathomimetic effects, which can result in vasoconstriction. The few human studies published concerning methamphetamine use in pregnancy have demonstrated an increased risk of preterm delivery, placental abruption, fetal growth restriction, and heart and brain abnormalities. However, these investigations have methodological flaws including small sample size, lack of a comparison group, and the confounding effect of multiple drug exposures. In the IDEAL (The Infant Development, Environment, and Lifestyle) study, a prospective longitudinal investigation that evaluated the effects of prenatal methamphetamine exposure on the newborn, there was an increased incidence of small for gestational age (SGA) and lower birth weight infants suggesting a direct methamphetamine-induced growth restrictive effect on the developing fetus. Neurobehavioral testing with the NNNS (NICU Network Neurobehavioral Scale) demonstrated decreased arousal, increased stress, and poor quality of movement. These results were affected by time of exposure as well as degree of use.

Like with many drugs, the environment of methamphetamine users is often characterized by chaos, neglect, abuse, and criminal activity, all of which can affect the outcome for the exposed child. In addition, these children face acute health and safety hazards from fires, explosions or toxic chemicals if exposed to a home methamphetamine lab. What little research is available regarding long-term effects of prenatal amphetamine exposure suggests that at birth, 1 and 4 years of age, mean weight, height, and head circumference are below the mean for their peers. In addition, there is a suggestion of a link between exposure and aggressive behavior, peer problems, and hyperactivity. These results are limited due to a lack of a matched comparison group, and the effect of other drug exposures. Additional work has suggested that prenatal methamphetamine exposure influences the development of the verbal memory system, long-term spatial memory, and visual motor integration. Confirmatory investigations in a prospective, controlled manner are vital so as to avoid drawing conclusions based on limited data as was the case with the early cocaine literature.

Marijuana

Marijuana is the most frequently used illicit drug among women of childbearing age in the US. Of the 3.3% of women who used illicit drugs noted in the 2002 SAMHSA report, 80% used marijuana. Marijuana abuse among pregnant teenagers has more than doubled from 1992 to 2007, accounting for 45.9% of the primary substance of abuse. The principal psychoactive component of marijuana is delta-9-tetrahydrocannabinol (THC), which rapidly crosses the placenta and can remain in the body for 30 days. Depending on frequency of use, cannabis can be detected in the urine between 2 and 4 days for infrequent users and up to 1 month for heavy chronic users. THC is secreted into the breast milk.

While infrequent marijuana use (less than once/weekly) is not associated with decreased birth weight, in a meta-analysis, a 131-g decrease in birth weight was noted in infants born to mothers who used marijuana >4 times weekly. Regular exposure to marijuana (six or more times weekly) has been associated with withdrawal-like symptoms, namely, excessive crying and tremors, as well as difficulty with state regulation. At school age, children exposed prenatally to marijuana have decreased impulse control and attention especially regarding problem solving, hypothesis testing, and planning, as well as poorer visual-spatial ability. Marijuana should not be considered a benign drug. Prevention programs aimed at adolescent pregnancy to address parenting skills, at risk behaviors, and comorbidities that lead to drug use should be incorporated into the reproductive health visit for the young adolescent teen.

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35 Common Procedures in Neonatology

Jayashree Ramasethu

The medical care of increasingly smaller and sicker newborn infants in the past century has been made possible by innovations in technology, but has not obviated the need for invasive procedures in the neonatal intensive care unit (NICU). In order to reduce iatrogenic morbidity, healthcare providers performing the procedures must be familiar with the indications, contraindications, and potential complications, and use appropriate equipment and precautions. The procedures should be performed or closely supervised by personnel with the necessary expertise. Documentation of the procedure in the records is important for patient care and is a medicolegal requirement in most institutions. The length of insertion of catheters and endotracheal tubes should be recorded for monitoring purposes, and details of problems encountered during the performance of a procedure may help if the procedure has to be repeated for any reason.

Informed Consent

Routine medical care is covered by the "general informed consent" obtained on admission of a patient, but the definition of "routine" varies from institution to institution and between NICUs. Consent is implied for certain procedures, such as intubation for respiratory support, obtaining blood samples, and venous access, when an infant is admitted to a NICU. It is judicious to obtain specific informed consent for invasive procedures from the parents or legal guardians whenever possible, unless a life-threatening emergency dictates immediate action. Consent should be obtained after a discussion of indications, important risks and benefits, and alternatives, if any, to the procedure and documented in the patient's records. While it is important to provide adequate information, too much information on every potential and rare complication may overwhelm and paralyze parents into being unable to make a decision and ultimately be detrimental to the patient.

Analgesia and Homeostasis

Adequate lighting and access to the infant are essential to allow procedures to be completed expeditiously. Nevertheless, every effort should be made to maintain homeostasis in infants undergoing procedures. Continuous cardiorespiratory monitoring is prudent to ensure stability, particularly if narcotic analgesics or sedatives are administered. Appropriate temperature and light control, calming touch and swaddling, kangaroo mother care and breast feeding all play a part in reducing stress. Sterile sucrose solution (12–50% concentration) on a pacifier is an effective analgesic for some procedures. Topical anesthetics such as lidocaine-prilocaine cream or tetracaine gel require application to the skin for 30–60 min under an occlusive dressing. They are appropriate for circumcisions but have not been shown to be effective in reducing the physiological responses associated with procedures such as peripheral IV cannulation or lumbar punctures in neonates. Local injection of 1% lidocaine is also effective for circumcisions, and has been shown to reduce traumatic lumbar punctures in children. Intravenous narcotic analgesics such as fentanyl or morphine are recommended for intubation or chest tube insertion.

Aseptic Preparation

Invasive procedures breach intact skin, a vital barrier to infection in neonates. Aseptic preparation for procedures includes the preparation of the personnel for the procedure, preparation of the patient's skin, and use of clean or sterile equipment as appropriate. Hand hygiene is the single most important intervention to prevent nosocomial infection. Hands should be decontaminated before and after any direct patient contact and before wearing sterile gowns or gloves to perform procedures. Current evidence indicates that alcohol-based rubs used for hand antisepsis in preparation for surgery are equally or more effective than aqueous scrubs. Chlorhexidine-based aqueous scrubs are more effective than povidone iodine-based aqueous scrubs in terms of the number of colony forming units on the hands. In neonates, the use of antiseptics is limited by the thinness of the stratum corneum and the possibility of absorption and toxicity. Hexachlorophene is not used in neonates because of its potential for transcutaneous absorption and central nervous system toxicity in

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infants. Alcohol (70–90%) is adequate for minor procedures such as peripheral IV catheter placement, since it is bactericidal, dries rapidly, and acts quickly. Iodophors and chlorhexidine have a longer duration of action. Iodine containing antiseptics may be absorbed through the skin and have the potential to suppress thyroid gland function in preterm infants. Although chlorhexidine gluconate in isopropyl alcohol has been found to provide persistent antimicrobial activity and reduces the rate of catheter-related bacteremia, it has the potential to cause burns in very immature infants. It is best to remove excess antiseptic from the procedure site by wiping with sterile water as soon as the procedure is completed. Masks, drapes, and gowns are important barriers to microorganisms shed into the air from skin and mucous membranes.

Preparation for procedures such as central venous or umbilical catheterization or chest tube insertion should be as rigorous as preparation for a major surgical procedure, with appropriate hand hygiene, wearing of sterile gowns and gloves, skin preparation, and draping of the "surgical" site. In extreme emergencies, such as pericardial tamponade or tension pneumothorax with severe hemodynamic compromise, the operator may be forced to omit certain steps in the interest of time. The aseptic preparation in these circumstances may simply be hurriedly swabbing the area with antiseptic or pouring antiseptic solution on the skin before using a needle and syringe to evacuate the air or fluid.

Capillary Heelstick Blood Sampling

Capillary blood sampling is the most common procedure performed on newborn infants. It is a simple technique to collect small volumes of blood. The advantage of capillary sampling is that repeated testing may be carried out, and peripheral veins may be saved for intravenous access. The preferred areas for sampling are the outer aspects of the heel (*Fig. 35.1*), avoiding the posterior aspect of the heel, which is close to the calcaneum. The skin to calcaneal perichondrium is at least 3 mm in most term babies and in 91% of babies at 33–37 weeks gestation; so the plantar surface of the heel may be used if the lateral aspects of the heel are compromised by previous repeated tests.

Equipment

Automated heel lancing devices, which have encased, sharp, spring-loaded, retractable blades provide a controlled and consistent width and depth of incision for blood testing. The incision depth/width ranges from 0.65/1.4 mm for babies weighing less than 1,000 g, to 1.0/2.5 mm for term infants. Manual stylets are not recommended for use in babies since the depth of incision cannot be controlled. Additional supplies required are a warm towel or heel warmer, heparinized capillary tubes for blood gas measurements, blood collection microtubes, antiseptic solution or wipes, and a small adhesive bandage.

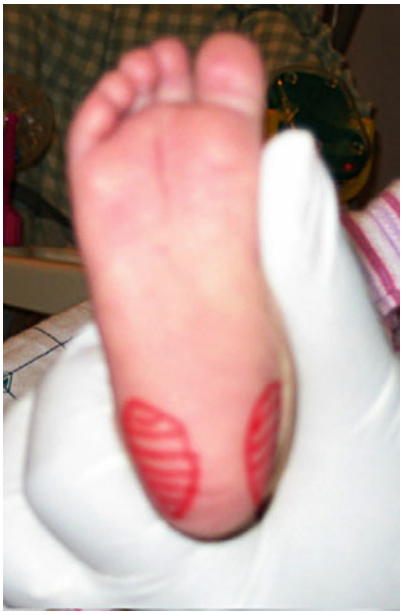

Figure 35.1
Recommended sites for capillary heelstick blood sampling in neonates

Procedure

Warm the heel by wrapping it in a warm towel or heel warmer for a few minutes just before the procedure. Swaddle the baby and provide non-pharmacologic pain control measures. Wash hands, wear gloves, and cleanse the site with antiseptic solution, followed by alcohol or sterile saline, and allow to air dry. Place automated heel lancing device on selected site and activate. Wipe away the first drop of blood with gauze and then collect samples required into capillary tube or blood collection microtubes. The calf may be squeezed gently intermittently to increase blood flow until all samples are obtained. Apply pressure to the puncture site to stop further bleeding and apply small adhesive bandage.

Complications

Hyperalgesia, cellulitis, abscess formation, perichondritis, osteomyelitis, and calcified nodules have all been described following heel stick sampling.

Peripheral Intravenous Cannulation

Intravenous cannulation of peripheral veins is most often performed for administration of fluids, medications, and for transfusion of blood products. The larger antecubital veins are preferred for venous blood sampling, particularly if volumes of 1 ml or more are required, since the smaller veins tend to collapse with the negative pressure exerted by the syringe when aspirating blood. A butterfly needle with most of the extension tubing cut off, leaving a 3–4 cm remnant, is useful to collect small samples of blood from the dorsum of the hand by the drip method. The veins useful for fluid administration are the dorsal venous plexus on the back of the hand, median antecubital vein or accessory cephalic vein on the forearm, basilic or cephalic vein in the antecubital fossa, or saphenous veins of the foot. The veins of the scalp may be used if none other is available. In critically ill neonates, it is judicious to reserve the veins in the antecubital fossa or the greater saphenous vein for potential percutaneous central venous catheterization.

Equipment

A variety of IV catheters made of polyethylene, polyvinylchloride, polyurethane, or Teflon ranging in size from 20 to 24 gauge and in length from 2 to 3 cm is available for use in neonates. In addition, a T-connector attached to a 3-ml syringe with sterile normal saline, transparent dressing, or adhesive tape for securing the cannula, additional adhesive tape for securing the arm or foot, and appropriate-sized arm board for restraint are required. A tourniquet and transilluminator are optional.

Procedure

Wash hands and wear gloves. Select an appropriate vein for cannulation. Apply a tourniquet proximal to the insertion site (optional). Prepare the selected area with antiseptic and allow drying for 30 s. Hold the limb with the nondominant hand, stretching the skin to immobilize the vein, and using the index finger and thumb as a tourniquet to distend the vein if a tourniquet is not used. Holding the catheter in the dominant hand, insert the needle into the skin a few millimeters distal to the point of entry into the vessel, at about a 30° angle (as in *Fig. 35.2*) and then maneuver it into the vessel in the same direction as the blood flow. When blood is visible in the cannula, withdraw the stylet and advance the cannula further into the vein, at a lower angle of 10–15°. Remove the tourniquet. Connect the T-connector to the hub of the cannula and flush 0.5–1 ml of normal saline to ensure that the cannula is within the vessel. Secure the cannula hub to the skin with adhesive tape or transparent dressing. Secure the limb to a board in an anatomically comfortable position, ensuring that all fingers and toes are visible and not constricted before taping. Attach the IV tubing to begin fluid administration.

Complications

Bruising and small hematomas are common if the procedure is unsuccessful. Extravasation or inadvertent infiltration of fluids into subcutaneous tissue from peripheral intravenous (IV) catheters is a frequent adverse event in neonates with complications ranging from minor transient swelling to loss of tissue and severe scarring, with resultant cosmetic or functional impairment. The recognition and management of extravasations has been addressed in several reviews.

Peripheral Artery Sampling or Cannulation

The radial, ulnar, posterior tibial, and dorsalis pedis arteries may be used for blood sampling or cannulated with

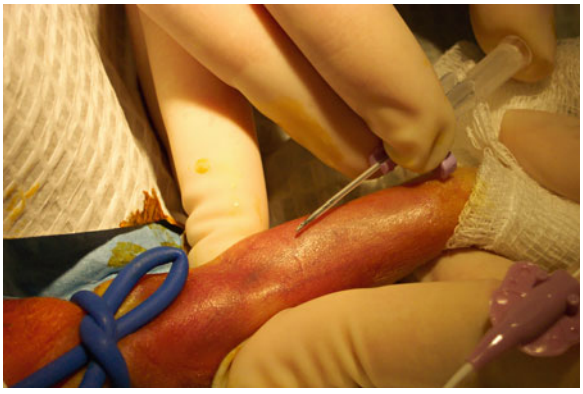

Figure 35.2
Introducer cannula with stylet for venipuncture prior to insertion of peripherally inserted central catheter (PICC)

indwelling venous cannulas for continuous blood pressure monitoring and for repeated blood sampling. Peripheral arterial catheters should be used only for blood sampling and continuous arterial blood pressure monitoring. No fluids other than heparinized saline should be administered through them and the rate of infusion should not exceed 2 ml/h.

Although the brachial and axillary arteries are easily accessible, catheterization of these vessels is not recommended because of the risk of vascular compromise to the arm. Catheterization of the temporal artery may be associated with neurological sequelae. The radial artery is preferred since the predominant blood supply to the hand is usually from the ulnar artery, but there are multiple variations in arterial vasculature. The modified Allen test has long been advocated to assess adequacy of the collateral circulation of the hand prior to radial artery catheterization, but the test is inaccurate and suffers from poor interobserver reliability. The radial artery is located at the proximal wrist crease by palpation or transillumination with the wrist supine and slightly extended. In extremely preterm infants, the vessel is superficial and often visible to the naked eye. In some infants, the ulnar artery is more easily located at the wrist than the radial artery. The posterior tibial artery is posterior to the medial malleolus with the foot in dorsiflexion. The dorsalis pedis is located in the dorsal midfoot between the first and second toes, but this artery is generally the last choice, since it may be very small or absent in some patients or may provide the main blood supply to the toes in others.

Equipment

Equipment for peripheral arterial blood sampling consists of sterile gloves, antiseptic solution, 23 or 25 gauge venipuncture (butterfly) needle with extension tubing, appropriate syringes, and blood collection tubes. Equipment for peripheral artery cannulation consists of sterile gloves, antiseptic solution, 22 or 24 gauge cannulas with stylets, T-connector with stopcock attached to 3-ml syringe flushed through with heparinized saline, sterile adhesive strips, materials for restraint of the arm or foot (arm board, adhesive tape, gauze pads, or cotton balls) arterial pressure transducer with extension tubing prepared with 0.5 N or Normal saline with 1 unit of heparin/ml, and continuous infusion pump capable of delivering 0.5–1 ml of fluid per hour. The importance of having the arterial pressure transducer and the continuous infusion pump ready before starting the cannulation cannot be overemphasized. The arteries are of very small caliber and need a continuous infusion of heparinized saline as soon as they are cannulated to remain patent.

Procedure

Arterial catheterization should be performed with sterile technique, preparing the area with antiseptic and using sterile gloves and equipment. For radial arterial sampling, puncture the skin just distal to the proximal skin crease with a butterfly needle and penetrate the artery at a 30–45° angle with the bevel of the needle facing upward (*Fig. 35.3*). Apply gentle suction on the syringe as soon as blood flow is observed. Maintain the needle in the same position until all blood samples have been collected. If no blood flow is obtained, or the blood flow ceases, the depth of penetration or the angle of the needle may have to be adjusted. After the needle is removed, apply direct pressure on the site for at least 2 min to secure hemostasis and inspect the fingers for circulatory compromise.

The procedure for peripheral arterial cannulation is similar. The artery is cannulated with an appropriate-sized cannula with stylet, instead of the butterfly needle. As soon as blood return is noted, decrease the angle to about 15° and advance the cannula forward up to the hub while withdrawing the needle (stylet), ensuring that the blood is continuing to flow. Inability to advance the catheter or the development of a hematoma at the insertion site usually means that the cannula/stylet has penetrated the dorsal or lateral wall of the vessel. The situation may be salvaged at times by withdrawing the cannula slightly and redirecting it. Attach a T-connector flushed with

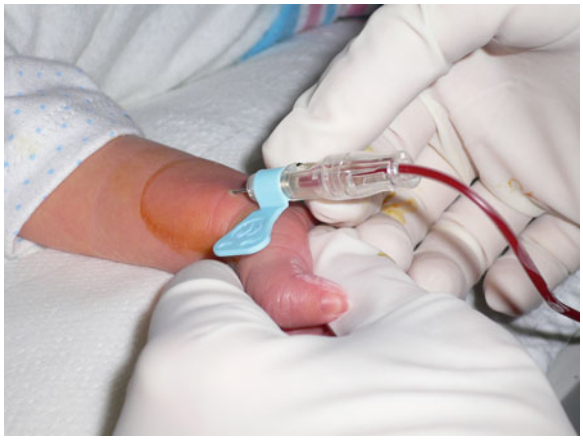

Figure 35.3
Radial arterial blood sampling using butterfly needle

heparinized saline to the hub of the cannula, aspirate to check for blood return, and then flush 0.5–1 ml of saline through gently. Use transparent semipermeable dressing or adhesive tape to secure the cannula in place, and restrain the hand and wrist on an arm board with adhesive tape, in a physiological position, making sure that *all* fingers are visible at *all* times for visual inspection. The T-connector must be attached immediately to extension tubing and pump with a constant infusion of 0.5–1 ml/h of heparinized saline to maintain patency of the catheter. The arterial pressure transducer may be connected for constant pressure monitoring.

Complications

Although there are multiple case reports of ischemic injury, and there are very limited data in extremely low birth weight infants, the overall risk of ischemic injury secondary to radial or ulnar artery catheterization appears to be approximately 5%. Peripheral ischemia may be immediately recognized as cyanosis or pallor of the fingers and the cannula removed to avoid gangrene and permanent loss of the digits. Topical nitroglycerine has been found to be effective in restoring perfusion in a few cases where radial artery catheterization has resulted in cold, cyanotic, and stiff hands with absent radial pulses.

Nonischemic complications of arterial catheterization or even repeated attempts at catheterization include bleeding, pseudo aneurysms, arteriovenous fistulae, median nerve palsy, carpal tunnel syndrome, and injury to the tendon sheaths.

Umbilical Arterial and Venous Catheterization

Catheterization of the umbilical vessels soon after birth provides immediate vascular access in critically ill infants. Umbilical arterial catheterization is vital for continuous blood pressure monitoring, and for blood sampling for arterial blood gases, biochemical and hematological testing. Umbilical venous catheterization provides stable intravenous access for infusion of parenteral nutrition, medications, and for exchange transfusions.

The umbilical arterial catheter (UAC) passes from the umbilical artery into the internal iliac and then the common iliac artery, into the descending aorta. The recommended placement of an UAC is such that the tip is located between vertebral bodies T6 and T9 or T10

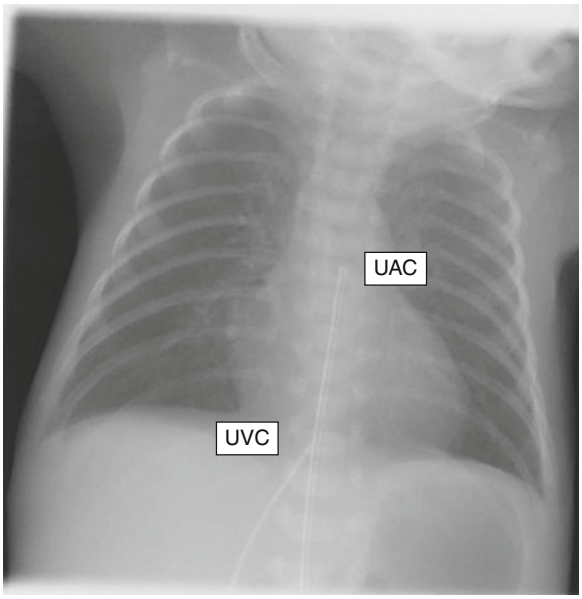

Figure 35.4
CXR showing appropriate location of tip of umbilical arterial catheter (UAC) and umbilical venous catheter (UVC)

(*Fig. 35.4*). The alternate location, "low aortic placement," below the level of the renal arteries and above the aortic bifurcation (vertebral bodies L3–4 on the X-ray) has been associated with increased risk of vascular complications. The UVC passes through the umbilical vein into the left branch of the portal vein, through the ductus venosus into the inferior vena cava (IVC). The tip is generally located at the junction of the IVC and the right atrium (*Fig. 35.4*). In an emergency situation, such as during resuscitation at birth, when immediate venous access is required, the UVC may be advanced to only a few centimeters into the umbilical vein, aspirated to ensure blood return and then used for administration of saline, dextrose, or epinephrine, without radiological confirmation of placement.

Prior to placement of the UAC or UVC, the length to which the catheter should be inserted to obtain proper placement should be estimated using standard formulae or published nomograms. The Shukla–Ferrara calculation (UAC length in cm = 3 × birth weight in kg+9; UVC length in cm = ½ × UA length calculation+1) is appropriate for most large babies, but has been found to overestimate catheter insertion length in very low birth weight (VLBW) infants. The modified formula of 4 × birth weight in kg +7 has been found to be more appropriate for UAC placement in VLBW infants.

Equipment

Sterile equipment for umbilical catheterization consists of gown and gloves, surgical drapes, cup with antiseptic solution, 4 × 4 in. gauze sponges, forceps to hold sponges, narrow umbilical tape tie, No.11 scalpel blade with holder, two curved mosquito hemostats, non-toothed iris forceps, small needle holder, 4–0 silk suture on small curved needle, suture scissors, 10-ml syringes, three-way stopcocks with Luer-Locks, 0.5 N or Normal saline flush solution (with 1 unit of heparin/ml of fluid), and the appropriate-sized catheters. Umbilical catheters may be made of polyvinyl chloride, polyurethane, or silicone. All have smooth non-thrombogenic ends, end holes, measurement markings, and are radiopaque. The use of feeding tubes as umbilical catheters is not recommended because they have side holes and are more thrombogenic. Single lumen catheters of 2.8 or 3.5 French (Fr) are used for UACs in babies weighing less than 1,200 g, and 5 Fr size catheters for larger infants. Single- or double-lumen catheters ranging in size from 2.8 to 8 Fr, depending upon the size of the infant may be used for UVCs. Single lumen catheters are recommended for exchange transfusions.

Procedure

The baby's limbs should be restrained to prevent contamination of the sterile area, but sedation or analgesia is not required. Standard aseptic precautions should be observed for placement of catheters, and sterile gowns and gloves are required. Hyperoxia causes potent constriction of the umbilical artery; therefore, weaning FiO_2 as appropriate to achieve saturation in the low normal range may facilitate UAC insertion.

Prepare the umbilical catheters by attaching a three-way stopcock to each catheter and flushing it with sterile-heparinized saline, making sure all air bubbles are removed. Clean the umbilical stump and the area around it with povidone iodine. Place a 10–15-cm piece of sterile umbilical tie tape around the umbilical stump loosely with a single knot. The knot may be quickly tightened to prevent blood loss if there is excessive bleeding when the umbilical cord is cut. Cut the umbilical cord horizontally with a scalpel blade approximately 1 cm from the skin surface. The umbilical arteries will be visible as two thick-walled, slightly protuberant vessels, while the umbilical vein appears larger, thin walled, and more patulous. Apply the two curved mosquito hemostats to the Wharton's jelly, on opposite sides of the cord, to stabilize the area (optional). Using the toothed forceps to grasp the stump, gently insert the tips of the curved iris forceps into the lumen of one of the umbilical arteries, initially keeping the points of the forceps together. Then allow the points to spring apart and maintain the forceps in this position for 15–30 s to dilate the artery. Grasp the saline-filled UAC about 1 cm from the tip, using non-toothed forceps, and insert the tip into the lumen of the artery between the prongs of the iris forceps, and advance it into the vessel with steady, firm pressure. The iris forceps may be removed once the catheter is inserted to a depth of 2–3 cm. It may be possible to pass the UAC into the artery without dilation in larger infants. Continue to advance the catheter into the vessel, 2–4 mm at a time, using non-toothed forceps, until the predetermined length has been reached. Mild traction of the cord toward the head of the infant will allow the UAC to navigate the slight angle between the cord and the abdominal wall. It should be possible to aspirate blood from the catheter after insertion of about 5–10 cm, to check its intraluminal position, but the blood should be cleared from the catheter by gently flushing 0.5–1 ml of heparinized saline intermittently, while the catheter is being advanced further to its final site. The UAC may be secured by a purse string suture through the Wharton's jelly, around the base of the cord, avoiding the vessels or the skin, after which the catheter itself is looped and taped to the abdomen with transparent semipermeable dressing. Other methods of securing the UAC are to enclose it within a tape bridge, or to suture a piece of tape attached to the catheter to the purse string suture. It is important to monitor the perfusion of the lower extremities immediately after the procedure and regularly thereafter while the UAC is in place (see "Complications").

Insertion of the UVC is often easier than inserting the UAC. The vessel walls are flaccid and dilation with iris forceps is not required. The iris forceps may be required to remove clots within the lumen. The saline-filled catheter is advanced gently into the vessel to the predetermined length and then sutured into position after ensuring that good blood return is obtained on aspirating the syringe attached to the catheter. Obstruction to easy passage of the catheter often implies that the catheter has wedged itself into an intrahepatic branch of the portal vein. The catheter may be withdrawn by 2–3 cm and reinsertion attempted. Occasionally a catheter in the portal circulation may be bypassed by the placement of another catheter in the same vessel with a 50% success rate.

Final placement of the UAC and UVC should be confirmed radiographically (*Fig. 35.4*) or by ultrasound scans.

Complications

The most serious complications of UACs are malposition, vascular spasm, and thromboembolic disease. Malpositions of the UAC into the femoral, gluteal, renal arteries, and into the celiac plexus have been noted, with severe complications in some cases. Numerous cases of gluteoperineal necrosis associated with sciatic nerve palsy secondary to thrombosis of the inferior gluteal artery have been recorded, some even when the catheter has been in an appropriate position and infused only with heparinized saline. Similarly, cases of acute and irreversible paraplegia following umbilical arterial catheterization have been attributed to infarction of the spinal cord following vasospasm or thromboembolic phenomena involving the artery of Adamkievicz, which supplies the anterior spinal artery. UACs may be associated with thromboembolic complications involving the aorta, iliac, renal, and mesenteric or other vessels. Symptoms of arterial TE include pallor or coldness of the lower extremities with diminished or absent pulses, and systemic hypertension, with or without renal failure if the renal arteries are affected. In a large systematic study of UAC-associated thrombosis, abdominal aortic thrombi have been detected by 2-D abdominal sonography in 32% of 99 patients in one study, which estimated that the risk of an aortic thrombus secondary to a UAC increased progressively from 16% after 1 day to 78% at 21 days. When vascular complications are noted, the catheter should be removed immediately.

Complications of umbilical venous catheterization are similar to that of peripheral central venous catheterization (described below). Portal vein thrombosis secondary to umbilical venous catheterization is a common cause of portal hypertension in childhood, and is more common in those with inappropriately placed umbilical venous catheters or with severe grades of thrombosis.

Percutaneous Central Venous Catheterization

Peripherally inserted central catheters (PICCs) are long, soft, flexible catheters made of silicone, polyurethane, polyethylene, or polyvinylchloride, inserted into a peripheral vein through a special breakaway or peel-away introducer needle and threaded into larger central veins. The advent of PICCs has significantly reduced the need for surgical placement of venous catheters in neonates. The peripheral veins usually used for placement of PICCs are the cephalic, basilic, median cubital, or axillary veins in the upper extremity, the saphenous vein in the lower extremity, and a scalp vein or external jugular vein in the head and neck. The tip of the PICC is typically positioned in the inferior vena cava (IVC) or superior vena cava (SVC), close to the heart (*Fig. 35.5*), to facilitate rapid hemodilution of the infusate. There is general consensus that the catheter tip should not be within the heart, because of the risk of pericardial effusions.

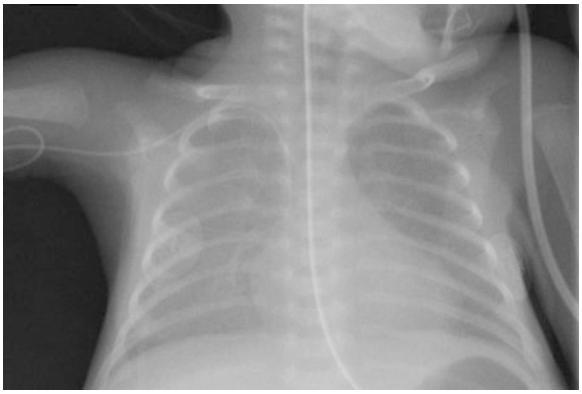

Figure 35.5
CXR showing tip of peripherally inserted central catheter (PICC) at junction of superior vena cava and right atrium

PICCs are placed in neonates primarily to provide stable intravenous access for parenteral alimentation, or for administration of medications or hyperosmolar fluids and medications that cannot be administered through peripheral IV cannulas. PICCs are not usually used for routine blood sampling or for blood transfusions in neonates because of their smaller caliber and propensity to clot.

Equipment

Commercially available PICC catheters used in neonates range in size from 1.2 to 3 Fr, and are usually single lumen, although a double-lumen version is now available. PICC introducer needles are available in 19, 20, 22, and 24 gauge with the size of the baby dictating the size of the introducer needle and the catheter. All equipment used, except for the head cover, mask, and tape measure, must be sterile. Many commercial kits contain the necessary equipment: catheter, introducer needle, 5–10-ml syringe with heparinized saline, forceps, gauze pads, antiseptic solution for skin preparation, transparent dressing, sterile tape strips, sterile surgical gown, gloves, and drapes.

Procedure

Restrain the infant by appropriate swaddling and provide non-pharmacologic comfort measures such as sucrose solution on a pacifier or a small dose of sedative or narcotic analgesic. Position the baby to facilitate a sterile field for insertion of the catheter, and using surface landmarks and tracing the approximate course of the vein, measure the distance from the insertion site to the point where the catheter tip will be placed. For catheters placed in the upper extremities or head and neck, the surface landmark for the SVC close to the heart is approximately at the second right intercostal space close to the sternum. For catheters placed in the lower extremity, the surface landmark for tip placement in the IVC would be at the infrasternal notch.

Wear the mask and cap, and then scrub hands thoroughly with antibacterial soap or alcohol-based scrub solution, and wear the sterile gown and gloves. Prepare the catheter by flushing it with sterile-heparinized saline using a 3- or 5-ml syringe. Smaller (1 ml) syringes may generate too much pressure, and are not recommended. Prepare the selected insertion site and the surrounding area with antiseptic solution. In small infants, it may be easier to swab the whole limb with sterile antiseptic than to prepare a small area. Drape the baby with sterile drapes leaving the insertion site exposed. A tourniquet may be applied on the limb proximal to the vein, if required.

Insert the introducer needle with the bevel up, about a centimeter distal to the insertion site at an angle of 15–30° and advance it into the vein (*Fig. 35.2*). As soon as a flashback of blood is obtained, decrease the angle, and advance the needle a few millimeters further to ensure that the entire bevel of the needle is within the vein. If an introducer cannula with a stylet is used, the same technique is used, but the stylet is removed as soon as the introducer cannula is well within the vein. Do not reintroduce the stylet into the introducer sheath if the venipuncture is unsuccessful. This could result in a severed sheath, which would be difficult to extract. If a tourniquet is used, it should be removed at this stage. Successful venipuncture is indicated by the steady flow of blood from the end of the needle or cannula. Gentle pressure over the insertion site can help to control bleeding.

Using fine non-toothed forceps, grasp the PICC about a centimeter from its end and insert it into the hub of the introducer needle/cannula, and then continue to nudge it along, a few millimeters at a time (*Fig. 35.6*). Do not advance the introducer needle or pull back to retract the catheter while it is in the introducer needle – it could result in shearing of the PICC, leaving a portion within the vein. When the PICC has advanced to a distance of 6 or 7 cm (or well beyond the length of the introducer), stabilize the catheter in the vein by applying digital pressure to the vein 2–3 cm distal to the introducer, withdraw the introducer needle or sheath carefully, and remove it by splitting or peeling the wings apart and away from the catheter. Complete catheter advancement to the premeasured length by nudging it further, a few millimeters at a time. Aspirate to check for easy blood return and flush with heparinized saline to clear the catheter. Verify the length of the catheter inserted and adjust if necessary. Apply gentle pressure with a sterile gauze pad at the insertion site to control any bleeding. Secure the catheter at the insertion site with a sterile tape strip. It is ideal to obtain radiographic confirmation of the position of the PICC tip before dressing the site so that adjustments may be made while the sterile field of operation is maintained. If the catheter has not been trimmed, the excess length may be coiled close to the insertion site and secured to the skin with sterile tape, ensuring that there is no kinking or stretching of the catheter under the tape (*Fig. 35.7*). Remove antimicrobial prep solution from the skin with sterile water or saline and dry before dressing the site with a semipermeable transparent dressing. Start fluid infusion through the catheter immediately after confirming appropriate placement.

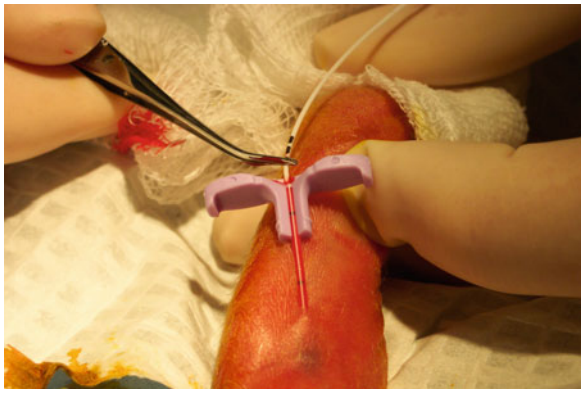

Figure 35.6
Threading PICC through the introducer sheath after removal of the needle

The care and maintenance of PICCs requires significant commitment for continued use and prevention of serious complications. Quality indicators such as infection rates, dwell times, and complications should be closely monitored. Dedicated PICC teams of doctors and nurses to insert PICCs and monitor adherence to policies and procedures help to reduce complication rates.

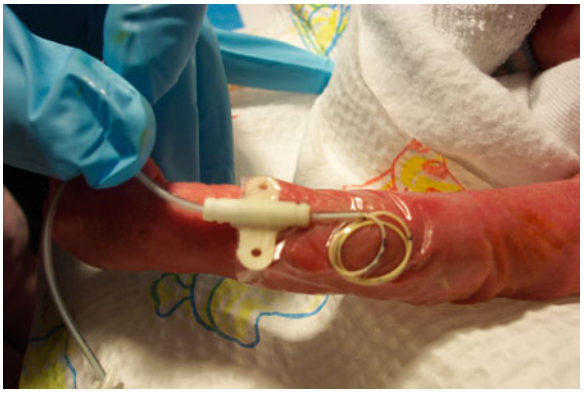

Figure 35.7
Excess PICC coiled and secured with sterile transparent dressing

The insertion site and dressing should be inspected daily and the dressing changed as needed. Transparent dressings should be changed every 7 days except in those patients where the risk of dislodging the catheter outweighs the benefit of changing the dressing. Sterile technique must be used for each dressing change. Aseptic technique is used for line changes, connecting medications, IV fluids. A continuous infusion of intravenous fluids of at least 1 ml/h is required to maintain patency for neonatal PICCs, with maximal flows dependent on catheter size and the manufacturer's recommendations. The addition of heparin (0.5–1 unit of heparin/ml of IV fluids) does appear to prevent occlusion of the catheter, but has not been shown to prevent thrombosis.

PICCs should be removed as soon as they are no longer medically necessary by gentle traction on the catheter at the insertion site after cleaning the area with antiseptic solution. There may be difficulty in removal of the catheter if a fibrin sheath has formed around it. The length of catheter removed must be crosschecked with the length that was originally inserted to ensure that no segment of the catheter has been left behind.

Complications

The major complications from PICCs (and from UVCs) are catheter migration or malposition, extravasation, infection, thromboembolism, catheter breakage, and dysfunction.

The tip of the catheter may inadvertently reach deep inside the cardiac chambers or fall short of the caval veins and end in the brachiocephalic or subclavian vein, or migrate through venous tributaries to entirely unexpected locations. Appropriate initial placement does not always ensure that the catheter will stay in place, since secondary catheter migration has also been described, possibly as a consequence of poor catheter fixation at the skin surface, or movements at joints. Sites of misplacement of PICCs include the cardiac chambers, internal jugular veins, contralateral subclavian vein, ascending lumbar, and superficial abdominal and renal veins. Extravasation of fluid from the catheters in each of these positions has led to serious, and occasionally, lethal complications. When the tip of the catheter is in the internal jugular vein or the contralateral brachiocephalic vein, spontaneous correction toward the superior vena cava can sometimes occur within 24 h, probably due to the direction of venous blood flow and may be facilitated by the movement of the arm.

Pericardial effusion with pericardial tamponade is a rare (estimated incidence ranges from 0.76–1.8%) but occasionally lethal complication, due to extravasation of the PICC fluid into the pericardial cavity. The tip of the catheter has been noted to be in the right atrium in most reports, with only rare reports of pericardial effusions occurring with the umbilical venous catheter tips in the "correct" location at the junction of the IVC and right atrium. Pericardial effusions have been described with all types of catheters including the very pliant silicone or Silastic catheters. The most common clinical presentation is sudden cardiovascular collapse. Unexplained or subacute cardiorespiratory instability and a sudden requirement for inotropic or respiratory support are present in about a third of patients. Urgent echocardiography is the mainstay of diagnosis and immediate pericardiocentesis the only lifesaving therapy. In a large series of 61 central venous catheter-related pericardial effusions in infants, mortality was reported to be 8% in patients who had pericardiocentesis, and 75% in patients who did not. The physical and biochemical characteristics of the pericardial fluid obtained by pericardiocentesis or noted at autopsy has been consistent with the infusate. Perforation with or without myocardial necrosis/thrombosis has been noted on autopsy, but in some cases no perforation has been detected. In view of this finding and the fact that the pericardial effusion is not bloody, it is postulated that constant abrasion of the endocardial wall by the tip of the catheter in the thin-walled right atrium leads to inflammation, and then necrosis or thrombosis with perforation that may self-seal or that there is transmural diffusion of hyperosmolar fluid across the injured endocardium and myocardium.

Pleural effusions due to extravasation of parenteral alimentation fluid are not an uncommon complication

of PICCs in the newborn, although the actual incidence is not known. Respiratory distress due to pleural effusions may arise within a few hours or several days after placement of the catheter. Although some effusions may be due to actual erosion or perforation of the intrathoracic veins, in other cases, migration of the catheter into the pulmonary artery or pulmonary vein has been described.

Inadvertent malposition of a PICC in the ascending lumbar vein after placement of the catheter in a vein in the lower extremity may lead to neurological complications, including seizures and flaccid paraplegia. The ascending lumbar vein drains the vertebral venous plexus into the common iliac vein, and is easily accessed by femoral or saphenous vein catheterization. On standard anteroposterior abdominal radiographs, the catheter may appear to be in the iliac vein or IVC, but cross-table lateral radiographs will reveal that the catheter is superimposed on the spinal canal or deviating posteriorly at the level of L4–L5, rather than anterior to the spinal column if the catheter is truly in the IVC. Symptoms in neonates may be nonspecific, prompting a "sepsis workup," but lumbar puncture reveals "milky" spinal fluid, with very elevated glucose or triglyceride levels, consistent with the composition of parenteral alimentation fluid.

Catheter-related sepsis is the most common complication of central venous catheters with rates ranging from 0% to 29% of catheters placed, and from 2 to 49 per 1,000 catheter days, with the smallest and most immature infants being at the greatest risk. The rate of infections also varies significantly among different neonatal units, secondary to differences in patient population, practice styles, and reporting variances. Removal of the catheter is often necessary for eradication of the infection but is not always possible in small and sick infants. The outcome for infants in whom the catheter is not removed within 24 h of identification of the organism is significantly worse than it is for those whose catheters are removed promptly, with increases in risks of end-organ damage or death. Prompt removal of the catheter is recommended for catheter-related sepsis due to *Staphylococcus aureus*, non-enteric gram negative bacteria, and candida. Treatment with appropriate antibiotics without removal of the catheter may be attempted for coagulase negative staphylococcal bacteremia, but removal of the line is essential if the blood cultures are repeatedly positive.

Catheter-related infection may be minimized with simple interventions, including the use of maximal barrier precautions (long sleeved gown, sterile gloves, mask, cap and large sterile sheet drape) during insertion of the catheter, use of chlorhexidine-containing antiseptics for preparing the catheter insertion site rather than povidone iodine, decreased manipulations of the catheter and the use of closed medication systems, and early feeding to reduce duration of catheter use. Strict protocols for central line care and education of physicians and nurses, with a methodology of surveillance and data feedback have been shown to reduce infection rates.

With the exception of renal vein thrombosis, almost all (approximately 90%) of venous thromboembolism (TE) in neonates is associated with central venous catheters. Catheter-related venous TE may be asymptomatic or result in severe complications such as deep vein thrombosis, portal vein thrombosis, superior vena cava syndrome, intracardiac thrombosis, or pulmonary embolism. Clinical manifestations of symptomatic catheter-related thrombosis in neonates depend on the site of the thrombosis. Catheter dysfunction, thrombocytopenia, or persistent bacteremia may be associated with vascular thrombosis at any site. Apart from the loss of venous access from catheter-related thrombosis, there is potential danger of injury to vital organs secondary to thrombus propagation, embolization, or infection. The management of catheter-related venous TE in neonates is controversial, and must be individualized. A full discussion of anticoagulants and thrombolytics in neonates is beyond the scope of this chapter; existing guidelines are updated as new data becomes available. A free consultative service, maintained 24 h a day for physicians caring for children with thrombosis, provides current management protocols and links to the network and its services. The toll-free number in the United States is 1-800-NO-CLOTS (Web site www.1800noclots.ca).

Endotracheal Intubation

Endotracheal intubation may be required for neonatal resuscitation, for endotracheal suctioning of meconium, surfactant administration, or for providing prolonged assisted ventilation.

Equipment

Supplies for endotracheal intubation should always be readily available in the delivery room, and the NICU, preferably in the form of a ready kit or tray. The supplies required are laryngoscope with extra batteries and bulbs; laryngoscope blades, preferably straight rather than curved blades (No. 1 for term infants, No. 0 for preterm infants, No. 00 for extremely preterm infants); endotracheal tubes with inside diameters of 2.5, 3.0, 3.5, and

4 mm; and stylets for the endotracheal tubes. Endotracheal tubes used in neonates are usually non-cuffed, have a uniform diameter through the length of the tube, and have centimeter markings. Tapered (shouldered) tubes are rarely used in the United States, but are popular in some parts of the world. Cuffed tubes are not recommended. A stylet provides additional stiffness and maintains the tube curvature during intubation, but its use is optional. The stylet should be secured so that the tip does not protrude from the end or side hole of the endotracheal tube; it should not slip further into the tube during intubation and yet should be easy to remove quickly as soon as intubation is accomplished. Additional equipment required is adhesive tape, scissors, stethoscope, suction equipment with 10 Fr suction catheter and size 5 or 6 Fr catheter for endotracheal tube suctioning, meconium aspirator, and a self-inflating or flow-inflating bag with mask or T-piece resuscitator and gas source.

Procedure

Premedication with a rapidly acting analgesic agent should be given intravenously just prior to the procedure for all endotracheal intubations in neonates, except for those in the delivery room or in acute emergencies in infants without venous access. Fentanyl at 1–4 μg/kg has almost immediate onset of action and lasts 30–60 min. Muscle relaxants and vagolytic agents may also be used in addition to the analgesic agents to facilitate intubation and prevent bradycardia.

Select the appropriate-sized laryngoscope blade and endotracheal tube (*Table 35.1*). Position the infant on a flat surface with the head in the midline and neck slightly extended. A small roll under the baby's shoulders may help, but it is important to avoid overextending the neck. Hold the laryngoscope in your left hand with the blade inferior and pointing away from you. If the laryngoscope is held in the right hand, the closed part of the blade will obscure your view of the glottis making intubation impossible. Insert the laryngoscope blade into the mouth, over the right side of the tongue, pushing the tongue to the left side of the mouth until the tip of the blade is in the vallecula or on the epiglottis. Lift the blade slightly, by pulling in the direction the handle is pointing, lifting the tongue out of the way to expose the pharyngeal area. Oral and pharyngeal secretions may need to be suctioned for better visibility of the glottis. If the tip of the blade is correctly positioned, the vocal cords should be visible on either side of the glottis as an inverted letter "V." Slight external pressure on the cricoid cartilage on the neck may help to bring the glottis into view. Holding the endotracheal tube in your right hand, introduce it into the right side of the baby's mouth, with the curve of the tube in the horizontal plane to prevent it from blocking your view of the glottis. *Keeping the glottis in view*, insert the tip of the tube between the vocal cords until the vocal cord guide markings on the tube are at the level of the cords. Do not force the tube through closed vocal cords, but wait for them to open. It is also important to actually visualize the tube passing between the vocal cords and not attempt to do it "blindly." Quickly verify the length of tube insertion of the tube at the level of the baby's lips, stabilize the tube by holding it between thumb and forefinger at the lips, and remove the laryngoscope blade from the mouth. The tube may now be stabilized by using a forefinger to hold it against the hard palate while the stylet is quickly but carefully removed. The tube is now ready for use. The meconium aspirator may be attached and meconium suctioned from the tube or positive pressure ventilation may be commenced. If the endotracheal tube is being used to provide respiratory support, it is important to ensure it is in correct position. Adequate chest movement with positive pressure ventilation, visible vapor condensing on the inside of the tube during exhalation, audible and equal breath sounds on auscultation high on the lateral sides of the chest bilaterally (in the axillae), and improving heart rate are reassuring signs. Colorimetric CO_2 detectors connected to the endotracheal tube change color in the presence of CO_2, indicating successful intubation, but do not indicate if the tube is correctly positioned. They are also unreliable in babies with very poor or no cardiac output as in cardiac arrest.

The endotracheal tube is probably not in the trachea if the baby remains cyanotic and bradycardic despite positive pressure ventilation or if the abdomen becomes

Table 35.1
Endotracheal tube size and depth of insertion in newborn infants

Weight (g)	Endotracheal tube size (inside diameter)	Depth of insertion (from upper lip)
<750 g	2.5 mm	5.5–6 cm
1,000 g	2.5–3.0 mm	7 cm
2,000 g	3.0–3.5 mm	8 cm
3,000 g	3.5 mm	9 cm
4,000 g	4.0 mm	10 cm

Source: Adapted from American Academy of Pediatrics and the American Heart Association (2006) Textbook of neonatal resuscitation, 5th edn. Chicago

distended or there are "sounds" over the abdomen but poor breath sounds over the chest, and no misting of the tube. In this situation, stabilize the tube with your right hand and reinsert the laryngoscope blade with your left hand to visualize the larynx and see if the tube is in the glottis or in the esophagus. Pull the tube back, visualize the glottis and reinsert the tube. It may be better to remove the tube, stabilize the baby's heart rate and oxygen saturation by bag and mask ventilation for a few minutes before the next attempt at endotracheal intubation.

If the endotracheal tube is required for positive pressure ventilation for more than a few minutes, it should be shortened to reduce the dead space and secured to the face as soon as it is judged to be in an appropriate position. The tube may be secured with a small piece of adhesive tape cut in an H shape with one limb of the H attached like a moustache to the upper lip and the other limb encircling the tube. Several proprietary devices are also available for securing endotracheal tubes. Radiographic confirmation of tube placement with the head in the midline is recommended to verify that the tube is in an appropriate position, preferably midway between the clavicle and carina.

Complications

Complications of endotracheal intubation include trauma to the lips, alveolar margins, and oropharynx from the laryngoscope. The stylet or endotracheal tube may cause trauma to the vocal cords, perforation of the trachea or esophagus, with pneumothorax, pneumomediastinum, or tracheoesophageal fistula as potential complications. The tube may be malpositioned in the right main-stem bronchus or the esophagus may be erroneously intubated. Prolonged fixation of the endotracheal tube may cause oral commissure defects or palatal deformity. The incidence of acquired subglottic stenosis has decreased in the past decade, and is estimated to range from 0% to 2%.

Lumbar Puncture

The primary indication for a lumbar puncture (LP) or spinal tap in a newborn infant is to obtain a sample of cerebrospinal fluid (CSF) for the diagnosis of meningitis or meningoencephalitis of bacterial, viral, or fungal origin. In neonates, specific signs of meningitis such as neck stiffness and bulging anterior fontanelle are often absent, and CSF cultures may be positive even when blood cultures are negative so an LP is generally included as part of the "complete sepsis workup." LPs are also performed to monitor efficacy of therapy in patients with meningitis, by monitoring changes in culture results, cell counts, and viral loads. In infants with posthemorrhagic hydrocephalus, drainage of CSF has been shown to improve cerebral hemodynamics. Although serial LPs have not been shown to reduce the need for shunt placement, drainage of 10–15 ml/kg of CSF two or three times a week in infants with posthemorrhagic communicating hydrocephalus permits deferment of ventriculo-peritoneal shunt placement until the baby is larger, more stable, and high CSF protein content has decreased to near normal levels.

Lumbar puncture is contraindicated if there is significant cardiorespiratory instability, which could be exacerbated during the procedure. Infection of the skin or tissues at or near the site is also a definite contraindication to the procedure. Thrombocytopenia (platelet count $< 100{,}000/mm^3$) or bleeding disorders should be corrected before an LP is attempted. The risk of transtentorial herniation following an LP due to increased intracranial tension is low since the sutures are open.

The spinal cord terminates at the L1/L2 spine in the majority of adults. Early in fetal life, the spinal cord stretches through the whole vertebral canal with the nerve roots traversing the intervertebral foramina horizontally. At 6 months of fetal life, the lowest limit of the spinal cord is at S1 level. Between 25 and 33 weeks gestation, the cord terminates at the level of L3 or above, but significant variation is present before 25 weeks. A line joining the most superior part of both iliac crests will intersect the midline at the L4 spine or the L4/L5 interspace, the recommended insertion site for lumbar punctures in infants.

Equipment

All equipment other than the cap and facemask is sterile. Spinal needles for neonatal use are available in 22 and 25 gauges, and have a short bevel and stylet. Other supplies required are sterile towels or drapes, iodophor antiseptic solution, gauze swabs, holder for the swabs, 3 or 4 specimen tubes with caps, adhesive bandage, 0.5 ml of 1% lidocaine in a 1-ml syringe with a 25 or 26 gauge small needle.

Procedure

The procedure may be done with the baby in the lateral decubitus position or in the sitting position. Continuous

cardiorespiratory monitoring during the procedure is recommended. Local anesthetic cream may be applied to the insertion site about 60 min before the procedure to reduce pain. An assistant should restrain the infant in the lateral decubitus position, keeping the back perpendicular to the surface on which the baby is lying, the hips perfectly symmetrical, flexing the spine by holding the shoulders and the legs. The neck should be in neutral position. The baby does not need to be held in tight flexion until the actual insertion of the spinal needle. Alternatively, the assistant may position the infant in a sitting position, with the back and neck flexed.

After putting on a cap and mask, wash hands thoroughly as for a major procedure and wear sterile gloves. Clean the lumbosacral area three times with antiseptic, using a fresh sterile gauze swab each time, starting at the L4–L5 interspace in the midline and cleaning in concentric circles toward the periphery. Allow antiseptic to dry for at least 30 s. Drape the baby's back and iliac region, leaving the puncture site exposed. Lidocaine (0.3–0.5 ml of 1% lidocaine) may be infiltrated into the subcutaneous space, if local anesthetic cream is not used. Increased volume or injection into deeper structures may make the procedure more difficult by making it more difficult to feel the spinous processes. Insert the spinal needle with the stylet in place in the midline, into the L4–L5 interspace, with the bevel of the needle in the sagittal plane, directing the needle slightly cephalad toward the umbilicus. The needle will pass through the supraspinous and interspinous ligaments, through the ligamentum flavum and dura mater into the subarachnoid space. In older children or adults, a change in resistance or "pop" is felt as the needle pierces the dura mater, but this is harder to appreciate in neonates. After the needle is inserted to 1 or 1.5 cm, continue to advance the needle by 1–2 mm at a time, removing the stylet intermittently to check for CSF flow, replacing the stylet each time before advancing the needle further. One may also have to wait for the CSF flow for a few seconds since it may be less brisk in neonates than in older children. If no fluid is obtained, rotate the needle about 90° to reorient the bevel. Allow the CSF to flow passively into the sterile collection tubes; never aspirate CSF with a syringe. Generally 0.5–1 ml per tube is adequate for most diagnostic studies; 10–15 ml/kg may be drained over 5–10 min for treatment of communicating hydrocephalus. If the spinal tap is traumatic and the fluid bloody, due to puncture of the epidural venous plexus on the posterior surface of the vertebral body, withdraw the needle by a few millimeters and allow the fluid to clear. Replace the stylet before removing the needle to prevent entrapment of spinal nerve roots. Place an adhesive bandage over the puncture site after removing the needle. Clean off the remnants of the antiseptic from the skin with sterile water.

Complications

The most common complication in neonates is transient hypoxemia during the procedure; this may be circumvented by careful attention to positioning and adjustments to the respiratory support. The other common complication is a traumatic or bloody tap, which is usually of no immediate consequence to the infant, but may lead to difficulty in interpretation of cerebrospinal fluid cell counts. Infections, bleeding into the spine, and spinal cord injury with nerve damage are very rare complications. Failure to use a stylet can lead to implantation of epithelial cells in the spinal canal with development of an intraspinal epidermoid tumor.

Thoracocentesis or Needle Aspiration of the Pleural Space

Needle aspiration of the pleural space is performed to evacuate air or fluid from the pleural space, sometimes as an emergency temporizing measure to recover cardiorespiratory stability while preparations are being made to insert a chest tube. The recommended site for aspiration of a pneumothorax is the third or fourth intercostal space at the anterior axillary line, while pleural fluid is more easily aspirated from the fourth intercostal space in the midaxillary line. The fourth intercostal space is located at the level of the nipples. The needle should be inserted over the upper border of the rib to avoid the intercostal vessels.

Equipment

Sterile gloves, antiseptic solution, 20, 22, or 23 gauge intravenous cannula or butterfly needle (based on the size of the baby), three-way stopcock, and 20-ml syringe.

Procedure

If possible, turn baby to the side, with the side of the pneumothorax superior, to allow the air to rise. Scrub hands, wear sterile gloves, and clean the insertion area with antiseptic solution. Insert the intravenous cannula perpendicular to the chest wall, just over the top of the rib in the fourth intercostal space. Remove the stylet and

attach the three-way stopcock and syringe to the hub of the catheter. Aspirate the air or fluid into the syringe. Turn the stopcock to close entry into the chest, while emptying the syringe, and then turn it again to allow further aspiration from the chest if required. If using the butterfly needle, attach a three-way stopcock and syringe to the needle. Insert the needle over the upper border of the rib, aspirating continuously with the attached syringe once the needle has punctured the skin. Stop advancing the needle when air or fluid flows back into the syringe. Remove the needle or cannula as soon as air/fluid aspiration is complete or a chest tube has been inserted. Apply a small adhesive dressing to the site.

Thoracostomy

Chest tube drainage of a pneumothorax is an emergency in infants with respiratory distress due to surfactant deficiency, meconium aspiration, or pulmonary hypoplasia. Chest tubes may also be required for drainage of large persistent pleural fluid collections.

Equipment

There are different types of chest tubes, with slightly different insertion techniques for each. The most commonly used chest tubes are polyvinyl chloride tubes, in sizes 8 (smallest), 10, and 12 Fr, which are available with or without trocars. Trocars are not recommended for use in neonates. An evacuation device consisting of extension tubing, connectors, and a bottle filled with sterile water for underwater seal is also necessary. Several proprietary evacuation devices are available. A general all-purpose surgical tray with curved hemostats, No. 15 surgical blade, nonabsorbable sutures on a small cutting needle are required, together with sterile drapes, petrolatum gauze, semipermeable transparent dressing, antiseptic skin solution, 1% lidocaine for local anesthesia or appropriate intravenous narcotic analgesic.

Procedure

Position the infant so that the side of the chest is accessible and restrain the arm over the head, away from the chest. Prepare as for a sterile procedure. Administer narcotic analgesic intravenously while preparing the skin over the lateral portion of the chest from the midclavicular line to the posterior axillary line with antiseptic solution. Cover the other areas with sterile drapes. Locate the nipple to ensure that the tube will be well away from the breast tissue. A vertical line at the level of the nipple will help to identify the fourth intercostal space. Locate the skin incision site at the fifth or sixth intercostal space between the anterior and midaxillary lines. Infiltrate the skin and subcutaneous tissue at the site with 0.5–1 ml of 1% lidocaine. Using the scalpel blade, make a small incision (0.5–1 cm) in the skin at the site, at the upper border of and parallel to the rib. Insert the curved hemostat through the incision and direct it superiorly in the subcutaneous plane to the fourth intercostal space. At the intersection of the nipple line with the anterior axillary line, apply pressure with the tip of the finger on the closed hemostat so the tip pushes through the intercostal muscles and parietal pleura to enter the pleural space in the fourth intercostal space. A slight "pop" or a rush of air may be felt at this point. Open the hemostat slightly and leave it in place. Remove the trocar from the chest tube and direct the tube into skin incision and through the opened tips of the hemostat into the pleural space. The curved points of the hemostat may then be rotated to direct the tube anteriorly and cephalad, the best position for evacuation of a pneumothorax in an infant who is lying in the supine position. A posteriorly placed chest tube would be appropriate for drainage of fluid. Remove the hemostat and advance the tube further to the predetermined length. Ensure that the side holes are within the pleural space. "Misting" of the chest tube indicates intrapleural position, which is further confirmed by bubbling when the tube is connected to the underwater drainage system. Apply 10–20 cm negative pressure to the underwater system to facilitate evacuation of the pneumothorax. Apply one or two interrupted sutures to close the skin incision and secure the tube by wrapping and tying the ends of the sutures to the tube. Purse string sutures are not recommended because the resultant scar may be puckered. Clean the remnants of antiseptic from the skin, and apply a small piece of petrolatum gauze at the incision site. Secure the chest tube to the skin with an adhesive tape bridge or with semitransparent dressing. Avoid a large dressing that could obscure chest examination or tube displacement. Obtain anteroposterior and lateral radiographic confirmation of appropriate positioning of the chest tube.

The chest tube may be removed when there has been no air or fluid draining for 24–48 h. The suction may be discontinued and the tube left to underwater drainage for a further 12–24 h, and transillumination or radiography used to document that there has been no re-accumulation of air or fluid. Administer analgesic medication intravenously just prior to removal of the tube. Remove the tape

bridge or dressing. Wearing sterile gloves, clean the incision site, the part of the tube entering the chest, and the surrounding area with antiseptic. Cut the sutures holding the tube to the skin. Hold a piece of sterile petrolatum gauze close to the insertion site and cover the site quickly with it as soon as the tube is withdrawn, to prevent air from entering the pleural space. If possible, remove the chest tube during the expiratory phase of respiration in spontaneously breathing infants and during inspiration in mechanically ventilated infants. Keep the skin sutures in place unless the skin is inflamed. The sutures may be removed later when healing is complete. If the skin is inflamed, remove the sutures and approximate the edges of the incision with sterile adhesive strips. Remove residual antiseptic and cover petrolatum gauze with dry gauze and small transparent dressing.

Complications

Chest tubes can cause perforation of the lung, bronchopleural fistulas, and hemorrhage from perforation of a major vessel such as the internal mammary or intercostal vessels, and diaphragmatic paralysis due to phrenic nerve injury.

Pericardiocentesis

Although pericardiocentesis is not a common procedure, it is described here since it could be lifesaving when performed for acute tamponade, a clinical condition with reduced cardiac output due to impaired ventricular filling, secondary to fluid or air in the pericardial space. Pericardial effusion can occur in the NICU secondary to perforation or transudate from an umbilical or percutaneous central venous catheter (see above). Ideally, pericardiocentesis should be performed with real-time ultrasound or guidance to determine the depth of penetration of the needle, but in an emergency, the procedure may be performed without sonographic imaging.

Equipment

The equipment for pericardiocentesis is readily available in any NICU, and consists of a standard 18–24 gauge intravenous cannula over a 1–2 in. needle, a three-way stopcock, extension tubing (optional), 10–20-ml syringes, local anesthetic, antiseptic solution, and sterile drapes and gloves. Two-D echocardiography equipment would be invaluable if available. A transilluminator may be useful to diagnose pneumopericardium and assess the efficacy of drainage, but does not reliably distinguish between air in the pericardial space or in the mediastinum.

Procedure

Wear a mask, wash hands, and wear sterile gloves. Clean the skin over the xiphoid, precordium, and epigastric area with sterile antiseptic, and cover the area with sterile drapes, leaving the subxiphoid area exposed. Inject local anesthetic (0.5–1 ml of lidocaine) subcutaneously near the xiphoid process, if time allows. Connect a 10-ml syringe to a three-way stopcock and an 18–24 gauge intravenous cannula over a 1–2 in. needle (depending upon the size of the baby), with the stopcock open to the needle and syringe. Insert the needle/cannula in the subxiphoid space, about 0.5–1 cm below the tip of the xiphoid process, in the midline or 0.5 cm to the left of the midline, directing the needle toward the left shoulder, at an angle of 30–40° to the skin. If 2-D echocardiography is used, finding the fluid-filled pericardial sac at the point closest to the body surface localizes the ideal entry site. While advancing the needle, apply gentle negative pressure with the syringe. Stop advancing the needle as soon as fluid or air is obtained, advance the cannula further and withdraw the steel needle. The position of the cannula in the pericardial space may be confirmed by echocardiography by the injection of a small amount of agitated saline. Aspirate as much fluid or air as possible from the pericardial space. The fluid may be bloody, serosanguineous, milky, or resemble the parenteral fluid infusing through the central venous catheter. A rhythmic tugging sensation, corresponding to the heart rate may be felt when the cannula is in the pericardial space, and does not necessarily mean that the cannula has entered the heart. Withdrawal of 5–10 ml of fluid from the pericardial space leads to improvement in the hemodynamic condition within seconds. Remove the cannula as soon as the aspiration is completed, and apply an adhesive bandage, after removing with antiseptic solution with sterile water.

Complications of pericardiocentesis include pneumopericardium, pneumomediastinum, pneumothorax, cardiac arrhythmia, cardiac perforation, and perforation of the liver. Complications are rare if echocardiography is used. Hypotension may occur when a large amount of effusion is drained rapidly, and may require fluid boluses.

Suprapubic Bladder Aspiration

Needle aspiration of the distended bladder is the recommended method of obtaining a specimen of urine for culture in infants. The risk of contamination and false positives is low, but success rates range from 25% to 100%. The use of portable ultrasound scan or transillumination to check if the bladder is full prior to the procedure can increase the likelihood of success. The procedure is contraindicated if the baby is dehydrated or if the abdomen is distended due to bowel dilatation or enlargement of other organs, or if there is evidence of a bleeding disorder or severe thrombocytopenia.

Equipment

Gloves, 3- or 5-ml syringe, 22 or 23 gauge straight or butterfly needle, antiseptic swabs, local anesthetic cream, and container for urine collection. All equipment is sterile.

Procedure

Ensure that the baby is well hydrated and has not voided in the last hour. Apply local anesthetic cream to the needle insertion site (1 cm above the symphysis pubis in the midline) at least 60 min before the procedure. Wash hands thoroughly and put on sterile gloves. Clean the suprapubic area in the midline including the symphysis pubis with antiseptic solution three times with antiseptic and wait for 30 s. Attach the needle to the syringe. Insert the needle 1 cm above the symphysis pubis in the midline, aiming the needle slightly cephalad. Aiming too far caudad will cause the needle to enter the bladder neck. Apply gentle negative pressure on the syringe once the needle has been inserted about a centimeter. Stop advancing the needle once urine is obtained or if the needle has been inserted up to approximately 2.5 cm in a term infant, less in a smaller baby. Do not manipulate the needle or redirect it in different directions if no urine is obtained. Remove the needle after the specimen is collected and apply gentle pressure over the puncture site with sterile gauze. Clean off any remaining antiseptic with water.

Complications

The most common complication is transient hematuria. Hematomas, abscesses, and symptomatic perforation of a viscus are rare complications. However, ultrasound observation indicates that the needle might easily enter the uterus or bowel when the bladder is not full and the needle inserted beyond 2 cm in preterm infants.

Bladder Catheterization

Catheterization of the bladder is an acceptable alternative method to obtain urine for culture. The procedure has a higher success rate, but is associated with higher contamination rates. Bladder catheterization may also be required for monitoring urinary output, relieving urinary retention, quantifying residual urine in the bladder, or to instill contrast agent in the bladder for cystourethrography. There are no definite contraindications to the procedure. Sterile precautions must be used for the procedure, regardless of the indication, since introduction of bacteria into the urinary tract during catheterization could lead to urinary infection and sepsis.

Equipment

All equipment must be sterile. Silicone urinary catheters in sizes 3.5, 5, or 6.5 Fr are suitable for neonates. A 5-Fr feeding tube or 3.5- or 5-Fr umbilical catheter may be used if urinary catheters are not available. The smaller 3.5-Fr catheters are more suitable for babies weighing less than 1,000 g. Catheters will need to be connected to a closed drainage system for monitoring urinary output; this may be accomplished with commercial prepackaged urinary drainage kits or by connecting the catheter with IV extension tubing to a collection burette. In addition, gloves, drapes, nonalcohol-based antiseptic solution, gauze sponges, and surgical lubricant are required.

Procedure

Restrain the infant in a supine frog-leg position. Wash hands thoroughly and put on sterile gloves. For a male infant, stabilize the shaft of the penis with the nondominant hand. This hand is now considered contaminated. Gently retract the foreskin to just enough to expose the meatus. Neonates have physiological phimosis and the foreskin cannot be fully retracted. Using the free hand, clean the glans three times with antiseptic solution, beginning at the meatus and cleaning down over the shaft of the penis. Use the "contaminated" hand to apply gentle pressure over the base of the penis to prevent reflex urination. Drape sterile towels over the lower abdomen and over the

infants' legs. Lubricate the tip of the catheter with sterile lubricant and gently insert it into the meatus. Gentle upward traction on the penis will prevent kinking of the urethra and aid in passage of the catheter. Slight resistance is sometimes met at the external sphincter, but the sphincter spasm generally relaxes in a brief period. Do not force the catheter if obstruction is encountered at any stage. The catheter should be advanced only to the length at which urine flow is obtained and no further, since additional length of catheter in the bladder could increase the risk of trauma and knotting of the catheter. Collect the urine specimen in a sterile container and remove the catheter, or, if continuous urinary drainage is required, connect the catheter to a closed system. For continuous drainage, the catheter should be taped securely to the inner thigh. If the foreskin has been retracted, ease it back over the glans following the procedure to prevent paraphimosis.

In a female infant, an assistant may be required to retract the labia with cotton-tipped applicators or gauze sponges. The area between the labia minora should be cleaned with antiseptic solution, swabbing from the anterior to the posterior direction to prevent fecal contamination of the sterile field. The urethral meatus lies anterior to the vaginal opening and may be difficult to see in extremely low birth weight infants. Advance the catheter a short distance until urine is obtained. The female urethra is very short; do not advance beyond 1–2 cm if no urine is obtained.

Complications

Urinary tract infection is the most common complication of bladder catheterization. Using a strict aseptic technique, maintaining a closed sterile collection system, and removing the catheter as quickly as possible decrease the risk of infection. Other complications such as perforation of the bladder or urethra and knotting of the catheter are rare.

Exchange Transfusion

An exchange transfusion (ET) involves replacing a major proportion of a patient's blood with donor blood, by repeatedly removing and replacing small aliquots of blood over a short time period, generally 1–2 h.

In newborn infants, the most common indication for an ET is severe unconjugated hyperbilirubinemia due to any cause, when intensive phototherapy has failed or there is a risk of kernicterus. ET may mitigate neurological abnormality even when there are signs of early or intermediate stages of acute bilirubin encephalopathy. The serum bilirubin level at which ET is recommended for smaller and more immature infants is variable and often individualized based on the risk benefit assessment, since ET in very immature infants is technically more difficult and can be associated with significant morbidity and mortality. In infants with severe alloimmune hemolytic disease of the newborn, ET may be performed early before the development of severe jaundice, both for the correction of severe anemia and also to replace antibody-coated neonatal red cells with antigen negative donor cells that are not susceptible to hemolysis. Partial ET has been used to correct anemia in neonates with severe anemia and congestive heart failure or hypervolemia. ET is also used in infants with polycythemia to reduce the hematocrit and therefore hyperviscosity, but there is no definitive evidence of clinically significant short- or long-term benefit of ET for this indication, particularly when the baby is asymptomatic. Other rare indications for ET in neonates include use in drug toxicity or overdose, the removal of metabolic toxins, such as in hyperammonemia, organic acidemia, and lead poisoning, removal of antibodies or abnormal proteins as in neonatal myasthenia, and in neonatal sepsis or malaria.

Communication with the blood bank is essential to determine and obtain the most appropriate blood product for the ET. The blood should be as fresh as possible (<7 days), and subjected to standard blood bank screening for HIV, Hepatitis B, etc. Donor blood should be screened for G6PD deficiency and sickle cells in populations endemic for these conditions. Plasma-reduced whole blood or packed red cells reconstituted with plasma with a packed cell volume adjusted to 0.50–0.60 is suitable for correction of anemia or hyperbilirubinemia. Blood may be anticoagulated with citrate phosphate dextrose (CPD or CPDA1) or with heparin. Red blood cells with additive anticoagulant solutions are generally avoided, but if this is the only blood product available, the additive solutions may be removed by washing or by centrifugation, prior to reconstitution of the red cells with plasma. Special attention has to be paid to compatibility testing in the presence of alloimmunization. If delivery of an infant with severe alloimmune hemolytic disease or any severe anemia is anticipated, O Rh-negative blood cross-matched against the mother may be prepared before the baby is born. Donor blood prepared after the baby's birth must be negative for the antigen responsible for the hemolytic disease, and the blood must be cross-matched against the infant. In Rh HDN, the blood should be Rh negative, and may be O group or the same group as the infant. In ABO HDN, the blood must be type O and either Rh negative or Rh compatible with the mother and

infant. The packed cells must be washed free of plasma or have low titer of anti-A or anti-B antibodies. Type O cells with AB plasma are suitable, but this results in two donor exposures per ET. Irradiated blood is recommended for all exchange transfusions, to prevent graft versus host disease, particularly if blood is obtained from first- or second-degree family members, or if postnatal ET follows an intrauterine fetal transfusion. There is a significant increase in potassium concentration in stored irradiated units, so irradiation should be performed as close to transfusion as possible (<24 h). In infants with polycythemia, the optimal dilutional fluid for a partial ET is isotonic saline rather than plasma or albumin.

A double volume ET, calculated as twice the infant's blood volume (2×80 ml/kg in term infants, 2×100–120 ml/kg in preterm infants), in fact exchanges only 85% of the infant's blood volume. Double volume ETs are performed for removal of bilirubin, antibodies, toxins, etc. A single volume ET results in approximately 60% of the infant's blood volume being replaced by donor blood, and may be adequate for correction of anemia or polycythemia. The volume of blood necessary for a partial ET for anemia may be calculated by the following formula:

$$\text{Volume(ml)} = \frac{\text{infant's blood volume} \times (\text{Hgb desired} - \text{Hgb initial})}{\text{Hgb of packed red cell unit} - \text{Hgb initial}}$$

The volume of saline for a partial ET for polycythemia is calculated as:

$$\text{Volume(ml)} = (\text{infant's blood volume} \times \text{desired hematocrit change}) / \text{initial HCT}.$$

Equipment

The equipment for neonatal ET consists of a suitable surface (infant warmer or incubator) with appropriate heat source, temperature and cardiorespiratory monitor, equipment for central and peripheral vascular access, and an exchange transfusion set. Sterile preassembled disposable sets with a special stopcock are available for ETs, but the procedure may be performed just as easily with sterile equipment assembled in the NICU, consisting of two three-way stopcocks with locking connections, IV connecting tubing, 5-, 10-, or 20-ml syringes, and a sterile waste receptacle like an empty IV bottle or bag. A thermostatically controlled blood warmer with appropriate coils is essential when an ET is performed on a small preterm infant, and is recommended even for larger infants. Resuscitation equipment and medications should be readily accessible.

Procedure

Two people are required to perform the ET. The person performing the ET should prepare as for a major surgical procedure with hand antisepsis, and wear a mask, head cover, sterile gown, and gloves. An assistant is required to monitor the infant closely, record vital signs and the volume of blood exchanged during the procedure.

Venous and arterial access should be obtained prior to the exchange transfusion based on the type of ET planned and may necessitate umbilical venous and arterial catheterization or peripheral venous and radial artery catheterization. The ET may be performed by a "push–pull" technique, generally through an umbilical venous catheter, or by an "isovolumeteric" technique with infusion of donor blood through a central or peripheral venous catheter and simultaneous removal of the patient's blood from an umbilical or radial arterial catheter. The isovolumetric technique is preferred for sick or unstable neonates since there is less fluctuation of blood pressure and alteration of cerebral hemodynamics. If an umbilical venous catheter is inserted for an ET, a single lumen catheter is recommended; double- or triple-lumen catheters have very small internal diameters and make withdrawal and infusion of blood extremely difficult. The position of the umbilical venous catheter should be verified to be in the IVC radiographically prior to the procedure. If the UVC cannot be positioned in the IVC, it may still be used for an ET in an emergency, when placed in the umbilical vein, if adequate blood return is obtained.

ET by the "push–pull" technique may be performed using an umbilical venous catheter and a special four-way stopcock or by using two three-way stopcocks in tandem. It is important to familiarize oneself with the setup and stopcock connections prior to the procedure. The special four-way stopcock has three ports to which a syringe and IV tubing are attached and a handle that points to the port that is open (*Fig. 35.8*). The handle and syringe may be rotated in a clockwise direction allowing the following sequence during the ET: (a) withdraw blood from the patient into the syringe, (b) eject the patient's blood into the waste bag or bottle, (c) draw donor blood into the syringe, and (d) inject donor blood into the baby. The sequence is repeated multiple times until the ET is completed. If the special four-way stopcock is not available, two standard three-way stopcocks may be used in tandem. The proximal stopcock is attached to the umbilical catheter and the IV extension tubing to the sterile waste blood container. The distal stopcock is attached to the tubing from the blood administration set/blood warmer and to the 10- or 20-ml syringe.

Restrain the baby suitably so that the sterile barrier is not compromised. Sedation or pain relief is not usually

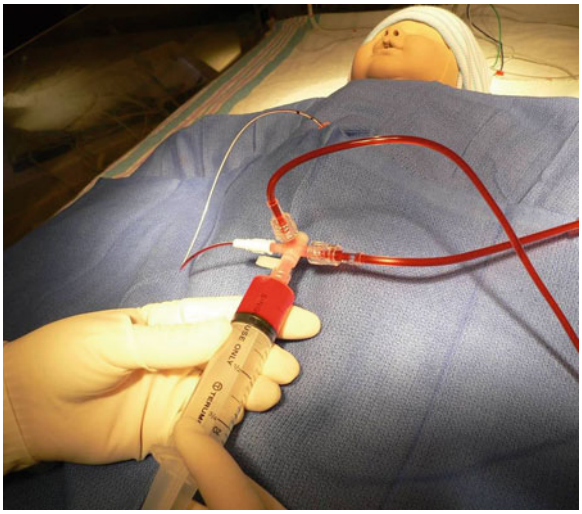

Figure 35.8
Demonstration of exchange transfusion using umbilical venous catheter (UVC) with special four-way stopcock and push–pull technique. Note that the direction in which the handle is pointing indicates the port that is open to the syringe, while other ports are closed. The handle and syringe ensemble are rotated clockwise to complete an exchange of one aliquot of blood

required. Conscious infants may suck on a pacifier during the procedure. The infant should not be fed for about 4 h prior to the procedure, if possible. Place an orogastric tube and empty the stomach prior to the procedure. Attach cardiorespiratory monitors and obtain baseline vital signs prior to the procedure. A peripheral intravenous line should be placed to provide IV infusions or medications as required.

Diagnostic laboratory tests in the infant such as antibody studies to evaluate hemolysis, antiviral antibody titers, metabolic screening, or genetic tests should be drawn prior to the ET. Pre-exchange blood tests include hematocrit, platelet counts, serum electrolyte, calcium, glucose and bilirubin levels, blood gases, and blood coagulation tests.

The principles and techniques for using the special stopcock or the three-way stopcocks are the same. It is important to ensure that all junctions are tight to produce a closed sterile system. Attach the blood administration set to the blood warmer tubing and the blood bag. Open the equipment tray using aseptic technique. Once all the connections are made, open the stopcock to the blood source and clear all air into the syringe and then into the waste bag. Consider measurement of central venous pressure using a pressure transducer in an unstable baby. Draw a sample of blood for pre-exchange laboratory tests. If the infant is hypovolemic, start the ET by transfusing an aliquot of 5-ml/kg into the catheter. If the infant has a high CVP or signs of congestive failure, start by withdrawing the pre-calculated aliquot. The usual rate of removal and replacement of blood during the ET is aliquots of 5 ml/kg over 2–4 min cycles. For example, in a baby weighing 3 kg, 15 ml of blood may be withdrawn from the UVC slowly taking about a minute and then flushed rapidly into the waste bag; 15 ml is drawn quickly from the blood administration set, and then given slowly over a minute to the baby through the UVC. Continue the sequence as described above with every withdrawal of an aliquot of infant's blood ("pull") being followed by ejection into the waste container, followed by a transfusion ("push") of an aliquot of fresh donor blood from the blood bag, with the assistant ensuring that the cumulative volumes are balanced throughout the exchange. The assistant should agitate the blood bag every 10–15 min to prevent red cell sedimentation, which may lead to exchange with relatively anemic blood toward the end of the exchange. Ensure that the stages of withdrawing and infusing blood from and into the infant are done slowly, taking at least a minute each to avoid fluctuations in systemic blood pressure, which may be accompanied by changes in intracranial pressure. Rapid withdrawal of blood from the umbilical vein may also induce a negative pressure that is transmitted to the mesenteric veins and may contribute to ischemic bowel complications. Continue exchanging aliquots of blood until the calculated volume is reached. Ensure that there is an adequate volume of donor blood left in the bag to infuse after the last withdrawal, so that the baby is not left with a net negative balance. Draw a post-exchange blood sample from the baby to check hematocrit, bilirubin levels, and necessary laboratory tests. The total duration of a double volume ET is usually 60–120 min.

If an isovolumetric technique is used for the ET, attach a three-way stopcock to the umbilical arterial catheter or a three-way stopcock with an extension tube to the peripheral arterial catheter. Attach an empty 5- or 10-ml syringe to one port and an IV extension tube connected to an empty sterile bag or bottle to another port. Attach a three-way stopcock and syringe to the umbilical or peripheral venous catheter and to the blood warming coil or blood administration set. Withdraw small aliquots of blood from the arterial line at the rate of 2–3 ml/kg/min and infuse the same volume drawn from the donor blood into the venous catheter simultaneously, keeping the flow as steady as possible and maintaining equal cumulative volumes on the arterial and venous sides. The arterial catheter may need to be flushed with small volumes of heparinized saline intermittently. The total duration of an isovolumetric ET is

usually about 60 min, but may take longer for sicker and smaller unstable infants.

Hypocalcemia may occur during the ET secondary to the use of citrated blood, and may be asymptomatic or manifested by changes in the Q-Tc interval or by agitation and tachycardia. If hypocalcemia is documented, 1 ml of 10% calcium gluconate may be administered slowly with careful observation of the heart rate and rhythm, after the line is cleared of blood with normal saline. Calcium will reverse the effect of the anticoagulant in the donor blood and may cause clotting of the umbilical venous catheter, so the UVC must be flushed clear with heparinized saline before resuming the ET.

Following the ET, continue to monitor vital signs closely for the next 6–12 h. Intravenous fluids should be continued to ensure normoglycemia. Infants are generally not fed for at least 4 h, and then feeds are restarted cautiously if the clinical condition is stable, with close monitoring of the abdominal girth, bowel sounds, and feeding tolerance if the umbilical vessels have been used for the ET. Serum ionized calcium and platelet counts should be rechecked immediately after the ET in sick infants and then as indicated. Hemoglobin and bilirubin levels should be checked immediately post exchange and further as clinically indicated. A double volume ET replaces 85% of the baby's blood volume, but eliminates only about 50% of the intravascular bilirubin. Bilirubin levels may rebound significantly within a few hours of the ET because of equilibration of intra- and extravascular bilirubin and continued breakdown of red cells by maternal antibody in alloimmune hemolytic disease of the newborn.

The risk of mortality or serious sequelae secondary to ET is estimated to be less than 1% in term otherwise healthy infants, but as high as 12% in sick infants. The most common complications of ET, noted during or soon after the ET in infants who are preterm and/or sick are apnea and bradycardia, hypocalcemia and thrombocytopenia. Other complications include derangements in acid–base balance and glucose concentrations, hematological problems such as neutropenia and coagulopathy, and vascular catheter-related complications such as vascular spasm and thromboembolism, and potential transfusion-related infection. Feeding intolerance and necrotizing enterocolitis have been described following ET, but the risk of omphalitis and septicemia should be low if strict aseptic technique is followed.

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36 Neurodevelopmental Follow-up and Outcomes

Betty R. Vohr · Bonnie E. Stephens

Prematurity continues to be a major public health problem, and despite advances in antenatal care, prematurity rates continue to rise in the United States. Advances in antenatal medicine, more aggressive delivery room resuscitation, and improved neonatal interventions and management have resulted in improved survival of preterm infants. The most dramatic improvements have been for infants born extremely low birth weight (ELBW, $\leq$1,000 g) and at the limits of viability (22–25 weeks). These improvements in survival have not been accompanied by proportional reductions in the incidence of neurologic, developmental, and behavioral disabilities in this population.

It has been almost universally accepted that neurodevelopmental outcome after preterm birth is the most important quality indicator for a neonatal intensive care unit. In addition, it is now accepted that there may be a disconnect between a neonatal intervention with positive short term results and an infant's subsequent long term outcome. Examples are the association of oxygen treatment for respiratory distress with blindness from retinopathy of prematurity, and the use of postnatal steroids to wean infants from a ventilator with subsequent cerebral palsy. These observations resulted in the current standard for the majority of large clinical trials in the field of neonatology to include a measure of post-discharge neurodevelopmental status as a component of the primary outcome.

Ideally there are three objectives for a Neonatal Follow-up Program that include the following:

1. Surveillance: The implementation of a database for the systematic monitoring of care and interventions for high risk infants during the neonatal hospitalization, and post-discharge, with assessments of general health, growth, vision, hearing, neurologic, developmental, and behavioral status, are an important component. The data gathered are used as feedback for staff, counseling of families, and system development.
2. Family Support: A fully developed follow-up program provides specialized, therapeutic, family-centered transition support, including education, evaluation, feedback, and referrals for families of high risk neonates, with the goal of preventing rehospitalization and maintaining close communication with primary care providers. When a formal program is not available, it is the obligation of the primary care provider to more closely follow, support, and refer, as needed, the high risk infant and family.
3. Research: Individual hospitals or networked follow-up programs that develop standardized protocols, assessments, and age of assessment can systematically investigate and report on the safety, efficacy, and impact of antenatal, perinatal, and neonatal interventions on both short term neonatal and long term post-discharge outcomes.

Eligibility for Follow-up

Most follow-up programs determine eligibility for follow-up by a birth weight or gestational age cutoff. The majority of published reports on outcomes of premature infants have focused on very low birth weight (VLBW) infants $\leq$1,500 g or extremely low birth weight (ELBW) infants $\leq$1,000 g. Recent interest in examining outcomes by gestational age has led to focus on the extremely low gestational age newborns (ELGAN; $\leq$27 weeks). In addition, study eligibility may be determined by the intervention studied (type of ventilation, phototherapy, steroids) or a specific morbidity (i.e., bronchopulmonary dysplasia or intra ventricular hemorrhage).

Age of Follow-up Assessment

While no single optimal age of assessment has been agreed upon, the current consensus among most investigators is the use of corrected age until 30 months of age. Corrected age is age from due date, rather than birth date, thus it takes prematurity into account. Subsequent assessments are completed at the chronologic age. Although follow-up

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to school age is optimal for determining ultimate function, this is usually not practical. Because of the administrative challenges and high cost of tracking, most clinical and research studies report outcomes between 18 months and 2 years corrected age.

What Are the Assessments?

Standard assessments for a follow-up program should include at a minimum health status, growth parameters, neurodevelopmental status, hearing, and vision. *Table 36.1* shows

Table 36.1
Categories of assessment at 18–24 months, 2–5 years, and school age

Assessment category	18–24 Months	3–5 Years	School age
Growth and Nutrition	Weight, length, head circumference, growth, velocity	Weight, length, head circumference, growth velocity	Weight, length, head circumference, growth velocity
	Skin folds, circumference, calorie and protein intake	Skin folds, circumference, calorie and protein intake	Skin folds, circumference, calorie and protein intake
	Body mass index, *z* scores	Body mass index, *z* scores	Body mass index, *z* scores
Neurologic assessment and neuroimaging	Standard for age	Standard for age	Standard for age
	Amiel Tison	Amiel Tison	
	MRI, DTI, DWI, CT	MRI, DTI, DWI, CT	MRI, DTI, DWI, CT
Vision	Eye exam and ophthalmologist reports	Eye exam	Eye exam
		Picture tests	Snellen letters or numbers, "E" test
		Ophthalmologist reports	Ophthalmologist reports
Hearing	Tympanometry, acoustic reflex	Tympanometry, acoustic reflex	Tympanometry, acoustic reflex
	Vision reinforcement audiometry	Behavioral audiometry	Standard audiometry
	Auditory brainstem response	Auditory brainstem response	
Gross Motor	Bayley III Motor Composite	GMFCS	GMFCS
	Bayley III gross motor scale score		
	GMFCS		
Fine Motor	Bayley III Motor Composite	Beery vision motor integration	Beery vision motor integration
	Bayley III fine motor scale score		
Cognition	Bayley III Cognitive Composite	Intelligence testing, executive function, vision motor skills	Intelligence testing, executive function, memory
Language	Bayley III Language Composite	Peabody Picture Vocabulary Test (PPVT)	PPVT, Reynell
	Bayley III receptive language scale score	Parent Checklists	
	Bayley III expressive language scale score		
	Parent checklists		
Functional	WeeFIM, Vineland, PEDI	WeeFIM, Vineland, PEDI	WeeFIM, Vineland, PEDI
Behavior	Child Behavior Checklist 1½–5	Child Behavior Checklist 1½–5	Child Behavior Checklist 4–18
		Child Behavior Checklist 4–18	Connors parent and teacher report
		Connor parent report	
Education	Early intervention	Preschool placement	Regular class, resource assistance, self-contained special education
		Special education preschool	

categories for assessment and the assessment tools used at three ages: 18–24 months, 3–5 years, and school age.

Growth parameters including weight, length/height, and head circumference should be obtained using standard techniques at each visit. If there are serial visits, longitudinal growth and growth velocities can be evaluated. Assessment of nutritional status including protein and calorie intake is most easily achieved during infancy. Subsequent collection of this information for clinical management can be achieved for research purposes but is costly and requires 3–5 day records. However, body mass index and *z* scores can be calculated and skin fold measurements obtained using calipers.

It is important to complete a neurologic assessment at each visit. The NICHD Neonatal Network uses the Amiel Tison examination for their 18–22 month and 30 month examinations. Important classifications of neurologic status need to be determined a priori; classifications which include normal, suspect, and abnormal, or moderate to severe cerebral palsy, mild cerebral palsy, and no cerebral palsy. Radiographic follow-up is currently being done for clinical management. Research studies have used this methodology for children age 7 and older when sedation is generally not needed.

Since blindness, myopia, amblyopia, and strabismus are common among preterms, an eye exam is recommended for each visit. By age 3 a standard picture test can be administered and children older than 5 can cooperate for a Snellen letters or numbers chart test.

Rates of congenital hearing loss and late onset loss are higher in the NICU population. In addition, VLBW infants are at increased risk of chronic middle ear effusions, thus tympanometry with acoustic reflex testing is recommended during the first 3 years. Follow-up with an audiologist for standardized audiology testing is recommended for all infants who passed the newborn hearing screen but have a risk factor for hearing loss (i.e., VLBW) by 24–30 months, or sooner if there is a suspicion of hearing loss.

Developmental outcome is a component of most follow-up studies. The new Bayley Scales of Infant and Toddler Development III was developed for infants 1–42 months. It contains separate composite scores for cognitive, motor, and language skills. In addition, it has scale cores for receptive language, expressive language, fine motor and gross motor skills.

The Gross Motor Function Classification System (GMFCS) is a reliable and validated system to describe severity of motor dysfunction in children with cerebral palsy and has been shown to be stable between 2 and 12 years of age. It is easy to administer and describes levels of function ranging from 1 (walks without restrictions) to 5. (Self-mobility is severely limited even with the use of assistive technology). The Bayley III gross motor scale can also be used between 1 and 42 months of age.

Fine motor skills can currently be assessed up to 42 months with the Bayley III fine motor scale. In older children the Beery Visual Motor Integration (VMI) test can be used in conjunction with fine motor skill assessment during the neurologic examination.

Cognitive abilities are assessed using the Bayley III cognitive composite score up to 42 months. In older children an intelligence test can be administered which may provide a verbal IQ, performance IQ, and full scale IQ in addition to a spectrum of subscores assessing discrete neuropsychological abilities. Mean normed scores on most of these assessments are 100 ± 15.

Preterm infants are at high risk of language delays and careful assessment of these skills is recommended. The previously used Bayley II had an MDI that contained both language-based and non-language-based tasks. The benefit of the new Bayley III is that cognition and language can be evaluated separately. Because of the influence of culture and primary language on test scores it is expected that the new cognitive composite score will be both more reliable and possibly higher than the Bayley II MDI. Prior to the development of the Bayley III language composite score, the primary mode of assessment was vocabulary checklists completed by parents. By 3 years, the Peabody Picture Vocabulary Test (receptive skills) can be administered in conjunction with a verbal IQ. The MacArthur Communicative Development Inventories (CDI) (parent report) was developed to serve as a valid and efficient measure of parental perception of a child's communicative development. The CDI Words and Gestures Inventory is designed to be completed by a caregiver of an 8–16 month old infant, and the CDI Words and Sentences Inventory is designed to be used with children between 16 and 30 months. A Spanish normed version is available. The Reynell is a standardized, individualized language assessment that utilizes toys and objects as manipulatives to assess verbal comprehension and expressive language skills. It is appropriate for children aged 12 months through 6 years 11 months.

Functional skills are essential skills of self-care, mobility, communication, and learning. Functional assessments can be administered to a reliable observer and by telephone interview. Examples include the Functional Independence Measure for Children (WeeFIM), the Vineland Adaptive Behavior Scales, the Battelle Developmental Inventory, and the Pediatric Evaluation of Disability Inventory (PEDI).

Assessment of behavior problems among former preterm infants continues to gain importance. The Child Behavior Checklist is a comprehensive measure of children's behaviors designed to assess in a standardized format the social competencies and behavioral problems of children 1 ½ to 5 years of age, as reported by their parents. Internalizing/externalizing and total problem scores are computed. The Conners Rating Scales-Revised (CRS-R) have three versions – parent, teacher, and adolescent self-report – all of which also have a short and long form available for assessing inattention, oppositionality, and hyperactivity.

Service utilization post-discharge for the former preterm population, many of whom are children with special health care needs, is also an important outcome. Education support services, physical therapy, occupational therapy, speech therapy, deaf educator services, and services for the blind should be recorded at each visit.

Current Status of Outcomes for Very Low Birth Weight Infants

Short Term Outcomes

Survival rates in the early 2000s are approximately 85% for very low birth weight (VLBW, $\leq$1,500 g) and 70% for ELBW infants. Survival has continued to improve for even the most preterm infants born at the limits of viability (23–25 weeks, $<$800 g) but few infants born $<$23 weeks or $<$500 g survive to discharge.

VLBW and ELBW infants who do survive remain at high risk for medical, neurodevelopmental, and behavioral morbidities which, like mortality, are inversely proportional to gestational age and birth weight. Due to these high rates of morbidities, many infants born extremely preterm are discharged home with special health care needs, including home oxygen and monitoring, multiple medications, growth failure, feeding difficulties, and need for gastrostomy tube feeds. Preterm infants are also at increased risk of rehospitalization within the first year of life.

Short term morbidities such as chronic lung disease, intraventricular hemorrhages, and periventricular leukomalacia also increase the risk of long term neurodevelopmental morbidities. Numerous authors have reported on the developmental outcomes of ELBW infants in infancy and early childhood and there is now increasing evidence of sustained adverse outcomes into school age and adolescence (*Table 36.2*).

Neurodevelopmental Outcomes

The primary focus of most published reports of neurodevelopmental outcome in infancy is the incidence of moderate to severe disability, often defined as mental retardation, cerebral palsy, blindness, and/or moderate to severe hearing impairment. This has been the outcome of interest due to the severity of the developmental impact of these severe and often combined morbidities. Unlike mortality rates which have dramatically improved, the incidence of moderate to severe disabilities has not changed significantly over the past 20 years. Rates of disability generally increase with decreasing gestational age and birth weight. In the NICHD Neonatal Network, rates of neurodevelopmental impairment (NDI) defined as the presence of any of the following: moderate to severe cerebral palsy, cognitive or motor scores more than two standard deviations below the population mean on standardized testing, bilateral hearing impairment requiring amplification, or bilateral blindness range from 28% to 40% in infants born 27–32 weeks and 45–50% in infants born 22–26 weeks. In two recent reports, only 21–27% of all ELBW infant survivors were unimpaired at 18 months.

Cerebral palsy (CP) is typically defined as a disorder of movement and posture that involves abnormalities in tone, reflexes, coordination and movement, delay in motor milestone achievement, and aberration in primitive reflexes. Rates of CP among ELBW survivors vary from 5% to 30% but are most recently sited at 5–12%. The most common form of CP in this population is spastic diplegia, accounting for 40–50% of all cases, followed by spastic quadriplegia and hemiplegia.

Arguably more important than the type or location of impairment is the functional level of the affected infant. A diagnosis of CP includes a wide spectrum of motor performance. In the Neonatal Network, 27% of ELBW infants diagnosed with CP at 18–22 months have moderate to severe gross motor function (Level 3–5), but 28% have gross motor function consistent with level 0 or 1 and are ambulatory when classified with the GMFCS.

Functional delays are observed in VLBW infants with and without severe impairments such as CP. While 93% of ELBW infants achieve sitting balance, 83% walk, and 86% feed themselves independently by 18–22 months corrected age, more subtle functional deficits become apparent later in life. At 10–14 years of age, 27% of children who were VLBW and 32% of those who were ELBW report restricted physical activity; 24% of VLBW and 29% of ELBW report they are unable to participate in sports.

Table 36.2
Outcomes for ELBW infants

Assessment category	18–24 Months	3–5 Years	School age
Growth and nutrition	Growth restriction: 30–33%	Shorter and weigh less than term controls	4–6 cm shorter and 4–6 kg less in weight
	Shorter and weigh less than term controls		
Neurologic assessment	NDI: 45–50% of 22–26 week infants 28–40% of 27–32 week infants	Decrease in NDI rates noted	History of brain injury: 50% NDI
			No History of brain injury: 7% NDI
Vision	Blind: 1–5%	Increasing diagnosis of myopia	Blind services:
	Myopia, strabismus, no stereopsis: 9–25%		History of brain injury 16%
			No History of brain injury 1.6%
			Glasses: 33–46%
Hearing	Require amplification: 1–9%	Gradual increase in rates of permanent HL seen	Hearing Aids:
	Mild hearing loss: 28%		History of brain injury: 12%
			No history of brain injury 2.5%
Gross motor	CP: 5–12%%	CP: 5–12%	CP: 5–12%
	Of those with CP: 28% GMFCS 0–1 45% GMFCS 2 27% GMFCS 3–5		DCD: 31–34% of VLBW 50% of ELBW
Fine motor	Bayley PDI $<$ 70: 20–30%	Increasing rates of fine motor impairments identified	Impairments in 70%
Cognition	Mean Developmental Quotient 70–89	Improving IQ with increasing rates of learning disability	Mean IQ 82–105
	Impairment: 37–47% of 22–26 week infants 23–30% of 27–32 week infants 34–37% of $<$1,000 g infants		Impairment: 16%
			Learning disability: 25–40%
			More subtle impairment: 50–70%
Language	Delayed receptive and expressive language scores	Improving language scores	Mean scores 85–90
			Impairment: 13–24%
Functional	93% sitting	Gross motor function improves but emerging fine motor dysfunction	27% restricted physical activity
	83% walking		24–29% unable to participate in sports
	86% independent feeding		
Behavior	Increased rates of behavior problems Autism: 21–25% screen positive True incidence unknown	Increased evidence of inattention and hyperactivity	Inattention/Hyperactivity: 23–27% VLBW 33–37% ELBW
			Anxiety/Social Withdrawal: 25–50%
			Generalized Anxiety Disorder: 8–14%
			Psychiatric Disorder: 25–28%
Education	Early intervention: 74–85%	Increased rates of preschool special education	Special education: 25–62%
	Increased needs for community supports		Grade repetition: 15–34%
			Graduation rate: 56–74%

While CP is the most well known and potentially most disabling motor abnormality associated with prematurity, infants born preterm often demonstrate less severe differences in their neurologic development. During the first year of life transient dystonia is a common deviation in the motor development of VLBW infants. Transient dystonia occurs in 21–36% of preterm infants with a peak incidence at 7 months corrected age. It involves increased extensor

tone of the trunk and lower extremities and increased adductor tone in the lower extremities, leading to shoulder retraction and hip rotation, persistent primitive reflexes, head lag on pull to sit, and delayed supportive responses. The presence of these findings increases the risk of later cognitive and motor problems including CP. Twenty percent of infants with transient dystonia go on to be diagnosed with CP. But the specificity of these findings is low, as they are truly transient in 80% of the infants in which they occur, disappearing gradually between 8 and 12 months of age.

Children born preterm are also more likely to have difficulty with motor coordination. In the past these children were often labeled as "clumsy" but in recent years the diagnosis of developmental coordination disorder (DCD) has been used. DCD is defined as impairment in motor performance sufficient to produce functional impairment that cannot be otherwise explained by the child's age, cognitive ability, or neurologic or psychiatric diagnosis. DCD is found in 31–34% of VLBW and 50% of ELBW infants at school age.

Difficulties with fine motor skills, visual perception, visual-motor control, hand–eye coordination, or visual-motor integration, are seen in as many as 70% of children born VLBW or ELBW. These difficulties can impact on academic performance and in functional abilities in 23% at 5 years of age.

While much less common than motor disabilities, rates of neurosensory disabilities are higher in ELBW infants than the general population. Unilateral or bilateral blindness occurs in up to 1–5% of ELBW infants. Milder visual impairments including myopia, strabismus, and lack of stereopsis (depth perception) occur at rates of 9–25%. Hearing impairment requiring amplification is reported in 1–9% of ELBW infants. Milder hearing impairment has been reported in up to an additional 28%.

The most common severe impairment seen in preterm infants at 18 and 30 months is cognitive impairment, defined as scores that are more than two standard deviations below the mean on standardized cognitive testing. Average scores on cognitive testing at 18 and 30 months range from 70 to 89 for ELBW infants, compared to 85–115 for the general population. Like rates of motor impairments, rates of cognitive impairment are inversely proportional to gestational age and birth weight. Rates of cognitive impairment at 18–22 months corrected age are reported at 37–47% in 22–26 week infants 23–30% in 27–32 week infants, and 34–37% in all infants $<$1,000 g in the NICHD Neonatal Network.

While cognitive functioning can be measured in infancy, it is not predictive of cognitive functioning later in life. The assessment of an infant's cognitive function is highly dependent on their motor, language, and social-emotional development. In one cohort of 330 ELBW infants, mean MDI at 20 months was 76 compared to a mean cognitive score of 88 at 8 years, and rate of cognitive impairment dropped from 39% at 20 months to 16% at 8 years. The positive predictive value of having a low cognitive score at 8 years ($<$70) given a low cognitive score at 20 months ($<$70) was only 0.37.

The mean intelligence quotient (IQ) for VLBW and ELBW infants during school age, adolescence, and adulthood is higher than at 18 and 30 months, ranging from 82 to 105. Although these mean IQs are within the average or low average range, they are 0.5–1.0 SD lower than those of normal birth weight peers and reflect significantly higher rates of cognitive impairment. Cognitive scores at school age and beyond remain reflect significantly correlated with gestational age and birth weight.

More subtle cognitive impairments are detected in 50–70% of children born VLBW at school age. These include relative impairments of executive functioning, visual-motor skills, and memory, especially verbal memory. These children score lower on tests of academic achievement, have poor perceptual-organizational skills, difficulty with visual processing tasks, and delays in adaptive functioning compared to their normal birth weight peers. Rates of learning disabilities are high, especially in mathematics, ranging from 25% to 40%.

Speech and language also develops atypically during early childhood in previously ELBW infants, with delays in the acquisition of expressive language, receptive language, and articulation. Children born at or before 25 weeks gestation have significantly lower scores on standardized language tests (90 vs 104) and higher rates of language impairment (16% vs 2%) than the general population at 6 years of age. Former ELBW infants continue to have significantly lower scores (92 vs 105) and higher rates of impairment (13% vs 4%) on the PPVT, as well as lower expressive, receptive, and total scores (85–87 vs 100–103) and higher rates of impairment (22–24% vs 3–4%) on the CELF at age 12.

While language development in infancy and early childhood is often an early proxy for overall cognitive development, specific language deficits have been described including phonological short term memory, and prosodic processing. At 12 years of age, children born $<$1,250 g have less pronounced differences on tests of lower level language skills (phonological processing, phonemic decoding, and sight word reading) compared to term controls, but exhibit significantly more difficulty with higher level skills (syntax, semantics, verbal language memory, and reading

comprehension). In addition, when given a semantic processing task, preterm children have abnormal patterns of brain activity on functional MRI, resembling the brain activity of term controls during phonologic processing.

Behavioral and Psychological Outcomes

Very low birth weight has been associated with a wide variety of behavioral and psychological diagnoses and disabilities. Recent concern has arisen that rates of Autism Spectrum Disorder (ASD) may be higher in ELBW infants than previously thought. Though low birth weight (<2,500 g) may result in a 2–3 fold increase in the risk of ASD, true risk of ASD in very preterm infants is unknown. Recent studies report that 21–25% of VLBW infants screen positive on the M-CHAT at 18 months. However VLBW infants with other severe impairments often have a false positive screen. The rate of positive screens in those without severe impairment was 10%. Neither of these studies performed diagnostic confirmation. Thus, further studies are needed to determine the true risk of autism in this population.

Parents and teachers of VLBW/ELBW infants report higher rates of inattention and hyperactivity at school age (8–12 years old), with rates of 23–27% in VLBW and 33–37% in ELBW infants. One quarter to one half of children born VLBW/ELBW have symptoms of anxiety and/or social withdrawal, 8–14% meet criteria for generalized anxiety disorder (compared to 1–4% of peers), and 25–28% meet criteria for a psychiatric disorder (compared to 7–10% of peers). These children continue to score higher on measures of inattention, anxiety/depression, withdrawn behavior, and social problems at 17 years of age.

Possibly as a result of higher rates of developmental and psychological sequelae, VLBW teens and adults score significantly lower on measures of self-esteem, and report less confidence in their athletic, school, romantic, and job related abilities. However they report lower rates of alcohol and drug use, sexual activity, and pregnancy than adults born normal birth weight.

Educational Outcomes

Due to high rates of impairments, ELBW infants have high rates of academic underachievement and increased needs for special education services. Teachers of VLBW infants report rates of below average school performance in all academic areas, ranging from 24% to 41%. Approximately 25% of VLBW infants and up to 62% of ELBW infants receive special education services. Between 15% and 34% require grade repetition. Only 56–74% of preterm children, significantly fewer than term birth weight teens, graduate from high school. Significant gender differences exist in graduation rates: 66% of VLBW males compared to 75% for term males and 81% for VLBW females compared to 90% for term females.

Late Preterm

The majority of neonatal outcomes research has focused on the ELBW infant. But during the 1990s the rates of delivery at 40 or more weeks gestation decreased while rates of deliveries between 34 and 36 weeks increased steadily, causing the rate of late preterm births to increase from 7.3% to 9.1% of all births between 1990 to 2005. These "late preterm infants" have higher mortality rates and higher rates of neonatal morbidities, with the potential to increase the risk of long term neurodevelopmental sequelae. Infants born 34–36 weeks are 3.39 times as likely as term infants to develop CP and 1.25 times more likely to have cognitive impairment than infants born at term. They are more likely to qualify for special needs preschool and are more likely to have problems with school readiness. In kindergarten and first grade they have lower reading scores, teachers report math skills below those of their full term peers, and they are more likely to qualify for special education services.

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37 Ethics and Decision Making in Neonatology

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Introduction

The history of neonatology parallels that of bioethics. Improvements in the care of neonates that led to major decreases in mortality are rather recent. Before the 1970s, babies born even mildly prematurely would usually die. Patrick Bouvier Kennedy, the son of the late US president John F Kennedy, provides a useful historical landmark. He was born in 1963, at a gestational age (GA) of 35 weeks and weighing 2 kg. He died in a hyperbaric oxygen chamber at Boston Children's Hospital on the second day of life. Even for the most powerful family in the world, doctors could do nothing.

Today, many more treatments are available and survival rates for premature babies are much better. Advances in treatment have led to new ethical dilemmas. The most common ethical dilemma involves a decision about withholding or withdrawing life-sustaining treatment in a situation where such treatment could save or prolong the life of a baby but might leave the baby with profound physical or neurologic deficits. In such cases, the traditional medical obligation to save life conflicts with the obligation to reduce pain and suffering.

These dilemmas are not unique to neonatal care. They also occur in other areas of pediatrics. Dialysis, heart surgery, extracorporeal membrane oxygenation (ECMO), or bone marrow transplant, for example, may save lives but may also leave survivors severely impaired. Neonatal issues are unique, however, for two reasons. First, decisions about newborns often take place at the moment when the fetus becomes a baby. At that moment, their legal status changes dramatically. The fetus does not have independent legal status. The newborn does. This legal change becomes the basis for a profound shift in moral obligations. Prior to birth, the doctors caring for a pregnant woman and her fetus must balance the risks and benefits of interventions that might help the fetus but harm the pregnant woman. After birth, the treatment decisions for the baby no longer need to consider the effects of those treatments on the woman's body. Second, decisions at the borderline of viability are associated with greater prognostic uncertainty than decisions in many other areas of pediatrics. Outcomes for tiny premature babies or asphyxiated infants cover the spectrum from completely unscathed to neurologically devastated. Much of the work of modern neonatal bioethics has been an attempt to develop coherent and consistent philosophical responses to such dilemmas.

The Evolution of Neonatology and Bioethics

The 1960–1990s brought a rapid evolution in neonatal care. Innovations such as amniocentesis and prenatal ultrasound allowed identification of high-risk pregnancies and earlier diagnosis of fetal anomalies. The regionalization of perinatal care allowed the concentration of expertise in regionalized referral centers. Antenatal corticosteroids and screening of pregnant women for group B streptococcal infections prevented or ameliorated the severity of newborn respiratory distress syndrome and neonatal sepsis. Better techniques for mechanical ventilation and parenteral nutrition supported fragile premature babies through the first perilous weeks of life. As a result, babies who would have died 20 years ago now routinely survive. Babies who would have been impaired as a result of sepsis or hypoxia now survive unimpaired. In the past 20 years, the disability rate has gone down at each gestational age, and for most neonatal problems. However, because more babies survive, the overall rate of disability as a result of perinatal complications has remained about the same. But the moral implications are different. In the past, babies used to survive or die in spite of our best efforts to save them. Now, often, a choice can be made about whether to allow them to die or to intervene.

Bioethics initially emerged as a response to dubious research protocols involving human subjects. After the birth of research ethics, clinical ethics has developed to answer questions often raised by the developing technologies and medical progress. For example, in vitro fertilization, organ transplants, ECMO, and open heart surgery have changed the way relationships, the human body, and

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life are looked at. They have also raised many ethical questions and dilemmas. One widely discussed approach to these dilemmas is the reliance on the four principles of Beauchamp and Childress. These principles are sometimes referred to as if they are "the" principles of bio-ethics: autonomy, beneficence, non-maleficence, and justice. Although these principles are valuable for framing the debate, they are no more objective than any other approach to ethical reasoning. Beneficence is in the eye of the beholder, an approach which is considered beneficent by one person, may seem excessively onerous and maleficent to another. Moreover, these four principles often contradict each other. The physician may think intervention is beneficent to an infant, but the baby's parents may disagree (autonomy), and they might also think that this disabled neonate is too much of a risk for their other children and their family life (distributive justice). Societies differ in the importance given to individual autonomy, as compared with community values. Other approaches (consequentialism, communitarism, feminist ethics, compassionate ethics, and others) are also valid and bring other insights to help address these dilemmas.

From Fetus to Person

Debates about neonatal bioethics have been inseparable from debates about abortion and the moral status of the fetus. This is because the bright legal dividing line between fetus and baby does not reflect the biological reality that is continuous rather than dichotomous. Intrauterine events influence neonatal outcomes. Antenatal decisions are as prognostically important as postnatal decisions. The instantaneous transition from intrauterine to extrauterine life has enormous moral and legal implications. Where abortion is legal, the fetus has no legal right to life, although most countries' abortion laws recognize a growing state interest in the life of the viable fetus.

This split between biological realities and legal realities is part of what makes neonatal bioethics unique. Neonatologists are physicians who can consult for patients who are not yet legal persons. They see mothers in consultation regarding problems which affect their fetuses. They create estimates regarding outcomes for patients who are not yet born. Sometimes, they never even meet their ex-fetus patients, either because the fetus dies in utero and never becomes a person, the pregnancy is terminated, or because the high-risk pregnancy is carried to term and the baby never needs to be admitted to the NICU.

The uniquely ambiguous moral status of the in utero patient shapes the ethical responses of the neonatologist. He or she must make decisions about what should or should not be done for the baby at the moments following birth, but those decisions are often somewhat tentative, being based on information that usually gives a wide range of possible outcomes, leaving enormous uncertainty.

NICU Patients and Ethical Questioning

The majority of babies in the NICU are there because they were born premature. Other babies are there because of infection (or suspicion of), congenital anomalies, asphyxia, metabolic disturbances, and other conditions that require them to be closely observed. About 12% of births in the United States and 8% in Canada are born preterm, before 37 weeks of gestational age. Of these, two thirds are born between 34 and 36 weeks and one third are before 34 weeks. Approximately half of late preterm babies, and virtually all babies born before 34 weeks are admitted to the NICU. About 3% of babies are born with a moderate to severe congenital anomaly, and approximately half are admitted to the NICU. Thus, roughly two third of NICU admissions are accounted for by prematurity. Although most articles in neonatal ethics have focused on extremely preterm infants, babies who are born severely asphyxiated, who have a grave metabolic disease, who have a serious neuromuscular disease, or congenital anomalies often raise many, if not more, ethical questions than extremely preterm infants.

Late preterm babies are at higher risk for long-term disabilities than full-term babies. Many late preterm births follow obstetrical decisions to medically induce delivery. These obstetric decisions require a complex trade-off between the risks of *in utero* insult (and liability) in a high-risk pregnancy and the risks of preterm delivery. The rate of medically induced preterm birth has been steadily rising in most industrialized countries and accounts for a big proportion of the rise in preterm births. More babies with disabilities originate each year from late preterms than from extremely preterm or full-term infants. Half the patients in cerebral palsy registries were not sick nor admitted to an NICU at birth. For the remaining half, most were of a gestation greater than 28 weeks at birth. In general, there would be no ethical question about whether to admit these babies to the NICU and offer active treatment. It is worth remembering, then, that policies to limit treatment for babies at the borderline of viability will not have much effect on the overall rate of cerebral palsy and disabilities in society.

Extremely premature babies, with a gestation of less than 28 weeks (Extremely Low Gestational Age Neonates,

ELGANs) or a weight of less than 1,000 g (also called Extremely Low Birth Weight babies, ELBW), comprise 0.8% of all deliveries and about 10% of NICU admissions. For these babies, birth weight and gestational age correlate with survival rates, although other factors are also very important. Infants weighing 1,000 g or born at 27 weeks gestation have an approximately 90% chance of survival. Infants who weigh 500 g at birth and are 23 or 24 weeks of gestational age have 30–60% chance of survival, but a high risk of severe neurodevelopmental disability.

For some babies in the NICU, multiple follow-up studies exist that can help parents and physicians predict outcomes. For example, for extreme prematurity and birth asphyxia probabilistic predictions of survival and disability can be made based on specific clinical features; one can question the utility of a prediction of a specific percentage risk of disability or survival, but some parents seem to appreciate this sort of information. The ethical dilemma here is dealing with the remaining considerable uncertainty. For a particular baby and family, statistics about cohorts of ELBWs might not be that helpful. An unborn ELBW baby with a 10% predicted risk of cerebral palsy will either have 0% or 100% cerebral palsy (albeit the severity of the affliction is highly variable, increasing the complexity of the decision-making). Other babies are born with multiple congenital anomalies, a specific syndrome, or serious metabolic diseases where research may be much scantier, but where babies are unambiguously impaired from birth. These diseases may have a narrower range of outcomes, but for some, there remains considerable uncertainty. For such babies, the ethical dilemma has less to do with weighing the probabilities and dealing with uncertainty; rather it is deciding what degree of impairment should be considered too severe and thus justifies limitation of life-sustaining therapy.

When medical technology develops quickly, many ethical and moral questions arise at the same time as a new development is made or, all too often, afterward. For what survival and long-term outcomes should very sick patients receive intervention? Do parents always have a choice when their newborn is at risk of disability, or is disabled? Should they be entirely responsible for the decisions, or should others also be involved? How are the neonate's best interest evaluated?

Prognostication and the Borderline of Viability

Prognostication in the NICU is difficult. There is no way to completely eliminate uncertainty. Babies who are doing well and who are predicted to survive may have an unexpected complication that leads to an unpredicted death. Babies who are not doing well may be predicted to die, but such predictions are often wrong. Both illness severity scores and our clinical intuitions are imperfect in predicting death or disability with high accuracy.

There are two possible responses to this uncertainty. One is to develop guidelines for treatment based upon probabilities. Given this uncertainty, many professional societies have developed policies about babies in the NICU. Unfortunately, these policies have described decision-making for babies born at the borderline of viability and ignored other equally important issues such as the baby with anomalies.

Such policies consider gestational age, birthweight, and other factors in order to classify babies as fitting into one of three "zones." One zone is that in which good outcomes are likely and thus in which treatment is considered morally obligatory. A second zone is often called "the gray zone." In the gray zone, outcomes are considered sufficiently ambiguous or uncertain as to allow non-treatment as an ethically defensible option. Finally, there is a zone in which newborns are not considered viable or, to put it another way, in which treatment is considered "futile." Today, in the policies of most developed countries, the "gray zone" is defined as between 22 and 26 weeks of gestation. It should be noted that in some countries, a baby in the gray zone could be in the futile zone in another country, or in the "good outcome" zone in yet another! Such policy statements are user friendly and simple. They are, however, both scientifically and morally problematic.

There are a number of problems with such algorithmic policies. First, these policies are often based on gestational age and prenatal determination of gestational age is imprecise. It can be off by a week or two in either direction. Thus, in the "gray zone," pre-birth decisions about resuscitation based on gestational age should be either tentative or avoided altogether. Second, birth weight, gender, place of birth, multiple birth, infection, and use of antenatal steroids are all independent predictors of outcome; adjusting for these factors improves the prognostic estimates. For example, a female infant born at 24 weeks weighing 700 g whose mother received steroids has a 74% chance of survival. A male infant born at the same gestational age but who weighs only 500 g and whose mother did not receive steroids has only a 26% chance of survival. Clearly, gestational age alone is not a very precise predictor of outcome.

A second approach to prognostic uncertainty would be to individualize treatment. By this approach, treatment could be initiated whenever there was a reasonable possibility of success, and decisions would be made about

whether to continue or to discontinue treatment based upon the baby's response to therapy. This approach also has disadvantages. Estimating "a reasonable possibility of success" is subjective. The problem with individualized treatment decisions is that prognosis does not necessarily improve with time. Some babies "declare themselves" by doing either better or worse than expected. This is particularly true for the tiniest babies. For many babies, however, there are no reliable predictors of outcome that can be assessed over time. For extremely preterm infants, resuscitation based upon an assessment of the newborn in the delivery room is also commonly offered. While this approach is appealing, epidemiologic studies suggest that there are no reliable predictors of outcome that can be obtained in the first minutes or hours of life.

Framing Issues and Informed Consent

Most professional guidelines suggest that doctors should share decision-making authority with parents for babies in the gray zone. Most doctors agree, in theory, with these guidelines. In practice, however, they often do not share decisions with parents. By their own self-report, they make unilateral decisions about resuscitation. Sometimes, they decide to resuscitate, sometimes not.

It is not clear whether physician paternalism with regard to extremely premature babies is more likely to lead to overtreatment of babies in situations when their parents would have wanted comfort care, or undertreatment of babies who had a reasonable chance for a good outcome. In all studies, parents are more likely than doctors or nurses to think that every effort should be made to save babies, regardless of their birthweight or chances for survival; parents also generally rate quality of life higher for babies with severe disabilities than do doctors or nurses. Interestingly, such differences are greater among parents who have had a premature baby than among parents of term babies.

In order for parents to give truly informed consent for treatment or for non-treatment, doctors need to be able to explain to them the complicated probabilities about survival and impairment. This task is complicated for a number of reasons. First, survival statistics differ at different units. Sometimes, these differences reflect policies about treatment in those units. Policies often turn into statistics. Thus, units that do not routinely resuscitate babies under 25 weeks will have much fewer survivors under 25 weeks. The policy becomes a self-fulfilling prophecy. It would be technically true to tell parents in such a unit that survival is extremely rare, in that unit, at 23 weeks. It would also be misleading, since other units, and even entire countries, report survival rates above 50% at 23 weeks.

A second reason why informed consent is complicated is that the information to be explained is inherently complex. For prenatal consults when there is a high risk of delivery of an extreme preterm in the "gray zone," the American Academy of Pediatrics (AAP) recommends physicians to inform parents of survival, and of all the relevant risks of short-term complications and long-term impairment. This risks swamping the parents with a potentially enormous quantity of information and percentage estimates. Parents in this extremely stressful situation need to be treated with compassion, and with realistic expectations of their abilities to recall information provided. Some parents want a lot of information, and knowing everything that can happen gives them some control. Other parents have difficulty dealing with everything the AAP recommends us to tell them. When families are counseled about these critical decisions their attention is often focused on a very different issue: they just want to continue the pregnancy.

A third complexity relates to framing issues. Psychometric studies show that people respond differently when told the same information in different ways. This has been directly confirmed in a study examining treatment decisions at extremely low gestations, volunteers were far more likely to decide for intensive care if the information was framed in a positive manner (for example, 25% survival), than if exactly the same information was framed negatively (75% will die).

One helpful way to break down the issues is to make sure that parents understand five possible scenarios for babies in the "gray zone": (1) Comfort care in the delivery room and death. (2) Admission to the NICU for a trial of therapy with possibility of withdrawal of intensive care if the infant develops severe illness or is predicted to survive with severe disabilities. (3) Admission to the NICU and death despite continued maximal medical therapy. (4) Admission to the NICU and survival with disability. (5) Admission to the NICU and survival without disability. Estimating the probability of options 2–5 might help parents decide whether or not to opt for option 1. All these options will directly affect parents and families for all their lives, including option 5. Interestingly, there are studies about how families cope with options 2, 5, but not option 1.

Disabilities and Quality of Life

Survival is not the only factor to consider. Other important considerations are the burden of prolonged intensive

care, and the risks of long-term disability, or of later death. Twelve to twenty-five percent of babies born before 27 weeks gestational age will have major neurological or developmental disabilities. These include cerebral palsy (8–10%), deafness (3%), blindness (3%), and developmental retardation (10–20%); up to 50% will have behavioral or educational problems: hyperactivity, learning difficulties, dyslexia, or behavioral problems. Rates of disability are higher in near-term babies than in term babies, and higher in ELGANs than in near-term babies, but, among ELGANs, gestational age does not correlate with the rate of long-term disability. Furthermore, the rate of severe disability is similar for babies at each gestational age between 22 and 25 weeks. In other words, for babies less than 26 weeks, the frequency of most disabilities, among survivors, changes very little and therefore, the chance of survival can be used as a proxy for all these outcomes. Mild cognitive deficits and learning problems are common. Severe deficits are rare. The mean IQ of ELBW infants is approximately 79, one standard deviation below that of control infants. It is interesting to note that for the past 10 years, surgeries and interventions for babies with Down syndrome are rarely questioned, and that their IQ is on average 42.

Motor dysfunction (cerebral palsy) may occur in up to 8–10% of very premature babies. Like the cognitive deficits, cerebral palsy is generally not catastrophic, compared for example, to babies born asphyxiated. The vast majority of babies with cerebral palsy are ambulatory without assistance. Importantly, some disabilities classified by physicians as being "minor," for example, hyperactivity or learning disability, can have far more devastating consequences to some families than some that are classified as "major" disabilities such as cerebral palsy and deafness. The way physicians place survivors in a "normal," "major disability," or "minor" disability category is necessary to scientifically quantify exactly adverse outcomes in this population, but it should be remembered that few studies look at functionality of these families. Multiple major disabilities that leave a child unable to ever live independently arise in less than 5–10% of babies born at less than 28 weeks.

The degree of disability is not correlated with either self-reported quality of life and parental reports of their child's quality of life. Parents of preterm infants, and the infants themselves when they are older, judge their quality of life to be much better than judgments made by health care providers. Not surprisingly, then, parents of both full term infants and of very premature babies are more likely than health professionals to favor the treatment of extremely premature infants. For example, 64% of parents were in agreement with the statement, "we should try to save all newborn infants independently of their birth weight," in comparison with 6% of healthcare providers.

Given these parental preferences, pediatricians often face a conflict between their negative assessment of an infant's long-term prognosis and the parents' desire for continued life-sustaining treatment. In such a situation, the burden of proof is on the physician who must be convinced that continued treatment is not in the interest of the baby. In the past, pediatricians have been criticized by advocates for the disabled for making decisions that undervalue the lives of people with disabilities. Moreover, it has been shown that non-treatment decisions are considered more often for extremely premature babies than for other patients with the same or even worse prognosis. When physicians are fairly certain that treatment will only lead to survival that is associated with intractable suffering for the infant, doctors should recommend non-intervention. Otherwise, they should defer to parents' wishes after they have informed parents of likely outcomes. Obviously, this standard requires careful judgments to be made under conditions of uncertainty: what life is worth being lived? When is death better than a life with disabilities? Are these decisions being taken for babies only, or also for their families, for ourselves, for society? Making a judgment of the value of the future for a small baby is never easy.

Practice Variation and Informed Consent

In all areas of medicine variations in practice occur. However when such decisions occur in life-or-death situations patients should be offered the same opportunities. In fact, decisions regarding whether or not to institute intensive care rather than palliation are much more variable in neonatology than in other domains: Although the initial therapy offered to women with advanced breast cancer varies across the USA, the number of women offered palliation as initial therapy does not (practically zero, everywhere). There are obvious differences in decision-making between resource-limited parts of the world with limited availability of intensive care facilities, equipment, and trained personnel and industrialized countries. However, enormous variations in survival of extremely preterm infants occur between countries with otherwise similar medical systems. In industrialized countries, most of this variation is due to differences in attitudes, infants being much more likely to die without an attempt at active intervention in some countries than in others. Some physician groups are prepared to institute palliative care for infants with an 83% chance of survival, an attitude which would be frankly unacceptable for older children, adults or

the elderly. Others are prepared to institute active care even when they feel that it is "futile." These variations in philosophy and approach lead both to avoidable deaths on the one hand, and avoidable intensive care with little or no hope of success on the other.

Consistency and consensus in these decisions is not by itself a worthwhile goal; it is possible to be consistently wrong! It seems, however, morally problematic that a mother presenting with the same high-risk pregnancy to two hospitals with the same capacity to intervene will have two discussions which are diametrically opposed, and will have her decisions influenced in opposite directions. The challenge is to find the right balance between consistency and local ethos.

Are Neonates Valued Differently from Older Individuals?

The Neonatal Resuscitation Program (NRP) textbook, which is the standard neonatal resuscitation text used in North America and many other parts of the world, states: "The ethical principles regarding resuscitation of newborns should be no different from those followed in resuscitating an older child or adult." On the other hand, current practice suggests that the principles are, in reality, very different. There is clear evidence of categorical separation of the ethical assessments associated with treatment or non-treatment decisions for newborns from similar decisions for older children or adults, assessments of whether resuscitation is in the best interests of a patient are not closely related to survival rates, nor to disability.

Setting an upper age limit for resuscitation is not a new concept, but is very controversial. While there appear to be no official policies or professional association guidelines which suggest an upper age limit for resuscitation, a lower age limit for the premature infant is almost universally promoted. At 24-weeks gestation, many national associations (for example, the Canadian Pediatric Society) deem prognosis to be so poor that life-saving interventions are considered to be futile, or optional. The current chances of an infant delivered at 24-weeks GA are a 50–70% survival rate and 50% "normal outcome" among survivors or better. There is no other group of incompetent patients for whom such results are thought to be too dismal to intervene, or to defer life and death decision entirely to the family. Policy statements for preterm infants often state survival and handicap as justification for optional intervention, the fact that such outcome statistics would not justify such approaches in other populations suggests that some other powerful factors are at work. These might include a sense that a premature baby is not yet a full-fledged person, that he does not have a "real" disease, a sense that neonatal care is disproportionately expensive, or an unduly pessimistic understanding of the likely outcomes.

Cost-Effectiveness of NICU Care

One concern often raised concerning neonatal intensive care is of its cost-effectiveness. Official guidelines have even invoked the expense of NICU care as a reason for denying intensive care to high risk infants. However, objective analyses of NICU care demonstrate that the large majority of NICU costs are expended on infants who will survive and have good outcomes. Because most infants who die do so within a few days, only 10% of NICU costs are expended on infants who do not survive. By this measure, NICUs are far more cost-effective than medical ICUs for adults, where 30–50% of expenditures go toward patients who do not survive until hospital discharge.

Another way to analyze cost-effectiveness is to calculate the dollars spent per quality adjusted life year (QALY) that results. By this measure, too, NICUs are highly cost-effective. For even the tiniest babies, NICUs achieve cost-effectiveness of <$10,000/QALY. This compares favorably to the $40,000–50,000/QALY benchmark that is used to evaluate many other medical therapies. NICU care is one of the most cost-effective tertiary care interventions in all of medicine. It is far more cost-effective than adult intensive care, coronary bypass surgery, solid organ transplantation, renal dialysis, or many other well-accepted interventions. If the provision of intensive care services were to be made on the basis of cost-effectiveness, NICUs would always be given the first priority in funding.

Preventing Prematurity

The rate of preterm birth in the United States has gone up by more than 50% over the last 25 years, from a little over 8–12.5%. The USA has the highest rate of preterm birth of any industrialized country, but preterm birth rates are rising in most industrialized countries. A critical (and maybe the most important) ethical issue in neonatology is how to prevent preterm birth.

Many approaches have been tried to decrease preterm birth. One approach is to provide better prenatal care. This was once thought to be the panacea, since preterm birth rates were much higher among women with inadequate or no prenatal care than with women who received

comprehensive prenatal care. Unfortunately, better access to prenatal care has not resulted in fewer preterm deliveries. More than half of preterm births are near term babies and many of those preterm deliveries are medically induced. Practice guidelines for Cesarean sections or inductions may lower the rate of unnecessary preterm delivery.

Another factor associated with the rise in preterm birth is the rise in treatments for infertility and delaying child birth. Both pharmacologic stimulation of ovulation and in vitro fertilization are associated with multiple pregnancies and multiple pregnancies are associate with preterm birth. Many countries have addressed the large increase in multiple births and the attendant complications by reimbursing costs of assisted reproduction technologies and adopting policies that mandate signle embryo transfer in IVF clinics. This has led to a progressive decrease in multiple gestations. In Sweden, only 5% of babies created through IVF are multiples; in the USA, it is 32%. In a North-American NICU study, iatrogenic avoidable multiple pregnancies from IVF were responsible for 16% of NICU admissions, and for significant avoidable mortality and morbidity, which produce unacceptable financial and emotional costs. If responsible fertility treatments were used in the USA and Canada, it would avoid many unnecessary NICU admissions and many complications to mothers and their children.

Global ethical issues include the world wide infant mortality. While ethical debate in developed countries focus on babies who are admitted to the NICU and are at elevated risk of later disabilities, many babies born in the world still die of benign infections, mild prematurity, and even malnutrition. This ongoing tragedy is beyond the scope of this chapter, but merits considerable reflection and thought.

Conclusions

Most babies who now survive intensive care would have died 40 years ago. Nature would have decided the outcomes. Ethical discussions about initiating or withholding resuscitation would have been unnecessary and irrelevant. Today, policy makers, administrators, families, and physicians often decide if a baby should be offered life-sustaining treatment. These decisions directly affect our society and our population health. A moral framework for making such decisions needs to consider the baby's interests, the family's interest, the cost of care, and availability of resources. While neonatal intensive care is often uncontroversial and beneficial, it can also lead to tragic outcomes that increase pain and suffering at enormous expense. Also, neonatal intensive care should not be seen as the only solution to preterm birth, prevention of prematurity is feasible and should be a public health proirity. Careful consideration of the medical facts, the issues of resource allocation, and the psychological implications of decisions will maximize benefit and minimize harm. While there are no easy formulae to "solve" these dilemmas, open discussion of these issues among clinicians, between clinicians and families will maximize the likelihood that the best decisions are made in each individual case.

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Inborn Errors of Metabolism

Pinar T. Ozand

38 Disorders of Organic Acid and Amino Acid Metabolism

Pinar T. Ozand · Mohammed Al-Essa

A large number of pediatric disorders occur as a result of inborn errors occurring in the metabolic pathways of amino acids or organic acids. These diseases are common pediatric problems with dramatic clinical presentations. Their initial clinical presentations differ according to age. A convenient manner of classification is as follows:

1. *Diseases of neonatal onset.* The first clinical symptoms appear soon after birth or within the first few weeks of life. Such diseases are always associated with central nervous system (CNS) symptoms. Occasionally an infant will be born with an encephalopathic picture and stupor, with profoundly disturbed neurologic function at birth. More often, an infant normal at birth will soon develop lethargy, progressing rapidly into coma in association with other severe neurologic signs. The disease will cause neurologic handicaps and death if intervention is not prompt. These diseases are therefore called "devastating metabolic diseases of the newborn." In this age group other systems, particularly the hematopoietic system and the liver, may also be involved.
2. *Diseases of later infancy or childhood.* In this age group amino acid and organic acid disorders will also lead to profound derangement of CNS functions. However, other systems, particularly the liver, might be involved. An important category of diseases is "silent," "neurologic," or "cerebral" organic acidemias. As the name implies, these are diseases that manifest only with progressive neurologic findings, without any disturbance in acidbase, ammonia, or glucose metabolism. As was the case for diseases of neonatal onset, if these disorders are not recognized early, they can lead to neurologic handicaps and death.

Devastating Metabolic Diseases of the Newborn

Clinical Presentations

The main diseases in this category are shown in *Table 38.1*, which does not include some of the rarer entities, but lists only common diseases.

Most of these patients will be normal at birth, except those with nonketotic hyperglycinemia and peroxisomal disorders who have severe stupor and encephalopathy. In the remainder, a prodrome with refusal to feed, vomiting, and lethargy that starts a few hours to days after birth rapidly evolves into profound coma in association with seizures and change of muscle tone. Vomiting may be so severe that occasionally the infant will be diagnosed as having intestinal obstruction or pyloric stenosis, and will undergo unnecessary laparotomy. The dramatic clinical picture is often interpreted as sepsis or meningitis without due consideration for an underlying metabolic disease. Since, at times, the metabolic disease leads to sepsis, proper diagnosis will be missed for many days and the underlying metabolic disease, since it is not treated appropriately, will lead to tragic consequences with irreversible neurologic damage. This is particularly true for maple syrup urine disease (MSUD or branched-chain aminoacidemia); such a patient, for example, is prone to a gram-negative or gram-positive sepsis, and will have no readily detectable clinical biochemical disturbance, leading to diagnosis only when the infant experiences a second devastating episode during the first month of life, by which time the patient will have suffered extensive CNS damage and will not have any hope of treatment.

Despite a great deal of similarity in their clinical presentation, several clinical symptoms give clues to the diagnosis. These clues are described in the following sections.

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Table 38.1
Devastating metabolic diseases of the newborn

Organic acidemias
Propionic academia
Methylmalonic academia
Isovaleric acidemia
3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) lyase deficiency
Multiple carboxylase deficiency
3-Methylglutaconic aciduria
Multiple acyl coenzyme A dehydrogenase deficiency (glutaric aciduria type 2)
Primary lactic acidosis:
Pyruvate carboxylase deficiency
Pyruvate dehydrogenase deficiency
Cytochrome *c* oxidase (COX) deficiency
5-Oxoprolinuria (pyroglutamic aciduria)
Amino acidemias
Urea cycle disorders:
Carbamylphosphate synthetase deficiency
Ornithine transcarbamylase deficiency
Citrullinemia
Argininosuccinic aciduria
Maple syrup urine disease, classic form (classic MSUD)
Diseases associated with encephalopathy and stupor
Nonketotic hyperglycinemia
Zellweger syndrome and neonatal adrenoleukodystrophy
Menkes disease
Miscellaneous disorders
Nesidioblastosis

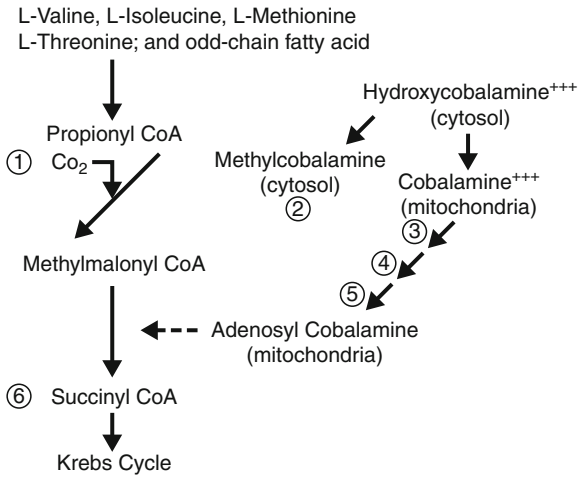


Figure 38.1
Metabolism of propionic and methylmalonic acid. Enzymes involved: (1) propionyl-CoA carboxylase, (2) methylcobalamin, which is involved in the methylation of homocysteine to methionine through the tetrahydrofolic acid methyltransferase, (3–5) two reductases and adenosyltransferase, and (6) methylmalonyl-CoA mutase, the cofactor of which is adenosylcobalamin. Diseases related to deficiency of the aforementioned enzymes: (1) propionic acidemia, (2) homocystinuria with methylmalonic acidemia, and (3–6) methylmalonic acidemia

Organic Acidemias

Propionic Acidemia

This is a disorder caused by the deficiency of propionyl coenzyme A (CoA) carboxylase (*Fig. 38.1*). Approximately half of the patients with propionic acidemia will present with devastating metabolic disease in the newborn period. The biochemical symptoms include metabolic acidosis, hyperammonemia, hypoglycemia, and hyperglycinemia, features shared by other organic acidemias such as methylmalonic acidemia. The pathogenesis is not clear. However, elevated propionic acid in the blood is implicated in the immune deficiency and thrombocytopenia. The central hypotonia is attributed to the neurotoxic effect of tiglyl-CoA that accumulates in the CNS. The hyperammonemia of propionic acidemia is usually severe (>400 μM). The reasons for these findings are shown in *Fig. 38.2*. These babies typically have a face with a depressed nasal bridge (organic acidemic face), except that they usually have a long philtrum of the upper lip (*Fig. 38.3*). A patient with propionic acidemia will almost always show profound central hypotonia. Approximately 25% of the patients will show nipple abnormalities, such as inverted, hypoplastic, or supernumerary nipples. Newborns with the severe form of propionic acidemia will quickly develop sepsis with *Candida* species or unusual bacteria, since the disease causes immune deficiency and hypoplasia of the thymus.

Propionic acidemia in the newborn may be a very confusing disease. It might have a prodrome of vomiting, leading to a misdiagnosis of intestinal obstruction or pyloric stenosis, and unnecessary surgery might be performed. In rare instances, the disease might manifest only with hyperammonemia and lead to an incorrect diagnosis of a urea cycle disorder. The acidosis of

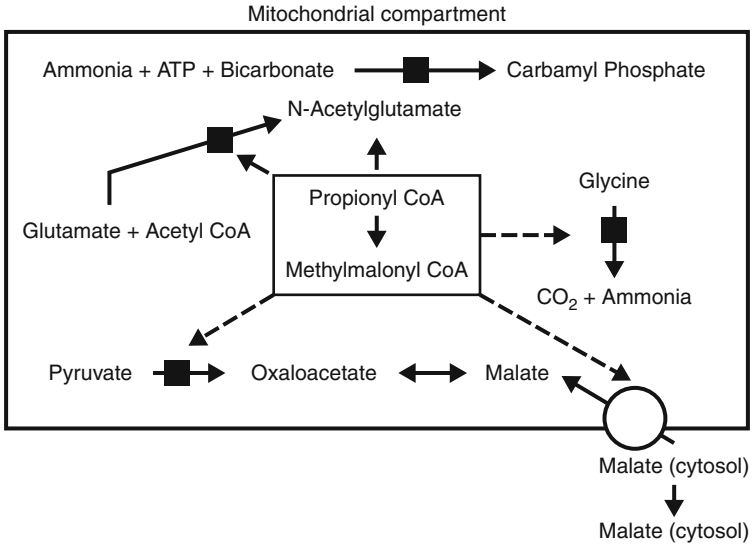


Figure 38.2

Mechanisms of hyperammonemia, hyperglycinemia, and hypoglycemia in patients with propionic acidemia and methylmalonic acidemia; the disturbed mitochondrial functions are indicated by *solid blocks*. Enzymes inhibited by propionyl-CoA or methylmalonyl-CoA and the resultant disturbed biochemical function: (1) pyruvate carboxylase (gluconeogenesis), (2) the transmitochondrial malate shuttle (gluconeogenesis), (3) glycinecleaving enzyme (hyperglycinemia), (4) carbamylphosphate synthetase (hyperammonemia), and (5) *N*-acetylglutamate synthetase (hyperammonemia). *Dashed arrows* indicate the site of inhibition

propionic acidemia is easier to correct than that of methylmalonic acidemia; a newborn with the metabolic crisis of propionic acidemia might have received enough alkalinizing treatment before referral, and only hyperammonemia may remain. A patient with propionic acidemia must be given large amounts of glucose, with insulin if necessary, to establish an anabolic state as quickly as possible. Patients with blood ammonia levels greater than 400 μM should receive peritoneal dialysis despite the danger of *Candida* peritonitis and sepsis, as well as sodium phenylbutyrate. Adequate management of coma can be measured by the disappearance of urine ketones. The disease causes neutropenia and an unusually severe and precipitous thrombocytopenia. Therefore, such a newborn should be monitored daily for platelet counts and must be given platelet transfusions when the count drops to 50,000/mm^3.

This is a disease that can fortunately be diagnosed within less than an hour when a tandem mass spectrometry (MS) system is available. Profound hypotonia in an acidotic baby with the aforementioned dysmorphic features should prompt a workup for propionic acidemia. Any child with hyperammonemia with or without acidosis, with or without treatment for urea cycle disorder, must be given large amounts of glucose and intravenous (IV) L-carnitine, until a definite diagnosis is reached.

Case History. Sultan was the product of a normal pregnancy and term delivery. On the second day of life he started to vomit bile and became lethargic. The parents were first cousins. The family history indicated the deaths of three previous newborns following a similar clinical history. On the third day of life Sultan developed labored respiration and became comatose, soon showing myoclonic seizures. The physical examination indicated a male infant who had no systemic findings, with normal abdominal sounds and a barely palpable liver. He could not be aroused and did not have sucking, rooting, or Moro reflexes. He was extremely floppy and the deep tendon reflexes could not be elicited. A catastrophic metabolic disease was suspected, and a preliminary workup indicated a blood glucose of 3 mM, bicarbonate of 10 mM, blood lactate of 5.6 mM (normal: $\leq$2 mM), blood ammonia of 235 μM (normal: $\leq$92 μM), blood pH of 7.32, base excess (BE) of −12 mEq/L, and 2+ ketonuria. This biochemical profile suggested either propionic acidemia, methylmalonic acidemia, or isovaleric acidemia. Considering that the infant had no foul smell in the diaper area, isovaleric acidemia was considered as remote. Since he was

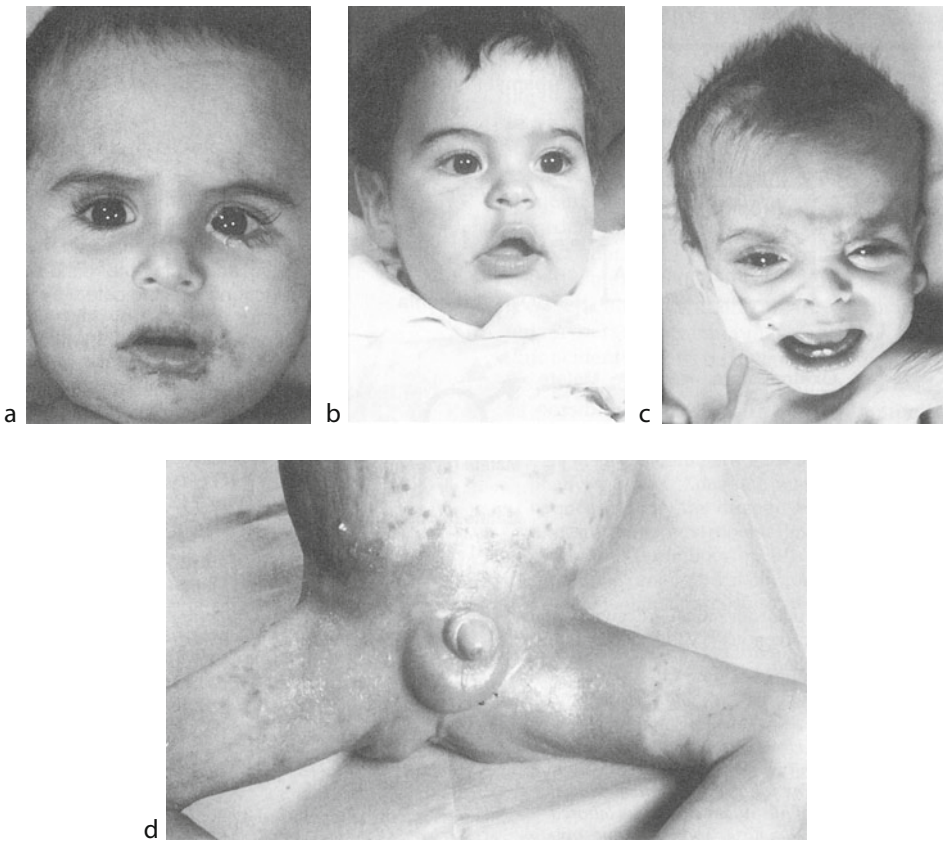


Figure 38.3
(a) An 8-month-old boy with propionic acidemia; note the depressed nasal bridge, partial epicanthic folds, and long philtrum of the upper lip, with *Candida* infection at the corner of lip (culture proven). (b) A 1-year-old girl with propionic acidemia successfully treated, showing the same type of face. (c) A 2-year-old patient with severe propionic acidemia; note the marasmus. He had severe anorexia and had to be fed by NG tube, and he had continuous diarrhea due to poliomyelitis infection. (d) Same patient with the severe *Candida* infection of the skin at the perineum

extremely floppy, a presumptive diagnosis of propionic acidemia was made. He was placed on propionic acidemia formula (a milk formula restricted in isoleucine, valine, threonine, and methionine), L-carnitine (IV 200 mg/kg/day), and biotin (10 mg/kg/day), and the acidosis was corrected by administration of sodium bicarbonate. He promptly responded and there remained no need for peritoneal dialysis or total parenteral nutrition (TPN) with insulin. A few days later the results of the plasma amino acids became available; glycine was 1,860 μM (normal: ≤500 μM; results indicated ketotic hyperglycinemia). A urine gas chromatography/mass spectrometry (GC/MS) revealed greatly increased excretion of 3-hydroxypropionic and methylcitric acids; a blood tandem MS revealed increased propionylcarnitine. All these results confirmed the clinical suspicion of propionic acidemia. Three months later, fibroblasts cultured from a skin biopsy indicated a profound deficiency of propionyl-CoA carboxylase (<5% of normal activity).

Methylmalonic Acidemia

This is a disorder caused by deficient activity of methylmalonyl-CoA mutase (*Fig. 38.1*). The cofactor of the enzyme is activated cobalamin (vitamin B_{12}), and methylmalonic acidemia can be caused by either deficiency of the mutase (mutant 0 or –) or deficiencies of cobalamin-activating enzymes (cobalamin a and b mutants). The pathogenesis of the disease is similar to that of propionic acidemia. Elevated methylmalonic acid is considered to be responsible for the bone marrow depression noted with the disease. The CNS toxicity has been attributed to the inhibition of succinyl-CoA

dehydrogenase, a key component of the tricarboxylic acid cycle, by methylmalonic acid. Patients with methylmalonic acidemia also show the same "organic acid face" (Fig. 38.4), but their muscle tone is usually increased. The ketolactic acidosis of the disease is protracted and will require a prolonged duration of treatment. The hyperammonemia in methylmalonic acidemia is not as pronounced as that of propionic acidemia. The thrombocytopenia and neutropenia during this period are either absent or mild. Such a patient must be administered large amounts of fluid in order to wash out the methylmalonic acid. Injections of 1 mg hydroxycobalamin should be given to any newborn with severe ketolactic acidosis, until the results of tandem MS or GC/MS become available. The tandem MS-based determinations will show elevated propionyl-carnitine in both propionic and methylmalonic acidemia. Therefore, the definitive diagnosis of methylmalonic acidemia is through detection of methylmalonic and methylcitric acids in urine by GC/MS. The response to treatment is easily followed by frequent measurement of urine ketones, which will become negative when the metabolic coma is under control.

Case History. Abdullah was born following an uneventful pregnancy. He was noted to have a heart murmur. The echocardiogram revealed a cribriform atrial septal defect. He refused feeding on the fifth day of life, with frequent vomiting and lethargy. The next day he had difficulty breathing and became comatose. The parents were closely related. The family history indicated the death of a previous infant with acidosis in the neonatal period. The physical examination indicated a 3-cm hepatomegaly, and neurologic examination indicated increased muscle tone and deep tendon reflexes. A metabolic disease was suspected, and biochemical workup indicated a blood pH of 7.20, plasma bicarbonate of 6 mM, blood glucose of 3.1 mM, lactate of 6 mM, and 3+ ketonuria. A presumptive diagnosis of methylmalonic acidemia was reached, and the patient was started on IV L-carnitine and daily intramuscular injection of 1 mg hydroxycobalamin, and his acidosis was corrected by IV administration of sodium bicarbonate. Within days, his clinical condition and acidosis improved. A urine sample obtained during the acute phase revealed a large peak of methylmalonic, methylcitric, and 3-hydroxypropionic acids. The blood acylcarnitine profile as analyzed by tandem MS showed a greatly increased peak of propionyl-carnitine. Therefore, the clinically presumed diagnosis was confirmed. He was placed on the propionic acidemia formula, since both diseases share a common pathway. He was kept on oral carnitine (200 mg/kg/day), daily intramuscular injections of 1 mg hydroxycobalamin, and oral tricitrates (Polycitra, 5 mEq/kg/day), and was discharged home in good condition. At present, Abdullah is 6 years old and has done well on the same regimen, experiencing only two or three acidotic crises in the interval. His intramuscular injections were substituted by intranasal vitamin B_{12} (Nascobal), 0.5 mg b.i.d.

Isovaleric Acidemia

This disorder is caused by the deficiency of isovaleryl-CoA dehydrogenase in the catabolic pathway of L-leucine (Fig. 38.5). The severe form of the disease will manifest

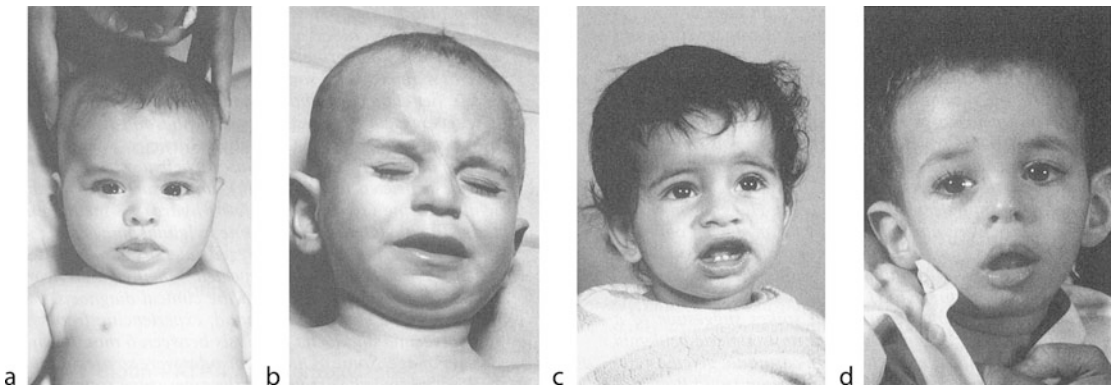


Figure 38.4

(a) A newborn with methylmalonic acidemia; note the wide nasal bridge with pseudoepicanthic folds, and upturned upper lip with short philtrum. (b) A 1-year-old boy with methylmalonic acidemia, with depressed nasal bridge, pseudoepicanthic folds, and upturned upper lip with short philtrum. (c) A 2-year-old boy with methylmalonic acidemia with similar facial features. (d) A 30-month-old girl with methylmalonic acidemia and similar face

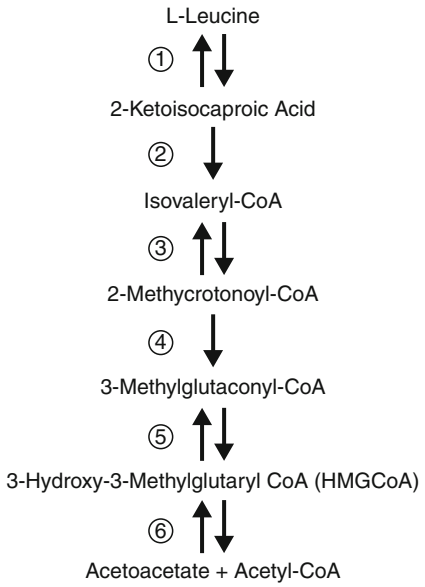


Figure 38.5
Breakdown of L-leucine and the enzymes lacking in various inborn errors of metabolism. Enzymes involved: (1) branched-chain amino acid transaminase, (2) branched-chain α-keto acid dehydrogenase, (3) isovaleryl-CoA dehydrogenase, (4) 3-methylcrotonyl-CoA carboxylase, (5) 3-methylglutaconyl-CoA hydratase, and (6) HMG-CoA lyase. Diseases related to deficiency of the aforementioned enzymes: (2) maple syrup urine disease (MSUD), (3) isovaleric acidemia, (4a) multiple carboxylase deficiency due to biotinidase deficiency, (4b) multiple carboxylase deficiency due to holocarboxylase synthetase deficiency, (4c) 3-methylcrotonyl-CoA carboxylase deficiency, (5) 3-methylglutaconic aciduria due to hydratase deficiency, and (6) HMG-CoA lyase deficiency

by devastating metabolic disease of the newborn. Isovaleric acid has a foul smell, like that of "unwashed feet" or "smelly cheese," and the disease can immediately be suspected by this unusual smell permeating the intensive care unit. The baby usually shows the typical face (i.e., depressed nasal bridge and upturned philtrum) of patients with organic acidemia. The muscle tone is usually increased. A severe form of the disease will cause profound thrombocytopenia and intracranial bleeding. The metabolic crisis will usually occur with sepsis, usually due to a gram-negative organism. This can lead to an erroneous diagnosis of disseminated intravascular coagulopathy (DIC). The DIC can also superimpose as a terminal event. Milder forms of the neonatal disease can have a prodrome of severe continuous vomiting, which can lead to the diagnosis of intestinal obstruction or pyloric stenosis and unnecessary laparotomy. Attacks later in life may be associated with acute pancreatitis. Any newborn with metabolic acidosis or sepsis with thrombocytopenia should receive a workup to rule out propionic acidemia (hypotonic baby), or isovaleric acidemia (baby with increased muscle tone), in order to prevent neurologic damage and death.

Case History. Hoda was 1 month old when she was first seen. The past history indicated that 3 days after birth she had vaginal bleeding that was attributed to maternally transmitted hormones. At 1 week of age severe bleeding from the mouth was observed, and she developed profound acidosis with severe thrombocytopenia and prolonged prothrombin time (PT) and partial thromboplastin time (PTT). The parents were first cousins. Despite the family history of death in the newborn period of an infant with acidosis, this child's condition was attributed to sepsis and DIC. She was treated with platelet transfusion and antibiotics. Her thrombocytopenia persisted and no bacteria could be isolated from the blood or from the cerebrospinal fluid (CSF). A few days after clinical stabilization, she developed a repeated episode of ketoacidosis and a urine sample revealed urine organic acids characteristic of isovaleric acidemia. She was transferred for management. At the time of admission she was jittery, had poor visual tracking, and had severely increased muscle tone and deep tendon reflexes. Her clinical chemistry values were normal, except for a platelet count of 50,000/mm^3. Computerized tomography (CT) studies of the brain revealed frontal white matter disease. The electroencephalogram (EEG) showed disorganized background activity and generalized spikes suggestive of a seizure disorder. She was placed on isovaleric acidemia formula (L-leucine restriction), L-carnitine, glycine (500 mg/kg/day), phenobarbital (5 mg/kg/day), and Polycitra (5 mEq/kg/day). She quickly stabilized. At present she is 5 years old and has no neurologic sequelae. CT of the brain and an EEG were normalized within 1 year. She never experienced a second metabolic attack on the treatment regimen given.

3-Hydroxy-3-Methylglutaryl Coenzyme A Lyase Deficiency

The disease is caused by the deficiency of 3-hydroxy-3-methylglutaryl (HMG)-CoA lyase, which is the final enzyme in the catabolic pathway of L-leucine (*Fig. 38.5*). The ethnic origin of most patients (more than 50%) is the Middle East. Approximately 70% of the cases will manifest before 24 h of life. A typical history is a devastating hypoglycemic lactic acidotic crisis after the first breast feeding. Despite profound acidosis,

there will be no ketones in the urine. The HMG-CoA inhibits gluconeogenesis. Synthesis of ketone bodies in the liver starts from the products of HMG-CoA lyase; therefore, when the enzyme is absent no ketogenesis occurs. This accounts for absent ketonemia in the presence of severe hypoglycemia and lactic acidosis. Upon appropriate treatment, the baby will recover quickly with no neurologic sequelae. A rapid clinical response to glucose and alkalinizing treatment in a newborn, and absent ketosis, strongly suggest the presence of HMG-CoA lyase deficiency. The presence of the deficiency must be quickly established in order to place the baby on appropriate formulas (low fat and leucine restricted) and L-carnitine, and to prevent further devastating attacks, which will recur when the patient fasts or is shifted to solid foods with high-fat and high-protein content.

Case History. Salha was delivered after a normal pregnancy and delivery. Six hours after birth, after first breast feeding, she experienced a devastating metabolic acidosis with severe hypoglycemia. The parents were second cousins. She came from a village where death due to the same disease was known to have occurred in at least six other infants. She was the second child in the family, and the previous sibling was normal. Her liver was 3 cm below the costal margin. The Moro, rooting, sucking, and tonic neck reflexes could not be elicited and she was in a deep coma. The blood pH was 7; CO_2 was 1 mM, blood glucose 0.5 mM, blood lactate 20 mM, and blood ammonia 235 μM, and urine ketones were negative. She was given IV glucose and sodium bicarbonate and, by 1 day of life, her clinical condition and chemistries normalized. The severe lactic acidosis, hypoglycemia, and absent ketonuria suggested HMG-CoA lyase deficiency. She was placed on an HMG-CoA lyase deficiency formula (L-leucine-restricted low-fat milk), and L-carnitine. Meanwhile, a urine GC/MS revealed 3-hydroxy-3-methylglutaric, 3-methylglutaric, and 3-methylglutaconic acids; the blood acylcarnitines as analyzed later by tandem MS, when she was 8 years old, revealed 3-methylglutarylcarnitine, all of which confirmed the clinical diagnosis.

Salha had a stormy childhood, experiencing frequent hypoglycemia and lactic acidosis between 6 months and 3 years of age. Some of these episodes were so precipitous and severe that she arrived at the emergency room (ER) and coded three times during this period, each time being successfully resuscitated. She developed a seizure disorder requiring anticonvulsant treatment. Meanwhile, fibroblasts grown from a skin biopsy revealed the absence of HMG-CoA lyase activity. After 5 years of age her disease became milder, with only infrequent mild acidotic comas. Despite a totally normal clinical appearance, she excretes the urine organic acids and has the acylcarnitine characteristic of HMG-CoA lyase deficiency. At present she is 14 years old, and is an excellent student with no neurologic sequelae or any evidence of seizure activity.

Multiple Carboxylase Deficiency

Multiple carboxylase deficiency (MCD) in the neonatal period is caused by the deficiency of holocarboxylase synthetase (HCS), an enzyme that activates and binds biotin to four apocarboxylases (propionyl-CoA carboxylase, pyruvate carboxylase, acetyl-CoA carboxylase, and 3-methylcrotonyl-CoA carboxylase) (*Fig. 38.6*). The neonatal form of the disease is very severe and will appear with severe ketolactic acidosis resistant to treatment. The symptoms may be attributed to the combination of severe propionic acidemia and pyruvate carboxylase deficiency. Such a newborn will usually show severe hypotonia, hepatomegaly, profound coma, and an irreversible acidosis, which will lead to death in a few days. Since some forms of the disease are responsive to biotin, large doses of this

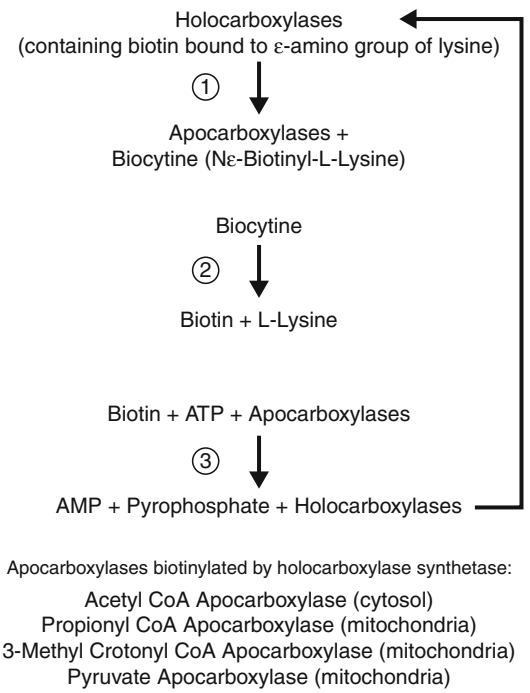


Figure 38.6

Endogenous biotin circle and biotin metabolism. Enzymes involved in biotin addition to apocarboxylases and biotin turnover: (1) normal proteolysis of holocarboxylases (biotin bound to active center), (2) biotinidase, and (3) holocarboxylase synthetase, which adds biotin to all four apocarboxylases indicated

vitamin must be provided in any newborn with ketolactic acidosis. The control of lactic acidosis within a few days in such a newborn will indicate biotin responsiveness, although neurologic damage due to severe acidosis may not be reversed. In families in which a previous sibling died of biotin-responsive HCS deficiency, the mother should be given 100–200 mg/day biotin during the last 1–2 months of pregnancy. If the disease is biotin responsive, the baby will be saved from neurologic crippling and certain death.

3-Methylglutaconic Aciduria

The cause of this disease is unknown, but possibly involves defective utilization of mevalonate (i.e., the mevalonate shunt), which is linked to oxidative phosphorylation. The mevalonate pathway is involved in the syntheses of cholesterol, ubiquinone, and dolichol, important key molecules of cell membranes and oxidative phosphorylation. Therefore, dysmorphic features are common, such as epicanthic folds and undescended testicles. Although a less severe form of 3-methylglutaconic aciduria occurs later during childhood, as a result of 3-methylglutaconyl-CoA hydratase deficiency (◉ *Fig. 38.5*), during the neonatal period it is the more severe form of the disease that will be encountered. Approximately half of the patients with the neonatal form of 3-methylglutaconic aciduria will have severe hypoglycemia (<1 mM) and lactic acidosis (in the range of 6–12 mM). Another variant with no neonatal acidosis and hypoglycemia will also show these biochemical findings periodically, later during infancy. Both variants lead to a rapidly progressive encephalopathy, characterized by severe spastic quadriplegia and death by 1–2 years of age. In both variants of 3-methylglutaconic aciduria, the newborn should be given ubiquinone, phytanedione, and ascorbic acid, since in some instances the disease might be responsive to this treatment. An example of the former variant, with neonatal hypoglycemia and lactic acidosis, is the following patient.

Case History. A male infant was born to first-cousin parents, with two previous children with 3-methylglutaconic aciduria, diagnosed after extensive neurologic damage had occurred. Both of his siblings had devastating metabolic disease with hypoglycemia and lactic acidosis at birth. Due to high risk, this patient was delivered under close observation. When examined at 2 h of age, he was a normal newborn with appropriate reflexes. The blood pH was 7.3, BE −7.5 mEq/L, glucose 3.1 mM, and lactate 3.5 mM at the age of 4 h. At the age of 10 h the baby became obtunded, with labored breathing and cortical fisting, and the blood pH was 7.20, BE −15 mEq/L, glucose 2 mM, and lactate 10.6 mM. He was immediately placed on IV glucose, sodium bicarbonate, phytanedione (0.2 mg/kg/day), ascorbic acid (20 mg/kg/day), coenzyme Q (10 mg/kg/day), L-carnitine, and riboflavin (100 mg/kg/day). His acidosis and hypoglycemia improved over the next week. His neurologic status also improved, and CT of the brain and an EEG were normal. The urine, during both the acute phase and recovery, showed 3-methylglutaconic acid and 3-hydroxyisovaleric acid, confirming the diagnosis. He was discharged home in stable condition without neurologic deficits. When seen next at the age of 3 months, he remained stable.

Multiple Acyl-CoA Dehydrogenase Deficiency

Multiple acyl-CoA dehydrogenase deficiency (MADD) is caused by defective riboflavin-dependent proteins (electron-transfer flavoproteins, or ETFs). The ETFs are essential parts of fatty acids and other dehydrogenases involved in the breakdown of fats: L-leucine, L-isoleucine, and L-lysine. In the absence of ETFs, a complex biochemical picture evolves with predominant formation of glutaric acid (◉ *Fig. 38.7*). This is the reason that the disease is also called glutaric aciduria type 2, implying the formation of glutaric acid from the breakdown of L-lysine. The disease is basically similar to profound riboflavin deficiency, and reflects the teratogenic effect of riboflavin absence on the developing fetus. Such patients show many dysmorphic features, increased muscle tone, and hepatomegaly (◉ *Fig. 38.8*). Eventually, they will develop severe cardiomyopathy and the infant will expire due to either heart or liver failure. The presence of hypoglycemia in a newborn with dysmorphic features should prompt a workup for this disease. The neonatal variant of MADD is usually not responsive to treatment with riboflavin and L-carnitine.

Primary Lactic Acidosis-Pyruvate Carboxylase Deficiency

Pyruvate carboxylase (PyC) is involved in the first step in gluconeogenesis (◉ *Fig. 38.9*). Besides gluconeogenesis, its activity is required for the transport of reducing equivalents from cytosol into mitochondria through the malate/aspartate shuttle. Malate can only enter into, and aspartate can only exit from, mitochondria (◉ *Fig. 38.10*). Therefore, when PyC is deficient, cytosol is in a more-than-normal reduced state and mitochondria are in a less-than-normal reduced state. This leads to a high ratio of blood lactate to blood pyruvate in the presence of low blood 3-hydroxybutyrate/acetoacetate ratios, which is diagnostic for this deficiency; these ratios are normal in pyruvate dehydrogenase (PDH) deficiency and are elevated in other oxidative phosphorylation disorders.

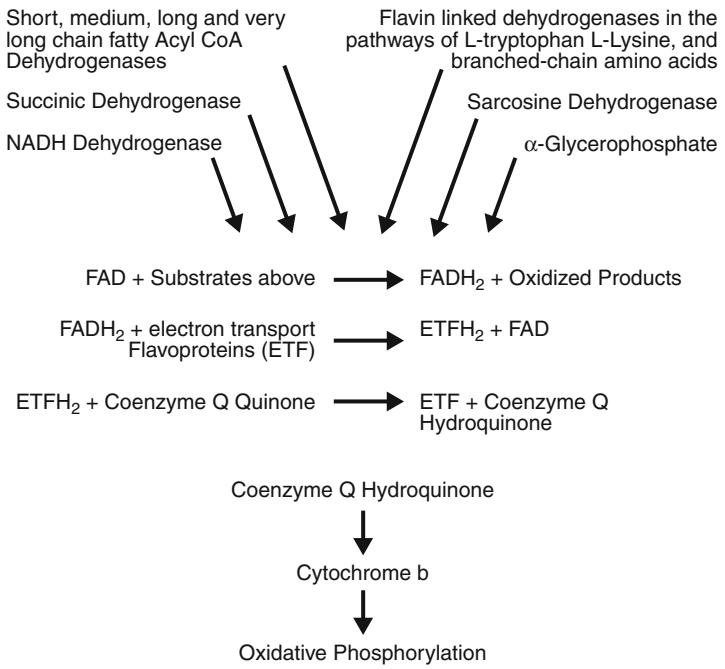


Figure 38.7
Flavin-linked oxidations in mitochondria

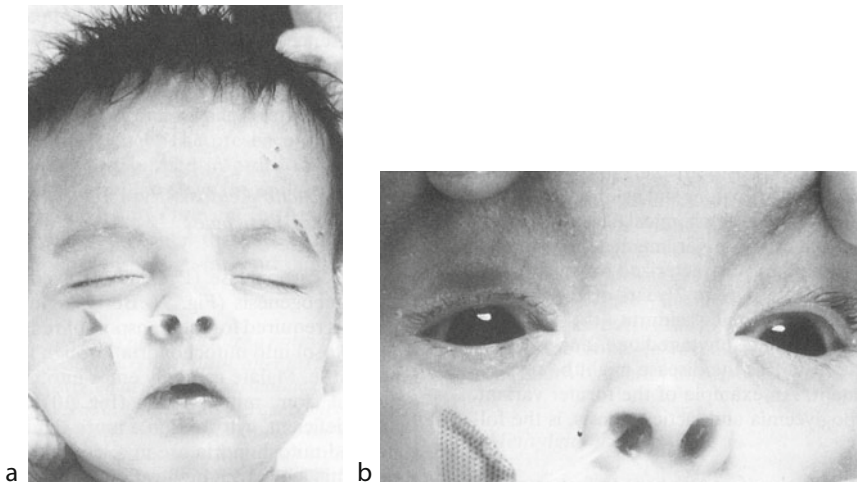


Figure 38.8
(a) Facial photo of a 1-month-old boy with type 2 glutaric aciduria (multiple acyl-CoA dehydrogenase deficiency); note the downward slanting of the eyes, depressed nasal bridge, and long philtrum of the upper lip. (b) Same patient; note the blepharophimosis

Approximately one third of cases with PyC deficiency will manifest at birth with severe refractory ketolactic acidosis, mild hypoglycemia in association with hepatomegaly, and increased muscle tone. The baby will not show intrauterine growth retardation (IUGR), which readily differentiates this acidosis from the primary lactic acidosis caused by PDH deficiency. Despite hepatomegaly, the liver functions are not unduly perturbed. The absence

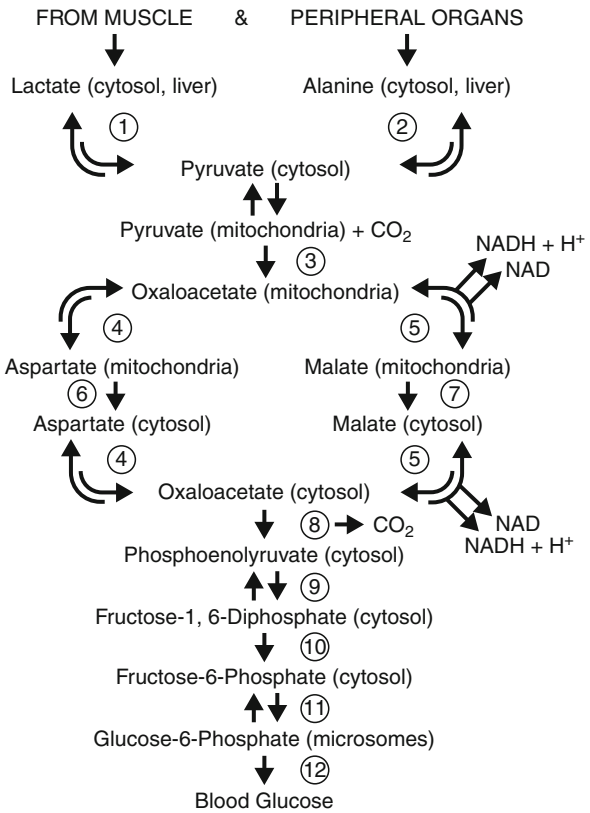


Figure 38.9
Gluconeogenesis in liver. Enzymes involved: (1) lactate dehydrogenase, (2) alanine transaminases, (3) pyruvate carboxylase, (4) oxaloacetate aspartate transaminase, (5) malic dehydrogenase, (6) aspartate port, (7) malate port, (8) phosphoenolpyruvate carboxykinase, (9) triosephosphate enzymes of glycolysis, (10) fructose-1,6-diphosphatase (FDPase), (11) phosphoglucose isomerase, and (12) glucose-6-phosphatase. Steps 3, 6, 7, 8, 10, and 12 are irreversible steps assuring the gluconeogenic flow

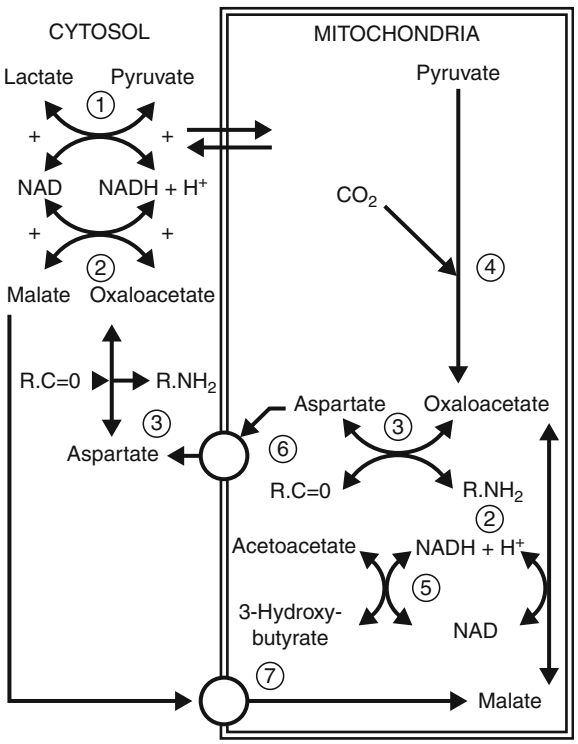


Figure 38.10
Malate-aspartate shuttle. Enzymes and transport systems involved: (1) lactate dehydrogenase, (2) malate dehydrogenase, (3) oxaloacetate aspartate transaminase, (4) pyruvate carboxylase (unidirectional reaction), (5) 3-hydroxybutyrate dehydrogenase, (6) aspartate port (unidirectional, transports aspartate only from mitochondria to cytosol), and (7) malate port (unidirectional, transports malate only from cytosol into mitochondria)

of severe liver and heart involvement differentiates PyC from cytochrome *c* oxidase deficiency. The blood lactate/pyruvate ratio will be greater than 25 (normal: $\leq$25), with elevated alanine. The absence of singly elevated glycine differentiates the disease from propionic, methylmalonic, and isovaleric acidemias of this age group. The blood tandem MS studies in PyC deficiency will indicate significantly elevated acetylearnitine, which is reduced in patients with PDH deficiency.

Case History. Maha was a 1-day-old who was referred for workup of severe neonatal lactic acidosis. She was born to first-cousin parents who lost two babies to a similar disease during the first week of life. She had no dysmorphic features; she showed hyperpnea and tachypnea and was mildly jaundiced. She stayed in the hospital for 6 days, during which time her blood pH ranged from 6.92 on admission to 7.30 at best, despite the administration of large amounts of bicarbonate and tromethamine (THAM). Her BE varied between −28 and −16.5 mEq/L, blood lactate between 12 and 30 mM, and plasma pyruvate between 200 and 400 μM (normal upper limit: 80 μM). The 3-hydroxybutyrate was 200 μM and acetoacetate 400 μM. The lactate/pyruvate rations ranged between 45 and 60 (normal: $\leq$25) and the 3-hydroxybutyrate/acetoacetate ratio was 0.5 (normal: >2). The plasma showed greatly increased alanine, threonine, citrulline, lysine, and phenylalanine. She had continuous

ketonuria, ranging from 2+ to 4+. An ultrasound of the head revealed marked cavitation in the region of the caudate nuclei with surrounding areas of increased echogenicity. CT of the brain further revealed extensive encephalomalacia within the bilateral temporal areas and severe periventricular white matter disease with scattered hypodense lesions throughout the brain. On the sixth day she developed a clinical picture of DIC, shock, hypotension, and bradycardia and died despite intensive support. Postmortem blood culture was sterile. Postmortem muscle biopsy did not show abnormal mitochondria. The muscle stain for cytochrome *c* oxidase was normal. Fibroblasts grown from a skin biopsy revealed profound deficiency of pyruvate carboxylase (3% of normal).

Primary Lactic Acidosis–Pyruvate Dehydrogenase Deficiency

Pyruvate dehydrogenase is active in the first step in the tricarboxylic acid cycle, converting pyruvic acid into acetyl-CoA. In its absence, pyruvate will be reduced into lactate.

The concept of anaerobic versus aerobic glycolysis is shown in Fig. 38.11. Anaerobic glycolysis provides scant ATP; therefore, when aerobic glycolysis is impaired, the newborn will suffer severe energy depletion. As the pathogenic considerations indicate, partial or total PDH deficiency also leads to stunted embryonic growth starting in the third trimester of pregnancy, and these babies will be born as IUGR infants. For the same reasons, the disease causes dysmorphia involving the face, brain, nipples, and viscera. The typical face of an infant with partial PDH deficiency is shown in Fig. 38.12.

The effect of energy deprivation will primarily manifest in the CNS. Therefore, PDH deficiency is incompatible with life if the enzyme is totally absent, or causes severe brain damage if the deficiency is partial. The phenotype is a Leigh encephalomyelopathy with severe lactic acidosis. Respiratory irregularities, such as apnea and "sighing," are common, and provide the most important clue for a diagnosis of PDH deficiency in an IUGR newborn. There will be early optic atrophy. Reflexes will be diminished, with early hypotonia. Magnetic resonance imaging (MRI) of the brain will reveal diffuse or patchy demyelination. The EEG will show a "burst suppression pattern" and profound background changes. The neonatal form of the disease is usually not responsive to treatment with thiamine, lipoic acid, dichloroacetate, or L-carnitine.

Primary Lactic Acidosis–Cytochrome *c* Oxidase Deficiency

The most common disease involving oxidative phosphorylation in the neonate is the deficiency of cytochrome *c* oxidase (COX; complex 4). The disease presents with severe ketolactic acidosis and multisystem involvement, with severe encephalopathy, liver failure, and cardiomyopathy. There is usually early optic atrophy. The presence of liver and cardiac involvement in a neonate should prompt a workup for COX deficiency, which can be achieved by immune histochemical studies for COX in a muscle or liver biospy or by measuring the COX activity in cultured cells. Milder forms of the disease due to partial

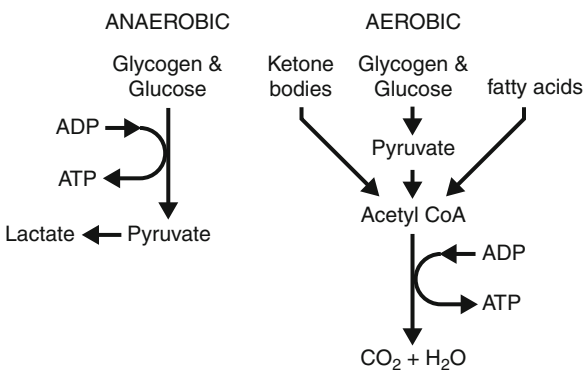


Figure 38.11
Two modes of cellular energy metabolism

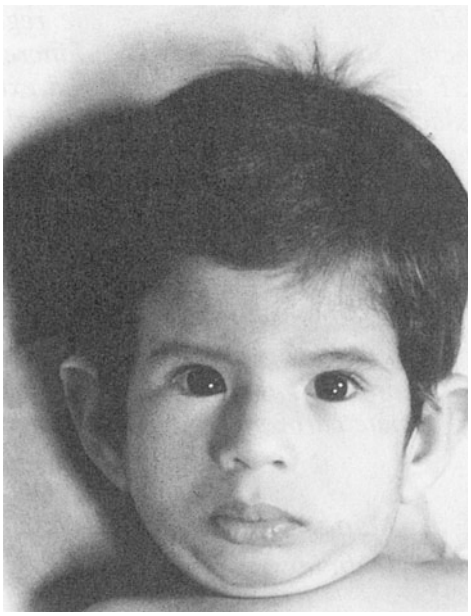


Figure 38.12
Facial photo of a 6-month-old girl with partial pyruvate dehydrogenase deficiency. Note the epicanthic folds, depressed nasal bridge, and the long philtrum of the upper lip

COX deficiency will appear with a similar clinical presentation later during infancy or in childhood. There is no treatment, and the neonatal form of the disease is incompatible with life.

Case History. A female infant developed respiratory distress, cyanosis, severe metabolic acidosis, and hypoglycemia at the age of 8 h in the referral hospital and was referred at the age of 7 days for diagnosis. The parents were first cousins, and three female siblings had died of a similar disease before 2 months of age. The patient's birth weight was 3.5 kg and she was appropriate for gestational age. Her admission weight, height, and head circumference were at the 50th percentile. She had a depressed nasal bridge and a long philtrum of the upper lip. The liver edge was 4 cm below the costal margin. She had mild central hypotonia and diminished deep tendon reflexes. She showed continuous myoclonic seizure activity. Chest x-ray indicated an enlarged heart. CT of the brain indicated cavum septum pellucidum, with bilateral frontal and bitemporoparietal white matter disease, The EEG showed poor background activity and spikes and polyspikes at the parieto-occipital and temporo-occipital areas. During admission her blood glucose values ranged from 3.3 to 5.4 mM; her blood lactate varied between 4.6 and 9.6 mM, and her pyruvate between 82 and 215 μM (normal: ≤80 μM). The lactate/pyruvate ratio varied between 36 and 53 (normal: <25). The muscle biopsy stained for COX revealed a deficiency of the enzyme. Her seizures responded to clonazepam, and she was discharged home. She died at home at the age of 4 months.

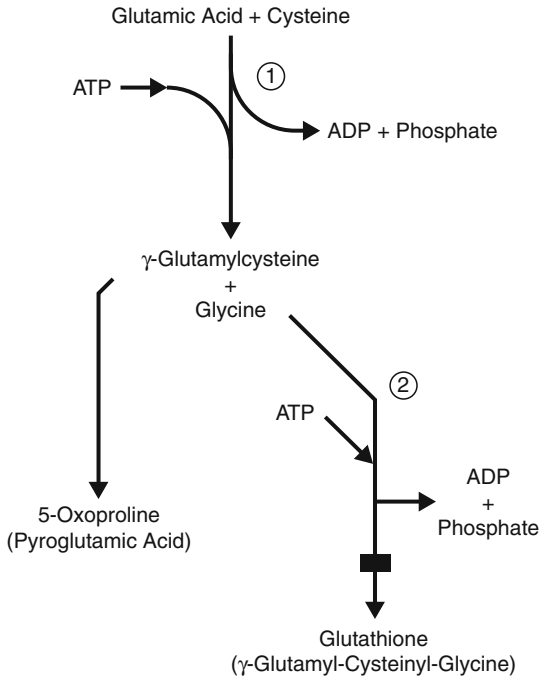


Figure 38.13
Metabolic pathway of glutathione synthesis. Enzymes involved in the pathway and deficiency responsible for pyroglutamic aciduria: (1) γ-glutamylcysteine synthetase, and (2) glutathione synthetase, deficiency of which results in deficiency of glutathione and increased excretion of 5-oxoproline (pyroglutamic acid)

Pyroglutamic Aciduria

This disease is caused by a deficiency of glutathione synthetase. The glutathione synthetic pathway is interrupted, and 5-oxoproline (pyroglutamic acid) is excreted in the urine in large quantities (*Fig. 38.13*). The disease appears as compensated/severe metabolic acidosis in association with mild to severe episodes of hemolytic anemia. Therefore, it combines the clinical features of glucose-6-phosphate dehydrogenase deficiency with those of an organic acidemia. The disease causes a slowly progressive encephalopathy and leads to mental retardation.

Case History. Hameed was referred at the age of 43 days for the evaluation of metabolic acidosis and hemolytic anemia. He developed severe metabolic acidosis at the age of 12 days, and a hemolysis diagnosed as ABO incompatibility. The parents were first cousins, and two of their offspring had expired with a similar disease within their first month of life. Despite the negative Coombs test in the referring hospital, Hameed received exchange transfusions twice. In between exchange transfusions he developed severe metabolic acidosis and increasing indirect hyperbilirubinemia. He also developed heart failure due to severe anemia and had to be digitalized. The urine ketones remained negative, there was no hyperammonemia, and blood lactic acid remained normal during acidotic attacks. At the time of transfer his weight was 2.1 kg, height 49 cm, and head circumference 35 cm. He had hepatosplenomegaly, with both organs measuring 4 cm below costal margins. He had Kussmaul breathing. The blood pH was 7.10, with an anion gap of 22; however, the lactic acid was normal (1 mM) and he had only trace ketonuria. He had glucosuria, phosphaturia, and proteinuria, indicating a renal Fanconi syndrome. Septic workup was negative, CSF analysis was normal, and there was no laboratory evidence of DIC. His hemoglobin was 70 g/L, and reticulocyte count 8%. His indirect bilirubin was markedly elevated (17.8 mg/dL), and liver enzymes were only mildly perturbed. The erythrocyte glucose-6-phosphate dehydrogenase was normal repeatedly, and no abnormal hemoglobin was found by repeated

electrophoresis. He was given continuous alkalinizing treatment by IV and oral bicarbonate solutions and repeated blood transfusions to combat the acidosis and anemia. His clinical condition eventually stabilized, and urine GC/MS revealed large amounts of 5-oxoproline. Further clinical follow-up revealed a child with mild mental retardation, with no renal sequelae of the disease. He had two further attacks between 6 months and 5 years of age, each time with hemolytic anemia and metabolic acidosis.

Amino Acid Disorders

Certain amino acid disorders will appear primarily during the neonatal period. These are the urea cycle disorders (UCDs) and MSUD.

Urea Cycle Disorders

Ammonia is converted into urea through a series of reactions known as the urea cycle (*Fig. 38.14*). The deficiencies of four of these enzymes are important causes of hyperammonemic devastating metabolic disease with normal or elevated blood pH during the neonatal period. The deficiencies of carbamyl phosphate synthetase (CPS) and ornithine transcarbamylase (OTC) are common diseases in the West. All four deficiencies present in a similar manner. The newborn is difficult to arouse to feed early on, and this evolves into a deep coma, which may be associated with myoclonic seizures. There are no associated dysmorphic features or other systemic findings. A normal or elevated blood pH and normal BE (which excludes organic acidemias), with profound coma and absence of alternating hypotonia with hypertonia (a hallmark of MSUD), should alert the pediatrician to a UCD. Such an infant found to have hyperammonemia (>200 μM) should receive either exchange transfusion, peritoneal dialysis, or preferably hemodialysis immediately. Treatment through a nasogastric (NG) tube with sodium phenylbutyrate (500 mg/kg/day) with L-arginine (500 mg/kg/day) should be initiated. L-Carnitine should be given until the absence of propionic acidemia can be established. The administration of L-arginine is essential to prevent CNS damage. The symptoms of UCD are caused by

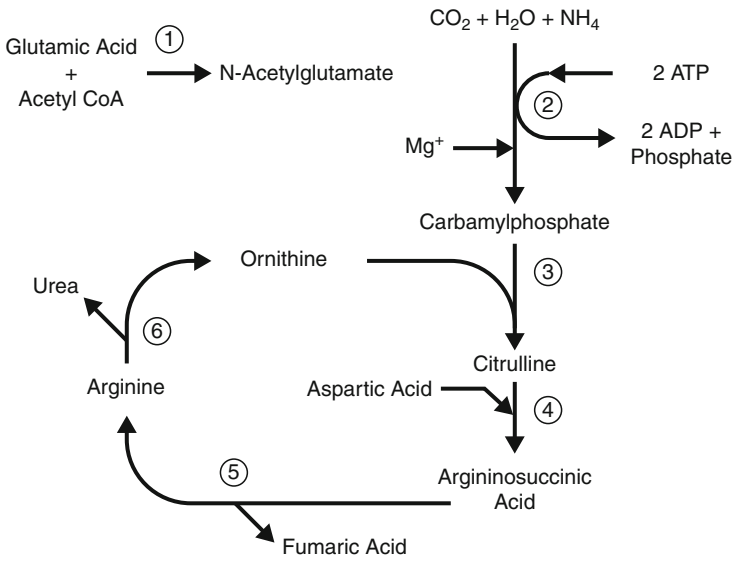


Figure 38.14

Urea cycle. Enzymes involved and related deficiencies: (1) *N*-acetylglutamate synthetase, deficiency of which causes hyperammonemia, (2) carbamylphosphate synthetase (CPS), deficiency of which causes severe hyperammonemia (the enzyme requires *N*-acetylglutamate as an activator), (3) ornithine transcarbamylase (OTC), deficiency of which is an X-linked disease (causes orotic aciduria in addition to hyperammonemia), (4) argininosuccinic acid synthetase, deficiency of which causes hyperammonemia and citrullinemia, (5) argininosuccinic acid lyase, deficiency of which causes hyperammonemia and argininosuccinic aciduria, and (6) arginase, deficiency of which causes periodic hyperammonemia and hyperargininemia

increased glutamine synthesis in glial cells in the CNS due to a high concentration of ammonia, which causes severe brain edema.

Among the four listed disorders, citrullinemia (due to the deficiency of argininosuccinic acid [ASA] synthetase) and argininosuccinic aciduria (due to deficiency of ASA lyase) may have more benign courses compatible with normal life. The hyperammonemia may also develop more slowly than in CPS or OTC deficiencies. There will be lactic acidosis and mild elevation of urinary orotic acid. In these latter diseases the same treatment modalities are used. Sodium phenylbutyrate is given with enough L-arginine to prevent hyperammonemia and the catastrophic elevation of citrulline in the blood. The photo of the patient with citrullinemia described in the following case history (◉ *Fig. 38.15*) shows the typical facial features of the disease. One form of argininosuccinic aciduria is mild and will manifest in later infancy or childhood.

Case History. Rakan developed lethargy progressing into deep coma, myoclonic seizures, difficulty feeding, hypothermia (33.5°C), and peripheral shock at the age of 5 days, for which he was admitted to another hospital. His chemistries at the time of that admission revealed a pH of 7.45, normal blood glucose and CO_2, but ammonia of 330 μM (normal: <129 μM). The symptoms and chemistries supported the diagnosis of a UCD; a Tenckoff catheter was placed and peritoneal dialysis was given. A blood amino acid study indicated L-citrulline to be extremely elevated, at 999 μM (normal: <40 μM), and showed absent argininosuccinic acid. A diagnosis of citrullinemia was reached and he was referred for detailed workup.

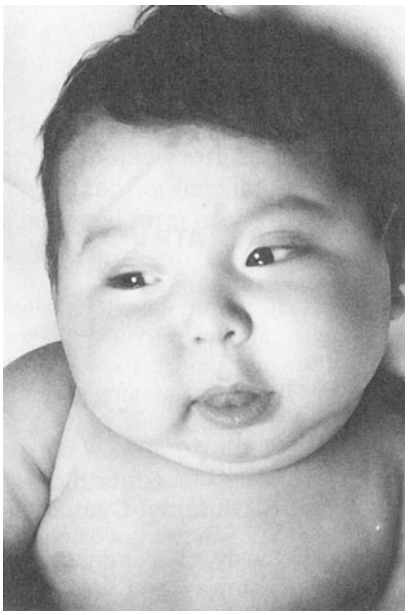


Figure 38.15
The facial appearance of a patient with citrullinemia; note the blepharophimosis, wide nasal bridge, epicanthic folds, and long philtrum of the upper lip

At the time of admission he was 12 days old, obtunded, and pale looking. He had an asymmetric tonic neck reflex and weak Moro, sucking, and rooting reflexes. He had spastic quadriparesis and 3+ increased deep tendon reflexes. The laboratory studies indicated low red blood cell count and hemoglobin (70 g/L). A bone marrow biopsy showed hypoplastic anemia. The ammonia was 168 μM, and citrulline 1,268 μM. He was placed on L-arginine (500 mg/kg), to which he responded promptly, and the ammonia decreased to 30 μM within 24 h. Although an EEG was normal, there was diffuse dysmyelination both infra- and supratentorially. He was discharged home on L-arginine, sodium benzoate (250 mg/kg/day), sodium phenylacetate (250 mg/kg/day), folic acid (5 mg/day), and pyridoxine (25 mg/day). Following a minor respiratory infection, he refused to eat and developed a second hyperammonemic episode at the age of 7 months and had to receive the same treatment. At present he is a very chubby boy and still has mild hypoplastic anemia. Neurologically he could sit independently at the age of 7 months, with good traction response, and he showed normal bipedal reflexes at the age of 8 months. Despite normal ammonia, his last citrulline level at the age of 9 months was 1,845 μM. Later, he had a sister who also had citrullinemia, but her disease was diagnosed at birth. She is growing as a totally normal child on the same therapy as her brother.

Maple Syrup Urine Disease (Branched-Chain Aminoacidemia): Classic Form

This disease is not common in the West, but it is the most common cause of devastating metabolic disease of the newborn in Middle Eastern countries. The disease is caused by a deficiency of branched-chain α-keto acid dehydrogenase (◉ *Fig. 38.16*). Since MSUD does not create biochemical disturbances readily detectable by the routinely available clinical biochemical analyses, it will be missed frequently. It has a typical prodrome. It remains asymptomatic for 5–7 days of neonatal life. The mother notices that the infant refuses to take the nipple and will spit out the milk as soon as it is given, but will tolerate water. The disease then rapidly progresses into a coma with myoclonic or grand mal seizures, and sepsis might be superimposed. Clinically the baby will show alternating

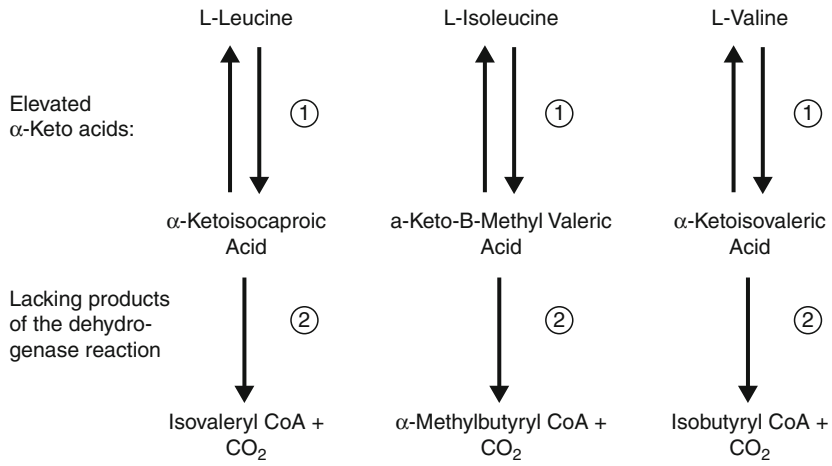


Figure 38.16
The branched-chain amino and α-keto acids elevated in maple syrup urine disease. (1) Branched-chain transaminase. (2) Branched-chain α-keto acid dehydrogenase that is missing in patients with MSUD

hypotonia and increased muscle tone and will show opisthotonus (*Fig. 38.17*). The reason for these symptoms is brain swelling or edema caused by elevated L-leucine, particularly in the brain stem. CT or MRI of the brain is so characteristic that an experienced radiologist can recognize MSUD and alert the pediatrician before laboratory results become available (*Fig. 38.17*). The keen clinician or parent will easily pick up the sweet smell of maple syrup coming from the diaper area, under the armpits, or the hair. A urine dinitrophenylhydrazine test will be strongly positive and can be secured within an hour in most settings. These two simple observations will raise suspicion in all cases. The diagnosis can then be confirmed by special analyses. Classic MSUD has poor prognosis if it is diagnosed after 2–3 weeks of life. Such a baby will incur such severe CNS damage, suffering frequent septic episodes and progression of the CNS damage, that the infant will not recover even after vigorous treatment. In the long run, even the best-controlled patients with MSUD may have some degree of neurologic damage. The disease is frequently associated with dermatitis due to disturbed L-leucine/L-isoleucine/L-valine ratios (*Fig. 38.17*). Poorly controlled patients will have abnormally long eyelashes and prominent fat pads in the cheeks due to malnutrition (*Fig. 38.17*).

MSUD is a true pediatric emergency and should be immediately and vigorously treated. The aim of the treatment is to reduce the blood level of branched-chain amino acids (BCAAs), particularly L-leucine, which are responsible for the brain edema. The primary source of L-leucine in a fasting infant is muscle, released through catabolism. In a newborn of 3 kg, 48 h of fasting will raise the blood leucine level to near 3,000 μM (normal upper limit: 120 μM). Therefore, the treatment includes administration of high levels of calories in the form of dextrose and lipids given together with regular insulin administration (1–1.5 U/kg) every 6–8 h, or given as a continuous drip. The blood glucose should be monitored to prevent hypoglycemia; when present, it should be corrected by extra glucose administration or by withholding the next injection of insulin. In a newborn with profound MSUD coma, peritoneal dialysis or exchange transfusion should be performed. If the newborn tolerates it, the MSUD formula should be slowly administered through the NG tube. The case histories of a poorly controlled and a well-managed MSUD patient are presented below.

Case History. Mohammed was the first child of a first-cousin marriage; he had poor Apgar scores, 3 at 1 min and 5 at 3 min, with meconium aspiration. He had continuous lethargy and was hospitalized in the neonatal intensive care unit for 10 days. At home he started to refuse breast feeding and developed generalized myoclonic seizures and opisthotonus with apneic spells at the age of 14 days. He was hospitalized at a peripheral hospital and suffered cardiorespiratory arrest at the age of 16 days. His blood gases, pH, glucose, CO_2, lactate, and ammonia were all within normal limits. The physician suspected MSUD, since the patient's urine and diaper area smelled of maple syrup. A blood sample revealed very elevated L-leucine, L-isoleucine, and L-valine levels of 2,030, 1,732, and 780 μM, respectively (normal upper limits: 175, 80, and 300 μM, respectively). He was referred for admission

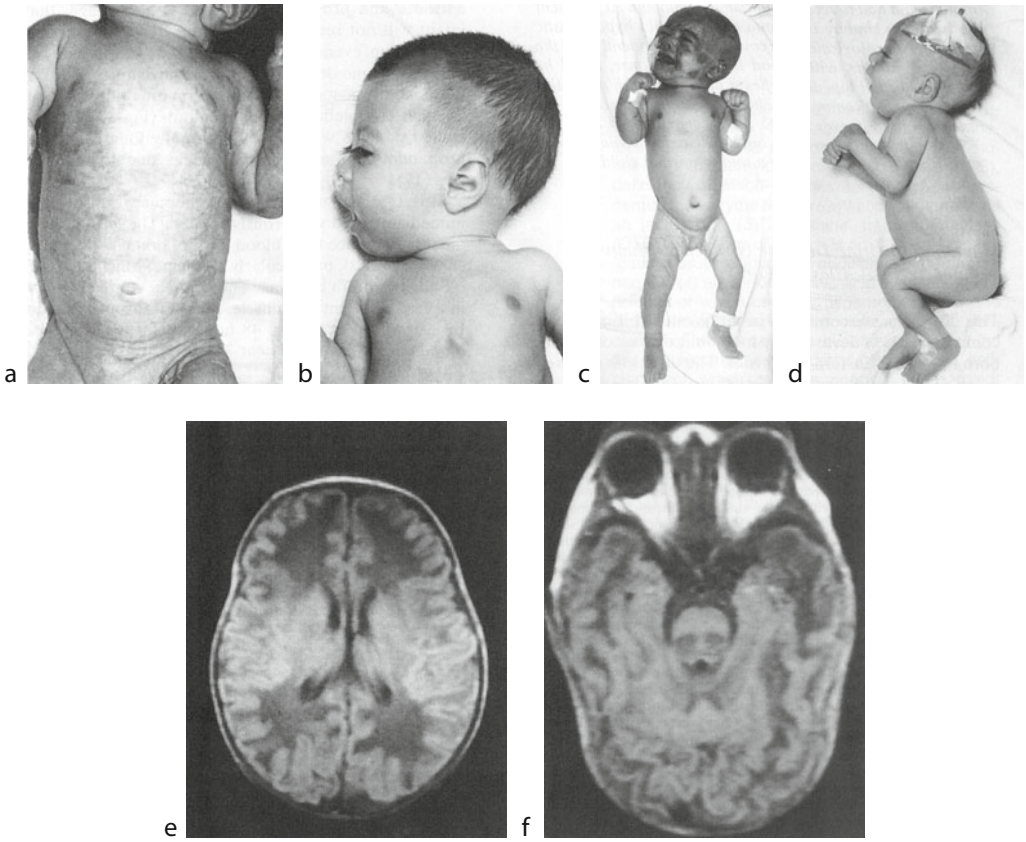


Figure 38.17

MSUD. (a) The body rash due to imbalance of branched-chain amino acids in blood. (b) Evidence of malnutrition on the face; very long eyelashes and fat accumulation in cheeks. (c) Skin lesions on cheek, severe pyramidal tract signs as evidenced by cortical fisting. (d) Opisthotonic posture is evidence of brain stem lesion. (e) MRI of the brain showing the severe central white matter disease in a neonate with MSUD. (f) MRI of the mesencephalon in the same infant showing the characteristic lesions of MSUD in the pons and brain stem

and management at the age of 3 weeks. Physical examination indicated optic atrophy, severe dermatitis in the diaper area, liver edge 2 cm below the costal margin, opisthotonus, and quadriplegia with increased deep tendon reflexes. CT of the brain indicated severe white matter disease. He was managed by an MSUD diet (L-leucine-, L-isoleucine, and L-valine-restricted milk), thiamine (100 mg/kg/day), and a pediatric trace element mixture (1 mL/day). He was discharged home in good clinical condition. The parents were extremely conscientious and followed the diet strictly. Over the subsequent 15 months, he never had another metabolic crisis and his blood levels of BCAAs returned to within normal limits. However, at the age of 15 months he still had mild optic atrophy, he could not sit independently, and he had central hypotonia. His verbal and social skills were approximately at the age level of 12 months. CT of the brain indicated generalized atrophy and a thin corpus callosum. The EEG was normal at the age of 15 months.

Case History. Lulwa was 8 days old at the time of admission. She was normal at birth. At the age of 5 days she started to refuse feeding, cried frequently, and showed myoclonic seizures and opisthotonus. The parents were first cousins and had 11 children, 6 of whom died of a presumed "hyperammonemic" disease. At the time of admission she was in deep coma, showing frequent myoclonic jerks, with alternating hypo- and hypertonia. She had opisthotonus, cortical fisting, and 4+ increased deep tendon reflexes. She had bilateral optic atrophy. An initial workup revealed normal blood gases, pH, glucose, CO_2, lactate, and ammonia. MSUD was suspected. A urine dinitrophenylhydrazine test was strongly positive. Plasma amino acids revealed the L-leucine level to be 3,127 μM (normal: $\leq$175 μM); L-isoleucine and L-valine were also

elevated, at 966 and 839 μM, respectively (normal: ≤80 and 300 μM, respectively). A Tenckoff catheter was placed and she was given peritoneal dialysis for the next 6 days. She developed coagulase-positive Staphylococcus aureus sepsis and peritonitis on day 15, but responded well to vancomycin treatment. She was placed on MSUD formula. CT of the brain at the age of 18 days showed severe demyelination. The EEG revealed no state transition and was disorganized. The brain stem auditory evoked response (BAER) showed severe brain stem dysfunction. The levels of BCAAs became normal by the tenth day of admission, and she was discharged for clinical follow-up.

Her subsequent clinical course has been very benign. The parents were most conscientious, and Lulwa never had a second metabolic crisis. At the age of 12 months the patient was so normal that the mother discontinued the diet, believing she was cured. Her blood BCAAs rapidly increased and she started to show cerebellar ataxia, irritability, and somnolence. She was placed on the diet again and improved quickly. At the age of 22 months she was age-appropriate neurologically. She did not have optic atrophy, and her BAER and EEG were normal. MRI of the brain was within normal limits except for mild periventricular demyelination. Her plasma BCAAs could be maintained near normal limits. At present she is 9 years old, and for all purposes she is a normal child with no neurologic sequelae, except for moderate attention-deficit disorder.

Diseases Associated with Neonatal Stupor and Encephalopathic Presentation

This category contains nonketotic hyperglycinemia, peroxisomal diseases, and Menkes disease. These three disorders do not show an evolving clinical picture, but are usually associated with severe encephalopathy in a newborn. Therefore, they are easily confused with the devastating metabolic diseases of the newborn since an accurate history might not always be available. They should always be included in the differential diagnosis.

Nonketotic Hyperglycinemia

This disease is caused by a defect in the glycine catabolic pathway, leading to accumulation of glycine in blood, CSF, and urine. Such babies are born with severe encephalopathy, showing myoclonic seizures, and the disease is usually confused with either 3-methylglutaconic aciduria or Zellweger syndrome. All three diseases show hypotonia, but the hypotonia in nonketotic hyperglycinemia is so severe that the patient has stridor. Glycine is the neurotransmitter for anterior horn cells in the spinal cord, and, when hyperglycinemia is present, hypotonia is observed. Patients with nonketotic hyperglycinemia do not have many facial dysmorphic features but may have partial or total agenesis of the corpus callosum. They will not have other systemic findings. Some cases of nonketotic hyperglycinemia can be managed with dextrometorphan (25–35 mg/kg/day) and sodium benzoate (500 mg/kg/day).

Case History. Hamad was 3 months old at the time of referral. His mother noted decreased fetal movements during pregnancy. At birth he was extremely hypotonic and required ventilatory support for 2 weeks. After discharge the parents noticed that he never vocalized and had very poor sucking. At home they also noticed him to have jerky movements of the neck and limbs. The parents were first cousins, and another baby had died soon after birth with a similar complaint. Hamad was referred with a presumed diagnosis of Menkes disease. At the time of admission he had a dolicocephalic head. His height, weight, and head circumference were all less than 3%. He showed polyfocal myoclonic jerks. He did not respond to visual threat, loud sound, or cueing. Eyegrounds examination showed pale optic discs and possible retinitis pigmentosa. The microscopy of the hair was normal. He never showed ketosis. Urine GC/MS for propionic acidemia was negative. Serum copper and ceruloplasmin were normal. Blood chemistries, including lactate, were normal. Plasma amino acids showed greatly increased glycine, at 1,123 μM (normal upper limit: 500 μM), and the glycine concentration in the CSF was 235 μM (normal upper limit: 10 μM), with a CSF glycine/blood glycine ratio of 20 (normal: 0.02), confirming the diagnosis of nonketotic hyperglycinemia. The knee x-ray did not indicate abnormal stippling seen in peroxisomal disorders. CT of the brain showed partial agenesis of the corpus callosum and severe diffuse dysmyelination or demyelination in the centrum ovale. The EEG was abnormal, with slow background, very frequent discharges, spikes, and polyspikes. He was placed on sodium benzoate (500 mg/kg/day) and dextromethorphan (35 mg/kg/day). He was lost to follow-up.

Zellweger Syndrome and Neonatal Adrenoleukodystrophy

The absence of peroxisomes due to a failure of peroxisomal assembly (Zellweger syndrome), or absence of oxidizing enzymes for very-long-chain fatty acids (neonatal adrenoleukodystrophy), is highly teratogenic to the developing fetus. Both diseases appear with severe myoclonic seizures. Patients with Zellweger syndrome have typical dysmorphic features, which may not be as

apparent in a patient with neonatal adrenoleukodystrophy. Zellweger syndrome is associated with systemic findings that include facial and cranial dysmorphia, earlobe creases, eye involvement in the form of cataracts and retinitis pigmentosa, hepatomegaly, skeletal findings indicating abnormal bone maturation in the form of stippling of the patella or femur heads, and severe central hypotonia. The appearance of a typical patient with Zellweger syndrome is shown in ❯ *Fig. 38.18*. These findings are missing in nonketotic hyperglycinemia. Most dysmorphic features characteristic of Zellweger syndrome might also be observed in another teratogenic disease, such as MADD; however, the latter will show intermittent severe hypoglycemia, while this is not a feature of peroxisomal diseases.

Case History. Hasna was a 2-month-old infant at the time of admission. She was the product of a 37-week gestation with assisted breech delivery. Her birth weight was 2.3 kg and she was extremely floppy at birth, unable to support respiration and requiring intubation and assisted ventilation for 3 weeks. The mother had a previous baby girl similar to Hasna who had numerous dysmorphic features, including a high forehead, depressed nasal bridge, cloudy cornea, cataracts, bilateral talipes, and elevated aspartate transaminase (AST) and alanine transaminase (ALT), who died at 7 months of age. On admission, Hasna's height and weight were 48.5 cm and 2.7 kg, respectively, significantly below the fifth percentile. She was jaundiced, with various dysmorphic features that included a broad forehead, shallow orbits, proptosis, depressed nasal bridge, wide anterior fontanel measuring 5 × 6 cm, highly arched palate, low-set ears, and micrognathia. She had an ejection systolic murmur. A firm and sharp liver edge was felt 3 cm below the costal margin. The spleen tip was palpable. She had normal external genitalia with a normal-size clitoris. She had severe central hypotonia and diminished reflexes. Pertinent laboratory findings were ALT of 402 U/L (normal upper limit: 43 U/L), AST of 578 U/L (normal upper limit: 40 U/L), and total bilirubin of 63 μM (normal upper limit: 21 μM). Plasma amino acids, blood gases, glucose, pH, urine ketones, and urine GC/MS were not remarkable. A skeletal survey indicated coronal clefts in the vertebrae and focal calcifications in the patella and in the posterior ends of the lower ribs. No cysts were observed in the liver, kidney, or spleen. EEG showed absent sleep spindles. The very-long-chain fatty acids in plasma were elevated: C26 was 3.33 μg/mL (normal upper limit: 0.24 μg/mL), with normal phytanic acid of 1.71 μg/mL (normal upper limit: 5.6 μg/mL), which confirmed the clinical diagnosis of Zellweger syndrome.

Menkes Disease

Menkes disease is caused by defective transport of copper into and out of cells, particularly neurons. The deprivation of copper in cells will impair oxidative phosphorylation

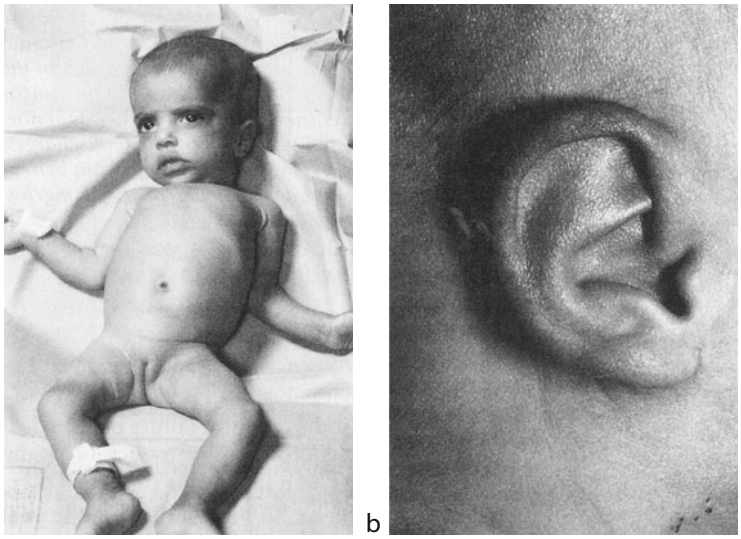


Figure 38.18
(a) A 1-month-old girl with Zellweger syndrome; note the head structure, severe hypotonia, and distended abdomen due to hepatomegaly. (b) The earlobe creases typical of Zellweger syndrome

and development of elastic tissue and hair. The consequences of the disease therefore are early dementia with typical facial structure due to sagging cheeks, abnormal hair structure or pili torti (Fig. 38.19), tortuous vessels in the brain and viscera leading to early subdural hematoma, diverticula in the bladder leading to rupture and acute abdomen, and copper-deficiency anemia. The disease is usually suspected in an infant with encephalopathy and stupor after one of the aforementioned complications occur. Early or prenatal administration of histidine-copper chelate (1 mg copper/day) has been found to be effective in the treatment of this disorder.

Case History. Nasser was 9 months old at the time of admission. The mother noted that he would not follow her visually at the age of 1 month, at which time he was severely floppy. He had myoclonic seizures at the age of 2 months following a febrile disease. He was admitted to another hospital at the age of 7 months, since the seizures could not be controlled. The family history indicated the death of another male sibling at 18 months and the presence of a normal boy at age 13 months. On examination the patient was found to have sagging cheeks, no visual tracking, no response to sounds, and severe central hypotonia. Microscopy of the hair indicated pili torti. MRI of the brain revealed a large bilateral subdural hematoma and diffuse white matter disease. A cystogram revealed no diverticula but right-sided reflux. Cerebral and abdominal angiograms did not reveal arterial tortuosity. Serum copper was 3 μM (normal: 11–22 μM), and ceruloplasmin was 50 mg/L (normal: 120–350 mg/L). Peripheral blood showed hypochromic, microcytic anemia with many target cells. He was not given chelated copper treatment, considering the advanced stage of disease. He was followed in the clinic until 3 years of age, at which time he died at home.

Miscellaneous Disorders

In the neonate with nesidioblastosis or in infants of diabetic mothers (IDMs), the severe hypoglycemia and seizures might be confused with the encephalopathies created by the deficiencies of fatty acid-oxidizing enzymes, and particularly by MADD.

Nesidioblastosis

At times a newborn with nesidioblastosis might be referred for the workup of an inborn error of metabolism. The hypoglycemia in an infant with nesidioblastosis is unremitting, but such a neonate is otherwise normal. Discordance between glycemia and blood insulin and elevated C-peptide levels easily reveals the disease. In borderline instances, a leucine provocation test by means of the administration of 100 mg/kg L-leucine will invariably cause hypoglycemia and an increase in blood insulin and C-peptide.

Diagnosis

Clinical Differential Diagnosis

The devastating metabolic diseases of the newborn are serious pediatric emergencies in most instances. The neonatologist must reach a quick presumptive diagnosis and initiate the treatment promptly. There are several clinical

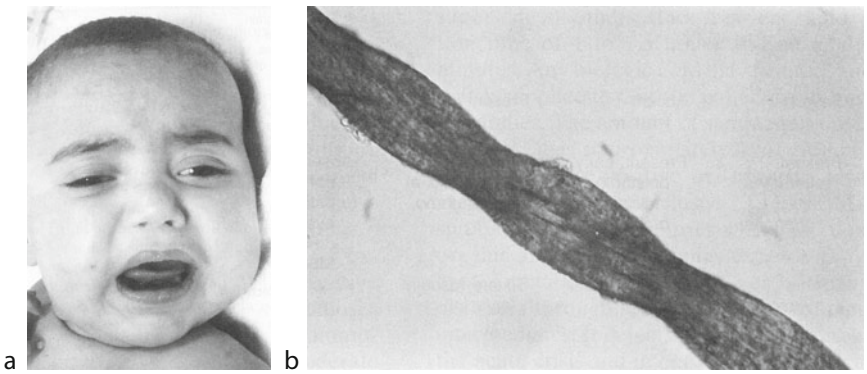


Figure 38.19
(a) Facial photo of an 8-month-old boy with Menkes disease; note the chubby cheeks. (b) Microscopic appearance of his hair, which shows ''pili torti''

and biochemical clues that will guide the pediatrician to a reasonably correct presumptive diagnosis. The helpful clinical signs are summarized in *Table 38.2*.

Certainly the tone of the infant is most helpful. For example, central hypotonia is suggestive of propionic acidemia and Zellweger syndrome. Alternating tone and opisthotonus are pathognomonic of MSUD. Hypertonia suggests methylmalonic acidemia or isovaleric acidemia. Seizures indicate primary gray matter involvement; they are very severe and invariably present in nonketotic hyperglycinemia, MSUD, and Zellweger syndrome. Unless hypoglycemia or anoxia and profound acidosis are present, seizures occur rarely in other devastating metabolic diseases. Subtle dysmorphic features are certainly most helpful indicators. In a case of primary lactic acidosis, for example, the presence of dysmorphia in an IUGR patient is very suggestive of PDH deficiency. In a baby with hypoglycemia, dysmorphic features support the diagnosis of MADD. Severe and persistent hypoglycemia in an otherwise normal infant suggests the presence of

Table 38.2
Devastating metabolic diseases of the newborn: clinical signs and symptoms

Category of diseases	Hypotonia	Hypertonia	Seizures	Dysmorphia	Liver disease	Associated infections
Organic acidemias	Present (e.g., propionic academia)	Present (e.g., methylmalocni academia, isovaleric academia)	Usually present (can be myoclonic or grand mal seizures)	Involving brain, midfacial structures, philtrum of the lip; different dysmorphia in different organic acidemias	Present in fatty acid oxidation disorders and diseases of oxidative phosphorylation	Almost always present, confusing the diagnosis; *Candida* species, gram-negative and -positive microorganisms
Urea cycle diseases	Severe	Absent	Present (usually myoclonic)	Absent	Preserved normal liver enzymes in plasma	May be present
Maple syrup urine disease (MSUD) (brached-chain) amino academia)	Present, alternates with hypertonia	Present, early opisthotonus indicating brain stem disease	Present (usually myoclonic, at times grand mal)	Absent at birth but all patients eventually develop the MSUD face	Absent	Almost always present, mainly gram-negative and unusual microorganisms
Nonketotic hyperglycinemia	Severe hypotonia, stridor, encephalopathy with stupor	Absent	Severe (usually myoclonic)	Absent	Absent	Usually absent
Zellweger syndrome and other peroxisome diseases	Severe encephalopathy with stupor	Absent	Severe (usually myoclonic)	Typical face, earlobe, abnormalities; dysgenesis of brain, retina, bones, liver, and kidney	Early liver disease with elevated bilirubin and liver enzymes in blood	Usually absent
Nesidiobastosis	Absent	Absent	Present (usually grand mal seizures)	Absent	Absent (inappropriately elevated insulin or C-peptide in the presence of hypoglycemia)	Absent

nesidioblastosis. Hepatomegaly and liver disease are associated with COX deficiency and MADD and Zellweger syndromes. Intercurrent infections with unusual organisms, and in terminal patients DIC, are almost always observed in cases of propionic acidemia and MSUD. Neonates with propionic acidemia are prone to infections with *Candida*.

Biochemical Differential Diagnosis

The presumed clinical diagnosis must be supported rapidly by chemical tests that are available in most clinical care settings. These are blood gases and pH, blood glucose, ammonia, lactic acid, and simple urine ketone testing. A combination of results of these tests will allow the clinical diagnosis to be refined. A summary of findings of these clinical chemistry tests is shown in ❯ *Table 38.3*.

The presence of overt or compensated acidosis, for example, in the presence of hyperammonemia is indicative of an organic acid disorder, while the absence of acidosis, with or without alkalosis, in a patient with hyperammonemia indicates a UCD. The absence of mild/moderate acidosis, hypoglycemia, and ketone bodies in a profoundly comatose newborn strongly suggests MSUD. The presence of severe hypoglycemia in an otherwise normal newborn is suggestive of nesidioblastosis, unless the baby is an IDM. The presence of severe persistent lactic acidosis suggests a primary lactic acidosis due to an oxidative phosphorylation defect, although urine ketones will test positive. In HMG-CoA lyase deficiency, on the other hand, urine ketones are absent despite severe lactic acidosis and hypoglycemia. The presence of severe ketolactic acidosis is suggestive of propionic acidemia, methylmalonic acidemia, and isovaleric acidemia. In patients with 5-oxoprolinuria despite severe acidosis, no lactic acid or ketones are detected, and the patient has hemolytic anemia.

Conclusive Diagnosis

Treatment must be initiated with the aforementioned clinical and biochemical clues. However, the diagnosis

Table 38.3
Devastating metabolic diseases of the newborn: associated biochemical findings

Category of disease	Blood pH	Blood glucose	Blood ammonia	Blood lactic acid	Urine ketone bodies
Organic acidemias	$<$7.35 or BE $>$ $-$5.0 mEq/L	Normal or mild/severe hypoglycemia	Usually mild/severe elevation	Usually mild/severe elevation	Normal or mild/severe positive
Urea cycle diseases	Normal or alkalotic with no appreciable BE	Normal	Rapidly rising within days or hours of birth, raising $>$400 μM	Normal; may be elevated in citrullinemia	Normal
Maple syrup urine disease (MSUD)	Normal	Normal in newborn; moderate hypoglycemia later during MSUD crisis in infancy	Normal	Normal	Normal in newborn but mildly/strongly positive later during MSUD crisis in infancy
Nonketotic hyperglycinemia	Normal	Normal	Normal	Normal	Normal
Zellweger syndrome and other peroxisome diseases	Normal	Normal	Normal	Normal	Normal
Nesidioblastosis	Normal	Severe hypoglycemia, either continuous or episodic	Normal	Normal	Normal

must then be confirmed at a tertiary care center where sophisticated specialized biochemical tests are available. These tests include GC/MS study of organic acids in the urine and CSF; amino acid quantification by high-performance liquid chromatography (HPLC) in blood; tandem MS studies in blood, urine, and CSF; and enzyme measurements in leukocytes, cultured fibroblasts, or lymphoblasts. The use of these tests and the findings in each disease are summarized in *Table 38.4*.

These tests, particularly GC/MS, require technical expertise, and they are usually time consuming. For example, GC/MS is an excellent method for the diagnosis of organic acidemias. However, it will require transport of the urine sample to the laboratory in a cold state, and the results will not usually be available in fewer than 2–3 days. Only a limited number of samples may be run per week (e.g., 40), which delays the reports further, unless several technicians and machines are present. In certain organic acidemias, such as fatty acid oxidation defects, the results of GC/MS will usually be equivocal. GC/MS is useful only for the analysis of organic acids during the metabolic crisis; the results might be equivocal in between attacks. The HPLC technique is excellent for quantification of amino acids, but it also has the same drawbacks listed for GC/MS. Unless a special request is made, argininosuccinic acid will not be measured.

Tandem MS is a new technique and will undoubtedly supersede all others, since it is very rapid, with a preparation time of 1–1.5 h and an analytical time of 2 min. Any biologic fluid may be used, and these samples may be applied to Gutherie paper, dried, and sent or mailed for studies. The amount of sample required is minimal; for example, it is approximately 7 μL for blood. There are few or no false-positive or false-negative results; the results are almost always conclusive. Tandem MS is particularly suitable for use in countries where the number of diverse organic and aminoacidemias exceeds all other inborn errors of metabolism. It detects over 30 organic or amino acid disorders through semiquantitative estimation of relevant intermediates. It detects most of these diseases both during the acute crisis and in between metabolic attacks. It is the gold standard for fatty acid oxidation disorders. The cost of reagents required is minimal. Since it detects only propionylcarnitine, it does not differentiate between propionic and methylmalonic acidemias. However, this does not pose a particular difficulty, since the treatments of both disorders are alike, and the newborn can be placed on treatment covering both possibilities until the results of GC/MS become available. Its only drawbacks are the substantial cost of the machine and the sophisticated technical expertise required.

Special enzyme tests, except in a few instances where red blood cells may be used, usually will not provide results before a couple of months, since cultured cells, and not leukocytes, are the preferred source. Only a few laboratories have the required expertise, and the maintenance of a cell culture laboratory and repository are very costly.

Genetics and Incidence

In the absence of a comprehensive neonatal screening for these disorders, it is impossible to state the incidence of devastating metabolic diseases of the newborn. In descending order, primary lactic acidosis, methylmalonic acidemia, propionic acidemia, and MSUD are the most frequently observed causes for devastating metabolic diseases of the newborn. These four account for approximately 60–80% of cases of these disorders. Isovaleric acidemia, HMG-CoA lyase deficiency, and 3-methylglutaconic aciduria occur less frequently.

With recent advances in molecular genetics, the gene locations for most of these disorders are increasingly established. The genes involved in causing devastating metabolic diseases of the newborn are listed in *Table 38.5*. An increasingly available diagnostic approach is to establish the diagnosis through genotyping, using the cDNAs available for the gene. Such a molecular genetic approach is particularly useful in screening the population for the prevalence of carriers once the mutation(s) involved are identified.

Prevention or Neonatal Screening

The diseases of organic and amino acids should be identified as early as possible, preferably before a metabolic crisis occurs. The period between birth and identification before damage occurs is called the "safety window." The safety window for some diseases is established. For example, in the case of classic phenylketonuria (PKU) it is 6 weeks, while in most of the organic acid disorders and MSUD it is probably only a few days after birth. In some other disorders, such as glutaric aciduria type 1 or homocystinuria, this period has not yet been established.

Most of the neonatal screening programs include only PKU, MSUD, and biotinidase deficiency. A broad-based neonatal screening program is highly desirable and should be mandatory in countries where these diseases prevail. The recent availability of tandem MS systems should

Table 38.4

Specialized biochemical tests required to confirm definite diagnosis in patients with organic and amino acid disorders (primarily devastating metabolic diseases of the newborn)[a]

Disease	GC/MS studies	HPLC studies for amino acids	Tandem MS studies	Enzyme studies or special tests[b]
Propionic acidemia	3-OH-propionic, methylcitric, propionylglycine	⇑ Glycine	Glycine, propionylcarnitine	Propionyl-CoA carboxylase (F)(L)
Methylmalonic acidemia	Methylmalonic, 3-OH-propionic, methylcitric	⇑ Glycine	Glycine, propionylcarnitine	Label fixation and complementation (F)
Isovaleric acidemia	3-OH-isovaleric, 4-OH-isovaleric, isovalerylglycine	Glycine may be elevated	C5-carnitine (isovaleryl carnitine)	Label release from [^{14}C] isovaleric acid or from 2,3-[^{3}H]isovaleryl-CoA (F)
HMG-CpA lyase deficiency	HMG (3-OH-3-methylglutaric), 3-methylglutaric, lactic, 3-methylglutaconic	N.P.	3-Methylglutarylcarnitine	HMG-CoA lyase (F)(L)
MCD (HCS) deficiency)	3-OH-propionic, 3-methylcrotonyl, 3-propionylglycine, methylcitric	N.P.	Propionylcarnitine methylcrotonylcarnitine	3-Methylcrotonyl-CoA, propionyl-CoA, and pyruvate carboxylase (F)(L)
3-Methylglutaconic aciduria	3-Methylglutaconic, 3-methylglutaric, HMG	N.P.	N.P.	N.P.
Glutaric aciduria type 2	Glutaric, 2-OH-glutaric, ethylmalonic	N.P.	Glutarylcarnitine, carnitine esters of short-, medium-, and long-chain fatty acids	ETF assays for various types of ETF (F)
Oxidative phosphorylation diseases[c]	Lactic, pyruvic, acetoacetic, 3-OH-butyric	Alanine	Alanine, acetylcarnitine	PyCD:PyC in (F((L) PDHD:PDH in liver, muscle COXD:COX in liver, muscle (F)(H)
5-Oxoprolinuria	5-Oxoprolice (pyroglutamic)	N.P.	5-Oxoproline (pyroglutamic)	⇓ Glutathione or its reductase (R)
UCD: CPS deficiency	N.P.	⇓ Citrulline ⇓ Arginine	N.P.	CPS in liver biopsy
UCD: OTC deficiency	Orotic acid	⇓ Citrulline ⇓ Arginine	N.P.	OTC in liver biopsy
UCD: citrullinemia	Orotic acid, lactic acid	⇑ Citrulline ⇓ Arginine ⇑ Glutamine ⇑ Alanine	Citrulline; mild hyperalaninemia	N.A.
UCD: argininosuccinic aciduria	N.P.: may have lactic aciduria	⇑ Argininosuccinic ⇑ Citrulline ⇓ Arginine ⇑ Glutamine ⇑ Alanine	Citrulline, argininosuccinic	N.A.
Maple syrup urine disease (MSUD)	Branched-chain α-keto acids	⇑ Leucine, valine, isoleucine	Leucine + isoleucine valine	^{14}CO2 released; [^{14}C]-branched-chain amino and α-keto acids (F)(L)

Table 38.4 (Continued)

Disease	GC/MS studies	HPLC studies for amino acids	Tandem MS studies	Enzyme studies or special tests[b]
Nonketotic hyperglycinemia	N.P.	⇑ Glycine in blood and CSF simultaneously	Glycine in blood and CSF simultaneously	N.A.
Neonatal peroxisomal disorders[d]	Pipecolic acid	N.P.	N.P.	Very-long-chain fatty acids and phytanic acid (serum)
Menkes disease	N.P.	N.P.	N.P.	⇓ Cu^{2+} and ceruloplasmin (serum)

GC/MS urine gas chromatography/mass spectrometry, *tandem MS* blood tandem mass spectrometry, *HPLC* blood high-performance liquid chromatography, *MCD* multiple carboxylase deficiency, *HCS* holocarboxylase synthetase, *ETF* electron-transfer flavoproteins, *UCD* urea cycle disorders, *CPS* carbamylphosphate synthetase, *OTC* ornithine transcarbamylase, *CSF* cerebrospinal fluid

[a]⇑, Pathognomonic elevation of the compound indicated; ⇓decreased concentration. N.P., not pathognomonic

[b]Enzyme activity can be tested; (F) in fibroblasts, (L) in leukocytes, lymphocytes or cultured B lymphoblasts, (H) histochemically, (R) in red blood cells, and N.A., not available routinely

[c]Pyruvate carboxylase (PyCD), pyruvate dehydrogenase (PDHD), cytochrome *c* oxidase (COXD) deficiencies

[d]Zellweger syndrome, neonatal adrenoleukodystrophy, neonatal Refsum disease

enable the implementation of such broad-based screening programs.

Previous screening procedures were based on the Guthrie test, that is, stimulation of bacterial growth in the presence of inhibitors (MSUD, PKU) or chemical reactions (biotinidase, galactosemia), based on a single mutation in the gene (cystic fibrosis, galactosemia). Besides the cumbersome technical nature of these tests, false-positives and false-negatives have always been a major problem. The principle of tandem MS technique is essentially different. It relies on identification and estimation based on molecular weight and a pathognomonic fragmentation pattern. Therefore, false-negative and false-positive results are not usually a problem. Despite the initial cost of the machine, it requires minimal chemical and technician costs, can be run automated, and is user friendly. The medium of choice is dried blood spots, but tandem MS can easily be applied to dried urine samples. The diseases listed in *Table 38.6* are detectable by this technique.

Treatment

Management of Acute Crisis

Fluid Therapy

Acidosis must be promptly corrected. For this purpose, $NaHCO_3$ should be administered at 1–2 mEq/kg over a period of 20 min to 1 h, and repeated every 1–4 h, depending on the severity of acidosis. The acidosis of methylmalonic acidemia can be very persistent, and soon hypernatremia may appear. In methylmalonic acidemia with severe acidosis, 1–2 days of adjunct treatment with 6 mL/kg THAM (a pharmaceutical preparation containing Tris buffer), administered slowly and repeated every 4 h, will usually normalize the pH within 24–36 h. Primary lactic acidosis is very resistant to alkaline administration, and a certain degree of acidosis (pH 7.20–7.30) is unavoidable. The acidosis in such patients might be treated by peritoneal dialysis using long-term indwelling peritoneal catheters. In patients with E_1 subunit abnormality of PDH, 50–100 mg/kg/day sodium dichloroacetate solution (pH = 7) might be tried orally, and might reduce the lactic acidosis without much benefit to the evolving encephalopathy. However, the pediatrician must use his or her judgment, since, except for those variants that are cofactor responsive, there is no long-term treatment for primary lactic acidosis. Depending on the severity and duration of acidosis, hypokalemia might be present, and should be treated cautiously, if the patient is passing urine, by adding potassium to the fluid, not to exceed 40 mEq/L.

A general rule is to overhydrate babies with methylmalonic acidemia and overfeed them with propionic acidemia or MSUD.

Treatment of Hyperammonemia

Hyperammonemia is a medical emergency and must be treated if it exceeds 300–400 μM. This is best achieved either by an exchange transfusion, by peritoneal dialysis using short-term indwelling catheters, or by hemodialysis.

Table 38.5

Location of genes of organic and amino acid disorders primarily related to devastating metabolic diseases of the newborn

Disease/enzyme	Chromosome location
Propionic acidemia/propionyl-CoA carboxylase	α Subunit: 13q32
	β Subunit: 3q21-q22
Methylmalonic acidemia/methylmalonyl-CoA mutase, hydroxycobalamin reductases, and adenosyltransferase (A, B, C, D, F complementation groups)	Multase: 6p21
	Cobalamin A, B, C, D, F: unknown
Isovaleric acidemia/isovaleryl-CoA dehydrogenase	15q14-q15
HMG-CoA lyase deficiency/HMG-CoA lyase	1pter-p33
HCS deficiency/holocarboxylase synthetase	21q22.1
3-Methylglutaconic aciduria/variety with unknown enzyme involvement	Unknown
Glutaric aciduria type 2/α-ETF, β-ETF, ETF-QO	α-eTF: 15q23-q25; β—*ETF*: 19; *ETF-QO*:? 4
Oxidative phosphorylation disease; pyruvate carboxylase	*PyC*: 11q13.4-q13.5
(PyC) deficiency; pyruvate dehydrogenase (PDH) deficiency; cytochrome *c* oxidase (COX) deficiency	*PDH*: $E_{1\alpha}$, Xp22.1-22.2; $E_{2\beta}$, 3p13-q23; E_3, 7q31-q32 Locations of its kinase and phosphatase are?
	COX: Contains 13 polypeptides; peptide, I, II, and III are coded on mitochondrial (mt) DNA gene locations of nuclear coded polypeptides are unknown
UCD/carbamylphosphate synthetase	2q35
UCD/ornithine transcarbamylase	Xp21.1
UCD/citrullinemia (argininosuccinic acid synthetase)	9q34
UCD/argininosuccinic aciduria (argininosuccinic acid lyase)	7cen-p21
Maple syrup urine disease/branched-chain a-keto acid dehydrogenase (E_1, E_2, E_3 subunits)	$E_{1\alpha}$: 19q13.1-q13.2; $E_{1\beta}$: 6p21-p22; E_2: 1p31 E_3:7q31-q32
5-Oxoprolinuria (pyroglutamic aciduria)/glutathione synthetase	20q11.2
Nonketotic hyperglycinemia/contains P, H, and T proteins	*P Protein*: 9p22; *T protein*: 3p21.2-p21.1; *H protein*: the cDNA is available
Neonatal peroxisomal disorders: Zellweger syndrome, neonatal adrenoleukodystrophy, infantile Refsum disease, and hyperpipecolic acidemia (contains 10 complementation groups)	*Peroxisomal assembly factor 1*: 8q21.1
	A peroxisomal marker is known on 7q11.23-q22.1
	PXPMP-1 marker: 1p21-p22
Menkes disease	Xq13

In patients with organic acidemia, particularly during the newborn period, the L-carnitine deficiency leads to the accumulation of organic acyl-CoA in liver mitochondria and causes hyperammonemia through inhibition of UCDs (see *Fig. 38.2*). In these diseases, administration of L-carnitine IV at a dose of 200–400 mg/kg/day, divided into four equal doses 6 h apart, given diluted in 5% dextrose in water and injected over 30 min, will control the hyperammonemia in 24–48 h. In UCDs, acute severe hyperammonemia is best treated by sodium phenylbutyrate (500 mg/kg/day given in four equal doses). All patients with UCDs must receive L-arginine (500 mg/kg/day divided into four equal doses) either orally or, in cases with acute hyperammonemia, IV at the same dose and intervals. In patients with argininosuccinic aciduria or citrullinemia, the administration of L-arginine will promptly reduce hyperammonemia, since the initial steps of the urea cycle are intact.

Treatment of Hypoglycemia

Hypoglycemia must be treated immediately by administering 10% dextrose (2–3 mL/kg), repeated as frequently as required. The blood glucose level at the bedside might be monitored by Dextrostix.

Table 38.6
Diseases that are screened in a neonate by tandem mass spectrometry

Isovaleric acidemia
3-Hydroxy-3-methylglutaric acidemia
Propionic acidemia
Methylmalonic acidemia
Cobalamin mutations with low methionine
Methylenetetrahydrofolate reductase deficiency
Holocarboxylase synthetase deficiency
Ethylmalonic acidemia
Medium-chain acyl-CoA dehydrogenase deficiency
Very-long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Short-chain acyl-CoA dehydrogenase deficiency
Glutaric acidemia type 1
Glutaric acidemia type 2
β-Kethothiolase deficiency
5-Oxoprolinuria (pyroglutamic acidemia)
Classic PKU
Biopterin-dependent PKU
Classic MSUD
Homocystinuria
Tyrosinemia type 1
Tyrosinemia type 2
Histidinemia
Citrullinemia
Argininosuccinic acidemia
Argininemia
Primary lactic acidemias
Pyruvate carboxylase deficiency
Nonketotic hyperglycinemia
Primary carnitine deficiency
Malonic aciduria

Total Parenteral Nutrition and Central Line Insertion

It is advisable that a central line be inserted in all newborns with devastating metabolic disease, since the clinical course will be labile, with the recurrence of metabolic attack or superimposed sepsis. A secure line should be present, usually for a period of 10–20 days, through which medications, fluids, and antibiotics can be immediately administered as required, until the patient can be stabilized.

Newborns with a severe crisis of propionic acidemia and MSUD must be treated with TPN. Both diseases require the administration of large amounts of calories to reinstate the anabolic state. Such TPN fluids usually contain 12.5–25% dextrose, and lipids are gradually increased depending on the liver enzymes, and per the discretion of the TPN pharmacists. Regular amino acid mixtures should not be used since they contain large amounts of BCAAs. The best option is to use specially prepared amino acid mixtures in TPN. These amino acid solutions lack BCAAs when used in patients with MSUD and lack L-isoleucine, L-valine, and methionine when used in case of propionic acidemia. If such special amino acid mixtures are not available, routinely available amino acid mixtures might be added at 0.5–1 g/kg/day. The special formulas available for propionic acid or MSUD should be given at half-strength by slow infusion through a NG feeding tube. The gastric residue must be checked every 4–6 h. After the first day of TPN, regular insulin injections (1 U/kg/dose) may be given every 6 h or insulin may be given through a continuous drip. The blood glucose must be monitored frequently, and extra glucose should be given if the infant becomes hypoglycemic. The efficacy of the treatment is best monitored by the daily weight gain in a nonedematous baby, by the decrease in phosphate and potassium, and by the increase in rate of glucose utilization per minute. When the daily weight gain plateaus, the baby can be gradually shifted to full oral administration of the special milk and gradual discontinuance of TPN.

Albumin and Blood Transfusion

Even the best-controlled newborn will develop hypoalbuminemia due to disturbed liver functions, hypercatabolism, and difficulties of providing adequate amounts of amino acids and protein. Albumin should be monitored biweekly in a nonedematous, and daily in an edematous, newborn. Albumin solution (1–2 g/kg) should be given to assure a normal blood albumin level and to prevent edema. Since the management of devastating metabolic disease will require very frequent and voluminous blood drawing, such babies will quickly develop anemia, and the hemoglobin should be maintained at greater than 100 g/L by blood transfusions.

Treatment of Thrombocytopenia

Infants with propionic acidemia will develop severe and precipitous thrombocytopenia, every time and at every age when they experience a metabolic crisis. Such a patient will die due to intracranial bleeding if the intercurrent thrombocytopenia is not suspected. A patient with propionic acidemia who develops a metabolic attack should receive daily platelet counts. Although less severely

and less commonly, patients with methylmalonic acidemia and isovaleric acidemia, particularly in the newborn period, might experience significant thrombocytopenia, and the same precautions should be observed.

Calcium and Other Supplements

During the management of the crisis, a patient with organic acidemia may develop hypocalcemia, which should be corrected by the administration of an appropriate dose of the available IV or oral calcium preparations. The TPN formula usually contains mixtures of trace elements. These babies, when shifted to oral formulas, should be given added trace element mixtures, and multivitamins in appropriate doses. Patients with UCDs should be given folic acid (5 mg) and pyridoxine (25 mg) daily. When large doses of hydroxycobalamin are used in the management of methylmalonic acidemia, folic acid (5 mg/day) must also be given.

Management of Chronic Disease

Patients with devastating metabolic diseases will require special care for their lifetimes. The parents must therefore be taught how to provide such care, and the pediatrician involved should frequently monitor the efficacy of the treatment. Noncompliance by parents and neglect by the pediatrician will only provoke frequent metabolic crises, each requiring costly hospitalization or intensive care. Therefore, a team consisting of a physician, nutritionist, and social worker is essential for successful management of these patients.

The principles of long-term management are to provide (a) chronic detoxification, (b) special foods restricted in certain amino acids, and (c) certain cofactors with the hope of activating a defective enzyme or stabilizing the small amounts of the existing enzyme.

Detoxification

L-Carnitine is the most important and most frequently used drug in the management of organic acid disorders. Under normal conditions, it is synthesized from L-lysine. It is responsible for the back-and-forth transport of acyl-CoA moieties from mitochondria and cytosol, since acyl-CoA cannot be transposed between these two compartments otherwise. Carnitine and acylcarnitines are water soluble and will be freely excreted into the urine. When an organic acidemia is present, L-carnitine soon will be depleted, since the rate of synthesis will not be able to cope with its rate of transacylation and eventual excessive loss of acylcarnitines through the urine. The transport role of L-carnitine is shown in *Fig. 38.20*. L-Carnitine is also considered to stabilize the dehydrogenase complexes and so is used, in addition to thiamine, in the management of patients with dehydrogenase deficiencies such as PDH and MSUD.

During acute attacks, L-carnitine should be used IV, at 200–300 mg/kg/day divided into four equal doses. When the patient is stable, it can be given at the same dose orally. No toxicity of the drug is known if the L-form is used. The DL-form shows CNS toxicity and must never be used. Oral absorption is usually less effective since only 10–20% of the drug is absorbed. Oral L-carnitine may

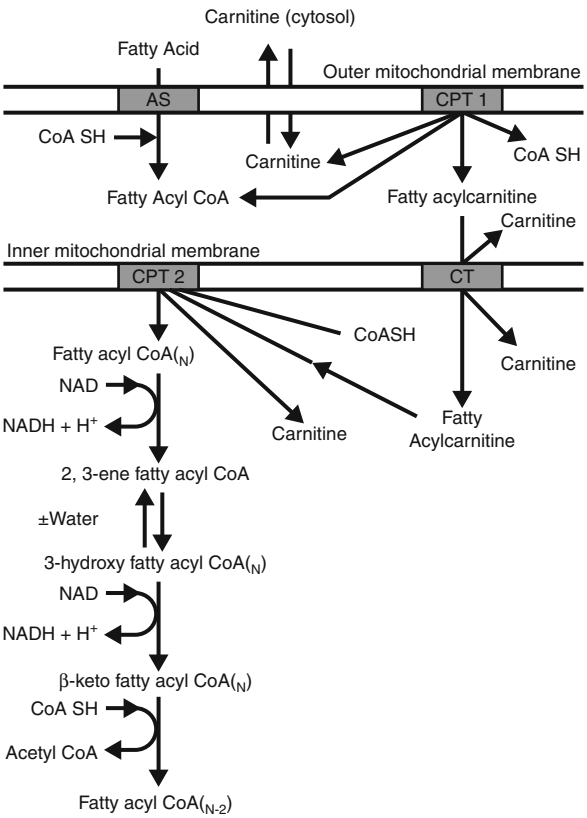


Figure 38.20
Fatty acid oxidation and role of carnitine. Enzymes involved: (AS) fatty acyl-CoA synthetase, (CPT 1) carnitine palmitoyl transferase 1, of outer mitochondrial membrane, (CPT 2) carnitine palmitoyl transferase 2, of inner membrane, (CT) carnitine/acylcarnitine translocase, (1) acyl-CoA dehydrogenase (short-, medium-, and very-long-chain specific (SCAD, MCAD, and VLCAD) types, (2) enoyl hydratase, (3) 3-hydroxyacyl-CoA dehydrogenase (LCHAD; trifunctional enzyme with broad specificity for chain length), and (4) β-keto-thiolase

cause some loose stools due to its high sorbitol content, and at times a fishy smell due to its breakdown by intestinal bacteria. None of these side effects should hinder its chronic use, since it truly is a life-saving drug.

In isovaleric acidemia and MADD, glycine is given at 500 mg/kg/day, divided into four equal doses, since isovaleryl-CoA and acyl-CoA intermediates of MADD can be detoxified by a liver enzyme that uses glycine (*N*-acylglycine conjugase).

In UCDs, L-arginine must be provided at 500 mg/kg/day divided into four equal doses. L-Arginine is an essential amino acid in the newborn period, cannot be synthesized in a patient with a UCD, and is absolutely essential for the normal development of the CNS.

Citric acid displaces methylcitric acid, which is produced from the condensation of propionyl-CoA with oxaloacetate, from mitochondria. Methylcitric acid inhibits numerous mitochondrial functions. Therefore, in diseases in which propionyl-CoA accumulates, such as propionic acidemia, methylmalonic acidemia, and MCD, citric acidcontaining preparations such as Polycitra or Shohl solution should be preferred over oral sodium bicarbonate therapy.

Special Formulas

The selectively amino acid–restricted formulas play a pivotal role in the long-term management of these disorders. These formulas are shown in *Table 38.7*. There are numerous commercial preparations, all equally effective. Some preparations contain L-carnitine already added to the formula, and are easier to use. Such formulas are for long-term usage; when the infant grows into a child, there are also special food substances that are deprived of selective amino acids. These are specially prepared flours and rice and pasta preparations that can be used in addition to formulas, together with other permissible food substances. The reader is referred to publications dedicated to this subject for detailed discussion of the use of available preparations.

Cofactors, Vitamins, and Medications Used in Long-Term Management

The medications used to treat devastating metabolic diseases of the newborn over the long term are shown in *Table 38.7*. Since L-carnitine is more or less universally used for most organic acidemias, it is not included in this table. In most of the disorders listed, fasting, or a fasting state created by vomiting, will prompt the crisis. In all such instances, the infant should be given IV dextrose solutions to prevent the breakdown of fats and proteins. Polycose, four to five scoops according to the age of the infant given ad lib in flavored electrolyte solution (Pedialyte), should be utilized upon minor vomiting, diarrhea, or anorexia since it prevents major hypoglycemia.

An important source of propionic acid is bacterial production in the intestines; therefore, metronidazole should be used during the acute crisis of propionic acidemia. The infant better tolerates Polycitra or Shohl solution, if sweetened. The treatment that may be effective in certain variants of 3-methylglutaconic aciduria should be tried in all patients with a mitochondrial disease.

Nonketotic hyperglycinemia is a very severe disease. Its outlined treatment will only make it less severe, and complete cure should not be anticipated.

There are several procedures to prepare copper-histidinate chelate, and either one may be used in the treatment of Menkes disease. A patient with Menkes disease should be delivered around 32 weeks of gestation, before the blood–brain barrier matures, in order to assure the entry of copper into the CNS.

A patient with 5-oxoprolinuria is severely deficient in reduced glutathione and should be carefully protected from exposure to oxidizing drugs and foods.

Outcome

The prognosis of these disorders depends on the genotype/phenotype and on the early or late detection of the disease. These considerations are summarized in *Table 38.8*. The prognoses cited are for patients in whom the disease is identified either early (i.e., within the period of the safety window) or before the first metabolic breakdown. Certain genotypes lead to very severe phenotypic presentations, while the reverse is also true. For example, methylmalonic acidemia due to cobalamin a mutation is a disease that allows rewarding treatment, while cobalamin c mutation or mutant 0 lead to very severe disease. The same disease in different children of the same family might also manifest either in severe or milder forms. All patients should receive vigorous treatment since it is next to impossible to assign a prognosis at the initial encounter. For example, MSUD causes such severe and early cerebral edema that mild to severe optic atrophy is invariably present at the time of initial encounter. Most MSUD patients will gain full visual function despite this finding if treated appropriately. In most instances, a primary lactic acidemia patient is abandoned because, despite vigorous therapy, including prolonged peritoneal dialysis, the physician will never be able to maintain a normal acid–base balance. Such an infant will develop severe pyramidal tract signs and loss of vision and

Table 38.7

Formulas and medications used for long-term management of infants who had devastating metabolic diseases of the newborn

Disease	Formulas[a]	Cofactors and medications[b]
Propionic acidemia	L-Isoleucine, L-valine, and L-methionine–restricted formulas	+LC. (Biotin, 5–10 mg/kg/day)[c]; metronidazole, 30 mg/kg/ ÷ t.i.d.; citrate, 4–6 mEq/kg/day
Methylmalonic acidemia	Same formula as described for propionic acidemia	+LC. *Acute crisis*: 1 or 2 × 1 mg IM daily hydroxycobalamin
		Chronic management: 1 or 2 × daily intranasal 0.5 mg B_{12}; citrate, 4–6 mEq/kg/day
Isovaleric acidemia	L-Leucine-restricted diet (not more than 83 mg/kg/day)	+LC. Glycine, 500 mg/kg/d; bicarbonate or citrate, 4–6 mEq/kg/d
HMG-CoA lyase deficiency	L-Leucine–restricted diet (as above); low-fat diet	+LC. Bicarbonate or citrate, 4–6 mEq/kg/day; Polycose for vomiting and diarrhea
Multiple carboxylase deficiency	N.R.	+LC. Biotin, 5–10 mg/kg/day; citrate, 4–6 mEq/kg/day
3-Methylgluaconic aciduria	N.R.	–LC. Ubiquinone, 25–50 mg/day; vitamin K_1, 5–10 mg/day; ascorbic acid, 250–500 mg/day; bicarbonate or citrate, 4–6 mEq/kg/day
Glutaric aciduria type 2	N.R.	+LC. (Riboflavin, 50–100 mg/kg/day); glycine, 200 mg/kg/day
Oxidative phosphorylation disease	N.R.	–LC. *PyC deficiency*: biotin, 5–10 mg/kg/day)
		±LC. *PDH deficiency*: thiamine, 50–100 mg/kg/d; (dichloroacetate, 50–100 mg/kg/day
		In all: bicarbonate or citrate, 4–6 mEq/kg/day
5-Oxoprolinuria	Same dietary precautions as for glucose-6-phosphate dehydrogenase deficiency	–LC. Same pharmacologic restrictions as for glucose-6-phosphate dehydrogenase deficiency; sodium bicarbonate or Polycitra 4–6 mEq/kg/day
Urea cycle disorders	UCD formula (mixture of essential amino acids and Polycose)	–LC. Sodium benzoate, sodium phenylacetate, or sodium phenylbutyrate, singly or in combination not to exceed 500 mg/kg/day[d]
		L-arginine, 250–500 mg/kg/day; folic acid 5, mg/day; pyridoxine, 25 mg/day
Maple syrup urine disease (MSUD)	MSUD (restricted in BCAA) formula	±LC. (Thiamine, 50–100 mg/kg/day); trace mineral mixture; zinc sulfate orally, 25 mg/kg/day; niacin, 50 mg/day; mixture of polyunsaturated fats, 1–2 g/day
Nonketotic Hyperglycinemia	N.R.	–LC. Sodium benzoate, 500 mg/kg/day; dextromethorphan, up to 35 mg/kg/day; folinic acid, 15 mg/day
Neonatal peroxisomal disorders	N.R.	(Oral bile acids)
Menkes disease	N.R.	–LC. Baby is delivered as early as compatible with life; copper-histidine chelate, 1 mg/M 2–3 × week

[a]N.R., not effective

[b]+LC, L-carnitine is used in these disorders at a dose of 200–400 mg/kg/day (it is administered IV during acute crisis); ±LC, L-carnitine may be of use in PDH deficiency and MSUD; −LC, L-carnitine not a part of the treatment. Treatments within parentheses are experimental, and might be effective in cofactor-responsive variants

[c]They may be beneficial

[d]Usually not used or used in reduced doses in patients with argininosuccinic aciduria, unless it is a severe case

Table 38.8
Outcome of devastating metabolic diseases of the newborn when diagnosed and treated early and appropriately

Disease	Outcome
Propionic acidemia	*Mild phenotype:* 20–30% compatible with a normal lifestyle; death is usually due to unsuspected thrombocytopenia during a crisis
	Severe phenotype: incompatible with life
Methylmalonic acidemia	*Most phenotypes:* easy to manage, leading to a normal lifestyle, except these children are prone to fulminant viral diseases
Isovaleric acidemia	*Most phenotypes:* easy to manage and are compatible with life, leading to normal lifestyle
HMG-CoA lyase deficiency	Excellent, except close supervision is required for the precipitous lactic acidotic hypoglycemia that will occur when the child has an infection and refuses to eat. Can be prevented by using Polycose
Holocarboxylase synthetase deficiency	Incompatible with life, except on rare occasion when the disease is biotin responsive and diagnosed early, receiving early and intensive treatment
3-Methylglutaconic aciduria: neonatal variants	Usually severe progressive encephalopathy leading to crippling and early death; except on rare occasions might be responsive to coenzyme Q and phytanedione
Multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria type 2)	Usually incompatible with life; rarely good response to cofactors in this age group
Oxidative phosphorylation diseases	*Pyruvate carboxylase deficiency:* usually fatal, except on rare occasions may be biotin responsive
	Pyruvate dehydrogenase and cytochrome c oxidase deficiencies: usually fatal
5-Oxoprolinuria (pyroglutamic aciduria)	Chronic and slowly progressive neurodegenerative disease with mental retardation
Urea cycle disorders	Compatible with near-normal lifestyle if diagnosed early and treated vigorously. Better prognosis for citrullinemia. Argininosuccinic aciduria, which might appear late, will have good prognosis if diagnosed and treated early
Maple syrup urine disease (MSUD)	*Classic MSUD:* if diagnosed early and treated vigorously, is compatible with normal lifestyle. Severe phenotypes and patients who are diagnosed late will develop severe neurologic sequel and will die
	Intermediate and intermittent phenotypes: excellent prognosis
Nonketotic hyperglycinemia	Moderate to severe neurologic crippling even in early-diagnosed and aggressively managed patients. Incompatible with life if diagnosed late and if not treated appropriately
Neonatal peroxisomal diseases	Incompatible with life
Menkes disease	Early delivery and treatment with copper-histidine chelate will be beneficial. Prenatally diagnosed and treated patients provide better results. Severe neurologic crippling and death in untreated cases

will eventually expire. The E_1 abnormal phenotype of PDH deficiency might respond to the administration of dichloroacetate, and the acid–base balance in such a neonate might be managed with more ease, delaying the eventual CNS manifestations. Some forms of pyruvate carboxylase, or holocarboxylase synthetase deficiency, are biotin responsive, and such a baby might be eventually managed without progression of the CNS disease. It is therefore recommended that, in each instance, the baby should be given at least 1 month of intensive cofactor treatment before any decision is made.

Diseases of Later Infancy and Childhood Involving Organic Acid, Amino Acid, and Carbohydrate Metabolism

Clinical Presentation

The list of diseases that will manifest periodically with metabolic crisis (e.g., acidosis, hypoglycemia, liver failure) in the period of later infancy and childhood includes organic and amino acid disorders as well as carbohydrate disorders. Among the latter, galactosemia is of special

importance since it may occur in the neonate but may also manifest at a few weeks to a few months of age. Since the acute or chronic manifestation of carbohydrate disorders is readily confused with organic acidemias, their manifestations are included in this chapter.

Organic Acidemias of Newborns that Also Occur in Later Infancy

The main diseases in this category are shown in *Table 38.9*. Some of these diseases have already been discussed in the section "Devastating Metabolic Diseases of the Newborn" and will not be presented again, with two exceptions.

Propionic Acidemia

A significant percentage of propionic acidemia will present in a different manner later during infancy, that is, it does not appear with devastating metabolic acidosis. Two significant presentations of the disease are one phenotype that presents primarily as a case of immune deficiency, and another that presents primarily with seizures or other neurologic manifestations. If these presentations are not recognized, the disease eventually will cause significant neurologic damage or death.

3-Methylglutaconic Aciduria with Extrapyramidal Tract Signs

The etiology of this organic acidemia is not known; circumstantial evidence suggests a block in the pathway of mevalonic acid that leads to the interruption of either cholesterol or ubiquinone (coenzyme Q) synthesis. Therefore, the clinical symptoms are those of either disturbed membrane function or an oxidative phosphorylation defect. A distinct subtype of the disease leads to the degeneration of basal ganglia and manifests with extrapyramidal tract signs. The presence of 3-methylglutaconic aciduria should be ruled out in any child who presents with rigidity, dystonia, or choreoathetiform movements. The dystonic posturing of a patient with this disease is shown in *Fig. 38.21*.

Table 38.9
Organic and amino acidemias of later childhood

Organic Acidemias
Neonatal disorders that also occur in later infancy
Propionic acidemia
Methylmalonic acidemia
Isovaleric acidemia
3-Hydroxy-3-methylglutaryl-CoA (HMG-CoA) lyase deficiency
Mild phenotypes of oxidative phosphorylation disease
3-Methylglutaconic aciduria with extrapyramidal symptoms
Diseases of primarily of infantile/childhood period
3-Ketothiolase deficiency
Glutaric aciduria type 1
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)
Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)
Biotinidase deficiency
Biotin-responsive holocarboxylase synthetase deficiency
4-Hydroxybutyric aciduria
Disorders of Carbohydrate Metabolism
Associated with either lactic acidosis, hypoglycemia, or both
Fructose sensitivity (fructose-1, 6-bisphosphatase [FDPase] deficiency)
Glycogen storage disease type 1
Galactosemia
Amino Acidemias
Hyperphenylalaninemia (classic PKU)
Biopterin-dependent hyperphenylalaninemia (malignant PKU)
Dihydrolipoyl dehydrogenase (E_3) deficiency
Homocystinuria (cystathionine β-synthetase deficiency)
Tyrosinemia type 1 (fumarylacetoacetate hydrolase deficiency)

Case History. A 4-year-old boy was the product of a first-cousin marriage with four normal siblings. He was normal at birth but experienced cyanosis within 2 h, requiring intensive care hospitalization. His further development was normal; he was sitting and crawling at 8 months and saying a few words. He started to lose milestones at 1 year and developed severe dystonic posturing. He had several tonic seizures after 2 years. He was small for stature, with his height, weight, and head circumference corresponding to median values of 12, 24, and 9 months, respectively, at the chronologic age of 48 months. He showed pseudobulbar affect, severe rigidity, and dystonic posture. Eyegrounds revealed optic atrophy; deep tendon reflexes were increased, with Babinski sign. Blood chemistries, lactic acid, pyruvate, pH, gases, ammonia, and blood count were normal. A urine GC/MS study revealed increased 3-methylglutaconic aciduria. The EEG showed diffuse background slowing. MRI of the

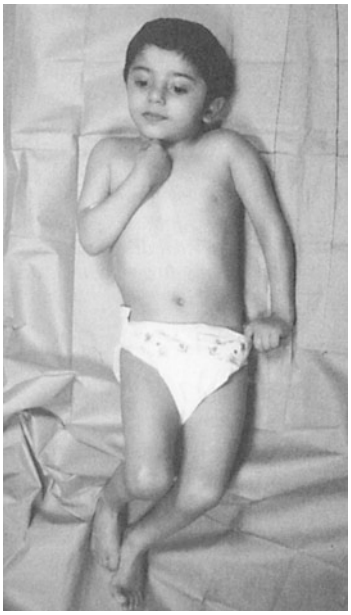


Figure 38.21
A 3-year-old boy with 3-methylglutaconic aciduria with putaminal necrosis; note the dystonic posturing

brain revealed atrophic changes in the posterior fossa, a small vermis, and delayed myelination with isointense subcortical white matter in the posterior parietal region. Lentiform nuclei bilaterally showed slit-like, low T1- and high T2-intensity lesions with involvement of the heads of the caudate nuclei.

Organic Acidemias Occurring Primarily in the Infantile/Childhood Period

Organic acidemias that occur primarily during this period are numerous; however, six of these are important, since they can be managed successfully and, if missed, cause severe neurologic handicap and death.

3-Ketothiolase Deficiency

This is a disease caused by the deficiency of the ketothiolase responsible for the breakdown of 2-methylacetoacetyl-CoA, the metabolite of the final step of degradation of L-isoleucine (*Fig. 38.22*). It causes periodic severe ketoacidosis and will require intensive measures to correct the acidosis. When the diagnosis is missed, the repeated acidosis causes CNS damage in approximately a third of the patients, while treatment with L-carnitine and a low-protein diet prevents the acidotic attacks as well as the neurologic sequelae.

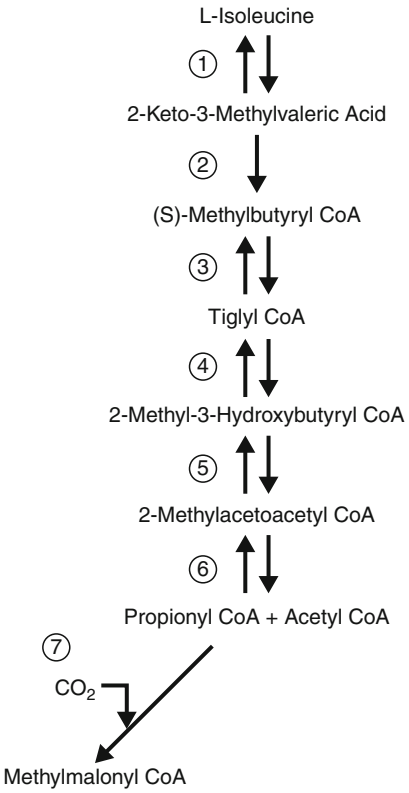


Figure 38.22
Breakdown of L-isoleucine and the enzymes lacking in various inborn errors of metabolism. Enzymes involved: (1) branched-chain amino acid transaminase, (2) branched-chain α-keto acid dehydrogenase, (3) 2-methyl branchedchain acyl-CoA dehydrogenase, (4) tiglyl-CoA hydratase, (5) 2-methyl-3-hydroxybutyryl-CoA dehydrogenase, (6) mitochondrial β-ketothiolase (2-methylacetoacetyl-CoA 3-ketothiolase), and (7) propionyl-CoA carboxylase. Diseases related to deficiency of the aforementioned enzymes: (2) MSUD, (6) mitochondrial β-ketothiolase deficiency, and (7) propionic acidemia

Case History. An 8-month-old boy was slow in achieving the appropriate developmental milestones, sitting only with support at 8 months. He had acute otitis media and developed fever, seizures, and vomiting with Kussmaul breathing. Examination revealed profound lethargy, a palpable liver edge, and central hypotonia. He had massive ketonuria; blood pH was 7.05, BE −26 mEq/L, pCO_2 1.45, and bicarbonate 2.5 mEq/L, with normal blood glucose. His EEG showed slow-wave discharges over the right anterior areas. MRI of the brain showed highintensity T2 lesions within the posterior lateral part

of the putamina, continuing toward the lower part of the corona radiata. The urine study showed massive amounts of acetoacetate, 3-hydroxybutyrate, and intermediates characteristic of the disease (i.e., 2-methylacetoacetate, 2-methyl-3-hydroxybutyrate, and tiglylglycine). His fibroblasts, grown from a skin biopsy, revealed a deficiency of mitochondrial 3-ketothiolase activity. He was placed on an L-isoleucine restricted diet, L-carnitine, and Polycitra. He did not have any further attacks. When last seen at the age of 2.5 years, he was normal and had no neurologic sequelae.

Glutaric Aciduria Type 1

This is a disease caused by the deficiency of glutaryl-CoA dehydrogenase, an enzyme on the breakdown pathway of L-lysine (*Fig. 38.23*). It leads to severe degenerative loss of basal ganglia and underdevelopment of anterior portions of the frontal and temporal lobes, causing a pathognomonic neuroradiologic sign known as "wide operculum" or very widened sylvian fissure. In addition, central white matter disease is observed. The pathogenesis remains unknown. Glutamate excitotoxicity due to glutamate accumulation in the basal ganglia as caused by the inhibitory action of glutaryl-CoA on glutamate decarboxylase has been implicated. Another hypothesis is the stimulation of alternate catabolic pathways of tryptophan and accumulation of quinolinic acid, which is highly toxic to the neurons in basal ganglia. Clinical signs reflect the neuropathology; such cases show macrocephaly and increased deep tendon reflexes in addition to basal ganglia symptoms such as severe dystonic posturing, rigidity, and choreoathetosis. The disease usually appears following either metabolic stress or an infection. The severe CNS signs that suddenly appear often lead to an erroneous diagnosis of meningitis or encephalitis while the underlying disease is missed. The disease then progresses, causing severe choreoathetotic cerebral palsy, and the patient will require placement in a handicapped-children's facility. If the disease is discovered before the first metabolic breakdown, during neonatal screening, it can be managed to prevent the appearance of neurologic signs. Such children will then lead a nearnormal life. The disease does not cause chemical disturbances detectable by routine laboratory chemistries, such as acidosis, hypoglycemia, or hyperammonemia; therefore, it is a "silent," "neurologic," or "cerebral" organic aciduria. Since the disease is panethnic, its detection should be part of neonatal screening programs universally. Its treatment or prevention includes the use of a lysine-restricted diet, riboflavin, carnitine, valproate, or baclofen, and rigorous management of even minor infections or metabolic stress. The characteristic dystonic posturing and the wide operculum sign are shown in *Fig. 38.24*.

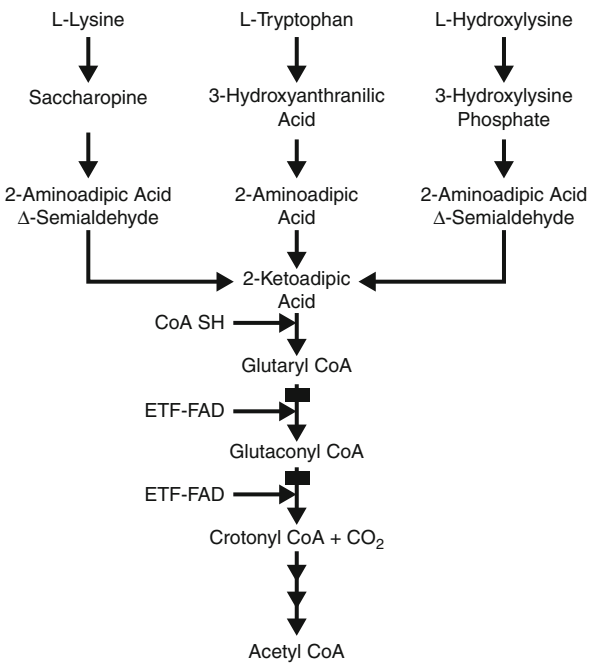


Figure 38.23
L-Lysine, L-hydroxylysine, and L-tryptophan metabolism and glutaric aciduria type 1. Defective enzyme in glutaric aciduria type 1: glutaryl CoA dehydrogenase; probably the same enzyme catalyzes the dehydrogenation of both glutaryl-CoA and glutaconyl-CoA. Defective enzyme in glutaric aciduria type 2 (multiple acyl-CoA dehydrogenase deficiency): flavin-adenine dinucleotide containing electron-transport flavoprotein (ETF-FAD)

Case History. A boy who was first seen at the age of 1 year had developed normally until 7 months, at which time he suffered a head trauma. The next day he developed fever, vomiting, and diarrhea; this was followed by focal seizures involving the left side of the body and the face, and oculogyric crisis. He was diagnosed to have encephalitis, and the CSF revealed elevated protein (500 mg/L). CT of the brain was obtained at the referring hospital; although the "wide operculum" sign, central white matter disease, and diffuse brain atrophy were observed, the significance of these neuroradiologic findings was not appreciated. He lost his acquired milestones and showed dystonic posturing of the hands and opisthotonus. On examination he had macrocephaly, rigid quadriplegia, increased deep tendon reflexes, and Babinski reflex. The routine laboratory examination was unremarkable, with

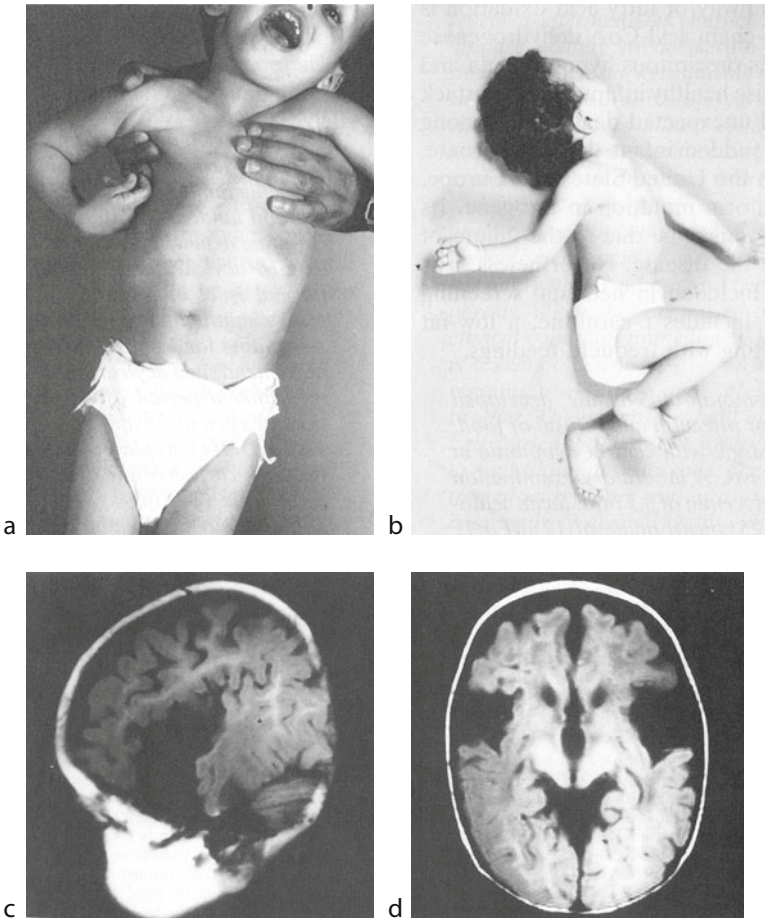


Figure 38.24
(a) A 2-year-old boy with glutaric aciduria type 1; note the choreic grimacing, dystonic posturing, and rigidity. (b) A 2-year-old girl with glutaric aciduria type 1; note severe dystonic posturing, rigidity, and macrocephaly. (c) MRI of the brain in glutaric aciduria type 1; note the widened arachnoid space at the sylvian fissure and the frontal and temporal lobe atrophy. (d) The wide operculum sign with frontotemporal lobe atrophy, generalized brain atrophy, some central white matter disease, and total degeneration of the basal ganglia, including the caudate nucleus

borderline elevated lactate (3 mM) and compensated metabolic acidosis, with BE −6.8 and −7.5 mEq/L on two occasions. MRI of the brain confirmed the findings of the previous CT of the brain. The EEG, visual-, and auditory-evoked potentials were normal. A urine GC/MS study revealed the characteristic intermediates of type 1 glutaric aciduria (i.e., glutaric, 3-hydroxy-glutaric, and glutaconic acid). He was placed on riboflavin (100 mg/kg/day), L-carnitine (200 mg/kg/day), valproic acid, niacin, and the lysine- and tryptophan-restricted diet used for type 1 glutaric aciduria. His disease did not progress over the next 3 years, but he did not regain the lost neurologic functions. The diagnosis was later reconfirmed by the detection of glutarylcarnitine in the blood by tandem MS, as well as the absent activity of glutaryl-CoA dehydrogenase in fibroblasts, at a referral laboratory.

Acyl-CoA Dehydrogenase Deficiencies

Medium-Chain Acyl-CoA Dehydrogenase Deficiency This is a disease caused by the deficiency of the initial dehydrogenase involved in the oxidation of medium-chain-length fatty acids. The pathway of fatty acid oxidation is shown in *Fig. 38.20*. Medium-chain acyl-CoA dehydrogenase deficiency (MCAD) causes precipitous hypoglycemia and lactic acidosis in an otherwise healthy infant. Such an attack might lead to sudden and unexpected death. It is among the recognized causes of sudden infant death syndrome. It is a common disorder in the United States and

Europe, and is due to a single uniform mutation in the gene. Its rare occurrence elsewhere might be due to the failure of pediatricians to recognize the disease. Nevertheless, it is treatable and it must be included in neonatal screening programs. The treatment includes L-carnitine, a low-fat diet, and avoidance of fasting with frequent feedings.

Case History. An 18-month-old female developed lethargy following a minor infection and refusal of food. She was profoundly lethargic with central hypotonia at the time of arrival at the ER. A laboratory examination revealed profound hypoglycemia of 0.5 mM, lactic acidosis of 8 mM, pH of 7.25, bicarbonate of 12 mEq/L, and BE of −10 mEq/L. The history failed to reveal any sensitivity to sweets and sucrose, and she had no hepatomegaly, which clinically ruled out a fructose sensitivity and glycogen storage disease type 1. She was revived with the administration of glucose, bicarbonate, and fluids. A urine examination revealed C6 and C8 dicarboxylic aciduria, and a study of the blood by tandem MS revealed elevated concentrations of C6 through C10 acylated carnitines, confirming the diagnosis. She had no further metabolic crisis; at present she is an entirely healthy 8-year-old girl.

Very-Long-Chain Acyl-CoA Dehydrogenase Deficiency This is a disease caused by deficiency of the initial dehydrogenase involved in the oxidation of long-chain fatty acids (*Fig. 38.20*). It appears that there are two enzymes involved with overlapping substrate specificity, a long-chain and a very-long-chain acyl-CoA dehydrogenase. The latter is more active with longer chain fatty acids, and its deficiency is known as very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD). Only the deficiency of VLCAD is known in humans. The clinical presentation of VLCAD can be mild to very severe. Mild forms will present with myopathy, cardiomyopathy, and periodic hypoglycemia with mild lactic acidosis. The severe disease manifests with severe hypertrophic cardiomyopathy, hepatomegaly, intractable hypoglycemia, and lactic acidosis. The mild form of the disease will respond to treatment with L-carnitine, medium-chain triglyceride (MCT) oil (1 g/kg/day), and a low-fat diet. The severe form of the disease is invariably lethal. VLCAD also may present with acute hepatic failure leading to precipitous death. This form is highly responsive to the aforementioned treatment.

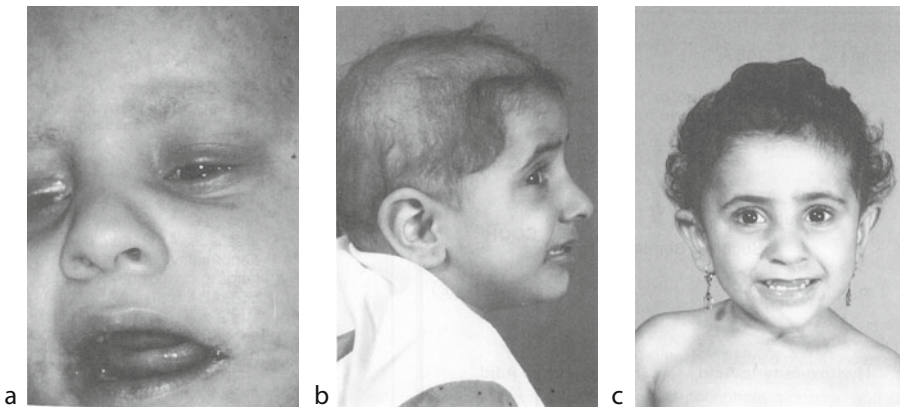
Case History. A 7-month-old boy was referred for the evaluation of his hepatomegaly, which was noticed soon after birth. The family history was interesting. The parents were first cousins; they had three normal children but had lost five infants to fulminant hepatic failure. According to the parents, these children, two girls and three boys, were normal and grew normally until the age of 4–8 months. They abruptly developed severe jaundice and died within 1–3 days with acute liver failure. The patient was a normal child whose growth parameters were at borderline normal percentile. His liver was enlarged 4–5 cm below the right costal margin and had a soft, blunt edge. He had no splenomegaly and neurologic examination was normal. The blood chemistries revealed lactate of 3.6 mM, glucose of 3.5 mM, ALT of 96 U/L (normal range: 10–40 U/L), and AST of 85 U/L (normal range: 10–40 U/L). Serum ammonia and amino acids were normal. Since the family history suggested death due to VLCAD, a blood tandem MS study was obtained, which showed carnitine deficiency and increased concentrations of C12–C18 acylcarnitines, including one to two times the normal level of unsaturated fatty acylcarnitines in the same chain-length range. When the patient was given an L-carnitine load of 200 mg/kg, the concentration of the aforementioned acylcarnitines increased. While on carnitine, after a period of 8 h of fasting, this increase became even more apparent, confirming the diagnosis of VLCAD. He was placed on frequent feedings with a low-fat, high-carbohydrate diet, MCT oil (1 g/kg/day), and L-carnitine (200 mg/kg/day). Over the next 2 years he grew without any metabolic crisis. At present he is 7 years old and his growth parameters are at the 95th percentile without any evidence of a liver disease.

Biotin Deficiency

Biotin deficiency does not occur in normal individuals, since a very effective physiologic mechanism exists that permits the preservation of biotin stores in the body. Biotin is a cofactor for various carboxylases, and the enzyme HCS binds biotin to the ε-amino group of lysine in the active center of carboxylases (*Fig. 38.6*). When carboxylases are biologically degraded, biotin is liberated bound to lysine, as biocytin (biotinyl-ε-aminolysine). This peptide is further broken down into free biotin and L-lysine through the action of a liver enzyme, biotinidase (*Fig. 38.6*). The small amount of biotin lost daily through urinary excretion is compensated by intestinal bacterial synthesis and through diet. When either biotinidase or HCS is deficient, biotin deficiency occurs. Both conditions are encountered during infancy. The symptoms of biotinidase deficiency are more severe in infants who are fed by breast milk, since it contains less biotin than commercial formulas. Although biochemically both of these diseases share a common pathology, their clinical presentations are significantly different.

Biotinidase Deficiency Two different phenotypes, one associated with absence and another one associated with deficiency, exist. The absence of biotinidase manifests during early infancy, initially with seizures and/or with loss of hair, eyebrows, and eyelashes and *Candida* dermatitis, particularly of the perineum. This is associated with early central deafness, and later in some instances by visual loss, pyramidal tract signs, and metabolic acidosis. The appearance of a patient with biotinidase deficiency before and after treatment is shown in ◉ *Fig. 38.25*. Any infant who has any one of the aforementioned symptoms should be tested for biotinidase absence, particularly when an etiologically obscure seizure disorder or loss of hair is encountered. The reason for the inclusion of biotinidase in the battery of neonatal screening is this multitude of nonspecific symptoms and early deafness associated with the disease. Upon appropriate treatment, most symptoms, including visual loss and pyramidal tract signs, disappear, but the deafness will remain. Biotinidase absence has one of the most rewarding outcomes of the inborn errors of metabolism in its treatment using biotin 1–5 mg/kg/day. Partial deficiency of biotinidase leads to a progressive encephalopathy with extrapyramidal tract signs and seizures. Finally, biotinidase will be detected to be transiently low in the presence of an ongoing liver disease. Therefore, when biotinidase is detected at a low level, it must be measured several times, months apart, while the patient is kept on biotin treatment, before a final verdict is reached.

Case History. A 3-year-old girl lost all her hair and eyelashes at the age of 20 days; however, both grew again a few weeks later, to be lost entirely again at 4 months. Since her primary dentition was also poor and she had extensive dermatitis, the primary physician diagnosed her tentatively as having ectodermal dysplasia. Her further development was delayed; she sat independently at 1 year, and never developed verbalization. Her hearing was tested at 18 months and she was found to be profoundly deaf. The parents noticed her to have poor vision at 20 months of age, and she developed spastic quadriparesis. She had several attacks of grand mal seizure at the age of 30 months and experienced a metabolic crisis with hypoglycemia, ketolactic acidosis, and hyperammonemia at 3 years, when she was referred for detailed investigations. At that time she had no hair, eyelashes, or eyebrows and had extensive Candida dermatitis under the armpits, neck, and arm folds, with severe inflammation of the perineum. She had bilateral optic atrophy, spastic quadriparesis, Babinski sign, and brisk deep tendon reflexes. The blood chemistries revealed lactic acid of 3.9 mmol/L (normal upper limit: 2 mmol/L); pyruvate of 219 μmol/L (normal upper limit: 80 μmol/L), ammonia of 71 μmol/L (normal upper limit: 55 μmol/L), zero to + ketonuria. The urine collected during the metabolic crisis revealed intermediates characteristic of MCD. The biotinidase activity in the serum was absent. The EEG showed diffuse background slowing, and CT of the brain showed diffuse brain atrophy with scattered foci of demyelination. She was placed on biotin 50 mg twice daily, with additional L-carnitine and Polycitra. Her response to treatment was dramatic, with hair growth after 3 weeks and improved spasticity and gain of visual acuity. The parents were not convinced of the value of treatment and discontinued biotin after 6 months of treatment. She lost her hair within 1 month and became spastic with quadriparesis. When she was placed on biotin



◘ Figure 38.25
(a) A 30-month-old girl with profound biotinidase deficiency, severe facial rash, and lack of eyebrows and eyelashes. (b) The alopecia of biotinidase deficiency. (c) Same girl after 1 month of biotin treatment

once again, her clinical condition immediately improved. At present she is 6 years old with nearly normal mentality, except she remains profoundly deaf. Meanwhile, she had a new brother. The parents brought him in for testing since his hair started to fall out at 3 weeks, and he was also found to have biotinidase absence. The brother was immediately treated with biotin, and at present he is 3 years old and is an entirely normal child with no hearing deficit.

Holocarboxylase Synthetase Deficiency The deficiency of this enzyme will lead to deficiencies of propionyl-CoA carboxylase, pyruvate carboxylase, 3-methylcrotonyl-CoA carboxylase, and acetyl-CoA carboxylase activities (*Fig. 38.6*). This form of multiple carboxylase deficiency often results in an early devastating metabolic disease of the newborn (see previous section) associated with hypoglycemia, hyperammonemia, and ketolactic acidosis. If the enzyme activity is totally deficient, the disease is not compatible with life; however, in some instances pharmacologic doses of biotin will restore enough activity of a deficient enzyme to secure near-normal biochemical function, and the child will survive.

Case History. A 10-day-old girl, the product of a normal pregnancy and delivery, suddenly developed coma and acidosis. At the time of initial encounter, she was comatose with acidotic breathing, and had severe hypotonia with diminished neonatal reflexes. The blood pH was 7.15, BE −21 mEq/L, blood glucose 1.5 mM, ammonia 176 μM, pyruvate 125 μM, and lactic acid 5 mM. The urine GC/MS revealed high amounts of lactic acid, 3-hydroxybutyric acid, 3-hydroxypropionic acid, 3-hydroxyvaleric acid, 3-hydroxyisovaleric acid, methylcitrate, 3-methylcrotonylglycine, propionylglycine, and propionylcarnitine, namely, the organic characteristic of MCD. The serum biotinidase was 5.6 U (normal: 4–8 U). She was given glucose, sodium bicarbonate, and large dose of biotin and L-carnitine. She recovered from this episode in 1 week and was maintained on the same medications. A fibroblast culture grown from a skin biopsy indicated low propionyl-CoA carboxylase, pyruvate carboxylase, and 3-methylcrotonyl-CoA carboxylase activities. The baby is now 2 years old, with only one further metabolic attack following a chest infection. She is neurologically intact with normal milestones. Undoubtedly she has a biotin-responsive holocarboxylase deficiency.

4-Hydroxybutyric Aciduria

This is a disease characterized by excessive formation of 4-hydroxybutyric acid. The enzyme responsible for the normal breakdown of succinic semialdehyde, succinic semialdehyde dehydrogenase, is deficient and, in place of the normal process of further oxidation, succinic semialdehyde is reduced to its alcohol, 4-hydroxybutyric acid (*Fig. 38.26*). The source of succinic semialdehyde is 4-aminobutyric acid or γ-aminobutyric acid (GABA), and it is formed by the transamination of the latter compound. 4-Hydroxybutyric acid is a very powerful neuropharmacologic agent with many actions in the CNS; at low concentrations it is excitatory, while at high concentrations it is inhibitory. Reflective of the diverse pharmacologic actions of 4-hydroxybutyric acid, the clinical presentation of succinic semialdehyde deficiency is nonspecific and is different at different age groups. In the neonate, it causes severe central hypotonia, to a degree compromising respiration, and myoclonic seizures probably due to the inhibition of oxidative phosphorylation by succinic semialdehyde. It is not unusual for such neonates to have retinitis pigmentosa or cataracts similar to the presentation of a mitochondrial disease. Later in life, ataxia, reflective of cerebellar involvement, and severe mental retardation complicate the clinical picture. The diagnosis of the disease depends upon the detection of 4-hydroxybutyric acid in the urine by GC/MS. This compound forms an inner ester (a lactone) easily, which is highly volatile and might be lost totally during the preparation of the sample. Since succinic semialdehyde inhibits various enzymes of oxidative phosphorylation, the urine of such a patient contains the intermediates characteristic of glutaric aciduria type 2, and the disease might easily be misdiagnosed as such. Approximately 60% of the reported patients are of Middle Eastern origin. The presence of 4-hydroxybutyric aciduria must be searched for in any profoundly hypotonic infant or in any mentally retarded child with ataxia. Vigabatrin (γ-vinyl GABA), a noncompetitive inhibitor of GABA transaminase, as well as dextromethorphan, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, have been used to manage the disease, but the results have not always been rewarding.

Case History. A 2.5-year-old girl was found to have profound hypotonia at birth, resulting in difficulty sucking and swallowing. She developed slowly and always showed severe central hypotonia, supporting the head only at 18 months and rolling over at 20 months. She could sit only with support at 26 months. She recognized her mother at 2 years. She never vocalized. The parents were first cousins, and she had a similarly affected brother and two profoundly mentally retarded aunts and an uncle. Despite central hypotonia, a myopathy was suspected and a muscle biopsy was obtained that showed few lipid droplets; urine GC/MS showed intermediates of type 2 glutaric

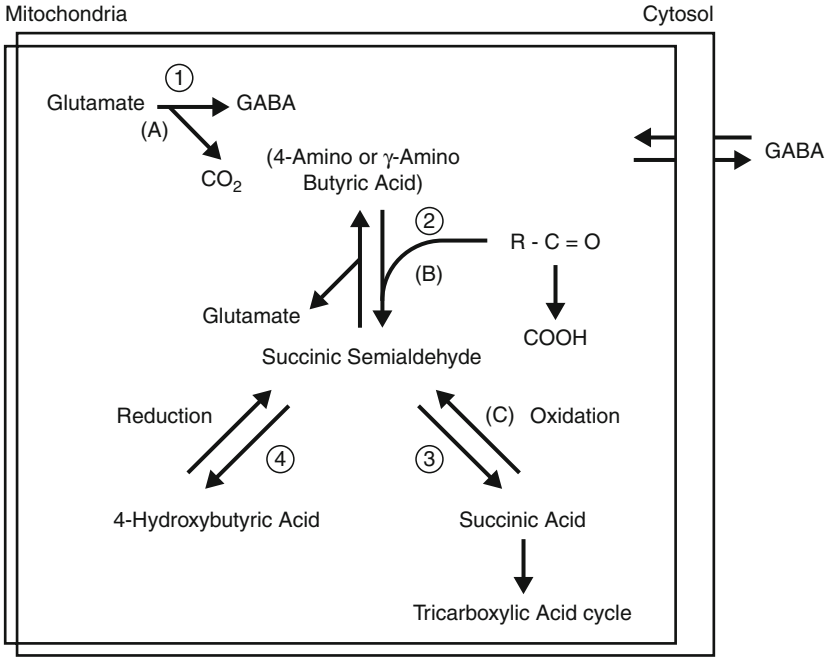


Figure 38.26

Metabolism of 4- (or γ)-aminobutyric acid and 4-hydroxybutyric aciduria. Enzymes involved and diseases caused by the deficiency of enzymes: (1) glutamate decarboxylase, (2) GABA transaminase, (3) succinic semialdehyde dehydrogenase, and (4) the reductase auxiliary pathway for succinic semialdehyde. (a) Glutamate decarboxylase abnormality or pyridoxine deficiency; leads to pyridoxine-dependent seizures. (b) GABA transaminase, the other substrate of which is α-ketoglutaric acid. Vigabatrine inhibits this enzyme noncompetitively. (c) The deficiency of this enzyme leads to 4-hydroxybutyric aciduria, since the indicated auxiliary pathway leads to the production of 4-hydroxybutyric acid, a powerful neuropharmacologic agent responsible for the symptoms of the disease

aciduria. She was considered to have a variant of this disease, or a mitochondropathy. She was referred to our center for further evaluation. At the time of admission she lay in the pithed-frog position; she had relative macrocephaly, poor eye contact, and mild temporal pallor of the optic discs, showing frequent choreoathetiform movements, severe central hypotonia, and diminished deep tendon reflexes. Her psychometric assessment was 8 months at 30 months of age. Her blood chemistries were normal and a repeat muscle biopsy was found to be normal. The EEG showed polyspike wave abnormalities. MRI of the brain indicated bilateral scattered high T2-intensity focal lesions. The urine GC/MS indicated large amounts of 4-hydroxybutyric acid, and, in addition, organic acids encountered in MADD (glutaric aciduria type 2). She was placed on vigabatrin (500 mg q.i.d.), dextromethorphan (30 mg/day), and clonazepam (6 mg/day) (weight 10 kg). Her seizures improved and her central hypotonia became less pronounced, but she has not gained speech or any new milestones. When assessed at 4 years of age, her intellectual development was found to remain at 8 months.

Disorders of Carbohydrate Metabolism

Three disorders listed in ❯ *Table 38.9* are of importance, since they manifest with dramatic metabolic disturbances.

Fructose-1, 6-Bisphosphatase Deficiency (Fructose Sensitivity)
This is a frequently encountered, but not frequently diagnosed, disorder. The presentation is usually after the infant has been exposed to food substances that are sweet, such as orange juice, honey, cereals, or milk with added sugar, or fasts for a prolonged period. The disease may be due either to a deficient or abnormal fructose-1-phosphate aldolase (aldolase B), or to the deficiency of fructose-1,6-bisphosphatase (FDPase) (❯ *Fig. 38.27*). The presentation of the former deficiency is early infantile, with a clinical picture more like that of galactosemia,

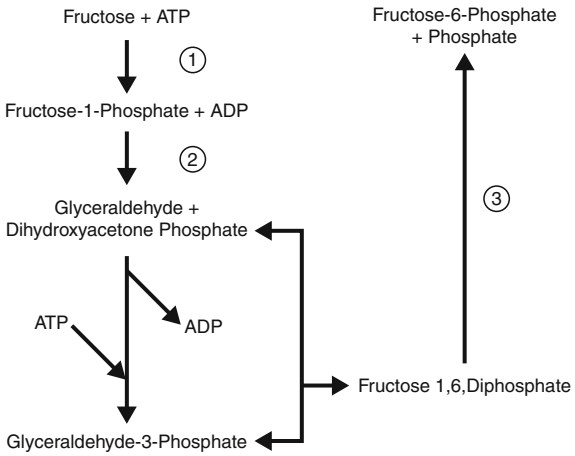


Figure 38.27
Fructose metabolism and enzyme deficiencies related to fructose metabolism. Enzymes involved in fructose metabolism: (1) fructokinase, (2) fructose-1-phosphate aldolase, and (3) fructose-1,6-diphosphatase (FDPASE). Diseases associated with enzyme deficiencies: (1) essential fructosuria, (2) aldolase deficiency, and (3) fructose-1,6-diphosphatase deficiency

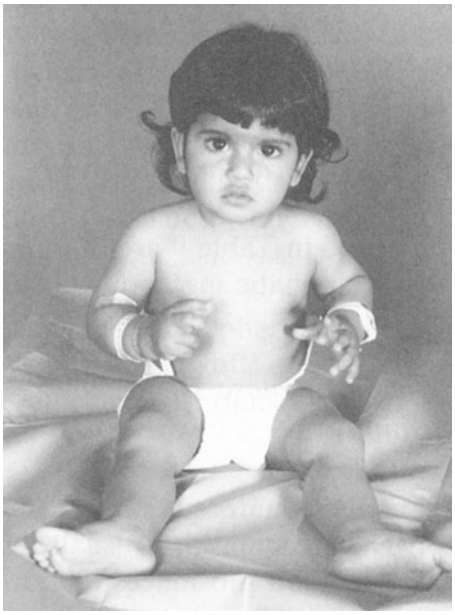


Figure 38.28
An 8-month-old girl with fructose-1, 6-diphosphatase deficiency. Her growth parameters were in the 90th percentile. There were no neurologic findings

while FDPase deficiency usually presents at 6–9 months, when the child first consumes fructose-containing food or fasts. The child may rapidly develop severe hypoglycemia, hypophosphatemia, and hyperlactic acidemia with coma and peripheral shock, which poses serious problems to the ER physician who has to manage the infant.

One suspects the presence of chronic subclinical hypoglycemia and chronic hyperinsulinism, since these infants are both bigger and heavier than their normal siblings (*Fig. 38.28*). The presence of ketone bodies in the urine at the time of crisis helps to differentiate the metabolic attack from that of HMG-CoA lyase deficiency, which never shows significant ketonuria. The hepatomegaly is not as pronounced as that of glycogen storage disease type 1. In a clinically suspect case, a liver biopsy may be obtained and measurement of the aforementioned enzymes may be attempted. A cautious fructose provocation with a small dose such as 200–250 mg/kg IV load, or short-term fasting, will lead to increased lactic acidemia, hypophosphatemia, and mild hypoglycemia, and will establish the diagnosis. If necessary, a glucagon provocation test (0.05–0.1 mg/kg glucagon injection followed by the measurement of blood glucose and lactic acid) will readily differentiate the disease from glycogen storage disease (GSD) type 1. A patient with FDPase deficiency is prone to develop precipitous metabolic crisis when fasting, or when given sugar containing antipyretic or antibiotic preparations for an infection. Fructose-containing food substances should be eliminated from the diet. Artificial sweeteners may be used. Such a patient will in time develop an aversion to sweet foods and, in an older child, the excellent condition of the teeth indicates avoidance of consumption of sweets.

Case History. A 2-year-old girl experienced a ketolactic acidotic hypoglycemia with hypocalcemia in the third month of life, and she had five further episodes with severe ketolactic acidosis, peripheral shock, and hypoglycemia during the first 2 years of life. The parents were not particularly attentive and did not note any relationship between acidotic episodes and consumption of sweet substances. She was admitted electively to prove the presumed clinical diagnosis of FDPase deficiency. Despite the short stature of the parents, her height on admission was 92 cm and weight 14.8 kg, which were in the 75th percentile. On examination she had 2-cm hepatomegaly below the right costal margin, with a smooth and round liver edge. The fasting blood glucose was 4.3 mM, lactate was 2.4 mM, and there was no BE; her other liver function tests were within normal limits and blood insulin was appropriate for glycemia. She was given a challenge of 250 mg/kg fructose. Blood glucose decreased gradually from 4.3 to 3 mM and blood lactate gradually increased to 5.7 mM at 90 min after

fructose loading. The test was discontinued in 3 h, at which time the blood glucose was 3.8 mM and lactate 4.2 mM. The BE at 90 min as well as at 3 h was −5.7 mEq/L. Thus the clinically presumed diagnosis of FDPase deficiency was proven and she was sent home on a strictly fructose-restricted diet. She came to the ER four times over the next 2 months with the same findings: peripheral shock, coma, acidosis, and hypoglycemia. It was learned that there were five normal children in the family, and that they were giving her candy behind the parents' backs, which was triggering the episodes. Since venous excess gradually became a problem and since she always reached the ER in shock, she was admitted and an indwelling catheter was placed. The parents became more attentive and during the next year she did not experience another episode, and the indwelling catheter was removed. At present, she is 8 years old, and her growth parameters are in the tenth percentile.

Glycogen Storage Disease Type 1 (von Gierke Disease)

This is a disease with a highly variable phenotype and etiologies. In its classic form, the infant starts experiencing early-morning hypoglycemia and lactic acidosis that usually are associated with grand mal seizures. History reveals a bleeding tendency, particularly from the nose, and failure to thrive, and the parents note the protuberant abdomen as early as 2–3 months of age. Physical examination will reveal impressive hepatomegaly in a child with abnormal fat distribution. The face will accumulate fat in the cheeks, looking like that of a trombone player (*Fig. 38.29*), while the extremities are thin. The skin may reveal ecchymoses or petechiae. The presence of almost continuous hyperlactic acidemia and low blood glucose alerts the pediatrician to the disease. The blood uric acid, triglyceride, and cholesterol levels are usually very high. Significant renal involvement may lead to a Fanconi syndrome–like urinary excretion pattern with significant aminoaciduria. Despite the bleeding tendency, both the number of platelets and bleeding and coagulation studies are normal. The metabolic crisis may be extremely severe, with pronounced hypoglycemia, hypokalemia, metabolic acidosis due to the accumulation of lactic acid, some degree of ketosis, and a serum that looks like milk, indicating fat mobilization from the adipose tissue. Such a crisis should be managed vigorously with glucose, potassium, and alkaline administration.

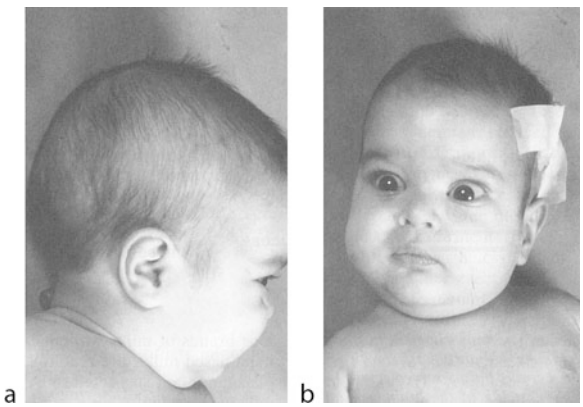


Figure 38.29
(a) Trombone player face of a patient with glycogen storage disease type 1A (von Gierke disease), lateral view. (b) Frontal view of the face in the same patient

The deficiency or abnormal structure of the microsomally located glucose-6-phosphatase (*Fig. 38.9*) causes GSD type 1A disease. The liver is unable to convert the lactic acid and alanine arriving from peripheral organs into blood glucose; therefore, continuous fat mobilization leads to fat infiltration in the liver. The liver biopsy will reveal large amounts of fat in addition to glycogen. Despite the severe liver involvement, liver enzymes in the circulation are elevated only slightly, certainly less than that observed in GSD type 3. Since this situation can be best described as "overfed liver and starving periphery," the treatment is aimed at reversing this cycle. In severe cases, the patient must be given a solution with glucose and high nitrogen (e.g., Vivonex) through a NG tube if he or she can tolerate it (e.g., if he or she does not develop difficult-to-control nosebleed). This feeding is done during the night by continuous administration of the solution through a pump; the child must be fed breakfast in the morning as soon as the pump feeding stops, otherwise he or she will develop a reactive hypoglycemia. When noctural feeding through a pump is not feasible, late-night feeding with a pudding prepared with uncooked starch and artificial sweeteners will prevent early-morning hypoglycemia. Successful management will lead to diminished liver size, improved growth, and improvement in the aforementioned biochemical parameters. The long-term complications of the disease are stunted growth, hepatomas, and uric acid nephropathy.

A distinct variety is GSD type 1B, in which the translocase for glucose 6-phosphate that carries the sugar phosphate to the compartment of glucose-6-phosphatase is deficient. This phenotype includes defective neutrophil leukocyte function and neutropenia, in addition to the features of GSD type 1A. The patient suffers from frequent infections. Treatment with granulocyte colony-stimulating factor may control these infections. The determination of glucose-6-phosphatase in liver biopsies, fresh

and frozenthawed, establishes the diagnosis. When the enzyme activity is absent both in fresh and frozen-thawed samples, it is type 1a; when it is absent in fresh but present in frozen-thawed samples, it is type 1B.

Case History. A 4-month-old boy at the time of admission was the product of a normal pregnancy and delivery, the second child of second-degree-cousin parents who were of Lebanese origin. The referral diagnosis was type 1 GSD, since he had a greatly enlarged liver. He experienced a devastating metabolic acidosis with a pH of 7.16, BE of −23 mEq/L, and blood glucose of 1 mM. At that time, he was found to have a hepatomegaly 3 cm below the right costal margin. He was treated with IV fluids and discharged home without a diagnosis. The mother noticed a distended abdomen at 3 months, with chubby cheeks. He was admitted to another hospital, where he was found to have a right liver edge at 7 cm and possibly a left lobe of the liver 3 cm below the costal margin. An abdominal ultrasound confirmed the enlarged organ on the left to be the liver and not the spleen. He did not have hypoglycemic seizures.

On admission his height, weight, and head circumference were at the 25th percentile. The liver on the right was 14 cm and on the left was 4 cm below the costal margin. He had evidence of nosebleed, but the platelet count was 440,000/mm^3. He had mild hypochromic, microcytic anemia. Hepatic profile indicated triglycerides of 20.3 mM (normal upper limit: 1.82 mM), cholesterol of 7.28 mM (normal upper limit: 4.7 mM), uric acid of 560 µM (normal upper limit: 240 µM), and alkaline phosphatase, ALT, and AST of 306, 173, and 199 U/L, respectively (normal upper limits: 240, 25, and 40 U/L, respectively). The abdominal ultrasound confirmed the enlarged liver and detected enlarged kidneys. An EEG was normal; MRI of the brain indicated mild delayed myelination and somewhat dilated ventricles, but there was no brain atrophy. A liver biopsy was done that indicated the presence of type 1A GSD. The glucose-6-phosphatase was 0.5 µmol/mg/h in both fresh and frozen-thawed samples (normal: 3.3 ± 1 µmol/mg/h); liver glycogen content was 5.3 µmol/g protein (normal upper limit: 1.2 µmol/g protein). The liver brancher enzyme, phosphorylase, phosphorylase b kinase, and debrancher enzyme activities were normal. He was placed on a fructose-restricted diet with frequent feedings. His growth and liver profile did not improve during the next year. He was then placed on Vivonex high-protein nocturnal feedings through a NG tube nightly for 10 h for 6 months at 33% of his daily caloric need. He suffered from frequent nosebleeds, at times copious, and had to have nasal septum cautery twice. The nocturnal feedings therefore had to be abandoned.

During the next 3 years his growth remained parallel to normal growth lines, but the height remained 4 standard deviations (SD) below the normal lower limit and weight at the fifth percentile. At present he is 5.5 years old. His liver size has decreased to 6 cm below the right costal margin; the left lobe of the liver is not palpable. The abdominal ultrasound indicates a normal echogenic liver with no focal lesions. Both kidneys remain enlarged, with increased echogenicity of the cortex but preserved echogenicity of the medulla. His last CT of the brain and EEG were normal. He never experienced hypoglycemic seizures, but continues to have bleeding diathesis and nasal bleeds. His chubby appearance has become less prominent. His disturbed liver profile with mildly increased liver enzymes, cholesterol, hypertriglyceridemia, lactate, and urate remain as before.

Galactosemia

Although the disease may manifest early during the neonatal period, its appearance may be delayed a few weeks to a few months after birth. In severe galactosemia the initial symptom might be sepsis, and, in all infants/neonates who have sepsis, galactosemia must be ruled out. There are several types of galactosemia with different enzyme defects in the pathway of galactose utilization (*Fig. 38.30*). Only classic galactosemia, that is, phosphogalactose (PGal) transferase deficiency, will be presented here. In most infants with classic galactosemia, the first symptoms are hepatomegaly, cataracts, and renal Fanconi syndrome. In many instances, it is the ophthalmologist who refers a child whose cataracts are surgically removed to the

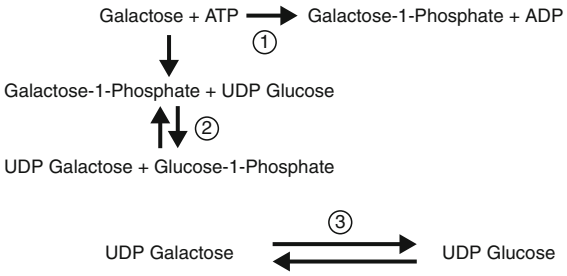


Figure 38.30
Pathway of galactose metabolism. Enzymes involved: (1) galactokinase, (2) galactose-1-phosphate uridyltransferase (PGal transferase), and (3) uridine diphosphate galactose 4-epimerase. Diseases related to deficiency of the aforementioned enzymes: (1) galactokinase deficiency, (2) classic galactosemia, and (3) epimerase-deficient galactosemia

pediatrician for evaluation, at which time the disease is diagnosed. A patient with PGal transferase deficiency whose cataracts have been removed is shown in *Fig. 38.31*. The patient will have hypoglycemia but no acidosis. The most important pathognomonic finding is positive reducing substance in the urine that tests negative with glucose oxidase-dipped paper. It must be remembered that any patient with severe primary or secondary liver disease will have tyrosinuria, which will react as a positive reducing substance. The identity of galactose in such urine samples must be proven by special biochemical tests. An alternative approach will be to determine the putative enzyme deficiency (i.e., PGal transferase) by directly testing in the red blood cells. A word of caution is that, in order to prevent false-positive and false-negative results, the patient must not have been transfused within 4 months, and the blood sample must be processed fresh, since the enzyme is labile and will lose its activity, even in the cold. The disease is best controlled by strictly restricting the galactose- or lactose-containing food substances in the diet. Various brands of milks without lactose, or soybean- or banana-based milks, are readily available. It is advisable to place an infant suspected to have galactosemia on such a milk product while waiting for the results of enzyme analysis. Long-term complications of the disease include sterility in female patients. The intelligence will be usually, but not always, normal in well-controlled patients. The mother of such a child must be placed on a galactose-restricted diet during subsequent pregnancies in order to prevent the emergence of cataracts in a galactosemic fetus.

Case History. A 14-month-old boy was noted to have poor development since birth. He was found to have cataracts at 1 year of age, and was referred for workup. His height and weight were 3 SD below the normal limit, and head circumference was at the fifth percentile. He could not sit without support and had no speech. The liver was enlarged 4 cm below the right costal margin. He had central hypotonia with head lag. His liver enzymes were mildly elevated but he had normal fasting glycemia. The uridine diphosophoglucose galactose-1-phosphate transferase (PGal transferase) in red blood cells was 2 U (normal: 20–40 U). The enzyme levels in the father and mother were 22 and 22 U, respectively. The EEG was normal; MRI of the brain revealed delayed myelination, particularly prominent at the frontal cortex. His cataracts were removed. He was placed on a galactose-free diet and was discharged home. He did well, and, when assessed at 43 months of age, his mental age was 16 months with pronounced linguistic delay, and he showed hyperactive behavior. At the age of 72 months, his mental age was 60 months, but he still showed hyperactive behavior. Retinal examination at that time indicated a prominent nerve fiber layer around the macula and optic disc. A recent MRI of the brain indicates improved myelination and no brain atrophy.

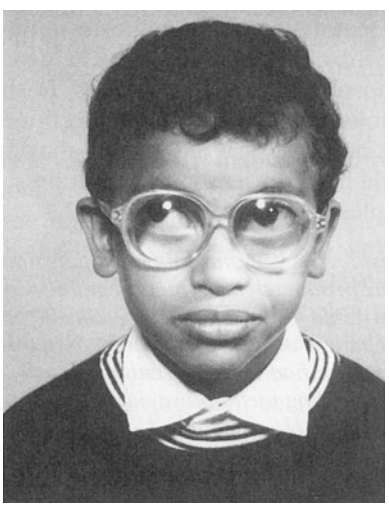


Figure 38.31
A boy with classic galactosemia due to uridine diphosphoglucose galactose-1-phosphate transferase (PGal transferase) deficiency. He had dense cataracts that had to be removed at 1 year of age. *Thick lenses* indicate the aphakia

Amino Acidemias

Although most amino acid disorders are of late infantile/childhood onset, only those five disorders listed in *Table 38.9* will be presented. Their diagnosis will often be missed in the absence of a neonatal screening program.

Hyperphenylalaninemia

This disease is due to a deficiency of phenylalanine hydroxylase, which catalyzes the conversion of phenylalanine to tyrosine (*Fig. 38.32*). Its deficiency leads to hyperphenylalaninemia, decreased tyrosinemia, and an increased phenylalanine/tyrosine ratio (>2). The hyperphenylalaninemia leads to an increased excretion of its catabolic product, phenylpyruvic acid, which reacts with ferric chloride at acid pH to give a dark green color, which was used in the past to diagnose the presence of the disease. The name PKU (phenylketonuria) was used to indicate

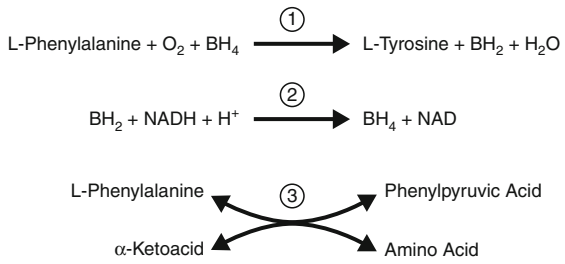


Figure 38.32
Metabolism of phenylalanine. Enzymes involved: (1) phenylalanine hydroxylase, (2) dihydropterin reductase (DHPR), and (3) transaminase. Diseases due to deficiency of the aforementioned enzymes: (1) classic PKU, and (2) biopterin-dependent PKU due to DHPR deficiency. (3) The transaminase pathway under normal conditions is a minor one; when phenylalanine hydroxylase is deficient, large amounts of phenylpyruvic acid are formed and excreted in the urine, which can be detected by the ferric chloride test

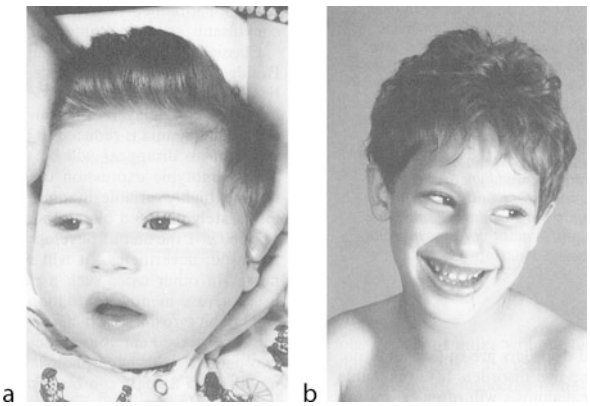


Figure 38.33
(a) A blond, 8-month-old infant who was referred for his myoclonic seizures and was found to have PKU. (b) An 8-year-old boy with PKU, whose disease was diagnosed at 1 year of age. He had mild disease that responded to dietary treatment. His school photo indicates his persistent light complexion

the excretion of phenylpyruvic acid in the urine. Hyperphenylalaninemia in infants is an insidious disease, which may show no symptoms until after 1 year of age. The initial rationale for many neonatal screening programs was this late presentation. Since the safety window for its diagnosis is only 6 weeks after birth, by the time the first symptoms appear the child will be microcephalic and moderately retarded, in which case the neurologic damage cannot be reversed. Occasionally the disease might manifest with myoclonic seizures as early as 4 months of life; such a child will be treated in vain with adrenocorticotropic hormone (ACTH) and anticonvulsants as having "infantile hypsarrhythmia."

Classic hyperphenylalaninemia is a panethnic disease. Besides seizures, the symptoms in an untreated older patient include severe attention-deficit disorder, hyperactive behavior, and delayed or absent speech. When the hyperphenylalaninemia is reduced to less than 800 μM, the first symptom to disappear will be the hyperactive behavior. The phenotypic expression of classic hyperphenylalaninemia is highly variable; in some patients, despite persistent moderately elevated blood phenylalanine values of 1,200–1,600 μM, the mental development might not be severely impaired; nevertheless, it will remain below the normal range. In other cases such a persistently high level will cause severe mental retardation. Hyperphenylalaninemia will inhibit tyrosinase, which causes light pigmentation that can be observed early in infancy. The light complexion of two patients with hyperphenylalaninemia at the age of 4 months and 8 years can be appreciated from the photos in *Fig. 38.33*. At times, an eczematous lesion will be apparent on the face or various parts of the body. Successful management leads to gradual darkening of the hair and skin color.

The infant with hyperphenylalaninemia must immediately be placed on phenylalanine-restricted formulas or food, with frequent monitoring of blood phenylalanine values, to assure a blood level of 300–800 μM. Well-managed patients will have normal mentality, and the diet may be relaxed after the teenage years. More recently, it has been shown that the supplementation of the diet with BCAAs and tryptophan will decrease the entry of phenylalanine into the CNS and ameliorate the deleterious effects of hyperphenylalaninemia. At a later age, a patient with hyperphenylalaninemia will have aversion to protein, since increased phenylalaninemia will cause cerebellar signs, in addition to speech difficulties and dull behavior. In female patients with hyperphenylalaninemia, if the blood phenylalanine level is not strictly controlled during pregnancy, the baby will be born with severe congenital defects, such as congenital heart disease, microcephaly, and severe brain damage (maternal PKU).

Case History. A 1-year-old boy was normal until 3 months of age, at which time he developed tonic seizures following a febrile episode. He had two to three seizures daily and was considered to have hypsarrhythmia, for which he was treated with ACTH. His seizures did not

improve; later he was given phenobarbital, which did not control the seizures either. He developed strabismus and nystagmus at 6 months of age. At the referral hospital his urine tested positive with a ferric chloride test and he was referred for detailed workup. He had started to sit with support at 6 months of age but lost all his milestones after 7 months. The parents noticed his visual loss at 8 months of age. At the time of the initial encounter at 1 year of age, he was an irritable child, continuously fussing, and he had no visual pursuit. He was blond and had fair features, while his parents and their other children were of darker complexion. He had severe nystagmus. He showed choreoballismus with occasional myoclonic twitching of the face and extremities. The height and weight were at the 50th percentile, while the head circumference was below 2 SD. His face had a cushingoid appearance, the result of the ACTH treatment. His eyegrounds showed bilateral moderately severe optic atrophy. He lay in the pithed-frog position, with severe central hypotonia. He did not have any parachute or magnetic response and had not developed primitive bipedal reflexes. He could not sit with support. He made cooing sounds but had no syllabic speech. He was assessed at a 2- to 3-month functional level at 12 months of age. His blood phenylalanine was 1,810 μM (normal: <120 μM). The early onset of severe encephalopathy and myoclonic activity suggested a biopterin-dependent PKU; however, his blood phenylalanine was not normalized when he was given tetrahydrobiopterin. The MRI of the brain indicated severe generalized white matter disease; a fibroblast culture was tested for metachromatic leukodystrophy as well as for Krabbe disease, both of which were negative. Carboxylase activities, blood very-long-chain fatty acids, and phytanic acid were also normal. The EEG showed poor background organization with discharges from the posterior quadrant. Visual evoked potentials indicated absent response. BAERs were also abnormal, with small peaks 3 and 5. The peripheral nerve conduction was normal. The CSF analysis indicated normal pterins and normal protein. He was diagnosed as having classic PKU of unusual severity and was placed on a phenylalanine-restricted diet. At present he is 9 years old and his mental age is 30 months; his motor skills are less impaired than his cognitive ability and speech. He is showing hyperactive behavior. The parents were not very compliant with the diet, and his blood phenylalanine level could be maintained only in the range of 700–1,600 μM. His nystagmus has disappeared, with only moderate left optic atrophy and alternating strabismus. Meanwhile, the parents had another male child who was diagnosed to have classic PKU at birth. He was placed on a phenylalanine-restricted diet. At present he is 5 years old and is totally normal, with no neurologic signs and with normal development.

Biopterin-Dependent Hyperphenylalaninemia (PKU)

Reduced biopterin (tetrahydrobiopterin or BH_4) is the cofactor of phenylalanine hydroxylase (◉ *Fig. 38.32*). BH_4 is synthesized from guanosine triphosphate (GTP) in several steps, the lack of any of which will cause its deficiency (◉ *Fig. 38.34*). The disease is known as malignant PKU. BH_4 is also a cofactor for other hydroxylases, namely, tyrosine hydroxylase and tryptophan hydroxylase, as well as for nitric oxide (NO) synthetase. This enzyme initiates pathways that lead to the synthesis of norepinephrine, epinephrine, and serotonin, and NO, a general neurotransmitter. Therefore, when BH_4 is deficient, in addition to the symptoms of hyperphenylalaninemia, serious autonomic and CNS dysfunction occurs. The CNS manifestations of the autonomic dysfunction include disturbed respiratory and cardiac rhythm. Immune function in these patients might also be disturbed. The presentation of this type of PKU is usually early, at 2–4 months of age, with infantile parkinsonian symptoms such as bradykinesia and cogwheel rigidity, indicating dihydroxyphenylalanine (DOPA) deficiency, in association with myoclonic seizures caused by the serotonin deficiency. A typical story is a consultation from the intensive care unit for an infant who developed bronchopneumonia and who has arrested with respiratory and cardiac irregularities, and who was found to have the aforementioned neurologic signs. The blood phenylalanine may not be as high as that in classic PKU, since some biopterin supplied through the milk or diet might be adequate to replenish the requirement of the liver phenylalanine hydroxylase. Since high doses of biopterin are required for its transport into the CNS, the neurologic symptoms will be severe in the face of mild hyperphenylalaninemia. The diagnosis can be easily verified by following the blood phenylalanine before, during, and after the administration of BH_4. Its values will be normalized within hours of administration of BH_4.

The determination of types of pterins excreted in the urine will establish an exact location of the enzyme defect. In GTP cyclohydrolase deficiency there will be no pterins in the urine. The clinical picture of this deficiency might be transient and may vary in its severity. In 6-pyruvoyltetrahydropterin synthetase (6PTS) deficiency, urine neopterin will be very high and biopterin will be very low. The clinical presentation of this disease is also variable, ranging from severe to mild. The fair features and rigidity of a patient with 6PTS deficiency are shown in ◉ *Fig. 38.35*. The prognosis of the mild variant of

Other reactions catalyzed by BH_4

(1) L-Tyrosine + BH_4 –> L-3,4-Dihydroxyphenylanine (DOPA) + BH_2
(2) L-Tryptophan + BH_4 –> L-5-Hydroxytryptophan + BH_2
BH_4
(3) L-Arginine + O_2 + NADPH + H^+ –> Nitric Oxide (NO) + L-Citrulline

Enzymes involved: (1) tyrosine hydroxylase; (2) tryptophan hydroxylase; (3) nitric oxide synthetase

Tetrahydrobiopterin Synthetic Pathway

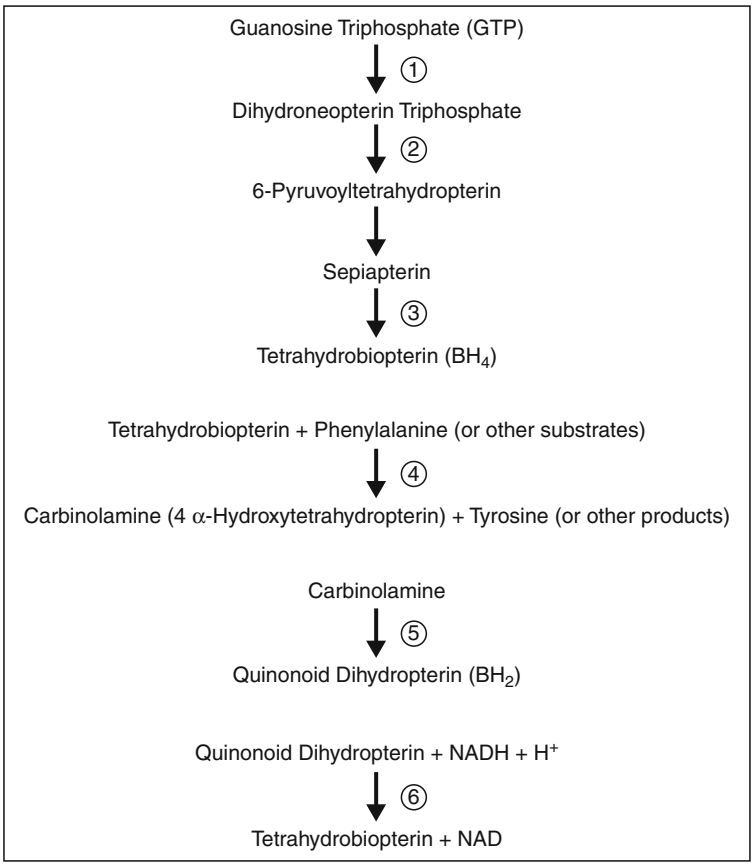


Figure 38.34

Reactions catalyzed by tetrahydrobiopterin and the tetrahydrobiopterin biosynthetic pathway. Deficiencies of several enzymes cause biopterin-dependent PKU. (1) GTP cyclohydrolase; in its deficiency there are no pterins in the urine. (2) 6-Pyruvoyltetrahydropterin synthase (6PTS); in its deficiency urine neopterin is high and urine biopterin is low. (3) Sepiapterin reductase; its deficiency-related condition is not known. (4) Hydroxylating enzymes such as phenylalanine, tyrosine, or tryptophan hydroxylases. (5) Carbinolamine dehydratase; when it is deficient, primapterinuria occurs. (6) Dihydropterin reductase; in its deficiency, increased urinary excretion of biopterin occurs. Folic acid deficiency also is observed since the enzyme also catalyzes the reduction of dehydrofolic acid

a 6PTS-deficient patient is excellent, as evidenced by the photo of the same patient together with another affected brother of school age (*Fig. 38.35*). In dihydropteridine reductase deficiency, there is excessive urinary excretion of biopterin. The clinical picture of this deficiency is very severe, and the clinical course might not be altered by the treatment procedures outlined later.

Once the diagnosis is established, the patient must be immediately provided the precursors of the aforementioned neurotransmitters, that is, the compounds subsequent to

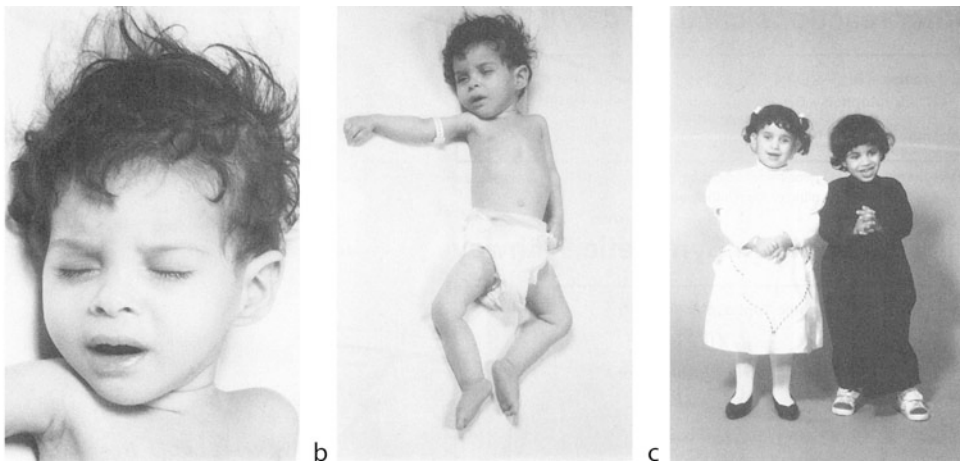


Figure 38.35
(a) Light complexion of a 1-year-old girl who was referred for rigidity, myoclonus, frequent chest infections, and cardiac arrest. She was found to have biopterin-dependent PKU due to 6-pyruvoyltetrahydropterin synthase (6PTS) deficiency. (b) Her rigid posture. (c) At the age of 7 years, she is attending normal school after rewarding response to the treatment. Her brother, at her side, was diagnosed very early to have 6PTS deficiency, and is a normal boy after the treatment

the step of hydroxylation reaction. These are DOPA and L-5-hydroxytryptophan, together with carbidopa to prevent their uptake by the peripheral tissues as well as assure adequate CNS uptake. The symptoms will resolve immediately except in late-diagnosed cases, in which, due to supersensitivity of the CNS autonomic neurons to the neurotransmitters, some symptoms suggestive of tardive dyskinesia, choreoathetosis, and at times high blood pressure might appear. In most instances tachyphylaxis will be established within a week, and the patient will tolerate the medication without side effects. A costly but effective treatment is to provide the patient with oral BH_4.

Case History. A 6-month-old boy who was an IUGR infant with 1.4-kg birth weight failed to thrive after birth, suffering from numerous chest infections requiring intensive care hospitalization three times. The parents were first cousins and the father had married twice. Previously he had a son from each wife, both of whom expired with a similar disease that led to sudden cardiorespiratory arrest. At the age of 5 months the patient suffered a cardiorespiratory arrest and the pediatric intensive care unit physician noticed truncal hypotonia, bradykinesia, and periods of "eye rolling." The patient was observed to have facial eczematous lesions and fair eye color with fair features. A metabolic disease was suspected and a blood test revealed hyperphenylalaninemia, at 1,632 μM (normal upper limit: 120 μM). At the time of initial encounter at 8 months of age, his weight was 2.76 kg and height 50 cm. He had a draining right otitis media and mild hepatomegaly. He was lying in a rigid posture with clenched hands and did not move, with eyes rolling upward periodically, increased reflexes, and severe head lag. A chest x-ray revealed minor infiltrates bilaterally. CT of the brain showed delayed myelination, and the EEG did not confirm the clinically observed myoclonus. Repeat sweat chloride tests were normal, and immunoglobulins G, A, D, and E were normal, although M was nine times elevated. Subclasses of immunoglobulin G were also normal. The clinical presentation strongly suggested a biopterin-dependent PKU. A urine study revealed ten times the elevated neopterin with barely detectable biopterin. When he was given BH_4 20 mg/kg/day, blood phenylalanine reduced to less than 120 μM within 24 h, with normalization of urinary neopterin and biopterin within 36 h. Initially the CSF neopterin was five times that of normal with no biopterin. Upon treatment with BH_4, the CSF neopterin decreased to normal levels and biopterin became detectable. He was kept on BH_4 treatment at the dose mentioned, and was also given DOPA (15 mg/kg/day), carbidopa (3.75 mg/kg/day), and L-5-hydroxytryptophan (4 mg/kg/day). During the initial month of this therapy he developed transient high blood pressure and mild choreoathetosis with mild symptoms of tardive dyskinesia. These symptoms eventually disappeared, and his further development has been normal and uneventful. His only problem has been a persistently draining right otitis media, which

unfortunately led to loss of function on that side. At present he is 12 years old and is attending grade school, where he is an average student. His height and weight remained 4 SD below the lower limit, but his growth velocity is normal. The father later had another daughter with the same disease. She was diagnosed soon after birth, was given appropriate treatment, and is growing normally.

Dihydrolipoyl Dehydrogenase (E_3) Deficiency

Dihydrolipoyl dehydrogenase, or E_3, is the common subunit of three dehydrogenases: pyruvic, α-ketoglutaric, and branched-chain α-keto acid dehydrogenases (*Fig. 38.36*). When defective, it leads to a clinical picture with periodic metabolic crisis, reminiscent of MSUD. Such a patient will be normal in between attacks, which are precipitated by heavy protein intake or infections. During the metabolic crisis, the patient will show cerebellar signs and, besides lactic acidosis, there will be significantly high α-ketoglutaric aciduria and branched-chain α-keto aciduria. The blood levels of BCAAs will be elevated four to eight times. These findings will establish the diagnosis, since the enzyme determination might not be always available. The disease is self-limiting, and the child should be managed by avoidance of fasting and frequent feeding of low-protein meals.

Case History. An 8-year-old boy had experienced two devastating metabolic episodes with severe ketolactic acidosis. Heavy meals or a minor respiratory infection triggered these episodes, and he vomited continuously for 1–2 days before becoming obtunded and sick and showing acidotic breathing. Intravenous fluids, glucose, and bicarbonate easily managed his symptoms, and he would recover without any neurologic deficits. These episodes took place at another hospital, and urine and blood samples from the time of the acute attacks were not available. During the next 3 years, he was followed up on an outpatient basis with extensive workup. Clinically he was normal, with no organomegaly or neurologic signs. He remained an excellent student in grade school, participating in all school activities. While he had no clinical complaints, numerous studies for urine, blood organic and amino acids, and blood acylcarnitines all remained within normal limits, except for lactic acid, which ranged from 2.4 to 2.8 mM. Finally, during one of these acidotic episodes, he was found to have five to six times elevated leucine, isoleucine, and valine in blood, with significant lactic acidosis of 5 mM and ketonuria. Urine GC/MS showed elevated 2-ketoisocaproic acid, 2-keto-3-methylisovaleric acid, and 2-ketoisovaleric acid (i.e., intermediates of MSUD). He was placed on a low-protein diet and frequent feedings. Over the next 2 years he did not have any further episodes. Dihydrolipoyl dehydrogenase activity in his fibroblasts could not be determined, and the diagnosis of E_3 deficiency was based on blood and urine biochemical findings observed during the acute attack.

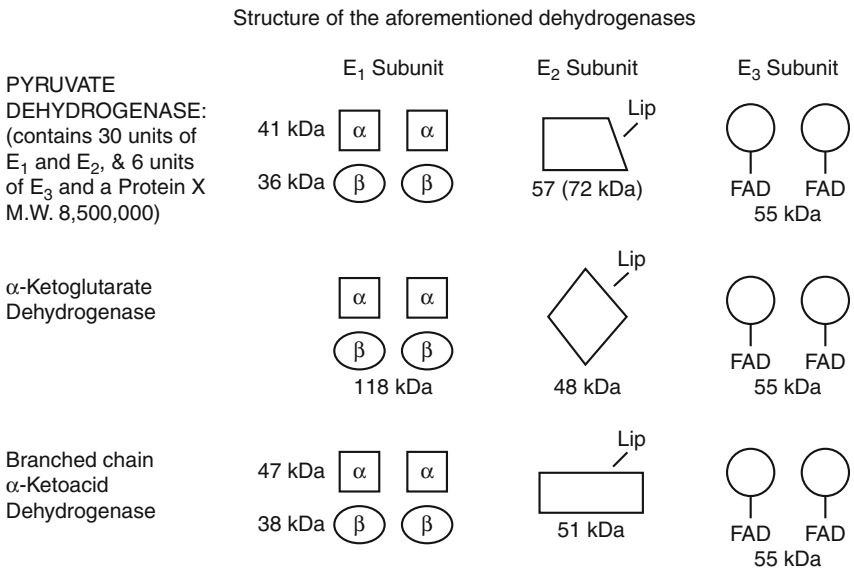


Figure 38.36

Important dehydrogenases that share the same E_3 subunit. kDa, molecular weight in kilodaltons; Lip, lipoamide; FAD, flavin-adenine dinucleotide

Homocystinuria

This disease truly poses a challenge to the pediatrician, since its presentation is highly variable. The usual presentation is with cataracts in an otherwise mildly delayed, shy young child. The slender, marfanoid appearance might not be noticeable early in life. At the later stage of the disease, the presentation is usually that of a neurologic catastrophe, such as seizures, dystonia, hemidystonia, or acute hemiplegia. These complications are caused by CNS infarcts due to a high level of blood homocystine caused by a deficiency of cystathionine β-synthase (◉ *Fig. 38.37*). Homocystine is highly toxic and at high blood levels will cause thrombosis. Homocystine also binds and destroys fibrillin, an important connective tissue component. The gradual destruction of fibrillin is responsible for lens subluxation and dolichostenomelia. These changes require several years, and the marfanoid features might be better appreciated after 4 or 5 years of age. The typical patient with homocystinuria has aphakia (thick cylindrical lenses), slender marfanoid appearance, and moderate arachnodactyly (◉ *Fig. 38.38*). The neurologic manifestations might be attributed to an entirely different etiology, and the missed diagnosis will cause further neurologic damage. Since a number of homocystinuria patients are pyridoxine responsive, early diagnosis and a high index of suspicion in a neurologically impaired child is of utmost importance. A simple special type of nitroprusside test of the urine, or detection of high methionine in the blood, will rapidly establish the diagnosis. High blood methionine levels might not always indicate homocystinuria, as summarized in ◉ *Table 38.10*. Its detection, however, should prompt a detailed diagnostic workup, including the measurement of cystathionine β-synthase activity in various cells. Determination of homocystine in the blood is cumbersome and, although a desirable adjunct, is not a readily available technique. At later stages the untreated disease will cause bone changes due to infarcts, and might be crippling. The treatment of the disease might be as simple as providing large doses of pyridoxine in pyridoxine-responsive patients. In pyridoxine-unresponsive cases, betaine and folic acid should be given, the reasons for which are illustrated in ◉ *Fig. 38.37*. In young infants, special formulas that restrict homocystine precursors, and in older children restricted protein diets, are used. In all cases, low doses of acetylsalicylic acid should be provided daily, to prevent clotting and infarcts.

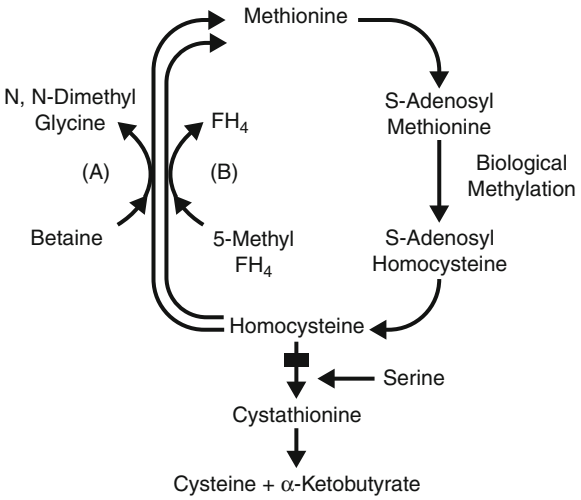


Figure 38.37
Metabolic pathways related to homocysteine. (1) Cystathionine β-synthase, the enzyme deficient in homocystinuria. (a) The mechanism of action of betaine used for treatment. (2) Methionine synthetase. (b) The mechanism of action of folic acid used in treatment. Methylcobalamin also participates in this methylation reaction. Therefore, the deficiency of this step is the etiology of homocystinuria and hypomethioninemia in the methylcobalamin-deficient type of methylmalonic acidemia

Case History. A 9-year-old girl was referred from an eye hospital with suspected homocystinuria. The teacher at school noticed her to have visual difficulties, and at the referral hospital she was found to have angle-closure glaucoma with inferiorly subluxated lenses bilaterally. Her school performance was average, and she did not have any neurologic complaints or findings. Her past history and development were normal. The parents were first cousins and had three normal children. On examination she had marfanoid features with arachnodactyly. A urine screening test for homocystinuria was positive, and blood amino acids indicated greatly elevated methionine, at 1,142 μM (normal upper limit: 50 μM). She was placed on a low-protein diet, betaine (100 mg/kg/day), folic acid (5 mg/day), pyridoxine (25 mg/kg/day), and aspirin (325 mg/day). The x-ray of the knees, obtained because of knee pain, and of the vertebral column revealed osteopenia, with mild compression of T-7 through T-12 vertebrae. A cardiac examination, echocardiogram, and electrocardiogram were normal. At 13 years of age she is attending a normal school but at fourth-grade level. Her participation in normal school activities is somewhat lower than average for the grade. She has chronic lung problems, and CT of the chest revealed widespread bronchiectasis with extensive bronchocentric infiltration

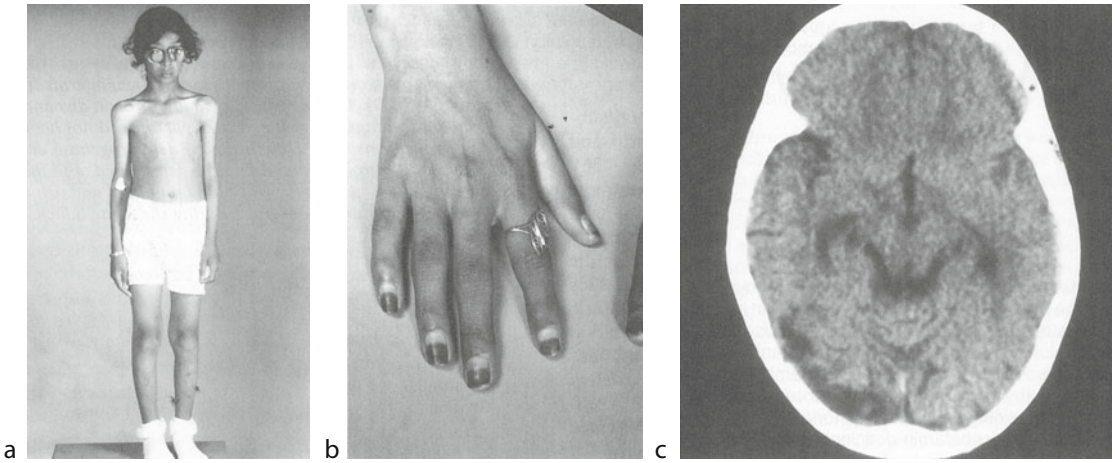


Figure 38.38
(a) Tall, slender marfanoid features of a 9-year-old girl with homocystinuria; note the aphakia and thick lenses. (b) Hands of the same patient showing slender and long fingers. (c) CT of the brain of a boy with homocystinuria showing the brain infarct

Table 38.10
Various etiologies involved in elevated blood methionine

Hypermethioninemia due to underutilization
Genetic deficiency of *S*-adenosylmethionine synthetase
Severe generalized liver disease
Tyrosinemia type 1
Hypermethioninemia due to overproduction
Cystathionine β-synthase deficiency (homocystinuria)
6-Azauridine administration
Hypermethioninemia due to uncertain causes
Transient hypermethioninemia of infants
Hypermethioninemia with elevated serum folate
Persistent hypermethioninemia with normal serum folate

scattered throughout both lungs. The lung problems were not caused by tuberculosis.

Tyrosinemia Type 1

This disease is caused by a deficiency of the enzyme in the last step of tyrosine breakdown (*Fig. 38.39*). The enzyme defect leads to the accumulation of fumarylacetoacetate, which is in isomeric equilibrium with the toxic compound maleylacetoacetate, which accounts for most of the clinical symptoms. Fumarylacetoacetate, through succinylacetoacetate, is further decarboxylated into succinylacetone, which is an inhibitor of porphyrin synthesis, leading to the accumulation of Δ-aminolevulinic acid. The disease may have mild to severe manifestations. In the severe form it manifests as early as 2 months of age, with liver derangement associated with normal liver enzymes but greatly increased α-fetoprotein and decreased prothrombin. The bone marrow involvement will cause thrombocytopenia, and the initial symptom might be bleeding. At times the disease is associated with cardiac valvular defects. The kidneys are affected and a renal Fanconi syndrome will be observed. When untreated, these symptoms will progress to rickets and terminal liver failure, and the patient will eventually expire due to liver failure or an acute porphyria crisis and brain edema caused by the accumulation of Δ-aminolevulinic acid. A patient with tyrosinemia type 1, her rickets in the wrist, and the rachitic rosary are shown in *Fig. 38.40*. In milder forms, the age of onset is usually 12–18 months and the initial symptoms might reflect the kidney involvement, such as renal diabetes insipidus and/or liver disease. The clinical course will end with the emergence of hepatomas, leading to death from malignancy.

The definitive mode of treatment is liver transplantation. However, a recent discovery permits a highly rewarding treatment. This is the use of a compound that inhibits the tyrosine breakdown pathway at the stage of *p*-hydroxyphenylpyruvic acid oxidase level. The compound, 2-(4-trifluoromethyl-2-nitrobenzoyl)-1,3-cyclohexanedione (NTBC), has been a life-saving drug, preventing galloping liver damage, reducing the accumulation of Δ-aminolevulinic acid, and preventing the formation of

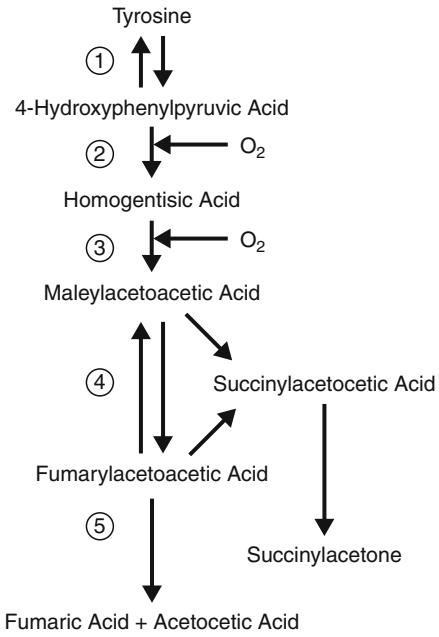


Figure 38.39
Catabolism of tyrosine. Enzymes involved: (1) tyrosine transaminase, (2) 4-hydroxyphenylpyruvic acid dioxygenase, (3) homogentisic acid oxidase, (4) maleylacetoacetic acid isomerase, and (5) fumarylacetoacetic acid hydrolase. Diseases due to deficiencies of the aforementioned enzymes: (1) tyrosinemia type 2 (Richner-Hahnhart syndrome), (3) alkaptonuria, and (5) tyrosinemia type 1. The deficiency of 4-hydroxyphenylpyruvic acid dioxygenase (2) is largely innocuous; this enzyme functions at the site of inhibition of the pathway by NTBC. Causes of hypertyrosinemia include inborn errors of metabolism (Tyrosinemia type 1, tyrosinemia type 2, 4-hydroxyphenylpyruvic acid dioxygenase deficiency), transient tyrosinemia of the newborn, severe hepatocelluar dysfunction, scurvy, hyperthyroidism, and postprandial effect

maleylacetoacetate. The circulating α-fetoprotein levels are reduced within months of its use, indicating prevention of liver damage. The drug is used in conjunction with a tyrosine-restricted diet. Tyrosinemia must be diligently searched for in any infant with any type of liver disease, since NTBC is life saving. Tyrosine and methionine are usually elevated in all types of liver disease (*Table 38.10*); therefore, the diagnosis of tyrosinemia type 1 can be firmly established only be detecting the elevated succinylacetone in the urine or Δ-aminolevulinic acid in blood.

Case History. A 10-month-old girl was referred for the workup of liver cirrhosis and Fanconi syndrome. She developed normally until 3 months of age, at which time she started to develop frequent chest infections and failed to develop in motor areas, although she continued to have normal social skills. The parents noted her failure to thrive, her poor feeding, and her constant ill health. She could never sit with support, but had developed syllabic speech. The parents were distantly related. They had eight normal children, but lost two girls and a boy to the same disease at 5, 7, and 9 months of age. A liver biopsy done at the referring hospital indicated prominent degenerative/regenerative changes in hepatocytes, with bile duct proliferation, cholestasis, and fibrosis indicating liver cirrhosis. On admission at 10 months, her height was 61 cm (corresponding to median age of 4 months) and her weight 4.8 kg (corresponding to median age of 2 months), with a head circumference of 41 cm (at lower limit of normal). Sclerae were mildly icteric. She had a rachitic rosary and enlarged epiphyses at the wrists. Her abdominal girth was 48 cm, enlarged with the liver 4 cm and spleen 5 cm below the costal margin. She showed muscle wasting, peripheral hypotonia, and no pyramidal or extrapyramidal tract signs. Her laboratory examinations indicated alkaline phosphatase of 1,530 U/L (normal upper limit: 350 U/L), but her ALT and AST were only borderline deranged. Bilirubin was 57 μM (normal upper limit: 21 μM). Her PT and PTT were elevated at 30.3 and 60.4 s, respectively (normal upper limits: 14.4 and 39 s, respectively). Her parathyroid hormone level was 430 pg/mL (normal upper limit: 65 pg/mL), her 25-hydroxy vitamin D was 66 nM (normal lower limit: 52 nM), and her 1,25 dihydroxy vitamin D was 360 pM (normal upper limit: 160 pM). The α-fetoprotein level was 240,000 U (normal upper limit: 15 U). Her urine tested positive for glucose at a blood glucose level of 4 mM. There was increased generalized aminoaciduria and phosphaturia; the urine pH was 7.5 and specific gravity 1.015. Her blood tyrosine and methionine were 310 and 210 μM, respectively (normal upper limits: 150 and 50 μM, respectively). The urine was tested three times for succinylacetone and was found to contain high amounts. Therefore, a conclusive diagnosis of tyrosinemia type 1 was reached. The abdominal ultrasound revealed abnormal echogenicity of the liver, with multiple nodular areas, the largest measuring 3 cm. The spleen was enlarged but had no focal lesions. There was a small amount of ascitic fluid. The enlarged kidneys were abnormal, with increased cortical echogenicity and prominent medulla. Chest x-ray revealed a consolidated right upper lobe. The child had had bacille Calmette-Guérin at birth. The sweat chloride test and α_1-antitrypsin activity

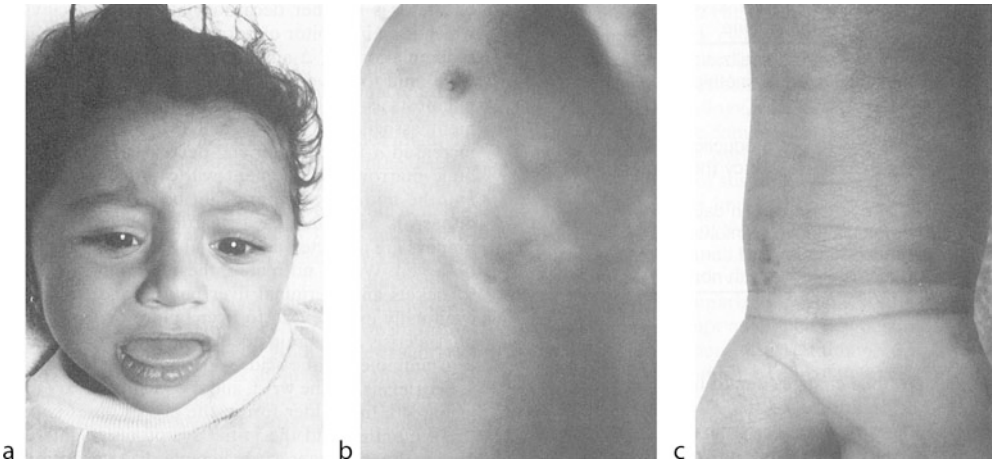


Figure 38.40
(a) A patient with tyrosinemia type 1. (b) Rachitic rosary in the same patient. (c) Changes of rickets evidenced by the enlarged wrist

were normal. The skeletal survey showed osteopenia and evidence of severe rickets. A cardiac workup was normal. CT of the brain and the EEG were normal. The child was placed on vitamin K_1 (5 mg), 1-Alpha (alpha-calcidiol) 0.3 μg (three drops), vitamin A (370 μg), and vitamin K (6 IU orally) daily. At the time, the hospital did not have NTBC for treatment. She was discharged to the referring hospital pending liver transplant. She developed sudden brain edema there and expired at the age of 14 months.

Diagnosis

Clinical and Biochemical Differential Diagnosis

In contrast to the devastating metabolic diseases of the newborn, the diseases listed in this section have more specific symptoms. A summary of the pertinent clinical and biochemical findings, as well as patients with a particular symptom that need to be investigated, are listed in *Table 38.11*.

Patients with the milder phenotypes of methylmalonic acidemia, isovaleric acidemia, HMG-CoA lyase deficiency, and oxidative phosphorylation diseases may experience their first metabolic attack later during the infancy or early childhood. Their clinical and biochemical presentations remain the same. Propionic acidemia that manifests in this age group usually has unusual symptomatology as presented; it may appear as an immune deficiency syndrome, as a basal ganglia disease, or as a seizure disorder.

The phenotype of 3-methylglutaconic aciduria in this age group is usually that of an extrapyramidal disease with prominent dystonia and choreoathetosis. It may be easily confused with glutaric aciduria type 1; however, a simple CT of the brain will reveal mainly putaminal lesions in the former and the "wide operculum sign" in the latter. Both diseases are "silent," "neurologic," or "cerebral" organic acidurias, since they are not associated with significant changes in acid-base balance, hyperammonemia, or hypoglycemia. It is important to reach an accurate diagnosis since both may be manageable but they require different treatments.

Besides those already listed in the section on devastating metabolic diseases of the newborn, the disorders that appear with periodic acidotic attacks that are particular to this age group are 3-ketothiolase deficiency, MCD, FDPase deficiency, GSD type 1, and E_3 deficiency.

In 3-ketothiolase deficiency the ketonuria is massive and blood glucose is normal; lactic acidemia is either normal or mildly elevated. The normoglycemia rules out FDPase deficiency and GSD type 1. Normal or near-normal lactic acidemia rules out MCD. The presentation of E_3 deficiency might be very similar to that of 3-ketothiolase deficiency (i.e., periodic acidotic attacks). However, E_3 deficiency usually occurs at a later age and is associated with acute cerebellar signs, and the biochemical findings suggest MSUD, with lactic and α-ketoglutaric aciduria.

Total biotinidase deficiency rarely manifests with acidotic crisis; its presentations may include pyramidal tract signs, dermatitis, hair loss, and seizures, which are easy to identify. Partial biotinidase deficiency is a progressive

Table 38.11

Brief synopsis of clinical and laboratory findings in organic acidemias of early infancy and childhood

Disease	Brief summary of clinical and laboratory findings	In which patient it should be investigated
3-Methylglutaconic aciduria	Progressive encephalopathy with dystonia, choreoathetosis, but with normal routine chemistries	Any infant or child who develops extrapyramidal signs with loss of milestones
3-Ketothiolase deficiency	Periodic metabolic crisis with acidosis following a prodrome of lethargy and vomiting	Any child who develops metabolic crisis with massive ketonuria but with normoglycemia (nonspecific symptomatology)
Glutaric aciduria type 1	Sudden extrapyramidal tract signs such as rigidity, dystonia, and choreoathetosis following a metabolic stress or infection. Macrocephaly, normal routine blood chemistries	Any child who develops extrapyramidal tract signs and has wide operculum sign on neuroradiologic studies
Medium-chain acyl-CoA dehydrogenase deficiency (MCAD)	Periodic metabolic crises with severe hypoglycemia and moderate lactic acidosis, with no neurologic or systemic findings	Any child who has a hypoglycemic episode with no systemic or neurologic findings
Very-long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	Acute hepatic failure, myopathy, cardiomyopathy, hepatomegaly and, during metabolic attacks with hypoglycemia, disturbed liver function and lactic acidosis	Any child with acute liver failure, hypertrophic cardiomyopathy, unexplained hepatomegaly, metabolic crisis with hypoglycemia and lactic acidosis
Biotinidase deficiency	Hair loss, deafness, visual difficulties, pyramidal tract signs, seizures, dermatitis; occasionally metabolic crisis with acidosis	Any child with etiology-unclear seizures, hair loss, deafness, or dermatitis with or without metabolic crises or long tract signs
Holocarboxylase sythetase deficiency	Severe early metabolic crisis with acidosis	Any infant who has severe metabolic crisis with ketolactic acidosis (nonspecific symptomatology)
4-Hydroxybutyric aciduria	Profound hypotonia with seizures, at times with extrapyramidal signs, or cerebellar signs or profound mental retardation; normal routine laboratory chemistries	Any infant or child with profound hypotonia, seizures, and cerebellar or extrapyramidal tract symptoms (nonspecific symptomatology)
Fructose sensitivity (fructose-1, 6-bisphosphatase or FDPase) deficiency	A big infant with mild hepatomegaly who develops profound lactic and ketoacidosis with severe hypoglycemia following ingestion of sweet substances, infections, or fasting	Any infant large in size who is always hungry, with mildly disturbed liver enzymes, mild lactic acidosis between attacks, and severe precipitous hypoglycemia and acidosis
Glycogen storage disease type 1A (von Gierke disease)	Massive hepatomegaly, history of hypoglycemia in the morning with prominent cheeks (trombone player's face) with episodes of hypoglycemia and profound lactic acidosis	Any infant with prominent hepatomegaly, with suggestive facial features, who has early morning hypoglycemia and metabolic crisis with hypoglycemia and lactic acidosis
Glycogen storage disease type 1B	Same as type 1A, but immune deficiency as a result of defective neutrophil function; frequent infections	Same as type 1A, neutropenia; enzyme activity appears after freeze-thawing the sample
Galactosemia due to UDPglucose galactose-1-phosphate transferase (PGal transferase) deficiency	Massive hepatomegaly with cataracts, history of hypoglycemia without acidosis, and amino aciduria with deeply disturbed live function tests, positive urine reducing substance	Any infant with cataracts, hepatomegaly, and reducing substance in the urine

Table 38.11 (Continued)

Disease	Brief summary of clinical and laboratory findings	In which patient it should be investigated
Hyperphenylalaninemia (classic PKU)	Early seizures, developmental delay mostly after 1 year; loss of 50% of the IQ by 1 year of age; fair features, eczematoid lesions	Neonatal screening must be performed since the clinical features before 1 year of life are not striking; child with mental retardation and/or seizures
Biopterin-dependent or malignant PKU	Early infantile myoclonic seizures, repeated early chest infections requiring hospitalization and PICU care due to cardiopulmonary arrest	Any infant with fair features and repeated chest infections or cardiopulmonary arrest without a good reason, with hypotonia and myoclonic seizures
E_3 deficiency	Infantile/childhood devastating metabolic disease with ketolactic acidosis and hypoglycemia; quick recovery upon appropriate treatment; the patient is normal between attacks	Any child who has periodic attacks of hypoglycemia and acidosis but is normal between attacks
Homocystinuria (cystathionine β-synthase deficiency)	Shy infant, with tall slender features, arachnodactyly and long toes; early visual difficulties with lens dislocation downward and early cataract; in late-diagnosed case, repeated thromboembolic attacks, with cerebrovascular accidents, extrapyramidal signs, and internal capsular lesions	Any child who had a cerebrovascular accident, unexplained hemidystonia, deep vein thrombosis of legs, long slender fingers and toes with slender body; any patient with cataracts
Tyrosinemia type 1	Several phenotypes exist: early presentation includes bleeding tendency with hepatomegaly and rickets; later during infancy it presents with diabetes insipidus (i.e., with reanal manifestations) and renal rickets, hepatomegaly, thrombocytopenia, disturbed liver functions; later in early childhood, it presents with chronic liver failure	Any infant with elevated PT and PTT, enlarged liver, elevated α-fetoprotein, thrombocytopenia but with other liver functions preserved, particularly if aortic or pulmonary valve disease is present; any older infant with renal rickets, diabetes insipidus and above-listed findings; any child with acute or chronic liver failure with any of the above-mentioned findings

PICU pediatric intensive care unit, *PT* prothrombin time, *PTT* partial thromboplastin time

encephalopathy primarily with seizures and pyramidal tract signs; its symptoms are nonspecific; therefore, biotinidase must be measured in all infants with a seizure disorder or with long tract signs. The assay of biotinidase does not require a sophisticated laboratory setting and can be accomplished anywhere.

In GSD type 1, the hepatomegaly is impressive, while in FDPase deficiency it is mild/moderate and is apparent only during crisis. A 4- to 12-month-old child who develops a precipitous hypoglycemic acidosis with peripheral shock either has HMG-CoA lyase or FDPase deficiency. Urine contains ketones in FDPase deficiency, but there is no ketonuria in HMG-CoA lyase deficiency.

Both MCAD and VLCAD are primarily hypoglycemic diseases; acidosis when present is due to increased lactic acid. An infant with MCAD with the milder phenotype does not have systemic symptoms. An infant with VLCAD will either have prominent cardiac symptoms, such as hypertrophic cardiomyopathy and myopathy, or liver findings such as increased enzymes, hepatomegaly, or impending liver failure. Again the acidosis is caused by the accumulation of lactic acid, and ketonuria is absent.

The presentation of 4-hydroxybutyric aciduria depends on the severity of the phenotype and is different at different age groups. The phenotype that appears early in infancy will manifest with severe central hypotonia and myoclonic seizures that are resistant to treatment, which are all non-specific symptoms. At a later age group, the past history usually includes infantile hypotonia and seizures, but the child shows profound mental retardation. 4-Hydroxybutyric aciduria is also a "silent" or "cerebral" organic aciduria (i.e., not associated with disturbed glucose, acid–base, or ammonia metabolism). The majority of the reported patients are of Middle Eastern origin.

The phenotype of galactosemia may vary from one country to another. In its classic form, the disease appears early during the neonatal period with sepsis; in the late-onset forms, the first symptoms occur at 2–12 months of life, and the presenting symptoms are cataracts and hepatomegaly. In fact, most such patients are referred from an eye hospital, where the infant is taken for cataracts. The hypoglycemia may be detected only in the laboratory, and sepsis may be uncommon. The presence of a renal Fanconi syndrome, in association with previously listed symptoms, will prompt a rapid diagnosis. Cataracts are a part of mitochondrial and peroxisomal diseases. In these latter diseases the child will show severe neurologic symptoms, while in galactosemia the CNS symptoms are milder. Homocystinuria will also show cataracts. Its presentation does not include hepatomegaly or the symptoms seen in mitochondrial or peroxisomal diseases.

Most amino acid disorders of this age group are associated primarily with severe neurologic symptoms and mental retardation. Noteworthy is classic PKU. The phenotype of classic PKU in the Middle East is highly variable. In some patients, despite very high phenylalaninemia, there may be only mild/moderate mental retardation, while in others hyperphenylalaninemia might not be impressive ($<$1,200 μM), but the infant will show early and severe myoclonus, myoclonic seizures, and early and severe regression of milestones with eventual severe mental retardation. Fair features are common but not always detected. The disease is easily identified through available neonatal screening programs. When neonatal screening is not performed, blood phenylalanine must be measured immediately in any young infant or child with the slightest suspicion of a neurologic finding. For this purpose various biochemical tests are available and can be applied in any setting. A ferric chloride test is useful if the urine is tested when fresh. It will yield false-negative results when the urine is stored cold more than a few hours. The treatment of classic PKU is very rewarding, particularly if identified early (i.e., less than 6 weeks of life).

A variant of PKU is "malignant PKU" or "biopterin-dependent PKU." Although four different types are known, the most common type in the world is 6PTS deficiency, a deficiency of the enzyme responsible for the second step of biopterin synthesis, namely, 6-pyruvoyltetrahy-dropterin synthase. An alert pediatrician may easily identify the 6PTS deficiency since it causes severe early parkinsonian signs such as bradykinesia and cogwheel rigidity, in addition to myoclonic seizures, cardiorespiratory rhythm abnormalities, and intrauterine and early infantile failure to thrive. Again, the skin and hair color are usually fair. The requirements of the liver phenylalanine hydroxylase for biopterin might be partially met by the small amounts of biopterin present in milk and other foods; therefore, hyperphenylalaninemia in this disease is not usually impressive. It may be easily missed in the neonatal screening programs. Its presence must be tested for in any small infant who experiences an unusually severe chest infection at 2–4 months of age. The treatment is most rewarding, and, if the infant survives the cardiorespiratory problems, and if the disorder is diagnosed before 6–12 months of age, minimal or no residual damage will be left upon appropriate treatment. All infants who test positive for PKU at any age should be tested for biopterin-dependent PKU. This is performed either by serially measuring blood phenylalanine level before, during, and after tetrahydrobiopterin administration, or by identifying and estimating the urine pterins.

In the absence of a neonatal screening program, most patients with homocystinuria will unfortunately be missed for a long period. The mental retardation and regression of milestones might not be very noticeable, and the child will arrive with a neurologic catastrophe. A lucky child will have his or her iridodonesis or cataracts noticed by an ophthalmologist who encounters the patient because of the complaint of visual difficulty, and the workup initiated will reveal the homocystinuria. The marfanoid features and arachnodactyly are usually noticed later during childhood. Any child with unusual CNS symptoms, particularly with hemiplegia, must be checked for homocystinuria. Hemiplegia is commonly caused in this age group by sickle cell disease, protein S deficiency, or anticardiolipin antibodies. Approximately 20% of the patients will have the "pyridoxine-responsive" phenotype of homocystinuria, which readily responds to treatment by large doses of pyridoxine, since cystathionine β-synthase in these cases carries a mutation that will be functional in the presence of a high concentration of pyridoxal-5′-phosphate. Early diagnosis of homocystinuria is a highly desirable goal, since the treatment of a neonate with homocystinuria with either phenotype, or of infants with the "pyridoxine-responsive" variant, is most rewarding, leading to an eventual normal lifestyle.

The presentation of tyrosinemia type 1 is essentially different from the diseases thus far presented. It can present with early derangement of certain liver functions, such as prothrombin synthesis in association with thrombocytopenia, presenting as a bleeding diathesis in an infant with mild hepatomegaly. Later presentations include renal Fanconi syndrome, diabetes insipidus, rickets, and the same liver symptoms as listed above. A simple determination of α-fetoprotein will reveal its very high

value, and will prompt the workup. In tyrosinemia type 1, besides elevated tyrosine and methionine, urine might contain large amounts of *N*-acetyltyrosine and 4-hydroxyphenylpyruvic and 4-hydroxyphenyllactic acids. These biochemical observations are also noted in patients with liver derangement due to other causes. The definitive diagnosis of tyrosinemia type 1 can only be reached by measuring urinary excretion of succinylacetone or the level of Δ-aminolevulinic acid in the blood. The ultrasound examination of the liver is also pathognomonic, with hepatomas and nonhomogeneous appearance. A patient with tyrosinemia type 1 is susceptible to intercurrent neurologic crisis with coma and death as a result of the brain edema caused by the porphyria, due to the inhibition of porphyrin synthesis by Δ-aminolevulinic acid. This compound is fat soluble and, if the patient fasts or is subjected to increased fat mobilization, it will be liberated from the adipose tissue, causing the neurologic crisis. Therefore, such patients should not be permitted to fast, and glucose should be administered when they develop an intercurrent infection. The disease is invariably fatal unless the patient receives a liver transplant, which is not always readily available. However, the recent discovery of a drug, NTBC, that inhibits the pathway before the formation of maleylacetoacetate, is life saving and probably permits the child to reach adolescence, when a liver transplant might be more feasible.

Conclusive Biochemical Diagnosis

The presumed diagnosis, based upon clinical and clinical biochemical findings, must then be confirmed by special biochemical tests that are available only in certain health care settings. These tests are listed in ❯ *Table 38.12*. The available tools include GC/MS analysis for organic acids, HPLC analysis for amino acids, tandem MS analysis for organic and amino acids, and special enzyme tests.

The pathognomonic organic acids will be identified during crisis in 3-ketothiolase deficiency, glutaric aciduria type 1, MCAD, VLCAD, MCD, FDPase deficiency, GSD type 1, and E_3 deficiency; however, they might not be readily detectable between crises. The elevated organic and amino acids are always detected in patients with 4-hydroxybutyric aciduria, classic PKU, biopterin-dependent PKU, homocystinuria, and tyrosinemia type 1. In this regard, tandem MS is a much superior tool, since it detects the carnitine esters of organic acids, as well as minor elevations of amino acids, at all times. So far, tandem MS has not been used to identify the diseases involving carbohydrate metabolism, and it will not detect 4-hydroxybutyric aciduria.

The disorders of fatty acid metabolism can be diagnosed accurately only through the use of tandem MS, since in these diseases the GC/MS findings are rarely conclusive. In most settings, E_3 deficiency is identified based only on amino acid and GC/MS findings, since the determination of enzyme activity is not readily available.

The definitive diagnosis of the disorders in this section must rely on confirmation by at least two different techniques. In certain cases, such as biotinidase deficiency or galactosemia, one of these is based on the determination of defective enzyme activity. Enzyme analysis is also recommended for 3-ketothiolase deficiency, galactosemia, and GSD type 1, since they have more than one phenotype.

Genetics and Incidence

The incidence for most of these disorders cannot be stated in the absence of neonatal screening programs. Glutaric aciduria type 1, 4-hydroxybutyric aciduria, FDPase deficiency, GSD type 1, homocystinuria, classic PKU, biopterin-dependent PKU, MCAD, VLCAD, biotinidase deficiency, galactosemia, E_3 deficiency, and tyrosinemia type 1 are not rare diseases.

The gene locations of most of these disorders have been identified (❯ *Table 38.13*), and the cDNAs of relevant enzymes are becoming increasingly available. Once the particular mutations of an enzyme in a population are identified, it will become increasingly possible to conduct screening procedures for the carriers.

Prevention Through Neonatal Screening

Most of these disorders are readily identifiable in a neonate, as listed in ❯ *Table 38.6*. The early identification, in most instances, will lead to rewarding treatment and normal or near-normal lifestyle in the child. Even glutaric aciduria type 1, a hitherto severly neurologically crippling disease, may be managed vigorously with medication and by early intervention at times of catabolic events such as infections, to an extent that is nearly compatible with a normal lifestyle, Delayed diagnosis in most instances, such as classic PKU, homocystinuria, and tyrosinemia type 1, will lead to severe crippling, mental retardation, or death, while the reverse is true when they are identified early.

In the absence of neonatal screening, it is the responsibility of the pediatrician to test all other children in the

Table 38.12

Specialized biochemical tests required to confirm diagnosis in patients with metabolic diseases primarily of late infantile or childhood onset[a]

Disease	GC/MS studies	HPLC studies for amino acids	Tandem MS studies	Enzyme studies or special tests[b]
β-Ketothiolase deficiency	2-Methylacetoacetic, 2-methyl-3-OH-butyric, tiglylglycine, 3-OH-butyric, acetoacetic	Glycine may be elevated	2-Methyl-3-OH-butyrylcarnitine, tiglylcarnitine	Mitochondrial β-ketothiolase (F)
Glutaric aciduria type 1	Glutaric, glutaconic, 3-OH-glutaric	N.P.	Glutarylcarnitine	Glutaryl-CoA dehydrogenase (F)
MCAD deficiency	Adipic, sebacic, 5-OH-hexanoic, 7-OH-octanoic, hexanoylglycine, suberylglycine	N.P.	Carnitine esters of C6, C8, and C10 fatty acids	MCAD assay (F) or gene mutation assay by PCR in blood spots or cells
VLCAD deficiency	Suberic, sebacic, dicarboxylic acids of C10 and C12 in urine	N.P.	Carnitine esters of C12, C14, C16, C18, and C20 and their mono-and diunsaturated forms	Mutations in the VLCAD gene must be assayed to confirm the clinical diagnosis (F)
Biotinidase deficiency	3-OH-Propionic, 3-methylcrotonyl, and 3-OH-propionylglycine, lactic, methylcitric (elevated only during acidotic crisis)	N.P.	Propionylcarnitine and methylcrotonylcarnitine (elevated only during acidotic crisis)	Biotinidase (serum)
4-Hydroxybutyric aciduria	4-Hydroxybutyric and its lactone, intermediates of MADD (GAT 2)	N.P.	N.P.	Succinic semialdehyde dehydrogenase (L)
Fructose-1,6-bisphosphatase deficiency	Lactic, pyruvic, acetoacetic, 3-OH-butyric	N.P.	N.P.	FDPase assay and fructose-1-phosphate aldolase assay in liver biopsy
Glycogen storage disease types 1A and 1B	Lactic, pyruvic, some ketone bodies	N.P.	N.P.	Glucose-6-phosphatase in liver; fresh and frozenthawed
Galactosemia	N.P.	N.P.	N.P.	PGal transferase and galactokinase (R)
Classic PKU	N.P.	⇑ Phenylalanine, ⇓ tyrosine	⇑ Phenylalanine, ⇓ tyrosine	N.P.
Biopterin-dependent PKU (6PTS deficiency)	N.P.	⇑ Phenylalanine, ⇓ tyrosine, ⇑ neopterin, and ⇓ biopterin in urine and CSF	⇑ Phnylalanine, ⇓ tyrosine, ⇑ neopterin, and ⇓ biopterin in urine and CSF	6PTS (R) Dihydrobiopterin reductase (R) GTP cyclohydrolase (L)
E_3 deficiency	Branched-chain α-keto acids, lactic acid, α-ketoglutaric	⇑ Branched-chain amino acids during the acute episode	⇑ Valine, leucine, isoleucine, alanine during the acute episode	N.A.
Homocystinuria	N.P.	Methionine	Methionine	Homocystine in serum and urine Cystathionine β-synthase (F)(L)
Tyrosinemia type 1	Succinylacetone	Tyrosine, methionine	Tyrosine, methionine	Δ-Aminolevulinic acid (serum) (R)

Table 38.13

The gene information contains consecutively: name of the deficient gene, number of the protein, symbol of the gene, chromosome location of the gene; the size of the gene; the number of introns and number of mRNA's. The annotation denotes (http://www.hgmd.cf.ac.uk/ac/index.php) consecutively the number of mutations, insertions, deletions, splicing errors, and other errors

Name of the disease	Gene information	Annotation
β-ketothiolase deficiency	Acetoacetyl coenzyme A transferase – EC 2.3.1.9 -ACAT 1; 11q22.3-q23.1; 31.56 kb; 19 different introns; 13 different mRNA	25/4/7/7/0
Glutaric aciduria type 1	Glutaryl Coenzyme A dehydrogenase; – EC 1.3.99.7 – GCDH; 19p13.13; 23.61 kb; 23 different introns, 20 different mRNA	92/0/7/9/0
MCAD deficiency	Acyl-Coenzyme A dehydrogenase, C-4 to C-12 straight chain; EC 1.3.99.3, 2.5.1; ACADM; 1p33.1; 76.8 kb; 49 introns, 26 different spliced mRNA	46/4/10/7/0
VLCAD deficiency	Acyl-Coenzyme A dehydrogenase, very long chain; EC 1.3.99.13; VLCAD; 17p13-p11; 8.14 kb; 33 different introns, 26 different mRNA	60/4/23/11/0
Biotinidase deficiency	Biotinidase, EC 3.5.1.12; BTD; 44.29 kb; 3p25; 13 different introns 14 alternatively spliced mRNA	85/3/12/2/1
4-Hydroxybutyric aciduria	Succinic semialdehyde deficiency; EC 1.2.1.24; ALDH5A1; 6p22.2-p22.3; 42.45 kb; 12 different introns, 5 alternatively spliced mRNA	19/4/9/7/0
Fructose bisphosphatase deficiency	Fructose 1, 6 bisphosphatase 1; EC 3.1.3.11; FBP1; 9q22.3; 37.35 kb; 11 introns, 8 different mRNA's	8/3/4/0/0
Fructose bisphosphate aldolase deficiency	Fructose 1, 6 bisphosphatase aldolase B; EC 4.1.2.13; ALDOB; 9q21.3-22.2; 16.84 kb; 11 different introns, 5 different mRNA's	23/3/10/7/0
Glycogen storage disease type 1 A	Glucose 6-phosphatase; EC 3.1.3.9; G6PC; 12.57 kb; 17 q21; 4 different introns, 2 alternatively spliced mRNAS;	63/7/11/4/1
Glycogen storage disease type 1 B	Glucose 6-phosphate transporter; SLC37A4; 11q23.3	62/7/16/7/0
Glycogen storage disease type 1 C&D	Glucose 6-phosphate transporter; SLC37A4; 11q23.3	6/0/0/0/0 and 1/0/0/0/0
Galactosemia, P-Gal transferase deficiency	Galactose-1-phosphate uridylyltransferase; EC 2.7.7.12; GALT; 9p13; 12.54 kb; 22 introns, 24 alternatively spliced mRNA's	146/4/23/11/0
Galactosemia; galactokinase deficiency	Galactokinase 1; EC 2.7.1.6; GALK; 17q24; 12.03 kb; 13 different introns; 8 alternatively spliced mRNA	18/4/4/0/0
Galactosemia; epimerase deficiency	UDP-galactose-4-epimerase; EC 5.1.3.2; GALE; 1p36-p-35; 38.27 kb; 11 exons;	20/0/0/0/0
Classic PKU	Phenylalanine hydroxylase deficiency; EC 1.14.16.1; PAH 12q22-q24.2; 120.68 kb; 26 different introns, 18 different mRNA	371/15/75/72/1
PKU; dihydropteridine reductase deficiency	Quinoid dihydropteridine reductase; EC 1.6.99.7; QDPR; 4p15.31; 29.21 kb; 19 different introns; 20 different mRNA's	20/4/2/6/0
PKU; 6-PTS deficiency	6-pyruvoyltetrahydropterin synthase. EC 4.6.1.10; PTS; 11q22.3-q23.3; 11.12 kb; 10 different introns; 8 different mRNA	34/1/5/5/0
PKU; cyclohydrolase deficiency (DOPA responsive dystonia)	GTP cyclohydrolase 1; EC 3.5.416; GCH1; 14q22.1-q22.2; 61.84 kb; 12 different introns; 11 different mRNA	80/8/18/15/2
E_3 deficiency	Dihydrolipoamide deficiency; EC 1.8.1.4; DLD; 7q.31-q32; 48.51 kb; 23 different introns; 13 different mRNA	10/1/1/1/1
Classic homocystinuria	Cystathionine beta-synthase; EC 4.2.1.22; CBS; 21q22.3; 23.93 kb; 26 introns, 29 different mRNA	105/8/22/11/1
Tyrosine type 1	Fumarylacetoacetate hydrolase; EC 3.7.1.2; FAH; 15q23-q25; 34.45 kb; 23 different introns, 16 different mRNA	26/1/3/13/0

Table 38.14

Formulas and medications used for long-term management of late infantile/childhood-onset metabolic diseases[a]

Disease	Formulas	Cofactors and medications
3-Ketothiolase deficiency	Low-protein or L-isoleucine-restricted formulas and diets	L-Carnitine, 200 mg/kg/day; bicarbonate or citrate 4–6 mEq/kg/day
Glutaric aciduria type 1	L-Lysine– and L-tryptophan–restricted or low-protein diet; IV dextrose during febrile disease	L-Carnitine, 200 mg/kg/day; riboflavin, 50–100 mg/kg/day; baclofen, 5–10 mg t.i.d.; vigabatrin 35–50 mg/kg/day; valproic acid, 25–35 mg/kg/day
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Frequent feeding with high- and slowly digested carbohydrate diets; avoidance of fasting	L-Carnitine, 200 mg/kg/day; Polycose in soft drinks upon vomiting
Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	Low-fat/high-carbohydrate diet; avoidance of fasting	Medium-chain triglycerides (MCT oil), 1–2 g/kg/day; L-carnitine, 200 mg/kg/day
Biotinidase and biotin-responsive holocarboxylase (HCS) deficiencies	N.R.	*Biotinidase deficiency*: Biotin, 5–10 mg/kg/day
		HCS deficiency: Biotin, 10 mg/kg/day; L-carnitine, 200 mg/kg/day; citrate, 4 mEq/kg/day
4-Hydroxybutyric aciduria	N.R.	Vigabatrin, 35–50 mg/kg/day; dextromethorpham 20–30 mg/kg/day[b]
Fructose sensitivity (FDPase deficiency)	Strict restriction of fructose- and sucrose-containing food substances	Bicarbonate or citrate 4–6 mEq/kg/day; Polycose in diet drinks upon vomiting or diarrhea
Glycogen storage disease (GSD) type 1	Frequent feeding with fructose restriction; late-night feeding with slowly digested glucose polymers; if and when possible, high-protein vivonex through NG tube by pump (33% of daily calories) nocturnally	N.R.
Galactosemia (PGal transferase deficiency)	Galactose- and lactose-restricted formulas and diets	N.R.
Hyperphenylalaninemia (classic PKU)	Galactose- and lactose-restricted formulas and diets	N.R.
	Phenylalanine-restricted milk formulas and food substances to assure blood phenylalanine between 300 and 800 μM	N.R.
Biopterin-dependent PKU	No phenylalanine restriction if the patient is given BH_4; otherwise same restrictions as in classic PKU	L-DOPA, 15–20 mg/kg/day; L-5-hydroxytryptophan, 4–5 mg/kg/day; carbidopa, 4–5 mg/kg/day; and if possible BH_4, 20 mg/kg/day[c], with folic acid, 5–10 mg/day
E_3 deficiency	High-carbohydrate diet; avoid fasting; during metabolic crisis, IV dextrose and alkalinizing agents	The use of lipoic acid or its amide its experimental but can be tried at 25 mg/day

Table 38.14 (Continued)

Disease	Formulas	Cofactors and medications
Homocystinuria (pyridoxine-responsive, -nonresponsive variants and in neonates)	*Neonates*: methionine-restricted formula	*Pyridoxine-responsive type*: pyridoxine, 10–20 mg/kg/day
	Pyridoxine-nonresponsive type: methionin-restricted or low-protein diet, whichever is possible	*Others*: Betaine, 100–200 mg/kg/day; folinic acid, 15 mg/day; aspirin, 65–325 mg/day
Tyrosinemia type 1	Tyrosine restriction will assure adequate growth and prevention of renal complications but will not prevent the liver disease	2-(2-Nitro, 4-trifluoromethyl benzoyl)-2,3-cyclohexanedione (NTBC), 0.1–0.6 mg/kg/day[d]; IV glucose in case of neurologic crisis. Hematin (experimental)

[a]N.R., not relevant
[b]The results are not always rewarding; however, the use of vigabatrin will improve the seizures
[c]Available only from Schirks Laboratories, Jona, Switzerland
[d]Although available commercially, it is advisable to use this compound according to a standard protocol, available from Dr. S. Lindstedt, Department of Clinical Chemistry, Sahlgrenska Hospital, Göteborg University, Göteborg, Sweden

extended family, as well as the future newborns, for the existence of the disease detected in the index case. Such an effort is mandatory for early diagnosis, treatment, prevention of crippling, mental retardation, and death.

Medications and Formulas Used in Acute and Long-Term Management

Acute Crisis

The management of acute events is pertinent to organic acidemias, and the same procedures and considerations cited for the management of devastating metabolic diseases of the newborn are also valid for the disorders encountered at this age group. Acute metabolic events in patients with 3-ketothiolase deficiency should be managed by vigorous use of IV sodium bicarbonate and L-carnitine. In glutaric aciduria type 1, even minor infections require hospitalization, IV administration of L-carnitine, and prevention of protein catabolism by IV glucose. The acute attacks of fatty acid oxidation disorders and HCS deficiency also require intravenous L-carnitine, large amounts of glucose, and bicarbonate treatment. The acute crises of FDPase deficiency, GSD type 1, and E_3 deficiency are managed by administration of bicarbonate and glucose. The neurologic crisis of tyrosinemia type 1 is managed by IV glucose administration.

Chronic Management

The diseases listed in this section, except for 4-hydroxybutyric aciduria and the cardiomyopathic phenotype of VLCAD, are all treatable disorders with eventual normal or near-normal lifestyle of the child. The formulas and medications used are shown in *Table 38.14*. The formulas are based on restricting the offending compound from the diet (e.g., fructose in FDPase deficiency and GSD type 1, galactose in galactosemia, and phenylalanine in classic PKU). Use of MCT oil in VLCAD deficiency and nocturnal feeding by Vivonex in GSD type 1 prevents the serious consequences of these diseases.

In some disorders, dietary intervention might be enough, but in most others, large doses of cofactors and specific medications must be used as adjuncts to achieve the best results (e.g., baclofen, vigabatrin, and valproic acid in glutaric aciduria type 1 and pyridoxine in homocystinuria). Although pyridoxine is essential for the "pyridoxine-responsive" phenotype, most pediatricians currently add this compound to the treatment of all patients with homocystinuria. This is permissible, as long as it is used in prescribed amounts that will not lead to peripheral neuropathy. The excess homocystine that is responsible for the thromboembolic phenomena in homocystinuria may be removed by its chemical methylation through betaine. In this disorder, aspirin is used also to delay clotting.

In certain diseases, only cofactors or medications without dietary therapy will prove effective. For example, in biopterin-dependent PKU, the precursors of neurotransmitters such as L-dopa, L-5-hydroxytryptophan, and BH_4 are used without any diet. In tyrosinemia type 1, strict dietary restriction of tyrosine is not required if NTBC is used. Biotinidase deficiency will be successfully treated by large doses of biotin. In other diseases, detoxification will be achieved by L-carnitine,

Table 38.15
Outcome of metabolic diseases of late infantile/early childhood onset, if treated early and appropriately

Disease	Outcome
3-Ketothiolase deficiency	Excellent, if metabolic crises are managed vigorously
Glutaric aciduria type 1	Minimal neurologic damage if it is diagnosed before the first neurologic crisis, and when all subsequent febrile episodes are treated vigorously through preventing protein catabolism
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency	Excellent if the disease is not of severe variety and if therapeutic precautions listed are followed
Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency	*Cardiomyopathic phenotype*: poor prognosis
	Phenotype with acute liver failure: good if the disease is diagnosed before the liver failure occurs and if it is treated vigorously
Biotinidase deficiency	Excellent; deafness if diagnosed late
Holocarboxylase synthetase deficiency	Good if the patient is biotin responsive and is closely followed and if metabolic crises are managed vigorously
4-Hydroxybutyric aciduria	Poor, with eventual severe mental retardation
Fructose sensitivity (FDPase deficiency)	Excellent
Glycogen storage disease types 1A and 1B	*Type 1A*
	Mild phenotype: very good, with adequate growth
	Severe phenotype: difficult to manage and establish adequate growth; late complications
	Type 1B: poor due to neutropenia and immune deficiency; infections may be treated by using granulocyte colony-stimulating factor
Hyperphenylalaninemia (classic PKU)	Normal intelligence if diagnosed and treated early, with minimal speech and behavioral deficits, in pregnant mother with PKU, teratogenic effect in fetus if her PKU is not controlled during pregnancy
Biopterin-dependent PKU	*Mild and transient phenotypes*: good, with minimal residual damage, speech and behavioral deficits
E_3 deficiency	*Severe phenotype*: microcephaly and spastic quadriplegia
	Excellent
Homocystinuria	*Neonate diagnosed early*: good, normal to near normal intelligence
	Pyridoxine-responsive phenotype: good if diagnosed early
	Pyridoxine-unresponsive phenotype: intelligence will not improve but thromboembolic phenomena will be controlled with the outlined therapies in late-diagnosed cases
Tyrosinemia type 1	Always fatal if the patient is not treated by liver transplantation; early trial results using NTBC are very rewarding, indicating it to be a life-saving medication

the use of which is necessary in glutaric aciduria type 1, biotin-responsive HCS deficiency, MCAD, and VLCAD.

Outcome

The outcomes of these disorders, when identified and treated early, are listed in *Table 38.15*. These are highly treatable disorders, except for 4-hydroxybutyric aciduria, the cardiomyopathic phenotype of VLCAD, GSD type 1B, and the severe phenotype of 6PTS-deficient PKU. When the diagnosis is late, the resultant CNS damage in glutaric aciduria type 1, VLCAD deficiency, classic PKU, and homocystinuria will be irreversible. This is the reason for a neonatal screening program to identify these diseases. If tyrosinemia type 1 is recognized late, the patient will expire before NTBC treatment can be initiated.

Acknowledgments

Excellent and detailed reviews of the diseases discussed in this chapter can be found in *The Metabolic and Molecular Bases of Inherited Disease* edited by C. R. Scriver, A. L. Beaudet, W. S. Sly, and D. Valle (New York, McGraw-Hill, 7th edition 1995). Suggested reading material for important aspects of each disease presented is listed in the sections below.

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39 Lysosomal Storage Diseases

Pinar T. Ozand · Mohammed Al-Essa

Many inborn errors of metabolism manifest with clinical evidence of a storage disease in the central nervous system (CNS) and/or peripheral organs. Since this storage occurs within the lysosomes, these inborn errors of metabolism are known as lysosomal storage diseases. In most types, the clinical presentation usually is similar, and there are only a few clinical hints that guide the pediatrician to the correct diagnosis. For example, only an experienced clinician can differentiate Hurler syndrome from Maroteaux–Lamy syndrome at the bedside early in infancy.

The diagnostic efforts are further complicated by the fact that the phenotypic expression of the disease varies according to its age of onset. For example, while G_{M2} gangliosidosis, either Sandhoff or Tay–Sachs variety, manifests first in early infancy with a severe dementing disease, the same disorder with a lesser degree of enzyme deficiency will manifest in late childhood or early adolescence with motor clumsiness or ataxia.

As the name implies, lysosomal storage diseases are usually associated with the enlargement of visceral organs. However, visceromegaly is also observed in other storage diseases that do not involve lysosomes. For example, glycogen storage disease (GSD) types 1, 3, and 4 cause significant hepatomegaly with or without splenomegaly and can easily be confused clinically with a lysosomal storage disease. The GSDs usually, but not always, lead to significant impairment of glucose and lipid metabolism, which are not seen in lysosomal storage diseases, and may be diagnosed through simple clinical laboratory tests. Some types of GSD, such as GSD type 3, cause early hepatosplenomegaly but no significant hypoglycemia or lactic acidosis. At early stages of the disease, it is nearly impossible to differentiate clinically GSD type 3 from Niemann–Pick disease type B, except that biochemical studies are helpful (e.g., GSD type 3, in contrast to Niemann–Pick disease, causes elevated creatine kinase [CK]).

A common misconception is that all lysosomal storage diseases cause clinically visible organomegaly or skeletal changes. A large group of them affect primarily the CNS, with little or no involvement of the peripheral organs. For example, Krabbe disease is associated with the storage of galactocerebrosides in the CNS, with no visceromegaly. Unless the pediatrician is aware that some storage diseases primarily affect the CNS, appropriate laboratory tests might not be ordered to reach the diagnosis.

This chapter is intended to provide a bedside guideline to the pediatrician for the diagnosis of lysosomal storage diseases. This is important since experimental therapies are available, such as enzyme replacement therapy. However, such therapeutic attempts require early diagnosis; for example, a bone marrow transplant (BMT) is rewarding only if the diagnosis is reached early. Newly available in utero BMT as well as the recent availability of gene therapy (e.g., for Hurler syndrome) make mandatory an accurate diagnosis of the disease in the index case, in order to provide intervention in future siblings or fetuses. The list of lysosomal storage diseases that are reviewed in this chapter is presented in *Table 39.1*.

Major Phenotypic Expressions and Alerting Signs of Lysosomal Storage Diseases

All lysosomal storage diseases are inherited as autosomal recessive traits except for Hunter syndrome (mucopolysaccharidosis type II) and Fabry disease, which are X-linked. In the following presentation, each disease is summarized with regard to its major phenotypic expression as well as the signs that should alert the pediatrician. An example case history with relevant physical or laboratory findings is also given when possible.

Mucopolysaccharidoses

Most patients with mucopolysaccharidosis (MPS) show similar physical features, such as coarse facies and physical appearance, macroglossia, stunted growth, corneal cloudiness, visceromegaly, umbilical and inguinal hernias, CNS involvement with mental retardation (MR), and skeletal changes known as dysostosis multiplex. The latter includes broadened metacarpal and metatarsal bones and ribs, severe deformities of the vertebral bodies, skull abnormalities with a "J-shaped" sella turcica and bony

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Table 39.1
List of lysosomal storage diseases

Mucopolysaccharidoses
Hurler, Hurler–Scheie, and Scheie syndromes (type, IH, IH/IS, and HS)
Hunter syndrome (type II)
Sanfilippo syndromes A, B, C, and D (type III)
Morquio syndrome (type IV A and B)
Maroteaux–Lamy syndrome (type VI)
Sly syndrome (type VII)
Glycogen storage disease type II (Pompe disease)
Wolman disease (Acid lipase deficiency)
Farber disease (Acid ceramidase deficiency)
Neuronal ceroid lipofuscinosis
Disorders of lysosomal enzyme phosphorylation
Mucolipidosis II (I-cell disease)
Mucolipidosis III (pseudo-Hurler polydystrophy)
Disorders of glycoprotein degradation
α-Mannosidosis
β-Mannosidosis
Fucosidosis
Sialidosis
Aspartylglucosaminuria
Disorders of glycolipid metabolism
Niemann–Pick disease types A and B
Niemann–Pick disease type C
Gaucher disease types I, II, and III
Galactosylceramide lipidosis (globoid cell leukodystrophy; Krabbe disease)
Metachromatic leukodystrophy
Multiple sulfatase deficiency
Fabry disease
Schindler disease
Gangliosidoses
G_{M1} gangliosidosis (infantile, late infantile, and chronic-on-set types)
Galactosialidosis (infantile–juvenile types)
G_{M2} gangliosidosis I (classic Tay–Sachs disease)
G_{M2} gangliosidosis II (Sandhoff disease)
G_{M2} gangliosidosis (activator protein deficiency)
G_{M2} gangliosidosis III (juvenile Tay–Sachs disease)
Cystinosis
Lysosomal transport disorders
Sialic acid storage disorder (infantile free sialic acid storage and Salla disease)
Chediak–Higashi syndrome

abnormalities of the basis cranii, and abnormalities of the hip joints, elbows, wrists, knees, and ankles. Both ligaments and joints are involved. This physical appearance of this symptom complex is referred to as "features of MPS."

Hurler Syndrome (Mucopolysaccharidosis Type IH)

The age of onset is usually between 6 and 24 months. Coarse facial features (gargoylism), macroglossia, stertorous breathing, persistent copious nasal discharge, cloudy cornea, glaucoma, hearing loss (conductive + neurosensory), cardiomyopathy, obstructive airway disease, umbilical and/or inguinal hernia, hepatosplenomegaly, dysostosis multiplex, joint stiffness, stunted growth, hydrocephalus, early developmental delay, and MR are present (*Fig. 39.1*). Death occurs in the first or second decade.

Alerting Signs. Hurler syndrome is marked by severe features of MPS such as coarse physical appearance, macroglossia, cloudy cornea, visceromegaly, hernias, dysostosis multiplex, and MR.

Case History. An 8-year-old boy was referred for the evaluation of coarse features, with a referral diagnosis of a dysmorphic syndrome. The parents noticed his features becoming coarse after 1 year of age. He developed stertorous breathing and continuous nasal discharge at approximately the same time. An umbilical hernia was noticed to grow in size before referral. Family history indicated the death of a previous sister at the age of 10 years. She was diagnosed to have Hurler syndrome. There were no normal children. The presence of a second affected child disrupted the family; they were divorced with acrimonious feelings and remarriage of the father. He had three normal children from the second marriage. On physical examination, the patient's growth parameters indicated severe dwarfism, corresponding to the development level of 3–4 years of age. He had coarse features suggestive of MPS. He had a large dolichocephalic head, severely clouded corneas, persistent nasal discharge with noisy breathing, macroglossia, shortened thick fingers and toes, narrowed intercostal spaces, kyphosis, a large umbilical hernia, and impressive hepatosplenomegaly. Cardiac examination indicated mitral and pulmonary valve regurgitation and he was placed on captopril and furosemide (Lasix). The skeletal survey showed dysostosis multiplex. The peripheral blood film showed leukocytes with metachromatic granules. An MPS screen of the urine indicated 4+ mucopolysaccharidiuria. Both leukocytes and cultured fibroblasts showed normal lysosomal enzymes, except for

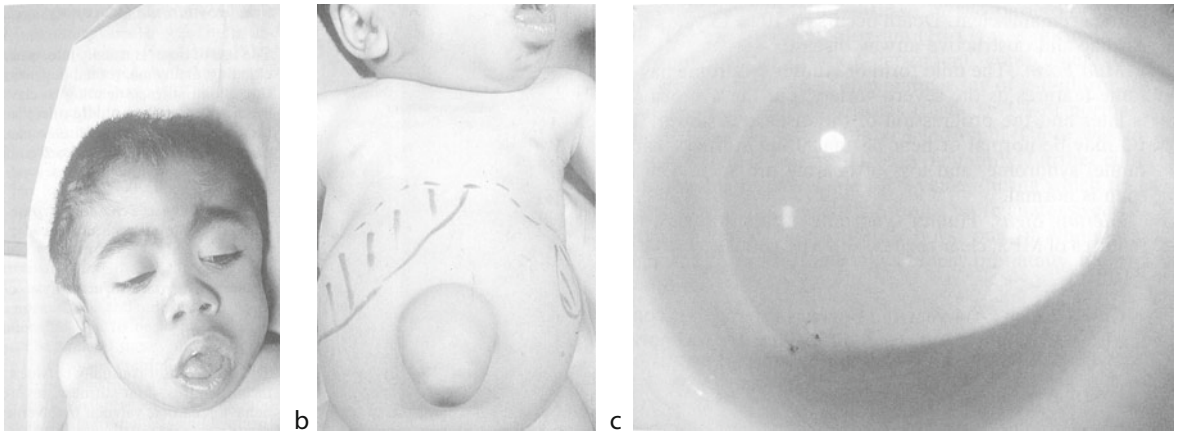

Figure 39.1
Hurler syndrome. (a) The coarse face and macroglossia. (b) The umbilical hernia. (c) The corneal cloudiness

α-L-iduronidase activity, which was less than 1% of normal. He suffered strangulation of his hernia and had to be operated on, following which he developed respiratory insufficiency due to upper airway obstruction and a tracheostomy had to be performed. At present he is at home under respiratory care.

Hurler–Scheie Syndrome (Mucopolysaccharidosis Type IH/IS)

The age of onset is around 1 year. Physical features are intermediate between Hurler and Scheie syndromes. Progressive dysostosis multiplex, coarse facial features, corneal clouding, severe joint stiffness, cervical cord compression, cardiac valvular involvement, and normal intelligence are observed. Death occurs usually late, in the teens and twenties, due to cardiac involvement and obstructive airway disease (◉ *Fig. 39.2*).

Alerting Signs. The physical features are like Hurler syndrome, but IQ is usually normal.

Case History. A 13-year-old boy, at the time of initial encounter, had chief complaints of coarsening of features, dwarfism, joint contractures, and lower back pain since 4 years of age. There was another sibling affected more severely with the same condition who died at the age of 20 years with cardiac complications of the disease. The parents were first-degree cousins. The patient's height and weight corresponded to median ages of 5 and 8 years, respectively, at the age of 13. He had a coarse face, widened fingers and toes with joint contractures, mild macroglossia, narrowed intercostal spaces, very cloudy corneas, mild hepatosplenomegaly, and an umbilical hernia. The psychometric examination indicated normal intelligence for age. He was attending school despite handicaps and was a good student. Neurologic examination

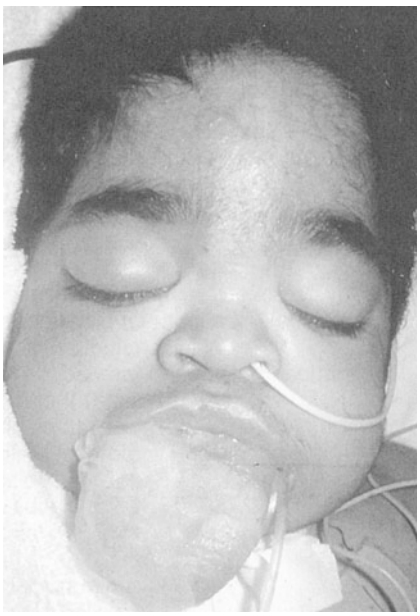

Figure 39.2
Hurler–Scheie syndrome in a 25-year-old male whose disease was first noticed at 6 years of age. He had severe pyramidal tract signs and upper airway obstruction due to the impressive macroglossia. He died despite intensive supportive measures

was normal; although they could not be visualized fully, the eyegrounds appeared normal. The level of α-L-iduronidase was 0.1% and 4% of normal in leukocytes and fibroblasts, respectively. An abdominal ultrasound indicated mild hepatosplenomegaly and no renomegaly. A skeletal survey indicated moderate dysostosis multiplex, with prominent involvement of pelvic bones and a "J-shaped" sella turcica. Magnetic resonance imaging (MRI) of the neck at 13 years of age indicated narrowing of the spinal canal at the C-1 to C-2 level with no compression.

He remained under clinical follow-up for over 12 years, during which time the disease progressed only mildly. Despite a large kinship, there was no human leukocyte antigen (HLA) match in the family for a possible BMT. During this time a cardiac workup indicated thickened mitral and tricuspid valves with no significant stenosis; heart function otherwise was normal. A dental workup indicated malocclusion. His large umbilical hernia required surgery. An ear, nose, and throat (ENT) examination indicated hearing loss of 30% at low frequencies at the age of 20 years. A chest x-ray at the age of 20 years indicated mild bronchiectasis despite no history of smoking. His joint contractures advanced to a stage at which he could not use his hands, and therefore could not be employed because of this handicap despite normal intelligence. He had bilateral corneal transplantation at the age of 18 years, with gain of some visual acuity. He suffered from gastroesophageal reflux and chronic hypertrophic gastritis that required treatment with antacid medication. A stomach biopsy did not show infiltration by MPS-loaded cells. He is now 25 years old and is maintaining a relatively normal lifestyle despite no occupation. He is married and has two normal children.

Scheie Syndrome (Mucopolysaccharidosis Type IS)

The age of onset is usually late, during childhood. Corneal clouding, glaucoma, retinal degeneration, mild coarse features, joint stiffness leading to claw hands, carpal tunnel syndrome, pes cavus, late-onset aortic regurgitation, at times obstructive airway disease causing sleep apnea, normal intelligence, and spinal cord compression and resultant signs of myelopathy are observed. Life span is usually normal.

Alerting Signs. Scheie syndrome is marked by cloudy cornea, stiff joints, and normal IQ.

Hunter Syndrome (Mucopolysaccharidosis Type II)

Severe Form. The age of onset is usually between 2 and 4 years. Coarse facial features, joint stiffness, severe MR with aggressive behavior, cardiac valvular involvement, obstructive airway disease, myocardial disease, mild hepatosplenomegaly, and subcutaneous "Hunter nodules" are observed (*Fig. 39.3*). The cornea remains clear. Death occurs by 10–15 years from cardiac and obstructive airway disease.

Mild Form. The mild form of Hunter syndrome has the same features as the severe variety, but the age of onset is later and the progression of the disease is slower. The IQ may be normal or near normal. Joint stiffness, carpal tunnel syndrome, and loss of hearing are seen. The life span is normal.

Alerting Signs. Hunter syndrome occurs in males, with features of MPS, clear cornea, and MR with aggressive behavior.

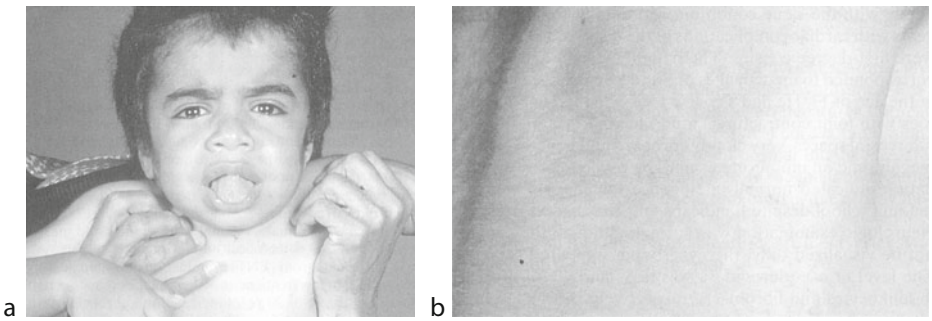

Figure 39.3
A boy with Hunter syndrome. (a) Coarse face but the corneas were clear. (b) Hunter nodules on pressure surface on the back (*See Color Fig.* 5–3*B*)

Case History. A 4-year-old boy was referred for coarse features, irritability, and social difficulties. He was normal until 1 year of age, when his parents noted him to show coarse features and irritable behavior. He was late in acquiring speech, but motor milestones were normal. He could not be toilet trained. He showed shy behavior and would cry if there were strangers around. The parents noticed him to have noisy breathing and persistent nasal discharge. The physical examination indicated a child at the 90th percentile of height and weight with macrocephaly (head circumference corresponding to 12 years of age at the age of 4 years). He had markedly coarse features, clear corneas, pectus carinatum, scoliosis, thoracolumbar kyphosis, and valgus deformity of the lower limbs. The eyegrounds examination was normal. The liver edge was 3 cm below the right costal margin and the spleen tip was palpable. He had a large umbilical hernia. Neurologic examination indicated normal tone and reflexes. A psychometric examination indicated him to be at a 24-months level at 4 years of age. The skeletal survey showed right-sided maxillary sinusitis, dysostosis multiplex with markedly enlarged and thickened calvarium, "J-shaped" sella turcica, markedly hypoplastic vertebrae, enlarged ribs, and enlarged metacarpals in addition to scoliosis and kyphosis of the thoracolumbar vertebrae. MRI of the brain showed subcortical white matter disease in the parieto-occipital area. The electroencephalogram (EEG) was normal. The radioactive sulfur fixation-dependent complementation analysis, and later direct enzymatic assay of α-L-iduronate sulfatase in cultured fibroblasts (result: <1% of normal), indicated him to have Hunter syndrome. There was no HLA-matched donor available in the family. Further clinical follow-up was available for 2 years, during which time he lost most of his speech, showing a more aggressive MR. Two subsequent siblings, both boys, one of whom was diagnosed from chorionic villus biopsy prenatally, had the same disease.

Sanfilippo Syndrome (Mucopolysaccharidosis Types IIIA, B, C, and D)

There are four forms of this disease, each with a different deficient enzyme. The most severe form is type A; type B is less severe, and the severity of type C is between A and B. Type D may have milder features.

Severe Forms. The age of onset is usually between 2 and 3 years, with previous normal development. Severe progressive CNS disease, little or no systemic involvement, severe MR and aggressive behavior, hirsutism and synophrys, sleep disorder with nocturnal insomnia, seizures, late onset of mild joint stiffness with minimal or absent dysostosis multiplex, and minimal or absent hepatosplenomegaly are seen (Fig. 39.4). No corneal cloudiness is observed. Death occurs by 10–30 years of age.

Mild Forms. Age of onset is usually late in childhood, with developmental regression and seizures.

Alerting Signs. Sanfilippo syndrome manifests with only mild features of MPS, extreme hirsutism with synophrys, and aggressive behavior with MR.

Case History (*Sanfilippo Syndrome Type B*). A 15-month-old boy was referred with a presumptive diagnosis of fetal Dilantin syndrome. The mother had a seizure disorder and was under therapy with heavy dose of phenytoin (Dilantin) during pregnancy. Mild coarse features, bilateral epicanthic folds, blepharophimosis, and mild central hypotonia were noticed at 1 year of age that were attributed to the teratogenic affect of phenytoin. The physical, social, mental, verbal, and psychological development remained normal. At the time of examination, coarse features, hirsutism particularly prominent on the forehead, and borderline hepatomegaly were found. He had no neurologic signs and was a happy, cooperative infant with severe atopic dermatitis on the cheeks.

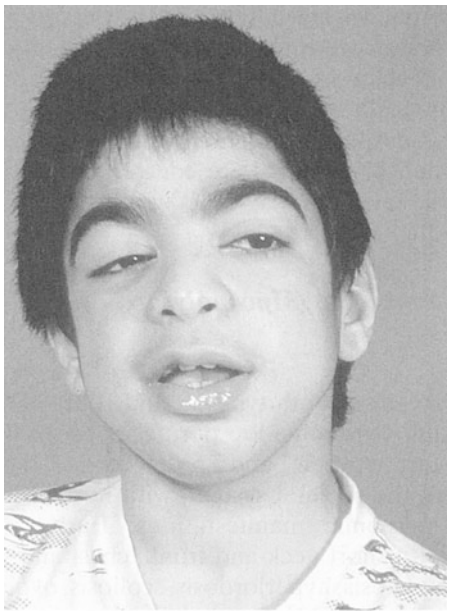

Figure 39.4
An 11-year-old boy with Sanfilippo syndrome type B, whose features coarsened in time, developing hirsutism and synophrys

A skeletal survey, computerized tomography (CT) of the brain, and the EEG were normal. There was no mucopolysaccharidiuria or metachromatic granulation of leukocytes. Since his coarse features suggested an MPS, a lysosomal battery was determined in lymphocytes and in cultured fibroblasts, which indicated absent α-*N*-acetylglucosaminidase, confirming the diagnosis of Sanfilippo syndrome type B.

The further clinical course is available until 11 years of age. Sequentially he started to show progressive encephalopathy with loss of mental, social, and verbal skills starting at 3 years of age but with preserved gross and fine motor function. Psychometric evaluations indicated the following developmental levels: 17 months at 3 years, 13 months at 5 years, 10 months at 7 years, and 6 months at 10 years of age. He developed an aggressive attitude at 5 years. CT of the brain showed mild/moderate atrophy until 5 years of age, at which time MRI of the brain indicated white matter disease, most prominent in the parietal area. The EEG remained normal until 6 years of age, at which time the background was found to be disturbed. He started to have frequent grand mal seizures at 9 years of age. Facial features started to become coarse, with hair on the forehead and synophrys. Bilateral contractures of the fifth fingers of the hand were noticed at 10 years of age. Ovoid vertebral bodies were first noticed at 6 years of age. He started to develop insomnia at 6 years of age. Eventually he had to be institutionalized at 10 years of age. At the age of 11 years, he is severely mentally retarded with aggressive behavior, and his seizures are controlled with phenobarbital.

Morquio Syndrome (Mucopolysaccharidosis Types IVA and B)

The phenotypes of both types A and B are alike. Infants with Morquio syndrome are normal at birth; skeletal deformities start between 1 and 3.5 years of age. It is primarily a disease of the skeletal system, with normal intelligence and mild systemic manifestations. Early and severe dwarfism with short neck and trunk, chest and sternal deformities, kyphosis, hyperlordosis, scoliosis, ovoid deformities of vertebrae with platyspondyly, ulnar deviation of the wrist, delayed ossification of carpal and metacarpal bones, hypermobile wrist joint due to ligament laxity and valgus deformity of the elbow, and odontoid hypoplasia leading to atlantoaxial instability, subsequent subluxation, and spinal cord compression occur (*Fig. 39.5*). All children with Morquio syndrome should have periodic examination of the neck by CT or MRI to detect impending cervical cord compression. Rare and mild systemic manifestations include mild corneal cloudiness, mild cardiac valvular lesions, and mild hepatomegaly. Patients with type A disease have enamel hypoplasia. The life span is normal.

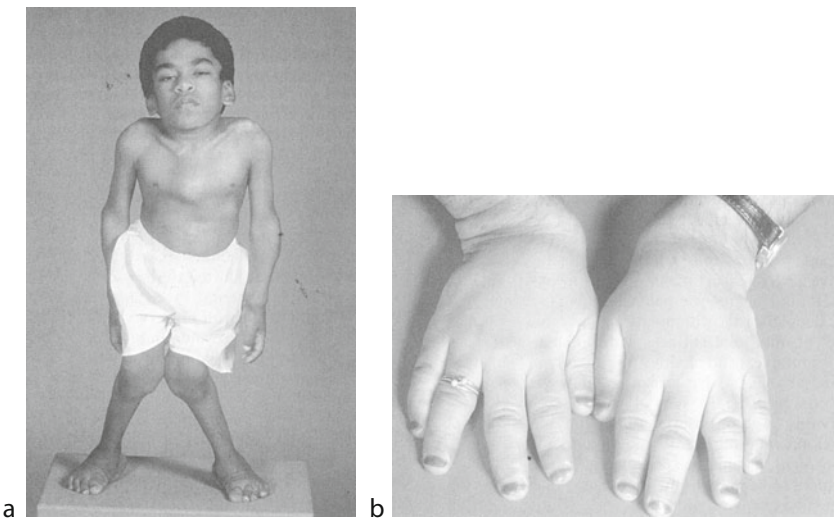

Figure 39.5
Morquio syndrome. (a) General appearance of a boy 16 years of age. (b) Wrists of a boy with deviation due to hypermobile joints

Alerting Signs. Morquio syndrome shows no features of MPS, but dwarfism, short neck, hypermobile joints, vertebral column and chest wall deformities are present, with normal IQ. *Type A* has enamel hypoplasia; *type B* has no enamel abnormalities.

Case History. A boy was diagnosed to have Morquio syndrome at birth by enzyme analysis (galactose-6-sulfatase < 2% of normal) and because of the family history (the presence of a previous sister who had already been diagnosed to have Morquio syndrome). During the first year of life he started to develop gradually the features of the disease, with stunted growth, shortened neck, and eventually kyphoscoliosis. His weight and head circumference remained normal; he did not develop hepatomegaly, and the corneas remained clear. At the age of 18 months a skeletal survey revealed platyspondyly with kyphoscoliosis, coxa valga with hypoplasia of the lateral aspect of the acetabular roof, and instability of the upper cervical spine, with displacement of C-1 in relation to C-2. Blood studies were normal and no metachromatic granules were found. At the age of 3 years, after a trivial pull of his head, the patient developed quadriparesis with increased deep tendon reflexes, bilateral ankle clonus, and Babinski sign. He lost sphincter control for urine and stool. Urgent MRI of the neck showed forward displacement of the C-1 in relation to the C-2 vertebra and hypoplastic odontoid process. He underwent emergency surgery for posterior fusion of the cervical spine. The patient improved gradually and started to walk again 4 months later. The abnormal deep tendon reflexes, Babinski sign, and ankle clonus disappeared 6 months after the surgery. He resumed control of his sphincters in 1 year. He had to wear a neck collar for more than a year. There was no HLA-matched donor in the family. At present he is 6 years old and has a normal IQ, and is leading a normal lifestyle despite worsening of his skeletal deformities.

Maroteaux–Lamy Syndrome (Mucopolysaccharidosis Type VI)

The symptoms are very similar to those of Hurler–Scheie syndrome. The development is normal for first few years of life, with the disease appearing after 2–4 years. The intelligence remains normal. The skeletal findings of dysostosis multiplex are severe; cervical cord compression from thickened dura might be seen. Death occurs in the late 20s to the 40s.

Alerting Signs. Maroteaux–Lamy syndrome is marked by severe features of MPS but normal IQ.

Sly Syndrome (Mucopolysaccharidosis Type VII)

The symptoms are similar to those of Hurler–Scheie syndrome. Severe forms may cause hydrops fetalis and abortions. The usual age of onset is after 4–5 years. Corneal clouding is variable; moderate MR or normal intelligence is seen.

Alerting Signs. Sly syndrome is marked by mild features of MPS, late age of onset, and normal or retarded IQ.

Glycogen Storage Disease Type II (Pompe Disease)

Severe Form

The age of onset is shortly after birth. Massive cardiomegaly with hypertrophic myocardium, macroglossia, hepatosplenomegaly, early feeding difficulties with poor sucking, marked peripheral hypotonia, and progressive muscle weakness including respiratory muscles, with usually firm muscles to palpation, are observed (*Fig. 39.6*). Rapid death occurs, usually before 1 year of age, with cardiorespiratory failure. The intelligence is normal.

Milder, Later Onset Forms. Those forms that present before 2 years show cardiomegaly and muscle weakness.

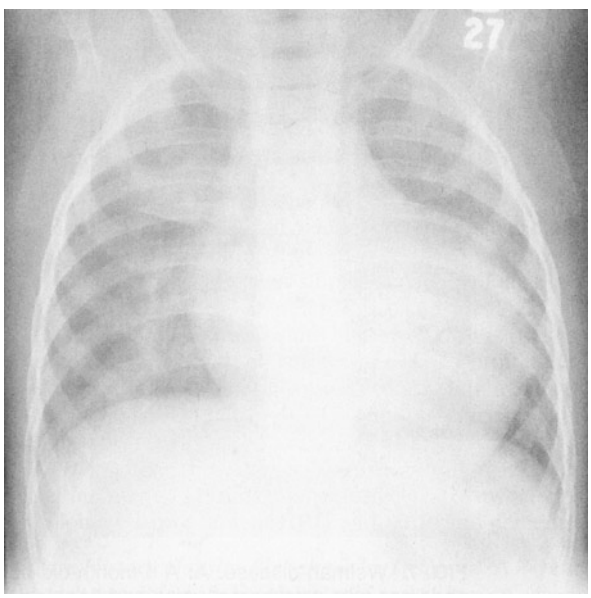

Figure 39.6
Pompe disease. Gross cardiomegaly due to hypertrophic cardiomyopathy

Those that manifest after 2 years of age show only muscle weakness. Muscle weakness is proximal, with involvement of respiratory muscles. Death is late, depending upon the severity of enzyme deficiency. Both severe and mild types show pseudomyotonic discharges on electromyography (EMG), namely, myotonic discharges without myotonia.

Alerting Signs. The *infantile-onset form* of Pompe disease shows massive hypertrophic cardiomyopathy, visceromegaly, and hypotonia. The *late-onset form* shows pseudomyotonic bursts in the EMG.

Case History (*Pompe Disease, Early Infantile Type*). An 8-month-old boy was referred for severe hypotonia. He was the product of a normal pregnancy and delivery. The parents noted him to be hypotonic since 2 weeks of age. The parents were first-degree relatives, with several normal children and no family history of a similar disease. Physical examination indicated height and weight below the fifth percentile. There was a grade 4 systolic murmur generalized over the pericardium with no heave. The liver was enlarged 6 cm below the costal margin; the spleen tip was palpable. There were severe peripheral hypotonia and diminished deep tendon reflexes. Primitive bipedal reflexes were absent. The muscles were very firm to palpation. The x-ray of the chest indicated gross cardiomegaly. Blood glucose and lactic and uric acid were normal. Pompe disease was suspected. Analysis of acid maltase (acidic α-glucosidase) in lymphocytes and, later, in cultured fibroblasts indicated acid maltase to be less than 2% of normal, confirming the clinical diagnosis. The general condition deteriorated rapidly, and the baby died because of heart failure.

Case History (*Pompe Disease, Late Infantile Onset*). The chief complaint of a 3-year-old girl was bilateral facial and diaphragmatic paralysis. She was normal until 30 months of age, at which time, after a chest infection, she could not maintain breathing and had to be placed on ventilatory support. At that time she was found to have severe peripheral hypotonia. She came off the respirator after 1 month and started to walk again with support. She had normal IQ for age. Three months later, she had to be admitted again with inability to support breathing, received a tracheostomy, and was referred for a diagnostic workup. At the time of admission she was alert but had respiratory distress. She had difficulty in swallowing. She had normal heart sounds and normal pulses. There was no visceromegaly.

Her muscle tone and deep tendon reflexes were greatly decreased. Blood chemistries indicated greatly increased CK, at 1,340 U/L (normal: <195 U/L); blood lactic acid and cerebrospinal fluid (CSF) protein were normal. Shortly after admission she developed atelectasis of the left lower lobe, requiring ventilatory support, and this time she could not be weaned off the ventilator. An EMG showed pseudomyotonic discharges without clinical myotonia. The electrocardiogram and echocardiogram revealed normal heart function. Peripheral nerve conduction was normal. Light microscopy of her muscle biopsy showed glycogen accumulation, and electron microscopy (EM) indicated widespread presence of glycogen both within and outside the lysosomes. The acid maltase (α-glucosidase) activity in her cultured fibroblasts was 6% of normal. She was placed on a high-protein (26%) diet, but her clinical status did not improve. She is alive after 3 years on a ventilator.

Wolman Disease (Acid Lipase Deficiency)

The age of onset is early during infancy, with failure to thrive (FTT), steatorrhea, massive hepatomegaly, occasionally splenomegaly, abdominal distention, markedly enlarged adrenals compressing the superior poles of the kidneys, and adrenal calcifications (Fig. 39.7). Mental development is normal. Eventually hepatic fibrosis occurs. Anemia, occasionally acanthocytosis, and vacuolated lymphocytes are seen.

Alerting Signs. Wolman disease is marked by massive hepatomegaly with FTT and adrenal calcifications.

Case History. A 3-month-old boy was referred for abdominal distention and FTT. He was small for gestational age, and abdominal distention had been noticed since birth. The family history revealed the presence of seven infant deaths due to Wolman disease as diagnosed enzymically. Four maternal and two paternal cousins also died of the same disease. On physical examination, he was an alert baby with height, weight, and head circumference corresponding to median ages of 1, 0.5, and 2.5 months, respectively. He had good visual following. There was no subcutaneous fat tissue; the marasmus was most apparent in the face. Protuberant veins were visible on the distended abdominal wall. Hepatomegaly filled the entire right half of the abdomen; the spleen was not enlarged. Neurologic examination was normal with mild hypotonia. The eyegrounds examination was normal. Blood chemistries were normal except for mildly elevated aspartate transaminase (AST) (139 U/L). Dihydroxycholecalciferol was low, at 11 ng/L (normal: >18 ng/L). Chest x-ray, skeletal survey, and CT of the brain were normal. Abdominal ultrasound and x-ray indicated focal areas of calcification in the suprarenal glands. There were acanthocytes in peripheral red blood cells. Bone marrow biopsy revealed histiocytes with hypervacuolization. Liver biopsy indicated small

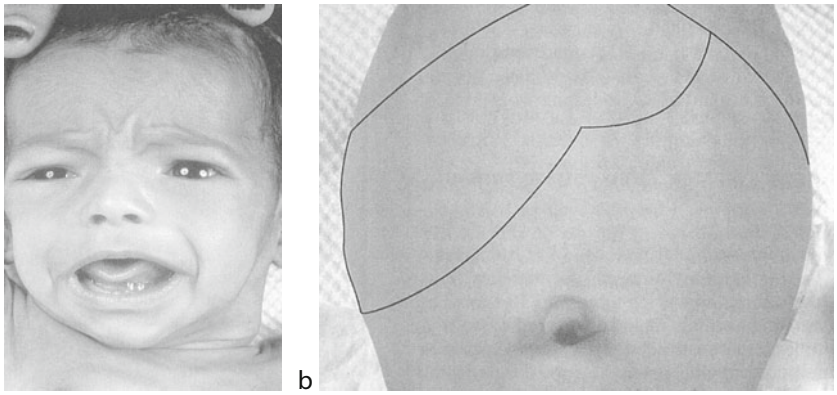

Figure 39.7
Wolman disease. (a) A 6-month-old boy with facial cachexia due to marasmus. (b) Distended abdomen with protuberant veins and hepatomegaly

and large fat vacuoles in hepatocytes, elliptical empty clefts in Kupffer cells, focal fibrosis, and thickened blood vessels. The acid lipase in leukocytes and cultured fibroblasts were 5% and 9% of normal, respectively, confirming the diagnosis of Wolman disease. The parents had previous experience with the fatal outcome of the disease and refused further intervention. He was discharged home, where he died 1 month later.

Farber Disease (Acid Ceramidase Deficiency)

Classic Variety (Severe, Intermediate, and Mild Phenotypes)

The age of onset is between 2 weeks and 2 months in the severe, birth to 9 months of age in the intermediate, and 2–20 months in the mild phenotype. Painful and progressively deformed joints suggest rheumatoid arthritis. Subcutaneous nodules are encountered near joints and at pressure points. Progressive hoarseness due to formation of nodules in the vocal cords; nodules on the external ear, nostrils, conjunctiva, and buccal mucosa; and cardiac valvular involvement due to granulomatous lesions are seen. Corneal opacities and cherry-red macula occur in 10% of the patients. Lung infiltrates, hepatomegaly, mild to moderate MR, and peripheral neuropathy with myopathy are usual. Mean age at the time of death is 1 year in the severe, 5 years in the intermediate, and 16–18 years in the mild phenotype.

Progressive Neurologic Variety. The age of onset is 1–2 years. Joint and nodule involvements are the same as in the classic type. However, the CNS disease predominates, with ataxia, polymyoclonia, rigidity, tremors, dementia, and cherry-red macula. No lung involvement and no corneal opacities are seen. Death usually occurs by 3 years of age.

Alerting Signs. Farber disease is marked by painful joints, subcutaneous nodules on joints and pressure surfaces, and hoarse voice. The neurologic variant also has progressive encephalopathy.

Neuronal Ceroid Lipofuscinosis

All forms of neuronal ceroid lipofuscinosis (NCL) are inherited as autosomal recessive disorders. This group of diseases is classified according to age of appearance.

Infantile Form (Santavuori Type)

The age of onset is 6–12 months, with motor regression, visual failure, and macular degeneration. These symptoms progress to truncal ataxia, dystonia, choreoathetosis, and stereotypic hand movements like those of Rett syndrome. Severe myoclonus and myoclonic seizures and eventually dementia are seen by 6–18 months. CT of the brain indicates dense thalami. The EEG flattens by 12 months, then becomes isoelectric. The visual evoked potentials (VEP) and electroretinogram (ERG) are absent by 12 months. Rectal biopsy shows ganglion cells with granular EM inclusions. Death occurs before 14 years. Subunit *c* of ATP synthetase does not accumulate in lysosomes.

Alerting Signs. Santavuori-type NCL manifests with myoclonus, myoclonic seizures, macular degeneration, dense thalami, and absent ERG or VEP.

Late Infantile Form (Jansky–Bielschowsky Disease)

The age of onset is 2–4 years. The neurologic findings and progressive encephalopathy are very similar to those of Santavuori disease, except stereotypic hand movements are absent and pigmented retinopathy is present. The EEG shows large polyspikes. The VEP and ERG show increased wave height. No dense thalami are seen in CT of the brain. MRI of the brain shows periventricular white matter disease. Death occurs by 10–15 years. Subunit *c* of ATP synthetase accumulates in lysosomes.

Alerting Signs. Jansky–Bielschowsky disease manifests with myoclonus, myoclonic seizures, pigmented retinopathy, periventricular white matter disease, and abnormal waves in the ERG and VEP.

Juvenile Form (Spielmeyer–Vogt Disease)

The age of onset is between 5 and 9 years. The neurologic findings and progression of the disease are similar to the late infantile variety, except slurred speech and echolalia are present. The EEG is not helpful, and the VEP and ERG are absent. Central white matter disease is present. The storage in the form of curvilinear or fingerprint bodies can be shown in peripheral lymphocytes. Death occurs by 20–40 years. Subunit *c* of ATP synthetase accumulates in lysosomes.

Alerting Signs. Spielmeyer–Vogt disease is marked by visual failure and retinitis pigmentosa (*Fig. 39.8*), myoclonus, myoclonic seizures, absent ERG and VEP, and dementia.

Case History (*Jansky–Bielschowsky Disease*). A 7-year-old girl was referred for myoclonic jerks, loss of vision, and spastic quadriplegia. She was doing well, acquiring milestones normally, until 4 years of age. She then started to have frequent, and later on continuous, jitters and lost her motor function gradually, becoming bedridden. Subsequently she lost her vision, speech, and sphincter control. She was immunized and had not had measles in the past. The parents were consanguineous, and other children in the family were normal with no familial history of a neurodegenerative disease. On physical examination, she showed continuous polymyoclonic jerks of the extremities and face. She was blind and deaf. There were no neurocutaneous lesions. The head was microcephalic. The eyegrounds examination revealed bilateral optic atrophy, retinal degeneration with pale retina, and very narrowed blood vessels. She had spastic quadriplegia, somewhat increased deep tendon reflexes, and Babinski sign. Blood chemistries, ammonia, lactate, tandem mass spectrometry studies, and urine organic acids were normal. MRI of the brain showed mild brain atrophy. The EEG showed diffuse background slowing and dysfunction at this late stage of the disease. The ERG indicated absent waves bilaterally. The nerve conduction studies were normal. These results suggested the diagnosis of NCL of the Jansky–Bielschowsky type. The EM analysis of lymphocytes of the buffy coat and a conjunctival biopsy revealed the curvilinear (fingerprint) bodies typical of NCL. The disease since then has progressed relentlessly, and she has become vegetative.

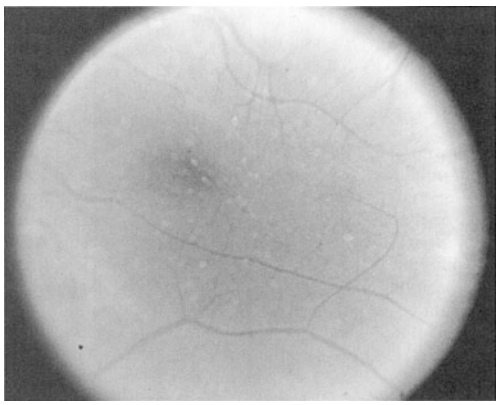

Figure 39.8
Neuronal ceroid lipofuscinosis (Spielmeyer–Vogt disease): retinitis pigmentosa in a 25-year-old girl whose disease started at 7 years of age (*See Color Fig.* 5–8)

Disorders of Lysosomal Enzyme Phosphorylation

Mucolipidosis II (I-Cell Disease)

The disease is always apparent at birth with somatic features and x-ray findings of dysostosis multiplex of Hurler syndrome. Its severe form causes hydrops fetalis. Birth weight and length are lower than normal. Coarse face, corneal cloudiness, aortic valvular disease, inguinal and umbilical hernias, bilateral talipes equinovarus, and congenital hip dislocation are seen. Striking gingival hyperplasia and absent mucopolysaccharidiuria as well as the features of MPS at birth differentiate I-cell disease from Hurler syndrome. Death usually occurs by 5–8 years of age. Those surviving show severe delay of motor function and moderate MR. The deficiency of a specific

phosphotransferase that phosphorylates a mannose residue on newly synthesized lysosomal enzymes leads to impaired uptake of all lysosomal enzymes by lysosomes and their excretion into medium, blood, or urine.

Alerting Signs. Mucolipidosis II shows severe features of MPS at birth and gingival hyperplasia (◉ *Fig. 39.9*).

Case History. A patient who was severely cyanotic and had respiratory distress was first seen at the age of 5 months in the company of her 2-year-old sister, who was already diagnosed to have I-cell disease. Her growth had completely stopped after birth; she had not grown an inch, had not gained 0.5 kg of weight, and had not increased her head circumference more than 1 cm. Physical examination indicated an infant with a weak cry, microcephaly, closed fontanel, significant gingival hyperplasia, odd coarse-looking features, an abnormal chest cage with flaring of the lower ribs, mild hepatosplenomegaly, increased muscle tone, and cortical fisting. The EEG showed mildly abnormal background. CT of the brain was normal. Skeletal survey indicated reduction of the sagittal diameter of vertebrae with bilateral convexity and bilateral dislocation of the hips with extreme acetabular dysplasia. Cardiac workup indicated pulmonary stenosis, severe dilation of the right atrium and right ventricle, severe tricuspid regurgitation with malaligned septum, ventricular septal defect, overriding aorta, and hypoplasia of the descending aorta. The lysosomal battery in lymphocytes and cultured fibroblasts revealed 3–8% of normal activity for all lysosomal enzymes tested, confirming the diagnosis of I-cell disease. The psychometric assessment at the age of 14 months showed her motor skills to be at less than 6 months of age, but her verbal and social skills at 10 months of age. By then the repeat EEG indicated markedly slow background. She survived until the age of 18 months, when she died of heart failure.

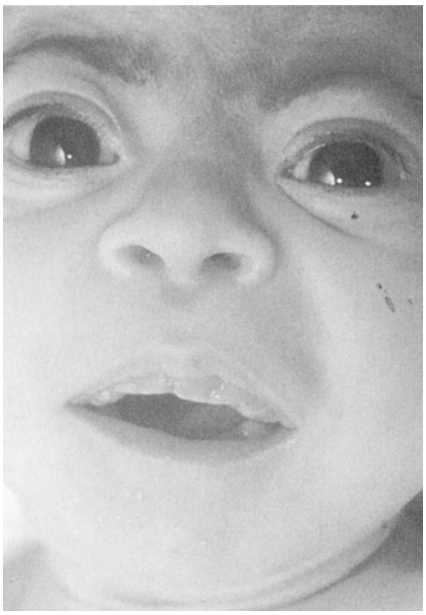

Figure 39.9
Mucolipidosis II (I-cell disease). A 1-year-old infant who had coarse features since birth; her hypertrophic gingiva are shown

Mucolipidosis III (Pseudo-Hurler Polydystrophy)

The age of onset is 2–4 years, with mild features of MPS. Prominent joint stiffness confuses the disease with rheumatoid arthritis. The characteristic ophthalmologic triad of corneal clouding, mild retinopathy, and hyperopic astigmatism appears by 7 years of age. Mild dysostosis multiplex evolves slowly. Mild to moderate MR is seen. Survival is until the 30s or 40s. The enzyme deficiency is the same as in mucolipidosis II, but it is milder.

Alerting Signs. Mucolipidosis III shows mild features of MPS with severe joint involvement.

Disorders of Glycoprotein Degradation

α-Mannosidosis (Severe and Mild Forms)

In the severe form, the age of onset is 3–12 months, and death occurs by 3–10 years. In the mild form, the age of onset is 1–4 years, and death occurs after 10 years of life. The phenotype includes coarse facial features, mild dysostosis multiplex, hernias, and hepatosplenomegaly. Corneal opacities are encountered mainly in the lower pole, and cataracts occur in a characteristic spoke-like pattern in the posterior lens. Severe to moderate MR is present. Recurrent bacterial infections due to impaired chemotaxis are frequent.

Alerting Signs. α-Mannosidosis shows features of MPS, opacities at the lower pole of the cornea, cataract, and frequent infections.

Case History (*α-Mannosidosis, Mild Form*). An 18-month-old boy was referred for hepatosplenomegaly, repeated chest infections, diarrhea, jaundice, and MR. He was a premature infant who sat at 6 months but could not walk at 18 months of age. He had no verbal skills. He had been hospitalized for chest and upper respiratory

infections three times previously, and had prolonged jaundice of unknown etiology for 3 months at the age of 14 months. The family history indicated five premature births who were now normal and a 6-year-old moderately mentally retarded sister with hepatosplenomegaly. According to the parents, the sister developed hazy corneas at 4 years of age and also had frequent chest infections. The patient's growth parameters were at the fifth percentile and the head circumference at the 50th percentile. He had the mildly coarse features of a patient with MPS. There was no corneal cloudiness. The cardiac workup was normal. The liver was 8 cm and spleen 4 cm below costal margins. Psychometric assessment placed him at 50% developmental level. Detailed ophthalmologic examination showed no cherry-red macula or corneal cloudiness. Neurologic examination showed normal muscle tone and reflexes. The peripheral blood and bone marrow examination indicated vacuolated lymphocytes. He had mild neutropenia. Liver enzymes were elevated (alanine transaminase [ALT] 354 U/L and AST 214 U/L). Skeletal survey indicated mild dysostosis multiplex, more prominent in the metacarpal bones, which showed proximal tapering. The lysosomal battery indicated α-mannosidase to be 6% of normal in leukocytes and 10% of normal in fibroblasts, indicating the presence of mannosidosis. There was no HLA-matched donor in the family. The patient was lost to follow-up.

β-Mannosidosis

The presentation is nonspecific, with MR, seizures, and, in the severe phenotype, spastic quadriplegia.

Alerting Signs. In β-mannosidosis there are none, except that it is a progressive encephalopathy.

Fucosidosis

Severe Form. The age of onset is around 1 year. Coarse facies, dysostosis multiplex, kyphoscoliosis, ovoid formation of vertebrae with beaking, joint contractures, hearing loss, tortuous conjunctival vessels, recurrent infections, cardiomegaly, hepatosplenomegaly, severe MR with aggressive behavior, seizures, and rapidly progressive encephalopathy are present. There is no corneal opacity. Sweat sodium chloride is elevated. Death occurs by 4–5 years of age.

Mild Form. The age of onset is around 2 years, with the same features as in the severe form, except they are milder. Angiokeratoma is seen only in this type (*Fig. 39.10*); sweat chloride is normal, but anhidrosis is present. Death occurs by 10–40 years of age.

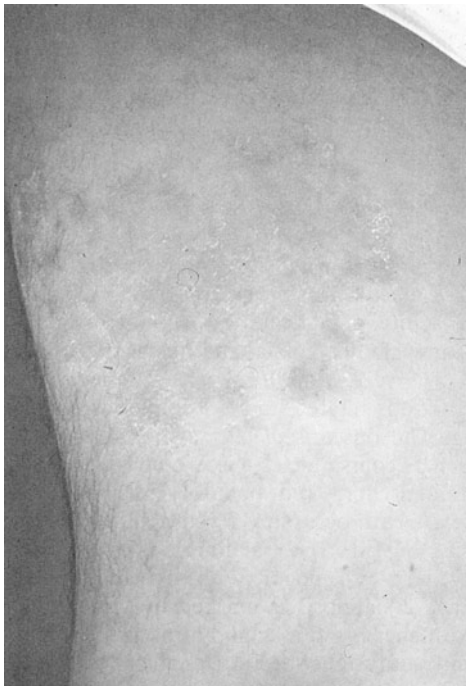

Figure 39.10
Fucosidosis. Angiokeratoma on abdominal wall (*See Color Fig.* 5–10)

Alerting Signs. Fucosidosis is similar to Sanfilippo syndrome but with prominent features of MPS and angiokeratoma.

Case History (*Fucosidosis, Mild Form*). A 5-year-old girl was referred for aggressive behavior and mildly coarse features. She developed normally until 18 months of age, at which time the parents noticed her to lose speech and show hyperactive behavior. The parents were first cousins, and they had one normal and two affected daughters. The physical examination indicated a girl with normal physical growth. Her lips were thick; she had mild hirsutism on her forehead, no corneal cloudiness, but mildly increased vascularity of conjunctiva. Her liver was 3 cm below the costal margin and the spleen tip was palpable. She showed aggressive behavior with mild spastic diparesis, increased deep tendon reflexes, and unsustained ankle clonus. Cardiac workup was normal. Skeletal survey indicated ovoid lumbar vertebrae with beaking. MRI of the brain revealed mild white matter disease in the centrum ovale. The EEG indicated slow background. Blood chemistries were normal. The clinical impression was a case of Sanfilippo syndrome. All four heparan sulfatase activities were tested

and were found to be normal. The α-fucosidase in her leukocytes and cultured fibroblasts indicated activity less than 1% of normal, indicating the diagnosis of fucosidosis. The younger, 3-year-old sister showed similar physical features; the 6-month-old sister physically appeared normal. Both children had absent α-fucosidase activity in their leukocytes. The youngest sister with the disease started to lose milestones at 2 years of age, with coarsening features and borderline hepatosplenomegaly. Sweat chloride test repeated twice was normal. During subsequent visits a peculiar rash was observed on the anterior and posterior wall of the abdomen; biopsy indicated it to be angiokeratoma. There was no HLA-matched donor in the family. She was lost to follow-up.

Sialidosis

Type I (*Cherry-Red Macula-Myoclonus Syndrome*). The age of onset is usually around the second decade, with cherry-red macula appearing later during the disease. Loss of visual acuity, night blindness, spontaneous or stimulus-induced myoclonus, ataxia, and nystagmus are seen.

Type II (*Severe, Infantile Form*). The more severe form causes hydrops fetalis, stippled epiphyses, and periosteal cloaking. The onset is usually at birth, with features of MPS such as coarse facies, visceromegaly, hernia, corneal clouding and cherry-red macula, seizures, and dysostosis multiplex. Death occurs by 2 years of age.

Alerting Signs. Type 1 sialidosis is marked by late-appearing cherry-red macula with myoclonus in an adolescent. *Type 2* sialidosis is marked by features of MPS at birth, with cherry-red macula but no gingival hyperplasia; it is easily confused with G_{M1} gangliosidosis.

Case History (*Sialidosis Type I*). A 14-year-old girl, at the time of initial encounter, had a chief complaint of action-induced myoclonus, with myoclonic jerks of the extremities that first appeared at 9 years of age and progressed to a stage such that she had stopped walking for the last 2 years. She had several grand mal seizures that were controlled by clonazepam. The parents were first cousins, and two of her cousins had the same disease. At the time of first visit her height, weight, and head circumference were normal, with no organomegaly or cherry-red macula. (The cherry-red macula appeared later, at the age of 22 years.) The deep tendon reflexes were normal. She had tremors of the hands throughout an intentional movement. She frequently showed exaggerated "startle response" followed by seizure and postictal sleep. She had severe action-induced myoclonus, bouncing up and down when standing. A psychometric assessment indicated normal intelligence and no dementia but depression. The level of neuraminidase (sialidase) in fibroblasts was 10% of control and was absent in leukocytes. Other lysosomal enzymes were normal. The 5-hydroxyindole acetic acid (in CSF) and homovanillic acid (in CSF and urine) were normal. CT of the brain was normal, and the EEG indicated poorly organized background. The VEP, brain stem auditory evoked potentials (BAEPs), and somatosensory evoked potentials were normal at the age of 16 years. She was placed on 5-hydroxy-tryptophan, which did not improve her myoclonus. Although her seizures could be controlled by valproic acid and clonazepam, the action myoclonus worsened to a degree that she eventually became totally wheelchair bound at the age of 24 years.

Aspartylglucosaminuria

The age of onset is few months after birth, with recurrent infections, diarrhea, and hernias. Subtle coarse features, macroglossia, hoarse voice, mild dysostosis multiplex, joint laxity, sagging skin folds, occasional hepatomegaly, and crystal-like lens opacities occur after 5–10 years; neutropenia, abnormal prothrombin time, and aspartylglucosaminuria also occur. Mental deterioration is seen between 6 and 10 years. Death occurs in the late 30s or 40s.

Alerting Signs. Aspartylglucosaminuria is marked by mild features of MPS with FTT and chronic diarrhea, neutropenia, and abnormal coagulation studies.

Disorders of Glycolipid Metabolism

Niemann–Pick Disease

Type A. The age of onset is usually 4–6 months after birth, with feeding difficulties, severe hypotonia, and distended abdomen due to hepatosplenomegaly. A cherry-red macula appears, and has a gray granular appearance (macular halo syndrome). Loss of motor function, dementia, striking emaciation with yellowish brown color of the skin, and at times xanthomas are seen. The pulmonary involvement is not prominent. The age of death is 2–3 years.

Type B. The age of onset is any time between early childhood and adolescence. Hepatosplenomegaly is impressive; the hepatomegaly is usually bigger than the splenomegaly and occurs earlier (Fig. 39.11). Neurologic findings and intelligence are normal. Cherry-red macula is usually present. Elevated ALT and AST are common. It is primarily a pulmonary disease, with lung

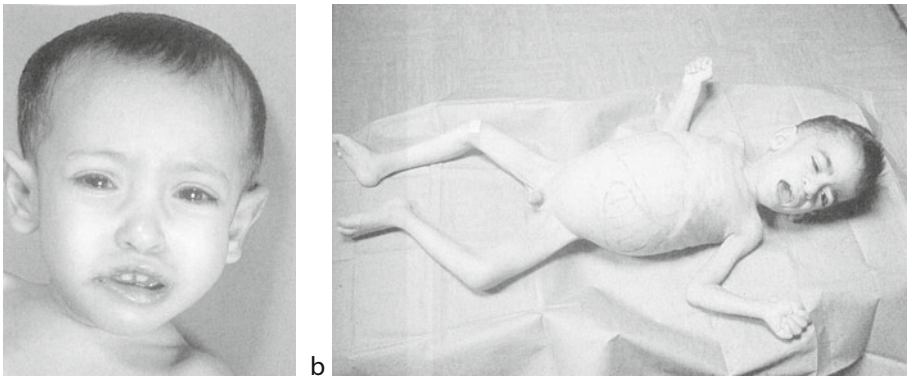

Figure 39.11
Niemann–Pick disease type B. (a) Typical marasmic face with loss of orbital fat tissue and prominent fat pad on nasal bridge. (b) A terminal patient with impressive hepatosplenomegaly and severe cachexia

infiltrates and eventually significant pulmonary compromise and death by 10–20 years of age. The Saudi and Middle Eastern variety appears as in type A, but with no neurologic involvement, very early pulmonary disease, emaciation, and death by 2–3 years of age.

Alerting Signs. Type A Niemann–Pick disease shows hepatosplenomegaly, cherry-red macula, and early emaciation with progressive encephalopathy; *type B* is similar to type A but with slow progression, elevated ALT and AST, and no neurologic involvement, and death is due to pulmonary infiltration.

Case History (*Niemann–Pick Disease, Type B, Middle Eastern Variety*). A 28-month-old boy was referred for hepatosplenomegaly. Birth and subsequent development were normal, and he acquiring the expected milestones. The parents noticed the abdominal distention at 9 months of age, and he started to lose weight and developed frequent chest infections that required repeated hospitalization. The abdominal distention progressed, and a biopsy of the liver at the referring hospital indicated cirrhotic changes and abundant foamy cells, typical of Niemann–Pick disease. The parents were first cousins and this was their first living child (the mother had had five miscarriages). The family history otherwise was not significant. The physical examination showed a cachectic child, with height, weight, and head circumference corresponding to median ages of 10, 6, and 18 months, respectively, at the age of 28 months. There was no subcutaneous fat tissue; he had sunken eyes and a marasmic face, except for a preserved fat pad on the nasal bridge (i.e., the typical face of a patient with Niemann–Pick disease). He responded poorly to visual stimuli and had a cherry-red macula. The hepatosplenomegaly was impressive, filling up the entire abdomen. He had mild central hypotonia. Blood chemistries indicated elevated ALT of 220 U/L, AST of 250 U/L, cholesterol of 6.5 mM (normal: <4.2 mM), and partial thromboplastin time of 45s (normal: < 35s). The sphingomyelinase in both leukocytes and cultured fibroblasts was less than 1% of normal, confirming the clinical diagnosis of Niemann–Pick disease. MRI of the brain revealed mild central white matter disease; the EEG revealed mild disturbance of the background. His clinical course progressed rapidly downhill. He eventually developed severe pulmonary disease with diffuse infiltrates and died as a result of his lung disease.

Type C. Severe forms of the disease may start neonatally, but the age of onset is usually after 4–5 years of age. Prolonged neonatal jaundice is always seen. The severe form of the disease manifests with terminal hepatic failure and pulmonary infiltrates in infancy. In its classic form, a slow dementia starts at school age with clumsiness, ataxia, dysarthria, dysphagia, and extrapyramidal signs such as dystonia, drooling, and seizures. Mild hepatosplenomegaly is usually first noticed at school age. Death occurs by puberty. The pathognomonic sign of the disease is vertical supranuclear ophthalmoplegia. Defective intracellular trafficking of exogenous cholesterol is shown by cholesterol accumulation in perinuclear lysosomes by a fluorescent stain, filipin.

Alerting Signs. Niemann–Pick disease type C shows progressive encephalopathy with splenomegaly and vertical supranuclear ophthalmoplegia.

Gaucher Disease

Type I. The age of onset varies between infancy and 33 years. Death occurs early in severe variants. Life span

is normal in late-onset variants. Early hepatosplenomegaly is observed, and the spleen is usually bigger than the liver. The skeletal involvement occurs early (Fig. 39.12). In a severe variant, hepatosplenomegaly may fill the abdomen. The abdominal protuberance is more marked than in Niemann–Pick disease type A or B. The early sign of bleeding is due to thrombocytopenia, which is not present in Niemann–Pick disease type A or B. The bone storage is debilitating, leading to an "Erlenmeyer flask" appearance of the distal femur, fractures in long bones and vertebrae, and painful "bone crisis." In severe cases, patient will be crippled due to multiple fractures. Lung infiltrates are common among Saudi and Middle Eastern patients. There is no CNS involvement, and the intelligence is normal.

Type II. The more severe form may occur at birth with hydrops fetalis and ichthyosis. The age of onset is usually early infancy, with death by 2 years of life. Extensive hepatosplenomegaly, severe early neurologic involvement with oculomotor apraxia, and the Gaucher triad of bilateral fixed strabismus, opisthotonus, and trismus are seen (Fig. 39.13).

Type III. The severity of this phenotype is between those of types I and II, with early hepatosplenomegaly that occurs at a median age of 1 year, and late neurologic manifestations that are seen at a median age of 2 years.

Alerting Signs. Type I Gaucher disease shows hepatosplenomegaly (spleen bigger), thrombocytopenia, normal ALT and AST, severe lytic bone changes, and normal neurologic findings. *Type II* Gaucher disease manifests as in type I but with severe CNS involvement (*Gaucher triad*: trismus, opisthotonus, strabismus); *type III* is milder than type II and more severe than type I.

Case History (*Gaucher Disease Type II*). A 3.5-year-old girl, at the time of initial encounter, had a chief complaint of abdominal distention, first noticed at the age of 12 months, which progressed to a size over the years that prevented her from achieving a sitting position. She had one chest infection before her first visit. Early developmental milestones were normal; she had developed good speech skills. The trismus and fixed strabismus were first noticed at 24 months. She was the second child born to a first cousin marriage, with one normal sibling. At the time of admission her height, weight, and head circumference corresponded to median ages of 18, 24, and 6 months, respectively, at the age of 42 months. The abdominal girth was 60 cm. She had marked rigidity of her neck, trismus, and strabismus (Gaucher triad). The liver span was 20 cm and the spleen span was 17 cm. She had severe anemia (61 g/L) and marked thrombocytopenia ($< 25{,}000/mm^3$) requiring repeated platelet transfusions. The β-glucosidase level in her cultured fibroblasts was 5% of normal value, with normal sphingomyelinase and other lysosomal enzymes. A bone marrow biopsy indicated the presence of Gaucher cells. A skeletal survey indicated collapsed L-4 vertebra and multiple cyst-like structures

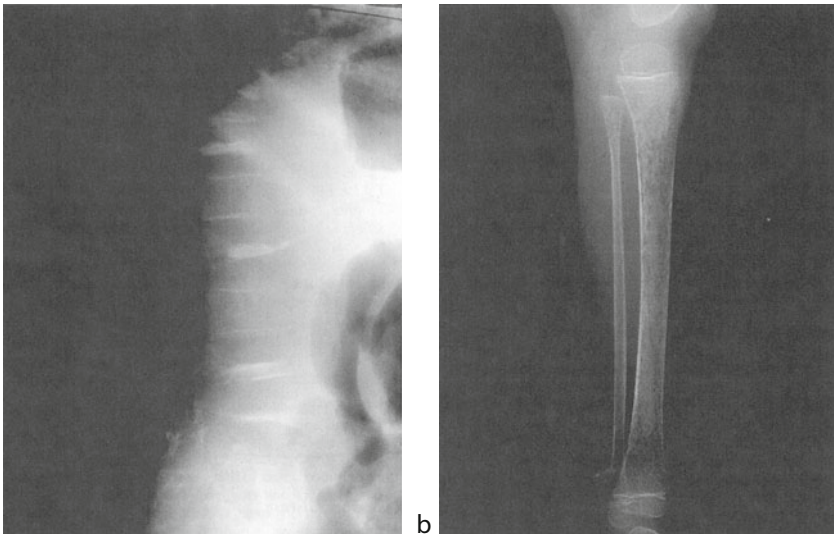

Figure 39.12
Skeletal changes in Gaucher disease. (a) Wasted vertebral body fractures and kyphosis in a patient with type I Gaucher disease. (b) "Moth-eaten" appearance of tibia in a patient with type II disease

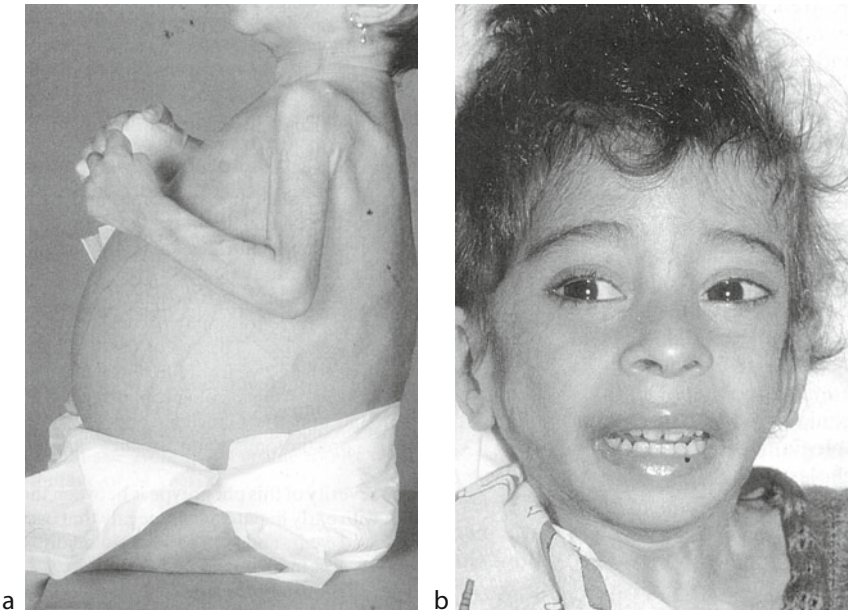

Figure 39.13
Gaucher disease type II. (a) The lateral view of a distended abdomen due to impressive hepatosplenomegaly. (b) Trismus in a patient with Gaucher triad

scattered through the long bones. Chest x-ray did not indicate lung infiltrates. There was mild white matter disease on CT of the brain with atrophy, and the EEG showed mildly slowed background activity. She underwent splenectomy, and the weight of the spleen removed was 2.5 kg (30% of her body weight). There was no HLA-matched donor in the family, and, given the CNS involvement, no effort was made to secure a BMT; the patient was discharged home and died later.

Galactosylceramide Lipidosis (Globoid Cell Leukodystrophy; Krabbe Disease)

The age of onset is usually 2–3 months in the early infantile and 6 months to 3 years in the late infantile form. Rare juvenile–adult types can start at 3–35 years of age. The infantile variety is characterized by extreme irritability (an unsoothable infant), with severe spasticity, blindness, optic atrophy, and rapidly progressive encephalopathy with dementia. Severe central white matter disease is seen in neuroradiologic studies. Pathognomonic findings are peripheral neuropathy, diminished to absent deep tendon reflexes in the presence of spasticity, prolonged nerve conduction time, and increased CSF protein. Death occurs by 1–3 years of age. The juvenile–adult forms start with psychomotor deterioration, ataxia, loss of vision, and pyramidal tract signs but occur usually without peripheral neuropathy.

Alerting Signs. Galactosylceramide lipidosis is marked by extreme irritability, spasticity with absent deep tendon reflexes due to peripheral neuropathy, and increased CSF protein.

Case History (*Krabbe Disease, Late Infantile Form*). A child was first encountered at 7 months of age with the chief complaint of developmental regression and extreme irritability. His early development was normal until 5–6 months of age, when he first started to show irritability, then losing the ability to smile at his mother and to sit with support. The growth parameters were normal. He was an unsoothable infant, whining continuously. He had midline hypotonia with hypertonic extremities. Deep tendon reflexes were normal. Primitive bipedal responses were absent. The eyegrounds examination indicated pale optic discs. A peripheral nerve conduction study indicated prolonged nerve conduction in the median and ulnar nerves and absent potential in the sural nerves bilaterally, with decreased amplitude in several motor nerves (i.e., evidence of peripheral neuropathy). The BAEP and ERG were normal; however, VEP were absent. MRI of the brain indicated areas of increased signal intensity in the centrum ovale, within the dentate nucleus of the cerebellum, and in the anterior limb of the internal and the posterior limb of the external capsule, indicating widespread white matter

disease. Brain positron emission tomography indicated markedly decreased glucose uptake widespread in the cortex, absent uptake in the caudate, and normal uptake in the thalamus and putamina bilaterally. The CSF protein was elevated, at 900 mg/L (normal: <450 mg/L). Lysosomal enzyme tests for arylsulfatase A and B, hexosaminidase, and β-mannosidase were normal, but the galactosylceramide-β-galactosidase activity was 3% of normal, confirming Krabbe disease. The further clinical course was that of a progressive encephalopathy at 2 years of age, with severe spastic quadriplegia developing and deep tendon reflexes disappearing. He had to be placed on gavage feeding since he could not swallow.

Metachromatic Leukodystrophy

The age of onset is different from that of classic forms of Krabbe disease, and the earliest age is about 2–3 years. The juvenile-onset (4–12 years) and adult-onset (mid-teens to seventh decade) forms are rare. The initial symptom is mental regression with gait disturbance and incontinence in a previously toilet-trained infant. This is followed by dementia, blindness, optic atrophy, quadriplegia, hypotonia, loss of verbal skills, and evidence of peripheral neuropathy with diminished deep tendon reflexes and prolonged nerve conduction time. The CSF protein is increased. Severe central white matter disease is seen in neuroradiologic studies. Eventually decerebrate posture with pseudobulbar signs and vegetative state emerge, leading to death by 5–8 years of age.

Alerting Signs. Metachromatic leukodystrophy shows progressive pyramidal tract disease with loss of milestones at 2–3 years of age, hypotonia, diminished deep tendon reflexes due to peripheral neuropathy, and increased CSF protein.

Multiple Sulfatase Deficiency (Austin Disease)

This disease combines features of MPS, particularly those of Maroteaux–Lamy syndrome and Morquio syndrome, with metachromatic leukodystrophy and features of deficiency of cholesterol sulfate sulfatase (i.e., ichthyosis). The age of onset of the disease is 1–2 years in the Middle East and Saudi Arabia. Psychomotor retardation in a shy child and some degree of hirsutism might initially suggest a Sanfilippo syndrome. Short neck and trunk, with odontoid hypoplasia and compression of the cervical cord, appear by 2–3 years of age. Hepatosplenomegaly, failure of growth, pyramidal tract signs, and progressive encephalopathy lead to death by 4–5 years of age. The IQ remains normal or near normal until late in the progression of the disease. In Japan and the United States, features of metachromatic leukodystrophy predominate, with lesser features of MPS. Pathognomonic features of the severe, early form of the disease are a poorly developed orbital cavity leading to proptosis in almost all patients and subtle to marked ichthyosis, which make rapid clinical diagnosis possible (Fig. 39.14).

Alerting Signs. Multiple sulfatase deficiency shows combined skeletal features of Morquio syndrome, hirsutism of Sanfilippo syndrome, and coarse features of Maroteaux–Lamy syndrome, with metachromatic leukodystrophy, ichthyosis, and proptosis.

Case History. A 2-year-old girl was referred for mildly coarse features and proptosis. She was slow in acquiring milestones, sitting at 1 year and able to take a few steps with help at 2 years of age. She had only two words, and had just started to transfer objects from one hand to the other and to hold her bottle. Her features became coarse at 1 year, and proptosis was observed shortly before referral. The parents were first cousins and were aware of the nature of her disease, since they previously had had a son who was diagnosed to have multiple sulfatase deficiency. They had refused clinical follow-up for him. He developed spastic quadriplegia after a sudden movement of the head, due to cervical cord compression by the dislocated C-1 vertebra, at 3 years of age. As a result, he was severely disabled and lived only another 3 years, to die at 6 years of age at home. The parents knew that this was a lethal disease, but wanted to prevent a cervical dislocation in this girl. On physical examination, her height was below the fifth percentile but her weight and head circumference were normal. The skin showed mild ichthyosis on the lower limbs. Her facial features were coarse and she had marked proptosis. Her nasal bridge was depressed and wide; there was some hirsutism on the forehead; and she had thick lips, broad, short, and stubby fingers, thoracolumbar kyphosis, and an umbilical hernia. Her corneas were cloudy; there was no cherry-red macula. There was a grade 3 systolic murmur over the precordium. The liver and spleen both were 4 cm below the costal margin. Neurologic examination revealed no pyramidal tract signs. An echocardiogram revealed a thickened mitral valve and mitral, tricuspid, and aortic valvular regurgitation with dilated left atrium and ventricle. The skeletal survey showed severe dysostosis multiplex. MRI of the brain showed mild white matter disease in the centrum ovale, and MRI of the neck showed instability of cervical vertebrae 1 and 2. The EEG was normal; however, VEP and BAEP indicated delayed responses. The following sulfatase

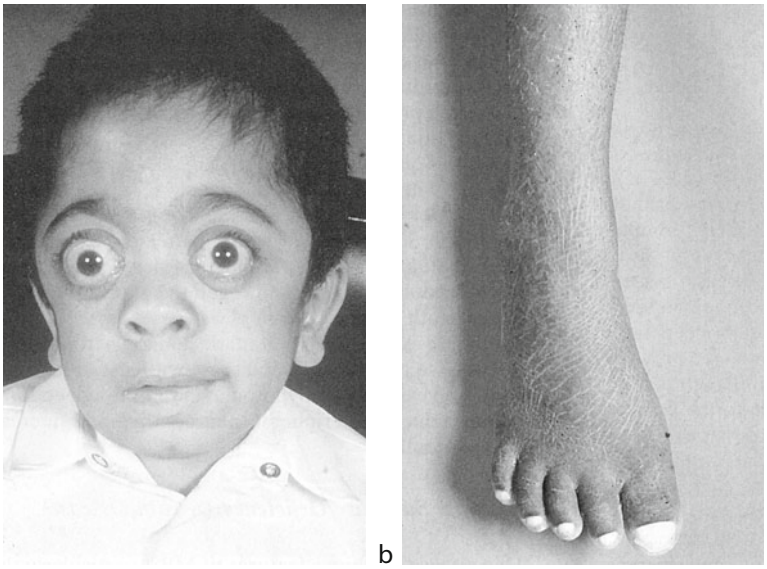

Figure 39.14
Multiple sulfatase deficiency. (a) The pathognomonic proptosis of the disease due to a shallow orbital cavity. (b) Ichthyosis on the leg

activities were below 10–15% in her cultured fibroblasts: arylsulfatase A and B, heparan sulfatase, keratan sulfatase, and steroid sulfate sulfatase, confirming the diagnosis of multiple sulfatase deficiency. She was operated on by a neurosurgeon, who immobilized her cervical vertebrae. There was no HLA-matched donor in the family. At present she is 5 years old, and the changes in her physical features and proptosis have become more pronounced. The mother subsequently gave birth to a normal child.

Fabry Disease

In the hemizygous male, the disease is of adult-age onset; the earliest age observed is late childhood or adolescence. The initial symptom is periodic severe excruciating pain in the extremities (acroparesthesia), hipohidrosis, angiokeratoma, and characteristic eye findings. These are whorl-like, cream-colored inferior corneal opacities; propeller-like inferior lenticular opacities; or spoke-like deposits of fine granular material in the posterior lens capsule. Later, during adult age, cardiac, renal, and cerebral disease due to vascular storage of globotriaosylceramide results in cardiac and brain ischemia, infarctions, and renal failure.

Alerting Signs. Fabry disease manifests with excruciating pain, corneal opacities, angiokeratomas, hipohidrosis, and, later, renal failure.

Schindler Disease (Neuroaxonal Dystrophy Types I and II)

Type 1 is a childhood and type 2 is an adult disease. Type 1 remains normal until 9–12 months of age. The early sign is developmental delay followed by progressive encephalopathy during the second year of life. This is followed by myoclonus, spasticity, hyperreflexia, reduced muscle mass, profound mental retardation, blindness, optic atrophy, and vegetative state with decorticate posturing.

Alerting Signs. Schindler disease is marked by nonspecific progressive encephalopathy with spinal cord disease and myoclonus.

Gangliosidoses

There is accumulation of various classes of gangliosides in this group of diseases. This accumulation occurs mainly in the CNS and, in severe forms, in other organs as well.

G_{M1} Gangliosidosis (Infantile, Late Infantile or Cerebral, and Chronic Late Onset)

Infantile Type. The infantile type presents with features of MPS at birth. Rapid dementia with pyramidal tract signs, hepatosplenomegaly, generalized dysostosis multiplex, and cherry-red macula with vegetative state are seen, and

occasionally dense thalami are observed in CT of the brain. Death occurs by 2 years of age.

Late Infantile Type (*Cerebral Type*). The age of onset is between 7 months and 3 years, with myoclonic or generalized tonic-clonic seizures and developmental regression developing into spastic quadriplegia, blindness, and optic atrophy. Cherry-red macula, visceromegaly, dysmorphic features of MPS, and dysostosis multiplex are absent.

Chronic Late Onset. The age of onset is 3–30 years, with mild symptoms. The disease is usually not suspected and remains undiagnosed before early adult age. The initial signs are gait and speech disturbances, usually with extrapyramidal signs. The only skeletal manifestation is flattening of vertebral bodies.

Alerting Signs. Infantile G_{M1} gangliosidosis shows features of MPS at birth and cherry-red macula; the *cerebral* type shows nonspecific progressive encephalopathy and no cherry-red macula; and the *chronic late-onset* type shows gait and speech disturbances.

Case History (*G_{M1} Gangliosidosis, Early Infantile Onset*). A 4-month-old boy was referred for the evaluation of coarse features, macrosomia, hepatosplenomegaly, and dementia. His coarse features and hepatosplenomegaly were noticed at birth. He also had nonimmune hydrops fetalis, albeit mild. He achieved no milestones. The parents were first-degree cousins and had two previous babies who died of a similar disease at 1–1.5 years of age. At the time of admission his height and weight were at the 90th percentile. The fontanel was 3 × 3 cm. He had mild macroglossia, some gingival hypertrophy, mildly coarse facial features, thickened fingers and toes, large umbilical and inguinal hernias, and hepatosplenomegaly, with liver span of 8 cm and spleen span of 7 cm. He had an increased amount of subcutaneous tissue. His eyegrounds examination revealed a cherry-red macula. Initially, the corneas were clear. He had severe central hypotonia with mild spasticity of the extremities; the deep tendon reflexes were mildly exaggerated. An acoustic myoclonus could be elicited but was not followed by myoclonic seizures. The blood chemistries indicated elevated AST (253 U/L) and ALT (298 U/L) and normal thyroxine and thyroid-stimulating hormone. CT of the brain indicated dense thalami. The EEG revealed disturbed background. The skeletal survey indicated dysostosis multiplex with involvement of vertebral bodies and a "J-shaped" sella turcica. The lysosomal enzymes in his cultured skin fibroblasts indicated normal levels except for β-galactosidase, which was less than 1% of normal. Neuraminidase was 35% of normal and carboxypeptidase Y 40% of normal. The diagnosis of G_{M1} gangliosidosis was reached. In further clinical follow-up, his height and weight deviated from established percentiles at 7 months of age, and he was eventually below the fifth percentile at the age of 15 months. Corneal cloudiness appeared at 1 year of age. He developed a difficult-to-control seizure disorder at 10 months of age. He died at home at 18 months of age.

Galactosialidosis (Infantile and Late Infantile/Juvenile Types)

The more severe form of the disease causes hydrops fetalis.

Infantile Type. The age of onset is birth to 3 months, with features of MPS such as coarse face, hepatosplenomegaly, hernias, cardiac valvular involvement, dysostosis multiplex, vertebral abnormalities, corneal clouding, cherry-red macula, blindness and hearing loss, dementia, and progressive encephalopathy. Occasionally dense thalami are seen in CT of the brain, and abnormal mottled dark pigmentation of the skin may be present (*Fig. 39.15*). Death occurs before 8 months with cardiac and renal failure.

Late Infantile/Juvenile Type. The age of onset is 12–36 months, with similar features as described for the infantile phenotype. The only difference is the benign neurologic course with no eventual MR. Cardiac valvular involvement is more prominent in this type. The life span is normal.

Alerting Signs. Early infantile galactosialidosis is similar to G_{M1} gangliosidosis; in the *late infantile* form, there are less apparent features of MPS and a benign clinical course with normal IQ.

Case History (*Galactosialidosis, Early Infantile Variety*). An 11-month-old boy was referred for abdominal distention, failure to thrive, repeated chest infections, and chronic diarrhea since 1–2 months of age. He never gained any milestones, never smiled, never had visual fixation, and needed nasogastric tube feeding because of his inability to suck since birth. He started to experience seizures at 5 months of age. The parents were first-degree cousins, with ten normal children and two children who died of the same disease at 1 year of age. On examination, his height, weight, and head circumference corresponded to the median ages of 6, 4, and 5 months, respectively, at 11 months. He had coarse features, long eyelashes, and hazy corneas. There was cherry-red macula. The skin showed spots of hyperpigmentation. The liver was 9 cm below the costal margin; the spleen tip was palpable. He had large bilateral hydroceles. Blood examination showed vacuolated lymphocytes that contained granular material. CT of the brain showed brain atrophy. The skeletal survey showed loss of modeling of long bones. Chest x-ray

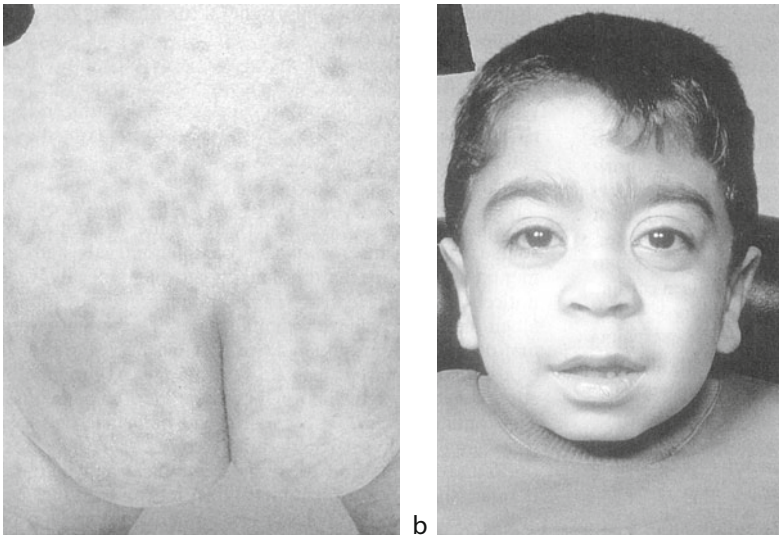

Figure 39.15
Galactosialidosis. (a) Skin marked with spots of pigmentation, a feature that is almost always associated with the severe infantile form of the disease in Saudi Arabia. (b) Mild coarse facial features of a 5-year-old boy with the late infantile form of the disease (*See Color Fig.* 5–15*A*)

indicated patchy lung infiltrates. Cardiac workup showed mild left ventricular hypertrophy with mitral regurgitation. The EEG was abnormal, with poor background activity and multifocal spikes at frontal areas bilaterally. The β-galactosidase, neuraminidase, and carboxypeptidase Y activities were 1%, 7%, and 5% of normal, respectively, in leukocytes and cultured fibroblasts. He was discharged home, where he died several months later.

Case History (*Galactosialidosis, Late Infantile Variety*). An 18-month-old boy was referred for evaluation of his coarse features, hepatosplenomegaly, bilateral inguinal hernia, and repeated chest infections. The parents noticed him to breathe noisily since first week of life. He had to be hospitalized numerous times for chest infections. His development has been relatively normal, sitting at 6 and walking at 16 months of age. He developed adequate verbal and social skills. At the age of 6 months he was found to have hepatosplenomegaly. His urine, sent by referring hospital to metabolic laboratory, indicated normal MPS excretion but increased intensity of oligosaccharides on thin-layer chromatography (TLC). The parents were first cousins with three normal children. The physical examination indicated height at the median of 10 months at 18 months and weight at the 25th and head circumference at the 50th percentiles. He had the coarse features of a patient with MPS, with broad hands and feet. The firm liver edge was 6 cm and the spleen 4 cm below the costal margin. He had macroglossia, kyphosis, bilateral inguinal hernias, and hydrocele. Neurologic examination indicated mildly increased muscle tone and increased reflexes with Babinski sign. The ophthalmologic examination indicated punctate densities in the stroma of the corneas and cherry-red macula. A cardiac workup was normal, with mild left ventricular hypertrophy. The chest x-ray showed patchy lung infiltrates. The skeletal survey indicated a "J-shaped" sella turcica, broadened metacarpals and fingers, broad ribs, and kyphosis. MRI of the brain indicated patchy leukodystrophy in the centrum ovale. The EEG was normal. The psychometric assessment indicated normal verbal and social skills. The lysosomal enzyme determination in serum indicated normal values, ruling out mucolipidosis. The β-galactosidase, neuraminidase, and carboxypeptidase Y activities in cultured fibroblasts were all less than 10% of normal, indicating the disease to be galactosialidosis of the late infantile variety. He was followed up until 5 years of age. His height at 5 years of age corresponded to the median age of 2 years; his weight and head circumference remained normal. At the age of 4 years he developed unusual capillary lesions on the lower part of the abdomen and scrotum. A biopsy revealed them to be angiokeratomas. His last psychometric assessment was borderline normal. Since they dropped out of the clinic, his fate is unknown. Molecular genetic analysis of carboxypeptidase Y revealed an unusual mutation, confirming the clinical and biochemical diagnosis of galactosialidosis.

G_{M2} Gangliosidosis

Infantile Tay–Sachs Disease (Type I) and Sandhoff Disease (Type II)

Both types I and II disease manifest similar symptoms. They differ only in the deficiency of the subunit of hexosaminidase: the α subunit is deficient in Tay–Sachs and the β subunit is deficient in Sandhoff disease. Most patients in the Arab world have Sandhoff disease, while Tay–Sachs is the disease of Ashkenazic Jews. The usual onset is at about 3–5 months with gelastic fits, followed by myoclonus, myoclonic seizures, hyperacusis (acoustic myoclonus), rapidly progressive pyramidal tract signs, early hypotonia and later spasticity, hyperreflexia, blindness, and dementia. They are usually beautiful babies. There is usually no systemic involvement, such as visceromegaly (can be observed rarely in type II) or dysostosis multiplex. The pathognomonic features of both type I and II diseases are the cherry-red macula in the presence of acoustic myoclonus. As a rule, dense thalami are observed in CT of the brain (*Fig. 39.16*). At later stages, macrocephaly due to increased CNS storage, vegetative state, and inability to swallow occur. Death usually occurs by 2–4 years of age and is due to aspiration pneumonia and inanition due to inability to feed.

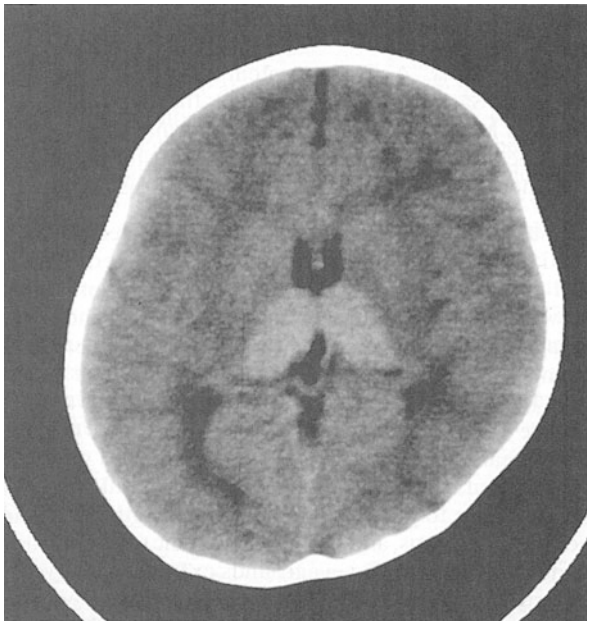

Figure 39.16
G_{M2} gangliosidosis. Dense thalami observed on CT of the brain are characteristic of gangliosidoses and early infantile neuronal ceroid lipofuscinosis

Alerting Signs. In Tay–Sachs/Sandhoff disease, a beautiful baby manifests gelastic fits, acoustic myoclonus, pyramidal tract signs, cherry-red macula, and late macrocephaly.

Case History (*Sandhoff Disease*). A 10-month-old boy was referred for myoclonic seizures and blindness after an ophthalmologic examination in another hospital had shown the presence of cherry-red macula. According to the parents, he was a slow infant from the beginning, never smiled, never reacted to maternal cues, never vocalized, and never could sit with support. They noticed the "acoustic startle" at the age of 4 months; he developed myoclonic seizures at 6 months of age. He began to have difficulty in swallowing at 9 months of age, and, by the time of referral, he was totally demented. The parents were first cousins who previously had had three children all of whom had the same disease and died; one of them was diagnosed to have Sandhoff disease. The unfortunate parents had no normal children and were aware of the grave prognosis of his disease. The physical examination indicated a beautiful baby boy lying motionless, but showing exaggerated startle upon acoustic stimuli; he also had action-induced myoclonus. His height and weight were at the fifth percentile, but his head circumference was at the 95th percentile. The anterior fontanel was open and measured 2 × 3 cm. He had searching nystagmus. The eyegrounds examination showed a cherry-red macula. The liver was enlarged 3 cm below the right costal margin; there was no splenomegaly. He had spastic quadriplegia with greatly increased deep tendon reflexes. CT of the brain revealed the characteristic dense thalami bilaterally. The hexosaminidase A and B activities in both leukocytes and cultured fibroblasts revealed both activities to be absent. Other lysosomal enzyme activities were normal. The diagnosis of Sandhoff disease was thus confirmed. He lived two more years, during which period he had to be given high-caloric nutrients by gavage feeding. He died at home of aspiration pneumonia. A chorionic villus biopsy sampling from the mother at the next pregnancy indicated another fetus with Sandhoff disease.

Activator Protein Deficiency

The presentation is similar to Tay–Sachs or Sandhoff disease, except the onset is somewhat delayed until 1–1.5 years of age. The diagnosis is reached by finding normal hexosaminidase activity when tested using an artificial substrate in a patient with typical symptoms of G_{M2} gangliosidosis, such as cherry-red macula, acoustic myoclonus, and dense thalami in CT of the brain. However, the hexosaminidase activity is absent when tested with the

natural substrate since this requires the activator protein for its hydrolysis.

Alerting Signs. Activator protein deficiency is similar to Tay–Sachs/Sandhoff disease, except the age of onset is later and hexosaminidase activity is normal with artificial substrate, while cherry-red macula, acoustic myoclonus, and other typical signs of a G_{M2} gangliosidosis are present.

Case History. An 18-month-old girl was referred for dementia. The history indicated she had developed normally until 1 year of age, at which time she had several words and was walking. Suddenly she stopped walking and started to have myoclonic jerks. The family history indicated the parents to be first-degree cousins; they had one normal child. Later on, a second sister was delivered and was found to have the same disease; she also developed normally until 1 year of age and then became demented gradually. The physical examination revealed a beautiful baby with little response to painful stimuli. She had an easily elicited acoustic myoclonus, and showed myoclonic seizures following acoustic startle. The eyegrounds examination revealed a cherry-red macula. There was no visceromegaly or dysostosis multiplex. Both the muscle tone and reflexes were increased. CT of the brain indicated bilateral thalamic densities. The clinical diagnosis was Sandhoff or Tay–Sachs disease. However, the enzyme assay for hexosaminidase activity as tested with artificial substrate was found normal on numerous occasions. As a result, hexosaminidase activity was assayed with labeled G_{M2} ganglioside and was found to be less than 1% of normal. Later on, molecular genetic analysis performed elsewhere confirmed the diagnosis by detecting the mutation. She lived until 5 years of age.

Juvenile Tay–Sachs Disease (G_{M2} Gangliosidosis Type III)

The age of onset is usually by 4–5 years. The initial symptoms of motor clumsiness, dystonia, choreoathetosis, and ataxia are followed by dementia. The clinical presentation resembles Niemann–Pick disease type C, except there is neither vertical gaze paralysis nor splenomegaly. There is no cherry-red macula. In some variants the predominant presentation is that of a spinocerebellar degeneration with ataxia, dysarthria, spasticity, and normal or increased deep tendon reflexes. The intelligence is preserved until late in the disease. Another subgroup manifests with a motor neuron disease as progressive muscle wasting and fasciculations resembling late-onset spinal muscular atrophy (Kugelberg–Wielander disease). The EMG shows chronic active denervation-reinnervation with fibrillation potentials, suggesting an anterior horn disease with normal nerve conduction. Eventually dementia and death occur late in the 20s.

Alerting Signs. Juvenile Tay–Sachs disease manifests with nonspecific progressive encephalopathy with symptoms of pyramidal, cerebellar, or anterior horn disease of the spinal cord, usually mistaken for Kugelberg–Wielander disease. Absence of vertical gaze paralysis and splenomegaly differentiate it from Niemann–Pick disease type C.

Case History. A 6-year-old boy presented with the chief complaint of loss of milestones (i.e., progressive encephalopathy). He was normal until 3 years of age, at which time he first lost his ability to walk, tripping and falling frequently. Then he lost comprehension of even simple commands, his speech, and eventually his vision. There was no precipitating illness. The parents were first-degree cousins and there was one normal sibling. On examination he showed pseudobulbar affect with bouts of crying and laughter for no reason or out of proportion to stimuli. There were no neurocutaneous stigmata. There was no cutaneous or buccal pigmentation suggesting Addison disease. There was no visceromegaly. Cranial nerve examination indicated bilateral optic atrophy and searching nystagmus. There was spasticity particularly of the lower extremities, with exaggerated deep tendon reflexes, ankle clonus, and Babinski sign. A presumptive diagnosis of X-linked adrenoleukodystrophy (X-ALD) was made, since MRI of the brain showed periventricular white matter disease, particularly prominent around the occipital horns. The CT scan did not show thalamic density. The abdominal ultrasound showed a nonhomogeneous appearance of the right lobe of the liver; otherwise, spleen and liver size were normal. AVEP showed prolonged P100 latency with atypical shape and characteristics. The plasma very-long-chain fatty acids and phytanic acid were found to be normal, ruling out X-ALD or a peroxisomal disease. A lysosomal battery in leukocytes revealed normal enzymes except for hexosaminidase A, which was not detectable, indicating the disease to be juvenile Tay–Sachs. The patient was lost to follow-up.

Lysosomal Transport Disorders

Cystinosis

The patient with cystinosis is normal at birth, developing renal Fanconi syndrome by 6–12 months of age. Growth fails, and severe dwarfism and hypophosphatemic rickets appear. Photophobia due to crystalline cystine storage in the corneas, hipohidrosis, and hypothyroidism are seen. The disease progresses to renal failure, causing death by 6–12 years of age.

Alerting Signs. Cystinosis, a common cause of renal Fanconi syndrome, presents as a blond and dwarfed baby with rickets and signs of corneal irritation (◉ *Fig. 39.17*).

Case History. A girl was first seen at 2 years of age for polyuria, polydipsia, poor growth, and weight gain. These complaints were noticed during early infancy, and the parents were particularly worried about her failure to gain height. The parents were first cousins and they had a normal child. The physical examination revealed a child whose height and weight were at the median ages of 10 and 16 months, respectively, at 24 months of age. Her head circumference was at the fifth percentile. She had very fair features, with blond hair, eyebrows, and eyelashes, while the other child in the family and the parents had dark complexions. Her wrists were enlarged and she had rachitic rosary. The x-ray of the wrist confirmed the rickets. Slitlamp examination of the cornea revealed extensive deposition of a crystalline material. The laboratory workup indicated proximal renal tubular disease and renal Fanconi syndrome, with renal tubular acidosis, proteinuria, phosphaturia, glucosuria, hypoisosthenuria, and generalized aminoaciduria. The amino acid pattern in blood was normal. Her hemoglobin was 85 g/L. A skin biopsy indicated the presence of many small, elongated crystals under light microscope by polarized light. The leukocyte cystine content was five times higher than normal. A diagnosis of cystinosis was reached. The patient was placed on oral supplement of phosphate, sodium bicarbonate, potassium chloride, and indomethacin, and treatment with phosphocysteamine was initiated. She has now been followed up for 5 years. Her growth in height and weight improved, with slow catch-up. She was given human growth hormone treatment to augment the growth. She was also started on treatment with erythropoietin and her hemoglobin values improved. The corneal crystals became less during this period. At the age of 7 years, abdominal ultrasound indicates both kidneys to be borderline small without any evidence of calculus or nephrocalcinosis.

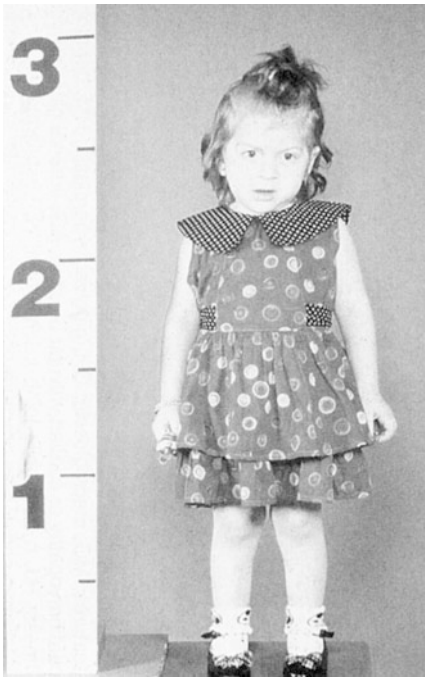

Figure 39.17
Cystinosis. Obvious fair features and short stature in a 6-year-old Arab girl

Sialic Acid Storage Disease

Infantile Sialic Acid Storage Disease

This disease presents at birth with severe FTT, severe developmental delay, coarse facial appearance, hepatosplenomegaly, and dysostosis multiplex; death usually occurs by 1 year of age. The urinary excretion of sialic acid is increased 2- to 200-fold.

Salla Disease

Salla disease starts at 6–9 months of age with axial hypotonia and horizontal nystagmus. After 1 year of age, ataxia, spasticity in the lower limbs with hyperreflexia, seizures, delayed speech, general developmental delay, and moderate to severe MR occur. Death is by 4–7 years of age. Sialic acid excretion in the urine is increased 10- to 100-fold.

Alerting Signs. The *infantile* form of sialic acid storage disease is marked by features of MPS with severe FTT and developmental delay; *Salla disease* is marked by spastic diplegia with ataxia, developmental delay, and MR. Both forms are associated with increased sialic acid excretion in the urine.

Chediak–Higashi Disease

This disease has been reviewed in detail elsewhere; only features pertinent to a lysosomal storage disease are summarized here. It is a disease of childhood onset, with susceptibility to bacterial infections, partial albinism,

photophobia, nystagmus, metallic silver-gray tint in the light brown hair, reduced and unevenly pigmented irises, giant peroxidase-positive lysosomal granules in the peripheral blood granulocytes, and bleeding (abnormal platelet aggregation). Death occurs by the accelerated phase of a lymphoma-like picture.

Alerting Signs. Chediak–Higashi disease is marked by frequent infections, albinism, abnormal distribution of pigment in the irises, and giant granules in leukocytes.

Differential Diagnosis

As this review indicates, a large number of systemic, visceral, skeletal, joint, skin, eye, ENT, and CNS findings are almost always associated with the lysosomal storage diseases. The clinical findings are not always pathognomonic for any particular disease. However, the alerting signs will raise a strong suspicion through the spectrum of clinical symptoms emphasized. The differential diagnosis should include consideration of many symptoms. In order to facilitate a bedside diagnosis, two diagnostic tables are presented. In *Table 39.2*, the prominent systemic, visceral, skeletal, and skin symptoms associated with major lysosomal storage diseases are tabulated. In *Table 39.3*, the prominent neurologic, eye, and ENT findings of the same diseases are presented.

Some specific features of lysosomal storage diseases deserve emphasis. For example, severe forms of these diseases present with hydrops fetalis at birth (*Table 39.4*). Hydrops fetalis may be caused by so many different etiologies that a neonatologist might neglect considering the presence of lysosomal storage disease, although such disorders are encountered rather frequently in consanguineous families. A detailed workup, including bone marrow biopsy to demonstrate storage cells, study of lymphocytes for vacuolization, enzyme measurements, and skeletal survey, should always be obtained in a neonate with hydrops fetalis, particularly when visceromegaly, coarse facial appearance, joint contractures, ichthyosis, and skeletal abnormalities are observed (*Fig. 39.18*).

A most important part of physical examination is the eyegrounds. So many times, in a baby with rapidly progressive encephalopathy, early dementia, and myoclonus, a rapid diagnosis of gangliosidosis may be reached simply by detecting a cherry-red macula. A number of lysosomal storage diseases lead to the accumulation of a storage substance within the ganglion cells around the retinal fovea, an area particularly rich in ganglion cells, while the fovea is poor in these cells. This accumulation causes a white halo around the fovea, the so-called cherry-red macula. This is most prominent in G_{M2} gangliosidosis (*Fig. 39.19a*) and can be seen in somewhat different form in galactosialidosis (*Fig. 39.19b*), while in Niemann–Pick disease the storage may just appear as a grayish and interrupted halo (*Fig. 39.19c*). Not only gangliosidoses, but also a variety of other lysosomal storage diseases, cause cherry-red macula; a comprehensive list is presented in *Table 39.5*.

Some lysosomal storage diseases primarily manifest as a progressive encephalopathy, with no or minimal evidence of peripheral tissue involvement. This may confuse the pediatrician accustomed to thinking in terms of visceromegaly, dysostosis, and skin findings in association with a lysosomal storage disease. A list of lysosomal storage diseases that manifest mainly, or only, with CNS symptomatology is presented in *Table 39.6*.

Since major forms of lysosomal storage diseases cause progressive encephalopathy and/or eventual MR, it is often forgotten that a number of them do not lead to MR, even in the presence of florid systemic symptomatology. A list of diseases that do not cause significant MR is presented in *Table 39.7*.

The aforementioned considerations will usually suffice to reach a presumptive diagnosis. Nevertheless, in all instances a definitive final diagnosis should be reached by specific enzyme or cellular morphologic studies.

Pathogenesis of Lysosomal Storage Diseases

It is important to know the pathophysiology of lysosomal storage diseases in order to understand their phenotypic manifestations and to order appropriate laboratory tests for diagnosis. For example, heparan sulfate is an integral part of plasma membranes, particularly in the CNS, and when heparan sulfate-catabolizing activities are absent (i.e., Sanfilippo syndrome types A through D), the phenotypic manifestation involves mostly the CNS. Iduronate sulfate is not present in significant quantities in the cornea; therefore, when iduronate sulfatase is deficient (i.e., Hunter syndrome), the cornea remains clear. Keratan sulfate is an important component of the skeletal system, joints, and ligaments, and, when keratan sulfatase is deficient (i.e., Morquio syndrome), the major phenotypic expression is in the skeleton and joints. Arylsulfatase A and galactosylceramide galactosidase are involved in the catabolism of components of myelin; in their absence (i.e., metachromatic leukodystrophy and Krabbe disease, respectively), white matter disease in the

Table 39.2

Prominent systemic, visceral, skeletal, and skin findings in lysosomal storage diseases[a]

Disease	AB	FTT	BI	CF	MG/GH	HM	SM	RD	AD	PD	CD	AG	DM	VC	JC	HJ	I	H	PA	SN	AK
Hurler syndrome				++	++	+	+		++		+		++	++	++			±			
Hurler–Scheie syndrome				++		+	+		+		+		++	+	++						
Scheie syndrome				±					+		+				+						
Hunter syndrome				++		±	±				+		+		+						
Sanfilippo syndromes						±							±		+					++	
Morquio syndrome						±							++	++		++		++			
Maroteaux–Lamy syndrome					++	+	+		+				++	++	++						
Glycogen storage disease type II (infantile)					+	+	+				++							±			
Glycogen storage disease type II (juvenile)																					
Wolman disease		++				++					+	++								++	
Farber disease						+			++	+	++										
Neuronal ceroid lipofuscinosis				+																	
I-cell disease	+				MG/GH	+	+				++		++	+	+						
Pseudo-Hurler disease				±									±		++						
α-Mannosidosis			++	++	+	+	+						+								
Fucosidosis			+	++		+					++		++	++							+
Sialidosis type I				++											+						
Sialidosis type II	+			++		++	++						++	+							
Aspartylglucosaminuria		+	++	+		±							+		+						
Niemann–Pick type A		++				++	++														
Niemann–Pick type B		+	++		++	++				++											
Niemann–Pick type C						+	++			+											
Gaucher type I[b]						++	++			+				++							
Gaucher type II[b]	May					++	++			+				++							
Krabbe disease																					
Metachromatic leukodystrophy																	+ +				
Multiple sulfatase deficiency	May			++		++	++				+			+	+						
Fabry disease								++			+		++								+
G_{M1} gangliosidosis (infantile variety)	+			++	+	+	+							+	+						
G_{M1} gangliosidosis (cerebral type)													++								
Galactosialidosis (infantile variety)	May			++		++	+						++								
Galactosialidosis (juvenile variety)				++		++	+				+		+	+	+						

Table 39.2 (Continued)

Disease	AB	FTT	BI	CF	MG/GH	HM	SM	RD	AD	PD	CD	AG	DM	VC	JC	HJ	I	H	PA	SN	AK
G_{M2} gangliosidosis, type I, II, III, AB						±[c]	±[c]														
Cystinosis								++					++					+			
Sialic acid storage disease (infantile type)	May			++		++	++														
Chediak–Higashi disease			++															++			

AB appears at birth, *FTT* failure to thrive, *BI* frequent bacterial infections, *CF* coarse face features, *MG* macroglossia, *GH* gingival hyperplasia, *HM* hepatomegaly, *SM* splenomegaly, *RD* renal disease, *AD* obstructive airway disease, *PD* pulmonary infiltrates with lung disease, *CD* cardiomyopathy or cardiac valvular disease, *AG* adrenal gland calcification, *DM* dysostosis multiplex, *VC* external and radiologic involvement of vertebral column, *JC* joint contractures and stiffness, *HJ* hypermobile joint, *I* ichthyosis, *H* hirsutism, *PA* abnormalities of pigmentation, such as hypopigmentation, pigment abnormalities in iris, or blotchy skin hyperpigmentation, *SN* subcutaneous nodules on pressure points or on joints, *AK* angiokeratoma

[a] ++, Severe; ++, Severe; +, present; ±, at times present

[b] The skeletal involvement in Gaucher diseases is lytic lesions in long bones (Erienmeyer flask appearance) and vertebrae

[c] May be present in Sandhoff disease

CNS and peripheral nerves emerges. When enzymes are involved in the breakdown of cellular components that are particularly rich in ganglion cells, cherry-red macula is seen (e.g., gangliosidoses, sialidoses, sphingomyelinase deficiency).

A lysosomal disease might be due to the deficiency of a single protein; most lysosomal diseases fall in this category. In another group of lysosomal diseases, the defect is in the processing of the proenzyme of the lysosomal activity in endoplasmic reticulum (ER). All lysosomal enzymes are synthesized on ER-bound ribosomes and all have a signaling sequence that enables them to dock onto a transport protein that carries them into the lumen of the ER. There, polymannose-containing oligosaccharides are attached. Then these oligosaccharides are trimmed to size back in the ER, and the proenzyme is transferred to the Golgi apparatus, where the mannose residues are phosphorylated into mannose 6-phosphate. The presence of mannose 6-phosphate is a prerequisite for the entry of all lysosomal enzymes into the lysosomes. The phosphorylation of the mannose residue is achieved by a specific phosphotransferase. The deficiency of this enzyme is responsible for mucolipidoses II and III. Although the lysosomal enzyme is now ready to enter the lysosomes, it must first travel across the cytosol. During this process a protective protein is needed, for example, for the cytosolic crossing of neuraminidase and β-galactosidase. When this protective protein is missing, both of these enzymes remain in the cytosol and are destroyed, leading to the combined deficiency of neuraminidase and galactosidase (i.e., galactosialidosis). In other instances, the active center of the lysosomal enzyme must be modified in order to create a functional protein, for example, all sulfatases share a common structure at their active center, and, when the enzyme responsible for the modification of their active center is lacking, multiple deficiencies of sulfatases occur (i.e., Austin disease).

Most enzymes of glycoprotein degradation are exoglycosidases, that is, they break down the mucopolysaccharide from the terminal end, removing one modified sugar residue at a time. For example, in the degradation of heparan sulfate, a key component of plasma membranes in neurons, the important first step is the removal of an N-terminal sulfate residue from heparan sulfate by an N-terminal heparan sulfatase. It is only after this step that the remainder of the glycoside residues in the molecule can be hydrolyzed sequentially. The more severe form of heparan sulfate-degrading diseases (i.e., Sanfilippo syndrome A) is due to the deficiency of this initial activity, since the sequential hydrolysis of heparan sulfate cannot be initiated. At times an inconsequential alternate pathway resumes importance due to a deficient enzyme activity. For example, in Krabbe disease a specific galactosidase, galactosylceramide galactosidase, is missing. Psychosine/sphingosine-galactose is a minor metabolite but requires galactosylceramide galactosidase for its breakdown. In the absence of this enzyme, psychosine accumulates in the oligodendroglia and, since it is extremely neurotoxic, it destroys the oligodendroglia, leading to the formation of "globoid cells."

This brief review indicates participation of multiple biochemical mechanisms in the pathogenesis of

Table 39.3

Prominent neurologic, eye, and ENT involvement in lysosomal storage diseases[a]

Disease	MR	HA	IN	DM	PT	CC	PN/AH	MP	SZ	MY	CI	EX	CL	LO	CM	RP	OA	VD	OP	DF	HV
Hurler syndrome	++			++									++							++	
Hurler–Scheie syndrome						++							++								
Scheie syndrome						+							++								
Hunter syndrome	++	++		+																	
Sanfilippo syndromes	++	++	+ +	++					+												
Morquio syndrome													±								
Maroteaux–Lamy syndrome													++								
Glycogen storage disease type II (infantile)								++													
Glycogen storage disease type II (juvenile)								++													
Wolman disease																					
Farber disease	+						PN	+					+		+						++
Neuronal ceroid lipofuscinosis	++			++	++				++	++	±	+				++	++	++			
I-cell disease	++																				
Pseudo-Hurler disease	±												++			++			b		
α-Mannosidosis	+												++	++							
Fucosidosis	++	++		++					+											+	
Sialidosis type I									+	++	+				++			++			
Sialidosis type II	++			++									+		++						
Aspartylglucosaminuria	+			++										++							++
Niemann–Pick type A	++			++	+										++						
Niemann–Pick type B															+						
Niemann–Pick type C	++			++					++		+	+							++		
Gaucher type I																					
Gaucher type II	++			++		c													++		
Krabbe disease	++			++	++		PN										++	++			
Metachromatic leukodystrophy	++			++	++		PN				+						++	++			
Multiple sulfatase deficiency	++			++	++	++							+	±				++			
Fabry diseases					d								++		++						
G_{M1} gangliosidosis (infantile variety)	++			++					+				++		++			++			
G_{M1} gangliosidosis (cerebral type)	++			++	++				++								++	++			
Galactosialidosis (infantile variety)	++			++					+				++		++			++			
Galactosialidosis (juvenile variety)													±		++						

Table 39.3 (Continued)

Disease	MR	HA	IN	DM	PT	CC	PN/AH	MP	SZ	MY	CI	EX	CL	LO	CM	RP	OA	VD	OP	DF	HV
G_{M2} gangliosidosis, types I, II, and AB	++			++	++				++	++					++			++			
G_{M2} gangliosidosis (juvenile Tay–Sachs)				++	++		AH	++	++		++	++									
Cystinosis													e								
Sialic acid storage disease (infantile type)	++																				
Chediak–Higashi disease	+																				

MR mental retardation or progressive development delay, *HA* aggressive behavior, *IN* reversal of sleep pattern and insomnia, *DM* dementia, *PT* pyramidal tract disease, *CC* cervical cord compression due to abnormalities at either C-1 vertebra or atlanto-occipital joint, *PN/AH* peripheral neuropathy or spinal cord anterior horn disease, *MP* myopathy, *SZ* seizure disorder, *MY* myoclonus, acoustic myoclonus, action myoclonus, *CI* cerebellar involvement, *EX* extrapyramidal tract involvement, CL corneal cloudiness, *LO* lens opacities, *CM* cherry-red macula, *RP* retinitis or retinitis pigmentosa, *OA* optic atrophy, *VD* visual difficulties such as night blindness, *OP* strabismus or external ophthalmoplegia, *DF* deafness, *HV* hoarse voice

[a] ++, severe; +, present; ±, at times present

[b] Hyperopic astigmatism

[c] Compression of brain stem due to meningeal storage, causing opisthotonus, trismus, and strabismus

[d] Cerebral ischemia, strokes

[e] Corneal crystals

Table 39.4
Lysosomal storage diseases that cause hydrops fetalis

Gaucher disease type II
G_{M1} gangliosidosis
Galactosialidosis
Sly disease
Sialidosis type II

lysosomal storage diseases. The defective enzymes in various lysosomal storage diseases are summarized in *Table 39.8*.

Specific Laboratory Studies Used in the Diagnosis of Lysosomal Storage Diseases

The diagnosis is based on the aforementioned pathogenic mechanisms. The strategies employed are (a) to measure directly or indirectly the putative defective enzyme activity, (b) to demonstrate the storage substance, (c) to seek additional evidence of the derangement in target organs of the disease or displacement of a lysosomal enzyme, and (d) prenatal diagnosis.

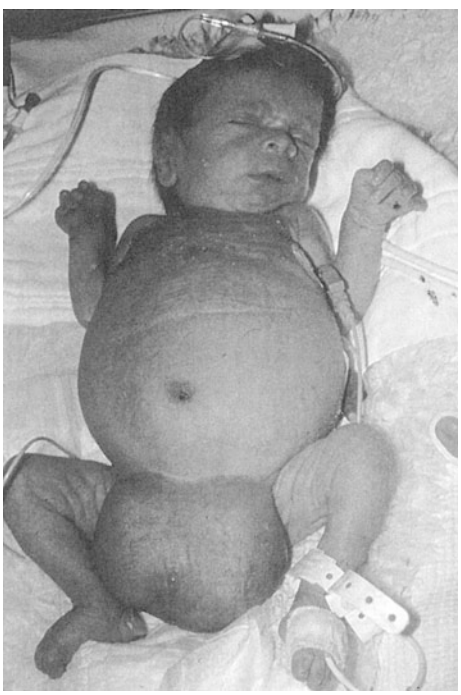

Figure 39.18
Hydrops fetalis in a newborn with the severe form of galactosialidosis

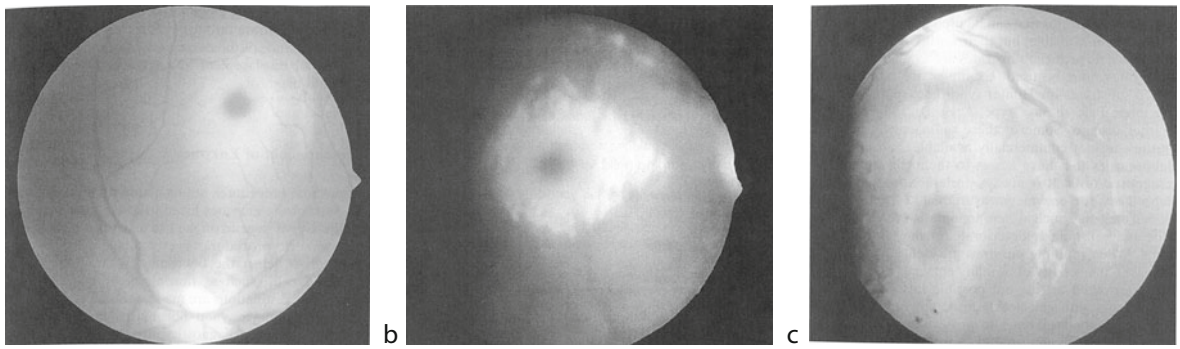

Figure 39.19
Cherry-red macula in a patient with G_{M2} gangliosidosis (a), in a patient with galactosialidosis (b), and in a patient with Niemann–Pick disease (c) (*See Color Fig.* 5–19)

Table 39.5
Lysosomal storage diseases that cause "cherry-red" macula

G_{M1} gangliosidosis (infantile–late infantile)
Galactosialidosis (infantile, juvenile, adult types)
G_{M2} gangliosidosis (Tay–Sachs disease)
G_{M2} gangliosidosis (Sandhoff disease)
G_{M2} gangliosidosis (activator protein deficiency)
Sialidosis type I
Sialidosis type II
Niemann–Pick disease type A, and less often in type B
Ceramidase deficiency, classic type 1 and frequently in the progressive neurologic type 5 variant
Multiple sulfatase deficiency (rare)

Table 39.6
Lysosomal storage diseases that manifest primarily with CNS involvement

Neuronal ceroid lipofuscinosis
β-Mannosidosis
Sialidosis type I
Niemann–Pick disease type C (except for splenomegaly)
Globoid cell leukodystrophy (Krabbe disease)
Metachromatic leukodystrophy
Schindler disease type I
G_{M1} gangliosidosis (cerebral type)
G_{M2} gangliosidosis, types I–III
Salla disease

Measurement of Enzymes

Analytical procedures are available for the measurement of most of the enzymes listed in *Table 39.8*. A large number of these tests depend on the use of artificial substrates, and fluorometric procedures are available that are sensitive enough to detect the deficiency in either leukocytes or cultured cells, such as fibroblasts or lymphoblasts. Although no distinctions are made between the use of leukocytes, lymphocytes, and fibroblasts, the latter source is more reliable for diagnostic purposes. In some instances this should be the preferred tissue (e.g., Pompe disease), since results with peripheral blood cells might be equivocal. Artificial substrates that can be used by colorimetric methods are also available, but their sensitivity is less. In some instances, no artificial substrates are available, and natural substrates must be used. Examples are radioactively labeled substrates for Hunter syndrome, sphingomyelin for Niemann–Pick disease type A or B, and ceramide for Farber disease. Some of these radioactively tagged substrates are not commercially available, and only the few laboratories that have access to them can perform these diagnostic tests. It is always preferable to use a reliable laboratory for enzyme measurements, since some lysosomal enzymes, such as neuraminidase, are very thermolabile and will quickly deteriorate, giving false-positive results. When multiple enzymes are deficient (e.g., Austin disease), the activity of as many enzymes as possible must be determined to rule out possible false-positive results. In patients with galactosialidosis, not only galactosidase and neuraminidase but also protective protein (carboxypeptidase Y) activity should be measured.

Table 39.7
Lysosomal storage diseases with no or minimal mental retardation

Hurler–Scheie syndrome
Scheie syndrome
Morquio syndrome
Maroteaux–Lamy syndrome
Glycogen storage disease type II, infantile and juvenile varieties
Wolman disease
Pseudo-Hurler syndrome (mild MR)
Sialidosis type I
Niemann–Pick disease type B
Gaucher disease type I
Fabry disease
Galactosialidosis, particularly late infantile/juvenile forms
Cystinosis
Chediak–Higashi disease (mild MR)

In other instances (e.g., activator protein deficiency), the hexosaminidase deficiency cannot be demonstrated by using the artificial substrates of hexosaminidase, but require the natural G_{M2} ganglioside. The presence of a pseudodeficiency gene for arylsulfatase A complicates the interpretation of results; therefore, the diagnosis of metachromatic leukodystrophy should also be performed with natural substrate, when possible, to rule out a disease in the unusual normal subject with a very low arylsulfatase A activity. Since various saposins participate in the action of arylsulfatases, they must be measured in clinically suspect cases of metachromatic leukodystrophy when arylsulfatase activity is found to be normal. The deficiency of β-galactosidase causes three different diseases: G_{M1} gangliosidosis with visceral and brain involvement, G_{M1} gangliosidosis with only cerebral involvement, and Morquio syndrome type B. This enzyme has two catalytic functions, one for the breakdown of keratan sulfate, an essential component of bone, and another one for the hydrolysis of G_{M1} gangliosides in the CNS. Most mutations of β-galactosidase lead to the loss of function of the enzyme for both compounds (i.e., the classic infantile variety of G_{M1} gangliosidosis). However, in rare instances, the mutation will affect only one function and not the other, leading to the emergence of either Morquio syndrome (catabolism of keratan by the enzyme is defective), or the cerebral variety of G_{M1} gangliosidosis (hydrolysis of ganglioside by the enzyme is defective). These two variants can only be diagnosed by the use of natural substrates.

An alternative indirect technique is complementation analysis. The cultured fibroblasts of an unknown case are grown together with fibroblasts from different patients with an already established diagnosis. Lysosomal enzymes released into the culture medium have the mannose 6-phosphate residue, and they are easily exchanged between cells. When radioactive sulfate is added into the culture medium, it is incorporated into the sulfated ground substance secreted by fibroblasts. In the absence of breakdown, this accumulation is much greater in the growth medium (e.g., of MPS cells) than in normal fibroblasts. When fibroblasts from two different types of MPS are grown together, both types of cells eventually end up containing a normal spectrum of enzyme activities, and the sulfate fixation into the ground substance decreases to normal limits. However, if both cell types have an identical enzyme deficiency, radioactive sulfate fixation remains high, establishing the diagnosis.

Demonstration of the Storage Substance

The original description of most of these disorders was based on the histological demonstration of the stored substance in tissues, peripheral blood cells, and cultured cells. At present, the ready availability of the substrates makes diagnosis possible through rapid enzyme measurements, which are universally preferred over the histologic procedures. It is still customary in many institutions that do not have access to enzyme measurements to use a bone marrow biopsy to show, for example, the Gaucher cell with its "creased silk" appearance (*Fig. 39.20*) or the Niemann–Pick type A or B cell with its "soap bubble" appearance (*Fig. 39.21*). A peripheral blood film will demonstrate vacuolated lymphocytes in most storage diseases or the presence of metachromatic granules in MPS (*Fig. 39.22*). The brain biopsy will indicate the typical "globoid cells" in Krabbe disease. Myelin degeneration can be shown in the biopsy of peripheral nerves in metachromatic leukodystrophy, appearing as "zebra bodies." Staining for glycogen or EM studies in muscle, for example, will show the presence of glycogen accumulation in the lysosomes in type II GSD.

Table 39.8

Deficient enzymes in lysosomal storage diseases

Disease	Deficient enzyme
Hurler, Hurler–Scheie, Scheie syndromes	α-L-Iduronidase deficiency is most severe in Hurler. There are several alleles for the enzyme; all are deficient in Hurler.
Hunter syndrome	α-L-Iduronate sulfate sulfatase
Sanfilippo syndromes	Four different enzymes for each phenotype (A, B, C, and D), all of which are involved in the breakdown of heparan sulfate.
Morquio syndrome	Galactose 6-sulfatase in type A; specific defect in β-galactosidase in type B
Maroteaux–Lamy syndrome	Arylsulfatase B
Sly syndrome	β-Glucuronidase
Glycogen storage disease type 2	Acid maltase (acid α-glucosidase); deficiency is less in late-onset type
Wolman disease	Acid lipase
Farber disease	Acid ceramidase
Santavuori disease	Unknown; subunit *c* of ATP synthetase does not accumulate in lysosomes
Jansky–Bielschowsky and Spielmeyer–Vogt diseases	Accumulation of subunit *c* of ATP synthetase
Mucolipidosis II and III	Defective mannose phosphorylating activity for newly synthesized lysosomal enzymes, deficiency of a specific phosphotransferase. The same enzyme defect in both diseases, except it is milder in mucolipidosis type III
α-Mannosidosis	α-Mannosidase
β-Mannosidosis	β-Mannosidase
Fucosidosis	α-Fucosidase
Sialidosis	Neuraminidase
Aspartylglucosaminuria	Aspartylglucosaminidase
Niemann–Pick disease types A and B	Sphingomyelinase; in type A: $<$5%; in type B: 5–10%.
Niemann–Pick disease type C	Intracellular trafficking defect of exogenous cholesterol
Gaucher disease type I–III	β-Glucosidase (glucocerebrosidase)
Krabbe disease	Galactosylceramide-β-galactosidase
Metachromatic leukodystrophy	Arysulfatase A
Multiple sulfatase deficiency	All lysosomal sulfatases are deficient; the enzyme that activates the active center of sulfatases is lacking
Fabry disease	α-Galactosidase
Schindler disease	α-*N*-acetylgalactosaminidase
G_{M1} gangliosidosis (infantile variety)	β-Galactosidase
G_{M1} gangliosidosis (cerebral variety)	A specific mutation in β-galactosidase
Galactosialidosis	Carboxypeptidase "Y" or protective protein that binds, carries, and modifies both β-galactosidase and neuraminidase before they enter into lysosomes
G_{M2} gangliosidosis, types I–III, and activator protein deficiency	Hexosaminidase in all, but α-chain defective in classic and juvenile Tay–Sachs disease, β-chain is defective in Sandhoff disease, and activator protein is deficient in activator protein deficiency
Cystinosis	Defect in carrier-mediated cystine transport from lysosomes
Sialic acid storage diseases	Defect in carrier-mediated sialic acid transport from lysosomes
Chediak–Higashi disease	Unknown

In only four instances is the only available diagnostic tool a histologic examination:

1. In Niemann–Pick disease type C, the storage of cholesterol in perinuclear lysosomes can only be demonstrated specifically by a special fluorescent staining technique, filipin.
2. NCL requires the EM demonstration of curvilinear "fingerprint" bodies or "beeswax" bodies.
3. Immunochemical techniques are used to show the accumulation of the subunit *c* of ATP synthetase in the Jansky–Bielschowsky and Spielmeyer–Vogt types of NCL.
4. Demonstration of giant lysosomes is accomplished by routine staining of leukocytes in the peripheral blood in Chediak–Higashi disease.

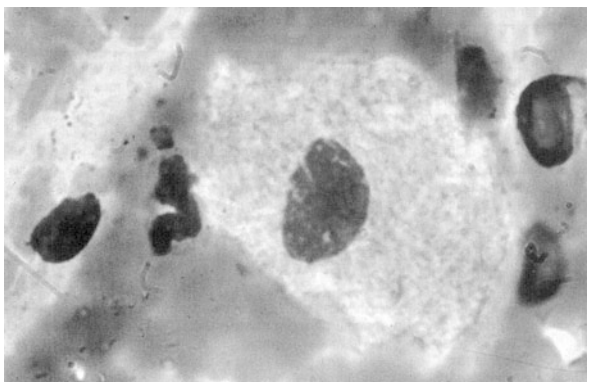

Figure 39.20
The light microscopic appearance of a typical Gaucher cell (*See Color Fig. 5–20*)

Seeking Additional Evidence of Storage

The accumulation of sphingomyelin in Niemann–Pick disease type A or B in the liver deranges the liver function, and both ALT and AST are increased in the circulation, while this is not true for Gaucher disease, which is clinically similar to Niemann–Pick disease. The only other visceral storage disease that causes elevated liver enzymes is deficiency of amylo-1,6-glucosidase (debrancher) (i.e., GSD type III).

Although there are methods to measure the phosphotransferase the deficiency of which is responsible for mucolipidosis II and III, they are difficult procedures, and these diseases can readily be detected by the increased levels of lysosomal enzymes (e.g., hexosaminidase) in blood and urine.

In cystinosis, the determination of increased accumulation of cystine can be shown in many tissues, but leukocytes are preferred. In sialic acid transport disorders the measurement of sialic acid, and in aspartylglucosaminuria the chromatographic measurement of aspartylglucosamine, in the urine will establish the

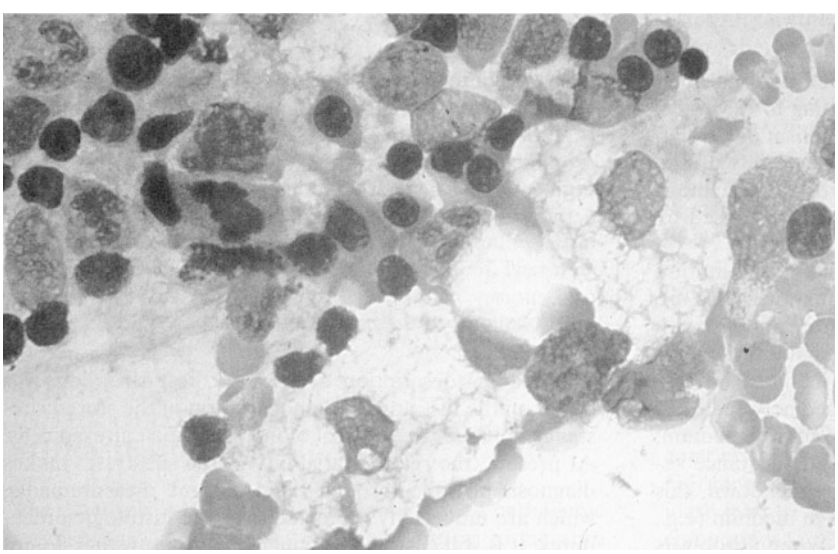

Figure 39.21
The light microscopic appearance of a typical Niemann–Pick cell (*See Color Fig. 5–21*)

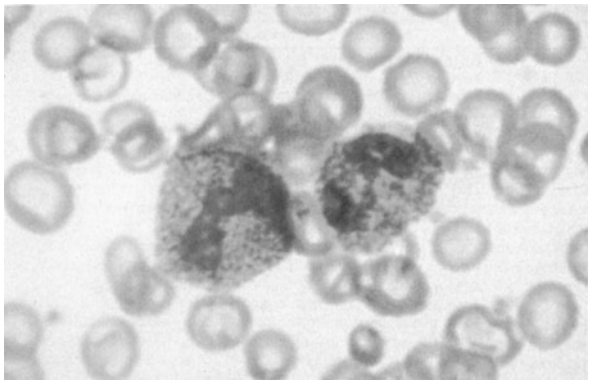

Figure 39.22
Increased metachromatic granulation in leukocytes in a patient with mucopolysaccharidosis (Hurler syndrome) (*See Color Fig. 5–22*)

diagnosis. A large number of institutions use a simple spot test or "screening test" to detect the increased mucopolysaccharide excretion in the urine to diagnose MPS. This test in inexperienced hands might give false-negative or false-positive results. A more sophisticated technique is the use of TLC or capillary electrophoresis in the urine to demonstrate the increased excretion of oligosaccharides or sialo-oligosaccharides that accompanies most of the lysosomal storage diseases. Although these latter tests lack specificity, they provide an excellent screening technique to show the presence of a lysosomal storage disease. In all instances it is advisable to measure the specific enzymes if the TLC or capillary electrophoresis test is positive.

Prenatal Diagnosis

Both chorionic villus biopsy and amniotic cell cultures have been used to show defective enzyme activity in the fetus. The main problem with this approach is the usually normal low expression of enzyme activity in a heterozygous fetus. In the prenatal testing for Hunter syndrome, the sex of the fetus should also be determined; a female hemizygous fetus might test deficient due to mosaicism. If a prenatal diagnosis is considered, particularly for intrauterine BMT, it is best to use molecular genetic methods. Although this technique is more complicated than is usually appreciated, requiring a specialized laboratory experienced in such diagnostic efforts, it is most reliable and will not provide false-positive or false-negative results. The gene locations and cDNA are available for most of the lysosomal storage diseases (*Table 39.9*).

Treatment of Lysosomal Storage Diseases

In most instances, the long-term management of a lysosomal storage disease is difficult. Most efforts involve supportive measures. In certain cases, the stored substance can be cleared through the administration of specific compounds or the synthesis of the storage substance can be inhibited. Some experimental therapies, such as administration of the enzyme that is deficient by BMT, either in utero or after birth, and gene therapies have been employed. Such experimental therapies are justified, since these are desperate diseases, and in so many instances show a protracted course causing intolerable pain and suffering to the patient and parents, and eventually death. A graphic summary of therapeutic interventions is shown in *Fig. 39.23*.

Supportive Measures

Lysosomal storage diseases cause significant CNS and systemic involvement, although, as the list in *Table 39.3* indicates, not all lysosomal storage diseases have CNS involvement. A dementing disease is a challenge to the pediatrician. Nutrition in a child who is unable to feed must be maintained by nasogastric tube feeding or by gastrostomy, using special formulas rich in calories. Such dementing diseases cause repeated aspirations and pneumonia, and the child usually expires due to inanition or pulmonary complications. The painful "bone crises" of Gaucher disease will often require use of narcotics. The patient with Gaucher disease will usually undergo splenectomy to manage the severe thrombocytopenia associated with the disease. When splenectomy is performed, it should be partial in order to prevent accumulation of glucocerebrosides in the lung. Such a patient should receive pneumococcal, meningococcal, and *Haemophilus influenzae* vaccinations and prophylactic antibiotics to prevent intervening life threatening bacterial sepsis. In patients with late-onset G_{M1} gangliosidosis, trihexyphenidy1 has been used to combat dystonia, since in such cases dopaminergic neurons are hypofunctional, while cholinergic neurons are hyperactive in basal ganglia. Several other aspects of lysosomal storage diseases deserve emphasis.

Patients with milder forms of MPS that have minimal CNS involvement, such as Hurler–Scheie and Scheie syndromes, Morquio syndrome, milder forms of Austin disease, and late-onset forms of galactosialidosis, have near-normal life spans, and the progressive skeletal

Table 39.9

Chromosome location of lysosomal storage diseases and prenatal diagnosis

Disease	Chromosome location
Hurler; Hurler–Scheie, Scheie syndromes	4p. 16.3[a,b]
Hunter syndrome	Xq28 together with sex determination[a,b]
Sanfilippo syndrome types A to D	Type A: 17q25.3; type B: 17q21; type C: chromosome 14: type D: 12q 14[a,b]
Morquio syndrome	Type A: 16q24.3; type B: 3p21.33[a,b]
Maroteaux–Lamy syndrome	5q11–q13[a,b]
Sly syndrome	7q21.11[a,b]
Glycogen storage disease type II	17q25.2-q25.3[a,b]
Wolman disease	10q24-q.25[a]
Farber disease	cDNA available[b]
Santavuori disease	1p.32
Spielmeyer–Vogt disease	16p12.1
Jansky–Bielschowsky disease	11p15.5
Mucolipidosis II and III	4q21.q23[b]
Mannosidosis, types α and β	Type α: 19cen-q12; type β: 4q22–q25[a,b]
Fucosidosis	1p34; pseudogene on 2q31.q32[a,b]
Neuraminidase	6p21.3[b]
Aspartylglucosaminuria	4q32.q33[a,b]
Niemann–Pick type A and B	11p15.4-p15.1[a,b]
Niemann–Pick type C	18q11-q12[a,b]
Gaucher disease I-III	1q21[a,b], pseudogene also on 1q, 16 kB (3.2 cM) downstream
Krabbe disease	14q31[a,b]
Metachromatic leukodystrophy	22q 13.31-qter [a,b], syndrome of pseudodeficiency is known; one form of MLD is caused by deficiency of saposin, a cerebroside sulfate activator
Fabry disease	Xq22[a,b]
Schindler disease	22q11
G_{M1} gangliosidosis	3p21.33[a,b]
Galactosialidosis	20q.13.1[a,b]
Tay–Sachs disease	15q23-q24[a,b]
Sandhoff disease	5q13[a,b]
G_{M2} gangliosidosis due to activator protein deficiency	5q31.3–q33.1
Cystinosis	17p13[a,b]
Salla disease	6q.14-q15

[a] Different mutations are known and reported in the literature that can be used for molecular genetics studies.
[b] Prenatal diagnosis has been achieved either by conventional enzyme measurement techniques or by molecular genetics studies.

deformities pose significant problems to the patient. They become orthopedic problems, and the skeletal deformities need to be corrected surgically. Atlanto-occipital joint, odontoid luxation, or C-1 vertebral abnormalities, as frequently observed in Hurler–Scheie and Scheie, Morquio, and Maroteaux–Lamy syndromes and Austin disease, lead to compression of the cervical cord and might transect the cord, causing paralysis. Such patients must have frequent and careful clinical follow-up to detect early signs of cord compression. When pyramidal tract signs such as bilateral ankle clonus or hyperreflexia are observed, the patient must receive CT or MRI of the cervical vertebrae, with

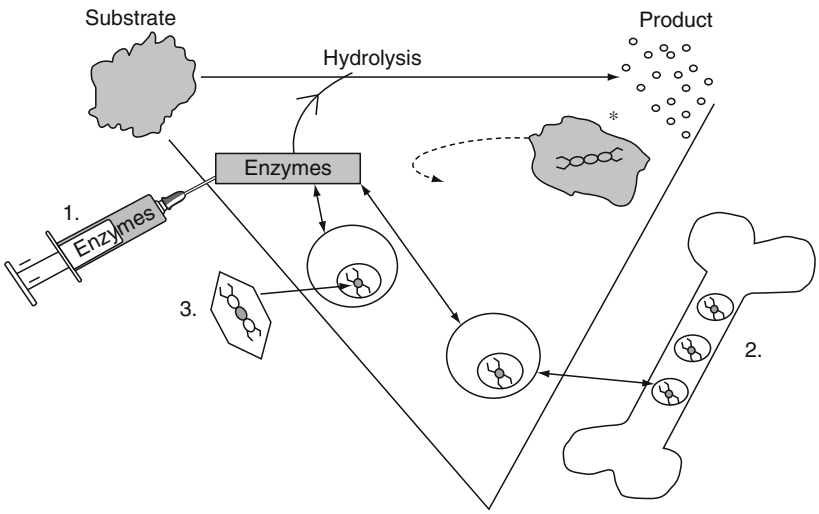

Fig. 39.23
A cartoon illustrating the principles of therapy in lysosomal diseases. The supply of exogenous enzyme (1), normal cells (2), and retrovirus-linked normal gene (3) are shown; the patient's defective cell is unable to produce the enzyme (*See Color Fig. 5–23*)

neurosurgical intervention when necessary to stabilize the atlanto-occipital joint.

Laryngeal obstruction in Hurler–Scheie syndrome and Farber disease might require tracheostomy. Large umbilical hernias of MPS, G_{M1} gangliosidosis, and galactosialidosis might require surgical intervention. Macroglossia in a teenage patient with Hurler–Scheie syndrome might require plastic surgery to keep the patient alive for a few more years. Craniofacial deformities in a patient with Hurler–Scheie syndrome can be debilitating, requiring surgery to alleviate the obstructive airway disease.

A patient with cystinosis or Fabry disease might develop chronic renal failure and will require hemodialysis for survival. Renal allografts have been attempted in cystinosis and fetal liver transplantation in Fabry disease, both of which have prolonged the survival of the patients. Corneal cloudiness in a patient with Hurler–Scheie syndrome will cause severe visual impairment in a mentally normal individual, requiring corneal transplantation from a healthy donor.

Clearing the Storage Substance and Enzyme Therapy

At present one of the preferred treatment procedures for Gaucher disease is periodic injection of a specially modified β-glucocerebrosidase. This commercially available enzyme, Ceredase or Cerezyme, is a biochemically modified human placental β-glucocerebrosidase in which the terminal mannose residues are exposed to assure its uptake by macrophages (*Fig. 39.23*). More than 600 patients with Gaucher disease at present are under treatment with Ceredase or Cerezyme. Most of these patients showed benefits such as decreased liver or spleen size, improved anemia and platelet counts, normalized pulmonary function, and normalized physical growth. This is a noninvasive method of treating Gaucher disease, but the cost involved is prohibitive, particularly when it is considered that the patient must receive this treatment lifelong. It is advisable to use Ceredase or Cerezyme until a suitably matched donor can be secured for BMT.

Case History (*Gaucher Disease Type I – Ceredase Treatment*). A child was admitted at the age of 6 years for fever of unknown origin, at which time he was discovered to have hepatosplenomegaly. The presumptive diagnosis of brucellosis was ruled out; a bone marrow biopsy done to rule out an early malignancy revealed the presence of Gaucher cells, and he was referred to the metabolic service. He was the only child of nonconsanguineous parents. At initial encounter his growth parameters were normal, but the liver span was 8 cm and the spleen span was 10 cm. Investigations revealed mild thrombocytopenia (90,000/mm^3) and prolonged bleeding time. There was no HLA-matched donor available, and he was followed without any therapeutic intervention for 3 years, during which period he suffered a linear fracture of his right femur neck after

jumping down from a height of 80 cm. He started to suffer from chronic anemia, with the hemoglobin dropping from 12 to 10 g/L in 3 years, and from chronic bone pain. His general well-being deteriorated and he was exhausted all the time. At the age of 9 years, the blood angiotensin-converting enzyme level was 72 U/L (normal: <42 U/L); the skeletal survey indicated mild/moderate involvement of long bones with Gaucher disease. The chest x-ray was clear. Eventually, he was started on Ceredase (90 U/kg every 2 weeks). His general health returned to normal, bone pain disappeared within a year, and liver and spleen size regressed to 2 cm below the costal margin in 2 years. His hemoglobin increased to 12 g/L and platelet count returned to normal within 1 year. At present he is a normal child for all purposes; he is an excellent student and a good football player, without suffering from fractures when he gets kicked accidentally.

More recently, purified α-L-iduronidase became available and was found to be useful in the canine model of Hurler syndrome; however, it has not been tested extensively yet in the human disease. As an experimental therapy, splenic α-galactosidase A has been found to be effective in clearing the globotriaosylceramide from the circulation and kidneys of two patients with Fabry disease. This enzyme is also not commercially available. An alternative approach is plasmapheresis to deplete the accumulated substrate in Fabry disease, which has been employed with some success.

An alternative therapeutic approach has been to reduce the production of the stored substance. For example, inhibitors of cholesterol synthesis, such as lovastatin, have been of some value in the management of Wolman disease. Furosimin, an inhibitor of sphingolipid synthesis, has been advised in the treatment of Farber disease. Dimethylsulfoxide, which reverses cholesterol trafficking, might be tried in patients with Niemann–Pick disease type C.

Maybe the most impressive use of a compound to clear the stored substance has been the use of cysteamine in cystinosis. The oral use of this compound has improved physical growth, particularly when used in conjunction with human growth hormone. Cysteamine has an unpleasant smell and taste, but a modified form of the drug, phosphocysteamine, is better tolerated by the patient and is equally, if not more, effective. The use of cysteamine/phosphocysteamine prevents the long-term renal complications of cystinosis; however, it is ineffective in clearing the corneal deposits, which is usually achieved by frequent and prolonged use of eyedrops containing these medications.

Bone Marrow Transplantation (BMT)

This therapeutic approach has been extensively used in the treatment of various types of lysosomal storage diseases (*Fig. 39.23*). The principle is to supply normal hematopoietic stem cells to the recipient. Adjacent cells will pick up the lysosomal enzymes released by a normal cell since they carry the mannose marker. One cell thus provides cure to many neighboring cells. Many reports indicate a dramatic improvement in the somatic features of MPS in Hurler disease after BMT. Over 140 patients with Hurler syndrome have received allogeneic BMT. Improvement and leukocyte enzyme levels maintain as long as the graft lasts. The problems with BMT are its cost, its invasive nature frequently leading to death in the hands of who are not experienced in BMT, rejection of the graft, graft-versus-host reaction, and finally loss of the chimera in the long term in many instances. BMT also is less effective in patients with advanced disease. In Hurler syndrome, although BMT has been curative, it does not prevent the long-term severe skeletal involvement, and such patients still require orthopedic interventions and correction of facial deformities that lead to obstructive airway disease.

BMT has been less effective in MPS II and III and metachromatic leukodystrophy. It has been ineffective in MPS IV, Krabbe disease, and G_{M1} and G_{M2} gangliosidosis. However, good results have been obtained in patients with MPS VI, Niemann–Pick disease type B, and Gaucher disease, and in these disorders the use of BMT is definitely advisable. Successful BMT in a patient with Niemann–Pick disease and in a patient with Gaucher disease are summarized in the case studies presented below.

Case History (*Niemann–Pick Disease – BMT*). A 1-year-old boy who had Niemann–Pick disease (sphingomyelinase <1%) had recurrent chronic chest infection, and his liver and spleen edges were 8–10 cm below the costal margin. He underwent splenectomy at 14 months of age and an allogeneic BMT from his sister at 16 months of age. He was followed for 5 years after BMT with the following clinical and biochemical changes:

1. Hepatomegaly decreased to normal in 4 years after BMT; the initial values of ALT (342 U/L) and AST (782 U/L) decreased to within normal range after 5 years, but cholesterol, which initially was 13.35 mM (normal: <4.2 mM), normalized only after 5 years.
2. The abnormal reticular granular pattern of the lung returned to normal in 1 year.
3. The height and weight at the time when he had BMT, at the age of 16 months, corresponded to 7 and

5 months, respectively; they increased to the fifth percentile at the age of 7 years.
4. The patient developed morphea (scleroderma) in the legs and around the laparotomy site for splenectomy 2 years after BMT, which prevented him from motion. This was due to chronic graft-versus-host reaction. These lesions became less indurated in the next 4 years after treatment with cyclosporin and prednisone.
5. He developed peripheral neuropathy 2 years after BMT, with nerve conduction times reverting to normal only after 4 years of therapy.
6. Initially he had mild demyelination of the central white matter, which became normal in 2 years after BMT.
7. A successful chimera was established as evidenced by repeat sphingomyelinase determination in leukocytes (10% of normal) and in fibroblasts (6% of normal) 4 years after BMT.

At the age of 7 years, he was in excellent health despite the handicaps caused by scleroderma. He had gained most of his motor function and was walking with crutches. He had started to attend school.

Case History (*Gaucher Type I – BMT*). A 1-year-old boy was referred for repeated chest infections, abdominal distention, and failure to grow. Biochemical studies revealed him to have Gaucher disease with a β-glucosidase of 5% of normal in his fibroblasts. During the next 6 months, he started to lose weight and the liver enlarged from 5 to 15 cm and the spleen from 8 to 18 cm below the costal margin. The chest x-ray revealed diffuse granular infiltrates. He developed severe thrombocytopenia, with the platelet count dropping to 10,000/mm^3, and a partial splenectomy had to be performed. Both the bone marrow biopsy and histology of the spleen removed showed numerous Gaucher cells. He received a BMT from an HLA-matched sibling at the age of 20 months. The further clinical course was complicated by chronic lung disease, with further loss of weight for 3 months. He was placed on cyclosporin, folic acid, and prophylactic penicillin. His general condition started to improve slowly, and the liver regressed to 4 cm below the costal margin in 2 and 2 cm below the costal margin in 3 years. Clinical and x-ray findings in the lungs disappeared in 2 years. The hemoglobin increased from the preoperative value of 60 g/L to 120 g/L in 2 years. The platelet count during the same period increased to 500,000/mm^3. The bone changes of Gaucher disease regressed only moderately, but he never suffered from bone pain or fractures. His general health improved so much that he could participate in games with other children. He started school at 6 years of age; at 8 years of age, he is an excellent student participating in all school activities at present. He is now a normal child.

Another experimental therapy, in utero BMT, has been advised for the treatment of lysosomal storage diseases that do not have prominent CNS involvement. The method employs intraperitoneal injection of hematopoietic cells isolated from the fetal liver of an electively aborted healthy fetus. This is best done before 13 weeks of gestation, before the fetus becomes immunocompetent. A patient with Niemann–Pick disease type B has already been treated with some success through this procedure. An alternative approach is the use of maternal stem cells, injected into the fetal circulation several times during the pregnancy in order to establish an immune tolerance. The neonate then receives a BMT from the mother after delivery. Although in utero BMT has proved to be most effective in the management of such hematologic diseases as thalassemia, and in various types of severe combined immunodeficiency, its efficacy in the treatment of lysosomal storage diseases has not been tested widely yet.

Gene Therapy

This mode of therapy is certainly more advantageous than BMT (*Fig. 39.23*). However, the difficulties in maintaining the gene introduced into the stem cell, as well as assuring that the gene is transferred with its regulator to a location where it can function appropriately, and the risks involved by the use of transfecting crippled virus vectors require adequate solutions before the widespread adoption of this technique. Recently, a multicenter effort has been initiated for the therapy of Hurler syndrome with the α-L-iduronidase gene.

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40 Osteopetrosis

Soud A. Al-Rasheed

Osteopetrosis (marble bone disease) is a rare condition characterized by marked radiodensity of bones throughout the skeleton and failure of remodeling of the metaphysis due to impaired lysosomal function of osteoclasts and their precursor cells, monocytes. The overall prevalence varies from 1:500,000 to 5.5:100,000. It is not a single disease but a syndrome with several variants defined on clinical criteria. These variants can be categorized as (a) infantile-malignant autosomal recessive, (b) intermediate autosomal recessive, and (c) autosomal dominant.

Infantile-Malignant Osteopetrosis

This form usually presents in infancy with failure to thrive, anemia with thrombocytopenia, severe, overwhelming infections, or fractures. The inheritance is usually autosomal recessive. Hyperostosis crowds the bone marrow cavity, leading to anemia, thrombocytopenia, and hepatosplenomegaly. The macrophage killing is defective, which may account for recurrent infections.

Other manifestations include growth and psychomotor retardation, optic atrophy, squint, deafness, and rickets. Radiologic features include generalized sclerosis of bone with metaphyseal widening, transverse striations, and bone-in-bone appearance that is most marked in the vertebral bodies. The base of the skull is dense.

Treatment is usually symptomatic, correcting anemia and thrombocytopenia, with aggressive treatment of infections. Other therapeutic measures include a low-calcium diet, prednisone, calcitriol, and more recently bone marrow transplantation. Neurosurgical unroofing of the optic foramina is necessary in some patients.

The prognosis for survival is poor, and death is usually from complications of anemia, thrombocytopenia, or infections.

Osteopetrosis with Renal Tubular Acidosis

This entity is the best example of the intermediate autosomal recessive group. The condition is caused by carbonic anhydrase (CA) II deficiency. It is the only type of human osteopetrosis that is understood at the biochemical/molecular level. The majority of patients with CA II deficiency have been reported from Saudi Arabia, Kuwait, and North Africa. In North America, the disorder has not been reported among ethnic groups of Western European descent. To date, the condition has not been described in blacks or Asians. It is discovered late in infancy or early childhood through developmental delay, short stature, fractures, weakness, cranial nerve compression, dental caries or malocclusion, and/or mental retardation.

The clinical expression is heterogeneous among different ethnic groups and is due to different mutations in the CA II candidate gene. Several mutations have been identified; a mildly affected Belgian patient homozygous for the HIO7Y mutation had frequent skeletal fractures and no mental retardation. Three American kindreds included three patients who were compound heterozygotes for the HIO7 mutation and for a splice junction mutation in intron 5. They had many skeletal fractures but were not mentally retarded. Many Arab patients were found to be homozygous for a splice junction mutation in intron 2. They had osteopetrosis, severe renal tubular acidosis, moderate to severe mental retardation, and infrequent fractures. Other mutations have also been reported.

Typical radiographic features of osteopetrosis are present (*Fig. 40.1*) and resemble those of other forms with two exemptions: the osteopetrosis and defective skeletal modeling can diminish spontaneously over decades, and there is cerebral calcification that usually appears at approximately 2–5 years of age. Deposits occur in the basal ganglia and affect cortical gray matter of all lobes of the brain. Bone scintigraphy shows characteristic features of widened metaphyses of all long bones that show increased tracer uptake, particularly in the distal femur and proximal tibia (*Fig. 40.2*). Dual x-ray absorptiometry shows increased bone density. Bone densitometry is a safe and noninvasive method of observing the natural history and therapeutic response.

The biochemical diagnosis of CA II deficiency can be achieved by demonstrating severe, selective reduction of CA II in erythrocyte lysates. Patients are usually not

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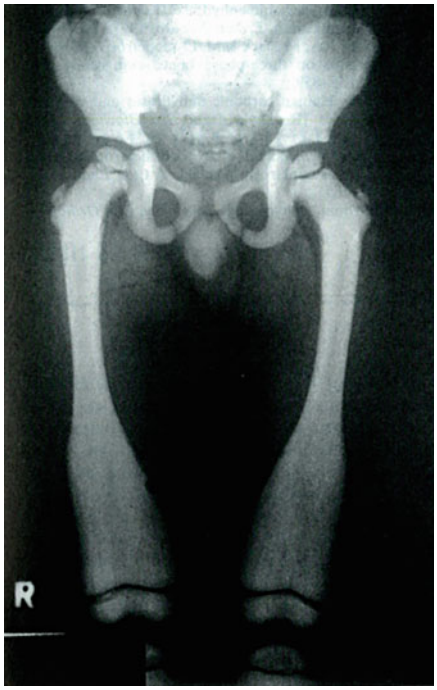

Figure 40.1
Roentgenography of both femora of a 7-year-old male with osteopetrosis showing generalized sclerosis of bones with widening of metaphysis and cortical thickening

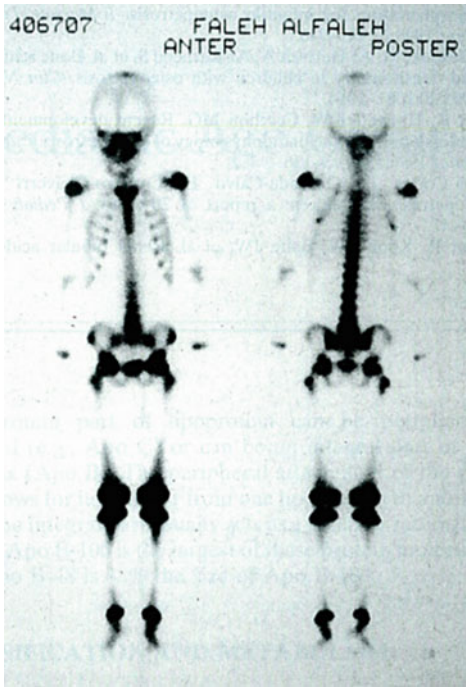

Figure 40.2
Bone scintigraphy demonstrating metaphyseal splaying with increased tracer activity in the femoral and tibial metaphyses (Courtesy of Dr. M. Elzouki, Umm Al Quara University, Makkah, Saudi Arabia)

anemic. A hyperchloremic metabolic acidosis, sometimes with hypokalemia, is caused by proximal, distal, or combined renal tubular acidosis. Serum levels of calcium, inorganic phosphate, magnesium, and parathyroid hormone are normal. Alkaline phosphatase and acid phosphatase activity in serum are usually normal but occasionally increased.

There is no established medical treatment for CA II deficiency. Some therapeutic trials with a low-calcium diet, alkali therapy, and high doses of 1,25 dihydroxy vitamin D3 have been tried in some patients.

The identification of the locus of the CA II gene on the long arm of chromosome 8 and the identification of its mutations provide a means for prenatal diagnosis. Carriers can be detected by the assay of erythrocyte CA II levels.

Autosomal Dominant Osteopetrosis

This is the most prevalent form of osteopetrosis and is often asymptomatic, and the diagnosis may be reached by chance. Autosomal dominant osteopetrosis is radiographically characterized by universal osteosclerosis involving the axial skeleton and symmetric involvement of the long bones without modeling defects. Based on radiographs, it is possible to describe two different subtypes. Type I is characterized by pronounced osteosclerosis of the cranial vault, whereas type II involves the endplate of the vertebrae (Rugger-Jersey spine) and pelvic bones. In the skull, the osteosclerosis is most pronounced at the base. In both types, the general physique, mentality, and life span are normal, and anemia is uncommon. Other clinical manifestations include bone pain, cranial nerve compression, recurrent fractures with delayed healing, and increased susceptibility to infections. The treatment is usually symptomatic.

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41 The Porphyrias

Hisham M. Nazer

The porphyrias are predominantly a group of inherited metabolic disorders which result from a specific deficiency of one of the eight enzymes along the pathway of heme biosynthesis and characterized by an excessive production of porphyrins or their precursors. Eight enzymatic steps (❯ *Fig. 41.1*) are involved in this pathway. There are eight clinical disorders of porphyrias associated with deficiencies of appropriate enzymes involved in the relevant steps in the heme biosynthetic pathway. In general, those disorders are characterized by photodermatitis, visceral and neuropsychiatric complaints of variable severity. The diagnosis of porphyria is usually triggered by a high index of suspicion that might save affected patients unnecessary investigations and ensure early management. Females are more commonly affected than males. Early intervention is important in porphyria, because most attacks can be prevented by avoidance of certain drugs with some dietary manipulation. The porphyrias are classified into acute porphyrias which present as intermittent attacks of neurogenic dysfunction and the non-acute porphyrias which are characterized by photosensitive skin eruptions. Acute porphyria is a life-threatening condition associated with a significant mortality of up to 10%. The porphyrias are also classified into hepatic and erythropoietic forms according to whether excessive production of porphyrins is predominantly in liver or the erythropoietic system. The estimated incidence is around 1 in 30,000 population; however porphyrias remain underdiagnosed. Increased awareness of the varied spectrum of clinical presentation in porphyrias contributes to early diagnosis and institution of appropriate therapeutic measures which will improve the overall outcome in this condition.

Precipitating factors can be identified in the majority of cases with drugs or alcohol most commonly implicated. Attacks of acute porphyria may also be precipitated by acute infection or fasting. Drugs that precipitate an attack of acute porphyria include barbiturates, sulphonamides, chloramphenicol, chloroquine, imipramine, pentazocine, oral contraceptives, phenytoin, and theophylline.

Classification of various disorders of heme biosynthesis related to porphyrias depends on the major site of overproduction of heme precursors as hepatic or erythropoietic porphyrias.

Porphyrias may also be classified into cutaneous and non-cutaneous forms or acute and non-acute forms. A definite diagnosis may not be always possible due to the varied spectrum of presentation in porphyries which could mimic several disease entities. However the diagnostic accuracy has improved recently with the advent of molecular biological techniques. Mutation screening of family members is recommended to identify presymptomatic carriers.

Diagnosis, especially in the acute form of the disease, is essential to avoid precipitating factors and the use of triggering drugs. In spite of the well-recognized role of genetics in confirming clinical suspicion, and in family screening, the diagnosis is still based mainly on clinical suspicion, course of the disease, as well as biochemical and clinical studies.

Hepatic Porphyrias

The clinical types of the different forms of hepatic porphyria have many features in common, e.g., neurovisceral, neuropsychiatric, and mental abnormalities. Hepatic porphyrias are mostly inherited in an autosomal dominant mode of inheritance associated with specific enzymatic deficiencies. The group of hepatic porphyria includes the following conditions:

1. 5-aminolevulinic acid dehydratase deficiency porphyria (ALAD porphyria)
2. Acute intermittent porphyria (AIP) due to porphobilinogen deaminase deficiency
3. Porphyria cutanea tarda (PCT) due to urogen decarboxylase deficiency
4. Hereditary coproporphyria (HCP) due to coproporphyrinogen oxidase deficiency
5. Variegate porphyria (VP) due to protoporphyrinogen oxidase deficiency

ALAD Deficiency Porphyria

This rare type of porphyria is due to deficiency of the enzyme 5-aminolevulinic acid dehydratase required for

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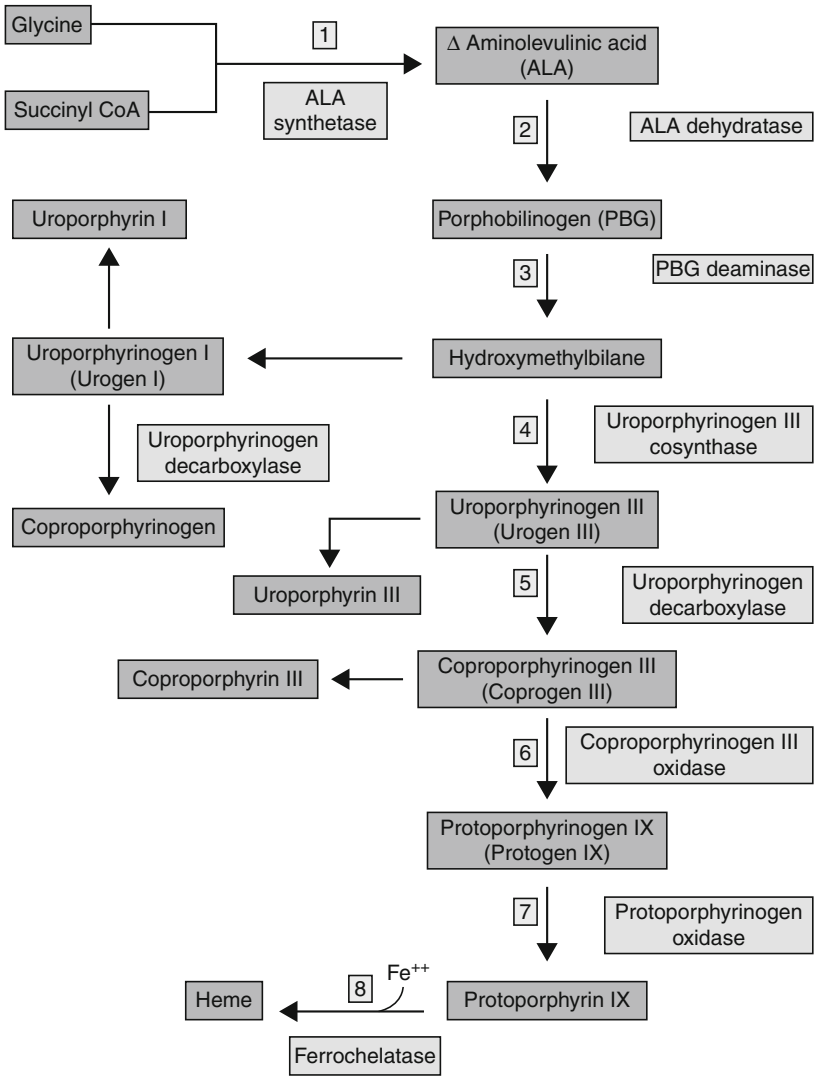

Figure 41.1
The heme biosynthesis pathway

the transformation of aminolevulinic acid (ALA) into porphobilinogen in the heme biosynthesis pathway. It is inherited in an autosomal recessive fashion. The onset is in the teenage years with acute clinical attacks similar to AIP.

Affected child suffers from systemic involvement in the form of abdominal pain, joints pain, hypotonia, and even paralysis. Laboratory investigations confirm the diagnosis by the presence of severe deficiency of the enzyme ALAD in the erythrocytes. Plweinska et al. reported the identification of the molecular lesions in severely affected homozygote. The mutation was confirmed in genomic DNA from family members by the competitive PCR technique. Treatment requires the administration of intravenous glucose during the acute episodes.

Acute Intermittent Porphyria (AIP)

Acute intermittent porphyria (AIP) is considered as the most common type of porphyria affecting pediatric age group. It results from the half-normal activity of the third enzyme in the heme biosynthetic pathway, porphobilinogen deaminase (PBGD), required for the transformation of porphobilinogen (PBG) into hydroxymethylbilane (HMB). The mode of inheritance is

an autosomal dominant. The defect has been located on the long arm of chromosome 11. AIP is due to mutation in the gene encoding for PBGD. Approximately only 10% of patients who inherit the gene have clinical symptoms. This type of porphyria has varied clinical presentations ranging from mild or even asymptomatic to those with severe abdominal pain, abdominal distension, vomiting, and constipation, a picture consistent with acute abdomen requiring surgical consultation. The vomiting may lead to malnutrition, dehydration, and renal failure. The urine has a port wine color. Other clinical features may include fever, diarrhea, and urinary retention. Hyponatremia due to the release of antidiuretic hormone from the hypothalamus may cause delirium, seizures, and coma. The gastrointestinal symptoms may be attributed to disturbances of the autonomic nervous system. Signs of sympathetic overload such as tachycardia and hypertension may occur. The patient may also have some psychiatric manifestations in the form of hallucination, anxiety, paranoia, and depression. Neuropathy, both motor and sensory, may develop with potential complication of bulbar paralysis and respiratory insufficiency. Episodes of neurovisceral disturbances typically begin in early adult life and are exceptional in childhood. The episodes vary in duration from days to weeks and may be intermittent. Life-threatening acute attacks may be precipitated by various factors, including drugs as steroids, sulfonamides, valproic acid, oral contraceptives, barbiturates, etc. Other predisposing factors to initiate acute attacks include fasting, stress, menstruation, and infections.

It is important to mention that symptoms of AIP may also be experienced by patients with tyrosinemia type 1. This may be attributed to the inhibition of δ-ALA dehydratase (Porphobilinogen synthetase) by succinylacetone which is known to accumulate in such patients due to fumarylacetoacetate deficiency.

Treatment includes removal of the causative agents, administration of carbohydrates, and may also include intravenous glucose and hemin to reduce the production of heme precursors.

Diagnosis is supported by the findings of high levels of porphobilinogen and aminolevulinic acid in the urine together with a variable level of reduction in the level of PBGD activity in the erythrocytes. In borderline case, cultured fibroblasts may have to be studied for the deficiency of PBGD activity.

Some individuals with decreased enzymatic activity do not have clinical features of the disease. Prenatal diagnosis has been reported by demonstrating the deficiency of the enzyme in cultured amniotic cells. Biochemical diagnosis is problematic, and the identification of mutations in the HMB-synthase gene could contribute to the accurate diagnosis of presymptomatic heterozygotes. The diagnosis of presymptomatic patients with AIP is recognized to be difficult in some cases due to the significant overlap between low, normal, and high heterozygote value for the enzyme.

Recently, accurate presymptomatic diagnosis was made possible by the identification of genetic mutations causing AIP. Lee et al. reported the identification of two mutations causing AIP: an adenine deletion at position 629 in exon 11 (629delA) and a nonsense mutation in exon 12 (R225X). Many different methods have been developed for mutation screening in AIP. Heteroduplex analysis method was recognized as an efficient mutation screening method.

Affected patients should not be exposed to the predisposing factors stated above including drugs, hormones, alcohol consumption, starvation, and other forms of stress. Should an episode develop in spite of all precautions, oral or even intravenous carbohydrates should be administered without delay. Beta-adrenergic blockers may be needed for control of tachycardia or hypertension. Analgesic as strong as morphine may be required to relieve associated pain. If the attack is severe enough and lasts for more than 48 h, with associated neurological involvement, intravenous hematin should be considered to facilitate resolution of neurological symptoms.

Porphyria Cutanea Tarda (PCT)

The disease is due to deficiency of the enzyme urogen decarboxylase which has been mapped on the short arm of chromosome 1. Mode of inheritance is in an autosomal recessive pattern. The enzyme catalyzes the decarboxylation of four acetic acid side chains of urogen III to yield coprogen III. The relevance of iron in the pathogenesis of PCT is well established. The clinical manifestation of the disease is often triggered by iron overload so that iron depletion remains the cornerstone of therapy in PCT. Specific treatment is accomplished by a series of phlebotomies and/or low-dose chloroquine administration. Two types of PCT have been recognized:

- *Type 1*: Sporadic PCT which usually affects adults
- *Type 2*: Familial PCT which usually affects children

PCT is probably the commonest type of porphyrias and is particularly prevalent in South Africa. It has been described in children in conjunction with either liver disease or prolonged iron therapy. Hift et al. reported

that viral hepatitis may precipitate overt PCT in the genetically predisposed child. The severity of the PCT declined as the hepatitis improved. PCT is rarely manifested in infancy or childhood. Most cases of childhood PCT are familial and some severe cases have been shown to have a hepatoerythropoietic porphyria or homozygous uroporphyrinogen decarboxylase deficiency.

Clinical manifestations are focused on the skin in the form of vesicles, bullae, scarring, crusting, and hyperpigmentation. Hepatic involvement may result in cirrhosis or even hepatocellular carcinoma. Diagnosis is confirmed by demonstration low level of the enzyme urogen decarboxylase in the liver or erythrocytes. Hepatic uroporphyrinogen decarboxylase activity is usually deficient but may be normal or increased in patients with PCT. Decarboxylase activity may return to normal after treatment, suggesting that the enzyme deficiency may be reversible. The characteristic pathological findings are alcoholic cirrhosis and excessive hepatic deposition of iron. The urine contains an excess of uroporphyrin. Acidified urine exhibits a pink fluorescence under UV light. Fecal porphyrin concentration may be normal or considerably increased. Serum concentration of iron and ferritin are increased in PCT.

Treatment includes avoidance of precipitating exposures as drugs (e.g., iron) or sunlight. Phlebotomy has been resorted to in some cases to decrease total body iron.

Hereditary Coproporphyria (HCP)

This type of hepatic porphyria with deficiency of the enzyme coprogen oxidase is also inherited in an autosomal dominant fashion with high penetrance and variable expressivity. HCP is considered to be the least common of the acute porphyrias. Affected patients present with neurovisceral, neurological, and mental manifestations usually indistinguishable from those of AIP. Clinical features also include gastrointestinal, neuropsychiatric, and respiratory manifestations together with sun intolerance. HCP is recognized by rather atypical clinical features and laboratory findings which could well attribute to the possible underdiagnosis of the condition.

Downey reported that a large number of patients with oral conditions and unknown pathophysiology had the clinical symptomatology and porphyrin abnormalities classically found in hereditary coproporphyria. Diagnosis is confirmed by the presence of low enzymatic activity of coprogen oxidase in the fibroblasts and leukocytes. Urine examination reveals excessive excretion of coproporphyrin, ALA, and porphobilinogen. The activity of hepatic δ-ALA synthetase is increased as in AIP.

Treatment is similar to AIP together with avoidance of exposure to predisposing factors as sunlight and drugs especially barbiturates.

Variegate Porphyria (VP)

The name "variegate" refers to the varied clinical features which may be exclusively predominantly cutaneous or neurovisceral. Variegate porphyria (VP) is also a type of hepatic porphyria with similar clinical features to other types of hepatic porphyrias especially AIP and HCP. VP has also been called South African genetic porphyria in reference to the studies of Dean who traced 236 cases of VP in 13 families which had descended from a Dutch couple who had settled in South Africa in 1688. The incidence among South African whites is about 1:333. The disease is inherited in an autosomal dominant pattern and characterized by the deficiency of the enzyme protoporphyrinogen (protogen) oxidase which is required for the transformation of protoporphyrinogen 1X (Protogen 1X) to protoporphyrin 1X in the heme biosynthesis pathway.

Clinical features usually involve the skin and nervous system. Over 80% of patients have skin involvement characterized by excessive fragility on mild trauma. Photosensitivity is usually mild but can be severe when there is concurrent liver damage.

The diagnosis is confirmed by the deficiency of the protogen oxidase enzyme in the lymphocytes and fibroblasts. There is excessive fecal excretion of protoporphyrin and coproporphyrin. During the acute neurovisceral attacks, there is considerable excretion in the urine of the porphyrin precursors δ-ALA and PBG, and of porphyrins.

Management of this disorder is similar to that of AIP.

Erythropoietic Porphyrias

These disorders are classified into two types of porphyrias.

Congenital Erythropoietic Porphyria (Gunther's Disease; CEP)

Congenital erythropoietic porphyria (CEP) is a rare metabolic disorder caused by deficiency of the enzyme uroporphyrinogen (urogen) III cosynthetase, the fourth enzyme of the heme biosynthetic pathway, which is required for the transfer of hydoxymethylbilane into uroporphyrinogen III. It is inherited in an autosomal

recessive pattern. This type has sometime been referred to as erythrohepatic protoporphyria in view of the evidence that liver may be also affected. There is a marked increase of porphyrins in the bone marrow, erythrocytes, spleen, urine, and feces.

The main clinical features of CEP are severe photosensitive dermatosis and hemolytic anemia. In the majority of reported cases, photosensitive skin lesions have occurred in the first few years of age. The disorder manifests clinically usually in the neonatal period with reddish brown staining of the diaper. Skin manifestations are prominent with the presence of photosensitive lesions in the exposed areas: vesicles, scarring, hyperpigmentation, and subsequent deformities of the phalanges, nose, and ears. There is blistering and bullous formation in the epidermis. Friable skin and hypertrichosis are present. Infections may cause extensive scarring and tissue loss, including loss of the eyelids and parts of the pinnae and fingers. The teeth may show reddish brown discoloration due to porphyrin deposits.

The disease may also manifest with other clinical features as pathological fractures, splenomegaly, and hemolytic anemia. Oguz et al. reported the presence of ocular involvement in two patients with congenital erythropoietic porphyria.

The prognosis is reported to be poor in severely affected patients. Death often occurs in early childhood. Diagnosis is confirmed by the deficient enzymatic activity of urogen III cosynthetase in the erythrocytes and fibroblasts. Erythrocyte protoporphyrin content is usually normal but exceptionally increased. There is excretion of large amounts of uroporphyrin I and coproporphyrin I in the urine and coproporphyrin I in the feces. The urobilinogen content of the feces is usually increased. In addition to the variable anemia, there is usually a reticulocytosis with normoblasts in the peripheral blood. The bone marrow shows erythroid hyperplasia.

Determination of the complementary DNA nucleotide sequence encoding the uroporphyrinogen III synthetase has helped to elucidate the molecular mechanisms underlying CEP.

Treatment includes avoidance of predisposing factors as sunlight, screening window light, protective clothing, barrier creams containing zinc or titanium oxide to improve light tolerance, together with hyper-transfusion regimen, and the administration of β-carotene. Splenectomy is indicated in the presence of hypersplenism. Oral administration of charcoal and hematin infusion have been used with good results. Cholestyramine may be used to bind and retard absorption of endogenous enteral porphyrins from the gut.

Bone Marrow Transplantation

Bone marrow transplantation (BMT) has significantly improved the outcome of severely affected patients with CEP. The role of BMT in many hematological and immunological disorders is well established. BMT in patients with CEP was first performed on a 10-year-old girl by Kauffman et al. The patient died of cytomegalovirus infection in spite of initial normalization of erythrocyte uroporphyrinogen synthetase activity. Thomas et al. reported the success of BMT performed on a 2-year-old girl with severe form of CEP. The authors recommended that HLA-identical allogeneic BMT should be proposed to severely affected patients with CEP as it might very well cure them.

Erythropoietic Protoporphyria (EPP)

Erythropoietic protoporphyria is a rare autosomal dominant disorder of erythropoietic porphyria, with variable penetrance, due to deficiency of the enzyme ferrochelatase, the final enzymatic step (step 8) in the heme biosynthetic pathway involved in the transfer of protoporphyrin IX to heme through the addition of iron. In children, it is recognized as the most common form of porphyria especially erythropoietic porphyria.

The disease is associated with excessive accumulation and excretion of protoporphyrin. EPP is also associated with mild cutaneous photosensitivity. Symptoms usually start in the first decade. Typically, within minutes or hours following exposure to sunlight, there is severe pain, pricking, itching, edema, and erythema of the skin. Blisters, cutaneous hemorrhages, and scarring are less common. EPP is the most common type of erythropoietic porphyrias. However hepatocellular disease, though rare, may be present and progress to cirrhosis. Cholelithiasis commonly occurs and often presents at an early age. The excess of protoporphyrin in protoporphyria is excreted exclusively by hepatic biliary secretion into the intestine for ultimate elimination in the feces. A significant proportion of protoporphyrin is reabsorbed in the intestine and may circulate through the enterohepatic circulation. The use of nonabsorbable binding agents as cholestyramine has been recommended for this reason. Rademakers et al. reported the presence of ultrastructural changes in the hepatic parenchymal cells even in early stages of the disease. The presence of changes in the bile canalicular ultrastructure suggests a defective hepatic excretory function, probably caused by the toxic effect of protoporphyrin. Liver damage is a significant complication in a small percentage of patients (5%) with protoporphyria.

Once jaundice develops, there is nearly always a rapid decline in liver function leading to death, unless liver transplantation is performed. It is not certain why some patients with EPP die of hepatic failure while most show no signs of liver disease. Rank et al. reported evidence of neurological dysfunction in end-stage protoporphyric liver disease due to protoporphyrin access to neural tissue when serum levels are markedly increased resulting in neurotoxicity. There is increasing evidence in the literature to suggest that protoporphyrin itself is a neurotoxin.

Diagnosis is confirmed by the low enzymatic assay of ferrochelatase in both erythrocytes and fibroblasts. Elevated free protoporphyrin IX is noted in the liver, erythrocytes, plasma, and bile. It is important not to miss the diagnosis of EPP because a number of patients may develop fatal liver disease. There is evidence that early detection can improve the outcome. The diagnosis of EPP is based on the presence of photocutaneous lesions, appropriate clinical and family histories, elevated levels of free erythrocyte protoporphyrin, and the absence of porphyrin in urine.

Treatment is focused mainly on prevention of exposure to sunlight and application of some sun protection measures. Sunscreens, particularly those blocking rays in the UV range, may offer some protection from the photodermatitis and other symptoms associated with sun exposure. Ross and Moss reported a reduction in the degree of photosensitivity with the use of oral pyridoxine. β-carotene has also been recommended but the dose required may be high enough to cause some side-effects as skin discoloration. Light-protective β-carotene is prescribed Cholestyramine and vitamin E have also been prescribed for patients with evidence of hepatocellular involvement. Cholestyramine helps to interrupt the enterohepatic circulation of protoporphyrin and lessen the level of hepatic protoporphyrin accumulation in patients with hepatic disorders.

Hepatoerythropoietic Porphyria (HEP)

This is a rare disorder due to the deficiency of the enzyme uroporphyrinogen decarboxylase (UROD), the fifth enzyme in the heme biosynthetic pathway. Decreased activity of UROD is responsible for three diseases:

1. Sporadic porphyria cutanea tarda
2. Familial porphyria cutanea tarda
3. Hepatoerythropoietic porphyria

HEP is inherited in an autosomal recessive fashion. The disease is a severe form of cutaneous porphyria that is usually manifest in early childhood.

The clinical entity is often difficult to distinguish from congenital erythropoietic porphyria. Clinical features include cutaneous photosensitivity, bullae, cutaneous erosions, discoloration of urine and teeth, hepatosplenomegaly, and hemolytic anemia.

Mutations of the UROD were identified. The first mutation in HEP, the substitution mutant G281E, was initially detected in a Tunisian family. Many other mutations were subsequently identified. Moran-Jimenez et al. reported two new missense mutations at the homoallelic state: P62L (proline-to-leucine substitution at codon 62) and Y311C (tyrosine-to-cysteine substitution at codon 311).

The identification of the molecular defects in UROD gene does allow*genetic counseling* and may hopefully lead to an effective*gene therapy* in the future.

Treatment is, at present, similar to that of CEP and EPP. It includes prevention of exposure to direct sunlight together with depletion of iron by repeated removal of blood to reduce urine porphyrin concentration to normal levels.

Screening for Porphyria

The porphyrias are group of inherited metabolic disorders in the pathway of heme biosynthesis. Relatives and siblings of index patients should be screened for latent porphyria. The finding of normal levels of porphyrin in the blood, feces, and urine does not rule out latent porphyria as these may only be raised during acute attacks. It is now possible to diagnose patients even with latent porphyria through the application of enzymatic assay.

It should also be possible that with the identification of the gene locus, a more reliable technique will be adopted to diagnose index cases and potentially affected relatives.

Secondary Porphyrinurias

Increased urinary excretion of porphyrin has been observed in many conditions as hemolytic anemia, pernicious anemia, liver diseases as chronic hepatitis, cirrhosis, Dubin–Johnson syndrome, diabetes mellitus, and heavy metal poisoning. These conditions must be differentiated from HCP and VP in remission by assessment of fecal porphyrins.

Differential Diagnosis

As porphyrias are recognized to have varied clinical manifestations with cutaneous, visceral, and neuropsychiatric

presentations, they should be included in the differential diagnosis of many disorders:

- Essential hypertension
- Hysteria and psychosis
- Acute surgical abdomen
- Hyperthyroidism
- Lead poisoning
- Tyrosinemia type 1

Safety of General Anesthesia and Surgery

It has long been recognized that patients with acute hepatic porphyria should be denied essential surgery because of the concern that general anesthesia, stress of surgery, operative medications, and surgery could well precipitate a life-threatening porphyric crisis. Dover et al. have reported following a major review of such an issue that major surgery can be undertaken safely in patients with porphyrias.

Postoperative complications have been reported mainly in patients prior to the diagnosis of porphyria. It is also important to ensure that patients with acute hepatic porphyrias undergoing surgery are kept on intravenous glucose infusion perioperatively until they are able to resume an adequate diet. It is also as important to choose the correct anesthetic agents and perioperative drugs and also to avoid starvation which could trigger an acute crisis.

Pseudoporphyria

Pseudoporphyria is defined as a cutaneous disorder characterized by skin fragility, vesiculation, and scarring in light-exposed areas affecting patients in the presence of normal porphyrin metabolism. This condition has been recognized recently associated with varied clinical conditions and medications. It has been reported in particular with naproxen therapy. Pseaudoporphyria has been induced not only by naproxen but also by other nonsteroidal anti-inflammatory drugs. Howard et al. were the first to report pseudoporphyria similar to porphyria cutanea tarda in patients with normal porphyrin metabolism but receiving naproxen therapy. Lang et al. reported that up to 12% of children with juvenile rheumatoid arthritis (JRA) receiving naproxen developed pseudoporphyria even without high sun exposure. Pseudoporphyria of the erythropoietic protoporphyria type has also been reported with naproxen therapy. The mechanisms of EPP-like-drug-induced pseudoporphyria remain unknown. Children with JRA should be protected from severe exposure to sunlight and should use broad-spectrum sunscreen and protective clothing including wearing a wide-brimmed hat while receiving naproxen therapy. Being aware of such complication, naproxen therapy should be discontinued in patients with JRA if they develop skin fragility or blistering.

Phototoxic reactions in patients taking nonsteroidal anti-inflammatory drugs should be well recognized. Moreover, since the recognition of pseudoporphyria-like eruptions in patients taking naproxen, other drugs such as ketoprofen, nabumetone, diflunisal, benoxaprofen, and tiaprofenic acid have also been recognized to induce pseudoporphyria.

Pseudoporphyria cutanea tarda has also been reported in patients undergoing peritoneal dialysis and receiving erythropoietin therapy. The clinical picture is similar to porphyria cutanea tarda but with a normal porphyrin profile. The mechanism of photosensitization due to erythropoietin therapy remains unknown.

Liver Transplantation

The recent adoption of liver transplantation in porphyria with end-stage liver disease has transformed the life of affected patients. Sarkany and Cox described a family in which two siblings with protoporphyria suffered from severe photosensitivity and developed hepatic failure requiring liver transplantation. It is not clear why some patients with EPP die of hepatic failure, while most show no signs of liver disease. Liver transplantation has been a life-saving procedure for patients who present with advanced liver failure where other available therapeutic modalities have proved ineffective. However, there are some operative hazards of liver transplantation in patients with protoporphyria. Exposure to bright surgical light during the operation may provoke a generalized motor neuropathy, hemolytic crises, or abdominal wall burns.

Polson et al. reported a successful outcome of liver transplantation in the treatment of EPP of a 13-year-old boy with end-stage cirrhosis and marked cholestatic jaundice. However, continued extrahepatic production of protoporphyrin was reported to result in recurrent allograft injury in patients with EPP. More recently, Meerman et al. reported two patients with EPP who were followed-up for 7 years after liver transplantation. Both patients have shown fibrosis with hepatocellular protoporphyrin accumulation 8 and 6 months, respectively, after liver transplantation. Reichheld et al. recommended the use of preoperative intravenous heme-albumin and plasmapheresis to reduce

the postoperative complications of orthotopic liver transplantation in patients with erythropoietic porphyria.

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Developmental, Learning and Behavioral Disorders

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42 Normal Child Development

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Introduction

Over the past centuries, there have been times when children were considered to be fully formed at birth and just needed feeding and education to prepare them for adulthood – such as during Victorian times. Caregivers and theorists assumed that the qualities of the child were already determined at birth. Child rearing was largely devoted to feeding, clothing, and providing formal education. Unfortunately this theory, in many cases, led to a failure to provide the caregiving environments that would foster child development and often led to children being punished for misbehavior that did not have the conscious intent that was assumed. Other times, experts postulated that parenting was the sole factor, or at least the main factor, which determined how a child matured into adulthood (such as during the period post World War II). Unfortunately, this led parents to be blamed (or to blame themselves) for developmental outcomes that they did not cause, such as when parents were thought to be responsible for autism in their child.

Current research has confirmed that development is partially determined by genetic and prenatal factors with the corresponding steps in neuromaturation that occur at each age. However, these steps are heavily influenced by other factors such as the interactions between the child and his environment, nutritional status, health, stresses, and, most importantly, interactions with key others.

Theories of Development

Several core theories of child development have influenced our understanding of children and how they develop. Each of these theories is based on extended observations of children and an effort to make sense of the developmental changes observed. These theories provide clinicians with insight about different components that likely play a role in child development. The patterns that theorists describe provide some insight into what is going on with the child, even if the theory eventually is "discredited." Some of the key theories that have helped shape our understanding of child development are described below.

Maturational Theory

This theory first emerged in the eighteenth century but subsequently most extensively developed by *Arnold Gesell* and his followers. It views the child as an immature organism who follows a predictable pattern and rate of maturation in the various developmental domains determined largely by internal factors controlled by genes. Maturational theory focuses on *fixed milestones* that the child achieves and a usual age range for acquiring those milestones. While maturational theory does acknowledge that environment can have an impact on development, this is largely seen in terms of environmental factors that might impede development rather than considering that environmental factors could enhance development. According to this theory, children must have an inner readiness to perform a task before they will be able to learn that task. The idea that development is linked to neuromaturational changes and proceeds in a predictable sequence is one that has stood up over time. The systematic look at developmental steps described by Gesell continues to be a useful way of thinking about the young child's development, although the model he proposed is more applicable to motor development and possibly early language development, and is weakest when applied to cognitive and emotional development.

Psychosexual Theories

These theories focus on the impact of early childhood experiences in shaping personality and emotional development. *Sigmund Freud* drew on his in-depth discussions with adult patients about their memories of their childhood experiences to develop a theory that proposes three parts of personality, the id, the ego, and the superego. In this theory, *the id* reflects basic drives or instincts and is the dominant force during early infancy. *The ego* is the aware or rational self and develops during late infancy and early toddlerhood. *The superego*, or the conscience, emerges during the preschool period between ages 3 and 6. He hypothesized that the way these components develop and are integrated during early childhood determines the

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individual's functioning into adulthood. He asserted that each stage has sexual meaning focused on a particular body part. Infancy is the *oral stage* (with sucking, feeding, biting as central). The *anal stage* follows during which the child masters control over his bowel functions with toilet training. The third phase is called the *phallic or the oedipal stage* and focuses on interest in genitals and resolving the competition with the same gender parent for the attention and love of the opposite gender parent. Freud believed that the successful resolution of the sexual conflicts of each of these stages results in a new level of emotional and social maturity.

Margaret Mahler proposed that a child's mental and physical relationship with his mother moves from one of *symbiosis to independence* through the first 3 years of life to allow the child to see himself as an independent person. According to this theory, the close relationship of a mother and infant was a crucial first step. *Erik Erikson*, in the mid 1960s, further expanded this to include psychosexual stages throughout the whole life cycle. He described each stage as tension between competing factors. Moving on to the next stage is only possible with resolution of the conflict. He also hypothesized that society and culture, in addition to family, play major roles in how successfully the individual is able to resolve the conflicts at each stage. The stages he describes for children include *trust versus mistrust* (birth to age 18 months), *autonomy versus shame and doubt* (18 months–3 years), *initiative versus guilt* (3–6 years), *industry versus inferiority* (6–11 years), and *identity versus role confusion* (adolescence).

Behavioral and Social Learning Theories

Behavioral theorists (*Ivan Pavlov, J. B. Watson, and B. F. Skinner)* believe that the environment is the primary source of change based on *patterns of reinforcement* of the child's behavior. They postulate that behaviors that are rewarded continue while those that are ignored or punished disappear. However, according to this theory, the child's own emotions, motivations, and styles of adapting play little role in shaping the child's development. As a result, this theory is limited in its contribution to the current understanding of child development, although it does provide important foundations for some of the interventions commonly used for problem behaviors.

Social learning theorists expanded on the work of the behaviorists by elucidating the role of *social models* in development. *Albert Bandura* one of the founders of social learning theory, describes children as mentally constructing models and developing behavior patterns on their own, learning from the models they see in their environment. This concept of the influence of the child's environment on his development and behavior is an important addition to current understanding of child development, although clearly only one factor in development.

Piaget

Jean Piaget published extensive theories of development of young children based on his detailed observations of the language and cognitive development of his own children. He is especially known for his observations that children think differently about things at different ages. He proposed that there were "stages of development" based on the way in which the child interacted with and interpreted the world around him. Piaget postulated that the sequence was fixed although the exact times of the shifts between stages vary from child to child.

He divided the child's approach to the world into four stages: the sensorimotor stage, preoperational stage, the stage of concrete operational thinking, and the stage of formal operations. In his *sensorimotor stage*, which usually occurs when babies are between birth and age 2, the child understands the world through direct sensations and motor actions. The child needs to master the concepts of *object permanence* (objects continue to exist, even when you can't see them), causality, spatial relationships, and the use of instruments (for instance using a rake to reach something beyond your reach) before moving on to the next stage. In the stage of *preoperational thinking*, usually occurring between ages 2 and 6, the child's thinking is egocentric. The child in this stage believes that the world is organized around him and his wishes. He needs to master his sense of animism (understanding that objects don't actually have a life although it is sometimes useful to describe them as doing so), egocentrism (the child is not the center of the world), idiosyncratic associations, and transductive reasoning (things are not necessarily linked just because they occurred at the same time) in order to move on to the next stage. In the stage of *concrete operational thinking* (usually ages 6–11), the child can reason through real and mental actions on real objects and can reverse changes in the world in his head in order to understand things. He can reason with a stable rule system and enjoys working with others to establish a set of rules. However, children in this stage continue to think about things in very concrete terms and have trouble imagining hypothetical situations. In order to move on to the next stage, the child must master the concepts of number, mass, volume, and linear time, deductive reasoning, and objective

causality. The final stage is called *formal operations* and occurs in youth sometime after the age of 12. In this stage, the youngster develops abstract thought, can reason about ideas, and can deal with broad abstract concepts. Steps for this stage include mastery of abstract thinking including inductive reasoning and complex deductive reasoning.

Moral Development

Lawrence *Kohlberg* builds on the basic Piagetian framework to describe children's moral problem solving. He proposes that children and adults solve moral dilemmas along a continuum but that the cultural context and values influence the stage in which the person thinks. *Carol Gilligan*, among others, objects to this schema, asserting that it is biased toward the male perspective and too much influenced by Western thinking. She points out that males and females tend to think about moral issues quite differently and that Kohlberg's concepts do not apply as well to children in non-Western cultures. However, there has been some evidence to support Kohlberg's theories that young children see rules as rigid and absolute while late school age children shift to understand that rules are things that a group of people agrees upon. Similarly, young children tend to view the damage done as determining their guilt while older children understand that intention to do wrong is a better determinant of degree of guilt.

Developmental and Behavioral Milestones

The developmental theorists described above tend to concentrate only on one or two realms of development at any given time. However, both parents and primary care providers are well aware that children develop in multiple areas simultaneously and that the child's development in one area impacts on the other areas of development. Observing and anticipating developmental milestones allows both parents and clinicians to provide and support experiences for the child that will enhance the development in each area. By convention, development is thought of as occurring in five areas: gross motor, fine motor, language, cognition, and social/emotional domains.

Infancy and Toddlerhood

During the first year and a half of life, the infant makes dramatic gains in gross motor skills. In general, gross motor development proceeds *centrally to distally* and *pronation precedes supination*. Typically, at birth, the child has little control over his motor state although should be able to move all of his extremities in a random fashion. Three developing processes allow him to acquire the skills to maintain upright posture and to move limbs across the midline of the body. These processes include the *balance between extensor and flexor tone*, *decline of the primitive reflexes* that the baby has at birth, and the *evolution/maturation of protective and equilibrium responses*. Evolution of these allow the infant to be able to hold up his head and later his chest when prone, roll over, sit with support, and get to sitting, and then develop the skills to be able to stand and then walk, such that the average youngster is walking by 12 months or soon afterward and running by 18 months of age. Fine motor skills move from being able to unfist hands, to reaching, transferring objects between hands, raking in objects, and then to developing a mature pincher grasp, all before 12 months of age (see *Table 42.1* for motor skills by age). Motor skills are less dramatic during the toddler years although there continue to be sizeable gains. Between 18 and 36 months of age, the youngster will become skillful in running, walking up and down stairs, jumping, and pedaling a tricycle. Similarly, the child will be skillful in scribbling and should be able to draw a vertical and horizontal line as well as a circle by age 3.

The rapid development in *sensory abilities* parallels and facilitates these changes. At birth babies already respond differentially to music they heard in utero. They quickly learn the sounds of their caregivers' voices and respond to them as well. At birth, a child can see clearly objects that are approximately a foot from his eyes, about the distance that the mother's face is from the baby when she is breast feeding her child. Objects that are closer than a foot or further away are seen much less clearly until around 2–3 months of age. This change at age 2–3 months, facilitates the development of motor skills with the child's hands. Vision further develops so that acuity and scope of visual fields is similar to adults later in the first year although full maturation does not occur until the preschool years. Sense of smell is also fairly well developed at birth. Soon after birth, babies can distinguish the smell of their mother's milk from the smell of other mother's milk. These rapidly evolving sensory skills contribute to and facilitate the attachment that is crucial for babies and their key caretakers. This attachment is key in social/emotional development.

Language development also has regular milestones related to maturational changes but seems to be more sensitive to environmental input than some other areas

Table 42.1
Motor and language development in infants and toddlers

Age	Gross motor skill	Fine motor skill	Receptive language skill	Expressive language skill
1 month	Head up when prone	Hold rattle	Responds to sound with startle or turns to look for source of sound	Crying
2 months	Chest up when prone	Grasps toy briefly	Turns to familiar voices	Smiles responsively, differentiated cry
3 months		Hands unfisted	Makes differentiated responses to familiar voices	Babbling vowels and few consonants
4 months	Rolls front to back	Hands to midline	Turns head to localize sounds	Laughs, squeals, says "ooh" and "ahh"
5 months	Sits with support	Transfers objects	Localizes sounds	Labial consonants (ba, ma, ga)
6–7 months	Sits without support	Rakes in toy, Bangs blocks together (7–8 months), transfers objects from hand to hand	Knows own name and familiar words (e.g., bath, doggy)	Repeats sounds
8–9 months	Pulls to stand	Immature pincher, feeds self pieces of food	Can do at least one simple "game" – peek-a-boo, so big, clap your hands, etc.	Jargon with the phonetic and intonation features of the child's native language
				Mama, dada nonspecific
10 months	Cruises holding onto furniture, Crawls or "cover territory"	Mature pincher – picks up small objects with thumb and fingers	Responds to simple commands – "say bye-bye"	Two syllable repetitions (baba, dada)
12 months	Cruises, beginning to walk alone	Releases – put down a small toy without dropping it	Points to objects – to share interest	Points to objects with vocalization; first words
15 months	Can bend over to pick up a toy on floor and then stand up without support	Scribbles on paper, uses a spoon to feed self but messy	Follows single step commands	Common to add and then lose words during this period
18 months	Walks up stairs, one stair at a time holding on	Tower of three cubes, Takes off shoes, socks	Points to body parts	10–50 words
24 months	Jumps with two feet, jumps down a step from last step	Uses a spoon without spilling much, uses turning motion with doorknobs or jars	Follows two step commands; Points at pictures in book	Two word sentences
30 months	Walks down stairs, both feet on each step, runs well, kicks a ball	Builds bridge from three blocks; copies vertical and horizontal lines	Can follow a simple story with pictures	Adjectives, possessives beginning to be used correctly
36 months	Walks up stairs alternating feet	Can string beads on shoestring; copies a circle, feeds self well with fork and spoon	Understands prepositions	Understood about three fourth of the time, beginning to use pronouns and plurals

of development and is closely linked with cognitive development. Although even deaf infants will develop initial sounds, if the sounds the infant makes are not reinforced by the responses of important people around them, these vocalizations will disappear. Hearing the sounds alone is not sufficient. For instance, hearing the sounds on TV or on audiotape does not result in the same mimicking of sounds after 8 or 9 months of age. By age 3–4 months, infants develop babbling repetition of all vowel sounds and some consonants. By 10 months, they start to produce two syllable repetitions such as dada, mama, and baba. Initially these are nonspecific, but as people surrounding them respond selectively to some and not to others, they begin to have a symbolic reference for the infant. The ability to attach a name for something requires a sense of object permanence. That is, they need to be able to hold an image of the object or person in their minds. Usually between 10 and 15 months, infants speak their first real words where there is a clear effort to name a person or object. They also begin to use symbolic gestures during this period, such as lifting their arms to indicate that they want to be picked up, pointing to objects that they want, and shaking their head to mean "no." Consistently, receptive language slightly precedes the same skill in expressive language. Children can point to pictures of animals or point to their body parts before they can name them directly. By age 2, they are putting words together and beginning to add adjectives as modifiers. By age 3 they are using prepositions correctly in sentences although they still may mix up pronouns. Their speech should be understandable by someone who does not know them about half of the time. Between 2 and 4, the clarity of their speech improves dramatically so that almost all of what they say should be understandable by age 4. They also will increase the complexity of their language by adding prepositions, correctly using pronouns, and beginning to use clauses.

Human understanding of children's cognitive development during infancy continues to evolve – partially because the ways of measuring and assessing cognitive development tend to be linked so closely to language and fine motor skills. Piaget vastly underestimated the cognitive skills of children because he was relying so heavily on language as a measure of their thinking skills. Even very young infants demonstrate signs of memory of auditory experiences, and appear to remember experiences that happened prior to birth. At birth infants already respond selectively to parent voices and maternal smells. They can learn simple patterns of behavior at quite a young age, even before they seem to understand the concept of object permanence, which does not appear until toward the end of the first year. By the end of the first year, they pay more attention to real words in the language of those around them as compared to nonsense sounds. By 18 months they are making categories of things, although these may not be the same categories adults might make. For instance, it is common for an 18 month old to call all animals "doggy." *Table 42.2* summarizes the major cognitive milestones of childhood.

For infants and toddlers, cognitive development, language development, and social/emotional development are completely intertwined. From very soon after birth, the infant fixes her eyes on key adults who are holding her and clearly pays attention more closely to those with whom she is attached. Very early on, the infant learns to engage in reciprocal interactions with those key adults, smiling at things they do and then laughing out loud when they do those things even more. The reciprocal interaction is key to development of both the cognitive connections in the brain and for the development of language skills. For the first few months, the infant's major goals are to learn how to regulate his systems, learn some self soothing, learn how to get assistance when he needs attention or tending to, and how to get comfort when he needs comfort. Once this self-regulation is in place, the infant turns her attention to interactions with those key adults, clearly responds differently to those important adults, and takes pleasure in those interactions. These interpersonal interactions are key for building the cognitive connections in the brain and for developing the initial components of language.

By 18 months, the toddler has developed a clear understanding that things continue to exist even when he can't see them, that his actions result in responses from both toys and people, and that he can manipulate the world around him, both literally and figuratively. After being closely linked to those key adults, the child now needs to exert his independence, to be able to function separately from those key people. This results in efforts on his part to begin to care for himself – feeding himself and beginning to use the toilet. He also is interested in the skill of removing his clothes and then later learning how to put them on himself. The toddler further exerts her independence by making liberal use of the word "no" just to stake out a position opposite that of the adult, even when she has conflicted feelings about it. Mastering that separation from those key adults is an important first step in growing to be an independent person.

Preschool Development

Gradually between the ages of 1 and 3, youngsters acquire the capacity to imagine things beyond what they can

Table 42.2
Childhood cognitive milestones

Milestone	Description	Approximate age of attainment
Early object permanence	Follows an object falling out of sight, search for a partially hidden object	4–8 months
Object permanence	Searches for an object completely hidden from view	9–12 months
Cause and effect	Realizes his/her action causes another action or is linked to a response	9 months
Functional use of objects	Realizes what objects are used for	12–15 months
Representational play	Pretends to use objects functionally on others, on dolls	18 months
Symbolic play	Uses an object to symbolize something else during pretend play	2–3 years
Pre-academic skills	Knows letters, numbers, shapes, colors, and counts	3–5 years
Logical thinking	Understands conservation of matter, multi-step problem solving; realizes there can be different perspectives	6–12 years
Abstract thinking	Able to hypothesize, think abstractly, draw conclusions	>13 years

directly see and, eventually, to imagine things beyond their experience. An 18-month-old child will pretend to drink from an empty cup while a 3 year old may pretend that that cup is a toy car on a trip to visit grandma. Throughout the preschool period, this imaginary play becomes increasingly complex and prolonged in duration so that, by the time the child is five, he may play an imaginary game all afternoon. This new imagination is both wonderful and very scary for these youngsters since they don't yet have a firm grip on what is real and what they just dreamed up in their heads. As a result, preschoolers tell wonderful tales but also can easily scare themselves with worries about monsters under the bed, or fears about all kinds of things from bugs to dogs. For many youngsters, the skill to be able to do a reality check and sort out real from imaginary doesn't fully mature until age 7 or 8. Even adults need to think hard about whether something is real or just imaginary sometimes.

At the same time, preschoolers become increasingly interested in interactive play with their peers. Prior to the preschool period, most enjoyed playing side by side with age mates and sometimes even stopped to watch what their peers were doing and then copied it. However, it is not until the preschool period that the play becomes truly interactive with multiple "turns" in the interactions. Preschoolers also develop a clear identity of themselves as a boy or a girl. This may involve excessive focus on activities that the child relates to his or her gender – such as always wanting to wear a dress – or it may involve "playing doctor" to check out the differences in anatomy between boys and girls. Often this exploration of gender includes being in competition with the same gender parent for the love and affection of the opposite gender parent (oedipal period). By the end of the preschool period, most youngsters resolve this by identifying more firmly with the same gender parent although the closeness with the opposite gender parent continues. Both motor skills and language skills also become more refined during this period. Preschoolers become adept at climbing and can convey their ideas in increasingly complex sentences.

School Age Development

The school age period is unique in that it is the one time during a child's life when the growth of his trunk and limbs proceeds at the same rate. This facilitates development of skills of coordination such as eye-hand coordination as well as kicking, batting, and throwing skills. The neurologic changes also facilitate development of fine motor skills such as writing and playing an instrument. At the same time, youngsters have acquired cognitive skills that facilitate learning to read and do math. The association between letters in certain patterns on the paper translating into words and sentences becomes something that early school age children find comes easily to them, especially if they acquired the building blocks for this during the toddler and preschool period. Key to learning to read is having had the experiences with books and being read to so that the youngster understands that print is a set of letters, which make up words and a story. Equally important is to have skills in "hearing" and appreciating that certain words begin and/or end with the same sound. Being able to come up with rhyming words and words that start with the same sound are important building blocks for reading. Similarly, in math, understanding the

concept of numbers and that number stays the same no matter how the items are arranged is a key concept to be able to understand the basic principles of addition and subtraction.

Later in elementary school, children become interested in classifying things and in learning about sets of things. In play this translates into interest in collections. In school, it translates into interest in learning about how things are similar and different and about categories of things – for instance learning about the differences between reptiles and mammals and which animals belong in each category.

Further developing skills in social interactions with peers is an important component of development for elementary school age children, both for the friendship skills that are acquired and because it gives the youngster perspectives about the world beyond those of his immediate family. Involvement in many activities for school age youngsters is motivated by two things – are there skills that will improve by participating in this activity and will she get to spend time with the kids she likes while doing this. Most commonly youngsters seek peer groups of the same gender during the early school age period although some youngsters seem to cross gender activities (such as the tomboy girl who loves sports) as part of the normal developmental process.

Adolescent Development

The teen years are a time of multiple physical and neurologic changes that have an impact on development and behavior. The hormonal changes, the rapid growth associated with puberty and the physical changes of puberty, and continuing evolution of brain development all have an impact on the adolescent's overall development. Recent studies suggest that the myelination of the areas that process motor and sensory information, as well as the areas connecting brain regions specialized for language and understanding spatial relationships is largely complete by the start of adolescence. However, the regions that deal with more advanced functions, including integrating information from the senses, reasoning, and other "executive functions" such as planning, organizing, and managing emotions, myelinate last and are not completely mature until the early to mid 20s. As a result, teens often misread emotional cues, especially in stressful situations, and are more likely to be risk takers because of the stage of their brain development.

In general, adolescent development is described as occurring in three phases: early, middle, and late adolescence. During adolescence, the teen needs to accomplish four goals. He needs to become independent from his parents, both psychologically and such that he is eventually capable of living on his own. She needs to establish her own identity, including a sexual identity. He needs to develop a career and a plan for his future. And she needs to develop a set of values congruent with society.

In *early adolescence*, the youngster is struggling to handle all of the changes of puberty – or struggling with why he or she has not yet started to have those pubertal changes. As a result, the teen often feels that his body is "out of control" with the rapid changes and may focus on the few things he or she does have control over such as hairstyle. Clothing choices often are made either to accent the changes or cover them up – thus the extremes of too revealing or very loose, baggy clothes that are often prevalent in early teen's attire. Early teens also focus on establishing their independence from parents as a first step in figuring out identity. In many ways it resembles the "terrible twos" in that early adolescents make every effort to be as different from their parents as possible in order to establish a separation. They may argue with their parents about trivial things, deliberately make choices that they know their parents would not approve of, and push the limits of whatever rules are set for them. The conflict of wanting to be independent but not truly able to be independent results in temper tantrums not dissimilar to those of the "terrible twos" although they usually involve more door slamming than kicking and screaming on the floor.

Middle teens' main focus is on establishing their identity including their sexual identity. They often take idealistic stances on things, reflecting some of their newfound ability to think in more abstract terms. For instance, it is common for a middle teen to become a vegetarian or be passionate about environmental causes. However, becoming independent is also a scary concept, so youngsters in early to mid adolescence typically are closely bound to their peer group and opt to dress and talk just like their peers. This often confuses parents because the parents correctly see this as not being independent at all, but just changing the dependent links. Early to mid teens may try out different persona, trying to find a role and style they are comfortable with. These efforts to sort out identity also apply to sexual identity. Early adolescents are coming to grips with their new sense of sexuality and will also experiment to figure out who they are in this arena. This is especially challenging for youths who come to sense that they may be gay or lesbian since both their school community and society as a whole may be very unsupportive of this identity.

While efforts to determine a career path may begin earlier, this is the main focus of late middle to *late*

adolescence. Prior to this time, most teens have trouble thinking ahead to next week much less thinking about long-term goals. However, by middle adolescence, the combination of a better sense of identity and more capacity to think long-term logically leads to efforts to set a career path. In addition, their increasing capacity for more complex and abstract thought leads them to establish a value system for themselves that allows them to function in society. These values may be very idealistic or very pragmatic depending on their experiences, both in their families and in their community, as well as their personal goals.

Screening and Assessment

Screening to determine children with early signs of developmental delay, followed by appropriate assessment and early intervention targeted at the specific documented problems, is crucial to enhancing child development. According to the guidelines set in the American Academy of Pediatrics 2006 Policy Statement, primary care providers should engage in *surveillance* for delays at each visit and *formal screening* for delays at the 9, 18, and 30 month (or 24 month if there is no planned 30 month) visits as well as formal screening when the question of delays occurs at other visits. This policy statement describes surveillance as consisting of five components: eliciting and attending to the parents' concerns, maintaining a developmental history, making accurate and informed observations of the child, identifying the presence of risk and protective factors, and documenting the process and the findings. Probably the most crucial of these is asking the parents about their concerns and taking their concerns seriously. Repeated studies have demonstrated that parents' identification of concerns has the highest correlation with a developmental disorder actually being diagnosed. However, for parents to feel comfortable voicing their concerns to their medical care provider, they must feel that the care provider is interested in their observations and plans to take their concerns seriously.

For the recommended *screening* at ages 9, 18, and 24 or 30 months as well as when parents have voiced concerns or when the other measures of surveillance suggest that there may be a concern, it is appropriate to complete a formal screening using a standardized test with a measure that has appropriate sensitivity and specificity. The goal is to identify which children need a full evaluation, missing as few as possible of those with a developmental disorder while not over identifying children. Over-identifying children can be a problem both because of the anxiety it provokes in parents and for the substantial costs of an appropriate evaluation.

The screening measure can be a parent questionnaire or a screening completed by staff in the office. Several are described in detail in the policy statement although most providers in the USA are choosing either the Ages and Stages Questionnaires (ASQ), which is available in English, Spanish, French, and Korean, or the Parents' Evaluation of Developmental Status (PEDS) (available in 14 languages). Both of these instruments are parent completed questionnaires that parents can complete while waiting for the visit and are easily scored in a matter of a few minutes. ASQ consists of a series of 19 age-specific questionnaires for children from 4 to 60 months of age. Each questionnaire asks questions pertaining to the domains of communication, gross motor, fine motor, problem-solving, and personal adaptive skills for that particular age child. It provides an option for the clinician to offer materials for parents to test if their child can do an item when they don't know the answer. Sensitivity is 0.70–0.90 and specificity is 0.76–0.9. PEDS is a parent-interview questionnaire with a single form used for any age of child (birth to age 8 years). Sensitivity is 0.74–0.79 and specificity is 0.70–0.80. The clinician or a member of the office staff can read the questions to the parent to obtain their observations of the child's development if parent literacy is limited for both of these parent report instruments.

The same guidelines note that using a general screen is best except in the case of autism since the symptoms of autism are quite different from other developmental disabilities. An autism-specific screening test should be used if there are parental concerns about autism, the clinician has concerns on surveillance, and routinely at a visit when the youngster is around 18–24 months of age. Unfortunately, there is not an excellent autism screening test at present. Currently most popular is the Modified Checklist of Autism in Toddlers (M-CHAT) (available in English, Spanish, Turkish, Chinese, and Japanese), a 23-item questionnaire that is intended for children ages 16–48 months. While the published sensitivity of this is 0.85–0.87 and the specificity is 0.93–0.99, subsequent studies have suggested that it has a strong tendency to over-identify children – in some studies only a third of the children identified by this screen were diagnosed with an autism spectrum disorder on further evaluation. Efforts are underway to add a second stage that may help address this problem with over-identification. Other social-emotional problems in children prior to school age can be identified via the Ages and Stages Social Emotional, the Brief Infant-Toddler Social and Emotional Assessment

(BITSEA), the Devereaux Early Childhood Assessment, or the Eyberg Child Behavior Inventory. Because of the complex interactions between environment and social-emotional status in young children, positive findings on any of these need to be investigated in depth before any diagnosis is given to the child. More typically, the sources of social/emotional problems in young children involve a complex interaction among many factors.

Older children's developmental delays usually are best identified by questions about their functioning in school since school performance relies on cognitive, language, and fine motor skills. However, screening for social/emotional delay and for behavior problems may require alternative measures. Asking about functioning within the family, with peers, and at school or daycare does give useful information. Probably the best accepted behavioral screen for school age children is Jellinek's Pediatric Symptoms Checklist. More in-depth questionnaires are available to use when questions have been raised and include the Behavior Assessment Scale Parent Rating Scale (BASC-P), the Conners' Rating Scale Revised (CRS-R), and Achenbach's Child Behavior Checklist (CBCL). Each of these has a parent form, a youth form, and a teacher form, is available in English and Spanish, and may help document the concerns in a systematic way, although none are diagnostic.

When children have a positive finding on a screen such as those described above, or when the parents or the clinician have sufficient concerns, even if the screen is not positive, a more extensive *evaluation* should occur. The primary care physician often completes at least part of this, reviewing the child's medical history, obtaining hearing evaluations if that is relevant to the concerns, and coordinating any further evaluation. The further evaluation could be done by a developmental-behavioral pediatrician in concert with appropriate other specialists such as speech and language clinicians, audiologists, and psychologists or could be done initially by an Early Intervention Team so that timely intervention can occur even if the medical component is delayed by long wait times for evaluation. In the USA these early intervention teams are linked to services available under Part C of the Individuals with Disability Act (IDEA), where services can be provided to the child and his family once developmental delay or certain specified risk factors for delay are documented. This more extensive evaluation should look in detail at the child's and family's medical history, and include the specific details about the child and his developmental skills, a physical exam, an assessment of his sensory capabilities (especially hearing and vision), an assessment of the child's strengths. Appropriate additional testing will be determined by the specific details about the findings.

Influences on Development

While developmental steps are determined by neuro-maturation, exactly how development proceeds for the child is influenced heavily by the child's experiences as well as by the child's nutritional status and exposure to toxins, the environmental stimulation and the quality of caregiving the child has had, stresses both for the child and his caregivers, and the child's health. Research has shown that the particular experiences the child has, especially during critical periods, lead to the creation of connections within the brain and the preservation of cells in the brain. Connections not made during certain critical periods and areas not used are pruned out. While there is some opportunity to establish new connections at later points, it often is accomplished in ways that are less efficient or less useful than if the connections had been established during the usual critical period. One example of this is the development of binocular vision. If the input from the eyes is such that a double image is created, as with children with ambylopia, the brain stops processing the image from one eye so that the input makes sense. Correction is possible up to a certain age but beyond that age (sometime in early elementary school), the brain will no longer process information from that one eye, even if the muscle imbalance between the eyes is fixed.

However, the impact of experience is not unidirectional. The child's behaviors and responsiveness have a profound effect on those around him and, in turn, influence the behaviors of people toward the developing child. This is referred to as the *transactional model* of development. When a child has a challenging temperament or when his style clashes with that of the parent, less than optimal interactions may result. Parents are less likely to interact with a child who is irritable or who is slow to respond to their efforts at interacting. So, the challenge is to foster optimal interactions and especially to identify situations which may interfere with optimal interactions, whether they are problems with the child or with the adults in the child's life.

Environmental Influences on Development

Many environmental factors influence development, including nutritional factors, presence or absence of toxins, and factors such as noise, light, and availability of appropriate toys, etc. Adequate nutrition including adequate protein, vitamins and essential minerals can have a profound effect on the child's development. For instance, Betsy Lozoff's studies of Costa Rican children

with iron deficiency anemia have documented that children with severe iron deficiency, even when the iron deficiency is promptly corrected once discovered, have lower cognitive skills and more behavior problems than their peers who never experienced iron deficiency. Clearly iron deficiency during critical periods of brain development has long lasting effects on the child's brain. Similarly, multiple studies document that children who experience failure to thrive, no matter what the cause, will have lower cognitive functioning, even when their growth rates return to normal.

Equally, it is known that toxins have long lasting impacts on growth and development. Children with elevated lead levels continue to have higher rates of behavior problems and lower cognitive scores than similar peers without lead exposure. Other toxins, such as mercury, have also been documented to have long lasting effects on brain functioning. Likely there are other substances that similarly interfere with optimal growth and development.

The physical environment also has an impact on youngsters. Studies have demonstrated that children respond differently to the sounds that they heard while in utero. Similarly, premature babies grow better when the noise level of the intensive care nursery can be kept down. Higher levels of ambient noise, caused by the elaborate machines used in caring for premature infants, inhibit growth in these small children. Equally, the availability of appropriate toys for a given age has an impact on development. For instance, multiple studies document that the presence of books in a household is correlated with the child's language development. While the key component of this language development is the adult–child interaction related to books, having books readily available is an important component to foster both language development and early literacy skills. The toys need not be elaborate or expensive, but can play a major role in facilitating development at a given age. For instance, for a toddler, access to a plastic cup and plate, as well as couple of pots and pans and a big wooden spoon will help foster imitation and early pretend play.

Familial Influences on Development

As mentioned above, families have a profound impact on their children's development, especially in the areas of cognition and language, although other areas of development can also be influenced by family environment. The time and attention given to the child by family members and the qualities of that attention play a major role in infant and toddler development. However, families continue to have a major impact on development in older children as well. For example, the academic success of high school age youngsters is highly correlated with whether or not the family eats meals together routinely as a family.

Children today are raised in families with a wide variety of family composition. Western countries are unique in having nuclear households be the norm. For most societies, extended families live in the same household or are frequent household visitors and all play a major role in child rearing. When the nuclear family assumes the major or sole responsibility, features about the family potentially can have more impact on the child. The idealized American two-parent household is only advantageous if the parents agree about basic childrearing and both are actively involved. Single parent households are more challenging, not because a single parent cannot do a good job of rearing his or her child, but because the stresses of earning a living, managing the day to day responsibilities and childrearing are falling on one person alone. This is complicated by the fact that many single parent households struggle much more financially, thus diverting time and energy from the tasks of child rearing. There are now multiple studies that also confirm that having gay or lesbian parents does not impact child development. Children reared by same sex couples do as well on average both developmentally and behaviorally as children reared in more traditional households.

Similarly, family composition in terms of number of children and the spacing of children has minimal effect on child development, if all other things are held constant. When family composition seems to be related to child development, the key factor is usually other stressors, such as the stress of more mouths to feed, challenges posed by a particular child in the household, or parental over-commitment to careers at the expense of time and energy devoted to child rearing.

Parental mental health has a clear impact on children's development. Young children with depressed mothers demonstrate substantial delays in cognition and language. They are likely to have a higher incidence of internalizing mental health problems as they get older as well. This impact can be moderated if there are other adults in the household who can take over the role of providing responsive, caring interactions with the young child on a regular basis. Similarly, there are several studies now that have shown an association between having a parent in the household who has aggressive behaviors or problems controlling his or her temper and a child's risk for demonstrating aggressive behaviors. Children in abusive households have long-term consequences for development,

their mental health, and their adult physical health at least partially related to the impact of stress on the developing brain.

Societal Influences on Development

Most children are influenced not just by their families but also by other social institutions in their communities. Multiple studies demonstrate that the quality of childcare has a clear impact on children's development. Children who are enrolled in high quality childcare with low child to caregiver ratios and with caregivers who are nurturing and provide a stimulating environment do well. For children from households where there is limited nurturing possibly due to financial hardships or exhausted parents, this quality childcare or preschool can make a dramatic difference in the child's success in language development and acquisition of academic skills. The long-term studies from the original Head Start Programs in the USA indicate that such a comprehensive preschool program can also have an impact on the children's ability to graduate from high school and avoid involvement in illegal behavior in adolescence.

Similarly several studies look at qualities of schools and the impact these qualities have on the academic and social success of their students. While class size does make a difference, it takes a dramatic decrease in class size to have a substantial impact on the children's academic success. On the other hand, schools with high expectations for their students' ability to be successful, who display and celebrate students' good work, and who encourage active involvement by students and faculty in decision making at the school level have students who perform better.

Extensive research has examined the impact of media on child development. Clearly there is a role for media in enhancing development, when media is used constructively, in moderation, and at the correct age. The American Academy of Pediatrics has strongly stated that children under age 2 should not watch television or videos, saying that it does not enhance development and detracts from time and energy that should be spent in interactive activities with the child. For older children, the impact of television watching is less clear, although children with high levels of television viewing are likely to have lower grades in school, more symptoms of depression, and more problems with obesity. Additional concerns center on the effects of violent programs for children and the impact these have on children's emotions and the strategies they use to address interpersonal conflicts.

The impact of institutional care can be profound on the children who need the help of institutions outside the family for their rearing. Research on children in orphanages in the former USSR countries by numerous authors has clearly demonstrated that those children from orphanages have long-term impairment in physical growth, cognition, and behavior, despite having their basic needs met. The staff members are too busy to have meaningful interpersonal interaction with their charges which leads to the deficits seen. Children who were removed and put into foster care in the same country had substantially better outcomes although the differences in outcome depended on what age they went to the orphanage, staffing at the particular orphanage, and how long the child stayed at the orphanage.

For children for whom home is not a safe or healthy place to remain, foster care remains a viable option. However, the stability of the placement and the quality of care have substantial impact on the development and mental health of the child. Long-term foster care, especially if it involves replacement in different households, clearly has negative consequences for the youngster. Children have better outcomes when foster placement is a short-term solution and the child is either reunited with their family who is now able to care for the child or who is adopted by a family committed to the development of the young child.

Chronic Illness and its Influence on Child Development

The impact of chronic illness on child development is dependent on multiple, complex factors. Development usually draws on input from all senses resulting in special challenges for children with sensory impairment. A child who cannot see will have difficulties in learning to name objects. A child who cannot hear will not be able to develop spoken language until the hearing problem is corrected. Children with cyanotic heart disease, chronic renal failure, or other disorders that affect their energy levels will be influenced by their lack of energy as well as by the altered focus of parent attention. However, in most chronic illnesses, the child's development can proceed normally. Some children may, in fact, have advanced understanding of some complex concepts such as illness causation.

Stress and Child Development

Stress is an inherent component of life. Research on stress suggests that some "stress" promotes child development by motivating the child to seek and master challenges. The steps to mastering those challenges may well be "stressful"

but the cognitive processes by which the child seeks to solve the problem to master the new skill enhances, not detracts, from his development.

However many stresses are beyond those of typical life. These can include illness or death of a family member, loss of family income, parental promotion at work, a household move, addition of a new sibling, parental separation or divorce, national or local disaster, etc. Refer to Chap. 50, "Children in Disasters", for a more extensive discussion of the effects of stress on the developing child.

Summary

Children's development is a complex process, partially determined by genetic factors but heavily influenced by the key people in the child's life and the events that happen throughout the developmental stages. Parents, and others caring for children, can play a central role in fostering development by being sensitive to the developmental stage of the child, his unique personality and temperament, and the kinds of stimulation and opportunities which will best foster development for the individual child. Helping the child build on his individual strengths and helping him find ways to master the developmental tasks of each stage and work around the challenges of his individual situation will help produce a mature, resilient young adult.

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43 Behavior Management of Medical Problems

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Introduction

In pediatric practice, it is common to encounter medical conditions that are complicated by the complex relationship between parent and child, as well as by the child's own temperament and beliefs about his or her own illness. For a number of common problems such as colic, encopresis, poor feeding, and insomnia, a combination of medical and behavioral interventions is often needed for optimal management. Furthermore, chronic medical illnesses in childhood often have behavioral comorbidities that complicate their treatment. As a result, pediatricians are often called upon to design behavior plans to complement medical treatments. The goal of this chapter is to help physicians understand and be able to develop and implement behavior plans with their patients.

In developing an effective behavioral program, the following components should be taken into consideration: (1) developing and maintaining positive parent–child interactions; (2) defining the behavior to be changed; (3) measuring and monitoring the target behavior; (4) setting a behavior change goal; (5) developing specific strategies to change the behavior; (6) implementing and evaluating the behavior program; and (7) maintaining behavior change (*Table 43.1*). Each of these steps will be discussed in detail, utilizing several case examples.

A basic knowledge of types of learning and common behavioral management techniques is also useful in designing a behavior plan, and these are summarized in *Tables 43.2* and *43.3* for your reference. These will be helpful to refer back to as three clinical cases are presented, each highlighting a different developmental stage, and addressing specific behavioral considerations and interventions.

Case 1: Infant with Colic and Feeding Problems

Ming is a 5-month-old infant, who was born to 29-year-old Suyin. Suyin has a history of depression and migraines. Ming was born full-term via C-section due to breech presentation. His father is away, fulfilling a military obligation. Because of long-standing fussiness around feeding, Suyin gave up nursing Ming. It now takes up to one hour to feed Ming with a bottle because he gags, spits up, and hiccups during and after his feedings. Physical examination is normal, weight gain has been appropriate, and he is developing well. His mother has tried three different formulas and many different nipples trying to get Ming to eat. She reports that he wakes every hour in the night to feed, and "catnaps" in the day in his mother's arms. She reports a total sleep time of 6–8 hours out of 24. Ming cries especially hard in the evenings and does not have a consistent bedtime. He has a hard time falling asleep at night. His mother sometimes resorts to running the vacuum close to him or taking him on a late-night car ride to get him to fall asleep. Suyin also reports that Ming wakes every hour at night requiring her help to return to sleep. Suyin admits that she is exhausted and near the end of her rope. She questions her adequacy as a mother.

Although crying is a common complaint among parents of infants, prolonged crying can negatively affect the parent–child relationship and can lead to increased parental symptoms of anxiety and depression. Infants with colic may also have difficulty with feeding, and the relationship between this infant's crying and feeding difficulties can be examined and addressed using the Seven Steps to Behavior Management model (*Table 43.1*).

1. *Developing and maintaining positive parent–child interactions*: Before implementing any behavior strategy, it is important to establish a foundation of trust and to nurture the bond between parent and child. In general, increasing the number of positive interactions parents have with their children leads to a decrease in the number of negative interactions between them. Enriched or enjoyable environments provide a basis for the use of time-out or ignoring as an effective deterrent of negative behaviors. Finding ways of rewarding a child, even an infant, for desired behaviors, rather than punishing him for undesired behaviors, tends to be a more effective way of changing behavior.

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Table 43.1
Seven steps to behavior management model

1. Develop and maintain positive parent–child interactions • Conflict related to medical and behavioral issues is common. Increasing positive interactions is essential to successful behavior management. A positive, soothing regular bedtime routine and a media-free family mealtime where parents and children share their daily experiences are two examples of ways to implement this.
2. Define the behavior to be changed • What behavior do parents want to change? Define a behavior that can be measured and tracked so that progress can be determined.
3. Measure and monitor the target behavior • Set up a recording chart, diary, or journal for baseline data collection of the target behavior.
4. Set a behavior change goal • Set a measurable, specific, obtainable goal
5. Develop specific strategies to change the behavior • Review all strategies to be implemented, have a recording system (sticker chart, diary) to monitor progress
6. Implement and evaluate the behavior program • Emphasize consistency, monitoring, and reinforcement as appropriate.
7. Maintain behavior change • Often involves gradually fading the external reinforcement

There may be many barriers that make it difficult to establish positive interactions between parents and their children. For example, parents may feel overwhelmed with the responsibilities of parenting; or other jobs or relationships may impact parents' abilities to enjoy their time with their children. In addition to teaching parents to attend to even small instances of positive child behavior, specific behavioral techniques such as *special time* (see *Table 43.3*) can be implemented to increase positive interactions between children and parents.

In this case, positive interactions between Suyin and Ming may be limited due to the stress of single parenting while Suyin's husband is completing military service, along with Ming's sleep difficulties and Suyin's resulting exhaustion from her own disrupted sleep. Screening for maternal depressive symptoms is important, given her history, and its potential influence on her parenting behaviors. Review of Ming's growth and development can provide reassurance to Suyin that her son is doing well despite his feeding and sleep issues. The clinician should help Suyin identify times when she can enjoy her time with Ming. Often early in the day is preferable, because both she and Ming may feel the most rested at that time. The provider/pediatrician could discuss simple activities such as singing, looking at books, cuddling together, "tummy-time," "peek-a-boo" and other play activities. When providers point out how well a child is growing and developing and compliment parents for their hard work and for being responsible for these gains, this enhances the provider–parent relationship and can also model how praise can also enhance the parent–child relationship.

2. *Defining the behavior to be changed*: It is important to be specific when determining what the goals are in behavior management. At the outset, it is often helpful to work collaboratively with parents to "break down" complex goals or behaviors into simpler component behaviors that can be measured and observed for improvement. Although the temptation may be to tackle the most bothersome behavior first, it is often helpful to choose a small and simple behavior to address initially, even if the family has many concerns. Success with changing the initial behavior will empower parents to have more confidence and become more invested in addressing additional, more difficult, behaviors.

In Case 1, Suyin is clear that she wants Ming to cry less and sleep more. During infancy, sleeping, crying, and feeding are very closely associated with one another. Before attempting to change these behaviors, it would be most helpful to understand Ming's crying, sleeping, and eating behaviors. Tracking when, how long, and where Ming is crying and sleeping, as well as how these interact with his feeding schedule is a logical first step.

3. *Measuring and monitoring the target behavior*: The effectiveness of any treatment is difficult to assess without a measurable outcome. As such, if a behavior cannot be measured and monitored, then it would be difficult to develop an intervention to change it, because any objective change would be very difficult to discern. Measuring and monitoring involves counting the frequency, the intensity, and the duration of a behavior. The "ABCs" – that is, the *Antecedents* to the *Behavior*, and its *Consequences* – should also be noted. These should all be documented in written form. Parents often learn about the behavior they are interested in changing during this step, for example, realizing that it happens more or less often than they thought or that it has a pattern of antecedents or consequences associated with it. Just by monitoring Ming's crying, feeding, and sleep, Suyin is likely to feel more in control of what is happening, and more likely to identify times where she can implement positive time or other helpful strategies. *Figure 43.1* (Infant Behavior, Cry and Sleep Diary) illustrates one tool that can be used to measure and monitor infant behaviors.

Table 43.2
Types of learning and their clinical application

Types of learning	Examples	Application
1) Classical Conditioning (also called *Pavlovian Conditioning*) is a type of learning related to an automatic or *reflexive response* to a specific stimulus	A child comes to associate the pediatrician's office with painful immunizations. When he goes to the office for any cause, the child becomes anxious, fearing getting a shot. A child with leukemia becomes nauseated while dressing to go to her chemotherapy appointment.	This type of learning plays a role in the development of phobias, food aversions, and school refusal. Interventions often include gradual exposure to the *conditioned stimulus* (pediatrician's office) paired with a more desirable stimulus (children's book or sticker rather than immunization) to decrease the response (fear). This is called *counter conditioning*. Classical conditioning can also teach desired behaviors: e.g., a bedwetting alarm wakes a child when she begins to wet.
2) Operant Conditioning (also called *Stimulant-Response Learning*) is a type of learning that occurs in response to environmental consequences. Operant behaviors are influenced either by *antecedents* to the behavior, or *consequences* of the behavior. Consequences may either increase the behavior (*positive and negative reinforcement*) or decrease the behaviors (*punishments or deterrents*).	A preschooler swears when he becomes frustrated. His older brother laughs when he hears it. The preschooler interprets his brother's laughter as approval and swears more because he enjoys his brother's attention.	This type of learning often plays a role in the development of 3 types of behavioral concerns: 1. *Behavioral excess* (e.g., aggression or tantrums) 2. *Behavioral deficiency* (e.g., toileting or food refusal) 3. *Inappropriate behaviors* (e.g., inappropriate dress, language, or touching). Interventions to increase or decrease the frequency of these behaviors focus on consequences following the behavior. Interventions aimed at changing the time or place of the behavior focus more on antecedent events.
3) Social or Observational Learning is a third type of learning that occurs through *modeling* or *imitation*. This learning may be either purposeful or incidental.	Parents may inadvertently promote undesired behaviors such as smoking by modeling them, even while talking about the dangers of this habit. Actions often speak louder than words.	Children learn most commonly by watching those most important in their world (family, friends, celebrities) and then by emulating them. The influence of the model on the child's behavior increases with the child's perceived similarity to the model and the status and success of the model in the child's view.

This Infant Behavior, Cry and Sleep Diary is used to monitor patterns of infant sleep, feeding, and crying behaviors. Number of hours spent fussing, crying, sleeping, awake, and eating should be totaled at the bottom as measurable data to be used for comparison. Diaries can be color-coded with highlighting markers to ease interpretation and to facilitate comparisons across 2–3 days and from week to week.

In this Case, a diary approach is useful, because the behaviors Suyin is trying to address are highly interrelated. This diary records feeding, crying, sleeping, and awake behaviors in 15 min intervals, as illustrated in ❯ *Fig. 43.1*, and should be kept for 2–3 days. Although monitoring behavior every 15 minutes for even a day or two is labor intensive, in clinical settings, in developed countries, more than 80% of parents can collect these data

Table 43.3

Behavior management techniques and their applications

Behavior management technique	Examples	Application
1) Time-in: Parents are encouraged to have frequent and brief positive physical, verbal, and visual contact with their child throughout the day, whenever the child is engaged in non-problematic behaviors. *When a child's behavior is praiseworthy, it should be praised consistently*. There are many variations of Time-In that are commonly advocated to teach children desired behaviors. These include advice to find moments to praise children in order to "*catch them being good*" and to have regular "*Special Time*" or "*Me Time*"	With "*Special Time*," parents plan an opportunity to observe their child's positive behaviors, perhaps during a creative activity and make sure that they praise the child for her effort and accomplishments. "*Me Time*" is time in which the child generally chooses what she wants to do within reason. The child is given choices from an array of desirable activities that usually include parental involvement. This should occur frequently, optimally daily. Naming the time "Me Time" or "Andrew Time" often elevates it in stature in the child's view.	"*Time-in*" *is an essential prerequisite for any behavioral management program*. *Special time* should not be removed as a punishment. *Time-in* and *special time* are conducive to a child's learning appropriate behaviors and her motivation to cooperate. They are more helpful when they occur often and regularly (but are not necessarily longer than 10–20 min), than when they are much longer but occur only rarely.
2) Time-out: The child is given time away from *positive reinforcers* such as desired activities or family attention. This is one of the most common forms of punishment used in most behavior management programs. In order to be effective, *time-out* should happen immediately and consistently after the targeted misbehavior. The duration of a *time-out* is generally short (approximately 1 min per year of child age) but may need to be extended if the child continues to misbehave or protest when the "time-out" would be expected to conclude (using a timer is recommended). *Time-out* is most effective with *time-in* and when applied to infrequent dangerous, or destructive behaviors.	1. Make a short and clear command or request of the child ("Please stop. . .") 2. Give a clear warning if the child does not respond to the request ("if you don't do what is asked, then you will have to sit in *time-out*"). 3. If the child does not complete the command or request, administer *time-out*. Select a location with as few pleasurable distractions as possible (i.e., the bottom step of a staircase, or a chair in a boring part of the room) and do not reason or talk with the child. *The child should be completely ignored during time-out*	*Time-out* is most effective in 2–6 year olds, but can be effective in older children as well. Be prepared in case the child refuses to go to time-out. Effective alternatives are adding additional time or, if the child still refuses, giving the child a choice of either going to *time-out* or losing a privilege. Following a *time-out*, the original command or request should be repeated. If the child does not comply, repeat the procedure. Once the child has complied with the request and the *time-out* is over, it should be forgotten, rather than dwelled upon.
3) Stimulus control: Controlling behavior by limiting access to antecedents that served to increase that behavior.	An overweight boy who drinks many sugar-filled sodas each day can be aided in decreasing this habit when his family decides that the whole family will only drink sodas on Sundays. Sodas are only available in the house on that day.	As in any technique, collaboration is key. Making sure the child is aware of the rule/expectation prior to implementing the strategy will be necessary in order to minimize protests from the child.
4) Differential reinforcement of incompatible behavior (DRI): Reinforcing a behavior that is not compatible with the behavior that is targeted for extinction.	A child with dermatitis exacerbates her condition by scratching in her sleep. *DRI* might include praise and a desired outing after a specified number of successes in wearing cotton gloves at night to limit scratching.	There are several types of differential reinforcement; however, the overarching principles include reinforcing wanted behaviors and withholding reinforcement for unwanted behavior.

Table 43.3 (Continued)

Behavior management technique	Examples	Application
5) Shaping: Gradually increasing a behavior by giving positive reinforcement to small increments (*successive approximations*) of the target behavior. Most commonly used to develop a new behavior pattern.	A preschooler who is refusing to eat vegetables is rewarded with a sticker first for allowing the vegetable to sit on her plate, then for touching the vegetable, then for smelling it, then for licking it, then for tasting it, then for eating a bite. A row of stickers earns a trip to the ice cream store.	*Steps* (*successive approximations*) should be identified before attempting to shape a behavior. Carefully outlining small increments of the behavior will facilitate success for the child and minimize frustration in the process.
6) Systematic desensitization: Gradually increasing a child's exposure to an anxiety-producing stimulus in order to enable him to gradually overcome his anxiety.	A child with school avoidance based on fear of bullying may be gradually exposed to school by attending one class on the first day, two classes on the second day, etc. while other supports like counseling are in place. This is also very effective with children who fear medical procedures.	*Systematic desensitization* is most commonly used in children who exhibit difficulties with anxiety. This technique usually includes careful instruction in relaxation training.
7) Fading: Gradually decreasing a *positive reinforcer* as a desired behavior becomes integrated into routine. This is the natural response once a new behavior is learned. Fading also refers to changing something gradually.	Once a toddler learns not to jump on the couch, he may not need to get hugs for each time period that he refrains from jumping. Gradually moving bedtime earlier by 15 min every 3 days is another use of fading.	*Fading* can often be used to reduce the level of protests displayed by a child. Gradually changing a behavior instead of abruptly changing it commonly results in less confrontation.
8) Planned ignoring (*extinction*): Withdrawal of all attention when a child is engaging in an unwanted behavior. Ignoring should only be used in situations that are nondangerous and nondestructive.	A toddler who often throws tantrums when wanting an unhealthy snack can be *ignored* by the parent who continues to perform another act (e.g., reading book, cleaning up, etc.) until the child's escalation ceases. Most useful for behaviors such as whining, tantrums, pouting, and arguing	*Ignoring* should include no physical contact, no verbal contact, and no communication non-verbally (i.e., no making faces, eye contact, etc.). Expect an *extinction burst* or an initial sharp increase in the child's unwanted behavior; however, with continued use, the unwanted behavior will decrease.
9) Redirecting: Changing the child's attention from one interest to another.	A toddler sees a child eating an apple and whines for an apple herself. Her mother does not have an apple to give and so she redirects her daughter's attention to the dogs across the street playing in the yard.	Redirection is most effective in younger children.
10) Corporal Punishment: Application of *physical pain* as a *punishment* with the goal of discouraging unwanted behavior.	Spanking and other physical punishments are commonly used for discipline. However, with recurring use, increasing intensity may be required to attain desired decrease in problem behavior, which can lead to significant injury. It can also result in other discipline methods losing their effectiveness. Parents should be assisted in learning other techniques to deal with problem behavior in children.	Research suggests that corporal punishment teaches children that hitting is acceptable, negatively alters parent–child relationships, and results in aggression in children. In addition, corporal punishment is not more effective than other discipline approaches.

Infant Behavior, Cry and Sleep Diary

During each 15 min period of the day you are to indicate the main activity of your baby.

The baby behaviors you will record are: **F** = Fussing **C** = Crying **S** = Sleeping **E** = Eating **A** = Awake

_____ _____ _____ _____
Day of the Week Month Day Year

12MN 1AM 2AM 3AM 4AM 5AM 6AM 7AM

8AM 9AM 10AM 11AM 12noon 1PM 2PM 3PM

4PM 5PM 6PM 7PM 8PM 9PM 10PM 11PM

Where baby falls asleep (**S** = swing, **A** = arms, **B** = parents' bed, **Ba** = bassinette, **C** = crib, **CS** = car seat)
Place above the block designating onset of a sleep episode. If baby is bottle feeding, put volume that is taken above times he/she is eating.

Best 5 min of the day _____

_____

For office use only:
Total Hours Fussing _____ Crying _____ Sleeping _____ Awake _____ Eating _____

Source: Adapted from the Brown Center for the Study of Children at Risk, Brown University and Women and Infants' Hospital, Providence, RI, USA

Figure 43.1
Infant Behavior, Cry and Sleep Diary

dependably and find the results informative and helpful. Diaries can also be used to prompt parents to note the "best 5 minutes of the day," which practitioners can use to help build on existing positive interactions between parent and child (as discussed in Step 1).

In review of her behavior diaries, Suyin noticed that Ming only woke up every 3 hours at night, not every hour. Ming slept only 10–11 hours out of 24; although this was more than his mother's perception, her concern was validated because it was less than what would be expected for his age. Furthermore, his sleep phase was noted to be shifted with a bedtime after midnight and late morning waking. Evenings were especially difficult with 3–4 hours of crying after 7 PM. His feeding times were prolonged, and she was feeding him only 1½–2 ounces every 1½–2 hours.

4. *Setting a behavior change goal*: After a period of monitoring, the clinician should help the parents identify patterns in the occurrence of the observed behavior, and help them develop a desired goal. It is important to set realistic goals so that the patient and family can experience success early in the course of treatment. Success encourages the family – and child – to continue the program. Over the course of an intervention, the patient and family should be encouraged to set a number of intermediate goals on the way to achieving the goal that is ultimately desired.

Because of Suyin's current level of stress, it will be especially important to set an initial behavior change goal that she thinks is attainable, even if it is only a relatively small step toward her ultimate goal for Ming. Going to bed earlier is a common goal for parents of infants, as is having their child learn to fall asleep without needing to be held, rocked, or otherwise loved to sleep. Decreasing the length of Ming's feedings may be another goal in this case. Based on review of the diaries, Suyin decided that she wanted Ming to fall asleep earlier in the evening, perhaps between 7 and 9 PM rather than after midnight, and to learn to fall asleep on his own.

5. *Developing specific strategies to change the behavior*: Once a goal has been established based on initial measuring and monitoring, specific strategies may be incorporated into a behavior plan aimed at changing the behavior in order to reach the goal. Selection of specific strategies should be based on what appears to maintain the unwanted behavior. The main components of the plan will be to alter the antecedents and the consequences of the behavior. In deciding what changes to make, it is

helpful to have the parent write down the specific changes/goals decided upon. This will help them remember what they plan to do after leaving the clinician's office.

With her behavior goals in mind, Suyin develops a plan with her clinician that utilizes many behavioral management elements. Moving Ming's crib out of her room will allow Suyin to sleep through normal sleep activity, such as Ming's sighs in his sleep, and attend only to clear signals requiring her help. Slowly shifting his bedtime earlier by about 30 min every few nights, while simultaneously moving his wake time earlier in the morning, will gradually *shape* his sleep cycle. Developing a soothing bedtime ritual such as giving him a bottle in his room with low lighting, then a quiet activity such as soothing music and reading together, ending with placing Ming in his crib drowsy, but awake, will help to develop pleasant sleep-onset associations. Keeping any night-wakings "business only" by feeding Ming and putting him back into his crib as quickly as possible will limit positive reinforcement for his waking in the night.

After waking him in the morning, she plans to keep him active for several hours, and space the amount of time between his feedings to every 3 hours. During the day, she will put him into his crib for naps at regular times after a shorter version of his bedtime routine, not letting naps exceed 2 hours. In addition, observation of Ming's feeding in clinic, in conjunction with his mother's diaries and reports, is suggestive for painful gastroesophageal reflux, and a trial of medication is simultaneously initiated.

6. *Implementing and evaluating the behavior program*: Following the development of specific behavioral strategies, parents are faced with the challenge of implementing the plan and evaluating their child's behavior change. It is okay to emphasize how difficult it is to start and maintain a program. Consistency is critical, however, and it is important to brainstorm things that might get in the way of consistency. For example, letting a child cry at night is very difficult for parents. If the plan includes leaving their baby in his crib after the nighttime routine, discussing what a family will do when the baby cries is important. It may be decided that the parent will check on the baby briefly to ensure that there is no immediate concern, say a soothing word or two, and then leave without picking the baby up. Working together with parents on how this will help them achieve their goal will likely increase the consistency in which parents are able to implement the plan set at home. A monitoring form should be part of this plan for parents and the clinician to see what changes are occurring. Often adjustments to the plan need to be made, and that is hard to do if ongoing monitoring is not done.

Once a program has been implemented for a specified period of time, usually a minimum of 1–2 weeks, behavioral change should be observable. The clinician should have the family carefully track targeted behaviors and should regularly meet with them to assess the quality and effectiveness of the strategies being implemented. Comparisons to monitoring from before the plan was implemented will help determine whether the behavioral goal is being met and when additional behavioral goals may be set. If behavioral goals are not being met, the clinician must discuss this with the family, explore possible reasons, and modify the behavioral program, usually by modifying antecedents and/or consequences.

Suyin will need to continue to keep diaries of Ming's behaviors and bring them to her next follow-up appointment. Based on progress, new intermediate goals and new strategies can be developed. At follow-up 2 weeks after implementing the plan, Ming is falling asleep by 9:30 PM in his crib with only a little whimpering and waking three times at night to feed. Naps are more problematic and sporadic. Ming continues to fall asleep in his mother's arms or in his swing for afternoon naps, but is sometimes placed in his crib once asleep. He is feeding a larger quantity of food, less often in the day. On medication, he continues to have occasional spitting up, but no longer cries during or after feeds, and the feeding duration has decreased to less than 30 min per feeding.

7. *Maintaining behavior change*: The ultimate goal of a behavioral program is to maintain behavior change. It is very easy for parents and children to fall back into old habits, as well as stop positively reinforcing the new habits. It is also important to predict that there will be setbacks, and discuss how to address them. In situations where parents and other parents are attempting to decrease an undesired behavior, clinicians should provide education about the likelihood of an *extinction burst*, a period when the frequency of the undesired behavior increases before decreasing. For example, it is important to remind the parents of infants that it will be difficult to ignore their baby's cries at night, because this will involve ignoring their own instincts to comfort their child. Once they have made the decision to do so, the baby will likely cry louder and harder in the attempt to gain his parents' attention. If the parents remain steadfast in their resolve to ignore his cries, their baby will quickly learn to go back to sleep again if extended crying does not get their parent's attention.

Suyin's ability to recognize improvement in Ming's sleep, and its association with her own improved sleep and mood, will encourage her to set additional goals, for example, providing a consistent routine for afternoon

naps in Ming's crib. She decides to wait for stronger signals from Ming at night before feeding him, thereby stretching out times between feedings in the night, *fading* (gradually eliminating) the reinforcement of prompt feeding in the night. Suyin does not interpret putting Ming down drowsy but awake and letting him settle and possibly fuss as a *time-out* or punishment, which would have been unacceptable to her. Instead she sees this strategy as teaching him an important skill, that he can put himself to sleep with supports (his regular bedtime and routine), and no longer need to listen to the vacuum to fall asleep. Of course, she may need to modify her responses in the night if Ming gets sick or if the family travels. Nonetheless, having successfully modified sleep behavior once, Suyin has a good chance of revising her strategies to help Ming get his sleep back on track after a disruption in schedule.

Case Summary

In this case of a 5-month-old infant with prolonged crying, decreased sleep, and symptomatic gastroesophageal reflux, a combination of medication and behavioral management has resulted in improved feeding, sleeping, and crying behavior patterns. Ming's bedtime routine and his mother's plan to encourage him to learn to fall asleep on his own in his crib utilizes both *classical* and *operant conditioning learning* techniques as described in Table 43.2 as well as many of the common behavior management techniques described in Table 43.3. Ming begins to associate his sleepiness, his bath, his full tummy, the low lights, the music, the room, and his crib with sleep onset. When he wakes in the morning, or after a sufficient nap, the positive attention he receives from his mother when they spend time playing together reinforces his appropriate sleep behavior.

Case 2: Child with Encopresis

Varesh is a 10-year-old boy who has been otherwise healthy, but who has 1–2 fecal soiling accidents per day. His parents report that he is very bright and is doing well in second grade. He has two older siblings, both of whom are toilet trained on time and had no problems. Varesh has soiling accidents occasionally at school, but mostly at home. He has never gone more than 2 days without a soiling accident, but has not had any eneuretic accidents since being fully toilet trained for urine by age 3. Varesh's parents do not understand why he continues to have accidents. They have tried everything, including yelling, pleading, bribing, and punishing him, and this has become a daily struggle. His medical history is otherwise benign, and his physical examination reveals fullness of the abdomen and a large amount of stool in his rectum.

Functional fecal incontinence with chronic constipation is a common problem among children which is often *silent* – that is, a family secret. What often begins as toilet avoidance, leads to chronic constipation. Retained stool in the distal colon becomes dehydrated and may become hard, forming a fecolith. Nerve endings become habituated to chronic distension of the colon, and become insensitive. The colonic wall musculature is distended around the fecolith, and becomes ineffective in contracting to propel it forward. Newly formed, softer stool leaks around the fecolith, resulting in incontinence. The child usually has no sensation that they are "leaking", and often have also become desensitized to the foul smell. Treatment requires a bowel "clean-out" that softens the impacted stool and empties the colon. Remission requires a long-term maintenance plan aimed at medication and dietary modifications to maintain softened stool, and ongoing monitoring to ensure that the child's stools are soft and that elimination occurs at least every 1–2 days.

1. *Developing and maintaining positive interactions*: In many cases of encopresis, parents and their children report increased negative interactions, largely around the incontinence, and a decrease in any positive interactions. In fact, almost all parent–child interactions may end up being about incontinence. It is important to find out what positive interactions are occurring with both parents and siblings. It is also important to assess the parent's beliefs about the cause of encopresis. For example, do they believe the child is doing it willfully? Such a belief will likely contribute to negative interactions and attributions, neither of which is helpful in resolving the encopresis. Prior to starting the intervention, parents should be educated about the pathophysiology of encopresis, have an open discussion about the shame the child and family may be feeling, and should find ways to enjoy some time together.

For Varesh, his incontinence is a source of embarrassment for him and his parents, and has become a source for contention in the household. His parents do not understand how a bright, social, second grader can have soiling accidents. All they talk about is how to make him stop soiling. Thus, the first step will be redefining some of their interactions, learning what they enjoy doing together, and what they would enjoy talking about if they were not spending time talking about his toileting behaviors.

2. *Defining the behavior to be changed*: With encopresis, the target behaviors are fairly easy to define – stop soiling and start having regular bowel movements in the toilet.

Everyone is in agreement with the goal, but they need guidance on how to achieve it. This is true for Varesh's family. Varesh has expressed interest in learning how to control his encopresis, but he feels hopeless. He also does not want to disappoint his parents again.

3. *Measuring and monitoring the target behavior*: The next step is to get an accurate assessment of the antecedents, behaviors, and consequences. This involves monitoring what happens prior to soiling incidents, including the time of day, location, and who the child is with; what happens during the soiling incident, including describing the incident itself and quality of stools; and what consequences follow the incident, such as whether he leaves his class, is punished, or loses some privileges. An example of an encopresis monitoring chart is seen in *Fig. 43.2*.

This monitoring sheet can be used for a child with toileting problems. This type of table is a useful tool which focuses on improving both quantitative (number of minutes spent sitting) and qualitative (attitude) measures.

Patterns may emerge that are helpful in both setting behavior change goals and identifying strategies that will be most helpful. Varesh's monitoring showed he consistently has two soiling accidents per day, typically on the way home from school and after dinner. He has mostly smearing and leakage, but occasionally a larger amount of watery stool. His current consequence included changing and washing his own clothes, as well as his parent's frustration and disappointment.

4. *Setting a behavior change goal*: A behavior change goal should be specific and measurable. Behavior change also targets the *behavior*, not the outcome. A certain outcome is expected when behavior changes, but if the outcome alone is targeted, it is likely to fail. Based on the patterns and behaviors that emerge from monitoring, a specific, measureable goal can be set. For encopresis, a typical goal is "sitting on the toilet" after meals, after school, and before bed each day. Clearly, it is expected that the child will start stooling in the toilet, and it will be tracked continuously, but the initial behavior goal is to comply with the toilet-sitting plan.

Varesh was not happy about starting a toilet-sitting plan and was worried about doing this at school. It was agreed to start on a long weekend, so that he could get used to the plan. His family also contacted the school nurse and a plan was set up for Varesh to use the private bathroom in her office after lunch and immediately prior

Varesh's daily monitoring sheet
Day of week:_____ **Date:**_____

Time/Activity	Time	Number of minutes	Amount of stool produced if any	Played videogame- Yes or NO	Attitude – scale 0 (problem) to 3 (pleasant)
Sat on toilet first thing in morning					
Took morning medication:____					
Sat on toilet after breakfast					
Sat on toilet after lunch					
Sat on toilet after dinner					
Sat on toilet at bedtime					
	Time	Amount	Attitude		
Soiled pants					
Soiled pants					
Wet pants					

Figure 43.2
Sample encopresis monitoring chart

to leaving school. A bowel cleanout was scheduled with his pediatrician for a Friday afternoon after school. His behavior change goal of sitting on the toilet at regularly scheduled intervals started immediately afterward, in conjunction with a plan for medications aimed at maintaining soft stools.

5. *Developing specific strategies to change the behavior*: A combination of *special time*, *stimulus control*, and *positive reinforcement* is used to address encopresis. Highlighting that parents need to have some *special time* with their child each day that does not revolve around the problem is a key strategy. Setting up a scheduled toilet-sitting plan provides *stimulus control* – increasing the opportunity for the desired behavior of stooling in the toilet and decreasing the opportunity for soiling accidents. *Positive reinforcement* is key to engaging the child in the plan. Given that no one enjoys spending extra time on the toilet, it is important to make this a time that is acceptable. For example, many children enjoy playing a handheld electronic game that is only available at this time. This can be designated as time to play for 10 minutes while trying to go to the bathroom. The child could also read a preferred book. The goal is to engage the child in making an attempt to stool in the toilet. In addition, a reward can be set up for consistent compliance with the behavior expected. For example, if a child complies with the toilet-sitting plan 85% of the time over a two day period they will earn a special reward. This reward is also an opportunity to reinforce special time with a parent, rather than an expensive, material reward.

Varesh and his family agreed to set up a chart to track his toilet-sitting time, taking of his medication, and his *special time* of playing one game of chess with his father each night. In addition, if he completes 90% of his sitting times without complaint, he will earn a movie out with a friend the following weekend. Note that a goal of 100% completion should not be set, because if the child cannot achieve perfection, motivation for continuing the behavior will plummet. Because Varesh was motivated to increase his time with his father and go out to the movie, he was less likely to resist sitting on the toilet at home and at school.

6. *Implementing and evaluating the behavior program*: In implementing a behavior strategy, all involved parents must be in agreement and demonstrate a clear understanding of the plan and be prepared to give rewards or punishments appropriately. The consistency, immediacy, and saliency of each reward or consequence should be emphasized to the parent. That is, rewards or consequences should be given each time the behavior occurs, should be given at the time it happens, and should be meaningful to the child. The clinician should model appropriate use of the techniques, and allow parents to practice in the office. Parents and older children might also work together to develop a behavioral "contract" that outlines the behavioral goals as well as the specific rewards and consequences that will be used; such contracts can be signed by parents and children to indicate their agreement with the plan.

Varesh's parents, although skeptical about a chart being effective when they had already "tried" everything, agreed to the plan and the rewards discussed. They did not want to involve the school at first, but agreed, given the frequent soiling accidents on the way home from school. In the first week, Varesh's accidents decreased by 50%. He was both surprised and proud, as were his parents. This helped increase his motivation for the second week. Over several weeks, his monitoring charts showed that he was more likely to have an accident in the early evening, and had only one all week on the way home from school. Thus, the plan was slowly modified to eliminate the "after lunch" sitting, and give him an additional sitting in the evening.

7. *Maintaining behavior change*: Once the behavior goal has been achieved, the clinician can help the parents begin the process of *fading* reinforcement in order to gradually decrease reliance on immediate reinforcement to maintain the behavior. For example, parents could offer reinforcement every two or three times a behavioral goal is met rather than every time; *fading* reinforcement would continue until the behavior is reinforced at a much lower rate. Other ways of decreasing reinforcement include reinforcing groups of behaviors, rather than single behaviors, or reinforcing with desired privileges rather than material rewards.

Varesh was able to decrease his soiling accidents to 1–2 per week within the first month. During this time, Varesh slowly trained his body to recognize the signs of having to go to the bathroom and became more aware of his own body's signals. With consistency maintained on his toilet-sitting plan, medication regimen, and increased positive time with his parents, he continued to experience increased success in staying continent. Varesh and his family agreed to maintain the toilet-sitting plan for several months after he was totally continent to maintain his success. At that time, they decreased the toilet-sitting plan slowly, first eliminating the morning sitting and the before bed sitting because these rarely produced stools.

Parents should be made aware of three challenges to maintaining behavior change: (a) reinforcers losing their saliency, (b) parents not naturally maintaining new behavioral methods once adequate behavior change is established, and (c) children not maintaining behaviors

as reinforcement is faded. Practitioners should talk with parents about these challenges in the context of follow-up appointments, the frequency of which will depend on how well the plan is working. For encopresis, maintenance must be attended to for at least 6 months, as the colon continues to heal. Setbacks should be expected, and a rescue plan to increase medication if stools harden should be an element of this plan. Ideally, just as parents fade reinforcement of established behaviors over time, practitioners will titrate the schedule of follow-up appointments such that families are seen less frequently over time.

Case Summary

In this case of a 10-year-old boy with primary encopresis, continence was achieved by establishing a medical bowel regimen, and implementing a behavior plan to increase compliance with appropriate toileting behaviors after a full bowel cleanout procedure. The plan was reinforced by positive time with his father and weekly rewards for adherence with the behavioral expectations. As a result, he achieved bowel continence for the first time and maintained his success.

Case 3: Adolescent with Difficulty Adhering to her Medical Regimen

Maria is a 16-year-old girl with insulin-dependent diabetes who had been controlled relatively well through close monitoring by her parents. Like most teenagers, Maria now spends more and more time with her friends, and her parents no longer provide the supervision that they once did. Her parents also think that because she is older, it is her responsibility to take charge of her own care. Unfortunately, Maria has not been testing her blood sugar or giving herself insulin as scheduled, nor has she been keeping to her diet, particularly when she is out with her friends. As her diabetic control has deteriorated, arguments in the home have increased.

Adherence to medical regimens among children and adolescents with chronic medical conditions is a common problem, and a combination of educational and behavioral approaches can be effective. Adolescence, in particular, can be a time of increased parent–child conflict as teenagers struggle to achieve independence from their parents. For the adolescent with a chronic disease, adherence to treatment can become another context in which parent–child conflict arises. From the parental perspective, the difficulty of altering adolescent adherence behaviors may be increased because of decreased supervision and a desire for the adolescent to take on more responsibility for their own health. But from the adolescent perspective, adherence is made difficult because of immature judgment and decision-making skills as well as the increasingly social context in which adherence behaviors must occur.

1. *Developing and maintaining positive interactions*: As in other cases, developing and maintaining positive parent–child interactions is important to provide the base from which to enact a behavioral plan to improve adolescent treatment adherence. Given the increased conflict that naturally occurs during adolescence, many parents step back too much and do not realize how important ongoing positive time with their teenager can be. Highlighting some positive time that is not related to any medical issue is critical. Another option is helping parents take advantage of the adolescent's natural drive for independence. The clinician can encourage parents to identify areas in which the adolescent can exercise independence without jeopardizing her health, such as how the adolescent dresses or keeps her room. Parents can also be encouraged to provide positive reinforcement for particular ways that the adolescent has asserted independence or responsibility in an appropriate way. For example, they should praise and reward her for helping to care for a younger sibling, or for working hard in school.

In the case of Maria and her parents, almost all of their interactions have become around medical care (or lack thereof), and being "grounded" from going out with her friends unless she takes better care of herself. Maria and her mother agreed to go get coffee together once a week and not discuss anything related to her diabetes during this time.

2. *Defining the behavior to be changed*: Ultimately, Maria's parents want her to take more responsibility for her own diabetes management. The clinician should help the family break down this goal into smaller parts by having the family outline the steps needed for diabetes management. They should then identify steps that she is already achieved, as well as areas with which she has difficulty. Outlining details in this way can have the effect of helping members of the family realize that adherence is difficult, because of everything it entails, and also aid in identifying areas of adherence that are more or less problematic. The clinician can then help Maria's family pick a specific aspect of adherence to be addressed initially. Research with adolescents with Type I Diabetes also shows that if parents collaborate with the teen on picking a specific goal, they are more likely to be successful.

Maria and her family decide to address the behavior of blood glucose testing and insulin administration when she is out with friends. Note that this assumes that Maria has the knowledge and technical skills necessary to perform these tasks; if this is not the case, then further diabetes education will be necessary before she can be expected to carry out these tasks with her peers.

3. *Measuring and monitoring the target behavior*: A behavior chart that lists the adherence behaviors to be monitored and allows for record-keeping each day as to whether the behavior was performed would be a useful way for Maria and her parents to monitor the chosen target behaviors. If possible, an electronic glucometer that records and reports time and results of blood glucose testing could be used to verify her records. *Figure 43.3* provides an example that can be modified depending on the age and specific behaviors targeted for increased medical adherence.

This type of chart is a variation of the standard "Sticker chart" used for encouraging typical childhood activities, such as chores and homework completion. In this case, it has been applied to diabetes care, but can be applied to any situation to empower children to take control of their own behavior. The level of detail and reward amount can be varied according to the developmental level of the child.

Maria and her family agree that she will monitor her blood glucose several times a day, and record when she administers her insulin. Each evening her mother will sit down with her to review the glucometer and write the blood sugar readings in her log.

4. *Setting a behavior change goal*: Although the ultimate goal is for Maria to fully perform her diabetic care when with peers, the clinician can help the family agree on some intermediate goals. For example, an initial goal could be for Maria to demonstrate increased independence in adherence behaviors at home. In addition, the family might agree to set a goal in which only a portion of adherence behaviors need to be done independently at the outset. Once this has been achieved, the family could then set goals for independent blood sugar testing in certain peer situations where success may be more likely, such as when Maria is with a small group of friends who know about her diabetes, before setting the goal for this to occur in all peer situations. For example, initially Maria needs to test her blood glucose 75% of the time while at home and

Maria's diabetes plan

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Test blood sugar 4x/day	★						
Give myself shots and write down on log	★						
Keep room clean							
Do homework before calling friends							
Eat Healthy							
Sit with mom to review glucometer							

35 Stars = Special activity with friends

Figure 43.3
Sample diabetes sticker plan

50% of the time while out with friends. Once she achieves this goal, she will earn an outing with her friends paid for by her parents. She will then be ready to increase the adherence necessary to earn the next reward.

5. *Developing specific strategies to change the behavior*: Identifying strategies for adolescents can be more complicated than with younger children. The keys are determining what motivates the adolescent, what stimulus control strategies would be effective for this family, and reinforcing the family collaboration. In Maria's case, her strong desire to spend time with her friends can be used as a motivator and to *positively reinforce* success with behavioral goals. A consequence for lack of diabetic care when with friends could be less time with friends. *Stimulus control* techniques, such as setting up times with friends to specifically include circumscribed needs for adherence behaviors (for example, meeting a friend for lunch for 1 hour) might also be employed, or having friends come to the house when it involves an extended period of time, so that parents are around to ensure adherence. Maria's family decided to use increased *time-in* with friends as a reward. They also agreed that parents could send Maria a text message when it was time to test her blood glucose if she was out.

6. *Implementing and evaluating the behavior program*: With respect to implementation, Maria and her family could consider what role Maria's friends might play. Her peers may be in a position to encourage and support her in meeting her adherence goals. Other issues to consider are that Maria's parents may be setting increased limits about the amount of time she is allowed to spend with peers, and this could increase conflict between them and Maria. One strategy to reduce this conflict may be for Maria's parents to help her identify times she can be with friends when diabetic adherence behaviors are not routinely required. If Maria's glucometer can provide electronic recording, there are ample data to evaluate whether adherence behaviors are being conducted and in what contexts. With such information, Maria and her parents will know whether the goals are being met and when additional goals, either with respect to achieving the same behaviors more often or in new contexts, or becoming more independent in other adherence behaviors (e.g., accurate carbohydrate counting) can be introduced.

7. *Maintaining behavior change*: One specific issue to maintaining behavior change in this case is Maria's ability to generalize the skills of independent adherence behaviors to new contexts such as summer jobs or after-school activities. Similar strategies of having Maria gradually increase her involvement in such activities as she demonstrates appropriate adherence could be considered. Another issue, that is similar to maintaining behavior change in other cases, is Maria's parents' ability to continue to monitor her success despite their desire for her to function independently. The clinician should provide praise and encouragement to the family, using the data of Maria's success as evidence of the importance of their efforts and to reinforce their continued involvement. Over time, the family can be guided to gradually reduce their involvement and assess the effect of that change on Maria's adherence.

Case Summary

Maria, a 16-year-old with Type I Diabetes, presented with her family due to non-adherence to her diabetic regimen. By helping the family reengage with positive interactions, identify all the aspects of Maria's regimen, and then target two specific behavioral goals, Maria was able to improve her self-care and continue to work collaboratively with her family to improve her diabetic control.

When to Refer

Given the constraints of the primary care clinician and the complexity of some cases, there are times when it advisable to refer the family to a behavioral specialist. In particular, this course of action is recommended in cases where the behavioral concerns are complicated by significant family dysfunction, child psychopathology, or when the practitioner does not have adequate time to provide such treatment.

Conclusions and Further Applications

A behavior management approach, involving the seven basic steps outlined in *Table 43.1*, can be effective in treating common medical problems in childhood. In this chapter, cases of colic, functional encopresis with constipation, and poor medication adherence have been presented, but these principles apply to numerous medical and behavioral concerns. This is also true in the case of children with autism and other developmental disabilities, where an applied behavioral approach has been used in helping children to work toward functional independence. For example, a behavioral program for parents of children with autism can be accessed at http://media.mindinstitute.org/education/ADEPT/Module1Menu.html. Resources have been included below for further reading and to direct practice.

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44 Sensory Disorders

Heidi M. Feldman · Maria A. Salinas · Brian G. Tang

Vignette

Jose was diagnosed in the newborn period with congenital cytomegalovirus infection because of a distinctive rash and liver enlargement. As part of the initial work-up, he had a full audiological assessment and was found to have mild to moderate sensorineural hearing loss. He was appropriately fitted with hearing aids by 6 months of age and tolerated the aids well. His first words emerged when he was 16 months old and he progressed steadily in language development for 2–3 years. However, repeat audiological testing at age 36 months revealed a moderate to moderately severe hearing loss. At that point, his parents began learning sign language and he became bilingual in spoken and signed language. By the time he was 5 years old, he was enrolled in a special education program for children with hearing impairment and deafness because his hearing continued to deteriorate. Though he was able to speak, he easily became fatigued in verbal environments when he had no interpreter for sign language. At age 9 years old, audiological assessment revealed a profound hearing loss and he became a candidate for cochlear implantation.

Introduction

Sensory impairments are a diverse set of problems in either sensing environmental stimuli using one of the five major senses, converting the information into nervous signals, passing the signals through the nervous system and brain, and/or using the information to accurately interpret objects and events in the world. Definitions, classifications, and causes of sensory impairments vary for the five sensory systems. This chapter focuses on impairments of vision and hearing. These senses are the best studied and most likely to have profound significance on the overall functioning of infants, children, and adolescents, as evidenced in the vignette described. The chapter will briefly discuss disorders of olfaction and gustation together because they are interrelated. It will also include a brief description of disorders of touch, including pain, though refer to Chap. XX for a more extensive discussion of pain.

Visual Impairment

Definitions/Classification

Visual acuity is typically assessed in terms of the ability to read fonts of specific sizes from specific distances. If normal vision is considered 20/20 in feet in the USA, visual impairment is defined as vision of 20/70 or worse after treatment or refractive correction. This fraction means that the person sees at 20 ft what individuals with normal vision see at 70 ft. Blindness is defined for legal purposes in the USA as visual acuity less than or equal to 20/200 in the better eye or a visual field of less than 20° diameter. The World Health Organization, using the metric system, defines low vision as the visual acuity after best correction of less than 6/18 m and equal to or better than 3/60 in the better eye. Blindness is defined as less than 3/60 or a visual field less than 10° from the point of fixation. The World Health Organization also has a functional definition of blindness that is the inability to use vision for the planning and/or execution of a task for which vision is essential.

Epidemiology

Approximately 1.4 million children in the world are blind. In low-income developing countries with high rates of mortality for children under age 5 years, the prevalence of visual impairment is 1.5 per 1,000 children. In high-income countries with low child mortality rates, the prevalence drops to 0.3 per 1,000 children. Approximately 87% of visually impaired people live in developing countries. More than 12 million children ages 5–15 are visually impaired because of uncorrected refractive errors (nearsightedness, farsightedness, or astigmatism); these are conditions that could be easily diagnosed and corrected with glasses, contact lenses or refractive surgery.

In the USA, in 2000, the Metropolitan Atlanta Developmental Disabilities Surveillance Program found 1.2 per 1,000 8-year-olds had vision impairment, or a rate of 1 in 833. Between 50% and 66% of these children had other impairments. The same survey found that 7/10,000 children were legally blind.

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Etiology and Pathogenesis

Abnormal vision may be categorized as myopia (near sightedness or limited ability to see distant objects), mydriasis (farsightedness or limited ability to see near objects), reduced visual fields, or imbalanced use or acuity of the two eyes (strabismus and amblyopia). Visual impairment in children can be acquired or congenital. In developed countries, genetic diseases of the optic nerve and higher visual pathways predominate. Retinopathy of prematurity is another important cause. In developing countries, acquired problems predominate. These include corneal scarring from measles; inadequate light sensitive pigments from vitamin A deficiency; trauma from the use of harmful traditional eye remedies; ophthalmia neonatorum and other eye infections from *Neisseria gonorrhoeae*, *Staphylococcus*, *Streptococcus pneumoniae*, and *Chlamydia trachomatis*; and cataracts from rubella. In all countries, congenital abnormalities such as cataracts, glaucoma, and hereditary retinal dystrophies are significant causes of visual impairment. The National Library of Medicine maintains a comprehensive list of genetic causes of visual impairment at (http://ghr.nlm.nih.gov/conditionCategory=eyesandvision).

The pathogenesis of visual impairment may be conceptualized as a disruption of one or more structures or functions of the eye and visual pathways. *Table 44.1* reviews some of the many causes of visual impairment as a function of the affected anatomical structure. For example, corneal opacities and blindness caused by *Chlamydia trachomatis* are highly prevalent in poor rural areas of Africa, Asia, Central and South America, Australia, and the Middle East. Onchocerciasis, an insect-borne disease caused by a parasite *Onchocerca volvulus*, is the world's second-leading infectious cause of blindness and is most prominent in African countries. Trauma, intraocular hemorrhage, ocular inflammatory disease, and intraocular tumor are important causes of glaucoma in the pediatric population. Infectious diseases are a frequent cause of cataracts in childhood and corticosteroids are the most important pharmacological agents that produce cataracts in the pediatric age group. Cataracts may be a sequela of eye trauma from child abuse.

Retinopathy of prematurity (ROP) is a pathologic process of immature retinal tissue that can progress to retinal detachment and functional or complete blindness. Children born prematurely should receive examinations by an experienced ophthalmologist to detect and treat ROP, following the guidelines and recommendations for management of ROP promulgated by professional organizations. Retinoblastoma is the most common primary malignant intraocular tumor of childhood. The initial sign in the majority of patients is often a white pupillary reflex (leukokororia), a reflection of light off the white tumor rather than the red retina.

Optic nerve hypoplasia is associated with defects of vision and of visual fields of varying severity, ranging from blindness to normal or near-normal vision.

Clinical Manifestations

The impact of visual impairment on an infant or child is highly variable, related to the age of onset, severity of and type of visual loss, the presence of other conditions, and psychosocial factors. Important signs of visual impairment in infancy may be poor tracking and following, nystagmus, and limited interest in brightly colored objects. Smiling may look unusual or may diminish over time. Parents may notice abnormalities in eye movements, including wandering eye movements or a gaze fixed in one direction. Infants may not blink or cry in response to a looming or threatening gesture. As children age, they may have complaints of poor vision. Mobile children tend to fall or bump into objects. School-aged children may be unable to read.

Even with typical intelligence, a child who is blind from birth or early childhood may experience delays in fine and gross motor development. Language development may also be delayed since speech is aided by imitating mouth movements as well as by listening to sounds. Clinical manifestations also relate to accompanying disabilities.

Diagnosis

Examination of the eyes should be performed beginning in the newborn period and at all well-child visits. Newborns should be examined for ocular structural abnormalities, such as cataract, corneal opacity, and ptosis. Vision assessment beginning at birth has been endorsed by US professional organizations. All children who are found to have an ocular abnormality or who fail vision assessment should be referred to a pediatric ophthalmologist or an eye care specialist trained to treat children.

The eye evaluation in the physician's office should include ocular history, vision assessment, external inspection of the eyes and lids, ocular motility assessment, pupil examination, and red reflex examination in infants birth to 3 years of age and older. In children 3 years and older, age-appropriate visual acuity measurement is important.

Table 44.1

Causes of visual impairment by type of condition and anatomic structure

Type of condition	Anatomical structures							
	Lid	Cornea	Anterior chamber	Iris	Lens	Retina	Optic nerve and visual pathway	Cortex
Structural or functional abnormality	Ptosis that obstructs vision Blepharophymosis	Clouding Keratopathy	Glaucoma	Coloboma	Cataract	Retinopathy	Optic nerve hypoplasia	Central visual impairment Occipital lobe lesions Amblyopia following strabismus
Genetic conditions and systemic disorders	Congenital Fibrosis Syndrome Combined levator/ superior rectus maldevelopment Muscular dystrophy Neurogenic retraction in Sylvian Aqueduct Syndrome or Hydrocephalus Myasthenia gravis	Congenital glaucoma Mucopolysaccridosis Fabray Disease Mitochondrial disease	Neurofibromatosis Sturge Weber Lowe syndrome Marfan syndrome Galactosemia Homocystinuria	Brachio-Oculo-Facial syndrome Cat-eye syndrome CHARGE anomalad Deletion 4Q Delection of 13Q	Trisomy 13 Trisomy 18 Trisomy 21 Turner syndrome Deletion 11 and 18 syndromes Duplication Syndromes (3q, 20p, 10q) Alport syndrome (nephritis, deafness, lens involvement)	Retinitis pigmentosa Retinopathy of prematurity Leber amaurosis Diabetes	Hydrancephaly Anencephaly Septo-optic dysplasia of de Morsier	Encephalo-ophthalmic dysplasia Focal dermal hypoplasia Hallerman–Streiff Syndrome Incontinentia Pigmenti Lenz's micropthalmia Syndrome Trisomy 13, 14, 15 or 2 Epilepsy
Infection or inflammation	Lagophthalmos with abnormal drying and keratopathy	Herpes simplex Congenital rubella Chlamydia trachomatis	Congenital Rubella Uveitis	Iritis from autoimmune disease Lyme disease Tb Syphilis	Toxoplasmosis CMV Syphillis Congenita Rubella HSV Perinatal measles Poliomyelitis	Uveitis Autoimmune disorders	Optic neuritis	Viral Meningitis Cytomegalovirus Toxopasmosis Onchocerciasis Untreated streptococcal disease and scarlet fever
Toxicity and metabolic conditions					Steroids Infant of diabetic mother Vitamin A deficiency		Dilantin LSD Alcohol Methanolingestion Infant of a diabetic mother	Mutiple metabolic diseases Neonatal hypoglycemia
Trauma	Ectropion with keratopathy	Birth trauma Trauma Corneal abrasions	Hypema	Iritis	Contusion or penetrating injury	Retinal detachment Retinal hemorrhage		Traumatic brain Injury Periventricular leukomalacia Hypoxic ischemic encephalopathy Stoke
Neoplasm	Capillary hemangiomas Lid tumors			Wilm's tumor with aniridia		Retinoblastoma	Pituitary adenoma	

Tests of visual acuity vary by age. Vision assessment in children younger than 3 years or any nonverbal child is usually limited to the child's ability to fixate on an object, maintain fixation, and then follow the object throughout various gaze positions. Failure of the child to perform these maneuvers may indicate significant visual impairment. If poor fixation and following is noted for both eyes after 3 months of age, a significant bilateral eye or brain abnormality should be suspected. Vision assessments in children older than 3 years can usually be accomplished in the pediatrician's office. *Table 44.2* summarizes methods for assessing vision in the pediatric office.

Photoscreening is an innovative adjunct to vision screening for children who are difficult to screen, including infants, toddlers, and children with developmental delays. A photograph is produced by a camera under specific lighting conditions, which shows a red reflex with both pupils. A trained observer can identify ocular abnormalities by identifying changes in the photographed pupillary reflex. This method does not substitute for testing visual acuity but it can identify strabismus, refractive errors, media opacities, and retinal abnormalities.

Tests of visual fields vary by patient cooperation. External examination of the eyes includes penlight examination of the lids, conjunctiva, sclera, cornea, and iris. Persistent discharge or tearing may be attributable to ocular infection, allergy, or glaucoma.

The assessment of ocular alignment in preschool children is important since the development of strabismus may occur. Slow or poorly reactive pupils may indicate significant retinal or optic nerve dysfunction. The red reflex test can be used to detect opacities along the visual axis, such as cataract or corneal abnormality, and abnormalities of the back of the eye, such as retinoblastoma or retinal detachment.

Treatment

The first step is treating the underlying condition causing visual impairment, such as using surgery to relieve hydrocephalus or antibiotics to cure infections. Treatment of clinically significant cataracts often requires surgical removal of the lens and subsequent correction of the resultant refractive error with glasses, contact lenses, or a lens implantation. Infantile glaucoma often requires surgical treatment. Treatment of ROP includes cryotherapy or laser photocoagulation of the retina to stop the progression of the disease. Advances in vitreoretinal surgical techniques have led to limited success in reattaching the retina in infants with total retinal detachment (ROP stage 5).

Glasses may correct refractive errors, disorders of eye movement and alignment. According to the World Health Organization, Vision 2020 partners have been actively involved in addressing the causes of childhood blindness and developing pediatric eye care services where interventions are amenable to prevention and treatment. Rehabilitation for individuals with visual impairment includes optimizing functional capabilities and quality of life. The multifaceted process involves the assessment of visual capabilities and the evaluation of functional performance (e.g., reading, writing, and mobility) within the context of employment, family activities, attitudes, and psychological well-being. Most vision rehabilitation strategies involve prescribing assistive devices (magnifiers and other optical devices) or providing training. Environmental interventions may help individuals to function well at home, in the workplace, and/or out in public places. For the child with low vision or blindness, reading readiness for Braille begins in kindergarten. Braille uses raised dots on a page to allow individuals who are blind to access written language. Research is focusing on the development of new devices and application of advanced technologies to develop visual and/or sensory substitution aids.

Prognosis

The prognosis for the child with severe visual impairment depends on the amount of residual vision, the child's intellectual functioning, the motivation of the child and the family, and the quality of education and training the child receives. Some eye conditions such as cataracts, glaucoma, diabetic retinopathy, and retinitis pigmentosa are progressive, worsening over time.

Prevention

Worldwide approximately 85% of visual impairment and 75% of blindness can be prevented or cured. Many strategies are available. Early detection and prompt treatment of ocular disorders in children is important to avoid lifelong visual impairment. Correction of refractive errors with glasses could restore normal vision to more than 12 million children ages 5–15 years old. Vitamin A supplements not only improve vision but also reduce child mortality in areas where Vitamin A deficiency is a public health problem. National vaccination programs have reduced the prevalence of eye complications of infectious diseases. Testing for and treating prenatal infections prior to delivery may prevent congenital infections. The use of silver nitrate or erythromycin prevents neonatal

Table 44.2
Eye examination guidelines

Function	Recommended tests	Stimuli	Response	Referral criteria ages 3–5 years	Referral criteria ages 6 years and older
Distance visual acuity	Snellen	Different letters and numbers on a wall chart 10 ft from child	Verbal identification	*For all tests*: <4 of 6 correct on 20-ft line with either eye tested at 10 ft monocularly (i.e., less than 10/20 or 20/40) Or Two-line difference between eyes, even within the passing range (i.e., 10/12.5 and 10/20 or 20/25 and 20/40)	*For all tests*: <4 of 6 correct on 15-ft line with either eye tested at 10 ft monocularly (i.e., less than 10/15 or 20/30) Or Two-line difference between eyes, even within the passing range (i.e., 10/10 and 10/15 or 20/20 and 20/30)
	Tumbling E	The capital letter "E" in different spatial orientation on a wall chart 10 ft from child	Manually showing the direction the E are pointing:		
	HOTV	Large H O T V letters on a wall chart 10 ft from child	Pointing to matching letter on the testing board		
	Allen figures	Seven schematic figures on wall chart 10 ft from child	Verbal identification		
	LEA symbols	Spiral flash cards with four figures	Verbal identification		
Ocular alignment	Cross-cover test	Distant object	Movement of the uncovered eye	Any eye movement in or out when shifting the cover indicates strabismus	Same referral criteria as ages 3–5 years
	Random dot E stereo test	Stereo blank card and the raised and recessed "E" card simultaneously	Manually showing the direction the "fingers" of the E are pointing	Fewer than 4 of 6 correct	Same referral criteria as ages 3–5 years
	Simultaneous red reflex test (Bruckner test)	Direct ophthalmoscope examination	Red reflexes seen from each eye	Any asymmetry of pupil color, size, or brightness	Same referral criteria as ages 3–5 years
Ocular media clarity (cataracts, tumors, etc.)	Red reflex	Direct ophthalmoscope examination of eyes separately	Red reflexes seen from each eye	White pupil, dark spots, absent reflex	Same referral criteria as ages 3–5 years

infectious eye disease. Prevention of ROP ultimately depends on prevention of premature births and its attendant problems. However, appropriate management of ROP can reduce visual impairment.

Over the life span, reducing exposure to UV-B with sun glasses reduces cataracts. Cataracts can also be prevented by reducing cigarette smoke and alcohol consumption. Protective eye wear is important for preventing eye injuries in certain sports.

Hearing Impairment

Definitions/Classification

Hearing acuity is assessed in terms of the amount of energy, measured in decibels (dB) that is required to detect sounds across a range of frequencies between 250 and 8,000 Hertz (Hz). Normal hearing in children is defined as a hearing threshold better than 20 dB,

depending on the reference. Hearing loss is defined as an inability to hear specific frequencies at the appropriate intensity. Hearing loss in childhood is classified as mild (20–40 dB threshold), moderate (41–54 dB threshold), moderate-severe (55–70 dB threshold), severe (71–90 dB threshold), and profound (>90 dB threshold). Thresholds can vary as a function of frequency. When differences in the threshold occur, higher frequencies are typically more severely affected than lower frequencies. Deafness is defined functionally as a hearing impairment that is sufficiently severe that the individual is impaired in processing linguistic information through hearing, even with amplification.

Epidemiology

The World Health Organization estimates that worldwide over 65 million people have hearing impairment that originated in childhood. Childhood hearing impairment affects 2–4 per 1,000 live births in developed countries and upwards of 6 per 1,000 in developing countries.

In 2000, The Metropolitan Atlanta Developmental Disabilities Surveillance Program reported that hearing loss was estimated at 1.2 per 1,000, or about 1 in 833, 8-year-olds. The same survey found that nearly 25–33% of children had one or more other developmental disabilities.

Etiology and Pathogenesis

Hearing loss generally falls into three categories – conductive, sensorineural, and mixed – related to the anatomic section of the ear in which an abnormality occurs. The external ear (pinna and ear canal) collects and focuses sound waves on the tympanic membrane, which converts acoustic energy into mechanical energy that pass through the ossicular chain of the middle ear. Conductive hearing loss occurs when transmission of sound information is mechanically disrupted through the external and/or middle ear. The cochlea of the inner ear converts these vibrations into hydraulic energy that move hair cells along the organ of Corti, causing neural impulses to be transmitted into the midbrain and higher cortical structures. Sensorineural hearing loss (SNHL) occurs when hair cells in the inner ear fail to transmit neural impulses normally within the cochlea or when problems disrupt nerve transmission down the acoustic division of the eighth cranial nerve (vestibulocochlear nerve). Mixed hearing loss involves both conductive hearing loss and SNHL, and typically represents damage to both middle and inner ear structures. A less common type of hearing loss in children is central hearing loss, in which the functional or structural lesion affects the auditory pathways from the brainstem to cerebral cortex.

Hearing loss can be acquired or congenital. *Table 44.3* reviews causes as a function of the anatomic structure affected. The most common form of hearing loss is genetic. Approximately 50% of SNHL cases are inherited, either with hearing loss isolated or associated with other abnormalities as one feature of a clinical syndrome. Over 500 syndromes with hearing loss have been characterized. Approximately 70% of inherited causes of SNHL are labeled nonsyndromic because they have no accompanying impairments. In this group, 80% have an autosomal-recessive mode of transmission. Mutations of the gene encoding the protein connexin 26 (Cx26) on chromosome 13 account for almost half of all nonsyndromic autosomal-recessive hearing loss representing the most common genetic cause of hearing loss. The National Library of Medicine maintains a comprehensive list of genetic causes of hearing loss at (http://ghr.nlm.nih.gov/conditionCategory=earnoseandthroat).

Cytomegalovirus (CMV) is the most common infectious cause of congenital SNHL. Congenital SNHL caused by maternal rubella, mumps, and measles have become uncommon in the developed world due to the advent of vaccination programs. These infectious diseases, however, continue to be significant risk factors for children born in developing countries where large segments of the population are unimmunized.

Extracorporeal membrane oxygenation (ECMO) is a significant risk factor for congenital SNHL that is progressive in nature. Hyperbilirubinemia and kernicterus are causes of damage to the auditory nerve that are more prevalent in the developing world than in the developed world.

Acquired causes of SNHL (e.g., high intensity noise, ototoxic medications, meningitis, and trauma) are progressive and permanent in most cases. Therefore, careful and close monitoring by an audiologist after one of these exposures is recommended, even when hearing tests are initially normal.

Most conductive hearing loss is acquired. The most frequent cause of conductive hearing loss is otitis media with effusion in which the hearing loss is transient and typically minimal to mild in severity. Structural anomalies of the external ear, canal, or middle ear are rare congenital causes of permanent conductive hearing loss.

Table 44.3
Causes of hearing impairment by type of condition and anatomic structure

Type of condition	Anatomical structure			
	Associated with conductive hearing loss		Associated with sensorineural hearing loss	
	Outer ear (e.g., external auditory meatus)	Middle ear (e.g., tympanic membrane, ossicular chain)	Inner ear (e.g., cochlea) and/or Auditory pathway	Cortex
Structural abnormality	Microtia Atresia of the ear canal	Congenital anomalies of the tympanic membrane Ossicular chain malformations	Anatomical abnormalities of the cochlea and temporal bone Auditory dysynchrony	Central hearing impairment
Genetic conditions and systemic disorders	Treacher–Collins syndrome Goldenhar hemifacial microsomia Branchio-oto-facial syndrome (BOF) Stickler syndrome Deletion 18 Q syndrome	Treacher–Collins syndrome Goldenhar hemifacial microsomia	Connexin 26 disorders Mitochondrial disorders Hyperbilirubinemia Waardenburg Syndrome Neurofibromatosis 2 Usher syndrome (problems of vision) Complications of Rh incompatibility	Neurodegenerative disorders Demyelinating disorders Alport syndrome (renal failure) Perinatal anoxia ECMO
Infection or inflammation	Otitis media externa Foreign body with inflammation	Tympanic membrane perforation Otitis media Cholesteatoma Mastoiditis	TORCHS infections Meningitis Lyme disease Measles HIV	Congenital rubella Encephalitis
Toxicity and metabolic conditions			Ototoxic drugs in pregnancy (e.g., isoretinoin) Aminoglycosides Loop diuretics (e.g., furosemide) Chemotherapy regimens (e.g., cisplatin)	
Trauma	Physical damage Cauliflower ear	Penetrating injury Scarring	Hypothyroidism Diabetes Noise-induced hearing loss Head trauma	Head trauma
Neoplasm			Acoustic neuroma	

Clinical Manifestations

The impact of hearing impairment on an infant or child is highly variable, related to the age of onset, severity of and type of hearing loss, the presence of other conditions, and psychosocial factors. Hearing loss in neonates and young infants may be associated with minimal clinical signs. For this reason, universal screening programs are important for early detection of hearing loss. Infants with hearing impairment may show diminished response to sounds and excessive vigilance toward visual stimuli. Delayed language milestones and age-inappropriate unintelligible speech are common associated findings of hearing loss in toddlers and young children. Other findings include behavioral difficulties or academic failure. Unilateral hearing loss may be detected when children show a unilateral preference for using a phone or appear disoriented when trying to indentify sources of sounds, such as turning toward people calling their names.

Older children, adolescents and adults with hearing loss may complain of decreased or muffled hearing or difficulty understanding what people say, particularly in the presence of competing auditory stimuli. Difficulties understanding language make it difficult to participate in social interactions. For this reason, affected individuals may complain of fatigue after a long social interaction. Some individuals experience tinnitus as the first symptom of hearing loss.

Screening and Diagnosis

Universal newborn hearing screening (UNHS) programs have been successfully implemented in several developed countries. Unfortunately, most developing nations lack such programs, contributing to a high rate of children and adults with undiagnosed hearing impairment. The Joint Committee on Infant Hearing recommends UNHS before 1 month of age. A behavioral or clinical assessment does not accurately detect hearing loss in children less than 6 months of age. Typically, screening occurs after birth in the hospital nursery using either evoked otoacoustic emission (OAE) or an automated auditory brainstem response (ABR). OAE detects emitted sounds generated by the cochlea in response to auditory bursts of clicks or tones. ABR detects and measures electroencephalographic waveforms in the auditory and brainstem nerve pathways via skin electrodes. OAE and ABR are both rapid and inexpensive screening tools that do not require voluntary responses from the child. Infants who fail this initial screen should be referred for a comprehensive audiology evaluation by 3 months of age and receive appropriate interventions by 6 months of age if diagnosed with a hearing loss. The full ABR, which includes frequency specific information, is the gold standard for determining hearing thresholds in infants younger than 6 months and in children who cannot be tested behaviorally. These recommendations were based on seminal studies showing that hearing impaired children developed language at the same rate as normal hearing peers if they were identified and treated by 6 months of age.

Some types of congenital hearing loss are late-onset or progressive and not evident until late childhood or even adolescence. Acquired hearing loss due to infections, trauma, or other genetic risk factors may present after infancy. Children with risk factors for hearing loss (*Table 44.4*) should be referred for a minimum of one diagnostic audiology assessment between 24 and 30 months of age, even if they passed newborn screening. One important risk factor is caregiver concern that a child might have hearing loss. In one study, caregiver concern was found to be a better predictor of hearing loss than an informal behavioral examination by the physician.

All children with possible hearing loss warrant a thorough physical examination as part of the evaluation and assessment. Careful examination of the ear canal and tympanic membrane may reveal causes of conductive hearing loss, including impacted cerumen, otitis media with effusion, foreign bodies, or a perforated tympanic membrane. Examination of the head and neck may reveal findings associated with several syndromic forms of hearing loss. Important physical findings include ear pits, microtia, cleft lip and palate, malformation of the external ear structures, and atypical pigmentation of the skin and eyes.

Any child who fails a hearing screen or shows signs or symptoms of hearing loss requires a referral to an audiologist for a comprehensive evaluation to confirm and define the nature of the hearing loss. Audiometry quantifies a child's hearing sensitivity, assists in qualifying the site of the lesion, and provides a clinical impression of the child's auditory functioning. Conventional behavioral audiometry is typically used to assess cooperative children 3–4 years or older. Tones of various frequencies (typically from 250 to 4,000 Hz) are delivered through headphones and various transducers (e.g., bone conduction oscillators). The child is instructed to respond when the tone is heard. For younger children, the use of play or visual reinforcements can condition and motivate a child to respond when auditory stimuli are presented. Often, these procedures are done in a sound field and the results represent the hearing of the better ear if a difference exists.

Tympanometry is a standard part of all audiology evaluations and can be performed in a general pediatrician's office. It measures the mobility of the tympanic membrane, providing a reliable assessment of middle ear pressure and function. Tympanometry is used to help diagnose middle ear disorders including otitis media with effusion and perforated tympanic membranes. It does not, however, directly assess hearing.

Treatment

Amplification through hearing aids is the most common treatment for children with SNHL. Hearing aids can be fitted on children as soon as the loss is identified. Regular audiology follow-up is necessary to monitor the child's hearing sensitivity and to make adjustments to the hearing aids. Children with hearing impairment, even with appropriate and early amplification, should be assessed

Table 44.4
Risk factors associated with hearing loss in childhood

Risk factors for early-onset hearing loss	Risk factors for delayed-onset or progressive hearing loss
Neonatal intensive care hospitalization >5 days	Caregiver concerns regarding hearing, speech, language, or developmental delay
Mechanical ventilation	Family history of progressive childhood hearing loss
Family history of permanent childhood hearing loss	Extracorporeal Membrane Oxygenation (ECMO)
Exposure to ototoxic medications (e.g., gentamicin, furosemide)	Head trauma, especially those requiring hospitalization or affecting the temporal/basilar region
Hyperbilirubinemia requiring exchange transfusion	Postnatal infections associated with sensorineural hearing loss, including confirmed bacterial and viral (herpes viruses and varicella) meningitis
In utero infections, such as herpes, rubella, syphilis, and toxoplasmosis	Cytomegalovirus in utero infection
Craniofacial anomalies, including those that involve the pinna, ear canal, ear tags, ear pits, and temporal bone anomalies	Chemotherapy (e.g., cisplatin)
Physical findings, associated with a syndrome known to include a sensorineural or conductive hearing loss	Syndromes associated with hearing loss or progressive or late-onset hearing loss (e.g., neurofibromatosis, Pendred syndrome, Usher syndrome)
Recurrent or persistent otitis media for at least 3 months	Neurodegenerative disorders (e.g., Hunter syndrome) or sensory motor neuropathies (e.g., Friedreich ataxia)
	Excessive noise exposure

Adopted from Joint Committee on Infant Hearing (2007) Year 2007 position statement: principles and guidelines for early hearing detection and intervention programs. Pediatrics 120(4):898–921

by a speech and language therapist and enrolled in treatment if necessary to improve their communication skills. Children with SNHL should also be followed by an audiologist for management of the hearing loss.

Cochlear implants are prosthetics that have been successful in improving outcomes for children with profound hearing loss, even if the loss is congenital or prelingual. These implants work by transforming sound that is picked up by an external microphone into digital neural impulses that are sent directly to the auditory nerve, bypassing the Organ of Corti. Hearing through a cochlear implant is qualitatively different than normal hearing. However, coupled with intensive postimplantation therapy, children can often acquire speech and language. Many children treated with cochlear implantation are able to participate in mainstream education. Early implantation during infancy has the advantage of exposing children to sounds during the period of development when children with normal hearing are acquiring speech and language skills.

Children with some types of conductive hearing loss are medically or surgically treatable and can restore normal hearing. Guidelines have been developed for the judicious use of antibiotics in acute otitis media and chronic otitis media. In some cases, surgical procedures are appropriate. Tympanostomy tube placement has not improved outcomes for otherwise healthy and typically developing children with persistent chronic otitis media with effusion. However, they may be important for children with preexisting hearing loss or other conditions. For children with severe to profound hearing loss, with or without cochlear implantation, education in sign language may provide the child with a useful primary or supplemental communication system. Sign language has all of the features of verbal language and uses hands, body postures, and facial expressions to convey meaning.

As molecular genetic testing becomes more refined and inexpensive, genetic testing will play a greater role in assisting clinicians in the treatment and management of children with hearing loss. Genetic testing and counseling is recommended for families of children with SNHL or a syndrome associated with hearing loss.

Hearing loss in children may result in significant impairment in function and developmental delay. These children depend on other senses to communicate. Therefore, an evaluation of the child's overall development and functioning, including vision, should be included in the work-up of all children with a hearing impairment.

In addition to the technologies used to treat children with hearing impairments, an interdisciplinary and family-centered approach is needed to ensure that these children have the educational and emotional supports to be successful in schools and their communities.

Prognosis

The early identification of children with hearing impairment provides opportunities for effective early treatments to prevent or minimize lifelong deficits in linguistic, cognitive, academic, and socio-emotional functioning. Successful treatment of hearing loss in children depends on several factors. The most important factor is the age at which the hearing loss was diagnosed and treatment initiated. When compared to delayed or no treatment, early treatment of hearing loss leads to early interventions and more favorable outcomes with regards to the child's language development, cognitive functioning, and future academic performance.

Prevention

The World Health Organization estimates that half of all cases of deafness and hearing impairment are avoidable through prevention, early diagnosis and appropriate management. Healthy People 2010 identifies several objectives for reducing the prevalence of functional problems caused by hearing loss. They include (1) increasing the number of newborns who get their first hearing test before they are 1 month old; children found to have a hearing loss should get additional testing before they are 3 months old, and should be enrolled in rehabilitative services by the time they are 6 months old, (2) decreasing the number of ear infections in children, and (3) increasing the number of individuals who are deaf or hard-of-hearing who use habilitation services and adaptive devices, such as hearing aids or cochlear implants. Immunizations have led to prevention of congenital hearing loss from rubella. Immunizations for *Haemophilus influenzae* and *Streptococcus pneumoniae* have led to reductions in rates of otitis media and meningitis with resulting prevention of hearing loss.

Another major initiative is to decrease noise-induced hearing loss. About 30 million Americans are exposed to dangerous levels of noise every day and 10 million Americans already have hearing loss from noise. Sounds that can cause damage include a chainsaw (110 decibels, or dB), ambulance siren (120 dB), 12-gauge shotgun (165 dB), hair dryer or gas-powered lawn mower (90 dB), and a rock concert or firecracker (140 dB). A common risk factor for hearing loss in children and adolescents today is the use of earbuds to listen to music on portable audio players. Regular exposure to 110 dB for more than 1 min risks permanent hearing loss. More than 15 min of unprotected exposure to 100 dB also is damaging. Prolonged exposure to any noise above 85 dB can cause gradual hearing loss. Prevention includes increasing the use of ear protection devices and equipment, such as earplugs or earmuffs as well as limiting exposure (National Institute of Deafness and Other Communication Disorders).

Olfaction and Gustation

Definitions/Classification

Olfaction (smell) and gustation (taste) are classified as the chemical senses. Together they allow full appreciation of the flavor and palatability of foods; serve as an early warning system given their ability to detect toxins, smoke, gas, and spoiled food; and aid in normal digestion by triggering gastrointestinal secretions. Humans can distinguish among hundreds of substances by smell, even in minute quantities. Disorders of olfaction represent a continuum from partial (hyposmia) to total impairment (anosmia). Humans can distinguish five distinct qualities of taste–salty, sweet, sour, bitter, and umami (a taste generated by the monosodium glutamate). However, because many nerves are responsible for transmitting taste information to the brain, total loss of taste (ageusia) is rare.

Epidemiology

A 1994 survey revealed that 2.7 million American adults have an olfactory problem, and 1.1 million report a gustatory problem. Many people are aware of a period in their life in which they had decreased smell or alterations in taste.

Etiology and Pathogenesis

As with the senses of vision and hearing, one method of classification of disorders of olfaction and taste relate to the anatomical structure that is abnormal. *Table 44.5* lists causes by anatomical structure affected. When individuals complain of problems with smell and taste, careful testing frequently reveals that the impairment is primarily

Table 44.5

Causes of disorders of smell and taste by type of condition and anatomic structure

Type of condition	Anatomical structure			
	Nose	Orbital cortex	Mouth and oral structures	Neural pathways and cortex
Structural abnormality	Chloanal atresia Nasal polyps Adenoidal hypertrophy	Nasal obstruction from chloanal atresia, polyps, deviated septum		
Genetic conditions and systemic disorders	Holoprosencephaly Encephalocele Dermoid cysts	Kallmann syndrome Congenital anosmia	Individual variation (non-tasters)	Malnutrition Chronic renal failure Liver disease (including cirrhosis) Cancer Acquired immunodeficiency syndrome
Infection or inflammation	Sinusitis Viral upper respiratory infection	Tympanic membrane perforation Systemic Lupus erythematosus	Oral and perioral infections (candidiasis, gingivitis, herpes simplex, periodontitis, sialadenitis) Sjögren's syndrome	Bell's palsy
Toxicity, metabolic and endocrine conditions	Cigarette smoking Cocaine abuse	Nutritional factors (e.g., vitamin deficiency [A, B_6, B_{12}], trace metal deficiency [zinc, copper]) Malnutrition Chronic renal failure Liver disease [including cirrhosis], cancer Endocrine disorders (adrenocortical insufficiency, Cushing's syndrome, diabetes mellitus, hypothyroidism, primary amenorrhea, pseudohypoparathyro, idism, Kallmann's syndrome, Turner's syndrome, pregnancy)	Toxic chemical exposure (benzene, benzol, butyl acetate, carbon disulfide, chlorine, ethyl acetate, formaldehyde, hydrogen selenide, paint solvents, sulfuric acid, thrichloro-ethylene) Industrial agent exposure (e.g., chromium, lead, copper) Radiation treatment of head and neck Anti-neoplastic, medications	Anti-neoplastic medications Nutritional factors (e.g., vitamin deficiency [B_3, B_{12}], trace metal deficiency [zinc, copper]) Endocrine disorders (e.g., adrenocortical insufficiency, Cushing's syndrome, diabetes mellitus, hypothyroidism, panhypopituitarism, pseudohypoparathyroidism) Kallmann's syndrome Turner's syndrome
Trauma	Physical damage to nasal structures	Frontal skull fracture Nasal fracture Disruption of cribiform plate Cerebrovascular accident	Burn to tongue or oral structures Dental surgery	Head trauma
Neoplasm		Brain tumor (osteoma, olfactory groove or cribiform plate meningioma, frontal lobe tumor, temporal lobe tumor, pituitary tumor Radiation treatment of head and neck		Tumor or lesions associated with taste pathways (oral cavity cancer, neoplasm of skull base

olfactory. Volatile airborne molecules pass through the nose and contact olfactory receptor cells. Flavors depend on stimulation of the smell receptors. Nasal blockage from any cause – polyps, upper respiratory infections, or sinusitis – may affect olfaction and result in the changes in the flavor of foods.

Impairments of olfaction can result from disruptions of the olfactory nerve fibers. Impairments of olfaction are prevalent after head trauma because of shearing injuries to the olfactory nerve fibers at the level of the cribiform plate. Central neural factors, such as tumor or epilepsy, particularly if injury is in the frontal or temporal lobes, may result in disruption of smell and taste.

Taste can be affected by changes in the oral cavity such as destruction of the taste buds from excessive dryness or burns. Gingivitis and sialadenitis or inflammation of the salivary glands may also disturb taste by creating products in the mouth that have bad tastes. Taste is affected by damage to one or more of the neural pathways innervating the taste buds from diverse causes, including Bell's palsy or dental surgical procedures.

Acquired causes of smell and taste disturbance are more common than congenital causes. Underlying basal cells generate olfactory neurons approximately every 30–60 days throughout life. Individual taste buds are modified epithelial cells with a short life span of approximately 10 days. Underlying basal cells replace them continuously in a process similar to olfactory receptor cells. For these reasons, most disturbances of smell and taste are transient. However, chronic use of nasal sprays that cause vasoconstriction of nasal circulation may ultimately lead to damage to olfactory receptor neurons and permanent damage.

Congenital causes of anosmia or hyposmia include Kallman syndrome, also known as hypothalamic hypogonadism or hypogonadotropic hypogonadism, a genetic disorder. Holoprosencephaly, a condition in which the forebrain fails to develop into two hemispheres from either genetic or nongenetic causes typically includes anosmia. *Table 44.5* includes additional conditions.

Congenital causes of taste disturbance includes an autosomal dominant inability to taste phenylthiourea (bitter) and other compounds with an –N-C= group. Type I familial dysautonomia (Riley–Day syndrome) causes severe hypogeusia or ageusia because of the absence of taste bud development.

Clinical Manifestations

Disorders of olfaction and gustation may be entirely silent, particularly in individuals with congenital conditions. Individuals with acquired and especially sudden onset anosmia may find food unappetizing and appetite diminished. Memories of smells are often intimately associated with emotional memories because of the connection of the olfactory bulb and the limbic system. Loss of smell has been associated with the onset of depression. Loss of olfaction in individuals with a previous intact sense may also lead to the loss of libido.

Diagnosis

Disorders of taste and smell generally have been difficult to diagnose. The process begins with a comprehensive history of infections, inflammation, diet, and medication use. A comprehensive physical examination focuses on the head and neck.

It is possible to make simple tests for olfaction, such as samples to sniff or taste. Commercial tests of olfactory function that evaluate threshold of odor detection and odor identification have been developed to provide a reliable measure of olfaction. The Cross-Cultural Smell Identification Test includes banana, chocolate, cinnamon, rose, and smoke because representatives of many different countries were able to identify these odors.

Evaluation of taste disorders is not as well developed as that of olfaction. No comparable approach to odor identification tests is available. Only four of the five basic tastes are typically tested (sweet, salty, bitter, and sour).

Treatment and Prognosis

Treatment of olfactory and gustatory disorders relies primarily on treatment of the specific underlying cause of the disturbance. Since many of the causes are transient, restoration of the senses is possible. Where cures are difficult to achieve or take time to accomplish, then acknowledgement of the disorder, reassurance, and treatment of secondary effects may be necessary.

Disorders of Touch

Definitions/Classification

Tactile sensations are received by nerve endings in the epidermis and sent to the brain via the spinal cord. The number and distribution of receptors vary across different body parts. Large sensory fibers sheathed in myelin register light touch, vibration, and position. Small sensory

fibers without myelin sheaths transmit pain and temperature. All of the sensory information flows along sensory or afferent tracts to the spinal cord, to the thalamus, and then usually into somatosensory areas of the parietal lobe of the cortex. Disorders of touch may involve reduced sensitivity, also known as hypoesthesia or increased sensitivity, also known as hyperesthesia. Hypersensitivity to touch may be sufficiently severe to be classified as pain. Allodynia is the term for painful sensations from stimuli that do not cause pain in other individuals.

Epidemiology

The prevalence of disorders of touch is not well established.

Etiology and Pathogenesis

Disorders of touch may arise from any anatomical structures involved in the pathway. Damage to the skin from trauma, burns, and surgery may affect touch sensation in that body part. Injury to peripheral sensory nerves may cause a neuropathy with resulting sensory changes. When other types of nerves are also involved, these problems may be accompanied by weakness and/or autonomic changes. Neuropathy is a feature of many conditions: metabolic and endocrine disorders, such as diabetes mellitus; toxic exposures, including alcoholism, heavy metals, and antineoplastic drugs; vitamin deficiencies, including B12, A, E, and B1; and infections, such as herpes varicella zoster. The dorsal root of the spinal cord may be affected in conditions such as Sjorgen syndrome. Central pain syndrome is caused by damage to the brain, brainstem, or spinal cord from any cause, including tumor or epilepsy.

Disorders of sensation may be part of a systemic condition. Riley–Day syndrome is an autosomal-recessive disorder that affects the development and function of nerves. The inability to feel pain and temperature in this condition can lead to significant injuries. Congenital insensitivity to pain and anhidrosis is one of a family of disorders known collectively as hereditary sensory and autonomic neuropathies. Children with these disorders do not respond to pain while they do respond appropriately to touch, pressure, heat, and vibration.

Clinical Manifestations

In the absence of disease or injury, children have highly variable responses to touch. Some children appear to be extremely insensitive. These children may bang their head on the corner of a table without crying or even slowing down. Such children may be oblivious to other sensory input as well. This pattern may affect children with certain specific neurodevelopmental diagnoses, including autism spectrum disorders, attention-deficit/hyperactivity disorder, and other mental health disorders. Other children appear to be overly sensitive to touch and related somatosensory input. These children complain about labels in their clothing, refuse to play with clay and sticky materials, and dislike hugs. They may be highly sensitive to other sensory input as well, refusing to try new foods or holding their ears when sirens go off. This pattern may affect some children with neurodevelopmental diagnoses, including autism spectrum disorders, attention-deficit/hyperactivity disorder, anxiety disorders, or intellectual disability.

Damage to large sensory fibers reduces the ability of the individual to sense vibration and touch, resulting in numbness, particularly in the hands and feet. Affected individuals may loose graphesthesia and may have a loss of position sense, compromising their motor skills. Damage to small sensory fibers may reduce sensitivity to touch and temperature. Affected individuals may not realize they have been injured. Pain receptors in the skin can become oversensitive so that individuals sense pain from stimuli that do not usually cause pain (allodynia). Disturbances of touch may also be associated with anorexia, poor appetite, sleep disturbance, and psychological symptoms.

Diagnosis

Establishing the diagnosis of disturbances of touch is very difficult because of the inherent subjectivity in testing. In addition, many factors besides the conditions of the sensory pathway may influence the response to touch, including the psychological state of the individual. More than 100 types of peripheral neuropathy have been identified, each with their own symptoms.

The medical work-up begins with a good history and physical examination. The pattern of involvement leads to specific testing. Nerve conduction studies and electromyelogram are used primarily for multifocal symptoms. Nerve biopsies can also assist in diagnosis.

Treatment and Prognosis

Treatment of disorders of pain is highly dependent on the nature of the disorder, its cause, and its functional implications. Analgesia may be appropriate for hyeralgesia and pain.

Prevention

Touch plays a prominent role in establishing the affectionate bond between parents and children. Touch and massage remain highly useful throughout the life span in reducing pain, anxiety, depression, and aggression.

Summary

Examination of the sensory systems is often challenging in infants and young children who cannot cooperate fully with testing. However, disorders in these systems may have profound functional consequences, particularly in learning, mobility, communication, and social interactions. Therefore, assessment of the sensory systems is a fundamental component of the neurological examination. Visual and hearing screening tests are appropriate at different times throughout childhood. It is particularly important to assess these senses in children with developmental disorders because sensory impairment frequently accompanies other conditions. Similarly, it is important to assess overall development in children with vision or hearing impairment because these might be part of a larger syndrome. Responses to smells and taste should be assessed in children with problems in anorexia, growth disturbance, or specific complaints. Response to touch is often assessed implicitly throughout a physical examination. Appropriate diagnosis and management of sensory disorders, as described above, may restore sensation with corresponding improvements in function. Prevention of sensory disorders, and in particular visual and hearing impairment, is a major focus of national and international public health efforts.

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45 Disorders of Cognition, Attention, Language, and Learning

Lynn M. Wegner · Jennifer K. Poon · Michelle M. Macias

Across all cultures, some children impress observers with their quick acquisition of developmental milestones and proficiency in understanding and mastery of information taught to them. If they live in societies with extensive formal systems of education, these children often do well in their classes, show strong performance on examinations, and are perceived as successful adults in their chosen vocational or professional fields. There are other children who do not show any notable delays in early developmental attainment, but struggle when the learning environment changes to formal instruction of reading, math, and written instruction. Sometimes children demonstrate uneven acquisition of academic skills. They may be advanced in math, but are slow and uncertain readers. Adults who endeavor to teach children face a quandary: What is hampering the child's progress in learning?

Educational attainment is multifactorial and very culture-dependent. The biology of the individual reflects genetics of the populace and the inheritance of their parents, nutrition, and environmental contaminants affecting the central nervous system. The social environment affects the teaching resources and the emphasis on academic success. There are individuals in all cultures, however, who are relatively not successful in academic endeavors. This chapter first will examine three domains affecting the ability to learn: cognitive profiles, selective attention (and executive functions), and language abilities. Specific disabilities in reading, math, and written expression will be presented. Most of the published literature in these topics is based on industrialized cultures; therefore, some bias may be noted. It is recognized that, despite the additional effort and expense required to educate special needs school-age children and adolescents, society as a whole benefits from helping them enter adulthood as capably as possible.

Cognition

Maria is 6 years old and her parents are upset that she is not interested in learning to read. Her teacher also has told them Maria's math abilities are not progressing like the other students. Maria had always needed more demonstration to learn games and home routines, but she has such a happy disposition that her parents and siblings did not mind giving her the extra help. When she is outside playing with other children, she seeks children 2–3 years younger than her for playmates. Her mother asks: "Isn't she as smart as my other children?"

Definition/Classification

Intelligence reflects the skills of logical reasoning, problem solving, critical thinking, and adaptation. Language, memory, processing speed, attention and executive function, and fluid intelligence are all components of most formal theories of intelligence. For example, memory is very important in learning and occurs in auditory, motor, perceptual, and visual domains. More recent conceptualizations of cognition include emotional, motor, and social intelligence.

In the USA, the terms "mental retardation (MR)" and "intellectual disability (ID)" are used synonymously, and current federal and state laws continue to contain the term "mental retardation." However, in 2007, the American Association on Mental Retardation (AAMR) changed its name to the American Association on Intellectual and Developmental Disabilities (AAIDD), and released its updated classification manual in 2010 in which "mental retardation" was universally replaced with "intellectual disability." The AAIDD defines ID as a disability characterized by significant limitations in both intellectual functioning and in adaptive behavior as expressed in conceptual, social, and practical adaptive skills. The AAIDD does not base their identification of an individual as "intellectually disabled" on cognitive testing standard scores alone, but rather the degree of external support the individual needs for life functioning. *Table 45.1* describes different levels of intellectual disability based on intelligence testing performance and level of external support needed by the individual.

Intellectual ability is presumed to occur in a population in a normally distributed manner. This is true for all societies. Children should be compared with

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children who live in similar cultures and communities. A normal distribution curve is symmetric around a mean value of 100 (50 percentile) and has a standard deviation of 15 points (Fig. 45.1). When percentages are examined on the normal curve, 2.14% of the population earns standard scores less than 70. The 2.14% of the population with intellectual abilities scores and adaptive functioning scores falling in this range fall within the category of ID. Not all countries use the terms "intellectual disability" or "mental retardation" to describe the individuals with intellectual testing and adaptive functioning in the lower 1–3% of the normally distributed population. The UK, for example, uses the term "learning disabilities" to describe individuals with ID as well as those with cognitive ability in the average range, but significantly weaker standardized academic achievement test scores. Regardless of the term used, common agreement is that the disordered cognition must be apparent before the age of 18 years.

Table 45.1
Intellectual disability: cognitive test level and external support needed

Descriptor	IQ	External support needed
Mild	55–70	Variable, situation dependent
Moderate	40–55	Minimal
Severe	25–40	Extended
Profound	<25	Complete in all situations

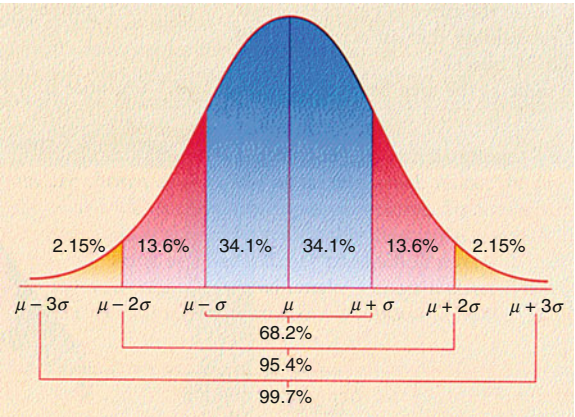

Figure 45.1
Normal distribution curve

Etiology/Pathogenesis

Identifying the etiology of ID may have more significance to the family than the medical provider unless there are associated conditions requiring ongoing medical monitoring and management. Prognosis for functioning as an older child and adult is a significant question and families may want to know the recurrence risk if additional children are planned. An important element of identifying the cause of the ID is dispelling myths and correcting any erroneous preconceived ideas of outcome the family may have.

The etiology of mild ID is identified in only 40% of patients. In children with moderate to more severe levels of ID, the etiology can be discerned more frequently, but specific identification still is unknown in 20% of these patients. Chromosome anomalies, metabolic disorders, extensive pre- and perinatal adverse events all have shown characteristic morphological and/or behavioral phenotypes. Some of the more well-recognized patterns are listed in Table 45.2.

Trisomy 21 is the most common genetic cause of ID; Fragile X is the most common inherited cause of ID; and fetal alcohol syndrome is the most preventable cause of ID.

Some children's ID is attributable to an identified pre- or postnatal event or condition. These include extreme prematurity (<30 weeks), congenital hypothyroidism, maternal untreated phenylketonuria, congenital hydrocephalus and other severe neural tube defects, severe intrauterine growth retardation or low birth weight, extensive intracranial bleeding, meningitis/encephalitis, and epilepsy. There also are external causes: head trauma; central nervous system infections and bleeding; heavy metal exposure (lead, manganese, methylmercury, and other forms of mercury, arsenic); exposure to polychlorinated biphenyls, organophosphates, chlorinated hydrocarbons; chronic hypoxemia; prenatal maternal medication and substances (antiepileptics, alcohol). Often, the end result of CNS dysfunction, whether prenatal, perinatal, or postnatal, results in ID. However, in the majority of individuals with ID, there may not be a specific structural abnormality identified.

Epidemiology

The prevalence of ID has slight variability due to the variations in diagnostic criteria. Although the prevalence was once thought to be as high as 3% it is now estimated to be between 0.78% and 1.27% of the US population. This discrepancy is due to the elimination of ID being diagnosed based solely on IQ scores, and now takes into

Table 45.2
Chromosomal and prenatal causes of intellectual disability

Disorder	Abnormality	Signs
Down syndrome	Trisomy 21	Hypotonia, small brachycephalic head, epicanthal folds, upslanting palpebral fissures, Brushfield spots in iris, single transverse palmar crease, flat nasal bridge, hypothyroidism, hearing loss, heart defects
Williams syndrome	(del) 7, 7q11	Periorbital fullness, short nose with bulbous nasal tip, long philtrum, wide mouth, and full lips; hypocalcemia, supravalvular aortic stenosis; "cocktail chatter"
Angelman syndrome	Four mechanisms: maternal (del) 15q11.2-q13; parental uniparental disomy; imprinting defects; mutation on UBE3A	Microcephaly, seizures, characteristic electroencephalogram; movement/gait disorder, happy demeanor
Smith–Magenis syndrome	(del) short arm 17, 17 p.11.2	Brachycephaly, broad face, midface hypoplasia, prognathism, short stature; hearing impairment
Fragile X syndrome	Trinucleotide repeat expansion (CGG; $\geq$200) in FMR1 gene	Mild-severe ID, autism
Prader–Willi syndrome	(del) 15q11.2-q13	Infancy: failure to thrive, hypotonia; obesity, hyperphagia, hypogonadism, short stature; almond-shaped eyes, hypopigmented hair; obsessive-compulsive disorder
Fetal alcohol syndrome	Not specified; associated with confirmed history of prenatal maternal ETOH use	Head circumference $\leq$10%; postnatal height or weight $\leq$10%; and at least two of these: short palpebral fissures, thin upper lip, smooth philtrum

account adaptive behavior. For example, in 1981, Swedish studies reported unequivocal ID in the school-aged Swedish population to be $<$1%.

Clinical Manifestations

Clinical presentation relies primarily on the degree of cognitive impairment. Initial presenting signs may include delayed language acquisition, cognitive skills, and adaptive skills. Children with severe to profound ID present at a very young age with globally delayed developmental skills. However, individuals with mild ID may be identified later, when they have difficulty with preacademic skills or multiple step instructions. Social skills may also be impacted, where a child may have more naive interests than his or her age-matched peers.

Diagnosis

The comprehensive evaluation of a child with ID can be coordinated by a primary pediatric health provider, but other professionals will have important roles. The focus of assessment is identifying etiology and extent of the intellectual disability. Family counseling should include discussion of prognosis and recurrence risk. The medical provider should be aware of any published guidelines for ongoing management. The child and family benefit from a comprehensive assessment as identifying the cause can lead to genetic counseling for future pregnancies and more accurate monitoring of the child for relevant physical conditions emerging in later years. Parents may be given a more accurate estimation of future developmental attainment and the frequent unspoken worry, "did I do anything to cause this?" may be answered.

A careful physical examination with measurements of: weight, height, frontal-occipital-head circumference, right auricle length, right palpebral length, philtrum length, testes volume (in postpubertal males) is needed. Hair patterns (including eyebrows), texture, density; skin texture and pigmentary changes (including nevus formation); examination of palmer creases and a careful neurological examination are essential parts the primary medical provider can do. Visual acuity and hearing thresholds should be documented as part of the examination.

The physical signs of Fragile X may not be obvious in very young children therefore all children with cognitive

delays should have specific DNA testing for Fragile X. Whole genome microarray testing can more precisely identify subtle chromosome abnormalities. Metabolic testing (plasma amino acids and urine organic acids) is indicated in the context of historical factors (parental consanguinity, family history, developmental regression, episodic decompensation) or physical examination findings suggestive of a specific etiology (coarse facial features, organomegaly). If the child shows abnormalities of head shape, microcephaly, or macrocephaly, neuroimaging (most often MRI) should be considered, but this is not a universal recommendation.

Formal psychometric testing is essential to establish the extent of ID. Psychologists customarily do this standardized testing, with instruments such as the *The Wechsler Intelligence Scale for Children*-Fourth Edition or the *Stanford Binet Intelligence Scale*-Fifth Edition and they often have adaptive functioning questionnaires, such as the Vineland Adaptive Behavior Scales for the parents (and sometimes teachers) with which the cognitive results are compared. Finally, it is very important to take into consideration the current functioning of the child and the "established" cognitive description. Children who entered high-quality daycare and preschools may perform at a transiently elevated cognitive level if their intelligence is tested as a young child. Their weaker cognitive level may be masked by this early intense stimulation. If an older child struggles in academics and adaptive functioning, yet has a record of "passing" early cognitive testing, an updated evaluation (with new cognitive testing and assessment of adaptive functioning) should be strongly considered.

Differential Diagnosis

If a child is labeled "mildly" ID but shows a variable profile of academic attainment (especially if math is strong) and age-appropriate adaptive skills (with the exception of weak communication), reassessment should be done with a comprehensive evaluation of expressive and receptive language abilities. If there is any question of the child's ability to understand what is said or to express herself/himself in an age-appropriate manner, a full language evaluation should be sought by a speech pathologist trained in evaluating children and adolescents. Weak language performance mandates the use of a cognitive test minimizing language during the testing and word use to solve the problems on the test in order to distinguish between a language disorder and ID. ● *Table 45.3* lists cognitive measures with minimal word knowledge required in the problem solving.

Children with impaired verbal IQ but normal nonverbal performance are likely to have a language-based learning disability rather than ID. Similarly, the opposite profile (below average nonverbal IQ but normal verbal scores) is more likely to represent a nonverbal learning disability. Children with autism often score in the impaired range on standardized assessments because of their language disorders or unwillingness to perform, but may not truly have ID.

Treatment

Supports for individuals with intellectual disability and their families are important. Much of the management for individuals with ID involves the educational setting, providing interventions and accommodations, while maintaining the least restrictive learning environment. Services such as physical, occupational and speech therapies, behavioral interventions, and/or specialized classrooms may be incorporated into the academic settings. It is also important to find extracurricular activities and social opportunities, which promote self-esteem. Transition planning should begin by early adolescence and focus

Table 45.3
Nonverbal intelligence tests

Instrument (year latest version)	Authors	Publisher (Web site)
Comprehensive Test of Nonverbal Intelligence-Second Edition; C-TONI-2 (2009)	Donald D. Hammill, Nils A. Pearson, and J. Lee Wiederholt	Pro-Ed www.proedinc.com
Differential Abilities Scale-Second Edition: DAS-II (2007)	Colin D. Elliott	Psychological Corporation www.psychcorp.com
Leiter International Performance Scale-Revised (1997)	Gale H. Roid and Lucy J. Miller	Stoelting Company www.stoeltingco.com
Raven's Progressive Matrices (2003)	J.C. Raven	Psychological Corporation www.psychcorp.com

on future medical care, work environment, and living environment. Furthermore, the development of a skill set for daily living is critical to foster maximum independence. Behavioral therapies should be utilized for maladaptive behaviors (e.g., aggression, self-injurious behaviors), including a functional behavior analysis. Pharmacologic management of impairing behaviors should be employed judiciously, and as an adjunct to behavior management strategies.

Prognosis

Long-term prognosis is difficult to predict in early childhood, as there may be variability in testing scores. However, in school-aged children, test scores become more consistent and more predictive. Individuals who have mild ID are commonly employed, and may support themselves and have a family of their own. Those who have moderate ID also may be able to work, but need more supervision. They may transition to a group home setting where they have higher levels of support. In individuals with severe and profound ID, more focus is placed on life skills and activities of daily living. Living arrangements will require constant supervision and assistance.

Attention Deficit Hyperactivity Disorder

Kashif is a 7-year-old boy who presents to your office with his mother for concerns of poor school performance. His mother complains that he has been doing poorly in his classes from a behavior and academic standpoint. You review notes from his teacher: "Kashif's behavior keeps him from learning. He leaves his seat during class and cannot keep his hands to himself. He talks while I am teaching. During reading, he stares off into the window and rarely completes his assignment. He forgets to bring home his assignment book."

When asked about how he is doing in the home, Kashif's mother has no major complaints. She says, "He is a typical boy and does not do anything around the house and at times, is impatient with his sisters, but otherwise there are no major problems." Upon further questioning, with simple chores like watering the plants, Kashif usually gets into something else before he finishes. He often fights with his younger siblings in playing games, as he does not have the patience to let them take a turn. Kashif's mother confides that his father does not believe that there is a problem at all. He says, "I was just like Kashif when I was his age. He is just a boy and he will be fine."

Attention deficit hyperactivity disorder (ADHD) is one of the most prevalent neurodevelopmental disorders of childhood. It can persist through adolescence and adulthood. While typically perceived as a pattern of overactivity, easy distractibility and impulsivity, there are other symptoms of poor planning, self-monitoring, organization, and task completion.

Definition/Classification

Attention Deficit/Hyperactivity Disorder (ADHD) is characterized by symptoms of hyperactivity, inattention, and impulsivity. The American Psychiatric Association's Diagnostic and Statistical Manual (DSM-IV) criteria for the disorder are: 6 out of 9 symptoms of inattention and/or 6 out of 9 symptoms of hyperactivity/impulsivity with noted impairment prior to 7 years of age, in two or more settings, and with clinically significant impairment in social, academic, or occupational functioning. Furthermore, the symptoms cannot occur with a pervasive developmental disorder, schizophrenia, or other psychotic disorder, nor can they be better accounted for by another mental disorder. DSM-IV categorizes ADHD into subtypes: (1) predominantly hyperactive/impulsive subtype, (2) predominantly inattentive subtype, and (3) combined hyperactive/impulsive and inattentive subtype. The proposed updated DSM-V changes the age of symptom onset. It proposes that in the evaluation of those over 17 years of age, 4 of 9 symptoms of inattention and/or 4 of 13 symptoms of hyperactivity/impulsivity are present. Furthermore, it raises the age of symptom presentation from 7 to 12 years. Similarly, the World Health Organization (WHO) classification under ICD-10 refers to hyperkinetic disorder and disturbance of activity and attention. These diagnostic criteria differ from DSM-IV in number of symptoms meeting threshold criteria, and differentiation of home vs. school as follows: Home: 3 of 5 symptoms of inattention, 3 of 5 activity problems, and 1 of 3 impulsivity problems; School: 2 out of 4 attention problems, 3 of 5 activity problems.

Etiology

ADHD is thought to be a genetically based neurobiological disorder, with multifactorial etiology. Genetic studies, neuroimaging studies, and environmental risk factor studies have provided evidence for this reasoning. Hereditability of the disorder is high, between 70% and 80% in studies involving families in the USA, Australia,

Scandinavia, and the European Union. A family history of ADHD has been shown to be higher in individuals with ADHD than their control counterparts. Twin studies have shown greater concordance for the disorder in monozygotic twins versus dizygotic twins.

Furthermore, genetic studies in families have found several genes that may be related to the disorder. Examples of genes related to ADHD include those related to dopamine (DRD4, DRD5, DAT1, DBH, and SNAP-25) and with serotonin (5-HTT, HTR1B). The International Multisite ADHD Gene identified 18 genes associated with ADHD.

The role of various environmental factors in the etiology of ADHD has been researched as well. However, as it is hard to control for confounding variables, the studies do not establish causality, but rather highlight attention to possible risk factors. Studies examining early risk factors for ADHD have identified prenatal exposure to maternal cigarette smoking as a consistent predictor of child ADHD, even when other factors are controlled. These findings are consistent internationally, including in the Netherlands, Finland, the UK, New Zealand, Australia, the USA, Canada, and Brazil and in animal models. Other prenatal and perinatal exposures that may be associated with ADHD are polysubstance abuse and alcohol exposure. The impact of these environmental exposures appears to function as part of a gene × environment interaction. For example, children exposed to prenatal nicotine and who have a polymorphism in the DRD4 are at the highest risk of developing ADHD. Similarly, children with the 10–10 allele for DAT who experience psychosocial adversity are more likely to develop ADHD.

Neuroimaging studies also suggest an association between structural abnormalities and ADHD. These associations may correspond to an underlying etiology of ADHD or may represent developmental adaptations to the disorder. A number of studies have demonstrated decreased volumes particularly in the caudate, globus pallidum, cerebellar vermis, anterior cerebrum, and white matter tracks. One study noted a correlation between cortical thinning in children with ADHD and the course of the disorder – children with persistent symptoms had persistently thin cortex, whereas those whose symptoms improved had normalized cortical thickness.

Epidemiology

World prevalence of ADHD ranges from 1% to 20%. The wide variability may be due to methodological differences among studies such as inclusion criteria, informants, instruments used, and the population studied. Studies within the USA alone have ranged between 4% and 12%. Studies in other countries' prevalence of ADHD include Canada 6%, Iceland 6%, Brazil 18%, Colombia 16%, the UK 17%, Germany 11%, India 11%, Israel 4%, Iran 6%, China 6%, and New Zealand 3%.

ADHD is diagnosed more frequently in males, with the ratio ranging from 2:1 to 4:1. Boys are more likely to be referred for evaluation as they tend to demonstrate disruptive behavior. There have been studies showing a higher prevalence of ADHD reported in urban versus rural children, although this may reflect more on disparities in health care.

Clinical Manifestations

ADHD is the most common childhood neurobehavioral disorder in primary care pediatrics. The core clinical features of ADHD are hyperactivity, inattention, and impulsivity. Not all of these symptoms manifest uniformly, and the clinician must remain vigilant to detect these problems.

Children with ADHD may first come to attention because they have symptoms of hyperactivity and trouble with impulse control. These symptoms may be seen early in the preschool years and at that time they may or may not be impairing. Trouble in the school setting often highlights symptoms. In school, the hyperactive–impulsive subtype of ADHD may manifest as a child who squirms in his or her seat, leaving it at inappropriate times. They may blurt out answers in the classroom or even talk to others while the teacher is teaching. In play and other peer interactions, they may have difficulty waiting their turn in games or conversation, often interrupting others. They can also have a higher rate of accidental injuries such as lacerations or fractures related to climbing or impulsive behaviors.

Children with the inattentive subtype of ADHD may be identified at a later time, as they are struggling with their academic work. Unfortunately, many are unidentified, as they may not be disruptive. However, these symptoms can be equally impairing as the hyperactive–impulsive subtype of ADHD. Inattention can present in a number of ways. For instance a child may appear to be staring at nothing, not listening, or not paying attention. They may forget easily about chores and assignments. Social skills may be impaired as they may not be able to pick up on others' social cues if they are distracted. Furthermore, inattention can result in poor planning, mistakes, and difficulty completing assignments.

Up to 75% of children with ADHD may also have existing comorbid conditions. Some of these conditions include oppositional defiant disorder, conduct

disorder, depression, anxiety, tic disorder, mania, and learning/academic problems. More than half of children with ADHD have sleep disorders as well. Learning problems and substance abuse disorders, including nicotine, also co-occur with ADHD. Similar patterns of comorbidity are present in children from eastern Asia and central Europe. In light of the high rate of comorbidities, it is important for the clinician to consider symptoms of these in the diagnosis and treatment plan of ADHD.

Diagnosis

There is no single test diagnostic for ADHD. Instead, it is a diagnosis based on clinical impressions and established criteria. Utilization of these criteria is important for a uniform standard of care and accurate diagnosis. Any school-aged child who presents with concerns about academic underachievement and/or behavioral concerns, including hyperactivity, inattention, and impulsivity should be evaluated for the disorder.

The clinician must gather information about the symptoms in multiple settings, the impairment from the symptoms, and any symptoms that may be related to comorbid diagnoses. It is important to discuss the age of onset, the frequency, duration, and level of impairment. As symptoms of ADHD manifest in differing environments, it is crucial to obtain information from both the home environment and an alternate setting, which is most often the school. Furthermore, the importance of the psychosocial history and family history should not be underestimated. A psychosocial history allows the clinician to look at other contributing factors to the behaviors at hand. Information such as the home environment, school setting, potential violence and/or trauma, and other stressors should be elicited. Family history can be valuable as ADHD is highly heritable.

Several ADHD-specific questionnaires and rating scales are available for both parents and teachers to complete in order to ascertain information from different environments. These questionnaires are valuable tools for the diagnosis of ADHD; however, they should not be viewed as the sole diagnostic tool, but instead, a supporting piece of evidence.

Vision and hearing should be screened to make sure there is no impairment causing the presenting symptoms. However, laboratory tests, such as lead levels or thyroid hormone levels are not advised, unless clinically indicated. Furthermore, brain imaging studies and electroencephalography have not consistently demonstrated differences between children with and without ADHD, and should not be relied upon to assist or confirm a diagnosis.

Differential Diagnosis

Hyperactivity is a nonspecific symptom that can occur in a range of other disorders. Hyperactivity that is situational or relationship specific may reflect anxiety or distress. Mania shares the hypermotoric patterns of ADHD, but can usually be differentiated by a decreased need for sleep (not simply sleep problems), euphoria or irritability, and grandiosity. Misbehavior only in classes may suggest a learning difficulty that must be assessed. Children with obstructive sleep apnea can also present with behaviors that are similar to ADHD and sleep patterns should be assessed as part of the assessment. Inattentive type ADHD symptoms must be distinguished from anxiety, including dissociative symptoms, from partial complex seizures, and either boredom in school or learning disabilities.

Treatment

Treatment should be based on the principles that ADHD is chronic, and often transcends into adulthood. Both the family and patient should be educated on the nature of the neurobiological basis of ADHD, the course of the disorder, and the treatment plan itself. In order to invest the family, including the child, in the treatment, they should have input in setting their goals for improvements in home life, academic settings, and interpersonal relationships. Treatment consists of both behavioral modifications and medication.

The Multimodal Treatment Study of ADHD provided significant knowledge to the understanding of treatments available for ADHD. The study was a multisite clinical trial to evaluate four treatment arms: (1) pharmacotherapy alone, (2) behavior-based treatment alone, (3) a combination of pharmacotherapy and behavioral treatment, and (4) community-based treatment. Results demonstrated that pharmacotherapy alone or a combination of pharmacotherapy with behavioral treatment resulted in the most significant improvement in ADHD symptoms. To date, there have been no studies supporting the efficacy of psychotherapy for ADHD.

Behavioral therapies should avoid focusing on negative behaviors and instead on promoting positive behaviors. Classroom modifications may improve academic performance. For instance, assignments may be broken into shorter segments, and timers may be used to encourage task completion. Children with ADHD may require lessons on note taking and organization, as these may not be intuitive. Furthermore, children with more prominent features of hyperactivity may require planned opportunities

for controlled movements. This may be in the form of helping with classroom housekeeping, passing out classroom materials, or even standing beside their desk periodically while doing classwork. The teacher may utilize positive reinforcement, token economy, and time-out.

While studies have shown the short-term effectiveness of behavioral modifications, often children with ADHD have trouble generalizing the modified behaviors to other situations. Furthermore, behavioral interventions are unable to ameliorate the neurobiological component of ADHD. Therefore, successful treatment involves a long-term combination approach and includes pharmacologic management.

Psychostimulants are considered first-line pharmacotherapy in the treatment of ADHD. They are the most studied of any medications and have a proven record of efficacy in over 70% of children with ADHD. The mechanism of action involves increasing the intersynaptic availability of the neurotransmitters, dopamine, and norepinephrine. The primary classes of stimulants include methylphenidate and the amphetamines. There are multiple formulations, from short to intermediate to long acting (see *Table 45.4*). The stimulants' onset of action is typically around 30 min. The most common side effects tend to be appetite suppression, insomnia, headaches, stomachaches, and irritability. These side effects may mostly be avoided and/or alleviated by adjusting the time or strength of the dose or to a different method of delivery. Unlike other medications, stimulants are not dosed according to weight, as each individual possesses a different dose-response curve. Patients should be started at a low dose and titrated up to maximum effect, with minimal to no side effects.

Stimulants do not induce seizures, and they may be used in children with tic disorders. While studies have shown that there may be some reduction in stature over the first year of treatment, this was not true for the long term and there was no overall affect on the ultimate height outcome. Teenagers who take stimulants for ADHD have been associated with better outcomes in the avoidance of substance abuse. While stimulants have been shown to have a statistically significant affect on blood pressure and heart rate this has not been clinically significant. The American Academy of Pediatrics recommends careful screening of children for whom stimulant medications may be indicated. This should include a good medical history and physical examination, including a cardiac history and examination, as well as a review of the family history, including a family history of unexplained sudden death in children and young adults, long Q-T syndrome, or hypertrophic obstructive cardiomyopathy. Any concerns from the history or physical examination should prompt further evaluation by a cardiologist prior to the initiation of a stimulant. Electrocardiograms and echocardiograms are not a necessary part of the screening, unless prompted by history or examination.

Table 45.4
Stimulant medications used in ADHD

Generic name	Trade name(s)	Doses	Dosing intervals
Amphetamine	Dexedrine	5,10,15 mg ER	Daily
	DextroStat	5,10 mg	Daily to three times daily
Dexmethylphenidate	Focalin	2.5,5,10 mg	Twice daily
	Focalin XR	5,10,15,20,30 mg ER	Daily
Lisdexamfetamine	Vyvanse	20,30,40,50,60,70 mg	Daily
Methylphenidate	Concerta	18,27,36,54 mg ER	Daily
	Daytrana	10,15,20,30 mg patch	Daily (9 h)
	Metadate CD	10,20,30,40,50,60 mg ER	Daily
	Metadate ER	10,20 mg ER	Daily to twice daily
	Methylin	5,10,20 mg; 2.5,5,10 mg chewable; 5,10 mg/5 mL	Twice to three times daily
	Ritalin	5,10,20 mg	Twice to three times daily
	Ritalin LA	10,20,30,40 mg ER	Daily
	Ritalin SR	20 mg ER	Daily to twice daily
Mixed amphetamine salts	Adderall	5,7.5,10,12.5,15,20,30 mg	Daily to twice daily
	Adderall XR	5,10,15,20,25,30 mg ER	Daily

Stimulant medications are typically titrated to effect, monitoring carefully for side effects, over the first month from initiation. Weight, height, blood pressure, and heart rate should be monitored at each visit. During this time, it is also important to obtain feedback from parents and teachers about how the child is responding to the medication. Objective measures in the form of brief follow-up rating scales can provide valuable information for the clinician to determine the optimal dosage for the medication. If a child is not responding favorably to one class of stimulants, despite proper administration, or if side effects cannot be avoided, the clinician should switch to the other class of stimulants. If the alternate class of stimulants is not effective, the clinician should consider one of the second-line medications, reevaluating for unrecognized coexisting disorders, and referral to a subspecialist.

Other medications that are also used include noradrenergic reuptake inhibitors, tricyclic antidepressants, and alpha-agonists (see *Table 45.5*). These are considered to be second-line agents in the treatment of ADHD. They may also be considered for patients who have had a history of substance abuse, as an alternative with less abuse potential than the stimulants.

Atomoxetine, a norepinephrine reuptake inhibitor, was developed as a nonstimulant treatment for ADHD. It is typically dosed once to twice daily and unlike stimulants, has a longer onset to action. Common side effects include gastrointestinal upset and sedation. There have been rare reports of liver dysfunction and failure, which were found to normalize after the cessation of the medication. Therefore, routine blood monitoring of liver function tests has not been recommended, unless there are signs and symptoms of liver dysfunction (e.g., right upper quadrant abdominal discomfort, jaundice). There is a black box warning regarding suicidal ideation; however, there have been no reported cases of suicide.

Tricyclic antidepressants have been used with success in the treatment of ADHD in children. They also inhibit the reuptake of norepinephrine. Because the tricyclic antidepressants present a cardiovascular risk, baseline electrocardiography should be obtained and monitored. Bupropion is another antidepressant that has been used for symptoms of ADHD. It is an aminoketone antidepressant that has noradrenergic effects.

Originally, clonidine and guanfacine, alpha 2 agonists, were developed to treat hypertension. Because these medications also have noradrenergic effects on the prefrontal cortex, they also help with hyperactivity and impulsivity. Improvements may not be seen for several weeks. Clonidine and guanfacine are typically dosed between two and four times a day, although recently, extended release versions of both medications have been introduced, reducing dosing to twice daily for clonidine and once daily for guanfacine. Side effects include sedation, fatigue, dry mouth, and hypotension. Furthermore, there is risk for rebound hypertension if the medication is stopped immediately.

Regular follow-up is important in the successful treatment of ADHD. Follow-up every 3–4 months allows reassessment of medication efficacy and provides the clinician time to help problem solve any issues that may

Table 45.5
Nonstimulant medications used in ADHD

Generic name	Trade name	Doses	Dosing intervals	Mechanism of action
Atomoxetine	Strattera	10,18,25,40,60,80,100 mg	Daily	Selective norepinephrine reuptake inhibitor
Buproprion	Wellbutrin	75,100 mg	Daily to three times daily	Norepinephrine dopamine reuptake inhibitor
Clonidine	Catapres	0.1 mg	Daily to four times daily	Nonselective alpha-2
Hydrochloride	Kapvay (extended release)	0.1,0.2 mg	Twice daily	Adrenergic agonist
Guanfacine	Tenex	1 mg	Daily to three times daily	Selective alpha-2a
	Intuniv (extended release)	0.1,0.2 mg	Twice daily	Adrenergic agonist
Impipramine, Desipramine	Tofranil	10,25,50 mg	Daily	Tricyclic antidepressant;
	Norpramin	10,25,50,75,100,150 mg	Daily	norepinephrine reuptake inhibitor
Modafinil	Provigil	100,200 mg	Daily	Unknown-CNS stimulant

be deterrents in the successful treatment of the disorder. Feedback, including objective measures, is important to obtain at these regular visits to track improvement, or lack thereof. Again, feedback should include both home and school settings.

Prognosis

ADHD often persists into adulthood. Up to 85% of children with ADHD continue to have impairment in adolescence and up to 60% in adulthood. Often the hyperactivity component of the disorder decreases with age, but the other symptoms of inattention and impulsivity persist. Studies have found that adults with a history of ADHD as a child are more likely to have criminal behavior, injuries, marital difficulties, job problems, and teen pregnancies. Outcomes have been found to be dependent on the quality of the symptoms, existing comorbidities, socioeconomic status, and history of treatment. Individuals who receive appropriate management and treatment tend to have improved outcomes. Some adults are able to accommodate the symptoms or choose careers in which the symptoms are less impairing.

Speech and Language Disorders

Levi is in your office for a routine health maintenance examination. He is 30 months old. His mother has no concerns about his health or development. In review of his developmental milestones, he runs well and he demonstrates that he can stand on one foot for 1 s, while smiling at you and his mother. He cooperates with your request to copy a horizontal and vertical line and as soon as you get out blocks, he stacks a tower of 10. He has five words that he uses consistently. He identifies his eyes, ears, and nose when you ask him; however, he looks away when you ask him to point to specific pictures. You ask his mother more about his language, and she says, "I am not concerned, Levi is a smart boy. Boys talk later than girls and he never has a chance to talk because his 5-year-old sister does all the talking for him."

Language acquisition is an extremely important component of a child's development. Language represents objects or actions in symbolic form and communicates ideas, intentions, and emotions. Speech and language disorders are the most common developmentally disabling disorders of childhood. Pediatric health-care providers are responsible for promoting language development, alleviating concerns about language development, and/or detecting language development problems. Early recognition and intervention are necessary to provide children with speech and/or language disorders with the best possible outcome. The reader is referred to ❯ Chap. 42, Normal Child Development, ❯ *Table 1*, for a detailed review of language milestones:

Speech produces complex acoustic signals that communicate meaning and is the result of interactions between the respiratory, laryngeal, and oral structures. This acoustic signal varies with regard to vocal pitch, intonation, and voice quality. The symbols need to conform to the language code so they can be decoded as meaningful communication.

Language involves both expressive and receptive components. Expressive language involves the communication of ideas, intentions, and emotions. Receptive language involves understanding what is said by someone else. Receptive language includes auditory comprehension (listening), literate decoding (reading), and mastery of visual signing.

Language has several components, as outlined in ❯ *Table 45.6*. The simplest "units" of language are *phonemes*, or individual sounds. Phonemes are combined to produce *morphemes*, which are the meaningful units of sound combined to produce a word. The *lexicon* (vocabulary) is the collection of all of the meaningful words in a language. *Syntax* (grammar) is the order of words in phrases and sentences. *Semantics* are the individual word and sentence meanings. The literal interpretation of words can be modified by *prosody* or vocal intonation. The social use of language is known as *pragmatics*.

Definition/Classification

A speech-language or communication disorder is defined as impairment in the ability to receive, send, process, and/or comprehend verbal, nonverbal, or graphic symbol systems. The most common variation in language development is language *delay*. The word *delay* inherently implies that catch-up will occur. Of children with early language delays, approximately 60% will catch up by 4 years of age with no persistent problems. Another variation is language *dissociation*. This can occur either within the domain, as seen when developmental rates differ between expressive and receptive language, or between different domains (e.g., language and motor skills). *Deviancy* of language development occurs when language development deviates from the norm, for example when children learn more advanced language-based concepts before they have mastered early language milestones. An example of

Table 45.6
Components of speech and language

Term	Definition
Speech	
Intelligibility	Ability of speech to be understood by others
Fluency	Flow of speech
Voice and resonance	Sound of speech, incorporating passage of air through larynx, mouth, and nose
Language	
Receptive language	Ability to understand language
Expressive language	Ability to produce language
Phoneme	Smallest units of sound that change the meaning of a word, e.g., "map" and "mop"
Morpheme	Smallest unit of meaning in language, e.g., adding –s to the end of a word to make it plural
Syntax	Set of rules for combining morphemes and words into sentences (grammar)
Semantics	The meaning of words and sentences
Pragmatics	The social use of language, including conversational skills, discourse, volume of speech, and body language

this is a child who is able to recite the alphabet or TV jingles but is not yet able to communicate needs using words and phrases. Deviant language development can often be a sign of autism spectrum disorders.

Etiology and Epidemiology

Language development occurs in an orderly and predictable manner for most children. However, virtually any disruption in brain function can affect language acquisition; therefore, a variety of conditions affecting the brain are associated with language problems. Delays in comprehension and/or expression not associated with other developmental or neurologic problems are found in 7.5–10% of North American preschool children with a significantly higher proportion of boys being affected.

The pediatric practitioner should not attribute cultural or gender differences as reasons for delayed language development. Children who learn two languages simultaneously follow the same pattern of speech and language development as monolingual language learners. The child may have a period when he or she mixes the two languages, but this should gradually disappear as language skills develop. Studies have shown that girls are more talkative (have more total words) than boys at all ages, with significant gender differences found between 1 and 2½ years of age. Although some boys may develop expressive language more slowly than girls, it is generally only by a few months and still within the accepted time frame. Language development is almost never delayed because the child "doesn't need to speak" (e.g., "her big sister always talks for her"). There is a tremendous motivation to improve communication, as the use of verbal labels allows the child to meet needs more efficiently than pointing.

The term *language delay* implies the delay will resolve and the child will catch up at some point. However, more than 40% of children whose early language delays show improvement have later reading or cognitive difficulties. Preschoolers with language disorders are at higher risk for language-based learning disorders, social, and behavioral problems. Speech and/or language concerns should not be dismissed with reassurance that the child will "catch up," given the possibility of future difficulties and better outcomes with earlier detection of these problems.

Pathogenesis and Genetics

The general location of basic language centers was determined in the nineteenth century by Paul Broca and Carl Wernicke, which then led to the theory of cerebral dominance. For virtually all right-handed people and two-thirds of left-handed people, speech and language are processed in the left cerebral hemisphere. Lesions bordering the sylvian fissure of the dominant hemisphere usually cause disturbances in speech and language. A functional anatomic loop connects the eyes and ears to the visual and auditory system, an intrahemispheral section through white matter connects the temporal with the frontal lobes, and the frontal lobes connect to the mouth and hand.

Meaning is provided to sounds and shapes through intrahemispheral and transcallosal pathways to the rest of the brain from the sylvian region. Recent advances in functional neuroimaging studies have suggested specific cortical areas associated with individual language skills. Positron emission tomography scans have shown increased metabolic activity across the left and right temporal and frontal cortex areas of the brain during speech and nonspeech acoustic processing. Functional magnetic resonance imaging studies show differences between the

sexes, with activation in the left inferior frontal gyrus for males and activation in both right and left inferior frontal areas for females during phonologic tasks. Word analysis and articulation has been mapped to Broca's area of the inferior frontal gyrus, whereas skilled word form discrimination involves the occipitotemporal region.

A substantial heritable component exists in speech and language disorders, but the underlying genetic basis is complex and involves different risk factors. Close examination of families with persistent signs of disordered language skills have suggested a genetic basis; however, exclusive of recognized genetic disorders with strong, specific language differences (e.g., velocardiofacial syndrome, Williams syndrome, or fragile X syndrome), no genetic markers for "developmental language disorder" have been clearly identified. Recent genome scanning techniques have identified chromosomes 2, 13, 16, and 19 as having potential candidate genes involved with more common forms of language impairment. Molecular genetic techniques are currently being utilized to investigate speech and language disorders.

Clinical Manifestations

Speech Disorders

Speech disorders reflect problems with creating the appropriate sounds representing the language symbols (the words). These problems include phonologic (*articulation*) disorders, speech fluency disorders (*stuttering*), and voice disorders. Speech disorders may or may not also include impairments in expressive language.

A phonologic or articulation disorder is characterized by the substitution, omission, addition, or distortion of phonemes and represents most speech therapy referrals. Children master sounds at different ages depending on the difficulty in producing the sound. In the first 2 years, children master simple sounds, including all vowels and the consonants /b/, /c/, /d/, /p/, and /m/. More difficult sounds, such as the consonants /j/, /r/, /l/, and /v/ and blends (i.e., sh, ch, th, st) may not be mastered until 5 or 6 years of age.

Dysarthrias are motor speech disorders that involve problems of articulation, respiration, phonation, or prosody as a result of paralysis, muscle weakness, or poor coordination. Dysarthric speech is characterized by weakness in specific speech sound production and is frequently associated with cerebral palsy. Dysarthric speech may also encompass problems in coordinated breath control and head posture.

Apraxia of speech or *dyspraxia* is a speech disorder involving problems in articulation, phonation, respiration, and resonance arising from difficulties in complex motor planning and movement. The child with apraxia/dyspraxia has problems putting syllables together to form words, and has more difficulty with longer words rather than shorter, simpler words. It is not due to weakness of the oromotor musculature as seen with dysarthria. Therefore, apraxia/dyspraxia can be differentiated from dysarthria by the lack of association with other oral-motor skills, such as chewing, swallowing, or spitting. Other neurologic "soft signs," such as generalized hypotonia, may be present on examination. Acquired apraxia/dyspraxia commonly results from head injury, tumor, stroke, or other problems affecting the parts of the brain involved with speaking and involves loss of previously acquired speech. It may co-occur with dysarthria or aphasia, a communication disorder impacting understanding or use of words caused by damage to the language centers of the brain. Developmental apraxia of speech is present from birth. Individuals with apraxia or aphasia might both have difficulty with verbal expression; however, apraxia on its own does not present a problem with language comprehension. Apraxia of speech is differentiated from an expressive language delay, in that children with expressive language delay typically follow a normal language trajectory but at a slower pace. Because individuals with apraxia of speech demonstrate similar language concerns as individuals with expressive language disorders, it is necessary for examiners to administer an oral-motor examination to help differentiate the two conditions.

Variations in pitch, volume, resonance, and voice quality can be seen in isolation or in combination with a language delay. Impaired modulation of pitch and volume can be seen in children with autism spectrum disorders, nonverbal learning disorders, and some genetic syndromes. Hyper- or hyponasal voice quality suggests anatomic differences or sometimes neurologic dysfunction, with hypernasal speech occurring secondary to velopharyngeal palatal incompetence and hyponasal speech arising from air impeded by large adenoids. Velopharyngeal palatine incompetence (insufficiency) can be a marker of velocardiofacial syndrome.

A fluency disorder involves the interruption in the flow of speaking. Examples of dysfluent speech include pauses, hesitations, interjections, prolongations, and interruptions. This is common in early childhood (age 2½–4 years) and at that time is categorized as *normal dysfluency of childhood*. Persistent or progressive dysfluency is more likely *stuttering*, which arises in the preschool years for most affected children. Red flags indicative of pathological dysfluency requiring speech therapy include repetitions associated with sound prolongations (e.g., "ca-caaaaa-caaaaat"), multiple part-word repetitions

(e.g., "ca-ca-ca-cat"), hurried and jerky repetitions with associated self-awareness and frustration, associated articulation problems, or a home environment with a low tolerance for stuttering or high pressure for verbal communication. Normal dysfluency usually improves over time.

Language Disorders

A language disorder, or specific language impairment (SLI), is an impairment in the ability to understand and/or use words in context, both verbally and nonverbally. The disorder may involve the form of language (phonology, morphology, and syntax), the content of language (semantics), and/or the function of language (pragmatics). Language disorders are also classified as receptive disorders (trouble understanding others), expressive disorders (trouble sharing thoughts, ideas, and feelings), or mixed receptive and expressive disorders.

Deficits in receptive language almost always occur in conjunction with expressive delays. There are situations where a child may appear to have an isolated receptive delay, but on careful evaluation, deficits in both areas are present. For example, a child with an autism spectrum disorder may appear to have normal or advanced expressive language skills due to extensive use of echolalia, but their functional communication delays are similar to their impaired receptive skills. Children with hydrocephalus (congenital or acquired) may have superficially appropriate or advanced expressive language skills but exhibit poor content of expression known as "cocktail party syndrome." In this case, receptive language lags behind expressive language and is felt to be secondary to hydrocephalus and related effects on the language centers of the brain.

Expressive language disorders represent a broad spectrum of delays, including developmentally inappropriate short length of utterances, word-finding weakness, semantic substitutions, and difficulty mastering grammatical morphemes that contribute to plurals or tense. Signs of weakness in expressive language include circumlocutions (using many words to explain a word instead of using the specific term), excessive use of place holders ("um," "uh"), nonspecific words ("stuff" or "like"), using gestures excessively, or difficulty generating an ordered narrative. Isolated expressive language delays are generally less indicative of organic pathology if not also associated with anatomic abnormalities.

Unless formal language testing using standardized instruments supports the presence solely of an isolated articulation disorder or specific receptive or expressive weakness, a child with a history of "language delays" should be presumed to have had some combination of language understanding and expression weaknesses. Impairment in both the receptive and expressive language domains raises the possibility of a more serious pathologic process, including intellectual disability (mental retardation), autism and other communication disorders, and deafness.

Deficits in pragmatic skills involve the inability to use language appropriately for social communication. A child may be unable to regulate social interactions or reciprocal body language or appropriately modulate their voice. They may stand too close or too far away from people or have improper voice pitch or volume. They commonly have difficulty initiating, maintaining, or terminating a conversation; modifying a topic for an audience; or including others in conversation. Pragmatic language disorders are often found in children with autism spectrum disorders and nonverbal learning disorders.

Diagnosis

The ICD-10 diagnostic criteria for speech and language disorders are outlined in *Table 45.7*.

Screening all children for delays in any of the developmental domains should be conducted at periodic intervals and whenever parents voice concerns about their child's development. This includes eliciting and attending to parental concerns, updating attainment of speech and language developmental milestones, determining risk and protective factors, and making accurate observations of the child. It is important to take parental concerns about speech or language development seriously, as these concerns are valid up to 75% of the time. A 25% delay in milestone attainment is cause for concern and indicates the need for more detailed screening and/or assessment of speech and language skills. Red flags for delayed language skills are outlined in *Table 45.8*.

The evaluation of a child suspected of having a speech or language delay should involve a thorough history and physical examination to determine the nature and extent of the problem but also uncover the etiology whenever possible. The clinician needs to determine whether the delay involves expression alone or both expressive and receptive language abilities. Parental concerns are often focused on a child's inability to express herself/himself and they may not be aware of associated delays in comprehension. Asking parents about any articulation or intelligibility difficulties is important. Inquiry about prenatal and delivery history, hearing loss, multiple ear infections, excessive drooling or difficulty feeding, and delays in other developmental domains will further

Table 45.7
ICD-10 criteria for specific developmental disorders of speech and language

F80.0 Specific speech articulation disorder
Note: Also referred to as Specific speech phonological disorder
A. Articulation (phonological) skills, as assessed on standardized tests, below the 2 standard deviations limit for the child's age
B. Articulation (phonological) skills at least 1 standard deviation below nonverbal IQ as assessed on a standardized test
C. Language expression and comprehension, as assessed on a standardized test, within the 2 standard deviation limit for the child's age
D. Absence of neurological, sensory, or physical impairments that directly affect speech sound production, or a pervasive developmental disorder (F84.-)
E. Most commonly used exclusion criterion: Nonverbal IQ below 70 on a standardized test
F80.1 Expressive language disorder
A. Expressive language skills, as assessed on standardized tests, below the 2 standard deviation limit for the child's age
B. Expressive language skills at least 1 standard deviation below nonverbal IQ as assessed on a standardized test
C. Receptive language skills, as assessed on standardized tests, within the 2 standard deviation limit for the child's age
D. Use and understanding of nonverbal communication and imaginative language functions within the normal range
E. Absence of neurological, sensory, or physical impairments that directly affect use of spoken language, or of a pervasive developmental disorder
F. *Most commonly used exclusion criterion*: Nonverbal IQ below 70 on a standardized test
F80.2 Receptive language disorder
Note: Also referred to as mixed receptive/expressive disorder
A. Language comprehension, as assessed on standardized tests, below the 2 standard deviations limit for the child's age
B. Receptive language skills at least 1 standard deviation below nonverbal IQ as assessed on a standardized test
C. Absence of neurological, sensory, or physical impairments that directly affect receptive language, or of a pervasive developmental disorder
D. *Most commonly used exclusion criterion*: Nonverbal IQ below 70 on a standardized test

Table 45.8
Red flags for delayed language development

Age	Milestone
6 months	No cooing responsively
10 months	No babbling
12 months	No basic gesturing (waving bye-bye, holding arms out to be picked up)
18 months	No words other than mama, dada
	No understanding of simple commands
	No pointing to what she/he wants
24 months	<50 words
	No two-word phrases
	<50% intelligibility
36 months	No three-word sentences
	<75% intelligibility
4–5 years	Not able to tell a simple story

elucidate an underlying cause. A detailed social history may uncover environmental causes of mild speech delay, including regression after a stressful event (e.g., divorce, birth of a sibling), lack of stimulation, or the over-anticipation of needs by older siblings and parents. Twin and family aggregation studies have demonstrated high heritability of language disorders therefore a detailed family history inquiring about speech and language or learning difficulties is important.

A simple conversation with the child may be all that is needed to determine the extent of their comprehension, expression, and deficits in speech delivery. This includes all attempts to communicate, whether it is verbal (e.g., babbling, jargoning, words) or nonverbal (e.g., facial expressions, gesturing or pointing, presence of joint attention, eye contact, and body posture). A neurologic examination focused on oromotor skills should be completed. The oromotor examination should include imitation of tongue movements in all directions, observance of palatal elevation on phonation, and evaluation of structural integrity of the oral cavity.

Evaluation of articulation disorders begins with good surveillance. A formula for the expected conversational intelligibility levels of preschoolers talking to unfamiliar listeners is: AGE IN YEARS/4 × 100 = % understood by strangers:

Child aged 1.0 = 1/4 or 25% intelligible to strangers
Child aged 2.0 = 2/4 or 50% intelligible to strangers
Child aged 3.0 = 3/4 or 75% intelligible to strangers
Child aged 4.0 = 4/4 or 100% intelligible to strangers

Any child older than 4 years with a speech intelligibility score of less than 66% (i.e., less than two-thirds of utterances understood by unfamiliar listeners) should be considered a candidate for intervention.

If a child is suspected of having a language disorder, evaluation by a speech-language pathologist is recommended. Referral to a developmental pediatric specialist or neurologist is also recommended if there is a history of language regression or if there are delays in other areas. Detailed genetic and neurologic evaluations for isolated speech and language impairments are of low yield, and an underlying etiology will be determined in less than 5% of cases. If hypernasality is noted with suspected velopharyngeal insufficiency, then further investigation for velocardiofacial disorder is indicated including referral to otorhinolaryngology and florescent in-situ hybridization study for 22q11.2. If a child has dysmorphic features or is found to have global developmental delays, then a full evaluation is recommended. This evaluation varies with the risk factors and findings and may include brain imaging, electroencephalogram, genetic testing, and/or metabolic testing.

Differential Diagnosis

If a speech or language delay is suspected, the child should be referred for a formal audiology examination, as a child may not have apparent hearing deficits by history. Even mild hearing loss can cause language delays and may not be picked up by newborn hearing screening. Evaluation of a child's nonverbal problem-solving and adaptive skills can determine whether the child may have an underlying cognitive impairment. If there are concerns related to a child's social relatedness and social interactions, an autism spectrum disorder should be suspected. There is considerable overlap among these underlying causes, especially considering the wide spectrum of severity in each area.

Language regression raises concerns for several disorders, including autism spectrum disorders, Rett Syndrome, or Landau–Kleffner syndrome (seizures accompanied by acquired aphasia).

Treatment

Even when there is a question regarding the underlying diagnosis, all young children suspected of having speech or language impairment should be referred promptly to their local Early Intervention Program (EIP). Such programs enrich a child's language experience through both parent training and provision of language-stimulating preschool environments. In addition, immediate speech and language therapy, which can be provided as a component of an EIP, has been shown to improve auditory comprehension and phonologic disorders. Additionally, speech and language therapy may prevent further delays and help reduce behavior difficulties associated with frustrated attempts to communicate.

Treatment of speech-language disorders includes three components: causal, habilitative, and supportive. Causal treatment is focused on repairing defects, correcting dysfunction, or eliminating factors that contribute to the language problem (e.g., cleft palate repair, hearing aids). Habilitative treatment is designed to directly improve the child's language skills (i.e., speech-language therapy, counseling of parents to actively engage in the child's language development). Supportive treatment aims to boost language acquisition (e.g., training programs for speech-related skills, increasing social contacts).

Goals for treatment depend on the nature of the child's speech or language impairment. The overall goal is to communicate with others, whether by spoken language or nonverbally through the use of sign language or communication systems, such as the Picture Exchange Communication System or an augmentative communication device. Some parents may voice concerns that early use of sign language or another communication system will impair a child's ability to speak, but there is evidence that using these systems may actually enhance a child's speech and language development.

In addition to therapy, parent education that focuses on language stimulation activities is essential. Structured/stimulating child care centers, preschool programs are also beneficial, particularly in children with isolated nonpathologic speech-language delay reflecting developmental variation or lack of a stimulating home environment.

Prognosis

While therapy may improve the degree of impairment and prognosis, many children do not "outgrow" speech and language disorders, although these disorders manifest in different ways over time. Developmental continuities exist between oral (including speech) and written (reading and written expression) language disorders. Oral language skills, including phonology, semantics, grammar, and pragmatics, are the foundation for reading. Children with language problems typically are at higher risk for

reading comprehension deficits. Children with persistent specific language impairment at 8½ years of age have been shown to have pervasive problems with spelling, word-level reading, and reading comprehension at 15 years of age. Developmental promotion of language and early identification and intervention for speech and language disorders are vital to provide the greatest long-term functional benefits.

Learning Disabilities

Issa is an 8-year-old boy in your office for concerns of school failure. He has a history of delayed speech and language development, which improved with speech therapy. This year, he had difficulty in his reading and writing class. So far, no behavioral problems have been revealed and he is diligent about studying and his homework. You decide to refer him for psychoeducational testing, requesting intelligence and achievement measures.

Definition

The term "learning disabilities" was used in 1963 by Samuel Kirk, PhD "to describe a group of children who have disorders in development in language, speech, reading and associated communication skills needed for social interaction." He carefully excluded children who had "sensory handicaps such as blindness or deafness. . .generalized mental retardation." Specific Learning Disabilities (SLDs) involve one or more disordered psychological processes involved in understanding or in using language, spoken or written, which may be manifested in problems with listening, speaking, reading, writing, spelling, or performing mathematical computations. Individuals with perceptual disabilities, brain injury, and developmental aphasia are included in this identification. Those who have problems resulting from visual, hearing or motor difficulties, intellectual disability, emotional dysregulation, or environmental, cultural, or economic disadvantages are usually excluded from meeting the criteria for SLD.

The discrepancy definition customarily assumes the child has been exposed to an adequate educational experience and yet shows a difference of one standard deviation or more (>15–20 points) between his/her intelligence level (IQ score) and standard score on achievement testing in oral expression, listening comprehension, basic reading skills, reading comprehension, written expression, or mathematics calculation or reasoning. For example, a 9-year-old with a full-scale IQ standard score of 100 in the mid-average range, would need to show a standard score of <85 in any of the aforementioned areas to be considered as meeting the "discrepancy criteria" for SLD.

Children also may be identified as SLD if they meet the "poor achievement" definition of SLD. The poor achievement is set as a standard score threshold (1½–2 standard deviations below the mean value) below which it is agreed academic performance is so weak there is a significant learning problem. The threshold usually translates into a 2-year lag in academic performance below that expected for the child's age. A standard score of 70 is 2 standard deviations below the mean and represents very weak performance. However, children whose educational achievement and cognitive levels overlap do not meet criteria for the diagnosis of SLD. With weaker cognition, educational achievement also is expected to be weaker.

Epidemiology

Learning disabilities are, by definition, only identified after a child enters a school where specific content instruction is given and performance is measured. For this reason, the incidence and prevalence statistics primarily reflect industrialized countries with government-supported school systems. Taking all categories of learning disabilities, the prevalence is estimated at 5–10% of the total school population. Boys appear to be overrepresented in learning disabilities with a ratio of boys to girls 4:1; however, girls may be underidentified because they often are not as behaviorally challenging in the classroom. Prevalence estimates of dyslexia in school-age children range from 7% to 15%. If the definition is broadened to include all reading disabilities, the prevalence may increase to as much as 18% of school-age children. Math learning disability incidence estimates range from 5.8% to 13.8%. Children with math disability who have comorbid reading disability are estimated at 35–56.7%. A 1992 study of unreferred primary grade children found that 1.3–2.7% had problems with handwriting; 3.7–4.0% had spelling weakness; and 1–3% had weakness in creating written narratives. In 1999, the National Assessment of Educational Progress reported that 77% of US fourth-grade students wrote at less than a fourth-grade level.

Etiology/Pathogenesis

Recent advances in functional neuroimaging have supported prior assertions that certain cognitive functions

can be localized to specific regions in the brain. Language-based learning disorders, such as reading, spelling, and written expression, comprise 90% of all SLD and are considered left hemisphere disorders. Right hemisphere SLD show weaknesses in spatial cognition and/or visuoperceptual abilities leading to difficulties in math calculation and reasoning. Genetic influences appear to be more prominent in children with phonological coding deficits than in those with visual coding deficits.

Clinical Manifestations

Reading Disorder/Dyslexia

While there are many components to reading weakness, it is currently held the most prevalent deficit is a specific language skill resulting in less ability in detecting and manipulating individual speech sounds (phonemes). This leads to poor word recognition and decoding. In the past, it was assumed that visual system deficits were the foundations for reading weakness and the term "dyslexia" was used to describe the pattern of reversing letters when reading and writing. Now "dyslexia" is used to refer to any reading weakness, including specific reading disability, phonemic awareness deficits, and rapid automatic naming weaknesses.

In typical reading development, the child realizes spoken words are comprised of parts (phonemic awareness). Once this recognition occurs, the child associates written letters with these phonemes and an appreciation of written language occurs. The printed words are now accepted by the inherent neural circuitry for processing spoken language. When the child reads the printed word, decoding into phonemes occurs where the words are automatically processing by the language system. The reading *code* is broken. In the USA, 70–80% of children successfully learn this skill. Skilled readers show strong activation in the posterior left occipitotemporal region. Children identified as dyslexic do not show this overactivation of the left occipitotemporal region even after repeated trials of word exposure. Phonologic weakness in the dyslexic reader is persistent and is seen irrespective of primary language, overall cognitive level, or educational level.

Reading ability is evaluated principally by assessing basic skills and comprehension. The best characterization of the child's reading skills will describe the most effective intervention program. The child's ability to assign sounds to letter combinations (phonological awareness), rapid automatic naming speed and accuracy, reading vocabulary, reading rate (basic speed of reading aloud), reading fluency (speed of reading without mistakes), and reading comprehension all should be described in the reading evaluation. A child with significant reading comprehension weakness should be seriously considered for a separate language evaluation. Weak grammatical understanding, often identified in those with language impairment clearly affects reading understanding.

Mathematical Disorder

Published information about math learning disabilities does not have the extensive breadth when compared with reading disabilities. The understanding of problems with math learning may be affected by the variety of yet unidentified cognitive processes involved in typical math competence. This contrasts with word reading which is largely subsumed by the phonological processing deficits. Math has many areas including number computation, algebra, geometry, measurement, and solving word problems, which has led to difficulty in developing specific definitions of math learning disabilities.

In the USA, current identification criteria developed by the U.S. Office of Education specify two types of math learning disabilities: disability in math calculation and disability in math reasoning. *Table 45.9* compares ICD-10 and DSM IV diagnostic criteria for math disorder.

There are no clearly identified areas of the brain presumed to provide the location for processing required in math learning. Certain neural functions appear essential for normal math development. Good attention, working memory, short- and long-term memory are all needed. *Semantic memory* allows number-symbol association, prompt recall of math facts, and contributes to phonologic memory. Long-term *procedural memory* underlies use of strategies and algorithms in math solutions. Developmentally normal *visual spatial abilities* allow the child to correctly align numbers, keep place values, and adhere to operational direction rules while performing operations.

Finally, information processing speed is very important while solving math problems and may be directly affected by the semantic, procedural, short- and long-term, and working memory. Weaknesses in any of these domains will result in slower rate of information assimilation and may result in failure of fact organization.

Evaluation of mathematical abilities usually includes an individually administered, standardized mathematical achievement test, and the performance standard scores are compared with the child's intelligence standard score. Specific areas of calculation, speed of calculation,

Table 45.9
Mathematical disorder criteria of ICD-10 and DSM-IV

	ICD-10	DSM-IV
Code	F81.2 Specific disorder of arithmetical skills	315.1 Mathematics Disorder
Description	Involves a specific impairment in arithmetical skills. The deficit concerns mastery of basic computational skills of addition, subtraction, multiplication, and division rather than of the more abstract mathematical skills involved in algebra, trigonometry, geometry, or calculus	A. Mathematical ability, as measured by individually administered standardized tests, is substantially below that expected given the person's chronological age, measured intelligence, and age appropriate education
	Includes: Developmental:	B. The disturbance in Criterion A significantly interferes with academic achievement or activities of daily living that require mathematical ability
	Acalculia	
	Arithmetical disorder	
	Gerstmann's syndrome	
		C. If a sensory deficit is present, the difficulties in mathematical ability are in excess of those usually associated with it
Excludes	Not solely explicable on the basis of general mental retardation, acalculia NOS (R48.8), arithmetical difficulties:	
	Associated with a reading or spelling disorder (F81.3)	
	Due to inadequate teaching (Z55.8)	

mathematical reasoning, and application of mathematical principles are usually assessed. It is not uncommon for children with language disorders to have acceptable calculation abilities, but struggle with mathematical problems presented in word format.

Disorders of Written Expression

Individuals with disorders of written expression have significant difficulty translating their thoughts into written format at a level consistent with their intelligence. Written expression involves many developmental abilities (fine motor skills, attention, language, and memory domains) and therefore is affected if any of these domains are weak. Variable difficulties may be observed in handwriting (mechanics), spelling, sentence development, punctuation, grammar, development of ideas, organization of those ideas, and developing a cogent written product. Both the quality and quantity of the written product can be affected.

Written expression puts coordination and integrative demands on many neurodevelopmental domains. Cognitive information processing areas involved include mentally resisting distractions and "overcoming inertia" to get started on a task, idea development, concept formation, thinking, reasoning, fluent retrieval of information from memory, expression of information, attention to detail, task analysis and prioritization, planning and organization, appropriate sequencing of ideas and activities, concentration, understanding of language and appropriate communication rules/syntax, working memory, and fine motor graphomotor skills. Individuals with language disorders, ADHD, fine motor weaknesses, visual impairment, and/or any other alternation of sustained alert status will be susceptible to impairment of written expression.

Written expression is assessed formally by administering standardized composite educational assessment instruments and informally by reviewing writing samples such as journal entries, book reports, themes written for class assignments, and even letters to family members or friends.

Diagnosis

It may not be practical to formally assess specific language-based learning problems in a school-aged child in the pediatric office setting. However, a few surveillance questions may help identify the presence of difficulties in language-based learning (*Table 45.10*).

The evaluation of learning disabilities includes taking a careful medical history. Extreme prematurity with or without cerebral hemorrhage, maternal prenatal risk

Table 45.10
Surveillance questions for language-based learning problems

1. Does she/he have trouble expressing her/his thoughts?
2. Is it difficult for her/him to understand or follow directions?
3. Does she/he express herself/himself through gestures rather than verbally?
4. Does she/he have trouble finding the correct word? (word retrieval)
5. Does she/he confuse words that sound alike (e.g., tornado for volcano)? (auditory discrimination)
6. Does it seem to take a long time for her/him to understand directions or answer questions? (processing speed)
7. Does she/he seem to have to repeat things (out loud or to self) in order to understand them? (processing speed)
8. Can she/he tell you the letter that comes after "s" without going through the alphabet? (could also use days of the week, months, etc.) (sequential processing)

factors (medications taken, substance abuse, poor nutrition, maternal chronic medical conditions), perinatal adverse events (severe hypoxia), significantly adverse postnatal course, and minimal developmental intervention are all risk factors for learning difficulties. Environmental adverse factors, such as excessive environmental lead and malnourishment should be identified. Early developmental progression and skills acquisition are important. Impact of any personal chronic medical conditions should be noted. Physical exam findings identifying any obvious or subtle dysmorphic features as well as screening for vision or hearing deficits are important.

The child's social emotional profile should be explored as there is a high degree of comorbid psychiatric diagnoses in children with SLD. Depression and anxiety may occur primarily or as secondary to the child's learning struggles. This assessment may be as brief as administration of an emotional screening instrument (e.g., Pediatric Symptom Checklist) or a more formal interview with the child and family. The family structure including their expectations and stability in the community can be important factors in academic success. Identifying support systems, economic resources available to the family and cultural forces impacting their decisions all should be taken into account when assessing a child who struggles academically.

Standardized intelligence testing is part of the learning disabilities assessment. Broad academic achievement tests are the usual instruments to obtain educational standard scores. In the USA, two widely used tests are the Wechsler Individual Achievement Tests-Fourth Edition (WIAT-4) and the Woodcock-Johnson Tests of Achievement-Third Edition (WJ-TOA-3) as these have corresponding intelligence measures: Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) and the Woodcock-Johnson Tests of Cognitive Abilities-Third Edition (WJ-TCA-III) respectively. More specific individual educational achievement tests also may be administered for more precise identification of particular educational strengths and weaknesses.

Treatment

In the USA, the determination of whether a child meets the criteria for supportive supplemental school services is reserved by the local school identification team. Students benefit from academic and classroom accommodations and modifications for learning disabilities. Specialized reading support is recommended for children with dyslexia. The National Early Literacy Panel endorses an evidence-based reading program that utilizes systematic instruction using a phonics-based, multisensory approach to teach the mechanics of reading and writing tasks (decoding and encoding), such as the Orton–Gillingham or Lindamood-Bell programs. Children with mathematics disorder may improve by supporting working memory through better attention and emphasizing the child's self-monitoring of calculation accuracy. Permitting the use of an electronic calculator may be an eventual bypass strategy for the child with persistent calculation inaccuracy. Disorders of written expression are treated by addressing the specific weaknesses that are involved. Children with SLD may develop poor self-confidence due to their academic struggles, which should be addressed with appropriate family and mental health supports.

Prognosis

Identification and intervention for reading disorders may not always guarantee completely normalized reading function. One study found that of those children identified as "reading disabled" in the third grade, 74% would meet that identification in the tenth grade. Children identified later as reading impaired need more time of individual remedial instruction. For example, if identified as reading disabled in kindergarten or the first grade, 30 min of daily remedial instruction can improve reading skills to grade level. If identification is not made until the third grade or

later, 2 h daily remedial instruction is necessary to make comparable progress. Often these students can be taught to compensate, but their phonological processing deficits persist to some degree.

Math computation weakness can have a good outcome with appropriate supports if the child does not have a primary problem of dyscalculia. Math reasoning weakness has a variable outcome as the reasoning weakness must be clearly identified during the evaluation process. Weakness in math reasoning may be due to weak conceptualization of the constructs, weakness in sequential processing, visual–spatial abilities, and cognitive flexibility. Language abilities also have a significant role in math reasoning.

The prognosis for a disorder of written expression is very dependent on the developmental skills weaknesses involved. If the child has poor fine motor skills, assisting with more precise handling of the writing implement and automaticity of letter formation will be very helpful. If vocabulary and/or spelling are not strong, then enhancing phonological skills and word knowledge will enhance written expression. Written expression, however, is very age-dependent and instruction sensitive and the expectations increase as the child becomes older. For this reason, many will have continued struggles with this domain.

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46 Behavioral Disorders of Childhood

Mary Margaret Gleason

Psychiatric disorders play an important role in pediatric practice. Worldwide, psychiatric disorders cause substantial suffering in both developing and developed countries, with as many as 20% of children affected by mental health problems that interfere with their functioning. Psychiatric problems have the potential to influence nearly every aspect of a child's life, with interference seen in family functioning, peer relationships, academic performance, and extracurricular activities. In addition, more than most other pediatric problems, psychiatric disorders are directly associated with substantial economic costs, including substantial medical, educational, and juvenile justice expenditures, as well as impact on parent income, even when the disorders are not identified as mental health problems. Most importantly, these disorders have the potential to cause suffering to the individual patient and family and to have adverse impact on future functioning.

In discussions of psychiatric disorders, it must be noted that, although symptoms and impairment can be identified at strikingly consistent rates around the globe, the diagnostic systems employed vary. The two major nosologies are derived from research in western cultures. The American Diagnostic and Statistical Manual (DSM) is currently in its fourth edition and the fifth edition is under development. This system includes a small section focused on disorders commonly seen in childhood, but for the most part, child psychiatric disorders are diagnosed using criteria developed using adult data. The World Health Organization publishes the International Classification of Diseases, a nosologic system in its tenth iteration. Like the DSM, the ICD includes a section focused on disorders specific to childhood, such as separation anxiety disorder, disruptive behavior disorders, attachment disorders, and hyperkinetic disorder, but prevalent emotional disorders are described for children in the same way they are for adults. Generally, the DSM and ICD systems describe similar syndromes, but the specific criteria vary.

The overwhelming majority of psychiatric research is in European and American settings. It is critical to note that, perhaps more than any other category of pediatric disorder, psychiatric disorders must be considered in the context of the child's cultural experience. Family structure and roles vary widely, and these structures shape the expectations of child development of autonomy, acceptable emotional expression, and even beliefs about perceptual experiences. These factors remind clinicians that assessment of family's view of the child's impairment is of utmost importance when assessing the mental health of a child, especially when the child's cultural background differs from those that have shaped the current diagnostic nosologies.

This chapter will review the major categories of psychiatric disorders, including the disorders affecting the youngest patients, attachment disorders, followed by a review of externalizing disorders, internalizing disorders, and psychotic disorders.

Reactive Attachment Disorder

Definition/Background

Attachment disorders are among the earliest presenting mental health disorders in young children. These disorders occur in children who have experienced adverse caregiving and who present with extreme behaviors suggestive of problems of attachment. Both diagnostic systems describe two similar forms of attachment disorders. In the DSM system, these are reactive attachment disorder (RAD), inhibited type and reactive attachment disorder, disinhibited type. The ICD system describes reactive attachment disorder of childhood, which focuses on the inhibited pattern and disinhibited attachment disorder of childhood. More recent research has focused on empirically derived criteria more closely linked to specific attachment behavior patterns which are included in the proposed criteria for DSM V (*Table 46.1*). To understand the concept of RAD, the fundamentals of attachment must be clear. The attachment system is thought to be activated when a child is under stress. In a healthy caregiving relationship, an infant or young child under stress will *preferentially* seek proximity to the primary caregiver and effectively derive comfort from the caregiver.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_46,

Table 46.1
Proposed criteria for DSM-V reactive attachment disorder

A. A pattern of markedly disturbed and developmentally inappropriate attachment behaviors, in which the child rarely or minimally turns preferentially to a discriminated attachment figure for comfort, support, protection, and nurturance. The disorder is manifest as (1), (2), or (3)
1. An inhibited, emotionally withdrawn pattern in which the child rarely or minimally directs attachment behaviors toward any adult caregivers, as manifest by three of the following:
(a) Rarely or minimally seeks comfort when distressed
(b) Rarely or minimally responds to comfort offered when distressed
(c) Limited positive affect and excessive levels of irritability, sadness or fear
(d) Reduced or absent social and emotional reciprocity (e.g., reduced affect-sharing social referencing, turn-taking, and eye contact)
2. A disinhibited, indiscriminate pattern in which the child directs attachment behavior non-selectively, as manifest by two of the following:
(a) Demonstrates overly familiar behavior and reduced or absent reticence around unfamiliar adults
(b) Rarely or minimally checks back with adult caregiver after venturing away even in unfamiliar settings
(c) Willing to go off with an unfamiliar adult with minimal or no hesitation.
3. A mixed pattern of inhibition and disinhibition characterized by two or more criteria from (1) and (2)
B. Child does not meet criteria for pervasive developmental disorder
C. The child has a developmental age of at least 9 months

RAD has been described as patterns of non-attachment, in which the child does not preferentially use the caregiver for comfort. In the emotionally withdrawn/inhibited form of RAD, children show few attachment behaviors, even when in distress, and appear inhibited, affectively negative, and lacking joyful reciprocity. In the socially indiscriminate/disinhibited form of RAD, children show excessive social indiscriminance, including not referencing their parents in new situations, approaching strangers without reticence, and leaving with a stranger.

Etiology

Both forms of RAD are associated with pathogenic caregiving conditions and appear to show a dose dependent response. Milder signs of RAD can be identified in children with lower caregiving adversity and more severe RADs are associated with severe caregiving adversity. It is important to note that adverse caregiving alone is not sufficient to cause RAD, as most children do not develop RAD, even in adverse caregiving situations. Studies are underway to identify prenatal or biological factors that explain individual variation.

Epidemiology

Systematic assessment of the prevalence of RAD is difficult. It is thought to be rare in the general population, although it has not been included in most population based studies of childhood psychopathology. In clinical samples, reports range from a low of 1–20%. This wide range likely represents differences in referral bases and diagnostic approaches. In maltreated samples, approximately 40% of children under 4 meet criteria for at least one form of RAD, and more than half of the children in institutions show the disorder. After removal from institutions, almost no cases of emotionally withdrawn/inhibited RAD are identifiable, although rates of socially indiscriminate/disinhibited RAD remain elevated.

Pathogenesis

To date, no research has identified the factors which put children at highest risk of developing RAD in high-risk caregiving settings. New research focused on institutionalized populations in Romania provide early hints that the inhibited form of RAD is, in fact, strongly related to attachment security and to the quality of caregiving but that the disinhibited form of RAD may have a different underlying deficit, including problems with committed social relationships, adaptive process in institutional care, or problems understanding other people's motivations and knowledge.

Clinical Manifestations

Children with RAD can be identified in clinical contexts by careful history and observation. Although pathogenic caregiving is required for the diagnosis, this requirement may be difficult to establish in an initial interview, especially if the child has been adopted or if the parent is guarded about parenting practices that would constitute maltreatment if they were disclosed. Thus, the lack of

confirmation should not preclude consideration of the diagnosis.

Children with the inhibited form of RAD will be described by their caregivers as seeking their caregivers out in only limited ways. The interview focuses on the signs of RAD described above. These children may have a flat affect or appear depressed. In a clinical interview and observation, such as a pediatric examination, these children are unlikely to use their parent for comfort during the physical exam or immunizations and may be difficult for even the most skilled pediatrician to engage.

Children with the socially indiscriminate form of RAD may be noted to approach unfamiliar adults in the waiting room or office setting without reticence, talking with them and even approaching them physically. The social impulsivity may resemble ADHD in the clinical setting. Older preschoolers with socially indiscriminate RAD may present with co-occurring aggression, but this is not seen in younger children and the data are mixed to date. Aggression and disruptive behaviors are not core symptoms of any form of RAD but may suggest comorbid conditions in these high-risk children.

There are few studies of RAD in children beyond the preschool years. The most rigorous studies examine a construct that defined as RAD, but which employs different criteria from those used in the more substantial literature in younger children. Thus, it is not clear whether the disorder described in school age children is the same disorder and the diagnosis should be applied with caution beyond the preschool years. Unfortunately, the internet abounds with descriptions of RAD which are not based upon peer-reviewed empirical literature. These descriptions characterize children with RAD as dangerous and having sociopathic traits. The risks to families reading these descriptions are multifold. Families who follow the paths suggested on these websites run the risk of missing the opportunity for a careful diagnostic assessment to identify the range of psychiatric disorders that may occur in children who have experienced severe adversity and miss opportunities for interventions for those disorders. Secondly, this characterization of vulnerable children as monsters tends to reduce the family bonds and empathy, both of which are necessary for recovery from the extremes of caregiving adversity.

General Care

Most importantly, clinicians treating children with RAD or suspected RAD should ensure that the child is in a safe caregiving situation now. If some degree of caregiving risk continues, it is critical that the clinician work with social service agencies to mitigate the risks to the child. In addition, because children with RAD are at risk of a range of adverse mental health and developmental outcomes because of their early risk exposure, a full developmental, medical, and mental health assessment should be completed and children with developmental delays, untreated medical conditions, and comorbid psychiatric conditions must be provided access to interventions to address those issues.

Specific Treatment and Prognosis

Only one study has used a randomized, controlled trial to examine the effects of an intervention on RAD. In the Bucharest Early Intervention Project, previously institutionalized Romanian children placed in foster care showed substantial improvement in both forms of RAD signs compared with institutionalized children who received care as usual. This finding related to inhibited RAD is consistent with other studies of post-institutionalized children, in which inhibited signs of RAD were virtually nonexistent after adoption. For the socially indiscriminate form of RAD, the effect was slower and of a lesser magnitude, but was associated with the quality of caregiving. Thus, children with RAD require warm, nurturing, consistent caregiving by someone who verbally engages with the child and is committed to the child's well-being. Even in such a circumstance, signs of socially indiscriminant RAD may persist over years.

Prevention

Because of the clear link with caregiving adversity, RAD can be prevented by ensuring that children worldwide are cared for by individuals who are committed to the child and available to the child when the child is in need. Institutional care that does not allow a child to learn that there is at least one and perhaps a small number of caregivers on whom the child can depend for comfort, nurturing, and love will continue to create cases of RAD. As societies, policies that protect children from pathogenic care are advocated.

Internalizing Disorders

Internalizing disorders include disorders whose symptoms are predominantly emotional and therefore

may be considered "internal" to the child. The main categories include mood disorders – depressive and bipolar disorders – and anxiety disorders. Each will be considered separately, as their presentation, trajectory, and treatment differ.

Depressive Disorders

The depressive disorders in childhood include major depressive disorder, dysthymic disorder, and depressive disorder not otherwise specified, that is, a constellation of depressive symptoms that interfere with a child's life, but do not meet the specific criteria described for the other two syndromes. In general, depressive disorders in children present with depressed or irritable mood, neurovegetative signs such as impaired sleep, appetite, or concentration, and impairment in functioning within important relationships or activities. In contrast to commonly held beliefs, younger children present with similar patterns of depressive symptoms as older children and adults.

Epidemiology

Depression affects a sizable group of children worldwide. In the USA and Europe, point prevalence rates of Major Depressive Disorder range from 1% to 2% in prepubertal children and 2–4% of adolescents, with lifetime prevalence rates up to 20% of children before the age of 18. There is no gender difference in rates of depression until puberty, when rates in girls are approximately double the rates in boys. Rates of depression also vary substantially across different risk groups. Poverty, chronic medical conditions, and exposure to violence are associated with higher rates of depression. A recent review of adverse outcomes of children living in low-income countries with extreme adversities including child soldier status, female genital mutilation, and child labor revealed that more than 50% had depression.

Etiology/Pathogenesis

Pediatric depressive disorders have multifactorial etiologies. As noted above, rates of depression vary with a number of physiologic and environmental risk factors. Major life stressors contribute to depression in children. Family factors and relationships such as harsh parenting, family discord and parental substance abuse all contribute to the risk of depression. The appearance of gender differences in rates of depression at puberty suggest that hormonal differences and social relationship differences may play important roles in the development of depression, although the causal mechanism has not yet been identified.

Heredity clearly plays a role in the development of depression. The transmission of the depression appears to be much more strongly related to the environmental risks associated with being parented by a depressed caregiver, although direct genetic influences exist as well. The environmental effect of parental depression can be relieved by successful treatment of parental depression. Twin studies suggest that in low-risk children, genetic factors appear to play important roles in the development of depression, but that for youth in high social risk settings, environmental factors are more powerful predictors of adolescent depression. Of these, early maltreatment has been most commonly studied. Specific genetic polymorphisms of genes associated with serotonin functioning, brain-derived neurotrophic factor, and cortisol all appear to play roles in development of depression, usually in conjunction with a range of environmental risk settings.

Clinical Manifestations

Pediatric depression has similar patterns of symptoms as depression in older children. Criteria in the DSM-IV and ICD-10 are quite similar and both require a depressed mood or irritability as the core symptoms. The DSM requires that the patient have six of the nine possible other symptoms. Children and adolescents with depression also present with associated neurovegetative signs including change in appetite, sleep, concentration, memory, energy. Appetite and sleep may change in either direction, with reductions or increases in appetite and weight and increase in sleep or decrease in sleep quality. Decreased quality of sleep in depressive disorders can be distinguished from changes in sleep in bipolar disorders because depressed children and adolescents continue to need their sleep and have reductions in their energy. The lack of enjoyment in activities that previously were enjoyable, "anhedonia," is a symptom specific to depression. It may be observed because a child begins to withdraw from social activities or from extracurricular activities, or when a patient doesn't appear happy doing activities he or she used to enjoy.

Suicidal ideation can also present in youth with depressive disorders. Suicidal thoughts can be characterized into two major categories. Active suicidal ideations include thoughts of taking an active step to end life (e.g., intentional ingestion, cutting) and passive suicidal

ideations, in which a person may wish he or she were dead and may not be taking usual safety precautions (e.g., not wearing a seatbelt), but does not have a plan to actively end her life. Suicidality is not uniquely associated with depressive disorders and can be seen in the context of other psychopathology or in general populations. Because completed suicides occur at relative low rates – although no rate is acceptable – reliable predictors are difficult to identify. However, family history of completed suicide, mania or agitation, and past suicide attempts are related to completed suicide. One study examined predictors of high-risk attempts that required medical attention and identified the following risk factors: a history of having been forced to have sex against their will, being a current cigarette smoker, lesbian, gay, bisexual, or unsure sexual identity, or not speaking English at home.

Children and adolescents presenting with depression may present with a chief complaint related to their mood. However, it is also not unusual for them to present with school failure, weight loss, or peer or family interaction problems.

Diagnosis

The diagnosis of major depression depends on a careful history. Children and parents should be interviewed together and separately. Every evaluation focused on psychiatric issues should begin with open ended questions about the patient's concern and current life context. The interview should include attention to potential triggers or exacerbating factors, such as recent breakup, family stressors, academic challenges, medical problems, child maltreatment, or partner violence. The history should review the symptoms of depression, including current and past suicidality. In addition, the history should review symptoms of frequently co-occurring disorders, especially anxiety disorders, disruptive behaviors, substance use or abuse, eating disorders, and sleep problems. Many of these can also be considered in the differential diagnosis. An evaluation of depression must include past medical and developmental history, looking for chronic illnesses that may be increasing the burden of stress on the child or developmental problems that may interfere with peer and/or academic functioning. Family history is of utmost importance, with attention to the psychiatric history of biological family members and household members. If a primary caregiver is reported to have symptoms of depression or other impairing psychiatric disorder, attention to the current level of symptoms and safety of the adult and their family is critical. In addition to the review of possible stressors, review of social functioning is another important facet of the assessment, with attention to school functioning, peer interactions and extracurricular activities.

The mental status and physical examination in children with possible depressive disorders may be normal in the pediatric setting. However, it is important to attend to the following components. Appearance and behavior may reflect limited ability to address hygiene or basic activities of daily living. Depressed children may be slowed in their movements, may make poor eye contact, and may be more withdrawn in their social interactions. Speech may be slowed or of lower than usual volume. In formal psychiatric terms, mood is the description that a patient uses for their own internal state. Affect is the word that describes the range of emotional content that is observable in the patient's facial expression and the degree to which the expressions match the content of discussion. Generally in depression, children's thought process remains intact, meaning that they can put thoughts together in an organized fashion. However, their thought content should be assessed for repetitive themes of hopelessness and explicitly assessed for active or passive suicidal ideation. All moderately or severely depressed patients should be asked about hallucinations and delusions. Since depression may interfere with concentration and memory, it can be useful to assess these formally.

Pediatricians add an important component to the mental health assessment. Physical examination should include height and weight measurements, careful skin examination for signs of self-injurious behaviors, especially cutting on forearms, inner thighs, and under breasts, and for metacarpal abrasions that might reflect purging. Physical exam should also include a thyroid palpation. Laboratory assessment is generally unnecessary, but specific clinical conditions might indicate the need for TSH to rule out hypothyroidism (weight gain, low energy, family history of autoimmune diseases), toxicology tests to identify illicit drug use, and pregnancy test if clinically indicated or if medications are being considered in a sexually active adolescent girl.

Differential Diagnosis

The differential diagnosis of major depressive disorder in children and adolescents is broad. *Table 46.2* reviews the differentiating factors between depression and anxiety disorders, other mood disorders, sleep disorders, substance abuse disorders, and eating disorders. It should be noted that comorbidity with many of these disorders is not uncommon.

Table 46.2
Differential diagnosis of major depressive disorder

Disorder	Similarities	Differences
Anxiety (GAD, panic disorder, separation anxiety, specific phobias, OCD, PTSD)	Sleep, concentration, memory problems, may withdraw from activities	No anhedonia (although avoidance), endorse prominent worrying, sympathetic activation
Adjustment D/O, dysthymia	Same symptoms	Time course, intensity
Sleep disorder	Sleep complaints, fatigue, concentration problems, irritability	Sleep disturbance predated mood symptoms, mood symptoms resolve with adequate sleep
Bipolar disorder	Depressive symptoms identical	Manic history, family history of bipolar disorder
Disruptive behavior disorders (ODD, CD)	Irritability, increased oppositional behaviors	Mood symptoms more situational/relationship specific; do not look depressed with peers
Substance abuse	Mood changes, sleep, energy, concentration, school problems	May be more variable patterns of moods, other social changes
Eating disorder	Weight loss, decreased energy, interest, concentration/memory problems	Body image distortion, refusal to gain weight, electrolyte and physical exam findings, generally more severe weight loss

Treatment of Depression

For children and adolescents with mild depression, non-pharmacological interventions including psychoeducation, school intervention, and supportive therapy should be used as first-line treatment. Mild depression does not include hopelessness, severe neurovegetative symptoms, and does not include active or intense suicidal ideation. For these patients, it is important for pediatricians to know that supportive therapy can be equally effective as evidence-based treatments such as Cognitive Behavioral Therapy (CBT), a form of treatment that focuses on helping the patient learn and use new thinking skills to modify negative behaviors and Interpersonal Therapy (IPT), in which the focus is on a patient's relationships with peers and family members and the way they see themselves. If a response is not seen within 4–6 weeks, more focused therapy should be considered.

For patients with moderate–severe depression or those who have mild depression that is unresponsive to supportive interventions, the evidence-based cognitive behavioral therapy, interpersonal therapy, and selective serotonin reuptake inhibitors should be considered. Although intuitively, the combination of an evidence-based treatment such as CBT and an SSRI might be expected to work synergistically, the combination has not been demonstrated to be more effective in reducing symptoms, although it shows a more rapid response rate than with CBT alone and less suicidal ideation than SSRI alone. It is possible that further follow-up will demonstrate a longer lasting effect of the CBT. Decisions about medication versus therapy can be made based upon availability of therapy, intensity of suicidal ideation or other indices of need for accelerated treatment response, family preference, and family history of response to treatment.

When psychopharmacological interventions are considered, fluoxetine is considered first line because it has the most substantial evidence supporting its efficacy and safety. Escitalopram and sertraline have also been shown to be superior to placebo in treating adolescent – but not school age child – depression. In youth who are at relatively higher risk of developing activation or mania, using a medication with a shorter half life, such as sertraline or citalopram, may be indicated. *Table 46.3* presents clinical indications, formulations, and general dosing targets for medications. Medications such as venlafaxine and buproprion have substantially less data supporting their use in pediatric depression than SSRI's and are not first-line interventions. Hypericum perforatum (St. John's Wort) is approved for use in European countries; however, a search of English language papers does not reveal evidence of randomized controlled trials showing this medication is superior to placebo for treatment of depression in children or adolescents.

All SSRI's are associated with a measurable risk of increased suicidal ideation. This risk has not been associated with an increased risk of completed suicide, but

Table 46.3
Selective serotonin reuptake inhibitor uses

Generic name	Brand name	RCT's support use in depression?	RCT's support use in anxiety disorders[a]?	RCT's support use in OCD?	RCT's support use in PTSD?	Pediatric doses
Citalopram	Celexa	7–17	No	No	No	–
Escitalopram	Lexapro	12–17	No	No	No	5–20 mg
Fluoxetine	Prozac	7–17	7–17	7–17	No	MDD: 5–20 mg OCD: 20–60 mg
Fluvoxamine	Luvox	No	Yes	8–17	No	50–200 mg
Sertraline	Zoloft	6–17	7–17	6–18	No[b]	25–200 mg

[a]Selective mutism, separation anxiety, generalized anxiety, disorder, panic disorder
[b]Specifically, does not add to effect of CBT when combined treatment provided

warrants careful monitoring of children and adolescents when starting an SSRI and with any dose changes. The US FDA recommends weekly monitoring for the first month and bimonthly monitoring for the second month after initiation or changes. Families should be instructed to seek emergency attention if they note signs of mania, activation, self-injurious behaviors, or voiced suicidal ideations. It should be noted that after the introduction of SSRI's in the 1990s, rates of completed suicides decreased, and that since the FDA's black box focused on the association between suicidal ideation and antidepressant use, the rates appear to be rising again.

Prognosis

Depression in children and adolescents is a chronic and relapsing disorder. Approximately 40% will experience a relapse in 2 years and nearly three fourths within 5 years. Better prognosis is associated with complete recovery from the initial incident of depression, parental mental health, lack of history of sexual abuse, and healthy family functioning.

Prevention

The impact of childhood depression and the long-term implications of childhood depression make prevention an important goal. One group at highest risk of depression is children of depressed adults. Family focused interventions show some effect compared with no intervention, but the effect sizes are modest. Treatment of parents with depression may also be an important preventive intervention for children at risk.

Bipolar Disorder

Bipolar disorder is characterized by periods of depression and of mania. Manic episodes classically include periods of elation that are accompanied by increased energy, rapid speech, and grandiosity. Both the DSM and ICD-10 definitions of manic episodes require a week of symptoms and associated symptoms of decreased need for sleep and pressured speech. In the DSM-IV, the primary mood can be either elation or irritability and the DSM specifies that 3 associated symptoms should accompany elation, adding grandiosity, flight of ideas, distractibility, increased goal-directed activity, and excessive risk taking. If the mood is irritable, the patient must demonstrate four associated symptoms. The ICD-10 is less specific, requires "several" associated symptoms, and does not include irritability. Depressive episodes must meet criteria for major depressive disorder, although there are variations of bipolar disorder either with a less intense manic episode (hypomania) or depressive episode (dysthymia). The characteristics of pediatric bipolar disorder continue to be the focus of debate. Specifically, the duration of episode, importance of the primary "cardinal" symptoms, and the intercurrent mood are all under active investigation.

Etiology/Pathogenesis

Bipolar disorder is highly familial. First-degree relatives of adults with bipolar disorder are at eight- to tenfold risk of developing the disorder. Studies in the USA and in Europe have yielded inconsistent findings related to genetic polymorphisms associated with pediatric bipolar disorder and candidate genes related to dopamine, serotonin, and catecholamine systems, and brain-derived

neurotrophic factors. Neuroimaging studies of pediatric bipolar disorder have revealed smaller amygdala, hippocampus, cingulated gyrus, and less gray matter in the dorsolateral prefrontal cortex. To date, the family and community risk factors related to the development of bipolar disorder have not been examined.

Epidemiology

Rates of pediatric bipolar disorder are estimated 1–2% in the general population, although large epidemiological studies have not reported rates of pediatric bipolar disorder in Europe or in the USA. Pediatric bipolar does not show significant gender differences. Rates of clinical diagnoses for bipolar disorder have increased substantially in the last decade, in the USA, as more encompassing diagnostic criteria have been proposed.

Clinical Manifestations

Children with bipolar disorder can present in the prepubertal period, but generally present during adolescence. Onset may be insidious or acute, but many children have a history of unipolar depressive symptoms prior to the onset of mania. The most commonly seen symptoms in pediatric bipolar disorder are increased energy, distractibility, pressured speech, irritability. The specificity of these symptoms is limited and can be seen with other psychiatric disorders. Of the symptoms with more specificity, decreased need for sleep and euphoria are seen in about 70% of patients. The DSM IV criteria require 1 week of symptoms nearly every day to meet the meet the criteria for a manic episode. This criterion should be maintained and children with shorter periods of mania may be considered to have bipolar disorder NOS.

Early research shows that a broadly defined disorder of chronic irritability without episodic mania has different familial patterns, different activity on functional neuroimaging, and different courses than strictly defined bipolar disorder. This empirically defined syndrome of chronic irritability and extreme reactivity in children who do not meet diagnostic criteria for MDD or bipolar disorder has been proposed as a separate mood disorder in the DSM V. The core deficit in this proposed disorder is of emotional regulation and it is considered to be a mood disorder, not a behavioral problem.

Comorbid conditions are common in youth with bipolar disorder, with as many as 50–80% meeting criteria for ADHD, 20–60% for disruptive behavior disorders and a similar rate for anxiety disorder. Youth with bipolar disorder are at elevated risk for suicide attempts and for completed suicide. Rates of substance abuse in this population are also elevated.

Diagnosis

Diagnosis of bipolar disorder depends on a careful history and sometimes multiple observations of a patient. Because of the nonspecificity of some symptoms of bipolar disorder, it is important to review all symptoms and to do a complete review of systems. Systematic measures like the Young Mania Rating Scale can be used to quantify the severity of the symptoms, but should not be considered diagnostic. A careful social history should investigate the social history, with attention to sexual abuse in children presenting with hypersexuality.

The validity of the diagnostic criteria for bipolar disorder in young children has been studied in only one published study to date and the controversy around applying current criteria to preschoolers is even more intense then for older children because of developmental issues, non-specificity of the symptoms, and risk of current treatments in young children.

Differential Diagnosis

The differential diagnosis of bipolar disorder should be considered carefully. Until diagnostic controversies are resolved, and to ensure effective communication across providers, the American Academy of Child and Adolescent Psychiatry Practice Parameters recommend applying the diagnostic criteria strictly. Many of the symptoms overlap with ADHD and the question of comorbidity versus differentiation should be considered. Bipolar disorder tends to present later than ADHD, does not respond to stimulants, and is more likely to be characterized by mood symptoms and fluctuating levels of symptoms, and actual *decreased need* for sleep. Bipolar disorder must also be distinguished from ODD in children who are negativistic, throw tantrums, and are easily annoyed. In children with bipolar disorder, behavioral difficulties should be present during mood episode but should resolve after the episode resolves.

General Care

As with all psychiatric disorders, psychoeducation is an important component of care. Reframing the behaviors as

part of the illness rather than intentionally problematic behaviors may be useful for families. Schools can be enlisted to support the child during transitions.

Treatment

Most research focused on treatment of bipolar disorder has focused on medication treatments and to date, the systematic research has focused solely on the treatment of acute mania rather than prospective treatment of bipolar disorder. Mood stabilizers and antiepileptic agents are commonly used to treat bipolar disorder. Although a number of open label trials have reported positive effects of a range of medications, the number of randomized controlled trials is limited. These studies, which generally last 4–8 weeks and focus on acute mania, have demonstrated that, compared to placebo, lithium, aripiprazole, ziprasidone, risperidone, divalproic acid and olanzapine are effective in treating acute mania. Efficacy is defined as 50% reduction in mania symptoms, and most report 40–61% response rates in the treatment arms and relapse rates are high, reflecting need for more effective treatments. As an adjunct to valproic acid, quetiapine reduces symptoms of acute mania more effectively than valproic acid alone. Published studies document a lack of effect of topiramate and oxcarbamazepine in treating acute mania.

In clinical practice, the AACAP's Practice Parameters recommend lithium, valproic acid, and atypical antipsychotic agents as first-line treatments for pediatric bipolar disorder. Because family history of response to pharmacological agent for bipolar disorder predicts a youth's response, family history may guide choice of a specific agent. In addition, presence of specific symptoms (e.g., psychosis), comorbid conditions such as obesity, or family ability to administer safely medications with a narrow therapeutic window may guide selection of an agent.

Side effects of these medications can be substantial. The atypical antipsychotic agents are associated with weight gain, hyperlipidemia, and glucose intolerance. Olanzapine is responsible for the most substantial weight gain, with a mean weight gain of 7 kg in an 8-week study of patients with psychotic disorders. Risperidone and quetiapine show moderate risk (~4 kg in 8 weeks), and aripirazole and ziprasidone are associated with the lowest risk of weight gain. A similar pattern is seen for the risk of diabetes and dyslipidemia. Extrapyramidal side effects may occur with any antipsychotic, but risperidone has the highest risk among the atypical agents. Ziprasidone is associated with prolonged QTc and should not be used in children with risk of arrhythmias. Preliminary findings focused on treatment for children with chronic irritability and emotional dysregulation, such as that described in the proposed DSM V diagnosis, suggest that these patients may respond to SSRI treatment, although more research is needed.

Studies focused on psychotherapeutic interventions for bipolar disorder are promising, although limited. The best studied psychotherapeutic intervention for pediatric bipolar disorder is child and family functioning cognitive behavioral therapy, which focuses on psychoeducation, developing routines, affect regulation, collaborative problem solving, and social supports. It reduces mood symptoms acutely and when followed, 3 years after treatment if booster sessions are provided. Unfortunately, most communities cannot access this sophisticated form of therapy. In all cases, psychoeducation, family and individual therapy, relapse prevention/medication compliance, and attention to academic supports are important components of treatment for bipolar disorder.

Prognosis

In pediatric bipolar disorder, a relapsing and remitting course is seen. More than two thirds of cases of pediatric bipolar disorder show recovery (at least 8 weeks without symptoms) within a year and more achieve recovery in 4 years. However, about half will relapse as well. Comorbid conditions, psychosis, low maternal warmth, low-income families, alcohol use, and medication nonadherence are all poor prognostic signs. Earlier age of onset of bipolar disorder is also associated with more recurrences and chronicity. Youth with bipolar disorder are twice as likely as children with major depression to make suicide attempts.

Prevention

Because of the high hereditability of bipolar disorder, attempts to provide early intervention and prevention are necessary. To date, two small, open trials have shown promising results of psychopharmacological preventive interventions for youth at risk of bipolar disorder because of their subsyndromal mood symptoms and family history of bipolar disorder. Further research is necessary to understand the role of psychotherapeutic and psychopharmacological interventions for children at high risk of bipolar disorder. Common sense suggests that these youth's prognosis is likely to be improved by adequate treatment for their parents or sibling with bipolar disorder.

Table 46.4
Characteristics of anxiety disorders

Disorder	Clinical characteristics	Common clinical presentation
Separation anxiety disorder	Preoccupation with and distress about separation from primary caregiver	Inability to separate to attend school or child care
Selective mutism	Inhibition of speaking and social interactions in specific social contexts (e.g., school, new people in a child who willingly speaks in familiar contexts)	May be acute onset
Social anxiety disorder	Anxiety related to embarrassing self in social situations or evaluative situations	Avoids large group activities, distress about school (may present with school avoidance)
Generalized anxiety disorder	Pervasive anxiety or worry about multiple (non-specific) topics	Sleep disturbance, concentration difficulties, muscle tension; often co-occurs with depressive symptoms
Panic disorder	Repetitive, non-triggered anxiety attacks including somatic symptoms, feeling of doom, and anticipatory anxiety about future attacks	May occur with or without agoraphobia (fear of not being able to escape a confined place)

Anxiety Disorders

Anxiety disorders are among the most common disorders in childhood. They can be considered excessive fear responses that interfere with adaptive functioning. A number of disorders fall under the broad umbrella of anxiety disorders. This section will focus on separation anxiety disorder, selective mutism, specific phobias, generalized anxiety disorders (GAD) and panic disorder, which seem to share some patterns of presentation and treatment responsiveness. Obsessive compulsive disorder and post-traumatic stress disorder will be addressed separately.

Descriptions of each of the forms of anxiety disorders are presented in *Table 46.4*. In general, classification of each these disorders in DSM and ICD systems are similar, except that in the ICD 10, children cannot meet criteria for both GAD and depression, although in the DSM system, these two disorders co-occur quite commonly.

Etiology

It appears that genes and environment play roles in the development of anxiety disorders in children. Family studies demonstrate that about half of children with anxiety disorders have parents with an anxiety disorder, but the transmission from parent to child is about only 30%. Polymorphisms in the promoter region of the serotonin transporter gene have been implicated as risk factors for development of anxiety disorders in children. Behaviorally inhibited temperament is an early manifestation of risk for anxiety disorder. Parenting practices are among the most powerful ways children learn to interpret possible risks. Parents' own anxiety, their messages to their children about safety or lack thereof, and the degree of intrusive protection all can shape children's anxiety patterns.

Epidemiology

Anxiety disorders occur at high rates across cultures. Between 2% and 25% of children experience anxiety disorders at some point in childhood. Separation anxiety disorder and selective mutism present in preschool and early school age, generally at equal distribution between girls and boys. Other disorders, including social anxiety disorder and panic disorder, are over-represented in girls even in the prepubertal period. GAD tends to show a predominance in girls starting at puberty.

Pathogenesis and Pathology

Increasingly, central nervous system correlates of anxiety can be identified through functional neuroimaging. Anatomical regions implicated in anxiety disorders include the amygdala, the orbitofrontal cortex, and the anterior cingulate cortex. Physiologic studies demonstrate that children with anxiety disorders have higher physiological arousal including increased heart rate under stress, elevated cortisol in response to stress, and increased startle response.

Clinical Manifestations

Although each anxiety disorder described in this section has its own unique characteristics, the comorbidity among these disorders is high. In clinical samples, 50% of children with an anxiety disorder have more than one anxiety disorder. Specifically, panic disorder, separation anxiety disorder, and specific phobia tend to cluster together. By contrast, generalized anxiety disorder and social anxiety disorder tend to be associated more commonly with major depressive disorder.

Anxiety disorders are also commonly comorbid with externalizing disorders. Because younger children may not have insight into their distress as anxiety, it is important that clinicians consider anxiety disorders when children present with school avoidance, oppositional behaviors related to social or evaluative experiences, or unexplained tantrumming. In preschoolers, it appears that anxiety disorders are more closely related to disruptive behavior disorders than to mood disorders, although they can also present with anxiety symptoms that cluster into the same categories as older children and adults.

Differential Diagnosis

The differential diagnosis of a pediatric anxiety disorder is also broad. First, a clinician must explore the specific anxiety symptoms and consider the specific anxiety disorders separately. Impairing separation anxiety symptoms can present when a child has experienced a traumatic event when separated from their parent. Some children may present with separation anxiety because they have concerns about their parent's well-being, such as a parent's medical illness, or a child's perception of parent's vulnerability related to parental mental health problems or family or community violence exposure. Thus, actual and perceived safety should be explored when a child presents with separation anxiety symptoms. In children presenting with selective mutism, it is essential to ensure that an appropriate language and hearing assessment has occurred. Again, if the disorder has an acute onset, consideration of a traumatic experience is warranted. Symptoms of autism spectrum disorder should be reviewed in children presenting with signs of social anxiety disorder. The disorder can be differentiated by good eye contact, reciprocity, language skills in children with social anxiety disorder when they are in comfortable situations. These children also do not generally present with stereotypical behaviors. Generalized anxiety disorder often co-occurs with depressive symptoms. In the ICD-10 system, used in most of the world, these disorders are mutually exclusive and a clinician must identify the syndrome that is most impairing for the patients.

All anxiety disorders can present with impairment in school functioning either because of concentration difficulties or peer interaction problems and sometimes they present with school avoidance. Careful attention should be paid to a child's developmental level and academic performance to ensure that learning disabilities are not overlooked and that bullying is not a contributing factor.

General Care

As with other psychiatric disorders, psychoeducation is especially important for children with anxiety disorders and their families, especially if the anxiety symptoms may have been interpreted as intentional or a sign of weakness. Psychoeducation in the educational setting may also be important if the child has been targeted by bullying or if the symptoms of anxiety have interfered with classroom experiences. In families in which parental anxiety is a contributing or perpetuating factor of the child's anxiety, referrals for the parent's mental health treatment can be an important intervention as well.

Treatment

Both psychotherapy and psychopharmacological interventions have been studied for the treatment of pediatric anxiety disorders. Data support the efficacy of both SSRI's and of cognitive behavioral therapy. Cognitive behavioral therapy for pediatric anxiety disorders includes parent involvement in psychoeducation, relaxation techniques such as diaphragmatic breathing and progressive muscle relaxation, cognitive coping strategies, graduated exposure to feared stimuli. Family workbooks, such as the *Coping Cat*, can be useful adjuncts for pediatricians to share with parents, especially if skilled cognitive behavioral therapists are not readily available. CBT for childhood anxiety is both effective for anxiety and also shows long-lasting effects.

Fluvoxamine, sertraline, and fluoxetine have all been studied as effective treatment for pediatric anxiety disorders in randomized controlled trials. Psychopharmacological treatment for panic disorder in children has not yet been established. To date, it is not clear how the association between suicidal ideation and SSRI's in depressed children may be applied to children with anxiety disorders. Judicious use of medications and careful monitoring of all children on SSRIs seems warranted.

One multi-site study has compared treatment outcomes between CBT and sertraline treatment. This study demonstrated that CBT and sertraline were equally effective in treating pediatric anxiety disorders, but that the combination of the two was more effective. After 12 weeks of treatment, 80% of children on the combination treatment were much improved or very much improved, compared to about 60% of children in each of the monotherapy arms. Thus, children should be treated with CBT and medication for most effective reduction of moderate–severe anxiety symptoms. Adding parent anxiety management training to CBT also adds to the effect of CBT, regardless of parent anxiety level.

Prognosis

The course of pediatric anxiety disorders vary. Typically, anxiety peaks in the general population in the preschool years and then declines. Children with anxiety disorders tend to continue to have anxiety, but the specific disorder may change over time. In a 5-year follow-up of children at risk for anxiety disorders, having separation anxiety disorder at baseline increased the risk of specific phobia, agoraphobia, and major depression four- to ninefold at follow-up. Early childhood agoraphobia increased the risk of GAD fourfold.

Prevention

Prevention of childhood anxiety disorders has not been studied. The evidence does suggest that children at high risk of anxiety disorders can be identified by identifying parents with anxiety disorders. Prevention strategies to be examined may include effective treatment of parent anxiety, early CBT, and other strategies for children at high risk of developing anxiety disorders.

Obsessive Compulsive Disorder

Obsessive compulsive disorder (OCD) is characterized by obsessions and compulsions. Both components of the disorder can cause substantial, though often unrecognized, impairment and distress in children and families. Obsessions are unwelcome intrusive, repetitive thoughts and worries that are not simply about real life worries. Compulsions are repetitive behaviors intended to reduce distress related to an obsession or that stem from rigid internal rules. In the DSM nosology, the symptoms of OCD must be distressing, time consuming (at least 1 h/day), or interfere with functioning. The ICD-10 does not specify the level of impairment or time consumption in OCD. Importantly, children do not necessarily recognize that their thoughts or compulsions are unreasonable.

Etiology/Pathogenesis

Strong evidence supports the role of heredity in OCD. In pediatric onset OCD, hereditability is thought to be between 45% and 65%. Between 10% and 30% of patients with OCD have a first-degree relative with OCD or OCD traits. Neuroimaging studies have identified associations between OCD symptoms and the cortico-striatal-thalamic pathways, with volumetric and metabolic differences in the orbitofrontal cortex, the globus pallidum, and the anterior cingulated gyrus. The pathway is thought to be associated with filtering consciousness and controlling stereotyped behavior patterns. It is clear that OCD is related to abnormalities in central nervous system serotonin. Serotonin is known to act in the frontal cortex-thalamocortical pathways, which are thought to be related to obsessions. Dopamine and glutamate have also been implicated in the pathogenesis of OCD. Perhaps the most controversial etiologic association of OCD is streptococcal infection, first described in 1998 by Swedo and Leonard. Pediatric autoimmune neurodevelopmental disorders associated with strep (PANDAS), describes a group of children with OCD who present with a course of abrupt onset of OCD and tic symptoms in the context of a recent streptococcal infection. The mechanism for this syndrome is thought to be an autoimmune process targeting the basal ganglia. Although a number of lines of research support the existence of a subgroup of children with OCD who have an autoimmune mediated disease, controversy remains. Strict application of the PANDAS criteria (more than one co-occurrence of onset of symptoms, immunologic evidence of streptococcal infection) is important to avoid overdiagnosis of PANDAS.

Epidemiology

Rates of OCD vary widely across studies and with methodologies. Best estimates suggest that prevalence of OCD is 1–3%. In younger children, patterns of magical thinking, ritualistic and rigid behaviors are normative and may not be impairing. Age of onset has two

peaks – first in the school age group and then in early adulthood. There is a slight predominance of boys over girls represented in pediatric OCD. Boys tend to present earlier than girls and present with different comorbities and symptom clusters.

Clinical Manifestations

Pediatric OCD tends to present with symptoms in four clusters – a focus on symmetry; on aggressive, sexual, religious, or somatic obsessions; on contamination/cleaning; or on hoarding. The first two clusters tend to present earlier than the latter two. Some studies suggest gender differences, with girls presenting with contamination-focused OCD and boys being more likely to have a focus on symmetry and "just right."

Another way of classifying the disorder is familial OCD, OCD with tics, sporadic OCD, and PANDAS. This classification system likely highlights the different etiologies among these different groups. Tic-related OCD may account for 10–40% of pediatric OCD and tends to be seen more often in boys and presents earlier than the other forms.

OCD is frequently comorbid with other conditions. In children, other anxiety conditions including separation anxiety disorder and specific phobias co-occur in as many as half of school age children with OCD. In adolescents, like adults, major depression is present in more than half of patients, and anxiety disorders are present in one quarter to one third of adolescents.

Pediatric OCD often presents with other chief complaints. Compulsions that interfere with family or classroom functioning may present with a chief complaint of behavioral difficulties. Even when patients feel that the OCD is a problem, it tends to be underreported because of shame and awareness that their worries are exaggerated or irrational. The average duration between onset of symptoms and diagnosis is 7–8 years.

Diagnosis

A comprehensive history from the parent and child is necessary to understand the range of symptoms. The Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) provides a structured way to review range of symptoms associated with OCD and the severity of the impairment associated with the disorder. In addition to the symptoms of OCD, it is important to review family history, tic and ADHD symptoms, and medical history. It is particularly important to examine the degree to which the symptoms impair the child or the degree to which the family has accommodated the symptoms.

Differential Diagnosis

OCD and autism spectrum disorders share obsessional patterns and some stereotyped behaviors. However, children with OCD show typical social reciprocity, have normal developmental trajectories, and may be aware that their patterns may seem unusual to others. Some compulsions may be so stereotyped that they must be distinguished from a tic disorder. The movement in OCD generally is voluntary and intended to accomplish something, albeit not always a necessary task. In a tic disorder, the movement is purposeless. Lastly, obsessions in OCD must be distinguished from auditory hallucinations. Usually, this distinction is not difficult, as children with OCD have organized thought processes, have very specific, focused unusual behaviors, and are able to describe that the thoughts are internal to them, rather than coming from outside of them.

General Care

Psychoeducation is the cornerstone of support for patients and families with OCD. Children and families can be taught that OCD is an external force which therapy will allow them to fight and overcome. The plan to "Beat back OCD" is used in the most effective forms of CBT for OCD. In addition, families with other affected members should be evaluated for the need for referrals or co-treatment.

Treatment

The treatment of OCD has been well studied in randomized clinical trial, most notably the Pediatric Obsessive Compulsive Treatment Study which compared sertraline to CBT. To date, fluoxetine, sertraline, and fluvoxamine have been shown to be more effective than placebo in treating pediatric OCD. However, an SSRI alone results in remission in only 20% of patients. For pediatric OCD, CBT alone is twice as effective as SSRI alone, with approximately 40% achieving remission. Again, as for other disorders, CBT has the advantage of durability, with

results that persist beyond 24 months even when the patient is no longer in treatment. Family involvement in CBT is essential to treat pediatric OCD. The combination of CBT and SSRI, specifically sertraline, is the most effective for adolescents, although still only 50% of patients remit within 12 weeks. Thus, the recommended treatment for OCD is CBT with an SSRI or CBT alone. When medications are used, doses to treat OCD tend to be higher than those used for depression or other anxiety disorders. In an analysis of the risk of SSRI-induced suicidality in a large group of children with OCD, there were no cases of suicidal ideations.

Prognosis

Studies of pediatric OCD show a heterogeneous course of illness. Generally speaking, about 40% of children and adolescents with OCD will meet full criteria for OCD as adults. An additional 20% continue to have some symptoms, although they do not meet criteria for the disorder. Comorbid disorders (especially disruptive behavior disorders), early onset of OCD, need for inpatient treatment, and poor initial treatment response are associated with more persistence of OCD. Checking/aggressive and cleaning patterns of OCD rather than hoarding are associated with functional impairment related to OCD. Importantly, parental accommodation to the symptoms, depressive symptoms, and limited insight are also associated with worse functioning with pediatric OCD.

A number of predictors of treatment outcome have also been identified. OCD is less responsive to medication treatment if a child has comorbid tics or comorbid externalizing disorders. CBT effectiveness is limited by family dysfunction and severity of OCD symptoms.

Prevention

There are no prevention approaches recognized for reducing the incidence of pediatric OCD. Tertiary prevention, that is reducing the impact of the disorder, may be possible with effective treatment with CBT. Reduction of the factors associated with persistence of OCD may be most important.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is a syndrome that can occur after exposure to extreme stress, particularly a stressor in which a child's safety or the safety of someone he loves may be threatened. In both the DSM and ICD systems, patients with PTSD suffer from re-experiencing symptoms that can include intrusive thoughts, reenactment, and nightmares related to the trauma. In children, this re-experiencing can present as themes of play and they may have nightmares without being aware of the content.

Epidemiology

Rates of PTSD vary by exposure to stressful events. Pediatric community studies suggest that approximately 5% of children and adolescents meet criteria for PTSD. Rates of exposure to potentially traumatic events vary widely. For example, 50% of preschoolers living in the Gaza strip have seen a home bombarded and 20% have heard a neighbor killed. Hundred percent of American children growing up in inner-city Los Angeles have heard gun shots. Rates of PTSD may vary by trauma type. Children exposed to natural disasters such as earthquakes, hurricanes, and tsunamis develop PTSD at rates between 10% and 50%. Between one third and one half of children exposed to war zones and terrorism meet criteria for PTSD. Unintentional injury and severe chronic medical illnesses have also been associated with elevated rates of PTSD. Interpersonal violence and assault are the most common causes of PTSD in children, with up to 90% of sexual abuse survivors showing PTSD, more than half of children exposed to domestic violence, and about 50% of children who have been physically abused. Factors such as family stability, degree of household disruption, parental safety, being believed when disclosing abuse, and lower chronicity of trauma exposure are all associated with lower rates of developing PTSD after trauma, although these moderators may act differently with different trauma types.

Etiology/Pathology

Clearly, trauma exposure is a necessary component for the development of PTSD. While necessary, it is not sufficient. In general, most social risk factors that increase the risk for mental health problems in general, including lack of social supports, maladaptive family functioning, poverty, and family history of psychiatric disorders, all increase the risk of PTSD. There are also data that suggest genetic factors also contribute to the development of PTSD, although most data are derived from adult studies. In adults, there is some speculation that lower hippocampal volume is a preexisting condition in people who develop PTSD, but this theory is not

supported by imaging studies in children. Early genetic studies suggest that the serotonin transporter and a polymorphism in the glucocorticoid receptor system may interact with trauma exposure to increase the risk of PTSD.

Children and adolescents with PTSD show a number of neurobiological abnormalities. For example, girls with a history of sexual abuse show elevated levels of urinary catecholamines, a marker of stress reaction. Kaufman et al. have demonstrated abnormalities of myelination in the corpus callosum in adolescents with PTSD.

Clinical Manifestations

Across diagnostic systems, PTSD includes re-experiencing symptoms, including play focused on the theme of the trauma, nightmares, and distress related to reminders of the traumatic event, and flashbacks in which the patient feels as if the trauma were reoccurring. The ICD also mentions, and the DSM requires, numbing and avoidance symptoms, dissociation, decreased interest in activities, and a foreshortened sense of future, meaning an inability to imagine the future. The DSM also requires arousal symptoms such as sleep difficulties, anger outbursts, hypervigilance (monitoring of the environment for safety, even when it is not necessary to do so), and hyperstartle responses. Trauma-related symptoms may present soon after the trauma but, in the DSM system, cannot be diagnosed as PTSD until they have been present for a month. Prior to that time, trauma-related symptoms are classified as acute stress disorder, which does not always foreshadow PTSD.

Symptoms of PTSD are often internal and may not have been identified by the patient or parent as being related to the trauma. It is important to ask both the parent and child about the symptoms to ensure the most sensitive assessment possible.

Comorbidity is the norm in PTSD, with nearly 75% experiencing another psychiatric diagnosis, most commonly depression. Other disorders, including externalizing disorders can also be seen with PTSD or after a traumatic experience in the absence of PTSD. Auditory perceptual events can be seen in trauma-exposed children without indicating a psychotic disorder, although these should be examined thoroughly.

Differential Diagnosis

PTSD should be considered whenever a traumatic event is identified and a trauma history is a necessary part of any psychiatric assessment. Although PTSD is most directly associated with trauma exposure, a careful assessment must be done to ensure that other diagnoses are not missed. The re-experiencing symptoms of PTSD are specific to PTSD. Psychotic processes can present with similar patterns, but children and adolescents with psychosis demonstrate disorganized patterns of behaviors and thought, whereas children with PTSD do not. PTSD may also be comorbid with other anxiety disorders, especially separation anxiety disorder and selective mutism in young children. In adolescents, substance abuse can also co-occur with PTSD.

General Care

The most important intervention for pediatric PTSD is ensuring safety. Children with PTSD who are unsafe in their home environment will experience both rational and irrational fears that can worsen symptoms synergistically. Pediatricians should be aware of resources in the community, including domestic violence shelters that may be available for the families. In environmental disasters or chronic war that impact the whole community, creating safety may be a difficult task and sometimes, unfortunately, impossible.

Treatment

Treatment for pediatric PTSD is primarily psychotherapeutic. CBT modified to address traumatic events (TF-CBT) has been shown to be a successful intervention in multiple studies for children with a range of trauma types. This form of CBT includes psychoeducation, focuses on behavioral and cognitive stress management and emotional regulation. When a patient has mastered these skills, they are gradually exposed to the traumatic experience by creating a trauma narrative. Pediatric TF-CBT also includes attention to oppositional behaviors and includes parents as partners. This intervention can be learned through web-based trainings http://tfcbt.musc.edu/. TF-CBT is associated with substantial decreases in PTSD symptoms that are maintained at least 1 year. A preschool version shows promising results as well. Child Parent Psychotherapy is another evidence-based treatment focused on young children. CPP has been shown to reduce symptoms of PTSD in young children exposed to domestic violence and maintain the results over at least 6 years.

Psychopharmacological interventions have received very little study in pediatric PTSD. One small study suggested that imipramine was effective in reducing the

progression from acute stress symptoms to PTSD. A more recent study examined the effect of adding sertraline to TF-CBT to treat PTSD in children with a history of sexual abuse, with only minimal differences between outcomes in the TF-CBT group compared with the combined group.

Despite the paucity of data, children frequently receive medication treatment for PTSD. In adults, SSRI's have been demonstrated to be effective in reducing symptoms of PTSD. Alpha agonists have shown some benefit in an open trial study. After an incomplete response to therapy, a clinician may consider medication, but must recognize that the randomized trials supporting psychopharmacological intervention have been done in adults. Comorbid conditions may be more amenable to psychopharmacological intervention.

Prevention

The most important step toward reducing the burden of PTSD is to reduce children's exposure to potentially traumatic events, including war, terrorism, abuse, and home and community violence. After a trauma has occurred, ensuring safety, reducing separation from parents, believing a child's report of sexual or physical abuse, and managing pain are paramount. Morphine has been shown to be effective in reducing PTSD in burns. Thus, physical and emotional comfort appears to be an important factor in resiliency. Children should be allowed to talk about the trauma at their own paces and parents should support "brave behaviors."

Prognosis

Prognosis for pediatric PTSD is variable. Generally, PTSD is considered a chronic disorder. Depending on the trauma type, more than one fourth of children with PTSD as children will continue to have PTSD as adults. The persistence of symptoms appears to be associated with history of prior trauma and major injury associated with the trauma.

Externalizing Disorders

The externalizing disorders comprise disorders of disruptive behaviors, in which patterns of behaviors interfere with functioning because of observable, "external" behaviors. The triad of disruptive behavior disorders includes attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) in the DSM system. In the ICD-10 system, these disorders are diagnosed under the umbrella of hyperkinetic disorders, of which there are two major forms: hyperkinetic disorder of activity and attention and hyperkinetic disorder of conduct.

ADHD will be discussed in Chap. 45, "Disorders Cognition, Attention, Language, and Learning".

Disruptive Behavior Disorders

Temper Tantrums

It is not unusual for the presenting concern to a child mental health provider is some form of "temper tantrums", usually describing emotional and behavioral dysregulation that may include crying, yelling, screaming, and aggression towards objects, other people, or self. There is no technical definition of such events and they do not represent a specific disorder, but parents and some providers will be tempted to consider such events to be behavioral difficulties because they may occur when an adult places a demand on the child. However, the differential diagnosis of such behaviors is wide and includes almost every category of mental health issue. For example, a child with a mood disorder, with prominent irritability, may react to perceived insults or injustices with extreme emotional reactions. Children with mood disorders should have concurrent neurovegetative signs such as sleep, appetite, or energy disturbances and may also experience difficulty with memory and concentration. On the other hand, a child with oppositional defiant disorder may react present with a similar patter of responding to adult directions, but would have a pervasive pattern of not following directions, arguing with adults, and/or intentionally annoying other people, but would not show neurovegetative signs. Children with anxiety disorders, including OCD, can present with "tantrums" when exposed to an event or situation that causes extreme anxiety and emotional dysregulation. Children and adolescents developing psychotic disorders may react in unpredictable ways to experiences they misperceive. Finally, children with developmental delays may exhibit tantrumming behaviors when asked to do things that are beyond their developmental level or as a sign of frustration. Thus, a single sign of difficulty organizing an emotional or behavioral reaction to a stressor cannot be considered pathognemonic for any single disorder.

Disruptive Behavior Disorder Diagnoses

Oppositional defiant disorder (ODD) and conduct disorder (CD) together comprise the disruptive behavior disorders (DBDs). In the DSM, ODD is characterized by four or more symptoms of oppositional and defiant behaviors, including losing temper easily, talking back to adults, intentionally defying adults, deliberately annoying others, blaming others for own transgressions, being touchy/easily resentful, easily annoyed, or spiteful and vindictive. In conduct disorder, children present with behaviors that reflect a disregard for the safety of others and of societal norms, including severe aggression, destruction of property, running away from home/school, and theft.

Etiology/Pathogenesis

The etiology of DBDs has been studied less than other disorders. Twin studies suggest some contribution of genetics in the development of DBDs. It is clear that there is a substantial familial nature to the disorders, and strong association with parental psychopathology including antisocial personality disorder as well as depression. One study showed an important interaction between genes and environment, namely that the combination of low activity level of monoamine oxidase-A activity and maltreatment put children at an especially high risk of showing persistent aggressive behaviors.

Prenatal environment, including toxin exposures such as nicotine, and environmental factors like early parenthood also predict persistence of aggression in children. Early parenthood, in combination with either maternal antisocial behaviors or low parental education achievement, increases risk of high aggression ten- or fourfold, respectively. One mediator of these associations appears to be harsh, punitive parenting style, which is among the most common risk factors for early childhood aggression. A cycle of harsh parenting and child disruptive behaviors that mutually reinforce each other can be seen in some families.

Reactive aggression has been thought to be associated with abnormal amygdale or frontal lobe function. On the other hand, premeditated, planful aggression and ODD have been associated with decreased autonomic reactivity.

Epidemiology

Disruptive behavior disorders occur in the community at rates between 5% and 10% of the population in the USA, New Zealand, and Canada, with ODD generally showing a much higher prevalence than CD. In general, boys have a higher risk compared to girls, although this gender difference does not appear until after age 6 and is less prominent than thought in the past. DBDs do seem to present at higher rates in lower socioeconomic groups, although further research is needed.

Clinical Signs

Disruptive behaviors are among the most common chief complaints in mental health settings and can be associated with a range of disorders, including DBDs. Children generally come to clinical attention because of concerns of parents or teachers but not because of the child's own distress related to the symptoms.

Few studies have examined the comorbid conditions of ODD, but the one study that did suggested that fewer than 20% had comorbid ADHD, mood disorders, or anxiety. On the other hand, about half of pediatric CD is associated with another disorder, most commonly ADHD, but also mood disorders and substance abuse. When associated with ADHD, CD is more severe, persistent, and has a earlier age of onset. Importantly, adolescent CD is highly associated with anxiety in girls, but not boys. Girls with aggression are also more likely to have mood disorders and suicidality than boys.

Diagnosis

Assessment of DBDs must be done using multiple reporters, as parents and children tend to report on different types of DBD symptoms. Teacher reports are important to understand the child's behavior in other contexts. Full history must include attention to parenting approaches (including question of abuse) and family history of psychopathology and criminal behaviors.

Differential Diagnosis

Mood disorders can present with irritability and problems with following directions and thus can be confused with ODD. Anxiety that causes social withdrawal may also be interpreted as oppositional behaviors by some adults and must be investigated. Severe aggression can be associated with unipolar depressive disorders, bipolar disorder, psychosis, re-experiencing symptoms of PTSD, and autism spectrum disorders, and each of these diagnoses must be

considered in the assessment of a patient with behavioral difficulties. Toddlers with immature language or older children with delayed language and other delays may also present with acting out behavior in response to frustration. Medical conditions, such as temporal lobe epilepsy are rare, but can present as unprovoked rage in adolescents.

General Care

Parents and children presenting with DBDs have generally heard from many child experts that they have failed. It is important, despite the obvious problems in behavior and possibly interactive difficulties, that the families experience the clinical setting as supportive and ready to problem solve. Scare tactics by parents and pediatricians are unlikely to change the patient's behaviors and have important negative impacts on relationships. General safety must be addressed, including the patients' safety toward themselves and toward other people, and caregivers' ability to keep the child safe and use safe behavioral management techniques.

Intervention approaches must include attention to the child, home life, educational experiences, and peer groups, all of which may influence the DBD. Comorbid conditions should be treated aggressively, as symptoms of mood disorders, ADHD, and substance abuse disorders all may exacerbate behavioral difficulties.

Treatment

Both psychotherapeutic and psychopharmacological interventions have been investigated to treat DBDs, and in general, a multipronged approach is indicated. In younger children in particular, parent management training (PMT) models have been shown to be particularly effective. Most effective PMT interventions focus on increasing parental attention to positive behaviors, planned ignoring, and consistent, structured, and safe consequences for misbehavior. They are associated with reduced signs of DBD, decreased parenting distress, and have sustained results up to 6 years later. Parent groups, such as the Incredible Years Series, and dyadic treatments like the Parent Child Interaction Therapy have been shown to be quite effective. In preschoolers, there are no systematic studies of medications for DBDs, and thus the balance of evidence is strongly in favor of these psychotherapeutic interventions.

For older children, wraparound services have been shown to be most effective for adolescents with severe behavioral difficulties. Multi-systemic therapy (MST) is a home-based, intensive therapy that uses a 7 days per week treatment approach with a Master's level team of therapists and a psychiatrist to provide a goal-directed treatment approach focused on crisis intervention, family systems therapy, and home-based behavioral treatment. It is effective in reducing recidivism, out of home placements, psychiatric symptoms, and substance abuse in adolescents with serious behavior problems. Medications can be useful adjuncts to psychotherapeutic interventions for youth with severe aggression related to a DBD. A recent meta-analysis revealed that methylphenidate can be effective in treating DBDs with or without comorbid ADHD and clonidine is equally effective. Lithium has been shown to be effective in reducing aggression in youth with conduct disorder. Antipsychotic agents, including haloperidol, thorazine, and risperidone are also effective in treating aggression in DBDs. Antiepileptic agents have shown mixed results in reducing aggression.

Prognosis

In preschoolers, rates of stability are somewhat lower and preschoolers with ODD appear to show heterotypic continuity. Most children continue to have a disorder, but a substantial proportion have anxiety in the school age years, while others continue to present with DBDs. The stability of disruptive behaviors from childhood to adolescence and beyond is consistently reported as above 50%, with the highest stability in children who have more severe DBDs. The long-term effects of the early childhood interventions for DBDs suggest that prognosis may be modified by early exposure to evidence-based treatments. Childhood DBDs are associated with antisocial personality disorder as well as with a range of other psychiatric disorders and adverse life events, including substance abuse, depression, delinquency, early pregnancy, and unemployment. However, it is important to note that the majority of children and adolescents with disruptive behavior disorders, especially those with ODD, do not develop psychopathology or delinquency in adulthood.

Prevention

The risk factors associated with DBDs provide guidance about possible prevention interventions. Reduction of prenatal exposures to potential toxins including smoking, substance use, and alcohol could decrease risk in susceptible patients. Secondary prevention programs that target positive parenting in children at high risk because of family poverty,

exposure to harsh parenting, or parental psychopathology can reduce risk of DBDs. One such program is the Nurse Family Partnership, in which prenatal home visits by nurses who continue to visit until the child's second birthday are associated with reduction in criminal behaviors when the children become adolescents. Access to parental psychiatric treatment may also reduce parent symptoms, which are shown to be associated with DBDs. Social service programs that create a safety net for low-income families and that reduce exposure to family and community violence are important preventive strategies.

Psychosis

Psychosis can be defined as a fundamental disturbance in thinking and perception, most commonly characterized by hallucinations and delusions that change a person's experience of reality. Primary disorders of psychosis, such as schizophrenia, are quite rare. Psychosis is more commonly seen as part of an affective disorder syndrome and perceptual abnormalities can also be experienced by patients with a history of trauma exposure or autism spectrum disorders. The major psychotic disorders in the DSM classification are schizophrenia and schizoaffective disorder. Schizophrenia is a disorder that includes psychotic symptoms as well as "negative symptoms" which include blunted or inappropriate affect. The DSM-IV and ICD-10 provide similar requirements for the diagnosis of schizophrenia. In the DSM-IV, two of the major symptoms of hallucinations, delusions, disorganized speech or behavior, and negative symptoms including flat affect, word-finding difficulties, and lack of motivation are needed, in addition to social functioning problems for at least 6 months. In the DSM system, psychotic illnesses with significant mood abnormalities are classified as schizoaffective disorder if the patient has periods of psychosis without mood symptoms or affective disorder with psychosis if affective symptoms have occurred independent of psychosis. The ICD-10 requires at least one major hallucination or delusional symptom or two minor symptoms for at least 1 month. Childhood onset schizophrenia (COS) is considered schizophrenia that presents in the prepubertal period. Adult onset schizophrenia typically presents in late adolescence or early adulthood.

Etiology/Pathology

The etiology of COS is poorly understood. Internationally, offspring of parents with psychosis have a 4–20-fold risk of developing schizophrenia. Data related to pre- and perinatal factors predicting COS are inconclusive. Genetic studies have identified a number of mutations seen at higher rates in COS, including those affecting dopamine, glucocorticoid, dysbindin, neuroregulin, and glutamate. Most importantly, about 4% of COS patients may have a deletion at 22q11, known as velo-cardio-facial syndrome. Mosaic Turner syndrome appears in COS patients at 500 times the rate expected in the general population. Neuroimaging studies of COS show increased ventricular size and associated loss of gray matter in the cortical, frontal, medial temporal, and parietal gray matter. The progression of the loss of gray matter reliably occurs in a progressive back to front pattern and seems to be related to the disease progression.

Epidemiology

The epidemiology of childhood onset schizophrenia (COS) has not been studied systematically, but it is thought to be rare. In the largest US epidemiological study that followed 1,420 children from age 9 to age 16, there is no mention of schizophrenia and rates of psychotic disorders appear to have been too small to report. COS appears to affect boys at approximately twice the rates of girls, until adolescence when the incidence is equal in the genders. The onset of COS is generally in the school age years. Preschool COS is nearly unheard of. The US study of 89 children with COS suggested that nonwhite patients were disproportionately represented, making up 52% of the children in that study. A similar pattern has been described in adult onset schizophrenia in the UK.

Clinical Manifestations

COS presents with an insidious prodromal course, which includes more negative symptoms. These symptoms include blunted or inappropriate affect, which may present similarly to a mood disorder, social withdrawal, disruptive behaviors including aggression, language deficits, academic problems, and other developmental difficulties. The onset of the full disorder usually includes so called positive symptoms, which include hallucinations and/or delusions, as well as negative symptoms, which include paucity of affect, decreased motivation, and low energy. COS presentation tends to also include depression, cognitive impairment, and hostility. COS is more likely to present with auditory hallucinations than delusions, which can include persecutory delusions and somatic

delusions. Children present with disorganized thought processes, which may be evident in their speech or in their play. Because of the insidious onset, children may present with unusual or odd behaviors before the positive symptoms are identified. Most children with COS will demonstrate cognitive decline with the presentation of their illness, with IQ's declining up to 20 points over their adolescence. COS commonly co-occurs with depressive disorders, obsessive compulsive disorder, and anxiety disorders. COS may also present in children with preexisting autism spectrum disorder. In adolescents, substance use is not uncommon with psychosis. Most strikingly, children with COS are severely impaired in most domains of their functioning, including family, peers, and academics.

Diagnosis

The diagnosis of COS requires multiple appointments, including interviews with the child and the parents, and observational assessments. Because the diagnostic criteria for schizophrenia include minimum duration of symptoms and because the disorder is associated with substantial stigma, it is reasonable to make a provisional diagnosis if there is any question about which psychotic disorder best matches the clinical presentation. Because COS is so rare, the diagnostic assessment should include careful assessment for more common disorders.

Differential Diagnosis

A number of disorders may overlap with the presentation of COS. Major depression with psychotic features and bipolar disorder both can present with psychotic symptoms. The differential diagnosis is made based upon the history of mood symptoms without co-occurring psychosis. Medical conditions including CNS lesions, metabolic derangements, and medications can present with psychosis and should be ruled out. Although medical testing should be tailored to the presentation, chemistry panel, thyroid function and liver function tests, and neuroimaging are generally part of the assessment to rule out organic processes. Substance use can also present with similar symptoms and also must be ruled out. Traumatic events can also trigger perceptual events as well as other trauma-related symptoms and must be examined.

General Care

Because psychotic illnesses interfere with every aspect of a child's life, it is important that the interventions focus not only on targeting the primary symptoms but also on providing support for the child. Psychoeducation about the disorder is important, and it can be helpful to provide opportunities for parents to process the diagnosis without the child as well. As with other chronic disorders, a diagnosis of COS may trigger a grief reaction in parents whose child will be expected to deteriorate substantially as the disorder progresses. School accommodations to address language, concentration, and academic processes are critical.

Treatment

The mainstay of treatment for COS is pharmacological. However, this disorder has been the focus of few studies. Early data demonstrated that haloperidol and loxapine, typical antipsychotic agents, reduced symptoms of COS. Two atypical antipsychotic agents, ziprasidone and aripiprazole, have also been shown to be more effective in reducing symptoms of COS than placebo, although it should be noted that in most studies of COS, "response" has been defined as a 30% decrease in symptoms, demonstrating a relatively low effect size. Most recently, molindone, olanzapine, and risperidone were shown to have generally equal efficacy in a 52 week controlled study without a placebo arm. All had high rates of discontinuation because of inadequate efficacy or adverse effects. Of the medications studied, clozapine is the most effective in reducing positive and negative symptoms. However, clozapine carries with it the risk of agranulocytosis, and higher rates of akathesia and weight gain than adults on clozapine. In clinical practice, polypharmacy is not uncommon, but it is clear that more research is needed to identify a safe and effective treatment for COS.

Prognosis

COS is a chronic disorder and appears to have continuity with adult schizophrenia. Earlier age of onset is associated with more severe disorder and worse prognosis. Lower premorbid functioning also predicts poorer outcome. In the past, it was thought that isolated psychotic symptoms in childhood or adolescence did not predict schizophrenia; however, a longitudinal study in New Zealand showed that nearly 10% of those with an isolated hallucination experience in adolescence developed a psychotic illness by age 26.

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47 Autism Spectrum Disorders

Kathleen Angkustsiri · Robin L. Hansen

Clinical Vignette

Steven is a 20-month-old boy born at term with no significant medical history except for recurrent ear infections. He had appropriate motor milestones, but his parents became concerned at 14 months because he was not using words and did not respond consistently to his name. He communicates by crying, whining, or leading his mother by the hand to a desired object. Steven does not point or use gestures such as waving or clapping, although will reach his hand toward things he wants. His parents find it difficult to get his attention, and he does not make eye contact readily. His favorite toy is a small car that he carries with him everywhere. He likes to spin the wheels with his finger and watch them out of the corner of his eye. Steven also lines up toys and occasionally flaps his hands.

Definition/Classification

The autism spectrum disorders (ASD) are a group of neurodevelopmental disorders affecting social communication. They include autistic disorder (autism), Asperger's disorder, and pervasive developmental disorder – not otherwise specified (PDD-NOS). The ASDs are currently included in the DSM-IV and ICD-10 under the category of Pervasive Developmental Disorders, which include autism, Asperger's disorder, PDD-NOS, Rett's disorder, and childhood disintegrative disorder. This chapter focuses on autism spectrum disorders (autism, Asperger's disorder, and PDD-NOS).

Etiology

ASDs are biologically based conditions that are thought to involve complex interactions between multiple genetic and environmental factors. There is no evidence to support that ASDs are caused by bad parenting or "refrigerator mothers," as described by Bettelheim. The ASDs are highly heritable, with a 2–8% sibling recurrence rate. The concordance rate for ASDs is 60–92% in monozygotic (MZ) twins compared to 0–10% in dizygotic (DZ) twins, supporting a strong genetic component. Although genetic causes such as chromosomal abnormalities and de novo copy number variations are implicated in 10–20% of cases with ASD, no single genetic etiology accounts for more than 1–2% of cases. ASD-associated syndromes (fragile X syndrome, Tuberous Sclerosis, chromosome 15q duplication syndrome, etc.) likely contribute to autism risk through common neural pathways related to early brain development. Carnitine deficiency and mitochondrial dysfunction may also be related to autism risk. Environmental influences have been implicated, including prenatal exposure to rubella, thalidomide, and valproic acid. Current theories propose that genetic susceptibility modulated by environmental factors is involved in the etiology of ASD.

Potential risk factors include prematurity, low birth weight, and parental age. While some individuals with ASD have dysfunctional immune responses, epidemiologic studies have not supported a causal link between immunization and the development of ASD.

Epidemiology

Autism was first described by Kanner in 1943 and was considered a rare disorder. In the late 1970s, prevalence in the UK, Denmark, and USA was estimated at 5/10,000. Prevalence has been increasing rapidly since then, and the most recent estimated prevalence of ASD worldwide is 63.7/10,000 or 1/157. In the USA, there was a 57% increase from 2002 to 2006. While some of the increase is attributable to better detection, increased awareness, and use of broader diagnostic criteria, some argue that these factors do not fully explain the dramatic rise in ASD. ASDs affect individuals of all social strata and ethnicity with a male to female ratio of 4:1. Exact prevalence data is not available for many countries, although some estimates ranging from 1/55 to 1/699 have been reported from population-based data as listed in *Table 47.1*.

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Table 47.1
ASD prevalence by country

Country	Prevalence	Year
USA	1/110	2006
UK	1/86	2006
Mexico	1/699	1996
Venezuela	1/588	2006
Hong Kong	1/621	2005
France	1/370	2002
Japan	1/55	1996
Canada	1/154	2004
Australia	1/255	2002
Denmark	1/188	2002

Clinical Manifestations/Diagnosis

There is considerable variability in the clinical features of ASD, which include significant impairment in three domains: social interaction, communication, and restricted/repetitive interests or behaviors. Screening is recommended at 18 and 24–30 months and early identification is important to maximize therapeutic effects of intervention ❯ *Table 47.2*. Diagnosis is made based on behavioral observations, history, and standardized assessment. Symptoms must be present by age 3. Diagnostic criteria are listed in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV, ❯ *Table 47.3*) and the International Statistical Classification of Diseases and Related Health Problems (ICD-10; ❯ *Table 47.4*). Revisions to the diagnostic criteria are anticipated in the next version of the DSM-V in 2013.

A diagnosis of autistic disorder requires impairment in a minimum of six total DSM-IV items, with at least two in social interaction and one from the other core domains. A diagnosis of Asperger's disorder requires impairment in at least two DSM-IV items under social interaction, one under restricted/stereotyped interests and behaviors, and no clinically significant language delay or cognitive/adaptive impairment in individuals who do not meet criteria for autistic disorder. PDD-NOS (ICD-10: atypical autism) is the term used when symptoms are subthreshold for autistic disorder or Asperger's disorder but cause pervasive impairment. Gold standard diagnostic tools include the Autism Diagnostic Observation Schedule (ADOS), a semi-structured behavioral assessment, and the Autism Diagnostic Interview-Revised, although the

Table 47.2
ASD screening tools

Modified checklist for autism in toddlers (M-CHAT)
Pervasive developmental disorders screening test-II (PDDST-II)
Social communication questionnaire (SCQ)
Autism spectrum screening questionnaire (ASSQ)
Early screening for autistic traits (ESAT)

See Johnson CP, Myers SM (2007) Identification and evaluation of children with autism spectrum disorders. Pediatrics 120:1183–1215 for other screening measures.

Table 47.3
Clinical Features/DSM-IV Criteria for autism

(A) *Qualitative impairment in social interaction:*
Marked impairments in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
Failure to develop peer relationships appropriate to developmental level
Lack of spontaneous seeking to share enjoyment, interests, or achievements with other people
Lack of social or emotional reciprocity
(B) *Qualitative impairments in communication:*
Delay in, or total lack of, the development of spoken language
Marked impairment in the ability to initiate or sustain a conversation with others in individuals with adequate speech
Stereotyped and repetitive use of language or idiosyncratic language
Lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
(C) *Restricted repetitive and stereotyped patterns of behavior, interests, and activities:*
Encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
Inflexible adherence to specific, nonfunctional routines or rituals
Stereotyped and repetitive motor mannerisms
Persistent preoccupation with parts of objects

A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)
Onset before age 3

Table 47.4
ICD-10 criteria for Pervasive Developmental Disorders (WHO 2007)

	Pervasive developmental disorders A group of disorders characterized by qualitative abnormalities in reciprocal social interactions and in patterns of communication, and by a restricted, stereotyped, repetitive repertoire of interests and activities. These qualitative abnormalities are a pervasive feature of the individual's functioning in all situations
F84.0	*Childhood autism* A type of pervasive developmental disorder that is defined by: (a) the presence of abnormal or impaired development that is manifest before the age of 3 years, and (b) the characteristic type of abnormal functioning in all the three areas of psychopathology: reciprocal social interaction, communication, and restricted, stereotyped, repetitive behavior. In addition to these specific diagnostic features, a range of other nonspecific problems are common, such as phobias, sleeping and eating disturbances, temper tantrums, and (self-directed) aggression
F84.1	*Atypical autism* A type of pervasive developmental disorder that differs from childhood autism either in age of onset or in failing to fulfill all three sets of diagnostic criteria. This subcategory should be used when there is abnormal and impaired development that is present only after age 3 years, and a lack of sufficient demonstrable abnormalities in one or two of the three areas of psychopathology required for the diagnosis of autism (namely, reciprocal social interactions, communication, and restricted, stereotyped, repetitive behavior) in spite of characteristic abnormalities in the other area(s). Atypical autism arises most often in profoundly retarded individuals and in individuals with a severe specific developmental disorder of receptive language
F84.5	*Asperger's syndrome* A disorder of uncertain nosological validity, characterized by the same type of qualitative abnormalities of reciprocal social interaction that typify autism, together with a restricted, stereotyped, repetitive repertoire of interests and activities. It differs from autism primarily in the fact that there is no general delay or retardation in language or in cognitive development. This disorder is often associated with marked clumsiness. There is a strong tendency for the abnormalities to persist into adolescence and adult life. Psychotic episodes occasionally occur in early adult life

Table 47.5
Red flags for ASD

Poor eye contact
No response to name at 12 months (with normal hearing)
No pointing by 14 months
No pretend play at 18 months
Echolalia
Loss of skills (regression)
No reciprocal social smile

administration of both tools may not be practical in all clinical practice. Warning signs that should prompt evaluation for ASD are listed in *Table 47.5*.

Social Deficits

Key features include difficulties with joint attention, social reciprocity, imitation, and nonverbal behaviors (eye contact and gestures). Joint attention develops as early as 8–10 months in typically developing children and includes following eye gaze, following a point (10–12 months), pointing to request ("protoimperative" 12–14 months), and pointing to express interest ("protodeclarative" 14–16 months). This is usually accompanied by directing eye gaze back and forth between another person's eyes and an object of interest. There may be a lack of social referencing, which is when a child looks to another person to share affect or, for example, to determine how to respond in an unfamiliar situation by looking for another person's facial expression. Shared enjoyment with others is limited, and there may be a lack of showing behaviors. One of the fundamental deficits in ASD is lack of emotional reciprocity and "theory of mind," the ability to understand and attribute the mental states (and emotions) of others as different from one's own.

Communication Deficits

Many children diagnosed with ASD are originally evaluated because of language delays. However, over 80% develop language. Individuals with Asperger's syndrome do not have clinically significant language delay by definition, but they may have the unusual speech patterns characteristic of ASD such as echolalia (repetition of words or phrases), difficulty with pronouns, and unusual prosody (stress, pitch, and intonation). There are also deficits in the semantic aspects of language, with difficulty

understanding abstract concepts. This tendency to be overly literal affects pretend play skills, and there may be difficulties with imitation. Individuals with ASD who have language often have trouble with the social use of language (pragmatics) such as turn taking and sustaining conversation.

Restricted Interests

Intense interests in restricted or repetitive patterns of behavior are common in ASD. This may involve unusual interests, such as a preoccupation with fans or license plates, or interests that are typical for developmental level (i.e., trains) but which are abnormal in intensity. There may also be a nonfunctional insistence on routines or sameness (lining up objects, etc.) and focus on parts of objects rather than the whole. Some individuals demonstrate repetitive and stereotyped behaviors, such as hand-flapping or finger flicking. Sensory differences (hyper- or hypo-sensitivity to noise, touch, etc.) are common although not universal. In a minority of cases, individuals with ASD may have savant skills, with isolated exceptional abilities in areas such as math or music.

Regression

Regression, or loss of previously acquired skills, is uncommon in typically developing children but affects 33–41% of children with ASD, typically between the ages of 15 and 24 months. Report of language loss alone may underestimate the prevalence of regression, since parents also report loss of social interest, eye contact, or use of gestures. Many parents report a period of typical development prior to the onset of regression, while others note the presence of developmental delay prior to regression.

IQ

As a result of early intervention, broader diagnostic criteria, and improved evaluative practices, the prevalence of global developmental delay or intellectual disability (ID) in individuals with ASD has decreased over the years, with recent estimates under 50%.

Differential Diagnosis

While some individuals with ASD may also have *intellectual disability* (ID), the distinguishing factor between ASD and ID is that people with ID have social and communication abilities appropriate for their developmental level. Children with *hearing impairment* may have difficulty with receptive language, similar to children with ASD. However, other aspects of communication, such as nonverbal behaviors, eye contact, and joint attention, are usually unimpaired. Many children with *visual impairment* may have poor eye contact and self-stimulatory behaviors that mimic symptoms of ASD. The *Landau–Kleffner syndrome* has a later onset of language regression and a characteristic EEG pattern. Poor eye contact is often attributable to *anxiety disorders*, and individuals with o*bsessive compulsive disorder* (OCD) may have intense preoccupations. However, in OCD, these behaviors cause distress whereas in ASD, individuals prefer activities related to their intense interests. Symptoms of *attention deficit hyperactivity disorder* (ADHD) may include social impairment, but communication and repetitive/restricted interests are not affected.

Management and Treatment

General Management and Treatment

Any child suspected of having an ASD should have a hearing evaluation and referral to a specialist for diagnostic assessment if available. Lead testing is appropriate if risk factors are present. Once diagnosed, high-resolution chromosomes/karyotype and fragile X DNA are indicated. Chromosomal microarray/comparative genomic hybridization (CGH) is gaining utility in identifying chromosomal duplications and deletions and may soon be first-line investigation. Targeted genetic testing, such as MECP2 mutations in females with acquired microcephaly, regression, and loss of purposeful hand movements, or FISH for chromosome 15q duplication in those with hypotonia, intellectual disability, and seizures, should be considered based on symptoms.

Routine MRI is not recommended unless there are clinically relevant findings, such as symptoms suggestive of tuberous sclerosis or increased intracranial pressure. Accelerated head growth and macrocephaly (head circumference >2 SD above population mean) has been reported in over 20% of children with ASD based on MRI and head circumference studies. Interestingly, head circumference is average or slightly lower than average at birth, with rapid growth in the first year of life. Structural differences in the frontal lobes, white matter, and cerebellum have all been identified.

EEG is recommended if there are clinical symptoms suspicious for seizures. Seizures have been reported in

approximately 25–30% of people with ASD, with a bimodal distribution in early childhood and adolescence. Abnormal EEGs in the absence of clinical seizures are reported even more frequently. The evidence relating a history of regression with EEG abnormalities is unclear, and treatment of EEG abnormalities in the absence of clinical symptoms is controversial.

Gastrointestinal (GI) problems, such as constipation and food selectivity/sensitivity, are reported frequently in ASD. A consensus report cited these recommendations with regard to GI disorders and ASD: Individuals with GI symptoms should be evaluated in the same manner as typically developing children; there is insufficient evidence to endorse the use of the gluten-free, casein-free diet to treat the core symptoms of autism, and growth and nutritional status (including protein, vitamin D, calcium, and iron) should be carefully monitored (given self-imposed or therapeutic diets). The report also highlights that GI symptoms may manifest as behavioral changes and despite reports of lymphonodular hyperplasia and increased intestinal permeability, there is no evidence at this time to suggest GI pathology specific to autism (since these findings are also found in typically developing populations). A detailed history and physical examination for immune-mediated food allergies should be pursued, with appropriate work-up if positive.

Sleep disturbances, including delayed sleep onset, night-time wakening, and decreased sleep duration, are reported more frequently in children with ASD. Behavioral interventions may successfully treat sleep problems. Melatonin, a hormone secreted by the pineal gland, is reduced in children with ASD and has shown to be safe and effective for improving sleep in ASD.

Psychiatric comorbidities are common, such as attention deficit hyperactivity disorder (ADHD), anxiety, and depression, especially in older children or adolescents. Screening for psychiatric problems, with proper behavioral and pharmacological intervention, should be performed routinely.

Educational Treatments

Behaviorally based interventions are the most effective treatments for ASD, and many types exist. Applied behavior analysis (ABA), which uses learning principles of how environment can change behavior, is perhaps the best documented, although other models such as developmental theory and relationship-based curricula have also proven effective. The evidence base for a variety of interventions is available at http://www.nationalautismcenter.org/about/national.php. Regardless of the modality, an intensive, comprehensive program which provides structured teaching tailored to the child's individual needs best benefits a child with ASD. Additional therapies important to consider include speech/language therapy, social skills instruction, and/or occupational therapy.

Early intervention agencies often provide intervention to toddlers, with transition to the school system after that. Many children require special education services and benefit from an individualized education plan (IEP). Goals for older children involve generalization of learned skills to new environments, functional skills that promote independence, and socialization with other children.

Pharmacological Treatments

The atypical antipsychotics risperidone and aripiprozole are FDA-approved to treat irritability in children aged 6–17 with ASD. Side effects include weight gain, sedation, and restlessness (akathisia). Rarely, there may be movement disorders as a result of these medications.

Current pharmacological treatments target associated symptoms, such as irritability, impulsivity, anxiety, or sleep. Clinical trials for medications to treat the core symptoms of autism are underway and include memantine, oxytocin, and other neuromodulators.

Prognosis

Due to early, intensive therapy, and broader diagnostic inclusion criteria, projected long-term outcomes have improved. While there is great heterogeneity in outcomes, most individuals continue to improve with milder symptoms into adulthood. However, the majority of individuals remain functionally impaired. The best predictors of good outcome are development of speech by age 5 and normal IQ. It is hoped that early diagnosis and continued autism-specific interventions will improve the long-term outcomes for individuals with ASD.

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Resources

American Academy of Pediatrics Autism Toolkit: http://www.aap.org/publiced/autismtoolkit.cfm

Autism Speaks 100 day kit: http://www.autismspeaks.org/community/family_services/100_day_kit.php

CDC information and statistics http://www.cdc.gov/ncbddd/autism/index.html

National Standards Project: http://www.nationalautismcenter.org/about/national.php

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48 Child Abuse and Neglect

Fadheela Al-Mahroos · Dena Nazer · Vincent J. Palusci · Rachel Clingenpeel

Overview of Child Maltreatment: An International Perspective

Child maltreatment consists of anything which individuals do or fail to do which directly or indirectly harms children or damages their prospect for safe and healthy development into adulthood. It includes physical, sexual, and emotional abuse and neglect.

Child abuse and neglect (CAN) has existed as long as humanity has existed. Infanticide was practiced in many societies and has been documented in China, India, and the Pre-Islamic Arabia. In the year 900 the prominent physician Al-Razi, attributed the prominence of umbilical hernia in children to "the child may have been intentionally struck." CAN cases are well documented in many writings, novels, and in medical professional literatures of the nineteenth century. The full scale of the problem, and the role of physicians in addressing it, has emerged in the latter half of the twentieth century, when documented in the medical literature by Henry Kempe and colleagues in the landmark article "The battered-child syndrome." This was followed in 1972 by another landmark article by Caffey describing "shaken-baby syndrome" consisting of diffuse subdural hemorrhage, diffuse multilayer retinal hemorrhage, and diffuse brain injury and swelling.

Since then, it is well-recognized that child abuse and neglect represent a common public health and social problem across the globe. The United Nations General Secretary's 2006 Study on Violence Against Children has documented that all forms of child maltreatment exist in every corner of the world and that no race or culture is exempted. According to this report, almost 53,000 children died worldwide in 2002 as a result of homicide, and up to 80–98% of children suffer physical punishment in their homes, with a third or more experiencing severe physical punishment resulting from the use of instruments. In addition, 150 million girls and 73 million boys under 18 have experienced forced sexual intercourse or other forms of sexual violence. Between 100 and 140 million girls and women in the world have undergone some form of female genital mutilation or cutting. In sub-Saharan Africa, Egypt, and the Sudan, 3 million girls and women are subjected to genital mutilation or cutting every year. In 2004, 218 million children were involved in child labor. Estimates from 2000 suggest that 1.8 million children were forced into prostitution and pornography, and 1.2 million were victims of trafficking.

The most recent large US study of CAN, conducted in 2005–2006, was the National Incidence Study (NIS–4). This revealed that nearly 3 million children experienced CAN as defined by the Endangerment Standard definition of maltreatment. This is equivalent to one child in every 25 in the United States being affected. Of the children identified as maltreated, 26% were identified as abused, and 77% were identified as neglected. Of the abused children, physical abuse was documented in 57%, emotional abuse in 36%, and sexual abuse in 22%. Another large scale research study is the Canadian Incidence Study of Reported Child Abuse and Neglect – 2003 (CIS-2003). This study revealed that an estimated 217,319 child investigations were conducted in Canada of which 103,297 (47%) child investigations were substantiated. Physical abuse was documented in 24%, sexual abuse in 3%, emotional abuse in 30%, exposure to domestic violence in 15%, and neglect in 28% of the substantiated cases.

A study which reviewed reported child abuse and neglect studies in the seven countries of the Arab Peninsula, documented child abuse in Bahrain, Kingdom of Saudi Arabia (KSA), Kuwait, Oman, and Yemen. The WorldSAFE study (2002) documented the rates of harsh forms of physical punishment in the previous 6 months as reported by mothers in four developing countries, and compared it with the rate in the USA. The rates of harsh treatment such as hitting a child with an object (not on buttocks) were significantly higher in Egypt and India (26% and 36%, respectively) in comparison with Chile and the US (4% each). However, the variation between the five countries is less in the rates of moderate forms of physical punishment. This illustrates that the limited amount of research about child abuse and neglect in developing countries does not imply less occurrence of child abuse and neglect. On the contrary, children in developing countries may be at higher risk due to high rates of poverty and political unrest in many of these countries.

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Root Causes of Child Abuse and Neglect

Child abuse and neglect result from the interplay of a constellation of factors in the victim, perpetrator, family, and society. The World Health Organization adopted the "ecological model" which identified the complex interplay of four risk factors that influence behavior. First are the individual characteristics of the victim and the perpetrator such as age, gender, education, substance abuse, childhood experiences of abuse, and personality traits. The second level is relationships with siblings, parents, and peers which might shape the victim or the perpetrator behaviors. The third is the community level, which is the social context within the neighborhood, school, and other institutions. These might include poverty, unemployment, social isolation, and high rates of drug addiction and alcoholism. The fourth level addresses societal factors such as the culture which accepts corporal punishment, gender inequality, and the use of violence in conflict resolution. Therefore, for every case of child abuse or neglect and in every culture, there is a complex interplay between protective and risk factors. The main challenge for professionals and communities is to determine how to exploit protective factors and control risk factors.

Case Presentation

A 10-week-old baby presented with a history of difficulty breathing, choking, and seizure 3 h ago. The baby was normal when the mother nursed her before she went to work 6 h ago. According to the father, he was trying to feed the child a bottle when she choked and had seizures. Father gave a history of the child slipping from his hand from a height of 1 ft into a plastic tub while he was bathing her. Physical examination showed a cyanotic infant with labored breathing and generalized tonic-clonic convulsions and a left parietal scalp swelling. No skin bruises were seen. Fundoscopy showed bilateral multilayer retinal hemorrhages. The patient expired after 4 days of ventilatory support and intensive care.

A non-contrast-enhanced CT of the brain showed diffuse cerebral edema, interhemispheric and peritentorial subdural hemorrhage, subarachnoid hemorrhage, bilateral cerebral contusions, left parietal scalp hematoma, bilateral temporal bone fracture and bilateral parietal bone fracture with comminuted fragment on the right, and separation of the lambdoid and coronal sutures (*Fig. 48.1*). Plain radiographs of the chest showed multiple rib fractures involving the anterior aspects of the right third to fifth ribs and the left third to seventh ribs with callus formation.

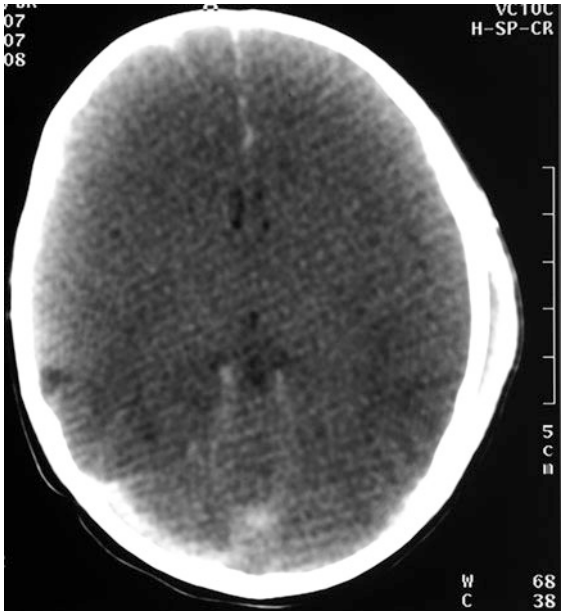

Figure 48.1
Non-intravenous contrast-enhanced CT of the brain showing diffuse brain edema with loss of gray-white matter differentiation, compression of the lateral ventricles, effacement of basal cisterns, interhemispheric and peritentorial subdural hemorrhage, subarachnoid hemorrhage at the cerebral convexity, and left parietal scalp hematoma

There are multiple posterior rib fractures on the left with callus formation involving the third to eighth ribs (*Fig. 48.2*).

The patient's history, physical exam, and radiologic findings are consistent with child abuse and fatal abusive head injuries.

Child Physical Abuse

Child physical abuse can be defined as the intentional use of force that results in physical injuries, including bruises, welts, cuts, burns, fractures, and internal injuries. It also may include shaking, deliberate poisoning, suffocation, drowning, and medical child abuse or factitious disorder by proxy.

Clinical presentation of child physical abuse ranges from normal physical examination to severe head injury and death. The main task in evaluating childhood injuries is to differentiate abusive from accidental injuries. This can be incurred from the location, size, pattern,

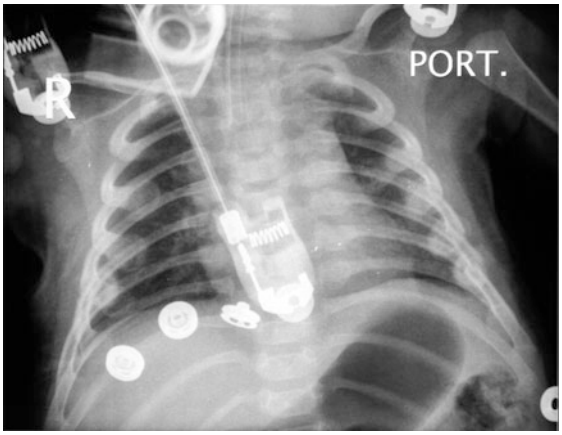

Figure 48.2
Plain radiograph of the chest showing multiple rib fractures involving the anterior ends of the *right* third to fifth ribs near the costochondral junction and the *left* third to seventh ribs with callus formation. There are multiple posterior rib fractures on the *left* with callus formation involving the third to eighth ribs

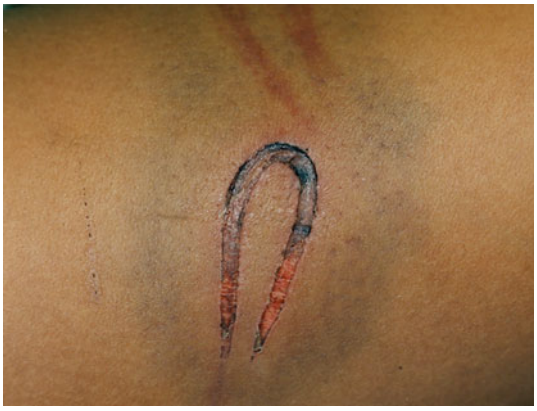

Figure 48.3
Large ecchymosis and loop bruise and burn on the thigh of a 9-year-old girl hit by her father

severity, possible force used, and the mechanism of injury. In addition, it is important to identify if the injury is developmentally conceivable for the child to sustain accidentally and whether the explanation by the caregiver is plausible.

Skin Injuries

Bruises are the most common presentation of child physical abuse. Bruises appear hours to days after injury. Color changes at different rates and different colors may be present in a bruise; therefore, it is not possible to date bruises based on the color. Bruises are also commonly found after accidental injury in mobile children. However, bruises are rare in pre-ambulatory normal infants. Therefore, any inadequately explained bruise in a nonmobile child should prompt further evaluation for child maltreatment, including a detailed history, careful and complete skin exam, a palpated exam for bony tenderness, and possible imaging.

The typical sites of accidental bruises are the bony prominences in the front of the body such as the forehead, nose, chin, elbows, knees, and shins. The history of an accidental bruise should be conceivable and compatible with the developmental abilities of the child. Injuries that involve soft tissue such as the eyes, ears, cheeks, neck, inner aspects of the arms, chest, abdomen, thighs, back, and buttocks are less common from accidents, and therefore more concerning for inflicted injury. Bruises may take the shape of the instrument used to inflict injury such as a hand, stick, cord, or belt (◉ *Fig. 48.3*). The caregiver's history of an inflicted injury may be vague or incompatible with the location, pattern, or severity of the injury.

Human bite marks are patterned injury typically 2–4 cm across that may include bruising, abrasion, laceration, or all of the above. The classic pattern is one of opposing semilunar marks composed of individual tooth marks. The bites of children typically leave impressions of both dental arches, whereas bites of adults often leave the impression of only one arch; however, this is not absolute. Bite marks should be photographed with and without a measurement standard and may help in forensic identification of the offender.

Accidental scald burns due to a spill of a hot liquid typically appear in a trickle-down or inverted triangle pattern, with the most severe burn at the point of first contact of the hot liquid with the body, and decreasing severity as the liquid flows in the direction of gravity and cools. The flow pattern of scald burns is influenced by the presence of clothing or diapers. Inflicted cigarette burns have a sharply defined "punched out" appearance and measure 0.8–1 cm, corresponding to the size of the cigarette (◉ *Fig. 48.4*). In contrast, accidental cigarette burns, resulting from the child running into a lit cigarette, have an ovoid or 'brushed' appearance resulting from the child's movement away from the hot stimulus, and generally do not have ulcerated centers. Inflicted burns may take the pattern of the inflicting instrument such as an iron, spoon, fork, or knife (◉ *Fig. 48.5*). Forced immersion burns may have a stocking-and-gloves appearance on the

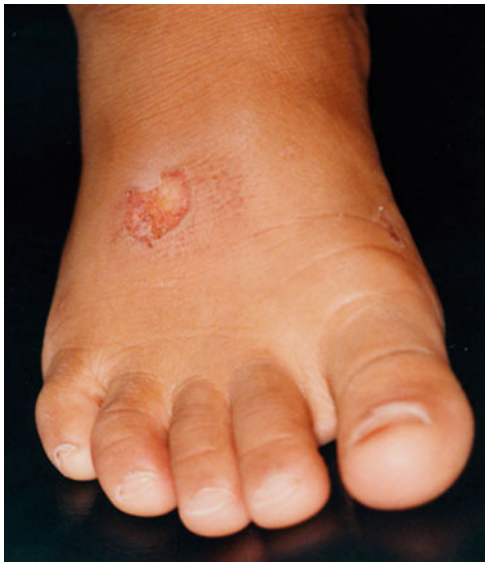

Figure 48.4
Three-year-old boy with a cigarette burn on the dorsum of the foot

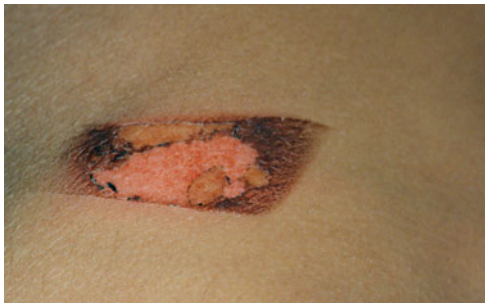

Figure 48.5
Hot knife burn on the thigh of an 8-year-old child punished by his mother for stool incontinence

extremities, or may spare flexor creases in the genital area. They produce a pattern of injury with more sharply demarcated proximal borders than accidental scalds, and the pattern of a flowing hot liquid typical of accidental scalds is absent or minimal.

Differential Diagnosis: Skin Injuries

There are many skin conditions that may be mistaken for inflicted injury. Accidental injuries (*Fig. 48.6*) must be distinguished based on appearance and plausibility of the history provided by the caregiver. Congenital skin lesions,

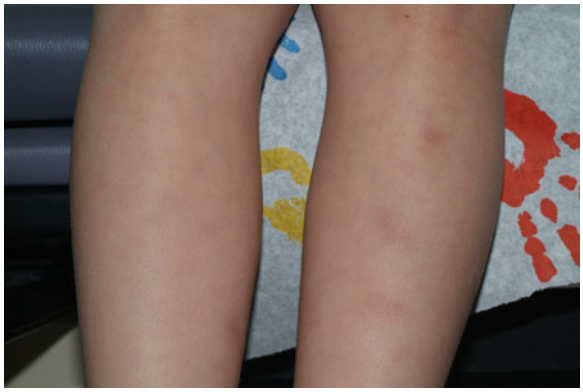

Figure 48.6
Legs of an active 3-year-old girl. Notice the multiple small bruises on her shins. Bruises are not patterned, consistent with the history of falling and are on bony prominences. Diagnosis: accidental bruising

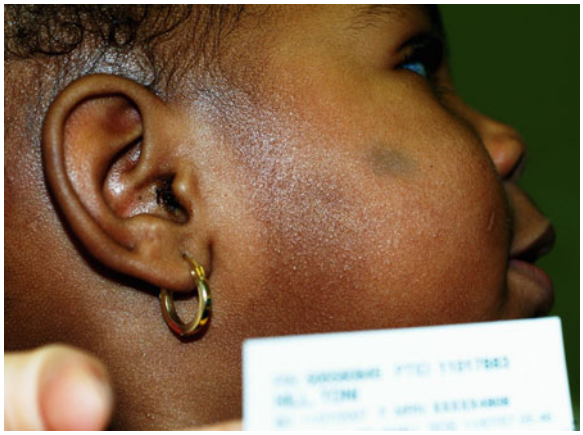

Figure 48.7
A child who presented for an evaluation of suspected abuse and had a hyperpigmented circular mark on her face. She had it since birth, is not tender and did not change in color. Diagnosis: Mongolian spot

such as slate gray nevi or Mongolian spots (*Fig. 48.7*) as well as hemangiomas (*Fig. 48.8*), may be mistaken for bruising. Bleeding diatheses, either congenital or acquired, may produce bleeding and bruising which seems out of proportion to the trauma history, or the patient may be lacking in any history of trauma. These may be distinguished by a careful bleeding history of the patient and family, concurrent symptoms, and laboratory testing if indicated. Skin infection such as bullous impetigo may be mistaken for cigarette burns; the phototoxic reaction

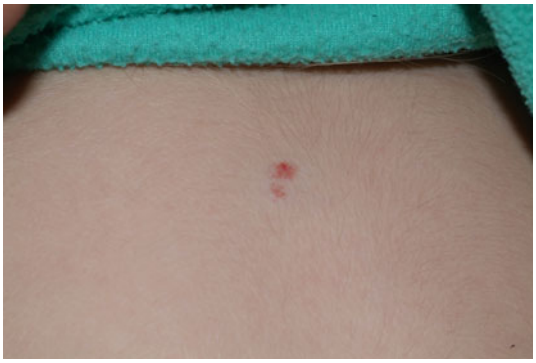

Figure 48.8
A child with a hemangioma on the back. It may be misdiagnosed as trauma and physical abuse

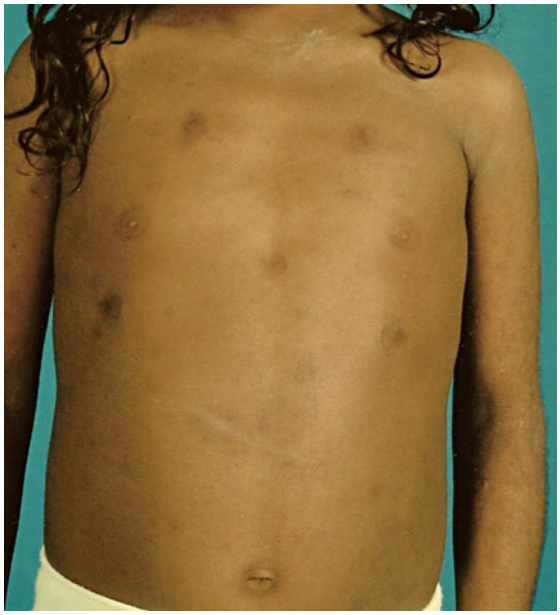

Figure 48.9
A child with multiple circular healed burns on the chest and abdomen. Diagnosis: Maquas (therapeutic burning) which involves using hot metal rods near an area of illness or pain (Photo courtesy of Hisham Nazer, MD)

phytophotodermatitis, resulting from sunlight exposure to skin after contact with psoralen-containing compounds, can also be mistaken for burns or bruises. Therapeutic cultural practices may produce skin findings that can be mistaken for bruises or burns inflicted with malicious intent. Coining (rubbing a coin over oiled skin) or cupping (applying a heated glass to the skin) may produce patterned ecchymoses or petechiae. Therapeutic burning practices may mimic inflicted burns. For example, Maquas (*Fig. 48.9*) involves placing hot metal or coals near areas of illness or pain, and moxibustion involves the burning of the herb moxa or mugwort at acupuncture points. Careful, nonjudgmental history and complete exam are usually sufficient to distinguish these conditions from abusive injury.

Fractures

There is no fracture type that is pathognomonic for abuse, and all fracture types can potentially result from inflicted injury. The diagnosis of inflicted fracture must therefore be made through careful correlation of the history provided by the caregiver with the child's developmental level and physical and radiographic findings. Although any fracture can be caused by abuse, certain patterns are strongly predictive of abuse. Classic metaphyseal lesions, rib fractures particularly posteriorly, scapular fractures, vertebral spinous process fractures, and sternal fractures all have a high specificity for abuse. Common, nonspecific injuries include subperiosteal new bone formation, clavicular fractures, diaphyseal fractures of long bones, and linear skull fractures. There are some fracture types and findings of intermediate specificity, which are concerning, but may be accidental if a clearly plausible mechanism is provided. This group includes multiple fracture, particularly when bilateral; fractures of different ages; epiphyseal separation; digital fractures; vertebral body fractures and subluxations; and complex skull fractures. Physical signs and symptoms of fractures may include swelling, tenderness, deformity, and limited range of motion with or without external bruising. The majority of fractures, both accidental and inflicted, are not associated with overlying bruising. Infants may present with irritability and/or not using the affected limb.

Classic metaphyseal lesions (CMLs), also known as corner fractures or bucket handle fractures, are highly specific for child abuse in children under 1 year of age. Metaphyseal fractures are the fracture type found most often in fatal child abuse cases, and are diagnosed most often in infants under 6 months of age. They represent a disruption of the primary spongiosa of the metaphyses under tension or shear mechanical loading. CMLs associated with subdural hematoma were first described by Caffey. The most common locations for CMLs are the proximal tibia, distal femur, and proximal humerus. CMLs can be easily missed because of subtle signs and

symptoms in the nonambulatory patients who sustain these fractures, and are often identified on skeletal surveys ordered due to other concerning historical or physical exam findings.

Rib fractures from accidental injuries are uncommon in young children, and when accidental rib fractures do occur, they are the result of high-force mechanisms, such as those involved in motor vehicle collisions. Posterior rib fractures in particular are highly specific for abuse (*Fig. 48.2*). Rib fractures may be identified incidentally when a chest film is taken for a respiratory problem or as part of skeletal survey for an infant with head injury. Infants with rib fractures due to abuse typically do not present with a history of trauma. In one study, for children younger than 3 years of age, the presence of a rib fracture had a 95% positive predictive value for child physical abuse.

A concern which is frequently raised is the possibility of cardiopulmonary resuscitation causing rib fractures. The published evidence indicates that rib fractures are exceedingly rare complications of CPR in children, seen in less than 2%, and that, when they do occur, they are likely to be anterior and not posterior rib fractures.

Long bone fractures are common fractures that have a low specificity for abuse. It is important to correlate the shape of the fracture line – transverse, oblique, spiral, or comminuted – with the described mechanism of injury. Spiral fractures have been strongly associated with abuse because of the torsion or twisting of the limb that is implied by this fracture morphology. Spiral fractures are more likely to be abusive in infants than in ambulatory children, but they commonly occur in accidentally injured mobile children, particularly of the femur, which has a relatively low injury threshold under a torsional mechanical load. Spiral fractures should not be considered innately more suspicious for abuse than other fracture morphologies; any long-bone fracture in a nonambulatory child is concerning and requires a plausible history to be considered accidental.

Skull fractures are relatively common after accidental falls in children; however, short falls typically result in simple linear fractures and are associated with a plausible history. In mobile children, the mechanism of injury may not have been witnessed, since they may have short periods of time out of the sight of a caregiver. However, they would have a period of crying or other behavioral indicator to the caregiver that the trauma had occurred. Fractures with a slightly depressed component may also occur from household falls if the fall is onto an object. Skull fractures are also commonly seen in abusive injury to the head, particularly in children under 2 years of age. No pattern of skull injury is diagnostic of abuse. However, diastatic, complex, or significantly depressed skull fractures are much more concerning for abusive injury and are caused by a greater degree of force than is associated with simple household falls.

The age of fractures can be helpful in assessing the plausibility of the fracture history, and multiple fractures of different ages raise the suspicion of abusive injury. Fracture healing manifests as periosteal reaction, also called callus, which is radiographically apparent after 10–14 days, and can be earlier in infants. Subperiosteal new bone formation can be a normal finding in infants under 6 months of age; as a physiologic finding, it is usually found along the shafts of long bones and is symmetrical on both sides of the body. A discrepancy between the history and signs of fracture healing is a red flag to initiate further scrutiny for child physical abuse. Skull fractures cannot be dated with accuracy.

Diagnosis: The Skeletal Survey

Skeletal survey is the standard diagnostic investigation when there is concern for physical abuse of infants and toddlers. It includes anteroposterior (AP) views of the extremities including feet, with the exception of the hands which are imaged in the posterioaterior view; AP and lateral skull; AP and lateral views of the thorax and oblique ribs; AP pelvis; and lateral views of the spine.

Differential Diagnosis: Fractures

In addition to accidental injuries, several bone diseases are considered in the differential diagnosis including rickets, bone infection, hypophosphatasia, and skeletal dysplasia including osteogenesis imperfecta (OI). History, physical examination, laboratory studies, and radiological findings will help identify medical causes of bone fragility. Differentiating OI from child abuse can be a challenge, but as in all forms of abuse, thorough patient and family history and concomitant findings are highly informative. The vast majority of patients who have bone disease increasing fracture susceptibility will have one or more laboratory abnormalities, abnormal-appearing bones on radiography, history of fractures with minor trauma, stereotypical morphologic features, or all of the above.

Osteogenesis imperfecta (OI) is a connective tissue disorder with a wide range of clinical severity, from pre- or perinatal lethality to only premature osteoporosis. Patients with OI have decreased bone formation and increased bone turnover. Ninety percent of affected

patients have a mutation in one of two genes for proteins in type I collagen. There are approximately two hundred genetic mutations that have been associated with OI. Clinical manifestations of OI might include blue sclerae, lucent teeth, hearing loss, easy bruisability, short stature, scoliosis, ligamentous laxity, and Wormian bones of the skull. The diagnosis of OI is predominantly a clinical one; no laboratory study is absolutely sensitive, but fibroblast culture from skin biopsy or DNA testing of leukocytes can verify the clinical assessment. Children with unexplained fractures are unlikely to have OI unless other features of OI are also present.

Abusive Head Trauma (AHT)

Abusive head trauma, previously referred to as "shaken-baby syndrome," is the most serious complication of child physical abuse and is responsible for about 80% of child abuse fatalities. It is predominantly a diagnosis of infancy, and is the leading cause of infant homicide in the United States. The term "abusive head trauma" is preferred because it reflects the various mechanisms or combinations of mechanisms which can produce inflicted head injury. Acute and long-term morbidities are high, and many patients end up with cerebral palsy, mental retardation, seizures, and visual loss. AHT can result from shaking or other causes of acceleration-deceleration and rotational forces, direct contact or impact forces, or combinations of these. The relatively large head size and weaker neck muscles make the infant more susceptible to injury from violent shaking. Analysis of information obtained from perpetrator confessions indicates that the shaking causing AHT is violent and is often repetitive, and is commonly triggered by caregiver frustration with infant crying.

Head injury may be the sole manifestation of AHT. However, it is often also associated with retinal hemorrhages, skeletal injuries, and/or cutaneous injuries. The patient may not have external signs of trauma. The presentation of abusive head trauma is often vague, nonspecific, and lacking in any immediately available history of trauma. Consequently, many cases are missed or misdiagnosed when they first present for medical care. Common presentations of abusive head injury in infants are altered states of consciousness, irritability, choking episodes, difficulty breathing or apnea, vomiting, and seizures. Children may also present with more indolent symptoms such as poor appetite, chronic vomiting, irritability, change in sleep pattern, and increasing head size after remote or repetitive episodes of trauma.

Subdural hematoma (SDH) is more common in AHT than other forms of extra-axial hemorrhages. Epidural hematomas are commonly present in accidental trauma. However, any type of extra-axial hemorrhage can be caused via an abusive mechanism, including subarachnoid, epidural, and intraventricular hemorrhage. The subdural space, between the arachnoid and dura mater, has bridging veins which cross this space, extending from the cortical surface into the dural sinuses. These bridging veins are torn during the abusive event, leading to subdural hematoma formation. The blood may spread into the hemispheric fissure and along the cerebral convexities. Many forms of intracranial injury can occur in cases of abusive head trauma, including cerebral contusion, axonal injuries, parencyhmal tears, and cerebral edema.

Retinal hemorrhages are often closely associated with abusive head trauma, though they are not universally present in these patients. Retinal hemorrhages have many possible causes, and are as a whole nonspecific. However, severe, bilateral, multilayer hemorrhages that extend to the periphery of the retina are highly specific for abusive injury when noted outside the neonatal period in the absence of medical disease or trauma history that adequately explains them. Retinal hemorrhages cannot be dated.

Diagnosis

The first step in diagnosing abusive head trauma is to include it on the differential diagnosis. This may not always occur due to the nonspecific nature of the presenting symptoms and often the absence of trauma in the history provided. Once concern for AHT is raised, CT scan is the preferred initial study for AHT because CT scans illustrate acute hemorrhage and skull fractures well, they are more readily available, require less time, and are more suitable for unstable patients. However, smaller hemorrhages and cerebral lesions can be missed on CT scans, which makes MRI the study of choice in subacute and chronic conditions due to its higher sensitivity and specificity. In comparison with large hematomas that cause symptoms due to mass effect, small subdural hematomas can be clinically silent and found incidentally. In addition, children with suspected abusive head trauma should have dilated eye examinations, preferably by a pediatric ophthalmologist; skeletal survey; and laboratory studies to include chemistry and blood count, urinalysis, liver and pancreas function tests to evaluate for occult abdominal injury, and screening coagulation studies.

Abusive Head Trauma: Differential Diagnosis

The differential diagnosis of abusive head injury is wide, and includes non-abusive trauma such as birth trauma, congenital conditions such as arteriovenous malformations, metabolic conditions such as glutaric aciduria type I, inherited or acquired bleeding diatheses, infectious causes such as meningitis or sepsis, and connective tissue disorders. The complete investigation of all of these entities in each case of suspected abusive head trauma would be not possible; fortunately, it is also not indicated. Patient and family history, clinical presentation, and associated findings should guide the clinician to those entities deserving of further diagnostic investigation.

Abdominal Trauma

Inflicted abdominal injuries are usually caused by blunt trauma resulting in injury to the liver, duodenum, pancreas, or bowel. The average age of children with abdominal trauma due to inflicted injury is 2 years. Symptoms may be vague or nonspecific and include vomiting, irritability, fever, and abdominal pain; therefore, clinical suspicion must remain high. Abdominal wall bruising is often absent. Delay in seeking medical care and the difficulty of diagnosis may lead to peritonitis, sepsis and death. The mortality rate in abdominal injuries is up to 50% and it is the second-leading cause of mortality from child physical abuse after head injuries.

Evaluation of Child Physical Abuse

Cases of abuse require strong skills and training in interacting with children and families. It is important to use non-leading questions when speaking with young children, who can be suggestible. It is also important to obtain the history from the child as well as each parent or other involved caregiver separately. That being said, the history taken in a case of suspected abuse is fundamentally the same as any good, thorough medical history. Good documentation is essential especially when the case is taken to court. Overall, maintaining a high index of suspicion and early detection is important in the evaluation and management of child physical abuse. Maintaining a trusted patient-doctor relationship is essential by emphasizing the role of a helper and a healer rather than a legal investigator. The main priorities are diagnosing and treating any injuries, protecting the child from further abuse, and meeting the child and family's needs. It is imperative to avoid premature accusation or judgment and seek help of a child abuse specialist when needed.

Treatment and Outcomes of Physical Abuse

Treatment of victims of child physical abuse depends on the nature and severity of the injuries. Protecting the child from further abuse is paramount along with the focus on addressing the underlying problems. In addition, removal of the child from his or her environment should be considered if it serves the best interest of the child, but should always be the last resort. Despite the seriousness of some of the physical injuries which can be fatal or result in severe disabilities, many of them will heal completely. However, it is the mental and emotional trauma that may have the most enduring effect and can result in long-term negative consequences including aggression, post-traumatic stress disorders, depression and anxiety, addiction, and other psychiatric conditions, as well as impaired attachment and chronic difficulty in relationships. Children who are physically abused are also more likely to accept and perpetrate violence in their relationships, as well as physically abuse their own children. Breaking this cycle of abuse requires appropriate mental health treatment of the child and the parent, and appropriate intervention to change the parent–child relational dynamic.

Child Sexual Abuse

Case Presentation

A 4-year-old girl is brought for medical evaluation because she was found naked in a bed with an unrelated adult male. She does not complain of pain, but appears frightened, clings to her mother, and says "the man hurt me." Her mother is concerned she may have been sexually abused, physically harmed, and can get an infection. How will you approach this patient? What are the physical and emotional manifestations of child sexual abuse, and what steps will you take for obtaining history, examination, diagnostic testing, treatment, and protection of the child?

Definitions/Classification

The World Health Organization has defined child sexual abuse and exploitation as the involvement of a child in sexual activity that he or she does not fully comprehend, is unable to give informed consent to, or for which the child

is not developmentally prepared and cannot give consent, or that violate the laws or social taboos of society. Child sexual abuse is evidenced by this activity between a child and an adult or another child who by age or development is in a relationship of responsibility, trust or power, the activity being intended to gratify or satisfy the needs of the other person. This may include but is not limited to:

(a) The inducement or coercion of a child to engage in any unlawful sexual activity
(b) The exploitative use of child in prostitution or other unlawful sexual practices
(c) The exploitative use of children in pornographic performances and materials

Rape is defined as forceful, penetrative sexual contact. *Sexual assault* refers to a broader collection of acts, including fondling and other non-penetrating acts and also is further refined in government codes. Other terms imply the relationship of the offender to the victim. *Incest* refers to sexual contact between family members, which is sometimes limited to immediate family but in other contexts can extend to fifth degree relationships (second cousin, once removed). *Sexual exploitation* generally refers to acts without sexual contact, such as having children pose for sexually explicit photographic or video images, having them witness sexual acts, internet solicitation, or by adults inappropriately exposing themselves to children, all for the sexual gratification of the adult. *Female genital mutilation* comprises all procedures that involve partial or total removal of the external female genitalia, or other injury to the female genital organs for nonmedical reasons.

Etiology

Child sexual abuse and sexual victimization are thought to occur because of several factors related to the behavior and mental status of the offender, the societal milieu, and the acceptance of sexuality and cultural history of violence toward women and children. Psychological harm occurs through direct emotional trauma and development of post-traumatic stress and later risk-taking behaviors in adolescence and adulthood. Physical harm occurs through tissue and organ trauma and infections with sexually transmitted agents.

Epidemiology

Although precise incidence data are lacking, sexual abuse of children occurs commonly throughout the world. In the USA, it has been estimated that one or more in four girls and one in ten boys will be victims of sexual abuse by the time they become adults. Similar or higher lifetime prevalence has been noted in Europe, Africa, and Australia. While boys are reported less often than girls, recent studies have suggested that the number of male victims may in fact be higher as a result of a reluctance to report cases among boys. The Canadian Incidence Study reported that confirmed sexual abuse reports involved 0.93 children per 1,000 in 1998. In the USA, the number of CSA victims, while rising during the late 1980s, actually declined during much of the 1990s and early into the twenty-first century. Cases declined from a peak of 144,760 cases in 1991 to 79,640 in 2006, with incidence rates declining from 2.2 per 1,000 children in 1990 to 1.1 per 1,000 in 2006. Early reports from professionals in countries associated with the United Kingdom noted lower rates (3 per 1,000), while later reports have rates similar to those in the USA. Reports from Asia, while limited, show smaller (but increasing) numbers.

Pathogenesis

Many cases of child sexual abuse follow a pattern of recurrent, escalating sexual contact with an offender in a position of authority to the child. A child is "groomed" for increasingly penetrative sexual contact beginning as fondling, then progressing to full sexual intercourse or sodomy. An offender who is known to a child and who victimizes the child over a period of time may pursue behavior to prevent detection and avoid physical injury, with repeated events of fondling or genital contact without full sexual penetration past the oral, anal, or genital openings.

Pathology

The most important determinant for indicating whether sexual abuse has occurred remains witness disclosure from the child, offender, and others. Most disclosures by children are delayed for weeks or more, and retrospective studies suggest that more than half are not revealed until adulthood, if ever. Most children have normal or nonspecific physical examinations. Physical findings diagnostic for acute sexual abuse are thought to be limited to acute lacerations or bruising of labia, penis, scrotum, perianal tissues, or perineum (Fig. 48.10). Laceration of the posterior fourchette or commissure not involving the hymen is also diagnostic of trauma. Acute ecchymosis,

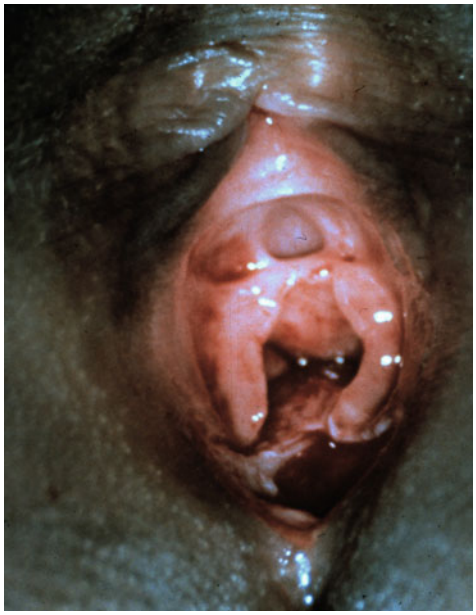

Figure 48.10
Infant with lacerated hymen, posterior commissure, perineum and vagina, with active bleeding. Exploration under anesthesia revealed posterior vaginal tear requiring surgical repair

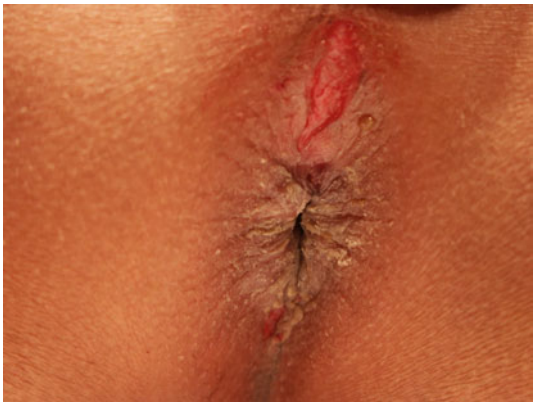

Figure 48.11
Superficial anal laceration affecting the anterior perianal tissues. Dried blood and forensic evidence present. No involvement of the external sphincter, rectum, or intestinal mucosa. No operative repair required

bruising, or laceration of the hymen and perianal lacerations extending deep to the external sphincter are also indicative, but rare case reports with unusual circumstances have been noted with accidental rather than sexual trauma (*Fig. 48.11*). A second category of diagnostic findings involves identifying residua of healed sexual trauma which can be difficult to interpret when the location, depth, and exact nature of the acute injury are not available for comparison. Healed lesions such as old hymenal transections, complete clefts to the vaginal wall in the posterior of the hymen, scars of the posterior fourchette or fossa navivularis, or missing segments of the posterior hymen are also diagnostic for prior sexual trauma. Untreated, sexually transmitted infections cause tissue and organ damage in patterns similar to but not identical with those found in adults.

Clinical Manifestations

Children can present with oral, anal, genital, or other physical injuries after sexual abuse. These can be mild to life-threatening. Most are brought for medical care with a disclosure of sexual contact, sexualized knowledge or behavior inappropriate for age, or physical symptoms indicating anogenital trauma or sexually acquired infection.

Differential Diagnosis

There are several medical conditions that can be confused with sexual abuse. Erythema and increased vascularity can reflect tissue irritation and inflammation associated with poor hygiene, chemical effects (urine, chlorine, stool, medications), self-manipulation, or nonsexual trauma. Irritation, coupled with the relative thinness of tissues, can lead to friability of the posterior fourchette or commisure and labial adhesions posteriorly, anteriorly, or both. Lichen sclerosis et atrophicus has been associated with easy tissue breakdown and genital bleeding. Accidental straddle injury causes replicable patterns of labial bruising and/or laceration over bony prominences with hymenal sparing. Hymenal and urethal opening size can vary widely in normal children without neurologic or urologic disease. Periurethral bands, intravaginal ridges and columns represent supportive ligaments and have bumps or mounds at their insertion. A linea vestibularis or "linea alba" is sometimes present in the midline and hypopigmentation of the labial or perianal tissues is usually unrelated to trauma. An annular hymen extends completely around the opening to the vagina while a crescentric opening lacks anterior tissue between

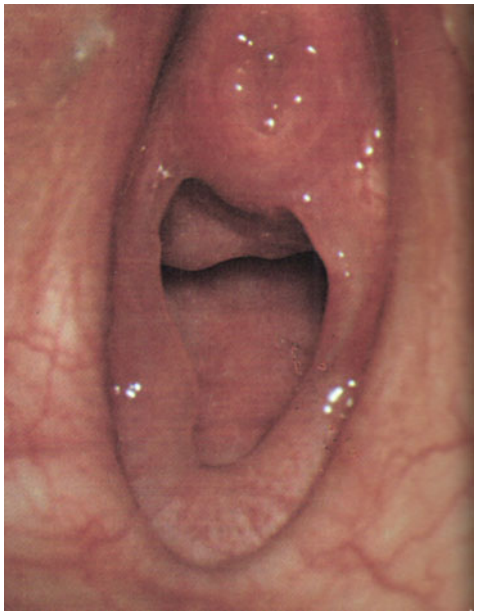

Figure 48.12
Normal female genital opening, with thin, almost translucent, hymenal tissue between 3 and 9 o'clock, fine vasculature, crescentric hymenal opening and normal labia, posterior commissure, and vaginal mucosa

10 and 2 o'clock (*Fig. 48.12*). Hymenal septa are present in 5–10% of girls at birth and can dehisce from their insertions spontaneously or with normal hygiene. Some girls have an imperforate hymen. Deep or complete hymenal notches or clefts at 3 and 9 o'clock in adolescents are normal findings, and those in the posterior hymenal tissue are difficult to interpret without knowledge of corresponding prior trauma. Posterior hymen width less than 1 mm has been considered an uncertain finding. Failure of midline fusion occurs when the external perianal epidermis appears to have remnant mucosal epithelium. Perianal venous congestion or pooling and flattened anal folds is normal or associated with constipation. A congenital absence of muscle tissue in the midline has been called diastasis ani. Children may have perianal skin tag formation associated with fissures and constipation.

Treatment

All sexually abused children should be referred for specialized medical and mental health assessment. Medical treatment for suspected sexual abuse includes obtaining medical history in a forensically sound manner, a comprehensive physical examination of extragenital sites, a noninvasive assessment for anogenital trauma, testing and treatment as indicated for sexually transmitted infections, and the collection of forensic trace evidence such as semen or sperm within 96 h of assault. Physicians should have familiarity with normal, nonspecific, and specific findings seen after sexual abuse. Examinations should not cause further trauma and should not be forced upon children. Specialized centers have been developed in several jurisdictions to provide these assessments while minimizing trauma to the child and family, enhancing prosecution, and providing supportive counseling. Children are typically examined while lying supine in the "frog-legged position." Any abnormal findings should be confirmed in the prone knee-chest position. For girls, the labia majora and minora are gently separated. Buttocks are separated gently to reveal the anus. In boys, the foreskin, if present, is gently retracted to reveal the glans penis and the scrotum and testes are palpated. The skin of the genitals and perineum are inspected. A dedicated light or otoscope should be used. A camera or colposcope can be used to record diagnostic, magnified images that can be simultaneously viewed by the child, caretaker, and examiner. In girls, penetrating genital injury can occur to the posterior vulva and hymenal rim, so these areas require careful inspection. Abrasions, bruising, and bleeding lacerations can all be seen in acute sexual assault and should be documented by diagram or photograph. Acute bleeding may warrant anesthesia and operative exploration or repair, but most children allow thorough examination without anesthesia or sedation if properly prepared. Although all sexually transmitted infections (STI) raise suspicion of sexual abuse, acquired HIV, gonorrhea, and syphilis are most diagnostic, whether or not there are other corroborating concerns. Specimens for STI and trace evidence are obtained using site-specific protocols and analyzed using procedures that are evolving. STI screening is not recommended in the USA, but should be obtained when:

(a) The child has signs or symptoms of an STI or an infection that can be sexually transmitted, such as vaginal discharge, genital itching or odor, urinary symptoms, or anogenital ulcers
(b) The suspected assailant is known to have an STI or be at high risk for STIs
(c) There is a sibling, another child, or adult in the child's environment who has an STI
(d) There is physical evidence of genital, oral, or anal penetration
(e) The child or parent requests testing
(f) The child is Tanner III or more advanced in sexual maturity rating

Prognosis

The outcome after child sexual abuse depends on the time to identification and treatment, number and severity of injuries produced, relationship with the offender, protection of the child from further harm, and other additional risk and protective factors. Children have improved prognosis when they are provided prompt, thorough, and compassionate care, appropriate supportive and long-term medical and mental health treatment, and protection from further victimization. Emotionally, many children will have little or no apparent behavioral effect acutely. Supportive parents (especially mothers), feeling safe and having access to resources are particularly protective. Some may experience the helplessness, secrecy and accommodation of the Child Sexual Abuse Accommodation Syndrome. Depression, anxiety, and post-traumatic stress disorder can affect all ages of children both acutely and over the longer term, with anxiety disorders, parenting and medical problems, and substance abuse and other risky behaviors becoming apparent in adolescence or adulthood. Treatment modalities (such as trauma-focused cognitive-behavioral therapy and multisystemic therapy) which directly address trauma and behavior problems and support certain coping strategies and family/peer relationships are most productive.

Prevention

David Finkelhor has noted that few studies have been done to assess the effectiveness of policy initiatives and laws intended to protect children from sex crimes by managing known sex offenders through restricting where they can live and work, how they are registered and monitored, and the length and terms of their incarceration. Prevention strategies that concern education programs for children, families, and youth serving organizations about how to prevent and respond to sex offenses and risky situations have been shown to reduce victimization but have not been universally supported by governments and practitioners.

Child Neglect

Case Presentation

A 16-year-old boy with cerebral palsy presented with severe malnutrition, weight loss, and hypothermia. His weight was 9 kg with a history of severe weight loss and missing medical and therapy appointments. He did not attend school for the past year. At the time of evaluation, his thigh was almost the same diameter as the urine catheter. This case illustrates physical neglect, medical neglect, and educational neglect. The family was assessed and it was determined that the mother was provided with the feedings through the insurance company. She had means of transportation and medical recommendations were conveyed to her multiple times previously. The child was placed in foster care and was admitted 6 months later for surgeries to release his contractures. At the time of this later admission, his weight had doubled and his spasticity had improved.

Definition

The establishment of a single, universal definition of neglect is challenging. Neglect has been defined as omission of care such as supervision or health care resulting in harm or potential harm to a child. However, a child-centered definition has been proposed which defines neglect as all circumstances where a child's basic needs are not met regardless of the contributor. Neglect is an act of omission rather than commission, and as such may be a more difficult form of maltreatment for the provider to diagnose. However, its effects on children can be among the most devastating.

Understanding the rights of children is a crucial point in understanding neglect. The Convention on the Rights of the Child was the first instrument to incorporate the complete range of international human rights as well as aspects of humanitarian law. The child's survival and development rights include rights to adequate food, shelter, clean water, formal education, primary health care, cultural activities and information about their rights. These rights require not only the existence of the means to fulfill the rights but also access to them. It is when any of these needs are not met that a child should be evaluated for neglect.

Etiology

Many factors contribute to neglect such as poverty, absence of community resources, parental characteristics (e.g., substance abuse, depression, intellectual impairment, domestic violence, unemployment, social isolation, and lack of education), and child related factors (e.g., prematurity, low birth weight, and disability) which

place additional demands on the caregivers and increase the likelihood of neglect.

Epidemiology

Neglect is the most prevalent form of child maltreatment in the US. As in other forms of child maltreatment, it is underreported. Neglect occurs worldwide and in all racial, educational and social backgrounds. According to United States data from 2007, an estimated 794,000 children were determined to be victims of child maltreatment. Of those, nearly 60% of victims suffered neglect.

Clinical Manifestations

The clinical manifestations of neglect vary depending on the type of neglect present, which reflect the various basic needs of a child that are not being met.

Physical neglect: Inadequate provision of food, clothing, shelter, and hygiene.

Medical Neglect: Caregivers may delay or fail to seek medical advice despite the presence of recognizable symptoms, they may not adhere to the healthcare recommendations, or they may refuse medical treatment. In diagnosing children with medical neglect, pediatricians should consider if the recommended care offers benefit to the child more than associated morbidity, the child is harmed or at risk of being harmed if the care is not provided, the caregivers understand the recommendations, and the health care is accessible but not used.

Educational Neglect: Children need to be in a learning environment that meets their specific needs whether at a school or through regulated home schooling. Neglect occurs when the child misses school with no satisfactory reason, or special educational needs are not met.

Supervisional Neglect: Failure to provide age-appropriate supervision, such that the child is placed at significant ongoing risk of harm.

Emotional Neglect: Failure to provide minimally adequate nurturance and affection or necessary psychological support.

Failure to Thrive, and Overweight: Both conditions have many etiologies and children need to be assessed carefully prior to diagnosing neglect. Most cases involve both psychological and nutritional problems, thus the classification into either organic or nonorganic is no longer used. These two conditions are discussed thoroughly in other chapters in this book.

Other forms of neglect may involve exposure of children to domestic violence, or encouraging them to participate in illegal activities.

Diagnosis

The same challenges that complicate the efforts to derive a clear and universal definition of neglect, also confront the provider in making the diagnosis. When evaluating children for suspected neglect, a thorough evaluation should be conducted to identify the child's needs that are not met, harm or potential harm resulting from neglect, and evaluation of the family for contributing factors. One should also ask if the family comprehends the needs of the child especially in children who have special needs due to a medical illness or disability. One also needs to assess if the family has the means and resources to meet the child's needs and if these needs were addressed properly by health care providers and necessary referrals and education provided to caregivers.

Prognosis

Neglect has been associated with substantial morbidity and mortality. The impact depends on the type of neglect, severity and the age of the child when it occurred. Adverse effects include behavior problems, academic underachievement, and cognitive deficits. Neglect is also associated with adverse effects on physical and mental health that can persist into adulthood.

Treatment

Health care providers should screen for risk factors for neglect and try and prevent neglect prior to its occurrence. A multidisciplinary approach with parental education, close clinical follow-up, home visitation programs, and referral to appropriate mental health and community services may help in amelioration and prevention of neglect. Individualized response taking into account the unique situation for each family is crucial for effective neglect intervention.

Prevention of Child Maltreatment

Preventing child maltreatment is resource-intensive and complex. This is, in part, due to the multifactorial nature

of child abuse. Public health approach to prevention (primary, secondary and tertiary) provides a structured approach to curtail the incidence and prevalence of child physical abuse. Primary prevention is directed toward the whole population and based on increasing the public awareness about child abuse, its indicators, consequences, normal child development, rearing practices, alternatives to corporal punishment, and anger control strategies. It also includes teaching children social skills and self-protection strategies without deemphasizing adults' primary responsibility for child protection. Secondary prevention focuses on families and children at risk of abuse such as single parents, poor socioeconomic status, and children with history of prematurity or disability or behavioral problems. Tertiary prevention is based on the response to victimized children and their families. It includes providing multidisciplinary child-centered services to meet the medical, social, psychological, and legal needs of children and their families. It also incorporates providing services for the victims and putting child protection laws and policies in accordance with the principles and the legal framework as outlined in the Convention on the Rights of the Child.

Consequences and Outcomes of Child Abuse and Neglect

Child maltreatment is a complex social problem with medical, mental, legal, and societal ramifications. The short and long-term impact of CAN is linked to several factors such as the child's age, the severity, frequency and duration of abuse, and the relationship of the perpetrator with the child. In addition, consequences are linked with the resources available to the family and the extent of treatment and rehabilitation of the child and family.

Younger victims of CAN are at more risk of developing serious mental disabilities. Extensive research indicates that prolonged and intense stress, especially during the brain's sensitive development period in early childhood, can lead to lasting changes in the central nervous system anatomy, physiology, and function. Long-term consequences of child abuse can include mental, behavioral, and psychological disorders such as mental retardation, psychosomatic disorders, poor school performance, addiction, risk-taking behavior, alcoholism, drug abuse, chronic anxiety disorders, depression and suicidal attempts, aggressive behaviors, and criminal acts which perpetuate the cycle of violence.

Several studies of the effects of adverse childhood experiences in adulthood document the increased risk for major causes of death such as coronary heart disease, diabetes, and hypertension among victims of child maltreatment as far as 50 years after the occurrence of abuse. This has been shown in the Adverse Childhood Experiences (ACE) study, from which numerous publications have been derived. A recent study found a significant link between child maltreatment and increased rates of poverty and unemployment.

However, in sharp contrast with the gloomy picture depicted by the aforementioned consequences, it is possible for maltreated children to recover and go on to lead happy and productive lives. Such resiliency is probably related to genetic factors and the presence of supportive circumstances such as supportive non-abusive adults, stable social and economic circumstances, and early intervention. Resiliency is currently the subject of intense research to improve the understanding of the phenomenon and to utilize it in the treatment of abused children.

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49 Global Perspectives on Child Development and Behavior

Ilgi O. Ertem · Vibha Krishnamurthy

Developmental Difficulties in Low- and Middle-Income Countries

The majority of the world's children live in low- and middle-income (LAMI) countries as defined by the World Bank. There is still unacceptable disparity between high-income and low- and middle-income countries with respect to indicators for child survival and health. Equally unacceptable is the disparity between countries in the range of supports that are given to children to optimize their developmental potential, and to prevent, detect, and intervene with developmental difficulties. Despite the fact that the United Nations Convention On The Rights Of The Child calls for countries to not only assure child survival, but also to support child development, an estimated minimum of 200 million children in low- and middle-income countries are not reaching their optimal developmental potential due to preventable causes. "Developmental difficulties" including problems in the areas of cognitive, language, social-emotional, behavioral, or neuromotor development will be used in this chapter in place of terms such as developmental disability, or developmental disorder. Approximately 10–20% of individuals around the world have developmental difficulties, most of which are preventable.

Health-care providers in LAMI countries have longstanding experience in combating childhood illness and mortality. The prevention, early identification, and management of developmental difficulties in childhood, however, are new challenges. Nevertheless, there is a wealth of information on this topic, which has been generated by researchers and clinicians working in resource-poor conditions. This chapter will provide information that is specific to low- and middle-income countries on: (1) Prevalence of developmental difficulties and risk factors that impinge on optimal child development; (2) Methods of early identification, assessment, and classification; and (3) Examples of interventions for developmental difficulties in low- and middle-income countries.

Prevalence of Developmental Difficulties and Risk Factors That Impinge on Optimal Child Development

Globally, the rates of developmental difficulties are higher than any other chronic morbidity and developmental difficulties are considered among disease control priorities in LAMI countries. There has been at least 3 decades of research on the prevalence of developmental difficulties in LAMI countries but the exact prevalence is unknown in most countries. This is due to the difficulties in conducting epidemiological studies and the lack of international standards for common definitions and population-based methods of appropriate detection. It is estimated that a minimum of 15–20% of children in LAMI countries experience developmental difficulties, with highest rates in populations where malnutrition and chronic illness such as HIV/AIDS is more prevalent.

Every condition that poses a risk for child survival may also be a risk factor to child development and conversely, factors that threaten child development are often risks to the survival of children. Clinicians and policy makers in LAMI countries need to know which risk factors require intervention at various times throughout the life cycle. Risk factors that can hamper optimal development and that need to be addressed across the life span include: physical and mental health impairments of parents or caregivers; deficiencies in the social and economic environment (including inadequate nutrition, safe housing, inadequate hygiene, lack of wages and jobs for caregivers, gender inequality, low caregiver education, inappropriate child care resources, lack of preschool opportunities and schools, inadequate access to health care and trained health-care providers), exposures to environmental toxins, and exposure to violence, war, and natural disasters.

During the pre-conceptional period, children's developmental outcomes are influenced by young and advanced maternal age, parental consanguinity, problems or deficiencies in maternal health and nutrition,

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inadequate birth intervals, and unintended pregnancies. During the perinatal period, asphyxia, low birth weight, prematurity, perinatal complications including preventable infections such as tetanus, and congenital abnormalities have a significant impact on child development. Maternal mortality, also not uncommon in LAMI countries, is a grave condition that jeopardizes the survival and development of the child at any age. Maternal depression is a prevalent and important risk for the survival, health, and development of the child during the neonatal and early infancy period, as are neonatal complications, neurological insults, and sensory impairments. During infancy and early childhood, malnutrition, iron and iodine deficiency, lack of appropriate child care and preschool programs, frequent acute health problems, chronic illness, inadequacies in nurturing and stimulating qualities of the home or living environment are risk factors that have adverse developmental and behavioral consequences. School-aged children are placed at additional risk from child labor, inadequate schooling and, particularly for girls, early pregnancies.

Methods of Early Identification, Assessment, and Classification

In LAMI countries, despite the overwhelming demands of large populations and poverty, the infrastructure to support child development within the health-care system is often present. For example, India has the world's largest integrated early childhood development services with the goal of improving the health and development of children and families. This system has been operational since 1975, functions in thousands of centers and covers millions of children and mothers. In Turkey, the government staffs local health-care facilities with physicians, nurses, and home-visiting midwives; these are located at a village level throughout the country. In some countries such as Azerbaijan and Georgia for example, widespread accessible health care to children is provided not by general practitioners but by pediatricians. Therefore, the health-care system in many countries can have a crucial role in promoting child development and the prevention, early detection and management of developmental difficulties. There are however, barriers within the health-care system that make the early identification process difficult. First, continuity in care (receiving health care continuously by the same provider), a crucial first step in delivering developmentally appropriate health care, may be absent in LAMI countries. Second, even if a child is followed by the same health-care provider, the amount of information, support, and intervention this provider can deliver will depend on his/her training and experience in providing guidance about child development concepts. Research indicates that health-care providers in LAMI countries do not have adequate training and experience in the prevention, early detection, and management of developmental difficulties in young children.

The third and perhaps most important barrier to early identification is the inadequacy of standardized methods and tools for the early detection of developmental difficulties across countries. Language, social-emotional, cognitive, and behavioral development and functional capacity have become essential components of instruments that aid clinicians in early detection. Developmental monitoring now emphasizes the importance of caregiver–clinician communication and partnership. The recent emphasis on family-centered care has changed the approach from models in which a parent watches while a clinician "tests" the child to models in which a caregiver and clinician use instruments to "talk" about the child's development and to build a joint understanding. Studies suggest that caregivers and health-care providers in LAMI countries may not be well equipped with knowledge about early childhood development, and, therefore, the need for standardized developmental tools is even more important than in high-income countries. However, developmental monitoring must not be based on a mere "screening approach." Developmental "surveillance" or "monitoring" should incorporate an understanding of risks and protective factors and methods for monitoring and support of the development of all children within a health-care system with direct links to available interventions. The following factors must be considered by health-care providers when choosing a method for developmental surveillance or monitoring in LAMI countries:

- Low caregiver education and literacy limit the use of written caregiver-completed questionnaires.
- Evidence suggests that reliance solely on caregiver concerns or checklists about milestones may not be sufficient to identify developmental delays. In populations where many children have delayed development, caregivers may not have a reference as to how children should typically develop. Furthermore, caregivers may not readily express concerns or admit that their child has not reached a certain milestone if they receive health care only sporadically, or do not receive their health care from the same trusted health-care provider each visit, do not believe that interventions exist, or are concerned about stigma related to developmental difficulties.

- The alternative reliance on "child testing" methods that involve direct elicitation of developmental skills by skilled professionals is neither practical nor desirable in LAMI countries. It is difficult and time consuming to elicit the optimal developmental functioning of young children during health-care visits. Testing of the child most often leaves the caregiver "watching" rather than participating in the evaluation, and, therefore, does not capitalize on the partnership of clinicians with caregivers. Caregivers do know their children best and, may be the key resource to support children's development, even more so than in Western countries. Furthermore, objects are often needed to elicit skills and the cleanliness of such objects may be a major concern in developing countries.

There have been two contrasting approaches to the selection of a population that constitutes a normative sample for a standard reference. In the United States, most studies involving cognitive assessment tools have been conducted on population-based samples that do not exclude children with health conditions that pose risks to development. LAMI countries have much higher rates of health-related problems that increase the likelihood of developmental difficulties, necessitating a different approach to standardization. The World Health Organization (WHO) recommends that in populations with a high prevalence of conditions that are hazardous to child health and development (such as malnutrition, low birth weight, chronic infections including HIV/AIDS, parasitic infestations, iron deficiency anemia, and perinatal complications) references for monitoring growth and development should be based on what the WHO refers to as a "prescriptive sample" of healthy, thriving children without these risks rather than geographic whole-population-based references. This approach was applied by the WHO in the construction of the newly launched WHO International Growth Standards and the WHO Motor Development Study. These studies have demonstrated that when child health is optimal, child growth and motor development are similar across countries with diverse backgrounds and one universal standard can be constructed. Conceptually, based on innate biological and psychosocial processes, children from different ethnic, geographic, or cultural backgrounds appear to have enough similarities in functional development that one standard can be constructed, at least for young children. The "prescriptive sample" approach is being used in LAMI countries as exemplified by the standardization studies for instruments developed in Argentina and in Turkey. In summary, the method used for developmental monitoring in LAMI countries should ideally be: (a) family centered; (b) scientifically reliable and valid for use in various cultures; (c) brief, user-friendly, easy to learn and administer, and require minimal documentation procedures; (d) be standardized using a prescriptive sample; and (e) linked seamlessly to systems of service delivery and support for identified difficulties. An example of such an instrument is the Guide for Monitoring Child Development (GMCD) which has been initially developed in Turkey and that is currently undergoing international standardization.

Similar to high-income countries, pediatricians and other primary health-care providers are predominantly responsible for the assessment, diagnosis, and referral to services for young children with developmental difficulties. Although LAMI countries may not have the infrastructure and resources for the multidisciplinary evaluations that are conducted in high-income children to diagnose developmental difficulties, the family-centered principles of a developmental assessment apply and can be adopted to all such clinical encounters around the world. Research on developmental assessment in LAMI countries has mostly been restricted to the use of specific instruments. Cognitive assessment tools have been the most frequently studied components of a developmental evaluation. Although to a very limited extent, a range of key components have also been studied in LAMI countries including the developmental interview, assessment of nurturance and stimulation in the home environment, family competence and social support systems, family mental health, functional development of the child, and language development. Universal systems and guidelines for developmental assessment that are supported by current scientific information and conceptualizations of child development are essential to improve the care of children in LAMI countries.

Research from LAMI countries on classification systems for young children with developmental difficulties is almost nonexistent. Internationally endorsed classifications are necessary to facilitate and advance communication among clinicians, researchers and policy makers as well as to advance clinical conceptualization, assessment, and formulation. Classification systems that can be used for young children with developmental difficulties do exist. The International Classification of Diseases (ICD), Diagnostic Statistical Manual of Mental Disorders (DSM), Diagnostic Classification of Mental Health and Developmental Disorders of Infancy and Early Childhood Revised (DC 0–3 R), and the World Health Organization International Classification of Functioning Children and Youth (ICF-CY), all offer promising approaches to the classification of developmental difficulties in children. The ICD-10 is a disease-oriented categorical approach, although some

codes do reference environmental/contextual aspects of child development. The DC 0–3 system offers a closer focus on the child–caregiver relationship than the DSM system, but both systems are limited to mental health disorders and do not address other developmental disabilities. The WHO promotes the use of the ICF-CY system alone or in conjunction with the ICD system in the classification of childhood disability across the world. The ICF-CY system is ideal in that it offers an approach that overlaps with the bioecological theory of child development and current concepts in developmental interventions. The ICF system classifies the following parameters for a given child: body structures, body functions, activities and participation in community and daily life, and environmental contextual factors such as family and home environment and community attitudes and services.

Examples of Interventions for Developmental Difficulties in Low- and Middle-Income Countries

1. *Community-Based Rehabilitation (CBR)* was introduced by the WHO in 1980s as a strategy for improving the quality of life of disabled people and their families around the world. By definition, the CBR aims to move away from center-based, or institution-based, specialist-based care of disability and move toward the building of local knowledge and practices to address the special needs of people with disabilities within the community. Since its introduction, CBR has been widely applied in many parts of the world for people of all age groups. The CBR also has been used as an intervention strategy for children with developmental difficulties and their caregivers. As defined by the WHO: "Community-based rehabilitation currently in practice in more than 90 countries around the world is a comprehensive strategy for involving people with disabilities in the development of their communities." CBR seeks to ensure that people with disabilities have equal access to rehabilitation and other services and opportunities – health, education, and income – as do all other members of society. The target populations are people with disabilities, families of people with disabilities, communities, Disabled People's Organizations, local, regional, and national governments, international organizations, nongovernmental organizations, medical and other professionals, business, industry, and private sector. A wide range of activities is included beyond medical care and rehabilitation. These are promoting positive attitudes toward people with disabilities, preventing the causes of disabilities, providing rehabilitation services, facilitating education and training opportunities, supporting local initiatives, monitoring and evaluating programs, supporting micro- and macro-income-generation opportunities. WHO is supporting United Nations member states in developing guidelines for CBR, conducting regional and country workshops to promote CBR and the guidelines, supporting member states to initiate CBR, and/or strengthening existing CBR programs. Despite the fragmented nature of the research on CBR, this model holds a promising venue to be used as an intervention approach to developmental difficulties in children.
2. *WHO/UNICEF Care for Child Development Intervention (CCDI)* developed by the World Health Organization Department of Child and Adolescent Health and Development and UNICEF, uses the window of opportunity that arises when the child comes in contact with the health-care system. The CCDI is a standardized interview, which assesses how the caretaker plays with and communicates with the child. Observations and intervention strategies offered to parents during the interview include listening to caregivers and giving specific reinforcement for ways they support their child's development; observing for positive interactions between infants and caregivers during the health-care visit; using basic homemade toys to facilitate interactions; pointing out responses of the infant and the role of the caregiver in eliciting these responses; and providing ideas for age-appropriate stimulation. Health-care workers then explore with the child's caregiver the potential for such interactions in the home; discuss obstacles that caregivers may face to help the child develop; and ways they can overcome these obstacles. The intervention can be delivered anywhere and adds approximately 10 min to the health visit. The training period is approximately 1.5 days. Training materials, comprising of workbooks and videotape for facilitators and trainees have been tested in the field and have been revised by the WHO and UNICEF to be used globally.
3. *Training of health-care professionals on child development and developmental difficulties: Turkey.* Over 2 decades, Ankara University School of Medicine Developmental-Behavioral Pediatrics (DBP) Unit has been collaborating with the Turkish Ministry of Health, the WHO, and UNICEF, to develop training programs for health-care clinicians on child development and children with developmental difficulties. As a result of

these collaborations, training programs have been developed for health-care clinicians at different levels, including general practitioners, home-visiting nurses/midwives, pediatricians, and developmental-behavioral pediatricians. The content of the training programs includes concepts and theories of ECD starting from pregnancy to preschool years, risks to optimal development, ways to decrease risks, preventing developmental delay, common psychosocial problems, techniques for developmental monitoring and for supporting child development, early identification of children with developmental delay, services for children with developmental difficulties, and community resources available for early intervention and rehabilitation. All training methods are interactive, experiential, and problem based. Materials include a book in Turkish on developmental-behavioral pediatrics, DVDs with slides presentations, local video recordings of children and caregivers demonstrating typical development and case scenarios for developmental difficulties. When introduced in a form that is appropriate to the context of their ongoing work, health-care professionals are highly motivated to take on as their mission the promotion of early childhood development.

4. *Training of community workers on child development and developmental difficulties: India.* Ummeed Child Development Center began in 2001 as a not-for-profit center to provide services for children and families with developmental disabilities. Initially, the organization was to provide interdisciplinary care, in a family-centered approach, to children with disabilities. As the center grew, it was evident that providing services to approximately 1,200 families per year was not even addressing the needs of Mumbai, leave alone the country. At current WHO disability estimates, Mumbai alone has 650,000 children with developmental disabilities. Further, children who are at high risk for developmental difficulties are often from families with no access to services.

Most young children in India do not receive routine health care from a physician. However, in many parts of the country, the government's Integrated Child Development Scheme provides services to children under five through anganwadi workers. In addition, there are hundreds of voluntary organizations working with young children in community-based programs. The workers within these organizations are a vital and already existing link to the community. Ummeed designed the Child Development Aide training program to give these individuals the skills to identify and intervene with children at risk and to promote good child development practices for all children.

Professionals from Ummeed, other parts of India, and around the world designed the course curriculum. The emphasis was to develop transdisciplinary community workers who would view the child and family as a whole. The curriculum's focus is the "transactional model" of child development with a family-centered approach to interventions for child development. The pilot project with ten trainees began in July 2009 with funding from USAID.

The trainees are chosen from organizations with a commitment to child development and disabilities and a willingness to support the candidate financially for 6 months. Because trainees are expected to return to the parent organization and train or influence their coworkers, leadership potential is an important factor in selection. After the 6-month training, the CDAs meet every month for 1 year for peer support and mentoring, facilitated by a professional at Ummeed. Future plans for scaling up include a "Train the trainer" program that will equip other organizations to run the CDA training program.

Case Vignette

Rashi works in the Mumbai-based Muktangan School, where most of her students are from the nearby Worli slums. She was chosen for the CDA training program when the school realized that 10–20% of the children enrolled had developmental difficulties, which they did not know how to address. One of her students is Eureka, a 5-year-old girl who lives in an orphanage. Since her arrival, Eureka had struggled with class work, and her teachers did not know what to do with her. They knew she had albinism, but they were puzzled by her inability to talk. She had no interest in playing with other children or communicating with her teachers. She wandered about the class all day, unable to do more than scribble on paper. The orphanage attendant told the teachers she was difficult to feed and mostly just drank milk out of a bottle. Rashi, who had just completed her CDA training, recognized that Eureka's development was like that of a child perhaps half her age. Tailoring her approach to this understanding, she began by guiding Eureka's class teacher on how to engage her in play and to develop communication skills. She asked the teachers to place Eureka's favorite foods and toys within sight but out of reach. She then encouraged Eureka to point to things she wanted. Next Rashi worked on helping the teacher make Eureka more a part of the class by sitting close to the teacher and helping her with simple errands like distributing worksheets and erasing the blackboard. During snack time, Rashi demonstrated to the orphanage attendant ways to encourage

Eureka to try new foods, and soon Eureka was eating with the other children. When Rashi found Eureka had been prescribed glasses but was refusing to wear them, she asked the attendant to bring them to school and convinced Eureka to wear them. Eureka is now an important part of her class. Her friends know her and greet her enthusiastically every morning when she arrives. The teachers and her classmates understand her many gestures, and she is speaking more. Most important, she loves to play with her friends and her teacher, and initiates her favorite games whenever she can. Rashi meets her for one-on-one sessions in the school's resource room to work on her IEP goals, which she has designed along with the class teacher and the orphanage attendant.

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50 Children in Disasters

David J. Schonfeld · Robin H. Gurwitch

Introduction

When disasters strike, children are one of the most vulnerable populations affected. The impact of a disaster on an individual child depends on a number of interrelated factors: the nature of the disaster itself including the extent and breadth of damage, loss, and disruption experienced by the child; the socio-emotional impact of the event on the child and family; the disruption of the child's extended support system; and the child's skills in coping with stressful experiences as well as the ability of the family and community to provide appropriate support to promote the child's recovery. In addition to the initial impact of the disaster, the effect on children is also exacerbated by secondary stressors and losses that result from the event and any delays in the recovery of the community and family. This chapter will begin by briefly reviewing a few selected findings from preclinical and clinical research on the impact of stress during critical periods of brain development in animals and humans that have implications for understanding the importance of early interventions for children in the aftermath of a disaster. Findings based on clinical experience and epidemiological research regarding the impact of disasters on children will be summarized and practical recommendations about how to address children's needs within clinical pediatric settings will be offered. Finally, as the acute and ongoing behavioral and mental health needs of children during the aftermath of a disaster are highly likely to exceed the capacity of clinical programs, attention will be given to the unique context of school settings as an important venue for both the identification of needs and the delivery of brief, supportive interventions to promote adjustment and recovery.

Implications from Preclinical and Clinical Research

From an extensive preclinical and growing clinical research literature on the impact of stress on young children, three findings will be highlighted: (1) Stressful situations, if not overwhelming, can promote development and learning. (2) Chronic stress during periods of brain development can lead to permanent changes in brain function and structure. (3) Parents and other caregivers play a key role in determining whether stress promotes or impairs children's development.

Stressful situations, if they are not overwhelming to the young child, can promote healthy development and learning. Indeed, all learning involves presenting novel situations or information. Research has shown that the removal of infant rats from their mother for brief periods of time for gentle handling by lab personnel does cause some distress for the infant rats, but if the infants are effectively nurtured and supported through this experience by their mothers when they are reunited, the rats are better able to tolerate subsequent stressors – they become less fearful in novel environments and more capable of learning in a laboratory model. This is good, since this is what humans do to their young. Preschool and early elementary school attendance can be viewed as such a brief separation that is hoped to enhance children's ability to learn.

Chronic stress leads to changes in brain function and structure. Gunna, Herrera, and Hostinar summarized findings from animal studies that show that severe early life stress leads to inhibition of neurogenesis, disruption of neuronal plasticity, neurotoxicity, and the development of abnormal synaptic connectivity. Young, developing brains are particularly vulnerable to these effects of stress hormones. As a result, uncompensated and chronic stress during critical periods of development increases the risk of difficulty in adjusting to stressful events later in life. In addition, animal models have shown that such chronic stress leads to changes in brain circuitry that limits subsequent learning and effective decision-making. Research involving children is also beginning to document comparable findings linking uncompensated and chronic stress (e.g., chronic abuse and neglect) to changes in brain structure and function.

The Adverse Childhood Experiences (ACEs) studies conducted by the Centers for Disease Control and Prevention and Kaiser Permanente found that the more ACEs children experience, the greater the risk for medical complications during adulthood, including heart disease, cancer, diabetes, liver disease, and emphysema. Contrary to

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folklore, stressful life experiences during childhood do not necessarily make children stronger or better able to cope with life, but in fact may result in increased morbidity during adulthood. Disaster exposure is a significant adverse childhood experience which adds to the cumulative exposure of adverse childhood experiences.

These findings underscore the need to protect young children from stressful situations as much as possible, intervene quickly after stressful events occur that impact children, and pay particular attention to subsequent stressors that may occur in the lives of children who have already been victims of disasters. It also should lead those in education to become concerned about the impact of stress on learning and to place greater emphasis on helping children impacted by disaster adjust in order to promote subsequent learning.

Parents and other caregivers play a key role in determining the difference between stress that promotes development and that which impairs development. In one set of experiments with rats described by Arie Kaffman, the investigators took advantage of the normal distribution of maternal nurturing behavior. Some rat mothers provide a much higher level of licking and grooming to their infants, and some mothers provide much less than average. Compared to infants raised by mothers that provided less of this nurturing behavior, infants raised by mothers that provided a higher level of licking and grooming were less fearful, less reactive to stressful situations, and performed better on several tasks that were felt to be dependent on the optimal functioning of the hippocampus. In a similar manner, data from a cohort from the National Collaborative Perinatal Project was used to demonstrate that the degree of maternal affection provided to human infants at 8 months of age, as measured by observations of maternal behavior during cognitive and developmental testing in a laboratory setting, predicts emotional distress in later adulthood.

It appears that this high frequency of nurturing behavior in rats during a critical period of brain development is necessary for removal of DNA methylation from the promoter element of DNA that controls the expression of the glucocorticoid receptor in the hippocampus. This in turn controls the rate by which the release of corticosterone in the rat after a stressor is terminated. Rats raised by mothers who were nurturing, in this model, had higher rates of expression of the glucocorticoid receptor in the hippocampus and therefore had shorter periods of exposure to corticosterone after stressful situations. Of particular interest, once established, this pattern of DNA methylation is stable. In this way, an epigenetic phenomenon can explain how early parental nurturance can result in less stress reactivity later in life. Research involving postmortem analysis of human brains from adults who died by suicide showed that those with a history of early life adversity had lower levels of glucocorticoid receptor messenger RNA in their hippocampus and higher levels of DNA methylation in the same promoter region found in the rat model.

Joan Kaufman and Dennis Charney showed that maternal rats respond with increased licking and grooming of their infants when reunited after brief separations; as already noted, this nurturing helps the infant adjust to the possible stress of such brief separations and results in positive infant outcome (i.e., less stress reactivity). When infants are instead removed from their mothers for prolonged separations, their mothers do not compensate when reunited for the prolonged separation through increased nurturing, but instead demonstrate lower rates of nurturing when subsequently reunited with their infants and the infants develop a negative outcome of more stress reactivity. If the infants assigned to the prolonged separations were then cross-fostered to other mothers that had been assigned to the brief separations condition, these "nurturing" mothers provided increased nurturing to these infants. And as a result, these infants initially assigned to the prolonged separation condition later appeared more similar to the infants who had only experienced brief separations. In other words, the foster mothers who had nurturing behavior were able to compensate for the impact of the prolonged separations. These findings have implications for how the caregiving and support of other adults can help to promote the development and adjustment of children impacted by a disaster.

Clinical research on the importance of nurturing adults for children's development is growing. While ACEs, including disasters, can have a significant negative impact on children's brain development and functioning, such damage is not guaranteed or irreversible. A mediating factor is the adults in a child's life. For example, stressed, exhausted, or depressed mothers show increased levels of cortisol and their young children also show increased levels of cortisol which may be even higher than their mother's level. Conversely, supportive, caring adults in a child's life can serve as a buffer for the hypothalamic–pituitary–adrenal (HPA) system, potentially protecting the brain from the harmful effects of significant stressors. Emotional support from adults is associated with improved overall adjustment and normative regulation of the HPA axis following stressful events in children's lives. These positive, supportive adults can provide a positive role model of how to cope with daily life stressors as well as unpredictable stressors such as disasters

or death of a loved one. Given that parental adjustment to a disaster is one of the best predictors of child adjustment, it is critical that when assessing children in the aftermath of these events, parental coping and adjustment is also assessed and supported.

Adjustment Reactions to Disasters in Children

- A survey was conducted by Hoven and colleagues six months after the terrorist attacks of September 11, 2001 of a representative sample of over 8,000 students attending grades 4–12 in New York City public schools. Among other variables, children were asked to provide self-reports of current mental health problems and self-reported impairment in functioning (e.g., not being able to do usual activities, having parents or teachers often upset with them, or having unexplained problems with school work). Children were felt to have a "probable psychiatric disorder" if they reported symptoms consistent with diagnostic criteria for that disorder and also reported impairment in functioning, which could be considered a fairly conservative self-report measure. One out of every four children (27%) met criteria for one or more of the probable psychiatric disorders assessed in the study and also reported problems in their day-to-day functioning. Approximately one out of ten had: post-traumatic stress disorder (PTSD) (11%), major depressive disorder (8%), separation anxiety disorder (12%), and panic attacks (9%). Agoraphobia (or fear of going out or taking public transportation) was reported in 15%. The vast majority (87%) of the students reported at least one ongoing symptom 6 months after the event: 76% reported often thinking about the attacks on the World Trade Center and 45% reported trying to avoid thinking, hearing, or talking about it; 25% found it harder to keep their mind focused; 24% were having problems sleeping; 17% were having nightmares; 18% stopped going to places or doing things that reminded them of the attacks; 11% reported at least six of the PTSD symptoms and qualified for probable PTSD. At least two-thirds of the children who self-reported both symptoms of PTSD and self-impairment also reported that they had not sought care.

Children's reactions to a disaster depend on a number of factors, including the nature of the event. Acts of terrorism, for example, are manmade and intentional and tend to create psychological reactions that are more prevalent and long-lasting when compared to natural disasters. There are as well factors which place children at greater risk for psychological difficulties after any type of disaster. These include: the extent of the children's and their family's direct involvement; the overall disruption of their routine resulting from the disaster; parental adjustment; children's preexisting mental health, coping skills, and vulnerabilities; and their age and developmental level. *Table 50.1* lists common adjustment difficulties that may be seen after a disaster. Reactions include symptoms consistent with acute stress reactions and posttraumatic stress disorder (PTSD). Although most children will experience distress and reactions to the disaster, most will not develop symptoms of sufficient severity or duration to qualify for a psychiatric diagnosis.

PTSD can occur after a traumatic event and is characterized by symptoms of re-experiencing, avoidance, and increased arousal that may occur immediately after a traumatic event and persist or may have a delayed onset. Symptoms of re-experiencing may take the form of dreams, with young children having nightmares that do not necessarily include content of the event. Children may have hallucinations or dissociative flashbacks in which

Table 50.1
Potential symptoms of adjustment reactions in children after a disaster

Sleep problems – difficulty falling or staying asleep; nightmares or frequent waking; resistance to sleeping alone; trouble waking in the morning
Separation anxiety or school avoidance
Anxiety, worries, and fears – worries of a repetition of the event; fears may be related to the event (e.g., fear of storms after a hurricane) or developmentally appropriate fears that may not be clearly associated with the traumatic event (e.g., fear of the dark even though the disaster occurred during daylight)
Irritability
Difficulties with concentration and academic work
Regression – developmental (e.g., secondary enuresis) or social (e.g., children – and adults – may become more clingy, less cooperative, more demanding, more self-centered, or less tolerant of others)
Sadness or depression; a sense of pessimism about the future or decreased future perspective
Avoidance of previously enjoyed activities; withdrawal and decrease in social interactions with peers
Onset of, or increase in, substance abuse
Somatization
Symptoms of posttraumatic stress disorder (PTSD)

they feel as if they are truly reliving the event or they may have intense reactions to cues that resemble the event. Young children may show they are re-experiencing the event through repetitive play. Avoidance after a traumatic event may be manifested by attempts to stay away from any activities, places, or people associated with the event, or efforts to avoid associated thoughts or feelings. Children may begin to withdraw from activities they previously enjoyed or become detached from others. Increased arousal may lead to problems falling or staying asleep, problems with concentration, increased irritability and anger outbursts, or becoming more hyper-alert with an increased startle response. All of these reactions individually are common after a disaster. To qualify for the diagnosis of PTSD, children must have symptoms for more than 1 month in all three areas (reexperiencing, avoidance, and increased arousal) that cause significant impairment in social, academic, or other areas of functioning.

Somatization is a common symptom of adjustment difficulties after a disaster. Because the difficulty is manifested as a physical complaint, this reaction is of direct relevance to all pediatric healthcare providers. Many of the children and families who would benefit from supportive services and/or counseling after a major crisis event will not identify their difficulties as psychological or emotional in nature, but instead may present with physical symptoms to their primary care providers, emergency departments, or pediatric subspecialists. It is therefore important to invite families to share information about recent losses or stressors and to inquire directly, especially after a disaster has occurred.

- Several months after Hurricane Katrina had caused devastating damage in New Orleans that was largely still not repaired, a group of pediatric healthcare providers commented that they had altered the structure of the routine healthcare visit. Now, in addition to the chief complaint, history of presenting illness, past medical history and physical exam, they found the need to add the "Katrina History." Several noted that it was this last additional element of history that often took the most time, yet yielded the information of most diagnostic and therapeutic utility.

Somatization underscores the need for all providers of healthcare to maintain a heightened sensitivity to the impact of trauma, loss, and stress on children and families and to develop effective partnerships with professionals who are able to address more fully these adjustment difficulties. Even when children are under marked distress after a disaster, they may not show any observable signs or may be reluctant to share their feelings with adults, especially those that are unfamiliar to them. It becomes especially important to establish a trusting relationship and create a safe environment where children can feel comfortable disclosing difficult feelings and concerns.

Posttraumatic stress reactions and disorders increase multifold after a disaster and often result in both acute and, if left untreated, long-term adjustment difficulties that can impair functioning in school (and at work when applicable), at home, and in social interactions. Because avoidance of thinking or talking about the disaster is one of the core features of PTSD, children and adults who are suffering from PTSD will often refrain from sharing their symptoms with others. Active screening and outreach become critical after a disaster event in order to identify those experiencing posttraumatic stress reactions.

It is important, though, to recognize that many of the difficulties children experience after a disaster may not be posttraumatic in nature. For example, if a disaster results in the death of someone close to the child, the child may experience bereavement that may be indistinguishable from bereavement resulting from a loss occurring outside the context of a disaster. Significant adjustment difficulties are typically seen as part of bereavement in children and may include any or all of the symptoms listed in *Table 50.1* as well as those seen in PTSD. In some situations, such as when the child witnesses the violent death of a loved one during a disaster, the child may experience a combination of posttraumatic reactions (to witnessing a horrific event) and bereavement (related to the loss of a loved one) which results in "traumatic grief" requiring treatment for both components. In too many situations, though, professionals assume that simply because a death occurred as a result of a disaster, that the child's symptoms are "posttraumatic." This may lead to a misguided focus on helping the child process the events of the disaster itself, rather than focusing on helping the child grieve an ongoing loss.

A major disaster typically initiates a cascade of secondary losses and stressors, any one of which may become the predominant problem for children and families. For example, the floods in the Gulf Coast from Hurricane Katrina resulted in a very large number of secondary losses and stressors including, among others: loss of belongings; loss of homes which often resulted in children experiencing one or multiple relocations; loss of social network of peers and supportive adults in the school and community; difficulty integrating into new peer networks, schools and communities; academic failure in part due to multiple school placements; financial stresses; and parental stress, mental health problems, and

substance abuse issues. Because of the prevalence of secondary stressors after a disaster, healthcare providers should not only inquire about the child's experience on the day of the flooding or other disaster, but also what other impact the evolving disaster and subsequent stressors are having on the child and the child's family. For example, a child may be demonstrating sleep difficulties or anxiety that is due to worries about financial problems and parental stress resulting from the loss of a parent's job due to the disaster, but not be having nightmares or anxiety because of the flood itself. It is critical that healthcare providers think more broadly about the impact of a disaster on children and families, rather than maintaining a narrow focus on posttraumatic symptoms and disorders hypothesized to originate from a singular traumatic event. Not only does this have implications for evaluation and treatment, but it provides important insights into the often lengthy process for community recovery seen after major disasters.

In many situations, the home, school, and community environments and supports for children can remain significantly impaired after a major community disaster for as long as years after the initial event. If one appreciates the impact of these secondary losses and stressors, then it would be anticipated that many children can also have some ongoing adjustment difficulties for many years. Given what is known from the research that chronic stress can cause changes in brain structure and function that has long-lasting impact, it becomes particularly critical that this phenomenon be anticipated. Interventions should begin promptly after disasters to provide support, promote adjustment, and help children and families deal with secondary stressors in order to minimize the cumulative stress experienced by these children.

Identifying Children at Highest Risk of Adjustment Difficulties

Given the high prevalence of adjustment difficulties among children after a disaster, it is important to employ approaches to identify which children are most likely to benefit from additional mental health evaluation and services. *Table 50.2* outlines some of the more common factors associated with an increased risk of adjustment problems in children after a disaster.

Children with prior (or concurrent) psychopathology or unaccommodated traumatic experiences or losses are at increased risk of maladjustment after a disaster. A crisis of any nature often awakens feelings related to a concurrent or even past crisis that were not fully resolved that may now assume a primary focus for the child. This may occur even if the prior event does not seem to be related to the disaster.

Table 50.2
Factors associated with an increased risk of adjustment problems after a disaster

Injury of the child, or death or injury of those close to the child
Child's perception (at the time of the event) that his or her life was in jeopardy
Exposure to horrific scenes (including indirectly through the media)
Prior psychopathology, significant losses, or traumatic events
Separation of child from parents or other important caregivers as result of event
Loss of property or belongings; disruption in daily routine or environment
Parental difficulty in coping
Lack of supportive family communication style
Inadequate community resources and support

- Students were inadvertently exposed to N-butyl mercaptan (an odorant with a skunk-like odor used in natural gas) when a student opened a personal protective device while on a bus. Dozens of children developed symptoms including vomiting, coughing, and choking, with a group requiring transport by emergency medical personnel to the hospital for treatment. The remaining students were transported via another bus to a local children's hospital where they underwent a controlled decontamination: children were greeted by a nurse and child life specialist who explained the decontamination process and children showered one at a time so that no child needed to undress in front of other children; the adults were decontaminated in another area of the hospital. Children were given clean, donated clothing and waited in a conference room where they could eat cookies, watch movies, and play games under the supervision of child life specialists, social workers, and chaplains, until reunited with their parents/caregivers. Despite the nearly ideal conditions for decontamination, two students continued to experience panic attacks for at least several weeks and had difficulty returning to school. The school inquired what could have been done differently to minimize the trauma of the event and it was suggested that they look instead to the histories of the two students. One student had recently transferred to the school and it became known that the reason

for the transfer was because of the very recent murder of a parent. For the other student, further investigation uncovered significant concurrent family issues that were the cause of her distress.

In addition to the risk factors outlined in *Table 50.2*, certain behaviors demonstrated by children in the immediate aftermath of a disaster may warrant immediate referral to mental health professionals for further assessment and appropriate services. These reactions include: dissociative symptoms (e.g., detachment, derealization, and depersonalization), extreme impairment in cognitive abilities or decision-making, panic or intense and unrelenting fear and anxiety, intense and uncontrollable grief, marked somatization, and suicidal ideation or intent.

Disasters challenge the assumptive world of children. Most of the time people function under certain assumptions which allows them to deny, or at least generally ignore, the nearly infinite risks they and those they care about face daily. People generally assume that they themselves and those they care about are healthy and safe and will remain that way – they will not personally experience earthquakes, lightning, random acts of violence, or tragic accidents. When a disaster occurs, even if it does not affect anyone the person knows, it has an impact on people's assumptive world. They are challenged by the reality that disasters do occur and people are killed and seriously injured and their homes and belongings destroyed. It causes people to question their prior assumptions, which had allowed them to conduct their day-to-day lives without becoming overwhelmed with all of the possible tragedies that can (and now they realize actually do) occur. It leaves people feeling anxious, vulnerable, or at least unsettled. Although it may be possible to identify children most likely to have more significant adjustment difficulties after a disaster, it is important to remember that major disasters impact virtually everyone, regardless of their personal involvement in the event or their preexisting risk factors.

Unfortunately, traumatic events and deaths of family and friends are extremely common in the lives of children; the vast majority of children experience the death of someone significant to them by the time they complete high school. Contrary to public perception that children who are raised in communities characterized by chronically high rates of violence "get used to loss," repetitive loss and trauma is instead sensitizing and cumulative. Children in these communities may learn that adequate external support is not provided by adults after each death or traumatic experience and may, therefore, not seek such support or request assistance, but this should not be confused with adjustment and coping. Support may be absent due to lack of awareness and understanding of the problems, lack of resources, or discomfort by adults and child-serving systems such as schools in addressing the situation. Whatever the reasons, the children remain underserved and their coping and long-term outcome likely compromised.

Adults Often Underestimate the Extent of Children's Distress

Parents, teachers, and other adults that support children tend to underestimate the extent of children's reactions to a disaster, especially as it relates to their internalizing symptoms (such as depression). There are a number of reasons why this may occur. Because of the stigma associated with mental illness and therefore even with seeking mental health services in most societies, children may be inclined to keep their adjustment problems to themselves. Parents, too, may have concerns about the stigma of their children needing such services and overlook or discount reactions. Parents and other caregivers who are struggling themselves may be unable or unwilling to recognize their children's distress – they want and often need their children to be coping and therefore fail to see signs of distress. When children see their parents upset, children may also withhold their complaints in hopes of protecting their parents from further distress. Or, children may misinterpret the discomfort that adults demonstrate when they ask questions about the disaster or its implications as a sign that such questions are inappropriate or discouraged and therefore, parents will not know of their children's worries or distress. Parents may not know for which signs or symptoms to look that may suggest distress after a disaster or any stressful or traumatic event. Lack of knowledge or awareness, rather than a lack of concern, is often the reason why parents underestimate their children's adjustment difficulties after a disaster.

Even when parents are aware of their children's distress, they may fail to bring this to the attention of healthcare providers because they may not perceive that they are interested or able to address these concerns. It is often said that adjustment difficulties after a disaster are "just a normal reaction to an abnormal event." But this would suggest that there is no need or benefit in bringing such reactions to the attention of professionals. It implies instead that they should be ignored, suffered in silence, while waiting for spontaneous remission. Healthcare

providers instead need to communicate that adjustment reactions after a disaster may be seen even in individuals that are otherwise psychologically healthy, but can cause significant distress and impairment. They need to convey to children and their families that reactions most often respond to assistance and support. Healthcare providers need to offer that support and/or provide advice on how it can be accessed through other sources.

Psychological First Aid and Basic Supportive Services

The goal of short-term interventions after a disaster is to minimize the onset and duration of adjustment difficulties and to promote children's recovery. In the aftermath of a disaster, children should be helped to understand not only what happened, but what is being done on all levels to assist in recovery, and be provided with a brief intervention that may help to reduce mental health challenges. This intervention, Psychological First Aid (PFA), involves a set of actions intended to provide immediate support to anyone impacted, both directly as well as indirectly, by the disaster. PFA is one of the first steps to helping children build or enhance their resilience, thus increasing their ability to recover quickly and effectively after a crisis event.

PFA ensures that basic needs are met. Children need assistance to meet their basic needs, including safety, security, food, shelter, and communication and reunification with family and other significant caregivers, before they are able to acknowledge and address their emotional needs. This is true for adults, including healthcare professionals – disaster preparedness and response plans should anticipate and actively address the basic needs of these professionals. Efforts to address basic needs also constitute important mental health services; approaches to meet basic needs should be informed by the potential to concurrently provide emotional support. For example, food provided in the aftermath of a disaster can not only provide caloric requirements, but can be used to provide nurturance. Shelters can not only shield people from the elements, but can also provide comfort and a supportive environment.

PFA involves psychoeducation and supportive services which can be provided by anyone (e.g., parents, teachers, neighbors, health and mental health professionals) when they encounter someone in distress. In applying PFA to children, psychoeducation consists of listening to how the child understands the disaster and gently correcting misperceptions and misattributions. The focus of explanations about what has happened should be on a developmentally-appropriate level, providing basic information that is directly relevant; graphic details, speculation, and irrelevant information should be avoided.

PFA includes providing information about common reactions that may occur in the aftermath of a disaster or crisis event; this action often serves to help children recognize that their reactions are not aberrant and can often lead to discussion of concerns and worries (see *Table 50.1* for list of common reactions). Realistic assurances are offered in a timely manner. PFA includes talking to children about how they have coped with challenging situations in the past, even though the disaster situation may be unique. Using positive coping strategies that they found helpful in the past may help in disaster situations. Adults can also model effective coping strategies; children look to adults for not only information but also for how to manage distress.

Because excessive exposure to media coverage of disasters has been linked to increased stress reactions, caregivers should monitor children's exposure to such coverage. Likewise, as children may not have a full understanding of adult conversations about the event, adults should be mindful when talking about the event in the presence of children. Children worry about what is being done and what could happen next. PFA actions also include giving realistic assurances and ongoing information in a timely manner, including what actions are being taken by the family, schools, community, and beyond in the case of federal involvement to address the aftermath of the disaster.

PFA actions include connecting children with others (family, friends, teachers, etc.) and with steps they can take to aid their recovery. Information about available resources that may benefit children is important to communicate to the family, including faith-based and culturally-based resources. Encouraging a return, as available, to the child's school and extracurricular activities can aid in recovery. When children reach out to help others, they also help their own recovery and build resilience. Adults should help children identify ways they can assist others that are personally meaningful and developmentally-appropriate. Finally, PFA includes recognizing when a child may require more help than support and psychoeducation. Risk factors that may necessitate a referral to more comprehensive services are listed in *Table 50.2*. To provide a continuum of care to children after a disaster, it is important that healthcare providers have ready access to mental health professionals with expertise in working with children who have experienced a traumatic or crisis event.

If properly prepared, all adults that interact with children, not just medical staff or mental health providers, have the opportunity to provide assistance to children in the aftermath of disaster. Adults who are less well informed risk either inadvertently contributing to their distress through insensitive comments or, more typically, by ignoring their signs of distress, their requests for assistance, or by trivializing the impact of losses or traumatic experiences.

- A high school experienced a very traumatic school shooting that resulted in the death of one of the students. A few months after the event, cafeteria staff observed that girls within the school were wearing long sleeve shirts when not indicated by the weather. When asked why they thought this was significant, they commented that when the girls held out their trays in the lunch-line, their sleeves retracted and they noticed marks indicating increased cutting behavior. The cafeteria staff explained that they felt it unlikely that other staff or parents had made this observation. In the same school, custodial staff commented that the students appeared more "out of control" since the school crisis. They reported observations of sexual behavior on campus and students rudely refusing to follow well accepted rules – both indications to them that the students were experiencing great distress. They correctly observed that such behaviors were unlikely to be displayed in the presence of authority figures within the school or the children's parents. Within this school, the cafeteria and custodial staff had unique observations regarding the impact of the disaster on students. They also had different access to the students that allowed them to observe and address their distress in ways that likely were not as available to teachers, school administration, and the children's parents.

Providing Advice to Parents

Pediatric healthcare providers can, and should, play an important role in the aftermath of a disaster by conducting their care in a way that minimizes further distress for children and families and by providing anticipatory guidance to parents about approaches that they can take within the home setting to support their children's recovery. This includes advising parents to reduce their children's exposure to frightening reminders of the disaster, including sights, sounds, and even smells. Within a healthcare setting, this might involve ensuring televisions are turned off in waiting rooms and patient treatment areas. Parents and other caregivers should avoid, or at least limit the amount of, exposure of children to news and other depictions of the disaster on television and through other media. When children do view television coverage, parents and other adults should consider watching it along with them to assist them in understanding what they are seeing and to monitor its impact on the children, discussing afterward what they think about the coverage and addressing any concerns that arise. If possible, parents may consider videotaping the coverage for later viewing. This provides an opportunity to pause the coverage to explore comprehension and reactions and, when indicated, to discontinue viewing until a later time.

Healthcare providers should be conscious that children often overhear conversations. Even if they cannot understand what is being said, children can pick up readily on the affective tone and become concerned if the speakers appear distressed (especially if they cannot figure out why). Extra care should be taken to close doors or curtains to minimize children's exposure to others who are injured or suffering. To the extent possible, healthcare providers should convey a sense of control of the situation and interact with children and their families in a calm, gentle, and compassionate manner. Children and families can sense when those in authority are panicked or overwhelmed and in turn become more anxious themselves. Healthcare providers should not only model such behavior for parents, but when they suspect or observe that parents are highly distressed, encourage them to seek their own support so that they can provide a more effective model of coping for their children.

Children are generally aided in stressful situations by the support provided by trusted caregivers. Healthcare providers should, therefore, minimize the need to separate children from important caregivers. When children are unaccompanied, healthcare sites should attempt to assign volunteers to provide consistent support to injured children until they can be reunited with family or other caregivers. Staff within the healthcare settings should provide guidance to the adults accompanying children about how they can support the children and reduce their distress. Having parents and other caregivers serve an active and positive role in the evaluation and treatment process will minimize the likelihood that either the children, or their parents/caregivers, will be disruptive to the delivery of care.

Psychotropic medication is *rarely* indicated for adjustment reactions in the immediate aftermath of a disaster and should be prescribed in consultation with a mental health provider who is experienced in the treatment of posttraumatic disorders and stress reactions in children. Such medication should not be used in order to suppress normative reactions (e.g., crying) or feelings (e.g., sadness)

in response to a disaster or to blunt children's awareness of the event. Awareness of the event and the expression of normative feelings are necessary for children to understand and ultimately adjust to the situation.

Schools as a Site for the Delivery of Recovery Services

- Following a devastating earthquake in a large rural area of Asia, hundreds of thousands of children and families were relocated to temporary housing communities. As the communities sought a return to normalcy, temporary classrooms were established. However, as teachers sought to cover lesson plans, many children would be crying in class or otherwise distressed. Teachers, also impacted by the earthquake, had little tolerance for the crying or other disruptive behaviors. They told children this was a sign of weakness and that they needed to be strong for the younger students. Although the children tried, they continued to show extreme distress in the classrooms. The local and federal government joined with agencies and outside experts to begin to address the distress in the children. Training and consultation about the impact of disasters on children was provided and alternative approaches were offered that were culturally appropriate to address the crying and other signs of distress. Also, simple techniques were taught, such as relaxation exercises, for use with children to reduce their distress. These exercises served as a way to increase positive coping for distress related to the disaster or other stressful situations.

After a major disaster, the number of children that would benefit from additional supportive services will likely exceed the capacity for traditional mental health services. Therefore, alternative models are needed for the delivery of basic supportive services to large numbers of children with minimal additional professional staff and at a site where children can go without feeling stigmatized. Schools emerge as one of the most viable and effective sites to accomplish these goals. School staff are well positioned to provide Psychological First Aid and brief supportive services to large numbers of children in the aftermath of a disaster. They can help to normalize both reactions and acceptance of assistance. They can identify children whose needs exceed those likely to be met through school-based support services based on children's risk factors for distress after disaster (see *Table 50.2*) and/or their level of reactions. Schools can also serve as a venue for provision of more intensive intervention services for identified students, reducing barriers such as transportation and stigma that may prevent students or their families from seeking help. Given that recovery from a disaster typically occurs over months and years, schools are uniquely suited to providing the long-term, longitudinal support and monitoring that is required.

- After an earthquake and tsunami struck a rural area in the Pacific, school staff were eager to learn from experts about how to support and respond to children in need. They shared their cultural considerations with trainers and the trainers provided information and modeling in working with children and families. This allowed for the best level of care to be provided to this small island community. Continued follow-up ensured that as the needs changed with time, these could also be addressed. For example, one small 8-year old boy whose parents had to leave the island to find work was living with relatives. He was extremely anxious and had begun avoiding school. He began drawing images of people drowning and no one around to help. With encouragement, he was able to talk about worries for the safety and security of his relatives. Who would help them if another tsunami occurred? He needed to be home just in case something happened so that he could offer assistance. He worried about the safety of his parents and who would take care of them. Support and acceptance of his concerns and psychoeducation about common worries was provided. Information about how the island was prepared for any future problems was given as were simple ideas for coping with his stress reactions. He was included in developing a preparedness plan for his new home. Slowly, this boy began to return to school. Weekly contact was established with his family so that he knew they were safe. Although small steps, each piece aided in reduction of stress such that he could begin to return to his school routine and begin to see the world with a more positive perspective.

While it is true that the primary mission of schools is to support academic achievement and not to provide counseling, it is also true that in the absence of effective interventions, disasters often have profound and sustained impacts on children's ability to succeed academically. *Figure 50.1* summarizes the impact of disasters on academic functioning, as well as the contributory factors. Despite this, most teachers and school staff (including mental health staff in school settings) have had only limited, if any, professional training on the impact of loss and crisis on children and strategies to provide effective support. Pediatric healthcare providers can, therefore, provide a critical role in advocating for schools to be better prepared to respond to crisis events and providing continued training and consultation on these issues.

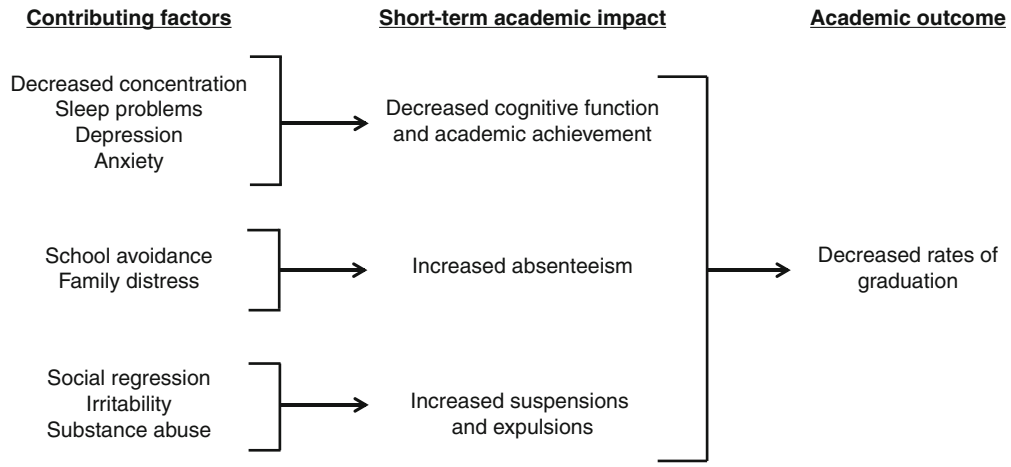

Figure 50.1
Possible impact of disasters on academic functioning in children in the absence of intervention

Long-Term Recovery

The question is often asked by parents and other caregivers: "When can children be expected to 'get over' a disaster?" or, "When can the family and community be expected to be 'back to normal'?" Disasters like other life-changing events – whether they be positive or negative events – do exactly that: They change the lives of all involved. They create indelible marks on a child's life course and have lasting impact. But this does not mean that children are permanently damaged or that long-term adverse impacts are inevitable.

Children's ability to cope and adjust to a disaster is initially compromised in the immediate aftermath of the event. Generally, in the period that immediately follows the event, there is an outpouring of concern and resources; families and communities come together and the resulting sense of cohesion can be uplifting. As a result, children begin to return to school and other routine activities. Parents, caregivers, and others serving children may interpret the return to routine as an indication that nothing else is needed. Unfortunately, while this return to routine is necessary for coping and recovery, it is not sufficient. Children may continue to need supportive services or even more intensive interventions. Many children may appear to be fine and have their needs overlooked.

Unfortunately, typically even modest improvement is seen as a sign that children are resilient and it is assumed that since they have started to "bounce back," they will return to their prior level of adjustment spontaneously. Although the majority of children will continue to improve over time after a disaster, many will not. If supports and assistance are withdrawn, before full recovery has occurred, these children will not return to their baseline adjustment levels but instead establish new baselines characterized by ongoing impairment. Children and school staff must instead be provided sufficient support until they are able to regain at least their baseline level of coping. For some children, if they have adequate internal resources and are provided sufficient support, they may even attain a higher level of adjustment. This posttraumatic growth occurs when children are helped to increase their resilience and learn new coping skills that they can call upon when faced with subsequent challenges. As the research has shown, adults who are in a position to support children play a key role in determining the difference between two ultimate outcomes – stress that promotes development and that which impairs development.

Commemorative and memorial activities often serve as effective mechanisms for promoting a group understanding of the event and acceptance of the resulting circumstances. Schools and other community sites can be important venues after a disaster to provide children with memorial and commemorative activities to help them express and cope with difficult feelings and to draw on the support of a caring community. By planning and taking part in a commemorative event, children can exercise at least some control over how they will remember the events – even if they felt powerless to prevent the disaster – as well as what and how they wish to honor what was lost or permanently altered.

The key to successful commemorative and memorial activities is to ensure that the students are actively involved in the planning and carrying out of the activity, which should be relevant to their interests and developmental needs and employ symbolic activities that are meaningful to survivors. Children are also helped to achieve long-term recovery when given opportunities to contribute actively to assisting others, whether that be victims of the disaster or others in need within their community. Healthcare professionals can lend their voices in support of children's involvement in these activities.

Professional Self-Care

- In the aftermath of a large-scale and devastating earthquake in Asia, paraprofessional mental health workers began to talk with children impacted by this disaster. Each day, they would venture out to the impacted areas and hear story after story of death and destruction. They would listen to the worries, fears, and anxieties of the children of all ages. They would listen as parents, relatives, and other adults would talk about the children and their worries. This began to take a toll on the workers. They were tearful and showing signs of compassion fatigue. The workers received specialized training in the impact of trauma, disaster, and bereavement on children as well ideas to support children's healing and resilience. This helped workers feel better able to meet the needs of those they encountered. However, this alone was not sufficient to address the compassion fatigue. Information about the importance of self-care was discussed and ideas offered, with workers contributing suggestions. Time to talk about the stories they had heard that day was established as one way to process all they were experiencing vicariously. The combination of these efforts led to a reduction in worker distress and an increased energy and new ideas about how to reach out to those in need, thereby contributing to improved services to members of the community.

Disasters that impact children generally also impact the adults within the community. This is true as well for professionals who reside or work within the same community.

Even if not impacted directly, healthcare professionals who have to bear witness to the suffering and distress of children and their families will also find themselves impacted. This is known as vicarious traumatization or secondary traumatization. Those working with children are particularly susceptible and are at high risk for compassion fatigue. As such, disaster response plans should anticipate ways to provide professional consultation and direct support to healthcare providers as they meet the mental health needs of children and families in the aftermath of a disaster. This is particularly important when providers are involved in providing complex services such as death notification (for practical guidelines on death notification in the aftermath of a disaster, see Foltin GL, Schonfeld DJ, Shannon MW, 2006). How well providers are faring also has a direct effect on how those they serve will cope.

Healthcare providers may need to respond to a dramatic surge in the number and acuity of patient demands at the same time they may be struggling to meet increased needs of family members and friends, or feel torn by the competing need to respond to damage to their home or personal belongings. Many of the secondary stressors experienced in the aftermath of a disaster are also present in healthcare settings – economic forces may result in reductions in workforce or loss of support staff or resources. Healthcare workers may find themselves needing to respond to increased demands in often more austere working conditions, especially when working in settings that have experienced devastation or major impacts on the infrastructure of the healthcare delivery system.

To reduce vicarious traumatization and other adjustment difficulties after a disaster, it is critical that professionals identify, acknowledge, and meet their own needs and utilize healthy ways of coping with the distress. For example, developing family disaster plans prior to any disaster may increase healthcare providers' ability to focus on the needs of patients and families, knowing that their family is safe. Healthcare institutions should also establish plans by which they can assist their staff with basic needs and ongoing support of family members (e.g., providing daycare or elder care to allow healthcare workers to increase their working hours without compromising the safety or well-being of loved ones, or supplying temporary housing when the disaster has destroyed or damaged the homes of staff). Such support can mitigate the additional stress that may otherwise impact negatively the quality of care delivered by healthcare workers.

It is important to acknowledge that the same emotional reactions that can be seen in adults within the broader community can also be experienced by healthcare professionals. They should therefore also receive Psychological First Aid, brief supportive interventions, and access to additional mental health services as indicated. Those professionals experiencing marked or persistent distress or demonstrating unhealthy attempts at coping (e.g.,

increased use of alcohol or other substances) should have ready access to services, such as through an Employee Assistance Program.

When healthcare providers can identify personally meaningful ways to help others in the community recover and rebuild after a disaster, they may experience an increased sense of personal and professional satisfaction and increased feelings of self-efficacy. Many healthcare providers are motivated to pursue their careers out of a desire to help others and derive personal fulfillment by doing so.

In summary, there are few situations where people are more in need than in the aftermath of a disaster and where healthcare providers are in a better position to provide the necessary care and support. Understanding the impact on children and families, they can provide guidance and support the recovery of this vulnerable population.

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Web-Sites

www.aap.org/disasters/adjustment.cfm Website maintained by the American Academy of Pediatrics that includes a range of resources related to mental health needs of children and families in the aftermath of a disaster that can be freely downloaded by healthcare providers, families, and others

www.cincinnatichildrens.org/school-crisis Website maintained by the National Center for School Crisis and Bereavement that includes a range of resources for school personnel and parents of how to support children dealing with loss and crisis that can be freely downloaded by school personnel, families, and others

Pediatric Nutrition

Hisham M. Nazer

51 Breast Feeding

Salah Shohieb · Hisham M. Nazer

There is growing interest in ensuring an adequate and appropriate nutrition for the infant from early days of life. Infant nutrition is a well-recognized major determinant of growth and development that has also a considerable influence on health later in adulthood.

Infants should normally be exclusively breast-fed at least until the age of 4–6 months or given expressed breast milk especially if premature or small for dates. If such an option is not possible, a modified artificial formula close to breast milk in composition should be given as an alternative.

The nutritional adequacy of any diet is determined by the clinical status, growth, and development of the child. Parents are extremely receptive to advice regarding a proper feeding regimen for their children to ensure a healthy lifestyle as they grow older.

Breast Feeding

The first half of the twentieth century was marked by decline in breast feeding in the industrialized world and that was followed by a similar decline in developing countries. However, the latter half of the century and extending into the twenty-first century witnessed an upsurge in breast feeding.

The duration of breast feeding varied from 9–12 months in some areas of the world to 2–3 years in others but most children were suckled usually on demand for a year either by their mother or by a wet nurse.

The volume of breast milk that a woman can produce varies widely, from as little as 400–600 mL per day to around 1,200 mL per day. Following birth, the placental inhibition of milk synthesis is removed with rapid decline of the mother's progesterone blood level. The breast fills with high density milk called colostrum.

Changes of the Breast During Pregnancy

There is visible enlargement of the nipple with an increased pigmentation. Each of the right and left breast has an average weight of 150–200 g, which increases to 400–500 g during lactation. Numerous sebaceous glands (Montgomery's glands) produce small elevations on the surface of the areola. These glands secrete a light lipoid material that lubricates and protects the nipple during nursing. Frequent use of soap to wash the nipples is not recommended. This will not only dry them but wash away the natural lubrication as well.

Galactogenesis begins immediately after delivery. For successful lactation, the breast must be primed by different hormones: estrogens, progestins, corticosteroids, insulin, thyroid, and parathyroid hormones.

After delivery, a sharp drop in estrogen levels triggers lactation. Optimal milk quality depends on the availability of thyroid, insulin, and cortisol and on sufficient intake of nutrients and fluids.

Frequent feeding is the only way to prevent engorged breasts. Normal newborn should be placed at the mother's breast every 2–3 h. Five minutes is more than enough time to stimulate the lactational reflexes. Breast-fed infants ingest 50% of the milk in the first 2 min of nursing, 80–90% in the first 4 min and nearly 100% in the first 7 min. The nutritional requirements of the newborn varies according to weight, gestational age, and environmental factors.

Night feeding should be encouraged because they take the advantage of the circadian nature of the prolactin secretion that occurs 60–90 min after sleep onset.

Breast Milk and Premature Newborns

Human milk is of great benefit in the management of premature infants. It improves the digestion and absorption of nutrients, gastrointestinal functions, host defenses, neurodevelopmental outcomes, and maternal psychological well-being.

Human milk may be used as such without any additives (unfortified) or with some additions (fortified).

Unfortified Human Milk for Prematures

Feeding of the premature infants by the breast milk without any additions leads to the following benefits:

- *Host defense benefits:* Where there is decreased rate of various infections due to the presence of specific

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bioactive factors such as secretory IgA, lactoferrin, lysozyme, oligosaccharides nucleotides, cytokines, growth factors, enzymes, antioxidants, and cellular components.

- *Neurodevelopmental benefits:* Visual functions may be improved due to high quantity of very long-chain poly-unsaturated fatty acids (PUFA) and antioxidant activity.
- *Gastrointestinal benefits:* Human milk promotes rapid gastric emptying and also activates intestinal lactase more than if the preterm baby is formula fed.

Fortified Human Milk for Prematures

Premature infants fed fortified human milk had significantly better growth i.e., positive increments in weight, length, head circumferences, nitrogen balance, and bone mineral content.

Human Milk Fortifiers

This can be performed using a commercially available liquid formula to be mixed with the human milk or a powdered product that has the advantage of not diluting the human milk. Most fortifiers are powdered nutrient preparations that contain protein, carbohydrate, calcium, phosphorus, magnesium, and sodium. The contents of zinc, copper, and vitamins vary.

With the increasing knowledge of the advantages of breast feeding, there is a positive changing trend among mothers to breast-feed their babies for the first 6 months of age. However, it has been seen, in the industrialized countries, that despite all knowledge about the superiority of breast milk, nearly one mother in two discontinues breast feeding before the infant is 6 months of age. This is usually due to the mother's belief that their milk production is becoming too little to benefit their babies (i.e., "the insufficient milk syndrome"). This phenomenon is precipitated by early introduction of supplementary feed and the mother's lack of motivation toward long-term breast feeding. Some have demonstrated that emotional factors could contribute to reduced milk consumption by the baby and subsequently reduced milk supply by the mother. Another cause for the reluctance the mothers have toward breast feeding or prolonged breast feeding is their belief that breast feeding will adversely affect their figures.

The test weighing method for measuring breast-milk consumption remains a valid and reliable method, especially in field studies.

There is a consensus that the appropriate time to start weaning and introducing additional foods to the infants is around 6 months of age, prior to which the baby should be on exclusive breast feeding.

Evidences Concerning the Superiority of Breast Feeding

1. Breast-milk composition includes: immunoglobulins, lactoferrin, lysozyme, oligosaccharides, and lymphocytes and these could well contribute to the protection of the breast-fed infant from infection.
2. Breast feeding is a preventive measure in programs to control diarrhea. In fact, both the promotion of breast feeding in general as well as stressing on the continuation of breast feeding during diarrhea are well-recognized important components of programs against diarrhea.
3. While women are suckling their babies, menstruation does not usually occur (i.e., lactation amenorrhea), nor do they conceive. Breast feeding can reduce the risk of breast cancer to nearly half relative to that in women who bottle feed their babies.
4. The maximum birth-spacing effect of breast feeding is achieved when a mother "fully" or nearly fully breast-feeds and remains amenorrheic. Exclusive breast feeding provides more than 98% protection from pregnancy in the first 6 months.
5. In much of the "Third World," breast-feeding rates are highest among the rural women and those with least education. On the other hand, women who work find it difficult to breast-feed their babies for long.

If breast feeding continues after the age of 6 months, some attention to a dietary source of iron is necessary. Semisolid foods containing meat or vegetable sources of iron plus vitamin C should be given. Bottle-fed infants should continue with their formula fortified with iron or change into follow-on-milk formula. All breast-fed infants require vitamin supplement after the age of 6 months. A limited exposure to the sun is advisable.

Breast feeding secures optimum health, growth, and development for babies and ensures they receive the vital immunity they need to protect them against childhood illnesses. Breast feeding is recognized to reduce the risk of developing gastrointestinal illnesses, especially gastroenteritis, which is a major cause of infant morbidity and mortality in the developing world. It also reduces the risk of other infections of the middle ear, and respiratory system. In later life, breast feeding is associated with

a reduced risk of allergies such as eczema and of insulin-dependent diabetes mellitus.

Mothers who breast-feed also have a reduced risk of developing premenopausal breast cancer as well as some forms of ovarian cancer.

As to the practice of breast feeding in rural areas of the developing world as well as in some traditional societies and Islamic communities, mothers continue to breast-feed their infants until 2 years of age, though partially but still with the supplement of other formulas or even solid foods.

Galactosemia is considered an absolute contraindication for continued breast feeding; however, in conditions like phenylketonuria, because breast milk contains a low concentration of the amino acid phenylalanine, breast feeding may be continued, provided there is regular monitoring of the serum phenylalanine. Occasionally, breast feeding may have to be supplemented with a special low-phenylalanine formula.

A summary of the situations where breast feeding is considered absolutely or relatively contraindicated is listed in *Table 51.1*.

Every effort should be made not to deprive the baby of the mother's breast milk and if needed, the baby's feed may be supplemented with formula feeds.

Maternal tuberculosis remains a serious health hazard in the developing world. Active tuberculosis should be diagnosed and managed antenatally. Contacts should also be investigated and treated accordingly. However, if the diagnosis was made after birth there is a significant risk to the newborn of tuberculosis not only through the mother's milk but also through the direct contact. The mother should therefore be treated with triple therapy while her baby is being isolated from her in the initial weeks of therapy. The baby should also receive a prophylactic dose of isoniazid for 6–12 months in a daily dose of 10 mg/kg body weight.

Table 51.1
Conditions associated with contraindications (absolute or relative) to breast feeding

Absolute	Relative
• Inborn errors of metabolism	• Hare lip and cleft palate
– Galactosemia	• Lactation failure
– Maple syrup urine disease	• Mastitis
• Serious maternal illness	• Maternal tuberculosis
– Psychosis	• Maternal hepatitis B infection
– End-stage liver or renal disease	• Breast cancer
– Heart failure	• Inverted nipples
– Human immunodeficiency virus (HIV)	• Drug therapy
	• Exposure to chemicals as herbicides, pesticides, heavy metals

Changes in Breast Milk After Delivery

There are three phases of milk production: colostrum, transition, and mature milk.

Colostrum is present from delivery to approximately 5 days postpartum. It has the highest concentration of protein, of most immunoglobulin (especially S IgA), and lactoferrin. It is lower in fat compared to mature milk (2% versus 3.5%) and has higher cholesterol levels than mature milk. It provides approximately 67 cal/100 mL. Major functions of colostrum are to provide substances for rapid growth, protect the gastrointestinal tract, and assist in increasing the level of *Bifidobacteria* of the gut. The amounts of colostrums secreted vary widely, ranging from 10 to 100 mL/day with a mean of about 30 mL.

Transitional milk is present between 6 and 15 days postpartum. Immunoglobulin level decreases while lactose and fat levels increase.

It provides between 67 and 75 cal/100 mL.

Mature milk is present from day 15 to weaning. It provides 75 cal/100 mL. One third of mature milk is foremilk, which is thin and low in fat. Two thirds of mature milk is hind-milk. This milk is about four times higher in fat than foremilk.

The composition of breast milk varies with the duration of lactation as well as with the infant feeding practice. Mature breast milk is variable in composition not only between mothers but also in the same mothers between breasts, between feeds, and even during a single feed as well over the course of lactation.

More information on the subject of breast feeding is available in the section on neonatology.

Breast-Milk Jaundice

This is a rare type of jaundice that develops in breast-fed infants around the age of 1 week and lasts for up to

3 months. The specific mechanism responsible for this condition is not identified. Abnormal bilirubin metabolism associated with breast feeding has been considered a possible etiology.

A high level of unconjugated bilirubin in breast-fed infants may be due to various proposed factors. It has been suggested that the unusual steroid metabolite of progesterone, pregnane-3(α) 20 (B)-diol, inhibits the activity of hepatic glucuronyl transferase in vitro. This observation was not confirmed by some subsequent studies. Other observations indicated that the breast milk from mothers with breast-milk jaundice does not inhibit the intestinal absorption of bilirubin. Other factors included the presence of free fatty acids, which are also known to inhibit the conjugation of bilirubin, resulting in jaundice due to accumulation of unconjugated bilirubin. However, there are reports to contradict those in support of the role of free fatty acids and milk lipases in the pathogenesis of breast-milk jaundice.

Subsequently, other factors such as the higher milk glucuronidase in breast milk of mothers with breast-milk jaundice have been suggested. Moreover, infants with breast-milk jaundice had higher concentration of epidermal growth factor in the serum and in the breast milk compared with that of infants without breast-milk jaundice. Although the exact mechanism of the hyperbilirubinemia of the epidermal growth factor are not completely known, the inhibition of gastric motility, increased absorption, and activations of bilirubin transport have been suggested as possible mechanisms.

Recently, prolonged unconjugated hyperbilirubinemia associated with the heam oxygenase-1 gene promoter polymorphism may be a factor in hyperbilirubinemia of these neonates.

However, maternal serum aflatoxin is a risk factor for jaundice in infants where studies reported that maternal breast milk in developing countries had higher rates of aflatoxin concentration than in high-income countries.

Breast-feeding infants remain in good general health, feeding well, and growing normally. This is why breast feeding should not be discontinued. In an attempt to the diagnosis, the breast feeding is discontinued for 1 or 2 days, following which the serum unconjugated bilirubin decreases, to rise again after the reintroduction of breast feeding.

Breast Milk and Gastrointestinal Health

The importance of breast milk in the prevention of neonatal and the preterm gastrointestinal disease states will be illustrated in the following paragraphs expressing worldwide clinical and laboratory experiences:

1. Protective properties of human breast milk:
   This may be *passive protection* of breast milk by lactoferrin and nucleotides and *active protection* by *growth factors*, *cytokines*, and *hormones.*
   These protective factors act as a barrier to antigen absorption in the immature infant's human intestine as a background for three accelerated gastrointestinal diseases as: necrotizing enterocolitis, intestinal allergy, and bacterial gastroenteritis.
2. Human milk actively stimulates the *infant's immune system* by the bioactive factors such as hormones, growth factors, and colony stimulating factors. In addition other factors in breast milk promote gastrointestinal mucosal maturation, decrease the incidence of infection, alter gut microflora, and have *immunomodulatory* and anti-inflammatory functions.
3. *Heparin-binding epidermal growth factor in breast milk:* This epidermal growth factor protects against intestinal epithelial cell apoptosis and necrosis and intestinal ischemia and reperfusion injury.
4. *Soluble CD14 in breast milk*, an important component of the lipopolysaccharide receptor complex, promotes the innate immunity and helps reduce gastrointestinal gram-negative infections.
5. *Breast milk probiotic potential* by 3 lactobacilli strains – 2 lactobacillus gasseri and 1 lactobacillus fermentum lactic acid producing bacteria – was isolated from milk of healthy mothers. The probiotic potential of lactobacilli isolated from milk of healthy mothers is at least similar to those strains commonly used in commercial probiotic products. This fact, together with the presence of prebiotic substances indicates that breast milk is a natural synbiotic food.
6. Breast milk *erythropoietin:* Mammary epithelial cells contribute to the production of erythropoietin in human milk. Erythropoietin receptors are widely distributed in human tissues including the gastrointestinal tract, endothelial cells, spinal cord, and brain. Thus erythropoietin may play a pleomorphic role in erythropoiesis, neurodevelopment, maturation of the gut, apoptosis, and immunity.
7. Breast milk: *essential fatty acids* (long chain) (LCPUFAS) as possible enhancers of the beneficial action of probiotics. Breast milk is rich in long-chain poly-unsaturated fatty acids that have immunomodulatory actions. LCPUFAS promote the adhesion of probiotics to mucosal surfaces, thus augmenting the health promoting effect of probiotics.

8. *Anti-complement activities* of human breast milk: Several natural components abundant in the fluid phase of breast milk have been shown to be inhibitors of complement activation. These include lysozyme, lactoferrin, lactalbumin-alpha, complement regulator protein, and other specific soluble inhibitors of complement activation.
9. *Human-milk glycans* inhibit pathogen in the gastrointestinal tract from adhering to their target receptors on the mucosal surface of the gut. The human milk glycans includes the oligosaccharides in their free and conjugated forms function as soluble receptors thus preventing morbidity and mortality in infancy.
10. *Haptocorrin* (Vitamin-B_{12} binding protein): in human milk with a host-defense role in the gastrointestinal tract of breast-fed infants. It is expressed by human mammary epithelial cells. It may exert a host-defense function, i.e., antimicrobial function against pathogens in the gastrointestinal tract of breast-fed infants.
11. *Hepatocyte growth factors in human milk:* The hepatocyte growth factor is present in sufficient amounts to profoundly affect gastrointestinal maturation in the fetus via the swallowed amniotic fluid and neonate via breast milk and help explain the increased rate of necrotizing enterocolitis in infants of premature rupture of membranes, complicated pregnancies, and the decreased rate in breast-fed neonates.
12. *Prostaglandins in human milk:* Prostaglandins (E2 and F2-alpha) are present in breast milk and may protect and maintain intestinal epithelial cell integrity. The cytoprotective effect of prostaglandins on the gastrointestinal tract may be related to their stability and lack of degradation in milk and gastric digestive juices.
13. *Secretory Immunoglobulin A* (*S IgA*) antibodies in breast milk. A fully breast-fed infant receives as much as 0.5–1.0 g of secretory immunoglobin A (SIgA) antibodies daily. These (SIgA) antibodies have been shown to protect against *Vibrio cholerae*, ETEC, *Campylobacter*, *Shigella*, and *Giardia*.
14. Importance of *breast-milk mucin:* The Rotavirus specifically binds to the milk mucin complex and thus viral replication is inhibited both in vitro and in vivo. Variations in milk mucin glycoproteins may be associated with different levels of protection against infection with gastrointestinal pathogens.
15. Human milk *nucleotides:* The dietary nucleotides optimize the function of rapidly dividing tissues such as those of the gastrointestinal and immune systems. Infants receive nucleotides in human milk where they are present as nucleic acids, nucleosides, and related metabolic products. The nucleotide content of human milk is significantly higher than most cow's milk–based infant formula.
16. Gastrointestinal *regulatory peptides* in human milk: These gut neuropeptides in milk may be important for growth and maturation of the gastrointestinal system in neonates. Neuropeptides were at the same or lower concentrations in milk than in plasma. These neuropeptides are: gastric inhibitory peptide, bombesin, gastrin cholecystokinin, peptide histidine-methionine, and neurotensin.
17. Human *milk proteins:* Human milk contains a wide variety of proteins as:
    (a) Many of these proteins are digested and provide a well-balanced source of amino acids to the rapidly growing infants.
    (b) Some proteins such as lipase, amylase, beta-casein, lactoferrin, haptocorrin, and alpha-antitrypsin assist in digestion and utilization of micronutrient and macronutrients.
    (c) Proteins with antimicrobial activity – immunoglobulins, kappa-casein, lysozyme, lactoferrin, haptocorrin, alpha-lactalbumin, and lactoperoxidase – contribute to the defense of breast-fed infants against pathogenic bacteria and viruses.
    (d) Prebiotic activity such as the promotion of the growth of beneficial bacteria such as lactobacilli and bifidobacteria, may also be provided by human milk proteins.
    (e) Some proteins and peptides have immunomodulatory activities (e.g., cytokines and lactoferrin) whereas others such as insulin-growth factors and epidermal growth factor are likely to be involved in the development of the intestinal mucosa and other organs of the newborn.

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52 Formula Feeding

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Exclusive breast feeding is the norm in infant feeding. Human milk remains the ideal milk for human babies in spite of all modern and modified commercial formulas available. It remains a superior formula not only because of its content and composition that varies with time, environment, emotions, and many other factors, but because it is safer with better psychological effects due to bonding and contact between mother and baby. All fluid, energy, and nutrients are provided for by breast milk, adapted for every child's age, with few exceptions of small amounts of medicinal supplements.

In a small number of situations there may be a medical indication for supplementing breast milk or for not recommending breast milk at all.

It is useful to distinguish between

1. Infants who cannot be fed at the breast but for whom breast milk remains the food of choice (may include infants who are very weak, have sucking difficulties or oral abnormalities, or are separated from their mother who is providing milk). These infants may be fed expressed milk by tube, cup, or spoon or by wet nurse (another mother).
2. Infants who may need other nutrition in addition to breast milk, like premature infants or infants with other medical diseases.

Infants that should not receive breast milk, or any other milk, including the usual breast milk substitutes and need a specialized formula (may include infants with certain rare metabolic conditions such as galactosemia who may need feeding with a galactose-free special formula or phenylketonuria where some breast feeding may be possible, partly replaced with phenylalanine-free formula).

The general decline in breast feeding is certainly linked to the far-reaching changes that have taken place in modern society.

There are, however, certain situations where breast milk is insufficient to maintain adequate weight gain or some relative or absolute contraindication to breast feeding exist for which reason the baby has to be placed on or supplemented with artificial formula.

In developed countries mothers who are infected with human immunodeficiency virus (HIV) have been advised not to breast-feed their infants. In developing areas of the world with populations at increased risk of other infectious diseases and nutritional deficiencies resulting in increased infant death rates, the mortality risks associated with artificial feeding may outweigh the possible risks of acquiring (HIV) infection.

Bottle formula is resorted to in infants born to mothers who are hepatitis B surface antigen positive, or who are infected with hepatitis C virus (persons with hepatitis C virus antibody or hepatitis C virus RNA-positive blood), febrile mothers, and mothers who are seropositive carriers of cytomegalovirus (CMV).

Switching to bottle formula from the mother's side reflects one of many causes: insufficient prenatal education about breast feeding, inappropriate breast-feeding technique, early hospital discharge, lack of follow-up care and postpartum home health visits, maternal employment, lack of family and broad societal support, commercial promotion, distribution of hospital discharge packs, media commercials, television and general magazine advertising, misinformation, and lack of guidance and encouragement from health-care professionals.

Complementary Feeding

The process starts when breast milk alone is no longer sufficient to meet the nutritional requirements of infants and therefore other foods and liquids are needed, along with breast milk.

Introduction of complementary feeding before 6 months of age generally does not increase total caloric intake or rate of growth and only substitutes foods that lack the protective components of human milk.

Every effort should be made not to deprive the baby of the mother's breast milk. If needed the baby's feedings may be supplemented with formula.

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Nutrient and Water Requirement

Water

Water is required for maintenance, excretion of excess protein, electrolyte intake, and changes in body composition.

Water constitutes approximately 78% of the body weight at birth and decreases to about 60% by the end of the first year of life.

Water requirement of an average newborn weighing about 3 kg is expected to be 80–100 mL/kg; it then increases to about 140–160 mL/kg at around 3 months of age.

The energy needs from complementary foods for infants with "average" breast milk intake in developing countries are approximately 200 kcal/day at 6–8 months of age, 300 kcal/day at 9–11 months of age, and 550 kcal/day at 12–23 months of age. In industrialized countries these estimates differ slightly (130, 310, and 580 kcal/day at 6–8, 9–11, and 12–23 months, respectively).

Estimated Energy Requirement

Estimated energy requirement during the neonatal period is about 120 kcal/kg/day, which is more than the child's requirement during later part of the first year, about 100 kcal/kg/day.

Human milk provides about 40–50% of energy as fat.

Protein

Human milk has the lowest protein concentration among mammals. Average protein content is estimated to be 1.15g/dL except during the first month, when it is 1.3 g/dL.

The total protein content of artificial formula should be lowered in order to be close to that of breast milk. Proteins are made of different amino acids that are linked together. They provide both calories and the amino acid building blocks that are necessary for proper growth. The protein in human milk provides between 10% and 15% of an infant's daily caloric need. Casein and whey are the two major proteins of human milk and most milk-based formulas.

Immunoglobulin, a type of protein unique to breast milk, provides passive transient infection-fighting immunity and is not considered as a nutritional source and is not efficiently metabolized.

Some 0.5–7.5% of infants have a true allergy to the cow's milk proteins that are in cow's milk-based formulas. Infants with true cow's milk allergy can develop abdominal pain, diarrhea, rectal bleeding, skin rash, and wheezing when given milk-based formulas. These symptoms will disappear as soon the milk-based formula is removed from the diet. Since allergy to cow milk protein is different from lactose intolerance, treatment of cow milk protein allergy involves using formulas that are not based on cow's milk or using formulas that contain "predigested" casein and whey proteins. The predigesting process breaks the whole proteins into smaller pieces or into amino acids.

Soy-protein formulas contain no cow's milk, and are reasonable alternatives for infants with true cow's milk protein allergy. Since most soy-protein formulas also contain no lactose, they are also suitable for infants with lactose intolerance. The carbohydrates in soy-protein formulas are sucrose, corn syrup solids, and cornstarch or glucose polymers.

Certain infants have allergy to both cow milk proteins and soy proteins. These infants require a formula in which the cow milk protein (casein) has been "predigested" and specific amino acids added to give a formula that can provide proper nutrition.

Carbohydrate

Lactose is the major carbohydrate in human milk. Galactose and fructose are present in human milk but to a much lesser concentration. Lactose is present in a concentration of 4% in colostrums and 7% in the mature human milk.

Lactose supplies about 40% of the energy needs but also has other functions. It is metabolized into glucose used for energy and galactose needed for development of the central nervous system. Carbohydrates (glucose, lactose, sucrose, galactose, etc.) are sugars or several sugars linked together. Carbohydrates provide energy (calories) for the brain tissues, muscles, and other organs. Lactose is a carbohydrate consisting of glucose linked to galactose. Lactose is the major carbohydrate in human breast milk, cow's milk, and in most milk-based infant formulas. While most infants will thrive on a formula that contains lactose, some infants are lactose intolerant.

Primary lactose intolerance is "rare congenital anomaly."

Temporary lactose intolerance may occur with any condition that damages the intestinal brush border with loss of the lactase activity. Lactose intolerance is due to a lactase enzyme deficiency (low levels of enzyme activity)

in the small intestines. Lactase enzymes are necessary for "digesting" lactose by breaking the link between glucose and galactose. The intestines can then absorb the smaller glucose and galactose molecules. In infants who are lactase deficient, the undigested lactose cannot be absorbed. This, in turn, can cause diarrhea, cramps, bloating, vomiting, and gas. Lactase deficiency is more common in premature infants than in full-term babies.

Lactase deficiency can also develop temporarily during recovery from viral gastroenteritis. For infants with lactose intolerance, formulas that contain no lactose should be used. There are quite a good number of breast milk substitutes that do not contain lactose.

Fat

Fat concentration is about 2 g/dL in the colostrums and increases up to 4 g/dL or even more. Fat is the most variable of human milk constituents. There is a recognized circadian fluctuation in the concentration of fat in human milk with highest concentration in the late morning and early afternoon.

The fatty acid composition of the human milk is relatively stable, with about 42% saturated and 57% unsaturated. Fat in human milk provides 30–35% of the total daily caloric needs for a growing infant. The fats are comprised of cholesterol, triglycerides, short-chain fatty acids, and long-chain polyunsaturated (LCP) fatty acids. The LCP fatty acids (18–22-carbon length) are needed for brain and retinal development. Large amounts of omega-6 and omega-3 LCP fatty acids, predominately the 20-carbon arachidonic acid (AA) and the 22-carbon docosahexaenoic acids (DHAs), are deposited in the developing brain and retina during prenatal and early postnatal growth.

An infant, particularly a preterm infant, may have a limited ability to synthesize optimal levels of AA and DHA from linoleic and linolenic acids. These two fatty acids may be essential. Recently, some infant formulas have added AA or DHA. Increasing evidence suggests that breast-fed infants have better visual acuity at 4 months and slightly enhanced cognitive development than formula-fed infants, even when socioeconomic factors are taken into account. These differences are more pronounced in premature infants.

Breast milk may somehow protect the developing neonatal brain from injury or less optimal development by providing necessary building materials and growth factors.

Human milk is rich in long-chain polyunsaturated fatty acids, which are important in brain development and enhance nervous tissue myelinization.

Vitamins and Minerals

Vitamins

In general, vitamin concentrations in human milk are usually sufficient to meet the newborn's needs.

Vitamin K

Vitamin K is present in higher concentration in both the colostrums and early breast milk than in later milk or breast milk substitute. This is helpful in reducing the incidence of hemorrhagic disease on the newborn.

Vitamin D

Vitamin D content of human milk is low and insufficient to meet the needs of the newborn infant. A brief exposure to sunlight produces sufficient vitamin D to satisfy the breast-fed baby's needs.

Minerals

Mineral concentrations (e.g., calcium, magnesium, zinc, iron) are lower in human milk than in artificial milk. Calcium is more efficiently absorbed because of human milk's high calcium phosphorus ratio of 2:1. Neonatal hypocalcaemia is more common among artificially fed infants due to its higher phosphorus concentration.

Iron

Complementary foods rich in iron should be introduced gradually beginning around 6 months of age. Preterm and low birth weight infants and infants with hematologic disorders or infants who had inadequate iron stores at birth generally require iron supplementation before 6 months of age. Iron may be administered while continuing exclusive breast feeding.

Iron deficiency anemia is extremely rare in young infants fed exclusively on breast milk during the first

6 months, due to many supportive factors that increase iron absorption (70%) compared to those (30%) in cow's milk.

In developing countries, the mother herself may suffer from iron deficiency anemia for which reason an iron supplement in therapeutic dose is needed, compared to a lower dose (5–6 mg/day) for mothers in developed countries aimed at only compensating for increased need in pregnancy.

Many baby milk formulas are fortified with iron including prepacked feeds.

Zinc

The amount of zinc in human milk, though small, is sufficient to meet the requirement of the newborn infant. Acrodermatitis enteropathica is reported to be far more common among artificially fed infants than among those who are breast-fed.

Trace Elements

Human milk also has the added advantage of providing sufficient amount of trace elements that meet the baby's requirement.

The levels of trace elements (e.g., copper, selenium, cobalt) are higher in human milk than in cow's milk.

Weaning

It is the process of introducing breast milk substitutes and/or complementary foods thereby decreasing lactation stimulation and milk production and eventually ending lactation and breast feeding.

Weaning is a crucial and important event in infant nutrition.

In the developed world, almost half of the mothers who start breast feeding stop within 6 weeks. The reasons vary, but in many instances they arise from difficulties that can be overcome with some encouragement and support.

The age at the initiation of weaning varies substantially in both developed and developing countries. Weaning in the developed countries starts early (i.e., before the age of 6 months), with the increasing number of working mothers.

In the developing countries, weaning may be earlier or later than in the developed countries. Most children continue to receive breast milk or an infant formula during weaning till the age of 24 months.

Many commercial formulas have been introduced in the process of weaning. These formulas are less modified forms of cow's milk than the starting formula. Iron deficiency anemia is an important cause of anemia in children in the developing world and is the commonest nutritional disorder during weaning. Weaning milk formulas are usually fortified with iron and vitamin D.

Weaning may start by introduction of formula feeding or water and fruit juice. Gradually the baby will be offered more of the artificial formula and less of the human milk. The process of weaning is not recommended to start before the age of 4–6 months in the exclusively breast-fed infant.

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53 Malnutrition in Infancy

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Concept

Moving from Malnutrition to Subnutrition

Malnutrition is one of the most common causes of mortality and morbidity among children under the age of 5 years in the developing countries. It is also an associated feature of some pediatric disorders in the developed world. Traditionally, malnutrition has mostly been associated with poverty, which should mean not only lack of food but also lack of security, psychomotor stimulation, and affection. Severe malnutrition represents the most dangerous degree of malnutrition; it requires special care in hospital with special management.

Although nowadays the term *subnutrition* is preferred to malnutrition, it is necessary to use the latter when referred to the past. In the decade of the 1960s, it was estimated that there were 300 million children in the world affected by under/malnutrition. In the 1980s, this figure had reduced by half, and in the year 2000, the figure given by WHO was 146 million. This implied a further reduction due to the population increase in the developing World. UNICEF's report that the annual subnutrition percentage reduction all over the world was 1.7% for the period 1966–2005. This figure is important from a global health focus as in developed countries, all chronic pediatric malnutrition is stable at less than 1%. The decrease in poverty, thanks to the development of the most heavily populated countries (China and India), has improved the prevalence and also infant mortality rates.

The WHO defines *"malnutrition,"* from a conceptual point of view, as the imbalance between the intake of nutrients and energy and the bodily requirements to live, grow, and carry out specific functions, especially before reaching the age of 5. This initial concept has changed from a mere lack of calories and protein to the present one including other specific deficiencies, a presence of illnesses, and lesser education. Nowadays *the term "subnutrition" is preferred as malnutrition* can exist without weight loss and even in cases of obesity. The term "underweight" is necessary because it signals the first degree of subnutrition (BMI-zs from −1.0 to −2.0 SD) and is the most common situation in developed and developing countries. The term *"stunting"* meaning height reduction (different from short height) from a nutritional origin is interesting as in westernized and transitional countries heights can be seen as shorter than the target height as consequence of a suboptimal nutrition. On clinical grounds, the term *"failure to thrive"* is sometimes used to refer to the state of "underweight" as it sounds less pejorative. The term *"wasted"* indicates an extreme and dangerous thinness. Finally, the terms *"food insecurity"* and *"hunger"* are used but with a more sociological focus. Owing to the lack of a precise measurement for both, they are evaluated according to the degree of subnutrition. With appropriate care management in hospitals and follow-up care, the lives of many such children can be saved.

Recognized risk factors that could lead to severe malnutrition in the developing countries are rural areas, low socioeconomic status, and young age of parents and patients.

The term *"protein-calorie malnutrition"* (PCM) was introduced in the 1920s by Jellife to describe this situation in developing countries, although in developed countries, it was also applied to a very minor population of children in hospital or chronically ill. PCM is usually a result of a diet deficient in energy and protein. PCM and infections such as measles or gastroenteritis are largely responsible for the very high infant mortality rate in the developing countries. Its two most well-known forms are *marasmus* and *kwashiorkor.*

Marasmus is an insufficient intake of proteins and energy while *kwashiorkor* is an almost sufficient intake of calories, but not proteins and because of this, such patients develop edema besides other specific clinical symptoms. Marasmus may follow recurrent attacks of gastroenteritis or intractable diarrhea.

Anthropometrics of Subnutrition

The methods must be *quantitative* and initially *simple* so as to be able to apply to any infant population. Anthropometric evaluation offers a crude assessment of the state

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of malnutrition. It has a recognized limitation, as it refers to a set of references applicable to children not necessarily the same as the ones under study.

The anthropometric measurements usually include length or stature, weight, skin-fold thickness of the triceps, subscapular region and circumference of the head, upper arm, and upper thigh. Efforts should be focused on establishing the norms for these items applicable to the indigenous population. Undoubtedly, the most used method for subnutrition screening is weight below 3rd centile for age and gender. In a rather imprecise way, this will indicate chronic and recent subnutrition. It is also considered when the weight curve has down crossed more than 2 centile lines on the chart. In an undernourished child, a decrease in height below 3 centile (stunting) indicates an accumulative effect of subnutrition, but to be more certain, at least the height of both parents should be known. This initial procedure should give way to the methods which incorporate height as a reference element for weight and which indicate the most recent effects related to nutrition. This is known as the *Quetelet index* (kg/m^2) which is more generally known as *body mass index (BMI)* which is very informative in the case of an adult whose growth has stopped. In the pediatric and adolescent stages with such variable growth speeds (4.0–15.5 cm/year), it is necessary to have more accuracy.

The relative body mass index (rBMI) is probably the least erroneous when it comes to fixing the degree of nonchronic subnutrition. This is due to the fact that height is used and this quotient is referred to the same quotient as 50 percentile of the age and gender reference population charts according to the formula ($kg/m^2/kgp50/m^2p50) \times 100$ and accurately identifies cases of acute subnutrition.

For *rBMI*, the figures of 85–90% are accepted as underweight and as subnutrition when they are below 85%. The advantage is that it can be calculated just with a growth chart and a simple calculator. The rBMI is less accurate in the cases of stunting where the accumulative effects of subnutrition have diminished the height. In these cases, and before qualifying this lack of height as nutritional, it should be ruled out as familial short height by means of target height which is obtained according to the *formula (paternal height + maternal height)/2 + 12 in the case of boys and −12 in the case of girls*, all data in centimeters. Also the neonatal status must be known (*small gestational age*) because it could affect the growth velocity. Finally, considering previous heights, specially in the first 2 years of life is of a great help as well as evaluating genetic and medical causes for short height.

In practice, the basic measurements usually focus on height (or length) and weight. Weight may be measured fairly accurately if the proper scale applicable to each age group is available and well calibrated. The physician may face some difficulties in trying to get the exact height (length) for the young infant. Such an exercise may often require more than one person and more than one measurement to be exact. In spite of all the difficulties and limitations, the anthropometric measurements remain valuable in the overall evaluation of children with malnutrition.

The body mass index z-score: zs = (BMI patient – BMI p50)/standard deviation of BMI for age and gender gives analogous information to that of the rBMI, the cutoff points are: *underweight – 1 – 2 SD* and subnutrition when it is greater than −2SD. *The z-score* when calculated for weight alone in relation to age and gender enables also to evaluate with greater accuracy chronic and recent subnutrition than the percentile plotting. The incorporation into the clinic of computer programs (*Seinaptracker*) makes this calculation easier and allows a wider use and more accurate diagnosis for the present situation and evolution of the patient. The advantages of using z-score are that it allows to quantitate the degree of underweight (or overweight) estimated by means of the BMI in relation to a national reference growth chart. Then the distance from individual BMI to the mean (or median), evaluated in SD units, permits a comparison with other pediatric population, and particularly to follow quite accurately the evolution of a child or of a determined group (Fig. 53.1).

Causes

In Developed Countries

In developed countries, as opposed to those developing countries, inadequate quantities of food, lesser degree of family education, or a poor health system are rare causes of undernutrition. Catastrophes, economic crises, or war can lead to the appearance of these factors, although they do not usually last as long as in developing countries. On the contrary, illnesses, especially chronic, play a more important role since they can imply anorexia, higher caloric requirements (infections, fever), or impair digestive and absorption functions. In practice, these situations, once the so called *infant – dystrophy* has gone, are represented by the following illnesses: cystic fibrosis, illnesses of the digestive tract which have not been diagnosed in time, chronic renal failure, cancer and its (chemo and radio) therapy, congenital heart disease and neurological (cerebral palsy),

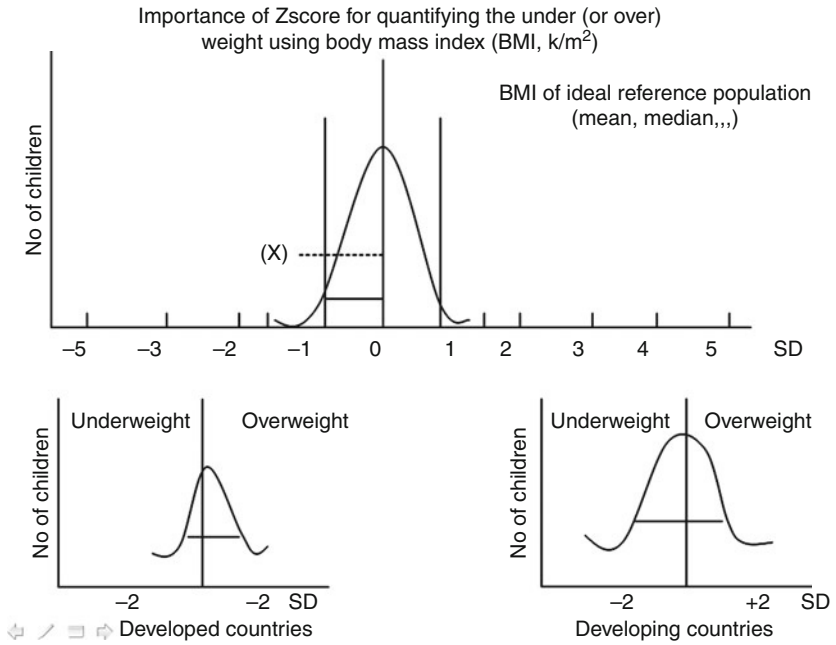

Figure 53.1

In the *upper* part, a normal distribution of BMI is shown. The distance from any individual case (x) to the mean of the reference population by gender and age can be evaluated by means of the z-score formula, obtaining accurate results expressed in standard deviation units. In the *lower* part of the figure, a representative curve of the nutritional status in developed countries is shown, with skewness toward the *right*. In developing countries, there is a skewness toward the *left* but also with a modest increase toward the *right* due to the obesity rise

and muscular illnesses. Less frequent causes but with potential capacity for malnourishment are lead poisoning, severe burns, HIV infections, and anorexia nervosa.

Prematurity must be taken into account, especially when these children are small for gestational age and if they are symmetrical (weight, height, and head circumference all below the 3rd centile) since these will have a poorer growth recuperation in spite of correct nutrition or even if supplemented. On the contrary, an asymmetrical child (reduced weight but with normal height and head circumference) responds better to these nutritional practices. The preterm adequate for gestational age is also a candidate to suffer from malnourishment at a later stage or earlier as consequence of common complications (bronchodysplasia, postsurgical short intestine, oral aversion, etc.); this implies special nutritional attention and focus on food from the beginning.

Another group of interest in the genesis of malnourishment are the *congenital anomalies* such as cleft palate or genetic syndromes in some of which short height is a part and therefore stunting must be discarded.

Within the family atmosphere, it is essential that taste perception of the newborn must be stimulated at the right time (*beikost*) because if this is not the case, the intake of solid food becomes difficult and results therefore in a reduction of food quantity and quality. This block of factors is also known as psychosocial subnutrition (and stunting). This is also known as the *syndrome of lack of affection, negligence, etc.* which although not reaching the stage of child abuse, goes on for a longer period of time. This is discovered on occasion when the family describes the child as temperamental, with sleeping problems and generally difficult to bring up.

The presence of the polymorphism C825T in the gene GNB3 brings less sensation of hunger and less sensation of discomfort or unease about this; this leads to a lower food intake in these patients. It is also possible in this way that a malfunction of satiation gut hormones (CCK, PYY, and GLP) can also contribute in certain cases.

In Developing Countries

In developing countries, the protein-calorie deficiency and also deficiencies in the most common specific nutrients, such as iron, zinc, iodine, and vitamin A among,

primarily exist. To these, other social factors like maternal malnutrition, ignorance, demographic explosion, poor housing conditions, lack of hygiene, poorly developed sanitary system, low family income, and difficult access to basic medical care must be added. Severe repetitive acute infections (diarrhea) or chronic (HIV) are other frequent circumstances predisposing toward malnutrition. These factors are more important than the protein-calorie deficit itself, as are also some previous actions (being given food versus agricultural teaching) with the aim to make up for this scarcity. An important factor is the stopping of breastfeeding early on, specially in circumstances when Beikost is for most part subject to carbohydrates. Food insecurity for young children formerly described in developed countries, occuring when nonfinancial factors such as maternal mental problems are widely applicable here, not only for the low socioeconomic status but also for depression or domestic violence. Nevertheless, it is important to conclude with the idea that malnutrition in developing countries is not due to one single cause and these other factors will certainly contribute.

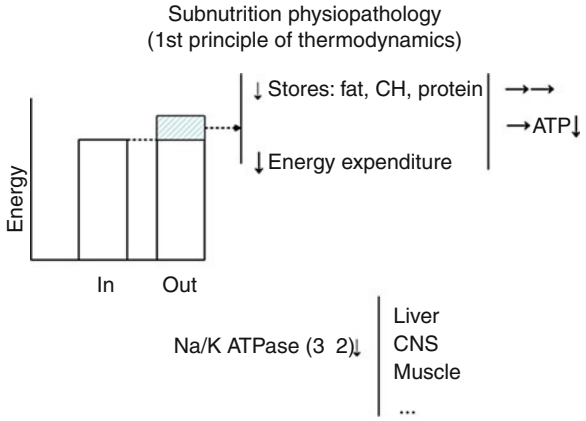

Figure 53.2
Subnutrition pathophysiology. According to the first principle of thermodynamics, the negative energetic balance is covered by a diminution of the stores and also by reducing physical activity (energy expenditure). After a long metabolic path, a reduction of ATP synthesis occurs. This will impair many functions as is shown in the *lower* part of the figure

Physiopathology

The child with severe malnutrition must be treated differently, because his physiology is seriously abnormal due to reductive adaptation. The system slows down and does less activities in order to allow survival on limited calories. This slowing down is known as reductive adaptation. As the child is treated, the body's system must gradually learn to function fully again.

A nutrition deficiency affects practically all organs and systems, especially in a phase of growth. Dietary proteins must provide essential amino acids for diverse synthesis in both facets, the structural and functional roles. Energy supplied by fat and carbohydrates is fundamental for all biochemical and physiological functions of the organs. When faced with a deficiency, the equilibrium is initially reached by metabolizing the energy stores and by a reduction of energy expenditure, mainly on physical activity, growth velocity, and body temperature, because the greater quota (resting energy expenditure 70%) is hardly modified at least in the initial and medium phases and so will be the diet-induced thermogenesis or energy used in digestion, absorption, and transport of nutrients (10%). As a consequence of this adaptation, changes appear which will be analyzed below. Besides the energetic aspect, the adequate intake of micronutrients must be taken into account as these are essential for different metabolic functions as they are components and cofactors in multiple enzymatic processes (*Fig. 53.2*). The physiopathological consequences of energy reduction depend on four major factors:

1. The type of energy restriction
2. The age at which it starts and its duration
3. The previous nutritional state
4. The existence or not of acute repetitive or chronic infections

The classic animal experiences with food restrictions and studies on children with malnutrition have allowed one to show how initially there is a depletion of fat and later a depletion of glycogen. If the situation persists, the protein catabolism will maintain basal needs. Hormonal changes are in a certain way responsible for these situations and among these must be considered the rise in cortisol, the lesser secretion of insulin, as a certain marginal resistance to this. An increase of GH but with a poor response of IGF1 and an increase in production of aldosterone also are found. The fact of a lesser synthesis of ATP in this last context brings with it an impaired function of Na/K ATPase, a sodium pump for the interchange of sodium for potassium at a rate of 3 x 2 with the consequent increase of intracellular Na and a reduction of K. But depending on the tissue where this reduction of

exchange takes place, the clinical consequences are different and of course do not make clear the initial implication in the genesis of the edema. Probably the reduced synthesis of albumin in the liver (fatty or not) could be the most important factor.

Another approach for water retention should be considered. Edema is a well-recognized clinical manifestation of subnutrition of childhood. The relationship between hypoalbuminemia and edema formation is well recognized in kwashiorkor. Since the early 1970s, it has been suggested that the cause of edema in kwashiorkor is hypoalbuminemia followed by reduced oncotic pressure. In marasmus, the low-energy supply stimulates cortisol secretion, which results in wasting of the muscles and as a consequence, essential amino acids become available for albumin synthesis. However, in recent years, the contributory factor of hypoalbuminemia in the pathogenesis of edema in kwashiorkor has been challenged. Further studies have demonstrated that the degree of the edema shows poor correlation with plasma protein concentration. The edema often resolves despite continued hypoalbuminemia. Edema in kwashiorkor was reported among affected children with a serum albumin higher than 17 g/L. The occurrence of edema in subnutrition may be a result of misdistribution of excess water between extra- and intracellular compartments. *Renin* activity in plasma is also increased in kwashiorkor. Subnutrition can also be associated with deficient ability to concentrate urine. The presence of aminoaciduria in this situation points to proximal tubular dysfunction. It is therefore appropriate to consider that the retention of water and salt in kwashiorkor is at least partly caused by altered renal function. Studies on groups of affected children have also shown that the average blood creatinine concentration was higher than in the well-nourished ones, while the urine volume was significantly lower in the group with subnutrition. Furthermore, they show a tendency to retain sodium and fluid whether they are edematous or not. Plasma *free iron* was also claimed to contribute to the mechanism of edema in kwashiorkor.

Clinical Manifestations

A meticulous history and physical examination are fundamental here since laboratory tests yield very little for an early diagnosis of subnutrition. It must be taken into account that the feeling of hunger is rarely expressed and an absence of other symptoms is the norm except for very severe cases. The mother's circumstances must be recorded in the anamnesis. The questions related to the child imply his efficient incorporation into the health system; if he can attend primary care regularly (vaccination, oral hygiene, etc.), developmental milestones and illnesses suffered, especially infections. The somatometric history is of an utmost importance and if possible should include weight and height of parents and of siblings and also previous data of the child. This can signal the beginning and evolution of subnutrition indicated by less weight and height gain. A nutritional record is also extremely important: Probably the most reliable is an absolute recall of what has been eaten in the last 24 h, but this is not fully representative. A prospective record is better of all the food to be taken in the next 5 days which is a way to assess the intake of proteins and energy. It is necessary to know for certain if the child feels hungry. The data related to family food habits and how meals are eaten is fundamental in cases of subnutrition. The following point is the social situation: age and occupation of the parents, possible family stress, and the economic situation in the home. In all cases of subnutrition or underweight, the anamnesis must be oriented toward the coexistence (classic secondary subnutrition) of organic illnesses by means of the presence of other signs and symptoms like anorexia, mood swings, dysphagia or vomiting, the type and number of stools, recurrent fever, and polyuria.

The 5 principles clinical signs of severe malnutrition are: severe wasting, edema, dermatosis, eye signs, and stunting.

Severe Wasting

The outline of the child's ribs are easily seen, skin of the upper arms looks loose, the skin of the thighs looks loose, the ribs and shoulder bones are easily seen, and flesh is missing from the buttocks.

Edema

The extent of edema is common rated in the following way:

+ Mild: both feet.
+ + Moderate: both feet, plus lower legs, hands, or lower arms.
+ + + Severe: generalized edema including feet, legs, hands, arms, and face.

Dermatosis

It is more common in children who have edema than in wasted children.

The dermatosis is classified in the following classification:

+ Mild: discoloration or a few rough patches of skin.
+ + Moderate: multiple patches on arms and/or legs.
+ + + Severe: flaking skin, raw skin, fissures.

Eye Signs

Children with severe malnutrition may have signs of eye infection and/or vitamin A deficiency.

Bitot 's spots : superficial foamy white spots on the conjunctiva.

Pus and inflammation.

Corneal clouding.

Corneal ulceration: which is a dangerous and urgent situation that requires immediate treatment with vitamin A and atropine.

Stunting

Which is unusually low height or length for age, often due to chronic malnutrition.

The standard deviation (SD) is a way of comparing the weight with height of the patient, Patient is considered as severely malnourished if his SD – score is < 3 SD.

The physical examination should be preceded by very precise height and weight measurements as the diagnosis of subnutrition will only be reliably given if the data is accurate. Genetically small children (normal variant of short height) usually have a normal weight for their height (rBMI 90–110%); they even usually have a head circumference in the same percentage. When subnutrition (and stunting) exists, a fall in the weight chart is first seen, and later is the height, but to assess them, a prolonged observation with monthly intervals is required. A thorough examination of systems is necessary for the diagnosis of underlying illnesses which may cause subnutrition or undernutrition. Apart from this quantifiable and clinical data, there is also present a less interaction between mother and child, with less visual, physical, or verbal communication.

The presence of lack of hygiene, nappy/diaper rash, or deficient buccal care implies a situation of abandonment or negligence. This is being so frequent in failure-to-thrive cases. If it is more severe (emaciation), then the skin is dry, inelastic, pale and cold, hair is sparse and falls easily, there is less muscle-mass and easy fatigue, a lack of interest in what is going on, more frequent infections, and slow healing of wounds.

To end this clinical context, it is necessary to mention the social risks of undernutrition. Children are targeted by bullies, judged as unhealthy and faible and if adolescent, rejected by classmates.

Complementary tests: This can be limited initially to a complete blood test, CPR, albumin, alkaline phosphatase, total cholesterol with a urine analysis and culture. One must remember that the markers are never too early and for caloric deficiency are the serum reduction of albumin and total cholesterol. The classic malnutrition markers (IGF 1, pre-albumin, RBP, test for immune responses, amino acid levels, essential fatty acids, vitamins, and trace elements) are found to be altered in only 1% of the cases which occur in the western world, while their determination in developing areas is more complicated and resource consuming. At least one must make sure that there is no lack of iodines, or of vitamins A and D, and specially iron. Cases with an important malnutrition are also candidates to studies of endocrinology, hepatology, cardiology, and especially for gastrointestinal tract disorders due to the therapeutic implications and prognosis that they may have.

Marasmus and kwashiorkor: These are the two syndromes mentioned by McCance as representative of a serious protein-calorie malnutrition.

The marasmus (non-edematous malnutrition) is produced by global energy deficit and comes between 6–18 months of age coinciding with an insufficiency of breast milk, use of formulas, or a too diluted milk, all this accompanied by frequent infections. It is characterized by a slowing down or even stop in weight increase, then followed by a loss of subcutaneous fatty tissue. If the situation continues, then muscular devastation appears also. There are general irritability and usually constipation but with occasional bouts of diarrhea which is difficult to treat. Examination reveals a chronically ill child with apathy and wizened (old man) face attributable to the disappearance of the buccal fat. The child looks thin, wasted, with loss of fat and muscles (Fig. 53.3) but also with distended or scaphoid abdomen and delayed physical development. The eventual development of lactose malabsorption contributes to the abdominal distention. There is an obvious loss of subcutaneous fat with decreased skin-fold thickness, the loss of subcutaneous fat around the buttock shoulder,

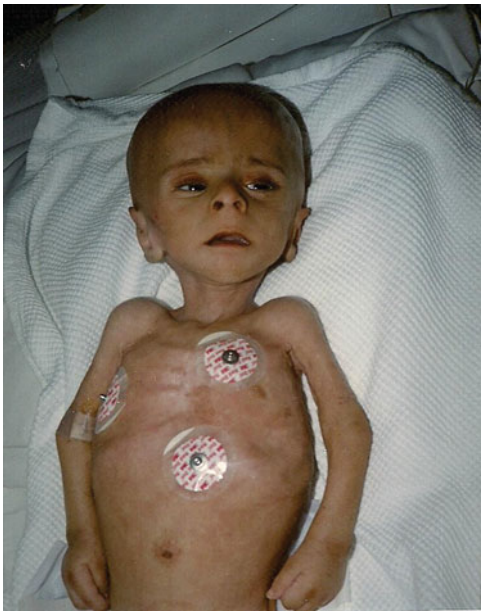

Figure 53.3
A marasmic young infant with classic features of apathy, marked wasting with easily seen ribs, and loss of subcutaneous fat

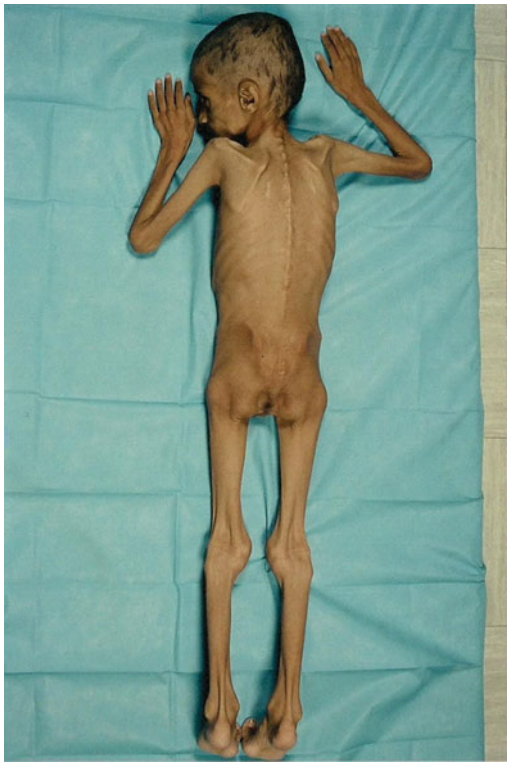

Figure 53.4
A child with severe wasting: **The outline of the child's ribs is easily seen, skin of the upper and lower limbs looks loose, the ribs and shoulder bones are easily seen, and flesh is missing from the buttocks as well as from the rest of the body**

and trunk and limbs complete the clinical appearance (*Fig. 53.4*). Marasmic children are often hypotensive; the presence of bradycardia and hypothermia is ominous. Hypoglycemia is common, but serum albumin and electrolytes are usually normal. It is important to screen marasmic children for associated infections and vitamin deficiencies.

The name *kwashiorkor* (edematous malnutrition) is identified as disease affecting the deposed child, the disease that the first child gets as the mother is expecting another child and tends to neglect the first one or following the arrival of the new baby. In the kwashiorkor, there is an energy intake at the limit but with a predominant protein deficiency generally coming between 18 months and 5 years of age.

Clinical Manifestations. The sign which best defines it is the presence of edema initially in the lower limbs and rapidly ascending even as far as the face. This can conceal the weight loss which always exists, but with growth delay, muscular devastation, anorexia, psychomotor alterations, gastrointestinal disorders with a tendency toward prolonged diarrhea, liver enlargement (steatosis), skin wounds or ulcers, and the hair is sparse, depigmented, reddish gray in color, and falls easily. All of these allow a simple, clinical diagnosis. When this situation continues, initial lethargy and apathy advance to a state of hypotension, hypothermia, coma, and death. Fortunately, both conditions are becoming rare and rarer in the developing countries, where once they widely existed.

Evolution and Prognosis

Long-Term Effects of Subnutrition

A prospective study on children with severe malnutrition addressed the issue of whether early malnutrition results in permanent physical and behavioral deficits or not. The study, which began in the early 1960s and ended in the following decade, demonstrated both *physical stunting and intellectual impairment* among those children. Other studies have also shown some permanent

defect in stature if growth was arrested by malnutrition in early infancy.

Subnutrition is associated with evidence of gastrointestinal damage manifested as chronic diarrhea and failure to thrive. There is also a variable degree of mucosal atrophy of the small and large intestines, with plasma cell infiltration of the lamina propria. The disease is also associated with evidence of pancreatic insufficiency.

Animal studies have further reported that malnutrition resulted in retardation of cellular growth as well as cell division of the brain.

Malnutrition was also demonstrated to adversely affect the IQ status of schoolchildren who were hospitalized during their first year of life. The difficulties of such studies are in the selection of which controls and which standard to use.

Early malnutrition may also result in long-standing *behavioral deficits*. Such observation remains a subject of debate, as it does not apply on certain conditions associated with malnutrition such as cystic fibrosis, where affected children do not necessarily demonstrate reduction in IQ or school performance.

Subnutrition may also be associated with *respiratory* and *myocardial dysfunction*.

Night blindness is a major public health hazard in developing countries caused by insufficient consumption of beta-carotene-rich foods and high prevalence of PEM. An association between PCM, *xerophthalmia*, and night blindness has been reported from Bangladesh as well as from other developing countries. Children with PCM are more susceptible to infections that result in further deterioration of their nutritional status as well as further depiction of vitamin A stores.

In the short term, in the cases of severe malnutrition (weight ZS greater than −4 SD or weight for age at 60–70% or rBMI <70%), death occurs in half of the children under 5 years of age. Even when this reduction is 80%, the risk of death is superior to that of the normal local population and always closely related to infections. Recent data from Ethiopia show a mortality of 21.3% of hospitalized children under 5 years. These figures cannot be applied to the westernized world, where death by this cause is really exceptional.

In the long term, children with chronic malnutrition, even when this has been cleared up, show behavioral disorders such as irritability, apathy, anxiety, and lack of attention. This implies a reduction of about 10 points in cognitive function in relation to children with normal nutrition in the same environment. This will continue beyond adolescence with a weight and height deficit, poor muscle structure which results in less capacity for work.

An association between adiposity and stunting has been described particularly when undernutrition is over; therefore, attention should be paid to the changes in body composition, particularly in abdominal fat accumulation for the risks that it implies. Infertility when adult ages are reached is another risk of long-lasting children and adolescent undernutrition. Both these factors lead to a poor economic level and the situation carries on. These consequences have been shown in the long term even with patients studied recently in the USA. When will these consequences be reverted? This cannot be known, but the sooner the causes are solved and social environment improves, the better.

Treatment

In secondary subnutrition, the treatment of the underlying illness is the first and most important step. The nature of the originating illness makes the second step, dietary therapy, to be more or less effective, as for example in the case of cystic fibrosis. In the cases of primary malnutrition owing to an inadequate intake of energy and/or protein, the nutritional therapy is the most important. A properly selected and available diet is the mainstay of treatment of PCM. Improvement of the general diet with increased consumption of dietary vitamin A to reduce the risk of night blindness and other complications of vitamin A deficiencies is advised. It has been implicated that supplementation with vitamin A capsules alone without dietary supplements may not result in a sustainable reduction in vitamin A-related morbidity.

The association of subnutrition and being in hospital must be taken into account even in the developed world; criteria for hospital admittance is as follows.

Serious and severe subnutrition (rBMI < 80%) Concomitant dehydration, adverse family circumstances, and Failure of primary care therapy.

Treatment of Moderate Subnutrition

This is the most frequent. The energy supply can be increased by intake of higher caloric food than previously taken and nutritional supplements, but in a flexible and progressive way. By doing this, the intake of macronutrients is fundamentally increased, but it is important to keep in mind that this will not prove very effective unless family environment and factors also improve. In the case of

formula-fed babies, it is sufficient if the formula has a correct concentration and its volume is adequate for the weight of the baby.

In the case of children, the caloric intake can follow the *simple rule: kcal per day = height (cm) × 15* and is to be divided between four meals a day; these can be enriched with oils, butter, full fat milk, and cheese. When dealing with moderately undernourished children in a low socioeconomic scenario, dietary counseling can be as effective as food supply itself in medium-term subnutrition, particularly when the cereal-dominated diet is common. Plant foods should be processed to maintain the energy density (avoid diluted gruels) or diminishing the eventual antinutrients (protease and amylase inhibitors or lectins) in pulses by a thorough cooking. The beneficial quality of animal-source foods should be stressed because of their quality of protective nutrient. They should be taken whenever possible, although there is no factorial approach for minimums, due to high-quality protein, high level of minerals (milk), and lack of antinutrients. From a complementary point of view, a multivitamin and microminerals product especially with iron and zinc should be administered.

There is no need to use hydrolysate; the prevalence of Cow's milk allergy in severely malnourished patients is not higher than the habitual incidence (5% of the severe malnutrition cases).

Apart from the treatment, social and economical aspects play a fundamental role and on many occasions escape medical attention. When social workers are available, the weekly house visit has been shown to be very effective. Alternatively, the patient may go to appointments at outpatients to control weight evolution and diet planning. Another factor to keep in mind is behavioral attitude with respect to mealtimes, avoiding distractions (TV) and sweets or snacks between meals.

Treatment of Severe Subnutrition

When talking about prognosis, it has been seen how in children under 5 years of age, half of the deaths are related to severe malnutrition. It must be added here that after analyzing more than 60 studies throughout the world, this mortality figure has not gone down in the last five decades. In 1999, WHO published a manual for the management of severe malnutrition which could be applied to a great number of children even in rather unfavorable hospital conditions. It establishes the following phases.

Initial or acute phase (2–10 days), here preferably oral rehydration is set up (Na 45 mmol/L; K 40 mmol/L). Treatment of hypoglycemia is also set up and of any infections or infestations. Dietary therapy is also started. The formula "F75" (75 kcal/kg and 1 g/kg/day of protein) put forward by WHO has not been tested very thoroughly, and in the cases of marasmus, the use of a conventional formula gives good results. In any case, calorie density should be between 75 and 100 kcal/kg/d and must never exceed 100 kcal/kg/day. If the child was breastfed, this should be kept up, but with the certainty that additional intake will be necessary.

The IV fluids administration is limited in case of shock from dehydration or sepsis. In this case, 15 ml/kg over 1 h should be given. Repeat the same amount of IV fluids for another hour,with one of the following solutions (listed in order of preference):

- Half-strength Darrow's solution with 5% glucose (dextrose)
- Ringer's lactate solution with 5% glucose
- 0.45% (half-normal) saline with 5% glucose.

After 2 h of IV fluids: use of oral or nasogastric rehydration with ReSoMal (5–10 ml/kg) in alternate hours with F-75 for up to 10 h.

If the child fails to improve after the first hour of IV fluids, a septic shock is possible. The blood transfusion is necessary, with 10 ml/kg over 3 h, in association of diuretics administration to avoid the heart failure. (In case of heart failure, give packed cells instead of whole blood) . The risk of developing cardiac arrhythmia could be prevented by starting the treatment with progressive energetic quantity (100 k.cal/kg/day). The energetic quantity will be increased meal by meal after the stabilization of the child's status, to arrive at the end of the protocol to 220 k.cal/kg/day.

Starting with high quantity of liquids could provoke cardiac failure by overload, which explains the necessity of the avoidance of IV fluids as possible.

The second phase or rehabilitation (2–6 weeks) is the one in which the child increases both his dietary intake and weight, and this period supposedly should be spent in hospital. The treatment from the acute phase would be complemented and a diet ("F100" formula or conventional) would be established. In this, there is an increase of 25 kcal/kg/day until a good tolerance is reached always inferior to 150 kcal/kg/d and to 4 g/kg/d of proteins so as to avoid the "*refeeding syndrome*" (fall in plasma Pi due to intracellular migration) which can lead to death by cardiac arrest.

The third phase or follow-up implies the child going back to his family environment which has supposedly improved, at least educationally and to set up an outpatients follow-up.

This plan widely disseminated in the developing world has not, at least initially, lived up to its expectations.

Feeding is a critical part of severe malnutrition management; feeding should begin as soon as possible to prevent fatal complications. The feeding is based on the use of special solutions: F75 (used in the acute phase) and F100 (used in the stabilized phase).

The use of these solutions is based on the physiopathological guidelines; F75 contains 75 K.Cal/100 ml, and F100 contains 100 k.cal. F75 is low in proteins (0.9 g/100 ml) and sodium, high in carbohydrates, which decreases the risk of the renal overload and prevent the hypoglycemia; F100 provides high quantity of calories in limited volume, which prevents all possible cardiac dysfunctions.

The F75 and F100 are given to patients in a special protocol to avoid all possible complications.

The F-75 and F100 could be prepared in hospitals using different types of dried or whole or skimmed cow milk.

Weight Gain During Treatment

Weight gain is classified in three categories and estimated in g/kg/day: well weight gain is >10 g/kg/day, moderate weight gain is: 5–10 g/kg/day, poor weight gain is $<$ 5 g/kg/day.

The causes of the poor weight gain are: feeding preparation errors, tuberculosis, or infections. Tuberculosis is too difficult to be diagnosed; the presence of adenopathy or poor weight gain are the most common signs. The tuberculin test is always negative secondary to the cellular immune deficiency, and the treatment has to be started when the weight gain is absent for more than 10 days after a standard management.

Prevention

The severely malnourished infant is at risk of developing a number of complications such as hypothermia, hypoglycemia, encephalopathy, intractable diarrhea, cardiac failure, and infections. The increase in birth weight should be accompanied by a significant decrease in neonatal morbidity and mortality. Supplementation during late pregnancy can have a significant beneficial effect on birth weight in women who are genuinely at risk because of an inadequate food intake. With appropriate care management in hospitals and follow-up care, the lives of many children can be saved; the fatality rate could be reduced from over 30% in the old protocol to less than 5% if the new protocol is well applied.

At an individual level, the prevention of subnutrition in the pediatric age starts with prenatal nutrition, encouraging breastfeeding, the wise introduction of beikost, and the often ignored food control in the second year of life. All of this is relatively simple for developed countries which also have over 90% coverage of vaccinations and a good health system. However, in the developing countries, this is more complicated, even in situations where nutritional support is offered by other countries.

On certain occasions, pediatric subnutrition is only secondary to the health system shortcomings and which are not easily recognized by those responsible. The importance of political intervention for prevention can be seen here. A preventive chain at national, community, family, and child levels must function (as it did in India with the administration of vitamin A) with specific programs aimed at not only providing adequate nutrition but also for the prevention of infections and hygiene improvement, although these are not always given the priority they deserve. In general, subnutrition is decreasing at the same rate as poverty.

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54 Nutritional Modulation of Intestinal Gene Expression

Ian R. Sanderson

Childhood is a time of great change in nutrient intake. This review will examine how nutritional changes alter the expression of genes in the intestine (the point of interaction between the child and the nutritional environment). Unlike other organs, the intestine is not shielded from the major environmental changes of childhood. In the fetus, the intestinal lumen is sterile and the fetal circulation provides nourishment. But after birth, it interacts with an extremely complex environment containing nutrients in varying concentrations. At weaning, this level of complexity increases further.

Altering the expression of genes has become a rapidly developing area of research in medicine. The realization that gene expression is important in a wide range of diseases (and not just in inherited disease) has resulted in the whole field of gene expression being recognized as one which may bring new therapeutic options. Although most recent attention has focused on the benefits of altering gene expression by inserting new genetic material into cells, the expression of genes can also be altered by other means, most notably by changing the molecular environment that cells inhabit. Utilizing the natural responses of a cell to changes in its surroundings offers a new and amenable way to alter the expression of its genes. Many ways of altering these surroundings can be proposed, but no single act alters the environment of the cells of the intestine more than the ingestion of food. Thus, the future of nutrition as a therapeutic tool may lie in its potential for influencing gene regulation. This chapter will examine this emerging field and will lay down some concepts which may prove useful in establishing the scientific basis from which future treatments may develop.

The survival of a child to reproductive age and beyond requires an ability to respond to external demands. Every organ in the body is attuned to this need. Many organ systems have two levels of response to external changes. There is a rapid response, often occurring within seconds of a new stimulus: the contraction of muscle fibers following a neuronal impulse, or the breakdown of glycogen by the liver during hypoglycemia are examples of how cells can quickly change. Such responses do not involve changes in gene expression. The cells maintain themselves in a state of readiness by synthesizing proteins whose activity can quickly alter in response to external stimuli. Behind this immediate response, there lie other slower, but more lasting, responses that require genetic control. For example, when exercise increases on a regular basis, muscle mass increases, as does the activity of the attendant enzymes that serve the increased metabolic needs. Similarly, regular exposure of the liver to drugs induces the expression of enzymes that catalyze their breakdown.

There are few external stimuli on a child more important than its nutritional environment. The metabolic processes underlying the rapid response of cells to nutritional variations have long been documented in humans and other mammals. However, the mechanisms whereby gene expression changes in response to nutritional stimuli are still poorly understood in humans or indeed in any multiorgan animal. This is, at first, surprising because in bacteria, the study of nutritional changes led to the understanding of some of the most fundamental mechanisms of gene expression. The elucidation of the induction of proteins that transport and hydrolyze lactose (the lac operon) after adding lactose to bacterial culture media was the first examination of any form of gene regulation. These observations spawned an explosion of research in other regulatory genes in bacteria and in unicellular, eukaryotic organisms such as yeast. The upregulation of the bacterial genes that handle tryptophan when this amino acid is scarce (the trp operon) has become another well-understood example of nutrient–gene interaction.

Progress in the study of nutrient–gene interaction in eukaryotic cells has been slower for two main reasons. *First*, the molecular mechanisms controlling gene expression are more complex than in bacteria; *second*, it is more difficult to identify the metabolites of nutrients that may be responsible for inducing such changes. This chapter will therefore cover some of the advances in the study of nutrition on gene expression in the human and, where necessary, in other mammals. Nutritional changes ultimately impinge on most cells in the body; however, it is the epithelium of the gastrointestinal tract that first

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encounters any variation in nutrient intake. Much of this chapter will therefore concentrate on how nutritional factors can alter the expression of genes in intestinal epithelial cells. The relevance of nutrient–gene interactions to human physiology will also be stressed. Finally, because manipulating nutritional intake may be a way of treating disease in children, the chapter will discuss nutritional therapy in childhood in the light of its effects on gene expression.

The effect of nutrients on gene expression may have different implications in different individual situations:

First, genes may be upregulated to better utilize the supply of a particular nutrient when it is scarce. Transporters of nutrients and the enzymes that metabolize them are examples of proteins that may be induced by nutrients.

Second, the expression of genes required for the storage of a particular nutrient may be altered according to that nutrient's abundance.

Third, nutrients regulate the secretion of hormones that control the homeostasis of metabolic processes. For example, insulin synthesis increases after increased carbohydrate intake to maintain glucose homeostasis.

Finally, food is part of our external environment and as such represents a challenge to the cells that come into intimate contact with it. This challenge is met, in the main, the epithelial cells lining the gastrointestinal tract. The ability of these cells to alter the expression of their genes with changes in food intake is one of the ways by which the intestinal epithelium can dominate the intestinal environment.

Certain fundamental characteristics are found in the mechanisms that underlie each of these different aspects of nutrient–gene interactions. They include a specific interaction between the cell and a particular nutrient (sensing) and a pathway by which such an interaction may translate into alterations in gene expression (signal transduction). There is little understanding of these mechanisms at the present time. However, some aspects of the molecular biology of these two functions will be examined later in this chapter.

Effect of Intestinal Contents on Genes in the Intestinal Epithelium

The gastrointestinal tract is the only part of the body that normally comes into contact with nutrients before they are absorbed. The GI tract is therefore exposed with a wider variety of nutrient molecules than any other organ of the body. The picture is further complicated because the lumen of the intestine is not a direct reflection of the food ingested. It also contains bacteria and their by-products and factors secreted into lumen in response to the ingestion of food. The study of nutrients on the enterocyte therefore should consider how changes in diet may affect the area around the apical aspect of a particular epithelial cell. The dissociation between nutrients ingested and the changes observed in the bowel lumen become greater the further one proceeds down the GI tract. The contents of the distal colon are completely different from food, although even here they are affected to some extent by dietary intake. This relationship between ingested nutrients and the local environment of the lumen is a separate issue from the interaction of that local environment with genes in the enterocyte.

It has been traditional to assume that the expression of genes in the small intestinal epithelium is preprogrammed and that their expression is not influenced by events in the lumen of the intestine. However, this view may be incomplete. An alteration in epithelial cell phenotype secondary to nutritional factors would have three possible advantages:

First, the intestine could adapt to absorb nutrients more effectively if specific digestive enzymes and transporters of the epithelium were upregulated by the repeated intake of a particular nutrient.

Second, as all mammals are fed from mother's milk, the opportunity exists for breast milk to influence the development of the epithelium through actions of its own constituents.

Third, if the genes affected in the epithelium were immunologically important, the intestinal epithelium could influence mucosal immune responses, by signaling information to the mucosal immune system and beyond through changes in the expression of epithelial cell genes. Each of these areas is likely to represent important physiological mechanisms which have implications for child health.

Polarity of Epithelia

Many cells in the body do not depend on a separation of functions to different cellular poles. For example, muscle cells receive signals from the entry of glucose at any point on the plasma membrane and, as far as can be judged, the changes in gene expression are not affected by the site of glucose entry. Cells that form epithelia are different in that they exhibit polarity. This separation between the apical side (bordering the lumen in the case of the intestinal epithelium) and the basolateral side is central to epithelial activity. This property is well recognized in the

field of intestinal transport. Ions, small molecules, and macromolecules are all transported differently across the apical membrane than across the basolateral membrane. It is the polarity of the epithelium that gives direction to the movement of these substances across the epithelium into or out of the body. But this property must also be considered when examining all aspects of intestinal epithelial cell function. *Polarity* is also of fundamental relevance in the study of nutrient–gene interactions in the intestinal epithelium. The polarity of the epithelial cells distinguishes the two major mechanisms by which nutrients (and other luminal factors) affect genes – that of a direct luminal effect on enterocytes from an indirect effect mediated through hormones, growth factor, and cytokines.

Furthermore, the intestinal epithelium acts as a barrier to the external environment contained within the gut lumen. The barrier is not complete as the intestine allows macromolecules to be sampled and actively absorbs nutrients. It has become increasingly realized that the enterocyte itself acts as an immune cell. For example, it has receptors for bacterial products, as well as expressing a wide variety of molecules on its surface that contain immunoglobulin domains. The epithelial cell also expresses proteins that may interact with immunocytes within the intestine. These include surface molecules such as class II MHC and cytokines that are released from the epithelium such as chemokines or IL-6.

These signaling proteins enable the epithelial cell to orchestrate events in the intestine. In our research group, the hypothesis used is that changes in the intestinal lumen regulate the expression of signaling molecules by the epithelial cell. By this means, the dietary effects on the intestinal lumen acts through the epithelium to alter indirectly events in the intestine, particularly those of the mucosal immune system.

There are *two* components within the signaling pathway linking diet and luminal bacteria to the mucosal immune system:

First, the afferent limb comprises the mechanisms whereby luminal changes alter gene expression within the epithelium.

Second, the efferent limb is the effect of proteins expressed by the epithelial cell acting on the immune system of the intestine. There is now good evidence for both these pathways.

It is possible to examine molecular events in the epithelium induced by changes in diet (the afferent limb). A useful model is the expression of class II MHC in the epithelium following weaning of mice. Class II MHC is responsible for presentation of antigen and its expression on the intestinal epithelium of the mouse occurs after weaning. It is therefore possible to wean mice on to a normal diet (mouse chow) or defined liquid formula (enteral nutrition) to examine the difference between these types of nutrition. The epithelial cells can then be isolated from the mice at varying time points after weaning to study the expression of class II MHC and invariant chain, which is co-expressed. The effect of the enteral feeding (vivonex) was dramatically different from normal mouse chow. Normal mice chow induced an expression of these genes between 20 and 30 days of age; whereas during this time period, enteral feeding did not result in their expression in the intestinal epithelium. It is known that the class II transactivator (a regulatory nuclear protein) is, for all cell types so far examined, both necessary and sufficient for class II MHC expression.

Experiments were, therefore, designed to examine whether the diet acted through the class II transactivator (CIITA). In the mouse, there are three isoforms of CIITA. Interestingly, a normal complex diet increased the expression of class II MHC through CIITA IV.

In addition to the dietary regulation of class II MHC, there was a slow, time-dependent regulation and this was found to be due to CIITA III. These experiments show that alterations in the diet have recognizable molecular pathways between the intestinal lumen and the signal transduction machinery of the epithelial cell.

Bacterial fermentation of unabsorbed carbohydrate in the intestine results in short chain fatty acid production. Butyrate levels therefore reflect changes in bacterial populations and in the substrates available for bacterial metabolism. Butyrate levels vary greatly in response to external changes. For example, newborn babies have very low butyrate levels in either the small or large intestine. However, with time, butyrate levels rise to adult levels by 2 years. Interestingly, butyrate levels are much higher in bottle-fed babies than they are in breast-fed babies during the first 6 months of life.

Butyrate levels therefore reflect events in the intestinal lumen and we hypothesized that their concentrations may alter epithelial cell signaling. Its effects on IL-8 and monocyte chemotactic protein-1 (MCP-1) expression were examined. Increasing the concentration of sodium butyrate increased IL-8 secretion while simultaneously decreasing MCP-1 expression. These effects were seen in resting epithelial cell lines but were much more marked in cells that have been stimulated with a pro-inflammatory agent such as LPS or IL-1b.

It is known that sodium butyrate alters histone acetylation. The nucleosome consists of a solenoid of histones wrapped around by an integral of two turns of DNA. Butyrate increases histone acetylation and this reduces

the compactness of the histone. The DNA cannot wrap around the large nucleosome in an integral number of turns. The nucleosome can no longer be packaged into tight bundles. This exposes the DNA and makes it more amenable to transcription factors. The working hypothesis is that butyrate altered the expression of chemokines by this process.

To test this hypothesis, a fungicide, trichostatin A (TSA), which is 700 times more potent in inducing histone acetylation than butyrate, was used. If the effects of butyrate on chemokine secretion were due to increased histone acetylation, the TSA would be expected to reproduce them. Experiments with TSA showed that TSA increased IL-8 secretion and decreased MCP 1 secretion. Both TSA and butyrate increased the acetylation of histone. Furthermore, the degree of this increase in IL-8 varies with the degree of histone acetylation. The effect of butyrate on histone acetylation was also reversible.

In summary: These experiments show that sodium butyrate alters the expression of chemokines in the epithelial cell. In addition, short-chain fatty acids alter this expression through histone acetylation. These experiments, however, do not exclude the possibility that additional effects of sodium butyrate may occur through promoter systems. Indeed, recent studies have demonstrated that butyrate downregulates insulin-like growth factor binding protein-3 (IGFBP-3) through acetylation of an inhibitory DNA binding protein. It is a challenge of future work to examine the interaction between chromosomal regulation, as is seen in these experiments, and promoter-based regulation with both butyrate and other luminal molecules.

Evidence for the effect of epithelial cell gene expression on the mucosal immune system (the efferent limb) has come from the ability to selectively alter the expression of genes in the intestinal epithelial cell by transgenic techniques. Chemokine expression by the epithelium has been used as a model to show that the epithelium can orchestrate the mucosal immune system. The chemokine, IL-8 which, in the human, results in the recruitment of neutrophils was the first identified chemotactic cytokine. However, IL-8 is not expressed in the mouse.

To examine the effects of chemokines on the mucosal immune system, a system was developed whereby the chemokine, macrophage inflammatory protein-2 (MIP-2), whose effects are very similar to those IL-8 in the human, was linked to an FABPI (fatty acid binding protein of the intestine) promoter. The promoter is only active in the epithelial cells of the small intestine and proximal colon. The transgenic mice had an increased recruitment of neutrophils into the lamina propria, and into the epithelial cell fraction, where the FABPI promoter was active. These data show for the first time that the epithelial cell can, through the release of chemokines, alter the mucosal immune function of the intestine in vivo. However, changes in the intestinal lumen may affect many chemokines as well as other cytokines which alter immune function. It is likely therefore that the changes in gene expression in the epithelium have far-reaching effects on the rest of the mucosal immune system.

These signaling processes are important not only in health but also in the treatment of disease. For example, the primary therapy of children with Crohn's disease in the UK is treatment with enteral feeds. Although there are many mechanisms by which enteral feeds may have their activity, it is possible that one of them is by radically altering the luminal environment to such an extent that it varies the signals from the intestinal epithelium to the mucosal immune element. This results in a downregulation of the inflammation of Crohn's disease. By this means, there is a decrease in the inflammatory activity of Crohn's disease.

DNA Methylation and Imprinting

The chapter has described examples of nutrient regulation of gene expression in the intestine. However, mechanisms exist within the genome for affecting gene expression throughout the body. Imprinting is an important example of this. Genomic imprinting is the silencing of one of a pair of alleles, allowing preferential expression of a particular gene from either father or mother. For example, the maternally inherited allele of the gene encoding IGF-II is silenced, resulting in expression that is derived almost entirely from the father's DNA.

Elegant studies in the late 1990s demonstrated that the phenomenon was due to differences in DNA methylation between the two alleles. Around 10% of adults exhibit some loss of imprinting (LOI). LOI of the IGF-II is often present in a condition familiar to neonatologists, the Beckwith–Weidman syndrome, where infants are born with abdominal wall defects in association with hypoglycemia and large organs, most noticeably the tongue. In addition, LOI of IGF-II is associated with certain tumors of childhood, particularly nephroblastoma (Wilms' tumor) and hepatoblastoma.

The variable yellow allele (A^{vy}) of the agouti mouse is an excellent tool in which to study DNA methylation. Expression of A^{vy} depends on a specific long terminal repeat (LTR). DNA methylation changes the gene's expression (and yellow color) by different amounts in genetically

identical mice. Although the level of agouti expression alters a number of downstream processes such as obesity and longevity, the relation between DNA methylation and the coat color has enabled researchers to show that diets rich in nutrients that increase donation of methyl groups cause changes in DNA methylation in coat color. These experiments raise the possibly that there is a direct relationship between diet, DNA methylation, and gene expression. More recently, Waterland and colleagues have varied postweaning diet and altered the DNA methylation and imprinting of the IGF-II gene in the maternal of non-agouti mice, thus confirming that diet can alter the expression of genes through LOI.

Conclusions

The possible number of interactions between nutrients and genes is very large, but this chapter has focused on specific examples where such phenomena may be important in childhood health and disease. The contents of the gastrointestinal tract have a major influence on gastrointestinal disease. It is believed that the luminal regulation of epithelial signaling affects the intestinal inflammatory process, especially because the intestine is an organ where the variations of nutrients are greatest.

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55 Enteral Feeding

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Enteral nutrition is a safe and effective mode of nutrition in most critically ill children. The early initiation of enteral nutrition may preserve mechanical and immunological gut barrier function and reduce bacterial translocation and the incidence of sepsis and multisystem failure.

Enteral nutrition is a widely used therapy for nutritional treatment of patients with multiple pathologies.

Most babies are expected to respond well on breast milk as on formula feeding. However, there are well-recognized conditions in which special dietary formula and regimens should be adopted. Dietary manipulation from early infancy has made it possible to ensure adequate enteral nutrition to such affected groups. These measures have saved a good percentage of affected children from having to go on to a parenteral nutrition program. The trophic effects of enteral nutrition are such that it is always advisable to try the effect of their continued administration in continuous nasogastric drip infusion even in a nutritionally insignificant amount. It is only in those children with frank intestinal failure that long-term parenteral nutrition should be considered. Total parenteral nutrition is recognized to result in functional and structural atrophy of the gut.

Enteral nutrition has also enhanced the adaptive process in babies with short bowel syndrome, enabling them to tolerate earlier and better enteral nutrition and to gradually do without parenteral nutrition.

The enteral feeding formula should contain a high percentage of medium chain triglycerides, essential fatty acids, fat-soluble vitamins, as well as glucose polymers. In patients with advanced liver disease, up to 4 g/kg/day of protein may be tolerated.

There are well-recognized conditions in which special dietary formula and regimen should be adopted. Adequate enteral nutrition to such group of children saved them from having to go on to a parenteral nutrition program.

Human milk contains many nonnutritional substances such as immunoglobulins, lactoferrin, lysozyme, and macrophages that enhance host defense. The risk of infection is far greater in formula-fed infants than in breast-fed infants

The introduction of an *elemental diet* has also made it possible for patients such as those with Crohn's disease to go into remission without having to suffer from the side effects of prolonged steroid therapy. An elemental diet as the sole means of nutrition for about 6 weeks was reported to be as effective as oral steroids in inducing remission. The exact mechanism of action of an elemental diet in this regard remains uncertain.

Although many patients manipulate their diets to help treat their inflammatory bowel disease, only parenteral nutrition with bowel rest and exclusive enteral nutrition therapy have been shown effective for the treatment of inflammatory bowel disease. Furthermore, literature supports the use of enteral nutrition in benign and malignant diseases. Studies have shown that infections, sepsis scores, and hospital stays were significantly reduced in the enteral nutrition–supplemented group.

Recent evidence demonstrates that early nutritional support is not only safe but likely necessary to optimize infant growth and neurodevelopment.

The use of synbiotics and probiotics is gaining further acceptance. Supplementation with glutamine may be important for wound healing. Enteral feeding in malnourished child may result in rapid growth of gut mucosal protein.

Polymeric formula has direct anti-inflammatory effects on enterocytes in an in vivo model of intestinal inflammation. The precise mechanism by which total enteral nutrition suppresses inflammation, however, is unknown.

The nutritional status of a patient is believed to have a significant effect on wound healing. Early enteral nutrition with or without glutamine reduces anastomatic inflammation. Several reports indicated the favorable response to the introduction of glutamine in the therapeutic management of children with short bowel syndrome.

Immunonutrition with formulas containing immunonutrients such as glutamine, arginine, omega-3 fatty acids, and nucleic acids have been shown effective in reducing the number of postoperative infectious process.

Enteral nutrition is also introduced in the management of children with various hepatic disorders associated

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with severe malnutrition. Enteral nutrition is safer than parenteral nutrition and is associated with a reduction in infectious complications.

Indications

Enteral nutrition is indicated in varied spectrum of clinical conditions in which regular oral feeding is not possible as in:

- Inflammatory bowel disease
- Digestive motility disorders
- Pancreatitis
- Radiotherapy or chemotherapy cases
- Some cases of esophagitis
- Some metabolic disorders
- Neurological dysphagia

The types of enteral feeding, or tube feeding, are named according to the feeding route used, the site where the feeding tube enters the body, and the point at which the formula is delivered: nasogastric, nasoduodenal, nasojejunal, gastrostomy, and jejunostomy.

The decision of which type of feeding to use is based on the expected duration of tube feeding as well as physiologic and patient-related factors.

The types of tube feeding most commonly used are nasogastric feeding and gastrostomy feeding.

Nasogastric (*NG*) *tube* is usually used when tube feeding will be required for a short time (i.e., less than 3 months).

Gastrostomy tubes are well suited for long-term enteral feeding or in cases of swallowing difficulties.

Jejunal Tube Feeding is used in children who cannot use their upper gastrointestinal (GI) tract because of congenital anomalies, GI surgery, immature or inadequate gastric motility, or a high risk of aspiration.

Types of Feeding

Tube feedings can be administered by bolus feedings, continuous drip feedings, or a combination of both.

Bolus feedings are delivered four to eight times per day. Each feed lasts about 15–30 min. Bolus feedings are more similar to a normal feeding pattern. In some children this pattern may cause bloating, cramping, nausea, and diarrhea.

Continuous drip feeding may be delivered without interruption for an unlimited period of time each day. However, it is best to limit feeding to 18 h or less.

In some cases (like in inflammatory bowel disease), continuous drip feeding is used for 8–10 h during the night, so that it will not interfere with daytime activities. The infusion pump is a better method of delivery than gravity drip.

Nutritional Considerations

The nutritional liquids are almost ready to use, and do not need to be prepared manually. The age and the nature of the disease determine the chosen liquid for enteral feeding.

Addition of a multifiber mixture with prebiotic components to pediatric enteral nutrition is well tolerated, promotes bifidobacteria and reduces stool Ph, indicating an improved gut health. The use of fiber-containing formula should become a standard practice for the majority of children on enteral feeds. It is likely that the available formulas require higher level of fiber.

The enteral feeding formula should contain a high percentage of medium chain triglycerides, essential fatty acids, fat-soluble vitamins as well as glucose polymers. In patients with advanced liver disease, up to 4 g/kg/day of protein may be tolerated.

Pediatric formulas have been designed for different age groups, and for children with certain diseases: examples are special formulation for regurgitating infants; metabolic diseases; cow's milk or multiple food allergies; and intestinal, pancreatic, renal, and hepatic insufficiency.

Exclusive enteral nutrition is a therapeutic concept to induce remission in children and adolescents with active Crohn's disease.

Some Guidelines to Determine the Liquids

1. Proteins: The daily requirement varies with the age and clinical situation, but on average it is about 1.5–3 g/kg/day.
2. Carbohydrates: The majority of enteral nutrition liquid preparation is free of lactose because of potential lactose intolerance in many affected patients. Carbohydrates present 50–55% of the total caloric intake. The daily needs could start from 10 to 14 g/kg/day.
3. Lipids: The long chain lipids are used in almost all enteral nutrition solutions. Lipids present 35% of the total caloric intake. The daily needs are about 2.5 g/kg/day.

In order to determine the energy and nutrient needs, nutritional status should be assessed before tube feeding is started.

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56 Parenteral Nutrition

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Introduction

Parenteral nutrition (PN) refers to intravenous infusion of nutrients, including glucose, amino acids, lipids, vitamins, and minerals; it provides a total or supplemental nutrition source for an infant or a child.

Maintaining or treating nutritional status is important and increasingly recognized as a major player in recovery and improving mortality and morbidity. Furthermore, as nutritional components increasingly include properties formerly ascribed solely to medications, the term "nutritional pharmacology" has been coined to more accurately describe these nutrients.

Only about four decades old, the science of parenteral nutrition is recognized as one of the most important therapeutic advances in pediatric gastroenterology and continues to improve the survival and clinical outcome of children with medical as well as surgical conditions.

PN demands a high degree of nursing and medical expertise. It remains a priceless therapeutic method of prolonging survival and ensuring adequate growth and development despite the potential complications, the technical challenges, and negative psychological consequences of oral aversion. Major strides have been made in improving its efficiency and minimizing the risk of complications.

PN is indicated when other means of nutrition have failed or are expected to fail as a short- or long- term therapy to prevent and correct malnutrition and to maintain appropriate growth and development. Maintaining good nutritional status is essential in growing children.

In general, PN is indicated when the use of the gastrointestinal tract is not possible or if the absorptive ability is insufficient to meet nutritional requirements. Early prophylactic PN is also required in the very small infants in whom the enteral route fails to work or work adequately. Enteral nutrition, when possible, is always considered the preferred mode of nutrition.

Indications

When enteral feeding is not possible for a variety of medical, surgical, and metabolic reasons, PN is indicated to prevent malnutrition. The list of PN indications has become longer over the past several years and now encompasses a multitude of gastrointestinal and non-gastrointestinal conditions.

Gastrointestinal related indications can be categorized into three main indications (Table 56.1):

1. Malabsorption syndromes: whether it is secondary to medical or surgical causes. Short bowel syndrome remains the commonest and most classic indication for long-term TPN.
2. Need for bowel rest as in acute pancreatitis or Crohn's disease.
3. Congenital or acquired neonatal pathology of the GI tract.

Non- gastrointestinal indications are many (Table 56.2), and may be categorized into the following:

1. High catabolic states: for example, children with malignant disease, post organ transplant or major surgery.
2. Metabolic disorders: like inborn errors of metabolism or end-stage liver disease: in these cases, PN with appropriate amino acid composition is used with close monitoring.
3. Renal: end-stage renal disease, severe tubulopathy, in these cases PN with appropriate electrolyte constituents is used with close monitoring and frequent adjustments.
4. Hematologic/oncologic: may include children with malignant disease or post bone marrow transplant. Children with malignant disease are unable to take adequate amounts of calories enterally due to anorexia, mucositis, and emesis related to chemotherapy.

Children with radiation enteritis may also suffer from GI dysmotility. PN has had a big impact on the management of patients with malignancies.

Contraindications

In general, PN should not be used in clinically unstable patient. Medical disorders in otherwise relatively stable

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Table 56.1
Gastrointestinal-related indications for parenteral nutrition

I. Malabsorption syndromes:
Short bowel syndrome
Congenital microvillus atrophy
Neonatal surgical emergencies
Multiple intestinal atresia
Intractable diarrhea of infancy
Autoimmune enteropathy
Acquired immunodeficiency syndrome
Intestinal bacterial overgrowth
II. Indication for bowel rest
Acute pancreatitis
Crohn's disease
Ulcerative colitis
Low birth weight, prematurity
Necrotizing enterocolitis
Radiation enteritis
Henoch Schönlein purpura
Intestinal lymphangiectasia
III. Congenital or acquired neonatal pathology of the GI tract
Necrotizing enterocolitis
Extensive small-bowel resection
Omphalocele
Gastroschisis
Meconium ileus
Hirschsprung's disease
Severe motility disorders
Hypo-peristalsis syndrome
Chronic intestinal pseudo-obstruction syndrome

Table 56.2
Non-gastrointestinal indications for parenteral nutrition

V. High catabolic states
Malignant disease
Organ transplant
Major surgery
Significant trauma
Severe burns
VI. Metabolic disorders
Inborn errors of metabolism
Cystic fibrosis
End-stage liver disease
VII. Renal
End-stage renal disease
Kidney transplant
Severe tubulopathy
VIII. Hematologic/oncologic
Malignant disease
Solid tumors
Leukemia
Bone marrow transplant

patient can usually be managed with appropriate adjustment of PN constituents. Fat emulsions have undeniable benefits of providing more than double the amount of calories per gram as compared to carbohydrates or proteins; they also correct essential fatty acids deficiency and these benefits are not to be underestimated. Medical management should be individualized so as the benefits outweigh the risks.

Lipoprotein lipase (LPL) activity is significantly reduced in profound malnutrition, but rapidly improves with the start of anabolism. Malnourished infants and preemies are at a higher risk of developing hypertriglyceridemia secondary to a much slower clearance of the intravenous fat emulsions (IVFEs). Inadequate clearance of IVFEs may result in overload of the reticulo–endothelial system. In such patients it is prudent to start with a relatively small amount and advance slowly with close monitoring.

The contraindications to the use of IVFE may include severe sepsis, metabolic acidosis, respiratory distress syndrome, disseminated intravascular coagulation, and thrombocytopenia. In neonatal hyperbilirubinemia, caution is advised as free fatty acids may displace the unconjugated bilirubin from albumin.

Daily Requirements of Parenteral Nutrition

The total amount of calories, including enteral and parenteral, and other specific nutrients, should meet the child's needs. This section will present general guidelines of the estimated caloric needs according to different age groups. It is important to remember that different disease states may have specific energy, fluid, and nutrient requirements or restrictions. Energy in a child is required for both maintenance of body metabolism as well as for balanced growth and these may dictate the needs. The PN constituents should be adjusted according to the child specific requirements, clinical progress, and monitoring of lab results. The protein requirements of neonates and children will vary according to age. The Dietary Reference Intake (DRI) for total energy and protein intake varies with age.

The recommended DRI for total energy is 102 kcal/kg/day in the first 3 months of age and is less later in life up to the age of 3 years (80 kcal//kg/day). The DRI for total energy decreases gradually with age to become about 47 kcal/kg/day for children over 10 years of age. Furthermore, the DRI for protein also changes with age from 1.52 g/kg/day for the first 6 months of age and gradually becomes 0.95 g/kg/day for children from 3 to 14 years of age.

It is obvious that neonates require more protein per kilogram of body weight than children, and children require more protein than adults. Providing amino acids is a priority and should be started as soon as possible to reverse a negative nitrogen balance. The infused amino acids are primarily to provide structural and visceral proteins and enzymes and not to supply energy. It is customary to start with lower than required amount of amino acids and increase it slowly over few days. Adapting such practices may carry the risk of delay in achieving adequate intake and this should be avoided at all cost.

It is not recommended to exceed 4 g protein/kg/day since it may result in azotemia. It is not only the amount of protein that matters, but the quality of the protein too. For example histidine has been shown to be a conditionally essential amino acid in neonates up to 6 months of age, growth is compromised in its absence. Cysteine prevents calcium and phosphorus precipitation by increasing the acidity of the PN solution; this particularly might be helpful in patients who require higher amounts of calcium or phosphorus.

There is no essential amount of carbohydrate needed by the body; in its absence the human body can synthesize it from proteins and lipids. It is quite important to provide enough carbohydrate to prevent catabolism of body proteins and fats. Carbohydrates are provided as dextrose in PN solution. Generally, carbohydrates should comprise 40–50% of the total caloric intake in infants and children. Carbohydrates are usually calculated as glucose infusion rate (GIR) (mg/kg/min) in children the goal should be 10–14 mg/kg/min achieved slowly and advanced as tolerated. Restrict dextrose to 12.5% when administered by peripheral line.

Lipids are infused as a fat emulsion; they provide essential fatty acids and are caloric-dense energy source. The usual starting dose is 0.5–1.0 g/kg/day and increased as tolerated gradually up to 3 g/kg/day. Lipid emulsions come in 10% and 20% concentrations. The 20% emulsion (50% linoleic acid), 2 kcal/mL, is preferred over 10% lipid emulsion because of improved triglyceride clearance. Infusion of 0.5–1 g/kg/day is enough to avoid essential fatty acid deficiency. It is not recommended to exceed 4 g/kg/day or to exceed 60% of total calories due to the risk of ketosis.

Daily requirements of different electrolytes are estimated to be 2–3 mEq/kg/day for sodium and chloride, 1–2 mEq/kg/day for potassium, 0.65–2 mEq/kg/day for phosphorus, 0.3–2 mEq/kg/day for calcium, and 0.13–0.5 mEq/kg/day for magnesium.

All the above-mentioned requirements should be used as general guidelines and should not replace professional judgment. In general, appropriate weight gain is a sign of adequate intake.

When?

The decision when to start PN, and the route of supplementation, depends on several factors. These include:

- Preexisting nutritional status
- The anticipated course of the underlying disease
- Other organ system involvement
- Energy intake by mouth
- Other patient-specific considerations

Preexisting nutritional status: It is one of the most determinate factors. Patients who are malnourished prior to hospitalization should be identified at the time of admission by nutritional status assessment. Hospitalized pediatric patients have a high prevalence of malnutrition. Moreover, sick patients requiring hospital stay for prolonged periods of time or in the intensive care units are subject to iatrogenic starvation. Unintentional weight loss or failure to gain weight in a growing child should prompt evaluation and intervention. Subjective Global Nutritional Assessment is a tool that has been developed and used to identify children at risk of infectious and other complications due to compromised nutritional status.

The anticipated course of the underlying disease: Diseases that are anticipated to take longer duration before recovery call for PN support earlier.

Significant other organ system involvement: might interfere with oral intake (e.g., neurological or respiratory disorders) or ability to use the enteral route (e.g., postoperative ileus, severe sepsis, hemodynamic instability). Some disease are associated with significant catabolic stress that enteral intake may not be able to keep up with (e.g., malignancy, massive burns, congenital heart disease, chronic lung disease).

Energy intake by mouth: both actual and anticipated. The body can compensate for inadequate nutrient intake for certain period of time, depending on previous nutritional status. It can compensate by breaking down glycogen stores, gluconeogenesis, peripheral lipolysis, and amino acid oxidation from muscle stores. Because of the fact that infants and children have proportionately lower reserves of body protein, carbohydrate, fat than adults, and also have increased metabolic needs, they may require earlier intervention. In general, insufficient oral intake for 3–7 days should trigger for intervention in previously well-nourished children.

Other patient-specific considerations: Decisions about PN are also affected by patient-specific factors including the severity of underlying disease state, duration of potential starvation, and prognosis.

The optimal timing of initiation of PN has not been established, and the decision is based upon clinical

judgment. Earlier initiation of PN is recommended in patients with lower energy reserves such as those with failure to thrive, weight loss, prematurity, or low birth weight, or patients with chronic illnesses.

How?

PN can be delivered via a peripheral or central access. A peripheral access is when the catheter tip is in a vein other than the superior or inferior vena cava. A central access is when the catheter tip is located at or near the right atrium, superior or inferior vena cava.

High-concentration solutions (hypertonic >1,000 mOsm) can be infused safely in central access catheters with high blood flow; this will cause rapid dilution, thereby reducing the risk of thrombophlebitis. This is not possible using peripheral access because of the risk of intimal damage from the catheter and infusate. In peripheral access catheters, it is recommended to use less concentrated solutions (<900 mOsm). Usually PN administered through peripheral access cannot meet the nutritional requirements, except if it is used as a supplement in addition to enteral feeding. Central access catheters can be single, double, or triple lumen catheters, which allow other infusates (like blood products or other medications) to be administered simultaneously without having to interrupt PN infusion. The use of tunneled catheters versus non-tunneled central catheters may decrease the risk of line-associated infections.

The most widely used way of PN administration is by using two bags: the first one contains amino acids, dextrose, electrolytes, vitamins, trace elements, and sometimes medications. The second bag contains the lipid solution. Other less commonly used methods include the administration of all components in one bag or the use of three separate bags (amino acid, dextrose, and lipid bags).

Components

Glucose is the vital energetic substrate especially for the cell, and is stored in the body in the form of glycogen. Glucose is utilized in all tissues. Constant normoglycemia is necessary for efficient functioning of the brain, myocardium, and all nervous tissues. When considering the rate of glucose administration, one should bear in mind that this should not exceed the maximal rate of glucose oxidation, which varies significantly depending on the clinical situation and age. When compared to adults, infants and children have a much higher glucose brain consumption and higher rate of glucose oxidation; this can be up to 15 mg/kg/min. The maximal rate of glucose oxidation is much lower in the critically ill children and premature infants to about 5–6 mg/kg/min. Gluconeogenesis contributes significantly to glucose supply. Carbohydrates should constitute 60% of the total calories provided. Dextrose is provided at an initial dose of 6 mg/kg/min to be increased gradually up to dose of 15 mg/kg/min. One gram of dextrose provides 3.4 kcal.

In addition to hyperglycemia, glycosuria and insulin resistance, excessive glucose intake has other negative consequences of increased energy expenditure, inducing steatosis and liver dysfunction as the liver derives its energy from carbohydrate oxidation as opposed to fatty acid oxidation, and the fatty acids are directed toward VLDL triglyceride production and lipogenesis. Hyperglycemia is also a risk factor for infection, particularly in the critically ill children.

Fat should be used as an extra energy source; intravenous fat emulsions (IVFEs) improve net nitrogen balance, provide a concentrated source of calories in a relatively low osmotic load as more than double the amount of calories are provided per gram of fat compared to carbohydrates and proteins. This also allows a more diversified energy input and reduces the recognized consequences of using glucose alone as the source of energy of fatty infiltration of the liver and greater water retention.

Fat is formed mainly of essential linoleic acid stabilized by egg yolk phospholipids to a mean particle size of 0.13 μm. Linoleic acid is required for cell membrane synthesis and stabilization and a variety of physiological functions; therefore, clinical situation permitting IVFEs should be started as soon as possible in a patient on total PN to prevent essential fatty acid deficiency. Since glucose infusions stimulate insulin secretion and that reduces lipolytic activity and prevents release of tissue linoleic acid stores; the use of IVFEs in the PN also ensures an adequate supplementation of essential fatty acids.

Infants and children at special risk to developing essential fatty acid deficiency are those with malnutrition, small-for-gestational-age newborns, and premature neonates. They have very low stores of essential fatty acids, and will more likely develop essential fatty acid deficiency within 1–2 weeks of lipid-free PN with the restart of anabolism.

Lipids should not exceed 60% of the total calorie input in PN, ideally less than 30% of nonprotein energy intake. Fat is usually administered to provide 20–40% of the total calories. Use of 20% lipid emulsion provides ~2 kcal/mL compared to 0.68 kcal/mL for a 20% dextrose solution. The start dose is usually 0.5 g/kg/day and increased gradually up to a maximum of 3 g/kg/day. The infusion rate should be as slow as 0.10–0.15 g/kg/h to allow fat clearance from the blood. Plasma triglyceride level, liver function

tests, and platelet counts should be routinely monitored. Increased caution is required in the application of parenteral lipid emulsions in the neonate. The glucose/lipid ratio should be optimized for maximal fatty acid oxidation, prevention of steatosis and liver dysfunction, and VLDL triglyceride production and fat overload.

Protein: Amino acids are the vital components of body protein that provide proper nitrogen utilization and retention. The nitrogen source of PN may be selected from a list of available amino acid mixtures designed specifically for infants and children. The nitrogen intake depends on the age, degree of malnutrition, presence of nitrogen losses from the GI tract, and nitrogen losses induced by catabolism. Energy supply should be closely correlated with nitrogen supply. Excessive amounts of nitrogen intake carry the risks of metabolic acidosis, iso-osmolar coma and hyper aminoacidemia, calcium and phosphorus urinary loss, and bone demineralization. Amino acids in PN prevent the breakdown of muscle protein and disturbances of blood clotting and the negative consequences of prolonged catabolic state of delayed wound healing, loss of muscle strength, and immunosuppression. The initial dose is 1 g/kg/day and is increased gradually up to 3 g/kg/day.

Special amino acid formulations have been designed to fit the patients' needs depending on the age and clinical situation. Amino acid solutions in PN can vary in terms of amino acid nitrogen content, electrolyte content, osmolality, and amount of essential amino acids per gram of total nitrogen. Products containing only essential amino acids have been formulated for children with renal failure. Amino acid solutions designed for prematures and malnourished infants have a higher amount of essential amino acids per gram of total nitrogen, higher percent of branched-chain amino acids, and contain taurine, which is absent from standard solutions.

Glutamine: Glutamine supplementation was found to reduce the length of hospitalization and promote enteral nutrition in neonates receiving PN. Glutamine is the most abundant amino acid in muscle and plasma and serves as the primary fuel for rapidly dividing cells, promotes cell growth and synthesis. It was also recognized that glutamine is an essential nutrient for the replication of cells in tissue culture; it is therefore expected that glutamine nutritional requirements are not the same during high catabolic states as compared to during health. It also plays a key role in acid-base homeostasis.

Glutamine supplementation is of particular benefit to preterm infants receiving PN. Recent studies have shown that glutamine-supplemented PN has clinical benefit on preserving gut structure and preventing intestinal atrophy. It is therefore empirical that large multicenter trials be conducted to confirm these observations and evaluate the efficacy of glutamine in high-risk preterm infants.

Other Components of PN Solutions

Electrolytes are also added to the PN infusion in a dose relevant to the patient's age and existing electrolyte imbalance and any associated factor leading to abnormal losses of electrolytes as in intractable diarrhea or the presence of an enterostomy. *Sodium* is the most important cation of the extracellular fluid with a basic requirement of about 2–4 mEq/kg/day. *Potassium* is the most important cation of the intracellular fluid. It is also responsible for the transport of glucose across the cell membrane. The effects of potassium deficiency or excess on muscle excitability, acid-base balance, and cardiac rhythm cannot be overemphasized. Potassium is usually administered at a dose of 2–4 mEq/kg/day. In the case of intractable vomiting or nasogastric suction, sodium, potassium, and chloride supplementations are higher to replace the losses. In the case of an enterostomy, more bicarbonate should be added in addition to higher replacement of sodium.

Other important constituents of parenteral infusion include *magnesium, phosphate, calcium, and trace elements* such as chromium, copper, selenium, zinc, and manganese. Trace elements are added to parenteral fluids to prevent the development of deficiency syndromes depending on the intake of the respective nutrients and their anabolism. The provision of appropriate nutrient solutions requires an understanding of the nutritional relationships between nutrients, electrolytes, vitamins, and trace elements. Zinc is one of the most important trace elements. It plays an important role in cell metabolism.

Many of the nutrient or additives used in parenteral solutions may be contaminated with metals. Trace metal monitoring has been more critical in patients on long-term PN. A proper balance of trace metals can contribute positively to the nutritional metabolism of patients receiving PN.

Multivitamins are also important for metabolic processes. PN fluids usually include vitamin B complex, vitamin C, and fat-soluble vitamins. The precise amount of vitamins to add to various parenteral fluid regimens is not yet resolved because these supplements are very difficult to measure and only few reference laboratories have such facilities. Furthermore, the intakes should be adjusted in patients with high catabolic states and intestinal losses.

The addition of *carnitine* supplement helps optimize fatty acid oxidation. Carnitine levels are very low in prematures and low-birth-weight newborns and should be supplemented, although there are currently no specific

recommendations regarding its supplementation. It is also advisable to add alpha-tocopherol to the IVFEs as an antioxidant.

Prescribing Parenteral Nutrition

At the initiation of PN, it is recommended to start with lower amounts than the set goals and advance slowly depending on the tolerance. Usually it takes several days before achieving patient-specific goals. Double checking the calculations is strongly recommended as calculation mistakes can be hazardous. Different hospitals have their own protocols. This section will describe general practical steps.

Step 1:

The initial step in PN calculations should be to asses protein and energy requirements. In general, energy requirements for children receiving PN may be 10% less than the DRI of enteral intake. For patients who are malnourished, energy requirements should be determined using ideal body weight (IBW) (weight-for-length at the 50th percentile) to allow for appropriate catch-up growth. Similarly, the IBW should be used in overweight or obese patients.

The total energy (kcal)/day = energy (kcal/kg/day) × weight (kg) (or IBW).

The total protein g/day = protein (kcal/kg/day) × weight (kg) (or IBW).

Contribution of energy from different components, generally dextrose and amino acids provide about 70% of the calories, and fat emulsions provide about 30% of calories.

Total energy (kcal/day) × 0.3 = energy from fat (kcal/day)

Total energy (kcal/day) × 0.7 = energy from dextrose and amino acid (kcal/day)

It cannot be stressed more that the requirements are variable and are dependent on the patients' needs dictated by their nutritional and health status, some patients may require much more than their DRI for age.

Step 2:

Calculate the maintenance fluid requirements. This may vary from patient to patient and may also vary overtime according to the child's health condition. Some medical conditions may require restriction of fluid intake, e.g., cardiac or renal disorder. Fluid requirements will be higher in patients with excessive losses, e.g., diarrhea, draining fistulas, fever.

Step 3:

Determination of the volumes of different components. Using a standard 20% lipid solution (1g = 5 mL), it is easy to calculate the daily lipid volume, then divide it over the number of hours of PN infusion. It is recommended to start the lipids at a lower amount at the initiation of PN (e.g., 0.5–1g/kg/day) and advance slowly depending on tolerance.

The rest of the required volume will be the amino acid and dextrose solution. Calculate amino acids, as above, a suggested start is to add 0.5–1g/kg/day and increase according to the DRI and the tolerance. Similar procedure should be used to calculate dextrose (see above daily requirements of PN).

Step 4:

Calculate electrolyte requirements and add that to the amino acid/dextrose solution. See above daily requirements of PN. Adjust as needed.

Step 5:

Calculate the calories in PN and lipid solution, adjust if needed. Keep in mind that these might not match the goals at the initiation of PN.

Step 6:

Additives. If a base is required to be added to PN solution, to treat acidosis, then it should be acetate (sodium or potassium); in such case balance the total amount of Na or K. Bicarbonate should never be added because it will result in precipitation of calcium and phosphorus in the PN solution. Zinc is often added in patients with gastrointestinal losses (e.g., diarrhea, ostomy output), inflammatory bowel disease, cystic fibrosis, or fistulas.

For other additives, suggest checking with pharmacy for compatibility and solubility of the PN solution.

Step 7:

Compare your results with requirements for accuracy (double checking). It is recommended that the clinical pharmacist double check the calculations for accuracy too.

When PN is to be stopped, it should not be stopped suddenly, it should be tapered off slowly, usually over 1–2 h with close monitoring. Avoid any sudden discontinuation of PN, especially in younger children or children with no enteral intake; this carries the risk of hypoglycemia and fluid deficit.

Monitoring

Close monitoring of patients' "tolerance" to PN is extremely important. Although there is no agreed regimen of monitoring, some monitoring parameters needs to be checked daily, others less frequently (weekly, monthly, and annually). The type and frequency of laboratory testing will depend on the stability of the patient and other body system involvement. Institutions usually develop their own monitoring protocols.

There are some general principles that are agreed upon: a baseline laboratory testing should be obtained before starting PN. This may include: complete blood count, electrolytes, glucose, calcium, magnesium, phosphorous levels, as well as kidney and liver profiles.

After initiation of PN, labs are frequently ordered until the goals are reached. It is wise to remember that patients differ in their "tolerance" to PN depending on several factors, these include: their current nutritional status, underlying disease, ability to take enteral feed, age, and several others. The PN composition may need to be adjusted accordingly.

Daily monitoring may include: careful measurements of fluid intake and output, weight, selected laboratory studies (e.g., serum electrolytes, bicarbonate and blood urea nitrogen (BUN), glucose, calcium, magnesium, phosphate, triglycerides), and urine glucose. We would suggest doing the above daily at the initiation of PN, whenever significant changes in the composition of PN are made, and significant change in the patient's condition. Later on, and depending on patient's condition and stability, monitoring may be spaced out.

Weekly monitoring in addition to the above may include: liver aminotransferases, bilirubin, albumin, prealbumin, and complete blood count. Later on, these labs may be checked once a month for more stable patients and for patients on home PN. Monthly labs may also include iron studies. Less frequent labs (biannually or annually) may include trace elements levels (Zn, selenium, and Cu) and vitamins levels.

Adequacy of the amino acid intake in the short term can be determined by either BUN or prealbumin measurements. Both will reflect changes in amino acid intake within 24–48 h. The BUN is a readily available test to titrate amino acid intake provided that the child is well hydrated with normal renal function.

Tolerance to lipid infusion can be judged by triglycerides measurement. Ideally, the triglyceride level should be less than 100 mg/dL. There are no data defining the level at which one should be concerned. The American Gastroenterological Association Technical Review on PN states that IVFE should not be administered to patients whose serum triglyceride levels exceed 400 mg/dL. It is recommended to measure a baseline level in these patients before starting lipids. Intralipids may need to be decreased with triglycerides >250 mg/dL. Sustained levels of serum triglycerides >400 mg/dL may require discontinuation of the fat emulsion. Interpretation of the data linking intravenous fat emulsions to pulmonary dysfunction, and immune function, is complicated, at the best controversial and beyond the scope of this discussion. Some studies show a beneficial effect, some no effect, and some an adverse effect of fat emulsion infusion.

The use of intravenous fat emulsions in patients with coagulation abnormalities is complicated too. In rare cases, intravenous fat emulsion has been associated with thrombocytopenia. Under normal circumstances, they do not induce thrombocytopenia. It should be kept in mind that essential fatty acid deficiency itself is a cause of hematologic abnormalities.

Other causes of elevation of triglyceride levels include sepsis, pancreatic disease, renal disease, and diabetes.

Patients receiving long term PN (especially with limited enteral intake) are at risk for developing iron deficiency since most PN solutions do not contain iron.

Complications

PN has become an essential therapy in most neonatal, medical, and surgical units. The noticeable improvement in techniques and fluid composition have enabled the selected patients to survive longer but at the same time have made them prone to developing some added complications that were not as common previously when PN did not last as long. In spite of all improvement in techniques and adherence to various aseptic measures together with a multidisciplinary approach, PN is not without hazards.

Catheterization of central veins for long-term PN should be performed by one who does such procedures fairly regularly. Complications of insertion are many. Pneumothorax is the most prevalent complication of subclavian vein puncture occurring in up to 5% of attempted catheterization. The pneumothorax may be asymptomatic and resolve spontaneously or may require needle aspiration or closed tube thoracostomy.

Air embolism is a potentially fatal complication of percutaneous catheterization of the subclavian and internal jugular veins or during routine tube changes. Other mechanical complications include: bleeding, especially with blind insertion techniques, pneumomediastinum, hemothorax, and hydrothorax.

Cardiac tamponade and arrythmias may also complicate the central venous catheter (CVC) insertion. Other recognized complications of catheter insertion include *injuries to the trachea, thoracic ducts, and brachial plexus.*

With increased application of PN and improved technical application, the number and frequency of such complications have become much less.

Other recognized complications include *metabolic disorders* like hypoglycemia, hyperglycemia, hypokalemia, hyperkalemia, and hypocalcemia. There is also a potential

complication of *electrolyte disturbances* precipitated by excess gastrointestinal losses resulting in hyponatremia.

Catheter-Related Sepsis

Central line-related sepsis is a serious complication of PN. The incidence varies, but it is reported to be in the range of 5%. This tends to happen more frequently with the surgically inserted CVCs particularly in the event of local hemorrhage following CVC insertion and local suppuration at the skin exit site. This is suggested by temperature variations, hypotension, oliguria, and general deterioration in the clinical condition. Any fever in the absence of an obvious focus of infection must be attributed to catheter-related sepsis until proved otherwise. Sepsis may occur at any time after catheter insertion. Repeated central line infections with septicemia are recognized serious complications associated occasionally with major clinical deterioration of the child who will require not only intensive antibiotic therapy but also replacement of the central line catheter.

Symptoms or signs of sepsis warrant thorough investigations for a focus including complete blood count, C-reactive protein, coagulation studies, blood cultures both central and peripheral.

Antibiotic treatment should be started promptly and should include anti-staphylococcus antibiotics, coagulase-negative staphylococci being the commonest blood culture growth.

All PN solutions must be prepared under a laminar flow hood and filtered. The PN team strongly emphasizes the importance of aseptic techniques not only during the insertion of the catheter but also during changing of dressings, infusion set, and intravenous fluids. Daily care of the CVC skin exit site is required, especially in those who are enrolled for home PN. The caring nurse should be specifically trained in this technique.

Full septic screen is required as soon as such a complication is suspected. The child should be treated with broad-spectrum antibiotics while awaiting the results of cultures.

Outbreaks of *Candidal bacteremia* have been reported in patients receiving PN. Investigations of outbreaks of Candida infections among neonates receiving PN have indicated that the outbreaks were terminated by using syringes only once and resuming intravenous tube changes every 24 h. Very often the source of the Candida could not be identified.

If fever persists over 48 h in spite of therapy, a serious consideration should be made for removing the catheter as well as the addition of antifungal medication especially in immunocompromised patients. Once the catheter is removed, the tip of the catheter should always be sent for culture and sensitivity. The child should be placed on peripheral infusion for a few days before insertion of new central line catheter.

Respiratory failure is also a recognized complication of high daily dextrose loads in PN in patients with obstructive airways disease.

A variety of CVC-associated infection prevention strategies are currently evaluated for efficacy. Intraluminal ethanol lock is showing promising results so far in terms of infection prevention, reduction of relapse rate, and catheter salvage. Ethanol has antimicrobial effects on *Staphylococcus aureus*, *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, and *Escherichia coli*. Ethanol lock has a multitude of advantages. It is an inexpensive excellent disinfectant with intrinsic anticoagulant activity and may be able to clear yeast, which is hard to treat with other locks.

Metabolic Complications of PN

Essentially all kinds of metabolic and electrolyte derangements can happen. The best way to avoid this is by careful calculation and frequent monitoring with prompt intervention.

Hyperglycemia: to avoid this dextrose initial infusion should be limited to 10–15%; increments should be limited to 5% per day.

Hypoglycemia: could be caused by abrupt cessation of PN, which should be avoided.

Hypercapnia: may be due to excessive caloric or dextrose infusion and should be avoided.

Azotemia: ensuring adequate hydration prior to PN initiation is essential; excessive amino acid infusion should be avoided.

Hypertriglyceridemia: serum triglycerides should be monitored frequently. Lipids should be infused over 18–20 h and may be given every other day.

Hypokalemia/hyperkalemia: serum potassium should be monitored daily until stable, then biweekly. Restriction and monitoring are especially necessary in patients with renal insufficiency.

Hyponatremia/hypernatremia: excessive fluid administration should be avoided. Intake/output should be monitored in addition to urine sodium and osmolarity.

Metabolic acidosis/alkalosis: acid–base balance derangements can happen in patients receiving PN. Intestinal or NG output losses should be replaced. May need to add acetate in cases of metabolic acidosis.

Hypocalcemia/hypercalcemia: ionized calcium, PTH, and vitamin D levels should be monitored.

Hypomagnesemia/hypermagnesemia: serum magnesium should be monitored until stable, more relevant in patients with renal insufficiency.

Hypophosphatemia/hyperphosphatemia: serum phosphorus should be monitored daily until stable.

Parenteral Nutrition-Related Bone Disease

PN-related bone disease is a well-known complication that is reported in patients of all ages. The clinician is alerted to this more common than previously thought complication by the findings of high serum alkaline phosphatase, low/normal vitamin D and PTH levels, and hypercalciuria.

Osteodystrophy is a known complication recently recognized in children receiving long-term PN. The patients suffer from bone pain and pathological fractures.

Radiological manifestations include osteopenia, fractures, and rickets. Histopathology reveals osteomalacia, decreased bone mineralization, and osteoid tissue excess.

The exact nature of this disorder is poorly understood. Caution is advised with vitamin D supplementation in long-term PN. Hypercalciuria may be decreased by reducing the sulfur-containing amino acids in particular and balancing the supplies of phosphorus, nitrogen, and energy.

The incidence of PN-related bone disease may be higher than considered at present if more sensitive radiological and biochemical criteria are applied. Children on long-term PN should have their serum alkaline phosphatase and urinary calcium checked routinely. *Dual X-ray absorptiometry (DEXA)* scan can assess the bone mineral density in children on long-term PN.

Parenteral Nutrition-Related Liver Disease and Hepatobiliary Complications

Hepatotoxicity is a well-recognized serious complication of long-term PN. It occurs in up to 90% of patients receiving long-term PN. PN-related liver disease may appear as early as after a few weeks of PN therapy.

The underlying digestive disease plays a role in the development of PN-related liver disease. Ileal resection in short bowel syndrome results in impairment of enterohepatic circulation of bile acids, bacterial overgrowth following ileocecal valve resection, and the impairment of bile secretion without enteral feeding.

Factors playing a role in the pathogenesis of hepatotoxicity in patients receiving PN include the duration of PN, prematurity, primary liver disease, hepatotoxic medications, and infections including bacterial translocation secondary to gut mucosal atrophy, bacterial overgrowth with gram negative sepsis as well as recurrent line sepsis.

Causes of hepatotoxicity also include the direct effect of the artificial nutrition. Excessive glucose supply may induce hyperinsulinism and de novo lipogenesis and steatosis. Metabolic dysfunction may be related to inadequate amino acid supply, presence of toxic products of amino acids metabolites. Liver injury can also result from excess iron, aluminium, and other micronutrient overload.

Hepatomegaly may become clinically apparent as early as within a few days of starting PN. Elevation of the serum alkaline phosphatase and gamma glutamyl transferase activities are the earliest and most sensitive laboratory markers, though not specific. *Hyperbilirubinemia* is a late marker of cholestasis.

Histologically: Hepatic steatosis is the most common and first morphological change seen as a sequel to PN. Cholestasis, portal, and peri-portal cell infiltration may progress to fibrosis, cirrhosis, and end-stage liver disease if PN is not performed correctly.

In an effort to reduce the hepatotoxicity due to PN, *enteral feeding*, even if tolerated in small quantities, should be introduced as early as possible. It has been hypothesized that PN-associated cholestasis is caused by a lack of enteral feeding, impaired bile acid secretion, gut mucosal atrophy and secondary bacterial translocation, and a sequel of events and complications. Therefore, in many centers and certainly in neonatal intensive care units, the trend nowadays is toward earlier enteral feeding in an otherwise healthy premature infant. Recent reviews recommend early introduction of partial enteral feeding to preserve liver functions.

It is essential to closely monitor hepatic function and minimize or reverse the development of liver disease by limiting glucose supply to prevent de novo lipogenesis and steatosis. Moreover, minimizing metabolic dysfunction by using pediatric-adapted amino acid solutions that include taurine, minimizing liver injury caused by excess iron, aluminium overload, providing essential fatty acids in the intravenous fat emulsion, monitoring platelet count and serum bilirubin level and stopping the intravenous fat emulsion in the case of thrombocytopenia or hyperbilirubinemia until they normalize, restarting the IVFE under very close monitoring, cycling the PN

to reduce hyperinsulinism and liver steatosis, using metronidazole to reduce bacterial overgrowth, using ursodeoxycholic acid to minimize liver injury.

All of the above-mentioned complications can be life threatening. But it is the associated cholestasis leading to liver failure that is the most common serious long-term complication, especially among neonates receiving PN.

Home Parenteral Nutrition

Major strides have been made toward lower morbidity and mortality rates associated with PN, and more infants and children are on long-term PN therapy. With the continuing improvement in the parenteral feeding regimens and appropriate provision of macro- and micronutrients, the improved care and insertion techniques of central venous catheters, home PN is the only alternative to prolonged hospitalization for patients requiring long-term PN. Prolonged hospitalization exhausts hospital resources and consumes a great deal of the physicians' and nurses' time as well as that of all members of the PN team.

Home PN helps minimize these costs and care, improves the psychological development of the child, enables the older children to attend school, and offers the patients and their families the best possible quality of life.

Candidates for home PN may be exclusively on PN, or on mixed enteral and PN. This will depend on their clinical condition and diagnosis, the progress made in intestinal adaptation and their tolerance to enteral feeds. These include children with severe and persistent genetic malabsorption syndromes, intractable diarrhea of infancy, villous atrophy, infants with short bowel syndrome secondary to intestinal resection, chronic intestinal pseudo-obstruction syndromes, and some cases of inflammatory bowel disease. The objective of long-term PN in these cases is to ensure normal growth of the child while the inflammatory syndrome subsides or while waiting for the residual intestinal condition to become stable.

Home PN protocols are mainly directed to the group of infants and children whose medical condition is stable on PN in hospital with or without enteral nutrition. With few exceptions, the parents usually express their readiness and competence to care for their child at home. The parents should undergo proper training sessions supervised by the PN team prior to discharging the patient home. Patients and their parents should be intellectually and emotionally able to cope with the heavy burden of daily management of PN. It is also practiced that after discharge, the family will receive regular visits at close intervals by trained personnel to ensure the smooth operation of home PN and to respond to any difficulties or queries that parents may have had in between visits. It is important to ensure that the parents are handling the therapy using fairly aseptic techniques. The parent should also be taught about the early signs of sepsis and be advised to bring their child back to the hospital for further evaluation or to call the team member on duty for further advice on management.

Home PN is usually administered in the same manner as in the hospital. The fluid is infused through a surgically inserted catheter, with its tip in the right atrium (Hickman-Broviac catheter) or through infusion ports under the skin (Port-a-cath).

It is important to program the hours of administration of home PN to run, if possible throughout the night, and allow the family and the child normal activity or schooling during the day. It is also easier to formulate the home PN all in one bag, which facilitated the procedure even further by requiring only one infusion pump. In the course of regular medical checkups and home visits, an attempt should be continued to increase the amount of enteral nutrition to save the child some of the risks of long-term PN.

Reports have recommended home PN programs based on the finding that central line-related infections are far less frequent among these children compared to those receiving their PN in hospital. Recent reports have, however, indicated that complications such as catheter-related thrombosis in children receiving PN at home remain high. While the most life-threatening home PN-related complication is liver disease, several reports suggest that home PN remains the best option for children in need of long-term PN.

Children who will require lifelong PN should be considered for intestinal transplantation as an alternative to lifelong PN and its related long-term complications including PN-related liver disease. This group includes infants with massive intestinal resection and extreme short bowel syndrome, severe motility disorders, intractable diarrhea of infancy, and microvillous inclusion disease.

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57 Vitamin Deficiencies and Excess

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Vitamins are natural chemical compounds required in minute quantities for health and normal nutrition in humans. They are divided into two groups, namely, water and fat-soluble vitamins. The former are procoenzymes that provide active substances necessary for enzyme synthesis and the latter alter conformation of complex molecules and membranes.

Water-Soluble Vitamins

Vitamin B Group Deficiencies

As the sources of vitamin B are present in more or less the same type of animal and vegetable foods, X and X deficiency of one is likely to be associated with deficiencies of others. Clinical manifestations of B vitamin deficiencies are usually seen in famine situations in developing countries, where there is also the added potential risk of improper preparation of food with long-term storage due to shortage of water and cooking facilities. Unlike fat-soluble vitamins, excess of water-soluble vitamins is not of significant concern.

Thiamine (B1)

Thiamine forms the heat labile portion of the B complex and its metabolites are important in carbohydrate metabolism. Thiamine pyrophosphate takes part as the coenzyme of carboxylase in the oxidative of carboxylase in the oxydative decarboxylation of α-keto acids such as pyruvic and α-ketoglutaric acids, where acetylcoenzyme A is subsequently formed. Thiamine pyrophosphate is also a coenzyme for transketolase which works as a direct oxidative pathway of glucose and consequently generates NADP and pentose. Thiamine is also required for the synthesis of acetylcholine required for the central nervous system.

Thiamine is found in unpolished grains, sunflower seeds, brown rice, asparagus, cauliflower, potatoes, oranges, liver, and eggs.

Thiamine Deficiency

Thiamine derivatives and thiamine-dependent enzymes are present in all body cells, thus deficiency could adversely affect all organ systems. However, the nervous system and heart are particularly sensitive due to their high oxidative metabolism.

Thiamine deficiency results in a condition called *beriberi*. Infantile beriberi primarily affects the cardiovascular system with dilatation of the heart and fatty degeneration of the myocardium. Generalized or localized body edema may occur. Nervous system involvement is associated with vascular dilatation and hemorrhage in the brain and peripheral nerve degeneration. Its etiology, epidemiology, and clinical manifestations have special features in infancy.

Epidemiology

In infancy, the disease is virtually confined to breast-fed infants of thiamine-deficient mothers who are subsistent on polished rice and minimal or absent additional food supplements. The peak mortality is usually from 2 to 5 months of age.

The infantile form is an acute disease unlike in adults. The early signs may be subtle and easily missed by the mother. It proves rapidly fatal without treatment; it is acutely fulminate between 2 and 5 months and is milder and less common after 6 months. Beriberi is rare after the age of 1 year. In older children, the disease is similar to that of adults, namely, wet, dry forms, and acute cerebral beriberi.

The prevalence seems to have diminished considerably worldwide, and it has not been a public hazard in recent years, especially in previously endemic areas, due to various interventions including fortification of rice with thiamine.

Clinical Features

Beriberi manifests with pallor, restlessness, vomiting, constipation, poor mental concentration, and apathy. Cardiac

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involvement is of sudden nature and manifests with restlessness, bouts of screaming, and breathlessness. The baby is pale but cyanosed. It is associated with acute output cardiac failure resulting in death due to peripheral vasodilatation, high output cariomyopathy, and salt and water retention. Chest radiography demonstrates evidence of pulmonary edema and cardiomegaly. Pericardial and pleural effusion may be present. Death may occur within minutes or hours from the onset of the disease. This is referred to as *wet beriberi*.

The aphonic form is another type that presents acutely. It manifests with distressing and increasing cough and choking that commence between the age of 5–7 months. This is rapidly followed by hoarseness, dysphonia, and aphonia, which gives rise to noiseless cry due to laryngeal nerve paralysis or edema of the larynx.

CNS involvement may appear later as peripheral neuritis associated with parasthesia, hyperesthesia, and burning feet. The child finds it difficult to rise from a sitting position due to muscle weakness and tenderness and this is followed by ataxia, loss of coordination, and loss of deep sensation. Polyneuropathy is described as *dry beriberi*.

Wernicke's encephalopathy is a recognized complication of thiamine deficiency and is associated with confusion, apathy, drowsiness, head retraction, signs of meningism and increased intracranial pressure. This usually occurs in children aged 8–10 months.

Diagnosis

The diagnosis rests upon reduced urinary thiamine excretion and is confirmed by absent thiamine pyrophosphate. A loading dose of 10 mg thiamine and lack of response in urinary excretion of thiamine in a deficient child have been suggested as a diagnostic test. The erythrocyte transketolase activity is lowered and blood or urinary glyoxylate values are high. Clinical response to thiamine administration remains the best test for thiamine deficiency. Thiamine as well as its derivatives can be measured quantitatively by high-performance liquid chromatography (HPLC).

Diffferential Diagnosis

Differential diagnosis include meningitis, encephalitis, laryngitis, tetany, congenital heart disease, kwashiorkor and acute poisoning. Therapeutic dose with thiamine is decisive and safe.

Treatment

Immediate: 50–100 mg of I.M./I.V. thiamine hydrochloride and Oxygen therapy give dramatic response within a few hours. Maintenance consists of 5–10 mg/daily for several days. Breast feeding mother should receive similar treatment. Other B vitamins should also be given in addition.

Prognosis: excellent if diagnosed and treated early

Prevention: Education and avoidance of over-dependence on polished rice; and mixed diets should be encouraged.

In *thiamine dependency*, which is rare, large doses of thiamine will be required.

Riboflavin (Vitamin B2)

Riboflavin is important in the formation of the coenzymes flavin mononucleotide and flavin adenine dinucleotide. Riboflavin is important for growth and tissue respiration. It is destroyed by light and is stable to boiling in acid solution. In tissues it forms mononucleotides with phosphoric acid which are coenzymes in flavoproteins. These coenzymes are essential in many oxidation–reduction reactions in the body.

Riboflavin Deficiency

Riboflavin deficiency is usually mild and results from low intake of riboflavin-rich diets, such as pulses, legumes, and animal products including liver, kidney, milk, and cheese. Breast milk or artifical milk intake is sufficient in preventing riboflavin deficiency. A diet is rarely deficient in riboflavin alone and signs usually accompany other deficiency states, like pellagra or severe protein calorie malnutrition.

Clinical Manifestations

The skin and mucus membranes are affected. Sebaceous glands become prominent in the nasolabial folds, alae nasi, external ears, eye lids, and scrotum in males and labia majora in females. Inspissated sebum accumulates in hair follicles, producing plugs of material. Angular stomatitis occurs in the acute form and rhagades in chronic deficiency. Cheilosis of lips and the tongue may be acutely painful and may have magenta color. Photophopia, lacrimation, and conjuctival injection may be present.

Diagnosis

Plugs in hair follicles tend to be rather specific for riboflavin deficiency. The other signs may be caused by other B complex deficiencies. Diagnosis is suspected on clinical grounds and confirmed by low urinary riboflavin excretion of less than 30 μg/day, and by an enzymatic test, reduced red blood cell glutathione reductase is found.

Treatment

This includes dietary support to ensure adequate supply of vitamin B as well as giving 3–10 mg of riboflavin daily. If there is no response within a few days, then it should be given by the intramuscular route as 2 mgs daily.

Nicotinic Acid (Niacin)

Nicotinic acid is a water-soluble vitamin and functions as a coenzyme required for a wide variety of essential metabolic processes. Nicotinamide adenine (NAD) and its phosphorelated form NADP are coenzymes for oxidation–reduction reactions including synthesis of high-energy phosphate compounds, glycolysis, pyrovate metabolism, pentose biothensysis, glycerol and fatty acid metabolism, and for obtaining energy from proteins. Conversion of tryptophan to nicotinic acid may be partially sufficient to meet body requirements.

Liver, salmon, poultry, and red meat are good sources. Breast milk supplies relatively high content of niacin and this meets the needs for infants until the age of 6 months.

Niacin Deficiency (Pellagra)

The disease typically occurs in adults, some cases can appear in children of all ages and manifestations are similar to those in adults. Pellagra is commonly seen in communities whose diet consists of maize as stable diet and this has been shown to have low content of tryptophan or niacin. It used to occur in endemic proportions in parts of the Middle East, Africa, and Southeast Europe. Pellagra also affects communities in India, Brazil, and Cuba that are not maize eaters.

Tryptophan gives rise to nicotinic acid in the body and very low levels of this essential amino acid may result clinically as pellagra. Some drugs like isoniazid compete with pyrodoxal phosphate, a coenzyme required on the metabolic pathway of tryptophan to nicotinic acid. Similarly pyridoxine deficiency from any cause may have the same effect.

Hartnup disease is a rare genetic metabolic disorder where the basic defect involves the intestinal and renal transport of many amino acids, and tryptophan is not exempt. Patients have the typical photosensitive rash and later, the skin becomes rough.

Cerebellar ataxia and psychiatric disturbances may occur; however, these signs are reversed with treatment. The diagnosis can be confirmed by presence of large amounts of monoamino monocabocyclic amino acids in the urine.

Clinical Manifestations

Niacin deficiency is characterized by "dermatitis, diarrhea, dementia, and depression." Other associated features include angular stomatitis and peripheral neuritis.

Prodromal symptoms include stomatitis, glossitis, vomiting, or diarrhea that may precede skin lesions. However, characteristic skin changes are commonly the first manifestation to be noted. The dermatosis is symmetrical and appears on parts exposed to sunlight and trauma, which is sharply demarcated. Erythema progresses to keratosis, scaling, and pigmentation. The hands, wrists, forearms, face, and neck are usually involved, but it may involve the feet and legs.

Mucocutaneous junctions, like the outer canthus of the eye, edge of alae nasi, anus, and genitalia are often fissured and sore. The tongue is described as "raw beef" in appearance which is red, swollen, and painful. Gastritis, diarrhea, and malabsorption may occur.

Neurological changes are usually late and rare in children. CNS symptoms include depression, disorientation, insomnia, and delirium. Encephalopathy is more characteristic than cord, pyramidal tract, or peripheral nerve damage. In advanced cases, demylination of parts of the spinal cord involving the lateral and posterior columns and also the cerebellum may occur.

Laboratory Tests

Excretion in urine of *N*-methylnicotinamide is undetected and its pyridone is reduced. Plasma tryptophan is very low. Clinical features and clinical response to niacin is best to confirm the deficiency state.

Treatment

In critically ill patients, 50–100 mg of niacin should be given intravenously. This treatment may be followed by flushing and burning sensation of the skin. Large doses of niacin may be complicated by cholestatic jaundice or hepatotoxicity.

In the acute form, nicotinamide is given subcutaneously three times a day for several days until marked improvement occurs when an oral dose of 20 mg/day can be substituted. Tryptophan-containing foods supplemented with other B complex vitamins should be added.

Pyridoxine (Vitamin B6)

Pyridoxine consists of three closely related compounds: pyroxine, pyridoxal, and pyridoxamine and their respective 5-phosphorylated forms. The coenzyme pyridoxal-5-phosphate has many roles in amino acid metabolism as well as in lipid, nucleic acid, and glycogen metabolism.

Deficiency

This rarely occurs as an isolated clinical entity as most food stuffs contain this vitamin. Pyridoxine deficiency results from poor intake as in malabsorption and severe malnutrition. It may result from drug antagonism such as isoniazid, oestrogens hydralazine, and penicillamine. It may also result from excessive loss and increased metabolic activity.

The developing nervous system of infants appears susceptible to pyridoxine deficiency. Gamma amino butyric acid (GABA) is present in high concentrations in the developing brain and is formed by decarboxilation from glutamic acid through pyridoxal phosphate as a coenzyme. GABA inhibits synaptic transmission and when its concentration is lowered in pyridoxine deficiency, the threshold of irritability is reduced and convulsions may occur as a result.

Clinical Manifestations

Clinical manifestations include convulsions, especially in infants, peripheral neuropathy, seborrhoeic dermatosis, glossitis, angular stomatitis, cheilosis, and normoblastic normochromic anemia.

Laboratory Tests

Diagnosis is confirmed by the presence of low serum pyridoxal 5 phosphate.

Treatment

In the case of neonatal convulsions suspected to be due to pyridoxine deficiency, up to 100 mg of pyridoxine may be given intramuscularly and a single dose may be sufficient. In case of good response, this may be confirmatory of the diagnosis. In other situations, an oral dose of 10 mg pyridoxine should be given, which is ten times the normal requirements of 1.0 mg/day, and this should give a good response.

Dependency

Myoclonic seizures may occur from birth up to 6 months of age. In B6-dependent anemia, although the blood picture is microcytic hypochromic anemia, yet patients have increased serum iron concentration, saturation of iron binding protein, deposition of iron in the liver and bone marrow, suggesting failure of utilization of iron for hemoglobin synthesis. Treatment consists of vitamin B6 given in a dose of 2–10 mg I.M. or 10–100 mg orally on daily basis.

Toxicity

Excessive intake may cause neuropathy; however, the few studies that have been conducted, have not been substantiated by further studies.

Vitamin B12

Also called cobalamin, vitamin B12 is a water-soluble vitamin with a key role in functioning of the brain and nervous system and also for mylin synthesis. It is a class of chemically related compounds that contain cobalt. Biosynthesis of the basic structure can only be accomplished by bacteria, but transformation into other derivatives occurs in the human body. Its derivatives function as cofactor of 5-methyltetrahydrofolate-homocysteine methyltransferase (methionine synthase).

It is involved in the metabolism of every cell affecting DNA synthesis and regulation, but it is also important in fatty acid synthesis and energy production.

It is found in fish, meat, poultry, milk and milk products, and eggs.

Deficiency

As B12 is found in many animal foods, dietary deficiency is unlikely except in strict vegetarians. Other recognized causes of deficiency include increased requirements as in blind loop syndrome, bacterial overgrowth and parasitic infestation of the small intestine, and due to fish tapeworm infestation.

B12 deficiency can potentially cause severe and irreversible damage to the brain and nervous system. Deficiency at lower levels causes fatigue, depression, and poor memory. It has also been suggested as a cause of mania and psychosis. Early changes lead to spongiform state of neural tissue along with edema of fibers. At later stages, this is followed by decay of meylin in the dorsal parts of the spinal cord, leading to subacute combined degeneration of the cord.

Deficiency may be caused by poor intake or poor absorption. It is rare for features of B12 to develop in early childhood. However, rare congenital defects have been described affecting assimilation of B12. These are less common than acquired deficiency in malabsorption and secondary to terminal illeal resection. In *juvenile pernicious anemia*, intrinsic factor production in the stomach is defective and this leads to megaloblastic anemia, and growth failure.

Clinical Manifestations

Clinical manifestations include anemia, jaundice, glossitis, paresthesia, dementia, and ataxia. Pernicious anemia is characterized by megaloblastic anemia, gastrointestinal symptoms, and neurological symptoms.

The neurological system may present with subacute combined degeneration of the cord with peripheral neuritis and other symptoms include impaired perception of deep, pressure and vibration sense, abolishment of sense of touch and persistent paraesthesias, ataxia of dorsal cord type, decrease or abolishment of deep tendon reflexes.

Diagnosis

Megaloblastic anemia, hypersegmented neutrophils, and thromocyopenia suggest B12 deficiency. Excessive excretion of methylmalonic acid in urine is a reliable index of B12 deficiency (normal amounts 0–3.5 mg/24 h). The diagnosis is confirmed by finding of low plasma level of less than 100 pg/mL.

When B 12 malabsorption results from defective absorptive ileal sites or due to other intestinal causes. The schilling test remains abnormal in pernicious anemia, even though therapy has completely reversed the hematological and neurological manifestations of the disease.

Treatment

Treatment of B12 deficiency depends on the cause. In pernicious anemia, treatment involves parentral administration of 1 mg and this is followed by reticulocytosis within a few days. Pernicious anemia due to B12 deficiency responds to folate therapy, but this has no effect on neurological complications.

In the event of neurological complications, a dose of 1 mg should be given daily for 2 weeks, followed by the same dose as IM on monthly basis route as maintenance therapy for life.

In the case of malabsorption, intramuscular injections of B12 are advisable to ensure a satisfactory response.

B12 is also used in the treatment of cyanide poisoning acting as a blocking agent.

Toxicity: No toxic dose is established.

Folic Acid

Folic acid (vitamin B9) is a water-soluble vitamin and it occurs naturally as folate, pteroyl-glutamic acid, and pteroyl L-glutamate. Folic acid is not biologically active, but its active form, tetrahydrofolate depends on the activity of the enzyme dehydrofolate reductase in the liver. Other derivatives are also produced in the liver or in the upper small intestine. It is essential for formation of nucleotide biosynthesis and homocystine.

Its importance relates to synthesis of DNA and RNA and similarly its action as cofactor in many biological reactions. Thus it is especially important for cell development during rapid cell division and growth, including the red cell development and maturation.

Folic acid is found in many plants and animal tissues. Leafy vegetables such as spinach, lettuce, beans and peas, tomatoes, and sunflower seeds are a principal source of folic acid. Fruits include orange, grapefruit, banana, raspberry, strawberry are recognized source of folic acid, which is also found in animal liver.

Folate Deficiency

Folate deficiency may result from poor intake or secondary to poor absorption as in malabsorption syndromes or due to specific malabsorption of folate. It can occur in the presence of folic acid antagonists, increased requirement as in prematurity, lymphoproliferative malignancy, or increased hemopoesis in different types of hemolytic diseases.

It is the commonest cause of megaloblastic anemia in children. Since folate deficiency limits cell division, erythropoiesis is impaired leading to megaloblastic anemia and hypersegmented neutrophils.

Deficiency of folate in pregnant women has been implicated in neural tube defects in fetuses, especially if this occurred during early pregnancy.

Some drugs interfere with biosynthesis of folic acid such as dihydrofolate reductase inhibitors such as trimethoprin, pyrimethamine, methotrexate, and sulphonamides.

DNA synthesis and repair are also impaired and this has been suggested as a cause of cancer.

Clinical Manifestations

The hemopoetic system is mainly affected leading to megaloblastic anemia although some skin changes and neurological problems do occur. Nonspecific features that may be shared with other water-soluble vitamins include glossitis, diarrhea, depression, and confusion.

Deficiency of folic acid during early pregnancy has been associated with serious neurological abnormalities during fetal development, including neural tube defects and also other brain defects.

Diagnosis

Peripheral blood picture and bone marrow changes show the specific features of megaloblastic anemia, which is not distinguishable from B12 deficiency; however, the shorter time frame suggests the former. Measurement of serum folate level reflects folate status, but the erythrocyte folate level is more specific in determining inadequate folate status.

Treatment

Folate deficiency is treated with supplemental oral folate of 1–5 mg daily. Patients with coeliac disease have a greater chance of developing folate deficiency as well as iron deficiency anemia.

Folic Acid Supplementation Risk for Children

Excessive supplementation of folic acid has been shown to increase the risk of developing malaria and increased mortality. This has prompted WHO to alter their policies for malaria endemic areas like India.

Vitamin C

Vitamin C or ascorbic acid is water -soluble vitamin, which is required for the synthesis of collagen. It plays an important role in the synthesis of the neurotransmitter, norepinepherine essential for brain function. It activates enzymes for hydroxylation of protocollagen proline and lysine to collagen hydoxyproline and hydroxylysine.

It is a potent antioxidant agent that is easily oxidized and destroyed by heat. It can regenerate other antioxidants such as vitamin E from its oxidized form.

Deficiency

Vitamin C deficiency results in scurvy, but is now a rare event worldwide due to availability of dietary sources rich in vitamin C such as citrus fruits, strawberries, tomatoes, and green vegetables. Breast milk contains sufficient quantities for the baby.

Clinical Manifestations

Symptoms of scurvy include bleeding and bruising, hair and tooth loss, joint pain and swelling. In severe cases, tenderness and swelling of legs, knees and ankles, and consequent pseudoparalysis may be present. The child appears weak, in severe pain with arthralgia and joint effusions, thus adopting a frog-like position to relief his pains. The detection of brawny edema often overlies subperiosteal hemorrhage, which occurs at ends of the femur and tibia.

The gums may be affected, leading to bleeding and tooth loss. Subconjuntival hemorrhage occurs and peticheal hemorrhages may result in the skin and mucus membranes. Delayed wound healing is a recognized complication. Such symptoms appear to be related to

weakening of collagen in blood vessels. Microcytic hypochromic anemia due to vitamin C deficiency may be detected.

Early symptoms like fatigue may result from diminished levels of carnitine, which is needed for production of energy from fat, or from decreased synthesis of norepinephrine.

Severe scurvy may cause degeneration of skeletal muscles, bone marrow depression, and adrenal atrophy.

Diagnosis

The diagnosis is based mainly on the characteristic clinical picture and is supported by radiological finding of subperiosteal hemorrhage with calcification and ground glass appearance of metaphysis due to atrophy of bone trabeculae. The diagnosis is confirmed by plasma concentration of vitamin C of less than 1 mg/L.

Treatment

Scurvy is treated by oral supplement of vitamin C of 100–200 mg daily for 1 week followed by 25–50 mg/day given orally. Treatment should be started early once the diagnosis is suspected. Diet should include juices rich in vitamin C.

Transient tyrisonemia in the neonatal period in low birth babies is corrected by administration of vitamin C.

X-Ray changes may take up to a year to disappear.

Toxicity

There has been no reliable scientific evidence that large doses of vitamin C are toxic or detrimental to health.

Fat-Soluble Vitamins

Vitamin A

Vitamin A is essential for vision, growth, cellular differentiation, reproduction, and the integrity of the immune system. There is a close metabolic relationship between vitamin A and protein. It is necessary to maintain a satisfactory level known as total body pool to meet physiological needs in addition to a constant liver reserve that may be required during stress. This is achieved by taking vitamin A (ratinol) and various carotenoids such as B- carotine, a-caroten, and cryptoxanthin that biologically functions as vitamin A.

The best sources are animal liver and fish liver oil, milk, whole egg, and other dairy and egg products. Active carotenoids are abundant in carrots, dark green leafy vegetables like spinach, lettuce, tomatoes, sweet potatoes, and in some fruits like papaya. The absorption and utilization of vitamin A and carotinoides are enhanced by dietary fat, protein, and vitamin E.

Properties

Vitamin A has several functions in the human body of which vision seems most important. Ratinol is combined with the protein opsin forming the photosensitive pigment of the rods, which is required for vision in dim light. The photorecepters of cones contain the same chrophore (ratinal) that are linked with protein iodopsin, which is important for color vision. The influx of calcium as a mediator triggers a nerve impulse allowing light to be perceived by the brain.

Vitamin A acts as a growth promoter. Linear growth of children is significantly associated with plasma retinol concentration. It is also necessary for morphological and functional integrity of the skin.

Vitamin A has anti-infective action and its metabolites are essential to T and B cell growth and function. It enhances immunity, thereby has been demonstrated to reduce childhood morbidity and mortality from common intercurrent infectious diseases including diarrheal diseases, respiratory infections, and proved to have a substantial impact on measles morbidity and mortality.

Vitamin A is important in iron-deficient patients not responding to medicinal iron therapy. There is a strong correlation between serum retinol and hemoglobin in children and pregnant women. Supplementation shows significant increase in retionol, hemoglobin, hematocrit, serum iron, and saturation of transferin. Recent reports have also indicated that vitamin A is essential for hemopoiesis.

Vitamin A functions as regulator of intracranial pressure and it influences the rate of secretion of the cerebrospinal fluid. Hence hyper or hypo-vitaminosis A may lead to increased intracranial pressure. β-carotene and vitamin A have also been shown to be effective in the prevention and treatment of different types of cancer.

Normal serum levels in pregnant women, especially during the first trimester, protects against the recognized association of neural tube defects of babies born to vitamin A-deficient mothers and similarly for meningomyloceles. Vitamin-deficient mothers have less

amounts of vitamin A in their breast milk and newborns usually have little liver stores.

Vitamin A Deficiency

Vitamin A is endemic in many developing countries and its prevalence is particularly high in southeast Asia including India, Indonesia, Bangladesh, and the Philippines. Vitamin A deficiency does not occur as an isolated problem, but it is invariably accompanied by PEM and infections like diarrheal diseases, respiratory infections, measles, malaria, and urinary tract infections, which are common childhood diseases.

Its deficiency interferes with rhodopsin production, impairs rod function, and results in impairment of dark adaptation, leading to night blindness that constitutes the early sign of vitamin A deficiency. This is followed by conjunctiva xerosis where epithelial cells undergo squamous metaplasia, the tear glands become blocked with horny plugs of keratin with diminution of secretions and dryness of cornea. It appears in the temporal quadrant and gives rise to formation of Bitot spots. These are considered early signs of vitamin A deficiency and are particularly responsive to treatment.

If untreated this will lead to corneal xerosis when dryness spreads to the cornea with keritinization of epithelial surface resulting in a dull, hazy, and lusterless dry appearance. This may be followed by keratomalcia or corneal ulceration, which presents as erosion of part or whole thickness of the corneal thickness at its periphery. This may lead to perforation of the retina, extrusion of intraocular contents and loss of the globe, and subsequently lead to corneal scars and xerophthalmic fundus. Treatment of patients suffering from malnutrition should be preceded by restoration of liver stores, else keratomalcia may pursue rapidly.

Deficiency is associated with increased morbidity and mortality from infectious diseases, like diarrheal diseases, acute respiratory infections, measles, malaria, TB, and HIV. Episodes of infection hasten the depletion of vitamin A stores and mild deficiency is associated with increased mortality. It has been demonstrated that deficiency is associated with impaired phagocytosis, reduced activity of T- killer cells, and impaired immunoglobulin response to antigens.

Chronic or acute deficiency leads to deceleration or cessation of linear growth while supplementation leads to restoration of normal growth. It equally leads to metaplasia of skin cells, thus blocks sebaceous glands and hair follicles. Hypovitaminosis A leads to increased intracranial pressure (pseudotumor cerebri) similar to hypervitaminosis A.

Diagnosis

Vitamin A deficiency is suspected by its characteristic clinical manifestations and confirmed by detection of low serum vitamin A of less than 200 ug/L and carotenoids of less than 500 μg/L. Dark adaptation tests may be helpful in the diagnosis. Xerosis conjunctivae can be detected by microscopic examination of the conjunctiva. Examination of scraping from the eye and vagina is recommended as diagnostic test. Vitamin A and retinol in serum is measured by high performance liquid chromatography (HPLC).

Treatment

In the acute phase of Vitamin A deficiency like xerophthamia, treatment involves administration of 1,500 μg/day of retinol orally for 5 days and then continued with IM injections of vitamin A in a dose of 7,500 μg daily until recovery occurs.

In latent vitamin A deficiency, a single dose of 1,500 μg is usually sufficient.

Prevention

Prevention of vitamin A deficiency among young children in developing countries is essential to reduce its complications and to achieve reduction of the high infant morbidity and mortality noted in these countries. Raising vitamin A status in communities with high prevalence of xerophthalmia is an urgent necessity and should be considered a national health priority.

Nationwide program to ensure adequate intake of vitamin A is an essential step in the management. Water misciple oral preparations are preferable since, in the presence of fat malabsorption, absorption of oily preparations may be poor. Deficiency of vitamin A in endemic areas may be prevented with a recommended daily intake of 800 μg retinol in premature infants, 400 μg in term and older infants, and 700–1000 μg in older children.

As for affected children and those at high risk, a periodic administration of large doses is recommended.

200,000 units of vitamin A should be given prophylacticaly every 6 months to pre-school children. This approach should be complemented by fortified food rich in vitamin A like milk, margarine, and bread. Similarly, well-balanced diets should also be encouraged through health education and school health programs.

Vitamin A Toxicity

When ingested in very high doses of preformed vitamin A, either acutely or chronically, it causes many toxic manifestations including headaches, nausea, vomiting, abdominal pain, diplopia, irritability, seizures, alopecia, dryness of mucus membranes, desquamation of the skin, bone abnormalities, and liver damage.

Signs of toxicity appear when chronic daily intakes of 20,000 IU in infants and young children are given. High incidence of >20% of spontaneous abortions, birth defects including malformations of the cranium, face, heart, thymus, and central nervous system was observed in fetuses of women ingesting therapeutic doses of 0.5–2.5 mg/kg of 13-*cis* retinoic acid (isotretinoin) during the first trimester of pregnancy.

Carotinoids in food, if ingested chronically in very large doses, are not known to produce toxic manifestations. They can, however, produce yellow discoloration of the skin and palms, but not the sclera, which differentiates it from jaundice. Hypercarotenosis is benign and can be corrected by lowering of intake of carotenoids.

Hypervitaminosis A leads to increased intracranial pressure (pseudotumor cerebri). Symptoms include vomiting, irritability, drowsiness, bulging of the fontanel, hydrocephalus, diplopia, papillodema, and cranial nerve palsies.

Excessive ingestion of vitamin A for several weeks leads to pruritis, alopecia, seborrheic cutaneous lesions, fissuring of the corners of the mouth, and desquamation of palms and soles.

Vitamin E

Vitamin E comprises a family of eight antioxidants; however, α-tocopherol is probably the only active form. It is found in large quantities in the body and appears to have the greatest nutritional significance. It is a fat-soluble antioxidant and direct hydrogen donor. It intercepts free radicals known to destroy fats, which form an integral part of the cell membrane. It also protects low-density lipoproteins (LDLs) from oxidation. LDLs transports cholesterol from the liver to different tissues in the body and have been demonstrated to inhibit platelet aggregation and enhance vasodilation.

It is found naturally in foods in varying amounts. Its major sources include vegetable oils like sunflower and olive oils, nuts, whole grain, and green leafy vegetables.

Deficiency and Clinical Manifestations

Serum levels tend to be low at birth, particularly in low-birth-weight infants and babies fed on formula milk high in polyunsaturated fat. Vitamin E is associated with hemolysis in the preterm infants at age of 6–10 weeks and hemolytic anemia is perhaps the only commonly observed abnormality in children. Secondary deficiency occurs in severe malnutrition, fat malabsorption syndromes like cystic fibrosis, biliary atresia, coeliac disease, and abetalipoproteinemia.

The developing nervous system is particularly vulnerable to vitamin E deficiency. Severe deficiency results mainly in neurological symptoms including cerebellar ataxia, polineuropathy, myopathy, and pigmented retinopathy.

Diagnosis

Diagnosis is confirmed by a low serum level of less than 5 mg/L (11μmol/L).

Treatment

Treatment includes dietary support with foods rich in vitamin E together with vitamin E supplementation in clinically affected patients. The dose of vitamin E (tocopherol acetate) ranges from 10 to 20 mg/K/day.

Toxicity

Premature infants appear to be vulnerable to a-tocopherol supplementation as a possible cause of hemorrhage. Excessive supplementation has been suggested to accelerate progression of retnitis pigmentosa.

Vitamin K

Vitamin K (phytomenanadione) has a recognized role in controlling the formation of prothrombin and acts as cofactor for synthesis of clotting factors II, VII, IX, and X in the liver. It has a biological role as cofactor for an enzyme that catalyses the carboxylation of glutamic acid resulting in its conversion to gamma-carboxyglutamic acid, which is important in the calcium-binding function of some proteins. The ability to bind to calcium ions is required for activation of vitamin K-dependent coagulation factors.

Vitamin K1 is a naturally occurring fat-soluble compound and it found in high concentrations in liver, soya beans, cotton and olive oil. It is, however, found in smaller quantities in vegetables such as spinach and tomatoes. *Vitamin K2*, on the other hand, is produced by gut flora in the body.

Deficiency

Vitamin K is usually obtained from intestinal bacterial synthesis and only a small proportion comes from external sources. Breast milk is an especially poor source and thus, breast-fed infants are susceptible to deficiency. In the first few days of life, the gut is sterile and hypoprothrombinemia may occur. Deficiency may occur in malabsorption or by impaired entrohepatic circulation.

Vitamin K deficiency may manifest from early life as hemorrhagic disease of the newborn. Bleeding may occur in the umbilicus, gums, nose, intestine, or under the skin, and massive hemorrhage may occur in the gastrintestinal tract. Intracranial hemorrhage may also occur.

Later in life, vitamin K deficiency is a potential hazard in malabsorption, progressive liver disease, resulting in prolonged prothrombin time and tendency to bleeding.

All coagulation factors dependent on vitamin K including prothrombin, factors II, VII, IX, and X are depressed; therefore, remain as a cause of bleeding.

Warfarin, an anticoagulant, interferes with vitamin K function, while broad-spectrum antibiotics can interfere with endogenous production of vitamin K by bacteria. Cyclosporines and salicylates, on the other hand, interfere with vitamin K recycling in the gut.

Diagnosis

The diagnosis is established by prolongation of blood coagulation time, prolonged prothrombin time and partial thromboplastin time.

Treatment

In cases of hemorrhagic disease of the newborn, 1 mg of vitamin K should be given. In later childhood, the dose is increased to 5 mg daily. I.M. injections are best avoided in the presence of severe bleeding. Fresh frozen plasma or whole blood transfusion may be necessary in some patients.

Prevention

Because of the risk of bleeding, breast-fed infants should receive prophylaxis of 1 mg vitamin A. preterm infants may receive 0.5 mg intramuscularly.

Toxicity

Vitamin K and its water-soluble analogues, except phytonadione, have induced hemolysis in large doses and children with G6PD are especially susceptible. Large doses in the newborn have caused anemia, hyperbilirubinaemia, and kernicterus in preterm infants.

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58 Rickets

Trond Markestad

Nutritional rickets due to deficiency of vitamin D, dietary calcium, or both is among the most common disease entities among young children in the Middle East, Asia, and Africa. It has also reoccurred in high-income countries among immigrants from parts of the world where rickets is common and among children on restricted diets. Rare forms of rickets are due to genetic diseases affecting vitamin D metabolism or response to vitamin D, or diseases resulting in renal loss of phosphate.

Definition and Pathology

Osteomalacia denotes inadequate mineralization of organic bone tissue, both children and adults, while *rickets* is the manifestation of inadequate mineralization of *growing* bone, i.e., before the fusion of the epiphyses. As the proliferating osteoid tissue in the metaphysis fails to mineralize, deformation and stunted growth occur. Inadequate mineralization also occurs in the shafts of the long bones and in membranous bone leading to pathologic softness and deformation.

Pathogenesis

The extracellular fluid concentration of calcium (Ca) and phosphate (P) are tightly regulated, mainly through the actions of parathyroid hormone (PTH) and the hormonal form of vitamin D, 1,25-$(OH)_2$D (*Fig. 58.1*). Both Ca and P concentrations must be appropriate to permit adequate deposition of Ca-Pi crystals in the bone matrix.

Ca homeostasis is mainly controlled at the intestine in that serum concentration of 1,25-$(OH)_2$D determines how large a fraction of the dietary Ca that is absorbed. When serum Ca drops (i.e., as a result of low dietary intake), 1,25-$(OH)_2$D synthesis is stimulated. This stimulation is indirect in that hypocalcemia initiates increased synthesis of PTH which, in turn, stimulates the synthesis of 1,25-$(OH)_2$D from 25-OHD in the renal tubular cells. The increased 1,25-$(OH)_2$D level raises serum Ca by promoting intestinal Ca absorption. High PTH and 1,25-$(OH)_2$D may together also mobilize Ca from bone and reduce Ca excretion in the kidneys. In this way, an adequate extracellular concentration of Ca, which is of vital importance for the living organism, may be maintained at the expense of bone mineralization.

Phosphate (P) homeostasis is mainly controlled at the kidney, since intestinal P absorption is nearly complete and largely independent of hormonal regulation. A high phosphate content of the diet will lead to a high serum concentration of P, which, in turn, will cause a drop in serum Ca, partially through a direct inhibitory effect on 1,25-$(OH)_2$D synthesis. The fall in serum Ca will stimulate PTH secretion which, in turn, will induce phosphaturia and raise serum Ca. On the other hand, a low serum concentration of P promotes 1,25-$(OH)_2$D synthesis and inhibits PTH secretion, and consequently reabsorption of P is increased in the kidneys.

Lack of vitamin D, disorders in the regulation of vitamin D metabolism or response to 1,25-$(OH)_2$D, and inadequate supplies or pathologic losses of Ca or P may all cause rickets. On the basis of etiology and pathogenesis, rickets may be classified as *calciopenic* or *phosphopenic* rickets (*Table 58.1*).

Symptoms and Signs

Skeletal

The most important symptoms of rickets are bone deformity and, in advanced cases, stunted growth (rachitic dwarfism). Bone pain and tenderness may be significant symptoms in *calciopenic* rickets.

The relative growth rates of different bones and therefore the relative distribution of skeletal manifestations change with age, since the most rapidly growing bones will be the most severely affected. Thus, symptoms and signs will be particularly prominent in the skull at birth and in early infancy; in the wrist, costochondral junction, and knee during the first year of life; and in the lower extremities later during childhood. The weight bearing will increase the deformity of the lower limbs when the young child begins to walk.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_58,

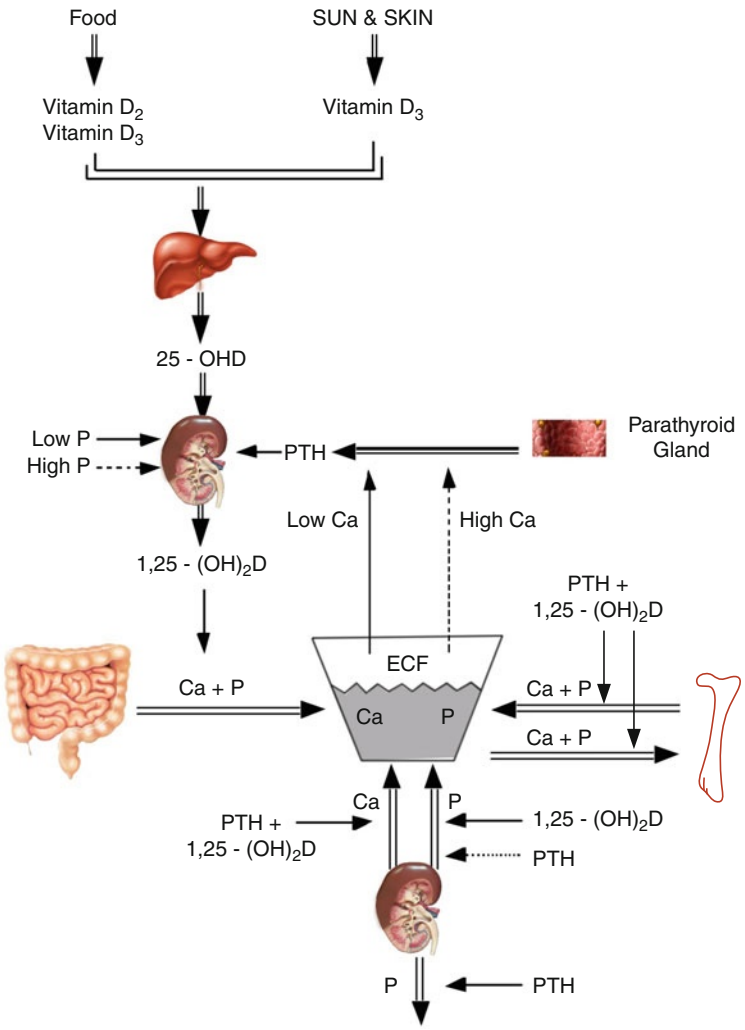

Figure 58.1
Biochemical pathways of vitamin D, and endocrine regulation of Ca and P homeostasis. ECF, extracellular fluid, PTH, parathyroid hormone, ⟶ stimulation; ⇢ inhibition

Skull

Craniotabes describes the thinning of the skull, and is detected as a "ping-pong ball" consistency when pressing on the parietal or occipital bones. It is important to note, however, that craniotabes along suture lines may be normal in breast-fed and in preterm babies in early infancy, and that localized craniotabes is a frequent and normal finding in newborns, particularly if the head has been engaged in the pelvis for a long time. Craniotabes is also seen in other diseases, such as osteogenesis imperfecta. *Frontal bossing* describes a prominence of the central parts of the frontal and parietal bones giving the head a box-like appearance (caput quadratum). This impression may be augmented by flattening of the head (particularly the occiput) or asymmetry caused by the softness of the skull and relative immobility of the infant. *Wide sutures*, a large *anterior fontanelle* and delayed closure of the fontanelle, may be other features, but they are nonspecific and may be normal variants.

Extremities

Swelling around joints because of widening and lateral bulging of uncalcified tissue at the metaphysis is

Table 58.1
Biochemical characteristics of various forms of rickets

Type of rickets	Serum Ca	Serum P	ALP	PTH	25(OH)D	1,25-$(OH)_2$D	Urine AA
Calciopenic rickets							
1,25-$(OH)_2$D deficiency due to	N or ↓	↓	↑	↑	↓	N, ↓ (or↑)[a]	↑
- Lack of sunshine/dietary							
- Malabsorption							
- Severe liver disease							
- Anticonvulsants							
1,25-$(OH)_2$D deficiency due to deficient synthesis							
- Vitamin D-dependent type I	N or ↓	↓	↑	↑	N	↓	↑
- Renal failure	N or ↓	↑	↑	↑	N	N or ↓	V
End organ resistance to 1,25-$(OH)_2$D							
- Vitamin D-dependent type II	N or ↓	↓	↑	↑	N	↑	↑
Calcium deficiency[b]	N or ↓	↓	↑	↑	N	↑	
- Dietary							
- Malabsorption							
Phosphopenic rickets							
Dietary deficiency	N or ↑	↓	↑	N	N	↑	N
- Parenteral nutrition							
- Prematurity							
Increased renal loss							
- Familial hypophosphatemia	N	↓	↑	N	N	N[c]	N
- Tumor	N	↓	↑	N	N	↓	N
- Hereditary hypophosphatemic rickets with hypercalciuria	N	↓	↑	↓	N	↑	N
- Fanconi syndromes	N	↓	↑	N	N	N[c]	↑
- Renal tubular acidosis	N	↓	↑	N	N	N[c]	N

↓=Decreased, ↑=Increased, Urine AA=urine aminoacids, N=Normal, V=Variable
[a]May be elevated on diagnosis if received even small doses of vitamin D within the last few days
[b]Rare as a single cause, more often seen together with vitamin D deficiency
[c]Within normal reference range, but inappropriately low considered low serum P

particularly noticeable at the wrist, knee, and ankle. Increased width of the epiphyseal line can be palpated at the wrist and ankle (*double malleolus*). After the first year, *deformities* like genu varum, genu valgum, coxa vara, and saber shins (anterior convexity of the tibia) may develop.

Thorax

Rachitic rosary describes the enlargement of costochondral junctions of the ribs (◉ *Fig 58.2*), and *Harrison's groove* the horizontal depression of the chest wall corresponding to the insertion of the diaphragm. *Pectus carinatum* (pigeon chest) and other thoracic deformities may also develop.

Spine and Pelvis

Scoliosis, dorsolumbar kyphosis, and lumbar lordosis may develop. Children with lordosis commonly have a deformity of the pelvis, particularly forward projection of the promontory, sacrum, and coccyx. In females, these changes may later cause difficulties during pregnancy and childbirth.

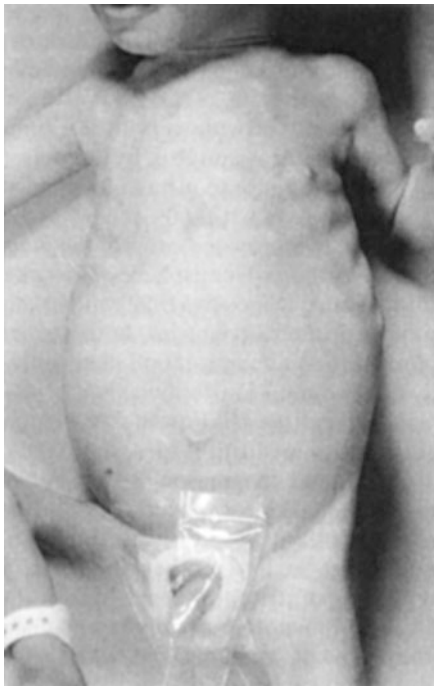

Figure 58.2
Rachitic rosary in a patient with florid rickets. (Courtesy of Prof. Hishan Nazer, Amman, Jordan)

Teeth

The temporary and permanent teeth may be abnormal, with delayed eruption, enemal hypoplasia and irregular pits, and increased tendency to caries.

Muscular

Muscular hypotonia is typical of *calciopenic* rickets and may be caused by 1,25-$(OH)_2$D deficiency. Hypotonia may be marked during infancy (floppy infant) and cause delayed motor development.

Tetany

Hypocalcemic tetany may occur at any stage of *calciopenic* rickets and even before other clinical findings or radiographic features are evident, but is *not* a feature of *phosphopenic* rickets. In latent tetany (serum Ca usually 1.75 to 1.90 mmol/L), the child may be irritable and show positive Chvostek or Trousseau signs. In manifest tetany, convulsions are most frequently observed, but carpopedal spasm and laryngospasms may occur. Serum Ca levels are usually below 1.60 mmol/L.

Malnutrition and Infection

Children with *calciopenic* rickets, especially caused by vitamin D deficiency, are often wasted in addition to being stunted in growth. Poor muscular development, possibly because of 1,25-$(OH)_2$D deficiency, association of vitamin D deficiency with a poor social environment, and poor feeding because of muscular hypotonia and malaise, may all contribute. Pot belly is also a characteristic feature of the muscular hypotonia of rachitic babies, so rickets per se may be confused with primary malnutrition and malabsorption syndromes.

Children with calciopenic rickets (particularly vitamin D deficiency rickets) are prone to infections, especially pneumonia. The soft thorax, muscular hypotonia, and concomitant malnutrition may represent the most significant risk factors, but active vitamin D metabolites may also have a direct effect on the immune system.

Radiographic Signs

The pathologic features discussed above are best visualized by x-ray film. In the metaphysis of the long bones, the following features are typical and most easily seen in the distal end of the radius and ulna: wide and irregularly calcified epiphyseal cartilage (the growth plate), concave and ragged border between calcified and noncalcified structures ("cupping" and "fraying"), and increased width of the metaphysis ("splaying") (*Fig. 58.3*). In more advanced cases, changes are also observed in the shaft, namely, diffuse rarefaction, thinning of the cortex, radiolucent transverse bands, greenstick fractures, and deformities.

The first sign of healing is typically the reappearance of a calcified transverse line that is separated from the distal end of the shaft by a radiolucent zone of osteoid tissue. The calcified line may appear within 2 weeks of the vitamin D and Ca treatment in nutritional rickets. As the osteoid tissue becomes calcified, the radiolucent zone between the calcified line and the shaft gradually disappears. The recalcification of the rachitic metaphysis may, however, also start at the visible end of the shaft and progress toward the epiphyseal cartilage. In the healing of advanced rickets, calcification of osteoid tissue under the periosteum of the shaft may present radiographically as a cortical envelope of uniform or lamellated density.

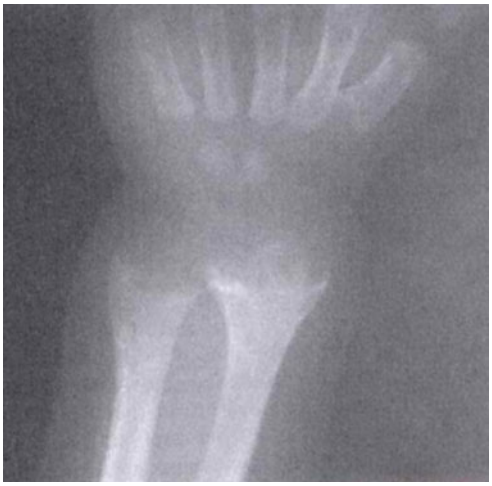

Figure 58.3
X-ray film of the wrist in a patient with rickets. Note cupping, fraying, and widening of the metaphysic. (Courtesy of Prof. Hisham Nazer, Amman, Jordan)

Biochemical Signs

Serum alkaline phosphatase (ALP) is almost always elevated. The serum concentrations and urinary excretion of Ca and P, urinary excretion of aminoacids, and serum concentrations of PTH and vitamin D metabolites will vary according to the etiology and stage of disease as discussed below for each rachitic syndrome (*Table 58.1*).

Differential Diagnosis

The combination of clinical signs, biochemical and radiographic features are rather specific. The main challenge is to define the specific cause of rickets. However, various *clinical* skeletal deformities may also be normal variants (e.g., bow legs, thorax deformities, and craniotabes), or represent a multitude of skeletal dysplasias. *Hypocalcemia* of rickets may be confused with hypocalcemia of hypoparathyroidism and magnesium deficiency, especially since tetany may occur before bony changes are evident on radiographs or serum ALP is significantly elevated. However, serum P is high in hypoparathyroidism and hypomagnesemia, but normal or low in rickets, except when rickets is caused by renal failure. It is important to note that serum P is normally considerably higher in children than in adults, and that an improper technique of sampling blood may give a falsely high value because of hemolysis.

Calciopenic Rickets

Calciopenic rickets denotes that the Ca supply is inadequate for normal bone mineralization. By far, the most common cause is *nutritional rickets*, i.e., vitamin D deficiency, lack of Ca in the diet, or a combination of both. Intestinal malabsorption of vitamin D or Ca (e.g., celiac disease) may be underlying causes. Inadequate synthesis of 25-OHD, which is the substrate for 1,25-$(OH)_2$D synthesis, may occasionally fail in cases of severe liver failure. Very rare causes are genetic disorders of vitamin D metabolism or end-organ resistance to the effect of 1,25-$(OH)_2$D.

Nutritional Rickets

Until recent years, nutritional rickets was thought to be due to vitamin D deficiency, except in rare cases of extreme diets with a very low Ca content. It is now acknowledged that low Ca diets may be the most important cause in parts of Africa (e.g., Nigeria and South Africa) and Asia (e.g., Bangladesh), and that a combination of low Ca intake and lack of vitamin D may be a quite common cause in many parts of the world and among some ethnic groups. Diets with less than approximately 300 mg elemental Ca per day have been identified as a major risk factor. Inhibition of Ca absorption by diets rich in oxalates (green, leafy vegetables) or phytate (unleavened bread) may add to the Ca deficiency. With a low Ca diet, vitamin D metabolism is stimulated to increase fractional absorption of Ca from the intestines. The increased synthesis of 1,25-$(OH)_2$D leads to a higher consumption and subsequent risk of frank vitamin D deficiency in children who are inadequately exposed to sunshine or vitamin D supplementation.

In nutritional rickets from vitamin D deficiency, lack of sunshine exposure or insufficient dietary intake of vitamin D leads to inadequate synthesis of 1,25-$(OH)_2$D.

Food items generally provide very little vitamin D, although fatty fish are important sources in some areas. The most important natural source is, by far, dermal synthesis of vitamin D_3 in response to ultraviolet (UV) irradiation from sunshine. This is why as much as 60–90% of the children in the polluted and overcrowded cities in the industrialized nations of the northern hemisphere had rickets in the late ninteenth and early twentieth century. Since the 1930s–1940s, the disease has become rare in these countries, however, because of vitamin D fortification of central food items or widespread use of individual vitamin D prophylaxis.

Paradoxically, the disease is now most common in the sunny subtropical countries in North Africa, the Arab countries, India, and China, and the main reason is that cultural habits cause inadequate sunshine exposure of women of childbearing age, and of infants. Typically, the infant with rickets is born to and breast-fed by a mother who herself is vitamin D deficient because of strict adherence to the cultural habit of wearing a veil. The mother usually has no clinical symptoms or signs of osteomalacia. Vitamin D is stored in the body, mainly in fatty tissues. The infant is born vitamin D deficient because the stores acquired in utero are proportional to the mother's vitamin D nutritional status during pregnancy. Furthermore, the vitamin D content of breast milk is proportional to the nursing mother's vitamin D nutritional status. The lack of vitamin D in breast milk will augment the infant's deficiency, but the vitamin D content of breast milk is inadequate even when the mother has a normal vitamin D nutritional status.

In Northern Europe and North America, nutritional rickets has reappeared as a significant clinical problem among children of families with extreme vegetarian diets, and among immigrants, particularly from Asia and Africa. Increased skin pigmentation, habits of clothing, traditional diets that limit vitamin D and Ca uptake and lack of tradition to take vitamin D supplements may all contribute to the risk of rickets in immigrant populations.

Clinical Features

Nutritional rickets during infancy and early childhood is usually due to vitamin D deficiency. Congenital rickets and rickets in early infancy occur, but the typical age of manifestation is between 4 and 18 months. When dietary Ca deficiency is the major cause, the typical age of debut is 3–6 years or during the pubertal growth spurt (adolescent rickets).

Symptoms and signs are described above. Important but not obligatory features of advanced rickets are muscuar hypotonia, irritability, and malnutrition. At least for rickets due to vitamin D deficiency, *three stages are described* on the basis of clinical and laboratory data:

- *Stage 1*: is characterized by low serum Ca, occasionally to the point of causing tetany, but normal serum P, and normal or minimal changes on radiographs. This stage is caused by insufficient intestinal Ca absorption, and is transient until compensatory mechanisms come into play.
- *Stage 2*: Secondary hyperparathyroidism has reestablished a normal serum Ca by mobilizing bone release and renal reabsorption of Ca, but serum P is decreased because of increased renal excretion. Clinical and radiographic signs of rickets become evident.
- *Stage 3*: Continued deficiency of 1,25-$(OH)_2$D and hyperparathyroidism result in insufficient mobilization of Ca from bone to maintain normal serum Ca. Hypocalcemia as well as hypophosphatemia evolves. Clinical symptoms, findings, and radiographic changes are more severe. Tetany may again become an important symptom.

Diagnosis and Differential Diagnosis

The diagnosis of nutritional rickets is based on a typical history, clinical findings and laboratory data, and a rapid response to vitamin D treatment. Muscular hypotonia may improve within days, radiographs within 2–3 weeks, and healing usually occurs within 8–12 weeks.

Serum concentrations of Ca and P are normal or low, dependent on the stage of rickets as described above. Serum ALP is elevated except that it may occasionally be normal in early stage1 rickets. Generalized aminoaciduria reflects secondary hyperparathyroidism and is not specific for nutritional rickets.

Measurement of vitamin D and its metabolites in serum is not uniformly available, not always diagnostic, and usually not necessary. Typically, 25-OHD, which reflects the vitamin D nutritional status, is below 25 nmol/L and PTH is elevated (secondary hyperparathyroidism). The 1,25-$(OH)_2$D is low or normal (but inappropriately low given the hyperparathyroidism) at diagnosis, but increases to very high levels within days of starting vitamin D therapy. High levels of 1,25-$(OH)_2$D may be seen even at the time of diagnosis due to recent sunshine exposure or inadvertent intake of vitamin D through food items.

If the medical history is not typical for vitamin D or Ca deficiency, malabsorption syndromes may need to be considered. Vitamin D is a lipid-soluble vitamin, and malabsorption may per se result in vitamin D deficiency if the child is not exposed to sunshine. Children on antiepileptic medication, especially phenytoin and phenobarbital, may develop vitamin D deficiency because of drug induction of hepatic enzymes that degrade vitamin D.

Iron deficiency anemia is commonly associated with viamin D deficiency rickets, and a hematological syndrome with anemia, leucomoid blood smear, and hepatosplenomegaly has been described.

Treatment and Prophylaxis

Sunshine exposure or artificial ultraviolet light will cure vitamin D deficiency rickets, but oral or intramuscular administration of vitamin D_3 or D_2 is needed for reliable treatment. A daily intake of 50–100 μg (2000–4000 IU) until healing, or a dose of 10–15 mg (400,000 to 600,000 IU) given as one dose or divided into two to four doses over 2–4 days with no further vitamin D therapy, are equally effective. The large dose may be given intramuscularly, but oral administration is probably equally or more effective, except if the child is vomiting. One dose of 15 mg will not cause vitamin D toxicity in a child with rickets, and it will not disguise vitamin D-resistant forms of rickets.

With malabsorption, a daily oral vitamin D intake of 100–200 μg, or one or a divided dose of 15 mg is usually adequate to cure rickets, but higher doses or the active metabolite 1,25-$(OH)_2$D may rarely be indicated, particularly if the child has severe liver disease.

Tetany should be treated with 10% calcium gluconate by slow intravenous infusions, 1–2 ml/kg up to a total of 10 ml over 10 min. Vitamin D treatment may trigger a further temporary drop in serum Ca due to rapid deposition in mineral-deficient bone ("hungry bone syndrome"). Therefore, oral Ca should be given, at least during the first 1–2 weeks of vitamin D therapy. If the diet is low in Ca, tapering doses of Ca supplements are advantageous until the healing of rickets. Ca supplementation is particularly important if serum Ca is low. If serum Ca is very low, hospitalization may be necessary the first few days of treatment to observe for tetany. A recommended early dose is 1 g of elemental Ca per day in divided doses as, for example, calcium lactate or calcium carbonate.

After healing of rickets, a daily oral prophylactic dose of 10 μg (400 IU) of vitamin D or sunshine exposure of the skin should be provided. Commercial infant formulas are generally fortified with vitamin D and no supplements are needed.

Prognosis

Nutritional rickets rarely cause permanent sequelae, but it may take 4–5 years before skeletal deformities are corrected.

Vitamin D-Dependent Rickets Type I

In this rare disorder, there is a lack of renal tubular enzymes converting 25-OHD to 1,25-$(OH)_2$D. Serum concentrations of 1,25- $(OH)_2$D are therefore very low, or inappropriately low given the secondary hyperparathyroidism despite adequate 25-OHD levels. The disease is inherited in an autosomal recessive mode. Clinical and standard laboratory findings are similar to those described for nutritional rickets, and become manifest during the first year of life.

The treatment of choice is lifelong physiological doses (0.25–2 μg/day) of alpha-calcidiol (1α-OHD) or calcitriol (1,25-$(OH)_2$D). Initially, Ca supplementation may be beneficial. The aim is radiographic healing and maintenance of serum Ca in the low, P in the normal, and PTH in the high range of normal in order to avoid hypercalciuria and nephrocalcinosis. It is important to note that hypercalcemia can evolve rapidly during calcitriol treatment, particularly at the time when rickets is healed and the need for 1,25-$(OH)_2$D is reduced. The family should therefore be warned of symptoms of hypercalcemia, such as lethargy, poor feeding, nausea, vomiting, constipation, or abdominal pain. Pharmacological doses of vitamin D may also be effective, but is not recommended because of the long half-life and unpredictable effect, particularly a risk of vitamin D toxicity.

Vitamin D-Dependent Rickets Type II

These rare patients have end-organ resistance to the effect of 1,25-$(OH)_2$D, and calciopenic rickets develop despite extremely high serum levels of 1,25-$(OH)_2$D. The disease is inherited as an autosomal recessive trait, and the onset is usually between 6 months and 3 years. There are several clinical variants, and some have alopecia as a distinctive feature.

The patients may benefit from large doses of alpha-calcidiol or calcitriol (15–50 μg/day) and large dietary supplements of Ca. Intravenous Ca may be necessary to initiate healing.

Renal Osteodystrophy (Renal Rickets)

The pathogenesis of renal osteodystrophy is complex and includes renal phosphate retention, malabsorption of Ca secondary to inadequate 1,25-$(OH)_2$D synthesis, and secondary hyperparathyroidism.

Clinical and Investigational Features

Growth failure occurs early. Serum P and the Ca x P product and PTH are elevated, although the Ca value

may be decreased. Serum ALP may be increased. On radiographs, subperiosteal erosions of the middle and distal phalanges typical of hyperparathyroidism may be seen in addition to typical features of rickets.

Prophylaxis and Treatment

Prophylaxis should be started before growth failure is significant and before any radiographic or biochemical evidence of osteodystrophy. Hyperphosphatemia should be controlled by judicious dietary restrictions and the use of phosphate binders, such as calcium carbonate, calcium acetate, or non-calcium binders if there is tendency to hypercalcemia. Acidosis may be controlled with sodium bicarbonate. Calcitriol or alpha-calcidiol is given in doses of 15–50 ng/kg/day (0.01 – 0.05 μg/kg/day) to increase intestinal absorption of Ca and to counteract hyperparathyroidism. As noted above, hypercalcemia can occur rapidly during treatment with active vitamin D metabolites, making clear instructions and close monitoring necessary.

Phosphopenic Rickets

The primary causes of rickets in these conditions are nutritional deficiency, which is limited to specific circumstances such as prolonged parenteral nutrition, feeding of small premature infants, severe malabsorption, or increased renal loss. Serum P is low and, typically, serum Ca is normal and PTH normal or mildly elevated.

Rickets of Prematurity

The fetus acquires 80% of bone minerals during the last trimester. For infants born preterm, it is not possible to provide Ca and P anywhere near the rate of placental transfer through the diet. Small premature babies (particularly babies with a birth weight less than 1000–1500 g) who are fed breast milk or a regular commercial infant formula may therefore develop osteopenia and rickets even if the vitamin D intake is adequate. Preterm babies fed breast milk are at particular risk of rickets because of the low P content of the milk although the Ca content is also too low for adequate mineralization. Biochemical evidence of P depletion (low serum P and low urinary excretion of P, but normal serum Ca and relatively high urinary excretion of Ca) may develop within 2–4 weeks, and rickets within 2–4 months of age. Preterm infants with bronchopulmonary dysplasia are at particular risk. ALP is usually, but not always, markedly elevated, and 1,25-$(OH)_2$D levels are high.

Craniotabes may be obvious, but there are generally few or no physical signs of rickets. Severe osteopenia and typical metaphyseal features of rickets are seen on radiographs, often together with fractures, particularly of the ribs.

Rickets may be prevented by securing a daily intake of 10 μg of vitamin D from the first week of life, and a supplement of 50–60 mg of elemental Ca and 30–40 mg of inorganic phosphorus per kilogram per day to infants with a birth weight below 1500 g, who receive breast milk. For infants on a regular formula, the dose may be somewhat lower. For preterm infants fed breast milk, supplements containing Ca, P, and other nutrients that are insufficient in breast milk, are commercially available. The amount of Ca and P does not prevent some degree of osteopenia, but larger doses may be poorly tolerated and cause malabsorption of other nutrients. However, if biochemical evidence of bone disease (ALP $>$ 1000 U and/or P below 1.7–1.8 mmol/L) or radiographic changes occur, the mineral supplements may be increased. Commercial formulas specially designed for preterm infants have higher contents of Ca and P and do not need to be supplemented.

Hypophosphatemic Rickets due to Renal Loss of Phosphate

Increased renal loss of inorganic phosphate (P) can be caused by a number of complex primary or secondary renal tubular defects, such as the Fanconi syndromes and distal renal tubular acidosis, or by conditions with isolated renal phosphate leak, particularly X-linked, autosomal dominant, and autosomal recessive hypophosphatemic rickets.

In isolated renal phosphate loss, a group of hormones, *phosphatonins*, plays a central role in that they stimulate phosphaturia. The best-described phosphatonin is fibroblast growth factor-23 (**FGF23**). The mechanisms of control of FGF23 and its role in normal P homeostasis are not well understood, but a kidney–intestine–bone hormonal axis controlling P homeostasis and bone mineralization exists. In the inheritable entities with isolated phosphaturia, genetic mutations cause increases in FGF23 and possibly other phosphatonin levels, which inhibit reabsorption of P in the proximal renal tubules. The phosphatonins also lower 1,25-$(OH)_2$D somewhat due to suppression of the 1 alpha-hydroxylase activity in

the renal tubular cells. In these conditions, the serum 1,25-$(OH)_2$D levels are usually still within the normal reference range, but inappropriately low given the low serum P, and PTH is normal or only slightly increased.

Familial Hypophosphatemic Rickets

This group is the most common cause of rickets in populations where nutritional rickets is combated through general prophylactic programs.

X-linked hypophosphatemic rickets (XLH) is the most common entity in this group with a prevalence of approximately 1 in 25,000. A mutation in the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X-chromosome), which is situated on chromosome Xp22.1, results in phosphaturia, at least partially through increased FGF23 levels. *Autosomal dominant hypophosphatemic rickets* and *autosomal recessive hypophosphatemic rickets* are very rare conditions.

In XLH, symptoms usually appear between the end of the first year to 3 years of age and are dominated by slow growth, bowing of the legs, and clinical findings of rickets. The patients may have poor dental development and tooth abscesses, but usually not the enamel defects typical of calciopenic rickets. Muscular hypotonia, bone tenderness, and tetany are not features of this condition. In XLH, the male is generally more severely affected than the heterozygous female who does not even need to show any clinical evidence of disease, but just fasting hypophosphatemia. The clinical expression may, however, be extremely variable. The autosomal and recessive forms usually present later in childhood than XLH or even in adulthood.

In XLH, serum P is always low (usually < 0.9 mmol/L), but serum Ca is normal, and there is no evidence of hyperparathyroidism (normal PTH and no aminoaciduria) or general tubular defects (no glucosuria, proteinuria, bicarbonaturia, or kaliuria). Since reduced tubular reabsorption of P is the primary defect, urinary excretion of P is high despite low serum P.

Treatment

The mainstay of therapy is a combination of active vitamin D metabolites (calcitriol or alpha-calcidiol) and phosphate supplementation. In XLH, a dose of 20–60 ng/kg/day divided in two doses (usual total maintenance dose, 0.5–1.0 μg/day) and phosphate in a dose of 0.5–1.0 g/day elemental phosphorus for young children and 1–4 g/day for older children. Phosphate intake may be limited by diarrhea and needs to be increased gradually, starting with approximately 40 mg elemental phosphorus per kg/day. Because of rapid urinary excretion of P, the phosphate supplement needs to be divided in four to six doses per 24 h. Phosphate may be supplied as Joulie solution or neutral phosphate tablets. The doses of active vitamin D metabolites and phosphate must be adjusted by close monitoring of serum Ca, P, ALP and PTH, and urinary excretion of Ca. Excessive vitamin D metabolites may lead to hypercalcemia, hypercalciuria, and nephrocalcinosis, while excess phosphate may lead to decreased intestinal Ca absorption resulting in secondary hyperparathyroidism and more bone lesions. Urine Ca/creatinine ratio above 0.25 mg/dl or above 0.7 mmol/L in the second morning void, or greater than 4 mg Ca per kilogram per day may cause nephrocalcinosis and progressive deterioration of renal function. Renal ultrasound should be performed regularly to monitor for nephrocalcinosis. The aim of the therapy is healing of rickets, normal linear growth rate, and avoidance of complications.

Low serum P and elevated serum ALP may be detected several months before rickets develops, and with early treatment rickets may be avoided.

Corrective osteotomies should not be attempted until active rickets is healed, judged by radiographs and normal serum ALP and Ca levels. Active vitamin D metabolites should be discontinued 1 week before surgery if surgery requires immobilization because of risk of postoperative hypercalcemia.

Hereditary Hypophosphatemic Rickets with Hypercalciuria

This rare genetic condition is mainly reported from the Middle East. Renal loss of P leads to hypophosphatemia and subsequent elevated serum 1,25-$(OH)_2$D and ALP. High 1,25-$(OH)_2$D levels leads to increased intestinal Ca absorption, hypercalcemia, hypercalciuria (even when the serum Ca is normal), and decreased serum PTH. Most patients present with rickets and short stature. The patients frequently develop renal stones as a result of increased urinary secretions of both Ca and P. Therapy consists of oral phosphate supplementation in frequent doses.

Tumor-Induced Rickets (TIO)

Small tumors of mesenchymal origin may cause hypophosphatemic rickets or osteomalacia through the secretion of phosphatonins from the tumor. Such tumors are mainly seen in adults, but pediatric cases have been

reported. The tumors are very small but may be detected with specific scintigraphic methods. A typical feature is very low serum 1,25-$(OH)_2$D levels. Removal of the tumor will cure the condition.

Other Rare Causes of Isolated Hypophosphatemic Rickets

Renal loss of P may occasionally occur in *polyostotic fibrous dysplasia* (as in McCune-Albright syndrome), neurocutaneous syndromes (e.g., epidermal nevus syndrome and neurofibomatosis) because of increased production of phosphatonin.

Fanconi Syndromes

Hypophosphatemic rickets may accompany multiple defects in the proximal renal tubule. Such defects may be part of the clinical picture of a variety of genetically transmitted inborn errors of metabolism (cystinosis, fructose intolerance, galactosemia, Lowe syndrome, tyrosinemia, and Wilson's disease), and some acquired diseases such as exposure to toxins (cadmium, lead, and mercury). Most commonly, however, it is idiopathic, and occurs sporadically or as a dominant or recessive trait.

Hypophosphatemia and increased urinary loss of P is accompanied by excessive loss of all or some of the following substances: bicarbonate leading to metabolic acidosis, potassium leading to hypokalemia and sodium leading to hyponatremia. Glucosuria, proteinuria, aminoaciduria, and hyposthenuria may be detected.

Clinical expression and age of debut vary according to the primary defect. Idiophatic Fanconi syndrome may present as early as during the first year of life. The idiopathic form is diagnosed by identifying the general tubular defect and by excluding the variety of secondary forms.

The idiopathic form is treated similarly to familial hypophosphatemic rickets. Management of secondary forms depends on the primary disorder.

Renal Tubular Acidosis (RTA)

Osteopenia and rickets may develop in these conditions through two mechanisms: In proximal renal tubular acidosis (RTA), phosphate is lost in the proximal renal tubules due to the tubular defect, and in both proximal and distal RTA, metabolic acidosis causes dissolution of bone to buffer a persistent acidosis.

Administration of bicarbonate to correct metabolic acidosis will stop bone dissolution and the secondary hypercalciuria. In proximal RTA with phosphate loss, oral phosphate and active vitamin D metabolites, similar to what is described for familial hypophosphatemic rickets, are needed in addition to bicarbonate.

Conditions Resembling Rickets

Hypophosphatasia

Hypophosphatasia is an autosomal recessive disorder that may present as a congenital lethal form with extremely poor mineralization, a severe infantile form, and later milder forms where the clinical and radiographic features may be confused with those of rickets. Important diagnostic characteristics are low serum ALP concentrations and large quantities of phosphoethanolamine in the urine.

Hyperphosphatasia

Hyperphosphatasia is an autosomal recessive disorder with elevated serum ALP, but normal serum Ca and P concentrations. Bowing and thickening of the diaphysis, variable bony texture with dense and radiolucent areas, and general demineralization on radiographs are other typical features.

Skeletal Dysplasias

Some of these conditions may be confused with rickets because of bone deformity and occasionally because of metaphyseal changes on radiography (metaphyseal chondrodysplasia). However, serum Ca, P, ALP, PTH, and vitamin D metabolites are normal.

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59 Obesity

Mohammad El Baba

Over the past three decades, the prevalence of obesity and overweight has increased throughout the world in both adults and children. Once considered a problem only in developed countries, overweight and obesity are now dramatically increasing in low- and middle-income countries. Children around the world are becoming more vulnerable to overweight and obesity-related health risks both in the short- and long term.

Definition

Obesity is defined as excessive fat accumulation that presents a risk to health. Body mass index *(BMI)* is widely accepted method to screen for overweight and obesity for children aged 2–19 years. *BMI* is defined as the ratio of an individual's weight to height squared (kilogram/meter^2) or determined from published tables, nomograms, or calculators. *BMI* is often used to assess weight status, because it is relatively easy to measure and correlates with body fat. It is also used to estimate a person's risk of weight-related health problems.

The World Health Organization (WHO) defines "overweight" as a *BMI* equal to or more than 25, and "*obesity*" as a BMI equal to or more than 30. Outside the United States, *The International Obesity Task Force (IOTF)* standards have been widely used to classify overweight and obesity in children. The standards are based on data from six different international countries and provide age and gender-specific cutoff points for BMI for overweight (25 kg/m^2) and obesity (30 kg/m^2) in children 2–18 years of age using dataset-specific centiles linked to adult cutoff points. In general, ***IOTF*** data appears to give lower estimates for the prevalence of obesity, especially in younger children.

In the United States, the percentile distributions relative to gender and age in the *Centers for Disease Control and Prevention (CDC)* 2000 growth charts are now the preferred reference.

BMI-for-age weight status and the corresponding percentiles are divided into four categories:

1. Underweight: Less than the 5th percentile
2. Healthy weight: 5th percentile to less than the 85th percentile
3. Overweight: 85th to less than the 95th percentile
4. Obese: Equal to or greater than the 95th percentile (BMI of >30 kg/m^2)

For children 0–2 years of age, the weight-for-recumbent length percentiles from the CDC 2000 growth charts are appropriate for evaluating weight relative to linear growth. Children with weight-for-length percentiles more than the 95th are considered overweight.

When compared with WHO child growth standards, CDC charts reflect a heavier, and somewhat shorter, sample than the WHO sample. This results in lower rates of under nutrition (except during the first 6 months of life) and higher rates of overweight and obesity when based on the WHO standards.

Alternative Measures of Fatness

Skinfold Thickness

This is a measurement of double layer of skin and subcutaneous fat at certain sites of the body by using special calibers. Sites commonly used are triceps and subscapular areas. Equations can then be used to estimate fat mass from the skinfold measurements. It is considered an attractive tool because measurements are noninvasive, predictive of total body fat, and may be useful in the monitoring of nutritional therapy in children. Limitations for routine clinical use of skinfold thickness measurements include the lack of validated reference data for different population groups and the considerable potential for measurement errors without training and experience.

Waist Circumference

Abdominal obesity is evaluated clinically by measuring the waist circumference or the ratio of waist circumference to the hip circumference. Compared with BMI, waist circumference in children provides a better estimate of visceral fat whereas BMI is better at estimating subcutaneous fat. Research has linked accumulated

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visceral fat to increased risk for cardiovascular disease in adults and an adverse lipid profile and hyperinsulinaemia in children.

Prevalence

Using the IOTF standard definition of pediatric overweight and obesity, the worldwide prevalence of overweight and obesity in children and young people aged 5–17 years is approximately 10%, with that of obesity alone being 2–3%. Certain regions and countries have particularly high rates of pediatric obesity: more than 30% of children and adolescents in the Americas, and approximately 20% of those in Europe, are overweight or obese, with lower prevalence rates being seen in the Asia-Pacific region.

Data from *National Health and Nutrition Examination Surveys (NHANES)* (1976–1980 and 2003–2006) show that the prevalence of obesity in the United States has increased: for children aged 2–5 years, prevalence increased from 5.0% to 12.4%; for those aged 6–11 years, prevalence increased from 6.5% to 17.0%; and for those aged 12–19 years, prevalence increased from 5.0% to 17.6%.

The relationship between socioeconomic status and childhood obesity has been observed. Overweight tends to be more prevalent amongst lower socioeconomic status children in developed countries, while developing countries show obesity to be more prevalent among higher income sectors of the population, and among urban rather than rural populations.

Etiology

Obesity results when body fat accumulates as a result of imbalance between energy intake and expenditure. Etiology is multifactorial and obesity is viewed as a neuroendocrine and metabolic disorder, which results from interaction between environmental, behavioral, and genetic factors. Etiologic classification of obesity is summarized in *Table 59.1*.

Table 59.1
Etiology of obesity in children and adolescents

Acquired Obesity
Environmental and behavioral factors:
Decreased physical activity
Prolonged television viewing
Dietary factors
Social factors:
Socioeconomic status
Ethnicity
Iatrogenic factors:
Medications
Endocrine disorders:
Hypothyroidism
Cushing syndrome
Growth hormone deficiency
Insulinoma
Pseudohypoparathyroidism
Hypothalamic lesions
Genetic obesity:
Single gene disorders
Polygenic obesity
Syndromic obesity
Others:
Parental factors
Intrauterine factors and birth weight
Breast feeding
Viral infection
Sleep deprivation

Decreased Physical Activity

Lack of physical activity is a major factor in increasing the risk of obesity. Studies from United States and Europe have demonstrated a decreasing trend in physical activity among children and adolescents.

Decreased physical activity in children is attributed to several factors. Walking and cycle riding has decreased in frequency, along with increasing use of cars and public transportation. Living in an unsafe neighborhood is another barrier to exercise.

Daily participation in school physical education among adolescents dropped from 42% in 1991 to 28% in 2003. In addition, less than one-third of high school students meet recommended levels of physical activity.

Television Viewing

Television viewing is one of the most studied factors that influence childhood obesity. Prolonged television viewing

may increase the risk by decreasing energy expenditure and increasing food intake. The amount of time spent in watching television was found to be closely associated with increased levels of childhood obesity and that reducing television, computer, and video game use could be an effective intervention to prevent childhood obesity.

Some data have linked television food advertising and childhood obesity and proposed that limiting the exposure of children to marketing of high-caloric food could be part of the efforts to reduce childhood obesity.

Dietary Factors

A recent cross-sectional study demonstrated an association between the patterns of food intake during adolescence and the prevalence of excess central body fat. The intakes of dairy and grains, especially whole grains, as well as total fruits and vegetables were inversely associated with central obesity among adolescents.

Several studies have linked obesity in children to the consumption of large amounts of sweetened drinks and 100% fruit juice.

Evidence is limited on dietary patterns that contribute to excessive energy intake in children and teens. However, large food and beverages portion sizes, eating meals away from home, frequent snacking on energy-dense foods, and consuming beverages with added sugar are often assumed as contributing to excess energy intake of children and teens. Obese children tend to skip breakfast. Several studies suggest that eating breakfast is associated with a reduced risk of becoming overweight and a reduction in the BMI in children and adolescents.

Socioeconomic Status

Overweight tends to be more prevalent among socioeconomically disadvantaged children in developed countries and children of higher socioeconomic status in developing countries. In more recent years, most studies have demonstrated an inverse relationship, and, in contrast to former times, very few positive associations were found. Parental education seems to be the major factor underlying the relationship between low socioeconomic status and elevated childhood obesity rates.

With regards to ethnicity, data from the United States indicate that differences in prevalence of obesity exist among Hispanic (21.8%), African American (21.5%), and white children (12.3%), with rapid increases occurring among African American and Hispanic children.

Iatrogenic

Medications

Obesity can result as a side effect to several medications such as valproate, cyproheptadine, steroids, and progestins. Overeating and weight gain have been observed in children and adolescents receiving Lithium and antipsychotic medications such as olanzapine and clozapine.

Endocrine Disorders

Endocrine disorders comprise less than 1% of children and adolescents with obesity and frequently associated with other symptoms. Most children with endocrine disorders have short stature and delayed puberty. The disorders are usually identified by means of characteristic clinical symptoms and not by laboratory screening.

Hypothyroidism: Common findings in hypothyroid children are short stature, fluid retention, and apparent overweight.

Cushing syndrome: Cushing syndrome in children usually causes short stature and generalized obesity. Central obesity is more common in adults and usually involving face, neck, trunk, and abdomen.

Growth hormone deficiency (GHD): Children with GHD present with growth failure, increased weight/height ratio, and delayed puberty. Obese children without endocrine disorders usually have decreased growth hormone levels and diminished response to pharmacologic stimuli.

Hypothalamic lesions: Hypothalamic insults such as infections, trauma, neoplasm, or surgical resections are usually associated with obesity.

Insulinoma: Extremely rare in children. Obesity is explained by low blood sugar resulting in increase food intake.

Genetic Obesity

Single gene disorders: Single gene mutations leading to obesity in humans are rare and accounts for severe early onset obesity induced by an increased energy intake. Mutations in the genes for leptin, leptin receptor, prohormone convertase 1 (PC1), and pro-opiomelanocortin (POMC) have been shown to lead to autosomal recessive forms of

obesity in humans. Mutations in the melanocortin-4 receptor gene (MC4R) are the most common single gene defects currently identified in populations with severe obesity. It accounts for 2–6% of extreme obesity in children and adolescents.

Polygenic obesity: Whole-genome scan studies have demonstrated the presence of different obesity susceptibility loci in different ethnic groups, which supports the notion that different gene combinations are responsible for the pathogenesis of obesity in different populations. A genome-wide association studies of obesity-related traits showed that a polymorphism of the fat mass- and obesity-associated gene was correlated with childhood and adult obesity in different populations.

Syndromic Obesity

Genetic obesity syndromes arise from genetic or chromosomal defects and involve obesity as part of their presentation.

Prader–Willi syndrome: is the most common syndromic form of obesity. Features of the syndrome include central obesity, neonatal hypotonia, hyperphagia, hypogonadism, short stature, behavioral abnormalities, and mild-to-moderate cognitive impairment. The syndrome is caused by the deficiency of one or more paternally expressed imprinted transcripts within chromosome 15q11–q13.

Bardet–Biedl syndrome: is characterized by early onset truncal obesity associated with rod-cone dystrophy, polydactyly, learning disabilities, and progressive renal disease.

Alstrom syndrome: is characterized by mild truncal obesity, short stature, dilated cardiomyopathy, and type 2 diabetes.

Others

Parental obesity: Parental obesity, especially maternal, is one of the strong risk factors for childhood and adolescent obesity.

Intrauterine factors and birth weight: Small for gestational age babies who are given high-caloric diet are at higher risk for obesity. Maternal smoking during pregnancy is another risk factor for childhood obesity.

Breast feeding: Several studies have demonstrated that breastfeeding is associated with a modest but consistent protective effect against later obesity.

Viral infection: Prevalence studies suggest that humans with antibodies to one strain of adenovirus tend to have higher rates of obesity and lower serum cholesterol and triglycerides.

Sleep: Cross-sectional studies have shown a consistent increased risk of obesity amongst short sleepers in children and adults. The mechanism may include activation of hormonal responses leading to an increase in appetite. Activation of inflammatory pathways by short sleep may also be implicated in the development of obesity.

Comorbid Conditions of Childhood Obesity

Self-esteem: Studies have shown a modest relationship between obesity and low self-esteem in children. The risk is increased in children who were subjects to parental criticism and weight-based teasing from peers. Other potential risk factors include: adolescents appear more at risk than young children; girls are more affected than boys; and children who believe that they were responsible for being overweight than children who attributed their weight to external causes.

Body image: Many studies have linked overweight and body dissatisfaction.

Depression: The relationship between obesity and depression in children and adolescents has not yet been established. However, clinical samples of obese children display higher levels of depression compared to average-weight-controlled children. A recent study has shown an increased risk for depression amongst overweight and underweight girls as well as obese boys.

Social stigma: Overweight and obese children are particularly vulnerable to weight bias from their peers, which can begin as early as age 3. The trend continues and, in some cases, worsens among elementary and middle school children. In several studies, school children tend to associate obese children with negative characteristics such as being lazy, dirty, lying, argues, mean, and stupid. Obese children are also more likely to be victims of bullying by their peers. Obese adolescents are commonly stereotyped as being lazy, eating too much, and unable to participate in sports.

Some studies have even suggested that overweight children may be vulnerable to weight bias at school by teachers and educators. Another surprising and unfortunate source of weight stigma toward obese children is parents.

Endocrine

Insulin resistance: Childhood obesity, specifically truncal obesity, is associated with insulin resistance *(IR)*, which is considered to be an important link between adiposity and

the risk of type 2 diabetes, fatty infiltration of the liver, and cardiovascular disease. IR is defined as a decrease in the ability of insulin to stimulate the utilization of glucose by muscles and adipose tissue and to suppress hepatic glucose production and output. Beside obesity, other factors can influence insulin sensitivity, such as physical activity, ethnicity, and gender.

The standard method for measuring IR is the euglycemic-hyperinsulinemic clamp, but this study is invasive and time-consuming. Simpler methods have been developed to assess IR based on markers derived from an oral glucose tolerance test or fasting insulin level and fasting glucose-to-insulin ratio.

Failure of pancreatic B-cell to maintain normoglycmia will lead to impaired fasting glucose *(IFG),* impaired glucose tolerance *(IGT)*, and eventually to overt type 2 diabetes. Individuals with IFG and/or IGT have been referred to as having prediabetes, indicating the relatively high risk for the development of diabetes. Diabetes mellitus is defined as a fasting glucose greater than or equal to 126; IFG, a fasting glucose 101–125; and IGT, a blood glucose between 140 and 200 mg/dL after an oral glucose challenge.

Metabolic syndrome: Metabolic syndrome refers to a combination of clinical findings and metabolic disorders comprising of abdominal obesity, insulin resistance, hypertension, and dyslipidaemia. Although there is no universally accepted definition of metabolic syndrome in children, modified adult criteria have been used to identify children and adolescents with metabolic syndrome, which include the presence of at least three of the following abnormalities: obesity (usually with a waist circumference higher than the ninetieth percentile), dyslipidemia (increase of triglycerides and decrease of high-density lipoprotein or HDL), hypertension, and abnormal glucose metabolism (elevated fasting glucose or type 2 diabetes).

Hyperandrogenism and *Polycystic Ovarian Syndrome (PCOS)*: Obesity in adolescent girls and women is associated with hyperandrogenism and PCOS. It is believed that visceral obesity and insulin resistance have a role in promoting adrenal hyperandrogenemia as well as a tendency toward glycemic intolerance. PCOS is characterized by menstrual irregularity, acne, hirsutism, and hyperandrogenemia.

Early menarche: Obese girls are observed to experience earlier menarche. A cross-sectional study has linked higher relative weight with early menarche after controlling for age and race.

Delayed maturation in adolescent boys: Overweight boys tend to show delayed onset of sexual maturation.

Pulmonary

Sleep disorder and obstructive sleep apnea: Several studies have shown that obese children are at higher risk for abnormal sleep patterns, decreased oxygen saturation during sleep, hypoventilation, and obstructive sleep apnea.

Obesity hypoventilation syndrome (OHS, Pickwickian syndrome): This syndrome is defined as obesity and alveolar hypoventilation. The classic symptoms consist of severe obesity associated with hypoventilation, somnolence, polycythemia, and right ventricular hypertrophy and failure. Most patients with OHS have obstructive sleep apnea, loud snoring, choking during sleep hypersomnolence, fatigue, and impaired concentration and memory.

Asthma: The relationship between asthma and obesity is controversial. However, several cross-sectional studies have suggested an association between childhood overweight and asthma. A meta-analysis of 12 studies examining the relationship between weight and asthma has shown that both high birth weight and high BMI during childhood were predictive of future asthma.

Obese children may also have more severe asthma symptoms and more medications use than normal-weight children.

Gastroenterological

Liver steatosis (nonalcoholic fatty liver disease NAFLD): This refers to a spectrum ranging from a relatively benign fatty liver infiltration to nonalcoholic steatohepatitis (NASH) that can potentially progress to fibrosis, cirrhosis, and liver failure.

The pathogenesis of NAFLD and its sequelae are incompletely understood but probably involve abdominal obesity with insulin resistance leading to accumulation of fat in hepatocytes and the generation of reactive oxidative species resulting in oxidative hepatocyte damage. NAFLD associates with clinical elements of the metabolic syndrome including insulin resistance, dyslipidemia, and hypertension.

Most children with NAFLD/NASH are asymptomatic. Some patients complain of fatigue, malaise and, vague right upper quadrant abdominal discomfort. Acanthosis nigricans can be found in up to 50% of children with NASH. Elevations of hepatic transaminases are predictors of the presence of NAFLD and NASH although degree of elevation has little predictive value and does not distinguish between steatosis and steatohepatitis. Hepatic ultrasound or magnetic resonance imaging may confirm the presence of fatty liver but they provide little or no information on the presence or degree of fibrosis or cirrhosis.

Liver biopsy is the only reliable means to distinguish between steatosis and steatohepatitis fibrosis or cirrhosis. It is indicated in selected cases with persistent elevation of transaminases to determine the severity of the fatty liver disease and to exclude other causes of liver disease. Weight reduction and regular exercising are the only established treatments for NASH. Efficacy of pharmacologic approaches remains to be proven and include Vitamin E and metformin.

Gallstones: Obesity accounts for the majority of gallstones in children with no underlying medical conditions. One study from Germany confirmed a higher prevalence of gallstones in obese asymptomatic children and adolescent (2%) compared to a prevalence of 0.6% in unselected cohort of children and adolescents.

Gastroesophageal reflux disease (GERD): Morbidly obesity is a risk factor for the development of GERD. Although the exact mechanism linking GERD to high BMI is not known, increased intragastric pressure, incompetence of the lower esophageal sphincter, and frequency of lower esophageal sphincter relaxation may be involved in the pathophysiology of this disease in morbidly obese patients.

Cardiovascular

Hypertension: Obesity is frequently associated with hypertension in both adults and children. In many screening studies, the prevalence of hypertension in children and adolescents has been shown to be as high as 10% among those with BMI $\geq$97th percentile. In addition, overweight adolescents have more than an eightfold increased risk of developing hypertension as adults.

Hyperlipidemia: Increased levels of LDL cholesterol, decreased levels of HDL cholesterol, and raised serum triglyceride levels occur among obese children and adolescents, particularly those with increased triceps skinfold.

Obese children and adolescents are also at higher risk for abnormal vascular wall thickness, endothelial dysfunction, left ventricular hypertrophy, and the development of early aortic and coronary arterial fatty streaks and fibrous plaques. In a recent cohort study, it was demonstrated that children with higher BMI were at increased risk for coronary heart disease in adulthood.

Neurologic

Pseudotumor cerebri: Also known as idiopathic intracranial hypertension *(IIH)* is a condition characterized by increased intracranial pressure in the absence of clinical, laboratory, or radiologic evidence of intracranial pathology. The etiology of IIH is unclear but some studies suggest that obesity, particularly in females, is a risk factor. Pediatric studies have suggested that older children with IIH were more likely to be obese than younger children.

Presenting symptoms are usually headache, vomiting, altered vision, papilledema, and isolated sixth cranial nerve palsy. Young children may present with irritability, listlessness, somnolence, and diplopia. In the setting of obesity, weight loss has been associated with resolution of papilledema and of IIH.

Orthopedic

Slipped capital femoral epiphysis (SCFE): Obesity is a significant risk factor in the development of idiopathic SCFE. Patients commonly present in early adolescence with symptoms of hip or referred knee pain.

Blount disease (Tibia vara): is more common in obese children and is characterized by progressive bowed legs and tibial torsion.

Others: Obese children are more likely to report fractures, musculoskeletal pain, and impaired mobility.

Skin

Obesity is associated with a number of dermatologic diseases including acanthosis nigricans, keratosis pilaris, hyperandrogenism and hirsutism, striae distensae, and with fat redistribution. Acanthosis nigricans is the most common skin manifestation of obesity and appears as symmetric, velvety, hyperpigmented plaques most commonly observed in the axilla, groin, and posterior neck. It is frequently associated with hyperinsulinemia and insulin resistance. Obesity also increases the incidence of cutaneous infections, including candidiasis, furunculosis, and folliculitis.

Prevention and Treatment

Pediatrician and primary care providers should assess obesity risk in all children by integrating information about the patient's BMI, risk factors, and current eating and physical activity behaviors. The likelihood of health risks increases in the overweight category (85th to 94th percentile) and is influenced by parental obesity, current lifestyle habits, as well as BMI trajectory and current cardiovascular risk factors. Those children should receive

prevention counseling, and should receive support in establishing healthy life style.

Obese children (BMI above the 95th percentile) are very likely to have obesity-related health risks, and should be encouraged to focus on weight control practices.

Prevention strategy should be performed at every stage including perinatal period. In a recent systematic review, prenatal insults including maternal smoking, malnutrition, and diabetes were found as particularly important determinants of future obesity risk.

Perinatal measures should include:

1. Careful control of gestational diabetes to avoid large for gestational age infants, which could lead to obesity.
2. Careful control of maternal weight before pregnancy and careful control of maternal weight gain during pregnancy.
3. Discourage smoking as smoking during pregnancy is an important risk factor for childhood obesity at any age.
4. Breast feeding should be encouraged as systematic reviews concluded that breastfeeding has a protective effect against later obesity both in childhood and adulthood, although degree of protection was small in some cases. Longer duration of breast feeding was associated with a reduced risk of obesity during early childhood.
5. Avoid prolonged bottle feeding and avoid early introduction of solid food as both may increase obesity risk.

Dietary Prevention and Treatment Option

Based on evidence-based data and clinical experience, the 2007 Expert Committee recommended that clinicians advise patients and their families to adopt and maintain the following specific eating behaviors:

- Limiting consumption of sugar-sweetened beverages.
- Encouraging consumption of diets with recommended quantities of fruits, vegetables, and dietary fiber.
- Limiting television time to <2 h/day and removing televisions from children's primary sleeping areas. If the child is less than 2 years of age, then no television viewing should be the goal.
- Eating timely regular meals, particularly breakfast, and avoiding snacking throughout the day.
- Limiting eating out at restaurants, particularly fast food restaurants and restaurants that serve large portions of energy-dense foods.
- Encouraging family meals in which parents and children eat together.

In the management of obesity, dietary changes alone are insufficient to have much effect without other long-term lifestyle changes, such as increased physical activity and psychological support. Dietary intervention in combination with exercise programs has been reported to have better success rates than dietary modulation alone.

For the management of mildly to moderately obese child without complications, a weight maintenance regimen is usually preferred. For the very obese child, or the moderately obese child with significant comorbidity, a balanced low-caloric diet is recommended. A more restricted very low calorie diet is only recommended when children suffer severe obesity with complications that justify such treatment. Risks associated with the rapid weight loss include cholelithiasis, hyperuricemia, decreased serum proteins, and diarrhea. Long-term effects of strict dietary control include reduced linear growth and loss of lean body mass.

Exercise

Assessment of physical activity levels should be performed at each well-child visit to determine whether they are meeting recommendations of adequate physical activity per day. Assessment and anticipatory guidance of decreasing time spent in sedentary behaviors such as television-viewing, playing video games, and using the computer should be performed at each well-child visit.

Programs designed to promote exercise should contain activities modified to the specific physical and emotional needs of the child. Parental modeling and supportive help from family and school is crucial to guarantee lasting positive effects of physical activity therapy.

Medications

Pharmacotherapy for childhood obesity should be limited to those with BMI over the 95th percentile, who have failed diet and intensive lifestyle modification, or those who have significant comorbidities of their obesity.

The Food and Drug Administration in the United States has approved two medications for the treatment of adolescent obesity: sibutramine for patients >16 years of age and orlistat for patients >12 years of age.

Sibutramine: a serotonin and norepinephrine reuptake inhibitor thus promotes satiety and decrease hunger.

In a multicenter randomized placebo-controlled trial, a significant decrease in BMI was noted in adolescent patients 12–16 years of age treated with sibutramine. Side effects include tachycardia, hypertension, insomnia, and anxiety.

Orlistat: an intestinal lipase inhibitor acts by blocking absorption of fat from the diet. Side effects include steatorrhea, oily spotting from the rectum, and abdominal cramping.

Metformin: inhibits hepatic gluconeogenesis and enhances insulin sensitivity. It is approved for the treatment of type 2 diabetes mellitus in children 10 years and older. Its long-term effect on weight reduction is still unknown but may be useful for the treatment of obese adolescents who are at risk for type 2 diabetes mellitus or have insulin insensitivity associated with polycystic ovary syndrome.

Bariatric Surgery

Bariatric surgery is becoming more commonly offered to severely obese adolescents. Most centers recommend strict selection criteria that include: BMI more than 50 or more than 40 with medical condition; physical, emotional, and cognitive maturity; insufficient weight loss from at least a 6 month effort in a formal program of lifestyle modification.

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Infectious Diseases

Richard J. Whitley

60 Animal and Human Bites

Richard J. Whitley

Introduction

Animal and human bites are among the most common causes for evaluation in physicians' offices and emergency departments, particularly during summer months. While dog bites are the most common, accounting for approximately 80% of all such visits, cat bites are associated with the highest rate of common infections, namely 50%. Certain bites (rabid animals) and at-risk populations warrant special consideration.

Etiology

Dog, cat, or mammal bites are most frequently associated with infection caused by *Pasteurella multocida* (as well as other species), *Staphylococcus aureus*, streptococci, anaerobes, and, less frequently, *Capnocytophagia* species, *Moraxella* species, *Corynebacterium* species, and *Neisseria* species. Rodent bites can be a source of *Streptobacillus moniliformis, Streptobacillus minus*, the cause of rat-bite fever. Reptile bites are usually attributed to gram-negative enteric bacteria or anaerobes. Lastly, human bites are usually associated with *S. aureus*, *Haemophilus* species, *Eikenella corrodens*, and anaerobes. Human bites should also raise concern for the possibility of transmission of hepatitis B virus and human immunodeficiency virus. Wild animal bites, including foxes, skunks, raccoons, bats, or unprovoked bites by ill-appearing dogs, should raise the concern for the possibility of rabies.

Management of Human and Animal Bite Wounds

The first and most important intervention is to vigorously clean and irrigate the wound bite with the exception of puncture wounds. For fresh wounds, a culture is not required. However, for wounds greater than 8–12 h in duration that have evidence of infection (see below), cultures should be obtained. Radiographs are appropriate if there are penetrating wounds of joints or underlying bones. For bites that are infected, a decision regarding debridement should be made. Wound closure is only appropriate for selected fresh and non-puncture bite wounds. Assessment must include evaluation for tetanus immunization, risk of rabies, risk of hepatitis B virus from human bites, and human immunodeficiency virus. Antimicrobial therapy should be initiated for moderate or severe bite wounds, facial bites, wounds in immunocompromised and asplenic individuals, as well as bites with obvious signs of infection. Follow-up should be within approximately 48 h. For individuals known to be hepatitis B virus and human immunodeficiency virus infected, standard prophylactic precautions should be instituted. For individuals who are bitten by wild animals (raccoon, foxes, bats), as well as unprovoked bites from ill-appearing domestic animals, they should receive rabies immune-prophylaxis in consultation with local infectious diseases specialists. In the developed world, most domestic animals are immunized against rabies and, therefore, concern for acquisition from cats and dogs is minimal.

Clinical Findings

Clinical findings usually involve localized rubror and edema at the site of the bite. There may be evidence of lymphadenitis or lymphangetic spread. Pain can be significant. Usually, localized warmth is present at the site of infection.

Treatment

First-line oral therapy consists of amoxicillin-clavulanate. Alternative oral antibiotics would include a regimen of extended spectrum cephalosporin or trimethoprin-sulfamethoxazole plus clindamycin. If intravenous therapy is required, the treatment of choice would include

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ampicillin sulbactam or, with reptile bites, ampicillin sulbactam plus gentamicin. For individuals who are allergic to penicillin, the primary regimen should include trimethoprim and sulfamethazole plus clindamycin or, alternatively, gentamicin.

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61 Bacterial Sepsis and Shock

Jeffrey Alten · Priya Prabhakaran

Introduction

Severe sepsis and septic shock caused by bacterial infections are important causes of mortality and morbidity among children worldwide. Severe sepsis has a mortality of about 4.2% (2.3% in previously healthy children and 7.8% in chronically ill children). The incidence is greatest in children less than 1 year of age and contributes to 50% of the mortality in this age group. Survival from severe sepsis has improved from earlier years, attributable to the discovery that early recognition, aggressive resuscitation, and timely treatment improve outcomes in infants and children with severe sepsis.

Microbiology of Sepsis in Children

The epidemiology of sepsis varies depending on the age of the child, immunization status, integrity of the immune system, and presence of comorbidities. The etiologies of invasive childhood bacterial infections have been significantly modified by widespread immunization against Hemophilus influenza type B (Hib), as well as pneumococcal serotypes. It is convenient to classify the most common bacterial infections based on age of the child. The organisms that should be considered in the septic neonate include Group B Streptococcus, Listeria monocytogenes, and Gram-negative enteric bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, Enterobacter species, and *Pseudomonas aeruginosa*. Staphylococci, particularly coagulase negative species, are becoming an important cause of sepsis in hospitalized neonates. Of note, herpes simplex virus can cause septic shock often indistinguishable from bacterial septic shock. It is not uncommon for neonates with severe herpes infections to have a concomitant bacteremia due to Gram-negative organisms, presumably caused by bacterial translocation from the intestines. In a recent large international severe sepsis therapy trial, *Staphylococcus* species were the most common cause of sepsis in children. In children under 1 year of age, community-acquired organisms such as *Pneumococcus* and *Neisseria meningitides* are frequent causes of sepsis. In the developing world, these two organisms, in addition to Salmonella species and Hemophilus influenza type B, are the most frequent causes of sepsis in infants. The most frequent pathogens remain the same in healthy school-aged children. In addition, sepsis without a clearly defined focus of infection such as meningococcemia becomes more common in this age group. Disseminated staphylococcal and streptococcal infections, often associated with a source in bone, joint, lung, or heart is a frequent cause of sepsis in children over 6 years of age. The incidence of methicillin resistance among *Staphylococcus* species has increased dramatically in developed countries.

Children with preexisting morbidities, such as congenital heart disease, genitourinary abnormalities, cancer, burns, sickle cell disease, severe malnutrition, and immune deficiencies, are at an increased risk of developing severe sepsis. In addition, neonates and other children that are hospitalized or who have had significant exposure to health care facilities are at increased risk of developing sepsis; importantly with infections caused by atypical organisms which may be resistant to the usual, first-line antibiotic therapy. Multidrug-resistant Gram-negative organisms have become increasingly prevalent among hospitalized children, especially in developing countries, and should influence the choice of initial antibiotic therapy. Knowledge of specific bacterial infections associated with underlying dysfunction in specific components of the immune system is essential. ❯ *Table 61.1* shows the common bacterial infections that are associated with specific pediatric conditions.

Definition of Sepsis and Septic Shock

The clinical spectrum of bacterial sepsis ranges from the early signs of bacterial invasion or toxin release in the body (such as tachycardia and fever) to circulatory collapse, multiple organ system failure, and death. To further classify this spectrum, consensus definitions for pediatric sepsis were developed by pediatric experts to help determine the severity of a child's illness and follow response to treatment. Each category represents an increase in severity of illness.

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Table 61.1
Specific organisms associated with sepsis in pediatric patients with comorbidities

Condition	Organism
Sickle cell disease (asplenia)	*Pneumococcus*, *Salmonella*
Asplenia, polysplenia	*Pneumococcus*, *Salmonella*
Nephrotic syndrome (complement deficiency)	*Pneumococcus*
Complement deficiency (C6-9)	*Neisseria* species (meningococcus, gonococcus)
Neutropenia	*Streptococcus mitis*, *Streptococcus* viridans, Gram-negative
AIDS	Pneumococcus
Burns	*Pseudomonas*

Systemic inflammatory response syndrome (*SIRS*): An inflammatory state affecting the entire body that represents the body's immune response to an insult that may or may not be infection. The presence of two or more of the following criteria (one of which must be abnormal leukocyte count or temperature) identify patients with SIRS:

1. Core temperature (rectal, oral, bladder, esophageal) $> 38.5°C$ of $< 36°C$
2. Tachycardia > 2 standard deviations above a child's normal-for-age heart rate, or for children < 1 year, bradycardia $<$ 10th percentile
3. Respiratory rate > 2 standard deviations above child's normal for age
4. Leukocyte count either high or low for age or leukocyte differential with greater than $> 10\%$ immature neutrophil forms

Sepsis: Systemic inflammatory response syndrome (SIRS) due to suspected or proven infection.

Severe sepsis: Sepsis associated with either cardiovascular organ dysfunction, acute respiratory distress syndrome, or with any two or more other organ dysfunctions. The consensus definitions for organ dysfunction are the following:

1. *Cardiovascular*: Hypotension or need for vasoactive medicine to keep BP in the normal range, or two or more of the following: unexplained metabolic or lactic acidosis, oliguria, capillary refill > 5 s
2. *Respiratory*: PaO_2/FiO_2 ratio < 300 or $PaCO_2 > 65$ Torr or > 0.5 FiO_2 to maintain saturations $> 92\%$ or need for mechanical ventilation
3. *Neurologic*: Glasgow Coma Score ≤ 11 or acute deterioration in mental status
4. *Hematologic*: Platelet count $< 80{,}000/mm^3$ or 50% decrease in platelet count or INR > 2
5. *Renal*: Serum creatinine ≥ 2 times upper limit for normal or twofold increase in baseline creatinine
6. *Hepatic*: Total bilirubin ≥ 4 mg/dL (not applicable for newborn) or ALT > 2 times upper limit for age

Septic Shock: Sepsis with cardiovascular dysfunction despite administration of ≥ 40 mL/kg isotonic fluid over 1 h.

While these categorical definitions do not exactly define prognosis, morbidity and mortality likely increases along the continuum of SIRS to septic shock. Increasing number of organ dysfunction in children with severe sepsis increases the likelihood of mortality.

Pathophysiology of Shock

Shock can be defined as a condition of insufficient delivery of oxygen and nutrients to meet the metabolic demands of the body. Oxygen delivery (DO_2) is directly proportional to cardiac output and the oxygen content in arterial blood (CaO_2). Cardiac output depends on heart rate (HR) and stroke volume. Stroke volume is a function of preload, myocardial contractility, and afterload.

$$DO_2 = CO \times CaO_2$$
$$CO = HR \times SV$$
$$CaO_2 = (Hb \times 1.34 \times SaO_2) + (0.003 \times PaO_2)$$

Oxygen delivery is an estimate of global oxygen availability, and may not be reflective of regional hypoperfusion and or ischemia. Severe sepsis induces a state of very high metabolic and oxygen demand. Inadequate DO_2 evokes compensatory mechanisms in an attempt to restore the balance between oxygen demand and delivery. In the early stages of shock, abnormalities in oxygen transport balance are compensated via tachycardia and systemic vasoconstriction to improve organ perfusion and oxygen delivery. The ability of children to vasoconstrict causes systemic blood pressure to be preserved until later stages of shock when frank decompensation may occur. Children who have compensated shock frequently have normal or even elevated blood pressure, and as the shock state progresses, compensatory mechanisms are overwhelmed leading to hypotension and organ dysfunction. Irreversible shock follows when cellular dysfunction is so severe that death occurs even if

cardiovascular function is restored to an adequate level. In order to achieve the best possible outcomes, shock should be diagnosed early and treated aggressively, before decompensation occurs.

Early Recognition of Septic Shock

History

A history focused on the child's activity level, intake and output, presence of fever, skin color or temperature, abnormal breathing, or rash is invaluable in making the diagnosis promptly, and may also aid in localizing the site of infection. History of risk factors for severe infection should be obtained, including immunization status, recent exposure to infectious illnesses, medication history (particularly recent use of systemic steroids), and presence of chronic illness.

Clinical Findings and Physical Exam

Rapid and repeated careful physical examination is essential to diagnose early shock and help localize the most likely source of the precipitating infection. Early recognition of shock requires a high index of suspicion, as only subtle changes in vital signs (i.e., mild tachycardia, mild tachypnea, or slight delayed capillary refill) may be the first signs of developing septic shock. In some forms of severe sepsis and septic shock, children present with "warm shock." Patients in warm shock have decreased systemic vascular resistance (SVR) with relative hypovolemia from vasodilatation and venous pooling of blood. There is low diastolic blood pressure, and wide pulse pressure with resultant clinical findings of "bounding pulses and warm extremities." Despite the potential reassurance of "adequate pulses," the oxygen delivery in these patients is not adequate, thus they are in shock. Children (especially infants and neonates) will more commonly present with "cold shock." These patients have elevated SVR, with a narrow pulse pressure, cool mottled extremities, and reduced peripheral pulses. There will often be tachypnea as a compensation for metabolic acidosis, which may develop into increased work of breathing if ARDS develops or there is underlying pulmonary disease. The child will frequently have fever and a "toxic" or ill appearance. Of note, neonates and young infants may have septic shock without fever. As shock evolves, there will start to be clinical evidence of compromised organ function with worsening tachycardia, tachypnea, decreased urine output, and altered mental status. Decrease in systolic blood pressure is a late finding in septic shock, and represents decompensated stage of shock, which can rapidly be fatal. As the child progresses to irreversible shock, severe hypotension, lethargy, and respiratory failure are late and ominous findings.

Diagnostic Testing

Cultures should be obtained from all pertinent sites (CSF, blood, urine, genitourinary tract, skin lesions), if possible before initiation of antibiotics. Antibiotic therapy should not be delayed while waiting to obtain cultures, though. There are no specific laboratory tests to diagnose shock. Leukocyte count obtained on complete blood count may help support the diagnosis; while platelet count, liver function tests, coagulation studies, arterial blood gases, serum lactic acid, and serum creatinine will all help determine the degree of organ dysfunction. Serial blood gases and/or lactate levels may be useful in assessing the response to treatment. Bedside glucose measurement should be performed in all infants and neonates with septic shock, as their limited glycogen stores put them at risk for severe hypoglycemia. Ionized calcium should also be measured in all infants and neonates as it is often low in septic shock which may decrease myocardial contractility. Chest x-ray should be performed to evaluate for pulmonary disease. Echocardiography to assess cardiac function should be performed, especially in children with evidence of compromised cardiac output in cold shock states.

Management of Septic Shock

Successful management and treatment of septic shock requires timely treatment of underlying cause and immediate reversal and stabilization of the hemodynamic derangements to optimize perfusion to compromised vital organs and limit the cellular damage before it becomes irreversible.

Antibiotics

Once the diagnosis of septic shock has been made, appropriate antibiotic therapy must be administered immediately, as ineffective or delayed antibiotic therapy is associated with increased mortality from septic shock. Antibiotics should not be delayed because of inability to obtain cultures. Broad-spectrum empiric antibiotics must

be chosen based on the most likely organism implicated. This will depend upon the age of the child (see ❯ Microbiology of Sepsis in Children above), location of infection, and the severity of illness. Knowledge of local sensitivity patterns is also very important in choosing antibiotics that are likely to be effective. In addition to initial broad-spectrum antibiotics to cover all of the most likely pathogens, some special considerations include: empiric treatment for MRSA should be considered in all children; Gram-negative and anaerobic coverage should be added for children with potential GI or GU source; immunocompromised, malnourished, and hospitalized children should receive initial empiric treatment with anti-pseudomonal antibiotics; and neonates should receive treatment for Listeria monocytogenes and herpes simplex virus. The antibiotic coverage should be tailored to the results of initial and repeat cultures as well as poor clinical response to initial empiric coverage.

Initial Treatment of Shock

The principle of treating shock is to reduce the imbalance between the oxygen demands of the tissues and oxygen delivery. While most therapy in early shock is directed toward increasing oxygen delivery, measures to curtail oxygen requirement are equally important and become more so as the shock state progresses. Fever, pain, and agitation all increase the metabolic rate and oxygen demand significantly. Children in shock frequently have increased oxygen demand by the muscles of respiration as they attempt to hyperventilate to compensate for metabolic acidosis. Aggressive control of fever, management of pain and sedation, and consideration of early intubation and mechanical ventilation to reduce oxygen demand of work of breathing, even in the absence of respiratory failure, are all very effective methods of decreasing oxygen requirements.

Airway and Breathing

As with all critically ill children, the first step of management is to support the airway and ensure adequate oxygenation and ventilation. Most children with septic shock will be tachypneic as compensation for their underlying metabolic acidosis, and should be given oxygen via face mask to help improve oxygen delivery to tissues. Children with septic shock can have as much as 40% of their cardiac output shunted to their respiratory muscles to support increased work of breathing. Mechanical ventilation can eliminate the excessive oxygen demand and help restore the balance between oxygen delivery and consumption by shunting cardiac output from the respiratory muscles to other vital organs. In addition, mechanical ventilation can help facilitate the use of sedation and improve fever control, which will also decrease the patient's oxygen demand and consumption. In the later stages of shock, there may be more recognized clinical indications for mechanical ventilation such as respiratory failure – in the presence of inadequate ventilation and/or oxygenation, obstructed airway, excessive work of breathing, or altered mental status, endotracheal intubation and mechanical ventilation should be instituted.

Caution should be exercised when performing endotracheal intubation in children with septic shock, as they are at risk for developing a sudden decrease in cardiac output from acute drop in preload. This may occur due to positive intrathoracic pressure caused by mechanical ventilation, inhibiting blood return back to the heart. Hypotension in this situation should be treated by aggressive fluid resuscitation (see below). The decrease in CO may also be due to the vasodilating properties of the medicines used to intubate the child with – which neutralize the compensatory endogenous vasoconstriction that is occurring in the child with septic shock. Medicines such as benzodiazepines, propofol, barbiturates, and opiates should be used with extreme caution for this reason. Some have suggested ketamine as the premedication of choice to facilitate mechanical ventilation due to its ability to release endogenous catecholamines with resultant increase in SVR and relative preservation of cardiovascular stability. Despites its ability to preserve hemodynamics, etomidate should not be used in children with septic shock because it suppresses the child's adrenal axis.

Fluid Resuscitation

Management of decreased oxygen delivery in shock begins with rapid intravenous administration of isotonic fluids. Vascular access should be established quickly, and placement of intraosseous catheter should be performed if IV access cannot be obtained within minutes. Children in septic shock have relative (due to vasodilation and capillary leak) and/or absolute hypovolemia. Early restoration of effective circulating volume is associated with improved outcomes. A 20 mL/kg bolus of isotonic fluid such as 0.9% normal saline or Lactated Ringer's should be given as rapidly as possible (over 5 min) for initial resuscitation.

Reassessment of the child's end-organ perfusion and vital signs should be performed after this and any repeat fluid bolus to determine if the child needs continued fluid resuscitation. The following are physiologic goals that should guide the fluid resuscitation: normalization of heart rate and blood pressure, improvement in capillary refill and perfusion to the extremities, normal mental status, and urine output $>$ 1 mL/kg/h. Repeated 20 mL/kg isotonic fluid boluses should be given until these physiologic goals are met. Patients with severe septic shock will often require 60–80 mL/kg or more of isotonic fluid in the first hour of resuscitation. Ongoing capillary leak must be monitored and adequate volume should be administered to prevent further hypovolemia. Hypocalcemia and hypoglycemia should be evaluated for and corrected during the fluid resuscitation. A urinary catheter should be placed to accurately follow urine output continuously. Central venous access should be established in children who respond poorly to the first 3–4 boluses, and those with insufficient physiologic physiologic reserves at baseline. Central venous pressure (CVP) monitoring may be a helpful adjunct for monitoring. The development of hepatomegaly, gallop rhythm or new crackles on auscultation, in addition to a marked increase in CVP without concomitant improvement in hemodynamics are signs of possible fluid overload denoting that more fluid is unlikely to be beneficial. Children in septic shock frequently become progressively more edematous with ongoing resuscitation due to continuing capillary leak. The development of edema or anasarca should not deter continuing fluid administration, if it is indicated for restoration of hemodynamics and improvement in oxygen delivery. Serial physical examinations are crucial, and resuscitation should be modified based on the evolving clinical scenario.

The use of colloid for fluid resuscitation in children with septic shock is controversial. A large randomized controlled trial of crystalloids versus colloids (4% albumin) for resuscitation of shock in adults showed that these were equivalent. In a subgroup analysis, patients with severe sepsis had a trend toward improved mortality when resuscitated with 4% albumin as opposed to normal saline. In children, a randomized controlled trial in children with dengue shock demonstrated earlier reversal of shock in patients who received 5% albumin, and a clinical practice paper on meningococcal septic shock in children used 5% albumin for resuscitation with mortality lower (5%) than predicted. Crystalloids are less expensive and more readily available than albumin and should be used for initial resuscitation. Until there is more evidence on the safety and efficacy of albumin resuscitation in children with septic shock, it should be reserved for consideration in children that have already received over 60 mL/kg fluid resuscitation with isotonic crystalloid.

Due to its crucial role in oxygen delivery, packed red blood cell transfusion should be given to keep the hemoglobin above 10 g/dL, and can be used as colloid during fluid resuscitation. This hemoglobin goal is part of an algorithm that has demonstrated decreased mortality in adult septic patients, and has been adopted as a pediatric goal in septic shock by expert consensus.

Vasoactive Medications

Children who remain in shock despite 60 mL/kg of fluid resuscitation (fluid-refractory shock) should be started on vasoactive infusions preferably via a central venous line. Children with fluid-refractory shock should be treated in a pediatric intensive care unit with invasive monitoring devices such as central venous and arterial lines.

Low dose dopamine may be started in a peripheral IV while central venous access is obtained. Dopamine is the first-line vasoactive drug of choice in pediatric septic shock not responsive to fluid resuscitation alone. It may be started at 5 μg/kg/min and rapidly titrated up to 10 μg/kg/min for goals of improved perfusion and blood pressure. If physiologic hemodynamic goals are not met with dopamine and fluid alone (fluid-refractory, dopamine-resistant shock), epinephrine (titrated between 0.02 and 0.3 μg/kg/min) is indicated for children who are hypotensive and in "cold shock." Vasoconstrictors such as norepinephrine (titrated between 0.02 and 0.3 μg/kg/min) are the treatment of choice in children who are vasodilated and in warm shock. For children with warm shock and lowblood pressure resistant to norepinephrine, the addition of vasopressin has been used with some success.

Fluid resuscitation should continue while titrating up on vasoactive medications unless hepatomegaly or pulmonary edema develops. In addition to the physiologic goals mentioned above, titration of vasoactive medicines can also be guided by serial serum lactate levels and superior vena cava saturations, with goal $\geq$ 70%. In children with femoral venous access, the trend in inferior vena cava saturations can be used to assess the adequacy of resuscitation. For children with normal blood pressure and cold shock, afterload reduction may be an important adjunct as these patients often have some level of myocardial dysfunction contributing to their shock; type III

phosphodieterase inhibitors (Milrinone 0.5 mcg/kg/min) or vasodilators such as sodium nitroprusside and nitroglycerin may be beneficial.

Hormonal Therapy

Children with septic shock are at risk for adrenal insufficiency. The exact role of steroid replacement therapy, its safety, and the identification of pediatric septic patients that will benefit from steroid therapy is not well defined. At this point, there is no high-level evidence to support the use of steroids in children who are not at risk for adrenal insufficiency. The consensus of experts recommend patients with septic shock at risk for adrenal insufficiency (recent systemic steroid exposure, purpura fulminans, congenital adrenal hyperplasia, or history of hypothalamic/pituitary insufficiency) or patients that have catecholamine resistant shock should receive hydrocortisone therapy after a random serum cortisol is drawn, if possible. There has not been consensus on the exact dose of shock or stress dose steroids. The dose range has been reported from 2 mg/kg/day to 100 mg/kg/day. The common practice at our institution is to send a random serum cortisol, followed by 100 mg/m^2 dose of hydrocortisone IV and treatment with 100 mg/m^2/day to be continued until the child's shock resolves if there is evidence of adrenal insufficiency (defined as dramatic hemodynamic improvement with steroid therapy or random cortisol less than 18 mg/μL). Steroids are stopped if there is no evidence of adrenal insufficiency or clinical improvement in the child's hemodynamics after the initial hydrocortisone bolus.

Children with septic shock are at risk for hypocalcemia which may contribute to myocardial dysfunction. Serial serum–ionized calcium should be monitored and corrected to the normal value. Due to the risk of neurologic injury and myocardial dysfunction, hypoglycemia must be avoided. Neonates and infants are especially at risk due to their poor glycogen stores. Children in septic shock should receive continuous infusion of 10% dextrose in their intravenous fluids. Hyperglycemia may be a risk factor for mortality in children with septic shock. Some clinicians advocate treatment with insulin infusions to keep glucose in the normal range, although the validity of this therapy is still under investigation.

Refractory Shock

Patients with refractory shock despite all the above measures should have all reversible causes of refractory shock ruled out (pericardial tamopnade, tension pneumothorax, intrabdominal hypertension, adrenal insufficiency, and hypothyroidism) and then referred to a center capable of providing pediatric ECMO support.

Summary

Bacterial sepsis continues to be a major source of morbidity and mortality in children worldwide. Early recognition (fever, tachycardia, tachypnea, abnormal white blood cell count, and presence of organ dysfunction) and immediate aggressive treatment has been shown to improve outcomes in pediatric patients with bacterial sepsis. Within the first hour of treatment, in addition to the standard ABCs of resuscitation, the child should receive up to 60 mL/kg fluid boluses and dopamine initiation if still in shock after 60 mL/kg of fluid. Blood, urine, respiratory, and other indicated cultures should be sent, and appropriate broad-spectrum antibiotics should also be initiated within the first hour. Fever control and consideration of early intubation and mechanical ventilation to significantly decrease the body's oxygen demand should be given to any child in septic shock. Escalation and direction of further fluid and vasoactive medicine resuscitation is determined by repeated examination and clinical response to the first hour of therapy.

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62 Bone and Joint Infections

Mohammad Al-Shaalan

Skeletal infections are not uncommon in children. They form a group of infections which involve bones and joints. Being deep, their presentations and diagnosis may be difficult. Therefore a high index of suspicion is always needed in their identification.

Osteomyelitis

Osteomyelitis means inflammation of the bone, which is most of the time caused by a microbial infection. Most of the cases occur in children and elderly. Approximately 1 in 5,000 children is affected.

Etiology

The causes of osteomyelitis vary according to age. However, *Staphylococcus aureus* predominates in all age groups. Other causes include *Streptococcus pyogenes*, *Streptococcus pneumonia*, *Kingella kingae*, and rarely gram-negative bacilli. Vaccination against *Haemophilus influenza* type b has eliminated this organism as a cause in children below 3 years of age. It is likely that conjugate pneumococcal vaccine will reduce the impact of pneumococcus as well. *K. kingae* has been reported to cause small outbreaks in childcare centers. Community acquired methicillin-resistant S*taphylococcus aureus* has emerged as an important cause of osteomyelitis constituting up to 10% of staphylococcal cause. Therefore this should be considered when empiric therapy is started bending the culture results (*Tables 62.1–62.3*).

Some underlying diseases may predispose the host to osteomyelitis that is caused by certain organisms like *Salmonella* in patients with sickle cell anemia, *Streptococcus pneumoniae* in asplenic patients, and *Serratia* or *Aspergillus* in patients with chronic granulomatous disease.

Pathogenesis

The organisms get access to the bone through one of the following routes: (1) hematogenous spread, (2) direct inoculation, (3) spread from infected contiguous site. In children, most of the infections occur by hematogenous route. Thirty to 40% of infected patients report a history of preceding trauma. Recent study implicated trauma as one of the predisposing factor for osteomyelitis as it may cause some contusion in the bone, which acts as a nidus for infection.

Metaphyses of long bones are involved in most of the cases. The blood vessels at the metaphysis are tortuous and the circulation is sluggish. Therefore, the organism has a chance to proliferate in that area and form a nidus of infection.

In infants up to 18 months of age, there are transphyseal vessels through which the infecting organism may get access to epiphysis causing inflammation there and pyogenic arthritis. In addition, the cortex of the infant bone is thin and thus it is easy for the infected material to escape through the cortex into the subperiosteal space and the surrounding softer tissues. In joints where the joint capsule is inserted, distal to metaphyseal plate as in hip, ankle, elbow, and shoulder, the pus may track through the cortex into the joint space. After infancy, transphyseal vessels are obliterated and thus the growth plate acts as a barrier to dissemination of the infection. However, the periosteum is loosely attached to the cortex and the pus may break through the cortex, resulting in subperiosteal abscess with periosteal reaction and bone formation.

Once the child reaches the adolescent age, the periosteum is attached firmly to the cortex and the infected material may erode through the periosteom to form a chronic sinus. It may as well spread through the Haversian Canals to the other nearby bony structure.

Clinical Features

Acute Hematogenous Osteomyelitis

Acute hematogenous osteomyelitis (AHO) is defined as a clinical episode in which a patient had at least one or more of the following: fever higher than 37.5°C, leucocytosis (white blood cell count (WBC) >13,000/mm^3), raised erythrocyte sedimentation rate (ESR) (>20 mm), or

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a positive blood culture plus one or more of the following: positive technetium bone scan, bony point tenderness and/or swelling, and redness or findings consistent with osteomyelitis on plain x-ray, CT scan or MRI or a positive microbiological culture from a bone biopsy or bone aspirate. Patients with AHO with septic arthritis (SA) of the adjacent joint were considered to have AHO. Presentation varies according to age. In newborn, systemic signs are minimal. The baby usually has pseudoparesis, erythema, soft tissue swelling, abscess or joint swelling, and erythema. Thirty to 40% of newborn with osteomyelitis have multiple bony involvement. In infants and children, the systemic signs are prominent with fever, poor appetite, pain at the site of infection, and severe tenderness over the area involved.

Table 62.1
Organisms causing osteomyelitis in children

Age group	Main causes
Neonates	*Staphylococcus aureus*
	Group B Streptococcus
	Group A Streptococcus
	Enterobacteria
	Streptococcus pneumonia
	Candida
Infants and children <5 years	*Staphylococcus aureus*
	Haemophilus influenzae
	Streptococcus pneumoniae
	Group A Streptococcus
	Brucella
Children >5 years	*Staphylococcus aureus*
	Streptococcus pneumoniae
	Group A Streptococcus

Subacute Osteomyelitis

Some patients may have an insidious onset with low-grade fever and minimal local signs extending more than 2 weeks.

Chronic Osteomyelitis

Patients with chronic osteomyelitis present with signs and symptoms of chronic illness like loss of appetite, loss of weight, anemia, and generalized weakness. Locally, there could be disuse atrophy and draining sinuses.

Special Presentations of Osteomyelitis

Osteochondritis

Osteochondritis occurs following injuries with nail or sharp objects that penetrate through sneaker. The floor of the sneaker is usually colonized with *Pseudomonas*. Thus the penetrating nail becomes contaminated with

Table 62.2
Causative organisms according to age

Organism	0–4 years (n = 28)	5–9 years (n = 18)	10–14 years (n = 16)	Total (n = 62)
Staphylococcus sp.	14 (50%)	11 (61%)	14 (88%)	39 (63%)
Staphylococcus aureus	8 (28%)	9 (50%)	14 (88%)	31 (50%)
Coagulase-negative	6 (21%)	2 (11%)	14 (88%)	8 (13%)
Staphylococcus sp.	8 (29%)	4 (22%)	2 (12%)	14 (23%)
Streptococcus pyogenes	3 (11%)	4 (22%)	2 (12%)	9 (15%)
P. pneumoniae	3 (11%)	0	0	3 (5%)
Streptococcus agalacticae	2 (7%)	0	0	2 (3%)
Haemophilus influenzae	4 (14%)	0	0	4 (6%)
Others	2 (7%)	3 (16%)	0	5 (8%)

Source: Bonhoeffer J et al (2001) Diagnosis of acute haematogenous osteomyelitis and septic arthritis: 20 years experience at the University Children's Hospital Basel. Swiss Med Wkly 131:575–581

Table 62.3
Acute haematogenous osteomyelitis: comparison of isolated organisms

Isolated organism	Current study no. (%)	Nade study no. (%)
Staphylococcus aureus	34 (76%)	42 (75%)
Methicillin-resistant *Staphylococcus aureus*	4 (9%)	0
Streptococcus pneumoniae	2 (4%)	3 (5%)
Streptococcus pyogenes	2 (4%)	6 (11%)
Group B *Streptococcus*	2 (4%)	0
Yersinia entercolitica	1 (2%)	0
Haemophilus influenzae	0	2 (4%)
Staphylococcus haemolyticus	0	1 (2%)
Escherichia coli	0	1 (2%)
Bacillus proteus	0	1 (2%)

Source: Goergens E et al (2005) Acute osteomyelitis and septic arthritis in children. J Paediatr Child Health 41:59–62; Nade S et al (1974) Antibiotics in the treatment of acute osteomyelitis and acute septic arthritis in children. Med J Aust 2:703–705

Pseudomonas, which results in implanting it into the foot causing localized infection, which is called osteochondritis. Unlike other forms of osteomyelitis, osteochondritis does not cause major damage to the bone and therefore it needs only a short course of antibiotic therapy directed against *Pseudomonas* usually for 7–10 days in addition to local debridement.

Vertebral Osteomyelitis

In children, vertebral osteomyelitis occurs secondary to hematogenous spread. In rare occasions, spread from contagious pyelonephritis may be the source. In drug addicts, gram-negative bacillary vertebral osteomyelitis may occur. Lumbar area is the most commonly involved part of spine. Affected children usually present with high fever, back pain, and local tenderness over the involved vertebra. Young infants usually present with fever, refusal to walk, or abdominal pain. Plain bone radiography findings may be subtle; however, most of the affected children will have destruction of the anterior part of the involved vertebra with new bone deposition and osteophyte formation. This is in contrast to tuberculous spondylitis in which new bone formation and osteosclerosis does not occur.

Diskitis

Intervertebral disks continue to have blood supply from the nearby vertebra up to 30 years of age. Therefore hematogenous infection of the intervertebral disk can occur. Infection usually starts with disk destruction followed by loss of intervertebral space. Later on, infection extends into the anterior part of the vertebra endplate cartilage. Wedging of the vertebra and paraspinous abscess are rare.

On isotope scanning, there is increased uptake at the site of infection. MRI is very sensitive in outlining the involved disk and nearby soft tissues. Therefore it is the investigation of choice.

In 50–60% of the patients, organism can be grown from the aspirate or biopsy of the involved disk. Most commonly isolated organism is *Staphylococcus aureus.*

Osteomyelitis in Sickle Cell Disease Patients

Bone pain in sicklers is a challenge to the treating physician. This is because of common vaso-occlusive crisis in patients with sickle cell disease, which results in bone infarction and pain and fever. This causes confusion in differentiating it from osteomyelitis to which these patients are at higher risk. Around 18% of sicklers will develop osteomyelitis at one time or another. The clinical features of osteomyelitis resemble those of vaso-occlusive crisis. Even ESR and c-reactive protein (CRP) are of little help in differentiating between the two. Blood culture can be positive in up to 30–50% of cases with osteomyelitis. *Salmonella nontyphi* species are the most commonly isolated organisms (*Table 62.4*). *Staphylococcus aureus* and gram-negative bacilli may be the cause but at a lesser frequency. Diagnosis of osteomyelitis in sicklers relies on radiological studies. Plain x-ray is of little help. Radioisotope bone scan has low sensitivity and specificity. However when combined with bone marrow isotope scan, sensitivity improves. In osteomyelitis, bone marrow scan is normal and bone scan shows high uptake. In bone infarction, both bone marrow scan and bone scan show reduced uptake. MRI is becoming the radiological method of choice for diagnosing osteomyelitis in sicklers. It is more sensitive than other modalities. In typical osteomyelitis with squestra, T2-weighted scan will show high-intensity uptake with central low intensity. T1-weighted with gadolinium will show an area of increased uptake around an area of nonenchancing center. If there is a defect in the periosteum, the MRI will show the communication between the marrow and the surrounding soft tissue collection.

Table 62.4
Relative prevalence of *Salmonella* in sicklemic patients with osteomyelitis

Study	No. of patients	% of isolates		
		Salmonella	*Staphylococcus aureus*	Others
Nelson	8	50	8	42
Givner	3	100		
Barett-Connor	12	42	8	50
Seeler	9	77	11	11

Chronic Multifocal Osteomyelitis

This is a disease of older children, 8–12 years of age. However, other age groups can be involved. It is characterized by recurrent episodes of pain and fever. The disease involves multiple sites of long bones, which range in number from 2 to 18 and characteristically involves the metaphysis. On plain x-ray, it is characterized by bone rarefaction and marginal osteosclerosis. Histologically there is evidence of chronic inflammation with plasma cell infiltration. No organisms are isolated from these lesions. Prognosis is good and treatment consists of non-steroidal anti-inflammatory drugs or steroids.

Osteomyelitis Associated with Brucellosis

Brucellosis rarely results in osteomyelitis in children. However when it occurs it is usually in the form of spondylitis. Other sites like long bones can be involved but is very rare.

Diagnosis

It is usually difficult to diagnose osteomyelitis. Presence of clinical features is the first clue to diagnosis. Some blood tests may be helpful including total white blood cell count (WBC), c-reactive protein (CRP), and erythrocyte sedimentation rate (ESR). WBC is not very sensitive and not very useful. CRP is raised in 82–96% of the affected patients and it usually rises early and declines within 1 week of therapy. ESR is also helpful being raised in 70–100% of affected patients. It may rise early in the therapy and then decline within 3 weeks of therapy. Aspiration and culturing of infected tissue from involved site is the gold standard; however this is not achievable all the time. It is usually positive in 45–83% of patients. Blood culture is positive in 24–74% of patients. Collectively, having tissue and blood cultures may give a yield up to 70%. Imaging studies play a major role in diagnosing osteomyelitis. Plain x-ray is not very sensitive and usually lags behind clinical presentation by 10–14 days. The major findings in plain x-ray are osteolytic lesion with periosteal reaction *Table 62.5*.

Table 62.5
Radiographic findings among 153 patients with osteomyelitis

Radiographic findings	Days from onset				
	1–6	7–10	11–20	21–30	31–
Bony destruction	5	17	31	17	6
New bone formation		4	19	15	1
Periosteal reaction		5	9	1	1

Radionuclide studies are more sensitive and usually show positive results earlier. Bone scan or Gallium scan are of similar sensitivity, approaching 80%. Indium-labeled WBC, technetium-labeled WBC, or indium-labeled immunoglobulin have a better sensitivity and specificity and are particularly helpful in cases where there is an implanted devise and in osteomyelitis of small appendicular bones. Magnetic resonance imaging has emerged as an excellent tool of diagnosing osteomyelitis. Its sensitivity approaches 100% and it is very helpful in detecting soft tissue and bone marrow infections. It is particularly helpful in differentiating osteomyelitis form soft tissue infections.

Management

There are special considerations in treating osteomyelitis. These include

1. Trial to reach a microbial diagnosis as much as possible
2. Prolonged duration of therapy
3. Close follow-up
4. Looking for complications

Taking in consideration the age of the patients, the initial empirical therapy is as follows:

1. Medical:
   (a) Initial antibiotics coverage:

(a) Neonates:	Cefotaxime and Nafcillin
(b) Children <5 years:	Cefuroxime
(c) Children >5 years:	B-lactamase resistant penicillins like Cloxacillin

In areas where the prevalence of MRSA is high, a consideration of starting vancomycin initially is warranted, especially in seriously sick children.

2. Surgical:

Initially, bone aspiration for diagnosis and debridement should be done, especially if there is evidence of subperiosteal abscess. In addition, for patients with traumatic bone injury, surgical debridement is required as part of management.

Sequential therapy starting with intravenous therapy followed by oral therapy is now the method of choice. Most of the patients will require intravenous medication for 5–7 days, after which the child becomes afebrile and his/her clinical symptoms improve. The criteria to switch to oral therapy include: (1) resolution of clinical symptoms, (2) availability of adequate oral therapy, (3) assured compliance, and (4) close follow-up. When switching to oral therapy, the antibiotic dosage should be the high dose, and the antibiotic of choice is usually directed by the isolated organism if any, or the used parenteral antibiotic ◉ *Table 62.6*.

The duration of therapy is usually 4–6 weeks for acute infection. However, shorter duration of therapy for 3 weeks has been advocated recently for patients with acute and non-complicated osteomyelitis. Chronic osteomyelitis may require a prolonged period of treatment.

Periodic follow-up of affected patients is mandatory. The check-up list includes clinical examination, plain bone radiography of the affected bone, and ESR. ESR takes 7–14 days to decrease. Therefore a slight increase in the first 5–7 days of therapy is expected and does not indicate worsening of the condition as long as there is clinical response.

Table 62.6
Commonly used antibiotics to treat osteomyelitis and septic arthritis

Antibiotic	Intravenous dose (mg/kg/day)	No. of doses/day	Oral dose (mg/kg/day)	No. of doses/day
Cloxacillin	150	4	75–100 (bad taste)	4
Vancomycin	45	3		
Cefuroxime	150	3		
Cephalexin			100	4
Clindamycin	30	3	30	3
Ceftriaxone	100	2		
Cefotaxime	150	3		

Prognosis

This depends on how prompt and adequate therapy was given. However neonates are at an increased risk of developing complications such as disruption of growth phase, which may result in shortening or elongation of the affected bone.

Septic Arthritis

Septic arthritis is a serious infection which affects 2–40/100,000 children. Special consideration of septic arthritis in children includes the variability of the causative organisms according to the age and geographical areas. In addition the clinical presentation may be subtle, which makes high index of suspecting the prime factor in diagnosis. Septic arthritis is defined as a clinical episode in which a patient had at least one or more of the following: fever higher than 37.5°C, leucocytosis (WBC $>$ 13,000/mm^3), raised ESR ($>$20 mm), or a positive blood culture plus one or more of the following: technetium bone scan consistent with septic arthritis (and not osteomyelitis), joint pain and tenderness and restricted range of movement, joint effusion detected clinically or with ultrasound or a positive culture from aspirated joint fluid or pus cells, and/or bacteria detected on microscopy of joint fluid and a negative culture (only acceptable if patients had received prior antibiotic therapy).

Etiology

In developing countries where *H. influenzae* type b vaccine is not universally adopted, *H. influenzae* continues to play a major role in causing septic arthritis among children 3 months to 5 years of age. In addition, Brucellosis is endemic in many of the Middle East countries and one of the major presentations of brucellosis in children is arthritis or arthralgia (◉ *Table 62.7*).

Clinical Features

Newborn and infants have subtle symptoms, which include joint swelling, erythema and tenderness, fever, and pseudoparalysis. Usually, there is no limitation of movement at the affected joint.

Older children have more severe symptoms with joint swelling, erythema, and tenderness associated with significant limitation of joint movement. Fever and other systemic signs of infections are prominent.

Diagnosis and Differential Diagnosis

Septic arthritis should be differentiated from other causes of arthritis, which include trauma, hemarthrosis in hemophiliacs, collagen vascular disease, transient toxic synovitis, bursitis, cellulitis, and malignancy. Clinical features in addition to supportive laboratory tests are usually helpful in diagnosing septic arthritis. Acute reactants are usually raised. Aspirated synovial fluid has special characteristics, which vary with different causes of arthritis (Table 62.8).

All patients with suspected septic arthritis should undergo aspiration of the affected joint by an experienced person. The aspirated fluid should be sent for analysis and culture. Special consideration and advice to the lab are warranted when organisms like brucella or mycobacteria are suspected because special culturing procedures are required.

Other helpful diagnostic tests include imaging studies. Plain radiography usually shows widening of the joint space, but this is a nonspecific finding. Ultrasound scan is very helpful in assessing the amount of effusion in the affected joint and also could be used to help for aspiration.

Radionuclide studies show an increased uptake in the affected joint and may help in differentiating septic arthritis from inflammation of surrounding soft tissues.

Table 62.7
The predominant organisms at different age groups

Age group	Causative organisms
In infants <3 months	*Staphylococcus aureus*
	Group B Streptococcus
	Enteric organisms
	Group A Streptococcus
	Haemophilus influenzae
	Candida
In older infants and children <5 years of age	*H. influenzae*
	Staphylococcus aureus
	Streptococcus pneumoniae
	Group A Streptococcus
	Salmonella
	Brucella
Children >5 years of age	*Staphylococcus aureus*
	Streptococcus pneumoniae
	Brucellosis
	Salmonella

Treatment

Medical Therapy

The choice of antibiotic depends on the suspected causative organism.

1. In neonates, a third-generation cephalosporin and anti-staphylococcal antibiotic like cloxacillin or naficillin are good initial antibiotic coverage until the causative organism is identified. Most of the neonates will require 4–6 weeks parenteral therapy as there are no studies showing efficacy of oral antibiotics.
2. Infants and children <5 years of age:

   Coverage in these patients should include *H. influenzae* and *Staphylococcus aureus*. Therefore,

Table 62.8
Synovial fluid characteristics

	Pyogenic infection	Chronic granulomatous diseases	Collagen vascular
Appearance	Turbid	Turbid serosanguinous	Turbid
Cell count	15,000–200,000	2,500–100,000	200–70,000
(average)	(65,000)	(28,000)	(15,000)
Glucose	Very low	Low	Mildly low
Culture	Usually positive	May be positive	Negative
Mucin clot	Poor	Poor	Fair–poor
Viscosity	Decreases	Decreased	Decreased

cefuroxime is good initial choice. Alternatives include penicillinase-resistant penicillin like cloxacillin and third-generation cephalosporin like cefotaxime. After discovering the causative organism, the specific antibiotic should be given. The initial therapy is usually parenteral. After clinical improvement (resolution of fever, improved movement at the affected joint), the antibiotic can be changed to oral route as long as compliance is assured and follow-up of serum bactericidal titter is available.

3. Children >5 years of age:

   Only staphylococcal coverage is required initially until the causative organism is discovered. The rest of management is similar to infant and children <5 years of age.

Surgical Therapy

All patients with hip and most of those with shoulder involvement should undergo arthrotomy to preserve the blood supply.

Physiotherapy

Initial bed rest and placing the affected joint in physiological position is required until the pain eases and the child starts to feel better. This can be achieved by splint, traction, or cast.

After the pain eases (usually in 3–5 days), passive movement should be encouraged in order to prevent contracture.

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63 Congenital Infections

Sami Al-Hajjar

The infant who is born with an infection acquired transplacentally during the first, second, or early third trimester may have what is termed *congenital infection.* Infection acquired in utero may result in abortion, stillbirth, developmental anomalies, intrauterine growth retardation, or clinical or asymptomatic infection, with the risk of subsequent sequelae of chronic postnatal infection.

Table 63.1 lists the different etiologic agents of congenital infections and possible sequelae.

The most common causes of congenital infections are cytomegalovirus (CMV), rubella, *Toxoplasma gondii, Treponema pallidum*, herpes simplex virus (HSV), human immunodeficiency virus (HIV), human parvovirus B19, hepatitis B virus, and Epstein-Barr virus. In rare instances, these infections are due to varicella-zoster virus, *Mycobacterium tuberculosis* and *Listeria moncytogenes.*

The acronym TORCH (*Toxoplasma, gondii* other, rubella, CMV, herpes simplex) has been used for the last two decades to increase awareness of the common etiologic agents in congenital infection. The "O" in TORCH (other) includes a list of pathogens that grows longer over time, including not only syphilis and varicella but also newer pathogens such as HIV and parvovirus B19 (*Table 63.1*). Lymphocytic choriomeningitis virus (LCMV) is a significant teratogen whose role in congenital infections has only recently gained appreciation. Approximately 88–93% of infants have chorioretinopathy and/or other ocular manifestations, including chorioretinitis, scarring, atrophy, nystagmus, esotropia, microphthalmos, cataracts, and vitreitis. Individuals who are exposed to rodents from living conditions or other exposure, such as pet handlers and laboratory personnel, are at particular risk for infection.

Certain other organisms may cause intrauterine infection but are usually transmitted just before delivery. This pattern is characteristic of HSV, *Enterovirus* group B streptococci, *Listeria*, and others. These intrauterine infections differ little from those caused by the same organisms when acquired just after delivery or during the first week or so of extrauterine life. For this reason, they are usually classified as "perinatal" rather than congenital infection. Recognition of pathogens causing congenital infection is critical, and the validity of the TORCH designation and screening for limited pathogens has been questioned.

Pathogenesis

Congenital infection occurs secondary to the exposure of the fetus during maternal infection. Most infections that occur in the mother during pregnancy appear to be limited to the respiratory or gastrointestinal tracts, and either resolve spontaneously without therapy or are treated with antimicrobial agents, and therefore do not pose a risk to the fetus. However, the infecting organism may invade the bloodstream, and this can lead to fetal infection. Transplacental spread after maternal infection and invasion of the bloodstream is the usual route by which the fetus becomes infected. Less frequently, the fetus may be infected by extension of the infection into the adjacent tissues and organs, including the peritoneum or the genitalia, or as a result of invasive methods for the diagnosis and therapy of fetal disorders such as the use of monitors, sampling of the fetal blood, and intrauterine transfusion.

Clinical Manifestations

Congenital infection in the great majority of infants will be missed during the early months of life. Ninety-five percent or more of newborn infants with congenital CMV have inapparent infection; comparable figures for the other congenital infections are toxoplasomis, 75%; rubells, 65%; syphilis, 50%; and most hepatitis B. In contrast, less than 1% of HSV infections in the neonate are subclinical. Despite striking differences in the nature of the microorganisms involved, signs and symptoms in the symptomatic cases overlap to a considerable extent. In fact, most of the clinical manifestations of congenital infections are also common to other noninfectious disease states. *Table 63.2* illustrates the frequency of clinical finding in infants with congenital infection.

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Table 63.1
Congenital infections associated with prematurity, intrauterine growth retardation, developmental anomalies, and persistent postnatal infection

Organism	Prematurity	Intrauterine growth retardation	Developmental anomalies	Persistent postnatal infection
TORCH Group	*Toxoplasma gondii*	*Toxoplasma gondii*	Rubella	*Toxoplasma gondii*
	Cytomegalovirus (CMV)	CMV	HSV	Rubella
	Herpes simplex virus (HSV)[a]	Rubella		CMV
				HSV
				HIV
				Hepatitis B
				Plasmodium
Others	*Treponema pallidum*	HIV[a]	VZV	HIV
	Mycobacteria	*Plasmodium*	HIV[a]	Hepatitis B
	Tuberculosis	*Trypanosoma cruzi*	Coxsackieviruses B[a]	*Plasmodium*
	Human Immunodeficiency virus (HIV)[a]	Varicella-zoster virus (VZV)[a]		
	Hepatitis B			
	Rubella			
	Plasmodium			
	Trypanosoma cruzi			
	Listeria monocytogenes			
	Coxsackieviruses B			
	Lymphocytic chorimeningitis virus			

Modified from Klein JO, Remington JS (2005) Current concepts of infections of the fetus and newborn infant. In: Remington JS, Klein JO (eds) Infectious diseases of the fetus and newborn infant 6th edn, vol 5. WB Saunders, Philadelphia, pp 1–19, with permission
[a]Association of effect with infection has been suggested and is under consideration

Diagnosis

Because the incidence of congenital infection in the fetus and newborn infant is high (0.5–2.5%) and because a significant number of congenitally infected infants are asymptomatic, the diagnosis of congenital infection in the infant relies on a high index of suspicion plus a combination of clinical and laboratory evaluations. The maternal history may provide important information about maternal infection. For example, the occurrence of maternal viral illness with an associated maculopapular rash suggests rubella in the neonate, whereas ulcerative genital lesions point toward HSV. It should be noted, however, that most maternal viral infections that lead to fetal or neonatal infection are asymptomatic in the mother. Therefore, the absence of a history of viral infection in the mother certainly does not rule out the possibility of such infection in her neonate.

Certain specific neonatal manifestation may provide helpful clues to strongly suspect specific etiologic agents on clinical grounds alone. For example, congenital rubella is characterized by purpura, heart defect, bone lesions, a "salt and pepper" appearance of the retina, and central cataract. An infant with a pink or dark red maculopapular or vesicolobullous skin, rash, rhinitis, and osteochondritis or periosteitis should be suspected of having congenital syphilis. Congenital CMV is probable in the infant with microcephaly, periventricular calcification, and "blueberry muffin" skin rash (*Fig. 63.1*), whereas toxoplasmosis is probable in infant with hydrocephalus, diffuse intracranial calcifications, and chorioretinitis. Chorioretinitis in the absence of major findings such as microcephaly is more likely due to toxoplasmosis and not CMV. LCM virus infection should be considered among infants who have chorioretinitis and congenital hydrocephalus or microcephaly, lack hepatosplenomegaly. However, the signs

Table 63.2
Prevalence of clinical findings in infants with congenital infections[a]

Clinical findings	Congenital infections[a]				
	Rubella	*Toxoplasma gondii*	CMV	Syphillis	HSV
Reticuloendothelial system					
Jaundice	+	++	+++	+++	–
Hepatitis	±	+	+++	+++	+
Hepatosplenomegaly	+++	++	+++	+++	+
Anemia	+	+++	++	++++	–
Thrompocytopenia	++	±	+++	++	–
Disseminated intravascular coagulation	–	–	±	–	–
Adenopathy	++	++	–	++	–
Dermal erythropoiesis	+	–	+	–	–
Skin rash	–	+	–	++	+++
Bone abnormalities	++	+	±	+++	–
Eye					
Cataracts	++	±	–	–	–
Retinopathy	++	+++	+	±	+++
Microphthalma	+	±	–	–	+
Central nervous system					
Microcephaly	+	±	++	–	+++
Meningoencephalitis	++	±±±	+++	++	+++
Brain calcification	±	±±	++	–	+
Hydrocephalus	–	±±	±	±	++
Hearing defect	++	±	++	+	–
Pneumonitis	++	±	+	+	–
Cardiovascular					
Mycocarditis	+	–	±	±	–

+ rare, ++ less common, +++ common, ++++ frequent, ± can or cannot be present
[a]None

and symptoms of many infections can overlap, and co-infection with more than one organism is possible. Therefore, in most cases, the investigation of suspected congenital infection usually requires simultaneous testing for a number of organisms. This should be tailored to the clinical situation.

The possibility of sepsis must always be considered, and the differential diagnosis of a symptomatic infant also includes hemolytic diseases and metabolic disorders such as galactosemia and tyrosinemia. The laboratory diagnostic approach to congenital has been tempered by the TORCH designation as TORCH titers are most frequently ordered by clinicians to diagnose congenital infection. In most case, however, the test is used inappropriately and is nondiagnostic. It must be remembered that a single investigation or specimen cannot be used to confirm the presence of one or the whole series of agents that can cause congenital infection.

The TORCH battery of serology tests has a poor diagnostic yield, and the appropriate diagnostic studies should be selected for each etiologic agent under consideration. Neonatal immunoglobulin G (IgG) titers are often difficult to interpret because IgG is acquired from the mother by transplacental passage. Of course, a negative antibody titer in the cord and maternal serum is sufficient evidence to exclude the diagnosis of congenital infection. Immunoglobulin M (IgM) titers to specific pathogens have high specificity and moderate sensitivity; they should not be

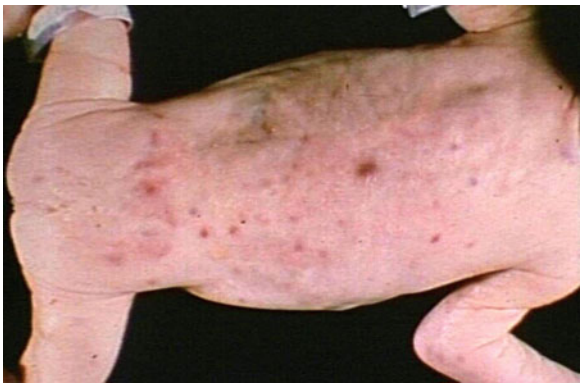

Figure 63.1
Purpuric "blueberry muffin" skin lesions in a newborn with congenital CMV infecion

employed to exclude infection. It is well known that IgM antibodies to rubella, CMV, and toxoplasma infection are long lasting. In many cases, IgM antibodies last for several months after primary infection with these pathogens . Because of this, it is very difficult to differentiate between acute and past infection utilizing current available IgM immunoassays. Recently, IgG avidity assays, which measure antibody maturity, have been shown to reliably discriminate between acute and past infection .Thus, in recent (acute) infection, for example, CMV, the body produces low-avidity IgG. After 2–4 months, the body begins to produce high-avidity CMV IgG. Low CMV IgG avidity suggests acute CMV infection occurred within the past 2–4 months. High CMV IgG avidity suggests that CMV infection occurred at some point in the past. This has been demonstrated to be the case for CMV, toxoplasma, and rubella. Avidity indices of 50% or less are considered low-avidity indices.

Total cord IgM level has been used as a screening test for congenital infection, but it lacks both sensitivity and specificity. Increased levels of total IgM ($\geq$20 mg/dL) occur only in one third of asymptomatic newborn infants with congenital infection and approximately 3% of uninfected infants. It is now apparent that infected fetuses first produce specific IgM between 19 and 24 h of gestation. When cordocentesis is performed before 20 weeks of gestation, the diagnosis of fetal infection can be made by isolation or detection of the agent itself, for example, by culture (CMV), by demonstration of the organism in inoculated mice (*Toxoplasma)* or by detection of both CMV or *Toxoplasma gondii* by polymerase chain reaction (PCR). The nonspecific and specific diagnostic tests are outlined in *Table 63.3*. It is important to remember that serologic tests not specific for IgM antibody require maternal serum for interpretation. Establishment of the specific agent is important for prognostic evaluation and for possible treatment. A combination of tests, including serology, avidity, and polymerase chain reaction, may be necessary to improve accuracy of diagnosis.

Table 63.3
Diagnostic evaluation of suspected congenital infection

Nonspecific tests	Specific tests[a]
Complete blood and platelet counts	**Viral culture**[b]
Lumbar puncture	Nasopharynx, urine, stool, skin lesion
Roentgenogram of long bones	Blood for HIV
Computerized tomography scan of head	Optional: cerebrospinal fluid (CSF), conjunctiva
Ophthalmologic evaluation	**Smears of skin lesion**
Audiology evaluation	FA stain
	Dark field examination
	Serology
	Rubella: IgG antibody (HAI, ELISA, FA, avidity) or IgM antibody (IFA) or
	Toxoplasma: IgG antibody (SF, IFA, ELISA, avidity) or IgM antibody (IFA, ELISA) or PCR
	Syphillis: VDRL or RPR, FTA-Abs test
	CMV: IgG (HAI, ELISA, FA, avidity)/ IgM antibody (ELISA)
	HIV: HIV DNA or RNA (PCR)
	Hepatitis B: HBsAg
	LCM: IgG and IgM antibody (IFA) and CSF IgG and IgM (ELISA)

[a]ELISA, enzyme-linked immunosorbent assay; FA, fluorescent antibody; FTA-Abs, fluorescent treponemal antibody test-absorbed; HAI, hemagglutination inhibition; HBsAg, hepatitis B surface antigen; IFA, immunofluorescent antibody; RPR, rapid plasma regain; SF, Sabin–Feldman dye test; VDRL, Venereal Disease Research Laboratory (test for syphilis). PCR, polymerase chain reaction
[b]African green monkey kidney cell line must be inoculated. Modified from Alpert G, Plotlein SA. A practical guide to the diagnosis of congenital infection in the newborn infant. *Pediatr Clin North Am* 1986;33:465, with permission

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64 Endocarditis

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Infective endocarditis (IE) is a dreaded, albeit uncommon, complication of structural heart disease. Mortality was exceedingly high in the pre-antibiotic era, but has subsequently improved. Morbidity, including prolonged antibiotic administration and surgery, remains significant. This chapter will give an overview of IE in pediatric patients including those without structural heart disease.

Definition

IE is a microbial infection on the endocardial surface of the heart. IE typically involves native or prosthetic valves, but can also involve septal defects and intravascular foreign objects. Infective endarteritis is a similar infection involving arteries such as the ductus arteriosus. Historically, the terms acute and subacute have been used to classify endocarditis. Acute IE was usually due to *Staphylococcus aureus*, *Streptococcus pyogenes*, or *Streptococcus pneumoniae* while the subacute form typically involved viridans streptococci. Currently, IE is classified by the causative organism.

Epidemiology

IE is a rare disorder and occurs less frequently in children than adults. Approximately 1 of every 1,280 hospital admissions in American children in the early 1980s was for IE. This rate represents an increase from the mid-1900s. The underlining epidemiology of structural heart disease in children has also changed since the mid-1900s in the Western world, leading to changes in the predisposing factors for IE.

The incidence of rheumatic heart disease (RHD) has significantly decreased since the mid-twentieth century. At that time, 30–50% of pediatric IE cases were associated with RHD. Currently, IE patients rarely have underlying RHD in the Western world. However, RHD remains a problem in the developing world and is presumably a significant factor in the development of IE in these areas.

Patients with congenital heart disease (CHD) are living longer and now account for the largest percentage of IE cases. A recent nationwide database search showed that CHD was present in approximately 42% of IE admission in the United States. The most common underlying CHD diagnoses in this database were tetralogy of Fallot (TOF), ventricular septal defect (VSD), hypoplastic left heart syndrome, and aortic valve disease. However, these results do not necessarily represent the absolute risk of acquiring IE due to a specific congenital lesion. For example, VSDs are one of the most common forms of CHD. However, the lifetime risk for acquiring IE in patients with a VSD is lower than many other lesions. The highest lifetime risks for IE per 100,000 patient years are: prosthetic valve replacement after prosthetic valve IE, 2160; previous IE, 740; and valve surgery for native valve IE, 630. These lesions, along with cyanotic congenital heart disease and surgically constructed systemic-pulmonary shunts and conduits, are generally considered the highest risk groups for acquiring IE. Acquired valvular dysfunction (such as from RHD), hypertrophic cardiomyopathy and most other forms of CHD increase the risk of IE over the general population, but to a lesser degree than the highest risk group. For example, the risk per 100,000 patient years with congenital aortic stenosis is 271 and with a VSD is 145. For comparison, the lifetime risk in adults without cardiac disease is 5 per 100,000 patient years. Isolated secundum atrial septal defects and mitral valve prolapse without regurgitation do not increase the risk of IE above the general population. Finally, corrective procedures, whether surgical or percutaneous, eliminate the attributable risk for IE after 6 months as long as there is no residual defect.

In the absence of structural heart disease, IE is often associated in patients with central indwelling catheters or in patients with *S. aureus* bacteremia. Children with congenital or acquired immunodeficiencies (but no structural heart disease) do not appear to be at an increased risk for IE.

Pathogenesis

Microorganisms have a difficult time attaching to and propagating on intact cardiac endothelium. Most experts believe the following sequence of events is necessary for the development of IE: formation of nonbacterial thrombotic

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endocarditis (NBTE) on the surface of a cardiac valve or other location of endothelial damage, bacteremia, adherence of the bacteria in the bloodstream to the NBTE and proliferation of the bacteria within a vegetation. As noted, endothelial damage is often the inciting event. Structural heart disease often creates turbulent blood flow and high-velocity jet streams. This abnormal flow damages the cardiac endothelium and creates a substrate for thrombogenesis. Depositions of sterile clumps of platelets, fibrin, and occasionally red blood cells adhere to the damaged endothelium and form a NBTE. Central IV catheters can also cause a NBTE by rubbing against and damaging endothelium. When a NBTE becomes colonized with microorganisms, IE ensues.

Endogenous microorganisms populate all mucosal surfaces. Trauma to these surfaces transiently releases many different microbial species into the blood stream. Examples of activities that can lead to bacteremia include tooth extractions, teeth cleanings, flossing, brushing teeth, or even chewing food. However, bacteremia alone is not sufficient for IE. The inoculation number and type of microorganism appear to be critical factors. Mediators of bacterial adherence serve as virulence factors in the development of IE. Bacterial surface structures present on streptococci, staphylococci, and enterococci serve as important adhesins in animal models of IE. Organisms with these structures are responsible for the majority of cases of IE.

After colonization, bacteria within the vegetation proliferate. Adherent microorganisms trigger further deposition of fibrin and platelets; essentially isolating the bacteria from host immune defenses. The bacteria rapidly multiply and reach maximal microbial densities of 10^8 to 10^{11} colony-forming units per gram of vegetation on left-sided lesions. The innermost organisms become metabolically inactive, reducing the action of many antimicrobial agents.

Pathology

Vegetations usually occur on the atrial side of atrioventricular valves (tricuspid and mitral valves) and the ventricular side of semilunar valves. Vegetations also occur on prosthetic material (for example, VSD patches or artificial valves) in the heart or vasculature. Local extension of the infection produces many of the pathological complications in the heart. Large vegetations can lead to obstruction of surgical shunts. Valvular involvement can cause hemodynamically important regurgitation and new-onset heart failure. Other described cardiovascular complications include ruptured cordae tendineae, perivalvular abscess, fistulas, pericardial empyema and tamponade, sinus of Valsalva or ventricular aneurysms, and myocardial infarction due to embolism.

Distant organs are also affected by IE. Renal pathology, such as glomerulonephritis or infarction, can result from either embolic events or an immune complex–mediated process. Embolism can also cause ischemia and hemorrhage to other organ systems such as the central nervous system or abdominal organs.

Clinical Manifestations

IE is often an indolent disease and many clinical findings are nonspecific. Common symptoms include prolonged low-grade fever, myalgias, arthralagias, headaches, generalized malaise, history of anorexia, rigors, diaphoresis and weight loss. These features constitute the so-called subacute form of endocarditis. Any patient with structural heart disease and this cluster of symptoms requires evaluation for IE.

Occasionally, patients present in a toxic state with high, spiking fevers and/or heart failure. This constitutes the "acute" form of IE, which is often associated with *S. aureus* infection. Urgent intervention may be necessary including early antibiotics, intensive care, and surgery.

Neonatal IE presents in a similar manner to sepsis or heart failure from other causes. Feeding difficulties, respiratory distress, and tachycardia are common. Septic emboli occur more frequently than in older children. The emboli lead to infections outside of the heart such as meningitis, pneumonia, and osteomyelitis. Neurologic signs and symptoms may also occur and include new-onset seizures, apnea, and hemiparesis.

Specific extracardiac manifestations of IE are well described in adults. These findings include Roth spots, Osler nodes, and Janeway lesions. Roth spots are exudative, edematous hemorrhagic lesions of the retina. Osler's nodes are painful, violaceous nodules on the pulp of the fingers and toes. Janeway lesions are macular, blanching, nonpainful, erythematous lesions on the palms are soles. In children, these findings are uncommon. Splinter hemorrhages are also commonly described in adults with IE, but this is considered a nonspecific finding in children.

The cardiac examination in children with IE is highly variable. The type of underlying structural heart disease and the site of infection have major implications on the findings. Valvular infections can produce leaflet destruction leading to a new or worsening regurgitant murmur. With severe regurgitation, patients may present with new-onset heart failure. Cyanotic heart disease often requires

systemic to pulmonary artery shunts for pulmonary blood flow and maintenance of acceptable systemic oxygen saturations. IE of these shunts may not a significantly change in a patient's murmur. However, oxygen saturations may decrease due to partial obstruction and decreased pulmonary blood flow. Finally, patients with catheter-related IE may have no cardiac findings at all.

Diagnosis and Laboratory Evaluation

The signs and symptoms of IE can be nonspecific; therefore criteria were developed to aid diagnosis. The Modified Duke Criteria employs a combination of clinical, microbiologic and echocardiographic criteria to determine the likelihood of IE. This criterion is the current diagnostic standard and has been confirmed in the pediatric age group. Patients are stratified into to definite, possible or rejected IE. The Modified Duke Criteria for definite IE is met with two major, or one major and three minor or five minor criteria. Possible IE is defined as one major and one minor or three minor criteria. Rejected IE occurs with any of the following: a firm alternate diagnosis; "IE syndrome" resolves within 4 days of antibiotic therapy; or if the case does not meet "possible IE" criteria. The two major clinical criteria are evidence of endocardial involvement and a positive blood culture typical for IE. Evidence of endocardial involvement includes a positive echocardiogram (specifically defined as a vegetation, paravalvular abscess, or valve dehiscence after surgery) or new valvular regurgitation (by auscultation, not echocardiogram). A positive blood culture is a major criterion when there is any of the following: growth on two occasions of a microorganism "typical for" IE (*S. viridans*, *S. aureus*, *S. bovis*, HACEK group or community-acquired enterococcus); at least two persistently positive cultures drawn >12 h apart; all of three or a majority of ≥4 separate cultures are positive (with the first and last sample drawn at least 1 h apart); or evidence of infection with *Coxiella burnetii*. Minor criteria are as follows: a predisposing heart condition or injection drug use; fever ≥38°C; vascular phenomena (major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions); immunologic phenomena (glomerulonephritis, Osler's nodes, Roth spots, rheumatoid factor); microbiologic evidence consisting of either a positive blood culture not meeting major criterion as noted above (excluding single positive cultures for coagulase-negative staphylococci and organisms that do not cause endocarditis) or serologic evidence of active infection with organism consistent with IE.

Blood Cultures

Positive blood cultures are a major criterion and are also important for antibiotic selection. In suspected IE, three blood cultures over 24 h from separate venipuncture sites are recommended. If the cultures are negative at 24 h, then an additional two cultures may be obtained. Bacteremia from IE is continuous; therefore it is not necessary to obtain cultures during fever spikes. In adults, 20–30 ml of blood per culture is recommended. This amount is not feasible in children. Typically, 5–7 ml of blood in children and 1–3 ml of blood in infants are recommended. Anaerobic organisms rarely cause IE, therefore emphasis is placed obtaining aerobic cultures. If possible, antibiotics are not started until blood cultures are obtained.

The most commonly cultured organisms in IE are the gram positives *S. aureus*, viridans group streptococci and coagulase-negative staphylococci. Recently, IE discharge data on children was compiled from a large collection of American hospitals. This data showed that *S. aureus* was the most common organism (57% of cases), followed by viridans group streptococci (20% of cases) and coagulase-negative staphylococci (14% of cases). Other studies have shown that viridian group streptococci is slightly more common than *S. aureus*. Rarely encountered gram positive causative organisms include pneumococcus, *Escherichia coli*, *Hemophilus influenzae*, group A streptococcus, group B streptococcus, group D streptococcus.

Gram negative bacteria are the causative agents in less than 10% of cases of pediatric IE and are primarily due to the HACEK group of fastidious coccobacilli. The HACEK group includes *Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *Actinobacillus [Haemophilus] actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella* species, and *Kingella kingae*. These organisms grow slowly in standard culture media. Therefore, the laboratory should retain initially negative blood cultures for at least 2 weeks to evaluate for gram negatives. Certain groups are at higher risk for these organisms and include neonates, immunocompromised patients, and injection drug users.

Fungal endocarditis is usually caused by *Candida* species and rarely *Aspergillus*. The use of central venous catheters to deliver hyperalimentation and high glucose solutions appears to be associated with Candida endocarditis. Additional risk factors include injection drug users and immunocompromised individuals. Fungal vegetations are often large and friable leading to embolization and serious complication.

Culture-negative endocarditis is diagnosed when a patient has clinical and/or echocardiographic evidence

of IE but the blood cultures are repeatedly negative. This occurs in about 5–7% of cases. The most common cause of culture-negative IE is current or recent antibiotic treatment or infection with a fastidious organism that grows poorly in vitro. These fastidious organisms include filamentous fungus, *Coxella burnetti* (Q fever), *Brucella, Legionella, Bartonella* (*Rochalimaea*), and *Chlamydia*. When the clinician encounters culture-negative IE, it is important to consult with the microbiology lab in order to maximize the chance of culturing the causative organism.

IE associated with central venous catheters, prosthetic material, or prosthetic heart valves is usually caused by *S. aureus* or coagulase-negative staphylococci. These infections may be inoculated at the time of the procedure and typically present within 60 days of surgery. However, coagulase-negative staphylococci can present up to 1 year after surgery.

Echocardiography

Echocardiography is the primary modality for detection of endocarditis as well as being a major diagnostic criterion. Echocardiograms can establish vegetation location, size, and response to therapy. Associated problems can also be determined such as the extent of valvular damage, ventricular size and function, the presence of pericardial effusion, and abscess formation. In adults, transthoracic echocardiography (TTE) is not considered sensitive enough for vegetation detection; therefore transesphogeal echocardiograms (TEE) are recommended. TTE is usually sufficient in pediatric IE with a reported sensitivity of 81%. TEE can be a useful adjunct in children with poor echocardiographic imaging (due to body habits or pulmonary hyperinflation), a prosthetic valve causing acoustic "shadowing" or in those with a normal TTE despite a high index of suspicion for IE. It is important to note that the absence of vegetation on echocardiography does not rule out IE. Conversely, an echogenic mass may represent a sterile thrombus, sterile prosthetic material (such as a surgical stitch), or normal anatomic variation. *Figure 64.1* shows an example of a mitral valve vegetation in a child imaged by TTE.

Serial echocardiography is an important part of the ongoing care for acute IE. Certain echocardiographic findings are predictive of complications and may require surgical intervention. These features include: persistent vegetation after systemic embolization, anterior mitral valve vegetation particularly if greater than 10 mm in size, one or more embolic events during the first 2 weeks of antimicrobial therapy, increase in vegetation size after 4 weeks of antimicrobial treatment, acute valvular dysfunction leading to heart failure and a large abscess or extension of the abscess despite appropriate antibiotic treatment.

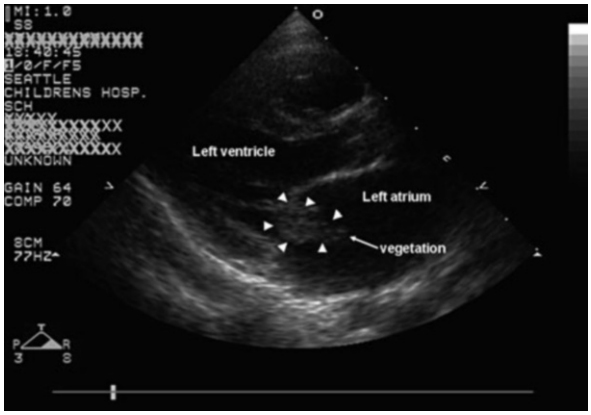

Figure 64.1
An example of mitral valve endocarditis in a child as visualized with a transthroacic echocardiogram. The margins of the vegetation are demarcated by arrowheads. The large size (~20 mm) of this vegetation required surgical removal due to a high risk of embolization

Other

Additional laboratory abnormalities are often present. An electrocardiogram should be performed to evaluate for arrhythmias and atrioventricular block, which may be a sign of an abscess within the conduction system. IE can cause anemia either through hemolysis or chronic disease. Leukocytosis is not always present, but immature cells are often present on blood smear. Elevations in the inflammatory markers C-reactive protein and erythrocyte sedimentation rate are common. Hematuria and other renal abnormalities can be found in IE patients who develop immune complex–mediated glomerulonephritis. Rheumatoid factor is also often elevated.

Differential Diagnosis

As noted, the clinical manifestations of endocarditis are usually nonspecific. Many disorders share similar features including other infections, malignancies, and rheumatologic conditions. However, it remains incumbent upon the clinician to strongly consider IE in any child with an unexplained fever and a history of structural heart disease.

Treatment

Antibiotics are the mainstay of IE treatment. A complete discussion of antibiotic treatment for every potential organism and clinical situation is beyond the scope of this chapter. For in-depth recommendations, the reader is encouraged to consult the American Heart Association (AHA) statement (most recently updated in 2005) entitled, "Infective Endocarditis: Diagnosis, Antimicrobial Therapy, and Management of Complication." Several general principles provide the basis for antibiotic treatment in IE. In clinically stable patients, antibiotics may be withheld for 48 h or longer until information from the blood cultures is available. The choice of antibiotics is then based upon the cultured organism and sensitivity to various antibiotics. Evolving antibiotic resistance patterns makes consultation with an expert in infectious disease necessary to assure proper therapy. Antibiotics are typically administered for 2–8 weeks. Additionally, bacteriocidal antibiotics should be chosen if available to minimize the possibility of a treatment failure or relapse. Intravenous treatment is the preferred route in order to achieve high bacteriocidal concentrations in the relatively avascular vegetations.

Occasionally, patients with IE present in an unstable hemodynamic condition; the so-called acute endocarditis. This situation warrants initiation of antibiotics prior to obtaining results from the blood cultures. Empiric treatment should focus on covering streptococci and staphylococci, the most common causative organisms in IE. The antibiotic coverage should include a penicillinase-resistant penicillin, penicillin G, and gentamicin. Vancomycin should be considered where rates of methicillin-resistant *S. aureus* are high. Blood cultures from three separate venipuncture sites are still recommended. However, the cultures can be obtained over 1 h.

As noted, viridans Group Streptococci is one of the most common causes of IE. For penicillin-susceptible streptococci IE of native valves, 4 weeks of IV treatment with penicillin G or ceftriaxone is recommended. A 2-week course of therapy with either of these antibiotics combined with gentamycin is an alternative strategy. However, this should only be used in uncomplicated cases of patients with symptoms for less than 3 months.

Staphylococci are classified as either coagulase-positive (*S. aureus)* or coagulase-negative (including *S. epidermidis*). Antibiotic recommendations are similar between the classes. For the purpose of this chapter, only recommendations for native valve staphylococcal IE will be discussed. Importantly, the vast majority of staphylococci are resistant to penicillin G and ampicillin. For methicillin-susceptible *S. aureus*, a semisynthetic penicillinase-resistant penicillin, such as Nafcillin, is given for 6 weeks. 3–5 days of gentamycin is sometimes added in seriously ill patients, however the clinical utility of this is unclear. Vancomycin treatment for at least 6 weeks is used in cases of methicillin-resistant staphylococci (which includes virtually all cases of coagulase-negative staphylococci). In addition, rifapin (at least 6 weeks) or gentamicin (2 weeks) is used with vancomycin for coagulase-negative staphylococci IE.

Gram negative IE is most commonly caused by the HACEK group of fastidious coccobacilli in children. Uncomplicated native valve infections should be treated for 4 weeks with ceftriaxone or another appropriate third or fourth generation cephalosporin or ampicillin/salbactum.

Fungal IE is rare and has a poor prognosis. Antifungal agents alone are almost always ineffective. Surgery (discussed below) is necessary to treat the infection and prevent complications. Surgical treatment is recommended after 1–2 weeks of medical therapy if the patient's status permits, but should be done earlier if embolic events occur. Amphotericin B is the most effective antifungal agent and should be given for 6–8 weeks.

In cases of culture-negative IE, empiric therapy with two or more agents is used for 6 weeks. During this time, continuing efforts to identify an organism should be pursued.

In general, the bacteremia from IE typically resolves within several days after initiating appropriate antibiotic therapy. S. *aureus* bacteremia may persist for 5–10 days when vancomycin is used. During treatment, repeat blood cultures should be obtained to assess the adequacy of the antibiotics and to document the resolution of bacteremia. Finally, blood cultures should be performed once or twice after antibiotic completion to ensure a successful cure.

Medical therapy alone is not always adequate for successful IE treatment. Surgery may be necessary during an active infection depending on the location and clinical course. Surgical indications typically fall into three categories. First, surgery may be necessary when antimicrobial treatment is unsuccessful or has a high likely hood of being unsuccessful. Persistent bacteremia after 2 weeks of appropriate antibiotics is generally considered a treatment failure necessitating surgery. Abscesses and fungal vegetations are exceedingly difficult to eradicate medically and therefore, surgery is recommended. Second, experts recommend removal of vegetations showering systemic emboli or at high risk of embolizing with a catastrophic consequence. The risk of embolization is associated with vegetation size and infecting organism. Fungal IE and vegetations

measuring greater than 10 mm are at high risk for embolization and should be removed surgically. Finally, valvular damage from IE may lead to uncontrollable heart failure, requiring surgery for hemodynamic stability. Other rarely encountered indications for surgery include myocotic aneurysms and unstable prosthetic valves.

Prognosis

The prognosis of children with IE depends on a number of factors including the severity of the underlying cardiac lesion, the causative organism, presence of prosthetic material, and the clinical course of the patient. Overall mortality from IE has significantly dropped. In the pre-antibiotic era, IE was almost uniformly fatal. Currently, reported mortality rates in children are between 5% and 11%. However, mortality approaches 50% in select patients such as those with Tetralogy of Fallot/pulmonary atresia. In adults and children with congenital heart disease, risk factors for mortality include vegetation size of 20 mm or greater, age <1 year, heart failure, and *S. aureus* as a causative organism. In patients without preexisting heart disease, risk factors for mortality included premature/neonatal age and *S. aureus* infections.

Patients may need surgery after an episode of IE has resolved. Because a previous episode of IE places a patient at high risk for recurrence, experts recommend closing a hemodynamically unimportant VSD following successful treatment. Additionally, valvular damage from IE may worsen over time and eventually require valve replacement or repair.

Prevention

Antibiotic prophylaxis to prevent IE during certain medical and dental procedures has been a standard part of the care for patients with structural heart disease for the last half century. However, no prospective randomized trial has been undertaken to demonstrate the effectiveness of this practice. The rational for prophylaxis is that certain medical and dental procedures cause bacteremia which, in turn, can lead to IE in patients with predisposing conditions. Administration of antibiotics just prior to these procedures may reduce the bacteremia and prevent IE. While the biologic plausibility is high, the results of observational studies have not demonstrated any benefit from IE prophylaxis. At best, research has shown that a large number of prophylaxis doses would be necessary to prevent a very small number of IE cases.

Given this and other data, the American Heart Association (AHA) and other international organization significantly revised IE prophylaxis guidelines. Importantly, these recommendations are only guidelines and clinical judgment is still indicated. The AHA cited four key points as support for these changes. First, IE is much more likely to result from frequent exposure to random bacteremias associated with daily activities (e.g., tooth brushing) than from bacteremia caused by a dental, gastrointestinal, or genitourinary procedure. Second, prophylaxis may prevent an exceedingly small number of cases of IE, if any, in individuals who undergo these procedures. Third, the risk of antibiotic-associated adverse events may exceed the benefit from prophylactic antibiotic therapy. Finally, maintenance of optimal oral health and hygiene may reduce the incidence of bacteremia from daily activities and is therefore more important than prophylactic antibiotics for a dental procedure to reduce the risk of IE.

A complete description of the IE prophylaxis guidelines is beyond the scope of this chapter. For complete details, the reader is referred to the 2007 AHA guidelines entitled, "Prevention of Infective Endocarditis." To summarize, antibiotic prophylaxis is now reserved only for patients with the highest risk of developing adverse outcomes from IE. The high-risk group includes those with prosthetic heart valves, a history of IE, unrepaired cyanotic congenital heart disease (including palliative shunts and conduits), completely repaired congenital heart defects with prosthetic material or device (whether placed by surgery or by catheter intervention) during the first 6 months after the procedure, repaired congenital heart disease with residual defects at the site or adjacent to the site of the prosthetic device and cardiac valvulopathy in a transplanted heart. The procedures for which prophylaxis is recommended include all dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa; procedures on the respiratory tract that involve incision or biopsy of the respiratory mucosa; procedures in patients with ongoing GI or GU tract infection; procedures on infected skin, skin structure, or musculoskeletal tissue; and surgery to place prosthetic heart valves or prosthetic intravascular or intracardiac materials. The choice of antibiotics depends upon type of procedure, patient allergies, and concurrent antibiotic treatment. In general, amoxicillin is the first choice and is given as a single oral dose 30–60 min before the procedure. The amoxicillin dosage is 50 mg/kg up to a maximum of 2 g. The guidelines also give recommendations for patients unable to take oral medications, already on antibiotics or with allergies to penicillins.

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65 Fever of Unknown Origin

Asa'd Al-Toonsi

Fever is a universal phenomenon of illness and occurs as part of the acute inflammatory response, which includes leukocytosis, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and a drop in levels of free serum iron. A useful definition of fever is a temperature more than 38°C. The most accurate method of measuring temperature is rectally or from freshly voided urine, followed by orally, which may be affected by drinking hot or cold liquid. Measuring the skin temperature, or the use of thermometers that measure tympanic temperature, is not reliable as skin temperature may be affected by environmental factors, and the infrared beams from tympanic thermometers may hit the external ear canal wall instead of the tympanic membrane.

Fever results from pyrogens such as interleukins 1 and 6 and tumor necrosis factor released from monocytes and tissue macrophages in response to infection, injury, autoimmune disease, or malignancy. Regardless of the triggering factor, the response is the same. These pyrogens act on the temperature-regulating centers in the hypothalamus to elevate the thermostat set point. The body then initiates heat conservation measures, including vasoconstriction, piloerection, and shivering, to drive body temperature up to a new level. These mechanisms, together with conscious heat conservation measures such as covering the body with blankets, act to bring up the body temperature to the new set point, which may be 38–40°C. When the set point is reached, or the stimulus is removed, the body initiates cooling measures, including vasodilation and sweating, in order to maintain the set point. There are also endogenous antipyretics, or cryogens (e.g., arginine, vasopressin, α-melanocyte-stimulating hormone, glucocorticoids, and, in some cases, tumor necrosis factor), that act to modulate the increase in body temperature to prevent it from rising to dangerous levels.

A second mechanism of fever involves increased heat production that exceeds heat loss, which may be seen in hyperthyroidism; exposure to excessive environmental temperature; or malignant hyperthermia. The third mechanism includes defective heat loss, as seen with ectodermal dysplasia, heat stroke, and poisoning with anticholinergic drugs.

Fever enhances host defense responses by enhancing neutrophil migration, increasing antibacterial substances produced by neutrophils (e.g., superoxide dismutase), increasing antiviral and antitumor activities of interferon, increasing T-cell proliferation, and decreasing growth of microorganisms in the fever-induced iron-poor environment. However, fever sometimes may be maladaptive (e.g., in association with hypoglycemia and shock). Drugs such as acetaminophen, aspirin, and nonsteroidal anti-inflammatory drugs act by interfering with prostaglandin synthesis through inhibition of cyclooxygenase. Because they do not suppress interleukin-1, they have no effect on the proliferation of T-helper cells and thus do not adversely affect the body's ability to fight infection. On the other hand, corticosteroids decrease the quantity of interleukin-1 released from monocytes and macrophages, thereby decreasing the body's ability to fight infection.

The pattern of fever is of minimal significance as an indicator of a specific disease but may provide a clue to the diagnosis on a few occasions. Intermittent fever is characterized by the return of temperature to normal at least once a day. This pattern of fever is seen in pyogenic infections, especially abscess collections, but it may also be seen in tuberculosis, lymphoma, or juvenile rheumatoid arthritis (JRA). Remittent fever is also fluctuating but does not return to normal. Sustained fever has little or no fluctuation and may be seen in typhoid fever. Relapsing fever is characterized by afebrile periods of one or more days between the episodes of fever. This pattern of fever is classically seen in malaria, but it may also be seen in rat-bite fever and lymphoma.

Fever Without Localizing Signs

Fever is the single most common chief complaint made to physicians who evaluate ambulatory children. Febrile illnesses account for 30% of outpatient visits and 20% of emergency department encounters. Fever without localizing signs is fever of acute onset and short duration, with no apparent etiology after careful history and physical examination. It has been estimated that between 5% and 10% of children presenting with fever will have no localizing signs, although in some series, this figure has been as high as 22%, with peak incidence during the second year of life.

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Approximately 5% of children with fever without localizing signs are bacteremic. A number of studies showed that if these children are not treated with antibiotics at the time of initial presentation, 5–10% will return with meningitis, 10% with localized bacterial infection, and another 30% with continued fever and persistent bacteremia, depending on the type of organism isolated. Children with fever without localizing signs may be at high risk of having serious infection, including infants younger than 2 months, those who appear toxic, or those with temperatures above 40°C, especially when accompanied by leukocytosis of more than 15,000/mm^3 and left shift. Children at low risk of having serious illness are those who are younger than 36 months, those appearing well, or those with fevers less than 39.4°C or leukocytosis less than 15,000/mm^3.

The management of high-risk children varies from septic workup with complete blood count and differential, with or without expectant treatment with empirical antibiotic coverage (e.g., amoxicillin-clavulanate or ceftriaxone) on an outpatient basis pending culture results, to hospitalization for those who appear seriously ill. On the other hand, low-risk children are managed more conservatively; they may not require any investigation, or only simple investigations, such as complete blood count or urinalysis, and follow-up may be all they require.

Fever and Occult Bacteremia

The incidence of bacteremia in children aged 3–36 months presenting with fever greater than 39°C is 3–5%. The child with bacteremia may appear clinically well apart from fever with or without an identifiable focus of infection. Bacteremia may be transient with spontaneous resolution, especially in cases with quantitatively low colony counts. Persistent bacteremia may be complicated with serious focal or generalized infection. For a bacteremic child discharged from the emergency department, the overall risk is 35% for persistent fever, 12% for persistent bacteremia, and 7% for meningitis, depending on the pathogen isolated.

The likelihood of a child with fever having an infectious disease depends on the age of the patient, the degree of fever, and the clinical status. In younger children, hypothermia may be seen with equal or greater frequency than fever in the course of septicemia. Infants 2–3 months of age are more likely to have focal bacterial infections with bacteremia or overwhelming sepsis when their temperature exceeds 40°C. After 3 months of age, the severity of illness and likelihood of bacteremia or septicemia is proportional to the degree of temperature elevation. With rectal temperature less than 38.9°C, the rate of bacteremia is 1%. It increases to 4% with temperatures of 38.0–39.4°C, and then to 8% with temperatures of 39.4–40°C. At temperatures of 40–41.4°C, the rate of bacteremia becomes 11%. Children with temperatures above 41.1°C have rates of serious illness exceeding 60%.

Fever of Unknown Origin

There is no general consensus on the definition of fever of unknown origin (FUO), especially in children. A reasonable definition of FUO in children is fever exceeding 38.3°C orally in children more than 3 years old or rectally in children less than 3 years old of more than 2 weeks' duration and uncertain diagnosis after 1 week of study in the hospital. It is important to differentiate FUO from fever without localizing signs because the differential diagnosis of each clinical condition is different. In patients with fever without localizing signs, urgent investigation to rule out sepsis is required, and it is acceptable to start expectant treatment. In patients with FUO, on the other hand, hospitalization is usually required but expectant treatment is not required.

Epidemiology

The results from old studies of children with FUO show that infection was found in 28–52% of these children, mainly as systemic illness, upper and lower respiratory tract infections, and skeletal infections. Unusual infections constituted 10–15% of all infections responsible for FUO (*Table 65.1*). Collagen-vascular diseases comprised 5–20% of the causes of FUO. Malignancy, mainly leukemia and lymphoma, contributed to 2–13% of cases, miscellaneous causes were responsible for 10–16%, and 5–30% of all cases of FUO were undiagnosed.

More recent studies of children with FUO did not differ much in their findings from the old series (*Table 65.1*). The findings from studies in the English literature show that infections were found in 22–43% of children with FUO, with infections such as Epstein-Barr virus (EBV) and *Bartonella henselae* (cat-scratch disease) becoming more frequent causes of FUO. In one study, EBV was the leading infectious cause of FUO, while bartonellosis was the third-leading infectious cause in those children. This finding may be explained by the fact that such diseases were probably underdiagnosed in the past and are diagnosed more frequently today due to

Table 65.1
Results from studies of children with fever of unknown origin

Diagnostic category	5–7 days	3 week outpatient or 1 week inpatient	2 week	>1 week, no diagnosis after 1 week in hospital	3 week outpatient or 1 week inpatient	≥3 week	≥3 week	≥2 week
Number	165	99	100	20	54	109	113	146
Infection	91	29	52	7	18	24	41	64
Collagen-vascular	9	11	20	3	8	7	15	11
Neoplasm	3	8	6	1	7	2	11	4
Miscellaneous (including inflammatory bowel disease)	18	24	10	3	11	3	25	5
No diagnosis	9	11	12	6	10	73	22	62

the availability of more sensitive and specific tests and better understanding of such diseases, or it may truly be due to increased incidences of these diseases. Collagen-vascular diseases were diagnosed in 6–13% and malignancy in 2–10% of cases, while miscellaneous causes were found in 3–18% of cases of FUO in these recent studies. An interesting finding is that, despite extensive workup and the utilization of modern technology, a large number of children with FUO remained with no diagnosis.

Clinical Presentation

FUO, in most instances, is an unusual presentation of a common illness rather than a presentation of a rare disease. However, the physician should be open-minded and not disregard rare diseases, especially when investigative procedures are exhausted. Systemic infections presenting as FUO include tuberculosis, brucellosis, salmonellosis, rickettsial diseases, spirochetes (such as leptospirosis), and viral infections such as EBV, cytomegalovirus, human immunodeficiency virus (HIV), and hepatitis viruses. Localized infections include upper respiratory infections, urinary tract infections, osteomyelitis, and occult abscesses. In certain parts of the world, other infections, such as malaria or leishmaniasis, may be seen more frequently as causes of FUO.

Fever may precede the appearance of other manifestations of illnesses such as rheumatoid arthritis (which constitutes 90% of collagen-vascular disease presenting with FUO) or systemic lupus erythematosus (SLE) by weeks or months, occurring when the serologic markers for these diseases are not yet present. Acute rheumatic fever should be considered in the differential diagnosis of FUO, as the fever sometimes predates other clinical features that may be discovered during subsequent clinical examination. Vasculitic diseases, such as Kawasaki disease and Wegener granulomatosis, may present as FUO. The former should be considered when the acute-phase reactants are extremely elevated.

Inflammatory bowel disease (IBD) accounts for 4% of FUO in children, with the majority due to Crohn disease, which may present with fever months or years before gastrointestinal symptoms become apparent. The finding of growth failure, as well as finger clubbing, reactive arthritis, pyoderma gangrenosum, iron deficiency anemia, and elevated ESR, are additional clues to the diagnosis.

Evaluation of the Child with Fever of Unknown Origin

Hospitalization is usually required for proper evaluation of the patient with FUO for many reasons (*Fig. 65.1*):

To try to relieve parents' anxiety and fears and gain their confidence to encourage cooperation

To document the fever and determine if there is any specific pattern to it that could help in reaching the diagnosis

To allow observation and daily evaluation of the child for appearance of new signs or availability of new information that may direct the diagnosis toward a specific etiology

To try to identify causes (*Table 65.2*), including such unusual causes as Munchausen syndrome by proxy or pseudo-FUO

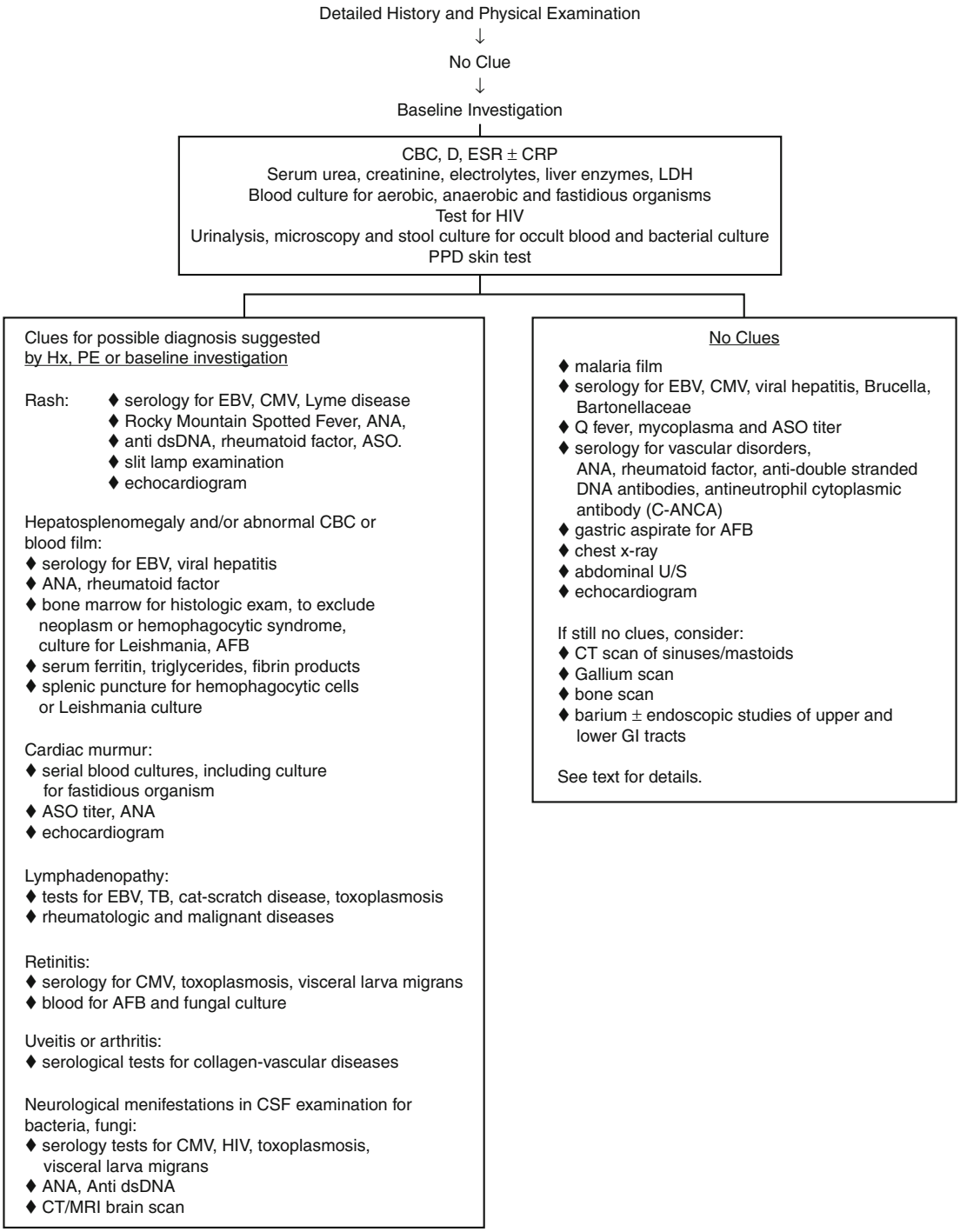

Figure 65.1

Evaluation of the child with fever of unknown origin. *AFB* acid-fast bacilli, *ANA* antinuclear antibodies, *ASO* antistreptolysin O, *CBC* complete blood count, *CMV* cytomegalovirus, *CRP* C-reactive protein, *CSF* cerebrospinal fluid, *CT/MRI* computerized tomography/magnetic resonance imaging, *D* differential leukocyte count, *EBV* Epstein-Barr virus, *ESR* erythrocyte sedimentation rate, *GI* gastrointestinal, *HIV* human immunodeficiency virus, *Hx* history, *LDH* lactate dehydrogenase, *PE* physical examination, *PPD* purified protein derivative (of tuberculin), *TB* tuberculosis, *U/S* ultrasound

Table 65.2
Some causes of fever of unknown origin

Infections (22–52%)	Collagen-vascular diseases (5–20%)
By site	Rheumatoid arthritis
Upper and lower respiratory infections	Systemic lupus erythematosus
Urinary tract infection	Polyarteritis nodosa
Osteoarticular	Behçet disease
Endocarditis	*Neoplasm (2–13%)*
Periodontal	Leukemia
Meningitis	Lymphoma
By organism:	Neuroblastoma
Salmonellosis	Histiocytosis
Shigellosis	*Miscellaneous (3–18%)*
Yersiniosis	Inflammatory bowel disease
Brucellosis	Hemophagocytic syndrome
Tuberculosis	Pseudo-fever
Tularemia	Munchausen syndrome by proxy
Chronic meningococcemia	Drug fever
Cat-scratch disease	Diabetes insipidus
Q fever	Thyrotoxicosis
Mycoplasma	Fever secondary to brain injury
Lyme disease	Ectodermal dysplasia
Malaria	Familial dysautonomia
Leishmaniasis	Atypical Kawasaki disease
Visceral larva migrans	Rheumatic fever
Leptospirosis	Periodic fever
Epstein-Barr virus	Sarcoidosis
Cytomegalovirus	Wegener granulomatosis
Viral hepatitis	
Human immunodeficiency virus	
Histoplasmosis	
Blastomycosis	

History

A careful history, with all the details of the present illness, should be taken. Minor complaints should not be ignored. Special attention should be paid to signs that may suggest specific organ involvement. History of rash may indicate a specific infection. JRA may be associated with a salmon-pink rash that appears with spikes of temperature and disappears when the fever subsides. While rheumatic fever is associated with the characteristic rash of erythema marginatum, it usually does not last more than a day or two. Joint pain or swelling raises the possibility of collagen-vascular disease. However, arthritis may also be an extraintestinal manifestation of IBD. Back pain associated with limping indicates diskitis or a vertebral abscess. Bone pain may be due to osteomyelitis or the expanding bone marrow from malignant cells in leukemia. A history of diarrhea may be important when diagnoses such as IBD, amebiasis, or giardiasis are considered. Genitourinary or respiratory symptoms may be due to a specific infection or be part of vasculitis syndromes such as Behçet disease or Wegener granulomatosis.

History of contact with a person who is ill is important in diseases such as tuberculosis. History of exposure to pets can be valuable in zoonotic diseases such as brucellosis, toxoplasmosis, cat-scratch disease, or visceral larva migrans. History of ingestion of undercooked meat or unpasteurized milk or dairy products may give clues to the diagnosis of brucellosis or Q fever. History of travel to areas endemic for certain diseases, such as malaria or leishmaniasis, should not be overlooked. Even a history of travel many years in the past to an endemic area might be relevant, as in histoplasmosis, coccidioidomycosis, or blastomycosis infections. A detailed history of all medications, including topical medications, should be obtained. Family history may reveal hereditary or familial conditions such as diabetes insipidus, familial dysautonomia, and familial Mediterranean fever, or direct the diagnosis toward an underlying immune deficiency disease that is presenting with FUO due to an unusual infection with opportunistic organisms or chronic viral infections. Social history may give clues to the diagnosis of Munchausen syndrome by proxy, pseudo-fever, or certain infections that may be seen with more frequency in people of low socioeconomic status, such as tuberculosis.

Physical Examination

Physical examination should be thoroughly performed at initial evaluation and at repeated evaluations. The general condition, and how well the child appears, usually indicate how serious the disease is. Measurements of growth parameters are important, as they may be the only clue to the diagnosis of IBD. Growth failure may also be associated with infection due to HIV or tuberculosis. Hypertension may be part of polyarteritis nodosa or SLE.

Absence of sweating and dehydration are seen in fevers due to diabetes insipidus or ectodermal dysplasia. Ophthalmoscopic examination should be done for all patients being evaluated for FUO. Retinal lesions may be seen in cytomegalovirus infection, toxoplasmosis, visceral larva migrans, disseminated tuberculosis, and disseminated fungal infections.

Skin rashes with specific distribution or a particular appearance may be diagnostic, such as erythema migrans associated with Lyme disease or the butterfly rash that is one of the features of SLE. Other important skin lesions are pyoderma gangrenosum and erythema nodosum, which are seen in patients with IBD. Mouth ulcers, in association with perineal ulcerations, uveitis, and central nervous system involvement, are diagnostic of Behçet disease. Perianal fistulas or skin tags are seen in patients with Crohn disease. The finding of cardiac murmur should alert the physician to the possibility of endocarditis. The murmur of mitral valve regurgitation is often the first clinical sign that gives a clue to the diagnosis of rheumatic fever presenting as FUO. Hepatomegaly, splenomegaly, and lymphadenopathy indicate a systemic disease, such as viral infections (e.g., EBV, cytomegalovirus) as well as toxoplasmosis, lymphoma, leukemia, hemophagocytic syndrome, histiocytosis, or rheumatoid arthritis.

Examination of the patient for gait abnormalities and assessment of individual muscle strength may demonstrate proximal muscle weakness suggesting inflammatory myositis, such as dermatomyositis. Joints must be examined for range of movement and signs of arthritis, such as redness, hotness, or swelling. Point tenderness and asymmetry in position or movement of the extremities, especially in the young child, indicate possible osteomyelitis, while point tenderness over the back may indicate diskitis.

Laboratory Evaluations

Baseline laboratory investigation is necessary at the initial assessment of the child with FUO. In many cases, the history, physical examination, and baseline laboratory investigation do not give clues to the diagnosis. At this stage, a more detailed investigation is required and, as more and more results of these investigations become available, rare causes of FUO are considered.

The baseline investigation should include a complete blood count and differential leukocyte count. An elevated leukocyte count with predominant immature forms and toxic granulations suggests a bacterial infection, especially when the patient appears toxic, but normal or low leukocyte counts could still be seen in bacterial infections. The presence of atypical lymphocytes in the peripheral blood smear suggests a viral infection, while the presence of blasts may indicate leukemia. Pancytopenia may be due to leukemia, leishmaniasis, parvovirus B19 infection, or overwhelming sepsis. Significant thrombocytosis, usually present in the second week of illness, may be the only clue to the diagnosis of atypical Kawasaki disease. The ESR is a nonspecific marker of inflammation. Markedly elevated values may determine the need for further evaluation, and the ESR is a helpful tool in monitoring disease activity.

In laboratories with the facility to measure the CRP, a single measurement may be normal in the presence of infection. However, there are some studies that show increased sensitivity of CRP as a marker of infection when measured serially over 24–48 h following presentation. Elevated CRP may be seen in patients with rheumatic fever, Kawasaki disease, or other inflammatory conditions. A renal profile, including serum creatinine, urea, sodium, and potassium, may help in pointing toward nephritis, which may be seen in SLE or polyarteritis nodosa. Abnormally elevated values may be seen in the child with fever due to dehydration from diabetes insipidus or ectodermal dysplasia. Liver enzymes may be abnormal in many conditions that could cause FUO, such as viral hepatitis, EBV infection, and several other infections. Elevated serum transaminases may be seen in diseases with multiorgan involvement, such as Kawasaki disease and hemophagocytic syndrome. Elevated serum lactate dehydrogenase suggests malignancy.

Blood should be cultured for aerobic and anaerobic bacteria. The blood culture should be incubated for 3–4 weeks to detect slow-growing, fastidious organisms, such as *Brucella* or the HACEK organisms (*Haemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens*, and *Kingella kingae*), which have a predilection for bacterial endocarditis. A series of three to five blood cultures, obtained at intervals within 24 h from different sites, are recommended when bacterial endocarditis is suspected. A blood smear for malaria becomes part of the initial investigation in patients living in an endemic area, with a history of malaria, or with a history of visiting endemic areas.

Urinalysis and microscopy may show red blood cell casts or granular casts that indicate nephritis. Hemoglobinuria may be due to hemolysis associated with malaria, and hematuria may be seen with leptospirosis. Urine culture should be part of the initial investigation even if the patient has no urinary symptoms suggestive of urinary tract infection. The stool should be tested for the presence of occult blood and cultured for enteric pathogens such as *Salmonella*, *Shigella*, and *Yersinia*.

Bone marrow aspiration for histologic or microbiologic evaluation should not be part of the initial baseline investigation unless there is an indication from the history, physical examination, or blood count and peripheral blood smear. Lumbar puncture for cerebrospinal fluid examination is indicated when the clinical picture suggests central nervous system disease.

A tuberculin test should be done on all patients. A positive test can help in the diagnosis, but a negative test does not rule out tuberculosis. Tests for HIV infection are an important part of the baseline investigation of FUO, particularly when there is a prolonged history of fever and/or chronic ill health, if the patient has recurrent or unusual infections, or in the presence of risk factors for HIV.

Radiologic studies should not be done routinely for every patient with FUO. Chest radiographs should be obtained only if there are signs of pulmonary disease. However, some authorities advocate a chest radiograph as part of the routine screening procedures for the child with FUO. Other radiologic studies, such as computerized tomography (CT), magnetic resonance imaging, isotope bone scans, or gallium scanning, also should not be done routinely, particularly cranial CT, which is the least helpful in the absence of clinical signs. They may be indicated when focal lesions are suspected.

When the initial clinical evaluation and baseline laboratory investigations give no clue to the diagnosis, more detailed investigations are performed, including serologic tests for cytomegalovirus, EBV, viral hepatitis, *Brucella* titers, and *Leishmania* antibodies. Additional tests include antinuclear antibodies, rheumatoid factor, anti-double-stranded DNA antibodies, antistreptolysin O titer, slit-lamp examination of the eyes for the presence of uveitis, abdominal ultrasound, CT scan of the sinuses and mastoids, and an echocardiogram.

Unusual Causes of Fever of Unknown Origin

Pseudo-Fever of Unknown Origin

A significant number of children, initially thought to have FUO, have pseudo-fever (no documented fever or insignificant fever). Common features of pseudo-FUO include mild self-limited illnesses, lack of objective abnormal physical findings, discordance of fever and pulse rate, behavioral problems, parents with misconceptions concerning health and disease or families under stress, and normal ESR and platelets. The physician evaluating children for FUO should pay particular attention to excluding this group of children from those with true FUO.

Children with pseudo-FUO are recognized by the physician after a careful, timely history is obtained, interviewing the parents and sometimes the grandparents. These individuals may be overly concerned about the possibility of a serious disease such as malignancy, or may have had previous experience of a serious or life-threatening illness, or may be from disturbed families. The historical interview allows them to express their concerns about the child's condition. Details about the timing and degree of fever and how the temperature was measured, and the number of days missed from school due to subjective morning complaints, should be obtained. The clinical examination should reveal a healthy child with no significant illness. The physician should then attempt to relieve the parents', grandparents', or child's fears and concerns about illness and reassure them.

Munchausen Syndrome by Proxy

Munchausen syndrome by proxy is a form of child abuse in which a disease is inflicted on the child by one of the parents, usually the mother, or by a child guardian who has psychosocial disturbances. The child can present with several forms of complaint that may be recurrent or changing. One presentation of this syndrome is FUO, in which the parent falsely reports a rise in temperature at home or in the hospital, or immerses the thermometer in hot water or shakes it to obtain a high reading. The diagnosis can be very difficult and requires a high index of suspicion. A timely evaluation of the child in the hospital and documentation of absence of fever, measured by a nurse who should be attending during the period when temperature is checked, particularly at the time when the parent reports fever, as well as observation of the parent–child interaction, may help in establishing the diagnosis. A test that may also be helpful in such cases is concomitant measurement of urinary temperature on a specimen supposedly collected for urinalysis.

Drug Fever

Drug fever is found in 1.5% of children with FUO in reported series and can be caused by many drugs. The diagnosis is established by the disappearance of fever within 48 h or three to five half-lives from discontinuation of the drug and the reappearance of fever within hours when the drug is restarted. Five mechanisms have been described for drug fever. The most common mechanism is a hypersensitivity reaction in which the patient may have

rash, urticaria, or symptoms of serum sickness. This type of reaction can occur with any drug. Altered thermoregulatory mechanisms include those seen with thyroid hormone supplement, which raises body temperature by increasing heat production from the increased metabolic rate, or decreased heat loss due to impaired sweating caused by the anticholinergic activity of atropine, tricyclic antidepressants, and phenothiazines. Fever can occur in relation to administration of drugs that have intrinsic pyrogenic activity (e.g., amphotericin B and bleomycin). Fever also can be caused by the pharmacologic effect of the drug; examples include the febrile reaction seen when antibiotics are given to patients with syphilis or leptospirosis (the Jarisch–Herxheimer reaction) and idiosyncratic reactions such as malignant hyperthermia in susceptible patients when given an inhaled anesthetic such as halothane or isoflurane.

Prognosis

The outlook for children with FUO is better than that for adults. Studies on pediatric patients show that the risk for serious illness in children with FUO is around 40%, compared to approximately 70% in adults. Also, malignancy is less common in children than adults.

Most of the children with FUO have a self-limiting or treatable illness. The fever occasionally disappears during evaluation of the patient in the hospital. Some children continue to have fever without diagnosis. Most of these children appear well on long-term follow-up. One study followed 40 children with FUO and prolonged fever referred for rheumatologic evaluation. Most of them had complete recovery within 24–48 months, while eight had neurologic abnormalities on follow-up. Whether these abnormalities were complications of prolonged fever could not be determined by the study group. This finding raises the possibility of neurologic and possibly other complications of prolonged fever.

The mortality rate from FUO varies between different pediatric studies. In one study, 9 of 54 children with FUO died. In another study, 9% of children with FUO died. Other pediatric series had a much lower mortality from FUO. These figures demonstrate the seriousness of FUO and the need for meticulous evaluation to reach the diagnosis.

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66 Healthcare-Associated Infections in Pediatrics

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Introduction/Definitions

Formerly, infections associated with hospitalization were termed nosocomial infections but in recent years, the term healthcare-associated infections (HAI) has been considered a better term to indicate that the issues extend to physicians offices, home nursing, and any interactions with healthcare facilities. Thus, HAI are infections that patients acquire during the course of interacting with a healthcare setting. HAI are not infrequent complications of serious illnesses. HAI occurring in hospitals are defined as infections not present or incubating at the time of admission that develop during admission or less than one incubation period after discharge. Illness from HAI may be any degree from minor infections to life-threatening ones. In practice, infections with an onset 48 h or more after admission are assumed to be HAI unless the infection is clearly community-acquired and follow-up surveillance 1 or 2 weeks after discharge should be sufficient to detect infections that were not apparent during admission. Severely ill and immunocompromised patients have a greater risk of acquiring HAI, so this problem is greatest in intensive care units (ICUs), transplant centers, and oncology units. Studies have demonstrated that nosocomial infections are frequently associated with preventable risk factors. Adherence to recommended techniques for patient care will benefit all patients but have the greatest effect in units where the sickest patients are cared for.

Certain patients are at increased risk because of the severity and possible immunosuppressive nature of their illness, and their need for invasive monitoring and life-support equipment. Studies of HAI rates in Pediatrics have therefore been largely limited to neonatal intensive care units and critical care units that care for children beyond the neonatal period. The epidemiologic factors which are associated with high susceptibility to nosocomial infection have been studied in infants, children, and adults.

Epidemiology and Rate of Nosocomial Infections in Pediatrics

Rates of nosocomial infections in pediatrics. Several studies have established the expected rates of HAIs in children hospitalized in general care wards and have defined the most common types of HAIs, the organisms responsible, and the risk factors. Rates of HAIs have generally been defined as the number of HAIs divided by the number of patients at risk times 100. The denominator is usually the number of admissions or discharges in the unit studied. This rate is sometimes expressed as a percentage. Risk may also be calculated according to the rate of infection per day of hospitalization. This is usually expressed as number of HAIs or specific types of HAIs such as bloodstream infections (BSI), or infection associated with the presence of certain devices (e.g., urinary catheters, assisted ventilation) per 100, 1,000, or 10,000 patient-days or device-days.

The method of obtaining data to determine the rate of infection may vary from one institution to another. Research surveillance studies use defined methodology that needs to be uniform if multiple institutions combine their data. As shown in ❯ *Table 66.1* there are many resources that can be used to identify nosocomial infections. Clinical ward rounds by a trained surveyor generally yields the most information but other sources may add information not available at the bedside or the patient's chart. ❯ *Table 66.2* lists the relative sensitivity of various sources of data indicating that active surveillance on a continuous basis is the most accurate method and data obtained from either the microbiology laboratory or the pharmacy is considerably less sensitive. Relying on clinicians to report nosocomial infections to a central collection point (passive surveillance) is notoriously inaccurate and greatly underestimates the rate of infection. Total daily hospital bedside surveillance is usually impractical as there is often neither sufficient time nor personnel to carry it out. Therefore, intensive surveillance is often limited to the highest-risk units such as the intensive care

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Table 66.1
Sources of information for surveillance of nosocomial infections

Clinical ward rounds
Microbiology laboratory reports
Radiology reports
Pharmacy data
Admissions department
Medical records department
Operating room activity reports
Post discharge surveillance
Regional health resources

Table 66.2
Relative "sensitivity" of selected methods of surveillance for nosocomial infections[a]

"Ideal" continuous active surveillance	+++++
Total chart review	++++
Microbiology reports	++ to +++
Fever plus antibiotic use	+++
Fever	++
Antibiotic use	++
Physician self-report forms	+ to ++

[a]+, least sensitive; +++++, most sensitive

units, oncology units, and surveillance of surgical procedure outcomes.

Each hospital must have a source of information for the criteria of diagnosing nosocomial infections. In the United States, most collaborative studies use the definitions recommended by the Centers for Disease Control and used in the National Healthcare Safety Network (NHSN).

In the United States, it has been estimated that one-third of infections in hospitalized patients are nosocomial. Thus, nosocomial infections occur in two million patients per year, result in four million extra days of hospitalization with costs of 4.5 billion dollars.

One of the earliest reported studies having to do with rates and risk factors for nosocomial infections dealt with children. In the early 1960s, T.E. Roy and associates reported on an extensive survey of hospital infections at the hospital for sick children in Toronto, Ontario, Canada. They found a 6.5% overall rate of hospital-acquired infections. This figure is somewhat higher than the rate of 3.2% reported in a 1970 study from Children's Hospital Medical Center in Boston, in which there were twice as many surgical patients as medical patients. In both studies, the rates were substantially higher on those services that dealt with debilitated patients and certain types of surgical patients. In the Toronto study, the two surgical wards had rates of 10.55% and 24.64%; however, rates were lower than average when surgery was performed on "clean" sites (2.1%).

Clean surgical cases are those in which there is an incision through prepared normal skin and the operative field does not include infected tissue, abscess, or entry into normally unsterile areas such as the bowel, the upper respiratory tract, or the lower female genital tract. *Table 66.3* shows that in surgically related HAI, the type of surgery and the degree to which the surgical field is likely to be contaminated with microorganisms determines the risk of infection.

In the Boston study, higher than average HAI rates were found among debilitated patients (e.g., a rate of 21.4% in patients on the tumor therapy ward,) and surgical patients (neurosurgery patients, 18.5%), but they were lower than average on services whose patients enjoyed good general health and had short hospital stays such as dental, ophthalmology, and otolaryngology patients.

More recent studies by The Pediatric Prevention Network Study in the United States (Stover et al.) looked at HAI rates in 43 Children's hospitals. In 1998, the nosocomial infection rate was 8.9 nosocomial infections per 1,000 patient days in newborn ICUs (NICUs) and 13.9 nosocomial infections per 1,000 patient days in pediatric ICUs (PICUs). In that study in the NICU, the device-associated rates were reported by device-days by birthweight ($>$2,500, 1,501–2,500, 1,001–1,500, and $\leq$1,000 g), bloodstream infections 4.4, 4.7, 8.9 and 12.6 per 1,000 device-days, and ventilator-associated pneumonia 0.9, 1.1, 4.9 and 3.5 per 1,000 device-days, respectively. In the PICU, the median nosocomial infection rates were 6.5 for BSI, 3.7 for ventilator-associated pneumonia, and 5.4 for urinary tract infection all per 1,000 device-days.

In a report from the Centers for Disease Control and Prevention in the United States, the overall rate of nosocomial infections in all services was 3.37% in 1978 and on pediatric services, it was 1.2%. The sites of infection were more commonly the gastrointestinal (GI) tract and the respiratory tract in children than in adults. A study published in 1984 from the Children's Hospital of Buffalo was one of the very few to examine the rate of nosocomial infections in various units within a children's hospital.

Table 66.3
Surgical wound classification

Type of wound	Definition	Estimated rate of infection
Clean	Elective surgery with primary closure and no drains: No breaks in sterile technique nor entry into non-sterile organs	<5%
Clean-contaminated	The alimentary or respiratory tract is entered without significant spillage or mechanical drainage	~10%
Contaminated	Fresh trauma or operations with a major break in sterile technique, gross spillage from the GI, infected biliary, urinary tract, etc.	~20%
Dirty wound	Presence of organisms in ordinarily sterile tissue before the operation – "Clean" incision into a collection of pus – Traumatic wounds with devitalized tissue – Fecal contamination – Delayed surgical treatment of dirty contaminated wounds	~30% or greater

The rate of nosocomial infections was 4.1 nosocomial infections per 100 patients discharged. The rate in the intensive care nursery unit was 22.2 infections per 100 discharges and the rate in the pediatric intensive care unit was 11.0 infections per 100 discharges.

The most common sites of nosocomial infection in pediatric patients are bloodstream infections followed by surgical site infections, lower respiratory tract and urinary tract infections. In adults, the most common sites are urinary tract infections followed by surgical site infections, lower respiratory tract and bloodstream infections. For pediatric patients outside of the neonatal period, the most common organism causing nosocomial infections is *Staphylococcus aureus*, followed by *Escherichia coli*, coagulase negative staphylococci, and *Klebsiella* species. Nosocomial infections in neonates are most commonly caused by coagulase negative *staphylococci*, followed by *Staphylococcus aureus*, *E. coli*, group *B Streptococcus* and *Klebsiella* species.

Neonatal intensive care unit rates. The pediatric population in which HAI have been studied most extensively is the patients in the neonatal ICU (NICU). In an early report, Hemming and associates demonstrated a high rate of nosocomial infections (24.6%) at the University of Utah Medical Center, neonatal regional ICU for infants hospitalized for greater than 48 h. By comparison, the nosocomial infection rate for the entire hospital was 7.3%. It was 5.4% for the general pediatric ward and 0.6% for the well-baby nursery. In another study of nosocomial infection in a neonatal ICU from Boston, it was hypothesized that proper staffing, adequate working space around incubators, control of traffic flow, and the presence of convenient scrub areas would decrease the rate of nosocomial infections. This was confirmed in a prospective study when a new nursery was built with improvements in all of these areas. The nosocomial infection rate for serious infections fell from 5.2% to 0.9%. The rates in this study were lower than in others because the unit transferred out newborns who required surgery. In the Pediatric Prevention Network study, the overall nosocomial infection rate was 8.9 per 1,000 patient-days, the bloodstream infection rate in the NICU was a median of 8.6 per 1,000 central venous catheter-days, and the ventilator-associated pneumonia rate was a mean of 2.5 per 1,000 ventilator-days. For all categories, the infection rates were inversely proportional to the birthweight. In a more recent study by the Centers for Disease control, the rate for HAIs for NICUs was 16.2–17.6 per 100 patients or 5.2–5.9 cases per 1,000 patient-days.

Pediatric and adult intensive care units. In an early study of patients in an adult surgical ICU by Northey and associates reported a nosocomial infection rate of 23.4% in 1974. Upper respiratory and urinary tract infections were the most common. If one takes into consideration the published nosocomial infection rates in pediatric patients with the underlying predisposing illnesses, the rate is similar to patients in a pediatric ICU and the data for neonatal and adult ICUs; 15–20% is a good approximation of the expected rate in a pediatric ICU. In the Pediatric Prevention Network study, the overall PICU HAI rate was a median of 13.9 per 1,000 patient-days; the bloodstream infection rate was 8.5 per 1,000 central venous catheter days, and the ventilator-associated pneumonia rate was 3.7 per 1,000 ventilator-days. In the later CDC study, HAI rate was 12.2–14.9 per 100 patients, or 5.8–19.0 per 1,000 patient-days.

Risk of Nosocomial Infections

General Risk Factors

Prior colonization with healthcare-acquired microorganisms. Several classic studies have addressed the question of the risk factors associated with the development of HAI. Most of the earlier studies were in adult populations. Studies from the Denver Veterans Administration Hospital by Selden and associates attempted to quantify the factors associated with risk of infection from a strain of *Klebsiella pneumoniae*, which was the cause of a large cluster of nosocomial infections, primarily in ICU patients, and was resistant to multiple antibiotics. They found that asymptomatic gastrointestinal colonization frequently preceded manifest infection. In a prevalence study, it was shown that 18% of those who were GI carriers of the *Klebsiella* strain had an infection due to the organism during their admission, while only 3% of those who were not colonized were infected. In a separate prospective longitudinal study, those who became carriers of *Klebsiella* during hospitalization, but were culture-negative on admission, had a 48% incidence of nosocomial *Klebsiella* infection. Length of hospitalization was another major factor. The rate of colonization rose steeply after 3 days of hospitalization to a maximum prevalence of 66% for those who were hospitalized for longer than 30 days. The therapeutic interventions associated with acquisition of *Klebsiella* in the gastrointestinal tract were inhalation therapy, nasogastric suction, and antibiotic therapy. These factors probably account for the high rates of HAI in patients who have been in an ICU. These findings were validated in subsequent studies.

Colonization of the upper respiratory tract with hospital-acquired flora is also associated with the development of nosocomial infections. The prevalence of pharyngeal colonization with gram-negative bacilli was studied in Texas by Johanson and associates. Colonization rate was proportional to the estimated degree of illness: it was low (2%) in physiologically normal inpatients and nonhospitalized normal subjects; moderately ill patients had a 16% rate of colonization, and moribund patients had a rate of 57%. It was assumed that the sicker patients had defective clearance mechanisms and that they also had more contact with contaminated materials. Patients receiving antibiotics also had a higher prevalence of gram-negative bacilli in the pharynx. This is attributed to the suppression of normal flora by antibiotics, allowing new organisms to colonize mucosal surfaces. Although pharyngeal colonization does not mean that there is active infection, it frequently precedes invasion, especially in patients who aspirate or already have other respiratory infections.

Catheters. The use of intravascular catheters and intravenous (IV) infusions are frequently implicated in the development of HAI. Septicemia rates associated with IV cannulae have varied in studies from 0% to 8%. The care of the infusion set and the cannulation site are important variables. The degree of risk is related to the method of insertion, type of catheter, type of infusion, and, to a very large extent, duration of catheter placement. There have been extensive studies of colonization of the catheter insertion site in the skin but it is related only indirectly to the development of sepsis. Bloodstream invasion, local skin infection, thrombophlebitis, and a particularly virulent form of septic thrombophlebitis are associated with IV catheters in the critically ill. Numerous studies of risk factors for nosocomial infections in sick neonates have shown that catheters are a major risk factor for nosocomial bloodstream infections, possibly the most important single factor.

The factors predisposing to nosocomial urinary tract infection are related to instrumentation (including surgery) and indwelling urethral catheters. Rates are higher among females, the elderly, and the critically ill. Breaks in the closed system or improper care of the drainage bag predispose to bacteruria. To reduce the rate of nosocomial urinary tract infections, it is important to preserve a closed system, and to reduce the length of catheterization or the number of catheterizations as much as possible.

Exposure to antibiotics. Prior use of broad spectrum antibiotics appears to be an important risk factor for the development of nosocomial infections. Some recent studies have focused on the particular importance of the expanded-spectrum cephalosporins and have shown that prior exposure to these antibiotics is a risk for colonization with antibiotic-resistant nosocomial bacterial flora. Susceptibility to colonization with nosocomial flora increases the risk of HAI and is the main reason of controlling the rate of HAI by reducing unnecessary use of antibiotics.

The indigenous microbial flora present on the skin and mucus membranes play an important function in protecting from invasion by pathogens and may therefore be considered part of host defenses. Established colonization with numerous organisms of low virulence limits dominance of any one species, and minimizes acquisition of exogenous pathogenic organisms. The mechanisms by which indigenous flora afford protection include competition for the host nutrient sources (bacterial interference), and blocking of cell-surface receptors or mucus blanket adhesions by other bacteria (colonization resistance). Both normal flora as well as pathogens appear to attach

to human tissue by very specific binding between specialized surface elements of the microorganisms (pili, and other specific proteins and carbohydrates) and molecules on the skin and mucosal surfaces. There is some evidence that if normal flora microorganisms, principally nonpathogenic bacteria and fungi, are abundant, there are very few molecules on host surfaces for pathogens to attach to. However, the more numerous and well-established normal flora can be partially or totally eradicated by the use of antibiotics. Should normal flora be lacking, new flora will more easily attach to the exposed receptor molecules on these surfaces. If these new flora have pathogenic potential, such as the ability to invade, generate toxins, or resist antibiotics they may proliferate more quickly than the normal flora can regenerate. This is felt to be the major mechanism for the spread of antibiotic-resistant flora in the hospital because so many patients have a disturbance of their usual normal flora.

Specific Environmental Risk Factors

A number of general principles of risk for nosocomial infections have been discussed above. In addition, there have been large numbers of reports of increased risk of nosocomial infections associated with environmental contamination and the use of devices discussed below. In many cases, problems with these devices have been reduced through recognition of their potential to cause HAI.

Inhalation equipment. While it has been recognized for a long time that the use of inhalation equipment was associated with risk of nosocomial respiratory infection, the mechanism was unknown until the equipment itself was studied. Pierce and Associates reported on the relationship between contamination of reservoir nebulizers and the occurrence of nosocomial necrotizing pneumonia. Aerosols from this type of equipment may contain large numbers of gram-negative bacilli, which are blown from the contaminated reservoir fluid into the patient's respiratory tract. Decontamination of this equipment virtually eliminated nosocomial gram-negative necrotizing pneumonias. Outbreaks of gram-negative pneumonia have been reported to be due to contaminated nebulized medication. The use of room humidifiers in the hospital has also been linked to the aerosolization of bacteria and colonization of exposed patients.

Intravenous solutions and catheters. Infections associated with infected intravenous infusion sites and contaminated IV solutions have become a major source of concern for infection control physicians. All patients who require intravascular fluid therapy are at risk for infection from contaminated IV solutions, medication, and tubing. A tragic example of this risk was a large multistate outbreak of infection due to *Erwinia* and *Enterobacter* in the 1970s from a defect in the manufacturing of the infusion bottles, which was subsequently corrected. Many hospitals reported unexpected episodes of sepsis due to these species with rates of infection and death that were related to the seriousness of the underlying diseases of these patients, although occasionally otherwise healthy patients were infected. Held and Associates recently reported two cases of life-threatening sepsis due to *Burkholderia cepacia* in children with hemophilia. Both had indwelling central venous catheters that were flushed with a heparin-vancomycin solution. This solution was prepared by an out-of-state pharmacy and investigation traced the source of the bacteria to the flush solution. In the past decade, there have been numerous reports of solutions contaminated with this particular species.

Viral Infections

In pediatric practice, there is a great risk of nosocomial infection from viruses. Spread of viruses does not appear to be as clearly related to contaminated equipment, antibiotic use, or inanimate reservoirs as is found in bacterial infection. Viral infections are introduced by infected patients, healthcare workers, or parents, and then spread to patients via infected secretions or direct person-to-person spread. Almost any virus that is spread by respiratory or gastrointestinal tract secretions or excreta can cause HAI if routine care techniques are not enforced or if a particularly infectious virus disease goes undetected. Strict observance of special transmission-based precautions (Droplet, contact or both, see *Table 66.4*) plus respiratory etiquette (*Table 66.5*) are important in limiting spread in healthcare setting. Surveillance studies have indicated certain viruses discussed below to be of special concern for nosocomial infections in pediatrics.

Respiratory syncytial virus has been shown in several studies by Hall and colleagues to be a significant nosocomial pathogen in pediatric hospital units. Infection due to respiratory syncytial virus can cause significant disease in any infant and could be responsible for life-threatening decompensation in infants who are already in an unstable state. Infants with congenital cardiac disease and those with pulmonary disease such as bronchopulmonary dysplasia are at especial risk. Studies have shown that transmission by close contact is responsible for dissemination to noninfected individuals; aerosols traveling a

Table 66.4
Transmission-based precautions

Precaution category	Components	Typical organisms
Contact precautions	• Private room • Requires putting on gown and gloves before room entry • Remove gown and gloves before the leaving room • Perform hand hygiene immediately after removal of gown and gloves before touching anything • Dedicated equipment • Essential movement/transport only	• Vancomycin-resistant enterococcus (colonization or infection) • Methicillin-resistant staphylococcus (colonization or infection) • Resistant gram-negative rods • Clostridium difficile colitis • Zoster in a normal host • Respiratory syncytial virus • Parainfluenza virus • Rotavirus
Droplet precautions	• Private room • Masks if within 3 ft of patient • Essential movement/transport only • Mask on patient during transport	• Influenza • Invasive meningococcal disease • Pertussis • Mycoplasma pneumoniae
Airborne precautions	• Private room – door closed • Negative-pressure room • Masks – N95 or HEPA • Essential movement/transport only • N95 mask during transport	• Suspected or confirmed Tuberculosis • Varicella/chickenpox[a] • Disseminated zoster[a] • Zoster in an immunocompromised host[a] • Measles

[a]Requires contact precautions as well

Table 66.5
Components of universal respiratory etiquette (also known as respiratory hygiene/cough etiquette)

• Applies to all patients, persons accompanying patients, visitors

• Source control measures
  • Cover the mouth/nose when coughing
  • Give the patient a surgical mask to wear
  • Use tissues if surgical mask is not available to contain secretions

• Hand hygiene after contact with respiratory secretions
• Spatial separation of person with respiratory infections in common waiting areas

considerable distance are not a major factor. Appropriate handwashing as well as limiting of number of contacts should be emphasized as the major means of infection control. The use of masks and goggles has been shown to further reduce dissemination of respiratory syncytial virus but is not ordinarily employed due to expense, interference with care activities, and marginal effect.

Varicella (chickenpox) is often transmitted in pediatric hospitals via aerosol dissemination. This viral infection is a particular threat to immunocompromised patients who can develop a progressive fulminant form of the disease, which has a high mortality. Immunosuppressed patients who lack antibody to varicella virus must be separated from any patients with chickenpox to prevent exposure to aerosols of their respiratory secretions. Therefore, patients with varicella, those suspected of having varicella or nonimmune patients exposed to varicella 8–21 days after exposure (the shortest and longest possible incubation periods) must be isolated in negative-pressure rooms that do not exhaust back into the hospital. Screening hospital personnel for antibody to varicella virus can pinpoint those individuals who could become infected and, therefore, transmit chickenpox to patients at risk. With varicella vaccine now available, the safest policy for hospital personnel is either to vaccinate all individuals who lack a history of having had chicken pox or who are determined by testing to lack a protective level of antibodies to the virus.

Influenza. Ordinarily, influenza is spread by droplets and the major precaution in addition to standard precautions is wearing a simple surgical-type mask. In recent years, there has occasionally been a requirement for additional precautions including gown, and gloves as well as negative-pressure rooms because of fear of spread of particularly virulent infection. The pandemics of Severe Acute Respiratory Syndrome (SARS caused by coronavirus) and

H1N1 influenza outbreaks demonstrated such a tendency for spread that, in many locales, simple droplet precautions were deemed insufficient.

Diarrheal disease due to viruses has long been noted to cause considerable morbidity in children's hospitals but only in the past few years have these viruses been identifiable. Rotavirus, the most common viral diarrheal agent, has been extensively studied in children and an enzyme-linked immunoassay (ELISA) is available for rapid and specific identification of the agent in stool. In neonates and young infants, this assay is not helpful as it is often positive in asymptomatic patients. In addition, other viruses such as norovirus (formerly Norwalk agent), astrovirus, minirotavirus, and calicivirus have been identified in infantile gastroenteritis. Methods for identification of some of these viruses may not be available except in specialized centers.

Prevention and Control of Nosocomial Infections

Physicians should be familiar with current recommendations concerning the control of the factors most frequently associated with transmission of HAI. Discussion of all of these measures is beyond this chapter and the reader is referred to contemporary texts for a fuller discussion. The Centers for Disease Control and Prevention is actively involved in prevention of HAI and keeps the medical community informed about risk factors and control through the journal *Morbidity and Mortality Weekly Report* and their Web site at www.cdc.gov.

General measures. Routine culturing of the environment, preparation of equipment, isolation techniques, and disinfection should be under the control of the surveillance and control team. The guidelines for these operations will not be dealt with here. Physicians need to be familiar with the appropriate precautions necessary to prevent spread of infection from patients to hospital staff, visitors, and other patients. Recommendations are usually modified for the needs of a specific hospital and incorporated in an infection control manual, which may be in the form of a printed text or available through the institution's computer workstation. The recommendations may allow significant individualization for a particular patient's age, mental status, underlying disease, local epidemiology, and hospital resources.

Standard precautions (Table 66.6). Standard precautions combine the major features of previously recommended Universal Precautions and Body Substance Isolation (Table 66.6). They are based on the principle that all blood, body fluids, secretions, excretions (except sweat), nonintact skin, and mucous membranes may contain transmissible infectious agents. Standard precautions apply to all patients, regardless of suspected or confirmed infection status, in any setting in which healthcare is delivered. The components include hand hygiene (Table 66.7); use of gloves, gown, mask, eye protection, or face shield, depending on the anticipated exposure; and safe injection practices. Equipment or items in the patient environment likely to have been contaminated with infectious body fluids must be handled in a manner to prevent transmission of infectious agents. For some interactions (e.g., performing venipuncture), only gloves may be needed; during other interactions (e.g., intubation), use of gloves, gown, and face shield or mask and goggles is necessary.

Universal Respiratory Etiquette

Universal respiratory hygiene/cough etiquette has been added to the other elements of standard precautions. These elements were initially deemed necessary during the SARS-Coronavirus activity in emergency departments and other outpatient areas during the widespread SARS outbreaks in 2003. The strategy proposed has been termed respiratory hygiene/cough etiquette (Table 66.5). The strategy is targeted at patients and accompanying family members and friends with undiagnosed transmissible respiratory infections, and applies to any person with signs of illness including cough, congestion, rhinorrhea, or increased production of respiratory secretions when entering a healthcare facility such as an emergency department, outpatient clinic, or any waiting area.

The elements of respiratory hygiene/cough etiquette include (1) education of healthcare facility staff, patients, and visitors; (2) posted signs, in language(s) appropriate to the population served, with instructions to patients and accompanying family members or friends; (3) source control measures (e.g., covering the mouth/nose with a tissue when coughing and prompt disposal of used tissues, using surgical masks on the coughing person when tolerated and appropriate); (4) hand hygiene after contact with respiratory secretions; (5) spatial separation, ideally >3 ft, of persons with respiratory infections in common waiting areas when possible; and (6) covering sneezes and coughs and placing masks on coughing patients.

Special Precautions

Special precautions are care elements required to prevent transmission of infections and are employed in addition to standard precautions. Decisions about which precautions are

Table 66.6

Recommendations for application of standard precautions for the care of all patients in all healthcare settings applies to all body fluids except sweat[a]

Component	Recommendations[b]
Hand hygiene	After touching blood, body fluids, secretions, excretions, contaminated items; immediately after removing gloves; between patient contacts
Personal protective equipment (PPE)	
Gloves	For touching blood, body fluids, secretions, excretions, contaminated items; for touching mucous membranes and nonintact skin
Gown	During procedures and patient-care activities when contact of clothing/exposed skin with blood/body fluids, secretions, and excretions is anticipated
Mask, eye protection (goggles), face shield	During procedures and patient-care activities likely to generate splashes or sprays of blood, body fluids, secretions, especially suctioning, endotracheal intubation
Soiled patient-care equipment	Handle in a manner that prevents transfer of microorganisms to others and to the environment; wear gloves if visibly contaminated; perform hand hygiene
Environmental control	Develop procedures for routine care, cleaning, and disinfection of environmental surfaces, especially frequently touched surfaces in patient-care areas
Textiles and laundry	Handle in a manner that prevents transfer of microorganisms to others and to the environment
Needles and other sharps	Do not recap, bend, break, or hand-manipulate used needles; if recapping is required, use a one-handed scoop technique only; use safety features when available; place used sharps in puncture-resistant container
Patient resuscitation	Use mouthpiece, resuscitation bag, other ventilation devices to prevent contact with mouth and oral secretions

[a]Table adapted from http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf (Accessed July 28, 2010)
[b]Subsequent updates include wearing surgical masks for performing lumbar punctures for diagnosis or for injections and for application of universal respiratory etuquette

to be employed in specific situation require categorization of diseases by how they are transmitted. The term *transmission-based precautions* is used to indicate that infectious diseases are categorized by whether they are spread by droplets, aerosols, or direct contact. The appropriate special precautions for hospitalized patients are determined by the mode of transmission of each suspected or proven infection.

Hand hygiene (Table 66.7). The term "hand hygiene" has replaced "handwashing" to emphasize the importance of alcohol gel hand rubs that can be used in place of soap and running water for most situations calling for cleansing of the hands in routine medical practice. Infection control experts consider hand hygiene to be the single most effective and certainly least expensive practice to prevent transmission of pathogens and prevention of HAI. Nevertheless, one recent review documents that even this simple directive has been insufficiently adhered to by medical personnel. In a review of 12 published studies, compliance with recommended hand hygiene was under 50% even in intensive care units. Proper handwashing methodology is summarized in Table 66.7. For handwashing, other than presurgical scrubs, hands should be vigorously lathered and rubbed together for at least 15 s with soap and warm running water. Hands should be rinsed and dried with a paper towel and the towel used to turn off the faucet. Gloves should be worn when touching blood or other body fluids and mucous membranes, to reduce the likelihood of transmitting organisms to patients during invasive procedures, and to prevent transmission of pathogens from an infected patient to another patient. Wearing gloves does not replace the need for handwashing. Adherence to handwashing recommendations is important as contamination of skin due to punctures or defects in a glove is possible. With the widespread use of alcohol-based hand rubs, there is evidence of improvement in hand hygiene compliance among healthcare personnel at many healthcare centers.

Intravenous Therapy

Intravenous devices are associated with a large proportion of HAI. Proper insertion and use of these devices is

Table 66.7
Hand hygiene

When	Before and after every patient contact
	Before and after putting on gloves (sterile or non-sterile)
	Before doing invasive procedures
	After use of bathroom facilities
	Between contaminated body sites
	Before eating or drinking
	After contact with laboratory specimens
	Whenever hands are contaminated
With what	*Soap and water hand hygiene* • Turn on faucet • Apply soap to all surfaces of hands • Rub hands together for 15 s • Make sure to cover thumbs, areas in between fingers, under nails • Rinse thoroughly • Pat dry with clean paper or cloth towel instead of rubbing • Use towel to turn off faucet

	Alcohol-based hand rub hygiene[a]
	• Push dispenser once
	• Coat all surfaces of your hands including
	  • Between fingers
	  • Under fingernails
	  • Back of hands and wrists
	• Rub hands together briskly, until dry
	• No rinsing needed

[a]Soap and water hand hygiene should be employed when hands are grossly contaminated or visibly dirty or when in contact with patients colonized or infected with Clostridium difficile or items contaminated by such patients. Alcohol-based hand rubs are not effective when there is visible dirt on the hands and are not optimally effective in decontamination of spores.

recommended as a method of reducing risk of infection. Because central catheters remain in place for an extended period of time, they have been especially concerning as a source of nosocomial bloodstream infections (central line–associated bloodstream infection – CLABSI). In the United States, it has been estimated that there are 9.7 million central catheter-days in ICUs (54% of ICU days). There have been an estimated 48,600 patients in the ICUs who have a CLABSI (5 BSI/1,000 catheter days) and of major concern, there have been 17,000 deaths attributable to CLABSIs in the ICU. Although the catheter utilization rate is lower outside of the ICU setting, as many or more CLABSIs occur outside the ICU setting.

Certain factors have been shown to increase the risk of catheter-related infections. In adults, the duration of catheterization is >3–4 days adds additional risk of infection but in children duration has not been demonstrated to be associated with extra risk. Other factors increasing risk of infection are increased diameter and number of ports on catheter, location (risk greater for femoral, less for internal jugular, and less for subclavian), and type of catheter (tunneled catheters have a lower risk than non-tunneled catheters). Antimicrobial/Antiseptic coated catheters may have a lower risk than non-coated catheters. Additional risk factors include thrombosis at the site of a central catheter, infusion with TPN or other lipid-rich infusate, and impaired skin integrity such as with burns, and dermatitis.

Recently recommendations for intravenous therapy have been revised and expanded. While it is beyond the scope of this chapter to discuss the use of each type of intravascular device available, among the recommendations for prevention of IV catheter-associated infections are the following general suggestions from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines. Additional recommendations can be found in the referenced articles and detailed information regarding diagnosis and management of intravascular catheter-related infections are contained in a practice guideline of the Infectious Diseases Society of America.

- Intravenous cannulae should be inserted only when clearly indicated. In general, "keep open" intravenous infusion should be discouraged if it is for the convenience of the medical staff. Remove any device as soon as its use is no longer indicated.
- Educate healthcare workers regarding the indications for intravascular catheter use, proper procedures for the insertion and maintenance of intravascular catheters, and appropriate infection control measures to prevent intravascular catheter-related infections.
- Use a catheter checklist to ensure adherence to infection prevention practices at the time of central catheter insertion and for dressing changes.
- Assess knowledge of and adherence to guidelines periodically for all persons who insert and manage intravascular catheters.
- Monitor the catheter sites visually or by palpation through the intact dressing on a regular basis, depending on the clinical situation of individual patients. If patients have tenderness at the insertion site, fever without obvious source, or other manifestations suggesting local or BSI, the dressing should be removed to allow thorough examination of the site.
- Record the operator, date, and time of catheter insertion and removal, and dressing changes on a standardized form.

- Observe proper hand hygiene procedures either by washing hands with conventional antiseptic-containing soap and water or with waterless alcohol-based gels or foams. Observe hand hygiene before and after palpating catheter insertion sites, as well as before and after inserting, replacing, accessing, repairing, or dressing an intravascular catheter. Palpation of the insertion site should not be performed after the application of antiseptic, unless aseptic technique is maintained.
- Maintain aseptic technique for the insertion and care of intravascular catheters.
- Wear clean or sterile gloves when inserting an intravascular catheter as required by the Occupational Safety and Health Administration Bloodborne Pathogens Standard.
- Sterile gloves should be worn for the insertion of arterial and central catheters.
- Wear clean or sterile gloves when changing the dressing on intravascular catheters.

Catheter Site Care

- Disinfect clean skin with an appropriate antiseptic before catheter insertion and during dressing changes. Although a 2% chlorhexidine-based preparation is preferred, tincture of iodine, an iodophor, or 70% alcohol can be used.
- No recommendation can be made for the use of chlorhexidine in infants aged <2 months.
- Do not submerge the catheter under water. Showering should be permitted if precautions can be taken to reduce the likelihood of introducing organisms into the catheter (e.g., if the catheter and connecting device are protected with an impermeable cover during the shower).
- Use aseptic technique including the use of a cap, mask, sterile gown, sterile gloves, and a large sterile sheet for the insertion of central catheters or for guidewire exchange.
- Do not routinely replace CVCs, PICCs, hemodialysis catheters, or pulmonary artery catheters to prevent catheter-related infections.
- Do not use guidewire exchanges routinely for non-tunneled catheters to prevent infection.
- For catheter-site dressing changes, use either sterile gauze or sterile, transparent, semipermeable dressing to cover the catheter site.
- Replace catheter-site dressing if the dressing becomes damp, loosened, or visibly soiled.
- Change dressings at least weekly for adult and adolescent patients depending on the circumstances of the individual patient.
- Do not use topical antibiotic ointment or creams on insertion sites (except when using dialysis catheters) because of their potential to promote fungal infections and antimicrobial resistance.

Recommendations for Umbilical Catheters

1. Remove and do not replace umbilical artery catheters if any signs of CLABSI, vascular insufficiency, or thrombosis are present.
2. Remove and do not replace umbilical venous catheters if any signs of CLABSI or thrombosis are present.
3. Replace umbilical venous catheters only if the catheter malfunctions.
   (a) Cleanse the umbilical insertion site with an antiseptic before catheter insertion. Avoid tincture of iodine because of the potential effect on the neonatal thyroid. Other iodine-containing products (e.g., povidone-iodine) can be used.
   (b) Do not use topical antibiotic ointment or creams on umbilical catheter insertion sites because of the potential to promote fungal infections and antimicrobial resistance.
   (c) Add low doses of heparin (0.25–1.0 U/mL) to the fluid infused through umbilical arterial catheters.
4. Remove umbilical catheters as soon as possible when no longer needed or when any sign of vascular insufficiency to the lower extremities is observed. Optimally, umbilical artery catheters should not be left in place >5 days.
5. Umbilical venous catheters should be removed as soon as possible when no longer needed but can be used up to 14 days if managed aseptically.

A milestone in improving the safety of catheter-related bloodstream infections in the ICU was achieved by Pronovost and associates who virtually eliminated central line–related infections by following the above recommendations as a "bundle" in a study of 103 ICUs.

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67 Infection Associated with Medical Devices

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Healthcare-associated infections (HAIs) occur worldwide and affect both developed and resource-poor countries. Infections acquired in healthcare settings are major causes of death and morbidity among hospitalized patients. They are a significant burden both for patient and for public health. The World Health Organization conducted a study in 55 hospitals of 14 countries representing four WHO Regions (Europe, Eastern Mediterranean, Southeast Asia, and Western Pacific). This prevalence study found that on average 8.7% of hospital patients had HAIs; data from the United States of America (USA) reveal a similar prevalence. Based on these figures, at any given time, over 1.4 million people worldwide suffer from infectious complications acquired while in the hospital. In December of 2010, the *Lancet* published a review of available scientific data on HAIs in countries with limited resources. In developing countries, the number of HAIs is 15.5 per 100 patients; this is in sharp contrast with the 8–10 per 100 patients reported in the USA and Europe. This review demonstrated for the first time the magnitude of HAIs as a major patient safety problem in the developing world.

The WHO and the Centers for Disease Control (CDC) define a HAI, formerly called a nosocomial infection, as "a localized or systemic condition that results from an adverse reaction to the presence of an infectious agent (s) or its toxin(s)." There must be no evidence that the infection was present or incubating at the time of admission to the acute care setting. Infections acquired in the hospital but appearing after discharge are also considered HAIs. HAIs may be caused by infectious agents from endogenous or exogenous sources. Endogenous sources are body sites, such as the skin, nose, mouth, gastrointestinal tract, or vagina that are normally inhabited by microorganisms. Exogenous sources are those external to the patient, such as patient care personnel, visitors, patient care equipment, medical devices, or the healthcare environment. Medicine has become more complex with new invasive technologies creating potential routes of infection. Further, aggressive and irresponsible use of antibiotics has created a cadre of drug-resistant bacteria. HAIs have become more prevalent. Nowhere is this more notable than in the intensive care unit (ICU). The frequency of infections associated with the use of invasive devices (central vascular lines, ventilators and urinary catheters) is exponentially higher in the ICU. This chapter will explore HAIs acquired due to commonly used medical devices.

Catheter-Associated Bloodstream Infections

Central venous catheters (CVCs) are used extensively worldwide for the delivery of vasoactive and/or high-osmolarity medications, monitoring of intravascular status, and removal of blood for laboratory evaluation. More than five million patients in the USA received central venous access in 2007. As central venous catheters have become more common, so have the many complications that are associated with them. The most common complications are infectious and thrombotic, both of which are associated with increased length of intensive care unit (ICU) and hospital stay, increased medical costs, and increased morbidity and mortality. The most common adverse result of CVC use in the ICU is catheter-associated bloodstream infection (CA-BSI). In the USA, CA-BSIs have been reported to occur in 3–8% of placed CVCs. Mortality from CA-BSIs has been quoted as high as 30%, depending on the severity of the patient's underlying illness. CA-BSIs can be difficult to treat and increase hospital length of stay by an average of 2 weeks. Mermel's study from 2001 estimated that the annual cost of managing CA-BSIs in the USA could be as high as $2.3 billion.

There are two different types of CVCs: those placed percutaneously and those placed surgically. Percutaneous CVCs come in two forms: (1) temporary, CVCs, which are placed centrally into the subclavian, jugular, or femoral veins via direct access of the vein; (2) percutaneously inserted central venous catheters (PICCs), which are entered in a peripheral vein and threaded to a central location.

Tunneled catheters and totally implantable venous access devices represent two different types of surgically

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implanted CVCs. Totally implantable venous access devices, often called portacaths, are fully enclosed beneath the skin. They are accessed via an infusion port that is connected to a catheter that enters a central vein. This type of access device is frequently used in hematology/oncology patients. There are lower size limits for portacath use; so, typically these are found in school-aged children and up. They have a lower infection risk than tunneled CVCs, as they are completely enclosed by skin when deaccessed. Tunneled catheters are surgically implanted CVCs in which the distal end of the catheter exits the skin. Catheters may contain a Dacron cuff, located just before the exit site, which keeps the CVC from migrating. These devices are used in patients who require very long-term central venous access, i.e., for chemotherapy or hemodialysis. Rates of infection associated with this type of catheter are lower than those for percutaneously placed CVCs.

A myriad of risk factors for CA-BSIs have been defined. Several studies have identified weight under 8 kg, duration of catheter placement, severity of underlying disease, changing the CVC over a guide wire, and obstruction with thrombus as risk factors. Cardiac failure and cancer are two disease processes that carry a high risk for CA-BSI. An increased number of catheter lumens may also increase the risk of infection. In the adult population, the location of the CVC is directly associated with increased risk of infection. The subclavian or jugular is preferred over the femoral vein. The higher levels of skin flora in the femoral region make infection more common in those CVCs in adults. This assertion has not been borne out in pediatric studies.

There is controversy about whether or not catheter material is a risk factor for infection. Catheters are commonly made from one of three materials: polyvinyl chloride (PVC), silicone, or polyurethane. Many companies have stopped producing PVC catheters because of the risk that phthalates or other organic plasticizers might leach out during use. In 2002, the US Food and Drug Association expressed concerns regarding exposure to the PVC plasticizer DEHP (bis(2-ethylhexyl)phthalate). DEHP was widely found in many medical devices such as IV catheters and tubing, blood bags, and extracorporeal support tubing. Animals exposed to DEHP in the laboratory experienced a variety of adverse effects, to include testicular atrophy and liver dysfunction. The FDA recommended that exposure to DEHP be limited in infants and children, particularly in the developing male. Subsequently, given this public health concern, PVC is being utilized with far less frequency than other materials. Silicones are one of the most thoroughly tested and widely used groups of biomaterials; they are well known for their intrinsic biocompatibility and biodurability. They are soft and relatively nonthrombogenic. Polyurethane is being increasingly used for catheters. Compared with silicone catheters of the same French size, polyurethane catheters have a larger internal diameter, allowing increased flow rates. Polyurethane is also biocompatible and nonthrombogenic.

The greatest controversy amongst experts in this area is the duration of use of CVCs. There have been very few studies to adequately address this question. There is consensus that prolonged duration of central venous access is a consistent risk for CA-BSI. What is debated is what length of time "prolonged duration" represents. Many authors feel that, in the setting of proper management, CVCs can be safely left in place for up to 14 days before the risk of infection begins to increase dramatically. Early removal of CVCs has been the focus of several US national CA-BSI prevention strategies. Unfortunately, long-term CVC use is often unavoidable in many critically ill children.

Multiple studies have also demonstrated that total parenteral nutrition (TPN) is also a known risk factor for CA-BSI, as the intralipid component is at high risk for bacterial and fungal contaminations. Further, lack of enteral nutrition is thought to lead to changes in the mucosa of the gastrointestinal tract, leading to bacterial translocation. Early institution of even low volume, trophic feeds reduces the risk of CA-BSI. A recent study from 2010 also lists transfusion of blood products as a risk factor for bloodstream infections. The authors do note that this may be because patients receiving multiple blood product transfusions tend to be sicker and thus have a higher baseline risk for CA-BSI.

For many years, there has been research on the best way to either interrupt or slow down the bacterial colonization on the plastic surface of the CVC. Initial research focused on coating the extraluminal surface of the catheter with the goal of preventing bacteria from adhering. This provided some reduction in the occurrence of CA-BSI; however, newer technologic innovation has resulted in the ability to bind antibiotics to the inner lumen. Intraluminal colonization is also a major source of infection; this is particularly true in patients receiving complex infusion therapies, especially blood products and intralipids. Catheters coated with antimicrobial or antiseptic agents decrease microorganism adhesion and biofilm production. Biofilm provides an ideal surface for microbial adherence; hence, decreasing the formation of biofilm should decrease the risk of catheter-related infection. Commercially available CVCs are typically coated with either chlorhexidine/silver sulfadiazine or

minocycline/rifampin. These catheters release silver, antimicrobials, and/or disinfecting agents in an untargeted way to kill the bacteria in the ambient surroundings of the catheter. In 2010, a major biomedical supply company released a newly developed plastic surface which kills bacteria on contact. This represents a novel and very promising approach to effectively tackle the problem of catheter-associated infection. Both of these types of CVCs are more expensive than traditional CVCs which may limit their use in some institutions. However, given the cost of managing a CA-BSI, the acquisition and use of antibiotic-coated CVCs may prove to be significantly less costly. There are an increasing number of studies that suggest that antimicrobial catheters may provide a decrease in infection in patients with a short-term need for CVCs.

Coagulase-negative staphylococci are the most common microorganisms associated with CA-BSIs. Other microorganisms commonly involved include *Staphylococcus aureus*, *Candida* species, *Enterococci*, and gram-negative bacilli.

Fever is the most frequent clinical and the most sensitive manifestation of a CA-BSI. Hemodynamic instability, respiratory decompensation, and altered mental status may also be manifestation of a CA-BSI. Inflammation and purulence at the insertion site are relatively uncommon but are generally fairly specific indicators of infection. CVC dysfunction (i.e., difficulty flushing or failure to draw) may be an indicator of distal thrombus, which has been shown to be associated with CA-BSI. Suppurative thrombophlebitis, endocarditis, osteomyelitis, and sepsis are all potential complication of a CA-BSI.

Given any of the previously detailed clinical findings, pursuit of laboratory confirmation of infection should be undertaken. The Centers for Disease Control in the USA gives strict criteria for determining a CA-BSI; the World Health Organization criteria are essentially identical. A CA-BSI must meet at least one of the following criteria:

1. Have a recognized pathogen cultured from one or more blood cultures
2. At least one of the following signs or symptoms: fever (>38.8°C), chills, or hypotension and signs and symptoms of bacteremia or sepsis
3. If the patient is an infant of less than 1 year of age, she must have at least one of the following signs or symptoms: fever (>38.8°C, rectal), hypothermia (>37.8°C, rectal), hypotension, apnea, or bradycardia

Common skin flora (i.e., coagulase-negative staphylococci, viridans group streptococci) must be cultured from two or more blood cultures drawn on separate occasions. This means that blood from at least two blood draws was collected within 2 days of each other and both cultures are growing the same common organism. Classifying a CA-BSI requires that the organism that is cultured from the blood cannot be related to an infection at another site. That is to say that a patient who has surgical site infection with *Klebsiella* and subsequently a blood culture that is positive for the same organism does not have a CA-BSI. The CDC recommends that blood cultures be drawn from the CVC and from a peripheral vein prior to initiation of antibiotic therapy. Interestingly, there is little evidence to support obtaining blood cultures from each lumen of multilumen CVC.

Treatment of CA-BSIs has two main components: antimicrobial therapy and catheter management. The former involves the early selection of broad empiric antimicrobials with subsequent narrowing of coverage once organism and sensitivity data are available. The second component involves decision making about whether the catheter should be removed, exchanged, or if it can be salvaged with therapy. As with all HAIs, the authors recommend consultation with the Infectious Diseases Service for assistance with antibiotic selection and duration of therapy.

The initial choices for empiric CA-BSI therapy are determined by suspected causative organism, the patient's underlying risk factors, and severity of illness. As a rule of thumb, empiric therapy should consist of an antimicrobial for treatment of coagulase-negative staphylococci (the most common causative organism) and one for treatment of gram-negative organisms. Vancomycin remains a common choice for coverage of coagulase-negative staphylococci where methicillin resistance is high. Patients who are neutropenic in the setting of their CA-BSI must have empiric antibiotic therapy that covers gram-negative bacilli (particularly Pseudomonas). A beta-lactam (i.e., piperacillin-tazobactam), a carbepenem (i.e., meropenem), or third or fourth generation cephalosporin (i.e., ceftazidime) are all appropriate empiric choices. The risk of infection with a multidrug resistant (MDR) organism must be considered when selecting empiric antibiotic therapy. Heretofore, amphotericin B and fluconazole have been the antifungal agents of choice for the treatment of candidemia. Amphotericin B has a sizeable side-effect profile. Fluconazole does not provide adequate coverage against *Candida glabrata* or *Candida kruzei*, both of which are increasingly common etiologies of fungemia. Azoles (i.e., voriconazole) and echinocandins (i.e., micafungin) are increasingly being used in the pediatric population with good success.

In general, duration of therapy is guided by the patient's clinical course; 10–14 days of therapy is the

current baseline. However, patients with persistent bacteremia (defined as a positive blood culture after >72 h of antibiotic therapy) may require weeks of antibiotics, especially if the CVC cannot be removed or replaced.

In general, the decision to remove a CVC in a pediatric patient is often fraught with difficulty. Our population has a much greater vascular access challenge than does the adult population. The risks and benefits of CVC removal for CA-BSI must be weighed on an individual basis. Many providers prefer to attempt to "treat through the line" instead of empirically removing it, given the greater challenge of vascular access in the pediatric population. However, there are occasions when CVC removal is warranted; the primary of these is fungemia. Treatment of fungemic CA-BSI without removing the CVC is rarely successful and carries a high mortality. Conversely, there are studies that report successful pediatric bacterial CA-BSI management without CVC removal. Very careful monitoring of patient status and the acquisition of blood cultures is required. The CVC should be promptly removed if there is evidence of clinical worsening or persistent positive blood cultures. Antibiotic lock therapy (ALT) may be warranted in patients with tunneled CVCs.

ALT works on the hypothesis that organisms living within the biofilm on the luminal surfaces of a CVC represent a reservoir for infection and are difficult to eradicate with systemic therapy alone. ALT is not sufficient as a sole therapeutic modality; it must be used in conjunction with systemic antibiotic treatment. It can be particularly useful in patients with tunneled CVCs and frequent CA-BSIs for whom CVC removal is not an option. ALT has been noted to be quite effective for intraluminal infections due to coagulase-negative staphylococci and gram-negative organisms. ALT has not been found to be effective for extraluminal infections. While there are case and anecdotal reports to the contrary, ALT has also not been a useful adjunct for management of infections due to *S. aureus*, *Pseudomonas aeruginosa*, MDR organisms, or *Candida*.

ALT consists of filling the CVC lumen(s) with a high-concentration antibiotic heparin or a 70% ethanol solution for hours or days at a time. Antibiotic concentrations needed to kill bacteria living within a biofilm are 100–1,000 higher than those needed to kill bacteria floating freely within the bloodstream. The choice of antibiotic lock solution will vary from institution to institution. However, the most common antibiotics are vancomycin, ceftazidime, and clindamycin. The antibiotic lock solution should be instilled into each lumen of the CVC for 8–12 h, once or twice per day. If a catheter has more than one lumen and both cannot be accessed simultaneously, then alternate lumens with each dose of the antibiotic lock solution. Some institutions report the use of 72 h dwell time for high-concentration vancomycin lock in hemodialysis catheters only. ALT should be continued for a minimum of 7–14 days or until resolution of bacteremia and clinical symptoms. The potential risks of fungal superinfection and emergence of antimicrobial resistance secondary to ALT have not been fully elucidated by current studies.

Prevention measures should address those areas of known risk for CVC infection. Type (temporary versus permanent), location, and duration of CVC placement are three risk factors that can be addressed through prevention strategies. Hospitals can also select the material from which a catheter is made with a goal to decrease CA-BSIs. The most important CA-BSI prevention measures are diligent hand hygiene and use of sterile technique with CVC insertion and dressing changes.

Strategies for prevention of CVC infections

Effective	Ineffective
Strict hand hygiene	Antimicrobial creams
Closed system for blood draws and medication administration	Antibiotic or antiseptic impregnated dressings
Limit duration	Changing CVC over a guide wire
Local skin preparation	Routine changing of CVC to different sites
Aseptic technique	Antibiotic prophylaxis
Removal if infection suspected	
Limiting entry to central lines	
Surgical asepsis for insertion	
Established frequency of dressing change	
Antibiotic-coated catheter for short-term use	

CVC insertion should be performed using sterile technique. This includes hand hygiene, sterile equipment setup, sterile gloves, long-sleeved surgical gown, a surgical cap and mask, and a full barrier sterile drape. All persons in the room should have on a surgical cap and mask, to include the patient if she is not intubated or on positive pressure ventilation. Prior to starting the insertion procedure, the site should be cleaned with antiseptic solution (i.e., chlorhexidine gluconate or povidone-iodine). Sterile technique should be maintained throughout CVC placement. The CVC insertion site should be dressed with a semiocclusive

sterile dressing. The use of antiseptic impregnated dressings remains controversial and has not shown a clear impact on reduction of BSIs.

An equally important part of the prevention process is CVC maintenance, both of the line and the insertion site. Well-recognized sources for CA-BSI are needleless connectors, catheter hubs, and injection ports that have become contaminated during patient care. Attempting to limit the number of times the CVC is accessed represents one way to address this problem. Another is to decrease contamination risk by vigorously cleaning access ports with an appropriate antiseptic, as well as accessing the port only with sterile equipment. The most common antiseptics used are chlorhexidine gluconate (CHG) and 70% isopropyl alcohol. The exact duration of cleaning remains up for debate; times found in the literature vary from 15 to 60 s, not counting the drying time. "Scrub the hub" campaigns have been used in many medical centers to educate bedside providers about methods to reduce the risk of infection. Daily CHG bathing has been shown to decrease colonization with MRSA and VRE; it is also thought to decrease the risk of CA-BSI.

Consistent, daily review of the need for continued central venous access is associated with a reduction in CA-BSI rates. This practice reminds providers to remove CVCs that are not longer necessary and posing a preventable infection risk.

In 2006, Pronovost et al. reported that the use of insertion and maintenance bundles for CVCs was directly associated with decreased infection rates. His group implemented bundles in 103 adult ICUs in the USA and found a reduction in CA-BSIs by up to 66% in some centers. These bundles were comprised of features that were known to reduce infection. These include use of sterile technique and a full field barrier during CVC placement, adherence to strict hand hygiene policies, limiting the number of times the CVC is accessed, and strict observance of the CDC line maintenance policy. Care bundles are a group of processes that have been created to ensure the delivery of quality health care. They represent a group of medical interventions that, when used conjunctively, improve clinical outcomes. Bundles can provide a link between evidence and its application at the bedside. A well-designed bundle also includes a metric for measuring the processes. An evaluation of CA-BSI reduction via the use of insertion and maintenance care bundles in PICUs was done by Jeffries et al. in 2009. This observational study of 26 freestanding children's hospitals found that implementation of care bundles, staff empowerment to implement best practices, and improved communication between members of the care team led to a significant decrease in BSIs.

Central venous catheter insertion and maintenance bundles (used with permission from Jeffries et al.)

Category	Insertion	Maintenance
Hand hygiene	Hand hygiene consistent with local guidelines and/or policies	Hand hygiene consistent with local guidelines and/or policies
Dressings	Apply transparent semipermeable dressing (use gauze only with bleeding and/or oozing)	Replace dressing if it becomes damp, loosened, or visibly soiled; apply transparent semipermeable dressing (use gauze only with bleeding and/or oozing)
Sterile barrier	Maximum sterile barrier (large sterile drape, sterile gloves, sterile gown, cap, and mask)	Aseptic gloves and sterile dressing
Sterile technique	Maintain sterile technique throughout	Use aseptic technique throughout
Skin preparation	Prepare skin with antiseptic/detergent CHG 2% except for patients with a contraindication	Prepare skin with antiseptic/detergent CHG 2% except for patients with a contraindication

Summary recommendations for the prevention of CVC infection:

1. Hand hygiene with every CVC contact.
2. Sterile technique during catheter insertion and care.
3. Disinfection of access ports with CHG or 70% alcohol before accessing. CHG requires longer scrub and dry times (30 s each) than does alcohol.
4. Remove any intravascular catheter that is no longer essential.
5. Healthcare worker education and training regarding the severity of CA-BSIs, proper CVC insertion and maintenance techniques, and prevention procedures.

Ventilator-Associated Pneumonia

Hospital-acquired pneumonia (HAP) is defined as pneumonia that occurs 48 h or more after admission and was

not developing at the time of admission. Ventilator-associated pneumonia (VAP) is a type of HAP that appears greater than 48 h after endotracheal intubation. Healthcare-associated pneumonia (HCAP) is defined as pneumonia that occurs in a nonhospitalized patient with extensive healthcare contact. It will not be discussed in this chapter. VAPs are the second most common HAI. Many physicians use the terms HAP and VAP interchangeably, as the vast majority of HAPs are VAPs. The most significant risk factor for HAP is mechanical ventilation. Intubation increases the risk of pneumonia 6- to 21-fold. VAP occurs in about 5% of mechanically ventilated patients and carries a 20% mortality rate.

Significant risk factors for developing VAP include:

- Chronic lung disease
- Reintubation and/or prolonged intubation
- Altered mental status or coma
- Neuromuscular blockade
- Immunodeficiencies
- Genetic syndromes, particularly those with associated neuromuscular weakness
- History of aspiration
- Cardiothoracic surgery
- H_2 blocker or proton pump inhibitor (PPI) therapy
- Transport out of the PICU
- Previous antibiotic exposure
- Hospitalization during the fall or winter season
- Mechanical ventilation for acute respiratory distress syndrome
- Frequent ventilator circuit changes

Tracheal intubation bypasses the protective mechanisms of the upper airway and allows bacteria to enter the lower respiratory tract, possibly leading to pneumonia. The pathogenesis of VAP is related to the bacterial load entering the lower respiratory tract and the relative virulence of those microorganisms. Microaspiration of oropharyngeal and gastric secretions is thought to be the primary manner in which the lungs are infected with organisms. Approximately, 45% of healthy adult subjects aspirate during sleep; this number increases in the severely ill. While there is not equivalent data in the pediatric populations, we do know that a reasonable number of healthy children have gastroesophageal reflux (GER) that is severe enough to require pharmacologic therapy. GER is often more severe in chronically ill and/or developmentally disabled children. It follows that these groups may also be at a greater risk of VAP in the setting of respiratory failure and need for mechanical ventilation. The stomach and upper gastrointestinal tract are relatively sterile secondary to the bactericidal activity of acidic gastric secretions. Gastric pH is increased due to severe illness, acid suppressing medications, and enteric feedings. A number of adult studies have demonstrated that gastric ulcer prophylaxis increases the risk of VAP.

Hospitalized patients often become colonized with microorganisms acquired from the hospital environment. There is data to support the assertion that over half of critically ill patients may be colonized with hospital flora within 72 h of admission. Tracheostomy or endotracheal tubes may become contaminated in the process of routine nursing care or via the contaminated hands of medical team members. Poor infection control processes can lead to cross-contamination of organisms between patients.

VAP can be caused by a wide variety of pathogens. Differences in host factors and in the local hospital flora also influence the patterns of pathogens seen. The vast majority of bacteria isolated from VAP patients are gram-negative aerobes, i.e., *Pseudomonas*, *Escherichia coli*, and *Klebsiella pneumoniae*. *S. aureus*, both methicillin resistant and sensitive, and *Streptococcus* species can be the causative agents of VAPs. Immunocompromised patients may develop VAPs secondary to fungi and viruses. A study comparing bronchioalveolar lavage (BAL) and protective brush specimens (PSB) in adults with VAP found that PSB are as effective in identifying infectious pathogens. Interestingly, this study also found very few instances of pneumonia caused by anaerobes.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a serious pathogen that has become endemic in some areas. In many ICUs, patients are screened on admission for MRSA colonization; MRSA pneumonia carries a higher mortality rate in the pediatric population. Infection with MDR organisms is a growing problem in many hospitals. Risk factors for acquiring an infection caused by a MDR organism include antibiotic use within the last 30 days, prolonged hospitalization, and high prevalence antibiotic resistance in the community and/or hospital. The definition of multidrug resistance in gram-negative organisms is not standard across infectious disease experts. The number of antibiotics to which an organism must be resistant varies from at least two up to at least eight, depending on the source used. Pan-resistance rates also exhibit local variability. However, the term defines organisms with diminished susceptibility to all of the antibiotics recommended for the empiric treatment of VAP. Broadly, these antibiotic categories might include carbapenems, beta-lactams, and cephalosporins (third and fourth generation).

A mechanically ventilated patient with, purulent tracheobronchial secretions in conjunction with a new or progressive pulmonary infiltrate on chest x-ray, should raise concerns about VAP and should be followed by the initiation of empiric antibiotic therapy. Additional signs of possible VAP include tachypnea, worsening pulmonary function, worsening hypoxemia, and/or increasing inspired oxygen need.

Establishing the diagnosis of VAP in mechanically ventilated pediatric patients can be quite challenging. In addition to the presence of clinical and radiologic findings that can be attributed to other causes, the diagnostic criteria for pediatric patients can be cumbersome and confusing. Unlike other HAIs, there is no laboratory standard for the diagnosis of VAP. No recommendations exist for invasive testing for children with VAPs. The CDC and WHO agree on the general requirements for diagnosing VAP; the CDC's criteria are a bit more specific, dividing criteria in to age-specific categories. The key criterion that must be met by all patients is having two or more serial chest radiographs with at least one of the following: a new or progressive, persistent infiltrate, consolidation or cavitation appearing greater than 48 h after initiation of mechanical ventilation. In infants less than 1 year old, pneumatoceles are also acceptable chest x-ray findings. Pediatric patients must also have at least three of the clinical criteria listed in the table below.

Clinical Criteria for VAPs

- Temperature instability with no other recognized cause (for children >1 year old or <12 years old, fever >38.4°C or hypothermia <36.5°C; for children ≥12 years old, fever >38.4°C)
- Leukopenia (<4,000 WBC/mm^3) or leukocytosis (≥15,000 WBC/mm^3) with a bandemia (≥10% of total WBCs)
- New onset of purulent sputum (≥25 neutrophils/hpf) or a change in character/volume of Respiratory derangement; apnea, tachypnea, increased work of breathing
- Change in auscultated lung exam: wheezing, rales, rhonchi
- Worsening gas exchange ($PaO_2/FiO_2 \leq 240$)
- Bradycardia (<100 beats/min) or tachycardia (>170 beats/min)

If there is laboratory data available, then the patient need only have one of the aforementioned clinical criteria and one of the laboratory criteria listed below.

Laboratory Criteria for VAPs

At least one of the following:

- Positive blood culture not related to another source of infection.
- Positive pleural fluid culture.
- Positive quantitative culture from a BAL or PSB.
- On microscopic exam, ≥5% of BAL-obtained cells contain intracellular bacteria.
- Histopathologic exam with at least one of the following:
  - Abscess formation or foci of consolidation with polymorphonucleocyte accumulation in bronchioles and alveoli
  - Positive culture of lung parenchyma
  - Evidence of fungal hyphae or pseudohyphae

Empiric antimicrobial choice should be based on available gram stain or culture data, the presence of underlying disease processes, recent antibiotic therapy, and any risk factors for MDR organisms. These include prolonged hospitalization, recent antibiotic treatment, high frequency of antibiotic resistance in the hospital or community, and immunosuppressive disease and/or therapy. One should also take into consideration the local bacterial flora of the hospital and community. For critically ill patients and for those with risk factors for MDR organisms, broad-spectrum, multidrug therapy is recommended. Antimicrobial therapy should be narrowed as soon as the infecting organism and its susceptibility pattern have been identified.

In patients with no known risk factors for MDR pathogens, third generation cephalosporins (i.e., ceftriaxone) or beta-lactams (i.e., piperacillin-tazobactam) are acceptable empiric choices. For those with known risk factors for infection with an MDR organism, empiric two- or three-drug combination therapy is recommended. The therapeutic regimen should include either an antipseudomonal cephalosporin (i.e., ceftazidime) or an antipseudomonal carbapenem (i.e., meropenem), or a beta-lactam. An aminoglycoside such as gentamicin should represent the second class of antimicrobials. Finally, vancomycin should be added to the drug regimen if MRSA is a frequent nosocomial pathogen in the institution or in the community. Linezolid is another agent with excellent MRSA coverage; it may be particularly useful in patients with renal dysfunction. Resistance to linezolid is uncommon, as is treatment failure. These antimicrobials should be immediately discontinued if the culture is not positive for MRSA. Use of all three drug classes may be acceptable in a severely unstable ICU patient with VAP.

If patients have recently received antibiotics, empiric therapy should generally be with a drug from a different class since earlier treatment may have selected pathogens resistant to the initial class.

Colistin, polymyxin, or inhaled aminoglycosides (i.e., tobramycin) may be considered as potential additional antibiotics in patients with MDR gram-negative bacilli. Aerosolization may increase antibiotic concentrations at the site of infection. This method of antibiotic delivery is common in patients with cystic fibrosis.

There are many causes of pulmonary infiltrates and fever, which can be difficult to distinguish from VAP. Leukocytosis, purulent tracheobronchial secretions, or respiratory abnormalities can be associated with most of these causes.

The differential diagnosis of VAP includes the following:

- Acute respiratory distress syndrome
- Aspiration pneumonitis
- Atelectasis
- Infiltrative tumor
- Lung contusion (especially following a trauma)
- Pulmonary embolism
- Pulmonary hemorrhage
- Radiation pneumonitis

The mouths of ICU patients become colonized with aerobic pathogens due to an inability to maintain normal oral hygiene. Decontamination of the oropharynx with CHG and other antiseptics or antibiotics has been evaluated in numerous studies. A 2007 study in adults found that CHG oral care significantly reduced the incidence of VAP. However, within the last year, there was a report about CHG staining tooth enamel; per the report, this could be reversed by routine dental cleaning. CHG use remains contraindicated in the neonate due to concerns about systemic absorption.

The goal of selective decontamination of the digestive tract (SDD) is to prevent oropharyngeal and gastric colonization with aerobic gram-negative bacilli and *Candida* species and thereby prevent VAPs. The most commonly cited regimen includes a mixture of antibiotics that are applied topically to the oropharynx or administered through a nasogastric tube. SDD has not been studied in the pediatric population.

Aspiration of oral and/or gastric secretions is the primary route of bacterial entry into the lungs and is believed to be a primary factor in the development of VAP. Elevating the head of the bed 15–45° is thought to decrease the likelihood of aspiration by decreasing the risk of reflux of gastric contents.

Secretions and gastric microaspirate pool below the glottis, just on top of the endotracheal tube cuff. The continuous aspiration of subglottic secretions (CASS) has been shown, in adult studies, to decrease the incidence of VAP. There are special endotracheal tubes that allow for CASS via a suction port just above the cuff. These endotracheal tubes are considerably more expensive than traditional ones. Furthermore, they are not made for patients who require a tube size less than 6.0.

Several companies manufacture silver coated endotracheal tubes. These have been demonstrated to delay the onset of VAP. However, these tubes did not decrease length of stay (ICU or hospital), duration of ventilator days, or mortality. Again, these tubes are primarily manufactured for the adult population, given that they are infrequently made in pediatric sizes.

Several studies have noted an increased incidence of VAP when the gastric pH is increased with the use of H2 blockers, antacids, or proton pump inhibitors (PPIs). Sucralfate was found to have lower association with VAP when compared with H2 blockers and antacids. However, this is an infrequently used medication in the PICU.

Strategies to prevent ventilator-associated pneumonia

General strategies	Strategies to prevent aspiration	Strategies to reduce colonization of the gastrointestinal tract
Minimize the duration of ventilation	Elevate the head of the bed of intubated patients to between 15° and 45°, unless there are contraindications	Orotracheal intubation is preferable to nasotracheal intubation
Perform daily spontaneous breathing trials	Avoid gastric distention	Perform regular oral care with an antiseptic solution at least twice daily
Use weaning protocols	Minimize unplanned estuations and reintubations	Limit GI prophylaxis to patients who are at high risk for developing a stress ulcer or stress gastritis

Use noninvasive ventilation when possible	Use a cuffed endotracheal tube with inline or subglottic suctioning	Replace oral suction devices daily to minimize contamination
Adhere to infection control guidelines from the CDC and WHO	Maintain an endotracheal cuff pressure of at least 10 cm H_2O	Use sterile water to rinse reusable respiratory equipment
Conduct active surveillance for VAP		Remove condensate from ventilatory circuits before moving or turning patient
Educate healthcare personnel who care for patients undergoing ventilation about VAP		Change the ventilatory circuit only when visibly soiled or malfunctioning
		Store and disinfect respiratory therapy equipment properly

Catheter-Associated Urinary Tract Infections

Urinary tract infections account for over 40% of all HAIs. Eighty percent of these infections are associated with indwelling urinary catheters. While UTIs are associated with less morbidity than other HAIs, they should not be taken lightly. UTIs in the critically ill patient can lead to bacteremia, urosepsis, and death. The acquisition of urinary tract infections following urinary bladder catheterizations is associated with nearly a threefold increase in mortality among hospitalized adult patients. An estimate of the economic impact of CA-UTIs suggests that patients with HA-UTIs secondary to indwelling catheters spend an average of 2.4 additional days in the hospital.

Urinary catheters should be used only when necessary and left in place for as little time as medically feasible. They should not be used solely for the convenience of healthcare workers. The need for continued indwelling catheter use should be addressed daily on rounds by the medical team. Intermittent or "straight" urethral catheterization can be a useful alternative to indwelling catheterization, though this is not without infectious risks.

The WHO and the CDC have defined bacteriuria as the presence of $\geq 10^5$ colony forming units (cfu)/mL of bacteria from a urine culture with a maximum of two isolated species. Bacteriuria in patients with indwelling urinary catheters occurs at a rate of approximately 3–10% per day of catheterization. It can be further subdivided into asymptomatic or symptomatic. Asymptomatic bacteriuria occurs in the absence of fever $>38^\circ$C and suprapubic or costovertebral angle tenderness, with a urine culture of $\geq 10^5$ cfu/mL of bacteria. The clinical significance of asymptomatic bacteriuria in catheterized patients is unclear. Only about 20% of these patients go on to develop symptomatic UTIs.

Symptomatic bacteriuria (the traditional "UTI") is defined as urine culture with greater than 10^5 cfu/ml, presence of fever $>38^\circ$C, suprapubic or costovertebral angle tenderness, and/or otherwise unexplained systemic symptoms. Examples of these include worsening respiratory status, hypotension, presence of systemic inflammatory response syndrome, and altered mental status. A UTI is still present if the patient has a urine culture with $>10^3$ cfu/mL, in conjunction with pyuria, leukocyte esterase, or nitrite on urinalysis, and systemic symptoms. Of note, per CDC definitions, if a patient develops the aforementioned symptoms within 48 h of removal of a urinary catheter, she is still considered to have a CA-UTI.

Patients with indwelling catheters often do not develop the "classic" signs (abdominal and/or costovertebral angle pain, dysuria, or frequency) of a UTI. Hence, evaluation for UTI is warranted when a patient with an indwelling urinary catheter develops fever and unexplained systemic symptoms.

Female sex and diabetes mellitus are independent risk factors for both asymptomatic bacteriuria and UTIs. Other risks include prolonged catheterization and improper catheter and collection system management.

Similar to CA-BSIs, infection associated with urinary catheterization may be extraluminal or intraluminal. A biofilm forms along the outside of the catheter in the urethra, leading to entry of bacteria into the bladder. This is called extraluminal infection. Intraluminal infection is an ascending infection and is directly associated with bedside management of the catheter. Urinary stasis because of drainage failure and contamination of the collection system are the most common reasons for

intraluminal infection. Notably, with CA-UTIs, extraluminal is far more common than intraluminal infection.

The bacteria responsible for the majority of UTIs come from gastrointestinal tract flora. These bacteria can represent normal flora such as *Escherichia coli* and *Proteus* or hospital acquired such as multidrug resistant *Klebsiella*. *Candida* is a common colonizing organism of urinary catheters. These Candidal infections are frequently asymptomatic and do not commonly progress to candidemia.

Most studies suggest that antimicrobial prophylaxis is not useful for prevention of bacteriuria. Indeed, antibiotics are frequently ineffective in the treatment of bacteriuria in the asymptomatic catheterized patient. For symptomatic patients with fever or signs of sepsis, treatment of bacteriuria with appropriate systemic antibiotics, as well as removal or replacement of the urinary catheter, is warranted.

Empiric antibiotic treatment should be started in a clinically symptomatic patient with a suspected CA-UTI. Empiric therapy should, ideally, be based on local antibiograms, the urine Gram stain, and, if present, previous culture results. Gram-negative bacilli may be treated empirically with a third-generation cephalosporin (i.e., ceftriaxone) or a beta-lactam (i.e., pipercillin-tazobactam). Older children and teenagers may be treated with a fluoroquinolone (i.e., ciprofloxacin). Gram-positive cocci are less common pathogens. Typically, these represent enterococci or staphylococci. Again, pipercillin-tazobactam or another beta-lactam antibiotic would be an appropriate choice here. The addition of vancomycin may be appropriate if there is a high level of resistant gram-positive organisms in your geographic area. Antimicrobial choice should be narrowed as soon as culture and susceptibility results become available. There is controversy in the literature about the optimal duration of therapy. The prevailing opinion is that treatment for 10–14 days is generally appropriate. Another source of discussion is when to transition to enteral antibiotics. When the patient has had resolution of systemic symptoms, is able to tolerate enteral feedings, and has a negative urine culture, the medical team can consider a change to enteral antibiotics.

Only two interventions are consistently effective in preventing CA-UTI. They are avoiding urethral catheterization unless there is a compelling indication and prompt removal of unnecessary catheters. Given that it is not always possible to forgo urinary catheterization, other methods of prevention of UTIs must be investigated.

UTI Prevention Strategies

Effective prevention	Ineffective prevention
Limit duration of catheter use	Systemic antibiotic prophylaxis
Use sterile technique at insertion	Bladder irrigation with normal saline or antibiotic containing solution
Maintain closed drainage system	Antiseptic added to drainage bag
	Antimicrobial-coated catheter
	Daily antiseptic perineal cleaning

Handwashing with soap and water or an alcohol-based product should be done immediately before and after any manipulation of the catheter site or apparatus. To minimize the risk of infection, urinary catheters should be always placed using sterile technique and equipment. Sterile gloves, a perineal drape, sponges, an appropriate antiseptic solution for periurethral cleaning, and a single-use packet of lubricant jelly should be used for catheter placement. Use of the smallest catheter that allows good urinary drainage is associated with a decreased risk of infection. Indwelling catheters should be properly secured after insertion to prevent meatal injury and traction on the urethra.

A sterile, continuously closed collection system should be used with indwelling catheters. If the system is disconnected from the catheter without maintenance of sterile technique, it should be replaced. Ideally, the indwelling catheter and collecting system should not be disconnected. Irrigation should be avoided unless obstruction is a serious concern (i.e., in hemorrhagic cystitis associated with chemotherapy). There are newer catheter types that have ports through which closed irrigation may be done. Neither continuous nor intermittent irrigation of the bladder with antimicrobials has been shown to decrease CA-UTIs and should not be performed as a routine infection prevention measure. When irrigation is performed, aseptic technique should be pursued. The catheter-collecting system junction should be cleaned with chlorhexidine gluconate, a povidone iodine solution, or a 70% isopropyl alcohol solution before disconnection. A large-volume sterile syringe and sterile irrigant should be used. These supplies should be discarded after each irrigation event. If the catheter becomes chronically obstructed and requires frequent irrigation, it should be removed and replaced only if medically necessary. There is a strong

possibility that the catheter itself is contributing to the obstruction. Further, catheter concretions that lead to obstruction can harbor bacteria. Unobstructed flow of urine should be maintained at all times. The catheter and collecting tube should be neatly secured to the patient's thigh to prevent meatal trauma. The drainage bag should be below the level of the bladder and should be emptied regularly using a separate collecting container for each patient. Avoid contacting the draining spigot and nonsterile collecting container with each other.

At times a small volume of fresh urine is necessary for analysis and bacterial culture. Ideally, there is a sampling port through which a sample can be obtained using aseptic technique. If this is not available, the distal end of the catheter can be cleansed with a chlorhexidine gluconate, a povidone iodine solution, or a 70% isopropyl alcohol solution; subsequently, urine can then be aspirated with a sterile needle and syringe. Larger volumes of urine (i.e., a 24-h urine collection) can obtained from the drainage bag of the collecting system.

Daily cleansing of the urethral meatus with povidone-iodine solution, soap and water, or CHG impregnated wipes has not been shown to reduce CA-UTIs. In fact, there is evidence that frequent meatal cleaning can lead to mucosal irritation and breakdown that actually increases risk of infection.

Indwelling catheters should not be changed at arbitrary fixed intervals. Instead, there should be daily review of the need for continued indwelling catheterization.

Conclusion

Hospital-acquired infections add to the functional disability and emotional stress of the patient and, in some cases, lead to disabling conditions that reduce the quality of life. HAIs are also one of the leading causes of death for hospitalized patients. The economic costs of management are considerable. The increased length of stay for infected patients is the greatest contributor to cost. Prolonged stay not only increases direct costs to patients and payers but also indirect costs due to lost work and diminished productivity. The increased use of drugs, the need for isolation, and the use of additional laboratory and other diagnostic studies also contribute to costs.

The CDC has extensive guidelines for diagnosis, management, and reporting of HAIs in the USA. The majority of so-called developed nations have a similarly complex system for monitoring HAIs. However, in developing nations HAIs are a serious and undermanaged problem. The burden of HAIs is one of the key areas of work of the WHO First Global Patient Safety Challenge: Clean Care is Safer Care. The WHO recently released data that demonstrated that the number of HAIs in developing nations was twice as high as that of their high income counterparts. Inadequate infrastructure and equipment, poor hygiene and waste disposal, lack of basic infection control knowledge and methods of implementation, as well as a lack of medical and nursing practice guidelines and policies are among the key factors that increase the risk of HAIs. Implementing system-wide surveillance, training, education, using indwelling devices appropriately and following proper procedures, and ensuring optimal hand hygiene practices are some of the solutions that must be tailored to the reality of these settings. To be successful, these solutions ultimately require a change in healthcare workers' behavior. Surveillance is the key to the reduction of HAI, as it enables hospitals to understand the magnitude of the problem, what interventions are needed, and to assess their impact. While HAI surveillance systems exist in many developed countries, only 23 out of 147 developing countries, or 16%, report a functioning national surveillance system.

HAIs are caused by a wide variety of pathogens during the course of medical care treatment. These infections can be devastating and even deadly. As our ability to prevent HAIs grows, these infections are becoming increasingly unacceptable. Elimination of HAIs is of major importance for both developed and developing nations. Infection control, provider education programs, and continued surveillance lead to decreased HAIs and improve outcomes in medical care.

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68 Infections in the Immunocompromised Host

Ibrahim Bin-Hussain

Introduction

Infections are considered a major cause of morbidity and mortality in immunocompromised children. The survival rate in this particular population has increased over the last 3 decades. This is mainly due to the advancement in medical technology leading to improvement in diagnosis capabilities as well as supportive care including antimicrobial therapy.

Immunodeficiency can be divided into primary and secondary immunodeficiency disorders. Primary immunodeficiency disorders including combined T-cell and B-cell immunodeficiencies, antibody deficiency, disease of immune dysregulation, congenital defects of Phagocyte number or function or both, defects in innate immunity, autoimmunity disorders, complement deficiencies, and cytokine defects. Secondary immunodeficiency disorders include human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) – both of which lead to altered cellular immunity – dysgammaglobulinemia, defective phagocytic function or neutropenia. Cancer leading to neutropenia, lymphopenia, humoral deficiencies and altered physical integrity especially with the use of chemotherapeutic agents leading to disruption barrier integrity with mucositis leading to easy access of microorganisms, solid organ transplant leading to deficiencies in cellular and phagocytic immunity, malnutrition which leads to impaired immunity, and complement activity.

Fever is the main manifestation and occasionally the only sign of infection in immunocompromised children. When approaching a patient with immunodeficiency in the context of infection, one needs to look at the net state of immunosuppression. The net state of immunosuppression can be evaluated by the host defense defects caused by the primary disease, dose and duration of the immunosuppressive therapy (the longer duration of immunosuppressive therapy, the higher risk of infection), presence of neutropenia, and anatomical and functional integrity because defect in the skin or mucosa can lead to easy access for the microorganisms, metabolic factors, and infection with immunomodulating viruses (HIV, HBV, HCV, CMV, EBV, and HHV-6).

Risk of infections can be classified as high, intermediate, and low. High risk includes hematologic malignancies, AIDS, HSCT, splenectomized patient, and congenital immunodeficiency especially severe combined immune deficiency (SCID). Intermediate risk includes solid tumors, HIV/AIDS, and solid organ transplantation. Low-risk patients include patients with corticosteroid therapy, local defects, and diabetes.

Etiology

The pathogens in immunocompromised patients can be predicted based on the immune defect. For example, if there is an anatomical disruption in the oral cavity it lead to infections caused by alpha hemolytic streptococci, anaerobes, *Candida* species, and herpes simplex virus (HSV). Patients with urinary catheters will be at risk for infection caused by gram negative bacteria including *Pseudomonas* spp., enterococci, and possibly candida. If there is a skin defect including central venous catheter (CVC), the patient will be at risk of *Staphylococcus* species (both coagulase-negative *staphylococci* and *Staphylococcus aureus, Bacillus* species, atypical *Mycobacterium*, and Gram-negative organism. If a defect in the phagocytic function, either quantitative or qualitative, predispose what to invasive diseases like invasive pneumonia caused by bacterial pathogens: Gram-positive (staphylococci, streptococci, and *Nocardia* species) and Gram-negative bacilli (*Escherichia coli, Klebsiella pneumoniae, P. aeruginosa)*, other enterobacteriaceae, and fungal pathogens like *Candida* species and *Aspergillus* species.

Patients with defective cell-mediated immunity are at risk of infections caused by intracellular pathogens (i.e., viral, fungi, mycobacterial, and intracellular bacteria). Intracellular pathogens include *Legionella* species, *Salmonella* species, *Mycobacteria*, and *Listeria* species, *Histoplasma capsulatum*, *Coccidioides immitis*, *Cryptococcus neoformens*, *Candida* species, *Pneumocystis jiroveci*, cytomegalovirus, Varicella-zoster virus, Epstein-Barr virus, live viral vaccines (measles, mumps, rubella, and

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polio) and protozoal, *Toxoplasma gondii*, *Strongyloides stercoralis*, *Cryptosporidia*, *Microsporidia*, and *Isospora* species.

Patients with immunoglobulin deficiencyo are at risk of sinupulmonary infection caused by *S. pneumoniae, Haemophilus influenzae, and* CNS infection from viral infections, especially enterovirus, leading to chronic meningoencephalitis as well as gastrointestinal infection due to giardiasis. Patients with complement deficiency are at risk of diseases caused by *S. pneumoniae, H. influenzae, and Neisseria* species. Splenectomized patients are at risk of invasive diseases (e.g., sepsis, meningitis) caused by encapsulated organism including *S. pneumoniae*, *H. influenzae*, and *Neisseria meningitidis*.

In evaluating patients with immunodeficiency, one can predict the pathogen based on the primary immune defects, the organs involved, and the clinical presentation of the patient. For instance, *Staphylococcus aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Pseudomonas* and *aspergillous* infection should be considered for a chronic granulomatous diseased (CGD) patient with soft tissue infection, lymphadenitis, liver abscess, osteomyelitis, pneumonia, and sepsis.

Diagnosis

In centers dealing with immunocompromised patients, the microbiology laboratory as well as the radiology service need to be well equipped and trained in diagnosing these patients. Patients with fever should be worked up with complete blood count with differential, renal, and hepatic profile, blood culture from central line (if present), and peripheral culture. Chest X-rays are not done routinely unless the patients have respiratory symptoms. Other investigations need to be guided by the presentation of the patient. Patients with diarrhea should have stool checked for bacterial culture, ova and parasite, viral culture, rotavirus, and electron microscopy for viral studies, in addition to microspora, cryptosporidium, and isospora. In addition to chest X-ray, patients with respiratory symptoms required nasopharyngeal aspirate for rapid test for viruses and PCR multiplex – a newly developed laboratory procedure that can screen multiple viruses and other respiratory pathogens in the same setting. Patients with skin lesions should have skin biopsy from the lesion, which will be sent for culture (bacterial, fungal, and mycobacterium) in addition to histopathology for Gram-stain and special staining for fungal as well as acid fast stain (AFB stain).

Management

There are several objectives in managing infections in immunocompromised patients. The first and foremost objective is to assure patients' survival and prevent infectious morbidity. Decrease days of hospitalization and decrease exposure to multidrug resistance organism, decrease number of days of antibiotic use to minimize selection of resistance organism. Modification of antimicrobial therapy in immunocompromised patients is the rule rather than the exception. Timely modification of antibiotic therapy is very important to control breakthrough infection.

There are several questions to be addressed to choose the effective antimicrobial therapy when evaluating patients. In addition to history and physical examination, it is important to determine which arm/arms of the immune systems that is/are affected? what the clinical syndrome/site of infection is? (to predict what are the likely pathogens), what clinical specimen(s) should be obtained (empiric/definitive therapy)? and which antimicrobial agents have predictable activity against pathogens? With these in mind, one can predict pathogen and choose the right antimicrobial agents.

Patients with Wiskott–Aldrich syndrome are at risk of bacterial pneumonia as well as sepsis with Gram-positive organisms including MRSA. In this situation, medication should include agents active against Gram-negative pathogen plus anti-staphylococcus agents, for example, cefotaxime or ceftriaxone plus naficillin; if MRSA or penicillin resistant *S. pneumonia* is suspected, one can use vancomycin.

The pathogen in immunocompromised patients can be predicted by the system involved during the presentation. For example, the presentation and etiological agents in pneumonia in immunocompromised patients are different than immunocompetent persons. In evaluating pneumonia in immunocompromised patients, one needs to know that the pulmonary complication is present in up to 60% of immunocompromised patients and mortality is up to 80% of those who require mechanical ventilation. The initial evaluation needs rapid assessment of the vital signs including oxygen saturation, complete blood count with differential, renal profile, blood culture, and imaging of the lung either chest X-ray or CT scan. The organism can be predicted based on the primary immune defect. At certain point in the history, the defect in the immune system, the presence or absence of neutropenia, history of antimicrobial exposure, the presence of potential pulmonary pathogens in previous cultures, and the presence of indwelling catheters should be looked at.

The pattern and distribution of radiological abnormalities can predict the pathogen and the time and the rate of progression and time to resolution of pulmonary abnormalities.

For definitive diagnoses invasive procedures may be needed including bronchoalveolar lavage (BAL), transbronchial biopsy, needless biopsy, thorascopic biopsy, and open lung biopsy. In obtaining the biopsy from this patient, it is very important to send it for histopathology for special staining, for viruses, bacteria, fungi, pneumocystis, mycobacterial pathogen, and also culture for viral, fungal, bacterial, and mycobacterium.

Other laboratory tests that will help in diagnosing pneumonia are nasal washings or swabs for direct fluorescent antibody, PCR for respiratory viruses and atypical pneumonia, culture and staining, CMV antigenemia or CMV viral load testing, *Aspergillus* galactomannan assay, and 1,3 beta D glucan.

The radiological finding in immunocompromised patient can be focal (lobar or segmental infiltrate), diffuse interstitial infiltrate or nodular (with or without cavitation). Focal infiltrate can be due to Gram-positive or Gram-negative bacteria, *Legionella*, mycobacteria, and fungal infection. Also the noninfectious etiology includes infarction, radiation, and drug-related bronchiolitis obliterans organizing pneumonia (BOOP). Diffuse interstitial infiltrate is caused by viral infection, *Pneumocystis jiroveci*, less likely mycobacterium, disseminated fungal infection, atypical pneumonium including *Chlamydia*, *Legionella*, and *mycoplasma*. Other noninfectious etiology causing diffuse interstitial infiltrate include edema, acute respiratory distress syndrome (ARDS), and drug-related radiation. For nodular infiltrate with or without cavitation the infectious etiology include *Aspergillus* infection, and other mycoses, *Nocardia*, bacteria either Gram-positive or Gram-negative, anaerobes, and *Mycobacterium* TB, as well as noninfectious etiology including disease progression like metastasis and drug toxicity.

The management of immunocompromised patients with pulmonary infiltrate will depend on the patient presentation. If the patient is acutely ill, it is very important to begin empiric therapy to cover the likely pathogen based on the presentation of the patient and the primary immune defect with simultaneously comprehensive evaluation.

Subsequently, therapy should be adjusted based on culture and clinical response. In providing empirical antibiotic therapy in patient with pulmonary infiltrate and defect in cell-mediated immunity one need to consider *Pneumocystis jiroveci*, nocardia, legionella, mycoplasma, in addition to aerobic Gram-positive cocci and Gram-negative bacilli therefore it is advised to use trimethoprim-sulfamethoxazole, macrolides including erythromycin or clarithromycin and agent active against Gram-positive and Gram-negative; for example, third-generation cephalosporin with or without aminoglycoside with anti-Gram-positive either nafcillin or vancomycin based on the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) and penicillin resistant *Streptococcus pneumoniae*.

Infection in Cancer Patients with Fever and Neutropenia

The fever is defined in the context of febrile neutropenia as a single oral temperature of more than 38.3°C or more than 38.0°C for at least 1 h and is not related to the administration of pyrexial agents including blood, blood product, IVIG, and pyrogenic drugs, especially Ara C.

Neutropenia is defined as absolute neutrophil count (ANC) less than 500/mm^3 or less than 1,000/mm^3 with predictive decline to less 500/mm^3 48 h.

Risk Factor for Infection in Cancer Patients

The most important risk factor is the presence of neutropenia as well as the degree and duration of neutropenia. The lower the neutrophil count, the higher the risk of infection. The longer the duration of neutropenia, the higher the risk of infection. Usually, neutropenia is considered high risk if $\geq$ 7 days and low risk $<$ 7 days. Other risk factors include associated medical comorbidity, primary disease, and status (remission or relapse). Low-risk patients are clinically defined by neutropenia as anticipated lasting less than 7 days, clinically stable, and having no medical comorbid conditions.

Epidemiology

About 50% of neutropenic patients who become febrile have established or occult infections and about 25% of patients with ANC less than 100 cells/mm^3 have bacteremia.

The risk varies depending on the underlying disease, for example, patients post allogenic bone marrow transplantation are at higher risk than autologous bone marrow transplantation while AML has the higher risk than ALL. The lowest risk is in patients with cyclic neutropenia.

Evaluation

In evaluating a patient with fever and neutropenia, it is important to keep in mind that signs and symptoms can be muted or subtle. Profoundly neutropenic patients can sometime have life-threatening infections and yet be afebrile especially if they presented with abdominal pain. Careful and comprehensive physical examination is critical and should be repeated at least daily because these patients are dynamic and their condition can change rapidly.

Other important points in the history include the nature of chemotherapeutic agents, steroids, or other immunosuppressive agents because these can predict the degree of immunosuppression, the duration of neutropenia, and the severity of neutropenia. The history of antibiotic prophylaxis is also important because the antibiotic used as prophylaxis should be avoided in treating these patients. Reviewing the recent documented infection with susceptibility can help in determining the empiric therapy. For example, if the patient has a previous infection with multidrug resistance pathogen, empiric therapy can be used to cover these pathogens. If the patient had recent surgical procedure, this means there is break of the skin and is at risk for certain pathogens including Gram-positive cocci (coagulase negative *Staphylococci and Staphylococcus aureus*). Allergy history is an important factor in selecting empirical therapy as allergic medications need to be avoided.

Detailed and thorough physical examination is important with focus on certain sites that can be a portal of entry of pathogens including periodontium, pharynx, lower esophagus, lung, skin, perineum, bone marrow aspiration site, and catheter entry and exit sites.

After history and thorough physical examinations, blood culture from central and peripheral lines should done in order to identify the source of infection. For example, if the blood culture is positive from the central culture but negative from peripheral culture, the likely source is the central line. If both are positive, time is needed to positively determine the source of infection. Routine surveillance culture is not indicated as it is not cost effective and has low predictive value. Other cultures should be guided by the sites of infection. For example, a patient with respiratory symptoms needs to have nasapharyngeal aspirate for viral study, PCR multiplex, and atypical pneumonia. Patients with gastrointestinal symptoms, for example, with diarrhea, the stool needs to be sent for viral study, culture and sensitivity, ova and parasite. Chest X-ray should not be done routinely in all patients with fever and neutropenia because it has low yield in patients without respiratory symptoms. It is only done in children who have respiratory symptoms. If negative, a chest CT scan to be considered to better evaluate patient not responding to therapy.

Site of Infection

Most patients with fever and neutropenia have no identifiable site of infection and no positive culture results. Bloodstream infection is documented in about 20% of patients with fever and neutropenia. Disruption of the skin or soft tissue including vascular access or catheter insertion site can be a point of entry. In those centers, who are dealing with cancer patients, it is very important to monitor the infection rate and pathogen as well as the resistance pattern in the same center. The local data will help to select the appropriate empirical antimicrobial therapy (*Table 68.1*).

Management

There is no ideal regimen because there are variables which include the risk status of the patient, microflora and their sensitivity patterns, toxicity indication, preference, and the cost. Prompt initiation of broad-spectrum therapy when neutropenic patients became febrile is the key to successful management. In 1960 the mortality rate was up to 80% initially but with the introduction of empiric therapy against gram-negative organism the mortality rate now is close to 5%. There is no ideal regimen because this can be determined based on the isolate and its susceptibility in the same center as each center for example, one cannot extrapolate from different centers the likely pathogen, the same thing that a center can have a different pathogen and different susceptibility pattern in adult versus pediatric population with febrile neutropenia (*Table 68.2*).

Monotherapy Versus Combination Therapy

Monotherapy and combination therapy has equal efficacy. The monotherapy needs to have antipseudomonal activities including antipseudomonal penicillin with or without beta-lactamase inhibitor, carbapenem, and third- or fourth-generation antipseudomonal cephalosporins. The combination therapy includes antipseudomonal beta-lactam with Aminoglycoside. Both monotherapy and combination therapy have equal efficacy but it is important to look at the local data to be able to predict the empiric therapy either combination therapy or monotherapy.

Table 68.1
Common bacterial pathogens in neutropenic patients

Common Gram-positive pathogens
Coagulase-negative staphylococci
Staphylococcus aureus, including methicillin-resistant strains
Enterococcus species, including vancomycin-resistant strains
Viridans group streptococci
Streptococci pneumonia
Streptococcus pyogenes
Common Gram-negative pathogens
Escherichia coli
Klebsiella species
Enterobacter species
Pseudomonas aeruginosa
Citrobacter species
Acinetobacter species
Stenotrophomonas maltophilia

Table 68.2
Recommendation from Clinical Practice Guidelines for empirical initial therapy in neutropenic patients with fever

Guidelines	Monotherapy	Combination therapy
IDSA (Infectious Disease Society of America), Freifeld et al. CID 2011	High Risk:* Cefepime Imipenem-cilasiatin Meropenem Piperacillin-tazobactam	Low Risk:
NCCN (National Comprehensive Cancer Network) 2008	Ceftazidime Cefepime Imipenem-cilasiatin Meropenem	Aminoglycoside + antipseudomonal penicillin Aminoglycoside + extended spectrum cephalosporin Ciprofloxacin + antipseudomonal penicillin
IHQ (infectious Diseases Working Party of the German Society of Hematology and Oncology) Link et al. 2003	Piperacillin-tazobactam Ceftazidime Cefepime Imipenem-cilasiatin Meropenem	Aminoglycoside + acylaminopenicillin Aminoglycoside + third-or fourth-generation cephalosporin
SEQ (Chemotherapy Society of Spain), 2001	Cefepime Meropenem	Not recommended for routine use

*Other antimicrobials (aminoglycosides, fluoropuinolone, and/or vancomycin) may be added to initial regimen for complicated presentation or if resistance is suspected or proven

It is worth stressing that vancomycin should not be used routinely for empiric therapy in febrile neutropenia and there is a special indication for vancomycin. The vancomycin indication includes hemodynamic instability or other evidence of severe sepsis, pneumonia documented radiographically, positive blood culture for gram-positive bacteria before final identification and susceptibility testing is available, clinically suspected catheter-related infections (e.g., chills or rigors with infusion through catheter and cellulitis around the catheter entry/exit site), skin or soft-tissue infection at any site, colonization with methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus, or penicillin-resistant *Streptococcus pneumoniae*, and severe mucositis, if fluoroquinolone prophylaxis has been given and ceftazidime is employed as empirical therapy. If the patient started empirically on vancomycin the need for continuation of vancomycin should be re-assessed on daily basis. Overuse of vancomycin in more than 90%, and selection for resistant organism and emergence of vancomycin resistance enterococci.

The factors influencing antimicrobial selection include the types of bacterial isolates found in the institution, antibiotic susceptibility patterns, drug allergies, presence of organ dysfunction, chemotherapeutic regimen whether the patient was receiving prophylactic antibiotics, and condition of the patient at diagnosis, for example, presence of signs and symptoms at initial evaluation and presence of documented sites requiring additional therapy.

The center-specific factors include the patterns of resistance, effect on microbial ecology, high presence of vancomycin resistance enterococci (VRE), or extended spectrum beta-lactamase (ESBL) producing organism. The patient-specific factors including recent antibiotic use such as current prophylaxis as drug allergy, and the underlying organ dysfunction. The signs and symptoms present at the initial evaluation determine.

In the recent year more interest in the outpatient therapy for patient with fever and neutropenia. The advantages of ambulatory management of febrile patients with neutropenia especially those at low risk include lower cost particularly with oral outpatient therapy, fewer superinfections caused by multidrug-resistant nosocomial pathogens, improved quality of life for patient, greater

convenience for family or other caregivers, and more efficient utilization of valuable and expensive resources. The disadvantage includes the potential risk for developing serious complications such as septic shock at home, risk of noncompliance particularly with oral therapy, false sense of security or inadequate monitoring for response to therapy or toxicity, and the need to develop a team and infrastructure capable of treating substantial numbers of low-risk patients.

There are several requirements for successful outpatient treatment programs for patients with febrile neutropenia which include institutional infrastructure and support, a dedicated and experienced team of healthcare providers, availability of institution-specific epidemiological data and susceptibility and resistance data, microbiologically appropriate treatment regimen, frequent follow-up monitoring of outpatient, adequate transportation and communication capabilities, and access to management team 24 h a day, 7 days a week.

Modification of Therapy

There are certain clinical events or manifestations that require modifying the initial antimicrobial therapy; for example, if a patient has breakthrough bacteremia and if Gram-positive is isolated (add vancomycin especially if there is a risk of MRSA or pneumococcal resistance penicillin). If Gram-negative organism is isolated consider resistant Gram-negative and can change the regimen or broaden the coverage (carbapenems if the data in the center showed that the carbapenems has better sensitivity than cephalosporin or beta-lactam antibiotic). If the patient has catheter-associated soft tissue infection, vancomycin should be added. Patients with severe oral mucositis or necrotizing gingivitis are at risk of anaerobic bacteria as well as viruses; add agent that is active against beta-lactamase-producing anaerobic bacteria including clindamycin, metronidazole, and acyclovir should be considered. If the patient has diffuse pneumonia, continue with the broad-spectrum anti-Gram-negative coverage (add trimethoprim-sulfamethoxazole and macrolide to the therapy). Increasing neutrophil count on patients who developed new infiltrates while on antibiotic can be related to the recovery of neutropenia. If the patient is stable observe if the neutrophil count is not rising, antifungal therapy should be considered as the patient is at risk for fungal infection. In addition to other evaluation *Aspergillus* galactomannan and B-D glucan (fungitell) should be done with chest CT scan. Depending on the CT scan findings bronchoalveolar lavage or lung biopsy should be considered. Patient with prolonged fever and neutropenia needs to be observed if recovery of neutropenia is not imminent. Antifungal therapy can include either regular amphotericin B, or lipid formulation of amphotericin B including liposomal amphotericin B (amBisome) or amphotericin B lipid complex (ABLC), caspofungin or voriconazole depending of the availability of medications and epidemiology of the institution.

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69 Meningitis

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Definition and Introduction

Meningitis is defined as an inflammation of the meninges, the protective membranes covering the brain and spinal cord. There are numerous causes of meningitis, the most common category being infectious, including viral, bacterial, fungal, and parasitic infections. Meningitis, particularly acute bacterial meningitis, is a pediatric illness that continues to cause significant disease burden, with mortality rates remaining unchanged in the last 15 years. The introduction of the pneumococcal, meningococcal, and *Haemophilus influenzae* type-B (HiB) vaccines has altered the epidemiology and prevalence of meningitis in developed countries. However, these vaccines are not available in many parts of the developing world, and bacterial meningitis caused by these vaccine-preventable infections continues to cause significant illness.

Etiology and Epidemiology

Bacterial Causes

In the United States, the majority of meningitis cases are due to viral agents, but the highest morbidity and mortality rates are due to bacterial meningitis. The predominant bacterial pathogens causing meningitis differ depending on the age and immune system of the host.

Neonates

Bacteria that cause meningitis in neonates (0–28 days) are distinct from those causing meningitis in older children and adults. Neonatal infections stem from exposure to maternal gastrointestinal and genitourinary flora and include Group B *Streptococcus* (GBS, *Streptococcus agalactiae*), *Escherichia coli,* and *Listeria monocytogenes.* In neonates, the highest meningitis disease burden is from GBS. Since the widespread initiation of intrapartum antibiotics in 1996, a decrease has occurred in the United States incidence of all early-onset GBS infections from approximately 2 cases per 1,000 live births in 1990 to 0.3 cases per 1,000 live births in 2004. The incidence of neonatal bacterial meningitis since intrapartum antibiotic initiation is approximately 0.25–1 cases per 1,000 live births, with premature infants being at higher risk with an incidence of 2.5 cases per 1,000.

Older Children and Adults

In the latest United States surveillance study, the most common etiologic agent of bacterial meningitis across all age groups was *Streptococcus pneumoniae* (61%), followed by *Neisseria meningitidis* (16%) and GBS (14%) (Table 69.1). *H. influenzae* and *L. monocytogenes* are less frequent causes of bacterial meningitis, accounting for 7% and 2% of cases, respectively.

S. pneumoniae is the second most common cause of meningitis in American children, and continues to be the leading cause of meningitis in both children and adults worldwide. *S. pneumoniae* is a ubiquitous organism with nasopharyngeal carriage rates ranging from 21% to 59%. Pneumococcal infections, including meningitis, are most prevalent in the winter months following upper respiratory tract viral infections. The incidence of pneumococcal meningitis peaks in children at 1 year of age, but is prevalent throughout childhood and peaks again in adults over 60 years of age. Children with certain congenital CSF abnormalities (i.e., spina bifida or meningoceles), cochlear implants, complement deficiencies, and asplenia are at an increased risk for acquiring bacterial meningitis. Approximately 20–25% of children with pneumococcal meningitis have a predisposing risk factor.

N. meningitidis is the second most common bacterial pathogen causing meningitis in the United States and is the leading pathogen in children 2–18 years of age. Two incidence peaks exist for meningococcal infection: the first peak occurs in children less than 5 years of age, and the second peak in people 15–24 years of age. Although the majority of meningococcal cases (95%) are endemic, outbreaks occur in association with daycare centers, college dorms, and military barracks. Meningococcal cases are more common in the winter months following influenza virus infections, which are thought to break down protective mucus membranes.

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Table 69.1
Meningitis epidemiology in the United States since the introduction of the HiB, pneumococcal, and meningococcal vaccines

Pathogen	1986	1998–2003
H. influenzae	45%	7%
S. pneumoniae	18%	61%
N. meningitidis	14%	16%
Group B *Streptococcus*	5.7%	14%
L. monocytogenes	3.2%	2%

Adapted from Dery MA, 2007

There are 13 identified *N. meningitidis* serogroups as determined by differences in the bacterial polysaccharide capsule. The serogroups have varying epidemiological features and are responsible for different disease manifestations. Serogroups B, C, and Y are the most prevalent serotypes in the United States. Worldwide, the majority of endemic meningococcal cases are caused by serogroups A, B, and C. Serogroups B and C cause disease in Europe and the Americas, and serogroups A and C cause disease in Asia and Africa. Although all serogroups have the potential to cause epidemic disease, certain serogroups have caused recurrent outbreaks. In the United States, the majority of these outbreaks are due to serogroup C and Y. Worldwide, serogroup A is the most common agent responsible for epidemics of meningococcal meningitis, especially in the sub-Saharan "meningitis belt" which extends from Ethiopia to Senegal.

H. influenzae type B (HiB) was the most common cause of bacterial meningitis in the United States prior to the introduction of the HiB vaccine. It now has been largely eradicated from the United States and other developed countries but continues to cause significant disease burden worldwide. According to the World Health Organization (WHO), HiB is estimated to cause approximately three million serious illnesses and an estimated 386,000 deaths annually in children less than 5 years old, chiefly through meningitis and pneumonia. The incidence of HiB meningitis is currently highest in sub-Saharan Africa and Latin America and typically occurs between 6 and 18 months of age. Sickle cell disease, asplenia, and HIV infection predispose children to HiB infection.

Other Bacterial Causes of Meningitis

Meningitis caused by *Mycobacterium tuberculosis* is a severe and deadly disease. The World Health Organization estimates that one third of the world's population is infected with tuberculosis. However, defining the incidence and prevalence of tuberculous meningitis has been challenging as diagnostic criteria are not universal and criteria for the initiation of empiric treatment differ. Tuberculous meningitis is estimated to complicate 0.3% of untreated tuberculosis infections in children, and more commonly affects children between 6 months of age and 4 years of age.

Borrelia burgdorferi (the etiologic agent of Lyme disease) causes meningitis in children living in endemic regions in the United States, such as the southern New England area, the eastern mid-Atlantic States, Wisconsin, and Minnesota. Other bacterial pathogens such as *Pseudomonas aeruginosa, Salmonella* species, *Klebsiella* species, and *L. monocytogenes* are rarer causes of meningitis and are more commonly identified in immunosuppressed or elderly patients. In particular, patients on chronic steroid treatment are at greater risk of contracting *Listeria* meningitis.

Viral Causes of Meningitis

While bacterial agents cause the majority of morbidity and mortality related to infectious meningitis, viral pathogens are the most common infectious cause of meningitis overall. Viruses cause an aseptic meningitis, which refers to meningeal inflammation not caused by a bacterial pathogen. The most common viral infections resulting in meningitis in children are enteroviruses, including coxsackieviruses and echoviruses. Enteroviruses predominate in the summer months and are most common in children younger than 1 year of age.

The herpes simplex virus (HSV) is an important cause of aseptic meningitis. HSV can cause neonatal meningitis as well as aseptic meningitis in older children and adults. HSV infection occurs in 1 in 3,200 deliveries in the United States; transmission of HSV occurs during delivery, either when mothers have an active primary infection, or less commonly through shedding and reactivation of latent virus.

Fungal and Parasitic Causes

Fungal and parasitic meningitis are uncommon and primarily restricted to patients with immunosuppression, such as HIV infection, autoimmune disease, diabetes, a history of solid organ or bone marrow transplantation, and cancer. The most common fungal meningitis worldwide is *Cryptococcus neoformans* in the HIV population.

Pathogenesis

Meningitis is usually caused by the hematogenous spread and subsequent seeding of organisms from a distant site, either from a local infection or colonization. Pathogenic bacteria often colonize the nasopharynx but can also arise from the genitourinary tract, gastrointestinal tract, or skin colonization. Bacteria seed the blood stream by damaging the local mucosa and are then transported to the vasculature surrounding the central nervous system (CNS). Organisms are thought to breach the blood–brain barrier through microbial interactions with host receptors, though the exact mechanism is still unclear. Infection subsequently spreads across the pia, arachnoid, and subarachnoid spaces. Once inside the CNS, pathogens are more likely to proliferate because of limited host defenses in the CNS. The subsequent inflammatory cascade that follows bacterial infiltration leads to the characteristic clinical symptoms of meningitis. Other rarer forms of CNS seeding are through retrograde neuronal spread and direct extension from a local infection.

History and Clinical Manifestations

Recognizing the signs and symptoms of meningitis is crucial; delays in treatment worsen outcomes. *Table 69.2* provides a list of important historical information when a diagnosis of meningitis is being considered.

Acutely, bacteremia can manifest as septic shock and cardiovascular instability. Patients with meningitis, particularly meningococcal meningitis, can have fulminant and rapidly progressive disseminated intravascular coagulation (DIC) characterized by petechiae and purpura. An initial bacteremia leads to meningeal seeding which causes an inflammatory reaction. Inflammation of spinal nerves causes neck pain and stiffness (meningismus) and is demonstrated using the Kernig and Brudzinski maneuvers. The Kernig sign is elicited by flexing the hips and extending the knees to elicit pain in the back and neck. The Brudzinski sign involves flexing the neck and eliciting involuntary flexion in the hips. The absence of meningeal signs lowers the likelihood of meningitis but can be absent in younger children. Importantly, the absence of fever does not rule out meningitis.

Clinical presentation in young infants differs in comparison to older children. Neonates and infants will often present with nonfocal symptoms such as irritability, temperature instability, jaundice, and poor feeding. Older children are better able to localize symptoms such as photophobia, and neck pain, and can display focal neurological findings and meningismus on examination. Occasionally, meningeal inflammation results in an increased intracranial pressure (ICP) which is a clinical emergency. Increased ICP can manifest as changes in consciousness, papilledema, diplopia, emesis, a bulging fontanelle, seizures and, in the late stages, Cushing's triad (hypertension, bradycardia, and hypopnea). Seizures from cerebritis, infarction, or electrolyte imbalances occur in up to 30% of patients with meningitis.

Tuberculous meningitis usually stems from a caseous lesion in the meninges or cortex that developed following lymphohematogenous seeding. Infection usually involves the brainstem and often presents with palsies of cranial nerves III, VI, or VII. Hydrocephalus and SIADH are common complications. Tuberculous meningitis typically progresses through three stages, and this progression of disease may be rapid, as is often seen in young children, or gradual. The first stage develops over 1–2 weeks and is characterized by general malaise and loss of developmental milestones. The second stage involves the more abrupt onset of neurological signs, including cranial nerve palsies, hypertonia, meningismus, emesis, and lethargy. The third stage is characterized by coma, paraplegia, decerebrate posturing, and death. Clinical outcome correlates to the

Table 69.2
Important historical information when considering a meningitis diagnosis

Neonates	All children
Maternal infection Maternal HSV status Prolonged rupture of membranes Prematurity	Chronic illness Recent illness Sickle cell disease Immunocompromised states (HIV, cancer, immunosuppressive agents) Cardiac disease Renal disease (especially nephritic syndrome) Diabetes mellitus Asplenia Central nervous system shunts Cochlear implants Immunization history Medication history (including IVIG, NSAIDS, and antibiotics) Ethnicity (specifically Alaska Natives and American Indian) Travel to endemic regions

HSV herpes simplex virus, *HIV* human immunodeficiency virus, *IVIG* intravenous immunoglobulin, *NSAIDS* nonsteroidal anti-inflammatory drugs

stage during which treatment in initiated, making early recognition essential. See Chap. 95, "Tuberculosis" for a more thorough discussion of *M. tuberculosis*.

Lyme meningitis often presents as cranial nerve palsies (particularly cranial nerve VII) with a lymphocytic basilar meningitis. Incidence is highest in the summer months and typically affects children between 5 and 9 years old. Compared to other causes of bacterial meningitis, Lyme meningitis typically has a less acute onset and progression. See Chap. 84, "Lyme Disease".

Viral meningitis usually presents as a nonspecific febrile illness, and while its clinical symptoms are generally less severe than those of bacterial meningitis, at times the symptoms can be indistinguishable from those of bacterial meningitis. Oftentimes, aseptic meningitis cannot therefore reliably be distinguished from bacterial meningitis on clinical exam alone, and further testing needs to be performed.

A third of neonatal HSV manifests as CNS disease and 60% of neonates with HSV meningitis will have skin lesions. Frequently, however, no maternal clinical evidence of HSV is present. HSV neonatal meningitis usually occurs within the first 6 weeks of life and can be a severe or fatal illness with CNS sequelae. In neonates, HSV meningitis can progress to encephalitis, which has a mortality rate of 75% in untreated infants. See Chap. 108, "Herpes Simplex Virus Infections" for more detail.

Diagnosis

Diagnosis of bacterial meningitis requires a lumbar puncture. Cerebrospinal fluid (CSF) should be sent for culture, and between 70% and 85% of CSF cultures are positive in non-pretreated patients. Analysis of the CSF should also include Gram stain and measurements of the cell count, glucose, and protein, as these measures can help to determine the etiology of meningitis while awaiting culture results. Interpretation of CSF findings in children can be challenging, however, given that CSF findings vary with age, particularly in neonates (*Table 69.3*). Slight elevations in white blood cell (WBC) count and elevations in protein can be normal in neonates.

The results of CSF analysis can indicate the most likely pathogens, with different typical profiles for bacterial, viral, Lyme, and tuberculous meningitis (*Table 69.4*). In general, children with bacterial meningitis have significantly elevated CSF leukocyte counts (pleocytosis) with a neutrophilic predominance, while children with viral or tuberculous meningitis have a lesser elevation in CSF WBC counts and a lymphocytic predominance. Glucose concentrations tend to be lower and protein concentrations higher in bacterial meningitis. The values in *Table 69.4* are general guidelines to assist with the interpretation of CSF values.

Occasionally, CSF can only be obtained following initiation of empiric antibiotics. Studies suggest that *N. meningitidis* is cleared from the CSF within 2–6 h of antibiotic administration, and *S. pneumoniae* within 4 h. However, no reliable data are available regarding CSF interpretation following antibiotic administration; consider consultation with an infectious diseases expert for assistance in interpreting CSF results obtained after antibiotic administration.

Differential Diagnosis

Signs and symptoms of infectious meningitis are often difficult to distinguish from other noninfectious causes of meningitis. Noninfectious meningitis, although rare, must be considered in the differential diagnosis. There are reported cases of drug-induced meningitis, particularly from nonsteroidal anti-inflammatory drugs, trimethoprim-sulfamethoxazole, intravenous immunoglobulin and the immunosuppressant OKT3. Autoimmune illnesses such as systemic lupus erythematosus and Kawasaki disease can also cause the symptoms of aseptic meningitis.

Table 69.3
Normal cerebrospinal fluid findings in healthy children

Age	WBC Count (cells/mm^3)	Protein (mg/dL)	Glucose (mg/dL)	Opening pressure (cmH_2O)
0–28 days	9 (0–19)	<115	>50 (or >75% of serum glucose)	5–10
29–56 days	3 (0–9)	<89	>50 (or >75% of serum glucose)	5–10
Children and adolescents	0–10	15–45	>50 (or >75% of serum glucose)	5–10

Table 69.4
Typical cerebrospinal fluid analysis by selected causes of meningitis

	WBC count (cells/mm^3)	Glucose (mg/dL)	Protein (g/L)	Opening pressure (cmH_2O)
Bacterial meningitis	>100 with a neutrophil predominance	<40 (or a CSF to serum ratio $\leq$ 0.4)	>100	>20
Viral meningitis	5–50 with a mononuclear predominance	normal	50–100	<20
Lyme meningitis	10–50 with a mononuclear predominance	10–45	50–150	<20
Tuberculous meningitis	10–50 with a mononuclear predominance	10–45	>100 (typically extremely elevated)	>20

Note: Children with a CSF WBC > 9 cells/mm^3 are thought to be at higher risk for having meningitis, although typical WBC counts in meningitis are higher

Many of the findings of meningitis, including an increased ICP, can also be caused by encephalitis, cerebral mass lesions, intracranial abscesses, epidural abscesses, strokes, and hydrocephalus. Neurologic changes can stem from a multitude of afflictions, including sepsis, toxic ingestions, seizures, and physical trauma.

Treatment

Bacterial meningitis is a clinical emergency that requires prompt, empiric treatment, without which mortality rates approach 100%. A suggested flowchart for the approach to the patient with suspected bacterial meningitis is presented in *Fig. 69.1*.

Antibiotics must be chosen based on pathogen probability (which is often dictated by age, clinical findings, and geographic location) and ability to attain bactericidal activity in the CSF. In neonates, conventional treatment includes ampicillin and cefotaxime to provide coverage against the most common pathogens in this age group. In children older than 1 month of age, treatment should include vancomycin plus a third generation cephalosporin to provide empiric treatment against resistant *S. pneumoniae* until culture results are available. Multidrug resistant *S. pneumoniae* is thought to account for approximately 30% of all cases of pneumococcal meningitis; this resistance pattern profile mandates that empiric treatment include antimicrobial agents that target resistant isolates of *S. pneumoniae*.

Once a bacterial pathogen is identified, antimicrobial treatment can be narrowed and tailored to the organism (*Table 69.5*). Individual patient treatment will vary based on organism susceptibilities. Typical first-line treatment selections are presented in *Table 69.6*. Typical treatment duration by pathogen is presented in *Fig. 69.1*. Repeat lumbar puncture after 24–48 h of antimicrobial therapy should be considered for patients with persistent symptoms or a known highly resistant isolate. Consultation with an infectious diseases expert should be sought for persistent symptoms despite appropriate antimicrobial therapy or persistently positive CSF cultures.

Treatment with dexamethasone is recommended in children older than 6 weeks with *H. influenzae* meningitis. Some studies suggest that dexamethasone may also curb the severity of hearing loss in *S. pneumoniae* bacterial meningitis if administered before the first dose of antibiotics, but the evidence is less clear and expert opinions vary.

Acyclovir is the drug of choice for neonatal HSV meningitis, dosed at 60 mg/kg/day divided every 8 h. Typical treatment duration is for at least 21 days; see Chap. 108, "Herpes Simplex Virus Infections", for more detail. The majority of other causes of viral meningitis, including enterovirus, are self-limited, and no treatment is recommended.

Cryptococcal meningitis is typically treated with Amphotericin B and flucytosine; consultation with an infectious diseases specialist is recommended.

Prognosis

Overall morbidity and mortality has significantly decreased since the introduction of HiB, pneumococcal, and meningococcal vaccines. However, survival rates for those who acquire bacterial meningitis have not changed in the last 15 years. The mortality rate is approximately 5–10%, with death being more likely in patients who

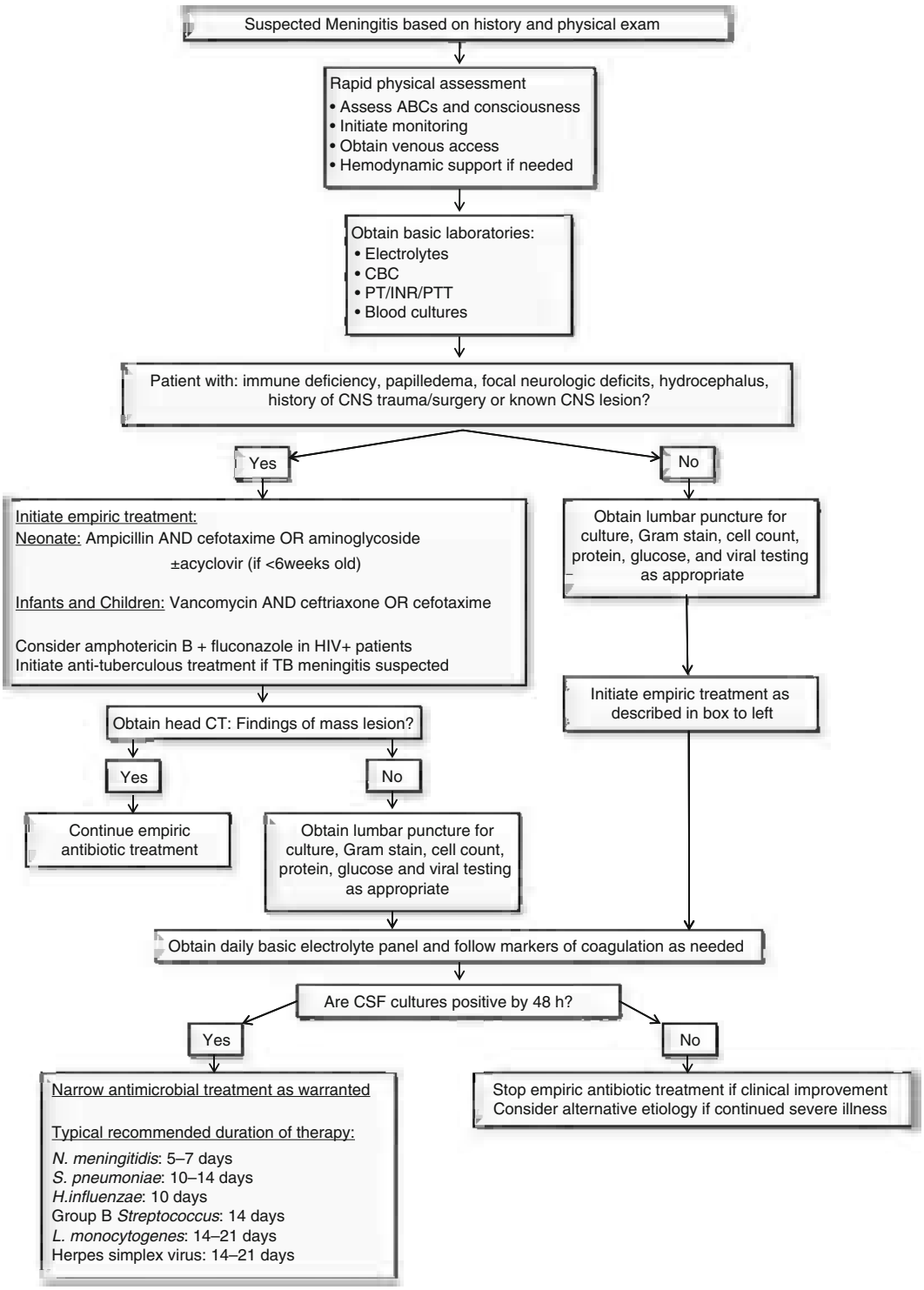

Figure 69.1

Recommended acute management of suspected meningitis. *CBC* complete blood count, *CNS* central nervous system, *CSF* cerebrospinal fluid, *HIV* Human immunodeficiency virus, *INR* international normalized ratio, *PT* prothrombin time, *PTT* partial thromboplastin time, *TB* tuberculosis

Table 69.5
Recommended empiric meningitis treatment by age group

Age group	Likely pathogen	Empiric treatment
Neonates (<28 days)	GBS, *E. coli, L. monocytogenes, Klebsiella* sp., HSV	Ampicillin + Cefotaxime or Aminoglycoside ± Acyclovir
Infants (1–23 months)	GBS, *E. coli, S. pneumoniae, N. meningitidis, H. influenzae*	Vancomycin + third generation cephalosporin[a]
Children and adults (2–50 years)	*S. pneumoniae, N. meningitidis, H. influenzae*	Vancomycin + third generation cephalosporin[a]
Adults >50 years	*S. pneumoniae, N. meningitidis, H. influenzae, L. monocytogenes,* aerobic gram-negative bacilli	Vancomycin + ampicillin + third generation cephalosporin[a]
Those with shunt devices or surgical intervention	*Staphylococcus aureus*, Coagulase-negative *Staphylococci, Propionibacterium acnes*, *P. aeruginosa*	Vancomycin + Cefepime or Meropenem
Those with compromised cellular immunity	*L. monocytogenes,* gram-negative enteric bacilli, *P. aeruginosa*	Vancomycin + Cefepime or Meropenem

GBS group B *Streptococcus*, *HSV* herpes simplex virus
[a]Ceftriaxone or cefotaxime

Table 69.6
Typical first-line treatment by causative organism

Microorganism	Typically recommended treatment
N. meningitidis	Penicillin G or Ampicillin
S. pneumoniae (Penicillin susceptible)	Penicillin G or Ampicillin or third generation cephalosporin[a]
S. pneumoniae (Penicillin-resistant)	Vancomycin + third generation cephalosporin[a]
H. influenzae	Third generation cephalosporin[a]
S. agalactiae (GBS)	Penicillin G or Ampicillin
L. monocytogenes	Penicillin G or Ampicillin
E. coli	Third generation cephalosporin[a]
P. aeruginosa	Cefepime or Ceftazidime ± Aminoglycoside
S. aureus (Methicillin susceptible)	Nafcillin or Oxacillin
S. aureus (Methicillin resistant)	Vancomycin
Enterococcus sp.	Ampicillin or Vancomycin + Gentamicin

[a]Ceftriaxone or cefotaxime

present with coma, prolonged seizures, shock, severe respiratory distress, a low peripheral WBC count, or a high CSF protein level. Those presenting with focal seizures are more likely to have adverse neurological outcomes. Young age, male gender, symptoms lasting greater than 48 h prior to admission, persistent fever (>7 days), delayed CSF clearance, and absence of petechiae also predict worse outcomes. It is likely that the absence of petechiae is related to the causative pathogen; petechiae are more common with *N. meningitidis* infection which, if treated, has better outcomes than *S. pneumoniae* meningitis. Penicillin-resistant *S. pneumoniae* is associated with poorer outcomes.

Morbidity following bacterial meningitis is approximately 15% and primarily consists of neurologic deficits, including hearing loss, hemiparesis, quadriparesis, facial nerve palsies, visual field defects, and developmental delays. Five percent to 30% of patients experience hearing loss, with a higher likelihood in patients infected with *S. pneumoniae* or with low CSF glucose levels. Other neurologic sequelae are more likely in patients with coma, seizures, fever greater than 7 days, and a low CSF-WBC count.

Prevention

Vaccines

The introduction of the pneumococcal, meningococcal, and HiB vaccines has led to a significant reduction in the number of bacterial meningitis infections and has changed meningitis epidemiology. However, these vaccines are not available in many developing countries where these three pathogens continue to cause significant disease burden.

The incidence of HiB meningitis in the United States has decreased by 94% since the introduction of the HiB conjugate vaccine in 1990. The HiB vaccine is administered as a 4-dose series at ages 2, 4, 6, and 12–15 months. Prior to its licensure, HiB accounted for approximately 45% of acute bacterial meningitis cases. Although there are occasional nontypable *H. influenzae* meningeal infections, HiB is now an uncommon pathogen.

The heptavalent pneumococcal conjugate vaccine (PCV7) was introduced in 2000 and included the seven serotypes that caused 83% of pneumococcal disease at that time. Since its introduction, the rates of pneumococcal meningitis have declined by approximately 30% overall, with the largest decrease (64% between 1998 and 2005) in children less than 2 years old. Although the overall rates of meningitis have decreased, the incidence of pneumococcal meningitis caused by serotypes not included in the vaccine (non-PCV7-serotypes) has increased by 60%. The introduction of PCV7 has also correlated with a decrease in antibiotic-resistant pneumococcal disease. In 2010, PCV7 was replaced by a 13-valent pneumococcal conjugate vaccine (PCV13), which is also administered as a four-dose series at ages 2, 4, 6, and 12–15 months. The impact of this vaccine has yet to be determined.

Since the introduction of the HiB and pneumococcal vaccines, *N. meningitidis* has emerged as the most common cause of meningitis in children greater than 2 years old in the United States. The conjugate meningococcal vaccine (MCV4) includes four common meningococcal serogroups (A, C, Y, and W-135) and was licensed in 2005. Most meningococcal disease is caused by these four strains. However, more than 50% of disease in younger children is caused by serogroup B, a serogroup not included in the vaccine. A new conjugate meningococcal vaccine against serogroup A was introduced to sub-Saharan Africa in late 2010, with a goal of widespread immunization to prevent *N. meningitidis* serogroup A epidemics in the Sub-Saharan "meningitis belt."

Since the introduction of these vaccines, the median age of patients with bacterial meningitis has increased from 15 months of age to 39 years of age between 1986 and 2003. The number of cases per year has also decreased from 12,920 to 4,450.

Chemoprophylaxis

Chemoprophylaxis is indicated for those exposed to patients with meningitis caused by HiB and *N. meningitidis*. Chemoprophylaxis is recommended for all household contacts exposed to HiB when there is an unvaccinated contact younger than 4 years old or a child younger than 12 months in the household. It is also recommended for childcare attendants when there are two or more cases occurring within 60 days at that facility. Four days of oral rifampin is the recommended chemoprophylaxis.

In cases of *N. meningitidis* meningitis, all household contacts, all daycare contacts present for 7 days before the onset of the illness, and those exposed to the patient's secretions should be treated with chemoprophylaxis. Recommended treatment is usually rifampin for 2 days, but ceftriaxone, ciprofloxacin, and azithromycin can also be used.

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70 Otitis Media

Marah Gotcsik

Definition/Classification

Otitis media is inflammation of the middle ear. Dependent upon presentation, associated symptoms, and duration of symptoms, the diagnosis can be further classified as follows:

Acute otitis media (AOM) is infection of the middle ear with acute onset, middle-ear effusion (MEE) on exam, and presence of signs and symptoms of middle-ear inflammation. *Treatment failure AOM* is defined by lack of improvement despite 48–72 h of appropriate antibiotic therapy. Diagnosis of *Recurrent AOM* requires three or more episodes in 6 months or four or more episodes in 12 months.

Otitis media with effusion (OME) is middle-ear effusion without signs or symptoms of active infection. *Chronic OME* (COME) is when this effusion persists for more than 3 months.

Chronic suppurative otitis media (CSOM) is chronic inflammation of the middle ear and mastoid cavity presenting with otorrhea through a perforated tympanic membrane. The World Health Organization definition requires 2 weeks of otorrhea for diagnosis, whereas others have suggested 6 weeks of symptoms as a diagnostic requirement.

Epidemiology

Otitis media is one of the most common pediatric diagnoses worldwide, and the prevalence may be increasing: United States surveillance data by the Centers for Disease Control showed a 150% increase to 24.5 million office visits per year with a principal diagnosis of otitis media from 1975 to 1990. At least 70% of children have at least one episode of AOM before 2 years of age, and AOM is the most common reason for antibiotic prescription for children in the United States.

Approximately 90% of children are diagnosed with OME before school age. Most episodes resolve spontaneously, but 30–40% of children have recurrent OME and 5–10% of episodes last 1 year or longer.

Numerous host and environmental risk factors have been studied in association with AOM and OME (see *Table 70.1*). The significance of genetic predisposition to the development of otitis media has been demonstrated with twin studies showing heritability as high as 70%. Studies have examined race and likelihood of developing otitis media without clear consensus.

CSOM, though rare in the developed world, remains a major cause of morbidity and mortality in the developing world and within certain racial groups. Unfortunately, the lack of consensus definition and variability in methods makes meta-analysis studies difficult. The highest prevalence of CSOM is in Alaska Native, Native Greenland, Native American, and Australian Aborigine children (prevalence 7–46%). Children in the South Pacific Islands, Africa, Korea, India, and Saudi Arabia have a relatively high prevalence of 1–6% with some subregions being more affected than others. Highly developed countries, such as the US and UK, have the lowest prevalence at $<1\%$.

Recurrent AOM is associated with development of CSOM, suggesting similar risk factors for both disease processes. In the antibiotic era, rates of CSOM have decreased, further supporting a link between nontreatment and progression to chronic disease. Additional identified risk factors include inadequate antibiotic treatment, frequent upper respiratory tract infections, nasal disease, and poor living conditions with poor access to medical care. It is encouraging that with intervention in these identified areas there can be a direct impact on health; one study targeting improvements in housing, hygiene, and nutrition resulted in a 50% decrease in CSOM in Maori children.

Pathogenesis

Development of otitis media is strongly associated with impairment of the structure and function of the eustachian tube. At baseline, the middle-ear space maintains a negative air pressure relative to the environment. This pressure is periodically relieved by opening the eustachian tube, for example, in the setting of yawning and chewing. If this pressure equalization cannot be achieved, inflammation can occur resulting in otitis media.

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Table 70.1
Risk factors for development of otitis media

Host factors	Environmental factors
Age <2 year	Bottle propping
Atopy	Child care attendance
Chronic sinusitis	Crowding in housing
Ciliary dysfunction	Low socioeconomic status
Cleft palate/Craniofacial anomalies	Non-breast feeding in infancy
Immunocompromise	Passive smoke exposure
Male sex	Winter season (respiratory virus exposure)
Trisomy 21	

Craniofacial anomalies with distortion of ear and eustachian tube anatomy are an obvious cause of eustachian tube dysfunction. However, normal pediatric anatomy is also associated with impairment of pressure equalization. In infants and children, the eustachian tube can be as short as half the length of the adult eustachian tube and is comprised of highly compliant cartilage positioned at a near horizontal angle (as opposed to the adult eustachian tube which is more firm and lies in a 45° angle in relation to the axial plane). The characteristics of the pediatric eustachian tube compromise the ability to effectively ventilate the middle ear. Inflammation due to upper respiratory tract infections (URI), allergic rhinitis, and gastro-esophageal reflux further impairs eustachian tube function. Additionally, nasopharyngeal secretions can reflux or be insufflated into the middle-ear space, serving as nidus for infection.

Both bacteria and viruses have been implicated in otitis media. AOM and OME have similar associated pathogens, whereas CSOM is has a distinct microbial profile (*Table 70.2*).

Upper respiratory tract infections are important in the pathogenesis of AOM. AOM has been identified as a complication of 37% of URIs in children, as high as 50% with coronavirus, respiratory syncytial virus (RSV), and adenovirus infection, and as high as 60% in human metapneumovirus infection.

In studies examining middle-ear fluid in patients with AOM, viruses are isolated 20–50% of the time, alone or together with bacterial otopathogens. The most frequently isolated virus types from middle-ear fluid are RSV, parainfluenza, and influenza (A and B).

Bacteria are isolated from middle-ear fluid in AOM 50–90% of the time. Historically, the most common bacteria associated with otitis media is *Streptococcus pneumoniae*. Following introduction of PCV7, vaccine serotypes of *S. pneumoniae* have been nearly completely eliminated, with *Haemophilus influenzae* becoming more prevalent. As with other *S. pneumoniae* infections, there is some evidence that non-vaccine serotypes are increasing to fill this niche – including identification of a multidrug resistant serotype 19A. The introduction of the 13-valent pneumococcal vaccine (PCV13) in 2010 will undoubtedly be associated with further changes in the bacterial otopathogens of AOM.

Development of OME is also associated with URI. URI can lead to OME nearly one quarter of the time, with a slightly higher incidence in the setting of influenza. Middle-ear fluid in COME was previously thought to be sterile based on culture results. However, the advent of PCR technology has allowed identification of bacterial DNA and mRNA in culture-negative middle-ear fluid. One hypothesis for this finding is the presence of biofilms – aggregated bacteria growing on a surface, surrounded by an extracellular matrix. Supporting this hypothesis are recent studies with visualization of biofilm on microscopy during placement of tympanostomy tubes in patients with COME.

Although CSOM is associated with recurrent AOM, the associated bacterial pathogens are different. Bacteria can reach the middle ear via the eustachian tube or via the external ear through the perforated tympanic membrane. There is wide variability in the prevalence of the pathogens; however, *Pseudomonas aeruginosa* is the most common, isolated from 18% to 67% of ear cultures. *P. aeruginosa* is implicated in the progressive destruction of middle-ear and mastoid structures. Unlike AOM and OME, fungi are a common pathogen, isolated from 50% of ear cultures from populations in hot, humid regions. Biofilms are also gaining attention as a possible cause for chronic infection in CSOM.

Pathology

The bony structures of the ear, the inner ear mucosa, and the tympanic membrane can readily heal from acute infection – including acute infection with perforation – without long term disability. In children with history of otitis media, tympanic membrane abnormalities present at 8 years of age nearly completely resolve by 18 years of age.

CSOM can result in damage of the typmanic membrane, the ossicles, and the mastoid space leading to osteoneogenesis, bony erosions, and osteitis of the temporal bones and ossicles.

Table 70.2
Pathogens identified by culture or PCR in middle-ear fluid of patients with AOM, OME, and CSOM

	AOM	OME	CSOM
Bacteria	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Aerobic
	Haemophilus influenzae	*Haemophilus influenzae*	*Pseudomonas aeruginosa*
	Moraxella catarrhalis	*Moraxella catarrhalis*	*Staphylococcus aureus*
	Streptococcus pyogenes		*Escherichia coli*
	Staphylococcus aureus		*Proteus mirabilis*
	Streptococcus agalactiae (neonates)		*Klebsiella* species
	Gram negative bacilli (neonates)		*Haemophilus influenzae*
			Anaerobic
			Bacteroides
			Fusobacterium
Viruses	Respiratory syncytial virus	Rhinovirus	
	Influenza	Respiratory syncytial virus	
	Adenovirus	Coronavirus	
	Parainfluenza		
	Rhinovirus		
	Coronavirus		
Fungi			*Aspergillus* species
			Candida species

Clinical Manifestations

Acute Otitis Media

Specific signs and symptoms: Otalgia is the most common complaint in children with AOM. Although not a sensitive marker of disease, it does have a high positive predictive value for presence of infection. Other specific signs are otorrhea following acute tympanic membrane perforation, hearing loss, vertigo, nystagmus, and tinnitus. Ear swelling and facial paralysis are signs that may suggest a more invasive process within the mastoid space or the temporal bone, respectively.

Nonspecific signs and symptoms: Fever is present in one third to two thirds of patients with AOM, although fever $>40^{\circ}$ may suggest bacteremia or alternate focal infection. Additional nonspecific symptoms are irritability, headache, anorexia, vomiting, and diarrhea.

Otitis Media with Effusion

OME, by definition, has minimal symptoms, with mild hearing loss being the most common complaint. Symptoms of an underlying process resulting in oropharyngeal inflammation (URI, allergic rhinitis, gastro-esophageal reflux) may be present.

Chronic Suppurative Otitis Media

Patients with CSOM present with chronic otorrhea and may also have significant hearing loss. Conductive hearing loss of 20–60 dB may be present due to tympanic membrane perforation and damage to the ossicles. Sensorineural hearing loss may also occur in CSOM in association with loss of cochlear hair cells due to inflammation.

Diagnosis

Proper diagnosis of otitis media is imperative, especially in the era of increasing antibiotic resistance. Unlike other disease processes, otitis media remains a clinical diagnosis based on history and physical exam with pneumatic otoscopy.

Assessment of the tympanic membrane (TM) should include color, translucency, position, and mobility. A normal TM has a ground glass appearance, is translucent with

clear visualization of the bony landmarks, and has good movement with pneumatic otoscopy.

Proper equipment is paramount to adequate visualization of the TM. The best light source is a halogen bulb with at least 100 ft-candles and a well-charged battery. Speculum choice is also important. When available, reusable specula are preferable because of their length, size options, and glossy finish which facilitates light transmission into the ear canal. In choosing a speculum, the largest lumen possible that can comfortably fit into the cartilaginous portion of the canal should be selected. Small speculums not only limit the field of view, but may pass into the bony portion of the canal resulting in pain.

Visualization alone can provide clues to the presence of effusion but is not adequate for diagnosis. Pneumatic otoscopy is highly sensitive and specific for the presence of middle ear effusion. Pneumatic otoscopy is a multistep procedure designed to assess the TM response to both positive and negative pressure. The speculum is inserted into the ear with the no pressure on the bulb. Slight pressure is applied to the bulb to create positive pressure. Next, the seal is momentarily broken to allow for neutralization of pressure. Finally, the bulb is released to create negative pressure. It is important to realize that a normal eardrum will move with 10–15 mm H_2O, whereas a pneumatic otoscope can deliver as much as 1,000 mm H_2O when the bulb is fully depressed.

Tympanometry may be used as an adjunct to pneumatic otoscopy if available. With a tympanometer, the compliance of the TM is assessed by the reflection of sound waves off the TM (*Fig. 70.1*).

Acute Otitis Media

Although AOM is a common pediatric problem throughout the world, development of international diagnostic criteria has proved challenging. Previous definitions have been too broad, without clear distinction between AOM and OME. This lack of consensus has limited the ability to study diagnosis and treatment practices.

In 2004, the American Academy of Pediatrics (AAP) and American Academy of Family Practice (AAFP) published clinical practice guidelines on diagnosis of acute otitis media with more specific criteria:

1. History of acute onset of signs and symptoms
2. Presence of MEE (bulging TM, limited or absent mobility of the TM, an air-fluid level behind the TM, or otorrhea)
3. Signs and symptoms of middle-ear inflammation (direct erythema of the TM, bullous myringitis, and distinct otalgia)

Otitis Media with Effusion

The commonly accepted diagnostic criteria for OME are:

1. Presence of MEE
2. No signs or symptoms of AOM

The 2004 AAP, AAFP, and American Academy of Otolaryngology – Head and Neck Surgery clinical practice guidelines strongly recommended that pneumatic

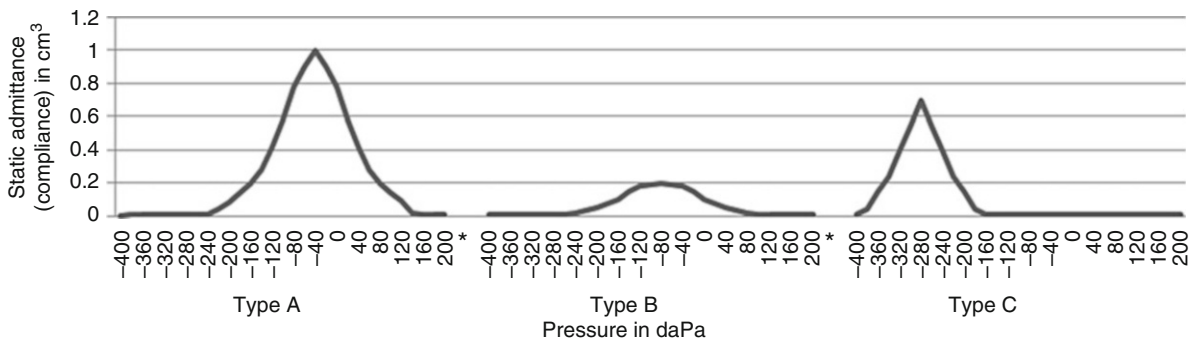

Figure 70.1

Examples of tympanometry curves Type A: Normal TM compliance. Type B: Poor compliance of TM with limited to no movement, in extreme cases can be flat. Type B curves are strongly associated with MEE. Type B curves can also be found with TM perforation in the setting of high measured volume. Type C: Decreased amplitude of compliance and shifted to the left, suggesting increased negative pressure in the middle ear. Type C curves are not diagnostic of middle-ear effusion

otoscopy should be used as the primary diagnostic method for OME to assess for MEE, based on grade A evidence.

Chronic Suppurative Otitis Media

The World Health Organization (WHO) diagnostic criteria of CSOM are:

1. Tympanic membrane perforation
2. Purulent otorrhea present continuously for at least two weeks

Treatment

Acute Otitis Media

In the developed world, there is large variation in practice of antibiotic prescription for AOM. In the setting of increasing antibiotic resistance, management practices for AOM have been reevaluated with emphasis on limiting antibiotic usage when possible. If left untreated, 61% of patients with AOM will have resolution of symptoms within 24 h, improving to 80% within 2–3 days. There is no significant difference in the incidence of suppurative complications, including mastoiditis, if antibiotics are initially withheld. This has led to a trend of expectant management with emphasis on pain control at the initial diagnosis of AOM. In certain groups with a high burden of disease, such as Australian Aborigines, national guidelines continue to support initiation of treatment at presentation. Rural populations may also not be appropriate for initial observation as close follow-up must be possible if a patient is not receiving antibiotics.

Numerous countries have adopted guidelines supporting a watch-and-wait approach to AOM, including the Netherlands, where there is the lowest rate of antibiotic prescription for AOM. The 2004 AAP guidelines stratify treatment by age and certainty of diagnosis. In otherwise healthy children with certain diagnosis, children under two years of age receive treatment, whereas those children greater that two years of age without significant ear pain or fever can be observed with follow-up. In cases of uncertain diagnosis, treatment is only recommended in children less than six months of age or if the child is six months to two years of age with significant ear pain or fever.

General Care

Supportive care is an important part of AOM management, including pain and fever control. There is no evidence for the use of antihistamines or decongestants in treatments of AOM.

Specific Treatment

Antibiotic choice in AOM is focused on medications with efficacy against *S. pneumoniae, H. influenzae,* and *Moraxella catarrhalis.*

First Line Therapy

Amoxicillin is widely accepted as first line therapy for non-penicillin allergic patients. However, the dosage and duration of treatment is highly variable. The Dutch College of General Practitioner Guidelines support lower dose therapy 30 mg/kg/day amoxicillin as compared to the AAP recommendations of 80–90 mg/kg/day. The rationale for higher dosing includes increased drug concentration in the middle ear and for the treatment of resistant strains of *S. pneumoniae*. In cases with fever >39 C or severe otalgia, the AAP recommends amoxicillin-clavulanic acid as first line therapy because of the potassium clavulanate's ability to inhibit B-lactamase-produced by many *H. influenzae* and *M. catarrhalis.*

In penicillin allergic patients there is less consensus, and recommendations include cephalosporins (cefdinir, cefuroxime, cefpodoxime, ceftriaxone), macrolides (azithromycin, clarithromycin, erythromycin), and sulfonamides (co-trimoxazole).

Treatment Failure Therapy

In cases of treatment failure, the AAP recommends amoxicillin-clavulanic acid, ceftriaxone, or clindamycin dependent on severity and if allergy to penicillin is present. The India-WHO Collaborative Programme also recommends amoxicillin-clavulanic acid as well as cefaclor.

Although tympanocentesis can be used in severe cases of treatment failure AOM, placement of tympanostomy tubes is reserved for children with recurrent otitis media. For children with tympanostomy tubes, AOM manifesting with otorrhea can be treated with ofloxacin otic solution or ciprofloxacin-dexamethasone otic solution.

Duration of Treatment

The recommended duration is also variable. The previous accepted duration of therapy for AOM was 10 days. Although this recommendation remains for younger children, children older than five years have demonstrated successful therapy with five to seven days of antibiotics. Older children may also be successfully treated with 1–5 days of azithromycin or 1–3 days of intramuscular ceftriaxone.

Future Development

As more national guidelines are endorsing the watch-and-wait approach to AOM, antibiotic prescribing patterns and development of complications must be monitored closely.

Otitis Media with Effusion

General Care

Just as with AOM, the rate of spontaneous resolution in OME is high. Of children with OME developing following AOM, 75% have spontaneous resolution of MEE in 3 months. Of children with incidentally identified OME, 42% have resolution within 6 months with 72% showing improvement in tympanometry curves at that time. Therefore, the watch-and-wait approach is also prudent in OME.

During this period of observation, hearing assessment every 3–6 months in addition to otoscopic evaluation with pneumatic otoscopy is important for ongoing surveillance. Asymptomatic effusions can be managed conservatively without intervention.

Specific Treatment

There is no clear role for medications in treatment of OME. Antihistamines and decongestants are not indicated for treatment. Antibiotics and corticosteroids have not been shown to have lasting effect. In children with persistent effusion lasting more than 4 months complicated by hearing loss, developmental delay (or risk for developmental delay), damage to the tympanic membrane, or otalgia or balance problems, tympanostomy tube placement may be indicated to remove the middle-ear effusion.

Future Development

Development of widely accepted and followed consensus guidelines may allow for further understanding of observation and management of OME.

Chronic Suppurative Otitis Media

The hallmarks of management of CSOM are treatment of the infection and closure of the tympanic membrane.

Mastoidectomy with tympanoplasty is curative, but there is limited access to tertiary centers offering these services for many of the children who are most affected. If the infection has spread deep into the middle ear, there is diffuse mucosal disease, or cholesteatoma has developed, the patient will likely be refractory to medical therapy alone. For patients without evidence of suppurative complication, the WHO has created a conservative medical management algorithm focused on aural toilet in conjunction with antibiotic treatment. Topical treatment has been shown to be superior to systemic therapy as well as being more cost-effective. Neomycin-polymyxin is recommended as first line therapy, with transition to quinolones, such as ofloxacin or ciprofloxacin, or gentamicin if drainage persists 2 weeks and ear culture is positive for *Pseudomonas*. If the drainage resolves on this regimen, the patient must then be followed for closure of the tympanic membrane. If the perforation persists, tympanoplasty can be performed with goal to restore hearing. If the perforation persists and otorrhea recurs, mastoidectomy is indicated.

Prognosis

In general, prognosis following an episode of otitis media is good. However, suspicion should be maintained for the many complications that can develop, most associated with local spread of infection.

Intratemporal Complications

Hearing loss is the most prevalent complication of otitis media. Conductive hearing loss is most commonly due to MEE and, less frequently, atelectasis of the middle ear due to high negative pressures. Average hearing loss is 20–30 dB, with a range of 0–60 dB. Sensorineural hearing loss can also be present due to increased tension on the round window membrane and inflammation of the cochlear hair cells. Hearing loss in CSOM is more severe than in AOM

and OME. Hearing loss may be associated with impaired development of speech and language with resultant poor school performance.

Tympanic membrane perforation can occur in AOM and OME. The TM usually heals within 2–3 months. For chronic perforations, lasting longer than 3 months, tympanoplasty is indicated.

Mastoiditis, although decreasing incidence in the antibiotic era, is the most common suppurative complication of otitis media. As the mastoid gas cell system is connected to the middle ear, all episodes of otitis media likely result in some degree of mastoiditis. If the infection spreads to the periosteum, mastoiditis with periosteitis develops. Presenting signs are fever, otalgia, postauricular erythema and mild tenderness, and possible anterior/inferior displacement of the pinna. The most severe form of mastoiditis occurs when infection spreads from the periosteum into the bone resulting in osteitis with potential for development of subperiosteal abscess. In mastoiditis with osteitis, postauricular erythema and tenderness are more pronounced, and the pinna is clearly displaced anteriorly and inferiorly. CT scan can be used to assess the extent of disease. Mastoiditis with periosteitis can be treated with parenteral antibiotics, tympanocentesis, and myringotomy. Mastoiditis with osteitis additionally requires mastoidectomy.

Cholesteatoma is a cystic mass of keratinized squamous cell epithelium and cholesterol in the middle ear. Cholesteatoma can be congenital or acquired, with acquired disease associated with chronic otitis media. Implantation cholesteatoma can develop following traumatic perforation of the TM or as a complication of ear surgery. In children, the most common location of cholesteatoma is the posterosuperior quadrant of the pars tensa. On otoscopy, a defect in the TM may be visualized with white greasy flakes of debris and sometimes foul smelling drainage. Findings on otoscopy can be subtle or difficult to visualize, making CT scan a useful diagnostic tool when there is high suspicion of disease. The squamous epithelium can extend inward, creating an expanding cystic cavity that causes progressive erosion of the ossicle, the mastoid space, and the temporal bone. Therefore, prompt surgical management is indicated.

Tympanosclerosis can occur with chronic middle-ear inflammation or as the result of trauma to the TM, including tympanostomy tube placement. On otoscopy, whitish plaques are visualized on the TM. Nodular deposits in the submucosal layers of the middle ear are also present. Conductive hearing loss can result if the ossicles become embedded in these deposits.

Suppurative labyrinthitis is a rare complication of AOM and OME, but can be seen in CSOM. The affected child presents with sudden onset of vertigo, nausea/vomiting, disequilibrium, and severe sensorineural hearing loss.

Facial paralysis can occur as a complication of AOM due to the facial nerve's course through the middle ear. Treatment consists of parenteral antibiotics, tympanocentesis, and myringotomy. Immediate surgical mastoidectomy is indicated in children with CSOM or cholesteatoma.

Intracranial Complications

Intracranial complications of meningitis, epidural abscess, subdural empyema, focal encephalitis, brain abscess, lateral sinus thrombosis, and otitic hydrocephalus have decreased in the antibiotic era, but remain a significant problem in underdeveloped countries, especially in the setting of cholesteatoma and CSOM. Due to spreading infection, 24–44% of children presenting with an intracranial complication will be found to have more than one intracranial complication at the time of diagnosis.

Meningitis can occur due to direct spread of infection through the dura, inflammation due to an alternate intracranial complication (such as abscess), or can be a concurrent infection with hematogenous spread from the upper respiratory tract. Hematogenous spread is the most common etiology. Treatment is parenteral antibiotics.

Epidural abscess is a collection of granulation tissue and pus between the dura and the temporal bone and can result when the temporal bone is compromised by cholesteatoma or infection. Earache, low-grade fever, and temporal headache may be present, as well as profuse, creamy, pulsatile otorrhea. Many cases of epidural abscess are asymptomatic. Treatment is surgical drainage and directed therapy with parenteral antibiotics.

Subdural empyema, although more common in sinusitis, is a rare but serious complication of otitis media. A pus collection develops in the subdural space, usually due to direct extension of infection. Presentation can be severe with toxic appearance, fever, and focal neurologic signs. Treatment is parenteral antibiotics and neurosurgical drainage if indicated.

Focal otitic encephalitis is non-suppurative brain inflammation associated with chronic otitis media or one of the associated suppurative complications. Presentation may be similar to brain abscess, necessitating MRI to distinguish the two entities. Treatment consists of antibiotics for the inciting infection.

Brain abscess can occur with AOM, CSOM, and cholesteatoma. Infection progresses to the brain from a localized subdural abscess or leptomeningitis. Otogenic

brain abscess are located in the temporal lobe or the cerebellum, depending on site of infection invasion. Multiple abscesses are common. The bacteria found in abscesses are the most common bacteria associated with AOM and CSOM. Signs of general and focal neurologic signs generally appear 1 month following acute infection. Systemic signs maybe absent. Treatment is surgical debridement and parenteral antibiotics.

Lateral sinus thrombosis can occur as a result of mastoid inflammation. The infection spreads though the mastoid space into the sinus, and finally into the venous system leading to thrombus formation. Signs of infection are signs of systemic infection, increased intracranial pressure, and sequelae of septic thromboembolism. Lateral sinus thrombosis has a high co-diagnosis with other intracranial complications. Treatment is parenteral antibiotics. There is no consensus on use of anticoagulation. Otitic hydrocephalus, markedly increased intracranial pressure, is highly associated with lateral sinus thrombosis.

Prevention

Otitis media is associated with environmental factors and genetic predisposition to disease. Some of the major environmental associations such as crowding and child care attendance may be difficult to impact in large scale prevention efforts. Due to these challenges, vaccines targeting the most frequent pathogens may be the most effective means to prevent otitis media. The introduction of PCV7 showed decrease in AOM diagnosis, but increase in presence of non-vaccine serotypes. Introduction of PCV13 as well as development of a vaccine against non-typable *H. influenzae* has the potential to substantially decrease rates of AOM.

For children with recurrent otitis media, daily antibiotic prophylaxis reduces the probability of developing AOM, OME, and CSOM. There is no continuing benefit after antibiotics are stopped, but this management strategy may be beneficial during high risk periods. Usual dosing regimens are half the daily treatment dose of amoxicillin or sulfonamides.

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71 Sexually Transmitted Diseases

Margaret R. Hammerschlag

Definition/Classification

Sexually transmitted diseases (STD) are infections caused by a varied group of organisms, including bacteria (*Neisseria gonorrhoeae, Chlamydia trachomatis, Treponema pallidum*), viruses (herpes simplex virus, HIV, human papilloma virus), and parasites (*Trichomonas vaginalis*) that are transmitted predominantly by sexual activity. STDs can also occur in young children, which can have serious social and medical legal implications. Children can acquire an STD during delivery from their mothers, if they happen to be infected, from sexual abuse or from consensual sexual activity as adolescents. Identification of an STD in a young child can initiate an investigation of sexual abuse. However, the diagnosis or how the infection was acquired may not be certain.

The Committee on Child Abuse and Neglect of the American Academy of Pediatrics defines child sexual abuse as "... when a child is engaged in sexual activities that he or she cannot comprehend, for which the child is developmentally unprepared and cannot give consent, and/or that violate the law or social taboos of society." Sexual activities can include all forms of oral–genital, genital, or anal contact by or to the child, and nontouching abuses, such as exhibitionism, voyeurism, or using the child in the production of pornography. Some of these activities are more likely to result in transmission of an STD. If the abuse is limited to nontouching activities, acquisition of an STD would be highly unlikely.

Epidemiology of STDs in Children Being Evaluated for Suspected Sexual Abuse

Studies of STDs in children over the past 20 years have demonstrated significant variability in the prevalence of infection. In many of the earlier studies, only symptomatic children were tested, which often gave higher prevalence of gonococcal infection than studies that tested all children being evaluated for suspected sexual abuse. Studies of *C. trachomatis* infection were not done until the 1980s. Studies of STDs in sexually abused children published since the 1990s have reported low rates of infection. Ingram et al. reported from North Carolina that among 1,538 children ages 1–12 years presenting to a tertiary referral center with a report of fondling, oral–genital and/or genital–genital sexual contact, 2.8% (39 females and 2 males) had *N. gonorrhoeae*, 1.2% had *C. trachomatis* (18 females and 0 males), 0.1% had syphilis, and 0.1% had herpes simplex virus (HSV). Robinson et al. isolated *N. gonorrhoeae* from 2/105 (1.9%) and *C. trachomatis* from 1/77 (1.3%) girls age 0–10 years attending a sexual abuse clinic in London. None of the males tested positive for an STD. Similarly, De Villiers and colleagues in South Africa detected *N. gonorrhoeae*, *C. trachomatis*, and syphilis in fewer than 2% of girls, no STI infections in boys, and no cases of HIV or HSV among 191 children presenting for sexual abuse; however, specific diagnostic methods were not described.

Four studies examining the epidemiology of STDs in children and adolescents being evaluated for suspected sexual abuse have been published since 2005 (*Table 71.1*). Three were retrospective chart reviews from Vienna, Austria, Auckland, New Zealand and Miami, Florida. Despite differences in population and methodologies, the results of the retrospective studies were fairly consistent. Charts from a total of 4,350 children were reviewed and included children from 0 to 17 years seen over a 4–7 year period. The prevalence of STDs, specifically gonorrhea and *C. trachomatis*, ranged from 0.4% to 1.8%. No child was found to have syphilis or HIV by serology. These findings are consistent with earlier published studies; however, the inclusion criteria varied greatly study to study; Simmons and Hicks only included girls who were seen within 72 h following an assault and were younger than 11 years of age, whereas the other studies included adolescents. Not every child was tested for every STD. Giradet et al. prospectively examined children 0–13 years of age being evaluated for suspected sexual abuse/assault at four tertiary care centers in the United States (Houston, TX, Atlanta, GA, Harrisburg, PA, and Brooklyn, NY). All children were tested at multiple anatomic sites for *N. gonorrhoeae* and *C. trachomatis* by culture and vaginal and urethral swabs and urine were also tested using two nucleic acid amplification tests (NAATs). Wet mounts were performed for *T. vaginalis* and cultures for HSV were done if lesions were present. Urine and

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Table 71.1
Selected studies published since 2005 of prevalence of STDs in children being evaluated for sexual abuse

N positive/tested (%)								
Study (ref)	N (total)/% Female	*N. gonorrhoeae*	*C. trachomatis*	Syphilis	HSV	*T. vaginalis*	HPV	HIV
Kelly and Koh[a]	2162 (85.8)	11/1690 (0.7)	20/1668 (1.2)	0/838	8[b]	6/1288 (0.5)	67/2162(3.1)	0/301
Kohlberger, et al.[a]	180 (100)	1/56 (1.8)	1/62 (1.6)	0/5	NS	1/136 (0.7)	NS	0/27
Simmons and Hicks[a]	2763 (100)	10/2007 (0.5)	10/2007 (0.5)	ND	ND	ND	ND	ND
Giradet, et al.[c]	536 (90.5)	16/483[d] (3.3)	15/482 (3.1)	1/384 (0.3)	5/12[e]	5/85 (5.9)	NS	0/384

ND not done, *NS* not specified
[a]Retrospective chart review
[b]Number of children tested not stated
[c]Prospective study
[d]Denominator females, none of the males were positive for any STI
[e]Testing only done in children with lesions suggestive of HSV

swabs of external genitalia were tested for HPV using L1 consensus PCR. Sera were also obtained for testing for syphilis, HIV, and type-specific antibody for HSV-1 and 2. A total of 536 children were enrolled, 485 (90.5%) were female. None of the 51 boys enrolled were positive for any infection. Forty (8.2%) of the girls were found to have one or more STDs. The prevalence of STDs varied between study sites, ranging from 1.7% in Texas to 7.8% in Atlanta. *C. trachomatis* and *N. gonorrhoeae* were detected by culture and/or NAAT in 15 (3.1%) and 16 (3.3%) of the girls enrolled, respectively. *T. vaginalis* was detected by wet mount in 5 of 85 (5.9%) symptomatic girls tested. Serologic evidence of syphilis was found in only one of 384 (0.3%) children. This child was also positive for *N. gonorrhoeae*. None of the children were positive for HIV. Cultures for HSV were obtained from only 12 children whose lesions were suggestive of herpes – five (41.7%) were positive, but only one of the culture-positive children had type-specific HSV-2 antibody. HPV DNA was detected in urine and/or genital swabs in 11.8% participants with adequate samples, but only 14 (2.6%) children had genital warts.

Clinical Manifestations: Symptoms, Signs

Most children being evaluated for suspected sexual abuse who are found to have an STD will be asymptomatic. Gonorrhea is more likely to be associated with purulent vaginitis, but rectal and pharyngeal infections are usually asymptomatic. Vaginal infection with *C. trachomatis* has not been consistently associated with vaginal discharge in children. Giradet et al. reported that the majority (67.5%) of the children with a confirmed STD had normal or nonspecific anogenital findings, only 53 (10.9%) presented with a history of a vaginal discharge and only 6.8% had clear evidence of penetrating anogenital trauma on physical examination. Of the girls with vaginal discharge, an STD was identified in 13(24.5%) compared to only 27 of 432 (6.3%) of girls who did not have a history of vaginal discharge ($p < 0.001$). Gonococcal infection was more likely to be associated with a vaginal discharge, 11 of 16 (68.8%) girls with a positive culture and/or NAAT for *N. gonorrhoeae* were symptomatic, compared to 8 of 15 (53.3%) girls with positive culture and/or NAAT for *C. trachomatis*. Three of five (60%) girls who had *T. vaginalis* identified on wet mount had a history of vaginal discharge. Clinical diagnosis of HSV infection can be problematic, only 5 of 12 (41.7%) children with genital lesions suggestive of herpes in the multicenter study were culture positive for HSV. Like adults, children with acquired genital herpes can have recurrences, although data on the duration and number are limited. Acute HSV-2 genital infection can also be associated with aseptic meningitis which is frequently self-limited (Mollaret's meningitis). This may also recur without recurrence of genital lesions.

Diagnosis

N. gonorrhoeae. The identification of *N. gonorrhoeae* in a child beyond the immediate neonatal period (defined as beginning at birth and including the first month of life) is indicative of some kind of sexual contact. The Centers for Disease Control and Prevention (CDC) 2010 STD Treatment Guidelines recommends that specimens for culture of *N. gonorrhoeae* be collected from the vagina in girls, the

pharynx and anus of girls and boys, and the urethra in boys being evaluated for suspected sexual abuse.

Culture remains the preferred method for detection of *N. gonorrhoeae* in children, primarily because it has the highest specificity. If possible, specimens should be plated directly onto selective media; however, this is generally not feasible in most practice situations. There are swab transport systems that can be used, including several commercially available systems that use selective media. Specimens then should be plated on enriched selective media. Presumptive isolates need to be confirmed as *N. gonorrhoeae,* Gram stain morphology and oxidase is not sufficient, especially when selective media are not used. The 2010 CDC STD Treatment Guidelines recommends that that presumptive isolates of *N. gonorrhoeae* obtained from children being evaluated for suspected sexual abuse be confirmed by at least two tests that involve different principles: biochemical, enzyme substrate, serological, or nucleic acid hybridization test methods. Use of multiple confirmatory tests is necessary as some of these confirmatory methods, specifically biochemical and serologic, can misidentify other Neisseria species as *N. gonorrhoeae.* This is especially important when testing specimens from the rectum and pharynx.

Use of NAATs has supplanted culture for detection of *N. gonorrhoeae* in adults in many laboratories. Currently, there are three commercially available, FDA-approved NAATs for *N. gonorrhoeae* and *C. trachomatis* in the United States: polymerase chain reaction (PCR) (Amplicor, Roche Molecular Diagnostics), strand displacement amplification (SDA) (ProbeTec, Becton Dickinson), and transcription-mediated amplification (TMA) (Aptima C2, GenProbe). PCR and SDA are DNA amplification; TMA is an RNA amplification assay. All three are FDA approved for use in genital sites (cervix, vagina, urethra) and urine from adolescents and adults. None are currently approved for extragential sites (pharynx or rectum) or have approval for any site in children. NAATs offer several advantages over culture-based methods including higher sensitivity and enabling the use of noninvasive specimens (urine, vaginal swabs), these assays have some limitations, especially for detection of *N. gonorrhoeae.* The gonococcus has the capacity for genetic variation and recombination that can affect the genetic sequences that are targets for amplification and are fully competent for exogenous DNA uptake throughout their life cycle. This enables frequent horizontal interspecies exchange of genetic material between *Neisseria* species leading to commensal *Neisseria* species acquiring gonococcal sequences and vice versa which can lead to both false-positive and false-negative results with certain NAATs. PCR and SDA have been demonstrated to have cross reactivity with other *Neisseria* species including *N. cinerea, N. flavescens, N. lactamica, N. sicca*, and *N. subflava.* This has important implications especially when testing extragential sites. Black et al. recently evaluated the use of SDA and TMA using urine and genital swabs versus culture for diagnosis of *N. gonorrhoeae* and *C. trachomatis* in children, 0–13 years of age. All children were tested at multiple sites for *N. gonorrhoeae* and *C. trachomatis* by culture and vaginal and urethral swabs and urine were also tested with SDA and TMA. Positive NAATs for *N. gonorrhoeae* were confirmed by an in-house PCR using an alternate target, the *Hinf*I fragment of the 4.2-kb cryptic plasmid. Sixteen of 485 (3.3%) girls had a positive result for *N. gonorrhoeae* by any test: 12 (2.5%) by culture, 14 (2.9%) by vaginal NAAT, and 14 (2.9%) by urine NAAT. All participants who had a positive vaginal culture for *N. gonorrhoeae* had positive urine NAATs. All positive NAAT results were confirmed by the alternative target PCR. These data suggest that NAATs, specifically SDA and TMA, may be alternatives to culture for the detection of *N. gonorrhoeae* in vaginal swabs and urine in prepubertal girls. As the prevalence of gonorrhea in children being evaluated for suspected sexual abuse is low, confirmatory testing is essential. Culture is still preferred for extragential specimens and any specimen from boys.

C. trachomatis. The CDC currently recommends that children being evaluated for suspected sexual abuse be tested for *C. trachomatis* at the anus in boys and girls and from the vagina in girls. The CDC does not recommend obtaining urethral specimens from boys as available data suggests that the likelihood of recovering *C. trachomatis* is too low to justify the trauma of obtaining an intraurethral specimen, but recommends a specimen from the meatus if obvious discharge is present. Pharyngeal specimens from children of either sex are also not recommended, as the prevalence of infection at this site is very low. Culture currently remains the method of choice for detection of *C. trachomatis* in children being evaluated for suspected sexual abuse. The CDC specifies that only standard tissue culture systems should be used. Cycloheximide-treated McCoy cells are used by most laboratories. The isolation of *C. trachomatis* in tissue culture should be confirmed by the microscopic identification of the characteristic intracytoplasmic inclusions, preferably by staining with a species-specific fluorescein-conjugated monoclonal antibody. Use of genus-specific antibody for culture confirmation can lead to misidentification of *C. pneumoniae* as *C. trachomatis* in pharyngeal specimens. Enzyme immunoassays (EIAs) are not acceptable as confirmatory tests and have been associated with

false-positive results, especially when used with vaginal and rectal specimens due to cross-reactions with bacteria present in the anogenital tract and nonspecifically react with fecal material. However, because confirmation is dependent on visual identification of inclusions, there is still a subjective component that could lead to misidentification of artifacts as chlamydial inclusions. This appears to have recently happened in a large commercial laboratory in the United States where instead of using a fresh positive control for each culture run they used a "previously positive" specimen to save time (M. Hammerschlag, personal communication). The incidence of *C. trachomatis* infection in children being evaluated for suspected sexual abuse increased from 2% to nearly 50% after the procedure was changed. Review of the laboratory's procedure confirmed that technicians were identifying cellular debris as inclusions.

NAATs are approved for detection of *C. trachomatis* from genital sites (cervix, vagina, urethra) and urine from adolescents and adults. None are approved for extragential sites (pharynx or rectum) or have approval for any site in children. These methods have been found to have excellent sensitivity for detection of *C. trachomatis*, >98%, in genital specimens and urine from adult men and women, while maintaining high specificity. As with *N. gonorrhoeae,* data on the use of available NAATs for detection of *C. trachomatis* in children are limited. The multicenter study by Black et al. also evaluated the use of SDA and TMA compared to culture for diagnosis of *C. trachomatis* in children. *C. trachomatis* cultures were performed at the clinical or hospital laboratories of each center, according to their own standard protocols. Fifteen (3.1%) of 485 female participants had a positive result for *C. trachomatis* by any test (7 [1.4%] by culture; 11 [2.3%] by vaginal NAAT; 13 [2.7%] by urine NAAT). All participants who had a positive vaginal culture had positive urine NAAT. Two girls had positive *C. trachomatis* cultures from rectal swab specimens, but negative vaginal swab specimens by both culture and NAATs (vagina and urine). All NAAT-positive/culture-negative specimens were confirmed by PCR testing at the CDC.

Syphilis. The prevalence of syphilis in children being evaluated for suspected sexual abuse is very low, <1% in most studies. The diagnosis of syphilis was based on serologic screening and the majority of these children were asymptomatic. Cases of symptomatic syphilis appear to be uncommon and are mostly limited to anecdotal reports. Clinical findings have included primary chancres, manifestations of secondary syphilis including rash and condyloma lata, which can be misdiagnosed as genital warts. The major confounding variable in the diagnosis of syphilis in children beyond the neonatal period is differentiating between acquired and congenital infection. As most pregnant women in the United States are screened for syphilis during pregnancy, congenital infection could be ruled out if maternal records can be accessed. However, this may not always be possible and for some the clinical manifestations of congenital syphilis may overlap with those of acquired syphilis. Serology remains the primary method for diagnosis. A non-treponemal test, either the rapid plasma reagin (RPR) or venereal disease research laboratory (VDRL) tests, which, if positive is then confirmed by a *T. pallidum*-specific test. These tests are useful for monitoring the efficacy of treatment; however, a number of other infections and diseases, including malaria, leprosy, and autoimmune conditions (systemic lupus erythematosus), can lead to the induction of anticardiolipin antibodies and cause false-positive results with RPR and VDRL (12, 24). The antibodies detected by RPR and VDRL are IgG and are transported across the placenta during pregnancy. The most frequently used *Treponema*-specific test is the fluorescent treponemal antibody absorption (FTA-ABS) test. Other available *Treponema*-specific tests are the *T. pallidum* hemagglutination assay (TPHA) and *T. pallidum* particle agglutination assay (TPPA). Anti-treponemal antibodies are usually present for life even after successful treatment, thus they cannot be used to monitor the efficacy of treatment or to distinguish between active and past infection. These assays also detect IgG antibody, thus will cross the placenta. Currently, there are no treponemal-specific IgM assays available. Because performance of the RPR and FTA-ABS is very labor intensive, many laboratories are now using treponemal EIAs for high-throughput screening, then confirming positive results with a non-treponemal test, reversing the traditional syphilis screening sequence. Currently, there are more than nine commercially available EIAs for *T. pallidum* antibodies. Some of these assays will also detect IgM antibodies in addition to IgG. As with FTA-ABS and other treponemal-specific tests, these antibodies remain positive throughout life. Several recent studies have demonstrated significant variation in performance of these assays; some may not be appropriate as stand-alone tests for screening or confirmatory syphilis serology. None of these assays have been evaluated for diagnosis of syphilis in children and are not recommended for diagnosis of congenital syphilis in infants.

If a child has lesions of primary or secondary syphilis, that is, chancre or condyloma lata, *T. pallidum* can be visualized in tissue exudates using dark-field microscopy and direct fluorescent-antibody-*T. pallidum* (DFA-TP) test or by PCR. Epidermal or mucosal lesions in primary

and secondary syphilis tend to contain high numbers of treponemes. Because of the technical challenges of dark-field microscopy and DFA-TPA should only be performed in an experienced laboratory. There are no FDA-approved, commercially available NAATs for detection of *T. pallidum*.

Herpes simplex virus (*HSV*). The overwhelming majority of published studies of STIs in children being evaluated for sexually abused have only tested for HSV in children who presented with suggestive genital lesions. The prevalence of HSV, mostly HSV-2, infection in these studies has been <5%. One study from South Africa performed cultures for HSV on all the children being evaluated ($n = 227$), none were positive for HSV. As most studies have only tested symptomatic children, there is no way of knowing how common asymptomatic infection may be in these children, even as more evidence emerges about the frequency of asymptomatic and subclinical infections in adults.

Culture. If active genital lesions are present, the vesicle should be unroofed for sampling of vesicular fluid for culture by swabbing the base of the lesion. However, the overall sensitivity of viral culture of genital lesions in adults is only approximately 50% compared to PCR. The diagnostic yield is highest in the early stages of disease when lesions are typically vesicular rather than in the later stages when lesions have largely crusted. Viral isolation rates are also higher with primary compared to recurrent genital herpes, particularly in the setting of asymptomatic recurrences with subclinical shedding.

NAATs. Real-time HSV PCR assays have emerged as a more sensitive method to confirm HSV infection in clinical specimens and are particularly useful for the detection of asymptomatic HSV shedding in adults. The main limiting factor in adopting real-time HSV PCR as the primary diagnostic tool in many clinical reference laboratories is the cost of the assay, which substantially exceeds that of viral isolation culture techniques. In addition, the lack of uniform validation of the PCR assay as a diagnostic method for detecting HSV in clinical specimens other than cerebrospinal fluid has limited its availability in some commercial laboratories. These are all in-house assays, there are no commercially available, FDA cleared PCR assays. PCR has not been evaluated at anogenital sites in children.

Tzanck smear. The Tzanck smear, which may demonstrate the cytopathic effect of the virus (multinucleate giant cells), and can be performed on lesion scrapings from patients with active genital lesions. However, it has limited utility since it has low sensitivity and specificity and should not be used in anogenital specimens from children and will not differentiate HSV from varicella-zoster virus.

Serology. Type-specific antibodies to HSV develop during the first several weeks after infection and persist indefinitely. The availability of type-specific serology using surface glycoproteins (Gg2 and Gg1 for HSV-2 and HSV-1, respectively) to distinguish HSV-1 and HSV-2 enables the clinician to determine if the patient is at risk of acquisition or has evidence of prior infection with either subtype. The presence of HSV-2 indicates anogenital infection, but the presence of HSV-1 can be consistent with either anogenital or orolabial infection. The sensitivities of HSV IgG type-specific tests vary from 80% to 98% in adults. False-negative results may occur at early stages of infection; the specificity of these assays is greater than 96%. Several FDA-approved type-specific HSV serologic tests are commercially available. Data on use of these assays in children are very limited. Giradet et al. tested sera from 283 children for HSV-1 and 2 antibodies using an immunodot enzyme assay with a monoclonal antibody inhibition for confirmation performed at the CDC. Antibody to HSV-1 was detected in 45.6%, antibody to HSV-2 was detected in seven (2.5%) children, three children had antibody to both. Only one of five culture-positive children had HSV-2 antibody. These data suggest that type-specific serology for HSV has a poor predictive value for diagnosis of HSV infection in children being evaluated for suspected child abuse. The performance of even FDA-approved tests can be inconsistent in a low-prevalence population.

Trichomonas vaginalis. Most published studies of STIs in sexually abused children have testing for *T. vaginalis* was limited to girls presenting with vaginal discharge. The presence of motile trichomonads on wet mount of vaginal secretions is diagnostic of infection, but this occurs in only 50–70% of culture-confirmed cases in adult women. The organisms remain motile in saline for 10–20 min after collection of the sample. Care should be taken in interpretation when trichomonads are reported present in urine specimens from children collected for another purpose. As the morphology of *Pentatrichomonas* (*Trichomonas*) *hominis,* a nonpathogenic intestinal flagellate, is very similar to that of *T. vaginalis*, care must be taken to make sure that specimens are not contaminated with fecal material. This could present a problem in children that are not toilet trained and in diapers and with bagged urine specimens.

Culture. Culture on Diamond's medium has a high sensitivity (95%) and specificity (>95%). Incubation periods of 2–7 days are needed to indentify *T. vaginalis* in culture. There are very few reports of use of culture in children. A commercial "In Pouch" *T. vaginalis* culture system can be used and is readily available (BioMed Diagnostics, White City, Oregon).

Rapid antigen and NAATs. Several rapid diagnostic kits using DNA probes and monoclonal antibodies have been developed commercially, with a sensitivity of 90% and a specificity of 99.8% in vaginal specimens from women with clinical vaginal discharge. The Affirm VP III Microbial Identification System (Becton Dickinson) test is a direct nucleic acid probe hybridization test for detection of *T. vaginalis, Gardnerella vaginalis*, and *Candida* spp. It has been reported to have sensitivities of 80–90% in adult women with vaginitis but has not been validated or approved for used in genital specimens from prepubertal girls or urethral specimens from men. False-positive results have been reported when used in children and adult men. The OSOM TV (Genzyme Diagnostics) is an objective rapid antigen detection test that has been demonstrated to perform very well in adolescent women with sensitivities significantly higher than wet mount or culture. Again, this test has not been validated or approved for use in children. GenProbe has introduced a TMA-based NAAT for *T. vaginalis* (APTIMA TV) that is expected to receive FDA clearance in 2011. Preliminary studies have demonstrated that this assay is highly sensitive and specific compared to wet mount microscopy, culture and an in-house PCR for the diagnosis of trichomoniasis in women and men. However, there are no data on use of this assay in children of either sex.

Human papillomavirus (*HPV*). The association of genital warts and sexual abuse in children is complicated by the long period of latency before lesions become clinically apparent and possibility of nonsexual transmission, either vertically during delivery or horizontally after birth. Criteria for diagnosis of HPV infection in children; clinical versus detection of HPV DNA, is also not standardized. Most published studies of HPV infection in children being evaluated for sexual abuse have relied on the presence of clinical lesions consistent with genital warts for the diagnosis of HPV infection.

Detection of HPV DNA. Several studies have evaluated detection of HPV DNA in children being evaluated for suspected sexual abuse; however, the results have been contradictory and have demonstrated poor correlation of detection of HPV DNA by PCR and presence of genital warts. There is also a great deal of heterogeneity of the PCR methods used; most were in-house assays which have used generic primers followed by either probing or sequencing of the products. Nested-PCR assays were used in some studies. Use of generic HPV PCRs may be less sensitive than specific HPV 16 PCR. Even so, the association of the presence of HPV DNA with abuse is not very strong; although HPV DNA has been detected in genital and rectal swabs in 15% of girls thought to be abused, it has also been detected in vaginal and/or anal specimens from 2.1% of healthy children with no history of abuse. There is only one FDA-approved test available for detection of HPV DNA in cervical specimens from adult women (Hybrid Capture II, Digene Corporation), and several more are currently being evaluated. The primary use of these assays is for detection of high-risk types HPV in the management and prevention of cervical cancer. HPV DNA testing is not recommended for persons with anogenital warts and has not been evaluated for detection of HPV in children. Routine screening of children suspected of being sexually abused for HPV DNA is not indicated at this time.

Treatment of STDs in Children

Because of the forensic implications and low prevalence of infection, the CDC recommends that children being evaluated for suspected sexual abuse not be treated prophylactically, but based on the results of microbiological studies.

Gonococcal infections. The treatment of choice for uncomplicated urogenital gonococcal infections in children is single-dose intramuscular ceftriaxone: for children <45 kg, 125 mg, >45 kg, 250 mg. Although oral single-dose cefixime is recommended for the treatment of uncomplicated genital gonococcal infections in adults, it has not been studied for this indication in children and is not recommended by the CDC. Single-dose cefixime is recommended for children by the Canadian Guidelines on Sexually Transmitted Infections: children under 9 years of age, 8 mg/kg PO in a single dose to a maximum of 400 mg, for children 9 years of age or older, 400 mg as a single oral dose. Quinolones are not recommended by either set of guidelines because of high level of quinolone resistance in many populations, in some area exceeding 60%. Options are limited for patients that are allergic to beta-lactam antibiotics. Spectinomycin is no longer available in the United States. Azithromycin as a single 2 g oral dose is an alternative regimen in adults but there are no data in children. Macrolide resistance has also been increasing, especially in Europe.

C. trachomatis. The current recommended regimen for children <45 kg is erythromycin base or ethylsuccinate, 50 mg/kg/day po in four divided doses for 14 days. For children who are ≥ 45 kg but <8 years of age, azithromycin, 1 g po in a single dose. Children ≥ 8 years can also be treated with 1 g azithromycin or doxycycline, 100 mg bid for 7 days.

Syphilis. Children with acquired primary or secondary syphilis should be treated with benzathine penicillin G, 50,000 Units/kg IM up to the adult dose of 2.4 million units in a single dose. If there is a credible history of penicillin allergy, the child should be desensitized. There are no alternatives to penicillin for the treatment of syphilis in children.

HSV. Recommended regimen for the first episode of genital HSV infection in children 2–12 years of age is acyclovir, 1,200 mg/day po divided q 8 h for 7–10 days, with a maximum of 80 mg/kg/day, for recurrences 1,200 mg/day po divided q 8 h for 5 days, with a maximum of 80 mg/kg/day or 1,600 mg/day po q 12 h. For suppressive therapy, 80 mg/kg/day in three divided doses to a maximum of 1,000 mg/day or 400 mg po bid. The need for continued suppression should be assessed after 1 year of treatment.

T. vaginalis. There are no regimens specifically recommended for treatment of children. One can use metronidazole, 30 mg/kg/day po qid to a maximum of 400 g/day for 7 days.

HPV. There are no regimens specifically recommended for treatment of genital warts due to HPV in children. Treatment should be done in consultation with a dermatologist.

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72 Viral Exanthem

Mohammad Al-Shaalan

Illustrative Case

An 18-month-old boy was brought to the clinic because of 1 day history of erythematous rash over hands and forearms as well as feet. This rash was associated with fever. The rash was judged by physician to be urticarial in nature and he was given oral prednisone for 3 days. His condition improved slightly but 1 day after stopping the steroid, fever recurred and the rash became more widespread to involve the trunk and face. It was noticed to be more pronounced in the diaper area. His conjunctiva and lips were also red. He was admitted to the hospital and was judged to have Steven-Johnson syndrome and was given parenteral methylprednisone for 5 days. His condition improved slightly and was discharged from the hospital. At home, he was noted to have skin peeling of the hands and feet. His fever relapsed 2 days after discharge. He was seen again in a tertiary hospital and he was found to have high fever of 39.7°C, strawberry tongue, fissured red lips, and maculopapular skin rash over the trunk and limps. His complete blood count showed a platelet of 768,000/mm^3 and his ESR was 105 mm/first h. He was diagnosed to have Kawasaki disease and was given intravenous immunoglobulin and his condition improved dramatically. Fortunately, his echocardiogram came to be normal and the repeated echocardiogram in 6 weeks was also normal.

Children presenting with rash and fever may face the treating physician with a challenge. Although some diseases have typical rashes (e.g., chicken pox), others may have rashes that are difficult to differentiate.

Therefore, such children need a systematic approach that could help in reaching correct diagnosis. Such approach includes:

1. Thorough history including antecedent symptoms; rash morphology, distribution and course; associated symptoms of itching or pain; contact with persons with similar rashes, travel, contact with pets, and drug history
2. Complete physical examination with attention to vital signs, mucus membrane involvement, lymphadenopathy, organomegaly, and distribution of the rashes, characters of the rashes, skin examination for ulcers, genital examination, and scalp examination

Once clinical assessment has been done, an initial idea may have been reached which will help in selecting laboratory aids to reach the diagnosis. For example, scalp involvement is rare except in chicken pox or ringworm infection. Palmer and solar involvement is common with secondary syphilis and blenorrhegica keratosis of Rieter's disease. Other diseases that involve palms and soles include hand-foot-mouth disease, chickenpox, herpes simplex, drugs, endocarditis, RMSF, EM, and atypical measles.

Definition of Exanthematous Lesions

Macular or Maculopapular Lesions

Macules are nonelevated discolored skin lesions. Papules are raised lesions that measure <0.5 cm in diameter. Most of the cases of maculopapular exanthems are caused by viral diseases; however, it may be caused by drug reaction or connective tissue diseases.

Vesiculopustular Lesions

Vesicles are small fluid-filled skin lesions that measure <0.5 cm in diameter, larger lesions are termed bulli. Vesicular lesions are caused by viral illness like herpes viruses and enteroviruses.

Nodular Lesions

Nodules are deep-seated skin lesions that are firm in consistency. These lesions are caused by fungal or mycobacterial infections especially when associated with local lymphadenopathies. Erythema nodosum is characterized by erythematous nodular lesions that are usually distributed symmetrically over the lower limbs. Rarely upper parts of the bodies may be involved. Erythema nodosum is commonly caused by streptococcal, fungal,

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and myobacterial infection, sarcoidosis, and drugs, for example, contraceptive pills.

Ulcerglandular Lesion

Ulcerated lesions that are associated with localized lymphadenopathy are mostly of infectious origin. Some of these diseases are associated with generalized maculopapular skin rashes. Therefore, any patient with generalized skin rashes should be examined for local eschar or ulcer.

Purpuric Lesions

These lesions represent extravasation of the blood from the vessels or severe vasculitis. They present as small petechiae, purpura, or ecchymoses. Purpuric lesions in children are of special concern to the pediatrician because they might be due to an overwhelming infection like meningococcemia or severe sepsis with DIC. Other diseases that my present with petechial lesions include RMSF and enteroviral infection.

Common Exanthematous Diseases of Childhood

Measles

Measles is an exanthematous disease caused by an RNA paramyxovirus. After an incubation period of 8–10 days, a prodrome of coryza and fever start. This prodrome is associated with the pathognomic feature of measles which is the Koplik's spots (*Fig. 72.1*). These Koplik's spots appear as salt-like dots on erythematous base. It occurs mainly over the buccal mucosa, but it can be seen in the conjunctiva and rectal mucosa. The prodrome lasts for 2–4 days to be followed by appearance of macular rashes which start in the face and proceed caudally and peripherally to involve the whole body in 2–3 days. The rash tends to coalesce and form blotchy spots. After 3–5 days, the rash fades in the same way it appeared. Measles is still a major disease of childhood mostly in some of the developing countries. It also causes outbreaks in many developed and developing countries. Around 450,000 deaths occur annually as a result of measles infection. Recent strategies for measles eradication included introduction of an extra vaccine dose at school entry as well as mass vaccination for children in areas where measles is still endemic.

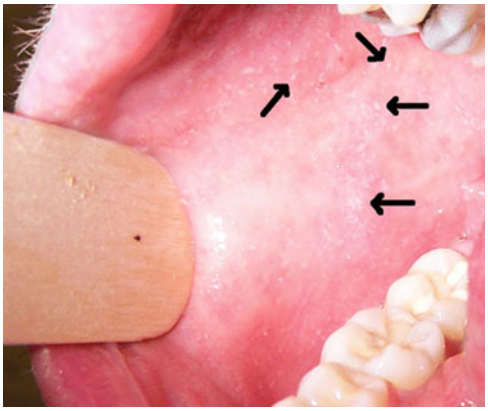

Figure 72.1
Koplik spots

Rubella

Rubella, or German measles, is caused by an RNA togavirus. Children of all ages may be affected but it occurs more commonly in adolescents. As many as 5% of 19–30 year old women are seronegative for rubella making them at high risk of acquiring infection during pregnancy and thus risking to have congenitally infected babies. Incubation period is 14–21 days. The rashes appear suddenly or after a prodrome of mild coryza. The rash is characterized by fine discrete macules that involve the trunk more than extremities. By 3–4 days of illness, the rashes spread to extremities and fade from the trunk. Most of the patients will have generalized lymphadenopathy with predilection to occipital region. Older patients may have an associated arthritis.

Erythema Infectiousum

Erythema infectiousum or fifth disease is caused by parvovirus B19. In children, it starts with erythematous rashes of both cheeks (slapped cheeks). Reticular or fine macular rashes appear on the trunk (*Figs. 72.2* and *72.3*). The rashes have a characteristic feature of fading and exacerbation triggered by local irritation, high temperature, and emotional stresses. Associated clinical features include lymphadenopathy and arthritis or arthralgia in older patients.

Exanthem Subitum

Roseola or sixth disease is caused by human herpes virus-6. Classic presentation includes 3–5 days of high fever in young

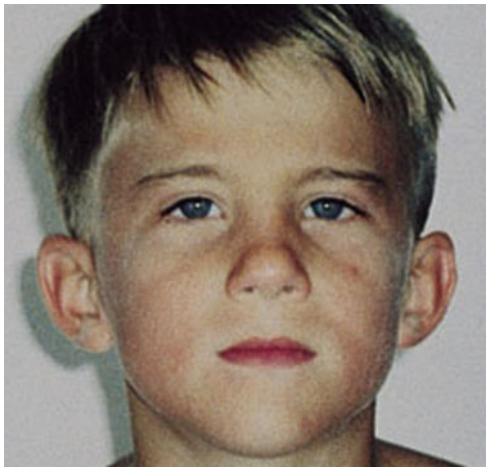

Figure 72.2
Slapped cheek erythema

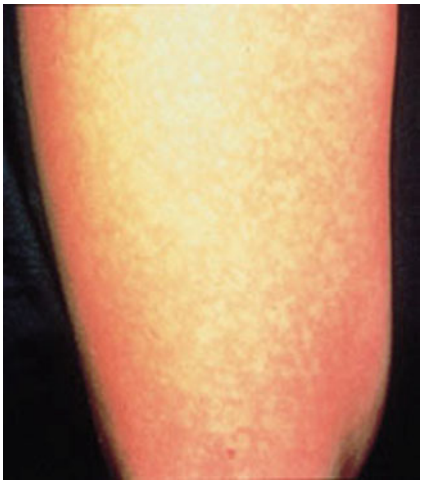

Figure 72.3
Reticular rashes

child without systemic toxicity followed by lysis of temperature and appearance of diffuse macular rashes. Most of the patients have lymphadenopathy especially of occipital region and more than 50% have red tympanic membranes. Recently, it has been found that roseola can present in atypical form with fever and rashes appearing at the same time. In older children, it may cause mononucleosis-like symptoms. After acute infection, the virus remain dormant in salivary gland cells, monocytes/macrophages, hematopoietic stem cells, and microglia cells.

Hand-Foot-Mouth Disease

This is an exanthem caused by enteroviruses, the commonest of which is coxsackei A16. It commonly affects young children. After an incubation period of 3–6 days, a prodrome of low-grade fever, sore throat, and abdominal pain begin, followed by eruption of exanthem over the dorsal surfaces of the hands and feet in 2–4 days, as well as palmar and solar surfaces. These exanthems are typically gray vesicles surrounded by erythematous border (*Fig. 72.4*). They are painful and last for 7–14 days. Mucous membranes of the mouth is also involved in most of the cases and characterized by vesicular lesions that are painful but not to the extent of the herpetic lesions. Also, the gingiva is not as involved as in herpes. Diagnosis is usually clinical, however when needed, viral culture of the vesicular fluid can be done. Treatment is supportive and most of the time self-resolving. Occasional cases of HFMD caused by enterovirus 71 may be severe and may cause some mortality.

Papular Purpuric Gloves and Socks Syndrome (PPGSS)

PPGSS is characterized by petechial and confluent purpuric rashes with edema that is limited to the hands and feet and associated with itching. Enanthem aphthous ulceration of mouth mucosa may occur. The disease is self-limiting and only needs analgesia.

Gianotti–Crosti Syndrome (GCS)

GCS is an acrodermatitis papulovesicular exanthema that occurs secondary to a number of viral infections including hepatitis B, EBV, RSV, parainfluenza, coxsackie, parvovirus, and HHV 6. The exanthematous rashes involve the cheeks, extensor aspects of extremities, and gluteal area (*Figs. 72.5* and *72.6*). Affected patients have positive Kobner phenomenon which is noticeable with tight clothing. GCS is a self-limited disease and only observation is needed.

Epstein–Barr Virus

It is a DNA virus belonging to herpes virus group. It causes a variety of clinical diseases. The most classical form is infectious mononucleosis, which is more common in adolescents. Its presentation consists of generalized lymphadenopathy, hepatosplenomegaly, facial and acral edema, and palatal enenthem. Diffuse skin rashes may be

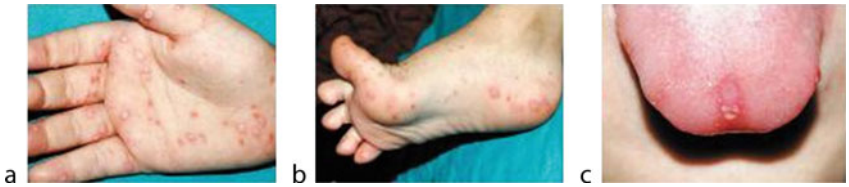

Figure 72.4
Hand foot mouth rashes

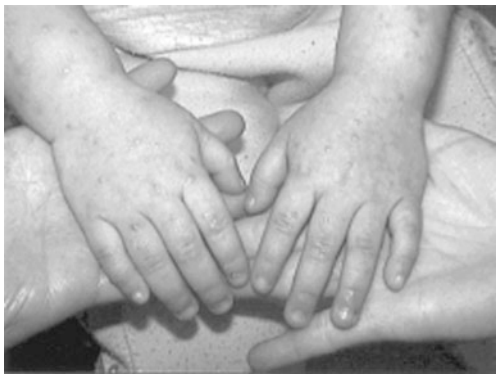

Figure 72.5
Gianitti Crosti rashes

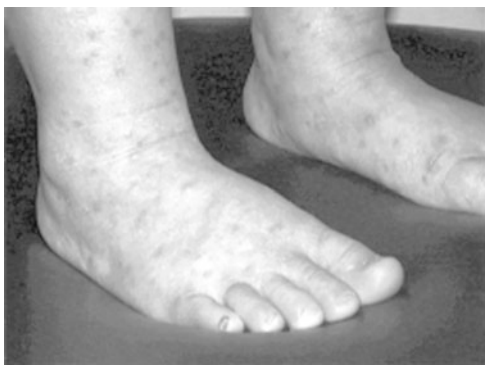

Figure 72.6
Gianitti Crosti rashes

present. Patients with IM who receive ampicillin therapy develop diffuse macular coalescent rashes 1 or 2 days after receiving ampicillin.

Cytomegalovirus (CMV)

CMV can cause infectious mononucleosis-like syndrome. In addition, it may present with subtle symptoms of upper respiratory tract infection and diffuse skin rash. Congenital CMV infection may present with diffuse petechial or purpuric rash.

Adenovirus Infections

Exanthem occurs less frequently with adenoviral infections. When present, it is usually in the form of diffuse macular rashes. Diseases that are commonly caused by adenoviral infections include pharyngoconjunctival fever, pneumonia, gastroenteritis, and cystitis.

Scalded Skin Syndrome (SSSS)

This illness is caused by *Staphylococcus aureus* phage II, which is able to produce an exfoliative toxin resulting in the manifestation of generalized erythoderma followed by skin peeling especially in areas which are exposed to friction or trauma (Nikolsky's sign). Most of the patients have a focus of staphylococcus infection including skin abscess, boil, osteomyelitis, septic arthritis, or other foci. Bacteremia and septicaemia are rare. It may resemble toxic epidermal necrolysis (TEN); however, in skin biopsy the line of separation of skin is intraepidermal in SSSS and subepidermal in TEN.

These patients require supportive therapy by maintaining hydration and relieving the pain. In addition, systemic antibiotics effective against *S. aureus* like cloxacillin or methicillin need to be administered to eradicate the organisms secreting the inflicting toxin.

Toxic Shock Syndrome (TSS)

When first identified, it was related to using tampons by menstruating women. However, it is now known to occur in children and persons who do not use tampons. The major causative organism is *S. aureus*; however, recently group A streptococcus is being recognized as another major cause.

Affected patients present with fever, hypotension, and generalized erythema. In addition, mucus membranes involvement is common with conjunctivitis and strawberry tongue manifestation. Case definition of TSS is based on the following criteria: fever of 38.9°C or more; presence of diffuse macular erythroderma; desequamation 1–2 weeks after onset of illness particularly of palms and soles; hypotension defined as a systolic blood pressure of 90 mmHg or less for adults and below the fifth percentile for children younger than 16 years of age; or an orthostatic drop in diastolic blood pressure of 15 mmHg or more with a change from lying to sitting, orthostatic syncope or orthostatic dizziness; Involvement of three or more of the following organ systems: gastrointestinal, muscular, mucus membrane, renal, hepatic, hematological, and central nervous system. TSS can be confused with many febrile illness with macular rashes and mucus membrane involvement like Kawasaki disease, scarlet fever, measles, RMSF, or leptospirosis.

Kawasaki Syndrome

First identified in Japan, this disease now occurs in all races and all communities. It commonly affects children <2 years of age; however, it can occur in children up to age 10 years. Affected children usually present with remittent fever and severe irritability. In 2–3 days, rash appears which is usually polymorphus; however, any type of rashes may occur. Perianal area erythema is common as well as erythema at the site of previous BCG vaccination. Hand and feet edema and erythema appear at the same time.

Periungunal skin peeling occurs by the end of 7–10 days. The peeling may involve the hands and rarely other part of the body. Thrombocytosis becomes apparent by the end of the first week.

Mucus membrane involvement is common with conjunctivitis and strawberry tongue, lip erythema and fissuring is characteristic. Cervical lymphadenopathy occurs in 50% of the patients with single or multiple lymphadenopathy. The lymph node may be tender.

Scarlet Fever

Scarlet fever is an exanthematous skin disease caused by Group A streptococcal infection. It is associated with systemic illness. The infection mostly occurs in the throat. However, skin lesion may result in surgical scarlet fever. The patient usually present with sore throat for 1–2 days followed by skin eruption that involves trunk and extremities. The rash is sandpaper in texture and is accentuated in the flexural surfaces resulting in Pastia's lines (*Fig. 72.7*). There is facial flushing with sparing of perioral area. The course of illness is 5–7 days and it responds to antibiotic therapy promptly.

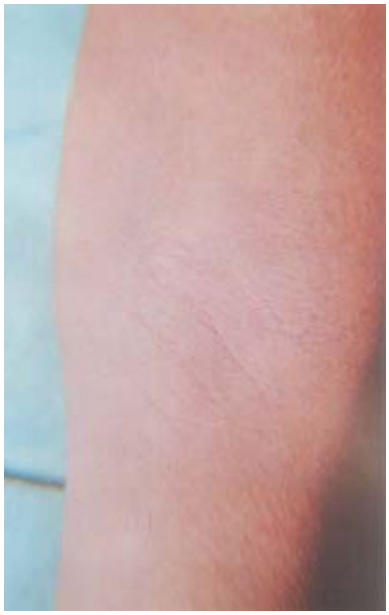

Figure 72.7
Pastia's lines in scarlet fever

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73 Antibacterial Therapy

Mohammad Al-Shaalan

Antibacterial therapy has made a big revolution in medicine; however, a judicious use of these drugs is very important in order to decrease the emergence of resistance. The antibiotic use can be one of the following ways:

- Empirical as in suspected sepsis in infant below 3 months of age and initial management of meningitis
- Specific as in streptococcal pharyngitis, otitis media, and cellulitis, or prophylaxis as in UTI prophylaxis

When used as empiric therapy, usually broad spectrum antibiotics are used, however this should only be for 24–48 h until the result of cultures are obtained and then narrowed to specific therapy according to isolated organism. Specific therapy should be chosen for the most likely organism, unless the patient is seriously sick in which case it should be broad until the causative organism is isolated (*Table 73.1*).

The duration of antibiotic therapy is mostly of arbitrary choice; however there is some agreed duration for specific conditions. Longer duration should be considered for those infection caused by slow-growing intracellular organism like Mycobacterium tuberculosis and Brucella spp, in situation where the achieved antibiotic level is usually low like bone and in situation where relapse is not desirable like CNS infection.

It is always advisable to monitor the use of antibiotics in each health center. Steps that are helpful to streamline the antibiotics use include:

- Appropriate history and physical examination leading to adequate tentative diagnosis
- Antibiotic use only if a bacterial infection is highly expected
- Obtaining cultures as possible
- Considering the use of the least expensive and narrowest spectrum antibiotic possible
- Attention for the side effects and drug interaction of the used antibiotic
- Prophylaxis antibiotic use should be limited to minimum and used in those situations where there is evidence of their value
- Follow the AAP/CDC guideline for judicious use of antibiotics

Pharmacokinesis

This indicates the mechanics of absorption, distribution, metabolism, and elimination. Antibiotics can be used orally, parenterally, or can be applied topically. All serious bacterial infections should be treated parenterally. Oral route can be used to treat mild to moderate infections like otitis media, sinusitis, or mild skin infection. Absorption of some antibiotics may be reduced if taken with foods; therefore, the patients should be advised to take them either 1 hour before or 2 hour after the meal. Examples of such antibiotics include azithromycin, clarithromycin, ampicillin, cloxacillin, clofazimine, doxycycline, piperazine citrate, rifampin, and thiabendazole. Topical antibiotics for which there is a systemic formulation should be limited in its use to decrease emergence of resistance.

The distribution of an antibiotic is determined by many factors which include molecular weight, lipid solubility, ionization, and protein binding. Drugs that have high volume of distribution tend to be of small molecular weight, water soluble and of low protein binding.

The two main routes of antibiotics elimination are either kidneys or liver or both. Accordingly, dosage should be modified if one of these organs is affected (*Table 73.2*). The following drugs need no modification with renal impairment; azithromycin, Ceftriaxone, chloramphenicol, clarithromycin, doxycycline, isoniazid, itraconazole, nafcillin, pyrimethamine, and rifampin.

Variations do exist among children of various age groups and between children and adults. Neonates tend to be a slow metabolizer, having large volume of distribution and having low excretion. This is due to immaturity of liver metabolism, larger extracellular water, and lower glomerular filtration, respectively.

Therefore, consideration for dosing as well as frequency of administration should be considered for younger age groups as well as in those with impaired liver or renal function.

Pharmacodynamics

The aim of using an antibiotic is to prevent the growth of bacteria either by suppressing their proliferation

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Table 73.1
Treatment of common infections

Condition	Management	Alternative therapy	Comment
Acute otitis media	Amoxicillin (high dose)	Cefuroxime axetile, augmentin, cefaclor, azithromycin, or clarithromycin	Recurrent or persistent OM need evaluation with tympanometry, tympanocentesis, and hearing assessment
Chronic suppurative OM	Coamox-clavulinate (augmentin) + local therapy	Ceftazidime or piperacillin	Use of ceftazidime or piperacillin require IV
Sinusitis	Same as otitis media		
Pharyngitis	Penicillin V	Ampicillin, amoxicillin, or cephalexine	
	1–5 years 125 mg PO BID		
	6–12 years 250 mg PO BID		
Peritonsiller cellulites or abscess	Clindamycin and cefotaxime	Tazocin or meropenem	Consider drainage for abscess
Retropharyngeal abscess	Clindamycin and cefotaxime	Tazocin or meropenem	Admission is indicated
Tracheitis	Cloxacillin+cefotaxime		Admission is indicated. In areas with high MRSA, consider vancomycin instead of cloxacillin
Epiglottitis	Cefuroxime	Cefotaxime	Admission is indicated
Pneumonia			
<3 months	Ampicillin+cefotaxime	Ceftriaxone	Usually need admission
3 months–5 years	Outpatient: amoxicillin Inpatient: cefuroxime		In community where MRSA prevalence is high, vancomycin should be considered especially in those who are toxic or has empyema
>5 years	Outpatient: azithromycin/ clarithromycin or erythromycin		
	Inpatient: Cefuroxime with or without azithromycin/ clarithromycin or erythromycin		
Osteomyelitis and septic arthritis	Neonates: cefotaxime Children >3 months of age: cloxacillin		In areas where MRSA prevalence is 5–10%, consider empiric therapy vancomycin or clindamycin Unvaccinated children <5 years of age need coverage for *H. influenzae* with cefotaxime or cefuroxime
Neonatal sepsis:	Gentamicin and ampicillin	Cefotaxime plus ampicillin	
Bacteremia	Ceftriaxone		
UTI	Mild: Coamox-clav, cotrimoxazole, cephalexine, cefuroxime, cefdinir, or cefpodixime		Consider prophylaxis if there are genitourinary abnormalities
	Severe: ceftriaxone		Need hospitalization
Brucellosis	Children <8 years : Rifampin and cotrimoxazole		Intravenous gentamicin for 5–7 days can be given to admitted patients
	children > 8 years : Rifampin and doxycycline		

Table 73.1 (Continued)

Condition	Management	Alternative therapy	Comment
Periorbital cellulitis	Cefuroxime	Cloxacillin and cefotaxime	In children <1 year without any precipitation wound or sinusitis, consider doing spinal tap and use of cefotaxime until meningitis is ruled out
Orbital cellulitis	Cefotaxime and cloxacillin		
Impetigo	Topical fusidin or mupirocin		Consider systemic cloxacillin if extensive

Amoxicillin high dose of 80–90 mg/kg/day PO in two divided doses for 5–7 days
Augmentin with high amoxicillin forms include 200 mg amoxicillin/28.5 mg clavulanic acid, augmentin 400 mg amoxicillin/57 mg clavulanic acid, and augmentin 600 mg amoxicillin/49 mg clavulanic acid. The dosage is based on amoxicillin at 80–90 mg/kg/day in two divided doses PO
Penicillin V 1–5 years 125 mg PO in two divided doses, 6–12 year 250 mg PO in two divided doses
Cephalexine 80–100 mg/kg/day in three or four divided doses PO
Cefdinir 14 mg/kg/day in two divided doses PO
Cefpodixime 10 mg/kg/day in two divided doses PO (maximum dose 400 mg/day)
Cefuroxime axetile 30 mg/kg/day in two divided doses PO
Cefuroxime 150 mg/kg/day IV every 8 h
Ampicillin 200–400 mg/kg/day IV in four to six divided doses
Azithromycin 10 mg/kg as loading dose then 5 mg/kg once daily for 4 days PO
Clarithromycin 14 mg/kg/day in two divided doses PO
Erythromycin 40 mg/kg/day in four divided doses PO or IV
Ceftriaxone 100 mg/kg/day once or twice daily IV
Cefotaxime 100–150 mg/kg/day in three divided doses IV
Gentamicin 7.5 mg/kg/day in three divided doses IV
Cloxacillin 150 mg/kg/day in four divided doses IV
Vancomycin 45 mg/kg/day in three divided doses IV
Clindamycin 30 mg/kg/day in three divided doses PO or IV
Rifampin 20 mg/kg/day in two divided doses PO
Cotrimoxazole 10 mg/kg/day in two divided doses PO
Doxycycline 4 mg/kg/day in two or single dose PO

(bacteriostatic) or by killing them (bactericidal). Antibiotics destroy organisms through various mechanisms (*Table 73.3*). The effect, activity, and toxicities of any medication are its pharmacodynamic characters. In order for a drug to have an activity against a specific organism, such organism must be susceptible. Some organisms are usually sensitive to certain antibiotic like Group A Streptococci is usually sensitive to penicillin.

Others are inherently resistant to some antibiotics, like Pseudomous is always resistant to first- and second-generation cephalosporins. Some organisms acquire resistance in response to antibiotic use or as a result of acquiring resistant gene through plasmid or transposone transfer such as methicillin-resistant *Staphylococcus aureus* and *Streptococcus pneumoniae*.

In order for an antibiotic to be effective, it must attain a level above or equal to organism MIC. MIC is the minimum antibiotic concentration required to kill the organism in vitro. Certain antibiotics are having an activity that is time dependent like β-lactam, macrolid, clindamycin, and vancomycin. These antibiotics need to have a level above MIC for at least 50% of the dose interval in order to be effective. Other antibiotics are concentration dependent, meaning that they have a post-antibiotic effect, which extends their killing ability even if concentration dropped below MIC. Such antibiotics include aminoglycosides and fluoroquinolones.

Instructive Case

A 3-month-old girl was admitted with history of fever and irritability. Anterior fontanelle was bulging and no focal neurological signs. Cerebrospinal fluid culture grew Streptococcus pneumoniae with the following MIC: penicillin 0.12 mcg/ml, cefotaxime 0.12 mcg/ml, and vancomycin 0.5 mcg/ml. In this case, the best treatment is cefotaxime because the cutoff point of sensitivity is 0.5 mcg/ml. This organism is intermediately resistant to penicillin and because the infection involves CNS, it is not suitable to use penicillin. However, if infection involves other part of the body, high-dose penicillin is usually effective.

Table 73.2
Modification of doses with renal and hepatic impairment

Modify in renal impairment	Modify in hepatic disease	Modify in both
Penicillins	Azithromycin	Aminosalicylic acid
Cephalosporins	Clindamycin	Amphotericin
Aminoglycosides	Clofazimine	Clarithromycin
Aztereonam	Erythromycin	Chloroquine
Imipenem	Isoniazid	Cotimoxazole
Capreomycin	Ketoconazole	Cycloserine
Vancomycin	Praziquantel	DDI
Acyclovir	Rifampin	Ethionamide
Amantidine		Grisovulvin
Foscarnet		Metronidazole
Ganciclovir		Pyrazinamide
Fluconazole		Thiabendazole
Flucytosine		
Paromomycin		
Quinacrine		
Quinine		

Table 73.3
Mechanisms of antibacterial action

Mechanism of action	Antibiotics	Type of activity
Inhibition of cell wall synthesis	Penicillins	Bactericidal, time dependant
	Cephalosporins	
	Vancomycin	
Protein synthesis inhibition	Clindamycin	Bacteriostatic, time dependant
50S inhibitor	Macrolide	
	Chloramphenicol	
30S inhibitor	Tetracyclines	Bacteriostatic, concentration dependant
	Aminoglycosides	
DNA gyrase inhibition	Fluoroquinolones	Bactericidal, time dependant
DNA synthesis inhibition	Metronidazole	Bactericidal
RNA polymerase inhibition	Rifampicin	Bactericidal
Cytoplasmic membrane destruction	Polymyxines	Bactericidal

Instructive Case

A 4-month-old boy with complex congenital heart disease was operated upon. Three days postoperatively, he started to have fever. His complete blood count showed elevated WBC and decreasing platelet. He was started empirically on ceftazidime and gentamicin. Blood culture grew Enterobacter cloacae. An Enterobacter cloaca is included in what is being known as SPICE organisms (Serratia, Pseudomonas, indole positive Acinetobacter and Morganella, Citrobacter and Enterobacter). These organisms are inherently resistant to β-lactam. Therefore, in such case, meropenem or an effective non-β-lactam antibiotic is advisable.

Mechanisms of Resistance

Some bacteria are de novo resistant to certain antibiotics, however with increasing pressure of antibiotics use, bacteria started to escape antimicrobial actions by acquiring resistance (Table 73.4). The major mechanisms of resistance are:

1. Production of an enzyme that degenerate or inactivate the antibiotic, for example, production of β-lactamases by *S. aureus* and *Enterobactericia*
2. Prevention of the antibiotic from reaching its site of action as in *Pseudomonas* and *S. epidermidis*
3. Altering the site of action as in *S. pneumoniae*
4. Increased efflux of antibiotics

Recently, there are major concerns of rising resistance against antibiotics. In some situations, these resistant organisms are the predominant cause of infections. There are situations where the resistant organism is resistant to all of the available antibiotics. This is apparent in some of the Gram-negative bacilli and vancomycin-resistant enterococci and vancomycin-resistant staphylococcus aureus. Table 73.5 shows some examples of these challenging organisms.

Penicillins

Penicillins are derivative of β-lactam. The basic constituent of all penicillins are β-lactam ring and thiazolidone ring. Penicillins vary in their characteristics by alteration in the side chains that are attached to the β-lactam ring. The mechanism of action of all penicillins is through attachment to penicillin-binding proteins (PBP). PBP(s) are transpeptidases that mediate the cross-linking of peptidoglycan polymers. This in turn results in inhibition of bacterial cell wall synthesis. Although they were effective against broad spectrum of organisms when initially introduced, resistance arose quickly. Most of the resistance to penicillin is by production of β-lactamases, which results

Table 73.4
Mechanisms of antibiotic resistance

Mechanism of resistance	Antibiotics affected	Organisms exhibiting
Detoxifying enzymes		
β-Lactamsases	β-Lactams antibiotics	S.spp., Enterobacteriaceae, Neisseria spp., Enterococci, Pseudomonas, Bacteroids
Acyltransferase, neucleotidyltransferas, phosphtransferas	aminoglycosides	Enterobacteriaceae, Pseudomonas, Enterococci, Staphylococci
Acetyltransferase	Chloramphenicol	Neisseria, *H. influenzae*, Enterobacteriacea
Methylating enzymes	Macrolides	Pneumococcus, Staphylococci
Alteration of the binding site	β-Lactams	Pneumococcus, MRSA, *H. influenzae*, Neisseria Streptococci
	Aminoglycosides	
	Macrolides	
	Vancomycin	
	Quinolones	
	Tetracycline	
	Vancomycin	
Impaired access of antibiotics		
Decreased permeability	β-Lactams	Pseudomonas, Enterobacter, Serratia, Klebsiella Pseudomonas, Enterobacteria
	Aminoglycosides	
	Tetracycline	
	Chloramphenicol	
	Quinolones	
Efflux of antibiotics	Tetracycline	
	Erythromycin	

in destruction of the penicillins. In addition, some bacteria acquire resistance by alteration of the PBP rendering them inaccessible to the antibiotics. The major side effect of penicillin is anaphylaxis, however it occurs rarely. Other side effects include autoimmune reactions like serum sickness and hemolytic anemia. Interstitial nephritis may occur especially with penicillinase-resistant penicillins. There are four classes of penicillins (◉ *Table 73.6*).

Natural Penicillins

These are penicillin V and penicillin G and its derivatives. Penicillin V is available in oral form and it has good bioavailability of 40%. Penicillin G is available in oral form (buffered penicillin G), intravenous form (aqueous penicillin G), and intramuscular forms (procaine penicillin and benzathine penicillin). Oral penicillin G has

Table 73.5
Challenging organisms

Organism	Challenge	Precaution
Streptococcus pneumoniae	Increasing resistance to penicillin	Resistant pneumococci is one of the cause of pyogenic meningitis
MRSA	Resistance to methicillin group	Community-acquired MRSA is increasing. MRSA should be considered as a cause of serious infections
SPICE (Serratia, Pseudomonas, indole positive Acinetobacter and Morganella, Citrobacter and Enterobacter)	Resistance to β-lactam and β-lactam-β-lactamase inhibitor	Becoming increasing cause of hospital-associated infections

Table 73.6
Commonly used penicillins

Drug	Dose	Route	Main uses	Side effects
Natural penicillin				
Penicillin G	400,000 U/kg/day q 4 h	IV, IM	Pharyngitis due to GAS, syphilis, peritonsiller abscess and retropharyngeal abscess	Anaphylaxis, intestitial nephritis
Penicillin G	25–50 mg/kg/day q 6 h	PO		
Penicillin G Procaine	25,000–50,000 U/kg od	IM		
Benzathine pen G	25,000 U/kg one dose	IM		
Penicillin V	25–50 mg/kg/day q 6h	PO		
Penicillinase resistant				
Cloxacillin	50–100 mg/kg/day q 6h	PO	Osteomyelitis, septic arthritis, infected implanted devices	Diarrhea, nausea, leukopenia, nephritis Interstitial nephritis I
	100–200 mg/kg/day 6h	IV		
Naficillin				
Methicillin				
Semisynthetic penicillin				
Ampicillin	200–400 mg/kg/day qh	IM, IV	Meningitis in neonates, UTI, shigellosis (if sensitive), otitis media, sinusitis, UTI	GIT symptoms, rash
Amoxicillin	50–100 mg/kg/day q 6h	PO		
Extended spectrum penicillin				
Pipercillin	200–400 mg/kg/day q 6h	IV	Pesudomonas infections, enterobacterecia and streptococci	Skin rashes, CNS effects like siezure and drowziness
Ticarcillin				
Mezlocillin				
Azlociilin				

a bioavailability of 20% of that achieved after similar dose given intramuscularly. Therefore, it can be used for treatment of mild infection; however, penicillin V has a better bioavailability. Procaine penicillin is available for intramuscular use and its main use is for treating syphilis except congenital syphilis when intravenous aqueous penicillin G is preferred. Benzathine penicillin is a long acting formula which maintains a detectable, although low, serum level of 1–2% of that achieved by similar dose of aqueous penicillin G given intravenously. Therefore, it is used for highly sensitive organisms, which can be inhibited by low serum concentration. Its main use is for rheumatic fever prophylaxis and Group A streptococcal infection.

Penicillins remain the drug of choice for Group A streptococcal infections, Group B streptococcal infections, syphilis, actinomycosis, leptospirosis, anthrax, and meningococcal infections. Once used to be 100% sensitive to penicillin, Streptococcus pneumoniae that are resistant to penicillin are increasing in number. In some countries, up to 50% of S. pneumoniae are relatively or highly resistant to penicillin. Therefore, in cases of pneumococcal meningitis, the initial therapy should be with third-generation cephalosporins and vancomycin until the availability of the sensitivity results. Most of the staphylococci and almost all Gram-negative bacilli are resistant to this group of penicillin antibiotics.

β-Lactamase-Resistant Penicillins

Soon after introduction of natural penicillins, staphylococci start to acquire resistance. Most of this resistance was mediated by inducible β-lactamases. Therefore, a search for alternative effective antibiotics resulted in introduction of penicillinase-resistant penicillins (oxacillin, methicillin, nafcillin, cloxacillin, and dicloxacillin). Methicillin is rarely used now except in neonates because of its low protein binding. Oxacillin and nafcillin are available in oral and parenteral forms; however their bioavailability when given orally is less than that of cloxacillin and dicloxacillin. Cloxacillin and dicloxacillin are available in oral forms only. This group of antibiotics is effective against most of the Staphylococcus aureus strains, 50–70% of the coagulase negative Staphylococci, Group A Streptococci, and Group B Streptococci. They are with the exception of methicillin also effective against Streptococcus pneumoniae. They share with the natural penicillins the hypersensitivity reactions in addition to interstitial nephritis, phlebotoxicity, neutropenia, and alteration in the liver transaminases. Soon after introduction of these antibiotics, resistant Staphylococci start to arise. Almost half of coagulase-negative Staphylococci are resistant to these antibiotics. Staphylococcus aureus that are methicillin resistant also start to appear. Their prevalence is variable; however, they are mostly nosocomially acquired and tend to be more prevalent in long-term care facilities and in large teaching hospitals. Methicillin-resistant Staphylococci are also resistant to all other penicillins, all cephalosporins, and most of the other antibiotics with the exception of vancomycin and teicoplanin. Some MRSA are also susceptible to trimethoprim-sulfamethoxazole, rifampicin, fluoroquinolones, and clindamycin.

Aminopenicillins

This group of penicillins is semisynthetics. They include ampicillin, amoxicillin, bacampicillin, and cyclacillin. Ampicillin is available in oral and parenteral forms whereas the others are available in oral form only. They are broader spectrum than the previous groups. Their activities encompass Group A Streptococci, Group B Streptococci, some of the Staphylococci, Enterococci, some of the Enterobacteriaceae (*E. coli*, Klebsiella, Enterobacter, Salmonella, and Shigella), Listeria monocytogenes, some of the Enterococci, and some of the Haemophilus influenzae type b. Recently, an increasing number of ampicillin-resistant Enterobacteriaceae, Haemophilus influenzae, and Enterococci are noticed especially in developing countries. Ten to fifty percent of Salmonella and Shigella are resistant to ampicillin. Twenty to thirty percent of *H. influenzae* is resistant to ampicillin.

Broad Spectrum Penicillins

This group of penicillins includes carboxypenicillins (carbenicillin and ticarcillin) and ureidopenicillins (piperacillin, mezlocillin, and azlocillin). These antibiotics are only available in parenteral form. Their spectrum of activity include most of the Enterobacteriaceae, Pseudomonas, Gram-positive cocci with the exception of most of the Staphylococci, oral anaerobes, some of Bacteriodes, and some of Enterococci. They are susceptible to penicillinase and therefore are ineffective against penicillinase producing bacteria like *H. influenzae*, enteric Gram-negative bacilli, and Staphylococci. Carbenicillin is rarely used nowadays because it is supplanted by more active ticarcillin. Ticarcillin and ureidopenicillin have similar range of activity and toxicity and therefore can be used interchangeably. The main use of these antibiotics is in

febrile neutropenic patients where they are used in combination with aminoglycoside as empiric therapy. In addition, they are effective in treating patients with intraabdominal infection when Pseudomonas is suspected to be one of the causative organisms. Pneumonia in cystic fibrosis patients is usually treated with a combination of one of these antibiotics and an aminoglycoside antibiotic. These antibiotics can be used alone in the treatment of pyelonephritis or pneumonia that is caused by Pseudomonas. The main side effects of this group of penicillin include, in addition to hypersensitivity reactions, hepatotoxicity, neutropenia, thrombocytopenia, and seizure when used in very high dosage.

Cephalosporins

Cephalosporins are another class of β-lactams. Their basic structure consists of β-lactam ring, dihydrothiazine ring, and variable side chains. β-Lactam ring and dihydrothiazine ring confer the basic antibiotic activity whereas the side chain determines the spectrum of activity and the pharmacokinesis of a specific antibiotic in the group. Cephalosporins act as bactericidal agents through inhibition of cell wall synthesis. As other β-lactam, they bind to PBP(s) on the bacterial cell membrane and thus interfere with the transpeptidation and cross-linking of the peptidoglycan segments. This in turn results in bacterial cell death. Although this is the basic mechanism of action, other additive or alternative action is speculated in which the autolysins play the major role. Most of the bacteria have their own autolysins, which are usually kept under control by protein inhibitors. When the β-lactam antibiotics bind to PBP(s), these inhibitors are released from the cells allowing the autolysins to act and lyse the cell. There are four generations of cephalosporins based on their spectrum of activities (*Table 73.7*).

First Generation

This class includes oral agents (cephalexin, cephradine, and cefadroxil) and parenteral agents (cephalothin, cephradine, cephapirin, and cefazolin). Cephalexin and cephradine have short half-life and thus need to be given four times daily whereas cefadroxil has a prolonged half-life allowing once or twice daily dosing. Among parenteral agents, cefazolin has the longest half-life and can be given every 8 h. In addition, it achieves higher blood level than the others and thus higher activities. These agents have a good activity against most Gram-positive cocci including *S. aureus*, *Streptococci* other than group D and viridans *Streptococci*. Their spectrum of activity against Gram-negative bacilli is limited to some of the E. coli, Kleibsiella species, and Proteus mirabilis. They are not effective against other Enterobacteriacea or Pseudomonas. The main use of these antibiotics is for mild to moderate infections like streptococcal pharyngitis, skin and soft tissue infection, and mild urinary tract infection caused by susceptible organisms. Cefazolin is used commonly as perioperative prophylaxis in orthopedic, cardiovascular, or abdominal procedures. Cephalothine is very painful if given intramuscularly and therefore it should be given by intravenous route only.

Second Generation

The members of this class have a better Gram-negative coverage with maintenance of Gram-positive coverage. This class includes agents that can be given orally (Cefaclor, cefuroxime axetil, cefprozil and loracarbef) and others that can be given parenterally (cefamandole, cefuroxime, cefoxitin, cefotetan, and cefmetazole). These antibiotics have almost the same range of activities with some minor differences. They have an excellent coverage for methicillin-sensitive Staphylococcus aureus, most of the Streptococci with the exception of some of the viridans group, Neisseria species, non-typable and typable Haemophilus influenzae, and some of the Enterobacteriaceae (E. coli and Klebsiella species). Their coverage for other Enterobacteriaceae is variable. These antibiotics are ineffective for Pseudomonas species. Cefoxitin, cefotetan, and cefmetazole are active against most of the anaerobes. Therefore, they are effective in treatment of intraabdominal infections like peritonitis following perforated viscus. In addition, they are effective in cases of pelvic inflammatory disease when given in combination with doxycycline or erythromycin. Cefuroxime is the safest and most stable for β-lactamase. Cefprozil and Cefaclor are less stable for β-lactamase. The main uses of second-generation antibiotics are in lower respiratory tract infections, otitis media that is resistant to therapy with amoxicillin, bone and joint infections in children below 5 years of age when the possibility of *S. aureus* and *H. influenzae* as causative agents is entertained, and urinary tract infection. The use of cefuroxime in treatment of meningitis is discouraged because of the delay in CSF sterilization in comparison with third-generation antibiotics.

Table 73.7
Commonly used cephalosporins

Drug	Dosage (mg/kg/day)	Route	Spectrum of activity	Side effects
First generation				Anaphylaxis is very rare Skin rashes Coagulopathy specially with moxalactam.
Cephalexine	50 QID	PO	Streptococci, S. aureus, some of the Enterobactercia	
Cephazoline	80 q 8 h	IV, IM		
Cephradine	25–50 QID	PO		
Cephalothine	80–160 QID	PO		
Second generation				
Cefuroxime axetile	40 BID	PO	S. aureus, Streptococi, Entrobactrecia, H. influenzae	
Cefaclor	40 TID	PO		
Cefuroxime	75–150 q8h	IV		
Cefamandole	100–150 q6h	IV, IM		
Cefotetan	40–80 q 12 h	IV, IM	Entrobactercia and anaerobes	
Cefoxitin	80–160 q8h	IV, IM		
Third generation				
Cefotaxime	150 q 6 h	IV, IM	Streptococci, S. aureus, Enterobactericia and H. influenza	
Ceftriaxone	100 q 12 h	IV, IM		
Ceftizoxime	150–200q6h	IV, IM		
Cefixime	8 od	PO		
Cefpodexime	10 od	PO		
Ceftazidime	100–150 q8h	IV, IM	Most of Gram-negative bacilli including Pseudomonas	
Cefperazone	100–150 q8h	IV, IM		
Fourth generation				
Cefpirome				
Cefepime				

Third Generation

This group of cephalosporins has a broad spectrum of activity against most of the Gram-negative bacilli including *Enterobacteria* and *H. influenzae*. Only ceftazidime and cefoperazone are active against *Pseudomonas*. Third-generation cephalosporins are generally β-lactamase stable, however some of the Gram-negative bacilli produce expanded spectrum β-lactamases that are able to hydrolyze these agents. This is mainly manifested by Pseudomonas aeruginosa, Klebsiella species, Enterobacter species, Citrobacter species, Serratia marcescens, and Acinetobacter species. Therefore, these antibiotics should be used with caution against these organisms, and preferably used in combination with an aminoglycoside when serious infection with these organisms is suspected. Cefotaxime and ceftriaxone have good coverage against *S. aureus*; however, they are not adequate to treat serious infections caused by this organism. All third-generation cephalosporins are effective therapy for *H. influenzae* and *S. pneumonia*; however, recently there are increasing reports of cephalosporin-resistant *S. pneumoniae*. When meningitis due to *S. pneumoniae* is suspected, the initial therapy should be with a combination of cefotaxime or ceftriaxone and vancomycin until the organism is proved to be susceptible to ceftriaxone or cefotaxime by susceptibility tests. This group of antibiotics is not effective against Enterococcus, methicillin-resistant *S. aureus*, *Listeria monocytogenes*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*. Third generation is generally safe with wide therapeutic-toxicity index. Mild to moderate hypersensitivity reactions occur in 3–5%. These are

mainly in the form of mild skin rashes. Type 1 reaction is very rare. Platelet aggregation defect and prolonged prothrombin time have been described with use of moxalactam and cefoperazone. Therefore, their use is limited. Mild anemia, thrombocytosis, and neutrophilia as well as mild elevation of the liver transaminases may occur with use of these antibiotics, but are usually transient and improve with discontinuation of the medication. Ceftriaxone is highly protein bound and thus may displace bilirubin, which may exacerbate neonatal hyperbilirubinemia and thus it should be avoided in neonates. In addition, pseudolithiasis and biliary sludging has been described with ceftriaxone use; however, this is usually transient and resolves after discontinuation of therapy.

Fourth Generation

These agents are just recently released for clinical use. They have a broad spectrum activity with effective coverage of almost all Gram-negative bacilli including *Enterobactericia* and Pseudomonas. They are effective againist *S. aureus* and *Streptococci*; however, they are not active against *Enterococci* or MRSA.

Aminoglycosides

Aminoglycosides are bactericidal agents. They act by inhibiting protein synthesis through inhibiting 30S ribosome. It remains controversial how aminoglycosides are bactericidal although inhibition of protein synthesis is not enough for organism killing. Aminoglycosides are highly polar and water soluble molecules, therefore their absorption after oral intake is poor and they should be given parenterally. Their volume of distribution is that of extracellular fluid and thus it is altered in cases of edema, heart failure, and dehydration. They poorly cross the cellular barrier and therefore their intracellular concentration is low except streptomycin. Because they poorly cross biological membrane, their concentration in CSF, bile prostate, and vitreous fluid is very low; however, they achieve a good level in bone, synovial fluid, and peritoneal cavity. The main excretion route is the kidneys and it is mainly through glomerular filtration. Aminoglycosides have almost similar spectrum of activities; however, amikacin is less susceptible to the modifying enzymes of other aminoglycosides and thus may be effective against some Gram-negative bacilli that are resistant to other aminoglycosides. Tobramycin is slightly superior to gentamicin, but this is not significant. The commonly used aminoglycoside is gentamicin because it is the least costly. The spectrum of activity of aminoglycosides includes Gram-negative bacilli, most of the Staphylococci, some of the Enterococci, Brucella, Francisella tularensis, Yersinia pestis, and some of the nontuberculous Mycobacteria. Aminoglycosides are used in combination with ampicillin or vancomycin in treatment of intraabdominal infections. Hospital-acquired Gram-negative bacilli infections are usually treated empirically with aminoglycosides until the sensitivity of the organism is available. In serious Pseudomonas infections, aminoglycosides are used in combination with an antipseudomonal β-lactam. Streptomycin is the drug of choice in cases of tularemia and plague. It is also used in combination with other antimicrobials to treat brucellosis, tuberculosis, and Enterococcus endocarditis when Enterococcus does not have high resistance (i.e., MIC $<$2,000 mcg/ml). Although resistance is not common, it is increasingly seen with increasing pressure of antibiotic use. The main mechanism of resistance is by production of modifying enzymes which include phosphoryltransferase, acetyltransferase, and adenyltransferase. These enzymes are found in some of Gram-positive cocci, like *Staphylococcus aures*, *Streptococcus pyogenes*, *Enterococcus fecalis*, and *Streptococcus pneumoniae*, and some of Enterobacteriaceae and Pseudomonas. In spite of this known mechanism of resistance, the prevalence of resistance to aminoglycosides among Enterobacteriaceae and Pseudomonas is still low. Other less common causes of resistance to aminoglycosides include alteration in the ribosomal binding or inhibition of transport of the antibiotic to the site of action. The main side effects of aminoglycosides are nephrotoxicity and ototoxicity. Nephrotoxicity is more common in those who have altered renal function either acutely or chronically. It is usually nonoliguric and reversible with discontinuation of therapy; however, it may prolong the illness of the affected patient and occasionally it may be permanent. In contrast to nephrotoxicity, ototoxicity is usually irreversible. These side effects are dose related and therefore it is advisable to maintain serum concentrations within the therapeutic range and to limit the duration of therapy to short periods (7–14 days). Use of single daily dose has shown to be of the same efficacy with reduction in the incidence of toxicity. The rationale behind the single daily dose is related to the dependence of aminoglycosides on their concentrations in bacterial killing. Therefore, with higher concentration achieved with single larger dose, the killing is better. ❯ *Table 73.8* lists commonly utilized aminoglycoside antibiotics.

Macrolides

These are bacteriostatic agents (Table 73.9). They act by inhibition of protein synthesis through binding to peptidyltransferase on 50S ribosome, and thus inhibit peptide bond formation. Erythromycin is the prime drug in this group. Erythromycin base is poorly water soluble, and thus its absorption after oral intake is poor. Therefore, it is linked to some salts that make it more stable in gastric acid and increase its absorption. The salt formulas that are available include: erythromycin stearate, erythromycin succinate, erythromycin propionate, and erythromycin estolate. Erythromycin has a broad spectrum of activity against most of *S. aureus*, some of Streptococcus pneumoniae, Group A and B Streptococci, Mycoplasma species, Chlamydia species, Campylobacter jejani, Bordetella pertussis, and Legionella. Erythromycin is the drug of choice for atypical pneumoniae caused by Mycoplasma pneumoniae, Legionella maltophila and Chlamydia pneumoniae, chlamydia psittaci, or Chlamydia trachomatis. It is also the drug of choice for Campylobacter enteritis. It can be used as an alternative therapy for Group A Streptococci pharyngitis and for syphilis in patients who are allergic to penicillin. It is also an alternative to penicillin for rheumatic fever and endocarditis prophylaxis. Although erythromycin is an effective medication against many of pediatric infections, it has a reputation of being not well tolerated due to high incidence of gastrointestinal upset, namely, gastritis, vomiting, and diarrhea. These symptoms occur in 25% of patients. Other than these, erythromycin is a fairly safe medication with low incidence of other side effects like skin rashes and cholestasis with estolate formula. Azithromycin and clarithromycin are the new macrolides that have the same efficacy as that of erythromycin and yet are less toxic to gastrointestinal system. These macrolides have better pharmacokinesis characteristics. Azithromycin is well absorbed with 37% bioavailability after a single 500 mg dose. It also has a prolonged half-life of 50 h that render it suitable to be given in single daily dose and for

Table 73.8
Commonly used aminoglycosides

Drug	Dose (mg/kg/day)	Route	Spectrum of activity	Side effects
Streptomycin	20 divided every 12 h	IM	M. tuberculosis, brucella, Yersinia pestis, tuleremia	Nephrotoxicity, ototoxicity, neuromuscular blockade, bone marrow suppression, and eosinophilia
Kanamycin	15–30 divided every 8 h	IV, IM	Rarely used, Enterobactericia, Klebsiella	
Gentamicin	7.5 divided every 8 h or once daily	IV, IM	Gram-negative bacilli, S. aureus, brucella	
Tobramycin		IV, IM		
Netilmicin		IV, IM		
Amikacin	15–22 divided every 8 h	IV, IM		
Spectinomycin	30–40 single dose	IM	For Neisseria gonorrhea	

Table 73.9
Macrolides in clinical use

Drug	Dose (mg/kg/day)	Route	Main uses	Side effects
Erythromycin	40 every 6 h	PO, IV	Otitis media, pharyngitis, pneumonia especially those due to chlamydia, mycoplasma, or legionella	Gastritis, vomiting, diarrhea, cholestasis especially estolate form
Azithromycin	10 mg as a loading dose then 5 mg once daily for 4 days	PO, IV	Same as above	Same as above but less frequent, mild elevation of liver transaminases and mild decrease in WBC
Clarithromycin	14 divided every 12 h	PO	Same as above, atypical mycobacteria and Helicobacter gastritis	Same as above

short duration course. Clarithromycin also has similar characteristics with oral bioavailability of 55%, however its half-life of 5–7 h is shorter than that of azithromycin and therefore it is given in twice daily dosage. Both of these new macrolides have broad spectrum of coverage with good activity against most *Streptococci* and *S. aureus* and excellent activity against *H. influenzae*, *Mycoplasma*, *Chlamydia*, *Legionella*, and *Bordetella*. Azithromycin has been reported to be active against *Brucella* and *Helicobacter pylori*. The main clinical uses of azithromycin are upper and lower respiratory tract infections. In children, it is used as a primary or alternative therapy for otitis media in a dose of 10 mg/kg in the first day followed by 5 mg/kg once daily for the subsequent 4 days. It is also used as an alternative to penicillin for treating Group A streptococcal infection in a dose of 12 mg/kg once daily for 5 days. Clarithromycin is one of the main drugs in treating atypical mycobacteria infections especially in AIDS patients. In addition, it is useful in the treatment of *Helicobacter pylori* gastritis. Both of these new macrolides are safe and have lesser incidence of gastrointestinal symptoms in comparison to erythromycin. Only 3–5% of patients using azithromycin and 5–9% of those using clarithromycin will report nausea, vomiting, or diarrhea. Other side effects of skin rashes and mild elevation of liver transaminases occur rarely. Unlike erythromycin, azithromycin has no reported drug interaction with terfenadine, warfarin, cyclosporine, theophylline, or carbamazepine.

Quinolones

The first quinolone known is nalidixic acid, which is mainly used in the treatment and prophylaxis for UTI. Recently, new derivatives are introduced, which are the fluoroquinolones. These antibiotics act by inhibition of DNA gyrase, which is responsible for DNA nicking and thus supercoiling. Although they have been claimed to cause cartilage defects in animals, this has never been proven in humans. Therefore, many authorities find no reason to contraindicate their use in children when needed.

Sulfonamides

Sulfonamides are synthetic agents that act by depriving bacteria from folic acid through their competitive inhibition of PABA, thus preventing conversion of PABA to dihydrofolic acid which is the precursor of folinic acid. They are used in children mainly for UTI and upper respiratory bacterial infections like sinusitis and otitis media. They are contraindicated to be used in jaundiced infants below 1 month of age as they displace bilirubin from albumin and thus may result in hyperbilirubinemia. Their other side effects include skin rashes and bone marrow suppression. Trimethoprim is another folate antagonist, which acts by inhibition of dihydrofolate reductase. In combination with sulfamethoxazole, trimethoprim has been used to treat common childhood respiratory problem like otitis media and sinusitis and urinary tract infections. In addition trimethoprim/sulfamethoxazole (cotrimoxazole) is the drug of choice for treatment of *Pneumocystis carinii* infection.

Carbapenem

Carbapenems are one of the β-lactam antibiotics. The basic constituents of these agents are β-lactam ring and formimidoyl thienamycin ring. The two known antibiotics of this group are imipenem-cilastatin (Primaxin) and meropenem. The third is biapenem and it is still investigational drug. Imipenem and meropenem have similar range of antibacterial activity but differ in their pharmacokinetic features. Imipenem is easily hydrolyzed by kidney dehydropeptidase I resulting in lower concentration of the patent drug in the urine and thus lesser efficacy in urinary infections. In addition, the metabolite is more toxic to the kidneys than patent drug. Combining imipenem with cilastatin in 1:1 ratio has decreased the hydrolysis of Imipenem by dehydropeptidase resulting in 70% of imipenem being secreted unchanged in the urine. Meropenem and biapenem are not metabolized in the kidney and are more stable.

Carbapenems drugs are small in size, are water soluble, and have low protein-binding tendency resulting in their large volume of distribution. Their concentration in all body fluids including CSF is excellent.

These antibiotics have broad spectrum activity, covering Gram-positive and Gram-negative cocci as well as Gram-negative bacilli. Also they are effective against most of anaerobic organisms. As β-lactam antibiotics, they may have cross allergy with other β-lactam but usually rare. Therefore, they can be used as alternative to other β-lactams unless there is history of anaphylaxis to penicillin in which case they should be used cautiously. The main side effects are similar to other β-lactams and include skin rashes and gastrointestinal symptoms. Anaphylaxis is very rare. The major side effect of imipenem is its high potential of inducing seizure especially in high doses which make it

unfavorable to use in meningitis. This has not been reported with the newer carbapenem agents. The recommended dose of imipenem is 50 mg/kg/day in four divided doses. 100 mg/kg/day can be used in life-threatening infections; however, lower dose is recommended for patients who have history of seizure. The maximum allowed daily dose is 4 g. Meropenem is used in a dosage of 20 mg/kg/dose every 8 h, however in meningitis higher dosage of 40 mg/kg/dose every 8 h is recommended.

Monobactam

The only available monobactam is aztreonam. It differs from other bicyclic β-lactam (penicillin, cephalosporins, and carbapenem) in having the nitrogen at the N-1 position replaced by sulfonic acid group. This has resulted in stabilization of the β-lactam ring and its assistance in acetylation of the transpeptidases of the organisms. Azterenam is stable to most of the β-lactamases with the exception of extended spectrum β-lactamases and metallo β-lactamases. It is available in parenteral form as its bioavailability after oral intake is poor. It has a serum half-life of 1.5–2 h and it is 50–70% protein bound. Aztereonam has a good activity against most of the Enterobacteriaceae, Neisseria meningitidis, Neisseria gonorrhea, Haemophilus influenzae, and Pseudomonas aeruginosa. It has limited activity against Acinetobacter, Stenotrophomonas maltophilia, and Flavobacterium. It has no activity against anaerobes or Gram-positive organism. Aztereonam has few side effects including skin rashes, nausea, vomiting, and diarrhea. Although it is one of the β-lactam group, it has no cross reaction with other β-lactam antibiotics. The main uses of aztreonam is in cases of urinary tract infection caused by susceptible organism, intraabdominal infection usually in combination with clindamycin or ampicillin and metronidazole, pelvic inflammatory disease in combination with clindamycin and tetracycline, and in febrile neutropenic patients in combination with an aminoglycoside and vancomycin. The recommended dose for children is 120 mg/kg/day in four divided doses. In cystic fibrosis patients, higher dose is required 200 mg/kg/day in four divided doses.

Vancomycin

Vancomycin is a glycopeptide that acts by inhibition of cell wall synthesis. It is not absorbed when given orally, therefore the only indications for oral vancomycin is pseudomembranous colitis, otherwise it should be given by intravenous route. Intramuscular route is not recommended because of pain associated with injection and inability to monitor the drug level due to variable absorption. The main uses of vancomycin are to treat infections caused by Gram-positive cocci including MRSA, coagulase negative *Staphylococci*, *Enterococci*, and *Corynebacterium jekium*. The last decade witnessed an increasing resistance of Streptococcus pneumoniae to penicillin and in these situations, vancomycin should be used especially in pneumococcal meningitis (◉ *Table 73.10*). The only Gram-negative organism covered by vancomycin is *Flavobacterium meningosepticum*, which is increasingly reported to cause meningitis in premature babies.

The main side effects are gastrointestinal (nausea and vomiting) and red man syndrome, a reaction manifested by macular erythematous eruption mainly over the neck. It is more common if vancomycin is infused rapidly.

Other Antibacterial Agents

Tetracyclines are not used frequently in children because they are contraindicated to be used in any child who is 8 years or lower. This is because of their tendency to accumulate in growing bone especially teeth resulting in permanent greenish-brown staining. They act by binding to ribosome 30S and thus inhibit the binding of aminoacyl-tRNA, which in turn cause disruption of peptide formation. These medications are the first choice in treatment of leptospirosis, Lyme disease, brucellosis, rickettsial diseases, cholera, relapsing fever, non-gonococcal urethritis, trachoma, and anthrax.

Clindamycin is a bacteriostatic antibiotic, which acts by inhibition of protein synthesis through binding to 505 ribosome and this prevents transpeptidation. It is effective in Gram-positive cocci and anaerobic organism. Its main uses are against anaerobic infections in cases of intraabdominal abscesses or diabetic foot. In children, it is more effective in eradicating the carriage state of

Table 73.10
Cutoff limit MIC of pneumococci

Pneumococci	Penicillin	Vancomycin
Susceptible	≤0.06 mcg/ml	≤1
Intermediately resistant	0.12–1	–
Resistant	≥2	–

group A Streptococci from the pharynx. The main side effect of clindamycin is pseudomembranous colitis.

Metronidazole is one of the standard agents for treatment of anaerobic infections. The mechanism of action of metronidazole is thought to be through production of toxic derivatives that destroy DNA. In addition to anaerobic infections, metronidazole uses include treatment of *Helicobacter* infections, intestinal protozoa infections, bacterial vaginosis, trichomoniasis, and pseudomembranous colitis. The major side effects of metronidazole include GIT symptoms, metallic taste, seizure, encephalopathy, skin rashes, and leukopenia; however, these are rare.

Chloramphenicol is a bactereostatic antibiotic that acts by binding to ribosome S 50 and prevents protein synthesis. Until the availability of third-generation cephalosporins, it was the standard choice of treating bacterial meningitis. The wide use of chloramphenicol is hampered by its hematological toxicities. Two types of hematological toxicities can arise: dose-related anemia which usually occurs by 3–5 days after starting therapy and idiosyncratic aplastic anemia that can arise 2 weeks to 12 months following chloramphenicol discontinuation. This idiosyncratic reaction is not related to the dose or route of administration and it can occur even after ophthalmic application. It is estimated to occur at a rate of 1/10,000–50,000 patients exposed to the drug. The other major side effect is gray baby syndrome, which arises when young infants are exposed to high serum level of the drug. It is attributed to cellular hyperventilation, which in turn results in hypotension, vasomotor collapse, pallid cyanosis, and abdominal distention with vomiting. This tragedy can be prevented through close monitoring of the level. In spite of all these drawbacks, chloramphenicol is a very potent antibiotic, which covers a wide variety of organisms including *S. aureus*, *S. pneumoniae*, *Neisseria*, *H. influenzae*, *Salmonella*, *Pseudomonas pseudomallei*, and anaerobic organisms. It has a good penetration to CSF and thus it suitable for treatment of brain abscess. It is also effective in treating rickettsial infections.

New Antibiotics for Gram-Positive Organisms

Gram-positive organisms (Staphylococcus aureus, coagulase-negative Staphylococci, Streptococcus pneumoniae, Enterococcus species, Streptococcus pyogenes, and Streptococcus agalactiae) are major causes of community as well as hospital infections. These organisms are becoming resistant to some of the antibiotics that are used to be effective. New antibiotics are therefore needed:

Linezolid: A new antibiotic that is effective for treating Gram-positive organism including MRSA, CONS, and VRE. This antibiotic is well tolerated by children and does not need dose modification with renal insufficiency. Myelosuppression is being reported rarely in adults and even less in children.
Daptomycin: This is a lipopeptide with good activity against most of the multiple-resistant Gram-positive cocci like MRSA, CoNS, enterococci, and pneumococci. For some patients, muscular bruising occurs, but it is reversible and it is advised that CPK be followed weekly while the patient is on daptomycin therapy. It is not recommended for pneumonia because it dose not achieve a good level in lung tissues.
New glycopeptide: Like oritavancin and dalbavancin, these are on the pipeline and have a better coverage than vancomycin and teicoplanin.
Ceftobiprole: This is a cephalosporin with a good coverage for Gram-positive cocci including MRSA. It also exhibits an extended acting against Gram-negative bacilli similar to that of cefepime.
Tigecycline: This is a tetracycline and therefore it should not be used in children below 8 years of age. It has an excellent coverage for multiple Gram-positive cocci including MRSA and enterococci.

Therapy of Multidrug-Resistant Gram-Negative Bacilli

The common GNB causing infection in human and specially hospitalized ones are becoming more resistant to available antibiotics.

This is exemplified by:

- Pseudomous resistance to ceftazidime, ciprofloxacine, and carbapenem
- Multiresistant acinetobacter species
- Expanded spectrum β-lactamase (ESBL) producing entrobacterecia (Escherechia coli 5%, Kleibsella pneumonie 20%, Enterobacter species 30%)

The increasing number of resistance is related to a number of factors:

- Long hospital stay
- Use of invasive devices

- Complicated surgery
- Extremes of ages
- Inadvertent use of antibiotics
- Immunocompromised status

Although it is recommended to limit the use of empirical antibiotics, there are situations where physicians are enforced to do them; however their use should be guided by the following:

1. Use of optimal dose as lower doses are known to promote resistance
2. Modify the antibiotic to the narrowest spectrum possible once the susceptibility is available
3. Try to obtain a microbiological diagnosis as much as you can, that is, get blood, urine, sputum cultures
4. Avoid prolonged use of antibiotics
5. Follow the center-based guideline for the use of antibiotics

What makes the problem worse is the shortage of available effective antibiotics for those hard and difficult to treat organisms. The armamentarium is really narrow and it includes only few antibiotics when faced by such multiresistant organisms. The available choices include:

- Colistin
- Tigacycline
- Fosfomycin

Colistin

It is an old drug that is now reinvented for use in infections caused by multiresistent Gram-negative bacilli. Colistin is a polypeptide that inhibits bacterial cell wall synthesis. It is available in two forms: colistin sulfate for oral and topical use and colistimethate sodium for parenteral use. Both forms can be delivered by inhalation. Colistin was available 50 years ago, but was abandoned because of its nephrotoxicity and neurotoxicity. However, with increasing resistance among Gram-negative bacilli bacteria and shortage of new effective antibiotics, it regains its popularity. It is now more pure and less toxic, but caution is warranted especially in those with impaired renal function. It is available in two brands: Colomycin at a dose of 6–9 mg/kg/day divided into two or three doses per day and ColyMycin at a dose of 2.5–5 mg/kg/day in two or three divided doses. The use of colistin is limited to infection with multiple-resistant Gram-negative bacilli including Pseudomonas aerogenosa, Enterobacterecia, and Acinetobacter bumanii. It is always recommended to contact the microbiology laboratory interpretation of susceptibility testing. Kidney function should be monitored regularly while the patient is receiving this medication.

Tigecycline

As mentioned above, this new tetracycline has an activity against some of the Gram-negative bacilli that are resistant to other antibiotics like Kleibsella pneumoniae, Serratia marcenense, Enterobacter cloacae, and Escherichia coli. It is not effective against Pseudomonas aerogenosa.

Fosfomycin

It is a phosphonic acid derivative that acts by inhibiting bacterial cell wall. It is available in oral and parenteral forms. In the USA, it is approved for treatment of uncomplicated lower urinary tract infection; however, in many other countries like Germany, Japan, Spain, Brazil, and others, it has been used for treatment of sepsis, deep-seated infection and soft tissue infection, and it is currently. It has an excellent activity against many of multiresistant organisms like methicillin-resistant staphylococcus auresus, Enterococcus faecalis, Pseudomonas aerogenosa, Kleibsella pneumoniae, Serratia marcescens, Escherichia coli, Proteus mirabilis, Haemophilus influenzae, and Streptococcus pneumoniae. It is one of the antibiotics that can be used as a salavage therapy in situation where a multiresistant organism is encountered.

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74 Antiviral Therapy

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Introduction

Though work on the synthesis and evaluation of compounds with antiviral activity began shortly after the discovery of penicillin in the 1940s, the rapid recent advances in antiviral development did not begin until several decades later. Much of the early emphasis in antiviral research focused on infections caused by the herpesviruses, in large part due to the recurrent or persistent nature of herpesvirus diseases. In the late 1940s and early 1950s, Hitchings and colleagues demonstrated that purine and pyrimidine antimetabolites, such as 5-bromouracil and 2,6-diaminopurine, inhibited the nucleic acid biosynthesis of viruses, bacteria, protozoa, and malignantly transformed cells. Direct clinical value of these observations was limited by both the toxicity and lack of potency of these early compounds. As such, these early landmark discoveries ultimately reinforced the widely held view of that era, as well as the subsequent two and a half decades, that chemotherapeutic agents with activity against DNA viruses are invariably toxic to the host. The scientific merit of this work was recognized by the global medical community in 1988 when Hitchings and Elion were awarded the Nobel Prize for their efforts in early antiviral development.

Despite these initial limitations, researchers steadfastly continued the quest for antiviral agents that were safe and effective, shifting focus from purine and pyrimidine bases to nucleosides. These compounds were screened against both tumor cells and viruses, reflecting the fact that they usually targeted active host cellular or viral replication processes. This resulted in the synthesis of 5-iododeoxyuridine (IUdR, idoxuridine) in 1959 by Prusoff, and the subsequent demonstration of its antiviral properties in vitro and in vivo. Due to its significant activity against herpes simplex virus (HSV) in 1962, IUdR became the first antiviral compound approved for clinical use, specifically for the topical therapy of primary and recurrent HSV ocular disease. Subsequent development of nucleoside analogues resulted in the synthesis of such compounds as 5-trifluoromethyl-2'-deoxyuridine (trifluorothymidine) and 9-(β-D-arabinofuranosyl)adenine (ara-A, vidarabine) in the 1960s. Due to the fact that most of these compounds did not distinguish between viral and host cellular functions, toxicity remained a significant problem with the systemic administration of these agents. Indeed, the first antiviral compound licensed for systemic use in the United States was not an anti-herpesvirus agent at all, but rather was amantadine, which was licensed in 1966 for the prophylaxis of influenza virus infections. In 1977, vidarabine became the first anti-herpesvirus agent to be licensed in the United States for systemic administration; this followed studies earlier in the 1970s demonstrating its utility in the management of infections caused by varicella-zoster virus (VZV) and HSV.

The obstacles encountered in the development of these first generation antiviral drugs emphasize several important generalizations that continue to influence the development of new antiviral compounds: (1) although many compounds demonstrate antiviral activity in vitro, most are associated with unacceptable toxicity due to interference with human host cell functions; (2) effective antiviral agents typically target a specific viral protein, thus producing a restricted spectrum of antiviral activity; (3) antiviral drug resistance is frequently the consequence of single nucleotide changes that result in critical amino acid substitutions in the target viral protein; (4) the presence of an intact host immune system is vital to the effective resolution of disease in the host, regardless of the presence or absence of an antiviral drug; (5) clinical efficacy is dependent upon adequate concentrations of the antiviral drug reaching the site of infection, including the achievement of adequate intracellular concentrations of drug; and (6) the in vitro assay systems utilized for the determination of antiviral susceptibility are not standardized, and correlation between in vitro drug concentration and in vivo clinical response is not established for most antiviral agents.

The significant progress in the development of effective anti-herpesvirus compounds in the 1970s directly paved the way for the dramatically rapid advances in the development of antiretroviral drugs in the 1980s and 1990s directed against human immunodeficiency virus (HIV). Likewise, the importance of advances in molecular biology and the resulting understanding of virus host-cell

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interactions cannot be overemphasized. The convergence of scientific experience with the emergence of a previously unknown viral entity (HIV) is stunning. A discussion of systemic antiviral small molecule drugs with activity against herpesviruses, respiratory viruses, and hepatitis B viruses will be presented in this chapter. However, the HIV-specific drugs (antiretroviral drugs and protease inhibitors) will not be reviewed due to the immensity of the subject and the extremely rapid therapeutic developments currently being enjoyed in that field.

Systemic Anti-Herpesvirus Agents

Acyclovir

The licensure of acyclovir in 1982 opened the field of clinical antiviral drug intervention and heralded the era of rapid development of new drugs. By requiring the presence of a virus-encoded enzyme to begin the process of intracellular phosphorylation, acyclovir became the first antiviral agent to target virus-infected cells rather than all host cells. Acyclovir's remarkable safety profile and impressive clinical utility have established the standard by which all subsequent antiviral drugs have been judged.

Antiviral Activity

Acyclovir (9-[2-hydroxyethoxymethyl]guanine) is a selective inhibitor of the replication of HSV-1, HSV-2, and VZV. Acyclovir concentrations required to inhibit the viral cytopathic effects of HSV-1, HSV-2, and VZV by 50% (ED_{50}s) are 0.04, 0.10, and 0.50 μg/mL, respectively. Acyclovir has a lesser degree of in vitro activity against Epstein-Barr virus (EBV) and human herpesvirus-6 (HHV-6) but lacks in vitro activity against cytomegalovirus (CMV).

Mechanism of Action

Acyclovir is converted by the HSV or VZV thymidine kinase (TK) to its monophosphate derivative, an event that occurs to a much lower extent in uninfected cells. Subsequent diphosphorylation and triphosphorylation are catalyzed by cellular enzymes, resulting in acyclovir triphosphate concentrations that are 40–100 times higher in HSV-infected cells than in uninfected cells. Acyclovir triphosphate prevents viral DNA synthesis by inhibiting the viral DNA polymerase. Acyclovir triphosphate is a much better substrate for the viral polymerase than for cellular DNA polymerase α, resulting in little incorporation of acyclovir into cellular DNA.

Pharmacokinetics

Bioavailability of the oral is only 15–30%. Steady-state peak plasma concentrations of 1.6 μg/mL and 20 μg/mL are achieved following an 800 mg oral dose and a 10 mg/kg intravenous dose, respectively. Acyclovir is minimally metabolized, and approximately 85% is excreted unchanged in the urine. In patients with normal renal function, the serum half-life is 2–3 h. The dosage of acyclovir must be adjusted in patients with impaired renal function.

Adverse Effects

Acyclovir has consistently demonstrated a remarkable safety profile. Reversible nephrotoxicity can occur, especially in patients receiving large doses of acyclovir by rapid intravenous infusion. In adults, however, oral acyclovir therapy has not been associated with nephrotoxicity. Acyclovir administration to neonates and young infants has been associated with neutropenia, although perhaps to a lesser degree ($\leq$20% developing neutropenia) than originally thought. High concentrations of acyclovir following intravenous administration in patients with impaired renal function can result in central nervous system complications such as agitation, hallucinations, disorientation, tremors, and myoclonus.

Resistance

Viral resistance to acyclovir can result from mutations in either the viral TK gene or the viral DNA polymerase gene. HSV isolates demonstrate acyclovir resistance in approximately 5% of transplant patients and patients with AIDS. Acyclovir-resistant HSV has also been documented rarely in immunocompetent adults and infants. Foscarnet is the drug of choice in the management of patients with acyclovir-resistant HSV and VZV infections.

Therapeutic Uses

HSV and VZV Infections Recommended doses of oral and intravenous acyclovir for clinical treatment are provided in *Table 74.1*. Acyclovir treatment is indicated for life-threatening infections and for disease associated with severe morbidity and death, such as HSV encephalitis, neonatal HSV infections, and VZV infections in compromised hosts. Acyclovir therapy is also indicated for mucocutaneous HSV infections in immunocompromised hosts and for disseminated HSV and VZV infections in otherwise normal hosts, including pregnant women. Acyclovir is effective for the treatment of primary genital HSV infections, reducing the median duration of viral shedding, pain, and length of time to complete healing. Intravenous and oral acyclovir therapies are almost

Table 74.1

Dosing of antiviral drugs in pediatric patients with normal renal function

Drug	Indication	Route	Age	Usually recommended dosage
Acyclovir	Neonatal HSV infection	IV	Birth to 3 months	60 mg/kg per day in three divided doses for 14–21 days
	HSV encephalitis	IV	≥3 months to 12 years	30–45 mg/kg per day in three divided doses for 14–21 days; FDA-approved dose for this indication and age range is 60 mg/kg per day in three divided doses, but nephrotoxicity may be increased at this higher dose
		IV	≥12 years	30 mg/kg per day in three divided doses for 14–21 days
	Varicella in immunocompetent host	Oral	≥2 years	80 mg/kg per day in four divided doses for 5 days; maximum dose, 3,200 mg/day
	Varicella in immunocompromised host	IV	<1 year	30 mg/kg per day in three divided doses for 7–10 days
		IV	≥1 year	1,500 mg/m^2 per day in three doses for 7–10 days; some experts recommend the 30 mg/kg per day dose
	Zoster in immunocompetent host	IV	All ages	Same as for varicella in immunocompromised host
		Oral	≥12 years	4,000 mg/day in five divided doses for 5–7 days
	Zoster in immunocompromised host	IV	<12 years	30 mg/kg per day in three divided doses, for 7–10 days
		IV	≥12 years	30 mg/kg per day in three divided doses, for 7–10 days
	HSV infection in immunocompromised host (localized, progressive, or disseminated)	IV	<12 years	30 mg/kg per day in three divided doses for 7–14 days
		IV	≥12 years	30 mg/kg per day in three divided doses for 7–14 days
		Oral	≥2 years	1,000 mg/day in three to five divided doses for 7–14 days
	Prophylaxis of HSV in immunocompromised hosts who are HSV seropositive	Oral	≥2 years	600–1,000 mg/day in three to five divided doses during period of risk
		IV	All ages	15 mg/kg in 3 divided doses during period of risk
	Genital HSV infection: first episode	Oral	≥12 years	1,000–1,200 mg/day in 3–5 divided doses for 7–10 days
				Oral pediatric dose: 40–80 mg/kg per day divided in three to four doses for 5–10 days (maximum 1.0 g/day)
		IV	≥12 years	15 mg/kg per day in three divided doses for 5–7 days
	Genital HSV infection: recurrence	Oral	≥12 years	1,000 mg in five divided doses for 5 days, or 1,600 mg in two divided doses for 5 days, or 2,400 mg in three divided doses for 2 days
	Chronic suppressive therapy for recurrent genital and cutaneous (ocular) HSV episodes	Oral	≥12 years	800 mg/day in two divided doses for as long as 12 continuous months

Table 74.1 (Continued)

Drug	Indication	Route	Age	Usually recommended dosage
Adefovir	Chronic hepatitis B	Oral	≥12 years	10 mg once daily in patients with adequate renal function; optimal duration of therapy unknown
Amantadine	Influenza A: treatment and prophylaxis	Oral	1–9 years	Treatment or prophylaxis: 5 mg/kg per day, maximum 150 mg/day, in two divided doses
		Oral	≥10 years	Treatment or prophylaxis: <40 kg: 5 mg/kg per day, in two divided doses; ≥40 kg: 200 mg/day in two divided doses
		Oral	Dose by weight, not age	Alternative prophylactic dose for children >20 kg and adults: 100 mg/day
Cidofovir (Vistide)	Cytomegalovirus (CMV) retinitis	IV	Adult dose	Induction: 5 mg/kg once weekly × two doses with probenecid and hydration
				Maintenance: 5 mg/kg once every 2 weeks with probenecid and hydration
Entecavir	Chronic hepatitis B	Oral	≥16 years	0.5 mg once daily in patients who have not received prior nucleoside therapy; 1 mg once daily in patients who are previously treated (not first choice in this setting); optimum duration of therapy unknown
Famciclovir	Genital HSV infection, episodic recurrent episodes	Oral	Adult dose	Immunocompetent: 2,000 mg/day in two divided doses for 1 day
				HIV-infected patients: 1,000 mg in two divided doses for 7 days
	Daily suppressive therapy	Oral	Adult dose	Immunocompetent: 500 mg/day in two divided doses for 1 year, then reassess for recurrence of HSV infection
	Recurrent herpes labialis	Oral	Adult dose	Immunocompetent: 1,500 mg as a single dose
				HIV-infected patients: 1,000 mg/day in two divided doses for 7 days
	Herpes zoster	Oral	Adult dose	1,500 mg/day in three divided doses for 7 days
Foscarnet	CMV retinitis in patients with acquired immunodeficiency syndrome	IV	Adult dose	180 mg/kg per day in two to three divided doses for 14–21 days, then 90–120 mg/kg once a day as maintenance dose
	HSV infection resistant to acyclovir in immunocompromised host	IV	Adult dose	80–120 mg/kg per day in two to three divided doses until infection resolves
	VZV infection resistant to acyclovir	IV	Adult dose	120 mg/kg/day, divided every 8 h, up to 3 weeks
Ganciclovir	Acquired CMV retinitis in immunocompromised host	IV	Adult dose	Treatment: 10 mg/kg per day in two divided doses for 14–21 days; Long-term suppression: 5 mg/kg per day for 7 days/week or 6 mg/kg per day for 5 days/week
	Prophylaxis of CMV in high-risk host	IV	Adult dose	10 mg/kg per day in two divided doses for 1–2 weeks, then 5 mg/kg per day in one dose for 100 days or 6 mg/kg per day for 5 days/week
Lamivudine	Treatment of chronic hepatitis B	Oral	≥2 years	3 mg/kg once day (maximum 100 mg/day) (children coinfected with HIV and hepatitis B should use the approved dose for HIV)

Oseltamivir	Influenza A and B: treatment	Oral	Birth to <12 months	3 mg/kg/dose twice daily
		Oral	1–12 years	≤15 kg: 30 mg, twice daily; 16–23 kg: 45 mg, twice daily; 24–40 kg: 60 mg, twice daily; >40 kg: 75 mg, twice daily
		Oral	≥13 years	75 mg twice daily for treatment
	Influenza A and B: prophylaxis	Oral	1–12 years	Same as treatment for patients 1–12 years of age, except dose given once daily
		Oral	≥13 years	75 mg once daily
Rimantadine	Influenza A: treatment	Oral	≥13 years	200 mg/day in two divided doses
	Influenza A: prophylaxis	Oral	≥1 year	1–9 years of age: 5 mg/kg per day, maximum 150 mg/day, once daily
				≥10 years of age, <40 kg: 5 mg/kg per day in two divided doses; ≥40 kg: 200 mg/day in two divided doses
Telbivudine	Chronic hepatitis B	Oral	Adult dose	600 mg once daily
Tenofovir	Chronic hepatitis B	Oral	Adult and adolescent dose	300 mg once daily
				8 mg/kg once daily
			2– 8 years old (for HIV)	
Valacyclovir	Chickenpox	Oral	2–<18 years	20 mg/kg per dose three times daily for 5 days, not to exceed 1 g per dose three times daily
	Genital HSV infection, first episode	Oral	Adult dose	2 g/day in two divided doses for 10 days
	Episodic recurrent genital HSV infection	Oral	Adult dose	1 g/day in two divided doses for 3 days
	Daily suppressive therapy for recurrent genital HSV infection	Oral	Adult dose	1,000 mg, once daily for 1 year, then reassess for recurrences
	Recurrent herpes labialis	Oral	>12 years	4 g/day in two divided doses for 1 day
	Herpes zoster	Oral	Adult dose	3 g/day in three divided doses for 7 days
Valganciclovir	Acquired CMV retinitis in immunocompromised host	Oral	Adult dose	Treatment: 900 mg twice daily for 3 weeks
				Long-term suppression: 900 mg once daily
	Prevention of CMV disease in kidney or heart transplant patients	Oral	4 months to 16 years	Dose once a day within 10 days of transplantation until 100 days post-transplantation according to dosage algorithm based on body surface area and creatinine clearance (see Drug Package Insert)
Zanamivir	Influenza A and B: treatment (see Influenza, p 400)	Inhalation	≥7 years (treatment)	10 mg twice daily for 5 days
	Influenza A and B: prophylaxis	Inhalation	≥5 years (prophylaxis)	10 mg, once daily for as long as 28 days (community outbreaks) or 10 days (household setting)

IV indicates intravenous, *IO* intraocular, *IM* Intramuscular, *SC* subcutaneous, *IU* international units

equally efficacious, with topical treatment providing less benefit. Acyclovir probably reduces the ocular morbidity of zoster ophthalmicus. The advantages of treating previously healthy individuals with herpes labialis, recurrent genital herpes, varicella, and herpes zoster are less dramatic, and the treatment of patients with these conditions should be individualized.

The most frequent indication for long-term suppressive oral therapy is in patients with frequently recurrent genital infections, in whom daily administration of acyclovir reduces the frequency of recurrences by at least 75%. Acyclovir has been shown to maintain a high degree of efficacy and little toxicity even after more than 5 years of continuous suppressive therapy. The use of prophylactic acyclovir therapy in pregnant women has been explored in several small studies, but the numbers of patients evaluated to date are insufficient to prove definitively its safety or efficacy in this population.

Valaciclovir

Valaciclovir (2-[2-amino-1,6-dihydro-6-oxo-9H-purin-9-yl-methothy]ethyl-L-valinate hydrochloride, Valtrex) is the L-valyl ester of acyclovir. This esterification serves only to increase the oral bioavailability of acyclovir, and administration of valaciclovir produces higher serum levels of acyclovir than comparable oral doses of acyclovir.

Antiviral Activity

Due to the fact that valaciclovir is converted to acyclovir prior to its monophosphorylation as acyclovir in HSV-infected cells, the spectrum of antiviral activity is identical to that of the parent compound.

Mechanism of Action

As expected with a prodrug, valaciclovir has the same mechanism of action as acyclovir and requires viral TK-dependent conversion of acyclovir to the monophosphate form.

Pharmacokinetics

After oral administration of valacyclovir, rapid and complete conversion to acyclovir occurs with first-pass intestinal and hepatic metabolism. The bioavailability of valacyclovir in adults exceeds 50%, which is 3 to 5 times greater than that of acyclovir. Peak serum concentrations, attained about 1.5 h after a dose has been given, are proportional to the amount of drug administration, and the area under the drug concentration time curve approximates that seen after intravenous acyclovir. All other pharmacokinetic characteristics are similar to those of acyclovir.

Valacyclovir oral suspension recently has been studied in children 1 month to 12 years of age. Bioavailability was estimated to be 45–51% in all age groups except 3–<6 month olds, in whom the bioavailability is lower at 22%. Approximate dose proportionality in C_{max} and AUC(0-∞) was seen across the 10–25 mg/kg dose range (i.e., dose-normalized differences generally within $\leq\sim$30%), with the exception of children in the 2–<6 year age range, for whom a near doubling in C_{max} and AUC(0-∞) was noted with only a modest increase in dose from 20 to 25 mg/kg in children beyond infancy (>12 months of age).

Adverse Effects

The safety profile of valaciclovir is similar to that of acyclovir. Clinical trials have shown that valaciclovir is very well tolerated and relatively nontoxic at dosages of up to 1 g three times per day. Primary side effects of the medication include gastrointestinal upset, vomiting, and headache.

Resistance

As valaciclovir is rapidly and efficiently converted to acyclovir following gastrointestinal absorption, the mechanisms of antiviral resistance are the same as for acyclovir.

Therapeutic Uses

Recommended doses of valacyclovir for clinical treatment are provided in ❯ *Table 74.1*. The indications for valacyclovir in adults are the same as those for acyclovir. In the United States, valacyclovir is licensed for the treatment of pediatric patients with orolabial HSV recurrences (12 years of age and older) and chickenpox (2–<18 years of age).

Famciclovir/Penciclovir

Penciclovir (9-[4-hydroxy-3-hydroxymethylbut-1-yl] guanine) is an acyclic nucleoside analog of guanosine. Famciclovir is the inactive diacetyl ester prodrug of penciclovir, with high oral bioavailability, rapid tissue distribution, and a long intracellular half-life.

Antiviral Activity

The spectrum of antiviral activity of penciclovir is similar to that of acyclovir. Penciclovir has demonstrable in vitro activity against HSV-1, HSV-2, VZV, EBV, and hepatitis B virus (HBV). As a prodrug, famciclovir lacks antiviral activity and, instead, produces antiviral effects only

following its conversion to penciclovir after oral administration.

Mechanism of Action

Penciclovir is the quite similar to acyclovir with respect to mechanism of activation. Like acyclovir, penciclovir is converted to its monophosphate form by viral TK. Penciclovir monophosphate is then converted to the triphosphate form by cellular enzymes. Like acyclovir triphosphate, penciclovir triphosphate serves as a competitive inhibitor of viral DNA polymerase and is incorporated into the nascent DNA chain. Penciclovir triphosphate has approximately 1/100th the potency of acyclovir triphosphate in inhibiting viral DNA polymerase, but by virtue of its high intracellular concentrations and long half-life, it remains an effective antiviral agent.

Pharmacokinetics

Hydrolysis in the intestinal wall and first-pass metabolism in the liver remove both acetyl moieties of famciclovir, converting it to penciclovir. Approximately 80% of the drug is absorbed after oral dosing, with drug absorption being unaffected by pH. Food delays absorption but does not affect the final plasma drug concentration. Peak serum concentrations of penciclovir are achieved 1 h following administration of a 500 mg dose of famciclovir, and the plasma half-life of penciclovir is 2 h. Renal clearance accounts for about 70% of drug elimination, with penciclovir being excreted unchanged in the urine by both glomerular filtration and tubular secretion. Dosage adjustment is required in patients with renal impairment.

Famciclovir pharmacokinetics have recently been assessed in a single-dose pediatric study of infants 1–12 months of age who were administered famciclovir sprinkles orally. Infants under 6 months of age had significantly lower systemic exposure compared with 6–12 month olds.

Adverse Effects

Safety analyses of famciclovir in humans have found the drug to be well tolerated and exceptionally nontoxic. Famciclovir increases digoxin levels and causes nausea (4.5%), diarrhea (2.4%), and headache (9.3%) in some patients.

Resistance

Penciclovir- and acyclovir-resistant mutants are roughly similar with respect to both phenotypic and genotypic alterations. Mutations in the viral TK that bestow acyclovir resistance will usually also confer cross-resistance to penciclovir.

Therapeutic Uses

Recommended doses of famciclovir for clinical treatment are provided in *Table 74.1*. Famciclovir is approved in the United States for treatment in immunocompetent hosts of primary and recurrent genital HSV infections and of herpes zoster. In placebo-controlled trials of the treatment and suppression of recurrent HSV lesions, famciclovir decreases pain and results in earlier healing of lesions by 2 days. In the management of herpes zoster, famciclovir accelerates cutaneous healing by 1 day and shortens the duration of postherpetic neuralgia when compared to placebo. A 7-day course of famciclovir (500 mg three times daily) is as efficacious as a 5-day course of acyclovir (800 mgfive times daily) for the treatment of herpes zoster in immunocompetent patients, with equivalent rates of healing, duration of acute pain, and drug side effects between the two treatments.

Ganciclovir

Ganciclovir (9-[1,3-dihydroxy-2-propoxymethyl] guanine) is another acyclic nucleoside analog of guanosine which, when compared to acyclovir, has an additional hydroxymethyl group. This additional group on the acyclic side chain conveys a markedly different spectrum of activity and adverse events profile than the previously discussed antiviral agents.

Antiviral Activity

Ganciclovir demonstrates striking activity against CMV, with inhibitory concentrations of 0.2–3.0 μg/mL for susceptible clinical isolates. Such marked anti-CMV activity is in contrast to that of acyclovir, penciclovir, and their respective prodrugs.

Mechanism of Action

As with acyclovir and penciclovir, ganciclovir requires intracellular phosphorylation to its active triphosphate derivative. In HSV- and VZV-infected cells, the initial monophosphorylation is accomplished by the viral TK. However, CMV does not encode a thymidine kinase; instead, the enzyme that catalyzes the initial phosphorylation of ganciclovir in CMV-infected cells is the phosphotransferase encoded by the UL97 gene. Cellular enzymes subsequently convert the monophosphate form to the active triphosphate derivative. Ganciclovir triphosphate serves as a competitive inhibitor of herpesviral DNA polymerases, though it has also some activity against cellular DNA polymerases. Incorporation of ganciclovir triphosphate into the growing viral DNA chain

results in slowing and subsequent cessation of DNA-chain elongation.

Pharmacokinetics

Following an intravenous dose of 5 mg/kg, ganciclovir peak and trough plasma concentrations average 8–11 μg/mL and 0.6–1.2 μg/mL, respectively. Concentrations of ganciclovir in the central nervous system range from 24% to 70% of those in the plasma, with brain concentrations of 38% of plasma levels. The pharmacokinetics of ganciclovir in the neonatal population are similar to those of adults. The plasma half-life of ganciclovir is 3–4 h, and the route of drug excretion is virtually entirely renal. In patients with renal impairment, therefore, dosage adjustments are required.

Adverse Effects

The primary adverse events attributable to ganciclovir therapy are hematologic. Up to 40% of adult patients and 68% of neonates receiving parenteral ganciclvoir experience neutropenia (absolute neutrophil counts $<$1,000 cells/mm^3), and thrombocytopenia occurs in up to 20% of adult ganciclovir recipients. The likelihood of neutropenia following oral administration of ganciclovir is lower, with 14–24% of patients developing an absolute neutrophil count of $<$1,000 cells/mm^3. These hematologic abnormalities are reversible upon cessation of drug. Alternatively, use of colony stimulating factors (G-CSF, GM-CSF) may also expedite bone marrow recovery from ganciclovir toxicity. Additional adverse effects seen with administration of ganciclovir include anemia, liver function abnormalities, headache, rash, fever, nausea/vomiting, and diarrhea.

Resistance

Ganciclovir resistance among CMV isolates is conferred by mutations in either the UL 97 gene or the CMV DNA polymerase gene. Of these two mechanisms of antiviral resistance, ganciclovir-resistant CMV isolates with mutations in the UL97 open reading frame are the predominant phenotype. Mutations in the CMV DNA polymerase can confer cross-resistance to foscarnet.

Therapeutic Uses

Recommended doses of ganciclovir for clinical treatment are provided in ❯ *Table 74.1*. The frequent occurrence of side effects limits the utilization of ganciclovir to those patients with potentially severe CMV disease. In the management of CMV retinitis, intravenous ganciclovir will result in stabilization or improvement of disease in approximately 75–85% of patients. Among solid organ transplant recipients, ganciclovir monotherapy is effective in the treatment of CMV pneumonia. In bone marrow transplant patients, however, CMV hyperimmune globulin should be administered concurrently with intravenous ganciclovir in the management of CMV lung disease. Ganciclovir monotherapy is ineffective in the treatment of CMV colitis in bone marrow transplant patients.

Prophylactic administration of intravenous ganciclovir is effective for the prevention of CMV disease in transplant patients. Several different regimens have been evaluated in these patients, including initiation of antiviral therapy at the time of transplantation, upon isolation of CMV from any body site following transplantation, and preemptively at the time of administration of antilymphocyte antibody. Prophylactic ganciclovir use also decreases HSV shedding in transplant patients.

Valganciclovir

Valganciclovir is the L-valine ester prodrug of ganciclovir. Because it is well absorbed after oral administration, it may represent a favorable option to intravenously administered ganciclovir for the treatment and suppression of CMV infections in immunocompromised hosts.

Antiviral Activity

Due to the fact that valaganciclovir is converted to ganciclovir prior to its phosphorylation in CMV-infected cells, the spectrum of antiviral activity is identical to that of the parent compound.

Mechanism of Action

As expected with a prodrug, valganciclovir has the same mechanism of action oas ganciclovir and requires phosphorylation by the UL97 gene product to the monophosphate form.

Pharmacokinetics

Valganciclovir is rapidly converted to ganciclovir, with a mean plasma half-life of about 30 min. The absolute bioavailability of valganciclovir exceeds 60% and is enhanced by about 30% with concomitant administration of food. Oral valganciclovir produces exposures of ganciclovir exceeding those attained with oral ganciclovir and similar to those reported after standard intravenous administration of ganciclovir. Oral valganciclovir pharmacokinetics in young infants have been compared with parenteral ganciclovir. Intravenous ganciclovir clearance nearly doubled and AUC_{12} was cut by almost half over the first 6 weeks of life. In comparison, only a marginal

decrease in AUC_{12} was noted following administration of valganciclovir oral solution, possibly due to the fact that bioavailability increased by 32% over the same time period.

Adverse Effects

The most common side effects associated with valganciclovir therapy include diarrhea (41%), nausea (30%), neutropenia (27%), anemia (26%), and headache (22%). Long-term (up to 5 years) treatment with valganciclovir is well tolerated in patients with AIDS, and the type and incidence of adverse events experienced long-term appear to be similar to those observed at 1 year.

Resistance

As valaganciclovir is rapidly and efficiently converted to ganciclovir following gastrointestinal absorption, the mechanisms of antiviral resistance are the same between the two drugs.

Therapeutic Uses

Recommended doses of valganciclovir for clinical treatment are provided in ❯ *Table 74.1*. Valganciclovir has similar indications to ganciclovir. However, based on limited controlled trials published to date, it is currently only approved for the induction and maintenance therapy of CMV retinitis. Orally administered valganciclovir appears to be as effective as intravenous ganciclovir for induction treatment and is convenient and effective for the long-term management of CMV retinitis in patients with AIDS.

The greater systemic exposure to ganciclovir delivered by valganciclovir when used prophylactically is safe and is associated with delayed development of viremia in solid organ transplant recipients, compared with oral ganciclovir. Valganciclovir is also effective as preemptive therapy and as treatment for CMV disease in solid organ transplant recipients.

Cidofovir

Cidofovir {(S)-1-[3-hydroxy-2 (phosphonylmethoxy)-propyl]cytosine} is a novel acyclic phosphonate nucleoside analog.

Antiviral Activity

Cidofovir has demonstrable activity against HSV and CMV. Due to its unique phosphorylation requirements for activation, the drug usually maintains activity against acyclovir- and foscarnet-resistant HSV isolates, as well as ganciclovir- and foscarnet-resistant CMV mutants. Cidofovir exhibits marked activity against CMV, with inhibitory concentrations of 0.1 μg/mL for susceptible clinical isolates.

Mechanism of Action

Cidofovir has a mechanism of action that is similar to other nucleoside analogues such as acyclovir and ganciclovir. In its native form, however, cidofovir already has a single phosphate group attached. As such, viral enzymes are not required for initial phosphorylation of drug. Rather, cellular kinases sequentially attach two additional phosphate groups, converting cidofovir to its active diphosphate form. This active compound then serves as a competitive inhibitor of DNA polymerase. While cidofovir is taken up by both virally infected and uninfected cells, the active form of the drug exhibits a 25- to 50-fold greater affinity for the viral DNA polymerase as compared to the cellular DNA polymerase, thereby selectively inhibiting viral replication.

Pharmacokinetics

Following intravenous administration of cidofovir, plasma half-life is 2.6 h, though cidofovir persists in cells for prolonged periods. In addition, active intracellular metabolites of cidofovir have long half-lives of 17–48 h. Such prolonged intracellular activity allows for an intermittent dosing schedule that is very attractive when compared to ganciclovir or foscarnet. Ninety percent of the drug is excreted in the urine, primarily by renal tubular secretion.

Adverse Effects

The principle adverse event associated with systemic administration of cidofovir is the development of nephrotoxicity. Cidofovir concentrates in renal cells in amounts 100 times greater than is seen in other tissues, producing severe proximal convoluted tubule nephrotoxicity when concomitant hydration and administration of probenicid are not employed. When present, renal toxicity manifests as proteinuria and glycosuria. Due to poor oral bioavailability (2–26%), cidofovir can only be administered intravenously or topically.

Resistance

Ganciclovir resistance conferred by mutations within the CMV DNA polymerase gene can be cross-resistant to cidofovir and sensitive to foscarnet.

Therapeutic Uses

Recommended doses of cidofovir for clinical treatment are provided in ❯ *Table 74.1*. Cidofovir has been evaluated

for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS), and it delays retinal disease progression. The drug should be administered with probenecid, and hydration should be assured. The safety and efficacy of cidofovir in children have not been studied.

Intralesional injection of cidofovir has been reported in several small, uncontrolled studies in patients with laryngeal papillomatosis caused by HPV infection. Recent uncontrolled studies, however, have reported less impressive therapeutic responses to cidofovir therapy, raising further questions about cidofovir's efficacy and safety in laryngeal papillomatosis. Case reports and small case series suggest that cidofovir may be beneficial in the management of adenovirus infections and BK virus infections in immunocompromised patients.

Foscarnet

Unlike the antiviral drugs discussed so far, foscarnet (trisodium phosphonoformate) is not a nucleoside derivative. Rather, this compound is an inorganic pyrophosphate analog. This basic difference provides foscarnet with a broader spectrum of activity than is available with the almost all of the other antiviral drugs discussed in this chapter.

Antiviral Activity

Foscarnet has demonstrable activity against all known human herpesviruses and HIV. While the drug concentrations required for inhibition of viral replication vary markedly, they generally range from 10 to 130 μM for HSV, 100–300 μM for CMV, and 10–25 μM for HIV. Foscarnet has proven useful in the treatment of disease caused by acyclovir- and ganciclovir-resistant isolates of HSV, VZV, and CMV.

Mechanism of Action

Foscarnet does not require intracellular metabolism to produce an active form of the drug. Rather, it directly inhibits viral DNA polymerase by blocking the pyrophosphate binding site and preventing cleavage of pyrophosphate from deoxynucleotide triphosphates. It is a noncompetitive inhibitor of viral DNA polymerases or HIV reverse transcriptase, and is not incorporated into the growing viral DNA chain. Once inside the cell, however, it is roughly 100-fold more active against viral DNA polymerases and HIV reverse transcriptase than cellular DNA polymerase α.

Pharmacokinetics

Plasma peak concentrations average 509 μM and 766 μM following intravenous administration of 60 mg/kg and 90 mg/kg foscarnet doses, respectively. Oral bioavailability is less than 20%. Initial plasma half-life ranges from 4 to 8 h in persons with normal renal function, but a more prolonged terminal half-life of up to 88 h occurs secondary to deposition of drug in bone. At steady state in CMV-infected individuals, the concentration of foscarnet achieved in the cerebrospinal fluid averages 66% of the plasma level. The major route of foscarnet elimination is renal, with most of the drug being excreted in an unmetabolized form. Dosage adjustments are required for the administration of foscarnet to patients with renal impairment.

Adverse Effects

The administration of foscarnet is frequently associated with the occurrence of adverse events, most commonly nephrotoxicity and metabolic derangements. Increases in serum creatinine occur in more than half of foscarnet recipients, though in most instances these adverse effects are reversible upon withdrawal of drug. Saline hydration can decrease the risk of nephrotoxicity. The metabolic abnormalities associated with foscarnet can include either elevations or decreases in serum calcium, phosphorus, and/or magnesium. Additional adverse effects include headache, tremor, altered sensorium, fever, nausea/vomiting, and abnormal liver function tests. Though hematologic abnormalities such as neutropenia and anemia also can occur, their incidence with foscarnet administration is much less than is seen with ganciclovir. The high concentrations of unmetabolized foscarnet excreted in the urine can produce genital ulcerations due to local toxicity from mucocutaneous contact. The skeletal and dental abnormalities seen in animals, as well as the fact that the drug must be diluted in large volumes of fluid, have precluded the systematic evaluation of foscarnet in infants and young children.

Resistance

Because foscarnet acts directly on the herpesviral DNA polymerase and does not require intracellular activation by viral or cellular enzymes, antiviral resistance is conferred only by mutations within the DNA polymerase gene. Passage of HSV and CMV isolates in the presence of drug can select for resistant variants. In addition, clinical HSV, VZV, and CMV isolates that are resistant to foscarnet have been reported. While cross-resistance with other antiherpesvirus agents has been described,

foscarnet-resistant mutants that remain amenable to treatment with acyclovir, ganciclovir, or cidofovir can occur.

Therapeutic Uses

Recommended doses of foscarnet for clinical treatment are provided in *Table 74.1*. Foscarnet administered intravenously has proven efficacious for the treatment of CMV retinitis, with approximately 90% of patients experiencing stabilization of their retinal disease; however, most will experience subsequent progression of infection and require re-induction. Foscarnet may also be effective in the management of CMV gastroenteritis or pulmonary infections in AIDS patients or transplant recipients, though studies of the drug in these conditions have not been well controlled. Notably, foscarnet is not beneficial in the treatment of CMV pneumonia in bone marrow transplant recipients.

Mucocutaneous disease produced by acyclovir-resistant HSV isolates is effectively treated with foscarnet. Additionally, acyclovir-resistant VZV disease in AIDS patients appears to respond to a change in antiviral therapy to foscarnet.

Antiviral Agents Active Against Respiratory Viruses

Oseltamivir

Oseltamivir is one of two licensed medications that specifically target the neuraminidase protein common to influenza A and B viruses.

Antiviral Activity

The influenza neuraminidase enzyme is highly conserved, being common to type A H1N1, type A H2N2, type A H3N2, type A H5N1, and type B influenza viruses. Therefore, this class of antiviral agents has activity against both influenza A and B viruses.

Mechanism of Action

The mechanism of action for this class of compounds is the specific inhibition of the influenza neuraminidase, with subsequent interference with the deaggregation and release of the viral progeny. Oseltamivir is an ethyl ester prodrug that, following hydrolysis by hepatic esterases, is converted to the active compound, oseltamivir carboxylate.

Pharmacokinetics

At least 75% of orally administered drug reaches the systemic circulation in the form of oseltamivir carboxylate. Coadministration with food has no significant effect on the peak plasma concentration. Neither oseltamivir nor oseltamivir carboxylate is metabolized by cytochrome P-450 isoforms. The primary route of elimination of oseltamivir is by conversion to the active drug, with more than 90% of the prodrug being metabolized to oseltamivir carboxylate. Oseltamivir carboxylate is not further metabolized, and it is entirely eliminated by renal excretion through glomerular filtration and anionic tubular secretion. Serum concentrations of oseltamivir carboxylate increase in the presence of declining renal function, and dose adjustment is recommended for patients with a CrCl below 30 mL/min.

Adverse Effects

The most common adverse effect reported with oseltamivir use is nausea, with or without vomiting. In controlled clinical trials, approximately 10% of patients reported nausea without vomiting, and an additional 10% experienced vomiting. The nausea and vomiting episodes were generally mild to moderate and usually occurred on the first 2 days of oseltamivir administration. Fewer than 1% of study subjects discontinued participation in the clinical trials prematurely because of nausea and/or vomiting. Food may help to alleviate these gastrointestinal side effects in some patients. Insomnia and vertigo were also reported more frequently among oseltamivir recipients than those receiving placebo.

Resistance

Oseltamivir-resistant influenza A viruses can emerge during treatment and also can be propogated in person-to-person spread during influenza epidemics. The seasonal influenza A H1N1 virus which predominated prior to the 2009 H1N1 pandemic was resistant to oseltamivir. However, 2009 H1N1 (which now has usurped the prior seasonal strain) is oseltamivir-susceptible. Thus, resistance patterns for oseltamivir must be monitored season by season to ascertain the utility of this antiviral agent.

Therapeutic Uses

Recommended doses of oseltamivir for clinical treatment are provided in *Table 74.1*. Oseltamivir is licensed for the treatment of influenza infection in patients 1 year of age and older, and is indicated for the prophylaxis of influenza in patients 13 years of age and older. Duration of illness is reduced by approximately 1.3 days when oseltamivir is administered within 2 days, compared to

placebo. Among patients treated within 24 h of the onset of symptoms, illness duration is reduced by almost 2 days. Oseltamivir recipients also had a more rapid return to normal health and activity compared with patients receiving placebo.

Compared with placebo, administration of oseltamivir for 6 weeks during the peak of influenza season significantly reduces the risk of contracting influenza. The protective efficacy for the prevention of culture-proven influenza approached 90%, which is comparable with that achievable with amantadine and rimantadine for influenza A.

Data generated by the NIAID Collaborative Antiviral Study Group before and during the 2009 H1N1 pandemic determined that the appropriate dose of oseltamivir in infants birth through 11 months of age is 3 mg/kg per dose given twice daily. This same group assessed dosing in premature neonates and estimated that 1 mg/kg per dose is the appropriate amount to administer in this at-risk group.

Zanamivir

Zanamivir is the second licensed medications that specifically target the neuraminidase protein common to influenza A and B viruses.

Antiviral Activity

Zanamivir also interferes with the function of the influenza neuraminidase enzyme, with subsequent interference with the deaggregation and release of the viral progeny.

Mechanism of Action

The mechanism of action for this class of compounds is the specific inhibition of the influenza neuraminidase, with subsequent interference with the deaggregation and release of the viral progeny.

Pharmacokinetics

Zanamivir has poor oral bioavailability and is therefore administered by oral inhalation. More than 75% of an orally inhaled dose of zanamivir is deposited in the oropharynx, most of which is swallowed. Approximately 13% of the dose distributes to the airways and lungs, and the remainder is retained in the delivery device. Inhaled zanamivir provides local concentrations in respiratory tract mucosa that greatly exceed inhibitory concentrations for influenza A and B viruses. Between 4% and 17% of an inhaled dose of zanamivir is absorbed systemically. Although serum zanamivir concentrations increase with decreasing CrCl, no adjustment in dosing is necessary in cases of renal insufficiency. Unabsorbed drug is excreted in the feces.

Adverse Effects

Zanamivir is well tolerated. The most serious adverse event associated with its use is respiratory distress. Decline in pulmonary function and bronchospasm have been reported in some patients receiving zanamivir. Many, but not all, of these patients had underlying airways disease, such as asthma or chronic obstructive pulmonary disease. Although influenza itself can cause such deteriorations, zanamivir is generally not recommended for the treatment of patients with underlying airways disease because of the risk of adverse events and the lack of demonstrated efficacy in this population.

Resistance

Antiviral resistance can be induced in vitro and has been detected in vivo. Cross-resistance between zanamivir and oseltamivir has been demonstrated as well in resistant isolates generated in vitro. Emergence of zanamivir resistance appears to occur less commonly than with oseltamivir or the adamantanes.

Therapeutic Uses

Recommended doses of oseltamivir for clinical treatment are provided in *Table 74.1*. Zanamivir is indicated for the treatment of uncomplicated illness due to influenza A and B virus of no more than 2 days' duration. Zanamivir therapy hastens clinical improvement by approximately 1.5 days in adults and children.

Inhaled zanamivir, 10 mg once daily administered for 4 weeks as seasonal prophylaxis, reduces the likelihood of laboratory-confirmed influenza infection (with or without symptoms) by 31%, influenza disease by 67%, and influenza disease with fever by 84%. A study of zanamivir administered once daily to healthy household contacts of influenza-infected index subjects demonstrated a 79% reduction in influenza illness.

Amantadine/Rimantadine

Amantadine (1-adamantanamine hydrochloride) and rimantadine (a-methyl-1-adamantane methylamine hydrochloride) are symmetric tricyclic amines that are closely related structurally to one another. Amantadine holds the unique status of having been the first antiviral agent to be licensed for systemic use in the United States for the prophylaxis of influenza.

Antiviral Activity

Both amantadine and rimantadine specifically inhibit the replication of influenza A. Inhibitory concentrations of susceptible isolates range from 0.1 to 0.4 μg/mL for amantadine and from 0.01 to 0.1 μg/mL for rimantadine. These concentrations are clinically relevant as the amount of either amantadine or rimantadine that is achievable in the blood or respiratory secretions is approximately 1.0 μg/mL. These compounds are not active against influenza B viruses.

Mechanism of Action

The target of the inhibitory action for both amantadine and rimantadine is the influenza A virus M2 protein. The M2 protein is an integral transmembrane protein that functions as an ion channel and is activated by pH. The M2 channel permits ions to enter the virion during the process of viral uncoating. This results in destabilization of protein–protein bonds, allowing the viral DNA to be transported into the nucleus. In addition, the M2 channel acts to modulate the pH of intracellular compartments, particularly the Golgi apparatus. In some species, this stabilizes the influenza A virus hemagglutinin (HA) during intracellular transport. These activities of the M2 ion channel are blocked by both rimantadine and amantadine.

Pharmacokinetics

Amantadine has a favorable oral bioavailability, with peak plasma concentrations being reached within 2–4 h following administration of the capsule, tablet, or liquid formulation of drug. As mentioned, levels achieved in respiratory secretions are similar to those of plasma. In healthy adults, plasma half-life of drug is 12–18 h, though this is prolonged in the elderly and in patients with renal insufficiency. Additionally, children with cystic fibrosis require larger doses of amantadine to achieve plasma concentrations similar to healthy adults. In excess of 90% of administered amantadine is excreted unchanged in the urine. Dosage adjustments are necessary when elderly persons or patients with renal insufficiency receive amantadine.

Rimantadine is also well absorbed orally, though time to peak plasma concentrations is somewhat longer at 2–6 h. While rimantadine levels in plasma are approximately half of those achieved with amantadine, rimantadine concentrates in nasal secretions and produces levels similar to amantadine at this site. Plasma half-life ranges from 24 to 36 h. Due to differences in the pharmacokinetics of rimantadine in elderly persons and patients with advanced hepatic or renal disease, the amount of drug administered to these persons should be decreased. Eighty-five percent of administered drug is metabolized by the liver, with the metabolites then being excreted in the urine; the 15% of administered drug that is not metabolized is excreted unchanged in the urine.

Adverse Effects

Minor dose-related gastric upset and central nervous system effects are quite common with administration of amantadine. Up to a third of healthy adult amantadine recipients will experience the somewhat disconcerting side effects of nervousness, insomnia, poor concentration, nausea, or anorexia. These central nervous system events are even more common in elderly patients, with 20 and 40% experiencing adverse CNS effects even when receiving reduced amantadine dosages. Discontinuation of drug due to unpleasant side effects occurs in 6–11% of patients taking amantadine as influenza prophylaxis. Extremely high plasma levels of amantadine in the setting of renal insufficiency or overdose can result in more severe reactions such as seizures, coma, cardiac arrythmias, and death. Long-term amantadine administration has been associated with livedo reticularis, peripheral edema, orthostatic hypotension, and urinary retention.

Rimantadine is much better tolerated than amantadine, with fewer than 5% of recipients of prophylactic rimantadine discontinuing drug due to unpleasant side effects, including neurotoxic effects. As compared to placebo, rimantadine (300 mg per day) administration is associated with higher rates of minor gastrointestinal complaints but not adverse neurologic events. Thus, rimantadine has a more favorable therapeutic index than does amantadine for the treatment and prevention of influenza A infections.

Resistance

Resistance of influenza A clinical isolates to amantadine and rimantadine is conferred by single amino acid substitutions at one of five positions (amino acids 26, 27, 30, 31, and 34) of the transmembrane domain of M2. Since 2005, virtually all circulating influenza A viruses have been resistant to amantadine and rimantadine, and for the time being, this class of drugs is no longer effective in the management of influenza disease in humans.

Therapeutic Uses

Prior to universal resistance among influenza A viruses worldwide, amantadine and rimantadine were used for the treatment and prophylaxis of influenza infection. Licensed doses of both drugs are provided in *Table 74.1*. However, at the current time neither amantadine nor

rimantadine are recommended for treatment or prophylaxis of influenza.

Antiviral Agents Active Against Hepatitis B Virus

Adefovir

Adefovir dipivoxil is one of three small molecules approved for use in the treatment of hepatitis B virus (HBV) infection in patients within the pediatric age range.

Antiviral Activity

In addition to HBV, adefovir diphosphate competitively inhibits deoxyadenosine triphosphate as a substrate for HIV-1 reverse transcriptase, resulting in chain termination following its incorporation in HIV DNA. The concentration required to inhibit enzymatic activity by 50% (IC_{50}) for HBV DNA polymerase is 0.1μmol/L, compared with >100 μmol/L for human DNA-α polymerase. In vitro, adefovir has an additive effect when combined with lamivudine, entecavir, or telbivudine.

Mechanism of Action

Adefovir dipivoxil is the oral prodrug of adefovir, which is an acyclic nucleotide analog of deoxyadenosine-5'-monophosphate (dAMP). Conversion of the prodrug to the active adefovir diphosphate is accomplished by cellular adenylate kinase. Adefovir diphosphate then acts as a competitive inhibitor of deoxyadenosine triphosphate for viral DNA polymerase, resulting in DNA chain termination following its incorporation in HBV DNA. The inhibition constant (K_i) for adefovir diphosphate against HBV DNA polymerase is 4-fold to 700-fold lower than the K_i for human DNA polymerases.

Pharmacokinetics

Adefovir dipivoxil is absorbed rapidly following oral administration. Following a single oral dose, the bioavailability is ∼59%. Food does not significantly impact absorption of adefovir dipivoxil, so the drug may be administered without regard to meals. Half-life at steady state is ∼7 h. Following absorption, adefovir dipivoxil is cleaved to adefovir by extracellular esterases. Adefovir then is phophorylated to the active moiety adefovir diphosphate by cellular adenylate kinase. The intracellular half-life of adefovir diphosphate is estimated to be 16–18 h. Adefovir is excreted renally as unchanged drug by tubular secretion and glomerular filtration. Dosing in patients with baseline creatinine clearance values <50 mL/min requires adjustment in the dosing interval. The dose of adefovir dipivoxil does not need to be adjusted in patients with hepatic impairment.

Adverse Effects

Adefovir dipivoxil generally is well tolerated over prolonged periods of administration. In randomized, controlled trials, diarrhea, headache, and abdominal pain occurred slightly more frequently in adefovir-treated patients compared with placebo-treated patients. Long-term administration may result in nephrotoxicity, but the risk in patients with adequate renal function is low. In vitro, adefovir does not inhibit cytochrome P450. No clinically relevant drug interactions have been reported in clinical trials.

Resistance

Resistance to adefovir becomes a limiting factor with prolonged use. The N236T mutation and the A181V mutationin the HBV polymerase both confer in vitro and in vivo antiviral resistance to adefovir diphosphate. Rates of resistance to adefovir at 1, 2, 4, and 5 years are 0%, 3%, 18%, and 29%, respectively. HBV strains with the A181V mutation also are resistant to lamivudine.

Therapeutic Uses

Recommended doses of adefovir dipivoxil for clinical treatment are provided in *Table 74.1*. Adefovir has been studied in pediatric patients with HBV infection and is approved for use in children 12 years of age and older. It is the preferred oral treatment option for children ages 12–15 (after which they can be treated with entecavir) who require antiviral treatment. In adults, adefovir dipivoxil therapy is associated with a 12% rate of HBeAg seroconversion, 21% rate of undetectable serum HBV DNA, and 53% rate of histological improvement in HBeAg-positive patients after 1 year of therapy. Once seroconversion occurs, it is sustained in 91% of patients. In adults, persistence of high levels of HBV DNA after 48 weeks of adefovir therapy predicts the emergence of resistance. The optimal duration of adefovir treatment in children is not known.

Entecavir

Entecavir is the second of the three small molecules approved for use in the treatment of hepatitis B virus (HBV) infection in patients within the pediatric age range, albeit the outer limits of this group (16 years of age and older).

Antiviral Activity

Entecavir triphosphate selectively inhibits HBV polymerase. It is only a weak inhibitor of cellular DNA polymerases and has no activity against HIV polymerase.

Mechanism of Action

Entecavir is a guanosine nucleoside analogue, which, following phosphorylation to the active triphosphate form, exhibits potent activity against HBV polymerase. Entecavir triphosphate inhibits HBV polymerase base priming, reverse transcription of the negative strand from the pregenomic messenger RNA, and synthesis of positive-strand HBV DNA.

Pharmacokinetics

Entecavir peak plasma concentrations occur between 0.5 and 1.5 h following oral administration in adults. Steady state is achieved following 6–10 days of once-daily administration, with approximately twofold accumulation. Due to decreases of approximately 20% in area under the curve (AUC) when administered with food, entecavir should only be given at least 2 h before or after a meal. The intracellular half-life of entecavir triphosphate is 15 h. Approximately two-thirds to three-quarters of drug is excreted unchanged in the urine. Pharmacokinetic studies of entecavir have not been conducted in children younger than 16 years of age.

Adverse Effects

Entecavir is not a substrate, inhibitor, or inducer of the cytochrome P-450 enzyme system. As such, entecavir pharmacokinetics are unlikely to be affected by drugs that affect or are metabolized by the cytochrome P-450 system. As with other therapies for chronic HBV infections, severe acute exacerbations of hepatitis B have been reported in patients who have discontinued entecavir therapy. Therefore, hepatic function should be closely monitored with both clinical and laboratory follow-up for at least several months in patients who discontinue HBV therapy.

Resistance

Both in vitro and in vivo data suggest that emergence of resistance to entecavir is rare in nucleoside-naive patients. However, approximately 7% of lamivudine-refractory patients with HBV infection develop entecavir resistance–associated substitutions when preexisting lamivudine resistance mutations are present. Additional mutations within the HBV viral polymerase are required for entecavir resistance to develop. Respective 5-year entecavir-resistance rates in nucleoside-naïve and lamivudine-refractory patients are 1.2% and 51%. Entecavir is active against adefovir-resistant mutants, and since additional mutations are required to develop resistance to entecavir, the drug also remains active against lamivudine-resistant mutants. Emergence of entecavir-resistance mutations is usually associated with virologic rebound during therapy.

Therapeutic Uses

Recommended doses of entecavir for clinical treatment are provided in *Table 74.1*. Entecavir is indicated for the treatment of chronic HBV infection in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active liver disease. Entecavir is superior to lamivudine in the treatment of chronic HBV infection and is the most potent anti-HBV agent available. Among patients with lamivudine-refractory chronic HBV infection, changing to entecavir (1 mg once daily) was superior to continuing lamivudine (100 mg once daily). Entecavir also is superior to adefovir dipivoxil in nucleoside-naïve, HBeAg-positive patients. The optimal duration of therapy with entecavir is not known. A Phase IIB pharmacokinetic and efficacy trial of entecavir in pediatric patients 2 years of age and older is nearing completion, and a Phase III trial in this age group has already started.

Lamivudine

Lamivudine is the third of the three small molecules approved for use in the treatment of hepatitis B virus (HBV) infection in patients within the pediatric age range. Of the three, it is licensed in the broadest age range, down to 3 years.

Antiviral Activity

Lamivudine inhibits the reverse transcriptase of both HBV and HIV, and is indicated for the treatment of HIV and chronic HBV infection.

Mechanism of Action

Lamivudine is a nucleoside analogue that is phosphorylated to lamivudine triphosphate by cellular kinases. As with other nucleoside analogues, lamivudine triphosphate exerts its antiviral effects via incorporation in the growing HBV DNA chain.

Pharmacokinetics

Lamivudine at a dose of 4 mg/kg administered twice daily produces an AUC_{12} of 5.16 mg·h/L and $t_{1/2}$ of 1.76 h. This $t_{1/2}$ in children is less than the $t_{1/2}$ in adults (3.5 h).

Adverse Effects

Adverse reactions include pancreatitis, paresthesia, peripheral neuropathy, neutropenia, anemia, rashes, nausea, vomiting, and hair loss.

Resistance

Lamivudine-resistant HBV mutants occur in up to one-third of subjects by the end of 1 year of therapy, and in up to two-thirds by the end of 4 years of drug exposure. Lamivudine resistance is usually manifest as breakthrough infection defined as reappearance of HBV DNA in serum after its initial disappearance. Most patients continue to have lower serum HBV DNA and ALT levels compared with pretreatment values, perhaps due to decreased fitness of the lamivudine-resistant mutants. Upon cessation of lamivudine therapy, most patients experience an increase in serum HBV DNA concentrations.

Therapeutic Uses

Recommended doses of lamivudine for clinical treatment are provided in *Table 74.1*. In the treatment of chronic HBV infection, lamivudine decreases serum HBV DNA by 3–4 log copies per mL in most patients. Among patients who are positive for HBeAg, approximately 20% achieve HBeAg seroconversion and undetectable serum HBV DNA at the end of 1 year of lamivudine therapy. Slightly more than half of patients experience improvement in histologic liver abnormalities. Similar findings have been seen in children.

Telbivudine

Telbivudine is the HBV antiviral drug which has been most recently approved by the FDA, in 2006. It is not licensed for use in children; it is approved for use in older adolescents and adults (16 years of age and older).

Antiviral Activity

Telbivudine preferentially inhibits HBV second strand (DNA-dependent) DNA synthesis. In comparison, lamivudine preferentially inhibits first strand (RNA-dependent) DNA synthesis. Telbivudine is active only against hepadnaviruses. In vitro, telbivudine-5'-triphosphate has no inhibitory effect on host cell DNA polymerases α, β, or γ at concentrations up to 100 μmol/L. In contrast, the mean 50% effective concentration (EC_{50}) inhibiting HBV DNA polymerase is 0.12–0.24 μmol/L, illustrating the specificity and potency of the drug for HBV replication. At concentrations up to 10 μmol/L, telbivudine has minimal toxic effect on host-cell mitochondria and does not increase lactic acid production.

Mechanism of Action

Telbivudine is the unmodified L-enantiomer of the naturally occurring nucleoside D-thymidine. Host-cell kinases phophorylate telbivudine to telbivudine-5'-triphosphate, which then is incorporated into HBV DNA, resulting in viral DNA chain termination. Coadministration of telbivudine with lamivudine does not produce additive or synergistic effects.

Pharmacokinetics

Telbivudine is rapidly absorbed after oral administration. Absorption is not influenced by food. The half-life of telbivudine is ~40 h. Approximately, 40% of the dose is excreted via the kidneys as the unchanged active substance, likely via renal filtration. Systemic exposure to telbivudine is increased in patients with impaired renal function, and in patients with moderate to severe renal impairment (creatinine clearance <50 mL/min) or end-stage renal disease requiring dialysis, the dosing interval requires adjustment. Dosage adjustment is not required for patients with impaired hepatic function.

Adverse Effects

Elevated blood CK concentrations are the most frequent adverse event possibly or probably related to telbivudine. Cases of myopathy during telbivudine therapy have been identified, but they did not correlate with the magnitude or timing of CK elevations. Nevertheless, treatment should be discontinued if persistent, unexplained muscle-related symptoms are noted. Patients receiving telbivudine along with other drugs associated with myopathy, such as cyclosporin or HMG-CoA reductase inhibitors, should be monitored closely for signs and symptoms of myopathy.

Resistance

The key determinant of telbivudine resistance is the M204I mutation in the YMDD motif. The principle mutations conferring in vivo lamivudine resistance do not produce cross-resistance to telbivudine, but cross-resistance can be induced in vitro. Telbivudine is active or has slightly reduced activity in vitro against adefovir-resistant HBV strains.

Therapeutic Uses

Recommended doses of telbivudine for clinical treatment are provided in *Table 74.1*. Telbivudine is licensed for use in adolescents and adults (≥16 years of age). It has not been studied in pediatric patients with HBV infection.

In HBeAg-seropositive and -seronegative adults, telbivudine is superior to lamivudine after 1 and 2 years of therapy. Telbivudine also has better early viral suppression compared to adefovir at week 24 in HBeAg-positive patients, regardless of whether the patients were treated initially with telbivudine or switched from adefovir to telbivudine. The early virological suppression resulted in better rates of HBeAg seroconversion, ALT normalization, and viral suppression.

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75 Laboratory Diagnosis of Viral Disease

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Unlike the automation and standardization of clinical chemistry and hematology laboratories, the only major changes in the methodology and operation of clinical microbiology laboratories since 1920 have been tests associated with antibacterial susceptibility. Although tissue culture techniques were introduced in diagnostic virology, their application was generally limited to a few large public health laboratories. However, with the development of newer simpler and rapid methods, the science is changing. This reflects evolving technology and differing priorities in various health-care settings. As the science pf antiviral chemotherapy advances, it is likely that priorities will come into a better focus and that hospitals will move toward a more standardized approach to viral illness and diagnostic laboratories.

Viral Diagnosis

There are a number of clinical situations where viral diagnosis may be particularly helpful. These include:

1. Viral diseases in which there are important public health considerations (e.g., influenza and arbovirus encephalitis)
2. Viral diseases in which there are significant risks to susceptible persons exposed to the patient (e.g., measles, hepatitis B, and varicella)
3. Situations involving important prognostic considerations (e.g., congenital infections, encephalitis, and infections in immunocompromised hosts)
4. Situations where withdrawal of antibiotics might serve the patient's interest (e.g., respiratory virus infections and viral meningitis)
5. Situations where therapeutic action depends on viral diagnosis (e.g., treatment with an antiviral agent, hospital infection control, and therapeutic abortion for rubella in pregnancy)
6. Cases where a viral diagnosis will teach the medical staff important lessons about diseases or epidemiology and improve subsequent care of similar patients

In order to identify the range of suspected viruses in any one individual patient, the onus is on the clinician to provide comprehensive information and/or liaise with laboratory staff.

Specimen Collection for Viral Diagnosis

It is difficult to overemphasize the importance of collecting proper clinical specimens for viral laboratory diagnostics. Unless the clinician pays close attention to the details of timing, collection, and handling, the laboratory can be of little help; for most acute viral illnesses, specimens obtained early in the illness (i.e., the first 1–4 days of symptoms) are most likely to contain recoverable virus.

Specimens should be collected with sterile implements and quickly transported to the laboratory (as any delay will mean some loss of virus particles). In addition to their heat lability, many viruses do not withstand drying. Swabs of mucosal surfaces, skin scrapings, and tissues are placed in a transport medium that contains a protein, a buffer at neutral pH, and antibiotics to kill or suppress the growth of bacteria and fungi.

Viruses vary in their ability to survive ambient temperatures. Specimens for virus isolation should always be transported to the diagnostic laboratory on ice, and, unless a delay of more than 4 days is anticipated, specimens should be held at 4°C and not frozen. If specimens are frozen, they should be kept at −70°C since conventional freezer temperatures (−10°C to −20°C) are detrimental to infectivity of many viruses.

The site of specimen collection should correlate with the clinical presentation and local epidemiology pattern. However, if there is deep or generalized disease (e.g., non-vesicular rash, meningitis, fever or unknown origin, congenital infection), it is advisable to sample multiple sites. *Table 75.1* shows a general listing of syndromes, common etiological agents, and appropriate specimens.

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Table 75.1
Specimens and viruses by clinical syndrome

Syndrome	Common	Uncommon	Specimens
Aseptic meningitis	Enteroviruses (Coxsackie, echo), mumps	Polio, LCMV, HSV-2, adenovirus	NP-throat, CSF, urine, stool, serum for LCMV
Encephalitis	Arboviruses[a], HSV-1, -2	Mumps, measles, influenza, rubella, VZV, rabies, EBV[a], enteroviruses	NP-throat, stool, CSF, brain biopsy (if herpes suspected), serum
URI, bronchitis, "flu"	Rhinovirus, parainfluenza, influenza, adenovirus, enterovirus, RSV	Measles, coronavirus (NL,HK), bocavirus	NP-throat, nasal aspirate
Croup	Parainfluenza	RSV, adenovirus, influenza	NP-throat, nasal aspirate
Pneumonia	RSV, adenovirus, influenza, metapneumovirus	Parainfluenza, CMV, rhinovirus, measles, rubella, HSV, VZV, enterovirus	NP-throat, stool, tracheal, aspirate, nasal aspirate, urine, serum
Bronchiolitis	RSV, influenza	Influenza, adenovirus, rhinovirus	NP-throat, nasal aspirate
Rashes – vesicular	VZV, HSV-1, -2	Vaccinia, enterovirus	Vesicular fluid, NP-throat, stool (for enterovirus), serum
Rashes – non-vesicular	Measles, rubella, enterovirus	EBV[a], Hepatitis B virus	NP-throat, stool (for enterovirus), serum
Congenital infection	CMV, HSV-2, rubella	Parvovirus B19	NP-throat, stool, pleural fluid, pericardial fluid, serum
Pleurodynia, pericarditis	Enterovirus (Coxsackie and echo)	Polio virus, mumps, influenza, adenovirus	NP-throat, stool, pleural fluid, pericardial fluid, serum
Eye lesions (keratitis, keratoconjunctivitis, conjunctivitis)	HSV-1, -2, adenovirus	Measles	Eye swabs, NP-throat, nasal washing
Gastroenteritis	Rotavirus norovirus[a], adenovirus	Enterovirus (newborns), influenza	Stool, NP-throat, urine
Hepatitis	Hepatitis A, B, C[a], D, EBV[a], CMV, VZV	Enterovirus, adenovirus, HSV-1, -2	Serum, NP-throat, stool, urine
Parotitis	Mumps parainfluenza, influenza	Adenovirus, LCMV, EBV[a], enterovirus	NP-throat, urine, nasal aspirate, serum

CMV cytomegalovirus; *CSF* cerebrospinal fluid; *EBV* Epstein-Barr virus; *HSV* herpes simplex virus; *LCMV* lymphocytic choriomeningitis virus; *NP* nasopharyngeal aspirate; *RSV* respiratory syncytial virus; *VZV* varicella-zoster virus
[a]Not cultivable in the routine laboratory; electron microscopy or serologic diagnosis available

Recognitions of Viruses in Clinical Specimens

Virus Isolation

The gold standard for viral isolation is the viral culture. Viruses are intracellular parasites and require living cells in order to replicate in the clinical laboratory. Living cells can be provided in the form of suckling mice, embryonated chicken eggs, and cell cultures. Today, most clinical laboratories prefer to use cell cultures rather than mouse and egg inoculation.

Virus identification depends on viral entry and proliferation in cells grown as a monolayer under sterile tissue culture conditions. Cytopathic effect (CPE) is a pattern of cell destruction resulting from viral infection that occurs in a characteristic pattern depending on the cell line and infecting virus. Members of the orthomyxovirus (influenza virus) and paramyxovirus (parainfluenza virus, or mumps) groups may fail to produce a clear-cut CPE in infected cell cultures, but they may be detected first, or sometimes exclusively, by demonstration of the phenomenon of hemabsorption (these viruses produce hemagglutinin molecules that protrude from the lipid bilayer of the

infected cell and bind to the guinea pig or other erythrocytes that are added to the tissue culture tube). Once CPE is detected by visual inspection under the microscope by a skilled technologist, confirmatory tests are performed to identify positively the virus.

A recent advance in a viral culture methodology involves centrifugation of the patient specimens onto cell monolayers in the bottom of glass shell vials, and, after a 1-to-2-day period of cultivation, staining for viral antigen in the cells by using a labeled monoclonal or polyclonal antibody. The centrifugation step shortens the time of development of viral antigen or CPE. The monoclonal antibody, if directed at viral antigens produced early in the replication cycle, can detect a virus even before the development of CPE. For example, use of the "shell vial" technique in the laboratory enables detection of 50–60% of cytomegalovirus (CMV)-positive specimens within 24 h and a cumulative total of 90% within 48 h. The remaining 10% are detected by traditional viral CPE and require a mean of 10 days for positive results. This technique has been applied to the rapid detection of several viruses, including herpes simplex, measles, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV), and varicella-zoster viruses.

Rapid Diagnostic Methods

Same-day diagnosis is the "wave of the future" in microbial diagnostics. However, rapid diagnosis is a "directed approach" that requires prior consideration of the virus suspected. Viral isolation, in contrast, is an "open-ended approach" that may yield interesting, unanticipated results.

Viral Cytopathology

The analysis of viral cytopathology is the oldest form of rapid diagnosis. An example of this form of testing is the Tzank preparation used to diagnose herpes virus infections. The technique is performed by scraping the base of a skin vesicle and transferring the scraping to a microscope slide. The slide is allowed to air dry and then stained with Giemsa, Wright, or Papanicolaou stain. Slides are viewed under a standard microscope. The finding of multinucleated giant cells is diagnostic of a herpesvirus infection. This method has been largely superseded by fluorescent antibody staining and other antigen detection methods that are more sensitive and can also identify the specific herpes virus present.

Electron Microscopy

Electron microscopy (EM) has been used for many years for the rapid detection of viruses in clinical specimens. This technique relies on the identification of viruses by their characteristic morphology. One limitation of EM is that virus must be present in sufficient quantity (approximately 10^5–10^6 particles/mL) in order to be detected. The most potent usefulness lies in detecting viruses in fecal contents; EM is not used widely for routine diagnosis because it is expensive, cumbersome, and insensitive. Newer rapid tests are available for most viruses that previously were diagnosed by EM.

Immunofluorescence

Immunofluorescence (IF) has been used for rapid diagnosis of respiratory tract infections, and vesicular exanthems and examination of tissues. The method is rapid, precise, and sensitive when careful attention is paid to be the technique of obtaining and processing the specimens, using appropriate controls, and having a well-trained laboratory staff to interpret the results. Clinical specimens are applied to a slide, dried, fixed, and stained. A fluorescence microscope is used to read the slides for either fluorescing organisms or infected cells. Staining may be direct, using a specific antimicrobial antibody with attached fluorescence dye, or indirect, using an unlabeled specific antimicrobial antibody followed by fluorescein-labeled antibody directed against the initial antibody.

The indirect test may be more sensitive than the direct test, although a recent study suggests the sensitivity is comparable. For RSV and measles, the sensitivity of IF exceeds that of cell culture. For the others, particularly when high-quality reagents are not available, the sensitivity appears to be somewhat lower. Immunofluorescence has also been successfully used to detect and distinguish herpes simplex and varicella-zoster viruses in vesicle fluids. The IF method is also very useful in the examination of tissue specimens. This technique is the preferred method for rapidly diagnosing (a) herpes simplex encephalitis in brain biopsies and (b) rabies in animal brain.

Immunofluorescence has the following advantages:

1. One can prepare a slide and stain for a number of different organisms at a single time; the adequacy of the specimen can be determined, and slides may be made and sent to the reference laboratory for reading.

2. IF is more sensitive than cultures since it does not require intact viable viruses; as a result, a specimen may be positive by IF in the face of negative cultures.

Enzyme Immunoassay

Enzyme immunoassay (EIA), or enzyme-linked immunosorbent assay, utilized multiple antigen–antibody reactions to detect low concentrations of microbial antigen. EIAs are available now for the diagnosis of respiratory viruses (RSV, influenza, parainfluenza, adenovirus, and metapneumovirus) enteric viruses (rotavirus, norovirus, and adenovirus), and herpes simplex virus. The major advantages of the EIA are ease of interpretation, objectivity, and ability to detect antigen in specimens collected and handled in a manner that disrupts intact infected cells needed for IF. These assays can be automated. The advantages of the EIA include the potential for nonspecific reactions that may give false-positive results and the ability of the test to identify the presence of only one infectious agent, unlike IF, in which the presence of any one of several agents can be determined on a single specimen by one procedure.

Nucleic Acid Hybridization

Recent advances in molecular cloning have made hybridization possible. With the availability of large quantities of cloned viral DNA, the use of nucleic acid hybridization has become practical possibility for detection of certain viruses in clinical specimens. Hybridization assays are available for the direct detection of herpes simplex virus, CMV, and human papillomavirus. Probes for hepatitis B core and surface antigen genes, human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), adenovirus, and type A rotavirus are currently available.

Polymerase Chain Reaction

The polymerase chain reaction (PCR) is the most sensitive method for revealing the presence of otherwise undetectable quantities of the genome of RNA or DNA of human viruses. PCR is a powerful new technique developed in 1985 and is an alternative to direct hybridization methods. It can be used to amplify a small piece of viral DNA or RNA in clinical specimens up to a millionfold, allowing detection of small quantities of infectious agent in a single sample. PCR has the sensitivity to detect as few as ten infected cells or one virus in as many as one million cells in clinical specimens. Because PCR is very sensitive, slight contamination of laboratory specimens by stray DNA can lead to amplification of DNA not in the original specimen. It is being used currently to detect HIV, herpesviruses, influenza virus, hepatitis viruses, rotavirus, EBV, CMV, and parvovirus. The use of PCR for the diagnosis of CNS disease has been well evaluated for HSV encephalitis and enterovirus meningitis. The use of this highly sensitive technique has increased our understanding of the etiological role of viruses in CNS disease. For example, it has been demonstrated that varicella-zoster virus (VZV) and HSV type 2 (HSV-2) can cause meningitic symptoms without causing concurrent skin lesions.

Multiplex PCR is a newer diagnostic technology that allows testing for multiple viruses simultaneously with a very high specificity and sensitivity. The xTAG RVP assay (Luminex Molecular Diagnostics; Toronto, ON, Canada) is one example and is approved by the US Food and Drug Administration (FDA). This test detects 12 different viruses and has a sensitivity of 96.4% and a specificity of 95.9%. Multiplex PCR is also available for diagnosis for CSF and enteric viruses.

Viral genome quantification (VL) has within a few years become an integral part of the clinical management of patients suffering from infection with HIV, HBV, HCV, or human CMV. Besides providing prognostic information on individual cases, particularly for HIV and human CMV, genome quantification plays a most important role in monitoring the patient's response to antiviral treatment. VL testing assesses the success of antiviral therapy, including, but unable to distinguish between, different factors involved. These include treatment failure due to viral (development of antiviral resistance) and host factors (one of which is noncompliance). Several studies have proven the value of VL determination as a surrogate marker for clinical markers of therapeutic success. The increasing availability and clinical use of potent anti-(retro)viral chemotherapy has sparked the development of a variety of commercial assays for viral genome quantification. It is being used currently to detect HIV and has been in use in research laboratories to identify other viruses, such as the herpesviruses, influenza virus, hepatitis viruses, rotavirus, EBV, CMV, and parvovirus.

Microchip Assay

DNA microarray testing, which so far is available only in research settings, is a newer technology designed for much broader-spectrum viral detection. The microchip has

approximately 22,000 oligonucleotide probes representing about 1,800 fully or partially sequenced viruses and it can detect all known viruses, as well as possible novel viruses that are related to known viral families, without a priori knowledge of their whole nucleotide sequences. This panviral microarray was used as part of the global effort to identify severe acute respiratory syndrome-associated coronavirus in 2003.

This method addresses the problems associated with both earlier methods, and reduces the detection time to less than 30 min. Because it is based on a rapid hybridization and no enzymatic amplification is used, it is not affected by impurities in the sample. At the present it can detect 500 copies or more of an infectious agent per sample. It can be adapted to any type of sample such as blood, stool, or tissues. The size of the chip is less than 1 cm^2 and the active site is less than 1 mm^2.

Serology

One of the classic methods of diagnosing viral infection is the detection of virus-specific antibodies or antigens in serum. Some of the assays, such as radioimmunoassays, EIAs, Western blots (protein is electrophoresed through a gel to separate molecules according to size, blotted onto a membrane, and then hybridized with antibody against a specific protein of interest), and IF, measure antigen–antibody interaction. Assays such as complement fixation, latex agglutination, and immune adherence hemagglutination depend on the capacity of antibody, upon interacting with antigen, to perform some non-virus-related function.

Most acute primary viral infections induce a dependable rise in antiviral immunoglobulin G antibody. Diagnosis can be made through measurement of antibody levels in paired sera obtained early in the course of disease (acute) and late or after recovery (convalescent) 14–21 days later. Exceptions involve the following situations:

1. Infections in immunodeficient hosts who cannot form antibody (including certain young infants).
2. Some superficial infections such as respiratory infections, which may occasionally fail to induce an antibody response despite significant illness (e.g., RSV in infants). Regardless of the method employed, serologic demonstration of an antibody response may provide evidence of infection in the absence of virus isolation from culture. Unfortunately, documentation of infection is delayed because of the need to assess convalescent serum for antibodies and is limited by the multiplicity of viruses infecting humans.
3. Acute infections acquired in the presence of passively transferred antibody (e.g., neonatally acquired CMV infection).

Most recent serologic diagnosis has emphasized the detection of specific immunoglobulin M (IgM) antibodies, which allows a diagnosis to be made from a single specimen obtained early in the illness. Specific IgM antibody testing is most useful in disease with a sufficiently long incubation period in which specific IgM antibodies are present at the time of clinical presentation; this is currently the method of choice for the diagnosis of rubella, measles, hepatitis A virus, and a number of arbovirus infections. There continues to be technical problems with many IgM assays, including interference with rheumatoid factors, which needs to be absorbed from serum.

Recently, IgG avidity assays, which measure antibody maturity, have been shown to reliably discriminate between acute and past infection. Thus in recent (acute) infection the body produces low-avidity IgG. After 2–4 months, the body begins to produce high-avidity IgG. For example, low CMV IgG avidity suggests acute CMV infection occurred within the past 2–4 months. High CMV IgG avidity suggests that CMV infection occurred at some point in the past. This has been demonstrated to be the case for CMV, toxoplasma, and rubella. Avidity indices of 50% or less are considered low-avidity indices.

For several infections, the testing of acute and convalescent specimens or the identification of virus-specific IgM antibodies is not necessary because the infections are typically chronic, and detection of any virus-specific antibodies more often signifies current infection. Examples include HIV, human lymphotropic T-cell virus, and hepatitis C virus.

The Future for Viral Diagnosis

Detection technologies will continue to evolve, allowing faster, more sensitive, and less extensive methods for pathogen discovery. Multiplex PCR assays are already widely implemented, but microarray technology is less advanced.

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76 Vaccination

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BCG Vaccine

Nature and Contents

Bacillus Calmette-Guérin (BCG) vaccine is an attenuated live vaccine containing suspension of a live attenuated strain of *Mycobacterium bovis*. The chemical composition of BCG vaccines varies widely among different preparations. Furthermore, the vaccines differ substantially in the level of residual virulence as well as immunogenicity. The vaccine is available in a lyophilized form, and sodium glutamate is used as a stabilizer in some products.

Mechanism of Protection

The mechanism of protection of BCG is largely unknown. Cellular immunity has been shown to play the major role in protection; however, the specific antigenic determinants and the mechanisms involved are not clear.

Storage and Handling

- Storage and shipment
  - Unreconstituted vaccine should be stored at 2–8°C and *never* frozen. Both forms should be protected from light.
- Stability
  - Unreconstituted form is stable for 1–2 years if stored as recommended within the expiry date specified. Products containing sodium glutamate may remain stable for up to 1 month at 37°C.
  - Reconstituted vaccine is stable for only few hours and should be discarded at the end of the vaccination session.

Efficacy

The effectiveness of BCG vaccine is difficult to determine and available data from field trials of the vaccine have yielded conflicting results. However, a meta-analysis of the published literature on BCG efficacy concluded that BCG significantly reduces the risk of T.B. infection by an average of 50%. Furthermore, protection against tuberculous meningitis was 64%, against disseminated T.B. 78%, and against death due to T.B. 71%. In another meta-analysis of 10 randomized clinical trials and eight case-controlled studies, the protective effect of BCG against serious forms of T.B. in children (meningitis and miliary T.B.) was found to be >80%. In a 60-year follow-up study, the long-term efficacy is estimated to be 52%.

Recommended Use

1. In areas with high incidence of T.B. (i.e., rate of new infection >1% per year), universal immunization of infants is recommended.
2. Newborn infants whose mothers have infectious tuberculosis at the time of delivery and isoniazide prophylaxis is not feasible (either due to resistant infecting strain or compliance cannot be assured).
3. Individuals with negative tuberculin skin tests who are continuously exposed to persons infected with bacilli resistant to isoniazide and rifampicin.

Adverse Reactions

Side effects of BCG vaccination are generally uncommon. Their rates, however, vary depending on the methods of administration, the strain and the dose of the vaccine, and the age and immune status of the vaccinee.

Local ulceration and regional lymphadenitis are the most common complications occurring in up to 5% of immunocompetent recipients following intradermal administration. Rates are higher among newborns than among older infants and children.

Moderately severe reactions include suppurative adenitis, and injection-site abscess may be seen in 1% of all vaccinee.

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Severe complications include osteitis and BCG dissemination which may be fatal. Dissemination occurs almost exclusively in persons with impaired immunity, and its frequency is approximately one in one million vaccinees.

Contraindications and Precautions

BCG is contraindicated in:

1. Individuals with altered immune status due to:
   (a) Primary immune deficiency involving cellular immunoresponses or interferon-gamma/IL-12 pathway defect.
   (b) Malignancy, e.g., leukemia, lymphoma.
   (c) Immunosuppressive therapy, e.g., corticosteroids, cytotoxic, etc.
   (d) Patients with confirmed HIV infection even if asymptomatic.
2. Persons with burns or extensive skin disease.
3. Individuals with positive tuberculin skin tests.
4. BCG should not be given within 4 weeks of development of, or vaccination against measles or mumps as these are known to suppress the tuberculin reaction.
5. Pregnancy: although no harmful effects on the fetus have been observed, it is preferable to delay BCG until after delivery.

Practical Hints

1. The normal local response to BCG vaccination includes formation of a papule which ulcerates within 2–3 weeks after vaccination and gradually heals with formation of a scar within 3 months.
2. In a newborn with a positive family history of congenital immunodeficiency in a sibling (e.g., severe combined immunodeficiency or interferon-gamma/IL-12 pathway defect), BCG vaccine should be withheld until such disorder is excluded in order to avoid BCG dissemination which may be fatal.
3. There is no correlation between presence or size of tuberculin delayed hypersensitivity reaction after BCG and protection against disease.
4. Tuberculin reactivity caused by BCG vaccination ranges from no indurations to an indurations of >15 mm. However, skin reactivity wanes with time and is unlikely to persist >10 years after vaccination in the absence of *M. tuberculosis* exposure and infection.
5. BCG-induced reactivity that has weakened might be boosted by administering a tuberculin test 1–2 weeks after the initial test. This phenomenon should not be confused with cutaneous conversion which may denote infection with T.B.
6. Malnutrition is not a contraindication for BCG vaccination.
7. Some authorities consider ulceration and scar formation at the BCG inoculation site as an indication of successful vaccination and immunity.

Diphtheria Toxoid

Nature and Contents

Diphtheria toxoid is prepared by formaldehyde detoxification of diphtheria toxin. The vaccine contains no bacterial antigens. The toxoid is available in monovalent preparations, in combination with tetanus toxoid (DT or Td) and in combination with tetanus toxoid and pertussis vaccine (DTP, DTaP) with or without other vaccines, including inactivated polio (IPV), Haemophiluse influanze b (HIB), and Hepatitis B virus (HBV) vaccines. The products are available in adsorbed form with Aluminum hydroxide or Aluminum phosphate. A plain (non-adsorbed) monovalent preparation is also available. Thimerosal is used as a preservative in some products.

The quantity of toxoid differs from one preparation to another and between different manufacturers. It ranges between 2 and 25 flocculation units (Lf) with the adult preparation (Td) containing the smallest amount (2 Lf).

Mechanisms of Protection

Immunization with diphtheria toxoid induces formation of neutralizing antibodies (antitoxin) which protect against the potentially lethal systemic effects of diphtheria toxin. The vaccine does not, however, prevent local infection with *C. diphtheriae.*

An antitoxin level of 0.01–0.02 U/mL is usually associated with a negative Schick test and may provide some protection; level of 0.1 U/mL or more provide full protection.

Storage and Handling

- Storage and shipment
  - All forms of adsorbed preparations should be stored and shipped at 2–8°C. No freezing is allowed.
- Stability
  - If stored as recommended, it is stable for approximately 2 years after leaving manufacturer's cold store.
  - Exposure to a higher ambient temperature for short period of time (<7 days) does not reduce the potency.
- Normal appearance
  - Turbid and whitish suspension. Vaccines that contain clumps of material that cannot be suspended with vigorous shaking should NOT be used.

Efficacy and Immunogenicity

Following completion of vaccination series, the risk of developing diphtheria is substantially reduced. Furthermore, vaccinated persons who develop disease have milder illness. Protection lasts at least for 10 years.

Recommended Use

1. Primary immunization
   (a) Three doses of diphtheria toxoid (as a component of DTP) starting at 6–8 weeks of age with 4–8 weeks interval between the doses is recommended for all infants.
   (b) A fourth dose is given 6–12 months from the third dose, and a booster dose is given at 4–6 years of age. Subsequently, a dose is given every 10 years.
2. Contacts of a diphtheria case
   (a) Immunized close contacts of a case of diphtheria should be given a booster dose of a preparation containing diphtheria toxoid unless they have received a dose within 5 years.
   (b) Unimmunized/incompletely immunized individuals should have their series initiated/completed in a timely fashion.
3. After recovery from diphtheria
   (a) Patients recovering from diphtheria do not necessarily become immune and should be immunized according to their age.

Dose and Route

The dose is usually 0.5 mL of a preparation appropriate for age and any special contraindication. All preparations with adjuvant should be given intramuscularly.

Adverse Reactions

Local reactions including swelling, redness, and pain at injection site are common after diphtheria toxoid, and most frequent and severe in older children and adults. Systemic reactions may occur particularly if preparations containing whole-cell pertussis vaccine (WCPV) are used.

Contraindications and Precautions

- Anaphylactic reaction to a vaccine component.
- Adults and children older than 7 years should only be vaccinated with Td preparation.
- When a combination vaccine is used, it is important to ensure that no contraindication to any component is present (see pertussis vaccines and tetanus toxoid below.

Practical Hints

1. Polysaccharide vaccines that are conjugated with CRM 197 (cross reacting material) diphtheria protein do not provide immunity to diphtheria.
2. Preparations containing between 15 and 25 Lf of diphtheria toxoid is intended for use in children <7 years and is marked as "D." The preparations for older children and adults contain 2 Lf and marked as "d."
3. Since diphtheria preparations are adsorbed products, it is important to ensure that it is given intramuscularly as spillage into subcutaneous tissue may lead to significant local reaction.
4. To further promote immunity against diphtheria, diphtheria toxoid and tetanus toxoid (Td) combination should be used whenever tetanus prophylaxis is needed following injuries if the last dose of diphtheria has not been given within 10 years.

5. Antibodies (antitoxin) passed through the placenta provides passive immunity to the newborn during the first few months of life.
6. Even when diphtheria booster doses are not received for 20–30 years, booster responses can still be elicited and no need for repeat of primary series.

Haemophilus Influenzae B Vaccine (HIB)

Nature and Contents

The currently available conjugated HIB vaccines are composed of a purified capsular polysaccharide of HIB, known as polyribosylribitol phosphate (PRP), linked (conjugated) to a protein carrier. The size of the polysaccharide, the type of the protein carrier, and the kind of linkage used is different from one vaccine to another. The characteristics of the four HIB conjugate vaccines are outlined in *Table 76.1*. Thimerosal is used in some vaccines as a preservative, and aluminum hydroxide is used as adjuvant in PRP-OMP.

Mechanism of Protection

HIB conjugate vaccines protect against invasive HIB diseases by:

- Induction of antibodies against HIB capsular polysaccharide, i.e., anti-PRP, which are bactericidal and opsonic.
- Reduction of asymptomatic HIB nasopharyngeal colonization rate, resulting in reduced exposure of unprotected individuals to HIB. This has probably contributed to the observed reduction of HIB diseases in non-vaccinated children after introduction of conjugate vaccines in several countries.

Table 76.1
Characteristics of HIB vaccines

Vaccine	Polysaccharide	Protein carrier	Link
PRP-D	Medium	Diphtheria toxoid	Spacer
PRP-CRM197	Small (Oligosaccharide)	CRM197 = nontoxic mutant diphtheria toxin	None
PRP-OMP	Medium	*N. Meningitidis* outer member protein complex	Spacer
PRP-T	Large	Tetanus toxoid	Spacer

Storage and Handling

- Storage and shipment
  - All forms of the vaccines should be stored at 2–8°C and should not be frozen.
- Stability
  - If stored as recommended, unreconstituted forms are stable for 2 years after leaving manufacturer's cold stores.
  - After reconstitution of lyophilized formulation, the vaccine should be used within 24 h.
- Normal appearance
  - Clear and colorless liquid except reconstituted PRP-OMP which is slightly opaque, white suspension.

Efficacy and Immunogenicity

All HIB conjugate vaccines are highly immunogenic after a single vaccine dose in children older than 18 months of age and in adults. However, significant differences exist in immunogenicity in infants among the different vaccines as outlined below.

PRP-D

Of the four conjugate vaccines, PRP-D is the least immunogenic in infants. Less than half of the fully vaccinated infants develop protective-antibody levels. In efficacy trials, it was found to be effective in Finland; however, it failed to show efficacy in Alaska.

PRP-CRM (HbOC) and PRP-T

The immune response to these two vaccines is roughly similar. After a single dose at 2–4 months of age, no significant response is elicited in most cases. However, after two doses and certainly after three doses, the immune response is excellent with almost 90–100% efficacy.

PRP-OMP

Unlike other conjugate vaccines, PRP-OMP induces a good immune response in the majority of infants after a single dose at 2 months of age. After two doses, more than 90% of infants will have protective antibodies. Of

note, a classical booster response is not seen after the second dose. Furthermore, addition of a third dose at 6 months of age does not boost levels or the proportion of responders. In efficacy trials, PRP-OMP has a proven efficacy even in a high-risk population.

Recommended Use

Vaccination with a conjugate HIB vaccine is recommended for all children below the age of 5 years, starting from 2 months of age. Older children and adults with increased risk of invasive HIB diseases such as those with sickle cell disease, bone marrow transplant, congenital or functional asplenia, HIV, or IgG2 deficiency are candidates for HIB conjugate vaccination.

- Any of the three conjugate vaccines (PRP-T, PRP-CRM, PRP-OMP) is acceptable for immunization of young infants. The number of doses recommended and the timing are summarized in *Table 76.2*.
- PRP-D is only acceptable for vaccination of older children (15 months of age) and for the booster dose in vaccinated infants.
- All the doses are given by intramuscular injection.

Table 76.2
Recommended schedule of vaccinations

Age at first immunization (months)	Product	Number of primary doses	Booster
2–6	HbOC	3	Yes
	PRP-T		(12–15 months)
	PRP-OMP	2	Yes
			(12–15 months)
7–11	HbOC	2	Yes
	PRP-T		(12–18 months)
	PRP-OMP		
12–14	HBOC	1	Yes
	HRP-T		(2 months Later)
	PRP-OMP		
≥15	HbOC	1	No
	PRP-T		
	PRP-OMP		
	PRP-D		

Adverse Events

Adverse events are few and usually mild. Local reactions include pain, redness, and/or swelling at injection site which are seen in approximately 25% of recipients but are typically mild and resolve within 24 h. Systemic reactions such as fever and irritability are infrequent. No severe adverse event has been reported.

Contraindications

Conjugate HIB vaccines are contraindicated in patients with history of severe allergic reaction to any component of the vaccines.

Practical Hints

1. Infants and children who experience an invasive HIB disease before the age of 2 years frequently remain susceptible after recovery, and therefore, they should be vaccinated according to the age-appropriate schedule. This can be done 1 month after onset of the disease or as early as possible after full recovery.
2. Children who develop invasive HIB diseases at or after the age of 2 years do not require vaccination after recovery as the infection will most likely induce formation of protective antibodies.
3. Children who develop invasive HIB disease after completing the recommended doses of conjugate HIB vaccines (i.e., one dose >15 months of age, or primary as well as booster doses <15 months of age) are at increased risk of having IgG2 deficiency, and immunological evaluation is recommended.
4. Following immunization with HIB vaccines, HIB antigen may be excreted in the urine for days to weeks and will be detected by latex particle agglutination. This should be considered when evaluating a febrile infant who has been immunized recently. Antigenemia is less common and occurs only very early post vaccination.
5. If possible, it is recommended to use the same vaccine product for all the primary doses. However, for the booster dose any of the four products is acceptable. When necessary, it is also acceptable to interchange the products.
6. It should be noted that carrier proteins do not induce sufficient immune responses to be considered immunizing agents versus diphtheria, tetanus, or meningiococcus.

Hepatitis A Vaccine

Nature and Contents

Hepatitis A vaccine (HAV) is an inactivated vaccine prepared by propagation of HA virus in human fibroblasts and inactivated by formalin. Aluminum hydroxide is used as adjuvant, and phenoxy ethanol is used as a preservative.

HAV is available either as a single agent or in combination with other vaccines like hepatitis B or typhoid vaccine.

HAV antigen content (expressed as IU) in the combined formulations is half that in the monovalent.

Mechanism of Protection

HAV induces anti-HAV protective antibody similar to natural infection.

Efficacy and Immunogenicity

All the licensed HAV have shown high levels of immunogenicity. Protective levels of anti-HAV develop in 95–100% of vaccinee 1 month after a single dose. Efficacy in preventing clinical disease is also high.

Recommended Use

1. Pre-exposure Prophylaxis
   (a) HAV is recommended for individuals at increased risk of infection or increased risk of severe disease.
   (b) Several countries have adopted universal HA vaccination and have included HAV in the routine childhood vaccination schedules starting from age of 1 year. Assessment of the disease burden and the local epidemiology of HA in each community is essential prior to consideration of universal vaccination.
   (c) HAV is recommended for the following individuals:
      (i) Residents of areas of intermediate or high endemicity.
      (ii) Travelers to areas with high rate of HA infection.
      (iii) People with high-risk behaviors such as illicit drug use.
      (iv) People with hemophilia A or B receiving plasma-derived replacement clotting factors.
      (v) Individuals who handle nonhuman primates such as veterinarians, researchers, zoo workers.
      (vi) Individuals who have chronic liver disease or those receiving hepatotoxic medications or infected with hepatitis C or B viruses as they are at increased risk of fulminant hepatitis if they became infected with HAV.
2. Post-exposure vaccination
   (a) HAV is possibly as effective as immunoglobulin in prevention of HA clinical disease following exposure if given within 1 week. All susceptible close contacts of patients with Hepatitis A should receive one dose of HAV as soon as possible.
3. Outbreak Control
   (a) HAV is effective in control of outbreaks and is preferred to immunoglobulin, particularly in outbreaks occurring among specific population.

Dose and Schedule

1. For monovalent formulations, two doses are required separated by at least 6 months. Currently, available vaccines are not approved for children younger than 1 year of age. The dose for adult is double that for children.
2. If the combined HA and HB vaccine formulation is used, three doses are given at 0, 1, and 6 months.
3. The vaccine is given by intramuscular injection.

Adverse Reactions

HAV is a safe vaccine with mainly local injection site reactions. Adults are affected more frequently than children. Malaise, headache, and fever were the reported systemic reaction.

Contraindication and Precautions

1. The only contraindication to HAV is severe allergy to any component of the vaccine.
2. If indicated, the vaccine can be given to pregnant women, breast-feeding mothers, and immunnocompromized individuals.

Practical Hints

1. Pre-immunization serologic testing for HAV antibody is neither necessary nor required. However, if the cost of vaccination is higher than serology testing, it may be considered in individuals who are likely to be previously infected.
2. Since only one dose is given for the vaccination with the combined HAV and typhoid vaccine, a booster dose using a monovalent HAV should be given 6 month later.
3. If the vaccination series was started with one formulation and that formulation is not available at the time of the booster dose any other formulation can be used.
4. Although the benefit from post-exposure vaccination is more when the vaccine is given within 7 days, it can be given after that period along with immunoglobulin if indicated at the same visit but at different site.

Hepatitis B Vaccine

Nature and Contents

Currently licensed hepatitis B vaccines (HBV) consist predominantly of purified particles of the surface antigen of hepatitis B (HBsAg). HBsAg is produced from recombinant yeast or cells (recombinant vaccines). An earlier vaccine derived from the plasma of chronic carriers (Plasma-derived vaccine) is no longer available.

Currently available HBV contain 5–40 μg HBsAg protein per milliliter adsorbed onto aluminum hydroxide. Thimerosal is used as a preservative in some products. The vaccine is available as a single agent and in fixed combination with other vaccines, including HAV, DTaP, IPV, HIB.

Mechanism of Protection

HB vaccines protect against HB infection and clinical disease by:

1. Inducing antibodies (anti-HBs) against HBsAg
2. Priming the immune system to form immune memory which protects against significant HBV infection (symptomatic and/or chronic infection) even though anti-HBs concentration may become low or undetectable.

Storage and Handling

- Storage and shipment
  - All types of HB vaccines should be stored at 2–8°C and must NOT be frozen
- Normal appearance
  - Slightly opaque, white suspension after thorough agitation.

Efficacy and Immunogenicity

A course of three intramuscular doses of HB vaccine induces formation of protective levels of anti-HBs $\geq$ 10 milli international units [mIU] per milliliter) in 90% of healthy adults and 95% of healthy infants and children. Seroconversion rate is lower in adults over 40 years of age, and it decreases with age. The immune response to the combined formulations is similar to that of single-agent vaccines. Immunocompromised individuals such as HIV patients and those on hemodialysis have poor antibody response to the vaccine. Although the incidence of loss of detectable serum antibody 10 years after vaccination is considerable, immune memory remains intact and protects against chronic HBV infection in vaccinees who have demonstrated initial seroconversion even though anti-HBs concentration may become undetectable.

Recommended Use

1. Universal vaccination of infants

   The World Health Organization recommends vaccination of all infants against Hepatitis B in countries with moderate or high endemicity. Failure of programs directed at vaccination of only high-risk groups in areas with low endemicity make universal vaccination of infants and children with HBV the preferred strategy in all countries. Furthermore, better immunogenicity of HBV in infants and children coupled with requirement of smaller doses than adults makes this the most cost-effective strategy.
2. Immunization of high-risks groups
   (a) Infants born to HBsAg-positive mothers
   (b) Those who are at increased risk of exposure to blood or blood products such as:
      (i) Patients receiving repeated infusions of blood (e.g., thalassemia) or certain blood products (e.g., Factor VIII or IX concentrate)
      (ii) Hemodialysis patients

(iii) Health-care workers who are at risk of needle-stick injury
(iv) Dentists, dental assistants, and hygienists
(c) Sexual and household contacts of hepatitis B virus carriers
(d) Patients with chronic liver diseases are at risk of severe acute infection should they become infected.

Schedules of Vaccination

- The routine HB vaccination schedule involves administering three doses of HBV with at least 1 month between first and second doses and 4 months between second and third doses.
- For infants of HBsAg-positive mothers, the first dose should be given at birth (along with hepatitis B immunoglobulin), the second dose at 1 month of age, and the third dose at 6 months of age.
- An alternative 4-doses schedule for post-exposure prophylaxis or for more rapid induction of immunity has been approved for one of the vaccines (Engerix-B) at 0, 1, 2, and 12 months.
- The doses recommended differ according to the indication and the particular product (see *Table 76.3*).
- All the doses should be administered by intramuscular injection at the anterolateral aspect of the thigh in infants and at deltoid in older children and adults.

Table 76.3
Recommended doses μg(mL) of Hepatitis B vaccines

Group	Recombinant	
	Recombivax HB	Engerix-B
Infants of HBsAg-negative mothers and children <15 years	2.5 (0.25)	10 (0.5)
Infants of HBsAg-positive mothers	5 (0.5)	10 (0.5)
Children and adolescents 15–19 years	5 (0.5)	20 (1)
Adults ≥ 20 years	10 (1)	20 (1)
Dialysis patients and other immunocompromised individuals	40 (1)[a]	40 (2.)[b]

[a]Special formulation for dialysis patients to be given at 0, 1, and 6 months
[b]Two 1.0 mL doses administered at one site in a four-dose schedule at 0,1,2, and 6–12 months

Adverse Reactions

- The most frequently reported adverse reactions after the vaccine are low-grade fever and pain at the injection site, which occur in 1–6% of children and adults.
- Allergic reactions are infrequent and anaphylaxis is very rare.

Contraindications

The only contraindication to the vaccine is hypersensitivity to any component of the vaccine. Pregnancy is not a contraindication, and the vaccine should be given to pregnant women if they are at risk of exposure to HB infection during pregnancy.

Practical Hints

1. The available vaccines are interchangeable, and the vaccination course may be completed using a single product or any combination of the available products.
2. Immunogenicity of HBV is diminished when it is administered in the buttock in adults and when given by the intradermal route; therefore, these practices should be avoided.
3. Concurrent administration of hepatitis B immunoglobuline (HBIG) does not interfere with the antibody response to HB vaccine. However, when HBIG is indicated, it should be given in a different syringe at a different site.
4. There is no increase in adverse effects when HBV are given to immune individuals (i.e., anti- HBs positive) or to carriers (HBsAg positive). However, it is not indicated in the first instance and not useful in the latter.
5. Routine prevaccination serologic testing to detect carriers or immune persons is not indicated and not cost-effective except may be in situations where the likelihood of previous exposure to HB infection is high.
6. Routine postvaccination testing for immunity is not indicated; however, in the following situations, it is recommended to test for anti-HBs level 1–3 months after the third dose of the vaccine:
   (a) In those who are known to be poor responders such as hemodialysis patients and immunocompromised individuals. In those who are at increased risk of exposure to HB infection and whose future management depends on knowledge of their response such as health-care workers.

7. Infants born to HBsAg-positive mothers should receive HBIG within 12 h of birth and HBV series should be started at birth. They should be tested 1–3 months after the third dose of vaccination for anti-HBs and HBsAg. If found to be negative for both, additional 1–3 doses of vaccine should be given followed by testing for anti-HBs.
8. Premature babies whose weight is less than 2,000 g have poor response to HBV, and the vaccine should be delayed till they reach 2 kg or their chronological age become 1 month. However, if the mother is HBsAg positive, HBV and HBIG should be given within 12 h of birth, and this dose of vaccine should not be counted.
9. At present, booster doses of vaccine are not recommended for children and adults with normal immune status. However, for hemodialysis patients, it is recommended to do annual testing for anti-HBs and to give a booster dose when the antibody level declines <10 mIU/mL.

Human Papilloma Virus Vaccine

Nature and Contents

The currently licensed human papillomavirus (HPV) vaccines are:

1. Quadrivalent HPV vaccine (Gardasil)
2. Bivalent HPV vaccine (cervarix)

The antigens of both vaccines are the L1 major capsid protein of HPV produced by using recombinant DNA technology. It is noninfectious and nononcogenic.

- *The Quadrivalent HPV*: each 0.5 mL dose contain between 20–40 μg of L1 proteins from HPV types 6, 11, 16, and 18. It is adsorbed on aluminum adjuvant, and it contains no thiomersal or antibiotics.
- *The bivalent HPV vaccine*: each 0.5 mL contain 20 μg each of HPV types 16 and 18 adjuvented with ASO4 (aluminum and lipid compound).

Mechanism of Protection

The mechanism of protection of HPV vaccine against cervical and other anogenital cancers is related to its efficacy in prevention of persistence of infection by HPV types 16 and18 which are implicated in the majority of cases of the histopathological changes leading to malignancy.

Following vaccination, neutralizing antibodies are produced in high levels which may be responsible for the prevention of persistence of infection by the viruses contained in the respective vaccine.

Storage and Handling

Both vaccines should be stored at 2–8°C and not be freezed. It should be protected from light.

Efficacy

- For females previously uninfected by vaccine-related HPV type, both vaccines are highly immunogenic and has proven efficacy in prevention of persistence of infection by vaccine virus and in prevention of precancerous and cancer lesions of cervix and other anogenital lesions.
- There is some evidence that some protection might be achieved against lesions caused by non-vaccine oncogenic HPV types particularly HPV type 31.
- In individuals who were previously infected by vaccine related HPV types, the vaccine efficacy is low.
- The duration of protection is not yet known. However, high neutralizing antibodies has been demonstrated for up to 5 years. Furthermore, robust immune memory is induced in vaccinees.

Recommended Use

Since the risk of infection and the burden of disease caused by HPV varies between different communities depending on the sexual behavior, the decision to adopt HPV vaccine requires consideration of these factors.

1. When it is indicated, HPV is recommended to be given prior to onset of sexual activity at or above 9 years of age.
2. Females $\geq$ 9–26 years of age maybe given the vaccine even if they have started sexual activity because they are unlikely to have been infected with all HPV types in the vaccine.
3. Females older than 26 years of age are not candidate for routine HPV vaccination.

4. HIV-infected females are at increased risk of infection and sequelae of HPV and should be vaccinated, although the efficacy of the vaccine may be reduced.
5. Males between 9 and 26 years of age may be vaccinated by the quadrivalent HPV vaccine to reduce their risk of genital warts.

Doses and Route

Both vaccines are administered in three dose schedule, at 0, 1 or 2, and 6 months by intramuscular route. The minimum interval between the first and second doses of vaccine is 4 weeks and between the second and third is 12 weeks. The minimum interval between the first and third dose is 24 weeks.

Adverse Reactions

Similar adverse reactions were reported from both vaccines. Local injection site reactions are common and include pain, redness, and swelling. Systematic reaction included fatigue, headache, and myalgia. No serious side effects were found.

Contraindications and Precautions

Both vaccines are contraindicated for persons with a history of immediate hypersensitivity to any vaccine component. The quadrivalent vaccine is produced in yeast and is contraindicated for individuals with immediate hypersensitivity to yeast.

- Anaplylactic latex allergy is contraindication for the prefilled syringes of the bivalent vaccine (single dose vials of the bivalent vaccine contain no latex)
- Both vaccines should not be used in pregnancy due to lack of data on safety.
- Syncope may occur after vaccinations in adolescents and young adult.

Practical Hints

1. Women should continue to receive regular cervical cancer screening (with pap smear) according to the recommendation even if they have received full course of HPV vaccine because the vaccine covers only 70% of the etiologies of cervical cancers.
2. Screening for infection with HPV or for changes in Pap smear is not recommended prior to vaccination.
3. Females who have had an abnormal Pap test or have current HPV infection or genital warts should get the vaccine. However, they should be informed that the vaccine will have no helpful effect on existing infection or abnormality.

Influenza Vaccine

Nature and Contents

Two types of influenza vaccine are currently in use:

- Trivalent inactivate influenza vaccine (TIV)
- Live attenuated influenza vaccine (LAIV)

The TIV is composed of either subvirion or purified surface antigens of three strains of influenza viruses prepared by propagation in embryonated eggs and chemical treatment for splitting (disruption) and inactivation.

Each 0.5 mL dose contains 15 μg of hemagglutinin of each of the three viral antigens. It may contain traces of antibiotics and egg proteins. In some products, thiomersal is used as a preservative.

The LAIV is a trivalent, cold adapted, temperature sensitive vaccine. It is produced by serial passages of the selected strains of influenza virus in chick kidney cells to produced attenuated strains with good replication at 25°C.

The three strains included in both vaccines are two subtypes of influenza A and one of influenza B. These are selected annually according to recommendations made by the WHO for the strains likely to circulate in the specific season in Northern or Southern Hemispheres.

Storage and Handling

TIV and LAIV should be stored at 2–8°C and should not be exposed to freezing temperature.

Efficacy and Immunogenicity

The effectiveness of influenza vaccine varies depending upon the age and immunocompetence status of the recipient as well as the degree of matching between vaccines and circulating influenza viruses. With good match,

TIV efficacy in children and healthy adults >65 years is 70–90%, but only 30–60% with incomplete match.

Among children 6–24 months old, efficacy is 60–70%. In elderly TIV is 50–60% effective in prevention of hospitalization and 80% in prevention of death.

LAIV efficacy in children 15–71 month old is 93% for culture-confirmed influenza with full match between vaccine and circulating viruses.

Recommended Use

Annual influenza vaccines are indicated for the following priority groups:

1. Individuals at high risk of influenza related complications or hospitalizations
   - Individual at high risk of complications or hospitalization include:
     (a) Elderly <65 years
     (b) Children 6–23 months of age
     (c) Children and adults with any of the following chronic conditions:
       (i) Cardiac disorders such as congenital heart disease
       (ii) Pulmonary disorders including bronchopulmonary dysplasia, cystic fibrosis, and asthma
       (iii) Diabetes mellitus, kidney disease, hematological diseases
       (iv) Cancer, immunodeficiency, immunosuppresion
       (v) Children and adolescent on long-term aspirin therapy
     (d) Residents of chronic care facilities
     (e) Pregnant women
2. Individuals capable of transmitting influenza to those high risk
   - Individuals capable of transmitting influenza to high-risk group include:
     (a) Health-care providers
     (b) Household contacts of any of the high-risk group
     (c) Household contacts of infants less than 6 months old

Dosages and Schedules

1. Influenza vaccines are given once per year. In children >9 years of age who are receiving the vaccine for the first time, two doses are required at least 4 weeks apart.
2. The dose for TIV is 0.5 mL given intramuscularly; children >3 years old should receive 0.25 mL.
3. LAIV is approved for use only in healthy 2–49 years old. It is given as a spray in the nose with 0.1 mL of the vaccine sprayed in each nostril.

Adverse Reactions

TIV

- Systemic adverse event reported after TIV vaccination of children include fever, malaise, and myalgia. These were observe more in young age groups (12% in those >5 years vs 5% <5 years).
- Local reactions are mild and included redness, swelling, and pain at injection site.

LAIV

- Among healthy children, the most frequently reported adverse reactions include: runny nose or nasal congestion, headache, fever, and wheezing. These symptoms were more reported after the first dose.
- Among healthy adults runny nose or nasal congestion, headache and sore throat were reported more in vaccine recipients than placebo recipients.

Contraindications and Precautions

- Contraindication and precautions for use of LAIV
  LAIV is contraindicated for the following groups:
  - Persons with severe allergy to any component of the vaccine or to egg.
  - Persons aged less than 2 years or above 50 years
  - Adults and children considered at high risk of complications of influenza
  - Adults and children who are immunosuppresed by diseases or by medication
  - Children between 2 and 4 years with wheezing episodes in the last 12 months
  - Children and adults on chronic aspirin use
  - Pregnant women

  The precautions include:
  - Moderate or severe illness
  - Contacts of patients with severe immunosuppression

- History of Guillain-Barré Syndrome (GBS) within 6 weeks following a previous dose of influenza vaccine

- *TIV* is contraindicated in persons with severe allergy to any vaccine component or to egg.
  Precaution should be observed in the following groups:
  - Moderate or severe illness
  - History of GBS within 6 weeks following a previous dose

Practical Hints

1. The optimal timing of vaccination in a given setting or geographical area depends on the local epidemiology data including the timing and intensity of influenza activity in that area. The principle, however, is to start vaccination prior to onset and continue throughout the season.
2. Individuals planning to travel to the tropics or with organized large tourist groups which may have people from different parts of the world are at risk of exposure to influenza viruses irrespective of the time of the year and should be encouraged to take the vaccine 2 weeks prior to the travel date.
3. Sneezing following LAIV administration does not warrant repeating the dose.
4. Children and adults vaccinated with LAIV can shed vaccine viruses after vaccination. However, transmission to unvaccinated contacts is rare and no serious illness has been reported as a result.
5. Both vaccines can be administered at the same visit with other routine childhood vaccines.

Measles Vaccine

Nature and Contents

Currently available measles vaccines are live attenuated viruses produced by several passages of the original virus strain in different cell cultures at different temperatures. Examples of such currently used vaccine strains include Schwarz, Moraten, Edmonston-Zagreb, Alk-C, etc. Usually, each dose contains trace amount of neomycin, sorbitol and hydrolyzed gelatine (as stabilizers), and at least 1,000 TCID50 of virus particles. The vaccine is available as a single agent and in combination with Mumps and Rubella (MMR) with or without varicella (MMRV).

Mechanism of Protection

Protection following successful vaccination is due to:

1. Induced IgG in serum and secretory IgA in nasal secretions.
2. Priming of the immune system so that a booster response is induced after exposure to natural virus.
3. Stimulation of cell-mediated immunity.

Storage and Handling

- Storage and shipment
  - Unreconstituted vaccine maybe stored at 2–8°C and maybe frozen.
  - Reconstituted form should be stored at 2–8°C.
  - Both forms should be protected from light (dark vials are usually used).
- Stability
  - If stored as recommended, unreconstituted form is stable for 2 years or more. Potency may be maintained for several months at room temperature and for up to 4 weeks at 37°C.
  - Reconstituted vaccine remains potent for up to 2 months at 2–8°C and for 2 days at room temperature. Potency is lost, however, after 7 h at 37°C.
- Normal appearance
  - Clear, yellow solution. If reconstituted vaccine is cloudy it should *not* be used.

Efficacy and Immunogenicity

Successful vaccination with measles vaccine induces an immune response very similar to that noted after natural infection. Both humoral (including IgG, IgM, and IgA) as well as cellular immunity are induced. Approximately 95% of children vaccinated after the first year of life develop seroconversion. The response to the vaccine in infants below 9 months of age is usually poor due likely to interference by maternal antibody. A protective efficacy study of a single dose given between 12 and 15 months of age was calculated to be more than 90–95%. After a second dose, almost 100% of children become immune. Although induced antibodies may decline with time, anamenstic responses follow exposure to wild or vaccine virus.

Recommended Use

1. Routine measles immunization
   (a) Measles vaccine is recommended to be given early in the second year of life (after interference by maternal antibodies have disappeared) in combination with Rubella and mumps (MMR).
   (b) Most countries have implemented two-dose schedule. The time for the second dose varies from one country to another. In some, it is one or more months from the first dose, and in others, several years later.
   (c) In areas in which measles is a significant problem in infants below 1 year of age (like most developing countries), a dose of a monovalent measles vaccine is recommended at 6–9 months of age. Use of vaccines containing Edmonston–Zagreb strain with intermediate titres provide better chance of seroconversion of infants vaccinated as early as 6 months of age.
2. Postexposure prophylaxis
   (a) Measles vaccine can be used to protect susceptible contacts following exposure to measles. The vaccine is likely to be protective only if given within 72 h of exposure.
3. Outbreak control
   (a) To help control an outbreak in a daycare, school, or a community, measles vaccine (or MMR) should be given to all individuals who have no proof of immunity or documented vaccination after first year of life. There are no ill effects from vaccinating individuals who are already immune.

Dose and Route

0.5 mL of reconstituted vaccine is given by subcutaneous injection.

Adverse Reactions

Fever >39°C occurs in 5–15% and a transient rash in 3–5% of vaccinees. These reactions usually occur 6–12 days post immunization. Predisposed children may develop febrile seizures associated with fever. Transient thrombocytopenia has been reported after measles-containing vaccines (MMR); however, it is usually benign and resolve spontaneously within 4 weeks.

High-titer measles vaccines (containing >100,000 TCID50) have been associated with increased mortality in recipients months to years after vaccination. Although the available data are not conclusive of unsafety of these vaccines, their use is discouraged.

There is no scientific evidence to support the claims that measles-containing vaccines cause autism, chronic inflammatory bowel diseases, or Guillain-Barré syndrome.

Contraindications and Precautions

Measles and measles-containing vaccines (MMR) are contraindicated in:

1. Individuals with altered immune status due to:
   (a) Primary immune deficiency
   (b) Malignancy, e.g., leukemia, lymphoma
   (c) Immunosuppressive therapy, e.g., corticosteroids, cytotoxic agents, etc.

   N.B.: Symptomatic and asymptomatic human immune deficiency (HIV) infection is not a contraindication for measles or MMR vaccine except if having severe immunosuppresion.
2. Individuals with history of anaphylactic reactions to a measles-containing vaccine, gelatine, or neomycin.
3. Pregnancy
4. Individuals who have recently received immunoglobulins or other blood products may not respond to the vaccine for 3–11 months due to passively acquired antibodies.

The following are *not* contraindications:

1. Mild febrile or nonfebrile illness such as upper respiratory tract infections.
2. Personal and/or family history of convulsions.
3. Allergic reactions to eggs.
4. Presence of immunocompromized patients in the household.
5. Penicillin allergy.
6. History of contact dermatitis to neomycin.

Practical Hints

1. Skin testing of individuals with anaphylactic reactions to eggs using dilute vaccine is not predictive of an allergic reaction to vaccination with measles-containing vaccine. Therefore, skin testing is not required in these individuals prior to vaccination.
2. If a patient receive immunoglobulins or other blood products within 2 weeks of measles vaccination, the

response to the vaccine may not be adequate and that vaccine dose should be repeated after the appropriate interval have passed.
3. Measles vaccination can temporarily suppress tuberculin reactivity; therefore, if there is indication to perform tuberculin skin test, this should be done either at the time of measles vaccination or 4–6 weeks later.
4. Although natural measles can exacerbate tuberculosis, live measles vaccines are not known to do so, and therefore, tuberculin skin testing is not a prerequisite for measles vaccination.
5. The infection induced by measles vaccine is not communicable even in vaccinees that develop rash or other measles manifestations.
6. The response of HIV patients to measles vaccine is not optimal, and the antibody response wane faster than uninfected children. Therefore, immunoglobuline should be administered after exposure even if previously vaccinated.

Meningococcal Vaccine

There are two different types of meningococcal vaccines available:

1. Plain Polysaccharide vaccines
2. Conjugated vaccines

Nature and Contents

The Plain polysaccharide meningococcal vaccines consist of purified capsular polysaccharides of sero group A, C, Y, and W135. The vaccine is available as either monovalent, bivalent, or a quadrivalent vaccine, depending on the polysaccharides contained in the product. It is produced as a freeze-dried preparation and is diluted with a sterile saline containing thimerosal as a preservative.

The conjugate vaccines are composed of purified capsular polysaccharide linked (conjugated) to a carrier protein. The carrier proteins used in the currently available vaccines are any of the following:

- Nontoxic, mutant diphtheria toxin (CRM197)
- Diphtheria toxoid
- Tetanus toxoid

This conjugation changes the nature of the immune response to the polysaccharide from the T-cell-independent to T-Cell-dependent response leading to improvement in immunogenicity in children less than 2 years old and anamenstic response in reexposure.

The currently available meningococcal conjugate vaccines are either quadrivalent vaccines containing capsular polysaccharide from serogroups A, C, Y, and W135 or monovalent vaccines containing polysaccharide from serogroup A or C alone or in combination with HIB vaccine.

Efficacy and Immunogenicity

1. Plain Polysaccharide vaccines

   All the four meningococcal polysaccharides are immunogenic in adults and children over 2 years of age. However, only group A polysaccharide is immunogenic in infants and children below 18 months. Clinical efficacy has been demonstrated for group A meningococcal vaccines in infants and young children given two doses of vaccine during epidemic situations, and both group A & C vaccines were protective to adults and older children after one dose. However, group C vaccine failed to protect infants and young children in epidemics. Antibody responses decline rapidly, particularly in children and adolescents. Furthermore, repeated vaccination with the polysaccharide vaccine result in hyporesponsiveness phenomenon (reduced antibody response compared with primary vaccination).
2. Conjugate Vaccines

   In older children and adults, the immunogenicity of conjugate vaccines is as good as that of polysaccharide. Furthermore, immunity persists longer and no hyporesponsiveness is observed after revaccination.

   In children less than 2 years of age, antibody response to all serogroups after two doses is better that that seen with polysaccharides vaccine.

   The response of serogroup C is comparable between quadrivalent and monovalent conjugate vaccine.

   Clinical efficacy has been demonstrated after introduction of the monovalent conjugate group C vaccine in UK.

Recommended Use

Meningococcal vaccines are indicated in the following situations:

1. Routine vaccination

   The adoption of universal routine meningococcal vaccination should be based on the local disease burden and other public health factors.

   When it is indicated the following apply:

   (a) For infants less than 1 year of age: two doses separated by 4–8 weeks should be given to those more than 2 months of age using the conjugate vaccine. A booster dose should be given at or after 12 months of age.
   (b) Children ≥1 year to >4 years: one dose of conjugate vaccine is adequate
   (c) Children more that 4 year and adults: one dose of conjugate vaccine is preferred, but polysaccharide vaccines will provide protection for 3–5 years.
2. Control of epidemics

   Conjugate vaccine containing the respective serotype causing the epidemic should be administered to all person over 2 months of age. In case of group A meningococcal epidemic, polysaccharide vaccine may be given to infants as young as 3 months of age. In the later situation, two doses separated by 2–3 months should be given to all children below 18 months of life.
3. Population at increase risk of meningococcal disease should be given conjugate vaccines. They include:
   (a) Patients with functional or anatomic asplenia
   (b) Patients with complement or properdine deficiency
   (c) Traveler and residents of areas with high risk of outbreaks
   (d) College students living in dormitories
   (e) Military recruit
   (f) Laboratory personal handling meningococci
   (g) The vaccine may be used as adjunct to chemoprophylaxis for contacts of patients with invasive meningococcal diseases.
   (h) The need for booster doses is not fully known. However, following plain polysaccharide vaccine, immunity is adequate for 3 years following vaccination of those older than 4 years of age and it declines markedly after 2 years in those vaccinated below 4 years of age. The conjugate vaccines are likely to provide longer lasting protection than the polysaccharide vaccines.

Adverse Reactions

Meningococcal vaccines are generally safe and associated with mainly local injection site reactions, including erythema, pain, or tenderness for 1 or 2 days. Fever occurs in <2% of vaccinees. Repeated boosters for adults within short interval may result in severe local reactions.

Practical Hints

1. If monovalent group A polysaccharide vaccine is not available, bivalent AC vaccines or quadrivalent vaccines may be used in infants and young children's for whom group A vaccine is indicated. However, the response to other components is usually poor.
2. Although the data on safety of meningococcal vaccine in pregnancy is not adequate, there is no clear contraindication to the use of the vaccine in pregnant women who are at increased risk of exposure to infection as the benefit outweighs the theoretical risk.
3. The preferred route is intramuscular to reduce reactogenicity, but it may be given subcutaneously.
4. Premature babies born below 28 weeks of gestation should be vaccinated according to chronological age and need respiratory monitoring. Should apnea, bradycardia, or desaturation occur after first dose, second dose should be given in hospitals with respiratory monitoring

Contraindications

A severe allergic reaction to a previous dose or to component of the vaccine is a contraindication.

Precautions

- In individuals with moderate to severe illness, vaccination should be deferred.
- Patient with past history of Guillain-Barré syndrome.

Mumps Vaccine

Nature and Contents

Current mumps vaccines are live attenuated viruses produced by serial passages of mumps virus in embryonated

eggs, chick embryo, and/or human diploid cell cultures. Several vaccine strains are in use throughout the world. However, most widely used strains are Jeryl Lynn, Urabe, and Leningrad strains. The vaccine is available in a monovalent form or combined with rubella or measles and rubella (MMR) vaccines with or without varicella vaccine. The vaccines contain trace amounts of neomycine as well as Sorbitol and hydrolyzed gelatine as stabilizers.

Mechanisms of Protection

Following vaccination with mumps vaccine neutralizing antibodies are induced in serum which prevent occurrence of viremia. Cell-mediated immune responses may also contribute to protection; however, the exact role is unknown.

Storage and Handling

- Storage and shipment
  - Unreconstituted vaccine may be stored at 2–8°C and may be frozen.
  - Reconstituted form: should be stored at 2–8°C
  - Both forms should be protected from light.
- Stability
  - Unreconstituted form is stable for 1–2 years if stored as recommended.
  - Reconstituted form is stable for 8 h at 4°C.
- Normal appearance
  - Clear, yellow solution. If reconstituted vaccine is cloudy, it should *not* be used.

Efficacy and Immunogenicity

Mumps vaccine induces formation of neutralizing antibodies in 80–100% of vaccinee. Clinical efficacy studies documented clinical protection in 90–95% of vaccinee. Although the induced antibodies are lower than those that follow natural disease, protection probably persists for over 17 years following a single dose. Responses to monovalent and combined vaccines are essentially the same.

Recommended Use

Routine Immunization

- Mumps vaccine is recommended to be given early in the second year of life along with measles and rubella (MMR) vaccines.
- In countries where two measles vaccine doses are recommended, it is preferred to use MMR for that purpose as it will reinforce mumps and rubella immunity.

Adverse Reactions

- Fever has been reported 10–14 days following vaccination with the vaccine.
- Transient skin rashes with pruritis have occasionally been reported but are uncommon.
- Aseptic meningitis may occur 2–3 weeks after vaccination, and its rate varies between the different strains. It ranges between 1 in 800,000 doses after Jeryl Lynn strain to as high as 1 in 1,000 for the Leningrad-3 strain. However, the course is usually benign and sequelae have been rare or absent.

Contraindications and Precautions

Mumps and mumps-containing vaccines (MMR) are contraindicated in:

1. Individuals with altered immune status due to:
   (a) Primary immune deficiency
   (b) Malignancy, e.g., leukemia, lymphoma
   (c) Immunosuppressive therapy, e.g., corticosteroids, cytotoxic agents, etc.

   N.B.: Symptomatic and asymptomatic HIV infection is not a contraindication for mumps or MMR vaccines except for those with severe immunosuppresion.
2. Individuals with anaphylactic reaction to neomycine or gelatin.
3. Pregnancy
4. Individuals who have recently received immunoglobulins or other blood products may not respond to the vaccine for 3 months or more due to passively acquired antibodies.

Practical Hints

1. Administration of MMR is not harmful if given to an individual already immune to one or more of the viruses.
2. The risk of mumps exposure for patients in whom mumps vaccine is contraindicated can be reduced by vaccinating their close susceptible contacts.

3. The infection induced by mumps vaccine is not communicable even in vaccinees who develop parotitis or other manifestations.
4. Mumps vaccine is not usually useful after exposure to the disease. However, vaccination of susceptible exposed persons is recommended as it will provide immunity to those individuals who will not develop mumps after their exposure and at the same time vaccination is not harmful to those incubating mumps.
5. If a patient receive immunoglobulins or other blood products within 2 weeks of mumps vaccination, the response to the vaccine may not be adequate and that vaccine dose should be repeated after the appropriate interval have passed.

Pertussis Vaccines

There are two different kinds of pertussis vaccines: whole-cell pertussis vaccines (wPV) and acellular pertussis vaccines (aPV).

Whole-Cell Pertussis Vaccine

Nature and Contents

Whole-cell pertussis vaccines (wPV) contain suspension of inactivated whole *Bordetella pertussis* bacteria. The vaccine is mostly available in combination with diphtheria and tetanus toxoides (DTP) with or without inactivated polio vaccine (IPV) and/or HIB conjugate and HBV vaccines. It is adsorbed in aluminum salts, and thimerosal is added as a preservative in some products. A single non-adsorbed preparation exists in some countries.

Mechanisms of Protection

1. Individual perspective

   Whole-cell pertussis vaccines induce antibodies to a number of *B. pertussis* antigens. However, it is not known which antibodies are responsible for protection.
2. Community perspective

   Pertussis vaccines probably decrease the spread of pertussis in the communities by reducing the intensity and duration of cough in vaccinated individuals who contract the disease.

Efficacy and Immunogenicity

The immune response to the wPV is directed against several antigen of whole bacterial cells. There are marked differences in the immune responses to various antigens among the different wP vaccines. It is difficult to have a precise estimate of efficacy of wPV. However, in a systematic review of efficacy of wPV including 49 controlled trials and three cohort studies using WHO case definition, the pooled efficacy of wPV in children was 78% but was variable among different vaccines. The protection from disease decreases as the time interval since vaccination increases.

Storage and Handling

- Storage and shipment
  - Adsorbed preparations containing pertussis vaccine should be stored and shipped at 2–8°C. No freezing is allowed.
- Stability
  - Exposure to temperatures <2°C or >25°C for as little as 24 h may precipitate suspended antigens and make it very difficult to resuspend normal appearance.
- Normal appearance
  - Turbid and whitish suspension. Vaccines that contain clumps of material that cannot be suspended with vigorous shaking should *not* be used.

Recommended Use

1. Primary immunization
   (a) Three doses of an adsorbed preparation containing pertussis vaccine is recommended for all infants starting at 4–8 weeks of age and separated by 4–8 weeks.
   (b) A fourth dose is given 6–12 months from the third dose, and a booster dose is administered at 4–6 years of age.
   (c) After the age of 7 years, wPV vaccine is not recommended because the morbidity from the vaccine is higher than that from the disease.
2. Close contacts of patients with pertussis
   (a) Close contacts younger than 7 years who are unimmunized or who have received fewer than four doses of pertussis vaccine should have

pertussis immunization initiated or completed according to recommended schedule. If the third dose was given more than 6 months before, a fourth dose should be given.

(b) Those under the age of 7 years who have received four previous doses of pertussis vaccine should be given a booster dose unless the fourth dose was given within 3 years.

Dose and Route

0.5 mL of preparations containing pertussis vaccine is given by intramuscular route. If non-adsorbed preparation is used, it can be given subcutaneously.

Adverse Reactions

Administration of wPV vaccine is associated with several local and systemic reactions as follows:

1. Local reactions: at the injection site include redness, swelling, pain, and tenderness which occur in approximately 50% of infants and may be higher in older children's. However, these are usually mild and resolve spontaneously. Rare local adverse events include pyogenic or sterile abscess (1 per 100,000 DPT injections).
2. Systemic reactions, including fever, irritability, drowsiness, and anorexia, occur in approximately 50–70% of vaccinees. More severe systemic reactions occasionally occur in some patients and include:
   (a) Seizures
      – These are mostly simple febrile convulsions and occur at a frequency of 1 per 1,750 injections. Predisposing factors to convulsions after pertussis vaccine include a personal or family history of convulsions. Rarely, a prolonged or complex convulsion occurs in association with pertussis vaccine. However, after prolonged follow-up, complete recovery without permanent sequelae has been observed in patients who developed a seizure disorder.
   (b) Hypotonic Hyporesponsive state
      – These episodes have been reported at the same rate of convulsion. Complete recovery occurs with no persistent neurologic or developmental defect on follow-up.
   (c) Unusual crying
      – Persistent, inconsolable crying lasting 3 or more hours is seen in 1% of vaccinee and high-pitched unusual screaming in 0.1%. The cause and significance of this observation is unknown.
   (d) Hyperpyrexia
      – Hyperpyrexia with fever greater than *40.5° C is seen in 0.3%.*

These severe systemic reactions are rarely reported after DT vaccines which suggest that the WC vaccines are responsible for their occurrence. It should be noted, however, that there is no scientific evidence to prove that wP vaccine cause encephalopathy, permanent brain damage, infantile spasm, or sudden infant death syndrome (SIDS).

Contraindications and Precautions

Contraindication to pertussis vaccine include:

1. History of anaphylactic reaction to a previous dose
2. Occurrence of encephalopathy within 7 days of a previous pertussis immunization
3. Acute febrile illness (but not mild upper respiratory infection)
4. Unstable or progressive neurological illness.
5. The following severe systemic reactions to a dose of pertussis vaccine are considered precautions for use of subsequent doses, and the potential benefits of administering the vaccine in the particular situation should be balanced against the possible risks:
   (a) Hyperpyrexia with temperature greater than 40.5°C within 48 h with no other identifiable cause.
   (b) Collapse (hypotonic hyporesponsive) state within 48 h.
   (c) Persistent, inconsolable crying lasting $\geq$3 h, occurring within 48 h.
   (d) Convulsions (febrile or afebrile) occurring within 3 days.

The followings are *not* contraindications:

1. Stable neurological conditions including well-controlled seizure disorders, cerebral palsy, hydrocephalus, etc.
2. Family history of convulsions or other neurological disorders.
3. Family history of SIDS
4. Family history of an adverse event following pertussis vaccine.

Practical Hints

1. Acetaminophene prophylaxis at 15 mg/kg/dose given at the time of immunization with DPT and again 4 h and 8 h later was found to markedly reduce the associated fever and local reactions, and is recommended for all infants and children.
2. In infants and children with personal or family history of febrile convulsion, use of acetaminophene prophylaxis at 4 hourly intervals is particularly important, and it can be continued for 24–48 h.
3. When pertussis immunization is contraindicated or deferred, immunization with diphtheria and tetanus toxoides can be continued using DT preparations. However, in communities where the risk of exposure to diphtheria and tetanus in the first year of life is minimal, DT immunization may be delayed until a decision is made regarding inclusion of pertussis component in the series. This, however, should not be delayed beyond first year of life.
4. If an infant developed a confirmed pertussis disease, pertussis vaccine should be omitted from his schedule. However, if the infant developed a pertussis-like illness, but with no confirmation of etiology as *B. pertussis*, the vaccine should be given.
5. Use of reduced doses of DPT vaccine in order to decrease the likelihood of adverse events has led to decreased protective efficacy of the vaccine and is not recommended.

Acellular Pertussis Vaccines

Nature and Contents

Acellular pertussis (aP) vaccines are composed of purified selected protein components of *B. pertussis* organisms. These include one or more of the following antigens: inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA), Pertactin (PRN) (a 69-kD outer membrane protein), and fimbrial agglutinogens (FIM). They are manufactured either by simultaneous purification of multiple antigens from culture supernatunt (T-type vaccine) or by combining individually purified antigens (B-type vaccines). The antigenic composition varies among different products. The components are adsorbed on aluminum salts, and a preservative is added to some products. Several products are available in combination with diphtheria and tetanus toxoids (DTaP) with or without inactivated polio (IPv) and/or HIB conjugate vaccine and hepatitis B vaccines (HBV).

Efficacy and Immunogenicity

aPV induce high concentrations of antibodies to the antigens included in the respective vaccine. However, because there is not yet a clearly defined serologic correlate of protection against pertussis, ability to protect against clinical infection (i.e., efficacy) of each particular vaccine should be demonstrated. Several studies have evaluated the efficacy of different aPV products in Japan, Europe, and United States. The results indicate that multicomponent aPV (i.e., >3 components) are more effective than single or two-components vaccines. Products containing PT, FHA, and PRN have shown consistent results. A recent Cochrane review concluded that all multicomponents aPV provided high-level protection against pertussis; the efficacy against severe pertussis was shown to be >80%.

Storage and Handling

Storage and handling of DTaP vaccines are similar to regular DTwP.

Recommended Use

If it is economically feasible, aP-containing vaccine is the recommended vaccine for all doses in the vaccination series due to the reduced local and systematic reactogenicity compared with wPV. aPVs are particularly useful for infants and children with tendency to develop seizure with fever. Furthermore, it is the only approved vaccine for vaccination of those >7 years and for the booster dose of adolescents and adults.

Adverse Reactions

All aPV are less reactogenic than wPV. The frequency of systemic as well as local reactions to aPV are approximately one-fifth to one-half that of wPV.

Contraindications and Precautions

Until further data are available, contraindications and precautions for aPV are the same as that for wPV.

Practical Tips

1. Although it is preferred to use same product for all the doses, it is unlikely that changing among or within the wP and aP vaccines will interfere with immunogenicity.
2. If the use of aPV for all the doses of vaccination is not feasible, priority should be for replacement of wPV by aPV for the booster doses.

Pneumococcal Vaccines

There are two types of pneumococcal vaccines available:

1. Pneumococcal polysaccharide vaccine (PPV)
2. Pneumococcal conjugate vaccines (PCV)

Nature and Contents

The polysaccharide vaccine is composed of purified capsular polysaccharides of 23 selected serotypes of *Streptococcus pneumoniae* which account for majority of invasive pneumococcal infections. These serotypes are (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, 33F).

Each 0.5 mL dose contains 25 μg of each polysaccharide with phenol or thimerosal as preservatives.

The currently available conjugate vaccines are composed of purified capsular polysaccharides of 7–13 *S. pneumoniae* serotypes individually conjugated (linked) to a carrier protein.

The carrier proteins currently in use are:

- Nontoxic diphtheria toxin (CRM197)
- Non-typeable *H. influenzae* protein-D (HiD)

This conjugation changes the nature of the immune response to the polysaccharide from the T-cell-independent to T-cell-dependent response, leading to improved immune response even in children below 2 years of age as well as inductions of immunological memory.

Currently available PCV include:

1. PCV-7 is the first licensed PCV. Each 0.5 mL dose contain 2 μg of capsular polysaccharide antigens from pneumococcal serotypes 4,9V,14,18C,19F,23F, and 4 μg of serotype 6 B.
2. PCV-13 is similar to PCV-7 with the addition of 6 serotypes, namely, 1,3,5,6A,7F,19A. In both PCV-7 and PCV-13, CRM 197 is utilized as the conjugate protein and both are adsorbed to aluminum salt as adjuvant.
3. PCV-10 is composed of capsular polysaccharides antigens from 10 pneumococcal serotypes which include the PCV-7 serotypes with the addition of (1,5,7F). The carrier protein used for conjugation is protein D of non-typeable *H. influenzae* for 8 of the 10 antigens. Tetanus toxoid and diphtheria toxoid are used for 18C and 19F antigens, respectively. Aluminum phosphate is used as adjuvant.

Mechanisms of Protection

Protection following successful immunization is due to induction of type-specific opsonic antibodies to the capsular polysaccharide which promote phagocytosis of the homologous pneumococcal organisms.

Furthermore, the PCV reduces nasopharyngeal colonization of vaccine recipients by serotypes in the vaccine which reduce transmission in the community.

Storage and Handling

- Storage and shipment
  - It should be stored at 2–8°C and should NOT be frozen.
- Stability
  - If stored as recommended, the vaccine is stable up to the expiration date.
- Normal appearance
  - Clear, colorless fluid

Efficacy and Immunogenicity

1. PPV

   Like other polysaccharide antigens, the immunogenicity of most pneumococcal serotypes in the current vaccine is poor in infants and children younger than 2 years. However, in healthy young adults and in older children's with increased susceptibility to invasive pneumococcal diseases (IPD), the vaccine has a proven efficacy in preventing pneumonia and reducing the likelihood of bacteremia.
2. PCV

   All PCV's induce protective antibodies against vaccine serotypes in infants and children younger than 2 years. Furthermore, PCV 7 and other PCVs

were demonstrated to be highly effective against IPD and moderately effective in preventing pneumonia caused by vaccine serotypes and some related ones in both developed and developing parts of the world.

In a Cochrane systematic review of five trials of PCV's efficacy conducted in both developed and developing countries, the pooled efficacy estimate of PCVs in children <2 years were found to be 80% for vaccine type IPD, 58% for IPD caused by all serotypes, and 27% for chest X-RAY defined pneumonia.

Recommended Use

- Vaccination with PCVs is recommended by WHO to be part of routine childhood immunization program starting from early infancy.
- The choice of the PCV should be based on assessment of the distribution of serotypes causing invasive pneumococcal disease in any specific population.
- The following groups are considered priority for PCVs:
  - All children <23 months of age
  - Children 24–59 months of age at high risk of IPD, including patients with:
    - Functional or anatomical asplenia, including sickle cell disease
    - HIV infection or other immunodeficiency state
    - Malignancy, immunodeficiency, or long-term immunosuppressive therapy, including steroids
    - Cerebrospinal fluid leaks
    - Chronic cardiovascular, pulmonary, or liver diseases
    - Nephrotic syndrome or chronic renal failure
    - Cochlear implants or scheduled to have it
- At-risk individuals 5 years of age or older should be given PPV.

Dosage and Schedule

- The dose for PPV & PCV is 0.5 mL given intramuscularly. PPV may also be given subcutaneously.
- The primary series for healthy infants is 2–3 doses of PCV staring after the age of 6 weeks and separated by 4–8 weeks. A booster dose is recommended at 12–15 months of age.
- At-risk children should be given a dose of PPV after the age of 2 years at least 8 weeks from the last PCV given.

Adverse Reactions

- Both PCV and PPV are well tolerated. The most commonly reported adverse reactions are pain and erythema at the injection site. However, it is usually mild except in adults after repeat doses.
- Systematic reactions are uncommon.

Contraindications and Precautions

- Confirmed anaphylactic reaction to a previous dose of the vaccine or to one of its component is a contraindication.
- Pregnancy and breast feeding is not a reason to delay pneumococcal vaccines
- As a precaution, patient with moderate to severe acute illness should be vaccinated when their illness subside.

Practical Hints

1. Whenever possible, pneumococcal vaccine should be given 2 weeks or more prior to the planned splenectomy or cancer chemotherapy in order to increase the likelihood of eliciting a protective antibody response.
2. At-risk children older than 2 years who were not previously vaccinated should be given a dose of PCV followed 8 weeks later with PPV.
3. At-risk children who had previously been vaccinated with PPV should be given a dose of PCV.
4. Revaccination with the PPV is recommended for certain high-risk groups, including those with sickle cell disease, asplenia, HIV infection or malignancy, or those who have conditions associated with a rapid decline after initial immunization (e.g., nephrotic syndrome). The interval between first and second dose should be 3–5 years.
5. Pneumococcal vaccine maybe given concurrently with other vaccines as there is no evidence of increases in adverse reactions or reduction in immunogenicity when administered with other vaccines

Oral Polio Vaccine (OPV)

Nature and Contents

The oral polio vaccine (OPV) is a live attenuated vaccine composed of one or more of the three types of polioviruses

(types 1, 2 and 3) propagated in tissue cultures. The vaccine is available mostly as trivalent (TOPV) vaccine. However monovalent (mOPV) and bivalent (Types 1 and 3) formulations are also available. A stabilizer (Magnesium Chloride [$MgCl_2$] or sorbitol) and trace amounts of streptomycin and neomycin are usually present in the mixture.

Mechanism of Protection

Individual Perspective

Live polio vaccine can prevent paralytic poliomyelitis by induction of:

1. Local secretory antibody (IgA) at the primary sites of virus multiplication in the gastrointestinal tract (thereby preventing implantation and multiplication of wild virus).
2. Humoral antibody (IgM and IgG) that prevent wild virus from reaching and invading central nervous system during periods of viremia.

Community Perspective

OPV protect against paralytic poliomyelitis at community level by:

1. Increasing the protected pool beyond those who received the vaccine (as vaccine strains get excreted in stools of vaccine recipients, providing opportunities for immunizing infections of unvaccinated contacts). This is particularly important in developing countries where vaccine coverage may not be optimal.
2. During epidemics, vaccine strains can preempt sites of multiplication within the host population, thus blocking implantation of the wild virus and interrupting its circulation.

Storage and Handling

Requirements for storage and handling of OPV depend on the stabilizer used in the particular product. Check your vaccine, and if it is stabilized with sorbitol, you need to observe the following recommendation:

- Storage and shipment
  - Must be at less than 14°C because of the sorbitol it will remain fluid at temperatures above −14°C).
- After thawing
  - Refrigerate or keep at temperature 4–8°C.
- Stability
  - If frozen, for 1 year from leaving manufacturer's cold stores.
  - After thawing for 30 days if kept refrigerated.
- Normal appearance
  - Clear solution, red or pink (due to phenol red added as a PH indicator).

Vaccines stabilized with $MgCl_2$ are significantly more tolerant of changes in temperatures. It was found that $MgCl_2$-stabilized vaccines retain potency in field and shipping conditions without refrigeration for up to 2 weeks.

Efficacy and Immunogenicity

Following administration of two doses of OPV 6–8 weeks apart, more than 90% of vaccinees will develop adequate protective antibodies to all the three strains of polio viruses. A third dose will ensure a long-lasting immunity to all strains in almost all vaccinees. Clinical efficacy of TOPV has been found to be >90% in some countries but lower than that in others. Immunological responses following mOPV and bOPV are superior to that of tOPV,

Recommended Use of OPV

1. Routine immunization of infants
   (a) The WHO recommends OPV alone for routine infant vaccination in all Polio-endemic countries and in countries at high risk for importation and subsequent spread.
   (b) In tropical countries and where the risk of encounter of wild polio virus at early age exists, it is recommended to start the vaccination at early age and to complete the primary series before the end of the first year of life. Four doses of TOPV are recommended starting at birth, and separated by 4–8 weeks. Although, the serological responses to TOPV in the first week of life is less than that of older infants, majority of neonates benefit by developing local immunity in the alimentary tract. Furthermore, it will make these infants immunologically primed, and they will respond promptly to subsequent doses. Supplementary doses are recommended at 18 months and 4–6 years of age.

2. Outbreak Control

   If a case of paralytic poliomyelitis caused by wild virus appears in a community, OPV should be administered to all individuals in the immediate neighborhood of the case (except those with an absolute contraindication) regardless of a previous history of immunization.

Adverse Reactions

Cases of vaccine-associated paralytic poliomyelitis have been reported in recipients of OPV and their contacts. The estimated risk is extremely small: the overall risk is approximately one case of paralytic poliomyelitis per 2.5 million doses distributed. The risk, however, is 10 times greater after the first dose than after all subsequent doses. Those at higher risk include immunodeficient individuals who get exposed to vaccine virus either from receiving the vaccine or from contact with a vaccine recipient. Unvaccinated healthy adults are at higher risk than children.

Contraindications and Precautions

OPV is contraindicated in:

1. Patients with altered immune status due to:
   (a) Primary immunodeficiency (humoral, cellular, or combined)
   (b) HIV-infection
   (c) Malignancy, e.g., leukemia, lymphoma
   (d) Immunosuppressive therapy, e.g., corticosteroids, cytotoxic agents, or radiation therapy.
2. Household contacts of persons with any of the conditions mentioned in (1).
3. Infants with family history of proven or suspected primary immunodeficiency disorder should NOT be given OPV until their immune status is determined and immunodeficiency is excluded.
4. Patients with history of anaphylactic reactions to neomaycin, streptomycin, or polymyxin B.

The following conditions are NOT contraindication for OPV:

1. Pregnancy

   There is no evidence to suggest that a pregnant women or her fetus is at greater risk from OPV than other persons. Therefore, OPV may be given during epidemic control or when immediate protection against poliomyelitis is needed.
2. Breast feeding

   Breast-feeding mothers can receive OPV without any interruption of feeding schedule.
3. Diarrhea
4. Current antimicrobial therapy

Practical Hints

1. If the infant spit out, regurgitate, or vomit a dose of OPV within 10 min of administration, another dose should be repeated at the same visit. If the second dose is not retained, neither dose should be counted and the vaccine should be readministered at the next visit.
2. Breast feeding does not interfere with successful immunization with OPV, and there is no need to withhold breast feeding before or after vaccination.
3. Due to excretion of polioviruses in the stool of OPV recipients and in order to prevent nosocomial transmission of vaccine viruses in nurseries and pediatric wards, OPV administration to hospitalized infants should be deferred until the day of discharge.
4. Administration of extra dose (or doses) of OPV (e.g., during outbreak control or national immunization campaigns) to a partially or fully vaccinated individual is a safe and acceptable practice when needed.

Inactivated Poliovirus Vaccine (IPV)

Nature and Contents

IPV contains a mixture of all the three types of polioviruses (1, 2, and 3) propagated in monkey kidney cell cultures or in human diploid cells and inactivated (killed) by formaldehyde. Trace amounts of streptomycine, neomycine, and polymyxine B are also included. The vaccine is available either as a standalone product or in combination with diphtheria, tetanus, and pertussis with or without conjugated HIB and HBV.

Mechanism of Protection

Individual Perspective

IPV protect against paralytic poliomyelitis by:

1. Induction of neutralizing antibodies in the serum of vaccinees.
2. Priming the immune system so that a prompt secondary response is elicited upon exposure to wild viruses.

Community Perspective

IPV use in a community induces herd immunity with resultant protection of unvaccinated individuals living in a well-vaccinated community. However, unlike OPV, IPV is not useful for outbreak control.

Efficacy and Immunogenicity

Following two doses of IPV given with interval of 4 weeks or more, almost 100% of individuals develop neutralizing antibodies for all the 3 strains of poliovirus. Furthermore, a long-term immunological memory is induced contributing to protection of vaccinees long after declining of serum antibodies.

Storage and Handling

The following recommendations apply for regular IPV as well as e IPV:

- Storage and shipment
  - Should be at 2–8°C and should not be freezed
- Normal Appearance

IPV is the recommended Polio vaccine for routine infant vaccination in areas with low risk for importation and transmission of wiled polio viruses. This is because it eliminates the risk of vaccine-associated paralytic polio (VAPP).

Clear suspension, red or pink (due to phenol red). Vaccine that contains particulate matter or develop turbidity should *not* be used.

Recommended Use

IPV only is the recommended polio vaccine for routine infant vaccination in areas with low risk for importation and transmission of wild polio virus. This is because it eliminates the risk of vaccine-associated paralytic polio (VAPP).

IPV is particularly recommended in the following situations:

1. Persons with compromised immunity who are unimmunized or partially immunized.
2. Symptomatic and asymptomatic individuals infected with HIV.
3. Household contacts of immunocompromised persons.
4. Unimmunized adults.
5. Persons refusing OPV.
6. Hospitalized infants if protection is needed soon after discharge.

For routine immunization of infants, three primary doses are recommended. The first dose starting at 6–12 weeks of age and subsequent doses given at interval of 4–8 weeks. The third dose may be given 6–12 months after the second. Supplementary doses are given at 1 1/2 and 4–6 years.

Dose and Route

0.5 mL is given by subcutaneous or intramuscular (IM) injection. If the used IPV preparation is combined with DPT, then it must be administered intramuscularly because of the presence of adsorbed tetanus and diptheria toxoids.

Adverse Reactions

Adverse events following IPV vaccination are limited to minor local reactions at injection site.

Contraindications and Precautions

IPV is contraindicated only in patients with history of anaphylactic reactions to neomycine, streptomycine, or polymyxine B.

Practical Hints

1. A combination schedule of IPV-OPV immunization has been adopted by several countries in order to avoid vaccine-associated paralysis while enjoying efficient mucosal immune response elicited by OPV. The regimen involve sequential administration of the first one or two doses as IPV (thereby protecting the vaccinee against the invasion of central nervous system by wild or vaccine virus) followed by OPV doses inducing additional protection at mucosal surfaces.
2. Any combination of IPV and OPV for vaccination is acceptable if the minimum interval between OPV doses is 6 weeks and between IPV doses is 4 weeks.
3. When IPV is given as a combined product with DPT, the schedule used is that for DPT, with 3 primary doses in early infancy. The extra dose of IPV is not strictly necessary, but it does not add to vaccine side-effects.

Rotavirus Vaccine

Nature and Contents

The two licensed rotavirus vaccines are:

1. Pentavalent (RV_5;RotaTeg) rotavirus vaccine.
2. Monovalent (RV_1;Rotarix).

Both are live vaccines administered orally. However, they differ in compositions as follows:

- Pentavalent (RV_5 RotaTeg): contain five live reassortant rotaviruses. The sources of the reassortant viruses are human and bovine strains. Four of the reassortant rotaviruses express the outer capsid proteins (G_1, G_2, G_3, G_4) from human rotavirus parent strain and the attachment protein P7 from the bovine rotavirus. The fifth reassortant rotavirus express the attachment protein P1[8] from the human rotavirus and the outer capsid protein G_6 from bovine.
  - Each 2 mL of vaccine dose contains a minimum level of the five reassortant rotaviruses, ranging from 2.0 to 2.8 $\times$ 10^6 infectious doses depending on the serotype.
  - These are suspended in a buffered stabilizer solution. The vaccine contains no preservative or thiomersal.
- Monovalent (RV1; Rotarix): contain one live attenuated human strain (P_1 A[8]G_1) strain. It is provided as lyophilized powder. Each 1 mL dose of the reconstituted vaccine contains at least 1 $\times$ 10^6 infectious doses.

Mechanism of Protection

The mechanism of protection is not fully clear. However, production of neutralizing antibodies to the vaccine strains and of specific IgA for rotavirus has been demonstrated in vaccine recipients and may play a role in protection.

Storage and Handling

- Storage and shipment: should be at a temperature between 2°C and 8°C and should not be exposed to freezing temperature. Should be protected from light as this may inactivate the vaccine viruses.
- Stability: Rota Teg (RV5) should be administered as soon as possible after removal from refrigeration, but may be used within 4 h if the vaccine has been maintained at temp $\leq$25°C. Rotarix should be administered within 24 h of reconstitution.

Efficacy

- The efficacy of three doses of RV5 (Rota Teg) vaccine against severe rotavirus gastroenteritis caused by G serotypes contained in the vaccine was 98.21, (95% CI 89.6–100%) and against rotavirus gastroenteritis of any severity was 73.8(95% CI 67.2–79.3%). In the large Rotavirus efficacy and safety trial (REST), Rota Teg reduces G_1-G_4 rotavirus-associated hospitalization or emergency visit by 94.5% (95%CI 91.2–92.5%).
- After completion of a two-dose RV1 (Rotarix) regimen, the efficacy against severe rotavirus gastroenteritis was 85% and against any rotavirus gastroenteritis was 87%. Hospitalization for rotavirus gastroenteritis was reduced by 85–100%.
- The duration of immunity from rotavirus vaccines is not known. Efficacy through 2 rotavirus seasons has been demonstrated for both vaccines, although generally the efficacy is lower in the second season than the first.

Recommended Use

1. Routine infant vaccination

   Several countries have adopted universal infant vaccination schedules, and it is recommended for all infants in the first half of the first year of life.
   (a) Rotarix (RV1): Infants should receive two doses of the RV1 (human monovalent rotavirus vaccine) at 2–4 months with the first dose between 6 weeks and <15 weeks of age. The second dose should be given at least 4 weeks from the first dose and not later than the 24 weeks of age.
   (b) Rota Teg (RV5): The vaccination course of RV_5 consists of three doses at approximately 2, 4, and 6 months of age. The first dose should be between 6 weeks and <13th week. The minimum interval between doses should be 4 weeks, and the upper age limit for the third dose should be <33 weeks of age.

2. Preterm infants

   Should be vaccinated at a chronological age of at least 5 weeks if clinically stable. Vaccination should preferably be done at or after the time of discharge from neonatal unit.

Adverse Reactions

- G.I symptoms (e.g., diarrhea or vomiting) occurred at an increasing rate (approximately 3% increase) in the first week following vaccination.
- No serious adverse events were noted particularly no increased risk of intussusceptions was observed.

Contraindications and Precautions

- Anaphylactic reaction to a prior dose of the vaccine or any of its components is a contraindication for its use.

Precautions

- Moderate or severe acute illness, including gastroenteritis.
- Immunodeficiency disorders.
- History of intussusceptions.
- The following are not considered precautions by many authorities:
  - Chronic GI disease.
  - Administration of antibody-containing blood products within the past 42 days. However, the interval between vaccination and the receipt of the blood products should be as long as possible but without delaying administration of vaccine beyond the age limits for dosing.

Practical Hints

1. If the first dose of RV vaccine is inadvertently administered at an age greater than the suggested cut-off, the remaining vaccine doses should be given as per the recommended schedule ensuring observation of the minimum interval between doses and the recommended upper age limit.
2. Since a single virus infection do not provide full immunity, RV vaccine should still be given to infants who develop RV infection before receiving the first dose or before completion of the recommended doses.
3. If the infant spits out, regurgitates, or vomit a vaccine dose, readministration of the dose is not necessary and not recommended.
4. If a recently vaccinated infant is hospitalized for any reason, no precaution other than routine standard precautions needs to be taken even if the vaccine virus is being shed in stool.
5. Following vaccination with RV_5 (Rota Teg), 9% of recipients in one study shed the virus in stool after the first dose but not after subsequent dose. Shedding occurred as early as 1 day and as late as 15 days after the dose.
   (a) Fecal shedding of rotavirus antigen after Rotarix was demonstrated in 50–80% of infants after the first dose at day 7 and in up to 24% at day 30. Following the second dose, fecal shedding was 4–18% at day 7 and 1–2% at day 30. No data are available on potential for transmission.
6. There is no reason to avoid exposure of pregnant women to vaccinated infants. Most pregnant women will have pre-existing immunity to rotavirus. Furthermore, vaccination of infant's contacts will reduce the chances of exposure of adults, including pregnant women, to wiled virus.
7. Due to lack of data on interchangeability of rotavirus vaccines, it is recommended to use the same vaccine for the whole schedule. However, if the same vaccine used in previous dose is not available or not known, completion of the dose with either vaccine is acceptable provided the upper age limit is observed.
8. Breast feeding does not diminish the efficacy of the vaccine, and hence, there is no need to withhold breast feeding in relation to vaccination.
9. Rota vaccines may be administered with all other infant vaccines. However, administration with oral polio vaccine should be avoided because no data is available on concomitant use of the two vaccines.

Rubella Vaccine

Nature and Contents

Rubella vaccine is a live attenuated virus prepared in human diploid cell culture from the strain RA 27/3 in most parts of the world. The unit dose usually contains

1,000 plaque-forming units (PFU). The vaccine is available in a monovalent formulation, a bivalent mumps-rubella and measles-rubella combinations and in a triple formulation measles-mumps-rubella (MMR) vaccine with or without Varicella vaccine (MMRV). The vaccines contain trace amount of antibiotic (e.g., neomycine) and sucrose or sorbitol.

Mechanisms of Protection

Following successful vaccination with rubella vaccine, the following responses are observed:

1. Induction of neutralizing antibodies in serum
2. Production of IgA antibodies in nasopharynx
3. Stimulation of cell-mediated immune response

Storage and Handling

- Storage and shipment
  - Unreconstituted vaccine may be stored at 2–8°C and may be frozen.
  - Reconstituted vaccine should be stored at 2–8°C
  - Both forms should be protected from light which may inactivate the virus.
- Stability
  - Unreconstituted form is highly stable in the frozen state. At 4°C, the potency is maintained for up to 5 years. Potency is markedly reduced after 3 months in room temperature and after 3 weeks at 37°C.
  - Reconstituted vaccine is very labile and should be used within 8 h.
- Normal appearance
  - Clear, yellow solution. If reconstituted vaccine is cloudy, it should *not* be used.

Efficacy and Immunogenicity

Rubella vaccine induces immune response similar qualitatively to that noted after natural infection. The magnitudes of the response are lower after the vaccine, however. Seroconversion and clinical protection occurs in >97% of vaccinees. The duration of protection persist for >20 years following vaccination and may be lifelong. There is no difference between the response to monovalent or to combination vaccines.

Recommended Use

1. Routine rubella immunization
   (a) Rubella vaccine should be given routinely to male and female children along with measles and mumps vaccines (MMR). The timing will be determined by the measles vaccination schedule.
2. Adolescents and adults

   Adolescents and adults who lack evidence of immunity to rubella (i.e., detectable antibody or documented vaccination) should be vaccinated against rubella especially if they belong to one of the following groups:
   - Postpubertal females
   - Postpartum women
   - Child-care personnel
   - College students
   - Health-care workers
   - Military personnel

Adverse Reactions

- Rash, lymphadenopathy, and fever simulating mild clinical rubella occurs in 5–10% of immunized children and may be higher in adults.
- Transient arthritis and arthralgia occurs in 10–15% of vaccinated adolescents and adults approximately 3 weeks post vaccination. Any joint may be involved but small joints of the hands and the knees are most affected. There are rare reports of recurrent or chronic arthritis after vaccination.
- Transient peripheral neuritis and parasthesias in the arms and legs have been reported rarely.
- Mild thrombocytopenia has been observed in some vaccinee rarely.

Contraindications and Precautions

Rubella and rubella-containing vaccines (MMR) are contraindicated in:

1. Individuals with altered immune status due to:
   (a) Primary immune deficiency
   (b) Malignancy, e.g., leukemia, lymphoma
   (c) Immunosuppressive therapy, e.g., corticosteroids, cytotoxic agents, etc.
2. Pregnancy – although there has been no reported fetal effects of mothers who were inadvertently immunized

while pregnant, it is prudent to avoid rubella vaccination during pregnancy because of the theoretical risk on the developing fetus. Vaccinated female should be advised not be pregnant for 1 month following immunization. However, should a mother discover that she was pregnant at the time of vaccination or she get pregnant within 1 month of immunization, she should be counseled on the theoretical risks to the fetus and be reassured of the very low risk. Such instances are not considered a reason to terminate pregnancy.

3. Anaphylactic reactions to vaccine components including the antibiotic used (e.g., neomycine).
4. Administration of immunoglobulins or other blood products 2 weeks before or within 3 months after rubella vaccination may interfere with successful immunization. However, the vaccine may be given to postpartum women at the same time as anti-Rho (O) IG or after blood products are given. In this situation, these women should be tested $\geq$8 weeks later to assure that seroconversion has occurred.

The following are *not* contraindications:

1. Mild febrile or nonfebrile illness such as upper respiratory tract infections.
2. Presence of immunocompromized patients or susceptible pregnant females in the household.
3. Non-anaphylactic allergic reactions to neomycin.
4. Breast feeding
5. Penicillin allergy

Practical Hints

1. The infection induced by rubella vaccine is not communicable even in vaccines that develop rash or other manifestations.
2. There are no known adverse effects to the administration of rubella vaccine to immune individuals or those incubating rubella infection, therefore, routine serological testing is not indicated prior to vaccination.
3. Unlike measles vaccine, the age of first vaccination does not seem to be as critical for development of immune responses to rubella vaccine. Successful vaccination is likely from 10 months of age.
4. Use of MMR instead of monovalent vaccines whenever an indication to either rubella or measles vaccination arise is recommended as this will provide an additional protection to the other components with little increase in the cost.
5. Rubella vaccination after exposure to the disease is not usually useful for prevention of the illness. However, immunization of exposed nonpregnant individuals is not harmful and will protect the individual in future if the current exposure does not result in infection.

Tetanus Toxoid

Nature and Contents

Tetanus toxoid is prepared by formaldehyde detoxification of tetanus toxin. The toxoid is available in monovalent preparation and in various combinations with some or all of diphtheria toxoid (DT or Td), pertussis vaccines (DTP and DTaP) with or without inactivated polio (IPv), conjugated HIB, and HBV vaccines. The toxoid is available in adsorbed formulation with Aluminum salt and in a plain form. The amount of toxoid in all the preparations is comparable and is usually 4–5 flocculation units (Lf).

Mechanisms of Protection

Immunization with tetanus toxoid induces production of neutralizing antibodies (antitoxin) which protect against the effects of the toxin. A level of 0.01 IU/mL of antitoxin is considered protective.

Storage and Handling

- Storage and shipment
  - All forms of adsorbed preparations should be stored and shipped at 2–8°C. No freezing is allowed.
- Stability
  - Exposure to a higher ambient temperature for short period of time (<7 days) do not reduce the potency.
- Normal appearance
  - Turbid and whitish suspension. Vaccines that contain clumps of material that cannot be suspended with vigorous shaking should *not* be used.

Efficacy and Immunogenicity

- Productions of protective concentrations of antitoxin are achieved in most vaccine recipient after two doses. Following a third dose, almost 100% become protected.

- Clinical efficacy has ranged from 80% to 100%. Infants born to mothers who received two or three doses of the vaccine were highly protected against neonatal tetanus.

Recommended Use

1. Universal immunization

   The primary immunization series consist of three doses of adsorbed tetanus toxoid separated by 4–8 weeks intervals. A fourth dose is given to children under the age of 6 years with a booster dose at 4–6 years of age unless the fourth dose was given after the age of 4 years. Subsequently, a booster dose is needed every 10 years.
2. Wound management
   (a) If the patient has received less than three doses of tetanus toxoid or if his immunization status is unknown, a dose of the toxoid should be given. Tetanus immunoglobulin (TIG) should also be administered unless the wound is clean and minor.
   (b) If the patient has received greater than three doses of the toxoid, no further doses are needed unless 10 years have lapsed since the last dose in cases of clean and minor wounds; or 5 years in other types of wound. TIG in these cases is not needed.
3. Prevention of neonatal tetanus

   This can be accomplished by (a) immunization of unvaccinated adolescent girls and women of child bearing age; (b) prenatal immunization of unimmunized pregnant mothers by administering two doses of the toxoid 4 weeks apart at least 2 weeks before delivery.
4. After recovery from tetanus

   Patient convalescing from tetanus should be immunized with tetanus toxoid as they are unlikely to acquire immunity from the disease.

Dose and Route

- The dose is usually 0.5 mL of a preparation containing tetanus toxoid as determined by age and special contraindication.
- The adsorbed forms should be given intramuscularly. Fluid preparation can be given subcutaneously.

Adverse Reactions

- Local reaction including pain, redness, and swelling at injection site are the commonest observed reactions. The frequency and severity of such reactions increase with successive doses of the toxoid and particularly in presence of high levels of circulating antitoxins resulting from too frequent immunization.
- Systemic reactions to the tetanus toxoid are rare but have included anaphylaxis reactions and peripheral neuropathy.

Contraindications and Precautions

Severe systemic reactions to a previous dose are a contraindication to further doses.

Patients who develop major local reactions or fever after a dose of toxoid should not be given another dose for at least 10 years.

Contraindications and precautions to other components of preparations containing tetanus toxoid should be observed.

Practical Hints

1. Administration of immunoglobulin does not interfere with the immune response to tetanus toxoid. However, when it is indicated, it should be administered by a different syringe at a different site than the toxoid.
2. Whenever immunization against tetanus is indicated, an appropriate combination is preferred to the single agent as this will also provide a chance to give booster of diphtheria and/or other agents.

Varicella Vaccines

Nature and Contents

The currently licensed varicella vaccine is a live-attenuated varicella-zoster virus (VZV) obtained after serial passages of the wild Oka virus strain in tissue cultures. Each dose contain $\geq$1,350 plaque-forming units of VZV. Some product may contain trace amounts of neomycin and gelatin. The vaccine is available as a monovalent vaccine or in combination with antigens of MMR vaccine.

Storage and Handling

- Unreconstituted vaccine and the diluent should be stored at +2°C to +8°C and should not be frozen.

- Reconstituted vaccine should be used within 30 min after reconstitution and, if necessary, it may be kept in 2–8°C for a maximum of 8 h but should not be frozen.
- The vaccine should be protected from light

Efficacy and Immunogenicity

In healthy children, 1–12 years of age, a single dose of Varicella vaccine results in a seroconversion rate of 97% or more. The clinical efficacy of a single dose exceeds 95% for severe disease and approximately 70% for any disease, over a 10-year period of follow-up. In persons 13 years of age and older, seroconversion rate are approximately 80% after a single dose and 99% after two doses. The magnitude of the antibody response after vaccination is lower than that after natural disease. However, the antibodies may persist for as long as 20 years following immunization.

Recommended Use

1. Healthy children, adolescents, and adults
   (a) In some countries, universal use of varicella vaccine in all healthy children between 1 and 12 years of age is currently recommended.
   (b) Susceptible adolescent and adults are encouraged to take the vaccine.
   (c) The vaccine is particularly indicated for any susceptible individual who belong to one of the following groups:
      (i) Health-care personnel
      (ii) Household contacts of immunosuppressed individuals
      (iii) Those at high risk of exposure such as teachers and college students
      (iv) Nonpregnant women at child-bearing age
      (v) Children and adolescent undergoing chronic salicylic acid therapy.
2. Individuals with isolated immunodeficiency diseases and know intact T-cell system are candidate for vaccination and include patients with:
   (a) Isolated immunoglobulin deficiency diseases
   (b) Neutrophil deficiency disorders
   (c) Complement deficiency diseases
   (d) Asplenia or splenic dysfunction
3. Individuals who could be vaccinated with fulfillment of pre-request:
   (a) Individuals with acute lymphocytic leukemia (ALL) may be vaccinated if the following prerequisites are fulfilled:
      (i) In remission for $\geq$1 year.
      (ii) Lymphocyte count of $\geq$1,200.
      (iii) Not receiving radiation.
   (b) HIV-infected children $\geq$1 year of age if asymptomatic or mildly symptomatic with age-specific CD4 count $\geq$25%.
   (c) Recipient of long-term immusuppresive therapy whose therapy has been discontinued for at least 6–12 weeks.
   (d) Patient who underwent solid organ or bone narrow or stem cell transplantation may be vaccinated 2 years after transplantation, provided they are on minimal immunosuppresion and not suffering from a major complication.
4. Post-exposure
   (a) Susceptible healthy individuals are candidate for vaccination after exposure if it can be given within 5 days of exposure. The effectiveness is high for prevention or reducing severity.

Dose and Schedule

The recommended dose of the vaccine is 0.5 mL given by subcutaneous injection. Children between 12 months and 12 years require at least one dose administered between 12 and 15 months. For optimal protection, however, a second dose should be given after an interval of 3 months. The decision to adopt two doses versus single dose schedule should be based on assessment of the cost-effectiveness in the particular setting. Individuals older than 12 years should be given two doses separated by 4–8 weeks.

Adverse Reactions

Adverse reactions following vaccination are generally minimal and include:

- A mild vaccine-associated maculopapular or varicelliform rash develops in approximately 7% of vaccinee with a median of two to five lesions.
- Injection site complaints such as transient pain, tenderness, or redness occurs in 20–30% of vaccinees.
- Systematic adverse reactions include fever (10–15%) and increase risk of febril seizure following vaccination with some products of MMRV.

- A mild zoster-like illness has been reported rarely after varicella vaccination. The frequency as well as the severity are much less following vaccination than after natural disease.

Contraindications and Precautions

Varicella vaccine is contraindicated in:

1. Individuals with altered immune status due to:
   (a) Primary immune deficiency involving T-cell system
   (b) Malignancy such as lymphoma and acute myelogenous leukemia
   (c) HIV infection
   (d) Immunosuppressive therapy including cytotoxic agents and high-dose corticosteroid therapy ($\geq$2 mg/kg of prednisone/day)
2. Individuals with anaphylactic reactions to any vaccine component
3. Pregnant Women
4. Individuals who have recently received immunoglobulins or other blood products may not respond to the vaccine for several months due to passively acquired antibodies. Therefore, the vaccine should not be given for at least 5 months after administration of immunoglobulins, VZIG, or plasma transfusion.

The following are *not* contraindications:

1. Mild febrile or nonfebrile illness
2. Presence of immunocompromised individuals including HIV-infected individuals in the household
3. Pregnancy of the mother
4. Lactation
5. Use of inhaled or topical corticosteroids

Practical Hints

1. Although the vaccine-virus has been recovered from vaccine recipients with skin lesions, the spread of the vaccine-virus from healthy vaccinees to others is very rare (<1%). The risk of transmission of the vaccine-virus is higher from vaccinated leukemic children with a skin rash.
2. Immunization of persons with prior immunity to varicella is not associated with an increase in adverse events, and therefore, serological proof of susceptibility to varicella is not a prerequisite in those uncertain of their susceptibility status.
3. In a child with history of congenital immunodeficiency in a sibling, varicella vaccine should not be given until immunodeficiency is excluded.
4. Varicella vaccine should not generally be given for at least 3 months following cessation of immunosuppressive therapy. However, except in children receiving high-dose corticosteroids, the vaccine maybe given 1 month after discontinuation.
5. Susceptible pregnant women and immodeficient patients who are not candidate for varicella vaccination should be given VZ immoglobuline within 96 h from exposure to a patient during infectivity period of varicella.

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77 Brucellosis

Youssef A. Al-Eissa

Brucellosis constitutes a major health and economic problem in many parts of the world, including the countries of the Mediterranean basin and the Middle East. The disease is primarily a contagious infection of animals, but it may be transmitted to humans through direct contact with infected animals, products of conception, or animal discharges, and through consumption of infected milk, dairy products, or meat. Although sporadic human cases of brucellosis were reported during the previous three decades in the Middle East, it was not until the early 1980s when the disease was first recognized as a major problem. Epidemiologic studies have shown that the disease is common and widespread, and it remains hyperendemic in certain rural areas of the Arab countries. This recent surge in the incidence of brucellosis in humans and animals has been linked to the uncontrolled importation of potentially infected animals, widespread animal husbandry, and the prevailing habit of ingesting raw milk or its products among the population of nomadic background.

Etiology

The disease is caused by small, fastidious, nonmotile, nonspore-forming, capnophilic, gram-negative coccobacilli of the genus *Brucella*. There are four important species pathogenic to humans: *Brucella melitensis* found primarily in goats, sheep, and camels; *Brucella abortus* found in cattle; *Brucella suis* found in swine; and *Brucella canis* found in dogs. The natural reservoir of brucellosis is domestic animals, and animal-to-animal transmission is usually venereal or by ingestion of infected tissue or milk. The *Brucella* species differ in degree of virulence and invasiveness. *B. melitensis* is the most invasive and produces the most severe disease. *B. abortus* is the least invasive and causes the mildest illness. *B. suis* is very invasive and often causes suppurative disease. In the Middle East, human infection with *B. melitensis* is commonly encountered and infection with *B. abortus* is less frequent, but infection with other species is rarely reported. Transplacental transmission of *B. melitensis* resulting in neonatal infection has been recently described. Although *Brucella* organisms have been isolated from human milk, no infection traced to this route has been documented.

Pathogenesis

Brucellae invade through the nasopharynx, gastrointestinal tract, conjunctiva, genital tract, abraded skin, or respiratory tract. Once the organisms have transgressed the mucous membrane or skin, they reach the regional lymph nodes by lymphatic spread. In the lymphatic tissues, brucellae multiply and invade the bloodstream, causing bacteremia. They are phagocytosed by polymorphonuclear leukocytes and monocytes and transported to various organs and tissues, particularly to those with abundant reticuloendothelial cells, including the spleen, liver, bone marrow, and lymph nodes. Brucellae are facultative intracellular pathogens with the ability to escape intracellular killing and even multiply within phagocytic cells of the host. Both host and pathogen factors are important to determine the clinical presentation and outcome of the *Brucella* infection.

The characteristic, but not specific, reaction of tissue to *Brucella* is the appearance of granulomas consisting of epithelioid histiocytes, lymphocytes, monocytes, plasma cells, and Langerhans and foreign body giant cells. These granulomas may have central hyaline necrosis but no caseaction necrosis. The granulomas are often found in biopsies of the bone marrow, lymph nodes, spleen, and liver.

Clinical Manifestations

Human brucellosis is notoriously a multisystem disease with varied manifestations, and the onset of the illness may be either acute or insidious. The latter mode of presentation has caused more difficulties in diagnosis. The incubation period is difficult to ascertain because of repeated exposures to the source of infection, but it varies from a few days to several months. Morbidity depends largely on the pathogenicity of the infecting *Brucella* species. Children infected with *B. abortus* are likely to have an

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asymptomatic or a mild illness. In contrast, children infected with *B. melitensis* often develop a severe disease.

Acute Brucellosis

The predominant presenting symptoms are fever, arthralgia, malaise, fatigue, and body aches. The fever may be associated with chills and drenching, malodorous sweats. Over half of patients complain of anorexia and experience a significant weight loss. In addition, patients may have abdominal pain, nausea, and vomiting. The most common signs of brucellosis in addition to fever are arthritis (up to 40%) (*Fig. 77.1*), splenomegaly (up to 35%), hepatomegaly (up to 30%), and lymphadenopathy (up to 20%).

Localized Disease and Complications

Localization of *Brucella* organisms may occur in any organ. Skeletal, gastrointestinal, and hematologic complications are the most common, but involvement of the heart and central nervous system are the most serious, albeit rare.

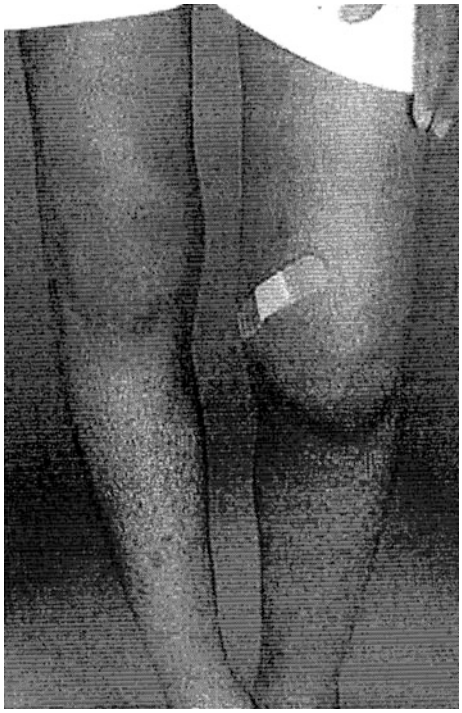

Figure 77.1
A patient with left knee brucella arthritis

Skeletal

Peripheral arthritis is the most common form of osteoarticular involvement in acute brucellosis. Arthritis is manifested by pain, periarticular soft tissue swelling with or without obvious intra-articular effusion, limitation of motion, various degrees of hotness, and, rarely, erythema. Arthritis is monoarticular in 70% of patients and has a predilection for large weight-bearing joints. Most patients with multiple joint involvement tend to have an additive rather than a migratory arthritis. The joints involved in order of frequency are hip, knee, sacroiliac, ankle, wrist, elbow, and shoulder. Small joint and spine involvement (*Fig. 77.2*) is rare in children, in contrast with the findings in adults. It is currently believed that suppurative and reactive arthritides occur in brucellosis, as in other bacterial infections. Osteomyelitis of the long bones, a rare osseous complication of brucellosis, has been reported in children.

Gastrointestinal

Hepatitis probably occurs in most infected patients during the course of their illness, and liver function tests commonly demonstrate hepatic involvement. Liver biopsy specimens have revealed nonspecific histologic abnormalities, including noncaseating granulomas. The spleen is a frequent site of localized brucellosis, and hypersplenism has resulted in abnormal alteration of the peripheral blood elements. Jaundice is very rare, and its appearance may be a manifestation of hepatic failure. Acute cholecystitis and hepatic or subdiaphragmatic abscesses are rare in children. However, acute ileitis and enterocolitis have been recently reported in pediatric patients.

Hematologic

Anemia (up to 50%), leukopenia (up to 35%), thrombocytopenia (up to 5%), and pancytopenia (up to 14%) have been associated with *B. melitensis* infection in children. Leukopenia is mainly accompanied by neutropenia or lymphopenia, but absolute or relative lymphocytosis is less frequently encountered in pediatric patients. Hemolytic anemia and disseminated intravascular coagulation are occasionally seen. Hypersplenism, hemophagocytosis, and granulomatosis lesions of the bone marrow appear to play a fundamental role in producing these abnormalities of the peripheral blood.

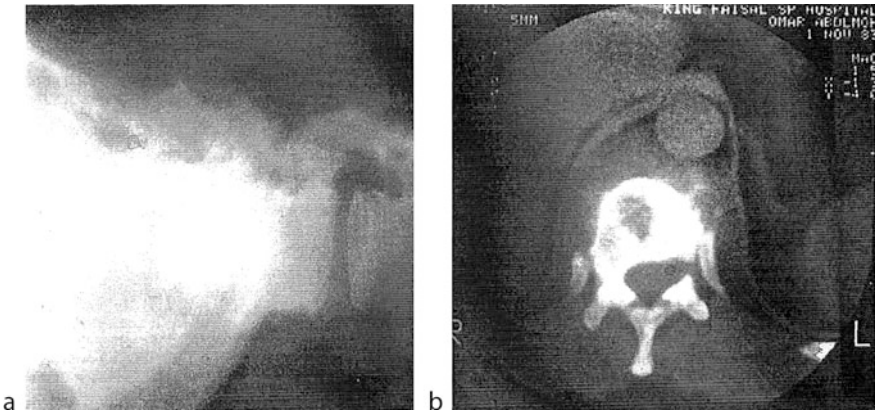

Figure 77.2
Destruction of intervertebral disk and bone, and soft tissue reaction caused by *Brucella* infection is seen in this plain film (a) and computerized tomography scan (b)

Psychiatric

Psychiatric disturbances seem to be frequent, but they are not clinically recognized. Profound depression (may be associated with suicidal thoughts), anxiety state, and hypochondriasis have been described. The severity of these manifestations is related in part to the duration of illness, being more common among patients with chronic brucellosis, but the pathogenesis of these disorders is poorly understood.

Neurologic

Involvement of the nervous system in systemic brucellosis is rare. The presentation of neurobrucellosis is diverse, and both central and peripheral nervous systems can be involved. Meningitis, encephalitis, meningoencephalitis, cerebellar ataxia, subarachnoid hemorrhage, myelitis, peripheral neuritis, radiculitis, Guillain–Barré syndrome, and cranial nerve palsy, particularly the eighth, have occurred in patients with brucellosis. In meningoencephalitis, the cerebrospinal fluid (CSF) shows a mildly elevated protein level, normal or low glucose level, and a lymphocytic cellular reaction. The syndrome of peripheral polyradiculitis with ascending weakness, tendon areflexia, intact sensation, and CSF lymphocytic pleocytosis has been reported. Cerebellar ataxia and profound sensorineural deafness are the presenting features of proximal polyradiculoneuropathy. Myelitis with spastic paraparesis, hyperreflexia, clonus, extensor plantar response, urine retention, and bilateral sensorineural deafness has been described.

Cardiovascular

Infective endocarditis is a potentially fatal complication, but the disease is fortunately rare. The development of endocarditis should be suspected in patients presenting with a heart murmur who have been exposed to a source of *Brucella* infection. It follows an indolent course and is accompanied by a high rate of congestive heart failure and arterial embolization. The aortic valve has been commonly involved, followed by the mitral valve alone or both valves concurrently. Endocarditis is the most common cause of death among patients with brucellosis. Myocarditis and pericarditis have been diagnosed in patients with brucellosis whose clinical presentations mimic findings usually noted in acute rheumatic fever.

Pulmonary

A variety of pulmonary manifestations of brucellosis, such as bronchitis, pneumonia, pleurisy, pleural effusion, empyema, hilar lymphadenopathy, single granulomatous coin lesion or isolated pulmonary nodule, and lung abscesses, have been reported. Brucellae have been occasionally cultured from sputum and pleural fluid. Pulmonary brucellosis can be clinically and radiologically indistinguishable from tuberculosis.

Genitourinary

Epididymo-orchitis, which is usually unilateral, is the most common genitourinary complication; sterility has

not been shown to follow such involvement. Other complications include cystitis, pyelonephritis, and acute glomerulonephritis.

Ocular

Ophthalmic manifestations have been considered to be quite rare. Pure ophthalmopathies have included keratitis, corneal ulcers, uveitis, and retinopathies. Neuro-ophthalmologic abnormalities comprise optic neuritis and atrophy, papillitis, and oculomotor dysfunction.

Dermatologic

Cutaneous manifestations are infrequent, and the reported skin lesions include nonspecific erythematous rash, petechiae and purpura, erythema nodosum, and subcutaneous nodules and abscesses.

Diagnosis

The diagnosis of brucellosis is based on epidemiologic evidence of a possible source of infection, clinical manifestations compatible with the disease, and one or more of three laboratory criteria: Isolation of the brucellae from blood or other body fluids and tissues; a *Brucella* agglutination titer of 1:160 or above; and a fourfold or greater rise in titers following the onset of symptoms. Brucellosis can display a variety of clinical pictures, and the diagnosis may be easily missed, particularly if there is no clear history of exposure to infected animals or their products. The clinical and routine laboratory findings of brucellosis are nonspecific, and the diagnosis is frequently overlooked or delayed until the more common childhood infections or diseases are excluded. Hence, the diagnosis of brucellosis should be entertained in every case of undefined fever or illness in a highly endemic area of animal brucellosis.

The definitive evidence of *Brucella* infection is by isolating the organisms from the patient. However, laboratory cultures of *Brucella* are often unsuccessful due to the slow-growing nature of these organisms, which may require up to 8 weeks to grow, and the requirement for special media and 5–10% CO_2. A variety of media have been found to produce satisfactory growth, such as tryptic soy broth or Albimi, and there is no convincing evidence that the use of Castaneda medium is superior. Approximately 50–85% of the patients whose blood is submitted for culture early in the course of infection, and who have not received antibiotics, will yield *Brucella* organisms from their blood when one or two samples are cultured. The isolation rate decreases with increasing duration of illness. Later in the course of the illness, organisms are more likely to be isolated from granulomas involving bone marrow or lymph nodes. *B. melitensis* is more successfully isolated from blood than *B. abortus*, but culture of the aspirated bone marrow is more likely to be successful for all species. All culture specimens from cases with a clinical suspicion of brucellosis should be clearly marked "possible brucellosis" for proper bacteriologic processing and because culturing brucellae may be dangerous to laboratory personnel. Blood culture sensitivity has improved significantly with the use of BACTEC system, which detects the majority of *B. melitensis* isolates within the routine 1-week blood culture schedule.

Brucella serologic tests have proved to be very valuable in screening for the disease. The most reliable test is the standard tube agglutination test using a serial tube-dilution technique of the patient's serum and a standardized suspension of *B. abortus* antigen that measures the total quantity of agglutinating immunoglobulin M (IgM) and immunoglobulin G (IgG) antibodies. This test will equally detect antibodies to the three major species (*B. abortus*, *B. melitensis*, and *B. suis*) due to cross-reactivity, but it will not detect *B. canis*. For the diagnosis of *B. canis* infection, antigen prepared from *B. canis* or *B. ovis* should be utilized. Most patients with acute brucellosis develop significant agglutination titers within 1–3 weeks of illness. In a typical acute infection, the agglutinating antibody level of the IgM class rises in the first week and peaks at approximately 3 months; low IgM levels may persist for several months or years, even after presumed complete cure of infection. Two to three weeks after the onset of acute infection, IgG antibodies rise to a high level over the course of 6–8 weeks, but these antibodies eventually disappear after recovery. Hence, with early diagnosis and prompt treatment of sufficient duration, IgG antibody titer rapidly declines and serves as an indicator of successful therapy. Antibodies of the immunoglobulin A (IgA) class rise soon after IgG antibodies and parallel the sequence of IgG. The IgG antibodies can be identified by the 2-mercaptoethanol (2-ME) agglutination test, as 2-ME destroys IgM antibody. The persistence of high serum IgG antibody titers in patients treated with antibrucella drugs could be due to a relapse because of inappropriate antibiotic therapy or poor compliance, a reinfection because of reexposure to a source of infection, the presence of focal disease, or high initial titers before initiating antimicrobial therapy. However, it is unusual to encounter a child with an agglutination titer of 1:160 or above without symptoms.

Only on rare instances has *Brucella* been recovered from the blood culture when the initial *Brucella* titers are negative. Serologic tests may remain negative in newborns with bacteriologically confirmed *Brucella* infection: Furthermore, patients may fail to mount a significant serologic response during the early stage of illness. Therefore, a negative serology should not preclude the diagnosis of brucellosis. Another cause of false-negative agglutination tests is the prozone phenomenon, due to blocking antibodies of the IgG and IgA classes appearing late in the course of the illness, which can be eliminated if dilutions are carried out to at least 1:1,280. Cholera vaccination, or infection with *Vibrio cholera*, *Francisella tularensis*, *Yersinia enterocolitica*, or *Salmonella* serogroups may, however, cause a false-positive *Brucella* agglutination test due to immunologic cross-reactivity.

A complement fixation test and antihuman globulin test (Coombs) have been used to detect mainly *Brucella* IgG antibody and have no associated prozone effect. Recently, the techniques of radioimmunoassay and enzyme-linked immunosorbent assay have been developed to measure all individual immunoglobulins. These tests have sensitivity and specificity that are similar to the standard tube agglutination test. However, their use may be limited only to cases where a relapse or failed therapy is suspected. Polymerase chain reaction test is available, but not widely used.

Routine laboratory tests are not helpful in making the diagnosis. Anemia has been found more often with *B. melitensis* infection than with other *Brucella* species and is noted in more than one third of the pediatric patients. Most patients have either a normal white blood cell count or leukopenia with lymphocytopenia or neutropenia. The erythrocyte sedimentation rate and C-reactive protein level may or may not be raised and are only of prognostic significance if they were previously raised. The liver enzymes are elevated in about two thirds of patients, and such abnormalities may reflect the severity of hepatic involvement.

Treatment

The efficacy of antimicrobial therapy for any infection is largely judged by the rate of cure and the incidence of sequelae. The purpose of chemotherapy for brucellosis in humans is to control the illness promptly and to prevent complications and relapses. Human brucellosis continues to pose a therapeutic problem, despite the susceptibility of the organisms to several antibiotics. This has been attributed to the intracellular localization of the brucellae within the reticuloendothelial cells of the host, a site that is relatively inaccessible to antibiotics. The unpredictable relapses after treatment are almost invariably associated with inappropriate choice, dosage, and length of antimicrobial therapy, or failure of patients to take prescribed drugs. Antibiotic-resistant *Brucella* strains are rarely a cause of therapy failure. Hence, the institution of the proper combination of antibiotics for a longer duration seems warranted to improve outcome and prevent relapses.

The standard therapy for acute brucellosis has been a combination of orally administered tetracycline (40 mg/kg/day, maximum 2 g daily, in four divided doses for 6 weeks) plus streptomycin (20 mg/kg/day, maximum 1 g daily, in one dose intramuscularly for the first 2–3 weeks); treatment with orally administered rifampin (20 mg/kg/day, maximum 600 mg daily, in one or two divided doses) together with tetracycline or doxycycline for at least 6 weeks is an effective alternative regimen. Tetracycline therapy is contraindicated in children 8 years of age and younger because of the risk of permanent teeth staining. Treatment with cotrimoxazole (trimethoprim 10 mg/kg/day and sulfamethoxazole 50 mg/kg/day, maximum 480 mg of trimethoprim and 2,400 mg sulfamethoxazole daily, in one or two divided doses) is an acceptable alternative to tetracycline/doxycycline for use in children less than 9 years of age. Relapses occur in less than 10% of cases when the patient receives proper therapy early in the course of illness, and they rapidly respond to a repeat course of antimicrobial therapy.

Although the antimicrobial therapy of systemic brucellosis is well established, the best regimen for the treatment of localized lesions or complications has not been clearly determined. Certain localized lesions require surgical intervention (e.g., drainage of an abscess or excision of infected tissue) in addition to prolonged combined chemotherapy. Bone infections can be effectively treated with 6- to 12-week courses of oral rifampin and doxycycline or cotrimoxazole combined for 2–3 weeks with intramuscular streptomycin. Successful treatment of neurobrucellosis with a combination of oral rifampin and cotrimoxazole for a 3-month course has been reported in isolated cases and in small series; the administration of streptomycin for 2–3 weeks has been recommended to ensure that at least two antituberculous drugs are given until results of acid-fast bacilli cultures become available. A brief course of corticosteroids for meningoencephalitis has been advocated. *Brucella* infective endocarditis is one of the most difficult forms of localized brucellosis to manage; treatment consists of early surgical removal of the infected valve and replacement with a mechanical or bioprosthetic valve, together

with early aggressive chemotherapy with a combination of intramuscular streptomycin or intravenous gentamicin for 1 month and oral cotrimoxazole, rifampin, and doxycycline for 3 months.

In pregnant women, recognition of brucellosis and effective antimicrobial chemotherapy can prevent infection of the fetus and abortion. The most effective, least toxic antibiotics for brucellosis in pregnancy remain to be fully established. Doxycycline has been given alone to pregnant women with favorable response, and the risk of tooth staining in the fetus is considered low in comparison with tetracycline. The administration of aminoglycosides, streptomycin, or gentamicin during pregnancy may subject the fetus to the risk of ototoxicity or nephrotoxicity. Both cotrimoxazole and rifampin have been advocated, but their use is also not without risks. Rifampin and trimethoprim are potential causes of fetal malformation, and in the last week of pregnancy sulfamethoxazole may cause kernicterus in the newborn. Based on the information available to date, oral doxycycline for 6 weeks is given if *Brucella* infection occurs during the first half of pregnancy, and oral cotrimoxazole and rifampin for 6 weeks plus supplemental folic acid is given for women infected with *Brucella* during the latter half of pregnancy.

In chronic brucellosis, several courses of antimicrobial therapy may be needed before cure is achieved. When the response even to prolonged treatment is poor, a chronic focus of infection must be sought, particularly with *B. melitensis* and *B. suis* infection.

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78 Chlamydial Infections

Margaret R. Hammerschlag

Definition/Classification

Chlamydiae are obligate intracellular bacteria that have established a unique niche within the host cell. They cause a variety of diseases in animal species at virtually all phylogenic levels. The genus has been reorganized with nine species: *Chlamydia trachomatis* and *C. pneumoniae*, which primarily cause disease in humans, and several species that have been split off from *C. psittaci* (Table 78.1). *C. psittaci* is primarily an avian pathogen, and is an important zoonosis in human. The new species include *C. pecorum*, which primarily infects cattle and other ruminants – there is no description of disease in humans; *C. muridarum* (formerly the agent of mouse pneumonitis – MoPn); *C. suis* (an important pathogen of swine); *C. abortus* (causes abortion in cattle and sheep, rarely has caused abortion in humans); *C. caviae* (formerly *C. psittaci* Guinea pig conjunctivitis strain); and *C. felis* (causes epidemic keratoconjunctivitis in cats).

All chlamydia species are characterized by a unique developmental cycle with morphologically distinct infectious and reproductive forms: the elementary body (EB) and reticulate body (RB). They have a gram-negative envelope without detectable peptidoglycan, although recent genomic analysis has revealed that both *C. trachomatis* and *C. pneumoniae* encode for proteins forming a nearly complete pathway for the synthesis of peptidoglycan, including penicillin-binding proteins. Chlamydiae also share a group-specific lipopolysaccharide (LPS) antigen and utilize host adenosine triphosphate (ATP) for the synthesis of chlamydial protein.

After infection, the infectious EBs, which are 200–400 μm in diameter, attach to the host cell by a process of electrostatic binding and are taken into the cell by endocytosis that does not depend on the microtubule system. Within the host cell, the EB remains within a membrane-lined phagosome. The phagosome does not fuse with the host cell lysosome. The inclusion membrane is devoid of host cell markers, but lipid markers traffic to the inclusion, which suggests functional interaction with the Golgi apparatus. The EBs then differentiate into RBs, which undergo binary fission. After approximately 36 h, RBs differentiate into EBs. At about 48–72 h, release may occur by cytolysis or by a process of exocytosis or extrusion of the whole inclusion, with the host cell left intact. Chlamydiae also may enter a persistent state after treatment with certain cytokines such as interferon gamma, treatment with antibiotics, or restriction of certain nutrients. While in the persistent state, metabolic activity is reduced. The ability to cause prolonged, often subclinical infection is one of the major characteristics of chlamydiae.

This chapter will cover infections in humans caused by *C. trachomatis*, *C. pneumoniae*, and *C. psittaci*.

Infections due to *Chlamydia trachomatis*

Etiology

C. trachomatis is an important cause of oculogenital infections in humans worldwide. There are 15 known serotypes that vary in tissue tropism and disease presentations.

Trachoma

Epidemiology

Trachoma is the most important preventable cause of blindness in the world. It is caused primarily by the A, B, Ba, and C serotypes of *C. trachomatis*. Blinding trachoma is believed to be endemic in 56 countries, mainly in sub-Saharan Africa, some areas of the Middle East, South and Southeast Asia, and in Aboriginal population in Australia. The disease is spread from eye to eye. Flies are a frequent vector. Poverty and lack of sanitation are important factors in the spread of trachoma. As socioeconomic conditions improve, the incidence of the disease decreases substantially.

Clinical Presentation/Pathology

Trachoma begins as a follicular conjunctivitis, usually in early childhood, often with copious purulent discharge. Active trachoma is seen predominantly in young children, becoming less frequent and shorter in duration with increasing age. Conjunctival scarring increases with age,

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_78,

Table 78.1
Classification of the genus *Chlamydia*

Species	Host(s)	Major diseases
Chlamydia trachomatis	Humans	Trachoma, urethritis, pelvic inflammatory disease, neonatal conjunctivitis and pneumonia, lymphogranuloma venereum
C. suis	Pigs	Gastrointestinal disease
C. muridarum	Mice	Pneumonia
C. pneumoniae	Humans	Pneumonia, bronchitis, exacerbations of asthma, asymptomatic infection
	Horse	
	Koalas	
	Bandicoots	
	Amphibians	
	Reptiles	
C. psittaci	Birds	Gastrointestinal disease
	Humans	Pneumonia (zoonosis)
C. abortus	Cattle	Abortion
	Sheep	
	Humans	Abortion (rare zoonosis)
C. pecorum	Cattle	Pneumonia, gastrointestinal disease, genital infections, conjunctivitis
	Sheep	
	Koalas	
C. felis	Cats	Keratoconjunctivitis
C. caviae	Guinea pigs	Conjunctivitis, genital Infections

not becoming evident until the second or third decade of life. Conjunctival scarring results in entropion, with the eyelid turning inward so that the lashes abrade the cornea, leading to corneal ulceration secondary to the constant trauma, eventually resulting in blindness. Bacterial superinfection may also contribute to scarring. The World Health Organization (WHO) suggests that at least two of the following four criteria must be present for a diagnosis of trachoma: (1) lymphoid follicles on the upper tarsal conjunctivae, (2) typical conjunctival scarring, (3) vascular pannus, and (4) limbal follicles.

Diagnosis

The diagnosis of trachoma is primarily clinical and can be confirmed by culture or NAATs for *C. trachomatis* performed during the active stage of disease. Serologic tests are not helpful clinically because of the long duration of the disease and the high seroprevalence in endemic populations.

Treatment/Prevention

The WHO currently recommends single-dose azithromycin (20 mg/kg, maximum 1 g) for the treatment of trachoma in children. Oral azithromycin is superior to treatment with topical antibiotics which require multiple dosing. Several studies conducted in trachoma endemic areas in several African countries have demonstrated that mass treatment with a single dose of azithromycin to all the residents of a village dramatically reduced the prevalence and intensity of infection. This effect continued for 2 years after treatment, probably by interrupting the transmission of ocular *C. trachomatis* infection.

Genital *Chlamydia trachomatis* Infections

Epidemiology

Genital chlamydial infections are caused by *C. trachomatis* serotypes D, E, F, G, H, I, J, and K. There are an estimated three million new cases of chlamydial sexually transmitted infections each year in the USA. In 2007, the overall rate of chlamydial infections in the USA among women (544.8 cases per 100,000) was almost three times the rate among men (190.4 cases per 100,000) (*Fig. 78.1*). Girls 15–19 years of age, had the highest rates of infection (3004.7 per 100,000) which is almost five times higher than in males in the same age group (615.0 per 100,000) (*Fig. 78.1*). This discrepancy is thought to be due in part to more extensive screening of women compared to men. However, with the introduction of noninvasive testing using urine, men are being tested more frequently. From 2003 through 2007, the rate of chlamydial infection in men increased by 43%.

Clinical Manifestations

Up to 75% of women with *C. trachomatis* cervical infection are asymptomatic. *C. trachomatis* can cause urethritis (acute urethral syndrome), epididymitis, cervicitis, salpingitis, proctitis, and pelvic inflammatory disease. The symptoms of chlamydial genital tract infections in men and women are less acute than those of gonorrhea, consisting of a discharge that is usually mucoid rather than purulent.

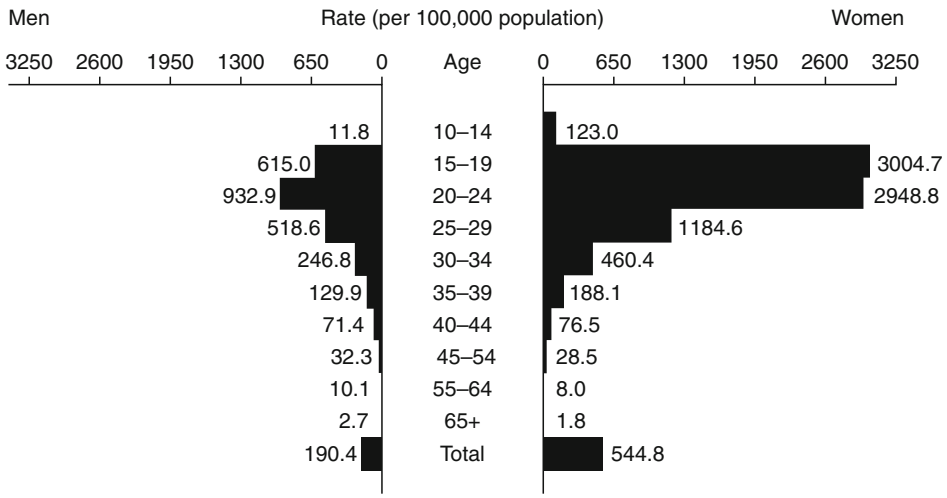

Figure 78.1
***Chlamydia trachomatis* – Age- and sex-specific rates: USA, 2007 (Reproduced from Centers for Disease Control and Prevention (2008) Sexually transmitted disease surveillance, 2007. U.S. Department of Health and Human Services, Atlanta, GA; December 2008) http://www.cdc.gov/std/pubs/**

In men, *C. trachomatis* can cause urethritis, proctitis, and epididymitis. Asymptomatic urethral infection is frequent in sexually active men. Autoinoculation from the genital tract to the eyes can lead to concomitant inclusion conjunctivitis.

Diagnosis

Diagnosis of genital chlamydial infection can be accomplished by isolation of the organism in tissue culture or by detection by a nucleic acid amplification test (NAATs). Care should be taken to obtain epithelial cells, not only discharge. *C. trachomatis* can be cultured in cycloheximide-treated HeLa, McCoy, and HEp-2 cells. Chlamydia culture has been further defined by the Centers for Disease Control and Prevention (CDC) as isolation of the organism in tissue culture and as confirmation of the characteristic intracytoplasmic inclusions by staining with *C. trachomatis* species–specific fluorescein-conjugated monoclonal antibody.

NAATs are now the standard for diagnosis of *C. trachomatis* infections in adults and adolescents. These tests have high sensitivity, 10–20% greater than culture, while retaining high specificity. There are currently three Food and Drug Administration (FDA)-approved, commercially available NAATs for detection of *C. trachomatis*: polymerase chain reaction (PCR; Amplicor Chlamydia test, Roche Molecular Diagnostics, Nutley, NJ), strand displacement amplification (SDA; ProbeTec, BD Diagnostic Systems, Sparks, MD), and transcription-mediated amplification (TMA; Amp CT, Gen-Probe, San Diego, CA). PCR and SDA are DNA amplification tests that use primers that target gene sequences on the cryptogenic *C. trachomatis* plasmid that are present at approximately ten copies in each infected cell. TMA is a ribosomal RNA amplification assay. All three assays are also available as co-amplification tests for simultaneously detecting *C. trachomatis* and *Neisseria gonorrhoeae*. There are several new NAATs that are undergoing clinical trials, all using a real-time PCR platform. The currently available commercial NAATs are FDA approved for cervical swabs from adolescent and adult women, urethral swabs from adolescent and adult men, and urine from adolescent and adult men and women. TMA and SDA have also been approved for use with vaginal swabs in adolescents and adults. The vaginal swab is now the specimen of choice in females, it is better than urine equivalent to endocervical swabs, and can be self-collected. Use of urine and vaginal swabs avoids the necessity for a urethra swab or clinical pelvic examination and may greatly facilitate screening in certain populations, especially adolescents. NAATs are currently not approved for use with extragential specimens. Several recent studies suggest that NAATs are sensitive and specific for detection of *C. trachomatis* from rectal specimens in adults.

Treatment

The first line treatment regimens recommended by the CDC for uncomplicated *C. trachomatis* genital infection in men and nonpregnant women are azithromycin (1 g orally PO as a single dose) or doxycycline (100 mg PO bid for 7 days). Alternative regimens are erythromycin base (500 mg PO qid for 7 days), erythromycin ethylsuccinate (800 mg PO qid for 7 days), ofloxacin (300 mg PO bid for 7 days), and levofloxacin (500 mg PO once daily for 7 days). The high erythromycin dosages may not be well tolerated. Doxycycline and ofloxacin or levofloxacin are contraindicated in pregnant women; quinolones are contraindicated in persons younger than 18 years of age. However, use of ofloxacin and levofloxacin offer no advantages over doxycycline. For pregnant women, the recommended treatment regimen is azithromycin (1 g PO in a single dose) or amoxicillin (500 mg PO tid for 7 days). Alternative regimens are erythromycin base (250 mg PO qid for 14 days), erythromycin ethylsuccinate (800 mg PO qid for 7 days or 400 mg PO qid for 14 days).

Prognosis

Complications of genital chlamydial infections in women include perihepatitis (Fitz-Hugh-Curtis syndrome) and salpingitis. Of women with untreated chlamydial infection who develop pelvic inflammatory disease, up to 40% will have significant sequelae; approximately 17% will suffer from chronic pelvic pain, approximately 17% will become infertile, and approximately 9% will have an ectopic (tubal) pregnancy. Adolescent girls may be at higher risk for developing complications, especially salpingitis, than older women. Salpingitis in adolescent girls is also more likely to lead to tubal scarring, subsequent obstruction with secondary infertility, and increased risk for ectopic pregnancy. Women with *C. trachomatis* infection have a three- to fivefold increased risk for acquiring HIV infection.

Prevention

Timely treatment of sex partners is essential for decreasing risk for reinfection. Sex partners should be evaluated and treated if they had sexual contact during the 60 days preceding onset of symptoms in the patient. The most recent sex partner should be treated even if the last sexual contact was >60 days. Patients and their sex partners should abstain from sexual intercourse until 7 days after a single-dose azithromycin or after completion of a 7-day regimen. Annual routine screening for *C. trachomatis* is recommended for all sexually active adolescents and females 20–25 years of age, and older women with risk factors such as new or multiple partners or inconsistent use of barrier contraceptives. Sexual risk assessment may indicate more frequent screening of some women, especially adolescents.

C. trachomatis Infection in Infants

Epidemiology

Approximately 50% of neonates born to pregnant women with untreated chlamydial infection will acquire *C. trachomatis* infection. Chlamydial genital infection has been reported in 5–30% of pregnant women. The infant may become infected at one or more sites, including the conjunctivae, nasopharynx, rectum, and vagina. Transmission is rare following cesarean section with intact membranes. The introduction of systematic prenatal screening for *C. trachomatis* infection and treatment of pregnant women has resulted in a dramatic decrease in the incidence of neonatal chlamydial infection in the USA. However, in countries where prenatal screening is not done, such as the Netherlands, *C. trachomatis* remains an important cause of neonatal infection, accounting for over 60% of cases of neonatal conjunctivitis.

Clinical Manifestations

Approximately 30–50% of infants born to mothers with active, untreated, chlamydial infection develop clinical conjunctivitis. Symptoms usually develop 5–14 days after delivery, or earlier with prolonged rupture of membranes. The presentation is extremely variable and ranges from mild conjunctival injection with scant mucoid discharge to severe conjunctivitis with copious purulent discharge, chemosis, and pseudomembrane formation. The conjunctiva may be very friable and may bleed when stroked with a swab. Chlamydial conjunctivitis must be differentiated from gonococcal ophthalmia, which is sight threatening. At least 50% of infants with chlamydial conjunctivitis also have nasopharyngeal infection.

Pneumonia due to *C. trachomatis* may develop in 10–20% of infants born to women with active, untreated chlamydial infection. Only about 25% of infants with nasopharyngeal chlamydial infection develop pneumonia. *C. trachomatis* pneumonia of infancy has a very

characteristic presentation. Onset is usually from 1 to 3 months of age and is often insidious with persistent cough, tachypnea, and absence of fever. Auscultation reveals rales; wheezing is uncommon. The absence of fever and wheezing helps to distinguish *C. trachomatis* pneumonia from respiratory syncytial virus pneumonia. A distinctive laboratory finding is the presence of peripheral eosinophilia (>400 cells/mm^3). The most consistent finding on chest radiograph is hyperinflation accompanied by minimal interstitial or alveolar infiltrates.

Infants born to mothers with *C. trachomatis* may develop infection in the rectum or vagina. Although infection in these sites appears to be totally asymptomatic, it may cause confusion if identified at a later date. Perinatally acquired rectal, vaginal, and nasopharyngeal infections may persist for ≥3 years. *C. pneumoniae* can also be confused with *C. trachomatis* infection in nasopharyngeal cultures if a genus-specific monoclonal antibody is used for culture confirmation.

Diagnosis

Definitive diagnosis of *C. trachomatis* infection in infants is isolation by culture in specimens obtained from the conjunctiva or nasopharynx. Limited data suggest that NAATs may be equivalent to culture for detection of *C. trachomatis* in the conjunctiva of infants with conjunctivitis, but none of the currently available assays are approved for this indication.

Treatment

The recommended treatment regimen for *C. trachomatis* conjunctivitis or pneumonia in infants is erythromycin (base or ethylsuccinate, 50 mg/kg/day divided qid PO for 14 days). The rationale for using oral therapy for conjunctivitis is that 50% or more of these infants have concomitant nasopharyngeal infection or disease at other sites, and studies have demonstrated that topical therapy with sulfonamide drops and erythromycin ointment is not effective. The failure rate with oral erythromycin remains 10–20%, and some infants require a second course of treatment. The results of one small study suggest that a short course of azithromycin (20 mg/kg/day once daily PO for 3 days) was as effective as 14 days of erythromycin. Mothers (and their sexual contacts) of infants with *C. trachomatis* infections should be empirically treated for genital infection. An association between treatment with oral erythromycin and infantile hypertrophic pyloric stenosis has been reported in infants <6 weeks of age who were given the drug for prophylaxis after nursery exposure to pertussis.

Prevention

The most effective method of controlling perinatal chlamydial infection is screening and treatment of pregnant women. Neonatal ocular prophylaxis with topical erythromycin or tetracycline ointment, or silver nitrate, does not prevent chlamydial ophthalmia or nasopharyngeal colonization with *C. trachomatis* or chlamydial pneumonia.

Lymphogranuloma Venerum

Etiology

LGV is a systemic sexually transmitted disease caused by the L_1, L_2, and L_3 serotypes of *C. trachomatis*. Unlike the serotyopes that cause oculogenital infections, LGV strains have a predilection for lymphoid tissue. About 20 cases of LGV have been reported in children, and <1,000 cases are reported in adults in the USA annually. Recently there has been a resurgence of LGV infections, due mostly to L_2 strains, among men who have sex with men in Europe and the USA, many of these individuals were also infected with HIV.

Clinical Manifestations

The first stage of LGV is characterized by the appearance of the primary lesion, a painless, usually transient papule on the genitals. The second stage is characterized by usually unilaterally femoral or inguinal lymphadenitis with enlarging, painful buboes. The nodes may break down and drain, especially in males. In females, the vulvar lymph drains to the retroperitoneal nodes, inquinal buboes are infrequent. Fever, myalgia, and headache are common. In the tertiary stage, a genitoanorectal syndrome occurs with rectovaginal fistulas, rectal strictures, urethral destruction, and lymphedema. Among men who have sex with men, especially if they are HIV positive, rectal infection with LGV can produce a severe, acute proctocolitis, which can be confused with inflammatory bowel disease or malignancy.

Diagnosis

LGV can be diagnosed by culture of *C. trachomatis* or NAAT from a specimen aspirated from a bubo or by

serologic testing. However, NAATs will not differentiate LGV strains from the other oculogenital serotypes. Most patients with LGV will have complement-fixing antibody titers of >16.

Differential Diagnosis

Chancroid and herpes simplex virus can be distinguished clinically from LGV by the concurrent presence of painful genital ulcers. Syphilis can be differentiated by serologic tests. However, coinfections can occur.

Treatment

Doxycycline (100 mg PO bid for 21 days) is the recommended treatment. The alternative regimen is erythromycin base (500 mg PO qid for 21 days). Azithromycin (1 g PO once weekly for 3 weeks) may also be effective but clinical data are lacking. Sex partners of patients with LGV should be treated if they have had sexual contact with the patient during the 30 days preceding the onset of symptoms.

Infections due to *C. pneumoniae*

Etiology

The first isolates of *C. pneumoniae* were obtained serendipitously during trachoma studies in the 1960s (). On the basis of inclusion morphology and staining characteristics in cell culture, *C. pneumoniae* initially was considered a *C. psittaci* strain. Subsequent analysis, however, has demonstrated that this organism is distinct from both *C. psittaci* and *C. trachomatis.* Sequencing has revealed that *C. pneumoniae* differs significantly from *C. trachomatis* in several areas. *C. pneumoniae* encodes for 21 polymorphic membrane proteins (PMPs) versus 9 in *C. trachomatis.* PMPs may be surface exposed in *C. pneumoniae.* Restriction endonuclease pattern analysis, nucleic acid hybridization studies, amplified fragment length polymorphism and sequencing analysis suggest a high degree of genetic relatedness (>95%) among the *C. pneumoniae* isolates examined thus far and less than 10% homology with either *C. trachomatis* or *C. psittaci.* At this point, we do not have a strain typing system for *C. pneumoniae. C. pneumoniae* has also been isolated from nonhuman species, including horse, Australian marsupials (koalas, bandicoots), reptiles, and amphibians, where it is frequently asymptomatic but can cause respiratory infection. The animal isolates were more diverse than isolates of human origin which appear to be essentially clonal. Additional data from Australia suggests that at least two separate animal-to-human cross species transfer events may have occurred during the evolution of this organism.

Epidemiology

Respiratory infection with *C. pneumoniae* affects individuals of all ages. The proportion of community-acquired pneumonias associated with *C. pneumoniae* infection is 2–19% varying with geographic location, the age group examined, and the diagnostic methods used. Several studies of the role of *C. pneumoniae* in lower respiratory tract infection in pediatric populations have found evidence of infection from 0 to more than 18%, depending on the population and methods used. Most of these studies have relied entirely on serology for diagnosis. *C. pneumoniae* may also be responsible for 10–20% of episodes of acute chest syndrome in children with sickle cell disease, 10% of episodes of bronchitis, and 5–10% episodes of pharyngitis in children. Transmission probably occurs from person to person through respiratory droplets. Spread of the infection can occur among members in the same household or individuals in enclosed populations, such as military recruits, and in nursing homes.

Clinical Manifestations

Respiratory infections caused by *C. pneumoniae* cannot be readily differentiated from those caused by other respiratory pathogens, especially *Mycoplasma pneumoniae.* Pneumonia usually presents as a classic atypical (or nonbacterial) pneumonia characterized by mild to moderate constitutional symptoms including fever, malaise, headache, cough, and frequently pharyngitis. However, severe pneumonia with pleural effusions and empyema has been described. *C. pneumoniae* can also serve as an infectious trigger for asthma and has been isolated from middle ear aspirates of children with acute otitis media, but is usually associated with bacterial otitis media. Asymptomatic respiratory infection has been documented in 2–5% of adults and children and may persist for a year or more.

Diagnosis

It is not possible to differentiate *C. pneumoniae* from other causes of atypical pneumonia on the basis of clinical

findings. Auscultation reveals the presence of rales and often wheezing. The chest radiograph often appears worse than the patient's clinical status would indicate and may show mild, diffuse involvement or lobar infiltrates with small pleural effusions. The complete blood count may be elevated with a left shift but is usually unremarkable.

Specific diagnosis of *C. pneumoniae* infection is based on isolation of the organism in tissue culture. *C. pneumoniae* grows best in cycloheximide-treated HEp-2 and HL cells. The optimum site for culture is the posterior nasopharynx; the specimen is collected with wire-shafted swabs in the same manner as that used for *C. trachomatis*. The organism can be isolated from sputum, throat cultures, bronchoalveolar lavage fluid, and pleural fluid, but few laboratories perform such cultures because of technical difficulties. Polymerase chain reaction (PCR) testing is the most promising technology in the development of a rapid, nonculture method for detection of *C. pneumoniae*. However, no PCR assay is commercially available or has FDA approval and no PCR is standardized or has been extensively validated compared with culture for detection of *C. pneumoniae* in respiratory specimens from adults or children.

Serology is of limited utility for the diagnosis of *C. pneumoniae* infection, especially in children. Studies of *C. pneumoniae* infection in children with pneumonia and asthma show that over 50% of children with culture-documented infection have no detectable antibody using the microimmunofluorescence (MIF) assay. Acute infection, using the MIF test, has been defined as a fourfold increase in immunoglobulin G (IgG) titer or an IgM titer $\geq$16. The presence of a single elevated IgG titer $\geq$516 has been used for diagnosis of acute or chronic infection, but this has never been validated compared to culture an/or PCR and studies have shown many discrepant results. Neither an elevated IgA titer nor any other serologic marker is a valid indicator of persistent or chronic infection. The CDC has not recommended the use of any enzyme-linked immune assay for detection of antibody to *C. pneumoniae* because there is concern about the inconsistent correlation of these results with culture results. Currently there are no MIF or EIA kits that have FDA approval for serologic diagnosis of *C. pneumoniae* infection.

Treatment

The optimum dose and duration of antimicrobial therapy for *C. pneumoniae* infections remain uncertain. As most published treatment studies have used serology only for diagnosis, microbiologic efficacy could not be assessed. Recrudescent symptoms and persistent positive cultures have been described following 2 weeks of erythromycin and 30 days of tetracycline or doxycycline. Tetracyclines, erythromycin, azithromycin, clarithromycin, and quinolones have good in vitro activity against *C. pneumoniae*. *C. pneumoniae* is constitutively resistant to sulfonamides. The results of several treatment studies that have utilized culture have shown that erythromycin (40 mg/kg/day divided bid PO for 10 days), clarithromycin (15 mg/kg/day divided bid PO for 10 days), and azithromycin (10 mg/kg PO on day 1, then 5 mg/kg/day PO on days 2–5) are effective for eradication of *C. pneumoniae* from the nasopharynx of children with pneumonia in approximately 80% of cases. Persistence is not due to the development of resistance as MICs of the isolates obtained before and after therapy were unchanged.

Infections due to *C. psittaci*

Etiology

C. psittaci, the agent of psittacosis (also known as parrot fever and ornithosis), is primarily an avian pathogen and causes human disease infrequently. *C. psittaci* affects psittacine birds (parrots, parakeets, macaws, etc.) and nonpsittacine birds as well (ducks, turkeys); the known host range includes 130 avian species. Strains of *C. psittaci* have been analyzed by patterns of pathogenicity, inclusion morphology in tissue culture, DNA restriction endonuclease analysis, and monoclonal antibodies, which indicate that there are seven avian serovars. Two of the avian serovars, psittacine and turkey, are of major importance in the avian population of the USA. Each is associated with important host preferences and disease characteristics.

Epidemiology

From 2001 to 2008, there were 128 reported cases of psittacosis in the USA. Of these, 85% were associated with exposure to birds, including 70% following exposure to caged pet birds, which were usually psittacine birds including cockatiels, parakeets, parrots, and macaws. Chlamydiosis among caged nonpsittacine birds occurs most frequently in pigeons, doves, and mynah birds. Persons at highest risk for acquiring psittacosis include bird fanciers and owners of pet birds (43% of cases) and pet shop employees (10% of cases). There have also been large

outbreaks associated with poultry processing (turkeys, ducks). Reported cases most likely underestimate the number of actual infections due to a lack of awareness.

Inhalation of aerosols from feces, fecal dust, and nasal secretions of animals infected with *C. psittaci* is the primary route of infection. Source birds are either asymptomatic or have anorexia, ruffled feathers, lethargy, and watery green droppings. Psittacosis is uncommon in children, in part because children may be less likely to have close contact with infected birds. One high-risk activity is cleaning the cage. Several major outbreaks of psittacosis have occurred in turkey processing plants; workers exposed to turkey viscera are at the highest risk for infection.

Clinical Manifestations

Infection with *C. psittaci* in humans ranges from clinically inapparent to severe infection involving multiple organ systems as well as pneumonia. The mean incubation period is 15 days after exposure, with a range of 5–21 days. Onset of disease is usually abrupt, with fever, cough, headache, and malaise. The fever is high and often is associated with rigors and sweats. The headache can be so severe that meningitis is considered. The cough is usually nonproductive. Gastointestinal symptoms are occasionally reported. Crackles may be heard on auscultation. Chest radiographs are usually abnormal with variable infiltrates, and pleural effusions may be present. The white blood cell count is usually not elevated, but a mild leukocytosis may be present. Elevated levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin are common.

Diagnosis

The diagnosis of psittacosis can be difficult because of the varying clinical presentations. A history of exposure to birds or association with an active case are important clues, but as many as 20% of patients with psittacosis have no known contact. Person-to-person spread has been suggested but not proved. Other infections that cause pneumonia with high fever, unusually severe headache, and myalgia include, most commonly, bacterial and viral respiratory infections as well as *Coxiella burnetii* (Q fever), *Mycoplasma pneumoniae, C. pneumoniae,* tularemia, tuberculosis, fungal infections, and Legionnaires disease.

The 2010 CDC case definition of psittacosis requires a compatible clinical illness, usually with a reliable history of avian exposure with laboratory confirmation by one of the following four methods: (1) culture of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid or tissue) or blood, (2) a fourfold or greater increase in CF or MIF titer in sera collected at least 2–4 weeks apart, (3) supportive serology (e.g., *C. psittaci* IgM titer of $\geq$32 in at least one serum sample obtained at onset of symptoms), or (4) detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by PCR. A probable case: An illness characterized by fever, chills, headache, cough, and myalgia that has either (1) supportive serology (e.g., *C. psittaci* IgM titer of $\geq$32 in at least one serum sample obtained at onset of symptoms) or (2) detection of *C. psittaci* DNA in a respiratory specimen (e.g., sputum, pleural fluid or tissue) via amplification of a specific target by PCR. A confirmed case would be a patient with the above clinical presentation with either (1) culture of *C. psittaci* from respiratory specimens (e.g., sputum, pleural fluid or tissue) or blood or (2) a fourfold or greater increase in complement fixation (CF) or MIF titer in sera collected at least 2–4 weeks apart. Although MIF has shown greater specificity for *C. psittaci* than CF, cross reactions with other *Chlamydia* species and bacteria can occur. To increase the reliability of the test results, acute and convalescent phase serum specimens should be analyzed in the same laboratory at the same time. Early treatment of psittacosis with tetracycline may abrogate the antibody response.

Although *C. psittaci* will grow in the same culture systems used for isolation of *C. trachomatis* and *C. pneumoniae,* very few laboratories culture for *C. psittaci,* mainly because of the potential biohazard (Table 78.2). PCR assays for detection of *C. psittaci* have been reported in the literature, but there are no FDA approved, commercially available kits for the diagnosis of infection in humans.

Treatment

Recommended treatment regimens for psittacosis are doxycycline (100 mg PO bid) or tetracycline (500 mg PO qid) for at least 10–14 days after the fever abates. The initial treatment of severely ill patients is doxycycline hyclate (4.4 mg/kg/day divided every 12 h IV, maximum 100 mg/dose). Erythromycin (500 mg qid PO) or azithromycin (10 mg/kg PO day 1, not to exceed 500 mg, followed by 5 mg/kg PO on days 2–5, not to exceed 250 mg) are alternative drugs if tetracyclines are contraindicated (e.g., children <8 years of age and pregnant women), but may be less effective. Remission is usually evident within 48–72 h. Initial infection does not appear to be followed by long-term immunity. Reinfection

Table 78.2
Laboratories that test human specimens for *Chlamydophila psittaci*

Laboratory	Tests performed	Telephone number web site
Focus Diagnostics Inc. (Quest subsidiary), Cypress, CA	Culture, MIF (IgM, IgA, IgG)	(800) 445-4032 www.focusdx.com
Laboratory Corporation of America, Burlington, NC	Culture, MIF (IgM, IgG)	(800) 222-7566 www.labcorp.com
Specialty Laboratories, Santa Monica, CA	MIF (IgM, IgG, IgA)	(800) 421-4449 www.specialtylabs.com
ViroMed Laboratories Minnetonka, MN	Culture, MIF (IgG, IgM)	(800) 582-0077 www.viromed.com
Response and Surveillance Laboratory, Respiratory Diseases Branch, CDC Atlanta, GA[a]	MIF (requires paired sera), PCR, culture, genotyping (multiple specimen types)	(404) 639-4921

Source: National Association of State Public Health Veterinarians (NASPV) (2010) Compendium of measures to control *Chlamydophila psittaci* infections among humans (psittacosis) and pet birds (avian chlamydiosis) http://www.nasphv.org/documentsCompendiaPsittacosis.html
MIF, microimmunofluorescence; PCR, polymerase chain reaction
[a]CDC is a reference laboratory and samples must be submitted through State Health Departments

and clinical disease can develop within 2 months of treatment; only two well-documented cases of reinfection have been reported in the literature.

Prognosis

The mortality rate of untreated psittacosis is 15–20%, but is <1% with appropriate treatment. Severe illness leading to respiratory failure and fetal death has been reported among pregnant women.

Prevention

Several control measures are recommended to prevent transmission of *C. psittaci* from birds. Bird fanciers should be cognizant of the potential risk. *C. psittaci* is susceptible to most disinfectants and detergents as well as heat, but is resistant to acid and alkali. Accurate records of all bird-related transactions aid in identifying sources of infected birds and potentially exposed persons. Newly acquired birds, including birds that have been to shows, exhibitions, fairs, or other events, should be isolated for 30–45 days or tested or treated prophylactically before adding them to a group of birds. Care should be taken to prevent transfer of fecal material, feathers, food, or other materials between birdcages. Birds with signs of avian chlamydiosis (e.g., ocular or nasal discharge, watery green droppings, or low body weight) should be isolated and should neither be sold nor purchased. Their handlers should wear protective clothing and a disposable surgical cap and use a respirator with an N95 or higher efficiency rating (not a surgical mask) when handling them or cleaning their cages. Infected birds should be isolated until fully treated, which is generally 45 days.

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79 Cholera

Louise Elaine Vaz

Case

A 6-year-old refugee child is brought to the camp hospital in the early morning hours by his parents. A review of the history is significant for abundant watery diarrhea and non-bilious emesis that began the night before. An older sibling had mild gastroenteritis earlier in the week but quickly recovered. Physical exam reveals a thin boy with sunken eyes, dry mucus membranes, and 3 second skin pinch of the abdomen. He is unable to take anything by mouth and is too tired to answer questions. How should you proceed?

The patient is assessed as severely dehydrated. Rehydration is immediately started with Lactated Ringers after IV access is established and continued with oral rehydration solution when the patient is able to drink. A sample of stool is collected and sent to the nearby field laboratory for diagnosis. Due to volume of watery stool, you suspect cholera and immediately notify the health directors to begin investigation of a new outbreak.

Definition/Classification

Cholera is one of the oldest and most notorious of epidemic diseases with the hallmark of profuse, severe watery diarrhea that can result in death over a matter of hours. Despite advances in the genetics of *Vibrio cholerae*, the pathophysiology of the disease, and advent of oral rehydration therapy, cholera can still cause significant morbidity and mortality throughout the developing world, particularly in vulnerable populations.

Vibrio cholerae belong to the family Vibrionaceae which shares characteristics with the Enterobacteriaceae. The organism is classified into serogroups according to the carbohydrate determinants of its somatic O antigen of the cell surface lipopolysaccharide. Over 200 serogroups have been discovered, classified broadly as those that agglutinate in anti-sera to the O1 group antigen or those that do not. Only the O1 and O139 serogroups are currently responsible for the epidemiologic characteristics and clinical picture of cholera. Non - O1 strains may be associated with a mild gastroenteritis.

There are two biotypes of O1 cholera: Classical and El Tor. Each differs in clinical presentation and biochemical properties. The El Tor biotype causes more asymptomatic infections with 20–100 asymptomatic infections to 1 symptomatic case. This is compared to 2–5 asymptomatic cases to 1 symptomatic case of the Classical biotype. O1 El Tor and Classical biotypes can each further be serotyped as Inaba, Ogawa, or (rare) Hikojima, distinguished by different expression of the O1 subspecific antigens A, B, and C.

Epidemiology

Allusions to a cholera - like illness have been made through ancient times. In the modern era, seven cholera pandemics have been recognized since the early 1800s. The first six pandemics, from 1817 to 1923, were thought to be of the O1 Classical biotype, largely originating from the Indian subcontinent with extension to Europe and the Americas. Transmission of the disease was recognized in the sentinel work in London in 1854 by John Snow, who recognized that transmission could be blocked by stopping access to a contaminated water source. The seventh and most recent pandemic started in 1961 in Indonesia, spread to Asia, Africa, and finally to Latin America, causing explosive epidemics in Peru in 1991. This pandemic has been the longest lasting and is caused by the O1 El Tor biotype.

In 1992, a non-O1 serogroup that caused an epidemic of a cholera-like illness was identified in Madras, India. It was named the O139 Bengal serogroup. O139 is a genetic derivative of El Tor biotype, is largely confined to Asia.

In 2009, 45 countries from all over the world reported a total of 221,226 cases of cholera to the World Health Organization. Most of the 4,946 deaths were recorded in Africa, with a worldwide overall case-fatality rate of 2.24%. The actual number of cholera cases worldwide can only be estimated due to limitations in surveillance systems, underreporting, and inconsistencies in the application of case definitions. As a result, the true burden of disease due to cholera is estimated at 3–5 million cases and 100,000–120,000 deaths each year. Reminders of this deadly disease are evident in recent times, such as the

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Goma experience in 1994 where over a 6 week period, an estimated 12,000 deaths and 70,000 cases occurred in eastern Zaire (currently the Democratic Republic of the Congo) among Rwandan refugees. Epidemics in Zimbabwe in 2008 and Haiti in 2010 highlight the continued need for surveillance and early response.

Among industrialized nations, imported cases of cholera have been reported in international travelers. Sporadic cases in the USA have occurred in the Gulf Coast region, with identification of an environmental reservoir of *V. cholerae* O1 El Tor Inaba. Seasonal variation in areas of endemic infection indicates the possible role of environmental factors in triggering the epidemic process. Humans are the only known host, but *Vibrio* organisms may exist in the dormant state in aquatic environments in association with copepods or other zooplankton. Transmission occurs by the fecal-oral route with ingestion of contaminated water and food.

Microbiology and Pathogenesis

Vibrio cholerae are gram-negative, comma-shaped, motile rods that are facultatively anaerobic. Genetic material consists of two circular chromosomes. Virulence factors are located on the larger chromosome and clustered on two main areas: a "pathogenicity island" and a prophage called CTXϕ which encodes the cholera toxin. The infectious dose causing disease varies from as few as 10^2 up to 10^6 organisms, depending on the vehicle of transmission and host characteristics. Once ingested, the acid content of the stomach may serve as a natural defense mechanism against *V. cholerae* which are killed at low pH.

Organisms multiply rapidly in the alkaline environment of the proximal portion of the small intestine and colonize, but do not invade, the mucosa of the small intestine with the aid of a pilus and other adherence factors. Inflammation is minimal and the epithelium remains intact. The cholera toxin is a multimeric protein and consists of two units: A (active) and B (binding). The B portion binds to the ganglioside receptor on local enterocytes. The A unit consists of A1 and A2 subunits. A2 connects A1 to the B unit. Internalization of the A1 subunit leads to transfer of an ADP-ribose molecule to a G-protein. This results in persistent activation of the G binding protein, upregulating cyclic adenosine monophosphate production. Elevated cAMP leads to the blocked absorption of sodium and chloride by microvilli and promotes the secretion of chloride and bicarbonate by intestinal crypt cells, resulting in massive of loss of water across the osmotic gradient.

It has been observed that individuals with *Heliobacter pylori* gastritis and those taking antacids or histamine blockers are at increased risk of cholera infection. Interestingly, persons with blood group O are at a higher risk of developing severe cholera, although the exact mechanism is unknown. Younger children are particularly vulnerable in endemic areas, as older children and adults benefit from some acquired immunity. Breast-fed children are normally protected against severe disease due to less exposure to contaminated water and foods and because of protective antibodies obtained in breast milk. Lack of breast feeding in parts of the world where mothers are unable to or opt not to breast-feed may demonstrate increased rates of cholera in infants.

Clinical Manifestations

The incubation period is dependent on the infectious dose and can vary from several hours up to 5 days. Most patients with cholera are asymptomatic, and some have mild or moderate diarrhea lasting up to 1 week. Vomiting, if it occurs, is usually early on in the disease course. Fever may be seen in children but because the bacteria are noninvasive, it is usually not present. Less than 5% of infected children develop *cholera gravis*, characterized by the sudden onset of profuse, painless watery diarrhea accompanied by emesis and severe dehydration that can occur over hours.

Stools are described as "rice water" due to the color and consistency resembling the water used to wash or cook rice. Cholera stools do not contain red blood cells or leukocytes. Diarrhea is uncontrollable and voluminous and may be accompanied by abdominal cramping, presumably due to fluid distension in the bowels. Urine output may decrease or cease. Within hours, metabolic acidosis, hypovolemic shock, renal failure, altered mental status, seizures, coma, or death may occur.

Electrolyte abnormalities are common. Hypokalemia may result in paralytic ileus, leading to severe distension of the abdomen. "Cholera sicca" ("*dry cholera*") can occur as intestinal secretions remain contained in the distended small intestine and colon, with little or no diarrhea. Hypoglycemia is more common in children and may result in altered mental status or seizures. After dehydration, hypoglycemia is the second most common cause of death in pediatric patients with cholera. Metabolic acidosis can result from bicarbonate loss in the stool and is exacerbated by hypoperfusion of tissues, leading to lactic acidosis. During the rehydration phase, patients are at risk for hypocalcemia, manifest by muscle cramping and tetany.

Diagnosis

Vibrio organisms can be identified by dark-field examination or wet preparation of stool. The use of specific cholera anti-sera to block the movement of the *V. cholerae* allows confirmation of the diagnosis. Rapid tests with direct antigen detection dipstick are now available, although results should be culture confirmed. Growth of *V. cholerae* on selective media, such as thiosulfate-citrate-bile salts-sucrose agar or tellurite taurocholate gelatin agar, remains the gold standard for diagnosis and analysis of microbial drug sensitivities. If laboratory facilities are not immediately available, Cary Blair transport medium can be used to transport or store a fecal or rectal swab. Stools can also be placed on blotting paper and kept in sealed plastic bags. Molecular assays, such as PCR, are available in certain reference laboratories. Acute and convalescent titer measurements are useful in epidemiological studies.

Cholera is a World Health Organization–reportable disease, recognized by its epidemic potential. The clinical case definition for suspected cholera by the WHO is as follows:

- Acute watery diarrhea (three or more loose stools in a 24 hour period) with or without vomiting in a patient age 5 or older in an *endemic* area.
- Severe dehydration or death from acute watery diarrhea in a patient age 5 or older in a *non-endemic* area.

By WHO standards, once laboratory confirmation of a single case of cholera has occurred, it becomes unnecessary to confirm all subsequent cases. In a cholera *outbreak*, any patient who has acute, profuse watery diarrhea should be treated as a cholera case. Intermittent laboratory confirmation of cholera cases in these settings is encouraged to monitor for drug sensitivities and to confirm the end of an outbreak.

Differential Diagnosis

Mild disease is often difficult to distinguish from gastroenteritis caused by other enteric pathogens such as *rotavirus, Enterotoxigenic Escherichia coli* (ETEC), or bacterial food poisoning with *Staphylococcus aureus* or *Bacillus cereus*.

Treatment

Treatment for dehydration should not be delayed for laboratory confirmation of disease. The World Health Organization outlines steps to the treatment of a patient with suspected cholera, which include the following:

1. Assess and classify the level the patient's of dehydration.
2. Rehydrate according to algorithm (*Fig. 79.1*) with frequent monitoring.
3. Maintain hydration and replacement of fluids until diarrhea stops.
4. Administer an oral antibiotic to patients with severe dehydration.
5. Resume food intake/breast feeding as soon as possible. Give zinc supplements.

Low osmolality oral rehydration solution (ORS) is the preferred first line treatment for children who have no or mild dehydration. Newer rice-based or amylase-resistant starch versions of ORS may be available. ORS can also be used to manage patients suffering from some dehydration who are able to drink. ORS can be administered via syringes or nasogastric infusions for infants and children unable to sip from a cup. Food should be offered as soon as children are able to eat. Mothers are encouraged to continue breast feeding.

Children unable to take ORS should have fluids administered intravenously. Access is critical, and larger veins may be utilized to enable boluses. The solutions of preference include Lactated Ringers or regional variants, such as Dhaka Solution or Peru Polyelectrolyte. ORS, which contains a higher amount of potassium compared to these IV solutions, should be started as soon as the patient is able to take fluids by mouth. The use of cholera cots, constructed with a hole in the center for stool and a collecting pot underneath, to accurately measure output is recommended. Fluid administration rates must be closely monitored, particularly in infants and severely malnourished children who are at risk for pulmonary edema and cardiac overload. Signs of over-hydration include periorbital edema, tachypnea, and crackles in the lungs.

Oral antibiotics may be used to decrease the volume and duration of diarrhea and shorten the period of communicability but are reserved for children who are severely ill. Mass chemoprophylaxis in the community is generally not warranted, but selective prophylaxis may be utilized in certain scenarios. Single dose or 3-day regimens exist, and antibiotic sensitivities should guide specific management in each outbreak (*Table 79.1*). IV or IM antibiotics are not necessary. The addition of 10–30 mg of elemental zinc for 2 weeks has been shown to decrease stool output and duration of diarrhea in children.

Cholera Treatment Algorithm

The *World Health Organization* has established guidelines* for rehydration and cholera treatment which have been adapted with permission and summarized below:

1. Assess and classify level of dehydration (severe, some, no/mild)
2. Rehydrate according to algorithm below with frequent monitoring
3. Maintain hydration and replacement of fluids until diarrhea stops
4. Administer an oral antibiotic to patients with severe dehydration (table 1)
5. Resume food intake / breastfeeding as soon as possible. Give zinc supplements

Severe Dehydration >10% loss of body weight	Treatment
At least 1 of the following: **Lethargy** **Unable to drink** **Skin pinch >2sec** Plus 1 or more: No tears Very sunken eyes Very dry mucus membrane Feeble pulse	Start IVF: Reassess every 15–30 min. 30 ml/kg / 70ml/kg <1 yr old: In 1st hr / Over 5 hrs >1 yr old: In 30 min / Over 2.5 hrs Then, **reclassify dehydration** [severe, some, none] and continue treatment as noted below **Be aware of hypoglycemia **Give ORS 5 ml/kg/hr as soon as able to take po **If no IV access: ORS by NG 20 ml/kg/hr x 6 hrs.

Some Dehydration 5–10% loss of body weight	Treatment
At least 1 of the following: **Irritability / fussy** **Thirsty, wants to drink** **Skin pinch 1–2 sec** Plus 1 or more: No tears Sunken eyes Dry mucus membrane Increased pulse rate	Start ORS: If weight is known calculate volume over 4 hrs by 75 ml x weight in kg If weight not known, use chart below. Reassess every 30 min. 0–4 mo: 200–400 ml over 4 hrs 4–12 mo: 400–700 ml over 4 hrs 12–24 mo: 700–900 ml over 4 hrs 2–5 yr: 900–1400 ml over 4 hrs 5–14 yrs: 1400–2200 ml overt 4 hrs 14 and above: 2200–4000 ml over 4 hrs Then, **reclassify dehydration** and continue treatment

No dehydration	Treatment
2 of the following: **Alert, well appearing** **Tears** **Mouth Moist** **Wants to drink** **Normal skin pinch**	After rehydration achieved, maintain hydration. Resume breast feeding and regular diet as soon as tolerated. Supplement with 10-30 mg of zinc daily. In an outpatient setting most patients can drink ORS to replace stool losses. Replacement of stool output: age <2: 50–100 ml/stool episode up to 500 mL per day. age 2–10: 100–200 ml/stool episode up to 1L per day. age 10+: po ad lib up to 2L per day **Reassess the patient** for signs of dehydration at least every four hours

*Department of Child and Adolescent Health and Development. (2005) Treatment of Diarrhoea. A Manual for physicians and senior health workers. World Health Organization. http://whqlibdoc.who.int/publications/2005/9241593180.pdf Accessed on Nov 15, 2010
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*World Health Organization. 2004. First steps for managing an outbreak of acute diarrhoea. http://www.who.int/topics/cholera/publications/en/first_steps.pdf Accessed Dec 2, 2010.

Figure 79.1
Cholera Treatment Algorithm

Table 79.1
Pediatric dosages for antibiotics in cholera

Antibiotic	Single dose regimen	Multiple dose regimen	Source
Erythromycin		12.5 mg QID × 3 days. Max 1 g/day	WHO First steps (2004)
Azithromycin	20 mg/kg Max 1 g	–	Khan et al. (2002)
Ciprofloxacin[a]	20 mg/kg max 1 g	–	Saha et al. (2005)
Doxycycline[b]	4–6 mg/kg . Max 300 mg	–	Alam et al. (1990), Sack et al. (1978)
Tetracycline[b]	–	12.5 QID × 3 days, Max 2 g/day	Roy et al. (1998)

Increasing resistance to TMP-SMX and furazolidone has limited their use in practice
[a]Fluoroquinolones are generally avoided in patients younger than 18 years because of concerns about arthropathy in animal studies. The AAP states use of fluoroquinolones may be justified in children <18 years of age in special circumstances after careful assessment of the risks and benefits for the individual patient and after these benefits and risks have been explained to the parents or caregivers
[b]Doxycycline and tetracycline doses are extrapolated from adult studies. Both are generally contraindicated for children under age 8 due to staining of permanent teeth. Short courses are not thought to contribute highly to this

Prognosis

Attack rates in endemic areas are highest in children under age five who have less acquired immunity. Immunologically naïve persons of all ages are at risk in a non-endemic setting. Mortality can approach 50% if treatment is unavailable or delayed. Pregnant women and infants are at particular risk for complications. For those that survive, cholera itself is self-limiting, with resolution in approximately 1 week. Stools may remain positive for *V. cholerae* up to 1–2 weeks after diarrhea ends, although occasionally the carrier state may persist for longer. With appropriate therapy, case-fatality rates should be less than 1%

Prevention and Control

Situations with overcrowding and poor sanitation can promote and perpetuate cholera epidemics. Epidemics often occur after man-made and natural disasters, particularly in complex emergencies and refugee camps, when water and food supplies become contaminated with *V. cholerae*. Social disruption, poor infrastructure, and poor access to health care can contribute to increased mortality. Systematic reporting to local, national, and international health bodies will help to coordinate the appropriate response and limit spread to other areas.

Once an outbreak has been identified, a multitiered approach is necessary, addressing public health education, treatment facilities, and ensuring safe water supply and maintenance of latrines. Hospitalization with enteric/contact precautions is desirable for severe cases. Less severe cases can be managed in an outpatient setting with ORS. Disinfection of articles used by patients, particularly linens and diapers is important.

The use of oral cholera vaccines is considered an additional public health tool that may be used in conjunction with the recommended cholera control measures such as ensuring safe water and adequate sanitation. Three oral cholera vaccines are available: WC/rBS (Dukoral) and the two versions of the variant WC (mOrcVax and Shanchol). Only one, WC/rBS, is currently prequalified by the WHO and available to purchase by UN agencies.

WC/rBS was developed in Sweden in 1991 and consists of killed whole-cell *Vibrio cholerae* O1 with a purified recombinant B-subunit of cholera toxin. It is not licensed for children less than 2 years of age and may be used in pregnant and HIV-positive individuals. Two doses a minimum of 7 days apart, if age greater than 6, or three doses, if between ages 2–5, is needed to induce immunity within 1 week after the last dose. Clinical trials in Bangladesh, Mozambique, and Peru conferred a range of protection from 78–90% for 4–6 months among all age groups. For children aged 2–5 years, 1 booster dose is recommended every 6 months and for those older than 6 years, one booster every 2 years. Reanalysis of data from clinical trials in Bangladesh revealed considerable herd protection from WC-rBS, including protection for children too young to be vaccinated.

Variants of the WC/rBS vaccine without the recombinant B-subunit resulted from transfer of technology to Vietnam and India. Both vaccines, mOrcvax (Vietnam) and Shanchol (India) are based on serogroups O1 and O139 and are identical in terms of strains but formulated by different manufacturers.

A recent reevaluation of parenteral cholera vaccines in a Cochrane review demonstrated an overall efficacy of 48% (95% CI: 35–58%, with protection for two years). Other cholera vaccines remain under development, with the goal to offer lifelong immunity in a single dose.

Useful Web Resources

World Health Organization: http://www.who.int/cholera/en/index.html

Centers for Disease Control: http://www.cdc.gov/cholera/

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80 Diphtheria

Mohammad Al-Shaalan

Diphtheria is a respiratory illness with systemic manifestations that are mediated by exotoxin. In addition, skin infection occurs in some patients. After introduction of diphtheria toxoid vaccine, the incidence of the disease has decreased dramatically. In 2008, only 7,088 cases are reported globally (*Fig. 80.1*). The decrement has been impressive over the last two decades; however there was a small outburst in the years of 1994 and 1995 due the outbreak that occurred in previous USSR where 60,000–80,000 cases were reported mostly among adults who were not or incompletely vaccinated. A significant number of cases are still reported from India, Sudan, and some other developing countries. The vaccine is effective but needs to be enforced and the immunity maintained by adhering to booster vaccination especially in adolescent and adults.

Organism

Diphtheria is caused by *Corynebacterium diphtheriae* – a Gram positive, facultative aerobic, nonmotile, and nonspore-forming bacillus. It can be grown in ordinary media like blood or chocolate agar; however selective media are required to distinguish it from other bacteria. Three biotypes of diphtheria can be identified in tellurite medium: gravis, intermedius, and mitis. Gravis biotype appears as semirough grayish colonies. Intermedius biotype appears as small smooth grayish colonies with black center. Mitis biotype appears as small smooth grayish colonies. Toxigenic strains can be smooth or rough and can be of any biotype, however intermedius is found more often to be toxigenic.

Pathogenesis

Infection is acquired by inhalation of infected droplets that are produced by an infected person or asymptomatic carrier. In addition inoculation of skin or other mucus membranes like nose, conjunctivae, and genitalia by droplets or with direct contact may result in localized disease. Once the organism has reached the mucus membrane of the pharynx and tonsils, it elicits an inflammatory response and causes necrosis. This results initially in small yellowish areas of exudates over the tonsils. These lesions coalesce to form a pseudomembrane that is formed by debris and inflammatory exudates. Necrosis of the underlying mucosa results in grayish discoloration of the membrane. The membrane is usually well demarcated and mainly covers the tonsils. In some instances it extends to uvula, pharynx, larynx, and trachea. It does not extend anteriorly.

Clinical Features

Tonsillopharyngeal Diphtheria

Incubation period of the disease is 2–7 days. The onset is usually insidious with illness progressing from mild sore throat and low grade fever to signs of increasing respiratory difficulty. Lymphadenopathy is usually mild and there is no tenderness. Throat examination will reveal grayish membrane that is well demarcated and usually extends beyond the tonsils. It bleeds upon trial of scraping. If the membrane involves the larynx, the patient will have inspiratory stridor and difficulty in breathing. Occasionally the disease may take a hyperacute course, with high fever, toxicity, cardiopulmonary collapse, and encephalopathy.

Nasal Diphtheria

Five to ten percent of diphtheria will present with nasal disease. It is usually mild and lacks systemic complication of myocarditis and neuropathy. The presentation starts with nasal mucoid discharge that proceeds to be bloody due to formation of necrotic tissue. The membrane can be visualized in the nostrils and there may be evidence of irritation on the upper lip.

Laryngeal Diphtheria

It is difficult to diagnose laryngeal diphtheria unless laryngoscopy or bronchoscopy is done to evaluate the upper airways anatomy. Systemic symptoms are minimal and the main presentation is inspiratory stridor that may progress to respiratory obstruction. As with nasal diphtheria cardiac and nervous systems complications are unusual.

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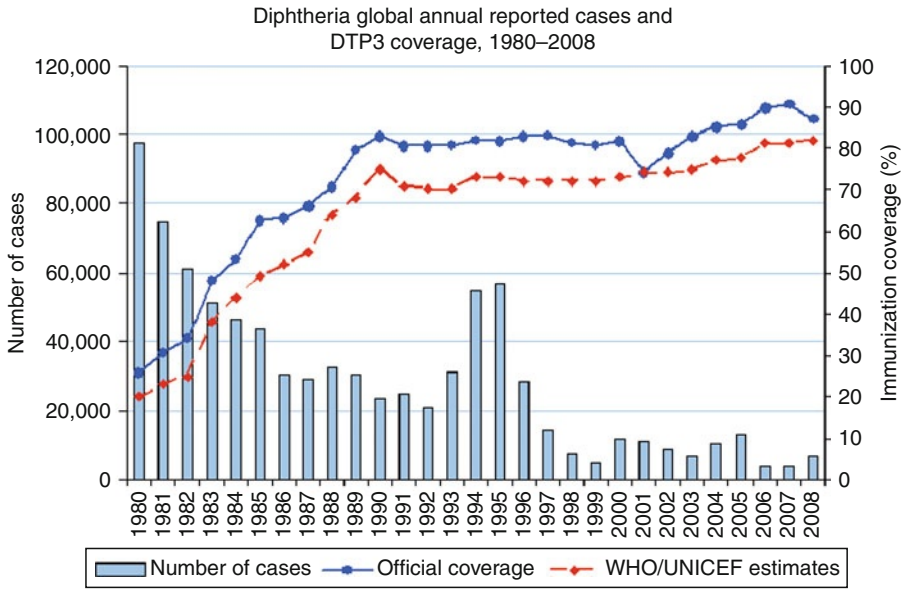

Figure 80.1
Global annual reported cases of diphtheria

Complications

Diphtheria complications are mediated by exotoxin that is produced by toxigenic strains of *C. diphtheria*. The toxin can cause damage to any organ; however CNS and heart are the most commonly involved.

Cardiac Complications

Diphtheria toxin causes myocardial degeneration with minimal inflammatory response. This degeneration also involves the conducting system. In addition to myocarditis, the affected patient usually has variable degrees of heart block and dysrhythmia. Actually the main cause of heart failure in these patients is usually dysrhythmias. Most of the toxin effects on the heart occur in the second week of illness but it can occur as early as few days and as late as 6 weeks. Early treatment will prevent or decrease the severity of heart involvement.

CNS Complications

CNS complications usually appear 4–7 weeks later. Diphtheria toxin has increased affinity to anterior horn neurons, cranial nerves neurons, as well as dorsal ganglion neurons. The most common CNS complication is bilateral motor ascending neuropathy with gradual flaccid paralysis and loss of deep tendon reflexes. Palatal and diaphragm palsies are the most common.

Cranial nerve palsies may occur. Brain stem involvement may occur with resultant blood pressure instability. There is usually no sensory impairment. Recovery is complete without any residual impairment.

Other Organ Complications

Hepatitis, nephritis, and gastritis are rare complications that have been reported in association with diphtheria. Adrenal hemorrhage also may occur with resultant adrenal failure. Hemolytic uremic syndrome has also been reported.

Diagnosis and Differential Diagnosis

Diphtheria mimics most of the upper respiratory infections like streptococcal pharyngitis, infectious mononucleosis, adenovirus infection, and Vincent's angina with faucial membrane. However the membrane in diphtheria usually extends beyond the tonsils whereas it does not in the others.

Laryngeal diphtheria has similar presentation to that of foreign body aspiration, peripharyngeal or retropharyngeal abscess, and laryngeal hemangiomas or papillomas.

In suspected cases of diphtheria, laboratory should be notified and both throat swab and nasopharyngeal aspirate be submitted. In the laboratory, specimens should be screened initially with Gram and methylene blue stains. At the same time blood agar, Loeffler's serum medium, and tellurite medium should be inoculated. Blood agar is used in order to diagnose any other or coexisting infection like streptococcal pharyngitis. Loeffler's medium is to isolate the organism in pure culture so it can be used for toxigenic evaluation or subculturing tellurite medium in case that initial inoculation was not informative. On tellurite medium *C. diphtheriae* has a characteristic appearance of black colonies surrounded by a brownish halo.

Schick test is an intradermal skin test that is used to determine the immunity status of the patient. Intradermal injection of diphtheria toxin will cause induration and erythema of >10 mm in patients who are not immune. Immune patients will not have a reaction as the toxin is neutralized with antitoxin. Some patients may show reaction secondary to hypersensitivity to the toxin or its constituents. To avoid such problem a control test with toxoid is injected into the other arm. In immune patients who are hypersensitive, a reaction will appear to both toxin and toxoid; however, it will disappear in 48–72 h. Nonimmune patients will have persistence of reaction to the toxin for more than 5 days and disappearance of reaction to toxoid in less than 5 days. Schick test is not widely used and its application in clinical practice is limited.

Treatment

Suspected cases of diphtheria should be given antitoxin and started on penicillin therapy. Antitoxin is equine derivative and therefore a test dose should be given. If there is any evidence of reaction then desensitization should be started. Penicillin can be given as procaine penicillin 25,000–50,000 units/kg/day for 14 days. Erythromycin is a good alternative for those who are allergic to penicillin.

Prevention

Isolation

Patients should be isolated for the whole duration of therapy. Two cultures from both nose and throat should be obtained 24 h apart after completion of therapy. If they are negative then isolation can be discontinued. If positive repeat the course of therapy.

Contacts

Close contacts should be cultured and given antibiotics prophylaxis with either erythromycin 40–50 mg/kg/day in four divided doses for 7 days or benzathine penicillin 600,000 units IM if the contact <30 kg in weight or 1.2 mega units IM if >30 kg in weight. Immunization status should be updated. A booster dose should be given to all contacts that have no diphtheria booster within 5 years.

Asymptomatic Carrier

Carrier patients should be treated with erythromycin 40 mg/kg/day in four divided doses for 7 days or single dose of benzathine penicillin 600,000 units IM for those below 30 kg in their weight or 1.2 mega units IM. Two throat cultures obtained 24 h apart should be obtained 2 weeks after completion of therapy. If still positive, therapy course needs to be repeated. Immunization should be updated. Those with uncertain history of immunization or who received less than four doses should be given a booster dose. In addition a booster should be given if the last vaccine dose was given 1 year or more prior to the illness.

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81 *Haemophilus influenzae* Infections

Mohammad Al-Shaalan

Haemophilus influenzae is a common cause of a wide variety of childhood diseases that cause significant morbidity and mortality. It is the serotype b that is known to be more invasive and cause most of severe diseases. Before introduction of the conjugate HIB vaccine, the incidence of serious disease due HIB is 50–300/100,000 children below 5 years of age. *H. influenzae* type b (HIB) is the most common causative organism of bacterial meningitis accounting for 50–70% childhood meningitis. Ninety-one percent of HIB meningitis occurred in children less than 2 years of age. Many studies from Saudi Arabia have shown HIB to be the cause of 50–60% of childhood meningitis. In 2000, HIB was estimated to cause around eight million serious illnesses worldwide with an estimated 371,000 deaths. Conjugated HIB vaccine that is effective in early infancy has been introduced into the national vaccination program in more than 150 countries. It has resulted in significant reduction in the disease burden in these countries (*Fig. 81.1*).

In many of the developing countries this vaccine has not yet been introduced probably due to cost limitations or the misconception that HIB is not a major cause of disease in these countries. In Asia there are many studies that showed HIB to be a significant cause of serious illnesses (*Table 81.1*). Studies from some developing countries showed that infection due to *H. influenzae*, mainly type b, is far more common than developed countries. In Papua New Guinea, 11% of children 6–24 months of age were colonized with HIB. This study was confirmed by other studies from Gambia. In these two countries, *H. influenzae* combined with *Streptococcus pneumoniae* were the commonest cause of bacterial acute lower respiratory intact infections, which are the commonest cause of mortality in children <5 years of age.

Microbiology

H. influenzae is a Gram negative, facultative aerobic, nonmotile, and pleomorphic bacilli and coccobacilli that grew better in aerobic environment with CO2 enrichment. *H. influenzae* requires hematin (X) and NAD (V) factors for growth. These factors are available in chocolate agar media because the hemolyzed RBC in such a medium release hematin and NAD. There are encapsulated and nonencapsulated strains of *H. influenzae.* Encapsulated strains are grouped into six serotypes (A–F) according to their capsular determinants.

Pathogenesis

HIB is the most invasive among all *H. influenzae* strains. Only 3% of children are colonized with HIB, however this number increases to 10–15% in developing countries. HIB gains entry into the blood through translocation across the nasopharyngeal epithelium. This translocation is mediated mainly by adherence of the organism to a previously damaged or breached epithelium. The adherent factors are thought to be fimbriae and the adherence is made easy by releasing IgA protease that inhibits the action of the SlgA. Once translocation occurred, HIB gains access to the blood where it is protected from immune reaction by its capsule. In the blood, the organism multiplicates to a critical level of 10^5 colonies/mL that is required for the organism to cause disease and invade CNS and other tissues.

The entry into the CNS occurs through choroidal plexus, although it may occur through the dural traversing veins. Once in subarachnoid space, the organism elicits a cascade of inflammatory response that damage the BBB (see Chap. 69, "Meningitis").

Clinical Features

H. influenzae Type B (HIB)

Bacteremia

Isolated bacteremia can be caused by HIB. It has decreased significantly after the introduction of the vaccine. Patients usually present with high fever without any localizing signs. In patients with HIB bacteremia, meningitis should always be ruled out. Haemophilus bacteremia is more

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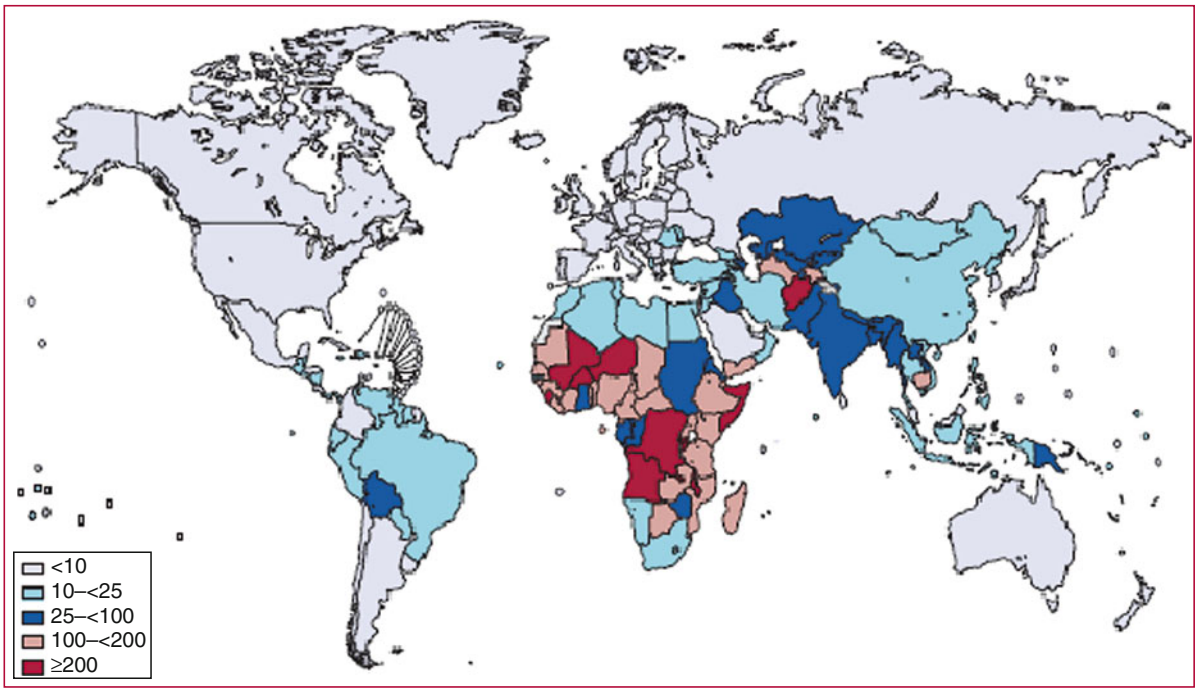

Figure 81.1
HIB mortality rate. HIB deaths in children aged 1–59 months per 100,000 children (HIV negative HIB deaths only) The boundaries shown and the designation used on this map do not imply the expression of any opinion by WHO concerning the legal status of any country, territory, city, or area, or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement

Table 81.1
Incidence of invasive HIB disease in children aged less than 5 years, by country

Country	Treatment setting	Study design	Incidence (per 100,000)	Reference
Hong Kong	Urban	Retrospective	2.7	Lau (1995)
Japan	Regional	Retrospective	4.3–56.8	Sakata (2007)
South Korea	Regional	Prospective	6.8	Kim (2004)
New Caledonia	Rural	Retrospective	54.6	Anglaret (1993)
Philippines	Regional	Population based	95	Limcangco (2000)
Saudi Arabia	Regional	Prospective, population based	17	Al-Mazrou (2004)
Saudi Arabia	Urban, tertiary hospital	Retrospective	40	Almuneef (2001)
Singapore	Urban, single center	Retrospective	4.4	Thoon (2007)
Taiwan	Regional	Population based	5.6 in 1997, 3.2 in 2000	Shao (2004)
Thailand	Regional	Prospective	3.8	Perks-Ngarm (2004)
Vietnam	Regional	Population based	12	Anh (2006)
Indonesia	Rural	Prospective	67–158 (meningitis), 1,561 (pneumonia)	Gessner (2005)

Source: Michael B (2009) Burden of invasive disease caused by *Haemophilus influenzae* type b in Asia. Jpn J infect Dis 62:87–92

likely to be associated with invasive diseases than that of *S. pneumoniae*. Therefore patients with Haemophilus bacteremia should be hospitalized and investigated thoroughly for focal infections. Parenteral therapy with appropriate antibiotic is indicated.

Meningitis

HIB is the commonest cause of meningitis in children 3 months to 5 years of age in developing countries. The introduction of HIB conjugate vaccine has resulted in dramatic decrease in the incidence of this illness, however this vaccine is not yet universal in most of the developing countries. HIB meningitis results in 5% mortality rate and around 20% morbidity rate. The percentage of hearing loss among HIB meningitis (10%) is less than that of pneumococcus (28%) but because of higher percentage of childhood meningitis caused by HIB, the number of patients with hearing deficit due to HIB is more than any other organism. Other neurological defects include: MR 6%, paresis 5%, and seizure disorder 6%. Dexamethasone adjunctive therapy has been shown to decrease the incidence of hearing loss but not other neurological sequelae.

Epiglottitis

In contrast to other HIB invasive diseases that usually occur during the first 2 years of life, epiglottitis tends to occur more commonly in children 2–4 years of age. The affected child usually presents with abrupt onset of high fever, inspiratory stridor, difficulty in breathing, muffled voice, and drooling. The child is toxic and adopts a characteristic sitting position with protrusion of the jaw and extension of the neck to ease the breathing. There is usually no associated cough. Cautious examination of such children is required. The throat examination should not be attempted until assurance that adequate intervention methods and expertise in intubation are available if needed. This means that the patient should be examined in operation room in the presence of an otolaryngologist and anesthetist. Lateral neck radiography will show enlarged epiglottis (thumb sign), however the patient should not be moved to the radiology department unless his or her condition is stable and should be associated with an expert physician should intervention be required.

Cellulitis

Facial cellulitis in children 3 months to 5 years of age is commonly due to HIB. Periorbital cellulitis is the most common presentation.

Acute Lower Respiratory Tract Infections

HIB constitutes a major cause of lower respiratory tract infections in developing countries. In Gambia, it is estimated that the incidence of pneumonia due to HIB is around 300/100,000 children/year resulting in 40 deaths/100,000 children/year. It is assumed that this high incidence is due to early colonization with HIB.

Septic Arthritis and Osteomyelitis

HIB is a common cause of septic arthritis in children between 3 months and 5 years of age. It rarely causes osteomyelitis at any age group.

Miscellaneous Infection

HIB can cause infection at any organ including endocarditis, pericarditis, conjunctivitis, peritonitis, liver abscess, salpingitis, vaginitis, and brain abscess.

Other *H. influenzae* Serotypes

These are rare cause of childhood infections, however they can cause similar spectrum of disease as that of HIB. It is not known whether introduction of HIB conjugate vaccine will result in increase in incidence of infections due to other serotypes, however this was not proved by a study done in United States that showed no difference before and after 3 years of introducing HIB vaccine.

Nonencapsulated *H. influenzae* Infection

These are common causes of otitis media and sinusitis preceded only by *S. pneumoniae*. Most of these strains are b-lactamase producers. HIB conjugate vaccine does not confer immunity against them. There are increasing reports of these organisms causing neonatal sepsis. They also can cause invasive diseases.

Illustrative Case

A 5-month-old girl who has a ventriculoperitoneal shunt presented with a 3-day history of fever and vomiting. Computed tomography scan of the brain showed an increase of ventricular size indicating shunt malfunction. Cerebrospinal fluid culture grew nontypeable *H. influenzae*. Intravenous ceftriaxone was given for 3 days with no response. Shunt was removed and external ventricular drain was inserted and CSF was obtained in 3 consecutive days and came to be negative. Shunt was reinserted after 7 days and ceftriaxone was given for a total of 14 days and the patient responded well.

H. influenzae Biotype Aegypticus

This is a common cause of epidemic conjunctivitis in different parts of the world. It is also the cause of distinctive invasive disease that is only recognized in Brazil. It is called Brazilian purpuric fever (BPF). BPF is a septicemia disease that is characterized by high fever, toxicity, shock, and purpura arising within 7–10 days after resolving conjunctivitis that is caused by *H. influenzae* biotype aegypticus. It results in high mortality rate and usually spare CNS.

Diagnosis

H. influenzae infections can be diagnosed by clinical features and isolating the organism from the site of infection. Antigen detection studies including counter current immunoelectrophoresis and latex agglutination test can be helpful in identifying the organism in CSF, urine, and serum. Latex agglutination test has a 90–95% sensitivity and specificity in identifying HIB in CSF.

Therapy

Currently the empiric therapy of suspected invasive haemophilus infection is third generation cephalosporins (ceftriaxone 100 mg/kg/day once or twice daily or cefotaxime 150 mg/kg/day three or four times daily). This is because of the increasing incidence of ampicillin resistance among HIB that varies between 20% and 70% in different parts of the world. Chloramphenicol resistance is very low, however because of its potential hematological toxicity and the availability of safer medications, its use is decreasing. HIB resistance to chloramphenicol is mediated by the enzyme acyltransferase. It is very rare to have HIB resistant to the ampicillin and chloramphenicol combination. Otitis media and sinusitis are usually responsive to amoxicillin even if they are resistant in vitro. This is because of the high level achieved in middle ear. Therefore the initial drug of choice for otitis media and sinusitis remains to be amoxicillin.

Prevention

Immunization

HIB conjugate vaccine is now available and proven to be immunogenic in young infants. Since its inclusion in the primary series of childhood immunization in some parts of the world, it resulted in significant reduction of diseases due to HIB.

Prophylaxis

Household Contacts

1. Household contacts with children <12 months of age should be prophylaxed regardless of the immunization status.
2. Household contacts with children >12 months of age who receive the primary series and booster at 12 months or older do not need to be prophylaxed.
3. Household contacts with children <4 years of age who are incompletely vaccinated should be prophylaxed.

Nursing Schools and Day Care Centers

1. If two cases arise in the same center within 60 days, all the contacts should be prophylaxed if there are children who are unvaccinated or incompletely vaccinated.
2. In day care attended by children below 2 years of age and whose contact is more than 25 h/week, all contact should be prophylaxed if there are non-vaccinated or incompletely vaccinated children.
3. Day care attended by children >2 years of age need not be prophylaxed regardless of vaccination status.
4. Pregnant women need not be prophylaxed because of the potential risk of rifampin on the fetus.
5. Prophylactic drugs – Rifampin 20 mg/kg once daily for 4 days.

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82 Infant Botulism

Mohammad Al-Shaalan

Botulism is a disease caused by *Clostridium botulinum* (*C. botulinum*). Three manifestations are known: food botulism, wound botulism, and infant botulism. Food botulism occurs as a result of exposure to botulinum toxin whereas infant botulism and wound botulism occur as a result to exposure to botulinum spores. Infant botulism is the most concerning for pediatricians. Infant botulism was first known in 1976 after Pickett et al. described an infant with hypotonia.

Causative Agent

C. botulinum is a Gram positive, spore forming, and nonmotile bacillus. It grows under anaerobic conditions and is distributed widely in the environment (soil, water, etc.). It produces very lethal toxins of many types, A through G. A and B are the most common toxins causing infantile botulism. Rare cases of toxin E disease due to *C. butyricum* and type F due to *C. baratii* have been reported. Type F toxin tend to produce disease in the very young infant and tend to be more severe. The only confirmed source of acquiring *C. botulinum* spores by an infant is ingestion of honey although this history is positive in only 20–35% of the cases.

Pathogenesis

Although honey is a known source of the spores, it is now rarely consumed by infants. Therefore the main source of botulinum spores is the environment, mainly the soil. Disruption of soil by farming or construction transmits the spores in dust particles to foods or water. Once consumed by the baby, spores germinate in the gastrointestinal tract producing the organisms which in turn produce the toxin. The toxin is absorbed and reaches the blood. From the blood it is distributed to cholinergic terminals including neuromuscular junction, ganglionic synapses, and parasympathetic postganglionic terminals. It binds to acetylcholine vesicles and thus prevents its secretion. This results in paralysis and hypotonia.

Clinical Manifestation

Infant botulism occurs in infants 6 days to 12 months of age and not later. Risk factors for acquiring botulism include consumption of honey, and constipation. The classic presentation is manifested by weak cry, poor oral intake, profound hypotonia, and constipation. Constipation usually precedes the other manifestations by 3 days to few weeks.

The hallmark of the disease is profound hypotonia. Characteristically it is descending in nature starting in the neck and proceeding caudally. In addition cranial nerves may be involved resulting in weakening of the pharyngeal muscles. This in turn results in weak, feeble cry, difficulty in swallowing, and regurgitation. Ophthalmoplegia and poor pupillary reaction to light may also occur.

Autonomic dysfunction may result in mucus membrane dryness and fluctuation in blood pressure and pulse rate.

Clinical diagnosis can be reached with certainty when full complement of symptoms and signs are present; however, infant botulism may present with a myriad of pictures ranging from asymptomatic disease to fulminant fatal disease.

Infantile botulism should be differentiated from other diseases that may present with similar picture including sepsis, Gullain-Barre disease, poliomyelitis, myasthenia gravis, heavy metal toxicity, organophosphorus toxicity, and metabolic diseases.

Lab Diagnosis

It is very rare to isolate *C. botulinum* from stool of normal infants; therefore isolating it from stool of an infant with clinical findings of botulism is regarded highly suggestive of infant botulism. *C. botulinum* can be isolated from the stool up to 150 days after infection. However, biologic mouse toxin assay is the only clinically evaluated diagnostic test. Recently ELISA has been developed for rapid detection of toxin A and B in the serum or fecal filtrate. This test allows detection in 24 h as compared to 4 days that are required for mouse assay.

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Table 82.1
Management targets to optimize outcome (in addition to use of BabyBIG®) (From: Long S (March 2007) Infant botulism and treatment with BIG-IV (BabyBIG_). The Pediatric Infectious Disease Journal • vol 26(3))

• Perform preemptive intubation when protection of airway is compromised; extubate when gag reflex, swallow, and sustained activity against gravity is restored
• Perform ventilator-associated pneumonia prevention "bundle"
• Differentiate hyponatremia due to dehydration vs. SIADH
• Position supine with head of planar mattress (not head of infant) raised 30°; small (washcloth size) roll behind neck; roll behind thighs (to minimize venous pooling & SIADH); smooth infant and bed clothing to avoid pressure from folds
• Institute nasojejunal feedings (continuous initially) within 48 h of admission, and remove intravenous catheter(s)
• Avoid use of unnecessary antibiotics, Foley catheters

Table 82.2
Differences in outcomes of infants treated with BIG-IV* (From: Arnon SS et al (2006) Human botulism immune globulin for infant botulism. N Engl J Med 354:462–471)

Randomized placebo-controlled trial (129 infants)[a]		
Duration of	Placebo	BIG-IV
Hospitalization	5.7 weeks	2.6 weeks
ICU care	5.0 weeks	1.8 weeks
Mechanical ventilation	4.4 weeks	1.8 weeks
Tube feeding	10.0 weeks	3.6 weeks
Total hospital charges	$163,000	$74,800
Open-label use (366 infants)		
Duration of hospitalization	BIG-IV @ 4–7 days hosp 2.9 weeks	BIG-IV @ <4 days hosp 2.0 weeks

*All differences statistically significant; *P* values ≤ 0.001
[a]Infants eligible only if <3 hospital days

Supportive tests include characteristic EMG picture of brief, small, abundant motor-unit potentials (BSAP). This can be observed in 90% of affected infants. Nerve conduction is usually normal.

Treatment

Management of infantile botulism relies mainly on supportive care (*Table 82.1*). This means supplying oxygen or artificial ventilation if needed. Two important factors have been associated with respiratory decompensation in these patients; administration of aminoglycoside antibiotics and neck flexion during positioning for lumbar puncture of computerized tomography. Aminoglycosides may potentiate neuromuscular blockade and therefore should be avoided in these patients. Most of the affected infants have poor suck and swallowing and therefore need nasogastric or nasojejunal feedings and occasionally parenteral nutrition. Care should be provided to prevent aspiration. Antibiotics have no room in treatment except for secondary bacterial infections. Botulism immunoglobulin intravenous (BIG-IV) is now available and has revolutionized therapy of infant botulism. It is derived from pooled human plasma of immunized adult volunteers and it neutralizes free toxin. Its use has improved morbidity significantly (*Table 82.2*). It should be given immediately based on clinical diagnosis without awaiting confirmatory test. It is most effective if given within the first 72 h of illness; however, it should be offered even after 72 h. With appropriate supportive management, the outcome is usually excellent with a mortality rate of less than 2%. The only preventive measure is avoiding honey in infant feeding. Relapse is rare and there are no special infection control issues.

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83 Listeria Monocytogenes (Including Listeriosis)

Benjamin Mackowiak

Definition/Classification

Listeriosis is an infection caused by the bacterium *Listeria monocytogenes* with a spectrum of disease ranging from asymptomatic infections in the immunocompetent patient to severe sepsis and death in certain populations including neonates. It is one of the three major worldwide causes of neonatal meningitis.

Etiology

The genus *Listeria* was named after Sir Joseph Lister, father of antiseptic surgery, while *monocytogenes* refers to the monocytosis often seen in animals infected with the bacteria. *Listeria* spp. are ubiquitous, gram-positive, facultatively anaerobic, intracellular, motile bacilli found in many environments including soil, water, and refrigerated foods. The organisms can survive in acidic, salty, and cold conditions. *Listeria* spp. can infect multiple animal species but, apart from scattered case reports involving *Listeria ivanovii*, *L. monocytogenes* is the main species to cause disease in humans. Furthermore, of the *Listeria monocytogenes* serotypes, three are responsible for 95% of infections in humans: 1/2a, 1/2b, and 4b. Serotype 4b appears to be more virulent than the others.

Epidemiology

Listeriosis is an uncommon cause of infection in the general population but it can lead to serious infections in pregnant women and their fetus, neonates, the elderly, and immunocompromised patients. While *Listeria* spp. are found throughout the world, listeriosis is more common in industrialized countries. Cases are mostly sporadic but can occur as part of an outbreak. The incidence varies from 0.1 to 11.3 per million in different countries. Infection rates also vary by age (*Fig. 83.1*) and are inversely proportional to gestational age. Males and females are affected equally. Women are 20 times more likely to develop a listerial infection during pregnancy, mostly in the third trimester. This is likely due to impaired cell-mediated immunity during the third trimester of pregnancy.

Several nations have seen decreases in incidence in the last 2 decades following public health and food industry initiatives in response to foodborne outbreaks. For example, France saw a 68% reduction in listeriosis from 1987 to 1997 while the United States of America saw a 40% decline from 1996 to 2004. Still, outbreaks have been reported in several countries in the past 10 years linked to dairy and ready-to-eat products. *Listeria* is also found in the stool of 5% of healthy adults.

Pathogenesis

Both early-onset and late-onset neonatal infections can be caused by transplacental transmission. The pregnant woman ingests *Listeria*. The bacterium then crosses the intestinal mucosa into the bloodstream where it travels to the placenta and infects the fetus. Ascending infection during pregnancy can also lead to early-onset listeriosis while late-onset infection can be acquired by exposure of the neonate to *Listeria* while passing through the contaminated birth canal. Infections after the neonatal period are all thought to be foodborne or via exposure to an extrinsic source.

The mechanism by which Listeria becomes pathogenic and invades cells continues to be studied. First, the bacteria gain access to the blood stream and other cells, including macrophages and placental trophoblasts, via the interaction of surface proteins such as internalin A and internalin B with cell-surface proteins like E-cadherin. One hypothesis explaining *Listeria*'s tropism for tissues like the central nervous system and the placental unit is that E-cadherin, for example, is found specifically on the cell surface of trophoblasts. Once endocytosed, the bacteria lyse the vacuoles which house them via the action of

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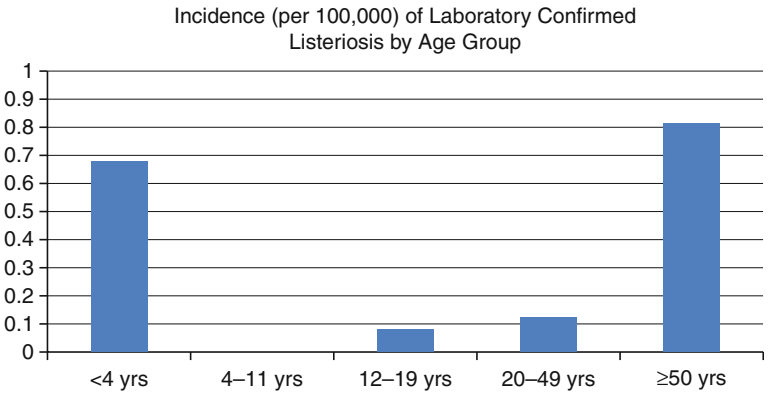

Figure 83.1
From preliminary FoodNet data on the incidence of infection in the USA with pathogens transmitted commonly through food – 10 states, 2009

proteins like lysteriolysin O and become motile within the cytoplasm by acquiring an actin-rich "comet-tail." *Listeria* then migrates to the cell periphery where it spreads to neighboring or immune cells like macrophages via cell wall protrusions that are endocytosed. The bacteria can therefore hijack the very cells, macrophages, which otherwise help clear intracellular infections.

Pathology

Placental pathology demonstrates multiple, well-defined macroabscesses while severe fetal infection is characterized by disseminated granulomatous lesions with microabscesses found throughout the body, including the skin.

Clinical Manifestations

Pregnant women infected with *Listeria* may be asymptomatic or have a flu-like illness. Fetal infection leads to premature birth or neonatal death in 22% of cases. While there are no pathognomic clinical features of listeriosis in the neonate, early-onset neonatal listeriosis presents on average at 1.5 days of life with signs and symptoms of sepsis. Other clinical manifestations include chorioamnionitis, meningitis, and pneumonia. In severe disease, granulomas and abscesses can be found disseminated throughout the body and skin, termed granulomatosis infantisepticum. The associated rash is characterized by lesions found mainly on the trunk or extremities which are maculopapular or papulovesicular in nature.

Late-onset listeriosis is less common than early-onset disease and presents around 2 weeks of life with nonspecific signs and symptoms of illness like fever, lethargy, and decreased feeding. It most frequently presents with meningitis and is associated with serotype 4b.

Non-neonatal pediatric listeriosis is rare even in the immunocompromised patient and has a variety of presentations ranging from self-limited gastroenteritis accompanied by fever and diarrhea to meningoencephalitis.

Diagnosis

The diagnosis of listeriosis is difficult to make on clinical presentation alone and therefore requires isolation of the bacteria from otherwise sterile sites such as the blood and cerebrospinal fluid (CSF). Identification can be challenging, however, as *Listeria* can look like cocci, diplococci, or diphtheroids under the microscope, often misleading the laboratory technician. Gram staining is only positive in approximately 30% patients. The organisms can be grown on selective media or using the cold enrichment technique and show a narrow zone of hemolysis. Rapid detection monoclonal antibody tests are available.

Unlike the name implies, infection in humans rarely leads to monocytosis. Instead, leukocytosis is more common with a predominance of polymorphonuclear cells. When meningitis is present, the CSF will usually be purulent with white blood cell counts ranging from 100 to 10,000 cells per mcL. The glucose levels are low in only 40% of the cases while protein levels are usually elevated.

Differential Diagnosis

Other neonatal sources of infection should be considered such as bacterial infections including group B streptococcus, *Escherichia coli*, and *Haemophilus influenza*. Other diagnoses may include disseminated herpes simplex virus, cytomegalovirus, rubella, or toxoplasmosis.

Treatment

While the diagnosis of maternofetal listeriosis is often missed due to the nonspecific symptoms associated with maternal infection, antimicrobial treatment of the mother during pregnancy can also treat the fetus and lead to a healthy newborn. Treatment of the neonate consists of supportive care in combination with antimicrobial therapy. High dose intravenous aminopenicillins such as ampicillin in combination with an aminoglycoside like gentamicin for synergy is the recommended treatment. Ampicillin alone is only weakly bactericidal and *Listeria* is resistant to all cephalosporins. An alternative in penicillin allergic patients is sulfamethazole-trimethoprim. Although there have been no randomized, controlled trials for the duration of therapy for listeriosis, the current recommendation is 10–14 days of IV therapy for invasive disease and 14–21 days for meningitis.

Prognosis

Twenty percent of *Listeria* infections during pregnancy will lead to stillbirth or spontaneous abortion while 68% of the surviving newborns will develop neonatal sepsis. Listeriosis has a 20–30% case fatality rate despite antimicrobial therapy. Non-neonatal cases who survive will have neurological sequelae in 30% of patients.

Prevention

There is no vaccine for *Listeria*. Avoidance of foods that are at high risk of being contaminated such as refrigerated deli meats, hot dogs/frankfurters, unpasteurized dairy products, and smoked fish is recommended in patients who are immunocompromised or pregnant. Other measures which may reduce the incidence of listeriosis include washing vegetables prior to consumption, keeping refrigerator temperature at 4.4°C or lower and freezer temperatures at −17.8°C or lower, and thoroughly heating all foods prior to consumption.

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84 Lyme Disease

Michael P. Koster

Definition/Classification

Lyme disease, also known as Lyme borreliosis (LB), is a vector-borne, bacterial illness caused by the spirochete *Borrelia burgdorferi* sensu lato (*B. borgdorferi* in the general sense). Infection of the skin occurs first, but LB can disseminate to multiple organ systems.

Etiology

Historically, descriptions of dermatologic manifestations date back 100 years; however, LB was officially described in 1977 among an epidemiological cluster of patients with oligoarticular arthritis in Lyme, Connecticut, USA. In 1982, *B. burgdorferi* sensu stricto was detected and isolated in culture (see ❯ *Fig. 84.1*), and since then *B. garinii*, *B. afzelii* (both in Europe), and *B. spielmani* (Asia) species have been described with LB.

LB is transmitted to humans by infected *Ixodes* spp. ticks, which take blood meals from humans during their nymphal (more infective) and adult life stages. It is not a simple bite, but prolonged attachment (∼48 h) that transmits disease, as *Borrelia* spp. are found in the tick gut, and engorgement is associated with higher transmission rates.

Epidemiology

LB has a worldwide distribution, but the majority of literature is from Europe and North America, where it is the most common vector-borne illness. The United States has adopted epidemiological definitions and national surveillance; reporting 29,959 confirmed and 8,509 probable cases in 2009, and an incidence of 13.4/100,000 persons (Delaware reports the highest at 111.2, followed by Connecticut at 78.2) with 5–10-year-old children comprising the largest affected group. In Europe, not all countries have universal reporting; however, in 2006 reported incidence in Slovenia was 155/100,000 persons, Austria 130, Sweden 80, Bulgaria 55, and Germany 25 (with highest reported total cases at 20,700). Asian countries including China, Indonesia, Japan, Korea, and Nepal also report LB.

Pathogenesis

Borrelia spp. regulate gene expression throughout the life cycle to adapt to different host and host defenses. Upregulation of plasmid-encoded outer-surface protein (Osp) C allows the spirochete to attach to tick salivary glands to facilitate transfer to the mammalian host. Another example is the antigenic variation of lipoprotein VlsE, which helps elude host immunity. Once transmitted to humans, *Borrelia* spp. infect the skin and the ensuing inflammation gives rise to the characteristic erythema migrans (EM) rash. *Borrelia* spp. bind many host receptors, including plasminogen and its activators, to help it spread through tissue matrices. Additionally, certain gene expressions of OspC have been associated with dissemination. Although it is not known what makes certain spirochetes more neurotropic or arthritogenic, ongoing investigations continue to elucidate the spirochete–host interplay.

Humans respond to infection through both innate (complement, chemokines, Toll-like receptors) and adaptive immune responses (opsonizing antibodies). There is evidence that LB can trigger autoimmune phenomena, exemplified in patients with certain HLA-DR allotypes who develop noninfectious, recalcitrant arthritis.

Pathology

Although not clinically indicated, skin biopsy of early erythema migrans (EM) lesion reveals a dense mononuclear infiltrate, mainly of T cells, plasma cells, and occasional macrophages. Two other skin manifestations, more common in Europe, often require biopsy (in conjunction with immunohistochemistry, culture, and PCR) to establish the diagnosis: borrelial lymphocytoma is characterized by B cell infiltration and observable germinal centers in the cutis and subcutis, and acrodermatitis chronica atrophicans (ACA) is associated with an inflammatory response of T cells and macrophages.

Disseminated disease occurs from direct bacterial invasion, as animal models demonstrate spirochetes within nervous, cardiac, and synovial tissue. In arthritis,

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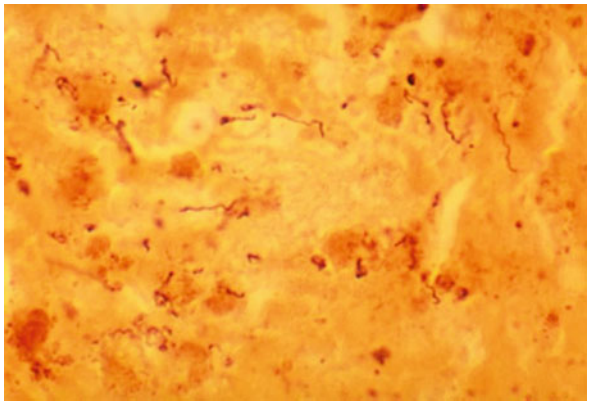

Figure 84.1
Histopathology showing *Borrelia burgdorferi* spirochetes in Lyme disease. Dieterle silver stain (Photo courtesy of CDC/Dr. Edwin P. Ewing, Jr. 1983)

joint aspiration will reveal a polynuclear leukocytosis. With meningeal involvement, cerebral spinal fluid will demonstrate a mild lymphocytic pleocytosis, moderately elevated protein, and typically normal glucose. Electrophysiological studies suggest that the bundle of His and AV node are the most commonly affected areas in cardiac disease associated with heart block.

Clinical Manifestations

Despite early and late clinical manifestations, symptoms do not necessarily present in a progressive linear fashion; however, the vast majority of patients (>90% in children) present with early localized disease, manifest by a single, circular, expanding (over days, at least 5 cm), macular, sometimes centrally-clearing (occasionally targetoid) lesion known as EM (see *Fig. 84.2*). EM typically occurs at the site of the tick bite approximately 10 days later (3–32 days), it can vary greatly in shape and infrequently can have a vesicular, scaly, or necrotic center. Careful examination is necessary as EM can be entirely within the hairline. Constitutional symptoms of myalgia, arthralgia, malaise, and/or headache can accompany EM or rarely be the only presenting symptoms. EM in Europe spreads slower, persists longer, and is associated with less symptoms of acute inflammation.

Multiple EM lesions are the most common presentation of early disseminated disease. Appearing days to weeks after a single EM in ~15–20% of cases, they are smaller, can

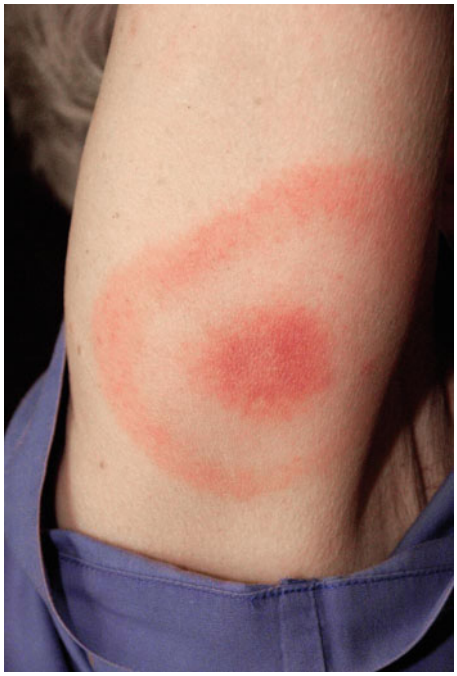

Figure 84.2
Erythema migrans rash with targetoid appearance (Photo courtesy of CDC/James Gathany 2007)

appear more linear, more often lack central clearing, and are often accompanied by constitutional symptoms. Neurological manifestations include isolated peripheral neuropathy, most commonly the facial nerve. Nuchal rigidity should prompt lumbar puncture for the evaluation of meningitis, but persistent and severe headaches are more typical. Increased intracranial pressure and papilledema, sometimes associated with abducens palsy, is well described in children with Lyme meningitis. Optic neuritis can also be seen. Cardiac involvement occurs in less than 1%, and presents as first-, second-, or third-degree heart block. Myocarditis can occur, but is less likely. An extremely rare and difficult to diagnose skin finding is borrelial lymphocytoma, which presents as a bluish-red swelling, mimicking a benign tumor, on the ear lobe or areola of the breast.

Arthritis, typically occurring months after infection, is the chief presentation of late disease and more common in North America (~10%). Monoarticular infection of the knee is most common; there is tremendous swelling with only mild-to-moderate pain and infrequently erythema overlies the joint. Occasionally, as described above, as a subset (~10%) of patients develop chronic arthritis. Polyneuropathy/ridiculoneuritis (Bannwarth syndrome)

is especially rare in children but should be suspected in endemic European areas when symptoms include muscle weakness, neuralgia, and/or paresthesias. Encephalomyelitis or encephalopathy (subtle cognitive dysfunction) is extremely rare in pediatrics, especially with better detection and earlier treatment. Also exceedingly rare (case reports in pediatrics), but historically important, ACA presents (typically in older women with *B. afzelii*) with a bluish-red lesion, atrophic skin, prominent vessels, and associated neuropathy.

Diagnosis

Serological testing is the mainstay for the diagnosis of LB. In North America, a two-tier testing system with excellent sensitivity and specificity has been adopted. Enzyme immunoassays (EIA) detect Lyme-specific antibodies quantitatively and if equivocal or positive (false positives occur), should be reflexed to a confirmatory Western immunoblot assay. The immunoblotting is considered positive if there are at least five of ten IgG bands or at least two of three IgM bands. Since immunoblotting can persist indefinitely after adequate treatment, a test which is positive by IgM alone would be considered false if symptoms had been present for longer than 1 month. Because of this, interpretation of testing can be very confusing, and testing should never be done for vague nonspecific symptoms, especially when the positive predictive value is low.

A clinical diagnosis of EM is pathognomonic for early localized disease, and serological testing should not be performed as it is unreliable at this stage.

Serological testing is invariably positive in early disseminated and late LB, although multiple EM is also specific enough to diagnose clinically. Especially in Europe where LB is more neurotropic, an antibody index or ratio of Lyme-specific immunoglobulins in the spinal fluid compared to the serum can elucidate neurological involvement.

Spirochete can be detected in affected sites by immunohistochemistry and culture, both with significant limitations to clinical practice. PCR has proven useful in diagnosing arthritis (not in meningitis).

Differential Diagnosis

The differential for EM includes, but is not limited to, other insect bites, granuloma annulare, nummular eczema, urticaria, pityriasis, tinea, drug eruption, erythema nodosum, and erythema multiforme. The expanding nature and persistence of EM, including the lack of scaliness and pruritus, help to distinguish it from the other rashes.

Lyme meningitis is indistinguishable from other forms of aseptic meningitis, but a larger percentage of monocytes in the spinal fluid, longer duration of symptoms, papilledema, and facial nerve palsy can be more telling.

Lyme arthritis can be mistaken for suppurative arthritis, reactive arthritis, juvenile idiopathic arthritis, rheumatic fever, or osteomyelitis with joint involvement. Ability to ambulate and only moderate pain, differentiate Lyme arthritis from suppurative arthritis, but serology (PCR if fluid is tapped) will decipher Lyme.

Coinfection (especially in North America) with other tick-borne illness like babesiosis should be considered in more severely ill-appearing patients and if leukopenia and thrombocytopenia are present ehrlichiosis should be suspected.

Treatment

Medication and duration are specific to the presenting symptoms of LB, best depicted in *Table 84.1*.

The use of macrolides (azithromycin 10 mg/kg/day (max 500 mg/day), clarithromycin 15 mg/kg/day in two divided doses (max 1,000 mg/day), erythromycin 50 mg/kg/day in 4 divided doses (max 2,000 mg/day)) should be reserved for those with true allergies to preferred regimens. Some patients may develop paradoxical worsening of symptoms soon after treatment begins that lasts about 24 h (Jarisch–Herxheimer). Few patients may have persistence of vague symptoms including fatigue, arthralgia, and headache that can last weeks to months after treatment. These post-Lyme syndromes are noninfectious, and should be treated supportively with nonsteroidal anti-inflammatory analgesic medications and reconditioning (there is no indication for prolonged antibiotics). For the few patients with recalcitrant arthritis, synovectomy or immune-modulating medications, like methotrexate, are treatment options.

Prognosis

LB has often been misdiagnosed, and has led to some confusion on treatment outcomes. Published data suggest that LB in children is completely treatable and outcomes for early and late disease are excellent.

Table 84.1
Treatment options based on symptomatology

Symptom	Drug	Duration
EM rash	1. Doxycycline[a] PO 4 mg/kg/day divided in two daily doses (max 200 mg/day) 2. Amoxicillin PO 50 mg/kg/day in three divided doses (max 1,500 mg/day) 3. Cefuroxime axetil PO 30 mg/kg/day in two divided doses (max 1,000 mg/day)	14 days (10–21 days)
Multiple EM rash	Same as for EM rash	21 days (21–28 days)
Borrelial lymphocytoma	Same as for EM rash	14 days (14–28 days)
Heart block/cardiac disease[b]	Same as for EM rash	21 days (21–28 days)
Isolated facial palsy	Same as for EM rash	28 days (14–28 days)
Meningitis,[c] polyneropathy, ridiculoneuritis, and other late neurological disease	1. Ceftriaxone 75–100 mg/kg/day IV once daily (max 2,000 mg/day) 2. Cefotaxime 150 mg/kg/day IV in three divided doses (max 6,000 mg/day) 3. Penicillin G 0.2–0.4 million units/kg/day in six divided doses (max 20 million units/day)	28 days (14–28 days)
Arthritis[d]	Same as for EM rash	28 days
ACA	Same as for EM rash	21 days

EM erythema migrans, PO per os, ACA acrodermatitis chonica atrohpicans
[a]Do not use in children <8 year and pregnant women due to teeth discoloration
[b]Third-degree heart block and severe cardiac disease requires hospitalization, sometimes pacing, and parenteral therapy initially
[c]Doxycycline has been studied extensively in Europe and can be used for acute uncomplicated neurological disease
[d]If arthritis needs to be re-treated some experts chose parenteral therapy

Prevention

The best way to prevent LB is to avoid tick-infested areas. In endemic residential areas, it is suggested to remove leaf litter and woodpiles, keep grass short, and apply pesticides. Using repellents such as DEET directly on the skin, and insecticides like permethrin on clothes, tents, and camping gear can be helpful. Also when anticipating exposure, wear long sleeves and tuck long pants into socks. Performing a careful skin inspection daily, when exposed, with prompt removal of ticks is most important as this dramatically decreases transmission rates (1–3%). Prophylaxis is not routinely recommended, only doxycycline has shown benefit in adults, and should be reserved for those who remove engorged ticks in endemic areas (children older than 8 years could take 4 mg/kg once, max 200 mg). Otherwise, patients who have been bitten should be monitored over the next month for the development of EM or constitutional symptoms and treated as needed.

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85 Mycoplasma Infection

Manika Suryadevara · Leonard Weiner

Etiology

Mycoplasma pneumoniae, originally called the Eaton agent, was first isolated from a sputum culture in a patient with atypical pneumonia in 1944. Twenty years later, it was ultimately identified to be a *Mycoplasma* not a virus as once thought. Mycoplasmas are the smallest self-repliacting prokaryotes with a size of approximately 120–150 nm. These organisms cannot be seen by light microscopy nor do they produce visible turbidity in liquid growth media.

Like other bacteria in its Mollicutes class, Mycoplasmas lack the gene necessary to synthesize peptidoglycan cell walls. The absence of a cell wall explains its pleomorphic phenotype, inability to stain with Gram stain, and its resistance to antibiotics that interfere with cell-wall synthesis such as beta-lactams. While Mycoplasmas are found in many animals and plants, humans are the only known host for *M. pneumoniae* infection.

For many years, it was believed that *M. pneumoniae* infections were self-limited, confined to the respiratory tract, and involved only adolescents and young adults. Over time, much has been learned about this pathogen, its epidemiology, pathogenesis, and variety of clinical manifestations.

Epidemiology

M. pneumoniae, an exclusively human pathogen, is a frequent respiratory pathogen causing up to 40% of outpatient pediatric community-acquired pneumonia and 12–25% of lower respiratory-tract infections in hospitalized children. Once thought to infect primarily adolescents and young adults, recent literature suggests increasing infection in younger children. Worldwide, the incidence of *M. pneumoniae* infection is highest in children aged 5–9 years. However, a study of community-acquired pneumonia in children in Korea found that children less than 5 years accounted for over 44% of the 568 *M. pneumoniae* cases. Infants have also been documented to have *M. pneumoniae* infection, however, rarely.

M. pneumoniae occurs endemically and epidemically worldwide and throughout the year, with peaks in the summer and early fall months when the frequency of other respiratory pathogens is low. Community epidemic infections can be seen in 3–5 year cycles, with each epidemic lasting a few months. The 2–3 week incubation period in combination with asymptomatic nasopharyngeal carriage that persists for months beyond the initial infection likely contribute to these lengthy periods. During these epidemics, the frequency of infection can be 5–20 times greater than during the endemic periods. As *M. pneumoniae* is transmissible by respiratory droplets during close contact with a symptomatic person, these outbreaks tend to occur in closed populations such as military bases, colleges, and summer camps.

Mycoplasma infection elicits protective immunity; however, it is short lived, and reinfections throughout life are common. Naturally acquired infection in which pneumonia develops results in longer protective immunity than mild or asymptomatic infection.

Pathogenesis

Respiratory disease caused by *M. pneumoniae* is dependent on the close association between the host respiratory epithelium and the pathogen. This cytadherence process, considered a major virulence factor of this organism, is essential to colonization and infection as alteration of any of these proteins results in the organism's inability to cause infection. Subsequently, the immune response elicited, while responsible for much of the disease process, does not effectively clear the organism or produce long-term immunity.

M. pneumoniae enters the respiratory tract via inhalation of aerosolized droplets spread by symptomatic close contacts. The pathogen, with the help of P1 adhesion protein and accessory proteins, attaches to the ciliated epithelium and is thus protected from the host's mucociliary clearance mechanism. Close contact between host cell and pathogen allows for the pathogen's release of hydrogen peroxide and superoxide radicals directly onto

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the cell, which in combination with the toxic oxygen molecules produced by the host induces oxidative stress on the respiratory epithelium causing local disruption and cytotoxicity. Clinically, this damage to the respiratory tract manifests as a prolonged and irritating cough.

M. pneumoniae then reaches the base of a ciliated cell in the lower respiratory tract, where multiplication of organism occurs. Here, Mycoplasma is opsonized by complement and antibody and then phagocytosed by activated macrophages drawn to site of infection by chemotaxis, inducing a cytokine release. CD4+ T cells and B cells infiltrate the lung resulting in lymphocyte proliferation, antibody production, and further cytokine production, including interleukins, interferons, and tumor necrosis factor, and thus the development of pulmonary infiltrates seen on radiologic imaging. The stronger the immune response and cytokine production, the more severe the clinical picture develops.

Extrapulmonary manifestations of Mycoplasma infection occur by a variety of mechanisms, involving both immune-mediated processes (including autoimmunity, cytokine production, and the development of immune complexes) and direct invasion with dissemination. The presence of cross-reactive antibodies results in autoimmune reactions leading to neurological and hematologic presentations specifically encephalitis, Guillain–Barre syndrome (GBS), cranial and peripheral neuropathies, and autoimmune hemolytic anemia. Autoantibodies to ganglioside GM1 and galactrocerebroside have been implicated in the development of *M. pneumoniae* associated GBS, while those recognizing the I antigen of human red blood cells leads to development of cold agglutinins, previously used as a diagnostic tool in identifying Mycoplasma infection. These above-mentioned pathways are not exclusive and, as a result of the multiple pathogenic mechanisms, clinical presentation can be complex with or without respiratory symptoms.

Pathology

There are currently no cases describing histopathology of Mycoplasma infection in the pediatric population. Histopathologic examination has been reported in a few adult cases, animal models, and tracheal organ cultures, revealing lesions of the epithelial lining of the mucosal surfaces, ulceration, and destruction of the ciliated epithelium of the bronchi and bronchioles, bronchial and bronchiolar edema, and bronchiolar and alveolar infiltrates of macrophages, lymphocytes, neutrophils, plasma cells, and fibrin. Reports have also described Type II pneumocyte hyperplasia, diffuse alveolar damage, fibrinous exudates in the pleura, and lung abscesses. In fatal cases, desquamative interstitial pneumonia with focal alveolar disease and bronchiolitis obliterans have been seen.

Clinical Manifestations

Respiratory Tract

M. pneumoniae the most common pathogen causing an "atypical pneumonia," is known to infect both the upper and lower respiratory tract. The illness is usually gradual in progression over days to weeks, although sudden onset of dyspnea and cough has been reported. Three to ten percent of patients infected with *M. pneumoniae* go on to develop pneumonia.

Children present most commonly with fever and cough. The cough initially is dry and nonproductive but may develop into a mucopurulent cough, occasionally with blood streaked sputum. Children with Mycoplasma pneumonia are more likely to have a have a history prolonged fever that does not respond to beta-lactam antibiotics than those with pneumonia of other infectious etiology. Other symptoms include sore throat, headache, lethargy, chills, myalgias, rash, and a protracted cough which may become paroxysmal. Younger children tend to present with more rhinorrhea, wheezing, vomiting, and diarrhea, whereas older children and adolescents complain about sinus fullness and ear pain and are more likely to develop bronchopneumonia. The clinical presentation of Mycoplasma respiratory infection can mimic that of both respiratory viruses and/or pertussis making the diagnosis more difficult.

Physical-exam findings are dependent on the site of infection and, early in illness, can include non-exudative pharyngitis, myringitis, and cervical adenopathy. The etiology of bullous myringitis, thought to be pathognomonic of *M. pneumoniae*, has been shown to be a variety of organisms with Mycoplasma being only a rare cause. As the illness progresses over days to a week, the fever and upper respiratory symptoms resolve, and the lower respiratory findings become more prominent including tachypnea, scattered rales, ronchi, and/or wheeze on auscultation of the chest. The presenting symptoms usually resolve within 2 weeks; however, symptom resolution can take months.

Chest x-rays are usually abnormal in patients with Mycoplasma pneumonia; however, the findings are variable and not specific for *M. pneumoniae*. Lobar consolidation (typically unilateral and involving lower lobes) is a common finding as well as bilateral interstitial changes.

Hyperinflation, bronchial thickening, and hilar lymphadenopathy can also be seen. Parapneumonic effusions can be seen in 4–20% of patients. Improvement of radiographic findings lags behind clinical improvement by months.

Extrapulmonary Manifestations

While the respiratory tract may be the most common site infected by *M. pnueumoniae*, any organ system can be involved. Twenty five percent of hospitalized patients with Mycoplasma infection have extrapulmonary manifestations. These symptoms can occur before, during, after, or in the absence of respiratory symptoms. Although the pathogenesis of extrapulmonary manifestations is unclear, it is hypothesized to include direct invasion and/or autoimmune processes.

Table 85.1 lists the extrapulmonary complications associated with *M. pneumoniae* infection. The most common of the extrapulmonary manifestations are dermatologic, affecting 25% of infected patients, and neurologic, seen in 7–10% of hospitalized patients with Mycoplasma infection. The skin presentations can be, but are not limited to urticarial, vesicular, or maculopapular. *M. pneumoniae* is one of the most common infectious agents associated with Stevens–Johnson syndrome both with and without rash. Central nervous system (CNS) manifestations most commonly are encephalitis, meningoencephalitis, polyradiculitis, and aseptic meningitis. *M. pneumoniae* encephalitis is more frequent in children than in adults, and this pathogen should be on the differential diagnosis of patients with CNS disease, especially if associated with pneumonia.

Table 85.1
Extrapulmonary manifestation with *Mycoplasma pneumoniae* infection

Organ system	Clinical manifestation
Dermatologic	Urticarial or vesicular rash
	Erythematous maculopapular rash
	Stevens–Johnson syndrome
	Erythema multiforme
Central Nervous System	Encephalitis, Meningoencephalitis
	Aseptic meningitis
	Cerebellar ataxia
	Cranial and peripheral neuropathy
	Transverse myelitis
	Guillan–Barre syndrome
	Confusion
	Psychosis
Ocular	Optic neuritis
	Diplopia
	Conjunctivitis
	Retinitis
	Anterior uveitis
	Retinal hemorrhage
	Iritis
Hematologic	Hemolytic anemia
	Intravascular coagulation
Gastrointestinal	Vomiting
	Diarrhea
	Mild elevation of hepatic enzyme
	Pancreatitis
Cardiac	Heart failure
	Myocarditis
	Pericarditis
	Pericardial effusion
Renal	Glomerulonephritis
	IgA nephropathy
Bone/Joint/Muscle	Myalgias
	Arthralgias

Special Circumstances

Children with underlying conditions, such as sickle-cell disease, Down syndrome, and immunosuppression, are more likely to develop severe Mycoplasma infection with fulminant pneumonia and joint infection. *M. pneumoniae* infection has been associated with acute chest syndrome and multilobar infiltrates with large bilateral pleural effusions in patients with sickle-cell disease.

There is little published data describing *M. pneumoniae* infection in the pediatric HIV population. Recently, a study in India evaluated 90 HIV seropositive children who were hospitalized with acute respiratory symptoms. IgM antibodies specific for *M. pneumoniae* were seen in 32% of these children, with the majority of these patients between 6 and 9 years of age. Cough and fever were the most common presenting symptoms, in combination with headache, joint pain, dyspnea, sore throat, and hemoptysis. Almost all of these children were anemic and many had elevated hepatic enzymes, a side effect seen with many anti-retrovirals as well.

Diagnosis

Growing Mycoplasma in culture is difficult, labor intensive, and expensive. Special care is required to meet the complex nutritional needs to achieve growth, which can take up to 4 weeks. The sensitivity of culture is low at 61% when compared to PCR. As Mycoplasma can persist in the nasopharynx for months after the initial infection, isolation of the pathogen does not necessarily implicate it as the etiology of the current illness. Therefore, culture for Mycoplasma is not recommended for routine diagnosis.

Bedside testing of cold agglutinins was once the primary diagnostic tool for Mycoplasma infection. Cold agglutinins are an early nonspecific IgM antibody against the "I" antigen of the human erythrocyte. These autoantibodies are most active at 4°C. To test for cold agglutinins, the patient's blood would be drawn into a tube containing anticoagulant. The tube would be placed in ice water for 30 s to 5 min and then examined for agglutination. The strength of the agglutination correlates with the severity of disease. Cold agglutinins can be seen in half of patients infected with *M. pneumoniae*; however, false positives can be seen in children with lymphoproliferative disorder, infectious mononucleosis, influenza, and adenovirus infections. Lack of sensitivity, specificity, and standards render this method impractical in clinical situations.

There are several serological tests of *M. pneumoniae*, including complement fixation, passive agglutination, immunofluorescent antibody assays, and enzyme immunoassays (EIAs) which are the most commonly used. Complement fixation, the first serological method developed for *M. pneumoniae*, measures early IgM response without differentiating between the antibody classes. Since it is now known that Mycoplasma antibody can persist for months to years, this differentiating between antibody classes is important in distinguishing acute infection from old infection. EIAs have become more widely used for *M. pneumoniae* detection. The sensitivity of EIAs in *M. pneumoniae* detection is higher than that of culture and is even comparable to that of PCR.

Serologically, the diagnosis is made retrospectively with collection of acute and convalescent sera 2–4 weeks apart to show evidence of seroconversion. A fourfold increase in antibody titer between acute and convalescent titers or a single anti-Mycoplasma antibody titer of $>$1:128 is diagnostic of acute Mycoplasma infection. Similar to the time needed for culture, the need for acute and convalescent titers is a limitation in acute management, and empiric treatment should be given based on clinical suspicion.

New molecular-based testing such as PCR has been increasingly used in Mycoplasma detection. PCR allows for same day results and detection of Mycoplasma from body fluids, such as blood and CSF. While PCR has high sensitivity, a positive PCR result from a patient with a negative culture without respiratory disease is difficult to interpret since this may represent persistence of pathogen without infection or asymptomatic carriage.

Differential Diagnosis

Respiratory infection caused by *M. pneumoniae* commonly shares clinical features with respiratory viruses such as influenza, adenovirus, parainfluenza virus, respiratory syncytial virus, and human metapneumovirus. Similarly, other bacteria and atypical organisms should be considered in the differential diagnosis, including *Streptococcus pneumoniae*, *Haemophilus influenzae, Staphylococcus aureus*, and *Chlamidyophila pneumoniae.* In patients who present with protracted, paroxysmal cough, the diagnosis of pertussis should be considered.

Treatment

When *M. pneumoniae* infections were first described, antibiotic therapy was thought to be unnecessary as these illnesses were mild and self-limiting. Over time, antibiotics have been shown to decrease duration of both fever and respiratory symptoms. As it is difficult to obtain a microbiologic result at the time of the patient visit, empiric therapy should be started with clinical suspicion of Mycoplasma associated lower respiratory tract infection.

Beta-lactams and glycopeptides, commonly used to treat community-acquired pneumonia, are ineffective against Mycoplasma since this organism lacks a cell wall. Macrolides are currently the recommended treatment of choice for infection with *M. pneumoniae*. Azithromycin and clarithromcyin are clinically as effective as erythromycin and are better tolerated, given only once or twice a day, and require shorter treatment duration in the case of azithromycin. Fluoroquinolones and tetracyclines are also effective antimicrobial agents and, unlike macrolides, there have been no reported Mycoplasma resistance to these classes. However, due to the significant toxicities associated with these medications in the pediatric population, macrolides remain the drugs of choice. While antibiotic therapy may decrease clinical symptoms, they do not eradicate the organism and asymptomatic carriage may persist and subsequent reinfection may occur.

Macrolide resistant strains of Mycoplasma contain a mutation in the 23S rRNA gene decreasing the affinity of these medications for the ribosomes. First described in Europe, clinical resistance to macrolides has been increasing worldwide over the past decade. Rates of macrolide resistance have ranged from a few case series in the United States to 3% in Germany and 13% in Japan to 69% in a study in China. Children with macrolide resistant Mycoplasma infection were found to have longer fever duration than those with infection with a susceptible organism.

There is little data available regarding the treatment of extrapulmonary manifestations of *M. pneumoniae*. The pathogenesis of these clinical presentations is unclear and thought to be due to direct invasion and dissemination and/or an autoimmune response. Therefore, treatments have included antibiotics, steroids, as well as plasmapheresis and intravenous immunoglobulin. There currently have been no controlled studies evaluating these treatment options with extrapulmonary systems and no consistent studies showing any benefit. It is reasonable, since Mycoplasma can cause severe disseminated disease, to start antibiotics in patients with central nervous system disease, hemolysis, or cardiac disease when infection with *M. pneumoniae* is suspected.

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86 Neisseria Infections

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Definition and Classification

Neisseria are aerobic, gram-negative, oxidase-positive coccoid bacteria, and most species are found in pairs (diplococci) on examination of the Gram stain. Two main pathogenic species exist, *N. meningitidis* (commonly referred to as meningococcus) and *N. gonorrhoeae* (commonly referred to as gonococcus). This chapter will focus on *N. meningitidis* and manifestations of *N. gonorrhoeae* outside the urogenital tract. For a detailed discussion of genitourinary infections caused by *N. gonorrhoeae*, please see Chap. 71, "Sexually Transmitted Diseases".

Other *Neisseria* species commonly colonize the human upper respiratory and female urogenital tracts, and can be distinguished from the more pathogenic *Neisseria* species on the basis of carbohydrate utilization and biochemical testing. These other species include *N. sicca*, *N. subflava*, *N. cinerea*, *N. lactamica*, *N. mucosa*, *N. flavescens*, *N. weaveri*, *N. polysaccharea*, and *N. elongata*.

Epidemiology

Annually, *N. meningitidis* causes disease in approximately 2,500 people in the United States, and 500,000 people worldwide, resulting in an estimated 50,000 deaths. Despite advances in therapy, the 10% mortality rate has remained unchanged in the last 20 years. Two incidence peaks exist for meningococcal infection: the first peak occurs in children less than 5 years of age, and the second peak in people 15–24 years of age. Although the vast majority of meningococcal cases (95%) are endemic, epidemic outbreaks have occurred in association with daycare centers, college dorms, and military barracks. Crowded living conditions promote the spread of the organism, placing those of low socioeconomic status at higher risk of meningococcal disease. In addition, tobacco smoke exposure and upper respiratory viral infections increase the risk of disease, likely through diminishing mucous membrane integrity. Meningococcal cases are reported more frequent in the winter months following influenza virus infections.

There are 13 identified *N. meningitidis* serogroups as determined by differences in the bacterial polysaccharide capsule. The serogroups have varying epidemiological features and are responsible for different disease manifestations. For example, serogroup C usually causes meningitis and septicemia, whereas serogroup W-135 also causes arthritis and pneumonia. Current meningococcal vaccines target specific serogroups and are likely going to change the epidemiology of disease in the future as vaccination rates increase.

Serogroups B, C, Y, and W-135 are the most common causes of endemic meningococcal disease in the United States. Of these, serogroups B and C are the most prevalent serogroups causing disease, but serogroup Y is emerging as a more common entity, causing up to a third of endemic cases in certain areas. Serogroup W-135 previously caused 20% of meningococcal cases but is now responsible for only 4% of cases in the United States.

Worldwide, the majority of endemic meningococcal cases are caused by serogroups A, B, and C. Serogroups B and C cause disease in Europe and the Americas, while serogroups A and C cause disease in Asia and Africa.

Although all serogroups have the potential to cause epidemic disease, certain serogroups have caused recurrent outbreaks. In the United States, the majority of these outbreaks are due to serogroup C, and more recently, due to serogroup Y. Although the frequency of epidemics has been increasing since the 1990s, epidemics in the United States typically account for only 2–3% of meningococcal cases.

Worldwide, serogroup A is the most common agent responsible for epidemics of meningococcal meningitis. Serogroup A causes outbreaks in the sub-Saharan "meningitis belt," which extends from Ethiopia to Senegal. In this region, serogroup A is responsible for both endemic meningococcal disease as well as recurrent epidemics occurring approximately every 7–10 years. Other serogroups that have caused epidemic disease include serogroup W-135, which was responsible for the Hajj epidemic in 2000, and serogroup B, which caused an epidemic in Oregon and Washington in 1990.

Overall, the incidence of gonococcal infections remains high, with an estimated 60 million cases annually

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worldwide, including approximately 300,000 annually in the United States. Disseminated gonococcal infection, however, is less common, with fewer than 5% of patients experiencing disseminated disease. Rates of disease in the United States have remained stable since the mid-1990s. Gonococcal infections are more common among those with lower socioeconomic status and earlier onset of sexual activity.

Resistance to multiple antibiotic classes has begun to develop among *Neisseria* species worldwide. In part, horizontal gene transfer between nonpathogenic colonizing *Neisseria* species and pathogenic *Neisseria* species is responsible for these increasing resistance patterns. Emerging resistance to penicillins, extended-spectrum cephalosporins, and fluoroquinolones has been documented.

Pathogenesis

Five to ten percent of adults are asymptomatic carriers of *N. meningitidis*. The organisms colonize the nasopharynx and are spread through secretions of aerosolized particles. Disease occurs when the epithelial cells engulf the bacteria, which then gain access to the bloodstream. For reasons that are still unclear, invasive disease tends to occur within 1 week of a new exposure to *N. meningitidis*.

People with deficiencies in antibody-dependent immunity are more susceptible to meningococcal disease. The specific immune deficiencies associated with meningococcal infection include infants with waning maternal antibodies, those with functional or anatomical asplenia, and those with terminal complement deficiencies. Terminal complement deficiencies are estimated to cause a 10,000-fold increased risk of acquiring meningococcal disease. However, the majority of meningococcal disease does not occur in people with intrinsic risk factors.

Clinical Manifestations

The common and uncommon clinical presentations of *N. meningitidis* and *N. gonorrhoeae* are presented in Table 86.1. *N. meningitidis* most commonly causes meningitis and meningococcal sepsis (meningococcemia), but can also cause less common infections such as arthritis, pneumonia, otitis media, conjunctivitis, epiglottitis, urethritis, pericarditis, and osteomyelitis.

Meningococcal sepsis manifests as an abrupt onset of fever and a characteristic petechial or purpuric rash. The rash that typically presents in meningococcemia is known as purpura fulminans and is a diffuse, non-blanching petechial or purpuric rash over the trunk and extremities. Progression of sepsis leads to hypotension and disseminated intravascular coagulation with end-organ failure. End-organ failure in meningococcal sepsis often involves the kidneys, lungs, and adrenal glands. Waterhouse–Friderichsen syndrome is an acute adrenal hemorrhage often seen in meningococcal sepsis, which leads to a subsequent cortisol deficiency.

Table 86.1
Clinical presentations *of Neisseria meningitidis and Neisseria gonorrhoeae* infections

Neisseria meningitidis	*Neisseria gonorrhoeae*
Most common	
Meningitis	Neonatal conjunctivitis
Bacteremia	Urethritis
Septic arthritis	Endocervicitis
	Salpingitis
Uncommon	
Otitis media	Septic arthritis
Pneumonia	Arthritis-dermatitis
Conjunctivitis	Bacteremia
Epiglottitis	Meningitis
Urethritis	Endocarditis
Pericarditis	
Vasculitis	
Osteomyelitis	

Chronic meningococcemia is a rare clinical manifestation of *N. meningitidis* and is defined as meningococcal sepsis of at least 1 week duration without meningeal symptoms. It is characterized by recurrent fevers, rash, migratory arthralgias, and headaches. The pathophysiology of chronic meningococcemia remains unclear.

The hematogenous spread of *N. meningitidis* can lead to meningitis, which is the most common presentation of invasive meningococcal disease (see Chap. 69, "Meningitis"). About 60% of patients with meningococcal meningitis present without septic shock. Clinical signs of meningococcal meningitis are typical of those of other causes of bacterial meningitis and include meningismus, headache, increased intracranial pressure, and mental status changes. In infants, meningitis can often present as poor feeding or lethargy without any focal signs.

N. meningitidis also causes arthritis. Two different types of arthritis result following infection: septic arthritis or an immune-complex-mediated arthritis. Septic

arthritis can occur as an isolated meningococcal infection, but it most commonly presents as a complication of meningococcemia or meningitis. Septic arthritis complicates approximately 10% of meningococcemia and is frequently preceded by an upper respiratory tract infection. It is usually monoarthritic, particularly affecting the knees, and is more common in men. The immune-mediated form of arthritis, which also primarily affects the large joints, results from the deposition of immune complexes in the joint space, and presents as a sterile effusion. The frequency of immune-mediated arthritis complicating acute meningococcal infection ranges from 4% to 50%.

N. meningitidis, particularly serogroup Y, can cause pneumonia as an isolated infection or concurrently with meningococcemia or meningitis. Meningococcal pneumonia occurs in approximately 5–15% of invasive meningococcal disease. Diagnosis of meningococcal pneumonia is challenging given that isolation of the organism in the sputum cannot distinguish between colonization and infection. Blood or pleural cultures that yield *N. meningitidis* can assist with the diagnosis.

Other meningococcal infections such as otitis media infections, epiglottitis, pericarditis, urethritis, and osteomyelitis are rare and may require consultation with an infectious diseases specialist.

Gonococcus is a common cause of neonatal conjunctivitis, also known as ophthalmia neonatorum. Neonates acquire the organism after exposure to maternal colonization; symptoms typically begin within 2–5 days after birth, though can arise in the first 3 weeks of life. Clinical features include prominent eyelid edema and significant mucopurulent discharge, often bilaterally. Rarely invasive gonococcal disease can occur with the microbial entry to the bloodstream via the conjunctivae.

Disseminated infections due to *N. gonorrhoeae* outside the genitourinary tract are uncommon, typically occurring in fewer than 5% of patients. The more common manifestations of disseminated gonococcal infection include bacteremia, septic arthritis, tenosynovitis, and an arthritis-dermatitis syndrome including multiple skin lesions with polyarthralgias. As with meningococcus, when septic arthritis is present, typically single large distal joints are affected, such as knees, wrists or ankles, but multiple joints and small joints (such as interphalangeal joints) can be affected. Likewise, arthritis in patients with gonococcal infections can also be immunologically mediated and sterile in nature. The skin lesions seen with disseminated gonococcal infections can be quite varied, including papules, pustules, and bullae. Gonococcal infections in children outside the neonatal period should prompt a consideration of sexual abuse; see Chap. 71, "Sexually Transmitted Diseases".

The other *Neisseria* species are typically nonpathogenic, but have been associated with bacteremia, meningitis, endocarditis, septic arthritis, and other invasive infections, most typically in immunocompromised hosts or after surgical procedures, but occasionally reported in previously healthy individuals. *N. cinerea* has been specifically linked to ocular infections in neonates. Because these *Neisseria* species are commensal oral flora, they have also occasionally been identified in bite wounds.

Diagnosis

Diagnosing meningococcal infection relies on recognition of clinical signs and symptoms and on isolating the organism from the appropriate body site. Gram stain and culture of blood, cerebrospinal fluid (CSF), and tissue remain the gold standard. In suspected meningococcal meningitis, diagnosis is made by performing a lumbar puncture and obtaining CSF for analysis. Typical CSF findings include an elevated opening pressure, a pleocytosis with a neutrophil predominance, an elevated protein level, and a low glucose level. While meningococcal meningitis can be diagnosed using an antigen test on the CSF, the antigen test is rapid but has poor sensitivity and is not commonly used. Narrowing empiric therapy based on the results of a rapid antigen test alone is therefore not recommended. Nucleic acid testing for *N. meningitidis*, although not commercially available in the United States, is being developed and used in other parts of the world.

Diagnosis of meningococcemia can be more challenging as typical clinical symptoms do not always manifest initially. Gram stain and culture of blood and skin lesions are most helpful in making the diagnosis. Diagnosis of septic arthritis should include joint aspiration with synovial fluid analysis for Gram stain and culture.

The diagnosis of meningococcal pneumonia is challenging as *N. meningitidis* isolated in the sputum cannot differentiate infection from colonization. Blood cultures positive for *N. meningitidis* support the diagnosis, but a pleural effusion sample or pleural biopsy confirms it.

Diagnosis of gonococcal infections can likewise be made in several ways. Diagnosis of genitourinary infections can be made rapidly using nucleic acid amplification methods on urine specimens (see Chap. 69, "Meningitis"). Blood cultures should be obtained if gonococcal bacteremia is suspected, and culture of synovial fluid is routinely indicated and may be positive in up to half of patients with gonococcal septic arthritis.

Differential Diagnosis

For a differential diagnosis of organisms that may cause a specific infectious syndrome (e.g., meningitis, septic arthritis, etc.), please refer to the appropriate chapter. Other gram-negative organisms that can appear coccoid upon microscopic examination include *Moraxella* species (formerly *Branhamella*) and *Kingella* species.

Treatment

The initial treatment of meningococcal disease depends on the severity of the presenting infection. If a patient presents with shock, disseminated intravascular coagulation, and increased intracranial pressure, resuscitation and supportive intensive care should be initiated. If septic shock or meningitis is the presenting illness and *N. meningitidis* is suspected, broad-spectrum antibiotics such as third-generation cephalosporins (cefotaxime or ceftriaxone) should be administered (see Chap. 69, "Meningitis"). Fluoroquinolones are not routinely recommended for empiric treatment of suspected invasive meningococcal disease due to reports of emerging resistance.

Once *N. meningitidis* has been identified on culture from a sterile site (such as blood, spinal fluid, or synovial fluid), antibiotics can be narrowed based on the susceptibility profile. Treatment of chronic meningococcemia is identical to that for acute meningococcemia. The majority of *N. meningitidis* isolates continue to be susceptible to penicillin, which is the preferred treatment. Treatment of meningococcemia for 5–7 days with penicillin is appropriate, although shorter antibiotic courses are being explored. However, cases of *N. meningitidis* infection with reduced susceptibility to penicillin have been documented in certain serogroups (W-135 and C) outside the United States. Alternative treatments in the case of penicillin-resistance or penicillin allergy include cefotaxime, ceftriaxone, and ampicillin. In the low-resource setting, a one-time intramuscular dose of chloramphenicol has also been shown to be effective.

If antibiotics are administered prior to obtaining CSF, interpretation of CSF analysis cannot be relied upon as *N. meningitidis* is killed within 3–4 h of antibiotic administration. Although a CSF pleocytosis may be seen, it is unlikely that culture will yield an organism. The benefit of corticosteroids in meningococcal meningitis has not been established.

In cases of less severe illness such as conjunctivitis, susceptibility testing is not always necessary and empiric treatment is recommended. Susceptibility testing should be initiated only in cases of treatment failures.

Recommended empiric treatment of disseminated gonococcal infections outside the central nervous system includes a third-generation cephalosporin (cefotaxime or ceftriaxone) for 7 days, and should be extended to 10–14 days if meningitis is confirmed or suspected. Antimicrobial treatment can be tailored when culture results are available.

Prognosis

Severe meningococcal disease such as meningitis and sepsis causes sequelae in up to 20% of survivors, including hearing loss, limb loss and skin scarring, seizures, and neurologic disabilities. Untreated neonatal conjunctivitis can progress to corneal ulceration and ultimately blindness, and was formerly a leading cause of blindness worldwide. Other *Neisseria* infections typically resolve without significant sequelae if diagnosed and treated in a timely manner.

Prevention

The quadrivalent conjugate meningococcal vaccine (MCV4) was licensed in 2005 and includes the four most common meningococcal serogroups encountered in the United States (serogroups A, C, Y, and W-135). Most meningococcal disease is caused by these four strains as well as serogroup B, which is not covered in any vaccine. More than 50% of disease in younger children is caused by serogroup B. The meningococcal vaccine is recommended routinely for adolescents 11–18 years of age, for children >2 years of age with risk factors (including terminal complement deficiencies and asplenia), children living in high-risk endemic areas, military recruits, and those living in college dormitories who were not previously vaccinated. A new, more affordably produced conjugate meningococcal vaccine against serogroup A was introduced to sub-Saharan Africa in late 2010 with a goal of widespread immunization to prevent epidemics of meningitis caused by *N. meningitidis* serogroup A. No vaccine is currently available for *N. gonorrhoeae.*

Close contacts of patients with invasive meningococcal disease are considered high risk and chemoprophylaxis is recommended. This includes all household members, persons sleeping in the same dwelling within 7 days of the index case, and all attendees of a daycare or preschool present within 7 days of the index case. Persons who

Table 86.2
Recommended chemoprophylaxis for exposed persons

Infants	Rifampin (2 days)
Children	Rifampin (2 days) or ceftriaxone (single dose)
Adolescents	Rifampin (2 days) or ceftriaxone (single dose) or azithromycin (single dose)
Adults	Rifampin (2 days) or ceftriaxone (single dose) or ciprofloxacin (single dose) or azithromycin (single dose)

came into contact with any secretions from the infected person, such as health care workers taking oral or nasal samples, or health care workers involved in airway management should receive chemoprophylaxis. Chemoprophylaxis is not necessary for health care workers coming into contact with secretions more than 24 h following antibiotic initiation. Persons seated next to the index case on a plane or confined space for more than 8 h should also receive chemoprophylaxis. All chemoprophylaxis should be initiated within 24 h of contact.

Rifampin should be used as chemoprophylaxis in children and rifampin, ceftriaxone, ciprofloxacin, or azithromycin can be used in older children and adults (*Table 86.2*). Chemoprophylaxis is also recommended in children treated for meningococcemia with penicillin or chloramphenicol as these antibiotics do not eradicate nasal carriage. Prophylaxis to prevent neonatal conjunctivitis is routinely and universally indicated, by applying either 1% tetracycline ophthalmic ointment or 0.5% erythromycin ointment to both eyes immediately after birth.

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87 Pertussis

Mohammad Al-Shaalan

Pertussis is an acute respiratory tract infection affecting all age groups. Pre-vaccine era witnessed a high prevalence of disease with a significant morbidity and mortality. Introduction of vaccine resulted in a significant decrease of the disease in children; however, because of waning immunity following natural disease in 7–14 years or vaccination in 4–12 years and because there is no booster vaccination after 7 years of age, the disease incidence increased in the adolescents and adults resulting in a pool of patients who remained a source for infecting others especially young infants who are not yet vaccinated or have received only one dose of the vaccine.

Because of these factors, the disease remained endemic in most of the countries with 50 million cases occurring annually resulting in 400,000 deaths. Most of the morbidity and mortality occur in young infants. However, the number of global reported cases is less than the estimated one (◉ *Fig. 87.1*).

The affected adolescents and adults usually present with a typical presentation of prolonged cough without classis whoop and therefore remain infectious for a long period.

Organism

Pertussis is mainly caused by *Bordetella pertussis* and *Bordetella parapertussis*. Bordetella is a Gram-negative fastidious aerobic, nonmotile bacillus. Therefore, it requires special media for its growth. The first media introduced was Bordet–Gengou agar. Bordet–Gengou medium is composed of potato, glycerol, and cephalexine. Recently, Regan–Lowe medium is being introduced. It is composed of charcoal agar, defibrinated horse blood, cephalexine, and amphoterecin B. In addition, there is a semisolid transport media of Regan–Lowe formula in case there is anticipated delay in culturing the specimen. Both media have similar yield although some studies showed Regan–Lowe to be superior. *B. pertussis* has also been shown to grow in some other media like buffered charcoal, yeast extract agar, and cyclodextrin solid medium.

Bordetella genus include other related species that may cause human disease but milder than that of *B. pertussis*. These species include:

- *Bordetella bronchoseptica*, which is primarily a pathogen in animals. It occasionally causes mild disease in humans.
- *Bordetella homesii* and *Bordetella hinzii* may be isolated from blood in patients with chronic illnesses. *B. henzii* has also been isolated from the respiratory tract of cystic fibrosis patients.
- *Bordetella trematum* is rarely isolated from wound and ear infections.
- *Bordetella petrii* has been isolated from patient with cystic fibrosis.

Pathogenesis

B. pertussis is acquired by inhalation of infected droplets. Once in the nasopharynx, they may invade the lower part of respiratory tract. It has a high preference for respiratory epithelium without systemic invasion. The attachment to respiratory epithelium is mediated by pertussis toxin and lymphocytosis promoting factor. The local damage is mediated by multiple factors that include in addition to pertussis toxin, tracheal cytotoxin, heat labile toxin, and other toxins. Adenylate cyclase and pertussis toxin inhibit the host immune response both by retarding chemotoxis and preventing phagocytosis and intracellular killing.

Clinical Features

After an incubation period of 7–10 days the symptoms start. The disease proceeds through three stages: catarrhal, paroxysmal, and convalescent.

Catarrhal Stage

In this stage, the child has nonspecific symptoms of fever, runny nose, conjunctivitis, and mild cough. This stage lasts for 1–2 weeks and it is usually very difficult to differentiate from symptoms of other respiratory infections.

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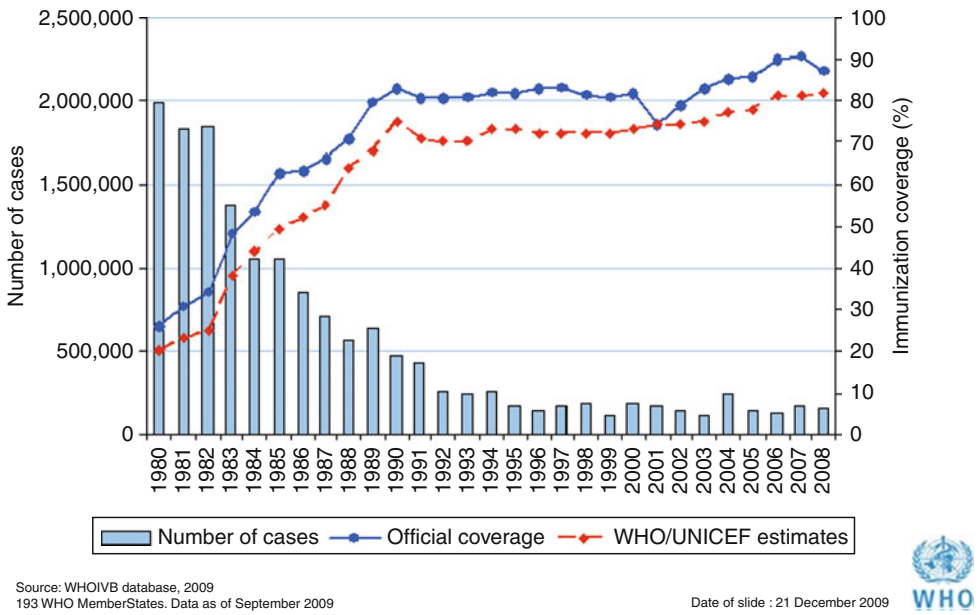

Figure 87.1
Pertussis global annual reported cases and DTP3 coverage, 1980–2008

Paroxysmal Stage

During this stage, the cough evolves into the characteristic pattern of paroxysms. Each paroxysm consists of 10–20 successive coughs that end by deep inspiration that may be associated with whoop due to forceful passage of air through narrow epiglottic opening. Young infants are less likely to have whoop; however, they are prone to develop apneic spells that may be prolonged and result in cyanosis and hypoxia. It is during this stage that hypoxemic insults may result. Such hypoxia may adversely affect brain and thus cause encephalopathy or seizure attacks.

Convalescent Stage

The cough decreases in its intensity; however, the child may remain to have episodes of cough that usually are not in paroxysm. This stage usually lasts for 1–2 weeks but it may persist for months. Recurrence of brief paroxysmal cough during this stage may occur but rare.

Complications

Pertussis is an acute disease that causes significant morbidity and mortality. Pneumonia whether primary or secondary is the most common complication and the most common cause of death among patients with pertussis. Pertussis results in atelectasis and bronchopneumonia in significant number of patients; however, long-term pulmonary sequelae are rare. Secondary bacterial pneumonia is common and therefore therapy directed for these pneumonias in addition to that of pertussis is required. Most common bacterial cases of pneumonia in such patients are *S. pneumoniae, H. ifluenzae*, and *S. aureus*.

Encephalopathy occurs in 8/1,000 and seizure occurs in 3% of affected patients. The presumed cause of these brain insults is hypoxia, toxins produced by *B. pertussis*, and intracerebral hemorrhage. Other complications include otitis media, sinusitis, subconjunctival hemorrhage, epistaxis, subdural hemorrhage, and melena.

Diagnosis

Culture, PCR, and serology are different methods of diagnosis but each has its limitation.

Culture

B. pertussis is fastidious organism that requires special growth media. Therefore in suspected cases, laboratory should be informed to prepare the appropriate media. Culture requires a collection of nasopharyngeal specimen

with a Dacron or calcium alginate swab and sending it immediately to the laboratory in a specific transport media, to be cultured in Regan–Lowe or Bordet–Gengou medium.

There are a number of factors which decrease the sensitivity of the culture:

1. Culture obtained after 7 days of illness.
2. Previous antibiotic usage.
3. Poor specimen collection or poor transportation or media contamination in the laboratory.
4. Previous immunization as the organism load is usually low.

Therefore, having a negative culture does not necessarily exclude the diagnosis:

PCR

A new modality for the diagnosis with a better sensitivity. It has the advantage of ability to be positive even if collected later in the disease course; however, sensitivity decreases after the 14th day of illness.

Serology

EIISA for IgG, IgA, and IgM against pertussis antigens can be done. The best antigen to be used is pertussis toxin. Previous immunization may result in positive test. Recent vaccination usually results in positive IgM and IgG. In acute infection IgA is usually positive; however, it is better to collect acute and convalescent sera for both IgA and IgG. A twofold rise is suggestive of acute infection. In adolescents and adults, a single IgG more than 100 unit/ml is highly suggestive of acute infection.

Antigen Detection Test

Direct fluorescent antibody (DFA) test is a rapid test that has 95% specificity but it is less sensitive 60%. The advantage of DFA is being rapid with result available in 2–4 h. Other experimental rapid tests are DNA hybridization and PCR-based tests but they are not yet widely used.

Treatment

Treatment of pertussis consists of nonspecific supportive measures and directed antibiotic therapy. Supportive measures include maintaining good nutrition, providing oxygen and supporting ventilation if needed. Nonspecific therapy with steroids and salbutamol has been used in few nonrandomized studies with some benefit; however, it cannot be recommended as a standard of therapy as it is not supported by controlled randomized studies. Young infants with severe leukocytosis exceeding 100,000/mm^3 may suffer from severe respiratory distress and pulmonary hypertension leading to respiratory and circulatory failure. Autopsy of such infants has shown obstruction of small- and medium-sized pulmonary arteries with lymphocytes without thrombosis. In such infants, there is some anecdotal report of some benefit from exchange transfusion to reduce the number of leukocytes. Specific antibiotic therapy is recommended in all patients with proven or suspected pertussis. Erythromycin especially the estolate form is very effective against *Bordetella*. The recommended dosage is 40–50 mg/kg/day in four divided doses. The new macrolides (azithromycin and clarithromycin) have been shown to be of equal efficacy with better tolerance. Use of antibiotic in the catarrhal stage (within 2 weeks of illness onset) may abort or ameliorate the progression of the disease. However, if it is not introduced until the paroxysmal stage is started, then there is no efficacy on the disease course; however, it will accelerate the eradication of the organism and thus its contagiousness. The recommended duration of therapy is 14 days; however, new studies have shown 7 days of therapy is equivalent to the longer duration and this has led many authorities to recommend the shorter course of therapy.

Resistance to erythromycin has been reported in occasional cases. Patients who do not tolerate erythromycin should be treated with cortimoxazol at a dosage of 8 mg of trimethoprim 40 mg of sulfamethoxazole/kg/day in two divided doses for 14 days.

Prevention

Isolation

Children suspected to have pertussis should be isolated if hospitalized until the culture is available or the patient is being treated for 5 days with appropriate antibiotics. They should also be prevented from school or day care attendance until they are 5 days on therapy.

Prophylaxis

Household contacts should be prophylaxed with erythromycin 40 mg/kg/day qid for 14 days.

Immunization

Killed whole cell vaccine has proven to be effective in decreasing the prevalence of pertussis and should be given to all infants. Recently, acellular pertussis vaccine with less side effects is being introduced and it may be the recommended future vaccine (see section on immunization).

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88 Pneumococcal Infections

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The pneumococcus *Streptococcus pneumoniae* continues to be a leading cause of morbidity and mortality in all age groups. In children, *S. pneumoniae* is the most common cause of community-acquired pneumonia, otitis media, and recently meningitis, due to the control of *Haemophilus influenzae* infection, which used to be the most common cause of bacterial meningitis, by the effective polysaccharide–protein conjugate vaccines. The significance of *Pneumococcus* is further accentuated because of the recent emergence of penicillin- and multidrug-resistant strains in many countries. The continued frequency and severity of pneumococcal disease, the emergence of penicillin resistance, and the fact that antimicrobial agents do not invariably prevent illness or death underscore the need for better understanding of pneumococcal infections and the development and use of appropriate vaccines.

Etiology

Streptococcus pneumoniae is a gram-positive, lancet-shaped, encapsulated diplococcus. There are 84 different serotypes that are identified by their type-specific capsular polysaccharides. Only smooth, encapsulated strains are pathogenic for humans. Capsular size varies considerably, with types 3, 8, and 37 having very thick capsules. Virulence is related in part to the size of the capsule. Capsular material impedes phagocytosis; therefore, fully encapsulated strains (e.g., type 3) are extraordinarily virulent.

Pneumococci are facultative anaerobes. On solid media, they form unpigmented colonies with α-hemolysis. Immediate and accurate identification can be made by exposing the pneumococcus to homologous type-specific antisera that combine with their respective capsular polysaccharides, thus rendering the capsule refractile (quelling reaction). Pneumococci also can be identified by rapid lysis after exposure to a 10% solution of bile salts.

In contrast to antibodies directed against the capsular polysaccharides, which are protective by promoting opsonization and phagocytosis, antibodies to various cell wall antigens such as C, R, and M antigens confer negligible immunity.

Epidemiology

Pneumococci normally reside in the pharynges of healthy people in all parts of the world. They spread from person to person in droplets of respiratory secretions, and infection of the upper respiratory tract aids spread. Therefore, both colonization and disease are more common in winter and spring. The colonization rate depends on age, exposure to young children, and the specific population studied. Maximum colonization rates occur in young children in institutions. Most children are colonized at some time during the course of a year. More than 90% of children between 6 months and 5 years carry *Pneumococcus* at some time. Adults with no contact with young children have a low colonization rate of 5%. Approximately 85% of infections are caused by serotypes 1, 4, 6, 9, 11, 14, 15, 18, 19, and 23, and 50% are caused by serotypes 6, 19, and 23.

Streptococcus pneumoniae is the most common cause of bacterial meningitis, otitis media, and pneumonia, with peak incidence at 3–6 months, 6–12 months, and 12–18 months, respectively. The increased susceptibility of children younger than 2 years of age to pneumococcal infection may be due at least in part to the inability of these infants to mount an antibody response to polysaccharide capsule antigens. In addition to young age, the frequency and severity of pneumococcal infections are increased in patients with sickle cell disease, asplenia, B-cell immune deficiencies, the acquired immunodeficiency syndrome, complement deficiencies, and underlying malignancy.

Pathogenesis

Pneumococci reach their target by direct extension from colonized mucosal surfaces or by hematogenous spread. Thus, most cases of otitis media result from extension of *Pneumococci* from the nasopharynx to the middle ear through the Eustachian tube, and most pneumococcal pneumonia cases spread from aspiration of pharyngeal secretions. Pneumococcal meningitis, in contrast, follows pneumococcal bacteremia except in the occasional case of

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direct spread to the meninges via a basilar or temporal skull fracture. It is believed that a preceding viral infection may enhance pneumococcal growth and invasion by producing mucosal damage, diminishing epithelial ciliary activity, and depressing the function of alveolar macrophages. In these tissues, *Pneumococci* can spread directly or invade the lymphatics and bloodstream.

Once *Pneumococci* reach the target tissue and multiply, severe inflammation ensues. Contrary to capsular polysaccharides, which have been shown to be nontoxic, cell wall active components of *Pneumococci* have been shown recently to induce severe inflammation in experimental animals. Exposure of tissues to such components has been associated with production of mediators of inflammation such as tumor necrosis factor and interleukins, among many others. These cytokines have been detected in high concentrations in body fluids infected with *Pneumococci*. Destruction of tissues results from direct bacterial invasion and the host inflammatory response incited by cell wall active components. (For details of pathogenesis at each site of infection [pneumonia, meningitis, otitis media], please refer to the respective chapter.) Severity of and survival from pneumococcal disease depends on the site of infection, underlying disease, and age of the patient. Infants and the elderly and patients with underlying immunodeficiency usually have severe disease and are more likely to have sequelae.

Deficiency of the terminal components of complement (C3 through C9) has been associated with recurrent pyogenic infections, including those caused by *Pneumococcus*. Splenectomized patients or patients with diseases that interfere with splenic functions are at an increased risk for severe pneumococcal infection, presumably related to deficient opsonization and the absent/decreased filtering functions of the spleen on circulating bacteria. In patients with sickle cell anemia, the greatest risk is in infants younger than 2 years of age. With advancing age, patients with sickle cell disease are able to mount an anticapsular antibody response, thereby reducing but not eliminating the risk of overwhelming pneumococcal sepsis.

Clinical Manifestations

The symptoms and signs of pneumococcal infections are related to the site of infection. Although *Pneumococci* most commonly cause bacteremia, otitis media, pneumonia, and meningitis, they can produce disease in virtually any organ. (Please refer to chapters addressing each specific site for detailed clinical presentation.)

Diagnosis

Isolation of *Pneumococci* from certain body fluids establishes a firm diagnosis. Examination of a Gram-stained smear offers prompt suggestive information, but both α-hemolytic streptococci and group B streptococci may closely mimic the appearance of *Pneumococci*. The quelling reaction is a helpful and rapid method in serotyping the bacteria. Blood cultures should be obtained in infants younger than 2 years of age who present without focal infection but who are toxic and not consolable, or have leukocytosis. Patients with focal infections such as pneumonia, arthritis, meningitis, and osteomyelitis should have blood cultures obtained before initiating antibiotic therapy.

Recently, the latex particle agglutination test has been shown to be helpful in establishing the diagnosis rapidly in patients with meningitis and bacteremic focal infections. The test is not sensitive enough in nonbacteremic pneumonia and otitis media. Although pneumococcal infections are associated with elevated erythrocyte sedimentation rate and leukocytosis, these findings are not specific.

Treatment

Penicillin has been the treatment of choice for pneumococcal infections. However, penicillin resistance among strains of *S. pneumoniae* has become a problem of international proportions. In certain areas of the world, most pneumococcal strains are either relatively or completely resistant to penicillin. Penicillin-resistant *Pneumococci* are not only resistant to other β-lactams but also to erythromycin, trimethoprim-sulfamethoxazole (TMP-SMX), tetracycline, and, in some countries, rifampin.

Acute otitis media and meningitis caused by penicillin- and cephalosporin-resistant pneumococci have been especially difficult for pediatricians to treat because traditional empirical therapy with β-lactams is often ineffective. Concentrations of the penicillins and cephalosporins in cerebrospinal fluid (CSF) and middle ear fluid are inadequate to achieve prompt eradication of some intermediate (minimal inhibitory concentration [MIC] 0.1–1.0 μg/mL) and most highly (MIC ≥2.0 μg/mL) penicillin-resistant pneumococcal strains. Therefore, unconventional therapeutic agents such as clindamycin and ceftriaxone for acute otitis media and vancomycin plus ceftriaxone or rifampin for meningitis might be necessary in these patients.

Penicillin G is the drug of choice for penicillin-susceptible strains. Oral penicillin V (50–100 mg/kg/day) for minor infections, intravenous penicillin G (200,000–250,000 U/kg/day) for bacteremia or pneumonia, and intravenous penicillin G (300,000 U/kg/day) for meningitis are recommended. Vancomycin (60 mg/kg/day) is effective in treatment of relatively or completely resistant pneumococcal strains. In areas with high or increasing incidence of penicillin-resistant *Pneumococci*, vancomycin should be the initial therapy for suspected pneumococcal meningitis or severe infections. For patients who are allergic to penicillin and do not have meningitis, erythromycin, cephalosporins, TMP/SMX, and chloramphenicol provide effective alternatives for susceptible strains.

Prevention

The presently available nonconjugated pneumococcal vaccine has proved to be immunologic and associated with few untoward reactions. However, responsiveness is unpredictable in children younger than 2 years of age, where the peak incidence of pneumococcal disease occurs. An effective protein-conjugate pneumococcal vaccine that can be given at 2, 4, and 6 months of age is now being evaluated.

Immunization with the available nonconjugated vaccine is recommended for children over 2 years of age who have sickle cell disease, functional or anatomic asplenia, nephrotic syndrome, or CSF leaks and children with human immunodeficiency virus infection. Reimmunization might be given to certain high-risk patients. Immunization does not completely prevent pneumococcal infections. Therefore, penicillin prophylaxis is still indicated in the high-risk patients. Recent data suggest that penicillin prophylaxis is not warranted in sickle cell anemia patients beyond 5 years of age.

Prognosis

Morbidity and mortality after pneumococcal infections is variable depending on the site of infection, the virulence of pneumococcus, host defense factors, and the adequacy of treatment (see chapters on specific diseases for details).

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89 Rickettsial Infections

Stephanie H. Stovall · Richard F. Jacobs

Definition

Rickettsiae are pleomorphic intracellular bacteria causing a variety of human diseases in all parts of the world. These organisms are transmitted by arthropod vectors and the mammals on which they feed. The prevalence of these infections is largely dependent upon the particular vectors that transmit them. The Rickettsiae are divided into the spotted fever group (SFG) and typhus groups. Rocky Mountain Spotted Fever (RMSF) is the most recognized rickettsial disease infecting humans in the United States, while Mediterranean Spotted Fever (MSF), which is also known as African tick-bite fever or Boutonnese Fever, is common in Europe and Africa. The typhus group is most known for endemic typhus and epidemic typhus. While it is not of the genus Rickettsia, scrub typhus (caused by *Orientia tsutsugamushi*) is a disease similar to the other typhus group diseases and will not be discussed in this chapter.

Etiology

Rickettsiae are obligate intracellular pleomorphic organisms that live inside eukaryotic cells and stain weakly Gram negative. Common agents in the SFG include *R. rickettsii* (RMSF), *R. akari* (Rickettsialpox), and *R. conorii* complex (MSF). Typhus group organisms include: *R. prowazekii* (epidemic), *R. felis* (endemic), and *R. typhi* (endemic). Scrub typhus is caused by *Orientia tsutsugamushi*.

Epidemiology

Diseases from the spotted fever group have been found in virtually all parts of the world.

Geography. RMSF is found primarily in the United States, but has also been found in Canada and Mexico and some parts of central/South America. The CDC reports the annual incidence of RMSF in the US is 2.2 cases per million persons with five states (North Carolina, South Carolina, Arkansas, Oklahoma, and Tennessee) reporting half the cases. Mediterranean Spotted Fever has been described in Europe and Africa with highest rates described in areas surrounding the Mediterranean. Incidence rates are reported around 50/100,000 persons per year in the Mediterranean region; however, the disease is not reportable in many European countries, so estimates may far underestimate true incidence. Both RMSF and MSF are more commonly diagnosed in the summer seasons corresponding with the highest tick burden. In the last decade there have been five other similar spotted fever diseases emerging caused by subspecies of *R. conorii*. Rickettsialpox is found in highly populated metropolitan cities of Asia and South Africa. Epidemic typhus (caused by *R. prowazekii*) is more prominent in periods of crowding, poverty, and poor hygiene. Historically it is thought to be the cause of massive numbers of deaths during times of war and famine. Most recently, it has been associated with outbreaks occurring in the late 1990s in sub-Saharan Africa and South America. Endemic (or murine) typhus is reported worldwide and is specifically associated with areas of high rodent burden, particularly near seaports and coastal regions.

Age, Sex. Approximately two thirds of reported cases of RMSF are in children under the age of 16, with the largest group 5–9 years. MSF occurs in all age-groups and both sexes. It is common for patients with MSF to have had contact with dogs. There are no age or sex discrepancies among the typhus group.

Vectors. *R. rickettsii* is transmitted to humans during the feeding process of several species of ticks found in North America including Dermacentor variabilis (American dog tick), Dermacentor andersonii (Rocky Mountain wood tick), and others. *R. conorii* is transmitted via the Rhipicephalus sanguineus (brown dog tick). Epidemic typhus is transmitted between people through bites from the human body louse. The louse becomes infected when feeding on an acutely infected person and then dies within 2 weeks. Unfortunately, *R. prowazekii* can persist even in the dead louse and serve as infectious material to those exposed. The rickettsiae are deposited in the louse feces during feeding and then are introduced into the bite, the conjunctiva or mucosa. Endemic typhus is transmitted by fleas that feed off rats. The fleas become

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Table 89.1
Rickettsial diseases, vector, clinical manifestations, mortality rates, and treatment

Rickettsial organism	Vector	Disease	Geographic location	Eschar at bite	Generalized rash	Mortality	Treatment
R. akari	Mites	Rickettsialpox	Widely distributed	Yes	Yes	No	Tetracycline
R. conorii complex	Tick	Mediterranean spotted fever	Europe and Africa	Yes	Yes	Rare	Doxycycline
R. conorii subsp israelensis	Tick	Israel spotted fever	Europe	Yes	Yes	~20%	Doxycycline
R. prowazekii	Louse	Epidemic typhus	Worldwide (historically); South America and Africa	Yes	Yes	Yes if untreated	Doxycycline
T. typhi	Flea	Endemic typhus	worldwide	Yes	Yes	<4% untreated	Doxycycline
Orientia tsutsugamushi	Mites	Scrub typhus	Asian Pacific; New Guinea	Yes	<50%	Rare if treated	Doxycycline; chloramphenicol; rifampin; azithromycin

Adapted from Table 179-1, Eremeeva ME, Dasch GA (2008) Other Rickettsia species. In: Long SS (ed) Principles and practice of pediatric infectious diseases, 3rd edn. Philadelphia, pp 925–926

infected for life and transovarially infect their progeny. These fleas deposit rickettsia in feces that are introduced into the bite wound or through the conjunctiva.

Table 89.1 provides additional epidemiologic information.

Pathogenesis

Rickettsiae infect endothelial cells producing a small vessel vasculitis. They can multiply in the cytosol or nucleus of the cells.

Rocky Mountain Spotted Fever. *R. rickettsii* is inoculated into the human skin by the tick vector. The organism attaches to endothelial cells of the host by means of a rickettsial outer membrane protein which triggers endocytosis. Release of the organism from the endosome and subsequent replication triggers polymerization of actin in the host cell which allows intracellular movement of rickettsia. Oxidative injury to host cells causes irreversible damage to infected cells leading to diffuse endothelial injury and vascular leak. This vasculitis causes multisystem disease manifesting in a variety of clinical signs and symptoms affecting potentially ever organ system.

Mediterranean spotted fever. A dark eschar forms as a result of mononuclear infiltration at the site of the bite causing the classic tache noire lesion. These lesions are more commonly found on the head of children and the extremities of adults. Similar to RMSF, a diffuse vasculitis results, involving endothelial cells of blood vessels throughout the body. Any organ can be involved with a wide variety of symptoms and signs including but not limited to: phlebitis, pericarditis, myocarditis, pleuritis, ARDS, nephritis, conjunctivitis, delirium, elevation of transaminases, and mild hepatomegaly.

Epidemic typhus. *R. prowazekii* infect endothelial cells preferentially using a rickettsial adhesion protein and can multiply in the cytoplasm. After killing of the host cell, these rickettsia are released and must infect other endothelial cells in order to continue to replicate. Vasculitis can be complicated by intravascular clotting or even gangrene.

Endemic typhus. *R. typhi* behaves similar to *R. prowazekii*; however, it can polymerize intracellular actin allowing some organisms to escape before cell death.

Pathology

The small vessel vasculitis caused by the offending Rickettsiae may produce various rashes that may be macular or petechial in nature. This vasculitis may also cause significant capillary leak and hypotension. Vasculitis of end organs (i.e., lungs or brain) may lead to respiratory failure or death.

Some rickettsial diseases (scrub typhus) commonly cause an eschar with perivascular inflammation at the site of inoculation.

Clinical Manifestations: Symptoms, Signs

Multisystem involvement particularly with rash, fever, and headache should trigger the clinician to consider rickettsial diseases. Many also exhibit an eschar at the site of inoculation.

Rocky Mountain Spotted Fever typically begins with fever, myalgia, and headache starting approximately 1 week after infection. In the United States it is frequently referred to as the "summertime flu" because the early symptoms are often "flu-like." Around the second to fourth day a rash begins to develop. Early on it appears macular and later progressing to petechial. It classically begins at the ankles and/or wrists with progression centrally and distally including the palms and soles. The full evolution of the rash may take 5 days. Most patients will present with ambulatory mild symptoms; however, untreated, many will progress to septic shock with or without respiratory failure. Many patients with RMSF will exhibit signs of central nervous system involvement which may be as mild as headache or as severe as seizures and coma. *Table 89.2* shows clinical and laboratory signs and relative frequency of occurrence. In the first 3 days of the illness, most patients have minimal symptoms that can easily be mistaken for a viral prodrome. In fact, many patients who seek medical care within the first few days of RMSF are treated symptomatically for viral illnesses. Few patients present for care with the classic triad of "fever, rash, and history of a tick bite." Less than half of patients with proven RMSF report a history of a tick bite even in retrospect. The characteristic rash of RMSF is seldom present at the onset of illness typically beginning around day 3 of symptoms; however, up to 20% of patients never develop a rash. Many adolescent and adult patients complain of an unremitting headache but young children are unlikely to verbalize this complaint. Of the three most common complaints recognized with RMSF (fever, headache, and rash), less that 60% of patients exhibit all three simultaneously. Absence of the classic triad should never be cause for delaying or avoiding therapy if RMSF is suspected because once the diagnosis is confirmed; the patient may well have developed severe morbidity or succumbed to the disease. The vasculitis of RMSF can involve any organ or system and frequently involves more than one system at the time of presentation, though early signs may be mild. Common signs may include nausea or vomiting (up to 70%), elevations of transaminases, pulmonary edema, or infiltrates sometimes severe enough to cause acute respiratory distress syndrome (ARDS), congestive heart failure, cardiac arrhythmia, mild CSF lymphocytosis, alteration of mental status, retinitis, conjunctival suffusion, and nephritis with resulting renal failure.

Table 89.2
Clinical signs and symptoms of RMSF in pediatric patients described in the published literature

Fever >39°C	>95%
Headache	~60%
Rash	80–95%
Myalgia	<50%
Respiratory symptoms	10–40%
Altered level of consciousness	~33%
History of tick bite	<50%
Thrombocytopenia $<150 \times 10^3$	~60%
Hyponatemia (<137)	>50%

Resources for parents
http://www.cdc.gov/ticks/diseases/rocky_mountain_spotted_fever/faq.html
http://www.cdc.gov/ticks/avoid/index.html
http://www.cdc.gov/ticks/removing_a_tick.html

Laboratory studies that support a diagnosis of RMSF are also highly variable. For instance depending on the stage of disease, the patient may have a normal, elevated, or low serum white blood cell count. Findings of hyponatremia and hypoalbuminemia often reflect the degree of vascular permeability. Thrombocytopenia is common, occurring in approximately 60% of pediatric patients.

Mediterranean Spotted Fever. Approximately 1 week after inoculation, the symptoms start abruptly with fever (>93%), myalgia, maculopapular rash (>94%), and headache. The rash typically involves the entire body including the palms and soles. Many patients (>60%) will also have a characteristic eschar at the site of inoculation (taché noire).

Epidemic typhus. High grade fever, severe headache, and rash occur 1–2 weeks after inoculation. The rash typically starts as macular and blanching on the trunk and spreads to extremities (sparing the palms and soles) while becoming fixed and sometimes purpuric or hemorrhagic. In extremely dark-skinned individuals the rash may not be appreciated, but evidence of vasculitis can sometimes be seen on the soft palate. Many will develop

constipation, dry cough, and jaundice. Neurologic abnormalities ranging from drowsiness to delirium or meningoencephalitic syndrome resulting in deafness or coma can occur. Patients have persistent symptoms until treatment or recovery. Prompt treatment relieves symptoms rapidly, typically without sequelae. Patients may have recrudescent symptoms up to many years later (Brill-Zinser disease). Recrudescent disease is similar but often less severe. Untreated, mortality rates are as high as 10–50%, with highest rates in those with malnutrition or chronic illnesses.

Endemic typhus. The initial symptoms of infection with *R. typhi* include fever, headache, and rash occurring approximately 5–10 days after inoculation. The headache and fever are usually milder than that found in epidemic typhus and symptoms resolve without treatment after 2–3 weeks. Treated patients will recover within 3 days. Mortality rate is <1%.

Diagnosis

The diagnosis of any rickettsial infection requires the clinician to consider the possibility or probability of exposure to the vectors which transmit these diseases. None of the rickettsial diseases can be reliably detected by commercially available rapid diagnostic tests during the acute phase of illness and many of the diseases left untreated will incur significant increases in morbidity and mortality.

Rocky Mountain Spotted Fever. Many patients seeking care for RMSF will be misdiagnosed early in the course due to nonspecific symptoms. Early laboratory findings may include hyponatremia and thrombocytopenia, but these are only found in about half of pediatric patients. Antibody-based testing through latex agglutination, indirect immunofluorescent antibody (IFA), enzyme immunoassay (EIA), or complement fixation can be helpful if positive, but are typically only positive after the first week of illness. A definitive diagnosis can be made by acute and convalescent serologic testing 2–3 weeks apart demonstrating a fourfold rise in titers. PCR testing is not commercially available, but is available through the Centers for Disease Control and Prevention. Sensitivity and specificity of Weil-Felix testing is poor and should not be used for diagnosis of RMSF.

Epidemic typhus. A fourfold rise between acute and convalescent serology (2–3 weeks apart) by IFA, EIA, or latex agglutination can establish the diagnosis. Likewise, testing is available though the CDC by immunohistochemistry or PCR of tissues.

Endemic typhus. A fourfold rise between acute and convalescent serology (2–3 weeks apart) by IFA, EIA, complement fixation, or latex agglutination confirms the diagnosis, and specific IgM by EIA can distinguish endemic and epidemic typhus if necessary. PCR or immunohistochemistry staining of tissues is available through the CDC.

Differential Diagnosis

Contact and exposure history is necessary to assess the likelihood of rickettsial diseases in patients presenting with symptoms of fever and rash.

Diseases causing fever and rash in childhood that can mimic the symptoms of RMSF include: meningococcemia, enteroviral sepsis, pneumococcal sepsis, typhoid fever, leptospirosis, secondary syphilis, rubella, scarlet fever, ricketsialpox, murine typhus, or ehrlichiosis.

After the rash of MSF appears it can look similar to measles, meningococcemia, secondary syphilis, or other rickettsial spotted fever group infections, particularly in cases where the tache noire is absent.

The progression of rash in patients infected with epidemic typhus is opposite to that of RMSF as it appears on the trunk and spreads peripherally and uncommonly involves palms and soles. Endemic typhus is usually mild with an evanescent rash without petechial character and may be mistaken for a viral exanthem.

Treatment

General Care. Patients presenting with shock should be volume resuscitated aggressively. Electrolyte abnormalities rarely require replacement once perfusion has normalized. Treatment for other infectious causes of septic shock should be administered simultaneously until certain diagnoses are excluded (i.e., meningococcemia, pneumococcal sepsis).

Rocky Mountain Spotted Fever. The treatment of choice for RMSF is doxycycline at 2.2 mg/kg/dose given twice daily (adult maximum dose: 200 mg/day). Administration of doxycycline is dependent upon the patient's clinical condition. Many ambulatory patients and those hospitalized for hydration and febrile illness of undetermined significance can receive doxycycline orally. Patients with septic shock, severe dehydration, vomiting, or significantly altered mental status should receive doxycycline orally to assure adequate absorption. Length of

therapy is dependent upon duration of fever. Doxycycline should be given at least 3 days beyond clinical improvement. Most patients will require 5–7 days of total therapy. Tetracycline antimicrobials have been associated with staining of permanent teeth. For this reason, they are not routinely recommended for children under 8 years of age while the enamel of permanent teeth is developing. However, because RMSF is a life-threatening infection and there is no evidence of tooth staining in patients treated with a single course of doxycycline, it is preferred treatment for this disease in all age-groups. One study shows that it requires more than six courses of tetracycline therapy in patients with developing teeth to cause significantly recognizable tooth staining. The only other potential therapeutic agent is chloramphenicol which is currently unavailable in the United States. Chloramphenicol has been associated with poorer outcomes compared to tetracyclines and is inferior treatment for Ehrlichiosis and Anaplasmosis which can occur in similar geographic areas and are often clinically indistinguishable from RMSF. Coupled with these findings and the high risk of aplastic anemia associated with chloramphenicol administration, doxycycline is the mainstay of treatment for RMSF in the United States.

Mediterranean Spotted Fever. The treatment of choice for MSF is doxycycline (same dose as RMSF); however, alternatives include chloramphenicol, ciprofloxacin, clarithromycin, or azithromycin.

Epidemic typhus. Effective treatment includes doxycycline (2.2 mg/kg/dose) twice daily for 7–10 days or chloramphenicol (12.5 mg/kg/dose) every 6 h for 7–10 days. Like in RMSF, use of chloramphenicol is associated with worse outcomes in children compared with tetracycline therapy. Single dose therapy for adults has been used for control in outbreak situations.

Endemic typhus. Like epidemic typhus, the treatment of choice is doxycycycline; chloramphenicol treatment increases the risk of relapse. Ciprofloxacin has been used successfully in adults. There appears to be no advantage to combination therapy.

Prognosis

Rocky Mountain Spotted Fever. Prior to the widespread use of anti-rickettsial therapy, the mortality rate of RMSF was 10–30% with surviving, untreated patients recovering after 2–3 weeks of illness. The majority of patients treated within the first 5 days of symptoms will recover completely without sequelae; however, even with treatment, approximately 3–5% of infected patients die usually within the first week of illness. Kirkland et al. noted the increased risk of death in patients treated beyond 5 days of initial symptoms (22.9%) compared with those treated within the first 5 days of symptoms (6.5%).

Mediterranean Spotted Fever. Fatality rates are up to 2.5%; however some studies have suggested an increase in severe disease and higher prevalence of sequelae in the last decade, some of which is likely related to particular subtypes of R. conorii (e.g., Israeli subtype). Patients who have renal failure are more likely to have a fatal outcome, and those with significant neurologic involvement have high rates of persistent neurologic sequelae.

Epidemic typhus. Untreated, 10–50% of infected people will die. Patients severely affected may have persistent neurologic sequelae including transverse myelitis, hemiparesis, or neuropathy. Recovered patients may also develop recrudescent disease, sometimes even decades later. Patients treated early in the course of illness typically recover uneventfully without lasting sequelae.

Endemic typhus. Untreated, mortality rates are approximately 4%, but with treatment fatalities are minimal. Elderly patients or those with underlying diseases affecting the liver or kidneys have more severe disease when infected with R. typhi.

Patients with Glucose-6-Phosphate Deficieny (G-6PD) are at increased risk of morbidity and mortality if they become infected with any rickettsial disease.

Prevention

Rocky Mountain Spotted Fever, Mediterranean Spotted Fever, and other tick-borne rickettsioses. Use of DEET during activities likely to encounter ticks, inspection for ticks after outdoor exposure, and environmental control of ticks is effective at preventing tick-borne spotted fever group rickettisioses. There is no vaccine available to prevent infection with *R. rickettsii* or *R conorii.* Removal of attached ticks should be done with tweezers or similar device by grasping the tick gently, close to the attachment point and pulling straight upward evenly while avoiding crushing the body.

Epidemic typhus. Insecticides containing pyrethrin to treat areas of infestation, decontamination of body louse infested clothing, and treatment of people infested with body lice are necessary to prevent epidemic typhus. There is currently no vaccine available to prevent epidemic typhus.

Endemic typhus. Prevention of endemic typhus includes avoidance of rodent infested surroundings and flea and rodent control programs. There is no vaccine to prevent endemic typhus.

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90 *Salmonella* Infections

Mohammad Al-Shaalan

Salmonella is a gram-negative bacillus that results in a myriad of human diseases ranging from mild gastroenteritis to severe typhoid fever. Non-typhoidal *Salmonella* infections are a major cause of diarrheal disease in children accounting for 20% of the two million death that occur annually due to diarrheal illnesses especially in developing world. Typhoid or enteric fever is still endemic in many of the developing countries, particularly south central and southeastern Asia. Worldwide, almost 21 million cases of typhoid fever occur every year, resulting in 217,000 deaths. *Salmonella paratyphi* is increasing in incidence in many of Asian countries as a cause of enteric fever.

Microbiology

Salmonella is a gram-negative, motile, flagellated, and encapsulated bacillus that belongs to Enterobacteriaceae family. It is non-lactose fermenter. It grows in most artificial culture media; however, selective media are used to inhibit the other bacteria and allow *Salmonella* to grow in pure culture so it can be identified.

Salmonella nomenclature is confusing; however, the last agreement was to divide *Salmonella* into three species: *Salmonella enterica*, *Salmonella bongari*, and *Salmonella subterraned*. Each species has a number of subspecies, and each subspecies has a number of serotypes or serovars Table 90.1. Most cases of gastroenteritis are caused by *S. enteritides* group, whereas enteric fever is caused by *S. typhi, S. paratyphi A, B, and* C.

Pathogenesis

Salmonella reaches the gastrointestinal tract after ingesting contaminated foods or drinks, especially poultry or dairy products. The infecting dose is usually 10^5–10^6 organisms; however, lower doses produce illness in more vulnerable hosts like young infants, immunocompromised patients, patients with hemoglobinopathies, elderly patients, and patients with achlorohydria or who have gastrectomy.

Once in the intestine, it adheres to the mucosa and then passes to the lamina propria where they proliferate and stimulate an inflammatory response which is mainly of polymorphonuclear cells in cases of gastroenteritis and mononuclear cells in cases of enteric fever. Polymorphonuclear cells stimulate production of prostaglandins which in turn stimulate fluid secretion and diarrhea. In cases of enteric fever, mononuclear cells travel from lamina propria via lymphatics into local lymphoid tissue in the Peyer's patches and then via thoracic duct into systemic circulation (primary bacteremia) where they then disseminate into the reticuloendothelial tissues in the liver, spleen, and bone marrow. From there, they then invade blood, causing secondary bacteremia with resultant dissemination to different organs.

Clinical Features

Non-typhoidal Salmonellosis

Almost all species of *Salmonella* can cause human diseases mostly in the form of enteritis. However the most common serovars belong to *Salmonella enterica*. The acquisition of infection occurs through eating contaminated foods or water. Most of culprit foods are those of poultry origin, specifically eggs. Many outbreaks have been attributed to eating contaminated eggs. Other sources include contact with infected animals, especially birds and reptiles.

Gastroenteritis

Gastroenteritis is the most common presentation of *Salmonella* infections. After an incubation period of 6–48 h, the patient starts to have diarrhea which is usually watery and associated with blood in some occasions. In contrast to shigellosis, there is not much mucoid secretion with diarrhea. Other symptoms of fever, abdominal pain, and dehydration are usually present. The symptoms persist for 2–7 days and then resolve spontaneously.

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Table 90.1
Current *Salmonella* nomenclature

Taxonomic position (writing format) and nomenclature				No. of serotypes in each species or subspecies [22]
Genus (capitalized, italic)	Species (italic)	Subspecies (italic)	Serotypes (or serovars) (capitalized, not italic)	
Salmonella	*enterica*	*enterica* (or subspecies I)	Choleraesuis, Enteritidis, Paratyphi, Typhi, Typhimurium	1,504
		salamae (or subspecies II)	9,46:z:z39	502
		arizonae (or subspecies IIIa)	43:z29:-	95
		diarizonae (or subspecies IIIb)	6,7:1,v:1,5,7	333
		houtenae (or subspecies IV)	21:m,t:-	72
		indica (or subspecies VI)	59:z36:-	13
	bongori	subspecies V	13,22:z39:-	22
	subteranea			

From Su L-H, Chiu C-H (2007) *Salmonella:* clinical importance and evolution of nomenclature. Chang Gung Med J 30(3):210–219

Bacteremia

Five percent to 10% of patients with *Salmonella* infections may develop bacteremia. This might have been preceded by diarrhea, or it may arise without any preceding gastrointestinal symptoms. In immunocompetent children, it is rare and usually transient and benign. However, invasive disease in association with bacteremia is more common in certain groups of hosts, including those who are 3 months old or younger and immunocompromised hosts. Affected patients usually present with fever, lethargy, loss of weight, and headache. Most of the patients have isolated bacteremia; however, 10% may have their bacteremia complicated by local suppuration which most commonly involves meninges, bones, or lungs. Other organs may be involved like joints, liver, kidneys, prostate, testicles, pericardium, or endocardium. A rare complication that is more common in adults is aortitis. This complication is associated with high mortality. Recurrent bacteremia is an indication of an underlying immunodeficiency status, especially interleukin-12 deficiency.

Illustrative case:

A 2-year-old girl presented with history of fever and diarrhea. Blood culture grew *Salmonella enteritidis*. There was no evidence of any focal infection. Her symptoms recovered after receiving appropriate antibiotic. Two weeks after discharge, she presented with fever. Blood culture grew again *Salmonella enteritidis*. She was treated with antibiotic and responded well. She was investigated for possible focal lesion, including CT scan of brain, which came to be normal. CSF analysis was normal, and CSF culture was negative. Bone scan was negative. She was discharged home after treatment completion. Again she came back 2 weeks later with fever and blood culture grew *Salmonella enteritidis*. At this point, immunological work up was done and came to be normal. Interleukin 12 assay was done and came to be deficient. She was placed on cotrimoxazole prophylaxis after completion of therapy and continued to do well.

Enteric Fever

S. typhi and *S. paratyphi* A, B, or C may result in a severe form of infection, called enteric fever. Enteric fever is a syndrome characterized by insidious onset of lethargy, myalgia, headache, loss of appetite and loss of weight, and fever. It is still a major cause of morbidity and mortality in developing countries, especially Asian ones. In year 2000, almost 21 million cases of *Salmonella typhi* and five million of *Salmonella paratyphi* occurred worldwide. Endemic persistence in these countries is attributed to poor sanitarian conditions. Although there has been success with use of typhoid vaccine, paratyphi is becoming more in frequency. The other concern about enteric fever endemicity is increasing incidence of resistance to fluoroquinolones and third-generation cephalosporins. The main clinical feature of enteric fever is the presence of fever which follows a stepladder pattern starting to increase gradually until it reaches a maximum of 40–41°C in 5–7 days. Some patients present with fulminant illness with high fever, drowsiness, anemia, and shock, but this is rare. During the first week of illness, most patients are constipated; however, by the second week, diarrhea

develops. Rose spot rashes usually appear by end of the first week as faint blanching macular erythematous or rose-colored lesions over the chest and upper abdomen. They last for 2–3 days and then disappear.

Complications of enteric fever occur in up to 3–5% of patients and include intestinal hemorrhage and perforation (the most common) occurring by the second to third week of illness. Other complications include arthritis, osteomyelitis, pneumonia, meningitis, pyelonephritis, hepatitis, cholecystitis, orchitis, parotitis, tonsillitis, and lymphadenitis.

Diagnosis

The gold standard method of diagnosis is isolating the organism from infected specimens. In cases of gastroenteritis, stool can be cultured on Xylose-Lysine-Deoxycholate (XLD) medium or Hekton enteric medium. These media are used to prevent the growth of other normal flora of the intestine.

Specimens from sterile body sites can be cultured on blood or chocolate agar, and the organism can be identified by microscan or ABI-20 identification system. In addition, biochemical characters of *Salmonella* can help in identification.

These include ability to ferment glucose but not lactose. On TSI or KIA tube, they form alkaline slant and acid butt with gas and H_2S production. *S. typhi* produces only a scant amount of H_2S.

In cases of enteric fever, *Salmonella* can be isolated from blood during the first week and from stool or urine by the second week of illness. However, bone marrow remains the most sensitive specimen for isolating the organism even if the patient has been pretreated with antibiotics.

Other diagnostic aids include WBC, which is usually low in count and is associated with neutropenia and bandemia. Liver transaminases, alkaline phosphatase, and LDH are usually elevated. Serology remains shorthanded in diagnosing *Salmonella*. The standard test is Widal test; however, it lacks sensitivity and specificity and cannot be relied upon in diagnosing *Salmonella* infections.

New serology test for detecting antibodies and antigens are in progress. Currently, there is latex agglutination slide test which is used to identify organism isolated in the culture media therefore shortening the period of identifying the organism.

Treatment

Antibiotic therapy of *Salmonella* infections is indicated in the following situations:

1. Gastroenteritis in infants <3 months of age, in immunocompromised hosts, in patients with hemoglobinopathies, in patients who are toxic and moribund, and in those with associated bacteremia
2. Any patients with bacteremia
3. Enteric fever
4. Patient with focal suppuration like meningitis, osteomyelitis, etc.

Over the last two decades, there has been increasing emergence of multiresistant *Salmonella,* especially *S. typhi,* which renders therapy difficult. Therefore, therapy should be directed by local sensitivity pattern of the organism. Based on available data, a significant portion of *S. typhi* is resistant to chloramphenicol, amoxicillin, and trimethoprim/sulfamethoxazole in most of the developing countries. The available alternative includes third-generation cephalosporins (cefotaxime or ceftriaxone) and fluoroquinolones which are not recommended in children. Recently, there is an increasing report of some *Salmonella* strains that have reduced susceptibility to fluoroquinolones. These strains have an MIC between 0.25–1 mg/L. In addition these strains are usually resistant to nalidexic acid. Therefore strains that are resistant to nalidexic acid should be checked for reduced susceptibility to flouroquinolones. The empiric therapy of strains suspected to have reduced susceptibility to flouroquinolones is usually cefotaxime or ceftriaxone. Azithromycin may be an alternative therapy for multi-drug resistance strains.

Aminoglycosides, tetracyclines, and first- and second-generation cephalosporins should not be used in treating enteric fever, even if in vitro sensitivity showed them to be effective as they are ineffective in vivo. Chronic carriers are better treated by cholecystectomy preceded and followed by antibiotics therapy with either ampicillin or fluoroquinolones. Chloramphenicol should be avoided in treatment of chronic carrier status.

Prevention

Hygiene, improved sanitation, improved food (poultry) processing are the most important methods in decreasing the infection rate. Surveillance of food handlers and removing those who are infected from contact with foods is also important.

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91 Shigellosis

Mohammad Al-shaalan

Shigella is not uncommon cause of bacterial enteritis in children. It is a Gram-negative non-lactose fermenter rod. Worldwide, 90 million cases are reported annually, 89 million of which occur in developing countries. Almost 70% of cases occur in children under 5 years of age. Every year 110,000 death occurs due to shigellosis, 65% of which occur in children below 5 years of age. The main clinical presentation is that of enteritis: vomiting and diarrhea.

Microbiology

Shigella is a Gram-negative, nonmotile bacillus. There are around 36 serotypes of *Shigella* which are divided into four groups: *S. dysenteriae* (group A) including 13 serotypes, *S. flexneri* (group B) including 13 serotypes, *S. boydii* (group C) including 18 serotypes, and *S. sonnei* (group D) with one serotype. The most pathogenic type is *S. dysenteriae*, which cause a significant proportion of shigellosis in developing countries; however, it is rare in developed countries. *Shigella* can be grown on MacConkey, xylose lysine deoxycholate (XLD), and Hektoen enteric media. It is identified by its inability to ferment lactose, inability to produce H_2S, and being urease negative. Most of the cases are caused by *Shigella sonnei* (*Table 91.1*).

Pathogenesis

Shigellosis is transmitted from humans to humans by the fecal–oral route via contaminated food and water or through person-to-person contact. Few organisms 10–100 are enough to cause infections. This in addition to its ability to withstand the stomach acidity makes it easy to establish infection. After passing from the stomach, they start to multiply in the small intestine to a large number that pass to the colon where they enter the mucosal cells by induced macropinocytosis, escape from the macropinocytic vacuole, multiply and spread within the cytoplasm, and pass into adjacent cells by way of fingerlike protrusions from the cell surface. Additional pathogenic factors include elaboration of three distinct enterotoxins: members of all four species produce the virulence plasmid-encoded ShET2, strains of *S. flexneri* 2a produce the chromosomally encoded ShET1, and *S. dysenteriae* 1 produce Shiga toxin (Stx). All of these enterotoxins are able to promote the secretion of solutes and water. However, they are not the only cause of the disease due to Shigella, as non-toxigenic strains cause similar disease. *Shigella dysenteriae* 1 is able to produce a shiga toxin similar to that produced by enterohemorrhagic *Escherichia coli* O157:H7 and thus may cause hemolytic uremic syndrome.

Recently, a 110-kDa heat and trypsin-labile cytotoxin was identified and implicated to be the cause of seizure and encephalopathy that associate shigellosis.

Clinical Features

Gastrointestinal Manifestations

Shigellosis is an enteric bacterial disease that commonly manifests with diarrhea. The incubation period is usually 2–4 days ranging from 1 to 7 days. Initially, the diarrhea is watery and of large amount due to involvement of small intestine. 24–48 h later, the disease progresses to involve large intestine with the production of small frequent bowel motions that are bloody and mucoid and associated with abdominal cramps and tenesmus (bacillary dysentery). The disease is usually self-limiting and lasts for 1–2 weeks. Most of the affected children have other systemic manifestations that include fever, vomiting, and dehydration (*Table 91.2*).

Extraintestinal Manifestation of Shigellosis

Ten to 40% of patients with shigellosis may manifest seizure activity. Other CNS symptoms include headache, drowsiness, and lethargy. Bacteremia and septicemia are rare in children; however, it occurs more commonly in young infants. Vaginitis and cystitis may occur in some patients. Conjunctivitis and keratitis are also rare complications. Reactive arthritis and Rieter's disease may occur in some patients, especially in sexually active patients.

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Table 91.1
Isolated *Shigella* species from a stool culture of children at King Fahad National Guard Hospital

Shigella species	Number (%)
Shigella dysenteriae	4 (1%)
Non-speciated	22 (5%)
S. boydii	45 (9%)
S. flexneri	193 (41%)
S. sonnei	207 (44%)

Table 91.2
Clinical features due to Shigellosis

Clinical feature	Number (%)
Diarrhea	432 (92%)
Fever	393 (83%)
Vomiting	311 (66%)
Bloody stool	147 (31%)
Abdominal pain	112 (24%)
Seizure	50 (11%)

Ekiri syndrome is characterized by a fulminant course with severe dysentery, hypoperfusion, hyperpyrexia, and central nervous symptoms of convulsion and sensory impairment that progress rapidly to death. This syndrome has been described initially in Japan. Although it is rare it is being reported from other countries. Hemolytic uremic syndrome is rare and occurs mainly with *S. dysenteriae* infections and rarely with *S. flexneri* infection.

Diagnosis

The diagnostic method of choice of shigellosis is stool culture; however, stool culture is not justified in all children with diarrhea. Therefore, it should be limited to those with bloody stools or those with positive stool for leukocytes in toxic patients. Rapid test using latex agglutination test to identify *Shigella* spp. grown in the culture media is commercially available. Other diagnostic aids include leukopenia or leukocytosis with bandemia. In cases with seizures, CSF is usually normal although minority may have mild lymphoid pleocytosis. EEG is usually normal.

Treatment

Antibiotic therapy should be offered to all patients with symptomatic shigellosis. Treatment will decrease the duration of illness and also will shorten the period of organism shedding and thus will reduce secondary cases. The pattern of antimicrobial susceptibility of shigellosis is changing overtime. An increasing resistance of shigellosis to ampicillin and trimethoprim/sulfamethoxazole has been observed. Studies have shown a resistance rate of 40–80% to ampicillin and trimethoprim/sulfamethoxazole. Resistance to flouroquinolones and third-generation cephalosporins are still low in the range of 1–2%; however, regularly updated local or regional antibiotic sensitivity patterns to different species and strains of *Shigella* are required to guide empiric therapy. Empirical therapy for patient admitted with moderate or severe disease is usually by ceftriaxone until antibiotic susceptibility is available. Alternative therapy is ciprofloxacin which should not be used unless the organism is proven to be resistant to ceftriaxone. For oral therapy, cefixime and azithromycin have a good coverage in the range of 80–90%. Nalidexic acid is also a good choice but resistance is increasing.

Prevention

Hospitalized patient should be enterically isolated and hand washing should be emphasized in all contacts. No vaccine is available yet.

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92 Staphylococcal Infections

Mohammad Al-Shaalan

In spite of the availability of adequate antibiotics, *Staphylococci* continue to challenge the treating physicians. New disease entities, new emerging species, and the changing spectrum of antibiotic susceptibility are examples of such challenges. Early in this century and before the advent of antibiotics, *Staphylococcus* was a major cause of morbidity and mortality. With the discovery of penicillin, it was thought that an upper hand had been achieved; however, *Staphylococcus aureus* (*S. aureus*) escaped this threat by producing b lactamase that renders them resistant to penicillin. This stimulated the research for an alternative antibiotic, penicillinase-resistant penicillin, namely, cloxacillin and others. Again *Staphylococci* start to have some resistance, methicillin-resistant *Staphylococcus aureus* (MRSA) which is now one of the major problems in health-care facilities. In addition, coagulase-negative *Staphylococci* are becoming important pathogens in many situations including neonates, immunocompromised host, and patient with implanted prosthetic devices.

Organism

Staphylococci are Gram-positive cocci that are catalase positive and non-spore forming. Staphylococcus genus includes a number of species that are classified to coagulase positive and coagulase negative according to production of a coagulation enzyme that aggregate sheep RBC.

The coagulase-positive staphylococcus is *Staphylococcus aureus. Staphylococcus aureus* is the commonest cause of human infections. It produces a variety of diseases that could be severe or mild. When antibiotics were initially introduced in the 1940s, *S. aureus* was sensitive to penicillin, and then it quickly became resistant which led to the introduction of b lactamase–resistant b lactam (methicillin, cloxacillin, and others). In the last 2 decades, methicillin-resistant *S. aureus* (MRSA) emerged as an important pathogen, initially in health-care settings, but recently it is becoming common in community-acquired infections. MRSA carry a chromosomally mediated gene that mediates resistance through alteration of penicillin-binding proteins (PBP). MRSA is one of the major problems in hospital-acquired infections, especially in hospitals with burn and intensive care units. Many epidemics due to MRSA have been reported in NICU, PICU, and burn units. MRSA is not more virulent than methicillin-sensitive *S. aureus*; however, it is difficult to treat because of its nature of being multiply resistant to many antibiotics including cephalosporins and aminoglycosides. They are usually susceptible to vancomycin, teicoplanin, linezolide, and daptomycin. Most of the hospital-associated MRSA strains are also resistant to other antibiotics like clindamycin, TMP/SMX, rifampin, and fluoroquinolones. Community-associated MRSA (CA-MRSA) are less resistant and it tends to be sensitive to clindamycin, cotrimoxazole, erythromycin, and tetracycline. However, attention should be paid that some of CA-MRSA is also multidrug resistant. When an MRSA is sensitive to clindamycin

The approach to treating patients with MRSA infection relies on a comprehensive surveillance for such organism in patients in the high-risk areas like burn unit and PICU. Patients who are colonized with MRSA but have no disease should be isolated in private rooms and barrier precaution are applied. Treatment of such patients has failed to eradicate colonization. If epidemics arise due to MRSA, a trial to eradicate infection by treating all colonized patients with TMP/SMX combined with rifampin or ciprofloxacin may be beneficial. Patients who develop diseases due to MRSA should be treated with vancomycin and if they have intravascular devices attempts to remove such devices is advisable. Application of mupirocin cream locally to the colonized areas has shown some success in eradicating infection.

There are almost 39 species of coagulase-negative *Staphylococcus* (CONS), the most important of which are *S. epidermidis*, *S. heminis*, *S. hemolyticus*, *S. werneri*, *S. lugodensis,* and *S. saprophyticus. Staphylococci* are facultative, nonfastidious organisms which can be cultured in ordinary media like blood or chocolate agars. Both *S. aureus* and some species of CONS are normal commensal of human skin.

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Staphylococcus aureus

S. aureus is a primary human pathogen that is a major cause of human disease. In the 1960s, it was the commonest cause of neonatal sepsis. Nowadays, it is the major cause of nosocomial and community-associated infections. *Staphylococcus aureus* causes a variety of illnesses which are divided into:

(a) Skin and soft tissue infections
(b) Deep-seated infections
(c) Bacteremia and sepsis

Cutaneous Infections

Impetigo

Ten to twenty percent of impetigo is caused by *S. aureus*. In another 10–20% of cases of impetigo, the causative agents are *S. aureus* and Group A *Streptococci* (GAS). The remainder is caused by GAS. Impetigo is a skin disease that starts as a macular erythematous lesion which changes soon to pustule that then form a honey-colored crust. Any part of the body surface can be involved and the patient may infect himself at multiple sites by self-inoculation of the organism through scratching. Other siblings in the family may be affected. *S. aureus* is the main cause of bullous impetigo. In recent years, spiderlike or herpeslike lesions may be the presentation of staphylococcal skin infections. This presentation is being attributed to a staphylococcus that produces Panton–Valentine leukocidin (PVL).

Illustrated Case

A 13-month-old girl was admitted because of fever and skin lesions. The lesions were erythematous papule with necrotic center (spider like lesions). It was thought to be herpetic lesion and she was given intravenous acyclovir. Twelve hours later she started to be hypotensive and was in respiratory distress. Chest radiography showed bilateral patchy consolidation and pleural effusion. She was transferred to intensive care unit and was started on vancomycin and ceftriaxone. She required ventilation and chest tube insertion. Pleural fluid was bloody. Blood and pleural fluid cultures grew methicillin-sensitive *S. aureus*. She required pleural decortication and her condition improved.

Cellulitis

Rarely, *S. aureus* may cause cellulitis especially in young children. However, GAS is the commonest cause of cellulitis. Treatment can be achieved by using penicillinase-resistant penicillin like cloxacillin.

Folliculitis

Folliculitis is a mild superficial skin infection that appears as small yellowish pimples. They are self-limiting and can be treated by using a topical disinfectant.

Furunculosis or Boils

This is a staphylococcal infection of hair follicle. It starts as erythematous lesion which then becomes pus-containing vesicle. Treatment can be achieved by evacuation and topical antibiotics.

Carbuncles

Carbuncle is defined as infection of multiple hair follicles which usually coalesce and form large abscess with multiple draining sinuses. This type of infection is more common in patients who have phagocytic impairment either quantitatively or qualitatively. Local debridement and systemic cloxacillin are the therapies of choice.

Tracheitis

Although not common in children, it is a life-threatening condition that usually presents with high fever, toxic appearance, inspiratory stridor, drooling, and cough that is productive of tenacious sputum and retrosternal pain. In addition to *S. aureus*, GAS and other *Streptococci* are other causes. Tracheitis may arise without any preceding illness; however, it may complicate a preceding viral illness like varicella or influenza virus infections. Diagnosis can be achieved by obtaining sputum for culture. Intravenous therapy with an antibiotic agent that is effective against *S. aureus* and *Streptococci* should be instituted promptly. Cefuroxime or cloxacillin is appropriate. In patients with tracheostomy and thought to have tracheitis

Enterobacteriaceae like *E. coli*, *Klebsiella pneumoniae* and *Enterocobacter* as well as *Pseudomonas* may be involved as causative agents and this should be considered in the antibiotic coverage. In these cases, adding aminoglycoside or ceftazidime is recommended.

Pneumonia

In infants, *S. aureus* is one of the major causes of bacterial pneumonia and it is only preceded by *S. pneumoniae* and *H. influenzae*. However, *H. influenzae* is decreasing in frequency with the introduction of the conjugate Hib vaccine. Staphylococcal pneumonia is usually severe with complicating pleural effusions and empyema occurring in 30–50% of the cases. Diagnosis is achieved by positive blood culture, pleural fluid, or specimens obtained by bronchoscope. In addition to supportive therapy with oxygen and artificial ventilation if needed, intravenous antibiotics with cloxacillin or nafcillin should be used.

Chest tube drainage of pleural effusion may not be effective because of early loculations; therefore, the trend now is to use antibiotic therapy and observe the patient. If there is no response to this therapy within 7–10 days, then decortication may be needed after a trial of chest tube drainage.

Bacteremia

S. aureus is one of the major causes of nosocomial infections. Bacteremia is the third commonest cause of nosocomial infection in pediatric hospitals and the *S. aureus* is the commonest cause of nosocomial bacteremia. In addition, *S. aureus* can cause community-acquired bacteremia, but this is rare. Any patient with staphylococcal bacteremia should be investigated for an underlying focal infection like osteomyelitis, endocarditis, or deep abscess. Recently, fulminant sepsis that can be fatal is being reported.

Illustrated Case

An 8-year-old healthy boy brought to emergency room by his father after complaining of being tired and unable to walk for few hours. He was very well until around 15:00 same day of presentation; at which time he started to have generalized malaise and not feeling well and at around 19:00 he was unable to walk and therefore he was brought to ER. Upon arrival to ER, he was conscious and alert; however, he looks sick. His vital signs showed a temperature of 36.7°C, pulse rate 150 beats/min, respiratory rate 30/min, blood pressure 117/70, and pulse oximetry 98% in room air. He has normal chest and cardiovascular examination. His abdomen was soft. He has ice cold extremities with mottled skin and delayed capillary refill of around 6 s. He was judged to be in compensated shock likely of sepsis origin. Two boluses of intravenous normal saline at 20 ml/kg were given as well as a shot of ceftriaxone and vancomycin. His condition was worsening gradually with increasing work of breathing and desaturation. Arterial blood gas was done and showed pH 7.12, PCO2 52, PO2 28, HCO3 17, and base access 12.2 and therefore oxygen 5 L/min by face mask was given and he was continued on intravenous maintenance fluid. His initial laboratory workup revealed WBC 1,000/mm3, hemoglobin 95 g/L, platelet 41,000/mm3, CPK 9,315 U/L, lactic acid 12.9 mmol/L, CRP 330 mg/L, and D-dimer 2,279 mcg/L. By 23:45, he started to desaturate in spite of being on 10 L/min and therefore he was intubated and mechanically ventilated. His condition deteriorated farther with drop in blood pressure and increasing difficulty in ventilating him. Chest x-ray showed white out lungs suggestive of ARDS. He was started on dopamine, dobutamine, and norepinephrine but his blood pressure remained low and his heart rate started to drop and became asystolic and not responding to resuscitation. He died by 3:30 next morning. Two bottles of blood culture was positive for gram-positive cocci in clusters, which was identified as *S. aureus*; methicillin resistant based on MicroScan result which was confirmed by cefoxitin diffusion disk as well as positive PBP. Bacterial isolate underwent molecular characterization using multilocus sequence typing, staphylococcal cassette chromosome mec (SCCmec) typing, and PCR for the presence of the genes encoding Panton–Valentine leukocidin (PVL) and confirm a positive PVL.

Endocarditis

S. aureus is the second commonest cause of endocarditis; however, it is the commonest cause of endocarditis in patients with drug abuse.

Osteomyelitis and Septic Arthritis

S. aureus is the commonest cause of skeletal infection in all age groups. Although sicklemic patients have an increased susceptibility to *Salmonella* osteomyelitis, *S. aureus* is still common cause of osteoarticular infection.

Meningitis

S. aureus is a very rare cause of meningitis, but it is one of the major causes of brain abscess.

Therapy of Staphylococcal Infections

Soft Tissue and Skin Infections

Impetigo

Most of the time, topical therapy is enough; however, if there is systemic manifestation, then an oral antibiotic with a drug that is effective against both *Staphylococcus aureus* and *Streptococcus pyogenes* is needed. Usually, a first-generation cephalosporin like cephalexin is enough. However, if MRSA prevalence in the community is high, ≥10%, then clindamycin is advised.

Folliculitis

Topical antibiotic is usually effective.

Furunculosis, Carbuncles, and Abscesses

If there is fluctuation and there are no systemic symptoms, then drainage is usually enough. If there is systemic manifestation like fever, then oral antibiotics like first-generation cephalosporin is added to the drainage.

Cellulitis

Cellulitis is usually associated with some systemic manifestations. Antibiotic therapy is needed. Because both streptococcus and staphylococcus can cause cellulitis, TMP/sulfisoxazole is not adequate. Other antibiotic like first-generation cephalosporin is recommended. In community where community-associated methicillin-resistant *S. aureus* (CA-MRSA) prevalence is high (>10%), clindamycin is advised. In some area, clindamycin resistance is high and in such areas other antibiotics like vancomycin, linezolid, and daptomycin can be used. It is always recommended that local susceptibility pattern of the CA-MRSA should be checked and antibiotics should be advised accordingly (Table 92.1).

Deep-Seated Infection

When having deep-seated infection due to staphylococcal infection, some consideration should be taken into account:

1. Prevalence of CA-MRSA
2. Severe systemic manifestations
3. Comorbid conditions

As eluted to in the chapter about musculoskeletal infection, the recommended initial therapy is usually parenteral penicillinase-resistant penicillin like cloxacillin (Tables 92.2 and 92.3).

However, in areas where CA-MRSA prevalence is high, other antibiotic is usually recommended like clindamycin if the clindamycin resistance is not high or vancomycin if clindamycin resistance is high.

Table 92.1
Skin and soft tissue infections

Disease	Management	
	No systemic signs	Systemic signs
Impetigo	Topical therapy	
Folliculitis	Topical therapy	
Furunculosis	Drainage	Add first-generation cephalosporin or clindamycin
Carbuncles	Drainage	Add first-generation cephalosporin or clindamycin
Abscess	Drainage	Add first-generation cephalosporin or clindamycin
Cellulitis		First-generation cephalosporin or clindamycin

Table 92.2
Treatment of noncomplicated invasive infections

Treatment	Antibiotic
Empiric treatment	
Low CA-MRSA prev and low C-R prev	Cloxacillin[a]
High CA-MRSA prev and low C-R prev	Cloxacillin + clindamycin
High CA-MRSA prev and high C-R prev	Cloxacillin + linezolid
Directed treatment	
CA-MSSA PVL-negative	Cloxacillin[a]
CA-MSSA PVL-positive	Clindamycin
CA-MRSA PVL-negative	Clindamycin
CA-MRSA PVL-positive	Clindamycin
CA-MRSA PVL-negative C-R	Linezolid
CA-MRSA PVL-positive C-R	Linezolid

[a]Cloxacillin could be changed with a first-generation cephalosporin such as cephazolin. *CA-MRSA* community-associated methicillin-resistant *S. aureus, CA-MSSA* community-associated methicillin-susceptible *S. aureus, C-R* clindamycin resistant, *Prev* prevalence, *PVL* Panton–Valentine leukocidin
Source: Rojo P et al. (2010) Community-associated *Staphylococcus aureus* infections in children. Expert Rev Anti Infect Ther 8(5):541–554

In cases when severe systemic manifestations are present, a combination of cloxacillin and vancomycin is recommended until the susceptibility result is available.

Bacteremia

Most of the staphylococcal bacteremia has a predisposing factor like musculoskeletal infections, implanted devices, or endocarditis.

When bacteremia is isolated and no focal infection is identified, then a suitable parenteral antibiotic should be given for 10 days. In community where CA-MRSA is rare, cloxacillin or similar drugs can be used. In areas where CA-MRSA prevalence is high, the choice will be either clindamycin if clindamycin resistance is low or vancomycin if clindamycin resistance is high. Other agents like linezolid and daptomycin may be used.

When bacteremia is associated with a central line, then the duration should be expanded to 14 days besides that blood culture is cleared promptly and the central line is removed.

Table 92.3
Treatment of severe invasive infections

Treatment	Antibiotic
Empiric treatment	
Vancomycin + clindamycin ± rifampin ± IVIG	
Directed treatment	
CA-MSSA PVL-negative	Cloxacillin[a]
CA-MSSA PVL-positive	Cloxacillin[a] + clindamycin + IVIG
CA-MRSA PVL-negative	Clindamycin
CA-MRSA PVL-positive	Vancomycin + clindamycin + IVIG
CA-MRSA PVL-negative C-R	Linezolid
CA-MRSA PVL-positive C-R	Vancomycin + linezolid + IVIG

[a]Cloxacillin could be changed with a first-generation cephalosporin such as cephazolin. *CA-MRSA* community-associated methicillin-resistant *S. aureus, CA-MSSA* community-associated methicillin-susceptible *S. aureus, C-R* clindamycin-resistant, *IVIG* intravenous immunoglobulin, *PVL* Panton–Valentine leukocidin
Source: Rojo P et al. (2010) Community-associated *Staphylococcus aureus* infections in children. Expert Rev Anti Infect Ther 8(5):541–554

Bacteremia associated with infective endocarditis requires a minimum of 4 weeks of parenteral therapy.

Coagulase-Negative Staphylococci (CONS)

CONS have emerged as a major cause of nosocomial infections. There are more than 39 species, the most common of which are *S. epidermidis*, *S. homonis*, *S. hemolyticus*, *S. werneri*, *S. lugodensis*, and *S. saprophyticus*. Most of the infections due to CONS occur in patients who have underlying predisposing factors like those who are immunocompromised and those who have implanted prosthesis. Other susceptible patients are neonates who are born prematurely and being cared for in NICU with a number of invasive procedures.

Neonatal Infections

Many reports have shown that CONS are becoming the most common cause of nosocomial infection in NICU, especially among premature neonates. Many factors predispose premature neonates to CONS infections including

prolonged hospitalization, intravascular devices, and TPN infusion. Varied presentations occur among infected neonates, the most common of which is bacteremia.

Bacteremia

Premature neonates are found to be more prone to bacteremia due to CONS. Some epidemiologic studies have shown that 10–25% of nosocomial neonatal bacteremia to be caused by CONS. The bacteremia due to CONS is usually indolent in its presentation with main manifestations including feeding intolerance, lethargy, apnea, bradycardia, decreased perfusion, hypotension, and temperature instability. Laboratory tests that frequently associate bacteremia include increased immature neutrophils, hyperglycemia, thrombocytopenia, and increased C-reactive protein. The major difficulty in diagnosing CONS bacteremia is the differentiation between true infection and contamination. However, in the presence of clinical signs, isolation of CONS indicates true infection.

Central Line Infection

Umbilical arterial catheter (UAC), umbilical vein catheter (UVC), or central lines can be colonized with CONS and become the cause of bacteremia. Polyvinyl catheters are more susceptible to be colonized than silastic catheter. TPN especially with intralipid infusion increases the susceptibility to infection. Diagnosis is by isolating CONS from blood that is drawn from the central line. Some quantitative estimates of the number of CONS colonies can help in differentiating colonization from infection. This can be done by semiquantitative method in which the intravascular tip of the catheter is rolled over the culture media.

If the number of colonies grown is more than 15 colonies then it indicates significant growth. If the line cannot be removed then comparing the colonies count of blood drawn from central line with that drawn from peripheral vein will give an idea of the source of infection. If the central count is more than peripheral one then this is likely to be central line infection. However, these methods are not standardized and cumbersome to do. Treatment requires removal of the central line and administration of appropriate antibiotics; however, in cases where removal of the line is not feasible, a trial of antibiotic therapy may result in cure although the failure rate is more common. The recommended therapy is vancomycin given through the central line for 10–14 days. Blood culture should be repeated in 24–48 h after starting the antibiotics. If the culture remained positive then central line should be removed.

Pneumonia

Reports of pneumonia caused by CONS have been increasing, especially congenital pneumonia and pneumonia in intubated neonates. Congenital pneumonia has been confirmed by isolating only CONS from placenta or from lung at autopsy.

Meningitis

CONS rarely causes meningitis; however, a number of cases have been reported. Characteristically, meningitis occurs in premature babies who have intraventricular hemorrhage. Meningitis due to CONS is characterized by minimal or absent abnormalities in CSF cell count, protein, and glucose. It is presumed that CONS are of low virulence and thus elicit minimal inflammatory response in CSF.

Enterocolitis

Narcotizing enterocolitis (NEC) is not uncommon in premature babies. Although the disease has been characterized and its pathology is known, its cause remains enigmatic. Delta toxin produced by CONS has been claimed to be a factor that may precipitate NEC.

Wound Infections

Surgical wound infection and local skin infections may be caused by CONS. In NICU and PICU, CONS share with *S. aureus* the cause of such infections.

Endocarditis

Few cases of endocarditis have been reported in neonates who have UVC inserted in the right atrium. The endocarditis involves mainly the right side of the heart with the tricuspid valve being commonly involved. Such patients usually present with persistent bacteremia associated with thrombocytopenia.

Bacteremia

CONS has emerged as a major cause of nosocomial bacteremia in children's hospitals. 20–30% of all nosocomial bacteremias are attributed to CONS.

CONS bacteremia is usually a disease of patients who have underlying predisposing factors, especially patients with malignancies or those who have undergone bone marrow transplant. Not all patients with CONS bacteremia have central lines or indwelling catheters. It is assumed that gastrointestinal tract may be the port of entry of CONS in the cases that have no indwelling catheters.

Urinary Tract Infection

S. saprophyticus is one of the principal causes of UTI in sexually active adolescent girls; however, it can cause UTI at any age group. *S. saprophyticus* has a specific adhesion that has higher affinity to attach to urogenital epithelium. Other CONS species can cause UTI. Because of their low virulence, even low colonies count may indicate a true infection rather than contaminant. Isolation of CONS species from urine in patients who are at risk of developing invasive disease may indicate the presence of bacteremia.

Endocarditis

Commonly arise following heart surgery especially during the first 3 months postsurgery. However, native value endocarditis may be caused by CONS. In one study, 26% of native valve endocarditis was caused by CONS.

Infection of Intravascular Catheters and Related Devices

Central Venous Catheter

CONS is the major cause of central line–related bacteremia. CONS is also the major cause of other central line–related infections like exit site or tunnel infections. Diagnosis of central line–related bacteremia is difficult. The comparison of central and peripheral blood cultures may be useful with the presence of five- to tenfold higher colonies in blood drawn from central line indicating central line infection. However, not all laboratories perform quantitative cultures. If the line is removed then culturing the tip of the catheter by rolling it over a blood agar plate and then counting the colonies may give a clue to the source of infection. Count that are >15 colonies indicate that the central line is the likely cause of bacteremia.

Ventriculoperitoneal Shunt Infection

Ventriculoperitoneal (VP) shunt infection can occur in 3–40% of the cases. Most of the infections are caused by CONS and most of them occur in the first 2 months after insertion. Diagnosis of shunt infection depends on isolation of the organism from CSF obtained by shunt-tapping. The changes in the CSF parameters may be minimal, but the culture usually yields the organism. Clinical presentations of shunt infection are variable, but mostly present with signs of shunt malfunction and increased intracranial pressure including headache, vomiting, and fever. Some patients may have associated signs of peritonitis. Treatment of VP shunt infection has been controversial. The recommended treatment is shunt removal with systemic antibiotics administration. Alternatively, success has been achieved with externalizing the peritoneal end of the shunt and systemic antibiotics administration until the CSF culture is negative in 3 consecutive days then reimplantation of the shunt and continuation of systemic antibiotics for 10–14 days. Intraventricular administration of antibiotics has shown some contradictory results; however, most of the studies show no additional benefit of such therapy.

Peritonitis

CONS is the major cause of peritonitis in patients undergoing peritoneal dialysis. Affected patients usually present with symptoms and signs of peritonitis: fever, abdominal pain, and vomiting, as well as changes in the color of peritoneal dialysate. Most cases of the peritonitis are associated with peritoneal fluid white cell count of more than 100; however, some have reported peritonitis with lower cell count. Treatment can be achieved by administering appropriate antibiotics with the peritoneal dialysate for 10–14 days. Removal of the catheter is unnecessary unless the infection cannot be controlled by antibiotics.

Other Prosthetic Devices Infections

CONS has been reported as causing infections in almost any implanted devices including implanted lens, pacemaker, and joint and vascular grafts.

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93 Streptococcal Infections

Mahmoud M. Mustafa

Streptococci are among the most common pathogenic bacteria isolated from children. They are associated with a wide variety of disease states. In this chapter, diseases that are caused by group A and group B β-hemolytic streptococci are discussed.

Bacteriology

Streptococci are gram-positive cocci that form either short or long chains. They are classified according to their ability to hemolyze red blood cells when grown on sheep blood agar plates. They may produce complete hemolysis (β-hemolytic), resulting in a clear zone around the colonies; partial hemolysis (β-hemolytic), resulting in a green color around the colonies, hence the name *viridans*; or no hemolysis (γ-hemolysis).

Streptococci are further separated according to differences of carbohydrate components of the cell wall; so far, they have been divided into groups A through H and K through V. Therefore, there are group A β-hemolytic streptococci, group B β-hemolytic streptococci, and so on. Group A streptococci can be divided into more than 81 different types on the basis of a series of serologically distinct surface proteins, the M proteins. M proteins are components of the outer portion of the streptococcal cell wall. M antigen renders group A streptococci resistant to phagocytosis and is the major virulence factor. Other virulence factors include lipoteichoic acid and hyaluronic acid.

Streptococci produce and release into the surrounding medium a large number of biologically active extracellular products, many of which are of clinical significance. Pyrogenic exotoxins A, B, and C are responsible for the rash of scarlet fever and the shock in the toxic shock syndromes. Both streptolysin O and S injure cell membranes, not only lysing red blood cells but also damaging neutrophils and platelets. Streptolysin O is antigenic while streptolysin S is not. Many of the streptococcal extracellular products are digestive enzymes such as streptokinase, hyaluronidase, amylase, esterase, and proteinase that liquefy pus and facilitate rapid spread through tissue planes. The latter enzyme is associated with tissue destruction of severe invasive streptococcal disease. Other products include nicotinamide adenine dinucleotidase (NADase) and deoxyribonuclease (DNAse A, B, C, and D); both are antigenic. Measuring antibodies to the antigenic substances (e.g., antistreptolysin O [ASO], anti-DNAse, and antistreptokinase) can be clinically useful. M-type–specific antibodies are detectable 4–8 weeks after infection; antibiotic therapy ablates this response.

Group A Streptococci

Epidemiology

Group A streptococci are identified most frequently in humans and are rarely found in other species. They are normal inhabitants of the nasopharynx. The colonization rate varies from 15% to 20% of children. There are different epidemiologic features of streptococcal skin and throat infections. Streptococcal impetigo occurs frequently in preschool children, whereas streptococcal pharyngitis is predominantly a disease of school-age children. Streptococcal disease is uncommon in children younger than 3 years of age; however, outbreaks of streptococcal respiratory tract infections have been observed in day care centers. Streptococcal tonsillitis and pharyngitis are common in temperate and cold climates, whereas streptococcal impetigo or pyoderma occur with greater frequency in hot or tropical climates.

Transmission of group A β-hemolytic streptococci, from one person to another and from one body site to another varies according to the clinical type of infection. Infection may be spread by droplets or by contact with skin lesions or transmitted by water, milk, and food. Nasal and pharyngeal carriers are effective disseminators. Crowding is the most important factor that helps spread the disease, particularly in schools, homes, military installations, and sleeping quarters. Acquisition of streptococci from an infected individual is most common during the acute illness and decreases during colonization stage. Once acquired, group A β-hemolytic streptococci readily establish infection of the intact epithelial surface of the upper respiratory tract. In contrast, the production of streptococcal impetigo or pyoderma requires disruption of the

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cutaneous epithelium by trauma, insect bites, or a preexisting skin condition.

Infection as well as a carrier state may produce type-specific immunity. As immunity to different streptococcal strains develops after repeated exposures, the risk of streptococcal infection diminishes during adult life.

Pathogenesis

After acquisition of streptococci, the first step in disease pathogenesis is attachment to the mucous membranes of the upper respiratory tract or the skin. The reason(s) why certain M types produce pharyngitis or tonsillitis and others produce impetigo or pyoderma is not known. Invasion of tissues by group A streptococci is facilitated by damage to leukocytes and fixed tissue cells by release of extracellular digestive enzymes. Spread of infection to adjacent tissues is enhanced by enzymes such as streptokinase, DNAase, hyaluronidase, and proteinase, producing such complications as retropharyngeal or peritonsillar abscesses, sinusitis, lymphadenitis, and otitis media. Access of streptococci to the bloodstream can result in septicemia, pneumonia, and osteomyelitis.

The rash and toxic manifestations of scarlet fever are due to the development of hypersensitivity to pyrogenic toxins (A through C). The toxic manifestations of streptococcal toxic shock-like syndrome are attributed to direct influence of pyrogenic toxins such as tumor necrosis factor. The exact pathogenetic mechanism of rheumatic fever and glomerulonephritis is not known, but most theories invoke immunologic processes in one way or another.

Clinical Manifestations

The most common suppurative complications of group A β-hemolytic streptococci involve the respiratory tract, skin, soft tissues, and blood. The nonsuppurative complications, acute rheumatic fever and glomerulonephritis, are discussed in Chaps. 196, "Short Bowel Syndrome" and 249, "Cyanotic Heart Disease", respectively.

Respiratory Tract

Streptococcal pharyngitis or tonsillitis (*Fig. 93.1*) is an acute, suppurative, short-term illness with an incubation period of 12 h to 4 days. Its severity is greatly variable. In 30–50% of infections the disease is subclinical. Severe toxicity with high fever, nausea, vomiting, and collapse occurs in 10% of infections and is particularly more frequent in epidemic situations. Typically the onset of illness is acute and characterized by fever, sore throat, headache, and abdominal pain. The pharynx or the tonsils typically appear congested but may appear pale in the presence of marked edema. In 50–90% of the cases, exudate is present and usually appears by the second day. The exudate is typically whitish yellow and discrete but may become confluent the second day. Cervical lymphadenitis occurs in almost half of the cases. Unless complicated by otitis media, sinusitis, or peritonsillar abscess, the symptoms and signs disappear in 3–5 days. The average latent periods for glomerulonephritis and acute rheumatic fever are 10 and 18 days, respectively, during which the patient appears well.

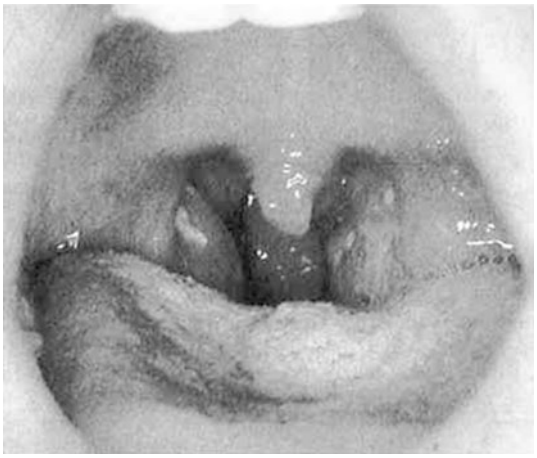

Figure 93.1
Inflammation with tonsillar exudate in a patient with streptococcal tonsillitis. Note the white-coated tongue

In infants, group A streptococcal infection may take the form of persistent mucoserous nasal discharge, generalized lymphadenopathy, and chronic low-grade fever with little or no inflammation in the pharynx or tonsils. This form of disease is called streptococcal fever. Other infections associated with the upper respiratory tract that may be caused by group A streptococci include otitis media, sinusitis, mastoiditis, pneumonia, and empyema. Subpectoral abscess and pleural effusion may develop as complications of streptococcal infections of the thumb through lymphatic drainage.

Skin

Impetigo (superficial pyoderma) is the most common form of streptococcal skin infection. Colonization of intact skin precedes impetigo by approximately 10 days. The infection is frequently painless and the patient is afebrile. The initial lesion is a superficial vesicle with little

surrounding erythema that progresses rapidly to a pustule and then forms a thick, honey-colored crust; this stage may last for a few days to several weeks. The lesions are most common on the lower extremities and do not leave permanent scars. Impetigo may be superimposed upon scabies, eczema, burns, insect bites, and wounds.

Streptococcal cellulitis, an infection of skin and subcutaneous tissues, frequently complicates varicella skin infection and may develop into severe necrotizing fasciitis or myositis. Lymphatic spread to draining nodes is common. Ecthyma is a chronic and more deep-seated infection than impetigo; it is found predominantly in tropical areas.

Erysipelas is streptococcal infection involving the skin and sometimes the adjacent mucous membranes. The skin is erythematous and indurated with elevated margins. Erysipelas most often involves the face, but extremities and other parts of the body can be involved. The onset is acute and often accompanied by systemic manifestations. The lesion may last a few days to several weeks and relapses are rather common.

Scarlet fever results from infection by streptococci that elaborate pyrogenic exotoxins. The primary site of infection is usually the pharyngeal area, but it may follow infections of wounds or burns or other skin infections. The average incubation period is 3 days (range, 1–7 days), and the onset is sudden, with fever, headache, chills, sore throat, and vomiting. The typical rash appears within 24–48 h. Physical signs include signs of primary site of infection (pharyngitis or skin infection) in addition to the characteristic mouth and skin findings. During the early phase of illness the tongue has a white coat through which red, hypertrophied papillae project (white strawberry tongue) (*Fig. 93.2*). Several days later the white coat desquamates, leaving a red tongue with hypertrophied papillae (red strawberry tongue). The palate may show petechiae. The characteristic rash is red and finely punctate and may be palpated more readily than seen, having the texture of sandpaper. It appears initially on the trunk or axillae, groin, and neck but rapidly spreads to cover all the body. The rash fades on pressure and typically leads to desquamation toward the end of the first week of illness. Desquamation starts on the face and ends on the hands and feet. Other characteristic signs include circumoral pallor, pastia lines (areas of hyperpigmentation and petechiae appear in the deep creases, particularly the antecubital fossa), and, in severe cases, miliary sudamina (small vesicular lesions over the abdomen, hands, and feet).

The differential diagnoses of scarlet fever include measles, rubella, infectious mononucleosis, enteroviral infections, and roseola infantum. Severe forms of scarlet fever that are associated with marked toxicity, bacteremia, jaundice, arthritis, and hydrops of the gallbladder occur infrequently. Streptococcal toxic shock-like syndrome has been well described.

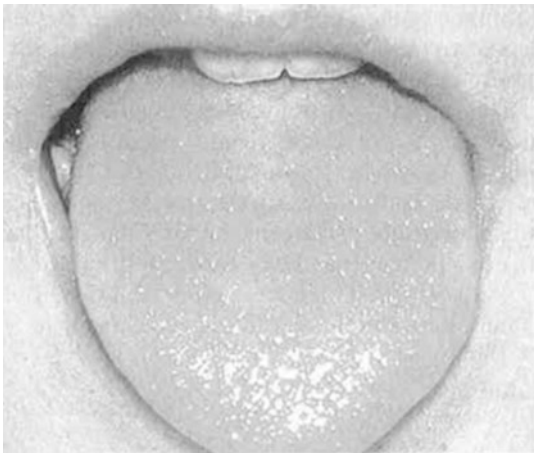

Figure 93.2
Strawberry tongue in a patient with scarlet fever

Bacteremia

Streptococcal bacteremia is usually secondary to a localized infection. However, primary streptococcal bacteremia has been described. The disease is severe and usually rapidly progressive, leading to severe systemic symptoms and organ dysfunction. Metastatic foci may complicate the course of infection, resulting in bacterial meningitis, osteomyelitis, arthritis, pneumonia, and endocarditis.

Diagnosis

Pharyngitis caused by group A streptococci is clinically indistinguishable from that caused by a variety of other etiologic agents, such as Epstein–Barr virus, *Corynebacterium diphtheriae*, *Arcanobacterium hemolyticum*, *Mycoplasma*, and groups C and G streptococci. Only 15% of children with pharyngitis and 25% of those with exudates have streptococcal infection; 10–50% of patients with streptococcal pharyngitis do not have tonsillary exudates. The diagnostic problem is especially difficult because group A streptococci can be found in the throats of normal children. Therefore, the pediatrician must rely on a combination of the clinical presentation, bacteriologic results, and epidemiologic findings to confirm the probability of streptococcal infection.

Isolation of the streptococci from the throat and evidence of host response are confirmatory of true

infection. Throat culture is the gold standard method for securing a safe diagnosis. However, isolation of group A streptococci from the pharynx of a child with pharyngeal infection does not necessarily indicate that the disease is caused by this organism. In recent years, a number of rapid techniques for direct identification of group A streptococci from the upper respiratory tract have become commercially available. Although they have relatively high specificity (~90%), they are not highly sensitive (50–90%). Therefore, rapid antigen detection tests are not sufficiently sensitive to be used without a backup culture.

Humoral antibodies to specific streptococcal extracellular products can be readily demonstrated by neutralizing assays. The ASO assay is the most commonly used. An increase in ASO titer to more than 166 Todd units is seen in more than 80% of untreated children with acute streptococcal pharyngitis within 3–6 weeks following infection. Early antibiotic treatment might diminish or abolish this response. It should be noted that, because streptolysin O is also produced by groups C and G streptococci, the test is not specific for group A infection. The ASO response can be feeble in patients with streptococcal pyoderma, and therefore its usefulness in this condition is limited. In contrast, the antideoxyribonuclease B (anti-DNAse B) and the antihyaluronidase responses are good after skin as well as throat infection. Titers start to rise 6–8 weeks after infection. Although the streptozyme agglutination slide test is inexpensive, simple, and fast to perform and detects antibody responses within 7–10 days, there are problems with standardization of its reagents, and it may not be specific for antibodies to extracellular products of group A streptococci. Furthermore, the test is not group-specific.

Changes in the peripheral white blood cell count, C-reactive protein, and erythrocyte sedimentation rate are nonspecific.

Treatment

Immediate antibiotic therapy is indicated to relieve symptoms and prevent suppurative, septic, and nonsuppurative complications. In patients with strong clinical epidemiologic evidence of streptococcal infection, therapy may be initiated before the results of throat culture are available. Although group A streptococci are generally susceptible to a number of antibiotics, penicillin remains the drug of choice except in those patients who have penicillin allergy. All strains of group A β-hemolytic streptococci are penicillin-sensitive. Although penicillin tolerance has been described, its clinical significance has not been defined. Penicillin V (125–250 mg three or four times per day) is the treatment of choice. Therapy must be continued for at least 10 days. If noncompliance is expected or the patient has nausea, vomiting, or diarrhea, we recommend a single intramuscular injection of a long-acting benzathine penicillin G (600,000 units for children less than 30 kg and 1.2 million units for children more than 30 kg). In patients with suspected allergy to penicillin, erythromycin (40 mg/kg/day), clindamycin (30 mg/kg/day), or cefadroxil monohydrate (15 mg/kg/day) may be used.

Repeating throat culture after a course of antibiotic therapy is indicated only in certain circumstances, such as patients with a history of rheumatic fever, a household member with rheumatic fever, and possibly when epidemic streptococcal disease is present in the community. Between 5% and 20% of children might have persistence of streptococci (treatment failure) after a complete course of penicillin. Treatment failures are more common with oral than intramuscular penicillin therapy or nonpenicillin antibiotic therapy. Treatment failure has not been adequately explained, but it may be due to poor compliance, presence in the throat of β-lactamase–producing organisms, tolerance to penicillin, reinfection, or presence of a carrier state. In these cases we recommend a second course of antibiotics, preferably an intramuscular penicillin preparation. Persistence of positive culture after a second course of antibiotics indicates a carrier state and need not be retreated.

Intravenous penicillin therapy should be used in patients with severe streptococcal infections such as pneumonia, deep soft tissue infections, meningitis, and toxic shock syndrome. For streptococcal impetigo, we recommend local hygienic measures plus oral antibiotics.

Prevention

Administration of antibiotics before the onset of symptoms is effective in preventing streptococcal disease. The best returns can be obtained from secondary prevention programs in patients with previously diagnosed rheumatic fever and perhaps from primary prevention programs in school-age children of low socioeconomic status and in institutional epidemics. For details of prevention of streptococcal infection in patients with rheumatic fever, see Chap. 196, "Short Bowel Syndrome".

In institutional epidemics and school exposure, the dose and duration of penicillin therapy is similar to that described under "Treatment" above. Management of the carrier state is controversial. Treatment with nonpenicillin antibiotics (erythromycin, a cephalosporin, or clindamycin) may be useful in eradicating the carrier state but should be reserved for the rare problem case.

Prognosis

Patients with streptococcal pharyngitis recover spontaneously. The prognosis for adequately treated patients is excellent. A few may develop suppurative complications, and an occasional patient may develop a nonsuppurative sequela. The risk of developing rheumatic fever after untreated streptococcal infection of the upper respiratory tract is about 3% after epidemic infections and 0.3% in endemic situations. However, 15–50% of patients who have had a previous attack of rheumatic fever might have a recurrence of acute rheumatic fever. There is no risk of rheumatic fever after skin streptococcal infection. The risk of poststreptococcal glomerulonephritis is dependent on whether the infection is caused by a nephrogenic strain or not. With a nephrogenic-strain throat or skin infection, up to 15% of patients can develop glomerulonephritis.

Group B Streptococci

Group B streptococcus is the most frequent bacterial pathogen responsible for neonatal sepsis in the United States and Western Europe. In other parts of the world, including the Middle East, the incidence of infection by this organism is lower, and in some countries it is rare. Besides neonatal infections, group B streptococci are occasionally responsible for other serious infections such as those in patients with malignancy, diabetic patients, obstetric patients, and patients with other chronic diseases. Asymptomatic bacteremia has been reported.

Group B streptococci are facultative, gram-positive, encapsulated, chain-forming β-hemolytic cocci. Based on type-specific capsular carbohydrates, together with C protein, most strains are classified into one of six relatively common serotypes, Ia, Ib, Ia/c, II, Iic, and III. Types IV and V are rare. The antiphagocytic polysaccharide capsule is the most important pathogenic factor. Increased capsular content of sialic acid has been associated with increased pathogenicity. Other virulence factors include C proteins, extracellular neuraminidase, and lipoteichoic acid.

Epidemiology

Group B streptococci have been recovered from birth canal cultures of 2–25% of pregnant and postpartum women. The majority (50–75%) of infants of culture-positive women are colonized in the first few days of life. In contrast, only 1–25% of infants born to culture-negative women have been shown to acquire group B streptococci. The transmission rate is increased in heavily colonized women. Cesarean section has little effect on transmission. Only 1–2% of colonized infants get systemic disease. The organism can also be transmitted to neonates after birth by health care providers; nosocomial nursery outbreaks have been reported.

Clinical Manifestations

The two most commonly encountered clinical presentations of group B streptococci in the neonate are early-onset and late-onset diseases. The clinical features of each are variable, and overlap is common. The early-onset disease is characterized by rapid-onset fulminant sepsis and pneumonia, typically associated with low birth weight, prolonged rupture of membranes, maternal peripartum fever, or difficult, traumatic delivery. Symptoms and signs begin within hours of birth and progress rapidly. The clinical and radiologic features are indistinguishable from those of hyaline membrane disease. Laboratory results may show leukopenia and gram-positive cocci in the tracheal aspirate. Mortality is approximately 50%. Group B streptococcal isolates from neonates with early-onset disease have been roughly even in their distribution among the major serotypes.

The late-onset disease, in contrast, is predominantly caused by type III group B streptococci. The disease is of slow onset and manifests as meningitis. The disease has a mortality of 10–15% and long-term neurologic morbidity of approximately 50%. Other presentations of late-onset disease include focal infections such as cellulitis, osteomyelitis, and arthritis.

Diagnosis

A high index of suspicion should always be maintained, and, when the diagnosis is considered, appropriate cultures should be obtained and prompt antibiotic therapy should be initiated. Infection is established by isolation of the organism from sterile body fluids. Antigen detection in these fluids using latex agglutination or counterimmunoelectrophoresis can be helpful. Changes in the complete blood count are not specific.

Treatment

Penicillin G is the antibiotic of choice for proven group B streptococcal disease. Intravenous penicillin should be administered in daily doses of 100,000–150,000 U/kg

(divided into two to three doses) in the first week of life and 150,000–200,000 U/kg (divided into three to four doses) thereafter. The dose should be doubled for meningitis. Duration of therapy should be 10–14 days for uncomplicated bacteremia, 2–3 weeks for meningitis and septic arthritis, and 3–4 weeks for osteomyelitis.

Ampicillin and gentamicin, commonly used for empirical treatment of infections in the neonate, is an effective combination. It may result in more rapid killing of streptococci in the blood and vascular tissues due to the synergistic activity of the two antibiotic agents against group B streptococci. Combination therapy should be continued for the first several days until a good clinical and bacteriologic response is obtained. Penicillin or ampicillin alone could then be used to complete the course of therapy.

Granulocyte-colony stimulating factor and streptococcal hyperimmune gammaglobulin have been used as adjuvant treatment to antibiotics with some promising results. More research is required before their routine use is recommended.

Prevention

Chemoprophylaxis and immunoprophylaxis have been tried to reduce neonatal infections, particularly in high-risk deliveries. The most successful chemoprophylactic approach is intrapartum administration of ampicillin to group B streptococcus-colonized mothers. Penicillin prophylaxis of an asymptomatic sibling of an infected twin may be justified. Because high levels of maternal type-specific antibody should protect full-term infants, the immunization of pregnant women with purified type-specific vaccine is a rational approach. The immunogenicity of capsular polysaccharide, however, has been low, with response rates of 40–80%. Protein conjugate vaccines are more immunogenic and might provide better protection. They are being investigated.

Group B streptococcal hyperimmune globulin has been used in some high-risk infants. Further studies are needed to confirm its efficacy.

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94 Tetanus

Sulaiman Al Alola

Tetanus is an old disease that has been described vividly in medical history as far back as the second century AD.

Etiology and Pathogenesis

Tetanus is caused by the anaerobic, spore-forming, motile, gram-positive bacillus *Clostridium tetani*, which is present in soil and human and animal feces. This organism was isolated by Ketaset in 1889. The disease manifestation is not due to infection with *C. tetani* but rather is secondary to the specific neurotoxins produced by the vegetative form of *C. tetani* at the site of infection, which usually starts by the inoculation of the spore forms of the organism at the site of injury. The spores then turn into vegetative forms that flourish and multiply to produce the neurotoxins. *C. tetani* does not cause any tissue destruction nor inflammatory response.

There are two exotoxins produced by *C. tetani*, tetanolysin and tetanospasmin. Tetanolysin causes only hemolysis and has no role in the clinical manifestation of the disease. Tetanospasmin is the exotoxin responsible for the clinical features of the disease. It is a protein of 67,000 Da. It is a very potent toxin, next only to the poison produced by *Clostridium botulinum*. Humans are very susceptible to tetanospasmin, requiring only 1/2,500 and 1/35,000 of the dose fatal to cats and chickens, respectively, to show symptoms. Tetanospasmin inhibits release of acetylcholine in the neuromuscular junctions.

Clinical Features

The incubation period is usually 3–21 days, but it could be as short as 1 day or as long as several months. There is a direct relationship between the incubation period and the distance between the site of infection and the central nervous system. Tetanus may manifest in two forms, local or generalized. Tetanus diagnosis is totally clinical after excluding other causes of tetanic spasms, e.g., hypocalcemic tetany, phenothiazine reaction, strychnine poisoning and hysterical reactions.

Local Tetanus

This is an infrequent form of tetanus in which there is painful spasm of the muscles at the site of infection. It can be a precedent of the generalized form of tetanus. Cephalic tetanus is a variant of local tetanus. It usually follows the introduction of *C. tetani* in the course of injuries to the scalp, eye, face, ear or neck; chronic otitis media; or rarely tonsillectomy. The incubation period of this form of tetanus is usually 1–2 days. It is characterized by palsy of cranial nerves III, IV, VII, IX, X, and XII, singly or in any combination. Generally, the prognosis of cephalic tetanus is poor.

Generalized Tetanus

This is the most common presentation of tetanus. It usually follows deep penetrating injuries in which there is tissue damage, but, in the majority of cases, simple insignificant injury was the cause of the disease. Trismus, or spasm of the masseters muscles, is the hallmark of the disease. It may be unilateral early in the disease but becomes bilateral within a short time. In some cases, it may be absent during the entire course of the disease or appear only after other abnormalities have become apparent. Severe, unrelenting trismus leads to the development of a characteristic facial expression, the sardonic smile (risus sardonicus).

Generalized seizures (produced by tetanospasmin) usually start as sudden bursts of tonic contractions of all groups of muscles that lead to the development of opisthotonus, flexion and abduction of the arms, clenching of the fists on the chest, and extension of the legs. This tonic muscle contraction is very painful and is precipitated by the slightest noise or disturbance to the patient.

Neonatal Tetanus

Neonatal tetanus is still a major health problem in the developing world and is directly related to the local customs and handling of the birth process, particularly

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Table 94.1
Tetanus prophylaxis after injury

	Type of wound			
	Clean minor wound		Dirty, complicated wound	
History of immunization	Td	TIG	Td	TIG
Unknown or <3 doses given	Yes	No	Yes	Yes
≥3 doses of immunization given	No	No	No	No

cutting the umbilical cord and taking care of the umbilical stump. Neonatal tetanus is the cause of 45–75% of all deaths secondary to tetanus. The primary cause of death in neonatal tetanus is bronchopneumonia or hemorrhage in the lungs, singly or together. Among the nonpulmonary causes of death in neonatal tetanus are hepatitis, omphalitis, cerebral hemorrhage, and thrombosis and rupture of the renal vein.

Treatment

Treatment of generalized tetanus is directed to the following goals:

1. Neutralization of the circulating tetanospasmin before it gets attached to the nervous system by administration of antitoxin
2. Surgical débridement of the site of entry of the organism, when possible
3. Constant sedation and anticonvulsant treatment, or even complete paralysis of the patient, especially in neonatal tetanus, and mechanical ventilation, together with meticulous nursing care
4. Close monitoring of fluid, electrolyte, caloric, and acid–base balance
5. Intravenous or oral metronidazole (30 mg/kg/day) Q 6 hrs is the recommended first line treatment for 10–14 days. Penicillin given intravenously in a dose of 100,000 U/kg/day in four divided doses for 10 days to kill the vegetative forms of *C. tetani* at the site of injury is an alternative.

The antitoxin, human tetanus immunoglobulin (TIG), is given in a dose of 3,000–6,000 U intramuscularly (IM). If human TIG is not available, horse serum tetanus antitoxin is given in a dose of 100,000 U. Half of this dose is given IM after appropriate testing to rule out sensitivity to horse serum. If this dose is tolerated well, the other half is given intravenously (IV) slowly. Diazepam IV has proven very effective in controlling the tonic spasms of neonatal tetanus. Immune Globulin Intravenous (IGIV) can be given if TIG is not available. The IGIV dose recommended is 200–400 mg/kg.

Prevention

Tetanus is a preventable disease. Active immunization has proved to be very effective in decreasing the incidence of tetanus. In USA only 40 or fewer cases of tetanus have been reported annually since 1999. Tetanus is not tranmissble from person to person. After the initial basic course of tetanus immunization in children, a protective level of antitoxin is present in the serum for 5–10 years after the last dose of immunization. Prevention of neonatal tetanus can be accomplished by prenatal immunization of the previously unimmunized mother. The mother should be given two doses of tetanus toxoid at least 4 weeks apart, and the second dose should be given at least 2 weeks before delivery.

For the patient who recovers from tetanus, active immunization should be given because having tetanus does not confer lifelong immunity. The need for tetanus prophylaxis after receiving a wound is summarized in *Table 94.1*.

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95 Tuberculosis

Suliman Al Jumaah

Etiology

Tuberculosis is caused by *Mycobacterium tuberculosis* (MTB) bacilli which are an aerobic nonmotile and nonspore-forming organism that range in size from 1 to 10 μm. These organisms do not take up usual stain for bacteria but rather stain strongly with special stains after treatment with acid and alcohol. Those characteristics are demonstrated by basic fuchsin stain technique (Ziehl–Neelsen and Kinyoun) or flourochrome method using auramine and rhodamine stains. Mycobacterium species include *Mycobacterium tuberculosis*, *Mycobaterium bovis*, and *Mycobacterium Africanum*.

Epidemiology

Tuberculosis is a major health problem worldwide. In 2009, WHO estimated 9.4 million incident cases of TB globally, accounting for an incidence of 137 per 100,000 with more than one million deaths. The global TB burden is falling slowly and the incidence rates have been declining since 2004 despite an increase in absolute TB cases due to population growth. There is a striking difference of TB among developed countries where incidence rate is generally less than 10/100,000 and low-income countries where incidence generally exceeds 100/100,000. In some regions like Africa, the incidence is still increasing. There is limited surveillance data that accurately quantify TB in pediatric population. In the year 2000, 884,019 (11%) of the estimated 8.3 million TB cases were in children, with 75% occurred in the 22 high-burden countries. The proportion of pediatric TB cases occurring in low-income countries is around 15% of total incident TB cases compared with 6% in the USA. In developed countries, like the USA, TB incidence is much less reduced. In 2009, the USA reported 11,545 total TB cases accounting for a rate of 3.8/100,000, representing 57% decline compared with 1992 resurgence peak. Six hundred and forty-six cases were among children, with an incidence rate of 1/100,000. Due to paucibacillary nature of TB disease in children, it is receiving less attention in TB control programs and most of the emphasis is directed toward the more infectious smear-positive TB. Recently, there has been an increased awareness regarding TB burden in children. In 2006, WHO compiled first guidance on the management of childhood TB and also requested all countries to include pediatric TB data in all future reports. In addition, in 2007, Global Drug Facility (GDF) made child-friendly TB drug formulation available for poor countries.

Infection with human immunodeficiency virus (HIV) is associated with tremendous risk of developing TB disease. Growing adult population coinfected with TB and HIV posed a major impact on TB incidence among their children due to more exposure and infection among those children. In addition, children infected with HIV and TB had a big impact on TB epidemiology in many countries, but no accurate data on actual burden.

Definitions

It is important to clarify some terminologies like TB exposure, latent TB infection (LTBI), and TB disease which are sometimes a source of confusions. Individuals who have been in contact with a case of tuberculosis but whose status is not clear because there is not enough time to rely on result of tuberculin skin test (TST) are defined as TB exposed. Asymptomatic individuals who have positive TST but no clinical or radiological finding of TB disease are referred to as latent TB infected. TB disease implies clinical or radiological findings consistent with Tuberculosis.

Pathogenesis

Mycobacterium tuberculosis is mostly acquired by inhalation of droplet nuclei containing the bacilli which reach the alveoli. Localized pneumonic process will form the primary (Ghon) focus. During the first 4–6 weeks, multiplication of bacilli within the primary focus will occur and bacilli will drain via lymphatic to regional lymph nodes. The upper lobes drain to ipsilateral–paratracheal nodes, whereas the rest of the lung drains to perihilar and subcarinal nodes, with dominant lymph flow from left to

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right. The Ghon complex (primary complex) is represented by both the Ghon focus, with or without some overlying pleural reaction, and the affected regional lymph nodes.

During this stage, occult dissemination occurs (primary bacillemia) to most of body organs including liver, spleen, bone marrow, and kidneys. This happens before cell-mediated immunity is reactivated. Most of this hematogenous spread is asymptomatic and few children progress to TB disease. After this primary dissemination, cell-mediated immune system is stimulated resulting in lymphocytic infiltration of the infected foci. Histologically, the infected foci become surrounded by lymphocytes and epitheloid cells, forming granuloma. In most of the situation, the immune system will control the disease which remains dormant as latent TB; however, this depends on various factors. Age and immune status are the most important factors determining disease progression. The risk of progression from tuberculosis (TB) infection to disease is generally small (5–10% lifetime risk) in immunocompetent older children and adults. However, in infants and children less than 2 years, the risk is increased to 40–50%. In untreated HIV-infected patients, there is 5–10% annual risk of disease progression. Risk is the lowest (2%) for children of 5–10 years of age. Fifty percent of disease progression occurs within the first 2 years.

Clinical Manifestations

Tuberculosis may involve any organ in the body. Pulmonary TB is the commonest form accounting for 60–80% of all cases. Extrapulmonary TB present with various forms with lymphadenopathy being the commonest (67%), followed by the central nervous system disease (13%), pleural disease (6%), miliary (5%), and skeletal (5%).

Pulmonary Tuberculosis

Inhalation of *Mycobacterium tuberculosis* bacilli results in Ghon complex causing parenchymal disease and intrathoracic adenopathy. The natural history of the disease illustrates that it either gets controlled by the immune system leading to LTBI or progress leading to primary parenchymal disease or progressive primary disease. LTBI may later reactivate leading to reactivation disease in adolescents or immunocompromised children.

Infants, young children, and adolescents are more likely to be symptomatic. Symptoms are usually vague with low-grade fever, malaise, cough, loss of appetite, and weight loss. Symptoms may result from enlarging lymph nodes compressing bronchus leading to collapse consolidation, hypoaeration, and segmental or lobar atelectasis. Progressive pulmonary tuberculosis results from poor containment of the initial infection, leading to tissue destruction and sometimes cavity formation (*Figs. 95.1* and *95.2*).

Reactivation form of the disease occurs usually in adolescents with fever, cough, and night sweats. It is not clear why adolescents are more prone to this form of disease. Radiological findings overlap with primary disease.

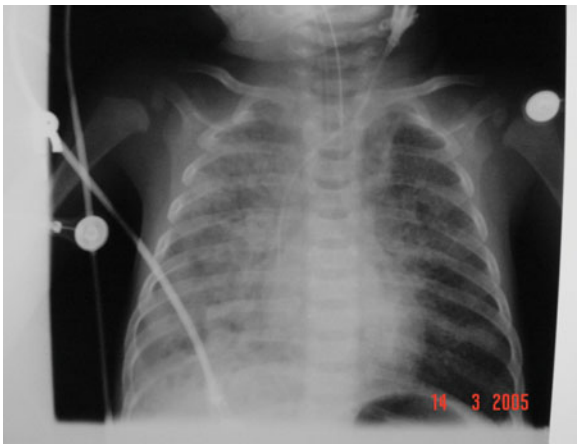

Figure 95.1
Chest radiograph of a 6-month-old infant with extensive consolidation, both gastric aspirate and tracheal aspirate grew *Mycobacterium tuberculosis*

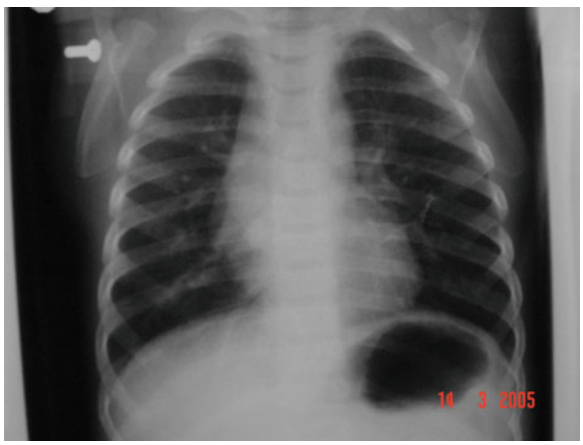

Figure 95.2
Chest radiograph of same infant showing marked improvement 6 months after therapy

The most common radiological finding is hilar, mediastinal adenopathy, followed by segment or lobar consolidation. Hilar adenopathy has been noted in about 50% of asymptomatic children as transient phenomenon which may be discovered in the context of contact tracing. However, this is conventionally treated as disease.

Pleural Disease

Pleural disease may result from primary infection or reactivation. In primary infection, there is direct invasion of pleural space after primary bacillemia, followed 6–12 weeks later by hypersensitivity reaction leading to pleural effusion. In reactivation form of the disease, there is usually parenchymal lung focus with secondary pleural involvement. Pleural TB occurs more in adolescents and rare in younger children.

Lymphatic Disease

Tuberculous lymphadenopathy occurs in 10–15% of children with TB and is the commonest form of extrapulmonary TB. Most cases of adenitis occur within 6–9 months of initial infection. Supraclavicular, anterior cervical, tonsillar, and submandibular nodes are involved secondary to extension of primary lesion of the upper lung fields or abdomen. Nodes are usually unilateral, firm, and non-tender. A primary pulmonary focus is visible in 30–70% of cases. Untreated lymph nodes can resolve but may also progress to caseating necrosis, capsule rupture with spread to adjacent nodes and overlying skin which will become shiny and red. If skin ruptures, this will lead to sinus formation. It is important to distinguish lymphadenitis due to *Mycobacterium tuberculosis* from that due to nontuberculous mycobacteria (NTM). Chest x-ray is usually normal in NTM adenitis and TST is negative or weakly positive and child is usually less than 3 years old with absence of systemic illness. History of contact in case of tuberculosis may be helpful, but generally excisional biopsy is required to confirm the diagnosis (*Fig. 95.3*).

Central Nervous System Tuberculosis

Central nervous system tuberculosis (CNSTB) is the most serious form of extrapulmonary TB, which is frequently fatal if untreated. CNSTB usually occurs within 6 months of primary infection, and 50% of patients are under 2 years. It complicates 0.5–2% of primary infection and 50% of military TB. The disease originates from caseous

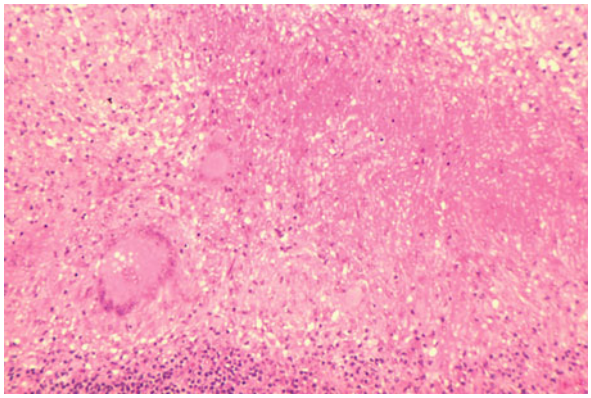

Figure 95.3
Lymph node biopsy from a child with tuberculosis lymphadenitis showing typical caseous necrosis

meningeal focus lesion in the cerebral cortex or meninges that were formed during the stage of hematogenous spread that release bacilli into subarachnoid space. The most common manifestation of CNSTB is meningitis in 95% and tuberculoma in 5%. The onset can be rapid but more often is insidious with nonspecific symptoms like fever, fussiness, and nausea. This is followed by cranial nerve palsy and meningeal irritation, and finally stupor and coma. CT scan of the brain frequently (>80%) shows hydrocephalus with basilar enhancement. Chest x-ray is abnormal in up to 90% and TST is positive in 30% of children. CSF shows high white cell count with lymphocyte predominance, low sugar, and high protein. AFB stain is positive in only 10–30% of patients, and culture is positive in 30–70% if enough CSF sample cultured (5–15 mL). Gastric aspirate is positive in about 10% of children.

Tuberculoma manifest as space-occupying lesion, which may involve any part of the brain but tend to be infratentorial in children (*Figs. 95.4* and *95.5*).

The most common symptoms are headache, fever, and convulsion. It needs to be differentiated from tumor and neurocysticercosis. The disease may be suspected on epidemiological ground, but biopsy is often needed for diagnosis. Tuberculoma may paradoxically increase in size or appear upon starting effective TB treatment. This phenomenon is probably immune mediated and does not signify failure of therapy.

Osteoarticular TB

Osteoarticular tuberculosis results from hematogenous seeding after primary infection. Interval between infection

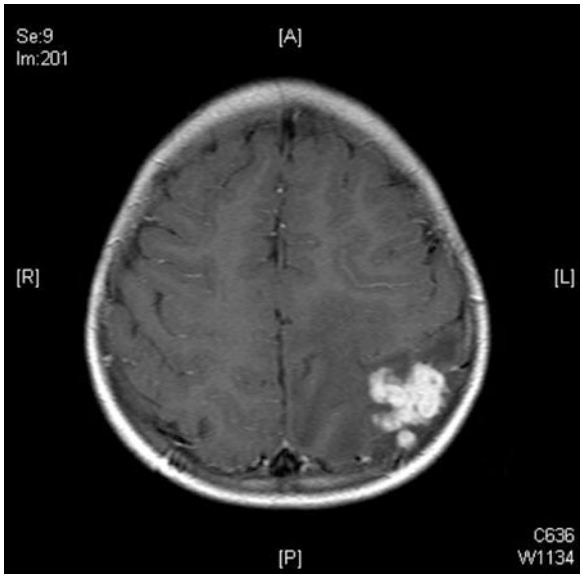

Figure 95.4
MRI brain, T1-weighted image of a child showing enhancing temporoparietal lesion proven by biopsy to be due *Mycobacterium tuberculosis*

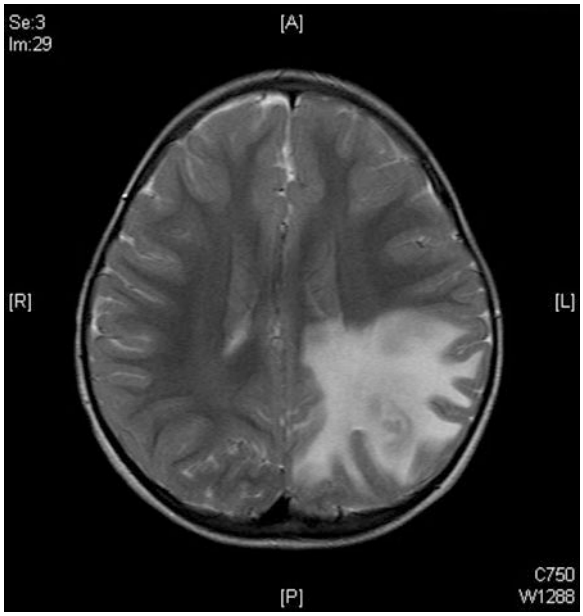

Figure 95.5
MRI brain, T2-weighted image of same child showing temporoparietal lesion with surrounding extensive edema

and clinical manifestation is usually several years but may be as short as 1 month like in tuberculous dactylitis in infants. Infection usually starts in the metaphysis of bone causing necrosis and caseation. Abscess formation and extension of infection to nearby joint complicate bone infection. Vertebrae are the most commonly affected bone, which is called Pott disease. It may affect any one or multiple vertebral bodies but mostly lower thoracic and upper lumbar. Wedging of the involved vertebrae results in Kyphosis and Gibbus deformity. Extension of infection to surrounding soft tissue causes paraspinal abscess, psoas abscess, or retropharyngeal abscess.

Vertebral diseases present with back pain, paraparesis, and parasthesia. CT and MRI will aid in diagnosis.

Other sites of involvement include knee, hip, elbow, and ankle. Involvement ranges from mild joint effusion to bone destruction with restriction of joint movement. TST is usually positive in 80–90%.

Other form of TB peculiar to infant is tuberculous dactylitits, which is present with swelling of hands, feet, and cystic bony lesions.

Miliary TB

Miliary TB results from lymphohematogenous spread with multiorgan involvement. It is commonly seen in infants and immuncompromised host including children with rheumatological disease receiving antitumor necrosis factors agent. Organisms seed many organs like lung, liver, spleen, meninges, bone marrow, and retina. Meningitis is seen in about 20–50% of cases.

Chest x-ray shows classic miliary pattern with multiple small nodules in 50%. There may also be airspace consolidation.

TST is usually negative due to anergy. AFB culture has a yield of 30–60%.

TB Diagnosis

Diagnosis of TB in children is a major challenge. Clinically, diagnosis is usually based on (1) known contact with an index case, (2) positive tuberculin skin test, (3) suggestive finding on chest radiograph.

In most situations, diagnosis of TB relies on clinical and epidemiological background. Unfortunately, there is no single test which could confirm the diagnosis in all situations. Bacteriological confirmation is possible in less than 50% of the cases.

Tuberculin Skin Test (TST)

TST using five tuberculin unit is the standard method. The antigens trigger delayed-type hypersensitivity reaction in persons previously exposed to TB. Induration is measured in millimeters after 48–72 h. Negative TST does not rule out TB since 10% of culture-confirmed TB cases have negative TST. False-negative results may be due to severe disease, debilitated children, malnutrition, immunosuppression, or if TST is done early after exposure. False-positive results are seen in infections due to NTM or previous vaccination with BCG. However, BCG vaccination is unlikely to give positive TST results after 3–5 years.

TST is interpreted taking in consideration risk of TB and immune status of the host. A cutoff of 5 mm or more is considered positive in persons with history of contact with TB case; chest radiograph is consistent with TB, HIV, and other immunosuppressive state. Ten millimeters or more is considered significant in health-care worker, population at risk, children in contact with adult at high risk. Fifteen millimeters is considered positive in low-risk group.

Mycobacterial Culture

Confirmation of TB in children is hampered by sampling difficulties since young children are not able to cough up the sputum. In addition, TB in children is paucibacilliary and AFB sputum smear is positive only in about 15–20% of cases. Early morning gastric aspirate yields positive culture in 37–45% which is better than bronchoalveolar lavage (yield 13–30%). Induced sputum has a yield of about 10%. Traditional solid culture medium (Lowenstein–Jensen medium and Middlebrook), takes 4–6 weeks to yield growth and in additional 2–4 weeks for susceptibility test. More recent fluid-based medium (radiometric and non-radiometric) has a better yield (10 days to 2 weeks). Other new method, microscopic observation susceptibility test (MODS) has median time of recovery of 7 days. It depends on direct inoculation of processed sputum into 24 well plates containing or not containing the drug. Growth is detected by examination under inverted microscope.

Nucleic Acid Amplification Methods

These tests are used to directly detect DNA on clinical samples. The principle is based on using high conserved segment to amplicate DNA. Polymerase chain reaction (PCR Amplicor, Roche) approved in the USA for adults with smear-positive sputum and Amplified *Mycobacterium Tuberculosis* Direct Test, Gene-probe (AMTD) is approved in adults for both smear positive and smear negative. These tests are very specific (95–98%), but sensitivity ranges from 35% to 75%. Limited studies in pediatric showed sensitivity of 25–83% in children with pulmonary TB. Those tests may help in diagnosis of TB in children but negative PCR does not exclude diagnosis of TB.

Interferon-γ Release Assays

These tests are based on in vitro stimulation of lymphocyte by specific mycobacterial antigen, early secretory antigen (ESAT), and culture filtrate protein (CFP). T cell of patients exposed to MTB will release interferon gamma. Released interferon gamma that reflects T-cell response will be measured.

Three tests are available: Quantiferon-TB Gold, Quantiferon-TB Gold in-tube (Cellestis, Victoria, Australia), and T-SPOT-TB (Oxford Immunotee, UK). Interferon gamma is measured by Elisa (Quantiferon) or by counting spot-forming T cells (T-SPOT-TB). Most of the studies were done on adults and there is limited data in pediatrics. Results of these tests are not influenced by previous receipt of BCG. Both tests are endorsed by FDA for diagnosis of LTBI and TB disease.

Recent meta-analysis of studies done on latent TB infection showed sensitivity of 70% for Quantiferon-TB Gold, 78% for Quantiferon-TB Gold in-tube, and 90% for T-SPOT-TB compared with 77% for TST. Both tests are fairly specific (96–99%) in both BCG vaccinated and non-vaccinated, but TST has specificity of 59% in BCG vaccinated and 97% in BCG non-vaccinated.

Both tests are promising but it is early to recommend their use in pediatrics.

Treatment of TB

One of the major problems with treating TB is the noncompliance which may lead to failure of therapy, relapse, and development of drug resistance which is already a growing problem worldwide. Adoption of directly observed therapy (DOT) is recommended for children and adolescents with tuberculosis. The American Academy of Pediatrics (AAP) recommends treatment of tuberculosis disease with 2 months of isoniazid, rifampin,

pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampin. Some experts recommend starting three-drug regimens (isoniazid, rifampin, and pyrazinamide) as initial regimen if a source case is known to be sensitive or reside in low-resistance area. WHO recommends starting four-drug regimens if INH resistance is more than 4%. Majority of extrapulmonary TB is treated with same regimen as for pulmonary tuberculosis. Exceptions are children who have CNSTB, disseminated TB, or severe cavitory TB where treatment course is 9–12 months (*Tables 95.1* and *95.2*).

Corticosteroids have been used as an adjunctive therapy in some forms of TB to decrease damage caused by inflammatory response. Indication to use steroids includes CNSTB, pleural, severe miliary TB, pericarditis, endobronchial and abdominal TB. Dose is 2 mg/kg per day of prednisone for 4–6 weeks followed by tapering dose.

The rationale of using multiple chemotherapy is to ensure mycobacteriologic cure, because resistance to one of the antimycobacterial drugs occurs naturally (INH, 1 in 10^6; rifampin, 1 in 10^6; streptomycin, 1 in 10^5; and ethambutol, 1 in 10^6). Therefore, in lesions with high population size, such as the cavitary lesion, which contains 10^7–10^9 mycobacteria, there is a high chance of having colonies resistant to one of the drugs. However, the chance of having resistance to two drugs is 1 in 10^{13}–10^{17}. In children, tuberculosis is a result of primary infection, which usually results in small caseous lesions that contain a smaller number of mycobacteria (10^6–10^7), and therefore the cure rate is excellent. However, due to increasing incidence of multidrug-resistant (MDR) mycobacteria, attention should be paid to therapeutic response, and every effort should be made to obtain susceptibility testing.

Table 95.1
Treatment of tuberculosis in children

Infection or disease category	Regimen
Latent tuberculosis infection (positive TST)	
Isoniazid susceptible	9 months of isoniazid, once a day
Isoniazid resistant	6 months of rifampin, once a day
Pulmonary and extrapulmonary (except meningitis, disseminated disease, and severe cavitory TB)	2 months of isoniazid, rifampin, pyrazinamide, and streptomycin/ethambutol daily, followed by 4 months of isoniazid and rifampin by DOT for drug-susceptible *Mycobacterium tuberculosis*
Meningitis, disseminated disease, and severe cavitory TB	2 months of isoniazid, rifampin, pyrazinamide, and an aminoglycoside or ethambutol or ethionamide, once a day, followed by 7–10 months of isoniazid and rifampin once a day or twice a week (9–12 months total) for drug-susceptible *M tuberculosis*

Table 95.2
Commonly used drugs for treatment of tuberculosis in children

Drugs	Dosage forms	Daily dosage, mg/kg	Side effects
Isoniazid	Scored tablets 100 mg 300 mg Syrup 10 mg/mL	10–15	Mild hepatic enzyme elevation, hepatitis, peripheral neuritis, hypersensitivity Diarrhea and gastric irritation caused by vehicle in the syrup
Rifampin	Capsules 150 mg 300 mg Syrup formulated Capsules	10–20	Orange discoloration of secretions or urine, staining of contact lenses, vomiting, hepatitis, influenza-like reaction, thrombocytopenia, pruritus; oral contraceptives may be effective
Pyrazinamide	Scored tablets 500 mg	30–40	Hepatotoxic effect, hyperuricemia, arthralgia, gastrointestinal tract upset
Ethambutol	Tablets 100 mg 400 mg	20–25	Optic neuritis (usually reversible), decreased red-green color discrimination, gastrointestinal tract disturbances, hypersensitivity
Streptomycin	Vials 1 g 4 g	20–40 (IM)	Hearing loss Nephrotoxicity

Treatment of LTBI

Tracing contacts and treating individuals with LTBI is one of the most effective ways of controlling TB. INH therapy was shown to reduce TB disease by 94%. INH should be administered to all children (and adults) with positive TST. High-risk children (<5 years) and infants need to be started on INH therapy even initial TST is negative. TST should be repeated in 3 months and if still negative, INH may be discontinued.

Prevention of TB

BCG is the only available vaccine and still recommended by WHO in high-endemic countries. It is live attenuated vaccine derived from *M. bovis* strain that has been attenuated by serial passages. It has modest effect in preventing TB. Meta-analysis of randomized clinic trial showed an overall efficacy of 74%. Efficacy for disseminated TB was 78% and 64% for TB meningitis. Its main side effect is local adenitis. It may also cause fatal disseminated diseases in SCID patients and patient with gamma interferon axis defect.

Drug-Resistant TB

Drug-resistant TB is a growing concern all over the world. Resistant may be to single agent (like isozianizid) or resistant to multiple drugs. Multidrug resistance TB (IMDR) is defined as resistant to at least isoniazid and rifampin. Many factors had contributed to the increase in drug resistance, mostly noncompliance with medication, poor therapy, and epidemic of HIV. Prevalence of INH resistance or MDR is variable among different countries. In the USA, the prevalence of INH resistance among patients with pulmonary tuberculosis has increased from 2% to 9%.

Consideration of local drug resistance has major impact on choice of initial regimen and retreatment of tuberculosis. It is advised to start a four-drug regimen if local INH resistance >4% and a three-drug regimen if INH resistance is less than 4%. Prevalence of MDR is variable. A survey by WHO showed an overall prevalence 2.2% but 13% in retreated patients. The prevalence data in children are limited. MDR is always difficult to treat with approximately 50% failure rate. Therapy should include five- or six-drug regimens for 12–18 months. In these situations, second-line agents like ciprofloxacin, levofloxacin, ethionamide, amikacin, and cycloserine are used. However, those agents are generally less effective than first-line agents.

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96 Fungal Infections

Ibrahim Bin-Hussain

Introduction

The number of patients at risk for fungal infection has increased dramatically over the last 3 decades. However, with the advances in medical technology and development of new antifungal agents, the diagnosis and treatment of fungal infections have been improved.

In the past, fungi were used by human in preparation of food, but over the last 3 decades the relation between fungi and human has been reversed with the emergence of new or previously rare fungal infections with an increased morbidity and mortality and development of drug-resistant strains.

In this chapter, the changing epidemiology of invasive fungal infections in pediatric patients is described, and the challenges with the diagnosis and treatment of fungal infections are discussed. The primary defense mechanisms against fungal infections are the skin and mucous membrane; these are fragile and easily colonized in children as well, as the functional immaturity of phagocytes and T lymphocytes put pediatric patients at higher risk for fungal infection. Interestingly, pediatric patients tolerate the intensive antifungal therapy much more than the adult patients.

Epidemiology

Fungi are present in the environment. The reservoirs for *Aspergillus* and *Zygomycetes* include unfiltered air-ventilation system, contaminated dust during construction. In contrast to candida, it is mostly acquired indigenously through prior colonization of the mouth, vagina, skin, and gastrointestinal tract, which can be transmitted to patient by the healthcare personnel; therefore, it is very important to practice infection control measures including hand hygiene to prevent transmission.

The systemic fungal infections are major causes of morbidity and mortality in the immuncompromised patients and the incidence of fungal infection is up to 40% in patient with acute leukemia and hematopoeitic stem cell transplant, 35% in patient with post heart transplant, up to 40% for post liver transplant, for other solid organ transplant is about 5% including kidney transplant.

Risk Factors

The most important defects that predispose to fungal Infections are neutrophil defects (either quantitative or qualitative) and defect in T-cell mediated immunity which are commonly seen in primary condition such as immunodeficiency either primary or secondary, leukemia, lymphoma, bone marrow transplant recipient, organ transplant, acquired immunodeficiency syndrome, primary immune disorder, gastrointestinal disease, severe burns, premature births, diabetes, and IV drug abuser. Other factors related to medical interventions (iatrogenic) include chemotherapy, immunosuppressive drugs, prolonged use of broad-spectrum antibiotics, breaks in skin or mucosa, indwelling catheters, peritoneal dialysis, prolonged hospitalizations, and total parenteral nutrition.

The classic risk factors for candidiasis include the use of multiple antibiotics, presence of central venous catheter, total parenteral nutrition, and colonization with candida. The specific risk factors in neonates, which are unique to this group, include low birth weight (90% of affected neonates) instrumentation like intubation and prolonged ventilation, prolonged use of third-generation cephalosporin, congenital malformation (frequently seen in infants with birth weight more than 2,500 g at birth with prolonged NICU hospitalization), gastrointestinal tract disease, necrotizing enterocolitis and anatomical abnormalities requiring surgery, and low Apgar score at 5 min.

In the invasive aspergillosis in children, the highest incidence are in patients post allogeneic bone marrow transplant, followed by patients with acute myloid leukemia (AML), congenital immunodeficiency; other groups at risks include aplastic anemia, acute lymphoblastic leukemia (ALL), lymphoma, autologous bone marrow transplant, and solid tumor. 74% of invasive

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Aspergillosis are related to oncological disorders both hematological and oncological malignancy and post bone marrow transplant.

Other predisposing factors for fungal infection include high dose and prolonged use of corticosteroid therapy. Other risk factors include Graft-versus-host disease, congenital immunodeficiency, and solid organ transplant. Interestingly, 90% of the patients have more than one of these risk factors.

Candidemia represent up to 15% of all bloodstream infections and is the third most common bloodstream isolate in the USA. The fungal sepsis is associated with second highest case fatality in children up to 13%. Comparing the pediatric patients and adult, the highest incidence per admission is in neonates up to 150 in 100,000 admissions, followed by children about 47 per 100,000 admissions and adult 30 per 100,000 admissions. The incidence in neonates increased with low birth weight and there is a reverse relationship between the birth weight and the incidence of fungal infection, mainly candidiasis.

In addition to fungal infection in high-risk patient, there is emerging fungal pathogen which can be varied from location to location. For example, in southern part of Saudi Arabia, there are pediatric patients reported with gastrointestinal basidiobolomycosis. Usually, these patients are present with huge abdominal mass that usually confuse with lymphoma or other solid organ tumor including rhabdomyosarcoma, and gastrointestinal tuberculosis. The clue for the diagnosis of gastrointestinal basidiobolomycosis is intense tissue eosinophilia surrounding the fungal structure (Splendore Hoeppli) phenomena and the special fungal stain (GMS) will show the fungal pathogen (*Fig. 96.1*).

Etiology

The predominant pathogen in immunocompromised patient is invasive candidiasis, followed by aspergillosis and mucormycosis. The candida species causing infection in immunocompromised patients are *candida albican*, which are most frequently isolated, but recently non-albicans candida species has emerged as a major pathogen including *Candida tropicales, Candida glabrata,* and *Candida parapsilosis*, in addition to other rarely isolated candida spp. including *Candida krusei* and *Candida lusitaniae*. The predominant aspergillus species is *Aspergillus fumigatos* in USA but other reported *Aspergillus flavus* is more frequently isolated.

Mortality in patients with invasive fungal infection is high. The mortality rate in patients post bone marrow transplant with invasive aspergillosis can exceed 70% and close to 30% in patients with candidemia.

The clinical manifestation of fungal infection varies depending on the immune status of the host. For example, Candida cause mucocutaneous candidiasis in neonate and patients or with prolonged use of broad-spectrum antibiotics. It is usually transient but if prolonged primary immunodeficiency should be looked at. Patients with polygandular endocrinopathy can present with recalcitrant mucocutaneous candidiasis.

Invasive candida infection involved wide spectrum of diseases from catheter-related candidemia to deep organ involvement. There are four forms of invasive candidiadis: candidemia usually catheter-related candidemia, acute disseminated candidiasis, chronic disseminated candidiasis, and deep organ candidiasis.

In aspergillosis, the targeted organs are lungs and paranasal sinuses. These patients can present with prolonged fever and neutropenia not responding to

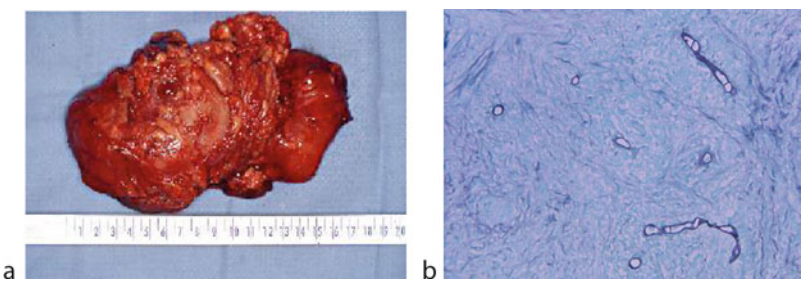

Figure 96.1
(a) Gross macroscopy of the mass after resection. (b) Silver stain showing branching septate hyphae of variable but generally wide diameter

broad-spectrum antiobiotics with few localizing signs. In adult series, the patient can have chest pain and hemoptysis but these are rare presentation in pediatric patient. Patient with paranasal sinusitis can present with localized facial swelling; with or without intracranial involvement.

Diagnosis

The diagnosis of fungal infection is a difficult task and it needs high index of clinical suspicion. Early diagnosis is very essential as the survival of patient often depends on the prompt initiation of appropriate therapeutic measure. Knowledge about spectrum of presentation is needed to predict the likely pathogen. Majority of these patients present with prolonged febrile neutropenia not responding to broad-spectrum antibacterial therapy. Few patients present with signs suggestive of fungal infection, for example, skin lesion, facial swelling, or necrotic lesion on hard palate. It is important to examine the patient thoroughly with good exposure to avoid missing an important clue for diagnosis. *Figure 96.2* shows patient presented with prolonged febrile and neutropenia, not responding to broad spectrum of antibiotic. This is the only clue for the diagnosis. If this patient is not exposed well, it will be easily missed as these lesions usually are asymptomatic and painless. It is also important to look in the oral cavity, for example, patient with acute lymphoplastic leukemia not responding to broad spectrum of antibiotic and with prolonged neutropenia, the examination for oral cavity can see the scar as shown in *Fig. 96.3* with necrotic ulcer in the hard palate.

Chest radiograph has low negative and positive predictive value in immunocompromised patients; therefore, it can be normal up to 25–50% of patient with invasive aspergillosis at the onset of the disease. The lesion in the chest x-ray can be patchy, peripheral, bilateral infiltrate, or solitary or multiple nodules. These lesions may progress over a period of days to weeks to form dense consolidated infiltrate or cavitation. Most of the patients who are at risk for fungal infection usually require high-resolution CT scan because it can give earlier and better assessment than chest radiograph. Findings from CT scan include halo sign, which is an early manifestation while the patient is neutropenic and usually appears as a rim of round glass–glass attenuation surrounding the nodule which usually corresponds to the rim of hemorrhage surrounding the pulmonary infarction. Other sign of invasive fungal infection includes air crescent sign. The problem in the air crescent sign is that the diagnostic usefulness is limited by the late occurrence which is usually seen about 1–3 weeks after the halo sign when neutropenia is resolved. This corresponds to the cavitations at the time of neutrophil recovery. In the recent publications in pediatrics, cavitation lessions is rarely manifested in pediatrics compared to adult. It is very difficult to depend on the air crescent sign and halo sign in pediatric patients. The difference in the manifestation radiologically between adult and pediatric is not understood.

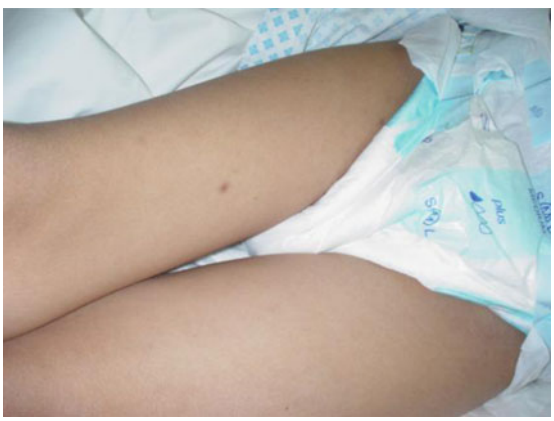

Figure 96.2
12-year-old with ALL with small nodula shown on her right thigh culture from *C. albican*

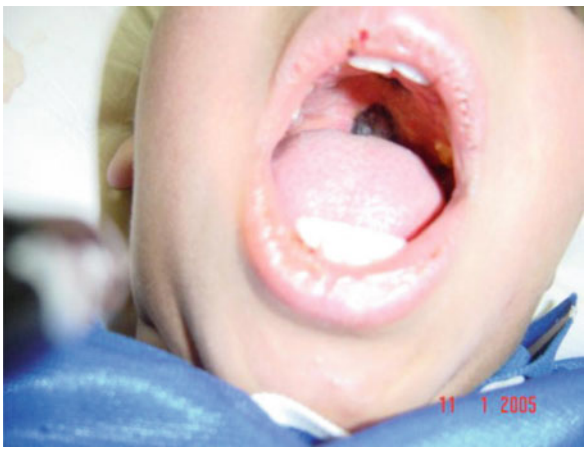

Figure 96.3
14-year with AML with necrotic hand pilace session, biopsy showed fungal hyphere culture from *A. flavus*

The radiological diagnosis of chronic disseminated candidiasis, the lesion may not be detected early in the course while the patients are neutropenic because these patients are unable to mount immunological response. The MRI and CT are more sensitive than the ultrasound in diagnosing chronic disseminated candidiasis as both MRI and CT scan can detect characteristic lesion in about 90% of patients compared to 75% with ultrasound but the ultrasound is a suitable alternative for monitoring the progress of the lesion during therapy.

The blood culture is useful for the detection of candida blood stream infections. The yield of blood culture for candidemia is up to 50% but with the new advancement in the microbiology the detection rate increased up to 80%.

Because of the difficulty in the diagnosis of fungal infection, there is surrogate marker including new diagnostic test that can help in diagnosis. For example, for candidiasis, markers which can help diagnosing candidemia in the blood includes 1, 3 Beta D Glucan which is approved to help in diagnosing invasive fungal infections. Marker for Aspergillosis include aspergillus galactomannan, both in the blood, broncoalveolar lavage fluid and CSF in addition to 1,3 Beta D Glucan.

The Galactomannan assay performance in children is lower compared to adult. The reason for the high false-positive Galactomannan antigenemia in pediatrics is not clear but one postulation could be related to the dietary difference in dairy products. The performance of Galactomannan assay for primary immunodeficiency, non-neutropenic patients is poor compared to other patient population as studies have shown that Galactomannan antigenemia detected in only 4 out of 15 cases of chronic granulamatous disease (CGD) and hyper IgE syndrome versus 24 out of 30 cases of all other immunocompromised conditions with significant statistical difference.

Because the clinical and radiological manifestations of fungal infection are often nonspecific, definitive diagnosis of fungal infection requires the performance of procedures with some degree of invasiveness. These procedures will depend on the condition of the patients, the clinical finding, as well as the finding on the radiological evaluations. Lesions need to be biopsied to guide therapy. Specimens need to be sent to microbiology as well as histopathology laboratories for fungal staining and cultures. The presence of branching, septate hyphae on direct microscopy suggest Aspergillus spp. but need to be confirmed by culture. Gomori methenamine stain is helpful for better visualization of the fungal structure. Only microbiological culture can identify the pathogen with accuracy.

Management

There are three important factors to consider in caring for patient at risk of fungal infection: the environmental controls and the use of cytokines as immunomodulator and antifungal agents. For the environmental control, there are strategies to control infections and to reduce exposure to pathogen. The infection control measures in the hospital setting is paramount important to prevent the spread of nosocomial infection. Environmental control such as minimizing exposure to dust especially from building construction and the use of air filter are crucial to prevent acquisition of organisms such as aspergillus. Infection control measures, in particular, hand hygiene, can minimize the spread of indigenous organisms such as candida species. Suppression of colonization using antifungal agent such as nystatin, clotrimazole, and fluconazole has limited success. The deficiency in number on function of white cell counts is correlated with the degree of progression of the disease. Cytokines as an immune modulator act on both neutropenic and non-neutropenic patients. These cytokines including granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor show a promising adjunct therapy for proven fungal infection. Regarding reducing exposure to fungal pathogen, it is important to avoid area of construction or renovation. Nosocomial *Aspergillus* infections result primarily from inhalation of fungal conidia. Rooms for high-risk patients should be equipped with high-efficiency particulate air (HEPA) filters, high rates of air exchange, and positive pressure so that air from the patient's room flows into the hallway.

Most cases of invasive candidiasis are caused by endogenous *Candida* organisms colonizing the gastrointestinal tract. *Candida* species can be carried on the hands of health-care workers, who need to follow appropriate hand washing precautions to prevent the nosocomial spread of organisms.

Patients at high risk for infections should avoid food known to be frequently contaminated with fungi (e.g., teas, herbal medicines, nonprocessed peanuts) and avoid activities that would provide large exposures (e.g., gardening, construction).

Antifungal Therapy

Significant antifungal chemotherapy began in 1903, with the successful use of potassium iodide (KI) for the treatment of sporotrichosis. There was little progress for the next 50 years until nystatin, the first useful polyene, was introduced in 1951. This was soon followed by

amphotericin B in 1956, still the standard against which new systemic antifungals are compared. Except for the development of flucytosine (1964), there was little progress until early 1972 in the development of the azole drugs. The current era, which is characterized largely by the modifications of azole drugs, began with miconazole (1978) and ketoconazole (1981) and brought the agents fluconazole (1990) and itraconazole (1992), which can be given orally and have increasing potency, decreased toxicity, and a broader spectrum of activity. The development of lipid formulation ameliorate the well-known toxicities of the amphotericin B. But from 2000 onward, there is a plethora of antifungal agents including IV itraconazole in 2000, caspofungin in 2001, voriconazole in 2002, micafungin in 2005, posaconazole in 2006, and anidulafungin in 2006.

The Mechanism of Action of Antifungals

Polyenes including amphotericin bind to ergosterol in fungal cell membranes, resulting in altered permeability and cell death. The azole antifungals including itraconazole, fluconazole, and voriconazole inhibit CYP450-dependent 14-alpha-lanosterol demethylase required for ergosterol biosynthesis. The echinocandins including caspofungin, micafungin, and anidulafungin inhibit the synthesis of 1,3-beta-D-glucan synthesis complex, which is a major component of the fungal cell wall.

Amphotericin B

The amphotericin deoxycholate B has a broad spectrum of activity which is active against yeast and filamentous fungi but has low activity against *Aspergillus terreus*, *Candida lusitaniae*, *Trichosporon ashaii*, *Sedosporium prolificans*, and *Pseudoalisteria boydii* which are usually resistant. Other limitation is the toxicity both infusion toxicity and non-infusion related toxicity. The infusion toxicity includes fever, rigors, chills, anorexia, nausea, vomiting, phlebitis, and anaphylaxis. The non-infusion toxicity includes nephrotoxicity (leading to hypokalemia, hypomagnesemia, tubular acidosis) anemia, and thrombocytopenia. Nephrotoxicity can be ameliorated with good hydration. Majority of patients who are receiving regular amphotericin B require potassium supplement. Because of the broad spectrum of amphotericin B, it continues to be in use for a long period and continues to be the standard for antifungal therapy, but the disadvantage is the major side effect; therefore, the pharmaceutical company worked to modify structure to decrease the side effect of amphotericin B while keeping its efficacy. There are three lipid formulations of amphotericin B, which include amphotericin B lipid complex (ABLC), amphotericin B colloidal dispersion, and liposomal amphotericin B (amBisome). The advantage of the lipid formulation of amphotericin B is that the efficacy is similar to regular amphotericin B but less nephrotoxic than amphotericin B. The liposomal amphotericin B (amBisome) has the lowest infusion-related reactions and best pharmacokinetic properties. The amBisome has fewer breakthroughs in fungal infection in febrile neutropenic patients when compared to regular amphotericin B. The CNS penetration is better with amBisome compared to amphotericin B lipid complex or ABLC. The disadvantage of lipid formulations is the higher cost compared to amphotericin B deoxycholate.

The nephrotoxicity of amphotericin B is less severe in children compared to adults. The pharmacokinetic study of ambisome in children showed that there is no dose limiting trend in adverse events up to 10 mg/kg/day. ABLC was assessed in more than 540 children with similar efficacy of amphotericin deoxycholate in children and adults.

Azoles

The fluconazole has broad-spectrum activity against candidiasis, cryptococcosis, trichosporum spp., and dermatophytes. It has very good bioavailability with high urine concentration. The limitation of fluconazole is the Candida krusei, which is intrinsically resistant to fluconazole, and resistance can develop in candida glabrata. Fluconazole has no activity against filamentous fungi including aspergillosis. The clearance in children is more rapid compared to adult with lower half-life. Children more than 3 months require to double the daily dose up to 12 mg/kg/day; the neonate showed slow elimination of drug due to reduced hepatic enzyme and reduced GFR.

The second agent in this class is the itraconazole. It is active against yeast and filamentous fungi includes aspergillosis but the activity is limited against fusarium and zygomytes. The limitation of oral capsule of itraconazole is erratic absorption. Other formulation of itraconazole is itraconazole cyclodextrin oral suspension and IV formulation.

Because of the erratic absorption of itraconazole and the limited spectrum activity of fluconazole, there are new generation triazoles including voriconazole. The voriconazole is available both in IV and oral, and has better candida activity, has a very potent anti aspergillus activity

but it is not active against zygomyces. Voriconazole has been approved as the primary treatment for invasive aspergillosis. In adult, it follows a nonlinear pharmacokinetics but in pediatrics it is a linear pharmacokinetic with accelerated metabolic clearance in children, therefore it needs higher dose without loading dose. The bioavailability of oral voriconazole is less in children (65%) than in adults (96%). In certain patients who are failing to respond to voriconazole, consider therapeutic drug monitoring.

Posaconazole

Posaconazole was approved by European Union in 2005 and by FDA in 2006 and is active against yeast and filamentous fungi including zygomyces. Only oral formulation is present at the time being. There is very limited data in pediatric patients. The pharmacokinetics studies of posaconazole are similar in adults. The dose for pediatric patients for posaconazole is not yet established.

Echinocandins

The third class is echinocandins, which include caspofungin, anidulafungin, and micafungin. These agents are acting in the cell wall and the cell wall is an important structure element in the fungal cell which is not found in other eukaryotic cells and therefore fulfill the criteria for selective toxicity.

The indication of echinocandins includes systemic candidiasis, esophageal candidiasis, and refractory invasive aspergillosis. The pediatric caspofungin dosing should be based on body surface areas and not on weight as weight-based dosing results in suboptimal plasma concentration. 70 mg/m^2 loading is used, then 50 mg/m^2 daily for children more than 3 months of age, and 25 mg/m^2 daily for children younger than 3 months of age as well as neonate. The half-life of caspofungin is about one third less in children. The Food and Drug Administration approved the caspofungin in pediatrics in July 2008.

The micafungin has similar activities with caspofungin and has been licensed for prophylaxis and treatment of invasive candidiasis in children.

The anidulafungin is not well studied in pediatric. There were phase I and phase II dose escalations study that showed pediatric patients more than 2 years of age receiving 0.75 or 1.5 mg/kg/day have PK similar to adults receiving 50–100 mg/kg/day. Based from the limited data, anidulafungin can be dosed based on body weight area (*Table 96.1*).

Table 96.1
Antifungal dosing for children

Drug	Formulation	Pediatric dose
Conventional AB	IV	0.6–1.5mg/kg/day
LAB (Ambisome)	IV	1–5 mg/kg/ day
ABCD	IV	3–5 mg/ kg/day
ABLC	IV	5 mg/kg/day
Fluconazole	Capsule, suspension, IV	6–12 mg/kg/day
Itraconazole	Capsule, suspension, IV	2.5–5 mg/kg q12
Voriconazole	Capsule, suspension, IV	6–8 mg/kg q12
Posaconazole	Suspension	400–800 mg/day in 2–4 divided doses
Caspofungin	IV	50 mg/m^2 daily Neonate 2 mg/kg or 25 mg/m^2
Micafungin	IV	1–4 mg/kg/day
Anidulafungin	IV	1.5–3 mg/kg load d1 followed by 0.75–1.5 mg/kg/day

In Managing Fungal Invasive there are four antifungal therapeutic strategies:

Antifungal prophylaxis is based on the risk factors in the absence of infection.

Empirical antifungal therapy for patients with risk factors and signs of infection of unclear etiology and the possibility of fungal origin, prolonged febrile neutropenia.

Pre-emptive antifungal therapy for patients with risk factors and additional evidence for the presence of a fungal pathogen including abnormal CT scan and/or abnormal aspergillus Galactomannan assay or 1,3 D Beta Glucan.

Definite therapy is treatment of proven infection.

In definite therapy, the prognosis will be poor if one waits for immunocompromised patient to establish the diagnosis of fungal infection before the initiation of antifungal therapy. The best approach is better utilization of preemptive antifungal therapy with monitoring of surrogate marker for the fungal diagnosis. The prophylaxis and empiric antifungal therapy will expose large number of patients to antifungal therapy and there is a potential of side effects and emergence of resistance.

Treatment of neonatal candidiasis: The regular Amphotericin is still the drug of choice followed by lipid formulation amphotericin B, and then fluconazole. If the patient is not receiving prophylaxis, echinocandins can be used with caution in neonates. Usually, neonate with candidemia will be treated for 3 weeks but all neonates with candidemia need LP and CSF study to exclude meningitis. Patient also needs serial eye exam to exclude involvement of the eye.

In other patient population, the algorithm below, can be followed. The first question is the patient is hemodynamically unstable or neutropenic; if yes, strongly considered avoiding the use of fluconazole. If the answer is no, move to the second question "Is *Candida glabrata or Candida krusei* likely to be the cause?" A yes strongly considers avoiding the use of fluconazole but use of echinocandin or polyene is preferred; use of voriconazole is an alternative option. If the answer for both questions is "NO" considers use of fluconazole.

The current practice of treating candidemia is to continue the treatment for 2 weeks after the last negative blood culture with resolution of neutropenia and signs and symptoms of infections. Patients with extensive visceral involvement will require longer therapy till all lesions seen on radiology are resolved or calcified. Follow-up with oral fluconazole provides the opportunity to manage these patients on outpatient therapy if the isolate is susceptible; other option is to use voriconazole as outpatient therapy. Most of the studies indicate that the removal of central venous catheter is important factor to clear the infection and decrease the complication of candidiasis. The mortality of candidemia and the contributing factor will approach 40–50%.

In the treatment of aspergillosis or mold infection, the first question to ask is the infection is likely to be caused by voriconazole susceptibility strain; if yes, use voriconazole, if no (the patient is exposed to voriconazole or other azoles or high incidence of zygomycosis in the

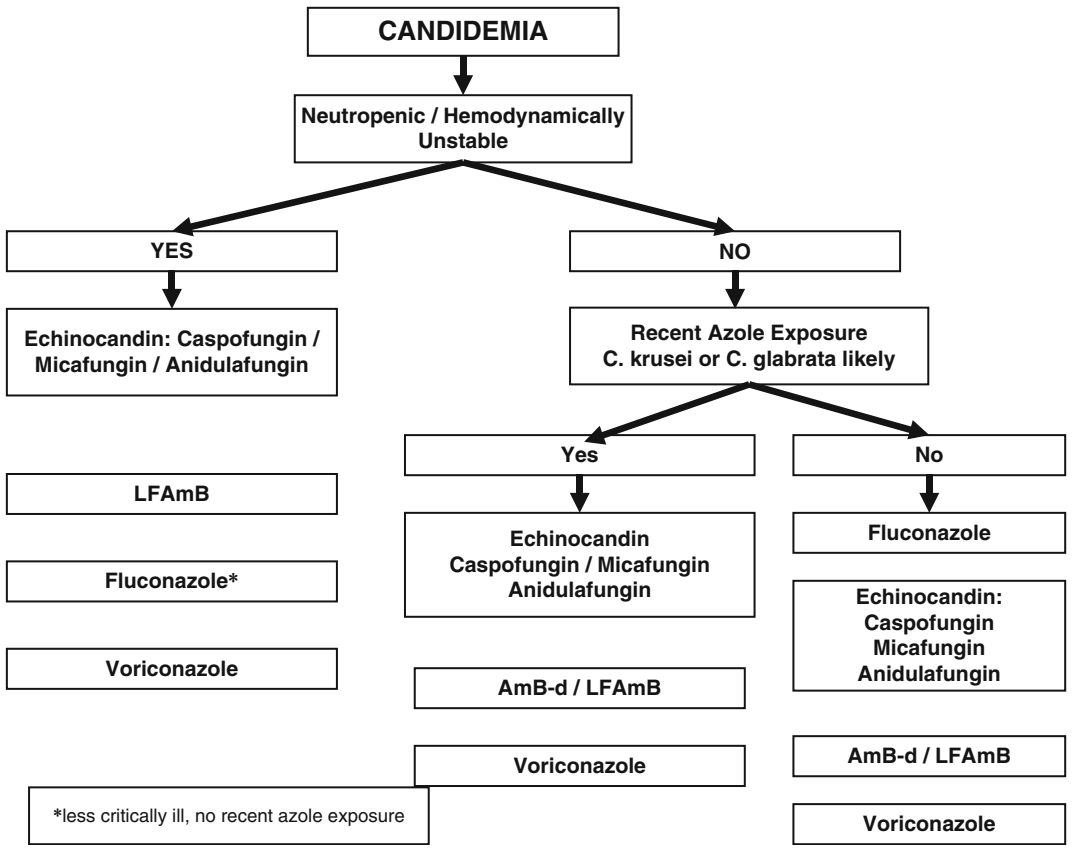

Fig 96.4
Approach to Patient with Candidemia

Table 96.2
Spectrum of activity of antifungal agents

Antifungal	Important clinical uses	Not/limited activity
Amphotericin B (including lipid formulation)	Cryptococcus neoformans, most candida species, aspergillus, mucoromycosis	Candida lusitaniae, scedosporium, fusarium, trichosporon
5-Fluorocytosine	Combination therapy yeasts	
Fluconazole	Most candida, C. neoformans	Candida krusei, candida glabrata, aspergillus
Itraconazole	Candida, aspergillus	
Voriconazole	Candida, aspergillus, fusarium, scedosporium	Mucormycosis caution: C. glabrata
Echinocandins	Candida, aspergillus	C. neoformans, fusarium, mucormycosis

center), use liposomal amphotericin B. Modification is guided by species identified response and tolerance.

The treatment must be started early and a definitive diagnosis must be pursued to exclude other pathogens. Once invasive aspergillosis is confirmed, the voriconazole is the treatment of choice. Variconazole has increased efficacy and improved survival when compared with amphotericin B as first-line therapy for invasive aspergillosis.

The echonicandins especially caspofungin have shown good efficacy and safety in patients with documented invasive aspergillosis not responding to or intolerant to other antifungal therapy.

Oral itraconazole can be used as chronic therapy but oral voriconazole is preferred.

The outcomes of invasive aspergillosis depend on the primary diseases, predisposing factors, as well as the location of the fungal infection. The highest mortality is in patient post bone marrow transplant followed by leukemia but if the CNS is involved in the immunocompromised patient the mortality is close to 95% and for non-immunocompromised patient with CNS involvement the mortality is much lower close to 13%.

The patient with invasive aspergillosis has higher hospital mortality rate than in patient with no invasive aspergillosis.

It is very important to know the susceptibility of the isolate before the selection of antifungal therapy. Aspergillosis is usually sensitive to voriconazole, itraconazole, amphotericin B, and echinocandins but aspergillosis terreus are usually resistant to amphotericin B. Voriconazole has no activity whereas posaconazole has some activity against zygomytes. Amphotericin B including the lipid formulation has limited activity against *Candida lusitaniae*, *Scedosporium*, *Fusarium*, and *Trichosporon*, but it is active against *Cryptococcus neoforms*, most Candida species, Aspergillus, and Mucoromycosis (*Table 96.2*).

The 5-flucytosine should not be used alone because development of resistant. Fluconazole is not active against *Candida krusei* as it is natively resistant to fluconazole no activity against aspergillus species but active against most of the candida and *Cryptococcus neoforms*. Itraconazole has activity against candida as well aspergillus but has limited activity zygomyces. Voriconazole is active against *Candida spp*, *Aspergillus spp*, *Fusarium spp*, and *Scedosporium spp* but has no activity against mucormycosis and caution has to be taken when the isolate is *Candida glabrata*. Echinocandins has activity against candida and aspergillus but has no activity against *Cryptococcus neoformans*, *Fusarium* and mucormycosis.

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97 Intestinal Infections

Mohammad Al-Shaalan

Parasitic (protozoa and helminths) intestinal infections are common in children (*Fig. 97.1*, *Tables 97.1* and *97.2*). Many of the infections are asymptomatic; however, they play a major role in childhood morbidity. Some protozoa are not pathogenic. These include Iodameba buetschlii, Endolimax nana, Entameba nana, and Entameba hartmanii. Others are pathogenic but rare like Dientameba fragilis, Balantidium coli, and Entameba polecki.

Protozoal Infections

Giardiasis

Giardiasis is a protozoal intestinal disease caused by *Giardia lamblia*. It is probably the most common parasitic infection worldwide. Infection is acquired by drinking water or ingesting food contaminated with infectious cyst. Person-to-person transmission as well as infection through contaminated inanimate objects can occur.

Clinical Features

Asymptomatic infection is common accounting for 50% of cases. Symptomatic infection is varied in presentation. Some patients present with mild diarrhea that is self-limiting, others present with decreased appetite, loss of weight, and signs of malabsorption (large greasy stools and signs of vitamin A, vitamin B12, and protein deficiencies).

Extraintestinal symptoms are rare and include fever, urticaria, reactive arthritis, pancreatitis, mesenteric adenitis, erythema nodosum, peripheral neuropathy, iridocyclitis, and biliary tract disease.

Diagnosis

Stool microscopy is the golden standard of diagnosis. When three stool specimens are examined, 90% of infected patients will have positive test. The stool should be processed in three fractions. The first is fresh stool that can be prepared as wet mount or stained with iodine and examined for motile trophozoites or the presence of the cyst. The second should be preserved in polyvinyl alcohol and stained with trichrome or iron hematoxylin stain. The third fraction is concentrated by formalin-ethyl acetate or zinc sulfate floatation which may increase the yield of stool microscopy.

Other diagnostic modalities include serology, antigen detection, or DNA probing. Antigen detection in the stool using EIA or IFA techniques is very sensitive and specific; however, in areas where the incidence of mixed parasitic infection is high, this technique is not practical and will miss diagnosing mixed parasitic infection, therefore in such areas stool microscopy should be the primary diagnostic method.

Serology testing to detect IgM and IgG are useful, however they are epidemiological studies.

Treatment

Recently some controversy has been raised on whether all patients with Giardia infection should be treated.

Asymptomatic Cyst Passers

It is recommended that all infected patients be treated in order to prevent future complications; however, some argue against such strategy as reinfection is common in endemic areas and thus asymptomatic patients need not be treated. The recommended therapy is metronidazole 15 mg/kg/day in three divided doses for 5 days. Alternative therapy can be achieved with quinacrine 6 mg/kg/day in three divided doses for 5 days. Other effective therapies include furazolidone, tinidazole, and paromomycin.

Symptomatic Infection

All patients should be treated and cure should be proved by negative stool microscopy or antigen test. Both

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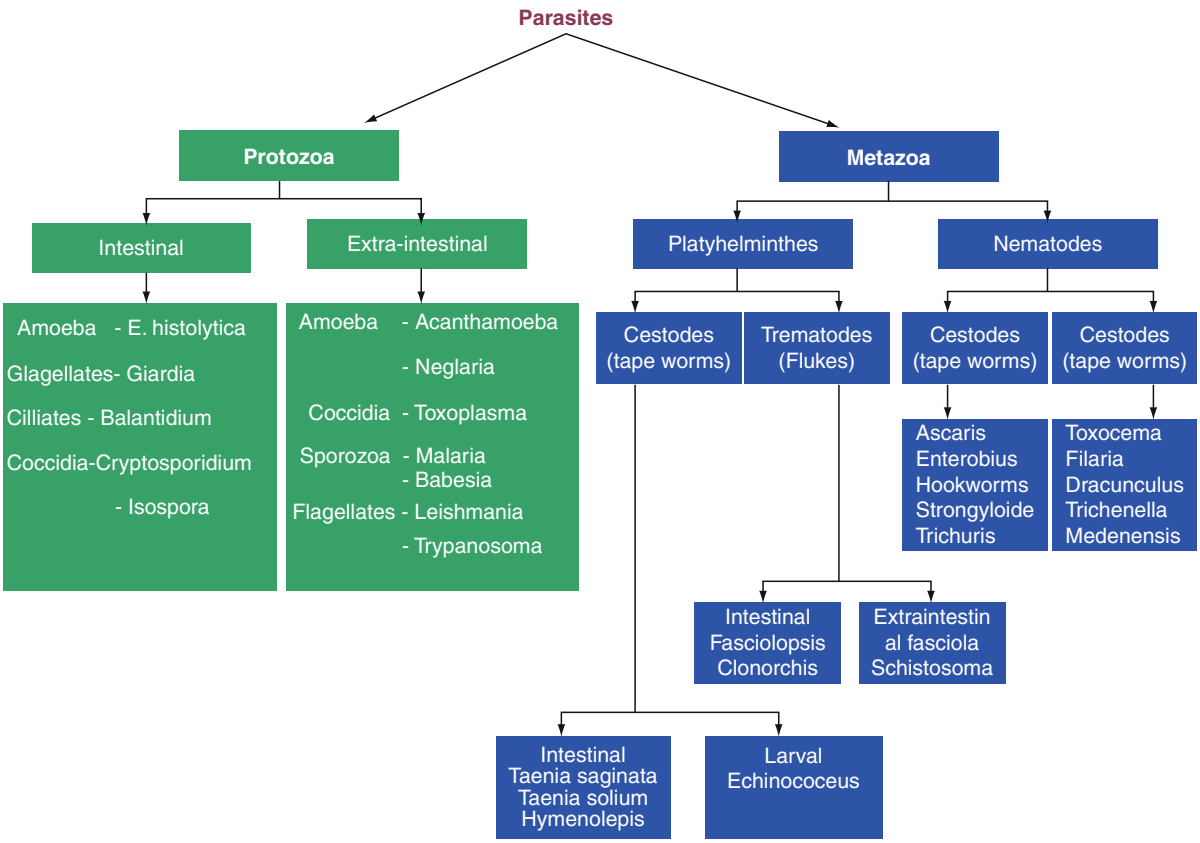

Figure 97.1
Simple classification of pathogenic parasites

quinacrine 2 mg/kg three times daily for 5 days or metronidazole 5 mg/kg three times daily for 5 days are equally effective; however, metronidazole is more widely used. Alternative drugs include furazolidone, mebendazole, albendazole, tinidazole, and paromomycin. Azithromycin has also shown to be effective against Giardia. Cases that fail to respond to therapy should be investigated for possibility of re-exposure and re-infection or whether the organism is resistant to therapy. In cases that are thought to be due to resistant organism, shifting to another drug is indicated. In those that remain resistant to therapy in spite of using different drug combinations, therapy with metronidazole and quinacrine is recommended.

Prevention

Assurance of water purity and sewage sanitation is of prime importance in decreasing the incidence of Giardia infection. Giardia is resistant to usual concentration of chlorine that is used to disinfect water. Therefore, Giardia is responsible for many outbreaks occurring in water recreation facilities. To increase the purity of water, it should be processed by sedimentation, filtration, and flocculation.

Preventing infected child from attending school or day care until he/she is cured was not proven effective. Personal hygiene remains the mainstay of protection.

Cryptosporidiasis

Cryptosporidium is a common cause of diarrhea especially in immunocompromised children. It is also a common cause of waterborne diarrheal illness in developed countries, and as a pathogen with long-term effect on childhood growth and development in impoverished areas.

Table 97.1
Protozoa

Protozoa	Diagnostic tests	Infection stage	Drug of choice	Alternative therapy
Giardia	• Cyst or trophozoite in the stool • Antigen detection in the stool using EIA	Cyst	Quinacrine 6 mg/kg/day in three divided doses for 5 days OR Metronidazole 15 mg/kg/day in three divided doses for 5 days	Tinidazole 50 mg/kg once Furazolidone 6 mg/kg/day in four divided doses for 7–10 days Paromomycin 25–30 mg/kg/day in three divided doses for 7 days
Amebiasis: Asymptomatic Carrier	• Cyst or trophozoite in the stool • Serology: IHA, ELISA	Cyst	Not recommended	Iodoquinol 30 mg/kg/day in three divided doses for 2 days or Paromomycin 30 mg/kg/day in three divided doses for 7 days
Symptomatic intestinal and hepatic			Metronidazole 35 mg/kg/day in three divided doses for 10 days OR Tinidazole 50 mg/kg/day once daily for 3 days Followed by carrier treatment	Dehydrocortine 1 mg/kg/day IM in two divided doses for 5 days
Dientameba fragilis	Trophozoite in the stool	Trophozoite	Iodoquinol 40 mg/kg/day in three divided doses for 20 days	Paromomycin 30 mg/kg/day in three divided doses for 7 days
Cryptosporidium	Oocyst in the stool by AFB stain IFA or EIA	Oocyst	Nitazoxanide: 1–3 years: 100 mg bid for 3 days 4–11 years: 200 mg bid for 3 days >12 years: 500 mg bid for 3 days	Azithromycin and paromomycin orally in AIDS patients
Balantidiasis	Cyst or trophozoite in the stool	Cyst	Iodoquinol 40 mg/kg/day in three divided doses for 20 days OR Metronidazole 35 mg/k/day in three divided doses for 5 days	
Blastocystis	Cyst in the stool	Cyst		
Isospora	Oocyst in the stool	Oocyst	TMP/SMX	

Causative Agent

Cryptosporidium is coccidian protozoa. Many species and subspecies are known; however, cryptosporidium parvum is the commonest cause. The oocyst is the infectious stage and it is sporulated and chlorine-resistant. After ingestion of the cyst, excystation occurs in the intestine. The released sporozoites penetrate the enterocytes of terminal jejunum and ileum and envelope themselves. They mature into type I meronts that release merozoites, which in turn invade the adjacent enterocytes. These merozoites mature into type I meronts (source of autoinfection) or type II meronts, which mature into micro- and macrogametocytes. Microgametocytes fuse with macrogametocytes and form zygotes that mature into cysts, which are passed with stool.

Epidemiology

Cryptosporidium is ubiquitous in both developed and developing countries. Serologic prevalence varies in different countries ranging from 10% to 80%. It constitutes 1–37% of diarrheal causes among Saudi children. Factors contributing to its high prevalence include small size of infectious oocyst, low infection dose, high chlorine resistance, and its ability to be transmitted from animals to humans.

Table 97.2
Helminthes

Parasite	Drug of choice	Alternative	Diagnostic method
Ascariasis	Mebendazole 100 mg PO bid × 3 days	Pyrantel pamoate 11 mg/kg once Albendazole 400 mg once	Ova in the stool and rarely in sputum
Trichuris	Mebendazole 100 mg bid × 3 days Pyrantel pamoate 11 mg/kg/ once	Albendazole 400 mg once	Ova in the stool
Enterobius Verimcularis	Mebendazole 100 mg single dose repeat in 2 weeks	Pyrantel pamoase 11 mg/kg/ once Albendazole 400 mg once (repeat in 2 weeks)	Ova seen on the Scotch tape or finger nail scraping
Strongyloides	Thiabendazole 50 mg/kg/day bid × 2 days	Ivermectin 200 mcg/kg/d for 1–2 days	Larva in the stool or duodenal aspirate Serology (ELISA)
Hookworms	Mebendazole 100 mg bid × 3 days	Pyrantel pamoate 11 mg/kg/d × 3 days Albendazole 400 mg once	Ova in the stool
Taeniasis	Praziquantel 5–10 mg/kg/once	Niclosamide 11–34 kg: single dose of two tablets >34 kg: single dose of three tables	Ova or gravid proglottid in the stool
Hymenolepis nana	Praziquantel 25 mg/kg once	Niclosamide	Ova in the stool
Diphyllobothrium latum	Praziquantel 25 mg/kg once	Niclosamide	Ova in the stool
Fasciolopsis buski	Praziquantel 25 mg/kg once		Ova in the stool
Toxocariasis	Diethylcarbamazine 2 mg/kg tid × 10 days	Albendazole 400 mg bid × 5 days Mebendazole 100 mg bid × 5 days	Serology
Trichinosis	Prednisone and mebendazole		Serology
Dracunculus Medinensis	Metronidaole 25 mg/kg/d in three doses × 10 days	Thiabendazole 50–75 mg/k/day in two doses × 3 days	Adult worm at the site of ulcer
Hydatid disease	Albendazole 15 mg/kg/d bid × 28 days, repeat as necessary		CT scan Serology (ELISA or HAI are sensitive and Immunoblot are specific) Skin test
Cysticercosis	Praziquantel 50 mg/kg/d in three doses for 15 days	Albendazole 15 mg/kg/day in three divided doses for 8 days	CT scan, serology (ELISA)
Schistosomiasis	Praziquantel 20 mg/kg q4h for two doses		Ova in stool or urine Serology
Opisthorchis	Praziquantel 25 mg/kg for three doses for 1 day		Ova in the stool
Fascioliasis	Bitgiomol 30 mg/kg on alternate days for 15 doses		Ova in the stool

Clinical Features

Cryptosporidiosis manifests as one of three patterns:

1. Self-limiting acute diarrheal illness: This is the presentation in immunocompetent hosts. It usually starts after an incubation period of 7 days with fever, diarrhea, abdominal cramps, and vomiting. This illness lasts 7–10 days and resolves spontaneously.
2. Chronic or recurrent diarrheal illness which occurs mainly in immunocompromised hosts, especially patients with AIDS. It is found that the disease is more severe with decreasing CD4 counts.
3. Growth deficit in impoverished children in developing countries.

Diagnosis

The widely available method of diagnosis is acid fast stain for stool specimen. However, this method is not sensitive or specific enough. Direct fluorescent antibody test and ELISA and PCR are now available. All of these tests have high sensitivity and specificity and will replace the standard acid fast staining in the future.

Treatment

Acute diarrhea in immunocompetent hosts is usually self-limiting and only supportive therapy with fluids is needed.

Non-HIV immunocompromised patients who are infected with *Cryptosporidium* pose a challenge to treating physicians as there is no effective therapy. Use of paromomycin and nitazoxanide, either singly or in combination, has some efficacy but not optimal.

Use of HAART in AIDS patients has resulted in decrease in infections with C*ryptosporidium* in these patients. Use of azithromycin and promomycin has shown some efficacy.

Amebiasis

Amebiasis represents a spectrum of diseases caused by *Entameba histolytica*, a protozoan parasite that is one of the major causes of morbidity and mortality especially in developing countries. More than 50 million people are infected annually with a mortality of around 1,00,000, ranking the second to malaria as the commonest cause of death from parasitic diseases.

The prevalence and incidence of E. histolytica cannot be precisely attained because of low sensitivity of stool microscopy, high proportion of asymptomatic infection, and inability to differentiate the pathogenic E. histolytica from nonpathogenic E. dispar and E. moshkovskii.

Pathogenesis

E. histolytica has three virulent factors: parasite surface protein (lectin), amebapore, and cytoproteins (cysteine proteases). Once ingested, cyst reaches the intestine, excystation occurs, releasing trophozoite. The trophozoite surface lectin recognizes the sugars galactose and *N*-acetylgalactosamine (GalNAc) on the host cell surface. If the lectin attaches to mucin galactose, noninvasive infection occurs and the trophozoite completes its life cycle and passes with the stool after encystations. However, if trophozoite penetrates the mucin layer and the lectin attaches to host cell surface GalNAc, then invasion ensues and the cascade of host cell death occurs with resultant ulceration and sometimes extraintestinal invasion. E. histolytica trophozoite has the ability to kill a wide variety of tissue cell lines including neutrophils, T. lymphocytes, and macrophages which explain the lack of inflammatory cells in the amebic ulcers.

Clinical Features

E. histolytica is acquired by ingesting infectious cyst with contaminated foods or water. Person-to-person fecal–oral transmission can occur. Incubation period ranges from few days to months or years. *Entameba* strains are classified as pathogenic or nonpathogenic according to specific pattern of isoenzymes (desmosomes) electrophoresis. Only 10% of infections are caused by the pathogenic *E. histolytica*, and only 10% of those develop symptomatic infection. Most of the positive stool microscopy will yield the cyst of nonpathogenic Entameba (E. dispar and E. moshkovskii).

Amebic Colitis

Amebic colitis usually presents as mild diarrhea that may be bloody. However, in some patients, the diarrhea may be severe, frequent, and associated with blood and mucus. There is usually no systemic manifestation of fever or lethargy. When colonoscopy is done, there are usually shallow flask-shaped ulcers that mostly involve the mucosa only. These pathologic lesions are produced as

a sequence of production of lysing enzymes that lyse not only mucus cells but also the macrophages and neutrophils. Therefore, on microscopic examination of scraping done from the edge of the ulcer, no neutrophils or other inflammatory cells are seen; however, most of the specimen will show trophozoites that may be containing RBC (hematophagous trophozoites).

Fulminating Enterocolitis

In some occasions, the disease may become severe enough that toxic megacolon or perforation may occur. Up to 75% of children with fulminant colitis develop perforation. The patient will present, in addition to dysentery, with diffuse abdominal pain and abdominal distention. The patient will be toxic and may be mistaken to have fulminant ulcerative colitis. In such patients, colonoscopy should be done with caution. The presence of trophozoites on biopsy will confirm amebiasis.

Ameboma

About 1% of patients with intestinal amebiasis will develop ameboma. It is a mass lesion that forms as a result of inflammatory and granulation tissue. It can be mistaken for malignant tumor.

Amebic Liver Abscess

Most commonly encountered in adults, but children may be affected. Patients usually present with abrupt onset of fever associated with right upper quadrant abdominal pain. The liver is usually diffusely enlarged, but in few occasions a single or multiple masses may be palpable. Pyogenic liver abscess may have similar presentation, but it usually has predisposing factors such as previous abdominal surgery or presence of intravascular devices. Ultrasound of the abdomen will show a single hypoechogenic lesion that usually involves the right lobe of the liver; however, multiple abscesses and involvement of other parts of liver may occur. Ultrasound may not detect small abscesses and in such cases, CT scan may be indicated. Echinococcal liver cyst may have similar appearance; however, such patients usually have no associated systemic manifestation of fever or toxicity. Diagnosis of amebic abscess can be confirmed by positive stool analysis for *E. histolytica* cyst and serology test that is positive in 90% of patients by day 7 of illness.

Diagnosis

Stool examination for Entameba cyst or trophozoite is the usual method of diagnosis; however, it lacks sensitivity and specificity. It will never be able to differentiate the pathogenic E. histolytica from the similarly appearing nonpathogenic E. dispar and E. moshkovskii. Therefore, depending solely on stool microscopy to decide about treating an asymptomatic patient who has Entameba cyst in the stool is not appropriate. Polymerase chain reaction, isoenzyme analysis, and monoclonal antibody-based antigen detection assays can differentiate E. histolytica, E. dispar, and E. moshkovskii. However, these tests are not available widely and therefore positive stool microscopy should be augmented by having clinical features suggestive of amebic infection to decide about initiating therapy.

Indirect hemagglutination (IHA) test has been replaced by enzyme immunoassay (EIA) test for routine serodiagnosis of amebiasis. EIA is 95% positive for extraintestinal amebiasis, 70% positive for active intestinal infections, and less than 10% for cyst passers. Aspiration of abscess under CT scan guidance may show the trophozoite and it is advisable in doubtful cases.

Treatment

Asymptomatic Cyst Passers

Treatment is not advisable.

Amebic Dysentery and Ameboma

Metronidazole 10 mg/kg three times daily for 10 days followed by luminal therapy with iodoquinol 30–40 mg/kg/day for 20 days or paromomycin for 7 days. In patients with microperforation, conservative therapy with antibiotics without surgical intervention is advisable. Nitazoxanide may be effective for mild to moderate intestinal infection.

Amebic Liver Abscesses

Metronidazole 10 mg/kg three times daily for 10 days followed by intraluminal therapy with iodoquinol 30–40 mg/kg/day for 20 days or paromomycin. Chloroquine phosphate may be used in combination with metronidazole for a better response. The cavity of the abscess may remain forever; therefore, there is no need to do any surgical intervention if the patient responds clinically to the treatment. When the abscess is large and risk of perforation is high, aspiration under ultrasound or CT scan guidance is advisable. It is also advisable to do aspiration when the response to medical therapy is poor.

Nematode Infections

More than one billion worldwide are infected with intestinal nematodes (round worm); most of them reside in developing countries. These infections play a major role in morbidity of infected persons as a major cause of anemia and malnutrition.

Ascariasis

Ascaris lumbricoides, the cause of ascariasis, is a 15–40 cm long round worm. It is pink-whitish in color and it is of smooth surface. The life cycle of this parasite starts by ingesting foods that are contaminated with the infectious ova. The ova pass to the duodenum and jejunum where they hatch into the rhabditiform larvae, which in turn penetrate the mucosa and travel by blood into the lung. They then pass into the alveoli and migrate upward through trachea into the pharynx and then pass into the intestine where they mature into adult form. The adult worm deposits 2,00,000 ova daily which pass with the stools and contaminate the soil or vegetations.

Clinical Features

Most of the ascaris infestations are asymptomatic; however, it tends to cause symptoms in children even with one worm.

The most common symptoms are abdominal pain and flatulence. In areas where recurrent infection is common, the number of parasites may be enormous to cause mechanical intestinal obstruction. In some occasions, the parasite may migrate through the ampulla of Vater and cause biliary symptoms, obstructive jaundice, cholangitis, or cholecystitis. In rare occasions, the pancreatic duct may get obstructed and pancreatitis may result.

During the initial passage of larva through the lungs, eosinophilic pneumonitis may occur especially when the infection is heavy. The patients usually have cough and shortness of breath. Chest x-ray may reveal some infiltrates.

Diagnosis

Clinical symptoms may not be helpful unless the patient has the complications. Most of the patients have moderate eosinophilia. Stool examination for ova and parasites is very sensitive.

Barium study may show the parasite in the intestinal lumen and ultrasound of the abdomen may show the parasite floating in the gallbladder. Endoscopic retrograde cholangiopancreaticography (ERCP) may show the parasite in the common bile duct.

Treatment

Ascaris is very sensitive to pyrantel pamoate, piperazine, or mebendazole. Patients who have intestinal or biliary complications need to be assessed by surgeons and gastroenterologist as they will need some surgical intervention. Patients with biliary ascariasis may develop cholangitis caused by the bacteria that migrate with worms and they should be treated with broad spectrum antibiotics like ampicillin, gentamicin, and metronidazole or third-generation cephalosporins.

Hookworm Infections

Necator americanus and *Anclyostoma duodenale* are common causes of intestinal parasitic infections. Infected persons are prone to develop anemia and hypoproteinemia.

Life Cycle

The infectious stage is filiform larvae which penetrate the skin and travel through the blood into the lung. From there, they migrate up to the trachea and then downward through pharynx and esophagus until they reside in the upper part of small intestine. There they mature into adult form which attach into the mucosa by their hooklets. *N. Americanus* and *A. duodenale* are 7–12 mm long.

Clinical Features

Heavy infections are usually associated with abdominal pain, diarrhea, anemia, and hypoproteinemia.

During the initial larva migration through the lungs, mild respiratory symptoms of cough occur. Eosinophilia is usually present.

Diagnosis

Microscopic stool examination will show the characteristic ova of the hookworms. Mild anemia and hypoproteinemia are usually present. Most of the patients will have eosinophilia.

Treatment

Mebendazole, pyrantel pamoate, and piperazidine are very effective in eradicating these infections. The response to therapy is associated with resolution of anemia and hypoproteinaemia. It also results in improvement of malnutrition and behavioral disturbances.

Trichuriasis "Whipworm Infection"

Common parasitic infection in developing countries. The causative parasite is *Trichuris trichura*, which is 30–50 mm long and resides in the cecum and colon. Most of the infections are asymptomatic; however, with severe infection, the worms may migrate into the rectum and cause rectal prolapse. Diagnosis can be made by finding ova in the stool. Mebendazole as a single dose is very effective in eradicating the infection.

Enterobiasis "Pinworm Infection"

The commonest parasitic infection with high incidence in developed and developing countries. It is caused by roundworm *Enterobius vermicularis*, which is 8–13 mm long and resides mainly in the cecum. The main presentation of the infection is pruritus ani which occurs as a result of migration of the parasite into the perianal area during the night time. In girls, vaginitis and peritoneal granuloma may occur on rare occasions.

Diagnosis does not depend on finding the parasite ova in the stool, but by applying scotch tape over the anal area and then adhesing it into a slide. The ova can be seen adhesing into the tape. The best time for applying the tape is early morning at a time when the parasite has laid many ova in the area.

Mebendazole given in two doses 2 weeks apart is very effective. In cases which are resistant to treatment, mass treatment of the whole family members with the same regime is advisable.

Strongyloidiasis

Strongyloides stercoralis is an intestinal nematode that is common in most of the developing countries. It gains more importance after emergence of HIV epidemics as a cause of disseminated and hyperinfectious disease.

Life Cycle

Strongyloides stercoralis has a distinctive life cycle with ability to produce autoinfection, intestinal multiplication, and free-living adult worms. The infectious stage is filiform larva which upon penetration of the skin travels with blood into the lungs. Then it passes into the alveoli and migrates along the trachea into the pharynx and then down to the upper intestine. It penetrates the mucosa and resides in the submucosa where it matures into adult form. In the submucosa, the female adult does not need male for fertilization and reproduces by parthenogenesis and lays ova in the submucosa. The ova hatch into rhabditiform larvae that pass into the lumen and pass with feces; however, some of these rhabditiform larvae mature into filiform larvae in the lumen before excretion. These filariform larvae are able to autoinfect the host by penetrating the intestine and passing with the blood into the lungs and then complete the cycle. The excreted rhabditiform larvae pursue one of two pathways of maturation: either maturing into an adult form or maturing into filiform larvae. The adult forms will lay ova in the soil that mature into filiform larvae.

Clinical Features

Immunocompetent Patients

The infection is mostly asymptomatic; however, when symptoms occur they consist of abdominal pain, diarrhea, urticaria, and loss of weight. Some patients may develop severe disease with severe abdominal pain, bloody diarrhea, protein enteropathy, and urticaria.

The disease may run a fluctuant course of symptomatic period followed by asymptomatic ones. During the initial stage of larva passage through the lungs, Loffler's pneumoniae may develop.

Immunocompromised patients may develop hyperinfection and/or disseminated disease. Because of the immunosuppression, the multiplication of the organism in the intestine goes unchecked which in turn results in heavy infection that is associated with severe enterocolitis, abdominal pain, protein-losing enteropathy, and intestinal bleeding. Lungs are involved frequently with parenchymal infiltrates that may be severe enough to cause adult respiratory distress syndrome. Filiform larvae may disseminate to other organs like liver, kidneys, and brain. Passage of gut flora with larva may result in septicemia and septic shock. Although HIV is one of the immunocompromised diseases, there was no noticed increased severity of strongyloides in such patients.

Diagnosis

Stool Microscopy

The main diagnostic method is finding rhabditiform larva in the stool, sputum, or duodenal aspirate. It is unusual to find adult forms or ova in the stool because these stages are located in the submucosa.

Serology

In endemic areas, it is of limited help because the available ELISA test does not differentiate between acute or chronic infection.

DNA Probe and PCR

Are still investigational but has some promises.

Treatment

The drug of choice is thiabendazole 25 mg/kg three times daily for 2 days. Recently, the efficacy of thiabendazole has been questioned; therefore, a more potent alternative has been sought. Albendazole 400 mg once daily for 3 days and ivermectin 200 mcg/kg/day for 2 days have shown very good activity in treating strongyloidiasis with efficacy of 80–90%. Cyclosporin has shown also to be very effective in spite of being immunosuppressive.

Toxocariaris

Toxocariaris is a zoonotic disease that is widely distributed all over the world. The causative agents are nematodes *Toxocara canis* and *Toxocara catti* that have their reservoir in the gut of dogs and cats, respectively. Infections commonly occur in children 3–10 years of age who have the habits of playing outdoors in areas that might be contaminated with dogs and cats excrete.

Life Cycle

Ova are produced with excreta of infected dog or cat. When a child encounters them during his play, they might be ingested orally if they remain on his hands at the time of eating or drinking. Other ways of acquiring infection is the ingestion of infectious ova with contaminated foods. Once the ova reach the intestine, they hatch and produce larvae. Larvae penetrate the intestine and reach the blood where they then may migrate to any organ including liver, eyes, brain, kidneys, lungs, and heart, however liver is the most commonly involved organ.

Clinical Features

Viscera Larva Migrans (VLM)

Most of the infections are asymptomatic. In symptomatic cases, symptoms depend on organ involved. However, general symptoms of malaise, urticaria, and gastrointestinal symptoms may occur. Liver may be enlarged and tender. Patients may present with respiratory symptoms of cough, wheezing, and shortness of breath with radiological appearance of lung infiltrations. Seizure may occur in patients who have encysted brain lesions. With severe infection, encephalitis may occur.

Ocular Larva Migrans (OLM)

Larvae may localize to any part of the eye and stimulate inflammatory response causing fibrosis, vitreous fibrosis, and retinal detachment. Ophthalmoscopy may reveal Leukocoria and may be difficult to differentiate from retinoblastoma.

Diagnosis

VLM diagnosis depends mainly on serological testing using fluorescent antibody test or ELISA. In infected tissue, larvae may be seen by histopathology examination. With invasive disease, eosinophilia is usually prominent. Western blot test is used for confirmation of infection because it is more specific.

In OLM, positive serum serology is usually negative or low. Therefore, confirmation of diagnosis requires estimation of antibody titer and eosinophilia in vitreous fluid.

Treatment

Asymptomatic patients require no therapy. However, those with symptoms need anti-helminthic therapy. Diethylcarbamazine 2 mg/kg three times daily for 10 days is the most effective therapy. Albendazole and thiabendazole are adequate alternatives although less effective. Adjunctive therapy with steroids in cases of severe systemic inflammatory response as in pulmonary, CNS, or cardiac disease may be life saving. In OLM, steroid therapy with prednisone 1 mg/kg/day for 2–4 weeks is the mainstay of therapy. Diethylcarbamazine is effective in eradicating the infection.

Cutaneous Larva Migrans (Creeping Eruption)
A zoonotic dermatologic disease that is caused by larvae of *Ancylostoma caninum* or *A. braziliensis*. Upon exposure, the larvae penetrate the skin and start migrating in the skin resulting in formation of serpiginous tracts. Each larvae form one tract and there may be many of them. The larva advance a few millimeters every day. The migration is associated with pruritus. Rarely, systemic invasion by larvae may occur. Treatment with single dose of albendazole 400 mg or ivermectin 150 mcg/kg is very effective and the migration stops within 48 h.

Trematodes

Intestinal Trematodes

Fasciolopsis buski is the commonest intestinal trematode infection. Infection is acquired by ingesting infectious metacercaria with contaminated water chestnuts. Most of the infection is asymptomatic. However, symptomatic cases may occur with presentation of abdominal pain, diarrhea, decreased appetite, and change in behavior. Treatment is achieved by giving one dose of praziquantel at a dose of 25 mg/kg.

Liver Flukes

Opisthorchiasis and Clonorchiasis

Both clonorchis and opisthorchis cause the same disease in humans and both are acquired by ingesting raw fish that is harboring the infecting metacercaria. In the intestine, the metacercaria mature into the adult form that migrate into the biliary system and reside mainly in the common bile duct. Adult worms lay ova there which in turn pass through the bile into the intestine and then are excreted with feces. They then mature into metacercaria which is the infection stage to humans. Opisthorchis is common in Southeast Asia where it is common to consume raw fish.

Clinical Features

In children, most of the infections are asymptomatic and are diagnosed by investigation for eosinophilia. However, some infections cause an acute illness that manifests with fever, abdominal pain, nausea, vomiting, loss of appetite, and loss of weight. With chronic infection, complications may arise; however, they require 15–30 years to develop, thus they are rare in children. Such complications include cholangitis, obstructive jaundice, biliary cirrhosis, and cholangiocarcinoma.

Diagnosis

Diagnosis can be achieved by finding the characteristic ova in the stool. Serology is limited in its application.

Treatment

Praziquantel 25 mg/kg/dose for three doses in 1 day is a very effective therapy. Response can be monitored by resolution of eosinophilia and if there are gallbladder changes on initial ultrasound of abdomen, this also can be followed sequentially, however it is very rare to see such changes in children.

Fascioliasis

Two species of Fasciola cause human diseases; *F. hepatica* and *F. gigantica*. Infection is acquired by ingesting the metacercaria with contaminated water plants. Some infection may occur after ingesting raw or undercooked sheep or goat liver which contains the adult form that may attach to the pharynx and cause laryngopharyngitis (Halzoun disease). Once in the intestine, the larva excyst the metacercaria and penetrate into the peritoneal cavity. From peritoneal cavity, it migrates through the liver capsule into the liver parenchyma. There are two stages of symptomatology. First stage lasts for 6–9 weeks and it coincides with the period of larva migration in the liver tissue. It is associated with fever, abdominal pain, hepatomegaly, and urticaria. The second stage coincides with the residence of the adult form in the biliary tree. Most of the patients have no symptoms in this stage unless the burden of the organism is high which may result in chronic biliary disease.

Diagnosis

Stool microscopy to visualize the characteristic ova is the gold standard of diagnosis. Most patients have an associated eosinophilia.

Treatment

Praziquantel 25 mg/kg three times daily for 6 days is the recommended therapy of choice.

Lung Fluke

Paragnomiasis

Paragnomiasis or lung fluke is a disease most commonly seen in Southeast Asia and Central and South America. It is acquired by eating raw fish that contain metacercaria. These metacercaria hatch into larvae and mature in the small intestine. From there, they pass through intestinal wall into the peritoneal cavity and then migrate through diaphragm into the lungs resulting in mass lesion that locate most commonly in the right lung. The mature worms lay ova in the lungs that can be expectorated or swallowed to be passed with stool.

Clinical Features

Some infections are asymptomatic. In others, the symptoms may be mild with cough, fever, chest pain, diarrhea, and urticaria. Some of these patients progress into a chronic disease and present with cough that is productive of rusty or golden-colored sputum, loss of weight, night sweating, and fever. The disease may have a prolonged course and mimic tuberculosis or aspergillosis.

Complications

Some patients develop local complications and in rare instances other distant organs may be involved. Local complications include bronchiectasis, fibrosis, pleural effusion and empyema. In rare instances, the adult forms and eggs may get access into the blood vessel and implant into various organs, most distinctly brain; however, other organs like liver, kidneys, testes, spleen, and skin may be invaded.

Diagnosis

Microscopy of the sputum or feces may show the ova of infecting organism; however, sensitivity may be limited. If surgical resection of the lesion is done, adult worms and ova may be seen in histopathology. ELISA and skin test are excellent in confirming diagnosis.

Treatment

Praziquantel 25 mg/kg three times daily for 3 days is very effective in curing the infection. Bithionol is an alternative therapy but more toxic.

Schistosomiasis

Schistosomal infection has its major burden in developing countries. Most of the cases in developed countries are imported with the exception of schistosomal dermatitis caused by avian schistosoma that has its vector in the lakes of Canada and USA.

It is estimated that 200 million people worldwide are infected with schistosoma with annual fatality of 2,00,000.

The various species of schistosoma are distributed among countries according to the availability of their intermediate snail host. *Schistosoma hematobium* (*S. hematobium*) infect 90 million persons and it is distributed in more than 50 countries in Africa, East Mediterranean and Southeast Asia. In Saudi Arabia, Jizan area in the south is the main endemic focus with a prevalence rate of 10–13%. Egypt also has a focus of infection mainly along Nile River with a prevalence of 10–15%. Currently, *S. hematobium* is the predominant species in Egypt due to the shift in the intermediate snail. *Schistosoma mansoni* (*S. mansoni*) infects 65 million people and causes 80,000 deaths annually. It has a prevalence of 1–7% in Saudi Arabia and mainly found in the western regions; however, an estimated prevalence in Riyadh is 7%, probably related to population movement to the capital from endemic areas. Nile delta is the main endemic focus for most of S. mansoni in Egypt. Other species are not common in Arab countries, *Schistosoma japonicum* (*S. japonicum*) is mainly found in Southeast and Far East Asian countries. *Schistosoma intercalatum* (*S. intercalatum*) is restricted to forest areas of Western and Central Africa. *Schistosoma mattheei* (*S. mattheei*) is reported in South Africa, Zaire, and Zimbabwe. *Schistosoma megoki* (*S. megoki*) is restricted to Cambodia and Laos.

Life Cycle

Humans and other mammals are the main reservoir for schistosoma species whereas different species of freshwater snails act as intermediate hosts. After being excreted with feces or urine into fresh water, the schistosomal ova hatch into mobile miracidia. The miracidia then enter a specific snail and mature into cercaria. The cercaria then is released into the water and upon encountering susceptible host, it penetrates through the skin. In subcutaneous tissue, cercaria matures into schistosomule which in turn passes with blood into the lungs. From the lungs, the schistosomule passes into their final residence in either mesenteric venous plexus in case of *S. mansoni* and vesical venous plexus in case of *S. hematobium*. In the venous

plexuses, the schistosomule mature into adult forms and start laying 200–300 ova/day.

Pathogenesis

The acute symptoms of schistosoma are related to local destruction of infected tissues as well as immune complex formation resulting in serum-sickness-like reactions. However, the main investigations were aimed at understanding the mechanism of chronic illness. It is thought that both parasite and host factors are responsible for the illness. The ova stimulate granuloma and fibrosis formation. The main contributing factor in such process is the release of cytokines, mainly alpha-TNF. In addition, T-cell subset Th1 has been shown to participate in the process of granuloma formation.

Some patients were found not to develop chronic disease and in these patients, it was found that they have some genetic constitution that makes them resistant to the infection.

Clinical Features

Acute Infection

In endemic areas, most of the infections are asymptomatic. At the time of skin penetration by cercaria, the patient may have itching and papular eruptions at the site of penetration. By 5–30 days after exposure, the patient starts to have symptoms of Katayama fever, which consists of fever, myalgia, arthralgia, and skin rashes that are usually papular and itchy. These symptoms last for 2–3 days and then resolve spontaneously. In cases of *S. mansoni*, *S. intercalatum*, *S. megonki*, and *S. japonicum*, the patients may have abdominal pain, diarrhea that is sometimes bloody and enlarged liver especially with heavy infection. *S. hematobium* may cause dysuria, frequency, and microscopic or gross terminal hematuria.

Chronic Infections

Without treatment, adult worms' life span is prolonged for 10–30 years. During this period, these worms lay a large number of eggs that usually remain in the venous channels and stimulate formation of granulomas and fibrous tissues.

S. hematobium results in formation of granulomas in the bladder. These granuloma cause bladder contracture and stricture of the ureter, which may lead to secondary hydronephrosis and obstructive nephropathy. Additional complications include vesical stone formation and bladder carcinoma.

S. mansoni, *S. japonicum*, *S. intercalatum* and *S. megonki* result in formation of fibroocclusive disease of the hepatic periportal areas resulting in presinusoidal portal hypertension with hepatomegaly, splenomegaly, and sequence of portosystemic shunting (esophageal varices, hemorrhoids, and ascites).

Swimmer's Itch

Some patients develop papular eruption following contact with cercaria especially those of avian schistosoma. History reveals a complaint of itching following a swimming in a freshwater lake. The itching evolves into papular eruption that is usually generalized. The symptoms resolve spontaneously in 2–3 days.

Diagnosis

Clinical suspicion should be the primary step in diagnosis of patients living in or returning from endemic areas. Laboratory diagnosis relies mainly on identifying the characteristic egg in the stool, urine, or infected tissue biopsies like rectal snip.

1. Stool microscopy: Ova of Schistosoma species other than *S. hematobium* can be identified in stool microscopy. *S. hematobium* ova can be seen in stool microscopy in rare occasions. Concentration of the stool is required to improve the yield of microscopy.
2. Urinalysis: For *S. hematobium*, urine microscopy will show the characteristic ova with terminal spike. It is recommended to collect urine between 10 a.m. and 2 p.m. as it is the best time when the ova concentration is high. In addition, filtration and sedimentation method is used to increase the yield of recovering the ova from the urine. *S. intercalatum* and *S. mansoni* ova can be seen in the urine microscopy in 10–15% of patients infected with these species.
3. Serology: HAI is the standard serology used in detecting IgG against Schistosoma. It is a genus specific and thus cannot differentiate between species. Also, it cannot differentiate between acute and chronic infection and thus it has limited role in diagnosing schistosomal infection in endemic areas. Other serological tests include EIA, RIA, IFA, and latex agglutination test. Using keyhole limpet hemocyanin, ELISA

can distinguish between acute and chronic infection but its use is restricted to research laboratories.

4. Antigen detection tests: Using EIA, two Schistosoma genus–specific antigens can be detected in the serum or urine. These two antigens are circulating anodic antigen (CAA) and circulating cathodic antigen (CCA). They are very sensitive and very specific but expensive and require special expertise and therefore not widely used.
5. Imaging studies: Plain radiography may be useful in showing bladder stones that could arise secondary to *S. hematobium* infection. Ultrasonography studies of liver are very specific and sensitive in showing periportal fibrosis that usually occurs with chronic *S. mansoni* infection. These changes also have been described rarely with *S. hematobium* infection. Ultrasound changes have been staged according to the severity of the infection and can be used to follow the response of therapy.
6. Supportive laboratory tests: Eosinophilia is present in most of the infected patients as well as leukocytosis. Urinalysis will show hematuria in those infected with *S. hematobium*. Stool may show hematochezia in *S. mansoni* infection. In chronic infection with fibroocclusive disease, there is raised bilirubin with normal liver transaminases. In fact, if liver transaminases are raised, then it is mandatory to rule out coexisting viral hepatitis.

Treatment

Treatment of Established Infections

Appropriate and very effective medication is available to treat Schistosomiasis. Praziquantel is effective against all human schistosomal infections. The recommended dosage is 30 mg/kg/dose in two doses given 4–6 h apart. Oxamniquine is effective against *S. mansoni*. Metriphonate is effective against *S. hematobium*. So far Schistosoma remain. Schistosoma responds to therapy very well with resultant resolution of acute symptoms, prevention of complication if used early, and halting the progression of the disease.

Response to therapy should be assessed by following stool and urine microscopy at 4–6 weeks and 3–6 months. Once antigen detection test is available, it will replace microscopy because it is more sensitive and specific.

Mass Therapy

In areas where schistosomal infection is endemic and involving a large proportion of population, mass therapy of the whole population proved to be effective in reducing the burden of infection. This can be achieved by giving praziquantel 40 mg/kg as a single dose.

Special Presentations of Schistosoma Infection

Central Nervous System Infections Schistosoma can infect both brain parenchyma and spinal cord. Encephalitis, meningoencephalitis, and focal brain lesions have been described in some cases of schistosoma infection especially *S. intercalatum*. Transverse myelitis and myelopathy can occur secondary to migration of schistosoma eggs into the spinal cord from the nearby venous plexuses. Early diagnosis and therapy may halt the infection and improve the outcome. Diagnosis can be achieved by myelography and finding schistosoma ova in the stool or urine. Steroid therapy in these cases is controversial but some showed it to be helpful.

Hepatitis B and C Infection Although incidence of hepatitis infection is reported to be high among patient with schistosoma infection, there is no scientific evidence that schistosoma infection increases host susceptibility to hepatitis.

Persistent Salmonella Bacteremia in Patients with Schistosoma Infection Salmonella bacteremia may be difficult to treat in patients with schistosoma infection as it may be kept hidden from antibiotics and host immunity in the tegument of schistosoma egg. Therefore, in such patients schistosoma should be treated in order to be able to eradicate schistosoma.

HIV and Schistosomiasis Again there is no proof that either infection predispose to the other.

Prevention This can be achieved through one of the following methods:

1. Immunization:

   Although there are efforts to find adequate vaccine, nothing yet comes in the surface. There is a need for vaccine because trials to decrease transmission have failed.
2. Decrease transmission:

   This can be tackled through the following methods:
   (a) Decrease the source of infectious eggs through mass therapy of all persons suspected to be infected.
   (b) Decrease the chance of encountering infectious ova by improving sanitation and decreasing the chance of having infected persons to contaminate water.
   (c) Decrease the loud of intermediate snails through using mollucicides.

Cestodes

Taeniasis

Taeniasis is a common intestinal cestode infection caused by either *Taenia saginata* or *Taenia solium*. Infection is acquired by ingestion of undercooked meat which is pork in case of *T. solium* and beef in case of *T saginata*. The infecting stage is cysticercus which upon reaching the stomach and small intestine degenerates to produce larva that mature to adult form. The adult forms are 8–12 m long (T. sagmata) or 4–8 m (T. solium) and contain many numbers of proglottids 1000–2000. The proglottids contain the reproductive system which upon fertilization, are replaced by gravid uterus that contain many eggs. These gravid proglottids then detach and pass with stool resulting in contamination of soil and vegetations. Beef and pork then ingest the eggs with their food which upon reaching intestine hatch to larvae that penetrate intestinal wall and travel to reside in the muscle to form cysticerci.

Clinical Features

Mostly asymptomatic and can stay so up to 25 years. When symptomatic, the manifestations include abdominal pain, vomiting, constipation or diarrhea, loss of appetite or increased appetite, and psychologic disturbances. The patient may give history of passing proglottids, which give a sensation of being passing a muscular tube that produces wave of movement upon passing through the rectum.

In few occasions, local complications may arise in the form of intestinal obstruction, pancreatitis, or biliary obstruction.

Diagnosis

In addition to clinical diagnosis, confirmation can be made by stool microscopy which sometimes may be negative because the proglottids release eggs upon passing through the rectum and in such cases perianal swab or scotch tape method may have a better yield.

Treatment

These patients respond very well to praziquantel 5–10 mg/kg as a single dose. Emetics should be avoided as gravid proglottid may be regurgitated and in this way may rupture and release the eggs in the intestine which in case of *T. solium* may result in cysticercosis.

Cysticercosis

Cysticercosis is a systemic parasitic disease that is caused by T. solium. In this disease, the human acts as an intermediate host who ingest eggs with contaminated foods or drinks. In the intestine, the egg hatches and produces larva that penetrates through the intestine and passes through blood to reside in any organs with particular predilection to the central nervous system.

Neurocysticercosis

Although not common in children, it can occur especially in the residents of endemic areas of Central and South America and some parts of Africa. The disease takes 3–5 years to develop and become symptomatic in 50% of the cases.

There are two types of neurocysticercosis, parenchymal and extraparenchymal. The parenchymal disease is localized in the brain tissue of cerebral cortex. The extraparenchymal disease may be intraventricular, subarachnoid, or spinal.

The symptoms associated with neurocysticercosis are variable and range from incidental finding of space-occupying lesion in the CT scan of the head, to a severe disease with meningoencephalitis that is manifested by fever, altered sensorium, headache, signs of increased intracranial pressure, and visual abnormalities. Majority of the affected patients present with epilepsy. Others may present with focal neurologic deficit.

Other Types of Cysticercosis

1. Muscular cysticercosis occurs in some patients but rare.
2. Cutaneous cystelcosis manifest by cutaneous nodules which may be calcified.
3. Eye cystelcosis which may involve any part of the eye.

Other organs: Any organ can be involved including heart, liver, kidneys, lungs, and spleen.

Diagnosis

Serology by ELISA is the mainstay of diagnosis in combination with compatible clinical signs and imaging studies. CT scan and MRI are very sensitive in elucidating the cerebral lesions which are variable in appearance from hypodense to isodense or hyperdense areas. Calcification may be present and usually indicates inactive disease. Brain biopsy is not indicated except in patients with negative serology in whom other causes of space-occupying lesions should be ruled out.

Treatment

In asymptomatic patients with calcified lesions, treatment may not be justified. Symptomatic patients should receive specific anti-helminthic therapy in addition to therapies to reduce the mass effects of the lesions such as steroids, mannitol, and diuretics as well as anticonvulsants. Specific anti-helminthics include praziquantel in a dose of 50 mg/kg/day for 15–28 days or albendazole 15 mg/kg/day in three divided doses for 28 days. Duration may need to be extended in cases that are not promptly responsive.

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98 Actinomycosis

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The genus Actinomyces consists of a heterogeneous group of gram-positive, non-spore forming catalase-negative pleomorphic rods that form a significant component of the commensal microflora of the oral, gastrointestinal, and female genital tracts and that are generally of low pathogenicity. Actinomyces species may invade via damaged mucosa, leading to bacteremia and systemic infections in both healthy individuals and immunocompromised patients. Actinomycosis is a catalase-negative infection and important to consider in chronic granulomatous disease (CGD).

Etiology

Of the 14 human actinomyces species, six may cause disease in humans, including the facultative anaerobic A. israelli, A. naeslundii, A. odontolyticus, A. visosus, A. meyeri, and A. gerencseriae. Actinomyces are fastidious bacteria that require cultures enriched with brain-heart infusion media, may be aided in growth by an atmosphere of 6–10% ambient CO_2, and grow best at 37°C. Colonies may appear after 3–7 days of incubation, but for adequate detection of slow growth, cultures should be observed for $>$ 21 days. Characteristically, actinomyces species appear "molar-tooth" colonies on agar or as "breadcrumb" colonies suspended in broth media.

Epidemiology

Human actinomycosis was first described in 1878 by Israel, who along with Wolfe first isolated that causative agent in culture and defined the organism's anaerobic nature. Actinomycosis occurs worldwide, with likely higher prevalence rate in areas with low socioeconomic status and poor dental hygiene. Humans are themselves the natural reservoir of the Actinomycyes species that cause actinomycosis. No external environmental reservoir such as soil or straw had been documented. There is no person-to-person transmission of the pathogenic actinomyces species. Actinomycosis in cattle, horses, and other animals is caused by other species, usually actinomyces bovis.

Pathogenesis and Pathology

Four clinical forms of actimonmycosis, i.e., cervicofacial, thoracic, abdominopelvic, and cerebral, account for the majority of infections in humans. Actinomycosis usually occurs in immunocompetent persons but may occur in persons with diminished host defenses.

The portal of entry of Actinomyces species is typically a break in the mucosa or the gastrointestinal tract, anywhere from the mouth to the rectum; such a break may occur as a result of a dental procedure, overt or covert dental sepsis, bacterial suppuration, diverticulitis, appendicitis, surgery or trauma.

In tissues, infecting Actinomyces species grow in microscopic or macroscopic clusters of tangled filaments that are surrounded by polymorphonuclear neutrophils. Subacute or chronic inflammation with granulation tissue, extensive fibrosis, and sinus tract is present in the surrounding tissues, but giant cells and cassation necrosis are generally not seen. When grossly visible, clusters exude from the soft tissues through sinus tracts, are pale yellow in color, and are called sulfur granules. Sulfur granules are not unique to actinomycosis. They occur in case of nocordiosis, chromomycosis eumycetoma, and botryomycosis. The causative organism can be recognized by their particular morphological features and cultural characteristics. The absence of sulfur granules from any lesion, however, does not exclude the diagnosis of actinomycosis; culture-proven case of actinomycotic cerebral lesions lacks this feature.

Diagnosis

The diagnosis of *actinomycosis* is made most accurately by isolating *Actinomyces* species in cultures specimens. However, the demonstration of actinomycotic granules in exudates or in histological sections of tissues not connected to hollow organs is strongly supportive of the diagnosis. Whether the sulfur granules are microscopic or macroscopic, they consist of tangled filaments of *Actinomyces* species, which becomes apparent on microscopic examination of a gram-stained smear of a crushed granule.

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Manifestations

Cervicofacial Actinomycosis

The face and neck are the most common sites of actinomycosis. The frequency of this location among cases of actinomycosis ranges from 11% to 96% with a mean frequency of 55%. Actinomyces species are normally present in high concentrations in the tonsillar crypts and gingivodental crevices, and many actinomycosis infections are odontogenic in origin. In addition to poor dentition and recent dental manipulation, chronic tonsillitis otitis and mastoiditis are important risk factors for these infections. External trauma may result in the introduction of Actinomyces species into the head and neck tissues.

Lesions are frequently located at the angle of the jaw or in the submandibular region. Cervicofacial actinomycosis may extend to the underlying mandible or facial bones, leading to the development of periostitis or osteomyelitis. Human cervicofacial actinomycoses can be diagnosed reliably only by adequate microbiological method. Histological procedures often do not provide conclusive result, because characteristic sulfur granules are often low in number and not always easy to identify or differentiate from granules of various other origins.

Thoracic Actinomycosis

Thoracic actimonmycosis accounts for 15–20% of cases and may involve the lungs, pleura mediastinum, or the chest wall. Routes of infection include aspiration of oropharyngeal secretions or gastric contents; direct extension of cervicofacial infraction in the mediastinum, along the deep facial planes of the neck; transdiaphagmatic or retroperitoneal spread from the abdomen; or rarely hematogenous dissemination. Infection in the lung usually leads to the development of chronic pneumonia with or without associated pleural effusion. The clinical picture of thoracic actinomycosis most often mimics that of tuberculosis or malignancy with findings of cough, low-grade fever, weight loss, and chest pain. Pulmonary actinomycosis presented as a mass-like consolidation. Response to antibiotics was facilitated by a removal of the airway plug through bronchoscopy. Airway obstruction may contribute to the prolonged medical treatment of pulmonary actinomycosis. The plug formation from fibrous material generated by the bacteria may obstruct bronchial orifices and account for the recurrence. Thus, periodic bronchoscopy to inspect and remove the airway plug may facilitate medical treatment.

Chest radiographs may reveal infiltrates suggestive of aspiration pneumonitis, firbronodular and cavitary parenchymal disease, or a mass in the lung. Contiguous extension from a chronic pulmonary focus may lead to empyema; vicinal destruction of the ribs, sternum, or shoulder girdle; involvement of the chest-wall muscles and soft tissues; and the formation of sinus tracts extending to the skin. Involvement of the mediastinal structures rarely leads to obstruction of the superior vena cava, formation of a trachoesophageal fistula, vertebral or paravertebral extension, or the development of pericarditis or myocarditis.

Abdominal and Pelvic Actinomycosis

Actinomycosis of the abdomen and pelvis accounts for 10–20% of reported cases. Actinomyces species are frequently part of the normal flora of the gastrointestinal and female genital tracts. Abdominal actinomycosis usually occurs following penetrating trauma, perforation of the gut, or surgical manipulation of the gastrointestinal tract. Abdominal actinomyocosis may be the most indolent and latent of all of the clinical forms of the disease; diagnosis may be delayed months or years after the inciting event. There is a predilection for involvement of the ileocecal region of the gut; thus, chronic abdominal actinomycosis may be confused with intestinal tuberculosis, ameboma, or chronic appendicitis.

Anorectal disease is not uncommon, and may present as rectal stricture, perirectal or ischiorectal abscess, or recurrent draining sinuses and fistulae. The primary site may be an anal crypt, or there may be direct extension from an intra-abdominal focus of infection. Gastric and perigastric, hepatic, splenic, and renal involvements are uncommon forms of abdominal actinomycosis. Actinomycosis species may reach these viscera through direct extension from the bowel or an intra-abdominal or intrathoracic site or via seeding through the portal vein or systemic circulation. Similar to intestinal infection, pelvic actinomycosis is typically insidious in its course and easily confused with other inflammatory or malignant pelvic disorders. Nonspecific symptoms of this form of the disease (lower quadrant abdominal pain and weight loss) and low-grade fever (or no fever) may persist for months to years. If pelvic actinomycosis is secondary to intestinal infection, the usual source is indolent ileocecal disease that extends to the right adnexa in 80% of cases. The ovary is most commonly affected, followed by the fallopian tubes, uterus, vulva, and cervix.

Central Nervous System

Actinomycosis of the CNS may present as a brain abscess, meningitis or meningoencephalitis, subdural empyema, actnomycoma, and spinal and cranial epidural abscess. Brain abscess accounts for almost 75% of all CNS lesions. Actinomycosis of the CNS is usually secondary to hematogenous spread from a primary infection in the lung, abdomen, or pelvis. However, extension form foci of infection in the ears, para nasal sinuses, and cervicofacial regions may proceed along the connective tissue planes or trough foramina at the base of the skull, causing focal infection of the CNS or diffuse basilar meningitis.

Actinomycotic cerebral abscesses are usually singular but may be multiple, unilocular, or multilocular, encapsulated or less frequently, un-encapsulated. The interval from the onset of symptoms to diagnosis is typically longer than that for pyogenic brain abscesses. There is a predilection for involvement of the temporal and frontal lobes. Cerebral actinomycosis may also be a component of disseminated disease that occurs in three or more noncontiguous body sites.

Involvement of the meninges results in basilar meningitis; the signs and symptoms mimic those of other chronic meningiticides. Because of the indolent nature of this form of the infection, frequent lack of acute toxicity, and findings in the CSF (e.g., mononuclear pleocytosis, an elevated protein concentration, and normal or low glucose concentrations), the disease is frequently misdiagnosed as tuberculous meningitis. Actinomycomas may occur at various sites within the CNS, i.e., as space-occupying lesions in the cerebral cortexes, as masses of the gasserian ganglion, or as lesions simulating tumors in the posterior or third ventricle.

Primary cutaneous actinomycosis is rare, and the diagnosis requires a high index of clinical suspicion.

Treatment and Prognosis

Actinomyces species are susceptible in vitro to several antimicrobials including penicillin G., chloramphenicol, the tetracyclines, erythromycin, clindamycin, imipenem, streptomycin, and the cephalosporins. Fluoroquinolones, aztreonam, fosfomycin, and other aminoglycosides generally have poor activity against *Actinomyces* species and *P.propionicus*. The clinical experience with actinomycosis has been extensive and supports the use of penicillin G as the drug of choice for all clinical forms of the disease. Mild cervicofacial infections maybe adequately managed with a 2-month course of peroral penicillin V or one of the tetracyclines (e.g., doxycycline, 100 mg given orally twice daily), without surgical intervention.

For other more complicated forms of actinomycoses, parenteral penicillin G, 10–20 million U/d divided every 6 h, should be administered for 4–6 weeks, followed by oral penicillin V, 2–4 g/d divided every 6 h, for 6–12 months. For penicillin-allergic patients, a tetracycline, erythromycin, clindamycin, and cephalosporins are suitable alternatives. Chloramphenicol, given orally or intravenously in a dosage of 50–60 mg/(kg/d) divided every 6 h, is probably the preferred agent for treating actinomycosis of the CNS in patients who are allergic to the penicillins. Risk factors significantly correlated with a poor outcome (death or relapse) for patients with CNS actinomycosis include the onset of disease $>$2 months before presentation, lack of antibiotic therapy or surgery, and the performance of needle aspiration drainage rather than open drainage or excision.

In light of the potential for relapse of actinomycosis, prolonged antibiotic treatment is prudent; the exact duration of therapy depends on the site and severity of disease. Prolonged observation of patients after treatment is necessary to detect recurrence.

Prevention

There are no specific measures for preventing actinomycosis; however, maintenance of good personal orodental hygiene, and in particular, removal of dental plaque, may reduce the density if not the incidence of colonization and low-grade periodontal infection with *Actinomyces* species.

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99 Hydatid Disease

Mohammed El-Bali · Adetunji Adeyokunnu

Hydatid disease is a cosmopolitan infection of humans and certain other mammals caused by cestodes belonging to the genus *Echinococcus*. *Echinococcus granulosus* is the main infection, with infection with *E. multilocularis* occurring to some extent and *E. vogeli* occasionally; *E. oligarthrus* is very rarely known to cause disease in humans. Infection is acquired by ingestion of ova from feces of carnivorous definitive hosts. The larvae most frequently develop in the liver but may occur in many different tissues, such as the lungs, spleen, and other organ systems, including the brain, eye, heart, bone, and genitourinary system. Although the disease is often referred to as hydatid disease, it may also be designated according to the morphology of the larval stages: unilocular echinococcosis, caused by *E. granulosus*; multilocular or alveolar echinococcosis, caused by *E. multilocularis*; and polycystic echinococcosis, caused by *E. vogeli*.

Etiology

The life cycles of the main species of *Echinococcus* are similar, but significant differences occur in the geographical distribution, types of host, and morphology of the parasite. *E. granulosus*, the most common species found in human infections, is of two major strains: the domestic or pastoral strain and the sylvatic strain. The small adult worm lives in the intestine of dogs, the main definitive host, and related canids such as the fox and wolf. Infective eggs are passed in the feces of these animals and may be ingested by sheep, cattle, camels, goats, or humans, who are usually the intermediate hosts. The eggs hatch in the small intestine and the embryos (in a larval stage called oncosphere) burrow through the intestinal wall and gain access to the portal circulation. Many embryos are destroyed, but those that survive may develop in many tissues, most commonly the liver or lung, where they become the cystic larval structures called hydatid cysts. The cyst is made up of an outer laminated acellular membrane lined by a thin, cellular germinal membrane. Spherical structures called brood capsules grow from the germinal membrane. Protoscolices develop within the brood capsules. These structures contain suckers and hooks and become scolices of adult worms. The cycle is maintained when dogs or wolves eat carcasses of the intermediate hosts. Unilocular cysts, which may contain daughter cysts, develop most commonly in the liver, with the second most common site being the lungs. In children, pulmonary involvement may be more common than hepatic involvement.

E. multilocularis typically involves foxes as definitive hosts and mice as intermediate hosts. Because the cysts lack a containing capsule, they progressively invade involved tissues and produce honeycombed alveolar hydatid cysts. The larvae may invade contiguous structures and rarely may metastasize. When *E. vogeli* infection occurs in humans, the germinal membrane of the larval cyst grows externally to form additional cysts and also develops septa within the original cyst. This is the polycystic variety of hydatid disease.

Transmission

Humans acquire hydatid disease by ingestion of food or drink contaminated with feces from the infected definitive hosts, usually dogs. The eggs can be found on the dog's perianal hear, muzzle, and paws. Children become particularly susceptible because of their intimate contact with dogs. They may pick up eggs contaminating the animal's coat or ingest eggs from the dog's tongue after being licked. Flies may disseminate the eggs from dog feces. The practice of tanning leather with a mixture of water and dog feces might be responsible for the high prevalence of infection among shoemakers in Lebanon. Major differences between the human-dog parasite and cattle-dog organism have been detected, thus raising doubt about the infectivity of the cattle and camel strains to humans.

Epidemiology

E. granulosus is the most common species found to infect humans and has a global distribution, being endemic in sheep-rearing regions such as the Mediterranean basin, the Middle East, East Africa, Latin America, southwestern

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Canada, Australia, South America, and New Zealand. *E. multilocularis* is confined to the northern hemisphere, including Europe, Canada, Alaska, Japan, the north central United States, Russia, and Turkey. *E. vogeli* is found in South America, and *E. oligarthrus* was discovered in Central and South America, where it is a rare infection in humans.

Pathogenesis

The development of disease is related to compression or displacement of host tissue. Unilocular hydatid cysts, for example, enlarge concentrically, increasing in diameter by 1–5 cm a year. A cyst may exceed 35 cm in diameter in the abdominal cavity. When there is rupture of or leakage from a cyst, an allergic reaction caused by the antigenic cyst content usually occurs. Patients may experience bronchospasm, urticaria, or anaphylaxix. Blood eosinophilia is usual. Cysts may calcify after many years, signifying the death of the parasite. The cysts may form foci for secondary bacterial infection. Infection of the cyst can facilitate the development of liver abscesses and mechanic local complications, such as mass effect on bile duct and vessels that can induce cholestasis or portal hypertension.

Clinical Manifestation

Many cases of hydatid disease are silent. When symptoms occur, they are caused by pressure produced by the expanding cyst, and its location determines the clinical presentation. Thus recurrent fever, proxysmal cough, chest pain, and hemoptysis are common symptoms of pulmonary hydatidosis. When pulmonary cysts rupture into the bronchus, the patient may describe "coughing up grape skins." Constant or intermittent right upper quadrant abdominal pain, vomiting, hepatomegaly, and jaundice may indicate liver involvement. Lung disease is reported to be most common form of presentation. It is thought, because of the slowly growing nature of the liver and lung hydatid cysts, even when such infections are acquired in childhood, most cases become symptomatic and are diagnosed in adult ages, and only 10–20% of cases are diagnosed in patients younger than 16 years. But cysts located in other organs like the brain or an eye can cause clinical symptoms even when small; thus, most cases are diagnosed in children. Central nervous system involvement is also much more common in children than in adults. Intracranial localization produces symptoms indistinguishable from those of a tumor, seizures, personality changes, intellectual deterioration, signs of increased intracranial pressure, or neurologic abnormalities. Orbital cysts produce proptosis. Bone cysts, which may be seen in preschool children, are most common in the vertebral and long bones. Unlike cysts in other sites, bone hydatids are characteristically multilocular and contain little fluid. Bone pain and pathologic fractures have been reported. Vertebral hydatid disease causes spinal cord compression.

Serious morbidity is the consequence of enlargement, secondary infection, or a cyst rupture. Some children with hydatid disease also show retarded growth patterns. Sensitivity to cyst contents due to slow leak of fluid may develop, with resulting allergic symptoms, notably urticaria.

Diagnosis

Diagnosis of human equinococcosis is made by a combination of clinical, imaging, serological, and molecular techniques. Diagnosis of hydatid disease depends initially upon clinical awareness of the condition. This includes history of residence in endemic areas. Physical examination is rarely definitive. Certainly, hydatid cysts are most commonly found in the liver and lungs, but other locations have been reported and prevalently in children and young adults. A moderate eosinophilia is almost invariably present in childhood cases except during febrile illnesses. Only about 50% of patients with hepatic hydatids have abnormal liver function tests. Immunoglobulin E levels characteristically are elevated.

A noninvasive confirmation of the diagnosis can usually be accomplished with the combined use of radiologic imaging and immunodiagnostic techniques. Results of radiologic and imaging studies can strongly suggest the diagnosis of hydatidosis. Plain x-ray of the chest may suggest pulmonary cysts. It will not differentiate such cysts from pyogenic lung abscess, lung tumor, metastatic deposits, or cavitating tuberculosis. Such x-rays will not visualize cysts in other organs unless they are calcified, as often is seen in hepatic cysts. However, since calcification takes years to occur, this procedure is unhelpful in childhood hydatid disease. Ultrasound techniques (*Fig. 99.1*) can be used to differentiate fluid-filled cysts from solid tumors. The expanded use of ultrasonography has improved the potential of diagnostic techniques in cystic echinococcosis, and the availability of portable ultrasound units facilitates epidemiological screenings in remote endemic areas. World Health Organization

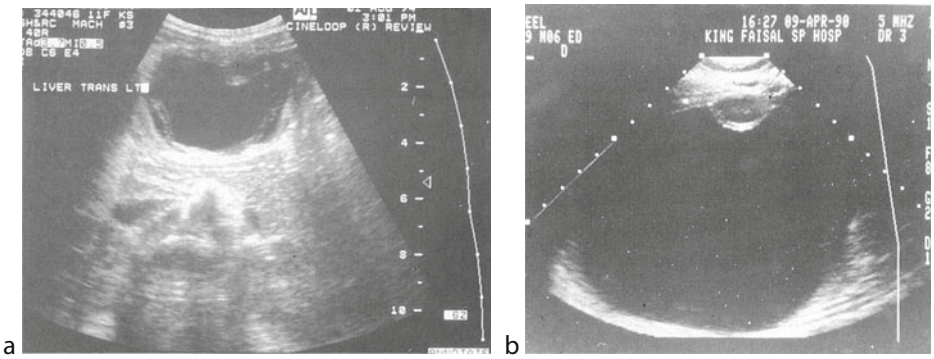

Figure 99.1
Ultrasonographs showing typical unilocular hydatid cysts of the liver. Notice the highly characteristic daughter cyst (b) and the double-layer lining (a)

developed a standardized classification system for hepatic hydatidosis cysts detected by ultrasonography. Briefly, this classification system includes the following types: CL, unilocular cyst(s) with uniform anechoic content, but no pathognomonic signs are detectable; CE1, active unilocular cyst with uniform anechoic content and cystic wall well visible; CE2, active multiseptated, rosette-like cyst with visible wall; CE3, cyst with anechoic content and inner floating detached membranes or daughter vesicles in solid matrix; CE4, inactive cysts with hypoechoic or hyperechoic degenerative content and no daughter cysts; and CE5, inactive cyst with wall calcification varying from partial to complete. A pathognomonic computerized tomography (CT) finding, in addition to the intact cyst (*Fig. 99.2*), is the presence of daughter cysts that are either free within the cyst or adherent to the inner germinal layer. Magnetic resonance imaging scans can add precision to equivocal results of CT scanning or ultrasonography.

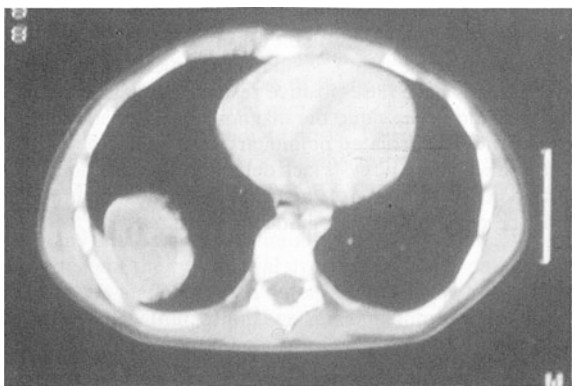

Figure 99.2
CT scan of chest showing the characteristic cannon-ball appearance of pulmonary hydatid cyst (Courtesy of Haysam Tufenkeji, FAAP)

Antibody assays are useful to confirm presumptive imaging diagnoses, although some patients do not demonstrate a detectable immune response. Intact cysts can elicit a minimally detectable response, whereas previously ruptured or leaking cysts are associated with strong responses. Several immunodiagnostic tests are available for detecting antibodies in the sera of patients with hydatid cysts. Casoni intradermal test has an accuracy of between 50% and 80%. However, sensitivity is variable, specificity is low, and false positives may be encountered in patients with schistosomiasis or neoplasia of the liver or lungs. The test may remain positive for several years after removal or death of the parasite. The complement fixation test (CFT) has an overall sensitivity of 70%. False positivity has been recorded in patients suffering from pancreatic or lung cancers or sarcomas. Results of the CFT revert to negative more quickly than those of agglutination reactions following surgical removal of hydatid cyst from the body. It is, however, a reliable method for monitoring continued infection and detecting reinfection. The indirect hemagglutination test and enzyme linked immunosorbent assay can be performed first in acute cases to record a presumptive diagnosis of hydatidosis. Both tests are simple, highly sensitive, and amenable to automation, but, because of the possibility of false-positive results produced by cross-reacting helminthic infections, specificity must be confirmed using the immunoassays with Arc-5 antigen, which so far is considered by

many to be the only absolutely specific serologic test available for hydatidosis. Em2, a species-specific native antigen isolated from the metacestode of *E. multilocularis* has been used successfully over a long period for immunodiagnosis of alveolar echinococcosis in ELISA format with a sensitivity ranging between 77% and 92%.

Even with these assays, 5–25% of patients with neurocysticercosis have false-positive results. Conversely, negative tests do not exclude the diagnosis because about 50% of patients with isolated pulmonary cysts and 10–15% of those with hepatic cysts lack detectable antiechinococcal antibodies. In seronegative individuals, a presumptive diagnosis can be confirmed by the demonstration of protoscolices or hydatid membranes in the aspirates obtained by percutaneous aspiration of the cyst, preferably guided by ultrasonography and under anthelmintic coverage.

Treatment

The definitive therapy for echinococcosis has been surgical excision. Success depends upon the size and location of cysts and the skill of the surgeon for removal of *E. granulosus* cysts and resection of tissues containing *E. multilocularis* cysts. In all cases, care must be taken during surgery to avoid spilling the cyst contents, which carries an immediate risk of anaphylaxis, spread of infection, and delayed risk of disseminated echinococcosis. Before excision, the cyst may be aspirated and scolicidal solutions such as hypertonic saline or ethanol cetrimide instilled into the cavity. Fear has been expressed that such a precautionary procedure may produce its own problems, such as hypernatremia, alcohol intoxication, and, with communicating hepatic lesions, sclerosing cholangitis. Albendazol has been used during surgery in the hope of reducing the risk of secondary spread of infection. Medical treatment before, during, and after surgery may be beneficial in some cases. For inoperable lesions, or when there is no consent for surgery, percutaneous cyst drainage followed by alcohol injection and reaspiration can be carried out with ultrasound guidance. The mortality from surgery is around 3–5%.

Chemotherapeutic agents are no substitute for surgery as their effect on available evidence seems to be palliative rather than curative. When surgery is not feasible because of poor general condition of the patient, the disease is too widespread to permit curative surgery, or the location of the cyst makes it technically inaccessible, then one of the two available agents, mebendazole or albendazole, may be used.

Mebendazol is a synthetic benzimidazol derivative. It was the first drug to be tried against echinococcal infection in humans. It is larvicidal to *E. granulosus* and *E. multilocularis* by limiting their cellular glucose uptake. It is also known to kill the germinative membrane of peritoneal hydatid cysts in experimental animals. A dose of 50 mg/kg body weight per day in three divided doses taken orally with meals for 3 months is probably the minimum effective dose for treating *E. granulosus* infection. Low-grade fever, pruritus, urticaria, exfoliative dermatitis, bone marrow toxicity and neutropenia, transient liver toxicity, and glomerulonephritis have been recorded complications. The initial abdominal discomfort and nausea can be lessened if the drug is taken with meals. Albendazole, another benzimidazole carbonate, was meant to be an improvement over mebendazole. The drug seems to induce degeneration of the germinal layer of the hydatid cysts and to kill protoscolices. The dose is 5–7 mg/kg twice daily to be taken at mealtimes. The treatment should be in the form of 30-day courses separated by 2-week intervals.

Response to chemotherapeutic agents can be monitored using ultrasonography and serial CT to detect changes in the size and contour of soft tissue cysts. Serial chest x-rays may also be helpful in monitoring pulmonary cysts. Serologic tests should also be employed to monitor disease activity during treatment. The prognosis of hydatid disease is widely variable. In 25% of cases, hepatic cysts may undergo spontaneous death and calcification, but, once patients become symptomatic, the prognosis without intervention is very poor.

Prevention

There are currently no effective drug treatments or vaccines to protect humans against the disease. Prevention of the disease requires elimination of infection in dogs, the main definitive host. This can be achieved by regular treatment of dogs with an effective teniafuge, such as praziquantel or mebendazole, at least twice yearly. Also, dogs should not be allowed to have access to carcasses of intermediate hosts like sheep. Control and prohibition of farm and home slaughter were key features in successful programs of eradication in countries like Iceland, New Zealand, and Tasmania.

Populations need constant education and to be alert to the possibility of infected eggs contaminating their foods, greens, and water, and they should be encouraged to take effective measures.

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100 Leishmaniasis

Mohammed El-Bali · Adetunji Adeyokunnu

Leishmaniasis refers to a group of parasitic diseases caused by protozoan flagellates of the genus *Leishmania*. The infection is transmitted to humans through the bite of *phlebotomine* sandflies that have fed on an infected host. The pattern of disease produced varies from innocuous self-limiting cutaneous lesions to potentially lethal visceral leishmaniasis depending on the infecting species of *Leishmania* and the host's immune response to infection. The disease is endemic in large areas of the tropics, subtropics, and the Mediterranean basin.

Etiology

Leishmaniasis is mainly a zoonosis, where human beings are incidental hosts of infection, and other mammals, such as rodents and canines, are reservoir hosts, although in certain areas of the world, it is primarily anthroponotic, with human–vector–human transmission (e.g., anthroponotic visceral leishmaniasis due to *L. donovani* and anthroponotic cutaneous leishmaniasis due to *L. tropica*).

Leishmania parasites are transmitted to humans predominantly through biting sandflies vectors of several species and subspecies of *Phlebotomus* in the Old World and *Lutzomyia* in the New World. The disease can also be transmitted by close contact with a contaminated bite wound, blood transfusions, congenitally from mother to infant and by shared blood-contaminated syringes among intravenous drug users, though; these are rare modes of contracting the disease.

The protozoal parasite *Leishmania* exists in two distinct morphologic forms: flagellated promastigotes, which replicate extracellularly within the sandfly vector gut and also in axenic cultures, and aflagellated amastigotes, which are obligate intracellular parasites of mononuclear phagocytes in mammalian hosts. When the vector, a sandfly, feeds on an infected host, it may ingest an infected cell from blood or tissue. The amastigotes are liberated in the fly's midgut and, within a few hours, transformation to the promastigote occurs. Binary fission then begins, and large numbers of promastigotes are produced that gradually move forward to the buccal cavity and mouth parts of the fly. The organisms may remain in the fly's mouth parts for between 1 and 3 weeks before dislodging into the bite wound when the fly next takes a blood meal.

Once inoculated, many of the promastigotes do not survive because vertebrate host tissue fluids contain cytolytic substances. On the other hand, the organisms that are phagocytized transform to amastigotes and initiate replication. They are round to oval bodies about 2–4 μm in diameter that possess a single nucleus and kinetoplast; they lack free flagellum. They are also referred to as Leishman–Donovan bodies. The organism can be seen readily in tissues or smears by light microscopy, especially with Giemsa staining.

Epidemiology

Leishmaniasis is found in all continents and is endemic in the tropical and subtropical regions of 88 countries. There is an overall prevalence of 12 million cases worldwide, and 350 million people are considered at risk. Each year, about 1.5–2 million new cases of cutaneous leishmaniasis occur, 90% of them registered in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Sudan, and some 500,000 new cases of visceral leishmaniasis, mostly in Bangladesh, Brazil, India, Nepal, and Sudan. In visceral leishmaniasis endemic areas, children and young adults are especially affected. Visceral leishmaniasis is also prone to large-scale epidemics with high fatality rates.

The number of leishmaniasis cases is increasing, mostly because of climate change, mass population movements, exposure of people who are not immune, deterioration of living conditions in outlying urban areas, and malnutrition. *Leishmania*/HIV coinfection has emerged as a result of the increasing overlap between both diseases. Visceral leishmaniasis is the clinical form most frequently associated with HIV/AIDS. Although, some coinfection cases with cutaneous forms have been reported.

Clinical Manifestations

Leishmania infection can in general manifest in three broad clinical forms: visceral, cutaneous, and mucocutaneous. These depend on the tissue tropism of the

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leishmanial species and the host's immune response, principally the cell-mediated component of immunity. Other variants of the disease are also well known, namely, post-kala-azar dermal leishmaniasis, diffuse cutaneous leishmaniasis, and recidivans cutaneous leishmaniasis.

Visceral Leishmaniasis

Certain *Leishmania* species show exaggerated viscerotropism in humans and cause the potentially lethal kala azar or visceral leishmaniasis. These organisms are grouped under the *L. donovani* complex and comprise the subtypes *L. donovani* and *L. infantum* in the Old World, and *L. chagasi* in the New World. In *L. infantum*, children are involved almost entirely and dogs or foxes are among the extrahuman vertebrate hosts, and *L. chagasi* is similar epidemiologically. In infections with *L. donovani*, adults tend to be involved more, and there is no extrahuman vertebrate. Few cases of visceral leishmaniasis caused by *L. tropica* have been also reported.

Typically, symptoms appear between 2 and 6 months following sandfly bite, although incubation periods of up to 3 years have been reported. Lesions at the inoculation site are rarely observed when the patient first comes to medical attention. In infants, an acute onset is associated usually with high fever, sometimes vomiting, and occasionally rigors. In younger infants, mild to moderate toxemia is commonly seen. Temperature is variable, irregular remittent, or intermittent, sometimes showing double or even triple peaks in 24 h. Congenital kala azar, though very rare, has been reported in infants whose mothers were affected with the disease during pregnancy.

In older children, the onset of disease is usually insidious, with low-grade fever that is also irregular, remittent, intermittent, or continuous with an uneven plateau. Apyrexial periods may intervene during the pyrexial course of the disease. During the early course of the disease, children may remain ambulatory with temperatures of 40°C and appear less ill than the height of the temperatures would suggest. Nonspecific complaints include vomiting, diarrhea, anorexia, and unproductive cough. Thereafter, the fever may recede, and the patient becomes weak and complains of symptoms due to an enlarged spleen, such as abdominal discomfort and early satiety. Physical examination will reveal splenomegaly. The spleen may so enlarge as to expand to the iliac fossa, but splenomegaly is an invariable finding. Hepatomegaly and less frequently lymphadenopathy are associated features. Well-established cases are characterized by pallor and later by ashen gray skin color.

Kala azar means "black poison," a terminology derived from the increased skin pigmentation in the malar region, the temples, and around the mouth that can be seen in dark-skinned races. There is wasting and drying of the skin; sparseness of the hair, which becomes thin and brittle; and varying degrees of abdominal protuberance due to gross splenic enlargement (*Fig. 100.1*). Petechiae, ecchymoses, and mild edema appear. Jaundice and ascites are rare. Anemia, leukopenia, and thrombocytopenia are common.

Kala azar should be suspected in any patient from an endemic area presenting with fever, splenomegaly, pancytopenia, hypoalbuminemia, and hyperglobulinemia. The disease may simulate malaria, salmonellosis, brucellosis, miliary tuberculosis, subacute bacterial endocarditis, and leptospirosis in general, as well as schistosomiasis, leukemia, reticulosis, glucagon storage disorder, tropical splenomegaly syndrome, and histoplasmosis with respect to the splenomegaly particularly.

Post-kala-azar dermal leishmaniasis is a complication of visceral leishmaniasis. A varying proportion of recovered visceral cases may evolve into a cutaneous form characterized by a macular, maculopapular, and nodular rash starting usually around the mouth and spreading to other parts of the body. It is mainly seen in East Africa (Sudan and Kenya) where usually it appears within the first 6 months post treatment, and in Indian subcontinent where most patients present after 2–3 years. Post-kala-azar dermal leishmaniasis cases are highly infectious because the nodular lesions contain many parasites. The post-kala-azar dermal leishmaniasis, although not as deadly as visceral leishmaniasis, requires a lengthy expensive treatment program.

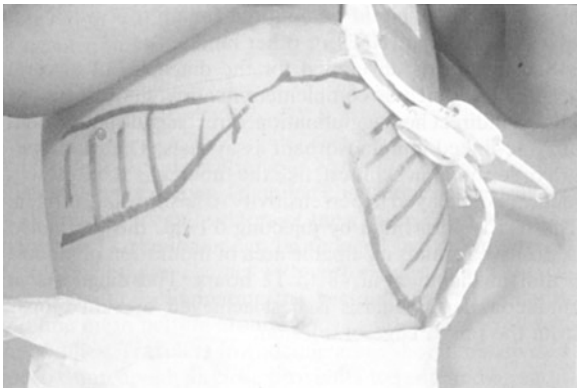

Figure 100.1
Hepatosplenomegaly in a patient with kala azar (Courtesy of Haysam Tufenkeji, FAAP)

Cutaneous Leishmaniasis

This type of infection is traditionally divided into Old World and New World cutaneous leishmaniasis. Old World (the Mediterranean basin, Africa, India, China, the former Soviet Union, the Middle East, and Asia Minor) cutaneous leishmaniasis is caused by three species of *Leishmania* that belong to the *L. tropica* complex: *L. tropica* is present in the Middle East and the Mediterranean littoral; *L. major* is found in the Middle East, Arabia, the former Soviet Union, India, and sub-Saharan Africa; and *L. aethiopica* is found principally in Ethiopia and Kenya. New World (primarily Central and South America) cutaneous leishmanasis arises from infection with parasites belonging to the *L. mexicana* or the *L. braziliensis* complexes. In most geographic areas, these parasites are maintained by transmission in nonhuman reservoirs, usually rodents, but person–vector–person transmission can also occur. The differential diagnosis of cutaneous leishmaniasis includes yaws, syphilis, leprosy, tuberculosis, basal cell carcinoma, sarcoid, and fungal infections.

The characteristic skin lesion begins as an erythematous papule or macule that may ulcerate after several weeks (*Fig. 100.2*). The lesions are generally painless, nontender, and nonpruritic unless superinfection with bacteria has occurred, in which case there may be regional lymphadenopathy. The lesions are often solitary, but multiple bites can produce several concurrent lesions. Satellite lesions containing parasites may form adjacent to the primary one. In Old World cutaneous leishmaniasis, spontaneous healing usually occurs over a period of months.

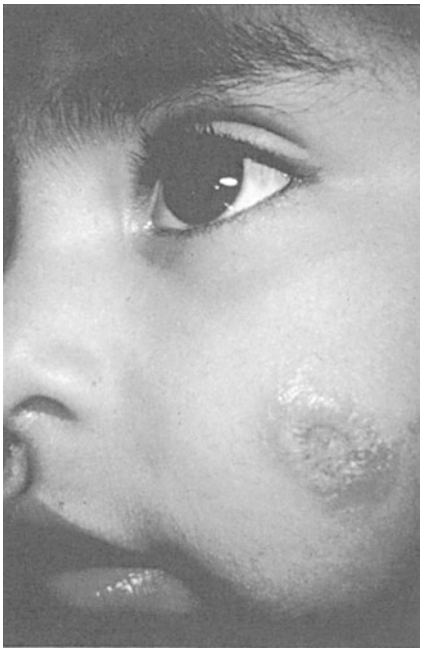

Figure 100.2
Cutaneous leishmaniasis. Note the raised edges and central ulcer (Courtesy of Haysam Tufenkeji, FAAP)

In humans, infection with *L. tropica* usually produces self-limited skin ulcers in which amastigotes can be found situated in macrophages in and about the lesions. However, military personnel in the Middle East have acquired cutaneous leishmaniasis with *L. major* as well as viscerotropic infection with *L. tropica*. It should be noted that, in the wet form of cutaneous leishmaniasis caused by *L. major*, the incubation period is short, rapid healing ensues, and few parasites are found in the skin; various rodents, for example, the fat gerbil (*Psommosys obesus*), are the main reservoir.

Cutaneous leishmaniasis, depending on the species of the causal agent, may evolve into diffuse cutaneous leishmaniasis, recidivans leishmaniasis, or mucocutaneous leishmaniasis.

Diffuse Cutaneous Leishmaniasis

Diffuse cutaneous leishmaniasis occurs most often in Ethiopia, Brazil, Dominican Republic, and Venezuela. It is an anergic form of cutaneous leishmaniasis in which neither cellular nor humoral immune responses are functional. This form of leishmaniasis is characterized by disseminated and chronic skin lesions very similar to those of localized cutaneous leishmaniasis and those of lepromatous leprosy. It occurs with extensive and widespread proliferation of parasites in the skin but without apparent inflammation or tendency for visceralization. The disease is usually refractory to treatment.

Recidivans Cutaneous Leishmaniasis

Leishmaniasis recidivans, also known as lupoid or tuberculoid leishmaniasis, is a chronic form of anthroponotic cutaneous leishmaniasis that may occur years after a localized cutaneous lesion has healed and lasts for many years. The lesions, commonly presenting on the face and exposed areas, form over the edge of the old scar. Untreated, the disease is destructive and disfiguring. Parasites are few or not detectable, but they may be isolated by culture.

Mucocutaneous Leishmaniasis

Infections with strains of *L. braziliensis* and *L. panamensis*, which are endemic in various areas of South America, mostly in Bolivia, Brazil, and Peru, cause cutaneous leishmaniasis, which may result in later development of mucocutaneous leishmaniasis. Such mucocutaneous disease (also known as espundia) involves the nasal or oropharyngeal mucosa or both, causing gross mutilation of the nose and palate. Lesions, almost never heal spontaneously and are usually seen months or years after a first episode of cutaneous leishmaniasis. Secondary bacterial infections are frequent and the disease may prove fatal.

In the Old World, mucosal lesions are rarely seen, but any species of *Leishmania* can cause them. Patients with anthroponotic visceral leishmaniasis, post-kala-azar dermal leishmaniasis or HIV coinfection, may develop lesions in the mouth or nose.

Diagnosis

Definitive laboratory diagnosis of *Leishmania* infection requires demonstration of the parasite in smears, in biopsies, or by isolation in culture media or in experimental animals. Histochemical and immunohistochemical methods for the demonstration of the parasite are also available. Different serologic methods for detecting the presence of antibodies against *Leishmania* parasites are available. Other laboratory methods, such as antigen detection by latex agglutination test and specific DNA detection by molecular techniques, have also been described for the diagnosis of leishmaniasis.

When kala azar is suspected based on the observation of a patient with fever, hepatosplenomegaly, and a history of exposure in endemic areas in addition to laboratory findings of anemia, leucopenia, thrombocytopenia, marked polyclonal hypergammaglobulinemia, and hypoalbuminemia, diagnosis can be confirmed by spleen or bone marrow aspiration looking for amastigotes in stained samples (*Fig. 100.3*). Tissue specimens can also be obtained from lymph nodes aspiration and liver biopsy. Microscopy shows high specificity, but its sensitivity varies. Although, splenic aspirates have been found to have the highest yields (93–99%), they are not without risk. The procedure should be avoided in individuals with a bleeding diathesis. Other contraindications include a soft or diffluent, acutely enlarging spleen; low platelets; and/or prolonged prothrombin time. In children younger than 5 years of age, splenic aspiration should be performed only by a fully experienced physician. Aspiration of lymph nodes has provided diagnosis in patients with kala azar and significant lymphadenopathy. Aspirated or homogenized biopsy material should be cultured for up to 4 weeks on specialized media (NNN or other medium).

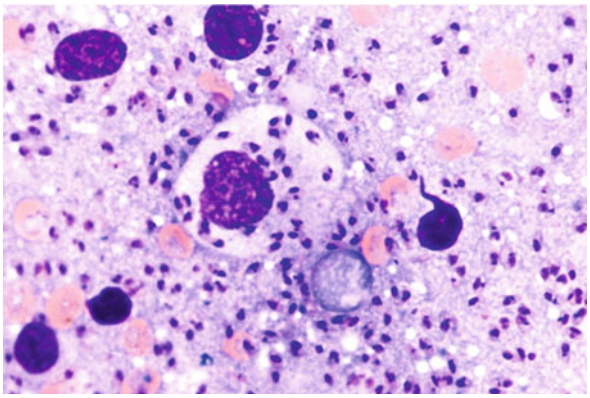

Figure 100.3
Stained spleen aspirate smear showing *Leishmania donovani* amastigotes

Several serological tests have been developed for the diagnosis of visceral leishmaniasis. These include antibody-detection tests, such as complement fixation (CF), indirect fluorescent antibody test (IFAT), indirect hemagglutination (IHA), enzyme-linked immunosorbent assay (ELISA) tests, direct agglutination test (DAT), and an immunochromatographic test (rK39-ICT). These last two tests are specifically adapted for field use. The DAT is a semiquantitative test using freeze-dried stained *Leishmania* promastigotes to detect and quantify specific anti-*Leishmania* antibodies in serially diluted sera of suspected individuals. Results are obtained after 18 h incubation, and positive reactions are visible with the naked eye. Sensitivity and specificity of the DAT were estimated about 95% and 97%, respectively. A rapid diagnostic test in format of dipstick or ICT using a recombinant *Leishmania* antigen (rK39) showed excellent sensitivity 93.9% and specificity 95.3% in several studies. rK39-ICT is proven to have a crucial importance for early diagnosis of visceral leishmaniasis cases in remote areas of endemic countries.

The leishmanin skin test (LST) or Montenegro test, like the tuberculin test, measures delayed type hypersensitivity (DTH) to leishmanial antigen, an important feature of cutaneous forms of leishmaniasis. The test is performed by injecting a suspension of killed promastigotes intradermally. A positive result is a palpable area of induration of at least 5 mm in diameter in 48–72 h. Particularly, the

delayed-type hypersensitivity to leishmanial antigens is associated with cutaneous, mucocutaneous, post-kala-azar dermal and cured visceral forms of the disease. The diagnosis of cutaneous leishmaniasis is best achieved by skin biopsy from the raised edge of a lesion.

Molecular techniques, such as PCR, developed for diagnosis of leishmaniasis using different specimens, are more sensitive and accurate, but these assays remain restricted to equipped centers and hospitals.

Treatment

Specific treatment of visceral leishmaniasis involves the use of chemotherapeutic agents. The pentavalent antimony compounds, sodium stibogluconate (Pentostam) and meglumine antimonate (Glucantime), have been the mainstays of antileishmanial therapy. The pediatric dose of Pentostam is 20 mg/kg/day intravenously or intramuscularly (maximum dose 800 mg). There is no unanimity of opinion as to how long it should be given. In most centers, 20 days appear sufficient. Pentamidine and amphotericin B, classical alternatives to antimonials, were relegated to second line because they were considered more likely to cause irreversible toxic effects, are now being resurrected particularly in antimony-resistant cases. Amphotericin B in a dose of 0.25 mg to 1 mg/kg by slow infusion daily or every 2 days for up to 8 weeks is proving effective in antimony-resistant cases. Commercial lipid formulations of amphotericin B are recommended for treatment of visceral leishmaniasis, but unfortunately, are too expensive for use in the countries where leishmaniasis is more prevalent.

Old World cutaneous leishmaniasis lesions are usually self-healing and confer immunity to people living in endemic areas. But, when complications or disfiguring scarring are expected, chemotherapy should be given. If there are only a small number of lesions, local infiltration of pentavalent antimonials can be employed. Cryotherapy and curettage can also be used in some cases of cutaneous leishmaniasis. Systemic treatment is recommended for cutaneous leishmaniasis cases with large and/or multiple lesions, with recidivans or disseminated cutaneous types, or with the risk of mucosal involvement.

Prognosis

Visceral leishmaniasis left untreated in childhood results in 75–85% mortality, but, properly treated at an early stage, 85–95% of cases can be cured. Patients with underlying malnutrition and acquired immunodeficiency syndrome and those who develop pancytopenia or bleeding diathesis or who fail to develop a delayed hypersensitivity skin reaction fare badly.

Prevention

Any meaningful prevention of *Leishmania* infection of humans will depend upon a detailed knowledge of the ecology of the reservoirs and vectors of the various forms of leishmaniasis. Transmission can be reduced by treating cases, decreasing human contact with vectors, destroying animal reservoirs, and eliminating the vectors. Insect repellents and insecticide-impregnated bednets can decrease exposure to sandflies. Travelers to endemic areas should be advised not to camp openly in close proximity farmland or naturally vegetated areas, which provide a habitat for rodents and thus an environment for the rodent–sandfly life cycle of the different forms of *Leishmania*. Sandflies are tiny (2–3 mm long) and their mobility is limited by wind speed. As wind speed increase with height, they do not fly high; they stay close to the ground. Thus, where situations permit, people should sleep in upper floors of their houses.

No chemoprophylactic agents are available. Although, Leishmanization, by intradermal inoculation of live virulent *L. major* promastigotes harvested from fresh culture has been practiced intermittently for many years in certain countries, such as the former Soviet Union, Israel, and Iran in large-scale vaccination trials. The procedure has its drawbacks. It may induce severe cutaneous lesions and should not be used under normal conditions, and in the case of American leishmaniasis, delayed sequelae such as mucocutaneous lesions are distinct deterrents for its use. The observation that curing an infection appears to impart protection against reinfection with homologous parasite species rekindled hope for the development of an effective safe vaccine in the future.

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101 Malaria

Shireesha Dhanireddy · John B. Lynch

Case

A 3-year-old child is brought into clinic with 3 days of headache, vomiting, and fever. On exam, he is coughing, tachypneic, and somnolent. Retinal exam shows retinal whitening and hemorrhages accompanied by papilledema (Fig. 101.1).

Initial laboratories return with a hemoglobin of 45 g/L a serum glucose of 2.0 mmol/L and a metabolic acidosis. As you evaluate the labs, the child has a seizure. As part of the work-up, a *Plasmodium falciparum* specific rapid diagnostic test is positive and antimalarial therapy with intravenous artesunate is started in addition to blood transfusion and treatment for hypoglycemia. Within 24 h of initiating therapy and careful monitoring of vital signs and serum glucose, the patient is awake and interactive. She goes on to make an uneventful recovery after completing a course of oral artemether-lumefantrine.

Introduction

For clinicians living and working in malaria endemic regions, the enormous scope of the problems associated with these infections is unfortunately all too well known. In a world with individuals and populations traveling across country lines and between continents in such large numbers, malaria also has the potential to affect children living in non-endemic areas, such as those emigrating from and traveling to endemic areas. Families traveling with children need to be aware of these risks and to know how to minimize them. Clinicians also need to be ready to recognize the symptoms and signs of malaria in any at-risk child. Malaria remains a major global threat that continues to preferentially injure and kill children and, as a result, the clinician must remain vigilant to this infection.

Epidemiology

Malaria continues to disproportionately affect the young, particularly those under 5 years of age. Of the estimated 1–2 million deaths each year due to malaria, greater than 80% are in children under 5 years, most of who live in sub-Saharan Africa. In the pediatric population, however, the effects of malaria extend well beyond mortality. Infection is associated with anemia, poor growth and development, intrauterine growth restriction, low birth weight, and school absenteeism, all of which have profound effects on child health. Taken as a whole, "at risk" African children on average have two to five episodes of malarial fever per year. Given this environment the United Nations Children's Fund (UNICEF) includes malaria prevention and control interventions as integral parts of the high-impact interventions to improve maternal and child survival.

As of 2010, there are five species that cause malaria in humans, all belonging to the genus plasmodium: *P. falciparum, P. ovale, P. vivax, P. malariae,* and *P. knowlesi. Plasmodium knowlesi*, which also infects macaques (*Macaca fascicularis)*, is the only zoonotic species known to infect humans, with the first published reports in 2004. Although *P. vivax* infections occur over a greater geographic area and affect a similar number of people, *P. falciparum* is responsible for the majority of deaths globally. It is important to recognize, however, that in many parts of the world, the attributable morbidity of *P. vivax* infections remains substantial.

The habitable parts of the planet can be separated into three general areas based on malaria risk due to the activity of the mosquito vector: little to no risk (e.g., Europe), unstable (seasonal) risk (e.g., South Africa and much of South America), and stable (year round) risk (e.g., The Gambia). The level of endemicity (variation in the level of the disease) is the result of a number of factors, including the level of specific immunity in the population, the presence of gametocytes in that population, and an environment suitable to anopheline mosquitoes (the vector). Endemicity is influenced by the *entomological inoculation rate* (EIR = mosquito biting rate × proportion of mosquitoes carrying sporozoites), which can range from <1 to $>1{,}000$ infectious bites per person per year. In high EIR areas, mortality is mainly clustered in children under a year old due to cerebral malaria, and adults with malaria in these areas are commonly found to be anemic. In low

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_101,

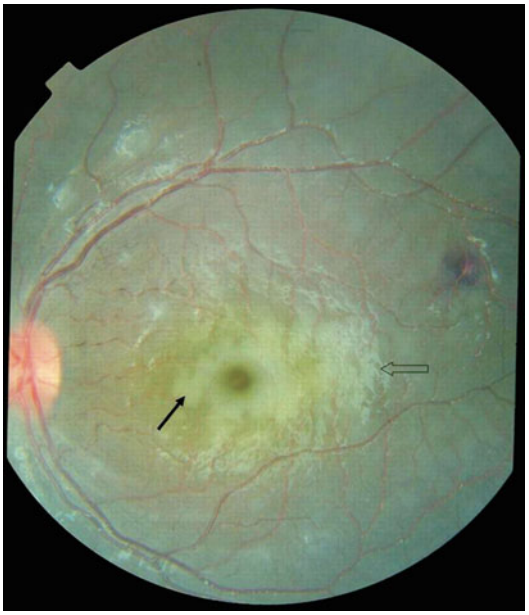

Figure 101.1
Retinal exam (Image from Beare, Tayler, Harding, Lewallen and Molyneaux, Trop Med Hygeine, 2006, p. 790)

EIR areas, the highest mortality rates are seen in children less than 5 years of age, again due to cerebral malaria.

Although *Anopheles* mosquito species are limited by temperature (18–29°C) and altitude (<6,000 ft above sea level), much of the rural and urban parts of the planet remain quite hospitable to these insects. As a result of this geography, between 3.3 and 5 billion individuals (over half the world's population) in ~100 countries are at risk of infection with *Plasmodium* species. Most (~70%) at-risk individuals live in areas of unstable transmission, where transmission intensity varies with the seasons and weather. As a result of this unstable transmission pattern, these populations do not develop the same level of acquired immunity as those living in highly endemic settings and tend to present with more severe disease, such as cerebral malaria. Similarly, individuals living in areas where malaria has been eliminated (both native born and migrant) have no immunity, putting them at high risk for progressive infection when exposed in endemic settings. These latter individuals without any immunity have benefited from programs that used a combination of approaches under the umbrella of the World Health Organization (WHO) Global Malaria Eradication Program (1955–1969) that successfully eliminated malaria from much of Europe and North America, notably in the absence of a vaccine. Due to increased awareness and new technologies, a similar, multifaceted approach to malaria elimination appears to be a realistic goal in over 20 of the more heavily affected countries of the world. Although the pursuit of an effective vaccine faces significant barriers due to the incredible complexity of the parasite's life cycle, a number of candidates are undergoing testing in humans, including one in phase III studies in African children.

The number of cases of malaria imported from endemic to non-endemic settings has risen dramatically over the last 30 years, with children accounting for 15–20% of all cases, although this may be an underestimate. In a 2009 study that reviewed cases of imported malaria in children between 1992 and 2002, over 17,000 cases were reported in 11 countries (predominantly France, UK, and USA). The children at highest risk were those returning to visit friends and relatives. Given the inappropriately high level of incorrect chemoprophylactic recommendations and issues with adherence, it is critical that children visiting endemic regions undergo appropriate pre-travel counseling and receive active chemoprophylaxis, with or without subsidies, in order to prevent infection.

Pathogenesis/Pathology

Anopheles mosquitoes serve as the only organism in which sexual reproduction occurs for the *Plasmodium* species that cause human disease. Humans act as "intermediaries" between mosquitoes in which a sexual reproduction of the parasites takes place as part of an amazingly complex life cycle (*Fig. 101.2*).

Following a mosquito blood meal, sporozoites are delivered from the salivary glands of the mosquito into the skin of the human, where they may remain for up to 2 h, postulated by some as the "skin stage" of infection. These sporozoites enter the blood stream, where they are rapidly cleared (<30 min) and circulate to the liver sinusoids where they infect hepatocytes (the pre- or exoerythrocytic cycle). In the liver cells, the sporozoites develop into liver stage schizonts containing haploid merozoites. Within 7–14 days, these merozoites are released in plumes from the infected liver cells back into the circulation where they can infect red blood cells (the erythrocytic stage of infection). Both *P. ovale* and *P. vivax* can also remain in quiescent hypnozoites in the liver, which can rupture and release merozoites months or years later, leading to relapses. The merozoites enter red blood cells by binding specific cell surface receptors, fusing with the cell membrane and vacuolization. Following red blood cell invasion, the parasites mature into trophozoites and undergo asexual reproduction to generate blood stage

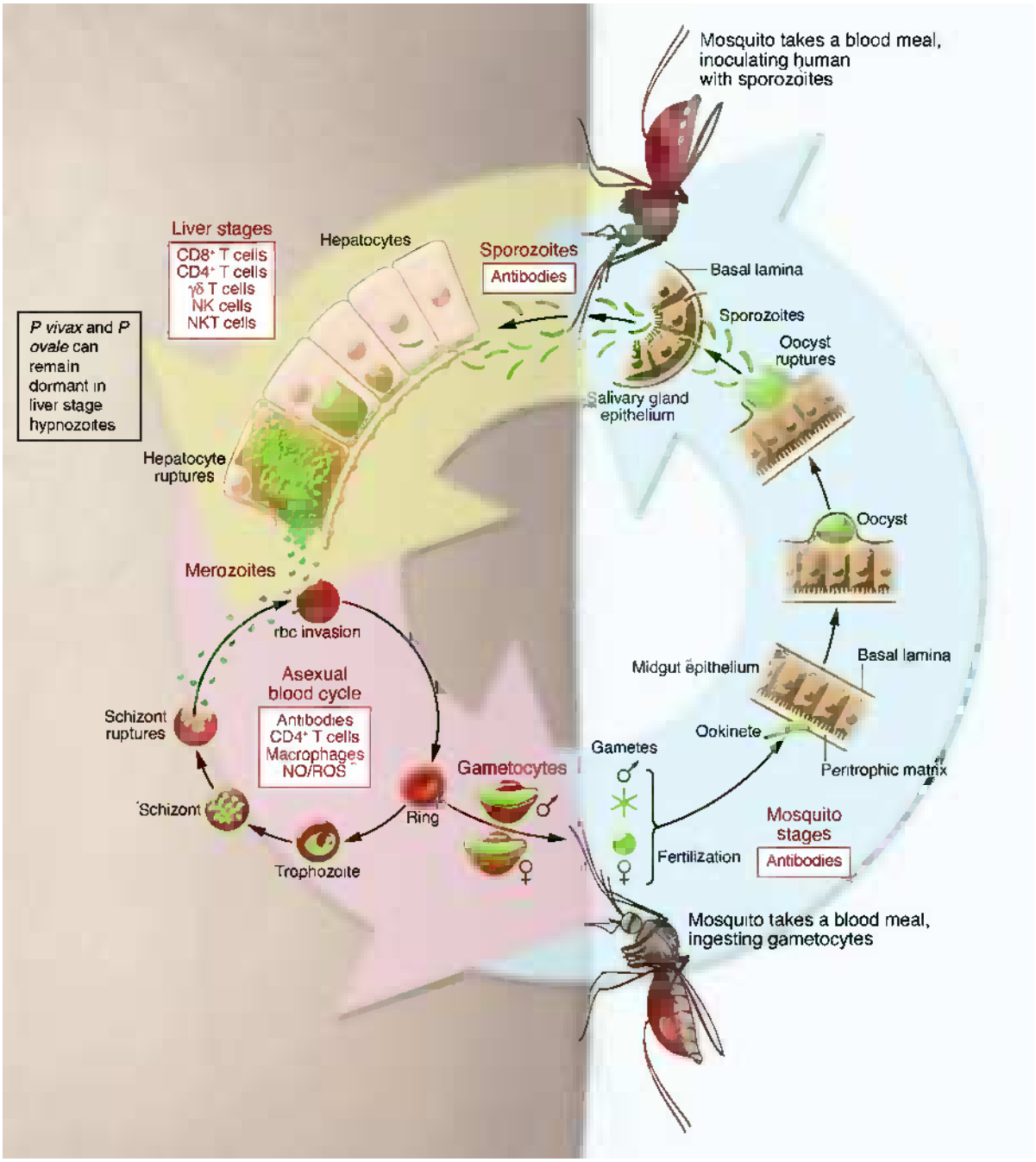

Figure 101.2
Life cycle. *Plasmodium* life cycle (Modified from Crompton PD, et al. (2010) J Clin Invest. (Modification is the addition of the box just to the left of "Hepatocyte ruptures")

schizonts followed by rupture of the red blood cell and release of blood stage merozoites. These merozoites are free to infect more red blood cells, creating more and more merozoites. With each cycle of asexual reproduction, the parasite burden increases, producing the classic recrudescent symptoms of malaria: fevers, chills, headache, nausea, and diaphoresis. The timing of the rupture of blood stage schizonts is the etiology of the various fever patterns

attributed to each species (subtertian, q36–48 h, *P. falciparum*; tertian, q48h, *P. ovale* and *P. vivax*; and quartan, q72h, *P. malariae*). Importantly, microscopy, the classic method of malaria diagnosis, detects only the erythrocytic (clinically active) stages of infection. Mixed infections are not uncommon, but what impact each species has on the other and how this changes the course of disease remains unclear.

Some blood stage merozoites develop into male or female gametocytes that are ready to be taken up by the next mosquito bite and undergo sexual reproduction (sporogenic cycle) in the gut to generate more sporozoites and complete the cycle.

The key pathophysiological feature of malaria is the effect that infection has on red blood cells. Once the merozoites enter the cells, they become adherent to the endothelial lining of the blood vessels and fixed in place. Given a sufficient density of infected cells, small vessels can become obstructed, leading to ischemia and destruction of the vessel itself. The signs and symptoms of infection are the result of the anatomical areas affected by the clogged vessel. As the blood stage schizonts mature and rupture the red blood cells, anemia results, and with advanced infection, hyponatremia and hypoglycemia. Infected cells are taken up by the reticuloendothelial system, leading to splenomegaly and hepatomegaly.

The severity of anemia is strongly influenced by the specific red cell stages targeted by the different *Plasmodium spp. P. falciparum* is able to enter erythrocytes of all stages, hence its ability to achieve the highest parasite densities (over 50%). *P. vivax* and *P. ovale* are only able to infect reticulocytes and so uncommonly can infect more than 2–5% of circulating erythrocytes. *P. malariae* infects senescent red cells and rarely exceeds a parasite count greater than 2%. This can lead to clinically latent infection and late (decades) manifestation of disease.

The coexistence of *Plasmodium* species and humans has led to a high degree of selective pressure on the human genome and, as a result, a spectrum of susceptibility and disease. A number of erythrocyte gene disorders offer some benefit to individuals, most often in the heterozygous state (e.g., alpha- and beta-thalassemia, elliptocytosis, G6PD deficiency), as well as the ability to generate potent, specific immune responses (e.g., HLA-B53, Fc-gamma receptors, and toll-like receptor 4).

While many factors influence the population prevalence of each of the five species of disease-causing *Plasmodium* species, the presence of a specific human Duffy blood group antigen gene (the Fy (a-b-) silent allele) in western and southern SSA populations appears to be a dominant factor, at least for *P. vivax*. This protein serves as the only red cell receptor for *P. vivax*, and in these populations there is very low to no expressed antigen on the surface of red blood cells, thus markedly limiting the spread of this species in that area. *P. ovale* is very similar to *P. vivax* in biology and microscopic appearance, but does not need the Duffy antigen. As a result, it is much more prevalent than *P. vivax* in Africa. Conversely, *P. vivax* is found throughout much of Asia and Latin America. *P. knowlesi*, a zoonosis also found in macaques, appears to be limited to Southeast Asia.

Clinical Manifestations

The clinical features of malaria vary depending on the endemicity (or EIR) in the geographic area as well as the species of malaria. Children less than 5 years of age are susceptible to more severe forms of disease and suffer a higher mortality rate, particularly in areas with low transmission rates. The incubation period, which is the time from infection with sporozoites to onset of symptoms, varies depending on species: 12 days for *P. falciparum*; 12–17 days for *P. vivax* and *P. ovale*; and 30 days for *P. malariae*.

A common feature of all types of malaria is paroxysms of fever, occurring every 48–72 h, which coincide with rupture of schizonts from the erythrocyte. In the early stages of the disease, pyrexial episodes may be somewhat irregular in occurrence, but later they tend to settle to the 48-h pattern of *P. vivax* infection or the 72-h pattern of *P. malariae* infection. Other characteristic features of malaria include headache, nausea, vomiting, abdominal pain, diarrhea, and myalgias. These paroxysms may be less apparent in young children. Children can also present with lethargy and decreased level of consciousness, organomegaly, and cytopenias.

In young nonimmune children, symptoms may consist of fever, listlessness, restlessness or drowsiness, vomiting, diarrhea with watery, dark green, mucous-containing stools, and seizures. In nonimmune older children, in addition to the above signs and symptoms, children may complain of headache, nausea, generalized aching, as well as abdominal pain as a result of splenomegaly.

In areas of stable malaria, infected children may die early as a result of overwhelming infection or may develop ill-defined subacute symptoms, possibly as a result of natural immunity. By 5 years of age, children in highly endemic regions have typically developed immunity to malaria that significantly modifies the clinical manifestations of the

disease. Heavy parasitemia may exist in children of school age without any symptoms. When symptoms do occur, they may be mild in severity, such as low-grade fevers, moderate degree of anemia, and hepatosplenomegaly.

Disease from *P. falciparum* is associated with higher degrees of parasitemia, as this species can infect all stages of erythrocytes, and is therefore associated with higher mortality, up to 30% in nonimmune infants. Disease caused by *P. vivax*, *P. ovale*, or *P. malariae* is typically less severe as these species generally result in <2% parasitemia. In addition, *P. vivax* and *P. ovale* can also result in recrudescence of symptoms months to even years later as they can remain as quiescent hypnozoites.

Human disease from *P. knowlesi* has only recently been described and mostly in adults in Southeast Asia. Most patients with disease from this species may present with a nonspecific febrile illness associated with thrombocytopenia, but approximately 10% can develop severe complications such as respiratory distress, renal failure, and hypotension. *P. knowlesi* has only a 24-h erythrocytic cycle, unlike the other known species to cause human disease which have longer cycles, which may explain the significant rates of severe disease that have been reported. Given that *P. knowlesi* appears nearly identical to *P. malariae* based on microscopic appearance, epidemiologic clues such as travel or residence in Southeast Asia, particularly near forested regions, are important in making the diagnosis.

Most of the severe complications of malaria result from infection with *P. falciparum*, given the potential for higher levels of parasitemia. Cerebral malaria is most common among children less than 5 years of age and can present with altered mental status, delirium, or even coma and carries a morality rate of up to 40%. Typically, children present with high fevers, seizures, and/or focal neurologic deficits. Cerebrospinal fluid analysis is generally unrevealing, but opening pressure is typically elevated. Despite the severe symptoms at presentation and high mortality, children who survive do not classically have residual neurologic deficits.

Hypoglycemia is another complication, which is associated with a poor prognosis in children with malaria, particularly in sub-Saharan Africa. Renal failure from malaria occurs as a result of several mechanisms, including decreased renal perfusion, acute tubular necrosis, hemoglobin deposition in tubules, or from antibody-mediated hemolysis. The latter results in a rare syndrome called blackwater fever, which is characterized by renal failure and severe hemolytic anemia. Other complications include thrombocytopenia, splenic rupture, pulmonary edema, and septic shock (algid malaria).

Diagnosis

The WHO recommends diagnostic testing of all cases of suspected malaria prior to treatment. This is a significant change from the prior recommendation to treat all febrile children in endemic areas for presumptive malaria. The new recommendations are in response to data from increased surveillance and testing, which revealed that other common causes of fever were not being diagnosed or treated.

The signs and symptoms of malaria in a child are nonspecific: fever, rigors, nausea, vomiting, headache, and listlessness, and as a result are not sufficient for diagnosis. A parasitological diagnosis should always be pursued if at all possible. In high resource, usually non-endemic, settings, the major barrier to diagnosis is considering malaria as a potential disease process. Once considered, however, testing for the presence of parasites should be pursued, often using a combination of technologies. For suspected cases, thick and thin blood smears should be sent in addition to blood cultures (to evaluate for other sources of fever), liver enzymes, complete blood count, blood urea nitrogen, and creatinine. Care must be given to not miss an alternative or concurrent infection, even when the clinical picture is consistent with malaria. This approach is also appropriate in low resource settings where the disease is seen much more commonly. Testing of suspect cases, preferably within 2 h of presentation, should be sought unless none are available. In the absence of a parasitological diagnosis, the clinician has to depend on the clinical exam and history, which, like all tests, depends on the prevalence of the test in the population. Where the risk of malaria is low, the diagnosis of malaria should meet stricter criteria (e.g., exposure, fever in last 3 days, signs of advanced illness, no other obvious disease processes such as rhinorrhea or measles). In higher prevalence settings, fever within the last 24 h and supporting findings, such as anemia or stiff neck, support the clinical diagnosis and indicate initiation of treatment. The WHO/UNICEF provides a guided approach to assist the Integrated Management of Childhood Illness (IMCI), a guide for the assessment and treatment of children 5 years of age and younger (http://www.who.int/child_adolescent_health/documents/IMCI_chartbooklet/en/index.html). It is critical to remember that other diseases, including other infections, can present in a manner similar to malaria in children. Continued testing and treatment for other disease are appropriate in the absence of a laboratory diagnosis. In non-endemic settings the diagnosis of malaria in children either emigrating from an endemic

area or returning from travel to such an area are likely underestimated. The infection might be missed on microscopy due to any number of issues, but most commonly is missed due to failure to consider the diagnosis.

Microscopy remains the gold standard for the diagnosis of malaria, but requires training and quality control (http://www.searo.who.int/LinkFiles/Malaria_malaria_microscopy_Learners_guide2010.pdf). Definitive diagnosis relies upon the *identification of the parasite on stained blood films.* For diagnosis, both thick and thin films of the blood should be prepared using a Romanovsky-type stain (most commonly Giemsa), with initially negative samples repeated every 12–24 h for a total of three samples, looking for parasite forms within erythrocytes. The concentrated, thick film allows for greater sensitivity, even with fairly low parasite density. Thin films are more useful for species identification and quantification. The percentage of infected red blood cells on a thin film can be used as a marker of illness severity and can contribute to species identification (e.g., *P. falciparum* is the only species able to infect up to 50% of erythrocytes). Alternatives to microscopy include molecular assays, serology, and immunochromatography. The utility of microscopy also has the potential to be improved with adjunctive techniques, such as the addition of fluorescent agents.

Given the challenges to the diagnosis of malaria, the use of rapid diagnostic tests (RDTs) is replacing microscopy, even in areas where the latter is available. The WHO currently lists over 40 different RDTs on its procurement list, with many undergoing large-scale testing of efficacy and effectiveness. These tests are antigen detection assays that use specific monoclonal antibodies to bind histidine-rich protein 2 (HRP-2, specific to *P. falciparum*), parasite lactate dehydrogenase (LDH, depending on antibody used can detect *P. falciparum* or mixed infections), or aldolase (used to determine non-*P. falciparum* infection versus mixed infection) in blood. LDH is only found with active infection, whereas HRP-2 can be found for weeks after effective treatment. This latter fact increases the false positivity rate. Whether to use an RDT or microscopy depends on many factors, including cost, availability of electricity, and technical support. RDTs are often more expensive, but offer the ability to test affected children in a much wider set of circumstances. With rapidly developing and spreading drug resistance, testing at the point of care has the potential to both improve treatment for the individual and prevent the increase of drug resistance in the community. Ultimately, the availability of microscopy or RDTs is usually made at a country or district level.

Molecular methods, including PCR and NAAT, are commonly used for a number of pathogens, but require high-level laboratory capabilities. Newer molecular assays, such as loop-mediated isothermal amplification (LAMP), exist that do not require temperature changes to amplify genes, overcoming a significant hurdle to use in very limited resource settings. Serological assays continue to have problems with cross-reactivity and can remain persistently positive long after primary infection. They remain useful for surveillance, but not necessarily for diagnosis of an acute infection.

Treatment

The primary goal of treatment of malaria is to avoid mortality. In the case of uncomplicated malaria, the goal is cure to prevent disease progression, whereas in severe malaria, the main goal is to maintain life. The widespread emergence of resistance, to all classes of antimalarials, has made treatment challenging. Another challenge in the pediatric population is the limited data about safety and proper dosing, particularly in children aged <12 months.

The WHO released new treatment guidelines in 2010 (*Table 101.1*), in response to increasing resistance and availability of newer drugs. The new strategy for treatment involves combination therapy with two or more antimalarials with different mechanisms of action to effectively treat malaria by overcoming resistance possibly present as well as preventing the development of resistance.

The approach to treatment of malaria is based on the severity of disease as well as suspected species. For uncomplicated malaria due to confirmed or suspected *P. falciparum*, which typically manifests as a febrile illness without organ dysfunction or hemodynamic instability, artemisinin-based combination therapy (ACT) is preferred. The benefits of ACTs include rapid clearance of parasitemia, leading to faster resolution of system, as well as reduction of gametocyte carriage, which can lead to decreased malaria transmission. Several ACT options are available, including artemether plus lumefantrine (pediatric formulation available), artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin plus piperaquine. Unfortunately, sufficient data about safety and dosing are lacking for any of the ACT options for children less than 5 kg.

Dosing is ideally based on body surface area but can also be weight-based. Given the lack of pediatric formulations readily available for most medications, adult tablets are often divided, which can lead to inaccurate dosing. For children unable to take oral medications due to nausea, the WHO does recommend a single dose of rectal

Table 101.1
WHO malaria treatment recommendations

Uncomplicated *P. falciparum* or species unknown malaria		
Preferred/first line	**Alternative options**	**Not recommended for use**
Artemether + lumefantrine (pediatric formulation available) OR Artesunate + amodiaquine OR Artesunate + mefloquine OR Artesunate + sulfadoxine-pyrimethamine OR Dihydroartemisinin + piperaquine	If child cannot take po and medical facility >6 h away, rectal artesunate (10 mg/kg) can be given Artesunate + (doxycyline or tetracycline or clindamycin) – should be reserved for treatment failures and only in the hospital setting	Tetracyclines should be avoided throughout infancy and in children <8 years of age Sulfadoxine-pyrimethamine should be avoided in first 2 weeks of life
Uncomplicated *P. vivax* or *P. ovale* malaria		
Chloroquine 10 mg/kg po, followed by 5 mg/kg at 6 h, 24 h, and 48 h (total dose 25 mg/kg) + primaquine 0.5 mg/kg po qday x 14 days *In areas of chloroquine-resistant P vivax* DHA-PPQ + primaquine		In patients with mild-to-moderate G6PD deficiency, primaquine dose should be reduced to 0.75 mg/kg once a week for 8 weeks. Primaquine should be avoided in patients with severe G6PD deficiency and in children < 4 years of age.
Uncomplicated *P. malariae* or *P. knowlesi* malaria		
Chloroquine 10 mg/kg po, followed by 5 mg/kg at 6 h, 24 h, and 48 h (total dose 25 mg/kg)		
Severe *P. falciparum* malaria		
Preferred/first line	**Alternative options**	**Comments**
Artesunate 2.4 mg/kg IV or IM on admission, then at 12h and 24h, then once a day OR Quinine 20 mg salt/kg IV infusion or divided IM infection on admission, then 10 mg/kg q8h	If child cannot take po and medical facility > 6 h away, rectal artesunate (10 mg/kg) can be given Artemether 3.2 mg/kg IM on admission, then 1.5 mg/kg qday (absorption is variable)	Parenteral therapy should be continued for at least 24 h and then consider changing to oral ACT regimen when clinically improved and able to take po

artesunate until the child can present to a medical facility for further care and appropriate treatment.

Treatment with ACTs has been shown to be generally well tolerated but severe nausea has been reported in children treated with mefloquine. Sulfadoxine-pyrimethamine can lead to neonatal hyperbilirubinemia and should be avoided for the first few weeks of life. Primaquine should also be avoided in the first month of life as well as in children with G6PD deficiency. Tetracyclines should be avoided by all children under 8 years of age due to its effects on bone development.

Treatment of uncomplicated *P. vivax* and *P. ovale* malaria is generally with chloroquine as these species remain susceptible to this drug in most areas of the world. In certain areas where chloroquine-resistant *P. vivax* exists, such as Indonesia, treatment with ACTs such as dihydroartemisinin plus piperaquine is recommended. Effective treatment of these species also requires treatment of the liver forms to prevent relapse of disease known as radical cure. Primaquine is the drug of choice for radical cure, but its use is limited to children greater than 4 years of age due to risk of hemolysis. Also,

primaquine is contraindicated in children with severe G6PD deficiency, and dose adjusted is recommended in children with mild to moderate G6PD deficiency.

The mainstay for the treatment of severe malaria had been quinine therapy, which is derived from the bark of the Cinchona tree. However, the availability of artemisinin-based therapies has changed the treatment paradigm for severe malaria. A systematic review of 12 trials comparing artemisinin derivatives and quinine in children with severe malaria found no difference in mortality or long-term morbidity. More recently, a large open-label, randomized trial of artesunate versus quinine in African children with severe malaria demonstrated that artesunate led to a significant reduction in mortality compared to standard quinine therapy. Artesunate was also shown to be well tolerated without serious adverse effects. These data were not available when the latest WHO guidelines were published. Unfortunately, parenteral artesunate is not readily available in many countries at this time. Treatment with parenteral chloroquine or sulfadoxine-pyrimethamine is no longer recommended due to significant resistance worldwide.

The effect of nutritional status on antimalarial absorption, distribution, metabolism, and elimination has been evaluated in mostly small studies, and studies are ongoing to determine the extent of this effect. In general, dose adjustment for protein-calorie malnutrition is not recommended.

In addition to antimalarial therapy, patients with severe malaria need intensive supportive care of symptoms and potential complications. Treatment with antipyretics for fever, glucose infusions for hypoglycemia, transfusions for anemia, and hemodialysis for renal failure may be necessary. In addition, children with altered mental status and seizures require airway management and anticonvulsant therapy.

Prevention

No single control strategy is sufficient to prevent malaria infection from occurring in individuals or populations. Conversely, combination approaches to prevention can have profound impacts on individual child and population morbidity and mortality.

Malaria remains a disease that disproportionally affects the poor, and poverty acts as a barrier to treatment and prevention. Most travelers do not avail themselves of appropriate malaria risk–reduction measures. This is especially true for children of immigrants returning to endemic areas to visit friends and family.

Tried and true basic advice continues to hold true. Children should wear loose clothing with long sleeves and pants. Exposed skin can be treated with N,N-diethyl-meta-toluamide (DEET) in concentrations not exceeding 35%. The choice of chemoprophylaxis should be a considered one made with a specialist in this area if possible. A growing number of drugs are available, tolerable and safe for use in the pediatric population. (*Table 101.2*)

Insecticide-treated bed nets (ITNs) and long-lasting insecticidal nets (LLINs) are a proven method of preventing childhood malaria and can last for between 6 months (ITNs) and 5 years (LLINs) depending on the handling and type of net. The materials used for these nets are usually impregnated with pyrethroids such as permethrin or deltamethrin, commonly used insecticides. Unfortunately, a growing number of *Anopheles* species are now resistant to this chemical. Nets also have been shown to act in a manner analogous to the herd immunity provided by vaccinations. When coverage with bed nets is high enough in a community (greater than 80%), even those without nets appear to benefit from some level of protection. In Eritrea, there was a significant drop in malaria cases following the distribution of free ITNs. For families and children traveling to at-risk regions, impregnated nets can be purchased before departing and used during the entire trip, especially if sleeping in non-air-conditioned spaces.

Indoor residual spraying (IRS) of insecticide is, according to WHO recommendations, the most effective method of quickly reducing mosquito density. Once applied, preferably to at least 80% of the premises, the residual spray appears to be effective for between 3 and 12 months depending on the chemical used. The only caveat is increasing resistance to the commonly used insecticides, such as DDT and the pyrethroids, especially in Africa.

There are two methods of intermittent preventative treatments (IPT) that affect the pediatric populations: IPT prenatal (IPTp) and IPT infant (IPTi). IPTp provides at least two doses of the antimalarial drug sulphadoxine-pyrimethamine (SP) at each scheduled antenatal visit after the first trimester. This intervention substantially reduces the risk of anemia and low birth weight. IPTi is an inexpensive and cost-effective intervention, costing between USD $0.13–$0.23 per child, and appears to be effective in reducing anemia and clinically apparent malaria in young children. In a study carried out in four African countries over 9 years, IPTi reduced malaria cases in infants by 30% and reduced all-cause hospital mortality. IPTi with SP is recommended in areas of moderate to high levels of transmission and low to moderate levels of parasite resistance.

Table 101.2
Prevention

Mediation	Restrictions	Common doses	Advantages	Disadvantages/ side effects	Resistance	Affected phase of the *plasmodium* life cycle
Chloroquine	All ages, all weights	5 mg/kg PO once per week, start 1–2 week prior to arrival and continue for 4 weeks after departing from endemic area	Inexpensive, weekly dosing	Resistance is common	Common	Erythrocytic
Doxycycline	>7 years, all weights	2 mg/kg PO daily (max 100 mg PO daily, starting 1–2 days before arrival and continuing for 4 weeks after departing endemic area)	Inexpensive	Age restriction, nausea, sun sensitivity, daily dosing		Erythrocytic
Atovaquone/ Proguanil	>10 kg	11–20 kg – 62.5 mg/25 mg PO daily 21–30 kg – 125 mg/50 PO daily 31–40 kg – 187.5 mg/75 mg PO daily >40 kg 250 mg/100 mg PO daily Start 1–2 days prior to arrival and continue for 7 days after departing	Shortest length of therapy, pediatric tablets available	Expensive, daily dosing		Exoerythrocytic, not including hypnozoites
Mefloquine	>3 months, >4 kg Seizure disorders Cardiac arrhythmias Psychiatric history	>3 months, 5–45 kg- 5 mg/kg PO once per week >45 kg – 250 mg PO once per week, start 1–2 weeks prior to arrival and for 4 weeks after departing	Weekly dosing	More nausea in children, neuropsychiatric effects	Border areas shared by Thailand, Myanmar and Cambodia	Erythrocytic
Primaquine	Normal G6PD status Rarely used, but best drug for prophylaxis in areas with predominantly *P vivax*	0.6 mg/kg PO daily × 14 days concurrent or following chloroquine treatment to prevent relapse	Inexpensive, prevents late relapses with *P ovale* and *P vivax* Daily dosing	Requires G6PD testing, daily dosing		Exoerythrocytic, including hypnozoites

An effective vaccine in the near future remains a possibility. Although correlates of immunity remain unknown, clinical immunity that improves with exposure time (age) appears to be commonplace and effective (unlike HIV). In vivo studies dating back to the 1960s documented high-level sterilizing protection (>90%) afforded by vaccination by irradiated sporozoites, indicating a role for the immune response prior to the clinically latent stage. Unfortunately, this method of vaccination has proven to be a technological barrier thus far, leading to an emphasis on vaccines that focus on other, later stages of infection. Currently, a large number of candidate vaccines

are currently being tested in humans (www.who.int/index.html) including one in phase III study in African children. Some level of protection can be achieved by passive transfer of hyperimmune immunoglobulin, implicating a role for antibodies in protection. There is likely a role for the innate immune system in early infection and T cells in clearance, but these responses have yet to be characterized. It is likely that any vaccine that goes into use will do so with an incomplete understanding of the immunology of malaria-host response.

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102 Nocardiosis

Rana AlMaghrabi · Ibrahim Bin-Hussain

Introduction

Nocardia, also called as nocardiosis, is a bacterial infection which tends to strike the lungs, brain, and skin, particularly in people with an impaired immune system. Majority of the cases of nocardiosis involves lung infection, brain abscess, or disseminated disease from nocardia. The cases are localized to the skin and cause cellulitis or skin infection.

The most common symptoms with the pulmonary form of nocardiosis are fever, cough, and chest pain. The symptoms of brain nocardiosis are usually headache, lethargy, confusion, seizures, and sudden onset of neurologic problems.

Epidemiology

Nocardia species have been identified in house dust, garden soil, beach sand, and swimming pools. Pathogenic species usually arise from direct inoculation of the skin or by inhalation. Underlying pulmonary dysfunction with decreased bronchobiliary clearance mechanisms is predisposed to colonization. This is the most common nocardial infection reported from tropical regions of southern United States.

Incidence estimates vary in immunocompromised populations. In patients who undergo renal transplant, the incidence rate is 0.20%. In patients who undergo bone marrow transplant the incidence rate is 0.3% and that is marginally associated with increased mortality among long-term survivors of allergenic marrow transplantation. In patients with systemic lupus erythematosus, the incidence rate is 2.8%. Nocardiosis is an uncommon cause of morbidity in heart-lung transplant recipients.

The risk factors for nocardial infection in transplanted patients show that high-dose steroids, CMV disease, and high levels of calcineurin inhibitors are independent risk factors. Nocardia infections in patients with CGD are not usually fatal if treated properly, and prophylaxis with IFN-y and sulfonamide may protect against dissemination.

Pathogenesis

Inhalation of *Nocardia* spp. can lead to primary pulmonary disease. Disseminated infection occurs via haematogenous spread from respiratory tract, especially immunocompromised hosts. Primary cutaneous infections usually result from trauma with soil contamination of the wound keratitis, either posttraumatic or associated with lens use. Patients with deficient host defenses are at high risk of invasive nocardiosis. Chronic lung disease and alcoholism are additional risk factors for pulmonary nocardiosis.

Clinical Manifestations

Pulmonary Manifestations

The most common clinical manifestation of nocardiosis is pulmonary disease occurring in more than two-thirds of the cases. Almost 90% of cases are caused by members of the *N. asteroides* complex. Pulmonary infection can present through cough or dyspnea as a well as nonspecific symptoms such as anorexia and weight loss. Chest radiographic findings are variable which include bronchopneumonia, alveolar infiltrates, interstitial reticular infiltrates, and abscesses. Complications such as empyema, mediastinitis, and pericarditis can occur following contagious spread from lung, pleural, or cutaneous focus.

Superficial Infection and Mycetoma

Skin manifestation includes cellulites. Subcutaneous abscesses and mycetoma (a glaucomatous mass associated with nodules, sinuses, and granules) can occur from days to months after inoculation and typically located distally on the limbs.

Disseminated Disease

CNS involvement was recognized in more than 44% of the cases, the hallmark of CNS nocardiosis is formation of

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parenchymal abscess that can occur in any region of the brain. The disease frequently progresses over months to years and causes a broad range of neurologic deficits. The most commonly involved sites, other than pulmonary, CNS, and cutaneous, are bone, heart, eye, kidneys, joints, spleen, and liver.

Laboratory Diagnosis

A definitive diagnosis of nocardiosis requires the isolation and identification of the organism from a clinical specimen. Direct smear from the specimens typically show gram-positive, beaded fine right-angled branching filaments that are usually acid fast. Nocardia species will grow on most nonselective media; growth of *Nocardia* species may take 48 h to several weeks. It appears as either buff or pigmented, waxy cerebriform colonies.

PCR provides a more accurate and rapid molecular identification of *Nocardia* species than conventional methods. Clinical laboratory performance of susceptibility testing on *Nocardia* spp. has been standardized and micro-broth dilution methods are used.

Treatment

Sulfonamide is the treatment of choice for nocardiosis since the 1940s in conjunction with appropriate surgical drainage or excision of empyema or large abscesses. The efficacy of sulfonamides and TMP-SMX is maximal against *N. brasiliensis*, *N. nova*, and *N. transvalensis*, variable against *N. farcinica*, but poor against *N. otitidiscaviarum*. Combination therapy, with a carbapenem or third-generation cephalosporin with or without amikacin, is usually recommended for severely ill patients or for those with CNS involvement.

Minocycline has excellent activity in vitro against many strains and is considered a reliable alternative to the sulfonamide in adults. Amikacin and imipenem, followed by cefotaxime and ceftriaxone, are the most active parental agents against the largest percentage of nocardia isolates, although *N. farcinica* and *N. transvalences* are usually resistant to imipenem and the cephalosporins. Meropenem has been shown to be more active than imipenem in vitro against *N. otitidiscaviarum* and *N. brasiliensis*.

Amoxicillin-clavulanate is active against most strains of Nocardia with the exception of *N. nova*, *N. otitidiscaviarum*, and *N. transvalensis*, which are resistant to the medication. Linezolid appears to be an effective alternative for the treatment of nocardiosis.

Because there are no optimal recommendations for all nocardia and the increasing in vitro sulfa resistance is associated with worsening the patient's outcomes, physicians should use empirical combination therapy until susceptibility results are available.

Duration of therapy for nocardial infection depends on the site of infection and the immune status of the host. For primary cutaneous nocardiosis, a course of 6–12 weeks of sulfonamide therapy is appropriate. For individuals with isolated pulmonary disease, 6–12 months of therapy is preferred. Brain abscesses or meningitis require longer therapy with a duration of at least 12 months in most cases.

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103 Schistosomiasis

Elizabeth M. Keating · Andrea P. Summer · Philip R. Fischer

Definition/Classification

Schistosomiasis is a chronic disease caused by parasites of the genus *Schistosoma*. More than 207 million individuals are infected with it worldwide, while 700 million are at risk of infection due to exposure from agricultural, domestic, and recreational activities. Symptomatology is variable and ranges from subclinical infection to severe disease with potentially fatal portal hypertension, urinary tract involvement, renal failure, and bladder cancer.

Hygiene and play habits make children especially susceptible to infection, so in endemic areas initial infection occurs most often during childhood. Schistosomiasis usually peaks in the teen years and most of the morbidity occurs in adults. However, symptomatic disease does develop in millions of children.

Etiology and Epidemiology

There is historical evidence of schistosomiasis occurrence as early as 2000 BCE. In fact, schistosoma eggs have been found in mummies from the 20th dynasty in ancient Egypt and ancient China. The etiology of schistosomiasis in humans was first discovered in 1851 by Theodore Bilharz who identified the parasitic cause of endemic hematuria to be *Schistosoma haematobium*. Consequently, clinical human disease caused by schistosomes was initially referred to as bilharziasis. During the same time period, the association between acute infection with schistosoma parasites and Katayama fever was recognized in Japan.

In the first decades of the twentieth century, the complete life cycle of the schistosoma parasite was identified. Until the development of effective curative medication in the 1970s, schistosomiasis was considered to be the "most dreadful of the remaining plagues of Egypt." Efforts to control this disease continue and eradication measures are still in the early stages of implementation.

Schistosomiasis is caused by helminths of the class Trematoda. Unlike other human flukes, schistosomes can invade through the skin and live in the vascular system. Additionally, they have separate male and female sexes. Humans are definitive hosts for five different species within the *Schistosoma* genus: *Schistosoma haematobium, Schistosoma japonicum, Schistosoma mansoni, Schistosoma mekongi, and Schistosoma intercalatum*. All of these species infect the intestinal vasculature except *S. haematobium,* which is the cause of urinary schistosomiasis. *S. japonicum* and *S. mansoni* have a global distribution, while *Schistosoma mekongi* and *Schistosoma intercalatum* are more restricted geographically. There are also avian species of schistosomes, but these are not able to penetrate fully through the human skin and thus cause a non-definitive pruritic rash, more commonly known as swimmer's itch.

Each of the aforementioned species uses freshwater snails as obligate intermediate hosts. The geographic distribution of each species is limited by the habitat of the snails. *S. japonicum* lives in *Oncomelania* snails, which inhabit moist soil along slow-flowing streams and irrigation canals limited to parts of China, the Philippines, and Indonesia. For its host, *S. haematobium* uses *Bulinus* snails that live in shaded, slow-flowing, shallow water primarily in tropical Africa, along the Nile River, and in the Middle East. The *Bulinus* snail is also a host to *S. intercalatum*, which occurs only in Cameroon and the Democratic Republic of the Congo. *S. mansoni,* on the other hand, inhabits *Biomphalaria* snails that live in shaded, slow-flowing, shallow water across tropical Africa, along the Atlantic Coast of South America, and on some Caribbean islands. The *Tricula* snail is the host for *S. mekongi*, and is limited to the Mekong River in Laos and Cambodia. In the United States, infection is seen only in immigrants and travelers from endemic regions. There is no transmission within the United States.

Most schistosomiasis infections in humans originate during childhood, when children come into direct contact with freshwater streams, rivers, or lakes that house infected snails. This contact occurs during everyday activities such as bathing, fishing, irrigating fields, or obtaining water for household use. Exposure to freshwater sources that harbor the parasite is greatest in boys aged 5–10 years. However, infection is seen in children of all ages and has been observed in infants as young as 6 months. In some African villages along Lake Victoria (shown to have heavy

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parasite loads), nearly half the children are infected with schistosomiasis within the first 7 years of life. The peak intensity of infection, which is measured by counting egg excretion, occurs in children as young as 8–12 years of age in heavily infected areas and in the teenage years in lightly infected areas. Males are more often infected because of their increased recreational exposure to water. After the adolescent years the incidence and intensity of egg excretion decreases, possibly due to hormonal changes during puberty that are associated with increased resistance to infection.

Pathogenesis and Pathology

Upon contact, the fork-tailed schistosomal cercariae penetrate the skin using secreted serine proteases (Fig. 103.1). Once they have penetrated, the cercariae lose their tails and modify their tegument to form the schistosomula stage. The schistosomulae then enter the bloodstream and travel to the lungs, where they exit the pulmonary arterial system and enter the venous circulation. From here, the schistosomulae travel through the systemic system until they reach the splanchnic vessels and gain access to the portal system.

Over a period of a few weeks, the parasites live in the portal system maturing and developing into male and female adults that mate persistently. Adult schistosoma worms can be from 1 to 3 cm long, and live for 3–7 years. As mentioned above, the Schistosoma species differ in the locations of the body that they infect. *S. haematobium* infects the venules of the urinary bladder, while *S. japonicum* and *S. mansoni* infect the mesenteric vessels (*S. japonicum* superior and *S. mansoni* inferior). Thus, the pregnant mature female parasites migrate up the bloodstream to lay eggs near either the bladder or the

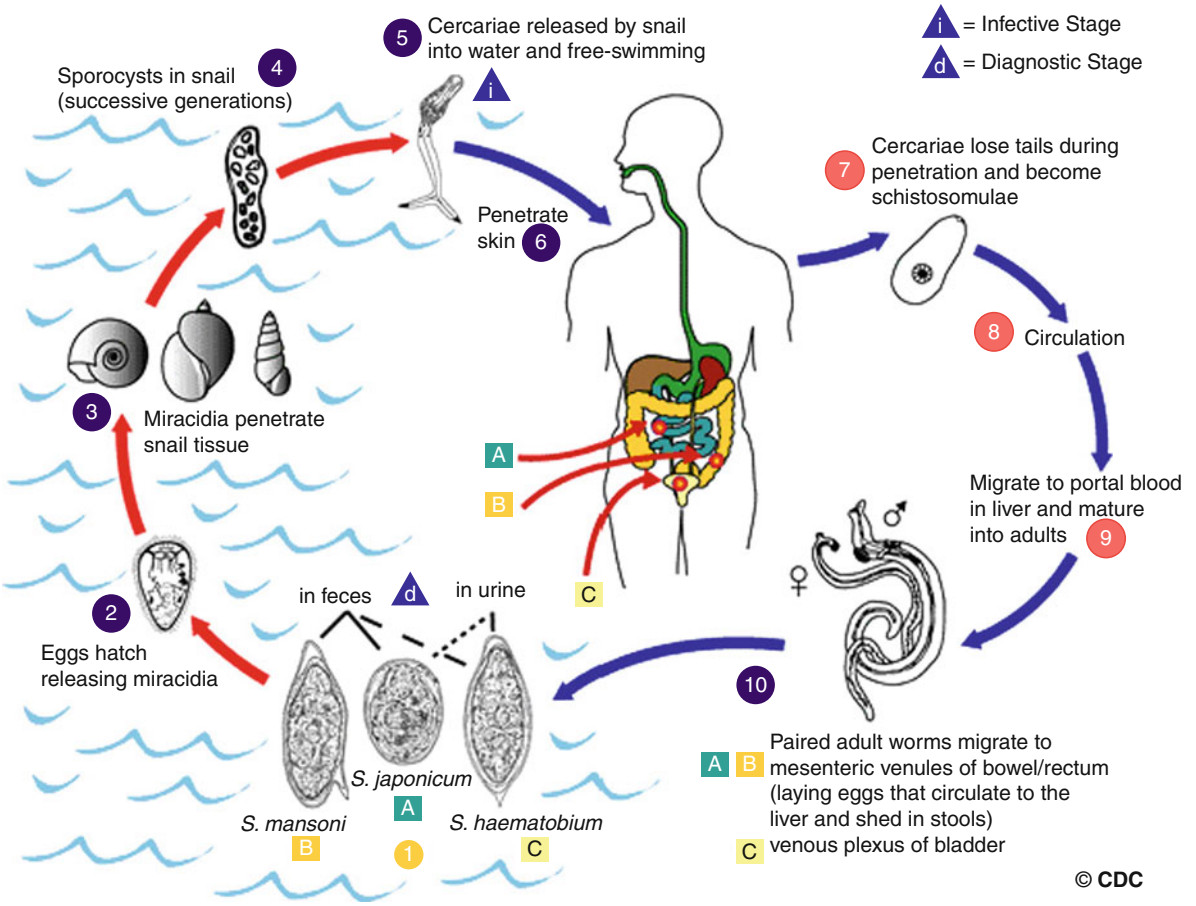

Figure 103.1
Life cycle of *Schistosoma* parasites

intestines, depending on the species. These females can lay up to hundreds of thousands of eggs per day.

Once they are laid, the parasitic eggs become embedded in the vessel walls causing reaction and disease. Additionally, some eggs can flow down the bloodstream and cause reactions at other sites. A localized granulomatous response allows the eggs to travel through the wall of the bladder (with *S. haematobium*) or the intestine (other *Schistosoma* species) and be released into the urine or stool. A week after being laid, the eggs mature and hatch, releasing miracidia. When released into freshwater sources, the miracidia are then able to reinfect their host snails to begin their life cycle once again. In the snails, they mature into hundreds of cercariae that can affect humans, and the cycle continues.

Initial Reaction

Within hours of penetration of the skin by the Schistosoma parasite, local erythema and inflammation may result from activation of parasite proteases. These papules are caused by infiltration of the dermis or epidermis with mononuclear cells and eosinophils, and is commonly referred to as swimmer's itch. Most often, swimmer's itch is associated with avian schistosomes, which are unable to penetrate fully through human skin into the circulation and consequently die in human tissue. If the person infected has been previously sensitized to the parasite, a delayed immune reaction can cause papular or vesicular lesions on the skin that may last for 7–10 days.

When the schistosomula initially infect the lungs from the bloodstream, they may migrate through unnoticed. If the person is heavily infected, fever, pneumonitis, pulmonary infiltrates, and eosinophilia may develop. However, these symptoms most often resolve with no intervention.

Acute Schistosomiasis (Katayama Fever)

Four to eight weeks after exposure, acute schistosomiasis may occur as the female parasites begin to produce eggs. This condition resembles serum sickness and is more often associated with *S. japonicum* infection than with *S. mansoni*, and rarely with *S. haematobium*. During acute schistosomiasis, patients have marked eosinophilia and immune complex deposition. This leads to the clinical manifestations of fever, myalgia, urticarial rash, and bloody diarrhea, which is commonly called Katayama fever. Severity of these clinical manifestations is determined by cercarial burden and the host immune response to parasite antigens. Pulmonary nodules and infiltrates may also be noted. In addition, acute infection can be complicated by ectopic egg production, and patients with acute *S. mansoni* or *S. haematobium* infection occasionally can have neurologic involvement. Interestingly, acute disease rarely occurs in endemic populations, possibly because the immune response is desensitized to parasite antigens from exposure in utero. In nonimmune travelers, on the other hand, acute disease is more common, with studies estimating rates of 39–100%.

Chronic Schistosomiasis

Chronic schistosomiasis is possible due to the evasion tactics of adult worms living in the bloodstream, which enable them to cause little host response. Their parasite surface incorporates blood group glycoproteins and downregulates expression of its own surface proteins, which may help them evade immune system attack. Chronic infection is caused by localized granulomata surrounding the parasite eggs. The granulomata form in order to protect the host from the injury caused by the egg antigens, which are cytotoxic to host cells. The granulomata also facilitate transfer of eggs into the stool and urine.

The two principal disease patterns observed in chronic schistosomiasis are gastrointestinal and urinary due to the egg-laying preferences of schistosome species. Other chronic manifestations may occur because of embolic egg deposition or heavy worm burdens.

When the egg count is high enough, eggs may stay in the venous vasculature and migrate back to the liver. Once here, granulomata form around the eggs and the liver becomes congested. This can eventually lead to hepatosplenic disease and portal hypertension.

In children with advanced hepatosplenic schistosomiasis and portal hypertension, eggs can bypass the liver and flow from the abdominal and pelvic veins in the small lung vessels. Localized granulomata form around the eggs lodged in the lungs, and after time children can develop fatigue, cough, and right-sided heart failure, cor pulmonale. Although medical therapy will stop the progression of cor pulmonale and decrease the ongoing inflammatory responses, right-heart failure is not fully reversible once it is established.

Urinary Schistosomiasis

Genital and urinary schistosomiasis is also the result of granuloma formation. Granulomata can form in the

ureters and bladder wall, blocking ureteral emptying and thus causing abnormal ureteral flow, dilatation, and hydronephrosis. Eventually, scarring and calcifications form and can be associated with chronic hydronephrosis, even with cured or light chronic infection. This chronic hydronephrosis and urinary stasis often predisposes patients to chronic bacteriuria and urinary tract infections. Other common complications in *S. haematobium* infection are glomerulonephritis from immune complex depositions in the patients' glomeruli, nephrotic syndrome, and amyloid deposition in the kidneys.

Squamous cell carcinoma of the bladder, although normally rare, is a common occurrence in areas of heavy infection with *S. haematobium*. It is thought that the prolonged irritation of the bladder epithelium by schistosome eggs and the resulting immune response triggers hyperplasia in the bladder and subsequent malignant disease.

Schistosomiasis in the Central Nervous System

The involvement of the central nervous system in schistosomiasis results in neurologic manifestations that are rare, yet often dramatic. Schistosomiasis worms do not always follow the usual routes described for urinary and intestinal schistosomiasis. Sometimes, worms migrate instead to the cerebral blood vessels and produce eggs there. This production can lead to seizures and headaches in children. On occasion, localized space-occupying inflammatory reactions that develop around the worms or eggs seem to result in optical field defects and dysarthria. Due to the space-occupying lesions, spinal fluid pressure may be elevated, and protein concentrations and lymphocyte counts in spinal fluid may both be increased. Cerebral schistosomiasis occurs more commonly with *S. japonicum* infection and is thought to develop in as many as 2% of children infected with this parasite.

S. mansoni infection and, even rarer, *S. haematobium* infection can produce eggs that embolize to the spinal cord. The eggs or associated granulomata can then cause transverse myelitis. Initially, paraplegia along with urinary and fecal incontinence are common problems in children with spinal schistosomiasis infection.

Clinical Manifestations

The main clinical manifestations of schistosomiasis vary greatly both with the stage of the life cycle and the species of parasite. Many patients are asymptomatic and can be identified during community screening programs in endemic areas, in immigrant or returned traveler evaluations in nonendemic areas, or when diagnostic tests such as urine or stool analysis are done to analyze other seemingly unrelated symptoms. Only a minority of children with heavy infections are likely to develop early symptoms, and these children are at greatest risk for major health complications.

Pruritus

After cercarial penetration through the skin, some children develop pruritus, or swimmer's itch. This response is more common in nonimmune travelers than in those indigenous residents of endemic areas. Additionally, the response is more pronounced upon repeated exposures. Pruritus occurs after contact with any human Schistosoma species, but more commonly results after contact with avian schistosomes. The rash that develops is erythematous and sometime papular, and usually disappears during a period of 2–10 days without scarring whether or not treatment is given.

Acute Schistosomiasis (Katayama Fever)

Acute schistosomiasis, on the other hand, is a more serious infection. It is sometimes referred to as Katayama fever, and begins 4–8 weeks after exposure upon egg production by the female worms. Clinical manifestations of acute schistosomiasis are high fever, chills, myalgia, headache, and general ill appearance. Additionally, urticarial rash and diffuse lymphadenopathy may be seen. In the lungs, cough, rales, and pulmonary infiltrates may be noticed, even without fever. Further, gastrointestinal symptoms of anorexia, abdominal pain, and loose stools may sometimes be noted. With heavy infections of *S. japonicum* and *S. mansoni,* which both infect the intestinal vasculature, bloody diarrhea can be seen acutely. In approximately 30% of children with Katayama fever, hepatomegaly and mild splenomegaly develop. A number of reports suggest that myelopathies are also a common partner to schistosomiasis. Genital symptoms and marked eosinophilia are also often seen with acute schistosomiasis.

Urinary Schistosomiasis

The classic finding of *S. haematobium* infection is painless hematuria. In fact, in some highly endemic areas, it is

considered abnormal for boys nearing puberty to *not* display this sign of "male menstruation." In urinary schistosomiasis, the hematuria results from the release of blood from irritated and inflamed areas about the granulomata in the bladder wall as the bladder contracts during micturition. Thus, there is typically "terminal hematuria," in which blood is most obvious at the end of the urine stream when bladder contraction is greatest. Although the hematuria is painless, it is sometimes accompanied by dysuria. In children who are either not treated or reinfected, chronic infection can develop and lead to obstructive uropathy. In fact, in community surveys completed in endemic areas, 40% of children were found to have significant renal or uretal abnormalities (often both). Hematuria and dysuria are found more often in children than adults, possibly due to the higher parasite loads in children. However, hydronephrosis is seen more often in adults, likely due to its chronic development.

Another complication that can develop as a result of urinary schistosomiasis is bacterial urinary tract infection. This complication is most likely secondary to urinary obstruction. The bacteriuria is sometimes caused by unusual urinary pathogens including Salmonella, which has been shown to cause recurrent Salmonella bacteremia. Chronic urinary infection can also lead to eventual renal failure. Additionally, obstructive uropathy can lead to a loss of renal function whether or not urinary tract infections are involved. Children with schistosomiasis can also have glomerulonephritis and nephrotic syndrome, and bladder cancer can occur in the context of untreated, heavy chronic urinary schistosomiasis.

Genital Schistosomiasis

Many studies have also identified the genital tract as an important site of schistosomiasis infection in both males and females. In women, granulomata can form around eggs in the cervix, uterus, or fallopian tubes. These granulomata can cause irritation, ulceration, vaginal bleeding, infertility, or ectopic pregnancy. Often, genital schistosomiasis is confused with cancer. In males, the prostate and seminal vesicles can become involved, especially in adolescent boys. Eggs were noted in the semen from 43% of men in an area endemic for *S. haematobium*. The main clinical finding of genital schistosomiasis is haematospermia, which may occur with either acute or chronic disease. In Africa, genital schistosomiasis may be an important cofactor in transmission of human immunodeficiency virus infection.

Intestinal Schistosomiasis

Most children with intestinal schistosomiasis do not present with intestinal symptoms. Thus, even finding eggs in the stool does not mean that symptoms are necessarily from a schistosomiasis infection. However, in some instances schistosomiasis can involve both the small and large intestines. Irritation of the bowel wall from inflammatory reactions induced by the eggs may cause diarrhea that can contain blood or mucus. Bowel wall granulomas can serve as the lead point for intussusceptions. Anorectal disease including abscesses and fistulas has also been described. Further, crampy abdominal pain and generalized malaise may occur. When endoscopy is performed, it can show granular inflammation with hyperemic areas, ulceration, hemorrhage, or polyps. Polyps can develop around the granulomata and can also be identified by contrast radiography. Protein-losing enteropathy and blood loss can cause malnutrition and iron deficiency, especially in cases with significant coexisting bowel disease. The role of schistosomiasis in malnutrition was illustrated by studies of mass chemotherapy, which resulted in improved nutrition and a lower prevalence of anemia.

Hepatosplenic Manifestations

Hepatosplenic disease can be caused by *S. japonicum* and *S. mansoni*, and can result in life-threatening complications. These complications are the result of eggs that stay in the venous vasculature and migrate back to the liver. The greatest predictor of hepatic involvement seems to be the total egg count, but some link with HLA type has been suggested.

Children with hepatosplenic disease that is compensated initially may show few symptoms, which may include anorexia, malaise, and abdominal fullness. These children exhibit hepatosplenomegaly even without significant portal hypertension. The enlarged liver is firm with fine nodules and either minimally tender or nontender. Splenic enlargement may be seen and can be massive. Liver function is affected only late in the course of hepatic schistosomiasis, so jaundice and liver enzyme elevations are unusual. As fibrosis develops over time around the eggs in the liver, portal hypertension occurs. Ascites develops slowly over a number of years, and the spleen may become very large. In the beginning stages of the disease, liver function usually remains sufficient. During the late adolescent and early adult years, however, worsening esophageal varices can cause death. Thus, bleeding

esophageal varices are a common cause of death in patients who had heavy schistosomiasis infections during childhood. Such individuals may come to medical attention due to the related symptoms of melena or hematemesis. Initial episodes are most often not serious, but with progressive liver decompensation variceal bleeding can be fatal. Additionally, children with severe hepatosplenic schistosomiasis often do not grow as well as other children.

Larval Pneumonitis

Occasionally, children have initial low-grade fever and cough as the schistosome larvae migrate through their lungs. This can occur with either an initial heavy infection, in which eggs will not yet be detectable, or in a heavy reinfection, when eggs will be detectable in urine or stool from the previous infection. This larval pneumonitis can be noted on lung examination as basilar rales and wheezing. Radiographic images may show basilar mottling in the lung fields. This condition usually resolves in 2–4 weeks, even without treatment. Similar symptoms also may be seen as a reactive pneumonitis when treatment of patients with heavy parasite burdens occurs.

Salmonellosis Coinfection

In endemic areas, some children have both salmonellosis and schistosomiasis at the same time. These children present with chronic low-grade fever, fatigue, malaise, and poor growth. Blood cultures frequently demonstrate *Salmonella* bacteremia, but stool does not always contain these bacteria. Some children have chronic *Salmonella* bacteriuria, yet despite the persistent bacterial infections are seldom affected with sepsis and mortality. Relapse of the *Salmonella* infection occurs commonly unless the coexisting schistosomiasis is treated. Bacteria apparently hide within the parasitic worms, evading host defenses since antibiotic penetration is poor within the worms.

Diagnosis

A clinical diagnosis of schistosomiasis should be given in the presence of the typical clinical findings and features. These features might be obvious, as with a painless hematuria in a child in a region endemic for *S. haematobium*, or less so, as with portal hypertension noted late in the second decade of life in an otherwise healthy adolescent from an area endemic for *S. mansoni* or *S. japonicum*. The other clinical findings described should also prompt the clinician to consider a diagnosis of schistosomiasis when the child has resided in or traveled through a *Schistosoma*-endemic area. In traveling children, the level of suspicion should be particularly high because patients may be asymptomatic or have atypical symptoms, they may not have a clear history of exposure to contaminated water, and parasitologic examination findings are often negative.

Reinfection is not typical outside endemic areas. Thus, a reasonable approach would be to test all children, including asymptomatic children, who have returned or emigrated from an endemic area where they had potential exposure to fresh water. This testing would involve all travelers who sat in, waded in, or even touched suspicious water, and it could involve immigrants who have spent time in endemic areas. Definitely, any child outside an endemic area who has even remote history of having had possible contact with cercariae along with clinical findings suggestive of any form of schistosomiasis should be tested. Testing is appropriate even at a later stage because even late therapy can have benefit to the course and outcome of schistosomiasis. In some highly endemic areas, diagnostic testing has limited feasibility or questionable reliability – or both – and curative medications are readily available. In these cases, establishing a proven diagnosis might not be completely necessary. For example, in a highly endemic setting, a simple urine paper strip test result positive for hematuria could provide sufficient suspicion of infection to justify administration of specific antischistosomal therapy. In populations with known high rates of infection, mass treatment without expensive diagnostic testing is reasonable and efficient.

In non-acute heavy infections, eggs can usually be found easily on microscopic examination of urine or stool. Urine samples collected between 10 am and 2 pm are more likely to be positive because this is when peak excretion of schistosome eggs tends to occur. For lighter infections, urine concentrating techniques may be necessary and useful. To do this, urine can be centrifuged and filtered to increase the yield of eggs. The result of a urine examination is most likely to be positive when urine is collected at midday and at the end of the urine stream. When infection is suspected and urine findings are negative, a bladder wall biopsy can be performed. The procedure is usually not necessary, however, because urine microscopy is usually positive, especially with concentrated or filtered samples. Additionally, in the instance of negative urine findings, multiple samples can be collected and examined to increase the egg yield.

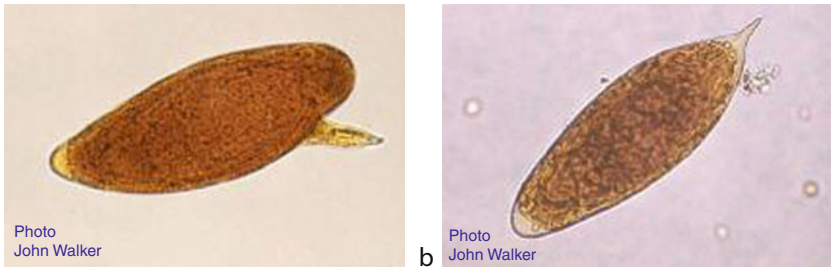

Figure 103.2
Eggs of *Schistosoma mansoni* and *S. haematobium*

Determination of the species of infection can be done by examining the yielded eggs microscopically. The eggs of *S. haematobium* and *S. mansoni* are approximately 90 mm in diameter, while the eggs of *S. japonicum* and *S. mekongi* are slightly smaller. As demonstrated in *Fig. 103.2*, identification of the specific species can be done by examining the spine, which is small for *S. japonicum* and *S. mekongi*, on only one end for *S. haematobium*, lateral for *S. mansoni*, and broad at each end for *S. intercalatum*. Additionally, plain radiographs of the bladder may show some calcification in the bladder wall around chronic granulomata. If cystoscopy is performed, it can reveal bladder wall hyperemia and consequent nodular lesions and fibrosis that give rise to "sandy patches" on the bladder wall. Granulomata can protrude from the bladder wall into the lumen and, along with edema, can cause obstruction of uretal orifices.

In light or acute infections, examination of urine or stool samples may not show eggs due to intermittent or low-volume shedding. Thus, negative stool or urine test results do not necessarily rule out schistosomiasis. When stools are repeatedly negative for ova, a rectal biopsy may be done. This can be performed by random punch biopsy, but the yield is increased when samples are taken from inflamed sites under direct visualization. Eggs are detected most often in unstained smears made by placing the tissue sample between a glass slide and a coverslip, but eggs can also be seen with standard histologic stains.

After successful treatment, nonviable eggs can be excreted for months or even years. With good medical treatment, eggs usually are inviable within a week of initiating therapy. However, with ineffective treatment or re-infection, viable eggs may continue to be passed. On microscopic examination, living ova contain transparent miracidia within the egg, which are often motile. To further prove their viability, the eggs may be hatched by placing them in freshwater exposed to light for 20 min. Afterward, observation with a hand lens can reveal swimming miracidia.

Since acute infections may occur before eggs are excreted or with eggs in ectopic locations, serologic tests may be needed for diagnosis since they are more sensitive and specific. For travelers with limited exposure and the likelihood of having either an acute or a limited chronic infection, serology is the principle diagnostic tool, even if it does not provide information about worm burden or clinical status. Delaying serology in asymptomatic but exposed individuals until 3 months after the exposures seems to be ideal to prevent pre-seroconversion false negative findings. Currently, the most common screening serologic test is the FAST-ELISA (the Falcon assay screening test-enzyme-linked immunosorbent assay) using *S. mansoni* adult worm microsomal antigen. It also cross-reacts with *S. haematobium* but is less sensitive for *S. japonicum* or *S. mekongi* infection. Species can be confirmed by the use of an immunoblot assay (enzyme-linked immunotransfer blot). This technique is also available for S. japonicum. Antigen-detection assays may be helpful, but they are not available in the United States.

A potential future option for diagnosis that, like serologic tests, does not rely on high egg yields is in vivo imaging using positron emission tomography (PET). This technique has been performed in mice and utilizes the *S. mansoni* species' high metabolic demand for glucose by measuring uptake of radiolabeled glucose with PET. Although still in the development states, in vivo imaging with PET based on animal data has been predicted to possibly better assess disease burden, improve the management of schistosomiasis, and enhance study of the parasite's biology.

The main imaging technique used in schistosomiasis is ultrasonography. This is because it is able to document involvement of the portal and urinary tracts and, in certain cases, can be diagnostic of schistosomiasis. Ultrasonography can identify bladder polyps, ureteral dilatation, hydronephrosis, and calcifications within the urinary tract. When possible, any child found to be infected with

S. haematobium should have an ultrasound evaluation of the urinary tract done. For older adolescents with persistent urinary symptoms such as dysuria, suprapubic pain, or hematuria despite having received good medical treatment, a cystoscopy could be considered to screen for bladder cancer. Other radiographs and tests of renal function and excretion are usually not performed unless the ultrasound evaluation shows significant urologic disease.

With hepatic involvement, portal ultrasonography is the imaging study of choice. The presence of periportal fibrosis with thickening of the portal tracts and vein walls correlates with parasite burden and hepatic disease. Experienced clinicians are able to distinguish schistosomiasis from cirrhosis and other chronic liver diseases.

Differential Diagnosis

Pruritis

When considering the pruritic rash that occurs upon schistosomal cercariae penetration, it is important to consider penetration by avian trematode cercariae, visceral leishmaniasis (kala-azar), and visceral larva migrans (toxocariasis and other common forms of dermatitis).

Acute Schistosomiasis

The differential diagnosis for acute schistosomiasis includes amebiasis, bacterial dysentery caused by Shigella or Salmonella, viral hepatitis, typhoid fever, malaria, fever of undetermined origin, or visceral larva migrans (toxocariasis).

Chronic Schistosomiasis

Chronic schistosomiasis, on the other hand, can present like visceral leishmaniasis (kala-azar), lymphoma, amebiasis, portal hypertension due to cirrhosis or portal vein thrombosis, tuberculosis, or trichinellosis infection. Additionally, chronic schistosomiasis can sometimes hide infection with *S. typhi* and is unrecognized until investigation is undertaken for recurrent typhoid fever.

Urinary Schistosomiasis

Schistosomiasis with urinary tract involvement presents with hematuria, which could also be due to a urinary tract infection, nephritis, or renal cell carcinoma.

Genital Schistosomiasis

Some types of genital schistosomiasis, such as *S. haematobium,* cause genital itch and vaginal discharge also common in irritant and infectious vulvovaginitis and with sexually transmitted diseases.

Intestinal Schistosomiasis

Since schistosomiasis in the intestine can present with diarrhea and abdominal discomfort, there is a large number of possible differential diagnoses for these symptoms. They include irritable bowel syndrome, Celiac disease, lactose intolerance, inflammatory bowel disease, chronic infections such as Whipple's Disease, or other parasitic infections.

Hepatosplenic Manifestations

The hepatosplenomegaly manifestations of schistosomiasis could also be due to Gaucher's disease, liver abscesses, or chronic heart failure causing hepatosplenomegaly.

Treatment

The optimal treatment of schistosomiasis depends on the stage of the disease. For the early stage of cercarial dermatitis, no antiparasitic treatment is necessary; it resolves on its own. However, oral antihistamine agents can be given for severe itching. When the human schistosomes gain access to the bloodstream and cause schistosomiasis infection, medical therapy has been shown to be effective and well tolerated without significant complications. Thus, there is no good medical reason to allow schistosomiasis to go untreated. However, the cost of treatment is a limiting factor in resource-poor areas of the world. If they can be obtained, several different medications can be considered to cure schistosomiasis.

The most effective agent against each of the five human schistosome species is praziquantel, a broad-spectrum oral anthelmintic agent. Praziquantel is a mixture of stereoisomers of pyrazinoisoquinoline ring structures, and is thought to unmask parasite antigens with subsequent killing by the host immune response. However, patients with acquired immunodeficiency syndrome respond well to praziquantel, raising questions about other concurrent mechanisms of action.

Praziquantel is given as full curative treatment in divided doses on a single day. For infection with *S. haematobium, S. mansoni,* and *S. intercalatum*, the dose is 40 mg/kg in two divided doses given on the same day. For infections with *S. japonicum* or *S. mekongi*, the dose is 60 mg/kg in three divided doses given the same day. Heavily infected children can sometimes experience nausea, vomiting, and abdominal cramping with praziquantel treatment. Rare side effects such as headache, pruritus, bloody stools, and fever are brief and resolve 1–2 days after treatment initiation. Since praziquantel mainly kills mature adult worms, a second course is recommended for the treatment of acute infection. Praziquantel has been shown to be effective in more than 90% of treated children. Unfortunately, some studies suggest that resistance may be emerging. However, these studies were performed in areas where there is frequent reinfection and high parasite burden, so the poor response may be due to the fact that young worm forms are not as susceptible to praziquantel. On the other hand, studies from nonendemic areas continue to demonstrate superb efficacy. In addition to curing schistosome infection, treatment with praziquantel has been linked with improved growth and a reduction in anemia. In endemic areas with high rates of infection, school-based and community-based treatment strategies without confirmatory diagnostic testing are effective, yet expensive. Due to this, cost issues raise concerns for program sustainability.

Oxamniquine, a tetrahydroquinoline compound, is an alternative treatment effective only against *S. mansoni.* Like praziquantel, the mechanism of this agent is unknown. The effective dose varies with the geographic origin of the schistosomal infection, and some resistance has been reported. Current recommendations are that children treated with oxamniquine be given 40–60 mg/kg divided into two doses administered on 1 day or four doses given over 2 days. Treatment can result in mild side effects including nausea, headache, and fever. Seizures are a rare side effect of treatment with oxamniquine, so children with seizure disorders should not receive this medication. Cure rates of more than 90% have been reported with oxamniquine.

Another treatment option is metrifonate, an organophosphate compound that causes paralysis of the schistosome parasite. It has been shown to be 70–80% effective against *S. haematobium* when it is used at a dose of 10 mg/kg orally once every 2 weeks for a total of 6 weeks. It decreases the child's own plasma and erythrocyte cholinesterase activity, yet actual cholinergic symptoms seldom occur. This medication is less expensive than the other two options mentioned, but it generally is not used when praziquantel is available.

When treatment is given, there is clear improvement in the patient's disease burden. In fact, even established uropathy and portal hypertension are often reversible. Surgical procedures usually are only done in children with complications related to long-term infection, such as persistent portal hypertension. Propranolol prophylaxis and sclerotherapy or banding can reduce rebleeding from esophageal varices. In addition, some cases require surgical decompression of portal hypertension. One way to do this is by using a splenorenal shunt, but these are associated with high rates of hepatic encephalopathy. However, comparative studies suggest that as long as a clinician is experienced enough, esophagogastric devascularization with splenectomy is the procedure of choice.

In severely ill children with Katayama fever or severe larval pneumonitis, systemic steroids may be useful. They may also be helpful in cases with granulomata in the central nervous system. However, corticosteroids have not been proven effective treatments in other forms of the disease, and thus should be restricted to use in patient with systemic complications of acute schistosomiasis.

Prognosis

Early medical treatment is most often effective for children with schistosomiasis infection, even with advanced disease. Thus, children with schistosomiasis have an excellent chance for full recovery. Recent studies have shown cure rates for children treated for schistosomias infection ranging from 70% to 100%. The remaining children who were not cured often showed persistent infection. This persistent infection is likely due to reinfection since it is common in endemic areas. Factors that affect prognosis are severity of schistosomiasis disease and the presence of comorbidities, which are fortunately not as common in children.

Prevention

The first step to prevention is limiting the risk of initial cercarial penetration. This can be done by applying *N*, *N*-Diethyl-meta-toluamide (DEET) to the skin when it is available. However, it is not always available in endemic countries.

Additionally, prevention can include travelers and emigrants in endemic areas limiting exposure to infectious fresh water. While in an endemic area, these people should avoid swimming in freshwater streams and lakes. Additionally, the cercaria can be eliminated by chlorination

or by allowing water to settle for 24 h before using it to bathe or wash.

The use of effective medical therapy combined with improved urine and stool hygiene has the potential to eradicate schistosomiasis from endemic areas. Elimination of the snails that serve as intermediate hosts would also be effective, but implementation of such elimination programs has been unsuccessful to date. In the past, national control programs in China focusing on snail control, sanitation, and improved water supplies have led to sustained reductions in infection rates, even apart from the influence of chemotherapy. For specific endemic populations, health education can lead to significant beneficial changes in knowledge about the illness, water-exposure activities, and reinfection rates in school-age children. In recent years, control efforts have focused on mass chemotherapy, with particular emphasis on school-based therapy. Treatment programs in which the entire school-age population is treated, typically with praziquantel, have resulted in an overall improvement in the levels of nutrition and in reducing the prevalence of anemia. However, in areas where reinfection occurs often, the effects of mass treatment programs are of limited duration, and treatment must be repeated every 6 months to a year. Sustainability of national control programs and of favorable outcomes thus remains challenging in Africa.

Artemisinin derivatives can prevent development of infection and decrease the worm burden in those exposed to both *S. mansoni* and *S. japonicum*. They are less effective for chemotherapy than praziquantel, however, probably because antiparasitic activity is limited to the juvenile forms of the parasite. Further, the public health role of chemoprophylaxis in preventing infection has not been established.

Prevention of experimental schistosomiasis can be achieved via immunization of experimental animals with irradiated cercariae. Thus, development of a vaccine to prevent humans against schistosomiasis is theoretically possible. Several potentially protective antigens have been identified on schistosomes, and they are being used as targets for vaccine development. However, the associates of protective immunity in humans are not well defined. Currently, vaccines using combinations of antigens are being studied for *S. mansoni*. Early stage clinical trials have been performed for *S. haematobium* glutathione S-transferase-containing vaccines. Very recently, the genomes of *S. mansoni* and *S. japonicum* were published, taking the world a step closer to the identification of key protective molecules and the development and implementation of effective anti-schistosome vaccines. Indeed, numerous proteins that play a role in *S. japonicum* parasite development and pathogenesis have been identified as possible new drug targets or vaccine candidates. It is uncertain whether development of a vaccine to prevent schistosomiasis infection in humans is a real possibility, and it is unlikely that any vaccine will be ready for clinical use in the very near future.

The best options for schistosomiasis control are multifaceted, integrated control programs that incorporate praziquantel treatment with transmission reduction through additional control measures such as the use of molluscicides, environmental modification, health education, and improved sanitation. Continued various avenues of schistosomiasis research should include vaccine development and the search for alternative drugs to praziquantel, because resistance against the drug in the future cannot be ruled out. Even if only partially effective, anti-schistosome vaccines that are incorporated as part of an integrated control strategy will be needed to hasten efforts to eliminate a disease that has existed for thousands of years. This combined-approach model has the potential to improve the health of a billion of the world's poorest people and its effect cannot and should not be underestimated.

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104 Hemorrhagic Fevers Including Dengue Fever

Richard J. Whitley

Introduction

Viral hemorrhagic fevers (VHFs) refer to a group of illnesses that are caused by one of four distinct families of viruses. The phrase viral hemorrhagic fever descriptively defines the clinical findings in patients who suffer from these illnesses. Generally, the integrity of the vascular system is compromised, resulting in hemorrhage and, potentially, life-threatening disease. These agents are broadly distributed across the globe.

Etiology

Viral hemorrhagic fevers are caused by four families of viruses: arenaviruses, filoviruses, bunyaviruses, and flaviviruses. Each of these viruses is zoonotic, being totally dependent upon an animal reservoir or arthropod vector for replication. Rodents and arthropods are, for the most part, the main reservoirs for viruses that cause VHFs.

All members of these four viral families are RNA viruses that have a lipid envelope. Because they are zoonotic, these viruses are restricted to the host range. Each of these four families will be considered separately.

Arenaviruses

Old World arenaviruses including lassa virus, the cause of lassa fever, a disease that occurs in West Africa, and lymphocytic choriomeningitis virus, cause less severe infections than the major New World arenavirus hemorrhagic fevers. Argentine hemorrhagic fever is caused by junin virus, Bolivian hemorrhagic fever is the consequence of machupo virus, and Venezuelan hemorrhagic fever is the consequence of guanarito virus. The first arenavirus isolated was lymphocytic choriomeningitis virus in 1933. Of note, new arenaviruses are identified at regular intervals.

The virus particles are spherical with an average diameter of 110–130 nm. Their name is derived from Latin which means "sandy."

Epidemiology and Pathogenesis

Arenaviruses are maintained in nature in rodent hosts in which chronic viremia persists. Infection of humans is the consequence of inhalation or contact of virus with mucus membranes and abraded skin. All arenaviruses can be transmitted by an airborne route. Of these agents, Argentine hemorrhagic fever was the most common, accounting for a few hundred cases annually, until a vaccine was developed. Disease caused by the remainder of this family of viruses is sporadic.

Clinical Manifestations

Following an incubation period of 6–17 days, illness can range from a mild, acute febrile infection to severe, life-threatening illness associated with multiorgan dysfunction and a bleeding diathesis. With all infections, fever, myalgia, headache, abdominal pain, and bleeding, particularly of the conjunctiva, are all common.

Diagnosis of Arenavirus Infections

Currently the standard diagnostic approach is the detection of virus-specific antibodies directed against either IgM or IgG. In addition, polymerase chain reaction will detect evidence of viral RNA. Virus can be recovered from the blood and transmitted to uninfected individuals. Thus, tissues and body fluids obtained from patients suspected to have an arenavirus infection should only be evaluated in Biosafety Level IV conditions.

Treatment of Arenavirus Infections

Intravenous ribavirin has been reported to decrease mortality in patients with severe lassa fever. However, no data are available regarding its use in the treatment of other

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arenavirus hemorrhagic fever infections. The role of immune globulin in preventing hemorrhagic fevers of arenavirus etiology is unclear.

Other Considerations

Patients with suspect arenavirus infections should be managed in an isolation room with careful attention to infection control procedures. A negative pressure room is recommended for these individuals. For Argentine hemorrhagic fever, a vaccine is available in South America, but is not licensed in North America. Zoonotic control, particularly reduction of the rodent community, has contributed significantly to the reduction of Argentine hemorrhagic fever and Venezuelan hemorrhagic fever.

Bunyaviridae Hemorrhagic Fevers

Etiology

Three syndromes are associated with bunyavirus infections: hemorrhagic fever with renal syndrome (HFRS), Crimean-Congo hemorrhagic fever (CCHF), and Rift Valley fever (RVF). HFRS is caused by hantaviruses and includes Korean hemorrhagic fever, epidemic hemorrhagic fever, and nephropathia epidemica. Crimean-Congo hemorrhagic fever is caused by a tick-borne nairovirus, a member of the *Bunyaviridae* family. Rift Valley fever is attributed to phlebovirus.

Epidemiology and Pathogenesis

All of the viruses that cause viral hemorrhagic fevers are associated with arthropod vectors except hantaviruses, which are associated with exposure to infected rodents. Hemorrhagic fever with renal syndrome accounts for approximately 100,000 cases annually in Asia and throughout Eastern and Western Europe. The incubation period ranges from 7 to 42 days. The vector for HFRS is the aedes mosquito.

Crimean-Congo hemorrhagic fever occurs through much of sub-Saharan Africa, the Middle East, Western and Central Asia, and the Balkans. It is transmitted by *Hyalomma* ticks. The incubation period ranges from 2 to 10 days.

Rift Valley fever occurs throughout sub-Saharan Africa and has caused epidemics in the Middle East, particularly Egypt, Saudi Arabia, Yemen, and Kenya. The virus is arthropod-borne and is transmitted from livestock to humans by mosquitos. It can also be transmitted by aerosol. Again, the incubation period is 2–10 days.

Clinical Manifestations

All three of these diseases are severe febrile illnesses that are associated with shock and bleeding. Multiple organs are usually involved. Of these three syndromes, HFRS and CCHF are the most severe as both involve vascular instability and varying degrees of renal insufficiency, accompanied by bleeding and fever. Additional findings include headache, myalgia, and hypotension. HFRS is associated with oliguria and renal insufficiency. Rift Valley fever is usually self-limited.

Diagnosis

While CCHF and RVF viruses are readily culturable from tissue and body fluids, working with such materials requires Biosafety Level 4 laboratories. Alternatively, enzyme immunoassays will detect viral antigen in blood and other body fluids. In addition, serum IgM and IgG virus-specific antibodies develop with convalescence and can be a useful retrospective diagnostic test. On the other hand, infections caused by HFRS are associated with the rapid clearance of virus, requiring the use of serologic assays for confirmation.

Treatment

There are reports that HFRS can be successfully treated with ribavirin. However, supportive care for all of these clinical illnesses is required, usually requiring management at a tertiary care facility in an intensive care unit.

Filoviruses

Introduction

Among the filoviruses, only Marburg virus and Ebola virus have been found to infect humans. Four species of Ebola virus have been identified and named according to the area of isolation, namely, Ivory Coast, Sudan, Zaire,

and Reston. Of these four viruses, Ebola-Reston does not cause severe disease in humans. These viruses exhibit pleomorphism upon replication, as characterized by both long and short filaments.

Etiology

Marburg hemorrhagic fever is a rare hemorrhagic fever that affects both humans and nonhuman primates. This virus was first isolated in 1967 when outbreaks occurred simultaneously in laboratories in Marburg and Frankfurt, Germany and in Yugoslavia. The most recent severe outbreaks occurred in the Democratic Republic of Congo (1998–2000), accounting for 154 cases with a mortality of 83%. Subsequently, in 2004–2005, an additional outbreak occurred in Angola, accounting for 252 cases with 227 deaths. Since then, cases have been sporadic.

Ebola virus was first identified in the mid-1970s when two outbreaks occurred in the current Democratic Republic of Congo and southern Sudan. The mortality of both outbreaks was exceedingly high. Since the mid-1970s, Ebola virus has appeared sporadically in Africa; however, large epidemics have occurred in Zaire and Uganda.

In the twenty-first century there have been ten outbreaks of Ebola, six of which have been attributed to Ebola-Zaire and two to Ebola-Reston. For the former strain, mortality has consistently exceeded 75% while with the latter strain, mortality remains about 50%.

Epidemiology and Pathogenesis

Transmission of Marburg virus to humans is unknown. Nevertheless, individuals with Marburg hemorrhagic fever can transmit infection to other humans. Similarly, persons who have handled infected monkeys have become infected. The natural reservoir of Ebola virus remains unknown. Thus, the mechanism by which humans become infected is also unknown. Nevertheless, people exposed to infected individuals and their bodily fluids can become infected. There has been documented spread of Ebola virus within the health care setting.

The incubation for Marburg virus hemorrhagic fever is approximately 5–10 days and disease is marked by the sudden onset of fever, chills, headache, and myalgia. A maculopapular rash involving the trunk appears approximately 5 days into the course of illness. As the disease progresses, multiorgan dysfunction becomes apparent.

In contrast, Ebola infection has an incubation period that appears to be longer, ranging from 2 to 21 days. The onset of illness is abrupt and characterized by fever, headache, myalgia, and weakness. A bleeding diathesis may occur.

Diagnosis

Specific laboratory diagnostic tests for Ebola and Marburg viruses include virus-specific antigen capture enzyme-linked immunosorbent assays (ELISA), and polymerase chain reaction detection of viral RNA. The detection of both IgM and IgG antibodies has been useful for both infections.

Treatment

There is no treatment for either Marburg virus or Ebola virus infections. The standard of care is supportive management.

Dengue

Introduction

There are four closely related dengue viruses, identified as dengue-1, dengue-2, dengue-3, and dengue-4. These viruses are transmitted to humans by the bite of infected mosquitoes. The dengue virus is a member of the *flavivirus* family and is considered an arbovirus since transmission occurs through a mosquito vector. The arthropod vector for transmission of virus to humans is most frequently by *Aedes aegypti.*

Epidemiology and Pathogenesis

Dengue viruses are transmitted by either *Aedes aegypti* or *Aedes albopictus.* The incubation period is usually 4–7 days and disease persists for 3–10 days. Dengue is endemic in many parts of the world, particularly in tropical and subtropical regions, especially during the rainy season when mosquitoes are breeding.

Approximately 40% of the world's population resides in areas at risk for dengue transmission. Dengue is endemic in at least 100 countries, causing between fifty and one hundred million infections annually. Dengue hemorrhagic fever accounts for approximately 500,000 cases. The mortality of dengue in children is approximately 22,000 deaths globally. Recently, dengue has been

detected in the continental USA. This is not surprising since *Aedes aegypti* is detected in these areas of the USA.

Clinical Manifestations

Dengue fever is characterized by what has been described as "bone-crushing" pain, rash, ocular pain, joint pain and mucosal bleeding. As noted above, the duration of disease is approximately 5–7 days. As illness ebbs, the patient is more likely to develop a capillary leak syndrome with bleeding diathesis, accounting for the hemorrhagic nature of the disease.

Diagnosis

The utilization of EIA-specific antibodies or polymerase chain reaction can be used to detect evidence of dengue virus.

Of note, infection with one dengue virus does not provide protection against the other three dengue virus strains. In fact, with infection caused by an additional strain, illness is reported to be more severe.

Treatment

Treatment is supportive. There is no specific therapy for dengue virus hemorrhagic fever.

Avoiding exposure to mosquitoes or the use of mosquito repellents in dengue virus endemic areas is of importance. In addition, the use of mosquito nets decreases the risk of acquisition of infection.

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105 Hepatitis Viruses A Through G

Daniel P. Mallon

The Hepatitis viruses A, B, C, delta (D), E, and G comprise a group of viruses that infect humans and display hepatic tropism. Each virus has an individual disease profile ranging from asymptomatic, to self-resolving acute infection, to chronic infection and, in some cases, liver failure and death. The burden that viral hepatitis places on individuals and communities is great, and the worthwhile work of developing new therapies and prevention strategies to mitigate that burden is ongoing.

Hepatitis A

Definition/Classification

Hepatitis A virus is one of two primarily water-borne hepatitis viruses. It is a single-stranded ribonucleic acid (RNA), non-enveloped virus in the Picornaviridae family, which can withstand harsh extracorporeal environments. The hearty virus can withstand heat and common solvents, but is inactivated by autoclaving, UV radiation, chlorine, and concentrated formalin.

Pathogenesis

The virus is usually spread via a fecal–oral route through contaminated water and food. Once ingested, it infects and replicates in the oropharynx and small bowel epithelial cells. From here, the virus then enters the blood, resulting in transient viremia, before it infects the liver. There the virus elicits an inflammatory response that leads to hepatocellular necrosis. Occasionally, the virus is spread parenterally, owing to the transient viremia.

Epidemiology

Hepatitis A is ubiquitous around the world, but its prevalence varies widely, with seroprevalence of anti-HAV antibodies ranging from 15% to 100%. Low-income countries have the highest incidence and prevalence, whereas high-income countries and countries with better access to clean water have low prevalence. In addition to varying levels of endemicity throughout the world, Hepatitis A also commonly occurs in sporadic outbreaks.

In highly endemic areas, nearly all young children are exposed in early childhood and gain immunity, resulting in low rates of infection in older children and adults. In areas of low or intermediate endemicity, there is little immunity in older children and adults, except where vaccination programs are in place. For example, the virus is common in the United States, but yearly incidence has been declining steadily in the past 15 years, especially in Western states, Alaska Native and Native American populations, which were areas of intermediate endemicity in which routine vaccination was instituted. These populations, the incidence has fallen from over 25 cases/100,000 to about <5 cases/100,000, which matches the rest of the country.

Pathology

Histologic changes are consistent with acute inflammation of the liver parenchyma and include hepatocellular necrosis and regeneration, leukocyte invasion of the parenchyma and portal tracts, and proliferation of bile ducts and Kupffer cells. However, obtaining a biopsy is rarely indicated in the management of patients with Hepatitis A.

Clinical Manifestations

Clinical disease manifests in phases (*Fig. 105.1*). After exposure, the incubation period lasts 28 days on average. As with the other hepatitis virus disease courses, there is a prodromal phase that can include nausea, vomiting, malaise, abdominal pain, and fever. Many patients, especially young children in highly endemic areas, may be completely asymptomatic or have only the above nonspecific viral symptoms. About 10% of children under 6 years of age enter a 1–2 week icteric phase, during which they exhibit jaundice and often have tender hepatomegaly. Most patients then enter a convalescent phase during which their clinical symptoms and signs improve

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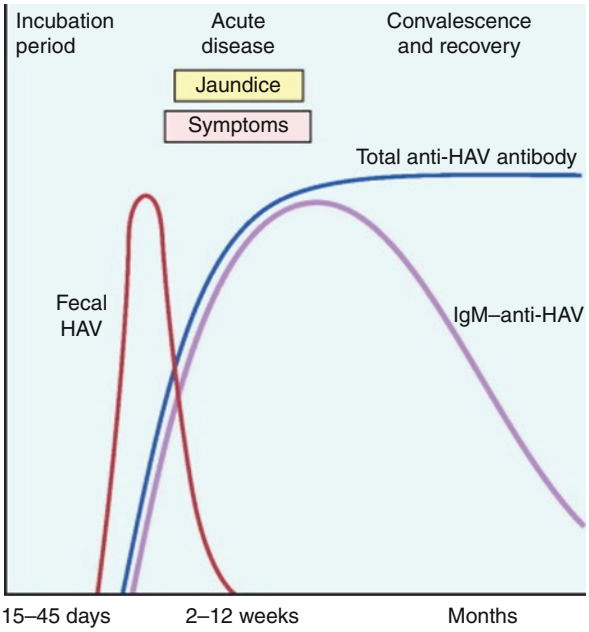

Figure 105.1
Serology and clinical manifestations of hepatitis A infection. *HAV* hepatitis A virus (Adapted from Crawford J, Liu C (2010) Liver and biliary tract. In: Kumar V et al (eds) Robbins and Cotran pathologic basis of disease, 8th edn. Saunders Elsevier, Philadelphia)

and resolve over 2–4 weeks. Occasionally, the acute signs and symptoms can abate and relapse over several weeks. Rarely (0.2% of icteric patients), they develop acute liver failure, and some progress to coma or death. The US mortality rate from Hepatitis A in children less than 14 years is 0.1%, while in adults it is 1.1%.

Diagnosis

Diagnosis begins with recognition of clinical signs of intestinal and hepatic disease and is aided by the measurement of markers of liver damage. Hepatic transaminases, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) become markedly elevated up to 10–100-fold as a result of hepatocellular damage. They peak 3–10 days after the onset of clinical symptoms and can remain abnormal for 2–4 weeks. Hyperbilirubinemia and bilirubinuria is also seen in patients who become icteric.

Anti-HAV antibodies confirm exposure to the virus, with anti-HAV IgM confirming recent infection in symptomatic patients and IgG confirming exposure in the more remote past. Anti-HAV IgG persists and confers lifelong protection. Testing a patient's stool for HAV virus in culture or genetic material is often of little use because the virus is so common.

Differential Diagnosis

The symptoms and signs of the prodromal phase of infection are nonspecific and can be similar to those seen in acute viral gastroenteritis, bacterial or parasitic gastritis or enteritis, pancreatitis, abdominal trauma, ischemic bowel disease, intussusception, or small bowel obstruction. Hepatitis may be caused by other viruses like Epstein-Barr virus, herpes viruses, adenovirus, enterovirus, parvovirus B19, Lassa fever, Dengue, and Yellow Fever viruses. Similar symptoms and signs are also seen in bacterial, parasitic or fungal hepatitis or liver abscess, as well as biliary disease including cholangitis, cholecystitis, and cholelithiasis.

Therapy

Specific therapy against hepatitis A viral infection is not usually necessary, and treatment is supportive to prevent dehydration, malnutrition, and spread of disease. In the case of acute hepatic failure, more aggressive supportive therapy is necessary and may include parenteral nutrition, fluid management, repletion of coagulation factors, medical management of increased intracranial pressure, endotracheal intubation and mechanical ventilation, and sometimes liver transplantation.

Prevention

For areas of high endemicity, where almost all children are exposed to the virus, primary prevention aims at improved water sanitation, but immunoprophylaxis with vaccines is too costly to be recommended. In areas of intermediate endemicity, the World Health Organization (WHO) recommends consideration of large-scale vaccination programs with the caveat that cost-benefit calculations should consider the relative benefits of vaccination against other diseases like Haemophilus influenza or pneumococcal disease. In areas of low endemicity, the WHO recommends vaccination for high-risk groups such as intravenous drug users, men who have sex with men (MSM), certain ethnic groups and travelers to intermediate or high endemic areas. In the United States, the

Advisory Council for Immunization Practices and Centers for Disease Control and Prevention (CDC) currently recommend routine vaccination for all children ≥12 months of age, MSM, persons who are at risk of occupational exposure, use illicit drugs, have chronic liver disease or receive regular administration of clotting factors, and those traveling to endemic areas.

There are four commercially available vaccines, all of which are highly immunogenic and effective. Some are available as two-dose regimens given 6–18 months apart, and one that is a combination vaccine with recombinant Hepatitis B vaccine is given in a three-dose regimen on a 0, 1, and 6 months schedule. Exact recommended schedules vary by manufacturer; none are licensed for infants younger than 1 year of age.

Postexposure prophylaxis (PEP) in areas of low or intermediate endemicity can be given to certain individuals with possible HAV exposure to prevent symptoms and spread of the virus. Household and sexual contacts of any index case and regular caretakers of children with confirmed HAV infection should be considered for PEP. If an index case is a child who attends a day care where children wear diapers, staff, other attendees, and household contacts of attendees should also receive PEP. The Centers for Disease control and the UK Health Protection Agency suggest similar algorithms regarding who to treat and what agent(s) to choose. In general, monovalent anti-HAV vaccine is sufficient PEP for children and adults 12 months to 40–50 years of age. Anti-HAV immune globulin should be given to infants <12 months, adults over 40 years, and anyone who is immunocompromised, has chronic liver disease, or is allergic to the vaccine. Special consideration is given when the index case or exposed individual is a food handler, and those organizations offer detailed recommendations.

Hepatitis B

Definition

Hepatitis B virus (HBV) is a virus in the Hepadnaviridae family whose virion is small, only 42 nm in diameter, and consists of an envelope that includes the Hepatitis B surface antigen (HBsAg) protein, glycoproteins, and lipids. Within the envelope, there is a capsid containing Hepatitis B core antigen (HBcAg), a molecule of partially double-stranded deoxyribonucleic acid (DNA), DNA polymerase, protein kinase and the nonstructural, soluble Hepatitis B e antigen (HBeAg). The presence and absence of these specific antigenic proteins as well as the patient's antibodies to them provide important clinical information. The virus targets the liver primarily, replicating in hepatocytes, but some chronically infected patients may have detectable virus in their circulating mononuclear cells, polymorphonuclear leukocytes, bone marrow, pancreas, kidneys, spleen, and even skin.

Epidemiology

The incidence of hepatitis B infection varies across the world, but overall, the WHO estimates that over two billion people living today have been infected with hepatitis B. It is also estimated that about 350 million individuals are chronically infected and that 600,000 people die every year due to the virus. A person's risk of being infected is influenced by endemicity, vaccination, and certain behaviors.

Areas of high prevalence include Sub-Saharan Africa, Southeast Asia, Eastern Mediterranean countries, south and west Pacific Islands, Caribbean Islands, and Amazon basin countries. High prevalence is defined as having greater than 8% prevalence, but in some areas, up to 20% of the population may be chronically infected. In these areas, mother-to-child perinatal transmission, child-to-child transmission, and sexual contact are the major ways the virus is spread. In areas of low endemicity (<2% prevalence), like North America, Northern and Western Europe, Australia, and New Zealand, homosexual and heterosexual sex and use of contaminated needles, especially among intravenous drug users, are major modes of transmission.

Pathogenesis

Hepatitis B is spread via parenteral routes including transfusion, blood exposure, or via sexual contact and enter the liver through direct hematogenous spread. Acute infection includes intracellular viral replication and causes an inflammatory immune response, which causes varying amounts of hepatocellular necrosis and degeneration. Although uncommon, acute liver failure due to extensive liver necrosis can be fatal. While the apparent lack of symptoms despite continued viral replication observed in many chronically HBV-infected individuals suggests the virus is not directly cytotoxic, the possibility that overwhelming viral replication can exacerbate disease remains, and is observed in chronically infected persons with immune systems compromised by chemotherapy or other immunosuppressive agents.

Pathology

The histological changes and chemical markers of hepatic injury, like elevations of serum aminotransferases, seen in the acute hepatitis phase are indistinguishable between different hepatitis viruses. Chronic hepatitis, caused primarily by HBV, Hepatitis C and D viruses (HCV, HDV), is characterized by persistent elevations of liver aminotransferases, hyperbilirubinemia, and detectable viral antigens and genetic material. Histologically, chronically HBV-infected patients have livers that can appear normal after the initial inflammatory response, injury, and regeneration of hepatocytes. However, biopsy specimens often show cells that display evidence of accumulated viral antigens referred to as "ground glass" hepatocytes (*Fig. 105.2*). Ongoing inflammation with lymphocytic/mononuclear infiltrates in the parenchyma and portal tracts, or the spectrum of fibrotic changes of cirrhosis can also be seen.

Clinical Manifestations

The clinical course of infection with Hepatitis B is similar to that of the other hepatitis viruses in the acute phase (*Fig. 105.3*). The incubation period is variable, lasting 4–26 weeks before viral antigens appear in the serum. Clinical signs and symptoms of acute infection may be absent or may range from mild to severe. A prodromal phase may include headache, nausea, vomiting, abdominal pain, malaise, and fever. Rarely, patients may experience symptoms similar to serum-sickness with fever, arthralgia or arthritis, and an erythematous maculopapular rash. An icteric phase then follows and can include jaundice, pruritus (especially in infants), dark urine, and light-colored stool. The rash of Gianotti-Crosti syndrome, papular acrodermatitis, has a long-recognized association with Hepatitis B infection. Physical exam may show the above mentioned skin findings, scleral or buccal icterus, lymphadenopathy, jaundiced skin, a tender right upper quadrant, hepatomegaly and/or splenomegaly. Injury may subside and symptoms usually resolve over the course of 6–8 weeks.

Acute HBV infection may cause extrahepatic phenomena including urticarial rash, vasculitis, polyarteritis nodosa, pericarditis, serositis, Henoch–Schönlein Purpura, thrombocytopenia, cryoglobulinemia, and aplastic anemia. Multiple types of glomerulonephritis can occur in association with HBV, especially in the setting of chronic infection, the most common of which is membranous glomerulonephritis due to deposition of HBV antigen–antibody complexes in the basement membranes of glomerular capillaries.

Worldwide, acute liver failure occurs more often as a result of Hepatitis B viral infection than the other hepatitis viruses, affecting 0.1–0.5% of those infected. Coinfection with Hepatitis D virus increases a patient's risk of developing this serious complication.

Age, immune status, viral genotype, and the HBV infecting dose all affect the clinical outcome of HBV infection. Infection is more likely to become chronic with young age at exposure to the virus, occurring in up to 90% of exposed neonates. In contrast, 30% of children ages 1–5 years, and only 5–10% of immunocompetent adults develop chronic HBV infection. Most infections that

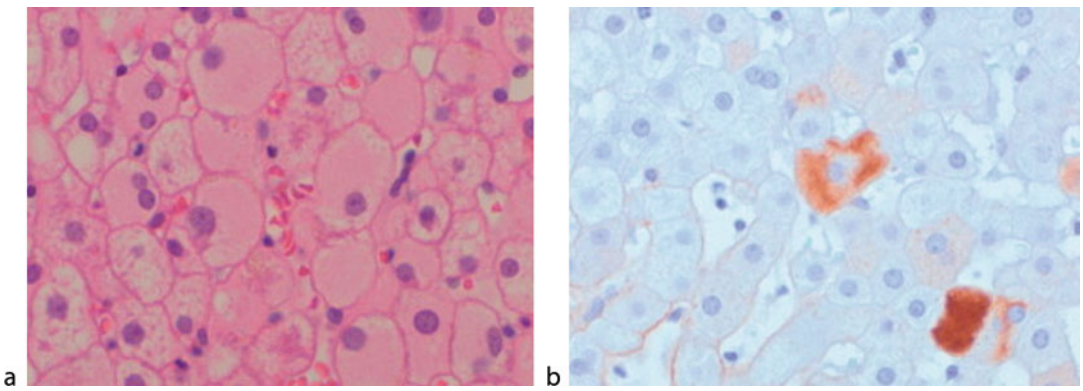

Figure 105.2
Chronic hepatitis B infection with "ground-glass" hepatocytes (a) and immunoperoxidase stain for hepatitis B surface antigen (b) showing cytoplasmic inclusions of viral particles (Adapted from Crawford J, Liu C (2010) Liver and biliary tract. In: Kumar V et al (eds) Robbins and Cotran pathologic basis of disease, 8th edn. Saunders Elsevier, Philadelphia)

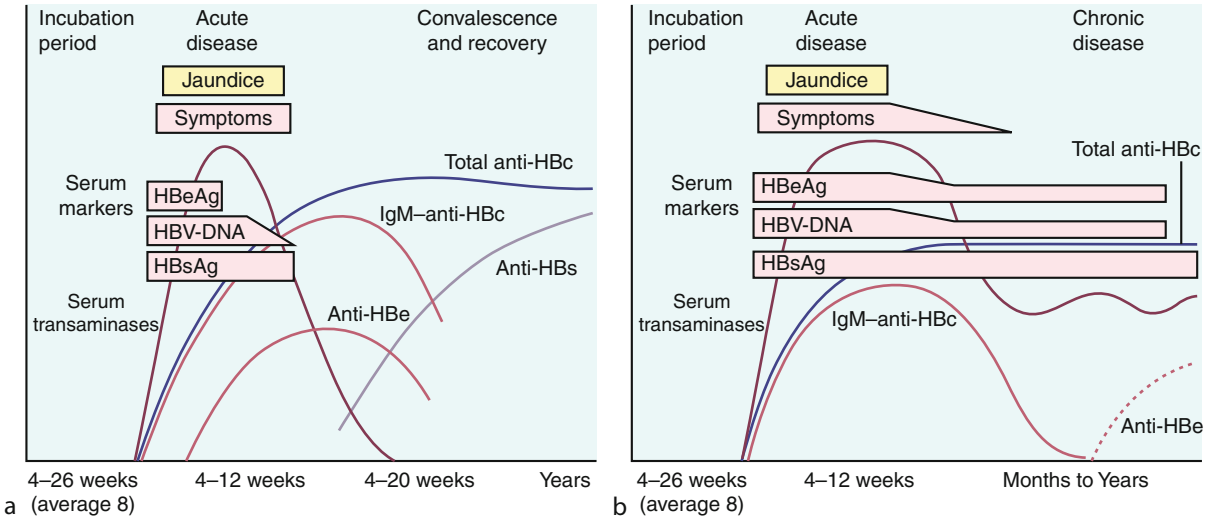

Figure 105.3

Serology and clinical manifestations of acute (a) and chronic (b) hepatitis B infection. *HBV* hepatitis B virus, *HBc* hepatitis B core antigen, *HBsAg* hepatitis B surface antigen, *HBeAg* hepatitis B e antigen (Adapted from Crawford J, Liu C (2010) Liver and biliary tract. In: Kumar V et al (eds) Robbins and Cotran pathologic basis of disease, 8th edn. Saunders Elsevier, Philadelphia)

occur in the perinatal or young childhood period are asymptomatic in the acute period, and clinical signs of disease rarely arise before the second or third decade of life.

Those with chronic infection pass through four phases. (1) *Immune tolerance* is the first phase, during which the virus replicates relatively freely (HBeAg +, ↑ HBV DNA) without hepatic disease (normal ALT). This phase characterizes most infants and young children who were infected perinatally by vertical transmission. Available evidence suggests that immune tolerance may be induced by transplacental passage of HBeAg and fetal thymic restriction of T cells that would respond to these "self-antigens." (2) *HBeAg-positive chronic hepatitis* is defined by active viral replication (HBeAg+, ↑HBV DNA), high infectivity, and elevated liver transaminases. Seroconversion to HBeAg-negative/anti-HBe-positive status indicates host immune response, which can attenuate active disease and usher in the next stage. (3) *Inactive carriers* have positive HBsAg and normal aminotransferases, are asymptomatic, have low or undetectable levels of viremia (HBV DNA), and are not as infectious. Patients may remain in this stage for many years. (4) *HBeAg-negative chronic hepatitis* is present when patients remain HBeAg-negative, HBsAg positive, and develop elevated transaminases and higher levels of viremia (HBV DNA). Patients in the stages of chronic hepatitis are at higher risk of developing cirrhosis and hepatocellular carcinoma.

Diagnosis

Diagnosis and determination of chronicity and infectivity depend primarily on serology (*Table 105.1*). Detection of HBcAg or HBsAg in the absence of vaccination confirms infection. Presence of HBeAg suggests active viral replication and high infectivity. Seroconversion occurs with the production of antibodies to HBsAg, HBcAg and HBeAb, anti-HBs, anti-HBc and anti-HBe, respectively, but there exists a "window period" during which HBsAg may be negative before anti-HBs is detectable. Anti-HBc antibodies of the IgM type can be very helpful in diagnosing recent infection, whereas IgG antibodies to any of the antigens indicate past infection only. Advances in polymerase chain reaction (PCR) techniques allow detection of lower levels of HBV DNA.

Differential Diagnosis

The differential diagnosis of acute liver injury in Hepatitis B is similar to that of Hepatitis A. Hepatitis B is an important cause of chronic hepatitis in children, but it is important to consider other causes, including autoimmune hepatitis, which is the most common cause of chronic hepatitis in children. Other etiologies include Hepatitis C infection, alpha-1 antitrypsin deficiency, Wilson's disease, cystic fibrosis, and drug-induced

Table 105.1
Serology in Hepatitis B infection

	Non-infected non-immune	Non-infected immune (vaccinated)	Acute infection	Chronic infection high infectivity	Chronic infection low infectivity	Resolved infection
HBsAg	–	–	+	+	+	–
HBeAg	–	–	+/–	+/–[a]	–	–
Anti-HBs IgG	–	+	–	–	–	+
Anti-HBc IgM	–	–	+	–	–	–
Anti-HBc IgG	–	–	–	+	+	+
Anti-HBe IgG	–	–	–	–	+	+/–

HBsAg Hepatitis B surface antigen, *HBeAg* Hepatitis B e antigen, *anti-HBs* anti-Hepatitis B surface antigen antibody, *anti-HBc* anti-Hepatitis B core antigen antibody, *anti-HBe* anti-Hepatitis B e antigen antibody
[a]Patients with HBeAg-negative chronic hepatitis may have significant liver damage, viremia with higher HBV DNA

hepatitis. Chronic hepatitis of many etiologies is often asymptomatic, with only elevated serum aminotransferases prompting evaluation.

Treatment

General Care

For those with confirmed acute infection, care is mostly supportive, as with Hepatitis A. Children diagnosed with acute or chronic infection with hepatitis B should be screened for HDV, which can coinfect persons with HBV, and be followed with regular monitoring of ALT and HBeAg for evidence of active liver disease and seroconversion. Abdominal ultrasound can be useful in evaluating for hepatocellular carcinoma. Liver biopsy gives definitive measure of inflammatory acuity and fibrosis, aids in prognosticating advancement of disease and need for therapy, and may help rule out other conditions.

Specific Treatment

Treatment options for children with chronic infection are limited, and optimal care is aided by referral to a pediatric liver specialist when possible. The goals of therapy are to reduce the morbidity and mortality of chronic infection and to slow or stop viral replication as evidenced by normalization of liver transaminases and clearance of HBV DNA and HBeAg. With the available treatment options, treatment is reserved for chronically infected children with active liver disease (↑ ALT) and active viral replication (↑ HBV DNA). However, children with cirrhosis, coinfection with HDV, rapidly deteriorating liver function, and those expected to begin immunosuppressive or cytotoxic chemotherapy should be considered for treatment regardless of ALT or DNA levels.

Currently, only a few drugs are approved for use in young children: interferon-α, which has an immune modulating as well as antiviral effect, and the antiviral nucleos(t)ide analogs lamivudine and adefovir. Interferon-α is modestly effective, yielding clearance of both HBV DNA and HBeAg in 23% of children versus 10% spontaneous clearance in controls. Important side effects include fever, malaise, and myelosuppression. A pegylated form may be better tolerated with its less frequent administration and is the subject of ongoing research.

Lamivudine is also effective, but is limited by viral resistance that frequently develops with prolonged use. Limited research of adefovir showed little efficacy in children under 12 years of age. Combination therapy of the above agents and promising new antivirals that have been used in adults are under pediatric study.

Prevention

Vaccines against Hepatitis B have been available since 1982, and have been very effective in preventing disease. Since 1992, when the WHO issued a global recommendation to routinely vaccinate all infants, the number of countries that have Hepatitis B vaccination programs increased fivefold, up to 164 countries in 2006. Such programs have taken prevalence levels in some countries from high to below 1%. Vaccination is also recommended for older

children and adults at high risk of exposure to or morbidity with HBV infection, including health care workers and those with occupational exposure to blood products, those who use injection drugs, persons with multiple sexual partners, and persons with chronic liver disease.

Currently, recombinant vaccines derived from modified yeast have mostly replaced plasma-derived vaccines. Both are equally effective and interchangeable within regimens. Preexposure immunization schedules are somewhat flexible, usually require three doses of vaccine, and individual doses vary by age and manufacturer. These can be initiated at birth, or for convenience, simultaneously with other vaccines (*Table 105.2*). The three-dose regimen is recommended for preexposure prophylaxis, and the four-dose regimen is recommended for use in immunocompromised patients or for older children as postexposure prophylaxis. Postvaccine testing and provision of booster doses are not routinely recommended, but may be appropriate in some cases, (e.g., immunocompromised patients).

Postexposure prophylaxis for infants born to chronically infected mothers should include administering a birth dose of hepatitis B vaccine and a dose of Hepatitis B immune globulin (HBIG), preferably within 24 h after delivery. Thereafter, the usual three-dose schedule of vaccine is recommended. Of note, the four-dose schedule without HBIG has been shown to be similarly effective in preventing vertical transmission, but is not currently recommended.

Two recent meta-analyses showed both lamivudine and HBIG to be individually effective in reducing the risk of mother to child transmission when administered to late-gestation HBsAg-positive mothers. Infants with mothers who are HBeAg-positive or have high serum levels of HBV DNA are at higher risk of vertical transmission, and these agents may augment prevention when added to HBIG and HBV vaccine regimen given to the infant at birth.

Hepatitis C

The hepatitis C virus is also transmitted parenterally and causes chronic infection and serious sequelae. Prior to its identification in 1989, it was the predominant cause of so-called non-A, non-B chronic hepatitis in the world. It is an enveloped, single-stranded RNA virus in the *Flaviviridae* family that is very heterogeneous genetically, with six separate genotypes and multiple subtypes that have diverse geographical distributions. Its ability to mutate rapidly allows it to elude host immune systems as well as scientists' efforts to develop an effective vaccine.

Epidemiology

Worldwide prevalence has been estimated at 3%, but ranges from 1.7% in the United States to 5.3% in Africa. Transfusions, while once a major source of HCV infections, are less risky due to widespread donor-blood screening for HCV. Now, vertical transmission is the most common way children acquire the infection, accounting for about 60% of cases of pediatric chronic infection. In contrast to vertical transmission rates seen with HBV, only about 5–7% of infants born to mothers with chronic HCV infection will acquire the infection themselves. Risk factors for vertical transmission include high levels of viremia, coinfection with HIV, prolonged or difficult delivery, and the use of internal fetal monitoring. Hepatitis C is also transmitted via other parenteral routes including sexual contact, use of contaminated needles, and via transfusion of donor blood products.

The different genotypes are clustered geographically around the globe. Genotypes 1–3 are prevalent worldwide. Genotype 1 is the most common in the United States and Europe. Genotype 2 accounts for less than 20% of all infections in all regions. Genotype 3 is most common in

Table 105.2
Recommended Hepatitis B immunization and postexposure prophylaxis schedules for infants

	Option I		Option II		Option III		PEP		
	Mono	Combo	Mono	Combo	Mono	Combo	Mono	Mono or combo	HBIG
Birth			x		x		x		x
2 months		x		x		x		x	
4 months		x				x			
6 months		x		x		x		x	

PEP postexposure prophylaxis for infants of HBsAg-positive mothers, *mono* monovalent hepatitis B vaccine, *combo* combination vaccine including hepatitis B vaccine, *HBIG* Hepatitis B immune globulin

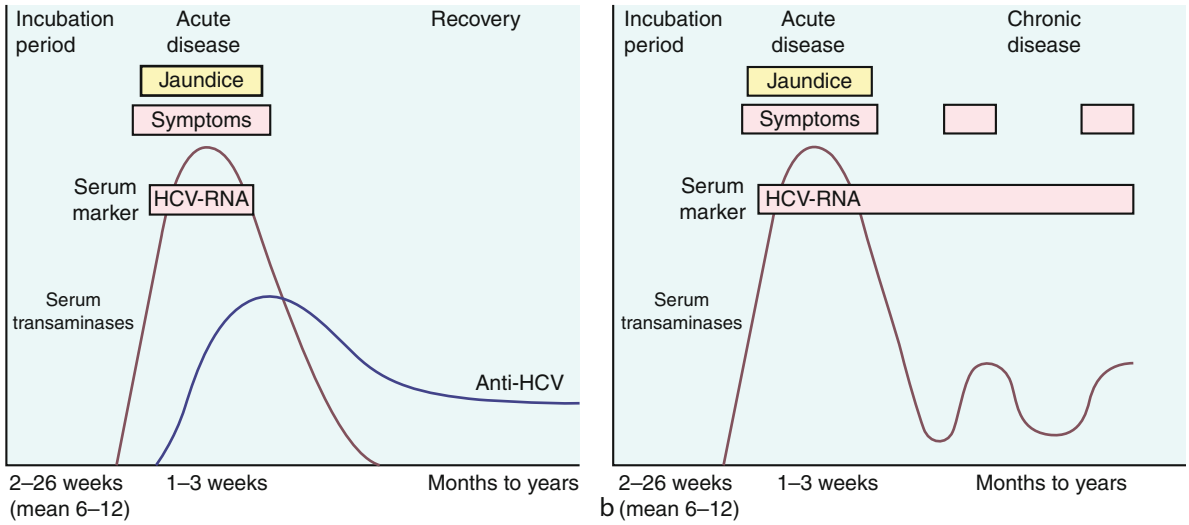

Figure 105.4
Serology and clinical manifestations of acute (a) and chronic (b) hepatitis C infection. *HCV* hepatitis C virus (Adapted from Crawford J, Liu C (2010) Liver and biliary tract. In: Kumar V et al (eds) Robbins and Cotran pathologic basis of disease, 8th edn. Saunders Elsevier, Philadelphia)

Australia, South America and India, 4 in Egypt, the Middle East and central Africa, and 5 and 6 are most common in South Africa and southeast Asia.

Pathology

Histologic changes due to HCV infection do not necessarily correlate with liver aminotransferase levels, but are similar to those seen with the other hepatitis viruses. Chronic infection carries a high risk of development of cirrhosis. Hepatocellular carcinoma can also be seen in chronically infected persons.

Clinical Manifestations

Children with hepatitis C are generally asymptomatic, but may have mild nonspecific malaise, anorexia, or abdominal pain. Hepatomegaly is the most frequent sign of disease in young children. Acute hepatic failure has not been reported in children and is rare in adults. Clinical progression of disease in those with chronic HCV infection is often indolent, with fluctuating serum transaminases and recurrent or chronic evidence of inflammation, but leads to cirrhosis in up to 25% in that population (*Fig. 105.4*). Hepatocellular carcinoma is associated with chronic HCV infection, though the mechanism of oncogenesis is yet unclear.

Diagnosis

Diagnosis is based on detection of viral RNA, which can be done by PCR or other assays. Chronic infection is determined by detecting HCV RNA in serum twice, at least 6 months apart. Measuring anti-HCV antibodies is useful to screen for past exposure, but they may be absent in recent infection, and in infants, may represent maternally transmitted antibody up to 18 months of age. Spontaneous clearance of virus is uncommon, occurring in about 15% of patients, and is seen more often in transfusion-acquired infection and when initial ALT levels are >5 times the upper limit of normal.

Differential Diagnosis

The differential diagnosis of chronic hepatitis C seen in children is similar to that of Hepatitis B, discussed above.

Treatment

General Care

Management of patients with chronic hepatitis C infection aims to reduce the risk of morbidity and mortality due to long-term sequelae including cirrhosis, liver failure, and

hepatocellular carcinoma. Evaluation should include laboratory monitoring of liver aminotransferases and HCV RNA, since the course of progression can vary widely and viremia can sometimes recur even after a period of undetectability. Genotype determination can lend very helpful prognostic information, especially related to expected response to therapy. Liver biopsy can be helpful in evaluating degree of liver injury, but must be weighed against its invasiveness, risk of complication, and the likelihood of sustained response to therapy. Some centers prefer to obtain ultrasounds every 3–5 years to evaluate for changes in liver size, echotexture, and for hepatocellular carcinoma, though the latter is rare in childhood. The intervals at which laboratory studies, imaging, and histology should be monitored have not been codified in current recommendations, but experts agree that therapy and monitoring should be prescribed and supervised by experienced providers.

Counseling of patients and families with an aim to prevent spread of disease should include avoidance of behaviors that would increase the risk of transmission like donating blood and sharing razors, toothbrushes, or injection needles. Immunization against HAV and HBV should be performed or confirmed in all patients with chronic HCV infection.

Specific Treatment

Antiviral therapy has the potential to eradicate infection, thereby reducing the risk of transmitting infection and developing severe liver disease or hepatocellular carcinoma. These risks, weighed against the risks of therapy and the possibility of spontaneous viral clearance, inform decisions about whether and when to treat. Patients with genotypes 2 and 3, rather than genotype 1, and those with lower pretreatment HCV RNA levels respond better to therapy.

Interferon, injected subcutaneously, was once the main therapeutic agent and was effective at inducing sustained viral response (SVR; undetectable serum HCV RNA 24 weeks after the end of therapy) in about 10–15% of patients. Addition of ribavirin improved rates of SVR. Pegylated interferon (PEG-IFN) is superior to interferon at viral suppression and allows for once weekly dosing. PEG-IFN combined with ribavirin is currently recommended for adults, and the first large controlled trial of PEG-IFN showed that combination therapy with PEG-IFN and ribavirin was similarly effective in children as in adults, inducing SVR in 53% of all subjects.

The typical suggested duration of therapy for children is 48 weeks, but this may be extended to 72 weeks for patients who have persistently detectable HCV RNA at 48 weeks. Therapy can be stopped after 24 weeks in patients who do not show adequate response to therapy. Patients should be monitored for adverse effects of therapy, which include leukopenia, neutropenia, and autoimmune hypothyroidism. Patients with co-morbid diseases including thalassemia, HBV infection, and HIV infection deserve special attention. The iron overload associated with transfusion-dependent thalassemia worsens liver disease and requires active management in addition to antiviral therapy. Coinfection with HBV can worsen liver disease, and treatment with PEG-IFN and ribavirin is recommended. Coinfection with HIV can accelerate HCV liver disease, but this effect may be ameliorated with highly active antiretroviral therapy (HAART).

Future Development

New promising agents include new formulations of interferon, better-tolerated ribavirin-like drugs, and agents that inhibit enzymes involved in viral replication. Albeit challenged by the genetic heterogeneity and great propensity for mutation of the virus, efforts to develop effective vaccine products are underway.

Prevention

The most effective measure in reducing the incidence of HCV worldwide has been the widespread screening of donated blood for HCV, thereby reducing the risk of transfusion-related transmission. Because screening of donated blood products is not 100% effective, transfusion should be recommended judiciously. Avoidance of high-risk behaviors as well as screening and counseling those who engage in high-risk behaviors such as those with multiple heterosexual or same-sex partners and those who use injection drugs may help prevent the spread of disease.

Screening is not recommended for pregnant women owing to the lack of available measures to prevent mother-to-child vertical transmission, and though HCV RNA can be detected in breast milk, there is not sufficient evidence regarding any increased risk of transmission to discourage breastfeeding.

Hepatitis D

Hepatitis D virus (HDV) consists of its single-stranded, circular RNA molecule and its only protein product, the

delta antigen. Infection with HDV requires coinfection with Hepatitis B, as it requires the latter's outer coat for extracellular spread. Coinfection of HBV with HDV is associated with higher risk of acute liver failure as well as severe liver disease and cirrhosis. Infection may be acquired simultaneously with hepatitis B or via similar parenteral routes after infection with Hepatitis B. Prevalence is high in the Amazon and Mediterranean Basins, the Middle East, Central Asia, West Africa, and south Pacific islands, and higher in those who use intravenous drugs and themophiliacs. Epidemics have been observed, especially in the Amazon Basin.

Liver transplantation may be necessary for those with acute hepatic failure. In chronically infected patients, treatment with high-dose interferon can improve liver disease, but has a low likelihood of eradicating the virus. Control of this disease relies on improved prevention of hepatitis B infection through immunization.

Hepatitis E

Hepatitis E virus (HEV) is the other water-borne hepatitis virus, like Hepatitis A. Once classified in the Calicivirus family, the enveloped, single-stranded RNA virus is now unclassified. It is the primary cause of enterically transmitted non-A, non-B hepatitis, and is the most common cause of symptomatic hepatitis in children in endemic areas, including central and southeast Asia, India, China, Africa, and Mexico. Anti-HEV antibodies have been detected in sera of individuals in all areas of the world, but the only symptomatic cases reported in the United States or Europe have been in travelers to endemic areas. This incongruity is yet unexplained but may be related to subclinical disease, attenuated viral strains or cross-reactivity of anti-HEV antibodies to other antigens.

Symptoms are similar to acute hepatitis of other etiologies, include malaise, anorexia, abdominal pain, hepatomegaly, and jaundice, and are usually mild. Mortality is generally low, ranging from 0.4% to 4%. For reasons that are not yet clear, infection during pregnancy is much more dangerous with mortality around 20%, higher risk of acute liver failure, intrauterine fetal demise, preterm delivery, and stillbirth. Maternal-fetal and/or perinatal transmission is likely possible, and very poor outcomes in neonates born to mothers with acute HEV infection have been reported.

No specific treatment is available beyond supportive therapy. Most infected persons develop anti-HEV IgG, which is protective of future disease for up to 14 years, but development of a therapeutic anti-HEV immune globulin has not yet been successful. A recent large-scale randomized controlled trial of a recombinant bacteria-derived vaccine in adults in an endemic area of China showed significant protective effect and appears promising. Its use in outbreaks, endemic areas, and travelers will depend on the usual cost-benefit analysis and requires much further study. Prevention currently relies on safe systems of water sanitation and proper counseling of travelers to avoid unsafe drinking water, uncooked fruits, vegetables and shellfish, and to practice good handwashing.

Hepatitis F

A novel hepatitis F virus was proposed after a virus resembling those in the Togaviridae family was isolated from the livers of a few patients with fulminant hepatitis, but subsequent research has not confirmed it as a novel distinct hepatotropic virus.

Hepatitis G

A novel virus, initially named GB agent, referring to the young British surgeon from whose liver it was isolated, was inoculated into tamarins and caused hepatitis. Subsequent research has elucidated that at least four subtypes of GB virus exist: GBV-A; GBV-B (the likely agent originally isolated from the surgeon); GBV-C, which is identical to the simultaneously discovered virus called Hepatitis G virus (HGV); and GBV-D. GBV-C/HGV has been found in many patients with chronic Hepatitis B or C as well as the stool of normal children, and has been proven to be transmissible by transfusion. Infection is usually persistent, and studies suggest that anti-HGV antibodies are present in the blood of nearly one-quarter of the world's population. Despite its prevalence, the ability of the GB viruses to cause hepatitis in other animals and its attractiveness as a possible etiology of non-ABCDE hepatitis, HGV is not associated with human disease, and testing is not indicated in patients with hepatitis.

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106 CMV Infections

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The Virus

CMV (human herpesvirus 5) is the largest and most complex member of the family of herpesviruses. The virion consists of three regions: the capsid containing the double-stranded DNA viral genome, the tegument, and the envelope. The viral genome consists of more than 235 kbp, which contain more than 252 open reading frames. The complexity of CMV's genetic makeup confers extensive genetic variability among strains. Restriction fragment length polymorphism analysis as well as DNA sequence analysis has demonstrated that no two clinical isolates are alike. The viral tegument contains viral proteins that function to maintain the structural integrity of the virion, are important for assembly of an infectious particle, and are involved in regulatory activities in the replicative cycle of the virus. The viral envelope contains eight glycoproteins that have been described, as well as an unknown number of additional proteins. The most abundant envelope glycoproteins are the gM/gN, the gB, and the gH/gL/gO complexes, which are all important for virus infectivity. In addition, gB, gH, and gM/gN have been shown to induce an antibody response in the infected host and are major components of the protective response to the virus.

Epidemiology

Cytomegalovirus infections have been recognized in all human populations. CMV is acquired early in life in most populations, with the exception of people in the economically well-developed countries of northern Europe and North America. The patterns of CMV acquisition vary greatly based on geographic and socioeconomic backgrounds and seroprevalence generally increases with age. Studies have shown that most preschool children (>90%) in South America, sub-Saharan Africa, East Asia, and India are CMV antibody positive. In contrast, seroepidemiologic surveys in Great Britain and in the USA have found that less than 20% of children of similar age are seropositive. A recent study of CMV seroprevalence that utilized samples from the National Health and Examination Survey (NHANES), 1988–2004 showed that the overall age-adjusted CMV seroprevalence in the USA was 50.4%. That study also showed that CMV seroprevalence was higher among non-Hispanic black children and Mexican-American children compared with non-Hispanic white children.

Transmission of CMV

Although the exact mode of CMV acquisition is unknown, it is assumed to be through direct contact with body fluids from an infected person. Breastfeeding, group care of children, crowded living conditions, and sexual activity have all been associated with high rates of CMV infection. Sources of the virus include oropharyngeal secretions, urine, cervical and vaginal secretions, semen, breast milk, blood products, and allografts (*Table 106.1*). Presumably, exposure to saliva and other body fluids containing infectious virus is a primary mode of spread because infected infants typically excrete significant amounts of CMV for months to years following infection. Even older children and adults shed virus for prolonged periods (>6 months) following primary CMV infection. In addition, a significant proportion of seropositive individuals continue to shed virus intermittently. An important determinant of the frequency of congenital and perinatal CMV infection is the seroprevalence rate in women of childbearing age. Studies from the USA and Europe have shown that the seropositivity rates in young women range from less than 50–85%. In contrast, most women of childbearing age in less well-developed regions are CMV antibody positive.

Vertical transmission: CMV can be transmitted from mother to child transplacentally, during birth, and in the postpartum period via breast milk. Congenital CMV infection rates are directly related to maternal seroprevalence rates (*Table 106.2*). Rates of congenital CMV infection are higher in developing countries and for low-income groups in developed countries. Although the reasons for this increased rate of congenital CMV in populations with high seroprevalence rates are not clear, recent demonstration that infection with new or different virus strains occurs commonly in previously seropositive

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Table 106.1
Sources and routes of transmission of CMV infection

Mode of exposure and transmission	
Community acquired	
Age	
Perinatal	Intrauterine fetal infection (congenital); intrapartum exposure to virus; breast milk acquired; mother-to-infant transmission
Infancy and childhood	Exposure to saliva and other body fluids; child-to-child transmission
Adolescence and adulthood	Exposure to young children; sexual transmission; possible occupational exposures
Hospital acquired	
Source	
Blood products	Blood products from seropositive donors; multiple transfusions; white blood cell containing blood products
Allograft recipients	Allograft from seropositive donors

Source: Reproduced with permission from Boppana SB, Fowler KB (2006) Persistence in the population: epidemiology and transmission. In Arvin A, Campadelli-Fiume G, Mocarski E, Moore PS, Roizman B, Whitley R, Yamanishi K (eds) Human herpesviruses: biology, therapy, and immunoprophylaxis. Cambridge University Press, Cambridge

Table 106.2
Rates of maternal CMV seroprevalence and congenital CMV infection in different populations

Location	Maternal CMV seroprevalence (%)	Congenital CMV infection (%)	Reference
Aarhus-Viborg, Denmark	52	0.4	Andersen et al (1979)
Abidjan, Ivory Coast	100	1.4	Schopfer et al (1978)
Birmingham, USA			
Low income	77	1.25	Fowler et al (1993)
Middle income	36	0.53	Fowler et al (1993)
Hamilton, Ontario, Canada	44	0.42	Larke et al (1980)
London, UK	56	0.3	Peckham et al (1983)
Seoul, South Korea	96	1.2	Sohn et al (1992)
New Delhi, India	99	2.1	Dar et al (2008)
Ribeirão Preto, Brazil	96	1.1	Mussi-Pinhata et al (2009)
Sukuta, The Gambia	96	5.4	van der Sande et al (2007)

individuals in a variety of settings suggests that frequent exposure to CMV could be an important determinant of maternal reinfections and subsequent intrauterine transmission. Studies of risk factors for congenital CMV infection showed that young maternal age, nonwhite race, single marital status, and history of sexually transmitted diseases have been associated with increased rates of congenital CMV infection.

Intrapartum transmission: Transmission of CMV during delivery occurs in approximately 50% of infants born to mothers shedding CMV from the cervix or vagina at the time of delivery. Genital tract shedding of CMV has been associated with younger age, other STDs, and greater number of sexual partners.

Postnatal transmission: Breastfeeding practices have a major influence on the epidemiology of postnatal CMV infections. CMV has been detected in breast milk in 13–50% of lactating women tested with conventional virus isolation techniques. Recent studies utilizing the more sensitive PCR technology demonstrated the presence of CMV DNA in breast milk from >90% of seropositive women. The early appearance of viral DNA in milk whey, the presence of infectious virus in milk whey, and higher viral load in breast milk have been shown to be risk factors for transmission of CMV infection. The consequences of CMV infection acquired via breast milk are negligible in full-term infants. In contrast, postnatal CMV infection can lead to symptomatic infection in about 10–50% of preterm infants leading to significant morbidity. Although an earlier study suggested an association between postnatal CMV infection and adverse neurodevelopmental outcome in preterm infants, a more recent prospective study demonstrated that none of the 22 preterm infants with early postnatally acquired CMV infection developed hearing loss or other neurologic sequelae.

Nosocomial transmission: Blood products and transplanted organs are the most important vehicles of transmission of CMV in the hospital setting; the latter is

unlikely to be of concern during pregnancy. Transmission of CMV through packed red blood cell, leukocyte and platelet transfusions poses a risk of severe disease for seronegative small premature infants and immunocompromised patients. Prevention of blood product transmission of CMV can be achieved by using seronegative donors or by special filters that remove white blood cells. Another potential source of nosocomial CMV infection that is of particular concern to those in reproductive medicine is semen donated for artificial insemination. Person-to-person transmission of CMV requires contact with infected body fluids and therefore should be prevented by routine hospital infection control precautions. Studies in health care settings found no evidence of increased risk of CMV infection in settings in which patients shedding CMV are encountered.

Child-to-child transmission: Young children are a known source of CMV infection. After early infancy, young children likely acquire CMV through horizontal transmission from other children or possibly indirectly through environmental contamination. Studies in day care centers throughout the world have demonstrated that young children shed virus in saliva and urine creating exposure opportunities for virus transmission to other children in the day care setting, to their parents, and to the day care or nursery workers. Besides child-to-child transmission, CMV is also found on toys and other environmental surfaces in day cares providing another viral source for CMV infection.

CMV transmission through sexual activity: An important source of CMV infection is through intimate contact with oral and genital secretions. Salivary glands are a site of persistent virus in humans, and it is likely that reactivations lead to the presence of infectious virus in oral secretions. Infectious virus can often be cultured from cervical secretions, and semen has been shown to be a rich source of virus in seropositive men. The association between sexual activity and CMV transmission can be summarized as follows: (a) the prevalence of CMV antibody more than doubles during the years of beginning sexual activity (15–30 years), (b) higher rates of seropositivity are found in male partners of seropositive women as compared to seronegative women, (c) CMV has been isolated from the cervix of 13–35% of women with suspected STDs, (d) seropositivity correlated with the presence of other STDs, (e) among seronegative women attending an STD clinic, the annual CMV seroconversion rate was noted to be 37% versus 1–2% per year in the general population, (f) seropositivity correlated with number of lifetime sexual partners and young age at onset of sexual activity, and (g) a negative correlation was made between the use of barrier contraception and seropositivity. Thus, there is strong epidemiological evidence that acquisition and transmission of CMV infection is associated with sexual activity and STDs.

Transmission of CMV to child care providers: Children in day care settings may also be a source of CMV infection for child care personnel. Numerous studies in the past decades have described the risk of CMV infection for women who provide care for children in an occupational setting. Risk factors for CMV seroconversion of child care providers have included workers <30 years of age, not wearing gloves when changing diapers, and caring for children ≤ 3 years of age for 20 h a week.

Pathogenesis

The pathogenesis of CMV infection in the naïve host has been characterized in humans as well as in animal models. After entry into a naïve host, cytomegalovirus infection induces a primary viremia with initial viral replication occurring in reticuloendothelial organs (liver and spleen). Secondary viremia subsequently ensues with viral dissemination to end organs. In healthy humans, both primary and secondary viremia may be asymptomatic, or the secondary viremia may be associated with mononucleosis-like symptoms including fever, transaminase elevation, and atypical lymphocytosis.

After immune-mediated clearance of acute viremia, the immunocompetent host may remain asymptomatic for life. Reservoirs of latent infection are not clearly defined but are thought to include monocytes and marrow progenitors of myeloid lineage, as well as possibly endothelium and secretory glandular epithelium such as the salivary, breast, prostate, and renal epithelium. The control of latency and reactivation is not well understood and has been intensively studied both in vitro and in animal models. It is believed that viral reactivation occurs intermittently in the immunocompetent host but fails to induce clinical disease secondary to intact immune control mechanisms. Up to 10% of the memory T-lymphocyte repertoire may be directed against CMV in the healthy host, and immune senescence ("T-cell exhaustion") may contribute to susceptibility to reactivation and reduced immunity to other infections in the elderly.

Immune Response to Infection

The innate immune system, particularly natural killer (NK) cells are responsible for initial control of viremia in

the normal host. Animal models demonstrate that activation of NK cells by virus-infected host cells contributes to viral clearance. Consistent with this, patients with NK cell deficiencies may develop life-threatening CMV disease as well as disease from other herpesviruses. Long-term control of CMV is maintained by adaptive immunity. Serum antibodies against CMV gB, gM/gN, and gH neutralize infection in vitro. IgM and IgG titers are used to determine clinical immunity and history of past infection. IgM is an indicator of recent infection, although IgM may persist for many months after primary infection. In addition, IgM antibodies can also appear during reactivations of CMV infection. However, hypogammaglobulinemia does not appear to be a risk factor for severe CMV disease except in conjunction with other forms of immunosuppression (e.g., transplant recipients). CMV-specific T-lymphocytes are critical for long-term control of chronic infection. The essential nature of CD4+ T-helper cells is demonstrated in HIV-infected patients who may develop CMV retinitis, colitis or esophagitis, hepatitis, or ventriculoencephalitis with loss of T-helper cell control of viral replication during late stages of HIV infection (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5804a1.htm). Immunorestoration of CD4+ and CD8+ T-lymphocytes in patients with AIDS after initiation of antiretroviral therapy correlates with control of CMV retinitis. The T-lymphocyte response has also been correlated with protection from CMV viremia in solid organ and stem cell transplant recipients.

CMV Immune Evasion Genes

CMV has evolved numerous immune evasion functions to permit coexistence in the normal host, which have been extensively reviewed elsewhere. For example, CMV downregulates MHC class I molecules on the infected cell surface, and encodes an MHC I homologue to inhibit immune recognition of the infected host cell. CMV encodes cytokine homologues such as UL111a mimicking human IL-10, chemokine receptors such as US28, and other immunomodulatory gene products which have been characterized in vitro.

As new pharmacologic immunomodulatory agents are developed to treat autoimmune diseases, the roles of specific cytokine pathways in the control of CMV infection are being elucidated. For example, patients with inflammatory bowel disease or rheumatologic diseases who are treated with monoclonal antibodies against TNF-α (etanercept or infliximab) have developed severe CMV disease, implicating this cytokine in the control of CMV.

Pathogenesis of Congenital Infection

The pathogenesis of central nervous system disease and sequelae including hearing loss in congenital CMV infection is not well understood. Few autopsy specimens are available for study and, because of the species specificity of the virus, human congenital CMV infection lacks a well-developed animal model that truly emulates human disease. Imaging studies of infants and children with congenital CMV infection reveal a variety of CNS abnormalities including periventricular calcifications, ventriculomegaly, and loss of white-gray matter demarcations. Histological examinations from CMV-infected fetuses has demonstrated evidence of virus by immunohistochemical staining for CMV proteins in a variety of brain tissue including cortex, white matter, germinal matrix, neurons of the basal ganglia and thalamus, ependyma, endothelium, and leptomeningeal epithelial cells. In most cases, virus was accompanied by an inflammatory response, sometimes severe and associated with necrosis. These findings together suggest that lytic infection as well as inflammation in response to infection contribute to the pathology in CNS infection. The neurological manifestations are unique in congenital CMV infection, leading to the hypothesis that the immature brain is more susceptible to infection. Animal models have supported this theory, wherein infection of the developing CNS leads to widespread lytic virus replication in neuronal progenitor cells of the subventricular gray area and endothelium.

Few temporal bones from congenitally infected children have been studied and described in the literature. Specimens displayed evidence of endolabyrinthitis and virus has been isolated from the endolymph and the perilymph. Cochlear and vestibular findings were variable, ranging from an occasional inclusion bearing cell within or adjacent to sensory epithelium of the cochlea or vestibular system to more extensive involvement of the non-sensory epithelium. Interestingly, inflammatory cell infiltrates were minimal and only reported in three cases. In contrast to the findings in infants, a study of the temporal bones from a 14-year-old with severe congenital CMV infection revealed extensive cellular degeneration, fibrosis, and calcifications in the cochlea and vestibular system. Studies in the guinea pig model of congenital CMV infection have shed some additional information on the possible mechanisms of CMV-related hearing loss and have demonstrated that not only was viral gene expression a prerequisite for damage to the inner ear and auditory abnormalities, but that an intact host immune response was also required.

From these studies in animal models and from the limited studies of human temporal bones, two mechanisms of hearing loss in congenital CMV infection are suggested. The presence of viral antigens or inclusions in the cochlea and/or vestibular apparatus of human temporal bones suggest that CMV can readily infect both the epithelium and neural cells in the inner ear and that hearing loss can occur as a result of direct virus-mediated damage to neural tissue. Alternatively, the host-derived inflammatory responses secondary to viral infection in the inner ear could also be responsible for damage leading to sensorineural hearing loss (SNHL).

Pathology

Cytomegalovirus was originally named for the cytomegalic changes and intracellular inclusions observed within infected cells during histologic analysis of infected tissues. The classic histologic finding in CMV pathology is the "owl's eye" nucleus, which is a large intranuclear basophilic viral inclusion spanning half the nuclear diameter, surrounded by a clear intranuclear halo beneath the nuclear membrane. Smaller cytoplasmic basophilic inclusions may also be seen in infected cells. Infected cell types include epithelial and endothelial cells, neurons, and macrophages, and can be found in biopsies of numerous tissues including brain, lung, liver, salivary glands, and kidneys. CMV-infected tissues may show minimal inflammation, or may demonstrate an interstitial mononuclear infiltrate with focal necrosis. In the intestine, CMV may induce ulceration and pseudomembrane formation. In congenital infection, chorioretinitis may be found in the eye, and pathologic findings in the central nervous system include microcephaly, focal calcifications, ventricular dilatation, cysts, and lenticulostriate vasculopathy.

Clinical Manifestations

Congenital Infection

Of the 20,000–40,000 children born with congenital CMV infection each year, the majority (approximately 85–90%) exhibit no clinical abnormalities at birth (asymptomatic congenital CMV infection). The remaining 10–15% are born with clinical abnormalities and are thus classified as having clinically apparent or symptomatic congenital infection. The infection involves multiple organ systems with particular predilection for the reticuloendothelial and central nervous system (*Table 106.3*). The most commonly observed physical signs are petechiae, jaundice, and hepatosplenomegaly with neurologic abnormalities such as microcephaly and lethargy affecting a significant proportion of symptomatic children. Ophthalmologic examination is abnormal in approximately 10%, with chorioretinitis and/or optic atrophy most commonly observed. Approximately half of symptomatic children are small for gestational age and one-third are born prior to 38 weeks gestational age.

Table 106.3
Clinical findings in 106 infants with symptomatic congenital CMV infection in the newborn period

Abnormality	Positive/total examined (%)
Prematurity[a]	36/106 (34)
Small for gestational age[b]	56/106 (50)
Petechiae	80/106 (76)
Jaundice	69/103 (67)
Hepatosplenomegaly	63/105 (60)
Purpura	14/105 (13)
Microcephaly[c]	54/102 (53)
Lethargy/hypotonia	25/104 (27)
Poor suck	20/103 (19)
Seizures	7/105 (7)

Source: Adapted from Boppana SB, Pass RF, Britt WJ et al (1992) Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J 11:93–99, with permission
[a]Gestational age less than 38 weeks
[b]Weight less than 10th percentile for gestational age
[c]Head circumference less than 10th percentile

Laboratory findings in children with symptomatic infection reflect the involvement of the hepatobiliary and reticuloendothelial systems and include conjugated hyperbilirubinemia, thrombocytopenia, and elevations of hepatic transaminases in over half of symptomatic newborns. Transaminases and bilirubin levels typically peak within the first 2 weeks of life and can remain elevated for several weeks thereafter while thrombocytopenia reaches its nadir by the second week of life and normalizes within 3–4 weeks of age. Radiographic imaging of the head is abnormal in approximately 50–70% of children with symptomatic infection at birth. The most common finding is intracranial calcifications, with ventricular dilatation, cysts, and lenticulostriate vasculopathy also observed.

Perinatal Infection

CMV infection acquired perinatally in a healthy, full-term infant is typically asymptomatic and without sequelae.

However, premature infants, particularly those with very low birth weight (VLBW) are at risk for life-threatening disease. Transfusion-acquired CMV infection in the VLBW infant can result in a sepsis-like syndrome with hepatosplenomegaly, thrombocytopenia, and respiratory deterioration. However, transfusion-associated CMV infections in neonates are now prevented through the use of blood from CMV-seronegative donors or blood that has undergone blood filtration to remove leukocytes.

Breast milk is currently the most common route of transmission in newborns, with preterm VLBW infants at highest risk for acquisition of the virus and symptomatic disease. Unlike congenital CMV infection, there has been no documentation of an association of perinatal CMV infection with sensorineural hearing loss or delay in neuromotor development.

Infection in the Healthy Host

CMV infection among infants, children, and adults with normally functioning immune systems is generally asymptomatic. However, CMV can cause a mononucleosis-type illness in healthy hosts. Patients most commonly present with fever and malaise, and elevated serum hepatic transaminase levels are commonly seen. Lymphocytosis is common and atypical lymphocytes may be seen. CMV infections in healthy individuals completely resolve; however, symptoms can persist for several weeks with a mean duration of symptoms of 7–8 weeks in one study of 124 adults with primary CMV infection. Severe infection due to CMV in the healthy host has rarely been described. Most commonly it involves overwhelming, multi-organ involvement but can involve only the central nervous system and present with encephalitis. Guillain–Barre syndrome, myocarditis and pneumonia requiring mechanical ventilation have also been reported to be associated with CMV infection in immunocompetent patients.

Infection in the Immunocompromised Host

CMV manifestations vary in the immunocompromised host depending upon the nature of the immunosuppression. In HIV-infected persons, CMV disease generally arises via reactivation from latency as the HIV infection induces progressive T-helper immunodeficiency. CMV retinitis and end organ disease (colitis, esophagitis, encephalitis, hepatitis) are opportunistic infections that may develop in patients with AIDS.

In transplant recipients, infection can be transmitted by the donor organ or by infected blood products, or may reactivate in the latently infected recipient. Acute CMV disease manifests as febrile syndromes, pneumonitis, hepatitis, splenomegaly, or bone marrow suppression. CMV infection (blood antigenemia or positive DNA PCR test) generally precedes onset of clinical disease. CMV disease in patients not receiving antiviral prophylaxis may develop around the first 30 days after transplant. Use of antiviral prophylaxis in high-risk patients (donor or recipient CMV seropositive transplants) delays the onset of CMV infection and disease, which may arise after discontinuation of antiviral prophylaxis. In solid organ transplant patients, CMV is also thought to exert immunomodulatory effects possibly related to dysregulation of CMV immune evasion functions in the immunocompromised host, rendering the patient more susceptible to coinfections with bacterial, fungal, and other viral pathogens.

CMV can induce colitis in patients with inflammatory bowel disease (IBD) and can mimic IBD exacerbations. Endoscopy and biopsy are often required to establish this diagnosis and to distinguish CMV colitis from that due to IBD. CMV disease and retinitis have also been associated with use of TNF-α inhibitors for IBD and for rheumatologic conditions.

Laboratory Diagnosis

Serology: Serological tests are useful for determining whether an individual has had CMV infection in the past, determined by the presence or absence of CMV IgG antibodies. The detection of IgM antibodies has been used as an indicator of acute or recent infection. However, assays for IgM antibody lack specificity for primary infection because IgM can persist for months after primary infection, and because IgM can be positive in reactivated CMV infections. Because of the limitations of the IgM assays, IgG avidity assays are utilized in some populations to help distinguish primary from non-primary CMV infection. These assays are based on the observation that IgG antibodies of low avidity are present during the first few months after the onset of infection and avidity increases over time, reflecting maturation of the immune response. Thus, the presence of high-avidity anti-CMV IgG is considered as evidence of long-standing infection in an individual.

Viral culture: The traditional method for detecting CMV is conventional cell culture. Clinical specimens are inoculated onto human fibroblast cells and incubated and observed for the appearance of characteristic cytopathic

effect (CPE) for a period of time ranging from 2 to 21 days. The shell vial assay is a viral culture modified by a centrifugation-amplification technique designed to decrease the length of time needed for virus detection. Centrifugation of the specimen onto the cell monolayer assists adsorption of virus, effectively increasing infectivity of the viral inoculum. Viral antigens then may be detected by monoclonal antibody directed at a CMV immediate-early (IE) antigen by indirect immunofluorescence after 16 h of incubation. This method was adapted to be performed in 96-well microtiter plates allowing for the screening of larger numbers of samples.

Antigen detection assays: The antigenemia assay has been commonly used for more than a decade for CMV virus quantification in blood specimens. Antigenemia is measured by the quantitation of positive leukocyte nuclei in an immunofluorescence assay for the CMV matrix phosphoprotein pp65 in a cytospin preparation of 2×10^5 peripheral blood leukocytes (PBL). This test not only gives a qualitative result but is also quantitative, correlating closely with viremia and clinical disease severity in immunosuppressed populations. The disadvantages of the antigenemia assay are that it is labor-intensive with low throughput and is not amenable to automation. It may also be affected by subjective bias. The samples have to be processed immediately (within 6 h) since delay greatly reduces the assay's sensitivity. Particularly in neutropenic patients, false-negative results may occur, since the antigenemia test depends on the presence of a sufficient number of polymorphonuclear leukocytes.

Polymerase chain reaction: PCR is a widely available rapid and sensitive method of CMV detection based on amplification of nucleic acids. The techniques usually target highly conserved regions of major IE and late antigen genes, but a number of other genes have also been used as targets for detection of CMV DNA. DNA can be extracted from whole blood, leukocytes, plasma, or any other tissue (biopsy samples) or fluid (urine, cerebrospinal fluid [CSF], bronchoalveolar lavage [BAL] fluid). PCR for CMV DNA can be either qualitative or quantitative, in which the amount of viral DNA in the sample is measured. Qualitative PCR has been largely replaced by quantitative assays due to increased sensitivity for detecting CMV and because quantitative PCR (Real-Time PCR) allows for continuous monitoring of immunocompromised individuals to identify patients at risk for CMV disease for preemptive therapy and to determine response to treatment. This method is generally more expensive compared to the antigenemia assay, but it is rapid and can be automated. Results are usually reported as number of copies/mL of blood or plasma.

Immunohistochemistry: Immunohistochemistry is performed primarily on tissue or body fluid samples. Slides are made from frozen or paraffin-embedded sections of biopsy tissue samples (e.g., liver, lung) or by centrifuging cells onto a slide. Monoclonal or polyclonal antibodies against early CMV antigens are applied to the slides and visualized by fluorescently labeled antibodies or enzyme-labeled secondary antibodies, which are detected by the change of color of the substrate. The stained slides are examined by fluorescent or light microscopy.

Antigen-specific cytokine release assay: The Quantiferon-Gold-CMV® is a recently commercialized enzyme-linked immunosorbent assay (ELISA) measuring gamma-interferon release by CMV-specific lymphocytes in response to peptide antigens containing sequences of CMV proteins and human MHC class I haplotypes. The patient's blood is incubated in a test tube containing these stimulating proteins, which induce any of the patient's CD8+ cytotoxic T-lymphocytes (CTLs) that have been primed against CMV proteins to release gamma-interferon. The cytokine is then measured by standard ELISA. Positive tests represent cytokine release by CMV-primed CTLs suggesting that the patient possesses an intact lymphocytic response to CMV antigens. The clinical indications for use of this test and interpretation of results in select patient populations have not yet been well established.

Congenital Infection

The diagnosis of congenital CMV infection is typically made by the demonstration of the virus, viral antigens, or viral genome in newborn urine or saliva (*Table 106.4*). The detection of virus in urine or saliva within the first 2 weeks of life is considered the gold standard for the diagnosis of congenital CMV infection. Since the detection of the virus or viral genome in samples obtained from infants after the first 2–3 weeks of life may represent natal or postnatal acquisition of CMV, it is not possible to confirm congenital CMV infection in infants older than 3 weeks. Serological methods are unreliable for the diagnosis of congenital infection. Detection of CMV IgG antibody is complicated by transplacental transfer of maternal antibodies, and the currently available CMV IgM antibody assays do not have the high level of sensitivity and specificity of virus culture or PCR.

Traditional tissue culture techniques or shell vial assay for the detection of CMV in saliva or urine are considered the standard methods for the diagnosis of congenital CMV infection (*Table 106.4*). Rapid culture methods have

Table 106.4
Laboratory diagnosis of cytomegalovirus infection by patient population

Congenital infection	Detection of virus or viral antigens in saliva or urine using standard or rapid culture methods; CMV PCR of blood is highly specific but insufficiently sensitive; PCR assays of saliva and urine are promising
Perinatal infection	Viral culture or PCR of urine; proof of absence of CMV shedding in the first 2 weeks of life
Healthy host	Detection of virus or viral antigens in saliva, urine, BAL washings
Immunocompromised host	Culture; antigenemia; PCR of blood or body fluids; immunohistochemistry; cytokine release assay

comparable sensitivity and specificity to the standard cell culture assays and the results are available within 24–36 h. A rapid method using a 96-well microtiter plate and a monoclonal antibody to the CMV IE antigen was shown to be 94.5% sensitive and 100% specific for detecting CMV in the urine of congenitally infected infants. This microtiter plate assay has been adapted for use with saliva specimens with comparable sensitivity and specificity. The utility of antigenemia assay in the diagnosis of congenital CMV infection has not been established.

Although PCR amplification of virus DNA is a very sensitive method for the detection of CMV in a variety of clinical specimens, the utility of PCR or other nucleic acid amplification assays for the diagnosis of congenital CMV infection has not been defined. Several studies have shown that PCR of saliva and urine specimens could be useful for the identification of infants with congenital CMV infection. Since dried blood spots (DBS) are collected for routine metabolic screening from all infants born in the USA, there has been increasing interest in utilizing PCR-based assays for the detection of CMV in newborn DBS samples. Most early reports have studied selected infant populations and did not include a direct comparison of PCR with a standard (i.e., tissue culture) method for identifying CMV infection. The sensitivity of DBS PCR in the diagnosis of congenital CMV infection may vary with the amount of blood collected on the filter card, the method used for DNA extraction, and the PCR protocol. Early studies have examined the utility of PCR on DBS obtained from infants in the nursery to diagnose congenital CMV infection retrospectively at the time of detection of SNHL. A number of studies from a group of investigators in Italy examined DBS from newborns and reported a sensitivity of the DBS PCR assay approaching 100% with a specificity of 99%. However, in a large multicenter study of more than 20,000 newborns, a DBS real-time PCR assay was compared with saliva rapid culture for identification of infants with congenital CMV infection and demonstrated that DBS PCR could only detect less than 40% of congenitally infected infants. The sensitivity and specificity of the DBS PCR assay when compared with the saliva rapid culture were 30.4% (95% confidence interval [CI], 21.5–41.0%) and 99.9% (95% CI, 99.9–100%), respectively. These results indicate that such methods as currently performed will not be suitable for the mass screening of newborns for congenital CMV infection. The high specificity of the DBS PCR assay suggests that a positive DBS PCR result will identify infants with congenital CMV infection. However, the negative DBS PCR assay result does not exclude congenital CMV infection. These findings underscore the need for further evaluation of high-throughput methods performed on saliva or other samples that can be adapted to large-scale newborn CMV screening.

Several previous studies that included smaller numbers of subjects examined the utility of testing saliva samples with PCR-based methods and demonstrated the feasibility and high sensitivity of these methods. However, none of these studies have included screening of unselected newborns or a direct comparison of a saliva PCR assay to the standard rapid culture method on saliva or urine. Although a more recent study from Brazil, in which more than 8,000 newborns were screened for congenital CMV infection, demonstrated the utility of a saliva PCR assay to screen newborns for CMV, the PCR assay was not directly compared to the standard culture-based assay. The utility of real-time PCR of saliva samples to identify infants with congenital CMV infections was evaluated in a multicenter newborn screening study of approximately 35,000 infants using rapid culture and PCR of saliva specimens. The findings of this study showed that PCR testing of both liquid and dried saliva specimens has excellent sensitivity (>97%) and specificity (99.9%).

There is growing interest in examining the feasibility of a newborn CMV screening program in conjunction with universal newborn hearing screening. Although DBS PCR assays have been shown to have insufficient sensitivity for the identification of most infants with congenital CMV infection, the development of saliva PCR assays could have the potential to adapt these methods in a high-throughput approach to screen large number of newborns for congenital CMV infection.

Perinatal Infection

For definitive diagnosis of perinatal CMV infection, it is important to demonstrate no viral shedding in the first 2 weeks of life, since CMV excretion does not begin until 3–12 weeks after exposure (Table 106.4). There is no agreed-upon standard method for diagnosis of perinatal CMV infections, however. Viral culture and CMV DNA detection by PCR using urine or saliva are the preferred diagnostic methods.

Healthy Host

Active CMV infection can be diagnosed through virus isolation from sites of viral shedding (e.g., urine, saliva, or bronchoalveolar washings) and the shell vial assay allows for this to be done within a 24 h period (Table 106.4). Serology is only useful for determining primary CMV infection by documenting seroconversion or by documenting IgM and low-avidity IgG. PCR for viral DNA in the blood or plasma may occasionally be used as supportive data to diagnose primary CMV in the healthy host but is rarely used in clinical evaluation of otherwise healthy patients.

Immunocompromised Host

Serologic detection of CMV infection in the immunocompromised host is limited by the abnormal host response to viral infection. Serology may be used in the transplant setting to determine the risk of transmission from a seropositive donor or reactivation from a seropositive recipient posttransplant, and has been used to guide the usage of prophylactic antiviral therapy or preemptive viral monitoring and therapy. Blood antigenemia and quantitative DNA PCR tests are commonly used for posttransplant surveillance to determine onset of CMV infection prior to clinical disease, and to monitor response to antiviral therapy (Table 106.4). It is anticipated that the Quantiferon-Gold CMV test may be utilized in the posttransplant setting to determine whether a patient has developed a CMV-specific (protective) T-lymphocyte response posttransplant. However, this test is not yet in common clinical usage. After clinical disease has developed, CMV may be isolated by culture, PCR, or histology of relevant tissues (BAL in pneumonitis; biopsy in hepatitis; endoscopy and biopsy in colitis) (Table 106.4).

In patients with HIV infection, serology may be used to determine whether the patient is at risk for primary disease (e.g., from blood transfusions) or reactivation when severely immunocompromised. However, because of impaired antibody responses in AIDS patients, serology may not be useful during severe immunocompromise to diagnose CMV disease. Diagnosis is generally directed toward the involved organ. Retinitis may be diagnosed by slit lamp/ophthalmologic evaluation. CMV colitis or esophagitis may be diagnosed by endoscopic evaluation and biopsy, and may be identified from biopsies by culture, immunohistochemistry, or rarely by PCR. CMV encephalitis may be evaluated by culture and PCR of CSF, or rarely by brain biopsy and immunohistochemistry. Neuroimaging may be used to support the diagnosis of CMV encephalitis.

CMV colitis in IBD patients is generally diagnosed by endoscopy and biopsy, with analysis as in colitis in AIDS patients. Diagnosis of CMV in other immunocompromised hosts should be directed toward the disease entity encountered, as for AIDS and transplant patients.

Differential Diagnosis

The differential diagnosis of CMV disease is broad. For mononucleosis-like illness and pharyngitis, the differential may include EBV infection, HHV-6, HSV-1, Group A strep, toxoplasmosis, acute HIV infection (acute retroviral syndrome), enterovirus, and adenovirus. Other infectious and noninfectious conditions may be considered based upon clinical features that may be found during acute CMV disease (fever, myelosuppression, etc.) and have been reviewed elsewhere.

Treatment

General Care

Treatment in the immunocompetent host generally consists of supportive care. Patients with acute mononucleosis-like syndrome may use analgesics, antipyretics, and supportive hydration. Acute CMV disease is self-limited in the immunocompetent host, and steroids and antiviral treatments are not indicated in these patients.

Antiviral therapy: Ganciclovir (GCV) is a nucleoside analogue of guanosine, which inhibits the CMV DNA polymerase. Ganciclovir requires phosphorylation by viral and cellular polymerases to acquire activity. Valganciclovir is an orally bioavailable analogue of ganciclovir. Cidofovir (CDV) is a nucleotide analogue of

cytosine which, unlike ganciclovir, is phosphorylated to the active form by cellular kinases without the requirement for viral kinase activity. CDV inhibits viral DNA polymerase similar to GCV. The primary complication of this treatment is nephrotoxicity. CDV does not cross the blood–brain barrier efficiently. Foscarnet is a pyrophosphate analogue that requires no intracellular metabolism to directly inhibit the viral DNA polymerase. Foscarnet is indicated for use in CMV retinitis and is also used in patients with suspected or proven CMV infection resistant to GCV and CDV. Metabolic derangements and nephrotoxicity are associated with foscarnet administration. Intravenous immunoglobulin (IVIG) and CMV hyperimmune immunoglobulin (CMVIg) may be used as adjunctive therapy to treat or prevent CMV disease.

Congenital Infection

Antiviral therapy for congenital CMV infection is limited. Only one randomized controlled trial has been performed to assess the effect of 6 weeks of intravenous ganciclovir therapy on hearing outcomes in infants with symptomatic congenital infection with involvement of the central nervous system. Although this study suffered from patient attrition, treatment suggested a possible benefit with hearing thresholds declining in 20% of ganciclovir recipients at 1 year of age or older compared with worsening of hearing in 70% of subjects that did not receive treatment. Time to resolution of clinical symptoms including splenomegaly, hepatomegaly, and retinitis were not different between the control and treatment group. Treatment was associated with significant neutropenia in 63% of ganciclovir recipients. The American Academy of Pediatrics Committee on Infectious Diseases thus states that "therapy is not recommended routinely in this population of infected infants because of possible toxicities and adverse events associated with prolonged intravenous therapy. . . ." Because congenital CMV infection is a chronic infection, little data is available to suggest the best time to begin therapy and the ideal length of therapy. Currently, the National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group is conducting a randomized placebo controlled study to compare a 6-week versus 6-month course of oral valganciclovir in babies born with symptomatic CMV infection to assess the safety and efficacy in regards to hearing and development outcome (http://clinicaltrials.gov/ct2/show/NCT00466817?term=congenital+cmv+infection&rank=3). No studies have been conducted in children with asymptomatic infection at birth; therefore, antiviral therapy is generally not recommended in these patients as the risks of treatment far outweigh the potential benefit.

Immunocompromised Host

Ganciclovir is the primary antiviral drug used to treat active CMV infections in immunocompromised hosts. Ganciclovir and valganciclovir are also used in prophylactic and preemptive treatment to prevent CMV disease in high-risk transplant patients. Both prophylactic and preemptive strategies have been shown to be efficacious in prevention of CMV disease in high-risk transplant recipients. Ganciclovir may cause marrow suppression (neutropenia, thrombocytopenia) particularly during long-term usage, which may limit its utility in hematopoietic stem cell transplant recipients prior to engraftment. Marrow toxicity must be monitored while patients are receiving ganciclovir and is reversible with discontinuation of the drug. Drug-induced neutropenia has also been treated anecdotally with granulocyte-colony stimulating factor (G-CSF). In cases where GCV-resistant CMV is suspected or demonstrated, cidofovir or foscarnet may be utilized. However, depending upon the mechanism of resistance, GCV-resistant CMV may also be resistant to CDV.

Intravenous immunoglobulin (IVIG) and CMV hyperimmune immunoglobulin (CMVIg) have been used in high-risk immunocompromised patients who have or are at risk for hypogammaglobulinemia (e.g., solid organ and stem cell transplant recipients), to prevent acute CMV disease. Both IVIG and CMVIg are also thought to have broadly immunomodulatory functions that may have benefit to the patient. However, the efficacy of immunoglobulin prophylaxis to prevent CMV disease is not well documented and generally has not been recommended as a strategy to prevent CMV disease. CMVIg has also been used as adjunctive therapy in addition to antiviral treatment in hematopoietic stem cell transplant patients with CMV disease. Again, the efficacy of this therapy is not well established and if used should be accompanied by use of specific antiviral drugs to limit direct viral replication.

Prognosis

Congenital infection: Early studies of outcome in symptomatic congenital CMV infection demonstrated that approximately 10% of symptomatic infants will die in the newborn period. However, more recent data suggests

that the mortality rate is probably less than 5%. However, the majority of symptomatic children will suffer sequelae ranging from mild to severe psychomotor and perceptual handicaps. Multiple prospective studies have shown that approximately half of the children born with symptomatic infection will develop sensorineural hearing loss (SNHL), mental retardation with IQs less than 70, and microcephaly. Predictors of adverse neurological outcome in children with symptomatic congenital CMV infection include microcephaly, chorioretinitis, the presence of other neurologic abnormalities at birth or in early infancy, and cranial imaging abnormalities detected within the first month of life. In a recent study, Rivera et al. analyzed newborn findings and hearing outcome data on 190 children with symptomatic infection to identify clinical predictors of hearing loss. Univariate analysis revealed that intrauterine growth retardation, petechiae, hepatosplenomegaly, hepatitis, thrombocytopenia, and intracerebral calcifications were associated with the development of hearing loss. Logistic regression analysis showed that petechiae and intrauterine growth retardation were the only factors that were independently predictive of hearing loss.

In general, asymptomatic children have a better long-term prognosis than children with symptomatic congenital infection. However, approximately 10% of asymptomatic children will develop SNHL (*Table 106.5*). Many prospective studies of children with asymptomatic CMV infection have been performed to define the natural history of hearing loss in this group. These studies show that approximately one-half of children with asymptomatic infection who develop hearing loss will have bilateral deficits, which can vary from mild high-frequency loss to profound impairment. Additionally, hearing loss in these children is often progressive and/or of delayed onset requiring ongoing audiological evaluation. Other neurological complications can also occur in asymptomatic congenital CMV infection but at a much lower frequency than in symptomatic infection.

Perinatal infection: Unlike congenital CMV infection, no association of perinatal CMV infection and sensorineural hearing loss or delay in neuromotor development has been documented.

Healthy host: Immunocompetent hosts with acute CMV disease should experience complete recovery. Long-term sequelae are not associated with CMV infection. CMV does cause persistent lifelong infection, but after acute infection usually remains latent for the lifetime of the normal host.

Immunocompromised host: After acute disease, immunocompromised hosts may be able to develop protective immunity that would prevent additional episodes of clinical disease. However, depending on the source and duration of immunocompromise, patients may continue to be at risk for additional episodes of disease from reactivation or from reinfection.

Table 106.5
Audiologic results for children with congenital cytomegalovirus infection

	Symptomatic	Asymptomatic
No. (%) of children with SNHL	40.7%	7.4%
Bilateral loss	67.1%	47.9%
High-frequency loss only (4,000–8,000 Hz)	12.9%	37.5%
Delayed-onset loss	27.1%	37.5%
Median age (range) of delayed onset	33 month (6–197)	44 month (24–182)
Progressive loss	54.1%	54.2%
Fluctuating loss	29.4%	54.1%
Improvement of loss	21.1%	47.9%

Source: Adapted from Dahle AJ, Fowler KB, Wright JD et al (2000) Longitudinal investigations of hearing disorders in children with congenital cytomegalovirus. J Am Acad Audiol 11:283–290, with permission

Prevention

Hand washing is considered an effective means to limit spread of CMV in the community among immunocompetent hosts as well as nosocomial spread. Disinfectants such as chlorine, alcohol, and detergents (soap) destroy the viral envelope and render the virus noninfectious. It has been suggested that all women of childbearing age should know their CMV serostatus; however, this is controversial. There is evidence that hygiene counseling and change in behavior can decrease the rate of primary CMV infections in seronegative women during pregnancy.

For immunocompromised hosts, contact precautions including gown and gloves with hand washing/disinfection may prevent transmission in the hospital setting but are not feasible in the community. Use of disinfectants, soap, and avoidance of sharing food and beverages may limit exposure to CMV in the community for immunocompromised patients. Prophylactic antiviral therapy (ganciclovir or valganciclovir) may be used in high-risk transplant recipients to prevent CMV infection and disease. Research is ongoing to develop adoptive immunotherapy strategies in hematopoietic stem cell recipients at high risk for CMV

disease posttransplant, whereby lymphocytes are stimulated ex vivo with CMV antigens and subsequently infused into the at-risk transplant recipient, presumably providing virus-specific cytotoxic and/or memory T cells to the recipient. However, such treatments currently remain available only under research auspices.

Passive immunization with CMV hyperimmune globulin to prevent transmission and treat infected fetuses has been evaluated in one study of pregnant women with primary CMV infection. However, the study lacked randomization and a control group, thus the use of passive immunoprophylaxis in pregnancy awaits further studies.

Vaccine prevention of congenital CMV infection has been considered since the 1970s and directed toward prevention of primary CMV infection during pregnancy. Several vaccine candidates have been studied including an attenuated, replication-competent virus and an adjuvanted glycoprotein subunit vaccine. Both appear to induce an immune response and both produce at least some level of cellular immunity. In a phase 2 trial that included 464 CMV-seronegative women of childbearing age, an MF59-adjuvanted CMV glycoprotein B subunit vaccine had 50% efficacy (95% CI, 7–73) at preventing CMV infection. The overall benefits were modest and the study was not powered to assess efficacy in preventing maternal–fetal transmission. In addition, the strategy of preventing primary maternal infections does not address the CMV-associated hearing loss and other neurologic sequelae in congenitally infected children born to women with preexisting CMV immunity. Considerable interest exists regarding the potential use of a CMV vaccine in transplant candidates prior to transplantation, but no studies have been performed in this population.

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107 Epstein-Barr Virus Infection

Sami Al-Hajjar

Epstein-Barr virus (EBV) is a ubiquitous virus that is widespread in the human population. Its distribution seems to be influenced by age, socioeconomic status, climate, and race, although all of these factors may simply reflect close contact and the ease of transmissibility. In developing countries, primary EBV infections occur in 80–100% of children by 3–6 years of age. In developed countries, only 30–60% of 6-year-olds have serologic evidence of EBV infection. Seroepidemiologic studies in Saudi Arabia have shown that 50% of children up to the age of 4 years have antibodies to EBV. In these settings, the vast majority of primary infections are usually asymptomatic. Among susceptible adolescents and young adults, primary EBV infection presents with symptomatic disease, the hallmark being infectious mononucleosis (IM).

Etiology

EBV or human herpesvirus 4 is a gamma-herpesvirus that establishes latency in memory B cells to persist in the host. A relatively unstable virus, EBV has not been recovered from environmental surfaces or formites. Two types of EBV (type A and B) have been recognized on the basis of divergence of several Epstein-Barr nuclear antigens. There is currently no evidence that type difference accounts for the wide range of conditions associated with EBV infection.

Epidemiology

Humans are the only known reservoir. Human-to-human transmission of EBV occurs mainly via saliva. Palatine tonsils act as an important site used by EBV for invasion of the host and as a reservoir. EBV is transmitted via salivary contact through kissing or exchange of saliva from child to child, such as that which occurs in day care centers. The incubation period is estimated at 4–7 weeks. Once transmitted, the virus infects the epithelial cells of the oropharynx and the salivary gland ducts. Periodic shedding from such tissue is linked to virus reactivation from latency. Shedding is sustained for months after infection and then falls gradually; in 15–20% of all attempts, the virus can be recovered from saliva. Immunocompromised hosts, including human immunodeficiency virus type 1–infected patients and allograft recipients, have higher rates of shedding (average 50–80%). Evidence of the virus presence in cervical epithelium and semen has emerged, but sexual transmission has not been proved. The virus can be transmitted to susceptible recipients by blood transfusion or bone marrow transplantation.

Pathogenesis

EBV infects epithelial cells of the oropharynx and the cervix and resting B lymphocytes. Infection of the epithelial cells results in replication of the virus, with the release of virions from the cells. In contrast, infection of B lymphocytes usually results in latent infection without replication or release of virus.

EBV enters B lymphocytes by means of the CD21 receptor, which is also the receptor of the C3d component of complement; 18–24 h later, EBV nuclear antigens are detectable within the nucleus of infected cells. Expression of the viral genome, which encodes at least two viral proteins, is associated with immortalization and proliferation of the cell. The EBV-infected B lymphocytes are polyclonally activated to produce immunoglobulin and express a lymphocyte-determined membrane antigen that is the target of host cellular responses to virus-infected B lymphocytes. The host mounts a cellular immune response to control B-cell proliferation (the characteristic atypical lymphocytes found in the peripheral blood). Cytotoxic lymphocytes (CD8) are activated for this function; later memory T cells maintain the capacity to limit proliferation of EBV-infected B cells to less than one per 10^6 circulating B cells.

Clinical Manifestation

Most early infections are asymptomatic in children. The full clinical picture of IM may take days or even weeks to

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evolve. The classic manifestation typically includes fever, tonsillopharyngitis usually accompanied by exudates, lymphadenopathy, malaise, and splenic or liver enlargement. In general, the spectrum of IM in children is similar to the classic form described in young adults (Table 107.1).

The fever is usually not higher than 39.5°C and lasts 1–2 weeks, but it may persist for 4–5 weeks. The enlarged lymph nodes are usually non-tender or minimally tender and have no overlying skin erythema. The affected lymph nodes are located principally along the cervical chains in a bilateral fashion, and generalized adenopathy also may occur. Children younger than 4 years frequently display hepatosplenomegaly, skin rashes, and abdominal pain than do older children and young adults. The skin rashes in young children appear to be spontaneous and do not correlate, as they do in young adults, with the administration of ampicillin. The reasons for these differences are not clear. The clinical manifestations of the illness last approximately 2–3 weeks, with peak involvement during the second week.

EBV has been linked with a number of malignancies, including Burkitt lymphoma, Hodgkin disease, and nasopharyngeal carcinoma. Transplant recipients, especially those who have received cyclosporine A, FK506 (tacrolimus), or anti-CD3 (OKT3) antibody, are at increased risk of developing a potentially fatal lymphoproliferative disorder resembling IM that often occurs within the first year after transplantation. They are also at risk of developing focal tumors, generally of the non-Burkitt lymphoma type; these usually occur more than 1 year after transplantation. Either specific antigens or the genome of EBV has been found in most of these tumors. Uncontrolled EBV-induced lymphoproliferation may occur in patients with the X-linked lymphoproliferative syndrome (Duncan syndrome). Within families with this syndrome, individual cases may end in overwhelming infection and death during the acute phase of the illness.

EBV is associated with the variety of other disorders in AIDS patients. At least four EBV-related disorders – non-Hodgkin lymphomas (Burkitt or non-Burkitt), leiomyosarcomas, lymphocytic interstitial pneumonitis, and oral hairy leukoplakia – may develop in patients with AIDS. In children with AIDS, EBV DNA has been demonstrated in non-Hodgkin lymphoma tissues, muscle cells of leiomyosarcomas, and lung biopsies in which there is histologic evidence of lymphocytic interstitial pneumonitis.

The initially suspected etiologic association between EBV or IM and the chronic fatigue syndrome now appears to be inaccurate. Chronic fatigue syndrome (chronic debilitating illness characterized by extreme fatigue syndrome, neuropsychological abnormalities, and myriad other problems) is now thought to be caused by an as-yet-unidentified retrovirus.

Table 107.1
Clinical findings in children with documented Epstein-Barr virus infectious mononucleosis by age group

Clinical findings (%)	Age of patient (yr)	
	<4	4–16
Fever	90	100
Lymphadenopathy	94	94
Sore throat/tonsillopharyngitis	68	76
Splenomegaly	80	51
Hepatomegaly	63	30
Cutaneous rashes[a]	34	27

[a]Cutaneous rashes can be erythematous, petechial, erythema multiforme-like, urticarial, or scarlatiniform

Diagnosis

Most acute EBV illnesses can be diagnosed by the presence of typical clinical, hematologic, and serologic findings. Patients with IM typically demonstrate an absolute lymphocytosis of 50% or more. Lymphocytosis is most severe during the second and third weeks of illness and lasts for 2–6 weeks. Usually, 20–40% of the lymphocytes are atypical, although not all patients have more than 10% atypical lymphocytes. The atypical lymphocyte is generally larger than the mature lymphocyte encountered in peripheral blood. The cytoplasm is often vacuolated and basophilic, and its edges have a rolled-up appearance. Nuclei are often lobulated and are eccentrically located. It should be remembered that atypical lymphocytes are not pathognomonic for IM and can also be noted in other illnesses (Table 107.2). Liver function tests (LFTs) are abnormal in more than 90% of patients with infectious mononucleosis.

Identification of heterophil antibodies, originally described by Paul and Bunnel, is the cornerstone of laboratory diagnosis. These antibodies are directed at antigens present on erythrocytes obtained from sheep, horses, or cattle. In the heterophil antibody test, the patient's serum is first absorbed with guinea pig kidney homogenate to remove cross-reacting antibodies such as Forssman antibodies and those naturally occurring in serum sickness. With IM, heterophil antibody is still present and is usually

detected by agglutination of sheep red blood cells. The heterophil antibody titer is the higher dilution of the absorbed serum required to agglutinate these erythrocytes. Horse red cell agglutination is more sensitive than are tests for sheep or beef red cell agglutination. Among school-age children and young adults, heterophil antibodies become detectable 80–90% of the time during the second week of clinical illness. This antibody will present in only 50% of children younger than 4 years of age. Heterophil antibodies may persist for 6–12 months after recovery from the illness. Most laboratories use one of many rapid agglutination tests, such as Monospot, to screen for EBV instead of the standard tube heterophil titer, which is labor intensive. The correlation between the results is obtained by the use of these rapid agglutination tests and those from the classic tube heterophil test.

Although EBV accounts for over 90% of mononucleosis syndrome cases, cytomegalovirus, rubella, adenovirus, Toxoplasma gondii, hepatitis A virus, human immunodeficiency virus, and human herpesvirus occasionally are responsible for a heterophil-negative mononucleosis-like syndrome. Virus-specific antibodies to EBV viral capsid antigen or nuclear antigen are usually demonstrable when patients develop EBV infection.

Table 107.2
Other infectious mononucleosis-like illnesses associated with atypical lymphocytosis

Cytomegalovirus infections
Toxoplasmosis
Acute viral hepatitis
Adenovirus infection
Rubella
Drug reaction

If a typical clinical syndrome is accompanied by detectable heterophil antibodies, EBV-specific serologic studies are not indicated. However, in children less than 4 years old, in whom heterophil antibodies may never turn positive, EBV-specific serology should be performed (*Table 107.3*).

The acute phase of IM is characterized by serum immunoglobulin M (IgM) and immunoglobulin G (IgG) antibody responses to EBV capsid antigen and in most cases an IgG response to EBV early antigen complex. The IgM response to EBV capsid antigen is transient, lasting only one or two months and even less in very young children. The IgG response remains for life. Antibodies to EBV early antigen complex may last several months or even years after resolution of the IM episode. Antibodies to EBV nuclear antigen are typically late in onset, gradually emerging over several months following the acute IM episode, and may remain for life.

In some patients with lymphoproliferative disorders or atypical clinical disease, the serologic response to EBV antigens may be incomplete or even lacking. In such cases, it may be necessary to demonstrate the presence of EBV antigen using immunofluorescence or immunoblot techniques, or the presence of EBV nucleic acid in tissue sections or Quantitative polymerase chain reaction (PCR) can be used to measure Epstein-Barr virus DNA in plasma. Because of the narrow host range and long incubation period, culture of EBV for diagnostic purposes is not useful.

Complications

Most persons with IM will recover uneventfully. Approximately 20% of children will develop some type of complication (*Table 107.4*). Death from IM is rare. Of 20 deaths clearly associated with IM in one series, 9 were of neurologic origin, 3 each were caused by secondary

Table 107.3
Serologic profiles of Epstein-Barr virus infection

Pattern of antibodies to[a]					
Paul–Bunnel heterophil test	VCA IgM	VCA IgG	EA (IgG)	EBNA	Interpretation
–	–	–	–	–	Susceptible
+	+	+	+/–	–	Acute primary disease
–	–	+	+	–	Recent primary
–	–	+	–	+	Past infection

VCA viral capsid antigen, EA early antigen, IgM immunoglobulin M, IgG immunoglobulin G, EBNA Epstein-Barr virus-associated nuclear antigen
[a]Negative (<+, positive (>1:10)

Table 107.4
Complication in children with Epstein-Barr virus infectious mononucleosis

Neurologic	Seizures, meningitis/encephalitis, Guillian-Barre Syndrome, peripheral fascial nerve paralysis.
Respiratory	Pneumonia, severe airway obstruction
Hepatic	Hepatitis, Jaundice
Renal	Glomerulonephritis
Genital	Orchitis
Hematologic	Hemolytic anemia, thrombocytopenia with hemorrhages
Infectious	Recurrent tonsillopharyngitis, bacteremia

infection or splenic rupture, 2 by hepatic failure, and 1 by probable myocarditis. EBV has been also implicated in hemophagocytic syndrome.

Treatment

Supportive therapy is usually all that is required in uncomplicated IM because more than 90% of patients recover uneventfully without specific therapy. Supportive therapy includes bed rest, drinking fluids, and administration of aspirin or acetaminophen. Because of the infrequent complication of splenic rupture, patients should be advised to avoid contact sports or strenuous physical exercise until the spleen is no longer palpable. Clinically, rupture is suggested by the presence of abdominal pain, hypotension, and/or shock-like syndrome. In some patients who are severely asymptomatic (e.g., impending airway obstruction) or patients with complicated illness (hematologic or neurologic complications), steroid therapy should be considered.

The use of antiviral drugs (acyclovir) in IM has been evaluated in double-blind placebo-controlled studies without any significant reduction of clinical symptoms in the early course of IM. In immunosuppressed patients with EBV-related lymphoproliferative disorders, acyclovir has shown some effects in some cases. Several other agents, such as ganciclovir, E-5 (2-bromovinyl)-2-deoxyuridine (VDU), and several other nucleoside analogues, exhibit greater effect in vitro than does acyclovir but have not been adequately evaluated by clinical trials.

Intravenous immunoglobulin is used to modulate immune function in the presence of autoantibodies. It has been used successfully in the treatment of immune thrombocytopenia associated with IM and for the treatment of EBV-driven posttransplant lymphoproliferative disease (PTLD) in combination with other treatment.

Some early case reports on the use of anti-B-cell antibodies for the treatment of lymphoproliferative disorders have suggested that this approach may have therapeutic value in the control of EBV-driven PTLD. Rituximab (a humanized murine monoclonal antibody that recognizes the CD20 antigen on B cells) is the next-generation immunoreagent that has recently been approved for the treatment of certain CD20-positive-B-cell non-Hodgkins lymphomas and anecdotal studies have reported favorable responses in PTLD patients.

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108 Herpes Simplex Virus Infections

David W. Kimberlin

Introduction

Herpes simplex virus (HSV) infections are extremely common in people. Fortunately, most HSV infections are neither life threatening nor incapacitating. Generally speaking, HSV type 1 (HSV-1) infects above the belt, and HSV type 2 (HSV-2) infects below the belt. The most common disease manifestations of HSV are fever blisters (HSV-1) and genital herpes (HSV-2). Severe life-threatening disease can occur with either viral type in the neonate, with HSV-1 brain infection, or with either viral type in immunocompromised patients. Fortunately, safe and effective antiviral therapies exist for both mucocutaneous and life-threatening HSV infections.

Epidemiology

HSV Infections in Children and Nonpregnant Adults

General

Transmission of HSV occurs when the mucous membranes or abraded skin of a susceptible person come in contact with virus from the lesion of an infected host who is actively shedding infectious particles. This most often occurs during close, intimate contact. If a person who is susceptible to HSV infection (who lacks preexisting antibody) is exposed to HSV-1 or HSV-2, then a *first-episode primary infection* may result. Viral reactivation after the establishment of latency may result in a *recurrent infection*. If, however, a person with preexisting antibody to one type of HSV experiences a first infection with the opposite virus type, then a *first episode non-primary infection* will result. An example of a first episode non-primary infection is the person with preexisting HSV-1 antibodies from an episode of gingivostomatitis earlier in life who later acquires a genital HSV-2 infection.

Oropharyngeal HSV Infection

Herpes simplex virus-1 is found most commonly in the oropharynx. Primary infection with HSV-1 occurs most commonly in young children and is usually asymptomatic; when symptomatic, the child usually presents with gingivostomatitis. Primary infection in young adults has been associated with pharyngitis and, often, a mononucleosis-like syndrome. Primary gingivostomatitis results in viral shedding in oral secretions for an average of 7–10 days, but may occur for as long as 23 days. Neutralizing antibodies begin to appear between days 4 and 7 after clinical onset of disease, peaking at approximately 3 weeks. Virus can be isolated from the saliva of asymptomatic children and adults as well.

Factors which influence the frequency of primary HSV-1 infection include geographic location, socioeconomic status, and age. In the United States, one-quarter of white children and one-half of black children are infected with HSV-1 during their pre-adolescent years. Seroprevalence rates for both racial groups reach 85–90% by 60 years of age. HSV-1 antibody prevalence is higher in developing countries and in the lower socioeconomic classes of developed countries, illustrating the role that crowded living conditions plays in the epidemiology of infection. Recurrent herpes labialis accounts for the largest proportion of HSV infections. As with primary infections, recurrent disease may occur in the absence of clinical symptoms. At any given time, approximately 1% in normal children and between 1% and 5% in normal adults will be asymptomatically shedding HSV.

Genital HSV Infection

Genital HSV infections are usually caused by HSV-2, although in the United States at least 20% are attributable to HSV-1 and the frequency appears to be increasing. Conversely, in Japan and in Sheffield, England, these figures have been reported to be as high as 35% and 50%, respectively. Genital HSV-1 infections have been reported to be less severe and to recur less frequently than HSV-2 infections, a finding which could explain why recurrent genital herpes infections are caused by HSV-2 in 99% of cases.

The primary route of acquisition of HSV-2 infections is via sexual contact with an infected partner. As with oropharyngeal HSV-1 infection, HSV-2 can be recovered

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Table 108.1
HSV-2 antibody prevalence in the United States, 1999–2004

Sample Size		HSV-2 Seroprevalence (95% CI)	P-value
Overall	11,508	17.2 (15.9–18.7)	
Gender			
Male	5,511	11.2 (9.9–12.8)	<0.001
Female	5,997	23.1 (21.5–24.9)	
Race/ethnicity			
Non-Hispanic white	4,311	13.7 (12.5–15.0)	<0.001
Non-Hispanic black	2,926	40.3 (37.3–43.5)	
Mexican American	3,406	11.9 (10.4–13.5)	
Other	865	17.7 (14.2–22.1)	
Age group, years			
14–19	4,650	1.6 (1.3–2.0)	<0.001
20–29	2,412	10.6 (8.9–12.5)	
30–39	2,251	22.1 (20.1–24.3)	
40–49	2,195	26.3 (24.2–28.7)	
Marital Status			
Never married	6,154	10.3 (8.8–12.0)	<0.001
Living with partner	682	24.9 (20.9–29.6)	
Married	3,595	16.8 (15.1–18.7)	
Divorced	486	35.9 (29.8–43.2)	
Separated	274	34.5 (28.5–41.9)	
Widowed	48	47.4 (27.1–83.0)	
Lifetime Number of Sex Partners			
0	2,342	2.6 (1.4–5.0)	<0.001
1	1,568	3.8 (2.6–5.7)	
2–4	2,432	13.3 (11.4–15.6)	
5–9	1,843	20.8 (18.5–23.5)	
10–49	1,847	27.2 (25.0–29.6)	
≥ 50	284	39.9 (33.7–47.3)	

Adapted from Xu F, Sternberg MR, Kottiri BJ et al (2006) Trends in herpes simplex virus type 1 and type 2 seroprevalence in the United States. J Am Med Assoc 296(8):964–973

from the genital tract of asymptomatic patients with primary, initial, or recurrent HSV-2 infection. As would be expected, antibodies to this virus are rarely found prior to the onset of sexual activity. As demonstrated in *Table 108.1*, gender, race, age, marital status, and lifetime number of sexual partners each correlates with likelihood of having antibody to HSV-2.

Recurrent genital HSV-2 infection can be either symptomatic (recognized by the patient) or asymptomatic (unrecognized throughout the time of recurrence). The duration of viral shedding is shorter during recurrent infection, and there are fewer lesions present.

Maternal Genital HSV Infection

It is apparent from the seroprevalence data that genital HSV infection in women is not uncommon. The clinical presentation of HSV infection during pregnancy is varied. The most common form of maternal HSV infection during pregnancy is localized genital infection. On the other extreme, pregnant women can develop life-threatening disseminate HSV disease due to the relative immunosuppression incumbent in pregnancy. More extensive disease is more likely to occur in women with first-episode genital herpes; the fact that approximately 10% of pregnant

women are at risk of contracting a primary HSV-2 infection from their HSV-2-seropositive sexual partners is noteworthy. Primary infections are associated with fever, malaise, myalgias, and other signs and symptoms of systemic illness. Eight percent of such patients develop aseptic meningitis, and 2% have sacral autonomic nervous system dysfunction with associated urinary retention. In contrast, systemic symptoms are distinctly uncommon in recurrent infections.

Between 60% and 80% of women who deliver an HSV infected infant have neither a past history of genital herpes nor a sexual partner reporting a history of genital HSV. In order for significant improvement in the prevention of neonatal HSV to occur, the means of identifying women who are seropositive but have no known history of genital herpes, as well as of identifying seronegative women at risk for acquiring infection from a seropositive sexual partner, must be greatly improved.

Neonatal Herpes Simplex Infection

Factors Influencing Transmission of Infection to the Fetus

Five factors increase the likelihood that a woman shedding HSV in her genital tract at the time of delivery will transmit the virus to her neonate. The most important of these is the category of maternal infection she is experiencing. The infants at highest risk for neonatal disease are those delivered to a mother with primary or initial HSV infection. If a woman is shedding HSV in her genital tract at the time of delivery, the risk of neonatal acquisition is almost 60% if she is experiencing a first-episode primary infection, 25% if she is experiencing a first-episode non-primary infection, but only 2% if she is experiencing a recurrent infection. The duration and quantity of viral excretion as well as the time to complete healing vary according to whether maternal genital infection is first-episode primary, first-episode non-primary, or recurrent. With primary infection, larger concentrations of virus are shed in the genital tract ($>10^6$ viral particles per 0.2 mL of inoculum) for a longer duration of time (up to 21 days). In contrast, virus is shed for an average of only 2–5 days and at lower concentrations (10^2–10^3 viral particles per 0.2 mL of inoculum) in women with recurrent genital infections.

The pregnant woman's antibody status at delivery also influences the severity of infection and the likelihood of viral transmission. Transplacentally acquired maternal neutralizing antibodies have a protective effect both on the acquisition of and the outcome from infection following neonatal exposure to HSV during delivery. Complete neutralization of virus by antibody may occur in some infants, and prolongation of the incubation period and modification of the infection may occur in others.

Additionally, the duration of membrane rupture and mode of delivery both impact the risk for acquisition of neonatal infection. Cesarean delivery in a woman with active genital lesions can reduce but not completely eliminate the infant's risk of acquiring HSV, especially if performed within 4 h of rupture of membrane. Based on this observation, it is recommended that women with active genital lesions at the time of onset of labor be delivered by cesarean section. Importantly, neonatal infection has occurred in spite of cesarean delivery performed prior to the rupture of membranes.

Lastly, the application of fetal scalp monitors around the time of delivery may increase the risk of neonatal HSV infection by providing a site of inoculation for the virus. The risks and benefits of such devices should be considered carefully for women with a history of recurrent genital HSV infections.

Incidence of Newborn Infection

While fluctuations in the incidence of neonatal HSV disease have been observed, the current estimated rate of occurrence is approximately one in 3,200 deliveries. Over the past 25 years, a progressive increase in the number of cases of neonatal HSV infection has been noted in some areas, paralleling the increased prevalence of genital HSV infection noted over the same time period. Still, neonatal HSV infections occur far less frequently than do genital HSV infections in the adult child-bearing population. Overall, the United States, with approximately 4.0 million deliveries per year, has an estimated 1,500 cases of neonatal HSV infection annually.

Times of Transmission of Infection

Herpes simplex virus infection of the newborn can be acquired at one of three times: in utero, intrapartum, and postnatal. Though the overwhelming majority of cases are acquired during the intrapartum passage through an infected birth canal, the other two modes of transmission must be recognized and identified in infants with HSV disease for both public health and prognostic purposes. Regardless of the route by which a neonate becomes infected with HSV, the potential for mortality and devastating morbidity is equally ominous.

Intrauterine acquisition of HSV accounts for about 5% of all neonatal HSV infections. Neonates typically present at delivery (and by definition within the first 24 h of life) with findings suggestive of in utero infection. Intrauterine infection occurs as a consequence of either transplacental or ascending infection. In the former case, the placenta may demonstrate necrosis and inclusions in the trophoblasts. Alternatively, histopathologic evidence of chorioamnionitis in other cases support ascending infection as an alternate mode of intrauterine acquisition of HSV infection. Risk factors associated with intrauterine transmission are unknown at this time. Both primary and recurrent maternal infection can result in infection of the fetus in utero.

Intrapartum contact of the fetus with an infected maternal genital tract is by far the most common source of neonatal HSV infection, accounting for about 85% of all cases. Risk factors associated with intrapartum transmission of virus are discussed above.

Postnatal acquisition of HSV accounts for roughly 10% of all cases of neonatal HSV infection. The possibility for postnatal acquisition of virus is especially concerning when HSV-1 is isolated from an infant. With at least 20% of genital herpes now caused by HSV-1, detection of this virus in the neonate does not prove that the timing of viral acquisition was postnatal; however, given the very large reservoir of HSV-1 in children and adults who have had orolabial infection, one should consider the possibility of postnatal acquisition when HSV-1 is determined to be the cause of neonatal infection. Relatives and hospital personnel with orolabial herpetic lesions may serve as a source of virus for infection of the newborn.

Clinical Presentation

Neonatal HSV Infection

The clinical presentations of neonatal HSV infections are a manifestation of both the site and extent of viral replication. Herpes simplex virus infection acquired either intrapartum or postnatally can be classified as: (1) disease localized to the skin, eye, and/or mouth; (2) encephalitis, with or without skin, eye, and/or mouth involvement; and (3) disseminated infection that involves multiple organs, including the central nervous system, lung, liver, adrenals, skin, eye, and/or mouth. The presentation and outcome of infection, particularly prognosis after therapy, vary significantly according to category. *Table 108.2* summarizes disease characteristics of 186 infants with neonatal HSV infections treated with intravenous acyclovir from 1981 through 1997 as part of studies conducted by the National Institute of Allergy and Infectious Diseases (NIAID)

Table 108.2

Characteristics of neonates enrolled in CASG protocols and treated with intravenous acyclovir, by extent of disease and year

	SEM			CNS			Disseminated		
	1981–1988	1989–1997[a]		1981–1988	1989–1997		1981–1988	1989–1997	
Characteristic	*n* = 54	*n* = 10	*P*	*n* = 35	*n* = 28	*P*	*n* = 18	*n* = 41	*P*
Number premature	20 (41%)	2 (20%)	0.294	9 (27%)	10 (36%)	0.582	5 (28%)	17 (41%)	0.389
Mean age at study enrollment (days ± SE)	11.2 ± 0.9	12.0 ± 2.2	0.719	15.2 ± 1.3	19.7 ± 1.6	0.031	10.3 ± 1.1	11.4 ± 0.8	0.442
Mean time (days ± SE) between earliest HSV symptom and enrollment	5.9 ± 0.7	5.7 ± 1.3	0.901	6.6 ± 0.8	7.4 ± 1.3	0.607	5.3 ± 0.7	5.6 ± 0.7	0.764
Time between earliest HSV symptom and age at enrollment									
0–1 days	9 (17%)	2 (20%)	0.524	3 (9%)	2 (7%)	0.895	1 (6%)	8 (20%)	0.314
2–4 days	16 (31%)	2 (20%)		12 (35%)	9 (33%)		8 (44%)	10 (25%)	
5–8 days	17 (33%)	2 (20%)		8 (24%)	9 (33%)		7 (39%)	14 (35%)	
>8 days	10 (19%)	4 (40%)		11 (32%)	7 (26%)		2 (11%)	8 (20%)	
Unknown	2 (–)	0 (–)		1 (–)	1 (–)		0 (–)	1 (–)	

From Kimberlin DW, Lin CY, Jacobs RF et al (2001) Natural history of neonatal herpes simplex virus infections in the acyclovir era. Pediatrics 108(2):223–229

[a]Patients with CNS and disseminated HSV disease were disproportionately enrolled in the high-dose acyclovir study spanning 1989–1997. This fact accounts for the relatively lower percentage of patients with SEM disease in this report

Collaborative Antiviral Study Group. Table 108.3 summarizes the clinical characteristics that influence mortality on the basis of relative risk after multivariate adjustments.

Intrauterine Infection

Intrauterine infection accounts for about 5% of neonatal HSV infections. Thus, about one in 300,000 deliveries results in a child with intrauterine HSV infection. Manifestations of intrauterine HSV infection may be obvious or very subtle, closely resembling those findings encountered in other congenital infections. Since infection of the fetus can occur at any time during gestation, the earlier in gestation the infection occurs, the greater the likelihood of significant damage. Intrauterine infection is characterized by the triad of skin manifestations, chorioretinitis, and central nervous system involvement. A summary of 71 patients who have been reported in the literature is presented in Table 108.4.

Disseminated Disease

Infants with disseminated infection typically present to tertiary care centers around 10 or 11 days of life, although signs of infection usually begin an average of 5–6 days earlier (Table 108.2). Historically, this group of babies has accounted for approximately one-half to two-thirds of all children with neonatal HSV infection. However, this figure has been reduced to about 25% since the introduction of early antiviral therapy, likely the consequence of recognizing and treating SEM infection before its progression to more severe disease.

The principle organs involved during the course of disseminated infection are the liver and adrenal glands. Other organs which may be involved include the larynx, trachea, lungs, esophagus, stomach, lower gastrointestinal tract, spleen, kidneys, pancreas, central nervous system, and heart. Constitutional signs and symptoms include irritability, seizures, respiratory distress, jaundice, disseminated intravascular coagulopathy, shock, and, in 58% of patients with disseminated disease, the characteristic vesicular exanthem of HSV infections. Encephalitis is a common component of this category of infection, occurring in about 60–75% of infants with disseminated disease. While the presence of a vesicular rash can greatly facilitate the diagnosis of HSV infection, over 40% of neonates with disseminated HSV disease will not develop cutaneous vesicles during the course of their illness.

Prior to the advent of effective antiviral therapy for disseminated neonatal HSV disease, mortality exceeded 80%. With antiviral therapy, however, mortality from this category of disease has been decreased to approximately 30% (Fig. 108.1). The significant predictors of mortality in infants with disseminated disease are pneumonia, depressed levels of consciousness at presentation, and disseminated intravascular coagulopathy. Over 80% of survivors of disseminated neonatal HSV disease will have normal neurologic development at 12 months of age (Fig. 108.3).

Evidence of bone marrow dysfunction (leukopenia, thrombocytopenia), liver dysfunction (elevated AST, GGT; direct hyperbilirubinemia), coagulation problems (disseminated intravascular coagulopathy), and pneumonia (diffuse interstitial pattern on chest radiographs, progressing to hemorrhagic pneumonitis) are the best indicators of visceral involvement and thus disseminated infection. As such, the clinical laboratory and the radiology department are invaluable in monitoring extent of disease and disease progression.

CNS Disease

Infants with HSV infection can have involvement of the central nervous system as a manifestation of: (1) disseminated disease, or (2) encephalitis with or without skin, eye, and/or mouth involvement. Infants with disseminated infection probably seed the brain by a blood-borne route, resulting in multiple areas of cortical hemorrhagic necrosis. In contrast, neonates who present with only encephalitis likely develop brain disease as a consequence of retrograde axonal transmission of virus to the central nervous system, with a more focal pattern of CNS involvement. This contention is supported by the finding that neonates with encephalitis alone (those who do not have encephalitis as a manifestation of disseminated infection) usually present to tertiary care centers at approximately 19 days of life, whereas those with the more fulminate disseminated disease present at 10–11 days of life.

One-third of all neonates with HSV infection are categorized as having encephalitis with or without skin, eye, and/or mouth involvement. Clinical manifestations of encephalitis, either alone or in association with disseminated disease, include seizures (both focal and generalized), lethargy, irritability, tremors, poor feeding, temperature instability, and bulging fontanel. Of those infants with encephalitis without visceral dissemination, 63% have associated skin vesicles at any point in the disease course. Cultures of cerebrospinal fluid yield virus in 25–40% of all cases of neonatal HSV encephalitis. This is a significantly higher yield than the ~4% of positive CSF

Table 108.3

Prognostic factors identified by multivariate analyses for neonates with HSV

Infection	Relative Risk	
	Mortality	Morbidity
Total group (*n* = 202)		
Extent of disease		
Skin, eyes, or mouth	1	1
CNS	5.8*	4.4*
Disseminated	33*	2.1*
Level of consciousness		
Alert or lethargic	1	NS
Semicomatose or comatose	5.2*	NS
Disseminated intravascular coagulopathy	3.8*	NS
Prematurity	3.7*	NS
Virus type		
HSV-1	2.3**	1
HSV-2	1	4.9*
Seizures	NS	3.0*
Infants with disseminated disease (*n* = 46)		
Disseminated intravascular coagulopathy	3.5*	NS
Level of consciousness		
Alert or lethargic	1	1
Semicomatose or comatose	3.9*	4.0*
Pneumonia	3.6*	NS
Infants with CNS involvement (*n* = 71)		
Level of consciousness		
Alert or lethargic	1	NS
Semicomatose or comatose	6.1*	NS
Prematurity	5.2*	NS
Seizures	NS	3.4*
Infants with infection of the skin, eyes, or mouth (*n* = 85)		
No. of skin-vesicle recurrences		
< 3	NA	1
≥ 3	NA	21*
Virus type		
HSV-1	NA	1
HSV-2	NA	14**,[a]

Adapted from Whitley R, Arvin A, Prober C et al (1991) Predictors of morbidity and mortality in neonates with herpes simplex virus infections. New Engl J Med 324(7):450–454

CNS denotes central nervous system, *NS* not statistically significant ($P > 0.05$), and *NA* not applicable (no baby with disease confined to the skin, eyes, or mouth died)

*$P < 0.01$

**$P < 0.05$

[a]Because of the correlation between virus type and skin-vesicle recurrence, virus type was not significant in the multivariate model; however, it was significant as a single factor

Table 108.4
Summary of 71 patients reported with intrauterine HSV infection

	Number of Cases (%) (*N*=71)
Sex	
Male	17 (24)
Female	26 (37)
Not reported	28 (39)
Virus	
HSV-1	5 (7)
HSV-2	43 (61)
Not reported	23 (32)
Findings	
Prematurity	42 (59)
Small for gestational age	17 (24)
Spectrum of disease	
Cutaneous lesions/scarring alone	5 (7)
Ocular+CNS lesions	4 (6)
Cutaneous+ocular lesions	10 (14)
Cutaneous+CNS lesions	24 (34)
Cutaneous+ocular+CNS lesions	28 (39)
Hepatitis	10 (14)
Associated dysmorphic abnormalities	6 (8)

From Baldwin S, Whitley RJ (1989) Intrauterine herpes simplex virus infection. Teratology 39(1):1–10

cultures from adult patients with HSV encephalitis. Anticipated cerebrospinal fluid indices include a mild pleocytosis (usually 50–150 cells) with a predominance of mononuclear cells (>70%), an elevated protein (>100 mg/dL), and a normal or slightly decreased glucose. The presence of red blood cells in CSF obtained from an atraumatic lumbar puncture is a reflection of cortical necrosis secondary to the viral infection. Serial examinations of cerebrospinal fluid in a neonate with encephalitis demonstrate progressive increases in the protein concentration. It is possible to have central nervous system involvement (as determined by a positive polymerase chain reaction test) but no abnormalities of CSF indices. The importance of cerebrospinal fluid examinations in all infants with suspected HSV infection is underscored by the finding that even subtle abnormalities have been associated with significant developmental delay.

Additional studies which are of benefit in the evaluation of the infant with suspected HSV encephalitis include electroencephalography (EEG) and computed tomography (CT) or magnetic resonance imaging (MRI). The EEG is diffusely abnormal in 80% of neonates with CNS involvement at the time of presentation; however, cranial CT scan at the time of presentation is usually normal.

Prior to the use of antiviral agents, mortality from neonatal HSV encephalitis with or without skin, eye, and/or mouth involvement was 50%. Since the advent of vidarabine and acyclovir therapy, though, this mortality rate has decreased to 6% (*Fig. 108.2*). As shown in *Table 108.3*, a semicomatose or comatose level of consciousness, as well as prematurity, significantly predict mortality in infants with encephalitis.

The impact of antiviral therapy on morbidity in neonatal HSV encephalitis is less impressive. More than two-thirds of survivors of neonatal CNS disease have neurologic impairment at 1 year of age and beyond (*Fig. 108.3*). The only factor which has been found to predict morbidity in patients with CNS disease is the presence of seizures. Neurologic sequelae of neonatal HSV encephalitis include microcephaly, spastic quadriplegia, persistent seizure disorder, blindness, and developmental delay.

Skin, Eye, and/or Mouth (SEM) Disease

Infection localized to the skin, eye, and/or mouth has historically accounted for approximately 18% of all cases of neonatal HSV disease. With the introduction of early antiviral therapy, this frequency has increased to approximately 45%. The association between this increase in SEM disease and the decrease in disseminated infection is likely the consequence of recognizing and treating SEM infection before its progression to more severe disease. By definition, SEM disease does not result in mortality. It is not known at this time whether the neurologic morbidity previously attributed to SEM disease actually related to subclinical CNS involvement which was not recognizable prior to the development of polymerase chain reaction technology. Regardless, neurologic morbidity following SEM disease, if it occurs at all, is an unusual event.

Neonates with HSV infection localized to the skin, eye, and/or mouth generally present for medical attention around 11 or 12 days of life, although evidence of the disease usually has been present for 5–6 days. The skin vesicles are typically 1–2 mm in diameter and erupt from an erythematous base. They may progress to larger, bullous lesions greater than 1 cm in diameter. Clusters of vesicles often appear initially on the presenting part of

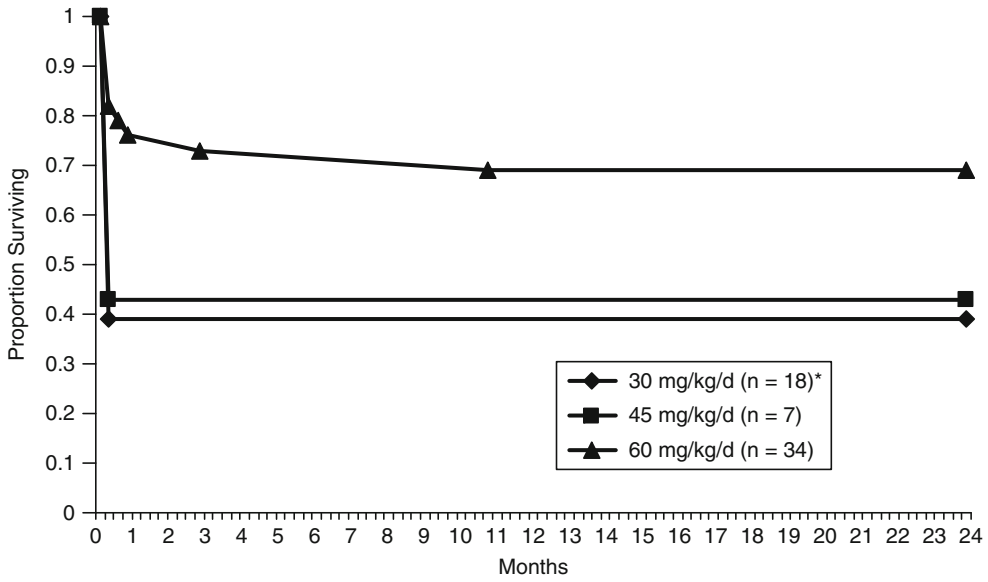

Figure 108.1
Mortality in neonatal HSV patients with disseminated disease

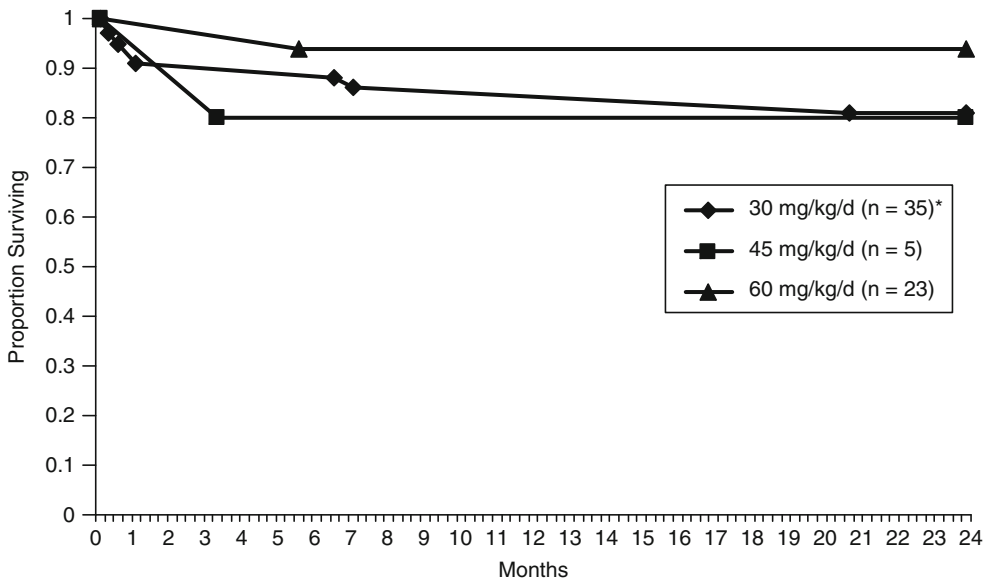

Figure 108.2
Mortality in neonatal HSV patients with CNS disease

the body that was in direct contact with the virus during birth. The rash may then progress to involve other areas of the body as well. While discrete vesicles on various parts of the body are usually encountered, crops and clusters of vesicles may also be seen. Such clusters of HSV vesicles have been described in a dermatomal, zosteriform pattern.

Oropharyngeal HSV lesions may occur with or without systemic involvement. Approximately 10% of all neonates with HSV infection have evidence of virus in the oropharynx. It is not clear, however, what proportion of these infants are excreting virus from this site in the absence of clinically apparent oropharyngeal lesions.

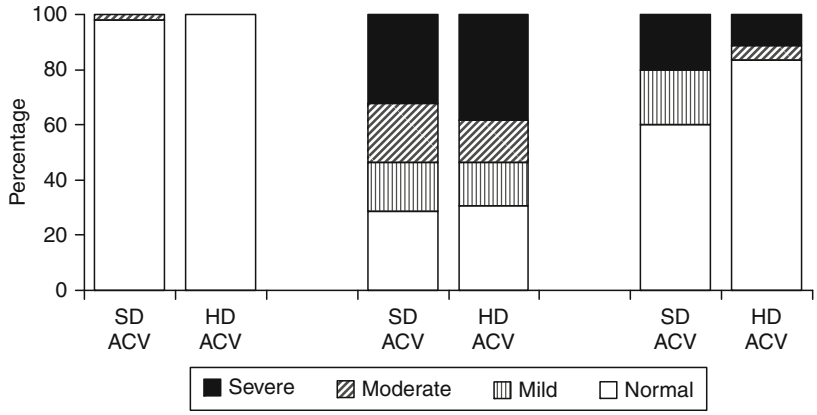

Figure 108.3
Morbidity among neonatal HSV patients with known outcomes after 12 months of age

Pediatric and Adolescent HSV Infections Beyond the Neonatal Period

Oropharyngeal HSV Disease

Most cases of primary HSV-1 infection in the pediatric age group are asymptomatic. When symptoms are present, they consist of variable combinations of fever, sore throat, ulcerative and vesicular oral lesions, gingivostomatitis, edema, localized lymphadenopathy, anorexia, and malaise. The incubation period for HSV-1 oropharyngeal infection ranges from 2 to 12 days, with a mean of approximately 4 days.

Symptomatic primary HSV-1 infection in children is characterized by buccal and gingival mucosal involvement. Clinical illness can last from 2 to 3 weeks, and fevers during that time can range from 101°F to 104°F. The degree of oropharyngeal involvement can predispose to dehydration due to the significant edema of the mucosal membranes and the associated pain. Oropharyngeal lesions evolve from vesicles to shallow ulcerations on erythematous bases, with subsequent slow healing. Intraoral vesicles are quite fragile and frequently rupture to leave the shallow ulcerations before being appreciated by the patient or his/her caregivers. Submandibular lymphadenopathy is a frequent component of primary HSV-1 illness, but is only rarely seen in recurrent disease. Other clinical signs and symptoms include sore throat, oral pain, malaise, tender cervical adenopathy, and an inability to eat or drink.

Symptomatic primary HSV-1 infection in adolescents and young adults is commonly associated with pharyngitis and a mononucleosis syndrome. Pharyngeal findings include tonsilar ulcerative lesions on erythematous bases and submandibular lymphadenopathy.

Within 24–48 h of clinical recurrence of HSV-1 vesicular lesions, a prodrome of pain, burning, tingling, or itching lasting fewer than 6 h commonly occurs. Vesicles most commonly appear at the vermillion border of the lip, persisting for only 48 h in most patients. Within 72–96 h, the lesions progress through ulceration to crusting, with a diminution of pain during this period. Healing is complete in 8–10 days. A typical recurrence consists of 3–5 vesicles localized to a small region of the vermillion border of the lip. The frequency of recurrences varies from person to person. Factors associated with recurrences of HSV-1 lesions include fever, stress, and exposure to UV light. HSV infection in patients with underlying eczema can result in severe cutaneous infection.

Genital HSV Disease

As is true with oropharyngeal HSV-1 infection, genital HSV-2 infection is more likely to produce symptoms when acquired for the first time, as opposed to recurrent infections. Primary HSV-2 infections can have associated fever, dysuria, localized inguinal adenopathy, and malaise. For reasons that are poorly understood, the severity of primary infection and complications thereof are higher in women than in men. Overall, systemic complaints occur in almost 70% of all cases of primary genital HSV infection.

Symptomatic primary genital HSV infections in women invariably involve the cervix, and vulvar lesions are usually bilateral. Additional sites of involvement can include the vagina, perineum, and buttocks. Lesions are usually exquisitely painful, with associated inguinal

adenopathy and dysuria. Eight percent of patients develop aseptic meningitis, and 2% have sacral autonomic nervous system dysfunction with associated urinary retention.

In men, symptomatic primary genital HSV infections manifest as clusters of vesicular lesions superimposed on erythematous bases, appearing usually on the glans penis or penile shaft. Numbers of vesicles are highly variable from patient to patient. Systemic complications in men with primary genital HSV infections are relatively uncommon, though aseptic meningitis can occur.

First-episode non-primary genital infection is associated with fewer and less severe systemic symptoms than primary disease. The number of lesions, severity of pain, and likelihood of complications are all notably decreased, likely due to the ameliorative effect of preexisting HSV-1 antibodies.

Herpes Simplex Encephalitis

Herpes simplex virus-1 causes encephalitis (HSE) in individuals of all ages and remains the most common cause of sporadic fatal encephalitis in the United States, accounting for approximately 1,250 cases yearly. The incidence of severe hemorrhagic focal encephalitis due to herpes simplex virus is approximately one in 200,000 persons per year. Mortality in untreated patients exceeds 70%, and only 2.5% of all patients return to completely normal neurologic function.

Clinical signs and symptoms which may be associated with HSE include focal neurologic findings, fever, altered consciousness, bizarre behavior, disordered mentation, and cerebrospinal fluid pleocytosis. Neuroimaging studies frequently demonstrate localized temporal lobe involvement. However, there are no characteristic series of findings which are pathognomonic for HSE. Thus, a high index of suspicion is crucial for the prompt diagnosis of this devastating disease. In pursuing this evaluation, however, other diagnostic possibilities should also be considered, as other treatable diseases can mimic HSE.

Herpes Simplex Keratoconjunctivitis

Primary herpetic keratoconjunctivitis initially manifests as either unilateral or bilateral conjunctivitis, followed by preauricular adenopathy. Associated symptoms include photophobia, tearing, eyelid edema, and chemosis. Herpetic ophthalmic infections beyond the neonatal period are usually caused by HSV-1, with approximately 300,000 cases diagnosed annually in the United States. Branching dendritic lesions are typically seen, and geographic ulcer of the cornea can occur in advanced ophthalmic disease. Recurrent HSV ophthalmic infections are common.

Diagnosis

Isolation of HSV by culture remains the definitive diagnostic method of determining HSV disease. If skin lesions are present, a scraping of the vesicles should be transferred in appropriate viral transport media on ice to a diagnostic virology laboratory. Such specimens are inoculated into cell culture systems, which are then monitored for cytopathic effects characteristic of HSV replication. Other sites from which virus may be isolated include the cerebrospinal fluid, urine, throat, nasopharynx, and conjunctivae. Duodenal aspirates for HSV isolation may be indicated in infants with hepatitis, necrotizing enterocolitis, or other gastrointestinal manifestations of disease. Typing of a HSV isolate may be done by one of several techniques and can be of value in determining the cause of the infection and prognosis for recurrence.

The diagnosis of HSV infections of the CNS and genital tract has been revolutionized by the development of polymerase chain reaction technology. PCR is now the gold standard for diagnosis of CNS involvement in neonatal HSV and in HSE. Increasingly, it also is used to detect viremia in neonatal HSV, and to document the presence of HSV in skin and mucosal surface lesions in HSV of all age groups. The test is now standardized to the point of being reliable in commercial laboratories, and has a much more rapid turnaround time compared with culture. With the exception of detection of viral DNA in CSF, if PCR is sent on non-CSF specimens, it generally is recommended that a specimen also be sent for HSV culture. The rationale for this apparent diagnostic duplication is that the sensitivity of HSV PCR is not as well defined in the non-CNS disease manifestations, and a positive viral culture will result in a viral isolate that can be studied further if needed.

In contrast to other congenital and neonatal infections, serologic diagnosis of HSV infection is not of great clinical value. The presence of transplacentally acquired maternal IgG confounds the assessment of the neonatal antibody status during acute infection. Serial antibody assessment may be useful in the very specific circumstance of a mother who has a primary infection late in gestation and transfers very little or no antibody to the fetus. Reliable, type-specific serologic assays are now commercially available and can be used to determine prior HSV-1 or HSV-2 infection in persons beyond the neonatal and infantile periods.

Treatment

Oropharyngeal HSV Disease

Orally administered acyclovir at a dose of 200 mg five times daily for 5 days reduces the length of time to the loss of crusts by approximately 1 day but does not alter the duration of pain or the length of time to complete healing. Increasing the dose to 400 mg five times daily for 5 days reduces duration of pain and length of time to the loss of crusts by about one-third, but only if treatment is started during the prodromal or erythematous stages of recurrent infection. Oral acyclovir begun within 96 h at a dose of 600 mg/m^2 four times daily for 10 days provides both virologic and clinical benefit when compared to placebo, though the duration of symptoms is decreased by only 2 days. Thus, oral acyclovir has a slight clinical benefit only if initiated very early after recurrence and cannot be recommended as routine treatment for herpes labialis in immunocompetent patients. Pediatric dosing of the valine ester prodrug of acyclovir, valacyclovir, has recently been defined.

Genital HSV Disease

Acyclovir administered topically, orally, and intravenously is effective in the treatment of primary genital herpes in the normal host, decreasing the duration of symptoms, viral shedding, and time to healing of lesions (*Table 108.5*). However, neither intravenous nor topical treatment of primary HSV lesions reduces the frequency or severity of recurrences. Episodic administration of oral or topical acyclovir for the treatment of recurrent genital HSV lesions provides only a modest benefit, with duration of lesions being shortened at most by 1–2 days. However, daily administration of oral acyclovir can effectively suppress recurrences of genital herpes in 60–90% of patients. There is no evidence that the frequency or severity of recurrent genital herpes is increased after cessation of long-term suppression therapy, and studies have evaluated suppressive therapy for as long as 3 years without evidence of substantial adverse effects. Treatment should be interrupted every 12 months to reassess the need for continued suppression. Valacyclovir and famciclovir are not more effective than acyclovir and cost more, but have

Table 108.5
Antiviral therapy in herpes simplex virus infections

Type of infection	Drug	Route and dosage[a]	Comments
Genital HSV			
Initial episode	Acyclovir	200 mg po 5 times/d × 10 day	Preferred route in normal host
		5 mg/kg IV q 8 h × 5 day	Reserved for severe cases
		5% ointment topically q 6 h × 7 day	Less effective than po
Recurrent episode	Acyclovir	200 mg po 5 times/day × 5 day	Limited clinical benefit
Suppression	Acyclovir	400 mg po BID	Titrate dose as required
Mucocutaneous HSV in immunocompromised patient	Acyclovir	200–400 mg po 5 times/day × 10 day	
		5 mg/kg IV q 8 h × 7–10 day[b]	
		5% ointment topically q 6 h × 7 day	For minor lesions only
HSV encephalitis	Acyclovir	10 mg/kg IV q 8 h × 10–14 day[c]	
Neonatal HSV	Acyclovir[d]	20 mg/kg IV q 8 h × 14–21 day	
Herpetic conjunctivitis	Trifluoridine	1 drop q 2 h while awake × 7–14 day	Alternate:
			Vidarabine
			Ointment

Adapted from Whitley RJ, Gnann J (1992) Acyclovir: a decade later. New Engl J Med 327:782–789
[a]The doses are for adults with normal renal function unless otherwise noted
[b]A dose of 250 mg/m^2 should be given to children <12 years of age
[c]A dose of 500 mg/m^2 should be given to children <12 years of age
[d]Acyclovir is not approved by the FDA for this indication

more favorable dosing intervals due to better oral bioavailability.

Mucocutaneous HSV Infections in Immunocompromised Patients

Topical acyclovir diminishes the duration of viral shedding and substantially improves time to cessation of pain and to total healing of HSV lesions in this patient population. Oral and intravenous acyclovirs are even more effective in improving outcome.

Prophylactic administration of oral or intravenous acyclovir to severely immunocompromised patients significantly reduces the incidence of symptomatic HSV infection (◉ *Table 108.5*). A sequential regimen of intravenous followed by oral acyclovir for 3–6 months can virtually eliminate symptomatic HSV infections in transplant recipients. Of note, however, acyclovir-resistant isolates have been identified in this group of highly immunocompromised patients.

Herpes Simplex Keratoconjunctivitis

Idoxuridine (Stoxil), trifluorothymidine (trifluridine, Viroptic), and vidarabine ophthalmic drops are effective and licensed for treatment of HSV keratitis. Of these compounds, trifluorothymidine is the most efficacious and the easiest to administer. In addition, trifluorothymidine is the compound most likely to penetrate the cornea, and thus may prove beneficial in the treatment of stromal keratitis and uveitis. As such, trifluorothymidine is the drug of choice for HSV ocular disease (◉ *Table 108.5*). Each of these ophthalmic preparations may cause local irritation, photophobia, edema of the eyelids and cornea, and superficial punctate keratopathy. Oral administration of acyclovir has been suggested as useful for both therapy and suppression of recurrent HSV ocular infections.

Herpes Simplex Encephalitis

Intravenous acyclovir is the drug of choice for the treatment of herpes simplex encephalitis (◉ *Table 108.5*). For the most favorable outcome, therapy must be instituted before semicoma or coma develops. While higher doses of parenteral acyclovir (45–60 mg/kg/day) are commonly used in the treatment of HSE, efficacy has not been studied and safety (particularly nephrotoxicity) should be assessed closely.

Neonatal HSV Infections

High-dose intravenous acyclovir (60 mg/kg/day in three divided daily doses) improves mortality following neonatal HSV disease. Treatment duration is 21 days for both CNS and disseminated disease, and is 14 days for SEM disease. Infants who have CNS involvement should have a repeat lumbar puncture obtained near the end of therapy to document clearance of viral DNA; in the unlikely event that the PCR remains positive, treatment should be extended for another week, with resampling of CSF for HSV DNA near the end of that extension as well. As such, treatment is extended until viral clearance is documented (◉ *Table 108.5*). Infants with ocular involvement caused by HSV should receive topical antiviral medication in addition to parenteral therapy. Trifluorothymidine (Viroptic) is the treatment of choice for HSV infection of the eyes of the neonate.

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109 Human Herpes Viruses Type 6 and 7

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Introduction

In 1986, a novel virus was isolated from six patients with lymphoproliferative syndromes, two of whom were also infected with the human immunodeficiency virus (HIV). Molecular and structural characterization of the new virus revealed an icosahedral core structure of 162 capsomeres, indicating that it was a herpesvirus. However, serological comparisons failed to demonstrate immunologic cross-reactivity with the five human herpesviruses known to exist at the time. Subsequent genomic analysis confirmed that the newly isolated virus was distinct from herpes simplex virus-1 (HSV-1), herpes simplex virus-2 (HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV). Due to the initial belief that the new virus selectively infected freshly isolated human B cells, the virus was given the name human B-lymphotropic virus (HBLV). Subsequent investigation revealed a broader cell tropism, with notable T-cell lymphotropism. For this reason, current nomenclature refers to this virus as human herpesvirus-6 (HHV-6).

Four years following the discovery of HHV-6, Frenkel and colleagues isolated another novel virus from the $CD4^+$ lymphocytes of a healthy adult. Designated human herpesvirus-7 (HHV-7), this new virus is closely related to HHV-6, exhibiting partial antigenic cross-reactivity with HHV-6. This rapid pace of discovery continued during the early 1990s, with DNA from the eighth member of the human herpesvirus family being isolated from Kaposi's sarcoma lesions of HIV-infected individuals in 1994. Thus, in less than a decade, the number of known human herpesviruses increased from five to eight. New technologic advances [peripheral blood mononuclear cell (PBMC) culture, representational difference analysis (RDA)] and the emergence of the acquired immunodeficiency syndrome (AIDS) epidemic converged to create the circumstances necessary for this remarkable pace of discovery. This chapter will review the current knowledge of HHV-6 and HHV-7 biology, of the pathology resulting from infection with these viruses in normal hosts, and of the possible impact of these viruses in immunocompromised persons.

Etiology

HHV-6 and HHV-7 are lymphotropic members of the *Herpesviridae* family. Genomic analysis places both among the β-herpesviruses, along with human CMV. Similarities with respect to amino acid sequences, gene organization, and putative protein functions suggest that HHV-6 is closely related phylogenetically to CMV. On the basis of DNA restriction analysis, in vitro tropism studies, and antigenic relationships defined by reactivities of monoclonal antibodies, HHV-6 can be separated into two variants, designated variant A (HHV-6A) and variant B (HHV-6B). Essentially all postnatally acquired primary infections in children are caused by variant B strains, except infections in some parts of Africa. Among congenital HHV-6 infections, however, as many as one-third may be variant A.

Epidemiology

HHV-6 and HHV-7 infections are ubiquitous in children worldwide. Humans are the only known natural host for these viruses. Epidemiologic studies in normal children have shown that the vast majority of primary HHV-6 infections occur within the first year of life. Human herpesvirus-6 IgG can be detected in more than 90% of neonates, reflecting both the high seroprevalence of HHV-6 among adults and the active transport of HHV-6 IgG across the placenta. The prevalence of HHV-6 IgG drops significantly by 4–6 months of life as maternal antibodies decline, then increases through the third year of life and remains high into adulthood. The highest geometric mean titers of HHV-6 antibody occur in the first 3 years of life, indicating a predominant clustering of primary infections in infants and toddlers. More than 90% of normal children become infected with HHV-6 by 12 months of life, and virtually 100% acquire infection by 3 years of age.

Transmission of HHV-6 in these early childhood years probably results from asymptomatic shedding of infectious virus in secretions of a healthy family member or

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other close contact. Reports of isolation of HHV-6 from the saliva of healthy adults and patients infected with HIV document salivary shedding in more than 85% of persons. Thus, immunosuppression is not a prerequisite for recovery of HHV-6 from saliva. Viral shedding in saliva is intermittent, and serum antibody titer to HHV-6 does not correlate with the ability to isolate HHV-6 from saliva samples. Human herpesvirus-6 DNA can be detected by polymerase chain reaction (PCR) in saliva or PBMCs of 90% of healthy individuals, and viral DNA may be detected throughout life by PCR assay in multiple body sites, including the brain or cerebrospinal fluid (CSF). Breast milk is unlikely to be an important source of early HHV-6 infection. Infections occur throughout the year without a seasonal pattern. Secondary cases rarely are identified. Congenital infection of HHV-6 occurs in about 1% of newborns as determined by the presence of HHV-6 DNA in cord blood. Most congenital infections appear to result from the germline passage of maternal or paternal chromosomally integrated HHV-6, a unique mechanism of transmission of human viral congenital infection. Transplacental HHV-6 infection also may occur from reinfection or reactivation of maternal HHV-6 infection or from reactivated maternal chromosomally integrated HHV-6.

HHV-7 infection usually occurs later in childhood compared with HHV-6. By adulthood, the seroprevalence of HHV-7 is approximately 85%. Infectious HHV-7 is present in more than 75% of saliva specimens obtained from healthy adults. Contact with infected respiratory tract secretions of healthy contacts is the probable mode of transmission of HHV-7 to young children. HHV-7 has been detected in breast milk, peripheral blood mononuclear cells, cervical secretions, and other body sites. Congenital HHV-7 infection has not been demonstrated by the examination of large numbers of cord bloods for HHV-7 DNA.

The mean incubation period for HHV-6 may be 9–10 days. For HHV-7, the incubation period is not known.

Clinical Presentation

Primary HHV-6 infection can be symptomatic or asymptomatic. In approximately 20% of children, infection will manifest as exanthem subitum, or roseola. A common disease of childhood, exanthem subitum was first described in 1910 by Zahorsky, who termed the illness roseola infantum. In 1921, Veeder helped confirm this syndrome as a specific pathologic entity and suggested the name exanthem subitum. Illness is characterized by a constant or intermittent, high fever to 104–105°F for 3–5 days in a patient who appears relatively well. The patient may have mild catarrhal inflammation of the pharyngeal mucosa and otitis media. Coincident with or immediately following the return of the temperature to normal, a rose pink macular rash appears predominantly on the neck and trunk, although it may involve the proximal extremities, postaural regions, and face. The rash is not pruritic, does not desquamate, and fades after 24–48 h.

As early as 1950, a possible viral etiology of exanthem subitum was proposed. In that year, Kempe and colleagues demonstrated direct person-to-person transmission by inoculation of blood from a patient symptomatic with roseola and speculated that a herpes-like virus might be the cause of the illness. Hellstrom and Vahlquist also succeeded in transmitting the infection by intramuscular injection into children. It was not until 1988, however, that Yamanishi and colleagues definitively proved the viral pathogenesis of exanthem subitum by successfully isolating HHV-6 from the peripheral blood lymphocytes of four infants in the febrile phase of exanthem subitum and by documenting seroconversion to HHV-6 in these patients. Subsequent studies have confirmed exanthem subitum as a manifestation of primary HHV-6 infection.

Primary HHV-6 infection also can manifest as an undifferentiated febrile illness without rash or localizing signs, as well as other acute febrile illnesses, often accompanied by cervical and characteristic postoccipital lymphadenopathy, gastrointestinal tract or respiratory tract signs, and inflamed tympanic membranes. As with exanthem subitum, fever is usually high (temperature greater than 39.5°C [103.0°F]) and persists for 3–7 days. Approximately 20% of all emergency department visits for febrile children 6 through 12 months of age are attributable to HHV-6.

Febrile seizures are the most common complication and reason for hospitalization among children with primary HHV-6 infection. Approximately 10–15% of children with primary HHV-6 illnesses develop febrile seizures, predominantly between the ages of 6–18 months. Other neurologic manifestations which may accompany primary infection include a bulging fontanelle and encephalopathy or encephalitis. Hepatitis has been reported as a rare manifestation of initial illness. Congenital HHV-6 infection is generally asymptomatic at birth. Whether clinical manifestations subsequently develop is unknown.

Primary HHV-7 infection is not strongly associated with a specific clinical entity. Most primary infections with HHV-7 presumably are asymptomatic or mild and not distinctive. Second or recurrent cases of roseola can be

caused by HHV-7, and the virus also may produce mild upper respiratory tract symptoms. HHV-7 also has been isolated from a child with fever, hepatosplenomegaly, and pancytopenia who subsequently developed hemophagocytic syndrome. HHV-7 also may be associated with febrile seizures, although to a much lesser extent than HHV-6.

Following primary infection, both HHV-6 and HHV-7 remain in a persistent or latent state and may reactivate. The clinical circumstances and manifestations of reactivation in healthy people are unclear. Illness associated with HHV-6 reactivation has been described primarily among immunocompromised recipients of solid organ and hematopoietic stem cell transplants. Among the clinical findings associated with HHV-6 reactivation in these patients are fever, rash, hepatitis, bone marrow suppression, graft rejection, pneumonia, and encephalitis. A few cases of CNS symptoms have been reported in association with HHV-7 reactivation in immunocompromised hosts, but clinical findings generally have been less frequently reported with HHV-7 than with HHV-6 reactivation.

Some investigators suggest that the association of HHV-7 with these clinical manifestations results from the ability of HHV-7 to reactivate HHV-6 from latency.

Diagnosis

Multiple assays for the detection of HHV-6 and HHV-7 have been developed, but few are commercially available and many do not differentiate between new, past, and reactivated infection. Diagnostic assays include serology, isolation of the virus from tissue culture, detection of viral DNA by qualitative and quantitative PCR, and of RNA by reverse-transcriptase PCR in blood, secretions, and tissues. Most of these assays are available only in research laboratories. Some serologic and DNA detection assays are commercially available.

Serologic tests currently used include immunofluorescent antibody, neutralization, immunoblot, and enzyme-linked immunosorbent (ELISA) assays. A fourfold increase in serum antibody concentration alone does not necessarily indicate new infection, since an increase in titer also may occur with reactivation and in association with other infections. Seroconversion from negative to positive in paired sera is good evidence of recent primary infection. Detection of specific immunoglobulin (Ig) M antibody also is not reliable for diagnosing new infection, as IgM antibodies to HHV-6 and HHV-7 are not always detectable in children with primary infection and also may be present in some asymptomatic previously infected individuals. Antibody assays to HHV-6 do not differentiate between HHV-6A and HHV-6B.

Diagnosis of primary HHV-7 infection in a child with previous HHV-6 infection is confounded by antigenic cross-reactivity between the two viruses. HHV-6 antibody titers will rise during a new HHV-7 infection, as well as during periods of reactivation of HHV-6 from latency. Detection of low-avidity HHV-6 or HHV-7 antibody with subsequent maturation to high-avidity antibody has been used in such situations to identify recent primary infection. Isolation of HHV-6 or HHV-7 in conjunction with seroconversion or, in the infant with maternal antibody, a fourfold titer rise confirms primary infection.

Polymerase chain reaction detection of HHV-6 DNA from blood and CSF is available through several commercial laboratories. However, detection of HHV-6 DNA or HHV-7 DNA in peripheral blood mononuclear cells, other body fluids, and tissues does not differentiate between new infection and reactivation of latent virus from a prior infection. As such, their interpretation can be challenging. Chromosomal integration of HHV-6 is indicated by consistently positive PCR tests for HHV-6 DNA in blood with high viral loads ($\geq$ 1 copy of HHV-6 DNA per leukocyte), and is confirmed by the detection of HHV-6 DNA in hair follicles.

Treatment

Antiviral susceptibility patterns of HHV-6 in vitro closely resemble those of CMV. HHV-6 multiplication is readily inhibited by ganciclovir at concentrations of 2–10 μmol/L and by foscarnet at a concentration of 66 μmol/L, both of which are easily achievable in the plasma of humans. Cidofovir also has demonstrable in vitro activity against HHV-6. While acyclovir has an inhibitory effect in vitro against HHV-6, it is much less active than either ganciclovir or foscarnet. Despite these in vitro findings, controlled prospective clinical evaluations of antiviral therapy for HHV-6 infections have not been conducted. Individual case reports in bone marrow transplant patients with HHV-6 encephalitis, however, suggest that ganciclovir, foscarnet, or a combination of these drugs can be beneficial, but that antiviral resistance may occur.

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110 Varicella-Zoster Virus Infections

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Definition/Classification

Varicella-zoster virus (VZV) is a DNA virus and a member of the herpesvirus family. VZV is classified as an alphaherpesvirus and is related most closely to herpes simplex virus types 1 and 2. Like other herpesviruses, VZV has the capacity to persist in the body after primary infection as a latent infection.

Etiology

Varicella-zoster virus (VZV) is so named because it causes two distinct diseases, varicella and zoster. Primary infection with VZV causes varicella, commonly referred to as chickenpox. After the primary infection, VZV establishes latency in dorsal nerve root ganglion and can reactivate, usually many years later, to cause herpes zoster, also referred to as shingles.

Epidemiology

Varicella and herpes zoster are human diseases. Humans are the only reservoir of VZV. VZV infections occur worldwide. In temperate climates, it is estimated that 90–95% of individuals acquire VZV in childhood as a result of annual varicella epidemics. Varicella tends to be less of a childhood illness in the tropics, with higher rates of susceptibility in adults. Some data suggest that in tropical areas, varicella infection occurs more commonly among adults than children. The reasons for this difference in age distribution is not known, but may be related to lack of childhood varicella infection in rural populations. In temperate areas, varicella has a distinct seasonal fluctuation, with the highest incidence occurring in winter and early spring. Less seasonality is reported in tropical areas. Herpes zoster has no seasonal variation and occurs throughout the year.

Varicella is a highly contagious disease with an attack rate of 65–86% in susceptible individuals following household exposure. It is less contagious than measles, but more so than mumps and rubella. Patients who have zoster can transmit varicella to others because the vesicular lesions contain infectious VZV. Zoster however is less contagious than varicella.

In the United States, prior to the introduction of varicella vaccine in 1995, an estimated four million cases of varicella occurred annually. In the prevaccine era, approximately 85% of cases occurred among children younger than 15 years of age. The highest age-specific incidence of varicella just prior to the introduction of vaccine was among children 1–4 years of age, who accounted for 39% of all cases. This age distribution was probably a result of exposure to VZV in preschool and child care settings. Children 5–9 years of age accounted for 38% of cases. Adults 20 years of age and older accounted for only 7% of cases. The implementation of the varicella vaccination program in the United States has lead to a steady decline in the incidence of varicella in all age groups, with the greatest decline among children 1–4 years of age.

In the prevaccine era in the United States, there were approximately 11,000 hospitalizations for varicella or varicella-related complications each year. Hospitalization rates were approximately 2–3 per 1,000 cases among healthy children and 8 per 1,000 cases among adults. Death occurred in approximately 1 in 60,000 cases. From 1990 through 1996, an average of 103 deaths from varicella was reported each year. Most deaths occurred in immunocompetent children and adults. After introduction of varicella vaccine, the number of hospitalizations and deaths from varicella has declined more than 90%.

Despite high one-dose vaccination coverage and success of the vaccination program in the United States in reducing varicella morbidity and mortality, data from varicella surveillance from 2001 to 2005 indicated that the number of reported varicella cases reached a plateau, and increasing proportion of cases represented breakthrough infection (chickenpox occurring in a previously vaccinated person). Outbreaks were reported in schools with high varicella vaccination coverage (96–100%). These outbreaks had many similarities: all occurred in elementary schools; vaccine effectiveness was within the expected range (72–85%); the highest attack rates occurred among the younger students; each outbreak lasted about

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2 months; and persons with breakthrough infection transmitted the virus although the breakthrough disease was mild. Overall attack rates among vaccinated children were 11–17%, with attack rates in some classrooms as high as 40%. These data indicated that even in settings where almost everyone was vaccinated and vaccine performed as expected, varicella outbreaks could not be prevented with a one-dose vaccination policy. These observations led to the recommendation in 2006 for a second routine dose of varicella vaccine in the United States.

Patients who develop zoster usually have a history of previous varicella. Zoster remains an illness of individuals over the age of 50 years and immunocompromised persons, especially bone marrow transplant recipients and children with human immunodeficiency virus. Zoster also develops commonly in patients treated for cancer and after organ transplantation. An estimated 500,000 to 1 million episodes of zoster occur annually in the United States. The lifetime risk of zoster is estimated to be at least 32%. Increasing age and cellular immunosuppression are the most important risk factors; 50% of persons living until age 85 years will develop zoster.

Zoster can occur in childhood. The incidence of zoster is increased by a factor of as much as 20 in those who had varicella in utero or before age 2 years, possibly because the immune response to VZV in young infants is immature. Children who develop zoster should be screened for possible risk factors such as HIV infection and underlying immunodeficiency; however, predisposing factors rarely are identified. On occasion, zoster occurs in healthy children or young adults. Presumably, such infection is a result of a transient decrease in cell-mediated immunity caused perhaps by another inapparent viral infection.

Pathogenesis

VZV is transmitted from person to person by direct contact, inhalation of aerosols from vesicular fluid of skin lesions of acute varicella or zoster, or infected respiratory tract secretions that might also be aerosolized. The period of contagiousness is estimated to begin 1–2 days before the onset of rash and to end when all lesions are crusted, typically 4–7 days after onset of rash in immunocompetent persons, but this period may be longer in immunocompromised persons.

VZV enters the host through the upper respiratory tract. Early studies of pathogenesis suggested that the virus replicated at the site of entry in the nasopharynx and in regional lymph nodes. A primary viremia followed 4–6 days after infection and disseminated the virus to other organs, such as the liver, spleen, and sensory ganglia. Further replication occurred in the viscera, followed by a secondary viremia, with viral infection of the skin.

More recent studies show the virus infects the respiratory epithelial cells from which the virus gains access to highly permissive T lymphocytes in the tonsillar lymphoid tissue. The virus is transferred to skin sites of replication by infected T lymphocytes within 24 h of infection. The formation of skin lesions that penetrate the skin surfaces requires 10–21 days because cell-to-cell spread of the virus after T lymphocyte transfer is countered by the potent innate antiviral responses of epidermal cells. VZV may also replicate in reticuloendothelial organs, such as the liver and the spleen. Uninfected T lymphocytes that traffic through sites of VZV lesion formation may amplify VZV viremia. The virus can be cultured from mononuclear cells of an infected person from 5 days before to 1 or 2 days after the appearance of the rash. VZV reaches neurons in dorsal nerve root ganglia during primary infection either by the hematogenous route or by anteretrograde transport along neurons from skin lesions. VZV then establishes latency in dorsal nerve root ganglia.

VZV reactivation causes a localized vesicular rash that usually involves the dermatomal distribution of a single sensory nerve. Infectious VZV is present in herpes zoster lesions, but the virus does not appear to be released into respiratory secretions during reactivation. Although subclinical reactivation has been difficult to document, it is likely to occur.

Primary VZV infection elicits antibodies directed against viral proteins which have neutralizing activity and mediate destruction of infected cells by antibody mediated cellular cytotoxicity. However, intact cellular immunity appears to be critical for the host to terminate viremia and virus replication at localized cutaneous sites. Children with untreated agammaglobulinemia generally have uncomplicated varicella, whereas those with primary immunodeficiency diseases affecting cell mediated immunity often die. Persistent VZV immunity may be maintained by periodic reexposure to the virus during annual epidemics or by repeated antigenic stimulation from subclinical reactivation of latent VZV.

Pathology

The skin lesions of varicella and herpes zoster are identical to each other and also to the lesions of herpes simplex virus. Vesicles fill with neutrophils and soon erode to become shallow ulcers. In infected cells, VZV produces a characteristic cytopathic effect, consisting of intranuclear

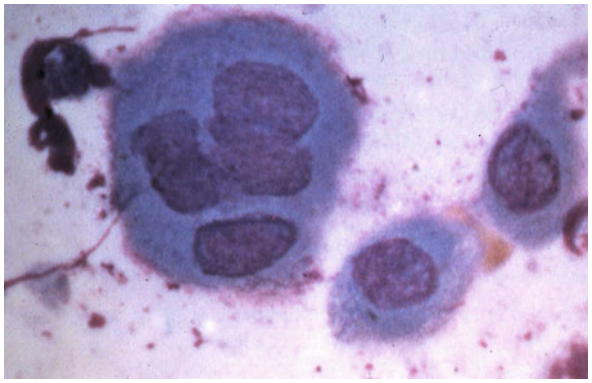

Figure 110.1
A Tzanck smear from a vesicular lesion showing multinucleated epithelial cells

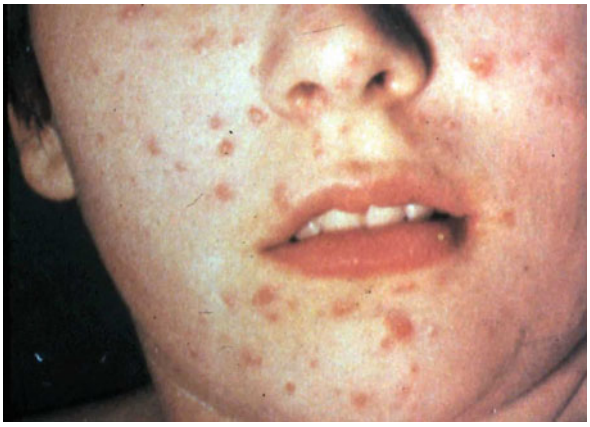

Figure 110.2
Papules, vesicles, pustules and crusts may be present at the same time

inclusions (Cowdry type A). The inclusion is large and eosinophilic and is separated from the nuclear membrane by a clear zone (halo). Multinucleated cells are common (*Fig. 110.1*). Over several days, vesicles become pustules and then rupture and heal.

In herpes zoster, the dorsal nerve root ganglion typically exhibits intense inflammation accompanied by hemorrhagic necrosis of nerve cells. The ganglion undergoes eventual neuronal loss with subsequent fibrosis of afferent nerve fibers, particularly type-C nociceptors.

Clinical Manifestations

Varicella

The average incubation period for varicella is 14–16 days with a range of 10–21 days. The incubation period may be prolonged in immunocompromised patients and those who have received postexposure treatment with a varicella antibody–containing product.

Varicella usually lasts 4–7 days and is characterized a pruritic rash consisting of crops of macules, papules, and vesicles which appear in three or more successive waves and resolve by crusting. A mild prodrome may precede the onset of a rash. Adults may have 1–2 days of fever and malaise prior to rash onset, but in children the rash is often the first sign of disease. The rash is generalized and pruritic and progresses rapidly from macules to papules to vesicular lesions before crusting. The rash usually appears first on the head, then on the trunk, and then the extremities; the highest concentration of lesions is on the trunk (centripetal distribution). Lesions also can occur on mucous membranes of the oropharynx, respiratory tract, vagina, conjunctiva, and the cornea. Lesions are usually 1–4 mm in diameter. The vesicles are superficial and delicate and contain clear fluid on an erythematous base. Vesicles may rupture or become purulent before they dry and crust. Successive crops appear over several days, with lesions present in several stages of development (*Fig. 110.2*). For example, macular lesions may be observed in the same area of skin as mature vesicles. Healthy children usually have 200–500 lesions in two to four successive crops.

The clinical course in healthy children is generally mild, with malaise, pruritus (itching), and temperature up to 102°F (38.9°C) for 2–3 days. Adults may have more severe disease and have a higher incidence of complications. Respiratory and gastrointestinal symptoms are absent. Children with lymphoma and leukemia may develop a severe progressive form of varicella characterized by high fever, extensive vesicular eruption, and high complication rates. Children infected with human immunodeficiency virus also may have severe, prolonged illness. Recovery from primary varicella infection usually results in lifetime immunity.

Most VZV infections result in clinical illness, but about 5% of primary infections are subclinical. Second attacks of varicella are unusual in otherwise healthy individuals, although they are recognized to occur. One estimate is that 1 in 500 persons with a prior history of varicella will experience a second attack after a household exposure to varicella. As with other viral diseases, reexposure to varicella may lead to reinfection that boosts antibody titers without causing clinical illness or detectable viremia.

A modified varicella, known as breakthrough disease, can occur in some vaccinated persons because the vaccine is only 70–90% effective in preventing disease. Breakthrough varicella is mild in 70–80% of cases, with <50 skin lesions, less fever, and shorter duration of rash. The rash may be atypical in appearance with fewer vesicles and predominance of maculopapular lesions. Nevertheless, breakthrough varicella is infectious (although less than varicella in unvaccinated persons).

In utero infection can occur as a result of transplacental passage of virus during maternal varicella infection. Primary maternal varicella infection in the first 20 weeks of gestation is occasionally associated with a variety of abnormalities in the newborn, including low birth weight, hypoplasia of an extremity, skin scarring, localized muscular atrophy, encephalitis, cortical atrophy, chorioretinitis, and microcephaly. This constellation of abnormalities, known as congenital varicella syndrome, was first recognized in 1947. The risk of congenital abnormalities from primary maternal varicella infection appears to be less than 2%. Rare reports of congenital birth defects following maternal zoster exist, but virologic confirmation of maternal lesions is lacking.

Herpes Zoster

Herpes zoster, or shingles, occurs when latent VZV reactivates and causes recurrent disease. Zoster usually appears as a unilateral vesicular skin eruption involving one to three dermatomes (*Fig. 110.3*). Most often, this involves the trunk or the fifth cranial nerve. Two to four days prior to the eruption, there may be pain and paresthesia in the involved area. Skin vesicles may be pruritic or painful, especially in adults. Zoster generally is a milder disease in children than in adults. There are few systemic symptoms. In immunocompromised persons, zoster may disseminate, causing generalized skin lesions and central nervous system, pulmonary, and hepatic involvement.

From 25–50% of persons older than 50 years of age and the same proportion of immunocompromised patients who acquire zoster experience serious pain, termed postherpetic neuralgia, after the rash has healed. The cause of postherpetic neuralgia is unknown.

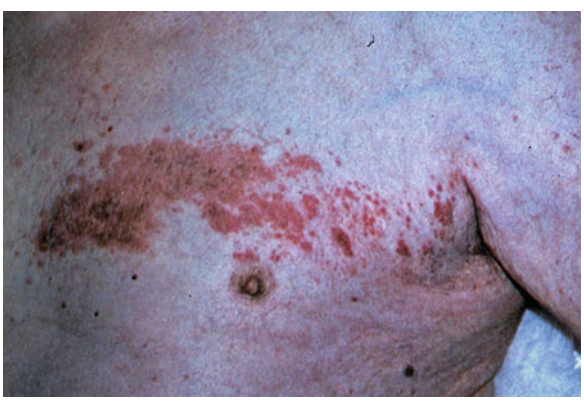

Figure 110.3
A zoster rash showing the distinctive unilateral dermatomal distribution

Diagnosis

Varicella generally is diagnosed clinically because of the characteristic vesicular rash and its distribution, as well as through epidemiologic information such as history of exposure and absence of prior varicella. Zoster also presents with a distinctive unilateral, dermatomal, vesicular rash that is diagnosed clinically. Laboratory diagnosis is not routinely required, but is useful if confirmation of the diagnosis or determination of susceptibility is necessary. The dramatic decline in varicella incidence as a result of routine varicella immunization in the United States has had the combined effect of increasing the number of atypical cases and of reducing physicians' experience in diagnosing varicella. As a result, the need for laboratory confirmation of varicella has increased.

Rapid varicella virus identification techniques are helpful for a case with severe or unusual disease to aid in the decision to initiate specific antiviral therapy. The diagnosis of varicella or zoster is made most definitively by demonstration of specific viral antigens in skin scrapings by immunofluorescence using a commercial monoclonal antibody to VZV conjugated to fluorescein (DFA) or by polymerase chain reaction (PCR). These diagnostic methods are highly sensitive and rapid. Real-time PCR methods are widely available and are the most sensitive and specific method of the available tests. Results are available within several hours. If real-time PCR is unavailable, DFA can be used, although it is less sensitive than PCR and requires more meticulous specimen collection and handling. Diagnosis also may be made by isolating virus from skin lesions, but this technique is more complicated and expensive, is less sensitive, and takes longer than DFA or PCR. The Tzanck test is not recommended because it lacks sensitivity and specificity. PCR can distinguish between vaccine and wild type VZV.

Skin lesions are the preferred specimen for laboratory confirmation of varicella disease. Specimens are best collected by unroofing a vesicle, preferably a fresh fluid-filled vesicle, and then rubbing the base of a skin lesion with a polyester swab. Crusts from lesions are also excellent specimens for PCR. Other specimen sources such as nasopharyngeal secretions, saliva, blood, urine, bronchial washings, and cerebrospinal fluid are considered less desirable sources than skin lesions because positive test results from such specimens are much less likely. Because viral proteins persist after cessation of viral replication, PCR and DFA may be positive when viral cultures are negative.

A reliable history of chickenpox has been found to be a valid measure of immunity to varicella because the rash is distinctive and subclinical cases are unusual. As a result, serologic testing of children is generally not necessary. However, serologic testing may be useful in adults where as many as 50% of those without a history of varicella will be found to be immune.

A variety of serologic tests for varicella antibody are available. Available tests include complement fixation (CF), indirect fluorescent antibody (IFA), fluorescent antibody to membrane antigen (FAMA), neutralization, indirect hemagglutination (IHA), immune adherence hemagglutination (IAHA), radioimmunoassay (RIA), latex agglutination (LA), and enzyme-linked immunosorbent assay (ELISA). ELISA is sensitive and specific, simple to perform, and widely available commercially. A commercially available LA assay is sensitive, simple, and rapid to perform. LA is generally more sensitive than commercial ELISAs, although it can result in false-positive results, leading to failure to identify persons without evidence of varicella immunity. This latter concern can be minimized by performing LA as a dilution series. Either of these tests would be useful for screening for varicella immunity.

Antibody resulting from vaccination is generally of lower titer than antibody resulting from varicella disease. Commercial antibody assays, particularly the LA test, may not be sensitive enough to detect vaccine-induced antibody in some recipients. Because of the potential for false-negative serologic tests, routine postvaccination serologic testing is not recommended.

For diagnosis of acute varicella infection, serologic confirmation would include a significant rise in varicella IgG by any standard serologic assay. Testing using commercial kits for IgM antibody is not recommended since available methods lack sensitivity and specificity; false-positive IgM results are common in the presence of high IgG levels.

Differential Diagnosis

In most cases, the characteristic features of the vesicular varicella rash establish the clinical diagnosis. The differential diagnosis consists mainly of allergic reactions, insect bites, Stevens–Johnson syndrome, generalized herpes zoster or herpes simplex infections, enterovirus infections, pityriasis lichenoides et varioliformis acuta (PLEVA) and guttate psoriasis. In the newborn, varicella must be differentiated from syphilis and incontinentia pigmenti. Before eradication of smallpox and in post-eradication surveillance, varicella was the disease most commonly confused with smallpox.

Treatment

General Care

Nonspecific treatment for varicella includes oral antihistamines, frequent bathing, calamine lotion, oatmeal baths, and the trimming of fingernails to discourage scratching. Fever should be controlled with acetaminophen. Use of aspirin for this purpose may predispose to Reye syndrome, and ibuprofen may predispose to Group A streptococcal infection.

Specific Treatment

Because most varicella infections are not serious and the illness usually is self-limited in otherwise healthy children less than 12 years of age, oral acyclovir is not administered routinely. Further, the drug is not well absorbed from the gastrointestinal tract. Specific therapy is reserved for those at higher risk for developing severe varicella and those who already have severe disease. Oral acyclovir should be considered for otherwise healthy people at increased risk for moderate to severe disease, e.g., persons aged >12 years; people with chronic cutaneous or pulmonary disorders; receiving long-term salicylate therapy; and receiving short, intermittent, or aerosolized courses of corticosteroids. Secondary contacts in household exposures may also be treated since these individuals also are at increased risk for more severe disease. Because controlled studies in children and adolescents given oral acyclovir for 5 days starting within 24 h of the rash of varicella have shown a modest benefit, prompt oral acyclovir therapy usually is recommended for healthy adolescents and young adults who are at moderately high risk for developing severe illness. The oral dose is 20 mg/kg PO four times daily for

5 days. Children who are relatively immunocompromised, such as those who have early seemingly mild varicella and those who have early HIV infection, may be given a closely monitored treatment trial of oral acyclovir and switched to intravenous acyclovir if clinically necessary.

Intravenous antiviral therapy, when administered within 24 h of onset of rash, is recommended for immunocompromised persons, including patients being treated with chronic corticosteroids. Patients at serious risk for or who have severe or potentially severe VZV infections should be treated with intravenous acyclovir (10 mg/kg every 8 h). There is a high correlation between early treatment and a successful outcome. Antiviral therapy for varicella does not prevent latent VZV infection. Acyclovir usually is very well tolerated. Adverse effects include phlebitis, rash, nausea, and neurologic symptoms such as headache. Patients whose creatinine clearance is less than 50 mL/min/1.73 m^2 are given one half to one third of the normal dosage with slow infusion, making sure that that hydration is adequate to avoid crystallization of acyclovir in the renal tubules.

Treatment of herpes zoster is associated with earlier healing of lesions and prevention of complications, particularly postherpetic neuralgia. Most available data regarding treatment of herpes zoster involves patients over 50 years of age. The three antivirals used for treatment of zoster are acyclovir, valacyclovir, and famciclovir. In general, these medications are well tolerated. Although oral acyclovir (800 mg five times daily) has been the mainstay of herpes zoster treatment, its poor bioavailability and need for frequent daily dosing prompted the development of later generation antiviral agents, valacyclovir and famciclovir, with improved pharmacokinetics and lower dosing frequency. Valacyclovir (1 g three times daily for 7 days) is now the drug of choice due to its increased bioavailability. The use of acyclovir may still be favored, however, if cost is an issue. Although famciclovir is now available in a generic formulation, its cost is still approximately threefold higher than acyclovir. If famciclovir is used, the standard dosing is 500 or 750 mg three times daily. Valacyclovir and famciclovir are not licensed in the United States for use in children or for the treatment of varicella.

Antiviral therapy is recommended for patients >50 years of age with uncomplicated herpes zoster who present within 72 h of clinical symptoms. The benefit of antiviral therapy in younger patients is not as clear, although the risk of adverse events is low. As a result, antiviral therapy is recommended for patients <50 years of age with herpes zoster who present within 72 h of clinical symptoms. All HIV-infected patients should be treated with antiviral therapy for episodes of uncomplicated herpes zoster, regardless of the age of onset. Intravenous acyclovir may be considered for more severe infections, such as disseminated disease or ophthalmic involvement.

Analgesic drugs are often needed in adult patients at presentation to address symptoms of acute neuritis. Most trials have demonstrated that early antiviral treatment for herpes zoster reduces the duration or incidence of postherpetic neuralgia. The routine use of corticosteroid therapy is not recommended since glucocorticoids do not decrease the risk of postherpetic neuralgia.

Prognosis

Acute varicella is generally mild and self-limited. Serious complications can occur, mainly in infants, adolescents, adults, and immunocompromised persons and include secondary bacterial infections of skin lesions, pneumonia, cerebellar ataxia, and encephalitis. Secondary bacterial infections of skin lesions with Staphylococcus or Streptococcus are the most common cause of hospitalization and outpatient medical visits. Secondary infection with invasive group A streptococci may cause serious illness and lead to hospitalization or death. Pneumonia following varicella is usually viral but may be bacterial. Secondary bacterial pneumonia is more common in children younger than 1 year of age. Central nervous system manifestations of varicella range from aseptic meningitis to encephalitis. Involvement of the cerebellum, with resulting cerebellar ataxia, is the most common and generally has a good outcome. Encephalitis is an infrequent complication of varicella (estimated 1.8 per 10,000 cases) and may lead to seizures and coma. Diffuse cerebral involvement is more common in adults than in children. Reye syndrome is an unusual complication of varicella and influenza and occurs almost exclusively in children who take aspirin during the acute illness. The etiology of Reye syndrome is unknown. There has been a dramatic decrease in the incidence of Reye syndrome during the past decade, presumably related to decreased use of aspirin by children. Rare complications of varicella include aseptic meningitis, transverse myelitis, Guillain–Barré syndrome, thrombocytopenia, hemorrhagic varicella, purpura fulminans, glomerulonephritis, myocarditis, arthritis, orchitis, uveitis, iritis, and hepatitis.

The risk of complications from varicella varies with age. Complications are infrequent among healthy children. They occur much more frequently in persons older than 15 years of age and infants younger than 1 year of age. For instance, among children 1–14 years of age, the fatality rate

of varicella is approximately 1 per 100,000 cases; among persons 15–19 years, it is 2.7 per 100,000 cases; and among adults 30–49 years of age, 25.2 per 100,000 cases. Adults account for only 5% of reported cases of varicella but approximately 35% of deaths from varicella.

Immunocompromised persons have a high risk of disseminated disease (up to 36% in one report). These persons may have multiple organ-system involvement, and the disease may become fulminant and hemorrhagic. The most frequent complications in immunocompromised persons are pneumonia and encephalitis. Children who have leukemia have a 30% rate of disseminated varicella, with a 7% mortality rate. Children with HIV infection are also at increased risk for morbidity from varicella and herpes zoster with the most severe infections and mortality occurring in those with AIDS.

The onset of maternal varicella from 5 days before to 2 days after delivery may result in overwhelming infection of the neonate and a fatality rate as high as 30%. This severe disease is believed to result from fetal exposure to varicella virus without the benefit of passive maternal antibody. Infants born to mothers with onset of maternal varicella 5 days or more prior to delivery usually have a benign course, presumably due to passive transfer of maternal antibody across the placenta.

Postherpetic neuralgia is a distressing complication of zoster. Postherpetic neuralgia is most likely to afflict the elderly and highly immunocompromised patients and is rare in healthy children with zoster. There is currently no adequate therapy available. The pain with postherpetic neuralgia may last a year or longer after the episode of zoster. Ocular nerve and other organ involvement with zoster can occur, often with severe sequelae.

Prevention

Varicella Vaccine

Varicella vaccine is routinely used for vaccination of healthy children in only some countries, including the United States, Uruguay, Qatar, Australia, Canada, Costa Rica, Germany, and South Korea. Varicella vaccine contains live, attenuated VZV. It is available as a monovalent formulation and in combination formulation, as measles–mumps–rubella–varicella (MMRV) vaccine, which is licensed in the United States for children 1–12 years only. In the United States, two doses of varicella-containing vaccine are now recommended for all susceptible persons older than 1 year without contraindications. The first dose should be administered at 12–15 months of age and the second dose at 4–6 years of age. A second catch-up dose of varicella vaccination is recommended for children, adolescents and adults who previously have received one dose. The minimum interval for children younger than 13 years is 3 months. The Centers for Disease Control's Advisory Committee on Immunization Practices (ACIP) now recommends that all others at least 13 years of age without evidence of immunity be vaccinated with two doses of varicella vaccine at an interval of 4–8 weeks. In cases with uncertain history, prior varicella disease is not a contraindication to varicella vaccination. Evidence of immunity to varicella includes any of the following:

1. Documentation of age-appropriate vaccination:
   - Preschool-age children aged $\geq$12 months: one dose
   - School-age children, adolescents, and adults: two doses
2. Laboratory evidence of immunity or laboratory confirmation of disease
3. Birth in the United States before 1980 (not a criterion for health-care personnel, pregnant women, and immunocompromised persons)
4. A health-care provider diagnosis of varicella or a health-care provider verification of a history of varicella disease
5. A health-care provider diagnosis of herpes zoster or a health-care provider verification of a history of herpes zoster disease

The most common adverse reactions following varicella vaccine are injection-site complaints (pain, soreness, redness, and swelling) that are self-limited. Fever was reported in uncontrolled trials in 15% of children and 10% of adolescents and adults. A macular or vesicular rash usually consisting of a few lesions at the injection site was reported in 3% and 1% of persons receiving the first and second dose, respectively. A generalized rash with a small number of lesions may rarely occur, within 3 weeks of vaccination.

Varicella vaccine induces latent infection similar to that caused by wild VZV. Consequently, zoster caused by vaccine virus has been reported. This appears to occur at a lower rate than following natural infection but longer-term follow-up is needed.

Contraindications to varicella immunization include: a severe allergic reaction to a vaccine component or following a prior dose, pregnancy or planned pregnancy within 4 weeks of vaccination, and immunosuppression. Single-antigen varicella vaccine does not contain egg protein or preservative. For the combination MMRV vaccine, live measles and live mumps vaccine are produced in chick

embryo culture. However, the risk for serious allergic reactions after administration of measles- or mumps-containing vaccines in persons who are allergic to eggs is low.

Persons with immunosuppression of cellular immune function resulting from leukemia, lymphomas of any type, generalized malignancy, immunodeficiency disease, or immunosuppressive therapy should not be vaccinated. Treatment with low-dose prednisone (e.g., <2 mg/kg of body weight/day or <20 mg/day) or aerosolized steroid preparations is not a contraindication to varicella vaccination. Persons whose immunosuppressive therapy with steroids has been stopped for 1 month (3 months for chemotherapy) may be vaccinated. Persons with impaired humoral immunity may be vaccinated. Because children infected with HIV are at greater risk for morbidity from varicella and herpes zoster than are healthy children, the ACIP recommends that varicella vaccine should be considered for HIV-infected children at least 12 months of age with CD4+ T-lymphocyte percentages ≥15% and without evidence of varicella immunity. Eligible children should receive two doses of single-antigen varicella vaccine, with a minimum 3-month interval between doses. Vaccination (two doses, administered 3 months apart) may be considered for HIV-infected older children, adolescents, and adults with CD4+T-lymphocyte count ≥200 cells/mL after weighing the risks and benefits.

Women known to be pregnant or attempting to become pregnant should not receive varicella vaccine. Pregnancy should be avoided for 1 month following varicella vaccination. The ACIP recommends prenatal assessment and postpartum vaccination for varicella. To date, no adverse outcomes of pregnancy or in a fetus have been reported among women who inadvertently received varicella vaccine shortly before or during pregnancy. The manufacturer, in collaboration with CDC, has established a Varicella Vaccination in Pregnancy registry to monitor the maternal–fetal outcomes of pregnant women inadvertently given varicella vaccine. The telephone number for the Registry is 800-986-8999. Breastfeeding is not a contraindication to the varicella vaccination.

The effect of the administration of immune globulin (IG) on the response to varicella virus vaccine is unknown. Because of the potential inhibition of the antibody response by passively transferred antibodies, varicella vaccines should not be administered for 3–11 months, depending on the dosage, after administration of blood (except washed red cells), plasma, or IG.

No adverse events following varicella vaccination related to the use of salicylates (e.g., aspirin) have been reported to date. However, the manufacturer recommends that vaccine recipients avoid the use of salicylates for 6 weeks after receiving varicella vaccine because of the association between aspirin use and Reye syndrome following varicella.

Available data suggest that transmission of varicella vaccine virus is a rare event. Instances of suspected secondary transmission of vaccine virus have been reported, but in few instances has the secondary clinical illness been shown to be caused by vaccine virus. It appears that transmission occurs mainly and perhaps only when the vaccinee develops a rash. If a vaccinated child develops a rash, it is recommended that close contact with persons who do not have evidence of varicella immunity and who are at high risk of complications of varicella, such as immunocompromised persons, be avoided until the rash has resolved.

A vaccine for zoster is available in the United States for use in adults 60 years of age and older. The primary clinical trial for this vaccine included more than 38,000 adults 60–80 years of age with no history of prior shingles. Efficacy was highest for persons 60–69 years of age (64%) and declined with increasing age. Vaccine recipients who developed zoster generally had less severe disease. Vaccine recipients also had about 66% less postherpetic neuralgia. The duration of reduction of risk of zoster is not known. As with all vaccines, a severe allergic reaction to a vaccine component or following a prior dose is a contraindication to zoster vaccination. As with other live virus vaccines, immunosuppression is a contraindication to zoster vaccination.

Postexposure Prophylaxis

Varicella vaccine is recommended for postexposure administration for healthy unvaccinated persons without other evidence of immunity. Administration of varicella vaccine to exposed susceptible persons ≥12 months of age, as soon as possible within 72 h and possibly up to 120 h after exposure, may prevent or modify disease and is recommended if there are no contraindications to its use. In several studies, protective efficacy was reported as ≥90% when children were vaccinated within 3 days of exposure.

In certain circumstances, postexposure prophylaxis with varicella zoster immune globulin is recommended. In 2004, the only US-licensed manufacturer of varicella zoster immune globulin (VZIG) (Massachusetts Public Health Biologic Laboratories, Boston, Massachusetts) discontinued production of VZIG. The supply of the licensed VZIG product was depleted in early 2006. In February 2006, an investigational (not licensed) VZIG product, VariZIG (Cangene Corporation, Winnipeg,

Canada) became available under an investigational new drug application (IND) submitted to the FDA. This product can be requested from the sole authorized US distributor, FFF Enterprises (Temecula, California). The investigational VariZIG, similar to licensed VZIG, is a purified human immune globulin preparation made from plasma containing high levels of anti-varicella antibodies. Unlike the previous product, the investigational product is lyophilized. When properly reconstituted, VariZIG is approximately a 5% solution of IgG that can be administered intramuscularly. As with any product used under IND, patients must be informed of potential risks and benefits and must give informed consent before receiving the product.

The decision to administer VariZIG to a person exposed to varicella should be based on (1) whether the person is susceptible, (2) whether the exposure is likely to result in infection, and (3) whether the person is at greater risk for complications than the general population. Persons at greater risk for severe complications who are not candidates for varicella vaccination who may benefit from postexposure prophylaxis with VariZIG include: susceptible immunocompromised persons (including people being treated with chronic corticosteroids $\geq$2 mg/kg of body weight or a total of 20 mg/day of prednisone or equivalent), susceptible pregnant women, newborns whose mothers had onset of varicella within 5 days before and 2 days after delivery, preterm infants at $\geq$28 weeks gestation whose mothers are susceptible to varicella, and preterm infants at $<$28 weeks gestation or $\leq$1,000 g birth weight, regardless of maternal history or serostatus. VariZIG provides maximum benefit when administered as soon as possible after exposure, but may be effective if administered as late as 96 h after exposure.

If administration of VariZIG does not appear possible within 96 h of exposure, administration of immune globulin intravenous (IGIV) should be considered as an alternative (IGIV should also be administered within 96 h of exposure).

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111 Human Immunodeficiency Virus

Sami Al-Hajjar

General Considerations

It has been slightly more than one 25 years since the first cases of human immunodeficiency virus (HIV) were identified in children. HIV is the most common cause of acquired immunodeficiency syndrome (AIDS) in children. The virus is a member of the lentivirus subgroup of human retroviruses (RNA viruses). HIV selectively infects human helper T cells, the virus enters cell by attachment to the CD4 molecule and fusion with cell membrane, which results in the lytic degeneration of helper T cells. The destruction of helper T cells profoundly affects B-cell function, suppressor T cells, and cell-mediated immunity and results in a profound combined (B- and T-cell) immunodeficiency. HIV also infects macrophages, monocytes, neural cells, Kuppler cells in the liver, Langerhans cells in the dermis, and Hofbauer cells of the placenta.

The profound immunodeficiency places HIV-infected children at risk of a wide variety of infections (common and opportunistic). Among the common bacterial infections are otitis media, sinusitis, pneumonia, and meningitis. Serious invasive bacterial infections occur in 20% or more of immunocompromised HIV-infected children. The agents responsible for these invasive bacterial infections include common childhood agents such as *Pneumococcus*, *Staphylococcus aureus*, *Enterococcus*, *Haemophilus influenzae* type B (HIB), *Salmonella*, and *Pseudomonas*. *Pneumococcus* is responsible for the greatest number of infections, including 30% of all bacteremias. Somewhat later in the course of the disease, T-cell deficiency results in susceptibility to *Pneumocystis carinii* pneumonia (PCP) fungal, viral, and other opportunistic infections. Central nervous system (CNS) involvement is frequent in children and is usually a direct result of infections of the CNS with HIV-1, leading to loss of milestones and brain atrophy.

In 1994, a new classification system for HIV-infected children was established by the Centers for Diseases Control and Prevention (CDC). In the new system, infected children are classified into mutually exclusive categories according to three parameters: (a) infections, (b) clinical status (*Table 111.1*), and (c) immunologic status. Once classified, an HIV-infected child cannot be classified in a less severe category even if the child's clinical or immunologic status improves.

Epidemiology

Almost all HIV-infected children acquire the virus from their mothers before or during birth or through breastfeeding. Mother-to-child-transmission (MTCT), estimated to cause more than 90% of infections worldwide in infants and children, probably occurs late in pregnancy or during birth. Studies have suggested that breastfeeding introduces an additional risk of HIV transmission of approximately 10–14% among women with chronic HIV infection. In developing countries, an estimated one-third to one-half of all HIV infections are transmitted through breastfeeding; the rest are infected from contaminated blood and blood products, infected organs, and sexual abuse. As adolescents become sexually active and experiment with intravenous drugs, their modes of acquisition are similar to those in adults. Therefore, the epidemiology of childhood transmission is essentially the epidemiology of transmission in childbearing women. The majority of women (70%) are infected as a result of personal drug abuse or drug abuse by a sexual partner. The rest acquire HIV from sexual transmission or from blood transfusion. The estimated risk perinatal transmission from an infected mother is between 15% and 40%. (The risk varies significantly according to the maternal immunologic and virologic status as well as placental membrane inflammation).

HIV infection is concentrated in certain geographic areas and socioeconomic groups, particularly large cities of Southeast Asia, sub-Saharan Africa, India, the islands of the Caribbean, South America, and the inner-city areas of major cities of Europe and the United States. Statistics on the prevalence of HIV/AIDS in the Middle East are hard to come. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS) about 460,000 people are living with HIV in the Middle East and North Africa and more than 22,000 children infected mainly by MTCT and other

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Table 111.1
Summary of the 1994 revised clinical classification of human immunodeficiency virus in children under 13 years of age (Adapted from Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR Morbid Mortal Wkly Rep 1994;43 (No. RR-121): 1–10, with permission)

Category N: nonsymptomatic
Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A
Category A: mildly symptomatic
Children with two or more of the conditions listed below but none of the conditions listed in categories B and C – Lymphadenopathy (≥0.5 cm at more than two sites, bilateral = one site) – Hepatomegaly – Splenomegaly – Dermatitis – Parotitis – Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media
Category B: moderately symptomatic
Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection listed in CDC clinical categories surveillance
Category C: severely symptomatic
Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of lymphocytic interstitial pneumonitis

routes of transmission exist, however notably blood/blood product transfusion and from kidney's transplanted from paid high risk, live, and non-related donor.

Clinical Manifestations

There are two general patterns of congenital or perinatal infection. About 20% of infected child develop early disease. Common early manifestation includes failure to thrive or wasting, recurrent thrush, chronic or recurrent diarrhea unresponsive to treatment and without definable cause, parotitis, and a variety of recurrent bacterial infections, including otitis media, sepsis, pneumonia, and meningitis. PCP is the most common opportunistic infection in children who have AIDS; it is more likely to be acute. Fever, tachypnea, retractions, and reduced breath sounds are frequent findings. CNS involvement occurs in about 50–60% of HIV-infected children. Cardiomyopathy, hepatitis, and nephropathy occur in some children.

In the second pattern, seen in the remaining 80% of infected children, HIV infection tends to progress less rapidly, with many children not developing frank AIDS until they are in school or even in adolescence. Hepatosplenomegaly, lymphadenopathy, diarrhea, thrush, and a variety of recurrent infections are common. Lymphocyte interstitial pneumonitis is seen in this group, and cough, digital clubbing, and lymphadenopathy are frequent findings. Lung disease is characterized by micronodular infiltrates on chest x-ray. As the disease progresses, all HIV-infected children developed profound T4-cell deficiency, multiple organ system involvement, and array of opportunistic infections.

Diagnosis

A diagnosis of HIV infection or AIDS depends on establishing the presence of HIV infection, defining the immunologic status of the child, and diagnosing the pattern of clinical illnesses that occur secondary to infection and loss of immune function. In children older than 18 months, the diagnosis of infection can be made by using a standard anti-HIV immunoglobulin G (IgG) antibody test, which is usually confirmed by Western blot. In children born to HIV-infected mothers, diagnosis is complicated by the presence or maternal anti-HIV IgG. The majority of these children are HIV-antibody positive at birth, although only 15–30% are usually infected. Maternal antibody may persist up to 18 months in uninfected infants. Polymerase chain reaction (PCR) and virus culture are currently the most sensitive and specific assays for detection of HIV infection in children born to infected mothers. Use of these assays can identify approximately 30–50% of infected infants at birth and nearly 100% of infected infants by 3–6 months of age. The standard P24 antigen assay and anti-HIV IgG are less sensitive than either viral culture or PCR.

In HIV infection, abnormalities of humoral immunity precede those of cell-mediated immunity. Earlier in the illness, polyclonal hypergammaglobulinemia and decreased or absent response of lymphocytes to mitogens and antigens are common. A late manifestation may be hypogammaglobulinemia. A typical indicator of progression of disease is a decrease in the ratio of T4 (helper) to T8 (suppressor/inducer) lymphocytes. In infants and young children, CD4+ lymphocyte counts and

percentages are higher than in older children and adults. Therefore, the recommendation for initiation of prophylaxis for PCP must be based on age-related criteria.

Differential Diagnosis

In children with recurrent, severe, or unusual infections or unexplained failure to thrive, consideration should be given to both congenital and acquired immunologic deficiencies. Wiskott–Aldrich syndrome, severe combined immunodeficiency, complement deficiency, immunoglobulin deficiency, and DiGeorge syndrome are among the possibilities.

Management

There have been many improvements in the management of children with HIV infection. However, HIV is still a lifelong, usually fatal infection for which no cure is available or likely to be found in the near future. The most successful approach requires a multidisciplinary team approach. Objectives fall into three categories: supportive care and adequate nutrition, prevention of infectious complications, and specific antiretroviral therapy.

Supportive Care and Adequate Nutrition

Important aspects of this category include monitoring of growth and immunization against childhood diseases.

Monitoring of Growth and Development

Failure to thrive is common, so ensuring adequate nutrition is essential. Anorexia, impaired absorption, and increased utilization of calories require caloric intakes that exceed expected requirement. Supplementation of the diet with a number of commercially available products may be required.

Immunization

HIV-infected children should receive all routine non-live-viral immunizations, as recommended by national immunization programs. Routine immunization with combined diphtheria-tetanus-pertussis, hepatitis B, hepatitis A, conjugated HIB, conjugated pneumococcal and conjugated quadrivalent meningococcal (MCV4), and inactivated poliovirus vaccines should be given according to the usual immunization schedule.

Live virus (e.g., oral poliovirus) and live bacterial (e.g., bacillus Calmette–Guerin) vaccines should not be given to patients with AIDS or other clinical manifestations of HIV infection who are immunocompromised. Combined measles-mumps-rubella and varicella, rotavirus vaccines may be given to children with HIV infection with mildly impaired immunity. Children exposed to varicella or measles should receive varicella-zoster immune globulin. Annual influenza vaccination should be given to all children $\geq$6 months of age.

Prevention of Infectious Complications

Pneumocystis jiroveci pneumonia (PCP) remains a major cause of morbidity and mortality in HIV-infected children. New guidelines for PCP prophylaxis recommend beginning PCP prophylaxis (low-dose trimethoprim-sulfamethoxazole) at 4–6 weeks of age for all children who have been perinatally exposed to HIV until they determined to be HIV uninfected or presumptively uninfected with HIV. HIV can be presumptively excluded in nonbreasted infants with two or more negative virologics tests, with one obtained >14 days of age, and one obtained >1 month of age; or one negative virologic test obtained >2 months of age; or one negative HIV-antibody test result >6 months. For patients who cannot tolerate trimethoprim-sulfamethoxazole, intravenous pentamidine is an alternative. Aerosolized pentamidine for those 5 years or older has also been used.

Prophylaxis should continue throughout infancy for all children with definite HIV infection but should be discontinued for those found to be uninfected. For the remaining children with HIV infection, the age-adjusted CD4 lymphocyte counts at which PCP prophylaxis is recommended are as follows: 1–11 months, 1.500/mm^3 or less; 12–23 months, 750/mm^3 or less; 2–5 years, 500/mm^3 or less; and 6 years and older, 200/mm^3 or less. Intravenous immunoglobulin is indicated for children with hypogammaglobulinemia.

Specific Antiretroviral Therapy (ART)

The National Pediatric Resource Center Working Group on ART recommended that CD4 + cell count on percentage be used as a criterion for intuition of ART in children

with HIV infection. As of August 2010, 22 drugs have been approved for infected adults and adolescents, 17 of them have been approved for pediatric treatment indication in children, and 15 in pediatric formulation or capsule. Combination therapy with at least three drugs, including either a protease inhibitor or non-nucleoside reverse transcriptase inhibitor plus a dual nucleoside analogue reverse transcriptase inhibitor backbone, is recommended for initial treatment of HIV-infected children, because it provides the best opportunity to preserve immune function and delay disease progression. The goal of therapy in treatment naïve-children is to reduce HIV RNA levels to below the level of detection (if possible, determined using ultrasensitive assays) and preserve immune function for as long as possible. ART is recommended in all infants <12 months of age, regardless of clinical status, CD4%, or viral load. In children >1 year the decision to start ART depends upon HIV-related symptoms and CD4% +/− viral load.

Prevention

One of the most important successes is the intervention in transmission of HIV from mother to child. Recent clinical trials have provided strong evidence that the administration of a regimen consisting of AZT given antepartum and intrapartum to the HIV-infected pregnant woman and to the newborn for 6 weeks reduces the risk of mother-infant HIV transmission by approximately two thirds. Route of delivery depends on VL prior to delivery (at 36–38 weeks gestation) and general obstetrical considerations. If viral load is (VL) > 1,000, labor has not started, and rupture of membrane (ROM) has not occurred, schedule elective C-section (no evidence of benefit after onset of labor or ROM). Data support vaginal delivery when VL < 1,000 and on ART, unless other obstetrical indications. Breastfeeding is contraindicated where safe alternatives exist; replacement feeding is essential to reduce transmission risk in industrialized countries. However, formula feeding increases mortality in resource-limited settings; thus, breastfeeding with infant prophylaxis or maternal ART is recommended in those settings. Screening of blood and plasma for HIV antibody has markedly reduced the risk of infection through transfusion. Adolescent education is extremely important. Information regarding HIV infection should include mode of transmission, implications of infection, and strategies for prevention, including abstinence or safe sex and avoidance of intravenous drugs.

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112 Influenza

Jonathan A. McCullers

Definition/Classification

Influenza is an acute, respiratory infection caused by members of the Orthomyxovirus family. Influenza viruses are enveloped, irregular, spherical particles containing a segmented, negative-sense RNA genome (*Fig. 112.1*). Three distinct types exist, termed influenza A, B, and C. Influenza A viruses are zoonoses derived from the wild bird population, while influenza B and C viruses are human pathogens. Influenza virus strains are named according to a standard nomenclature defining the type, the host species if not human, the geographic source, the isolate number from that geographic region, and the year, for example, B/Memphis/13/03. For influenza A viruses, the subtype is based on antigenic variation in the two major surface glycoproteins, the hemagglutinin (HA or H) and neuraminidase (NA or N), and this is indicated in parentheses during designation of strains (*Fig. 112.2*). There are 16 distinct HA subtypes and 9 NA subtypes in birds, although only 3 HA and 2 NA subtypes have to our knowledge established long-term lineages in human populations.

Etiology

Disease from influenza manifests from a complex mixture of direct viral damage, host responses, and the effects of co-pathogens. Primary influenza is considered a viral infection of the upper and lower respiratory tract. However, much of the disease that occurs during influenza epidemics and pandemics is mediated by secondary pathogens or host responses. The most common agents complicating influenza are the gram-positive bacteria *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Streptococcus pyogenes* (Group A streptococcus). Bacterial otitis media, sinusitis, pneumonia, and meningitis can all be mediated by co-pathogens in the setting of influenza. In addition, influenza interacts with host factors in vulnerable populations to cause disease through exacerbation of preexisting conditions. Acute worsening of cardiac disease, diabetes, asthma, and chronic obstructive pulmonary disease (COPD) are common accompanying morbidities during influenza. Deaths during influenza epidemics are often described as "excess" mortality since the underlying chronic diseases are classified in vital statistics as the official causes of death, even though influenza was the inciting factor.

Epidemiology

Seasonal influenza is primarily a disease of children, with clinical attack rates of 20–30% annually, concentrated in naive hosts. Children are also the primary vectors of disease due to this high clinical attack rate, their high social contact rate, and a relative lack of cross-reactive immunity allowing unrestricted replication and shedding of large quantities of the virus. However, most deaths are in persons with chronic comorbidities, so mortality is mostly in the elderly. Annual death rates are approximately 1 in 10,000 in developed countries and are presumed to be higher in the developing world, although data are lacking. The excess mortality rate for influenza A viruses varies significantly by strain and season, based on both the degree of preexisting immunity in the population, the potency of viral virulence factors, and how well the circulating viruses support secondary bacterial infections from regionally endemic bacterial strains. Since influenza B viruses do not have an animal reservoir and are well adapted to humans, their epidemiology resembles that of well-adapted seasonal strains with a high clinical attack rate in children, and little mortality outside of those with underlying chronic illnesses. The epidemiology of influenza C viruses is poorly understood, but it is not thought that significant disease results from typical infections.

Pandemics of influenza occur several times a century when a novel influenza A virus enters humans and achieves worldwide spread. A virus must meet three criteria to be considered pandemic: (1) a novel HA protein to which most of the population is immunologically naive, which allows a high clinical attack rate; (2) ease of transmission enabling worldwide spread; and (3) ability to cause severe disease. Four pandemics have taken place in the last 100 years. In 1918, an H1N1 subtype virus entered humans from the animal reservoir, causing severe disease and killing more than 40 million people worldwide.

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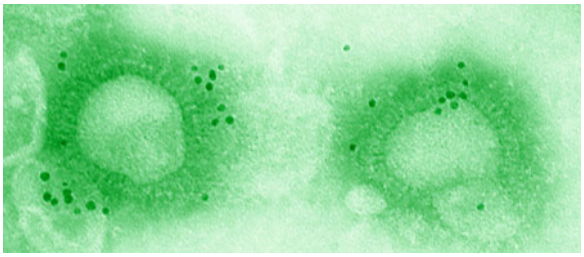

Figure 112.1
Influenza virions. Influenza virions as seen by electron microscopy. The dark beads are gold particles labeling neuraminidase spikes on the surface of the virions

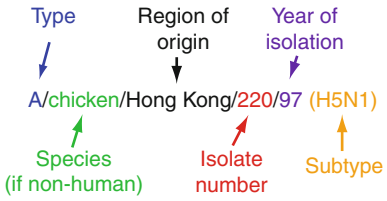

Figure 112.2
Nomenclature of influenza viruses

This virus adapted to humans and circulated until 1957, when it was replaced by an H2N2 subtype virus that took part of its gene constellation from the circulating H1N1 strain (since influenza viruses have a segmented genome, they can swap genes through a process called reassortment in intermediate hosts such as pigs), and the remainder from an avian source. The 1957 pandemic was severe, but not on the same scale as that of 1918, killing several million persons. In 1968, another novel strain emerged, again by reassortment. This H3N2 virus had a novel HA, but retained the NA and several other genes from the 1957 strain. Disease and mortality were milder than in previous pandemics, perhaps because of the retention of the NA antigen from the previously circulating strain. Adapted versions of this virus continue to circulate today. This virus was joined in circulation in humans in 1977 when a 1950 version of the previously circulating H1N1 strain was released from a frozen source. Although this virus achieved worldwide circulation and continues to be endemic in humans today, co-circulating with H3N2 strains, this event was not considered to be a pandemic since much of the population was immune and little disease ensued.

In 2009, the most recent pandemic strain emerged as a complex mixture of genes of avian, human, and swine derivation. It was again of the H1N1 subtype, but was most antigenically similar to the 1918 strain among viruses that circulated in the twentieth century. Because of this, only elderly persons who experienced influenza in the 1930s and 1940s had any cross-reactive immunity. Sero-archaeologic evidence suggests that as far back as the mid-1850s, H1, H2, and H3 subtype viruses have successively replaced each other as pandemic strains. It is not known whether this recycling phenomenon is limited to these subtypes due to factors presently not understood, or whether other subtypes are also capable of causing pandemics. The repeated incursions of highly pathogenic avian influenza viruses of the H5N1 subtype into humans since 1997 have created significant concern that a truly novel pandemic strain could arise, but as of yet these viruses seem incapable of sustaining chains of transmission in humans.

The 2009 H1N1 pandemic was marked by a high clinical attack rate in children, severe disease in older children and young adults, and relative sparing of the elderly due to cross-reactive immunity. Most cases of severe disease were found in persons with preexisting comorbidities, especially asthma, chronic cardiac or respiratory disease, and obesity. Bacterial pneumonia complicated the clinical course of about 30% of severe or fatal cases. The phenomenon whereby the elderly experience relatively less disease during pandemics than young persons appears to be related to the recycling phenomenon; the repeating reintroduction of the three most common subtypes leads to protection in the oldest sections of the populations as they will have antigenic experience with these unadapted viruses. Most disease is thus seen in younger persons. This is the inverse of the pattern of disease during seasonal epidemics with adapted viruses. Because most epidemics occur with drift variants that have been selected for their ability to cause disease in an immune population, the elderly are susceptible, and the relatively higher prevalence of comorbidities with increasing age drives higher rates of hospitalization and mortality. In pandemics, more than 90% of deaths are typically in younger age groups in whom the clinical attack rate is highest. During seasonal outbreaks, although young persons remain the primary vectors of transmission and are most likely to be infected, persons over 65 years account for about 95% of all mortality.

Transmission of influenza viruses can occur by contact, large droplet, and aerosol routes. Since most viruses are expelled during coughing and sneezing, direct contact with infected secretions or contaminated objects is thought to dominate in most settings. Transmission is affected by both temperature and humidity, and is favored in cold conditions and significantly diminished in the setting of high humidity. It has been suggested that aerosol transmission is more efficient in cool, dry environments,

facilitating explosive outbreaks when conditions are right. Most outbreaks in temperate climes are seasonal and occur in cooler, winter months when transmission is favored. However, a low level of infection can be detected year-round. In tropical parts of the world, circulation of viruses occurs all year, with inconsistent peaks related to poorly understood climactic changes. Herd immunity plays some role in the seasonality of influenza as well, since pandemic strains appear to transmit efficiently in the summer in temperate climes. The increased availability of susceptible hosts may overcome the temperature and humidity barriers to transmission of seasonal strains. The relative ability of influenza viruses to transmit is expressed by a term called the reproductive number R_0, which represents the average number of persons an infected individual will themselves infect. Any value over 1.0 suggests that sustained transmission is possible and therefore an outbreak can occur. Pandemic viruses may have an R_0 in the 2–3 range, higher than the average seasonal virus which may be $\sim$1.4, but much lower than comparable viruses such as measles which may have an R_0 of about 10–15.

Pathogenesis

Influenza viruses are segmented RNA viruses that encode 10–11 proteins. There are two surface glycoproteins, HA and NA, which are involved in attachment and budding, respectively, and are the main targets of antibodies. In addition to structural and polymerase proteins, the virus also encodes nonstructural proteins PB1-F2, which is a cytotoxin, and NS-1, which is an interferon antagonist. The lack of proofreading mechanisms for the polymerase complex during replication leads to a high mutation rate, which generates a multitude of variants within any population of viruses, termed a quasispecies. In the presence of selective pressure, such as adaptation to a new host or upon encountering antibody-mediated immunity, this breadth of options allows selection of fitter viruses. In the context of seasonal epidemics, the resulting drift of the surface antigens allows new variants to arise that can escape immune pressure in an experienced population, generating new epidemics. In addition, the segmented genome allows reassortment between two viruses infecting the same cell, which can lead to the genesis of a pandemic strain if the nascent virus encodes a novel HA from the animal reservoir.

The first encounter of the virus with the host is typically at a mucosal surface in the upper respiratory tract, where infection is initiated in epithelial cells. Clinically, influenza can be limited to this site or may spread down to the trachea and major bronchi. Penetration into the lower lung is limited by innate defenses such as collagenous lectins, which can bind glycoconjugates on the major surface glycoproteins HA and NA and neutralize infectivity. However, poorly glycosylated viruses, such as those recently emerging from avian sources, can evade this barrier and cause pneumonitis. The epithelial damage influenza viruses cause during replication can expose basement membrane, allowing adherence of bacteria and facilitating secondary infections. Severity of disease is thus a combination of the effective site of infection, which modulates both the viral syndrome and the type of secondary bacterial disease that might occur, together with the host response. The host response can be either helpful, by clearing the virus, or detrimental by furthering lung damage. Primary influenza is cleared by a combination of innate host defenses, IgM antibody, and a CD8+ T-cell response, which recognizes and kills infected cells. During this resolution stage, CD4+ T-cells facilitate class-switching of antibodies to IgG and induction of long-term memory. Thus, on later rechallenge with a related strain, infection is prevented or rapidly cleared through antibody-mediated neutralization of infecting particles. In the event that the new virus has drifted sufficiently that antibodies no longer recognize the surface proteins, infection is not prevented, but again the CD8+ T-cell response will clear the virus. This reliance of cellular immunity can be problematic in a compromised host, such as the elderly, who cannot clear virus as well and may suffer more severe disease. Paradoxically, robust immunity in older children can also contribute to disease if the T-cell response is strongly induced but cross-reactive antibodies are not present. Most of the clinical symptoms of influenza are due to either direct viral damage or the immune response.

Pathology

The hallmark of pandemic influenza is pneumonitis with diffuse alveolar damage, since these viruses typically penetrate well into the lower respiratory tract. Hemorrhage, fibrin deposition, edema, and formation of hyaline membranes are common. In severe cases, typical features of acute respiratory distress syndrome (ARDS) are seen. Findings suggestive of bacterial pneumonia, primarily manifest as a neutrophilic infiltrate with consolidation, may be superimposed on this pathologic picture. Antigen testing for bacteria in autopsy cases has been useful in recent studies to define the differences between primary viral and secondary bacterial pneumonia. Seasonal influenza rarely presents as severe, primary viral lower

respiratory tract disease; a mild to moderate tracheobronchitis is a more common presentation. Infiltration of lymphocytes in a peribronchial and perivascular distribution is typical. The epithelial lining of the major airways is predominantly affected, with cell death and sloughing of epithelial cells exposing basement membrane elements, upon which extracellular matrix material is deposited. Ciliated cells may also be killed during infection or may merely be functionally disrupted so that beat frequency and coordination of beat direction are altered, reducing clearance of mucus secretions. Pathologic alterations in other affected organs (e.g., heart, brain) are most commonly nonspecific, with edema and inflammatory changes present.

Clinical Manifestations: Symptoms, Signs

Influenza is a disease of rapid onset with both respiratory and systemic symptoms appearing together after a short, 2–3-day incubation period. After the first several days of illness when systemic symptoms dominate the clinical course, a transition takes place and systemic symptoms subside and cough and other respiratory tract–related symptoms become more prominent. Systemic symptoms include fever, chills, malaise, headache, dizziness, gastrointestinal disturbances, and myalgias. An erythematous maculopapular rash may be present briefly but it is not a common or prominent sign of infection. Common respiratory symptoms include cough, sore throat, rhinitis, nasal congestion, and eye irritation. Cough may be productive or nonproductive and may persist for weeks or longer. Typical features of bacterial pneumonia may be superimposed on this clinical presentation. Disease in adolescents and older children is similar to that of adults, and is dominated by the triad of fever, cough, and myalgias (*Table 112.1*). Cough is less prominent in younger children, and is sometimes absent entirely in infants. Myalgias are much less frequent in children than adults. Gastrointestinal symptoms are frequent in young children, and can manifest as vomiting, diarrhea, or abdominal pain. Infants may have fever and diarrhea as their sole presenting signs. Gastrointestinal symptomatology was more common during the 2009 H1N1 pandemic than is typically observed in seasonal influenza, and commonly affected older children and adults. Apnea and a sepsis-like syndrome can also occur in neonates and infants. Most children with influenza have a normal white blood cell count, but both leukopenia and leukocytosis can be seen. Leukocytosis with a predominance of neutrophils can be a sign of secondary bacterial infection, but can also occur with uncomplicated influenza. Blood chemistries are typically normal unless dehydration or complications are present. Influenza A and influenza B are indistinguishable clinically, although specific strains may have a predilection for certain clinical syndromes, and influenza B is more likely to cause clinical disease in younger children than in adults. Influenza C viruses typically cause more limited illness, with less-severe clinical presentations and a shorter duration of illness.

Table 112.1
Clinical manifestations of influenza

Symptoms	Infants	Children	Adults
Fever	++	+++	+++
Cough	+	++	+++
Myalgias	–	+	++
Sore throat	–	+	++
Headache	–	++	++
Conjunctivitis	++	++	++
Cervical adenopathy	+	+	–
Anorexia	++	++	+
Diarrhea	++	+[a]	–[a]
Vomiting	++	+[a]	–[a]
Rhinitis	++	+	+
Malaise/lethargy	++	+	+
Neurological symptoms	+	–[a]	–

– Rare, + uncommon, ++ common, +++ very common
[a]Common (++) with 2009 pandemic influenza

Both viral and bacterial complications are common during childhood influenza. Otitis media, sinusitis, and pneumonia can all be due to either the primary viral infection or can be manifestations of coinfecting bacteria. Otitis media may present as a mild, serous exudate if it is solely due to the virus, but in young children mixed viral–bacterial infections are common and a painful, purulent exudate may result. Symptoms of sinusitis are common during acute influenza, and opacification of the sinuses can be seen on computed tomography in a significant proportion of affected persons. Bacterial sinusitis may result as a secondary complication, manifest as increased pain and a return of fever after an initial period of recovery. Laryngotracheobronchitis (croup) can be a manifestation of acute influenza in young children, and is often more severe than is typical for parainfluenzaviruses. An acute myositis manifest by severe pain and tenderness of both calves may occur during the early convalescence stage. This syndrome typically has an acute onset and is accompanied by elevations of serum creatine kinase and aspartate

aminotransferase and, occasionally, rhabdomyolysis in severe cases. Cardiac complications including myocarditis and pericarditis are associated rarely with influenza. The pathogenesis of these complications is unclear, as virus is rarely identified in affected tissues.

Neurological symptoms associated with influenza are confined almost exclusively to young children who are naive to the virus and have never received the influenza vaccine. Febrile seizures are relatively common and uncomplicated in this group, and up to 30% of all febrile seizures of childhood are due to influenza. Encephalopathy from influenza can present with a variety of symptoms and signs, but mental status changes ranging from delirium to behavioral disturbances to coma are most prominent. Cranial nerve pareses are unusual, as are meningitic presentations. Cerebrospinal fluid (CSF) examination is typically normal or reveals a mild pleocytosis, and virus can be detected in CSF by polymerase chain reaction (PCR) or in biopsy or autopsy material from affected brains in about 15% of cases. Electroencephalography (EEG) typically shows a general slowing without an acute focus, and computed tomography (CT) scans are either normal or demonstrate diffuse edema. A subset of patients present with a more fulminant course and have findings on CT suggestive of necrosis in the subthalamic regions, a syndrome termed "acute necrotizing encephalopathy." Influenza-associated encephalopathy is uncommon in much of the world, but was relatively common in Japan in the late 1990s and early 2000s for reasons that remain unclear. During the 2009 H1N1 pandemic, older children were affected more commonly than is typically seen with seasonal influenza, likely because of lack of preexisting cross-reactive immunity.

Diagnosis

Classically, influenza has been diagnosed on the basis of a compatible clinical presentation in the setting of supportive epidemiology. Local or regional data suggesting increased presentation to primary care centers coupled with an increased rate of laboratory diagnosis of influenza can usually be relied on to indicate the start of winter-time epidemics in temperate climes. Sentinel programs to track influenza are in place in many countries (e.g., through the Centers for Disease Control in the United States) and internationally through the World Health Organization. As an important epidemiologic clue, influenza will more frequently affect both adults and children together than other causes of similar clinical syndromes. In this context, an age-appropriate clinical presentation can usually be assumed to be influenza and appropriate measures taken without specific diagnostic testing. Chest radiographs may be employed to confirm lower respiratory tract involvement or define a complicating bacterial pneumonia. Recently, two factors have altered the utility of clinical diagnosis alone. First, co-circulation of viruses with disparate antiviral susceptibility patterns has created a need to not only to definitively diagnose, but also determine the subtype of an infecting influenza virus so that treatment can be targeted with specific antivirals, and unnecessary drug use can be avoided. Second, during circulation of the 2009 H1N1 pandemic strain, infection control measures in hospitals differed for this strain compared to seasonal influenza. Strain identity had to be established to provide appropriate health-care worker protections. These factors, coupled with increased use of antiviral medications with their associated expense, have led to an increased demand for accurate, point of care diagnostic methodologies.

Three methods of diagnosis of influenza are in widespread use at present. Point of care testing in outpatient settings is typically limited to antigen based testing. This is accomplished through the use of inexpensive kits that utilize colorimetric changes upon antibody recognition of virus in nasal swab material to rapidly demonstrate the presence of antigen. Some tests can distinguish type A from type B influenza, but none can currently subtype influenza A strains or distinguish specific strains within an influenza A subtype or between the two major influenza B lineages. These kits uniformly have a low sensitivity, so while a positive result is useful for directing care, a negative result does not rule out influenza. Rapid antigen testing is also commonly employed in hospitals as a point of care diagnostic in acute care settings such as emergency rooms, but typically with a more sensitive and specific test as a backup, performed in a central laboratory. Two methods are commonly employed. A fluorescent antibody test, where clinical material from a nasal swab or nasal wash is incubated in susceptible cell culture, and the presence of virus is determined by microscopy to detect fluorescence of dyes bound to antibodies which recognize the virus, has been in common use for decades. This method is more sensitive and specific than rapid antigen tests, but may take several days to achieve a result. This is being replaced in many centers by the use of PCR-based testing, particularly using rapid and sensitive real-time PCR assays. These assays have the advantages of quick turn-around times, improved sensitivity and specificity compared to all other methods, and can be designed to differentiate viruses by type, subtype, and even strain. In parallel, similar methods are now available to rapidly sequence portions of the viral genome to provide

indicators of the most common resistance mutations. Other potential methods to diagnose influenza, such as virus isolation or acute and convalescent serology, are now confined to research settings.

Differential Diagnosis

Because influenza can manifest as a variety of clinical syndromes, the differential diagnosis is broad. This is particularly true in infants, who may not have common signs of infection such as cough. Depending on the particular disease manifestations, many other pathogens can either be the primary cause or a co-pathogen. Other respiratory viruses such as parainfluenzaviruses, respiratory syncytial virus, human metapneumovirus, rhinoviruses, and coronaviruses should be considered in the differential diagnosis for upper respiratory tract infections, otitis media, and laryngotracheobronchitis (croup). Bacterial causes of epiglottitis, such as *Haemophilus influenzae*, *S. aureus*, and *S. pneumoniae*, must also be considered in the child with croup, particularly if acutely ill. *S. pneumoniae*, *S. aureus*, and *S. pyogenes* are common lower respiratory tract co-pathogens with influenza, but must also be considered in the differential diagnosis as primary agents of disease along with other common causes of community-acquired pneumonia such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Numerous viral and bacterial pathogens can also present with fever and diarrhea, although gastrointestinal symptomatology with influenza is generally mild and the diarrhea non-bloody. The encephalopathy syndrome associated with influenza can mimic either bacterial meningitis or a viral encephalitis, so multiple causes must be considered. Finally, neonates with influenza can present with lethargy, poor circulation, and apnea, so other causes of sepsis must be considered.

Treatment

There are two classes of antiviral drugs approved for use against influenza viruses (*Table 112.2*). The adamantanes amantadine and rimantadine act by blocking the M2 ion channel, which prevents acidification of the virion during uncoating early in infection. Adamantanes have been in clinical use since the late 1960s for both prophylaxis and treatment of symptomatic influenza. Insomnia and difficulty concentrating are common side effects of amantadine that are less problematic with rimantadine due to its extensive metabolism in the liver. The NA inhibitors (NAIs) act by binding to and blocking the enzymatic activity of NA. This prevents budding of newly produced virions from infected cells, enhances aggregation at cell surfaces, and blocks escape from sialylated mucins. The NAIs oseltamivir and zanamivir were first licensed in the United States in 1999 and are now in widespread use throughout most of the world. Oseltamivir is available in a form that can be taken orally, while zanamivir is administered as a powder that must be inhaled with the use of a device. An intravenous form of zanamivir was made available in 2009 through an investigational new drug process to provide an alternative form of the drug for patients severely affected by pandemic H1N1 and unable to take oral or inhaled medications. A second NAI that can be administered intravenously, peramivir, was also made available during the recent pandemic through an emergency use authorization from the US Food and Drug Administration, and was licensed for clinical use in Japan. However, both of the US authorizations were withdrawn during the summer of 2010 at the conclusion of the pandemic, so licensed intravenous agents are not currently commercially available in any countries except Japan.

The primary clinical utility of existing antiviral agents is to halt progression of disease by preventing new host cells from being infected. If this intervention is administered early in the clinical course, it may alter the tempo of infection, allowing normal immune mechanisms to clear the virus. Earlier treatment works better in most cases because the infection is not yet widespread. Thus, the major effects of treatment are symptom reduction and a more rapid recovery, not immediate clinical cure. In clinical trials of NAIs, illness severity, ancillary medication use, and the frequency of prescriptions for lower respiratory complications were all reduced. The time to cessation of fever, alleviation of illness, and return to normal activity was decreased by about 24 h. Treatment of critically ill patients is complicated by lack of data regarding duration of therapy (all published data from prospective trials use short courses with a goal of symptom alleviation in acute, uncomplicated influenza) and by lack of a licensed intravenous formulation. Resistance has been a clinically significant issue for the adamantanes for years, limiting their utility. Widespread resistance to oseltamivir appeared in H3N2 viruses in 2007, and sporadic resistance in both seasonal and pandemic H1N1 viruses has been reported. Clinically significant resistance has not been seen with zanamivir, but viruses resistant to oseltamivir are typically also resistant to peramivir. Thus, while both zanamivir and peramivir could be considered for patients in need of intravenous therapy if they can be obtained, only zanamivir is currently an option for those with resistance

Table 112.2
Antiviral drugs available for treatment of influenza

Characteristics	Adamantanes[a]	Zanamivir	Oseltamivir	Peramivir
Licensure	1966, 1973	1999	1999	2009[b]
Target	M2 ion channel	Neuraminidase	Neuraminidase	Neuraminidase
Activity	Influenza A virus	Influenza A and B virus	Influenza A and B virus	Influenza A and B virus
Route	Oral	Inhaled, intravenous[c]	Oral	Intravenous
Effective against secondary bacterial infections	No	Yes	Yes	No data
Resistance[d]				
Seasonal H3N2	Resistant	Susceptible	Susceptible	Susceptible
Seasonal H1N1	Susceptible	Susceptible	Resistant	Resistant
Pandemic H1N1	Resistant	Susceptible	Susceptible	Susceptible

[a]Amantadine and rimantadine
[b]Emergency use authorization during 2009 pandemic only in United States; licensed in Japan
[c]Intravenous formulation available through investigational new drug (IND) application during 2009 pandemic only
[d]Based on 2008–2009 data

to both adamantanes and oseltamivir. The disparate resistance patterns of multiple viruses co-circulating over the last several years have made utilization of diagnostic PCR methodologies which can subtype viruses critical for appropriate management of severely ill patients. Combination therapy with multiple drugs within or across classes has been modeled in animals, and may improve effectiveness. However, these findings have not yet been proved in clinical trials.

Importantly, the effects on resolution of symptoms and the recommended duration of therapy (5 days) are based on studies in healthy persons with mild disease. It is not clear whether the dose, duration of therapy, and expectation of benefit should be the same in immunocompromised patients or in patients who have severe or complex disease manifestations. In regard to complications, oseltamivir both decreases the incidence of secondary bacterial pneumonia and reduces the severity of complications in animal models. Similar data are not available from a single, well-powered trial in humans, although a meta-analysis of data from multiple trials including unpublished data suggests these results can be extrapolated at least to healthy adults. In children, however, oseltamivir was shown to reduce the occurrence of otitis media by 44% compared to placebo. Retrospective reviews of insurance claims databases suggest that NA inhibitors reduce the risk of otitis media, pneumonia, respiratory illnesses other than pneumonia, and hospitalization in both adults and children, including in some at-risk groups such as diabetics. The best treatment for encephalopathy associated with influenza infection is uncertain. If viral replication in the brain is involved, effective antiviral treatment may not be possible, since neuraminidase inhibitors do not cross the blood–brain barrier (as do the adamantanes), and resistance to the adamantanes and lack of effect against influenza B viruses generally precludes their use. Reduction of virus titer in the lung with a neuraminidase inhibitor and supportive care may be the best available options.

The majority of clinically apparent cases of influenza can be managed as outpatients. The systemic symptoms that are prominent in the first several days of the acute infection often limit normal activity, causing missed school or work. General supportive care is often recommended, including antipyretics, rest, and hydration. Care must be taken in use of analgesics in children due to a past association of aspirin with an unusual manifestation of influenza known as Reye's syndrome and due to a concern that specific antipyretics or other herbal remedies in widespread use in Japan in the 1990s contributed to that country's high rate of influenza-associated encephalopathy. There is currently disagreement over the most appropriate use of antiviral medications. Most expert groups providing guidance have suggested that, at a minimum, persons at high risk for complications of influenza should receive early treatment with antivirals active against circulating strains of influenza. This guidance is tempered by a lack of study of these drugs in these specific groups. Clinical trials of these

compounds have typically been conducted in healthy persons, and clinical outcome measures have focused on reductions in symptoms and in duration of illness. Thus, whether these drugs are as active in persons with chronic medical conditions or are capable of preventing complications such as hospitalization and death are unclear. Duration of therapy and effective dose in critically ill patients and immunocompromised patients who may exhibit prolonged shedding are similarly unclear. There is currently little consensus on the issue of antiviral use in healthy persons including children, who have higher rates of hospitalization than adults. Some experts advocate withholding antivirals from healthy, well-appearing children on the basis of limited effectiveness data for significant outcomes such as hospitalization, coupled with the economic consideration of cost. However, the strategy of waiting to treat until complications develop may limit the effectiveness of therapy since early treatment has been proved to be superior to later treatment. In addition, many deaths in children are in otherwise healthy young persons of school age, and it has been argued that early intervention may prevent some of this mortality.

Numerous antiviral drugs directed against multiple targets of the influenza virus life cycle have progressed to preclinical or early clinical stages. As described above, intravenous formulations have seen some limited clinical use and at least one is now licensed in Japan. A long-acting drug in the NAI class has advanced through Phase III clinical trials, and may offer a single-dose option for uncomplicated influenza. Inhibitors of the HA, the polymerase complex, and combination chemotherapy approaches are also in various stages of clinical development and testing. Because of the prominent involvement of host immune responses in generation of symptoms and in the pathogenesis of severe influenza, immunomodulatory approaches have also been contemplated. Systemic steroids have been utilized to treat ARDS from H5N1 or pandemic H1N1 influenza, but the results have been generally disappointing, including some evidence that the disease may have been worsened by immunosuppression in some cases. Nonspecific anti-inflammatory therapies such as statins have also been utilized clinically, but no definitive, positive results have been reported. Use of antimicrobials is generally reserved for the treatment of complicated influenza when there is evidence of a secondary bacterial infection present. However, many pediatric deaths have been reported in recent years due to necrotizing *S. aureus* pneumonia, and this often presents as a fulminant disease. Early, directed anti-staphylococcal therapy should be considered in any critically ill child who presents with influenza-like illness or a confirmed diagnosis of influenza.

Prognosis

Viral disease from seasonal influenza is typically a self-limited illness in all but the most severe cases. Hospitalization and death are mainly due to complications, such as secondary bacterial infections, unusual non-pulmonary presentations (e.g., encephalopathy), or exacerbation of underlying illness. Bacterial disease when it accompanies influenza is often more severe than primary bacterial illness, and more difficult to treat. In particular, necrotizing staphylococcal pneumonia in association with influenza is considered an emerging disease in children. It presents as fulminant pneumonia progressing rapidly to respiratory failure, often with accompanying sepsis and multisystem organ failure, and may not respond to antibiotic therapy. Influenza-associated encephalopathy carries a high mortality rate. The severity of the initial presentation is considered a prognostic factor, with cases presenting in a comatose state carrying a high mortality rate and similarly high rate of severe neurologic deficit in survivors. Outcomes in immunocompromised children or in persons with chronic diseases are dependent on the severity of underlying illness and response to treatment. Need for hospitalization and the clinical course from influenza in the setting of preexisting cardiac or pulmonary disease is more often related to the underlying disease than to the inciting infection. Most children with cancer who contract influenza have a clinical course similar to that of immunocompetent children, but serious complications such as respiratory failure are more common. Disruptions of chemotherapy and hospitalization for fever in the setting of neutropenia are major problems in this group of patients. Prolonged viral shedding can occur, and in this setting prolonged antiviral therapy often leads to induction of resistance.

Prevention

Children experience the highest clinical attack rates, have the highest social contact rates to facilitate spread, and are the main vectors of transmission into vulnerable populations. Although mortality is unusual in children, more than 50% of rare complications and deaths are in healthy children without typical risk factors for hospitalization from influenza. For these reasons, universal influenza vaccination against children has been strongly advocated by most experts for many years. Current guidelines for vaccination of children vary widely between countries, but have been generally moving over time toward more inclusive recommendations. Vaccination of all children is now recommended in the

United States, as well as in many central European states, and is being considered in other countries. Prevention of influenza is clearly a cost-effective strategy compared to any currently available treatment options.

There are two basic types of influenza vaccines presently in use in children. Chemically inactivated, split-antigen vaccines grown in eggs (the "flu shot") are the standard vaccines that have been in use for more than 50 years and are licensed for children greater than 6 months of age. A cold-adapted, live, attenuated vaccine was introduced within the last decade and is licensed for use in children greater than 2 years of age. Both vaccines contain three antigens, one from the dominant, circulating type B strain, and the latest drift variants of each of the H1N1 and H3N2 subtypes of influenza A. The trivalent, inactivated vaccine (TIV) typically requires multiple exposures to achieve acceptable immunogenicity, efficacy, and durability in children under the age of 9 years, so current recommendations suggest two doses in anyone within this age group with fewer than two previous lifetime exposures. TIV is safe, with mild to moderate local soreness at the injection site the only common side effect. Guillaine–Barre syndrome does occur at a very low frequency after TIV, but at a lower rate than it does in association with influenza virus itself, the infection that the vaccine prevents.

The live, attenuated influenza vaccine (LAIV), which is administered as a nasal spray, appears to induce better initial immunity than TIV in young children who lack prior exposure, leading to better efficacy, longer durability, and improved cross-protection against drifted strains. It is unclear whether these advantages extend out of early childhood since available data suggest that LAIV has inferior efficacy in adults in some circumstances. This may be due to cross-protective antibody responses in more immunologically experienced hosts limiting replication of the vaccine virus. LAIV appears to be safe, with no evidence of reversion to wild type or transmission from vaccinated hosts. LAIV has been shown in one clinical trial to increase wheezing in children under 2 years of age, so administration to children with asthma or to those under 5 years of age with a history of wheezing is not currently recommended. Safety and efficacy have not been established in high-risk groups, so TIV is typically used for children with underlying chronic medical conditions.

Multiple alternative methods of producing influenza vaccines are either in clinical trials or already in use in adults. High-dose versions of standard TIV with four times the amount of each antigen show modestly increased immunogenicity in elderly adults, in whom vaccine effectiveness is generally poor, and are now licensed for this age group in many European countries and, more recently, in the United States. Adjuvanted vaccines, typically containing oil-in-water emulsions and lipids such as squalene or tocopherol, have also been extensively used in elderly adults in Europe to increase immunogenicity. Several of these vaccines that are in use in the elderly are in clinical trials in children, and may be available in the coming years as alternatives, where they might be particularly useful in at-risk groups where standard vaccine approaches are poorly immunogenic.

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113 2009-H1N1

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Introduction

With the emergence of the second wave of the 2009 influenza A (H1N1) virus, there have been concerns that this pandemic may rival those of 1957, 1968, and even 1918 in which not thousands, but millions of people around the world died from the disease (*Table 113.1*). WHO is advising the countries of the northern and southern hemisphere to prepare for a second wave of H1N1 pandemic in which large numbers of severely ill patients requiring more and more intensive care infrastructure are likely to be seen, creating pressures that could overwhelm in hospitals and intensive care units, and possibly disrupt the provision of care of other diseases. The newly developed H1N1 vaccine is expected to reduce the impact of the second wave of H1N1 influenza pandemic in the population, especially, on high risk groups, with diminished complications, hospitalization rates, and mortality. On the other hand, previous H1N1 strains have developed antiviral resistance, and this, as well as mutation to greater virulence, remain concerns for the future. Past pandemics were characterized by several features that have been seen since March 2009: the rapid spread of a virus with novel antigenic determinants, a change in pathogenicity with high death rates in younger age groups, successive pandemic waves, apparent higher transmissibility than that of the seasonal influenza,; and differences in impact in different geographic region. The overall mortality in the previous century's three pandemics ranged from 1 million to more than 45 million deaths. In the three previous influenza pandemics, vaccines were not produced in time to have any substantial impact. Even though the technology of vaccine manufacture, produced in embryonated eggs, has changed little since the 1930s, there is some hope that vaccines will be available to mitigate the force of later waves of the current epidemic. In addition, several clinically useful antiviral drugs are now available, although there are still concerns about development of resistance.

Influenza Virus: Back to Basics

The viruses that cause influenza are influenza A, B, and C belonging to the family Orthomyxoviridae, which is characterized by segmented minus-strand RNA genome. Influenza A and B viruses' genomes consist of eight separate segments. These include the following: three transcriptases (PB_1, PB_2, and PA); two surface glycoproteins, the hemagglutinin (H or HA) and neuramidase (N & NA); two matrix proteins (M_1 and M_2); and one nucleocapsid protein (NP). Epidemic disease is caused by influenza virus type A and B. Influenza C viruses cause sporadic mild influenza-like illness in children. The focus of this chapter will be on influenza A virus, which may infect humans and birds, and most importantly has the capability of developing into pandemic virus. Influenza A virus has been divided into multiple subtypes, and the natural host for most of these is various avian species. In addition, influenza A viruses of a few distinct subtypes have been isolated from pigs, horses, seals, whales, and human beings, and the genome of the virus codes for two important surface glycoproteins, the hemagglutinin (H or HA) and the neuraminidase (N or NA), have been identified. Based on both sequence and antigenic analysis, 16 distinct H (H1-H16) and 9 distinct N (N1-N9) subtypes are now recognized in animal and avian influenza viruses, but only 3 H subtypes (H1, H2, and H3) and 2 N subtypes (N1, N2) have caused extensive outbreaks in human beings. The influenza virus has a poor ability to proofread its genetic material while replicating, which results in frequent errors in progeny genes, and thus frequent mutations. When such minor changes occur in the H and N proteins, they result in "antigenic drift," the slow but significant change in antigenicity that occurs over time in both influenza A and influenza B, and that requires periodic changes in the yearly vaccine. An example of such drift occurred during the 2003/2004 influenza season when the H3N2 circulating virus developed over 80% drift from the virus that was used to make one of the three major vaccine components that year (*Table 113.2*). Further, marked changes in H, with or without similar changes in N, termed "antigenic shift" occur when new H or N gene segments are acquired by a process known as "reassortment." This may take place by the mixing of genetic segments during dual infection of cells by a human and an animal virus. When such viruses containing reassorted gene segments are introduced into

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Table 113.1
Influenza pandemic of the twentieth century

Date	Strain	Estimate number of worldwide deaths	Comments
1918–1919 (Spanish Flu)	H1N1	Over 50 million	• Three waves: A first, mild wave in the spring of 1918 was replaced by a second wave in September to November, 1918 that resulted in a mortality rate over 2.5%. A third wave with equally high mortality rates swept around the world in 1919 • The virus probably originated from the United States and then spread to Europe
1957–1958 (Asian Flu)	H2N2	1–1.5 million	Two waves: The virus originated in Southern China in February 1957 and spread over 3 months to Singapore, Hong Kong, and Japan and in October 1957 reached United Kingdom and United States. A second wave was detected in January 1958
1968–1969 (Hong Kong Flu)	H3N2	3/4 million	Two waves in winters of 1968–1969 and 1969–1970. The virus originated from Hong Kong in July 1968

Table 113.2
Antigenic drift and shift

Drift	Shift
Minor change within subtype	Major change, new subtype
Point mutations	Exchange of gene segments
Occurs in A and B subtypes	Occurs in A subtypes only
May cause epidemics	May cause pandemic
Example: A/Fujian (H3N2) replaced A/Panama (H3N2) in 2003–2004	Example: H3N2 replaced H2N2 in 1968

a population that has no pre-existing immunity, they may lead to a pandemic. This happened in 1957 and 1968.

Devastating pandemics take place when populations are exposed to a new viral subtype in the absence of pre-existing immunity. The infectious capabilities of a new virus that emerges in this way through reassortment are likely to be acquired from one or more of the human influenza gene segments. Conditions favorable for the emergence of an antigenic shift (reassortment) involve humans living in close proximity to domestic poultry and pigs. Pigs play an important role in interspecies-transmission of influenza virus. Susceptible pig cells process receptors for both avian and human influenza strains, which allow the pigs to serve as mixing vessels for the exchange of genetic material between human and avian viruses, resulting in the appearance of novel subtypes. Analysis of the 1957 H2N2 pandemic strain found that the emergent virus resulted from the acquisition by previously circulating human H1N1 of three new gene segments of avian origin (the H2 gene, the N2 gene, and one other). Similarly, the 1968 pandemic H3N2 virus acquired two new genes from an avian virus closely related to viruses isolated from ducks in Asia in 1963. In contrast, the 1918 H1N1 virus appears to have been an avian-like influenza virus derived from an unknown source. The currently circulating novel influenza H1N1 viruses that have been isolated around the globe during 2009 appear to have originated from two unrelated swine viruses, one of them a derivative of the 1918 human virus (*Table 113.3*).

Evolution, Zoonotic Transmission, and Possible Origin of 2009 H1N1 (Swine Influenza)

The 1918 H1N1 pandemic is believed to have also affected swine at that time. Its descendents have been enzootic in pigs up ever since. The first influenza A isolated from diseased pigs in United States (USA) was in 1930. These H1N1 swine viruses are called the classical swine H1N1 viruses and have continued to circulate in pigs in the Americas, Asia, and, until 1980, also in Europe, and they remain relatively antigenically stable. This swine H1N1 subtype has crossed over to

Table 113.3
Evolution of swine Influenza A virus

1918–1919	H1N1 pandemic also affected swine
1930	The first isolation of H1N1 in pigs
1968	H3N2 infect swine in Asia after human pandemic
1976	Outbreak of new H1N1 swine strain of A/New Jersey/1976 occurred in military personnel at Fort Dix, New Jersey
1998	Triple reassortment viruses were isolated from pigs
1958–2005	37 human swine-origin influenza were reported
2005–2009	11 sporadic triple reassortment swine viruses were reported
2009	New strain of H1N1 influenza emerge is A /California/07/2009

humans periodically, including the Fort Dix outbreak in 1976, resulting in infections that have been occasionally fatal, particularly in pregnant or immunocompromised persons, but not producing human epidemics. Moreover, following the human pandemic of the H3N2 subtype in 1968, H3N2 influenza virus infected pigs, although such porcine strains have shown less antigenic drift in swine than in humans. In 1998, H3N2 viruses with genes derived from human, swine, and avian genes of North America ("Triple reassortant viruses") were first isolated from pigs in the USA. The triple reassortant H3N2 viruses also continue to acquire other virus genes via reassortment to generate triple reassortant H1N2 or H1N1 viruses. Swine viruses of subtypes H1N1, H1N2, and H3N2 have been reported to cause occasional human infection during this time. Between 1958 and 2005, 37 human swine-origin influenzas were reported. Twenty-two (51%) of these cases reported recent exposure to pigs. The overall fatality rate was 17%. Prior to the current pandemic, but after December 2005, 11 sporadic cases of triple reassortant H1 viruses were reported to the Centers for Disease Control and Prevention (CDC) in the USA, 10 carrying H1N1 genes and 1 carrying H1N2 genes. Some of the patients had close exposure to pigs. Possible limited human-to-human transmission was reported in several situations. Genetic analysis of 2009 H1N1 viruses isolated in North America, Europe, and Asia revealed quadruple reassortant swine influenza A viruses that have not been recognized previously in pigs or human. The virus resulted from the reassortment of North American H3N2 and H1N2 swine viruses (triple reassortment viruses: avian/swine/human with Eurasian swine viruses). Sequence analysis also suggests that PB2 and PA genes originated from American H3N2 avian virus; a PB1 originated from H3N2; HA, NP, and NS genes originated from classical swine virus; and NA and M genes originated from Eurasian swine virus (*Fig. 113.1*). One of the swine genes of this new virus has been derived from the 1918 human virus, so the strain causing the 2009 pandemic is a fourth generation descendant of the 1918 virus. The 2009 H1N1 viruses are more pathogenic in mammalian models than seasonal H1N1 viruses, showing the ability to replicate and cause appreciable pathology in the lungs of mice, ferrets, and non-human primates. The pathologic changes seen were similar to those found in the lungs of animals infected with the highly pathogenic H5N1 avian influenza virus.

Epidemiology and Impact

Epidemiological data now indicate that 2009 H1N1 influenza virus pandemic started as an outbreak of influenza like illness in the Mexican town of La Gloria, Veracruse in mid-February 2009. In mid-April, the Center of Disease Control (CDC) identified swine origin H1N1 influenza virus in two specimens, independently collected in southern California. By the end of April, international spread and human-to-human transmission prompted the WHO to increase the pandemic alert from Phase 3 to Phase 4 and shortly after to Phase 5. On June 11, 2009, the WHO raised its pandemic to the highest level, Phase 6, indicating widespread community transmission on at least two continents (*Table 113.4*). As of December 6, 2009, more than 208 countries and overseas territories/communities have each reported at least one laboratory-confirmed case of pandemic H1N1 influenza, with a total or more than 622,000 laboratory confirmed cases and at least 9,596 deaths. However, the number of cases reported vastly underestimates the real number of cases; the WHO ceased regular reporting of case counts on July 16, 2009, because many countries were having difficulty tracking their numbers, and the WHO judged that their time would be better spent on investigating severe cases and other exceptional events. Most patients in the world with 2009 H1N1 have been teenagers and young adults, with rates of hospitalization highest in very young children. Between 1% and 10% with clinical illness require hospitalization. Overall, 7% to 10% of all hospitalized patients are pregnant

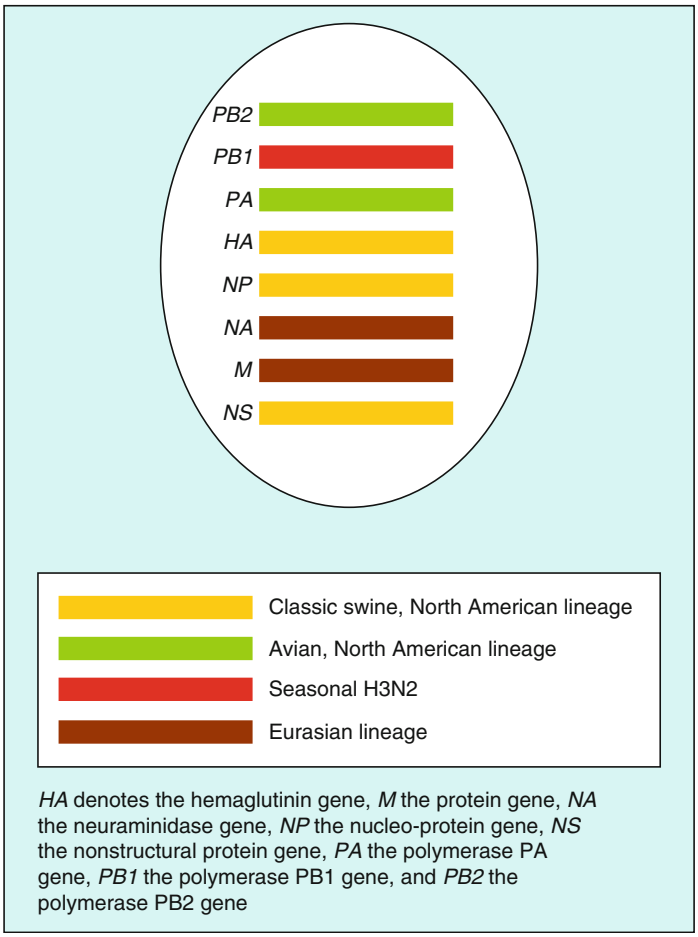

Figure 113.1
2009 Influenza A (H1N1) virus genotype

women in their second or third trimester. Of the hospitalized patients, 10% to 25% have required admission to intensive care, and 2–9% have died. Little is known about the level of pre-existing immunity to the 2009 H1N1 virus. Recent studies suggest that persons under the age of 30 years have little evidence of protective antibodies. However, a portion of older adults have pre-existing cross-reactive antibodies, presumably as a result of exposure to H1N1 strains circulating before 1957. Transmission of 2009 H1N1 virus from person to person is similar to that of other influenza viruses. The main route of transmission is respiratory through inhalation of large-particle respiratory droplets, and possibly via droplet nuclei. Transmission via large-particle droplets requires close contact because these droplets do not remain suspended in the air and generally travel only short distances (less than 2 m). Contact with contaminated surfaces is another possible source of transmission. All respiratory secretions and bodily fluids (e.g., fomites, diarrheal stool) of infected person should be considered potentially infectious. The secondary attack rates in households were estimated to be 27.3%, and in school settings, an infected school child was estimated to infect 2.4 other children within the school. The estimated incubation period could range from 1 to 7 days, but is most likely 1–4 days. Infected persons can be assumed to be shedding virus from 1 day prior to illness-onset until resolution of symptoms (up to 7 days following illness-onset). Children and immunocompromised or immunosuppressed persons may be contagious for longer periods. The amount of virus shed is greatest during the first 2–3 days of infection and appears to correlate directly with the height of fever. The 2009 pandemic H1N1 virus is expected to come in waves, and the middle of the second

wave is going on. This wave may continue during winter, or there may be a third wave. As of today no increase of severity has been seen, and genetic mutations have been minimal.

Clinical Features

The clinical manifestations can vary from asymptomatic infection to serious fatal illness that may include exacerbation of other underlying conditions or severe viral pneumonia with multi-organ failure. The Centers for Disease Control and Prevention (CDC) defines cases as influenza-like illness (ILI), if there is a fever of >37.8°C (>100°F) plus cough and/or sore throat in the absence of a known cause other than influenza. In the outbreak of 2009 H1N1 influenza pandemic in New York City, 95% of virologically proven cases satisfied the ILI definition. Fever has been absent in some outpatients and in, up to one in six surviving hospitalized patients. Vomiting and or diarrhea have occurred in up to 38% of outpatients in United States. Young children may have atypical influenza illness with the absence of fever and cough.

Table 113.4
World Health Organization pandemic levels

Phase 1 – No viruses circulating among animals have been reported to cause infections in humans
Phase 2 – An animal influenza virus circulating among domesticated or wild animals is known to have caused infection in humans, and is therefore considered a potential pandemic threat
Phase 3 – An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks. Limited human-to-human transmission may occur when there is close contact between an infected person and an unprotected caregiver, but the virus is not widely transmitted among humans
Phase 4 – Verified human-to-human transmission of an animal or human-animal influenza reassortant virus able to cause "community-level outbreaks." The risk of pandemic is significantly raised
Phase 5 – Human-to-human spread of the virus into at least two countries in one WHO region. The declaration of Phase 5 is a strong signal that a pandemic is imminent
Phase 6 – The pandemic phase is characterized by community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5. A global pandemic is under way

Among 89 children with confirmed H1N1 who required hospitalization in Birmingham, United Kingdom, the most common symptoms were fever (81%), cough (73%), and diarrhea (62%). Infant may present with fever and lethargy. The CDC case definitions for confirmed, probable, and suspected cases are in *Table 113.5*.

Three categories of clinical presentations have been seen during the current pandemic:

1. Mild illness is characterized by fever (some patients had no fever), cough, sore throat, diarrhea, myalgias, and headache. Other frequent findings have included chills and malaise. Vomiting and diarrhea have been reported in some patients, but no shortness of breath, dyspnea, or severe dehydration.
2. Progressive illness is characterized by mild illness in addition to signs or symptoms suggesting a progressive illness which include (*Table 113.6*):
   (a) Chest pain, tachypnea, or labored breathing in children
   (b) Hypotension
   (c) Confusion or altered mental status
   (d) Severe dehydration or exacerbations of chronic conditions (e.g. asthma, cardiovascular conditions)
3. Severe illness characterized by the following:
   (a) Profound hypoxemia, abnormal chest radiograph, and mechanical ventilation
   (b) Encephalitis or encephalopathy
   (c) Shock, multisystem organ failure
   (d) Myocarditis and rhabdomyolysis
   (e) Invasive secondary bacterial infection (e.g. pneumococcal disease)

Table 113.5
CDC: case definition for 2009 H1N1 Influenza virus

Confirmed case	An individual with an acute febrile respiratory illness with laboratory confirmed 2009 H1N1 infection by one or more of the following tests: • Real time reverse-transcription polymerase (rRT-PCR) or • Viral culture
Probable case	An individual with influenza like illness (i.e., an illness with a fever and cough or sore throat) who is positive for influenza A, but negative for H1 and H3 by rRT-PCR
Suspected case	An individual who does not meet the definitions of confirmed or probable pandemic H1N1 influenza A, but has ILI an epidemiologic link (e.g., likely exposure to a confirmed or probable case within the past 7 days)

Table 113.6
Clinical signs indicating rapid progression and need for urgent medical care

In adults	In children
• Difficult breathing or shortness of breath	• Tachypnea or labored breathing
• Pain or pressure in the chest or abdomen	• Skin color change, gray or blue
• Episodes of sudden dizziness	• Inadequate intake of oral fluids
• Severe or continuous vomiting	• Severe or continuous vomiting
• Influenza-like illness that improves but then returns with fever and cough	• Influenza-like illness that improves but then returns with fever and cough
• Confusion	• Irritable or not waking up

Complications

Most patients appear to have mild illness and recover spontaneously. Approximately 2–5% of laboratory-confirmed 2009 A (H1N1) influenza in Canada, and in the United States, as well as 8% in Mexico have required hospitalization. Nearly three quarters of cases in the USA requiring hospitalization, as well as 21 (46%) of 45 fatal cases in Mexico, involved one or more underlying conditions including asthma, diabetes, heart or lung disease, neurologic disease, pregnancy, morbid obesity, autoimmune disorders, and associated immunosuppressive therapies. Forty-five percent of patients admitted to intensive care units in the USA were children under the age of 18 years, and 5% were 65 years of age or older. Surveillance of pediatric deaths reported by CDC indicated that, of 36 children who died, 7 (19%) were aged <5 years, and 24 (67%) had one or more high-risk medical conditions. Twenty-two (92%) of the twenty-four children with high-risk medical condition had neuro-developmental disabilities which included cerebral palsy, developmental delay, autism, congenital neurological disorders, and other central nervous system disorders. Pneumonia is the most common and serious complication of the 2009 H1N1 pandemic influenza. The clinical course of 45 fatal cases in Mexico was characterized by severe pneumonia, hypoxemia with multifocal infiltrates including nodular alveolar, or basilar opacities on chest X-ray, and rapid progression to acute respiratory distress syndrome (ARDS) and renal or multi-organ failure. A similar experience was reported from Canada, Australia, and New Zealand. Some patients who required intensive care required advanced mechanical ventilation with high-frequency oscillatory bi-level ventilation and mean airway pressures of 32–55 cm/H_2O or veno-venous extracorporeal membrane oxygenation (ECMO) support. Bacterial co-infections likely played a role in almost one third of fatal cases of 2009 pandemic influenza A (H1N1) in the USA. The CDC investigators found evidence of concurrent bacterial infection in lung specimens from 22 of 77 patients (29%) with fatal pandemic H1N1 infection. A total of ten cases were co-infections with *Streptococcus pneumoniae*, six with *Streptococcus pyogenes*, seven with *Staphylococcus aureus*, two with *Streptococcus mitis*, and one with *Haemophilus influenza*. Four of the fatal cases involved multiple pathogens. The age of patients ranged from 2 months to 56 years, with a median of 31 years. Among other complications of pandemic H1N1 are acute neurologic syndromes reported in four patients aged 7–17 years who were admitted with signs of ILI, and findings that included seizures or altered mental status in two children, encephalitis in two, and ataxia in one. Three of the four patients had abnormal electroencephalogram (EEG). In all patients, pandemic H1N1 viral RNA was detected in nasopharyngeal specimen, but not in cerebrospinal fluids (CSF). All were recovered without sequelae. The overall case-fatality rate was 0.4% (compared with 2.4% for the 1918–1919 influenza pandemic) based on surveillance data from Mexico and mathematical modeling. There was a documented underlying medical condition in at least 49% of global documented fatal case.

Diagnosis

When influenza viruses are known to be circulating in the community, patients presenting with mild influenza can be diagnosed on clinical and epidemiological grounds alone. All patients should be instructed to return for follow-up should they develop any signs or symptoms of progressive disease (*Table 113.6*) or fail to improve within 72 h of the onset of symptoms. Under no

circumstances should influenza diagnostic tests delay initiation of infection control practices or antiviral treatment, if 2009 H1N1 pandemic disease is suspected. Laboratory testing should be prioritized to include hospitalized patients; patients where a diagnosis of influenza will inform decisions regarding clinical care, infection control or management of close contacts; and patients who have died of an acute illness in which influenza was suspected.

The gold standard for laboratory diagnosis of the 2009 H1N1 influenza is the real-timereverse transcriptase polymerase chain reaction (rRT-PCR) test, using primer and detector sequences tailored to the specific detection of this virus. A number of other diagnostic tests are available to detect the presence of 2009 H1N1 influenza in clinical specimens, but they differ in their sensitivity and specificity. Rapid influenza diagnostic tests (RIDTs) are based on various forms of antigen detection and have high specificity (>95%), but variable sensitivity (10–70%). Preferred respiratory specimens include a nasopharyngeal swab with a synthetic tip (e.g., polyester or dacron), nasal wash, bronchoalveolar lavage (BAL) or endotracheal aspirate. Lower respiratory tract specimens have a higher yield in patients with pneumonia due to viral replication in the lower respiratory tract. Many experts advise the use of a combination of nasopharyngeal swab with oropharyngeal swab. Isolation of H1N1 virus in cell culture or embryonated eggs is a diagnostic for infection but it may not yield timely result for clinical management; in addition, a negative viral culture does not exclude infection. All diagnostic laboratory work on clinical sample from patients, who are suspected cases of influenza H1N1 virus infection, should be done in a biosafety level (BSL) laboratory. Growth of H1N1 virus in cell culture or embryonated eggs should be performed in a BSL-2 laboratory using BSL-3 practices.

Management of 2009 H1N1 Influenza

The majority of individuals infected with the pandemic H1N1 influenza A virus can be treated with simple supportive care at home using antipyretics (e.g., acetaminophen or ibuprofen). Aspirin (acetylsalicylic acid) or aspirin-containing products (e.g., bismuth, subsalicylate-PeptoBismo) should not be used in children <18 years due to the risk of Reye's syndrome.

Empiric antiviral therapy should be started as soon as possible for persons with suspected, probable, or confirmed influenza and for:

Table 113.7
High risk groups for severe illness

1	Children younger than 2 years old
2	Pregnant woman up to 2 weeks post partum (regardless how the pregnancy ended)
3	Adult, 65 years of age or older
4	Persons younger than 19 years who are receiving long-term aspirin therapy
5	Persons with medical condition including asthma, neurological and neurodevelopmental conditions (including disorder of the brain, spinal cord, peripheral nerve and muscle such as cerebral palsy), chronic obstructive lung disease, cardiac disease, diabetes mellitus, and immunosuppressive conditions (including HIV/AIDS and cancer)

1. Illness requiring hospitalization
2. Progressive, severe, or complicated illness regardless of previous health status and/or
3. High risk for severe disease (*Table 113.7*)

Recent reports have shown that 21–25% of hospitalized patients with confirmed 2009 H1N1 infections have not received antivirals or have delay in receiving antivirals. Among 27 fatal cases in Mexico, the median time from the appearance of symptoms to treatment with antivirals was 8 days (range: 1–26 days).

Antiviral Drugs for Treatment of 2009 H1N1 Influenza

The neuraminidase inhibitors, oseltamivir (Tamiflu^{R}) and zanamivir (Relenza^{R}) are the drugs of choice for treatment and while the vast majority of pandemic H1N1 circulating strains are sensitive to these medications, all strains tested are resistant to amantadine and rimantadine (*Table 113.8*).

Oseltamivir and zanamivir are generally well-tolerated. Nausea and vomiting were reported with moderate frequency among adults receiving oseltamivir for treatment (nausea without vomiting, 10%; vomiting 9%). In children treated with oseltamivir, 14% reported vomiting. Oseltamivir suspension is formulated with sorbitol, which may be associated with diarrhea, and abdominal pain in patients who are fructose-intolerant. Zanamivir is formulated for oral inhalation and is contraindicated in patients with asthma or chronic obstructive disease. As of November 18, 2009, 39 isolates (among more than 1,000 tested) of pandemic H1N1 were resistant to oseltamivir. Among

Table 113.8
Antiviral treatment and chemoprophylaxis of 2009 H1N1 influenza

Medication/age groups		Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir			
Adults		75 mg twice daily	75 mg once per day
Children (age ≥12 months), weight	≤15 kg	30 mg twice daily	30 mg once per day
	15–23 kg	45 mg twice daily	30 mg once per day
	24–40 kg	60 mg twice daily	60 mg once per day
	>40 kg	75 mg twice daily	75 mg once per day
Children (age 3 months to <12 months)		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
Children (0–<3 months)		3 mg/kg/dose twice daily	Not recommended, unless situation judged critical (limited data)
Zanamivir			
Adults		Two 5-mg inhalations (10 mg total) twice daily	Two 5-mg inhalations (10 mg total) daily
Children	≥7 years or older for treatment	Two 5-mg inhalations (10 mg total) twice daily	Two 5-mg inhalations (10 mg total) daily
	≥5 years for chemoprophylaxis		

the 32 cases for which detailed information were available, 16 were associated with antiviral prophylaxis, and 3 had no history of exposure to oseltamivir. Resistance was associated with the common H275Y mutation, with retention of zanamivir susceptibility. Antiviral therapy is most effective when started within 48 h after the onset of symptoms; however, evidence suggests that treatment may benefit patients with prolonged or severe illness, even when started more than 48 h after the onset of illness. The recommended duration of treatment is 5 days. Hospitalized patients with severe infection might require longer antiviral courses. Some experts have advocated use of double doses of oseltamivir in critically ill patient, despite lack of published dates about efficacy. Zanavimir-inhaled formulation is not designed to be used in any nebulizer or mechanical ventilator as there is a risk that lactose drug carrier can obstruct ventilator equipment. For patients who are unable to take oral medication or in whom oral medication appears to be ineffective, peramavir, which is an investigational neuraminidase inhibitor formulated for intravenous administration, can be requested from the CDC under Food and Drug Administration (FDA) and emergency use authorization, although studies on efficacy and safety are limited.

Symptomatic patients who have highly suspected or documented oseltamivir resistance should not be treated with peramivir, because strains with the H275Y mutation have demonstrated reduced in vitro susceptibility to peramivir. These patients should be treated with intravenous zanamivir, which is an investigational drug that can be requested from the FDA for compassionate use. The CDC suggests limiting the use of antiviral chemoprophylaxis to specific groups. Antiviral doses recommended for treatment and prophylaxis of 2009 H1N1 influenza in adult and children are listed in *Table 113.8*. Clinicians should consider empiric treatment with antibacterial drugs if bacterial co-infection is suspected during or after influenza. Antibiotics selection should take into consideration, local data regarding frequency of pathogen causing secondary infection and pattern of drug resistance. When pneumonia is present, treatment with antibiotics should follow evidence-based guidelines for community acquired pneumonia.

The use of corticosteroids for H1N1 influenza is controversial. High-dose systemic steroid are not recommended for use in viral penumonitis outside clinical trials. However, low-dose steroids may be considered in patient with septic shock who require vasopressors.

Isolation of the Hospitalized Patient with 2009 H1N1 Infection

CDC recommends standard, droplet, and contact precautions for care of patients with suspected or confirmed 2009 H1N1 influenza infection. Health care workers should use

Table 113.9
ACIP priority target groups for H1N1 influenza vaccine

• Pregnant woman
• Household contact and caregivers for infant younger than 6 months of age
• All people from 6 months through 24 years of age
• Persons aged 25 through 64 years who have health conditions associated with high risk of medical complications from influenza (table)

surgical masks for routine non-aerosolizing patient care and N95-respirators for aerosol-generating procedures. Isolation precautions should continue for 7 days after illness-onset or until 24 h after the resolution of fever and respiratory symptoms. A longer period of isolation may be considered in the case of young children and severely immunocompromised patients.

2009 H1N1 Vaccine

An effective vaccine is the best tool to prevent the unpredictable spread of the current influenza pandemic. The 2009 H1N1 virus has the potential to cause severe disease, deaths, and potential socioeconomic dysfunction, and mathematical modeling suggests that the effect of the virus can be reduced by immunization. Two types of H1N1 vaccines have been prepared and have received approval from the FDA or the European Medicine Agency (EMEA) for use in the prevention of influenza caused by the 2009 pandemic influenza A (H1N1) virus. Both "adjuvanted" and "unadjuvanted" vaccine formulations are available. An adjuvant is a substance that boosts the immune response. It is made up of naturally occurring oil, water, and vitamin E. The "unadjuvanted" vaccine does not include this material. Vaccination campaigns are currently underway to protect populations from pandemic H1N1. Preliminary data indicate that both vaccines are safe and immunogenic. The Advisory Committee on Immunization Practice (ACIP) recommends that vaccination efforts should focus initially on persons in five target groups at high risk for influenza related complications (*Table 113.9*).

On November 19, 2009, the WHO estimated that around 80 million doses of pandemic vaccine had been distributed globally and around 65 million people had been vaccinated. The side-effect profile of the H1N1 vaccine ("adjuvanted" and "unadjuvanted"), particularly the frequency and severity of solicited adverse events, is consistent with previous experience from seasonal influenza vaccine. To date, less than ten suspected cases of Guillan-Barre syndrome have been reported in people who have received vaccines. These numbers are in line with normal background rates of this illness as recently reported. All such cases are being investigated to determine whether these are randomly occurring events or whether they might be associated with vaccination. WHO has received no reports of fatal outcome or confirmed cases of Guillain-Barre syndrome, since the H1N1 vaccination campaigns began. All cases have recovered. Intense active monitoring for rare adverse reactions of H1N1 vaccine is ongoing, but all data compiled to date indicate that pandemic H1N1 vaccines match the excellent safety profile of the seasonal influenza vaccines which has been used for more than 60 years.

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114 Measles

Najwa Khuri-Bulos

Definition

Measles is a systemic viral infection which is characterized by fever, cough, coryza, and conjunctivitis followed by a characteristic enanthem and a maculopapular rash with distinct progression and dissemination. Measles virus is one of the most infectious agents known and its host range is limited to humans only. Before the introduction of measles vaccine in the 1960s, infection with measles virus was a universal occurrence by late childhood unless people lived in secluded island communities. In addition, measles was a major cause of mortality and morbidity causing more than one million deaths annually occurring mainly in underdeveloped countries and affecting primarily children less than 5 years of age. The most important complications of measles include pneumonia, diarrhea, otitis media, and encephalitis. All of these are more common in the very young, malnourished, and immune compromised individuals. Despite major advances at controlling measles by widespread use of measles vaccine, measles continues to be a major cause of concern since reemergence of measles easily occurs if the immune status in the population is allowed to wane by delays or incomplete vaccination in the population.

Etiology

Measles virus is an RNA virus that belongs to the genus morbilliviridae in the family paramyxoviridae. It is closely linked to two other animal viruses, rinderpest and canine distemper viruses. While there are theoretical considerations that measles virus emerged as a zoonotic agent in the distant past, measles virus has evolved to be restricted in its host range to humans only though nonhuman primates can be infected in the laboratory. The virus is a spherical, single-stranded enveloped RNA virus that is light and heat sensitive. The viral genome encodes for eight proteins two of which are surface proteins that play a major role in pathogenesis and in producing immunity. The H (hemagglutinin) protein helps in attachment of the virus to host cell surfaces while the F (fusion) protein facilitates entry of the virus into host cells. This later leads to fusion of the infected cells leading to large multinucleated cells in tissue culture as well as in humans pathologically. Morbillivirus is the only paramyxovirus that characteristically produces inclusion bodies in culture. Measles neutralizing antibodies that protect the host against measles and confer lifelong immunity against infection are mainly directed against the H protein. Even though RNA viruses are prone to mutations, there is no evidence that the surface proteins of measles virus have changed over the years and measles virus is monotypic. This is an important consideration for use of the measles vaccine which was formulated more than 40 years ago but continues to confer immunity till the present time. Based on the C terminal 450 nucleotide of the N gene or the entire coding region of the H protein, 8 clades, A-H have been described. New genotype designation is done when there is $>2\%$ variance in the nucleotide sequence in the H or 2.5% in the N protein. However, even though measles vaccine in use belongs to the A clade which has not been circulating widely in recent years, measles vaccine continues to be effective. While 23 genotypes have been described and gene sequencing has proved useful in epidemiological tracking of measles outbreaks, there is no evidence that genotype variation impacts on immunity to measles. Measles virus genome has also been sequenced and it is now possible to distinguish wild from vaccine strains which is also an important consideration as measles elimination activities intensify. Measles virus is light and temperature sensitive which is also applicable to measles vaccines making it necessary to keep the vaccine under strict environmental control in order to assure effectiveness in the host.

Epidemiology

Measles virus is one of the most contagious pathogens known in humans. Infection rate exceeds 90% among the exposed nonimmune individuals regardless of age and even brief exposure to measles can lead to infection in the nonimmune exposed individuals. Measles can be transmitted by different routes including contact, droplet, and airborne. It is noteworthy that the virus can remain

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viable and infectious up to 1 h in room air and outbreaks have been described in pediatric clinics even with no direct contact between patients. Respiratory secretions from sick patients are contagious 4 days before and 4 days after appearance of the rash. Since measles virus can remain infectious when suspended in air for up to 1 h, patients should be placed in single rooms and airborne isolation should be instituted upon hospitalization. Measles virus shedding may continue in immune compromised hosts for longer periods and isolation of these patients should continue for the duration of the illness which is an important consideration for their nonimmune contacts. The incubation period of measles is 8–14 days and the average number of secondary cases after exposure to an infectious case is 15–20 cases. Mathematical modeling has postulated that endemic spread of measles in a community can be maintained with a population of 250,000–500,000. The typical epidemiological pattern of measles infection before introduction of the vaccine was widespread infection with recurrent outbreaks every 1–2 years involving mainly very young children, less than 2 years of age in developing countries while in developed countries the age group tended to be older. During the same period, marked differences between these countries were noted in outcome and prognosis. In many of these developing countries, measles mortality was between 5% and 10% of cases while this was <0.1% in developed countries. In addition to the very young age of infection, malnutrition, which was also more prevalent in developing countries, was found to be a risk factor for poor outcome with measles. After introduction of measles vaccine the infected age group was older and the intervals between outbreaks became longer. This trend was associated with decrease in mortality and morbidity khuri-bulos. However despite a high level of immunization, outbreaks of measles continued to occur in both developed and developing countries. The last such outbreak in the USA occurred in 1991 when even though more than 90% of the population was immunized, a pool of susceptible individuals increased to the point and a widespread outbreak occurred. This was associated with 55,000 cases and more than 10,000 hospitalizations and 1,023 deaths. Since this failure to control the spread of measles was found to be due to vaccine failure in a small number of older children and low immunization coverage in younger ones, it was recommended that each child should receive two doses of measles vaccine after the age of 1 year. Following this two dose schedule in the USA, endemic transmission of measles ceased since 1993. Another initiative in Latin America to control measles was applied by PAHO. In this program of accelerated measles control, a combination of strategies including high routine immunization coverage coupled with supplemental immunization activities (SIAs) administered intermittently to all children led to interruption of measles transmission in the whole continent of South America since 2002. Following these successful strategies introduction of similar initiatives at measles mortality reduction and later elimination were started in many other regions of the world. The impact of these programs to control measles has been great and it was estimated that 23% of mortality reduction in children less than 5 years of age which occurred lately is due to the widespread use of measles vaccine with resultant reduction in measles cases (P. Strebel, personal information WHO). The success of these strategies coupled with the characteristics of the infectious agents and the disease itself makes measles eradication eminently feasible. At the present time measles is also considered one of the major indicators for achieving the MDG4 aimed at decreasing less than five mortalities by two thirds by 2015. The MDGs were undertaken by the United Nations in 2000 when measles was found to be the fifth major cause of death in children worldwide and the leading cause of vaccine preventable deaths in children globally.

Pathogenesis

Measles virus gains entry into the host through infection of the epithelial cells of the respiratory tract. The surface proteins H and F interact with the cell receptors CD46 and SLAM (signaling lymphocytic activation molecule or CD 150); CD 46 is a widely distributed human complement regulatory protein expressed on all cells. This normally acts as a cofactor for the inactivation of C3b. SLAM is expressed on all immune cells, immature lymphocytes, T, B cells and monocytes as well as mature dendritic cells. This explains the widespread dissemination of the virus. Both vaccine and wild strains bind on these receptors though to varying degrees. Once the virus gains entry into the cells there is local replication followed by spread to the regional lymph nodes where amplification of the virus occurs. This leads to entry of the virus into the reticuloendothelial cells in the spleen, liver, and lymph nodes where viral multiplication continues leading after a brief period to secondary viremia and spread of the virus to the skin, conjunctiva, lungs, and other organs. Pathologically, the most important distinguishing feature is the presence of giant cells, which are present in the lymph nodes and other tissues including the skin. The prodromal stage coincides with the onset of secondary viremia about 8–12 days after infection. During this period,

cell-associated viremia can be detected until appearance of the rash when virus-specific immune response appears and virus starts to disappear at the same time; however, while measles virus may not be detectable after appearance of antibodies by culture methods, viral RNA can be demonstrated for several weeks by PCR indicating slow clearance of the virus. The immune response to measles virus is a major determinant of the clinical manifestations of measles. In response to measles virus, CD4 cells are activated. Initially there is an increase in the IFN gamma levels, which is followed by a shift to IL4 and IL10 responses in the convalescent phase. While measles antibodies play a major role in prevention of infection from measles they are not as important in clearing the virus once infection has occurred and viral clearance is mainly attributed to the cellular immune response. Patients who have immunoglobulin deficiency develop typical measles rash and recover from measles, while patients with T cell immune deficiency frequently do not develop the typical measles rash and have difficulty in clearing the virus and develop a more protracted and severe illness often ending in death.

The initial antibody response following measles consists of production of IgM antibodies followed by a switch to IgG2 and IgG4 followed by IgG1 and IgG3 antibodies. In addition to immune activation, measles also leads to immune suppression. This includes lymphopenia and reduction in both CD4 and CD8 T lymphocytes and may lead to a falsely negative PPD and in some cases reactivation of tuberculosis.

Pathology

Similar to cells seen by tissue culture, the most characteristic lesion pathologically is giant cell formation that is seen in many tissues including lymph nodes, spleen, and the lungs in immunocompromised individuals who may develop giant cell pneumonia. In the central nervous system, demyelination is the major pathological finding in acute disseminated encephalomyelitis (ADEM) with no evidence of virus or inclusion bodies in the brain on microscopic examination. In these patients, there is no viral antigen or antibody detected in these brains or the cerebrospinal fluid. On the other hand in patients who suffer from T cell immune deficiency measles inclusion body encephalitis (MIBE) occurs. In this entity both inclusion bodies and measles antigen are detected in the brain. A third CNS complication of measles is subacute sclerosing panencephalitis (SSPE) which manifests many years after measles infection in what are apparently normal hosts. Pathologically, both inclusion bodies and measles virus antigen have been detected in the brain of these patients.

Clinical Manifestations

Classical Measles

Before the introduction of measles vaccine, measles infection was easy to diagnose with confidence depending on clinical manifestations alone. Following an incubation period of 8–14 days, there is onset of fever accompanied by what was termed the three "Cs" consisting of conjunctivitis, coryza, and cough. These increase along with the fever for a prodromal period of 3–4 days at the end of which the pathognomonic enanthem, the Koplic spots appear in the buccal mucosa. Koplic spots appear as pinpoint white blue lesions on the buccal mucosa best seen opposite the lower molars one day before and on the day of appearance of the rash. At the end of the prodromal phase, measles rash, which is a maculopapular rash, appears initially behind the ears and spread quickly to the face and over a period of 2–3 days in a centrifugal manner to the trunk and extremities involving on occasion the palms and soles. The rash may be so intense as to coalesce. Even though the characteristic measles is maculopapular on rare occasions the rash may be hemorrhagic. By the third day, the rash starts to fade in the same order it appeared. On occasion, fine peeling may occur. Fever, which continues during the appearance of the rash, disappears with disappearance of the rash. Fever extending beyond the fourth day of rash may indicate secondary bacterial infection. On occasion, patients with measles may also develop lymphadenopathy and splenomegaly.

Modified Measles

In situations where the host may have partial immunity to measles due to preformed antibodies, such as infants who still have persisting maternal antibodies or in recipients of intravenous gamma globulin or antibody containing blood products, clinical manifestations of measles may be modified leading to a longer incubation period, shorter prodromal illness with lower grade fever and a faint rash. Modified measles is also associated with fewer complications. In fact, the clinical manifestations maybe so mild as

to lead to misdiagnosis unless these cases are linked epidemiologically to a classical case of measles.

Atypical Measles

Contrary to modified measles, which is similar to classic measles but milder in severity, atypical measles is a distinct entity that occurs in patients who are infected with wild measles virus after having received killed measles vaccine, which was available between 1963 and 1968. Atypical measles is distinctly dissimilar to classical measles since it is characterized by sudden onset of high fever with abdominal and chest pain with cough and vomiting. The rash appears in the distal extremities initially and may progress from maculopapular to vesicular or even purpuric rash which does not occur with natural measles infection. Recovery may take 2–3 weeks. Atypical measles does not occur after live measles vaccine.

Complications

Even though otitis media is the most common complication of measles, pneumonia remains the most important cause of death following measles. It is important to note that measles virus itself infects the respiratory epithelium and while cough and bronchitis are common in the first 3 days of measles due to viral invasion of the respiratory epithelium, bacterial superinfection follows later in the course of the disease, usually 3–4 days after onset of the rash leading to bacterial bronchopneumonia. The most common pathogens leading to this complication include *H. influenzae*, *Streptococcus pneumoniae*, and staph aureus. Diarrhea is also an important complication especially in developing countries. This may be caused by the virus itself or maybe due to bacterial superinfection. Diarrhea exacerbates malnutrition in many of these children decreasing the immune response of the host further and increasing the risk of superinfection with resultant increase in mortality and morbidity.

Central Nervous System (CNS) Complications

An important major complication of measles is CNS involvement. Even in the absence of neurological manifestations clinically abnormal CSF and EEG findings have been reported. Measles virus can affect the CNS in several ways and clinically apparent neurologic complications of measles include three entities: measles encephalomyelitis or acute disseminated encephalomyelitis (ADEM), measles inclusion body encephalitis (MIBE), and subacute sclerosing pan encephalitis (SSPE). These three complications differ significantly in their pathogenesis, the time of onset, and clinical manifestations. The first to appear infection is measles encephalomyelitis or acute dissiminated encephalomyelitis (ADEM). This occurs in the recovery phase, about 2 weeks after the onset of rash, after acute measles infection with the onset of high fever, decreased level of consciousness, and seizures. The pathogenesis of this entity is an autoimmune demyelinating illness. No viral antigen or antibody has been detected in the CSF or the brain. Acute dissiminated encephalomyelitis occurs in about 1/1,000 patients following acute measles infection. It is a monophasic illness with guarded prognosis since a majority of these patients develop long-term sequelae. Another form of CNS involvement is measles inclusion body encephalitis (MIBE). This complication occurs primarily in patients who suffer from immune deficiency especially in decreased or abnormal T cells. It may follow both wild measles infection and administration of attenuated live measles vaccine. The onset is relatively rapid, 1–2 months following exposure, though some of these patients do not develop the characteristic measles rash and hence the acute measles infection may be missed. Disease manifestations include behavioral abnormalities, myoclonus, focal seizures, confusion, and coma. At biopsy, there is gliosis and inclusion bodies in neurons and glial cells. Measles virus can be detected though it might be defective. The third form of CNS involvement is subacute sclerosing pan encephalitis (SSPE). This is a very rare complication of measles with an incidence rate of ??2–40/1,000,000 population annually. The disease starts many years after measles with a latent period ranging from 2 to 22 years, usually 2–10, and is more common in patients who develop measles before the age of 1 year. SSPE follows wild measles infection mainly. The initial manifestation is deterioration in mental capacity with myoclonic jerks progressing to optic atrophy, followed by akinetic mutism and death over a period of several months to years. Patients have characteristic electroencephalographic changes and on CSF examination measles virus antibodies are detected. On pathology, inclusion bodies are present in neurons and glial cells and defective measles virus is identified. SSPE is very similar to MBIE but with immune deficiency the incubation period in MIBE is shorter than that seen in SSPE.

Measles in the Immunecompromised Host

A group of patients who have an exceptionally serious course with poor outcome following measles are the immune compromised, especially patients with T cell deficiency, since cell-mediated immunity is necessary for adequate response to measles virus. Following measles infection, these patients develop a widespread infection involving many organs with giant cell formation but no rash. Giant cell pneumonia and measles inclusion body encephalitis are major complications that frequently end fatally.

Diagnosis

During endemic conditions, the diagnosis of classic measles is possible using clinical criteria alone. In fact the clinical presentation is so characteristic that no further diagnostic test is needed in these situations. The introduction of measles vaccine on a wide scale, however, modified some of this classical clinical presentation and in these situations diagnosis is dependent on demonstration of antibody to infection. Antimeasles IgM antibodies are usually present by the time of appearance of the rash. Viral isolation is not necessary though demonstration of viral antigen by PCR is possible.

Differential Diagnosis

While measles has to be distinguished from several diseases leading to maculopapular rashes, the classical presentation with prodromal fever accompanied by coryza, conjunctivitis, and cough followed by the classical distribution of maculopapular rash with fever is almost diagnostic. Other diseases that can lead to a similar rash, however, include rubella, though the illness is less severe and there is a milder prodrome with no cough and the rash is milder; roseola infantum where there is little or no cough or conjunctivitis and fever subsides when the rash appears; parvovirus (fifth disease) with maculopapular rash but with no prodromal stage; scarlet fever is associated with sore throat and fever with no conjunctivitis or coryza. An important noninfectious disease to consider, however, is Kawasaki which gives rise to high fever and conjunctivitis and rash which maybe confused with measles. There is, however, no cough or koplik spots and the progression of the rash is dissimilar. Kawasaki may also lead to joint swelling which is absent with measles. However, since measles may be modified by partial immunity in some hosts, it is important to obtain laboratory confirmation of measles in some of these patients so as to make sure that control measures are started. This is becoming increasingly important as efforts at measles elimination and possible eradication are adopted.

Treatment

Even though antiviral agents such as ribavirin and isoprinosine have been tried there is no proved antiviral therapy for measles and treatment continues to be mainly supportive. Patients with acute measles should be well hydrated and offered antipyretics. These patients should also continue to be fed since many of them are living in poor conditions where their nutritional status is marginal. Patients who have suspected bacterial superinfection should be treated with appropriate therapy since pneumonia continues to be the major cause of death in measles. Another supportive measure that has proved beneficial is vitamin A. This vitamin has been found to improve the outcome with measles and vitamin A administration is recommended to patients with acute measles regardless of vitamin A status. A Cochrane review showed that two doses given on 2 consecutive days is recommended in order to decrease complications. The WHO recommends this for all children regardless of country of residence (*Table 114.1*).

Patients who have vitamin A deficiency should receive a third dose 2–4 weeks later.

Prognosis

Measles mortality and morbidity are increased at the extremes of age. Other factors that increase mortality include malnutrition, immune suppression especially

Table 114.1
Vitamin A treatment for measles

Age	Vitamin A dose	Two doses on 2 consecutive days
< 6 months	50,000 units	Two doses on 2 consecutive days
6–11 months	100,000 units	Two doses on 2 consecutive days
>12 months	200,000 units	Two doses on 2 consecutive days

T cell deficiency, chronic disease, and poor access to care. Mortality rates in children living in developing countries may be as high as 6% while this is less than 0.1% in developed countries.

Prevention

Natural measles infection leads to lifelong immunity. However, since measles infections lead to major complications and are associated with great mortality and morbidity, prevention of measles by immunization is mandatory. Immunization using the live attenuated measles is necessary to prevent measles and in patients who are immunocompromised, prevention of measles is possible by administration of immunoglobulin within 4 days of exposure to measles. Immunoglobulins, however, play no role in the treatment of measles once the infection has occurred.

Active immunization by the use of measles vaccine became possible with isolation and cultivation of measles virus by Enders. The first measles vaccine to be used was the killed measles vaccine which was introduced in 1963. This was later withdrawn from the market due to the occurrence of atypical measles in immunized individuals upon exposure to wild measles infection. This led to introduction of the first attenuated live measles vaccine in use. The first live measles vaccine in use was the Edmonston B strain which was associated with major side effects often necessitating the use of gamma globulin along with the vaccine. This strain was "further" attenuated leading to two strains the Moraten and Schwartz strains. These are the most widely used strains in Europe and the USA though other strains such as the Edmonston Zaghreb and other regionally attenuated strains are in use in other parts of the world.

Moraten and Schwartz strains are genetically identical and belong to the A genotype. While the original A genotype is not the commonly circulating genotype at the present time, individuals who have received measles vaccine in the past continue to be immune to measles and there is no need to change the formulation of the vaccine. Measles vaccine is also available as a combination vaccine with mumps and rubella vaccines. It contains no thimerosal but may contain sorbitol or gelatin as stabilizers. The vaccine is stable in the frozen state but the reconstituted vaccine is light and heat sensitive.

Measles vaccine induces antibody responses of the IgM class followed by IgG and IgA antibodies. Long-term immunological T cell memory is induced by CD4 and CD8 measles specific cells. The immune response to measles vaccine is dependent on absence of preformed measles antibodies which may inactivate the live vaccine. This may occur in infants who receive the vaccine at an early age during which maternal antibody may still be able to inactivate the vaccine. Measles vaccine may also be inactivated by blood or blood products. In these situations, measles vaccine should be delayed for several months depending on the product received. If a child received measles vaccine during that period this should be repeated at a later time. Another determinant of the immune response is the age at immunization and the viral dose and strain of the vaccine used. In most studies, the proportion of children who developed measles antibodies after receiving the vaccine was less than 75% in infants who received the vaccine before the age of 9 months and increased to 85% after the age of 9 months. This proportion increases gradually till 12 months of age when most studies show that 90–95% of recipients develop antibodies. Since measles is a very highly infectious disease and outbreaks can occur even in a highly immunized population a second dose of measles vaccine is recommended. This second dose is not a booster dose but is intended to lead to antibody response in the few who did not develop antibodies with the first vaccination effort. In studies of children who failed to respond to the first dose of measles vaccine, the seroconversion rate was in excess of 90% upon revaccination. After the age of 1 year, measles vaccine should be preferentially offered in combination with mumps and rubella vaccines which is not associated with increased risk of side effects and leads to immunity to all three antigens (MMR). A recently introduced formulation of MMR combined with varicella (MMRV), however, has been associated with a small increased incidence of seizures in recipients (1/2,000). This is mainly seen in patients who received the MMRV as a first dose between the ages of 12 and 48 months. A second dose can be administered using MMRV, however, with no increased risk of seizures.

The vaccine schedule for measles in many of the developing countries includes a dose to be administered at 9 months of age. This dose is necessary in order to prevent occurrence of measles infection in children who are less than 1 year of age in endemic countries. This group frequently has a higher mortality and morbidity than older children. In these situations, it is recommended that the MMR be administered again at 12–15 months of age and a second MMR be administered at 18 months or at 4 years of age. This strategy led to a major decrease in the number of cases of measles and measles elimination from many parts of the world. In the USA and Latin America, measles transmission has been interrupted since 1993 and 2002, respectively.

Side effects of measles vaccination in normal hosts are usually mild and self-limited. Fever occurs in 5–15% of vaccine recipients about 6–12 days following vaccination. Mild rash has also been reported in 5% of individuals. More serious side effects including thrombocytopenia occurs in less than 1/25,000 recipients while encephalitis has been reported in one in one million individuals.

Measles vaccine is contraindicated in patients who are immune compromised or are recipients of high dose steroids. This is defined as having received 2 mg/kg of >20 mg of prednisone for more than 14 days. Such patients can receive the measles vaccine 1 month after discontinuing steroids. Patients on inhaled steroids can receive measles vaccine, however. Measles vaccine is contraindicated in pregnancy, but children of pregnant women should be vaccinated and there is no evidence of transmission of the measles vaccine to contacts.

Care of exposed susceptible individuals includes administration of human immunoglobulin in a dose of 0.25 ml/kg in normal individuals and 0.5 ml/kg in immune compromised hosts within 6 days of exposure. Measles vaccine is not contraindicated in these situations, however, and may help protect the host if given in the first 3 days of exposure.

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115 Mumps

Richard J. Whitley

Introduction

Mumps is an acute viral illness that has been recognized for millennia, first being identified by Hippocrates who described parotitis and orchitis. In the 1930s mumps was proven to be caused by a filterable agent from saliva that could be transmitted from infected patients to rhesus monkeys. Prior to the development of a vaccine, mumps was a frequent cause of outbreaks among military personnel. In spite of the availability of an excellent vaccine (measles, mumps, rubella with or without varicella), there have been outbreaks of mumps. In 2006, there was a multi-state outbreak of mumps that involved over 6,500 cases in the United States, occurring predominantly among Midwestern College students. A similar outbreak occurred in the summer of 2009, resulting in over 4,000 cases. On average, however, only 20 cases occur annually in the United States. Similar outbreaks have been reported globally by the World Health Organization.

Etiology

Mumps is a single-stranded RNA virus that is in the paramyxovirus family. Other members of this family include parainfluenza and Newcastle disease virus. Mumps virus grows readily in various human and subhuman primate cultures. It can be isolated from humans from multiple sites in those individuals who are infected.

Epidemiology

Mumps is transmitted by direct contact with infected oropharyngeal secretions. It occurs worldwide and humans are the only reservoir for disease. The highest incidence of mumps is late winter and early spring. Transmissibility of mumps is similar to that of influenza and rubella. Individuals with mumps are considered infectious 3 days before the onset of clinical illness to approximately 4 days after the onset of disease. Most cases occurred in young children between 5 and 9 years of age with 90% of cases occurring among children less than 15 years of age. Prior to vaccine licensure, it is estimated that there were over 200,000 cases of mumps annually in the United States. Males and females are equally affected. With widespread vaccination programs, current outbreaks, as noted above, tend to occur in older individuals, particularly those in college.

Clinical Manifestations

The case definition of mumps is acute onset of unilateral or bilateral tender, self-limited swelling of the parotid or salivary glands lasting greater than 2 days. The incubation period averages 14–18 days. Prodromal symptoms are usually nonspecific and include fever, malaise, anorexia, and myalgia. Approximately 20% of cases are asymptomatic.

Mild and self-limiting parotitis characterizes the clinical symptomatology and occurs in 30–40% of infected individuals. Symptoms tend to resolve over the first week of illness.

Importantly, mumps can be associated with significant medical complications, including orchitis, the most common of complications that occurs in post-pubertal males. Orchitis is associated with the acute onset of testicular swelling, pain, nausea, vomiting, and fever. It occurs in approximately 50% of individuals with clinical disease. Aseptic meningitis will also occur in approximately 15% of patients and tends to resolve without sequelae over a period of a week. Encephalitis is significantly less common.

Other complications include oophoritis (5% of post-pubertal females), pancreatitis, and myocarditis. Hearing loss attributed to mumps virus infection has been reported to occur in 1 in 20,000 cases.

Diagnosis

The diagnosis of mumps is usually made on the basis of clinical presentation. Specimens of saliva can be obtained either for isolation of virus in cell culture or for detection of viral DNA by polymerase chain reaction. The

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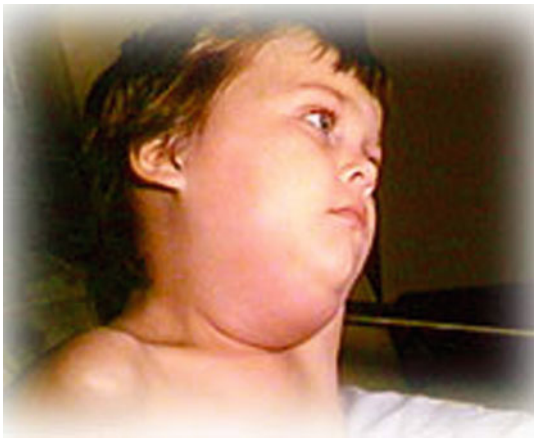

Figure 115.1

evaluation of acute and convalescent sera by enzyme immunoassay (EIA) is an easy way to determine evidence of acute infection. Reliable EIA assays to detect both evidence of IgM and IgG antibodies are available.

Prevention and Therapy

No therapy exists for the treatment of mumps infection. Similarly, the use of high-tittered immune globulin or routine IgG has not proven effective in post-exposure prophylaxis. Thus, current efforts focus on deployment of an efficacious vaccine.

The current vaccine strain Jeryl Lynn was a virus isolated from Dr. Maurice Hilleman's daughter and subsequently developed into a vaccine that was licensed in 1967. The mumps vaccine is available in combination with measles and rubella (MMR) or as a quadrivalent vaccine that includes varicella. The efficacy of the vaccine is considered to be in excess of 95% with immunity persisting greater than 25 years. Vaccine is routinely administered at greater than 12 months of age. A second dose of vaccine has been recommended for school age children by the Advisory Committee of Immunization Practices, Centers for Disease Control and Prevention.

The vaccine is considered contraindicated in individuals who are immunocompromised, pregnant women, or those who have had a severe allergic reaction to prior immunization. Since the MMR vaccine is a live attenuated vaccine, it requires a cold chain at all times.

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116 Non-Polio Enterovirus: Infections

Sami Al-Hajjar

Enteroviruses (EVs) comprise nearly 72 serotypes within the family *Picomaviridae* (pico, small; ma, their characteristic nucleic acid component). Control of poliovirus in much of the world has focused attention on the nonpolio EVs which include Coxsackieviruses A and B, echoviruses, and the newer members of the EVs (*Table 116.1*). In recent years all newly identified enterovirus types have been designated simply as "enterovirus" followed by a number beginning with 68.

Morphologic and Biologic Features

The EVs are extremely small (22–30 nm in diameter), naked virions with icosahedral symmetry. They possess single-stranded positive RNA and four major polypeptides. EVs are distinguished from rhinoviruses (the other large genus of picomaviruses) by their resistance to acid (pH 3.0), the capability to replicate efficiently at 37°C, and a higher buoyant density.

Pathogenesis

The mechanism of pathogenicity of EV infection is the lytic infection of the host cell, resulting in severe cytopathic effects. EVs replicate in the lymphoid tissue of the oropharynx and gut. This phase occurs over 1–3 days and is symptom free. There follows a minor viremia with spread of virions to the reticuloendothelial system at 3–5 days. A subsequent major viremia results in viral dissemination to secondary organs such as the central nervous system, lungs, heart, and liver. This phase frequently is responsible for symptomatic illnesses.

Epidemiology

EVs are ubiquitous in humans, and humans are their only natural host. The EVs have a worldwide distribution, with a marked summer/fall seasonality in temperate climates and high year-round incidence in tropical and subtropical areas. The epidemiology of EV infections is not well studied in the Middle East and Arab Gulf Region. Early and recent reports have concentrated on the identification of wild polioviruses. In Saudi Arabia, there has been a significant increase in EVs during midwinter and early spring in addition to a year-round incidence of infection. Each enterovirus season in each part of the world is dominated by a few serotypes. Young children are most susceptible. As many as 13% of infants are born in the summer of life and one fifth of them are hospitalized with suspected bacterial sepsis and receive unnecessary antibiotics.

EVs can be isolated from the lower and/or upper alimentary tract and therefore can be spread both by fecal-oral and respiratory routes. In areas with poor sanitary conditions, fecal-oral transmission predominates. Transmission by respiratory routes can occur early in infection because the virus replicates in the upper respiratory tract.

After infection the viruses will persist in the oropharynx for 1–4 weeks, and they can be shed in the feces for 1–18 weeks. Sexual transmission of EVs has not been reported, and blood transfusions and insect bites seem not to be responsible for virus transmission. EVs can be isolated from sewage; therefore, a fecal-water-oral route of transmission is possible. Nosocomial transmission of EVs typically takes place in newborn nurseries and has been reported for several Coxsackieviruses of groups A and B and echoviruses. Incubation periods vary, but relatively short intervals (3–6 days) are frequent. Often illness will be seen concurrently in more than one family member, and the clinical features will vary within the household.

Clinical Manifestations

EVs are responsible for significant and frequent illnesses in infant and children and result in an array of clinical manifestations (*Table 116.2*). The most common presentations are nonspecific febrile illness or rashes. No disease is uniquely associated with specific EV serotype, and no serotype is uniquely associated with any one disease.

Of great clinical importance is enteroviral aseptic meningitis frequently caused by a group A or B Coxsackievirus or an echovirus. Onset of meningitis usually is sudden and

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Table 116.1
Nonpolio enterovirus: human serotypes

Group name	Serotypes
Coxsackieviruses, Group A	23 (A_1–$A2_2$, A_{24})
Coxsackieviruses, Group B	6, (B_1–B_6)
Echoviruses	31 types (types 1–9, 11–27, 29–33)
Enteroviruses	5 types (68–71)

fever of 38–40°C is the most consistent clinical finding. Headache and nuchal rigidity are more common in the school-age child. Cerebrospinal fluid (SF) analysis shows a moderate pleocytosis with a predominance of lymphocytes (early in the course the polymorphonuclear cell type is predominant), normal glucose, and slightly increased protein level. The duration of illness due to enteroviral meningitis is less than 1 week. Several studies indicate that as many as 10% of survivors of aseptic meningitis occurring before 3 months of age may suffer long-term neurologic sequelae, especially speech and language delay. Older children apparently recovered completely. Neurotropic strains, such as enterovirus 71, can cause aggressive central nervous system infection, and have overall fatality rate of 14%.

Coxsackieviruses B_1 through B_5 are among the most important pathogens of acute and chronic myocarditis and cardiomyopathy; also they are often implicated in pleurodynia (Bornholm disease), which is most common among children 5–15 years of age. It is characterized by the abrupt onset of pain over the lower rib cage or upper abdomen with moderate fever. Cough is notably absent.

Group A Coxsackieviruses usually cause herpangina, which is characterized by an eruption of tiny oral vesicles and ulcers (particularly concentrated on the posterior pharynx), high fever, anorexia, sore throat, and dysphagia. Complications are unusual and the child is generally asymptomatic by the seventh day.

Hand-foot-mouth syndrome, most commonly due to Coxsackievirus A_{16}, occurs particularly among children less than 5 years old. The course is similar to that of herpangina, but a vesicular exanthema is distrusted over the buccal mucosa and plate, with similar lesions appearing on the hands more commonly than the feet. Trunks, thighs, and buttocks may be involved. Recently strains of enterovirus 71 circulating in East Asia caused outbreaks of hand-foot-mouth disease that are associated with a severe rhombencephalitis (inflammation of brain stem),with significant mortality.

Acute hemorrhagic conjunctivitis, usually associated with Coxsackievirus A_{24} and Enterovirus 70, occurs in epidemics and pandemics, affecting as many as 50% of the entire population of a community. Typically patients have sudden onset of severe eye pain, tearing, photopia, swelling, and dramatic subconjunctival hemorrhage. Recovery occurs in a week to 10 days.

Approximately 2,500 babies each year develop perinatal disseminated EV infection. The risk of severe morbidity and mortality is highest in the first day of life. Meningoencephalitis, myocarditis, hepatic necrosis, and necrotizing enterocarditis may develop as well as disseminated intravascular coagulation, making this syndrome indistinguishable from overwhelming bacterial infection.

Unusual EV-associated illnesses include chronic meningitis or meningoencephalitis occurring in antibody-deficient individuals, inflammatory myositis, and rare cases of juvenile diabetes mellitus that have been related to Coxsackievirus B.

Diagnosis

Diagnosis of nonpolio EV infection is more readily established by virus isolation from throat swabs, stool or rectal swabs, body fluids, and occasionally tissues. Direct isolation of virus from affected tissues or body fluids in enclosed spaces (e.g., pleural, joint, pericardial, or cerebrospinal) usually confirms the diagnosis. Because EVs can persist in the lower gastrointestinal tract for as long as 8–12 weeks, fecal isolates may not be causally related to the patient's illness.

When there is central nervous system involvement, CSF cultures taken during the acute phase of the disease may be positive in 10–85% of cases, the mean time to grow EVs from the CSF ranges from 4 to 8 days. Recently a polymerase chain reaction assay was proven to be more sensitive (95–100%) and as specific (97%) as cell culture for detection of EVs in CSF of patients with aseptic meningitis and meningoencephalitis. Serologic screening without viral isolation is generally not indicated.

Treatment

Treatment is supportive only. Although there is no approved antiviral therapy for any enteroviral infection, pleconaril, a capsid-inhibiting compound, may play a role in the treatment plan for serious infections in the future. Intravenous immune globulin (IVIG) has been administered to B-cell-deficient patients (such as

Table 116.2
Clinical infections associated with nonpolio enteroviruses

	Coxsackieviruses A	Coxsackieviruses B	Echovirus	Enterovirus (other)
Asymptomatic infection	*	*	*	*
Nonspecific febrile illness	*	*	*	*
Aseptic meningitis	*	*	*	*
Croup		*	*	
Pneumonia		*	*	
Pleurodynia		*		
Myocarditis		*		
Pericarditis		*		
Hepatitis	*	*	*	*
Panreatitis		*		
Gastroenteritis	*	*	*	*
Conjunctivitis	*			*
Herpangina	*			
Hand-foot-mouth disease	*			.
Rash	*	*	*	*
Diabetes mellitus		*		
Fulminant neonatal disease		*	*	
Chronic meningoencephalitis		*	*	

agammaglobulinemia) with chronic meningoencephalitis, and in neonates with overwhelming EV infection with some benefit (uncontrolled trials).

Isolation and Control Measures

Enteric precautions must be observed for hospitalized patients during their hospital course. Particular attention should be given to hand washing and personal hygiene, especially after diaper changing.

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117 Parvovirus B 19

Mahmoud M. Mustafa · Kenneth L. McClain

Parvovirus B 19 (B19) is the only known human pathogenic parvovirus. It was discovered accidentally in 1974 during a study screening healthy blood donors for hepatitis B using panels of serum samples. One sample (coded 19 in panel B) gave a positive result in counterimmunoelectrophoresis (CIE) but negative results in more sensitive assays. Electron microscopic examination of the excised precipitin line from the CIE showed the presence of 23-nm particles resembling parvovirus. Since that time, serologic surveys have demonstrated that B19 is a ubiquitous agent. Thirty percent to 60% of adults have antibody to the new virus. Systematic search of blood samples to identify infected patients and possible clinical correlates resulted in 1981 in the discovery of B19 in the serum of sickle cell anemia patients with aplastic crises. The next major association was made in 1983 when B19 infection was found to be the causative agent of erythema infectiosum. Since then, the spectrum of illness with which B19 is associated has grown to include intrauterine infection with hydrops, arthritis, idiopathic thrombocytopenic purpura, transient erythroblastopenia of childhood, neutropenia, hemophagocytic syndrome, encephalitis, pseudoappendicitis, and purpura. This chapter reviews the present knowledge on Parvovirus B 19 virology and epidemiology and its associated clinical manifestations.

Virologic Aspects of B19 Infection

Parvovirus B 19 is a small (*parvum* is Latin for small), nonenveloped, single-stranded DNA virus that belongs to the family Parvoviridae and is a member of the genus *Parvovirus*. As result of its lack of envelope and limited DNA content, B19 is extremely stable to physical inactivation by such mechanisms as heat (60 min at 56°C) and lipid solvents. Parvoviruses are species specific, and no animal model has been identified that permits the replication of B19. In addition, although the virus can be grown in fresh human bone marrow cells, erythroid cells derived from fetal liver, and erythroid leukemic cells, there is no practical in vitro system for isolation of B19 from clinical specimens.

Epidemiology

Infection with B19 is common. The reported prevalence of immunoglobulin G (IgG) antibodies ranges from 2% to 15% in children 1–5 years old, from 15% to 60% in children 5–19 years old, from 30% to 60% in adults, and up to 90% in the elderly. Women of child-bearing age show an annual seroconversion rate of 1.5%. Viremia in the general population, however, is rare. A study of the prevalence in blood donors showed that 1:20,000–1:40,000 units of blood contain high titers of B19 during the epidemic season. This is important to consider when many thousands of units of blood are pooled to make factor concentrates used for treatment of patients with hemophilia.

The distribution of B19 is worldwide. Seroprevalence studies from the United States, Western Europe, and Japan show similar patterns. The prevalence rates are slightly higher in developing countries. Infection in temperate climates is common in late winter, spring, and early summer. Infection with B19 follows a cyclic pattern, with increased rates of infection occurring every 4–5 years. The infection may be either epidemic or sporadic. The major route of transmission is through respiratory secretions of viremic patients. Transmission may occur among family members, from patient to patient, and from patient to health care or day care provider. The secondary attack rate among household contact is approximately 50%, and during school epidemics 10–60% of schoolchildren will develop erythema infectiosum. Outbreaks of erythema infectiosum in schools may be prolonged over months, suggesting close contact transmission rather than an aerosol transmission mode. Patients with erythema infectiosum are beyond their period of infectivity and present a low risk for further transmission; therefore, they need not be isolated. The principal risk in clinical settings appears to come from patients with high-titer viremia, such as patients with sickle cell anemia and aplastic crisis, or those with chronic pure red cell aplasia, such as human immunodeficiency virus–infected patients. These patients should be in contact and respiratory isolation, and pregnant health care workers should not take direct care of such patients.

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Other routes of transmission include vertical and parenteral transmission and as an occupational hazard in medical laboratory workers. Vertical transmission may occur from mother to fetus in approximately one third of cases of serologically confirmed maternal infection. B19 has been shown to be transmissible in factor VIII and factor IX concentrates. B19 is heat resistant and can withstand the usual heat treatment (80°C for 72 h) used to destroy infectivity of factor concentrates. In addition, solvent detergent methods only inactivate lipid-enveloped viruses (B19 is a nonenveloped virus). B19 has been transmitted by steam- or dry-heated factor VIII and IX concentrates. The question of whether measures should be taken to reduce B19 infection by transfusion of blood components and clotting factor concentrates is eloquently discussed in a recent publication. Immunoglobulin products have not been associated with B19 transmission and may present a low risk because they contain high B19 antibody titer.

Pathogenesis

B19 has tropism for erythroid progenitor cells, including erythroid colony-forming and burst-forming units. The major receptor for B19 on erythroid target cells is the P antigen; B19 capsids bind to P antigen. B19 is critically dependent for its replication upon actively dividing cells. Virus replication occurs in the nuclei of the pronormoblasts. During its replication, B19 is cytotoxic to the infected cells.

The diverse clinical manifestations of B19 infection are the result of either erythroid progenitor (and/or possibly other hematopoietic progenitor cell) aplasia or host immune response. In the immunocompetent host, B19 infection typically results in a self-limited febrile illness characterized by asymptomatic red cell aplasia followed by a rash or arthropathy presumed to be immunologically mediated. Recovery is associated with the production of specific antibodies and probably lifelong immunity. Asymptomatic infection is common. In one study of a school outbreak, B19 caused asymptomatic infection in approximately 25% of adults. If the immunocompetent host has an underlying hematologic disorder (typically characterized by increased cell destruction) (*Table 117.1*), B19 may result in severe symptomatic anemia. However, in all such cases the aplastic anemia is transient. In contrast, B19 infection in immunocompromised patients may become persistent and results in chronic anemia. The fetus is particularly vulnerable because it might develop severe anemia and persistent infection due to its decreased red cell survival (about half that of a normal adult) and inability to mount an adequate immune response to clear the infection.

Table 117.1
Hematologic conditions predisposing patients to Parvovirus B 19–associated acute aplastic crisis

Hereditary disorders
Sickle cell anemia
Hereditary spherocytosis and stomatocytosis
Thalassemia
Glucose-6-phosphase dehydrogenase deficiency
Pyruvate kinase deficiency
Pyrimidine-5′-nucleotidase deficiency
Congenital dyserythropoietic anemia
Acquired disorders
Iron deficiency anemia
Chronic autoimmune hemolytic anemia
Cold antibody-mediated autoimmune hemolytic anemia
Malaria
Blood loss
Paroxysmal nocturnal hemoglobinuria
Normal host

The cause of transient neutropenia has not been well defined. Parvovirus has been detected in granulocytic- and erythroid-line cells in a patient with B19-induced pancytopenia. In addition, replicative forms of B19 DNA have been found in granulocyte-enriched fractions of human serum, suggesting a role for direct infection by B19. B19 has not been shown to replicate in megakaryocytes, but in vitro it inhibits megakaryocyte colony formation.

Diagnosis

For optimal diagnostic yield, the patient's clinical presentation, stage of disease at presentation, and the underlying hematologic and immunologic conditions must be considered when ordering a laboratory test. In a previously normal host who presents with erythema infectiosum or arthropathy, for example, a single immunoglobulin M (IgM) antibody assay is the only test required to confirm infection. IgM is detectable within 3 days after onset of disease, peaks in 2–3 weeks, and then begins to decline in 1–2 months. B19 IgM can be measured in patients' serum or saliva. Saliva can be a convenient alternative to

serum for the diagnosis of recent infection, particularly during outbreaks. Patients with chronic hematologic disorders, on the other hand, may present with aplastic crises before IgM or IgG antibodies are detectable. Furthermore, the fetus or patients with immune deficiency may have an unpredictable antibody response.

Serologic tests of viral infections can be confusing when more than one virus is sought as the cause of a particular set of symptoms. Some samples positive for *Parvovirus* IgM often give positive results for other viruses. In one study, of 25 initially B19 IgM-positive sera, 20% cross-reacted in an Epstein–Barr virus viral capsid antigen IgM test and 8% in a cytomegalovirus IgM test. Another report compared several enzyme immunoassays for the detection of parvovirus to a radioimmunoassay developed by the authors, which used baculovirus-expressed B19 protein. From 88 sera tested, approximately 50% agreement between tests was found. Test sensitivity ranged from 70% to 100% and specificity from 76% to 100%.

Tests of B19 DNA or viral antigens are most useful for patients with aplastic crises or immune deficiency states. The most sensitive assays for B19 DNA detection are polymerase chain reaction (PCR) and hybridization assays. Recent and rapid methods for detection of B19 DNA using a nested PCR reaction have been developed. PCR and hybridization assays have been applied successfully to a variety of clinical samples. B19 DNA may be detectable in serum of patients for several months even after an uncomplicated infection. Because of extreme sensitivity, meticulous care and adequate controls must be used to ensure reliable results. The PCR is often considered to be a specific and highly sensitive test for the viruses in clinical specimens. The nested PCR method for parvovirus was able to detect as low as 3–30 viral genome copies.

Assays for B19 antigens are available but are relatively insensitive. Electron microscopy can also be used to detect B19. In anemic patients, bone marrow aspirate examination shows giant cell proerythroblasts, which constitute strong evidence of B19 infection. In situ hybridization and immunohistochemical studies can be used to confirm the diagnosis. These studies can be used also on tissue obtained from other infected sites.

Clinical Overview of Nonhematologic Effects

In the normal host, B19 infection can be asymptomatic or causes disease such as erythema infectiosum, polyarthropathy syndrome, acute hepatitis, and Behçet's disease. Asymptomatic infection occurs in as high as 20–50% of children and adults. Most people with B19-specific antibody have no recollection of any specific symptoms.

Erythema Infectiosum (Fifth Disease)

Erythema infectiosum is the most common clinical manifestation of B19 infection. It is a moderately contagious disease affecting mainly children. It is called the fifth disease because it was the fifth of five illnesses described exhibiting somewhat similar skin rash. (The other four diseases were rubella, measles, scarlet fever, and Filatov–Dukes disease, the last of which is now considered a mild atypical form of scarlet fever.) Histopathologic changes of the skin include edema and lymphocytic infiltrate. The disease affects mainly children, is infrequently encountered in infants and adults, and is characterized by an initial nonspecific prodromal illness followed in 2–5 days with marked erythema of the cheeks sparing the circumoral and bridge of the nose regions (giving the child a slapped-cheek appearance) and a lacy rash on the trunk and extremities. The rash may involve the palms and soles. Infrequently the body rash may precede the facial one. It may be transient or recurrent over 1–3 weeks. Recrudescence may occur with exercise, warm baths, rubbing of the skin, or emotional upset. There may be great variation in the skin rash appearance. Pruritus may occur in as much as 70% of patients. The rash lasts from 2 to 39 days (mean, 11 days) and resolves without desquamation. Constitutional symptoms such as headache, pharyngeal pain, myalgia, arthralgia, and gastrointestinal disturbances are more frequent and more severe in adults. Less than 10% of children will have arthralgias or joint swelling.

Complications of erythema infectiosum are rare. Arthritis, hemolytic anemia, pneumonitis, and encephalopathy have been reported. No treatment is indicated and isolation is not required. Because the disease is mild and the duration of the rash is prolonged, affected children should be allowed to attend school.

Polyarthropathy Syndrome

The polyarthropathy syndrome in children is usually mild and of short duration. The role of viral infections in the etiology of acute and chronic arthritides of childhood is incompletely understood. There are several viruses that are known to cause acute arthritis, including rubella,

influenza, and B19. Among the many aspects of acute polyarthritis, B19 has been found associated with carpal tunnel syndrome, hepatic dysfunction, and possibly angioedema.

Myocarditis

Parvovirus has been identified as the cause of acute myocarditis and pericarditis in adults and children and may cause cardiac transplant rejection.

Hepatitis

Hepatic dysfunction has been noted in some children with erythema infectiosum. A retrospective investigation by PCR for *Parvovirus* in serum from 773 patients found four children with acute hepatitis of unknown origin who had B19 DNA. These four patients were between 7 months and 5 years old, and other common viral causes of hepatitis were excluded, including hepatitis A, B, or C viruses and Epstein–Barr virus.

Effects on Fetus

Seroprevalence studies have shown that 25–75% of pregnant women are seropositive and that the annual incidence of B19 infection in women of reproductive age is approximately 1.5%. Maternal infection during pregnancy, whether symptomatic or not, is usually followed by a successful outcome with delivery of a normal child. The risk of an adverse outcome in women with serologically confirmed B19 infection is less than 10%, and that in women with unknown immunity who are exposed in the household or in the school is 2.3% and 1.4%, respectively. Infection in the first 20 weeks of pregnancy is associated with the greatest risk of fetal loss, especially between weeks 10 and 20, which coincide with the development of erythroid precursors. The interval between maternal illness and fetal death is usually 3–5 weeks but may be as long as 11 weeks. All pregnancies complicated with nonimmune hydrops should be investigated by fetal blood sampling looking for the evidence of *Parvovirus* infection. Intrauterine transfusion should be reserved for hydropic fetuses with a low hematocrit.

A study of 618 pregnant women exposed to B19 found that 50% were immune to B19 and 259 remained susceptible after exposure, but only 52 (16.7% of all those susceptible) contracted B19 infection. None of the 52 fetuses of infected women developed nonimmune hydrops, and there were no fetal deaths attributable to B19 in this group. The relative risk of maternal B19 infection was 2.8 if the source was a related child living in the household, and the mother's occupation had no significant correlation. Symptoms reported by the women included polyarthralgia (46%), fever (19%), and nonspecific rash (38%) and were significantly more common ($p < 0.001$) in IgM-positive patients than in noninfected women. About one third of the IgM-positive women were entirely asymptomatic. The authors concluded that exclusion of pregnant women from the workplace during endemic periods with seasonal clusters of cases is not justified.

There is some controversy as to whether a child born to a mother with acute *Parvovirus* infection is at risk for developmental delay. A study of over 100 women who became seropositive for parvovirus during pregnancy revealed that there is no apparent increase in the frequency of developmental delays in children with exposure in utero to *Parvovirus*, but the authors stated that larger studies were needed.

The most common abnormality reported in the affected fetuses is hydrops fetalis. B19 infection accounts for up to one fourth of cases of nonimmune hydrops. The pathogenesis of B19-associated fetal damage is probably similar to that leading to aplastic crises in other conditions in which the red cells have a shortened life span. The resultant anemia is thought to cause cardiac failure and hydrops. However, anemia is not profound in all cases, and red blood cell lysis, myocarditis, and liver disease may contribute to the development of hydrops and fetal loss. Hydrops can resolve without treatment and result in the delivery of a normal infant. Intrauterine blood transfusion has been tried with successful outcome. However, this procedure is not without hazards, and the risk–benefit ratio must be calculated carefully before recommending such treatment.

B19 Infection in Patients with an Underlying Hematologic Disorder

The sudden onset of markedly lower red cell numbers in patients with sickle cell anemia and hereditary spherocytosis has been called "aplastic crisis" or transient aplastic crisis. An infectious etiology for aplastic crisis in sickle cell anemia patients had been hypothesized since the early 1980s because of clustering of cases and periodic epidemics. In 1981, two groups published evidence that linked acute parvovirus infection to the onset of aplastic

crisis in patients with sickle cell anemia. Since then, numerous additional chronic hemolytic anemias have been documented to have the same hematologic pathophysiologic findings (Table 117.1). B19 infection can occur, interestingly, without inducing an aplastic crisis even in patients with chronic hemolytic anemias. Recent transfusions could explain some of these cases.

The usual presentation includes a prodrome of fever and constitutional symptoms suggesting a viral illness from 1 to 17 days before the aplasia. Shortly afterward, the patient has extreme pallor and fatigue. More than half report abdominal pain, vomiting, or nausea. Nearly three quarters of the patients have aches and pains or distinct arthralgias. About one quarter of these patients also have faint maculopapular skin rashes. Patients with hepatic or splenic sequestration with the aplastic crisis have also been reported. Although life threatening and occasionally fatal, the aplastic episode is self-limited. Of considerable interest are the reports of aplastic crisis in individuals with previously undiagnosed and unsuspected compensated hereditary or acquired hemolytic anemia. Reticulocytopenia (reticulocyte counts 0–2.2%) and profound anemia with hematocrits as low as 7% are common. Bone marrow aspirates reveal marked erythroid hypoplasia with characteristic inclusions in the giant pronormoblasts. Reticulocytosis occurs from 2 to 14 days after presentation with the aplastic crisis. Most of these patients require red cell transfusions.

Any person with a chronic hemolytic anemia is at risk for aplastic crises because of the rapid turnover of their erythroid progenitors. It is important to note that occasional instances of aplastic crisis have been reported with pneumococcal, other streptococcal, and *Salmonella* infections. B19-associated aplastic crises have been reported in patients with hereditary spherocytosis, pyruvate kinase deficiency, autoimmune hemolytic anemia, thalassemia, and hereditary erythroblastic multinuclearity associated with a positive acidified serum test (Table 117.1).

Transient Erythroblastopenia of Childhood

Transient erythroblastopenia of childhood is a temporary failure of erythropoiesis in previously hematologically normal children. In the few cases that have been described with B19 infection, anemia was associated with thrombocytopenia, whereas in the classic transient erythroblastopenia of childhood the platelet count is high, suggesting that the two conditions are different. This entity does not appear to be caused by B19 infection.

B19 and Idiopathic Thrombocytopenic Purpura

Thrombocytopenia associated with B19 infection may occur before or after the rash appears in a patient with erythema infectiosum. In vitro studies have shown that B19 can suppress megakaryocyte formation and that B19 RNA may be found in the megakaryocytes. Typical immune thrombocytopenia (ITP) has been reported shortly after the onset of erythema infectiosum.

A longitudinal study to determine a possible role of B19 in ITP patients seen at one center over a 12-month period was reported. B19 DNA was detected by PCR in 17/35 ITP patients (49%). Of these, six had anti-B19 IgM titers and eight were seropositive for anti-B19 IgG. It was hypothesized that a chronic B19 infection would permit PCR detection of B19 DNA long after the acute viral infection, thus providing the association of IgG titers but no IgM anti-B19 antibodies. There has been some speculation that ITP patients have altered immune systems, but there are conflicting data on lymphocyte function and subsets. *Parvovirus* infection is known to induce anti-DNA and anti-lymphocyte antibodies in some individuals.

Neutropenia Secondary to Parvovirus Infection

Infection of normal individuals with B19 is accompanied by mild neutropenia 10–14 days after an intranasal injection; this is the time of fever, maximum viremia, and the IgM response to the viral infection. The neutropenia lasts for approximately a week. There have been several reports dealing with the effects of B19 infection and anemia, but also accompanied by lower numbers of myeloid precursors or mature neutrophils. Typically the neutropenia would only last a few days. One study found IgG antibodies to red cells, neutrophils, or platelets in four children with B19 infection. The neutropenia resolved within 10 days in all of these children, who were subsequently proven to have acute *Parvovirus* infection by elevated IgM titers. Interestingly, the anti-B19 IgM was detected after the neutropenia resolved in one patient.

Parvovirus has also been linked to autoimmune neutropenia in children. Typically the neutropenia lasts a median of 19 months (range: 6–64 months), with spontaneous recovery. IgM antibody to B19 has been found in a series of five patients with autoimmune neutropenia and accompanying anti-neutrophil NA-1 antibody. These authors failed to find the viral DNA by PCR analysis.

A larger study of children with chronic autoimmune neutropenia showed evidence of B19 DNA by PCR in the bone marrow of 15/19 children tested. Four of six sera specimens taken at the time of the bone marrow sample had IgG antibody to B19. None had IgM titers, although the immune response to B19 is often defective or delayed in chronic B19 infection. Since no control patients had evidence of B19 in their bone marrow, it is unlikely that contamination of the DNA specimens could be blamed for the 15/19 positives in the neutropenic patients.

B19 Infection in Patients with Congenital or Acquired Immunodeficiency States

In patients with either congenital or acquired immunodeficiency, B19 infection may become chronic, resulting in persistent viremia and chronic bone marrow failure. The clinical illness in such patients is usually characterized by acute anemia that is persistent, with or without neutropenia or thrombocytopenia; chronic viremia; and, on bone marrow examination, erythroid hypoplasia with giant vacuolated proerythroblasts similar to those described in acute B19 infection. Spontaneous recovery has been reported. Temporary cessation of immunosuppressive agents usually results in clearance of viremia and resolution of hematologic manifestations. Prompt decrease in viremia, increase in reticulocyte count, and increase in hemoglobin usually follow intravenous immunoglobulin (IVIG) administration. Long-term remissions have been documented, but repeated administrations are frequently necessary to sustain or reinduce remissions. Chronic B19 infection has been reported to occur in patients with a variety of underlying immunodeficiency states (*Table 117.2*).

Effective therapy of B19-induced pure red cell aplasia in immunocompromised patients consists of infusion of commercially available immunoglobulin preparations. These are good sources of neutralizing antibodies because most adult populations have been exposed to the virus. Patients with acquired immunodeficiency syndrome respond to a 5–10-day course of IVIG, but relapses are common. A second course or maintenance IVIG infusions may be required. In patients who are undergoing therapy with immunosuppressant drugs, temporary cessation of therapy may result in clearance of viremia and recovery of cytopenia. Measurement of serum virus can be helpful in determining optimal therapy and predicting relapse.

Table 117.2
Immunodeficiency disorders that have been associated with chronic Parvovirus B 19 infection

Congenital immunodeficiency
Nezelof syndrome
Common variable immunodeficiency
Severe combined immunodeficiency
Fetus
Others
Acquired immunodeficiency
Human immunodeficiency virus infection
Malignancy
Acute lymphoblastic leukemia
Acute myeloid leukemia
Non-Hodgkin lymphoma
Brain tumors
Wilms tumor
Rhabdomyosarcoma
Organ transplant recipients
Renal transplantation
Liver transplantation
Cardiac transplantation
Bone marrow transplant recipients
Collagen-vascular diseases
Systemic lupus erythematosus
Rheumatoid arthritis

Vaccine Development

Effective vaccines have been developed for animals, and the prospects for a human Parvovirus B 19 vaccine are good. The availability of a genetically engineered expression system capable of producing unlimited quantities of B19 viral capsid antigens has made it possible to consider vaccine development. Viable candidates for B19 vaccines are now available, and vaccines should be in human trials soon.

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118 Poliomyelitis

Mohammad Al-Shaalan

Poliomyelitis is a paralytic viral illness that is getting less in incidence with the implementation of the effective vaccine. Poliovirus belongs to enterovirus group and has three serotypes 1, 2, and 3. Most of the wild poliovirus infections are caused by serotype 1, whereas infections acquired from vaccine are caused by serotypes 2 and 3.

Epidemiology

After the introduction of the vaccine in 1950s, the incidence of poliomyelitis has decreased dramatically. America has been declared free of wild poliomyelitis in 1995. In addition, the disease is completely controlled in Western Europe and most of the countries in Asia and some countries of Africa. In 1995, 6,000 cases of poliomyelitis worldwide has been reported; 205 cases from Europe; 3,398 cases from southeast Asia, mostly from India; 738 cases from Eastern Mediterranean; and 344 cases from far east region. The main remaining endemic areas for poliomyelitis are the Indian subcontinent and some parts of USSR. This remaining endemicity is attributed to lack of proper vaccination and not to the failure of the vaccine.

Pathogenesis

The infection is acquired by oral route. The virus then multiplies in the pharyngeal and intestinal lymph nodes. From there the virus spreads via blood into the terminal nerves, where it travels along the axons into the neuronal cells mainly in the anterior horn; however, neurons in the intermediate gray matter and dorsal ganglion may be involved. Neurons in the brain stem and cranial nerves nuclei are also susceptible and may be involved. The cortex is spared with the exception of the immediate precentral area of the motor cortex.

The virus multiply in these areas and result in cellular destruction and degeneration with resultant neuropathy and musculopathy. Because of the edema involved with initial infection, an apparent more diffuse involvement of neurons occurs, but after the acute infection, the edema resolves and recovery of some involved neurons occurs. Most of the time only parts of neurons are involved and compensation by other surviving neurons occurs, and paralysis may resolve if the neuron destruction is not extensive.

Clinical Features

Asymptomatic Infections

Ninety percent to 93% of poliovirus infections are asymptomatic.

Abortive Poliomyelitis (Minor Illness)

In 2–5% of the cases, the infection is manifested by mild illness of low-grade fever, headache, myalgia, vomiting, and diarrhea. The disease is self-limiting and does not result in any sequelae.

Aseptic Meningitis

In 2–3% of the cases and after few days from subsiding symptoms of minor illness, symptoms of meningitis may develop with manifestation of headache, neck pain, and low-grade fever. CSF reveals elevated protein, normal sugar, and mild pleocytosis, usually of 10–200 cells/mL, which is initially neutrophilic and then shifts to be lymphocytic in 1 or 2 days. The disease lasts for 2–8 days and then resolves spontaneously.

Paralytic Poliomyelitis

One percent of symptomatic infections (i.e., 1/1,000 of poliomyelitis infections) results in flaccid (lower motor

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neuron) paralysis. The paralysis involves different muscle groups, and usually it is patchy in distribution. In addition to skeletal muscles, cranial nerves involvement may occur with resultant bulbar palsy.

Diagnosis

The mainstay of diagnosis is the isolation of poliovirus from throat, stool, urine or, rarely, CSF. The virus can be recovered shortly before symptoms and up to 2 weeks after the infection. In stool, the virus can be isolated up to 2 months after infection. Immunocompromised patients secrete the virus for a longer period of time. Serology tests, acute and convalescent are helpful. Recently, PCR is being developed, and it will help to differentiate between wild virus infection and infection acquired by vaccination.

Treatment

Treatment is supportive to decrease pain and fear by using analgesics. In those who develop respiratory failure, artificial ventilation may be needed. Swallowing may be impaired, and thus nutritional support by nasogastric tube feeds or total parenteral nutrition may be needed. Once the acute stage is passed and fever is resolved, the passive and active muscle movement should be initiated to prevent contracture and deformities.

Late Complications of Poliomyelitis

Late Post-Polio Syndrome

Some patients who had poliomyelitis may present 10–40 years later with new onset of weakness, decreased daily activities, and/or muscle atrophy. This is defined as progressive postpolio muscular atrophy. Other manifestations of post-polio syndrome include muscle pain, musculoskeletal deformities, fatigue, and cramps. This syndrome is usually associated with electrophysiological evidence of acute denervation superimposed on chronic denervation–inervation process. The progress of muscle deterioration in post-polio syndrome is usually slow and, in some cases, it may not be appreciated on year to year basis.

Orthopedic Deformities

Due to muscle weakness, bone deformities may arise due to malpositioning. This may result in scoliosis and cervical radiculopathy.

Neurological Abnormalities

Nerve entrapment may occur in polio patients and result in exacerbation of muscle atrophy and weakness.

Respiratory Complications

Scoliosis and muscle atrophy may result in restrictive lung disease which in turn results in respiratory insufficiency and core pulmonale.

Prevention

Enteric precaution is advised for all contacts of the patients with poliomyelitis. Immunocompromised patients and their contacts should not receive live attenuated vaccine. For vaccination recommendation, see section on immunization.

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119 Respiratory Syncytial Virus

Suliman Al Jumaah

Respiratory syncytial virus (RSV) is the major respiratory pathogen in infants and young children. It is the most common cause of hospitalization for respiratory illness among children. Young age, chronic heart or lung disease, and immunosuppression are risk factors for sever RSV infection.

Etiology

RSV is an enveloped RNA virus that belongs to the Paramyxoviridae family. The RSV genome encodes for ten viral proteins. The F and G proteins are envelope-associated proteins, which were studied extensively as a vaccine candidate. F glycoprotein mediates fusion of the virus with the host cell. G protein is the attachment protein that mediates attachment of the virus to host cells. It is the most variable protein among RSV strains, while F glycoprotein is highly conserved among major RSV strains. RSV isolates fall into two groups, A and B. The major antigenic differences between group A and group B RSV are largely due to variability within G glycoproteins, with only 53% homology in amino acids between the two strains. In RSV season, both groups circulate concurrently. However, group A usually predominates, comprising 70–80% of isolates.

Epidemiology

RSV is the most important cause of lower respiratory tract infection (LRI) (bronchiolitis and pneumonia) in infants and young children, accounting for 60–90% of cases of bronchiolitis and 5–40% of cases pneumonia. In the United States, RSV isolation strongly correlates with LRI-associated deaths in children 1–11 months of age, with the strongest association among those less than 5 months. The virus infects one half of children by 1 year of age, and virtually all children are infected by 2 years of age. Reinfection with RSV is common, but the disease tends to be mild with repeated infection. One percent to 2% of RSV-infected children are admitted to the hospital. In the United States, RSV infection is responsible for 40–50% of the hospitalizations for bronchiolitis and 25% of pediatric hospitalization for pneumonia, of a total of 91,000 admissions annually at a cost of about $300 million. RSV infection occurs yearly as an outbreak between late fall and early spring. In addition to mortality and morbidity in the acute phase, RSV infection may be associated with abnormalities in pulmonary function testing in late childhood as well as development of asthma and chronic lung disease. However, causality has not been proven.

Certain factors are associated with an increased risk of repeated RSV illness. These include a family history of atopy, presence of older siblings, and exposure to passive smoking. Age is associated with increase severity and frequency of infection, with severe RSV disease occurring most commonly in early infancy. RSV LRI in patients with underlying cardiac and lung disease causes significant morbidity, with early estimates of mortality of up to 30%. More recent studies have shown that the mortality is one tenth of these earlier estimates. This may reflect the overall improvement in management of the underlying illness of such patients, resulting in a better clinical condition prior to RSV infection.

Morbidity due to RSV, in the form of prolonged of complicated hospitalization, remains high among patients with underlying cardiac or pulmonary disease. In retrospective and prospective studies examining the outcome of RSV infection in high-risk patients, the Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) group observed that patients with underlying illness had significantly prolonged hospitalization, ventilatory support, and oxygenation days as compared to other risk groups, including premature infants and infants less than 6 weeks old at the time of RSV infection.

Pathogenesis

The incubation period ranges from 2 to 8 days. The virus is usually inoculated through the upper airway passages, although the infection may extend to the lower respiratory tract. The pathology affects primarily the small airways, where the airways are infiltrated with lymphocyte and

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plasma cells, with syncytia formation. Subsequently, there will be sloughing and necrosis of the epithelium, resulting in airway obstruction evidenced by expiratory wheezing in bronchiolitis. There will be hyperinfiltration due to air trapping. These changes are due to direct viral invasion; however, an immune-mediated process may contribute to the pathogenesis of the disease.

Clinical Manifestations

RSV infection has a wide spectrum of clinical manifestations. These include bronchiolitis, pneumonia, tracheobronchitis, and upper respiratory tract infection. Young infants may present with a sepsis-like picture or apnea. The most important clinical presentation is bronchiolitis, which usually affects infants less than 1 year of age, with peak incidence at 6 months of age. Illness starts usually with upper respiratory tract infection with nasal discharge and pharyngitis that may be associated with fever. Cough may be present. After several days, infection may progress to involve the lower respiratory tract, with development of respiratory distress, wheezing, irritability, and feeding difficulty. Primary infection in young infants is more likely to involve the lower respiratory tract. In most cases the infection is mild and resolves in 1–3 days; however, on occasion, the infection can be quite severe.

The typical chest x-ray, showing hyperexpansion, is evident in 50% of cases. Peribronchial thickening and interstitial pneumonia are seen in 50–80% of cases. Consolidation is seen in 20–25% of cases. Among high-risk hospitalized infants, the mortality is about 1% from recent studies. Complicated RSV infection is most likely to occur in patients with underlying congenital heart disease, chronic lung disease of prematurity (CLD) or cystic fibrosis, and young and premature infants and post stem cell transplant patients. These patients are more likely to have prolonged hospitalization and require intensive care. Children with congenital immunodeficiency are at risk of severe RSV infection and prolonged viral shedding.

RSV infection may cause acute otitis media. Treatment failure and persistent middle ear effusion are high in the presence of coinfection of RSV and bacterial pathogens.

Diagnosis

Diagnosis of RSV LRI is usually made on the basis of clinical and epidemiologic findings. Confirmation of infection may be made by isolation of the virus on the proper cell culture line from secretions obtained by nasopharyngeal aspirate or nasal swab. The characteristic cytopathic effect is usually evident by 2–10 days. Rapid diagnostic tests such as direct fluorescent antibody staining and enzyme immunoassay are widely used because the results can be available within several hours. The sensitivity of these tests varies from 53% to 96%, mostly in the range of 80–90%, and the specificity approaches 100%.

Treatment and Prevention

Ribavirin is the only specific antiviral agent available for treatment of RSV infection. It is a synthetic guanosine analogue with broad-spectrum antiviral activity. The antiviral properties of rivabirin were first demonstrated in vitro and subsequently confirmed in the cotton rat model. Several controlled trials of aerosolized ribavirin in infants hospitalized with RSV LRI were carried out. Some of these studies were done in previously healthy infants and others included infants with underlying illnesses. Ribavirin improved respiratory score and oxygenation but was not shown to decrease hospital stay. Meta-analysis of all controlled trials showed that ribavirin therapy did not decrease mortality or respiratory deterioration. In ventilated infants, ribavirin therapy reduced days of ventilation; however, this reduction was sensitive to the exclusion of one study.

Ribavirin was approved by the US Food and Drug Administration in 1986. The aerosol route of administration and potential toxic side effects on health care provider in addition to modest clinical efficacy led to decrease in the use of ribavirin. The Committee on Infectious Diseases of the American Academy of Pediatrics stated that ribavirin is not recommended for routine use but may be considered for use in select patients with documented potentially life threatening RSV infection. Randomized clinical trials of bronchodilators have yielded conflicting results. Some studies comparing bronchodilators are beneficial, while others have shown no benefit. Corticosteroids failed to show a beneficial effect. Supportive treatment in the form of adequate oxygenation and hydration is the most important line of management of severe RSV infection.

Prophylaxis and treatment of RSV infection with pooled human immune globulin in laboratory animals was well tolerated and reduced viral shedding was not associated with duration of hospitalization. Monthly prophylaxis with standard intravenous immunoglobulin does not achieve an adequate titer of RSV-neutralizing antibodies (RSV-IGIV) for protection. More recently, randomized controlled trials have shown that monthly

prophylaxis with high-titer RSV immunoglobulin may prevent LRI in infants and young children with underlying cardiac or pulmonary disease and in premature infants. RSV-IGIV is no longer available.

The only available passive prophylaxis for RSV is Palivizumab, which is a humanized monoclonal immunoglobulin G-1 directed against an epitope on the F glycoprotein of RSV and is produced by recombinant DNA technology and approved for use since 2002. Palivizumab consists of 95% human and 5% murine amino acid sequences. Palivizumab is not derived from human immune globulin. It is highly active in vitro against type A and type B RSV isolates, where it was 50–100 times more potent than similar concentrations of RSV-IGIV. Two randomized controlled clinical trials have demonstrated that palivizumab results in significant reductions in the incidence of RSV hospitalizations in premature infants and infants with hemodynamically significant heart disease.

Palivizumab is administered monthly during RSV season. The period of exposure has been assumed to be 5 months during the winter season beginning in November or December, with the last dose given in March or April; however, this depends on local epidemiology of RSV.

RSV prophylaxis is recommended for children younger than 24 months of age with CLD of a prematurity who require on-going therapy within 6 months receiving the RSV season. It is recommended for children younger than 24 months with hemodynamically significant cyanotic and acyanotic heart disease and also for infants born at or before 32 weeks of gestation who are 6 months of age at the start of RSV season. Infants born between 32 and 35 weeks of gestation may be given prophylaxis if there are other risk factors.

Immunization

Currently, there is no effective vaccine against RSV. Children who received inactivated RSV vaccine in 1969 remained susceptible to infection and developed more severe disease after acquiring RSV infections than controls. The mechanism of this susceptibility remains unknown. Successful RSV vaccine has to be immunogenic in young infants, where the risk is maximal, and must not be hampered by passively transferred maternal antibodies. Live attenuated and subunit (utilizing F glycoprotein) vaccines are being developed to prevent RSV infection. Purified fusion protein vaccines (PFP1 and PFP2) are under investigation. These vaccines were shown to be safe and immunogenic in RSV-seropositive children. Enhanced pulmonary pathology was not noticed. Subunit vaccine induces systemic but not local immunity, and children who received the vaccine were not protected against RSV infection. Studies in cystic fibrosis patients showed that the vaccine was not protective against RSV infection; however, the number of LRIs was significantly reduced. Despite many attempts to generate RSV vaccine, using various technologies, no vaccine has been licensed for human use.

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120 Rotavirus and Noro- and Caliciviruses

Namita Singh · Tyler Burpee

Rotavirus

Introduction

Rotavirus is the most common cause of severe diarrhea in infants and children of developed and developing countries worldwide. Globally, rotavirus gastroenteritis causes the death of more than half a million children younger than 5 years of age. This illness creates a disease burden to virtually all societies around the world.

Etiology

Rotaviruses are included in genus *Rotavirus*, part of the *Reoviridae* family. Negative contrast electron microscopy reveals the viral particles take on a wheel-like appearance in feces, leading to the prefix "rota."

Rotavirus particles are large in size (1,000 Å), nonenveloped, and have three concentric layers of proteins surrounding a viral genome. The genome is comprised of 11 segments of double-stranded RNA, a characteristic that allows reassortment during natural infection to yield new strains. These segments encode six structural viral proteins (VPs) that form virus particles and six nonstructural proteins (NSPs). The NSPs are synthesized in infected cells and interact with host proteins to influence pathogenesis and the immune response to infection.

The rotavirus outer capsid shell is made of the protein VP7. Spike-like projections protrude through the capsid shell and are formed by the glycoprotein VP4. The three-layered capsid renders it stable and resistant to the acidic pH in the stomach and to the digestive enzymes in the small intestine. This eases the fecal-oral transmission and delivery of the virus into the small intestine, where rotavirus causes pathological changes in structure and function.

Rotaviruses can be classified into Groups A-E, according to antigenic groups on the major capsid antigen, VP6. Only groups A, B, and C have been shown to infect humans, with group A causing the preponderance of human rotaviral gastrointestinal disease.

Rotaviruses are further classified into G and P types based on the identification of antigens on the outer capsid proteins VP7 and VP4. Most severe infections in young children are caused by serotypes G1-4. In general, the more densely populated countries show the most complex patterns of serotype prevalence. During the last two decades, G1 infections appear to have predominated globally.

Epidemiology

Worldwide, approximately 40% of hospitalizations for diarrhea in children younger than 5 years of age are attributable to rotavirus infection. The virus is identified in the stool in 10–40% of children admitted for acute diarrhea in developing countries and 35–50% in developed countries. Over 525,000 children younger than 5 years of age die annually from rotavirus, with more than 85% of these deaths occurring in African and Asian nations. In the United States, prior to the vaccine's introduction, rotavirus infection accounted for 400,000 doctor visits, 200,000 emergency room visits, 50,000 hospitalizations, and 20–60 deaths per year, with costs amounting to $1 billion yearly. See *Fig. 120.1*: Rotavirus disease burden.

Virtually all children have been infected with rotavirus by the age of 5, with various degrees of severity. It is common to have progressively less severe subsequent rotavirus infections as each causes a boost in mucosal immunity. Serious rotavirus infections occur most often in children 4–24 months of age. Neonatal infection is often asymptomatic in healthy, full-term infants, presumably due to passive immunity from transplacental and breast-milk antibodies. Adults are rarely severely affected, but roughly 20% of adult household contacts of an infected infant may develop symptomatic disease.

Rotavirus gastroenteritis has a seasonal variation pattern. In the United States and other countries with a temperate climate, infections predominate during the winter months, with annual epidemics occurring between December and June. Regional variations also exist within particular climates or countries. For example, the United States rotavirus season starts in the southwest in the fall and ends in the northeast

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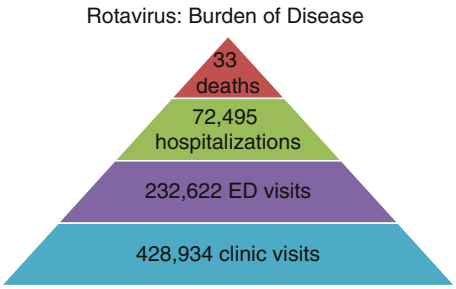

Figure 120.1
Annual rotavirus disease burden in the United States prior to vaccine introduction

in the spring. In Europe, the season begins in the southern region and spreads north over the fall to spring months. Rotavirus infections fluctuate less in the tropics, though a recent systematic review of 26 studies from tropical areas concluded that infections were more prominent in the coolest and driest months of the year.

Rotavirus is primarily transmitted person-to-person via the fecal-oral route. In developing regions, it may also be spread via fecally contaminated water. Infected individuals usually shed large quantities of virus, up to 10^10 particles per gram of stool. As few as ten viral particles may cause infection in rotavirus-naïve patients. Viral shedding may occur up to 2 days prior to the initiation of symptoms and continues for an average of 4 days, though shedding has been reported for up to 21 days in immunocompetent patients. Immunocompromised patients may excrete the virus for even longer periods.

The virus may survive at least 4 h on hands, days to weeks on environmental surfaces, and up to weeks in drinking water. Transmission is increased in settings such as child day-care centers and family homes, where diaper changing has been identified to be the highest-risk activity. Additionally, rotavirus has been found on toys, faucets, hand-washing areas, and even food preparation areas, indicating that fomites may play a role in viral transmission. The high infectivity, presymptomatic shedding, and prolonged environmental life span are all important factors in the transmission of rotavirus.

The transmission from animals to humans is rare. There is evidence, however, that animal rotaviruses can infect humans via direct transmission of the virus or by contributing one or more RNA segments to reassortants with human strains.

The respiratory spread of rotavirus via aerosolized particles has also been suggested. Rotavirus has been detected in respiratory secretions in a small number of patients, and cases of pneumonia have been described. Rotavirus RNA from air samples taken from rooms of hospitalized children with rotavirus gastroenteritis indicate that airborne spread may be a route of transmission of rotavirus, especially in hospital and day-care settings.

Rotavirus has its most profound effects in the gastrointestinal tract, yet systemic infection has been reported. RNA and proteins of rotavirus have frequently been detected in the blood of infected children, as well as the liver, heart, lung, and central nervous system.

Pathogenesis

Rotavirus particles are ingested orally. In the small intestine, the VP4 spikes on the capsid surface may be proteolyzed by the enzyme trypsin. This cleavage causes a conformational change in the spike structure, which then exposes other attachment sites on the surface glycoprotein. The virus is then attached to host receptors on enterocytes, and the entry process begins. The outer capsid shell is removed, and double-layered particles are inserted into the cytoplasm. These particles produce capped viral messenger RNAs (mRNAs) that are then displaced from the transcribing particles into the cell cytoplasm. There, they are then translated into proteins and replicated to new genomic RNA. This viral replication process is unique and occurs in viroplasms, electron-dense structures near the cell nucleus, and endoplasmic reticulum. Newly assembled particles with newly replicated dsRNA bud into the endoplasmic reticulum from the viroplasm and are equipped with outer capsid proteins. Fully developed virus particles are released from enterocytes via cell lysis or delivery of particles to the apical plasma membrane of cells.

Rotavirus primarily invades mature enterocyte villi, sparing the intestinal crypts. With enterocyte destruction, fluid moves into the intestinal lumen, resulting in a net loss of fluid and electrolytes in stool. Malabsorption occurs secondary to the loss of absorptive enterocytes, the decreased synthesis of lactase and other digestive enzymes, and the alteration of tight junctions between enterocytes that leads to paracellular leakage.

The rotavirus toxin, NSP4, is a nonstructural glycoprotein that may contribute to the pathophysiology by inducing a secretory component to the diarrhea. This viral enterotoxin is reported to increase intracellular calcium and activate cellular chloride channels, in turn increasing the secretion of chloride and consequently water into the lumen. NSP4 has also been found to activate the secretory reflexes of the enteric nervous system (ENS), further contributing to diarrhea.

Microischemia of villi, impaired polar transport of sucrase-isomaltase to the membrane surface, neuronally mediated intestinal hypersecretion, and altered intestinal motility are other possible mechanisms of rotavirus injury.

Pathology

Histologically, rotavirus is associated with a wide spectrum of changes, ranging from virtually normal mucosa or mild enterocyte vacuolization and loss to more significant villous blunting and crypt hyperplasia. The degree of inflammation is usually milder than that caused by other intestinal pathogens. There appears to be no direct correlation between histological findings and disease symptoms.

Clinical Manifestations

After a 2–7 day incubation period, symptoms often start abruptly with vomiting, followed by watery diarrhea. This is a noninflammatory process, with blood and white cells typically absent from the stool. In about one-third of patients, fever of over 38.9°C is reported. Other clinical features of acute rotaviral infection include anorexia and lethargy, with abdominal cramping being less common. The diarrhea can range from mild to severe, with resultant dehydration, shock, electrolyte imbalance, and even death. Severe, dehydrating rotavirus infection occurs mostly in children age 3–35 months. Rotavirus is generally a self-limited virus, with vomiting settling within 24–48 h and diarrhea in 2–7 days. Some studies have noted respiratory symptoms and otitis media in up to half of patients with rotavirus infection.

Intussusception in rotavirus infection may be caused by a disturbance in the motility of the gastrointestinal tract during an acute infection, as opposed to a typical lead point. Lipopolysaccharides may slow intestinal motility through the induction of various inflammatory agents, such as prostaglandins, cytokines, and nitric oxide.

Diagnosis

The Center for Disease Control and Prevention (CDC) defines a confirmed case of rotavirus gastroenteritis as diarrhea (3 or more loose stools within 24 h) or vomiting (1 or more episodes in a 24 h period) in a child with a positive stool detection of rotavirus by a standard assay, such as an enzyme immunoassay (EIA).

Confirmation of rotavirus infection is necessary for reliable surveillance and can be clinically useful to avoid inappropriate antimicrobial use. The most widely used method to detect rotavirus antigen in stool is EIA. These assays typically detect the rotavirus group antigen present on VP6. Many EIA kits are commercially available, providing rapid, inexpensive results with 90–100% sensitivity. Strains may be further characterized by additional enzyme immunoassay or reverse transcriptase polymerase chain reaction (RT-PCR).

Research centers use other techniques for detection and surveillance of rotavirus, including electron microscopy, RT-PCR, nucleic acid hybridization, sequence analysis, and culture. These techniques are more labor intensive and provide little additional clinical utility.

Differential Diagnosis

The non-bloody, watery diarrhea of rotavirus gastroenteritis is clinically indistinguishable from that caused by other enteric viruses, including norovirus and other caliciviruses, enteric adenovirus, and astrovirus. That said, rotavirus associated acute diarrhea may be more severe and more frequently associated with fever and vomiting. The presence of blood or leukocytes in the stool should suggest alternative diagnoses, including bacterial etiologies such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Escherichia coli*. Noninfectious etiologies, including intussusception, must also be considered in the infant with this presentation. Protozoal infection, particularly *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*, should also be included in the differential diagnosis.

Prognosis

As mentioned, rotavirus infection is most frequently self-limited, with cessation of vomiting within 2 days and diarrhea within 7 days. Severe, dehydrating infection occurs more often in young children from age 3–35 months. Malnutrition is known to increase the severity of infection, with delayed small intestinal recovery and altered inflammatory responses.

Acute complications include dehydration, sodium imbalance, and possible seizures. Reye syndrome, encephalitis, rectal bleeding, and intussusception have all been associated with rotavirus, but evidence showing a causative effect is lacking.

Treatment

Rotavirus gastroenteritis is generally a self-limited illness, and treatment is largely supportive. Initial management should focus on the identification and correction of any underlying fluid and electrolyte imbalance. The assessment of dehydration and the use of oral rehydration therapy are critical and are reviewed elsewhere in this text (Chap. 187, "Acute Gastroenteritis in Infants and Children"). Undernourished children are particularly at risk of severe and/or persistent symptoms, and great care must be taken to encourage early resumption of normal feeding, typically including breastfeeding. There is no role for antibiotics in the treatment of rotavirus gastroenteritis. The use of antiemetics and antidiarrheals is generally avoided. Please see Chap. 187, "Acute Gastroenteritis in Infants and Children" for further details.

The oral administration of a probiotic, Lactobacillus GG, is effective in both reducing viral shedding and shortening symptom duration by roughly 1 day. This improvement is most notable when the probiotic is given early in the course of the illness and seems most prominent in young children. The mechanism may be due to an enhancement of the immune response against the virus.

Orally administered Human Immune Globulin, as an investigational therapy in immunocompromised patients, was found to shorten the course of diarrhea and decrease viral excretion. Further investigation is required, and the cost-benefit ratio may not justify usage of this therapy on a wide-scale basis.

Prevention

Rotavirus attack rates are similar between developed and developing regions, suggesting that improved sanitation is unlikely to play a significant part in disease prevention. The high infectivity of the virus makes control measures difficult.

Rotaviruses are relatively resistant to chemical disinfectants used widely in hospitals. Effective agents include chlorhexidine gluconate and quaternary ammonium compounds with high alcohol content (70%). Hand washing with plain soap is often ineffective against rotavirus and may even spread the virus over a larger area of the hands. The use of a waterless, alcohol-based hand-cleaning agent before and after patient contact is recommended.

Breastfeeding plays a protective role against acquiring rotavirus. This may be due to the presence of anti-rotaviral secretory IgA and trypsin inhibitors in breast milk. Breast-fed infants also excrete fewer viruses than formula-fed infants.

Based upon the significant morbidity and mortality of childhood rotaviral infection worldwide, great attention has been focused upon the development of a successful vaccine. Since 1983, multiple candidate vaccines have been tried. Initially, vaccines based upon the use of animal rotavirus strains that are not pathogenic in humans failed to provide sufficient clinical protection. Rotashield (Wyeth-Lederle Vaccines, Philadelphia, PA), a tetravalent simian/human reassortant rotavirus vaccine, was licensed by the FDA in 1998, based upon data showing an 80–100% protection against dehydrating rotavirus diarrhea. Within 9 months of its release, the CDC's Vaccine Adverse Event Reporting System (VAERS) reported 15 cases of intussusception in infants who had received the vaccine. Subsequent case control and retrospective cohort studies verified a temporal association. The relative risk for intussusception within 2 weeks following the first vaccine dose exceeded 20 in both studies, prompting the vaccine's withdrawal from the market.

Two subsequent oral rotavirus vaccines are now licensed in many nations around the world, including the United States. These vaccines have led to the decline of rotaviral infection and mortality worldwide. Rotarix™ (GlaxoSmithKline Biologicals, Rixensart, Belgium, 2006) is based on a live attenuated human rotavirus strain, G1P. RotaTeq™ (Merck & Co., Inc., Whitehouse Station, NJ, USA, 2008) is a pentavalent human–bovine reassortant, with a low rate of replication in the human gastrointestinal tract and a low rate of fecal shedding. Large phase III clinical trials have demonstrated that both Rotarix™ and RotaTeq™ are well tolerated. They have also been demonstrated to be immunogenic and highly efficacious, preventing 74–87% of all cases of rotavirus gastroenteritis and greater than 85% of those associated with severe diarrhea. In Africa and Asia, where more than 85% of rotavirus associated deaths occur, RotaTeq™ vaccination reduced cases of severe rotavirus diarrhea by greater than 50% during the first year of life when the disease burden and mortality is greatest. The World Health Organization's Strategic Advisory Group of Experts declared that rotavirus vaccines should be included in national immunization programs worldwide, particularly in nations with high diarrheal fatalities. Diarrhea-associated deaths in these developing countries could be reduced by 25%.

The RotaTeq™ vaccine is recommended to be given as a three-dose series to infants between the ages of 6–32 weeks. The Rotarix™ vaccine is recommended to be administered as a two-dose series at the ages of 2–4 months. Details of the vaccine schedules are provided in

Table 120.1

Rotavirus vaccine schedule per the Advisory Committee on Immunization Practices (ACIP) recommendations, 2009

	2 Months	4 Months	6 Months
Rotarix® (RV1)	Rotarix® #1	Rotarix® #2	NA
	*Minimum age 6 weeks, maximum age 14 weeks 6 days	*Minimum 4 weeks between doses;	
		Not to be given after 8 months of age	
RotaTeq® (RV5)	RotaTeq® #1	RotaTeq® #2	RotaTeq® #3
	*Minimum age 6 weeks, maximum age 14 weeks 6 days	*Minimum 4 weeks between doses #1 and #2	*Minimum 4 weeks between doses #2 and #3;
			Not to be given after 8 months of age

Table 120.1. Contraindications to the rotavirus vaccine include a previous severe life-threatening allergic reaction to any components of the vaccine and some immunocompromised states.

Data from the CDC's VAERS has shown that the observed rate of intussusception in RotaTeq™-vaccinated children is not higher than the age-adjusted background rate of intussusception. Similarly, studies show no increased risk of Kawasaki syndrome with the administration of RotaTeq™ vaccine.

Since the introduction of these vaccines in 2006, the incidence of rotavirus diarrhea in infants has dramatically decreased. One study noted that from 1986 to 2006, nearly 20% of hospitalized gastroenteritis patients younger than 5 years of age tested positive for rotavirus in the stool. In the three seasons after vaccine introduction (2007–2009), the percentage dropped to 12.4%, 9.6%, and 6.4%, resulting in a decline of 66% by the study's termination. Furthermore, the rotavirus season has been found to be shortened and delayed. See *Fig. 120.2*: Hospitalizations in children due to laboratory-confirmed rotavirus gastroenteritis.

Newer approaches, such as non-replicating virus-like particle (VLP) vaccines, are presently being evaluated. Meanwhile, the current rotavirus vaccines remain a success in decreasing the morbidity and mortality from this global health disease.

Noro-Caliciviruses

Etiology

Norwalk virus carries historical import as the first confirmed viral etiology for human gastroenteritis when it was identified by electron microscopy in stools from a severe outbreak of diarrhea in Norwalk, Ohio in 1972. Subsequently, similar appearing viruses were often called "Norwalk-like viruses." Recent reclassifications now define the family as *Caliciviridae*, which are 20–40 nm, non-enveloped, single-stranded RNA viruses. Within this family are four distinct genera. The *Norovirus* genus accounts for roughly 95% of Calicivirus-associated gastroenteritis and is discussed here in greater detail. The other three genera (Sapovirus, Lagovirus, and Vesivirus) are less clinically relevant.

Human norovirus strains are classified into several distinct genogroups and subgroups. Genogroup II has been identified as the most common strain infecting humans worldwide. A new pandemic strain emerges every 2 –4 years.

Epidemiology

Noroviruses are the most common cause of nonbacterial gastroenteritis outbreaks worldwide. Infections may occur year round, though more cases are reported during winter months. Both children and adults can be affected. The Center for Disease Control (CDC) estimates that noroviruses cause 21 million cases of gastrointestinal illness annually in the United States, accounting for half of all foodborne disease outbreaks. Norovirus infection leads to an estimated 70,000 hospitalizations and 500 deaths annually in the United States. There, only rotavirus leads to more hospitalizations for gastroenteritis in children. In developing countries, norovirus is also a common etiology for diarrhea. In India and Peru, 15% and 31%, respectively, of stool samples in hospitalized pediatric gastroenteritis patients tested positive for norovirus via PCR (*Table 120.2*).

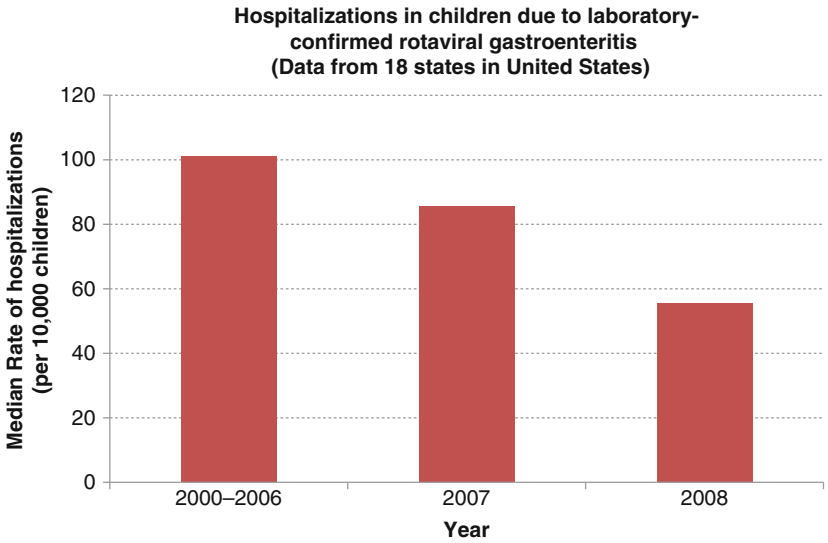

Figure 120.2

Hospitalizations in children due to rotavirus-confirmed gastroenteritis in 18 states of the United States, with data including pre-vaccination years 2000–2006 and 2 years following the introduction of a rotavirus vaccine

Table 120.2

Characteristics of rotavirus and norovirus infection

	Rotavirus	Norovirus
Genome	Non-enveloped; 11 segments of dsRNA	Non-enveloped; ssRNA
Population most affected	Children <5 years of age	Children and adults
Mode of transmission	Fecal-oral	Fecal-oral
Incubation period	2–7 days	12 h–2 days
Length of symptoms	2–7 days	< 3 days
Diagnostic testing	EIA most widely available	EIA for outbreaks
	Also RT-PCR, nucleic acid hybridization, sequence analysis, and culture	RT-PCR (limited availability)
Vaccine?	Yes; Rotateq® and Rotarix®	No

ds = double stranded
ss = single stranded
EIA = enzyme immunoassay
RT-PCR = Reverse transcriptase polymerase chain reaction

Norovirus outbreaks frequently occur in closed environments, such as cruise ships, camps, nursing homes, or schools. Typically, the outbreaks originate from direct contamination by an infected food handler. Food contaminated at its source, such as oysters from contaminated water, has also been described. As the viruses are highly contagious, outbreaks can be explosive, with potentially thousands of people being infected in a short period of time.

Norovirus is typically transmitted via the fecal-oral route or through the ingestion of contaminated food or water. Additionally, vomitus has been shown to contain infectious particles. As few as 10–100 virions are required for infection. Once exposed, roughly 30% of individuals may shed the virus prior to the onset of symptoms. Viral shedding then peaks 1–3 days after illness develops and may persist for up to 3 weeks. The virus is stable from freezing temperatures up to 60°C. All of these factors contribute to the ease of spread and the potential for large outbreaks.

Clinical Manifestations

The incubation period ranges from 12 – 48 h. Disease onset is then quite rapid, with vomiting and non-bloody, watery diarrhea. Fever occurs in roughly 40% of cases, and other constitutional symptoms such as headache, myalgias, and chills are common. In one-third of patients,

asymptomatic infection and viral shedding occur, playing a large part in viral transmission.

The illness is often mild and short-lived, with 85% of patients experiencing less than 3 days of vomiting and diarrhea. The risk for dehydration requiring hospitalization is greatest in children less than 5 years of age and in adults 65 years and older.

Pathogenesis and Pathology

In the infected host, the proximal duodenum demonstrates villous broadening and blunting, crypt-cell hyperplasia, cytoplasmic vacuolization, and inflammatory cell infiltration into the lamina propria. Histologically, the stomach and colon are spared. Intestinal brush border enzymes are diminished during acute infection, with resultant carbohydrate malabsorption. Mild steatorrhea is also noted. The prominent nausea and vomiting associated with norovirus gastroenteritis may relate to delayed gastric emptying, which has been documented in symptomatic adults.

Differential Diagnosis

The preponderance of vomiting and the high attack rate across all age groups are characteristic features of calicivirus gastroenteritis. Norovirus outbreaks can be distinguished from those caused by preformed toxins by the slightly longer incubation period (12–48 h vs. 2–6 h for toxins) and the emergence of secondary cases in household contacts. In general, calicivirus infection tends to have a milder, less dehydrating course than rotavirus. That said, the illness is not reliably clinically distinguishable from that caused by other enteric viruses, including rotavirus, enteric coronavirus, enteric adenovirus, and astrovirus.

Diagnosis

Human noroviruses cannot be cultured. Reverse transcriptase polymerase chain reaction (RT-PCR) can be used to detect viral RNA from stool or emesis samples, in addition to environmental swabs from food or water, in special circumstances. The technique is challenging as human caliciviruses are genetically diverse. Consequently, several sets of primers must be used to confirm infection. Real-time quantitative RT-PCR assays have increased both the sensitivity and specificity of this diagnostic modality. RT-PCR detection is available in some public health and research laboratories but is not readily commercially available in most areas.

Enzyme immune assays (EIAs) for norovirus detection have been approved for commercial use in some countries, though the poor sensitivity of current assays (<50%) limits their use in sporadic cases. In outbreak situations, however, they can be used to rapidly identify norovirus as the causative agent.

In many situations, microbiologic confirmation of a suspected norovirus outbreak is not possible. The "Kaplan criteria" were developed in 1982 to distinguish outbreaks caused by norovirus from those caused by bacterial etiologies. The criteria (vomiting in greater than 50% of affected persons, a mean illness duration of 12–60 h, a mean incubation period of 24–48 h, and no bacterial pathogen identified in stool culture) are highly specific (99%) and moderately sensitive (68%) in this regard. As roughly 30% of norovirus-induced outbreaks will not satisfy all four criteria, it is still important to consider this virus in the appropriate clinical setting. Until norovirus diagnostic tests become widely available, the application of these criteria may be the most useful diagnostic aid in identifying food-borne gastroenteritis outbreaks due to norovirus.

Prognosis

As noted above, Calicivirus gastroenteritis is, in general, fairly mild and self-limited. Immunocompromised hosts, infants, and the elderly are at the highest risk for protracted illness and more severe dehydration. Reports have arisen suggesting an association of norovirus with necrotizing enterocolitis in newborns, benign seizures in infants, and inflammatory bowel disease exacerbations in pediatric patient. Further studies are required to investigate these possible links.

Treatment and Prevention

There is no specific treatment available. As with other causes of viral gastroenteritis, supportive care and attention to fluid and electrolyte balance is crucial. Please see Chap. 187, "Acute Gastroenteritis in Infants and Children" for additional details.

During an outbreak, preventing secondary spread is important in halting further progression. Enforcing personal hygiene, using contact precautions, decontaminating environmental surfaces, and using an

alcohol-based hand sanitizer have all been found to decrease the spread of infection. People with diarrhea due to norovirus refrain should refrain from the use of recreational water venues, such as pools and lakes, for at least 2 week following the resolution of symptoms.

The development of effective preventative measures is of great interest, given the significant socioeconomic burden of large, prolonged outbreaks. In contrast to rotavirus, humans do not acquire long-term immunity with norovirus infection, making vaccine development challenging. A virus-like particle vaccine is currently being evaluated.

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121 Rubella

Richard J. Whitley

Introduction

Initially, rubella was considered to be a variant of measles or scarlet fever; however, in 1814, rubella was recognized as a distinct clinical entity. In 1866, Veale introduced the name rubella for the clinical syndrome associated with a maculopapular rash of children and young adults. Rubella is frequently called "German measles" and is the third of six viral exanthems of childhood, with measles and scarlet fever being the first and second. In 1914, Hess suggested a viral etiology predicated on work performed in animal models; however, the etiology was never firmly established until 1938 when Hiro and Tosaka confirmed the viral origin by passing disease to children using filtered nasal washings (16 nonimmune children).

Rubella was considered a benign disease until the early 1940s when, following a widespread outbreak in Australia, an Australian ophthalmologist, Norman Gregg, first described congenital defects, as described below, of infants born to mothers who developed rubella early in pregnancy. With an increasing recognition of the congenital rubella syndrome and after pandemics between 1962 and 1965, a definitive need for the development of a vaccine became apparent. Parkman and Weller first isolated rubella in cell culture in 1962, which ultimately led to the development and licensure of a vaccine in 1969.

Etiology

Rubella is a single negative stranded RNA virus that is enveloped. It is classified as a togavirus, genus rubivirus of the togaviridae family. The other genus in the family of togaviridae is alphavirus. In contrast to the alphaviruses, which replicate in arthropods and invertebrates, rubella virus has no invertebrate host. The only known host of rubella is humans. This virus is relatively unstable and is inactivated by lipid solvents, formalin, ultraviolet light, low pH, and heat. There is only one immunologically distinct serotype of rubella virus. The spherical particles of rubella virus measure 50–70 nm in diameter.

Pathogenesis

Rubella virus is transmitted by the respiratory route. After exposure, replication of the virus is thought to occur in the upper respiratory tract including the nasopharnyx and regional lymph nodes. Viremia ensues approximately 5–7 days after exposure. During periods of viremia, transplacental infection can take place, resulting in fetal damage, particularly during the first trimester of gestation. In studies conducted with volunteers, virus can be detected 7 days prior to and approximately 14 days after the onset of rash. Rubella has a worldwide distribution, although clinically recognized disease occurs less frequently in tropical regions than in temperate zones. Humans are the only known host. As noted above, rubella is spread from person to person via airborne transmission. Rubella is highly contagious and the incidence of infection during an epidemic cycle approaches 100% for susceptible individuals.

In temperate climates such as North America and Europe, rubella is most prevalent from March through May. Persons with subclinical infection are contagious and can transmit infection to others.

Fetal infection can occur at any time during pregnancy; however, the risk is greatest during the first trimester and decreases thereafter. The risk of congenital anomalies in live-born children following fetal infection varies according to the month of pregnancy in which maternal infection occurred, being the highest during the first 8 weeks at 85%.

Clinical Manifestations

The incubation period for rubella is approximately two weeks with a range of 12–23 days. Symptoms are generally mild and many infections are totally asymptomatic. A maculopapular rash is characteristic of infection, as illustrated in *Fig. 121.1*. The rash begins on the face and progresses distally, persisting approximately 3 days. Arthralgia and arthritis are frequent complications in adults (occurring in as many as 70% of adult women).

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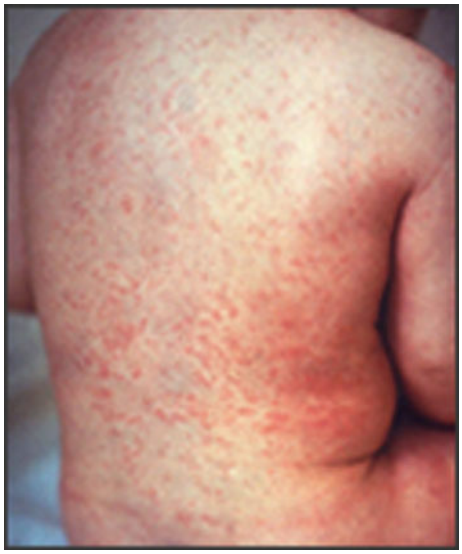

Figure 121.1

When arthritis occurs, it frequently involves the fingers, wrists, and knees. Encephalitis is a rare complication, occurring in approximately 1 in 6,000 cases. Additional complications include orchitis, neuritis, and a late-onset syndrome of progressive pan encephalitis. In addition, hemorrhagic manifestations may be present during the acute illness.

The most significant complication of rubella is the congenital rubella syndrome. Prevention of this syndrome has been the main objective of rubella vaccination programs worldwide. Fetal infection may lead to death, or premature delivery. The congenital rubella syndrome involves virtually all organ systems. Deafness is the most common finding of congenital infection. Other manifestations include ocular abnormalities of cataracts, glaucoma, retinopathy, and microphthalmia. Cardiac defects include peripheral pulmonic stenosis and coarctation of the aorta. Neurologic abnormalities include microcephaly and, ultimately mental retardation. A late-onset congenital rubella syndrome has been described that results in diabetes mellitus and a progressive encephalopathy.

Diagnosis

While clinical findings can suggest a diagnosis of rubella, maculopapular rashes can be attributed to a variety of other etiologies. Thus, laboratory confirmation is required. Definitive diagnosis is achieved by isolation of virus either in cell culture or by polymerase chain reaction. Rubella virus can be detected in blood, urine, cerebrospinal fluid, and nasal and throat swabs. It is present generally 1 week prior to the onset of illness and 2 weeks after rash onset.

Serology is a common method for confirmation of diagnosis. Acute and convalescent serospecimens can be tested by enzyme-linked immunosorbent assays for evidence of antibodies directed against rubella virus. The application of IgM antibodies for confirmation of diagnosis has been used; however, infection attributed to parvoviruses will cause false-positive IgM tests.

Treatment and Prevention

There is no definitive antiviral therapy for rubella infection. Administration of immunoglobulin to susceptible persons experimentally exposed to rubella can prevent clinical disease; however, there have been many reports of failure. As a consequence, it is not routinely recommended.

Since 1979, the RA27/3 rubella vaccine, a live attenuated virus, has been used for the prevention of rubella. The vaccine virus is not communicable except in the setting of breast feeding. It is combined with measles and mumps as an MMR vaccine, or, in addition, with varicella as MMRV. Over 90% of vaccinated individuals will derive significant protection from both clinical disease as well as blood-borne infection for a minimum of 15 years. The first dose of vaccine is recommended for administration between 12 and 15 months of age, with a subsequent dose at school entry (4–6 years of age).

The vaccine can be administered to individuals exposed to rubella within 3 days of exposure.

The vaccine is contraindicated for pregnant women and those who are immunodeficient or receiving immunosuppressive therapies, including individuals with leukemia, human immunodeficiency virus infection, lymphoma, or other malignancies.

Adverse reactions to the vaccine have included arthralgia and arthritis, attributed to the rubella component of MMR. The development of a rash is most likely attributed to the measles component of the vaccine. Additional common complaints include fever, lymphadenopathy, and arthralgia.

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Primary Immunodeficiency Disorders

Harb A. Harfi

122 The Immune System: Development and the Immune Response

Michael Loubser

Development of the Immune System

The immune system develops from gut-associated tissues. Multipotential hemopoietic stem cells first appear in the yolk sac at approximately two and a half weeks of gestation and migrate to fetal liver by the fifth week. They later migrate to the bone marrow where they remain throughout life. The cells of the lymphoid system develop from these multipotential stem cells and differentiate to T- and B-lymphocytes or NK cells depending upon the organs or tissues to which the stem cells traffic. Primary lymphoid organs (thymus and bone marrow) develop during the middle of the first trimester. Secondary lymphoid organs (spleen, lymph nodes, tonsils, Payers patches) develop a little later. These organs serve as sites of differentiation and maturation of T-lymphocytes, B-lymphocytes and natural killer cells throughout life. Both initial organogenesis and continued cell differentiation occur as a consequence of the interaction of lymphocytes with a great number of micro-environmental cells, surface molecules, and proteins.

Lymphoid Organ Development

Lymphoid tissue is proportionately smaller but rather well developed at birth and matures rapidly in the postnatal period. The thymus is largest relative to body size during the fetal life and at birth is ordinarily two thirds of its mature weight. It attains its mature weight during the first year of life. The peak mass is however attained just prior to puberty and it gradually involutes thereafter. By a year of age all lymphoid structures are mature histologically. Absolute histiocyte counts in the peripheral blood reach a peak during the first year of life. Peripheral lymphoid tissue increases rapidly in mass during infancy and childhood, reaches adult size by approximately 6 years of age and reaches those dimensions during the prepubertal years, and then undergoes involution coincident with puberty. Spleen gradually increases its mass during maturation and does not reach full weight until adulthood. The mean number of Payers patches in the gut is approximately one half of the adult number at birth and gradually increases until the adult mean number is reached during the adolescent years.

T- and B-lymphocytes are the components of the immune system which are responsible for adaptive immunity. The adaptive immune response is characterized by antigen specificity and the development of immunologic memory. Natural killer (NK) cells are lymphocytes that are also derived from hemopoietic stem cells; there is evidence that they share some of the development pathways of T-cells. NK cells have a role in host defense against viral infection and tumor surveillance. The proteins synthesized and secreted by T, B, and natural killer cells and by the cells with which they interact, for example, macrophages and endothelial cells, are referred to as cytokines. Cytokines have the ability to act in an autocrine, paracrine, and/or endocrine manner to promote and facilitate differentiation and proliferation of the cells in the immune system.

T-Cell Development and Differentiation

The thymic rudiment develops from ectoderm of the third brachial cleft and endoderm of the third branchial pouch during the fourth week of gestation. Beginning in the seventh to eighth week, the right and left rudiments move caudally and fuse in the midline. Blood-borne T-cell precursors, initially from the yolk sac and fetal liver and later from the bone marrow, colonize the perithymic mesenchyme in a number of waves at approximately 8 weeks of gestation. Clear delineation of the thymic cortical and medullary regions becomes discernable by the 12th week of gestation.

The pro-T-cells are identified by the presence of surface proteins CD7 and CD34 and the absence of CD3, the T-cell receptor (TCR), and CD4 and 8 – so-called triple negative thymocytes (*Table 122.1*). The role of CD 7

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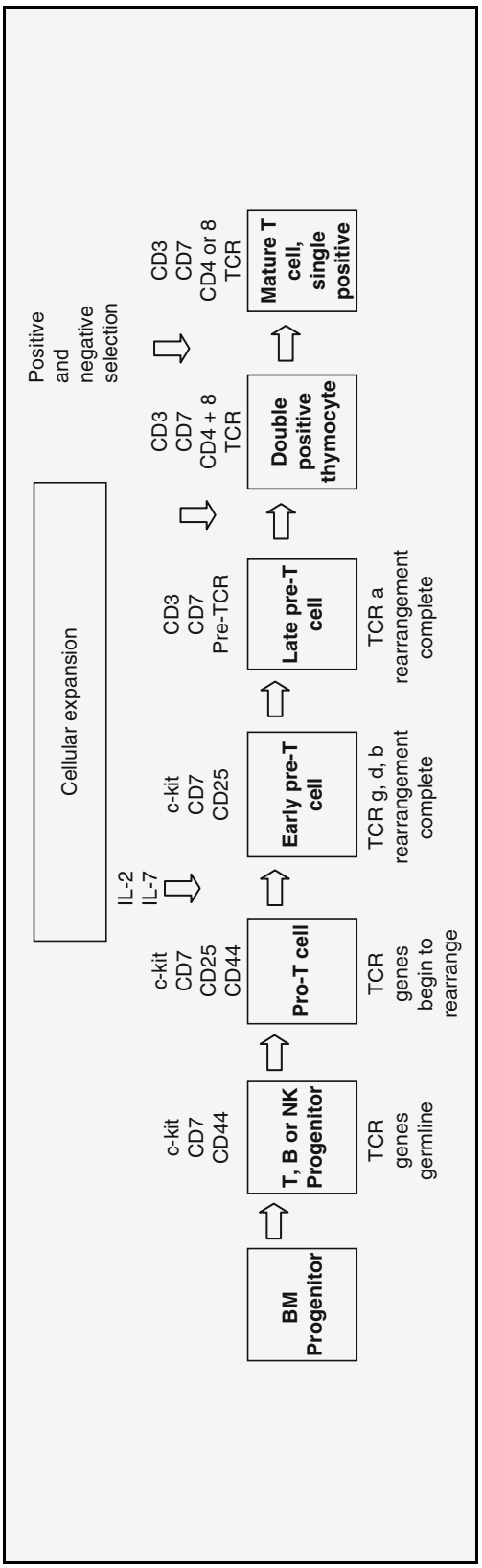
Table 122.1
Thymic development of T-lymphocytes



in T-cell differentiation is not known. It may be a ligand for a complex family of glycoproteins called galectins, whose physiology remains unclear. Toward the end of the eighth week CD7 positive cells are found in the thymus, some of them co-express CD4 and CD8 – so-called double positive thymocytes. Also at this time a number of cells are found bearing incomplete T-cell receptor (TCR) molecules. The mature TCR is a heterodimer comprising either α and β or γ and δ chains; 95% of circulating mature T-cells express a TCR composed of α and β chains. Much of the biology of γδ T-cells remains to be elucidated. TCR αβ or γδ chains are co-expressed on the cell's surface with the CD3 complex which is composed of five polypeptide chains, CD3 γ, δ, ε, ζ, η. TCR diversity is achieved by a process of TCR gene rearrangement. TCR gene rearrangement begins shortly after colonization of the thymic cortex with stem cells between the eighth and tenth weeks of gestation. By 9½ to 10 weeks of gestation, 95% of thymocytes are CD7, CD2, CD4, CD8 positive and have cytoplasmic CD3. By 10 weeks, 25% of thymocytes have functional αβ TCRs. This process is crucial for normal T-cell maturation and involves a mechanism in which large non-contiguous blocks of DNA are spliced together. These segments known as variable (V), diversity (D), and joining (J) each have a number of variants. The VDJ segments are joined at a constant region on the alpha gene and the VJ segments are joined to the beta gene to complete the receptor polypeptide gene. Random combinations of these segments account for much of the enormous diversity of TCR, giving human fetal lymphocytes the ability to recognize millions of different antigens at birth. The development of this vast antigenic repertoire occurs in the absence of exposure to antigen. TCR gene rearrangement is facilitated by recombinase activity genes. Some of these recombinases are specific to the lymphoid cells and others are more generally distributed. The generally expressed recombinase enzymes are KU 80, DNA-PK, and XRCC-4. They are responsible for repair of double-stranded breaks within the genetic replication machinery. More specific to the immune system, however, are two recombinase activating genes referred to as Rag-1 and Rag-2. Lack of recombinase activity resulting from mutations in Rag-1 and/or Rag-2 genes has clinical significance in that there are both animal and human forms of severe combined immunodeficiency resulting from these defects. Affected individuals have low or undetectable levels of circulating T- and B-lymphocytes, the so-called $T^{-}B^{-}$ phenotype.

Rearrangement of TCR genes signifies a developmental step in which pro-T-cells become committed to the T-cell lineage as so-called pre-T-cells. As the immature cortical thymocytes begin to express T-cell receptors, the process of positive and negative selection takes place. This process occurs at the thymic corticomedullary junction. In order for the immune system to be effective, T-lymphocytes must be able to recognize the multitude of foreign antigens that they will encounter over the lifetime of the individual while at the same time they must avoid self-antigens – this differentiation is achieved by positive and negative selection.

Positive selection occurs through the interaction of the TCR of thymocytes with major histocompatibility complex (MHC) antigens present on cortical thymic epithelial cells. There is emerging evidence that normal self-peptides associated with self-MHC capable of having low-affinity interactions with TCRs mediate positive selection. Positive selection is critical for determining the T-cell repertoire and early clonal proliferation. Positive selection is, in fact, the rescue from certain programmed cell death, the eventual fate of the vast majority of thymocytes. Those thymocytes that recognize antigen in the context of MHC class II are selected to become single positive $CD4^{+}$ lymphocytes and conversely those that recognize antigen in the context of MHC class I are selected to become single positive $CD8^{+}$ lymphocytes.

Negative selection is mediated by interaction of the surviving thymocytes with host peptides presented by MHC class I or II antigens on bone marrow–derived macrophages, Langerhans cells, and possibly B-cells. Lymphocytes bearing TCRs with high affinity for self-antigens undergo genetically programmed cell death (apoptosis). In this way autoreactive lymphocyte clones are deleted. Fetal cortical thymocytes are among the most rapidly dividing cells in the body, but as a consequence of positive and negative selection, approximately 97% die. The surviving cells are no longer CD4 and 8 double positive but remain singly positive for one or the other. The single positive, mature cells migrate to the thymic medulla. The medullary thymocytes emigrate from the thymus to the periarteriolar areas of spleen, paracortical areas of the lymph nodes, and appendix at approximately 12 weeks of embryonic life and into the tonsils by 14–15 weeks. They are found in great numbers in the thoracic duct lymph. By the 12th week of gestation T-cells are able to proliferate in response to plant lectins (phytohaemagglutinin and concanavalon A) and allogeneic cells. Lymphocytes capable of responding to exogenous antigen are found by 20 weeks of gestation. Hassell's corpuscles (swirls of terminally differentiated medullary epithelial cells) are first seen in the thymic medulla at 16–18 weeks of embryonic life.

B-Cell Development and Differentiation

B-cell development begins in the fetal liver prior to the 11th week of gestation. Fetal liver CD34 positive stem cells are seeded to the bone marrow of the clavicles by 8 weeks of embryonic life and to the long bones by 10 weeks. There are two broad developmental steps in the maturation of B-cells. These stages of development are defined by cell surface markers (Table 122.2). The first step is antigen independent while the second step leading to the production of high-affinity immunoglobulins is antigen dependent.

Antigen-independent development: Stages of development from pre-pro-B-cell to mature, resting, or virgin B-cell are defined by expression of specific surface proteins and immunoglobulin gene rearrangement patterns (Table 122.2). The precise combination of signals resulting in the differentiation of hemopoietic stem cells into B-cell progenitors is not fully understood. Various cytokines such as interleukins (IL)-3 and IL-7, insulin-like growth factor 1, and stem cell factor (SCF) are known to promote development of B-cell precursors. The earliest detectable cellular markers of B-cell development are D-JH gene rearrangement and the surface expression of CD7, CD10, and CD19.

During the process of B-cell development, B-cell receptor (immunoglobulin) genes undergo rearrangement in much the same way as TCR genes rearrange during T-cell development. The immunoglobulin (Ig) heavy chain genes usually rearrange first, and early B-cell stages express a complex of an Ig heavy chain together with molecules called surrogate light chains. The first heavy chain to be expressed is the μ heavy chain. The surrogate light chains are the products of genes close to the lambda light chain locus. They have some homology with Ig light chain V and C regions, but are not true lambda light chains.

Several of these genes have been identified in humans. V pre-B is a non-rearranging gene encoding most of an Ig V domain. The other genes are a family called lambda 5. The surrogate light chain genes are expressed only in pre-B-cells, and the complex containing the Ig heavy chain with surrogate light chain is called the pre-B-cell receptor.

Genetic defects that prevent expression or interfere with the pre-B-cell receptor function lead to an absence of B-cells and agammaglobulinemia. This has been described in humans with mutations involving.

IgM C region genes, lambda 5 surrogate light chain gene, signal transducing molecules Ig-alpha genes, Bruton's tyrosine kinase (btk) genes, and B-cell linker

Table 122.2
Surface markers defining stages of B-cell development

	Antigen-independent phase					Antigen-dependent phase			
	Pre-pro- B-cell	Pro-B-cell	Pre- B-cell	Immature B-cell	Mature B-cell	Activated B-cell	Blast B-cell	Memory B-cell	Plasma B-cell
MHC Class II	+	+	+	+	+	+	+	+	
CD10*	+	+					+		
CD19*	+	+	+	+	+	+	+	+	
CD20*		+	+	+	+	+	+	+	
CD21*			+	+	+	+			
CD23				+	+	+	+		
CD25, IL-2R alpha						+	+		
CD32, Fc gamma RII				+	+	+	+	+	
CD34	+	+	+						
CD35, CR1				+	+	+	+	+	
CD40		+	+	+	+	+	+	+	
CD80/86, B7-1/2						+	+		

Data from Bona CA, Bonilla FA (1996) Textbook of immunology, 2nd edn. Harwood Academic, Amsterdam, p 102

protein (BLNK) genes. In addition, a V pre-B gene mutation has been described in mice.

Protein tyrosine kinases (PTK) predominantly expressed in T-lymphocytes and natural killer cells, ZAP-70, and a Syk-family PTK also appear to play a role in the transition of pro-B to pre-B-cells.

Following successful production of a true Ig light chain and its combination with the heavy chain, a complete IgM antibody molecule appears on the cell surface. This is the hallmark of the immature B-cell stage – by this stage CD10 and CD34 surface expression has been lost.

In a process closely mirroring negative selection during T-cell development, an immature B-cell expressing surface IgM that has a strong interaction with membrane-bound self-antigen (such as MHC) on other cells, results in that B-cell either undergoing apoptosis, or further Ig gene rearrangement to create a new Ig with a different specificity – a process known as receptor editing.

After exiting the bone marrow, B-cells complete their development in the spleen. The mature, resting, or virgin B-cell expresses surface IgM and IgD.

Antigen-dependent development of B-cells occurs after the mature or virgin B-cell is stimulated by antigen through its antigen receptor. As previously noted, the antigen receptor in the case of the B-cell is surface immunoglobulin. The outcome of the antigen-dependent maturational stage is the production of plasma cells which synthesize and secrete antigen-specific immunoglobulin and the production of surface immunoglobulin positive memory B-cells. There are five immunoglobulin isotypes, IgM, IgG, IgA, IgE, and IgD, each determined by the immunoglobulin heavy chain that it bears, μ, γ, α, ε, and δ, respectively. IgG and IgM are the only complement fixing isotypes and are the most important immunoglobulins in the blood and other internal body fluids. IgM is confined primarily to the intravascular compartment because of its large size. IgG is present in all body fluids. IgA is the predominant immunoglobulin in external secretions and plays a major role in mucosal immunity. IgE is present in both internal and external body fluids and plays a major role in host defense against parasites. Because of the high-affinity IgE receptors on basophils and mast cells, IgE is the principal mediator of immediate-type hypersensitivity. The significance of IgD is not clear. There are also subclasses of immunoglobulins, again defined by unique heavy chains. IgA and IgG have two and four subclasses, respectively. These subclasses have different biologic roles, antibodies directed primarily against protein antigens are found in the IgG_1 and IgG_3 subclasses whereas those directed predominantly against polysaccharide antigens are found in the IgG_2 and IgG_4 subclasses.

Although fetal B-lymphocytes are able to differentiate into immunoglobulin-synthesizing plasma cells, they are not found in fetal tissues until about 20 weeks of gestation. This is primarily because the uterine environment is sterile and the antigen-dependent steps of B-cell development do not occur. Prior to birth, lymph nodes have primary but not secondary follicles. The human fetus receives significant quantities of maternal IgG transplacentally from the 12th week of gestation. This quantity steadily increases until cord blood serum concentrations of IgG are comparable to or greater than maternal serum. IgG is the only class of immunoglobulin to cross the placenta. All four subclasses of IgG cross the placenta but IgG_2 does so to a lesser degree. Small quantities of IgM, IgA, IgD, and IgE are present in cord blood. None of these proteins cross the placenta so they are therefore presumed to be of fetal origin.

Natural Killer Cell Development

Natural killer cell (NK cell) activity is found in the fetal liver by about 8–11 weeks of gestation. NK cells are derived from bone marrow precursors and share some of the developmental features of T-lymphocytes. Thymic processing appears not to be necessary for NK cell development. NK cells are defined by their capacity to mediate non-MHC-restricted cytotoxicity. NK cells do not rearrange antigen receptor genes during their development. Virtually all NK cells express CD56 and greater than 90% express CD16. Other CD antigens found on the NK cells include CD57, CD7, CD2, and CD8. NK cells, therefore, share surface antigens common to T-lymphocytes and myeloid cells, leading to some ambiguity as to their ontogeny. Humans who have deficiencies in T- and B-cells often have a relative increase of NK cells. Deficiencies of NK cells have been described and these individuals have normal T- and B-cell development. After release from bone marrow NK cells enter the circulation and migrate to the spleen. There are very few natural killer cells in the lymph node. NK cells recognize virally infected or tumor cells by the absence or decreased expression of MHC class 1 on their surfaces. This MHC-unrestricted killing is mediated by perforin/granzyme apoptotic pathways. A second mechanism of cytolysis is antibody mediated and is termed antibody-dependent cell-mediated cytotoxicity (ADCC). Here, target cells that have bound IgG_1 or IgG_3 trigger the FcRIIIa on NK cells and induce cytolysis. In normal individuals, NK cells compromise approximately 10% of lymphocytes. This percentage is often slightly lower in cord blood.

The Immune Response and Effector Mechanisms

The T-Cell Response: Cell-Mediated Immunity and Cell-Mediated Cytotoxicity

T-lymphocytes may be conceptualized as the conductors of the immune orchestra. They provide help for antibody production by B-cells while participating actively in antigen-specific cell-mediated immunity (CMI). CMI plays a central role in elimination of cells infected by intracellular organisms (viruses and certain bacteria) as well as cells that exhibit abnormal growth and development (neoplastic cells). CMI plays an important role in allograft rejection and in some autoimmune disorders.

The T-cell receptor is made up of a complex of molecules and is exclusively membrane bound – unlike the B-cell receptor – immunoglobulins – that secrete into plasma. T-cell receptors recognize foreign peptides bound to the MHC molecules expressed on the surface of antigen-presenting cells or on the surface of cells that become the target of cytotoxicity.

Antigen-presenting cells are key to the initiation of the T-cell effector mechanism. Common to all antigen-presenting cells is the constitutive or inducible expression of MHC class II; examples of these cells are dendritic cells, monocytes, and macrophages. Antigens presented in the groove of MHC class II have the capacity to interact with the TCR on lymphocytes co-expressing CD4 – this interaction initiates a complex process of cytokine production and co-stimulatory molecule interaction that results in activation and clonal proliferation of the specific T-cell as well as B-cell help. In general, antigens presented on the context of MHC II have arisen from extracellular sources. Almost all somatic cells express MHC I. In general, antigens presented in the context of MHC I have resulted from intracellular processes (viral or intracellular bacterial infection, tumor, etc.). Cells expressing MHC I are capable of binding to TCRs that exist on lymphocytes co-expressing CD8 – the so-called cytotoxic T-cells. This interaction results in lysis of the affected cell. B-cells express MHC II and are able to activate memory T-cells but cannot activate resting naïve T-cells.

The details of antigen processing and presentation are beyond the scope of this chapter, briefly though; professional antigen-presenting cells such as dendritic cells utilize surface receptors, e.g., Toll-like proteins that bind to a variety of microbiological products, e.g., lipopolysaccharide. When the receptor is bound by its ligand, the dendritic cell undergoes maturation and, under the influence of cytokines, migrates to the secondary lymphoid organs where it interacts with the T- and B-cells. The dendritic cell takes up the antigen and in the cytoplasm degrades it into smaller peptides that are loaded onto MHC I or II molecules for later presentation to the relevant lymphocyte.

T-Cell Activation: Essential for T-cell activation is an intact TCR complex, interaction with antigen in the context of MHC, the interaction of a number of co-stimulatory molecules, and an intact transmembrane and intracellular signaling network. The outcome of the activation process is the production of various cytokines that ultimately dictate the outcome of the activation process.

The T-cell receptor complex is comprised of the CD3 complex and a heterodimer comprising either α and β or γ and δ subunits. The so-called $\alpha\beta$ T-cells account for the majority of circulating lymphocytes (90%) and their biology is best understood while the $\gamma\delta$ T-cells are found predominantly in the gut-associated lymphoid tissues and their function is incompletely elucidated.

Each mature T-lymphocyte co-expresses either a CD4 or a CD8 molecule. As mentioned previously, the interaction between the TCR and MHC II bearing a foreign antigen, in the presence of the CD4 molecule is largely responsible for activation of T-cells that produce an array of cytokines that ultimately facilitate the cell-mediated immune response. Conversely, the interaction of a lymphocyte bearing TCR and CD8 with a cell-presenting antigen in the context or MHC I will ultimately lead to the production of a variety of cytokines that ultimately facilitate cell-mediated cytotoxicity and cell lysis.

The above-mentioned interaction is, however, insufficient to activate the naïve T-cell. In fact, binding of TCD–CD3 complex without engaging any co-stimulatory molecules leads to a state of unresponsiveness (anergy) and even death by apoptosis. This may be an important mechanism in T-cell tolerance. One important interaction is that between CD28 on the T-cell with CD80 on the antigen-presenting cell. In the primed T-cell, this interaction triggers the production of interleukin-2 (IL-2) and cellular proliferation. This is at least partially mediated by a positive feedback mechanism between IL-2 and its receptor, CD25.

The process whereby TCR–CD3 complex binds to MHC antigen complex and co-stimulatory molecules triggers a cascade of intracellular events. The details of these biochemical events are beyond the scope of a general pediatric text. Briefly, the intracellular components of the receptor molecules interact with protein tyrosine kinases, triggering three major pathways, mitogen-activated tyrosine kinases (MAPK), Rho family GTPases, and the phosphoinositol regulated pathways. The ultimate result

of these interactions is to send signals to the nucleus via nuclear transcription factors that ultimately result in the production of cytokines.

Based upon the patterns of cytokine production observed for different T-cells, attempts have been made to classify T-cells as either Th0, Th1, Th2, or Th3. This classification is useful from a descriptive point of view, but it is not clear whether truly distinct functional subgroups of T-cells actually exist in the human. The Th0 subgroup is thought to represent undifferentiated T-cells. Cells exhibiting the Th1 cytokine profile (interferon gamma and IL-2) are predominantly involved in macrophage activation and the induction of cellular cytotoxicity, whereas Th2 cells produce cytokines (IL-4 and IL-10) that stimulate IgE, IgG_2, and eosinophil production – all involved in the immunological response to parasites. In clinical practice, the Th2 response seems to be the predominant profile of the atopic reaction. Th3 cells produce transforming growth factor beta (TGF-beta) and are thought to play a role in suppression or negative regulation of the immune response.

Regulation of the immune response is critical to the maintenance of health. Unchecked activity of the effector mechanisms leads to tissue damage as evidenced by the autoimmune connective tissue diseases. T-cells play a central role in the regulation of both T- and B-cell-mediated immunologic processes. The regulatory process is complex and involves both cell-to-cell contact and the production of circulating factors. Two specific receptors play an important role in negatively regulating T-cells – CD 95 and Tumor necrosis factor-2 (TNF-2). When bound to their extracellular ligands, these molecules promote cell death and hence a down regulation of the inflammatory response. The role of Th3 cells in negative regulation has also been alluded to previously.

The B-Cell Response: Humoral Immune Response

Circulating antibodies are acquired either *passively* (during human gestation by the transplacental transfer of maternal IgG, and postnatally via colostrum and breast milk through transepithelial Ig transport by the neonatal Fc receptor, FcRn) or *actively* by natural infection or immunization with vaccines. During the second trimester of pregnancy, IgG crosses the placenta and enters the fetal circulation; IgA and IgM are not transported across the placenta and occur in only very small concentrations in the fetus. Maternally acquired IgG is gradually lost and essentially disappears by 6 months of postnatal age.

Active (or adaptive) immunity is the response generated during the encounter of the immune system with antigen, either naturally occurring or in the form of vaccination. These interactions are responsible for the antigen-dependent stage of B-cell development. This process involves B-cell activation, proliferation, and eventually differentiation into memory B-cells or antibody-secreting plasma cells. Broadly speaking, there are two types of antibody response, one that is independent of T-cell help and the other that is regarded as being T-cell dependent.

T-independent B-cell responses – occur in response to a number of different antigens; some plant and microbial antigens are capable of stimulating polyclonal (i.e., nonspecific) responses and are called mitogens.

Certain strains of Epstein Barr virus can transform B-cells to proliferate in the absence of T-cell regulation. Finally and perhaps most importantly the majority of carbohydrate antigens are handled in this way, one of the most significant organisms being *Streptococcus Pneumonia*. Surface Ig cross-linking is insufficient to induce B-cell proliferation and differentiation, but renders B-cells receptive to T-cell signals (cytokines) which further stimulate their progression toward antibody-secreting cells. In this setting, T-helper-cells do not need to make physical contact with B-cells. This is referred to as non-cognate T-cell help.

T-cell-dependent B-cell responses – account for the majority of responses to protein and glycoprotein antigens. In this instance, antibody production requires close collaboration between T- and B-cells. Initially, T-cells are activated by recognizing antigen associated with MHC molecules presented to them by an antigen-presenting cell. The activated T-cell produces cytokines and becomes capable of providing help to a B-cell for antibody production. A second interaction involves direct contact between a B-cell and the T-helper-cell. B-cells internalize antigen that binds specifically to the B-cell receptor (Ig molecule); the antigen is processed and associated with MHC class II molecules, as occurs with the professional antigen-presenting cells. This action is necessary for a T-helper-cell to be able to recognize appropriate B-cells to which they deliver stimulating signals. Analgous to T-cell activation, B-cells additionally require interaction with other molecules to complete and mature the humoral immune response – examples include interactions with complement proteins, activation molecules such as CD21 and molecules that mediate class-switching from IgM to other classes, specifically CD40L (CD154). Once a sufficient set of activating signals are received, the B-cell enters a differentiation pathway leading either toward a plasma cell, or a memory cell. By influencing the process of Ig class-switching,

cytokines also influence the relative proportions of various Ig isotypes produced in antibody responses.

Intracellular signaling in B-cells is regulated by tyrosine, serine, or threonine phosphorylation of one or more components of the pathway. Protein kinases (PTKs) and phosphatases, respectively, phosphorylate and dephosphorylate their various substrates ultimately leading to nuclear activation and protein synthesis.

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123 Innate Immune Defects

Jordan S. Orange · Nina Poliak

The innate immune system serves as an initial immunologic defense against microorganisms. Once a microorganism penetrates the body's physical barriers, the innate immune system responds almost immediately. Steps in function of the innate immune system include *recognition* of danger, *amplification* of a signal, and a functional *response* to foreign material. As a whole, the innate immune system utilizes numerous individual components to affect these objectives. Almost any of these have the potential to be defective in children, leading to susceptibility to infection and environmental exposures. There are many individual different known defects of the innate immune system, some of which define specific syndromes or disorders. The individual diagnoses are best suspected after characteristic patterns of infection that suggest a particular defective element of innate immune defense. The recognition of these infectious paradigms can facilitate the consideration of a particular disorder and help target an appropriate diagnostic approach. In this chapter, individual defective elements of innate immunity as well as specific disorders are reviewed. Emphasis is placed upon the infectious susceptibility demonstrated by the "typical" patient affected by the given disorder.

Phagocyte Defects

Neutrophils are the chief phagocyte of the immune system and function to isolate, engulf, and kill pathogens. Neutrophils express adhesion receptors, such as integrins, and immunoglobulin (Ig) receptors, and complement receptors to facilitate uptake of opsonized dangerous elements. Defects in neutrophils are the cause of several diseases of innate immunity and comprise approximately 18% of all primary immunodeficiencies. These are presented in ❯ *Table 123.1* along with the respective genes impaired in each and include chronic granulomatous disease, Chediak–Higashi syndrome (CHS), Griscelli syndrome (GS), Hermansky–Pudlak syndrome (HPS) type 2, leukocyte adhesion deficiency (LAD) (Type I, Type II, and Type III), neutrophil-specific granule deficiency, myeloperoxidase deficiency, cyclic neutropenia, severe congenital neutropenia (Kostmann syndrome), X-linked neutropenia, and hyper-IgE syndrome (HIES).

Chronic granulomatous disease (*CGD*) occurs in approximately 1 in 200,000 live births and is caused by a defect in the NADPH oxidase complex and resulting inability of phagocytes to produce a respiratory burst. There are several individual components of the NADPH oxidase complex and deficiencies of any one can cause CGD. Since one, $GP91^{phox}$ is encoded by a gene on the X chromosome, CGD can be either X-linked or autosomal recessive. In general, the X-linked form is both more common and more severe. Patients usually present in early childhood with abscesses of skin and deep-seated infections of lungs, lymph nodes, liver, and bones. The most common pathogens are catalase-positive bacteria such as *Staphylacoccus, Klebsiella, Serratia, and Burkholderia*. Fungal infections also represent a major susceptibility of CGD patients and most commonly are caused by *Aspergillus species*. Aspergillus pneumonia is historically the leading cause of fatal infection in CGD. Approximately 17% of patients with CGD develop a difficult–to-treat form of inflammatory bowel disease. Patients also develop inflammatory granulomas in sites such as the stomach, esophagus, ureter, and bladder, which can lead to obstructive symptoms. CGD can be diagnosed by determining phagocyte oxidase activity by measuring the reduction of a fluorescent dye such as dihydrorhodamine (DHR). DHR reduction after cell activation will produce a quantitative change in fluorescence that can be easily measured by flow cytometry.

Treatment of CGD focuses on the prevention of life-threatening infections through the use of indefinite antibiotic prophylaxis. The currently recommended prophylactic regimen includes both trimethoprim-sulfamethoxazole and itraconazole and has been validated to substantially reduce infection in placebo-controlled studies of CGD patients. Studies have also demonstrated a benefit for prophylaxis with Interferon–γ in reducing infections. Hematopoietic stem cell transplantation (HSCT) has more recently been demonstrated to correct immune defects in CGD patients and thus has the

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Table 123.1
Phagocytic cell disorders and its characteristics

Phagocytic cell disorders	Inheritance	Gene	Defective immune mechanism	Clinical presentation susceptibility	Diagnosis	Treatment
Chronic granulomatous disease (CGD)	75% XR	CYBB	Mutations in phagocyte NADPH oxidase complex. XR: defect in the gene for gp91phox	Recurrent, pyogenic, deep-seated, granulomatous infections of skin and internal organs with catalase-positive bacteria (S. aureus, Serratia, Klebsiella, Aerobacter, Salmonella, Burkholderia cepacia,), and fungi (Aspergillus, Nocardia, Candida). ~17% of patients develop IBD Granulomas can cause obstruction of stomach, ureter, or esophagus.	Measurement of phagocyte oxidase activity via dihydrorhodamine reduction assay (or similar) Specific gene sequence	1. Prophylactic antimicrobial and antifungal therapy or 2. IFN-γ injections 3. Granulocyte transfusions 4. HSCT 5. Gene therapy
	25% AR	CYBA NCF1 NCF2 RAC2	AR: defects in genes p47phox or p67phox or p22phox, or RAC2			
Chediak–Higashi syndrome (CHS)	AR	LYST	Mutations of LYST causing abnormal lysosomal trafficking leading to aberrant formation and function of phagolysosomes and melanosomes.	Pyogenic infections of skin, respiratory tract Partial oculocutaneous albinism, photophobia Nystagmus, ataxia, peripheral neuropathy. Accelerated phase: lymphoproliferative disease with hemophagocytosis that is often fatal.	Microscopic evaluation of neutrophils to demonstrate the presence of giant azurophilic granules Reduced or absent NK cell cytotoxicity Specific gene sequence	1. Prophylactic antibiotics 2. HLA-identical HSCT Allogeneic HSCT 3. High-dose cocorticosteroids and chemotherapy for accelerated phase
Griscelli Syndrome (GS)-II	AR	RAB27A	RAB27A mutation leading to defective transit of phagolysosomes, lytic granules, and melanosomes	Pyogenic infections Pigmentary changes in hair (large melanin clumps in the shaft) and skin Accelerated phase like Chediak–Higashi	Reduced or absent NK cell cytotoxicity Specific gene sequence	1. Prophylactic antimicrobial therapy 2. Chemotherapy for accelerated phase 3. HSCT

Table 123.1 (Continued)

Phagocytic cell disorders	Inheritance	Gene	Defective immune mechanism	Clinical presentation susceptibility	Diagnosis	Treatment
Hermansky–Pudlak syndrome (HPS) type 2	AR	AP3B1	Abnormal formation of neutrophil granules Mutation of the adaptor protein complex 3 subunit	Same as for Chediak–Higashi with the addition of: Severe thrombasthenia-Congenital neutropenia	Neutropenia Reduced or absent NK cell cytotoxicity Prolonged bleeding time Specific gene sequence	1. Prophylactic antimicrobial therapy 2. Control of bleeding 3. Chemotherapy for HLH 4. HSCT
Leukocyte adhesion deficiency (LAD), Type I	AR	ITGB2	Absence or partial deficiency of adhesive integrins on neutrophils and lymphocytes (CD11/CD18 deficiency)	Recurrent non-purulent soft tissue and mucous membrane infections such as gingivitis, stomatitis, otitis, perirectal abscesses; Destructive periodontitis Impaired wound healing Delayed umbilical cord separation	Decreased or absent expression of CD18 on neutrophils by flow cytometry Elevated white blood cell counts Specific gene sequence	1. Prophylactic antimicrobial therapy 2. Surgical debridement of wounds 3. HSCT
LAD, Type II	AR	FUCT1	GDP-fucose transporter gene defect Decreased level of Sialyl Lewis X protein (CD15)	Recurrent infections especially of lungs Coarse facial features Developmental delay and mental retardation Bombay blood type and leukocytosis	Decreased or absent Sialyl Lewis X by flow cytometry (CD15) Specific gene sequence	1. Prophylactic antimicrobials 2. Fucose supplementation 3. HSCT
LAD, Type III	AR	CALDAG-GEF1	CALDAG GEF1 mutation Integrin activation defect on leukocytes also affecting platelets	Recurrent severe non-purulent infections Petechiae or severe bleeding from birth, Leukocytosis	Specific gene sequence	1. Prophylactic antimicrobials 2. Blood transfusions 3. HSCT
Specific granule deficiency	AR	CEBPE	Absence of neutrophil-specific granules resulting from absent function of the transcription factor C-EBPε.	Recurrent skin and respiratory tract infections with S. aureus, Pseudomonas, Candida.	Microscopic examination of stained eutrophils Specific gene sequence	1. Supportive treatment of infections

Table 123.1 (Continued)

Phagocytic cell disorders	Inheritance	Gene	Defective immune mechanism	Clinical presentation susceptibility	Diagnosis	Treatment
Severe congenital neutropenia (including Kostmann syndrome)	AR	HAX1 ELA2 G6PR P14 GCSFR	Various depending upon the specific gene mutation all resulting in the near absence of neutrophils in peripheral blood	Bacterial respiratory tract infections Otitis, gingivostomatitis, perineal and vaginal ulcerations, fever and malaise	Serial measurements of neutrophil counts Specific gene sequence	1. Therapy with granulocyte colony stimulating factor (G-CSF) 2. Supportive treatment of infections
Cyclic neutropenia	AD	ELA2	Deficiency of elastase 2 (ELA2)	Low neutrophil counts approximately every 21 days (range 14–36 days) Neutrophil counts nadirs usually present for 3–6 days Fever, stomatitis, periodontitis, and skin infections when neutrophil counts are low.	CBC check $\geq$ weekly for 6–8 weeks Specific gene sequence	1. G-CSF 2. Supportive treatment for infections
X-linked neutropenia	XR	WASP	Constitutively activating mutation in Wiskott–Aldreich syndrome protein	Bacterial infections	Serial CBC Specific gene sequence	G-CSF
Myeloperoxidase deficiency	AR	MPO	Diminished capacity to enhance hydrogen peroxide-mediated microbicidal activity	Healthy individuals who can develop fungal infections when deficiency is associated with systemic diseases (e.g., diabetes, lupus)	Diminished or absent myeloperoxidase	Therapy for fungal infections
Hyper-IgE syndrome (HIES)	AD AR	STAT3 DOCK8 TYK2	Defective function of STAT3 transcription factor and absence of Th17 cells	Recurrent lung infections with Staphylococcus and Aspergillus Bronchiectasis Pneumatoceles Recurrent skin infections Chronic eczematous dermatitis with frequent superinfections S. aureus. Coarse facial features	Elevated IgE levels Eosinophilia Specific gene sequence	1. Aggressive and prophylactic antibiotics 2. antifungal 3. dental evaluation for retained primary teeth 4. HSCT is not curative as disease recurs.

AR autosomal-recessive, *AD* autosomal dominant, *XR* X-linked recessive

potential to "cure" the immunodeficiency. Preliminary evidence with gene therapy in the X-linked form has identified some potential benefits.

CHS is characterized by abnormal neutrophil granules and subsequent defective antimicrobial killing. Partial oculocutaneous albinism, neurological symptoms, and increased susceptibility to pyogenic infections affecting skin, respiratory tract, and other organs are typical. Microscopic examination of neutrophils can reveal giant azurophilic granules that result from the defective formation of these and related cell organelles in CHS and lead to impaired function. Patients with CHS can develop an "accelerated phase" after certain types of viral infections, which is characterized by unchecked systemic inflammation and can be fatal without aggressive immunosuppressive therapy. HSCT can cure the immunologic abnormalities in CHS.

GS is a heterogeneous disorder and has several distinct phenotypes, with the feature common to all being a global pigmentary dilution with silvery gray hair. While there are features characteristic of each form of GS, GS2 includes a phagocytic immunodeficiency that is similar to CHS and results from abnormal management of intracellular granules. This results in a susceptibility to pyogenic infections and similar to CHS can also develop an accelerated phase. HSCT can also cure immunologic abnormalities in GS.

HPS is similar to CHS and GS as it results from abnormal generation of phagocytic granules. It also presents with oculocutaneous hypopigmentation, susceptibility to bacterial infections, and developmental delay, and can be associated with an accelerated phase. There are several forms of HPS, and it is HPS2 that is associated with immunologic abnormalities. Unlike CHS and GS, HPS is associated with bleeding as certain platelet granules are also affected. Treatment of HPS includes antibiotics prophylaxis, control of bleeding, and the use of HSCT, which can cure immunologic abnormalities.

LAD is extremely rare and represents an inability of leukocytes to localize to sites of inflammation due to defective adherence mechanisms. As a result, there are extraordinarily high numbers of white blood cells in the circulation. LAD is autosomal recessive and has three distinctive subtypes. *LAD Type I* patients present with recurrent non-purulent infections of the skin such as cellulitis, omphalitis, poor wound healing, severe periodontitis, and respiratory tract and intestinal infections. Diagnosis can be established by detection of absent or severely decreased CD11a/b and CD18 integrin components on leukocytes using flow cytometry. This disorder has been classically associated with delayed separation of the umbilical cord stump in the perinatal period. This, however, is quite common, while LAD is very rare. In addition, the delayed separation of the cord in LAD is almost always associated with omphalitis and elevated white blood cell counts. Prophylactic and therapeutic antimicrobial regimens and early HSCT are the current management strategies for LAD Type I. *LAD Type II* is similar to LAD Type I clinically, but also presents with severe mental retardation, growth delay, and dysmorphic facial features. In contrast to LAD type I, decreased or absent CD15 by flow cytometry is diagnostic for LAD Type II, and this deficiency results in the inability of leukocytes to marginate to sites of inflammation. *LAD Type III* is also clinically similar to the others, but here integrins are present on leukocytes, but cannot be activated. This also affects platelets and thus patients develop petechiae and hemorrhage in early infancy.

Severe congenital, cyclic, or X-linked neutropenias are characterized by susceptibility to septicemia, bacterial respiratory tract infections, soft tissue infections, gingivostomatitis, periodontitis, and oral vaginal and rectal mucosal ulcerations. The severity of the infectious complications parallels the severity of neutropenia. Serial measurements of neutrophil counts are necessary to distinguish persistent from cyclic neutropenia and to establish the diagnosis.

Neutropenia in severe congenital neutropenia and X-linked neutropenia is persistent, while in cyclic neutropenia, decreased cell counts typically occur every 21 days but may range from 14 to 36 days.

HIES is a rare primary immunodeficiency that involves the immune and musculoskeletal systems. Patients with HIES present with eczema, recurrent staphylococcal furunculosis and abscesses, mucocutaneous candidiasis, and respiratory infections. The clinical hallmark of HIES is recurrent pneumonia with pneumatoceles and bronchiectasis. Patients with HIES develop characteristic facial features including prominent forehead, wide-set eyes, and thickening of the ears and nose. Skeletal abnormalities lead to recurrent pathological bone fractures and prolonged retention of primary teeth. Laboratory findings include elevated polyclonal IgE (IgE levels of more than 2,000 IU/ml), eosinophilia, and absence of TH17 cells. Treatment of HIES consists of aggressive skin care, prophylactic and therapeutic antibiotics. Immunoglobulin replacement therapy is held to be useful in some patients as deficiencies in polysaccharide-specific antibodies can be documented. HSCT is not curative in HIES as the symptoms are not ameliorated and IgE levels return after transplant to pre-transplant levels.

Natural Killer Cell Defects

Natural killer (NK) cells are lymphocytes of the innate immune system that function to help control of infection through cytotoxicity, cytokine production, or costimulation of other immune cells. There are isolated NK cell deficiencies in addition to immunologic syndromes associated with NK cells defects. A wide variety of combined primary immunodeficiencies affect NK cells as part of the overall immunological defect in that disease. These include severe combined immunodeficiency, CHS, GS type II, the X-linked lymphoproliferative syndrome (XLP), Wiskott–Aldrich syndrome, and *NF-κB essential modulator* (NEMO) deficiency.

Isolated NK cell deficiencies (not affecting other components of the immune system) are rare and are characterized by the absence of NK cells or their functions. Presently, only one genetic aberration has been associated with this diagnostic category, and thus they are categorized phenotypically (◉ *Table 123.2*). Patients with NK cell deficiencies typically have increased susceptibility to herpesviral infections and treatment includes therapeutic and prophylactic administration of antiviral medications.

Familial Hemophagocytic Lymphohistiocytosis (*FHL*) has five different forms (FHL1-5) and represents a serious life-threatening disease that manifests early in life as hematophagocytic lymphohistiocytosis (HLH). The symptoms and laboratory findings of HLH include high, prolonged fever without evidence of bacterial infection, hepatosplenomegaly, pancytopenia, and elevated inflammatory markers/acute phase reactants. This symptomatic phase of FHL is lethal if not treated and is often triggered by herpesvirus infection. Absent cytotoxic activity of NK cells is a characteristic feature of FHL and relates to the underlying defective mechanism. FHL type 1, does not have an identifiable genetic cause but types 2–5 are caused by mutations in specific genes (◉ *Table 123.3*). Specific

Table 123.2
Isolated natural killer cells deficiencies

NK defects	Inheritance	Gene	Peripheral blood NK cells	Clinical susceptibility	Diagnosis	Treatment
Absolute NK deficiency	Unknown	Unknown	Absent NK cells and NKT cells	Severe VZV, CMV, HSV, bacterial and mycobacterial infections	No CD56+ cells_	1. Treatment and prophylaxis of infections 2. HSCT
Classical NK deficiency	unknown	unknown	Absent NK cells with present T cells	HPV, trichophyton	Absent classic NK cells (CD56+/CD3−) and absent NK cytotoxicity	1. Prophylaxis against herpes viruses 2. aggressive therapy of HPV 3. HPV vaccination 4. HSCT
Functional NK deficiency	Unknown	Unknown	NK cells present, but unable to mediate cytotoxicity	EBV, HSV	Presence of NK cells but absence of their activity	1. Prophylaxis against herpes viruses 2. Possibly cytokine therapy (IL-2)
NK cell deficiency due to CD16 impairment	AR	FCGR3A	NK cells present, have impaired spontaneous cytotoxicity	Severe HSV, VZV, EBV	Flow cytometry showing absent CD16 as recognized by mAb B73.1 (CD16 is present when assessed using mAb 3G8)	1. Prophylaxis against herpes virus

Table 123.3
Primary immunodeficiencies associated with defect in natural killer cells

Defects involving NK cells	Inheritance	Gene	Defect	Susceptibility	Diagnosis	Treatment
Familial erythrophagocytic lymphohistiocytosis	AR	PFP1 MUNC13–4 STX11 MUNC18–2	Defect in perforin (PFP1) or the ability to appropriately release the contents of lytic granules	EBV, CMV, VZV, HSV	Reduced NK cell cytotoxicity, Flow cytometry for absence of perforin (PFP1) or degranulation via CD107a upregulation in NK cells Fulfillment of FHL diagnostic criteria (5/8) Specific gene sequence	1. Treatment of infection. 2. Immunosuppression 3. Chemotherapy 4. HSCT
XLP	XR	SH2D1A XIAP (BIRC4)	Ligation of 2B4 fails to induce lysis of EBV-infected cells	EBV	Specific gene sequence Reduced NK cell cytotoxicity Elevated CD8+ cells Absence of SAP protein by flow cytometry	1. Treatment and prophylaxis of EBV 2. IVIG 3. Immunosuppression 4. HSCT

guidelines for the diagnosis of FHL have been published and require the presence of 5/8 criteria, or the definition of a known associated gene mutation. Management of FHL immunosuppression during the acute phase of the illness and ultimately HSCT, as it is the only curative treatment.

XLP presents clinically in previously healthy individuals after infection with Epstein-Barr virus (EBV). These patients develop extreme symptoms of their EBV infection and demonstrate a profound proliferation of infected B cells, leading to multiorgan system abnormalities. Once triggered, clinical disease in XLP patients is difficult to manage and frequently, lethal. Thirty percent of XLP patients have B cell lymphoma as an initial presentation and normal immunologic functions become impaired in most. Treatment includes immunoglobulin replacement, antiviral therapy, rituximab, immunosuppressants, and HSCT. Prognosis of patients with XLP is poor with mortality of 10% within the first 10 years of life and early transplantation after diagnosis (even if not yet symptomatic) is recommended.

Cytokine Deficiencies

Cytokines are a heterogeneous group of soluble glycoproteins that serve important roles in inducing innate immunity are produced by the innate immune system to facilitate adaptive immunity. While many cytokines function in innate immunity, a family of defects referred to as the Type I cytokine pathway defects are especially relevant. These include IFN gamma receptor (R1 or R2) deficiency, IL-12 receptor deficiency, IL-12 p40 deficiency, and STAT1 deficiency. All these deficiencies are inherited as autosomal recessive disorders and result in susceptibility to atypical mycobacterial disease. Specifically, the actions of these cytokines and the STAT1 transcription factor used by these cytokines allow for the appropriate activation of monocytic cells so that they can destroy mycobacteria in the phagosome. Patients with IL-12 defects also are susceptible to Salmonellosis. Diagnosis can be suspected on account of an aberrant production of IFN-γ (in IL-12 deficiencies), or response to IFN-γ. In the IFN-γ receptor deficiencies, there are also elevated

levels of serum IFN-γ. Treatment includes antimycobacterial regimens, antimycobacterial prophylaxis, IFN-γ for the IL-12 and partial IFN-γ receptor deficiencies, and potentially HSCT.

Toll-like Receptor Function Defects

Ten toll-like receptors (TLRs) have been described in humans and serve as pattern recognition receptors for dozens of molecules (both foreign and self) that contain motifs signifying danger. As a result, they represent key initiators of the innate immune response. Patients with defective function of the TLR system have specific infectious susceptibilities (*Table 123.4*). Some defects affect a number of TLRs by impairing common signaling pathways downstream of the receptors. Examples include IRAK-4 and MyD88 deficiency in which patients are susceptible to pyogenic infections. Laboratory evaluation of patients with suspected defect in TLR includes a TLR

Table 123.4
Primary immunodeficiencies involving TLR

Immunodeficiency	Inheritance	Gene	Defect	Susceptibility	Diagnosis	Treatment
Interleukin-1 receptor associated kinase 4 (IRAK-4) deficiency	AR	IRAK4	TLR-IRAK signaling pathway	Pyogenic infection	TLR assay abnormality Direct gene sequence	1. prophylactic antibiotic treatment 2. IVIG
MyD88 deficiency	AR	MYD88	Deficiency of downstream adaptor of TLR	Pyogenic infection	TLR assay abnormality Direct gene sequence	1. prophylactic antibiotic treatment 2. IVIG
Herpes simplex encephalitis (HSE)	AR	UNC93B1	Defect in UNC-93B dependent IFN induction	HSV encephalitis	TLR assay – measurement of IFN-λ Direct gene sequence	Prophylaxis and treatment of HSV
	AD	TLR3	Defect in TLR3 dependent IFN induction	HSV encephalitis Influenza cerebritis	TLR assay - measurement of IFN-λ Direct gene sequence	Prophylaxis and treatment of HSV
NEMO Deficiency (some with Ectodermal dysplasia with immunodeficiency)	XR	NEMO (IKBKG) mutation	Defective NF-κB activation downstream of TLR and other immunoreceptors	Pyogenic bacteria, mycobacteria, pneumocystis, DNA viruses	NEMO gene sequencing TLR assay NK cell abnormality Low immunoglobulins Impaired specific antibody production	1. Myocbacterial and Viral prophylaxis 2. IVIG 3. HSCT
Ectodermal dysplasia with immunodeficiency (AD)	AD	IKBA	Defective NF-κB activation downstream of TLR and other immunoreceptors due to gain of function alteration in IκBα	Pyogenic bacterial infection, mycobacteria, and Anhidrotic ectodermal dysplasia	Same as for NEMO, except sequencing of IKBA	1. Bacterial prophylaxis 2. IVIG 3. HSCT

assay to measure the production of proinflammatory cytokines after exposure of PBMC to TLR ligands. Therapy includes prompt antimicrobial treatment of infections as well as antibiotic prophylaxis and IVIG therapy. Other deficiencies of TLR are less intuitive biologically, but important nonetheless. These include TLR3 and UNC93B deficiencies, which result in a susceptibility to herpes simplex virus encephalitis.

NF-κB essential modulator (*NEMO*) *and the inhibitor of NF-κB-α* (*IκBα*) *deficiency* can result in *anhidrotic ectodermal dysplasia with immunodeficiency* (EDA-ID), interfering with the signaling downstream of most TLRs. Thus, patients share much of the infectious susceptibility associated with IRAK-4 and MyD88 deficiency. These patients, however, also have signals interrupted downstream of other important immunological receptors and thus have a broader immunodeficiency syndrome; they are frequently infected with atypical mycobacteria, pneumocystis, and DNA viruses. A majority of patients will have the EDA-ID phenotype, but many will not, and the diagnosis should not be excluded on that basis alone. Diagnosis can be suspected by identifying a combined immunodeficiency, which in most cases will include a demonstrable impairment of TLR function and can be confirmed by direct gene sequencing. NEMO deficiency is X-linked recessive and IκBα is autosomal dominant. Treatment includes immunoglobulin replacement therapy, prophylactic antibiotics and HSCT has been curative for some, but not all patients.

Complement Deficiency

Complement deficiencies comprise approximately 2% of all primary immunodeficiencies. Deficiencies of almost all soluble complement components have been described and the most common are of C2 and C9. *Deficiency of the early classical complement pathway components* usually present with susceptibility to bacterial infection and autoimmunity (including systemic lupus erythematosus, polymyositis, and vasculitis). *Terminal complement component deficiencies* present with increased susceptibility to Niesserial infections and recurrent disease is characteristic. Thus, meningococcal vaccination and antibiotic prophylaxis is essential. Diagnostic assessments can include a total hemolytic complement of the classical (CH50) and alternative (AH50) pathways for screening for defects in the complement system. Both will be abnormal in deficiencies of terminal complement components. The levels of individual complement components can also be measured directly or functionally.

Hereditary angioedema (*HAE*) is an unusual deficiency of the C1 esterase inhibitor, which presents with angioedema, but not with increased risk of infections. HAE is diagnosed by the presence of significant angioedema, depressed C4 levels, and absent C1 esterase inhibitor. It is treated by replacement of C1 esterase inhibitor for prevention and treatment of attacks. Therapeutic androgens can increase the level of functioning C1 esterase inhibitor and can be used for the prevention of exacerbations.

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124 Humoral Immune Defect

Mark Ballow · Brian Safier

Early B-Cell Differentiation Defects

Definition/Classification

These defects disturb the maturation of the B-cell lineage, and result in agammaglobulinemia. B-cell development is arrested at the level of the pro-B-cell or early pre-B-cell stage (*Table 124.1*).

Etiology

This category of B-cell defects results from gene mutations associated with X-linked or autosomal recessive inheritance, or sporadic genetic mutation: X-linked agammaglobulinema (XLA) and various autosomal recessive forms of agammaglobulinemia, including mutations affecting the Ig μ heavy chain, the Igα (CD79A) component, the adaptor protein BLNK (B-cell linker protein), and the λ5/14.1 surrogate light chain (*IGLL1*). One third to one half of XLA cases are sporadic.

Epidemiology

The estimated minimal birth rate of XLA in the USA is 1:379,000 total births per year, or 1:190,000 male births per year. The mean age at diagnosis of patients with sporadic XLA is 35 months old. Most patients with familial XLA are diagnosed before the age of 2 months. XLA represents approximately 85% of early B-cell differentiation defects. Defects in μ heavy chain are the most common of the autosomal recessive agammaglobulinemias. The mean age at diagnosis for patients with μ heavy chain defects is 11 months old.

Pathogenesis

Mutation in Bruton's tyrosine kinase (Btk) is X-linked; the *BTK* gene maps to the mid-portion of the long arm of the X-chromosome at Xq21.2-22.2. Btk is expressed at all stages of B-cell development but is down-regulated in plasma cells. Btk is required for B-cell receptor signaling. The pre-B-cell receptor consists of the μ heavy chain, surrogate light chain (Vpre-B and λ5/14.1), and transmembrane signal transduction components Igα and Igβ. Mutation of these structures follows an autosomal recessive inheritance pattern, and manifests with a phenotype similar to XLA (Vpre-B mutations have not been identified in patients with agammaglobulinemia). Pre-B-cell receptor expression and signaling is necessary for positive selection of B-cells, prevention of apoptosis, and progression of B-cell development. Gene mutations in BLNK, necessary for receptor signaling, also block B-cell differentiation (*Fig. 124.1*).

Pathology

The lymphoid tissues (e.g., adenoids, lymph nodes, tonsils, and spleen) are absent or markedly hypoplastic.

Clinical Manifestations: Symptoms and Signs

The onset of recurrent bacterial infection is typically during the latter part of the first year of life, when maternal antibodies are reduced below protective levels. However, a significant number of patients may present at 3–5 years of age (10–20%), and may present even later in life as misdiagnosed common variable immunodeficiency (CVID). The sinopulmonary tract is a frequent site of infection (60% of patients). Other types of infection include gastroenteritis (35%), pyoderma (25%), meningoencephalitis (16%), septicemia (10%), chronic conjunctivitis (8%), and osteomyelitis (3%). *S. pneumonia* and *H. influenzae* are commonly associated with these infections. Poorly treated pulmonary infections eventually lead to bronchiectasis. Chronic lung disease is one of the most common complications of XLA, and may be seen without an overt case of acute pneumonia. Patients with XLA are not at increased risk of viral infection, fungal infection, or

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Table 124.1
Early B-cell differentiation defects

Disease	Laboratory features	Clinical features	Gene defects
X-linked agammaglobulinemia	• B-cells <2% of lymphocytes • Agammaglobulinemia or severe hypogamaglobulinemia • Poor specific antibody responses • Absent isohemagglutinins	• Absent/hypoplastic lymphoid tissue • Recurrent and severe bacterial infection • Enteroviral infection • Chronic lung disease • Increased malignancy risk	• *BTK*
Autosomal recessive agammaglobulinemias	• Same as XLA	• Same as XLA, with earlier onset and more severe complications	• μ heavy chain, Igα, Igβ, BLNK, λ5 (*IGLL1*)

tuberculosis, because cellular immunity is intact. Exceptions to this include viral hepatitis; enteroviral infections such as polio (vaccine-associated poliomyelitis may occur), echovirus, or coxsackievirus; and chronic enteroviral meningoencephalitis.

Repeated bacterial infections of susceptible target organs, such as the middle ear, sinuses, and lungs, lead to positive physical findings of active inflammation, with eventual scarring or damage to the site. Infections caused by enteroviruses or *Ureaplasma urealyticum* may cause arthritis. Enteroviruses may also cause a dermatomyositis-like syndrome. Gastroenteritis is not uncommon, and may be caused by *Giardia lamblia*, *Campylobacter* species, or rotavirus.

Patients with autosomal recessive agammaglobulinemia have an earlier onset of disease compared with patients with XLA, and they are more likely to have severe complications.

Diagnosis

Definitive diagnosis of XLA requires that a male patient have less than 2% mature B-cells (CD19+ B-cells), and at least one of the following: mutation in Btk; absent Btk mRNA on Northern blot analysis of neutrophils or monocytes; absent Btk protein in monocytes or platelets (Western blot or flow cytometry); maternal cousins, uncles, or nephews with less than 2% CD19+ B-cells.

Diagnosis is likely in a male patient with less than 2% CD19+ B-cells in whom all of the following are positive: onset of recurrent bacterial infections in the first 5 years of life; serum IgG, IgM, and IgA more than 2 SD below normal for age; absent isohemagglutinins and/or poor response to vaccines; other causes of hypogammaglobulinemia have been excluded.

If a mutation in Btk is not identified and findings are consistent with a diagnosis of XLA, it may be worthwhile to screen for defects in the components of the pre-B-cell receptor complex, or B-cell signaling pathway, e.g., Igα and Igβ, and BLNK.

Differential Diagnosis

Other causes for severe hypogammaglobulinemia. Myelodysplasia, including those with monosomy 7, trisomy 8, or dyskeratosis congenita.

Treatment

Aggressive treatment of acute or chronic infections is essential. Patients should be treated with replacement doses of IgG immunoglobulin, intravenous (IVIG) or subcutaneous (SCIG), to obtain serum IgG levels of >750 mg/dL. Infections are usually well controlled on IVIG. However, the use of prophylactic antibiotics may be needed. Live viral vaccines are contraindicated. Disseminated enteroviral infections have been treated with high doses of IVIG.

Prognosis

Prognosis is variable depending on the disease. Some patients have life-threatening or fatal infections in the first year of life. With early diagnosis and appropriate treatment with IVIG most patients live into adulthood. Nevertheless, mortality rates can be as high as 30% over 10

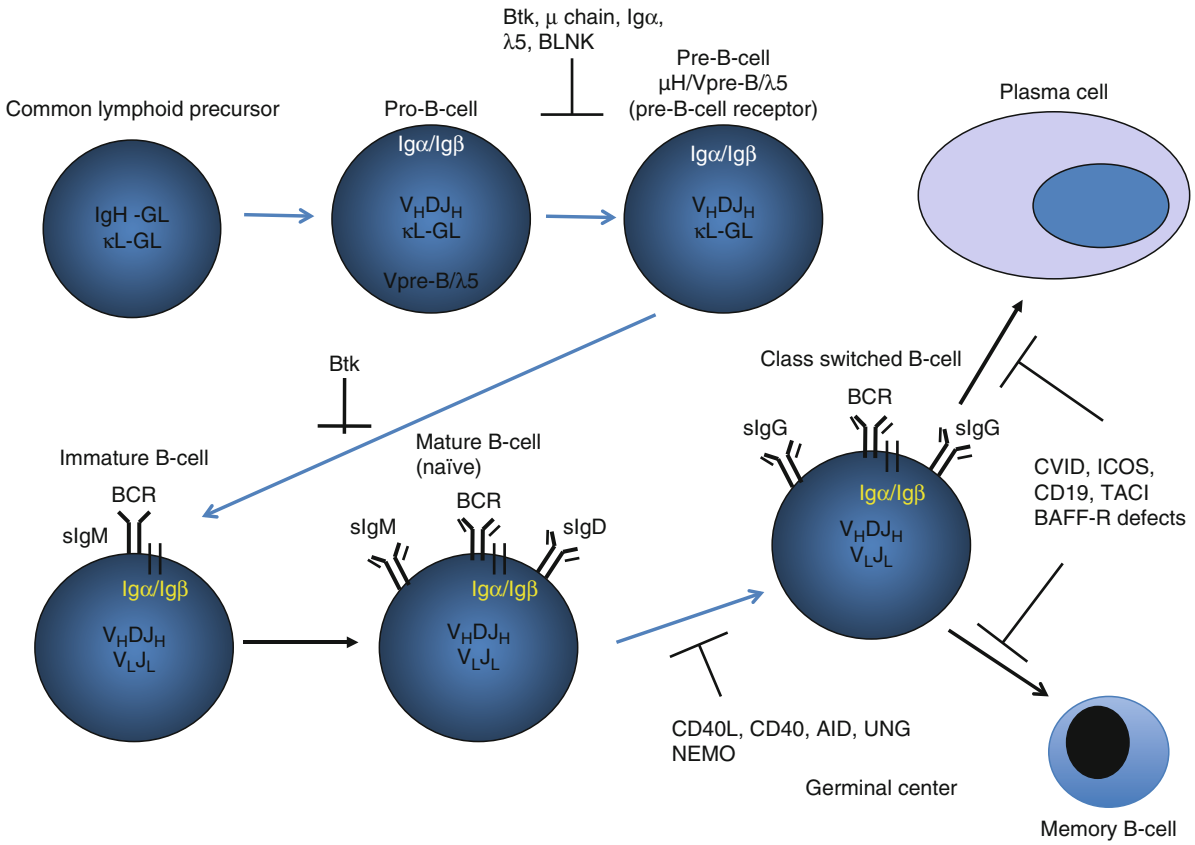

Figure 124.1

Common lymphoid precursor cells give rise to pro-B-cells, in which the germline heavy chain genes (IgH-GL) undergo rearrangement of their immunoglobulin heavy-chain gene segments ($V(D)J_H$). Subsequently, the immunoglobulin heavy-chain gene segments join with the surrogate light chain gene products (Vpre-B/λ5) to form the pre-B-cell receptor (μH/Vpre-B) with Igα and Igβ, cytoplasmic signaling molecules. The immunoglobulin light-chain genes in the germ line configuration (kL-GL) undergo rearrangement to complete the formation of a functional IgM B-cell receptor on immature B-cells. Engagement of the B-cell receptor on immature B-cells results in the proliferation and differentiation of these immature B-cells with class switch recombination and somatic hypermutation leading to antibody secreting plasma cells and long-lived memory B-cells. Genetic mutations have been identified to cause disruption at distinct junctures of this developmental process, as indicated in the figure above. Defects in the genes encoding Btk, μ heavy chain, Igα, λ5 surrogate light chain, and BLNK lead to a block in the generation of pre-B-cells. Gene mutations in CD40L, CD40 receptor, AID, UNG, and NEMO lead to abnormalities in class switch recombination and somatic hypermutation. Gene defects associated with ICOS, CD19, TACI, and BAFF-R are associated with abnormalities in terminal B-cell differentiation. *AID* activation-induced cytidine deaminase, *BAFF-R* B-cell activating factor receptor, *BCR* B-cell receptor, *BLNK* B-cell linker, *Btk* Bruton's tyrosine kinase, *CD40L* CD40 ligand, *CVID* common variable immunodeficiency, *ICOS* inducible T-cell co-stimulator, *NEMO* nuclear factor κB essential modulator, *TACI* transmembrane activator and calcium-modulating cyclophilin-ligand interactor, *UNG* uracil *N*-glycosylase

years even with comprehensive care. Lung complications are the most common issue especially with undertreatment with replacement IVIG. XLA patients have an increased incidence of lymphoreticular malignancies of 0.5–6%.

Prevention

Early diagnosis and proper treatment may prevent some infectious complications. Maternal and family testing with genetic counseling is important.

Late B-Cell Differentiation Defects

Definition/Classification

These defects involve processes of late B-cell differentiation and interfere with the development of properly functioning memory B-cells and plasma cells. This category of B-cell defects includes common variable immunodeficiency (CVID) and selective IgA deficiency (IgAD) (Table 124.2).

Etiology

Approximately 10–20% of CVID and IgAD are inherited, and the pattern of inheritance is variable. Familial studies suggest an allelic relationship between IgAD and CVID. In some patients, IgAD may be the early manifestation of CVID.

Epidemiology

CVID is the most common symptomatic primary immunodeficiency, with an estimated incidence in Europe and North America between 1:10,000 and 1:50,000. CVID is rare among Asians and blacks. With CVID, the mean age of onset of symptoms lies in the third decade of life and the age at diagnosis in the fourth decade of life. The variable in CVID denotes variability in the age at presentation (e.g., early childhood, adolescence, or as young adults) and variability in the degree and type of hypogammaglobulinemia. There is no gender predisposition.

The prevalence of selective IgA deficiency is estimated to be 1:400 to 1:3,000. The frequency is significantly lower in Japanese and Chinese populations. It is the most common form of primary immunodeficiency.

Pathogenesis

CVID is a heterogeneous group of disorders involving both B-cell and T-cell immune function, the predominant manifestation of which is hypogammaglobulinemia. Serum Ig levels are markedly diminished but are usually higher than those found in XLA. There can be tremendous variability in the degree of hypogammaglobulinemia; any or all isotypes of Ig can be affected. Specific antibodies are absent or reduced, and isohemagglutinin titers are usually diminished. The proportions of circulating B-cells in the peripheral blood are usually normal, but a subset of CVID patients may have very low circulating B-cells. T-cell function can be variable. Approximately half of the patients have absent delayed skin hypersensitivity to recall antigens, low numbers of circulating T-cells, and depressed in vitro responses to mitogens and specific antigens.

Several mechanisms have been proposed to explain the immune abnormalities in patients with CVID, including an intrinsic B-cell defect, excessive T-suppresser cell activity, deficient T-cell helper function, cytokine deficiencies, suboptimal T-cell–B-cell interactions through deficient expression of the CD40 ligand, and defects of antigen-

Table 124.2
Late B-cell differentiation defects

Disease	Laboratory features	Clinical features	Gene defects
CVID	• IgG, and IgA or IgM >2 SD below mean for age • Poor specific antibody responses • Absent isohemagglutinins • B-cell numbers usually normal; reduction in memory B-cells • T-cell function variable	• Sinopulmonary infection with encapsulated pathogens • Bronchiectasis • Autoimmune disease • Malignancy –lymphoma and gastric • Liver disease • Gastrointestinal disease-infection, NLH, granulomas, IBD • Granulomatous inflammation	• ICOS, TACI (TNFRSF13B), CD19, BAFF-R (TNFRSF13C), MSH5 • Mostly unknown
IgA deficiency	• IgA <7mg/dL • Normal IgM and IgG • Normal specific antibody responses • Normal B-cell numbers	• Mostly asymptomatic • Sinopulmonary and gastrointestinal disease • Autoimmunity • Atopy	• TACI, MSH5 • Mostly unknown

NLH nodular lymphoid hyperplasia, *IBD* inflammatory bowel disease

presenting cells. Studies have demonstrated each of these immune dysregulations independently.

Approximately 10–20% of CVID is familial, with the majority of these cases being transmitted in an autosomal dominant manner with variable penetrance; approximately 10–20% is inherited in an autosomal recessive fashion. Most of these families have members affected by CVID, selective IgA deficiency, or intermediate states of humoral immunodeficiency. Family members of patients with CVID also have an unusually high incidence of autoimmunity and malignancy. Genetic linkage studies have identified genetic susceptibility loci near the HLA region on chromosomes 6, 4q, and 16q, though responsible genes within these regions have yet to be identified.

Mutations in several genes have been implicated in contributing to the CVID phenotype, including *ICOS*, *TNFRSF13B* (encoding TACI), *CD19*, and *TNFRSF13C* (encoding BAFF-R). Polymorphism in the encoding gene for a repair protein involved in class switch recombination (*MSH5*) has been associated with IgA deficiency and CVID.

With IgA deficiency peripheral blood B-cells co-express IgA, IgM, and IgD, similar to IgA-bearing B-cells found in cord blood. However, these cells fail to mature into IgA-secreting plasma cells. The pathogenesis of IgA deficiency is unknown, although abnormalities in Ig class switching and the cytokines involved in isotype switching have been implicated. IgA deficiency shares with CVID the inheritance of a restricted MHC extended haplotype, and may share a common cause with CVID since these two disorders share many immune aspects. Mutations in TACI and polymorphisms in the gene encoding Msh5 have been identified in patients with IgAD, further supporting the link between IgAD and CVID. However, T- and B-lymphocyte subpopulations and activation/differentiation markers differ significantly between the two entities (*Fig. 124.1*).

Pathology

Hypertrophy of lymphoid tissues, including peripheral lymph nodes, the spleen, and occasionally the liver, are frequently seen. Secondary neutropenia or thrombocytopenia may result from the hepatosplenomegaly.

Clinical Manifestations

CVID patients most frequently have sinopulmonary tract infection. The most common pathogens are encapsulated bacteria such as *H. influenza*, *S. penumoniae*, and *M. catharralis*. Recurrent pneumonia often results in bronchiectasis, as well as lung fibrosis and emphysema, though pneumonia occurs frequently before the diagnosis of CVID and subsequent initiation of replacement IVIG. Despite appropriate treatment, chronic lung disease, e.g., bronchiectasis is among the most common causes of morbidity and mortality in these patients. Infrequently, patients may have recurrent *Herpes zoster* and infections with *Mycoplasma* spp. which is often associated with arthritis. Chronic CNS infections with enteroviruses are found in patients with CVID, though less commonly than with XLA. Opportunistic infections are rare.

Gastrointestinal disease is present in approximately 21% of CVID patients, presenting with malabsorption, weight loss, and chronic diarrhea. Lactose intolerance, celiac disease, protein-losing enteropathy, or superimposed infection of the small bowel with *Campylobacter*, *Salmonella*, or *Yersinia* species or the parasite *Giardia lamblia* contribute to the gastrointestinal symptoms. Atrophic gastritis with achlorhydria may lead to pernicious anemia. Nodular lymphoid hyperplasia (e.g., hypertrophy of the Peyer's patches in the small bowel), diffuse lymphoid infiltration, and loss of villi are characteristic in patients with CVID.

Autoimmune disorders occur in approximately 22% of patients with CVID and include rheumatoid arthritis and seronegative arthritis; autoimmune hematologic disorders, such as hemolytic anemia, idiopathic thrombocytopenic purpura, and pernicious anemia; autoimmune neurologic diseases, such as Guillain-Barré syndrome; chronic active hepatitis often related to hepatitis C virus; autoimmune endocrinopathies, particularly involving the thyroid; and vasculitides. More commonly seen in CVID patients with autoimmune disorders, though not exclusively, are noncaseating granulomatous lesions infiltrating organs such as the liver, lymph nodes, lungs, and skin. These lesions are often confused with sarcoidosis.

The incidence of malignancy is increased (11–13%) in CVID during the fifth and sixth decades of life. The majority of these malignancies involve the gastrointestinal tract and the lymphoid tissues. As many as one third of CVID patients will develop a nonmalignant lymphoproliferative disease.

Up to 90% of individuals with IgA deficiency are clinically asymptomatic. IgAD patients with compensatory increase in secretory monomeric IgM in their upper respiratory tract secretions and gastrointestinal fluids tend to be less symptomatic. IgAD patients with more severe and recurrent sinopulmonary infection tend to have an associated IgG2/IgG4 or IgG4 subclass deficiency.

Patients with symptoms have sinopulmonary infections and involvement of the gastrointestinal tract with giardiasis and nodular lymphoid hyperplasia. An increased frequency of autoimmune disorders has also been associated with IgA deficiency, including arthritis, a lupus-like illness, autoimmune endocrinopathies, chronic active hepatitis, ulcerative colitis, Crohn's disease, a sprue-like disease, and autoimmune hematologic disorders. IgAD is also strongly associated with atopy.

IgAD may be found in association with other immune abnormalities, including ataxia-telangiectasia. It may also occur in association with the administration of drugs, such as phenytoin, sulfasalazine, hydroxychloroquine, and D-penicillamine. IgAD has been described in association with a number of chromosomal abnormalities, especially on chromosome 18.

Diagnosis

CVID requires a reduction, at least two standard deviations below normal, in two immunoglobulin isotypes: IgG and IgA or IgM, an onset of immunodeficiency after the age of 2 years, and absent isohemagglutinins and/or defective vaccination responses. IgA deficiency is defined as a patient greater than 4 years of age who has a serum IgA of less than 7mg/dL with normal serum IgM and IgG levels. Both IgA subclasses, IgA1 and IgA2, are usually markedly reduced or absent, although isolated deficiencies have been described. Other causes of hypogammaglobulinemia must be excluded. Patients with IgA deficiency have a normal IgG antibody response to vaccination.

Differential Diagnosis

Excessive loss of immunoglobulins (e.g., nephrosis, protein-losing enteropathy, severe burns)
Hypercatabolism of immunoglobulin (e.g., proximal myotonic myopathy)
Malignancy (e.g., chronic lymphocytic leukemia, Good's syndrome, non-Hodgkin's B-cell lymphoma, myeloma)
Drug-induced (anticonvulsants, gold salts, glucocorticoids, δ-penicillamine, antimalarial agents, methotrexate)
Infectious disease (e.g., Epstein-Barr virus, HIV, and congenital rubella, CMV, Chlamydia, mycoplasma, HSV, cytomegalovirus, or *Toxoplasma gondii*)
X-linked agammaglobulinemia
Hyper-IgM syndromes
Ataxia-telangiectasia
Late-onset adenosine deaminase deficiency
Atypical forms of severe combined immunodeficiency
X-linked lymphoproliferative disorder (Epstein-Barr virus-associated)
Warts, hypogammaglobulinemia, infections, and myelokathexis syndrome
Immunodeficiency, centromeric instability, and facial anomalies
Chromosomal anomalies (e.g., chromosome 18q syndrome, monosomy 22, trisomy 8, trisomy 21)
Vitamin B12 deficiency

Treatment

Replacement immunoglobulin (IgG) therapy with IVIG is key in the prevention of recurrent and chronic lung infections. Close monitoring and aggressive treatment of acute or chronic infections are essential with antibiotic therapy for breakthrough infections, and treatment of associated disease complications and sequelae. Additionally, prophylactic antibiotics may be considered in select patients.

Replacement immunoglobulin therapy is generally not indicated in IgA deficiency. Prophylactic antibiotics are indicated for patients with recurrent infection. In symptomatic patients with IgAD and IgG subclass deficiency immunoglobulin replacement must be used with caution. IgAD patients with IgA levels less than 7 mg/dL are at risk for developing anti-IgA antibodies on receipt of blood products, including immunoglobulin replacement. Medic-Alert bracelets may be useful with these patients.

Complete blood count with differential, a comprehensive metabolic panel, serum immunoglobulins, and pulmonary function tests should be obtained every 6–12 months. Chest computed tomography should be done at diagnosis, and periodically thereafter to monitor for bronchiectasis.

Prognosis

In CVID, lower levels of IgG at the time of diagnosis and poor T-cell function are associated with an earlier age of death. The 20-year survival rate after diagnosis is approximately 65–67%, which when compared to the general population is about 30% lower.

The prognosis for IgAD patients is usually not associated with a shortened life expectancy. Rare instances of disease resolution have been observed, particularly in young patients. A small percentage of patients evolve into CVID.

Prevention

Early diagnosis and proper treatment may prevent complications of infection and associated conditions.

Class Switch Defects and Defects of Somatic Hypermutation

Definition/Classification

These defects involve defects in the ability of the B-cell to undergo isotype switching, e.g., from IgM to IgG, IgA or IgE, and/or increase antigen specificity through somatic hypermutation. This category of B-cell defects includes the hyper-IgM syndromes (HIGM1-4) and gene mutations associated with impaired nuclear factor (NF) κB activation (Table 124.3).

Etiology

HIGM1 (or X-linked HIGM) is caused by defects in CD40 ligand (CD40L/*TNFSF5*). Autosomal recessive forms include HIGM2 which is the result of defects in activation-induced cytidine deaminase (*AID*) gene (HIGM2), or uracil N-glycosylase (*UNG*) gene (HIGM4); and absence of CD40 receptor on B-cells (HIGM3; *TNFRSF5*). HIGM4 (UNG deficiency) is downstream of AID activity, and is characterized by defective class switch recombination with preserved somatic hypermutation. Other similar entities in clinical phenotype, e.g., normal or elevated IgM with low serum IgG and IgA, include defects in nuclear factor-κB essential modulator (NEMO, also known as IKK-γ gene (*IKBKG*)) that is present on the X-chromosome, or gene mutations in IκBα (*NFKBIA*). Many of these patients also have ectodermal dysplasia and dyshidrosis.

Epidemiology

These groups of patients are very rare, and are usually associated with consanguineous families. The prevalence of HIGM is estimated to be approximately 1:500,000 in the Caucasian population, and represents between 0.3% and 2.9% of all patients with primary immunodeficiency in registries from Europe, Asia, and South America. The estimated minimal incidence of HIGM1 in the USA is 1:1,030,000, which represents two thirds of all HIGM

Table 124.3
Class switch defects and defects of somatic hypermutation

Disease	Laboratory features	Clinical features	Gene defects
HIGM1	• Normal or elevated IgM with IgA and IgG >2 SD below mean for age • Normal T-cell number, abnormal function • Normal or elevated B-cell number • Poor specific antibody responses • Neutropenia in 50%	• Recurrent bacterial infection of sinopulmonary and gastrointestinal tracts • Opportunistic infection, particularly *P. jiroveci* • Sclerosing cholangitis • Parvovirus-induced aplastic anemia • Autoimmunity and malignancy	• CD40L (*TNFSF5)*
HIGM2	• Normal or elevated IgM with IgA and IgG >2 SD below mean for age • Normal B-cell number • Poor specific antibody responses	• Recurrent bacterial infection of sinopulmonary and gastrointestinal tracts • Lymphoid hyperplasia (large germinal centers)	• *AID*
HIGM3	• Normal or elevated IgM with IgA and IgG >2 SD below mean for age • Normal T-cell number, abnormal function • Poor specific antibody responses	• Recurrent bacterial infection of sinopulmonary and gastrointestinal tracts • Opportunistic infection, particularly *P. jiroveci* • Lymphoid hypoplasia	• CD40 (*TNFRSF5)*
HIGM4	• Normal or elevated IgM with IgA and IgG >2 SD below mean for age • Poor specific antibody responses	• Recurrent bacterial infection of sinopulmonary and gastrointestinal tracts • Lymphoid hyperplasia	• *UNG*
NEMO defect	• Normal or elevated IgM with IgA and IgG >2 SD below mean for age • Impaired NK cell function and Toll-like receptor signaling	• Hypohydrotic ectodermal dysplasia • Pyogenic bacterial infection • Herpes, CMV, and HPV infection • Atypical mycobacterial infection	• IKBKG (NEMO) • NFKBIA (IκBα)

patients; more than half of these patients are diagnosed by 1 year of age, and almost all by 4 years of age. HIGM2 is typically diagnosed in the second or third decade of life. The mean age at diagnosis for HIGM4 is 8.8 years old. 55–65% of HIGM patients are male.

Pathogenesis

Appropriate interaction between CD40L on the activated T-cell and CD40 constitutively expressed on the B-cell is essential for switching of IgM to another Ig isotype. AID is only present on activated B-cells, and is one of the enzymes triggered by CD40 engagement and activation. The role of AID is to deaminate DNA cysteine to uracil with subsequent initiation of a base excision repair process. UNG removes uracil to form abasic sites allowing for cleavage at these DNA sites and eventual class switching. These components are also all essential for somatic hypermutation which is the process of genetic alteration that allows for the development and selection of antibodies with increased affinity for antigen. The result is patients with normal or elevated levels of IgM, with decreased IgG, IgA, and IgE, and generally low antibody affinity for antigen.

IKBKG (NEMO) and *NFKBIA* (IκBα) mutations cause abnormal activation of NFκB. NFκB affects AID and UNG transcription; therefore some of these patients have decreased class switching and somatic hypermutation, leading to the observed increase in IgM levels. With *IKKG* mutation, there is abnormal toll-like receptor signaling (including lipopolysaccharides responses), deficient production of antibody specific for carbohydrate antigens, variable degrees of total antibody deficiency, and defective NK cell function. *NFKBIA* mutation is associated with T-cell deficiency (Fig. 124.1).

Pathology

The patients with autosomal recessive inheritance of hyper-IgM syndrome have enlarged secondary lymphoid tissues, and show marked follicular hyperplasia with abnormally large germinal centers. In contrast, patients with the x-linked form of hyper-IgM syndrome have no germinal centers in their lymph nodes.

Clinical Manifestations

HIGM patients are characterized by severe recurrent bacterial infections, particularly of the sinopulmonary and gastrointestinal tracts. HIGM1 and HIGM3 patients are susceptible to opportunistic infections, especially for pneumonia caused by *Pneumocystis jiroveci*. This is due to defective T-cell CD40L interaction with CD40 on monocytes/dendritic cells, resulting in abnormal cellular immune responses. HIGM2 and HIGM4 patients are not susceptible to opportunistic infections and typically present later in childhood. Liver disease is common in HIGM1, and is often associated with *Cryptosporidium* or CMV infection. HIGM1 is also associated with autoimmune disease and malignancy (particularly gastrointestinal, hepatic and biliary). Neutropenia is common (50%) in HIGM1.

NEMO mutations cause a variable clinical phenotype of hypohydrotic ectodermal dysplasia and immunodeficiency including susceptibility to pyogenic bacterial infection in early childhood, atypical mycobacterial infections in early or late childhood, and viral infection, particularly herpesviruses, CMV, and human papilloma virus.

Diagnosis

Diagnosis of HIGM1 is definitive in a male patient with serum IgG concentration at least 2 SD below normal for age and one of the following: mutation in the CD40L gene; maternal cousins, uncles, or nephews with confirmed diagnosis of HIGM1. Diagnosis is likely in a male patient with a serum IgG concentration at least 2 SD below normal for age and all of the following: normal number of T-cells and normal T-cell proliferation to mitogens; normal or elevated numbers of B-cells but no antigen-specific IgG antibody; absent CD40 ligand cell surface staining on activated CD4+ T-cells as assessed by binding to soluble CD40 or by binding of monoclonal antibody to CD40 ligand; one or more of the following infections or complications: recurrent bacterial infections in the first 5 years of life, *P. jiroveci* infection in the first year of life, neutropenia, cryptosporidium-related diarrhea, sclerosing cholangitis, parvovirus-induced aplastic anemia.

Other forms are diagnosed based on normal or elevated IgM with IgA and IgG levels at least two SD below normal, and normal numbers of B-cells (some HIGM4 patients have decreased memory B-cells). Diagnosis is confirmed using flow cytometry and/or mutational analysis.

Patients with NEMO have impaired NK cell function, and Toll-like receptor signaling is impaired in the majority of patients.

Differential Diagnosis

X-Linked agammaglobulinemia
Common variable immunodeficiency
Transient hypogammaglobulinemia of infancy
Severe combined immunodeficiency
Secondary causes of agammaglobulinemia, e.g., congenital rubella

Treatment

These patients require replacement immunoglobulin therapy, but this does not decrease susceptibility to opportunistic infections. Therefore, the use of prophylactic antibiotics for *P. jiroveci* is indicated for HIGM1 and HIGM3 patients. G-CSF may be necessary to treat neutropenia in HIGM1 and HIGM3 patients. Bone marrow transplant may be considered in HIGM1 patients $\leq$8 years old without serious infection if an optimal donor is available. Prevention of *Cryptosporidium* infection using boiled or filtered water is recommended. Baseline and follow-up pulmonary function tests, chest and sinus X-Rays or CT scans, CBC, and CMP are important.

For patients with NEMO, antibacterial, antimycobacterial, and antiviral prophylaxis should be considered.

Prognosis

The most common cause of death in HIGM1 patients is opportunistic infection, followed by liver disease and malignancy. A European study suggests that only 20% survive past 25 years of age.

Prevention

Early diagnosis and proper treatment may prevent complications of infection and associated conditions.

B-Cell Defects of Unknown Etiology

Definition/Classification

B-cell immunodeficiency of unknown etiology. This group of B-cell abnormalities includes transient hypogammaglobulinemia of infancy (THI), IgG subclass deficiencies, and selective antibody deficiency (*Table 124.4*).

Epidemiology

An exact incidence of these disorders is not known. These conditions are rarely familial and are more common in males.

Clinical Manifestations

THI is an exaggeration and prolongation of the normal physiologic hypogammaglobulinemia that occurs between 2 and 4 months of age, which may persist to age 3–5 years.

Table 124.4
B-cell defects of unknown etiology

Disease	Laboratory features	Clinical features	Gene defects
Transient hypogammaglobulinemia of infancy	• Low IgG levels +/−low IgA and/or IgM • Normal antibody responses to protein antigens • Viral respiratory antigen antibody response may be reduced	• Recurrent upper respiratory tract infection • Hematologic abnormalities (e.g., neutropenia) • Atopy	• Unknown
IgG subclass deficiency	• Reduced >2 SD below mean for age • Normal total IgG • May have poor specific antibody responses, especially to polysaccharide antigens	• Recurrent respiratory tract infection • Atopy • Autoimmunity • Associated with IgA deficiency and ataxia-telangiectasia	• Unknown
Selective antibody deficiency	• Normal serum Ig and IgG subclass levels • Abnormal response to immunization with unconjugated polysaccharide vaccine	• Recurrent sinopulmonary infection	• Unknown

Patients may have recurrent upper respiratory infections, including otitis media, sinusitis, and less commonly, pneumonia. Often, hematologic abnormalities are present, most notably neutropenia. Less frequently, gastroenteritis and failure to thrive occur in this patient population. There is an increased incidence of atopy in this patient population.

IgG subclass deficiency is defined as low serum levels of one or more IgG subclasses (more than 2 SD below normal serum levels for age). However, even healthy individuals without recurrent infection can have low IgG subclass levels. Some immunologists question whether the entity represents a true immunodeficiency disease. However, IgG subclass deficiency has been associated with recurrent respiratory tract infection, bacterial and viral. Symptomatic IgG2 subclass-deficient patients typically have infections with *H. influenza* or *S. pneumoniae*, and most are unable to produce specific antibodies after immunization with unconjugated polysaccharide antigens (e.g., Pneumovax). The authors believe that this entity is a developmental immune delay since most of these children eventually stop having recurrent infections and are able to produce specific antibodies to polysaccharide antigens. IgG2 subclass deficiency is the most common subclass deficiency in children, whereas in adults IgG3 subclass deficiency is the most common. IgG subclass deficiency may be seen in conjunction with other primary immune deficiency disorders, such as ataxia-telangiectasia and IgA deficiency. Atopy and autoimmunity are frequent in patients with IgG subclass deficiency.

Selective antibody deficiency is defined by normal serum immunoglobulins but poor ability to make specific antibodies to polysaccharide encapsulated bacterial antigens. Patients have recurrent sinopulmonary infections. Most of these patients are between 3 and 6 years of age, possibly reflecting a maturational delay of the humoral immune system.

Diagnosis

THI is best defined as low levels of IgG, with or without depression of IgA and/or IgM, in a child older than 6 months of age in which other primary immune deficiencies have been excluded. Antibody responses to protein antigens are normal, but may be reduced to viral respiratory antigens.

IgG subclass deficiency is defined as the presence of one or more IgG subclasses more than 2 SD below the mean with normal total IgG levels, in a patient with recurrent infections and a significant defect in antibody responsiveness.

Selective antibody deficiency is defined as normal serum Ig and IgG subclass levels with abnormal response to immunization with unconjugated polysaccharides, such as Hib capsular antigen, or to pneumococcal polysaccharide antigens.

Differential Diagnosis

Primary and secondary causes of hypogammaglobulinemia
CVID
Protein losing enteropathy or nephropathy

Treatment

For each of these entities, Ig levels, including IgG subclasses, and antibody responses should be evaluated every 6–12 months to monitor for disease resolution or progression to other immunodeficiencies, such as CVID. Chest and sinus radiographs or CT scan may also be indicated.

Patients with recurrent infections may be treated with prophylactic antibiotics. Immunoglobulin replacement therapy is typically not indicated but may be considered if recurrent infection is poorly controlled with antibiotics. For patients with selective antibody deficiency and recurrent acute sinusitis, immunization with conjugate vaccines to Hib or pneumococcal polysaccharide can be helpful in decreasing the frequency of infection including booster vaccination after the primary conjugate series has been administered. This is because antibody responses to conjugate polysaccharide vaccine tend to fall within the IgG1 subclass instead of the IgG2 subclass.

Prognosis

THI is a self-limited disorder with no long-term sequelae.

Most IgG subclass deficiency patients do well with appropriate supportive therapy and prophylactic antibiotics. Children under 10 years of age may recover spontaneously, whereas adults may progress to CVID. Children with selective antibody deficiency usually recover over time. Those who do not recover may develop CVID. Adults are more likely to have this condition indefinitely.

Prevention

Early diagnosis and proper treatment may prevent complications of infection and associated conditions.

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Web Links for Families and Healthcare Professionals

www.primaryimmune.org, through which physicians may get a free immunology consult via email or phone

www.jmfworld.org – Jeffrey Modell Foundation – the ten warning signs of primary immune deficiency

125 T-Cell Immune Defects

Evelina Mazzolari · Luigi D. Notarangelo

T-cell immunodeficiency comprises a heterogeneous group of disorders with impaired development and/or function of T lymphocytes (◉ *Fig. 125.1*). The thymus is the primary lymphoid organs where development of T lymphocytes takes place, starting from a common lymphoid progenitor that originates from a bone-marow-derived hematopoietic stem cell. Within the thymus, several differentiation steps mark progressive maturation of thymocytes, and ultimately lead to generation of mature naïve T lymphocytes. The earliest stages of T-cell development are characterized by lack of CD4 and CD8 expression (double negative T cells). This is followed by co-expression of CD4 and CD8 molecules, along with expression of the T-cell receptor (TCR), at the double-positive (DP) stage of T-cell differentiation. Expression of the TCR enables positive selection of thymocytes in the thymic cortex, followed by further differentiation into single positive (SP) CD4 or CD8 thymocytes that migrate to the thymic medulla, where negative selection of self-reactive T cells takes place. Eventually, mature naïve T lymphocytes leave the thymus and reach the periphery, where they colonize the lymph nodes, the spleen, and patrol the skin, the mucosa, and peripheral tissues.

Development of T lymphocytes is under strict genetic control. Sigle-gene disorders that affect the early stages in T-cell development (up to DP stage of differentiation) are associated with Severe Combined Immune Deficiency (SCID), with lack of circulating T lymphocytes. Some of these genetic disorders may also compromise development of B and/or NK lymphocytes. Defects that affect later stages in T-cell development and/or function are also known as Combined Immune Deficiencies (CID), and are characterized by the presence of a variable number of circulating T lymphocytes. Finally, defects in the ontogeny of the thymus also compromise development of T lymphocytes. DiGeorge syndrome represents the prototype of such conditions. In this chapter, we will review the clinical features, pathophysiology, diagnostic approach, and treatment to human T-cell immunodeficiencies.

Severe Combined Immunodeficiencies (SCID)

Clinical Presentation

SCID include a heterogeneous group of genetic disorders characterized by inability to generate mature T lymphocytes. While some of these defects also affect development of B and/or NK lymphocytes, all forms of SCID are characterized by impaired humoral immunity, due to the lack of helper T-cell activity. Hence, the clinical presentation of SCID is marked by early onset and severe infections of bacterial, viral, or fungal origin. Opportunistic infections are very common. Interstitial pneumonia is very frequent and may be due to *P. jiroveci*, cytomegalovirus (CMV), adenovirus, parainfluenza 3, and respiratory syncitial virus (RSV). Chronic diarrhea typically leads to failure to thrive. Persistent candidiasis is also common. Typically, infections develop already in the first months of life, reflecting the essential role of T lymphocytes in mediating and orchestrating pathogen-specific immune responses. The early onset and the severity of infections in infants with SCID mark a clear difference vs. pure antibody deficiencies, whose clinical manifestations most often consist of recurrent bacterial infections, that tend to become more prominent when maternally derived immunoglobulins have disappeared. Skin manifestations (maculopapular rash, erythroderma, alopecia) may also be observed in patients with SCID, and often represent manifestations of immune dysregulation due to infiltration by maternal T lymphocytes that have engrafted into the fetus, or the presence of a residual number of autologous and activated T lymphocytes. Infants with SCID typically have hypoplastic lymphoid tissue (tonsils, lymph nodes), and absence of a thymic shadow can be demonstrated on chest X-ray. Additional features are characteristically associated with specific forms of SCID. For instance, microcephaly is present in most infants with SCID due to defects in DNA repair. Sensorineural deafness is observed in infants with reticular dysgenesis, but may also be present in patients with adenosine deaminase

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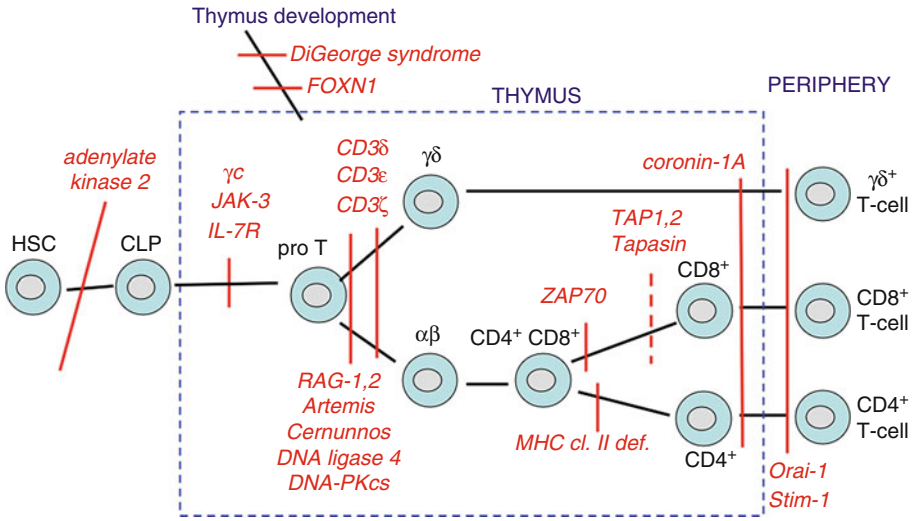

Figure 125.1

Schematic representation of defects along human T-cell development that cause SCID or other severe T-cell immunodeficiencies. Red lines identify specific blocks in development, and the genes involved are annotated. HSE: hematopoietic stem cell; CLP: common lymphoid progenitor

(ADA) deficiency. Progressive neurological deterioration is often seen in patients with purine nucleoside phosphorylase (PNP) deficiency, and neurobehavioral problems are common also in ADA deficiency. ADA-deficient patients also often have flaring of the ribs at chest X-ray.

Pathogenesis and Genetics

SCID comprise a heterogeneous group of mendelian disorders, and their overall prevalence is estimated to be 1:50,000 to 1:100,000 births, with significant geographic variability. In Western countries, the most common form of SCID is inherited as an X-linked trait; however, a variety of autosomal recessive (AR) forms are also known. AR-SCID are more common in countries with higher consanguinity rate or among restricted ethnic groups.

The pathophysiology of the various forms of SCID reflects distinct defects in critical steps along T-cell development. In some cases, these defects may also involve additional blood lineages, including B and/or NK lymphocytes or myeloid cells, or may affect non-hematopoietic cells as well.

Increased apoptosis of lymphoid precursors is observed in reticular dysgenesis (RD), ADA deficiency, and PNP deficiency, three autosomal recessive forms of SCID. RD is due to mutations of the *AK2* gene, encoding for adenylate kinase 2. This defect is associated with perturbed homeostasis of ADP and ATP levels in mitochondria, resulting in increased cell death. The defect is not restricted to T lymphocytes, but also involves myeloid neutrophil progenitors and the inner ear, accounting for severe neutropenia and sensorineural deafness.

ADA and PNP are two enzymes of the purine salvage pathway. ADA converts adenosine (Ado) and deoxy-adenosine (dAdo) into inosine and deoxy-inosine, respectively. In the absence of ADA, high intracellular levels of Ado, dAdo, and their toxic phosphorylated metabolites cause apoptosis of lymphoid precursors, and hence result in the virtual absence of T lymphocytes that is usually associated with marked reduction of B and NK lymphocytes ($T^-B^-NK^-$ SCID). PNP catalyzes the phosphorylation of inosine, guanosine, and deoxyguanosine. In the absence of PNP, high intracellular levels of dGTP cause lymphoid and neuronal toxicity. Immature thymocytes are particularly susceptible to PNP deficiency. Accordingly, the immunological phenotype of PNP deficiency is characterized by decreased T-cell counts, whereas B and NK lymphocytes are often unaffected. Both ADA and PNP deficiency have extraimmune manifestations, reflecting the ubiquitous expression of these genes.

Interleukin-7 (IL-7)-mediated signaling plays a critical role in the expansion of early thymocyte progenitors, which express IL-7 receptor (IL-7R), composed of an IL-7R α chain and a common γ chain (γc), also shared by

receptors for IL-2, IL-4, IL-9, IL-15, and IL-21. In all of these receptors, the γc is coupled to the intracellular tyrosine kinase JAK3. In humans, defects of IL-7-mediated signaling abrogate T-cell development, whereas impaired signaling through IL-15R affects development of NK cells. X-linked SCID, due to *IL2RG* mutations, represents approximately 40% of all cases of SCID, and is characterized by lack of T and NK lymphocytes but normal development of B cells ($T^-B^+NK^-$ SCID). B lymphocyte function, however, is severely compromised by both the lack of T-cell help and γc. JAK3 deficiency is inherited as an autosomal recessive trait, and its phenotype is identical to that of X-linked SCID ($T^-B^+NK^-$ SCID). In contrast, autosomal recessive IL7R deficiency due to mutation of the α chain is characterized by the selective lack of T cells ($T^-B^+NK^+$ SCID).

Expression of the pre-T-cell receptor (pre-TCR), which is composed of a pre-Tα chain, a TCR β chain, and the CD3 γ,δ,ε, and ζ chains, marks the next step in T-cell development. Signaling through the pre-TCR permits rearrangement of the TCRα chain and expression of a mature TCRαβ. Alternatively, thymocytes may express the γδ chains of the TCR. Signaling through the TCR is essential for positive selection of cortical thymocytes. Defects in the mechanisms of assembly and signaling of the pre-TCR and TCR complexes result in SCID in humans. Rearrangement of the TCR loci is accomplished by means of the V(D)J recombination, whereby the lymphoid specific RAG1 and RAG2 proteins mediate DNA cleavage at the Variable (V), Diversity (D), and Joining (J) elements of the TCR loci. DNA Double Strand Breaks (DSB) at the coding ends are initially sealed as a hairpin, which are then resolved by Artemis (encoded by the *DCLRE1C* gene). Eventually, sealing of coding and signal joins is mediated by the Ku70/80 heterodimer, XRCC4, DNA ligase IV (LIG4), DNA-Protein Kinase catalystic subunit (DNA-PKcs), and Cernunnos/XLF. The V(D)J recombination process is essential not only in T cell development, but also for B cell development, where it mediates rearrangement at the immunoglobulin heavy and light chain loci. Hence, defects in any of the steps of the V(D)J recombination process cause $T^-B^-NK^+$ SCID. RAG1 or RAG2 deficiencies are the most common V(D)J recombination defect and account for about 10% of all forms of SCID. Defects in Artemis, DNA-PKcs, LIG4, and Cernunnos/XLF are less frequent. Importantly, while expression of the *RAG1* and *RAG2* genes is restricted to lymphocytes, Artemis, DNA-PJcs, LIG4, and Cernunnos/XLF are ubiquitously expressed and mediate nonhomologous end joining (NHEJ) DNA repair. Accordingly, deficiency in any of these proteins is associated with increased cellular radiosensitivity and extraimmune clinical manifestations (microcephaly, growth and developmental defects, increased risk of malignancies).

The CD3 δ,ε, or ζ chains represent the signaling elements of the pre-TCR and of the TCR. Defects in these molecules cause autosomal recessive $T^-B^+NK^+$ SCID. In contrast, CD3γ deficiency is associated with mild T-cell lymphopenia and a variable clinical phenotype.

CD45 is a tyrosine phosphatase that is also involved in signaling through the TCR and the B-cell receptor (BCR). CD45 deficiency has been reported in few patients with $T^-B^+NK^+$ SCID.

Diagnostic Approach

Diagnosis of SCID is based on clinical and family history and on typical laboratory features. Presentation early in life with severe infections, especially if sustained by opportunistic pathogens, should always prompt to consider SCID as a possible diagnosis. Family history should be addressed to document other male subjects on the maternal side who presented and/or died with severe infections early in life (suggestive of a possible X-linked form of the disease) or the presence of parental consanguinity (indicative of possible autosomal recessive inheritance). Laboratory investigation should be primarily based on careful evaluation of the absolute lymphocyte count (ALC), and values should be compared with age-matched controls. The vast majority of infants with SCID present with severe lymphopenia. If the ALC is $<2{,}000/mm^3$, analysis of lymphocyte subsets should be immediately performed. Typically, infants with SCID have markedly reduced or absent circulating T cells. Depending on whether the development of B and/or NK lymphocytes is also affected, SCID can be classified into distinct immunological phenotypes: (a) $T^-B^+NK^-$ SCID (the most common variant), (b) $T^-B^+NK^+$ SCID, (c) $T^-B^-NK^+$ SCID, or (d) $T^-B^-NK^-$ SCID. These different immunological phenotypes reflect distinct genetic defects (*Table 125.1*) and thus may guide in the molecular diagnosis. However, a normal ALC does not rule out SCID, if suggestive clinical features are present. In particular, subnormal or even normal ALC in SCID may reflect maternal T-cell engraftment, a phenomenon observed in more than 50% of infants with SCID. Most often asymptomatic, it may cause skin rash or, less frequently, typical graft-versus-host disease (GvHD) with generalized rash, liver disease, profuse diarrhea, jaundice, and cytopenias (thrombocytopenia, anemia, leukopenia) due to bone

Table 125.1
Molecular basis of SCID, divided by immunological phenotype

Immunological phenotype	Underlying molecular defect	Inheritance
$T^- B^+ NK^-$	IL2RG (γc)	XL
	JAK3	AR
$T^- B^+ NK^+$	IL7R	AR
	CD3D	AR
	CD3E	AR
	CD3Z	AR
	CD45	AR
$T^- B^- NK^+$	RAG1	AR
	RAG2	AR
	Artemis	AR
	LIG4	AR
	DNA-PKcs	AR
	XLF	AR
$T^- B^- NK^-$	ADA	AR
	AK2	AR

XL: X-linked; AR: autosomal recessive

marrow damage. The presence of detectable T lymphocytes in peripheral blood in infants with SCID may also reflect hypomorphic mutations or somatic reversions in SCID-causing genes, which allow for residual development of autologous T cells, resulting in a "leaky" SCID phenotype. Characteristically, maternally engrafted T lymphocytes in patients with SCID, and autologous T cells in patients with leaky SCID, express the CD45R0 memory/activation antigen on their membrane, whereas most T cells in normal infants have a naive $CD45RA^+$ phenotype. Furthermore, autologous activated T cells in infants with leaky SCID have a restricted TCR repertoire, as indicated by expression of a limited set of TCR Vβ families with a restricted diversity of CDR3 length. Lymphocytes from SCID infants fail to proliferate in vitro to mitogens and specific antigens. Patients with PNP deficiency often show progressive decline of T lymphocyte number and function, and are at increased risk for autoimmune hemolytic anemia. Ineffective thymopoiesis in patients with SCID is also marked by very low or undetectable levels of T-cell receptor excision circles (TRECs) in circulating lymphocytes. TRECs are a by-product of V(D)J recombination that consist of circularized signal joins and are maintained in newly generated mature T lymphocytes that leave the thymus. Because TRECs cannot be detected in infants with SCID, assessment of TREC levels by polymerase chain reaction has been proposed for newborn screening for SCID.

Regardless of the presence or absence of circulating B lymphocytes, patients with SCID show hypogammaglobulinemia. However, normal IgG levels may be observed early in life, reflecting transplacental passage of maternal immunoglobulins. Specific antibody responses to immunization antigens are abolished. However, humoral immunity may be spared in patients with PNP deficiency.

Eosinophilia and elevated IgE levels are common, especially in patients with leaky SCID, whereas infections may associate with anemia, thrombocytopenia, and/or neutropenia. Bone marrow dysplastic changes may be observed, especially in patients with Cernunnos/XLF or with LIG4 deficiencies.

Differential diagnosis of SCID includes secondary forms of immunodeficiencies, especially HIV infection. Congenital rubella or CMV infections, severe malnutrition, and defects of vitamin B12 and folate metabolism may also mimic the SCID phenotype.

Treatment

SCID are inevitably and rapidly fatal unless immune reconstitution is attained by means of treatment. Treatment of active infections and initiation of appropriate laboratory testing should be immediately performed in infants with possible SCID. *P. jiroveci* pneumonia is usually treated with high-dose intravenous sulfamethoxazol/trimethoprim (20 mg/kg). CMV or adenoviral infections must be treated with gancyclovir or cidofovir, respectively. Administration of antitubercular Bacillus Calmette-Guerin (BCG) immunization at birth carries risk of BCGosis, and should prompt treatment with isoniazid and rifampicin, regardless of the presence of clinical signs of infection. Regular use of intravenous immunoglobulins and antimicrobial prophylaxis are part of the mainstay of therapy. Enteral or parenteral nutrition may be required in infants with chronic diarrhea and malnourishment.

Live-attenuated vaccines should not be administered to infants with SCID because of the risk of disseminated infection due to vaccine strain (59–61). All blood products should be irradiated to avoid fatal transfusional graft-versus-host disease (GvHD):

Ultimately, survival of SCID infants depends on attainment of robust immune reconstitution. Hematopoietic cell transplantation is the treatment of choice, and was successfully used for the first time in humans in a patient

with X-linked SCID. Excellent results, with >90% long-term survival, have been obtained with HCT from HLA-identical family donors, with no need of pre-transplant chemotherapy. However, this option is available only to 15–20% of patients. Excellent results without chemotherapy have been reported also after haploidentical transplantation, if performed in the neonatal period or in the first 3.5 months of life; however, survival is only 50–65% if haploidentical HCT is performed at a later age. Promising results have been reported with HCT from matched unrelated donors (MUD) and unrelated cord blood (UCB). Although graft rejection should not be possible in infants with SCID (making the use of pre-transplant chemotherapy not necessary), engraftment and immune reconstitution are problematic in recipients of haploidentical HCT, especially for $T^-B^-NK^+$ SCID, ADA deficiency, and reticular dysgenesis. Furthermore, B-cell reconstitution may not be achieved, unless pre-transplant conditioning that favors engraftment of donor stem cells is used.

Most patients with SCID enjoy good quality of life after transplant, however infections, autoimmune/inflammatory complications, and GvHD are observed in a significant fraction of patients. ADA or PNP deficiency and SCID with increased cellular radiosensitivity are at particularly higher risk for these complications, and for neurological and developmental problems, even if successful T-cell reconstitution is achieved.

For patients with ADA deficiency, an alternative form of treatment is represented by enzyme replacement therapy with weekly intramuscular injections of pegylated bovine ADA, although T-cell counts often remain low, in spite of successful detoxication.

Gene therapy has led to immune reconstitution in infants with X-linked SCID or with ADA deficiency; however, 5 out of 20 patients with X-linked SCID treated by gene therapy have developed leukemic proliferation due to insertional mutagenesis.

Other Combined Immunodeficiencies

Combined immune deficiencies (CID) include disorders with residual ability to support T-cell development and/or function. They may be due to either: (a) hypomorphic mutations in SCID-causing genes that allow for some T-cell development or (b) genetic defects that affect late stages in T-cell development or peripheral T-cell function. The clinical features of CID overlap with SCID, but also include autoimmunity and/or inflammatory manifestations reflecting unbalanced immune homeostasis.

Omenn Syndrome

Omenn syndrome (OS) is characterized by severe infections associated with early-onset generalized skin rash/erythroderma, alopecia, lymphadenopathy, hepatosplenomegaly, eosinophilia, and oligoclonal expansion of anergic, activated autologous T lymphocytes that infiltrate and damage target tissues. Serum immunoglobulins are usually very low, but IgE levels are increased. Hypoproteinemia is common, leading to edema. OS is associated with hypomorphic mutations in SCID-causing genes that allow for residual T-cell development. The few T cells that are generated in the thymus undergo extensive homeostatic proliferation in the periphery. Poor thymopoiesis in OS causes abnormalities of thymic stroma, with impairment in the mechanisms of negative selection of autoreactive T cells and of generation of regulatory T cells. These abnormalities contribute to the immunopathology of OS. Mutations in *RAG1* and *RAG2* are the most common genetic defect in OS; however, mutations in *DCLRE1C* (Artemis), *IL7R*, *LIG4*, *RMRP*, *IL-2RG*, *ADA*, and *ZAP70* have been also reported.

Patients with OS have a variable number of circulating T lymphocytes that carry a characteristic activated/memory ($CD45R0^+$) phenotype and have a restricted repertoire. The distribution of CD4 and CD8 subsets is generally skewed. The in vitro lymphocyte response to antigens is abolished; responses to mitogens are variable, but are often reduced. Depending on the nature of the underlying genetic defect, B and NK lymphocytes may be absent or present.

Differential diagnosis includes maternal T-cell engraftment and complete atypical DiGeorge syndrome. HCT represents the mainstay of treatment. In preparation for HCT, aggressive treatment of infection, nutritional support, correction of hypoproteinemia, and immune suppression with steroids and/or cyclosporine A to control extensive T-cell-mediated tissue damage are necessary.

ZAP-70 Deficiency

The Zeta-associated protein of 70 kDa (ZAP-70) is an intracellular kinase that is involved in TCR-mediated signaling. In humans, mutations of the *ZAP70* gene result in autosomal recessive CID with selective deficiency of CD8+ T cells. $CD4^+$ lymphocytes are present, but are functionally impaired. Variable defects have been reported in immunoglobulin levels and antibody responses. Clinical features do not differ from what observed in

SCID, however lymph nodes are palpable, and the thymus can be visualized by chest X-ray.

Differential diagnosis includes MHC class I deficiency and CD8α deficiency, two conditions also characterized by a severe reduction of $CD8^+$ lymphocytes (110, 111). The only curative treatment of ZAP-70 deficiency is HCT.

MHC Class I Deficiency

MHC class I deficiency is an autosomal recessive disorder, characterized by reduced expression of MHC class I molecules at the cell surface. It is caused by defects in the *TAP1* (112), *TAP2* (113), or Tapasin (114) genes, which encode for molecules involved in intracellular loading of peptide antigens MHC class I molecules, and cell surface expression of the complex.

Patients with MHC class I deficiency suffer from recurrent respiratory infections, chronic inflammatory lung disease, and skin lesions that resemble Wegener's granulomatosis. The number of circulating $CD8^+$ T cells is reduced because positive selection of $CD8^+$ lymphocytes in the thymus depends on the recognition of MHC class I molecules. In vitro lymphocyte proliferation is normal, facilitating differential diagnosis with ZAP-70 deficiency, and accounting for a less severe clinical phenotype. Levels of serum immunoglobulin may be variable.

Antibiotic prophylaxis to prevent recurrent respiratory infections, and topical treatment of the cutaneous granulomatous lesions, are the mainstay of treatment.

MHC Class II Deficiency

MHC class II molecules are constitutively expressed by B lymphocytes, monocytes, and dendritic cells, but may also be expressed by other cells (T lymphocytes, endothelial and certain epithelial cells) upon activation. Recognition of MHC class II molecules in the thymus promotes positive selection of $CD4^+$ thymocytes. In the periphery, recognition of antigens in the context of MHC class II molecules is essential to elicit $CD4^+$ T-cell-mediated responses.

MHC class II deficiency is inherited as an autosomal recessive trait and is caused by mutations in any of four different genes (*CIITA*, *RFXANK*, *RFX5*, and *RFXAP*) that encode for transcription factors that control MHC class II genes expression.

The clinical phenotype is marked by increased susceptibility to bacterial, viral, and opportunistic respiratory tract infections; chronic diarrhea; and sclerosing cholangitis, often secondary to *Cryptosporidium* or CMV infection. However, less severe presentations and survival into adulthood have been also reported.

The number of circulating $CD4^+$ T cells is markedly reduced, reflecting an impairment of positive selection in the thymus. Delayed-type hypersensitivity responses are absent, but in vitro proliferative responses to mitogens are preserved. Hypogammaglobulinemia and poor antibody response to immunization are also present. Differential diagnoses include HIV infection and idiopathic CD4 lymphopenia. Both these conditions are characterized by a reduced number of circulating $CD4^+$ lymphocytes; however, expression of MHC class II molecules is preserved.

Most patients with MHC class II deficiency die in their first years of life of severe infections. Antibiotic prophylaxis, immunoglobulin replacement therapy, and adequate nutritional support are an important part of treatment, but definitive cure can be only achieved with HCT. However, the results of HCT for this disease are far less satisfactory than in other forms of severe T-cell immunodeficiency.

Defects of Thymocyte Egress and of Lymphocyte Activation

Once they have completed their intrathymic maturation, T lymphocytes are exported to the periphery. This process requires active cytoskeleton reorganization. Coronin 1A is an actin regulator that plays a key role in regulating thymocytes egress and trafficking of naïve T lymphocytes to secondary lymphoid organs. Coronin 1A mutations have been shown to cause peripheral T-cell lymphopenia and severe and recurrent infections. The disease can be cured by HCT.

In the periphery, activation of T lymphocytes requires mobilization of intracellular calcium stores and influx of extracellular calcium across calcium-release activation channels (CRACs). Mutations of Orai1 (a component of CRAC channels) and of Stim1 (a sensor of Ca^{2+} concentration in the endoplasmic reticulum) have been identified in patients whose clinical features resembled SCID, associated with non progressive myopathy autoimmune cytopenias. In these patients, the number of circulating T lymphocytes is normal, but in vitro proliferation to mitogens is drastically decreased. The disease is fatal, unless immune reconstitution is achieved following HCT. However, myopathy persists.

Defects of Thymic Development

DiGeorge Syndrome

The DiGeorge Syndrome (DGS) is a disorder caused by impaired migration of neural crest cells of the third and fourth pharyngeal arches during early embryonic development. This abnormality causes impaired formation of the thymus and of the parathyroid glands, defects of the aortic arch, and facial dysmorphisms. However, significant variability of the clinical phenotype, and especially of the immunological phenotype, can be observed. Neonatal hypocalcemia is characteristic and reflects hypoparathyroidism. Approximately 80% of infants with DGS require calcium supplementation and/or treatment with calcitriol; however, hypoparathyroidism often resolves during the first year of life due to hypertrophy of residual parathyroid tissue. Cardiac malformations affect the outflow tract in particular. Interrupted aortic arch, Fallot's tetralogy, and truncus arteriosus are particularly common. Facial dysmorphisms include low-set ears with abnormal folding of the pinna, short nasal philtrum, and micrognathia. Velopharyngeal insufficiency is also very common. Feeding difficulties, mostly due to esophageal dysmotility and gastroesophageal reflux, may represent a significant concern. Laryngomalacia and aspiration pneumonia are common. During adult life, psychiatric and behavioral problems have been frequently diagnosed.

The immunodeficiency is an important component of DGS, but its severity is variable. Most patients present with *partial DiGeorge syndrome*, characterized by mild to moderate immune deficiency, with a low but detectable number of circulating T lymphocytes. The *complete DiGeorge syndrome* phenotype consists of congenital cardiac defects, hypocalcemia due to parathyroid insufficiency, and profound T-cell immune deficiency as a consequence of thymic aplasia. Finally, a few patients with DGS may present with an atypical phenotype characterized by a pronounced erythematous rash and lymphadenopathy, associated with oligoclonal, activated, and anergic T cells. This phenotype, which mimics Omenn syndrome, is also known as *complete atypical DiGeorge syndrome*. The different degrees of immunological impairment in patients with DGS dictate the spectrum of clinical manifestations related to immune dysfunction. Oral thrush and recurrent infections are common; however, patients with complete and atypical complete DGS suffer from early onset and severe infections (*P. jiroveci* pneumonia, interstitial pneumonia, or disseminated infections of viral origin) and warrant immediate attention. Autoimmune manifestations are also relatively common in patients with DGS.

DGS may be sustained by different mechanisms. Hemizygous deletion of chromosome 22q11.2 accounts for DGS in 55–65% of the patients. CHARGE association is responsible for about 25% of the cases of DGS, whereas diabetic embryopathy and monosomy of chromosome 10p have been documented in 15% and 2% of the patients, respectively. The 22q11.2 region contains the TBX1 gene that encodes for a transcription factor; isolated mutations of this gene have been identified in a few patients with DGS.

Diagnosis of DGS is based on typical clinical features, and should not be restricted to patients with 22q11 deletion, that can be demonstrated by FISH. ALC and enumeration of CD3 count is important to define the degree of immunological impairment. In most cases, variable CD3 lymphopenia is documented; however, a severe deficiency of circulating T cells is typical of complete DGS. The total CD3 count can be normal in patients with atypical complete DGS, but in these cases the circulating CD3+ T cells co-express activation (CD45R0, DR, CD25) antigens, there are very few if any recent thymic emigrants ($CD4^+$ $CD45RA^+$ $CD31^+$) in the peripheray, and the TCR repertoire of circulating T cells is severely restricted. In vitro proliferative responses are most often normal in patients with partial DGS, but are significantly reduced in the most severe cases. Most patients with DGS have normal immunoglobulin levels and antibody responses; however, impairment of humoral immunity can be also observed. Treatment of DGS consists of correction of congenital heart defects, when present, and of hypocalcemia. Depending on the severity of the immune deficiency, patients may require antibiotic prophylaxis; IVIG replacement therapy may be needed in selected cases. However, complete DGS (including atypical presentation) is associated with a very high mortality rate early in life. In such cases, survival strictly depends on immune reconstitution. Thymic transplantation is the treatment of choice. The thymus, usually obtained from infants undergoing partial thymectomy at the time of heart surgery, is sliced, cultured, and then implanted in the quadriceps muscle. T cells develop approximately 4–5 months after thymic transplantation in patients with complete DGS, and 1-year survival is close to 75%. Patients with complete atypical DGS often require immune suppression prior to thymic transplantation, to control the effects of activated and oligoclonal T cells. Unmanipulated bone marrow transpplantation from HLA-identical related donors has been also used with success in infants with complete DGS; in these cases, long-term immune reconstitution has been

provided by mature T cells contained in the graft, which have expanded and persisted for up to 20 years.

FOXN1 Deficiency

The transcription factor FOXN1 is essential to promote differentiation of thymic epithelial cells. In mice, Foxn1 mutations are associated with the nude/scid phenotype, with lack of circulating T cells and of hair. Mutations of the FOXN1 gene have been identified in Italian siblings who presented with severe infections, alopecia, and nail dystrophy. One of the affected siblings also showed features of Omenn syndrome. The immunological phenotype consisted of T-cell lymphopenia that involved predominantly the $CD4^+$ subset. Immune reconstitution was obtained in one of the siblings following unmanipulated bone marrow transplantation from her healthy HLA-matched brother.

Conclusions

Irrespective of the specific diagnosis, all forms of T-cell immunodeficiencies are characterized by significant morbidity and some of them also by high early-onset mortality rates, thus emphasizing the critical role played by T lymphocytes in ensuring effective immune defense mechanisms and in maintaining homeostasis. Therefore, accurate clinical and laboratory evaluation are critically important in patients with a putative T-cell immunodeficiency. Whereas the clinical and family history and physical examination may disclose the diagnosis in some forms of T-cell immunodeficiency, laboratory evaluation is most often required to provide a definitive diagnosis. Simple laboratory assays (total lymphocyte count and subsets distribution, in vitro proliferative responses) are usually sufficient to confirm the suspicion. Some forms of T-cell immunodeficiencies, and SCID in particular, represent true medical emergencies that warrant prompt and accurate evaluation and early treatment by HCT.

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On-Line Resources for Parents

For SCID: http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=syndromes&area=6&CFID=2813523&CFTOKEN=3

For DiGeorge Syndrome

http://www.info4pi.org/aboutPI/index.cfm?section=aboutPI&content=syndromes&area=3&CFID=2813523&CFTOKEN=3

On-Line Resources for Professionals

http://www.usidnet.org/

http://www.esid.org

126 Immune Dysregulation Disorders

Thomas A. Fleisher

Appropriate activation of the immune system in response to a microorganism is an absolute requirement for normal host defense. However, down regulation following an appropriate immune response is also an essential process to insure that the host does not suffer unnecessary and/or protracted inflammation and its consequences. In addition, normal homeostasis also requires the immune system develops in such a manner that it is not directly reactive against self. These processes fall under the general concept of immune homeostasis and include control mechanisms that prevent immunologic responses to self as well as control the extent of immune activation. Central to the prevention of auto-reactivity is a complex set of processes referred to as immunologic tolerance. These involve central tolerance that occurs in primary lymphoid organs (thymus, bone marrow) resulting in the eliminatation of self-reactive cells and peripheral mechanisms that maintain immunologic tolerance at the site of immunologic reactions. It is now clear that this homeostatic or regulatory side of the immune system is also subject to congenital defects that result in immune dysregulation disorders and these are typically accompanied by autoimmunity with or without increased susceptibility to infection. These "experiments of nature" represent prototypic disorders that provide important insights into mechanisms required for tolerance and the control of immune responses. In this chapter, congenital disorders that impact central deletion of autoreactive T cells in the thymus as well as those that impact other mechanisms involved in the maintenance of tolerance in the periphery will be discussed. In all of these disorders the clinical phenotype includes autoimmunity together with other manifestations of immune dysfunction.

Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy (APECED)

APECED (OMIM #240300) is a rare, autosomal recessive disorder of defective central immune tolerance that is found disproportionately in individuals with Finish, Sardinian, and Iranian Jewish backgrounds. It is characterized by systemic autoimmunity that primarily affects endocrine organs, particularly the parathyroid and adrenal glands. Hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis typically characterize the syndrome but patients may also develop type 1 diabetes, gonadal failure, pernicious anemia (secondary to atrophy of gastric parietal cells), autoimmune hepatitis, and other cutaneous manifestations.

Genetics and Immunopathogenesis

APECED is caused by mutations in the gene encoding the autoimmune regulator (AIRE) protein, a transcription factor that plays a role in ectopic expression of tissue-specific antigens expressed by thymic medullary epithelial cells (mTEC). Based on experimental models, this gene appears to play a significant role in facilitating the elimination of autoreactive T cells within the thymus before exit into the peripheral circulation where they could cause autoimmunity. Recent data suggest that AIRE also may play a role in the generation of functional regulatory T (T_{REG}) cells that act as immunologic suppressor cells suggesting that APECED may not only have a defect in central tolerance but also deficient peripheral mechanisms for maintaining tolerance.

Diagnosis and Treatment

APECED should be suspected in patients who have two of the following three primary symptoms: hypoparathyroidism (typically presenting as hypocalcemia), adrenal insufficiency, and mucocutaneous candidiasis. Suspicion is raised further by the presence of other autoimmune manifestations including diabetes, gonadal insufficiency, hepatitis, and pernicious anemia. There are no specific standard diagnostic lab tests and the definitive diagnosis can only be made by sequencing the *AIRE* gene.

Therapy for APECED is generally focused on symptomatic treatment including calcium supplementation, steroid replacement, as well as management of diabetes and other endocrinopathies. Mucocutaneous candidiasis

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can be a problem in that it often persists and can cause significant morbidity as well as increase the risk of oral malignancies. Over time, the Candidal species may become resistant to azole antifungals, further complicating long-term management. Immunosuppressants are not routinely used in APECED unless patients develop autoimmune hepatitis or renal disease in which case, azathioprine and cyclosporine A have shown benefit. Bone marrow transplantation generally has not been considered for APECED, even in severe cases.

Box 1: Key Concepts

Autoimmune Polyendocrinopathy, Candidiasis, Ectodermal Dystrophy (APECED)

- Hypoparathyroidism, adrenal insufficiency, and chronic mucocutaneous candidiasis typically characterize the syndrome
- Patients may also develop type 1 diabetes, gonadal failure, pernicious anemia, autoimmune hepatitis, and other cutaneous manifestations
- Autoimmunity due to a failure of central tolerance as a result of a defect in the gene encoding the autoimmune regulator (AIRE) protein

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX)

IPEX syndrome (OMIM #304930) is a rare X-linked recessive disorder that presents with a clinical triad including autoimmune enteropathy, early onset endocrinopathy, and dermatitis. The enteropathy typically presents very early in life as watery diarrhea, frequently resulting in malnutrition and failure to thrive. Type I diabetes is the most common endocrinopathy but clinical and/or laboratory evidence of thyroiditis is common as well. Eczema is the most common dermatitis in IPEX but erythroderma, psoriasiform dermatitis, and pemphigoid nodularis have also been observed.

In addition to the "IPEX-triad," most patients with IPEX also have other associated autoimmune disorders including autoimmune hemolytic anemia, thrombocytopenia, neutropenia, nephropathy, or hepatic disease (Torgerson & Ochs, unpublished data). These conditions contribute substantially to the morbidity of patients with IPEX and increase the risk of death from disease. Patients with the classical form of the disease typically die secondary to malnutrition, electrolyte imbalances, or infection before the age of 2 years unless treated with aggressive immunosuppression.

Genetics and Immunopathogenesis

IPEX is caused by mutations in FOXP3, a protein expressed by T_{REG} cells that act to suppress the immune response and in this capacity provide a critical means of maintaining immunologic tolerance in the periphery. Recent studies have demonstrated that FOXP3 is required for T_{REG} cells to develop suppressor function. A great deal of work remains to identify the key FOXP3-regulated gene (or genes) that confers suppressor function on T_{REG} cells.

Diagnosis and Treatment

IPEX is generally suspected in any patient who demonstrates at least two of the three basic clinical features of IPEX including enteropathy, endocrinopathy (type I diabetes or thyroiditis), and dermatitis. Evaluation for the expression of the FOXP3 protein in T_{REG} cells using flow cytometry is a valuable tool to rapidly screen for the absence of T_{REG} cells. Currently, identification of a mutation in *FOXP3* represents the definitive means for establishing the diagnosis of IPEX. This is complicated by the fact that in centers with substantial experience with IPEX, mutations are identified in less than 50% of patients in whom there is a clinical suspicion of disease. Patients with normal *FOXP3* analysis are often categorized as "IPEX-like" and generally have a somewhat less severe clinical phenotype. From a clinical laboratory standpoint, the most consistent abnormality among patients with IPEX is markedly elevated IgE, which is present in the majority of cases while "IPEX-like" patients tend to have normal or minimally elevated IgE levels.

Treatment of IPEX focuses primarily on suppression of the unregulated immune system using cyclosporine A, tacrolimus (FK506), or sirolimus (Rapamycin). These are often combined with steroids and/or other immunomodulatory agents and in cases where there is evidence for pathogenic autoantibodies; Rituximab (anti-CD20) has also proven to be effective in dampening the dysregulated inflammatory response. These therapies are often effective initially but long-term cure is currently only achievable with hematopoietic stem cell transplantation. Rapid diagnosis and transplantation early in the course of disease, before the pancreatic islet cells are destroyed, should be the therapeutic goal in IPEX.

Box 2: Key Concepts

Immune Dysregulation, Polyendocrinopathy, Enteropathy, X-Linked (IPEX)

- Clinical triad of autoimmune enteropathy, early onset endocrinopathy (diabetes and/or thyroid disease), and dermatitis (typically eczema)
- Often also associated with autoimmune hemolytic anemia, thrombocytopenia, neutropenia, nephropathy, or hepatic disease
- Results from a defect in the gene encoding FOXP3 resulting in an absence of T regulatory (T_{REG}) cells
- Highly lethal and hematopoietic stem cell transplantation is currently the only curative therapy

Defects in IL-2 Signaling

Recognition that experimental animals lacking CD25 (the α-chain of the three protein chain high-affinity receptor for IL-2) have a phenotype similar to IPEX raised the possibility that defects in IL-2 signaling in humans might lead to an IPEX-like presentation. This hypothesis is now supported by findings in a small number of patients with defective IL-2 signaling.

CD25 Deficiency

Two unrelated patients with CD25 deficiency (OMIM #606367) have been described. Similar to the clinical manifestations of IPEX, both patients developed severe, chronic diarrhea and villous atrophy in infancy (one at 6 weeks and the other at 8 months of age). One also developed early-onset insulin-dependent diabetes and later developed eczema. Subsequently, both patients developed autoantibodies, hepatosplenomegaly, lymphadenopathy, and lymphocytic infiltrates in various organs (e.g., gut, liver) indicative of ongoing immune dysregulation. In addition to autoimmune features, both CD25-deficient patients had infectious complications including recurrent CMV pneumonitis suggestive of a more extensive defect in cellular immunity that rendered the patients susceptible to opportunistic organisms.

Genetics and Immunopathogenesis

In each case, inheritance was found to be autosomal recessive leading to a complete lack of CD25 protein expression on activated T cells. Animal studies suggest that the failure to express CD25 is associated with a defect in the survival, maintenance, and competitive fitness of mature T_{REG} cells associated with immune dysregulation as well as defects in T cell responsiveness that underlie the immune deficiency that is seen in these very rare patients.

Diagnosis and Treatment

Both patients lacked CD25 expression on T cells suggesting that flow cytometry to evaluate expression of this protein should be an effective screening tool to identify CD25-deficient patients. Sequencing of the *CD25* gene, however, is recommended to confirm the diagnosis. Because of the "severe combined immunodeficiency (SCID)-like" features of this syndrome, one patient underwent a successful hematopoietic stem cell transplant from a matched sibling donor and has done well. It is possible, however, that patients may respond to IL-2 therapy at an appropriately modified dose based on the deficiency of the high-affinity IL-2 receptor although this has not been proven to date.

STAT5b Deficiency

Deficiency of STAT5b (OMIM #245590) causes a rare autosomal recessive disorder reported in only a small number of patients. STAT5b is an intracellular protein that mediates signaling by various growth factors (including cytokines). In this disorder, the most recognizable clinical features are dwarfism, a prominent forehead, a saddle nose, and a high-pitched voice. STAT5b is also critical in mediating the response of T cells to IL-2 so most of these patients also have a marked immunodeficiency similar to SCID, with recurrent Varicella virus, Herpes virus, and *Pneumocystis jiroveci* infections.

In addition to frank immunodeficiency, most patients who lack functional STAT5b also have symptoms suggestive of immune dysregulation including chronic, early onset diarrhea, eczema, and lymphocytic interstitial pneumonitis.

Genetics and Immunopathogenesis

This is an autosomal recessive disorder and patients studied to date have markedly reduced or absent STAT5b expression. In addition, these patients had significantly fewer T_{REG} cells than normal individuals and these cells

failed to demonstrate in vitro suppressive activity suggesting that maintenance of peripheral tolerance is likely abnormal in these patients.

Diagnosis and Treatment

Diagnosis of STAT5b deficiency is suspected in patients with the overt physical features of dwarfism combined with evidence of a significant immunodeficiency. Patients typically have normal serum growth hormone levels but very low insulin-like growth factor-1 (IGF-1) levels. Sequencing of the *STAT5b* gene should be done to confirm the diagnosis.

Treatment of patients with STAT5b deficiency is generally focused on symptomatic therapy and prophylaxis against infections. Hematopoietic stem cell transplantation has not been reported in this disorder although one would predict that the immune deficiency and immune dysregulation would be corrected by this therapy but that the non-immunologic problems would not.

Autoimmune Lymphoproliferative Syndrome (ALPS)

In 1967, Canale and Smith described a group of patients who presented in early childhood with generalized lymphadenopathy and hepatosplenomegaly associated with autoimmune anemia, thrombocytopenia, and increased gammaglobulins. In 1992, patients with similar features were noted to have a marked increase in a unique T cell referred to as an α/β–double-negative T (DNT) cell that normally constitutes a very small proportion of the peripheral lymphocytes. These patients had autoimmunity and lymphadenopathy as noted in the original description together with the expansion of α/β-DNT cells leading to the hypothesis that they had a disorder equivalent to the phenotype of certain murine models of autoimmunity. This led to an extensive evaluation based on the findings in the animal models that revealed an underlying defect in programmed cell death (apoptosis), one mechanism that plays a role in regulating the immune response.

The typical clinical course in ALPS (OMIM #601859) begins within the first 5 years of life with nonmalignant peripheral lymphadenopathy that is often associated with splenomegaly and hypersplenism that may necessitate splenectomy. Clinically apparent autoimmunity most commonly presents as autoimmune hemolytic anemia either alone or together with idiopathic thrombocytopenic purpura (ITP). Some ALPS patients may also develop neutropenia that can be immunologically mediated or secondary to hypersplenism. Dermatologic findings may be seen in ALPS, with urticarial rashes being the most common. Although less common, other autoimmune disorders may be present in ALPS including glomerulonephritis, polyneuropathy, autoimmune hepatitis, and Guillain–Barre syndrome. Perhaps the most life-threatening manifestation of ALPS is the dramatically increased incidence of lymphoma in individuals with *FAS* mutations, with an increased relative risk of 51-fold for Hodgkin disease and 14-fold for non-Hodgkin lymphoma.

Genetic and Immunopathogenesis

The majority (~65%) of ALPS patients have germline heterozygous (single allele) mutations in *FAS* with the site of the mutation having a direct impact on the development of disease manifestation. Recently, somatic mutations in *FAS*, affecting primarily DNT cells with variable presence in other leukocytes have been described in some patients with sporadic ALPS. The current classification scheme for ALPS is:

- ALPS-FAS: germline mutation in the gene encoding Fas *(TNFRSF6)*
- ALPS-sFAS: somatic mutation in the gene encoding Fas
- ALPS-FASLG: mutation in the gene encoding FasL *(TNFSF6)*
- ALPS-CASP10: mutation in the gene encoding caspase 10 *(CASP10)*
- ALPS-U: no known mutation
- RALD (RAS associated autoimmune leukoproliferative disorder): somatic mutation in the genes encoding NRAS (*NRAS*) or KRAS (*KRAS*)

Diagnosis and Treatment

The constellation of clinical and laboratory findings in ALPS patients is rather unique. However, the initial presentation of lymphadenopathy often raises the issue of malignancy that generally requires a biopsy to differentiate between these two diagnoses. The initial findings can also be suggestive of a chronic viral infection such as Epstein–Barr virus (EBV), although there are no serologic studies or in situ hybridization data that support a role for EBV in ALPS. The autoimmunity seen in ALPS patients is most commonly directed against red blood cells and platelets.

The laboratory findings include immunophenotyping that typically reveals peripheral lymphocytosis with expansion of αβ-DNT cells together with other changes in lymphocytes. A polyclonal increase in serum immunoglobulins is seen in virtually all patients. Typically, in the setting of autoimmune hemolytic anemia the direct Coombs' test is positive while autoantibodies directed to platelets and neutrophils are also found but may not directly correlate with the clinical manifestations of thrombocytopenia or neutropenia. Many of the laboratory findings associated with the autoimmunity do not distinguish patients with ALPS from those who do not have this disorder in that there is a broad range of autoantibody specificities observed. Interestingly, serum vitamin B12 levels are elevated in most ALPS patients, for unknown reasons. There also are markedly elevated serum levels of IL-10 and soluble Fas ligand (sFasL) in ALPS patients and these findings appear to correlate best with mutations affecting *FAS*. Finally, the histological findings of the enlarged lymph nodes are unique and typical for ALPS.

The initial diagnostic triad for ALPS was nonmalignant lymphoaccumulation, defective in vitro lymphocyte apoptosis, and increased levels of αβ-DNT cells. Flow cytometric evaluation of peripheral blood lymphocytes is necessary to evaluate increased levels of αβ-DNT cells. The assessment of lymphocyte apoptosis is only available in specialized centers and hence the identification of a disease associated genetic defect is now an alternative disease criteria (see Box 3).

The lymphoid expansion typically diminishes with age; thus, therapy directed at this feature of ALPS is generally not necessary. The finding of splenomegaly is often associated with hypersplenism, and splenectomy has commonly been performed among the ALPS patients referred to our institution. Because overwhelming infection with *Strep. pneumoniae* has been observed in ALPS patients postsplenectomy (perhaps at a higher rate than in other postsplenectomy patients), it is important to provide prophylactic antibiotic and vaccination protection in this setting. The autoimmune cytopenias typically respond to corticosteroids; this therapy is also associated with a decrease in lymphadenopathy but this rapidly reappears after discontinuation of therapy. Exacerbations of ALPS-related thrombocytopenia are not uncommon and these may become resistant to conventional therapy. The response to intravenous immunoglobulin therapy is less satisfactory than in childhood ITP cases. Preliminary data suggest that mycophenolate mofetil may be useful in the treatment of ALPS patients with ITP who are unresponsive to standard therapy. Importantly, the increased risk for the development of lymphoma appears to be lifelong and careful vigilance is required to monitor for this complication in all family members known to have *FAS* mutations.

Box 3: Key Concepts

Autoimmune Lymphoproliferative Syndrome (ALPS)
Required Criteria for Diagnosis

- Nonmalignant lymphadenopathy
- Increased percentage and/or numbers of α/β T cell receptor double-negative T cells

Plus one of the two following criteria:

- Defective in vitro lymphocyte apoptosis
- Identified deleterious mutation in *FAS*, *FASLG* or *CASP10*

Supportive Criteria for Diagnosis

- Elevated serum vitamin B12, IL-10, and/or soluble Fas ligand
- Autoimmune disease (typically autoimmune cytopenias)
- Family history
- Typical histologic findings on lymph node biopsy

Wiskott–Aldrich Syndrome

The Wiskott–Aldrich syndrome (WAS, OMIM 301000) was first described in the 1930s based on a family with multiple males who developed bleeding problems. It is now known to be an X-linked recessive immunodeficiency disease that has a characteristic clinical triad of bleeding associated with microthrombocytopenia, eczema, and increased susceptibility to infection. Microthrombocytopenia refers to the low numbers of platelets that are characteristically small and the immune dysfunction associated with WAS is not only accompanied by recurrent infections but also by a high incidence of autoimmunity and malignancy.

The typical presentation of a patient with WAS begins postpartum with the appearance of petechiae, easy bruising, and bloody diarrhea. In addition, there is typically excessive bleeding in WAS patients who undergo circumcision. Eczema often appears during infancy, is usually persistent and can be very severe. The recurrent infections often start with otitis media and pneumonia involving bacterial agents but over time, opportunistic infections evolve as a clinical problem. Bleeding remains a management issue throughout

a patient's life due to the persistence of microthrombocytopenia. This clinical story together with the laboratory finding of low numbers of small platelets are strongly suggestive for the diagnosis of either WAS or a related disease, X-linked thrombocytopenia (XLT).

Genetic and Immunopathogenesis

The WAS is caused by a mutation in the WAS protein gene (*WASP*) and interestingly defects in this gene have now been associated with four different related diseases: WAS, XLT, intermittent XLT, and X-linked neutropenia (XLN). The WAS protein (WASP) is directly involved in regulating actin polymerization in hematopoietic cells and mutations in *WASP* cause defects in cell signaling, cell locomotion, and immune synapse formation. A general genotype–phenotype relationship has emerged in which mutations that result in WASP absence typically present with WAS, mutations that impair WASP production usually result in XLT, and mutations that occur in one specific site within the gene produce a gain of function mutation that results in XLN. However, the genotype–phenotype relationship is not absolute and clinical findings in the patient dictate the clinical course regardless of the mutation identified.

The immunologic defects involve both the adaptive and innate immune systems. Humoral immunity is abnormal with decreased response to protein and polysaccharide antigens as well as low isohemagglutinin titers together with elevated serum IgE and IgA levels. T cell function is diminished based on ex vivo function testing, reduced T cell numbers, and opportunistic infections. Finally, NK cell function is also decreased when tested ex vivo. In addition to the increased susceptibility to infection, WAS patients have a very high incidence of autoimmunity (40–70% among European and US patients) that include autoimmune hemolytic anemia, vasculitis, arthritis, nephropathy, immune thrombocytopenia, neutropenia, and inflammatory bowel disease. The cytopenias were previously treated with splenectomy but follow-up has determined that this results in a poorer prognosis related to postsplenectomy infectious complications and thus, splenectomy is generally no longer recommended in WAS.

The frequency of malignancies in WAS was 13% in a North American cohort study with an average age at onset of 9.5 years. In this study, the most common malignancy was a B cell lymphoma that often was EBV positive. The outcome in these patients was poor with the majority not surviving beyond 2 years following the tumor diagnosis. Currently, there is no information regarding the risk of malignancy in patients with a *WASP* mutation associated with diagnoses other than WAS (i.e., XLT, XLN).

Diagnosis and Treatment

The diagnosis of WAS should be considered in any male child with bleeding problems that start early in life. The finding of thrombocytopenia with small platelets on the blood smear would be further evidence supporting this diagnosis. A significantly elevated IgE level is typical in WAS but is not a specific finding. A number of other immunologic tests are usually abnormal including lymphocyte proliferation, specific antibody production, and NK cell cytotoxicity. Definitive testing focuses on evaluating for WASP expression and performing mutation analysis for a defect in *WASP* gene.

Conventional management approaches include providing replacement immunoglobulins when there is evidence of abnormalities in specific antibody production. Prophylaxis for *Pneumocystis jirovecci* is also often utilized based on the defective T cell response. It is important to avoid live vaccines in patients with WAS as they are susceptible to infection with the modified vaccine strain virus. Therapy of eczema and autoimmunity should follow the standard approaches used in other patients. It is noteworthy that in the face of a cytopenia, splenectomy should be reserved as a last resort since WAS patients are particularly susceptible to postsplenectomy sepsis. In a situation where a patient is splenectomized, he must be placed on lifelong, appropriate prophylactic antibiotics. Currently, the only curative therapy for WAS is a hematopoietic stem cell transplant. The outcome has been good in settings where there is an HLA matched family, an unrelated matched, or a partially matched cord blood donor but far less satisfactory with a mismatched family donor. There are currently preclinical studies directed at determining the feasibility of gene therapy directed at the patient's hematopoietic stem cell.

Conclusions

In recent years, identification of the gene defects in a handful of clinical syndromes with congenital systemic autoimmunity has led to the definition of a new class of primary immune deficiency in which the defect involves specific features of the regulatory compartment of the immune system. Lessons learned from these disorders

have clarified aspects of thymic selection, T_{REG} function, and Fas-mediated apoptosis. There are a number of unresolved issues that include defining other contributing genetic and/or environmental factors and clarifying the basis for the specific patterns of autoimmunity seen in these disorders and the underlying basis for the marked increase in autoimmunity seen in WAS. In addition, defining the molecular basis that contribute to other findings in these various disorders will further our understanding of the immune system. Certainly, studying these experiments of nature will continue to be a fertile field of investigation over the coming years as we strive to uncover the basic mechanisms of immune homeostasis and immunologic tolerance.

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127 Miscellaneous Immunodeficiencies

Harb A. Harfi

Ataxia-Telangiectasia

This syndrome is characterized by telangiectasia, a progressive ataxia, sinopulmonary infections, hypersentivity to ionizing radiation, and combined immunodeficiency.

Clinical features: Clinical presentation is variable and may be of early or late onset. The ataxia is cerebellar but may become generalized. Apraxia is almost always present. Patients are normal until they start walking with an ataxic, unsteady gait with frequent falls. The face may appear expressionless and may give the impression of stupidity. The speech becomes slurred and handwriting is characteristic as the child becomes severely ataxic. Strabismus, drooling, and weakness are common features in older children. Mental retardation occurs in some patients.

Extrapyramidal and posterior column signs are common. Telangiectasia begins in the palpebral conjunctiva between 1 and 6 years. It may become generalized and visible on the earlobes, nose, and antecubital areas. Some patients have little or no telangiectasia. Other cutaneous manifestations may include premature graying, hypertrichosis, hyperpigmentation, hypopigmentation, atopic dermatitis, and pyoderma.

Infections are usually in the form of sinusitis and pneumonia. Bronchiectasis and chronic lung damage will eventually lead to right-sided heart failure. These patients are usually small and retarded in growth. Many may not develop secondary sex characteristics. Mitral valve prolapse may develop in some patients.

Malignancy is a real threat that interrupts the lives of many patients. It has been estimated that, in about 38% of those who die, the direct cause of death is malignancy. Such malignancies include lymphosarcoma, Hodgkin disease, leukemia, adenocarcinoma, gonadoblastoma, reticulum cell carcinoma, medulloblastoma, dysgerminoma, and T- and B-cell lymphomas. Family members are at an eightfold higher risk of developing breast cancer, compared to the general population.

Those who survive long enough into adulthood become wheelchair bound and, later on, bedridden.

Pathology: There is cerebellar atrophy with loss of Purkinje cells. Peripheral nerve cells have malformed nuclei of Schwann cells. The thymus is hypoplastic with absent Hassall corpuscles.

Genetics and immunopathogenesis: The syndrome of ataxia-telangiectasia (A-T) is inherited as an autosomal recessive disorder. The ATM gene is located on the 11q22–23 chromosome. There is lack of nuclear DNA repair that leads to extensive and wide-ranging cellular damage in different organs. Some of the organs affected include the central nervous system, endothelium of blood vessels, T- and B-lymphocytes, and thymus. There is increased production of alpha-fetoprotein (A-FP). There are both cellular and humoral immune defects.

Epidemiology: Carriers of defective AT gene are more common in Caucasians and is in the range of 1.4–2%. The incidence of the disease is around 1 in 20,000–100,000 live births.

Diagnosis: The clinical and phenotypic features are characteristic. Signs and symptoms of immunodeficiency with recurrent infections may not develop early. Laboratory diagnosis may reveal lymphopenia and eosinophilia. Immunologic abnormalities include one or more of the following: IgA deficiency (in about 70%); high IgA and low IgG; decreased IgG; decreased IgA and IgM; decreased IgG, IgA, and IgG2; decreased IgG and IgG4; depressed specific antibody response; increased autoantibodies; depressed T-cell number and function; and very high A-FP. There is excessive chromosomal breakage. Endocrine abnormalities include decreased 17-ketosteroids and high urinary follicle-stimulating hormone; also, these patients have abnormal response to insulin-induced hypoglycemia. Magnetic resonance imaging of the brain shows atrophy and dilated ventricles.

Treatment: There is no curative therapy. Propranolol can be used to decrease tremors. IVIG is not beneficial, and the prognosis is very gloomy.

Caution: Radiologic examinations should be avoided as much as possible. Exposure to ionizing radiation increases the chromosomal breakage and, hence, development of malignancy.

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Cartilage-Hair Syndrome

The syndrome is characterized by short stature, with short limbs, fine sparse hair, and immune deficiency mostly cellular. It is inherited in an autosomal recessive mode.

The immune deficiency is characterized by lymphopenia, defective delayed immune response, and markedly decreased T-cell response to mitogens. These patients are susceptible to fungal, bacterial, and viral infections. Antibody response is also poor in more than one third of the patients. Fatal varicella infections have been reported. Some of the patients may have severe anemia, Hirschsprung disease, and increased incidence of cancer. The phenotypic features, however, are variable with some patients having immunodeficiency with normal hair, and normal skeletal system. Others may have normal hair and intact immune system. Mutations in RNA processing (RMRP) gene have been reported in patients with immunodeficiency. The treatment is supportive with antibiotics in patients with immunodeficiency. Bone marrow transplant may cure some patients with immunodeficiency.

Partial Albinism, Immunodeficiency, and Progressive Neurologic Disease (PAID Syndrome/Griscelli Syndrome)

Some features of the syndrome were partially reported (Griscelli) in 1978 in two Tunisian girls.

Since then sporadic cases have been reported from different countries. The largest number of cases is reported from Saudi Arabia with new features of the syndrome being described. The syndrome is characterized by partial albinism, recurrent fever, and accelerated phase with pancytopenia and hemophagocytic lymphohistiocytosis. In the majority of cases the final course is characterized by organomegaly, with neurological involvement which progresses into coma and death.

Clinical features: The syndrome is so characteristic it can be recognized at birth especially in dark-skinned patients. The salient features of the syndrome are silvery tint to golden gray hair with a "dead ash" appearance especially on the eye brows (see ❯ *Fig. 127.1*); hypopigmented skin, recurrent fever, hepatosplenomegaly; CNS involvement with demyelination of the white matter, and early death, in the majority.

The syndrome is inherited in an autosomal recessive mode. Recently three mutations have been described with three different clinical presentations:

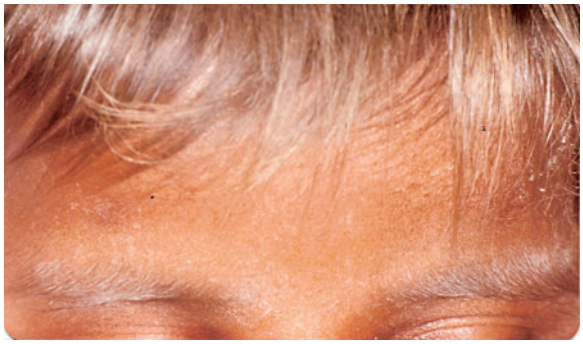

Figure 127.1
Close-up to show the typical hair and skin color in Griscelli syndrome

Type 1 Griscelli (GS1) is characterized by the presence of CNS disease with no hemophagocytic abnormalities and immunodeficiency.

Type 2 patients have hemophagocytic abnormalities, immunodeficiency, and variable neurological involvement.

Type 3 has abnormal melanin pigment distribution with partial albinism but no immunological, hematological, or neurological abnormalities. This type is more compatible with longer longevity.

Cutaneous manifestations: The skin is light in color, with areas of normal pigmentation and others without pigmentation giving freckled appearances. In some patients the skin is bronzy in color. The hair is grayish to silvery, or even golden gray, especially on the eyebrows. This is more apparent in brown or dark-colored skin and black hair. The parents usually make the diagnosis of the abnormality very early.

Recurrent fever: The clinical course in the majority of patients is characterized by frequent episodes of fever. Most febrile episodes yield negative cultures, but some may be indications of sepsis, pneumonia, or otitis media.

Neurological abnormalities: Neurological involvement is variable; some patients have hypotonia, or hyper reflexia in the lower extremities, others have seizures, coma, and death. Some patients may be mistakenly diagnosed as aseptic meningitis. The main lesion of the CNS is demyelination process that starts initially in the posterior fossa and spreads to the rest of the white matter (❯ *Fig. 127.2a, b*). CNS findings in 18 of our patients are summarized in the ❯ *Table 127.1*. Among the 18 patients (index cases) and their 16 affected siblings, 95% had CNS involvement. Four of the 18 patients had optic neuritis and visual loss. The

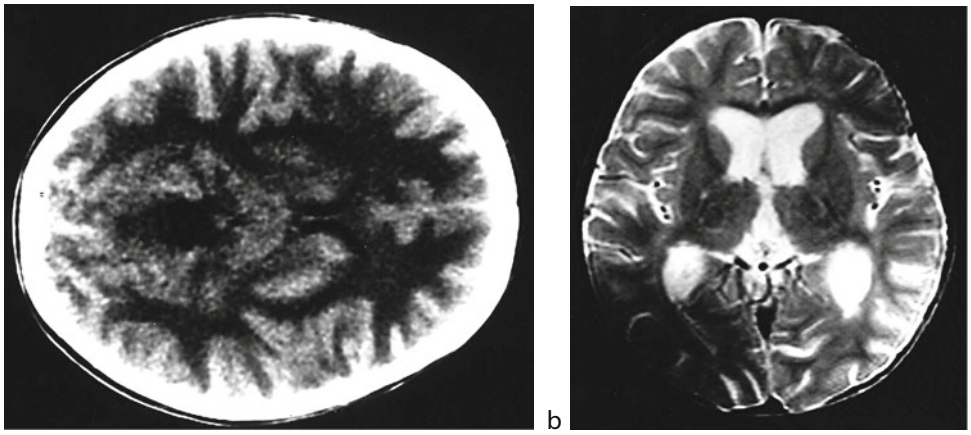

Figure 127.2
(a) CT of the brain of pt. with Griscelli syndrome. (b) MRI of the brain of pt. with Griscelli syndrome

Table 127.1
Clinical Findings in PAID (Griscelli disease)

		Findings
Total patients	18	Hypertonocity, ataxia-hyper reflexia, hemiparesis, facial palsy, coma, retinitis, mental retardation
Male/female	9/9	
CNS involvement	11(61%)	High protein mononuclear cells (50% B-cells, 50% CD4)
CFS involvement		
Abnormal EEG	11(61%)	Mild brain atrophy (two patients)
CT scan and MRI		White matter demyelination (11 patients)
Abnormal CT scan	11	Cerebellum alone (three patients)
Abnormal MRI	8	Generalized (four patients)

CNS involvement is at least partially reversible when treated early with a combination of immunosuppressive drugs.

Hematologic features: Very often these patients are anemic and they develop a picture reminiscent of the accelerated phase of Chediak–Higashi Syndrome. They develop pancytopenia, hepatosplenomegaly, and infiltration of the spleen, liver, bone marrow, and lungs with histiocytic mononuclear, atypical lymphocytes. CNS infiltration is evident by the presence of mononuclear cells in the CSF. Liver enzymes are elevated in all symptomatic patients.

Immunologic abnormalities: All patients with recurrent fever and infections have poor primary antibody response with very low isohemagglutinin antibody titer. They are anergic to recall antigens by skin test. As they become older, they develop a picture of combined immunodeficiency with low T- and B-cell count and defects in their function. Some patients had defective leukocyte chemotaxis.

Radiological findings: Computerized tomography (CT) and magnetic resonance imaging (MRI) may be normal in asymptomatic patients. Once the patient develops even mild neurologic manifestations, white matter changes will be detected. The early demyelination changes start in the cerebellum. As the disease progresses, the whole white matter disappears and the ventricles become dilated. This process is reversible when patients are treated early.

Histopathology findings: There is characteristic distribution of melanin pigment. The hair when examined under a high power lens shows areas of clumped pigment alternating with areas of no pigment. Skin biopsy shows melonocytes with short dendrites packed with mature pigment but very little pigment released in the epidermis. Langerhans cells may

be normal, decreased, or absent. The CSF cytology is 50% B-lymphocytes and 50% T-helper (CD4) lymphocytes. Over 78% of patients have high CSF proteins. Lungs, liver, and spleen and bone marrow are infiltrated by hemophogocytic histiocytes in symptomatic patients.

Epidemiology: The syndrome has been reported in case reports from different countries including Turkey, Mexico, Jordan, Kuwait, USA, and Europe but more than two thirds of the cases came from Saudi Arabia. Males and females are equally affected.

Pathogenesis and genetics: Consanguinity of parental marriages – usually first cousin – is the rule in all patients reported from the Arabian Peninsula. Mutations that have been identified are in MYO5A that encodes an unconventional myosin (GS1), mutation in RAB27A that encodes a GTP-binding protein of the Ras family (GS2), and MYO5A gene or gene that encodes for melanophilin (MLPH) in GS3.

Natural course: Untreated, patients die early in life, usually in the first decade of their lives. Before their demise patients become lethargic and stuporous followed by coma and death. They may develop septicemia or hepatitis with jaundice before they die. None of our patients survived beyond 6 years of age without BMT.

Diagnosis: Is made easy by the presence of the typical features confirmed by microscopic exam of the hair. The diagnosis can be made at birth.

Treatment: The disease is fatal if untreated. Rarely do patients survive beyond age 6–8 years. When patients are in accelerated phase with CNS involvement, chemotherapy with prednisolone, VPI6, with cyclosporine A, or antithymocyte immunoglobulins leads to temporary remission. If CNS is involved, intrathecal methotrexate can totally reverse the white matter changes, though partial response in relapse is the rule. The only curative treatment is allogeneic BMT or hematopoietic stem cell from a matched donor.

Prenatal diagnosis: Prenatal diagnosis can be achieved by examination of the fetal hair or and gene mutation of MYO5A or RAB27A in families with defined history.

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128 Approach to the Child with Recurrent Infections

Mohammad Almutawa · Zaina H. Albalawi

Introduction

Newborns exhibit a physiological immature immune system. As they grow and interact with the environment, they encounter pathogens for the first time that trigger their immune system to mount a response and to develop an immunological memory. It is common for children to experience frequent infections; however, a concern should arise when these infections become severe, refractory to therapy, recurrent, or caused by unusual organisms. In this case, the physician should consider the possibility of an underlying primary immunodeficiency disorder (PID).

Primary immunodeficiencies are inherited disorders of the immune system function that predispose affected individuals to an increased rate and severity of infection, immune dysregulation with autoimmune disease, and malignancy. There are over 100 distinctive genetic disorders that have been identified up to date, but less than 20 probably account for more than 90% of cases.

They are classified according to the principle immunologic mechanisms that are disrupted. These subdivisions include humoral, cellular deficiencies, combined immunodeficiencies that affect both humoral and cellular mechanisms, phagocytic, and compliment system defects.

Individual immunodeficiencies are rare, but altogether they occur in as many as 1 in 2,000 live births. Of all the previously mentioned immune system components, antibody deficiencies account for about half of all primary immunodeficiency disorders (PIDs).

It is important for a physician faced with a child with recurrent infections to first consider other medical conditions, potentially resulting in secondary immunodeficiency and other anatomical or biochemical conditions predisposing to infection. Once those have been excluded, or are not considered sufficient to explain the observed degree of infectious susceptibility, the physician should proceed in a stepwise manner to search for a diagnosis of PID.

Knowing the principal clinical manifestations of each subtype of PID provides a useful way to narrow down the differential diagnoses (◉ *Table 128.1*). In general, the initial evaluation is guided by the clinical presentation. Screening tests are applied followed by advanced tests as indicated. Early diagnosis and therapy are key for improved survival and better quality of life for immunodeficient patients. It is therefore important to have an approach to identify those patients and effectively direct them to the appropriate route.

Classification of Primary Immunodeficiency

The immune system is a large organization of many interdependent cell types that work cooperatively to defend the human body from invading organisms such as bacteria, viruses, parasites, and fungi.

Inherited disorders of the immune system are classified according to the arm of the immune system that they predominantly affect. Immunity is subdivided into two major components, the *innate* "nonspecific" and the *adaptive* "specific." The former is characterized by its faster and immediate maximal generic response with no resulting immunologic memory. It is provided by the surface barrier of the skin and the mucous membranes. In addition, the inflammatory process attracts leukocytes by the release of cytokines that is triggered by injured cells. *The complement system* is the major humoral component of the innate immune response. It is a biochemical cascade that attacks the surfaces of foreign cells and is named so for its ability to "complement" the killing of pathogens by antibodies. Finally, the *Cellular Barriers* "Leukocytes" act like independent, single-celled organisms and are the second arm of the innate system. The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms. Innate cells are also important mediators in the activation of the adaptive immune system. PIDs due to genetic defects in neutrophil development, toll-like receptor signaling and

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Table 128.1

Primary immunodeficiency disorders: examples of typical clinical presentations (Adapted from Elsevier © with permission. Bonilla FA, Bernstein IL, Khan DA et al. (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94(5):S1–S63

Category of immunodeficiency and examples	Characteristic presentation
Antibody deficiencies	
XLA, ARA, CVID, SIGAD, IGGSD, SAD, THI, hypogam	Recurrent sinopulmonary infections with encapsulated bacteria
Cellular deficiencies	
IL-12/IFN-γ axis	Atypical mycobacterial and salmonella infections
AIRE mutations	Mucocutaneous candidiasis and autoimmune endocrinopathy
Combined deficiencies	
SCID	Failure to thrive, diarrhea, opportunistic infection, rash
Wiskott–Aldrich syndrome	Thrombocytopenia with bleeding and bruising, eczema, recurrent infection with encapsulated organisms
Ataxia telangiectasis	Chronic sinopulmonary disease, cerebellar ataxia, oculocutaneous telangiectasis, malignancy
DiGeorge syndrome	Hypocalcemic seizures due to hypoparathyroidism, cardiac disease, abnormal facies, infection
CD40 ligand deficiency	Recurrent, serious pyogenic infections (also opportunistic infections)
Phagocyte defects	
Chronic granulomatous disease	Deep-seated infection, abscess with granuloma formation
Leukocyte adhesion deficiency	Recurrent serious bacterial infections, delayed separation of the umbilical cord, poor wound healing, lack of pus
Hyper-IgE syndrome	Chronic dermatitis, recurrent serious infection of lungs with pneumatoceles, skin infections, bone fragility, failure to shed primary teeth
Complement deficiencies	
Early classical pathway components	Autoimmune disease and bacterial infections
Late components	Neisserial infection
C3 and regulatory components	Recurrent infections with encapsulated bacterial

Abbreviations: *AIRE* autoimmune regular, *ARA* autosomal recessive agammaglobulinemia, *CVID* common variable immunodeficiency, *hypogam* hypogammaglobulinemia, *IFN-γ* interferon-γ, *IGGSD* IgG subclass deficiency, *IL*-12 interleukin 12, *SAD* specific antibody deficiency, *SCID* severe combined immunodeficiency, *SIGAD* selective IgA deficiency, *THI* transient hypergammaglobulinemia of infancy, *XLA* X-linked agammaglobulinemia

complement reveal the protective role played by the innate immune system.

The second major component of the immune system is the adaptive immunity. It exhibits brisker and more specific responses on second and subsequent encounters to foreign antigen. It can also provide long-lasting protection through its capacity of immunologic memory. The responses are carried out by lymphocytes. There are two broad classes of such responses, antibody responses and cell-mediated immune responses, and they are carried out by different classes of lymphocytes, called B-cells and T-cells, respectively. T- and B-lymphocytes are the main self-defense weapons of this system. Unlike innate immune responses, the adaptive responses are highly specific to the particular pathogen that induced them.

Humoral or antibody deficiency is the most common type of PID and accounts for approximately 60% of all primary immunodeficiency. Five to ten percent of affected individuals have abnormalities of cell-mediated immunity (T-Cells), while a further 20–25% have combined defects of both humoral and cellular function. Disorders of phagocyte account for approximately 10–15% of all PIDs, while Complement deficiency is the rarest, comprising less than 2% of all PIDs.

Another classification for PID is presented by the International Union of Immunological Societies Expert

Committee on Primary Immunodeficiencies, published in 2009 by Notarangelo et al. It includes a detailed list of all the identified PIDs and their genetic basis. It serves as a useful reference for the immunologist. The classification adopted in this chapter is meant to facilitate the approach for the general pediatrician.

Clinical Features of Primary Immunodeficiency

History and Examination

In evaluating a child with recurrent infection, it is critical as much as possible to document carefully the foci of infections, the organisms, and the response to treatment. This is necessary to distinguish infectious disease from others noninfectious conditions such as allergic diseases. Any other conditions that may increase the patient's susceptibility to infection, including congenital defects, allergy, and metabolic disorders, should be considered when appropriate.

Careful evaluation of the family history of a similar condition can be helpful in determining the likelihood of PID. Consanguinity is suggestive of autosomal recessive diseases. Several PIDs are X-linked; a history of male infection or unexplained infective deaths in infancy or early childhood on the maternal side of the family is significant. Death from infection in infancy is highly suggestive of severe combined immunodeficiency (SCID) and should be taken seriously even in families where there is no consanguinity. The age at onset of infections of unusual frequency or severity may yield important insights into possible underlying immune deficiencies. In addition, pregnancy history, previous blood transfusions and vaccination history are also important. The latter is important from the diagnostic perspective of which antigens the patient's immune system has been exposed to, and secondarily important to document live vaccines that may become pathogenic in the immunocompromised host.

Growth parameters and the general state of health of the child should be evaluated as children with cell-mediated immunodeficiency tend to appear chronically unwell and have features of malnutrition. Ear examination with attention to the tympanic membranes should be carefully inspected for evidence of acute inflammation or scarring. Examination of the lymphatic system for the presence/absence and size of the lymph nodes, spleen and tonsils is important. The skin should also be examined for vascular abnormalities as well as rashes, which may or may not be infectious, due to malnutrition or graft-versus-host disease.

Humoral Immunodeficiency

Antibody deficiency is the most common form of PID. Among its subtypes, selective IgA deficiency (SIGAD) is very common, affecting approximately 1 in 500. Most patients with SIGAD are asymptomatic.

The principle clinical manifestations of humoral immunodeficiency are recurrent bacterial infections of the respiratory tract. These infections tend to be recurrent, pyogenic, and present after 6 months of age. On average, the majority of maternally acquired Immunoglobulin G (IgG) has disappeared by 6 months of age. IgG production begins shortly after birth and reaches adult levels by the fifth year of life. The common organisms infecting these children are polysaccharide-encapsulated organisms, such as *Haemophilus influenzae* and *Streptococcus pneumonia*. In general, patients with disorders of the humoral immune system tend to grow well; failure to thrive is not a feature of these diseases. An overview of selected humoral immunodeficiencies is presented in (*Table 128.2*).

Cellular Immunodeficiency

Cellular immunodeficiency accounts for 5–10% of PIDs. When T-cell function is impaired, antibody formation is also affected. Children suffering from defects of the cell-mediated immune system are predisposed to developing viral, bacterial, fungal, and parasitic infections. Infective organisms are mostly intracellular, such as *Mycobacteria* and *Salmonella*. They usually present between 3 and 6 months of age. A major feature of this group is failure to thrive associated with persistent diarrhea and malabsorption. Other features include diseases due to BCG vaccine, disseminated TB, and severe herpes infections. These children may also present with skin rashes and chronic, persistent candidal infection of the nail, skin, and mucous membranes, as seen in Chronic Mucocutaneous Candidiasis (CMCC). A list of cellular immunodeficiencies is presented in *Table 128.3*.

Combined Immunodeficiency

It comprises 20–25% of PIDs. This is a heterogeneous group, characterized by the presence of T- and B-cell dysfunction, often associated with decreased numbers of T lymphocytes and immunoglobulin levels. The "combined" nature of these immune deficiencies results from

Table 128.2
Characteristic features of selected humoral immunodeficiency

Humoral deficiency	Age of onset	Infections	Characteristic features
XLA	>6 months	Otitis media, sinusitis, and pneumonia	Absence of lymph nodes and tonsils Agammaglobulinemia and very low/absent B-cell count
		CNS infection with ECHO-virus	Paralytic polio with live vaccine Absence of BTK protein
CVID	Recurrent infection in children >2 years	Otitis media, sinusitis, pneumonia, bronchitis, and enteric infection	GI tract (20–25%): lymphonodular hyperplasia, IBD, and malabsorption Autoimmune diseases (20%): AIHA, ITP, seronegative arthritis, and vasculitidis Lymphoproliferative disorders: splenomegaly and peripheral lymphadenopathy Malignancies: NHL and gastric cancer
SIGAD	>4 years	Viral, otitis media, sinopulmonary infection and GI infection	Serum IgA level <0.07 g/L with normal IgG and IgM levels GI: Crohn's, UC, and celiac disease Atopy: allergies and asthma Autoimmune: lupus-like illness and arthritis Malignancies: GI and lymphoid malignancies later in life

Abbreviations: *XLA* X-linked agammaglobulinemia, *ECHO* enterocytopathic human orphan, *BTK* bruton tyrosine kinase, *CVID* common variable immunodeficiency, *GI* gastrointestinal, *IBD* inflammatory bowel disease, *AIHA* autoimmune hemolytic anemia, *ITP* idiopathic thrombocytopenic purpura, *NHL* Non-Hodgkin lymphoma, *SIGAD* selective IgA deficiency, *UC* ulcerative colitis

Table 128.3
Diseases of cellular immunodeficiencies

Defect of the IL-12/IFN-γ axis
IFN-γ receptor α chain
IFN-γ receptor β chain
IL-12 p40
IL-12 receptor β1 chain
Signal transducer and activator of transcription 1
CMCC
CD16 deficiency
Idiopathic CD4+ T Lymphocytopenia
NK cell deficiency due to unknown defect
Cellular immunodeficiency, unspecified

Abbreviations: *IL* interleukins, *INF* interferon, *CMCC* chronic mucocutaneous candidiasis, *NK* natural killer, *CD* cluster differentiation

the inability of T-cells to provide immunological "help" to the antibody producing B-cells or a direct impact on B-cell development, resulting in the combined clinical features of both T-cell and B-cell dysfunction. Patients with Combined Immunodeficiency (CID) present within the first few months of life with recurrent, persistent, or severe bacterial, viral, or fungal infections. Failure to thrive, diarrhea, and rashes are frequently seen features. Common

pathogens are most often seen, in addition to nonpathogenic organisms (opportunistic infections). Infections usually do not remain localized; disseminated disease is frequent in those patients.

It is critical to deal with even a suspicion of severe combined immunodeficiency (SCID) as a medical emergency because of the rapidity with which these infants succumb to life-threatening infections, and early management is life saving.

Newborn screening provides a promising method for identifying these children as early as possible. The feasibility of newborn screening for SCID has been demonstrated by Baker et al. in their experience in Wisconsin. *Table 128.4* presents features of some CIDs.

Phagocytic Cell Disorders

This entity constitutes approximately 10–15% of all PIDs. It includes defects in neutrophil and monocyte maturation and differentiation, chemotaxis, phagocytosis, and intracellular killing. Phagocytic cell defects may present with deep-seated abscesses due to infections with *Staphylococcus aureus* or gram-negative organisms such as *Klebsiella pneumonia*, *Serratia*, and *Proteus* species. These individuals are also predisposed to fungal infections, especially *Aspergillus fumigatus* pneumonia. Infections of the skin and viscera can also be manifestations of a phagocytic cell disorder. *Table 128.5* displays some of the characteristic features of selected phagocytic cell disorders.

Complement Disorders

Complement disorders account for a small percentage of PIDs (less than 2%) and may coexist with autoimmune diseases, such as systemic lupus erythematosus (SLE). The clinical features of these disorders vary depending on which complement proteins are affected. The complement system consists of 30 proteins that work synergistically in defending against invading organisms. Of these complement proteins, the commonest is deficiency of C1 inhibitor causing hereditary angioedema, but not infection. A deficiency of C2 is associated with SLE-like syndrome, vasculitis, dermatomyositis, and predispose individuals to recurrent bacterial infections. C3 is the most abundant protein of the complement system. Its products play

Table 128.4
Characteristic features of selected combined immunodeficiency

CID	Age of onset	Infections	Characteristic features
SCID	3–9 months	Pneumonia, septicemia, gastrointestinal	Absence of lymphoid tissue and thymus Failure to thrive and diarrhea Skin disorders and GVHD (due to maternal T-Cells) Disseminated BCG infection. Chronic hepatitis and neutropenia
WAS	<6 months	Otitis media, pneumonia, skin (herpes)	Triad: eczema, thrombocytopenia, and immune deficiency Recurrent and severe infections Autoimmune disease: colitis, vasculitis, and glomerulonephritis EBV-related B-cell lymphoma 10–15%. Average age 10 years
DiGeorge syndrome	Birth	Pneumonia and gastrointestinal	Cardiac abnormality, abnormal facies, thymic aplasia, cleft palate, and primary hypoparathyroidism 80–90% associated with 22q11.2 deletion
CD40 and CD40-L Deficiency (previously known HIgM)	Infancy	Pneumonia, otitis media, gastrointestinal, soft tissue	Gastrointestinal complaints with malabsorption associated with cryptosporidium infection and cholangitis Lymphoid hyperplasia Chronic anemia and neutropenia

Abbreviations: *SCID* severe combined immunodeficiency, *GVHD* graft-versus-host disease, *BCG* Bacillus Calmette–Guérin, *WAS* Wiskott–Aldrich syndrome, *EBV* Epstein–Barr virus, *HIgM* hyper-IgM

Table 128.5
Characteristic features of selected phagocyte disorders

Phagocyte disorders	Age of onset	Infections	Characteristic features
CGD	Infancy	Skin, pneumonia, perianal abscess, osteomyelitis, multiple ulcers infected with *Serratia* species in young adults	Granulomatous abscesses: lungs, lymph nodes, skin, liver, bones, and brain Hepatosplenomegaly, dermatitis, pneumonitis, suppurative lymphadenitis Obstructive granulomas in the GU and GI systems
HIES (Job syndrome)	Early childhood	Pneumonia, skin, otitis media, mastoiditis	Markedly elevated serum IgE and eosinophilia Severe papular and pruritic rash, becomes lichenified. Coarse facies Hyperextensible joints, polyarticular arthritis, reduced bone density, and recurrent fractures Recurrent pneumonia with pneumatocele formation Cold abscesses
LAD	Early in life	Cellulitis, abscesses, bacterial and fungal respiratory tract infection	Significant neutrophilia, recurrent infections, along with absence of pus formation LAD type I: poor wound healing, delayed separation of the umbilical cord LAD type II: pulmonary infections and chronic severe periodontitis. Characteristic facies, growth and developmental delay, and mental retardation
CHS	–	Pyogenic, affect mainly skin and respiratory tract	Partial oculocutaneous albinism and pleomorphic neurologic manifestations; cognitive impairment, photophobia, nystagmus, and central and peripheral neuropathies. Giant Azurophilic granules are characteristic Lymphoproliferative disorder known as the accelerated phase causing lymphadenopathy, hepatosplenomegaly, and bone marrow failure

Abbreviations: *CGD* chronic granulomatous disease, *GU* genitourinary, *HIES* hyper-IgE syndrome, *LAD* leukocyte adhesion deficiency, *CHS* Chediak–Higashi syndrome

an important role in chemotaxis, opsonization, and regulation of the complement cascade. Deficiency of C3 predisposes affected individuals to severe pyogenic infections. Disorders of the terminal complement cascade (C6 through C9) are associated with predisposition to Neisserial meningitis.

Laboratory Investigations

Laboratory investigations are heavily relied on to reach a specific diagnosis of PID. Before proceeding with immunological tests, basic tests should be applied to detect any electrolyte or metabolic imbalances the child may have due to intractable diarrhea, or malabsorption. A complete blood count with a differential, as well as a coagulation profile is essential. Efforts must also be made to identify any infection the patient may have.

The history and physical examination findings serve as a guide to which investigations to start with. The general rule is that screening tests are applied first followed by advanced tests. *Table 128.6* serves as an outline for this approach.

Consultation with physicians experienced in the diagnosis of PIDs is essential wherever uncertainty regarding evaluation occurs, to aid in reaching an accurate diagnosis as quickly as possible, and enable directed therapy. Wherever possible, diagnosis at the molecular level is desirable to establish a clear diagnosis and permit accurate genetic counseling. It also assists in better defining of genotype-phenotype association and to identify candidates for gene-specific therapies.

Table 128.6

Laboratory tests for evaluation of immunodeficiency (Adapted with permission from Elsevier ©. Bonilla FA, Bernstein IL, Khan DA et al. (2005) Practice parameter for the diagnosis and management of primary immunodeficiency. Ann Allergy Asthma Immunol 94(5):S1–S63)

B-cell function
Screening tests Serum immunoglobulin levels Serum specific antibody titers Advanced tests Antibody response to booster immunization Flow cytometry to enumerate B-cells In vitro immunoglobulin production in response to mitogen In vitro immunoglobulin production in response to anti-CD40 and cytokines Antibody response to immunization with ϕ X174
Cellular immune function
Screening tests Flow cytometry to enumerate T-cells and natural killer cells Cutaneous delayed hypersensitivity Advanced tests Enzyme assays (ADA, PNP) FISH for 22q11 and 10p11 deletion In vitro proliferative response to mitogens and antigens Natural killer-cell cytotoxicity Cytokine production in response to mitogen or antigen stimulation Expression of surface markers after mitogen stimulation
Phagocytic cell function
Screening tests Blood cell count with differential Neutrophil staining, morphology Advanced tests Oxidase function (dihydrorhodamine, nitroblue tetrazolium, chemiluminescence) Flow cytometry for adhesion molecules Chemotaxis Phagocytosis Enzyme assays (myeloperoxidase, G6PDH) WBC turnover Bacterial or fungal killing Bone marrow biopsy
Complement function
Screening tests CH_{50} (total hemolytic complement activity) AH_{50} (alternative pathway hemolytic activity) Advanced tests Level or function of individual complement components Chemotactic activity of complement split products
General
Advanced tests Molecular methods including southern, northern, and western blots, PCR/SSCP, DNA fingerprinting, and nucleotide sequencing

Abbreviations: *ADA* adenosine deaminase, *FISH* fluorescent in situ hybridization, *G6PDH* glucose-6-phosphate dehydrogenase, *PCR* polymerase chain reaction, *PNP* purine nucleoside phosphorylase, *SSCP* single-strand conformation polymorphism, *WBC* white blood cell

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129 Primary Immunodeficiency Syndromes

Clinical Cases

Harb A. Harfi

Antibody Deficiency

Case History 1

Nada is a 12-year-old girl who was the product of a normal pregnancy and delivery, born to first-degree consanguineous cousins. At the age of 2 years, she had lobar pneumonia that required hospitalization for 15 days. At the age of 30 months, she had an episode of sinusitis and otitis media, which responded slowly to antibiotics. Between the ages of 3 and 5 years, she had several episodes of conjunctivitis, diarrhea, otitis media with bilateral ear canal discharge, and chronic productive cough. At the age of 5 years, she was diagnosed as having antibody deficiency. Her tonsils and adenoids were atrophic (*Fig. 129.1*). Her CD19 (B lymphocytes) was 3% and her serum IgM was 0.2 g/L (normal, 0.4–1.6 g/L), IgA was 0.3 g/L (slightly low), and IgG was 1.8 g/L (normal, 5–8 g/L). Chest and sinus x-rays showed a small area of bronchiectasis in the left lower lobe and bilateral maxillary sinusitis. She was started on trimethoprim/sulfamethoxazole (TMP/SMX) prophylaxis and monthly IVIG. She did well with no further infections other than mild conjunctivitis.

Nada has a 6-year-old sister and 4-year-old brother who were diagnosed with antibody deficiencies. Both are doing well on antibiotic prophylaxis and monthly IVIG.

Comment

The above case, with positive family history of both sexes and milder course, is an example of the autosomal recessive inheritance of antibody deficiency.

Case History 2

Mohammed is an 8-year-old boy who was well until the age of 2 years, when he started to have repeated episodes of fever and lymphadenopathy. He had one episode of pneumonia and two attacks of otitis media. He also presented with bilateral cervical and submandibular lymphadenopathy and organomegaly. He was anemic and had persistent neutropenia. He was hospitalized on four occasions because of fever. Lymph node biopsy on two occasions was nonspecific.

When the patient was referred to our Immunology Unit, he was small for his age, both in weight and height. He had splenomegaly of 6 cm and hepatomegaly of 5 cm below the costal margin. He had generalized lymphadenopathy of mediastinal, inguinal, axillary, and cervical areas. He had bull neck-like appearance, with hoarseness of his voice and inspiratory stridor. His eardrums looked thick and dull, and he had chronic sinusitis. His white blood cell count showed platelets of 120,000/mm^3 and his total neutrophils were 750/mm^3. His serum IgM ranged between 5.2 and 7.8 g/L (extremely high for his age). His serum IgG was 0.8 g/L and IgA less than 0.2 g/L. Lymph node biopsy from the cervical area on two occasions showed lymphoid hyperplasia. He was treated with TMP/SMX prophylaxis and monthly IVIG. Because of upper airway obstruction, dexamethasone was given orally for 10 days. His cervical lymphadenopathy decreased markedly in size and his spleen shrank to 2 cm below the costal margin. Both axillary and inguinal nodes became smaller. His upper airway obstruction and stridor cleared up. However, 6 months later, symptoms of upper airway obstruction with extremely large lymph nodes recurred. He responded modestly to dexamethasone. Flow cytometry with monoclonal antibody against CD40L showed lack of expression of the ligand on CD4+ cells, confirming the X-linked hyper-IgM syndrome. Repeat lymph node biopsy with DNA study showed B-cell lymphoma. Interferon alpha was added to his therapy and the patient did fairly well.

There is no family history of a similar case and the patient's parents are not consanguineous.

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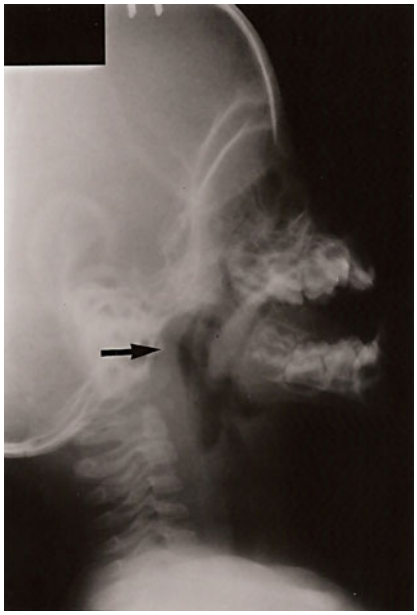

Figure 129.1
X-ray of the post nasal space shows atrophic adenoids in a patient with antibody deficiency

Case History 3

Othman is a 6-year-old boy referred because of recurrent meningitis. *Streptococcus pneumoniae* was isolated from the cerebrospinal fluid (CSF) on several occasions during his hospitalization. He was hospitalized on several occasions since the age of 2 years. As a consequence of recurrent meningitis, he became deaf. There was no history of trauma to the head. He had sepsis on one occasion and pneumonia on two occasions. Extensive radiologic and computerized tomography scans with thin cuts of the head, petrous bones, and cribriform plate failed to uncover communication with the CSF, nor were congenital anomalies detected. Serum IgG, IgA, and IgM were normal. Serum IgG subclass measurement showed IgG2 to be less than 0.01 mg/dL and IgG4 less than 0.001 mg/dL. No specific antibody was detected against *S. pneumoniae*. The patient was placed on antibiotic prophylaxis with TMP/SMX without much benefit. IVIG every 2 weeks reduced the frequency of meningitis to once every 9–12 months.

Comments

The above case is a classic example of the extreme presentation of IgG subclass deficiency. In such cases, trauma to the head and congenital skull bone defects should be excluded first before concluding that IgG subclass deficiency is the explanation for the recurrent meningitis.

Case History 4

Bander was 3 years old before he had his first episode of otitis media and left lobe pneumonia. He received a course of antibiotics and improved, though his improvement was slow. He continued to have low-grade cough with yellow, thick sputum. When he was evaluated in the Immunology Clinic at the age of 7 years, he was well developed with no apparent distress. His physical examination showed a few fine crepitations on the left lower lobe posteriorly. His serum IgG, IgA, and IgM levels were normal. IgG subclass assay showed his IgG3 level to be 0.1 mg/dL. Sputum and ear discharge cultures grew *Haemophilus influenzae* on several occasions. At the age of 11 years, he developed flat, hypopigmented maculopapular lesions on the forehead. Skin biopsy established verruca virus, a poxvirus, to be the cause of the skin lesion. Repeated extensive courses of antibiotics kept his lungs clean, except for a small area of bronchiectasis in the left lobe.

Comments

The above case illustrates another IgG subclass deficiency that ended up in mild bronchiectasis and failure to clear a viral infection. There was gradual improvement in the frequency and severity of infections as the patient grew older.

Case History 5

Abdulaziz was 14 months when he presented to the Immunology Clinic. According to his parents, his problems started at 10 months of age with upper respiratory tract infection and recurrent otitis media. He responded well to antibiotics. Since then, his history has been characterized by recurrent cough, fever, and sore throats. He had two episodes of bronchopneumonia between the ages of 14 and 24 months. He developed airway hyperreactivity with cough and wheezing that required bronchodilators. At the age of 14 months, his serum IgG was 2.1 g/L and the other immunoglobulins were normal. His serum IgG2 subclass was 0.15 mg/dL (normal, 0.28–0.8 mg/dL). Serial serum IgG and IgG subclass measurements showed gradual increase and normalization at 36 months, which

coincided with his clinical improvement. During this time he was placed on TMP/SMX three times per week.

During the follow-up, the parents had another boy, Saud. At the age of 4 months, Saud had his first upper respiratory tract infection. After that, he followed an identical course of clinical and laboratory findings as his brother. He recovered at 38 months of age.

Ataxia Telangiectasia

Case History 1

Shokri was a 2-year-old boy when he was examined because of unsteady gait and frequent falls. He was the product of a full-term pregnancy born to first-degree cousin parents. His examination showed expressionless face and ataxic (cerebellar) gait (*Fig. 129.2*). He also had telangiectasis of both conjunctivas (*Fig. 129.3*). As he grew older, he became more and more ataxic. He had horizontal and vertical nystagmus. He developed chronic cough and bronchiectasis. At age 21, he became wheelchair bound. Both weight and height were much below the fifth percentiles. His serum Alpha-FP was six times the upper normal value. His IgA is undetectable, and his serum IgG was 0.5 g/L. In vitro T-cell function was markedly depressed.

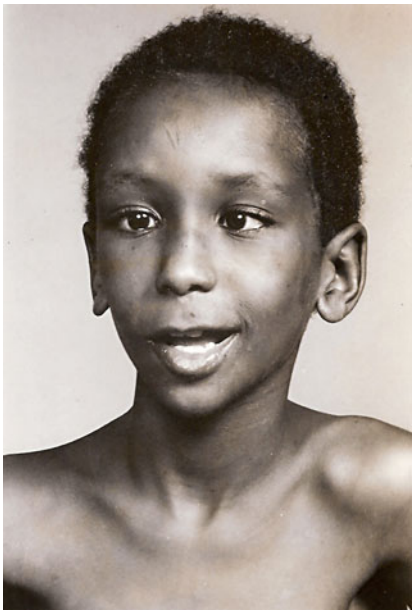

Figure 129.2
Patient with ataxia telangiectasia. Notice the expressionless face and masked appearance

His brother, Hussam, was seen at age 8 years with the same complaint of ataxia. On his initial visit, he was found to have matted, rubbery left cervical lymph nodes measuring 5 × 5 cm, which proved to be lymphoblastic lymphoma.

Case History 2

Abdulaziz and Abeer were two siblings, product of first-degree consanguineous cousin parents. They were diagnosed to have A-T at the age of 1 year. A third sibling, Bakr, was born and developed classic features of A-T at 10 months of age. All three siblings had classic immunologic and clinical features of A-T. Abdulaziz became wheelchair bound. He developed normal secondary sex characteristics at the age of 19 years, but his body was small. His sister, Abeer, developed cerebral infarction at the age of 10 years and became bedridden. None of the siblings suffered from serious infections other than mild sinusitis.

Case History 3

Noura is a 9-year-old girl who was diagnosed as having ataxia telangiectasia at 1 year of age. Since 7 years of age, she has been suffering from chronic sinopulmonary infections. Her IgG and IgG2 were very low, and her serum IgA was undetectable. Antibiotic therapy and TMP/SMX prophylaxis did not reduce her infections except temporarily. IVIG (400 mg/kg) was given slowly. Within minutes, the patient became diaphoretic and cyanotic with respiratory distress and expiratory wheezing. The infusion was stopped immediately and anti-anaphylactic treatment

Figure 129.3
Conjunctiva of a patient with ataxia telangiectasia. Notice the dilated Blood vessels

was given. The same reaction occurred when IVIG was attempted 1 month later. Therefore, replacement therapy with IVIG was abandoned.

DiGeorge Syndrome

Case History 1

Mabrook is an 8-year-old boy born to nonconsanguineous parents. Shortly after birth, he was observed to have abnormal congenital anomalies, including micrognathia, low-set deformed ears, broad depressed nasal bridge, high-arched palate, and Tetralogy of Fallot (*Fig. 129.4*) He developed hypocalcemic tetany 24 h after birth. His serum calcium was very low and his phosphorus was high. His parathyroid hormone was extremely low. Chest x-ray showed absent thymic shadow. The diagnosis of DiGeorge anomaly was made and he was started on calcium and vitamin D supplement; the latter was changed later on to calcitriol, 0.25 μ/day orally. His cardiac anomalies were corrected surgically at the age of 4 weeks.

Although in vitro assessment of his T and B lymphocyte function by culture with mitogens was normal, the patient had poor antibody response. He had several episodes of sepsis, otitis media, and oral thrush. He was placed on TMP/SMX prophylaxis and IVIG on a monthly basis. The patient did well, with no further pyogenic infections. He was slow in his language development and mental performance.

Figure 129.4
DiGeorge Syndrome notice the typical features

At the age of 5 years, the calcium and calcitriol were discontinued without the recurrence of tetany. His serum calcium and phosphorus remained normal. Repeated study of his T- and B-cell functions showed moderate in vitro suppression of his T cells when cultured with mitogens and allogenic cells.

Severe Combined Immunodeficiency (SCID)

Case History 1

Noura was 5 months old when she was referred to our Immunology Division. Her problem started in the second week of her life when she was noticed to have extensive oral thrush. She developed diarrhea and became emaciated. At 3 months of age, she developed a necrotic ulcer at the site of BCG vaccine on the left shoulder. She then developed generalized nodular cutaneous lesions. The lesions were 3–5 mm in diameter, and coppery red to dark brown in color, involving the scalp, palms, soles, and other areas of the body. Her lymph nodes were atrophic. She had hepatosplenomegaly, with her spleen being 5 cm below the costal margin. A complete blood count (CBC) showed extreme lymphopenia, with a white blood cell (WBC) count of 3,500/mm^3 and lymphocytes 8%. Total T cells were 185/mm^3, with CD4 less than 4 mm^3, CD8 84/mm^3, and B lymphocytes 21/mm^3. There were not enough lymphocytes for in vitro functional studies. X-ray of the chest showed absent thymic shadow. X-ray of the skull and long bones showed lytic small lesions with no bony reactions, involving all bones (*Fig. 129.5a*, *b*). Serum immunoglobulin levels were undetectable.

Biopsy of the skin nodules was full of acid-fast bacilli, confirmed by culture to be *Mycobacterium bovis*, compatible with disseminated BCG. The patient died shortly after admission before BMT could be given. Her parents were first-degree cousins. They lost two previous infants: a boy at the age of 4 months and a girl at the age of 7 months, both with a clinical history suggestive of SCID.

Case Histories 2 and 3

Abdulaziz and Abdulkareem were two full-term, identical twin brothers, born to first-degree cousins. The parents lost one boy at the age of 6 months with the diagnosis of

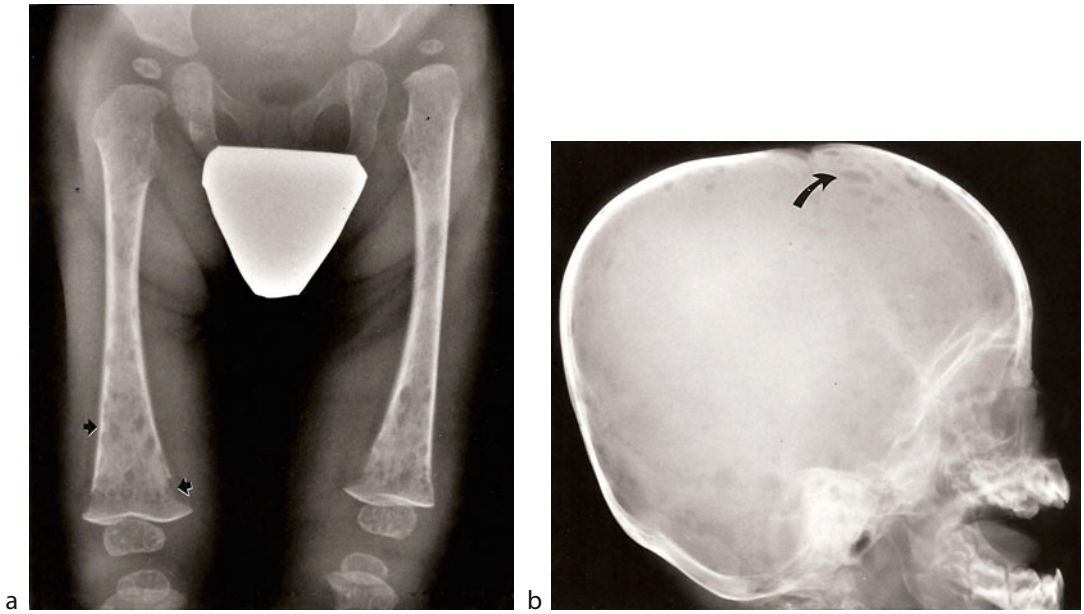

Figure 129.5
(a) X-ray of the long bones in a SCID patient with dessiminated BCG. Notice the lytic lesions due to absent immune. (b) X-ray of the skull in a SCID patient with dessiminated BCG. Notice the lytic lesions due to absent immune response

SCID. The twin brothers received BCG vaccine at the age of 24 h. Both developed oral thrush, recurrent otitis media, and lung infection. When they were examined at the age of 5 months, they were found to have atrophic lymphoid tissues, extensive oral thrush, and generalized dark brownish, nodular skin lesions. Both had hepatosplenomegaly but no BCG scar at the site of inoculation. Skin biopsies of the nodules were full of acid-fast bacilli; cultures grew *M. bovis*, compatible with BCG. Chest x-ray showed no thymic shadow; x-ray of other bones was negative. CBC showed extreme lymphopenia with very low percentages of CD4, CD8, CD3, and CD19 (B Cells). Serum immunoglobulin levels were undetectable. In vitro culture of lymphocytes with mitogens (phytohemagglutinin [PHA], concanavalin A [Con-A], pokeweed), pooled cells, and purified protein derivative (PPD) of tuberculin showed no response.

Human leukocyte antigen (HLA) typing of the patients and family members showed that the patients were full matches with their brother, Fahad. BMT was done on an emergency basis. Two weeks post-BMT, the patients became highly febrile with the appearance of more nodular lesions. Four weeks post-BMT, an abscess started to develop at the sites of BCG inoculation, coinciding with engraftment of bone marrow. Both patients were treated with a combination of four antituberculous drugs and biweekly IVIG and supportive therapy. During this time, the patients continued to be highly febrile, with temperatures ranging from 38–40°. They showed signs of engraftment 3 weeks post-BMT, with increasing lymphocyte count and normalization of serum immunoglobulins. Abdulkareem developed BCG osteomyelitis of the right metatarsal bone. At 4 months post-BMT, the skin lesions dried up and healed along with healing of the BCG inoculation site. Two years post-BMT, the two brothers were cured. They became immune competent with normal antibody response and normal in vitro T- and B-cell functions.

Comments

Disseminated BCG is uniformly fatal in SCID patients. The only chance for survival is aggressive antituberculosis therapy and emergency BMT form a full-match donor, such as what happened with these brothers. Once the patients engrafted, they started to be highly febrile. Localization of infection was reflected by the development of abscesses at the site of vaccination. The high fever reflects the response to endotoxin released from the dead organisms once the T cells became functionally competent and capable of mounting an immune response.

Case Histories 4 and 5

Amal is a 6-year-old girl, who had BMT at the age of 3 months. Because an older sister had SCID and died at the age of 6 months, Amal was diagnosed at 12 hours postnatally. She was placed in isolation and no BCG was given. Her CBC and leukocyte markers showed lymphopenia of both T and B lymphocytes. At the age of 3 months, her serum IgG, IgA, and IgM were undetectable. HLA and DR class typing showed her brother, Abdullah, to be a full match. She was transplanted without conditioning. Engraftment was apparent after 2 weeks. She reconstituted without complications.

The parents had another male child, Omar, who was diagnosed immediately after birth to have SCID. He was transplanted from his brother. He is alive and well 2 years post transplant. His transplant was across two A, B mismatch loci. He reconstituted for T cells but not for B cells. Currently, he is on IVIG replacement therapy.

Case History 6

Ahlam, a 5-month-old girl, was a product of a full-term, normal pregnancy and delivery. She was referred to the Immunology Service because of persistent thrush and recurrent febrile episodes. At the age of 2 months, she had gram-negative sepsis. At the age of 3 months, she had fever, anemia, and leukopenia. Her hemoglobin dropped to 6 g, and she was treated with nonirradiated packed red blood cells. She developed erythematous maculopapular rash on the cheeks, abdomen, and extensor surfaces of her upper and lower extremities. The rash was nonpruritic. She developed cough and low-grade fever. Her cough continued for 6 weeks until she was referred.

Her physical examination showed extensive oral thrush. She had no BCG scar at the site of inoculation. Her lymphoid system was atrophic, with very small adenoidal tissue. Her lungs were full of fine crepitations. A chest x-ray showed extensive interstitial pneumonia. CBC was remarkable with 15% eosinophilia and lymphopenia, with total T cells of 348/mm^3 and B cells of 108/mm^3. Skin biopsy was compatible with GVHD grade 2. Her serum immunoglobulin levels were extremely low. Lung biopsy was full of *Pneumocystis carinii*. The patient was treated with a combination of TMP/SMX and IVIG. She made a good recovery.

A search for a potential bone marrow donor was started. Her parents had no other children. Their first-born daughter died at the age of 7 months, with a history similar to Ahlam's. The patient received T-cell depleted marrow from her father, using soybean lectin. Her immediate post-BMT course was uncomplicated. She was continued on IVIG and *P. carinii* prophylaxis. There were no signs of engraftment 100 days post-BMT. Shortly after she went home, she developed fever, bilateral cervical lymphadenopathy, and hepatosplenomegaly. A chest x-ray showed bilateral lung infiltrate. The lymph nodes were matted together and rubbery. Cultures were negative. Lymph node biopsy showed lymphoproliferative disease with positive Epstein-Barr virus (EBV) capsid. Her condition deteriorated and she went into respiratory failure and died. Fine-needle aspiration from the lung was full of lymphoproliferative lymphoid cells, similar to histopathology of the lymph nodes.

Comments

This is a classic case of the autosomal recessive type of SCID. She developed a rare complication of depleted BMT (i.e., lymphoproliferative disease), which is uniformly fatal. She presented before 3 months of age and had opportunistic infection with *P. carinii*.

Bare Lymphocytic Syndrome

Case History 1

Bander was 9 months old when he presented to the Immunology Unit. He was the product of a full-term pregnancy, born to first-degree cousins. He had two brothers and four sisters. At the age of 2 months, he had one episode of fever, diarrhea, and dehydration. Since then, he had never been well; his life was characterized by chronic diarrhea and a distended abdomen, with both weight and height being below the fifth percentile. Recurrent fever, oral thrush, and chronically draining ears responded modestly to treatment.

At the age of 6 years, he developed extensive cutaneous atypical mycobacterial infection on both lower extremities (*Fig. 129.6*). The infection cleared up after 6 months of treatment with rifampin and isoniazid. Replacement with IVIG and prophylactic antibiotics reduced the severity and frequency of infections. CBC with differential showed normal numbers of T and B lymphocytes. His serum immunoglobulins were low, including IgG, IgA, and IgM. In vitro assessment of his T- and B-cell function showed moderate depression in response to both mitogens and antigens. HLA and DR typing failed because his cells

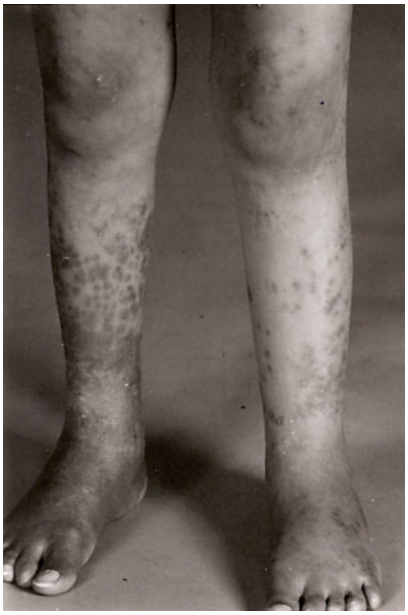

Figure 129.6
Atypical mycobacteria skin infection in a patient with Class II MHC deficiency (BARE Lymphocyte Syndrome)

were not typeable. He had class I and class II deficiency. The patient continued with ill health until he died outside the hospital at the age of 14 years. Since then, several members of the same tribe have been diagnosed with class II MHC deficiency (*Tables 129.1* and *129.2*).

Case History 2

Nahla was 3 months old when she was referred to the Immunology Unit. She was the product of a consanguineous marriage between two second-degree cousins. Early in life, she was noted to have erythematous skin rash that later became scaly. The rash involved the whole body, including the scalp. Her hair was sparse and she had generalized lymphadenopathy, mostly in the axillary areas. She also had hepatosplenomegaly. She developed otitis media and oral thrush. She had several episodes of fever and lung infections. Her in vitro lymphocyte blastogenesis was markedly depressed. Serum IgG was very low. Serum IgE was high; she had eosinophilia of 25% of the peripheral blood. Skin biopsy did not show evidence of GVHD.

The diagnosis of Omenn syndrome was made. HLA and DR class typing showed her mother to be a full match. She was transplanted after conditioning with busulfan and cyclophosphamide. The engraftment failed. Re-transplant was tried after adding radiation as part of her conditioning. The patient died with overwhelming sepsis during the acute stage of BMT.

After that, the parents had two healthy children, a boy and a girl. A third girl, Amal, was born with a clinical picture similar to Nahla at the age of 2 weeks. Successful BMT was performed at 2 months of age.

Table 129.1
Clinical features of 17 patients with the bare lymphocyte syndrome (MHC II & I)

Sex (M/F)	9/8
Clinical presentation in the first year	16/17
Parental consanguinity	15/17
MHC deficiency class II	16/17
MHC deficiency classes I & II	1/17
Chronic diarrhea and failure to thrive	16/17
Recurrent chest infection	14/17
Recurrent ear infection	6/17
Hepatomegaly	7/17
Encephalopathy	–
Truncal ataxia	–
Hypotonia	–
Neurologic involvement	10/17

Table 129.2
Organism associated with infection in 17 patients with bare lymphocyte syndrome (MHC II & I)

Escherichia coli	5/17
Salmonella species	5/17
S. aureus	5/17
Klebsiella species	3/17
Campylobacter	3/17
Streptococci	2/17
H. influenzae	2/17
Pseudomonas sp	2/17
Other bacteria (*Clostridium difficile*, *Citrobacter*, *Enterobacter* spp., atypical myobacteria)	4/17
Viral infections (rotavirus, poliovirus, adenovirus, herpesvirus, respiratory syncytial virus, echo-virus)	10/17
Fungal (*Candida*, *Aspergillus*)	3/17
P. carinii	1/17
Cryptosporidium	1/17

Phagocytic Cell Disorders

Leukocyte Adhesion Defect (LAD)

Case History 1

Laila is a 5-year-old girl seen in the Immunology Unit with the following history. She was born full term to first-degree cousin parents. Her umbilical cord stump fell off at 21 days. At that time she had periumbilical cellulitis with sepsis. She had conjunctivitis and cellulitis of the inner canthus of the right eye. The lesion became necrotic. Pseudomonas species was isolated from the lesion. The cellulitis healed with a scar that led to obstruction of the right nasolacrimal duct. At 11 months of age she was seen in our hospital for diagnosis and management. Earlier she had perianal cellulitis and two episodes of sepsis and one episode of otitis media. She was also found to have persistent leukocytosis and neutrophilia. Immunologic studies showed CD11 and CD18 to be less than 1%. HLA and DR class typing of the patient and her family showed her 6-year-old brother to be a full match. After conditioning with a combination of busulfan and cyclophosphamide, Laila was transplanted from her brother with no complications. Engraftment was evident 3 weeks post BMT. Post-BMT immunologic studies, including in vitro lymphocyte blastogenesis response to mitogens and specific antigens and antibody response, were normal. Four years post-BMT the patient had no infection. Her chromosome analysis revealed 46, XY.

HyperIgE Syndrome

Case History 1

Khalid is a 5-year-old boy whose problem started around 6 weeks of age with skin rash, severe itching, and recurrent sinopulmonary infection. The skin rash was eczematoid and generalized. He had several boils and skin abscesses that grew *Staphylococcus aureus*. His WBC count showed eosinophilia of 17% with a platelet count of 645,000/mm^3. His serum IgE was 115,000 IU/ml (normal, up to 1,200 IU/ml). At the age of 3 years, he had pneumonia that progressed to lung abscess and pneumatoceles (◉ *Fig. 129.7*). He failed to respond to antibiotics. A right lobectomy was performed and histopathology showed extensive inflammation with abscesses; *S. aureus* was isolated. The patient failed to thrive and developed several episodes of lung infections and otitis media. He also developed oral thrush and *Candida* of the thumbs. In vitro culture of his peripheral lymphocytes with mitogens and specific antigens was moderately depressed. His serum IgG2, IgA, and IgM were normal. His serum IgG2 was less than 0.15 mg/dL. The patient was placed on prophylactic antibiotics and monthly IVIG, but continued to have recurrent sinopulmonary infections. His facial features became coarse (◉ *Fig. 129.8*).

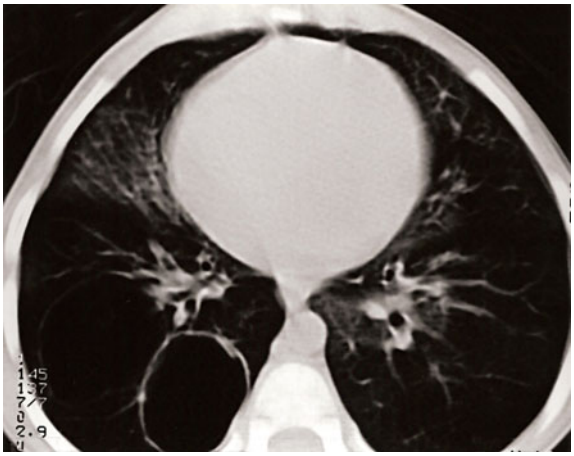

Figure 129.7
CT Chest showing pneumatocele in a patient with Hyper IgE

Chronic Granulomatous Disease (CGD)

Case History 1

Fatma is an 11-year-old girl who was diagnosed at the age of 3 years to have CGD. At the age of 6 weeks, she had perianal abscesses. After that she had several febrile episodes with cervical and gluteal abscesses that required surgical drainage and healed with scars. At the age of 3 years, she had another episode of perianal abscess that left a sinus track after it ruptured. She was found to have cervical and axillary lymphadenopathy. She had splenomegaly of 5 cm below the left costal margin. Her WBC count was 15,000/mm^3 with 78% neutrophils, her hemoglobin was 95 g/L, and her NBT test was 14% of the normal control. There was defective phagocytosis by chemiluminescence.

The patient was placed on prophylaxis with TMP/SMX on a daily basis. Between 3 and 6 years of age, the patient had

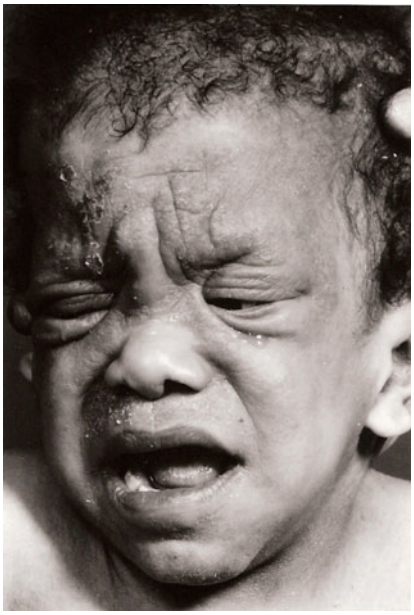

Figure 129.8
Coarse facial features in Hyper IgE

no serious infections. At the age of 7 she had fever and splenomegaly. Cultures were negative and antibiotics were given for 6 weeks with no response. On admission, she was found to have *Aspergillus* right lung pneumonia, empyema, and osteomyelitis of the seventh rib.

The patient was treated with a combination of surgical drainage and intravenous amphotericin B. She showed slow but steady improvement after 6 weeks of treatment. Her treatment was continued at home for 6 more weeks with 100 mg of itraconazole daily. The patient made a complete recovery. At the age of 8, she was placed on IFN-y, 50 $\mu g/m^2$ subcutaneously three times per week. While the patient was on IFN-y, she developed Salmonella sepsis, pneumonia on two occasions, one episode of liver abscess, and extensive pulmonary granulomas. The IFN-y was discontinued and the patient was placed on fluconazole and TMP/SMX prophylaxis. The patient failed to thrive and she looked small for her age.

Case History 2

Abdulrahman, a 3-year-old boy, is the product of nonconsanguineous parents. He was preferred at the age of 27 months because of persistent fever. He was noticed to have slight limping of the right leg and was complaining of abdominal pain in the pelvic area. There was tenderness to palpitation on the fourth and fifth lumbar vertebrae and on the pelvic area.

The WBC count was 18,000/mm^3 with 85% neutrophils. The erythrocyte sedimentation rate (ESR) was 120 mm in the first hour; the NBT test was 9% of the normal control. Magnetic resonance imaging of the abdomen and pelvic area, including vertebral column, showed pus collection in the spinal canal and the retroperitoneal space with osteomyelitis of the fourth and fifth vertebrae.

Laparatomy and drainage of the abscess grew *Aspergillus* species. The patient was treated with a combination of intravenous amphotericin B, leukocyte transfusion, and IFN-y. The response was very slow. The patient's ESR dropped gradually to 60 mm and then to 25 mm. After 6 months of therapy, the lesion started to heal with resolution of the abscess and osteomyelitis of the vertebrae with no residual neurologic deficit.

Case History 3

Sara is a 17-year-old black girl, diagnosed at the age of 6 years to have CGD because of recurrent folliculitis of her scalp and cervical lymphadenopathy. Her NBT test was 21% of the normal control. At the age of 12 years, she had a liver abscess that grew *S. aureus* though she was taking TMP/SMX and IFN-y prophylaxis. Her compliance with the treatment was poor. She developed bilateral pulmonary granulomas with fibrosis (*Fig. 129.9*). Sara had two other sisters, 3 and 5 years of age, diagnosed to have CGD. Their course is generally mild with no deep-seated abscesses. Their parents are first cousins and had five other healthy children, three girls and two boys.

Comments

The first case is a girl with an autosomal recessive disease with a mild course initially, but later on, she developed serious infections while on prophylactic treatment, including IFN-y. Case 2 is a classic X-linked CGD with very low NBT reduction. His disease was associated with abscesses and osteomyelitis early in life. His therapy was a combination of IFN-y, granulocyte transfusion, and antifungal treatment. There was no evidence that IFN-y made a difference in his response to treatment. Case 3 is an example of the mild autosomal recessive type of CGD. Three girls were affected in the family as a result of consanguineous marriage. Their NBT test results were higher than those in the X-linked CGD case, and their infections were generally milder.

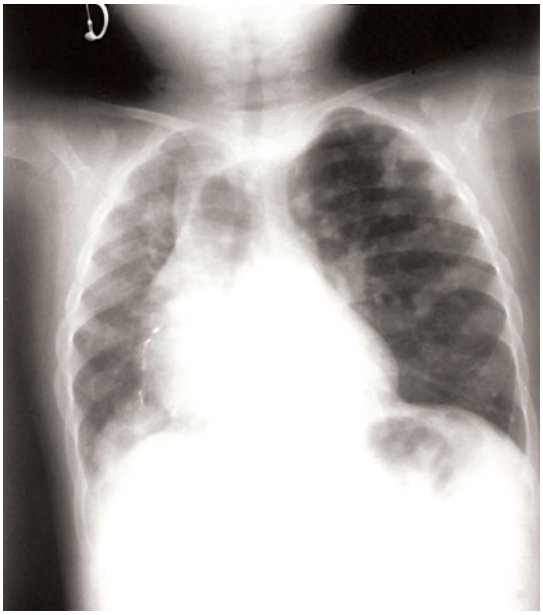

Figure 129.9
CXR in a patient with CGD. Granuloma in right upper lobe

Complement Deficiency

Case History 1

Najla was 3 years old when she was diagnosed for the first time with hereditary angioneurotic edema (HANE). She had repeated attacks of painful, nonpitting edema at different parts of her body that occurred initially once a month (*Fig. 129.10*). Each attack lasted 2–3 days. She had one attack that involved the right temporal area, which left her with a mild visual defect. Her serum C4 was less than 0.2 mg/dL and C1-esterase inhibitor (CTINH) was less than 1% of normal.

She was started on ε-aminocaproic acid in a dose of 6 g daily, which later was reduced to 0.5 g daily. The frequency of the attacks was reduced to once every 2–3 months. During this therapy, the patient complained of some leg aches, muscle weakness, and hypertrichosis when she was on the higher dose. Later on, she was switched to danazol (100 mg/day). The frequency of the attacks dropped to one every 6 months. The frequency increased when the patient forgot to take her hormone. When in remission, her C4 stayed low while the C1-esterase inhibitor increased to 3–5%.

When the patient got married at the age of 18 years, she had more frequent attacks. One of the attacks was associated with respiratory distress. Recently, pure C1-esterase inhibitor was used for treatment of her acute attacks and as prophylaxis before delivery. She had two healthy children with no serious attacks.

Figure 129.10
Nonpitting edema in right hand in patient with HANE

Case History 2

Sara was 9 years old when she had her first attack of *Neisseria meningitidis*. Since that time, she had at least one attack every 9–12 months. Every time, meningococcal meningitis was diagnosed. Her family history was unremarkable, with no similar condition. CBC and serum immunoglobulin levels were normal. Total hemolytic complement (CH50) was zero. Her C6, C7, C8, and C9 levels were very low. Serum C7 was undetectable. The diagnosis of C7 deficiency was made. The patient was placed on rifampicin prophylaxis (200 mg/day) with no recurrence of her meningitis.

Miscellaneous Immunodeficiencies

Mucocutaneous Candidiasis with Immunodeficiency and Endocrinopathy

Case History 1

Yousef was 3 months old when he was seen for consultation because of persistent oral thrush that covered his tongue, buccal mucosa, and angle of the mouth. He also had *Candida* of the nails and the foreskin of the penis (*Candida* phimosis). There was no Bacille Calmette-Guerin (BCG) scar at the site of the inoculation, but he had left axillary

lymphadenitis. Fine-needle aspiration of the fluctuant lymph node grew acid-fast bacilli. The patient was treated for 6 months with rifampin and isoniazid. The lymph node was drained surgically and healed very slowly.

Skin test with *Candida albicans* antigen was negative. Lymphocyte culture with mitogens and purified protein derivative (PPD) of tuberculin and *Candida* showed moderate depression of the response to mitogens but flat response to *Candida* and PPD antigens. Serum immunoglobulin assay showed deficient IgG2 and IgG4. Endocrine function assessment showed hypothyroidism. At the age of 3 years, the patient developed diabetes mellitus. During this time, the patient developed several episodes of sinopulmonary infections. His *Candida* was resistant to mycostatin and miconazole but temporarily responded to itraconazole. The patient developed overwhelming gram-negative septicemia and died at the age of 3½ years.

Case History 2

Ali and Noura are 12 and 9 years old brother and sister, respectively. They had persistent oral thrush and maculopapular rash on the forehead and upper part of the chest and neck (*Fig. 129.11*). Culture of the oral and skin lesions grew *C. albicans*. Skin tests with *Candida* antigen were negative after 48 h. Screening for endocrine function was normal. Serum immunoglobulin assay was normal. In vitro culture of the lymphocytes with mitogens and *Candida* antigen showed normal response to mitogens but absent proliferation with *Candida*.

The oral mucosa cleared partially after topical applications of gentian violet, but there was no response to mycostatin. Oral and topical use of miconazole and ketoconazole was ineffective in clearing the lesions. Long-term treatment with ketoconazole and fluconazole led to limited improvement that relapsed after the treatment was stooped.

There was no problem with recurrent infections, and no complications with immunization. They had mild neutropenia and anemia. Ali developed a small patch of alopecia on the scalp and a limited area of vitiligo on the chest; otherwise continued to be in good general health. This case is mucocutaneous candidiasis without immunodeficiency or endocrinopathy.

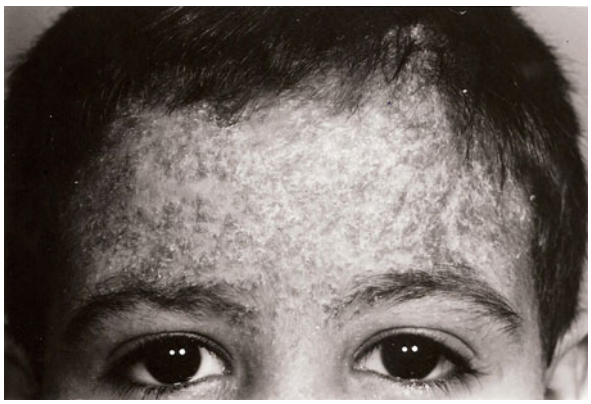

Figure 129.11
Patient with mucocutaneous candidiasis

Wiskott–Aldrich Syndrome

Case History 1

Riyadh was 8 months old when he was referred because of recurrent infections, thrombocytopenia, and eczema. He was full term and a product of nonconsanguineous parents. Two brothers died at the ages of 7 and 10 months because of bleeding, anemia, recurrent respiratory infections, sepsis, and eczema. Those brothers had history of rectal bleeding in the first week of their lives.

Riyadh was found to have thrombocytopenia and rectal bleeding since the first week of his life. He was hospitalized on two occasions for treatment of bleeding and anemia. One month before his referral, he was hospitalized with left pectoralis muscle abscess. He had generalized petechiae and bleeding eczema on the back of the neck, chest, cubital areas, and ankles. He had bilaterally draining ears, the culture of which grew a mixture of *S. pneumoniae* and H. influenza. He had chronic sinusitis. His parents reported history of stools with streaks of blood. He also had nosebleeds and bleeding when scratching his skin. He had small adenoids and atrophic lymphoid tissues. His complete blood count showed lymphopenia and eosinophilia with thrombocytopenia. Serum IgM was less than 0.1 g/L, isohemagglutinin antibody titer was less than 1:1, serum IgE was 5,000 IU/ml (normal up to 72 IU/ml), IgA was 2.1 g/L (normal, 0.3–1.2 g/L), and IgG was 4.8 g/L. Platelet histogram showed 90% of the platelets to be between 2 and 6.2 fL.

The patient was placed on TMP/SMX prophylaxis, IVIG, and transfusion with irradiated blood when indicated. He developed crops of molluscum contagiosum on the face and upper extremities. The skin lesions were treated with local applications of acanthritine and curretting with minimal effect. His hepatitis screening was positive for hepatitis B surface antigen.

At the age of 18 months, he received BMT from his full-matched 4-year-old sister after conditioning with busulfan and cyclophosphamide. The patient developed mild GVHD on day 12, which responded well to treatment. At 3 months, his chromosome analysis showed 46 XX. At 6 months, he was immune competent, and his immunizations were given with good antibody response and without complications. At age 13 years, Riyadh is completely healthy, without bleeding eczema or infections. His serum IgG, IgA, IgM, and IgE all returned to normal values.

Case History 2

Mohammad was 12 h when the diagnosis of WAS was made. He was found to have small sized platelets and a count of 17,000/mm^3. His older brother, Sagr, was known to have WAS. Mohammad had rectal bleeding 48 h postnatally and he developed staphylococcus septicemia with a stormy course. He had two brothers, Rakan, who died at age 2 years with thrombocytopenia of unknown etiology, and 3-year-old Sagr, who was diagnosed to have WAS. Both Mohammad and Sagr had several episodes of bleeding, including per rectum, in the first week of their lives, as well as recurrent otitis media.

As no full-match donor was found, other than a 6-year-old sister with two loci on A and B mismatched, splenectomy was done on both boys. Mohammad had intracranial bleeding that was treated with ventriculoperitoneal shunt. Both brothers had eczema, skin infections, high serum IgE and IgA, and low serum IgM. Both patients were given pneumococcal vaccine before splenectomy and were placed on penicillin prophylaxis. During this time, the older brother, Sagr, developed pneumococcal septicemia and meningitis and died 6 h after admission.

Because of what happened to the two brothers, it was decided to transplant Mohammad, though there were two HLA loci mismatched. The patient was transplanted after conditioning with busulfan and cyclophosphamide. He engrafted with no complications. His chromosome study, post-BMT, showed 46 XX. His serum immunoglobulins returned to normal values, and his platelet count and size normalized. Three years post transplant, the patient is doing well with no infections or eczema.

Chediak–Higashi Syndrome

Case History 1

Atef was 3 months old when he was diagnosed as having CHS; his parents suspected the diagnosis at birth because four of his brothers died with the syndrome. He had typical findings of partially gray hair and freckled skin, and recurrent fever. His peripheral blood and bone marrow had the pathognomonic giant lysosomal cytoplasmic granules. The patient had several febrile episodes with sepsis and pyogenic arthritis. He was treated with antibiotics and ascorbic acid (0.5 g daily).

At the age of 5 years, he developed hepatosplenomegaly, lymphadenopathy, and pancytopenia. In vitro studies showed defective chemotaxis. Biopsy of the liver, bone marrow, and lymph nodes showed infiltration by mononuclear cells. His cerebrospinal fluid (CSF) showed atypical lymphocytes. The patient was prepared for BMT from his 8-year-old sister. Unfortunately, he died from intracranial hemorrhage before he was transplanted.

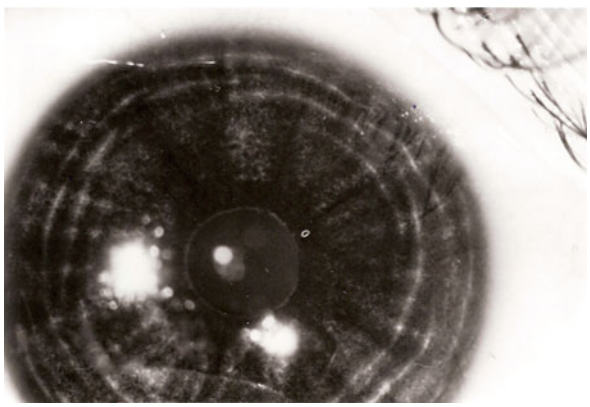

Figure 129.12
Note the partially hypopigmented iris in Chediak-Higashi Syndrome

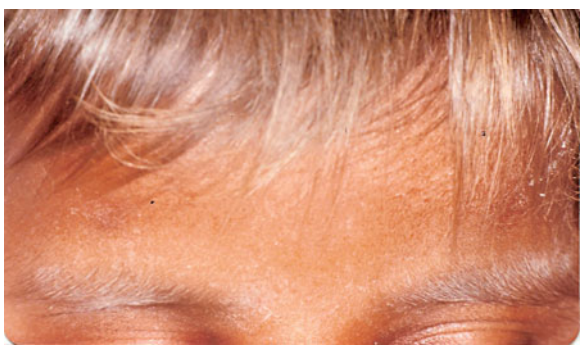

Figure 129.13
Close-up to show the typical hair and skin color in Griscelli Syndrome

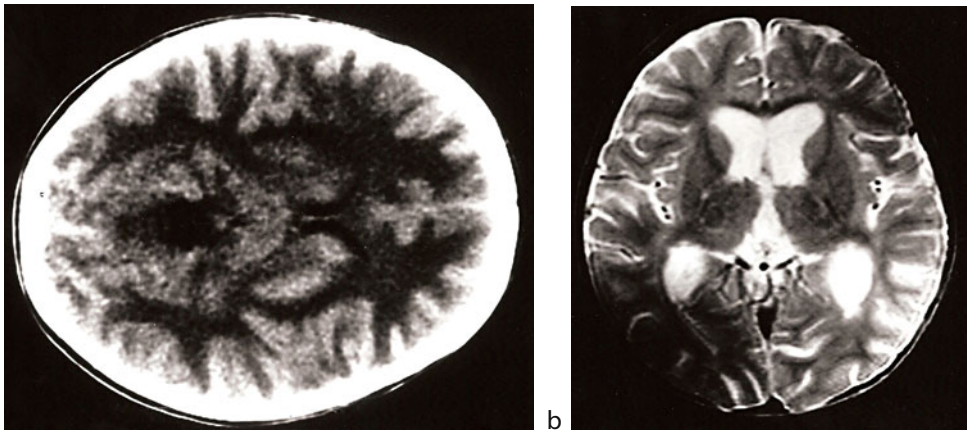

Figure 129.14
(a) CT of the brain of pt. with Griscelli Syndrome. (b) MRI of the brain of pt. with Griscelli Syndrome

Case History 2

Mohammad was a 10-year-old boy at the age of referral. He had lifelong history of recurrent fever and infections, viral, bacterial, and fungal. He was mentally retarded. His features were those of classic CHS, with partial oculocutaneous albinism (*Fig. 129.12*). His skin was very light in color compared to his parents. His white blood cells (WBCs) showed giant granules. He had peripheral neuropathy with foot drop. Sural nerve biopsy showed CHS cells infiltrating the nerve sheath. He had pancytopenia and giant splenomegaly. He required several blood transfusions with fresh frozen plasma, platelets, and packed red blood corpuscles, with no improvement. His leukocytes showed markedly depressed chemotactic activity. Splenectomy resulted in an immediate normalization of all blood elements. The histopathology of the spleen showed signs of hypersplenism and cells with cytoplasmic giant granules. Immunologic studies 6 weeks postsplenectomy showed reversal of the chemotactic activity, and no blood transfusion was needed. Six months postsplenectomy, the patient complained of sudden and severe headache and died within hours at home. The suspected cause of death was intracranial hemorrhage.

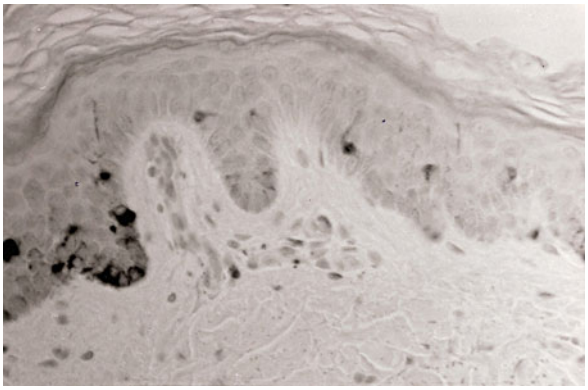

Figure 129.15
High power magnification of skin biopsy of pt. with Griscelli Syndrome

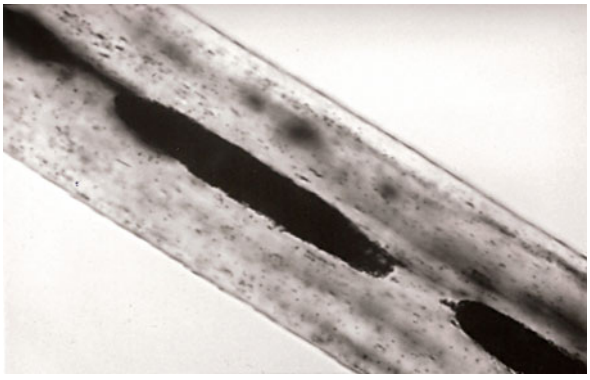

Figure 129.16
Typical appearance of hair under high magnification of Griscelli Syndrome

Griscelli Syndrome

Case History 1

Manal was 5 years old when she was referred to our hospital because of seizure, coma, and the suspected diagnosis of viral meningitis. She was the product of a

full-term pregnancy, born to first-degree cousin parents from the north of Saudi Arabia. She had four sisters and two brothers who were healthy. The parents lost two children, a 2-year-old boy and a 4-year-old girl with history of gray hair, light skin, recurrent fever, anemia, seizure, coma, and death. Their features and clinical history were similar to those of Manal.

Manal was noticed at birth to have freckles with areas of hypopigmented skin with alternating areas of normal skin. Her hair was golden to silvery gray in color, especially on the eyebrows. She had several episodes of fever and was found to have anemia and hepatosplenomegaly. She was given one blood transfusion. One month before her referral, she became febrile, complained of headache, and became lethargic. She also had three short attacks of clonic tonic seizures that lasted for 30 min each. The patient became unresponsive and comatose.

On examination, the patient had typical features of PAID (Griscelli/Harfi syndrome) (◉ *Fig. 129.13a*, *b*). She was deeply comatose and unresponsive to painful stimuli. Her pupils were sluggish in reaction, and her reflexes were depressed. Ophthalmologic exam showed bilateral optic neuritis. Complete blood count showed pancytopenia; her spleen was 8 cm below the costal margin and her liver was 6 cm down. Her alanine transaminase (ALT) was 120 U/L and aspartate transaminase (AST) was 95 U/L. Serum IgG, IgA, and IgM were normal. Isohemagglutinin antibody titer was less than 1:1, with blood group "O" positive. Her CSF showed a WBC count of 18/mm^3; all were lymphocytes. Cytospin and monoclonal study of these cells showed 50% to be B lymphocytes and 50% to be CD4 helper T lymphocytes. CSF protein was 980 mg/dL (normal, up to 450 mg/dL). CT scan and MRI of the head showed extensive white matter demyelination with ventricular dilation and brain atrophy (◉ *Fig. 129.14a*, *b*).

In vitro lymphocyte blastogenesis showed moderately depressed response to PHA, Con-A, and allogeneic pooled lymphocytes with a high response to pokeweed mitogen (2.5 times the control). A skin biopsy showed sparse Langerhans cells but a normal number of melanocytes, with very little melanin in the prickle cell layer of the epidermis. Microscopic examination of the hair showed characteristic distribution of melanin, with areas of clumping and areas of no pigment (◉ *Figs. 129.15* and ◉ *129.16*). The patient was started on a combination of prednisolone, methotrexate (12 mg/m^2 intrathecally, weekly for 6 weeks), and intravenous methotrexate (25 mg/kg every week). The patient started to respond gradually and was able to wake up from her coma. Repeat MRI of the head showed complete recovery of the white matter. The patient continued in remission for 6 months

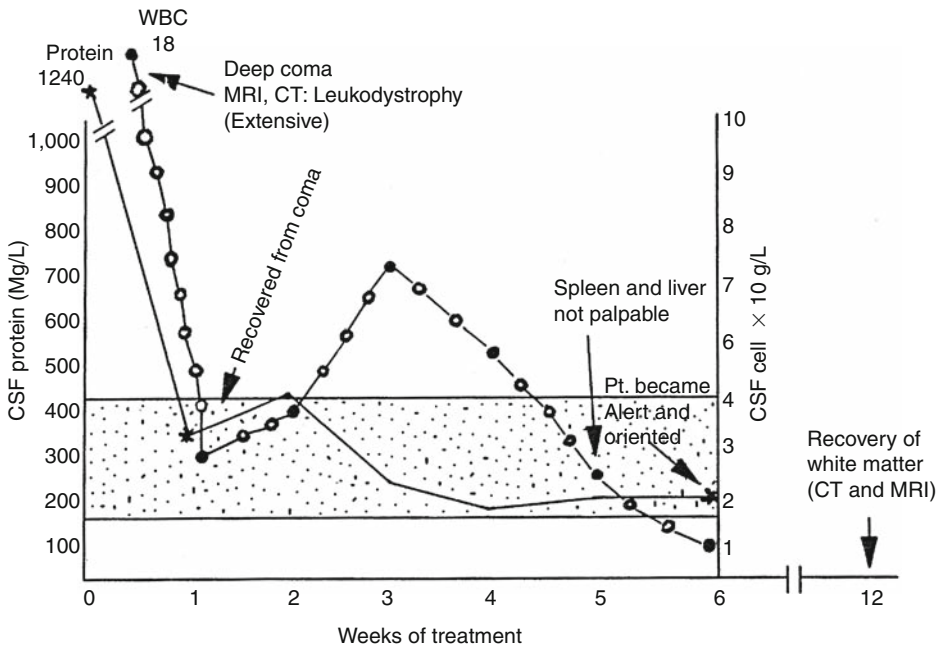

Figure 129.17
Clinical Course of a patient with Griscelli Syndrome

before she relapsed. Repeat of the same treatment failed to induce full remission, and the patient died at the age of 6½ years in a deep coma (Fig. 129.17).

During Manal's follow-up, her mother delivered another boy with the classic features of the syndrome. He was transplanted from his 4-year-old sister with good signs of early engraftment. Unfortunately, the baby developed gram-negative sepsis and died 28 days post-BMT. One year later, the parents had another boy with the same syndrome.

Case History 2

Lubna was the product of first-degree, double-consanguineous cousins. Because the parents had one son

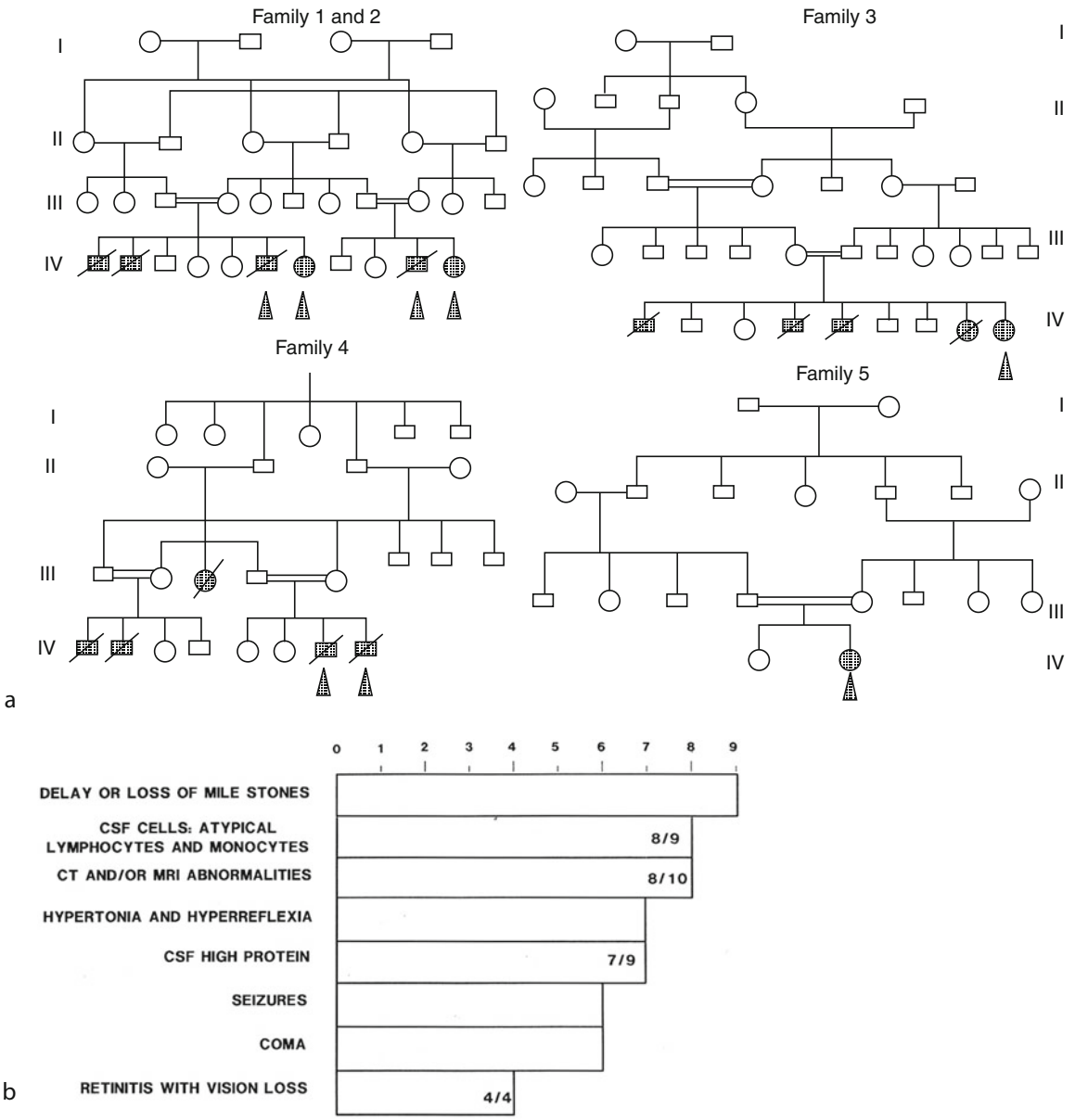

Figure 129.18
(a) Family pedigree of patients with Griscelli/PAID Syndrome. (b) CNS findings in 9 patients with Griscelli Syndrome

Table 129.3
Clinical findings in PAID (Griscelli disease)

Findings		
Total patients	18	Hypertonocity, ataxia-hyper reflexia, hemiparesis, facial palsy, coma, retinitis, mental retardation
Male /Female	9/9	
CNS involvement	11(61%)	High protein mononuclear cells (50% B-cells, 50% CD4)
CFS involvement		
Abnormal EEG	11(61%)	Mild brain atrophy (2 patients)
CT scan and MRI		White matter demyelination (11 patients)
Abnormal CT scan	11	Cerebellum alone (3 patients)
Abnormal MRI	8	generalized (4 patients)

who died a year earlier with the syndrome, and five of their nephews and nieces had the syndrome, they were able to make the diagnosis at birth (*Fig. 129.18*). When Lubna was seen at 1 month of age, she had the classic features of the syndrome. HLA and DR class typing showed one of her brothers to be a full match. After conditioning with busulfan and cyclophosphamide, Lubna was transplanted from her brother. She engrafted without complications. Four years post transplant, she is completely healthy with normal immune functions, but her phenotypic features in regard to hair and skin color did not change.

The father's sister was married to the mother's brother (Lubna's aunt and uncle) and both couples are from the southern part of the Arabian Peninsula. The second couple lost five children with the syndrome; one child died 3 years after BMT from overwhelming sepsis. Her four brothers died in coma as a result of CNS involvement. *Table 129.3* summarizes the clinical findings in 18 patients.

Comments

All 34 cases came from these two tribes, one from the far north and the other from the far south, with no blood relationships or intermarriage between the two tribes. It seems that the gene mutation occurred, probably simultaneously, in these two areas. Only one patient came from Bahrain and had no relationships to either tribe. The defect seems to be a stem cell defect, which can be corrected by early BMT from a full-match donor. *Figure 129.18* shows family pedigrees of some patients with Griscelli/PAID Syndrome.

Allergic Disorders

Harb A. Harfi

130 Allergy and the Allergic Diseases

Karthik Krishnan · William K. Dolen

The management of patients with the allergic diseases is a challenging and rewarding aspect of pediatric practice. It is estimated that 20% of the world's population suffer from one or more of the allergic diseases. For mysterious reasons, the prevalence of allergic diseases among children has increased significantly in the last few decades, resulting in considerable morbidity and mortality. Understanding basic concepts of the allergic diseases is essential to the timely diagnosis and effective management of children with these conditions and their comorbidities.

Definition of Allergy

In 1906, the Austrian pediatrician Clemens von Pirquet introduced the term "allergy" (from the Greek *allos*, "other," and *ergon*, "reaction") to describe a state of hypersensitivity, rather than simple immunity, to foreign proteins. Since then, the term has acquired many different meanings, in medicine, in pseudoscience, and in colloquial speech. Fundamentally, "allergy" is a state of sensitization of the immune system, a disease mechanism, rather than a specific disease entity.

Classification of Immunopathologic Mechanisms

In the modern era, Gell and Coombs have classified mechanisms of immunopathology for the purpose of study (*Table 130.1*). This classification remains very useful in the study of disease mechanisms, although a medical condition in an individual patient might simultaneously involve more than one mechanism. The European Academy of Allergology and Clinical Immunology (EAACI) defines the term "allergy" as inclusive of any of these mechanisms. In the United States, the term usually refers to Type I (IgE-mediated) hypersensitivity, unless otherwise qualified.

Type I Hypersensitivity

Type I hypersensitivity is IgE dependent. A sensitized patient has been exposed to an antigen and by a complex, highly regulated process has made a specific IgE antibody response. Antigens that produce IgE responses are called "allergens." These are typically protein antigens foreign to the body. IgE is a homocytotropic antibody that binds to various cells of the immune system via high-affinity and low-affinity receptors. In a sensitized patient, subsequent allergen exposure leads to cross-linking of allergen-specific IgE molecules bound to mast cells and basophils via high-affinity receptors. Receptor aggregation causes these cells to release preformed and newly synthesized mediators of immediate hypersensitivity, including histamine, tryptase, and leukotrienes (*Fig. 130.1*). In a patient who also has an allergic disease state (for example, anaphylaxis, rhinitis, asthma, and atopic dermatitis), these mediators will produce disease symptoms. Because the mast cell and basophil mediators are released so quickly (seconds to minutes) upon allergen exposure, these reactions are termed "immediate hypersensitivity."

Type II Hypersensitivity

These immunologic reactions are mediated by antigen-specific IgG or IgM class antibody bound to cell surfaces via specific receptors. Antigen binding by antibody causes lysis of sensitized cells, often by complement-dependent mechanisms. Clinical examples include hemolytic anemia of the newborn (which is not usually complement dependent), Goodpasture syndrome, and some types of transplant rejection.

Another disease mechanism now classified as Type II involves an autoantibody to a cell surface receptor. Antibody binding can either prevent receptor-mediated signaling, or induce it. In some cases of chronic urticaria, an autoantibody to a component of the high-affinity IgE receptor can cause mast cell activation in a non-IgE-mediated

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Table 130.1
The classic Gell and Coombs classification of hypersensitivity reactions

Class	Reaction type	Immunologic mechanism	Clinical disease example
Type I	Immediate hypersensitivity	IgE-mediated	Anaphylaxis
Type II[a]	Cytotoxic	Cell-bound IgG or IgM	Hemolytic anemia
Type III	Immune complex	IgG or IgM	Vasculitis
Type IV	Delayed hypersensitivity[b]	T lymphocyte mediated	Contact dermatitis

[a]A second mechanism now classified as Type II involves an autoantibody to a cell surface receptor
[b]Another mechanism involves T lymphocyte–dependent activation of eosinophils and other cells

manner. An autoantibody to the thyroid-stimulating hormone (TSH) receptor can cause unregulated thyroxin synthesis (Grave's disease), whereas a different autoantibody to the same receptor can block the action of TSH, resulting in hypothyroidism.

Type III Hypersensitivity

Type III hypersensitivity involves formation of immune complexes of antigen and antibody, of IgM or IgG class. The relative proportion of antigen and antibody determines immune complex size. When circulating immune complexes deposit in small blood vessels in tissue, they can activate the complement system, resulting in vasculitis with tissue destruction. Disease manifestations depend on which tissues are involved. Clinical examples include serum sickness, rheumatoid arthritis, and the Arthus reaction.

Type IV Hypersensitivity

Unlike the other three types of hypersensitivity, classic Type IV reactions are mediated by antigen-specific Th1 and cytotoxic T lymphocytes. Because T cell activation is a relatively slow process, it takes 1–3 days for disease manifestations to appear. Contact dermatitis is a clinical example. A different example of Type IV hypersensitivity involves T lymphocyte–dependent activation of eosinophils and other cells, resulting in non-IgE-mediated rhinitis or asthma.

Allergy and the Allergic Diseases

Sensitization to antigen, resulting in the formation of antigen-specific antibodies or T lymphocytes, is not necessarily a disease state. Sensitization is found in normal, asymptomatic individuals. In order for a sensitized individual to develop symptoms following antigen exposure, the patient must have a disease state in addition to immunologic sensitization. This concept will be explored in terms of Type I hypersensitivity.

The diseases commonly associated with Type I hypersensitivity are often called the "atopic diseases" or the "allergic diseases." The classic atopic diseases, which have a hereditary tendency, are rhinitis, asthma, and atopic dermatitis. These conditions are often called the "allergic triad" since they tend to occur together in the same patient at different stages of life. Disease symptoms can be produced by different immunologic mechanisms, primarily Type I IgE-mediated immediate hypersensitivity. However, they are not invariably IgE dependent; disease manifestations can be triggered by various immunologic and nonimmunologic mechanisms. For example, asthma can be triggered by respiratory virus infections (nonallergic, or "intrinsic," asthma) or by cat exposure in a cat-sensitized patient (allergic, or "extrinsic," asthma). Other diseases that can be triggered by IgE-dependent as well as non-IgE-dependent mechanisms include anaphylaxis, urticaria, and some types of conjunctivitis and gastroenteritis (in particular, eosinophilic gastroenteritis).

Risk Factors in the Development of the Allergic Diseases

The etiology and pathogenesis of the allergic diseases are the subject of worldwide research. The clinical manifestation of an allergic disease involves a complex interplay between host characteristics (i.e., race, gender), genetic influences, and a multitude of environmental factors. The contribution and interaction of these factors differ among the atopic diseases and are poorly understood.

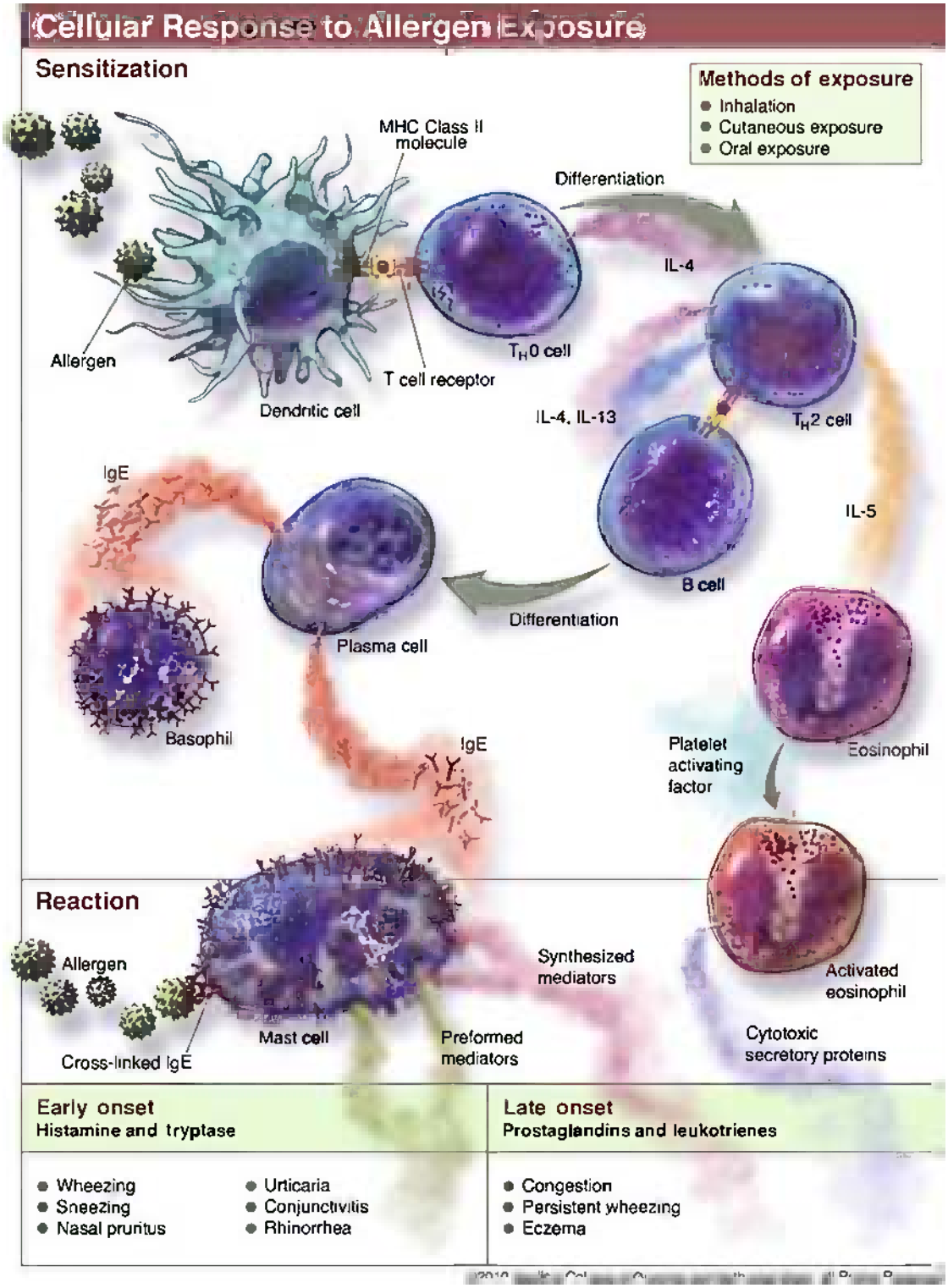

Figure 130.1
Cellular responses to allergen exposure: sensitization and reaction

Furthermore, whether an individual patient also has IgE-mediated allergic sensitization is an additional variable affecting disease expression.

The atopic diseases have a strong hereditary tendency, whereas the inheritance pattern of the other allergic diseases is highly variable, suggesting variable expression between different groups of genes. Certain individuals may co-express several atopic diseases while others manifest only one atopic disease. The atopic diseases can also occur without a family history of these diseases. The incidence of atopic disease is approximately 10% when neither parent has an atopic disease, 50% if one parent is atopic, and 66% when both parents have an atopic disease. Extensive genomic studies have identified specific genes associated with atopic diseases; however, no definitive casual genes have been discovered. Other factors involved in the development of atopic diseases are environmental factors such as allergens (both indoor and outdoor), animal exposure, air pollution, infections, gut flora and other microbes, antibiotics, air pollution (both indoor and outdoor), environmental tobacco smoke, maternal diet, obesity, and low vitamin D levels.

Children are not born with IgE-mediated allergic sensitization, but rather with the ability to produce specific IgE antibodies in response to environmental exposures. Reasons for this appear to be independent of, but somehow related to, mechanisms for developing the allergic disease state. External exposures are necessary for sensitization in susceptible individuals. Routes of exposure include inhalation, ingestion, or direct contact. The production of specific IgE antibody to allergens may take weeks to years of exposure.

Whether or not there is concomitant IgE-mediated allergic sensitization, a common feature of the chronic allergic diseases (such as rhinitis, asthma and atopic dermatitis) is eosinophilic inflammation. Successful management brings this inflammatory response under control.

Clinical Approach to Patients with Suspected Allergic Disease

Evaluation of all patients begins with a detailed medical history and physical examination, with the intent of establishing whether an allergic disease might be present, and determining what factors might be triggering acute symptoms and sustaining chronic inflammation. Symptoms of allergic diseases typically involve the eyes, nose, lungs, skin, and gastrointestinal system. Each symptom has a unique differential diagnosis based on the age of the patient. For instance, wheezing at birth is likely due to an anatomical defect, whereas the sudden onset of unilateral wheezing in a two-year-old is highly suspicious for a foreign body aspiration. Furthermore, symptoms such as wheezing, sneezing, and eczema are not specific for the allergic diseases but may be seen in many other conditions. The goal of the history and physical examination is to generate a differential diagnosis that will guide further evaluation, including any necessary diagnostic testing (laboratory or procedural).

A good medical history helps establish whether an allergic disease might be present, and identifies potential immunologic and nonimmunologic trigger factors. The history identifies which symptoms are (pertinent positive) or are not (pertinent negative) present, and carefully characterizes them by eliciting the onset, location, duration, characteristics, associated symptoms, relieving factors (including medications and other treatments), temporal factors, and severity of symptoms.

The history identifies the age at which symptoms began and how long they have been present. Atopic dermatitis begins in infancy, allergic rhinitis normally after two to three years of appropriate exposures, and eventually asthma. This sequence is commonly referred to as the "atopic march." The next line of questions should pertain to the symptom pattern. Are symptoms acute or chronic? Are they continuous (perennial), intermittent (seasonal), or intermittent exacerbations superimposed on a continuous background? Knowledge of pollination patterns of regional flora helps in correlating symptoms with the appropriate seasonal exposures. Environmental allergens such as house dust mites, animal dander, and fungi are present year round, albeit at different levels of exposure. An understanding of the frequency and severity of episodes reveals the impact on the quality of life of the patient. Children with mild symptoms that occur infrequently rarely come to the office. On the other hand, the allergic diseases can produce frequent episodes resulting in school absenteeism, considerable morbidity, and mortality. Symptom patterns that change in severity or character over the years may alter the diagnostic approach. For instance, a five-year-old who previously had nasal symptoms only in the spring, but now has symptoms in the fall, warrants repeat skin testing to identify sensitization to new triggers.

It is useful to ask the patient and parents what they suspect as triggers, exacerbating or precipitating symptoms such as pollens, dust, animals, foods, odors, and medications. Most patients are conscious of obvious triggers. Elicit whether symptoms are affected by infections, emotions, hormonal factors (pregnancy or menstruation), and changes in climate (humidity and temperature).

One asks whether symptoms occur at a particular time of day, such as upon awakening in the morning or worse at night. Are there particular locations where symptoms are worse or better such as a friend's home, school, hospital, indoors, or outdoors? Are the same symptoms present while visiting a different geographical location or while vacationing on a beach?

Details of timing and location of symptoms are relevant to correlating this information with suspected allergens and other trigger factors, allowing the clinician to identify potential causes of the patient's symptoms. Specific allergy testing, if indicated by the history, should confirm this impression. Positive skin test reactions with allergens are clinically relevant only if they correlate with the possibilities suggested by the history. If a skin test is negative to a particular allergen suspected to be relevant by history, this does not automatically dismiss the relevance of the history.

Information regarding previous and current medications should be reviewed. A detailed medication history should include dosage, frequency of usage, start date, efficacy, and adverse effects for all medications. A good response to medical therapy may suggest an allergic basis of the patient's symptoms. For instance, corticosteroids typically improve symptoms of allergic diseases. Lack of benefit may indicate other causes for the symptoms. However, medication failure may also result from improper use or lack of adherence. Certain medications, such as antihistamines, decongestants, and corticosteroids, may alter physical findings or skin test results. It is important to know when the last dose of antihistamine was taken since they can suppress skin test reactivity for days or weeks.

A detailed environmental history is a unique feature of an allergy history. An understanding of a patient's environment is important for identification of possible triggers and exposures to particular allergens (*Table 130.2*). It is also useful in planning environmental control measures. The indoor environment is the source for both allergens and non-specific irritants. The major indoor allergens include house dust mites, cockroaches, animal dander, and molds. A detailed description of indoor environment with special attention to the child's bedroom(s), pet exposures, and presence of a basement or water damage is helpful in determining the influence of the above indoor allergens in the home. Non-specific irritants include environmental tobacco smoke exposure, gas appliances, heating and cooling systems, and car exhaust fumes from attached garages.

The family history identifies the presence of atopic diseases in the parents and/or siblings. A family history of atopic disease increases the probability that the patient has an allergic disease. The social history should account normal daily activities, hobbies, and occupation of the patient. The past medical and surgical histories often reveal pertinent information. For instance, a history of extreme prematurity requiring prolonged assisted ventilation would be important in formulating the differential diagnosis of wheezing in a child. A thorough dietary history may reveal adverse food reactions that might be relevant to present symptoms. Hospitalizations and injuries should be documented. Operations such as tonsillectomy, adenoidectomy, and sinus surgery should be noted. The review of systems may uncover symptoms not reported in earlier parts of the history, suggest the presence of other diseases, or reveal comorbid conditions such as gastrointestinal reflux.

Table 130.2
Potential environmental triggers

Outdoor allergens	Indoor allergens	Irritants
Pollens	House dust mite	Tobacco smoke
Tree	Animal dander	Pollutants
Grass	Cockroach	Diesel exhaust particles
Weed	Other pests	Ozone
Fungi	Mouse	Cleaning chemicals
	Rat	Strong odors
	Molds	Perfumes
	Foods	Candles
		Air fresheners
		Temperature changes
		Cold air
		Humidity
		Emotions

The physical examination may provide additional clues for an accurate diagnosis. Vital signs and growth parameters warrant careful review. Children with chronic diseases may have poor growth either from the disease itself or from effects of therapy. The examination will report the overall general appearance of the child. Is he well developed and nourished? Does she have any obvious signs of allergic diseases? Following this brief visual inspection, an organized systematic approach to the examination is useful in identifying allergic manifestations in various organ systems. Particular features of the physical examination commonly seen in allergic diseases are conjunctival injection and edema, periorbital swelling, dark discoloration and/or wrinkles beneath the lower

eyelids, wrinkling of the nose, pale to blue mucosa with edematous nasal turbinates, pruritic, eczematous patches of skin, and presence of dermatographism. Abnormal findings on chest examination are usually seen in acutely sick children or children with severe, chronic asthma. The absence of lung findings does not exclude asthma.

Basic Testing

Laboratory and procedural evaluation should corroborate the clinical impression from a complete allergy history and physical examination. Basic testing is planned to address the differential diagnosis. Sometimes, no testing is indicated.

When asthma is suspected, spirometry, an objective measure of lung function, is indicated in children older than 4–5 years of age to evaluate for airway obstruction and reversibility. Regardless of pre-bronchodilator results, the initial evaluation should include a post-bronchodilator study to evaluate for reversibility of obstruction. Although no reversibility cutoff has been established in children, many have adopted the adult criterion of >12% reversibility (and >200 mL) in FEV1 following bronchodilator therapy to make a firm diagnosis of asthma. The lack of reversibility does not refute the diagnosis of asthma.

Bronchial provocation challenge can be used to assess airway responsiveness in patients with normal baseline spirometry. The agent most commonly used is methacholine, a potent non-specific bronchoconstrictor. Histamine, mannitol, exercise, and cold air are useful alternatives for some situations. Challenge testing determines the presence and magnitude of bronchial hyperreactivity in patients with normal or near-normal spirometry. The patient inhales increasing concentrations of methacholine until a 20% drop in FEV1 from baseline is noted. A negative methacholine challenge greatly lessens the likelihood of asthma; however, a positive challenge does not confirm the diagnosis of asthma, given the test's poor specificity.

The measurement of the level of fractional exhaled nitric oxide (FeNO) is being utilized both in asthma diagnosis and monitoring of asthma control. The FeNO level is a noninvasive biomarker of eosinophilic airway inflammation. Patients with uncontrolled asthma have higher levels of FeNO compared to those without asthma. FeNO concentrations acutely rise in conjunction with increased airway inflammation, sputum eosinophilia, and upper respiratory infections. Treatment of asthma with inhaled corticosteroids results in a decrease in FeNO levels. The equipment and supplies required to measure FeNO levels are affordable, simple to operate and maintain, and easily performed by most school-aged children, making it a very appealing tool. Reference values for FeNO concentration levels are based on age. FeNO levels are affected if performed after spirometry or after consuming foods high in nitrates.

However, the correlation between airway inflammation, FeNO levels, and asthma is not well delineated. It is not yet clear whether FeNO should be used as a diagnostic tool for asthma, to guide asthma management, or to monitor asthma control. Results of FeNO testing do have a high negative predictive value for the diagnosis of asthma (i.e., a low FeNO level lessens the likelihood of asthma), similar to methacholine challenge. There are conflicting results in the literature regarding the utility of serial FeNO levels to guide asthma management and predict asthma control following modifications in therapy. Further, controlled clinical trials may better define the role of FeNO measurement in the diagnosis and management of asthma.

Any child presenting with nasal obstruction warrants a detailed examination of the anterior and posterior nasal cavity. Rhinoscopy is a relatively simple and safe method for visualizing the upper airway anatomy in an office-based setting. Examiners can routinely identify the cause of the nasal obstruction, which may include mechanical obstruction from adenoidal hypertrophy, nasal polyps, or choanal stenosis.

In patients with suspected uncomplicated allergic disease, a complete blood count might show an elevated absolute peripheral eosinophil count (>500 cells per microliter). While this is a common finding in children with atopic diseases, it lacks diagnostic specificity. Other conditions associated with peripheral blood eosinophilia include malignancy, hypoadrenalism, drug reaction, collagen vascular disease, and parasitic infestation.

Allergy Testing

Because of the complexity of identifying triggers of allergic diseases, selecting appropriate test methods, performing testing, and interpreting results, allergy testing is fundamentally a subspecialty procedure. Various test methods are available.

Serum total IgE levels are not usually useful in the evaluation of patients with suspected allergic disease. While total IgE serum levels are often elevated in such patients, particularly in atopic dermatitis and asthma, an elevated serum total IgE level is not specific for the allergic

diseases. Consequently, this test has very limited value as a diagnostic tool for allergic disease.

Specific allergy testing by in vivo or in vitro methods is used to determine the presence of specific IgE to various allergens (*Table 130.3*). The presence of specific IgE indicates sensitization, not disease. The disease state occurs when only clinical symptoms correlate with results of allergy testing.

Allergen provocation testing is performed to determine the association between allergen exposure and the presence of symptoms. In provocation challenge testing, allergens are directly exposed to the skin, conjunctiva, nasal mucosa, or lungs.

Skin Testing (In Vivo)

When indicated, skin testing can be performed in patients of any age, including infants. The selection of allergen extracts (pollens, house dust mites, animal dander, molds, and foods) to be tested should be individualized based on the history. There are two skin testing techniques, namely, epicutaneous and intradermal, each with advantages and limitations. In the skin prick test, a drop of allergen extract is applied to the patient's skin, usually the back or ventral surface of the forearm. The allergen extract is introduced into the epidermis by a gentle needle prick or puncture through the drop of extract. A positive control (histamine) and a negative control (saline) are placed at the same time to assess skin reactivity. Patients with dermatographism may react to the skin pressure involved in performing testing, resulting in false-positive results. A poor histamine response indicates the presence of an antihistamine or related agent, resulting in false-negative results. The sizes of the wheal (swelling) and flare (erythema) are measured 15–20 min after test placement. There is international consensus that a wheal size at least 5 mm larger than the negative control is a "positive" result; some clinicians will accept smaller reactions as positive. The size of the reaction does not necessarily correlate with the severity of symptoms.

Intradermal skin testing is a more sensitive, but less specific, alternative to the skin prick test. A small amount (0.02 mL) of diluted allergen extract is injected into the dermis of the arm. It is often used for testing with low-potency extracts, such as drugs and insect venoms. Some clinicians apply intradermal tests when skin prick testing is negative, but the patient has a convincing history suggesting sensitization. It is controversial because of a lack of studies supporting clinical utility in this situation, and non-specific irritant reactions are commonly seen when concentrated extracts are used. Practice guidelines recommend not testing for food allergens by the intradermal technique due to the increased risk of systemic reactions (anaphylaxis). Skin testing is rapid, inexpensive, and correlates well with symptoms. Disadvantages include inconvenience of discontinuing antihistamine 3–7 days prior to testing, discomfort from pruritus, and minute risk of a systemic reaction.

In Vitro Testing

There are several immunoassay methods available to detect the presence of allergen-specific IgE antibody in the serum. The test is performed by incubating an allergen extract coupled to a solid phase matrix with a small amount of the patient's serum. Antibody present in the

Table 130.3
Comparison between specific allergy tests

	Skin test (in vivo)	Serum specific IgE (in vitro)
Test	Prick or intradermal test	Radioallergosorbent test (or modified version of assay)
Advantages	Immediate results	No risk of systemic reaction
	More sensitive than in vitro test	May continue antihistamine
	Inexpensive	
Disadvantages	Discontinue antihistamine use	Delayed results
	Risk of systemic reaction	Less sensitive than in vivo test
	Discomfort from pruritus	Increased cost
	Unable to perform in severe atopic dermatitis and dermatographism	

patient serum binds to the allergen-matrix. Specific IgE is detected by incubation with a labeled anti-human IgE antibody. The amount of IgE antibody bound to the allergen-matrix correlates to the quantity of serum allergen-specific IgE. Higher levels of allergen-specific IgE are more predictive of clinical symptoms. The main advantages of the blood allergy tests are safety (no risk of anaphylaxis, although there is a risk of phlebotomy-related syncope) and present no interference of results from medications, atopic dermatitis, or dermatographism. Although blood testing is less sensitive than skin testing, results correlate fairly well with skin testing. Disadvantages include cost and delay in results.

Food Challenge Testing

As noted above, allergen-specific IgE sensitization can occur without clinical manifestations. Oral food challenges determine whether a specific food has a causal relationship to symptoms and can help decide whether it is safe to re-introduce a specific food into a child's diet, given a history of an adverse reaction. There are three forms of oral food challenges: open, single blind, and double blind placebo-controlled. The latter is the gold standard for research, and is most appropriate clinically when the patient's symptoms are vague or subjective. In blinded studies, the smell and taste of the food being challenged is disguised. The patient is gradually challenged with increasing amounts of food at set time intervals until a reaction occurs or the patient tolerates an entire meal. Challenges are not commonly used to evaluate patients who have had severe anaphylaxis. In patients at risk, challenges should be performed in a medical facility with trained personnel equipped to treat anaphylaxis.

Unproven Tests

In the lay press and the pseudoscientific literature, various vague or subjective symptoms such as hyperactivity, fatigue, myalgia, and learning difficulties have been empirically attributed to "allergy." Specific IgE testing by any accepted method is not helpful in such situations. Unproven diagnostic tests, not based on sound scientific principles, are sometimes used to identify environmental triggers (inhalants and chemicals) or foods in order to explain a constellation of poorly characterized symptoms. The diagnostic value of these tests has not been examined or validated in rigorous controlled clinical trials. Furthermore, many of these tests are expensive and not covered by insurance companies. Examples of unproven tests include exposing various substances to the patient in an attempt to reproduce symptoms (provocation testing); presence of morphologic changes in peripheral blood leukocytes exposed to an allergen (the cytotoxic test); measuring changes in leukocyte cell volumes following allergen exposure; measuring electrical impedance of the skin exposed to various food or inhalant extracts (electrodermal testing); and estimating muscle strength while holding allergens (applied kinesiology).

Managing Patients with Allergic Diseases

General Principles of Management

There is presently no cure for any of the allergic diseases, whether allergen-specific IgE is playing a role, or not. Thus, the basic goals in the management of allergic diseases include symptom control, decreasing exacerbations, and improving quality of life. In patients with IgE-mediated sensitization, these goals are achieved by avoidance of allergens and irritants, appropriate pharmacotherapy, and allergen immunotherapy. For patients with allergic diseases without evidence of IgE-mediated sensitization, management focuses on avoidance of nonallergic triggers (such as irritants), and pharmacotherapy.

When symptoms are only triggered by IgE-dependent mechanisms, the most effective mode of treatment is avoidance of known allergens, which is possible for many foods and drugs. However, strict avoidance of other trigger factors is difficult and not practical. Pharmacotherapy offers a wide selection of medications and minimal side effects, providing control of underlying inflammation and relief of symptoms. Immunotherapy is the only treatment option that can alter the natural history of the disease, producing a long-term remission of symptoms. Immunotherapy demands a time commitment from the patient and is expensive. Symptoms of allergic diseases can be successfully controlled with a combination of management options along with regular patient education.

Allergen Avoidance

Patients with the allergic diseases report allergic (IgE-dependent) and nonallergic triggers. Environmental control measures are the most effective means of reducing symptoms precipitated by trigger factors. Most children spend the majority of their day indoors, at home, or school. House dust mites, cat, and cockroach are the most

significant triggers in the indoor environment. Other pets, pests, fungi, and non-specific irritants (tobacco smoke and strong odors) can also be problematic.

Although no measures are available to completely eradicate house dust mites, significant reduction in exposure can be achieved. In sensitized patients, dust mite avoidance practices should be emphasized in the child's bedroom and bed since one-third of their day is spent in this one room. Appropriate and effective control measures include impermeable encasings on pillows, the mattress, and box spring; washing beddings weekly in bleach and hot water; and minimizing or removing items that collect dust (i.e., carpet, drapes, upholstered furniture, and stuffed animals). Other possible measures include removing room humidifiers since dust mites do not survive in <50% relative humidity and vacuuming floors and furniture weekly.

Many families own pets, most commonly a cat or dog. The major allergen source for these animals is hair, dander, and saliva. When a family member is allergic to a beloved pet, some families will remove the pet from the home, and others will not. Even after pet removal, pet allergen may be present for many months. The major cat allergen, Fel d 1, is particularly problematic since it is highly charged and sticks to a variety of surfaces. As a result, cat allergen is ubiquitous and is commonly transported to public places, including schools where cat allergen can be found on clothes of children who do not have pets.

Non-specific irritants in the home are often overlooked as symptom triggers. The use of products that generate strong odors (e.g., candles, perfumes), kerosene heaters, and wood burning stoves should be discouraged. Environmental tobacco smoke is a major indoor pollutant, and smoking cessation should be encouraged and discussed on a regular basis.

Avoidance of outdoor allergens is impractical, although certain measures will limit exposure. Limiting certain outdoor activities such as mowing the lawn during the grass pollen season significantly decreases exposures. Windows and doors should be kept closed during periods of high pollen levels to minimize exposures.

Pharmacotherapy

For all of the allergic diseases, the goal of pharmacotherapy is to control the disease by reducing underlying inflammation, and to provide relief from breakthrough symptoms. At the same time, it is important to minimize adverse effects from therapy. Drugs alleviate symptoms in allergic diseases by inhibiting or downregulating inflammatory mediator production and/or release, acting as mediator receptor antagonists, or promoting sympathomimetic effects. Certain medication classes are used for controller (preventive) therapy while others are more appropriate for relief (rescue) therapy. Controller medications are taken on a regular basis while reliever drugs are used as needed for acute symptom relief. It is very important to educate patients about the difference between "controller" and "reliever" medications, so that they will be used appropriately. The allergic diseases affect different organ systems. The concepts of therapy are similar, but the specific medications differ (Table 130.4). Most importantly, regardless of which medications are used, adherence and education on the proper use of these medications is the key to successful management.

Controller Therapy

Asthma controller medications include inhaled corticosteroids, leukotriene synthesis inhibitors and receptor antagonists ("antileukotrienes"), and cromolyn. Long-acting beta-2 receptor agonists, and theophylline have some anti-inflammatory action, and are sometimes classified as asthma controller therapy. Inhaled corticosteroids are recommended as first-line therapy for persistent asthma symptoms because of their potent anti-inflammatory properties. The other medications listed above are alternatives or add-on therapy to gain improved control of symptoms. Antileukotrienes and long-acting beta agonists are the most common add-on controller medications used. Cromolyn and theophylline are less frequently used due to compliance issues and safety concerns, respectively. Anti-IgE therapy, using recombinant humanized monoclonal antibody to IgE, is used in patients with allergic asthma, and is being studied in other conditions.

Controller medications for allergic rhinitis include intranasal corticosteroids, intranasal cromolyn, and leukotriene synthesis inhibitors and receptor antagonists ("antileukotrienes"). The most effective first-line therapy for control of nasal symptoms is a topical intranasal corticosteroid. Intranasal cromolyn is effective and safe but requires frequent dosing. Antileukotrienes have most thoroughly been studied as reliever therapy for rhinitis symptoms, and seem to be effective controller therapy in a subset of patients. Oral and topical intranasal antihistamines are most often used as symptom reliever therapy, but some products do have some degree of anti-inflammatory effect. Regular therapy is an alternative to intranasal corticosteroid therapy. For patients with problematic ocular symptoms, an antihistamine and a mast cell stabilizer are most effective in controlling symptoms.

Table 130.4
Pharmacotherapy options

Disease	Controller therapy		Reliever therapy
	First-line	Add-on	
Asthma	Inhaled corticosteroid	Long-acting beta agonist	Short-acting beta agonist
		Antileukotriene	Anticholinergic agent
		Theophylline	
		Cromolyn	
Rhinitis	Intranasal corticosteroid	Antileukotriene	Oral or intranasal antihistamine
		Intranasal cromolyn	Decongestant
			Intranasal anticholinergic
Atopic dermatitis	Oral antihistamine	Calcineurin inhibitor	Oral antihistamine
	Topical corticosteroid		

Regular antihistamine therapy, and non-specific skin hydration measures can decrease pruritus in patients with atopic dermatitis. When needed to control an exacerbation, topical corticosteroids are appropriate controller medication for atopic dermatitis. Different potencies of topical corticosteroids are used based on the severity of disease. Topical calcineurin inhibitors are used as add-on therapy in cases of severe atopic dermatitis. Some experts recommend systemic immunosuppression for the most severe cases.

Reliever Therapy

Short-acting beta agonists are the medication of choice for acute relief of asthma symptoms. Anticholinergics have been used as reliever medications in asthma, benefitting a select group of patients. Some antihistamines have a mild bronchodilator effect, but none are used as reliever therapy in asthma.

Antihistamines (oral and intranasal), and sympathomimetic decongestants are most commonly used for acute relief of nasal symptoms. Oral decongestants should be used sparingly for short periods of time with caution in children due to concerns of side effects. Topical decongestant sprays are also only for short-term therapy. Anticholinergics are effective against rhinorrhea of various etiologies.

Immunotherapy

Specific allergen immunotherapy modifies the immune response to limit or prevent symptoms upon exposure to the putative allergen. Because of the complexity involved in identifying appropriate patients for treatment, identifying allergen extracts for therapy, and writing the immunotherapy prescription, it is primarily a subspecialty procedure. However, while subspecialists should prescribe immunotherapy, patients may prefer to receive injections in their pediatrician's office. Current practice guidelines do not support the giving of injections at home because of the complexity of treating anaphylaxis.

Three routes of administration that have been used for immunotherapy, subcutaneous, sublingual, and oral immunotherapy, have proven to be effective in inducing tolerance (*Table 130.5*). In the United States, subcutaneous immunotherapy is the most established and widely practiced, whereas sublingual immunotherapy is considered investigational. Oral immunotherapy for severe food allergy is in clinical trials with encouraging results. Each of these forms will be discussed.

Subcutaneous Immunotherapy

Conventional immunotherapy is a clearly effective treatment option for both seasonal and perennial allergic rhinitis, allergic asthma, and insect venom anaphylaxis. It has not been well-studied for food anaphylaxis, atopic dermatitis, or urticaria, and its use in treatment of these conditions is controversial. Immunotherapy involves the subcutaneous injection of increasing doses of specific allergens in individuals to induce tolerance upon natural exposure to the offending allergen. Successful immunotherapy diminishes and prevents symptoms by inducing immunologic changes, hence modifying disease duration and progression. Immunotherapy increases production of specific IgG-blocking antibodies, increases activity of specific regulatory

Table 130.5
Comparison between three forms of immunotherapy

Subcutaneous	Sublingual	Oral
Weekly to monthly injections	Daily doses of allergen under tongue	Variable food ingestion schedule
Multiple components can easily be given simultaneously	Usually given as monotherapy (one type of allergen)	Monotherapy (single food)
Low prevalence of systemic reaction (including fatal reactions)	Very low prevalence of systemic reactions	Safety, administration schedules, and dosing under investigation in clinical trials
Established schedules and allergen dosing ranges	Schedules and dosing under investigation	Administered in medical facility
Injection administered in medical facility	Self-administration at home	Must continue daily intake of sensitized food
3–5 year treatment course	Likely 3–5 year treatment course	
Documented long-term efficacy	Long-term benefits not known	

(suppressor) cells, causes a lymphocyte differentiation shift from the T_H2 phenotype to the T_H1 phenotype, decreases allergen-specific IgE levels; and decreases mediator release from sensitized mast cells and basophils.

Effective immunotherapy depends upon selection of appropriate patients whose disease is mostly triggered by IgE-dependent mechanisms, and upon administration of clinically relevant allergen extracts. Immunotherapy is appropriate when symptoms are not controlled with avoidance measures and a trial of pharmacotherapy for an appropriate length of time at recommended doses. The severity and duration of symptoms should justify the time commitment, cost, and risks associated with immunotherapy. Another important consideration is the age of the patient. Immunotherapy is not usually recommended for infants and small children due to the increased risk and difficulty in communicating systemic reactions and emotional distress associated with repeated injections. Other factors to consider prior to initiating immunotherapy include compliance of frequent injections over a 5-year time period and accessibility to a nearby medical facility willing and equipped to administer immunotherapy. The benefits versus risks of immunotherapy warrant careful consideration in children on beta-blocker therapy, with autoimmune disorders, psychiatric disorders, and other chronic medical conditions (or therapies) that would place the patient at increased risk for a severe systemic anaphylactic reaction.

The allergist should discuss benefits and risks of immunotherapy with the patient and family prior to initiating therapy. They should know exactly what to expect over the next 3–5 years, understanding that the benefits from immunotherapy are not immediate; rather immunotherapy is a long-term plan. The types of immunotherapy reactions, including fatal anaphylaxis, should be discussed. Reactions can be local or systemic (generalized); immediate or delayed. Local shot reactions consist of swelling or erythema at the site of injection and do not predict future systemic reactions. Systemic reactions involve two or more separate organ systems (e.g., skin and lungs) and can be fatal. Because of this, injections should only be given in a medical facility with personnel trained to administer shots and equipped to handle medical emergencies. Most systemic reactions occur within 30 min of receiving an injection; as a result, patients should be monitored in the office for 30 min following an injection. Current practice guidelines recommend that injections should not be given at home or by untrained personnel. Patients with an asthma exacerbation are at increased risk for an adverse reaction.

The mixture of allergen extracts administered in immunotherapy is based on the patient's history and the allergy test results. Immunotherapy vials may contain single component allergen extracts, or mixtures of pollens (tree, grass, and weeds), dust mite, cockroach, animal dander, or molds. High protease extracts (dust mite, cockroach, and molds) are mixed and stored separately from low protease extracts (pollens) to prevent degradation and loss of potency.

The prescribing allergist will provide a dosage schedule for administering injections. The basic principle of immunotherapy is to gradually inject increasing doses of an allergen extract mixture until a maintenance dose is achieved. Initial injections are typically given every 3–7 days until maximum ("maintenance") doses are reached. This usually requires 6 months, at which point the interval may be increased to every 2–4 weeks. The physician supervising the injections should ensure that reactions are monitored throughout the immunotherapy course, consulting with the prescribing allergist when reactions occur. Local reactions do not necessitate dose

reduction, unlike systemic reactions, which may require up to a 50% reduction in dose prior to the next injection. The typical course of immunotherapy lasts 5 years.

The response to therapy should also be monitored throughout the course of immunotherapy. Successful results include reduction in symptoms, decreased reliance on medications for symptomatic relief, and increased tolerance upon natural exposure of the offending allergen. If no significant clinical benefit is achieved after 1 year of maintenance therapy, the supervising physician should consult with the prescribing allergist to determine whether there should be a reassessment of sensitivities or a discontinuation of immunotherapy. When a course of immunotherapy has been successful, the majority of patients benefit from continued improvement after discontinuing immunotherapy, while some experience a gradual relapse of symptoms. Such patients may benefit from reevaluation and another course of treatment.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) involves the application of high doses of allergen extracts under the tongue, followed by swallowing. Compared to placebo therapy, SLIT is effective, but less effective than conventional subcutaneous immunotherapy. SLIT has been used mostly in patients sensitized to one type of allergenic substance. The appeal of sublingual immunotherapy includes lower rates of systemic reactions and patient convenience. Although there is a risk of systemic reactions, particular when high doses of mixtures containing multiple components are used in highly sensitive individuals, patients are usually permitted to self-administer SLIT at home. The main complaint from patients is local adverse reactions. Further investigation is required regarding optimal dosing, administration schedules, safety and efficacy of complex allergen mixtures, and long-term benefits.

Oral Immunotherapy (Desensitization): Food Allergy

Oral immunotherapy is a promising treatment option for children with severe food allergy manifesting as anaphylaxis or cutaneous symptoms. The use of oral desensitization in controlled clinical trials conducted in children with milk, egg, and peanut allergy has been effective. It is a potentially dangerous therapy, although it has been safe when used by highly experienced researchers. Treatment protocols involve gradually challenging patients with increasing amounts of the offending food allergen in rigorously supervised medical settings. Preliminary studies indicate oral tolerance to food allergens may be mediated by the same mechanisms involved in conventional immunotherapy.

Oral Desensitization: Drug Allergy

Oral desensitization is a form of immunotherapy used to induce clinical tolerance, primarily in patients with adverse drug reactions, IgE-mediated and non-IgE-mediated. Escalating doses of the offending drug are given in a fixed period of time until a tolerable, therapeutic drug dose is reached. Specific protocols for various drugs are available, including penicillin, aspirin, and trimethoprim/sulfamethoxazole. Following desensitization, patients must remain on the desensitized drug to preserve tolerance, or have repeat desensitization prior to future use.

Unproven Therapies

Unproven treatment methods are those that lack scientific validation in controlled clinical trials, or have not been studied to documented clinical efficacy and safety. Unproven treatments have been endorsed to alleviate or eliminate allergic diseases without scientific credibility. Examples of these methods include self-administration of a "neutralizing" substance when symptoms appear or prior to anticipated exposure to relieve symptoms (neutralization therapy); injecting a mixture of low-dose allergen with beta-glucuronidase prior to pollen season or every 2–6 months (enzyme-potentiated desensitization), chemical detoxification to remove toxic, synthetic chemicals in the body; injecting the patient's own urine to reduce symptoms (autogenous urine therapy); acupuncture, chiropractic manipulation, yoga, and homeopathic remedies. Perceived benefit from these therapies is likely placebo effect, and not physiologic. The clinician should be aware of these therapies to provide proper counseling of patients.

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131 Allergic Rhinitis

Michael S. Blaiss · Cyrus Nozad · Jeremy Katcher

Allergic rhinitis (AR) has become a global health problem affecting 10–25% of the population with the highest rate in the pediatric population. This figure underestimates the true prevalence of AR primarily secondary to under diagnosis, misdiagnosis, and patients not seeking medical attention. Allergic rhinitis affects 20–40 million people in the United States with its frequency continuing to increase especially in the younger population. Allergic rhinitis is one of the most common chronic allergic diseases of childhood, and one of the top ten reasons for visits to primary care physicians. The prevalence of seasonal AR (SAR) is higher in children and adolescents than adults, and according to the International Study of Asthma and Allergy in Children (ISAAC) Phase I study, the prevalence is 0.8–14.9% in 6- to 7-year-olds and 1.4–39.7 % in 13- to 14-year-olds. According to ISAAC, the prevalence of AR varies worldwide with the lowest prevalence rates in countries such as Indonesia, Greece, and Albania while the highest rates are seen in countries including the United States, United Kingdom, Australia, New Zealand, Nigeria, and Paraguay.

AR is rare below the age of 1, but 20% of the cases develop before the age of 3 years and 40% by the age of 6. In fact, 80% of people that are going to have symptoms of AR do so by the age of 20.

Classification

Allergic rhinitis is an IgE-mediated reaction triggered by allergens in nose that leads to the classic symptoms of sneezing, nasal itching, rhinorrhea, and nasal congestion (*Table 131.1*). The sneezing is usually repetitive and worse during the early morning hours. Rhinorrhea is profuse and watery. Nasal obstruction is worse at night and can interfere with sleep. Along with nasal symptoms, most children with allergic rhinitis will have eye involvement, which consists of itching, watering, and redness of the conjunctiva. Other less common symptoms that occur in children with allergic rhinitis include post-nasal drip, which leads to frequent clearing of the throat, cough, and headache. Children may also complain of itching of the soft palate and ears as accompanying symptoms of allergic rhinitis.

Classification of the types of allergic rhinitis has been going through a revision. Until recently, allergic rhinitis has been divided into two primary types, seasonal and perennial, which is based on the allergen(s), which lead to the symptoms. Seasonal allergic rhinitis is due to pollen that typically occurs during a particular season. In general, trees pollinate in the early spring, grass in the late spring and summer, and weeds in the fall. In certain climates, mold or fungus may be primarily found in the air during the summer. It is important to know what pollinates in your area at which time of year in making the diagnosis of seasonal allergic rhinitis in a patient. In contrast, perennial allergic rhinitis is due to allergens which are present on a year-round basis. The most common allergens leading to perennial disease are animal danders, dust mites, mold spores, and insect particles. In rare cases, foods may be a factor in perennial disease, but it appears to be restricted to infants. Seasonal allergy symptoms may differ with perennial ones, in that children with seasonal disease tend to have more sneezing and rhinorrhea with eye involvement where perennial disease is characterized by more nasal congestion and post-nasal drip.

In 1999, The World Health Organization commissioned a panel of global experts in the field of allergy to review the impact of allergic rhinitis, develop guidelines for management, and propose a new classification for allergic rhinitis (*Fig. 131.1*). Their classification divides allergic rhinitis into two subgroups, intermittent and persistent based on duration of symptoms. Intermittent allergic rhinitis means that symptoms are present for less than 4 days a week or for less than 4 consecutive weeks. Persistent allergic rhinitis is defined as symptoms for more than 4 days a week and for more than 4 consecutive weeks. Also under each classification, the patient is rated due to severity of symptoms and its effect on quality of life. It is mild disease if the patient has none of the following present: sleep disturbance, impairment of daily activities, leisure, and/or sports, impairment of work or school, and symptoms present but not troublesome. In contrast, moderate or severe disease has at least one of the above. This classification based on duration of symptoms and severity may be more accurate since the pathophysiology of allergic rhinitis is the same for seasonal and perennial disease

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Table 131.1
Symptoms of AR

Symptoms		
Nasal	Eyes	Other
Itching Sneezing Runny nose Post-nasal drip Nasal congestion	Itching Irritation Watering Puffiness Redness	Cough Decreased sense of taste Headache Sore throat Throat clearing Itching of soft palate Itching of the throat Snoring

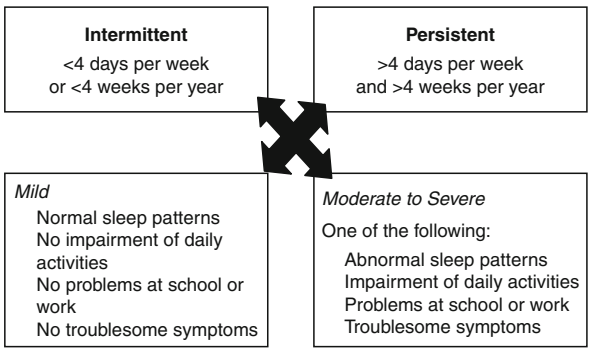

Figure 131.1
ARIA classifications of allergic rhinitis

and in some climates patients may have exposure to "seasonal" allergens throughout the year while some patients may have exposure to "perennial" allergens for only a short period of time each year, such as visiting a house with a pet.

Pathophysiology

Allergic rhinitis can manifest as an early-phase response characterized by itching and sneezing within seconds or minutes followed by nasal discharge and congestion at 15–30 min, but can also involve a late-phase response of nasal obstruction usually around 6–12 h post-exposure. The early allergic response is largely mast cell/basophil-dependent, and occurs when cross-linking of adjacent IgE molecules on the mast cell/basophil surface by allergen results in cell degranulation. This degranulation causes the release of immediate hypersensitivity mediators such as histamine and tryptase. In addition, there is neosynthesis of membrane-derived leukotrienes C4, D4, E4, and prostaglandin D2 (PGD2), as well as platelet-activating factor (PAF), TNF-α, IL-3, IL-4, IL-5, and IL-13. Histamine stimulates H1 receptors on sensory nerves causing vasodilation and increased vascular permeability; bradykinin production leading to nasal congestion. Tryptase indirectly leads to inflammation/tissue damage. Leukotrienes increase vascular permeability and induce mucus secretion from nasal glands, while PGD2 causes vasodilation and neutrophil chemotaxis. PAF causes chemotaxis, leukocyte activation, and vasodilation, while TNF-α promotes overall inflammation. IL-3 and IL-5 promote mast cell proliferation and eosinophil production/activation, while IL-4 and IL-13 promote Th2 differentiation.

Unlike the immediate response, the late-phase response is characterized by T cell recruitment and activation and tissue eosinophilia. Eosinophils degranulate and release tissue-damaging mediators such as major basic protein and peroxidases. Similar to the mast cell, eosinophils also generate leukotrienes C4, D4, E4, IL-3, and IL-5. However, they also secrete their unique set of cytokines that promote eosinophil activation and production, inflammation, and leukocyte chemotaxis. These cytokines include GM-CSF, IL-10, IL-8, RANTES, and eotaxin.

The development of allergic rhinitis involves a complex interaction between genetic predisposition and environmental exposures. Though allergic rhinitis does not exhibit a Mendelian hereditary pattern, twin studies have demonstrated a hereditary component (45–60% concordance for monozygous twins, 25% concordance for dizygous twins). It has been estimated that allergic rhinitis exhibits an inheritability of 0.33–0.75.

Diagnosis

Diagnosis of allergic rhinitis in the child is dependent on an accurate history and physical examination. As previously mentioned, the typical symptoms are repetitive sneezing, nasal itching, profuse rhinorrhea, and nasal congestion. Age of onset of symptoms and time of year that symptoms occur should be elicited from the parent/caregiver. Along with nasal symptoms, it is important to know question about the possibility of headaches, cough, and itching of the soft palate and ears in the child. Because of the nasal congestion, it is not uncommon for the child to have snoring associated with their nasal allergies. Also due to nasal congestion, children with allergic rhinitis have decreased sleep time and poorer quality of sleep, which can lead to poorer school performance and worsen their quality of life. Children with nasal allergies frequently have epistaxis due to fragility and congestion of the nasal

mucosa. A history of previous medications used for treatment of nasal symptoms can be beneficial in determining future treatment in the child.

Family history is pertinent as the child's risk of allergies is much higher than the general population if a first-degree relative has allergies. If one parent has allergies, a child's estimated risk of developing allergies increases to about 30%. If both parents have allergies, the child's risk nearly doubles again to 50–60%. The environmental history is paramount in learning about possible triggers of a child's allergy. Are there pets in the house? Is there carpet in the bedroom? Is there a basement or flooding in the home, which may suggest a mold problem? Are there smokers in the home? Though cigarette smoke is not an allergen, it is an irritant that can make nasal allergies worse.

On physical examination, numerous organ systems should be assessed in the child with AR (◉ *Table 131.2*) The child should also be observed for mouth breathing, repeated nose wiggling, wiping, and pushing up the tip of the nose (allergic salute), and a nasal crease, a transverse line across the bridge of the nose due to repeated allergic salutes for at least 2 years. Chronic mouth breathing due to nasal congestion can lead to allergic facies with development of an elevated upper lip and overbite along with a high arched palate.

Table 131.2
Physical examination characteristics of allergic rhinitis

Where to look	Relevant signs
General Observations	• Facial pallor • Allergic shiners • Allergic salute • Mouth breathing • Nasal (allergic) crease
Nose	• Pale, "boggy," swollen nasal mucosa • "Cobblestoning" of the posterior pharynx • Clear, watery discharge (but can be thick and white/yellow-green if concomitant sinusitis is present)
Eyes	• Conjunctivitis
Mouth	• Elevation of upper lip • Overbite (malocclusion) • High arched palate
Ears	• Abnormal tympanic membranes (retraction or immobility) • Serous fluid collection
Chest	• Persistent cough • Wheezing
Skin	• Eczema

Some children may have allergic shiners. These are dark circles in the eyes due to nasal blockage that acts as a dam in impeding venous drainage.

It is important to do an intranasal exam. Typically in children with allergic rhinitis, the turbinates are pale, boggy, and swollen with profuse serous drainage. On throat examination, it is not uncommon to see thick post-nasal drip and cobblestone appearance of posterior pharyngeal wall.

Because of the numerous co-morbidities associated with allergic rhinitis, other important organ systems should always be assessed. Eye symptoms are especially common with seasonal allergies. The conjunctiva may be inflamed and swollen. Skin manifestations that may be seen in children with nasal allergies are atopic dermatitis and urticaria. Examination of the tympanic membranes is needed to check for serous otitis media. Auscultation of the chest should be done to assess the possibility of expiratory wheezing as children with allergic rhinitis are three times more likely to develop asthma than children without allergies.

The most important diagnostic test is skin prick test using common allergens pertinent to the patient's history. Linking the history and physical examination with the positive skin prick tests will give an accurate diagnosis that can lead to proper management of the child's nasal allergies. In vitro diagnosis of specific allergens with the RAST is useful if a skin test cannot be performed or as a confirmatory test. Another diagnostic test is a nasal smear, which will contain eosinophils in an allergic patient, but does not differentiate from non-allergic eosinophillic rhinitis. In rare patients, there may be a need for CT or sinus x-ray when chronic or recurrent rhinosinusitis is suspected as a complicating factor.

Complications

Asthma

There is a strong epidemiologic link between allergic rhinitis and asthma with allergic rhinitis occurring in the vast majority of asthma patients. Allergic rhinitis often precedes the development of asthma in children, which is commonly called the "atopic march." Wright et al. showed that the presence of physician-diagnosed AR in infancy was independently associated with doubling the risk of developing asthma by the age of 11. They found that 32% of the children with rhinitis developed asthma while only 5% were without rhinitic symptoms. In the classic work by Greisner and Settipane, they followed 1,836 college freshman at Brown University for 23 years. They were evaluated

prospectively by questionnaires, interviews, and physical examinations, and allergy skin tests for the presence of asthma and allergic rhinitis for 23 years. It was found that allergic rhinitis and positive allergy skin tests are significant risk factors for developing new asthma. The freshman were three times more likely to develop asthma that had allergic rhinitis than the ones that did not have allergies

Numerous studies have documented that treatment of allergic rhinitis will improve asthma outcomes. Intranasal corticosteroids have been shown to decrease asthma symptoms and airway hyperreactivity. Leukotriene modifier agents, such as montelukast, have also been demonstrated to show efficacy in both allergic rhinitis and asthma.

Sinusitis

Sinusitis is a potential complication of allergic rhinitis. The relationship between rhinitis and sinusitis may involve inflammation in one compartment leading to secondary inflammation in the other compartment, such as in the case of rhinitis leading to obstruction of the osteomeatal complex. The relationship may also involve individual manifestations of a shared process, such as allergic disease. In a Los Angeles population of 70 children 3–16 years of age with allergic rhinitis, 53% had abnormal sinus radiography. In this subgroup, 4 children (6%) had marked thickening (>6 mm) of the maxillary sinus walls, and 15 children (21%) had complete opacification of 1 or more sinus cavity. Huang et al. studied 413 children for 5 years, of whom 215 had perennial allergic rhinitis and 198 had seasonal allergic rhinitis, to examine the prevalence of sinusitis in these patients. They found that the prevalence of sinusitis was significantly higher among patients with PAR than among those with SAR regardless of age or season, and that mold allergy is an important risk factor for sinusitis in these children.

The clinical presentation of chronic sinusitis in children can be very vague. Most commonly, it is associated with chronic post-nasal drip, cough, especially at night, and headaches. Though headaches are seen in children with chronic sinus disease, the symptoms are usually mild and not intense. Confirmatory diagnosis of chronic sinusitis requires CT scans of the paranasal sinuses.

Chronic Otitis Media with Effusion (OME)

Otitis media with effusion is a significant medical problem in the pediatric population. It is estimated that more than 80% of all children have at least one episode of otitis media by the age of 3 and that 40% will have three or more episodes.

Tomonaga et al. showed that in children with a primary diagnosis of allergic rhinitis, 21% had OME; in the control group representing the general population, only 6% had OME ($P < 0.01$). In children with a primary diagnosis of OME, 50% had allergic rhinitis; in the general population, only 17% had allergic rhinitis ($P < 0.01$). These results suggest that allergic rhinitis affects tubal function (even temporarily) and that allergic rhinitis may be a risk factor in children prone to OME.

Caffarelli et al. evaluated 172 children with OME and a control group of 200 children using a questionnaire for atopy, allergy skin tests, and a clinical evaluation of allergic symptoms and hypersensitivity to aeroallergens. They found that symptoms associated with atopy occurred significantly more frequently in the group with OME ($P<0.001$), and concluded that the association of OME with symptoms associated with atopy might play a part in the pathogenesis of the disorder.

Even though there is data suggesting a linkage between OME and allergic rhinitis, there is controversy on whether routine evaluation for allergies should be done in children with OME. A recent guideline on management of OME by The American Academy of Pediatrics, American Academy of Family Physicians, and American Academy of Otolaryngology-Head and Neck Surgery made no recommendations for allergy management as a treatment for OME. They based their recommendation on insufficient evidence of therapeutic efficacy or a causal relationship between allergy and OME. It appears prudent that if the child with OME has significant symptoms of allergic rhinitis, then evaluation of allergy as a factor in the child's OME should be entertained.

Snoring and Sleep Apnea

Another complication to consider in children with allergic rhinitis is snoring. Chng et al. administered a questionnaire on snoring to parents of 11,114 children aged 4–7 years in randomly selected preschools and primary schools in Singapore. They found that snoring and habitual snoring (snoring three or more time a week) were reported in 28.1% and in 6.0% of the children, respectively. On multivariate logistic regression analysis, it was found that one of the significant associations with snoring was atopy (asthma, allergic rhinitis, or atopic dermatitis). In fact, atopy was the strongest risk factor for habitual snoring. In children with snoring secondary to allergic rhinitis, obstructive sleep apnea syndrome may be present and

may lead to further medical problems. McColley et al. did a prospective study of 39 children with habitual snoring who were referred for polysomnography. RAST was performed to check for allergen sensitization. They found that 14 subjects (36%) demonstrated sensitivity to allergens; this is higher than expected for the general pediatric population. The frequency of sleep apnea was increased in subjects with positive RAST results compared to those with negative RAST results (57% vs 40%; $\chi^2 = 9.11$; $P < 0.01$) suggesting that allergy may be a risk for habitual snoring in children. Of course, not all snoring in children is due to allergic rhinitis, but it is important to include it in the differential diagnosis for evaluating the child that snores.

Differential Diagnosis

The differential diagnosis of allergic rhinitis is vast. Non-allergic rhinitis encompasses a large list of causes of rhinitis that do not have an allergic stimulus. Vasomotor or idiopathic rhinitis is the most frequent form of non-allergic rhinitis. It is characterized by sporadic or persistent nasal symptoms that are trigged by: strong smells, cold air, changes in temperature, humidity, barometric pressure, strong emotions, alcohol and changes in hormone levels. Diagnosis is made clinically and typically is adult onset.

Rhinitis medicamentosa is severe nasal congestion due to a rebound effect with overuse of topical decongestants, such as oxymetazoline and phenylephrine. Other medications that can lead to nasal symptoms, especially congestion, are ACE inhibitors, β-blockers, aspirin, and NSAIDs. Gustatory rhinitis occurs after eating heated foods, spicy foods, or alcohol. It may be vagally mediated, food allergy, and/or other undefined mechanisms. Hormonal-induced rhinitis includes menstrual cycle–related rhinitis and rhinitis of pregnancy. This condition typical begins in the 2nd trimester with severe congestion and resolves about 2 weeks postpartum. Infectious rhinitis may be acute or chronic. Symptoms include nasal congestion, mucopurulent nasal discharge, pain and pressure, headache, olfactory disturbance, post-nasal drainage, and cough. Viral infections account for as many as 98% of acute infectious rhinitis in young children. Non-allergic rhinitis with eosinophils (NARES) usually develops in adults and is characterized by year-round nasal symptoms primarily congestion with negative allergy skins and normal serum IgE levels. Classically, nasal smears on these patients have 20% or greater eosinophils. Many of these patients may develop ASA sensitivity, nasal polyps, and asthma. (◉ *Table 131.3*)

◉ **Table 131.3**
Differential of rhinitis in children

Differential	Examples
Allergic rhinitis	
Non-allergic rhinitis	Vasomotor Drug Induced Gustatory Hormonal Infectious NARES
Nasal polyps – may occur in conjunction with allergic rhinitis, chronic rhinitis, or sinusitis	
Anatomic abnormalities: Structural changes may cause symptoms	Deviated septum/ septal wall anomalies Adenoidal Hypertrophy Trauma Nasal tumors (Benign or Malignant)
CSF rhinorrhea: From accidental head trauma, surgery, tumors, or spontaneous	
Primary ciliary dykinesia: Autosomal recessive impairment of mucociliary clearance. Nasal polyposis is often present leading to nasal congestion, as well as failure of the frontal sinuses to develop	
Autoimmune: May be the cause of rhinosinusitis, which is seen in some vasculitities	SLE Churg–Straus syndrome Wegener's granulomatoisis
Foreign body	
Metabolic: Hormonal related, e.g., excess growth hormone	Hypothyroidism Acromegaly
Cystic fibrosis: Chronic rhinosinusitis may be associated with CFTR gene mutations. 10–32% develop nasal polyps, leading to nasal congestion	

Treatment

Allergen Avoidance

Treatment of allergic rhinitis requires education of the patient/parent/caregiver and is a threefold approach-allergen avoidance, appropriate pharmacotherapy, and allergen immunotherapy (in selected children).

The initial step in treatment of allergic rhinitis is to educate the patient/parent/caregiver about their condition and complications associated with allergic rhinitis. After allergic triggers have been identified, either through the patient's history or through diagnostic testing, the physician or office staff person can educate the patient on how to avoid specific allergens (*Table 131.4*). The most common allergens are house dust mites, cockroaches, molds, animal dander, and pollen.

Table 131.4
Allergen avoidance measures (Adapted from Urval, 1998)

Allergen	Control measure
House dust mites	• Remove dust collectors from bedroom. • Cover mattress, box springs, and pillow with allergen-proof coverings. • Wash uncovered bedding in 130°F at least once a week. • Maintain indoor humidity at less than 40%. • Remove carpeting throughout house, or at least in the bedroom.
Animal dander	• Remove the pet. • Keep pets out of bedroom at all times. • Note: No hypoallergenic dog or cat breeds have been identified.
Cockroaches	• Wash dishes promptly. • Keep garbage contained outside of the home. • Wipe up food spills immediately. • Keep food tightly sealed in containers. • Repair or remove sources of standing water.
Molds	• Avoid damp, musty basements. • Use a dehumidifier in areas of high humidity. • Avoid activities (such as raking leaves) that increase exposure to molds. • Houseplants should be kept at a minimum. Apply fungicides to appropriate surfaces with obvious contamination.
Pollens	• Monitor pollen forecasts and avoid high pollen areas. • Keep windows closed in the home and car. • Avoid activities (such as mowing the lawn) that increase pollen exposure. • Use air conditioning both in the house and car. • Immediately shower after being outside for an extended period of time.

House dust mites. These allergens are among the most common perennial allergens. They survive in all climates, except at high altitudes where reproduction is halted. While the entire home can be a source of dust mites, the bedroom should be of particular concern. Mattresses, box springs, and pillows should be encased in zippered, allergen-proof encasings. Bedding should be washed weekly in hot water. Ordinary dusting and vacuuming have little effect on dust mite control. If vacuuming is done, it should be done using a vacuum cleaner with an efficient double filtration system or a high-efficiency particulate air (HEPA) filter. When dusting, a damp cloth should be used, as it better picks up dust. Because it takes approximately 40 min for dust mites to settle after cleaning, the patient should leave the area immediately after cleaning. Ideally, the house should be cleaned when the patient is not home.

Dust collectors, such as stuffed animals and should be removed from the bedroom. When practical, carpeting should be removed throughout the house, or at least in the bedroom.

Animal dander. While cat and dog dander are the most common animal allergens, most other warm-blooded animals, including mice, rats, guinea pigs, horses and birds, can also cause allergic reactions. The best method of allergen avoidance in this case is removal of the animal from the home. However, because most people have strong attachments to their pets, this is often an unreasonable request. Also, it can take up to four months for all the dander to decompose after the pet is removed, so improvement in symptoms will not be immediate. After discussion, if the decision is made to keep the animal in the house, several steps can be taken. The pet should be kept out of the patient's bedroom at all times. Routine vacuuming of furniture and carpeting can also help. Ideally, the carpet should be removed from the bedroom floor and allergen-proof covering used for dust mite avoidance should also be used. Use of a HEPA filtering system in the bedroom can help decrease the level of animal dander in the air. At this time, no hypoallergenic breeds of cats or dogs have been identified.

Cockroaches. Cockroach allergy is a major trigger of allergic rhinitis. This is particularly evident in the inner cities. Although exposure to cockroaches is usually limited to the kitchen or dining rooms, the allergen can be passively transferred on clothing and shoes. Eradication of cockroaches may prove to be difficult, as the allergenic proteins can persist in the environment for months or even years. In addition, problems will often persist until food and garbage are disposed and packaged properly. Cockroaches also require water for survival. Therefore, it

is essential to repair leaking faucets or to clean up standing water in the basement.

Molds. Mold spores can be a source of both perennial and seasonal allergies. To avoid exposure to outdoor molds, keep car and house windows closed at all times. Outdoor activities that bring greater exposure to molds, such as raking leaves, should be avoided. In patients with mold allergies, limitation of outdoor activities during specific times may be necessary. Spore counts are often at their highest early in the morning or late in the evening when dampness is present. Numerous precautions can be taken indoors. Damp musty basements should be avoided, and the humidity level should be reduced within the house. A dehumidifier can be helpful during periods of high humidity. Live plants should be kept to a minimum, as they can promote the growth of mold. Finally, because mold spores can accumulate in bedding and carpeting, techniques such as those used for dust mites can be used.

Pollens. Pollen-induced allergy is probably the most difficult to control through allergen avoidance, because simply being exposed to outside air can trigger an attack. Patients should be given resources that allow them to monitor daily pollen counts and be advised to stay indoors on days when pollen counts are particularly high. Because remaining entirely indoors is impractical, the best prevention is to keep windows closed at all times, both in the house and in the car. Don't dry clothing outside, as the pollens will collect on the clothes. If available, air conditioning should be used both in the car and house; air filters should be replaced or cleaned on a regular basis. Certain activities that increase exposure, such as mowing the lawn, should be avoided. Finally, showering after spending time outdoors can remove pollen from hair and skin and avoids contamination of bedding.

Pharmacologic Agents in AR

There are several pharmacologic agents available: oral and topical H_1-antihistamines, intranasal glucocorticosteroids, leukotriene receptor antagonists, mast cell stabilizers, anticholinergic agents, and oral and topical decongestants (*Table 131.5*).

Medications used for AR are typically administered orally or intranasally. The intranasal route allows for higher concentrations of the drug to be delivered, thus minimizing the systemic side effects. However, many children with AR have an aversion using nasal spray and oral medications are typically used in these patients.

Oral H_1-Antihistamines

Histamine is an important chemical mediator of allergic inflammation and is released in large quantities from tissue mast cells and basophils.

H_1-antihistamines are inverse agonists, rather than H_1-antagonists, that combine with and stabilize the inactive form of the H_1 receptor, leading toward a shift in equilibrium to the inactive state. In addition to the inverse agonist effect at the H_1 receptor, the newer second-generation agents have both anti-allergic and anti-inflammatory properties.

The first-generation H_1 antihistamines such as diphenhydramine, chlorpheniramine, brompheniramine and hydroxyzine are also referred to as the sedating antihistamines. These agents are effective at controlling the rhinorrhea, sneezing, and pruritus associated with AR. Unfortunately, these agents cross the blood–brain barrier, thus producing undesirable side effects such as central

Table 131.5
Estimated symptom efficacy of agents used in management of AR

Drug class	Sneezing	Itching	Rhinorrhea	Congestion
Oral antihistamines	++	++	++	+
Intranasal antihistamines	+++	+++	+++	+++
Intranasal corticosteroids	++++	++++	++++	++++
Decongestants	_	_	_	++++
Cromolyn	+	+	+	+
Leukotriene receptor antagonists	++	++	++	+
Anticholinergic	_	_	++++	_

Excellent efficacy, ++++; Good efficacy, +++; Mild efficacy, ++; Questionable efficacy, +; No efficacy, –

nervous system depression, sedation leading to impaired performance at home, work, and school, and cardiotoxicity. There are no long-term safety studies on the first-generation antihistamines. These agents have poor H_1 receptor selectivity and act on muscarinic receptors, causing anticholinergic effects such as dry mouth, urinary retention, constipation, and tachycardia. The high risk to benefit ratio makes the first-generation H_1 antihistamines a less attractive therapeutic option and are not recommended as first-line therapy in AR.

The second-generation antihistamines developed in the early 1980s have improved H_1 receptor selectivity, absent or decreased sedation, faster onset and longer duration of action, and fewer adverse effects. To date, no clinically significant cardiotoxic effects have been reported for loratadine, desloratadine, fexofenadine, cetirizine, and levocetirizine. In general, second-generation antihistamines exhibit favorable pharmacokinetics. They have a relatively quick onset of action, near complete absorption, widespread tissue distribution with minimal CNS penetration unlike first-generation antihistamines and relatively long half-life allowing for once daily dosing.

Intranasal H_1-Antihistamines

Topical second-generation H_1-antihistamines are considered to be similar in efficacy to oral antihistamines and are also considered as first-line therapy for mild-moderate AR. Studies have shown that azelastine and olopatadine improved all symptoms in SAR and PAR including ocular symptoms and can also reduce nasal congestion. These agents have a quicker onset of action than oral antihistamines and intranasal corticosteroids. The most common side effects associated are mild sedation and bad taste.

Corticosteroids

Intranasal corticosteroids are recommended as first-line therapy for moderate-severe AR. Corticosteroids target the inflammatory mechanism of the early- and late-phase allergic processes and are therefore effective in treating most symptoms of AR including: congestion, sneezing, rhinorrhea, and nasal pruritus. They may also decrease eye symptoms by blocking the nasal-ocular reflex. Studies show that these agents are superior to all other classes of allergic rhinitis medications in controlling symptoms of AR.

Epistaxis, secondary to irritation of the nasal mucosa, is the most common adverse effect but diminishes over time. Therefore, patients should be instructed on proper technique for administration, which is to direct the spray away from the septum.

In children, there is a concern regarding suppression of linear growth, and, therefore, they should receive the lowest possible dose of intranasal corticosteroid and routine height monitoring.

Systemic corticosteroids should not be used for chronic management of allergic rhinitis due to their poor side effect profile. In moderate to severe flare-ups of AR, systemic corticosteroids may be used for a short course (3–7 days).

Leukotriene Receptor Antagonists

Leukotrienes appear to be important mediators of nasal allergic reactions, and their presence in the nose induces nasal obstruction. Montelukast has been generally accepted for treatment of mild to moderate AR with efficacy comparable to oral antihistamines. However, there are no data supporting the use of leukotriene receptor antagonists combined with oral or intranasal antihistamines, intranasal corticosteroids, or both in the treatment of AR.

Cromolyn

Mast cell stabilizers inhibit mast cell degranulation and thus inhibit the release of histamine and other mediators of the early phase of allergic inflammation. Cromolyn sodium is generally not as effective as antihistamines or intranasal corticosteroids but has been shown to be superior to placebo in reducing symptoms of the early phase. Although the safety profile of cromolyn is very good, the dosing interval of four times a day makes this a less attractive option.

Anticholinergics

Double-blind, placebo-controlled studies have shown that ipratropium bromide is effective in controlling watery nasal discharge, but that it does not affect sneezing or nasal obstruction. Anticholinergic side effects are uncommon and usually dose-dependent.

Decongestants

Decongestants reduce nasal congestion by activating α-adrenergic receptors on the nasal vasculature leading to vasoconstriction. Decongestants have not been shown to be effective with other symptoms of AR. Common side effects in children seen with oral decongestants include insomnia and agitation.

Topical decongestants, oxymetazoline and phenylephrine, are also available for the treatment of nasal congestion. Unfortunately, rebound nasal congestion, termed rhinitis medicamentosa, can occur if they are used for greater than 3–5 days.

Allergen Immunotherapy

Allergen immunotherapy is the only disease-modifying treatment for AR. During allergen immunotherapy, patients can be desensitized to their allergen triggers. During this process, the patient is injected subcutaneously or given sublingually increasing amounts of allergen until either a symptom-relieving dose is reached or a maximum tolerance dose is reached.

Children should be considered candidates for allergen immunotherapy when they fail to respond to a combination of allergen avoidance and pharmacotherapy. Also, patients with severe and persistent nasal symptoms are commonly referred for immunotherapy. Another indication for allergen immunotherapy would be a child with significant complications associated with their allergic rhinitis, such as asthma and chronic sinusitis.

Recent studies have suggested that allergen immunotherapy in children with allergic rhinitis may reduce the risk of developing asthma. Recent research has demonstrated that the use of allergen immunotherapy in children with allergic rhinitis can decrease the risk of development of asthma. Novembre et al. evaluated 113 children aged 5–14 years allergic rhinitis to grass pollen and no other clinically important allergies were randomized in an open study to receive specific sublingual immunotherapy (SLIT) for 3 years or standard symptomatic therapy. The children on SLIT were 3.8 times less likely to develop asthma after 3 years than the control subjects. Jacobsen et al recently published a 7-year follow-up of children treated for 3 years with specific subcutaneous immunotherapy for allergic rhinitis to grass and/or birch pollen. These children were compared to a control group of allergic rhinitis children for allergy symptoms and the development of asthma. The immunotherapy-treated children had significantly less asthma after 7 years as evaluated by clinical symptoms [odds ratio 4.6 (1.5–13.7)] in favor of specific subcutaneous immunotherapy for prevention of development of asthma.

Allergic Conjunctivitis

The most common associated condition with allergic rhinitis is allergic conjunctivitis. Studies suggest that all 90% of children with allergic rhinitis have eye symptoms especially those with seasonal pollen sensitivity. Typically, the child complains of itching, redness of the conjunctiva, and watering of the eyes. On examination, the conjunctiva is usually inflamed and in severe cases, swelling or chemosis of the conjunctiva can occur.

As with allergic rhinitis, the first step toward successful management of allergic conjunctivitis is to limit the exposure to the known allergens. Once symptoms have occurred, the use of cold compresses may provide temporary relief of symptoms. Lubricating the eye with saline solutions may help to alleviate the symptoms, as well as assist in the removal and dilution of allergens that may be in contact with ocular tissue.

There are a number of medications currently available to treat the symptoms of allergic conjunctivitis. Systemic first- and second-generation antihistamines may help stop the itching associated with allergic conjunctivitis though they are usually not effective for more moderate to severe eye symptoms. Topical antihistamines, such as emedastine and levocabastine, are effective in relieving symptoms of itching and redness. Topical non-steroidal anti-inflammatory agents such as ketorolac are effective in relieving not only the itching associated with allergic conjunctivitis, but also the redness, swelling, and tearing that often accompany the allergic reaction. Topical mast cell stabilizers such as cromolyn sodium, lodoxamide, or nedocromil are effective in relieving the itching, tearing, and redness associated with allergic rhinitis; however, as with the nasal products, mast cell stabilizers do not offer rapid relief. Instead, they must be used prophylactically. Some of the more effective treatments are dual-action antihistamines/mast cell stabilizers such as olopatadine, ketotifen, epinastine, bepotastine and azelastine. These agents have a rapid onset of action and relieve all the symptoms associated with allergic conjunctivitis. In addition, they are both very long lasting, and so compliance is easier to attain. In more severe cases of conjunctivitis, topical ocular corticosteroids may be used. However, these agents should be prescribed only by an eye specialist,

and only after a slit-lamp examination has been performed to make sure there is no evidence of a herpes infection. Use of a topical ocular corticosteroid in a patient with herpes infection in the eye can lead to severe complications, including blindness.

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132 Pediatric Asthma

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Introduction

A mother brings in her 3-year-old son because he has recurrent respiratory symptoms.

He coughs at night, when he laughs or cries, or runs outside. He has had post-tussive emesis on occasion. Colds settle into his chest and he has been diagnosed with bronchitis, croup, and pneumonia several times.

He is usually treated with antibiotics and has been given albuterol breathing treatments on several occasions which helped his symptoms. The last time he was sick he received 5 days of oral steroids, which was very beneficial. He is nasally congested on most days. His mother states he seems to be susceptible to colds and he is sick more frequently than he is well.

He was full term and his immunizations are up to date. He has not been hospitalized nor has he had surgical procedures. When he was an infant he had hives and vomiting with cow's milk formula and scrambled eggs. He tolerates dairy and eggs now.

He is an only child and he attends day care 5 days a week.

His mother has allergies and his father had asthma when he was a child. His maternal cousin has eczema and peanut allergy.

He is not presently on medications.

Physical exam reveals a well nourished happy 3 year old with height and weight at the 75%.

He has pale swollen nasal turbinates with clear discharge bilaterally. He has mild scarring of the tympanic membranes and shotty posterior cervical lymph nodes bilaterally. Cardiovascular exam is normal. His chest has normal configuration and his lungs are clear to auscultation; however, after running in the exam room he begins to cough.

The skin demonstrates dry, erythematous patches in the antecubital and popliteal fossae.

He does not have clubbing or cyanosis or edema of the extremities.

Does this child have asthma? Does he have risk factors for asthma? What is the differential diagnosis of a child with these recurrent respiratory symptoms? What is the severity classification? What is appropriate workup and treatment plan for this child?

Will his symptoms remit or persist over time?

Definition/Classification

The Global Initiative for Asthma (GINA) guidelines define asthma descriptively as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role. The chronic inflammation is associated with airway hyperresponsiveness that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and cough, particularly at night or in early morning. These episodes are usually associated with widespread but variable airflow obstruction which often is reversible either spontaneously or with treatment."

Asthma is a syndrome. A syndrome is defined as "an aggregate or set of concurrent symptoms indicating the presence and nature of a disease." Such an aggregate can be recognized only if it is associated with clear criteria for doing so. Asthma is a syndrome because there is no readily available genetic, blood, or pulmonary function test that can be used to objectively diagnose it, particularly in young children in whom it usually starts. Consequently, it is not surprising that a variety of underlying physiologic disorders may result in the constellation of symptoms that are consistent with asthma.

The diagnosis of asthma is usually made clinically based upon the history and response to asthma medications. In older children and adults, pulmonary function studies (spirometry) may be done before and after bronchodilator; however, many patients particularly those with cough variant asthma do not demonstrate obstruction on spirometry. To assist in making the diagnosis, the GINA guidelines recommend that the following questions be asked with positive responses increasing the likelihood that the patient has asthma.

- Has the patient had an attack or recurrent attacks of wheezing?
- Does the patient have a troublesome cough at night?
- Does the patient wheeze or cough after exercise?

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- Does the patient experience wheezing, chest tightness, or cough after exposure to airborne allergens or pollutants?
- Do the patient's colds "go to the chest" or take more than 10 days to clear up?
- Are symptoms improved by appropriate asthma treatment?

Etiology

Atopy

Many studies such as the Tucson study and the PEAK trial have shown that allergy plays an important role in the development of asthma. In addition, total IgE is a strongly heritable trait. In a genome-wide association study, functional variants in the gene encoding the alpha chain of the high affinity receptor for IgE (FCER1A) on chromosome 1q23 (rs2251746 and rs2427837) were strongly associated with total IgE. The most significant single nucleotide polymorphism (SNP) influenced the cell surface expression of FCER1A on basophiles, and genome-wide expression profiles indicated an interesting novel regulatory mechanism of FCER1A expression via GATA-2. Polymorphisms within the RAD50 gene on chromosome 5q31 were consistently associated with IgE levels and increased the risk for atopic eczema and asthma and STAT6 was confirmed as susceptibility locus modulating IgE levels.

Obesity

Obesity has been shown to be a risk factor for the development of asthma. Infant weight gain has been shown to be associated with the development of asthma later in childhood. Though weight gain is not associated with daily asthma symptoms or lung function it is associated with an increased need for prednisone and urgent care visits. Conversely, smaller weight gain is associated with fewer exacerbations.

Obese patients with asthma are more likely to report continuous symptoms, miss more work days, use short acting beta agonists, use inhaled corticosteroids (ICS), and use controller medication than matched nonobese asthmatics. They also are less likely to be in asthma remission and are more likely to have severe persistent asthma.

Environmental Factors

Environmental tobacco smoke (ETS) is the best understood and likely the most significant indoor air pollutant. It not only confers a significant increase in risk of developing asthma, it also causes an increase in IgE sensitization as well as an increase in asthma severity. Asthma is more severe in former smokers both before and after treatment than in those who have never smoked. Though smoking cessation is an important goal in treatment of asthmatic patients, smoking initiation needs to be reduced, especially in teenagers. This is because cigarette smoking has a persistent, dose-dependent, negative impact on the response to treatment in patients with uncontrolled asthma even after smoking cessation.

Outdoor air pollutants with significant impact on asthma include nitrogen oxides (NO_x), sulfur oxides (SO_x), and ozone along with particulates. Sensitivity to these exposures does vary and has a genetic component. For example, arginases (encoded by ARG1 and ARG2 genes) have an important effect on asthma pathogenesis through effects on nitrosative stress. Arginase expression is upregulated in asthma and varies with TH2 cytokine levels and oxidative stress. Both ARG1 and ARG2 genetic loci are significantly associated with asthma. Within each locus, the ARG1 haplotype is associated with reduced risk and the ARG2 haplotype is associated with increased risk of asthma. The effect of the ARG1 haplotype is associated with the presence of atopy and ambient ozone. Atopic children living in high-ozone communities with the ARG1 haplotype have a reduced asthma risk.

Infections

Many common respiratory viruses have been linked to recurrent wheezing in infancy and early childhood, including rhinovirus and respiratory syncytial virus. In addition, some of these viruses are linked to as high as a 40% increase in risk for asthma later in childhood. The "hygiene hypothesis" suggests, however, that infections during early childhood influence the immune system in such a way that the risk of developing asthma is reduced.

In the childhood origins of asthma study (COAST), 289 newborns were followed prospectively. The investigators found that even one moderate to severe rhinovirus infection during infancy drastically increases the risk of recurrent wheezing and possibly of the subsequent development of asthma. Apparently, healthy infants who experience repetitive severe viral respiratory infections develop recurrent wheezing, possibly as a consequence of lung damage and/or airway remodeling. It also seems that infants born with poor antiviral responses and/or airway hyperresponsiveness (AHR) are prone to have repetitive severe illnesses which may increase their risk of

developing asthma. This effect is most pronounced if the infants wheeze with rhinovirus infections as opposed to infections with RSV which is less specific for development of asthma.

Epidemiology

The world wide prevalence of asthma is increasing. Epidemiological studies based upon symptom questionnaires of parents of young children (6–7 years old) and older children (13–14 years old) in the ISAAC study Phase I (International Study of Asthma and Allergies in Children) show variability between countries with highest prevalence rates of asthma symptoms in 12 months in UK, Ireland, New Zealand, and Australia followed by South, Central, and North America, Kuwait, and South Africa. The lowest rates were reported in several Eastern European countries (Romania, Georgia, Albania, Uzbekistan), Greece, China, India, and Ethiopia. In Southeast Asia the lowest prevalence of symptoms was in Malaysia and China and the highest in Japan, Thailand, Philippines, and Hong Kong.

Studies show patterns of increasing prevalence of asthma worldwide especially in Western countries and as communities become more urbanized. Asthma symptoms in Chinese adolescents was lowest among residents of mainland China and greater for those in Hong Kong and for those who immigrated to Canada and was highest for those born in Canada. A significant increase in the prevalence of asthma in the Kingdom of Saudia Arabia was noted from 8% in 1985 to 23% in 1995 in a questionnaire of children between 8 and 16 years which was hypothesized to be related to changes in environmental factors of increased tobacco smoke and indoor animal exposure. Although the prevalence of asthma symptoms tends to be more common in affluent countries, the symptoms are more severe in less affluent countries.

According to data from the US National Center for Health Statistics, the burden from childhood asthma seems to have leveled off after many years of increasing. Asthma prevalence in the USA increased by an average of 4.3% per year (from 3.6% to 6.2%) between 1980 and 1996. Asthma attack prevalence remained constant between 1997 and 2000. After a decrease between 1980 and 1989, the asthma office visit rate increased by an average of 3.8% per year from 1989 to 1999. The asthma hospitalization rate grew by 1.4% per year from 1980 to 1999. Although childhood asthma deaths are rare, the asthma death rate increased by 3.4% per year from 1980 to 1998. Children aged 0–4 years had the largest increase in prevalence and had greater health care use, but adolescents had the highest mortality.

Unfortunately, racial and ethnic disparities remain large for asthma utilization and mortality. The asthma burden is borne disproportionately by black children. Racial disparities were largest for asthma hospitalizations and mortality: compared with white children. In 1998–1999, black children were more than three times as likely to be hospitalized, and in 1997–1998 they were more than four times as likely to die from asthma.

In the USA, the Centers for Disease Control and Surveillance published data from surveys of 2001–2003 reporting higher rates for current asthma for children (8.5%) than for adults (6.7%), for blacks (9.2%) than whites (6.9%) and for those of Puerto Rican descent (14.5%) than those of Mexican descent (3.9%) and the rates of asthma deaths in the USA increased during 1980–1990, but have decreased each year since 2000. In the2007 report of The National Health Interview Survey, the greater prevalence of asthma in minority populations occurred in non-Hispanic black children more likely to have ever been diagnosed with asthma (20%) than Hispanic children (13%) or non-Hispanic white children 11%).

In early childhood, asthma is twice as prevalent among boys as girls. As the asthma rate among young girls increases, however, the gap in prevalence of asthma in early childhood between boys and girls decreases. The ratio reverses in adolescence and early adulthood with asthma becoming more common in women though the reasons for this gender-related difference is unclear.

In a survey of randomly chosen adult patients and parents of children with current asthma in the USA, surveyors asked about short-term symptoms (4-week recall), long-term symptoms (past year), and activity limitation. The surveyors found that 10.7% had mild intermittent disease while 77.3% had moderate to severe persistent disease suggesting that a majority of the US population with asthma experiences persistent rather than intermittent asthma.

Pathogenesis: Including Genetics

Asthma is known to be an inheritable condition. Whole genome screens are beginning to identify gene-rich regions that are of special relevance to the development of asthma and atopy. Candidate genes for the development of asthma include the many genes that regulate IgE production, the proliferation and maturation of eosinophils and mast cells, and epithelial barrier function. Some

of the better defined genes contributing to the development of asthma, include Arg/Gly, 17q12–21, ADAM-33, and the filaggrin (FLG) gene. In addition, several genes have been identified that effect patient response to medications. These genes include Arg/Gly alleles of the beta2 receptor as well as components of the leukotriene pathway. The identification of novel genes for asthma suggests that many genes with small effects rather than few genes with strong effects contribute to the development of asthma. These genetic effects are modified interactions with a person's environmental exposures, though some genetic influences also operate independently of environmental factors. A number of important gene–environment interactions have been identified which may aid in the identification of individuals who are particularly susceptible to environmental hazards.

Since asthma is an inflammatory airway disease that is associated with upregulation of TH2-type cytokines, genes encoded in the corresponding cluster on chromosome 5q on T cells and inflammatory cells are of particular interest. This upregulation along with local airway susceptibility factors leads to airways hyperresponsiveness, variable airflow obstruction, and in some cases to airways remodeling. Two examples are polymorphisms involving IL-4 receptors and the enzymes controlling cysteinyl leukotriene production.

In addition to inflammation of the airways caused by atopy, interactions between the respiratory epithelium and other environmental factors such as virus infections, ETS, and pollutants also contribute to tissue damage and abnormal repair responses that can lead to remodeling. Previously unknown genes involved in this interaction have recently been identified. Dipeptidyl peptidase 10 (DPP10) and disintegrin and metalloproteinase-33 (ADAM-33) are examples of newly identified genes that are associated with asthma that are preferentially expressed in the airway epithelium and underlying mesenchyme.

Leukotrienes contribute to the inflammatory process in asthma, to the extent that leukotriene modifiers are mainstays in the therapy of asthma. Leukotriene pathway genes have been shown to be involved in the pathogenesis of and treatment response in asthma. Certain genetic variants in these pathway genes also appear to be associated with the development of aspirin-exacerbated respiratory disease, and pharmacogenetic response. Those specific variants include two variants in the 5-lipoxygenase gene that are both associated with response to 5-lipoxygenase inhibition and to leukotriene receptor antagonists (LTRA), variants in genes encoding the two cysteinyl LTRA, and a leukotriene C4 synthase promoter polymorphism that has been associated with the risk of asthma exacerbations.

Transcription factors control the development of TH1 and TH2 T-cells. Two of these, the T-box transcription factor and GATA3, appear to be involved in the development of asthma and atopic diseases. Another homeobox transcription factor H.20-like homeobox 1 (HLX1) interacts closely with the T-box transcription factor. Nineteen polymorphisms have been identified in this gene, and seven of these are associated with increased likelihood of developing childhood asthma. These appear to work by decreasing promoter transactivation disrupting specificity protein-transcription factor binding.

Another T cell-specific T-box transcription factor (TBX21) induces the differentiation of T-cells to a TH1 phenotype and prevents the formation of TH2 cells in combination with the homeobox transcription factor HLX1. Three SNPs in this gene increased the risk of developing childhood asthma significantly. In addition, two polymorphisms in the promoter region influence TBX21 promoter activity. A specific combination of TBX21 and HLX1 polymorphisms increases the asthma risk by more than threefold, which demonstrates a synergistic effect on asthma risk.

Null mutations in the FLG gene have been shown to be major risk factor for. A meta-analysis of 24 studies on FLG mutations, eczema, and asthma showed strong associations with eczema and also that certain mutations are significantly associated with asthma though the strongest effects were for the combination of asthma and eczema. No association between FLG mutations and asthma in the absence of eczema. The two common FLG-null mutations R501X and 2282del4 and three recently identified rare FLG variants (R2447X, S3247X, 3702delG) increased the risk for eczema more than threefold, conferred a substantial risk for allergic rhinitis, and increased the risk of asthma occurring in the context of eczema but not of asthma alone.

In addition to pathogenesis, genetic factors also may explain ethnic disparities not explained otherwise by environmental, social, cultural, or economic factors. In particular, differences in susceptibility allele frequencies have been observed that increase the risk of asthma in certain populations. A meta-analysis of African-ancestry populations yielded three SNPs in genes of potential biologic relevance to asthma and allergic disease: rs10515807, mapping to the alpha-1B-adrenergic receptor (ADRA1B) gene on chromosome 5q33; rs6052761, mapping to the prion-related protein (PRNP) gene on chromosome 20; and rs1435879, mapping to the DPP10 gene on chromosome 2q12.3–q14.2. Though certain forms of these SNPs are associated with minority populations in the USA, their

significance with respect to disparities remains to be determined.

Bronchial hyperresponsiveness (BHR) and asthma are linked to chromosome 5q31–q33 with some evidence that the protocadherin 1 gene (PCDH1) has several novel sequence variants. In seven out of eight populations from The Netherlands, UK, and USA, PCHD1 gene variants were significantly associated with BHR both in families with asthma and in general populations. PCDH1 mRNA and protein are expressed in airway epithelial cells and in macrophages.

Several studies have suggested that chromosome 19q13.1–3 contains asthma susceptibility genes. In particular, support has been found for an asthma/lung function susceptibility locus (48.9–49.1 Mbps) which apparently is localized to the plasma urokinase plasminogen activator receptor (PLAUR) gene. PLAUR SNPs in the 5′ region, intron 3, and 3′ region are associated with asthma and BHR susceptibility and predict FEV_1 and plasma PLAUR concentrations. SNPs in the 5′ region showed an association with asthma, FEV_1, and BHR. These same were associated with plasma PLAUR levels as well as with FEV_1 decline in subjects with asthma. The association of PLAUR with lung function decline appears to support a role for PLAUR in airway remodeling in asthma.

Pathology

The GINA guidelines first recommend that asthma severity be classified as intermittent, or as mild, moderate, or severe persistent based on specific criteria (Table 132.1). This classification is determined with the assumption that the patient has yet been treated since once treatment is initiated the symptoms are expected to improve. The NHLBI guidelines have similar criteria for the four categories of asthma severity.

Once treatment is initiated, both guidelines recommend that the degree of asthma control should be monitored to determine whether treatment needs to be increased, remains the same, or even decreases. The criteria for asthma control outlined in the GINA guidelines are shown in Table 132.2. In clinical practice, the need for simple methods to assess asthma control has led to investigation of a variety of candidate measures. The method that is most effective depends on the outcome that is to be achieved. If the goal is to minimize symptoms and exacerbations, then the measurement should utilize standardized measures of symptoms such as the Asthma Control Test (ACT). On the other hand, if reduction of eosinophilic pulmonary inflammation is the goal, then measures such as eosinophilic cationic protein (ECP) should be used. The question is how the various measures relate to each other and how well they lead to the ultimate asthma outcome, which is a reduction in long-term morbidity and mortality while maximizing the patient's quality of life.

Both the NHBLI guidelines and the GINA guidelines emphasize the need to monitor and maximize asthma control as a major goal of treatment. The main reason for this new emphasis on control is due to the recognition that the adverse effects of taking medications when they are not necessary may offset the advantage of complete medical control. It may be easy to prescribe all of the medicine all of the time; however, it is not as easy to prescribe just the right amount of treatment to reach a balance between the benefits of medical control and the

Table 132.1
Classification of asthma before treatment * (Gina Guidelines 2008, P23)

Intermittent Asthma
Symptoms less than once a week
Brief exacerbations
Nocturnal symptoms not more than twice a month
FEV1 or PEF >80% predicted
PEF or FEV1 variability <20%
Mild Persistent
Symptoms more than once a week but less than once a day
Exacerbations may affect activity and sleep
Nocturnal symptoms more than twice a month
FEV1 or PEF >80% predicted
PEF or FEV1 variability <20–30%
Moderate Persistent
Symptoms daily
Exacerbations may affect activity and sleep
Nocturnal symptoms more than once a week
Daily use of inhaled short-acting B2-agonist
FEV1 or PEF 60–80% predicted
PEF or FEV1 variability >30%
Severe Persistent
Symptoms daily
Frequent exacerbations
Frequent nocturnal asthma symptoms
Limitation of physical activities
FEV1 or PEF <60% predicted
PEF or FEV1 variability >30%

*The worst feature determines the severity classification

Table 132.2
Levels of asthma control (Gina Guidelines 2008, Chapter 2 Diagnosis and Classification P 23)

Characteristic	Controlled	Partly Controlled	Uncontrolled
Daytime symptoms	None (twice or less/week)	More than twice/week	Three or more features of partly controlled asthma present in any week
Limitations of activities	None	Any	
Nocturnal symptoms/ awakenings	None	Any	
Need for reliever/ Rescue treatment	None (twice or less/week)	More than twice/week	
Lung Functions (FEV or FEV1)	Normal	<80% predicted or personal best (if known)	
Exacerbations	None One or more/ year*	One in any week+	

*Any exacerbation should prompt review of maintenance treatment to ensure that it is adequate

+By definition, an exacerbation in any week makes that an uncontrolled asthma week

Lung function is not a reliable test for children 5 years and younger

There are several validated questionnaires which may be used to access asthma control including the Asthma Control Test (ACT) and Childhood Asthma Control Test (C-ACT) (http://www.asthmacontrol.com), the Asthma Therapy Assessment Questionnaire (ATAQ) (http://www.ataqinstrument.com), the Asthma Control Questionnaire (ACQ) (http://www.goltech.co.uk/Asthma1.htm).1 The questionnaires may be used by researchers and clinicians in the assessment of patient asthma control at follow up visits

harms of treatment. Patients have been asserting their desire to take less medicine for a long time by choosing to be nonadherent to recommendations made by their physicians. Their volitional decisions to take less medicine while physicians prescribe more medicine leads to a question of what the best method is for measuring asthma control and what effect such measurements could have on outcomes. For this reason, it is essential that any treatment of asthma consider both the reduced burden of disease while at the same time recognized reduction in the burden of treatment.

The measures of asthma control that will be considered in this chapter include validated measures of symptoms (e.g., ACT), pulmonary function testing (PFT), airway hyperresponsiveness (AHR), exhaled nitric oxide (eNO), induced sputum for eosinophils, ECP and exhaled breath condensates (EBC). Though other measures such as bronchial alveolar lavage and bronchial biopsy may provide a more definitive assessment of airways inflammation, they are not appropriate for routine clinical use in an outpatient setting.

Clinical Manifestations: Symptoms, Signs

The NHBLI guidelines emphasize the need for assessment of daytime and nighttime asthma symptoms as a measure of control. Symptoms of asthma generally consist of recurrent cough, wheeze, and difficulty breathing that vary in intensity spontaneously, or in response to bronchodilators or to provoking agents. To facilitate quantification of asthma symptoms as a measure of control, the five-item ACT was developed. As a screening tool, the ACT shows good agreement with specialist's rating of asthma control. The test has been validated for identifying patients with poorly controlled asthma. It also has been found to be a useful tool for helping physicians to identify patients with uncontrolled asthma and to help them follow patients' progress. It has been found to be internally consistent, repeatable, and sensitive to changes in asthma control. It correlates well with specialists' ratings of asthma control, pulmonary function tests, and with treatment recommendations. An ACT score of 19 or less provides an optimum balance of sensitivity and specificity for detecting uncontrolled asthma.

Pulmonary Function Testing

Asthma is a condition that is manifested by airways obstruction due to cellular infiltration and edema leading to narrowing. Since it is not practical to directly measure the degree of narrowing in a patient's airways, it is necessary to use surrogate measures of airflow resistance such as FEV_1 and FEV_1/FVC. Even so, there is some debate about the utility of measures of airflow limitation in patients with asthma. The NHLBI recommends that objective measures of airflow limitation be obtained at regular intervals and has included them as a component of asthma severity and control. The measurements are easy to perform, noninvasive, and relatively inexpensive. For these reasons, PFT has become the standard test used in clinical trials and it has achieved widespread use in clinical

practice. Use of PFT does have its limitations, however. Though patients with decreased FEV_1 have been shown to have an increased risk of having an asthma exacerbation, even patients with an $FEV_1 > 80\%$ predicted have a 20% of having an exacerbation.

Airway Hyperresponsiveness

AHR is defined as the concentration of a provoking agent that is required to reduce FEV_1 by 20% from baseline. This can be expressed either as the provocation concentration (PC20) or the provocation dose (PD20), which is the concentration multiplied by the volume delivered. AHR is used to measure the sensitivity of airways to provoking agents and also to define underlying mechanisms of drug action and bronchoconstriction. The most common agents used for AHR include methacholine, histamine, AMP, exercise, cold air, and dry air (eucapnic hyperpnea). Recently, hyperosmolar mannitol also has been used. Allergens can also be used to determine the sensitivity of an allergic individual over time in response to a new treatment.

In general, methacholine, an agent that directly activates smooth muscle cells in the lung, is used for making the diagnosis of asthma by identifying AHR and to guide treatment. Exercise is used as a model of exercise-induced asthma, though eucapnic hyperpnea also is being tested as a surrogate to identify exercise-induced asthma. These techniques indirectly cause AHR by enhancing the release of prostaglandins, leukotrienes, and histamine. There is increasing interest in agents that act indirectly to release mediators to better define the underlying mechanisms of inflammation.

To determine predictors for failed reduction of ICS in patients with well-controlled asthma taking a stable dose of an ICS, the ICS was halved every 8 weeks in a clinical trial. The significant predictors of a failure of ICS reduction were AHR to both histamine and mannitol at baseline and during the dose-reduction phase. Response to mannitol and percent sputum eosinophils were significantly greater before a failed ICS reduction than before the last successful ICS reduction, whereas there were no significant differences in symptoms, spirometry, or eNO.

Tests of AHR are well suited to monitor the success of a treatment strategy. In one study comparing AHR-guided treatment using methacholine with recommendations from the NHLBI guidelines, investigators found that the AHR-guided strategy led to more effective asthma control and greater improvement of airways inflammation. In particular, patients treated according to the AHR strategy had a 1.8-fold lower rate of mild exacerbations than did patients treated with the reference strategy. In addition, FEV_1 improved more and there was a greater reduction in thickness of the subepithelial reticular layer in the AHR strategy group.

Eosinophil Cationic Protein

Eosinophil cationic protein (ECP) is another measure that has been studied as a potential biomarker of eosinophilic airway inflammation. ECP has been measured in serum, plasma, sputum, saliva, and bronchoalveolar lavage (BAL) fluid; however, serum and sputum are the most common sources. The concentration of ECP correlates well with airway inflammation but not with AHR. Since it can be elevated in other atopic diseases, measurement of ECP is not diagnostic for asthma, though it has been shown to be useful for assessing asthma severity and compliance with anti-inflammatory medications. ECP also has the potential to be used as a guide for managing ICS therapy.

Serum concentrations of ECP are significantly higher during acute asthma exacerbations than during clinical remissions. In addition, patients with an FEV_1 less than 75% predicted have higher ECP concentrations than those with a higher FEV_1. ECP also is higher in children with chronic asthma symptoms compared with non-asthmatic, non-atopic children.

Induced Sputum

The value of sputum induction in pediatric asthma lies in its potential to directly and noninvasively assess airway inflammation in children. Induced sputum is one way to determine which types of cells (neutrophils or eosinophils) are predominant in the airways of a patient with asthma. The challenge is to get a good sample that is reflective of the pulmonary cellularity and that is not too contaminated by saliva. For adults, this is relatively straight forward though it is less easy in children due to their lack of cooperation in the maneuver and to their tendency to swallow sputum rather than spit it out. In one study using induced sputum neutrophil and eosinophil counts as markers of inflammation, the presence of sputum neutrophils but not eosinophils was associated with lower postbronchodilator FEV_1 suggesting that neutrophilic airway inflammation is associated with poorer response to treatment.

Since exacerbations of asthma are likely to be due to an increase in airway inflammation, an increase in the number of cells in induced sputum may prove to be a marker of an impending exacerbation. Both increases in sputum eosinophils and eNO correlate with decreased morning peak flows and FEV1. In addition, higher sputum percentage eosinophils are associated with atopy, increased bronchodilator reversibility, lower FEV_1/FVC ratio, higher eNO levels, circulating eosinophils, sputum and serum eosinophil cationic protein, and greater asthma severity. Tailored asthma interventions based on sputum eosinophils are beneficial in reducing the frequency of asthma exacerbations in patients with asthma.

Exhaled Breath Analysis

International asthma guidelines recommend that a variety of clinical tests be used to monitor asthma control. These have focused largely on identifying variable airflow obstruction and responses to provoking agents, bronchodilator, or corticosteroids. A growing interest has recently been directed toward identifying noninvasive markers of airway inflammation including gases such as nitric oxide and EBC collection. Exhaled breath analysis is used to measure inflammation and oxidative stress in the respiratory tract, to make a diagnosis of airway disease and as a guide to monitor and adjust therapy. EBC is obtained by cooling exhaled air. Its composition is believed to mirror that of the fluid lining the airways. While EBC is still considered to be a research tool, other exhaled components such as eNO measurement are closer to clinical practice.

Exhaled Nitric Oxide

Fractional eNO (FeNO) is a gas that is increased in atopic asthma, correlates with various inflammatory markers, and is reduced by treatment with corticosteroids and antileukotrienes but not by beta2-agonists. Since NO is a gas at room temperature, it does not liquefy on cooling and therefore it is not an EBC. FeNO is a reliable marker of eosinophilic airway inflammation that can be measured using standardized techniques in children as young as 4 years. FeNO is believed to be another surrogate marker of inflammation. Until recently, measurement of FeNO was limited to research facilities and secondary care institutions. With the development of portable nitric oxide analyzers (MINO; Aerocrine AB; Smidesvagen, Sweden) routine measurement of FeNO is more available for clinical practice without the need for the more expensive units (NIOX; Aerocrine) without losing any accuracy in measurement.

FeNO appears to represent a distinct parameter from other, more clinically based measurements. The concentration of FeNO is significantly elevated in uncontrolled asthma and decreases after anti-inflammatory therapy. A low eNO appears to be predictive of not having an exacerbation of asthma in the near term. An elevated FeNO in preschool-aged children with moderate-to-severe intermittent wheezing also is associated with an increased risk of respiratory tract infections and with aeroallergen sensitization.

Current asthma guidelines recommend adjusting treatment on the basis of lung function tests and symptoms. Unfortunately, neither of these has been shown to be closely associated with airway inflammation. This leads to the question of whether FeNO can be used to manage asthma as effectively as the more standard measurements. FeNO concentrations do seem to change more rapidly in response to administration of ICS than FEV_1 or AHR suggesting that it is more sensitive to changes in inflammation than these other measures. By using it to guide step-down treatment, FeNO measurement seems to reduce the use of ICS without compromising asthma control. There have been studies with different results. Clearly, further research is needed to fully define the value of FeNO measurements as a guide to asthma treatment.

Exhaled Breath Condensates

Collection of EBC is a noninvasive method for obtaining samples from the lungs to assess airway inflammation and oxidative stress and may be useful in the assessment of childhood asthma. EBC contains large number of mediators including adenosine, ammonia, hydrogen peroxide, isoprostanes, leukotrienes, nitrogen oxides, peptides, and cytokines. Concentrations of these mediators are affected by lung diseases and can be altered by therapeutic interventions. In addition, the pH of EBC changes in response to the presence of respiratory diseases. Recently, the American Thoracic Society/European Respiratory Society Task Force on EBC provided recommendations for the collection and measurement of EBC. The recommendations included instructions to "collect EBC during tidal breathing using a noseclip and a saliva trap; define

cooling temperature and collection time (10 min is generally sufficient to obtain 1–2 mL of sample and well tolerated by patients); use inert material for condenser; do not use resistor and do not use filter between the subject and the condenser."

Increased concentrations of 8-isoprostane, hydrogen peroxide, nitrite, and 3-nitrotyrosine are found in EBC in inflammatory lung diseases. Increased levels of lipid mediators are found in these diseases, with a differential pattern depending on the nature of the disease process. With the development of smaller, less expensive, and more sensitive analyzers, exhaled breath analysis may become available for diagnosis and monitoring of asthma in the routine clinical practice.

Exhaled 8-isoprostane is a stable marker of oxidative stress. Mean exhaled 8-isoprostane concentrations are significantly higher in steroid-naive asthmatic children than in healthy children. Children with asthma who take ICS also have higher 8-isoprostane levels than normal children suggesting that it is not normalized by inhaled steroid therapy. Exhaled 8-isoprostane also does not correlate with duration of asthma, dose of inhaled steroids, or FeNO.

Aldehydes and glutathione are additional biomarkers of oxidant and antioxidant status in asthma, respectively. Children with exacerbations had higher concentrations of malondialdehyde (an oxidant), that decreased after steroid therapy, than healthy controls. Conversely, glutathione (an antioxidant) concentrations are decreased during exacerbations and increased with steroid therapy.

Cysteinyl leukotrienes (Cys-LT) and isoprostanes are inflammatory metabolites derived from arachidonic acid whose levels are increased in the airways of asthmatic patients. Isoprostanes are relatively stable and specific for lipid peroxidation, which makes them potentially reliable biomarkers for oxidative stress found during asthma exacerbations. Both substances decrease with prednisone treatment but not as much as FeNO suggesting that corticosteroids may not be fully effective in reducing oxidative stress in children who are having an exacerbation of asthma.

EBC pH and ammonia concentrations have been used as a noninvasive method to measure acid-base status in the airways of asthmatics. Both pH and ammonia are lower in patients with asthma than in healthy control groups. In addition, both values increase with ICS-treatment. At low pH values found in the airways, nitrite, which is an endogenous airway compound, is converted to nitric oxide (NO) in quantities that may be sufficient to account for the concentrations of NO found in the expired air of asthmatics.

Diagnosis

2007 NHLBI Guidelines

In 2007, the NHLBI published the third complete update of its guidelines for the diagnosis and treatment of asthma. Though previous versions emphasized careful diagnosis of asthma, categorization of severity and treatment based on that severity, little emphasis was placed on long-term assessment of asthma control. The third update corrected that oversight with its emphasis on ongoing measurement of asthma control with corresponding modification of treatment. There are a number of reasons for this including a growing recognition that maintaining asthma control is an important component of prevention of adverse outcomes such as emergency department (ED) visits, hospitalizations, and death.

Since asthma is a heterogeneous syndrome with some phenotypes responding better to certain treatments than others, identification of markers that can help to predict asthma exacerbations is an important component of control, particularly since asthma severity changes frequently over time. This heterogeneity includes variability in clinical, physiologic, and pathologic parameters. Children with asthma frequently move between severity categories, particularly if they start with inadequate asthma control to begin with.

To achieve the best control, asthma severity needs to be determined repeatedly using assessments of lung function, albuterol use, and asthma symptoms along with new markers of eosinophilic airway inflammation. There is increasing evidence that management guided by measures of inflammation is superior to other measures leading to a reduction in exacerbation frequency and a reduction of inhaled corticosteroid dosage.

International GINA Guidelines

In addition to the NHLBI guidelines in the USA, the GINA guidelines have been accepted as an international set of asthma guidelines. Since it was formed in 1993, the GINA, a network of individuals, organizations, and public health officials, has played a leading role in disseminating information about the care of patients with asthma based on a process of continuous review of published scientific investigations. A comprehensive workshop report entitled "A Global Strategy for Asthma Management and Prevention," first published in 1995, has been widely adopted, translated, and reproduced, and forms the basis for many national guidelines. The 2006 report contains important

new themes. First, it asserts that "it is reasonable to expect that in most patients with asthma, control of the disease can and should be achieved and maintained," and recommends a change in approach to asthma management, with asthma control, rather than asthma severity, being the focus of treatment decisions. The importance of the patient–care giver partnership and guided self-management, along with setting goals for treatment, are also emphasized. Management of asthma according to the GINA guidelines has been shown to be associated with a decrease in asthma morbidity and mortality.

Differential Diagnosis

Since asthma is a heterogeneous syndrome that is defined clinically, a number of related diseases can have similar symptoms. It is important to distinguish between alternative diagnoses and conditions that trigger underlying asthma. For example, Respiratory Syncytial Virus and Rhinovirus are common triggers of asthma in young children. Though it is possible for a child with RSV to wheeze, it is more common for a patient with asthma to wheeze when infected with these viruses than for a nonasthmatic person. These viruses therefore are triggers of asthma and not alternative conditions. Similarly, Gastroesophageal Reflux Disease (GERD) is a trigger for asthma as opposed to an alternative disease since most children with this condition do not wheeze.

The most common alternative disorders in children include Cystic Fibrosis which often manifests as a chronic obstructive lung disease, Vocal cord dysfunction (VCD), congenital abnormalities of the lower airways (bronchogenic cysts, abnormal blood vessels, TE fistulae, etc.), Cardiac asthma which is actually congestive heart failure manifesting with wheezing, immotile cilia syndrome (Kartagener's syndrome if associated with situs inversus), and immunodeficiency. Other conditions such as foreign body aspiration must be considered along with various conditions associated with chronic cough such as post-viral cough, habit cough, and exposure to irritants. Children with alpha-1-antitrypsin deficiency usually present with liver disease, and COPD in a child is very rare.

Since most of these alternative diagnoses can be excluded either by history or simple diagnostic tests and most obstructive wheezing lung disorders in children actually are manifestations of asthma, it is not necessary to perform exhaustive testing in every child to rule out alternative conditions. Instead it is reasonable to prescribe a short trial of asthma treatment and evaluate the response to it. If the patient fails to improve significantly after a reasonable treatment trial, alternative conditions should then be considered.

Treatment

General Care

Trigger Avoidance

Allergen exposure in children with asthma with known sensitivity not only can increase asthma symptoms but can also trigger an asthma exacerbation. Therefore, patients with persistent asthma should be evaluated for atopy for potential of allergen exposure. This should be done by taking a careful allergy history and with either skin prick testing or in vitro testing for allergen-specific IgE. Sensitized patients should be encouraged to limit their allergen exposure.

The most common indoor allergens are dust mite, fungi, and animal dander. When indoor allergens are suspected to be present, consideration should be given to requesting an environmental home or school assessment by an environmental hygienist. Such assessments may help to identify the types and amount of exposure and can help guide avoidance recommendations.

Dust mites are considered to be an important trigger of asthma. These acarids are found in upholstered furniture, bedding, and carpeting and they feed on shed skin cells, fungi, and each other. They produce 5 μm fecal pellets that contain dust mite allergens and that become airborne when disturbed. Suggested methods for reducing exposure to dust mites include air filtration, reduction of humidity, chemical acaracides, and use of dust-mite impermeable mattress covers. Because the fecal pellets settle out of the air relatively quickly, air filtration has not been shown to be very effective for reducing dust mite exposure. Reduction of humidity to 35% can reduce dust mite populations but is hard to consistently achieve in microenvironments such as a bed because of respiration and perspiration by its human occupants. There is limited evidence that these simple interventions such as dust mite covers and chemical acaracides are effective for treating asthma. Instead, a comprehensive set of environmental control measures is likely to be required.

Exposure to pet dander from furry animals is another important trigger of asthma. There is some evidence that individuals born into houses with cats can become desensitized; however, once sensitization has occurred it is important to avoid exposure. While

avoidance would seem to be easily accomplished for sensitized individuals, the reality is that most households consider their pet to be a member of the family that they are very reluctant to part with. For that reason, a number of strategies have been evaluated for reducing pet allergen while retaining the dog or cat. The most effective has been to simply wash the dog or cat regularly to remove most of the allergen. Denaturants such as tannic acid and dilute bleach also have been proposed as ways to reduce allergen exposure. Regular use of a high-efficiency vacuum such as a HEPA or cyclonic vacuum also has been proposed as a way to reduce pet allergen exposure. Ultimately, it is likely that a combination of these approaches will be necessary to sufficiently reduce exposure so that the pet can remain in the home without triggering asthma.

Irritants trigger asthma symptoms by non-immunologic mechanisms. ETS is one of the most important indoor irritants. For that reason, all patients with asthma should be evaluated for exposure to ETS and referrals to smoking cessation programs should be offered when appropriate. Avoidance of smoke from wood burning stoves, fireplaces, and grills should be advised, as well as avoidance of strong odors, volatile organic compounds, and other respiratory irritants. Adolescents should also be screened for possible occupational exposures, particularly those who have new onset asthma.

Finally, a detailed history should be taken to identify possible, treatable comorbid conditions that may cause increased symptoms. Examples of these conditions include gastrointestinal reflux disease, aspirin sensitivity, rhinosinusitis, obesity, sleep apnea, and stress. If identified as a contributing factor, comorbid conditions should be aggressively treated.

Vaccinations

Patients with asthma are more likely to have serious health problems as the result of many infections. As a result, immunizations should be kept up-to-date with current recommendations. In particular, inactivated influenza vaccinations should be offered to all children greater than 6 months of age with asthma every fall. Children with asthma should not receive the live attenuated influenza vaccine. The 23-valent pneumococcal polysaccharide vaccine is currently only routinely recommended for adults with asthma. Children should continue to receive the 7-valent pneumococcal vaccine as part of their routine immunization schedule but it is not considered to be part of asthma treatment.

Asthma Self-management

Asthma education is an essential component of asthma management. Asthma care providers should teach patients and families the basics of asthma and medication techniques in simple language. Patients should be taught about asthma and step-down treatment. In addition, clinicians should provide written asthma action plans that include the patient's daily controller medications as well as how to recognize and handle worsening asthma symptoms. Action plans based on peak flow meter readings are no more effective than plans based on symptoms.

The Acute Intervention Management Strategies (AIMS) trial attempted to determine what management strategies are effective by following children with a variety of allergy, asthma, environmental, and quality of life assessments. They found that episodic use both of ICS and LTRA led to reductions in trouble breathing and interference with activity during episodes. This suggests that parents can use symptoms to guide the need for controller medications for long-term management of asthma.

The question of what intervention would be effective for treating an exacerbation of asthma has been extensively reviewed. There is limited evidence for the addition of a long acting beta-agonist (LABA) during an episode of asthma to prevent the need for oral steroids. Addition of or doubling the dose of an inhaled corticosteroid has not been shown to be effective. The one intervention that has been shown to be effective is to quadruple the dose of the inhaled corticosteroid at the onset of respiratory symptoms. If needed for an exacerbation, a short course of oral steroids has been found to effectively prevent relapses of asthma.

Spacers

Spacers should be considered for use with all metered dose inhalers (MDIs) when the patient is unable to coordinate an inhalation and actuation. In particular, spacers should be considered for infants and very young children. Though there does not appear to be a significant difference between the different types of spacer, it is important that it be fitted to the patient so that it can be used properly. Holding chambers, when used correctly, are as effective for

delivering an aerosol as is nebulizer delivery and they may be more effective for treating acute episodes of asthma.

The Future of Asthma

While asthma continues to be a significant global health problem, the future of asthma management appears to be bright. Over the next decade it is likely that genetic tests will identify individuals who are at high risk for developing asthma and that new treatments will be developed based on those new insights. Treatment will be personalized based on knowledge of a person's genetic makeup eliminating the "one size fits all" approach that is used today. In addition, asthma control will be monitored using sensitive biomarkers that relate to outcomes that are important. And finally, it is possible that preventative approaches to asthma will be developed so that the prevalence of this troublesome disease will decline.

Specific Treatment

The 2007 NHLBI guidelines for the diagnosis and management of asthma outline a stepwise approach to initiating various pharmacologic treatments. While initiation of treatment is based on the severity of asthma, long-term management is based on control. The recommendations are for patients to step-up treatment if control is inadequate and to maintain or step-down treatment when control is achieved to determine the least amount of treatment necessary to maintain optimal control. The specific medications recommended for each step are shown in *Table 132.3*.

Table 132.3
Stepwise approach for managing asthma

Stepwise approach for managing asthma in children 0–4 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Medium-dose ICS
Step 4	Medium-dose ICS and either LABA or montelukast
Step 5	High-dose ICS and either LABA or montelukast
Step 6	High-dose ICS and either LABA or montelukast and oral systemic corticosteroid
Stepwise approach for managing asthma in children 5–11 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Low-dose ICS and either LABA, LTRA, or theophylline or medium-dose ICS
Step 4	Medium-dose ICS and LABA
Step 5	High-dose ICS and LABA
Step 6	High-dose ICS and LABA and oral systemic corticosteroid
Stepwise approach for managing asthma in children >12 years of age	
	Preferred medications
Step 1	SABA PRN
Step 2	Low-dose ICS
Step 3	Low-dose ICS and LABA or medium-dose ICS
Step 4	Medium-dose ICS and LABA
Step 5	High-dose ICS and LABA and consider omalizumab
Step 6	High-dose ICS and LABA and oral systemic corticosteroid and consider omalizumab

Source: Reproduced from the NHLBI Asthma Guidelines 2007

Relievers

Short acting beta-agonists (SABAs) include albuterol, levalbuterol, and pirbuterol. These medications quickly relax bronchial smooth muscles leading to bronchodilation. These drugs are also beneficial for prevention of exercise-induced bronchospasm when used 15–20 min before exercise. The mechanism of action involves activation of adenlycyclase resulting in an increase in cAMP which in turn leads to activation of protein Kinase A which inhibits phosphorylation of myosin and lowers intracellular calcium resulting in relaxation of bronchial smooth muscle. Other benefits include reduced vascular permeability and edema and increased cillary beat frequency. Side effects include tremor, increase in heart rate, prolongation of QT interval and hypokalemia and hyperglycemia especially with frequent use.

Asthma mortality epidemics occurred in 6 countries in the early 1960s associated with the introduction of isoprenaline forte and in the 1970s in New Zealand with the introduction of fenoterol. Both of these beta adrenergic agents are nonselective with enhanced cardiovascular side effects especially in high doses and with frequent administration in persons with hypoxemia from asthma. Selective beta adrenergic agents currently in the market such as albuterol, salbuterol, and levalbuterol have not been associated with epidemics of asthma mortality.

In patients with mild asthma, scheduled use of albuterol does not provide either beneficial or deleterious effects on asthma control. Consequently, SABAs should be used as rescue medication and ideally should be necessary infrequently if the asthma is under good control. An increased need for SABA use should be viewed as a marker for increased inflammation and to signify the need to increase daily controller medications. A patient who requires frequent SABA use and is not controlled should receive stepped-up therapy with an inhaled corticosteroid and/or systemic corticosteroids because beta adrenergic agents do not provide the needed anti-inflammatory activity.

Inhaled Corticosteroids

ICS are the most potent and effective maintenance treatment of asthma and should be used in all patients who require more than infrequent use of SABA. ICS reduce airway inflammation and hyperresponsiveness. There are a large number of ICS currently available for the treatment of asthma. These medications can be increased in a stepwise fashion to obtain improved asthma control though most have a limited dose-response range. The NHBLI recommendations for the comparative daily doses of various ICS are shown in *Table 132.4*.

Table 132.4
Estimated comparative daily doses of inhaled corticosteroids

Drug	Low dose (mcg per day)			Medium dose (mcg per day)			High dose (mcg per day)		
	Age 0–4	Age 5–11	Age ≥ 12	Age 0–4	Age 5–11	Age ≥ 12	Age 0–4	Age 5–11	Age ≥ 12
Beclomethasone HFA 40 or 80 mcg/puff	N/A	80–160	80–240	N/A	>160–320	>240–480	N/A	>320	>480
Budesonide 90, 180, or 200 mcg/DPI	N/A	180–400	180–600	N/A	>400–800	>600–1,200	N/A	>800	>1,200
Budesonide inhalation suspension	250–500	500	N/A	>500–1,000	1,000	N/A	>1,000	2,000	N/A
Flunisolide 250 mcg/puff	N/A	500–750	500–1,000	N/A	1,000–1,250	1,000–2,000	N/A	>1,250	2,000
Fluticasone HFA 44, 110, or 220 mcg/puff	176	88–176	88–264	>176–352	>176–352	>264–440	>352	>352	>440
Mometasone 110 or 220 mcg/DPI	N/A	110	220	N/A	110	440	N/A	110	>440
Triamcinolone acetonide 75 mcg/puff	N/A	300–600	300–750	N/A	>600–900	>75–1,500	N/A	>900	>1,500

Source: Reproduced from the NHLBI Asthma Guidelines 2007

Though ICSs are the most commonly used asthma controller medications, responses to corticosteroids vary widely between individuals. Though it is difficult to predict who will respond and who will not, a genetic cause in the form of variations in corticotropin-releasing hormone receptor 1 (CRHR1) has been shown to be associated with enhanced response with individuals homozygous for the variants showing increased lung function response to corticosteroids.

Long Acting Beta-Agonists

LABAs are defined as beta-agonists whose half-lives are at least 12 h duration. LABAs are more lipophilic secondary to their extended side chain which leads to a longer duration of action. Medications in this class include salmeterol and formoterol. Formoterol has an onset of action within 15 min and salmeterol within 30 min. LABAs are used in combination with ICS in the maintenance of asthma and are not recommended for use as monotherapy. In the USA, packaging of LABA includes a black box warning from the Food and Drug Administration in which practitioners are advised to weigh the risks and benefits of this medication prior to use.

The GINA guidelines recommend increasing inhaled corticosteroid doses in all children with asthma not controlled on low-dose ICS before adding a long-acting beta2-adrenergic agonist, whereas NHLBI guidelines have different age-based recommendations for children. In patients younger than 5 years, NHLBI guidelines recommend increasing the inhaled corticosteroid dose before adding a LABA; in children aged 5–11 years, equal weight is given to increasing the inhaled corticosteroid dose or including add-on therapy to low-dose ICS. In adults and adolescents aged 12 years and older, GINA recommends adding a LABA to low-dose ICS in preference to increasing the dose of inhaled corticosteroid. The NHLBI guidelines give equal weight to these choices, with alternative, although not preferred, therapies including the addition of theophylline, zileuton, or LTRA to low-dose ICS.

A number of concerns were voiced in 2006 regarding the safety of the use of LABAs for treatment of asthma. These concerns included whether use of this class of drug increases the risk for hospitalization, near death, or death due to asthma, whether the increased risk was greater in African Americans, and whether individuals who are homozygous for arginine at the 16th codon of the beta2-adrenergic receptor have a poorer response or even deteriorate when prescribed LABAs. Subsequent studies addressed each of these concerns and have been consistently reassuring.

Leukotriene Modifiers

This class of medications include both LTRA (montelukast and zafirlukast) as well as a 5-lipoxygenase inhibitor (5-LO; zileuton). The NHLBI guidelines consider LTRAs to be an alternative, but not preferred monotherapy for the treatment of mild persistent asthma. They also are considered to be effective for adjunct therapy in children <12 years; however, LABAs are the preferred adjunct therapy in adults and children >12. Finally, LTRAs are indicated for treatment of exercise-induced bronchospasm. Zileuton is less preferred to LTRAs in children >12 years because of the need for liver function monitoring. LTRAs and Zileuton also may attenuate bronchoconstriction in aspirin sensitive individuals.

Oral Corticosteroids

Oral corticosteroids are potent anti-inflammatory agents whose efficacy in the treatment of asthma is well documented. Because of the many side effects, however, every consideration must be given to administering the lowest dose of oral corticosteroids for the shortest amount of time. Before prescribing oral corticosteroids for maintenance therapy it is important that the use of all other conventional asthma medications be maximized.

Short courses of oral corticosteroids have been shown to be effective for treatment of acute asthma exacerbations. In particular, when taken at the onset of a respiratory infection, a 3–5 days course of an oral steroid can reduce the risk of an ED visit or hospitalization for asthma. Once an asthma exacerbation has taken place, oral steroids are effective for treatment in the ED to reduce the likelihood of hospitalization, though they need to be given as early as possible.

Other Agents

Cromolyn sodium and nedocromil are similar but distinct medications whose anti-inflammatory properties are felt to occur via mast cell stabilization. They may be used as an alternative, but are not preferred treatment in mild persistent asthma. They also may be useful as preventative treatments prior to exercise and when a predictable

exposure to an allergen is unavoidable. Both of these agents are considered to have relatively weak anti-inflammatory effects that take time to become apparent. Their main benefit is their extremely low side effect profile.

Theophylline is a nonselective phophodiesterase inhibitor that provides some bronchodilation. Sustained-release theophylline is an alternative, but not preferred treatment of mild persistent asthma in children >5 years old. Theophylline was widely prescribed for treatment of asthma in the 1980s but fell into disuse in favor of ICS. The main drawback to theophylline is its relatively narrow therapeutic index and well-known side effects that include tachycardia, arrhythmias, nausea, hyperactivity and at higher concentrations, seizures. If theophylline is used it is necessary to monitor serum theophylline concentrations to ensure that the levels are therapeutic without becoming toxic. A number of medications interact with theophylline metabolism including cimetadine, ketaconazole, and many macrolide antibiotics.

Omalizumab

Omalizumab is a recombinant, humanized, monoclonal antibody directed to the portion of the IgE molecule that binds to mast cells and basophiles, thus preventing binding of IgE and subsequent degranulation of these cells. Omalizumab is considered to be an effective adjunct therapy in asthma patients >12 years old with moderate to severe persistent asthma and allergies documented by skin prick testing or in vitro testing. The safety and efficacy of omalizumab in children of ages 6–11 is currently under investigation.

Combinations

Given the extensive list of treatment options for controlling asthma, the question is how to determine which treatment is most appropriate for a particular individual. Both ICSs and LTRAs lead to improvement in most measures of asthma control. However, clinical outcomes, pulmonary responses, and inflammatory biomarkers such as exhaled nitric oxide eNO improve significantly more with ICS treatment than with LTRAs treatment. In addition, elevated FeNO seems to be a predictor of better response to ICS compared with an LTRA.

For moderate persistent asthma, ICSs are more effective. This was confirmed by the Pediatric Asthma Controller Trial (PACT) which found that fluticasone monotherapy and combination fluticasone/salmeterol combination provided greater improvements in asthma control days than montelukast alone. These results are not surprising given the greater anti-inflammatory effects of ICS; however, there is limited information comparing the two agents for patients with mild asthma where the anti-inflammatory effect required for control may be less.

For mild asthma it is possible that both ICS and LTRA would provide sufficient control assuming that patients respond to them equally. To determine how frequently children with asthma do respond to ICS or LTRA, a comparison study was performed in children 6–17 years of age with mild-to-moderate persistent asthma. While 17% responded to both medications, 23% responded only to fluticasone, 5% responded only to montelukast alone and surprisingly, 55% responded to neither medication. Since most patients with asthma improve with treatment, this result suggests that there is more going on than simple anti-inflammatory treatment with medications.

The GINA guidelines are similar to the NHLBI guidelines with an important difference. In the GINA and NHLBI guidelines, patients with moderate to severe asthma are advised to use ICS or an ICS/LABA combination with a SABA as reliever. Because some patients still fail to achieve guideline-defined asthma control leading to overuse of SABA reliever medication at the expense of ICS, the GINA guidelines recommend that such patients use an ICS/LABA combination for both maintenance and reliever therapy. This clearly is contrary to recommendations from the NHLBI guidelines. The GINA treatment strategy has been shown to significantly reduce the rate of severe asthma exacerbations compared with ICS/LABA plus SABA while achieving equivalent daily symptom control with a lower overall steroid load.

Finally, there has been controversy over whether ICS can modify the subsequent development of asthma in children at high risk for asthma. This is important because if ICS does modify subsequent disease development and severity, a stronger case can be made for more aggressive ICS use in young children even when they are asymptomatic. On the other hand, if disease progression is not affected by regular ICS use, it is hard to recommend that asymptomatic children receive aggressive treatment given the potential harms, both physiologic and psychological, that are associated with such treatment. In the one study that addressed this question in preschool children at high risk for asthma, 2 years of inhaled-corticosteroid therapy did not change the development of asthma symptoms or lung function during a third, treatment-free year. These findings suggest that ICS treatment does not lead to a subsequent disease-modifying effect after ICS treatment is discontinued.

Allergen Immunotherapy

Patients who do not respond adequately to pharmacotherapy or who wish to avoid long-term use of medications should be considered for allergen immunotherapy. Injection immunotherapy has been shown to be effective for the treatment of asthma in children in a meta-analysis of clinical trials In addition, sublingual immunotherapy has also shown substantial efficacy for treatment of asthma in children and may be as effective as an inhaled corticosteorid for mild persistent asthma.

Prognosis

Although many children wheeze within the first 3 years of life with viral infections, not all of these children continue to have asthma symptoms as they age. A prospective study of 6-year-old children in Tucson, Arizona found that 51% never wheezed, 19.9% wheezed at least once with viral illness during the first 3 years of life but not at 6 years (transient wheezing), 15% did not wheeze at 3 years but had wheezing at 6 years (late onset), and 13.7% had wheezing both at 3 and 6 years (persistent). Smoking by mother, lack of history of maternal atopy, and lower lung function of the child in the first 3 years of life were risk factors for transient wheezing whereas children who continued to wheeze at 6 years were more likely to have mothers with allergy and to have elevated serum IgE levels. In addition, young children were more likely to continue to wheeze at 6 and 13 years of age if they had risk factors including parental history of asthma or eczema, eosinophilia, wheezing apart from colds, and allergic rhinitis, and over 95% of children without these criteria never wheezed actively between 6 and 13 years.

Patterns of wheezing prevalence and levels of lung function appear to be established by age 6 years and do not change much after that. In a follow-up report, the prevalence of atopy and wheeze by age 16 years was similar for never and transient wheezers and for persistent and late-onset wheezers. Both transient early, and persistent wheezers had significantly lower FEF(25–75), FEV_1, and FEV_1:FVC ratio, respectively when compared to never wheezers.

The natural history of asthma is one of periods of remission followed by reemergence of symptoms in some individuals. A New Zealand cohort study of children with asthma followed into adulthood found that 14.5% continued to wheeze to age 26 years, 27.4% had remission at age 26 years, and 12.4% had a remission but relapsed by age 26 years. Risk factors for persistence and relapse of asthma were earlier onset of wheezing, sensitivity to dust mites, BHR, female sex, and smoking.

Another cohort study of babies at risk for atopy in the UK in which most of the children who wheezed before the age of 2 years and did not wheeze at 11 years did not develop allergies or bronchial hyperresponsiveness whereas 20 of 23 children who wheezed at 11 years had atopy and increased bronchial hyperresponsiveness. Those with positive skin test to egg and milk as infants correlated with asthma at 22 years of age.

Persistence of childhood asthma correlated with severity of asthma in a Canadian study. Children who were hospitalized during the first year after the diagnosis of asthma had a threefold risk of persistent asthma and those with at least four physician visits for asthma had a 2.6-fold increased risk of persistent asthma at age 12 years.

As to the long-term natural history, 30–80% of asthma patients seem to develop symptoms again later in life. This is because some patients who outgrow their asthma continue to have persistent airway eosinophilic inflammation, AHR and airway narrowing. In summary, family history of allergies, personal history of allergic rhinitis, wheezing apart from colds, more severe asthma symptoms in childhood, and lower lung function in childhood tends to be associated with persistence or relapse of asthma as adults.

Prevention

According to the NHLBI guidelines as outlined in *Table 132.5*, the goal for asthma treatment is to control asthma by reducing impairment and risk. This can be done using a stepwise approach to medications in which treatment increases as symptoms increase and decreases when symptoms decrease. To do this it is essential that patients be taught to monitor their degree of asthma control. Because asthma is a chronic disease, it is likely that the relationship between a patient and the asthma provider will be long-term necessitating that the two approach management of the asthma as partners. Referral to an asthma specialist should be considered for patients with persistent asthma for possible comanagement. Patients should receive information about identifying and avoiding asthma triggers including testing for specific IgE, environmental control and when indicated specific allergen immunotherapy. And finally, all patients with asthma should receive a written action plan so that they can control their asthma if and when it flares to reduce the likelihood of an ED visit, hospitalization, and most importantly, avoidance of death. By following these steps it

Table 132.5
Managing asthma long-term

• The goal for therapy is to control asthma by reducing impairment and risk (Evidence A).
• A stepwise approach to pharmacologic therapy is recommended to gain and maintain control of asthma in both the impairment and risk domains (Evidence A).
• Monitoring and follow-up is essential (Evidence B).
• Because asthma is a chronic inflammatory disorder of the airway, persistent asthma is most effectively controlled with daily long-term control medication directed toward suppression of airway inflammation (Evidence A).
• Therapeutic strategies should be considered in concert with clinician–patient partnership strategies; education of patients is essential for achieving optimal pharmacologic therapy (Evidence A).
• At each step, patients should be advised to avoid or control allergens (Evidence A), irritants, or comorbid conditions that make the patient's asthma worse (Evidence B).
• A written asthma action plan detailing for the individual patient the daily management (medications and environmental control strategies) and how to recognize and handle worsening asthma is recommended for all patients; it is particularly recommended for patients who have moderate or severe asthma, a history of severe exacerbations, or poorly controlled asthma (Evidence B). The written asthma action plan can be either symptom-based or peak-flow-based; evidence shows similar benefits for each (Evidence B).
• Referral to an asthma specialist for consultation or comanagement of the patient is recommended if there are difficulties achieving or maintaining control of asthma; if additional education is needed to improve adherence; if the patient requires step 4 care or higher (step 3 care or higher for children 0–4 years of age); or if the patient has had an exacerbation requiring hospitalization. Consider referral if a patient requires step 3 care (step 2 care for children 0–4 years of age) or if additional testing for the role of allergy is indicated (Evidence D).

Source: Reproduced from the NHLBI Asthma Guidelines 2007

should be possible for all patients with asthma to have well-controlled disease with little or no impairment.

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133 Atopic Dermatitis

Harb A. Harfi

Definition

Atopic dermatitis or infantile eczema is a skin inflammation characterized by intense pruritus and scratching, which result in skin damage. The skin lesions manifest in the form of papulation, excoriation, oozing, crusting, and secondary infection. The severity and intensity of symptoms vary from one patient to another. The hallmark of atopic dermatitis (AD) is itching. The skin changes that follow are due to traumatization of the skin by persistent scratching. The symptoms are made worse by increased heat, perspiration, excessive dryness, irritation, psychological tension, and secondary infections.

Epidemiology

Although AD is a common allergic disease of infancy and childhood, its exact incidence is not known. But the incidence seems to be increasing. There are no racial or geographical differences and girls may be slightly more affected. It may affect 5–20% of children, but some studies estimate the incidence to be between 1% and 4%, depending on the population studied and the methodology of the study. The higher figures are in urban population. Most infants develop AD below the age of 1 in 60% of cases and by the age of 5 in another 30%. It is unusual for an infant below 2 months of age to develop AD. The occurrence of AD is much higher in families with a history of allergy. About 75% of infants and children with AD either have another allergy or have a strong family history of atopy.

Pathogenesis and Genetics

The pathogenesis of AD is more complex than it was previously thought. This includes impaired epidermal barrier function, immune disorders in which T-cells, Langerhans cells, and immune effector cells induce inflammatory response to various environmental factors such as irritants, infections, chemicals, and allergens. The integrity of the epidermis is important for a healthy skin. This integrity is kept by the interaction of keratinocytes and a variety of proteins such as Filaggrin, enzymes, and lipids. Disruption of this barrier allows foreign antigen to penetrate and come in contact with immune cells and release proinflammatory agents that lead to the clinical and pathological manifestations of AD. Atopic skin keratinocytes are defective in binding water, which is important for a healthy epidermal barrier. This dryness leads to pruritus with scratching, skin trauma, and inflammation. Several genetic factors involved in the epidermal permeability barrier defect have been described. These include Filaggrin mutation that leads to icthyosin (R 501X and 2282dL4), and defective Spink5 that leads to cleavage of intercellular attachments, and hence, the corneocyte cohesion, which weakens the skin barrier function. The defects open the way for foreign antigens to enter through the epidermis and interact with immune cells, leading to sensitization and inflammation. AD is a genetic disease based on twin studies and family history. The trait is more often inherited through a maternal gene rather than a paternal one. Many patients have Filaggrin mutations.

Clinical Manifestations

Clinical features of atopic dermatitis depend on the severity and chronicity of inflammation. The most prominent feature of atopic dermatitis is itching. The skin is usually dry or erythematous with some degree of lichenification, or oozing, crusting, and acutely inflamed, depending on the stage of inflammation. Skin manifestations go through different stages, depending on the chronicity of symptoms and the age of the patient. Classification of atopic dermatitis in relation to age is divided into three groups:

1. Infantile – from 2 months to 2 years
2. Childhood – from 2 to 10 years
3. Adolescent – from 11 to 20 years

In infants, the early feature is dry erythema on the cheeks, which may become oozy with crust formation and secondary infection. The eczema may spread to involve the forehead, scalp, and postauricular areas. It may also

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involve the extensor surfaces of the upper and lower extremities and may become generalized. The baby is usually irritable and scratches the skin constantly. The baby may look unhappy due to severe itching, which may interfere with feeding and sleep. This stage has a tendency to improve as infants grow older. Once an infant starts crawling, the skin's dryness increases and the papules tend to become larger, confluent, and crusty. In older children, the skin lesions have a tendency to involve the flexural areas, with the antecubital and popliteal fossae and the back of the neck being the preferred areas. Skin infection may complicate the picture further and leads to confusion in diagnosis. In chronic severe eczema, the skin of the eyelids becomes thickened and forms transverse lines known as Dennie–Morgan lines.

Complications

Complications of atopic dermatitis in both infants and children include

1. Secondary infections with *Staphylococcus aureus*, herpes simplex, herpes zoster (eczema herpeticum), and molluscum contagiosum. Herpes simplex may become disseminated, causing serious consequences.
2. Subcapsular cataract occurs in about 16%.
3. Keratoconus and ulceration of the cornea.
4. In cases of severe generalized eczema, psychological complications may lead to withdrawal of the child from social activities.

Differential Diagnosis

Seborrheic dermatitis is easy to differentiate; it usually starts as cradle cap with thick, greasy, yellowish scales. It begins before the age of 2 months and causes minimal or no itching. In comparison, atopic dermatitis starts after the age of 2 months with intense itching. Classic seborrheic dermatitis follows the hairline with slight erythema, while atopic dermatitis is inflamed mostly at the center, and when scales are present, they are usually dry. In addition, the smell of seborrheic dermatitis (mouse-like) is characteristic.

Contact dermatitis is rather uncommon in infants and children. The common causes are earrings, wristwatches, and metal buttons in trousers. The site of dermatitis correlates with the size and site of the causative metal.

Primary immunodeficiency syndromes include *Wiskott–Aldrich syndrome*, which is characterized by eczema, immunodeficiency, thrombocytopenia, and bleeding early in infancy. It is X-linked, and there is usually a history of similar cases in the family. *Severe combined immunodeficiency (SCID)* is very easy to differentiate from atopic dermatitis. The history of severe infections with low virulence and uncommon organisms makes the diagnosis easy. The dermatitis in SCID is due to graft-versus-host disease, and pruritus is unusual. *Hyper-IgE syndrome* (Job syndrome) is very easily confused with atopic dermatitis. In hyper-IgE syndrome, the level of serum IgE is extremely high, and the infant has a history of deep-seated infections, including sinusitis and skin and pulmonary abscesses. The distribution of the eczematoid eruption in hyper-IgE syndrome is different from that of severe atopic dermatitis. The first involves the entire skin from head to toe, and patients have coarse facial features. The color of the eczema ranges from coppery red to violaceous red, with distribution mostly on the extensor surfaces. ➤ *Table 133.1* summarizes the most important differential points between atopic dermatitis and other conditions.

Diagnosis

History and physical examination are usually enough to make the diagnosis of atopic dermatitis. The minimal criteria to establish the diagnosis should include the followings: chronic or recurrent dermatitis with itching, characteristic distribution in relation to age, and white dermographism. The history should include detailed questioning regarding the age of onset, severity of symptoms, and manifestations of other allergic diseases, both in the patient and relatives. Evolution of the skin eruption, the presence of pruritus, and the effect of seasonal variations are pertinent questions in history taking. Triggers such as foods, clothes, drugs, and changes in weather should be inquired into. If food is suspected to be a trigger for the patient's symptoms, confirmation by oral challenge and appropriate tests, performed by a physician experienced in the field of allergy, should be sought. Frequency of bathing and showers are important to know, because of their drying effect on the skin. By physical examination, the patient may have a classic appearance and distribution of atopic dermatitis; in addition, other stigmata of allergy may be present.

Diagnostic procedures include skin prick test. Allergens should include inhalants and common foods consumed by the patient. All positive tests should be confirmed by elimination and oral challenge. Other diagnostic tests include complete blood count, serum IgE level, and culture from surfaces of the infected skin. If the child has extensive skin involvement, skin testing may not be possible. In this case,

Table 133.1
Differential diagnosis of atopic dermatitis

	AD	Seborrhea	Contact dermatitis	WAS	SCID/GVHD	HIE
Itching	+ + + +	+	+ + +	+ + +	0	+ + +
Age of onset	Early (>2 months)	<2 months	Late	V. early	<2 months	V. early
Bleaching	+	0	+	+ + +	0	+
Distribution	Typical	Typical	Localized and characteristic	0	0	Generalized
Deep infection	0	0	0	Yes	Yes	Yes
Crusts	With infection	Greasy	With infection	With infection	No	Abscesses
Serum IgE	↑↑↑	N	N	↑↑↑	↓	↑↑↑↑
Sex	Any	Any	Any	Male	Any	Any
Platelets	Normal	Normal	Normal	V. low	Normal	High
Allergens	Food and others	None	Metals and others	None	None	Food
Prognosis	Good; development of other allergies	Excellent	Excellent	Guarded unless transplanted	Guarded unless transplanted	Poor
Inheritance	±Atophy	0	0	X-linked	X-linked or autosomal recessive	Autosomal recessive

AD, atopic dermatitis; *WAS,* Wiskott–Aldrich syndrome; *SCID*, severe combined immunodeficiency; *GUHD,* graft-versus-host disease; *HIE*, hyper IgE

a radio allergo sorbent tes (RAST) for the common foods and inhalants allergens is an alternative diagnostic tool. Although the majority of infants and children with atopic dermatitis react to foods, the results should not be taken as cause and effect unless confirmed by elimination and challenge.

Management

Patients with atopic dermatitis live in a vicious cycle of scratching and skin inflammation, which aggravate each other. Therefore, the management of atopic dermatitis should attack two points in this vicious cycle: (1) stopping the itching and (2) healing the inflamed skin.

General Management

Excessive dryness, perspiration, and overheating should be avoided as much as possible. Rough fabrics in clothing should be avoided and soft fabrics made of cotton or silk should replace them. Nails should always be kept trimmed to minimize trauma to the skin from scratching.

To bathe or not to bathe? It is a known fact that frequent bathing with soap and water increases skin dryness and, hence, pruritus and scratching of the skin. The traditional teaching to the patient is not to bathe or at least to minimize bathing and showers to once a week. From a practical point of view, it is extremely difficult for the patient and family to accept this recommendation due to hygienic reasons. Therefore, the recommendations in this regard should take into account the social habits and living conditions of the patient and the family. The parents should follow their usual practice of bathing their child as long as they apply moisturizing creams and lotions immediately after the bath or shower. Soap that has a high content of fat is preferred, and it is also preferable not to use scented or perfumed soap. The parents should be encouraged to use creams and lotions of their choice as liberally and as often as they desire.

Antipruritic Medications

Any of the following antihistamines can be used to relieve itching. cyproheptadine (Periactin) in a dose of 2 mg every

6–8 h, or hydroxyzine 5 mg every 6 h, can be used in infants younger than 6 months. The dose can be increased to 10 mg every 6 h in older children. The latter drug is tolerated very well, and the dose can be increased by 6 mg every 5–7 days. Because itching is worse at night, it is advisable to double the dosage at bedtime. If hydroxyzine is not enough to relieve the symptoms, diphenhydramine (Benadryl) in a dose of 0.5–1 mg/kg (maximum 25 mg) every 6 h can be added. The treatment with antihistamines should be given on a continuous basis rather than intermittently. Relieving the itch will help the skin to heal faster, and therefore the need for anti-inflammatory drugs will decrease.

Control of Infection

If there is evidence of skin infection, antibiotics that are active against *S. aureus* should be used. Topical antibiotics should be completely avoided in patients with dermatitis. Patients with a history of frequent skin infections may benefit from prophylaxis with long-term antibiotics active against *S. aureus.* Erythromycin is an alternative drug when the patient is allergic to penicillins.

Dietary Manipulation

Dietary restriction should be reserved for those infants who have definite evidence of allergy to food. If there is evidence of coexistence of respiratory allergy, such as allergic rhinoconjunctivitis and/or bronchial asthma, and the allergen cannot be avoided, immunotherapy guided by history and skin tests may be added to the treatment.

Local Treatment

In the acute weeping phase, topical application of a wet dressing should be used at least four times a day on the oozing areas. Burow's solution is aluminum acetate 1:40 and can be prepared by dissolving Domeboro in 500 mL of tap water. A clean gauze is then soaked in the solution and applied to the oozing area. Once the skin becomes relatively dry and less inflamed, with no oozing, corticosteroid creams can be applied once to twice a day. In cases where the skin is thick and lichenified with no signs of infection, corticosteroid ointment can be applied but avoid skin folds and facial areas. Extremely thick eczematous areas on the extremities need an occlusive dressing with steroid ointment. In very severe cases, systemic, short-acting corticosteroid administration may become necessary for the control of inflammation. Ultraviolet light (PUVA) or cyclosporin A may be used in extremely resistant generalized dermatitis.

In some patients with atopic dermatitis, hypopigmented or discolored areas appear after healing and may be of concern to them. In these cases, reassurance is all that is needed, because the skin color will go back to normal in due time. Topical potent fluorinated corticosteroids should never be applied to facial areas, especially around the eyes. The preferred corticosteroid is 0.5–1% hydrocortisone cream applied twice to three times a day for facial dermatitis. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus applied twice daily have been introduced recently. In very severe cases, oral cyclosporine A may be used with caution.

Prognosis and Prevention

Although prognosis depends on the severity and extent of skin involvement, at least 50% of infants with atopic dermatitis become asymptomatic as they grow older. If there is a positive family history of allergy, atopic dermatitis in early infancy is an indication that other forms of allergy will follow. This knowledge is useful to the treating physician and the family in planning treatment and prophylaxis. Approximately 70% of infants and children who start with atopic dermatitis and have a positive family history of atopy end up with bronchial asthma and allergic rhinitis. If the cord blood IgE level of an infant is greater than 1 U/mL along with a positive family history, the chances of development of atopic dermatitis and other allergies in that infant are extremely high. Mothers of such infants should be advised to breast-feed their babies and to be cautious in introducing solid foods or cow's milk formula into their infant's diet before the age of 6 months. Mothers should also avoid potentially allergenic foods such as milk, eggs, peanuts, and fish in their diet while nursing their infants.

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134 Food Allergy

Justin Skripak · Hugh A. Sampson

Definition/Classification

Food allergy is broadly defined as an adverse reaction to a food resulting from an abnormal immunologic mechanism. "Food hypersensitivity" is generally used interchangeably with "food allergy." However, a European Academy of Allergy and Clinical Immunology subcommittee recently recommended using the term food hypersensitivity to describe any type of adverse reaction to a food, not just immunologically mediated reactions. There are indeed many types of adverse reactions to foods with no immunologic cause. These are best categorized as food intolerances. There are many examples of food intolerance, such as lactase deficiency, scombroid poisoning, or food poisoning when infectious bacteria are present (*Table 134.1*). Food allergy can be subdivided into three categories, based on various possible immunologic mechanisms, which are also described in *Table 134.1*.

Etiology

As food passes through the gastrointestinal tract, it is digested and subsequently presented to the immune system. This normally results in immunologic tolerance to the antigens in that food. A failure of this process to proceed normally is likely a contributing mechanism by which food allergy develops. Genetic and environmental influences on the development of allergic disease have been extensively studied, and the associations appear to be a complex web of multiple factors.

There clearly is a genetic component to the development of food allergy. A child with a food allergic first-degree relative has a significantly increased risk of being food allergic. Additionally, monozygotic twins have an estimated food allergy concordance rate of 64.3%, compared to only 6.8% for dizygotic twins. Lastly, although there have not been any "food allergy-specific" genes identified, there are some candidate genes for increased risk of food allergy, as well as other atopic diseases.

In addition, there are environmental exposures that likely influence the risk of developing food allergy. Vitamin D deficiency, exposure to certain microbes, and timing of food exposures have all been demonstrated in certain studies to contribute to the development of food allergy, but with limited degrees of association. However, all of these factors seem to rely on other complementary environmental, as well as genetic factors, being present simultaneously. The significance of early exposure to foods, in particular, has been challenging to sort out. An alternative to the long-standing approach of early avoidance of allergens in high-risk children has been challenged and is being studied. Some early evidence suggests that the opposite approach, that is, early exposure to allergens, may be beneficial.

Epidemiology

The prevalence of specific food allergies is not uniform around the globe. In Western countries, studies identify milk, egg, peanut, tree nuts, soy, and wheat as the most common allergens. In Spanish children, while egg and milk are also the two most common food allergens, fish may be the third most common one. Israeli children have also been found to be most commonly allergic to cow's milk and eggs, but in this case, sesame allergy appears to be the third most common. In a recent study of Turkish school-aged children, the most common food allergens were found to be beef, cow's milk, cocoa, egg, and kiwi.

Pathogenesis

There are a few aspects of the infant's or young child's *gastrointestinal tract* that differ from that of an adult. These include decreased acidity, decreased proteolytic activity, and an immature microvillus membrane. These factors may contribute to altering the process of food antigen uptake and subsequent presentation to the immune system, which reduces the normal tendency toward tolerance induction. Every individual who ingests food will subsequently have those antigens presented to their immune system. Normally, there is no immunologic

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Table 134.1
Causes of food-related symptoms

Food allergy		
IgE-mediated	**Cell-mediated**	**Mixed**
Anaphylaxis	Contact dermatitis	Atopic dermatitis
Urticaria/angioedema/ flushing	Dermatitis herpetiformis	Allergic eosinophilic esophagitis, gastritis, enteritis, or colitis
Gastrointestinal anaphylaxis	Food protein-induced enterocolitis, enterpoathy, or proctocolitis	Asthma
Oral allergy syndrome		
Rhinoconjunctivitis	Food protein-induced pulmonary hemosiderosis	
Anaphylaxis		
Food intolerances		
Carbohydrate intolerance (lactase, fructase, and sucrase-isomaltase deficiency)		
Food contaminant		
• Additives (sulfites, nitrites, azo dyes, acetylsalicylic acid)		
• Dyes		
• Infectious organisms		
• Bacterial (*Campylobacter*, *Salmonella*, *E. coli* O157:H7)		
• Viral (Norwalk-like virus)		
• Parasitic (Giardia, Cryptosporidia, Askis simplex)		
• Toxins		
• Fish-related (scombroid, ciguatera)		
• Fungal (aflatoxin)		
• Bacterial		
Pharmacologic effects (caffeine, histamine, serotonin, tryptamine, tyramine)		
Psychological (sometimes in conjunction with food allergies)		
Other		
Immunologic (celiac disease)		

response, as the process of *oral tolerance induction* to food antigens occurs. In children who acquire food allergies, this normal development of tolerance fails to occur. Exactly how this normal process fails is yet to be elucidated. It appears that T lymphocytes are intimately involved in the process. Induction of anergic T lymphocytes or T regulatory lymphocytes is essential for the development of oral tolerance.

One factor that clearly is involved in the development of food allergy is the presence of a *Th2*-type immune response. Th2 lymphocytes are defined by their production of certain cytokines that promote an allergic inflammatory response. (It is the interaction of the immune system with dietary antigen in the context of this Th2-type milieu that drives the development of sensitization and subsequent clinical allergy.)

Not all allergic disease is created equal. The IgE-mediated allergic response, such as those seen with typical allergic rhinitis or with anaphylaxis, is the classic pathway associated with allergic disease. However, there are other allergic disorders that appear to develop through a T cell-mediated pathway and do not involve allergen-specific IgE. Examples of such disorders include food protein-induced enterocolitis syndrome and food protein-induced proctocolitis. Finally, some allergic disorders appear to operate through both IgE-mediated and non-IgE-mediated mechanisms. Atopic dermatitis and eosinophilic esophagitis are conditions of this nature.

Clinical Manifestations

The most feared manifestation of food allergy is *anaphylaxis*. Although a precise definition for anaphylaxis remains debated, a working group assembled by the National Institute of Allergy and Infectious Disease and Food Allergy and Anaphylaxis Network in the USA defined it as a "serious allergic reaction that is rapid in onset and may cause death." Along with this definition, a set of diagnostic criteria were also put forth to aid in the diagnosis of anaphylaxis (Table 134.2). In general, these criteria state that symptoms involving two or more body systems must occur following the ingestion of a known allergen for a given patient.

Anaphylaxis typically occurs within minutes to a few hours of ingesting an allergenic food. One variation on this is food-dependent exercise-induced anaphylaxis. This condition requires the presence of two triggers: (1) a food allergen and (2) physical activity above a certain threshold, in order for anaphylaxis to develop. If the food allergen is ingested in the absence of significant physical activity, or if there is physical activity in the absence of the food allergen, no symptoms will develop. Symptoms are typical of those seen with conventional anaphylaxis.

Symptoms are not infrequently isolated to the *skin* during food IgE-mediated allergic reactions. These symptoms can include localized erythematous or urticarial rashes, or facial angioedema at the site of food contact. These symptoms can also develop as part of a systemic reaction. Another skin manifestation of food allergy can be atopic dermatitis. This is often a confusing clinical problem, since atopic dermatitis can be present in addition to food allergy and not necessarily always provoked by it. Additionally, false positive food-specific IgE tests are not uncommon in cases of significant atopic dermatitis. Therefore, attributing a given food as a factor in the exacerbation of atopic dermatitis must be based on symptoms that specifically improve with food elimination and recur with reintroduction of the particular food.

Gastrointestinal symptoms associated with food allergy can be separated into two large categories: those symptoms whose onset repeatedly follows each food allergen exposure, and those that are chronic and not temporally related to food allergen ingestion. In the first category, the abdominal pain, vomiting, and/or diarrhea associated with anaphylactic reactions would be included. The oral cavity sensations of pruritus or scratchiness associated with *oral allergy syndrome* would as well. Finally, although involving a different immunologic mechanism, the delayed onset of severe vomiting and diarrhea associated with *food protein-induced enterocolitis syndrome* also reliably follows each exposure to a given allergen.

Other food allergic conditions manifest as chronic symptoms that do not necessarily follow or are not recognized following each ingestion of a given allergen. *Food protein-induced proctocolitis* usually presents in infants, with bloody stools. Onset of these symptoms may not occur for hours, days, or even weeks following initial exposure to and repeated ingestion of a food. *Food protein-induced enteropathy* typically presents with diarrhea, vomiting, poor feeding, failure to thrive, and steatorrhea. *Allergic eosinophilic disease of the esophagus or gastrointestinal tract* may present at any age. Symptoms of *allergic eosinophilic esophagitis* in infants and young children typically include poor feeding, irritability, spitting-up [reflux], food refusal or early satiety, and sometimes failure to thrive. In older children and adults, difficulty in swallowing, abdominal pain, and impaction are common

Table 134.2
Diagnosing anaphylaxis

Anaphylaxis should meet one of these three criteria		
1. Acute onset of:	2. Acutely following a *likely* exposure to a known allergen (any two below):	3. Acutely reduced BP following a *known* allergen exposure
• Skin or mucosal symptoms *AND* • Respiratory compromise	• Skin or mucosal symptoms	• For infants and children, low age-specific systolic BP, *or* >30% decrease in systolic BP
OR • Reduced BP or symptoms of cardiovascular dysfunction	• Respiratory compromise	• For adults, systolic BP <90 mmHg or >30% decrease from the individual's baseline
	• Reduced BP or symptoms of cardiovascular dysfunction	
	• Persistent gastrointestinal symptoms	

symptoms. *Allergic eosinophilic gastroenteritis* may present with intermittent abdominal pain, poor appetite, and failure to thrive, and edema, hypoproteinemia, and anemia are not infrequent complications.

Respiratory symptoms and/or *cardiovascular* symptoms, such as throat tightness, coughing, wheezing, chest tightness, paleness, cyanosis, or passing out, are unusual as isolated symptoms of food allergy. These symptoms can occur during severe reactions, typically with other more common skin and/or gastrointestinal symptoms, as described above.

Diagnosis

As with all good medical practice, the diagnosis of food allergy is heavily dependent on obtaining a thorough *history.* Critical questions should include, but are not limited to the following: what are the symptoms of concern, when do they occur in relation to exposure to a given food, can the food be eaten without these symptoms occurring, and have the symptoms been present at times other than after exposure to a given food. Because children with food allergy are at significantly increased risk for the development of other atopic diseases, screening questions addressing those concerns should be posed as well. A *physical examination* should cover any areas of concern, with particular attention paid to body weight and height, rashes, and upper or lower respiratory stigmata of allergic disease or asthma.

When there is a suspicion of one or more food allergies, diagnostic testing can be used to help in the diagnosis. *Skin prick testing* and *serum food-specific IgE* levels are the two most appropriate tests to be utilized, although these test results often require careful interpretation. While the sensitivity is generally very good, clinically irrelevant (false-positive) tests are not uncommon. However, studies have indicated that increasing skin prick test wheal diameters or food-specific IgE levels correlate with an increasing likelihood of clinical reactivity. This concept is illustrated in further detail in ❯ *Fig. 134.1.*

Other forms of testing may be employed at times in food allergy evaluation. *Atopy skin patch testing* may have some limited value in assessing food allergies manifesting as delayed hypersensitivity reactions, atopic dermatitis, or eosinophilic esophagitis. Others have found that utilizing atopy patch testing in addition to skin prick and serum-specific IgE testing provides only a marginal increase in positive predictive values. Additionally, extracts for food testing are not standardized, nor is the interpretation of test results. This has resulted in patch testing not being considered a routine or reliable part of the evaluation of food-allergic patients at this time.

Food-specific IgG testing has been utilized from time to time by some physicians. However, there is no evidence that there is any clinical significance to the presence of food-specific IgG antibodies, and this test is not indicated in the routine evaluation of food allergy.

Differential Diagnosis

The key point in the accurate diagnosis of a food allergy is that reactions typically occur *consistently* with exposure to the particular food proteins. A deficiency of one of several enzymes responsible for carbohydrate digestion can result in the onset of gastrointestinal symptoms with or without rashes in some cases. However, symptoms will occur with exposures to foods containing various unrelated proteins. Symptoms occurring as a result of the ingestion of a food contaminant can mimic symptoms seen during anaphylaxis. This can be especially true with scombroid, following ingestion of contaminated fish. However, these reactions are sporadic, following many previous ingestions of the food with no problems, and frequently occur in more than one individual eating the meal. Again, the diagnosis of scombroid poisoning can be difficult since fish allergy is one of the few foods (along with shellfish) that cannot uncommonly have an onset during adulthood. Some foods have pharmacologically active substances, which that can cause symptoms as well. Examples of these include caffeine, histamine (e.g., in strawberries), or tyramine (e.g., in wine, dried cheeses, or sausages). Celiac disease can also present with a food allergy-like constellation of gastrointestinal symptoms. However, there are distinct diagnostic findings on serum testing (IgA anti-endomysial and anti-tissue transglutaminase antibodies) and histology of intestinal biopsies (flattened villi). Lastly, food phobias can cause multiple symptoms, including flushing, oropharyngeal sensations, chest tightness, light-headedness, and diaphoresis, which are similar to those seen with food allergy. A careful history and judicial use of diagnostic testing are important in making the appropriate diagnosis.

Treatment

For as long as food allergy has been recognized, the standard management has been total *avoidance* of responsible food allergens. This usually means not just avoidance of a given food in a concentrated form (e.g., a glass of milk

for a milk-allergic child), but avoiding even trace amounts (e.g., incompletely refined lactose [with protein contaminant] as an ingredient in a cookie). The latter can be quite difficult when deciding what packaged food products are safe to consume. The U.S. Government attempted to lessen the burden on parents by enacting legislation in 2004 requiring that the presence of any of eight "major" allergens be clearly indicated on a food's ingredient label (Food Allergen Labeling and Consumer Protection Act of 2004). Similar legislation was passed in the European Common Market countries. In addition to this, parents must be advised that certain types of foods (e.g., baked goods or candies), or types of cuisines (e.g., those of certain Asian countries), carry a relatively high risk of containing a particular food allergen (e.g., peanut).

It is no longer uncommon for children to have multiple food allergies. One common example in the USA is the infant who is allergic to milk, egg, and peanut. Although the prognosis for spontaneous resolution of cow's milk allergy has always been thought to be good, some studies have found more patients with milk allergies persisting through adolescence. Some combinations of food allergies can severely limit dietary options, placing those children at increased risk for the development of nutritional deficiencies. Since it appears that more and more children are developing food allergies, and that they may be lasting longer in some of those children, it is essential that adequate *nutritional counseling* be provided when necessary.

Even among the most well-educated and well-intentioned patients and their families, accidental exposures to food allergens occur. In fact, they are not uncommon, and when they do occur, can be relatively severe in about 10–15% of cases. Therefore, once the diagnosis of an IgE-mediated food allergy is made, families must be counseled on the signs and symptoms of anaphylaxis, and on how to treat such reactions appropriately. In the case of acute anaphylactic reactions, the primary treatment remains intramuscular epinephrine. In addition to this, antihistamines (oral, intramuscular, or intravenous depending upon the patient's symptoms), intravenous fluids, systemic corticosteroids, and inhaled beta-agonists should be used as clinically indicated.

It is worth noting that recently there has been a major increase in clinical trials investigating various forms of treatment for food allergy. Clinical trials of oral and sublingual immunotherapy, involving the administration of extremely small amounts of the food protein, and then progressively increasing the dose over time, have shown promising results. The majority of participants in these studies became "desensitized" to the particular food. However, most were not permanently cured, that is, "tolerized," and required continued regular exposure to the food to maintain the desensitized state. Allergic reactions to the treatment are common side effects: anaphylactic reactions occur in up to 10% of cases. Future research will attempt to improve on these initial trials, by improving both safety and efficacy of the approach. Another approach of interest involves the consumption of cow's milk or egg proteins in extensively heated (baked) forms, such as when they are contained in muffins, cakes, and cookies. It appears that a majority of children allergic to milk and eggs in the unheated form can tolerate them when extensively heated. The same is not likely to be effective for foods such as peanut, in which proteins are not similarly heat-labile. Most importantly though, these treatments are still considered experimental, and should only be implemented under the careful supervision of clinical trials at this time.

Prognosis

While allergies to milk, soy, egg, and wheat commonly present during the first or second year of life, they also tend to resolve spontaneously in the majority of cases. However, some recent retrospective studies of selected cohorts have found even milk, egg, and wheat allergies persisting into adolescence in a significant number of children with these allergies. Peanut, tree nuts, fish, and shellfish allergies, on the other hand, most often persist into adulthood. The natural history for other food allergens is not well studied. However, our clinical experience in the USA is that among other common allergens, allergies to meats, fruits, and vegetables are often outgrown during childhood. Allergy to seed proteins may be more likely to persist into adulthood, for example, sesame and mustard seed. One qualified exception to this is the oral allergy syndrome, a type of food allergy to raw fruits and vegetables, which typically has an onset in late childhood or adulthood, and is likely to persist. These allergies are not primary food allergies, but rather, allergies to plant pollens with secondary cross-reactivity to certain fruit and plant-based proteins, for example, birch pollen and apples, potatoes, carrots, etc., ragweed, and melons and bananas.

Prevention

There are no current measures that provide a clear and significant protective effect against the development of food allergies. A 2007 American Academy of Pediatrics report and an earlier report from European Society of

Pediatric Allergy and Clinical Immunology recommended breastfeeding until the age of 4 months, and delaying the introduction of solids until the age of 4–6 months because of a possible small impact on decreasing the risk for developing atopic disease. Infants who are not breastfed may gain some protection against the development of atopy when fed a hydrolyzed formula until the age of 4–6 months. Of note, neither organization's review of the literature found a discernible protective effect conferred by maternal food allergen avoidance during pregnancy or lactation.

Conclusion

Food allergy affects up to 6% of the pediatric population in the USA and Europe, and up to 2–3% of the general population, figures that may be on the increase. The diagnosis is established by typical history, laboratory studies, and food challenges. The prognosis for IgE-mediated food allergies in young children is for the eventual acquisition of tolerance. Although food allergen avoidance and counseling about how to treat reactions caused by accidental ingestions remains the mainstay of therapy, there has been a recent increase in clinical trials investigating various forms of immunotherapy.

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135 Urticaria

Harb A. Harfi

Definition

Urticaria is an intensely itchy, circumscribed, raised erythematous plaques usually pale in the center. Lesions may coalesce to form giant lesions. The lesions are usually evanescent and disappear in hours, rarely lasting more than 48 hours. The urticarial lesions clear up without leaving residual marks unless the skin is damaged by scratching.

In relation to the clinical course, urticaria can be divided into:

1. *Acute urticaria*: Acute urticaria is defined if the outbreak of the lesions does not last more than 6 weeks. This form is common and affects about 20% of the population, at least once in their lives. Usually, the cause of acute urticaria can be identified in most cases.
2. *Chronic urticaria*: Chronic urticaria is defined by urtical lesions that last more than 6 weeks and present most of the time. Chronic urticaria makes about one-third of all urticarial cases, both acute and chronic. In most cases of chronic urticaria, an underlying etiology is difficult to identify. Nearly 40% of patients with chronic urticaria have associated angioedema of lips, eyelids, cheeks, and extremities. Sometimes, angioedema also affects the tongue and genitalia.

Etiology

Anything under the sun can cause urticaria including the sun itself. Among the many causes of urticaria, drugs of all kinds are the most common. Others include insect stings, foods, food additives, pollens, parasitic infestations, contact allergens, and transfusion reactions and physical agents such as heat, cold, pressure, exercise, vibrations, water, and sunlight. Other causes include immune complex diseases and serum sickness, viral and bacterial infections, or it can be idiopathic or secondary to autoimmune thyroiditis.

Children with urticaria usually have manifestations of other atopic diseases such as allergic asthma, allergic rhinitis, and positive family history of allergy. Children with contact urticaria due to latex have other manifestations of allergy. Although chronic urticaria is not common in children, parasitic infections, drugs, physical factors, and foods are likely to cause it among them. In some studies, autoantibodies to high affinity IgE receptors were present in as high as 47% of the cases, similar to adults. Food allergy in children may contribute to 7–11% of the cases of urticaria. In a recent study, children with chronic urticaria, physical urticaria such as dermographism, cholinergic and mixed, formed 70% of the subtypes and 13% reported respiratory allergy.

Epidemiology

There are very few studies that define the prevalence of urticaria in children. The figure of 20% within the general population involves both adults and children. In one study, autoimmune chronic urticaria is found in 30% of children who have urticaria. Another study estimates the figure to be 47%. Chronic urticaria alone affects 1% of the general population.

Pathogenesis and Genetics

Several theories regarding the pathogenesis of chronic urticaria have been proposed such as autoimmunity, defective basophils signaling or function. But none of those theories have been helpful in investigating the disease.

Pathology

The pathology is usually heterogeneous, but usually there is interstitial edema and perivascular cellular infiltrates, including eosinophils, lymphocytes, neutrophils, and basophils.

Clinical Manifestations

The urticarial lesions are intensely pruritic, well defined, raised, red or pinkish in color, and usually pale in the

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center. The lesions can be a few millimeters or centimeters in diameter and may coalesce and form giant lesions. Very frequently, urticaria is associated with angioedema of the lips, tongue, or eyelids. Benign urticarial lesions are evanescent lasting few hours to less than 48 hours. It can involve any part of the body.

Diagnosis

The urticarial lesions are easy to identify. In acute urticaria, a careful history taking is important in identifying the cause. In children, food allergy, or drugs are the most likely causes. In endemic regions and areas of poor hygiene, stool examination for ova and parasites is indicated. In chronic urticaria, a careful history and limited laboratory testing may help to identify an underlying disease: CBC, ESR, TSH, and antithyroid antibodies are recommended. Serum IgE and specific IgE for foods and inhalants are recommended, especially if there is history of respiratory allergy. If the lesions last more than 48 hours, a punch biopsy to rule out vasculitis is indicated.

Differential Diagnosis

The pruritic skin lesions that need to be differential from urticaria include:

Drug eruptions, contact dermatitis, atopic dermatitis, pityriasis rosea, insect bites, Henoch–Schonlein purpura, plant-induced dermatitis, and erythema multiformed

Treatment

The most important part of the treatment is identification of the underlying cause and its elimination. However, in the majority of cases, the etiology of urticaria is difficult or impossible to identify. In these cases, pharmacological therapy is indicated. However, most cases of urticaria clear up spontaneously. Administration of antihistamines that relieve itching and suppress the lesions is the main treatment. In severe cases, corticosteroids may be used with other drugs. In autoimmune thyroid disease, with hypothyroidism, thyroxine replacement may be helpful. H1 and H2 antihistamines may be combined in resistant cases. Antileukotrienes, cyclosporine, and calcium channel blockers may be helpful in some difficult cases.

Prognosis and Prevention

Most cases of acute urticaria in children clear up with or without treatment. If urticaria is related to foods, pollens, or drugs, elimination and treatment of the etiology leads to cure. In most cases related to autoimmune thyroiditis, chronic urticaria usually clears up in weeks or years, usually less than 5 years.

Prevention of urticaria depends on recognition of the underlying cause or causes and treating it, or avoidance especially if it is food or drug.

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136 Anaphylaxis

Harb A. Harfi

Definition

As defined by international expert consensus, "Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death".

Etiology

Food is the most common cause of anaphylaxis, especially in infants. Other causes include medications, insect stings, rubber latex; vaccines, and idiopathic anaphylaxis are relatively rare in the pediatric age group. Other uncommon triggers of anaphylaxis in infants and children include inhalant allergens, especially animals and exposure to cold temperature.

Epidemiology of Anaphylaxis in Children

The true incidence of anaphylaxis in infants and children is not exactly known. In one study, it has been estimated to be 1/3,000 for both children and adults. In a recent study questionnaire in German children below 12 years, 103 cases were found. Foods were the most common, followed by insect stings and immunotherapy. The occurrence is increasing in industrialized countries.

Pathophysiology of Anaphylaxis

In anaphylaxis, there is massive and sudden release of mediators from mast cells and basophils into the circulation. The reaction results from immunologic response to foods, insect stings, or drugs, or foreign proteins. However, nonimmune mechanisms by contrast media or drugs can also lead to release of mediators. Genetic factors also may play a role. The immunologic reactions that lead to release of multiple mediators from mast cells and basophils are IgE-dependent. Sensitization by foreign proteins leads to formation of specific IgE. The IgE becomes cell bound to the surfaces of mast cells and basophils. On reexposure to the foreign protein, the protein (allergen) binds to the cell-bound IgE, leading to release of the mediators responsible for anaphylaxis. These include heparin, histamine, tryptase, chemochynes, leukotrienes, prostagladins, and platlets activating factor (PAF). These are responsible for signs and symptoms of anaphylactic reactions.

Pathology

In autopsy of fatal anaphylaxis, there are few or no pathological findings. This is related to the rapid onset of anaphylaxis. When pathologic findings are present, they include edema and hyperemia of the upper airway, hyperinflations of the lungs, cerebral edema, and urticaria on cutaneous erythema.

Clinical Manifestations

The clinical manifestations of anaphylaxis in infants up to 2 years can be difficult to recognize. Many of the signs are nonspecific, such as drooling, crying, vomiting and diarrhea after feedings, flushing, colics, and irritability, which can also be found in healthy infants. But in some infants, the onset of anaphylaxis can be seen in the form of sudden onset of lethargy or hypotonia and cessation of activity. Because food is the most important cause of anaphylaxis in infants, sudden onset of lethargy, irritability, colics, crying, flushing, and angioedema or cessation of activity should alert the mother or the caregiver to the possibility of anaphylaxis, and immediate resuscitative measures undertaken. In older children and adolescents, the clinical features of anaphylaxis are not different from those in adults. These include generalized hives, flushing, pruritus, vomiting, diarrhea, respiratory distress, sneezing, rhinorrhea, and nasal congestion, hoarseness, strider, laryngeal edema, wheezing, cough, dyspnea and cyanosis, dizziness, syncope, seizure, and, in severe cases, a sense of doom. There may be arrhythmia, tachycardia, hypotension or bradycardia, cardiac arrest, and death in very severe anaphylaxis.

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Diagnosis

The diagnosis of anaphylaxis is based on the clear history of exposure to a known allergen, followed by the symptoms such as, respiratory distress, angioedema, urticaria, tachycardia, choking, etc. Since foods and insect stings, in addition to drugs are the most common causes of anaphylaxis in infants and children, parents, caregivers, and physicians should suspect anaphylaxis if symptoms occur shortly after food ingestion or insect sting or drug administrator. Laboratory tests such as serum tryptase and serum IgE measurement for specific allergens are not much helpful.

Differential Diagnosis of Anaphylaxis

The conditions that may be confused with anaphylaxis include acute generalized urticaria and angioedema, acute asthma, vasovagal and syncope attacks, acute anxiety disorders, shock, and vocal cord dysfunction. In infants, inborn errors of metabolism and sudden infant death syndrome have to be considered in differential diagnosis.

Treatment

Immediate and effective treatment of anaphylaxis starts with assessment of the airway, skin, circulation, and response, followed by immediate administration of epinephrine intramuscular and intravenous fluids, in addition to antihistamines and corticosteroids.

To establish the diagnosis and differentiate it from other conditions in order to establish proper treatment, three criteria must be met:

1. Acute onset of an illness involving the skin, mucosal tissue or both and respiratory distress, and reduced blood pressure.
2. Two or more of the following occurring shortly after the exposure to an allergen: generalized hives and angioedema, respiratory compromise, hypotension, and gastrointestinal symptoms.
3. Hypotension after exposure to a known allergen for that patient, within minutes or hours. Hypotension in infants and children is defined as systolic pressure of 30% less for age normal BP.

Treatment of anaphylaxis has to be immediate. This includes administration of epinephrines, immediate intubation, and establishment of IV line if airway obstruction is anticipated, oxygen and intravenous bolous fluids, and inhalation of salbutamol if there is bronchospasm, and antihistamine diphenhydramine 1–2 mg/kg. Ranitidine 1 mg/kg can be given IV, and methylprednisolone 2 mg/kg to be given iv. In refractory cases, epinephrine and dopamine should be given, especially in hypotension. After recovery, the patient should be kept under observation at least for 6 hours.

Prognosis

If treated immediately with epinephrine the prognosis is good. However, fatalities and near fatalities occur in children if treatment is delayed or anaphylaxis is not recognized early. Fatalities are more common in patients who had asthma. Most fatalities followed ingestion of foods such as peanuts or tree nuts. Recurrence of anaphylaxis can be as high as 40–60% if the trigger is not avoided.

Prevention of Anaphylaxis

The most important measure is to identify the cause of the reaction and avoid future exposure. In case of food allergy, the parents and caregivers should be given a list of the foods that caused the reaction. Reading the labels of processed foods for ingredients is critical in prevention. If the trigger is a drug, an alternative drug should be prescribed in case it is needed. Avoidance of insect nestings and places of attraction is important. Epinephrine autoinjections should be kept on hand at home and school, and the patient should learn to inject himself. Patients who receive allergens immunotherapy should stay under observation in the physician's office at least for 20–30 min while the treatment is being updosed.

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137 Drug Allergy

Harb A. Harfi

Introduction

Drug hypersensitivity in children is not as common as in adults. The estimated occurrence of adverse drug reactions is more common in adults, especially hospitalized patients. The occurrence of drug reactions from different epidemiological studies ranges from 6% to 10%. True allergic drug reactions in children based on questionnaires and confirmation by skin testing, in vitro specific IgE antibodies, and challenge is rather low 3–5.8%. The most common drugs to cause allergic reactions are the beta-lactam group. Other drugs include anticonvulsants, sulfa, biological agents, chemotherapeutic agents, protamines, and others.

Clinical Manifestations of Drug Allergy

Skin eruptions are the most common presentation of drug allergy in children. The rash can be morbilliform, urticarial, bullous lesions or exathematous, or in the form of eczema or fixed drug eruptions. In some severe cases, it can be in the form of Stevens–Johnson syndrome or epidermolysis. Anaphylaxis with respiratory distress, angioedema, hypotension, and even death may occur in some cases, especially with beta-lactam antibiotics. Toxic immunologic reaction such as hemolysis may occur. Some patients may develop immune complex reactions such as serum sickness and vasculitis. Sometimes, drug fever may be the presenting symptom. Other clinical manifestations are fixed drug eruptions.

Diagnosis and Differential Diagnosis of Drug Allergy

Drug allergy is a great imitator of many skin diseases, especially viral exanthema. In case of skin eruptions, differential diagnosis should include measles, chicken pox, eczema, other causes of urticaria, and in patients with bone marrow transplant for immunodeficiency with graft versus host reactions.

The diagnosis of drug allergy is usually easy in children if the reaction occurs after the administration of a single drug.

The difficulty arises when a patient is taking multiple drugs when the reaction occurs.

- Practical approach to a child with suspected drug allergy
  1. Get a detailed medical history.
  2. Get history of atopy in the child or his family. Allergic drug reactions are more common in atopic families.
  3. Get information on the start and stop of each drug. Allergic reactions are more likely to occur with the lately introduced drug.
  4. Get history of previous reactions to a drug, dosage, and route of administration.
- Tests to establish the diagnosis of drug allergy.
  1. Skin Prick test: Very few drugs are available for skin test. These are mostly the beta-lactam antibiotics, insulin, and very few other drugs. Tests should not be done earlier than 2 weeks after anaphylaxis.
  2. Specific IgE in vitro using ImmunoCAP system or ELISA.
  3. Oral challenge, if feasible and no danger of anaphylaxis.

Management of Drug Allergy

The most important thing to do is to stop and withdraw the suspected drug. If the reaction is mild type 1 allergic reaction that is usually enough. However, in severe cases with anaphylaxis, resuscitative measures should be started immediately. These include administration of adrenaline, antihistamines, and corticosteroids, in addition to intravenous fluids, if there is hypotension. If the drug is life-saving such as the case of bacterial endocarditis, the patient should be desensitized and continued on penicillin. But in milder cases, an alternative antibiotic should be given. If the drug is very necessary and no alternative the patient should be desensitized under close observation

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in a hospital setting by an allergist or an experienced physician.

Once the culprit drug is identified, the patient should carry a card or a bracelet and his chart labeled "allergy to", with the name of the drug.

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138 Insect Allergy

Harb A. Harfi

Stinging insects are widespread and are of different orders. Most belong to hymenoptera. The hymenoptera that are important in allergy belong to three families: Vespidae, Apidae, and Formicidae. The Vespidae has the following subfamilies: yellow jacket, yellow hornet, paper wasp, and white-faced hornet. The Apidae has the honey bee, bumble bee, and sweet bee. The Formicidae has fire ant, harvester ant, jack jumper ant, and samsum (Mayr), Pachycondla sennaarensis ant. Usually, it is the female that stings, most often in defense of its nests.

The incidence of allergic reactions to insect stings in children is not exactly known. But figures from epidemiological studies in general populations showed allergic reactions in children to be around 3% of all those who reported history of insect stings.

Children have a different pattern of allergic reactions to insect stings compared to adults. Systemic reactions are less severe and mostly cutaneous in the form of urticaria. Honey bee is the commonest culprit. It is estimated that 60% of systemic reactions in children are mild. But 30% of those who have moderate to severe reaction will have a similar reaction 2 decades later. Although previous studies did not show correlationship between atopy and increased severity of reactions to insect stings, a recent study showed that school-age children with atopic diseases are at a higher risk of having more severe reactions.

Clinical Manifestations

Most insect stings in children cause painful local swelling, with redness and itching. This may last a few hours or a few days. Generalized or systemic reactions are mostly cutaneous: urticaria, flushing, and/or angioedema with pruritus. A small number of older children may develop respiratory symptoms in the form of hoarseness, shortness of breath, and wheezing. Only 30% of children may develop light-headedness, hypotension, and shock, with cardiopulmonary symptoms.

Diagnosis

The diagnosis of insect allergy is essentially clinical. History of exposure to outdoor insects, feeling of sudden pain at the site of sting, and identification of the insect are enough to establish the diagnosis. But, sometimes, identifying the insect may be difficult. Redness and itching at an exposed area of the skin point to an insect sting. Symptoms of anaphylaxis should be recognized immediately by the patient and the physician and the family members. It is very important to recognize symptoms such as nausea, light-headedness, vomiting or cramps, and diarrhea and flushing early after sting in order to establish diagnosis and start treatment immediately.

Laboratory diagnosis is limited to skin test with venom or whole body extract, or in vitro by specific IgE. In case of anaphylaxis, serum tryptase and histamine measurements can be helpful, but negative results do not exclude the diagnosis because they are transient.

Management

In children less than 16 years of age do not give epinephrine unless the reaction is more than cutaneous. For local reactions apply cold compresses. If the local reaction is large and troublesome to the child, give either one dose of prednisolone 2 mg/kg or tapering dose over 2–3 days. If the reaction is painful, a nonesteroidal anti-inflammatory drug should be given. If the lesion is pruritic, antihistamine may be given.

In cases of anaphylaxis, epinephrine intramuscular should be given immediately, in addition to other resuscitation measures with intravenous fluids, corticosteroids, antihistamines, and oxygen. Once these patients recover, they should be referred to an allergist for long-term management. Autoinjectable epinephrine such as EpiPen should be available at all times. Immunotherapy with venom vaccine did not show any difference in the course of insect stings in children, except in the small number with history of anaphylaxis. In the majority of children, venom immunotherapy is not indicated except in moderate to severe reactions. Children who received venom immunotherapy for 3–5 years fared better and had milder reactions on subsequent stings.

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Prognosis

Children aged less than 16 years who suffered a systemic reaction have about a 10% chance of a similar systemic reaction on subsequent sting. Children who were followed for 10–20 years, irrespective of whether they had received venom immunotherapy or not, continued to have reactions on subsequent stings. But those with moderate to severe reactions and venom immunotherapy fared better than those who did not receive venom immunotherapy. The effect of venom immunotherapy in these cases was long lasting.

Prevention

Hymenoptera, whether they are winged or nonwinged, are attracted to bright colors, perfumes, and rotten fruits. Some of them nest on the ground, such as ants and some wasps. Children with history of insect allergy should avoid wearing floral shirts and perfume when they are outdoors. In picnic areas and areas with vegetation, they should avoid walking barefoot and sitting next to garbage cans. Autoinjectable epinephrine such as EpiPen can be lifesaving in case of severe reactions and should be carried by the patient or the child's parents all the time when they are outdoors.

Summary

Allergic reactions to hymenoptera stings are usually mild and mostly cutaneous in nature in the majority of children. The incidence is not exactly known, but it is less than in adults. Long-term follow-up showed that children continue to have reactions on subsequent stings either the same or milder. In those who had moderate to severe reactions should be referred to a qualified allergist for care. Venom immunotherapy is not indicated in the majority of children with insect allergy. But those with moderate to severe reactions on subsequent stings may benefit from venom immunotherapy. Prognosis is generally good. Prevention is important and EpiPen is necessary in cases of severe reactions.

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139 Miscellaneous Allergies

Harb A. Harfi

Prevention of Sensitization and Allergic Diseases

Numerous publications dealt with ways of preventing the occurrence of allergic diseases in infants and children.

Breast Feedings

Numerous studies showed that breast feeding alone, at least in the first 4–6 months, delays or even prevents the early development of atopic dermatitis and respiratory allergy in high-risk infants. However, this issue is controversial since other studies showed breast feedings did not prevent the occurrence of allergic symptoms. However, it is generally recommended, in high-risk families for allergy, that mothers nurse their babies for the first 6 months. Also delay of introducing solid foods in infant's diet may help in delaying development of allergy symptoms. If breast milk is not available, an alternative is a highly hydrolyzed formula that may help in delaying or even decreasing the development of sensitization.

Smoking

Cigarette smoking in doors is a major pollutant factor that enhances the occurrence of allergy, especially asthma. In children of smoking parents, asthma symptoms and severity improve when parents quit smoking.

Dust-Mite-Sensitization Prevention

Early studies showed that exposure to house dust mite early in life is responsible for the development of respiratory allergy. Avoidance of exposure to dust mite allergens tends to result in less wheezing and other respiratory allergy. However, other studies showed dust mite avoidance reduced the indoor allergen level, but has no effect on respiratory symptoms or other atopic diseases and no effect on total or specific IgE level. So, encasing of beddings and expensive equipments and the use of acaricidal sprays do not seem to have big impact on reducing development of allergy in genetically susceptible infants and children.

Latex Allergy in Children

Latex is extracted from the tree *Heavia brasiliensis*. Rubber gloves and balloons are made of latex. The occurrence of sensitization to latex protein is very common in children with spina bifida. This is due to frequent exposure intermittently during surgery, catheterization, or removal of impacted stool. These children may develop urticaria, contact eczema, rhinitis, asthma, or even anaphylaxis. The higher the number of procedures, the greater the chance of allergic reactions. It is recommended that surgeons should use an alternative with non-latex gloves and catheters when they operate on these children.

Allergic Reactions to Vaccines

Anaphylaxis to vaccines in children is very rare and the estimated figures are between 0.65 and 1.53 per million. Most cases of vaccine allergic reactions are due to preservatives, such as gelatin, in the vaccine. Mumps and measles vaccines are grown in chick embryo fibroblast culture. Hundreds of thousands of children who are allergic to eggs are given the vaccine without reactions. Therefore, MMR vaccine can be given safely to egg allergic children if they can eat eggs without anaphylaxis. However, in influenza and yellow fever vaccines, patients who are egg allergic should be tested with the vaccine before it is administered. Reactions to meningococcus, pertussis, pneumococcus, rabies, tetanus, and varicella have rarely been reported. Most of those reactions were due to preservatives.

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Disorders of the Skin

Zbigniew Ruszczak

140 Pediatric Dermatology: Scope and Challenges

Zbigniew Ruszczak

Skin is the largest organ of the body and a very complex and dynamic structure consisting of many parts and appendages. The actual condition of the skin may reflect not only skin-specific or skin-limited disorders, but – in most cases – is a mirror of either the somatic or psychological status of the patient.

The outermost layer of the skin surface – the epidermis – is an effective barrier to the penetration of irritants, toxins, and organisms, as well as a membrane that holds in body fluids. It acts also as an immunologically active organ responding to external and internal stimuli, communicating with other parts of the skin and, through signaling molecules, transmitters, and neural connections, with different body structures including the central nervous system.

Beside the main cellular component – keratinocytes – epidermis contains specific and sophisticated cells such as melanocytes, which are important for protection against the harmful effects of ultraviolet (UV) light, and the Langerhans cells, a part of the body's first-line immunologic defense. In its basal layer epidermis also contains multipotent stem cells, which in physiologic condition reassure the normal turnover of this skin layer.

The dermis, consisting largely of fibroblasts and collagen, is a tough, leathery, mechanical barrier against cuts, bites, and bruises. Its collagenous matrix also provides structural support for a number of cutaneous appendages.

Hair, which grows from follicles deep within the dermis, is important for cosmesis as well as for protection from sunlight and particulate matter. The bulb part of a hair follicle is also the place from which the epidermis and hair regenerate, being the part of the skin richest in stem cells.

Sebaceous glands arise as an outgrowth of the hair follicles. Oil produced by these glands helps to lubricate the skin and contributes to the protective function of the ceramide-rich epidermal barrier.

The nails are specialized organs of manipulation that also protect sensitive digits.

Eccrine sweat glands accomplish skin thermoregulation.

Glomus cells regulate changes in the cutaneous blood flow.

The skin also contains specialized receptors for heat, pain, touch, and pressure, and the input from these structures helps to protect the skin surface against environmental influence or trauma.

Below the dermis, in the subcutaneous tissue, fat is stored as a source of energy, a reservoir of biologically active substances, vitamins, and hormones, and also acts as a soft protective cushion.

The newborn and neonatal skin is of special interest not only because the transition from an aqueous and sterile atmosphere to a dry and pathogen-rich environment is a tremendous challenge to the young skin. The functioning epidermal barrier is of great importance for the prevention of water loss and for the interaction with numerous microorganisms that colonize the neonatal skin from the moment of birth.

The anatomy of the epidermal and dermal components of the newborn and neonatal skin is the same as that of older skin. However, the process of postnatal maturation and adaptation to environmental stimuli is crucial for the further physiological condition of the skin. It is also important to know that the young skin is much more permeable than the skin of an older person, which implicates the need for appropriate dose adaptation of topically used agents.

The importance of appropriate neonatal skin care and treatment to maintain the protective function of the skin will be discussed later in this section.

Disorders of the skin in infants and young children vary from the occurrence and presentation of the same symptoms in older children and adults. Both diagnosis and treatment may be influenced by the more sensitive pattern of reaction and, in many cases, therapeutic regiments differ from those of adults.

In the beginning of any diagnostic process, a careful and adequate patient and family history should be obtained followed by a detailed physical examination of the child's body. Easy visibility of the lesion may sometimes lead to cursory examination and hasty diagnosis.

Examination of the entire skin including the scalp, oral and anogenital regions, periorbital skin and conjunctiva,

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palms and soles, as well as nails and hair should be routinely performed to obtain a clue for final diagnosis.

Examination should always be performed in a well-temperatured room. Overwarming or overcooling of sensitive skin, especially that of newborns and neonates may lead to wrong impressions and misdiagnosis of physiological skin response to environmental stimuli as a specific pathologic condition (i.e., vascular phenomenon).

The morphology and configuration of cutaneous lesions are not always specific, but are of great importance to the classification and, consequently, correct diagnosis of skin diseases. Therefore, understanding dermatologic terminology is of great importance to a physician who is not a dermatologist. This also helps to eliminate barriers in communication and misunderstandings if specific dermatologic consultation is requested and when a dermatologist is responding to pediatrician consultation using his or her specific "skin-derived" language.

It is important to understand that most dermatologic terms are descriptions of the morphology of the lesion and applicable to many different diseases. Appropriate description of the lesion, timeline of its appearance, changes over time, and associated symptoms (i.e., itching or burning versus asymptomatic course) are crucial in distinguishing between different pathologic conditions.

Annular, nummular, circinate, or *ring-shaped lesions* (ringworm-like) may most often be found in superficial fungal infections. However, ringed lesions can be seen in seborrheic dermatitis, nummular eczema, pityriasis rosea, erythema anulare, erythema migrans, erythema multiforme, lupus erythematosus, urticaria, lupus vulgaris, leprosy, tinea versicolor, secondary syphilis, and many others.

Lesions that have an arc-like configuration are named *arciform* or *arcuate*; if they show a tendency to merge they are described as *confluent* and most commonly occur in exanthemas, pityriasis rosea, urticaria, and erythema exsudativum multiforme.

Distribution of the lesion over specific dermatome (single or multiple) is described as *dermatomal* because it is most commonly seen in HSV-3 infection.

Lesions that are solid, infiltrated, and discus-shaped (solitary or multiple) are named *discoid*, as in lupus erythematosus, discoid eczema, granulomas.

If skin lesions are drop-like, infiltrated, and showing a covering scale, they are called *guttate* and are often seen in childhood psoriasis or in adolescents and often follow acute respiratory tract infections (i.e., early pityriasis rosea).

Lesions showing spiral-like, coiled, or twisted appearance are described as *gyrate* (i.e., in urticaria, erythema anulare).

If such lesions have more than one kind of shape, they are considered to be *multiform* or *polycyclic* (i.e., urticaria, erythema multiforme, polymorphous light eruption).

Serpentine or snake-like morphology is named *serpiginous* and is most commonly seen in larva migrans and elastosis perforans serpiginosa.

Lesions presenting with a central depression and shaped like an umbilicus are termed *umbilicated*, as is the case in molluscum contagiosum, varicella, variola, eczema herpeticum, or HSV-III infection.

Vesicular and papular lesions localized in clusters are referred to as *grouped*, as in cases of HSV infection (HSV-I, -II or -III), insect bites, bullous dermatosis of childhood, and less commonly in contact dermatitis.

Iris-like or *target* lesions are those having a concentric, ringed appearance most characteristic of erythema exsudativum multiforme and Stevens-Johnson syndrome.

Lesions having line or stripe form are defined as *linear* or *band-like* and are most commonly seen in epidermal nevi, linear morphea, lichen striatus, incontinentia pigmenti, hypomelanosis of Ito, acanthosis nigricans, etc.

Lesions demonstrating a *net-like* or *murmur-like* pattern are described as reticulated – i.e., in livedo reticularis, curis marmorata, and cutis telangiectatica congenital.

An important pattern of skin morphology often indicating a specific disease is called *isomorphic response* or *Koebner phenomenon*. This term describes the appearance of new lesions along the site of a superficial injury. The most prominent example is a linear development of new lesions in psoriasis vulgaris, lichen planus, or keratosis folicularis. Linear spreading of warts or molusca contagiosa after scratch inoculation is also an example of this phenomenon.

The morphological configuration and regional distribution of skin lesions, presence or absence of mucous membrane involvement, or coincidence of skin and nail lesions may also be of importance in the finding of correct diagnosis.

Dependence from exposure to UV light (i.e., sun exposure areas) is important in estimating a possible photosensitive background or establishing a relationship between medication and the appearance of skin lesions.

Coexistence of itching and aggravation of symptoms in a warm environment (e.g., nights at bedtime) together with specific localization (i.e., intertriginous areas, genitalia, interdigital spaces) and coexistence of similar symptoms in other family members in close contact with each other is specifically suggestive of infestations such as, scabies. However, in infants and small children this diagnosis may be difficult because the lesions are typically

localized on the palms and soles and often on the neck and the head. A change of skin color frequently helps in making the correct diagnosis.

Brown or brownish discolorations are often associated with postinflammatory hyperpigmentation, pigmented nevi, incontinentia pigmenti, café-au-lait spots, epidermal nevi (together with hyperkeratotic, villous-like structure), photodermatitis and phytophotodermatitis, acanthosis nigricans, or as iatrogenic-induced hyperpigmentation by use of local irritants or concentrated fragrances (melasma, chloasma).

Yellow discoloration, especially in infants, is often connected with the presence of carotene derived from food, particularly yellow vegetables and carrots. Examination of sclera helps in distinguishing this phenomenon from an icterus.

Red or purple lesions are usually of vascular origin like superficial hemangiomas, naevi flamei, or spider telangiectasias.

Rose color is often characteristic for active inflammation or in development of inflammatory lesions such as atopic dermatitis or psoriasis. The latter often show superficial scaling and pinpoint bleeding known as the Auspitz phenomenon.

Lesions with decreased pigmentation (hypopigmentation or depigmentation) may be seen in several pathologic conditions. Superficial tinea, pityriasis versicolor may be easily distinguished by Wood's lamp. Localized depigmentation in different shape and form may be seen in vitiligo, piebaldism (clinical picture, family history, and dynamics of lesion are important distinguishing factors), and chemically induced pigment loss or progressive macular hypomelanosis.

Postinflammatory lesions may also appear hypopigmented. In children with atopic constitution or atopic dermatitis, multiforme hypopigmentation is described as pityriasis alba. Generalized decrease in skin pigmentation may be seen in albinism or untreated phenyloketonuria.

Ethnic variations need to be taken into consideration in assessment of skin changes. Erythema or inflammation may be difficult to see in children with black skin; postinflammatory hyperpigmentation or hypopigmentation is usually much more prominent in black, Mediterranean, Arabic, and Asian populations.

Hyperpigmentation of flexure areas (neck, axilla, inguinal region, perianal region) are considered to be physiologic in children with colored skin. However, physicians may be confronted with the pressure of parents who are not willing to accept that their children have such normally occurring skin discoloration, even if the parents have the same skin symptoms.

Qualities of hair may also differ among individuals of different ethnic origins. African-American and African hair tends to be extensively curly, to tangle when dry, and becomes matte when wet. Due to the naturally curly or spiral nature of the hair and appearance of so-called bushy hair, folliculitis and pseudofolliculitis are more common in children of African, African-American and in some groups of Asian descent.

Prolonged and continuous traction on hair results more commonly in traction alopecia in African, Asian, and Arabic populations.

Wound healing complications, especially development of keloids and hypertrophic scars after surgery or burns, are reported more often in children of African, Asian, or Arabic origin. Similarly, keloid complications of acne or other follicular disorders are more prominent in children and adolescents with colored skin.

Skin is not just a cover of the human body. It helps to adapt to environmental conditions; communicate with the surrounding world in a physical, chemical, and immunologic manner; and is an organ of interpersonal communication.

Most important for appropriate skin function is to keep the skin barrier intact and to restore it as quickly as possible if the barrier function is impaired.

Interruption of disruption of the barrier may lead not only to skin dysfunction, but also to impaired function of other organs, i.e., to immunologic defects. Skin and mucous membranes are the targets of airborne and contact allergens.

There is a common belief that the best way to keep the skin barrier and skin itself in good shape is to make it moist and fat. However, this widely believed thinking is not correct. Use of fat lubricants (i.e., vaseline or liquid paraffin) may seal the skin surface, which increases the accumulation of water and heat below the applied product and leads to increased itching and worsening of skin lesions. This is of particular importance in hot and humid climate areas.

Many nondermatologists may be hesitant to use some specific agents in younger patients because of safety concerns.

Two groups of topical skin medication are of special interest: topical corticosteroids and emollients.

Emollients and moisturizers are of particular interest because fragile, young skin needs them more than adult skin and – because of high permeability – it may absorb applied ingredients in much higher concentrations.

Children's skin should be kept "not too dry" and "not too moist (fat)," and achieving this balance has become a science in itself.

In this section, dermatologic conditions most relevant in a pediatrician's daily practice are reviewed. Our goal is to give a practical overview and to help in the assessment and management of common skin diseases in neonatal, child, and adolescent populations. The intent is to not to deeply discuss etiologic, genetic or therapeutic issues, especially if they are in an experimental stage of medical knowledge or if only a single clinical report describes specific clinical outcome.

For detailed reviews and further studies, pediatric dermatology textbooks and monographs are recommended. A short list of such fundamental recent books is given below.

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141 Cutaneous Disorders of the Newborn

Shaden Abdel Hadi

Neonatal dermatology encompasses the spectrum of cutaneous conditions observed during the first 4 weeks of life. As it is practically impossible to discuss the full spectrum of neonatal dermatoses in one chapter, we have elected to focus on conditions that are most common in clinical practice.

Physiology of Neonatal Skin

From the moment at birth, the skin of the neonate is confronted with a significant challenge of transition from a sterile, thermally stable aqueous environment to a dry one, rich in pathogens, undergoing temperature changes, and exposed to friction. Therefore, the neonate's skin undergoes several changes in adapting to the new extrauterine environment. The stabilization of the epidermal barrier is the highlight of this dynamic adaptation process that involves acceleration of the stratum corneum maturation by increasing its thickness and normalizing the skin pH, stratum corneum hydration, and changing the lipid composition. Thus, the majority of premature infants develop intact barrier function by 2–3 weeks of age.

In addition to epidermal thickness, the neonatal skin differs from that of an adult in many other aspects. It is less hairy, secretes less sweat and sebum, has weaker intercellular and dermo-epidermal attachments, has fewer melanosomes, lacks protective skin flora at birth, and forms a higher surface area–body mass ratio. All these factors combined make the neonatal skin more vulnerable to external stresses and toxins than the adult skin.

Skin of the Premature Infant

The number of epidermal layers increases with fetal age along with stratum corneum thickness, which makes the extent of skin fragility in premature neonates directly proportional to the degree of prematurity. Infants born prior to 32–34 weeks of estimated gestational age have markedly decreased epidermal barrier function with a higher surface area–body mass ratio than that of full-term infants. Heat regulation, on the other hand, is dysfunctional in premature neonates due to reduced sweating, thin subcutaneous fat layer, and underdeveloped autonomic control of the skin vasculature. Moreover, immature organs of premature neonates may affect the metabolism of chemical agents administered topically or systemically.

The above-mentioned features of premature skin put it at a higher risk of thermal instability, percutaneous toxicity, mechanical injury, infections, and, finally, increased transepidermal water loss. The latter is particularly accompanied by increased morbidity, as it can lead to dehydration and electrolyte imbalance.

In extremely premature infants (<24 weeks), the skin is sticky, friable, and transparent, and lanugo hair is absent.

Skin of the Full-Term Infant

The skin of full-term infants seems to have a relatively sufficient barrier function; however, they still stand the risk of toxicity from topically applied products. As mentioned above, this is due to the high surface area–body mass ratio and the underdeveloped metabolism pathways.

Skin of the Postmature Infant

Postmature infants born at >40 weeks of gestation have a dry peeling skin soon after birth. This physiological shedding is usually superficial and much more prominent in postdate infants than in others, and may last for a maximum of 1 month.

Skin Care of the Newborn

Removal of Vernix Caseosa

In utero, fetal skin is covered by a protective biofilm known as vernix caseosa that prevents it from maceration in amniotic fluid. It is composed mainly of water, proteins, lipids

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from sebaceous gland secretions, and debris of fetal epidermal decomposition.

The thickness of this gray-white greasy layer varies depending on the gestational age at which the baby was born. It is thicker in full-term infants than in pre- or postmature ones. It is usually wiped off gently with a clean towel soon after delivery.

Washing and Bathing

There is a general consensus that cleansers used for washing newborns should be gentle, nontoxic, nonabrasive, pH-neutral, and free of dyes and fragrances. Antiseptic baths containing hexachlorophene, chlorhexidine, or iodine are not indicated in daily care due to the risk of absorption and systemic toxicity. Immersion of the newborn in water baths for more than 5 min increases skin fragility due to hyperhydration and therefore it should be avoided.

There is no single ideal method for umbilical cord care; however, a recent study revealed that wiping with sterile water and allowing it to dry naturally is superior to using isopropyl alcohol.

Ears should be cleaned gently with water, and ear swabs, if used, should never be inserted into the external ear canal.

Finally, too frequent washing with multiple products not only leads to irritation and dryness but also exposes the infant to a wide range of potentially allergenic chemicals and puts the infant at risk of sensitization. So, bathing the whole body twice a week might be enough, using the least needed number of topical products.

Napkin Change

Changing infant's napkin should be done frequently and as soon as it gets soiled. The area should be washed with running lukewarm water and dried carefully without rubbing, and then covered with a barrier product before placing a new diaper.

For more details, the reader is refered to standards of diaper area care shown in *Table 141.2*.

General Care of Newborn Skin

Emollients are generally used to enhance skin flexibility and reduce transepidermal water loss. The use of thick fatty products is generally discouraged for daily care, specifically in warm and humid climates, and incorporating these products into emulsions consisting of W/O (water in oil) appears to be more logical in terms of achieving skin hydration without paradoxical increase of occlusion.

Powder use is undesirable in infants due to the hazard of accidental inhalation and subsequent lung inflammation.

The skin of the newborn tends to be less pigmented in the first few months and, therefore, has less natural protection from sunlight. Considering the general concern around using topical sunscreens before the age of 6 months, it is appropriate to avoid prolonged sun exposure and use protective clothing whenever necessary.

Evidence-based guidelines for standard care of neonatal skin were recently published in the *Journal of Obstetric Gynecology and Neonatal Nursing*. A recent review of moisturizers and emollients used for appropriate skin care is given in the dermatology section of the *eMedicine* journal (see reference list for details).

Transient Benign Neonatal Dermatoses

The exact etiology behind many transient neonatal dermatoses remains unclear. Clinical recognition of these cutaneous lesions is essential not only to reassure the parents but also to rule out serious infections. When in doubt, skin scrapings and swab cultures taken from the lesions should be performed, and antimicrobial therapy should be initiated accordingly.

The most common transient skin findings in neonates include: desquamation (seen in 15–65% of the neonates, depending on their ethnic and geographic origin), Epstein' and Bohn's pearls (56–88% of neonates, depending on the study region), hyperplasia of sebaceous glands (32–48% of assessed children, depending on the geographic localization), milia (19–48% of the patients, depending on ethnic and geographic origin), toxic erythema (seen between 16% in Indian and 40% in Japanese neonates), perianal dermatitis (seen between 7% in African-Americans and 19% in Japanese patients), miliaria cristalina (seen between 3.1% in white skin children in the USA and 17% in neonates of African-American origin), and miliaria rubra (seen between 4% in Japanese and 5.5% in African neonates in the USA). Genital hyperpigmentation has been reported, for example, in 5% of Caucasian neonates and 20% of Mongolians. The phenomenon of cutis marmorata is a phenomenon described in 6.7% of neonates in France. Other transient skin changes that may affect neonatal population are sucking blisters (reported in approximately 10% of the children), acne neonatorum

(affecting approximately 1.2% of newborns in the USA) as well as harlequin color changes, jaundice, and undefined skin redness.

Vernix Caseosa

Vernix caseosa presents as a chalky white film covering the skin of infants at birth. It is a mixture of shed epithelial cells, sebum, and lanugo hair.

The vernix serves as a protective lubricant covering the infant from amniotic fluid and also as a natural defense from microbes due to its content of antimicrobial peptides and lipids. In infants who have suffered fetal distress, vernix might be stained with meconium (a yellow-brown color).

Neonatal Desquamation

Postmature infants (over 40 weeks of gestation) are often born with cracking and peeling of the skin that are much more clinically prominent in them in full-term or premature neonates. In severe cases, congenital ichthyosis can be considered as the condition might mimic collodion baby syndrome without ectropion, eclabion, or gloved appearance. Topical care is usually sufficient to control the desquamation and includes moisturization and avoidance of over-bathing.

Transient Vascular Phenomena

Harlequin Color Change

Harlequin color change is a rare phenomenon in which the amount of blood flow differs markedly between the right and left sides of the infant's body, particularly when lying on one side. A transient erythema appears on the dependent side due to vasodilatation while the upper half of the body exhibits simultaneous blanching with a sharp demarcation on the midline (◉ *Fig. 141.1*).

This phenomenon is believed to be related to abnormal hypothalamic control of skin vasculature within the first few weeks of life. It has also been observed in infants with severe intracranial injury that could have contributed to hypothalamic dysfunction.

The condition is more common in, but not limited to, premature/low-weight infants, usually in good general health. It typically occurs around days 3–5 of life and may last up to 3 weeks of age. The face and genitalia of the infant may be spared. Color changes are transient, lasting 20–30 min in each attack, and rapidly reversible when the infant's position is changed.

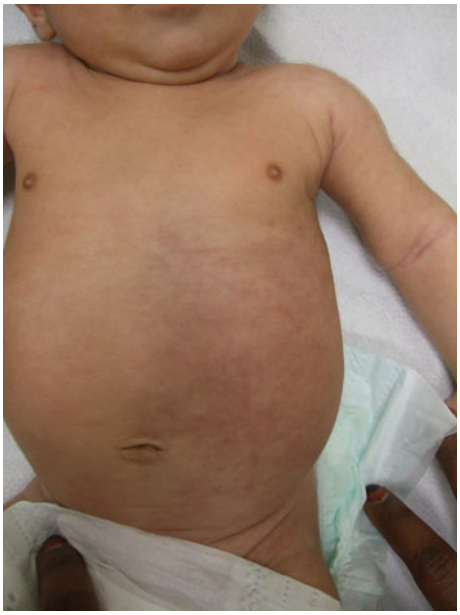

Figure 141.1
Harlequin color skin changes. Unilateral, transient net-like erythema

Harlequin color change is self-limiting, completely benign, and usually subsides after the third week of life without any treatment.

Acrocyanosis and Cutis Marmorata

Acrocyanosis is a condition in which the hands, feet, and/or lips become variably blue or violaceous in color without associated edema or other notable skin changes.

Cutis marmorata presents as a marble-like pattern or bluish mottling of the skin. This reticulated cyanosis is usually blanchable, symmetrically involving the trunk and extremities. Both patterns reflect an underlying vasoconstriction in a physiologic response to cold stress and usually resolve with warming of the skin.

If cutis marmorata persists over 1 month of age, other central nervous system–induced neurovascular dysfunctions (e.g., Down syndrome, Cornelia de Large syndrome, and hypothyroidism) should be considered.

Cutis marmorata telangiectatica congenita (CMTC) may also mimic cutis marmorata, but it is persistent in the form of localized patches on the trunk or extremities.

Erythema Toxicum Neonatorum (Toxic Erythema of the Newborn)

Erythema toxicum neonatorum is the most common, transient rash in neonates, occurring in approximately 50% of all full-term newborns, but virtually never seen in premature infants. Lesions may be seen at birth, but they usually appear in the first 2 days of life or later; some cases that appear at the age of 10 days have been reported. Lesions then wax and wane and rarely last for more than a week. They are clinically characterized by small erythematous macules with or without a central papule or pustule. These 1–3-mm sterile lesions show a follicular-based distribution and, therefore, can appear anywhere on the body except palms and soles. Histologically, pilosebaceous apparatus is filled with eosinophils, and therefore their pathogenesis has been mistakenly related to a fleabite.

The etiology of erythema toxicum neonatorum is not yet established and it has been considered to be idiopathic. Currently, there are several unproven etiological hypotheses including skin reaction to absorbed enterotoxines, hence the name "toxicum," an allergic reaction because of eosinophilia in lesions (and in peripheral blood of some patients); however, an allergic agent has so far never been identified. Transient adjustment of the skin of the newborn to mechanical/thermal stimuli, a decrease in corticosteroid blood levels following neonatal stress enhancing the eosinophilic response, maternofetal transfer of lymphocytes prior to, or during, delivery causing a minor transient form of acute GvH reaction, and activation of skin antimicrobial system prior to birth and strengthened in the first few days of life, all have also been postulated as factors causing this acute inflammatory response.

The disease is self-limiting and no therapy is needed. The parents can be reassured.

Transient Neonatal Pustular Melanosis

Transient neonatal pustular melanosis (TNPM) is clinically characterized by pustules that are present at birth but rapidly resolve leaving a fine colarette of scales rather than healing with hyperpigmented macules. The content of the pustule is mainly neutrophilic and sterile. The condition is more common among full-term neonates of African descent and is usually located on the chin, forehead, neck, nape, chest, back, and thighs. It can occasionally be found on the scalp, palms, and soles.

TNPM has no clear etiology. It is self-limiting in nature; pigmented freckles or lentigines may persist for a few months.

Transient neonatal pustular melanosis is considered to be a harmless condition that requires no treatment.

Miliaria

Miliaria is a general term that describes a group of transient eccrine disorders in which the sweat ducts are occluded by keratotic plugs at various levels, resulting in leakage of sweat to the surrounding tissue.

The pathophysiology is closely related to warm conditions (i.e., when an infant is overheated, over-wrapped with occlusive agents/materials, or febrile). It has been suggested that *Staphylococcus epidermidis* may have produced an occlusive substance that obstructed the delivery of sweat to the skin surface. Relative immaturity of the eccrine ducts favors the poral closure and subsequent sweat retention.

Several subtypes of miliaria have been described:

- *Miliaria crystallina (Sudamina)* is common during the summer and in neonates placed in incubators. Ductal obstruction occurs at the stratum corneum level. It is clinically characterized by 1–2 mm asymptomatic superficial clear noninflammatory vesicles, which desquamate in few days. They usually appear 1 week after delivery, mostly on the forehead and then the scalp, sparing the skin of palms, soles, and the mucosa. Rare congential cases have been reported and attributed to the occlusive environment of amniotic fluid and vernix caseosa.
- *Miliaria rubra (Prickly Heat)* typically occurs later than *Miliaria crystallina*, mostly between the 11th and the 15th day of life, usually in hot and humid conditions. It may be preceded by *Miliaria crystallina*. The level of ductal obstruction is still intraepidermal, but lower than that of *Miliaria crystallina*. It presents as nonfollicular erythematous 1–3-mm papules or pustules (*Miliaria pustulosa)* on the head, neck, trunk, diaper region, or any intertriginous area. Erythema reflects dermal inflammation around the occluded eccrine duct.
- *Miliaria profunda* is an obstruction at or below the dermo-epidermal junction. It presents as a firm pale papule on the trunk or extremities and may follow *Miliaria rubra*. It is unusual in a newborn.

Treatment for miliaria includes avoiding or correcting the overheating. In febrile condition, treating the underlying fever is helpful. Lightweight cotton clothing, cool baths, and air conditioning are all supportive measures.

Milia

Milia are small epidermal cysts commonly occurring on the face of newborns as a result of retention of keratin within the dermis. They present as pinpoint to 1-mm pearly white papules, more prominently on the nose, chin, cheeks, and forehead. They are usually spontaneously extruded in a few weeks, requiring no therapy.

Lesions may also be located in the oral cavity on the hard palate where they are called Epstein's pearls. These are present in the majority of newborn infants.

When such lesions occur on the alveolar gum margins, they are termed Bohn's cysts.

Similar to skin lesions, oral lesions also resolve spontaneously within few weeks.

Neonatal Acne (Neonatal Cephalic Pustulosis)

Acne neonatorum is a commonly observed, benign condition affecting many newborns. Historically, appearance of the lesions has been thought to be mediated hormonally. Recently, however, it has been proposed that the term "neonatal acne" should be replaced by "neonatal cephalic pustulosis," because there is no relation to androgen secretion, and classical acne comedones are usually absent. Latest hypotheses favor the theory that an inflammatory reaction to malassezia species (both *M. furfur* and *M. sympodialis*) may promote the development of such acneiform skin lesions in neonates.

Clinically, erythematous papules and pustules appear mainly on the cheeks, face, and sometimes on the scalp, either at birth or within the first few weeks of life, only to resolve spontaneously without requiring any treatment (*Fig. 141.2*).

In contrast to acne neonatorum, infantile acne presenting in children of 2–3 months of age has been considered to be androgen driven. The morphology of the lesions exhibits the classical picture of papules, pustules, and comedones located on the face. This condition may be severe and may require systemic treatment to prevent scar formation (*Fig. 141.3*).

Sebaceous Hyperplasia

Sebaceous hyperplasia is common in term neonates, but premature infants are less affected. It is present as follicular, regularly spaced smooth white papules grouped into plaques without surrounding erythema. In such cases, androgenic stimulation in utero, coming from either the mother or the infant, leads to hypertrophy of the sebaceous glands occurring in the last month of pregnancy. The lesions are found typically on the nose, cheeks, upper lip, and forehead. They gradually involute in the first few weeks of life.

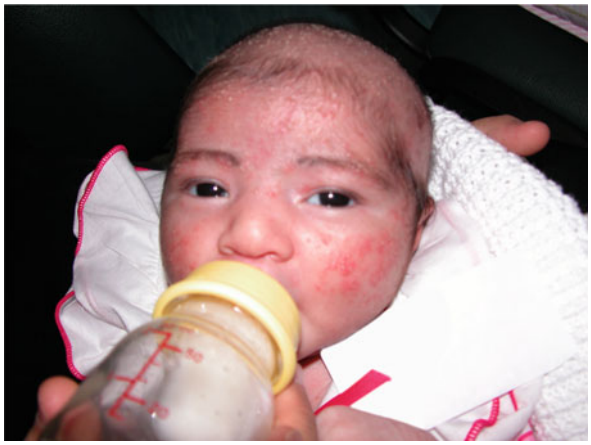

Figure 141.2
Neonatal cephalic pustulosis. Disseminated pustular lesion on the face and scalp

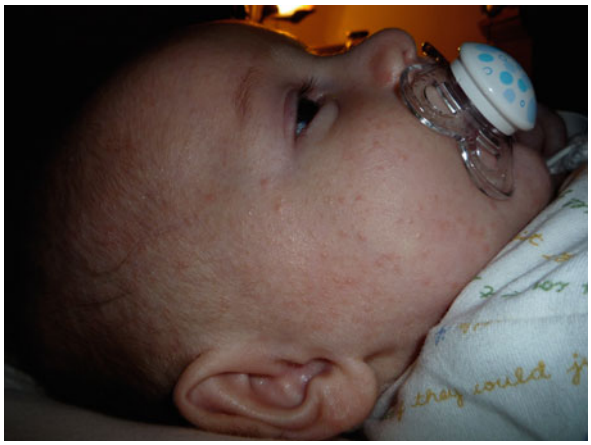

Figure 141.3
Infantile acne. Multiple acneiform lesions on the face of a 3 months old boy

Umbilical Granuloma

Failure of the umbilical stump to heal after the cord sloughs off may cause hyperproliferation of the endothelial cells in that area, clinically resulting in pink-gray

papules or nodules growing over the stump that are extremely friable and bleeding easily, resembling pyogenic granuloma. The term "granuloma" is, however, a misnomer as the condition is not related to any granulomatous skin reaction. A traditional treatment consists in gently touching the surface of the lesions with silver nitrate, and the lesion resolves without scaring.

Sucking Blisters

Sucking blisters are apparent at birth as a result of vigorous intrauterine sucking of a finger, thumb, wrist, lip, or forearm. It is an uncommon finding in a newborn and presents as a solitary oval-shaped 0.5–2-cm blister or erosion seen on noninflamed skin of the dorsal aspect of the affected site. It resolves rapidly without sequelae.

Disorders of Subcutaneous Tissue in the Newborn

A well-developed layer of subcutaneous fat (panniculus) is normally present at birth in the neonate, even when premature, which then grows until about 9 months of age giving the traditional chubby appearance to the healthy newborn.

A number of subcutaneous fat disorders have been described and recognized based on their distinctive clinical patterns, course, and both histopathological and biochemical markers. The neonatologist must differentiate disorders that have an innocent and self-limiting behavior from those that have systemic implications and are associated with significant morbidity.

Subcutaneous Fat Necrosis of the Newborn

Subcutaneous fat necrosis (SCFN) of the newborn is an uncommon skin disorder, which appears during the first few weeks of life, primarily in full-term and postmature infants. This condition may develop in infants with a normal delivery; however, it has been observed mostly in neonates who have suffered from perinatal complications.

The exact etiology of this disorder remains uncertain; however, some investigators have suggested that it occurs as a result of ischemic injury of fat by local trauma during or after delivery. The observation that lesions are commonly located over bony prominences supports this theory. Many affected neonates have had perinatal asphyxia with poor American Pediatric Gross Assessment Record (APGAR) scores, hypothermia, meconium aspiration, and fetal distress.

Other authors have hypothesized that the disorder may be related to an underlying defect in fat composition and metabolism in the newborn.

Neonatal fat is mainly composed of saturated fatty acids (stearic and palmitic) with a relatively high melting point when compared to adult fat, which is rich in unsaturated fatty acids (oleic acid) with a much lower melting point. This causes the neonatal fat to be more susceptible to crystallization and adipocyte damage in response to hypothermia.

Fat necrosis has been associated with hypercalcemia. It has been proposed that this is related to production of 1,25 dihydroxy-vitamin-D by macrophages in the granulomatous reaction around fat necrosis, subsequently increasing intestinal calcium uptake.

Another hypothesis tries to explain increased calcium serum level as a result of elevated levels of prostaglandin E2 which may have caused excess bone resorption. An increased level of parathyroid hormone has also been postulated as a potential promoting factor.

Overall, it seems that all of these mechanisms combined result in this fat necrosis. An abnormal fat composition in the newborn makes it susceptible to necrosis under a stressful event leading to a granulomatous skin reaction, which in turn predisposes the child to hypercalcemia.

Affected infants are usually in a good clinical condition. Lesions appear during the first month of life as single or multiple firm nodules or plaques that are localized and freely mobile (not attached to deeper structures), with or without erythema. These are usually painless, but may become tender. Sites of predilection are areas of trauma or ischemia including cheeks, back, buttocks, arms, and thighs (*Fig. 141.4*). The anterior trunk is usually spared. Lesions resolve spontaneously within weeks to months; however, they may occasionally calcify or ulcerate leaving mild atrophy of the skin after resolution.

Diagnosis is usually made clinically, but histological examinations reveal lobular panniculitis (inflammation of subcutaneous fat lobules) with granulomatous inflammatory infiltrate and characteristic needle-shaped clefts within adipocytes and calcification.

The prognosis for subcutaneous fat necrosis of the newborn is excellent. Most lesions undergo spontaneous resolution within several weeks to months.

Hypercalcemia is a rare association, but may be life threatening. The onset may be delayed for several months

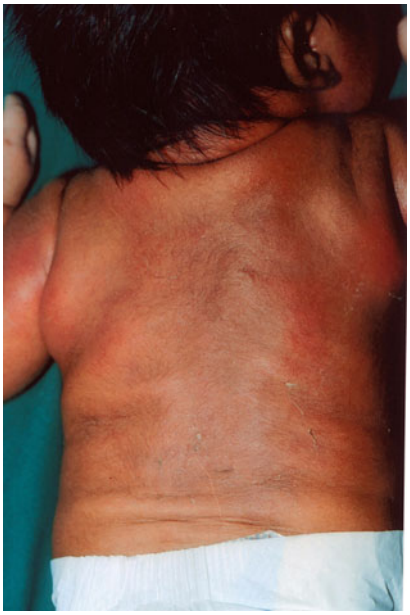

Figure 141.4
Subcutaneous fat necrosis. Atrophic changes in subcutaneous disuse in a newborn (Courtesy of Arti Nanda, MD)

after the appearance of skin lesions. Therefore, it is recommended to check the calcium level, vitamin-D level and parathyroid functions, and renal function for up to 6 months after appearance of the lesions. Children should also be observed closely for symptoms such as anorexia, vomiting, constipation, irritability, failure to thrive, and seizures. Unclear transient thrombocytopenia has been reported in a few cases.

In most cases, reassurance is the key due to the self-healing nature of the disease. If hypercalcemia occurs, treatment should include good hydration to increase renal excretions of calcium with or without calcium-wasting diuretics (e.g., furosemide). Systemic corticosteroids or etidronates are rarely needed.

Sclerema Neonatorum

Sclerema neonatorum is a diffuse, rapidly spreading hardening of the skin and subcutis that affects very sick, debilitated neonates in the first 1–2 weeks of life. This condition is becoming rare as neonatal care is improving worldwide.

The cause of this disorder seems to be multifactorial; it appears to represent a nonspecific sign of severe illness rather than a primary disease. Infants are characteristically small or premature, debilitated, cyanotic, and lethargic.

Immaturity of the neonatal lipoenzymes that are responsible for converting saturated fatty acids (palmitic and stearic) into unsaturated acids (oleic) is further compromised by hypothermia, severe metabolic disorders, infections, shock, or any other environmental stress. This enhances the subcutaneous fat predisposition for solidification (because of a defect in fatty acid mobilization) and subsequent development of sclerema.

Sudden diffuse hardening of the skin usually appears during the first week of life, from legs to thighs and buttocks to cheeks and trunk until it eventually involves most of the infant's skin except the palms, soles, and genitals. This woody-hard nonpitting induration renders the skin cold, smooth, and bound down, the joints immobile, and the face masklike. Prognosis is poor, with a high mortality rate in affected infants. In surviving infants, the skin findings resolve without residual sequelae.

No specific treatment is beneficial for sclerema neonatorum. Attention should be paid to the underlying general disorder (i.e., sepsis, dehydration, etc.) and adequately correcting it may improve the skin condition. The role of systemic steroids is still controversial. Exchange transfusion with fresh whole blood may improve the outcome. Comparison between sclerema neonatorum and subcutaneous fat necrosis of the newborn is shown in *Table 141.1*.

Table 141.1
Comparison between clinical features of sclerema neonatorum and subcutaneous fat necrosis of the newborn

	Sclerema neonatorum	Subcutaneous fat necrosis of the newborn
Affected neonates	Premature, critically ill newborns	Generally healthy full-term newborns, may have history of perinatal complications
Morphology	Diffuse, rapid hardening of skin and subcutis	Localized indurated nodules
Distribution	Whole body, sparing palms, soles, and genitals	Buttocks, cheeks, arms, and thighs
Prognosis	Poor	Excellent

Pedal Papules of Infancy (Congenital Pedal Papules)

Pedal papules of infancy are uncommon, soft, asymptomatic lesions located on the heels of the newborn's feet.

The etiology of pedal papules of infancy is unknown. This condition is considered to be distinct from the more common adult piezogenic pedal papules in which gravity on the heels leads to fat herniation through a defect in the dermis.

The presence of these papules at birth speaks clearly against this gravitational theory. The only plausible etiology is probably a developmental defect in the plantar fibrous fat trabeculae that allows fat herniation through it. The histological picture supports this theory showing normal fat globules protruding from the reticular dermis without inflammation.

Clinically, pedal papules of infancy are solitary asymptomatic, soft, skin-colored nodules seen on the medial plantar surface of a newborn's heel. It does not seem to accentuate with position.

Prognosis is unknown, and it is not clear if pedal papules of infancy predispose the child to painful piezogenic pedal papules. Pedal papules of infancy usually do not require treatment.

Iatrogenic and Traumatic Skin Disorders of the Newborn

Iatrogenic and traumatic skin disorders can occur before, during, or after delivery. Skin injury caused by medical procedures may be complicated by infection or scarring.

Iatrogenic Injuries During Pregnancy

Antenatal procedures performed for diagnostic or therapeutic purposes may be complicated by fetal skin injuries. There have been several observations that these wounds may heal without scarring. This could be attributed to either the presence of amniotic fluid or the nature of fetal skin, or both. The amniotic fluid provides a moist, sterile environment that is rich in growth factors and extracellular matrix components. On the other hand, fetal skin is covered, between 4 and 24 weeks of gestation, with a unique layer called "periderm" that is highly proliferative, facilitating wound closure by regeneration and growth rather than scarring. Despite this hypothesis, scars are often observed in newborns undergoing antenatal procedures.

Marks Related to Amniocentesis

Aspiration of amniotic fluid is a widely used procedure in obstetric practice. Since the introduction of ultrasound guidance under which amniocentesis is performed nowadays, fetal injuries have been greatly reduced.

Mid-trimester amniocentesis has the lowest risk of fetal injury since the fetus occupies only half of the amniotic cavity, whereas in the first and third trimesters there is less room to maneuver.

Marks caused by amniocentesis injuries are present at birth, but may go unnoticed for weeks. These marks may be scars, lacerations, depressions, or dimples, and may be solitary or multiple, located on the extremities, head, neck, or chest.

Serious complications are exceptional, and if they occur, include peripheral nerve damage, ocular penetration and blindness, arteriocutaneous fistulization, and exsanguinations of the fetus.

Injuries due to Chorionic Villus Sampling

Chorionic villus sampling is obtaining a small biopsy of villi from chorion fundosum under ultrasound guidance to analyze its DNA.

It has been reported that this procedure might be associated with increased risk of limb and jaw malformations; however, this notion has been disputed and confirmation is still lacking.

An increased risk of hemangioma has been reported in infants exposed to chorionic villus sampling antenatally, especially when performed by the transcervical route as opposed to the transabdominal approach. However, this association is now considered to be controversial.

Other Antenatal Procedures

Other procedures performed antenatally, which may leave marks on the skin of the newborn, include:

- Fetal biopsies taken for prenatal diagnosis of severe genodermatosis
- Fetal liver biopsy
- Fetal tumor biopsy
- Aspiration of fluid collection, such as fetal urine from bladder or pleural effusion
- Therapeutic procedures such as shunting of obstructive uropathy or hydrocephalus

Iatrogenic Injuries During Labor

Injuries due to Fetal Monitoring

Monitoring of the fetal heart rate during labor is a standard obstetric practice. This can be achieved either by placing an ultrasonic transducer on the mother's abdominal wall or by using an electrode attached to the presenting part of the fetus. The latter method is generally safe; infrequent complications include bleeding at various levels in the scalp, lacerations, ulcerations, scalp abscesses, and herpetic infections. Although herpes simplex virus infection is an extremely rare complication, it might become life threatening.

Scalp puncture for fetal blood gas sampling is less frequently performed, but it may cause scalp lacerations. Scalp abscess formation is an unusual complication.

Caput Succedaneum

A caput succedaneum is a diffuse soft-tissue edema with or without bruising involving the fetal presenting part (scalp, face, and scrotum). This occurs as a result of venous congestion during a prolonged labor. Accumulation of the fluid is external to the periosteum, which explains why the edema crosses the midline and is not limited to the suture lines.

The condition clears spontaneously in few days. No treatment is required except in the case of extensive bruising when early phototherapy for hyperbilirubinemia may be indicated. Another possible complication is the development of an annular alopecia presenting in a circumferential ring around the scalp, reflecting a pressure necrosis phenomenon (scalp ring halo) which may occasionally persist.

Cephalohematoma

A cephalohematoma is a subperiostial hematoma caused by rupture of skull veins due to shearing forces during prolonged delivery, particularly vacuum-assisted vaginal deliveries. Due to the slow process of periosteal bleeding, cephalohematoma may not become visible until several hours or even days after birth.

Cephalohematoma appears as a nonpulsating, often fluctuant, lump on one side of the scalp limited by cranial sutures, with a normal colored overlying scalp. Although the parietal bone is most commonly affected, occipital and frontal bones may also rarely be involved.

The cephalohematoma has no long-term implication, although it may last for months before it disappears. Treatment is not required, except in rare cases when it is complicated by infection or severe hemorrhage. In these cases, antibiotic treatment, blood transfusions, or phototherapy for eventual hyperbilirubinemia may be indicated.

Injuries due to Forceps Deliveries

Forceps deliveries can cause many injuries to the soft tissues of the face or scalp, corresponding to the area of application of the forceps. These injuries range from minimal erythema or bruising to abrasions or subcutaneous fat necrosis.

Injuries due to Vacuum Extractors

Vacuum extractors are occasionally used when there is slow progress of labor. Introduction of softer silicone cups has reduced the risk of fetal injuries.

When the fetal scalp is sucked inside the cup, a "chignon" might be produced; this is a small swelling of the scalp with a diameter larger than the rim of the vacuum cup. A chignon is a benign lesion which disappears in a few days in the majority of cases without scarring. In rare cases, it may become lacerated and infected that may end up in a localized alopecia. Abrasions of the scalp may also be seen especially with the rotation of the cup on the skin, or due to sudden detachment from the infant.

Injuries due to Cesarean Section

A potential injury from a cesarean section is lacerations to the infant caused by the scalpel, which may be deep enough to require suturing. This can be complicated by infection, scarring, and linear alopecia.

Iatrogenic Skin Disorders After Birth

Several untoward events may be related to technological advances that have become standard nursery practice. When describing these iatrogenic complications, one should keep in mind that these diagnostic and therapeutic procedures have significantly reduced morbidity and mortality in many infants. Injuries related to these procedures, if they occur, are minor and easily manageable in most cases (*Fig. 141.5*).

Figure 141.5
Iatrogenic skin injury. Skin ulceration after peri-partum superficial skin injury

Conditions Related to Arterial Catheterization

Catheterization of umbilical or peripheral arteries is a commonly performed procedure in neonatal intensive care units.

Damage or thrombosis of the artery caused by cannulation may lead to ischemia of the distal part of the limb. These are frequently seen on feet, hands, or buttocks.

Early skin changes include transient blanching, erythema, and bulla formation. Usually, this is reversible after early removal of the line. It may, however, progress to extensive skin necrosis and gangrene if the diagnosis and subsequent removal of the line were delayed.

Drug-Related Complications

Neonatal skin is uniquely vulnerable to the toxic effects of chemical substances. This has been attributed to their immature hepatic, renal, and central nervous systems, and to the high body surface to volume ratio.

Skin damage, burns, sloughing, and blistering have been reported from topical application of alcohol-based skin cleansers such as isopropyl alcohol and chlorhexidine gluconate. Moreover, toxic side effects of systemic absorption have been noted with some drugs such as neomycin, aniline dye, iodine, and hexachlorophene.

Infants born at 37 weeks of gestation or later seem to have an effective skin barrier as compared to infants born at 32 weeks or before. At 2 weeks of age, the skin of the most immature infant begins to function like that of full-term infants.

Skin Damage due to Adhesive Dressings

Adhesive tapes used frequently to secure intravenous catheters, endotracheal tubes, nasogastric tubes, monitor leads, or chest drains may damage the skin, especially that of premature infants. As a result, skin sloughing, blistering, and even hemorrhage, scarring, and pigmentary changes have been reported. Using pectin-based skin barriers directly on the skin under the adhesive tape may prevent these injuries. Careful and gentle removal of the tape is also helpful.

Needle Marks

Hypopigmented, pinhead-sized lesions, grouped together giving a speckled appearance, are frequently seen on distal extremities at sites of venous or arterial catheterization.

Heel prick marks may appear as dimpling, hard calcified nodules, hypertrophic scars, or even gangrene of the heel.

Anetoderma of Prematurity

Depressed atrophic patches or outpouching of the skin of a premature infant resulting from thinning of the dermis with loss of elastic fibers have been described, especially with extreme prematurity (less than 29 weeks of gestation). Lesions develop without a preceding inflammation 1–10 months after birth. These are mainly seen on the anterior trunk and proximal extremities, at sites of placement of adhesives or monitoring leads. The exact cause is not well understood, and lesions are believed to have lasted indefinitely.

Calcinosis Cutis

Calcinosis cutis is the deposition of hydroxyapatite crystals and calcium phosphate within the skin's soft tissue. Iatrogenic calcinosis cutis occurs as a result of tissue damage followed by deposition of these crystals with a normal calcium/phosphorus ratio. This usually occurs at sites of heel pricks, calcium administration for correction of hypocalcemia, electrocardiograph electrode placement, or any injury resulting in subcutaneous fat necrosis. Calcified nodules appear initially as depressed small macules, growing over months to turn into white-yellow papules or nodules and eventually extruding their content to the skin surface. These lesions disappear generally within 2–3 years.

Children may occasionally show signs of discomfort while standing. In such cases, gentle cryosurgery or curettage may be helpful. Using electrode pastes that do not contain calcium chloride may prevent calcinosis cutis secondary to electrode placement.

Bronze Baby Syndrome

The term "bronze baby syndrome" is used to describe infants who develop a diffuse gray-brown discoloration of the skin, serum, and urine 1–7 days after starting phototherapy for hyperbilirubinemia. This is considered to be a rare complication of phototherapy, developing particularly in infants with liver impairment, especially cholestasis. The pathophysiology seems to be related to photoisomers of bilirubin or biliverdin or to a copper-bound porphyrin photoproduct. This discoloration fades over weeks after phototherapy is discontinued without significant sequelae.

Bronze baby syndrome can easily be distinguished from transient porphyrinemia after phototherapy, as the latter causes a purpuric eruption sharply confined to the exposed skin areas.

Complications of Neonatal Circumcision

Meatal ulceration is a complication of circumcision that often goes unrecognized. This is probably due to its potentially delayed occurrence. Removal of the prepuce exposes the glans penis epithelium to diaper irritation, which in turn may lead to erosions and sometimes healing with stenosis.

Bleeding, infections, and direct injury to the glans penis or urethra are some of the uncommon complications of circumcision.

Dermatoses of Diaper Area

"Diaper dermatitis" is probably the most common dermatologic disorder in infancy and early childhood. The term is broadly used to describe any acute inflammatory skin reaction affecting the anogenital area of napkin-wearing infants. Thus, the term "diaper rash" should not be used as a specific diagnosis, but rather as a descriptive regional term that encompasses various skin disorders of multifactoral etiology. A prolonged contact with urine and feces, hydration, friction, occlusion and heat, allergic and irritant agents, and secondary infections may all play a causative role in napkin dermatitis, either separately or in combination with each other.

Eruptions of the diaper area may be classified into disorders that are directly related to the wearing of diapers in which the diaper environment plays a central role, disorders aggravated by wearing diapers, and disorders occurring in the diaper area regardless of the presence of diapers. This chapter will mainly review the first group of diseases directly related to diapers.

Clinical presentations of different diaper dermatoses may overlap significantly, and a specific diagnosis can be a real challenge in some cases. As a general rule, a diaper rash that does not respond to standard therapeutic measures or develop as expected should draw the physician's attention to alternative uncommon diagnoses, and further diagnostic evaluation should be performed.

Standard Care of the Diaper Area

The advent of superabsorbent disposable diapers in the 1990s has significantly reduced the frequency and severity of diaper rashes.

Normal care should be aimed at frequent changing of the diapers as soon as they get soiled, gently removing the residual feces preferably with running lukewarm water with or without a soap-free cleanser, drying the area gently without rubbing, applying a mild nonocclusive barrier product with every diaper change, and removing the diaper whenever possible to allow drying of the skin. Using baby wipes is generally not recommended, but, if needed, they should be free from fragrance and alcohol (*Table 141.2*).

It is not recommended to use talcum or baby powders due to their potential toxicities and the risk of inhalation by the infant.

Table 141.2
Simplified rules of diaper area care (ABCDE-rules)

ABCs of diaper area care
Air: Diapers should be left open when possible to allow aeration of area
Barrier ointments (zinc oxide paste) should be applied with each diaper change
Cleansing gently with plain water and a gentle cleanser without rubbing
Diapers changed frequently as soon as they get soiled
Education of parents and caregivers

Modified from Boiko S: Making rash decisions in the diaper area. Pediatr Ann 29:50, 2000.

Finally, parents can be reassured that even the most severe or extensive rash related to napkin wearing will resolve once toilet training is achieved.

Disorders Directly Related to the Use of Diaper

Irritant Contact Dermatitis

Chafing or frictional napkin dermatitis is by far the most prevalent type of diaper dermatoses affecting almost every infant at some point in his/her life. The disorder seems to be attributed to a combination of factors such as contact with proteolytic enzymes of the stool, especially in cases of diarrhea, irritant chemicals or soaps, moisture and occlusion leading to sweat retention, the warm environment of the diaper, and constant friction and rubbing. All these factors compromise the skin integrity and impair its barrier function. Although ammonia from urine was initially thought to cause irritant diaper dermatitis, subsequent evidence refers to feces as the principal culprit.

Clinically, the condition is characterized by shiny confluent erythema with or without shallow erosions and swelling involving the convexities of the perineum, genitals, and buttocks (areas of closest contact with irritants), and sparing creases of intertriginous areas. Rarely, in infants over 4 months of age, it may present with perianal erythema. A subtype of irritant contact dermatitis is the simple intertrigo that affects overweight infants, mostly on moist skin folds (*Fig. 141.6*).

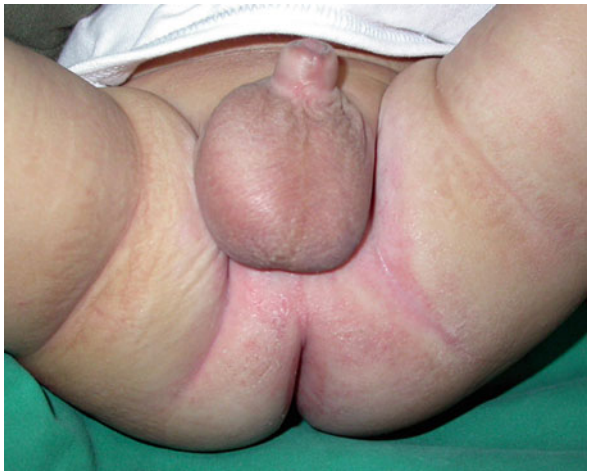

Figure 141.6
Contact dermatitis and secondary intertrigo in diaper area. (Courtesy of Arti Nanda, MD)

A severe form of irritant contact dermatitis is known as Jacquet's erosive dermatitis. This presents as well-demarcated punched out ulcers and erosions with elevated borders. Irritant contact dermatitis may occur any time during the diaper period. This condition has become uncommon since the advent of superabsorbent diapers.

Treatment includes minimizing contact with irritants by following the instructions previously mentioned (keeping the area clean and dry). A mild topical corticosteroid therapy (1% hydrocortisone cream for a short period of time) with a barrier product (zinc oxide soft paste) applied two to three times a day clears the condition rapidly. Stronger topical steroids should be avoided under diaper occlusion as it maximizes systemic absorption.

Allergic Contact Dermatitis of the Diaper Area

Allergic contact dermatitis is less common than irritant contact dermatitis in the diaper area, arising de novo or as a complication of another form of napkin rash. However, it should be considered if the infant does not respond to the usual therapeutic measures.

Offending agents include fragrance, dyes, and preservatives in topical baby products or other components of the diaper itself. An infant usually needs time to be sensitized, which is why this type of dermatitis is not generally seen in the first 6 months of life. Morphologically, it begins with erythema, small vesicles that rupture, giving the classical picture of an eczematous eruption. It mainly affects the convex surfaces under occlusion if the allergen was in the diaper, or may be more prominent in the flexural surfaces if the reaction is due to a topically applied product.

"Lucky Luke" dermatitis is a specific form of allergic contact dermatitis affecting the outer buttocks and hips, waistline, and proximal thighs. It indicates an allergy to rubber components in the elastic bands of the diaper. This is known as the holster sign (named after a cartoon character that carried its gun holster in the same area).

Strict avoidance of the suspected allergen with judicious use of topical corticosteroids is usually efficient in clearing this reaction in several days.

Granuloma Gluteale Infantum

Granuloma gluteale infantum is a rare condition characterized by firm, painless red-brown to purple dermal nodules varying in size from 0.5 to 4 cm, localized on the gluteal and convex surfaces of the diaper area in infants

between 2 and 9 months of age. It usually arises within the area of preexisting diaper dermatitis. The etiology is unclear, but it seems to be related to a combination of factors as an abnormal skin response to inflammation, local infection with candida, and the use of topical fluorinated steroids. Treatment is directed at correcting the underlying diaper rash and avoiding topical steroids and all irritants. Resolution occurs in several months, sometimes leaving atrophic skin patches.

Candida Diaper Dermatitis

Candidiasis is the most common infection in newborns. Candida diaper dermatitis in particular is the second most common type of diaper dermatitis. Provided there is sufficient warmth and moisture, candidiasis from lower intestinal flora frequently contaminates any form of diaper rash that lasts for over 3 days. Moreover, candidiasis is a possible sequela of systemic antibiotic therapy and should be considered when the rash develops during or shortly after antibiotic administration. Diarrhea also makes the infant more susceptible to candidiasis. Maternal mastitis during breast-feeding or presence of vaginitis at vaginal delivery could also be other sources.

Characteristic morphology is seldom seen before 6 weeks of age and presents as beefy red erythematous moist papules, patches, and plaques with pathognomonic satellite lesions, sharply defined with peripheral scale over the buttocks, abdomen, and the entire perineal area involving creases as well as convex surfaces. Oral thrush can also be associated with this type of diaper rash and it should be examined when candida is suspected.

The diagnosis is usually based on the characteristic clinical picture; however, potassium hydroxide scraping from peripheral scales may confirm it by revealing pseudohyphae and/or egg-shaped budding yeast.

Rarely, a psoriasiform skin eczematid ("Id reaction") may complicate a severe candidal napkin rash with scaly psoriasiform lesions appearing rapidly on the trunk and extremities.

Diaper candidiasis responds rapidly to topical antifungals such as nystatine, imidazoles, and ciclopirox. A brief course of low-potency topical steroids may speed up clinical improvement.

Perianal Pseudoverrucous Papules and Nodules

"Perianal pseudoverrucous papules and nodules" is a term used to describe a rare entity that represents a severe skin reaction following a chronic, unremitting irritation with feces, urine, or both. Therefore, it affects infants and older children with chronic diarrhea much more than newborns. Clinically, it presents as wart-like papules and nodules in the perianal and suprapubic areas. The lesions are usually red in color, moist, shiny, smooth, and flat topped.

Once the chronic irritation is removed, lesions regress spontaneously. The clinical importance of this condition lies in differentiating it from other serious dermatosis, especially candyloma accuminata.

Granular Parakeratosis

Infantile granular parakeratosis represents a rare, peculiar, idiopathic form of retention hyperkeratosis in diaper-wearing infants, rather than newborns.

There are two clinical patterns for this condition. The first one presents with asymptomatic geometric yellow-brown plaques with characteristic thick flake-like scales and underlying erythema over areas of friction or pressure. The second pattern presents with bilateral linear plaques appearing in the inguinal folds.

Treatment aims at reducing friction and following standard care of the diaper area; however, response is variable and spontaneous resolution after several months seems to be the rule.

Dermatoses Aggravated by Diaper Environment

Infantile Seborrheic Dermatitis

Infantile seborrheic dermatitis is an inflammatory skin disease, which may commonly affect the diaper area of infants, starting at 3–6 weeks of age and lasting for several months.

The condition occurs in "seborrheic areas" where sebum secretion is active, most commonly on the scalp, intertriginous areas of the diaper region, and may also involve the face, retroauricular area, neck, and axilla.

Classical presentation of infantile seborrheic diaper dermatitis includes a well-defined asymptomatic salmon-colored patch starting from the creases to the convex surfaces. Although classical seborrheic dermatitis is covered with thick greasy yellow scales, this feature in diaper areas is minimal or unusual, unless candida is secondarily involved. A major clue in the diagnosis is the characteristic sparing of the anogenital area.

The etiology of infantile seborrheic dermatitis is probably due to colonization of the yeast Malassiza furfur

(pityrosporum ovale) that thrives in an oily environment, explaining the special distribution of the patches.

The prognosis for infantile seborrheic dermatitis is generally good. It resolves spontaneously in most cases within the first year of life. Topical ketokonazole used two to three times daily may be useful.

Psoriasis

Psoriasis occasionally begins as a persistent diaper rash, with potential overlap with seborrheic dermatitis (sebopsoriasis). The appearance of psoriasis in the diaper area is attributed to the Koebner phenomenon caused by other types of diaper rashes.

Clinically, psoriasis presents as sharply defined erythematous plaques with much less scaliness than the classical psoriasis lesions due to hydration under the diaper (psoriasis inversa). These plaques involve both convex surfaces and inguinal folds. The lesions can potentially spread to the trunk and extremities or remain confined to the diaper region. Lesions tend to persist or heal and recur over months. Topical steroids usually achieve temporary improvement; new topical immunomodulators (pimecrolimus/tacrolimus) are also promising.

Other Dermatoses Affecting the Diaper Area

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is another rare disease that can cause atypical or persistent diaper rash as a part of periorificial distribution of the disease. In the recessively inherited form of the disease, there is an inborn defect in intestinal absorption of zinc. This typically affects infants when weaned from breast milk, which contains a zinc-ligand-binding protein. The other form of the disease is transient and is acquired due to nutritional zinc deficiency for any reason (e.g., low zinc in mother's breast milk, malabsorption, prematurity, etc.). Both types clinically present with crusting–scaling erosive diaper dermatitis, diarrhea, and hair loss. Affected infants are usually irritable and suffer from recurrent infections and failure to thrive. Eczematous lesions typically involve the face periorally and periorbitally with the acral areas of the digits (*Fig. 141.7*). Oral zinc supplementation clears the rash within several days. Infants with inherited forms require this supplementation for life, with dose adaptation according to the zinc serum levels.

Many other dermatoses may also affect the diaper area with or without affecting other areas of the infant's body that are not directly in contact with the diaper. These include:

- Atopic dermatitis
- Bullous impetigo
- Staphylococcal scalded skin syndrome
- Ecthyma gangrenosum
- Diaper dermatophytosis
- Herpes simplex
- HPV infection
- Molluscum contagiocum
- Coxsackie viral infection
- Cystic fibrosis
- Chronic bullous disease of childhood
- Langerhans cell histiocytosis (Letterer–Siwe disease)

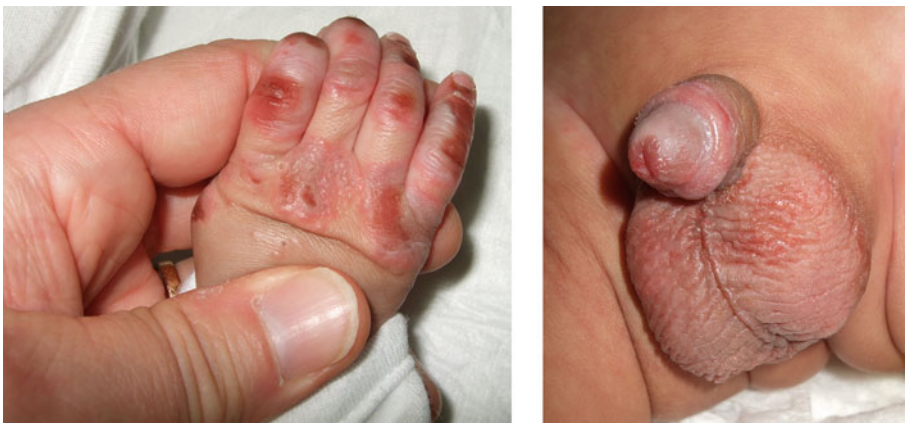

Figure 141.7
Acrodermatitis enteropathica. Typical erosive lesions on palms and genital area

- Kawasaki disease
- Hemangiomas
- Lichen sclerosus
- Pyoderma gangrenosum
- Bullous pemphigoid
- Child abuse
- Bullous mastocytosis
- Incontinentia pigmenti
- Congenital syphilis
- Scabies
- Perianal streptococcal disease and streptococcal intertrigo
- Perioral dermatitis with genital manifestations Crohn's disease
- Epidermolytic hyperkeratosis
- Epidermolysis bullosa

These diseases are much less common and relate to various etiologies, and therefore, are not discussed in this chapter. The reader is referred to the list of recommended references for further information.

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142 Eczematous Skin Disorders and Atopic Dermatitis in Childhood

Douglas W. Kress

Definition and Epidemiology

Atopic dermatitis (AD) is a genetically inherited papulosquamous skin disease most commonly seen in children. Seventy to ninety-five percent of cases present before the age of 5 years. The prevalence of AD in the western world is now between 10% and 20%, with the ratio of girls to boys being 1.3:1. Additionally, it is more likely for a child to inherit atopic dermatitis from a mother with atopy than from a father with atopy. This prevalence has steadily increased in North America and Europe since World War II. There are many theories that attempt to explain this increase ranging from environmental factors to the "Hygiene Hypothesis," many of which will be discussed later on in this chapter. The prevalence of AD varies worldwide. One very large study which looked at over 700,000 children in over 150 centers across the world showed the lowest prevalence in 6–7 year olds to be 2% in Iran and the highest prevalence in this age group to be 16% in Japan. In children 13–14 years of age, the lowest prevalence was 1% in Albania and the highest was over 17% in Nigeria.

Atopic dermatitis is commonly associated with asthma and allergic rhinitis, and the three together have historically been referred to as the "atopic triad." More recently, the finding of eosinophilic enteritis associated with severe food allergies has also been linked to these diseases. Food allergies can be seen in 40% of infants and children with moderate to severe AD. Eighty percent of individuals with AD will go on to develop either asthma or allergic rhinitis later on in life.

Etiology and Pathogenesis

From an etiologic perspective, AD is a multifactorial disease. First, there are several aspects of immune dysregulation. Seventy to eighty percent of patients with AD show elevated levels of IgE and eosinophilia. Biopsies of active skin lesions show a predominance of TH2 lymphocytes. Additionally, the skin of patients with AD produces lower levels of two families of antibacterial peptides known as B-defensins and cathelicidins. This is just one reason why atopics are much more susceptible to viral and bacterial infections than are non-atopics. Up to 90% of patients with AD will grow pathogenic *Staphylococcus aureus* from swab cultures taken from exudative skin lesions. *Staphylococcus* proteins can act as superantigens that can also flare AD.

Another pathomechanism, and another reason why atopics are so prone to infection, is that they have deficient epidermal skin barrier function. The stratum corneum of the skin of atopics contains much lower levels of ceramide proteins and filagrin than does the skin of non-atopics. Ceramides and filagrin are proteins that function to help the skin retain its moisture content. A hydrated epidermis keeps transepidermal water loss to a minimum, and also provides the best barrier against infection. There are many new topical products now available, both over the counter and by prescription, which contain both ceramides and filagrin. Their appropriate use as part of an overall treatment regimen for AD will be discussed at length in the treatment section to follow.

Clinical Manifestations

Clinically AD usually manifests itself in three phases, infantile, childhood, and an adolescent/adult phase. Infantile AD usually presents with a diffuse red scaly dermatitis mainly limited to the face and scalp (*Fig. 142.1*). Within the first 6–12 months of life, AD can overlap clinically with Seborrheic Dermatitis, also known as cradle cap. Usually, sometime between 12 and 18 months, the rash of AD leaves the face and scalp, and becomes more prominent on the popliteal (*Fig. 142.2*) and antecubital fossas (*Fig. 142.3*). This phase usually persists up through the early teenage years, by which point approximately 60% of patients will have grown out of their disease. In the up to 40% of atopics who carry their skin disease into adulthood, a number of different clinical patterns can be seen. These can include a chronic hand dermatitis, eyelid or neck eczema, or nipple eczema in young women. Many other clinical features can be seen

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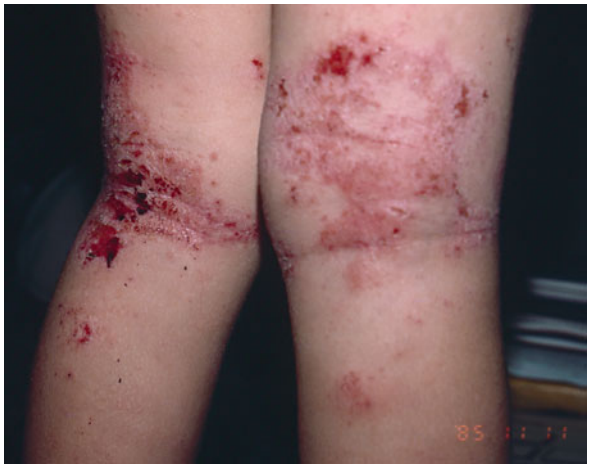

Figure 142.1
Facial atopic dermatitis in an infant

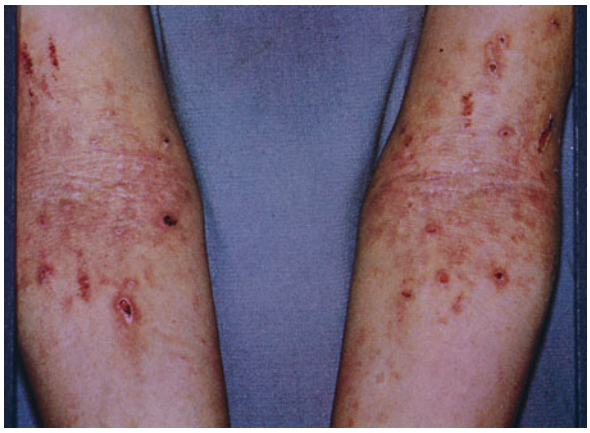

Figure 142.2
Popliteal fossa atopic dermatitis

at any age and make up a number of the minor criteria used to diagnose atopic dermatitis (see list below). From a morphological perspective, clinical lesions at each phase can also present in three different stages, acute, subacute, and chronic, which vary both clinically and histologically.

Major and minor criteria for the diagnosis of atopic dermatitis (adapted from Hanifin and Rajka's article) are as follows:

Major features

Pruritus
Typical morphology/distribution
Chronic and relapsing
Personal or family history

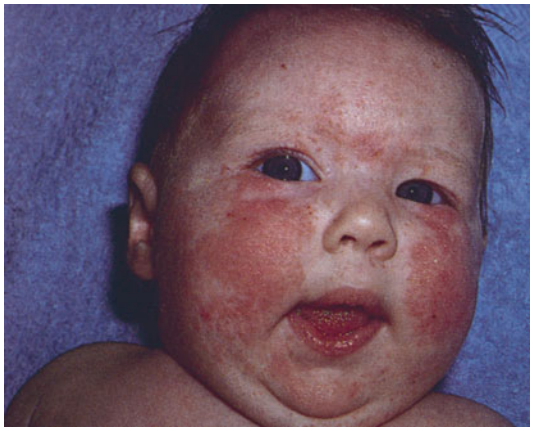

Figure 142.3
Antecubital fossa atopic dermatitis

Minor features

Xerosis
Ichthyosis/keratosis pilaris
Immediate Type 1 hypersensitivity
Elevated serum IgE
Early age of onset
Increased skin infections
Non-specific hand foot dermatitis
Nipple eczema
Chelitis
Recurrent conjunctivitis
Dennie–Morgan folds
Keratoconus
Anterior subcapsular cataracts
Orbital darkening
Facial pallor/erythema
Pityriasis alba
Anterior neck folds
Pruritus with sweating
Intolerance to wool
Perifollicular accentuation
Food intolerance
Influenced by environment
White dermatographism

Pathology

Histopathology varies at each stage. Acute eczema shows intraepidermal edema with microvesicles, also known as spongiosis. There is a perivascular lymphocytic infiltrate predominantly composed of CD4+ T cells extending from

the upper dermis into the epidermis. Langerhans cells and macrophages may also be seen in the infiltrate of acute eczema. Subacute eczema still shows some spongiosis and a less prominent lymphocytic infiltrate. Additionally, some epidermal thickening may be noted at this stage. Chronic eczema, which clinically appears as lichenification, shows only sparse to absent inflammation and spongiosis, with psoriasiform epidermal hyperplasia. Even the normal skin of patients with atopic dermatitis can show abnormal pathology, including a sparse perivascular infiltrate of T lymphocytes, eosinophils, and macrophages.

Differential Diagnosis

The differential diagnosis of AD is quite broad and is different for each phase, infantile, childhood, and adult. The differential includes other chronic dermatosis, infections and infestations, immunodeficiency syndromes, metabolic, genetic and autoimmune disorders, drug eruptions, and malignancies (*Table 142.1*).

Table 142.1
Differential diagnosis of atopic dermatitis (adapted from Bolognia)

Chronic dermatosis	
Seborrheic dermatitis	C
Contact dermatitis	B
Psoriasis	B
Nummular eczema	B
Asteatotic eczema	A
Lichen simplex chronicus	B
ID reaction	B
Infections and infestations	
Scabies	B
Tinea	B
Impetigo	B
Mucocutaneous candidiasis	C
Congenital syphilis	C
Primary immunodeficiencies	
Wiskott–Aldrich syndrome	C
Hyper IgE syndrome	C
Genetic syndromes	
Netherton syndrome	C
Ectodermal dysplasias	C
Autoimmune disorders	
Dermatitis herpetiformis	A>>C
Pemphigus foliaceus	A> > C
Dermatomyositis	B
Lupus	A>>C
Malignancies	
Cutaneous T cell lymphoma	A>> > C
Langerhans cell histiocytosis	C
Other	
Drug eruptions	B

A = adults, *B* = both, *C* = children

Treatment

Once the diagnosis is made, the treatment of AD varies based on the patient's age, the location of the eczematous lesions, and their morphology. Treatment of infantile AD, which mainly involves the face and scalp, should begin with mild soap-free cleansers, known as syndets, and with moisturizers which contain ceramides and/or filaggrin. If those are not effective, very mild topical steroids should be added. There are seven classes of topical steroids available to treat all types of skin disease in patients of all ages. Class 1 steroids are the strongest and Class 7 steroids are the weakest. Several agents in Classes 5–7 are approved for use as young as 3 months of age in the United States, including certain strengths of hydrocortisone, desonide, and fluticasone. These are the agents that should be used to treat eczema in young infants. The topical steroids should be used for no more than 2 weeks without taking a break to minimize their side effects, including the possibility of hypothalamic–pituitary–adrenal (HPA) axis suppression. They should be used in conjunction with the above cleansers and moisturizers. Pruritus can be seen in association with AD at any age. If numerous excoriations are noted, or the parents report poor sleep hygiene, a low nightly dose of a sedating antihistamine, such as hydroxizine, should be considered. Sometimes there is a clinical overlap between AD and seborrheic dermatitis. If this overlap is suspected, the addition of ketoconazole shampoo applied three times per week can be very helpful.

At some point between 12 and 18 months, most facial and scalp AD resolves, and many young children are left with a flexural dermatitis involving the popliteal and antecubital fossas. These skin lesions often exhibit accentuation of the skin lines, a clinical finding known as lichenification. Once lichenification is noted, it will probably become necessary to increase the strength of the topical steroid to one of mid potency, such as triamcinolone. As above, it continues to be important to use

soap-free cleansers and ceramide and filaggrin containing moisturizers. As the strength of the topical steroid use is increased, it is especially important to find ways to give the skin a break from steroid use. Twice daily use of a Class 4 steroid for only 2 weeks on greater than 10% of the body surface area of a child can be associated with statistically significant HPA axis suppression. If, as a clinician, one finds patients for whom the moisturizers and cleansers are not enough to allow the patient to not use topical steroids for at least 1 week per month, that patient may be a candidate for the use of one of the two calcineurin inhibitors/topical immunomodulators (TIMs), pimecrolimus or tacrolimus. In the United States, these two agents carry a Black Box Warning against the theoretical increased malignancy risk of using these agents in children under 2 years of age. This warning stems from the fact that the transplant patients taking oral tacrolimus for more than 5 years have an increased risk of malignancy, especially skin cancers and lymphomas. No malignancies have been definitively causally linked to the use of either topical pimecrolimus or topical tacrolimus.

For a very small percentage of patients who do not respond to aggressive moisturization, mid to high potently topical steroid use, oral antihistamines, and the addition of one of the TIMs, systemic therapy is sometimes necessary. Systemic therapy may also be appropriate for those patients with such a large percentage of body surface area involved (i.e., >20%) that topical therapy is not a tenable option. There are numerous systemic therapies ranging from oral antibiotics and oral steroids, threw light therapy, and up to other oral and injectable immunosuppressive agents such as Cyclosporin, Azathioprine, Methotrexate, Mycophenolate mofetil (MM), Intravenous immunoglobulin (IVIG), and Interferon gamma.

Prospective clinical trials evidence exists only for Cyclosporin, Azathioprine, Interferon gamma, Broadband UVB, and PUVA. Evidence at the level of retrospective clinical trials or large case series exists for systemic steroids, narrowband UVB, methotrexate, mycophenolate mofetil (MM), and intravenous immunoglobulin (IVIG). Although the scientific evidence for oral prednisone is not as strong as for some other agents, based on decades of clinical experience, many pediatric dermatologists will first try a 2–3 week taper of oral prednisone from a starting dose of 1 mg/kg/day. It is often necessary to overlap a 10–14-day course of a penicillin or cephalosporin antibiotic with the prednisone in these patients with severe atopic dermatitis due to their high risk of secondary bacterial infection. If the prednisone is either not effective or significant rebound in disease activity is noted rapidly, one of the steroid sparing agents should be considered.

Cyclosporin is the most effective of these other agents and should be given at a dose of 3–5 mg/kg/day for 3–6 months. Close monitoring of patients on cyclosporine is very important, and includes monthly blood pressure checks, complete blood counts, lipid profiles, BUN, creatinine, magnesium, and urinalysis. Azathioprine can also be very effective, but produces a slower clinical response. Dosing should be determined based on the patient's level of thiopurine methyl transferase. It is necessary to follow hepatic function tests and complete blood counts monthly. If cyclosporine and azathioprine are either ineffective or too toxic for a given individual, either methotrexate or MM can be given. Methotrexate is dosed weekly at 0.2–0.8 mg/kg/week, while MM is given daily at a dose of 10–30 mg/kg/day. It is important to follow hepatic function and complete blood counts monthly in patients on both of these drugs. Although there is a good evidence for the efficacy of several different types of light therapy in the treatment of atopic dermatitis, the technical difficulties involved in providing it to young children usually puts it far down the therapeutic ladder. Lastly, Interferon gamma and IVIG, although both effective, must be considered treatments of last resort due to their extremely high costs.

Prognosis and Prevention

Approximately 60% of individuals with AD will grow out of it by the early teenage years. Unfortunately, a small percentage of these patients will carry their tendencies toward asthma and food and environmental allergies into adulthood. Prevention can be viewed as either keeping the disease from ever developing or minimizing the level of disease activity once it has developed. Complete prevention has only been reported in a few small trials in the British medical literature that looked at the use of probiotics in pregnant and nursing mothers, and the incidence of AD in their infant children. From the point of view of prevention of active disease, once the diagnosis has been made, ceramide and filaggrin containing moisturizers have been shown in numerous studies to fill this roll.

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143 Acne and Related Disorders

Harald P. M. Gollnick

Introduction

Acne is a disease which encompasses a variety of clinical features and variants of which the most known is acne vulgaris. However, different courses exist due to several grades of severity, distribution in body areas, age, gender, and internal and external factors manifesting, exacerbating, or prolonging it. Acne is seen today as a chronic disease which continuously needs medical counseling. Physical and psychological scarring often accompanies the disease, and emotional distress is very commonly seen in all ages with manifestation of acne.

Historical Remarks

In the "Papyrus Eber," a disease named "Aku-t" was mentioned which was characterized by lesions well fitting the clinical picture of acne: boiling, blains, sores, pustules, and inflammation. The famous Greek physicians Hippocrates and Aristoteles saw an association with puberty. The Greeks named the disease "ionthos," the Latins "Varus." The pharao King Tut (135–1337 A.D.) undoubtedly had suffered from severe scarring. Most probably Atius, physician at the court of Justinian in East-Rom, used the term "acne" for the first time. Acne most probably arises from the greek "akme" but have been misspelled. It could also derive from aknesis, a rash which does not itch or from the greek word "akun." Lastly the Greeks took most probably over the term "aku-t" and then the word was introduced and finally came into medical latin language "acne."

Genetics and Epidemiology of Acne

Acne has a familial background, but a clear genetic inheritance has not been described yet. Genes encoding for cytochrome P450-1A1 and steroid-21-hydroxylase as well as 11- or 3-HSD may be involved. Environmental factors also appear to be of relevance. Especially, diet has recently gained attention. Populations with a balanced lifestyle seem not to develop significant acne and recent epidemiologic and investigative studies correlate acne with Western diets. The course of the disease in homozygotic twins is very similar, the sebum excretion rate is the same in more than 90%, whereas in heterozygotic ones it drops down to 40% and the severity is different. It has clearly been shown that seborrheic and acne patients have more lobules per single gland in the sebaceous apparatus than people with normal skin, which indicates a genetically prone situation. Nodulocystic courses of acne are more frequently seen in patients with the XYY genotype.

Acne today is regarded as one of the most frequent skin diseases worldwide in all ethnic groups. Epidemiologic studies in Western industrialized countries estimated the prevalence of acne in adolescents to be between 50% and 95%, depending on the method of lesion counting. In the USA, the prevalence in 15–17-year-old children is around 85%. If mild manifestations were excluded and only moderate or severe manifestations were considered, the frequency was still 20–35%. Acne is a disease primarily of adolescence. It is in parallel emerging in children at the start of puberty by the initiation of androgen production by the adrenal glands and gonads, and it usually subsides after the end of the growth period. Although comedo formation decreases significantly, the hyperseborrhea still exists up to the fourth or fifth life decade. However, to some degree, acne is going to persist beyond teenage in a significant proportion of individuals (*Fig. 143.1*).

There are not only cases with persisting acne, but also those with reoccurrence or with a first manifestation in the third decade of life. Even after the adolescent type of acne has ceased, scarring and hyper- and hypopigmentation are long-term visible postacne features affecting the patients with negative physical outcome needing further medical and cosmetic care. Recent publications show a higher incidence of facial and persisting acne in certain families with an odds ratio of about >4 in the UK and Han Chinese. The course of disease stops more abruptly in males as compared to

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Prevalence of Acne in Different Epidemiological Studies

Autor	Jahr	Alter (Jahre)	Prävalenz Männer (%)	Prävalenz Frauen (%)	Gruppengröße (n)	Ort
Bloch [20]	1931	15–18	87,8–99,4	87,8–96,6		Schweiz
Hellgren [21]	1963	15–24	29,3–28,8	12,0–24,5	7 495	Schweden
Burton et al. [4]	1971	15–18	100	95–100		UK
Larsson and Liden [22]	1980	15–16	48,3–53,3	37,0–38,8	8 290	Schweden
Rademaker et al. [1]	1989	15–17	85–96	81–85		UK
Bahamadan et al. [23]	1996	14–19	56,4–78,2	n.b.	647	Saudi-Arabien
Freyre et al. [24]	1998	15	50,9–78,4	40,0–59,0	1 087	Peru
Plunkett et al. [25]	1999	20+	9,4–14,2	11,2–16,1	1 457	Australien
Daniel et al. [26]	2000	11–18	69,3–74,7		913	Frankreich
Schäfer et al. [8]	2001	1–87	29,9	23,7	896	Deutschland
Jemec et al. [13]	2002	15–22	40,7	23,8	186	Dänemark

Schäfer et al. JDDG; 2010 • 8:S4–S6

Figure 143.1
Acne epidemiology

females in whom there is today up to 30% persisting acne cases. Interestingly these observations have been already made in a doctoral thesis from Breslau in the early 1900 on female medical students. This means it is not a clear observation in females today, however, it is increasing in number.

Acne is in general considered a disease starting in adolescence; however, acne lesions may already precede the natural signs of puberty and little tiny comedones like milia (acne miliaris) can be seen mostly in children from the seventh to ninth year of life at the sides of the upper nose/glabellar area and lateral cheeks. Rarely, inflammatory lesions are detected. In girls, it may precede the menarche by up to 2.5 years.

A special subtype of acne occurring in early childhood is acne neonatorum during the second and fourth week of life and acne infantum manifesting after the second or third months after birth. Whereas in the first case maternal androgens or intrauterine stress-induced adrenal androgens are responsible, in the second case a temporarily adrenal functional hyperplasia is the cause, which under normal circumstances will fade away after the 9th month of life. Persisting cases, however, are suspicious for adrenal or gonadal androgen–producing tumors or misfunction of 3-, 7-, 11-, or 21-steroidhydroxylases and a pubertas precox.

Prognostic Factors of Disease

A number of prognostic factors have to be considered and are more or less related to the severe courses of the disease. These are outlined and evidenced in a review paper published by Holland and Jeremy (2005) and Dreno et al. and include family history, course of inflammation, persistent or late onset disease, hyperseborrhea, androgenic triggers, scaring, truncal acne, and/or psychological sequelae. Infantile acne may also correlate with resurgence of acne at puberty and one should be aware – even though not clearly proven by statistical evidence that early age of onset with mid-facial comedones, early and more severe seborrhea, and earlier presentation relative to the menarche are connected to the incidence of acne as a baby.

Scarring Assessment/Potential for Scarring Influence on Management

Scarring usually follows deep-seated inflammatory lesions but may also occur as a result of more superficial inflamed lesions in scar-prone patients. Holland and Jeremy published their findings that patients with more severe inflammatory infiltrate in the biopsy have less scarring

than those with a less inflammatory one. If this can be used as a predictor is not clear yet. Ethnic predisposition plays, in addition, an important fact having more scarring in black and Indian skin. More recent results by S. Kang point toward the fact that scars may even arise from skin areas not having involved by a visible lesion at all. This implies that treatment has to be done as early and as sufficient as possible.

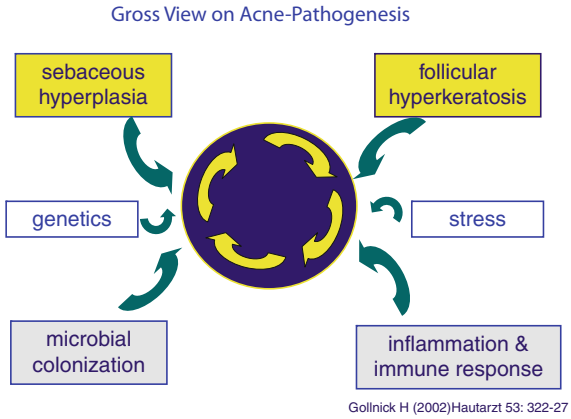
Acne scarring of different types, albeit mild, has been identified in up to 90% of patients attending a dermatology setting. Scars may show increased collagen (hypertrophic and keloid scars) or be associated with collagen loss (ice-pick, boxcar and rolling type of scars). The presence of scarring should support immediate onset of an interventional aggressive management and therapy should be considered as early as possible in the disease process. In the postacne situation, patients suffer long-standing sequelae and ask for additional support by peelings and lasers as well as psychological help.

Pathophysiology

Acne is an androgen-dependent and androgen-driven disorder of the pilosebaceous apparatus. At the beginning of its manifestation, the first nonvisible lesion is the microcomedo in which the colonization with *P. acnes* does not play any role, but sebaceous hyperplasia and increased pathologic cohesion of follicular corneocytes have led to the microscopic changes of the follicular milieu.

Today, four primary pathogenic factors are accepted in different grades of expression and at different time points involved or intermingled in the pathogenesis of acne. These are as follows: (1) increased sebum production by the sebaceous gland, (2) hyperproliferation and disturbed keratinization with increased cohesion of corneocytes in the follicular canal, (3) colonization with Propionibacterium acnes in the lower part of the infundibulum, and (4) release of several inflammatory mediators involved in innate and acquired immunity (◉ *Fig. 143.2*).

Patients with seborrhea and acne have a significantly higher number of lobules per gland as compared to normal healthy persons who never developed acne or seborrhea (so called genetically prone "Anlage"). This means that the androgenic event in puberty acts on a different Anlage. Inflammatory responses occur prior to hyperproliferation of keratinocytes. IL-1α upregulation participates in the development of comedones independent of the colonization with *P. acnes.* A relative linoleic acid



◘ Figure 143.2
Gross view on acne pathogenesis

deficiency has been described by Downing and Strauss, but this can only be a contributing factor because the deficit appearing in the lobules of the gland and consequently in the follicular corneocytes with less barrier function (ceramides) persists despite resolution of comedones in the third life decade when acne resolves but seborrhoea persists (◉ *Fig. 143.3*).

Cycling of the sebaceous follicle is an important part in the cascade of mechanisms interacting in the pathophysiology, leading to certain time points when the microcomedo formation becomes disposed to form a sensitive moment for an injury as a starting point of new lesions.

P. acnes colonizes the skin right after birth and an immune response with IgM and IgG follows. It seems that *P. acnes* at this time point is of a planctonic type, whereas later in puberty it becomes pathologic and starts biofilm production and increases its virulence. Acting on the inflammatory cascade of NF kappa and the proinflammatory cytokines via Toll-like receptor 2 it contributes to a continuous self-perpetuating vicious cycle. Activation of AP-1 induces matrix metalloproteinase genes, whose products degrade and alter the dermal matrix.

However, it should be noticed that inflamed follicles exist showing no *P. acnes* colonization at all. Oxidized squalene (squalene peroxide) can stimulate hyperproliferation in keratinocytes and those lipoperoxides can produce leukotriene B4, a powerful chemoattractant.

The role of free fatty acids formed after the splitting of triglycerides into FFAs and diglycerols has been long overestimated but still contributes to the different factors working in concert in the follicular milieu (◉ *Fig. 143.4*).

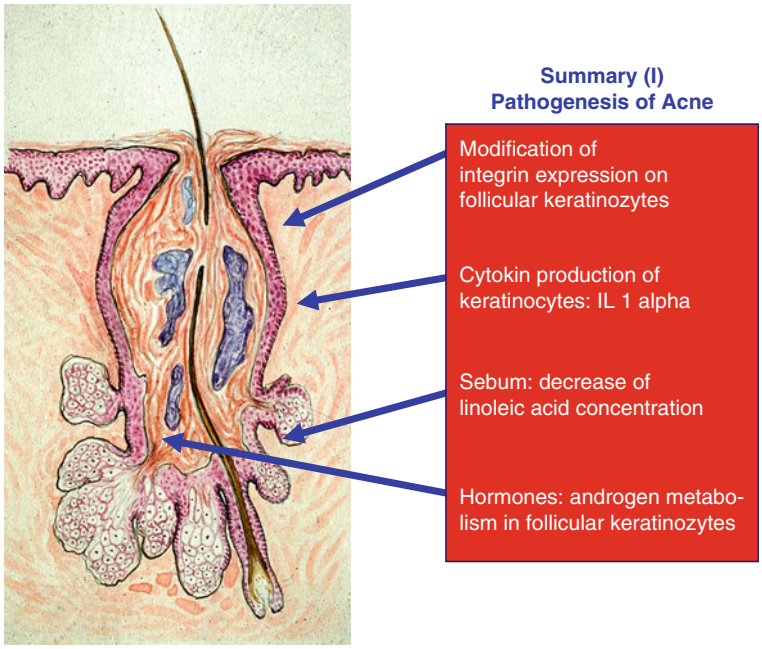


Figure 143.3
Summary of the pathogenesis of disturbed follicular keratinization processes in the follicular infundibulum

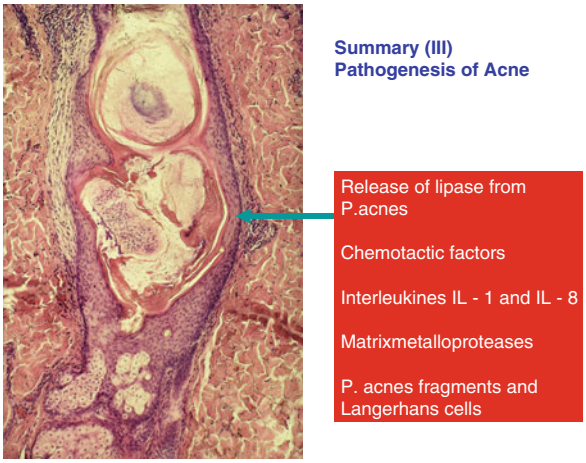


Figure 143.4
Summary of pathogenetic processes in the infundibulum related to P.acnes

Sebaceous lipids are regulated by peroxisome proliferator-activated receptors gamma and alpha (PPAR's) which act in concert with retinoid X receptors to regulate epidermal growth and differentiation as well as lipid metabolism. Sterol response element binding proteins (SREBP) mediate the increase in sebaceous lipid formation induced by insulin-like growth factor-1 via the PIK-3 or/and Akt-pathways. Substance P receptors, neuropeptidases, α-melanocyte stimulating hormone, IGF-1R, and CRH-R1 are also involved in regulating sebocyte activity, and finally the ectopeptidases such as dipeptidylpeptidase IV and animopeptidase N, which are distributed on activated keratinocytes, sebocytes, and T-cells in the inflammatory infiltrate. The sebaceous gland acts on the whole as an endocrine organ in response to changes in androgens and hormones (*Figs. 143.5* and *143.6*).

The role of FoxO1 and the relation of nuclear to cytoplasmic shifting with stimulation of the PPAR gamma and of the androgen receptor are not yet fully discovered; however, a connection to the IGF and insulin-related stimulation of this cascade is a further evidence for research (*Fig. 143.7*).

The improved understanding of acne development on a molecular level suggests that acne is a disease that involves the innate and adaptive immune system and inflammatory events as well as the local and systemic hormonal network. The "Switch-Off Signal" of acne, however, is not understood yet (*Fig. 143.8*).

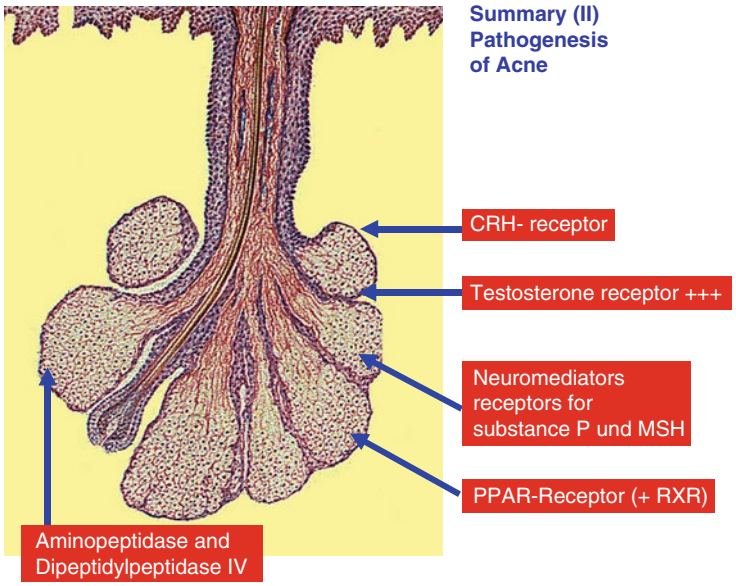


Figure 143.5
Summary of pathogenesis of processes leading to sebaceous hyperplasia

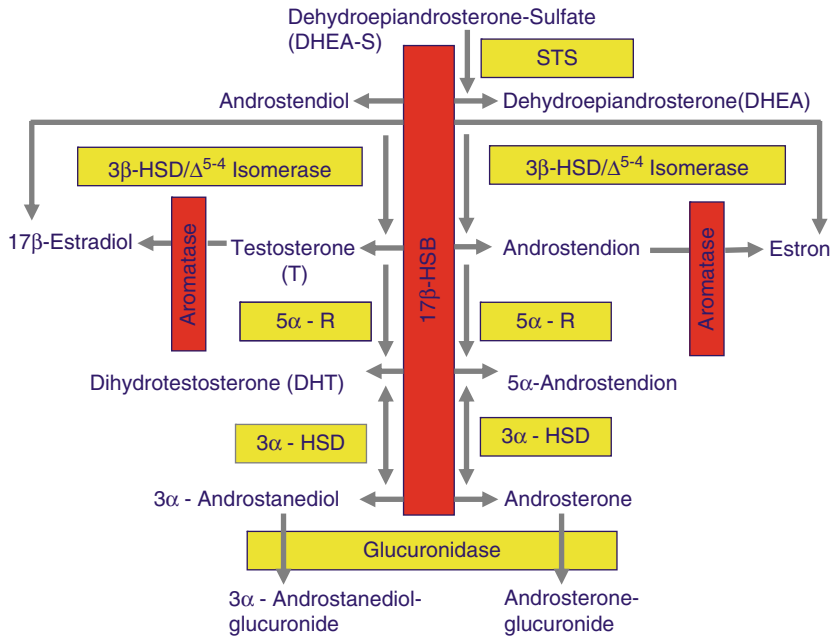


Figure 143.6
Androgen metabolism pathways important in the activation of sebocytes and follicular keratinocytes

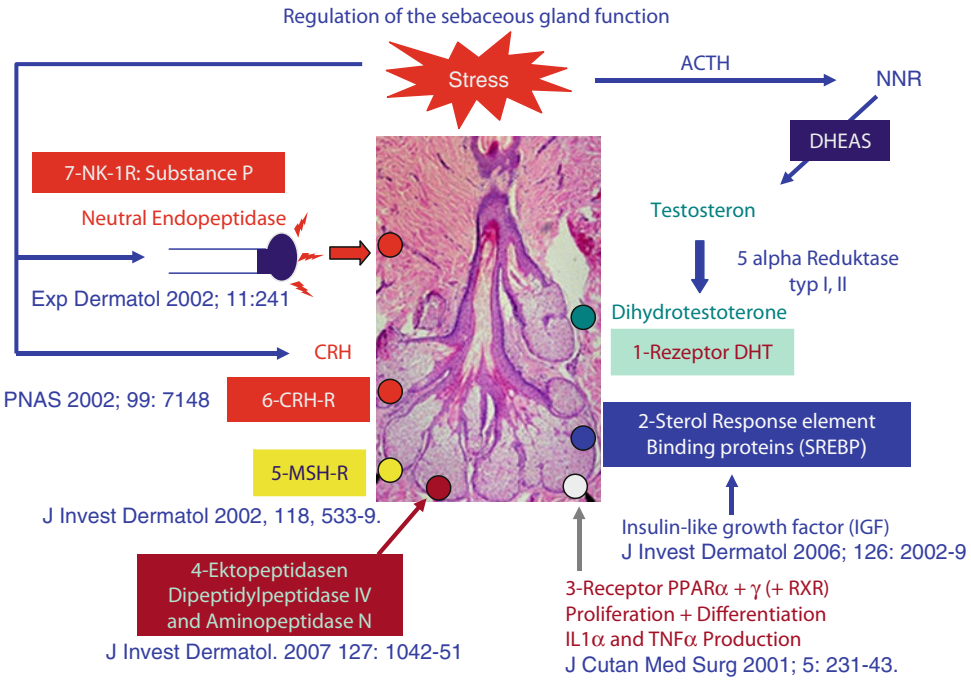


Figure 143.7
Details of the receptors and mediators acting on the sebaceous gland

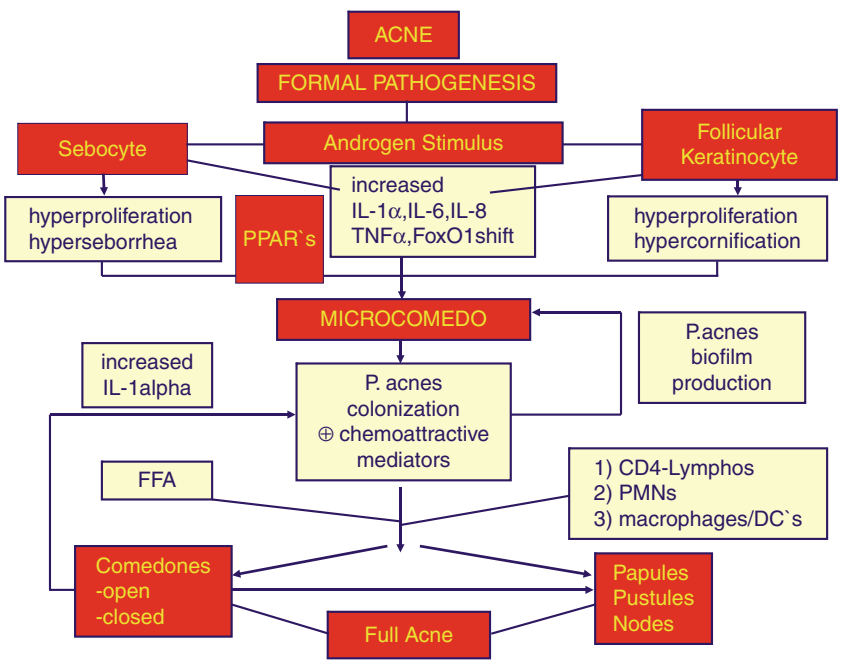


Figure 143.8
Detailed scheme on acne pathogenesis

Clinical Features and Variants

Vulgar acne, synonymous with "acne vulgaris," is a polymorphic, in the very beginning noninflammatory but then characteristically inflammatory skin disease most commonly affecting the face (in 99% of cases) and to a lesser extent the back (60%) and chest (15%). Seborrhea is a hallmark of acne.

The clinical picture embraces a spectrum of signs, ranging from mild comedonal acne, with or without sparse inflammatory lesions, to aggressive fulminate disease with deep-seated inflammation, nodules, and in some cases associated systemic upset. In addition, certain clinical subtypes provoked by internal and/or external factors exist (◉ *Fig. 143.9*).

Comedonal Acne

Clinically, noninflamed lesions develop from the subclinical microcomedo which is evident on histological examination early in acne development. At very early stage of puberty, the comedones are very small and monomorphic, white miliaria like, closely located at the sides of the cheeks at the nose and the outer cheek near the maxilla-orbital area and forehead near the hair margin. Noninflamed lesions encompass both open (blackheads) and closed (whiteheads) comedones which increase in size over the years. These comedones frequently appear in a mid-facial glabellar distribution in childhood and when evident early in the course of the disease; this pattern is probably indicative of poor prognosis. Closed comedones are often inconspicuous with no visible follicular opening and become more visible when stretching the skin or may be prominent producing a sandpaper-like pattern (◉ *Figs. 143.4*, ◉ *143.10*, ◉ *143.11*).

Papulo-Pustular Acne

Most patients with acne vulgaris (A.pap.pustulosa I–III according to Plewig and Kligman) have a mixture of noninflammatory and inflammatory lesions. Inflammatory lesions arise from the invisible microcomedo or noninflammatory lesions and may be superficial or deep in nature. Superficial inflammatory lesions include papules and pustules (5 mm or less in diameter) and these may evolve into deep pustules or nodules in more severe disease. Lesions with a size of 0.5–1 cm are small nodules and characterize the subtype of Acne pap.-pust.nodosa often in the course of the disease developing in addition nodes >1cm. Inflammatory macules represent either initial precursor lesions existing for a short time or regressing lesions that may persist for many weeks and contribute markedly to the general inflammatory erythematous pattern of acne. Scarring may even develop from macules (◉ *Figs. 143.12–143.15*).

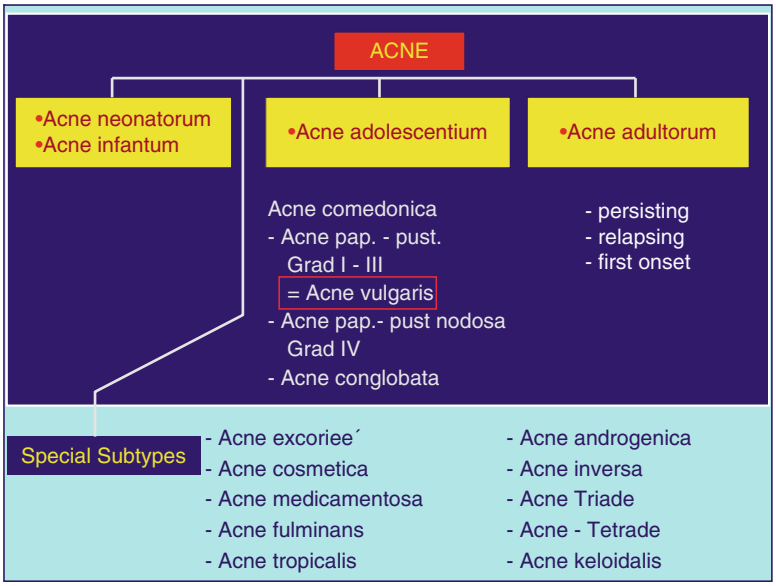


Figure 143.9
Classification of acne and specific subtypes

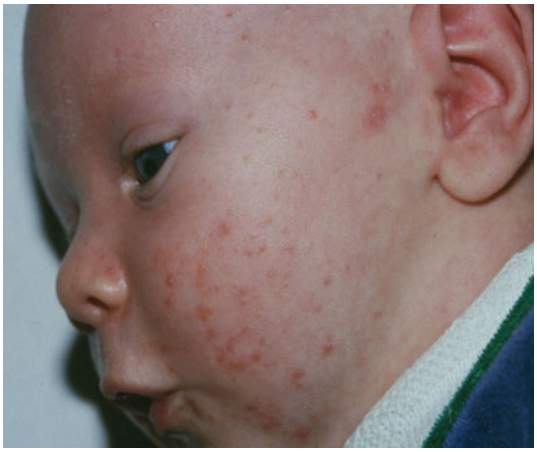


Figure 143.10
Figure Comedones and little papules in acne infantum

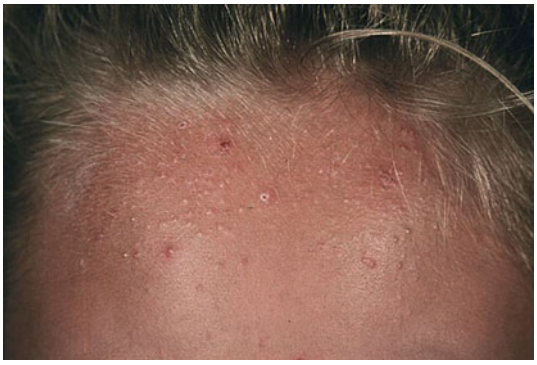


Figure 143.11
Tiny white closed comedones in early development of acne at begin of puberty

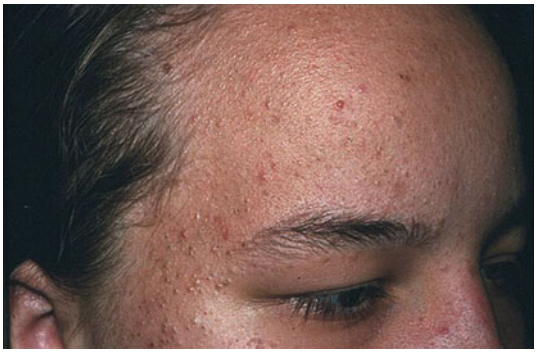


Figure 143.12
Dense distribution of comedones (sandpaper-like type)

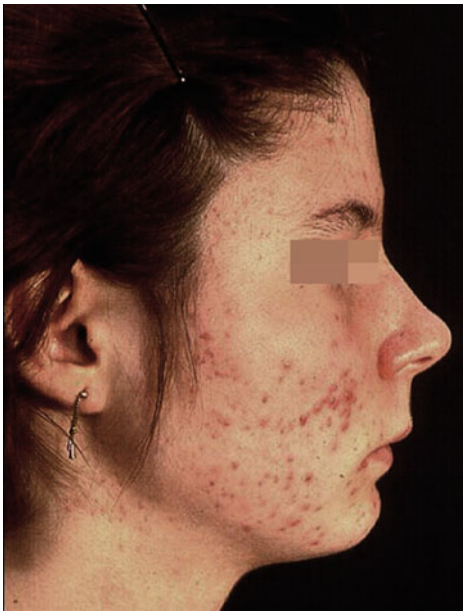


Figure 143.13
Papular-pustular acne grade III with small nodules (accord. Plewig & Kligman)

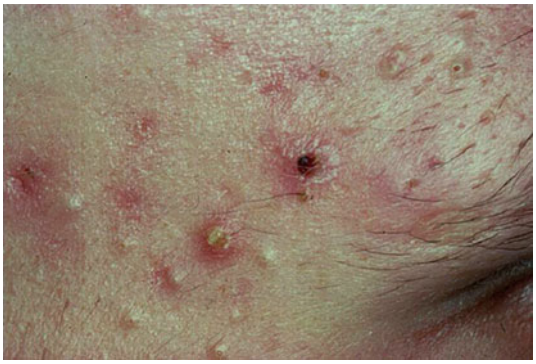


Figure 143.14
Polymorphous inflammatory picture of acne lesions with comedones, papules and pustules

Conglobate Acne

Small nodules are defined as firm, inflamed lesions >5 mm in diameter, painful already by palpation; large nodules are >1 cm in size and may extend to the subcutaneous tissue and confluate over large areas, frequently resulting in painful and exudative sinus tracts and tissue destruction. Conglobate acne (*A. conglobata*) is a rare but severe special form of acne found most commonly in adult males with no or little systemic involvement. Lesions

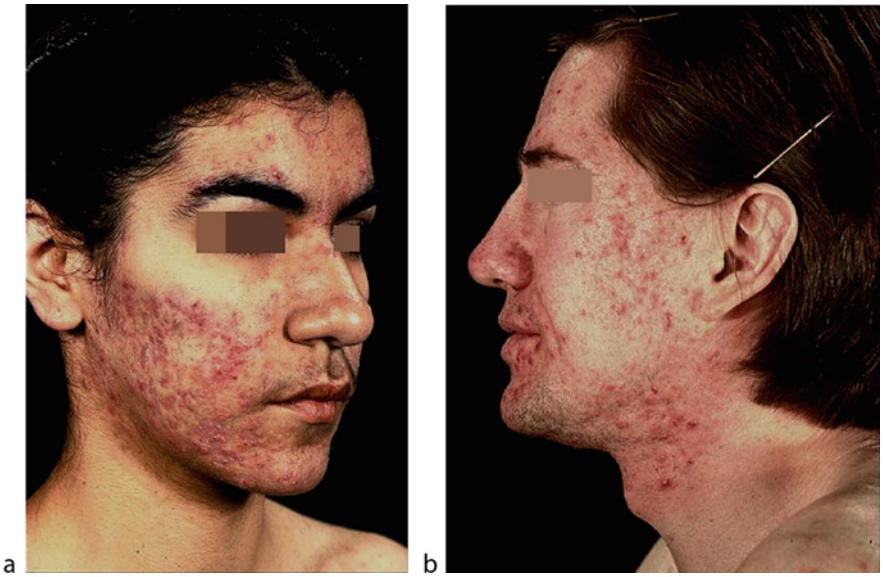


Figure 143.15
Acne papulo-pustulosa nodosa (grade IV accord.Plewig & Kligman)

usually occur on the trunk and upper limbs and frequently extend to the buttocks. In contrast to classic acne, facial lesions are less common or may be missing and only back or chest are involved, however, poor nodular pattern of the face without trunc involvement exists, however, severe only in the face localized cases with sinuses at the cheeks can be observed. The condition often presents in the second to third decade and may persist even into the sixth decade of life. Conglobate acne is characterized by multiple, grouped comedones amid inflammatory papules, tender, suppurative nodules which commonly coalesce to form sinus tracts or a network of rabbit-warren like small undermining fistules.

Extensive and disfiguring scarring of the hypertrophic and keloid type as well as icepick scars, boxcar scars and rolling scars in the face are frequent postacne sequelae (*Fig. 143.16*).

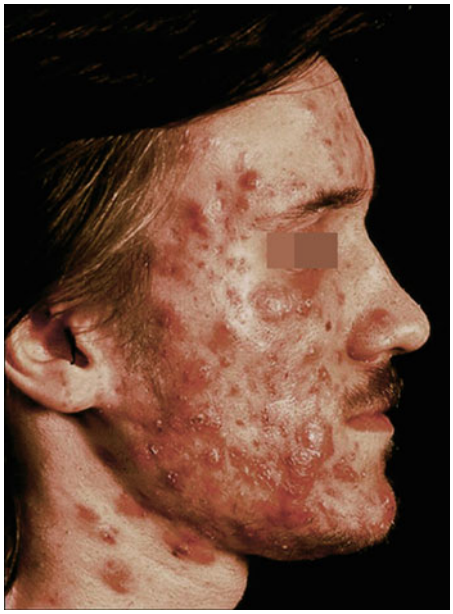


Figure 143.16
Conglobate acne of the face

Other Acne Variants

There are several mild to moderate to severe and clinical different variants or complications of the course of acne. These include acne conglobata as described earlier, but in particular acne fulminans, gram-negative folliculitis, pyoderma fulminans, vasculitic/pyoderma gangrenosum, acne mechanica, oil/tar acne, chloracne, acne in neonates and infants and late onset, adrenogenital syndromes, including HAIR-AN syndrome, Sapho-syndrome, and other rare syndromal manifestations, persistent acne sometimes associated to underlying inborn or iatrogenic-induced endocrinopathies as well as occupational derived provocations.

Therapy

General Remarks

Therapy in acne has changed over the last two decades significantly because new drugs and new formulations have become available. In general, there is a differentiation in acute intervention treatment and maintenance treatment with topical and systemic agents and a combination of both. In addition, adjunctive treatment procedures are available such as lasers and light and chemical peelings as well as cosmeceuticals for postacne or concomitant treatment. More and more guidelines and consensus papers with evidenced-based medicine-related studies support therapeutic decisions today. Acne treatment is long term. Not more than 50% improvement in a moderate acne under oral tetracycline plus topical benzoylperoxide can be achieved in 3 months, for milder cases earlier and for more severe cases even longer. Because of the relapsing character of acne as a chronic disease over 5–10 years, continuous medical counseling and prescriptions and additional adjunctive including psychologic counseling procedures are necessary (*Fig. 143.17*).

Topical Treatment

Topical treatment is based on three out of the four main pathophysiologic factors in acne which are normalization of the disturbed keratinization in the follicular apparatus, the reduction of hypercolonization of *P. acnes*, and anti-inflammatory actions. Until now, no effective drug is available which influences by the topical route the activity of gland hyperplasia with consecutive reduction of hyperseborrhea. Lasers and photodynamic therapy unfortunately reduce seborrhea by complete or partly irreversible damage to the gland followed by subclinical microscarring.

Three main classes of topical substances are on the market worldwide: the different generations of retinoids, benzoyl-peroxide (BPO), azelaic acid (AzA), and antibiotics. Retinoids and BPO function as so-called basic topical agents. Peeling substances are not well evidenced yet based on the interventional phase of treatment.

Retinoids

Within the classes of retinoids, the oldest (first reported in 1962) still in use is tretinoin (all-trans retinoic acid); later isotretinoin (13-cis retinoic acid) came on the market followed by tazarotene and adapalene.

All of them have very good efficacy in normalizing of the disturbed keratinization in the follicular canal by being comedolytic and anticomedogenic. The increased cohesion of corneocytes, filaggrin macroaggregates, tonofilaments, and lipid droplets is reduced. Upregulated and downregulated genes are directly influenced by the retinoids. In addition, there is evidence of an additional anti-inflammatory efficacy of adapalene and tretinoin in

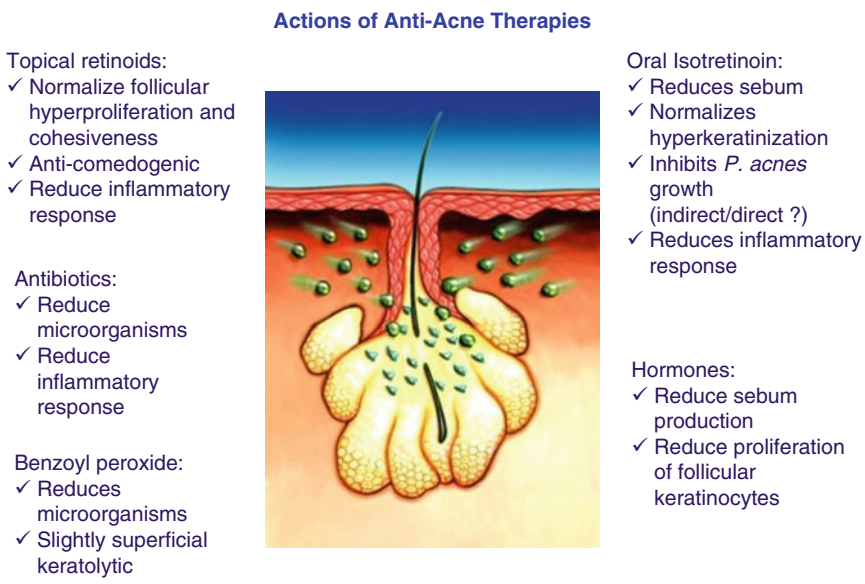


Figure 143.17
Overview of therapeutic armamentarium in acne

downregulating the activity of Toll-like receptor 2 (TLR-2) stimulated by *P. acnes* which finally leads to the activation of proinflammatory cytokines such as IL-6, IL-8, or TNFalpha. Adapalene is, in addition, capable of species-specific inhibition in humans certain lipoxygenases. The additional positive influence on postinflammatory hyperpigmentation and on the collagen matrix in the upper dermis is well known.

All retinoids significantly reduce the number of open and closed comedones and microcomedones as well. After 3 months of treatment, more than 50% of comedones are reduced. There are several types of formulations on the market which vary from country to country but are mostly gels and creams or solutions. All retinoids available are effective as single agents in mild to moderate acne. Tazarotene 0.1% is more effective than tretinoin 0.025% or the more modern galenic formulation 0.1% microsphere gel or adapalene 0.1% gel or cream (EBM level 2c). Adapalene 0.1% is equally effective as the above-mentioned tretinoin gel concentration or tretinoin 0.05% cream or isotretinoin 0.05% (EBM level 2c).

Retinoids are recommended as a monotherapy in comedonal acne and mild acne papulo-pustulosa. Grade II and III of papular-pustular acne according to the Plewig and Kligmans classification should be treated in sequential or fixed combinations with BPO or with topical antibiotics. In those combinations, in addition to the retinoid effects, a reduction of *P. acnes* is markedly achieved. There is one fixed combination of adapalene and BPO 2.5% on the market available now, the first combination of a retinoid with BPO that is pharmacologically compatible. Alternatively, one can use a topical antibiotic or BPO in the morning, followed by the application of the retinoid in the evening.

In severe forms of acne, retinoids are ideal partners in combination with oral antibiotics or in young females already under prescription for an antiandrogenic hormonal pill.

The irritative potential is the mildest with adapalene, followed by isotretinoin and tretinoin and tazarotene, respectively. One can mostly see an initial flare-up of lesions for a couple of days, in particular with tretinoin and tazarotene; erythema, desquamation, and dryness are common to all generations of retinoids. All adverse events fade away over the duration of treatment. In dry atmospheres in the house or in hot temperatures, a moisturizer should be applied in addition. Adapalene has nearly no phototoxicity compared to tretinoin or tazarotene which is important for treating patients in sunny countries. In young females of childbearing age and who wish to become pregnant, a retinoid should not be chosen because of the risk of teratogenicity (*Fig. 143.18*).

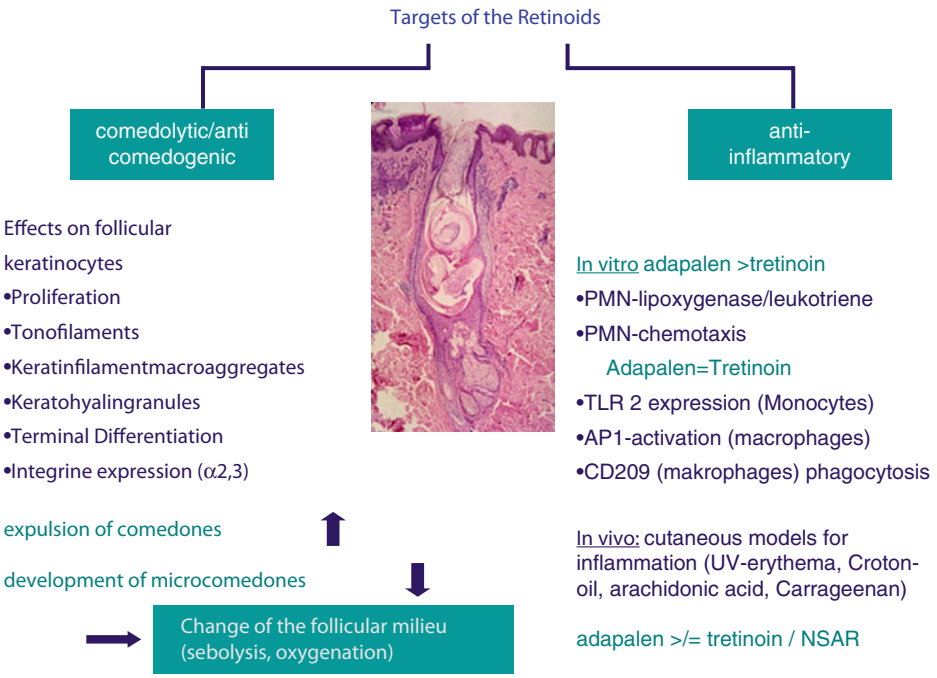


Figure 143.18
Targets for the actions of topical retinoids

Benzoyl-Peroxide

Benzoyl-peroxide is one of the oldest but very effective topical acne drugs introduced already in 1934. It is available in concentrations between 1% and 10% for acne treatment. Controlled studies revealed that a dose of 2.5% is enough for topical treatment in the face. For back and chest, a 5% concentration with more irritation can be applied, which is here better tolerated than in the face. One can use gels, lotions, or washes, the last also as a short contact therapy. As a monotherapy, BPO can be used in mild inflammatory acne, in moderate acne combinations with adapalene in a fixed form, or in sequential applications together with topical antibiotics or retinoids, as has been well documented and evidenced.

The efficacy of BPO is based on its strong antimicrobial potency which is achieved within 2 weeks by reducing *P. acnes* on two log scales from skin samples and in in vitro cultures. It does not allow the development of any resistance of *P. acnes* or staphylococci on the skin. Benzoyl-peroxide is the gold standard of antimicrobial acne treatment. It has only a slight anticomedolytic action by desquamating the upper corneocyte layers at the orifice of the follicular channel, but it is not anticomedogenic.

Depending on the concentration and galenic formulation, one can see a dose-dependent dryness and desquamation of the skin accompanied by burning and redness, which the patient will adapt to over time. Moisturizers will reduce adverse events. Bleaching of hair and clothes can occur and contact sensitization in acne is rare. Benzoyl-peroxide can be used during pregnancy.

In moderate forms in which internal drugs are not applied, as a first step, the combination with adapalene or other retinoids is to be preferred (see above), or the combination in either fixed ones or sequential ones with antibiotics (either erythromycin or clindamycin). Resistances toward topical antibiotics are reduced by these combinations.

For severe forms of acne, BPO can easily be combined with oral antibiotics which lead to an additional antimicrobial effect and a faster onset of therapeutic success. Resistant bacterial strains on the skin under oral antibiotics are reduced. The efficacy of the combination is enhanced and the treatment goal achieved faster.

Antibiotics

Currently, there are two antibiotics which are used most for the topical route: erythromycin and clindamycin. Tetracycline should not be used anymore on the topical way because of high bacterial resistances and phototoxicity. Nadifloxacin is chemically synthesized and belongs to the group of quinolones acting against gram-positive bacteria and gram-negative bacteria. Its use is critically seen because of the possibility of inducing quinolone-resistant staphylococci strains with consequences for negative systemic treatment outcomes.

Both antibiotics erythromycin and clindamycin are macrolides and act via bacteriostatic mechanisms using ribosomal protein synthesis inhibition.

Erythromycin and clindamycin are indicated for the mild papular-pustular acne; however, recent evidence-based guidelines do not recommend these agents as monotherapy but in combination with retinoids, BPO, or AzA. Fixed combinations are available on the market or a sequential use in the morning and the combination partner in the evening. The efficacy is significantly enhanced with reduction of the time course of treatment. A combination with oral antibiotics is obsolete and they should also not be used in comedonal acne. The efficacy of topical erythromycin and clindamycin monotherapy in mild inflammatory acne is evidence based on level 2b.

The local side-effect profile of topical antibiotics is different; on one side, they have a low irritative potential, on the other, they induce resistance in the skin bacterial populations and may even be resorbed and have systemic adverse events. Clindamycin in pregnancy should not be used because of rarely reported colitis events.

Azelaic Acid

Azelaic acid has been available since the beginning of 1980. It is a dicarbonic acid that occurs physiologically in the body. It reduces comedones by repairing the corneocyte dysfunction in the follicle, reducing the increased keratohyalin macroaggregates, and acts by reducing protein synthesis in the pathological proliferating cell. It has an antibacterial effect in reducing the *P. acnes* amount in vitro by one log step. In addition, it is an ROS scavenger and reduces the hyperreactivity of neutrophils. Recent evidence indicates a reduction of certain proinflammatory cytokines. It also restores the postinflammatory hyperpigmentation, similar to retinoids.

AzA is available in creams and gel or lotion in 20% and 15% formulations. It is indicated in comedonal acne and in inflammatory mild acne as a monotherapy. Evidenced studies show a 2b level of similar efficacy when the drug was compared to clindamycin, BPO, or tretinoin. In moderate acne it should be combined with topical antibiotics and retinoids or BPO. It can be well combined with oral

tetracyclines or with oral antiandrogenic drugs. In conglobate acne, a controlled study of minocycline and AzA with oral isotretinoin showed a similar efficacy, however, the long-term outcome was better with isotretinoin. When AzA was used as a maintenance topical treatment, it prevented the relapse to some extent.

The adverse drug profile shows, in particular, a stinging and burning or itching sensation at the beginning of treatment which persists for 10–20 min after application and generally fades within 1–2 weeks. It induces no bacterial resistances and can be used during pregnancy.

Other Topical Treatments

Local abrasives have additional value in comedonal acne, in particular to open the closed comedones to allow topical drugs to better penetrate and to desquamate the comedonal plug.

Topical dapsone is released on the market in the US, however, the efficacy is of minor value compared to other topicals mentioned before.

A large pile of topicals exist from the medico-comeceutical site, but good controlled studies are missing. Except the preparation of retynal ester and glycolic ester or niacinamide and salicylic acid for milder forms of acne and maintenance treatment.

There exist depending on regional availabilities a certain amount of topical formulations which are not proven for any evidence based use.

Systemic Treatment

Oral Antibiotics

Oral antibiotics mostly used in acne are doxycycline, lymecycline, and minocycline. Oral tetracycline hydrochloride is less used today. Other systemic antibiotics such as clindamycin or erythromycin are reserved for special situations. Quinolones, cotrimoxazole, and azithromycin are not well evidence based and should be used only with care and if specific resistances arise or mixed bacterial colonizations are detected on the skin (*Fig. 143.19*).

Tetracyclines, macrolides, and clindamycin inhibit the protein synthesis of bacteria in different ways; cotrimoxazole influences folate metabolism. The number of *P. acnes* is significantly reduced in a short time of 10–14 days.

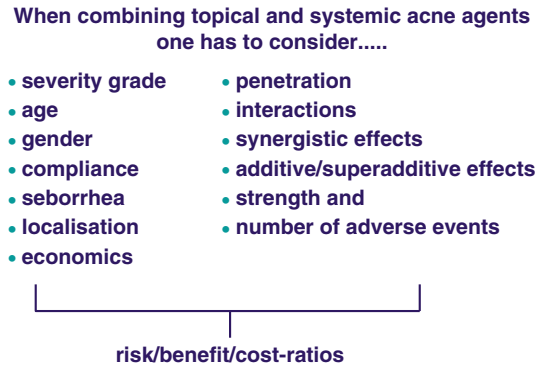


Figure 143.19
Considerations before selecting combination treatments

Today the focus is on the para-antibiotic mechanisms of actions of tetracycline, doxycycline, and minocycline. The inhibition of free fatty acids from the bacterial lipase of *P. acnes* is markedly reduced independent of killing *P. acnes*. In addition, increasing knowledge is being gained over the years in the dose-dependent and direct inhibition of lymphocyte mitosis, inhibition of chemotaxis which reduces pustular formation, and reduced phagocytosis. In particular, the reduced release of proinflammatory cytokines such as IL-1, IL-6, IL8-, and TNF alpha and increase of the anti-inflammatory IL-10 can be measured in vitro and in vivo as well. Furthermore the ROS release is significantly reduced.

Inflammatory moderate acne not responding to topical treatment and severe acne are good examples for evidence-based therapy for oral antibiotics.

A systematic review of all clinical studies between 1962 and 2008 with systemic tetracyclines confirms that no evidence of significant difference exists in terms of efficacy. A clear difference between dose and efficacy could not be figured out. In a double-blind randomized trial with minocycline and combination with and without tazarotene over 3 months and follow-up after another 3 months with oral placebo, minocycline, and tazarotene, a further increase of efficacy could not be found. Therefore, a 3-month oral antibiotic seems to be the appropriate length of application time.

Tetracyclines are usually given in a dosage of 2 × 250 mg/day, doxycycline 100 mg/day, and minocycline 100 mg/day. However, due to the changing view of the use of oral antibiotics as anti-inflammatory drugs, one is trying to apply lower doses. A slow-release minocycline formulation is going to be marketed for acne soon, and a doxycycline retarded formulation is already available on the market for rosacea.

Oral antibiotics can be combined preferentially on the topical route with retinoids and BPO and AzA as well. It significantly increases the efficacy and reduces the time to response >50% of inflammation and reduction of >50% total lesion count.

For the oral route, antibiotics can be combined with oral antiandrogens. In a comparative trial, the relapse rate was higher in the monotherapy arm with antibiotic alone.

The adverse drug profile of oral antibiotics is quite large and of different importance. Resistances of *P. acnes* occur with erythromycin and clindamycin, cross-resistances may come up, and transfer of resistances to other contact persons is possible. Concomitant use of topical BPO is preferable. Increased upper-respiratory infections have been reported.

Main contraindications are liver dysfunctions, hypersensitivity reactions, and renal insufficiency. These reactions are seen in adolescents less often than in patients with late type acne.

Gastrointestinal complaints, diarrhea, and candidiasis are mostly to be seen with tetracyclines. Minocycline can produce hyperpigmentations. Phototoxicity is dose dependent but less often observed with minocycline and doxycycline compared to oxytetracycline. All tetracyclines have the potency of increasing brain pressure.

Hypersensitivity syndrome with LE-like pattern and other autoimmune patterns have been, in particular, reported for minocycline. DRESS syndrome, even in children, exists as single reports with doxycycline and minocycline. Tetracyclines are not indicated in children before the end of dentation because of discoloration of teeth (Fig. 143.20).

Oral Isotretinoin

Oral isotretinoin was first reported as effective in 1971. Because of its teratogenicity it was not followed up longer by Stüttgen, but was then reported to be the most effective drug in conglobate acne by Peck in 1979.

Isotretinoin is the most potent antiacne drug available in particular for the most severe forms.

Isotretinoin is 13-cis retinoic acid, a naturally occurring product in the vitamin A metabolism. It is a monoaromatic retinoid which is chemically modified at the polar end group and the polyene side chain of the original vitamin A. It is related to the all-trans retinoic acid (tretinoin) to which it is under certain conditions converted.

Isotretinoin has multiple mechanisms of action, which are the suppression of the sebaceous gland hyperactivity by increased differentiation and reduced hyperproliferation of sebocytes, normalization of the disturbed keratinization, reduction of the inflammation at the humoral and cellular level, and indirect reduction of the amount of *P. acnes* in the follicle because of a change of the growth condition for the bacterium. In addition, matrix tissue metalloproteinases are normalized. Recent evidence from the lab shows that isotretinoin increases the skin surface levels of neutrophil gelatinase-associated lipocalin important in killing *P. acnes* and defense mechanisms as well as sebocyte apoptosis important in the action of this drug. Recently, a possible antiandrogenic action was discovered. It obviously inhibits the 3-alpha hydroxysteroid oxidation by retinol dehydrogenase which finally leads to reduced amounts of dihydrotestosterone and androstenedione. Both are involved in the activity of the sebocyte function

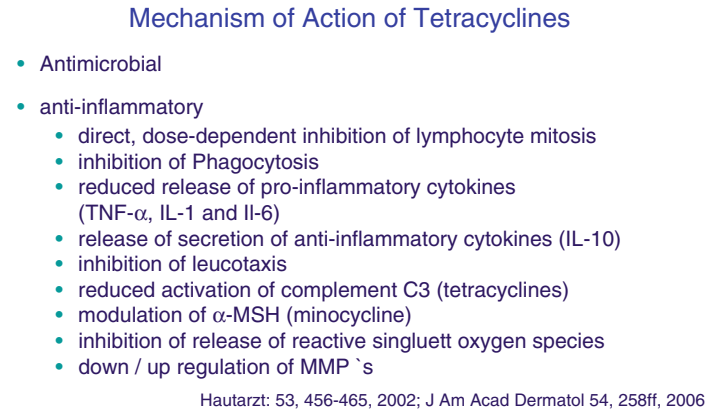


Figure 143.20
Mechanisms of actions of oral tetracyclines – the para-antibiotic anti-inflammatory efficacy

and therefore their reduction leads to a sebosuppressive effect (◉ *Figs. 143.4*, ◉ *143.6*, ◉ *143.7*, ◉ *143.9*, ◉ *143.17*).

Whereas in the past isotretinoin was the drug of first choice in severe recalcitrant nodular and conglobate acne, it was re-ranked by the FDA and the EMEA because of its adverse drug profile, in particular teratogenicity. This means that in those subtypes of acne, first a treatment with oral antibiotics combined with topical basic agents has to be given over 3 months; if this treatment approach is not successful it can be switched to oral isotretinoin. It should also not be given anymore to children under 12 years. The monitoring profile and time schedule of laboratory parameters have been intensified (◉ *Fig. 143.18*).

Isotretinoin is available in 10, 20, and 40-mg capsules. Several generic formulations are available on the market after Roche Comp. has discontinued the production of the original brand Roaccutane/Accutane. However, there is evidence from pharmacological reports that not all of them are of the same efficacy because of minor bioavailability. Eleven out of thirteen generics failed in several tests.

Today the range of doses given is 0.1–1.0 mg/kg bw/day. Usually one starts with 0.5 mg/kg, i.e., 20–40 mg/day, which can be increased to 40–80 mg/day according to the efficacy and side-effect profile, if necessary. There is evidence that a higher dose at the beginning and a cumulative dose of around 120 mg/kg given over a total of 12 months continuously have a lower relapse rate. Relapse rates in general are between 20% and 30% depending on the severity and the age of the patients. Patients respond without tachyphylaxia to a second course of the drug.

Isotretinoin compared to oral antibiotics is more cost effective having less long-term courses of the disease and less relapses.

The adverse drug profile is quite large and consists of mucocutaneous, systemic, and laboratory ones.

Dose-dependent cheilitis, xerosis, and skin fragility and dry nose are the most common skin symptoms. Systemically, myalgias, arthralgias, and headache are frequent and bone toxicity after long-term treatment is a complication; increased triglycerides and cholesterol are less common in adolescents but need to be monitored. The reader is referred to the special references and local regulations in his country.

The most important adverse effect is teratogenicity with craniofacial, cardiovascular, and CNS defects. Strong anticonceptive measurements (double method) and a clear indication in girls >12 years are demanded. Continuous negative pregnancy tests 1 month before treatment, monthly under treatment, and one menstrual cycle after cessation of the drug are necessary. Blood donation is prohibited during treatment and 1 year after.

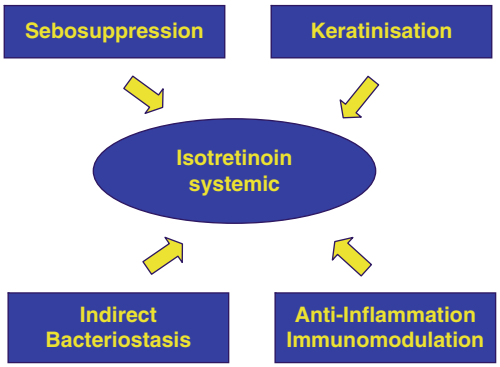


Figure 143.21
Effects of oral isotretinoin in acne

Psychiatric adverse events are critically evaluated over the last 10 years. Any psychiatric disorder, depression, or suicidal ideation is a strong contraindication for isotretinoin prescription. Two large retrospective cohort studies showed that the incidence of an increased risk of depressive mood or suicide attempts is not different in patients under isotretinoin compared to a group with the same severity grade of the disease under oral antibiotics (◉ *Fig. 143.21*).

Hormonal Antiandrogen Therapy

Antiandrogenic hormonal treatment was introduced in the early 1980s when cyproterone acetate and later chlormadinon acetate became available in combination with ethinylestradiol. These hormonal treatments are anticonceptive but in particular dedicated to the treatment of acne and seborrhea.

Acne often starts with adrenarche and the increased amount of circulating adrenal androgens producing hyperseborrhea from the sebaceous gland. Later, the effects from the ovaries and testes follow. Antiandrogenic therapy follows a reduction of circulating free testosterone. A classification of the mechanisms can be made as follows: blockade of the androgen receptor, suppression of ovarian-derived androgens, action on the hypophysis, suppression of the adrenal activity, and finally inhibition of the peripheral androgen metabolism.

The gestagens cyproterone acetate and chlormadinon acetate bind to the progesterone receptor and block the androgen receptor. Gonadotropin secretion is reduced

and consequently the production of androgens from the adrenals and the ovaries. Sexual hormone binding globulin is more available and free circulating testosterone is bound. Another antihormonal pill contains dienogest.

Drospirenone, a derivative of 17-alpha spironolactone, is antiandrogenic, and reduces antimineralocorticoidal efficacy in addition to causing premenstrual perifollicular edema.

Antiandrogenic treatment is foreseen for female patients only. It is indicated in young adolescents with sign of peripheral hyperandrogenism with and without hyperandrogenemia, early signs of the SAHA syndrome (seborrhea, acne, hirsutism, and alopecia), and in females with persisting acne as well as in females with acne and who wish for a hormonal anticonceptive.

Comparing these hormonal treatments the significant efficacy of cyproterone acetate and drospirenone are equivalent. Dienogest and chlormadinon acetate–containing pills are only slightly less effective. Different drugs are available in different countries and therefore all products cannot be mentioned here. Significant treatment effects can be seen on the comedo counts after 6 months, on the seborrhea after 6–9 months, and on hirsutism signs after a year. Monotherapy with antihormonal pills is not recommended. In general, depending on the type of acne, they have to be combined with topical drugs or oral antibiotics or isotretinoin.

Absolute and relative contraindications are, in particular, thrombophilia, chronic venous insufficiency, immobilization, severe obesity, migraine, and liver diseases; however, the individual risk and all other contraindications have to be evaluated with the first prescription by endocrinologic gynecologists.

Other Systemic Treatments

In children with acne and in adults, the use of diaminodisulphone (dapsone) does not have a very good evidence base. It can in certain situations be used as an adjunctive drug.

For oral zinc gluconate, some evidence exists. The use of flutamide is not recommended.

Maintenance Treatment

Acne is a chronic disease and therefore during the course of the disease over more than 5–10 years, long-term treatment is necessary (*Fig. 143.22*). In the center of relapse stands, the microcomedo from which either noninflammatory comedones or inflammatory papules and pustules develop. More than three evidence-based trials (level 2b) have been published in different types of acne in the last 5 years showing that after the interventional treatment phase using an additional course with

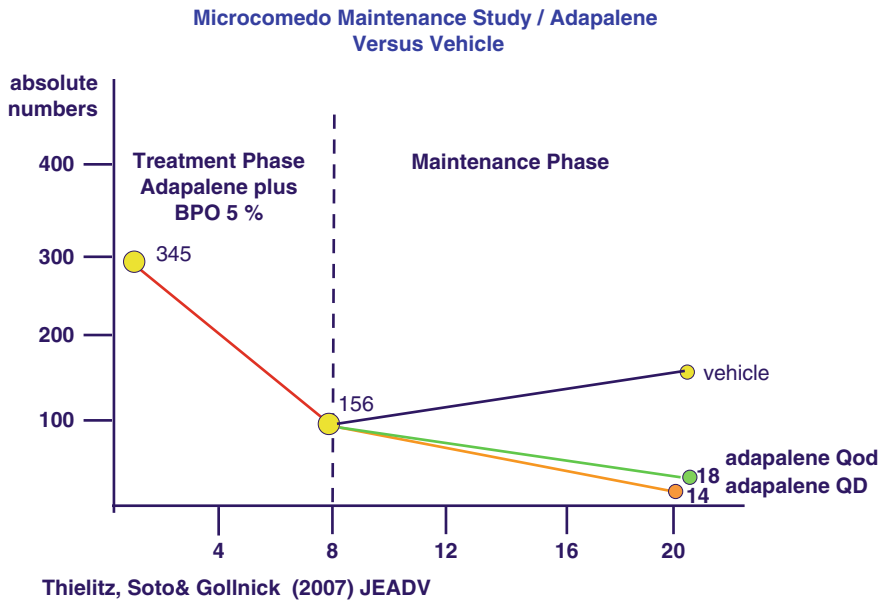


Figure 143.22
Effects of retinoids to prevent development of new microcomedones in maintenance treatment

Facts in Favour for Acne as a Chronic Disease

	Acne	Atopic Dermatitis
basic character	inflammatory	inflammatory
duration	>3 months → > 10–30yrs	>3 months → >5–40yrs
genetic background	yes, long term courses, polygenic	yes, polygenic
age of onset	~10	~1
self limiting	>80% ~3rd life decade	> 80% 2nd or 3rd lifedecade
relapses	frequently	frequently
counselling	intervals / years	intervals / years
medication	continously / intervals	continously / intervals
social impact	yes	yes
psychologic impact	yes	yes
post diseasesequelae		
physical	yes	yes
pychologic	yes	yes

Gollnick,Shear,Finlay(2008)AmJClinDerm 9:279-84

Figure 143.23
Acne as a chronic disease – comparison to atopic dermatitis

monotherapy of a retinoid (adapalene), a relapse could be prevented and even the outcome further improved. This has also been shown in one trial with tazarotene (*Fig. 143.23*).

Adjunctive Treatments

UV light should not be used for the treatment of acne, neither UVA which is comedogenic nor UVB which only produces a camouflage and, on the other hand, contributes to the lifelong cumulative dose of UV.

Visible light, in particular in the blue range (415 nm), can destroy *P. acnes* by activating porphyrins from the bacterium and production of ROS with consecutive destruction of the microbe. A comparative trial with BPO showed similar efficacy (EBM level 2b). Usually three to four applications per week are necessary and after 10 applications the treatment is successful.

Photodynamic therapy with visible light in the range of 550–770 nm plus topical 5-aminolevulinic ester showed, in a placebo-controlled study in mild to moderate acne, a significant improvement (EBM level 2b) and concomitant reduction of seborrhea and of *P. acnes*. Local pain during and shortly after irradiation followed by crusting and some pigmentation are the typical adverse events. It should be mentioned that significant destruction to the gland may harm the patient because the sebaceous gland today is seen as a small endocrinological adjacent organ of the skin which plays a role in the skin homeostasis.

Lasers are increasingly used in active acne with more or less good results depending on the type of laser. Mostly the trials are not well controlled and concomitant treatment is allowed or a conservative treatment arm is missing.

In mild comedonal acne, abrasives with aluminum particles can be used or manual comedo peeling by an experienced cosmetician can be done.

Chemical peeling as an intervention treatment is not established yet; however, it can be used in addition to topical treatments, oral antibiotics, or hormonal antiandrogens, but is contraindicated in parallel to oral isotretinoin. Peelings encompass salicylic acid, glycolic acid, and lactic acid.

Additional substances that can be considered in mild types of acne are retinaldehyde, genistein, and niacinamide.

Scarring

Acne scarring is the most prominent and unwanted outcome of acne. It starts in late puberty and progresses to late-type acne when acne does not cease naturally. It is quite common and because of its different types of scars and distribution it is difficult to treat. Acne scar types are

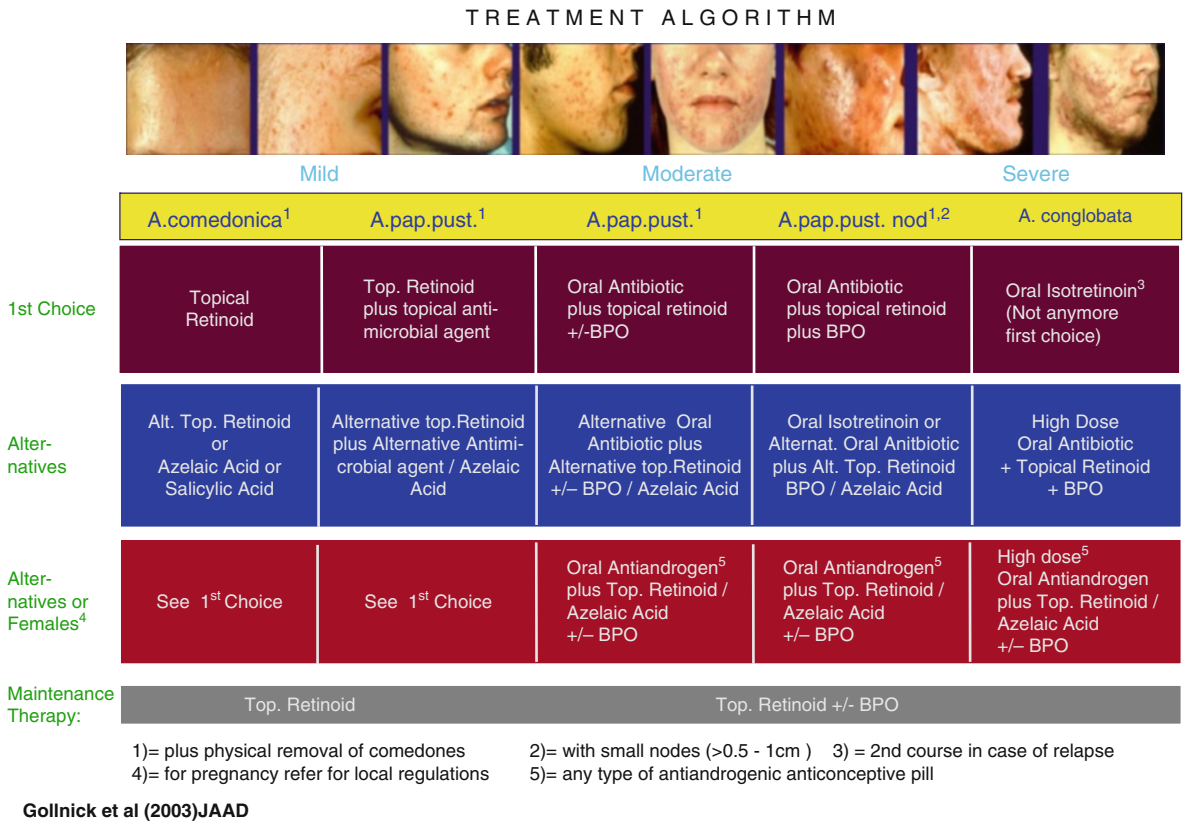


Figure 143.24
Acne treatment algorithm of the Global Alliance for Improvement of outcome in acne treatment

the following: hypertrophic and atrophic scars of which the latter consists of three types: icepick, boxcar, and rolling. All scar types can be mixed. Acne scars can be scored according to the ECCA (echelle d'evaluation clinique des cicatrices d'acne). In general, electrodesiccation, dermabrasion, punch elevation, small excisions or minitransplants, ablative and nonablative lasers, chemical peeling (CROSS technique), and dermafillers are used successfully in the hands of experienced dermatologists. Fractional lasers and microneedling are used in addition (*Fig. 143.24*).

Related Disorders

Hidradenitis Suppurativa

Hidradenitis suppurativa, formerly known as acne inversa, is an acne type of the elderly and therefore will not be discussed here. It is a disease of the terminal hair follicle. The apocrine gland is not the primary focus of the disease. A genetic background is increasingly being discussed. Radical dermatosurgical excisions of the involved areas at the axillas and groins or buttocks are essential. Reduction of smoking and obesity is essential. The use of biologics from the TNF alpha type may initially reduce the inflammatory process in preparation of the following surgery. Isotretinoin is less effective, only very early cases may respond. Acitretin affects positively the keratotic fistulas in the chronic stages.

Rosacea

Rosacea is rare in the second decade of life and a disease of the third and higher decades. However, some cases, in particular with strong family background, can be seen. Those are mostly of the telangiectatic type and have to be evaluated as differential diagnosis to cutaneous and systemic lupus erythematodes and dermatomyositis. Perniones or family related telangiectasia have to be considered.

Gram-negative Folliculitis

Gram-negative folliculitis of the minor or major type is a complication of long-standing oral and/or topical therapy. It is mostly located around the oral and perinasal area. Swabs from the pustules and inner nostrils reveal the pattern of a gram-negative microbial flora. The treatment is difficult and often frustrating. In general, a treatment with topical BPO and AzA alone or combined with oral co-trimoxazole should be used. Oral isotretinoin can be successful. Relapses with all treatments are quite common.

Perioral Dermatitis

Perioral dermatitis was in former times a disease of females in the third decade of life as a result of using excessive moisturizers and thereafter developing pustules around the mouth, which are consecutively treated by topical corticosteroids. Whenever the steroids were stopped a flare-up was observed and again corticosteroids were applied. This mostly led to a vicious cycle. Due to overprotection in skin care of the face with detergents and moisturizers and topical steroids, the disease was also seen around the periorbital area, not only in females but also in males and finally in younger adolescents and even in children in the first decade of life (❯ *Figs. 143.11*, ❯ *143.12*, ❯ *143.22–143.24*).

Most important is to cessation the usage of corticosteroids despite flare-ups. Short oral doxycycline can be used (caveat: not in children before end of dentation) with a local ketoconazole cream in combination with metronidazole (❯ *Figs. 143.10*, ❯ *143.13–143.15*). One crash type therapy is drying by lotio alba and oral doxcycline. Outcome is in general favorable.

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144 Contact Dermatitis: Diagnosis and Therapy

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Introduction

The term contact dermatitis refers to a group of exogenous dermatoses commonly affecting both children and adults, with irritant contact dermatitis (ICD) representing the vast majority of cases (~80%) and allergic contact dermatitis (ACD) accounting for the other large proportion (~20%). The current estimate is that ACD may actually account for as much as 20% of all childhood dermatitis. Patch testing is the gold standard for diagnosing ACD and a number of studies have demonstrated that appropriate epicutaneous patch testing improves quality of life measurements by directing the avoidance of inciting allergens.

In the last decade, multiple international tertiary care centers have reported clinically relevant positive patch test (PPT) reactions being identified in a relatively significant number of pediatric patients with prevalence rates ranging from 21% to 77%. These data sets, combined, serve as a useful guide in the selection of allergens used for patch testing, especially given that many of the same allergens appear across the lists globally. For example, Beattie et al. put forth the "allergens with a positive yield," Wöhrl et al. outlined the "allergen hit list," and Jacob et al. described a guide for screening allergens with the highest yield for patch testing children in particular locales.

Contact allergy (rates of positive responses to contact allergens) varies by referral patterns, regional and social variations in allergen exposure, selection criteria for patch testing, and the allergens tested. It is important to recognize the diagnostic clues, signs and symptoms which alert clinicians to the presence of ACD, especially in children where "eczema" and atopic dermatitis abound.

Pathophysiology

Contact dermatitis is a general term that encompasses adverse cutaneous reactions resulting from contact of the surface of the skin or mucous membrane with an exogenous agent. The type of reactions fall into several categories, namely ICD, ACD, as well as the less common IgE-mediated contact urticaria (CU).

Irritant Contact Dermatitis

Irritant contact dermatitis which accounts for approximately 80% of all contact dermatitis cases is a non-immunologic reaction which does not require prior sensitization or previous chemical exposure. The response is caused by contact with chemicals that directly injure the skin cells by abrasion or irritation**.** While damage to epidermal keratinocytes induces inflammation, it does not activate an immune cascade.

Onset of symptoms ranges from a few minutes to 48 h, appearing in any location on the skin or mucosa. The severity of the reaction is significantly affected by the concentration of the irritating substance and the duration of exposure**.** Patient history and clinical presentation are important clues to the diagnosis of ICD. Classically, acute ICD presents as a localized erythema, corresponding to the area of skin that was exposed to the offending agent; however, blistering and erosions may occur with strong or prolonged exposure. In addition, patients are more likely to complain of burning and pain rather than pruritus. Chronic cases can be more difficult to distinguish from ACD, especially when lichenification complicates the clinical and histopathologic picture. A common example of ICD in childhood is *liplicker dermatitis*, a perioral eruption caused by a series of events, such as irritation from cold, dry weather followed by subsequent lip licking to counteract the dryness leads to dermatitis, a secondary reaction from exposure to drying saliva.

Allergic Contact Dermatitis

It is important to differentiate sensitization (the ability to elicit a PPT, a contact allergy, in an asymptomatic person) from the clinical state of ACD, in which a sensitized person demonstrates a clinical dermatitis related to allergen exposure. Sensitization can occur very early in life. Bruckner et al.

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tested a group of asymptomatic patients and found that 45% of those with PPT reactions were younger than 18 months. The top five allergens were nickel (12.9%), thimerosal (9.4%), methylchloroisothiazolinone/methylisothiazolinone (2.4%), neomycin (1.2%), cobalt (1.2%), and p-tert butylphenol (1.2%). Of note, 7 of the eleven reactions to nickel were in children less than 16.5 months of age, with exposure sources related to jewelry and clothing fasteners. Of note, sensitization does not always correlate with clinical-allergic disease, ACD. For example, in both adults and children PPT reactions to thimerosal and gold frequently have little direct clinical relevance to the contemporaneous dermatitis; the source of these PPTs may be from past exposure to vaccinations and piercings, respectively.

Allergic contact dermatitis refers to a T-cell mediated, type IV, delayed hypersensitivity reaction (clinical-allergic disease) that results when a person is sensitized to an environmental chemical. Small lipophilic chemicals (haptens) with a low molecular weight (<1,000 Da) penetrate the skin and bind with self-proteins forming hapten–protein complexes (complete antigens). Dendritic cells, antigen presenting cells (APC) of the skin, then uptake these hapten–protein complexes and express them on cell surface major histocompatibility complex (MHC) molecules. In the regional lymph nodes, the APC presents the antigen to naïve antigen-specific T-cells, which in turn differentiate into effector T-cells capable of acting on target cells presenting the antigen in the future. This induction phase of sensitization is usually asymptomatic and takes about 10–15 days.

Subsequent exposure to the antigen, which may occur transepidermally or systemically, e.g., intravenously, by inhalation, or by ingestion, leads to the second or elicitation phase. Elicitation corresponds to the clinical picture of ACD, typically characterized by pruritic, erythematous, and edematous patches and plaques in the distribution of the contactant. Further exposure to the allergen may increase the reactivity pattern to one which is more diffuse and disseminated.

Recent studies have reported relevant PPTs in children at a frequency equivalent to those of adult populations. It is vital to note that the majority of children with ACD are not patch tested and that true prevalence rates may be significantly underestimated.

Demographics and Prevalence of Allergic Contact Dermatitis in Children

In the past 5 years, there has been an influx of reports demonstrating a high prevalence of ACD in pediatric patients. The majority come from tertiary care centers, with patients referred by dermatologists and allergists, where rates of PPT reactions are significantly higher (41–83%) than in unselected asymptomatic patients from the general population (13.5–24.5%).

In US-based referral center studies a significant number of tested patients have been Caucasian and Hispanic, with Asians and African Americans making up the minority. This data is primarily indicative of the distribution of patients in referral populations, rather than the prevalence of ACD in specific ethnic groups. These same studies have also shown that with respect to race and gender, the demographics for subjects within analyzed age groups have been similar to one another and to the population of all enrolled subjects. Differences in the prevalence rates of a given allergen among different age groups likely reflect the frequency, type, and length of exposure required to induce sensitization to specific chemicals and the age at exposure.

The true prevalence of contact allergy in both adults and children is largely unknown, because a significant number of affected patients are never patch tested.

Diagnosis

The diagnosis of ACD depends on a careful medical and environmental history, a high index of suspicion for ACD, and confirmation by diagnostic patch testing. In general, ACD presents as eczematous plaques largely localized to the site of allergen exposure. Pruritus is a main feature, in contrast to ICD, where burning is more common. Classic presentations, such as geometric shapes or linear streaks on the extremities, may be associated with plant contact dermatitis especially *Toxicodendron* spp. (e.g., poison ivy, poison oak, and poison sumac). Allergic contact dermatitis may also present in focal skin areas, such as the earlobes, periumbilical area, or eyelids.

Pediatric Patch Testing

Patch testing is the "*gold standard*" for the diagnosis of ACD and should be performed when there is a clinical suspicion and a suggestive history. Currently, there is no approved commercially available patch test screening kit for use in children in the USA. Moreover, in both Europe and the USA, the majority of centers comprehensively screen children with specific allergens selected for individual patients based on the history and clinical distribution

of dermatitis. Comprehensive patch testing is cumbersome and not always available; therefore, a large number of cases of ACD in children do go undetected. Patch test protocols, allergen selection, and interpretation of results are vital to proper diagnosis of ACD and techniques for patch testing children have been discussed in detail.

Special Considerations in Pediatric Patch Testing

Current consensus recommends using the same patch test chemical concentrations as in children as those used in adults. In children older than 12 years (adolescents), testing can basically be performed in the same manner as in adults. While patients as young as 2 years of age have been tested, most clinicians reserve testing for children under the age of 6 to cases in which they have a high index of suspicion, and even then, only selectively test with suspected contact allergens. In addition, the German Contact Dermatitis Research Group (DKG) proposed that patch test allergens be removed after only 24 h in younger children to reduce frequency of irritant reactions, with readings then performed at 48 and 72 h.

One of the intrinsic challenges in pediatric patch testing is the limitation imposed by the anatomically smaller back size of the young child, which translates into a smaller number of allergens applied. The emotional and psychological impact and inherent activity of children means that special attention is required to properly secure the patches. Tools such as games and videos to distract a child during application of the tests are helpful.

Interpretation and the assignment of relevance to PPT results are critical, since there may be only partial concordance between a PPT and ACD. A PPT indicates that an individual has developed sensitization to a chemical allergen, which may or may not be the cause of the patient's contemporaneous dermatitis. Patient history and allergen exposure lists are reviewed to help determine current, past, or uncertain relevance of the test results. Positive patch tests may account for all, part of, or none of the patient's dermatitis. Additionally more than one diagnosis may explain the patient's dermatitis. Allergic contact dermatitis ICD, atopic dermatitis, and CU may co-exist in the same patient. In addition to allergen avoidance, repeat open application use test (ROAT) may be employed by patients to assess improvement after the avoidance of putative allergens. In the ROAT, the patient applies the suspected substance (i.e., lotions, diaper creams, lip balms, etc.) twice daily to the upper arm or posterior auricular area on the same area for a week or more to observe if the dermatitis is reproduced.

Patient counseling is a key component of the patch test protocol, including instruction on keeping patch tests dry by avoiding bathing and sweat-provoking activities, as well as discontinuing the use of potentially interfering medications. For 2 weeks prior to testing, topical corticosteroids or calcineurin inhibitors should not be used in areas where the patches will be applied. Before testing, parents should be educated about the nature and causes of contact dermatitis, realistic expectations for outcome after testing, including allergen avoidance, and the potential for negative patch test results.

Side Effects of Patch Testing

The most common *side effects* of patch testing are the expected local pruritus, burning, and inflammation at the site of application. Pustular and blistering reactions rarely occur, and there is the potential for hypo/hyperpigmentation and persistent reactions. Exacerbations of the patient's presenting dermatitis are to be expected, and while this is usually minimal and bearable, it can serve as an important diagnostic clue in assigning clinical relevance. Information extrapolated from adult studies indicates that the risk of active sensitization to one of the tested allergens is extremely low. Serious adverse effects, such as anaphylactoid reactions to neomycin or bacitracin, are reported to be very rare. Potential benefits of patch testing clearly outweigh the procedure's potential risks and side effects. Use of commercially available patch test chemicals in generally accepted and published concentrations are associated with the fewest side effects.

Important Contact Allergens in Childhood

Table 144.1 lists the predominating 20 pediatric allergens found ubiquitously among patch testing reports from the USA, Canada, Europe (Germany, Italy, UK, France, Spain, Belgium), and Brazil.

Metal Allergens

Nickel is the most prevalent allergen in patch-tested patients of all ages (*Fig. 144.1*).

Nickel contact dermatitis classically presents as an eruption on the earlobes, face, and periumbilical area, as a result of contact with items such as jewelry and clothing

Table 144.1
Important allergens in children (USA, Canada, Europe, Brazil)

Rank	Allergen	Description	Source	Frequent distribution
1.	Nickel	Metal	Jewelry, buckles, snaps, eyeglasses, orthodontics, studs on school chairs, musical instruments, cell phones, keys, coins	Face/eyelids, earlobes, neck, wrists
2.	Cobalt	Metal	Jewelry, buttons/snaps, ceramics, cement, vitamin B12	Earlobes, neckline, umbilical area, hands
3.	Potassium dichromate	Metal	Tanned leather, matches, cement, pigments (green felt), dental implants	Hands, generalized
4.	Gold	Metal	Jewelry and dentistry products	Eyelids, mouth/lips
5.	Neomycin sulfate	Topical antibiotic	Topical antibiotic preparations	Foot, eczema sites, wounds
6.	Bacitracin	Topical antibiotic	Topical antibiotic preparations	Foot, eczema sites, wounds
7.	Tixocortol pivalate	Corticosteroid, especially hydrocortisone	OTC and prescription creams, lotions, and ointments	Any location topical is applied
8.	Sorbitan sesquioleate	Emulsifier	Pharmaceuticals, cosmetics, ointments, creams, lotions	Iatrogenic – sites of dermatitis
9.	Propylene glycol	Solvent/moistening agent	Pharmaceuticals, foods, cosmetics, personal care products	Face, perioral, in sites of dermatitis
10.	Lanolin	Emollient	Emollients, rust-preventative waxes, soaps, lip balms	Hands, any body area with emollient use
11.	Fragrance mix 1	Mix of 8 fragrances	Perfumes, personal care products, household products, soaps, detergents, cleaners, medicaments	Eyelids/face, neck, mouth/lips
12.	*Myroxylon pereirae* (balsam of Peru)	Fragrance/flavorant – tree resin	Perfumes and cosmetics, toothpaste, lozenges, flavoring agent	Eyelids/face, neck, mouth/lips
13.	Colophony	Fragrance/adhesive – distillation product of conifers	Personal care products, adhesive bandages, pine extracts	First aid bandage application sites, eyelids/face
14.	Cocamidopropyl betaine	Detergent, surfactant	Shampoo, liquid soap, bath gel, toothpaste, contact lens solutions, make-up removers	Face, scalp, and neck
15.	p-tert butyl formaldehyde resin	Adhesive and neoprene cement allergen	Leather shoes, athletic shoes, protective sports gear, neoprene	Foot, sports gear distribution
16.	Carbamates	Rubber accelerant	Elastic waistbands, shoes, socks, gloves, swimsuits, tires	Waistline, feet, hands
17.	Thiuram	Rubber accelerant	Elastic waistbands, socks, swimsuits, shoes (soles or insoles), gloves, pesticides	Waistline, feet, hands
18.	Para-phenylene diamine	Hair dye chemical	Hair dye, ''black-henna'' (PPD-adulterated henna) tattoos	Hairline, ears, hands, henna tattoo sites
19.	Disperse dyes (blue 106/124)	Aniline dye	Textiles, diapers, glasses	Peri-axillary bands, diaper edge
20.	Quaternium-15	Preservative-formaldehyde releasing	Cosmetics and topical medications – non-prescription and prescription	Face and body

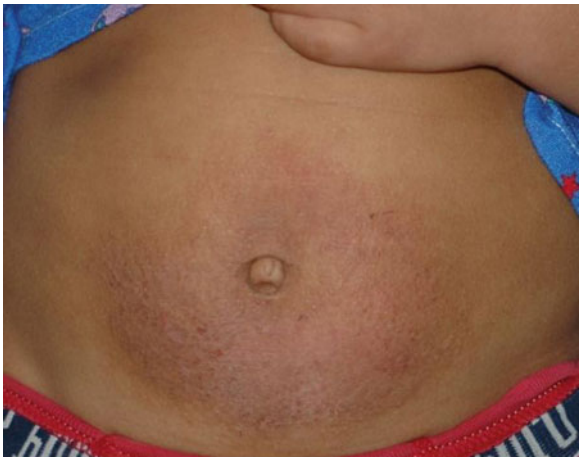

Figure 144.1
Nickel dermatitis

fasteners. With continued exposure and immune stimulation, involvement of distant sites, which are not in direct contact with the metal allergen, is seen in up to 50% of children. This is known as an *id*-reaction, where dermatitis affects sites such as the extremities and the upper trunk, is more diffuse, and may mimic follicular eczema.

Because nickel is so ubiquitous, allergic patients should purchase the commercially available dimethylglyoxime spot test kit to identify if nickel ions are released from metal objects. A few drops of 1% dimethylglyoxime-ammonia (DMG-A) are applied to a cotton tip applicator, which is rubbed against the object in question. If nickel is present at a concentration as low as 1:10,000 on a solid surface and 10 ppm in a liquid, the applicator will turn a pink color. Currently, in the U.S.A., there is an effort to encourage a limitation on the allowable release of nickel to be <0.2 mcg/cm^2/week in products with prolonged skin contact, as has been instituted in Europe since 2004.

Cobalt is also a metal that is naturally found in metal ore with nickel and is often used as an alloy with nickel. It can be used to increase the overall strength of other metals. Sensitizing exposures include jewelry, clothing snaps, buttons and metal objects, as well as cosmetics, joint replacements, ceramics, paints, cement, and multi-vitamins (vitamin B12/cyanocobalamine).

Another frequently sensitizing metal is *gold*, which is found in jewelry and dentistry. PPT reactions to gold do not always correlate with the area of suspected ACD. The most clinically relevant presentations usually include eyelid involvement and stomatitis.

Chromate (potassium dichromate), a metal salt derived from chromium, is the final metal to top the allergen chart. Tanned leather is a potential source of chromate exposure in the household and is found in couches, shoes, boots, belts, and gloves. Vegetable-tanned leather can be used as an alternative. Chromium is also used in dental implants and the metal wire used in orthodontia. Additional sources of chromium include orthopedic prostheses, suture materials (chromated catgut), vitamin supplements, green tattoo ink, some cosmetics with green tints, as well as dyes and pigments, paints, and ceramics.

Antibiotics and Medicament-Associated Allergens

Neomycin sulfate, a topical antibiotic, maintained second place on the list of most common sensitizing allergens for approximately 25 years. More recently, the prevalence has been on a decline, which may be a result of its replacement with other topical antibiotics, such as *bacitracin*. Neomycin, however, is still frequently found in many over-the-counter creams and ointments used for the treatment of superficial wounds or burns, as well as to treat skin, eye, and ear infections. Co-reactivity with other chemically unrelated substances has been noted, likely due to its use in formulations with other antibiotics, antifungals, or corticosteroids.

Corticosteroid allergy is becoming more widely recognized in children. In fact, 0.2–6% of patients have been found to display ACD to one of the five groups of *corticosteroids*. The sensitization potential of group A corticosteroids (e.g., Cortaid, Cortizone-10) is greater than that of the other structural classes [A (5.72%) > B (4.80%) > D1 (3.54%) > D2 (2.13%) > C (1.10%)], likely due to its over-the-counter usage. Tixocortol-21-pivalate is the screening substance for the group A corticosteroids (some investigators also screen with hydrocortisone 1% in alcohol), while budesonide and triamcinolone are the screening substances for class B, and hydrocortisone-17-butyrate for class D2. Cross-reactions between classes are possible, specifically between groups A and D2, as well as between certain corticosteroids in groups B and D2.

Personal Care Product and Vehicle Allergens

Another important and emerging allergen, especially in atopics, is *cocamidopropyl betaine (CAPB)*, a surfactant derived from coconut oil and commonly found in foaming

cleansers, shampoos (used in "no tear" formulations), and soaps. Thus, the distribution of dermatitis often involves the head and neck region. The true sensitizers in CAPB are thought to be the manufacturing contaminants, *amidoamine,* and *3-dimethylaminopropylamine* (DMAPA). Cosmetic manufacturers are being encouraged to remove these impurities, which may reduce sensitization rates from products containing CAPB.

Contact allergy to *fragrances* has also been associated with atopic individuals. One of the chemicals used to screen for fragrance allergy is *balsam of Peru (BOP),* a substance derived from the *Myroxylon pereirae* tree. Children (and adults) are commonly sensitized to this allergen. The distribution of dermatitis has a predilection for the face, neck, and axillae. BOP and/or cross-reacting chemicals can be found in cosmetic products, such as perfumes, lotions, diaper-area care products, and toothpastes and mouthwashes, which may cause contact stomatitis or cheilitis. Moreover, BOP may be found in pharmaceutical preparations, scents, and flavorings for foods, drinks, and liquid medicaments (i.e., tomato, soda, cinnamon, chocolate, and vanilla extract); it also may be associated with hand dermatitis.

Fragrance mix 1 (FM1) is a mixture of eight chemicals (geraniol, cinnamic aldehyde, hydroxycitronellal, cinnamic alcohol, eugenol, isoeugenol, oak moss absolute, and a-amylcinnamic alcohol) that is also used to screen for fragrance allergy. Since the products that incorporate these eight chemicals are similar to those that include BOP, the distribution of the dermatitis may be similar. In fact, some of the fragrances included in FM1 are constituents of BOP, which explains the cross-reactivity that may be seen between these allergens.

Colophony or rosin is a resin that is derived from the distillation products of pine and spruce trees. It is commonly used as an adhesive as well as in eyebrow wax, some cosmetics, and diapers (top-layer pad). There is cross-reactivity among colophony allergic patients with fragrance and BOP, as components of both colophony and BOP occur together in nature, and may be incorporated in fragrances.

Formaldehyde and formaldehyde-releasing preservatives (FRPs) are another group of allergens which may co-sensitize with fragrances due to similar product utilization patterns. Their widely effective antibacterial and antifungal properties have led to the FRPs use as disinfectants and preservatives in a number of products, such as lotions, shampoos, body washes, and even some medicaments (generic corticosteroid creams and permethrin cream). Many manufacturers have replaced formaldehyde with one of the FRPs in biocides and personal hygiene products. These FRPs include: *quaternium-15*, diazolidinyl urea (Germall II), DMDM hydantoin (Glydant), imidazolidinyl urea (Germall), 2-bromo-2-nitropropane-1,3-diol (Bronopol), and tris nitromethane (Tris Nitro). Systemic exposure to formaldehyde is possible through inhalation of cigarette smoke or ingestion of certain foods that metabolize into formic acid (i.e., aspartame-containing foods). These sources of exposure have been reported to stimulate allergic reactions, with some patients improving through dietary avoidance.

Sorbitan sesquioleate is an important emulsifier, specifically a fatty acid ester that is widely used in pharmaceuticals, such as topical corticosteroids, as well as in cosmetics, ointments, creams, and lotions; it has recently been shown to be a relevant contact allergen in the pediatric population. Its association with corticosteroids makes this allergen particularly relevant to those with atopic dermatitis, who often require topical corticosteroids for treatment.

Propylene glycol is a preservative and "wetting agent" found in a wide variety of products, including pharmaceuticals, foods (e.g., "moist" cakes), cosmetics, and personal care products, making allergen avoidance particularly challenging.

Lanolin (wool wax alcohol) is an emollient used for skin barrier protection and repair. It is made from the sebaceous excretions found on sheep's wool. Common sources are topical ointments, moisturizers, and lip balms. Lanolin allergy is difficult to diagnose clinically with "trial and error" product substitution; patch testing is essential.

Rubber Additives

The next category of allergens that commonly affect children is rubber accelerators, to which both *thiuram* and *carbamate* belong, in addition to mercaptobenzothiazole, mercapto mix, and diakylthioureas. These chemicals are major additives in most rubber products as they promote rubber's transformation from a liquid to a solid state. Sources of exposure include athletic shoes (insoles and soles), elastic waistbands, socks, swimwear, toys, pacifiers, cosmetic applicators, and adhesives.

Another allergen utilized with diakylthioureas in neoprene and athletic gear foam is *p-tert-butyl-formaldehyde resin.* The two are commonly referred to as the "neoprene cement" allergens. PTBFR is not a rubber accelerator, rather it is an adhesive that is used in the manufacture of shoes and cars, in addition to being an important component of neoprene and sports gear.

Dye and Textile Allergens

Para-phenylenediamine (PPDA) is a colorless aromatic amine commonly known for its use in permanent hair dye. Para-phenylendiamine acts as a primary intermediate in hair dyes, is oxidized by hydrogen peroxide, and then polymerized to a color within the hair by a coupler such as resorcinol. Although PPDA derivatives are used in screening chemicals for black rubber allergy (e.g., isopropyl-paraphenylenediamine and related chemicals), PPDA itself is a poor detector of sensitization for black rubber allergy and is usually patch test negative.

More recently PPDA is being used in temporary tattoos, where it is mixed with natural henna to make "black henna." Black henna tattoos may induce sensitization with severe bullous reactions and subsequent adverse reactions with hyper- and hypopigmentation and permanent scarring. While PPDA is the most commonly used "permanent hair dye" [limit permissible for hair dyes (<6%)], it has been detected in concentrations well above 15% in henna tattoo preparations. Due to this elevated concentration, adolescents that have become sensitized through "black-henna" tattoos at younger ages are at risk for unusually severe reactions to PPDA containing hair dyes. Potential for systemic reactions is also possible among PPDA-sensitized patients when exposed to cross-reactors, such as benzocaine, hydrochlorothiazide, and sulfonamide medications. Moreover, 25% of those allergic to PPDA can also be reactive to certain dark synthetic clothing, which may contain semi-permanent dyes.

Because of their sensitizing potential, *Disperse blue dyes 106 and 124* are often used to screen for textile dermatitis in pediatric patients. These partially water-soluble dyes easily leach out of fabrics onto the skin with normal wear and repeated washing. Allergic contact dermatitis in children has been reported from sensitization to aniline dyes found in clothes, undergarments, seatbelts, diapers, and eyeglass frames**.** In addition to patch testing with individual dyes, a swatch of the patient's suspect garment may also be directly applied, as many colors can make up a hue**.**

Another cause of textile dermatitis is *formaldehyde*, which may also cause hand and systemic contact dermatitis. In textiles, formaldehyde is used in resins to create "permanent press" or "wrinkle-resistant" clothing, and is associated with dermatitis in regions where clothing rubs against the skin, i.e., body folds. These chemicals are also used in rayon and corduroy, and patients that develop contact allergy to formaldehyde resins in textiles have also developed diffuse nummular eczema or erythroderma due to secondary sensitization from quaternium-15, a FRP.

Treating ACD

The basis of therapy for ACD is the avoidance of the causative agent(s). Once allergens are confirmed and identified through patch testing, patients are educated on allergen substitution, avoidance, and removal from their environment. With these interventions, it may be possible to "cure" dermatitis with a sustained remission.

At times, patch testing fails to identify the inciting agents, especially if multiple chemicals are involved; and in some instances, avoidance alone may not completely clear the ACD. In these cases, topical and/or systemic therapies will be necessary as an adjuvant. Cool, wet compresses are particularly useful in providing symptomatic relief to acutely inflamed skin. In cases of hand dermatitis and in "unavoidable exposures," such as toxicodendron exposure in a woodlands hiker on a trek or in the cases of aeroallergens, physical barrier creams can be utilized. With these, the patients apply the creams before and during the exposure in an effort to avoid absorption of the allergen.

First-line therapy is topical corticosteroids, which albeit effective, may have side effects with prolonged use. A word of caution is that corticosteroids themselves may be allergens or their vehicles may contain allergenic components. Thus, careful screening during patch testing and specific prescription of appropriate formulations is necessary. For atrophy-prone areas, such as the face and intertriginous areas, topical calcineurin inhibitors (TCIs) may need to be substituted. Also of note, ACD to the active ingredients pimecrolimus, and tacrolimus themselves, and to the benzyl alcohol component of pimecrolimus has been reported.

In particular cases, where dermatitis is severe or widespread, involves the mucous membranes, or continues to progress despite the use of topical agents, systemic therapies may be necessary. Oral corticosteroids, used at 1 mg/kg/day, can be effective for acute exacerbations or episodes of ACD. When dermatitis becomes severe and chronic, "steroid sparing" agents should be considered. These include ultraviolet light therapy, cyclosporine, mycophenolate mofetil, methotrexate, and azathioprine.

In conclusion, the most important first step in treating patients with patch test confirmed ACD is avoidance education. A number of resources are available to provide patients with easy-to-read facts on where their specific allergens are found and ways to avoid them. (http://www.contactderm.org/, http://www.truetest.com/, http://www.chemotechnique.se/). Furthermore, many physicians educate their patients on the substitution of safe alternatives by providing them detailed shopping list instructions formulated by software such as the new

Contact Allergen Management Program (CAMP), available to members of the American Contact Dermatitis Society at www.contactderm.org and the list of Alternatives for the 2007 NACDG Standard Screening Tray developed by the American Contact Alternative Group.

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145 Papulosquamous and Related Disorders Including Psoriasis

Eckart Haneke

In this entry, various skin diseases characterized by papules that develop scales are summarized. They differ widely in their etiology.

Psoriasis

Epidemiology

Psoriasis is a frequent disease with about 2–3% prevalence among light-skinned Caucasians, but it is also observed in dark-skinned individuals. Type 1 psoriasis has its first manifestation peak in the second decade and is thus the form mainly found in children. Roughly one-seventh gets the first manifestation before age 10, and more than one quarter before age 15. HLA-Cw6-positive children have earlier manifestation.

Genetics

Family history is usually positive in type 1, and there is an association with HLA-Cw6, B13, B57, and DR7. Molecular genetic investigations have identified seven loci as psoriasis genes, so-called PSORS.

Pathogenesis

Both genetic as well as environmental factors are important for the outbreak of psoriasis. Bacterial infections of the respiratory tract, particularly streptococcal ones, and also various stress situations and drugs may precipitate psoriasis. Inflammation of the dermis and hyperproliferation of the epidermis are the main events. There is a whole lot of cytokines, particularly TNF-α, interleukins 8, 12, 17, and 23, involved in the inflammation, which is mediated by T lymphocytes, monocytes, and granulocytes. The proliferation of the epidermis that normally takes 28 days is accelerated and shortened to 4–7 days.

Clinical Features

Psoriasis is a chronic relapsing, noncontagious and noninfectious, inflammatory, oligogenic multifactorial disease. The latter explains its enormous clinical variability, both morphologically and concerning its unpredictable course and treatment response.

Psoriasis vulgaris, the most frequent type, begins with small red papules that rapidly enlarge to well-circumscribed red plaques often covered with a thick layer of silvery-white scales. The elbows, knees, scalp, os sacrum, and intergluteal cleft, and particularly typical for children is the face (*Fig. 145.1*) and retroauricular fold, are mainly involved. Scalp psoriasis is often characterized by hair ensheathed in a mixture of scales and crusts (tinea asbestina or amiantacea) (*Fig. 145.2*).

Psoriasis guttata is a particular form characterized by acute onset, usually after a streptococcal infection, and widespread, small, drop-sized red lesions with relatively little desquamation (*Fig. 145.3*).

Psoriasis inversa is characterized by lesions mainly in the flexural areas like armpits, inguinal regions, palms, and soles. It is not rare to see diaper dermatitis transform into psoriasis in the genetically susceptible (*Fig. 145.4*).

Erythrodermic psoriasis covers the entire body. Pain, itching, and relatively little desquamation are typical.

Psoriasis pustulosa is also observed in children though less frequently than in adults. In the primary generalized pustular form, innumerable small pustules develop in fiercely red skin and the general condition of the patient is severely impaired. Palmo-plantar pustular psoriasis is very rare in children as is Hallopeau's acrodermatitis continua suppurativa that involves the tips of the digits and nails. Pustular outbreaks may occur during corticosteroid treatment of *P. vulgaris*. Annular lesions with or without visible pustules are the hallmark of erythema annulare centrifugum-like psoriasis.

Psoriasis arthropathica is rare in childhood. When the axial skeleton is involved, HLA B27 is often positive, but rheumatoid serology is usually negative.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_145,

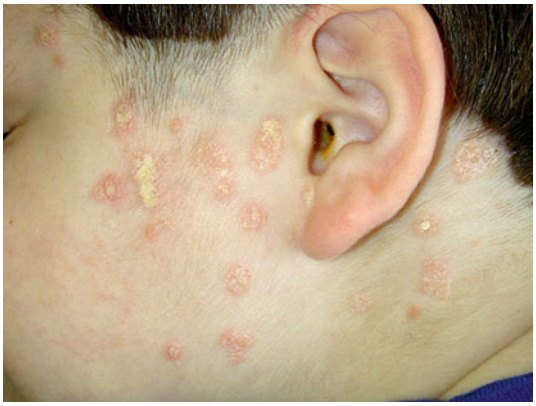

Figure 145.1
Psoriasis of the face in a 6-year-old boy after a respiratory infection

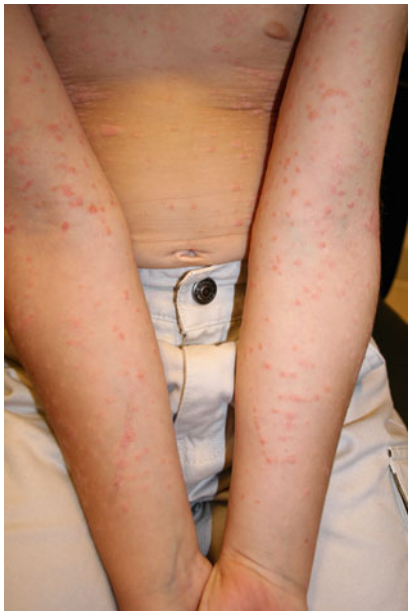

Figure 145.3
Psoriasis guttata with many small red scaly plaques

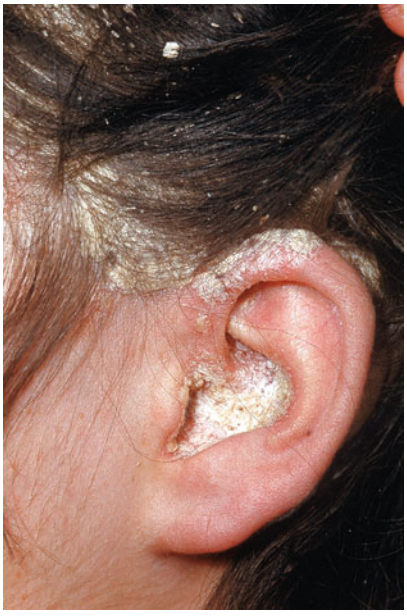

Figure 145.2
Psoriasis of the scalp and ears with thick white scales

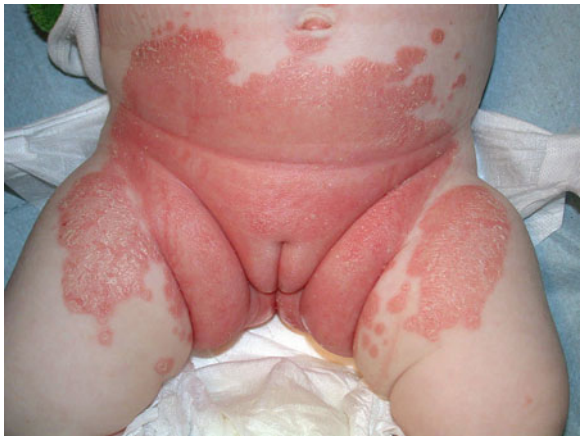

Figure 145.4
Ten-month-old girl with psoriasis of the diaper area that developed after a diaper rash

Diagnostic Measures

Psoriasis is diagnosed clinically. Typical clinical lesions and distribution allow the diagnosis to be made in more than 80% of cases. When a scale is scratched cautiously, first a red shiny moist surface appears as the parakeratosis is easily removed. One more scratch will remove the thinned epidermis over the elongated papillae, and capillary bleeding is seen as Auspitz' phenomenon. Often, nails show pitting, salmon spots, and subungual hyperkeratosis.

Radiographs may help to differentiate psoriatic arthritis from other types, and bone scans allow joint involvement to be detected much earlier.

Histopathology is diagnostic, particularly in pustular forms.

Differential Diagnosis

A variety of mainly exogenous factors may modify the clinical features. Itching and scratching irritate psoriasis and may lead to new lesions (Köbner's phenomenon). Eczematization makes it difficult to make the correct diagnosis, even histologically. Annular lesions resemble tinea corporis, and psoriasis guttata may be confused with pityriasis lichenoides (PL). Slightly erythematous lesions have to be differentiated from pityriasis rosea. Scalp lesions may look like seborrheic eczema, and in fact, they may be associated ("sebopsoriasis"). A diaper rash may be due to *Candida albicans*, but in psoriatic individuals may turn into diaper psoriasis.

Quality of Life in Psoriatic Children

Psoriatic children suffer from decreased self-esteem and often feel severely embarrassed by the skin lesions. This in turn negatively influences the disease.

Any trauma, including sunburns, has to be avoided. Some drugs may worsen psoriasis, e.g., chloroquine, aspirin, and beta blockers.

Treatment

While treating psoriasis, one has to consider that this is a chronic relapsing, often lifelong condition, a fact that has to be explained to the parent and patient. Even though trigger factors such as streptococcal infections play an important role, psoriasis is neither infectious nor contagious. Infant skin is more permeable for drugs, and thus topical treatment often has a systemic effect; this is true for the desired as well as undesired effects. Cytostatics are thus not indicated in childhood.

Topical Therapy

While treating the skin directly, the physician has to consider the age of the patient; the extent, the specific region, and acuity of the lesions; the patient's wishes; and the cost factors. Moisturizing creams and ointments, stress reduction, and light and climatotherapy are valuable adjuncts. Salicylic acid ointments are used to reduce the thick scales. Monotherapy or combinations as well as rotational treatments are helpful.

Topical steroids, usually class 2–3, are most widely prescribed and usually sufficiently efficient. Their drawbacks are skin atrophy, striae, systemic effects, and rebounds. The face and intertriginous areas are treated with milder steroids. Cyclical treatment is intended to reduce side effects.

Anthraline is not popular as it stains skin and clothes but is efficient and virtually without side effects even with decade-long application. Short-contact therapy with 0.1–1% anthraline ointment, with or without addition of salicylic acid, which is removed after 15–60 min, does not produce stains. Anthraline encapsulated in a matrix of semicrystalline monoglycerides (Micanol®) makes application even cleaner.

Coal tar is another staining and smelly, but very efficient, psoriasis drug for long-term use. It is particularly useful for the scalp and in itchy lesions. Refined tar extract (liquor carbonis detergens) is less active, but neither messy nor smelly.

Both anthraline and coal tar may be combined with ultraviolet radiation as the *Goeckerman* or *Ingram regimen*, respectively. The effects achieved with these regimens last much longer than those with topical steroids.

Vitamin D_3 analogs are indicated in mild-to-moderate psoriasis. Calcipotriol is as effective as potent steroids. It can be combined with steroids, usually betamethasone diproprionate or UV radiation. It may burn, particularly in the face of young children, but is otherwise well tolerated. A maximum dose of 50 mg/m^2/week should not be exceeded in order to prevent hypercalcemia.

Tazarotene is a topical retinoid for use in psoriasis. It is approved in adults, but has also shown efficacy in children.

Tacrolimus is a topical immunomodulator. In children above 2 years, 0.03% cream is applied twice daily to the lesions.

Phototherapy

Phototherapy with psoralens plus ultraviolet A or with narrow band UVB is seen critically in children because of its potential carcinogenicity. It is highly efficacious in plaque psoriasis.

Systemic Treatment

In children with guttate psoriasis, the use of penicillin over a week to 10 days for the treatment of streptococcal infection is often helpful.

Systemic treatments are only indicated for severe psoriasis not responding to topical treatments. They suppress

psoriasis; however, their potential side effects may be more serious than the disease.

Methotrexate is given 0.2–0.7 mg/kg/week PO/IM. The dose is elevated by 1.25–5 mg/week until the therapeutic effect is reached and then tapered to an effective maintenance dose.

Biologics have proven to be well tolerated and efficacious in treating psoriasis of adults and can also be applied in children. TNF-α inhibitors are particularly effective. Of the available biologics, etanercept is approved for use in children above 4 years and results in fewer and less severe side effects compared to infliximab in the juvenile rheumatoid arthritis population. Though biologics are generally safe and effective in the pediatric population, serious adverse effects, including infection, have been reported in the literature and have to be considered before beginning treatment with any biologic agent.

Reiter's Disease

Reiter's disease, also called reactive arthritis, is characterized by mucocutaneous, ocular, genitourinary, and joint lesions. There is a genetic background and most patients are HLA B27 positive. It is usually triggered by gastrointestinal infection and is very rare in children (mainly in boys). Conjunctivitis, asymmetric arthritis, dysuria, and psoriasiform skin lesions are the most common presenting symptoms. Mucosal lesions are seen as circinate balanitis or vulvitis. The arthritis is often self-limiting but may sometimes be debilitating. Enthesitis results in painful attachments of tendons and ligaments to the bones. Keratoderma blennorrhagicum is found in 10% of patients. Clear vesicles on an erythematous base develop to macules, papules, and nodules on the soles, toes, palms, scrotum, trunk, and scalp and progress to hyperkeratotic skin, resembling psoriatic lesions.

Treatment aims at removing triggering factors such as infections. Inflammation is controlled with aspirin or nonsteroidal anti-inflammatory agents, e.g., indomethacin 1–2 mg/kg/day PO, divided bid/qid. Acitretin may reduce the dose needed to control arthritic pain. Cutaneous lesions respond to topical steroids. Severe cases require systemic steroids. Alternatives are sulfasalazine, acitretin, cyclosporine, or methotrexate.

Pityriasis Rubra Pilaris Devergie

Pityriasis rubra pilaris is an uncommon condition in children. Familial cases are probably autosomal dominant. Five types were differentiated, of which three (approximately 40%) occur in children and adolescents. The skin is hyperkeratotic with a characteristic orange yellowish color and accentuation of the follicular openings resulting in a goose-skin appearance (◉ *Fig. 145.5*). The lesions gradually enlarge and typically spare some spots – nappes claires (clear spots or islands of sparing) or Leredde's sign. Palms and soles develop yellow hyperkeratoses with painful cracking on a red base (◉ *Fig. 145.6*). The nails may develop hyperkeratosis of the nail bed, become thickened, lose their shine, and shed. Oral mucosal involvement may lead to diffuse white appearance.

The classical infantile type III usually appears within the first 2 years of life. It is often associated with prior fever and involutes spontaneously in a year though protracted cases are known. Circumscribed juvenile PRP (type IV) rarely regresses (◉ *Fig. 145.7*). Atypical juvenile PRP (type V) runs a protracted course.

Basic treatment is application of emollients to reduce hard follicular hyperkeratoses and soften palmar plantar hyperkeratoses. Topical steroids may relieve itching but do not significantly improve the condition. Isotretinoin over several months is approved in adolescents over 12 years, and acitretin is also effective. Azathioprine and methotrexate are rarely indicated.

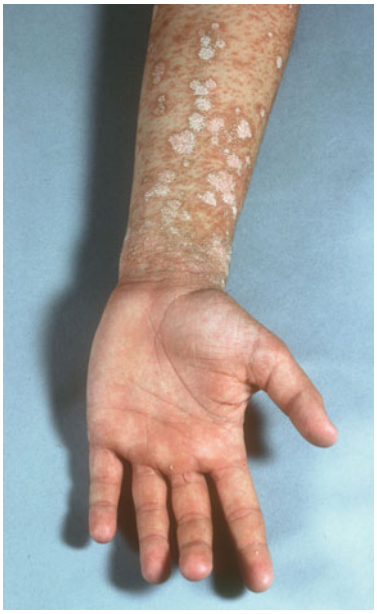

Figure 145.5
Pityriasis rubra pilaris type III showing red follicular papules and diffuse redness with scaling

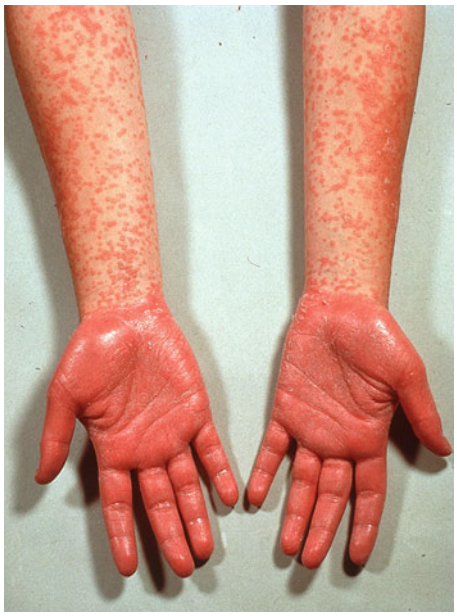

Figure 145.6
Pityriasis rubra pilaris with typical papules on the arms and diffuse hyperkeratosis of the palms on a red base

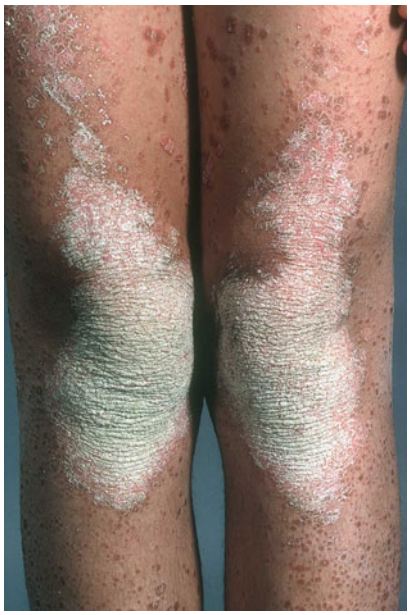

Figure 145.7
Pityriasis rubra pilaris on the knees is clinically similar to plaque psoriasis; however, the scales are much smaller and adhere firmly to the skin

Pityriasis Rosea Gibert

Pityriasis rosea is common in children and young adults and characterized by light-red oval spots with fine scaling and a slightly elevated margin with a collarette. It often begins with prodromal symptoms and usually starts a week later with a single herald patch that remains the largest of the lesions. Typically, the trunk and most proximal parts of the extremities are involved. The long axis of the lesions is oriented along Langer's lines giving a fir tree pattern (*Fig. 145.8*). Atypical involvement of the face and peripheral extremities may be seen in children. Oral lesions include red plaques, dot-like hemorrhages, and shallow ulcers. Human herpes virus types 6 and 7 were recently identified as a cause. A variety of drugs may cause pityriasiform rashes. Pityriasis rosea is not contagious.

The condition is self-limited. Treatment is symptomatic with dry lotions not containing sulfur as this may considerably irritate and eczematize pityriasis rosea. When itching is a dominant feature, an antipuritic lotion or steroid is used.

Lichen Planus

The prevalence of lichen planus in children is not known. There appears to be a link with HLA A3, B8, B16, Bw53, DR1, and DQw1. Association with other autoimmune conditions and hepatitis C infection is not rare.

Lichen planus is characterized by the sporadic appearance of polygonal, purple, pruritic papules with a flat surface and a tiny central depression. The most characteristic localization is the flexural aspect of the wrist

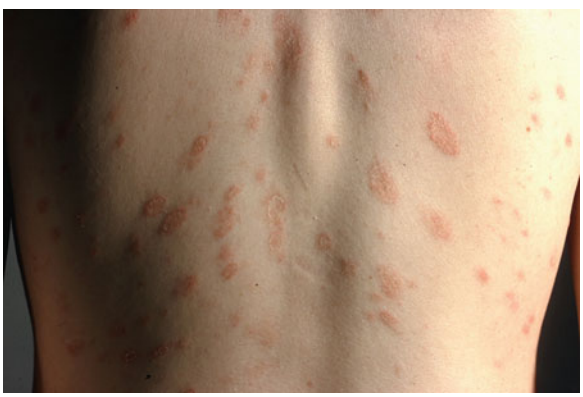

Figure 145.8
Pityriasis rosea with light-red oval lesions, a slightly elevated scaling margin, and arrangement in a fir tree pattern

(Fig. 145.9). The papules tend to accumulate and give the appearance of coarse skin relief. Making the covering keratin layer transparent with a drop of oil often reveals a network of very fine white lines, the Wickham striae. Oral mucosal involvement is usually seen as a net of coarse white lines and is less common in children. Trauma may induce papules, called Köbnerization (Fig. 145.9). The incidence in children is not exactly known.

Morphological variants of lichen planus are atrophic, hypertrophic, erosive, annular, pigmented, follicular, linear, vesiculo-bullous, and actinic (Fig. 145.10).

The etiology of LP is not known. Lichenoid drug reactions are not exceptional.

Histopathology is usually diagnostic.

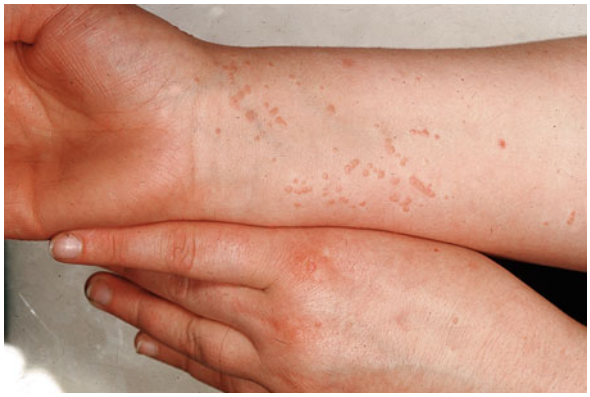

Figure 145.9
Lichen planus on the flexural aspect of the forearm showing flat red papules that are grouped or are in linear arrangement due to Köbnerization

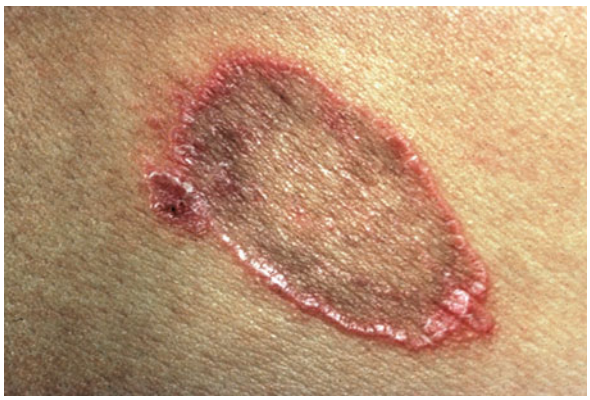

Figure 145.10
Annular lichen planus showing a ring of lichen planus papules around a hyperpigmented center

Most cases are self-limited and resolve within a year. Topical medium-potency steroids relieve itching and reduce skin lesions. Calcineurin inhibitors such as tacrolimus ointment twice daily as well as narrowband ultraviolet B are also effective. Retinoids in low dose over several months were also shown to help in nail LP. Sulfasalazine was effective in a controlled study.

Lichen Nitidus

Lichen nitidus is a granulomatous disease of unknown etiology. Tiny skin-colored papules (Fig. 145.11) arise, usually in a diffuse distribution on areas of the trunk, flexor aspects of the extremities, and dorsal aspects of the hands as well as genitalia of children and adolescents. Nail involvement may lead to longitudinal ridging. Histopathology shows a granuloma with an occasional giant cell that fills and widens a connective tissue papilla.

The condition usually runs an asymptomatic course. No etiological treatment is known, though phototherapy may be effective. Topical and systemic steroids, topical tacrolimus, cetirizine, levamisole, etretinate, acitretin, itraconazole, cyclosporine, topical dinitrochlorobenzene, psoralen plus UV-A light, and narrowband UV-B light have all been tried.

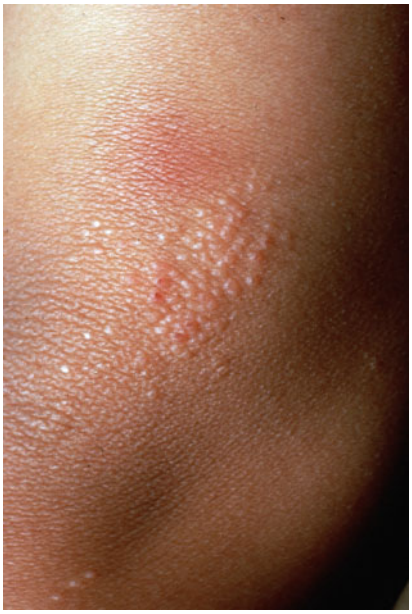

Figure 145.11
Lichen nitidus showing crops of small flesh-colored papules

Lichen Striatus

Lichen striatus is a rare, self-limited disorder mainly affecting children. It is characterized by flat-to-slightly follicular papules arranged in a linear pattern, commonly along Blaschko's lines. The cause is unknown, but an epigenetic mosaicism may be present. Histopathology shows a deep lymphocytic infiltrate mainly around follicles, thus allowing this condition to be differentiated from linear lichen planus. The disease is self-limited. Vitamin D_3 analogs may shorten the course.

Lichen Aureus

This is predominantly a disease of children. Grouped asymptomatic papules, usually as a short line, on a brownish background are characteristic. The legs are most frequently involved and almost every region of the body may show lesions. Histopathologically, there is a lichenoid lymphocytic infiltrate in the upper dermis with epidermotropism and erythrocyte extravasation; the red blood cells are degraded by macrophages and leave hemosiderin, hence the brown color.

Whereas purpuric dermatoses in adults are often due to different drugs, this has not been proven for lichen aureus in children.

No specific therapy is known.

Pityriasis Lichenoides

Pityriasis lichenoides (PL) is usually divided into an acute and a chronic form. Their etiology is unknown though infections – predominantly EBV, Toxplasma gondii, and HIV – have repeatedly been thought to be triggers.

Pityriasis lichenoides et varioliformis acuta (PLEVA) makes up for approximately one-quarter of the PL cases. Crops of symmetrically distributed red papules with a tendency to central hemorrhage and superficial necrosis appear within a short period (◉ *Fig. 145.12*).

Histology shows a so-called lymphocytic vasculitis with hydropic degeneration of the basal keratinocytes, often necrosis of the epidermis and erythrocyte extravasation.

Pityriasis lichenoides chronica (PLC) is more common. Red, sometimes lichenoid, lesions appear often over a course of months to years. They develop a characteristic hourglass scale (◉ *Fig. 145.13*) that can often be removed as a whole confirming the clinical diagnosis. Older and fresh lesions are seen together

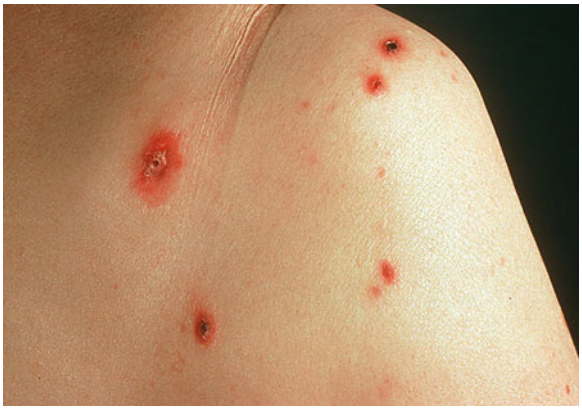

Figure 145.12
Pityriasis lichenoides et varioliformis acuta shows red papules of different sizes, the largest of which exhibits a hemorrhagic center

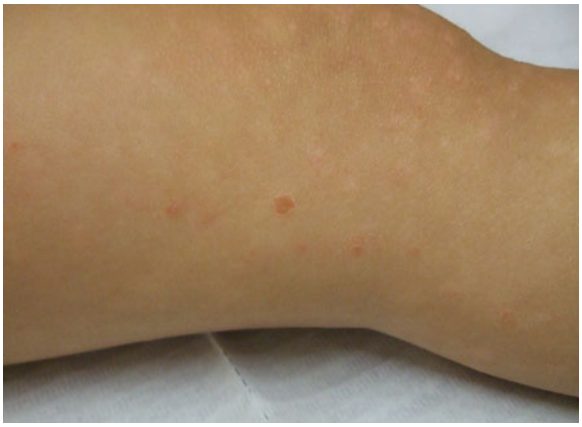

Figure 145.13
Pityriasis lichenoides chronica in a 2-year-old boy. The papules are covered with a single large transparent scale

(◉ *Fig. 145.14*). Histopathology demonstrates a band-like infiltrate and vacuolar degeneration of the basal cells.

There is no evidence-based treatment for PLC or PLEVA. Spontaneous resolution is the rule for PLEVA though waxing and waning is frequently seen in PLC. Narrowband ultraviolet B phototherapy and methotrexate may be tried in children. Tetracycline was effective in some cases; slow tapering maintained resolution and prevented recurrence.

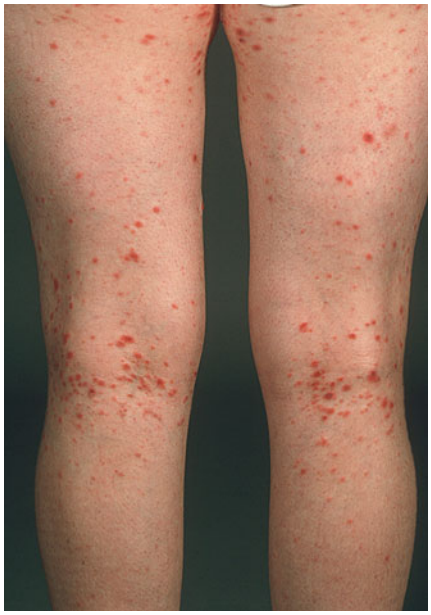

Figure 145.14
Multiple red papules with variable scales are seen in pityriasis lichenoides chronica

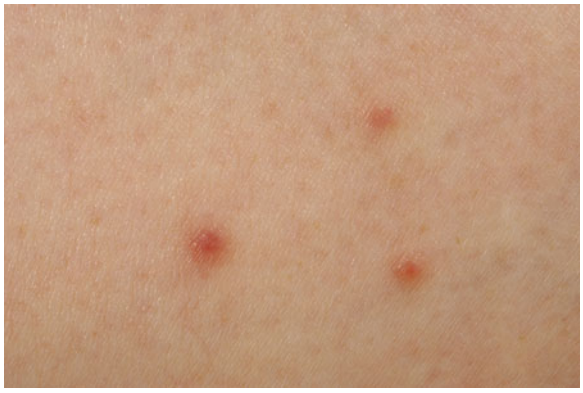

Figure 145.15
Lymphomatoid papulosis of a 14-year-old girl. The papules waxed and waned over many years

Lymphomatoid Papulosis

Crops of small red papules appear mainly on the trunk and extremities (*Fig. 145.15*) that involute within a few weeks but may recur over a period of decades. Pruritus is usually mild. Ulceration may occur giving a clinical picture similar to pityriasis lichenoides (*Fig. 145.16*). The hallmark of lymphomatoid papulosis in histopathology is a large proportion of CD30+ cells.

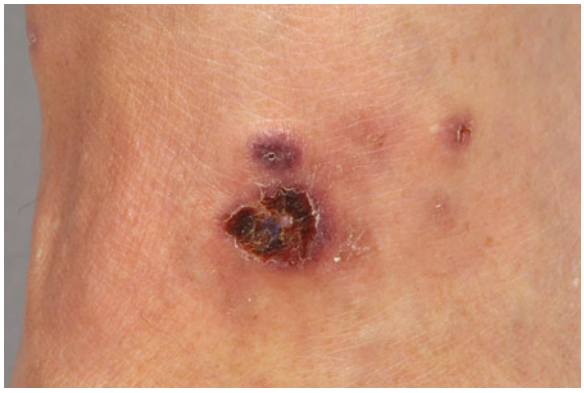

Figure 145.16
Lymphomatoid papulosis with central ulceration

Most cases remain benign, but in 10–20% the condition may be associated with, or progress to a malignant lymphoma.

Treatment is aimed at hastening of lesion resolution. Mid-potent steroids are used for itchy papules. The most consistent lesion suppression is achieved with low-dose methotrexate, but PUVA is also effective.

Parapsoriasis Group

Parapsoriasis is characterized by red scaly patches and plaques and a chronic course. The main localization is the trunk and upper extremities that are not chronically exposed to sunlight. Two types are commonly differentiated: small plaque and large plaque parapsoriasis. The former runs a protracted but benign course whereas the latter is thought to represent a cutaneous T cell lymphoma (mycosis fungoides). Both forms are rare in children. Small plaque parapsoriasis is often also referred to as digitate dermatitis as the lesions often show finger-like extensions, particularly those on the lateral aspects of the trunk. They are light red, finely scaly, smaller than 5 cm. Spontaneous resolution is common. Histopathology shows a mild superficial perivascular infiltrate in which CD4+ cells prevail.

Topical emollients and mild to medium-potency steroids as well as ultraviolet light are efficient.

Granuloma Anulare

Granuloma anulare (GA) is a benign condition of unknown etiology. Both the circumscribed (*Fig. 145.17*) as well as

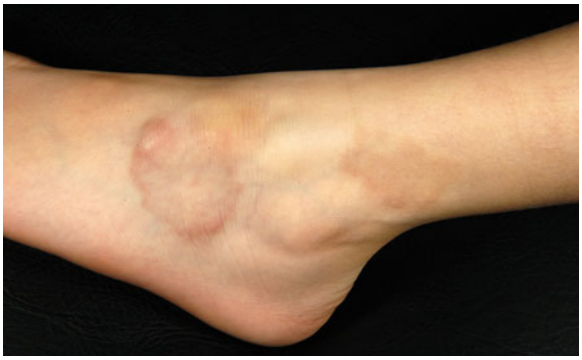

Figure 145.17
Granuloma annulare of the foot and ankle with one deeper area looking like a nodule

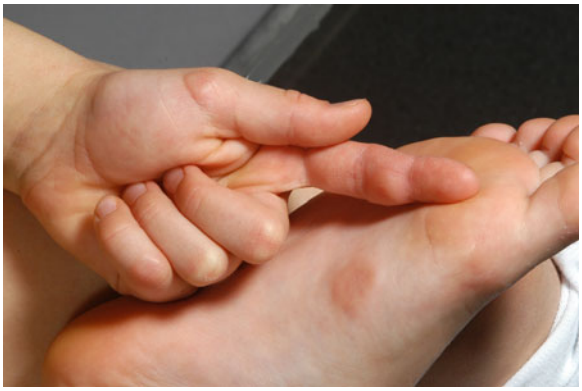

Figure 145.18
Granuloma anulare of the palm and sole. Note the subcutaneous nodule of GA on the palmar aspect of the index finger

the subcutaneous variants (*Fig. 145.18*) are common in childhood, although generalized GA is also seen in children under 10 years of age. Small, relatively hard, red papules with mild scaling develop that often form ring-like lesions with violaceous skin in the center. The subcutaneous form develops deep dermal to subcutaneous nodules up to 10–15 mm in diameter, mainly on the dorsa of the feet, hands, and eyelids. Transepidermal elimination of necrobiotic collagen leads to perforating GA (*Fig. 145.19*). Generalized GA shows up to several hundreds of small skin colored to red nodules. The lesions are usually asymptomatic. Histopathology shows a palisading granuloma with necrobiosis and mucin deposition in the center.

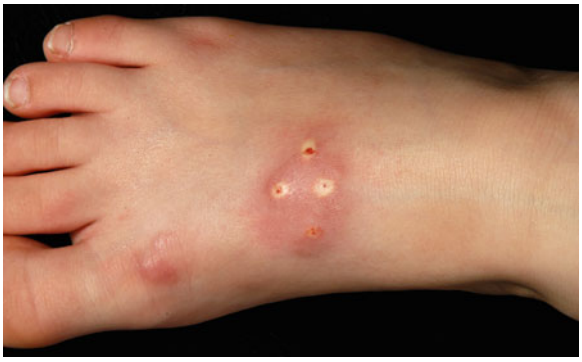

Figure 145.19
Perforating granuloma annulare on the dorsum of the foot

Healing is mostly spontaneous and without sequelae, but generalized GA is often chronic. Potent topical steroids are rarely necessary. Traumatization, such as a biopsy, cryotherapy, or occlusive tape, may induce involution.

Perforating Dermatoses

Several perforating dermatoses are known. They have a perforation of the epidermis with transepidermal elimination of connective tissue in common.

Elastosis Perforans Serpiginosa

This rare condition usually appears in the second decade but may occur in early childhood. Three forms are differentiated: idiopathic, reactive in association with Down, Marfan, Ehlers–Danlos syndrome, osteogenesis imperfecta and pseudoxanthoma elasticum, and drug induced by D-penicillamine. Small papules in a serpiginous or circular arrangement develop, most commonly on the neck. In their center, a plug of degenerated connective tissue emerges. The area they surround slowly enlarges until apparently all pathological material has been extruded and the activity stops. Histology, particularly with elastic stains, is diagnostic showing clumped elastic fibers together with collagen and cellular debris being expulsed through a channel of the overlying epidermis.

Treatment is often not necessary. Spontaneous resolution with mild scarring after some years is the rule. Destructive methods are not indicated. Tazarotene was observed to be helpful and is approved in children older than 12 years.

Reactive Perforating Collagenosis (RPC)

Reactive perforating collagenosis (RPC) is a rare condition, of which an inherited form appearing in infancy or early childhood and an acquired form developing in old age are known. Nodules in frequently traumatized areas, precipitation or aggravation by cold, Köbner phenomenon, and pruritus suggest that superficial trauma plays a role in the pathogenesis.

Small red papules develop after minor trauma and steadily enlarge in the course of a few weeks. The center develops a scab, then a necrosis. Degenerated collagenous material is extruded and the lesion heals slowly with a small scar.

Histopathology shows basophilic collagen that has lost its birefringence. There are no laboratory tests for the inherited form. However, renal function tests should be performed in older children.

There is no established treatment for RPC. Anecdotal reports describe retinoids, allopurinol, doxycycline, and PUVA.

Perforating Folliculitis

Reddish, scaly folliculocentric papules, 2–8 mm in size, develop on hair-bearing surfaces of the arms, thighs, and buttocks, predominantly in youngsters and adults (*Fig. 145.20*). Expression yields keratotic debris, sometimes with a coiled hair. Most cases are idiopathic but diabetes mellitus is a common association. Its relation to Kyrle's disease is not entirely clear.

The diagnosis is confirmed by histopathology demonstrating focal disruption of the wall of the acroinfundibulum; however, serial sections may be necessary to find these changes.

Of all the different treatments tried, ultraviolet B therapy appears to give the most consistent beneficial effects. Reassurance and information about the nature of the disease are necessary.

Kyrle's Disease

This condition, originally called hyperkeratosis follicularis et parafollicularis in cutem penetrans by Kyrle, is characterized by the appearance of relatively large nodules with a central keratotic plug (*Fig. 145.21*). Keratinization probably occurs at the expense of proliferation until no basal layer is left, giving the impression of penetration of the keratin plug into the epidermis.

Kyrle's disease is often associated with chronic renal failure and diabetes mellitus. It is very rare in children. Its relation to perforating folliculitis and perforating reactive collagenosis is not entirely clear.

No specific treatment is known, though therapy of its associated disorders may be beneficial.

Pseudoxanthoma Elasticum (PXE)

Pseudoxanthoma elasticum (PXE) is a rare genetic disorder due to mutations in the ATP-binding cassette

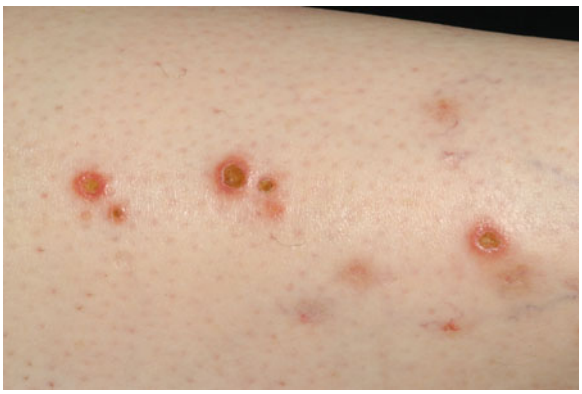

Figure 145.20
Perforating folliculitis shows slowly enlarging nodules that eventually ulcerate centrally forming a crust and heal with a small scar

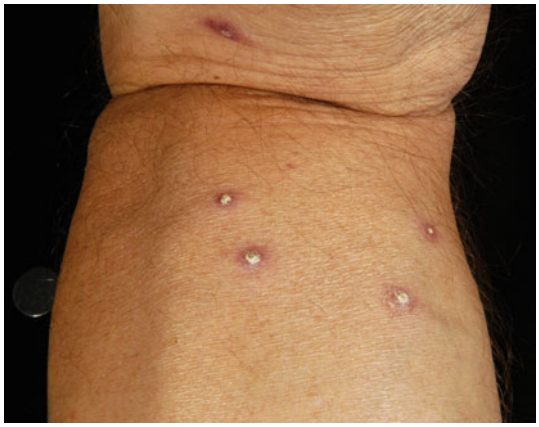

Figure 145.21
Hyperkeratosis follicularis et parafollicularis in cutem penetrans Kyrle in a 17-year-old adolescent showing nodules with massive circumscribed hyperkeratosis

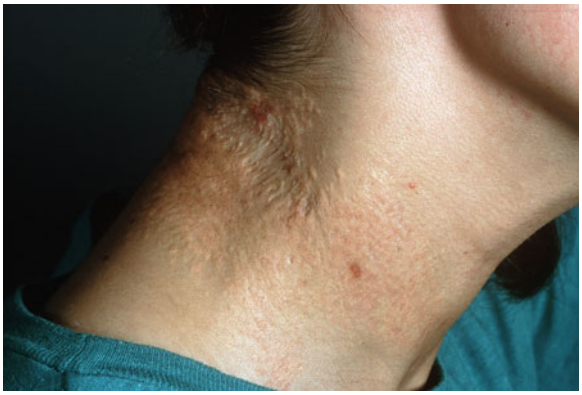

Figure 145.22
Pseudoxanthoma elasticum has its name from the yellow color of the lesions as seen in this 16-year-old boy on the lateral neck

transporter C6 (*ABCC6*) (multidrug resistance-associated protein 6 (*MRP6*) gene), mapped to 16p13.1. It is characterized by fragmentation and calcification of elastic fibers of the skin, eye (Bruch's membrane), and cardiovascular system. Recessive and dominant forms are believed to exist with the latter exhibiting more severe alterations. Skin lesions begin in childhood, but are rarely diagnosed at this time, mainly between 10 and 15 years. In the flexural areas and the lateral neck, flat yellowish papules in linear or reticular arrangement develop (*Fig. 145.22*), and with time, the surrounding skin becomes flaccid looking like a plucked chicken. In the labial mucosa, yellowish spots are seen on stretching it. Systemic signs such as gastrointestinal bleeding, intermittent claudication, and retinal hemorrhage occur later in life though gastric bleeding may occur in the second decade. Elastosis perforans serpiginosa is a relatively common association. Histology shows fragmented and often whorled elastic fibers with calcification.

Regular monitoring is mandatory. Once the lesions have developed, they are irreversible. As high serum lipids aggravate the lesions, diet and exercise are recommended. Calcium intake is to be restricted. Smoking has a deleterious effect. Fundoscopy shows the characteristic angioid streaks representing ruptures of Bruch's membrane. Early laser treatment may prevent ocular complications. Intravitreal injections of antivascular endothelial growth factor have been proposed. Vitamins A, C, E, and zinc are beneficial. Antibiotics prior to surgical and dental interventions are proposed, e.g., amoxicillin 50 mg/kg in children 1 h before.

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146 Hair Disorders and Alopecia

Zbigniew Ruszczak

Hair loss is a common problem in all ethnic groups. It may occur in all parts of the body; however, it more commonly affects the scalp, and the patient presents with major concerns about cosmetic effects, long-term outcome, and perspectives. Physiologically, hair is of minor benefit to humans. However, the psychological effect and disturbances of hair growth are a frequent source of concern to all age groups, including children and adolescents.

Hair is a protein product of follicles having periodic development phases, which assure physiologic regrowth. Hair is distributed everywhere on the body surface except palms, soles, vermilion part of the lips, glans penis and penile shaft, nail bed, and sides of the fingers and toes.

By week 22 of gestation, a developing fetus has all of its hair follicles formed. At this stage of life, there are about five million hair follicles on the body. There are a total of one million on the head, with 100,000 of those follicles residing on the scalp. This is the largest number of hair follicles a human will ever have, since no new hair follicles will be generated anytime during the course of one's life. The density of scalp hair reduces from childhood (1,135 hair per cm^2) to adulthood (615 hair per cm^2) since the scalp expands as we grow.

Each day the scalp hair grows approximately 0.35 mm (6 in. per year), while the scalp sheds approximately 100–150 hair per day, and more with shampooing. Because each follicle passes independently through three stages of growth, the normal process of hair loss is usually unnoticeable. At any one time, approximately 85–90% of scalp follicles are in the anagen phase of hair growth. Follicles remain in this phase for an average of 3 years (range, 2–6 years). The transitional, or catagen, phase of follicular regression follows, usually affecting 2–3% of hair follicles. Finally, the telogen phase occurs, during which 10–15% of hair follicles undergo a rest period of about 3 months. At the conclusion of this phase, the inactive or dead hair is ejected from the skin, leaving a solid, hard, white nodule at its proximal shaft. This cycle is then repeated.

Hair Growth Cycle

Unlike other mammals, human hair growth and shedding are random and not seasonal or cyclical. At any given time, a random number of hair will be in one of the three stages of growth and shedding: anagen, catagen, and telogen.

Anagen

Anagen is the active phase of the hair. The cells in the root of the hair divide rapidly. A new hair is formed and pushes the club hair (a hair that has stopped growing or is no longer in the anagen phase) up the follicle and eventually out.

During this phase, hair grows about 1 cm every 28 days. Scalp hair stays in this active phase of growth for 2–6 years.

Some individuals have difficulty growing their hair beyond a certain length because they have a short active phase of growth. On the other hand, individuals with very long hair have a long active phase of growth. The hair on the arms, legs, eyelashes, and eyebrows have a very short active growth phase of about 30–45 days, explaining why they are so much shorter than scalp hair.

Catagen

The catagen phase is a transitional stage and about 3% of all hair is in this phase at any time. This phase lasts for about 2–3 weeks. Growth stops and the outer root sheath shrinks and attaches to the root of the hair. This is the formation of what is known as club hair.

Telogen

Telogen is the resting phase and usually accounts for 6–8% of all the hair. This phase lasts for about 100 days for hair on the scalp, and longer for hair on the eyebrow, eyelash,

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arm, and leg. During this phase, the hair follicle is completely at rest and the club hair is completely formed. Pulling out a hair in this phase will reveal a solid, hard, dry, white material at the root. About 100–150 telogen hairs are shed normally each day.

A directed history and physical examination usually uncover the etiology of hair loss.

The history should focus on when the hair loss started; whether it was gradual or involved "handfuls" of hair; and if any physical, mental, or emotional stressors occurred within the previous 3–6 months. Determining whether the patient is complaining of hair thinning (i.e., gradually more scalp appears) or hair shedding (i.e., large quantities of hair falling out) may clarify the etiology of hair loss. The pattern of hair loss, especially whether it is focal or diffuse, also may be helpful. The hair-pull test gives a rough estimate of how much hair is being lost. It is done by grasping a small portion of hair and gently applying traction while sliding the fingers along the hair shafts. In the hair-pluck test, approximately 50 hairs are grasped with a hemostat and removed with one motion and prepared for microscopic examination. This test results in a trichogram that assesses the telogen/anagen ratio, but is rarely needed for clinical diagnosis of hair loss.

There is a necessity to distinguish age-related hair loss from hair loss that represents a true disease. There is also a need for patient education, especially when aggressive media is advertising full hair recovery in both medically promising and impossible situations.

The word "alopecia" is the medical term for hair loss. Alopecia does not refer to one specific hair-loss disease – any form of hair loss may be named an alopecia. The word alopecia is Latin, but can be traced to the Greek "alopekia," which itself comes from alopek, meaning "fox." Literally translated, the word alopecia (alopekia) is the term for mange in foxes.

Alopecia is usually categorized into nonscarring and scarring (critical, terminal) alopecia. Scarring alopecia may have either disease-related background or be genetically related and is much less predominant than the nonscarring one.

Hair loss on the scalp could then be classified as focal (areal) or diffuse, and may affect both sexes. This preliminary distinction is the first step in diagnosis and in determining further diagnostic and therapeutic procedures.

Some hair-loss conditions are named "effluvium," which means an outflow. Effluvia characteristically affect different phases of the hair growth cycle. Hair follicles on the scalp do not continuously produce hair. They cycle through a growth stage that can last 2 or more years, and then regress to a resting stage for up to 2 months before starting to grow a new hair fiber again. At any time on a healthy human scalp, about 80–90% of hair follicles grow hair. These active follicles are in what is called the anagen phase. That leaves up to 10–20% of scalp hair follicles in a resting state (telogen).

At birth, the hair is in the actively growing anagen phase, but within the first 2 days of life, there is a physiologic conversion to the telogen phase. Consequently, the majority of hair sheds within the first 4 months of life. This process, known as telogen effluvium of the newborn, usually occurs gradually. Sometimes, however, sudden hair loss is also possible. This physiologic hair loss may lead to either partial or total alopecia. At this stage, parents should be reassured that newborn hair loss is a normal process and that gradual replacement of the first terminal hair is generally completed before the first 6 months of life. This hair convert to vellus hair during the first year of life. At this time, scalp hair growth synchronously takes the typical adult pattern, which is usually achieved by the end of the first year. It is a gradual transition process of hair developing from an unmedullated, lightly pigmented hair having final length of less than 2 cm to terminal, pigmented, medullated, hair of thicker shaft with longer anagen phase and longer length. If light at birth, hair color usually tends to darken with age.

If born premature, newborns are covered with lanugo hair with main distribution over the face, limbs, and trunk. Lanugo hair may also be seen on the limbs and shoulders of full-term, normally developed newborns, but this hair should be shed within the first 2 months of age.

The examination of a child with hair loss should always be preceded by a profound medical history. Examination should include an entire skin inspection, and if indicated, also a microscopic examination of the hair bulb and shaft.

Basically, the scalp examination should distinguish whether the hair loss is diffuse, global, or focal. Diffuse hair loss may be either inherited, if hair development and/or hair follicle density is impaired, or acquired, in cases such as alopecia areata or telogen or anagen effluvium.

Examination of the scalp skin of patients with hair loss should determine if the hair follicles are still present (visible follicular openings), to rule out possible irreversible changes. This has not only diagnostic and therapeutic but also social implications.

It is important to distinguish if the hair loss depends on an abnormal growth rate or if abnormal hair shedding is occurring. The first can be simply evaluated by cutting a shaped hair window in an area that is difficult to manipulate by the patient (usually the back of the scalp) and

observing hair growth over few weeks. Even with underlying hair fragility problems, the hair should achieve a length of approximately 0.5 cm in 2–3 weeks.

If abnormal shedding occurs, hair-pull test mentioned earlier in the chapter and a subsequent microscopic examination is a simple and reproducible method to make correct diagnosis.

In some cases, the possibility of being confronted with a syndrome coexisting with hair loss should be ruled out. Multisystem abnormalities may include ectodermally derived organs (teeth, ears, eyes, central nervous system, and mammary glands), bone, cleft lips, or palate.

Hair-loss disorders are clinically and pathophysiologically divided into two main groups: congenital or acquired.

Acquired hair loss can be then divided into so-called nonscarring (noncicatricial) or scarring (cicatricial) alopecia.

Causes of nonscarring alopecia include alteration of hair growth cycle, structural abnormalities of hair, and inflammatory cutaneous diseases.

Traction alopecia or trichotillomania usually resolves without scarring as well.

Scarring alopecias tend to cause permanent hair loss and are part of disorders destroying hair follicles without regrowth and follow an irreversible course.

Congenital Hair Abnormalities

Congenital Hypotrichosis

Hypotrichosis is the term dermatologists use to describe a condition of reduced or no hair growth. Unlike alopecia, which describes hair loss where formerly there was hair growth, hypotrichosis describes a situation where there was no hair growth right from birth and which usually stays with the patient throughout its life.

The majority of hypotrichoses are due to genetic aberrations or defects of embryonic development. There are a multitude of types of genetic hypotrichoses. Often, affected individuals have other physical or mental problems beyond a lack of hair. Conditions such as Graham–Little syndrome, Ofuji syndrome, cartilage-hair hypoplasia, Jeanselme–Rime hypotrichosis, Marie–Unna hypotrichosis, and metaphyseal chondrodysplasia, among many others, can involve the symptom of hypotrichosis.

Despite a rapidly growing understanding of the human genome, the genetics and biochemistry behind hypotrichoses remain unknown and most conditions involving hypotrichosis have no known treatment.

The most common hypotrichosis will be discussed here also because they are interesting in terms of understanding hair follicle physiology.

Congenital Aplasia

Aplasia cutis congenita, or congenital aplasia, is a developmental defect where, for reasons not understood, the skin does not fully form as an embryo develops. A baby may be born with a patch of skin that is like an open wound or an ulcer. Often this defect occurs at the back of the scalp, at the center of the "whorl pattern" of hair growth. If the defect is small, the skin will grow over, closing the defect and the child is left with a hairless scar (*Fig. 146.1*).

Sometimes this healing process already occurs in utero, and all that can be seen at birth is a patch of scalp where there are no hair follicles. However, if a child is born with a large(er) surface congenital aplasia, it usually requires a surgical intervention and removal of the affected area to achieve the best cosmetic effect. This is especially necessary in cases when the open wound may be a site of potential hemorrhage and infection.

Triangular Alopecia

Triangular alopecia (alopecia triangularis) is a condition similar to congenital aplasia. It is usually apparent from

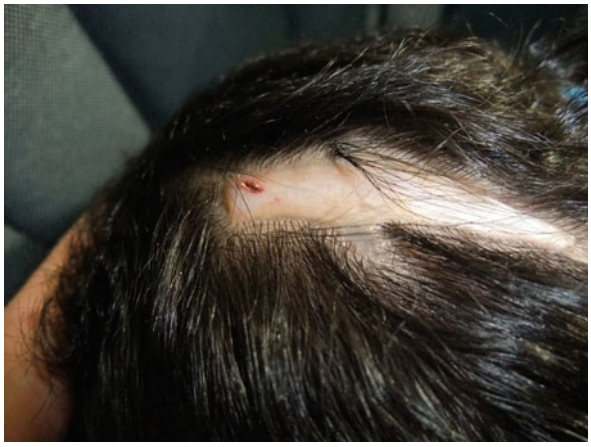

Figure 146.1
Aplasia cutis congenita. Aplasia cutis congenita in a 6-month-old girl. Typical, partially scarified, atrophic lesion of the scalp resulting in alopecia circumscripta

birth and tends to affect a triangular patch of skin and hair above the temples. For unknown reasons, the skin fails to grow hair follicles in this area. Even if children are not born with an open wound, as in the case of aplasia cutis congenita, the long-term result is the same – a bald patch where hair does not grow. To achieve better cosmetic result, the affected area can be surgically removed or implanted with hair follicles taken from elsewhere on the scalp.

Marie–Unna Hypotrichosis

Marie–Unna hypotrichosis is an autosomal-dominant genetic disorder in which scalp hair is sparse or absent at birth, but a coarse hair may grow in early childhood followed by a diffuse hair loss (especially over the vertex) at puberty. The hair morphology shows abnormal cuticula with longitudinal ridding and irregular twisting. Brows, lashes, and body hair are sparse or absent. Anodontia is common; nails are usually not affected. Increased tendency to atopy and early development of atopic dermatitis have been reported.

Congenital Atrichia

Congenital atrichia or papular atrichia is a unique condition in terms of hair-loss pattern. Inheritance (autosomal dominant versus recessive) is not fully clear even if hair-loss disease is postulated to be caused by a single gene defect. Although the condition is generally regarded as a hypotrichosis, it is not strictly so. Children with congenital atrichia can be born with normal, partial, or absent scalp hair. If not present at birth, hair will be successively lost within the first 2 years of life and never regrows. The only exception may be eyelashes, which can remain unchanged throughout the patients' lives.

Teeth and nails of patients with congenital atrichia are usually not affected; however, sweating may be impaired. Psychomotor retardation, ataxia, and hypogonadism have also been described to be associated.

Congenital atrichia has been studied as a model for understanding physiologic hair growth. Normal hair follicles rely on chemical communication between two basic cell types: bulb keratinocytes, which form both the hair papilla and the outer skin epithelium, and modified fibroblasts, the so-called dermal papilla cells. These two cell populations must permanently "talk" to each other through biochemical signals to ensure physiologic hair growth and cycling. The cells must keep close contact to each other to assure the continuation of this process. One cell population cannot exist and grow hair without receiving signals from the other cell population.

The mechanism of congenital atrichia is not fully understood yet. It is postulated that as the hair follicles enter their first resting (telogen) state in early childhood, the two cell types lose the ability to communicate with each other. It seems that when hair follicles go into the resting phase of the hair cycle, the dermal papilla cells lose their ability of reactivating them. Without this stimulation, a new anagen growth phase cannot occur and hair never grows again. While congenital atrichia is genetic, it is a gene defect that can spontaneously develop in some embryos born to parents who do not have such a condition.

Some patients diagnosed with alopecia universalis may, in fact, have congenital atrichia instead.

Some congenital hair shaft abnormalities may be associated with unruly hair.

Uncomable hair

Uncomable hair syndrome and woolly hair are the most prominent members of this group.

Uncomable Hair Syndrome

In uncomable hair syndrome, children have slowly growing silver-blond glossy hair that is disorderly and difficult to style or manage.

Potential explanation for this appearance is premature keratinization of the inner root sheath leading to triangular shape, longitudinal grooving, and expressing features of pili torti.

The condition can express an autosomal dominant pattern; however, in most cases it is sporadic and has no association with other abnormalities.

Uncomable hair syndrome usually improves with age; dietary supplementation has no effect. For better cosmetic effect, gentle hair styling and applying of hair conditioner may be beneficial.

Woolly Hair Syndrome

In woolly hair appearance, the hair is tightly coiled, but it has no typical shape of pili torti. The woolly hair is a styling or hair management problem since the hair becomes bushy or frizzy and the hair length is usually decreased.

Woolly hair is common in children of black African ancestry and usually does not have any specific associations or implications. An autosomal-dominant fashion has been postulated. In some cases, coexistence of woolly hair with enamel hypoplasia, ocular abnormalities, keratosis pilaris, or ichtiosis vulgaris has been reported.

In infants and children of non-African origin, the presence of woolly and curly hair may implicate the need to search for rare syndromes such as tricho-dento-osseous syndrome (small, sharp, widely spaced teeth, frontal bossing, and dolichocephaly) or CHAND syndrome (curly hair, ankyloblepharon, and nail dysplasia).

In general, woolly, curly, or difficult-to-style (comb) hair are common in black African, African-American, or Arabic population, expressing a normal phenomenon that should not be seen as a condition requiring medical intervention.

Hair Loss due to Increased Fragility

Variations in the structure of the hair may provide clues about possible pathologic abnormalities. Microscopic hair examination of snipped hair to find out possible hair shaft abnormalities (i.e., due to impaired keratinization or formation of hair shaft) may be helpful to verify if the hair loss depends on increased hair fragility.

There are multiple conditions where physical damage to the hair fiber results in hair loss. Sometimes this damage occurs to the hair which has been already improperly formed by the hair follicle, which increase the chance of hair loss. These conditions are usually determined by genetic defects. There are also conditions where physical damage of the hair fiber is caused by environmental influence, most often poor or inappropriate hair care.

Hair loss as a result of physical hair defects is very rare if compared to other causes of alopecia, but the most common ones are listed below.

Loose Anagen Hair Syndrome (LAS)

Loose anagen syndrome or loose hair syndrome describes hair that is "loose" and can be easily pulled out of the hair follicle. Loose anagen syndrome is most often first diagnosed in early childhood, more frequently in girls than in boys. Their scalp hair never seems to grow, they only rarely need a haircut, and the hair is usually thin, especially at the back of the scalp. The hair is easily pulled out by rubbing of the head on a pillow and explains why the back of the head is most affected. The remaining hair usually does not grow very long and it can be unruly and difficult to comb and style. Blond-haired children in the age of 2–5 years are most likely to be affected, but loose anagen syndrome can also appear later. The syndrome usually improves with age of its own, if symptoms first occurred in young children, but if symptoms develop in adolescents, the hair loss may be more persistent. The etiology of loose hair syndrome is not clear. It has been demonstrated that the root sheaths that normally surround and protect the hair shaft in the skin are not properly developed in children with loose anagen syndrome. Thus, there is a lack of adhesion between the hair shaft and the root sheath and the hair fiber is poorly anchored in the hair follicle.

The term "loose anagen hair syndrome" is also used for children with easily extracted hair having either patchy unruly hair (LAS type B) or otherwise normal hair with increased shedding in a subject of any age (LAS type A and C).

Genetic predisposition has been postulated, since the condition can occur in families; however, there are also many isolated case reports with no family history. Association with specific disorders has not been reported. There are no known effective treatments for loose anagen syndrome.

Trichorrhexis Nodosa

One of the most common hair shaft defects in children is trichorrhexis nodosa (also called trichonodosis). Trichorrhexis nodosa is a focal defect in the hair fiber. When observed under the microscope, isolated spots along the length of a fiber swelling and/or fracturing and splaying can be seen, giving broken hair a fan-like array. These focal defects develop where there is an absence of cuticle, which leads to exposed cortical fibers.

Causes of trichorrhexis nodosa can be congenital or acquired. Congenital trichorrhexis nodosa is very rare, but some patients have naturally weak hair where the cuticle is not properly produced. Congenital trichorrhexis nodosa is usually hereditary and it first develops in early childhood. Abnormal production of hair fiber that is irregular and brittle can also occur in metabolic disorders such as those involving abnormal urea synthesis, abnormal copper or zinc metabolism, or defective cysteine or sulfur incorporation into hair fiber (trichothiodystrophy). Acquired trichorrhexis nodosa is much more common and develops as a result of excessive hair manipulation and overprocessing. Extensive brushing, hairstyles that put constant stress on the hair, excessive washing, use of

chemicals for dying, and perming may disrupt the cuticle in focal areas along a hair shaft. Trichorrhexis nodosa is particularly seen in those patients whose parents overuse hot combs or permanent waves to style children's hair. Once the cuticle is removed from hair fiber, the hair cortex swiftly breaks down.

Trichorrhexis nodosa present in young children should trigger search for underlining metabolic disorders. One such association is argininosuccinic aciduria in which the absence of enzyme arginosuccinase leads to acidosis, hyperammonemia, low serum arginine, and increased serum and urine citrulline and argininosuccinic acid. In such children, psychomotor retardation, ataxia, and dull brittle hair with trichorrhexis nodosa occur usually at or after the age of 2 years.

Another disorder associated with trichorrhexis nodosa is citrullinemia with deficiency of the enzyme argininosuccinic acid synthetase. Children with this defect present scaly skin eruption and hair fragility. Microscopic hair examination shows trichorrhexis nodosa and pili torti.

Similarly, patients with trichopoliodystrophy (Menke's syndrome), an X-linked defect of MKN or ATP7A gene leading to disorder of copper transport, can have trichorrhexis nodosa and pili torti. In affected children, hair is normal at birth but is replaced by sparse, brittle, depigmented hair of steel wool-like appearance. This led to creation of a specific term for such a condition: a "steely hair syndrome." Associations with mental retardation, and degeneration of bone and connective tissue have been reported. A low serum ceruloplasmin is diagnostic. Copper supplementation is ineffective and most affected children die before the age of 3 years.

Trichorrhexis Invaginata

Trichorrhexis invaginata or "bamboo hair" is clinically present in infants with short, brittle, and sparse hair. Primary defect is an abnormal keratinization of the hair shaft allowing intussusceptions of the fully keratinized and hard distal shaft into incompletely keratinized and soft proximal portion of the shaft. In consequence, fraction of the hair in this particular area is very common. Usually, this hair anomaly is associated with the Netherton's syndrome, an autosomal recessive inherited disorder characterized by a triad of ichthyosis, atopic diathesis, and trichorrhexis invaginata. In Netherton's syndrome there is a mutation of the gene for serine protease inhibitor, SPINK5, localized on chromosome 5q32 has been postulated.

Pili Torti

Pili torti are characterized by short, brittle hair, which is flattered and twisted on its own axis, usually between 90° and 360°. Affected hairs usually fracture through the twist. To diagnose pili torti, there must be multiple twists at irregular intervals throughout the involved hair.

Pili torti can be present in association with or as a part of different hair shaft abnormalities and can be either inherited or acquired. The most prominent of such abnormalities are trichorrhexis nodosa and trichorrhexis invaginata (see above), but this phenomenon can also occur in monilethrix, pseudomonilethrix, or woolly hair. In the classic form of pili torti (so-called Ronchese type), the abnormality is autosomal dominant or can be found as a co-symptom of ectodermal dysplasia complex of findings.

Monilethrix and Pseudomonilethrix

The condition monilethrix makes hair fiber look like a string of beads. Along the length of a hair fiber, there are nodes and constrictions with regular, periodical appearance every 0.7–1.0 mm, making the edge of the fiber undulate. This hair beading weakens the fiber, and patients with monilethrix have diffuse hair loss. The back of the scalp and neck are most frequently affected, leaving the front of the head relatively unchanged. Monilethrix can also affect hair in other regions of the body. Microscopically, the hair fibers can be seen to have lost the cuticle covering over their nodes, while the constrictions keep their cuticle. The brittle hair easily breaks once it is exposed above the skin and, as a result, the fibers rarely grow very long. Monilethrix most often occurs in childhood but adolescents and young adults can also be affected. It is a genetically inherited disease, although different family members may be affected with different severities. This disorder has been linked to the mutations of keratin type-II gene cluster located on chromosome 12q13. The severity of monilethrix can also change with the seasons. It is often worse in winter and improves in summer. Monilethrix may spontaneously improve, although many patients have monilethrix for their entire lives.

Pseudomonilethrix is characterized by irregular beading along the hair shaft – opposite to the regular beading occurring in monilethrix. Current observations suggest that pseudomonilethrix is not a separate entity, but an artificial phenomenon.

Hair Damage due to Physical or Chemical Processes

Traction Alopecia and Trichotillomania

Based on the mechanical action, traction alopecia and trichotillomania are similar. Hair is plucked out of the skin, leaving clear bald patches or diffuse, thin hair. With traction alopecia, the cause may involve tight hat bands, pulling the hair into a tight pony tail, cornrow hair styles, and any other action that pulls on the roots of the hair. If traction alopecia continues for a long time and the same hair region is repeatedly pulled out, the hair follicles in this skin region become cumulatively damaged and they may stop growing hair permanently.

Trichotillomania is a psychiatric impulse control disorder. The mean age of onset is 8 years in boys and 12 years in girls, and it is the most common cause of childhood alopecia. Although any part of the body can be involved, the scalp is the most common. Patients also may eat their own hairs after plucking them (trichophagia), which may result in internal complications such as bowel obstruction. Hair loss often follows a bizarre pattern with incomplete areas of clearing. Often the hair on the scalp is plucked to leave bald patches, but the patient may also focus on the eyelashes, eyebrows, pubic hair, or any other hair-bearing region. There is a consensus that trichotillomania is not a habit like nail biting, but a real psychological problem.

The scalp may appear normal or have areas of erythema and pustule formation. A scalp biopsy may be necessary to rule out other etiologies, because patients may not acknowledge the habit. Because of its psychological nature, the mainstays of treatment are counseling, behavior modification techniques, and hypnosis. Treating trichotillomania is difficult; psychiatrists and psychotherapists can probably help more than dermatologists. Selective serotonin reuptake inhibitors or other antidepressants administered for other obsessive-compulsive disorders may be useful, although there are no specific FDA-approved medications for treatment of trichotillomania. If a more moth-eaten appearance of hair loss is present and no evidence of hair-pulling behavior can be elicited, syphilis should be suspected.

Traction Alopecia

In contrast to trichotillomania, traction alopecia involves unintentional hair loss secondary to grooming styles. It often occurs in patients who wear tight braids (especially "cornrows") that lead to high tension and breakage in the outermost hairs. Traction alopecia also occurs commonly in female athletes who pull their hair tightly in ponytails. It may also be connected with ethnic or religion-dependent way of hairdressing or hair cover. Hair loss usually occurs in the frontal and temporal areas but depends on the hairstyle used. Treatment involves a change in styling techniques. Other hair-growth promoters may be needed in end-stage disease, in which the hair loss can be permanent even if further trauma is avoided (*Fig. 146.2*).

Figure 146.2
Traction alopecia. Diffuse hair loss due to mechanical forces resulting in traction alopecia in a 7-year-old girl

Overprocessing, Cuticle Stripping, and Bubble Hair

Overprocessing the hair is the most common cause of physical hair damage. Perming, straightening, bleaching, and dyeing the hair all involve chemicals that can significantly affect the integrity of hair fiber. Using these approaches too frequently or inappropriately can lead to irreversible damage to the hair fiber. The more the hair fiber is damaged by these processes, the weaker it will be, and the more likely it will be for it to break off.

The hair cuticle is a very strong outer sleeve of highly keratinized cells that overlap each other like fish scales along the length of the hair fiber. The cuticle helps protect the softer inner cortex structure of the hair fiber from damage. The overlapping scales of the cuticle may become damaged and "flake up" if they are exposed to extensive processing. For perms, straighteners, bleaches, and dyes to

work, the cuticle has to be "opened up" so that chemicals can get into the hair cortex and rearrange the chemical bonds in the hair structure, as occurs with perms and straighteners, or to remove or add hair pigment, as occurs with bleaching and dyeing. If substances opening the cuticle are applied for too long, in an unsuitably high concentration, or too frequently, the cuticle may be irreversibly damaged or even completely stripped away. This leads to exposure of the softer cortex to the environment. The cortex with this rough surface is then directly visible, and the hair can look dull, "dry," and frizzy. Chemicals in shampoos, in the water, in air pollution, combined with UV light exposure can all contribute to further damage and weakening of the hair cortex. In consequence, the hair may become so weak that it splits or breaks off completely. More usually, this splitting and breakage occur to older part of the hair, toward the end of the hair fiber. However, if the chemical processing is very severe, it alone can damage the hair fiber, making the fiber at the root severely weakened. If this happens, the hair may break off at the skin surface.

In addition to chemical-induced damage, physical processes can also damage the hair. Aggressive brushing, backcombing, and other grooming techniques that put a lot of physical stress on the hair fiber can cause the cuticle to flake and strip away. Inappropriate use of the hair dryer can also cause hair damage. When patients wash the hair, water may penetrate under the cuticle and into the cortex. If the hair is then made to dry with a high heat, water gets heated up and expands inside the hair producing artificial spaces in the hair fiber. In severe cases, little bubbles develop within the hair shaft leading to so-called bubble hair. These bubbles make the hair much weaker and are likely to break off. Physical damage combined with damaging chemical processes aggravates all negative effects.

Physical and chemical damage to the hair through overprocessing are difficult to treat. The best is to avoid further processing, cut off as much damaged hair as possible, and wait for new, undamaged hair to grow. Some cosmetic treatments advertise to help "glue" damaged hair back together, but the end result is never as good as the original, undamaged hair.

Treatment of primarily defect hair depends on the considered cause of the focal defects. If the hair production is believed to be abnormal, then treatment will focus on the hair follicle and improving the strength of hair fiber. Where the defect is the result of excessive grooming, the obvious action is to reduce the amount of hair manipulation. Patients and parents should be encouraged to stop using brushes, avoid extensive hair styling involving chemical agents, and to use only very mild hair and scalp care products.

Infectious Condition Resulting in Hair Loss

Tinea Capitis (Ringworm)

The traditional term "ringworm" is used to describe a fungal infection (tinea) of the scalp and hair. Tinea is the most common infectious skin condition and can occur anywhere on the body, but if it develops on the scalp (tinea capitis) it may lead to patches of hair loss. It usually begins as a small, isolated area that progressively expands in size, leaving scaly patches of temporary baldness. Depending on the type, the fungus may penetrate into the hair fibers (exotrix or endotrix). In such cases, hair becomes brittle and breaks off easily on the skin surface. The affected areas are often itchy, red, inflamed, expressing scaly patches that may blister and ooze. The areas are usually more prominent (active) around the outside border of the lesions showing a more "normal" skin tone in the center. This phenomenon creates the appearance of a ring, leading to the common name, "ringworm."

The most common fungi causing tinea capitis in the North and South America and in Europe are *Microsporum audouini* and *Trichophyton tonsurans*. Other fungi that may cause tinea capitis include *Trichophyton schoenleinii*, *Trichophyton megninii* in Southern Europe and Africa, and *Trichophyton violaceum* in the Middle East. The fungus *Microsporum gypseum* can also cause tinea capitis in children. This fungus is common in soil and may be transferred to humans by contact with infected animals. A use of Wood's lamp may be helpful to confirm fungal infection, since several types of fungi fluorescents exist. However, the most common fungus in the United States (*Trichophyton tonsurans*) does not fluoresce, lessening the value of this test.

Children often get fungal infections from pets that carry the fungus, and cats in particular are the common carrier. Tinea capitis is a contagious disease. It can be passed from one child to the other by direct skin-to-skin contact and is often seen in siblings. Fungal skin and hair infections can also be transferred through contact with contaminated items such as combs, unwashed clothing, and shower or pool surfaces. The most severe form of tinea capitis is a kerion, a fluctuant, boggy lesion with overlying hair loss (*Figs. 146.3* and *146.4*).

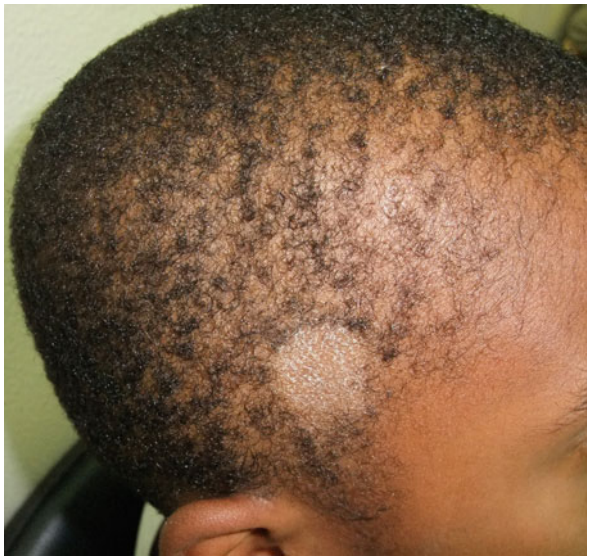

Figure 146.3
Tinea capitis 1 (*Mycosporum canis*). Mycosporum canis infection resulting in focal hair loss in a 7-year-old boy

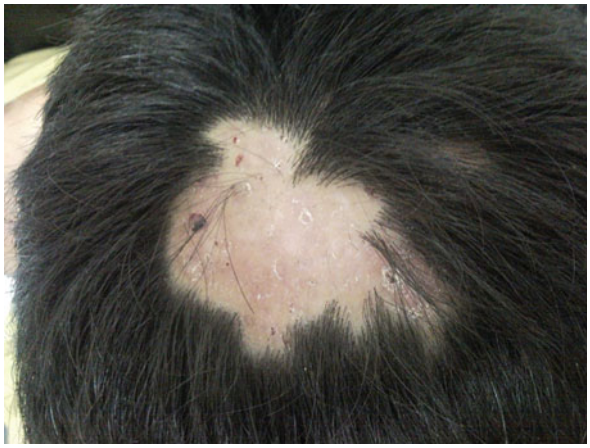

Figure 146.4
Tinea capitis 2. Pseudo-scaring alopecia areata due to deep tinea capitis in a 10-year-old boy. Hair regrowth completely after 12 weeks of terbinafine administration (125 mg per day)

Treatment for tinea capitis varies, depending on the particular fungus involved. Sometimes mild and localized fungal infection may resolve spontaneously. In general, however, tinea capitis needs specific antibiotic/antifungal treatment. In the United States, the most common agent is Griseofulvin. Griseofulvin is very effective due to keratine binding and gradual accumulation in both hair and skin, but it is not effective for treatment of yeast or bacterial infections. More recently, cases of tinea capitis have been showing signs of resistance to Griseofulvin necessitating higher doses and longer courses of treatment. This cheap and easily available drug remains, however, the first-line treatment of deep scalp tinea (kerion) in many regions of the world. As an alternative to Griseofulvin, other antifungal drugs such as Terbinafine, Itraconazole, and Fluconazole can be administrated. It is necessary to stress that systemic antifungal therapy in children, especially in cases of deep and prominent tinea capitis, requires often much longer and consequent administration than it is given by most standard protocols. By short course of treatment, relapses are preprogrammed and development of drug resistance may be the most negative outcome.

Folliculitis

Folliculitis describes a focal inflammation of hair follicles. In the early stages of a folliculitis, the hair fiber may still be present, but as the infection progresses, the hair often falls out. When folliculitis is severe, the inflammatory process can permanently destroy the hair follicles, leaving bald patches (*Figs. 146.5a, b*). There are rare forms of noninfectious hair follicle inflammation caused by oils and greases applied to the skin and clogging up the hair follicles. The most common infectious agent is *Staphylococcus aureus*. The so-called hot tub folliculitis is caused by *Pseudomonas aeruginosa* which grows in inadequately chlorinated water. In some cases, other infectious agents such as viruses, fungi, or yeast may contribute to pathogenesis of folliculitis involving *HSV-I*, *-II*, *and -III*, *Pityrosporum ovale*, and *Trichophyton rubrum*. For mild forms of bacterial or fungi folliculitis, over-the-counter topical antifungal agent or antibiotics such as bacitracin, mycitracin, or neomycin can be used. For more serious infections, oral antibiotics such as tertacyclines or antifungal agents such as griseofulvin or terbinafine are necessary.

Piedra

Piedra (*Trichomycosis nodularis*, piedra means stone in Spanish) is a condition where the hair fibers are infected by a fungus. The visible indicator of a piedra infection is development of hard perifollicular nodules (stone-like folliculitis). The nodules are a concretion of hyphae and

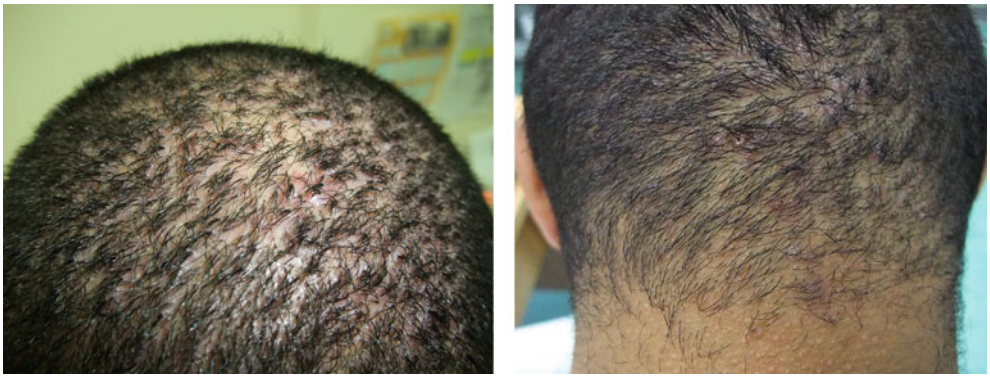

Figure 146.5
Chronic folliculitis (a and b). Chronic, scarifying folliculitis in a 14-year-old male patient with bush-like hire growth

fruiting bodies of the fungus, known as an ascostroma, from which the fungal spores are released. Two basic types of piedra have been described: black piedra and white piedra, referring to the color of the nodules formed around the hair fiber. The agent of black piedra is the fungus *Piedra iahortae* and is mostly found in tropical countries. The white piedra is due to *Trichosporon beigelii* and is common in Europe and North and Southern America.

The infection may affect hair of the scalp, body, and genital areas. Usually the infection is relatively benign. However, when the infection is severe, the fungus weakens the hair fiber, making it easy to break off, resulting in a patchy – diffuse hair loss. Treatment generally involves shaving off affected areas or a topical application of salicylic acid. White piedra is resistant to azole-based antifungals, but this category of treatments is effective for black piedra. Systemic therapy with terbinafine is usually very effective.

Seborrheic Dermatitis

Seborrheic dermatitis is not an infectious disease, but it can involve infection. Seborrheic dermatitis is, in many cases, one of the first of skin conditions seen in children and can involve temporary hair loss if the dermatitis is located on the scalp or other terminal-haired skin areas. The dermatitis presents as scaly, sometimes oily, inflamed skin that can be itchy or even painful to touch. In this inflammatory condition, the sebaceous glands produce a very rich form of sebum, which contains less free fatty acids and squalene, but increased amounts of triglycerides and cholesterol. Androgen steroids are considered to be a stimulating factor, and times of hormone fluctuation, such as during puberty, can activate the onset of seborrheic dermatitis. Seborrheic dermatitis can also be observed in some newborns, and maternal androgens that pass from the mother to the child across the placenta are considered to be involved.

Rich sebum production in seborrheic dermatitis can trigger the proliferation of skin flora. Yeast *Pityrosporon ovale* (also known as *Malassezia furfur*) has been shown to increase in numbers with the intensity of seborrheic dermatitis. Although this inflammation is not specifically directed at the hair follicle, hair growth can be adversely affected and seborrheic dermatitis may nonspecifically cause diffuse hair loss. This hair loss is reversible and hair fully regrows when inflammation dissolves. Although seborrheic dermatitis can involve a proliferation of years, it is important to stress that seborrheic dermatitis is not infectious (*Figs. 146.6a, b*).

There are several treatments for seborrheic dermatitis. The simplest treatment involves the use of medicated shampoos to suppress growth of involved microorganisms and control the skin proliferation and scaling. Shampoos for seborrheic dermatitis may contain sulfur, selenium sulfide, zinc pyrithione, tar, salicylic acid, or oil of Cade and have been available for many years. Azole-based shampoos (Ketoconazole) are very effective and have been recently made available over the counter in many countries. Other medicated shampoos may contain fluconazole. In some more severe cases, systemic antibiotics may be necessary to control the skin bacterial flora and reduce the inflammation.

Hair loss that may occur in severe cases of seborrheic dermatitis resolves and the hairs fully regrow as the inflammatory process is cured.

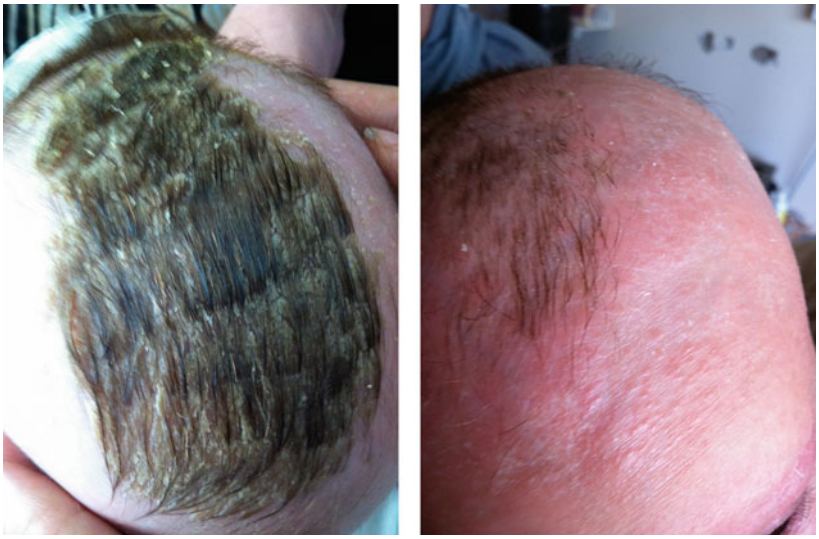

Figure 146.6
Seborrheic dermatitis (a and b). Hair loss associated to seborrheic dermatitis in a newborn with combined immunodefficiency

Noninfectious Hair Loss

Alopecia Areata

Alopecia areata (AA) is an autoimmune disease that presents as nonscarring hair loss and occurs in populations worldwide. The exact pathogenesis of the disease remains to be clarified. It is a common disease encountered by dermatologists, with a frequency ranging from 0.7% to 3.8%. In the United States, AA was estimated to occur in 0.1–0.2% of the general population, with a lifetime risk of 1.7%. AA can affect any hair-bearing area. It often presents as well-demarcated patches of nonscarring alopecia on skin of overtly normal appearance. The presence of AA is often associated with a higher frequency of other autoimmune diseases. Controversially, there may also be increased psychiatric morbidity in patients with AA.

Approximately 60% of patients with AA express their first patch before 20 years of age and pediatric cases constitute approximately 20% of all patients with AA. Although some AA features are known poor prognostic signs, the course of the disease is unpredictable and the response to treatment can be variable.

A history of allergy has been reported in 10–30% of cases with alopecia areata, but this association remains still unclear. In large studies, immunologic abnormalities, especially thyroid disorders, were found in approximately 10% of the patients with alopecia areata showing the main association with Hashimoto's autoimmune thyreoiditis. Recently, it has been postulated that all patients presenting with alopecia areata should obtain an ultrasensitive thyroid-stimulating hormone (TSH) assay and be tested for the presence of antithyroid antibodies.

Alopecia areata has been found to be present in 1.3–9% of the patients with Down's syndrome, but this association still remains unexplained.

Despite extensive studies and many interesting hypothesis, the pathogenesis of alopecia areata remains a puzzle. Without any doubt, several pathophysiological mechanisms and factors include autoimmune phenomena, and lymphocytotoxic phenomena triggering cytokine secretion may be involved. The role of specific cytokines has been recently discussed, but these phenomena are probably secondary and the initial factor still need to be discover.

In immunohistochemical and clinical studies, the role of viruses, especially CMV, activated T-lymphocytes attacking the hair follicle, keratinocytes and melanocytes, dysfunction of dermal papilla components, together with genetic predisposition (up to 47% of cases has been reported in identical twins) has been postulated.

Psychiatric studies suggest that the presence of alopecia areata may be associated with generalized anxiety disorders or depressions. The latter fact can be also explained by the great social impact of partial or total hair loss in any age groups, especially in children.

Lesions of alopecia areata can occur on any hair-bearing area of the body, but it affects the scalp in approximately 90% of cases. Typically, they appear suddenly overnight or within several days. The hair loss can present as single delimited patches (most common), multiple patches, or extensive, large-surface hair loss.

Based on the morphology of the lesion and involved skin area, the disease can be clinically classified as follows:

- Patchy AA, in which there is a partial, localized loss of scalp hair (*Fig. 146.7*)
- Alopecia totalis (AT), in which 100% of scalp hair is lost
- Alopecia universalis (AU), in which there is a 100% loss of all scalp and body hair. Approximately 5% of cases of patchy alopecia may progress to AT/AU.

The pattern of hair loss observed in alopecia areata can differ, showing reticular patches of hair loss, ophiasis type (band-like hair loss in parieto-temporo-occipital area), ophiasis inversus – a very rare band-like hair loss in the fronto-parieto-temporal region, and a diffuse thinning over part or all of the scalp.

The ophiasis pattern of alopecia areata begins as a hairless spot unilaterally or bilaterally located supraauricular at the posterior scalp and rarely on the anterior aspect of the scalp. This alopecia type occurs in approximately 5% of the children and is believed to have a poor prognosis.

Alopecia totalis is characterized by the loss of entire scalp hair and may develop in about 5% of patients with partial alopecia. Slow progress of partial alopecia into alopecia totalis is more common in children than in adults (*Fig. 146.8*).

Complete or almost complete hair loss of any localization (scalp, eyebrows, eyelashes, and genital area) occurs in alopecia universalis and may occur with or without prodromic appearance of alopecia areata.

Recently, another variant of acute diffuse and total alopecia has been described in larger series of patients showing similar characteristics. This new variant is characterized by its rapid progression of confluent alopecia patches and extensive skin involvement. Even if the onset and progression of the disease may be rapid, the prognosis is considered to be favorable.

In the classic form, alopecia areata lesions are well demarcated, round, or oval, complete bald patches with smooth and shiny surface. Hair follicle openings are present and are better visible under the dermatoscope. The skin within the patch appears normal, sometimes with a slightly peachy or reddened color. One of the common findings seen at the border of alopecia patches is "exclamation mark hair" – short hair tapered proximally and wider distally. In active disease, the hair-pull test may be positive if performed at the periphery of lesions.

Initial hair regrowth, whether spontaneous or induced by treatment, is typically non- or hypopigmented, but the color usually returns with time. The disease is frequently asymptomatic, although a few patients report pruritus, burning sensations, or pain before hair loss begins. The use of dermatoscopy or videodermoscopy with a magnification of 20–70 times may be a valuable, noninvasive tool in equivocal alopecia areata cases. Microscopic examination of the hair shafts of hair from the edge of lesions, particularly exclamation mark hairs, may reveal subtle defects in the structure and cuticle.

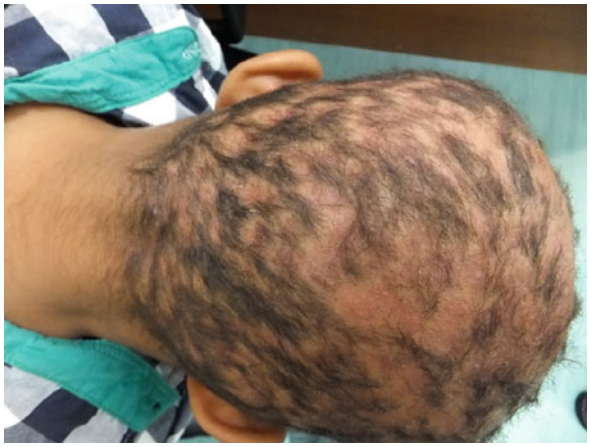

Figure 146.7
Alopecia areata. Alopecia areata in a 12-year-old boy

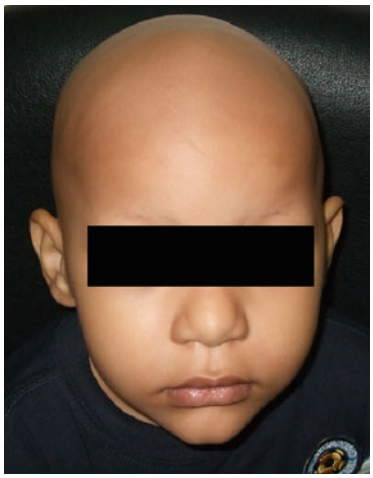

Figure 146.8
Alopecia totalis, hair loss all over the body

Nails changes are seen in 10–20% of children with alopecia areata. The most characteristic nail abnormality is a grid-like, fine stippling appearing in either vertical or horizontal rows, similar to changes seen in psoriasis. Other nail changes such as opacification, proximal shedding, and longitudinal ridging or more severe dystrophies seem to appear more common in patients with alopecia totalis and alopecia universalis.

The sudden hair loss and its unpredictable course seen in alopecia areata make this to be a challenge for both patients and their families and psychological support is usually required.

Only few therapies for alopecia areata have been comprehensively evaluated in randomized controlled trials. The lack of good evidence-based data for therapeutic approaches is a challenge to the dermatologist in choosing the most suitable treatment. Since there is no causal therapy of alopecia areata, the recommended regimens are designated to control the condition in the best possible manner.

It is important to stress that any therapeutic trial should be given for not less than 3–6 months since the scalp hair grows slow. Both patients and parents need to be educated about this issue.

In children, the most common therapy of alopecia areata is topical administration of potent steroids (class II steroids) without or with time-limited occlusion. Class I ultrapotent steroids can be used only in intermitted pulse regimens to avoid local skin atrophy and potential systemic effects of drug absorption.

Knowing that a high percentage of children with alopecia areata may demonstrate spontaneous hair regrowth, some physicians do not initiate any therapeutic action and instruct both patients and parents to wait for such spontaneous remission without initiating topical steroid administration as described above.

In general, however, patients with alopecia areata should be referred to a dermatologist for further evaluation and initiation of treatment.

For children less than 10 years of age, midpotent topical corticosteroid is the first line of therapy. Recently, a combination of 5% minoxidil solution twice daily and topical class II steroid has been recommended. If there is no response after 6 months, short-contact local sensitization (immunotherapy) with anthralin can be tried. For patients older than 10 years of age with less than 50% scalp involvement, intralesional injections of triamcinolone acetonide have been recently discussed by US authors to be the first option for therapy. However, if there is no improvement after 6 months, potent topical corticosteroid under occlusion at night and short-contact anthralin sensitization usually together with twice a day application of 5% topical minoxidil are also postulated.

For children and adolescents with more than 50% scalp involvement, topical immunotherapy with DPCP is the treatment of choice (*Fig. 146.9*).

Other therapy regimens include phototherapy and photochemotherapy, excimer laser application in limited patchy alopecia areata, infrared irradiation as monotherapy

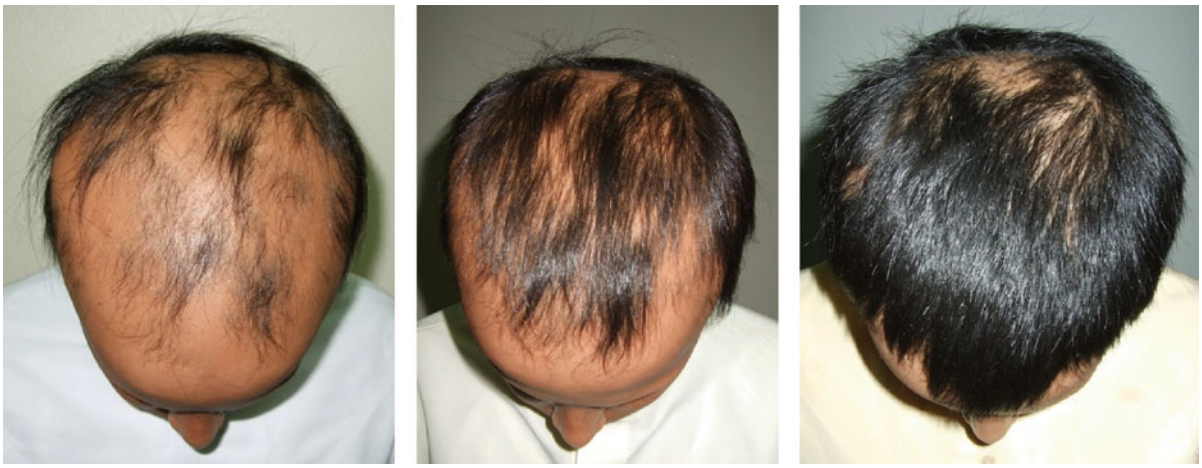

Figure 146.9
Alopecia areata in an adolescent male patient. Progress of hair regrowth under short-contact local sensitization with DPCP

or adjunctive to conventional therapy have been demonstrated to have some success. Photodynamic therapy is considered to be ineffective.

Several reports of the use of modern biologics, including etanercept, efalizumab, adalimumab, and infliximab failed to show any improvement in patients with alopecia areata. Similarly, the use of topical calcineurin inhibitors was found to be unsuccessful.

It has to be stressed that in any of the therapy regimens discussed above, only adjuvant acting drug should be considered. Concomitant use of irritating or immunomodulatory agents such as anthralin and DPCP with drugs having anti-inflammatory properties such as corticosteroids leads to mutual neutralization of the biologic activity of both individual components, making such combinations ineffective.

In many cases of alopecia areata, the common-sense perception "more brings more" is not applicable.

Despite intensive clinical trials, there is still a need of developing treatment options for refractory cases and for specific hair-bearing sites (i.e., eyelashes) where treatment choices are almost nonexistent. Because of higher psychiatric morbidity in patients with alopecia areata, psychosocial support is a valuable tool and should be an integral part of any management plan.

Telogen Effluvium

Telogen effluvium occurs when the normal balance of hair in growth and rest phases is disrupted, and the telogen phase predominates. Disproportionate shedding leads to a decrease in the total number of hair. All anatomical localizations may be equally involved. The hair-pluck test usually shows up to 50% of hair being in a telogen phase (normally 10–15%). These results can, however, vary in persons with advanced disease. Majority of patients with telogen effluvium have had inciting events in the 3–4 months before starting hair loss (*Figs. 146.10a, b*).

In patients with telogen effluvium, the physician should always look for causes of severe metabolic derangements, toxic exposures, or underlying chemotherapy. No specific treatment for hair loss is required because normal hair regrowth usually occurs with time. Lack of significant historical events and a delay in regrowth should raise suspicion for syphilitic-derived alopecia.

Three basic pathways can be seen in patients with telogen effluvium:

1. An environmental insult that "shocks" the growing hair follicles, arresting hair in its telogen phase. This results in an increase in hair shedding and a diffuse thinning of hair on the scalp. This form of telogen alopecia can develop rapidly with the onset 1–4 months after the shock incident. If the trigger is short lived, the hair follicles may quickly return to their growing state. This form of telogen effluvium usually lasts less than 6 months and the affected individuals regain their normal scalp hair density again within a year.
2. The second form of telogen effluvium develops more slowly and persists longer, most likely as a response to a persisting trigger factor. The hair follicles may not all of a sudden shed their hair fibers and enter a resting

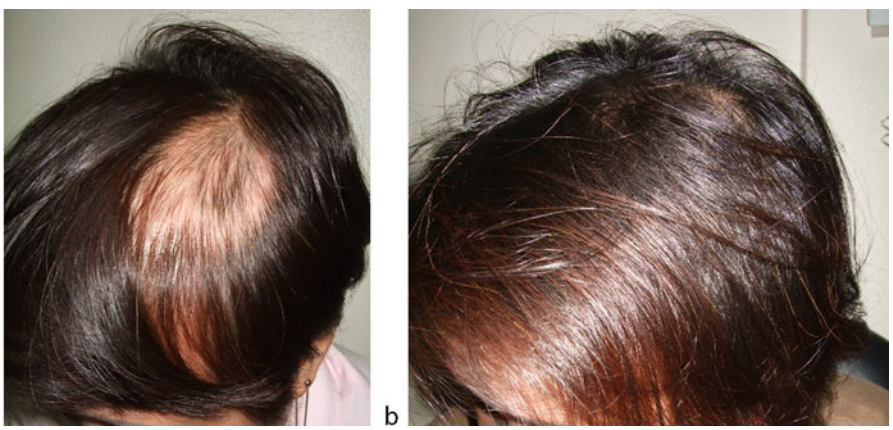

Figure 146.10
Telogen effluvium. (a) Telogen effluvium in a young girl to the stress resulting from surgery. (b) Full and quick hair regrowth without specific treatment after recovery from the surgery

telogen state. Instead, the follicles enter their resting phase but do not return to a new anagen hair-growing state and stay arrested in the telogen phase. This results in a gradual accumulation of telogen hair follicle state and progressive decrease of anagen hair follicles with growing hair. In this form of telogen effluvium, slow thinning of the scalp hair is more prominent than the noticeable hair shedding.

3. In a third type of telogen effluvium, the hair follicles do not stay in a resting state but rather cycle through truncated growth cycles. When this happens, the individual experiences thin scalp hair and persistent shedding of short, thin hair fibers.

Telogen effluvium can occur in many different conditions. In children, the most important causes of telogen hair loss include physiologic effluvium of the newborn, early stages of androgenic alopecia, injury or stress, high and prolonged fever (i.e., by malaria), severe infection, severe chronic illnesses or major surgeries, severe psychological stress, hypothyroidism and other endocrinopathies, and severe malnutrition. Telogen effluvium can also occur after treatment with specific antikeratinizing agents (i.e., etretinate), anticoagulants (especially heparin), antithyroid agents, or anticonvulsants and hormones.

There is no effective treatment for telogen effluvium. Educating both patients and parents about the pathophysiology of the disorder and its favorable prognosis can avoid unnecessary stress and desperate seeking for immediate solution.

However, adolescents predisposed to androgenic alopecia may show incomplete hair regrowth with the pattern typical for androgenic alopecia.

Anagen Effluvium

Anagen effluvium is a diffuse hair loss (similar to telogen effluvium), but it develops rapidly and affected individuals can lose all their hair. The main cause of anagen effluvium is the therapy with cytostatic drugs for cancer or those who have ingested toxic products. All these substances suppress cell proliferation. Cytostatic cancer drugs and various toxins and poisons arrest or inhibit the proliferation of cells in the hair follicles. The most common cytotoxic drugs causing telogen effluvium are cyclophosphamide, methotrexate, 6-mercaptopurine, doxorubicine, and vincristine. Anagen effluvium can be also associated with colchicine, toxic levels of boric acid, lead, thallium, arsenic, bismuth, and Coumadin. The result is a sudden stop of hair fiber generation and a very rapid onset of hair loss. Patients who start anticancer treatment can pull their hair out in clumps within the first 2 weeks of therapy, however the degree of hair loss varies from person to person. Some patients may have a mixture of anagen effluvium and telogen effluvium and have more limited hair loss. Some cancer treatment centers try to block the hair loss using a cold therapy. More popular in Europe than North America, cold therapy involves covering the scalp with ice packs or using a special hood filled with cold water while the anticancer drugs are given. The cold decreases the skin blood flow and sends the hair follicles into suspended animation prior to contact with the drug and prevent the hair follicle cells from accumulating the drug and being damaged by it.

The recovery from anagen effluvium is usually as rapid as its development. Because the follicles are just frozen in time, they are ready to grow once the factor causing the anagen effluvium has been removed. On completion of an anticancer drug treatment course, patients may notice new hair growth within a month. The hair follicles are not destroyed, so the hair growth speed and hair density remain normal. However, some patients may notice changes in the nature of the new hair finding them changed from straight to curly or vice versa, or changing hair color. Such changes are usually permanent.

Scarring (Cicatricial) Alopecia

Cicatricial alopecias cause permanent hair loss. These disorders destroy hair follicles without regrowth and follow an irreversible course. It is likely that they involve stem-cell failure at the base of the follicles, which inhibits follicular recovery from the telogen phase. Inflammatory processes, including repetitive trauma as in trichotillomania, also may lead to such stem-cell failure. Other processes may be caused by autoimmune, neoplastic, developmental, and hereditary disorders.

Among these disorders, discoid lupus, pseudopelade in Caucasian population, and follicular degeneration syndrome, especially in patients with African origin, are most common. Scarring alopecia may also be part of a severe condition such as systemic lupus erythematosus. Dissecting cellulitis, lichen planopilaris, and folliculitis decalvans also may cause scarring alopecia. In early stages of the disease, some lesions may respond to treatment with intralesional steroids or antimalarial agents. Patients suffering from scarring alopecia should, as early as possible, be referred to a physician who specializes in hair-loss disorders.

In all forms of scarring alopecia, the hair loss is potentially permanent, and irreversible destruction of the hair follicles is followed by their replacement with scar tissue. Most forms of scarring alopecia first occur as small patches of hair loss that may expand with time. In some cases, the hair loss is gradual, without noticeable symptoms, and may proceed unnoticed for a long period of time. In other cases, the hair loss is associated with severe itching, burning, and pain, and is rapidly progressive. The scarring alopecia patches usually look different from alopecia areata in that the edges of the bald patches are more "ragged." Affected areas may be smooth and clean, or may have redness, scaling, increased or decreased pigmentation, or may have raised blisters with fluids or pus coming from the affected area. These visual indicators may help with diagnosis, but it is difficult to diagnose a scarring alopecia just from the pattern of the hair loss and the nature of the scalp skin. If scarring alopecia is suspected, one or more skin biopsies need to be done to confirm the diagnosis and help identify the particular form of scarring alopecia. A small biopsy of 2–4 mm in diameter is enough for histological examination. Scarring alopecia usually burns out, hairless patches stop expanding, and inflammation, itching, burning, or pain successively reduces. Microscopically (dermatoscopy and videomicroscopy), no hair follicles can be detected. Rarely, a few hair follicles, at least at the periphery of a bald patch, may persist and the hairs can regrow in these areas.

Infection-Related Scarring Alopecias

Folliculitis Decalvans

Even if folliculitis decalvans is not a primary alopecia, it is an important part of diseases leading to focal hair loss. Folliculitis decalvans is a profound hair follicle infection showing crops of patchy lesions, which usually ends as postinflammatory scarring and permanent hair loss (*Fig. 146.11*).

This disorder is usually seen in adolescents and young male adults and is very rare in children. The scalp is most commonly affected, but the lesions may also appear on the trunk, axilla, and pubic region. In these localizations, folliculitis decalvans should be distinguished from acne inversa (hidradenitis suppurativa) demonstrating perifollicular nodules and cysts.

Typical lesions of folliculitis decalvans show painful follicular and perifollicular nodules, patches, and crusts, surrounding already atrophic and scarring areas. If the hair is coming out in tufts from enlarged follicular openings, this variant of folliculitis decalvans is known as "tufted folliculitis" and, if not sufficiently treated, always leads to irreversible hair loss and deep, painful scarring.

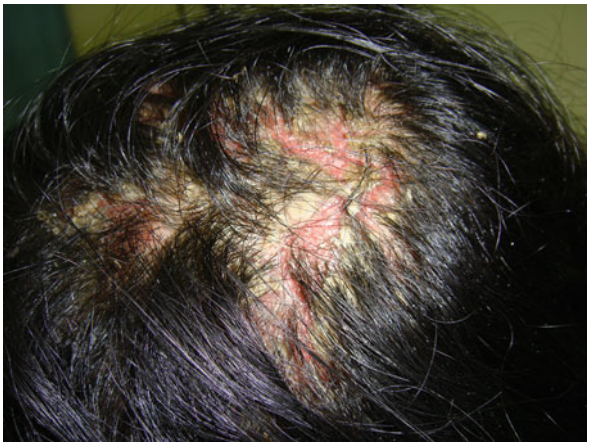

Figure 146.11
Folliculitis decalvans. Persistent, deep mixed fungal and bacterial infection of the scalp of a 15-year-old male

Therapy of folliculitis decalvans is difficult and usually frustrating for both patient and physician. From all available antibiotics, only those that sufficiently penetrate hair follicle such as tetracyclines, clindamycin, or erythromycin are recommended. Some authors recommend a combination therapy with one of these drugs and rifampicin. Treatment is, unfortunately, not curative but in most cases can suppress the disease and prevent spreading to surrounding scalp areas and prolong relapse intervals. Long-term administration of antibiotics is always needed to achieve satisfactory disease control.

Acne Keloidalis Nuchae

Acne keloidalis nuchae (also known as keloidal folliculitis) is clinically very similar to folliculitis decalvans showing deep folliculitis and perifolliculitis located in the upper neck and distal occipital scalp. In severe cases, deep abscess and interfollicular sinus formations are common. Lesions are often associated with pain and discomfort, especially if pressure is applied on affected areas (i.e., while sleeping).

Acne keloidalis nuchae affect mostly postpubertal males above the age of 12–14 years and is frequently seen in patients of African lineage, and is also common in Arabic patients, especially in warm and humid countries. In contrast to folliculitis decalvans, scars formed in acne

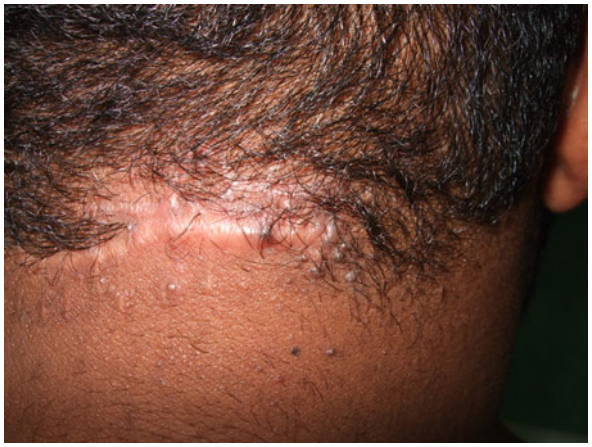

Figure 146.12
Acne keloidalis nuchae. Typical picture of acneiform lesions and deep keloidal scaring in a young male with acne keloidalis nuchae

keloidalis are often deep and nodular with polycyclic appearance. Lesions spread centrifugally and infection may be transmitted into other part of scalp by scratching. It is postulated that short haircut, especially in persons having thick and curly hair that can lead to development of ingrown hair, may promote the disease (*Fig. 146.12*).

Treatment is difficult and long-term systemic antibiotics that sufficiently penetrate into hair follicle (see above) are usually necessary. In many cases, combination with systemic or topical steroids may be helpful. In nonactive intervals, intralesional administration of steroid suspension may assist the treatment of persistent keloids. In some patients, surgical intervention and removal of deep, plaque-like keloids may be necessary.

Similar to folliculitis decalvans, the development of acne keloidalis nuchae may be promoted, and existing disease may often be accelerated by the use of hats, tight and occlusive-like caps or helmets, and stiff shirt collars, especially in hot and humid climate.

Dissecting cellulitis of the scalp (or perifolliculitis abscendens capitis) is a scalp skin disorder combining many clinical features of both folliculitis decalvans and acne keloidalis nuchae, even if the etiology may be different. In a typical situation, descending folliculitis begins on the occipital area of the vertex and spreads to the entire scalp showing follicular and perifollicular nodules often connected by deep sinuses and fistulae. Disintegration of the scalp skin and subcutaneous tissue may lead to the formation of pus reservoirs and dissection of skin from the underlining tissue – the phenomenon that, together with descending spreading of the lesion, gave the name to this pathological condition.

Descending cellulitis of the scalp usually leads to scarring and permanent hair loss. Treatment with systemic tetracyclines or erythromycin together with surgical intervention to drain deep debris collection is one of the possible options. Some studies, however, prefer the use of systemic isotretinoin as the first-line therapy.

Descending folliculitis occurs more frequently in adolescents and young adults having thick, curly hair and bushy hair growth with obstruction of sebum extraction. Upregulated inflammatory reaction to proprionibacterium acnes has been postulated as a possible causal factor, especially the association of descending folliculitis of the scalp with hydradenitis suppurativa and acne conglobata is not uncommon ("acne triad"). Since in many patients with acne triad pilonidal sinus is also present, all the disorders have now been grouped into a "follicular occlusion tetrad."

Disorders with Overgrowth of the Body Hair (Hypertrichoses)

Hypertrichosis – an abnormal or extensive hairiness – can be divided into congenital and acquired in terms of onset of the condition and localized or diffuse (generalized) in terms of affected body area. The term hypertrichosis is reserved to androgen-independent extensive hair growth in both female and male individuals. In females, hypertrichosis occurs without any evidences of abnormal menstrual cycles or masculinism. On the other hand, hirsutism refers to abnormally increased hair growth in girls and women showing typical, androgen-dependent hairiness in areas in which hair is usually not prominent. Hirsutism may also be seen as a "physiologic" variant of hair growth seen in different female members of the same family and does not need specific treatment. Affected girls and women are seeking medical intervention mostly because of individual or social pressure asking for removal of "overexposed" hair. In this respect, the frequent use of the terms "hypertrichosis" and "hirsutism" as synonyms is inappropriate from both an ethological and a clinical point of view. Hirsutism will not be discussed in this chapter.

One of the hereditary hypertrichoses is the general hypertrichosis lanuginosa, an autosomal-dominant disorder, in which the lanugo hair is confluent and generally cover the entire hair-bearing areas. In some cases, the hair may be then spontaneously lost during childhood; in most of the cases, however, the lanugo hair persist for life. Generalized hypertrichosis may create a real personal and social problem for children and their families.

General hypertrichosis has been described to be associated with different abnormalities, some of them have been connected with syndromes, for example, skeletal abnormalities, missing teeth, glaucoma, and many others. Over 25 different syndromes have been described as far. For more detailed information, we recommend consultation of genetic textbook or general monographs.

Localized inherited forms of hypertrichosis are usually divided into two groups – nevoid hypertrichosis and the so-called idiopathic hirsutism.

In the latter, extensive body hair of male pattern is present in girls without evidences of hormonal abnormalities or endocrine metabolic function. This may be understood as an overreacting response of the hair follicle to normal levels of androgenic hormones in genetically predisposed girls. Taking this into consideration, as per the definition above, the incorrect term "idiopathic hirsutism" should be replaced with "idiopathic inherited hypertrichosis."

Idiopathic inherited hypertrichosis (idiopathic "hirsutism") may often be seen in girls and women of particular ethnic origin, that is, in Mediterranean (Hispanic, Jewish, and Arabic) or Welsh girls. Physicians should, however, take into consideration that what is normal and acceptable in some regions may be seen as a handicap or disfiguration in others and that both children and their parents may force the doctor to treat this "wild disease."

Nevoid hypertrichosis describes an entity in which hair of abnormal length, diameter, or/and color may grow in different parts of the body often associated with other devoid abnormalities or localized developmental malformations.

Localized hypertrichosis is usually a part of large, congenital melanocytic nevi (i.e., Becker's nevus) or may be seen in plexiform neurofibroma, smooth muscle hamartoma, underlying kyphoscoliosis, duplication of the part of spinal cord, or tethered cord (as in faun-tail nevus). Localized hypertrichosis occurring in anterior cervical area is currently seen as a part of an autosomal recessive malformation connected with developmental delay and peripheral neuropathy.

In many cases, however, localized hypertrichosis is seen as a simple hair follicle hamartoma and does not have association with other defects.

Acquired Hypertrichosis

Several therapeutic agents may be related to the development of secondary or acquired hairiness. Newly stimulated hair is typically vellus-like.

One of the most prominent drugs causing diffuse hypertrichosis is minoxidil, a drug primarily developed and used to treat hypertension. Patients treated with this derivate of piperidinopyrimidine develop extensive new hair growing on the back, shoulders, extremities, and, especially on the face. This phenomenon occurs several weeks or even months after administration of the drug and slowly resolves after discontinuation of the drug. Young patient population is less affected by this drug when it is used systemically. However, similar development of localized hypertrichosis can be noticed in children and adolescents treated with topical minoxidil for diffuse scalp alopecia. This therapy is getting to be a standard adjuvant in older children, adolescents, and young adults (see treatment of alopecia areata section in this chapter). In such patients, hypertrichosis may develop on the lateral face, neck, and upper shoulder areas and resolves within months after discontinuation of the treatment.

Another prominent drug widely used in transplantology for prevention of organ rejection and causing diffuse hypertrichosis is cyclosporine. Children and adolescents obtaining the drug for treatment of graft versus host disease, develop gradual, sometimes extensive, hair growth within the first weeks after the drug has been introduced. Coexistence of insulin-dependent diabetes mellitus seems to aggravate the phenomenon. Discontinuation of cyclosporine leads to spontaneous decreasing of hypertrichosis. This process may, however, take months to resolve.

Children treated with phenytoin may also develop localized hypertrichosis. Extremities are the most common regions; face and trunk are usually less affected. Spontaneous regression occurs mostly within a year after discontinuation of the therapy.

Treatment of idiopathic hypoglycemia of the childhood with diazoxide may result in negative side effect in the form of localized forehead, neck, trunk, extremity, and eyebrow/eyelash hypertrichosis. It begins within the first few weeks of application of the drug and resolves usually during within a year after the drug has been stopped. Interestingly, increased hair growth similar to hypertrichosis lanuginosa of the newborns and neonates has been observed in cases when diabetic mother was treated with diazoxide during pregnancy.

Topical steroids are widely used in pediatric dermatology for treatment of inflammatory skin disorders and atopic dermatitis. One of the most prominent side effects of these drugs is extensive hypertrichosis localized to the places of prolonged application. Hair growing in this condition usually do not or only partially regress after discontinuation of the therapy (*Fig. 146.13*).

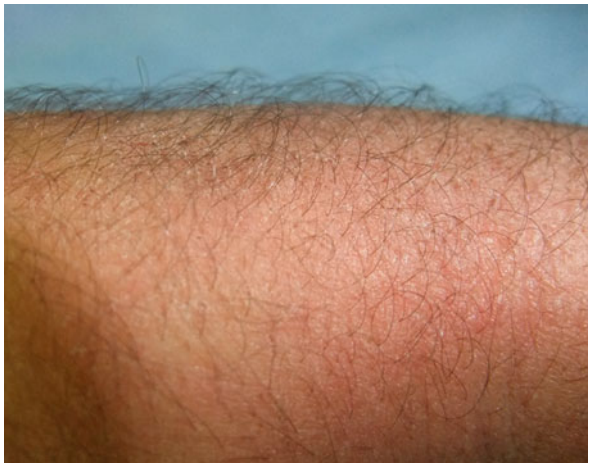

Figure 146.13
Acquired hypertrichosis. Acquired hypertrichosis on arms and legs due to long-term topical steroid application in an atopic dermatitis girl

Treatment of hypertrichosis is difficult. The most easy, but not always practicable, way is to shave the overgrowing hair. Even if there is an overall belief that this treatment may additionally stimulate the growth of the hair and result in thicker and faster hairiness, this has not been proved in clinical practice. In some regions of the world, depigmentation of hair using hydrogen peroxide is the most common to make the overgrowing hair less visible. Especially when after the use other bleaching agents in parson with dark(er) skin the contrast between the yellowish-white hair and the underlying skin becomes prominent. Applied in children, this technique may, however, lead to massive skin irritation and development of contact or irritative–toxic dermatitis. Chemical or mechanical depilation may be another option and, in large surface areas, is, however, less practicable and may also result in irritative–toxic dermatitis. Additionally, children with large-surface hypertrichosis should not be treated with chemical peels such as sulfides, or thioglycolates because of possible systemic absorption and toxic adverse reaction.

Recently, lasers or combination between laser and xenon pulse light has been successfully applied for treatment of hypertrichosis. It is necessary to stress that such techniques do not "remove" the hair, but primarily reduce their density. The principle of this therapy is a selective photo-chemo-destruction of melanin granules within the hair follicles, which together with thermal effect of laser light results in pigment and follicle destruction. If applied appropriately, this therapy is safe and effective. In less satisfactory outcome, extensive inflammation, postinflammatory patchy hyper- or hypopigmentation, or/and scarring due to thermal collateral damage of the tissue are the most common side effects. Repeated sessions are necessary to achieve satisfactory results.

Electric depilation (electrolysis) is an older, but still well-used, technique of hair removal. Based on thermal follicle destruction,this technique gives more permanent results but is very painful and almost not applicable in children. Side effects, if they occur, are similar to overdosed laser energy with inflammation, dyschromia, and focal perifollicular scarring. In individuals with African or Arabic origin having both ethnic and family predisposition to development of hypertrophic scars, this may lead to development of multiple small keloids in places of destructed hair follicles.

Supportive topical therapy decreasing hair growth through inhibition of ornithine decarboxylase (i.e., as 15% compound crème formulation) may be helpful.

Introduction of eventual systemic medication, however, needs profound endocrinological diagnosis and should always be done in close cooperation with an endocrinologist.

In case of hirsutism, all therapies listed above have only an ancillary value. The principle should be to refer the affected child to pediatric endocrinologist and/or gynecologist for appropriate diagnosis and treatment.

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147 Nail Disorders

Eckart Haneke

The nail is the biggest cutaneous appendage. It is an integral part of the functional unit tip of the digit, supports its sensory functions, and is an important tool for manual dexterity, for scratching, and for defense.

The nail develops from fetal week 9 onward and requires an intact terminal phalanx as well as a series of signaling proteins for its correct shape and size. At week 13, the nail field is fully developed and at week 14, the nail plate starts growing to cover the nail field almost completely by week 17. From week 20 onward, the digit and the nail grow synchronously, and at birth the nail plate has normally reached the distal ridge of the finger. If the nail is still shorter, the infant may be born with a distally ingrowing nail. Koilonychia is also frequently seen at birth, but usually disappears spontaneously.

The nail is a plate of keratin containing both hard "hair" keratins and soft epidermal keratins. It is transparent allowing the distal matrix – the lunula – and the nail bed to be seen. The nail is both physically and chemically resistant. Antimicrobial peptides in the nail protect it against bacterial and fungal attack even though it does not have any vascular supply.

The nail is formed in its entirety by the matrix (*Fig. 147.1*), which continuously produces nail substances during the whole life. Most of the matrix is covered by the proximal nail fold, the ventral surface of which forms a horny layer, the eponychium, that is firmly attached to the dorsal surface of the nail. When the nail grows out, it pulls part of this keratin layer with it forming the cuticle, which seals the nail pocket. When this attachment is lost, usually as a result of inflammation, infection, or trauma, the cuticle disappears and foreign material may enter under the proximal nail fold. This further irritates the tissue giving rise to paronychia. In newborns, this may be due to *Candida albicans*, probably acquired during the birth process.

The nail bed is seen as a pink structure through the normal nail. What gives it this pink color is still not completely understood, although it is thought to be due to the particular parallel arrangement of the capillaries running longitudinally in several layers one above the other. The nail is a window to the bed permitting the vascular supply and blood oxygenation to be evaluated. Even subtle color changes can be seen through the thin newborn nail and give important hints at general health indicators. The nail plate is very firmly attached to the nail bed, which produces just a thin layer of keratin allowing the nail to slide over it without losing its attachment.

The distal margin of the nail divides from the nail bed at the hyponychium. This, again, is a specialized structure preventing foreign substances from entering under the nail. Detachment of the nail from the nail bed is called onycholysis, usually, as a result of infection or trauma, and is mostly seen in girls due to overzealous manicure.

The lateral nail folds, together with the proximal one, form a frame for the nail ensheathing it on three sides.

The Newborn Nail

In the newborn, the nail is soft, thin, and pliable. If the big toenail has not yet overgrown the hyponychium, it may grow distal-laterally or laterally. This is easily treated by the mother: a lubricating ointment is applied on the tip of the toe, and in a warm bath, the distal and/or lateral nail folds are gently massaged away from the nail. Within a few weeks, the nail will have reached the tip of the toe.

Koilonychia or spoon nails are frequent and harmless. This minor abnormality disappears by itself within months or the first 2 years of life.

Some weeks after birth, transverse grooves running parallel to the lunula border may be seen. These Beau's lines are thought to be due to the trauma of birth that may temporarily slow down the nail growth rate.

A large number of congenital hereditary diseases and intrauterine damages can affect the nails (*Tables 147.1* and *147.2*). Ectodermal dysplasias (ED) may also affect the nails, particularly the group of tricho-onychotic EDs. Small and hypoplastic nails or fluting are the most common nail changes. Pachyonychia congenita type 1 is a disease of keratins 6a/16 and type 2 of 6b/17.

Nail Changes in Infants

Some infants develop a hypertrophic medial nail wall, which may cover up to one-half of the nail. Debris is

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_147,

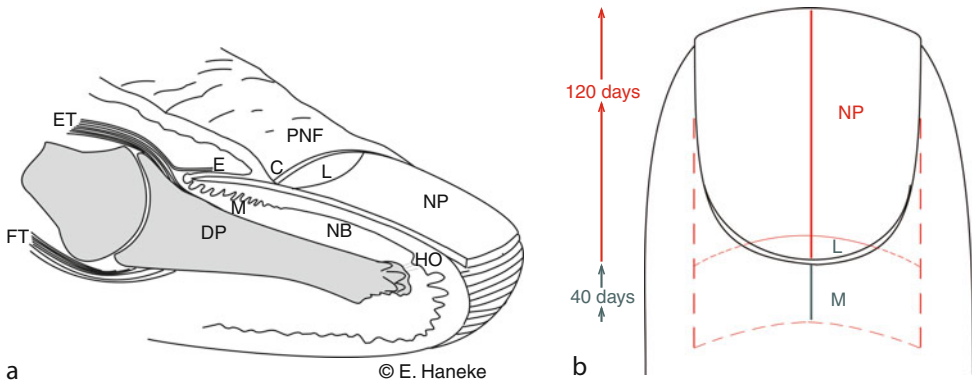

Figure 147.1
Schematic illustration of the nail. (a) Sagittal section through the distal phalanx of a finger. *C* Cuticle, *DP* Distal phalangeal bone, *E* Eponychium, *ET* Extensor tendon, *FT* Flexor tendon, *HO* Hyponychium, *L* Lunula, *M* Matrix, *NP* Nail plate, *PNF* Proximal nail fold. (b) Growth rate of a normal nail

Table 147.1
Nail alterations in chromosomal anomalies (Adapted from Haneke E (2006) Nagelkrankheiten. In: Hamm H (ed) Pädiatrische Dermatologie, 2nd edn. Springer, Heidelberg, pp 677–698)

Condition	Nail changes	Other symptoms
Trisomy 3q	Hypoplasia, anonychia	Hirsutism, synophris, eye anomalies, short neck
Monosomy 4p	Overconvex	Fish mouth, cheilopalatoschisis, head asymmetry, preauricular pits, retardation
Trisomy 7q	Overconvex	Facial asymmetry, retardation
Trisomy 8p	Hypoplasia, anonychia	Facial asymmetry, retardation
Monosomy 9p	Wide convex	Hypoplasia of middle face, trigonocephaly, upward slanted eyes, abnormal dermatoglyphics, retardation
Trisomy 9p	Dystrophic, claw-like	Downward slanted eyes, microcephaly, short digits, retardation
Trisomy 13	Narrow, convex, hypoplastic	Cheilopalatoschisis, aplasia cutis, polydactyly, hemangiomas, microcephaly, vitium cordis, genital hypoplasia
Trisomy 18	Hypoplasia of fifth finger and fifth toe	Cramped hands with overlapping fingers, short sternum, abnormal dermatoglyphics
Trisomy 21 (Down's syndrome)	Clubbing and macronychia	Upward slanted eyes, hypoplasia, short broad fingers, four-finger-fold, vitium cordis, cutis marmorata
X0 (Turner syndrome)	Small, convex, deep lying	Pterygium colli, short neck, congenital lymphedema, ovarial dysgenesis, cubitus valgus, nevi
Ring chromosome group C	Pachyonychia	Facial anomaly, retardation

collected in the deep fold leading to subacute inflammation. Massaging from the nail to the plantar surface of the tip of the toe is usually effective. When it does not respond, it may simply be removed and the small wound left for second intention healing.

Congenital malalignment, originally described as congenital dystrophy of big toenails, is another abnormality of infant nails. Often, the distal phalanx of the big toe is deviated laterally and the nail even more. This may lead to oblique shearing trauma causing onycholysis and, as its consequence, the nail becomes oystershell-like distorted, triangular, discolored, thickened, and sharply bent medially. The condition may improve spontaneously up to the age of 2 years; however,

Table 147.2
Teratogens and their effects on nails (Adapted from Haneke E (2006) Nagelkrankheiten. In: Hamm H (ed) Pädiatrische Dermatologie, 2nd edn. Springer, Heidelberg, pp 677–698)

Teratogen	Nail changes	Other symptoms
Alcohol	Hypoplasia, anonychia of fifth finger, convex	Microcephaly, small lid opening, epicanthus, short nose, flat philtrum, retardation
Phenytoin	Hypoplasia, longitudinal pigmented streaks	Cheilopalatoschisis, deep-set ears, hirsutism, sunk-in nasal bridge, broad mouth, short neck, finger-like thumbs, short tapering fingers, wide distance between nipples
Trimethadione	Hypoplasia	Microcephaly, V-shaped merging eyebrows, ptosis, malformed ears, small flat nose, deafness
Warfarin	Hypoplasia	Hypertelorism, small nose, short neck, brachydactyly, spotted epiphyses

if this does not occur, the nail bed shrinks permanently, a distal nail wall develops, and the nail becomes more and more unsightly, sometimes painful. Unfortunately, there is no sign indicating spontaneous healing. Treatment is surgical by the age of 2 years with rotation of the entire nail organ into its correct axis.

Nail Changes in School Children

Ingrown nails are a common condition in children from around 12 years onward. There is a discrepancy between a relatively wide nail and a narrow nail bed distally. In most cases, the nails are markedly curved. Usually, the patient tends to cut the distal corner of the nail, leaving small spicules in the depth of the distal lateral nail groove, which pierce into the soft tissue when the nail grows out. Three stages of ingrown nails are distinguished: (1) Reddening and swelling of the lateral nail fold. (2) Secretion. (3) Granulation tissue. There may be fluctuations between stages 1 and 3 depending on foot care and hygienic measures. Treatment may be conservative in early stages with taping, packing, gutter treatment, artificial nails, or nail braces. This is a long-term treatment and requires good patient compliance. When conservative treatment is not successful or feasible, definitive surgical cure is achieved by selective lateral matrix horn resection or phenolization. Wedge excisions are obsolete.

Nail Signs

There are some nail changes that may be – to a certain degree – a marker of an internal or general condition.

Beau's lines are transverse, slightly curved furrows that run parallel to the lunula border. They indicate a temporary slow down in the nail growth that had occurred some weeks ago, most commonly a disease with high fever. Beau's lines are more marked in fast-growing fingernails than in slow-growing toenails. Single-digit Beau's lines are typical sequelae of a past surgical intervention.

Koilonychia, also called spoon nails, is typically seen in iron deficiency. It is a frequent finding in the big toenails of newborns and usually disappears spontaneously within a few weeks.

Leukonychia occurs as small dots, short transverse lines, or rarely as narrow longitudinal lines. Punctate and striate leukonychia is frequent in young girls, mostly due to overzealous manicure. Longitudinal leukonychia is caused by a narrow rim of keratin running from the lunula to the free nail edge; its cause is usually an onychopapilloma.

Melanonychia most commonly occurs as a longitudinal brown streak. In children, it is usually due to either a lentigo or a junctional melanocytic nevus of the matrix; nail melanomas are extremely rare in children. In warmer climate, some pathogenic fungi may produce a soluble melanin that may give rise to a grayish-to-blackish spike in the nail. In contrast to true melanonychia, subungual hematomas never reach the free nail margin and can easily be diagnosed dermatoscopically. Most hematomas have a history of a previous trauma.

Most other colorations are due to exogenous dyes or drugs.

Onycholysis is the distal separation of the nail from the nail bed. It has often a curved smooth border; this is called onycholysis semilunaris and is a result of manicuring the nail with sharp instruments.

Proximal onycholysis is called *onychomadesis*. It develops when the nail stops growing for a certain period. Single-digit onychomadesis typically develops after a

run-around or acute paronychia, whereas general diseases cause onychomadesis in a symmetrical fashion. It may be followed by nail shedding.

Characteristic Nail Conditions

Twenty nail dystrophy is characterized by the gradual development of rough nails of both the fingers and toes, a phenomenon called trachyonychia. The nails show fine depressions on their surface. One nail after the other may be affected, but very often one single nail remains spared. In the more common form, the nails lose their shine, but there is also a shiny variant. Skin lesions are not found. In most cases, histopathology exhibits a spongiotic dermatitis of the matrix; less frequently, a lichen planus, psoriasis, or eczema may be seen. Whether or not the spongiotic changes indicate an isolated alopecia areata of the nails remains to be clarified. The course is usually benign in children with spontaneous resolution around the age of 16. A combination of topical calcipotriol with a potent steroid accelerates healing.

Twenty nail dystrophy must be differentiated from nail lichen planus as this may cause permanent nail dystrophy even in children. The nails are rough, ridged longitudinally, and tend to break.

Nail Psoriasis

Nail involvement in children with psoriasis is not rare (see Papulosquamous and Related Disorders Including Psoriasis). Subungual hyperkeratosis, distal onycholysis, pits (*Fig. 147.2*), and so-called salmon or oil spots are the most frequent signs. Pits and small whitish spots develop from tiny psoriatic lesions of the most proximal part of the matrix. Salmon spots represent psoriatic plaques of the nail bed. Psoriatic leukonychia is due to a psoriatic affection of the middle of the matrix. Complete nail destruction indicates psoriatic involvement of the entire nail organ and is often seen in arthropathic psoriasis. In children, the nails may also become very thick and rough with huge subungual hyperkeratosis. Treatment of nail psoriasis is difficult as the nail wall and plate cover the diseased portions of the nail organ. Any systemic therapy resulting in clearance of the skin potentially also improves nail psoriasis.

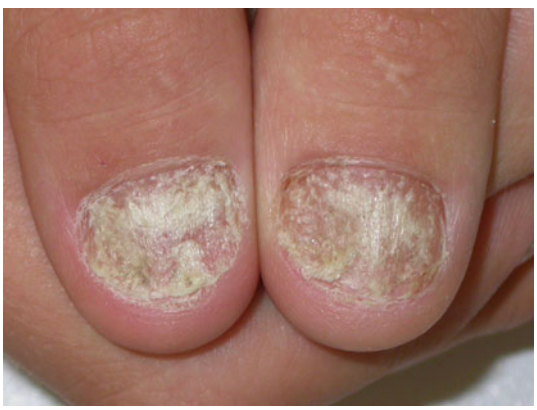

Figure 147.2
Psoriasis of the nails in a 13-year-old boy

Lichen Planus

Roughly one-tenth of the patients with lichen planus develop nail changes. In about one-quarter, the nail changes come after diagnosis of skin and mucosal lesions. Most characteristically, this condition affects the proximal and dorsal matrix with subsequent ridging, roughness, and loss of shine of the nail. The problem with nail lichen planus is its propensity to permanently destroy the nail. Early treatment is therefore mandatory. Topical vitamin D_3 analogues, best in combination with a steroid, should be started first. When this is ineffective over a course of >3 months, low-dose etretinate may be given. An alternative is intramuscular triamcinolone acetonide crystal injections, about 0.5 mg/kg bodyweight every 4–6 weeks.

Alopecia Areata

Alopecia areata often affects the nail. The more severe it is, the more likely are the nail changes. The nails become rough, nontransparent, and lose their shine. Thickening and brittleness occur when the nail plate contains a lot of serum inclusions. Histologically, alopecia of the nail represents a spongiotic dermatitis and it may be difficult to differentiate it from eczema. No specific treatment is known, but it appears that ungual alopecia areata runs a benign course.

Eczema

The different forms of eczema may cause variable nail changes. Rubbing with the surface of the nail in chronic atopic eczema is the main cause for the characteristic shiny nails. In dyshidrotic eczema, the periungual skin may be involved with small itching vesicles. Allergic contact dermatitis may cause nail deformation, particularly when the

allergen gets under the proximal nail fold and induces an eczematous change in the matrix. In chronic eczema, a thickening of the proximal nail walls develops with rounding of its free margin and spontaneous loss of the cuticle. This leads to separation of the nail fold's undersurface with the nail, and more foreign substances, including allergens, microbes, and dirt, may enter the nail pocket. In girls, nail cosmetics may play a causative role.

Erythema Multiforme

Erythema multiforme is a skin disease characterized by round erythematosus lesions that develop a central blister, the roof of which often becomes necrotic and thus gray. The tricolor appearance make the lesions look like targets. When the nail organ itself is involved, onychomadesis, nail dystrophy, and later shedding may develop.

Infections and Infestations

Viral warts are common in periungual locations and are less frequent subungually. They are often rather oval than round, grayish hard lesions with a rough and sometimes clefted surface. The problem is not the diagnosis, but rather their treatment. A conservative approach with aggressive keratolysis and regular cautious curettage of the necrotized wart keratin has been adopted. Saturated monochloroacetic acid is applied sparingly on the wart and allowed to dry. It is then covered with 50% salicylic acid plaster and fixed with adhesive band. With all this on, the patient has to perform a hand or footbath as hot as tolerated twice a day for about 10 min. After a week, the adhesive tape and salicylic acid plaster is removed, showing a white soft surface of the wart. This is gently curetted and the procedure repeated until the wart is gone. The success rate is over 90%. However, after several debridements, the monochloroacetic acid tends to cause a nagging pulsating pain, and the treatment has to be interrupted. Whether duct tape is an alternative remains to be seen. Cryotherapy has about the same cure rate, but is very painful at the nail. Lasers are not more effective than other destructive methods. Limited evidence exists for the efficacy of topical 5-fluorouracil, intralesional interferons, photodynamic therapy, imiquimod, and a variety of vaccinations. Bleomycin, dinitrochlorobenzene, and other obligate topical sensitizers, 5-fluorouracil, interferons, and photodynamic therapy, are potentially hazardous or toxic treatments.

Digital herpes simplex is often underdiagnosed. It is commonly misdiagnosed as a recurrent paronychia or felon. It presents with painful blisters around the nail or on the pulp of the digit that are barely visible under the thick horny layer of this region. Very often, a red stripe indicating lymphangitis is seen, sometimes even before any visible vesicle. Within a few days, the blisters may become putrid. When the diagnosis is made early enough, acyclovir may be used. Antibiotics are of no use.

Although *mollusca contagiosa* are probably transmitted with the scratching finger nail, their localization at the nail is very rare.

Cow pox, milker's nodule, and orf are clinically almost identical lesions caused by similar viruses. The first are usually acquired from wild living cats, the second from an infected udder, and the last from sheep. One to two weeks after infection, a nodule develops with sanguinolent secretion. Healing takes a few weeks.

The most common bacterial infection is *bulla repens*, also called run-around. This is often derived from hangnails that are torn out and leave a small wound. It is mostly due to staphylococcus aureus, less frequently streptococci. In the beginning, a clear blister develops, which soon becomes cloudy, and yellow pus can be seen. Pain is moderate to severe. Treatment of choice is opening of the blister and disinfective baths twice daily as well as dressings with antimicrobial ointments. Systemic treatment is rarely necessary.

A *whitlow* is a deeper infection due to pyogenic micrococci. Reddening, swelling, and pulsating pain are characteristic. A subungual felon may cause irreversible matrix damage within 24–48 h in children and should therefore be treated as an emergency. A swab has to be taken for bacterial culture and systemic treatment with a staphylococcus-specific antibiotic begun until the result of sensitivity testing has arrived.

Blistering dactylitis is a streptococcal infection that often remains undiagnosed as it usually causes no symptoms. Blisters occur on the tip of the digits and the horny layer later sheds off. They may represent a chronic streptococcal focus and require treatment. The blister roof is cut and the finger disinfected. Systemic penicillin treatment is recommended.

Onychomycoses are fungal infections, most commonly of the nail bed. Dermatophytes are responsible for more than 80% of the cases. They are rare in infants and increase in prevalence with age.

Distal lateral subungual onychomycosis is the most frequent type. The fungus infects the tip of the digit and then the hyponychium and nail bed, where it slowly grows proximally toward the matrix. The nail plate itself is rather an obstacle for the fungus than the site of infection; thus the nail plate covers the infection and makes it difficult to treat. The nail bed develops a subungual hyperkeratosis that is

seen as a yellowish substance through the nail. Only in late advanced stages will the plate be destroyed (Fig. 147.3).

In *proximal subungual onychomycosis*, the fungus breaks the barrier of the cuticle and grows along the underside of the proximal nail fold toward the matrix. Once this is reached, the fungus is included into the growing soft nail and penetrates it in virtually all layers. The nail bed does not produce a subungual hyperkeratosis. The nail that is invaded by the fungus takes on a whitish color; hence, the term proximal subungual white onychomycosis is often used (Fig. 147.4).

Superficial white onychomycosis is a peculiar infection of the surface of the nail plate. Several molds may be the causative pathogen, particularly in warm climate, whereas *Trichophyton mentagrophytes* is the common pathogen in temperate climate zones.

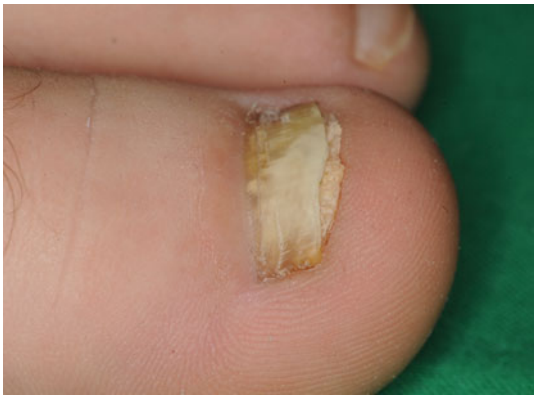

Figure 147.3
Onychomycosis in a 12-year-old boy

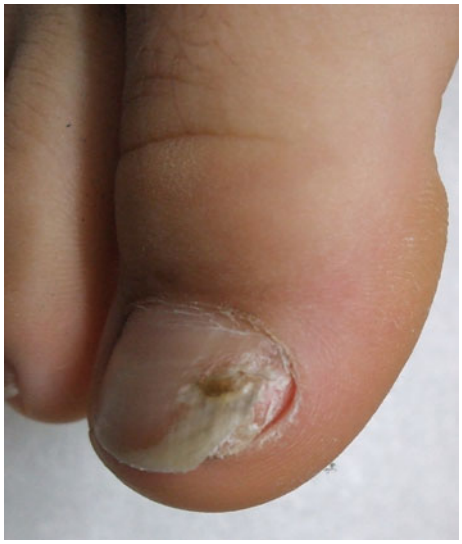

Figure 147.4
Subungual exostosis of the big toe in an 11-year-old girl

Endonyx onychomycosis is mainly caused by *T. soudanense* and *T. violaceum*. The pathogen grows entirely in the nail plate.

Any of these onychomycosis types may progress to *total dystrophic onychomycosis*. This, however, is also a common finding in *chronic mucocutaneous candidosis*.

Treatment of childhood onychomycoses is hampered by the fact that the potent systemic antifungals are often not approved for use in children. As long as the infection has not yet reached the matrix, an antimycotic lacquer may be used, but the treatment has to be performed with consistent compliance over many months. When the matrix is reached, in proximal subungual and total dystrophic onychomycosis, systemic treatment is advised. Depending of the age and weight, terbinafine, fluconazole, or itraconazole are the most potent drugs. In some countries, griseofulvin is still available. Chemical nail avulsion supports treatment in total dystrophic onychomycosis.

Nail involvement is not uncommon though often overlooked in *crustous scabies*. There is subungual hyperkeratosis and some nail roughness. There may be hundreds of mites under the nails, and failure to treat subungual scabies usually results in recurrence and spread of the infection. Treatment is with topical scabicide drugs, which have to be brushed in twice daily over several days. Ivermectin is an alternative.

Tungiasis is common in endemic regions and often causes some sort of paronychia. Under the nail in the region of the hyponychium, the female *tunga penetrans* digs itself into the skin and causes an itching nodule growing to the size of a pea. A small black dot represents the opening through which the sand flea lays its eggs. Treatment of choice is curettage of the hole in which the flea lives in order to prevent infectious complications such as erysipelas, cellulitis, or gangrene.

Tumors of the Nail Organ

Benign nail tumors are not exceptional in childhood. They often differ in their clinical appearance from the same tumors in other locations.

Koenen Tumors

Koenen tumors are round to sausage-shaped lesions that develop in about one-half of the patients with tuberous sclerosis from the age of 12 years onward. They are flesh

colored and asymptomatic. Most grow under the proximal nail fold and thus cause a groove in the nail plate. They may be severed at their base, but new lesions tend to develop.

Recurrent Digital Fibromatosis of Reye

In early infancy, reddish dome-shaped lesions develop on the digits with the exception of the thumbs and big toes. When they grow in the periungual skin, they may distort the nail. Treatment is not necessary as they disappear spontaneously.

Keloids

Keloids in the nail region are rare, but may be monstrous. The most common cause is electrosurgery for periungual warts, which should therefore be abandoned. They may be painful and cosmetically embarrassing.

Angiomas

Pyogenic granuloma, an eruptive angioma, is sometimes seen around or even under the nail. It presents as a rapidly growing red nodule that tends to erode, superficially ulcerate, and bleed easily. It responds to potent topical steroids under occlusion, but may also be carefully removed at its base with cautery of the feeder vessel. The specimen has to be examined histopathologically in order to rule out other tumors.

Port-wine stains rarely affect the nail region. Whereas the periungual skin is deep violaceous red, the nail itself is usually white.

Glomus tumors are exceptional in children.

Exostosis

Subungual exostosis is a reactive lesion that may occur at any age. The most characteristic localization is the medial dorsal aspect of the distal phalanx of the big toe, but other digits may be involved as well. They present as a stone-hard round lesion covered with skin that is extended and shiny, usually without the typical ridges of plantar skin. A radiograph confirms the diagnosis. Treatment of choice is the generous surgical removal at the base.

Diagnostic Measures

In most cases, nail alterations do not require many sophisticated and expensive tests. Careful clinical inspection of the digits in relaxed position and with pressure to check potential vascular changes is important. Probing can localize circumscribed pain. Transillumination is useful to check for a cystic lesion or a foreign body. Bacterial and fungal cultures are indicated when an infection is suspected. Radiographs have to be very soft in order not to overexpose the distal phalanx. Computed tomography and magnetic resonance imaging are sometimes helpful as is variable high-frequency ultrasound. Direct microscopy of subungual keratin allows to find fungi. However, the gold standard for diagnosis is histopathology, which requires a biopsy.

Nail Biopsy

In case of onychomycosis, a nail clipping stained with PAS is twice as sensitive as a fungal culture.

For an incisional biopsy, a local anesthesia is applied. This may be a distal or proximal digital block or a transthecal block. The biopsy site within the nail organ is crucial: Changes involving the nail surface require proximal matrix tissue, best as a lateral longitudinal nail biopsy. A punch may be taken for nail bed lesions but should not have a diameter greater than 3 mm.

Nail Avulsion

This is very rarely helpful and must never be done as a substitute for a diagnosis. Many conditions are worsened by avulsing the nail.

Under local anesthesia, a blunt, slightly curved nail elevator is inserted under the proximal nail fold to separate it from the underlying nail by careful back-and-forth movements from one side to the other. The elevator is then pushed through the hyponychium till the matrix to detach the plate from the nail bed and matrix. The proximal avulsion approach detaches the nail from the matrix; this is technically more demanding but less traumatizing.

When the nail plate is lacking after avulsion, the pulp of the tip of the digit may be dislodged dorsally; this is often the case in the big toenails. A distal nail wall develops that prevents the nail from growing out. Instead, it becomes thicker, yellowish, and intransparent. With time, it loses its attachment with the nail bed.

Subungual Hematoma

Children often traumatize a finger; most commonly it is a car door crash. The result is a hematoma that causes

considerable pain. When it stretches over more than 50% of the nail field, a fracture is likely and requires adequate repair. In smaller hematomas, drilling a hole over it and releasing the blood immediately relieves the pain.

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148 Pigmentary Disorders and Vitiligo

Arti Nanda

This chapter will review the common disorders of skin color including disorders of hyperpigmentation and hypopigmentation. People with colored skin including Asians, Mediterraneans, and Africans are more prone to pigmentary disorders. Parents of children with any deviation from normal pigmentation are concerned about the problem.

Pigment-producing cells called melanocytes are present in the bottom layer (basal cell layer) of skin's epidermis. They comprise 5–10% of cells in the basal layer of epidermis. Through the process called melanogenesis, these cells produce melanin, which is primarily responsible for the color of skin. Once made, melanin is moved along arm-like structures of melanocytes, called dendrites, in a special container called melanosomes and transferred to keratinocytes. The difference in skin color between different people is due not to the number (quantity) of melanocytes in their skin but to melanocytes level of activity of melanocytes.

Disorders of Hyperpigmentation

Hyperpigmentation is caused by the increase in melanin production. The disorders of skin hyperpigmentation will be discussed under the following sections:

1. Birth marks/Pigmented nevi
2. Benign hyperpigmented lesions
3. Postinflammatory hyperpigmentation
4. Hyperpigmentation related to systemic diseases/drugs

Birth Marks/Pigmented Nevi

Transient Pustular Melanosis of the Newborn

Transient pustular melanosis is characterized by pustules present at birth that evolve into macular pigmentation. The pigmented macules fade over 3–4 weeks' time. All areas of the body can be affected, including palms and soles. Gram or Giemsa staining of the pustule shows neutrophils and occasionally eosinophils. Clinical recognition of the condition can help physicians to avoid unnecessary diagnostic testing for infectious etiologies.

Mongolian Spots

Mongolian spots are the most frequently seen birthmarks in infants. These flat bluish grey or brown lesions occur on the back or buttocks. Their incidence varies among racial and ethnic groups and are more often seen in blacks, Native American, Asian, and Hispanic populations. The lesions may vary in size from a few millimeters to 10 cm. They tend to fade with advancing age. It is universally accepted that, in general, Mongolian spots are benign cutaneous manifestations that have no clinical significance. Their atypical or aberrant presentation (*Fig. 148.1*) may be associated with certain inborn errors of metabolism, including mucopolysaccharidosis, GMI ganglisidosis, and phacomatosis pigmentovascularis.

Café-Au-Lait Macules (CALMs)

CALMs present as uniform tan–brown, round or oval macules with distinct margins. They tend to enlarge in earlier years of life and then stabilize. They do not regress with advancing age. Their prevalence among children may vary from 0.3% to 36% depending upon the age of the pediatric population studied. Their prevalence increases during infancy and childhood.

Solitary CALMs usually have no clinical significance. The presence of multiple CALMs (*Fig. 148.2*) may indicate the presence of multiple systemic disorders, most important of which is neurofibromatosis type 1 (NF-1). It is generally assumed that the presence of six or more CALMs larger than 1.5 cm are pathognomic of NF-1.

Congenital Melanocytic Nevi

A congenital melanocytic nevus (CMN), also referred to as congenital nevocellular nevus, is considered to be nevomelanocytic proliferation with an estimated prevalence

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_148,

rate of 1–6%. The cause of CMN is not known. In normal human development *in utero*, melanocytes are derived from the neural crest as melanoblasts and migrate from a dorsal location in the embryo ventrally to the skin, the central nervous system, eyes, and adrenal glands between week 5 and 25 of gestation. Defects in migration or maturation are hypothesized.

The most commonly used classification for CMN is based on size, with small (<1.5 cm), medium (1.5–19 cm) (*Fig. 148.3*), and large (20 cm≥) (*Fig. 148.4*) CMN. The term giant CMN is used for nevi covering large segments of body. CMN can involve any location in the skin including mouth, palms, soles, and nails. One lesion is normally present, but multiple CMN can be present in the same patient, numbering hundreds. "Satellite nevi" describes the presence of multiple small congenital nevi in association with a large CMN.

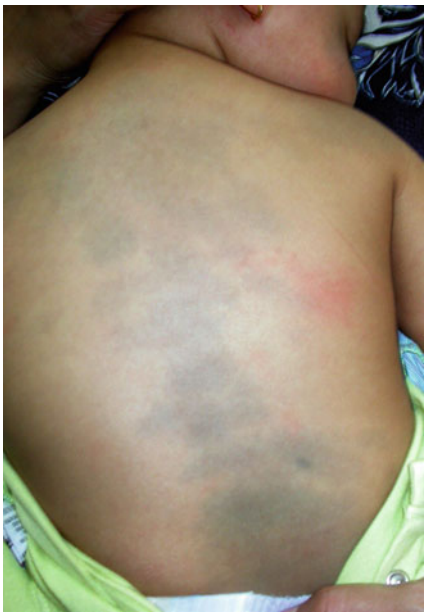

Figure 148.1
Multiple, widespread Mongolian spots on the back of an infant

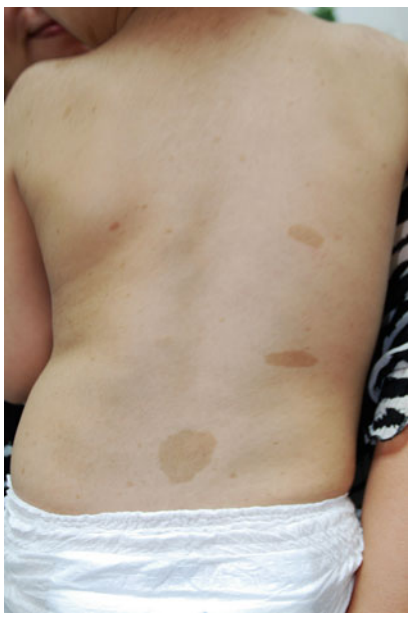

Figure 148.2
Multiple café-au-lait macules on the back of an infant

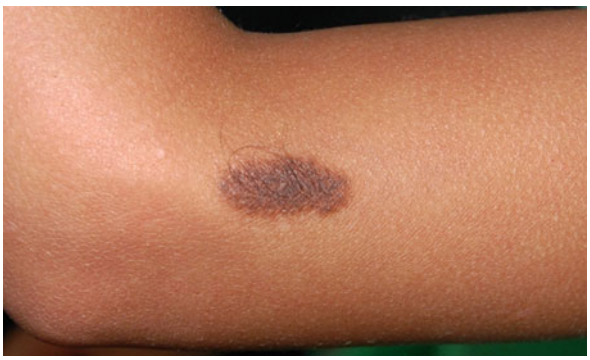

Figure 148.3
Medium sized congenital melanocytic nevus on the forearm of a child

Figure 148.4
Giant congenital melanocytic nevus on the face of an infant

The lesions usually are round to oval in shape and may be associated with the long axis along lines of skin development. The color is usually brown to dark brown or black plaque with rugose or black mamillated topography. The lesions can develop hypertrichosis. The clinical appearance is important for assessment of malignant potential with and without regard to size. A homogeneous uniform color and symmetric CMN with uniform topography (e.g., no distinct papules) is less concerning than a multicolored CMN with an uneven surface with irregular borders (◉ *Fig. 148.5*).

A CMN can have medical, cosmetic, and psychological implications. The most significant medical concern is risk associated with transformation to malignant melanoma. Estimates for risk transformation vary and lifetime risk ranges from 4% to 10%. Smaller lesions are thought to have lower risk for transformation than larger CMN relative to the nevus burden. The other medical concern is the association of CMN with neurocutaneous melanocytosis (NCM). NCM refers to increased melanocytes in the central nervous system in the presence of CMN. NCM is usually associated with large CMN. The exact incidence of NCM is unknown. It can be symptomatic or asymptomatic. Symptomatic NCM with features including seizures, developmental delay, motor delay, hydrocephalus, etc., is associated with grave prognosis. Patients who have a large CMN at the posterior head, neck, spine, or paravertical location have higher risk of NCM, especially those with multiple satellite lesions. Diagnosis of NCM is made by magnetic resonance imaging.

Treatment of CMN needs to be tailored according to the patient. Treatment options include surgical excision, lasers, or a combined approach. A multidisciplinary approach with plastic surgery, dermatology, pathology, radiology, and psychology is important.

Nevus of Ota

Nevus of Ota, also referred as oculodermal melanocytosis, arises from dermal melanocytes. The lesion appears as a blue-to-purple, mottled discoloration of the skin in the distribution of the ophthalmic and maxillary divisions of the trigeminal nerve (◉ *Fig. 148.6*). It is usually congenital and unilateral and frequently is associated with ipsilateral ocular melanocytosis involving the conjunctiva, sclera, and uveal tract. Diagnosis is based on the typical clinical appearance. Important associated disorders include ipsilateral glaucoma and intracranial melanocytosis. Malignant degeneration may occur, particularly in white, with choroid the most common site of involvement. Thus periodic dilated fundus examination is recommended. Treatment is indicated due to cosmetic concern. Treatment options include laser treatment with Q-switched Ruby laser and Q-Switched Nd:YAG laser.

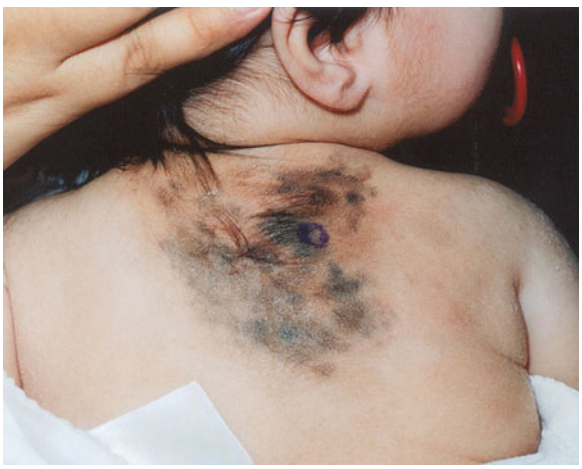

Figure 148.5
Giant congenital melanocytic nevus with a multicolored, uneven surface

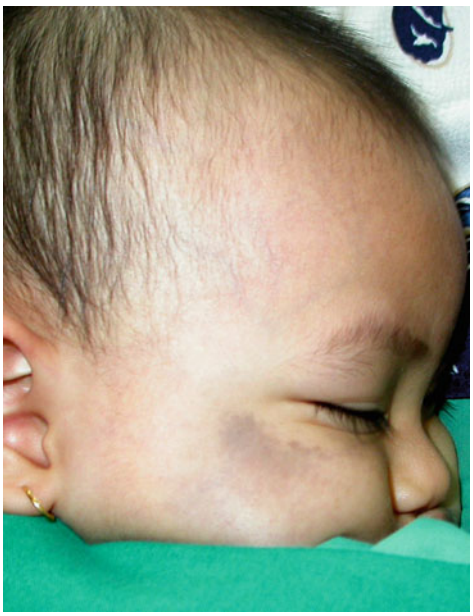

Figure 148.6
Nevus of Ota in the distribution of maxillary division of an infant

Becker's Nevus

Becker's nevus (Fig. 148.7) is a unilateral, solitary, acquired, localized, macular, light brown to hyperpigmented lesion of the skin. It is considered to be a cutaneous hamartoma and is covered more or less by terminal hair. Male-to-female ratio of occurrence is 2:1. It usually occurs in adolescence, but a congenital onset is also recorded. These lesions are usually localized on the shoulder, anterior chest, or upper arms, but lesions in other areas have been reported. Lesional tissue in Becker's nevus has been found to have an increased level of androgen receptors. Becker's nevus may occur in association with other conditions including breast hypoplasia, smooth muscle hamartoma, lipoatrophy, and acanthosis nigricans. "Becker's Nevus syndrome" refers to the occurrence of Becker's nevus with unilateral breast hypoplasia or other cutaneous, muscular, or skeletal defects. All of these anomalies tend to show a regional correspondence to the nevus and are mostly ipsilateral. No effective treatment for Becker's nevus is known. Er-YAG and Nd-YAG lasers have been used to improve cosmetic results.

Benign Hyperpigmented Lesions

Lentigines

Lentigines are small, tan, brown, or black, oval, or circular macules that may occur on any cutaneous surface and on mucous membrane. They do not darken on exposure to sunlight and do not disappear spontaneously. Histology of a lentigin shows elongation of epidermal rete ridges and increased activity of basal melanocytes without nesting of melanocytes, but melanocytes may be increased in number. Presence of multiple lentigines may be a sign of LEOPARD syndrome. The acronym LEOPARD stands for: *L*entigines; *E*lectrocardiographic abnormalities; *O*cular hypertelorism; *P*ulmonary stenosis; *A*bnormal genetalia; *R*etarded growth; and *D*eafness (sensory). Another multisystem disease associated with lentigines is Peutz-Jeghers syndrome, an autosomal dominant disorder that consists of multiple lentigines in the perioral area and elsewhere and gastrointestinal hamartomas situated most densely in the jejunum. No definite treatment of lentigines exists. Laser may be helpful in some cases.

Ephelides (Freckles)

Freckles are common in light skin, red-haired people and seem to be inherited as an autosomal dominant trait. The histology of ephelides shows increased melanin in epidermis without an increase in melanocytes and elongation of rete ridges. They are mainly present on sun-exposed areas, darken in summer and fade during winter months. They tend to fade in adults. Excessive, progressive freckling (Fig. 148.8) may be a feature of xeroderma

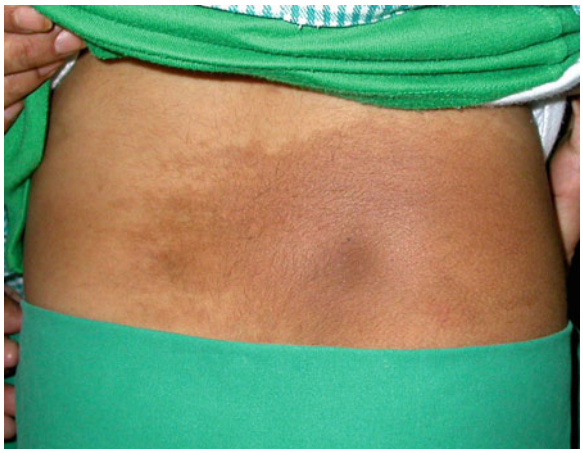

Figure 148.7
Becker's nevus on the lower back of a child

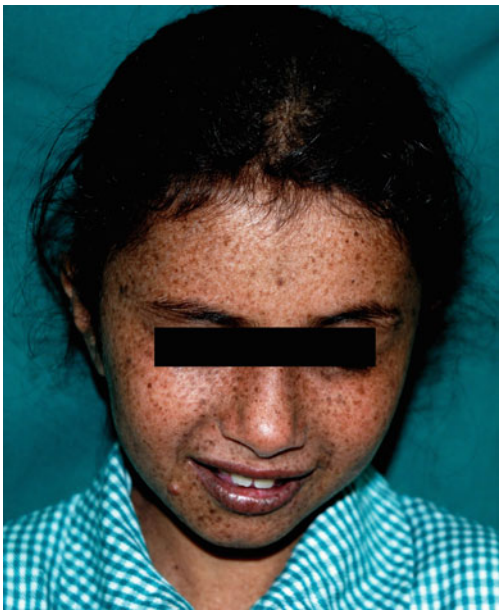

Figure 148.8
A child with xeroderma pigmentosum having multiple freckles

pigmentosum where it is associated with photosensitivity and photophobia. Patients with freckles should be advised about photoprotection. Treatment is for cosmetic reasons. Laser therapy may be useful in some cases.

Postinflammatory Hyperpigmentation

Postinflammatory hyperpigmentation refers to hyperpigmentation following skin inflammation or skin rashes, e.g., following sun damage, acne vulgaris, urticaria pigmentosa, etc. People with darker skin tones including Asians, Mediterraneans, or Africans are more prone to postinflammatory hyperpigmentation especially if they have excess sun exposure. Postinflammatory hyperpigmentation tends to fade with time.

Hyperpigmentation Related to Systemic Diseases/Drugs

Many endocrinological disorders including Addison's disease, Cushing's disease, and acanthosis nigricans are associated with different patterns of hyperpigmentation. Hyperpigmentation can also be induced by certain drugs including salicylic acid, bleomycin, psoralens, and cisplatin. A careful review of medical history, drug history, and relevant investigations are important in such cases.

Disorders of Hypopigmentation

Disorders of hypopigmentation are characterized by reduced melanin content in the skin that results in lightening of the skin. They can be congenital or acquired and may have hypopigmented or depigmented skin lesions.

Congenital Disorders of Hypopigmentation

Nevus Depigmentosus

Nevus depigmentosus (ND) is most frequently observed as a hypopigmented macule or patch in infants. Up to 1 in 130 otherwise healthy infants may have at least one ND. Most of the lesions appear during infancy and remain static throughout life. They are most commonly found on the trunk and can vary in size from 2–3 to 10 cm in diameter. The lesions are well circumscribed with irregular serrated borders, non-progressive, hypopigmented, lighter than the surrounding skin, seldom white, and without associated pathology. Occasionally, lesions may be segmental (◉ *Fig. 148.9*), linear with or without whorls, or block-like following Blashko's lines but without any other associated pathology; differential diagnosis includes hypomelanosis of Ito (HI). Histopathology and immunohistochemistry show that the melanin content is decreased in the affected skin, but there is no change in the number of melanocytes.

Nevus Anemicus

Nevus anemicus is a congenital lesion, 1–3 cm in diameter, round, slightly hypopchromatic with a ragged outline. Clinically, it may look like nevus depigmentosus. If pressure is applied with a convex glass, the nevus disappears, and if stroked, no flare is elicited. It is a congenital vascular anomaly and the lesional pallor is due to localized hypersensitivity to catecholamines with resultant vasoconstriction.

Ash-Leaf Macules

Ash-leaf macules are 1- to 3-cm hypopigmented macules that are ash-leaf in shape, i.e., oval at one end and pointed at the opposite. Lesions are most often found on the trunk, rarely on other sites, and are usually present at birth. Doubtful lesions should be visualized by Wood's light (ultraviolet light with 365-mm wavelength). They often

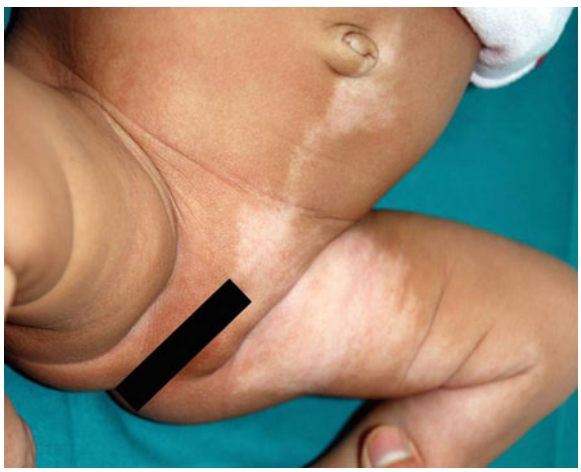

Figure 148.9
Nevus depigmentosus in a segmental distribution in an infant

are the first cutaneous sign of tuberous sclerosis complex (TSC). The diagnosis of TSC should be strongly suspected in patients having three or more ash-leaf macules (Fig. 148.10).

Hypomelanosis of Ito

The skin lesions in the HI include white, linear, extensive lesions usually affecting more than one body segment, unilateral or bilateral, whorls or whirl shaped (Fig. 148.11). They are not present at birth and have a tendency to disappear with age. Associated neurological and bone abnormalities may be present in 60% of the patients. HI is considered to be a heterogeneous disorder and its genetic nature is still not characterized. Chromosomal abnormalities (mosaicism and chimerism) are often detected in HI.

Piebaldism

Piebaldism is an autosomal dominant disorder caused by a defect in migration and maturation of melanoblasts from the neural crest. Clinically, it is characterized by congenital, extensive, and symmetrically distributed white patches on the forehead, anterior thorax, and limbs (Fig. 148.12), and a tuft of white hair on the forehead (white forelock). Small pigmented macules may be characteristically observed within the white patches with advancing age. The disorder is the result of the KIT gene mutation that encodes a tyrosine kinase receptor responsible for development of pigment cells and is located in chromosome 4q12.

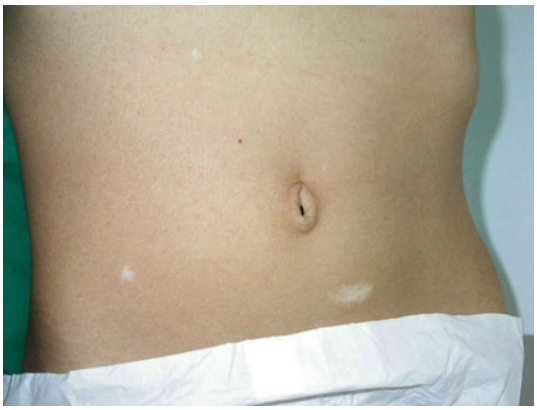

Figure 148.10
Ash-leaf macules in a patient with tuberous sclerosis complex

Waardenburg Syndrome

Waardenburg syndrome (WS) is a group of auditory-pigmentary syndromes that are caused by physical absence of melanocytes from skin, hair, eyes, and stria vascularis of

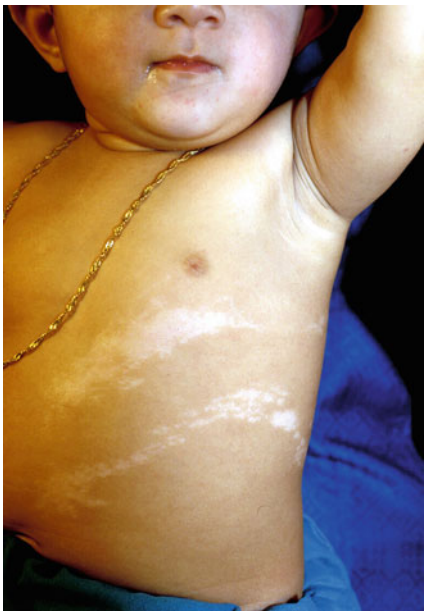

Figure 148.11
An infant with hypomelanosis of Ito having unilateral linear whorled hypopigmentation

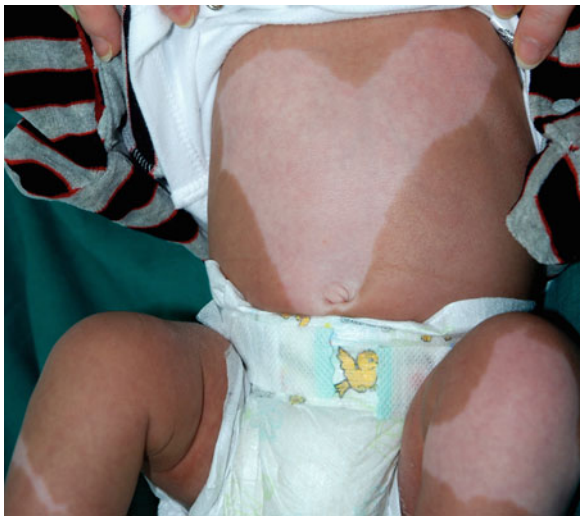

Figure 148.12
An infant with piebaldism having classic distribution of white patches

the cochlea. It is characterized by varying degree of sensorineural deafness, minor defects in the structures arising from the neural crest, and pigmentary abnormalities. Various clinical features include very pale or brilliantly blue eyes, eyes of two different colors (heterochromia) or eyes with one iris having two colors, a forelock of white hair (poliosis), premature graying of the hair, dystopia canthorum, moderate to profound hair loss, presence of white patches on the skin, and neurological abnormalities. At least four types of WS are described. *Table 148.1* summarizes the distinguishing clinical and molecular features of all the four types. A great inter- and intrafamilial variability among cases exist.

Others

Oculocutaneous albinism (OCA) is a heterogeneous group of disorders characterized by generalized reduction in pigmentation of skin, hair, and eyes. The clinical spectrum of OCA ranges, with OCA1A being the most severe type with complete lack of melanin production throughout life, while the milder forms of OCA1B, OCA2, OCA3, and OCA4 show some pigment accumulation over time. Clinical manifestations include various degrees of congenital nystagmus, iris hypopigmentation and translucency, reduced pigmentation of the retinal pigment epithelium, foveal hypoplasia, reduced visual acquity, refractory errors, color vision impairment, and prominent photophobia. The degree of skin and hair hypopigmentation varies the type of OCA. The incidence of skin cancer may be increased. All four types of OCA are inherited as autosomal recessive disorders. At least four genes are responsible for the different types of the disease (TYR, OCA2, TYRP1, and MATP). Persons with OCA have normal life span, development, intelligence, and fertility.

There are several syndromes of albinism associated with systemic pathology. These include Chediak-Higashi syndrome, Hermansky-Pudlack syndrome, Griscelli syndrome, and Elejalde syndrome. The genetic basis of some of these has been characterized.

Table 148.1
The four types of Waardenburg syndrome

Type	Inheritance	Distinguishing clinical features	Mutation
I	AD	Dystopia canthorum	Nearly all have PAX3 mutations
II	AD	No dystopia	Heterogeneous, MITF; SNAI2; SOX10 mutations
III	AD (most cases sporadic)	Hypoplasia of limb muscles, contractures of elbows, fingers	PAX3 heterozygotes; some may be homozygotes
IV	Mostly AR	Hircshsprung's disease	Heterogeneous; includes homozygotes for EDN3 or EDNRB mutations

AD autosomal dominant, *AR* autosomal recessive

Acquired Disorders of Hypopigmentation

Pityriasis Alba

Pityriasis alba is a common benign dermatosis usually seen in preadolescent children. It is characterized by the presence of hypopigmented, irregular, slightly scaly macules with well-defined borders that vary from 0.5 to 6 cm in diameter. The lesions are most commonly seen on the face and limbs. The trunk may also be affected. Males are thought to be affected more frequently, as are patients with darker skin color. The etiopathogenesis of pityriasis alba is still poorly understood. Excessive and unprotected sun exposure, frequent bathing, dry skin conditions, and atopic background are strongly linked to the development of pityriasis alba. The treatment should include sun protection, use of moisturizers, and mild potency topical steroid creams in resistant cases.

Pityriasis Versicolor

Pityriasis versicolor (PV) is a common benign recurrent superficial fungal disease that is caused by *Malassezia furfur* species. These yeasts are part of normal human skin flora and occur predominantly in seborrheic areas because of their lipid dependency. The prevalence is higher in hot and humid climates. Some host factors including use of anticoagulants, systemic corticosteroids, and immunosuppressive state are also noted to influence the development of disease. PV is most commonly seen in adolescents and young adults but has been reported in children as well. The disorder manifests as hypopigmented scaly macules on seborrheic areas. The lesions are usually oval or scalloped and tend to be asymptomatic. Diagnosis is made on clinical suspicion and can be confirmed by

examination of scales under a microscope using 10–20% potassium hydroxide alone or in combination with Parker ink in equal parts. This examination reveals a typical "spaghetti and meatballs" pattern that reflects the presence of hyphae and blastospores. Treatment includes various topical modalities including selenium sulfide 2.5% shampoo, ketoconazole shampoo, topical clotrimazole, miconazole creams, or lotions. Patients with recurrent or resistant disease may need systemic treatment with itraconazole or fluconazole.

Halo Nevus

A halo nevus is a pigmented nevus surrounded by a ring of depigmentation (◉ *Fig. 148.13*). The nevus usually undergoes progressive regression over a period of several months. The lesions usually develop in children and young adults and are preferentially located on the back. The pathophysiology of halo nevus is not well known. A cytotoxic cell-mediated immune response is suspected to be involved in the destruction of nevomelanocytes. Halo nevus and vitiligo seem to have different pathognomic mechanisms. Some patients with vitiligo after the appearance of halo nevus have been reported. Treatment options may include laser and noncultured epidermal cellular grafting.

Vitiligo

Vitiligo is an acquired disorder of depigmentation characterized by progressive loss of melanocytes from the epidermis and epidermal appendages that results in well-circumscribed milky white macules. It affects 1–2% of the world population. Approximately half the affected individuals develop the disease during childhood and adolescence. It affects all racial types but is a disease of major concern among those with dark skin. According to the distribution of the lesions, several types of vitiligo have been distinguished. Focal vitiligo refers to the presence of one or more macules in distant areas (◉ *Fig. 148.14*). Segmental vitiligo refers to the presence of one or more vitiligo lesions in segmental distribution (◉ *Fig. 148.15*). Acral vitiligo refers to that with predominant acral distribution including the hands, feet, and face (◉ *Fig. 148.16*). Most often the lesions are precipitated by trauma. Stress and infections may act as other precipitating factors. The etiopathogenesis of the disease is still not completely elucidated. Various theories including genetic, autoimmune, neural, and hormonal have been proposed. Its association with various autoimmune disorders including thyroid disease, pernicious anemia, etc., and the presence of

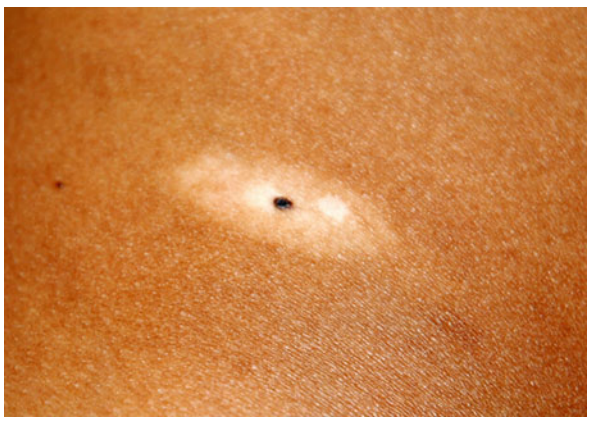

Figure 148.13
Halo nevus

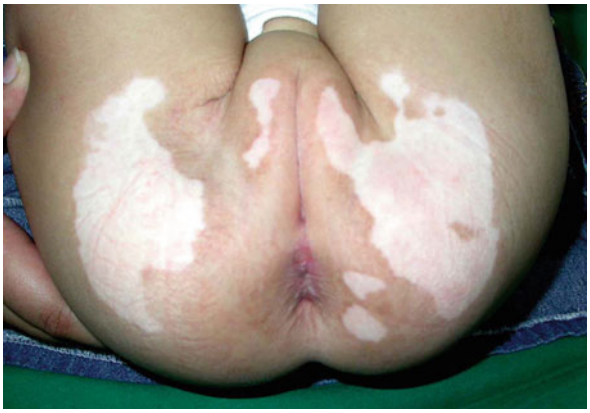

Figure 148.14
An infant with perianal vitiligo

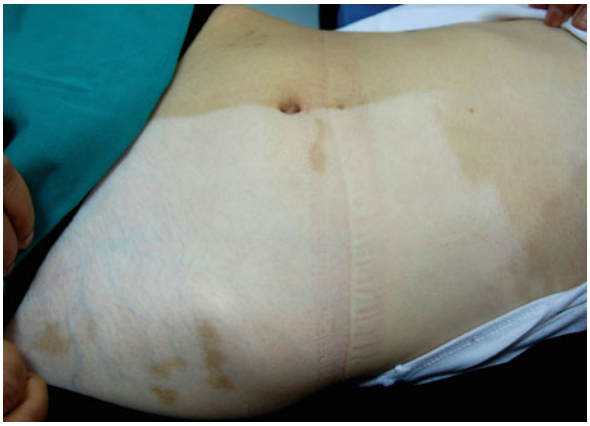

Figure 148.15
A child with segmental vitiligo

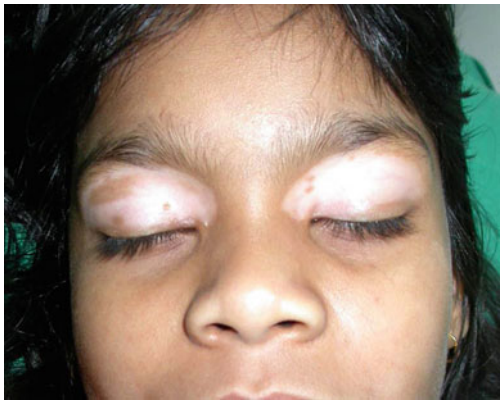

Figure 148.16
A child with periorbital vitiligo

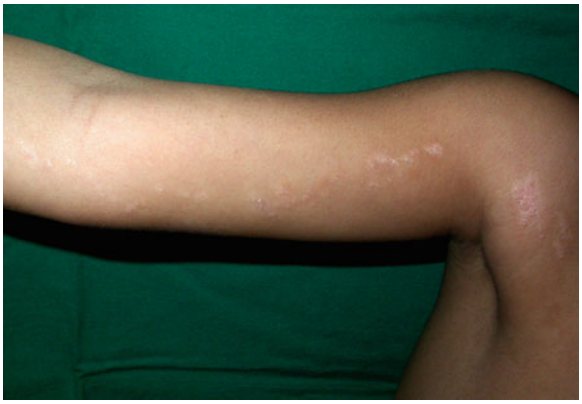

Figure 148.17
Lichen striatus on the arm of a child

organ specific autoantibodies in vitiligo patients favors an autoimmune etiology. The treatment of vitiligo is based on finding ways to stimulate melanocytes, stopping the destruction of melanocytes, and providing ways to allow for melanocyte migration. The choice of treatment depends upon the extent of the disease, sites affected, and age of the patient. For localized disease, topical modalities are preferred that include topical steroid creams, calcineurin inhibitors (pimecrolimus and tacrolimus), calcipotriene, pseudocatalase, and topical meladinine. Narrow band ultraviolet B (NB-UVB) phototherapy and photochemotherapy (PUVA) are indicated for extensive disease. PUVA is relatively contraindicated in young children. Excimer laser is indicated for localized, stable vitiligo that does not respond to conventional topical preparations. Surgical options include autologous punch grafting, suction blister grafting, split-thickness skin grafting, cultured-melanocyte transplantation, and noncultured-melanocyte transplantation. Surgical options are indicated for stable disease or segmental vitiligo where other treatments have failed and choice of surgical therapy depends upon availability and the experience of the treating physician. Combination therapies or a cyclic approach between various treatments is useful in several cases.

Lichen Striatus

Lichen striatus is usually characterized by a linear, finely popular, hypochromic asymptomatic skin eruption most frequently located on the extremities following lines of Blashko (*Fig. 148.17*). It spontaneously disappears in 1–2 years leaving behind hypopigmentation that slowly regresses. It is relatively common in children and adolescents and rare in infants. Lichen striatus has been histologically related to a virus.

Lichen Sclerosus et Atrophicus

Lichen sclerosus et atrophicus (LSA) is rare in children. The lesions are chalk white and are associated with pruritus. Lesions can happen anywhere but perivulval and perianal locations are more common (*Fig. 148.18*). Female children are more often affected than males. The etiopathogenesis is still not clear but several mechanisms including genetic, autoimmune, and hormonal are suspected to play a role. Typical lesions of LSA are milky white atrophic papules that coalesce to form plaques and may also show follicular plugging. The main differential diagnosis is vitiligo. Child abuse is also considered in some cases. Treatment possibilities are mid- to high-potency topical steroids, calcineurin inhibitors, and pimecrolimus. In female children the lesions tend to show spontaneous remission with the onset of menarche.

Hypopigmented Mycosis Fungoides

Mycosis fungoides (MF) is a variant of cutaneous T-cell lymphoma with an indolent course. It is rare in children and adolescents. Hypopigmented MF is a variant of patch stage MF that has been reported in races (*Fig. 148.19*) and is more often seen in younger patients including children and adolescents. The lesions may manifest as hypopigmented to depigmented macules with or without

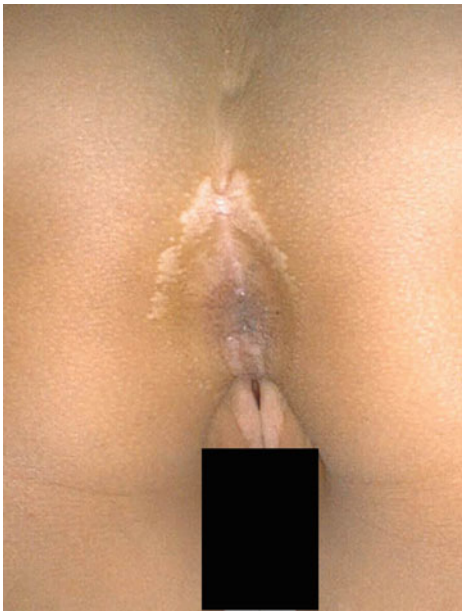

Figure 148.18
Lichen sclerosus et atrophicus on the perigenital distribution in a female child

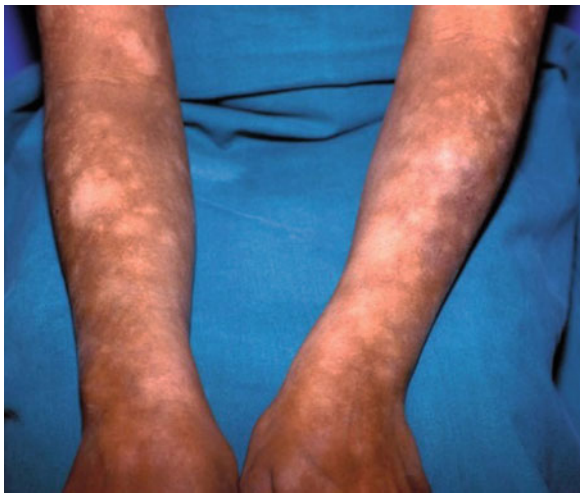

Figure 148.19
A child with multiple hypopigmented mycosis fungoides lesions on the forearms

scales present anywhere on the skin. Differential diagnosis includes vitiligo, pityriasis alba, and postinflammatory hypopigmentation. If suspected clinically diagnosis needs to be confirmed by histopathology. Phototherapy (NB-UVB) and photochemotherapy (PUVA) are the treatments of choice.

Postinflammatory Hypopigmentation

In colored races, skin inflammation and rashes may sometimes heal leaving behind postinflammatory hypopigmentation.

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149 Infectious Diseases of the Childhood, Including Fungal and Viral Infections

Sara A. Lohser · Camille Sabella · Kenneth J. Tomecki

Bacterial Infections

Bacterial infections are a common cause for medical appointments, emergency room visits, and hospital admissions among children. Such infections occur in both immunocompetent and immunocompromised children, the latter group being more susceptible to more serious and potentially resistant infections due to frequent use of antibiotics. The most common causes of infections are *Staphylococcus aureus* and group A beta hemolytic (GABHS), which is also known as *Streptococcus pyogenes*. In some instances, there can be overlap with multiple bacterial pathogens involved, e.g., *Corynebacterium, Pseudomonas* species, and *Neisseria meningitidis*.

MRSA

Folliculitis, Furuncles, and Carbuncles

Folliculitis is an infection of the hair follicle most commonly caused by *S. aureus*, less often, occlusion without bacteria, or *Pseudomonas* secondary to hot-tub exposure (see ❯ *Pseudomonas* Infections).

Patients have perifollicular erythematous papules with overlying pustules on the buttocks, axillae, chest, back, within areas of occlusion/friction/irritation (e.g., shaving), but may occur anywhere on the body. Folliculitis is often seen in immunocompetent patients, but obese, diabetic, and/or immunocompromised patients are at increased risk for this infection. A furuncle is a deeper infection of the follicular unit with spread into the surrounding tissue. A carbuncle is the fusion of several furuncles. Furuncles and carbuncles are generally painful, and purulent drainage is common (❯ *Figs. 149.1* and ❯ *149.2*).

The differential diagnosis includes molluscum contagiosum, keratosis pilaris, *Pseudomonas* folliculitis, ruptured epidermal inclusion cyst (which can look identical to a furuncle), hidradenitis suppurativa and acne conglobata (distinguished by negative cultures), *Pityrosporum* folliculitis, candidiasis, scabies, acne, miliaria rubra, and tinea corporis.

Evaluation should include KOH prep and culture with sensitivity, specifically for *S. aureus*, including methicillin-resistant *S. aureus* (MRSA). Treatment is directed at good hygiene, including bleach baths and antibacterial soaps, such as chlorhexidine or benzoyl peroxide. If the area of involvement is small, topical mupirocin is worthwhile. Widespread infections require oral antibiotics, such as first-generation cephalosporins or amoxicillin/clavulanic acid for methicillin-susceptible pathogens, clindmaycin, or trimthroprim sulfamethoxasole for MRSA infections.

Impetigo

The most common cause of impetigo in the USA and Europe is *S. aureus*, while in developing countries, *S. pyogenes* is the more prevalent causative agent. However, overlapping infections are becoming more common. MRSA has also been implicated and is seen more commonly in the nonbullous form of impetigo.

S. pyogenes typically colonizes the skin after trauma secondary to excoriations, bites, or dermatitis, and precedes the clinical appearance of erosions and resulting infection by approximately 2 weeks. Infection is superficial, contagious, and, most often, occurs in the summer months in children under age 6 years. Systemic signs and symptoms are common. Children develop oozing erosions, often on the face, specifically around the nose and mouth that form typical "honey-colored crusts" (❯ *Fig. 149.3*).

Bullous impetigo is a variant with bullae, often in the groin or intertriginous areas. Bullae are initially clear and become turbid and occasionally pustular. Ruptured bullae leave a raw, eroded base with a peripheral collarette of scale. Both nonbullous and bullous forms of impetigo heal without scarring.

The differential diagnosis of impetigo includes herpes simplex, diagnosed via Tzanck smear, PCR, or DFA; tinea infections, diagnosed via KOH; and contact or nummular dermatitis. Biopsy may be required to confirm the diagnosis.

Secondary glomerulonephritis may occur, but is rare. Treatment includes gentle debridement, cleansing with

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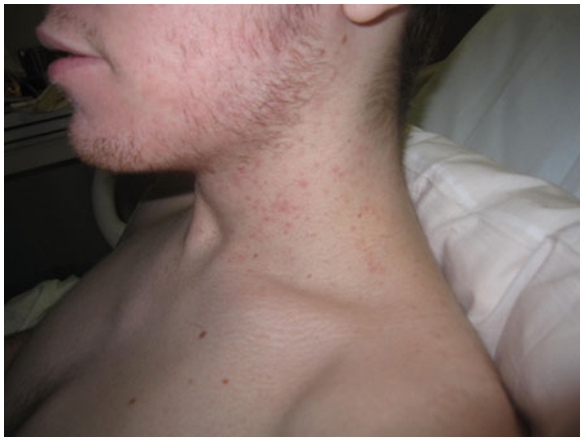


Figure 149.1
Folliculitis

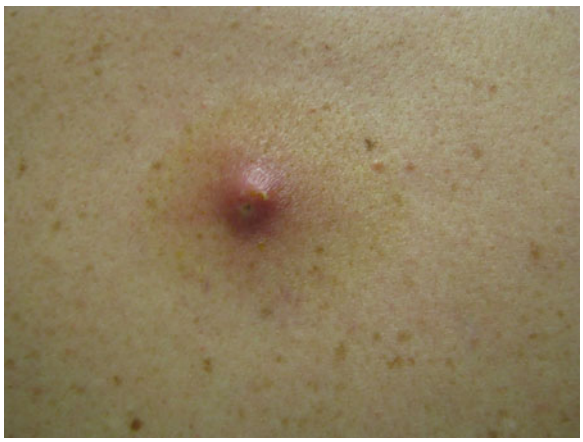


Figure 149.2
Carbuncle

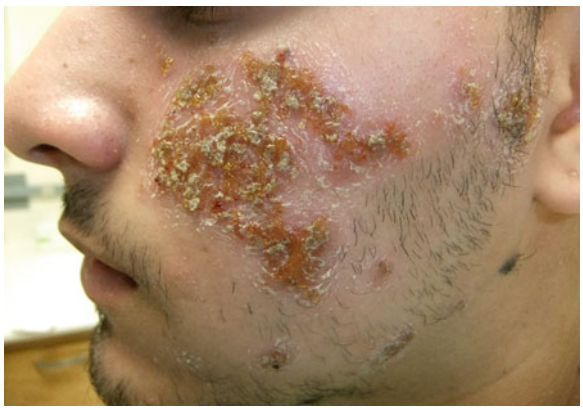


Figure 149.3
Impetigo

antibacterial soap or wash (chlorhexidine), and topical antibiotics (mupirocin or retapamulin). Retapamulin has better bacterial coverage than mupirocin, with less likelihood (thus far) of resistance. Fusidic acid is a useful alternative for treatment, but is not available in the USA. For patients with widespread involvement, oral antibiotics are necessary, e.g., first-generation cephalosporins (cephalexin), or beta lactam/beta lactamase inhibitors; for MRSA infection, tetracycline, trimethoprim/sulfamethoxazole, clindamycin, or linezolid may be required. Recurrence may be secondary to Staphylococcal carriage in the nares, axillae, groin, or umbilicus. Treatment with mupirocin ointment twice daily for 5 days may help eliminate colonization, but periodic retreatment is often required, and the long-term efficacy of decolonization is not clear.

Staphylococcal Scalded Skin Syndrome (SSSS)

SSSS is caused most commonly by a phage group 2 of *S. aureus*, which produces exfoliative toxins, ETA and ETB. The toxins are serine proteases targeting desmoglein 1 which produces a split within the epidermis at the granular cell layer. The toxins spread hematogenously from a localized source of epidermal damage, but the source of infection is often unknown; possible sites include wounds, nasopharynx, urinary tract, anus, umbilicus, conjunctiva, surgical site, or pneumonia.

SSSS typically affects children under age 2 (62%) and almost all affected patients are children under age 6 years (98%), due to decreased renal ability to excrete the ETA and ETB toxins. Clinically, children have severe irritability, skin tenderness, malaise, and +/− fever. Skin disease erupts rapidly with crusting and scaling occurring around the mouth or intertriginous areas, progressing until the entire body is covered with tender erythroderma. Patients may develop fragile bullae (with Nikolsky sign) that rupture easily yielding skin peeling in sheets. Healing typically begins in approximately 10 days without scarring, and mucosal surfaces are not involved.

Evaluation should include cultures obtained from the eye, nose, throat, axillae, groin, blood, or other suspected sites of infection. Cultures obtained from desquamative areas are negative since denuded skin is toxin-medicated. Frozen section of peeling skin may help differentiate toxic epidermal necrolysis.

Differential diagnosis includes toxic shock syndrome, pemphigus foliaceus, graft-versus-host disease, epidermolysis bullosa, thermal burn, Kawaski disease, nutritional deficiency, keratolysis exfoliativa, drug eruption, and viral exanthem.

Most patients require hospital admission unless there is very minimal involvement. Treatment includes rehydration, temperature control, topical wound care (often with burn unit treatment depending on level of severity), avoidance of handling infant/child as much as possible due to sensitivity of skin, analgesia, and parenteral antibiotics (e.g., nafcillin, oxacillin, or vancomycin). Most cases are resistant to penicillin.

Methicillin-Resistant *Staphylococcus aureus*

Historically MRSA infections occur in institutionalized and hospitalized populations. However, over the past few years these have become more common throughout the community. The clinical presentation is typically an abscess (often in the diaper area of infants) due to the Panton–Valentine leukocidin (PVL) toxin, which is lethal to neutrophils. MRSA infections can affect children of all ages, but those with increased risk factors include atopic patients and some athletes, e.g., wrestlers and football players.

Abscesses develop and may resolve without treatment especially when drained either manually or spontaneously. Hyperpigmentation persists after resolution and scarring is common. Though uncommon, MRSA can be potentially fatal if it progresses to sepsis, pneumonia, or osteomyelitis.

Evaluation includes bacterial culture with sensitivity of abscess and culture for potential colonization. The mainstay of therapy is incision and drainage of the abscess. With that simple approach, the vast majority of patients do well. Antibiotics are necessary for those patients with cellulitis, comorbidities, large lesions, and/or fever. Tetracycline, clindamycin, and trimethoprim-sulfamethoxazole generally provide good outpatient coverage, while intravenous vancomycin or linezolid are often required for hospitalized patients.

Streptococcal Infections

Perianal Streptococcal Dermatitis

Perianal streptococcal dermatitis is caused by group A ß-hemolytic *Streptococcus* (GABHS) and affects children aged 7 months to 10 years (mean age 4–5 years), more commonly males. Thirteen percent of patients have symptomatic pharyngitis, but 60% have a positive throat culture. Affected patients have tender, raw, well-demarcated, beefy red perianal erythema. As disease progresses, scaling develops, resembling inverse psoriasis. Other possible diagnoses include irritant dermatitis, candidiasis, and inflammatory bowel disease with cutaneous involvement. Dermatitis typically involves the perianal area, but buttocks and vagina or penis (balanitis) may also be affected. Associated signs/symptoms include painful defecation, fecal avoidance or incontinence, blood streaked stool, and anal fissures.

Bacterial culture should be obtained: standard treatment is penicillin for 14–21 days, and alternatives include amoxicillin or clarithromycin. A second course of antibiotics is sometimes required and recurrence is common. Bland emollients will help soothe the affected areas. Treatment is important to offset progression to post streptococcal glomerulonephritis, followed by posttreatment urinalysis and culture to confirm clearance. Guttate psoriasis may follow perianal streptococcal dermatitis in the same manner that it follows streptococcal pharyngitis.

Scarlatina

Scarlatina occurs in children aged 2–10 years after streptococcal pharyngitis or soft tissue infection. Children present with fever, sore throat, adenopathy, and strawberry tongue, and within 2–3 days, they develop a fine, sandpaper erythema on the face, posterior neck, and upper back that spreads downward over the body. Erythema is most notable in skin folds and fades in a week, followed by desquamation that may persist for days to weeks.

Erysipelas and Cellulitis

Erysipelas is a superficial cellulitis typically caused by group A ß-hemolytic *Streptococcus* (GABHS) with a recent shift toward non-group A *Streptococci*. Patients have a well-defined, erythematous, indurated, tender, warm, shiny plaque with a rapidly advancing border that develops as the bacteria spreads through lymphatic vessels. Infection is associated with fever (+/−), chills, and malaise. The legs are the most commonly affected areas, but infection may occur on the face and less often on other areas of the body.

Cellulitis is caused by GABHS, *S. aureus*, *Haemophilus* (incidence markedly decreased with advent of Hib vaccine), *Pasturella multocida* secondary to animal bites, *Klebsiella pneumoniae*, and *Yersinia enterocolitica*. Patients develop deep dermal or subcutaneous erythema with poorly defined borders at the site of a previous wound. As with erysipelas, a leading edge of erythema is often present, but cellulitis has no sharp demarcation from surrounding skin. Cellulitis has attendant warmth, edema, and pain often with fever, chills, and malaise. Bullae and petechiae may occur (*Fig. 149.4*).

The cause of both erysipelas and cellulitis is bacterial inoculation of the skin (skin trauma). Potential portals of entry include the nasopharynx (streptococcal pharyngitis in one-third of cases of facial erysipelas), abrasions, and

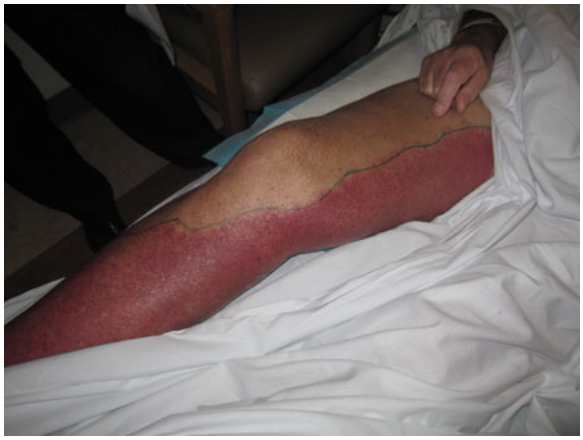


Figure 149.4
Cellulitis

ulcerations secondary to body piercing, venous insufficiency with stasis, inflammatory dermatoses, dermatophyte infections, insect bites, and surgical incisions. Patients with preexisting lymphedema secondary to past surgeries, trauma, thromboses, or congenital vascular malformations are at increased risk for erysipelas and cellulitis. Differential diagnosis includes contact dermatitis, arthropod bite dermatitis, necrotizing fasciitis, and eosinophilic cellulitis.

Treatment includes elevation of the affected area, compresses for ulcerated or necrotic areas, and antibiotics, e.g., penicillin for group A streptococcal infections, first-generation cephalosporin or clindamycin for staphylococcal infections, and in patients with penicillin allergy. Patients with facial or orbital cellulitis require hospitalization and parenteral antibiotics.

Corynebacterium Infections

Pitted Keratolysis (PK)

Pitted keratolysis caused by *Corynebacterium* species *Micrococcus sedentarius* and *Dermatophilus congolensis* is a superficial infection that occurs within the stratum corneum (SC) due to the bacterial production of proteolytic enzymes that digest the outermost layer of the skin. PK is malodorous, 1–2 mm craters, or shallow erosions that coalesce into depressed plaques with moist texture (+/− frank maceration) on the plantar feet and around the toes. It occurs more commonly in males and patients with excessively sweaty feet or exposure to wet environments or boots.

Tinea pedis is the differentiating diagnosis, and KOH prep can confirm or negate, though the distinct pungent odor of PK generally allows the distinction to be made clinically. Treatment includes clindamycin solution, erythromycin solution, mupirocin ointment, or benzoyl peroxide gel for 2–3 weeks. Excessive sweating can be addressed by the use of aluminum chloride preparations or botulinum toxin injections. Patients should avoid wet work and prolonged periods of wearing boots.

Erythrasma

Erythrasma caused by *Corynebacterium minutissimum*, a Gram-positive rod that produces porphyrins, mainly occurs in adults and only occasionally in children. Affected patients have pink to brownish scaling plaques most commonly in the groin and axillae, less so in the inframammary area, abdominal skin folds, gluteal cleft, and interdigital spaces of the toes. Infection is generally asymptomatic, but pruritus may occur, often exacerbated by heat and humidity.

The porphyrins produced by the positive rod cause a coral-pink fluorescence with Wood's light examination, which helps to clinch the diagnosis. Other entities to consider include: tinea infection, Candida or frictional intertrigo (KOH prep for diagnosis), psoriasis, and seborrheic or nonspecific dermatitis. Treatment with topical clindamycin or erythromycin is usually curative or oral antibiotics for extensive disease.

Neisseria meningitidis

Meningococcemia

Meningococcemia is caused by *Neisseria meningitidis*, a Gram-negative diplococcus bacterium spread to asymptomatic carriers via respiratory droplets. Infection is bimodal and typically occurs in children less than 4 years old (neonates <6 months are often protected due to maternal immunoglobulin G antibodies) or adolescents 15–19 years old. Meningococcemia is a viral-like illness with fever, headache, neck stiffness, and photophobia; these signs will often be absent making the diagnosis more difficult in children <2 years old. The infection rapidly evolves into meningitis or septicemia and irreversible shock and death may occur within hours of onset of symptoms.

Most patients (2/3) will initially have blanchable erythematous macules and papules and later small petechiae, usually on the trunk and lower extremities. The petechiae rapidly coalesce into well-demarcated ecchymoses. Extensive purpura with gunmetal gray color occur in fulminant infections, followed by sloughing of the skin, gangrene,

and loss of limbs. Patients with fulminant infections have CNS abnormalities and sepsis.

Patients with suspected infection need hospitalization. The workup should be prompt and includes blood and CSF Gram stain and culture, followed by empiric antibiotic treatment, with broad spectrum and/or multiple IV antibiotics, e.g., benzylpenicillin, cefotaxime, or ceftriaxone. Timely management is crucial since the mortality rate is 5% and 90% if DIC develops. To prevent outbreaks and further spread of infection, household and other close contacts deserve prophylaxis with rifampin, ceftriaxone, or ciprofloxacin.

Pseudomonal Infections

Pseudomonas is a Gram-negative, aerobic rod that produces pyocyanin which causes the notable green color, may be a normal part of the skin flora, especially in the ear canal, groin, and axillae. *Pseudomonas* has a fruity or grape-like aroma associated with infection, and although the odor is not always present or noted, it can be very helpful in making a diagnosis.

The most common cause of *Pseudomonas* infection in normal hosts is hot-tub folliculitis which occurs after exposure to improperly chlorinated hot tubs or spas. Children are particularly susceptible to the infection after bathtub toys or sponges are used in hot tubs and then stored in mesh containers without being rinsed, harboring *Pseudomonas*. Patients may have low-grade fever and malaise but, typically, they are asymptomatic with edematous perifollicular red papules and pustules on the trunk and proximal extremities, although may be pruritic and/or painful. The infection may be associated with otitis externa from the hot-tub exposure and may occur in swimmers secondary to water collection in the external auditory canal.

The differential diagnosis includes *S. aureus* folliculitis, bug bites, and nodular scabies. Culture should be obtained to confirm the diagnosis. Treatment is not necessary since papules resolve spontaneously; however, low-potency corticosteroid may be useful if pruritus is present. As prevention, hot-tub chlorination must be employed or properly adjusted (often necessary to drain hot tub), and toys must be cleaned with bleach, though discarding them would be best. Associated otitis externa deserves treatment with ototopic gentamycin, tobramycin, or ciprofloxacin solution.

Please refer to *Table 149.1* for additional examples of *Pseudomonas* infections.

Table 149.1
Other physical findings secondary to *Pseudomonas*

Condition	Signs/symptoms	Exacerbating factors	Treatment
Pseudomonas nail	Greenish-black discoloration of nails associated with onycholysis	Moist environments/ water work	Gentamycin, tobramycin, or ciprofloxacin solution
Interdigital infections	Macerated, erythematous plaques within toe spaces	Hyperhidrosis, chronic moisture, exposure to wet environments	Acetic acid soaks
			Decrease moisture with aluminum chloride or botulinum toxin injections for hyperhidrosis
Chronic wounds with secondary infection	Associated with wounds of epidermolysis bullosa, thermal burns, neuropathic ulcers, ulcerated hemangiomas of infancy	Uncontrolled/poorly controlled underlying disease	Topical or oral antibiotics depending on severity and distribution of wounds, coupled with treatment of underlying medical condition to prevent future colonization
Ecthyma gangrenosum	Edematous vesicopustule that becomes hemorrhagic and develops into punched-out ulcer with black eschar with surrounding edema	Immunocompromised patients	Hospitalization
			Culture suspected lesions
			Parenteral antibiotic treatment as soon as possible
			Blood cultures and biopsy to confirm diagnosis and rule out bacterial/fungal process, pyoderma gangrenosum, or Sweet's syndrome
	Patients are often bacteremic and septic		Debridement of necrotic tissue

Viral Infections

Viral infections are commonplace in the general pediatrician's office and often exhibit nonspecific skin findings, fever, and malaise. Most viral illnesses are self-limited and rarely warrant dermatologic management and treatment. The most common viral diseases for a dermatologist are molluscum contagiosum and warts.

Classic Exanthems of Childhood

Order	Exanthem
First	Rubeola or measles
Second	Scarlet fever
Third	Rubella or German measles
Fourth	Filatow–Dukes' disease[a]
Fifth	Erythema infectiosum or Parvovirus
Sixth	Roseola or exanthem subitum

[a]Not a separate exanthem, variant of scarlet fever or toxin-producing staphylococcal disease

Measles (Rubeola, First Disease)

Rubeola caused by an RNA morbillivirus, of the Paramyxoviridae family, is a common infectious disease with worldwide distribution and appreciable mortality often related to early age of exposure and poor nutritional status.

Transmission occurs via respiratory spread, 1–2 days before the prodrome until 4 days after the onset of exanthem; the incubation period is 8–12 days. Prodrome lasts 2–4 days, and patients experience high fever, coryza, cough, conjunctivitis, often with white spots on an erythematous base on the buccal mucosa opposite the molars which are Koplik spots and pathognomonic for the disease. The exanthem typically begins 14 days after exposure with red-brown pruritic macules and papules that initially begin along the hairline, behind the ears, and on the neck, which spread to the trunk and become generalized by day 3. The exanthem begins to fade within 5 days (*Fig. 149.5*).

Complications are more likely to occur in young children (<5 years old), young adults (>20 years old), and immunodeficient and malnourished (specifically with low levels of vitamin A) patients, most commonly otitis media and bronchopneumonia, less so encephalitis, myocarditis, pericarditis, and death due to respiratory and neurologic sequelae. The mortality rate in the USA is low, 0.1–0.2%, but worldwide, measles is still a leading cause of death accounting for 197,000 deaths annually.

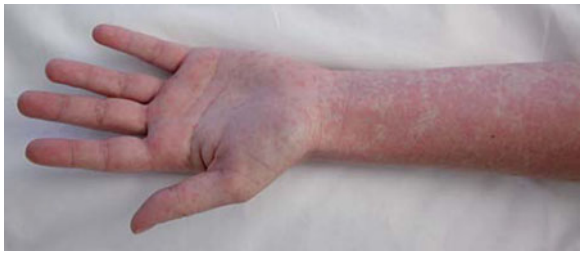


Figure 149.5
Measles

Patients with measles should be isolated and treated by supportive care measures. Oral rehydration may be all that is required; however, intravenous hydration may be necessary. Dietary supplementation with vitamin A is essential for all kids with measles and reduces mortality by 50% and helps prevent eye damage and blindness. Disease has diminished dramatically, especially in the USA since the advent of the measles vaccine in 1963. However, resurgence has occurred in the last two decades because of parental refusal of about vaccination and home schooling (loss of compulsory vaccination). The measles vaccine is a live attenuated virus and part of the measles, mumps, and rubella (MMR) vaccine. The first dose is given at 12–15 months and the second dose at 4–6 years. Mild exanthem may occur 10–14 days after administration of the vaccine.

Rubella (German Measles, Third Disease)

Rubella caused by Rubivirus, an RNA virus of the Togaviridae family, has worldwide distribution, and transmission occurs via respiratory droplets. The incubation period is 14–21 days, and the infection begins in the nasopharynx followed by a primary and secondary viremia, which causes a generalized systemic infection. Patients are infectious 5–7 days prior to exanthem and for 3–5 days afterward.

Children typically have no prodrome but, occasionally, they have low-grade fever, painful occipital lymphadenopathy, and ocular pain. Adolescents and adults are symptomatic during the prodrome with fever, malaise, sore throat, nausea, and anorexia. Children develop a mild exanthem, but infection is subclinical in 50% of cases. When present, the exanthem begins on the face and neck with pink to erythematous macules and papules that generalize within 24–48 h. An associated enanthem of petechiae on the hard palate, known as Forschheimer spots, may develop.

Arthritis and arthralgias occur with increased age and are more common among women. Within 2–3 days, the exanthem fades, initially on the face and then elsewhere.

In most cases, diagnosis is made clinically and, in more severe cases, serologic testing can be useful to rule out other viral exanthems. Detection of virus-specific immunoglobulin M (IgM) antibody in acute serum and a fourfold rise in antibody titer between acute and convalescent sera is diagnostic of rubella. Affected patients should be isolated and kept at home for 7 days following the onset of disease; given the mild nature, generally no treatment is required. Potential complications include peripheral neuritis, encephalitis, and thrombocytopenia purpura. If rubella is contracted during the first trimester of pregnancy, it can have devastating fetal effects, including intrauterine growth retardation, cataracts, glaucoma, microphthalmia, chorioretinitis, sensorineural deafness, patent ductus arteriosus, atrial and ventricular septal defects, and pulmonary stenosis. Neonates may have violaceous macules/papules secondary to extramedullary hematopoiesis ("blueberry muffin" baby), and 20% of patients will have hematologic abnormalities. The virus can be excreted for 1–2 years.

Introduction of the live vaccine in 1969 reduced the incidence of Rubella by 98%, and the vaccine produces seroconversion in 98% of patients. Today, cases are due to refusal or failure to be vaccinated. Children should receive the measles, mumps, and rubella (MMR) vaccine at 12–15 months and, then, at 4–6 years. Side effects occur in 5–15% of children and include exanthem, fever, and lymphadenopathy. Older children may have arthralgias and arthritis.

Erythema Infectiosum/Parvovirus (Fifth Disease)

Erythema Infectiosum, first recognized and described in 1889, represents infection with Parvovirus B19, a single-stranded DNA virus. The infection, like other viral exanthems, is widespread and typically occurs in young children. It is most common during the winter and spring, and transmission occurs via respiratory droplets, hematogenous spread, and transplacental exchange. The incubation period is 4–14 days and the prodrome is absent or minimal; if symptoms do occur, patients have low-grade fever, headache, sore throat, rhinorrhea, and malaise. The exanthem has two phases, the first, bright red erythematous patches on the cheeks with the characteristic "slapped cheek" appearance; the second, 1–4 days later, lacy, reticulated macules and papules on the proximal extremities, which spread to the trunk. Children, especially adolescents, may have arthralgias and arthritis (knees, ankles, wrists, and elbows most commonly affected). The exanthem is essentially asymptomatic but may be worsened with heat and sun exposure, and fades within a few days to weeks. It is important to counsel parents that the rash may recur with heat (including warm baths), sun exposure, friction, crying, or exercise for up to 4–6 weeks.

Another parvovirus infection is the papular-purpuric gloves and socks syndrome, an entity more commonly seen in adolescents and characterized by the sudden onset of erythema and edema of the palms and soles. Patients develop petechiae in the same distribution, which becomes sharply demarcated confluent purpura. Petechiae may also be found on other areas of the body and oral mucosa. Patients often have pain, burning, or itch, especially on the hands and feet.

The differential diagnosis of erythema infectiosum includes: scarlet fever, rubeola, rubella, roseola, other viral exanthems, erysipelas (face), and drug eruption. In patients with arthralgias and arthritis, lupus erythematosus, Henoch–Schonlein purpura, and juvenile rheumatoid arthritis should also be considered. Children with the papular-purpuric syndrome should be evaluated for Rocky Mountain Spotted Fever or meningococcemia. Parvovirus is a clinical diagnosis, but may be confirmed with elevated levels of IgG and IgM. IgM levels persist for 2–3 months following the infection. Erythema infectiosum may be complicated by anemia in many patients, which may progress to aplastic anemia in patients with sickle-cell disease, other hemoglobinopathies, or those on chemotherapy. Pregnant women with an active infection have a 33% chance of fetal infection, although the vast majority of these infants are born without sequelae. Women in the first and second trimester are at greatest risk. The infection can rarely cause significant anemia leading to hydrops fetalis and death. Children are viremic 1 week prior to exanthem, thus no isolation is recommended at the time of the appearance of the rash.

Children typically recover spontaneously, and no treatment is needed, unless complications arise. Supportive care with rehydration therapy, nonsteroidal anti-inflammatory agents for arthralgias and arthritis, and antipyretics for fever are generally all that is needed.

Herpes Viruses (Herpesviridae)

There are eight human herpes viruses (HHV) with skin manifestations and some with organ involvement. The

Table 149.2
Properties of Herpes viruses

Human Herpes type	Name	Subfamily	Target cell type	Latency	Transmission
1	Herpes simplex-1 (HSV-1)	Alpha	Mucoepithelia	Neuron	Close contact
2	Herpes simplex-2 (HSV-2)	Alpha	Mucoepithelia	Neuron	Close contact, usually sexual
3	Varicella Zoster virus (VZV)	Alpha	Mucoepithelia	Neuron	Contact or respiratory route
4	Epstein–Barr virus (EBV)	Gamma	B lymphocyte, epithelia	B lymphocytes	Saliva
5	Cytomegalovirus (CMV)	Beta	Epithelia, monocytes, lymphocytes	Monocytes, lymphocytes, and possibly others	Contact, blood transfusions, transplantation, congenital
6	Human herpes virus-6 (HHV-6)	Beta	T lymphocytes and others	T lymphocytes and others	Contact, respiratory route
7	Human herpes virus-7 (HHV-7)	Beta	T lymphocytes and others	T lymphocytes and others	Unknown
8	Human herpes virus-8 (HHV-8) Kaposi's sarcoma-associated herpes virus (KSHV)	Gamma	Endothelial cells	Unknown	Possibly exchange of body fluids

viruses have substantial morbidity and mortality in humans and a worldwide distribution. The unifying characteristic of all herpes viruses is the ability to remain latent in various cells (dependent on specific virus) after initial infection. Technological advances allow for earlier diagnosis and treatment. Cell culture and immunospecific or molecular methods are now available for rapid diagnosis of HSV, VZV, CMV, EBV, HHV 6, and HHV 8 (*Table 149.2*).

Herpes Simplex Virus (Human Herpes Virus 1 and 2)

HSV 1 and 2 are double-stranded DNA viruses which were first isolated in the 1960s. Infection is transmitted by direct contact, but viral shedding may occur during asymptomatic periods. HSV1 is usually associated with mucocutaneous disease, i.e., stomatitis, and HSV2 with genital disease. HSV1 remains latent in the trigeminal ganglia and reactivation affects the face and the oropharyngeal and ocular mucosae; HSV2 has a more efficient reactivation in the lumbosacral ganglia, affecting the hips, buttocks, genitalia, and lower extremities. HSV1 has been increasingly cited as the causative agent in genital herpes secondary to orogenital contact.

HSV 1 and 2 can infect people of all ages, causing a wide spectrum of disease, ranging from asymptomatic to severe systemic illness with a high fatality rate. The incubation period is typically 6–8 days but may vary from 1 to 26 days.

Children may be asymptomatic during primary HSV1 infection, usually a gingivostomatitis, or they may have high fever, malaise, irritability, lymphadenopathy, pain with swallowing, and mucosal erythema, ulcerations, exudates, and crusting. Dehydration may occur with oral disease. HSV1 recurrences are typically less severe and are for shorter duration, but secondary infections may occur with a prodrome of pain, tingling, itching, or burning at the affected site. Within 24 h of the prodrome, patients develop small, grouped vesicles on an erythematous base which coalesce into larger vesicles, bullae, pustules, and erosions that may crust. Disease typically occurs at the mucocutaneous junction of the lip and lasts 4–7 days, typically healing without scarring. Triggers and potentially exacerbating factors include sun exposure, illness (especially with fever), stress, and immunosuppression (*Fig. 149.6*).

Primary genital herpes is predominantly a sexually transmitted event, usually in sexually active adolescents or adults; it may occur in young children, raising the question of sexual abuse.

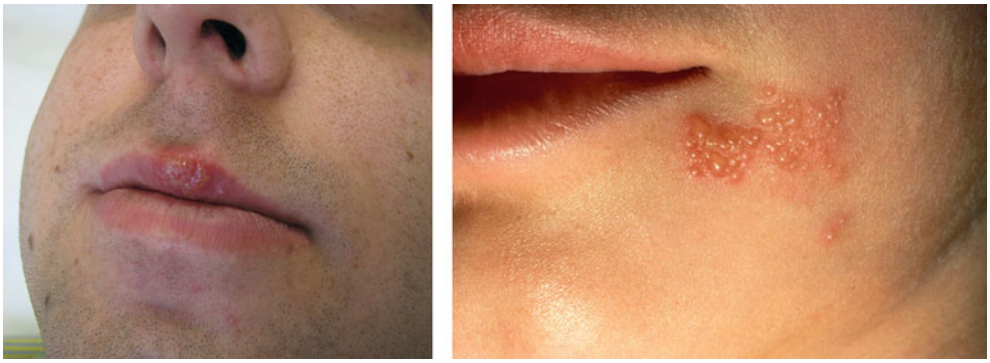


Figure 149.6
HSV1

Differential diagnosis includes impetigo, herpes zoster, hand foot and mouth disease, molluscum contagiosum, and allergic contact dermatitis. Infections may be complicated by erythema multiforme, often indistinguishable from HSV disease, especially with involvement of the oral muscosa. Diagnosis is often clinical, but Tzanck smear of vesicles, culture, direct fluorescent antibody, and PCR can help to confirm.

Patients are contagious until lesions have crusted; as such, parents and patients should be advised to avoid direct contact with other children and pregnant women. Treatment varies depending on the severity of the outbreak. Asymptomatic or mild cases of orolabial herpes simplex can be treated with compresses, bland emollients, and oral analgesics. For more severe or recurrent episodes, antivirals are the treatment of choice. Topical therapy with penciclovir or acyclovir may provide minimal improvement. Oral therapy is far more efficacious, although the dosing and cost may be prohibitive. Acyclovir, valacyclovir (approved in children >12 years old), and famciclovir (recently FDA approved in children) are available for oral use. In patients with frequent mucocutaneous or genital outbreaks or in immunosuppressed patients, prophylactic suppressive treatment may be necessary.

Herpetic Whitlow

Herpetic whitlow is a primary or secondary infection in children and health-care workers caused by HSV1 producing deep, tender vesicles and pustules on the fingers. In children, whitlow occurs when kids put their hands and fingers in the mouth of an infected person. Whitlow may also follow HSV2 infection in sexually active adolescents.

The differential diagnosis includes: blistering distal dactylitis secondary to *S. pyogenes*, orf (sheep pox), and milker's nodules (pseudocowpox). Clinical history will usually help differentiate these entities, but culture may be useful in unclear cases.

Neonatal Herpes

Neonatal herpes infection is acquired during delivery, rarely from intrauterine placental infections, from mothers who are infected with HSV1 or more commonly HSV2 (75% of cases), the latter associated with more severe disease.

The incidence of neonatal herpes is 1 per 3,000–3,200 live births. With an active lesion at the time of delivery, the risk of neonatal infection is 30–50% and women with primary infections are more likely to transmit the disease. With recurrent infections, the rate is significantly lower (2–5%). However, of all cases of neonatal herpes, 60–80% of the mothers have no history of genital infection and no evidence of infection at the time of delivery, thus making prevention difficult. With neonatal infection severe sequelae and death occur in greater than 50% of cases, most often due to rapidly progressive multiple organ failure.

Infants with neonatal herpes typically develop vesicles and bullae within the first 4 weeks of life. The disease can be categorized into three types: skin, eye, or mouth (SEM); CNS; and disseminated disease. SEM type has an excellent prognosis with antiviral therapy, but 75% of cases progress to disseminated disease if not treated. CNS and disseminated disease have a poor prognosis with high morbidity and mortality. If neonatal herpes is suspected, prompt

treatment with antiviral agents is essential to prevent CNS complications and death.

If a pregnant woman has a history of genital herpes, treatment with acyclovir 500 mg daily from 36 weeks until delivery may be attempted, but the efficacy of this approach in preventing transmission to the infant is not clear. If genital disease is present at the time of delivery, Cesarean section should be performed. If vaginal delivery takes place in a woman with HSV disease, neonate deserves careful monitoring. Physicians must be vigilant in regard to detecting and treating neonatal herpes. Acyclovir 20 mg/kg/day every 8 hours for a minimum of 14 days is the recommended treatment for suspected cases. Longer duration of therapy is often required for the treatment of disseminated and CNS infections.

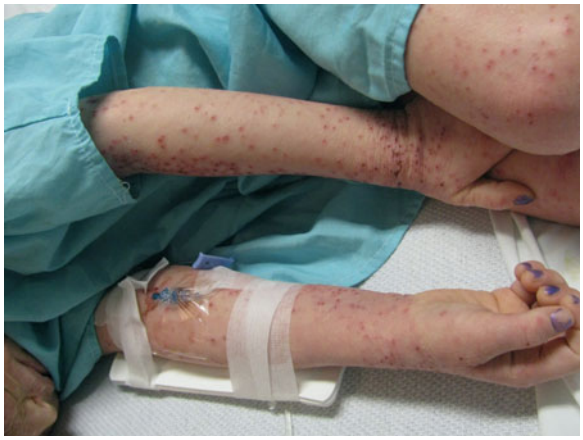


Figure 149.7
Eczema herpeticum

Eczema Herpeticum (Kaposi Varicellifom Eruption)

Eczema herpeticum is an HSV infection in a patient with a primary skin disease, most commonly, atopic dermatitis. The clinical presentation may vary from a few vesicles in areas of dermatitis to fulminating disseminated disease. Patients typically have fever, malaise, and extreme discomfort. Disseminated infection previously had a 20% mortality rate usually due to viremia or secondary bacterial infection, with the advent and use of antiviral treatment; morbidity and mortality have decreased significantly. Mild cases deserve treatment with acyclovir 20–30 mg/kg/day five times daily (up to 200 mg five times daily) or with valacyclovir. Most patients deserve hospitalization for supportive care and intravenous acyclovir. Eczema herpeticum may be complicated by secondary bacterial infection. If suspected, obtain culture and start antibiotic treatment (*Fig. 149.7*).

Varicella Zoster Virus (VZV, Human Herpes Virus 3)

Varicella zoster virus, a double-stranded DNA virus, is the cause of chickenpox, a highly infectious disease common worldwide. The advent of the chickenpox vaccine and the institution of routine immunization in 1995 have drastically reduced the frequency and prevalence of the disease. Chickenpox was primarily a disease of childhood, with more than 90% of cases occurring in children younger than 10 years and with only 2% of cases occurring in adults. Since vaccination began, the epidemiology has shifted; now disease occurs more commonly in adolescents and adults. Complications and more severe disease are also associated with increased age. Overall, the incidence in all ages has decreased with the vaccination.

Transmission occurs via direct skin contact and via respiratory droplets; the virus is commonly isolated from vesicles and is rarely isolated from the respiratory tract. The incubation period is 10–21 days (mean 14 days) and patients are contagious for 7 days, beginning 2 days before the onset of disease. Exclusion from school is routine, but may not prevent transmission. Children have a 2–3-day prodromal period prior to developing the disease and the prodrome varies from asymptomatic to a severe illness with fever, malaise, cough, coryza, and sore throat. Chickenpox begins on the scalp and trunk as erythematous macules that rapidly develop central vesicles on an erythematous base ("dew drop on a rose petal") and evolve into pustules or crusts. New crops of macules and vesicles continue to develop for approximately 7 days, and children may have disease in all stages of development. The polymorphous nature of chickenpox is characteristic. Infections are considered severe if the patient has more than 500 lesions (38% of cases). Crusting occurs within 2–12 days and healing in 16 days, typically without scars, but depressed or hypertrophic scars may occur. Scarring may follow excoriations due to pruritus, which ranges from minimal to intense. Oral disease occurs in 25% of cases. Subsequent attacks are rare clinically; however, serologic evidence of reinfection is common.

Complications in immunocompetent children include secondary bacterial infection (5–10%) and otitis media

(5%). High-risk individuals, i.e., older children, adults, or immunosuppressed patients, require hospitalization and may develop severe complications, including pneumonia, thrombocytopenia, encephalitis, cerebellar ataxia, aseptic meningitis, transverse myelitis, Guillain–Barre syndrome, nephritis, carditis, arthritis, orchitis, uveitis, purpura fulminans, and even death. Reye syndrome was once a complication but is now rare with the avoidance of aspirin in children.

Women in childbearing years without immunity to varicella have a 0.05–0.07% risk of developing chickenpox during pregnancy and potentially infecting the fetus. These women should be vaccinated and titers checked to ensure immunity. If a woman does develop chickenpox during pregnancy, there is a 2–4% chance of fetal infection and development of intrauterine varicella. The risk of fetal abnormalities is greatest if the maternal infection occurs during weeks 8–20 of pregnancy. Neonates with fetal infection have low birth weight, skin disease, and scars in a dermatomal distribution, cataracts, microphthalmia, chorioretinitis, bone and muscle hypoplasia, mental retardation, microcephaly, and dysfunction of bladder and bowel sphincters. If congenital infection occurs after 20 weeks, infants have increased risk of developing herpes zoster in the first few years of life.

Neonates born to a woman who develops chickenpox 5 days before or 2–5 days after delivery are at increased risk of developing disseminated chickenpox, with a 20–30% chance of fetal death usually from pneumonitis and hepatitis. The mortality has decreased considerably with the use of varicella-zoster immune globulin (VZIG) and acyclovir. If a woman develops chickenpox 5 days after delivery, the risk to the neonate is similar to those of older children.

The differential diagnosis of chickenpox includes arthropod bites, eczema herpeticum (patients with atopic dermatitis), herpes simplex infection, impetigo, folliculitis, hand foot and mouth disease, pityriasis lichenoides, scabies, bullous pemphigoid (adults), erythema multiforme, and drug eruption. The diagnosis is usually clinical given the distinct characteristics of chickenpox. A Tzanck smear allows for immediate confirmation, but successful interpretation requires skill and experience. VZV can be isolated from vesicles during the first 3 days of eruption with DFA or PCR. Serologic tests may also be used to determine immune status.

All chickenpox vaccines originate from the live Oka strain developed in Japan in 1970. The vaccine is well tolerated and safe for use in immunocompetent patients. Vaccine complications include erythema at the injection site (25%), and dermatitis within 1 month of vaccination (5%; with leukemic patients, 50%). Children aged 12 months through 18 years should receive two doses of the vaccine given 1 month apart. The vaccine is 70–85% effective in preventing infection and almost 100% effective in preventing severe infection. Breakthrough cases occur more commonly under the previous immunization recommendations (only one dose of the vaccine). Even in breakthrough cases, the number of lesions and length of time to healing were decreased.

In most cases of chickenpox, symptomatic treatment suffices, i.e., antihistamines, oatmeal baths, calamine lotion, Domeboro soaks, menthol-containing lotions, and bland emollients. Secondary infection should be treated with antibiotics. Fever and general discomfort should be treated with acetaminophen.

Varicella-zoster immune globulin (VZIG) is useful in preventing and modifying the development of chickenpox but must be administered within 96 h of exposure. It is recommended for immunocompromised patients and newborns whose mothers developed disease between 5 days before and 2 days after birth. VZIG has been effective in preventing disease in susceptible healthy adults and pregnant women who have had contact with infected individuals. Because VZIG is not currently available, intravenous immune globulin can be substituted when VZIG is indicated.

Acyclovir, a nucleoside analog, is a powerful and selective inhibitor of HSV, and to lesser extent VZV, by blocking viral DNA replication, which must be administered within 24 h of chickenpox lesions. It is not efficaciously used in otherwise healthy children given its expense, marginal effect, and difficulty of delivery within limited window. However, use in adolescents (>12 years of age) and adults, patients with chronic cutaneous or pulmonary disease, those receiving salicylates or corticosteroids, and in immunocompromised patients can reduce morbidity and mortality. The recommended dosage is 20 mg/kg four times per day (up to 800 mg four times per day) in adolescents and adults and 10–20 mg/kg intravenously every 8 h for 10–14 days in sick individuals or immunocompromised patients. If given at the time of exposure, acyclovir may modify or even prevent chickenpox infection. Valacyclovir and famciclovir are reasonable alternatives.

Herpes Zoster (Shingles)

Herpes zoster represents reactivation of latent VZV in the sensory ganglia after previous VZV infection. Zoster most often affects the elderly and children with

immunodeficiency or malignancy; it also occurs in immunocompetent children/adolescents who contacted chickenpox early in life. There have also been an increased number of cases in the last 15 years since the advent of the chickenpox vaccine. Patients generally experience a dull aching sensation, followed by urticarial papules then unilateral, grouped vesicles, and bullae on reddened skin in a dermatomal distribution. The dermatitis is generally accompanied by discomfort, described as a dull constant burning sensation, with intermittent sharp, stabbing pain. The dermatitis lasts for 10–14 days and usually heals without scarring. Involvement of the nasal tip indicates involvement of the nasociliary branch of the trigeminal nerve (V) which may forebode ocular complications, necessitating ophthalmologic consultation (◉ *Fig. 149.8*).

Herpes zoster can be difficult to distinguish from HSV, especially if the HSV infection occurs in a dermatomal distribution. Immunoflourescent microscopy (DFA) can help to confirm the diagnosis.

Zoster is not typically problematic in healthy children, but in immunocompromised patients, ulcerative lesions can occur, disease may involve several dermatomes, and there is increased risk of visceral dissemination causing significant morbidity and mortality. Postherpetic neuralgia may follow zoster and may last for months. Neuralgia is a common and often debilitating complication in elderly patients, less likely in younger patients.

Treatment is not usually required in children. For adolescents and adults, treatment is acyclovir 800 mg five times per day for 7–10 days and for immunocompromised patients 10 mg/kg every 8 h for 7–10 days. Healing is improved and severity of acute pain is diminished if antiviral treatment begins within 48–72 h of the disease onset.

Epstein–Barr Virus (EBV, Human Herpes Virus 4)

Epstein–Barr Virus, first described by Burkitt in 1958 as the causative agent of a lymphoma and the most common tumor in children in East Africa, is the etiologic agent of infectious mononucleosis, a major cause of Gianotti–Crosti syndrome, which is also linked to nasopharyngeal carcinoma. The infection is widespread and humans are the natural host. Primary infection occurs early in life, particularly in tropical climates and lower socioeconomic classes, and is usually asymptomatic.

Infectious Mononucleosis (IM)

IM is a self-limited lymphoproliferative disease characterized by fever, sore throat, lymphadenopathy, fatigue, and splenomegaly. The disease typically lasts for weeks,

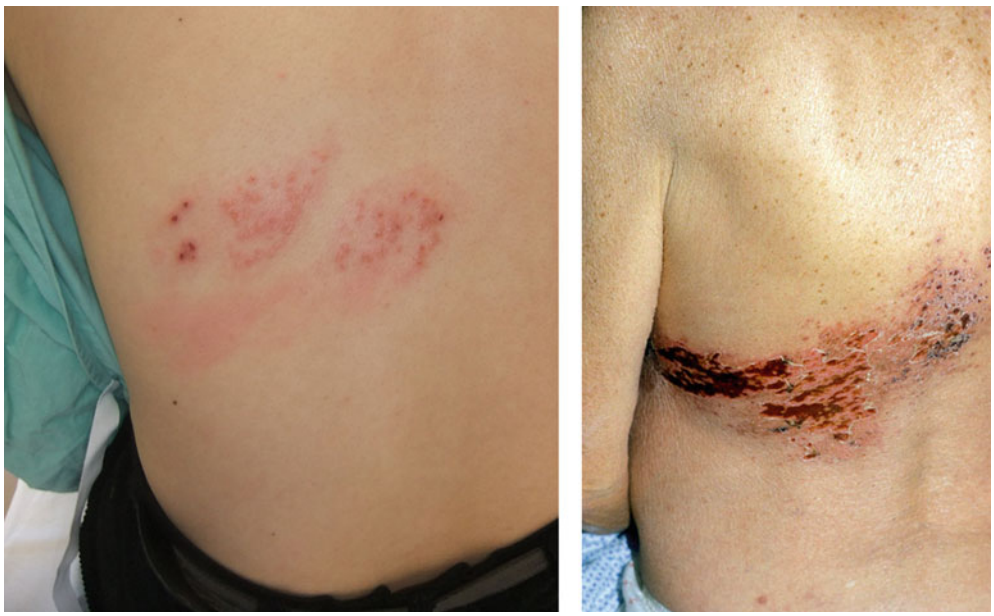


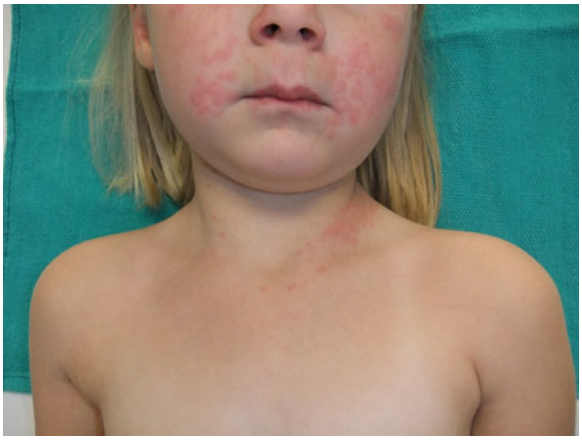
Figure 149.8
Zoster

although the fatigue associated with it may last for months. There is no evidence to implicate ongoing viral infection or replication in those with prolonged fatigue following infectious mononucleosis. Patients with infectious mononucleosis treated with ampicillin for suspected streptococcal pharyngitis often develop a hypersensitivity exanthem.

Gianotti–Crosti Syndrome (GCS, Papular Acral Dermatitis of Childhood, Papulovesicular Acrolocated Syndrome)

Gianotti–Crosti, first described in Italy in 1955, is a common exanthem of healthy young children, usually less than 5 years old. The syndrome was initially described in association with hepatitis B infection but has since been associated with parainfluenza virus, echovirus, enteroviruses, hepatitis A and C, cytomegalovirus, human herpesvirus-6, coxsackievirus, rotavirus, parvovirus, molluscum contagiosum virus, respiratory syncytial virus, mumps, human immunodeficiency virus (HIV), *Bartonella henselae*, *Streptococci*, *Borrelia burgdorferi*, *Mycoplasma pneumoniae*, and Epstein–Barr Virus. EBV is the most common etiology worldwide. Vaccinations have been linked to Gianotti–Crosti. GCS typically affects preschool children but may occur in children aged 3 months to 16 years. Prodrome is variable, i.e., upper respiratory or gastrointestinal infection, which leads to the exanthem. Children suddenly develop an asymptomatic exanthem of small pink/red/brown to flesh-colored 2–5 mm monomorphous papules or papulovesicles, symmetrically distributed on the face, buttocks, and extensor surfaces of the extremities. The trunk is usually spared. Patients may have purpura, inguinal or axillary lymphadenopathy, and hepatosplenomegaly (associated with hepatitis B). The exanthem lasts 4–6 weeks and disappears without sequelae.

The differential diagnosis includes: lichen planus, lichenoid drug eruption, papular eczema, Henoch–Schonlein purpura, arthropod reaction, keratosis pilaris, Langerhans cell histiocytosis, urticaria pigmentosa, molluscum contagiosum, erythema multiforme, drug reaction, and id reaction. Generally, the diagnosis is clinically apparent especially with absence of truncal involvement. A biopsy may be necessary for a definitive diagnosis and Epstein–Barr serologies can be obtained in inconclusive cases, along with liver function tests and hepatitis serologies in unimmunized children. Given the self-limited nature of Gianotti–Crosti, no treatment is necessary (◉ *Fig. 149.9*).



◘ Figure 149.9
Gianotti–Crosti

Cytomegalovirus (CMV, *Human Herpes Virus* 5)

CMV species–specific herpesviruses, discovered in the 1950s when human and murine varieties were isolated, are transmitted from person to person via close contact with high incidence in close contact quarters such as day-care centers. Age of infection and prevalence vary worldwide. In the USA and other developed countries, infection tends to occur later in life, while in developing countries children are more prone to infection. Rates of seropositivity are around 50% worldwide, approximating 90% in high-risk groups. Most CMV infections are subclinical, but can be significant in immunosuppressed and immunodeficient patients.

Neonatal CMV is a part of the TORCH infections (toxoplasmosis, other viruses – syphilis, varicella-zoster, parvovirus B19, rubella, CMV, Herpes/HIV). Maternal infection transmitted via the placenta or breast milk is most severe when the virus is contracted during the first half of pregnancy and 0.2–2% of neonates are infected in utero. Of those, only 2–10% will show signs of disease, e.g., intrauterine growth retardation, jaundice, petechiae, hepatosplenomegaly, microcephaly, and "blueberry muffin" skin disease. Even fewer patients develop severe sequelae, such as neurologic complications, mental retardation, and sensorineural deafness. Many infants (10–60%) are infected during the first 6 months of life, and they rarely show any signs of disease.

Most cases of CMV infection do not require treatment; but for severe cases in neonates, immunosuppressed or immunodeficient patients, antiviral treatment is

necessary. Ganciclovir and valganciclovir are the anti-viral agents of choice for the treatment of CMV infections.

Roseola Infantum (Exanthem Subitum, Human Herpes Virus 6 and 7)

HHV6, isolated in 1986 in patients with lymphoproliferative disease infects and replicates in T lymphocytes; two subtypes are known, A and B, and the latter (B) is the causative agent of roseola infantum. Ninety percent of adults have antibodies to HHV6, which is intermittently spread in saliva throughout life. After an incubation period of 9 days, children aged 6 months to 3 years typically develop fever for 3–4 days, but remain otherwise well except for mild, nonspecific upper respiratory or abdominal symptoms. As the fever resolves, the characteristic rose-colored, nonpruritic macules appear on the chest and arms and rapidly generalize. The exanthem fades within 24–48 h. Many children have subclinical cases of infection.

The differential diagnosis includes other causes of viral rashes, Scarlet fever, and drug eruption. The distinct time course of fever and rash helps to make the diagnosis. Isolation of the virus is not usually necessary but can be done by culture, immunohistochemical stains, serology, and polymerase chain reaction. The exanthem is self-limited, but convulsions secondary to high fever and/or direct infection of the meninges have been reported. In one study, one-third of children aged 12–15 months evaluated for febrile seizures had HHV6 infection. In another study, 20% of children with fever of unknown origin had positive IgM antibodies to HHV6. Severe complications, such as permanent neurologic damage following encephalitis, have been reported, but the exact role of HHV6 in these cases is not clear.

In most infants, treatment is supportive and some (13%) will require hospitalization due to febrile seizures. Immunosuppressed patients may require antiviral treatment such as ganciclovir or foscarnet.

HHV7 was isolated in 1990. Primary infection occurs during childhood; over 95% of adults have been infected and 75% were infected before age 6. HHV7 has been associated with roseola infantum and some reports of pityriasis rosea.

Hand–Foot–Mouth Disease (HFMD)

HFMD is a viral exanthem most commonly caused by Coxsackie A16, an Enterovirus, and part of the Picornaviridiae family. Alternative pathogens include other single-stranded RNA viruses such as Coxsackie B, ECHO, and Enterovirus (71). The disease tends to affect children aged 2–10 years old, and sometimes adults. Transmission occurs via the fecal–oral route or respiratory droplets, and the incubation period is 3–6 days. The virus is highly contagious and outbreaks commonly occur in late summer and early fall. Patients usually have a prodrome with low-grade fever (38°C), anorexia, malaise, cough, and sore throat/mouth 1–2 days prior to the development of mucosal and skin disease. Initially, patients have 1–3 mm vesicles on the buccal mucosa and tongue and, in one-third of patients, the palate, uvula, and anterior tonsillar pillars are also involved. The exanthem develops shortly after oral disease with gray-white, oval vesiculopustules that parallel skin lines on the palms and soles or on the dorsal/lateral surfaces of the hands and feet. The vesicles are typically flaccid, thin-walled, and erosions/ulcerations with crust may follow. Another common presentation is a maculopapular exanthem on the buttocks and genitalia. HFMD may be painful or pruritic, but is generally asymptomatic and heals without scarring in approximately 7 days.

The differential diagnosis of oral HFMD includes: HSV infection, aphthous ulcers, Streptococcal or Candida infection; the differential of hand lesions includes varicella, erythema multiforme, dyshidrotic eczema, meningococcemia, Rocky Mountain Spotted Fever, subacute bacterial endocarditis, gonococcemia, disseminated HSV/zoster, and papular acrodermatitis of childhood. Diagnosis is usually based on physical exam, but viral culture, DFA, and/or biopsy can help to clarify/confirm the diagnosis.

The disease is usually self-limited and treatment is not necessary. Though, supportive care may be necessary in some cases. Topical analgesics (viscous lidocaine) can help relieve oral pain, and rehydration may be necessary for some patients. Antipyretics and oral analgesics are also frequently used. In rare cases, due to Enterovirus 71, life-threatening complications such as encephalitis have been reported.

Herpangina

Herpangina is viral exanthem most commonly caused by Coxsackie A9, an Enterovirus, part of the Picornaviridiae family. The infection occurs in young children who exhibit fever and sore throat with a few scattered, discrete vesicles on the soft palate, uvula, tonsils, and tongue. The oral cavity and throat are typically erythematous and

hyperemic. Herpangina is more painful than HFMD but heals without scarring within days.

Mollusca Contagiosum

Molluscum contagiosum is an infection caused by large DNA poxvirus, with transmission through direct skin-to-skin contact, less commonly via fomites. The virus affects patients worldwide, and there is a bimodal distribution; the first in preschool aged children with transmission from nonsexual contact, and the second in early adulthood usually via sexual contact. Adults are rarely affected even with close contact with infected children, most likely due to universal exposure and long-standing immunity. Those at increased risk for developing Molluscum contagiosum include immunocompromised patients and those with atopic dermatitis.

The incubation period is between 2 and 8 weeks, and patients typically develop asymptomatic, flesh colored to erythematous, dome-shaped 1–5 mm papules, often with central umbilication. Papules larger than 5–10 mm are "giant molluscum." Molluscum commonly occur on the face, flanks, abdomen, axillae, thighs, buttocks, and groin, but may be found anywhere on the body. Local inoculation and spread may result in a linear distribution. Pruritic dermatitis may occur in 10% of patients, more so in patients with atopic dermatitis, and often complicates the molluscum treatment. Secondary infection or an inflammatory response to the virus may cause large, painful erythematous papules or pustules. With molluscum near the eye, conjunctivitis may occur (*Fig. 149.10*).

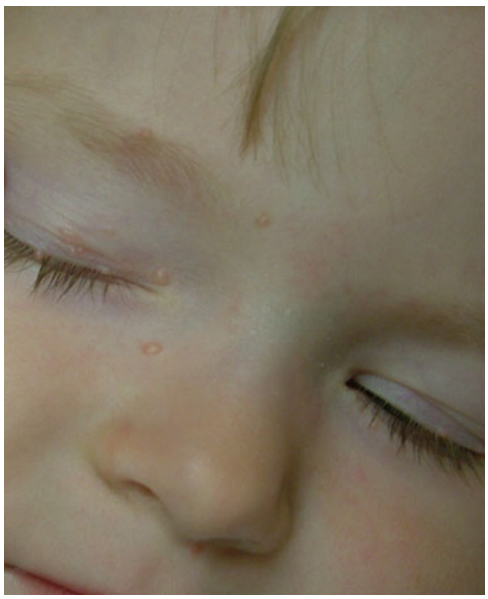


Figure 149.10
Molluscum

The differential diagnosis includes: HSV infection, warts, milia, folliculitis, and skin tags. Giant molluscum may mimic epidermoid cysts. Diagnosis is usually made clinically. A KOH prep and microscopy can assist in making the diagnosis but are not typically necessary. In rare cases, a biopsy may help to confirm the diagnosis, revealing large eosinophilic cytoplasmic inclusions (molluscum bodies). In children with strict genital involvement, child abuse needs to be explored.

Spontaneous regression usually occurs after 6 months to 4 years. Treatment may not be necessary, but per one study, 82% of parents and patients report concern about the lesions and are likely to pursue treatment. Treatment modalities vary depending on patient age and include imiquimod 5% (cost prohibitive), tretinoin 0.025%, salicylic acid, and benzoyl peroxide, with variable efficacy and are generally reserved for treatment of the face. Best results occur with cantharidin 1.5% applied to individual non-facial molluscum. The medication is applied and washed off with soap and water after 3–4 h, bullae may develop within hours to days. In older patients, options include curettage and cryotherapy. Scarring may occur with self-healing or with treatment.

Verrucae (Warts)

Warts are caused by the human papillomavirus (HPV), a subgroup of the Papovaviridae family with over 200 genotypes and 76 different site-specific subtypes. The incubation period for infection varies from months to 3 years. Transmission occurs via direct contact often through damaged skin; spread depends on the patient's immune status. Large warts tend to occur in transplant patients, HIV/AIDS patients, and patients receiving systemic steroids. Warts in immunosuppressed patients tend to be resistant to treatment, and patient comfort is often the mainstay of therapy.

Generally, warts are asymptomatic but may be associated with pain depending on size and where they occur. There are many commonly employed and reasonably effective treatments for warts, but failure rates are appreciable (30%) regardless of treatment modality. Fortunately, warts in healthy patients are self-limited and typically involute within 1–2 years. However, most patients or their parents desire treatment. In general, the goal of treatment is to create inflammation of the wart stimulating natural immunity to attack the wart virus. Several treatments may be

combined and employed at once, and most modalities will require a series of treatments to ensure clearance.

Treatment options include:

- Salicylic acid preparations (various strengths available) applied one to two times daily with or without occlusion
- Topical immunotherapy, i.e., sensitization and treatment with squaric acid solution or diphenylcyclopropenone
- Injected immunotherapy with Candida antigen
- Tretinoin (Retin A 0.1%) applied once to twice daily, often combined with imiquimod
- 5-Fluorouracil solution or cream applied BID
- Cimetidine (oral) 30–40 mg/kg/day for 2–3 months, effective especially in the treatment of genital and perigenital warts
- Cantharidin solution applied to warts and then washed off with soap and water after 8–10 h
- Podophyllin 25%, a metaphase inhibitor, applied to warts (usually genital warts) washed off with soap and water after 4–6 h
- Podophyllotoxin gel 5% (Condylox) used to treat genital warts
- Trichloroacetic acid used to treat genital warts
- Cryotherapy (liquid nitrogen) is often the mainstay of therapy in adolescents and adults, but can be painful and poorly tolerated by young children
- Pulsed dye laser or CO_2 laser treatment for resistant or stubborn warts
- Photodynamic therapy with red light, studies are currently underway and show promising results in the treatment some recalcitrant warts
- Surgical removal may be considered after failure of several other treatment modalities, avoid on the plantar surface due to painful scarring

Verruca Vulgaris (Common Warts)

Common warts, usually caused by HPV types 1, 2, 4, and 7 occur most often on the hands, feet, knees, and elbows but may be found on any body surface. Clinically, warts appear as asymptomatic flesh to white colored callus-like papules that may coalesce into plaques. On the face or mucous membranes, they may have a filiform appearance with a thin stalk. Warts around the fingernails may be large and very difficult to treat especially if the virus has migrated under the nail plate, a complication commonly seen in nail pickers/biters and in immunocompromised patients. The differential

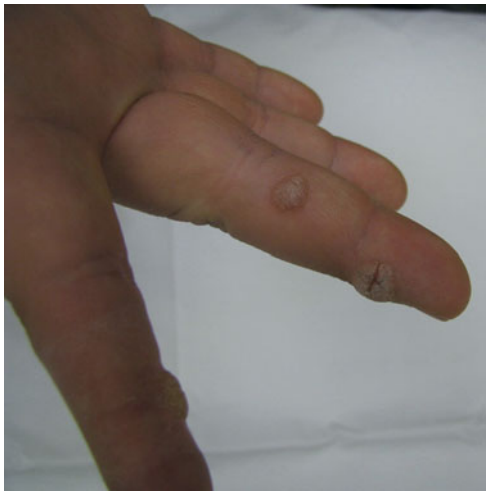


Figure 149.11
Common warts

diagnosis includes calluses, molluscum contagiosum, prurigo nodule, and knuckle pads. Small black dots within the wart are thrombosed superficial capillaries, "wart seeds"; cutting or paring results in pinpoint bleeding – a helpful diagnostic clue. Disruption or disappearance of dermatoglyphs within warts is another diagnostic clue (*Fig. 149.11*).

Verruca Plana (Flat Warts)

Flat warts, associated with HPV 3, 10, and 28, are yellow/white/red/brown to flesh-colored 2–4 mm flat topped papules that may occur in groups or in a linear distribution due to autoinnoculation. Flat warts commonly occur on the face, neck, wrists, and legs, but may be found anywhere on the body. They are often quite subtle and difficult to appreciate, and may be confused with lichen planus, lichen nitidus, mollusca contagiosa, keratosis pilaris, folliculitis, xanthogranulomas, acne, benign cephalic histiocytosis, granuloma annulare, or syringomas. Occasionally, biopsy is needed to confirm the diagnosis (*Fig. 149.12*).

Condyloma Accuminata (Genital Warts)

Condyloma accuminata, caused by HPV types 6 and 11 (90% of cases) and, occasionally, with types 2, 4, 16, 18, 30, 31, 33. Women with genital warts caused by types 16, 18, 31, and 33 have an increased risk of cervical and

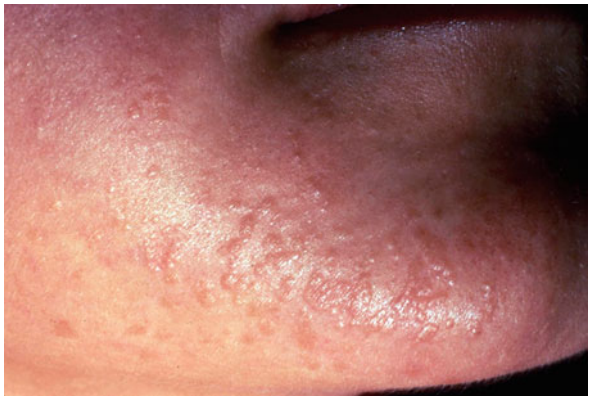


Figure 149.12
Flat warts

vulvar dysplasia. The main mode of transmission in infants/children is passage through the birth canal; the younger the child is at the time of presentation, the greater likelihood of transmission at birth. In older children, genital warts may be associated with sexual abuse in 5–10% of cases. The variable incubation period of 1–3 years often makes suspected cases of abuse more difficult to prove.

The appearance of condyloma accuminata is variable, e.g., red/brown/white to flesh-colored, raised or flat, single or grouped papules or plaques. Fusion of the papules can lead to large, moist, vegetative plaques that may fissure and ulcerate. The larger plaques are typically sexually transmitted, and the skin and mucous membranes of the anogenital area are most commonly affected. Other mucous membranes, e.g., the larynx may be affected if exposure occurs during vaginal delivery or in breastfeeding mothers with warts (*Fig. 149.13*).

The differential diagnosis of condyloma accuminata includes molluscum contagiosum, skin tags, anal fissures, and condyloma lata (secondary syphilis). Diagnosis is most often made clinically, but biopsy can help to confirm diagnosis. Treatment options are variable as mentioned above. With the advent of the HPV quadrivalent (HPV 6, 11, 16, 18) and bivalent vaccines, prevention of genital warts and ultimately cervical cancer has become a possibility. The vaccine is approved for use in boys and girls aged 9–26 years old. Vaccination protects against the two types of HPV, 6 and 11, which cause 90% of genital warts and the two types of HPV, 16 and 18, that cause 75% of cervical cancer. The vaccine is given as a series of three injections over 6 months, and the side effect profile is minimal, with injection site reaction being the most common complaint.

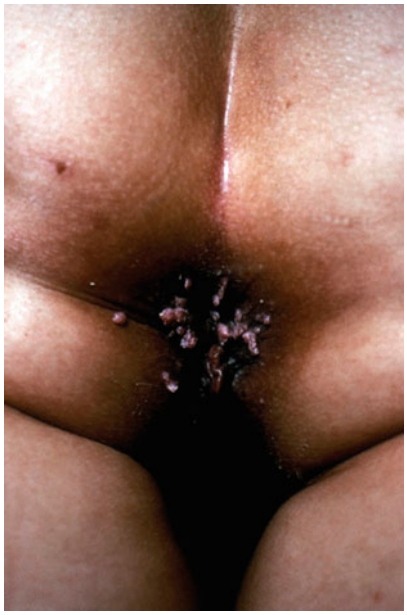


Figure 149.13
Condyloma acuminata

Fungal Infections

The two most common causative agents of fungal infections in children are Candida (yeast) and superficial dermatophytes (mold). *Trichophyton* and *Microsporum* species are both acquired through human or animal contact, while *Epidermophyton* is acquired only through human contact; these three species are the dermatophytes most commonly seen in kids. Examples of zoophilic organisms include *Microsporum canis* (cats and dogs) and *T. verrucosum* (cows and horses). Anthropophilic organisms include *Tinea mentagrophytes*, *Trichophyton tonsurans*, *Trichophyton rubrum*, and *E. floccosum*. Organisms produce keratinases which aid in invasion; however, most fungal infections are superficial and affect only the skin, hair, and nails. Less commonly, fungi may cause deep infections when they invade organs. Fungal infections are named using "tinea" (gnawing worm, from Latin) and the area of involvement: tinea capitis – scalp, tinea corporis – body, etc. Immune status dictates susceptibility to infections; the other likely risk factors include excessive moisture and occlusion, which may exacerbate fungal infections.

Tinea Capitis

Tinea capitis affects children worldwide and typically presents in children aged 3–7 years old, rarely in infants and

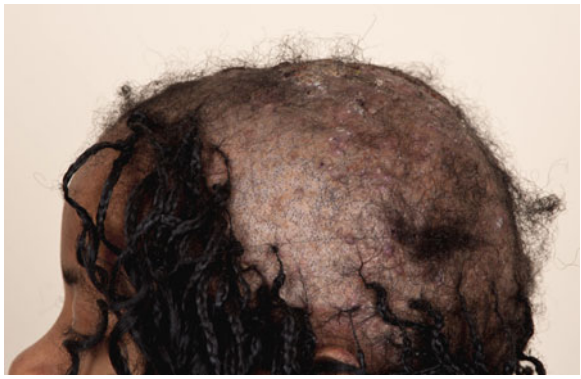
older children. Transmission occurs person to person, or through fomites, or infected animals. Tinea capitis is caused by a dermatophyte, and the most common causative organisms are *Trichophyton tonsurans* (most common in USA/Canada, most prevalent in black children), *Trichopyton soudanense*, *Trichopyton violaceum*, *Microsporum canis* (most common worldwide), and *M. audouinii*.

T. capitis has four different presentations:

1. Scaly plaques (resembling seborrheic dermatitis) without hair loss, often seen with *T. tonsurans* infection and associated with broken hairs, known as "black dot ringworm"
2. Alopecic patches and scaling with minimal inflammation
3. Scattered papules, pustules, and crusts
4. Kerion formation – an edematous, boggy, tender mass, which occurs as a result of an immunologic inflammatory reaction to the fungal infection (permanent scarring may result) (◉ *Figs. 149.14* and ◉ *149.15*)

Severe forms of tinea capitis may be associated with systemic symptoms such as fever, malaise, and cervical/occipital lymphadenopathy. Disease may be complicated by an id reaction, papulopustules on the face that may be mistaken as resistant disease; however, this reaction resolves with treatment of the tinea infection. If the id reaction is significant, an oral antihistamine and topical corticosteroids will help alleviate symptoms.

◘ Figure 149.14
Tinea capitis



◘ Figure 149.15
Large kerion

The differential diagnosis includes: alopecia areata, trichotillomania, seborrheic dermatitis, psoriasis, discoid lupus, lichenplanopilaris, and bacterial folliculitis. KOH prep helps to confirm diagnosis. Depending on the causative dermatophyte, spores may be within (endothrix) or outside of the infected hair shaft (ectothrix). Other diagnostic modalities include fungal culture (Sabouraud medium) and Wood's light examination. Fungal culture allows determination of the causative agent, especially important in the case of *M. canis* which is indicative of exposure to an animal that needs treatment as well. *M. canis* can be difficult to treat, often requiring longer treatment. Wood's light examination will yield green fluorescence if infection is caused by *Microsporum* (except *M. gypseum*). *Trichophyton* species do not fluoresce. Bacterial culture should be obtained if secondary infection is suspected.

Some individuals may be asymptomatic carriers of the disease, and spores are often difficult to eliminate, especially from fomites (children should avoid sharing helmets/head gear). Tinea capitis deserves treatment with an oral antifungal agent since organisms invade the hair follicle. The treatment of choice is griseofulvin 20–25 mg/kg/day for 6–8 weeks. *M. canis* typically requires extended treatment for 3–5 months or sometimes longer. For younger children, a liquid suspension (125 mg/teaspoon) is available. Parents should be instructed to give the medicine with fatty foods such as whole milk or ice cream to increase absorption. Side effects include headache and upset stomach but, generally, the medication is well tolerated and safe. Laboratory monitoring is not necessary in healthy children for treatment described above (6–8 weeks), but for kids with prolonged treatment or other illnesses/comorbidities, liver function studies and complete blood counts should be obtained. Alternative

regimens include: itraconazole 5 mg/kg/day for 2–3 weeks, fluconazole 6 mg/kg/day for 2–3 weeks, and terbinafine (dosing is weight dependent) <20 kg: 62.5 mg; 20–40 kg: 125 mg; >40 kg: 250 mg for 2–4 weeks. Additionally, topical antifungal shampoos, e.g., ketoconazole, can be used in conjunction with systemic therapy to help decrease scale, shedding, and contagiousness. Secondary bacterial infections should be treated with oral antibiotics.

Tinea Corporis (Ringworm)

Tinea corporis is a superficial fungal infection of the body, most commonly caused by *Trichophyton rubrum*, less so *M. audouinii* and *M. canis*. Transmission occurs by direct contact with those infected, through fomites or when children hold or play with infected cats/dogs (*M. canis*).

Patients develop pruritic, erythematous, circular, or annular plaques with central clearing that expand outward with a peripheral edge of scale/crust and darkening. Vesicles may appear at the periphery of the plaque, and multiple plaques may coalesce and give a polycyclic appearance. Plaques tend to affect the face and arms; however, they can occur at other sites. If the organisms invade the hair follicle or shaft, a deeper infection (Majocchi granuloma) occurs with reddened boggy papules, pustules, plaques, and nodules (*Fig. 149.16*).

Tinea corporis can be difficult to treat and may defy diagnosis. If initially treated with steroids, plaques expand and become more inflamed often with pustules on an erythematous base. If diagnostic clues, i.e., inflammation and scale, are absent, condition is known as tinea incognito. Differential diagnosis includes: psoriasis, granuloma annulare, nummular dermatitis, pityriasis rosea, and erythema annulare centrifugum.

KOH prep establishes diagnosis; culture (Sabouraud medium) confirms the specific causative agent. If a Majocchi granuloma is suspected, biopsy is recommended to confirm a deeper infection. If disease is limited, topical antifungals used twice daily for 2–4 weeks will generally provide clearance. Patients should continue treatment for approximately 1 week after clearance to ensure eradication. For extensive or resistant disease, oral antifungals should be provided, either terbinafine 6 mg/kg/day for 2 weeks or griseofulvin 20 mg/kg/day for 4–6 weeks.

Tinea Pedis

Tinea pedis ("athlete's foot") is more common in adults than in children and tends to develop after puberty. The causative organisms are *Tinea rubrum*, *Tinea mentagrophytes*, *and Epidermophyton floccosum*. Affected patients usually have scaling, erythema and maceration between the third, fourth, and fifth toe spaces (atopic dermatitis favors first and second toe spaces), and/or scaly plaques on the plantar foot. Pruritus and malodor are common and associated onychomycosis may occur.

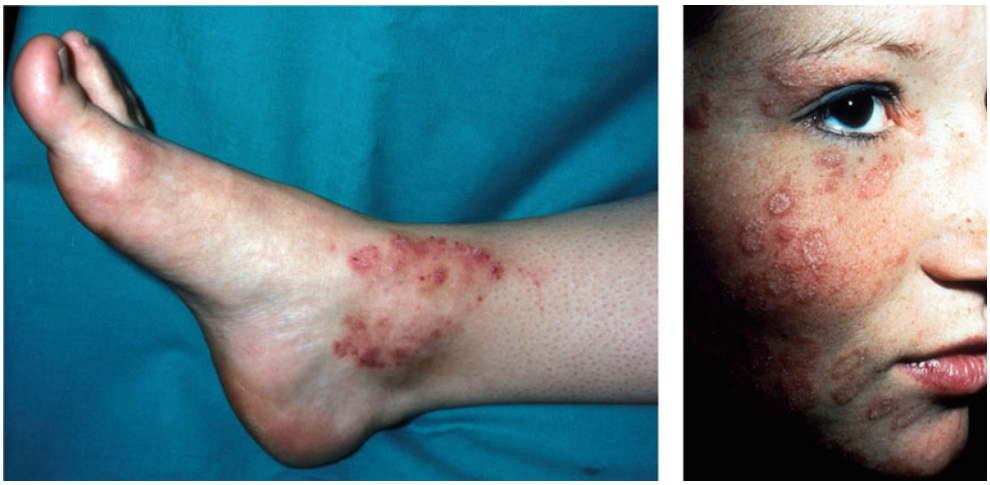


Figure 149.16
Tinea corporis

There are four recognized types of Tinea pedis:

1. Chronic intertriginous (most common) – erythema and scale of the web spaces and bacterial coinfection which can lead to maceration
2. Chronic hyperkeratotic/moccasin tinea pedis – erythema and scale on the plantar surface; one hand may also be involved (two feet–one hand syndrome)
3. Vesiculobullous – multiloculated, erythematous vesicles and bullae, often on the arch and heel
4. Acute ulcerative (rare in children) – vesicles and pustules that progress rapidly into ulcers and erosions, often with systemic signs of infection and typically seen in immunocompromised and diabetic patients

Many people will develop tinea pedis during their lifetime (70%). Those at increased risk are often exposed to high humidity, wear occlusive footwear, and use communal pools, showers, baths, or locker rooms regularly. Tinea pedis is quite common among athletes.

Secondary bacterial infections and id reactions, manifested as vesicles on the hands/feet or as dermatitis elsewhere on the body, can complicate tinea pedis. Differential diagnosis includes: granuloma annulare, contact dermatitis, psoriasis, juvenile plantar dermatosis, and hereditary keratodermas. KOH prep establishes diagnosis. Chlorazol black E or KOH, in conjunction with dimethylsulfoxide, may enhance visualization of the fungal hyphae. Fungal cultures to determine the causative agent may be helpful, but often not necessary. *M. canis* indicates an infected animal as source and *T. tonsurans* likely means someone in the home has tinea capitis. Bacterial cultures should be obtained if there is concern for secondary infection.

Most small, localized infections will respond to simple measures, including limited use of occlusive footwear, drying powders, and topical antifungal treatment for 4–6 weeks. In resistant or extensive cases, oral antifungal medications: terbinafine 6 mg/kg/day for 2 weeks or griseofulvin 20 mg/kg/day for 4 weeks may be necessary, coupled with topical antibiotics to treat secondary bacterial infections.

Onychomycosis

Onychomycosis is a fungal infection of the nails usually caused by *T. rubrum*. Other causative agents include *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, and *Candida albicans*, typically the cause of onychomycosis in infants and usually acquired intrauterine or via vaginal transmission. Though far more common in adults, onychomycosis can occur in children – prevalence 0.2–2.6%, accounting for 30% of all nail disease. Risk factors include family history of dermatophytosis, Down syndrome, diabetes, and immunosuppression due to HIV infection or medications. The infection is transmitted in shared settings such as swimming pools, baths, and locker rooms.

Clinically patients have dystrophic, hyperkeratotic, yellow-brown discoloration of the nails with onycholysis. The toenails are more commonly affected than the fingernails, generally only some nails are involved, and the infection is usually asymmetrical (*Fig. 149.17* and *Table 149.3*).

Patients often have coinfection with tinea pedis, tinea corporis, or tinea capitis. The differential diagnosis includes psoriasis, lichen planus, traumatic dystrophy, alopecia areata, 20-nail dystrophy (trachyonychia), and pachyonychia congenita. KOH prep establishes the diagnosis, and fungal culture will delineate specific pathogen. When direct microscopy and fungal culture fail to confirm infection, material should be collected from nail clippings, subungual debris, nail bed, or undersurface of the nail plate and sent for histopathology.

Treatment can be difficult, and it is important to weigh the risks and expense of systemic treatment given cure rates (65%) and high rate of recurrence (50%). Parents and children may opt for less invasive measures, such as simply paring and filing of the nail to relieve pressure points causing pain. Patients may also undergo mechanical debridement with total or partial surgical nail avulsion. Topical medications require rigorous compliance and sustained treatment which may not provide clearance. Ciclopirox 8% (Penlac) is a nail lacquer applied daily for 9–12 months (success rate 20%); bifonazole in 40% urea (Mycospor Onycho-Set) and amorolfine 5% with once weekly application are alternatives. Systemic treatment

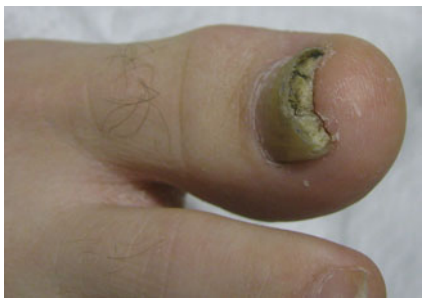


Figure 149.17
Onychomycosis

Table 149.3
Onychomycosis: Classified by mode and site of invasion

Type	Location	Features	Cause
Distal lateral subungual onychomycosis (DLSO)	Hyponychium	Spreads proximally along the nail bed and lateral nail grooves	Western countries causative agent: *Trichophyton rubrum*
Endonyx onychomycosis (EO)	Distal lateral onychomycosis	Involves nail plate/bed	*T. soudanense* and *T. violaceum*
Superficial onychomycosis (SO)	Dorsal plate		Superficial white onychomycosis-*T. mentagrophytes var interdigitale* and superficial black onychomycosis – *T. rubrum var melanoides* or *Scytalidium dimidiatum*
Proximal subungual onychomycosis (PSO)	Proximal nail fold	Spreads distally on nail plate	*T. rubrum*; PSO with paronychia – *Candida albicans*
Total dystrophic onychomycosis (TDO)		Most severe form Rarely seen in children	May occur as a result of immunodeficiency or culmination of other types of onychomycoses

Table 149.4
Systemic treatment options of onychomycosis

Medication	Properties	Dose	Duration
Itraconazole	Fungistatic against dermatophytes, molds, and yeasts	3–5 mg/kg/day up to 200 mg/day	12 weeks
Terbinafine	Fungistatic against dermatophytes, Aspergillus, Scopulariopsis	Weight dependent:	6–12 weeks for fingernails
		<20 kg: 62.5 mg/day or 125 mg every other day	12 weeks for toenails
		20–40 kg: 125 mg	
		>40 kg: 250 mg	
Fluconazole	Fungistatic against dermatophytes, Candida, nondermatophyte molds	3–6 mg/kg/dose given weekly	12 weeks for fingernails and 26 weeks for toenails
		or	or
		3–6 mg/kg/day (up to 300 mg/day) given daily	2 months for fingernails and 3 months for toenails

deserves confirmation of infection with positive culture (*Table 149.4*).

Tinea Versicolor (Pityriasis Versicolor)

Tinea versicolor (TV) is a common superficial fungal infection of the skin caused by *Malassezia furfur*, which exists in the yeast phase (*Pityrosporum orbiculare*) on normal skin. *M. furfur* produces disease only when substantial numbers of the hyphal form predominate on the skin. The reason for this proliferation of the hyphal form is unknown; however, it is more common in diabetics, patients treated with oral corticosteroids, or patients who have a genetic predisposition to TV. Tinea versicolor is common in tropical climates and areas with high humidity and temperatures.

Typically, adolescents and young adults are most susceptible, but the infection can occur in any age group, including infants. Patients develop scaling, oval-shaped

hyperpigmented (pink/brown) or hypopigmented plaques on the trunk (chest and back), arms and, occasionally, face (more common in infants). The plaques are usually asymptomatic or mildly pruritic and are more prominent during the summer months when patients tan and plaques remain hypopigmented. In the winter, plaques are typically hyperpigmented compared to the unaffected skin. Generally, the patient's concern is mainly cosmetic (*Fig. 149.18*).

The differential diagnosis includes: confluent and reticulated papillomatosis of Gougerot and Carteaud, pityriasis alba, postinflammatory hypo/hyperpigmentation, vitiligo, seborrheic dermatitis, atopic dermatitis, pityriasis rosea, tinea corporis, psoriasis, erythrasma, and secondary syphilis. The diagnosis is often clinical, and stretching of lesional skin helps elucidate fine scale, which is often imperceptible. KOH prep confirms diagnosis exhibiting pseudohyphae and spores ("spaghetti and meatballs"). Wood's lamp examination may be helpful by revealing orange or blue-white fluorescence.

Treatment can be very difficult due to recurrence and relapse. Topical treatment is standard, but compliance and difficulty of application may limit or prevent success. Topical medications include selenium sulfide shampoo 2.5% applied to the body for 10–15 min prior to showering for 7 days, and then weekly to monthly to prevent relapse. Alternative treatment is to apply from the neck down overnight and then wash off the following morning on two consecutive nights. This process is repeated 1 week later. Zinc pyrithione 2% shampoo or soap and ketoconazole shampoo are also effective when used in a similar manner. In patients with persistent infection or who are not amenable to the application of topical medications, oral antifungals may be beneficial and a single dose of fluconazole or ketoconazole 400 mg may be curative. With extensive or recurrent episodes, ketoconazole 200–400 mg daily for 5–10 days, or daily once a month for 6 months should eradicate TV. Itraconazole and fluconazole have also been shown to be effective. It is important to counsel patients that repigmentation may take months to occur, recurrence is common, and prophylactic treatments are usually necessary to prevent relapse.

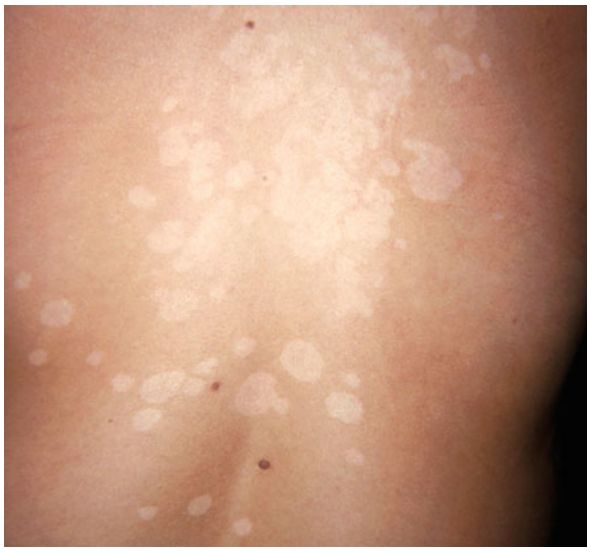


Figure 149.18
Tinea versicolor

Infestations and Bites

Scabies

Scabies is an infestation with the mite, *Sarcoptes scabiei var. hominis* which affects all age groups; in children, it occurs most commonly under the age of 2. The infestation occurs across all ethnic groups and socioeconomic levels. Outbreaks are typical in overcrowded areas such as daycare centers, elementary schools, and orphanages. Risk factors for scabies include: overcrowding, poverty, poor nutrition, poor hygiene, and homelessness.

Transmission occurs through prolonged skin-to-skin contact, rarely by indirect spread via infected bedding, clothing, etc. After a 3–6 week incubation period, the mite burrows into the stratum corneum and lays eggs that hatch and emerge as larva in 15 days. With recurrence or reinfection, infestation may develop within a few days. The mite is quite efficient and most healthy individuals harbor only 10–15 mites. Most of the resultant dermatitis is the result of an allergic reaction to the body parts of the mite.

Clinical Features

Patients develop a polymorphous pattern of papules, vesicles, pustules, nodules, urticarial plaques, and/or dermatitis. Favored sites are the fingers/hands (flexor wrists), finger and toe web spaces, intertriginous areas, axillae, nipples/areola, umbilicus, and genitalia. The distribution in infants who are crawling differs somewhat; papules and pustules may occur on the palms/soles as well as the head, neck, face (typically spared in older children), axillae, and

diaper area. The classic sign of disease in all age groups is the scabietic burrow, a serpiginous erythematous linear tract with a minute black dot (the mite) at one end. Patients typically develop intense itching, especially at night; with scratching, areas may become lichenified, purulent, or impetiginized. Secondary infection with *Streptococcus* and *Staphylococcus* is common due to excoriations, and id reactions may develop.

Differential Diagnosis

Scabies infestation may mimic atopic dermatitis in infants. Key features to help differentiate the two entities include xerosis and facial/flexural involvement – elements more commonly seen in atopic dermatitis, while burrows, hyperpigmented nodules, extensor involvement, and pruritus in other household members suggest scabies. Other entities to consider include: impetigo, insect bites, viral exanthem, dermatitis herpetiformis, eczema herpecticum, infantile acropustulosis, papular urticaria, tinea corporis, Langerhans cell histiocytosis, and pityriasis rosea.

Evaluation

Skin scraping of burrows or suspicious papules, using mineral oil or KOH for visualization, helps to identify mites, ova, or feces (scybala – only seen with mineral oil). Multiple scrapings from several different sites will increase the yield. Occasionally, dermatoscopy helps to identify mites (*Fig. 149.19*).

Treatment and Prognosis

- Permethrin 5% is the treatment of choice and is approved for infants >2 months old. After bathing, patients (or parents) apply the medication from the neck down, including genitalia (avoiding orifices), leave it on for 8–12 h (may be left on overnight), and shower off the following morning. Complete coverage is essential, parents/caregivers should cover every square centimeter of the body, even if no disease is apparent. Patients should be retreated 1 week later.
- Crotamiton 10% cream. Applied from neck down for 2 consecutive days and then rinsed off 48 h after last application.
- Precipitated sulfur 6–10% is approved for use in children under 2 months old and pregnant women. Applied for 3 consecutive days and then rinsed off 24 h after last application.
- Other reported treatment options: benzyl benzoate, allethrin.

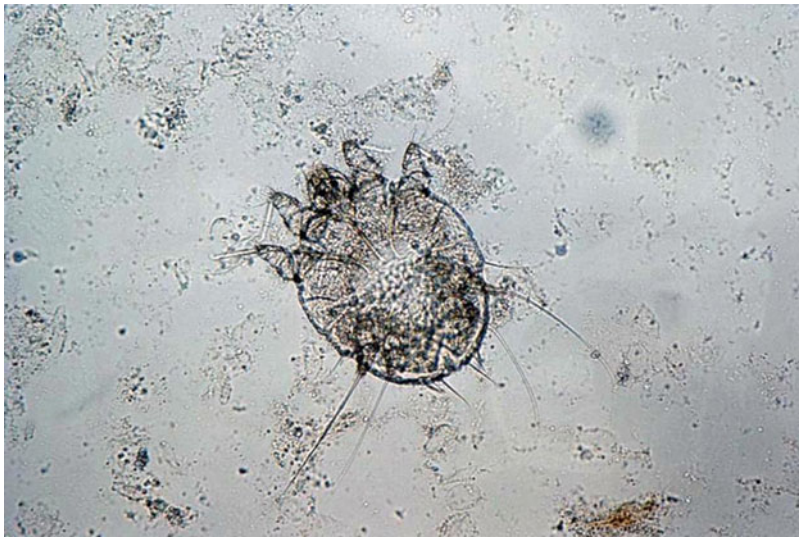


Figure 149.19
Scabies

- Persistent cases, epidemics and Norwegian scabies: treat with ivermectin 200 ug/kg, repeat 1–2 weeks (not to be used in children younger than 5 years or less than 15 kg or pregnant women).

When treating a patient with scabies infestation, all family members and close contacts (i.e., caregivers) should be treated simultaneously, even if asymptomatic. Recurrence rates are high, often related to lack of compliance and not treatment failure/resistant cases. Additional treatments include antihistamines for pruritus, systemic antibiotics for treating secondary infections, and washing linens and clothing in hot water. Mites can persist off the body for up to 2–3 days; any clothes and fomites that cannot be washed should be removed and quarantined for that period of time (at least 1 week). Despite successful treatment, postinflammatory changes and pruritus (a common issue) may persist for weeks to months. Treatment of post-scabietic pruritus with topical corticosteroids should help pruritus and any lingering dermatitis.

Scabies Variants

Nodular scabies is a bug bite like hypersensitivity reaction to the scabies mite. Patients have red-brown edematous papules (5–20 mm in size) and plaques, larger and more prominent than a typical scabies infestation. Nodular scabies affect the axillae, genitalia, buttocks, and groin. Treatment is the same as for traditional scabies, but after eradication of the mites, topical or intralesional steroids are often necessary for the nodules and plaques.

Norwegian scabies is a variant of human scabies that is highly contagious and commonly seen in institutionalized, immunosuppressed and elderly patients; it is uncommon in kids. The infestation is characterized by 1,000 mites, forming hyperkeratotic plaques (pachydermia) on the hands, elbows, knees, and soles, and nail thickening/dystrophy with extremely high elevations of serum IgE and IgG. A single treatment with ivermectin (200 ug/kg) is generally curative, but immunocompromised patients may require a second treatment (not to be used in children younger than 5 years or less than 15 kg or pregnant women). Keratolytics are also useful in removing the thick scale.

Canine scabies is a transient infection in humans caused by *Sarcoptes scabiei var. canis* and acquired after contact with a dog infected with mange. Children develop a pruritic papular dermatitis on the face, arms, chest, and abdomen in the distribution of contact with an infected animal, but patients do not harbor any mites. Skin disease is self-limited and lasts 5–10 days. No specific treatment is required, but topical steroids help to decrease pruritus. The affected animal should be treated by a veterinarian.

Pediculosis

Lice are insects with antennae and three body segments: head, thorax, and abdomen. Each segment has a pair of clawed legs; pubic louse have a small pair of legs and two pairs of legs with large crab like claws. Three types of lice parasitize humans: head lice (*Pediculosis humanis capitis*), pubic or crab lice (*Phthirus pubis*), and body lice (*Pediculosis humanis corporis*). Structurally, body lice and head lice have similar characteristics, both measuring 1–3 mm. The pubic louse is wider and only 1–2 mm in length. Once a female louse has infested a human, she deposits approximately ten eggs daily. These eggs take 7–10 days to hatch and another week to mature.

Pediculosis Capitis

Clinical Features

Pediculosis capitis is a lice infestation on the scalp. Throughout history, epidemics have waxed and waned. Over the past 30 years, incidence has risen and is reaching epidemic proportions in certain countries. Infections are common in elementary-school aged girls (aged 3–11 years old) of all socioeconomic groups and ethnicities, except African American children. Several potential theories have been suggested and include: oiling the scalp, which prevents the louse from adhering or causes suffocation and prevents movement; chemical and heat processing, which impacts the survival of the louse; and basic differences in hair texture and shaft properties.

Transmission occurs by direct contact, but lice may survive for 1–3 days off the infested host; thus, transmission can occur via fomites, e.g., combs, brushes, linens, hats, and clothes. Lice release a poisonous salivary secretion with their mouth parts when piercing the skin. This causes intense pruritus which produces scratching and excoriations, with resultant crusts and perhaps secondary impetiginization, dermatitis of the occipital scalp and postauricular area, and cervical/occipital lymphadenopathy.

Differential Diagnosis

Nits resemble hair casts, fragments of hairspray, and white piedra caused by *Trichosporon ovoides* and *Trichosporon inkin*. The scaling and dermatitis may resemble psoriasis, seborrheic dermatitis, and tinea capitis.

Evaluation

Identification of lice or nits establishes the diagnosis. Though difficult to see given the small, 1–3 mm size and rapid movements, they are most common at the nape of the neck at the hairline and behind the ears. Wetting the hair and combing with a fine-toothed comb may cause lice to fall from the hair and specs of fecal material may also be present on the scalp; well-lit exam rooms with the use of a magnifying glass will help make the diagnosis. The nits (ova) are translucent to opalescent 0.5–1 mm specks and are often detectable sticking to the hair shafts, thus making them difficult to remove (unlike hair casts that slide freely up and down the hair shaft). The nits are laid close to the scalp and grow upward as the hair grows downward. Microscopic exam of nits will show an oblong structure attached to the hair shaft at an acute angle and examination of whether the nit is full or empty may help determine active versus cleared infestation. Larger nits greater than 6 mm imply long-standing infection.

Treatment and Prognosis

Over-the-counter products (*Table 149.5*).
Prescription products (*Table 149.6*).

Other treatment modalities include:

- Single dose of Ivermectin mixed into shampoo, along with vigorous nit removal offers approximately 75% cure rate (not commercially available)
- Applying water/vinegar (4% acetic acid) solution (1:1 ratio) will help remove dead nits by dissolving the chitin in the exoskeleton

Table 149.5
Over-the-counter products (while using OTC products, advise parents/children to stop using cream rinse as it may prevent the medication from working)

Generic name	Trade name	Application	Repeat	Important facts
Permethrin 1%	Nix	Apply to dry hair Rinse after 5–10 min	1–2 weeks later	
Pryrethrins with piperonyl butoxide	RID Pronto	Apply to dry hair Rinse after 5–10 min	1–2 weeks later	Pryrethrins are natural extracts from Chrysanthemums – avoid in patients with contact allergy

Table 149.6
Prescription products

Generic name	Trade name	Application	Repeat	Important facts
Malathion 0.5% lotion	Ovide	Apply to dry hair Rinse after 8–12 h	Repeat 1–2 weeks later	Not for use in kids <6 years old
Permethrin 5%	Elimite	Apply to dry hair Rinse after 8–12 h	Repeat 1–2 weeks later	Not for use in infants <2 months old
Ivermectin 200 ug/kg	Stromectol	One dose	Repeat in 7–10 days	Not for use in children younger than 5 years or less than 15 kg or pregnant women
Trimethoprim-sulfamethoxazole		PO for 2 weeks		Results in clearance due to lice ingesting the antibiotic when obtaining blood meal

- Manual removal with fine tooth combing is possible but requires significant amount of time – unrealistic in most cases
- Suffocation therapy with oils, petrolatum, pomades, mayonnaise to the entire scalp two to three times overnight to kill the lice – somewhat efficacious; however, very messy
- Application and saturation of hair with cetaphil, followed by blow-drying introduced as new treatment modality appears to have similar efficacy rates of previous methods of suffocation, far less messy

In addition to the patient, all family members, close contacts, and caregivers should also be treated. Parents should inform the child's school about the infestation so that classmates may be examined and treated, especially if they are symptomatic. Children can still attend school once treated. Patients should be treated with over-the-counter products initially, and then prescription medications if necessary. Most "resistant" infections are due to improper use of medications.

Pediculosis Corporis and Pubis

Although pediculosis corporis may be spread by close contact among children playing, most cases of corporis and pubis are transmitted during sexual activity. Pediculosis pubis is especially unusual in young children, and if present, consider child abuse as explanation. In sexually active adolescents, pediculosis pubis is often seen in conjunction with other sexually transmitted diseases. The pubic louse is easier to see and may be found grabbing the base of pubic hairs or hairs elsewhere on the body. Nits are similar to those of pediculosis capitis; however, infestation of the eyelashes is common. Nits can be removed from the eyelashes by applying thick coats of petroleum two to three times daily. Any of the treatment modalities described above may be used for pubis, but the treatment of choice is permethrin cream 5% with or without hair removal.

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150 Vascular Malformations and Neoplasms in Childhood

Arti Nanda

Vascular malformations are rare disorders representing errors in vascular development. These malformations are often confused with most common vascular tumors, the infantile hemangiomas (IH), and other rare vascular neoplasms. This entry will review the recently adapted classification of various cutaneous vascular anomalies and distinguishing features between vascular malformations and IH as well as the clinical characteristics of significant vascular malformations, vascular neoplasms, and their related syndromes.

Classification of Vascular Anomalies

The recently adapted classification divides vascular anomalies into vascular malformations and vascular neoplasms. Cutaneous vascular birthmarks are rare errors of vascular development and occur in approximately 0.3–0.5% of the population. These lesions are much less common than the infantile hemangiomas but are often confused with them. *Table 150.1* shows the recently adapted classification by the International Society for the Study of Vascular Anomalies (ISSVA). Vascular malformations can be further subdivided into groups based on vessel type and flow characteristics. Capillary, venous, and lymphatic malformations (LM) are slow-flow lesions, and arteriovenous malformations (AVM) and fistulae are fast-flow lesions. Combined lesions may also occur (*Table 150.1*). *Table 150.2* shows distinguishing features between infantile hemangiomas (IH) and various vascular anomalies. Only the significant vascular malformations, vascular tumors, and their related syndromes will be covered in this entry.

Significant Vascular Anomalies and Related Syndromes

Capillary Malformations

Salmon Patch (Synonyms: Angel's Kiss; Stroke Bite)

Salmon patch is a subset of capillary malformation (CM) that is most commonly present on eyelids, glabella (*Fig. 150.1*), and nape of the neck. It is sometimes termed fading capillary stain rather than true CM, because it typically lightens significantly or disappears early in life. Some, often located on the nape of the neck, persist till adulthood without darkening. Salmon patch has no pathological significance, and no treatment is indicated.

Portwine Stain (PS)

Portwine stains (PS), also known as true CM, occur approximately in 3 of 1,000 infants, are present at birth, and have equal sex predisposition. They usually occur sporadically; however, familial cases with associated arteriovenous malformations (AVM) have been described. Portwine stains may arise on any surface of skin but is frequently present on the head and neck area. On the face, distribution usually corresponds to branche(s) of trigeminal nerve (*Fig. 150.2*). Mostly unilateral, occasionally bilateral, single, or multiple lesions may occur. When present on the face, PS may extend to the lips, and gingival or oral mucosa. As the patient matures, PS may become darker, more violaceous, thicker, and develop blebs. It may

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Table 150.1
Classification of vascular anomalies (Mulliken Classification [1996]. Adapted by International Society for Study of Vascular Anomalies [ISSVA])

Vascular malformations		Vascular neoplasms
Simple	Combined	
Capillary	AVF; AVM	Infantile hemangioma
Lymphatic	CVM; CLVM	Congenital hemangioma (RICH; NICH)
Venous	LVM; CAVM	Pyogenic granuloma
Arterial	CLAVM	Tufted angioma
		Hemangioendothelioma
		Hemangipericytoma

AVF arteriovenous fistula, *AVM* arteriovenous malformation, *CAVM* capillary AVM, *CLAVM* capillary-lymphatic AVM, *CLVM* capillary-lymphatic venous malformation, *CVM* capillary venous malformation, *LVM* lymphatic venous malformation, *RICH* rapidly involuting congenital hemangioma, *NICH* non-involuting congenital hemangioma

Table 150.2
Distinguishing features between infantile hemangiomas and vascular malformations

Characteristic	Infantile hemangiomas	Vascular malformations
Age of occurrence	At birth to neonatal period	Since birth
Sex prevalence (F:M)	3:1	1:1
Natural history	Rapid growth followed by involution	Proportional growth persist if untreated
GLUT-1	Specific immunohistochemical marker	Not expressed
Treatment	Spontaneous involution, pharmacological, surgical, or laser treatment if indicated	Lasers, sclerotherapy, surgery

GLUT-1 glucose transporter protein 1

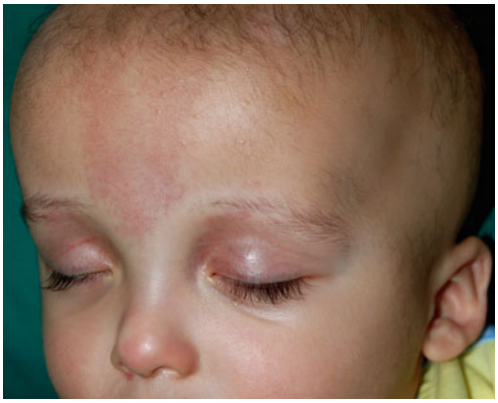

Figure 150.1
A neonate with salmon patches on eyelids and glabella

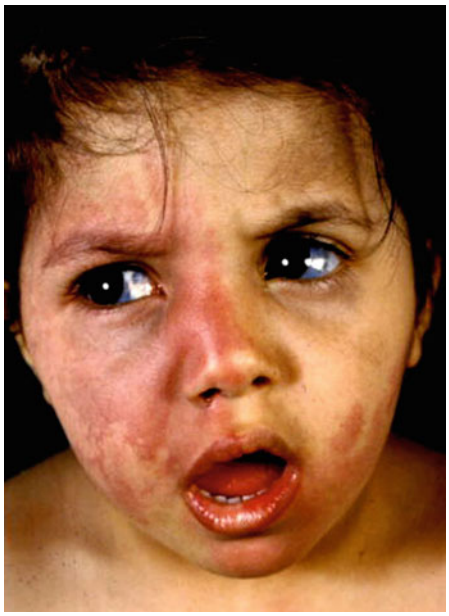

Figure 150.2
A child with capillary malformation (portwine stain) affecting right side of the face involving V1, V2, and V3 dermatomes of trigeminal nerve with some spilling on the left side. Child with this distribution has a higher risk of Sturge–Weber syndrome

be associated with underlying soft tissue hypertrophy. On limbs and trunk, PS may appear to be very red at birth and sometimes fades to lighter pink over time. Depending upon its location, PS may occur in association with various congenital malformations, including underlying vascular anomalies, or structural abnormalities of ectodermal origin, including bony or soft tissue hyperplasia or atrophy, neurological defects, eye abnormalities, spinal dysraphism, etc. The treatment options include pulsed dye laser and photodynamic therapy.

Venous Malformations (VM)

Venous malformations (VM) are slow-flow vascular malformations composed of anomalous dilated venous channels. Mucocutaneous VM are uncommon, but when present, they may have significant consequences. These lesions usually arise sporadically, but familial VM can occur and are inherited in an autosomal dominant fashion. Clinically, characteristic VM are usually noted at birth but in some cases may not become evident until the child matures. They typically become more prominent over time. They present as soft blue or purple masses that may be easily compressed with gentle pressure and become more prominent with activity or if the affected area is held in dependent position. Venous malformations do not demonstrate any warmth or thrill on palpation; if these features are present, a mixed arteriovenous malformation should be suspected. Venous malformations may arise on the skin surface or the mucosal surface and may be small focal lesions or larger covering a significant portion of head and neck or extremity. Treatment options include compression modalities, pulsed dye laser, and percutaneous sclerotherapy.

Lymphatic Malformations (LM)

Lymphatic malformations (LM) are developmental anomalies of the lymphatic system that result in abnormalities in lymphatic flow. Lymphatic malformations of the skin and subcutaneous tissue represent a diverse group of disorders that may be primary or secondary, localized or diffuse. A diffuse LM is also known as lymphedema. In this entry, we will briefly review localized LM.

Localized LM present during infancy or childhood and are often called lymphangiomas. They are classified as macrocystic or microcystic LM and arise as isolated or in combination with other vascular malformation. Macrocystic LM of the head and neck area are also called cystic hygromas. Lymphangioma circumscriptum is an older term used to describe microcystic LM with a superficial component. A common presentation of microcystic LM is that of a group of brown to tan papules, which may be mistaken for warts, overlying localized or larger area of the skin (*Fig. 150.3*). The papules may become hemorrhagic or crusted or develop black dots within them (*Fig. 150.3*). Secondary infection, skin erosions, and bleeding are frequently reported complications of microcystic LM. Squamous cell carcinoma has also been reported to arise within a long-standing microcystic LM. Surgical excision with or without grafting, Nd:YAG laser, and CO_2 laser are the treatment modalities reported for these lesions.

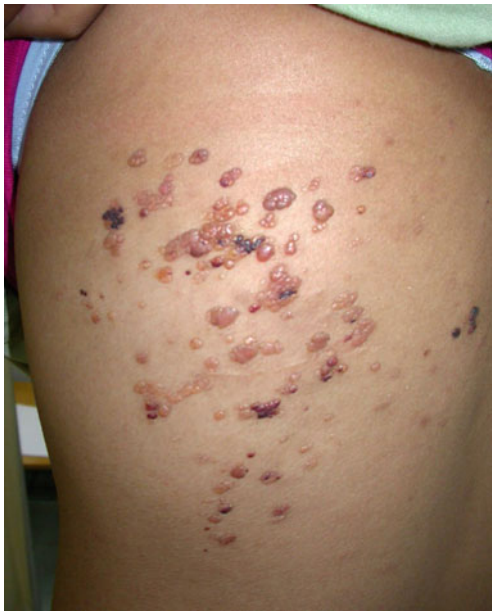

Figure 150.3
Microcystic lymphatic malformation on the thigh of a child. *Dark areas* represent hemorrhage in the lymphatic vesicles

Sturge–Weber Syndrome (SWS)

Sturge–Weber syndrome (SWS) is a sporadic congenital disorder characterized by a dermal capillary malformation (port-wine stain) occurring in association with vascular malformations of the leptomeninges and the eye. Since the original description, the syndrome has been variably defined in the literature. The complete syndrome generally includes the triad of facial dermal capillary malformation (PS), ipsilateral central nervous system (CNS) vascular malformation (leptomeningeal angiomatosis), and vascular malformation of the choroid of the eyes associated with glaucoma. Various CNS manifestations include epilepsy, headache, hemiplegia, and mental retardation. Syndrome may manifest with partial involvement. The risk of SWS may be determined by the distribution of PS. Occurrence of SWS is more often seen when PS is present is distribution of first branch (V1) of the trigeminal nerve. The incidence is higher when distribution of PS involves two (V1, V2) or all three divisions (V1, V2, V3), and the incidence of SWS is further higher if the lesions are distributed bilaterally (*Fig. 150.2*). The pathogenesis of SWS is still not clearly elucidated. It has been proposed that the ectomesenchyme for the nasofrontal bud (forehead and upper lid) and piamater (meninges) of the brain share a common progenitor in the anterior neural fold.

Therefore, it has been hypothesized that a common somatic mutation occurring early in embryogenesis in the anterior neural fold results in SWS.

Klippel–Trenaunay Syndrome (KTS)

Klippel–Trenaunay syndrome (KTS) is characterized by a superficial vascular stain (capillary malformation) of the skin in association with soft tissue and bony hypertrophy of the affected limb, and varicose veins with or without deep venous anomalies. The capillary malformation is noticed soon after birth and usually involves the whole limb. It may be accompanied by vascular and/or lymphatic malformation. Varicose veins are present at birth or appear during infancy and are associated with limb hypertrophy. Lower limb involvement is most common, followed by upper limb involvement (*Fig. 150.4a, b*). Involvement of both upper and lower limbs in the same patient may be seen in 10–15% of the cases. Once KTS is diagnosed, regular monitoring of limb length is mandatory. Many cases of KTS can be managed conservatively with elastic support garments. Several radiographic studies are helpful in follow-up and management of these cases. Echo/Doppler and duplex scans are the studies of choice to evaluate for superficial and deep venous anomalies and to rule out arteriovenous shunting. Plain radiographs or ortho-roentenography ("scanograms") can be used to evaluate bony hypertrophy, but in young patients the discrepancy may be subtle radiographic finding. MRI of the limb will help to delineate the extent of soft tissue hypertrophy, bone involvement, and presence of an associated lymphatic anomaly. If there is significant discrepancy in limb length, the orthopedic surgeon should be consulted as surgical correction may be indicated. Capillary malformation can be treated with pulse-dye laser and lymphatic blebs may require surgical excision or destructive laser techniques.

Cutis Marmorata Telangiectatica Congenita (CMTC)

Cutis marmorata telangiectatica congenita (CMTC) is a distinct cutaneous vascular malformation characterized by a fixed reticulated vascular pattern on the skin that resembles physiologic cutis marmorata. It can be differentiated from physiologic cutis marmorata by its persistence when the infant has been warmed. Cutis marmorata telangiectatica congenita may have a female preponderance and cutaneous lesions are usually noted at birth with localized, unilateral, or generalized distribution. The reticulated pattern may be fine or coarse, with broad streaks of discolored skin in a "tram-track-like pattern." Atrophy of the skin and subcutaneous tissue may supervene, resulting in limb hypoplasia (*Fig. 150.5*). Cutis marmorata telangiectatica congenita occurs as an isolated anomaly in the majority of localized cases; however, associated

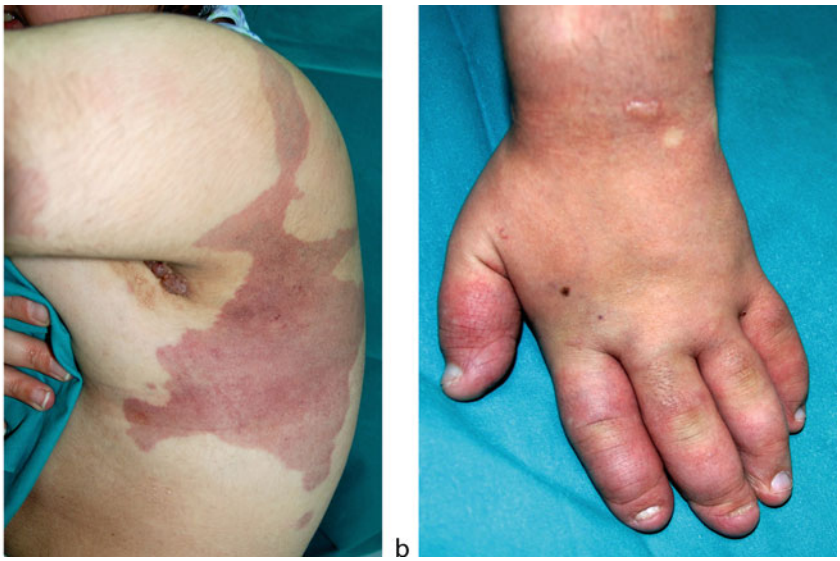

Figure 150.4
Klippel–Trenaunay syndrome with (a) large geographic vascular stain on the trunk, extending on to the arm and lymphatic malformation in the axilla, and (b) hypertrophy of the hand and forearm

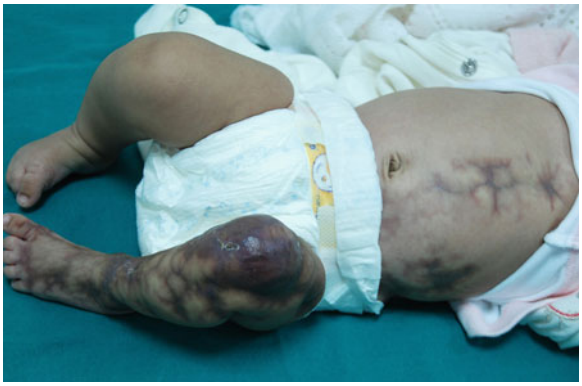

Figure 150.5
Cutis marmorata telangiectatica congenita in an infant affecting right lower limb and trunk with associated ipsilateral limb hypoplasia

congenital anomalies have been reported in 27–50% of cases. Associated abnormalities are more common in generalized cases. The most common associated congenital abnormality is limb hypoplasia. Other rare associations include limb hyperplasia, aplasia cutis congenita, congenital pigmented nevus, widespread dermal melanosis (Mongolian spot), skull asymmetry, syndactyly, scoliosis, hypothyroidism, developmental delay, and anogenital anomalies. Cutis marmorata telangiectatica congenita appears to occur sporadically; however, a genetic basis has been proposed suggesting paradominant inheritance. Cutis marmorata telangiectatica congenita has a tendency to lighten with maturity. In many patients, a marked improvement is often noted in the first 2 years of life. When lightening occurs, it is rarely complete and may have residual reticulate lesions. If lesions persist, they may be treated with pulsed dye laser, although the response is variable.

Significant Vascular Neoplasms and Related Syndromes

Infantile Hemangiomas (IH)

Infantile hemangiomas (IH) also known as hemangiomas of infancy, are the most common vascular tumors seen in childhood. Infantile hemangiomas are not noted at birth and rather become evident in the first few weeks of life as they begin to proliferate. The incidence of IH has been estimated to be 1–5%. Demographic risk factors for IH include female sex, Caucasian ethnicity, premature births, and low-birth-weight babies. Increased maternal age, multiple gestations, preeclampsia, maternal history of infertility, chorionic villus sampling, assisted reproductive technologies, and ovulation promotion have also been proven or suggested as potential risk factors. Although in many instances IH appear as sporadic lesions, recently, a familial tendency was reported in 12% of the patients.

Pathogenesis

The pathogenesis of IH is still not fully understood and is generally believed to be multifactorial. The various suggested pathogenic mechanisms include: (1) developmental theory, (2) placental theory, (3) vasculogenesis, and (4) genetic predisposition.

1. *Developmental Theory:* Developmental basis of IH is suggested due to their common occurrence on the head and neck region; frequent involvement of lines of fusion; and associations of IH with developmental anomalies. It is proposed that some arrest of mesodermal cells occurs during early embryogenesis (between the tenth and twelfth week) that later develop into IH.
2. *Placental Theory*: Frequent appearance of IH in infants with factors associated with placental insufficiency including preterm babies, small for date babies, chorionic villus sampling, etc. suggests a placental link. In addition, IH express GLUT-1 (erythrocyte-type glucose transporter protein), an exclusive marker for IH that is also expressed on chorionic villus cells of the placenta. A relationship to the placenta as the possible source of hemangioma endothelial cells has also been suggested given the presence of overlapping markers in both hemangioma and placental vessels. Infantile hemangiomas probably originate from invading angioblasts that have differentiated toward a placental phenotype or from embolized placental cells. The points against placental origin are lack of villus architecture in histopathology of IH, and IH do not express known placental trophoblastic markers.
3. *Vasculogenesis*: Infantile hemangiomas has long been considered an angiogenic disease because of the tangled disorganized mass of blood vessels in the tumor. The detection of angiogenic factors such as basic fibroblast growth factor (bFGF) and vascular endothelial growth factor-A (VEGF-A) within the tumor has supported this concept. However, an alternative is that IH arises by a process more akin to vasculogenesis, i.e., the de novo formation of vessels from progenitor cells. Children with proliferating IH have increased levels of circulating endothelial progenitor cells and surgical specimens of hemangiomas are positive for co-expression of progenitor specific markers such as CD34, CD133, and VEGF

receptor-2. Thus, VAGF signaling pathway seems to play an important role in the development of hemangiomas.

4. *Genetic Theory*: Familial occurrence of IH favors a genetic basis, and an autosomal dominant mode of inheritance has been proposed. Because of heterogeneity in clinical settings, a polygenic basis has also been proposed. Endothelial cells within the hemangioma lesions (hemEC) exhibit X-chromosome inactivation pattern of clonality with upregulated expression of some markers and downregulation of others. Various upregulating or downregulating mutations within the pathway of angiogenesis/vasculogenesis seem to be responsible for IH.

Clinical Features

Infantile hemangiomas have tremendous clinical heterogeneity in their appearance and behavior. They vary in presentation from small red plaques, nodules, to large and bulky tumors that may result in functional impairment or permanent disfigurement. Infantile hemangiomas often appear as a telangiectatic patch on an area of pallor during the first few weeks of life. Infantile hemangiomas may occur anywhere in the body but the most common location (60%) is the head and neck area. The natural history of IH is characterized by an initial proliferative or growth phase followed by a plateau, and finally the involution phase. Most hemangioma growth occurs in the first 5 months and by this time almost 80% of the final size has been achieved. On an average, IH achieve their maximum size by 9 months, but deep hemangiomas may proliferate little longer. Some IH exhibit minimal proliferation and may remain flat and some may have a network-like or reticulate appearance. Finally, an involutional phase occurs and most IH are involuted by the age 7–9 years. A change in color from bright red to purple or gray often signals transition to involutional phase.

Historically, IH have been classified by their depth into superficial, deep, and mixed types. Superficial hemangiomas involve the superficial dermis and appear as bright red lesions (*Fig. 150.6*). These lesions may be rounded nodules or plaques. Deep hemangiomas involve the deep dermis and subcutis and present as bluish-to-skin-colored nodules. Mixed hemangiomas have both superficial and deep components (*Fig. 150.7*). Another classification of IH is based on morphology and has proven to be more predictive of risk of complications or need for treatment. Under this classification, IH can be described as localized (focal), multifocal, or diffuse cutaneous hemangiomatosis. Localized hemangioma can be further classified as a localized nodule or plaque (*Fig. 150.6*),

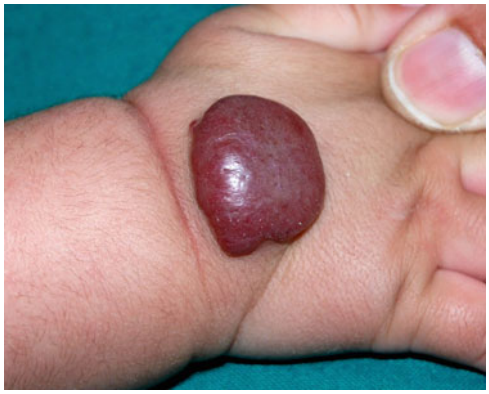

Figure 150.6
Localized hemangioma on the dorsum of the hand of an infant

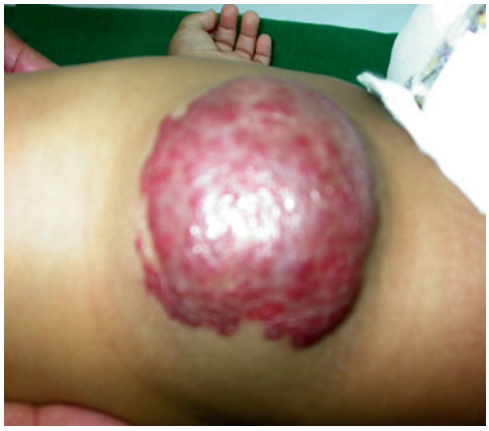

Figure 150.7
Mixed hemangioma with both superficial and deep components on the right flank of an infant

and segmental. Eighty percent of IH are focal and solitary. The term segmental has been used to describe hemangiomas that demonstrate a geographic shape and involve a broad anatomic region or a recognized developmental unit (*Figs. 150.8* and *150.9*). Segmental hemangiomas are at higher risk of complications and associated anomalies. The term multifocal refers to the presence of five or more hemangiomas (*Fig. 150.10*), and these infants are more at risk of visceral involvement. Diffuse cutaneous hemangiomatosis refers to the presence of multiple hemangiomas with a high risk of visceral involvement. They carry a great risk of high output cardiac failure and a high morbidity and mortality. *Table 150.3* enlists hemangiomas of concern and risks associated with them. Ulceration is the most common complication encountered with IH (*Fig. 150.11*). The erythrocyte-type glucose transporter protein 1(GLUT-1) has been shown to be an

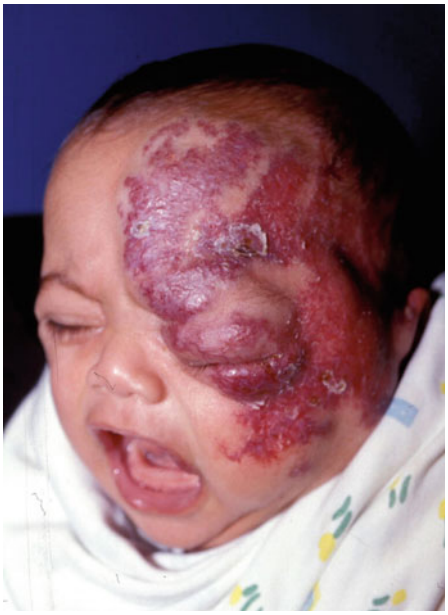

Figure 150.8
Segmental hemangioma on the left side of the face of an infant with *PHACE* syndrome

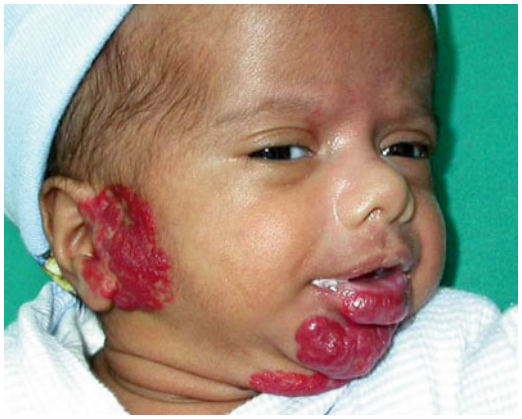

Figure 150.9
Segmental hemangiomas on the right mandibular area of an infant with associated airway hemangiomas

exclusive immunohistochemical marker of IH and is an invaluable tool used to distinguish IH from other vascular neoplasms and vascular malformations.

Congenital Hemangiomas

Unlike IH which arise in early infancy, congenital hemangiomas are rare fully grown solitary lesions that are present at birth. They occur at 1:1 gender ratio and are classified into two different types: noninvoluting congenital hemangioma (NICH), which undergoes proportional growth with the child but no regression; and rapidly involuting

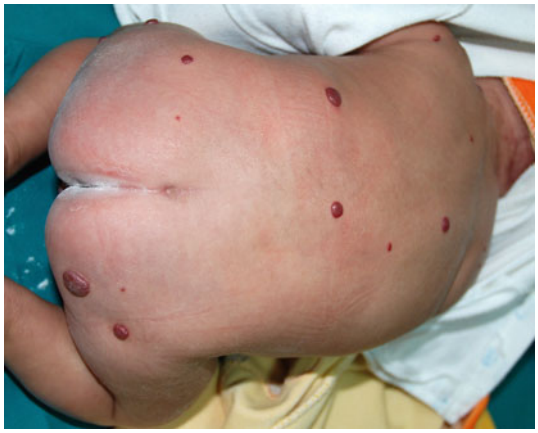

Figure 150.10
Multifocal hemangiomas on the back of an infant

Table 150.3
Infantile hemangiomas (IH) of concern and risks associated with them

IH	Associated risks
Ulcerated hemangioma	Bleeding; infection
Segmental hemangioma	
Ophthalmic	*PHACE/S* syndrome
Maxillary/mandibular	Airways obstruction/*PHACE/S* syndrome
Perineal	*PELVIS* syndrome
Midline lumbosacral	Tethered spinal cord, intraspinal hemangioma, intraspinal lipoma, genitourinary abnormalities
Large hemangioma on/around vital structure/s	
Periorbital	Visual axis occlusion, amblyopia, astigmatism, etc.
Lips/peri-oral	Feeding difficulty, cosmetic disfigurement, ulceration
Nose	Breathing difficulty, scarring, cosmetic disfigurement
Multifocal hemangioma	Visceral hemangiomas (liver, gastrointestinal most important)
Diffuse cutaneous hemangiomatosis	Visceral hemangiomas, high output cardiac failure

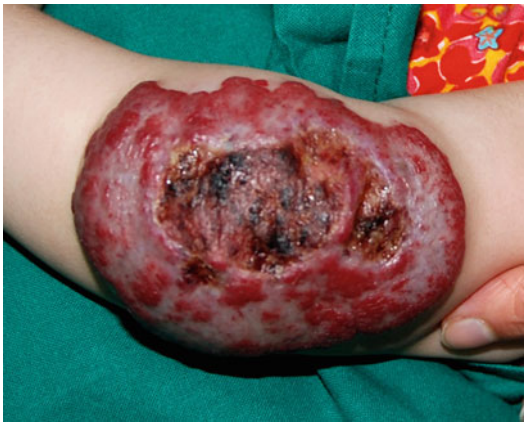

Figure 150.11
A large ulcerated hemangioma on the upper limb of an infant

congenital hemangioma (RICH), which regresses within 14–20 months of birth. Clinical appearance and histologically, both NICH and RICH are indistinguishable from infantile hemangiomas, but immunohistochemically neither NICH nor RICH show immunoreactivity for GLUT-1 which is a specific marker of IH.

Table 150.4 includes the syndromes associated with IH and their salient clinical features. Both the syndromes (*PHACE/s* and *PELVIS*) associated with IH are acronyms and are seen in infants with segmental hemangiomas affecting cervicofacial (*Figs. 150.8* and *150.9*) and perineal hemangiomas, respectively.

Table 150.4
Syndromes associated with infantile hemangiomas (IH)

IH	Associated syndrome	Clinical characteristics
Cervicofacial	*PHACE/S* syndrome	*P:* Posterior fossa malformation
		H: Hemangioma
		A: Arterial abnormalities
		C: Cardiac abnormalities/ coarctation of aorta
		E: Eye abnormalities
		S: Sternal clefting/suprapubic raphe
Perineal	*PELVIS* syndrome	*P:* Perineal hemangioma
		E: External genital malformations
		L: Lipomyelomeningocele
		V: Vesicorenal abnormalities
		I: Imperforate anus
		S: Skin tags

Treatment of Infantile Hemangiomas

The clinical heterogeneity and unpredictable and variable course of IH complicate management decisions. Physicians caring for an infant with IH must first determine whether treatment is indicated, as most hemangiomas are self-limited. Up to 38% of hemangiomas referred to tertiary care specialists require treatment due to complications such as ulceration, bleeding, risk of permanent disfigurement, obstruction of vision, airway obstruction, or high-output cardiac failure. Several factors outlined in *Table 150.3* must be considered by physicians managing patients with IH.

1. *Ulceration:* Initial therapy for most ulcerated hemangioma is local wound care. Gentle debridement of crust overlying the ulceration, antiseptic cleaning, and use of antiseptic barrier creams is required in most cases. Topical or systemic antibiotics based on culture and sensitivity are indicated in the presence of secondary infections. If ulceration is recalcitrant to initial topical measures, topical becaplermin gel, a recombinant human platelet-derived growth factor has been shown in a small series to be effective at speeding healing.
2. *Localized hemangiomas of cosmetic concern:* Although most localized IH do not require treatment, in many instances treatment may be indicated due to cosmetic concern, particularly hemangiomas located on the face or other cosmetic sites. Some of the treatment options for such cases include local compression, potent topical or intralesional steroids, cryotherapy, pulsed dye laser, and topical imiquimod (5% cream).
3. *High-risk IH*: High-risk hemangiomas include large, rapidly growing hemangiomas on vital structures, those associated with visceral hemangiomas or systemic anomalies, and diffuse cutaneous hemangiomatosis (*Tables 150.3* and *150.4*). Most cases necessitate a systemic therapy. Various treatment approaches that have been tried in such cases are:
   (a) *Systemic Steroids*: Systemic corticosteroids at a dose of 2–5 mg/kg/day (typically 2–3 mg/kg/day) used up to 6–8 months with slow tapering have historically been the mainstay of therapy. Response to treatment is variable with a reported

regression in one-third, stabilization of growth in another third, and minimal to no response in the final third. Adverse effects are common and include irritability, gastrointestinal upset, sleep disturbance, cushingoid features, adrenal suppression, immunosuppression, hypertension, bone demineralization, cardiomyopathy, and growth retardation.

(b) *Vincristine*: Vincristine has been reported to be effective in the treatment of IH and has historically been reserved for those IH that are resistant to corticosteroids or in patients intolerant to corticosteroids. Single weekly dose of 1–1.5 mg/m^2 has been used. Constipation is the most common side effect, but neuropathy, most commonly presenting as foot drop, is a potentially serious side effect. Administration of vincristine requires placement of central line; therefore, risks associated with it must also be considered.

(c) *Interferon-Alfa*: Recombinant interferon-alfa is an inhibitor of angiogenesis, administered as a subcutaneous injection of three million units per square meter per day, that has also been used successfully for the treatment of IH. Adverse effects include influenza-like symptoms, transient neutropenia, and abnormalities of liver enzymes. The side effect of great concern is spastic diplegia that has been observed more frequently in infants treated at an earlier age thus restricting its use.

(d) *Propanolol*: Propanolol has recently been used in the treatment of IH after growth arrest of an infant's hemangioma was incidentally noted when propanolol was started for obstructive hypertrophic cardiomyopathy. Subsequently, propanolol administered orally at 2–3 mg/kg/day has been shown to have a consistent, rapid, therapeutic effect, leading to considerable shortening of the natural course of IH, with good clinical tolerance. It has been recently proposed to be considered as first-line treatment for high-risk IH due to a better safety profile than other treatment modalities used for such cases. The most common serious side effects of propanolol include bradycardia and hypotension. Other side effects encountered rarely include hypoglycemia, bronchospasm, congestive heart failure, depression, nausea, vomiting, abdominal cramps, sleep disturbance, and night terrors.

(e) *Surgical Excision*: Surgical excision may be an option for function- or life-threatening hemangiomas when medical therapy fails or is not tolerated. Most commonly, surgical therapy is indicated for removal of residual fibrofatty tissue or correction of scarring after involution.

Kaposiform Hemangioendothelioma (KHE)

Kaposiform hemangioendothelioma (KHE) is a rare locally aggressive vascular tumor of the skin, deep soft tissue, and bone in infants and children, characterized by infiltrating nodules and sheets of spindle cells, and is often complicated by the Kassabach–Merritt syndrome. The use of the term "Kaposiform" relates to its unmistakable resemblance to Kaposi's sarcoma and the designation of "hemangioendothelioma" implies the uncertainty regarding the biologic behavior of such tumor, situated somewhere between hemangioma and angiosarcoma. It tends to be locally invasive, but is not known to produce distant metastases. It appears as one or multiple masses, and in most cases is associated with consumptive coagulopathy (Kassabach–Meritt syndrome). Most (75%) cases have skin involvement. Visceral involvement is very uncommon, but several cases with bone, retroperitoneal, or mediastinal involvement have been described. Various factors, including a large tumor, retroperitoneal or visceral involvement, resistance to treatment, presence of lymphangiomatosis, and Kassabach–Meritt syndrome, determine the poor outcome of KHE. Treatment options include surgical excision, systemic steroids, and interferon-alfa.

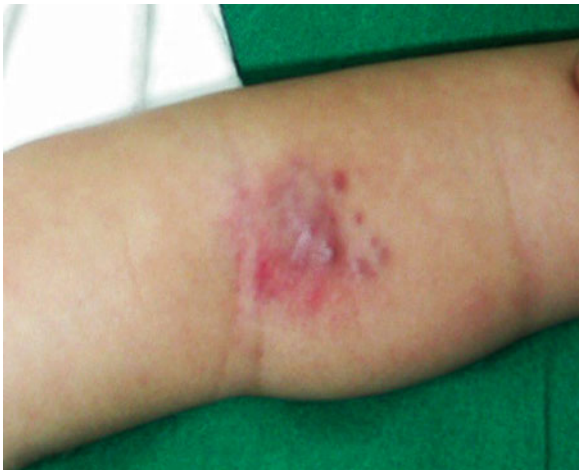

Figure 150.12
Tufted angioma on the cubital fossa of an infant

Tufted Angioma

Tufted angiomas (TA) are rare vascular tumors, most commonly localized to the skin and subcutaneous tissues and characterized by slow angiomatous proliferation. Tufted angiomas occur most frequently in children and 60–70% of the cases develop before the age of 5 years. Congenital cases are also reported. They are equally prevalent in both sexes and manifest as solitary brown, dull red, or purple patch or plaques (◉ *Fig. 150.12*) that slowly enlarge from 5 months to 10 years. Pain and tenderness are common associated symptoms and may also be accompanied by hyperhidrosis. They usually have a benign course. Rarely, TA may be complicated by the Kassabach–Meritt syndrome. A partial regression may be noticed, but complete regression is not a rule. However, a self-involution has been reported in some congenital TA cases. Surgical excision, cryotherapy, radiotherapy, and pulse-dye laser are the treatment options used for TA.

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151 Pediatric Surgical Dermatology

Kyle Anderson · Christopher Gasbarre

Surgical Considerations

Preoperative Assessment

In general, most children are healthy and require little specialized evaluation prior to dermatologic procedures. The most important component is a thorough history and physical ensuring proper diagnosis. Any existing conditions affecting surgical risk may require perioperative consultation or have implications for anesthesia. Patient and parents' expectations and goals for the final outcome must be understood prior to undergoing any procedure. The postoperative risks of scarring and possible incomplete resolution of a lesion must be explained by the surgeon. Each patient is unique and a specialized treatment plan must be formulated for their specific diagnosis.

Imaging

An important consideration is when to perform preoperative imaging. Midline lesions, especially on the scalp, are the most concerning for underlying developmental anomalies and can be a harbinger of more serious underlying defects. Nodules on the scalp may communicate with deeper structures and represent a dermoid cyst with a sinus tract, encephalocele, or heterotropic brain tissue. In addition, congenital midline skin lesions such as lipomas, dermal sinuses, acrochordons, or localized hypertrichosis can be the first recognized sign of spinal dysraphism. Most authors agree that magnetic resonance imaging (MRI) provides the best resolution and most accurate information for both superficial and deep structures of the head, neck, and spinal column. A drawback of this modality for infants and young children is the necessity for sedation. Ultrasound is also an effective imaging tool for dermatologic lesions of the midline. It does not require sedation and is far more cost effective, making ultrasound the imaging technique of choice in this age group. MRI or ultrasound is indicated prior to both biopsy and excision of congenital midline cranial masses.

Timing of Surgery

There is no single guideline among dermatologic surgeons about the optimal time to surgically intervene on nonlife-threatening conditions such as hemangiomas, vascular malformations, dermoid cysts, or congenital nevi. The final decision is best made through collaboration of both the surgeon and parents. There is no specific age when local anesthesia can be used over general anesthesia but, if a child is unable to cooperate through the entire procedure, general anesthesia must be used. Some authors feel 8 years in girls and 9 years in boys are the ideal ages, but this is highly variable. An excision performed at a younger age is able to benefit from increased skin mobility but will most likely require general anesthesia. While waiting until preadolescence could allow use of local anesthesia, a large lesion may require a staged excision due to decreased skin mobility. In general, elective procedures should be delayed until preadolescence, so the risk of general anesthesia can be avoided. Exceptions to this rule include certain vascular malformations and hemangiomas, where earlier intervention can prevent development of significant functional and cosmetic problems in the future. Capillary malformations can lead to tissue hypertrophy over time, making treatment more difficult. Venous and arteriovenous malformations are often more extensive than they appear on the surface of the skin, leading to damage of underlying structures with subsequent enlargement. Some proliferative infantile hemangiomas ulcerate or impair important structures. In these circumstances, a more prompt surgical intervention is warranted.

Anesthesia

Techniques to minimize pain during local injection are distractions such as video games or movies, topical anesthetics, lidocaine buffered with sodium bicarbonate, warming the anesthetic and slow infiltration of the anesthetic. Eutectic mixture of local anesthetics (EMLA) cream was the first widely used topical anesthetic used in children. EMLA is generally well tolerated, but there is an increased risk of methemoglobinemia when used in

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infants younger than 3 months of age. Liposomal lidocaine is a new formulation with similar efficacy to EMLA without the risk of methemoglobinemia. Viscous lidocaine and lidocaine patches are available in a variety of formulations. For pediatric patients, lidocaine 1% (10 mg/ml) is the preferred concentration buffered with 8.4% sodium bicarbonate in a 1:10 ratio. This lessens the injection pain without affecting the onset or duration of anesthesia. The maximum dose of 1% lidocaine without epinephrine is 5 mg/kg and with epinephrine is 7 mg/kg.

Most authorities agree the highest risk period for general anesthesia is within the first year of life. However, the overall risk in a dermatologic setting is low because of the short operation time, the nonemergent elective nature of the procedures, and the majority of patients being healthy. At our institution, general anesthesia is reserved for patients over 6 months of age unless special circumstances necessitate earlier intervention. In a recent multicenter retrospective review of 881 procedures, the most common complication was postoperative nausea seen in 4% of patients. The most common serious complications were hypoxia and aspiration which occurred in 0.1%. Overall, the risk was quite low with over 90% of procedures occurring without complications.

Common Lesions

Verruca Vulgaris

Human papillomavirus (HPV) types 1, 2, 4, 27, and 41 are frequent causes of common warts and infect 20% of school-age children. Warts are most frequently located on the fingers, hands, or feet but can occur anywhere. Numerous medical and surgical modalities are available, though a large percentage of lesions will spontaneously regress within 1–2 years. Conventional medical treatments consist of topical application of podophyllotoxin, cantharidin, salicylic acid, trichloroacetic acid, or lactic acid. Newer immunomodulators such as 5-fluorouracil and imiquimod have also been shown to be effective. In the pediatric population, these options are often difficult because of the frequency and length of application. Locally destructive therapy options include cryosurgery with liquid nitrogen, curettage, electrosurgery, or laser. First-line therapy is cryosurgery with two freeze thaw cycles which can be repeated every 4 weeks until the warts are gone. For recalcitrant lesions, pulsed-dye laser or potassium-titanyl-phosphate (KTP) laser can be used to target the rich supply of dermal capillary vessels present in warts. Combination therapy with a topical and a destructive option often provides the best results (*Fig. 151.1*).

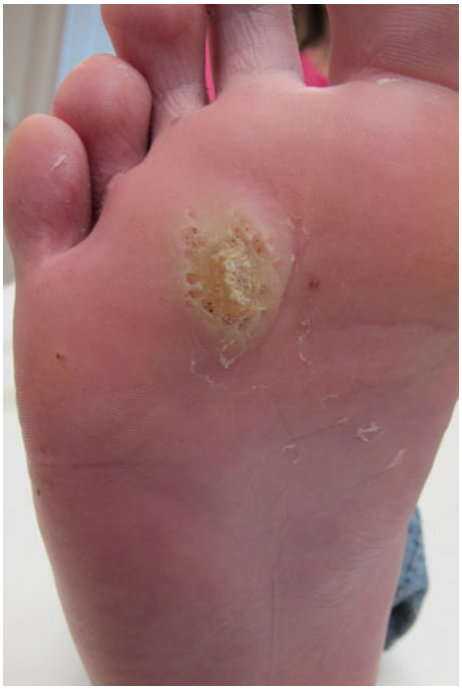

Figure 151.1

Molluscum

Molluscum contagiosum is a member of the poxvirus family and causes common cutaneous lesions in children. Transmission is via direct contact so the virus is often spread between children at daycares and school. The smooth, dome-shaped papules will spontaneously involute in 2–4 years, but treatment is usually requested. Along with numerous medical therapies, cryotherapy and curettage are potential surgical interventions. The limiting factor in the pediatric setting is pain of these procedures, so medical options such as cantharadin or imiquimod cream should be performed first (*Fig. 151.2*).

Congenital Nevi

Congenital nevi are divided into three categories: small, less than 1.5 cm, medium, 1.5–19.9 cm, and giant, 20 cm or greater. All nevi have the potential to develop

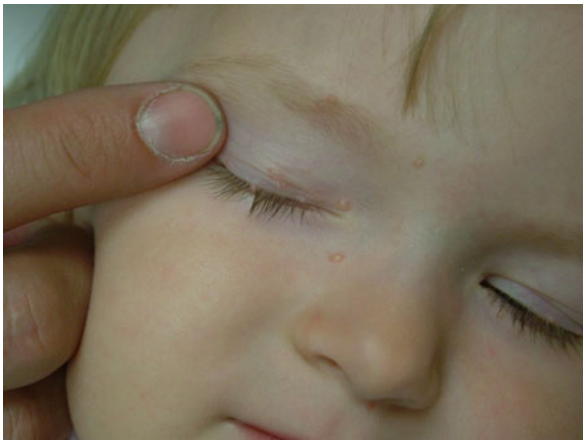

Figure 151.2

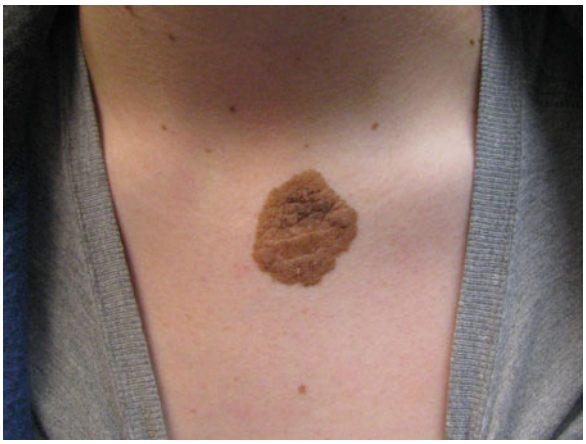

Figure 151.3

melanoma, but the risk of melanoma is directly related to the size. Most experts agree giant congenital nevi should be excised at a young age because of their increased risk of melanoma. Tissue expansion and staged excision are required in the majority of cases to preserve function and provide adequate cosmesis. For small and medium congenital nevi, careful surveillance is the best option. However, if the lesion begins to change color, shape, or size, it should immediately be evaluated by a dermatologist. Dermabrasion or curettage should not be performed because surgical excision is the only treatment that alleviates the risk of melanoma. Also, these procedures distort both the clinical and histologic architecture, making the diagnosis of a future melanoma far more difficult (*Fig. 151.3*).

Epidermal Nevi

Epidermal nevi are linear hyperpigmented papillomatous lesions distributed along the lines of Blaschko. They occur in 1 in 1,000 live births and are present at birth in 80% of cases. Complete excision to the dermis is required to prevent recurrence but is not always an option based on size or location. Laser ablation, cryosurgery, and medium-to-full-depth chemical peels may decrease symptoms and provide improved cosmesis but will not resolve the lesion (*Fig. 151.4*).

Pyogenic Granuloma

Pyogenic granulomas are solitary friable rapidly growing vascular proliferations usually occurring at sites of trauma. Minor trauma can cause extensive bleeding and be quite alarming to patient and family. These lesions can occur at any age but are more common in children and young adults. Scoop shave excision with electrodesiccation, excision with primary closure, or pulsed-dye laser are effective treatment options (*Fig. 151.5*).

Spider Angioma

Spider angiomas are bright red dilated vessels most commonly seen on the face, forearm, or hands. These lesions respond very well to treatment with pulsed-dye laser or electrofulguration. Multiple treatments maybe required with either method, but electrofulguration carries an increased risk of scarring (*Fig. 151.6*).

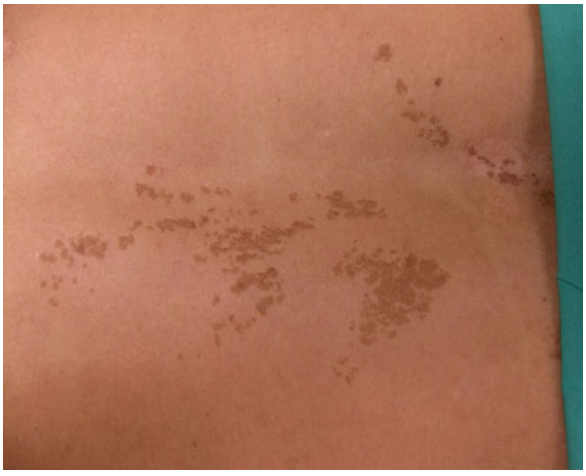

Figure 151.4

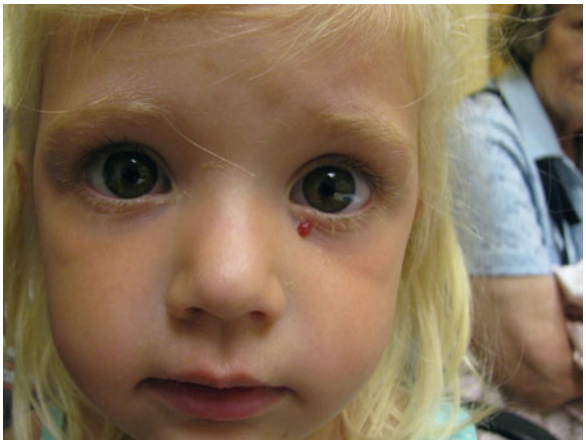

Figure 151.5

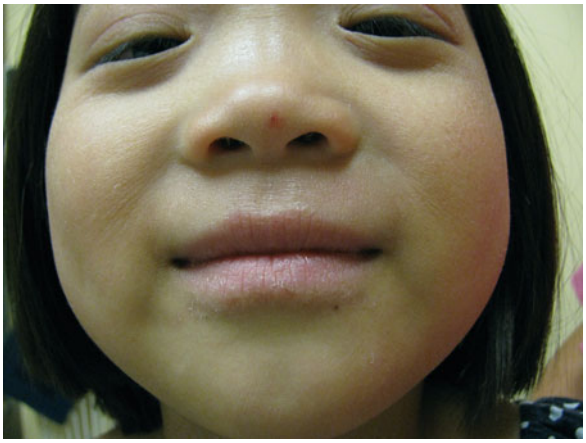

Figure 151.6

Birthmarks

Hemangiomas

Hemangiomas are benign, congenital vascular proliferations of endothelial cells occurring in 10% of newborns within the first year of life. Most hemangiomas typically undergo a proliferative phase of rapid growth during the first 3–6 months of life followed by a plateau phase and finally an involuting phase after 12 months. Studies have shown 30% of lesions involute when the child is 3 years old, 50% when 5 years old, and 90% when 9 years old. The majority of hemangiomas will involute completely, but 20–30% will leave a residual fibrofatty, atrophic, telangiectatic, hypopigmented, or hyperpigmented scar. These lesions are typically observed if they are limited, do not ulcerate, or do not impair a vital structure. Large segmental facial hemangiomas should raise the suspicion for PHACES syndrome which is an acronym standing for posterior fossa brain malformations, hemangioma, arterial anomalies of the aortic branches, eye anomalies, and sternal defects. Lower facial hemangiomas ("beard" hemangiomas) can be a marker for laryngeal involvement and subsequent airway obstruction. Recent studies support the use of propranolol for extensive hemangiomas that require treatment. Other modalities include intralesional corticosteroids, vascular laser, interferon alfa, and vincristine. After regression, pulsed-dye laser or surgical resection can be used to improve the residual thin skin, malformed vessels, or pigmentary changes.

Vascular Malformations

Nevus flammeus (salmon patch) is a common vascular birthmark located on the glabella, posterior scalp, or nape of neck. The majority of these lesions fade by 2 years of age. Treatment is usually not necessary, but low potency topical corticosteroids can be used with good results.

Port-wine stains are large capillary malformations present at birth in 0.3–0.5% of newborns. They commonly affect the face in the distribution of the trigeminal nerve but can present anywhere on the body. These lesions result in a significant cosmetic problem but can also be part of systemic syndromes. Sturge–Weber syndrome consists of a port-wine stain in the ophthalmic branch of the trigeminal nerve with or without maxillary or mandibular involvement along with glaucoma, seizures, and mental retardation. Klippel–Trénaunay syndrome consists of a port-wine stain usually on an extremity with associated venous malformations and hypertrophy of the affected limb. Proteus syndrome comprises port-wine stains with soft tissue hamartomas, asymmetric overgrowth of bones, and cerebriform connective tissue nevus of palms and soles. The gold standard for treatment of port-wine stains is pulsed-dye laser. Gradual fading will occur over successive treatments with as much as 80% resolution after eight to ten sessions. Best results are obtained when treatment begins prior to 1 year of age. Treatment is painful and requires general anesthesia when performed in young patients. Early laser treatment helps prevent later hypertrophy which is much more difficult to treat (*Fig. 151.7*).

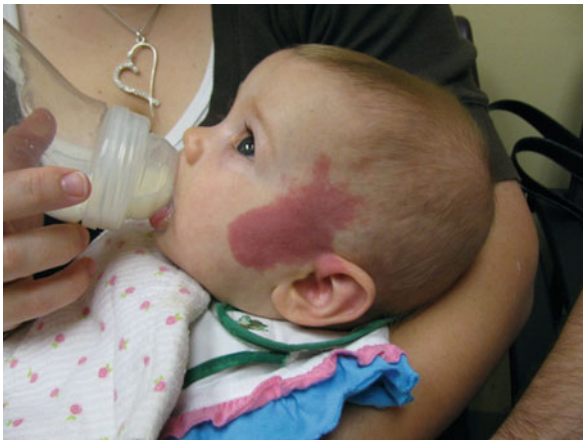

Figure 151.7

Figure 151.8

Café-au-Lait Macules

Café-au-lait macules are light or dark brown macules which can be located anywhere on the body. They are very common and reported in 10–20% of the population. Response to treatment is highly variable and must be explained to the patient and family prior to therapy. Prior to treatment of large or extensive café-au-lait macules, treating small test areas within a lesion is helpful to determine the best laser setting and outcome. This also tests for posttreatment hyper- or hypopigmentation which is an unfortunate side effect. Pigment lasers such as Q-switched ruby, Q-switched Nd:YAG, or Q-switched alexandrite are effective, but multiple treatment sessions are required, and as many as 50% of lesions may recur (*Fig. 151.8*).

Nevus of Ota and Mongolian Spots

Nevus of Ota is a congenital blue-gray hyperpigmentation in the distribution of the first and second branches of the trigeminal nerve seen more commonly in Asians. Mongolian spots are similar lesions located in the lumbar and sacral area but are more likely to regress during childhood. The discoloration is due to melanin-producing melanocytes within the dermis. Given the depth of dermal pigment, pigment lasers with longer wavelengths such as the Q-switched ruby, Q-switched Nd:YAG, or Q-switched alexandrite are effective treatment options. Like other melanocytic lesions, multiple treatments are required for successful removal and may not give total resolution (*Fig. 151.9*).

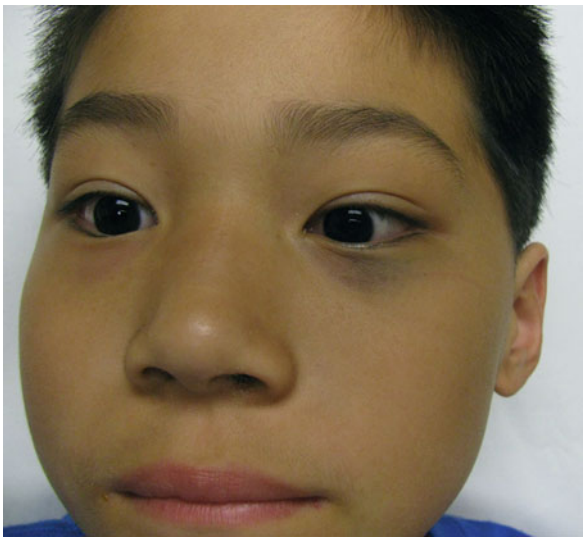

Figure 151.9

Becker's Nevus

Becker's nevus is an acquired hairy hyperpigmented plaque most commonly on the shoulder and upper arm of males. Malignant transformation has not been reported, so treatment is for improved cosmesis. The hyperpigmented component can be treated with pigmented lasers such as Q-switched ruby or Q-switched Nd:YAG, but recurrence is high. Fractional resurfacing has also been reported to be effective to lighten and improve texture. The hypertrichosis in Becker's nevus can be treated with hair removal lasers such as the long-pulsed

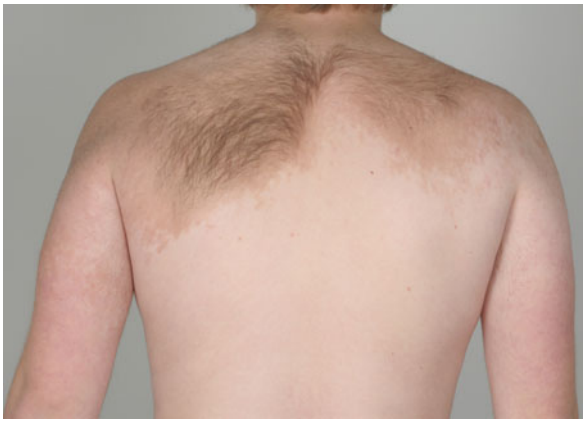

Figure 151.10

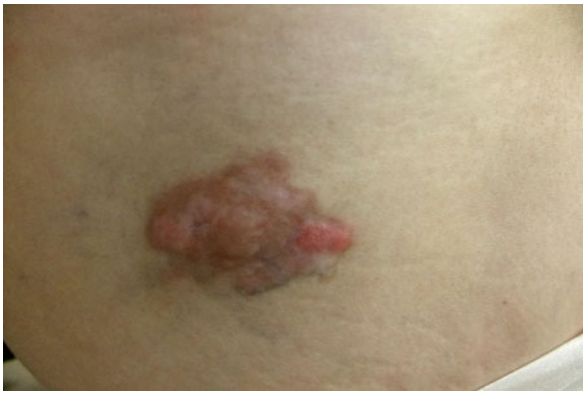

Figure 151.11

ruby, long-pulsed alexandrite, long-pulsed diode, long-pulsed Nd:YAG, or intense pulsed light (IPL) (Fig. 151.10).

Malignancies and Rare Tumors

Melanoma

Melanoma is very rare in children with only 2% of all melanomas occurring before the age of 20. In general, pediatric melanomas have thicker primaries than adults because of delayed time to diagnosis. Treatment in children is similar as in adults with wide local excision being the standard of care. The margins for re-excision are based on depth of tumor invasion on initial biopsy. The current recommendations for excision with tumor thickness <0.5 mm is 0.5 cm margins, 0.5–1.0 mm is 1.0 cm margins, 1.0–4.0 mm is 2.0 cm margins, and >4 mm is 2.0–3.0 cm margins.

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans is a rare spindle cell tumor occurring in 0.8 per million people, with only 6% of those in children less than 16 years of age. The preferred treatment of these tumors is Mohs micrographic surgery which gives clearance rates of 93–100% (Fig. 151.11).

Hyperhidrosis

First-line treatment for mild hyperhidrosis is topical 20% aluminum chloride hexahydrate or 6.25% aluminum tetrachloride daily for three to five consecutive nights, then once weekly. For more persistent hyperhidrosis, intradermal injection of botulinum toxin type A can produce near anhidrosis for 4–6 months. Oral anticholinergics will decrease sweating in most patients but have significant side effects such as dry eyes, dry mouth, palpitations, mental status changes, changes in vision, urinary retention, and bowel disturbances so should be used with caution. Excision of the sweat glands and sympathectomy are more radical procedures that should only be used in refractory cases.

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152 Pediatric Skin Care: Skin Barrier Management and Topical Treatment in Pediatric Dermatology

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Children's skin differs both physically and physiologically from adolescent and adult skin. Newborn skin is the most fragile and permeable, is affected by transepidermal water loss, and is susceptible to penetration by toxic environmental substances or drugs intentionally used to improve pathologic skin conditions. Children's skin is more likely to develop blisters or erosion in response to heat, chemical irritation, and mechanical trauma, including simple friction. Consequently, conditions that may not negatively affect adult skin need to be considered as potentially harmful to children's skin.

One of the most important functions of the human skin is its barrier function. In this respect, an appropriately functioning epidermis is one of the crucial elements. Normally, keratinization of the human epidermis begins at about the 24th week of gestation and is completed shortly before term, so that transepidermal water loss and transepidermal absorption of topically applied substances at birth are similar to those of older children. However, elasticity of young children's skin is much less than older children due to a deceased amount of collagen and elastic fibers. Response to ultraviolet (UV) light differs due to a low number of melanocytes, which still need to proliferate and to mature. Even though the sebaceous glands are fully developed, the numbers of eccrine and sebaceous glands are lower in newborns, children, and young adolescents. This phenomenon has practical clinical implications, i.e., in the development of acne, folliculitis, or pigmentary disorders potentially linked to functioning sebaceous glands (e.g., the so-called "progressive macular hypomelanosis").

In children, skin injuries, hyperemia, and inflammatory processes, as well as acidosis, ischemia, and systemic infections including sepsis, may negatively influence the skin's barrier function.

It is important to realize that in newborn and young children the skin surface:volume ratio is much higher than in older children, adolescents, and adults, and this may result in a higher cutaneous penetration ratio. This phenomenon influences the calculation of the applied dose of topically administered agents and always needs to be considered in therapy planning.

Skin permeability is inversely proportional to gestational age. Even in infants born at term, transcutaneous water loss and percutaneous absorption of topically applied substances, including intentionally given drugs, is two to three times higher than in older children and adults. Substances of low molecular weight and water-soluble substances penetrate very easy. Topically applied antiseptics and antibiotics, salicylates, urea, and alcohol-containing dressings have been associated with neonatal toxicity due to percutaneous absorption, especially in premature infants and newborns.

It is important to realize that the normal barrier function of the skin depends not only on the development of physically intact, cornified epidermis, but also on the quality of epidermal lipid composition. This has important implications in cases of so-called "dry skin" as, for example, in children with atopic dermatitis.

Skin pH is important in the regulation of antimicrobial barrier function and regulation of transepidermal penetration. At birth, the skin pH is usually neutral or slightly alkaline (pH of 6.2–7.5) and decreases rapidly during the first weeks, reaching the range of 5.0–5.5 at the fourth week of life.

Neonatal and newborn skin is more predisposed to heat loss, resulting more from evaporation of water from the skin's surface than from radiative heat loss. The vasoconstrictive response to reduced environmental temperature has practical clinical implications if neonates, newborns, and young children will be examined in cold rooms or left uncovered for a longer period of time before medical examination.

Different body sites have different permeability. Variations in the epidermis, especially in the stratum corneum, and its hydration status, density of hair follicles and sebaceous glands, thickness of the epidermis and dermis, local body temperature, and occlusion influence the penetration of topically applied agents through the epidermis into

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the dermal skin component, vasculature (and eventual further systemic effect), and subcutaneous fat.

Both long-term, practical experience and clinical experimental data support the simple and practical ranking of body sites from the highest to the potentially lowest permeability and absorption rate – scrotum, face and scalp, trunk and extremities, palms and soles, nails. Hair does not actively absorb or transport substances from the surface into the skin, but the absorption of agents applied to the hair may easily occur through the hair follicle and pilosebaceous units.

Topically applied substances are usually poorly absorbed and only a small portion of the drug penetrates through the stratum corneum. Most of the applied agent remains on the skin surface and is then actively or passively removed from the application area by exfoliation, sweating, wash-out, rub-off, penetration into clothing, or by time, pH, or UV exposure–related degradation.

Therefore, local application of a drug under occlusion (i.e., under polyethylene foils, colloidal, or hydrocolloidal patches) may dramatically increase the penetration and, consequently, local and systemic absorption.

A number of local or environmental factors can increase transepidermal and transdermal penetration of the active substance. Hydration of the skin due to occlusion (moisture retention) in intertriginous areas can increase absorption up to five- to tenfold. Removal of lipid components from the skin surface, for example, by alcohol swab, can also increase transepidermal penetration due to removal of the superficial fat and "opening" of the natural skin barrier. The addition of alcohol or polyethylene glycol to the drug-carrying vehicles also increases penetration of the active substances. This technique has been utilized in the manufacturing of vehicles for super- and high-potent steroids to maximize their bioavailability. On the other hand, extensive use of such substances along with, for example, dimethyl sulfoxide (DMSO), may lead to local adverse skin reactions in the form of burning, stinging, or maceration, especially in eroded skin, and may also lead to irritation or allergic contact dermatitis.

The "opening" or "expansion" of the stratum corneum by DMSO, glycols, water, and other solvents enhances the uptake of the drug and is often used to establish a "superficial skin reservoir" of the applied medication.

Appropriate skin function is best maintained by keeping the skin barrier intact and restoring it as quickly as possible if barrier function is impaired.

Historically, the best way to keep the skin barrier and the skin itself in good shape was to keep skin moist and lubricated. However, this conventional wisdom is not correct. Overwetting and overfatting, especially using semisolid lubricants like vaseline or liquid paraffin may lead to occlusion of the skin surface and retention of heat and fluid under the fat film, negatively influencing skin condition.

Many nondermatologists may be hesitant to use some specific medications in younger patients because of safety concerns. Two groups of topical skin medications are of special interest: corticosteroids and emollients.

Topical Steroids

The selection of a topical corticosteroid in terms of strength and vehicle depends on the nature, location, and extent of the skin lesion(s), the age of the patient, and the duration of treatment.

The vehicle is a crucial factor in topical delivery of active substances. An ointment is generally the most effective vehicle for treating thick, fissured, and lichenified skin lesions. The occlusive nature of the vehicle enhances corticosteroid penetration. In large surface areas it may, however, lead to accumulation of heat and moisture under the almost occlusive layer of the vehicle. Ointments may be considered aesthetically undesirable by some patients.

Creams are generally the vehicle of choice for acute and subacute dermatoses. They may be used on moist skin and in intertriginous areas and are generally aesthetically acceptable to patients. Cream vehicles may occasionally be considered drying, and some patients may benefit from the application of a moisturizer in addition to a corticosteroid cream. Cream formulations usually require the addition of preservatives, which may cause sensitivity.

Solutions, gels, and sprays are the most aesthetically elegant vehicles for use on the scalp. They also may be useful when, for aesthetic or medical reasons, a non-oil-based vehicle is needed. These vehicles frequently contain alcohol and propylene glycol, which may cause irritation or burning if applied to acute dermatoses, erosions, or fissures (see above).

Topical steroids are the most potent anti-inflammatory agents. The introduction of corticosteroids for systemic application in 1951 and topical administration in 1952 revolutionized the daily practice of dermatology.

Development of topical corticosteroids focused on enhancing biological potency and simultaneously minimizing side effects, retaining high activity in the skin and quick metabolism after absorption into inactive metabolites ("soft" corticosteroids). Mometasone and fluticasone propionate (see below) are examples.

Normally, only 1% of an applied corticosteroid dose is therapeutically active. Cutaneous side effects can result from this small percentage or from the transient presence of the initial amount on the skin surface, intended occlusion, large surface area application, or physiologic occlusion in intertriginous or diaper areas.

High-potency topical corticosteroids should be used briefly or intermittently, and potency and frequency should be reduced once partial improvement is achieved. Sudden discontinuation almost always leads to rebound effect and prolonged therapy to tachyphylaxis.

In infants and children the use of topical corticosteroids is influenced by the high ratio of surface area to body weight. Infants, especially premature infants, are less able to rapidly metabolize the quickly absorbed drug through their thin skin.

Topical corticosteroids are divided into seven classes according to their biological potency. Class I represents the most biologically active (potent) drugs, whereas class VII represents the weakest.

The potency of a topical steroid determines its clinical application, maximal surface area treated, duration of application, and potential local and systemic side effects.

It is important to note that a topically applied steroid may change its clinical potency not only due to the concentration, but also depending on the vehicle used, because the type of vehicle determines the bioavailability, penetration, and the length of time the drug stays on the skin surface, and therefore the vasoactive properties.

Some steroids have been chemically modified so that they retain their biological potency in all forms of vehicles used for application to the skin. This complicates the understanding of the biology of topical steroids.

To make this "science" simpler, the following classifications do not include the weight percentages of the particular steroid or the grams of vehicle, but focus on the chemical form of the vehicle itself (petrolatum-based ointment, cream, or lotion).

Class I (ultrapotent) steroids are clobetasol propionate, betamethasone dipropionate, diflorasone diacetate, and halobetasol propionate, all in an ointment vehicle. Clobetasol is also considered ultra-potent as a cream or lotion.

Class II (potent) steroids include betamethasone dipropionate (in a cream or lotion vehicle), mometasone furoate (in all forms – ointment, cream, gel, and lotion) diflorasone diacetate (ointment), halcinonide (ointment), triamcinolone acetonide (ointment), fluocinonide (ointment, cream, and gel), and desoximetasone (in all forms – ointment, cream, and gel).

Class III (high-mid strength) steroids include triamcinolone acetonide (ointment), fluticasone propionate (ointment), amcinonide (cream or lotion), diflorasone diacetate (ointment), halcinonide (in all forms – cream, ointment, and lotion), fluocinonide (ointment, cream, and gel), desoximetasone (ointment and cream), and betamethasone valerate (ointment).

Class IV (middle-mid strength) includes triamcinolone acetonide (cream), flurandrenolide (ointment, gel, and cream), prednicarbate (ointment), mometasone furoate (cream and lotion), triamcinolone acetonide (ointment), betamethasone valerate (foam or cream), fluocinolone acetonide (ointment), and hydrocortisone valerate (ointment).

Class V (low-mid strength) includes alclometasone dipropionate (ointment), flurandrenolide fluticasone propionate (lotion and cream), prednicarbate (cream), triamcinolone acetonide (lotion), hydrocortisone butyrate (ointment, cream, and solution), fluocinolone acetonide (cream), and hydrocortisone valerate (cream), and prednicarbate (cream).

Class VI (low strength) steroids, including alclometasone dipropionate (ointment, cream, and lotion), desonide (ointment and cream), and fluocinolone acetonide (solution).

Class VII (very low strength) steroids include hydrocortisone as a cream in all available concentrations: 0.5%, 1%, and 2.5%.

Structural modifications influence the efficacy of topical corticosteroids. Betamethasone dipropionate and clobetasol propionate, known as fifth-generation corticosteroids, are typical examples of super-potent molecules that can control specific dermatoses very rapidly, but that are associated with a high risk of topical and systemic adverse effects.

Recently, steroid components have been synthesized that aim to have adequate anti-inflammatory effects and minimal adverse effects. The topical corticosteroids widely used nowadays for the treatment of different dermatoses and allergic reactions of the respiratory tract (in particular asthma) are budesonide, mometasone furoate, prednicarbate, the di-esters 17,21-hydrocortisone aceponate and hydrocortisone-17-butyrate-21-propionate, methylprednisolone aceponate, alclometasone dipropionate, and carbothioates such as fluticasone propionate. These new formulations have higher anti-inflammatory effects and good compliance among patients (often only a once-daily application is needed), compared with well-known and established corticosteroids. They rarely induce cross-sensitivity reactions and have weak atrophogenicity.

Minimally infiltrate, acute, inflammatory skin lesions frequently respond to low- to medium-strength topical corticosteroids. Chronic, hyperkeratotic, lichenified, or indurated lesions may better respond to high- or very high-strength topical corticosteroid preparations.

Treatment of the face and intertriginous areas (axilla, groin, perineum, and inframammary area) needs special consideration. Because of the thin stratum corneum and possibly because of the nature of the pilosebaceous structures in the area, the face is particularly susceptible to local side effects. In intertriginous areas, heat, moisture, a thin stratum corneum, and self-occlusion enhance the penetration of topical corticosteroids that can cause both local side effects and potential systemic effects from the enhanced absorption. The occlusive effects of diapers enhance penetration in the groin area to an even greater extent.

For these reasons, low-strength preparations are preferred for the face and intertriginous areas. In some patients, especially if the lesions are indurated, lichenified, or impetiginized, short-term (generally for a week or 2 weeks) use of more potent agents is occasionally required. These agents should rarely, if ever, be used in the diaper area of infants.

Recalcitrant lesions of the face or intertriginous areas such as those of discoid lupus erythematosus and lichen sclerosus may require more potent corticosteroids or a longer duration of treatment.

Lesions on skin with a thick stratum corneum, such as the palms and soles, frequently require treatment with high- or very high-strength topical corticosteroids to achieve significant improvement.

The amount of body surface area to which the corticosteroid is to be applied will help determine the specific class of drug that should be used. Because of the likelihood of systemic absorption, corticosteroids of low to medium strength are preferred when large areas are to be treated.

It is important to make treatment simple for patients, parents, and physicians. Parents should be instructed on how to apply medications. It is important to prescribe the appropriate amount of the drug – too little leads to too quick an end to medication, provoking rebound effects after abrupt interruption; too much may lead parents to apply more than appropriate.

Thin application is desirable for most medicines except emollients, where thicker or multiple daily applications may be preferred. Moisturizers may be applied in the "steroid free intervals" to damp skin to retain hydration.

Estimates of coverage of the skin can be made by using the "rule of nines," in which the body surface is divided into 11 equal parts, each constituting ~9% of the total body surface area. Based on this, the following estimation can be made: 2 g of cream or ointment should be enough to cover each of the following body surface areas (thin application!): head, one arm, chest (anterior), back, abdomen, buttocks, lumbar area, one half of each leg.

Another practical way to measure the amount of topical steroids needed per application is the fingertip unit (FTU) and the rule of hand. An FTU is the amount of cream or ointment that can be pressed out onto the medial surface of the second finger of the adult hand. Two "mean" adult hand surfaces correspond to one FTU, which is approximately 0.5 g of the topically applied agent.

Unfortunately, both the opening of the tube (tube-size-dependent) and the adult finger are not standardized, so the rule has been established for practical demonstration to the patient/parent how much cream or ointment should be applied per surface area.

Factors that increase percutaneous absorption of a medication include inflammation, fresh skin hydration (after a bath), any type of occlusion (especially with plastic foils, films, or wraps or the use of diapers), epidermal breakage or injury, heat and hot, humid environment (climate should be considered), and type of vehicle (see above).

Age is a consideration in the selection of both the class of the steroid used and the vehicle, particularly in children and elderly patients, because of the body surface area to weight ratio in infants and the thinness and fragility of the skin of premature infants and the elderly.

In children, the duration of daily use of very-high-strength topical corticosteroids should not exceed 1–2 weeks and should be restricted only to the most affected areas and areas of concomitant lichenification. Recalcitrant lesions on small body surface areas may be eventually treated for a longer duration of time.

Higher to medium-strength corticosteroids should not be used in intertriginous areas, including diaper areas. Medium- and high-strength topical corticosteroids rarely cause side effects when used with caution for 3 months or less. Exceptions include use on the face and in intertriginous areas. For treatment of longer duration, intermittent therapy may be preferable to long-term continuous therapy.

Side effects are rare with the use of low-strength topical corticosteroids. However, even with these agents, intermittent therapy may be preferable to continuous therapy for long-term management of chronic skin diseases, particularly if large surface areas are being treated.

Allergic reactions should be considered in cases of persistence or worsening of the inflammatory dermatosis despite topical corticosteroid application (bacterial and/or fungal infections should be ruled out up-front).

Potential contact sensitizers in topical corticosteroids are vehicle components such as parabene, propylene glycol, benzyl alcohol, chlorocresol, ethylenediamine hydrochloride, isopropyl palmitate, polysorbate, stearyl alcohol, or the corticosteroid itself. Prevalence of corticosteroid-dependent sensitization is 0.2–6% and depends on the frequency, duration, and type of drug used.

Topical corticosteroids should be discontinued when the skin disease has resolved. Long-term therapy with topical corticosteroids may be used for a chronic skin disease that is responding to treatment with the medication. If continuous long-term treatment is needed, patients should be monitored for the development of side effects and tachyphylaxis (loss of clinical effect over time).

The recommended frequency of application varies depending on the topical corticosteroid selected and the site to be treated.

Once- or twice-daily applications are usually recommended for most preparations. Occasionally, more frequent application is necessary. Skin with a thick stratum corneum and from which the medication is easily removed during normal activity, such as the palms and soles, may require more frequent application. Other regimens, such as every-other-day therapy or weekend-only (pulse therapy) application, may be effective for chronic conditions in selected cases.

Generally, the lowest potency corticosteroid that is effective, especially in infants and children, should be used. Occlusion under polyurethane or polyethylene foils, tight-fitting clothing, or diapers increases absorption several-fold.

Prolonged use should be avoided in the periorbital area, face, and intertriginous areas.

Topical corticosteroids used in large amounts, for long time periods, and under occlusive conditions may cause different abnormalities. Reported side effects of topical corticosteroid use include cutaneous and/or local effects such as acneiform eruption, folliculitis, rosacea, periocular and perioral dermatitis, atrophy of the epidermis and dermis, skin fragility (young or sun-damaged skin, intertriginous areas, and the face are most susceptible), delayed wound healing, granulomas, purpura, telangiectasia and erythema, striae, hypopigmentation, and hypertrichosis. Use of topical steroids can mask or aggravate dermatophyte or bacterial infection or promote secondary infection.

Systemic side effects of appropriately administered topical steroids are rare. They are seen most frequently with prolonged and extensive use in infants and children of very-high-strength topical corticosteroid compounds. Such adverse reactions may lead to cataracts, glaucoma with periorbital use, adrenal suppression (hypothalamic-pituitary-adrenal axis), growth retardation (infants and young children), hypertension, and Cushing's syndrome.

In summary, topical corticosteroids, if used appropriately, are safe and effective.

Current advice to patients to apply topical corticosteroid preparations "sparingly" or "thinly" contributes to "steroid phobia," increasing the risk of poor clinical response and treatment failure.

In the patient's mind, the current advanced groups are mixed together with the old-generation steroids, regardless of their potential for adverse effects. The advice also tends to reinforce an erroneous concern that the risks from topical corticosteroids may be similar to those from systemic corticosteroids.

Recently, a change in the pharmacy labeling of topical corticosteroids has been proposed to more accurately reflect the low risk of harm from corticosteroids of low to moderate potency and the importance of applying sufficient medication to achieve a satisfactory clinical response. Patients are informed that treatment should not exceed prescribed quantities, and if used for a prolonged period of time careful medical supervision is required. The current recommendation of the European Dermatology Working Group stresses that topical corticosteroid product information should include clear "fingertip unit" instructions, preferably with images of an FTU and a chart to show the number of units required for specific areas of the body (see above for details).

The fear of use of topical steroids resulted in the development of products having steroid-like biological effect without steroid-like adverse reactions. Recently, two new topical immunosuppressive treatments, pimecrolimus and tacrolimus, were marketed to provide alternatives to topical corticosteroids without the associated long-term side effects. They both work by inhibiting calcineurin in the skin, which regulates the activity of several transcription factors that control cell division and trigger the early stages of T cell activation.

Tacrolimus 0.1% is as effective as potent corticosteroids for treating atopic dermatitis and more effective than mild preparations such as hydrocortisone acetate 1%.

Pimecrolimus is less effective than potent corticosteroids; it has not been compared with mild corticosteroids.

Both agents caused more burning of the skin than topical corticosteroids, but no differences were observed in rates of skin infections.

Both products would be interesting alternatives to topical corticosteroids, but they cannot be seen as a corticosteroid replacement, especially in the management of an acute phase of an inflammatory skin disease.

Moisturizers and Emollients

As mentioned previously, emollients (moisturizers) are essential not only to maintain the function of skin barrier but also to support hydration and integrity of the skin. Moisturizers are a group of cosmetic products designed for skin care and hygiene. They make the skin surface (stratum corneum) softer and more pliant by increasing its hydration. Among many moisturizing skin products on the market, some are marketed as so-called cosmetic and therapeutic adjuvants.

The beneficial effects of emollients include support of skin barrier functions and protection against transepidermal water loss and negative effect of exogenous or endogenous offenders that result in dry and/or scaly skin. Moisturizers are possibly the most prescribed products in dermatology, and, until recently, even dermatologists received little or no training regarding their ingredients, pharmacokinetics, benefits, and toxicities.

Naturally occurring skin lipids and sterols are often added to moisturizers. In the correct proportion, these agents can help promote repair of cutaneous barrier function. In the wrong proportion, they can delay repair or may have opposite effect.

The term "moisturizer" is often used synonymously for humectant, emollient, lubricant, oil, or grease, which is not fully correct since each term has a specific definition. A moisturizer is a substance that imparts or restores moisture. A humectant is a substance, such as glycerin, that absorbs or helps another substance retain moisture. The term "emollient" describes a substance that makes something soft or supple. Grease is rendered animal fat or a thick lubricant, usually oily matter. "Lubricant" is a term for a substance, such as grease, that is capable of reducing friction, heat, and wear when introduced as a film between solid surfaces; something that lessens or prevents destruction by rubbing.

Moisturizers claim to heal and prevent the dryness of the skin. Dry skin is not a unique, well-defined condition, but represents a medley of totally unrelated changes in the structure of the stratum corneum associated with environmental and systemic conditions that influence the properties of the skin surface.

Information about moisturizers has exponentially increased in recent years. Their structure and function are becoming very complex and sophisticated; many are equidistant between cosmetics and drugs. Modern moisturizers include agents that mimic natural ingredients and function as botanicals, including vitamins, hydroxy acids, and retinoids. Other common ingredients are metabolites of collagen, elastin, deoxyribonucleic acid, ribonucleic acid, lecithin, sodium hyaluronate, sodium passive cutaneous anaphylaxis, and ceramides.

Moisturizers impart a temporary barrier to the damaged stratum corneum, which allows time for repairing this layer. Two concepts have been proposed to explain water passage through the skin. First, the solubility-diffusion model postulates that water has a finite solubility in lipids; therefore, it can permeate through lipids. In this model, the water molecules are moving through the lipid barrier as individual entities, or one molecule at a time. This model is probably the best description of transepidermal water loss through the stratum corneum. The second model postulates that water passes through lipids through transient pores or water-filled channels. The evidence for the existence of such channels or pores is inconclusive in the case of most biomembranes and especially for the stratum corneum.

Emollients fill the spaces between the corneocytes, thus providing therapeutic improvement to defects in desquamation. Emollients function is to smoothen the roughened skin, changing its appearance, supplementing or replacing natural skin lipids, and providing occlusion. Emollients are usually composed of water in oil emulsions; thus, oil is the largest component, ranging from 3% to 25%. The concentration of oil in emollients is important for easier spreading and for the degree of occlusion that is desired.

Negative effects of the use of moisturizers are rare. Dermatitis is seldom observed with the application of moisturizers. When dermatitis occurs, the ingredients that are most frequently liable are fragrances, preservatives, lanolin, vehicles, and sunscreens. The most common offenders in fragrances are cinnamic alcohol, hydroxycitronella, and isoeugenol along with often reported and well-known potential sensitizers such as formaldehyde-releasing preservative systems, notably quaternium-15, imidazolidinyl urea, and bronopol.

The most important inflammatory skin disease in which moisturizers and emollients play a crucial role is atopic dermatitis. Therapy for atopic dermatitis still remains a challenge for the physician and patients and their parents. The success of any therapeutic concept is based on a broad and early diagnostic approach, which allows relevant provocation factors and allergens to be ruled out. During remission periods, the regular use of a topical basic therapy that consists of a drug-free, water-in-oil moisturizer has been shown to decrease relapses and severity.

The increasing prevalence, patient morbidity, health care costs, and potential toxicities of current therapies make the development of disease prevention strategies for atopic dermatitis an important goal. The development of new atopic dermatitis prevention strategies was one of

the six "urgent calls" for research in a systematic review of atopic dermatitis recently published in Europe. Despite decades of extensive research, primarily focusing on allergen avoidance, no accepted strategies exist for prevention of the disease. Most recently, probiotic supplementation and extensively hydrolyzed infant formulas have shown some promising results.

Skin barrier dysfunction plays a prominent role in the development of atopic dermatitis. Although advances have been made in understanding the genetic and biochemical basis for skin barrier defects seen in atopic dermatitis, there have been no primary prevention strategies that target the skin barrier.

Recently, an interesting and very promising concept of prevention of or, if prevention is not possible, significant delaying of the onset of atopic dermatitis in children of highly genetically predisposed families has been described.

This novel approach begins by "restoring" or "supporting" the skin barrier function from birth. It was found that an intervention with an oil-in-water, cream, used widely to treat dry skin and often recommended for the management of atopic dermatitis, dramatically decreases the symptoms up to achieving a clinical "normality" of the skin barrier. The therapy was particularly effective when the parents were encouraged to use the emollient immediately (within 3 min) after bathing.

Targeting the skin barrier for atopic dermatitis prevention is a novel concept which reveals the importance of the skin barrier in the development of this disease and possibly also of food allergy and asthma. Correcting skin barrier defects from birth may prevent atopic dermatitis onset or moderate disease severity.

Practical Approaches to the Use of Moisturizers and Emollients in Children

As mentioned above, emollients generally contain moisturizers. Water employed as an integral part of an emollient on the stratum corneum can be stabilized through the use of substances reducing dehydration. However, such substances usually have an occlusive effect and create a film resulting in a decrease or blocking of transepidermal water loss. These products can contain hydrocarbons (petrolatum derivates such as Vaseline or solid or liquid paraffin), cetyl or stearyl alcohol, waxes, lanolin or oils (mostly of plant origin), and ceramides.

Emollients having occlusive effect should never be used alone, in an extensive manner, or in areas of physiological moisture retention because their cosmetic and medical qualities are inadequate and their occlusive properties are too great.

The optimal emollient allows a sufficient quantity of water to remain in the stratum corneum but has no or only minimal occlusive effect. In this respect, oil-in-water emulsions and creams seem to be a good choice.

In areas of extensive keratinization, hyperceratosis, or thick seborrheic plaques, the short-term use of fatty emollients with or without combination with urea (in children not more than 5–10%) may increase the desquamative effect of the treatment.

In many countries, a simple formula utilizing natural olive oil and water has been used for generations as an adequate, simple, cheap, and satisfactory moisturizing emollient.

In daily practice a freshly prepared mixture or 50% olive oil with 50% lukewarm water is shaken ex tempore into dispersion and applied to the skin directly after bathing and gives excellent results in both "just dry" skin as well as in already damaged atopic dermatitis skin in children of all age groups.

Protective creams are usually used to reduce the risk of skin irritation, particularly in intertriginous areas (e.g., diaper areas). Such creams can be, however, paradoxically too occlusive if used in thick layers. Parents should be aware that "too much" is in this case really too much and that butter-like layers of cream (with or without zinc oxide) may harm and not help.

Powders are still widely used to prevent erythema or to "smooth" the skin, especially in newborns and neonates. The traditionally understood role of powders is to absorb moisture, especially in skin folds. However, after contact with water, powder often aggregates and forms clumps, which mechanically irritate the sensitive and fragile skin resulting in erosions, secondary infections, and contact dermatitis.

Antiseptics and antibiotics are widely used in pediatric skin care. However, it needs to be stressed that antiseptic baths, rubbing of children's skin with antiseptic solution (in many cases containing alcohol), or preventive use of antibiotic-containing creams is not recommended. These may increase skin dryness and irritation, promote paradoxical development of secondary infections, lead to increased sensitization, and, consequently, to the development of allergies and contact dermatitis.

In addition, saprophytic bacterial colonization is necessary for normal development of a functioning skin barrier, and destruction of this environment may contribute to development of skin diseases caused by a disrupted barrier.

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Rheumatology

Alberto Martini

153 Clinical Approach to a Child with Suspected Rheumatic Diseases

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Rheumatic disorders are systemic diseases in which joints are frequently involved. Arthritis may represent the main clinical feature, as in juvenile idiopathic arthritis (JIA), or a minor symptom as in systemic lupus erythematosus (SLE) where other features are much more important for the diagnosis as well as for long-term prognosis.

The pathogenesis of rheumatic diseases is still poorly understood but it is thought to be, depending on the disorder, autoimmune or/and autoinflammatory. Autoimmune means that abnormalities in adaptive immunity lead to an immune response against the "self." Autoinflammatory means that abnormalities in the regulation of the inflammatory process result in chronic inflammation: in recent years, several monogenic disorders (called autoinflammatory diseases) have been identified in which genetic defects affecting the innate immune response mechanisms lead to persistent or recurrent inflammation. Most of the rheumatic diseases are considered multigenic and multifactorial. Multifactorial means that not only genetic but also environmental factors are involved in the etiopathogenesis and multigenic that many different predisposing genes, each of which with a modest role, have to be present in the same patient.

Diagnostic Approach

There is no single sign, symptom, or laboratory examination that is specific for any of the rheumatic diseases which moreover may show symptoms that overlap with those seen in diseases belonging to almost every medical subspecialty. The diagnosis implies the exclusion of other conditions than can be responsible for the same symptoms. A typical example of the large variety of sign and symptoms that can characterize a rheumatic disease is given by SLE which can affect any organ and therefore mimic many different disorders.

The diagnosis of rheumatic diseases is therefore clinical; history, symptoms, laboratory examinations, and imaging, if indicated, should be consistent with the suspected disease and fit each other like the tesserae of a mosaic. The more they are and the better they fit, the clearer the image will appear.

The differential diagnosis of rheumatic disorders is very broad. Here we will take into consideration principally those aspects related to the assessment of a child presenting with arthritis. Arthralgia is just pain referred to a joint that appears normal and has a full range of motion; it is very common and, especially if transient, has low clinical significance. Arthritis implies the objective presence of signs of joint inflammation; its definition requires the presence of swelling and/or of joint pain with limitation of motion. Arthritis is an important symptom and mandates a careful diagnostic workup.

Many diseases, other than rheumatic, can cause joint involvement. They include trauma, infections, postinfectious, inflammatory or genetic diseases, malignancy, benign tumors, and orthopedic disorders. Moreover, a sizable proportion of children, especially adolescents, presenting with joint complains is affected by diseases of psychological origin including pain amplification syndrome.

Medical History and Physical Examination

Medical history and physical examination are of paramount importance in establishing the correct diagnosis.

Swelling of a single joint is frequently erroneously ascribed to a previous trauma which is often present in the medical history of any child. A false diagnosis of traumatic arthritis should be avoided since joint immobilization, in case of an inflammatory arthritis such as JIA, is contraindicated. An arthritis following after 1–3 weeks a gastrointestinal infection especially in an HLA-B27-positive patient may suggest post-dysenteric (reactive) arthritis. Morning stiffness or stiffness after long period of immobility with improvement of pain with subsequent activities is consistent with an inflammatory arthropathy. On the contrary, mechanical pain is not associated with stiffness and is usually worsened by movements that load the joint. Aching pain especially pronounced at nighttime

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may suggest malignancy (chiefly acute leukemias or metastatic neuroblastoma) or osteoid osteoma. In malignancy, pain is usually localized to the bone and especially to the metaphyseal region and is often out of proportion with respect to the objective findings. In plant thorns synovitis often weeks or months elapse between the entry of the fragment and its dissection into the joint; a careful search of the injury in the medical history should therefore be performed. A history of abdominal pain, diarrhea, weight loss, and blood in the stools can lead to suspect an inflammatory bowel disease. A history of tick exposure and of the typical annular rash (erythema migrans) is strongly suggestive for Lyme disease. Effusions in the large joints are observed in the camptodactyly – arthropathy-coxa vara-pericarditis syndrome (CAPS), a disease due to mutation in the gene of lubricin, a major joint lubrificant; the presence, since the first few months of life, of camptodactyly is very helpful to address the correct diagnosis. In relapsing polychondritis, arthritis is associated with a history of cartilage inflammation of ears, nose, and larynx.

The characteristics of arthritis could be helpful in addressing the correct diagnosis. An extremely painful monoarthritis with refusal to move the joint in a febrile child strongly suggests septic arthritis. Arthritis is fixed and persistent in JIA, while it is migratory in rheumatic fever; in migratory arthritis, the involvement of one or few joints is followed by the involvement of other joints while the previously affected joints improve. Moreover, arthritis in JIA is characterized more by swelling than by pain and is slowly sensitive to nonsteroidal antiinflammatory drugs (NSAIDs); the opposite is true for rheumatic fever in which arthritis is painful but with limited swelling and is extremely sensitive to NSAIDs. The inflammation of the enthesis (insertion of tendon or ligaments on the bone) is called enthesitis and is suggestive of a spondyloarthropathy; the most common sites are on the calcaneous at the insertion of the Achilles' tendon or of the plantar fascia. Joint contractures and limitation of motion in the small joints of the hand can be a feature of systemic scleroderma; the coexistence of a tightened skin, Raynaud phenomenon, and other features can address the diagnosis. Focal tenderness over a long bone in a febrile child is suggestive of osteomyelitis. If the metaphysis is intra-articulars, as is the case for the hip, osteomyelitis and septic arthritis coexist; if, as in the knee, it is extra-articular it can cause a reactive, sterile effusion in the joint. In an adolescent with a febrile polyarthritis involving the large joints and erytematous/vescicular/pustular cutaneous lesions, gonococcal arthritis should be suspected.

Disk space infection (diskitis) can be suspected in a child that does not want to move the legs, pelvis, or low back and has pain when standing or sitting. Musculoskeletal pain and dactylitis are common in sickle-cell disease. Several autoimmune manifestations including chronic arthritis can be observed in immunodeficiencies. In Scheie disease, a mucopolisaccharidosis, and in mucolipidose type III the disease can first present with progressive contractures of the joints of the hands. Another metabolic disease, lysinuric protein intolerance, may show features consistent with a rheumatic disease such as vasculitis, glomerulonephritis, autoimmune hemolytic anemia, circulating ANA, and low complement levels. Muscle weakness, joint contractures, and enlargement of the bone end of the interphalangeal joints (pseudorheumatoid arthritis) may represent the presenting features of a bone dysplasia, spondyloepiphyseal dysplasia tarda. Pain along the long bones with periostitis and polyarthritis (secondary hypertrophic osteoarthropathy) can be observed in patients with digital hippocratism and severe pulmonary impairment.

A marked joint laxity such as that observed in Ehlers–Danlos, Marfan, and Larsen syndromes can lead to joint swelling secondary to recurrent dislocations. Normal children with mild joint hypermobility can experience transient joint pain and, occasionally, small, transient joint effusions. Growing pains are often localized in the calf, over the anterior thigh or behind the knee, and are of short duration; physical examination as well as laboratory tests are normal.

Multisystemic involvement, usually in an inflammatory context, is suggestive for a rheumatic disease. Recurrent, self-limiting episodes of fever and arthritis are characteristic of autoinflammatory diseases. A high-spiking fever with an evanescent, nonfixed, erythematous rash that occurs with fever peaks suggests systemic JIA. New or changing heart murmurs in a febrile child are consistent with infective endocarditis. Involvement of specific organs can be of help in addressing the diagnosis. Kidney and/or central nervous system involvement is common in SLE and in systemic vasculitis. The involvement of coronary arteries and of heart valves is typical, respectively, of Kawasaki disease and of rheumatic fever. The lung is characteristically involved in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis and in systemic scleroderma. Recurrent, painful, shallow oral (and genital) ulcers are a feature of Behçet disease. Muscle weakness associated with typical cutaneous features characterizes juvenile dermatomyositis. Raynaud phenomenon in children is often associated with systemic scleroderma. Uveitis is mainly observed in oligoarticular antinuclear antibody (ANA)-positive JIA, spondyloarthropathies, Behçet disease, Blau syndrome, and sarcoidosis.

Laboratory Investigations

Laboratory tests can be diagnostic for diseases that mimic a rheumatic disorder (bone marrow aspiration for leukemias, genetic tests for genetic diseases, serology, blood and synovial cultures for infectious diseases, etc.). In rheumatic diseases they can be supportive for the diagnosis but not diagnostic and should be always interpreted according to the clinical findings.

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can help to differentiate inflammatory and infectious diseases and malignancy from other conditions (such as genetic or orthopedic diseases). However, in some rheumatic diseases, such as oligoarticular JIA, Henoch–Schöenlein purpura, and juvenile dermatomyositis, they can be normal. In SLE, ESR is elevated while CRP is usually only moderately increased or even normal.

Low white blood cell and/or platelet count is seen in viral infections, SLE, and infiltrative processes in the bone marrow. Urinalysis is of course essential to identify kidney involvement. Muscle-related enzymes, creatine kinase, transaminases, aldolases, and dehydrogenase, are useful if myositis is suspected. A Mantoux tuberculin skin test should be performed especially in case of monoarticular knee arthritis since tuberculous arthritis at onset can mimic monoarticular JIA.

Low complement values are characteristic of SLE and of hypocomplementemic urticarial vasculitis but can also be observed in some primary glomerulopathies (membranoprolipherative, post-streptococcal).

The diagnostic value of autoantibodies depends on their titers and on the clinical features they associate with. ANA may be positive in many rheumatic diseases but also in other non-rheumatic diseases and, in low titers, in a small percentage of normal children. In JIA, they identify a subset of patients at particular risk of developing chronic anterior uveitis. Some particular ANA specificities have been strongly associated with a particular disease: this is for instance the case for anti-double-stranded DNA or anti-Sm antibodies with SLE. Rheumatoid factor (RF) is useful for the diagnosis of RF-positive polyarticular JIA; it can be also positive in other rheumatic diseases, in some chronic infections, and in a very small percentage of normal children. Anticardiolipin antibodies and lupus anticoagulant are antiphospholipid antibodies that can be observed especially in SLE and are associated with predisposition to develop venous or arterial thrombosis. Antineutrophil cytoplasmic antibodies (ANCA) although nonspecific are especially associated with three types of vasculitis: Wegener's granulomatosis, Churg–Strauss syndrome, and microscopic polyangiitis.

Joint aspiration is mandatory in febrile children with extremely painful monoarthritis in which septic arthritis is suspected; in general, white blood cell count (WBC) is higher than 50,000/μL and >90% of leukocytes are neutrophils. Blood is recovered from joint fluid aspiration in case of hemophilia or synovial hemangioma. A chocolate-brown synovial fluid is characteristic of pigmented villonodular synovitis. Crystal-induced arthritis, common in adults, is very rare in children and therefore joint aspiration is almost never performed with this indication.

Synovial biopsy is rarely useful for diagnostic purposes. It is indicated in tuberculous arthritis, sarcoidosis, and a few other rare conditions.

Imaging

X-rays as well as the sophisticated imaging technique available nowadays can be very useful in the follow-up of patients with rheumatic diseases, but their role is more limited in the initial diagnostic workup of a child presenting with arthritis.

Plain-film radiographs are mainly useful in the diagnosis of malignancies and of bone and cartilage disorders, such as fractures, bone tumors, avascular necrosis, osteochondritis dissecans, slipped capital femoral epiphysis, and bone dysplasias. Multiple chronic lesions with osteolysis and encircling sclerosis are suggestive of chronic recurrent multifocal osteomyelitis (CRMO) once infections and malignancy have been excluded. Computed tomography is precious to image bone details in selected circumstances. Ultrasound is a very useful noninvasive technique to assess joints and tendons. Magnetic resonance imaging (MRI) using contrast enhancement can accurately visualize synovium, joint fluid, peri- and intra-articular structures, bone edema, and bone erosions. Technetium bone scanning is useful particularly for the early diagnosis of infections and malignancies.

Follow-up

An accurate follow-up is often an essential component of the diagnostic approach to rheumatic diseases. For instance, viral arthritis can often mimic different types of rheumatic disorders. It is however transient and symptoms disappear in the space of a few weeks and do not recur. For this reason, in the diagnostic criteria of JIA it is mentioned that the arthritis should last for at least 6 weeks. Transient monoarticular synovitis of the hip is one of the more common form of arthritis observed in

children. It often follows by 1 or 2 weeks an upper respiratory tract infection and resolves spontaneously in a few days or weeks; ESR is normal or only slightly elevated. The diagnosis of osteolysis or spondyloepiphyseal dysplasia tarda can be made only when the characteristic radiological features appear.

An adequate follow-up is also important because the clinical spectrum of rheumatic diseases may evolve over a period of months or years. It may be therefore necessary to follow the disease course before making a definite diagnosis. For instance in systemic JIA, the arthritis, which is of course essential for the diagnosis, may appear weeks or months after the beginning of systemic symptoms.

Some conditions should always been considered when assessing a child with rheumatic complaints since they all require a prompt diagnosis. They include septic arthritis, which is a real emergency since it can lead very rapidly to joint destruction, malignancies, Kawasaki disease, rheumatic fever, renal and cerebral involvement associated with SLE or vasculitis.

A web site with information for families of children with rheumatic diseases is available in 50 languages (http://www.printo.it/pediatric-rheumatology).

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154 Juvenile Idiopathic Arthritis

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Definition

Juvenile idiopathic arthritis (JIA) is not a single disease but a term which includes all forms of arthritis beginning before the 16th birthday, persisting for more than 6 weeks, and for which no cause is known. Therefore, there is no clinical or laboratory feature that is pathognomonic of JIA which represents an exclusion diagnosis that gather together all forms of childhood chronic arthritis of unknown cause.

This heterogeneous material has been analyzed in order to identify discrete clinical subsets that could correspond to different diseases. More than 30 years ago two classification systems were created one in USA and one in Europe. The condition was named juvenile rheumatoid arthritis (JRA) in USA and juvenile chronic arthritis (JCA) in Europe. Although similar in many respects, these two classifications had also some important differences that have prevented interchangeable use and comparative research. About 10 years ago the International League of Associations for Rheumatology (ILAR) proposed a new classification system to be shared between the two sides of the Atlantic. This classification, in which the term JIA has replaced JRA or JCA, has unified classification criteria and terminology and since then has represented a useful tool for international research. However, it has the limits inherent to any classification based on clinical criteria, and probably will be modified as new information on pathogenesis becomes available.

Epidemiology

JIA is the most common chronic rheumatic disease in childhood and an important cause of short- and long-term disability. Studies in American and Northern European countries have reported an incidence and a prevalence of JIA varying from 2 to 20 and from 16 to 150 per 100,000, respectively. Differences have been found in the incidence of the various JIA subtypes according to geographical areas or ethnicity. While in western countries the most common subtype is represented by oligoarthritis, this same subtype is rare in countries such as Costa Rica, India, New Zealand, and South Africa where polyarthritis predominates.

The JIA Subtypes

According to the current (ILAR) classification the various JIA subtypes or categories (*Table 154.1*) are identified by a definition and several exclusion items on the basis of the features presented in the first 6 months of disease. Seven different subtypes have been identified, many of which appear to represent different diseases. The seventh subtype however do not represent a definite entity but group together all the forms that according to the definitions and the exclusion criteria do not fit in any of the other categories.

Systemic Arthritis

Systemic arthritis is characterized with respect to the other JIA subtypes by prominent systemic manifestations. The disease occurs as often in boys as in girls, does not show a preferential age at onset, and represents about 10–15% of all JIA cases. It is observed also in adults where it is of rare occurrence and is known as "adult onset Still disease."

The characteristic of the disease is a high spiking daily fever greater than 39°C. Myalgias and abdominal pain may be intense during fever peaks. Another frequent feature is an evanescent, non-fixed, erythematous rash that typically occurs with fever peaks (*Fig. 154.1*); sometimes it can be urticaria-like and pruritic. Hepatomegaly, splenomegaly, and generalized lymph node enlargement, if present, are usually mild. Pericarditis or pleuritis are not rare but are more often mild and asymptomatic. Cardiorespiratory distress due to myocarditis or cardiac tamponade is very unusual. Arthritis is more often symmetrical and polyarticular. It may be absent at onset in about 30% of cases and develops during disease course, weeks or months after the onset of fever.

Laboratory examinations show leukocytosis (with neutrophilia), very high erythrocyte sedimentation rate

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Table 154.1

The International League of Associations for Rheumatology (ILAR) categories of juvenile idiopathic arthritis (Petty 2004). Frequency, preferential age at onset, and sex distribution. RF = rheumatoid factor

Onset type	% of all JIA	Onset age	Sex ratio
Systemic arthritis	10–15%	Any	M = F
Oligoarthritis	40–50%	<6 years	F >>> M
RF-positive polyarthritis	<5%	>10–12 years	F >>> M
RF-negative polyarthritis	15–20%	Variable	F >> M
Enthesitis-related arthritis	5–10%	>7 years	M >> F
Psoriatic arthritis	<5%	Variable	F > M
Undifferentiated arthritis	10–20%		

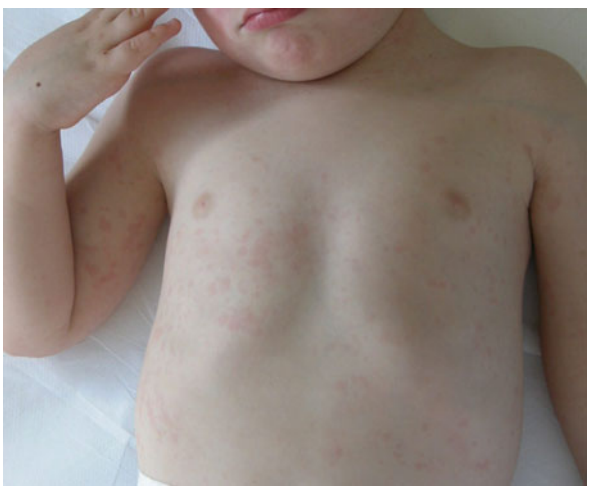

Figure 154.1

Rash associated with systemic JIA. Evanescent, non-fixed, salmon-colored rash that occurs with fever peaks

(ESR), and marked thrombocytosis. Anemia, sometimes profound, is common and is microcytic. For unknown reasons about 5–8% of patients with systemic arthritis may develop a life threatening complication called macrophage activation syndrome (MAS). It is a form of hemophagocytic lymphohistiocytosis and may follow an intercurrent viral illness or a change in medication. The syndrome includes a non-remitting (instead of a spiking) high fever, pancytopenia with marked neutropenia, hepatomegaly, a coagulopathy with hemorrhagic manifestations, and neurologic symptoms such as lethargy, disorientation, seizures, or coma. Laboratory features include elevated serum liver enzymes and triglycerides, low sodium levels, and markedly increased ferritin concentrations; the abnormal coagulation profile is characterized by the prolongation of prothrombin and partial thromboplastin time, hypofibrinogenemia (which causes a drop in ESR values), and detectable fibrin degradation products. The demonstration of active phagocytosis of hematopoietic cells by macrophage in the bone marrow is common. The syndrome is a life threatening complication that should be promptly recognized and treated.

Both disease characteristics and sensitivity to treatment with biological agents (see later) suggest that systemic JIA is a heterogeneous condition and that at least some forms are autoinflammatory in nature.

Oligoarthritis

It is characterized by the presence of an arthritis affecting 1–4 joints during the first 6 months of disease. Although oligoarthritis as a whole is probably heterogeneous, the large majority of patients belong to a quite well characterized type of disease. This form, which is typical of children and is not observed in adults, is characterized by an asymmetric arthritis, an early onset (before 6 years of age), a female predilection, a high frequency of positive antinuclear antibodies (ANA), and a high risk for developing a chronic iridocyclitis. In Europe and USA, oligoarthritis represents up to 50% of all forms of JIA while in other countries such as Costa Rica, India, New Zealand, and South Africa it is more seldom observed.

The disease affects predominantly the joints of the lower limbs; the knee is the most commonly affected joint followed by the ankle. In about 30–50% of cases a single joint is involved at presentation. Joints are obviously swollen but in general not particularly painful although joint contractures are frequent.

Acute phase reactants may be normal or moderately increased although in some instances ESR may be quite high. Antinuclear antibodies are detected in significant titers in about 70–80% of patients and represent a risk factor for the development of chronic iridocyclitis.

The ILAR classification distinguishes two categories in the oligoarthritis subtype based on the number of joints that are involved after the first 6 months of disease: *persistent oligoarthritis* in which the disease remains confined to 4 or less joints and *extended oligoarthritis* in which arthritis extend to more than 4 joints. However, the clinical characteristics of ANA positive patients belonging to these two categories are the same with respect to age at onset, sex ratio, asymmetry of articular involvement, and frequency of uveitis. This suggests that extended oligoarthritis is the same disease as persistent oligoarthritis and that the difference is only in the spread of arthritis. The involvement of an upper limb joint and a higher sedimentation rate at onset have been suggested to predict the evolution to the extended phenotype (which may occur in up to 50% of patients).

A chronic, asymptomatic, nongranulomatous, anterior, mono or bilateral uveitis affecting the iris and the ciliary body (iridocyclitis) and that can cause severe visual impairment is a characteristic feature of the disease and affects about one third of patients. The onset is insidious and very often entirely asymptomatic in contrast with the painful, acute uveitis that can be observed in enthesitis-related arthritis. In less than 10% of patients uveitis is detected before the onset of arthritis and in about half of patients it occurs at the time of JIA diagnosis or shortly thereafter. Most children who develop iridocyclitis do it within 5–7 years from the onset of arthritis. The onset before arthritis is unfortunate since, being the iridocyclitis initially asymptomatic, it is in this case usually diagnosed when damage is already established. ANA positive patients present a higher risk of developing uveitis. If left untreated or in most severe cases iridocyclitis can cause severe ocular damage.

Iridocyclitis can occur in other JIA subtypes such as RF-negative polyarthritis or psoriatic arthritis especially if ANA are positive. As discussed later there is evidence suggesting that ANA positive patients represent a single disease entity currently classified into different categories. Since uveitis is asymptomatic, children with JIA should be screened periodically by slit-lamp examination; the advised frequency of the examination reflects the anticipated frequency of the ocular complication. Any patient with oligoarthritis or polyarthritis of early-onset or, more in general, with ANA positive, RF-negative JIA should undergo slit-lamp examination at least every 3 months.

Rheumatoid Factor Positive Polyarthritis

It is defined as an arthritis that affects five or more joints during the first 6 months of disease and on the presence of high and persistent titers of the IgM rheumatoid factor (RF). It is the same disease as RF-positive rheumatoid arthritis (RA) in adults; however, while in adults it is the most common form of chronic arthritis, in children it represents a small minority (<5%) of all cases of JIA. Antibodies to cyclic citrullinated peptides (anti-CCP), as in adults, are often positive while they are not detected in the other forms of JIA.

The disease is much more frequent in females, is usually observed in adolescents, and is very rare before 8 years of age. It is characterized by a symmetrical polyarthritis with the early involvement of wrist, metacarpophalangeal and proximal interphalangeal joints, and a subsequent rapid spread with involvement of many joints. Low-grade fever may be present. It is practically only in this form that rheumatoid nodules are observed. They are firm, usually mobile and non-tender, and are usually located below the olecranon or at other pressure points.

Rheumatoid Factor Negative Polyarthritis

It is defined as an arthritis that affects five or more joints during the first 6 months of disease in the absence of IgM RF. It accounts for about 15–20% of all JIA cases and is the less defined and probably the most heterogeneous JIA subtype. This heterogeneity has also been supported by recent studies on peripheral blood gene expression profiles.

At least 3 distinct subsets can be identified from a clinical point of view.

Early-Onset, ANA Positive Polyarthritis

This form resembles in all respects, except for the number of joints affected in the first 6 months of disease, ANA positive oligoarticular JIA. It is indeed characterized, as the latter, by an asymmetric arthritis, an early onset (before 6 years of age), a female predominance, ANA positivity and an elevated risk to develop a chronic iridocyclitis. The hypothesis that ANA-positive RF-negative polyarthritis and ANA-positive oligoarthritis are the same disease, the former representing a rapid arthritis spread in the latter, is also strongly supported by studies on the frequency of the various JIA subsets in different

ethnic populations. Indeed, in those countries in which ANA positive, early onset, iridocyclitis-associated, oligoarthritis is rare, ANA positive, early onset, iridocyclitis-associated RF-negative polyarthritis is also seldom observed.

Prolific Symmetric Synovitis

This is the more classic form of RF-negative polyarthritis. Joint involvement is symmetric and affects large joints as well as the small joints of hands and feet. ESR is often elevated and ANA are usually negative. Age at onset is about 7–9 years. The relation between this form of arthritis and the RF-negative form that represent 25% of all forms of adult RA is unknown since no reliable markers exist for both conditions.

Dry Sinovitis

A small subgroup of patients with polyarticular RF-negative arthritis show little palpable synovial thickening but gradually contract up leading to marked loss of function. These children tend to be about 7 or 8 at presentation. There is usually little pain in the affected joints. ESR in these patients is often normal or only modestly raised and ANA are negative.

Enthesitis-Related Arthritis

It accounts for about 5–10% of JIA cases and mainly affects males after the age of 6 years. It is characterized by the association of enthesitis and arthritis. Enthesitis represent the inflammation of enthesis, which are the insertion of ligaments and tendons to the bone. The most common sites are the calcaneal insertions of the Achilles tendon or plantar fascia and the plantar fascia attachments to the metatarsal heads. Most patients are HLA-B27 positive. Arthritis commonly affects the joint of the lower extremities. At variance with the other JIA subtypes, hip involvement is common at disease presentation. The disease is often remitting and may be mild. A variable percentage progressively develops the involvement of the joints of the axial skeleton. Indeed, enthesitis-related arthritis is a spondyloarthropathy, a disease which is treated in detail in another chapter of this section (Chap.155, "Juvenile Ankylosing Spondylitis"). It overlaps with the previously defined seronegative enthesopathy and arthropathy (SEA) syndrome.

Psoriatic Arthritis

Represents less than 5% of all cases of JIA, although estimates of its prevalence are very variable. It is defined by the presence of arthritis plus a typical psoriatic rash or, if the latter is absent, the presence of any two of the following: family history of psoriasis in a first-degree relative; dactylitis (swelling of one or more digits that extend beyond the joint margins); and nail pitting. There is evidence that this subtype does not represent a clearly defined entity. In adults, psoriatic arthritis is a form of spondyloarthropathy. Many patients that meet the ILAR criteria for psoriatic arthritis, in which patients with enthesitis are by definition excluded, have features very similar to those observed in oligoarthritis: early onset, asymmetric arthritis, female predominance, risk for the development of iridocyclitis and ANA positivity. The main difference is that these patients have a higher frequency of the involvement of both small and large joints. In previous studies on children with psoriasis and arthritis in which patients with enthesitis were not excluded, a proportion of patients presented with arthritis and enthesitis and some developed sacroiliitis during follow-up similar to adult patient with psoriatic arthritis. So it appears that the association of psoriasis with arthritis does not define a unique entity.

Undifferentiated Arthritis

It does not represent a separate subset, but a category in which by definition patients that do not fulfill inclusion criteria for any category or that fulfill criteria for more than one are included.

Etiology and Pathogenesis

The etiopathogenesis of JIA is still poorly understood. Moreover, the heterogeneity of JIA implies that very probably multiple etiopathogenetic factors are involved. As for many other rheumatic diseases the etiopathogenesis appears to depend from alteration in innate and/or in adaptive immune response and is considered multigenic and multifactorial. Multifactorial means that both genetic and environmental factors are needed and multigenic that there are many different predisposing genes, each of which with a modest role, that have to be present in the same patient.

Data on disease concordance in identical twins are scanty. A concordance rate of 25% has been found in some studies. Several studies on disease concordance in

nontwins have suggested that genetic components are important especially for oligoarticular JIA. Oligoarticular JIA has also been consistently associated with some HLA antigens, in particular HLA-DRB1*08. As the other spondyloarthritides, enthesitis-related arthritis is strongly associated with HLA-B27. Rheumatoid factor positive polyarthritis is associated, as in adults, with the HLA-DRB1 alleles that share a particular epitope sequence (the shared epitope). The hypothesis that an infection triggers the disease in genetically susceptible individuals, although attractive, remains unproven.

The inflammatory synovitis in JIA is similar to that observed in adult RA and does not appear to differ significantly among the different JIA subtypes. The synovium shows marked hyperplasia of the lining layer and an exuberant infiltration of the sub-lining layer with mononuclear cells including T cells, B cells, macrophages, dendritic cells, and plasma cells. The T cell aggregates are composed predominantly of CD4+ cells. The inflammatory process leads to pannus formation with cartilage and bone erosions mediated by degradative enzymes such as metallo-proteinases. As for adult RA, the observed potent therapeutic effect of anti-tumor necrosis factor (TNF) agents in many patients supports an important pathogenic role for this cytokine.

Systemic JIA has some peculiar pathogenetic aspects. The driving cytokines here are represented by interleukin-1 and interleukin-6. The excellent response observed in some patients with anti-IL-1 therapy has lead to the suggestion that at least some forms of systemic JIA belong to autoinflammatory diseases. Another peculiar aspect of systemic JIA is the predisposition to develop MAS. The reasons of this predisposition are unknown but the pathogenesis of MAS seems to depend, as in the other forms of hemophagocytic lymphohistiocytosis, on the excessive expansion and activation of cytotoxic cells with hypersecretion of pro-inflammatory cytokines that in turn induce macrophage activation, further cytokine production and tissue infiltration.

Diagnosis

As previously mentioned JIA is defined as any arthritis of unknown origin, lasting for more than 6 weeks and with onset before 16 years of age. It is therefore an exclusion diagnosis and, by definition, any other cause of chronic arthritis has to be ruled out. As outlined in another chapter of this section (Clinical Approach to a Child with Suspected Rheumatic Diseases) many other diseases can indeed cause arthritis (*Table 154.2*).

Table 154.2
Main diseases that cause arthritis

Infectious
Septic arthritis
Gonococcal arthritis
Endocarditis
Mycobacterial arthritis
Lyme disease
Viral arthritis
Post-infectious (reactive)
Rheumatic fever
Post-dysenteric arthritis
Viral infections
Serum sickness
Rheumatic and inflammatory diseases
Juvenile idiopathic arthritis
Juvenile ankylosing spondylitis
Systemic lupus erythematosus
Juvenile dermatomyositis
Scleroderma
Overlap syndromes
Systemic vasculitis
Behcet disease
Autoinflammatory diseases
Chronic recurrent multifocal osteomyelitis
Sarcoidosis
Inflammatory bowel diseases
Neoplastic diseases
Leukemia
Lymphoma
Neuroblastoma
Malignant bone tumors
Osteoid osteoma
Synovial tumors
Bone and cartilage disorders
Trauma
Patellofemoral syndrome
Avascular necrosis
Osteochondritis dissecans
Slipped capital femoral epiphysis
Other diseases
Immunodeficiencies
Histiocytic syndromes
Hemophilia
Sickle cell disease
Mucopolysaccaridoses
Mucolipidoses
Spondyloepiphyseal dysplasia tarda
Osteolysis
Farber disease
Camptodactyly–arthropathy-coxa vara-pericarditis syndrome
Relapsing polychondritis

Table 154.2 (Continued)

Pigmented villonodular synovitis
Hypertrophic osteoarthropathy
Plant-torn synovitis
Joint hyperlaxity

In systemic JIA malignacies (in particular leukemia and lymphomas) and infections must be always considered and ruled out. In endemic areas, leishmaniosis and brucellosis should be excluded since, although in general associated with leucopenia, both diseases can mimic the systemic features of systemic JIA (sJIA) and moreover be a cause of MAS. Inflammatory bowel diseases, rheumatic fever, Kawasaki disease as well as other rheumatic diseases such as systemic lupus erythematosus and systemic vasculitis should also be ruled out. The differential diagnosis of systemic JIA can be particularly difficult at presentation in patients in whom systemic features precede the development of overt arthritis; a definite diagnosis cannot be made until the appearance of arthritis.

In a febrile child with a very painful monoarthritis septic arthritis has to be excluded. Tuberculous arthritis may cause a monoarticular arthritis usually of the knee that can initially mimic monoarticular JIA. For more details on the differential diagnosis of arthritis see Chap. 76 (Clinical Approach to a Child with Suspected Rheumatic Diseases).

Some characteristics of articular involvement in JIA may be helpful. With the exception of enthesitis-related arthritis, in which joint involvement can be quite painful or transient and recurrent, the arthritis of JIA is characterized by persistent joint swelling which is often not particularly painful especially in the oligoarticular subtype. Joint contractures are however frequent. Since joint involvement is not very painful physical examination can detect the involvement of joints that were not initially referred as affected. Morning stiffness or stiffness after long period of immobility with improvement of pain with subsequent activities is characteristic and its duration is proportional to disease activity.

Treatment

A treatment able to "cure" the disease is not available. However, the prognosis of JIA has improved very much in the last decade, thanks to substantial progresses in disease management. Since JIA is not a single disease the therapeutic strategy varies also according to the different JIA subtypes. It is often problematic to anticipate what strategy will be needed to control the disease since it is difficult to predict at onset, even within a definite subtype, which children will recover and which children will go on to have unremitting disease. Treatment therefore follows a step by step approach according to the severity of the disease and its sensitivity to therapies. The goal of treatment is to reach the complete control of the disease, to preserve the physical and psychological integrity of the child and to prevent any long-term consequence related to the disease or its therapy. This requires a careful long-term follow-up in which monitoring of treatment, disease activity and disease damage is critical. Periodic X-ray examinations of the affected joints are needed to document disease evolution.

Optimal management of JIA requires a multidisciplinary approach that involves pediatric rheumatologists, nurses, physical and occupational therapists, social workers and, when indicated, psychologists, orthopedic surgeons, and ophthalmologists.

Medical Treatment

Oligoarthritis and Polyarthritis

Nonsteroidal anti-inflammatory drugs (NSAIDs). NSIADs have been the mainstay of JIA treatment for decades. Their role remains important and most children with JIA are started on an NSAIDs. These drugs work primarily by inhibiting the enzyme cyclo-oxygenase (COX) that converts arachidonic acid to prostaglandin, a family of substances involved in inflammation. There are two COX, COX-1 which is considered a constitutive enzyme found in most mammalian cells and COX-2 which is undetectable in most normal tissues and is induced in activated macrophages and other cells at sites of inflammation.

Just a few NSAIDs are approved for use in children; the most commonly used include naproxen, ibuprofen, and indomethacin; acetylsalicylic acid is much less used than in the past because of the less favorable safety profile. They are all COX-1 inhibitors; experience with COX-2 inhibitors in children is very limited.

The anti-inflammatory effect of NSAIDs in JIA is slow and is usually achieved after several weeks of continuous administration. NSAIDs are usually quite well tolerated and side effects are less common than in adults. They include nausea, abdominal pain, mood changes, tinnitus, elevated liver enzymes, hematuria; gastric or duodenal ulcerations are less frequent than in adults.

Intra-articular steroid injections. Intra-articular steroid injections with triamcinolone hexacetonide are frequently

needed at disease onset or during disease course. In mono or oligoarticular arthritis they are used often in association with or in substitution for NSAIDs. They are specifically indicated in the presence of persistent joint contractures, susceptible to cause deformity. Indeed, they are rapidly effective and, most importantly, they break the vicious circle that leads to deformity, such as valgus deviation due to flexion contracture of the knee (*Fig. 154.2*). Although they are not curative, their effect may last for long periods.

Methotrexate. In those children in which the disease is not well controlled by NSAIDs and steroid injections, a second line agent is often needed. These patients have usually an arthritis with a polyarticular onset or course, and second line therapy should be introduced quite early in order to try to prevent disease progression. The second line agent of first choice in JIA is methotrexate (MTX). The effect of MTX on inflammation depends on the inhibition of purine synthesis. A controlled study has shown its efficacy at a dose of 10 mg/m^2/week. A further study has shown that the plateau of efficacy is reached at 15 mg/m^2/week and that higher doses are not accompanied by a better effect. At doses >10 mg/m^2/week parenteral administration is advisable. The effect is usually detectable within 6–12 weeks. MTX is usually well tolerated especially if associated with the administration of folic or folinic acid. The most common side effects are gastrointestinal toxicity and an increase in liver enzymes.

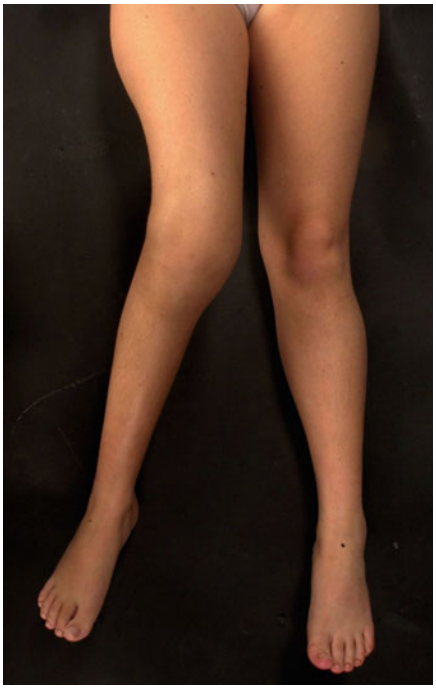

Figure 154.2
Severe valgus deformity secondary to long standing flexion contracture of the knee

Anti-TNF agents. In those patients that have an unsatisfactory response to MTX and in whom the disease remains active, treatment with anti-TNF agents is indicated. Usually the anti-TNF agent is added to MTX. The first anti-TNF agent used and registered both in Europe and in USA for JIA has been etanercept, a fusion protein consisting of two identical chains of the recombinant extracellular tumor necrosis factor monomer fused with the Fc domain of human IgG1. A controlled study has shown the efficacy of etanercept, at a dose of 0.4 mg/kg s.c. twice a week, in patients with JIA who were resistant or intolerant to MTX. Subsequently, other studies have confirmed the remarkable and rapid efficacy and, so far, the good safety profile of the drug in JIA. Since cases of reactivated tuberculosis have been reported during treatment with TNF inhibitors, all children should have a documented negative TB test before starting therapy. The overall safety of anti-TNF agents, including the potential of inducing malignancy, will be best assessed in the future with long-term studies.

Controlled trials with other anti-TNF agents such as Infliximab and Adalimubab have also been performed and have shown a similar profile of safety and efficacy with respect to etanercept. Both are monoclonal antibodies directed against TNF; Infliximab is a chimeric antibody (it has a mouse component) while Adalimumab is a fully human antibody. The Infliximab study has shown that although the dosages of 3 and 6 mg/kg (i.v. every 8 weeks) were both effective, children treated with 3 mg/kg developed in a higher percentage antibodies against Infliximab with a similar higher rate of infusion reactions. Adalimumab has been registered in USA for use in JIA at a dose of 20 mg (s.c. every other week) in children weighing 15–30 kg and of 40 mg for those weighing >30 kg; in Europe it has been so far registered only for children >30 kg. Indirect evidence suggests that, as in adults, anti-TNF agents are more effective if combined with MTX.

Other Drugs A controlled trial has recently shown the efficacy of Abatacept, an inhibitor of lymphocyte activation, in the treatment of MTX-resistant JIA. The percentage of response was similar to that observed with anti-TNF agents and the safety profile was good. Moreover, treatment showed an effect also in a discrete proportion of patients who had previously failed also anti-TNF agents. Abatacept is fully human fusion protein that consists of the

extracellular domain of the cytotoxic T-lymphocyte-associated antigen (CTLA)-4, linked to the constant portion of human immunoglobin. Activation of T cells requires 2 signals from the antigen-presenting cell (APC). One is the presentation of the antigen to the T-cell receptor in the context of a major histocompatibility complex molecule, the other is a costimulatory signal. One of the best characterized costimulatory signals is delivered by the APC molecules CD80 or CD86 to the T cell's CD28 molecule. CTLA-4 is a protein naturally expressed on the activated lymphocyte surface that avidly binds to CD80/86. Abatacept, therefore, by binding to costimulatory molecules on the surface of APC prevents their binding to CD28 and interferes with lymphocyte activation. Abatacept has been registered for use in JIA in Europe and in USA.

Studies are ongoing to assess the efficacy of anti-IL-6 therapies in polyarticular course JIA.

Studies performed many years ago have shown that hydroxychloroquine and D-penicillamine are not more effective than placebo in RF-negative JIA. Sulfasalazine is used in some center as a second line agent in patients with polyarticular JIA and in enthesitis-related arthritis. It should not be used in systemic JIA, for the increased risk of toxicity, in patients with porphyria or with glucose-6-phosphate dehydrogenase deficiency. A recent trial has shown the efficacy of leflonomide in JIA but the experience with this drug is still limited. In general the use of second line agents other than MTX has declined over the years with the introduction of the more efficacious anti-TNF agents.

In polyarticular JIA systemic steroids (prednisone) are used only as a bridge drug when the disease is very active and time is required before second line agents (as MTX) can show their efficacy.

Systemic Arthritis

Systemic arthritis frequently does not respond to NSAIDs alone. In this case, once infectious and neoplastic disorders have been excluded and the diagnosis is established, prednisone therapy is often indicated. Once disease control is reached, steroid therapy has to be progressively tapered. Indeed, the use of steroids should be limited as much as possible because of their severe, well-known side effects. Vitamin D and calcium supplements to try to prevent osteoporosis as well as dietary counseling to prevent fat increase secondary to increased appetite are indicated. Treatment of MAS relies on prompt recognition of this complication and the use of high dose steroids and cyclosporine which is usually highly and rapidly effective in this specific indication. In children characterized by a polycyclic course, steroids and NSAIDs may be sufficient to control episodes of disease activity. In unremitting disease, steroid tapering is often accompanied by recurrence of systemic symptoms and arthritis. While systemic symptoms often, but not always, fade during disease course, arthritis persists and often represents the main determinant for disease outcome. MTX is less effective in systemic arthritis than in other JIA subtypes. Anti-TNF agents also are less effective in systemic arthritis than in other JIA subtypes. The use of thalidomide has been proposed for resistant systemic arthritis. In patients with very severe unremitting disease autologous bone marrow transplantation has been performed. In the very rare cases that develop amyloidosis alkylating agents are indicated.

As mentioned above, the pathogenesis of systemic JIA seems to differ from that of the other JIA subtypes, and IL-6 as well as IL-1 appear to play a prominent role. Indeed, a controlled trial with Tocilizumab (an anti-IL-6 receptor humanized monoclonal antibody) has shown very promising results. Another confirmatory controlled trial is ongoing. Moreover, several noncontrolled studies with Anakinra (a recombinant form of the natural IL-1 receptor antagonist) have shown also the efficacy of IL-1 inhibition in the treatment of systemic JIA. In some patients, usually characterized by a lower number of joints involved, anti-IL-1 therapy has been shown to have a spectacular effect similar to that observed in some autoinflammatory diseases. This has suggested, as previously mentioned, that at least some form of systemic JIA could indeed represent autoinflammatory diseases. A controlled trial is ongoing using Canakinumab, a monoclonal fully human antibody which is a more potent inhibitor of IL-1 than Anakinra. It appears therefore that treatment with IL-6 and IL-1 inhibitors, if their safety will be confirmed, will represent a major advance in the treatment of systemic JIA and an opportunity to unravel the clinical heterogeneity of this disease.

Chronic Iridocyclitis

Early diagnosis is very important for the success of therapy. The initial approach consists of glucocorticoid eye drops associated with mydriatics to dilate the pupil and prevent the occurrence of posterior sinechiae. Concurrent therapy with NSAIDs is often used. In patients with disease resistance to topical therapy, systemic steroid administration and/or subtenon injection of corticosteroids are required. In disease not controlled by the above measures several drugs have been claimed to be effective including MTX, cyclosporine, and alkylating agents. However no controlled trials exist. The efficacy of etanercept is

controversial while Infliximab and Adalimumab have been anecdotally reported to be of benefit.

Other Therapeutic Aspects

Physiotherapy and occupational therapy are important components of the therapeutic approach to any patients with JIA. In general, children limit by themselves their activities and should not be restricted. Swimming and bicycle riding that do not put significant weight on the joints should be encouraged. An orthodontic approach is often indicated in case of temporomandibular joint involvement.

Arthroscopic synovectomy may be indicated in a few cases to debulk proliferative synovitis resistant to other treatments. Soft tissue release may be useful in selected cases but the intervention as well as the following postoperative rehabilitation have to be performed by experienced personnel. Total arthroplasty, in particular of the hip and knee, represents a successful option in the presence of severe functional impairment and is generally delayed until growth has stopped. It presents special problems and has to be performed by orthopedic surgeons with specific experience.

JIA has a great psychological impact on the child and his family. Children should be encouraged to normally attend school as well as all the activities that are appropriate for their age. Parents may tend to excessively protect the child and limit his activities; this can affect the proper development of the child personality and prevent him from acquiring adequate self-confidence and self-esteem. When indicated a psychological support can be required.

Course and Prognosis

A part from polyarticular RF-positive JIA that, like in adults, tends to run a progressive and aggressive course, the prognosis of the other JIA subsets differ greatly even among patients belonging to the same subset. Moreover, while in many cases of JIA the disease spontaneously remits with time, a sizable proportion of patients enter adult life still with an active disease. No reliable markers are available to predict early in the disease course the ultimate outcome in order to tailor treatment to the risk of disability.

Oligoarticular JIA

Patients with oligoarticular JIA have in general the best outcome. The early use of intra-articular steroids is very effective in preventing the deformities secondary to joint contractures such as valgus deformity in case of flexion contracture of the knee (*Fig. 154.2*) or leg-length inequality secondary to asymmetric knee involvement (*Fig. 154.3*). In the majority of children the disease tends to remit spontaneously with time although some series have reported that the rate of remission after 6–10 years from disease onset ranges only from 23% to 47%. The percent of patients that develop extended oligoarthritis has been reported to vary between 20% and 50%. Joint damage is more frequent in patients with a polyarticular course.

The outcome of uveitis depends very much on early diagnosis and treatment. Prior to careful monitoring for uveitis with periodic slit-lamp examinations, a severe outcome was observed in more than one third of patients. Now only a minority of patients suffer complications which can however be significant and include keratic precipitate, posterior synechiae between the iris and the anterior surface of the lens resulting in an irregular and poorly reactive pupil, band keratopathy, secondary cataracts, and glaucoma. A small minority of patient may experience a progressive disease that can lead to blindness despite adequate monitoring and treatment. The course of iridocyclitis may be relapsing or chronic and does not parallel the clinical course of arthritis.

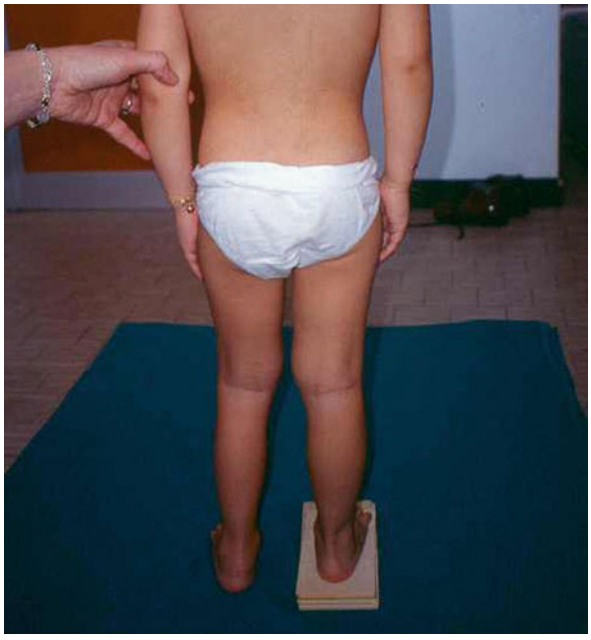

Figure 154.3
Leg-length inequality secondary to asymmetric knee involvement

Systemic Arthritis

Systemic arthritis has a variable course. In about half of patients the disease is characterized by a monocyclic or an intermittent course with relapses followed by intervals of remission; in these patients the arthritis accompanies the episodes of fever but remits when systemic features are controlled. The long-term prognosis of these patients is usually good since the disease tends to disappear with time without causing articular damage. In the other half of patients the disease follows an unremitting course. In many, but not all, cases systemic symptoms eventually resolve, leaving chronic arthritis as the major long-term problem. This second group of patients with an unremitting disease course is probably the most severe among all JIA subtypes with a high risk of severe joint destruction. Death were once principally related to the development of amyloidosis that now appears to be a very uncommon complication. Nowadays, MAS remains the most serious and potentially fatal threat and has to be promptly recognized and treated.

Other Subtypes

RF-positive polyarthritis is a chronic and aggressive disease and has the same poor long-term outcome as RF-positive adult RA. RF-negative polyarthritis has a variable outcome reflecting the heterogeneity of the subtype: the percent of patients with bad outcome varies widely among series probably reflecting different patient selection. The prognosis of psoriatic arthritis as defined by the current ILAR criteria is not yet defined; in general, in comparison with oligoarticular JIA, patients have a more frequent involvement of small joints and a higher number of affected joints.

A variable percentage of patients with enthesitis-related arthritis progressively develops a full blown picture of ankylosing spondylitis with involvement of the joints of the axial skeleton.

Growth Anomalies

A characteristic feature of chronic arthritis in children is the effect it may have on bone and joint development. Nowadays, thanks to intra-articular steroid injections and the use of more potent drugs such as anti-TNF agents these complications are observed much less frequently.

Local growth disturbances occur at sites of inflammation resulting in either overgrowth or undergrowth of the iuxta-articular bone extremities. Overgrowth is due to accelerated development of ossification centers, possibly related to increased vascularization and growth factor release secondary to inflammation. As previously mentioned flexion contracture of the knee can cause valgus deformity and asymmetric knee involvement can result in lengthening of the affected leg with leg-length inequality; both, if not very pronounced, tend to resolve with growth if arthritis is controlled.

Undergrowth is secondary to growth center damage or premature fusion of epiphyseal plates. When extremities are involved, it may be symmetric resulting in small hands or feet, or it may be isolated with selective brachydactyly. Arthritis of the wrist may cause growth failure of the ulnar head with shortened ulna and ulnar deviation of the carpus. Unilateral involvement of the temporomandibular joint may result in mandibular asymmetry, and bilateral involvement may cause marked micrognatia. The involvement of the temporomandibular joint is rather frequent and has to be carefully sought in order to start in time an adequate orthodontic treatment. Similarly, involvement of the cervical spine, which is frequent in patients with JIA, may cause undergrowth of the vertebral bodies resulting ultimately in a short neck. Involvement of the neck may make difficult intubation in case of general anesthesia. Atlantoaxial instability is rare in JIA but can be observed.

Anomalies in growth and morphogenesis of skeletal segments result also from anomalous tractions, on growing structures, secondary to muscular spasm and periarticular fibrosis. They are more marked in children with precocious onset of arthritis and very active disease. A characteristic developmental anomaly of the hip is often observed in children with early onset of arthritis. It includes enlargement and flattening of the femoral head, incompletely covered by an underdeveloped acetabulum, and a short, squat, valgus, and anteverted femoral neck.

General growth abnormalities may be secondary to the treatment with steroids as well as to the inflammatory process particularly in patients with severe, persistently active, systemic JIA.

In the affected joints periarticular osteoporosis is common. The use of corticosteroids may lead to generalized osteoporosis.

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155 Juvenile Ankylosing Spondylitis

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Definition

The term juvenile-onset ankylosing spondylitis (AS) refers to a disease, which onset of symptoms occurs before the age of 16 years and its main features are familial aggregation, strong association with HLA-B27, as well as peripheral arthritis and enthesitis at onset and sacroiliitis and spondylitis throughout the course of the disease. Juvenile-onset AS is the counterpart of adult-onset AS, the prototype of the group of disease and syndromes known as spondyloarthritis (SpA). Either in children or adults, the SpA group includes undifferentiated forms, psoriatic arthritis (PsA), reactive arthritis (ReA), ulcerative colitis, and Chron's disease.

Diagnosis

Juvenile-onset AS is diagnosed according to the modified New York criteria for AS (*Table 155.1*). The fulfillment of such criteria requires clinical and radiographic evidence of spinal and sacroiliac joint involvement, particularly structural radiographic changes of the sacroiliac joints. (*Fig. 155.1*). Since AS in children and adolescents usually presents with peripheral rather than axial arthritis and enthesitis, the diagnosis of AS is rarely made; in fact, most patients fulfill the modified New York criteria 5–10 years after the onset of peripheral symptoms.

Besides the diagnosis of AS reflects a considerable delay, the structural changes that had taken place throughout the course of the disease are certainly irreversible and represent the end of a disease spectrum, which starts with undifferentiated symptoms. It is therefore that the recognition of children with peripheral arthritis and/or enthesitis and the identification of bad prognostic factors (i.e., HLA-B27, polyarthritis, back or sacroiliac joint pain) are essential to provide the best available treatment in the earliest phase of the disease and attempt to halter disease progression.

The earliest form of juvenile-onset AS is equivalent to undifferentiated SpA according to the European SpA Study Group (ESSG) or enthesitis-related arthritis (ERA) according to the International League for Associations of Rheumatology (ILAR) classification criteria for juvenile idiopathic arthritis (JIA). Rarely, the diagnosis of AS is made in children with less than 3 years of disease duration.

Epidemiology

The incidence and prevalence of juvenile-onset AS in pediatric rheumatology clinics vary according to diagnostic criteria. The proportion of patients with juvenile-onset SpA whose final diagnosis was juvenile-onset AS varied between 13.1% and 25.4% in mid-1990s registries from Canada, the USA, and the UK. In a recent study, 2.5% of 3,269 patients seen throughout 23 years in specialized Canadian clinic had juvenile-onset AS. Finally, the percentage of HLA-B27 children with arthritis that actually have AS may be close to 75%. The proportion of juvenile-onset AS among patients with AS ranges from less than 21% in caucasian populations to 30–50% in Mexicans, Indians, North Africans, and Asians.

As mentioned before, the diagnosis of AS requires of axial symptoms and structural changes in the sacroiliac joints not present in the initial years of the disease. Therefore, epidemiological data only reflect the end of the spectrum. The earliest stage of AS corresponds to most epidemiological data on undifferentiated SpA, including the seronegative enthesopathy and arthropathy (SEA) syndrome.

The age of onset of juvenile-onset AS occurs between the ages of 6 and 12 years, but they may commence at any age below 16 years and is much more frequent in boys than in girls in the prepubescent years, but the proportion of affected girls increases with age.

Pathogenesis

The etiology of AS, including juvenile-onset AS is still unknown. Genetically determined susceptibility is a major factor, but the role of bacterial infections and perhaps mechanical, growth, and developmental factors needs to be investigated.

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Table 155.1
The modified New York classification criteria for ankylosing spondylitis

Clinical criteria
Low back pain and stiffness for at least 3 months, which improves with exercise, but is not relieved by rest
Limited lumbar spinal motion in sagittal (sideways) and frontal (forward and backward) planes
Chest expansion decreased relative to normal values corrected for age and sex
Radiologic criteria
Bilateral sacroiliitis grade 2 to 4
Unilateral sacroiliitis grade 3 or 4
Definite AS, if one radiologic criterion is associated with at least one clinical criterion
Probable AS, if three clinical criteria are present or one radiologic criterion is present without any clinical criterion

Source: Van der Linden S, Valkenburg HA, Cats A (1984) Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York Criteria. Arthritis Rheum 27:361–368

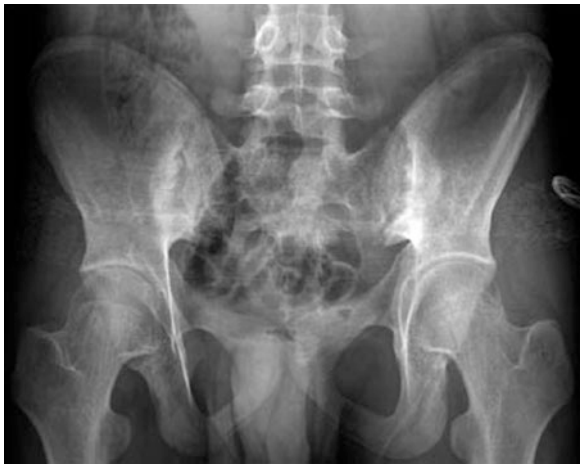


Figure 155.1
Grade 3 bilateral sacroiliitis in a 14-year-old boy with 6 years disease duration. There is subchondral sclerosis of the iliac bone, joint surface irregularities, which include some erosions on both sides, and joint space narrowing of the hips (From Burgos-Vargas R (2006) The juvenile-onset spondyloarthritides. In: Weisman MH, van der Heijde D, Reveille JD (eds) Ankylosing spondylitis and the Spondyloarthropathies. Mosby, Philadelphia, pp 94–106)

AS, including juvenile-onset AS, are strongly linked to HLA-B27, particularly B*2705. HLA-B27 association determines the prevalence of AS in the general population and familial aggregation of the disease. Four major hypotheses have been postulated to explain the role of HLA-B27 in the pathogenesis of AS. The arthritogenic peptide hypothesis suggests that the HLA-B27 molecule is able to bind a unique bacterial or self-antigenic peptide, which is then presented to a HLA-B27-restricted cytotoxic (CD8+) T cell. Such hypothesis assumes that a bacterial product and a self-tissue constituent share an aminoacid sequence that elicits an autoimmune response through molecular mimicry. The B27 misfolding hypothesis refers to the abnormally slow folding and accumulation of the B27 heavy chain as covalent homodimers and multimers in the endoplasmic reticulum (ER), ER stress, activation of the unfolded protein in macrophages, activation of the nuclear factor-kB, and cytokines production. The β2m hypothesis refers to the deposition of β2m in the synovium and perhaps other tissues. Finally, the surface homodimer hypothesis postulates that HLA-B27 heavy chain homodimers expressed at the cell surface are recognized by leukocyte receptors and upset the normal development of HLA class I–mediated responses; tissue-specific adaptation to stress at sites of tension may be modulated by a cytokine-mediated mechanism, but unusual signaling leads to excessive proinflammatory cytokine release.

Around 90% of the overall susceptibility to the development of AS is determined genetically. An autosomal dominant trait with 20% penetrance has been demonstrated in some studies. AS occurs 10–20 times more frequently in relatives of patients with AS and 50–80 in their siblings.

Nearly one-half of the genetic contribution to AS is attributed to HLA-B27 and other major histocompatibility complex (MHC) genes, including ERAP1 and IL23R. Thus, B27-postive individuals with a family history of AS have a tenfold greater risk of developing AS than those without familial aggregation.

Different MHC gene polymorphism associations have been described in AS and juvenile-onset AS in several populations including: HLA-DPB1*0301; HLA-DRB1*01, *04 *08, and LMP2 alleles; tumor necrosis factor (TNF); heat shock protein (HSP) and low molecular weight protein (LMP) polymorphism; and outside the MHC region with CYP2D6, ANKH, and IL-1 and IL-1RA.

Currently, three different genome-wide linkage scans and a formal meta-analysis with the whole genotype combination have confirmed the linkage between the MHC region and AS and nominal or suggestive linkage with 2q, 3p, 5q, 9q, 10q, 11q, 16q, 17p, and 19q. Derived from

multiplex case family studies, the best-fitting model involved in the AS genetics ranges from three to nine genes. ARTS1 and IL23R, which are responsible for 26% and 9% of population-attributable risk of AS are two of the three most important genes associated with AS.

Despite no clear triggers of AS and juvenile-onset AS have been found some data suggest a role for bacterial infections in the pathogenesis of the disease. Since killing of bacteria in B27-expressing cells is impaired, infective organisms persist within the host. On the other hand, HLA-B27 can modulate the production of cytokines, favor bacterial cell invasion, and delay bacterial killing. Further evidence include the presence of antibodies against bacterial peptidoglycan in children with juvenile-onset AS, creased T-cell responses to enteric bacteria and heat shock protein 65 in peripheral blood and synovial in HLA-B27 positive pauciarticular JCA, and cases of AS triggered by different microorganisms such as *Mycoplasma pneumoniae*. The synovial fluid of patients with juvenile-onset undifferentiated SpA or AS may contain *Salmonella*, *Shigella*, *Chlamydia*, *Campylobacter*, and *Mycobacterium tuberculosis* DNA.

Pathology

SpA and juvenile-onset SpA synovitis is milder and cartilage erosion less severe than in rheumatoid arthritis (RA). There is hyperplasia of the lining cell with CD68 expression and CD163+ macrophages in the sublining layer and marked neo-vascularity with increased numbers of CD146+ endothelial cells. TNF-α is prominently expressed in the synovium of peripheral joints and high levels of CD8-activated cells, TNF-β, γ interferon, and interleukins 2, 4, and 6. Most cells express TNF receptor p55 and p75 are expressed in most cells, but the former predominates in the vascular endothelium.

Enthesitis consists of a nonspecific inflammation accompanied by granulation tissue, lymphocytes, and plasma cells in the bone marrow, the fibrocartilage, and the interface between calcified fibrocartilage and subchondral bone. There is localized osteitis with marked bone proliferation and mucopolysaccharide deposits also found in tarsal soft tissues. Overall, the inflammatory infiltrates are mainly composed by CD3+, CD4+, and CD8+ T cells. Interestingly, osteocartilaginous proliferation and enthesophytosis may also occur in noninflammatory situations such as bone growth and development, particularly under the effect of trauma or mechanical stress. Cross-reactive humoral and T-cell immune responses to aggrecan G1 domain, a normal constituent of the enthesis, would explain the peculiar localization of the disease.

Clinical Manifestations

The clinical picture of AS in children in the early stages corresponds to undifferentiated SpA or SEA syndrome.

Arthritis. The commonest clinical presentation of juvenile-onset AS is lower-limb oligoarthritis. The joints most frequently affected are the knees and then the ankles and tarsus. Slight and mild cases may enter into sustained remission or have recurrent symptoms. Most patients attending specialized clinics have an increasing number of joints involved throughout the years. The second most frequent type of onset is the combination of arthritis and enthesitis; in such a case, the latter involves the plantar fascia and Achilles tendon's attachments as well as tarsal entheses. Rarely, AS starts with a combination of peripheral and axial symptoms, including back pain and sacroiliitis.

The severity, duration, and consequences of arthritis and enthesitis may not parallel each other and may differ between sites. The distinction between arthritis and enthesitis may be difficult in some sites, for example the sacroiliac joints and the feet. The long-term consequences of arthritis and enthesitis in certain regions, for example, the feet, may lead to ankylosing tarsitis, a peculiar form of disease accompanying AS and other juvenile SpA or a clinical situation presenting without symptoms of other SpA.

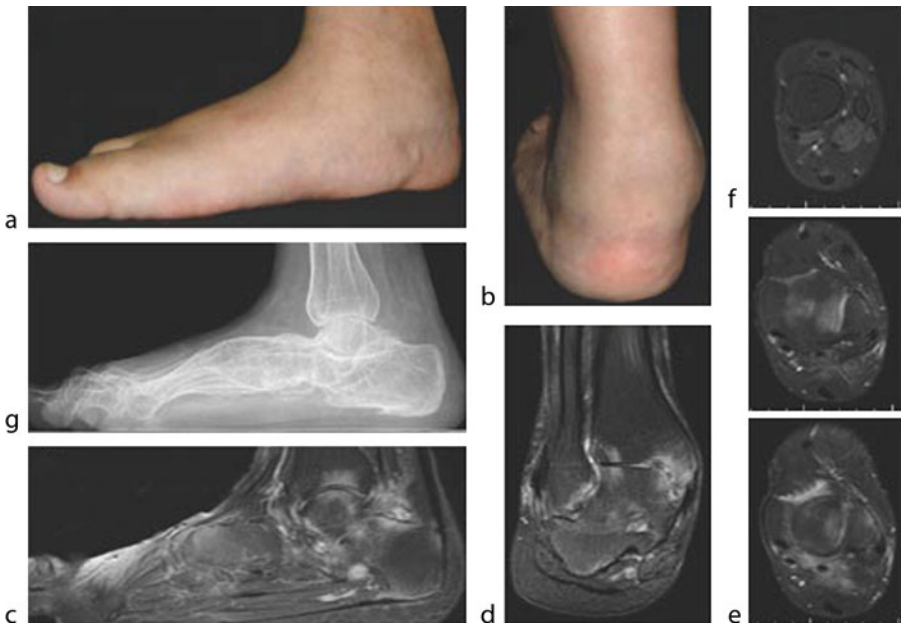
The course of arthritis is variable. Some patients have few episodes of mono or oligoarthritis for 3–6 months; others develop recurrent episodes of oligo or polyarthritis for longer periods followed by partial remission, and few develop severe and persistent bilateral polyarthritis; but generally by the end of the first year the majority has polyarthritis and some involvement of the upper extremity joints. The involvement of the hips, MTP, and foot IP joints as well as some of the upper extremities, particularly the shoulder increases during the course of the disease. Permanent joint damage, including joint contractures and limited mobility, muscle atrophy, and distorted bone alignment occur in some patients on the long term.

Enthesitis. Enthesitis and its consequences – osteocartilaginous proliferation and enthesophytosis – may occur within the joints (i.e., the sacroiliac joints) and in extra-articular sites (i.e., Achilles tendon and plantar fascia attachments to the calcaneus). Apart from the plantar fascia and Achilles tendon entheses, the functional entheses of the longitudinal apposition of the

peroneal and tibialis anterior and posterior, as well as extensor hallucis longus tendons to the tarsal bones), those of the knees (tibial anterior tuberosity), hips (greater trochanter), and pelvis (iliac crest and ischion) may be involved. Involvement of the upper-limb entheses is rare. Enthesitis presents with pain, swelling, and reduced mobility of the joints even in cases with no synovitis. The bursae and synovial sheaths of the feet may be swollen (◉ *Fig. 155.2*).

Axial involvement. By definition, all patients with juvenile-onset AS have spinal and sacroiliac joint involvement. In the Mexican and Canadian populations, 70–90% of patients with SEA syndrome fulfill adult-onset criteria for AS within 10 years of symptoms. Shorter follow-ups yield lower figures. Axial symptoms may accompany disease activity at peripheral sites, particularly in patients with severe polyarthritis and enthesitis. Spinal symptoms include pain, stiffness, and reduced mobility and in some patients correspond to typical signs of inflammatory back pain. The diagnosis of inflammatory back pain is the most characteristic symptom of axial disease in juvenile-onset AS – and other SpA – and relies on the following criteria: onset of pain or awakening because of pain in the second half of the night, spinal morning stiffness >30 min, and improvement with exercise, but not with rest. Some children and adolescents clearly fulfill such criteria, but the characteristics of spinal disease in other patients are different. Alternating gluteal – sacroiliac – and costosternal pain are uncommon at onset. All three segments of the spine may be involved, but the thoracolumbar junction and the cervical spine seem most frequently affected. Compared with healthy controls the anterior and lateral spinal flexion and less frequently chest expansion are reduced in parallel with axial symptoms. The involvement of the hips or knees may interfere with the assessment of the spinal mobility.

Extra-articular manifestations. During episodes of disease activity, 5–10% of patients have high-grade fever, weight loss, muscle weakness, fatigue, lymph node enlargement, leukocytosis, or anemia. Up to 27% have non-granulomatous acute uveitis, usually unilateral, frequently recurrent and rarely precedes the onset of the



◉ **Figure 155.2**

Composite images of ankylosing tarsitis in a 16-year-old boy with AS of 9 year's disease duration and complete ankylosis of the tarsal bones and grade 2 bilateral sacroiliitis. (a and b) Flat foot and swelling around the ankle. (c, d, e, and f) T2-weighted-fat suppressed MR imaging showing edema in various tarsal bones, joint spaces (c and d), and soft tissues (e and f) surrounding the tendons of the posterior aspect of the foot on the coronal view (arrows) fat. (g) Complete ankylosis of the tarsal bones and an enthesophyte at the plantar fascia attachment (Modified from Burgos-Vargas R (2009) A case of childhood-onset ankylosing spondylitis: diagnosis and treatment. Nat Clin Pract Rheumatol 5:52–57)

musculoskeletal manifestations. Uveitis seldom leaves ocular sequelae. At least between 40 to 60% of patients have nonspecific IBD. Rare manifestations in the initial years of disease are aortic valve lesion and nonspecific conduction disturbances, and other fewer miscellaneous findings. Pulmonary function test abnormalities, amyloidosis, and atlantoaxial subluxation may also occur.

Juvenile-onset and adult-onset AS. Most differences between juvenile and adult-onset AS consist in symptoms at onset. Children and adolescents with AS have peripheral arthritis and enthesitis in the initial years and axial symptoms 5–10 years later. In contrast, most adult patients complain of spinal and sacroiliac pain and stiffness. Peripheral joint disease is more common in juvenile-onset AS and persistent hip disease is associated with a poor functional outcome. Also, the severity of AS is greater in juveniles than in adults since more juvenile-onset AS patients require hip replacements, more patients are in functional classes III and IV, and Bath ankylosing spondylitis functional index (BASFI) mean scores are higher. However, the severity of spinal involvement seems lower than in adults.

Imaging Studies

Radiographic examination. The presence of bilateral grade 2 or unilateral grade 3 sacroiliitis is mandatory to establish the diagnosis of AS in patients with symptoms of axial disease (Fig. 155.1). These changes are usually not seen before 5–10 years after onset. Peripheral joints may show osteopenia, space narrowing, and even ankylosis; erosions and destructive changes are rare; when present, they are usually seen on the margins or the articular surface of some small joints of the feet or the hips. Collectively, osteopenia, joint space narrowing, bone ankylosis, and enthesophytes characterize ankylosing tarsitis, a radiographic event that may be present in juvenile-onset AS (Fig. 155.2). Generally, spinal radiographic changes occur much later than sacroiliac joints and are rarely seen in childhood or adolescence. Radiographic findings of enthesopathy include bone overgrowth, enthesophytosis, bone bridging, and ankylosis; less frequently, subcortical bone cysts and erosions at tendon attachments.

MR imaging. MR is the most sensitive indicator of inflammation in both the sacroiliac joints and the spine. The best MR sequences are T1-weighted and T2-weighted-fat suppressed or Short Tau (t) (inversion time) Inversion Recovery (STIR). Hyperintense signals in MR are interpreted as edema and inflammation in the bone, synovium, peritendineous tissue, and bursae (Fig. 155.3). Structural changes, specifically erosions, bone destruction, enthesophytosis, and ankylosis may also be seen on MR. Interestingly, MR studies may reveal inflammatory changes of the sacroiliac joints in asymptomatic children.

Other studies. Joint and entheses ultrasonography may provide useful information in active disease. Computed tomography may show structural changes. Finally, radionuclide imaging does not appear to be useful because the growing plates might show augmented periarticular radionuclide activity.

Differential Diagnosis

Early on the course of juvenile-onset AS, its recognition and differential diagnosis represent an important problem, particularly when some children present with nonspecific complaints (i.e., fatigue, tiredness, and ill-defined aches and pains), which are often related to growth, sexual maturation, and development. The involvement of joints and entheses are frequently attributed to injuries and overuse as consequence of games and sports; the diagnosis in such cases range from ankle sprain, meniscus rupture, to Leg–Calve–Perthes and Osgood–Schlatter diseases. Patients with monoarticular

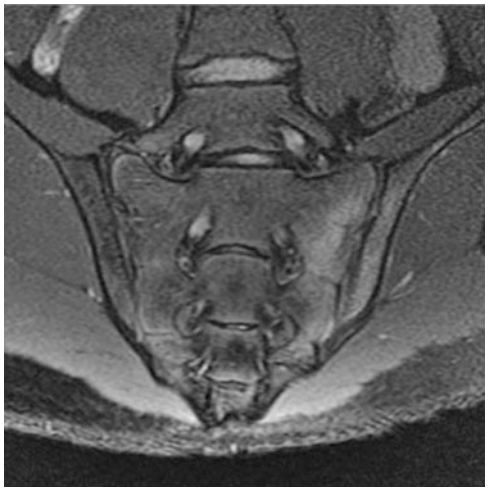


Figure 155.3
Short Tau (t) (inversion time) Inversion Recovery (STIR) MR imaging of the sacroiliac joints of a 16-year-old boy a 3-month history of gluteal pain and a 3-year history of peripheral arthritis and enthesitis. There is ample edema of the iliac bone and sacrum (line) and part of the sacrum inferior quadrant on the opposite side

involvement of the hips are often diagnosed as toxic synovitis of the hip or even tuberculosis and other types of septic arthritis. These circumstances yield mistreatment in early disease and late referral of patients to specialized departments.

Treatment

Currently, the main therapeutic goal in patients with juvenile-onset AS is to reduce the intensity and duration of signs and symptoms of disease, particularly of those related to inflammation (◉ *Table 155.2*). Ideally, therapy should also reduce the structural consequences of the disease, yet there is no evidence that any treatment may do so thus far and on the other by the time the diagnosis of AS is made, patients have structural changes already.

The multidisciplinary health team approach may provide education and relief of medical and nonmedical manifestations. Juvenile-onset AS patients require continuous care and treatment. Patients with juvenile-onset SpA should be enrolled in physical and occupational therapy programs to prevent the consequences of the disease, particularly, hip, foot, and spinal problems. Rest, dynamic splints, and exercise programs should be individualized. Juvenile-onset AS may profoundly harm the quality of life of children and adolescents, and, therefore, their transition to adulthood. Therefore, it is important to consider a number of issues including the psychological, educational, and socioeconomic aspects of life. Disease activity and later, disease damage, may affect these individuals' social life, including personal and family activities, education, and jobs.

Despite there are no guidelines or recommendations for the treatment of juvenile-AS, those issued for adult patients may be adapted at some extent. Treatment, particularly pharmacologic therapy should be individualized according to specific problems. Patients with high-level disease activity with involvement of peripheral and axial joints and entheses should be treated in a different way than children with mild involvement of few joints or entheses. Nonsteroidal anti-inflammatory drugs (NSAIDS) provide symptomatic relief for most patients with mild symptoms. The use of oral prednisone and deflazacort or intra-articular preparations of glucocorticoids may be beneficial in patients with moderate and severe disease activity not responding to NSAIDS or persistent swollen joints. Sulfasalazine might be useful in some patients with peripheral arthritis. Methotrexate is also frequently used to treat juvenile-onset SpA, but there is no clear evidence of improving disease activity in these patients. In adults with AS, the efficacy of sulfasalazine has also been questioned and there is no clear indication of methotrexate in such condition. In contrast, sulfasalazine or methotrexate may improve extra-articular manifestations such as anterior uveitis.

◘ Table 155.2
Medications used in the treatment of juvenile-onset SpA

Drug category	Major indication	Effect
NSAIDS	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	
Sulfasalazine	Pain and swelling	Symptomatic relief
	Peripheral arthritis and enthesitis	
	Psoriasis, uveitis, intestinal bowel disease	
Glucocorticoids	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	
	Uveitis, psoriasis	
Methotrexate	Pain and swelling	Symptomatic relief
	Peripheral arthritis	
	Uveitis, psoriasis	
Etanercept	Pain and swelling	Symptomatic relief Remission, probably
	Peripheral and axial arthritis and enthesitis	
Infliximab	Pain and swelling	Symptomatic relief
	Peripheral and axial arthritis and enthesitis	Remission, probably

The most significant advance in the therapy of adult and indeed juvenile SpA is the use of tumor necrosis factor alpha (TNF-α) blockers. The anti-inflammatory effect of etanercept and inflixmab in patients with juvenile-onset SpA, including juvenile-onset AS is clearly noticed within few weeks of treatment and their long-term administration provides sustained response. TNF-α blockers reduce the number of active joints, tender entheses, pain intensity, and acute phase reactants and improve functioning. MR imaging of peripheral and sacroiliac joints may also show significant changes with TNF-α blockers. Until now, TNF-α have been safety and well tolerated.

Surgical modalities such as soft tissue release, synovectomy, tendon repair, arthroplasty, and joint replacement may be indicated in some forms of hip, knee, and MTP disease.

Prognosis

Currently, accurate data on long-term prognosis are very limited and there are no validated measures of outcome for juvenile SpA or juvenile-onset AS. Disease activity and structural damage result in diverse degrees of pain, stiffness, loss of movement, functional impairment, and harm to quality of life. Information on juvenile-onset SpA, not exclusively juvenile-onset AS indicate that the probability of remission 5 years after onset only reaches 17% of patients with juvenile-onset SpA; by 10 years of disease less than 50% are in remission; and by 17 years after onset more than 50% of the patients still have active disease. Sixty percent of the patients have moderate to severe functional limitations 10 years after onset, particularly those with disease activity for more than 5 years; however, low-level disability has also been found after 27 years of disease. Compared with other subgroups of JIA, patients with juvenile-onset SpA have higher bodily pain and childhood health assessment questionnaire (C-HAQ) scores, poorer physical health and lower physical functioning and health-related quality of life.

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156 Post-infectious Arthritis and Related Conditions

Alberto Martini

In some instances, arthritis is not due to the direct invasion of the joint by the pathogen but rather to the immune response against the infectious agents. In this case, the eliciting infection precedes by a few weeks the onset of symptoms.

Post-streptococcal Arthritis

Acute rheumatic fever (ARF) is a classical post-infectious disease and arthritis is an integral part of its clinical picture (see Chap. 153, "Clinical Approach to a Child with Suspected Rheumatic Diseases"). Arthritis in ARF affects the large joints, is migratory, is characterized by pain, limitation of motion and limited joint swelling and is very sensitive to the treatment with non-steroidal anti-inflammatory drugs.

Post-streptococcal arthritis refers to a post-streptococcal syndrome characterized by an arthritis that is persistent rather than migratory, is less responsive to non-steroidal anti-inflammatory drugs, and occurs in patients whose illness does not fulfil the Jones criteria for the diagnosis of ARF. Usually, the latent period between the streptococcal pharyngitis and the onset of arthritis is shorter (<10 days) with respect to that usually observed in ARF. The course of arthritis is variable; it may last for a few or for several weeks and occasionally even for months. The treatment is based on the administration of non-steroidal anti-inflammatory drugs.

A small proportion of these patients develop valvular heart disease in the follow-up. It is still debated if post-streptococcal arthritis is a defined entity or a manifestation of ARF. This debate involves also the need and the duration of secondary penicillin prophylaxis. The more conservative approach is to follow a prophylactic regimen similar to that proposed for ARF patients who have arthritis but not carditis, that is, to continue prophylaxis until the patient reaches the age of 21 years and for a minimum of at least 5 years.

Reactive Arthritis

Reactive arthritis is a term that identifies an inflammatory arthritis that arises after certain types of gastrointestinal or genitourinary infections. It occurs most frequently in HLA-B27 positive individuals and is therefore considered to belong to the group of spondyloarthropathies (see Chaps. 154, "Juvenile Idiopathic Arthritis" and 155, "Juvenile Ankylosing Spondylitis"). The microorganisms most frequently involved are *Chlamydia trachomatis, Salmonella, Shigella, Campylobacter,* and *Yersinia*. The etiopathogenesis of reactive arthritis is unknown. One theory postulates a CD8-positive cross-reactive T cell response against peptides presented in the context of HLA-B27; this response would cross-react with bacterial epitopes.

The diagnosis associates the presence of an arthritis (usually asymmetric and involving predominantly the lower limbs) with the evidence of an infection, within the preceding 1–4 weeks, with one of the above mentioned microorganisms. Such evidence can be supported either by a history of diarrhea or urethritis or, in the absence of symptoms, by laboratory analysis.

The arthritis, which may be accompanied by fever, is similar to that observed in enthesitis-related arthritis (see Chap. 154, "Juvenile Idiopathic Arthritis"). It is usually asymmetric, predominantly affects the lower limbs, and is often associated with enthesitis and tenosynovitis. The simultaneous presence of arthritis, conjunctivitis, and urethritis constitutes the so-called Reiter's syndrome. Acute phase reactants may be elevated usually in proportion to the severity of clinical symptoms.

The course as well as the severity of arthritis are variable. After a period of weeks or months the arthritis can either go into permanent remission or follow a recurrent pattern which may evolve in a full blown picture of ankylosing spondylitis (see Chap. 155, "Juvenile Ankylosing Spondylitis").

Treatment depends from the severity and the duration of symptoms and is similar to that described in the chapters devoted to enthesitis-related arthritis (see Chap. 154, "Juvenile Idiopathic Arthritis").

Transient (Toxic) Synovitis of the Hip

Although it is often considered secondary to a viral illness its true etiology remains uncertain. It is a common cause

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of limping in children and is most prevalent between 3 and 10 years of age. In the majority of children it is preceded by 1 or 2 weeks by an upper respiratory tract infection.

The clinical picture is that of a monoarticular synovitis of the hip lasting for a few days and causing a limping gait; pain can be referred to the hip, thigh, or knee. Physical examination shows a limitation of the internal rotation of the affected hip. Children are often afebrile or have low grade fever. Acute phase reactants are normal or occasionally mildly elevated. Ultrasonography of the hip shows a joint effusion. The condition resolves spontaneously within 2 or 3 weeks; non-steroidal anti-inflammatory drugs are indicated.

The condition is usually easily differentiated from septic arthritis, which is characterized by a very painful arthritis accompanied by high fever and a marked elevation of acute phase reactants. If there are doubts, a joint aspiration has to be performed.

Viral Arthritis

Articular symptoms in viral infections are thought to be mainly secondary to the immune response against the virus. Several viruses cause post-infectious arthritis (*Table 156.1*). The clinical course of arthritis is typically self-limiting, usually lasting no longer than a few weeks. The diagnosis is usually made on clinical and serologic grounds and on the transient nature of arthritis.

Joint symptoms in the acute phase of alphavirus infection may be severe and consist of a migratory polyarthralgia or an arthritis affecting mainly the small joints of the hands, feet, wrists, and ankles. Diffuse myalgia and back or shoulder pains may also be present.

Parvovirus B19 associated joint symptoms are more frequent in adults where they usually present as a self-limited, acute symmetric polyarthritis affecting the small joints of the hands, wrists, and knees. In children, they often consist of an asymmetrical and oligoarticular arthritis, often involving the knee. Articular symptoms are usually preceded or accompanied by the classic manifestation of acute parvovirus B19 infection, the "slapped cheek" rash of the fifth disease (erythema infectiosum). In some patients, during the acute infection, autoantibodies can be transiently positive in low to moderate titers.

The arthritis associated with rubella usually follows natural infection or, more rarely, rubella vaccination. Uncommon in males and in prepubertal girls, it affects mainly adult females and appears soon after the onset of rash. Arthritis is frequently symmetrical and polyarticular.

Arthritis, although infrequent especially nowadays with the current available therapies, can occur at any stage of human immunodeficiency (HIV) virus infection, although it is more common in the advanced phases of the disease. Rarely it can be the presenting feature. The arthritis more often affects the large joints of the lower limbs. The defective immune response makes of course these children also at risk for infectious arthritis.

Arthritis may occasionally occur during cytomegalovirus or Epstein-Barr virus infection.

During the preicteric phase of acute hepatitis B infection a small proportion of patients develop a symmetric polyarthritis. Hepatitis C–related arthritis is rare in adults and even more in children.

In mumps, arthritis is unusual and predominantly affects young adult males; it may occur before, after, or even in the absence of parotitis.

Varicella-associated arthritis is uncommon in children. It usually occurs after or coincident with the onset of the disease and tends to affect large joints, especially the knees. Suppurative arthritis has also been reported as a complication of varicella.

Table 156.1
Viruses more frequently associated with arthritis

Alphaviruses
Human parvovirus B19
Rubella virus
HIV
Cytomegalovirus
Hepatitis B virus
Mumps
Varicella
Hepatitis C virus
Epstein-Barr virus (EBV)

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157 Miscellaneous Conditions Associated with Arthritis

Alexandre Belot · Pierre Quartier dit Maire

Relapsing Polychondritis

Relapsing polychondritis (RP) is a rare multisystem disorder characterized by widespread, destructive, inflammatory lesions of the cartilage. The peak incidence is between the fourth and the sixth decades and less than 5% of the published cases concern children. The disease includes cartilage inflammation of ears, nose, and larynx. Recurrent flares may lead to floppy ears, saddle nose, and laryngotracheal stenosis. Ear inflammation involves the cartilaginous portion of the pinna and spares the non-cartilaginous lobe. Arthritis is common and non-erosive. Most of the children present with conjunctivitis or episcleritis during the follow-up. Hearing impairment occurs in less than 10% of cases. Histology is not mandatory for the diagnosis and may show granular deposits of immunoglobulins and C3, as well as CD4+ lymphocytes and plasma cells associated to a loss of basophilic staining of the cartilage matrix. Erythrocyte sedimentation rate (ESR) is usually elevated but normality, a normal ESR, does not exclude the diagnosis of RP. Autoantibodies against collagen or matrilin-1 have been reported in some cases but with lack of specificity; therefore, the diagnosis remains mainly clinical and the Michet criteria can be used to diagnose childhood onset RP (*Table 157.1*). An association to other autoimmune disorders is less common than in adults (less than 15% of reported pediatric cases); when present, it may include hematologic diseases, inflammatory diseases (Goodpasture, Henloch-Shönlein purpura), and an overlapping syndrome with Behçet disease called MAGIC syndrome (Mouth And Genital ulcers with Inflammed Cartilage syndrome). Differential diagnoses in pediatric practice also include rare inherited degenerative chondropathies, Chronic Infantile Neurologic Cutaneous and Articular (CINCA) syndrome/Neonatal Onset Multisystem Inflammatory Disease (NOMID), Wegener's granulomatosis, and congenital syphilis. Silverman syndrome can be discussed in the presence of saddle nose and ear destruction, but normal X-rays usually rule out this diagnosis. Indeed, some pediatric RP cases have been first diagnosed as Silverman syndrome. Prognosis depends on associated vasculitis and laryngotracheal lesions which can lead to fatal aortic aneurysm and valvulopathy or laryngeal collapses and pulmonary infection, respectively. Treatment consists in nonsteroidal anti-inflammatory drugs in the mildest forms of the disease or steroids and immunosuppressants in the cases with systemic involvement. Few reports also suggest an efficacy of biologics.

Hypertrophic Osteoarthropathy

Hypertrophic osteoarthropathy (HOA) is a rare syndrome characterized by an excessive proliferation of skin and bone at the distal parts of the extremities and is closely associated with severe chronic disease such as cystic fibrosis, malignancies, and biliary atresia.

The hallmark of the disease is a unique bulbous deformity of the tips of the digits so-called finger clubbing and pain along the long bones with periostitis. Most patients have symmetric polyarthritis with pain and effusions in the knees, wrists, and ankles. Synovitis of the hand joints is far less common. Digital hippocratism is not rare and more often related to cystic fibrosis. Radiographs may also show a symmetrical periosteal new bone formation at the distal ends of the tibiae, radii, fibulae and ulnae and occasionally joint effusions that may be large. Correction of the underlying etiology leads to a quick regression of HOA. Several isolated reports suggest that biphosphonates are effective in relieving bone pain. Octreotide treatment was also associated with clinical improvement in a few case reports.

Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) may be involved in the pathogenesis of HOA. These growth factors represent potent stimuli for angiogenesis or osteoblast differentiation and are induced by hypoxia. Immunohistochemistry studies have shown increased VEGF and PDGF deposition in the stroma of clubbed digits. Recently, primary form of HOA has been demonstrated to be secondary to a mutation in the gene encoding for hydroxyprostaglandin

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Table 157.1
Diagnostic criteria for relapsing polychondritis

Michet et al. criteria (1 of 2 conditions necessary for diagnosis)
– Proven inflammation in 2 of 3 of the auricular, nasal, or laryngotracheal cartilages or – Proven inflammation in 1 of 3 of the auricular, nasal, or laryngotracheal cartilages plus 2 other signs including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, and hearing loss

dehydrogenase (HPGD). In this form starting early in the youth, features include skin thickening and excessive sweating ("pachydermoperiostosis"), delayed closure of the cranial sutures ("cranio-osteoarthropathy"), and congenital heart disease, especially patent ductus arteriosus. These symptoms may be related to a defect of prostaglandin E2 (PGE2) catabolism. Consequently, PGE2 and its inactive, HPGD-derived metabolite, 11a-hydroxy-9, 15-dioxo-2,3,4,5-tetranor-prostane-1,20-dioic acid (PGE-M) urine measurements may be useful to evocate the diagnosis, showing an increase of PGE2 and a reduction of PGE-M. Then HPGD mutation analysis is mandatory for the diagnosis.

Mucha-Habermann Disease

Pityriasis lichenoides et varioliformis acuta (PLEVA), also known as Mucha-Habermann disease, is a rare dermatosis characterized by erythematous, scaly papules often accompanied by hemorrhagic lesions. Febrile ulceronecrotic variant of PLEVA, also termed febrile ulceronecrotic Mucha-Habermann disease (FUMHD), is characterized by the acute onset of extensive ulceronecrotic skin lesions associated with high fever (up to 40°C), malaise, myalgia, arthralgia, gastrointestinal and central nervous system symptoms, interstitial pneumonitis, lymphocytic myocarditis, and death. Notably, there is a prognostic difference between adult and children for the FUMHD because all cases resulting in fatality are of the adult type, whereas no fatal cases have been reported among children. T cell clonality in FUMHD is a bad prognostic factor, mainly found in adult patients. Treatments of FUMHD are not standardized and are mainly related to single case reports in the literature. According to Yang, the initial combination use of high-dose corticosteroids rapidly brings down the inflammatory component of the FUMHD, and prolonged treatment with erythromycin can maintain the therapeutic effect. This sequence was successful for the treatment of a 14-year-old patient. Immunosuppressive drugs, phototherapy, antibiotics, or skin grafting may be of interest to treat pediatric FUMHD.

Plant-Thorn Synovitis

Plant-thorn synovitis, a severe foreign-body granulomatous inflammation induced by plant material, is an uncommon cause of arthritis. Injuries of rose thorn or date palm are frequent in the USA whereas, black thorn is the principal cause of thorn synovitis, in Europe. It frequently occurs incidentally when in contact with thorny plants and children are more often affected. The initial symptoms are usually transient and represented by a mild synovitis. Then, local arthritis or soft tissue swelling may develop. At a later stage, chronic or relapsing arthritis represent misleading symptoms for the clinician and can be reminiscent with a chronic inflammatory disease. Symptoms may occur long after the thorn injury has been forgotten, and the diagnosis is usually established at the time of the synovectomy. Histological findings show a sterile granulomatous synovitis. Plant thorns are usually not radiopaque and X-rays are useless. Recently, it has been shown that magnetic resonance imaging and sonography can be helpful for the diagnosis. Removal of the plant thorn with synovectomy is the only curative treatment.

Autoimmune Manifestations of Immunodeficiency

In the last decades, substantial progress led to a precise understanding of primary immunodeficiencies (PID) with the identification of more than 120 genes accounting for more than 150 distinct diseases. Notably, several PID are associated with autoimmunity and give rise to a better understanding of tolerance breakdown.

Autoimmune Manifestations Associated to B and/or T Cell Defects

Bruton's agammaglobulinemia, is an X-linked immune disease due to mutations in Bruton's tyrosine kinase (BTK), a signal transduction molecule essential for B-cell maturation. BTK-deficient B cells do not differentiate into antibody-producing plasma cells, and patients present

with pan-hypogammaglobulinema responsible for recurrent bacterial infections. Juvenile rheumatoid arthritis, dermatomyositis, aseptic polyarthritis, cytopenia, and chronic diarrhea mimicking inflammatory bowel disease have been reported. In some cases, chronic viral infection may explain the symptoms and careful screening for infection is mandatory.

IgA deficiency (IgAD) is the most common primary antibody deficiency and can be diagnosed in children older than 4 years. The most common infections associated with IgAD are sinopulmonary and gastrointestinal infections, especially with *Giardia lamblia*. The prevalence of autoimmune disorders in IgAD patients varies from 7% to 36%. It mainly consists in hematologic disorders, celiac disease and rheumatic disease such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Autoimmune thyroiditis is the most common manifestation of autoimmunity in these patients. The association between IgAD and primary antiphospholipid syndrome has been reported recently.

Hyper-IgM syndromes (HIGM) are primary immunodeficiencies secondary to mutations of various genes, including the genes including CD40 ligand (X-linked HIGM), CD40, NF-κB essential modulator (NEMO), activation induced cytidine deaminase (AID) or uracil DNA glycosylase (UNG). HIGM patients display low levels of IgG and IgA with normal or elevated IgM levels. These patients are prone to recurrent sinopulmonary and gastrointestinal infections. Patients with CD40 ligand mutations may also develop opportunistic infections, mainly *Pneumocystis carinii* infections and cryptosporidiosis. Autoimmunity has also been described in HIGM patient series including immune thrombocytopenia, Coombs positive hemolytic anemia and nephritis, suggesting that tolerance is breached in these patients. Several autoantibodies have been identified in the plasma of HIGM patients. Other autoimmune manifestations seen in these patients include inflammatory bowel disease, autoimmune hepatitis, seronegative arthritis, hypothyroidism, and discoid lupus erythematosus. In two cohorts of patients with X-linked HIGM, chronic neutropenia was found in 44–60% of the patients, anemia, or thrombocytopenia in 15% and 4%, respectively. Seronegative arthritis was seen in 11% and inflammatory bowel disease in 6% of the patients. Other HIGM also demonstrate autoimmunity with a large spectrum of symptoms including cytopenia, autoimmune hepatitis, SLE, diabetes mellitus, inflammatory bowel disease mimicking Crohn's disease and bilateral chronic uveitis. Lymph node, spleen, and liver hyperplasia is a common feature in patients with AID mutations and may also be seen in other HIGM syndromes.

Common variable immunodeficiency (CVID) usually appears later in life. In many cases, the underlying genetic defect is unknown. Some patients disclose mutations in genes encoding the inducible costimulator (ICOS), CD19, the transmembrane activator, calcium-modulator and cyclophilin ligand interactor (TACI) or B-cell activating factor of the tumor necrosis factor family receptor (BAFF-R). Autoimmune manifestations occur in about 22% of CVID patients and are organ specific in most of the cases, consisting in autoimmune cytopenias, pernicious anemia, Hashimoto's thyroiditis, rheumatoid arthritis, and/or vitiligo. In patients with CVID, idiopathic thrombopenia frequently precedes other clinical manifestations. However, cytopenias may also occur later in the disease course.

IgG subclass deficiency can be associated to autoimmune manifestations such as vasculitis, cytopenia, and arthritis. IgG2 is the most prevalent IgG subclass deficiency in childhood. The hallmark of IgG2 deficiency is a defect in anti-polysaccharidic antibody response with severe infections to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*.

Some patients with severe combined immunodeficiencies (SCID) and a high proportion of the patients with combined immunodeficiencies (CID) are prone to develop autoimmune manifestations. The paradox wherein severe T cell defect can be associated to severe self reactivity of the immune system can be explained, at least in part, by the rupture of central and peripheric tolerance in SCIDs and CIDs. Indeed central tolerance, which is in charge of elimination of autoreactive T cell clones, is impaired in SCID because of markedly reduced expression of Aire, a transcriptional regulator for the expression of tissue-specific antigens in the thymus. Peripheral tolerance is also markedly decreased in SCID because of several factors including the expansion of T cell clones as a consequence of the lymphopenia observed in these conditions as well as a diminished number of regulatory (FOXP3+) T cells, allowing autoreactive T cells to proliferate and infiltrate various organs in the body of SCID. Autoimmunity may also be observed in patients with DiGeorge syndrome (22q11.2 deletion syndrome), where it is more common among patients with a partial yet relatively pronounced deficiency of T cell development. Autoimmune manifestations of DiGeorge syndrome are found in about 10% of patients and consist in autoimmune cytopenias, juvenile arthritis, vitiligo, autoimmune endocrinopathy, or inflammatory bowel diseases. Haemolytic anemia, thrombocytopenia, insulin-dependent diabetes mellitus, asthma, and skin rash has also been reported in patients with SCIDs/CIDs due to

adenosine deaminase deficiency or purine phosphorylase deficiency. Wiskott–Aldrich syndrome (WAS) is a single-gene primary immunodeficiency associated with a remarkably high prevalence of autoimmunity, as high as 70% in retrospective cohorts, which is likely explained by a defect in T regulator differentiation. Omenn syndrome secondary to hypomorphic mutation of RAG1, RAG2, or ARTEMIS can develop autoimmune complications including lymphadenopathy, splenomegaly, erythroderma, and autoimmune hepatic dysfunction. These complications are associated with eosinophilia and elevated IgE, suggesting the involvement of the Th2 subset of T cells that produces IL-4, IL-6, and other cytokines that drive plasma cell differentiation and IgE production by B cells. Patients with these complications have been treated with high-dose steroids, antithymocyte globulin, and cyclosporin A, but bone marrow transplantation remains the only definitive treatment. Class I deficiency (TAP1 or TAP2 deficiency) can present as a granulomatous disease mimicking Wegener disease and recurrent infection in the context of a granulomatous disease should alert the clinicians. Class II deficiency starts earlier in life and is usually revealed by severe or recurrent infections.

Primary Immunodeficiencies Defined by Autoimmune Manifestations

Several monogenic primary immune deficiencies are defined by the occurrence of autoimmune manifestations. Among them are the Autoimmune lymphoproliferative syndromes (ALPS), the Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), the Autoimmune-Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) syndrome, CD25 deficiency, and the recently described syndrome of immunodeficiency and autoimmunity associated with mutations in the gene encoding the Stromal Interaction Molecule 1 (SIM1). The extended analysis of these diseases widely increases the understanding of human immune tolerance regulation. ALPS is secondary to a mutation of the death domain Fas or Fas-Ligand responsible for an uncontrolled proliferation of double negative CD4-CD8- T cells, with lymphadenopathy, splenomegaly, and polyclonal hypergammaglobulinemia. The diagnosis is often made before the age of 2. These patients may develop autoantibodies usually associated with systemic lupus erythematosus (SLE) without evidence of clinical manifestations of SLE. Autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and autoimmune neutropenia occur in 29–38%, 23–34%, and 19–27% of the cases, respectively. Glomerulonephritis, optic neuritis, Guillain–Barré syndrome, arthritis, cutaneous vasculitis, primary biliary cirrhosis, autoimmune hepatitis, blistering dermatosis, or acquired factor VIII deficiency have been reported in a few case reports.

IPEX is the consequence of mutation in Foxp3 transcriptional factor leading to a defective development of CD4+ CD25+ regulatory T cells. As a consequence, T cell activation and cytokine production are increased. Autoimmune manifestations are characterized by autoimmune enteritis, type 1 diabetes mellitus occurring during the first months of life, eczema, hypothyroidism, AIHA, membranous nephropathy, recurrent infections, and high titer of IgE. Patients presenting with IPEX syndrome usually die before the age of 2.

APECED (Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy) syndrome is a recessive autosomal disease secondary to a defect of the autoimmune regulator gene (AIRE). Symptoms include chronic mucocutaneous candidiasis, polyendocrinopathy and/or hepatitis, and dystrophy of dental enamel and nails. Candidiasis is usually the first clinical manifestation of the disease, occurring around the age of 5, followed in most cases by hypoparathyroidism before the age of 10 and adrenocortical failure before the age of 15. Other organ-specific autoimmune manifestations encountered in this condition include hypothyroidism, hypogonadism, type 1 diabetes mellitus, pernicious anemia, vitiligo, alopecia, and primary biliary cirrhosis.

Autoimmune Manifestations Associated to Hereditary Complement Deficiency

Primary complement defect, especially in early components of the classical pathway, leads to an increased susceptibility to SLE. C1q, C1s, and C1r complete deficiencies are rare and associated with a high risk to develop pediatric SLE. One of the mechanisms may be an impaired clearance of immune complexes and apoptotic cell debris. More than 90% of homozygous C1q deficient patients present with SLE-like syndrome, whereas SLE occurs in more than 50% of patients with C1s and/or C1r deficiencies. Homozygous C2 deficiency, which is the most frequent hereditary deficiency in classical pathway complement components (1/10,000 to 1/30,000 among Caucasian people), is associated with SLE in 10–30% of the cases.

Table 157.2

Autoimmune manifestation of primary immunodeficiencies (Modified from Goyal R, Bulua AC, Nikolov NP, Schwartzberg PL, Siegel RM (Jan 2009) Rheumatologic and autoimmune manifestations of primary immunodeficiency disorders. Curr Opin Rheumatol 21(1):78–84)

Disease or Syndrome	Mutant gene	Immunologic defect	Manifestations	Autoimmune manifestations
Bruton agammaglobulinemia	Bruton's tyrosine kinase	X-linked agammaglobulinemia	Recurrent bacterial infections and enteroviral infections	Recurrent arthritis, including aseptic arthritis, dermatomyositis-like syndrome, meningoencephalitis (enteroviral infection)
Hyper IgM syndrome (HIGM)	CD40 ligand	Ig class switching defect leading to decreased IgG with normal to elevated IgM	Sinopulmonary and gastrointestinal infections with encapsulated bacteria and lymphoid hyperplasia	Diabetes mellitus, autoimmune hepatitis, rheumatoid arthritis, inflammatory bowel disease, and uveitis
Common variable immunodeficiency (CVID)	TACI (TNFRSF13B)	Hypogammaglobulinemia, humoral and T-lymphocyte dysfunction	Recurrent chronic infections particularly respiratory	Inflammatory bowel disease, autoimmune hemolytic anemia, thrombocytopenia, rheumatoid arthritis pernicious anemia
Severe combined immunodeficiency	Multiple	Lymphocyte development	Failure to thrive, chronic mucocutaneous fungal infections or opportunistic infections, or both	Alopecia, autoimmune thrombocytopenia
Wiskott–Aldrich syndrome (WAS)	WASP	CD4 T-lymphocytes, regulatory T cells, NK cells	Micro-thrombocytopenia with bleeding diathesis, eczema, recurrent infections	Autoimmune hemolytic anemia, arthritis, vasculitis, inflammatory bowel disease, glomerulonephritis
Omenn syndrome	RAG1, RAG2, ARTEMIS	T-B-NK+	Exudative skin rash, lymphadenopathy, hepatosplenomegaly, eosinophilia, and hyper-IgE levels	Part of primary syndrome
Autoimmune polyendocrinopathy candidiasis-ectodermal dystrophy (APECED)	AIRE	Negative selection defect of autoreactive T cells in the thymus	Hypoparathyroidism, chronic mucocutaneous candidiasis, adrenal insufficiency, primary hypogonadism, alopecia, vitiligo, pernicious anemia	Part of primary syndrome

Table 157.2 (Continued)

Disease or Syndrome	Mutant gene	Immunologic defect	Manifestations	Autoimmune manifestations
Immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX)	Foxp3	Regulatory T cell defects	Autoimmune thyroid disease, excema, type I diabetes, eosinophilia, hyper IgE	Part of primary syndrome
Leukocyte adhesion deficiency (LAD1)	CD18, ITGB2	Monocytes and neutrophils adhesion defect	Recurrent bacterial infections	Inflammatory bowel disease
Chronic granulomatous disease (CGD)	CYBB and other components of the NOX2 NADPH oxidase complex	NADPH oxidase	Recurrent suppurative microbial infections, granuloma formation	Chronic inflammation with granuloma formation, inflammatory bowel disease

Autoimmune Manifestations Associated to Phagocytic Cell Defect

Chronic Granulomatous disease (CGD) is a genetic immunodeficiency secondary to a defect of NADPH oxydase complex in phagocytes enabling generation of superoxide and other reactive oxygen species (ROS). Systemic lupus erythematous, mouth ulcers and discoid lupus have been reported in many CGD patients; discoid lupus is also a common feature among X-linked CGD female carriers. Inflammatory bowel disease is the frequent inflammatory condition associated to CGD with symptoms mimicking Crohn's disease. Lung, urogenital tract, and eyes can also demonstrate germ-free granulomatous lesions. Steroids are helpful to resolve the symptoms but do not prevent relapses. Other autoimmune manifestations are represented by idiopathic thrombocytopenic purpura, myasthenia gravis, and juvenile rheumatoid arthritis in a few case reports. In some patients, the severity of autoimmune or inflammatory manifestations, usually associated with recurrent infections, may be part of the symptoms leading to the indication of allogeneic hematopoietic stem cell transplantation.

In conclusion, primary immunodeficiencies shed new lights into the pathogenesis of autoimmune diseases. Molecular identification of mechanisms involved in tolerance maintenance is crucial to develop new treatment as specific as possible of the underlying defect.

As primary immunodeficiencies can present with symptoms suggesting a rheumatic disease (*Table 157.2*), a careful assessment is mandatory in pediatric rheumatology practice to avoid, in particular, an inappropriate use of immunosuppressive drugs in these patients.

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158 Pain Amplification Syndromes

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Introduction

Pain is a common presenting complaint in the pediatrician's office. As many as 30% of children and adolescents experience significant muscular fatigue and chronic or recurrent musculoskeletal pain. The symptoms have many causes and the differential in children includes infectious and metabolic conditions, growing pains, overuse injuries, hyperextensibility, orthopedic problems, arthritis, and genetic syndromes.

Pain Amplification Syndromes are rarely recognized or diagnosed in a timely fashion by the primary care physician. These syndromes are characterized by a lack of physical or laboratory findings. Typically the child describes the pain as maximal (on a pain scale of 10/10). There is disability out of proportion to the physical findings, a sensation of pain to non-painful stimuli, psychological distress, an inappropriate indifferent affect (La Belle indifference), a significant family history of disability or chronic pain, and the presence of multiple somatic complaints. Indeed, the degree of pain and disability in these groups is strikingly high compared to children with Juvenile Idiopathic Arthritis or other classical rheumatic conditions where joint disease is readily demonstrable.

Given the lack of a diagnostic test and variability of presentation, as well as a large number of potential etiologies, Pain Amplification Syndromes have been called by many synonyms, despite the possibility that they all represent variations of a common process. Generalized pain syndromes include fibromyalgia, fibrositis, myofascial pain syndrome, pain amplification syndrome, and diffuse wide spread myofascial pain, while localized pain syndromes have been called reflex sympathetic dystrophy, reflex neurovascular dystrophy, causalgia, and Sudeck's atrophy.

Some authors suggest that the precise classification in children with pain and fatigue is not necessary because overlap in clinical presentation is frequent and all children with pain syndromes respond to a similar treatment programs.

Pathogenesis of Pain Amplification Syndromes

An understanding of the pathophysiology and pathogenesis of chronic central pain syndromes has evolved over recent years and is now known to involve multiple interrelated systems including genetic factors, environmental triggers, as well as the neuroendocrine and autonomic nervous system which are simultaneously involved in disordered pain regulation.

Genetic Factors

Studies among patients with central pain syndromes have noted a familial component. First degree relatives of individuals with a pain syndrome have an increased risk of developing a similar disorder, as well as being diagnosed with other concomitant pain disorders such as irritable bowel syndrome and temporomandibular disorders.

Recent studies have identified polymorphisms in genes encoding catechol-*O*-methyltransferase, an enzyme that inactivates catecholamines, as well as the serotonin 5-HT2A receptor and a dopamine D4 receptor. In all of these instances, monoamine metabolism or transport is affected. Monoamines appear to be key factors in the human stress response and these polymorphisms may contribute to abnormalities in pain and sensory processing.

Environmental Factors

Multiple environmental factors have been investigated as possible triggers in the development of central pain syndromes. Physical trauma especially truncal injury, infections (Hepatitis C, Lyme disease, Epstein-Barr Virus, Parvovirus, HIV), catastrophic events such as war, emotional/psychological stress, and the diagnosis of autoimmune diseases have been implicated as playing a role in triggering the onset of pain syndromes. Recent studies of patients with fibromyalgia and other related pain

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syndromes have noted that approximately 5–23% of patients have an identifiable precipitating event, such as a prolonged or painful episode early in life, prior to the onset of diagnosis. However, an overwhelming majority of patients diagnosed as having a pain syndrome have no known trigger at the onset of symptoms and diagnosis.

Behavioral and Psychologic Factors

Between 7% and 22% of patients with fibromyalgia and other central pain disorders suffer from comorbid psychiatric conditions such as depression. These conditions may also contribute to the symptomatology noted in central pain disorders. Depression is a frequent comorbid condition in pain amplification syndromes and may predate the pain syndrome or be a result of having chronic pain. Patients with depression or anxiety will not have improvement in their pain without proper evaluation and treatment of the underlying psychiatric problems. Therefore, it is imperative that a psychiatric evaluation be required as part of an initial work up for pain amplification syndromes.

Pathophysiology of Enhanced Pain Perception

There appears to be central augmentation of sensory input and altered pain inhibitory function in patients who suffer from central pain. This may be due to both neuroendocrine and autonomic nervous system dysregulation. The concept involves a stimulus being applied to a tissue resulting in sensory inputs from nerve receptors in the tissue being transmitted along primary afferent fibers in the dorsal horn of the spinal cord. Second order spinal neurons then transmit this information to the brain. Neurotransmitters such as Substance P and excitatory amino acids such as glutamate are released in this process and activate postsynaptic receptors which are thought to produce pain perception. Once the sensory input is eliminated, there is reduction of pain sensitivity. When there is a strong or prolonged sensory input there is an exaggerated release of neurotransmitters and excitatory amino acids which cause a hyper-excitable state. There is a positive feedback phenomenon which leads to prolongation of the hyper-excitable state. This model is felt to be responsible for central augmentation and for the low pain thresholds, and high pain intensity described in central pain syndromes. Notably, the source of the exaggerated or prolonged input is unknown in central pain syndromes. In favor of this theory are recent studies showing elevated levels of Substance P and excitatory amino acids glutamate and aspartate, in the cerebrospinal fluid of patients with central pain syndromes. This indicates that the pain is both real and inappropriate.

Is the Brain Responsible for All the Peripheral Pain?

There also appears to be a deficiency in serotonergic and noradrenergic transmission in the central nervous system, shown by a reduction in the levels of primary metabolites of both 5-HT and norepinephrine, but normal levels in the opioidergic system. 5-HT is involved in the inhibition of neurotransmitters and excitatory amino acids, as well as in mood, sleep, and pain regulation all of which are dysregulated in central pain syndromes. Decreased levels of 5-HT may lead to increased levels of Substance P and glutamate and further prolongation of a hyper-excitable state.

There appears to be dysregulation within the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous systems in patients with central pain syndromes. The dysregulation does not appear to occur at the pituitary or primary endocrine level. Rather, it implicates central nervous system dysregulation. Recent studies have shown elevated levels of adrenocorticotropic hormone (ACTH), follicle-stimulating hormone (FSH), and decreased levels of insulin growth factor-1 (IGF-1), growth hormone, and estrogen. IGF-1 deficiency has been postulated as a possible cause for sleep impairment commonly noted in central pain syndromes. It has been speculated that many of these hormonal abnormalities are secondary to the observed deficiencies in the serotonergic pathway which influences the HPA axis.

While great strides have been made in the understanding of central pain syndromes and their associated disordered pain regulation, much work is still needed to fully understand these abnormalities. It is unclear if the above processes are causal or secondary phenomena, and there is, as of yet, no identifiable sensory input which triggers these syndromes.

Clinical Characteristics

Overall, children with pain amplification syndromes have disturbed sleep patterns and poorer stress and pain coping mechanisms than age matched controls. This leads to nonrestorative sleep, poor school performance, inability to concentrate, and, oftentimes, withdrawal from school

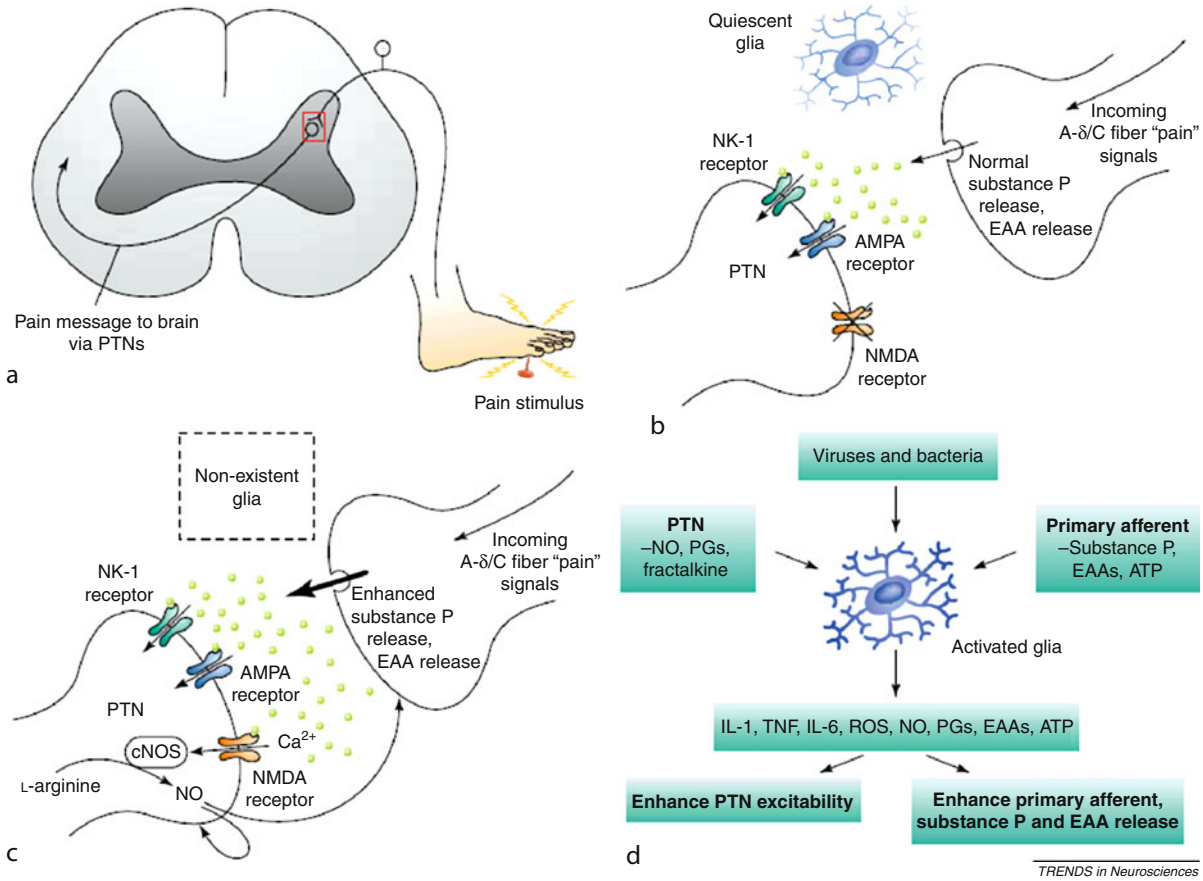

Figure 158.1

(a) Sensory input, (b) transmission within the dorsal horn, (c) neurotransmitters released that promote sensory transmission, and (d) Schematic of pain amplification neural pathway

altogether. Headaches, usually frontal, are common and often occur for hours each day. Some patients complain of numbness and paresthesias or vertigo but no underlying physiologic pathology can be demonstrated. Most patients have widespread musculoskeletal complaints of achiness, arthralgias, and myalgias often concentrated in the neck and upper back. Most patients feel worse after any type of exertion, exercise, or massage and prefer not to be touched. These symptoms respond poorly to over-the-counter medications.

Testing

Reasonable diagnostic studies are often unavoidable except in very early cases and they help to reassure both physician and family. Repeated investigations by inexperienced physicians may prolong the time to diagnosis and treatment. In these cases, x-rays will show patchy demineralization (Sudeck's atrophy), while Doppler studies, technetium, and gallium scans may reflect the excessive autonomic activity and increased or decreased blood flow. MRI evaluation may show dermal enhancement and edema. It is important not to misinterpret these findings as indicative of other disorders (*Fig. 158.1*).

Major Syndromes

Reflex Sympathetic Dystrophy

Reflex sympathetic dystrophy (RSD) (neurovascular dystrophy) is not rare in childhood but is difficult to diagnose. The important diagnostic clue is that the child suddenly assumes an immobile posture of a hand or foot that is soon accompanied by diffuse juxta-articular swelling and continuous burning pain (causalgia) that is greatly intensified by light touch (allodynia). The swelling is often

accompanied by color and temperature (trophic) autonomic changes often with coolness and sweating. RSD usually occurs distally involving one hand or foot. These children invariably refuse to bear weight on the foot or even wear shoes or socks. When the hand is involved the child protects the hand by curling it against the chest and the child refuses to use the hand for self care, eating, or writing. Even the lightest touch can cause excruciating pain.

Uniquely, the child refuses to move the hand or foot or holds it in an uncomfortable or bizarre posture. This disease occurs predominantly in teenage girls.

Fibromyalgia Syndrome

Fibromyalgia syndrome (FMS) is a descriptive syndrome that includes widespread musculoskeletal pain, fatigue, and multiple discrete tender points. Diagnostic guidelines for adults were published by the ACR in 1990 (add a link). The classification criteria dictate a history of chronic, diffuse pain with greater than 11 tender points on examination. There is limited published data in children and teenagers with FMS. Children tend to have fewer discrete tender points than adults, but usually develop the requisite number if they are followed over time. Many experts feel that the trigger point tenderness is not required to make the diagnosis of FMS in children.

At least 6% of children seen in pediatric rheumatology centers have this diagnosis, making it the third most common diagnosis in some clinics. The mean age of onset is 12.6 years and it is more common in teenage girls. It appears to be less prevalent in minority and urban populations.

Risk Factors. Primary fibromyalgia occurs without underlying illness. Teenage girls appear to be at higher risk with an increased prevalence of concomitant depression. Prolonged pain and trauma have been proposed as risk factors and have been studied in adult patients with a history of childhood physical or sexual abuse, PTSD, and other traumas. When compared with adult FMS patients, pediatric FMS patients have a higher percentage of secondary fibromyalgia with an underlying rheumatologic condition such as JIA, spondyloarthritis, or SLE.

Treatment Modalities of Pain Amplification Syndromes

The complex nature and unclear pathophysiology of pain amplification syndromes have led to difficulty in both the creation of pharmacologic and non-pharmacologic treatments and their testing in clinical trials. Most of the data and studies involve adult populations and to date there are few pediatric trials designed to examine the efficacy of different treatments. Management of pediatric pain amplification syndromes is similar to that used for adults, with modifications based on age and developmental level and there are fewer medications that are generally prescribed in children. In the initial stages of evaluation and diagnosis, it is of vital importance to establish a therapeutic relationship in which the pain symptoms of the child are validated and noted to be real. The general pediatrician must be sensitive to the diagnosis of a pain amplification syndrome and make an appropriate referral, to avoid misdiagnosis. Once an appropriate diagnosis is made, a multidisciplinary approach should be utilized in order to promote education, exercise, cognitive behavioral therapy, and medications when indicated.

The main goal of treatment should be complete return to school and normal activities. The family should be educated about the role of stress, sleep, pain, and exercise and its role in pediatric pain amplification syndromes. They must be supported in their successful reentry to school by providing whatever accommodations are needed, such as an extra set of school books, modified physical education program or beginning classes later in the morning. No treatment protocol has been completely successful, but incorporating psychological support and exercise reduces disability.

Non-pharmacologic Therapies

There are a plethora of non-pharmacologic therapies available which have been evaluated in the adult literature. Of note, cognitive behavioral therapy (CBT) and aerobic exercise have been used with the strongest evidence of success in treatment in the adult population and in the pediatric population.

Cognitive Behavioral Therapy

Management of psychological factors may play a role in decreasing the perception of chronic pain in these patients. Cognitive behavioral therapy helps patients control pain via guided imagery and distraction in order to help the patient cope with behavioral and cognitive responses to pain. By decreasing their daily stress levels through cognitive behavioral therapy, patients can improve physical functioning. There have been several small pediatric studies documenting the effectiveness of cognitive behavioral therapy in the context of juvenile primary fibromyalgia syndrome. Psychological support

should be provided with evaluation for coexisting conditions such as depression, anxiety and school phobia.

Exercise Interventions: Exercise has been shown to be effective in improving quality of life in pediatric patients with central pain syndromes. Chronic deconditioning secondary to pain leads to decreased physical activity and decreased functioning which becomes a cycle of inactivity. Aerobic programs have been found to have positive effects both on mood and physical functioning in patients. Cardiovascular exercise routines have had greater evidence of benefit then strength training or stretching. During the initiation of aerobic exercise, there may be increased reports of pain, followed by gradual improvement and an increase in energy level. There are also reports of improved sleep and mood with exercise initiation. A pilot study that examined a 12 week exercise intervention in children and adolescents with juvenile fibromyalgia and compared intense aerobic exercise with a light intensity program known as Qigong found improvements in both groups of patients with better response in several measures in the intense aerobic exercise group.

Physical and occupational therapy is an integral component of the treatment of RSD in an effort to reverse immobility and preserve function. Intensive daily desensitization with an experienced physical therapist and a home program is usually extremely successful in relieving and resolving the pain. The rehabilitation must begin immediately when the child is diagnosed. We generally begin with massage while examining the patient and direct them to bear weight or use their hand despite the pain. Once parents are educated about these mysterious symptoms and accept there is no harm in moving the painful limb they can carry out the program at home. Other therapeutic interventions that have had some success in treatment of RSD include nerve stimulation, lidocaine patches, and sympathetic blocks. Prolonged immobility will create symptoms that are more difficult to treat.

Sleep Hygiene: As children with central pain syndromes, most notably the juvenile primary fibromyalgia syndrome have disturbed sleep cycles, reinforcement of sleep hygiene should be an integral component of the multidisciplinary approach to treatment. Regular sleep schedules, avoidance of day time napping, and limitation of caffeine intake are important in establishing sleep-wake cycles.

Pharmacologic Therapies

Many classes of medications have been evaluated in adult literature in the treatment of pain amplification syndromes. The use of medication should be an adjunct to promote better sleep and tolerance to physical therapy. Medications are not curative by themselves. Drug treatment of pain amplification in children is off-label and the risk to benefit ratio should be evaluated prior to onset. Medications such as tricyclic antidepressants, SSRIs, Serotonin and Norepinephrine Dual Reuptake Inhibitors, and CNS acting medications (Pregabalin and Gabapentin), and analgesics have been evaluated in the adult population with variable efficacy. Currently, Duloxetine, Milnacipran, and Pregalbin are FDA approved in the treatment of adult pain amplification syndromes. The use of tramadol, an opioid and serotonin/norepinephrine reuptake inhibitor, has had some efficacy in treatment of fibromyalgia.

Prognosis

There are only limited studies that have examined follow up in pediatric pain amplification syndromes and the results vary between institutions. Overall, it appears that the prognosis is better for children than their adult counterparts. The majority of these children do not develop any other rheumatic diseases but they are prone to developing chronic pain in other organ systems especially headaches, abdominal pain, as well as other psychiatric disorders. Neither the rate of relapse nor long term functional outcome is known. Patients and their families must understand these syndromes are difficult to treat. A multidisciplinary approach appears to be the most comprehensive and successful treatment modality.

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159 Systemic Lupus Erythematosus

Bianca Lattanzi · Angelo Ravelli

Definition and Classification

Systemic lupus erythematosus (SLE) is a multisystem, inflammatory, autoimmune disease that can affect any organ system and is characterized by the presence of circulating antinuclear antibodies, especially antibodies to native (double-stranded) DNA. Its clinical manifestations are widely variable, and its course is unpredictable. If left untreated, SLE is often progressive and has a significant fatality rate. It is estimated that 15–20% of patients with SLE have their onset before 16 years of age. Although clinical and laboratory features in juvenile SLE are similar to those that are seen in adults, SLE that begins in childhood has been considered more severe than SLE with onset during adulthood. Furthermore, children diagnosed with SLE may need high-dose corticosteroids and immunosuppressive agents for disease control more often than do their adult counterpart.

In 1971, the American College of Rheumatology (formerly American Rheumatism Association) developed a set of criteria for the classification of SLE, which were revised in 1982 and modified in 1997 (◗ *Table 159.1*). SLE is established when a patient fulfills at least 4 of the 11 criteria. The criteria can be present simultaneously or occur with time along the disease course. The 1982 criteria have been determined to have a sensitivity of 96% and a specificity of 100% in juvenile SLE.

Etiology and Pathogenesis

The etiopathogenesis of SLE remains unknown. The disease is characterized by a dysregulation of the immune system with polyclonal B-cell activation, which appears to drive the production of self-reactive autoantibodies. The production of autoantibodies may represent the sentinel event in the pathogenesis of SLE as it has been found to antedate the onset of clinical symptoms by years. Production of autoantibodies leads to formation of immune complexes, with subsequent tissue deposition and complement activation. The mechanism for polyclonal activation and autoantibody production is not understood. Possible causes include nonspecific responses to antigenic stimuli, such as viral antigens, or loss of either B-cell immune tolerance to self-antigens or suppressor T-cell function. The role of interferon-α in the pathogenesis of SLE has received increasing attention in recent years. This cytokine has been found to be elevated in the serum of SLE patients, and its therapeutic administration in patients with hepatitis has been linked with the development of autoantibodies and lupus-like syndromes. It is hypothesized that interferon-α promotes B-cell responses and immunoglobulin class switching, which may in turn increase autoantibody production. Recent studies have implicated defective apoptosis in the pathogenesis of SLE. Failure of apoptosis may lead to the persistence of self-reactive lymphocytes that normally undergo programmed cell death. In addition to INF-α, other cytokines, such as interleukins-6, 10, 12, and 18, may be involved in the induction of the inflammatory process.

Other mechanisms may play a role in amplifying the manifestations of SLE. Defects in macrophage phagocytosis and processing immune complexes have been reported. The effects of sex hormones, namely estrogens, may account for the disease predominance in females. However, estrogen-containing contraceptives do not produce exacerbations of SLE. Furthermore, that female predilection is also seen among patients with prepubertal onset argues against a prominent responsibility of estrogens. Exposure to ultraviolet rays in sunlight is known to trigger lupus flares, perhaps through damage to skin cells, resulting in release of nuclear debris, such as DNA, which complexes with circulating anti-DNA antibodies. The administration of some drugs can lead to lupus-like serologic and clinical manifestations. However, their discontinuation is usually associated with complete remission.

Reports of clusters of SLE in some families suggests common genetic and/or environmental predisposition. Furthermore, a high concordance rate for monozygotic twins has been described. However, the inheritance of a predisposition to SLE is most likely multifactorial, and multiple genetic factors probably play an important role. The development of SLE has been associated with several HLA aplotypes, Fcγ receptor polymorphisms, and complement abnormalities, such as deficiencies in early components of the complement pathways, namely, C1q, C2,

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Table 159.1
Criteria for the classification of systemic lupus erythematosus

ACR 1982 criteria[a]	ACR 1997 criteria[b]
1. Malar "butterfly" rash	1. Malar "butterfly" rash
2. Discoid rash	2. Discoid rash
3. Photosensitivity	3. Photosensitivity
4. Oral or nasal mucocutaneous ulcerations	4. Oral or nasal mucocutaneous ulcerations
5. Nonerosive arthritis	5. Nonerosive arthritis
6. Nephritis[c] Proteinuria > 0.5 g/die Cellular casts	6. Nephritis[c] Proteinuria > 0.5 g/die Cellular casts
7. Encephalopathy[c] Seizures Psychosis	7. Encephalopaty[c] Seizures Psychosis
8. Pleuritis or pericarditis	8. Pleuritis or pericarditis
9. Cytopenia	9. Cytopenia
10. Positive immunoserology[c] Antibodies to dsDNA Antibodies to Sm nuclear antigen Positive LE-cell preparation Biologic false-positive test for syphilis	10. Positive immunoserology[c] Antibodies to dsDNA Antibodies to Sm nuclear antigen Positive finding of antiphospholipid antibodies based on: (a) IgG or IgM anticardiolipin antibodies *or* (b) Lupus anticoagulant *or* (c) False-positive serologic test for syphilis for at least 6 months, confirmed by Treponema pallidum immobilization of fluorescent treponemal antibody absorption test
11. Positive antinuclear antibody test	11. Positive antinuclear antibody test

[a]Adapted from Tan EM, Cohen AS, Fries JF, et al. (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277
[b]Adapted from Hochberg MC (1997) Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 40:1725
[c]The presence of any one item satisfies the criterion

and C4, high incidence of C4 null alleles and abnormal complement receptors. The genetic factors predisposing to juvenile SLE may differ across ethnic groups. Caucasians patients have a two-fold increase in the frequency of DR-B1 alleles, DR2, and DR3, but this association is not seen in non-Caucasians. Ethnic differences have been reported for Fcγ receptor polymorphisms as well.

Epidemiology

The median age at diagnosis in juvenile SLE ranges from 11–12 years, with disease onset under the age of 8 years occurring in <20% of cases. Although the disease is more common in females than males, the female:male ratio in juvenile SLE (4–5:1) is lower than that seen in adult-onset SLE (9:1). Similar to adult-onset SLE, juvenile SLE is more common and diagnosed at a younger age in non-Caucasian than in Caucasian patients. Incidence and prevalence rates of juvenile SLE have been reported to be 0.3–0.9 per 100,000 children/year and 3.3–8.8 per 100,000 children/year, respectively. The disease frequency differs between ethnic groups. Overall, it is more common in nonwhite populations, particularly in Hispanics, Afro-Americans, Afro-Caribbean, Native Americans, and Asians.

Clinical Manifestations

Children and adolescent with SLE often present with nonspecific constitutional symptoms, such as fever,

fatigue, malaise, and weight loss. Signs and symptoms related to involvement of visceral organs may be already detectable at disease onset or develop throughout the disease course.

Mucocutaneous manifestations. Skin disease is common in juvenile SLE, both at disease onset and during disease exacerbations, and is very heterogeneous (Table 159.2). The most characteristic manifestation is the classic "butterfly" or malar rash (Fig. 159.1), which is observed at onset in 30–50% of patients. It is characterized by symmetrical erythema and edema that are typically centered over the malar eminences and over the bridge of the nose, and sometimes extend to the forehead and the V area of the neck; the nasolabial folds are typically spared. The rash is usually confluent and well demarcated, and may be slightly raised. The malar rash may be precipitated by exposure to sunlight (photosensitivity) but is non-scarring.

A number of other dermatologic manifestations can occur in juvenile SLE. Maculopapular rashes resulting from vasculitis or perivasculitis may be seen anywhere in the body, particularly on sun-exposed areas, such as the face and the upper-anterior chest (Fig. 159.2). These lesions, that are sometimes painful, may also involve the palms and soles. More rarely, cutaneous disease may present as a more widespread morbilliform or exanthematous eruption, or in an extremely acute form that can simulate toxic epidermal necrolysis. Petechial and purpuric eruptions may be related to perivasculitis or be secondary to thrombocytopenia. Raynaud phenomenon is seen in some patients.

Discoid lupus occurs rarely in pediatric patients. The discoid lesions consist of areas of flat or slightly elevated, sharply demarcated, red–purple, papulosquamous patches with adherent scales and follicular plugging, which most commonly occur in sun-exposed areas, such as the scalp and the limbs, in an asymmetric distribution.

Alopecia is a common feature of juvenile SLE. It is associated with disease activity and is usually characterized by diffuse hair thinning, which initially affects frontal hairs. The hairs become brittle and kinky, and are prone to breaking off. This phenomenon is generally referred by the child or the parents as an excessive hair falling on the pillow, in the comb, or after shampooing. This alopecia is usually non-scarring and more often causes limited

Table 159.2
Cutaneous manifestation of SLE

Acute manifestations
Malar rash
Photosensitivity
Generalized erythema
Subacute manifestations
Annular lesions
Papulosquamous lesions
Chronic manifestations
Discoid lupus erythematosus
Lupus panniculitis
Lupus tumidus
Nonspecific manifestations
Alopecia
Urticarial lesions
Cutaneous vasculitis
Bullous lupus
Associated with antiphospholipid antibodies
Livedo reticularis
Leg ulcerations
Cutaneous necrosis or gangrene
Thrombophlebitis

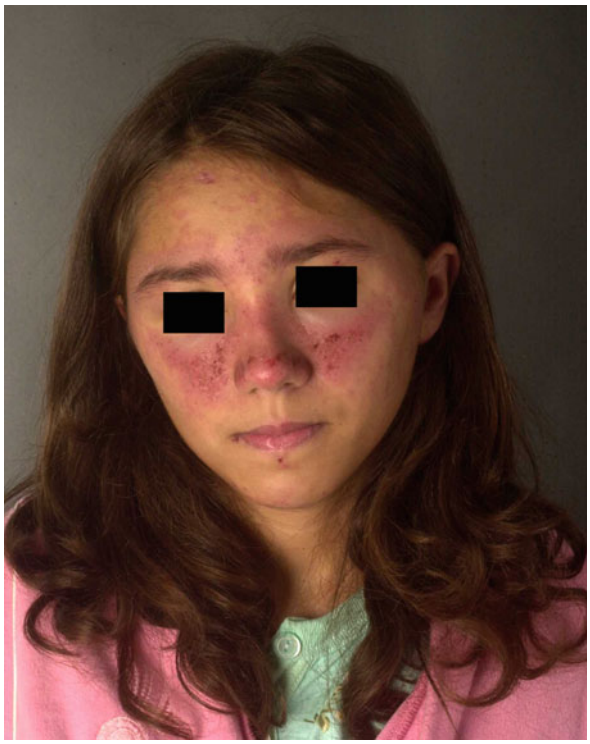

Figure 159.1
Malar "butterfly" rash in a 13-year-old girl with systemic lupus erythematosus

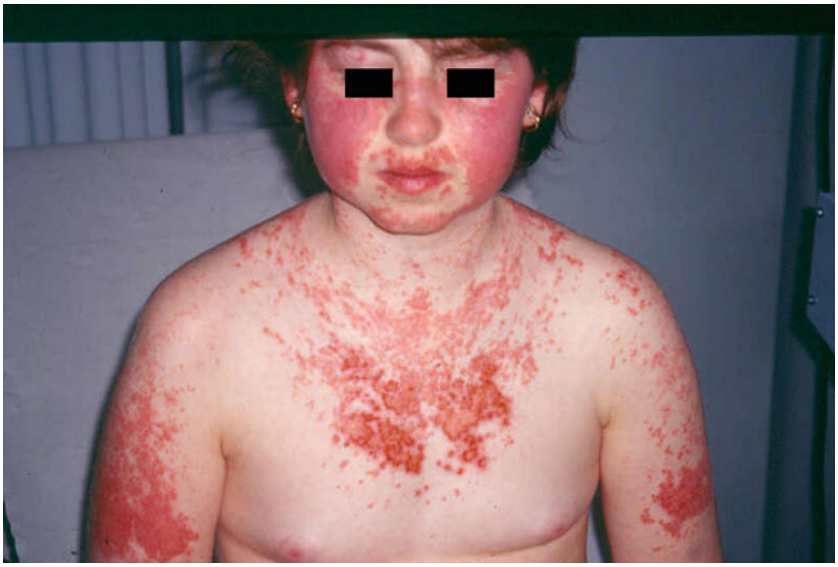

Figure 159.2
Vasculitic rash over the chest and arms in a 12-year-old girl with systemic lupus erythematosus

upset. In contrast, irreversible scarring alopecia from permanent follicular destruction is rare.

Other uncommon cutaneous manifestations of juvenile SLE are urticarial and bullous (pemphigoid-like) lesions. Fingers, toes, or face red–purple patches and plaques that are precipitated by cold exposure and are reminiscent of simple chilblains or pernio lesions are occasionally observed in children. Diffuse hyperpigmentation, usually most prominent on the light-exposed and extensor surfaces of the body, is another important, though rare, dermatologic feature of juvenile SLE. Shallow, painful ulcers of the lips, gums, palate, and nasal mucosa occur in 10–15% of patients and frequently occur during disease exacerbations. Similar lesions are seen occasionally on the vulvar surface.

A number of skin changes that may develop in patients with lupus have been associated with the presence of circulating antiphospholipid antibodies. They include leg ulcers, livedo reticularis, cutaneous necrosis, gangrene of the digits or extremities, thrombophlebitis, necrotizing purpura, and nailfold infarcts. Leg ulcers, which occur more often in the lower limbs, are painful and sharply marginated; they have a necrotic center or base and leave a white atrophic scar on healing. Livedo reticularis has been related to the stagnation of blood in dilated superficial capillaries and venules, and affects primarily the skin of the tights, shins, and forearms.

Musculoskeletal disease. Most patients with juvenile SLE have musculoskeletal involvement, mainly arthritis or arthralgia, with or without associated tenosynovitis. Arthritis is typically symmetric and nonerosive and affects large and small joints. Joint involvement is usually marked by only mild to moderate effusion; however, tenderness and pain on passive motion with reduced range of movements may be present. Deforming arthritis is uncommon, although hand arthritis can lead to ligament damage and significant joint laxity. Although myalgia is frequent, true myositis with muscle weakness is seen in less than 10% of patients. When present, myositis can be difficult to distinguish form steroid-related myopathy. Avascular necrosis is a known complication of corticosteroid therapy (*Fig. 159.3*). It is seen in 10% of cases and may be more common in children than in adults. The juxtaarticular regions of the large, weight-bearing joints, particularly hips and knees, are typically affected. Osteoporosis and vertebral fractures may occur in patients on long-term corticosteroid treatment and are often asymptomatic. Inflammatory musculoskeletal pain should be distinguished from noninflammatory pain than results from a pain amplification syndrome secondary to mood or emotional disturbance.

Renal disease. Overall, 60–80% of children with SLE have urinary or renal function abnormalities early in the disease course. Kidney involvement becomes manifest most frequently in the first 2 years from disease onset. However, lupus nephritis may also occur later in the disease course. Treating physicians should routinely screen for hematuria and proteinuria, as well as for laboratory

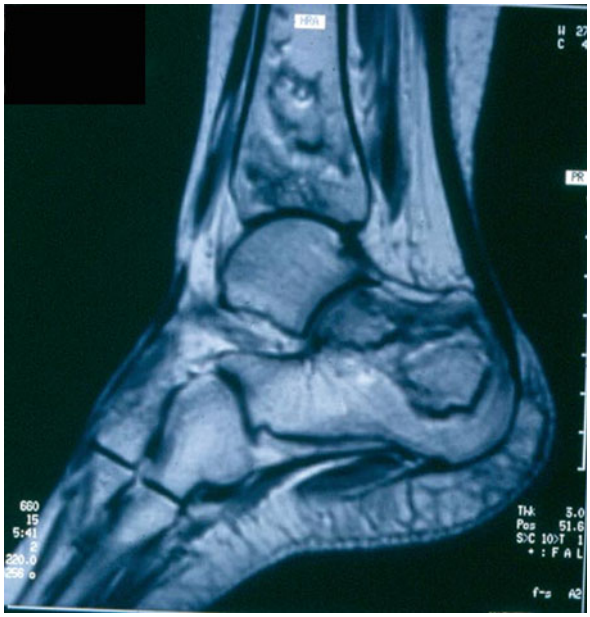

Figure 159.3
MRI of the right ankle showing avascular necrosis of the distal tibia, astragalus, and calcaneus

parameters of renal function and hypertension. A high index of suspicion should be maintained, and symptoms such as headache, weight gain, and swelling of the extremities should raise the alarm for possible renal involvement. Typically, microscopic hematuria and proteinuria precede more overt signs of nephritis. Although it may be easy to predict the histologic lesion in patients who present with severe renal failure and significant hypertension, in less severe cases, it is difficult to predict the morphologic pattern based on clinical and laboratory parameters, including urine sediment and the amount of proteinuria. For this reason and because treatment differs for diverse forms of SLE nephritis, it is suggested that renal biopsy be always performed at the time of initial presentation in patients who have significant abnormalities on urinalysis or abnormal renal function. It is common view that early diagnosis may improve the long-term outcome of patients with proliferative lupus nephritis.

The World Health Organization (WHO) has defined a morphologic classification of kidney biopsies in SLE, which was revised in 2003 by the International Society of Nephrology and the Renal Pathology Society (*Table 159.3*). The spectrum of lupus nephritis ranges from mild mesangial proliferation (class II) to diffuse proliferative glomerulonephritis (class IV) to membranous nephritis (class V). Patients with advanced glomerular sclerosis are classified in class VI. Among patients with

Table 159.3
Abbreviated International Society of Nephrology/Renal Pathology Society Working Group (ISN/RPS) classification of lupus nephritis 2003

Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis
Class V	Membranous lupus nephritis
Class VI	Advanced sclerosing lupus nephritis

Source: Adapted from Weening JJ, D'Agati VD, Schwartz MM et al. (2004) The classification of glomerulonephritis in systemic lupus erythematosus revisited. Kidney Int 65:521–530

active nephritis, those who have class III or class IV lupus nephritis carry the greatest risk of developing end-stage renal disease. Recently, definition of the degree of active inflammation and cumulative damage with activity and chronicity scores, respectively, has been proposed. However, the prognostic value of these scores is still uncertain.

Neuropsychiatric disease. Involvement of the CNS and peripheral nervous system is another major cause of morbidity and mortality in juvenile SLE. Overt neuropsychiatric disease may be seen in approximately one third of patients. However, a greater proportion of cases may have subtle manifestations, particularly cognitive dysfunction, when examined with specific neuropsychiatric testing. Patients with lupus may develop a wide variety of neuropsychiatric manifestations. In 1999, the American College of Rheumatology provided a classification of neuropsychiatric lupus into 19 separate disease entities (*Table 159.4*). However, patients with neuropsychiatric lupus may meet criteria for more than one of these entities. Although neuropsychiatric disease is seen more often in the first year after disease presentation, it can also occur later in the disease course in around one quarter of patients.

Headache is the most common neuropsychiatric manifestation. However, a mild isolated headache may be due to causes unrelated to SLE. A true lupus headache is refractory to standard analgesic treatment. When the headache is severe or unremitting, then investigations are warranted because it is often due to an organic cause, such as vasculitis, cerebral vein thrombosis, or raised intracranial pressure caused by CNS infection or pseudotumor cerebri.

Psychiatric manifestations occur in up to 40% of pediatric patients with SLE, and they are mostly characterized by psychosis, depression, cognitive dysfunction, or

Table 159.4
1999 ACR nomenclature and case definitions for neuropsychiatric SLE

Central nervous system	Peripheral nervous system
Aseptic meningitis	Guillan–Barrè syndrome
Cerebrovascular disease	Autonomic disorder
Demyelinating syndrome	Mononeuropathy
Headache	Cranial neuropathy
Movement disorder	Myastenia-like syndrome
Myelopathy	Plexopathy
Seizure disorder	Polyneuropathy
Acute confusional state	
Anxiety disorder	
Cognitive dysfunction	
Mood disorder/depression	
Psycosis	

Source: Adapted from The American College of Rheumatology nomenclature and case definitions for neuropsychiatric lupus syndromes. Arthritis Rheum 42:599–608

confusion. Psychiatric symptoms are frequently associated with headache. Laboratory markers of lupus activity can be negative, and brain parenchymal imaging studies, including MRI and CT scan, are frequently normal. The diagnosis is, therefore, solely based on clinical features. The differential diagnosis between lupus psychosis and steroid-induced psychosis is often difficult. The usefulness of single-emission computed tomography (SPECT) has been advocated by some authors but denied by others. It has been suggested that the presence of mania, head banging, and excessive crying (uncommon in neuropsychiatric lupus) are useful to differentiate lupus from steroid-induced psychosis.

Cognitive dysfunction occurs in about 30% of patients and may range from concentration and attention defect, memory loss, and decreased school performance, to frank confusion, and coma. Cerebrovascular disease is seen in up 25% of pediatric patients. It may be secondary to small vessel inflammation or to the presence of lupus anticoagulant and anticardiolipin antibodies (antiphospholipid syndrome). Seizures are frequent at disease presentation and are often associated with other CNS manifestation, but can also occur in isolation. Generalized seizures are more frequent that localized seizures. Seizures may also be secondary to uremia, hypertension, or CNS infection. Chorea is more common in juvenile than in adult-onset SLE. It is generally accompanied by the presence of antiphospholipid antibodies and may occur in isolation or together with other manifestations of the antiphospholipid syndrome.

Cranial and peripheral neuropathies are rare in juvenile SLE. Cranial nerve involvement is most common and may present with optic neuropathy, oculomotor palsy, facial palsy, or trigeminal neuropathy. Transverse myelitis may present with acute paraplegia or quadriplegia, and may be associated with antiphospholipid antibodies. Other clinical manifestations are polyneuropathy, mononeuritis, miastenia gravis-like syndrome, demyelinating disease, and Guillan–Barrè syndrome.

Cardiac involvement. The most common form of cardiac involvement is pericarditis with pericardial effusion. Myocarditis and valvular disease are less frequent, and ischemic heart disease secondary to coronary artery vasculitis is rare. Symptomatic pericarditis occurs in 15–25% of patients, whereas up to 68% of patients have echocardiographic abnormalities consistent with pericarditis. In case of severe pericardial effusion, constriction or tamponade may ensue. Valvular heart disease may be associated with the presence of antiphospholipis antibodies or Libman–Sacks endocarditis. Myocarditis can occur in about 15% of children and may lead to congestive heart failure, cardiomegaly, and arhitmias. For this reason, tachycardia without fever in lupus patients should be always investigated.

The major source of cardiac morbidity associated with juvenile SLE is premature artherosclerosis. A number of traditional and nontraditional atherosclerotic risk factors, including lipid abnormalities, abnormal endothelial function, nephritis, and heavy proteinuria, have been linked to the development of early atherosclerosis in juvenile SLE. Recent studies have shown that children and adolescents with lupus have myocardial perfusion defects, abnormal vascular reactivity, and increased carotid intima-media thickness, suggesting that pediatric patients are exposed to an increased risk for myocardial infarction and cerebral vascular events early in life. It is believed that the chronic inflammatory process of lupus is the leading risk factor for premature atherosclerosis. The responsibility of corticosteroids is less clear.

Pulmonary involvement. Pleuritis and pleural effusions are frequently seen in patients with juvenile SLE. Less common forms of pulmonary disease include lupus pneumonitis, pulmonary hemorrhage, pulmonary hypertension, pulmonary embolism, and pneumothorax. Symptoms suggesting lung disease include persistent dry cough, chest pain, dyspnea, and orthopnea, but the course can be occasionally subclinical. Acute lupus pneumonitis is characterized by bibasilar pulmonary infiltrates and atelectasia. It usually responds to corticosteroid therapy.

However, an infectious etiology for the pulmonary infiltrate should be always searched for. Pulmonary hemorrhage is rare but should be considered in children who develop sudden pallor, tachycardia, and falling hematocrit, even if hemoptysis is absent. Chronic interstitial lung disease is not described in children with lupus.

Hematologic manifestations. Leukopenia, anemia, and thrombocytopenia are commonly seen in pediatric patients with SLE. Cytopenia affecting one or more cell lines is frequent in poorly controlled disease and may be a marker of disease activity. Anemia is usually microcytic and hypocromic as related to chronic disease. Thrombocytopenia may be the presenting symptom of SLE in children and adolescents, and may predate the development of other signs and symptoms of SLE by many years. In general, isolated hematologic involvement at disease onset is observed more frequently in juvenile SLE than in adult-onset SLE. All children who have chronic autoimmune thrombocytopenic purpura should have antinuclear antibodies determined because, if positive, they are at high risk of developing SLE. The Coombs' test is positive in approximately 30–40% of patients, but less than 10% of patients have overt hemolysis. When present, autoimmune hemolytic anemia may be severe enough to require transfusion.

Leukopenia occurs in 20–40% of cases of juvenile SLE. It may consist of either lymphopenia or granolocytopenia, although lymphopenia is more common. Lymphopenia is a reliable indicator of general disease activity but does not require a specific therapy. A profound lymphopenia may herald a significant risk for serious infection. Neutropenia may be due to central depression of granulopoiesis, antigranulocyte antibodies, or splenic sequestration.

The most common coagulation abnormalities seen in juvenile SLE are related to the presence of lupus anticoagulant, which is observed in 20–30% of cases. Patients with lupus anticoagulant and other antiphospholipid antibodies, namely, anticardiolipin antibodies and anti-β2 glycoprotein I antibodies, have an increased incidence of venous and arterial thrombosis and other clinical manifestations, such as chorea, livedo reticularis, thrombocytopenia, Coombs' positive hemolytic anemia, cardiac-valve abnormalities, and skin ulcers (so-called antiphospholipid syndrome). Occasionally, patients with these antibodies may develop a catastrophic antiphospholipid syndrome, which is characterized by widespread microangiopathic changes and thrombosis in multiple organs. Because antiphospholid antibodies react with cardiolipin used in the serologic test for syphilis, their presence may result in a false-positive test.

Patients with juvenile SLE may develop macrophage activation syndrome, a severe, potentially life-threatening complication characterized clinically by nonremitting high fever, pancytopenia, hepatosplenomegaly, hepatic dysfunction, encephalopathy, coagulation abnormalities, and sharply increased levels of ferritin. The pathognomonic feature of the syndrome is seen on bone marrow examination, which reveals numerous morphologically benign macrophages actively phagocytosing hematopoietic cells. This syndrome is associated with an excessive activation and proliferation of T lymphocytes and macrophages with massive hypersecretion of proinflammatory cytokines. Macrophage activation syndrome may occur spontaneously, as a complication of active underlying disease, or may be triggered by an infection or a change in drug therapy.

Gastrointestinal and liver disease. The most common gastrointestinal complaint is abdominal pain, which can be related to peritoneal inflammation due to serositis, vasculitis, pancreatitis, pseudo-obstruction, or paralytic ileus. Lupus enteropathy may present as acute ischemic gut inflammation or protein-losing entheropathy. This condition is suggested by the occurrence of cramping abdominal pain and diarrhea. The same symptoms may also be secondary to mesenteric vasculitis or thrombosis, however. Gastrointestinal vasculitis carries a high risk for perforation, whose symptoms may be masked by ongoing high-dose corticosteroid therapy. Pancreatitis may occur in less than 5% of patients and may be secondary to active inflammation, infection, or corticosteroid or azathioprine therapy. Splenomegaly may reflect the generalized inflammatory state or, occasionally, macrophage activation syndrome. Hepatomegaly is frequent, as is the abnormality of liver function tests. Liver involvement may be due to lupoid hepatitis, Budd–Chiari syndrome, macrophage activation syndrome, or, more rarely, intrahepatic necrotizing arteritis with nodular regenerative hyperplasia. Mild liver function test increase may be secondary to fatty liver in patients who have received prolonged corticosteroid therapy.

Autoantibodies. The hallmark of SLE is the production of a wide array of autoantibodies directed against several antigens. The most common are the antinuclear antibodies, which are found in up to 100% of patients. ANA represent an excellent screening tool but lack specificity because they can be found in apparently healthy individuals and in patients with different rheumatic diseases or other conditions. Anti-double-stranded anti-DNA antibodies are more specific for lupus and often reflect the degree of serologic disease activity. Other autoantibodies seen in patients with

juvenile SLE include anti-RNP, anti-Sm, anti-Ro, anti-La, and antiphospholipid antibodies. Anti-ribosomal P antibodies have been linked to the development of psychosis.

Diagnosis

The diagnosis of juvenile SLE is based on the typical constellation of clinical and laboratory features. Although the American College of Rheumatology criteria (*Table 159.1*) were designed as classification criteria, they are widely used for diagnosis. However, not all patients have at least 4 criteria at the time of disease presentation. Indeed, the clinical spectrum of SLE is protean, and early identification can be challenging when the disease occurs in monosymptomatic or oligosymptomatic form, or presents with atypical clinical manifestations. Thus, patients suspected to have lupus who demonstrate fewer than four criteria should receive appropriate medical treatment

Differential Diagnosis

Because of the multisystem nature of SLE, lupus must be considered in the differential diagnosis of many conditions, ranging from fevers of unknown origin, to arthritis, anemia, thrombocytopenia, nephritis, and neurologic dysfunction. The differential diagnosis includes other rheumatic diseases, including rheumatic fever, post-streptococcal glomerulonephritis, hematologic malignancies, immune thrombocytopenic purpura, and idiopathic hemolytic anemia. In general, lupus should be considered in patients with a systemic inflammatory illness and multiorgan symptoms, especially if there are hematologic or urinalysis abnormalities, or if autoantibodies are found.

Drug-Induced Lupus

Exposure to some drugs, including anticonvulsivants, sulfonamides, and antiarrhythmic agents, may induce a lupus-like disease. Many of these patients have antihistone antibodies. The typical symptoms of fever, rash, and pleuro-pericardial disease usually abate with discontinuation of the inciting drug. Serum complement levels generally remain normal, and visceral organ involvement, namely renal disease, are rare.

Treatment

General Aspects of Management

The therapeutic management of juvenile SLE is driven by the affected target organs and disease severity. Early disease control and a comprehensive approach to care are crucial to reduce long-term morbidity and mortality. Meticulous and frequent reevaluation of clinical signs and laboratory tests is fundamental, especially for monitoring of renal disease and detection of disease flares. Prompt recognition and treatment of disease flare may improve patient outcome.

In all patients with hypertension, blood pressure should be tightly controlled with the use of antihypertensive agents. Because lupus patients are known to have an increased risk of early atherosclerosis, cardiac risk factors should be minimized with diet, exercise, and maintenance of a healthy life-style. In patients on long-term corticosteroid therapy, osteoporosis prevention with calcium and vitamin D supplementation is advocated. Sun exposure should be minimized and include use of a sunscreen, particularly in patients with photosensitive rash. Patients with antiphospholipid antibodies should be advised about the need of minimizing exposure to other pro-thrombotic factors, such as smoke, alcohol, and use of estrogen contraceptive pills. In case of development of antihospholipid antibody-related thrombotic complications, long-term anticoagulation is prescribed.

Pharmacologic Therapy

Nonsteroidal anti-inflammatory agents are used to treat arthralgia and arthritis. However, these medications should be used with caution because patients with lupus are more susceptible to hepatotoxicity. Ibuprofen is generally avoided because of reports of ibuprofen-related aseptic meningitis in SLE patients.

Hydroxychloroquine is often used to treat skin lesions and musculoskeletal manifestations. Because its major side effects are retinal maculopathy, ophthalmologic evaluation is required every 6 months. However, ocular toxicity is rare if the dose is kept to less than 6.5 mg/kg/day. Hydroxychloroquine may also reduce the risk of thromboembolic disease and lowers lipid levels. It might have a general effect on prevention of lupus flares as well.

The mainstay of pharmacological therapy of juvenile SLE is represented by corticosteroids, which can be administered orally or intravenously, depending on clinical manifestations and personal physician's experience.

Prednisone or prednisolone (1–2 mg/kg/day) are started at disease onset in order to attain remission. Initial dose may be divided into 2 or 3 daily doses, on the basis of disease severity. Administration of high-dose pulse intravenous methylprednisolone (30 mg/Kg/day to a maximum of 1 g/day for 1–3 consecutive days) is frequently used with the aim of achieving prompt control of active disease or disease exacerbation, particularly in the presence or severe renal, CNS, or hematologic involvement, and of preventing adverse effects of daily corticosteroid administration. Lower doses of prednisone (e.g., 0.5 mg/kg/day) may be used in patients with mild disease severity or for the treatment of skin rash or musculoskeletal manifestations. Once a satisfactory control of disease manifestations is obtained, corticosteroid dose is gradually reduced until the minimal dose that is sufficient to maintain remission over the long-term.

Patients with severe disease or major visceral organ involvement may require cytotoxic therapy. Pulse intravenous cyclophosphamide has been found to maintain renal function and prevent progression in patients with proliferative glomerulonephritis. However, the optimal therapeutic regimen and length of therapy remain controversial. Cyclophosphamide is also used to treat vasculitis, pulmonary hemorrhage, CNS involvement, and life-threatening hemolytic anemia. Adverse effects include secondary infections, gonadal dysfunction, and increased risk of later malignancies.

Azathioprine has been used to prevent renal progression, but nowadays its main indication is long-term maintenance therapy after induction with cyclophosphamide. This drug may have a steroid-sparing role in the treatment of other disease manifestations, namely, autoimmune cytopenia. Mycophenolate mophetil is an alternative to cyclophosphamide for some type of lupus nephritis, particularly membranous nephritis, and has an efficacy comparable to azathioprine as maintenance therapy in proliferative nephritis. This drug has been recently proposed as a less toxic and equally efficacious alternative to cyclophosphamide in the induction therapy of proliferative lupus nephritis. However, this indication is still controversial. Methotrexate and cyclosporine are also used as steroid-sparing agents for some specific disease manifestations, such as arthritis or cytopenia.

In recent years, there has been increasing interest for the use of biologic medications in SLE. The anti-CD20 monoclonal antibody rituximab has been tried, alone or in combination with cyclophosphamide, with encouraging results in the treatment of severe and refractory cases of proliferative glomerulonephritis, CNS disease, or cytopenia. Use of rituximab in the management of lupus nephritis is currently being explored with the aim of designing therapeutic protocols that allow for a lower cumulative cyclophosphamide dose. Side effects of rituximab include infusion reactions, increased risk for infection, and demyelinating syndromes. Autologous stem cell and allogeneic bone marrow transplantation have been proposed for patients with very severe, resistant disease.

Outcome and Prognosis

The natural history of juvenile SLE is widely variable, ranging from acute, life-threatening disease to long-lasting, smoldering disease. The prognosis is worse in patients with involvement of major visceral organs, particularly the kidney and the CNS. The major causes of death in patients with juvenile SLE currently include infection, nephritis, CNS disease, and pulmonary hemorrhage. However, over the past two decades there has been a marked improvement in survival among patients with juvenile SLE. In some recent reports, the 5-year survival rate approaches 100% and the 10-year survival rate is close to 90%.

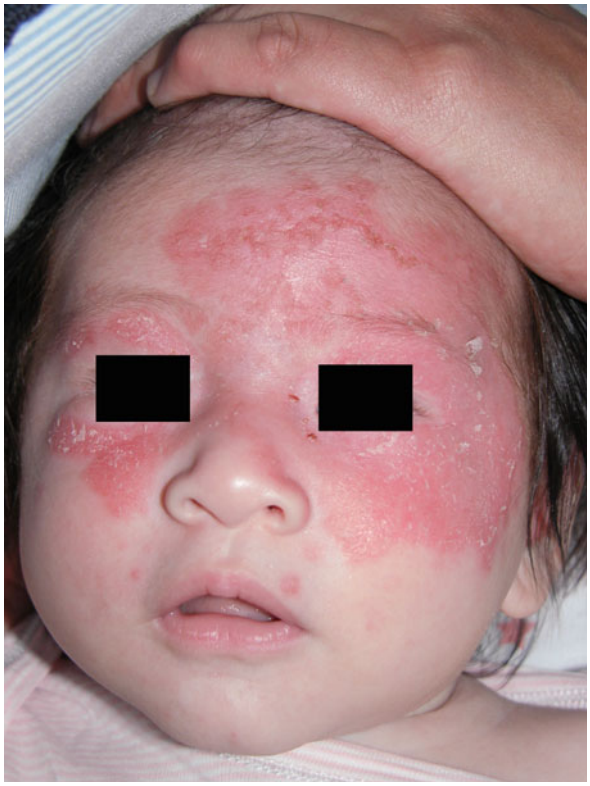

Figure 159.4
Typical cutaneous rash of neonatal lupus

As a result of the prolonged life expectancy, children and adolescents with SLE are now exposed to an increased risk of morbidity related to the sequelae of disease activity, side effects of medications, and comorbid conditions, such as recurrent infections, accelerated atherosclerosis, osteoporosis, and hypertension. The development of cumulative organ damage has been observed in 50–60% of patients, with the musculoskeletal, renal, and neuropsychiatric systems being most frequently affected. Furthermore, children and adolescents with SLE have been found to have poorer HRQL, particularly in the physical domain, and lower socioeconomic achievements than their healthy peers. These issues emphasize the need of continuing a careful long-term follow-up of currently treated patients in order to understand the overall impact of the disease and its therapy. Furthermore, future treatments and treatment strategies should be aimed not only at better controlling disease activity but also at reducing the development of nonreversible organ damage.

Neonatal Lupus

Newborns of mothers affected with SLE or Sjogren's syndrome, who possess anti-Ro/SSA or anti-La/SSB antibodies, may develop lupus manifestations. The disease results from transplacental transfer of these autoantibodies between the twelfth and sixteenth weeks of gestation. Symptoms include congenital heart block, cutaneous rashes, hepatitis, thrombocytopenia, neutropenia, and pulmonary and neurologic disease. The rash occurs most frequently on the face and scalp (◉ *Fig. 159.4*) and may leave scars in 25% of cases. Treatment is supportive in most cases, although a course of steroids may be required in patients with severe manifestations. Severe thrombocytopenia may require corticosteroid or intravenous immunoglobulin therapy. Most manifestations resolve spontaneously, although congenital heart block is permanent and often requires cardiac pacemaker, either after birth or, when detected and sever, antenatally. Corticosteroid treatment of the pregnant mother after heart block is detected early in utero, and postnatal corticosteroids may be effective.

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160 Antiphospholipid Antibody Syndrome

Tadej Avčin

Definition/Classification

The antiphospholipid antibody syndrome (APS) is a multisystemic autoimmune disease characterized by thromboembolic events, pregnancy morbidity, hematologic, dermatologic, neurologic, and other manifestations in the presence of elevated titers of antiphospholipid antibodies (aPL). Antiphospholipid antibodies are a heterogeneous group of autoantibodies directed against negatively charged phospholipids or phospholipid-binding plasma proteins. The most relevant aPL for identifying patients at risk for immune-mediated thrombosis are anticardiolipin antibodies (aCL), antibodies against β_2 glycoprotein I (anti-β_2GPI) and lupus anticoagulant (LA).

The classification criteria for APS were developed by consensus and designate patients who suffered from vascular thrombosis or pregnancy morbidity associated with the presence of aPL, detected on two or more occasions at least 12 weeks apart (*Table 160.1*). These criteria were developed for classification of adult patients with APS and include pregnancy morbidity as a clinical criterion, which is not applicable for the pediatric population. A classification of "probable APS" has been given to patients with aPL that have non-criteria clinical features associated with APS such as livedo reticularis, thrombocytopenia, nephropathy, and neurologic manifestations. Catastrophic antiphospholipid antibody syndrome (CAPS) is a rare, life-threatening variant of APS, characterized by acute microvascular occlusive disease involving at least three organ systems in less than a week.

Etiology

The cause of APS remains unknown. It may occur as an isolated clinical entity (primary APS) or in association with autoimmune diseases, infections and malignancies. Primary, isolated APS accounts for approximately half of all pediatric patients with APS. The majority of cases associated with underlying autoimmune disease occur in patients with systemic lupus erythematosus (SLE) and lupus-like disease. Preceding or concomitant infections were found in approximately 10% of children with primary APS or APS associated with autoimmune disease. APS associated with malignancies is exceedingly rare in childhood and accounts for less than 1% of all pediatric APS cases.

Epidemiology

APS is considered the most common acquired hypercoagulation state of autoimmune etiology, and aPL were reported in up to 25% of unselected children with thrombosis. The average age of onset in 121 pediatric APS patients included in an international registry was 10.7 years with the female-to-male ratio 1.2:1. Children of all ethnic background have been affected with APS.

Antiphospholipid antibodies can be found in a high percentage of children that do not experience thrombosis. SLE is the autoimmune disease in which aPL occurs in highest percentage, with the reported mean frequencies of 44% for aCL, 40% for anti-β_2GPI, and 22% for LA, respectively. The estimated incidence of thromboembolic events in pediatric SLE patients with positive LA was 54% and with positive aCL 22%.

Low levels of aPL can be found in children without any underlying disorder. These naturally occurring aPL are usually transient and could be the result of previous infections or vaccinations that are common in the pediatric population. LA can be rarely found in apparently healthy children as an incidental finding of prolonged activated partial thromboplastin time (aPTT) in pre-operative coagulation screening. The risk of future thrombosis is exceedingly low in otherwise healthy children who were incidentally found to have positive aPL.

Pathogenesis

There is an accumulating experimental evidence that aPL may directly contribute to disease pathogenesis and are not just a simple serological marker of APS. The dominant antigenic targets in APS are β_2GPI and prothrombin.

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Table 160.1
2006 revised classification criteria for the antiphospholipid antibody syndrome (APS)

Clinical criteria	1. Vascular thrombosis One or more clinical episodes of arterial, venous, or small-vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria (i.e., unequivocal findings of appropriate imaging studies or histopathology). For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
	2. Pregnancy morbidity One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria	1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Hemostasis. 2. Anticardiolipin antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer, on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA. 3. Anti-β_2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma, present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA.

APS is present if at least one of the clinical criteria and one of the laboratory criteria are met

Multiple pathogenic mechanisms have been proposed by which aPL may predispose to thrombosis including interaction between aPL and endothelial cells, platelets, monocytes, activation of the complement system, and interaction with the proteins involved in the regulation of the coagulation cascade. At present, it cannot be discerned whether one dominant mechanism is responsible for venous, arterial, or small-vessel thrombosis.

Genetic associations in APS are suggested by the frequent findings of aPL in first-degree relatives of people with APS or with SLE. Family studies support that APS and aPL can occur in family clusters, but this is so only in a minority of patients. Some HLA-DR and -DQ types (e.g., B1, B8, and DR3) may occur with increased frequency among patients with APS, depending on the racial and ethnic backgrounds of patients studied. Experimental animal models as well as preliminary studies on the polymorphisms of candidate genes of inflammatory mediators suggest the association between inflammatory gene single nucleotide polymorphisms and thrombosis in APS.

Pathology

The histopathologic alterations in APS have been described as thrombotic, microangiopathic, ischemic, or coincidental with underlying disease–related pathology. Thrombotic vaso-occlusive lesions in APS may involve any organ or system and, histopathologically, do not differ from those seen in other prothrombotic conditions. Thrombotic lesions are mainly non-inflammatory and may occur in large or small vessels. Some patients with APS can develop true vasculitis, which is in general causally not related to aPL but to the coexisting underlying disease, most commonly SLE.

Microangiopathic lesions can be characteristic of APS and appears to be significantly underestimated. A major role in the initiation and development of acute microangiopathic lesions is that of endothelial cells of the small blood vessels that are activated and injured by aPL.

Clinical Manifestations

Children with aPL can present with various thrombotic (*Table 160.2*) or nonthrombotic clinical manifestations (*Table 160.3*). The presence of vascular occlusive event is required for the diagnosis of definite APS, but children with aPL more frequently present with nonthrombotic clinical manifestations. At the time of the initial thrombotic event in children with definite APS, the estimated frequencies of associated nonthrombotic manifestations

Table 160.2
Venous and arterial thromboses manifestations of pediatric antiphospholipid syndrome

Vessel involved	Clinical manifestations
Venous sites	
Limbs	Deep vein thrombosis
Skin	Livedo reticularis, chronic leg ulcers, superficial thrombophlebitis
Large veins	Superior or inferior vena cava thrombosis
Lungs	Pulmonary thromboembolism, pulmonary hypertension
Brain	Cerebral venous sinus thrombosis
Eyes	Retinal vein thrombosis
Liver	Budd-Chiari syndrome, enzyme elevations
Adrenal glands	Hypoadrenalism, Addison's disease
Arterial sites	
Limbs	Ischemia, gangrene
Brain	Stroke, transient ischemic attack, acute ischemic encephalopathy
Eyes	Retinal artery thrombosis
Kidney	Renal artery thrombosis, renal thrombotic microangiopathy
Heart	Myocardial infarction, cardiomyopathy
Liver	Hepatic infarction
Gut	Mesenteric artery thrombosis
Bone	Infarction

Table 160.3
Nonthrombotic clinical manifestations associated with antiphospholipid antibodies in pediatric population

Organ system	Clinical manifestations
Hematologic	Thrombocytopenia
	Autoimmune hemolytic anemia
	Leucopenia
	Lupus anticoagulant-hypoprothrombinemia syndrome
Skin	Livedo reticularis
	Raynaud's phenomenon
	Subungual splinter hemorrhages
	Skin ulcers
	Cutaneous necrosis
Central nervous system	Chorea
	Epilepsy
	Migraine headache
	Transverse myelitis
	Multiple sclerosis-like disorders
	Sensorineural hearing loss
	Cognitive defects
	Psychosis
	Guillain–Barré syndrome
Heart	Libman–Sacks endocarditis

are 38% for hematologic manifestations, 18% for dermatologic manifestations, and 16% for nonthrombotic neurologic manifestations. All children with aPL presenting either with thrombotic or nonthrombotic manifestations require thorough assessment for evidence of underlying systemic disease, since APS may develop as an initial manifestation of SLE.

Thromboses

Vascular occlusive events in APS may involve arteries, veins, or small vessels in all organs (*Table 160.2*). Venous thrombosis is the most common thrombotic event occurring in up to 60% of pediatric APS patients. The most frequently reported site of venous thrombotic event is deep vein thrombosis in the lower extremities, followed by cerebral sinus vein thrombosis, portal vein thrombosis, deep vein thrombosis in the upper extremities, and superficial vein thrombosis. Venous thrombotic events are particularly common in APS associated with pediatric SLE, and the strongest predictor of thrombosis risk in these patients is persistent LA positivity. Arterial thrombosis occurs in approximately 30% of pediatric APS patients. The most frequently reported site of arterial thrombotic event is ischemic stroke, followed by peripheral arterial thrombosis.

Small-vessel thrombosis occurs in less than 10% of pediatric APS patients and may present as localized small-vessel thrombosis or an aggressive microvascular occlusive disease (*Fig. 160.1*). Localized small-vessel thrombosis most commonly appears as isolated thrombosis of digital vessels or renal thrombotic microangiopathy. Aggressive microvascular occlusive disease is characteristic of catastrophic APS, which is a potential life-threatening variant of APS leading to multiorgan failure. The most commonly affected organ systems include the kidney, lung, central nervous system, heart, and skin. Catastrophic APS in children is most frequently triggered by preceding infections, SLE flares, or in association with underlying malignancy.

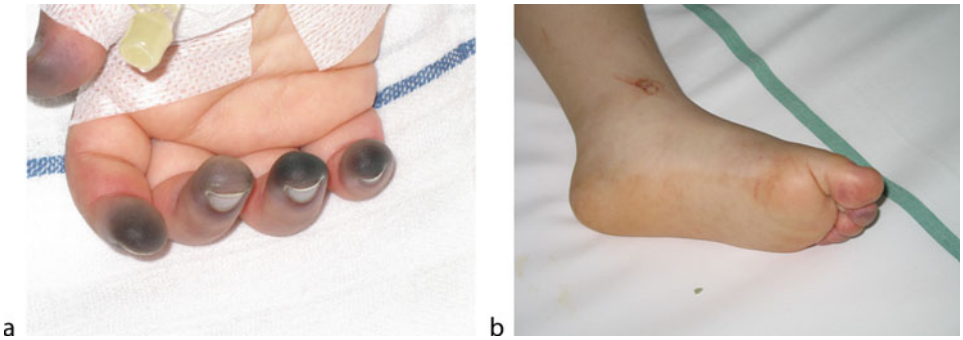

Figure 160.1
Necrotic changes on the fingertips (a) and toes (b) in a child with atypical hemolytic uremic syndrome complicated by thrombotic microangiopathy associated with antiphospholipid antibodies

Hematologic Manifestations

The characteristic hematologic manifestations associated with aPL in children are thrombocytopenia, autoimmune hemolytic anemia, and leucopenia. Thrombocytopenia is usually mild, with platelet counts greater than 50×10^9/L and is rarely associated with hemorrhagic phenomena. Thrombocytopenia may appear as an isolated clinical manifestation, associated with Coombs-positive hemolytic anemia (Evans syndrome) or along with other APS manifestations.

The acquired LA-hypoprothrombinemia syndrome is a rare hematologic complication consisting of a severe bleeding diathesis associated with the presence of a certain subtype of LA, namely the antiprothrombin antibodies that cause rapid depletion of plasma prothrombin.

Neurologic Manifestations

Typical neurologic manifestations are ischemic stroke and cerebral sinus vein thrombosis, both caused by thrombotic occlusion of cerebral vessels. Several other neurologic manifestations have been associated with the presence of aPL, including various movement disorders Video epilepsy, migraine, transverse myelitis, multiple sclerosis-like disorders, sensorineural hearing loss, cognitive defects, psychiatric diseases, and Guillain–Barré syndrome. These manifestations are not fully explained by the ischemic pathophysiologic mechanism, and primary immunologic effects of aPL have been suggested such as direct interaction with neuronal tissue or immune complex deposition in the cerebral blood vessels wall.

Other Manifestations

Dermatologic manifestations are frequently present in patients with APS, ranging from minor signs to life-threatening conditions such as widespread cutaneous necrosis. The most common findings are livedo reticularis, Raynaud's phenomenon, digital necrosis, subungual splinter hemorrhages, and skin ulcers. Livedo reticularis and especially the coarser variant called livedo racemosa are considered a major clinical feature of APS, strongly associated with cerebral and ocular ischemic arterial events.

Cardiac involvement may affect all tissues and include valvular disease (Libman–Sacks endocarditis), occlusive coronary artery disease, cardiomyopathy (due to multiple small vascular occlusions), and intracardiac thrombosis. Pulmonary manifestations include pulmonary embolism, infarction, and pulmonary hypertension. Antiphospholipid antibodies are also associated with renal, hepatic, digestive, and adrenal manifestations resulting from occlusive vascular disease of intra-abdominal vessels.

Osteoarticular manifestations such as avascular necrosis of bone, non-traumatic fractures, and bone marrow necrosis are rarely seen in APS patients. Association between aPL and Perthes disease has been suggested in pediatric population.

Perinatal Complications Associated with Antiphospholipid Antibodies

The presence of maternal aPL during pregnancy is associated with a number of serious obstetric and fetal

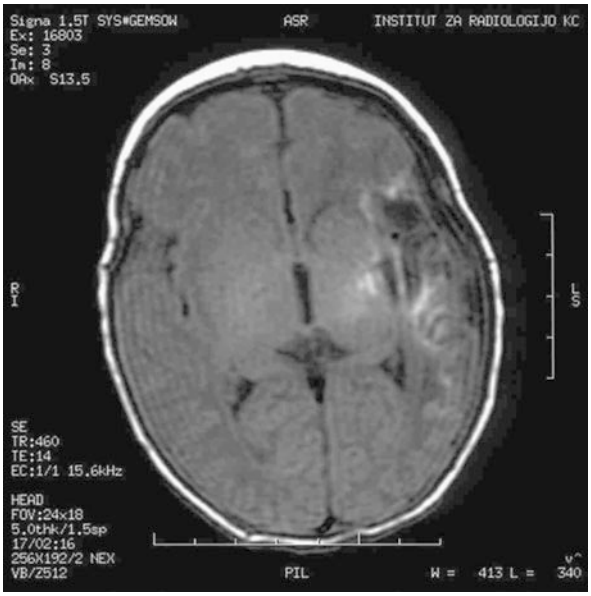

Figure 160.2
Magnetic resonance imaging of the head showing ischemic changes in the left hemisphere in a neonate with transplacentaly transferred IgG anticardiolipin antibodies and heterozygous methylenetetrahydrofolate reductase C677T and prothrombin G20210A gene mutations

complications including preeclampsia, utero-placental insufficiency, intra-uterine growth restriction, fetal distress, and premature birth. The prematurity rate in babies born to mothers with APS is 10–15% and the incidence of growth restriction is 15–20%.

Perinatal thrombotic events are exceedingly rare complication due to transplacental passage of maternal aPL (*Fig. 160.2*). Arterial thromboses were reported in 80% of the aPL-related perinatal thrombotic events and were frequently associated with additional thrombophilic risk factors such as arterial or venous catheters, sepsis, asphyxia, and/or congenital thrombophilia.

Children born to mothers with APS have increased risk of developing learning disabilities at a later stage in life and regular neuropsychological assessments are recommended for long-term follow-up.

Diagnosis

Classification criteria for the diagnosis of APS require the presence of at least one of the clinical criteria and one of the laboratory criteria (*Table 160.1*). Patients that have non-criteria clinical features associated with aPL are classified as probable APS. In clinical practice, testing for aPL should be performed in every child presenting with thrombosis or clinical features that are suggestive of APS, such as unexplained thrombocytopenia, hemolytic anemia, livedo reticularis, Raynaud phenomenon, and chorea.

Antiphospholipid antibodies can be detected by a variety of laboratory tests. The most sensitive test is the aCL test, which uses enzyme-linked immunosorbent assay (ELISA) to determine antibody binding to solid plates coated with cardiolipin. The specificity of aCL for APS increases with titer, and is higher for the IgG than for the IgM isotype. The anti-β_2GPI ELISA has improved specificities over the aCL test. The LA test is a functional assay measuring the ability of aPL to prolong in vitro phospholipid-dependent clotting reactions such as the aPTT, the Russell viper venom time, or the kaolin clotting time. The LA assay correlates better with the occurrence of thromboembolic events than the aCL or the anti-β_2GPI assays and is regarded as a less sensitive but more specific test for detection of aPL.

Persistent positivity of aPL is of major importance for diagnosing APS, and all abnormal aPL values should be verified on at least two occasions at least 12 weeks apart to demonstrate persistence. In a cohort of children included in the pediatric APS registry, the presence of aCL was detected in 81%, anti-β_2GPI in 67%, and LA in 72% of cases.

Imaging studies are aimed to detect thrombosis in target organs with the use of color-flow and pulsed Doppler ultrasound, echocardiography, computerized tomography plus angiography, and magnetic resonance imaging with or without angiography. Except during interventional procedures, venography and angiography are rarely used in children, because of technical difficulties, the requirement for iodinated contrast, and the possibility of extending thrombus. A tissue biopsy is required for definitive histopathologic confirmation of small-vessel occlusions in the target organ.

Differential Diagnosis

Because of its possible manifestations, APS must be considered in the differential diagnosis of many problems, ranging from thrombosis to unexplained thrombocytopenia, hemolytic anemia, livedo reticularis, Raynaud phenomenon, and various neurologic manifestations.

All children presenting with aPL-related thrombotic event should receive a broad investigation for additional congenital and acquired prothrombotic risk factors, and thorough evaluation for evidence of underlying SLE

or other systemic disease. The main congenital prothrombotic states to be considered include factor V Leiden, prothrombin G20210A mutation, deficiencies of antithrombin, protein C and protein S, total cholesterol, triglycerides, lipoprotein (a), fasting homocysteine concentration, and T677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene (297, 298). The most common acquired factors that may contribute to the risk of thrombosis are infection, malignancy, congenital heart disease, nephrotic syndrome, systemic vasculitis, central venous lines, surgery, and immobilization.

The differential diagnosis of nonthrombotic aPL-related clinical manifestations includes a variety of hematologic, dermatologic, neurologic, and other diseases. Catastrophic APS should be distinguished from severe SLE vasculitis, sepsis, thrombotic thrombocytopenic purpura, macrophage activation syndrome, and disseminated intravascular coagulation.

Treatment

Treatment strategies for children with APS are based on a few pediatric observational cohort studies and modified recommendations for adult patients with APS. General therapeutic measures in all children with APS include avoidance of additional risk factors for thrombosis such as smoking, hypertension, obesity, hypercholesterolemia, and use of estrogen-containing oral contraceptives in adolescent girls.

Treatment of the acute thrombotic event in children with APS is no different from that of thrombosis arising from other causes. Most patients receive anticoagulation therapy with unfractionated heparin as a loading bolus injection followed by continuous infusion. Low-molecular-weight heparins (LMWHs) are being used increasingly for initial therapy of acute thrombosis in children due to their subcutaneous administration, more predictable dose response, and reduced requirement for monitoring. The target therapeutic anti-Xa activity for children treated with LMWH ranges between 0.5 and 1.0 U/mL. Systemic or local thrombolytic therapy should be considered in difficult cases with high-risk clots.

Patients with persistently positive aPL, in particular those with LA, have a high risk for recurrent thrombosis and should receive long-term anticoagulation with warfarin. In the absence of controlled trials, the optimal intensity and duration of anticoagulation therapy in pediatric APS patients are still controversial. The standard treatment in adult APS patients with venous or non-cerebral arterial thromboembolism consists of oral anticoagulation at a target INR of 2.0–3.0, and in patients with ischemic stroke, either low-dose aspirin or moderate intensity warfarin with INR between 1.4 and 2.8. This recommendation has been challenged by a systematic review that included observational cohort studies and advised life-long anticoagulation at a target INR of 2.0–3.0 in patients with first venous events and above 3.0 for those with recurrent and/or arterial events. The major fear of high-intensity anticoagulation in children with APS is that secondary bleeding complications will exceed its beneficial effects. During the mean follow-up period of around 6 years, 20% of pediatric patients included in the international APS registry developed recurrent thrombotic events, which is significantly higher than recurrence rates reported in adult APS patients (3–11%). Given the higher recurrence rate of thrombosis, it seems reasonable to consider anticoagulation in all pediatric patients with definite APS at least at a target INR suggested for adult population. Moreover, it is essential to individualize treatment according to the presence of additional thrombophilic risk factors and the aPL profile (multiple aPL antibodies, high titers of aCL and/or anti-β_2GPI, presence of LA).

Patients with catastrophic APS require immediate aggressive treatment of the ongoing thrombotic events, suppression of the excessive cytokine storm, and elimination of possible precipitating factors such as infection or necrotic tissue. The highest recovery rate in catastrophic APS was achieved by the combination therapy of anticoagulants, corticosteroids, and plasma exchange.

In recurrent thrombosis, despite optimal anticoagulation, the first approach is usually adding low-dose aspirin and increasing the warfarin dose to achieve a higher INR. Additionally, an improved understanding of the pathogenic mechanisms by which aPL induce thrombosis has suggested some innovative treatments such as new anticoagulant and antiplatelet drugs, hydroxychloroquine, statins, complement inhibitors, rituximab, and other targeted therapies.

Prognosis

Pediatric APS is a serious and potentially life-threatening disease. During a 6-year follow-up period, 20% of children with APS develop recurrent thrombosis and the estimated mortality rate is 7%. Major causes of death in patients with APS are thrombotic events, SLE complications, and hemophagocytic syndrome.

Approximately 20% of children who initially present with primary APS may progress over time to develop

clear-cut SLE or a lupus-like disease. Therefore, all these patients need closer follow-up with regular clinical and immunological assessments for an underlying systemic connective tissue disease. The presence of aPL has also a negative impact on the global disease outcome in patients with SLE.

Prevention

The risk of future thrombosis is very low in asymptomatic children who are incidentally found to have positive aPL, high among those in whom thrombosis already occurred, and extremely high in patients with catastrophic APS. Primary prevention involves thromboprophylaxis in aPL positive asymptomatic children and patients with SLE but without previous thrombotic events.

Because of the increased risk of bleeding during play and sports, it is generally recommended that asymptomatic children with aPL do not need any long-term prophylactic treatment. The final decision on the use of specific prophylactic therapy such as low-dose aspirin (3–5 mg/kg/day) or warfarin should be individualized and based on the presence of additional congenital or acquired prothrombotic risk factors and the aPL profile. Prophylaxis with LMWH is generally recommended during high-risk situations, such as prolonged immobilization or surgery.

The coexistence of an underlying autoimmune disease, particularly SLE, significantly increases the thrombosis risk. Low-dose aspirin has been recommended as thromboprophylaxis in all pediatric SLE patients with persistently positive aPL. An additional protection may be provided by hydroxychloroquine, which has protective role against the development of both venous and arterial thromboses in SLE patients.

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161 Juvenile Dermatomyositis

Lucy R. Wedderburn

Definition and Classification of Juvenile Dermatomyositis (JDM)

The idiopathic inflammatory myopathies (IIM) of childhood are rare, multi-system serious conditions, characterized by inflammatory changes of muscle and other tissues with associated dysfunction, of which juvenile dermatomyositis (JDM) is the most common. JDM typically affects skin and muscle but can also affect other systems including gut, lungs, joints, and central nervous system. The current classification criteria for JDM remain those of Bohan and Peter, defined over 30 years ago. Efforts to generate new criteria which would more closely align with modern clinical diagnostic tests, such as magnetic resonance imaging (MRI), are underway. The Bohan and Peter criteria for definite JDM require the presence of characteristic rash, combined with three of: symmetric proximal muscle weakness, raised serum muscle enzymes (which may include creatine kinase (CK), transaminases, lactate dehydrogenase (LDH), and aldolase), and abnormal findings on muscle biopsy or electromyography (EMG). The presence of rash and any two of these features make a diagnosis of "probable" JDM. Since many centers no longer perform EMG, while some do not perform muscle biopsy except in atypical or difficult cases, many clinically typical cases of JDM may be classified as "probable" under this system. In addition to this need for more appropriate modern diagnostic criteria, evidence from serological studies suggests that a classification which incorporates autoantibody specificity would be clinically useful.

Epidemiology of JDM

The incidence of JDM is between two and four per million children under the age of 16 per year, while juvenile polymyositis (JPM) is very rare, (about 20 times less common than JDM). There have been few large epidemiological studies of JDM in different ethnic groups but some data suggest ethnic differences. JDM is more common in girls than boys (F:M ratio approximately 2.3:1) and has a mean age of onset of just over 7 years, although it can present at as young as 2 years and throughout childhood.

Etiology and Pathogenesis of JDM

The etiology of JDM remains unknown. As for other autoimmune conditions, a working hypothesis is that it is caused by interactions between environmental triggers, immune dysfunction, and specific tissue responses in genetically susceptible individuals. Some studies suggest a seasonal pattern to onset, or that infections may commonly precede the onset of JDM. Proposed infectious triggers include parvovirus or enteroviruses but definitive evidence for specific triggers of JDM remains lacking. Many genes influence susceptibility to myositis of which the best understood are the human leukocyte antigen (HLA) loci. The alleles HLA-B*08, DRB1*0301, and DQA1*0501 confer risk of myositis in both adults and children. HLA-DPB1*0101 also confers risk of myositis (adult and pediatric) especially in particular serological subgroups, and the DQA1*0301 allele is an additional risk factor for JDM. Many other genes likely contribute to susceptibility or subtype in JDM: to pursue these, large numbers of cases are required; the results of ongoing genome-wide studies in myositis are awaited.

Autoantibodies are common in JDM and can be divided into two categories: myositis specific antibodies (MSA), which are relatively specific for myositis or subtypes of disease; and myositis associated antibodies (MAA) which are also found in other autoimmune conditions. Between 60% and 75% of children with JDM are ANA positive and approximately 70% of children with JDM have one or more detectable MSA or MAA if full serological testing is used. Several novel autoantibodies have been identified in JDM including an antibody known as anti-p155/140, present in ~25% of JDM cases and associated with extensive skin involvement, and a novel antibody known as anti-p140, present in 23% of JDM patients and associated with risk of calcinosis. It is possible that in the future autoantibodies may provide

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valuable prognostic tools. The pathological role of autoantibodies in myositis remains unknown, but it is of interest that muscle tissue from adults with DM or PM has increased expression of several of the target antigens of such antibodies, and evidence suggests that immune complexes containing anti-Jo-1 or anti–Ro 52/anti–Ro60 autoantibodies induces type I interferon production.

Muscle biopsy from children with JDM may show small vessel endothelium abnormalities, including thickened endothelial cells, deposition of complement or immune complexes, and loss of capillary density, leading some researchers to propose that endothelium is the target of damage in JDM. Other changes on biopsy include inflammation, muscle fiber MHC class I protein overexpression, muscle fiber regeneration, and fiber atrophy (*Fig. 161.1*). Four "domains" of typical change have been defined in a proposed scoring system with which to assess JDM biopsy material. Recent studies suggest that type I interferons, made predominantly by dendritic cells, may induce this pathology, and that muscle from JDM patients shows a "signature" typical of a type I interferon-driven process, on gene expression profiling. Other cytokines thought to play a role in muscle damage in JDM include TNF and IL-1. These cytokines can upregulate MHC proteins on muscle fibers, which is increased in myositis including JDM. MHC over-expression is thought to cause muscle damage through a process called ER Stress in human myositis, and which in model systems is more severe in juvenile than adult muscle.

Clinical Manifestations of JDM

The onset of JDM may be gradual and insidious, which may lead to misdiagnosis for many months; alternatively children may progress from full health to being severely weak and unwell, in only a few weeks. The classical rash of JDM typically manifests as a periorbital "heliotrope" rash, and/or Gottron's papules over the extensor surfaces, commonly over metacarpophalangeal and interphalangeal joints. Less typical rashes, which may lead to a delay to diagnosis, can occur anywhere on the body, including other extensor surfaces but also ears, axillae, or trunk (*Fig. 161.2*).

Other skin features may include vasculitic rash, ulcerative change, and intradermal or subcutaneous calcification (calcinosis), all of which indicate a poor prognosis. Calcinosis can take the form of subcutaneous plaques or nodules, or extensive sheets of calcium which may encase a whole limb or the body. Severe cases may also present with severe widespread oedema which may cause diagnostic difficulty. Several skin scoring systems have been proposed, to ensure comprehensive assessment of skin involvement in JDM. The examination of nailfolds is simple and informative and may reveal periungual erythema or dilated capillary loops, associated with ongoing active disease, prolonged course, and poor prognosis. The skin rashes of JDM are often photosensitive, therefore history of exacerbation after sun exposure is important. With time, and in severe cases, serious complications of skin disease are ulceration of skin lesions (which can be in other sites such as axillae, eye lids, or pressure points) and calcinosis, and both should be examined for with great care, both on presentation and at every assessment.

The second cardinal feature of JDM is muscle weakness, which can be easily missed in a sick child especially if muscle strength is not formally tested. Weakness typically starts in proximal muscles, and again may be insidious or rapidly progressive. Proximal weakness leads to difficulty with stairs, dressing, or walking, and is frequently combined with tiredness or lethargy. Children may be mistakenly thought to be uncooperative when in fact weakness prevents them from performing tasks. On examination, the child may be unable to sit up from lying, or to hold the head off the bed, or to squat, and may also demonstrate Gower's sign, where the child uses his/her arms placed upon the legs to help themselves to stand up from the floor. Weakness in a sick child is easily missed; however, the Childhood Myositis Assessment Scale (CMAS) and manual muscle testing of a standard group of 8 muscles (MMT8) are available as validated tools for muscle assessment and can be performed in a few minutes. Weakness of the muscles of the palate or pharyngeal muscles can lead to dysphagia or dysphonia; therefore a history of altered speech (sometimes described as "Donald Duck") or trouble with swallowing should be asked about.

Children with JDM can have a wide range of other symptoms including irritability, fevers, anorexia, arthritis, myalgia, Raynaud's phenomenon, lethargy, dyspnoea, mood changes, headaches, and abdominal symptoms. More rare but also ominous signs include generalized peripheral oedema, which appears to be more common in younger children, and also lipodystrophy, where there is a marked atrophy of subcutaneous tissue.

Assessment, Diagnosis, and Differential Diagnosis in JDM

In specialist centers, the assessment and diagnostic workup for children suspected of having JDM will include careful clinical and functional assessment, blood testing,

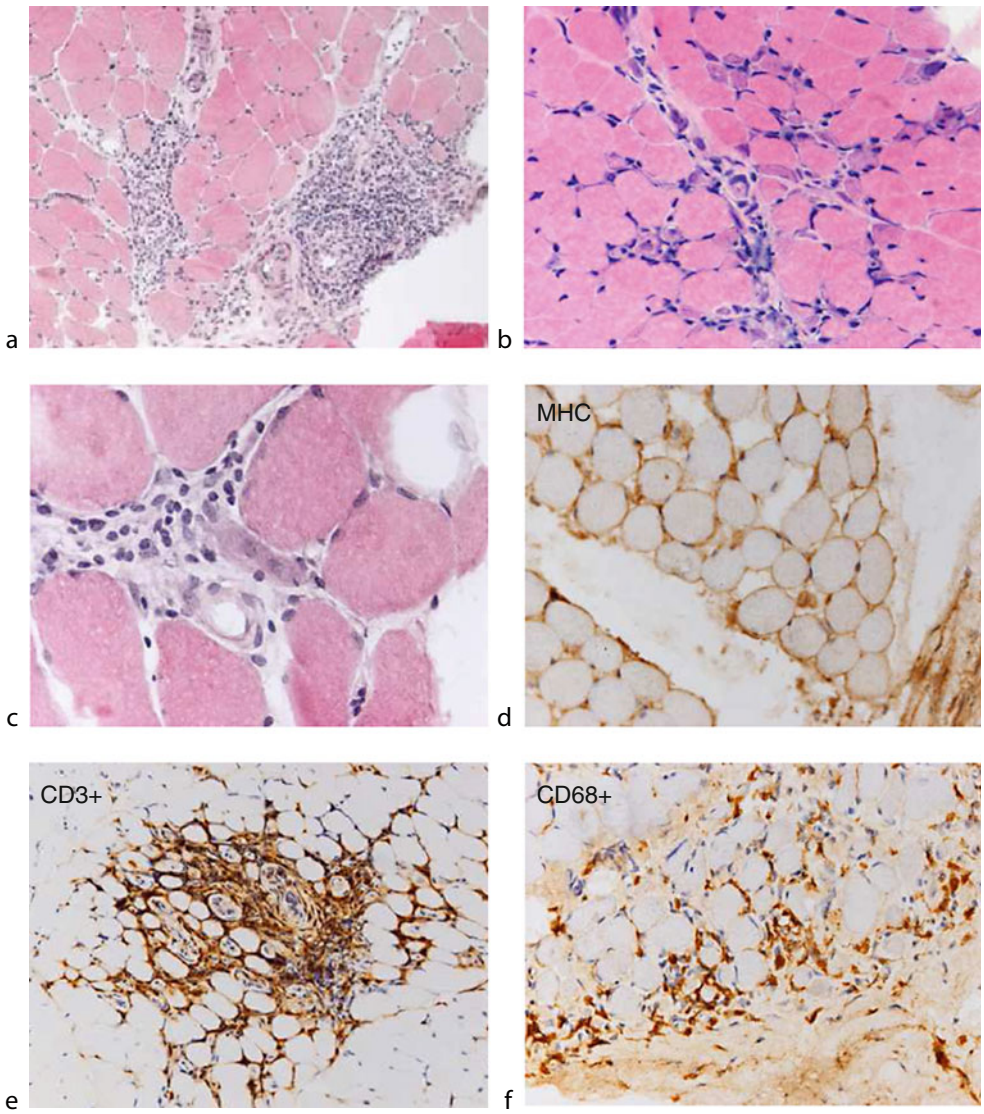

Figure 161.1

Histological features seen on muscle biopsy tissue from juvenile dermatomyositis patients. (a–c) Sections stained with haematoxylin and eosin, (d–f) immuno histochemistry for markers as shown. (a) Shows inflammatory infiltrate, largely preivascular, and variable muscle fiber size; (b) shows marked inflammation, as well as muscle fiber atrophy, and internal myonuclei; (c) shows variable muscle fiber size, regenerating basophilic fiber with central nuclei; (d) shows increased sarcolemmal expression of MHC class I (also known as HLA) on muscle fibers; (e) shows infiltrating T lymphocytes (CD3+) in a perivascular pattern; and (f) shows diffuse infiltration of myeloid cells (CD68+)

imaging (most commonly MRI), and, in many centers, muscle biopsy. Laboratory tests should include full blood count, ESR, muscle enzymes, renal and hepatic function, as well as analysis of autoantibody status (see above, pathogenesis section). Formal muscle testing and documentation of skin and nail fold changes is critical. Calcinosis should be looked for whenever it is suspected and can be confirmed by plain radiography. Inflammatory changes seen in muscle by MRI (typically assessed in T2 weighted images of quadriceps muscles) can be quantified and have been shown to correlate with disease activity. Although the Bohan and Peter criteria for

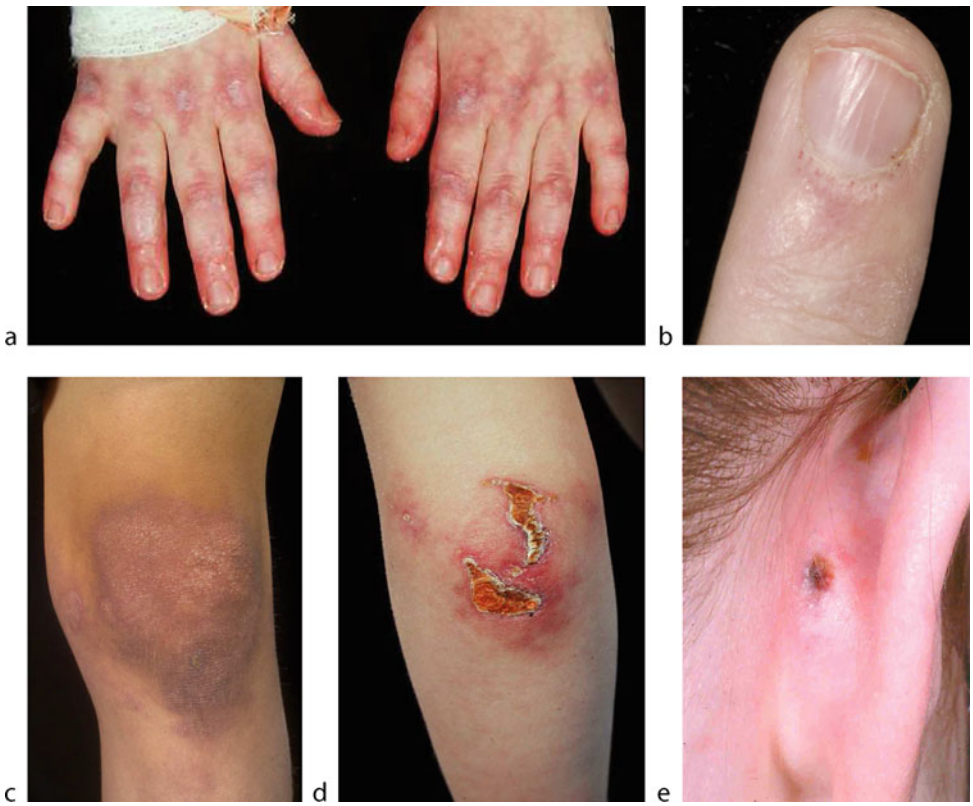

Figure 161.2

Cutaneous involvement in juvenile dermatomyositis. (a) Classical Gottrons papules over metacarpophalangeal joints (MCPs), distal and proximal interphalangeal joints, (PIPJ, DIPJ). (b) Periungual erythema and nail fold capillary loops. (c) Scaly erythematous rash over knee in a child with JDM, which may be mistaken for other diagnoses such as psoriasis. (d) Scarring lesions in a child with JDM with ulcerative skin disease. (e) Ulcerative lesion behind pinna in child with JDM

diagnosis of JDM include changes on EMG, many centers no longer routinely perform this test in children. Muscle biopsy is performed in many centers, but until recently the lack of a standardized system for analysis and assessment of histopathological features led to variable diagnostic or prognostic yield from this test. An International Consensus Group has recently proposed a formal system for analysis of changes on JDM muscle biopsy and assessment of severity. In addition to these tests, specific features may require further investigation such as high resolution pulmonary CT with lung involvement, or videofluroscopy in the presence of suspected pharyngeal involvement.

Although modern criteria for the diagnosis of juvenile inflammatory myositis are not yet agreed, tools for assessment of disease activity and damage have been proposed by two International collaborative groups, the Paediatric Rheumatology International Trials Organization (PRINTO) and the International Myositis Assessment and Clinical Studies Group (IMACS). Both proposed core sets include a parent/patient assessment, the physicians overall assessment, muscle strength measurement, functional assessment (e.g., Child Health Assessment Questionnaire), and assessment of extra-muscular disease and damage. The PRINTO set also includes a measure of quality of life, the Child Health Questionnaire (CHQ). Regular serial measurements and assessments are vital in order to monitor disease course and response to treatment. The PRINTO collaboration has tested the validity and consistency of the proposed set of tools in measuring response to treatment in JDM. It is important to be vigilant in monitoring for complications or signs of active disease including ongoing rash, nail fold abnormalities, new lesions of calcinosis, respiratory or gut involvement, or lipoatrophy.

The differential diagnosis of JDM includes other inflammatory myositis such as JPM, post infectious myositis, focal myositis, eosinophilic myositis, genetic dystrophies, and myositis, which is part of another connective tissue disease such as SLE or scleroderma. Pediatric myositis shows a higher rate of such "overlap" than seen in adults: for example, in a cohort of over 100 cases of JDM, almost a quarter had features suggestive of overlap with scleroderma. In JDM cases with minimal or no apparent muscle involvement, the differential diagnosis may include alternative causes of the rash such as psoriasis. Amyopathic dermatomyositis presents with classical rash but no muscle involvement; this is a rare but well-recognized entity, which still requires immunosuppressive therapy; muscle biopsy confirms lack of pathological change in these cases.

Treatment of JDM

The care of children with JDM is ideally delivered by a mutlidisciplinary team of specialists, including pediatric rheumatologists, specialist physiotherapists and nurses, speech/language therapists, and others. Modern management involves active early drug treatment, with the aim of rapid control of disease activity, combined with physiotherapy to maintain and regain muscle strength. There is a severe lack of evidence base for the drug management of JDM, but international efforts are now facilitating adequately powered drug trials. The mainstay of treatment of JDM remains corticosteroids, usually combined with disease modifying agents, most commonly methotrexate (MTX) or cyclosporin A. In most centers steroids are initially given as intravenous methylprednisolone (MP), with a total of six pulses given in two sets of three, a dose 30 mg/kg/day for 3 days, (maximum dose 1 g), repeated after a week, and oral steroids (1–2 mg/kg) between pulses and in weaning doses thereafter. Bioavailability of ivMP is thought to be higher than that of oral prednisone, particularly in children with vasculopathy and gut involvement. Methotrexate is given at a dose of 15 mg/m^2, preferably subcutaneously, with folic acid (typically 1 mg/day). Evidence suggests that early use of MTX with corticosteroid reduces overall steroid dose and long-term side effects, while providing equally good disease control as steroid alone. Other DMARD used for active JDM include Azathioprine 3–5 mg/kg/day, Hydroxychloroquine 3–6 mg/kg/day (especially for rash), and Ciclosporin (total of 4–10 mg/kg/day in two doses, aiming for trough level of 75–100 ng/mL). A recent large consensus study found that a majority of North American pediatric rheumatologists advise use of steroids with MTX for moderate to severe cases of JDM as first line of management. A multinational trail comparing steroids alone, to steroids with MTX or steroids with cyclosporin is underway. Intravenous immunoglobulin has been shown to be effective in adult DM and in small series of JDM cases, and is in use in some countries, in place of MTX of cyclosporin.

Concurrent with drug management, exercise under the supervision of a physiotherapist is very important in maintaining and restoring muscle strength and there is evidence that it is safe to muscles. Other measures required include strict sun protection advice, good dietary advice, and protection against osteoporosis. Specific management will depend on organ involvement, such as NG feeding for children with dysphagia and risk of aspiration pneumonia, specialist skin care for those with ulcerative disease, and speech and language therapy for children who have dysphonia.

Many cases of JDM respond well to combined treatment of steroid plus first DMARD such as MTX. However a proportion of children continue to show active disease, in particular rash, development of ulceration or calcinosis, or involvement of other organs such as pulmonary, GI, or CNS systems. For these severe or refractory cases the current choice of therapy is largely led by local experience. Cyclophosphamide, given IV monthly at 0.5–1 g/m^2 has been shown to be beneficial in a series of cases with severe features including severe weakness, dysphagia, skin or gastrointestinal ulceration, or CNS disease. A small number of severe cases have been successfully treated with anti-TNFα therapy (Infliximab). Anecdotal reports of treatment using Etanercept suggest that this may be less effective than Infliximab. The B cell depleting monoclonal antibody (anti-CD20) Rituximab has been found to be effective in a small case series, and children are currently included in a large international trial of Rituximab in myositis. A few severe cases of JDM have been successfully treated by autologous stem cell transplantation (ASCT); experience from other autoimmune conditions suggests that it may be important to consider ASCT before irreversible damage has taken place. The complication of calcinosis is difficult to treat but some centers advocate use of pamidronate and diltiazem. Comorbidities including those due to side effects of drugs need to be considered; in particular, cumulative doses of both steroids and cyclophosphamide should be monitored, and treatment to prevent osteoporosis, such as calcium supplementation or bisphosphonates, considered. Where multiple or high doses of cyclophosphamide are planned, gamete storage may be offered to teenage patients, in particular for boys.

Prognosis and Outcome in JDM

Before the use of steroids and more recently DMARDS, mortality associated with JDM was roughly 30% of children; recent data suggest that in the modern era mortality is much reduced, with one study involving 1,353 patient years estimating mortality at just under 1%. There is evidence that early aggressive treatment reduces time to remission and reduces morbidity in JDM. However despite this improved situation, the functional outcomes of JDM remain poor. It is estimated that 15–20% of cases continue to have active disease despite early treatment and run either a chronic, or a polyphasic, relapsing course; one study of 490 patients with mean follow-up of 7.7 years found that 69% had cumulative damage. Early persistence of rash and nailfold changes appears to predict a longer time to remission. Clinical features which indicate severe disease include ongoing rash or severe weakness despite treatment, ulcerative skin disease, calcinosis, dysphagia that is unresponsive to treatment, and other major organ involvement (gut, CNS, pulmonary). Recent reported deaths due to JDM have been due to respiratory failure, pancreatitis, cadiovascular failure or catastrophic gut vasculopathy.

The recent availability of internationally agreed measures of disease outcome and response to treatment, which are being prospectively validated, will make the assessment of outcome in JDM more amenable to robust analysis in the near future; in addition the existence of several large national and international collaborative cohort studies will facilitate collection of outcome data from large numbers of children. While it is now clear that with early and aggressive management a proportion of children with JDM can reach full remission, off medication, and can recover full muscle strength, predictors for complications, or response to treatment are still much needed. Long-term side effects of treatments include osteoporosis from steroids, and the as yet unknown risks of chronic immune blockade from treatment with biological agents. In addition, as for other pediatric chronic autoimmune disorders such as JSLE, there is preliminary evidence that children with JDM may have metabolic changes (such as alterations in lipid metabolism) which could lead to long-term increased risk of cardiovascular disease. In the future, improved outcomes for children with JDM will be driven by a combination of international research efforts, the use of modern treatments, an increasing opportunity to include children in international drug trials to generate a robust evidence base for this treatment, and improved access for children to specialized centers for care.

Acknowledgments

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162 Juvenile Scleroderma

Francesco Zulian

Juvenile scleroderma syndromes, although rare, represent the third most frequent chronic rheumatic conditions in pediatric rheumatology practice after juvenile idiopathic arthritis and systemic lupus erythematosus. They essentially include two varieties, juvenile systemic sclerosis (JSSc) and juvenile localized scleroderma (JLS).

Juvenile systemic sclerosis is quite rare and involves both skin and internal organs. Unlike adults, children with JSSc show a significantly less-frequent involvement of the internal organs and a slightly better outcome as far as mortality and morbidity are concerned.

Juvenile localized scleroderma, also known as morphea, is the more frequent subtype of scleroderma in childhood. It comprises a group of distinct conditions which involve the skin and subcutaneous tissues. They range from very small plaques of fibrosis involving only the skin, to diseases which may cause significant functional and cosmetic deformity.

Etiology and Pathogenesis

Although the cause of scleroderma, potential pathogenetic mechanisms include a tripartite process in which dysfunction of the *immune system, endothelium,* and *fibroblasts* gives rise to a heterogeneous phenotype that is characterized prominently by fibrosis.

Autoimmunity is evident by the elaboration of circulating disease-specific autoantibodies and multiple abnormalities of the inflammatory cell function. These include the presence of mononuclear cell (MNC) infiltrates in early lesions, altered function of helper T and NK cells, and release of cytokines, chemokines, and growth factors. Raynaud's phenomenon, capillary dropout, and abnormalities in vascular tone are manifestations of endothelial cell dysfunction, particularly evident in JSSc. Fibroblast dysfunction is represented by fibrosis as the result of increased synthesis and deposition of extracellular matrix proteins. These three areas of abnormal function, although apparently unassociated with each other, are closely linked by several immunologic alterations.

Juvenile Systemic Sclerosis

Definition/Classification

Juvenile systemic sclerosis (JSSc) is a chronic connective tissue disease characterized by symmetrical thickening and hardening of the skin, associated with fibrous changes in internal organs.

Although rare in children, it represents one of the most severe rheumatic conditions in pediatric rheumatology practice.

Very recently, an update of the Classification Criteria for JSSc has been proposed. On the basis of this new classification, a patient, aged less than 16 years, shall be classified as having JSSc if the one major, presence of proximal skin sclerosis/induration, and at least two of 20 minor criteria, grouped in nine main categories, are present (*Table 162.1*).

Epidemiology

The onset of JSSc in childhood is very uncommon: children under 16 years of age account for less than 5% of all cases. The onset occurs at a mean age of 8.1 years and the peak age is between 10 and 16 years. The disease is almost fourfold more frequent in female and there is no clear evidence for a racial predilection.

Clinical Manifestations

The onset is often insidious. The mean time between the first sign of the disease and the diagnosis of JSSc is between 1.9 and 2.8 years with a range between 0 and 12.2 years. Overlap syndromes, most frequently with polymyositis-dermatomyositis account for almost one third of all cases.

Raynaud's phenomenon (RP) is the first sign of the disease in 70% of the patients and in 10% it is complicated by digital infarcts. Proximal skin induration is the second

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Table 162.1
Classification criteria for juvenile systemic sclerosis

Major criterion	Proximal sclerosis/induration of the skin
Minor criteria	
– *Skin*	Sclerodactyly
– *Vascular*	Raynaud's phenomenon
	Nailfold capillary abnormalities
	Digital tip ulcers
– *Gastrointestinal*	Dysphagia
	Gastroesophageal reflux
– *Renal*	Renal crisis
	New onset arterial hypertension
– *Cardiac*	Arrhythmias
	Heart failure
– *Respiratory*	Pulmon fibrosis (HRCT/X-ray)
	Decreased DLCO
	Pulmonary hypertension
– *Muskulo Skeletal*	Tendon friction rubs
	Arthritis
	Myositis
– *Neurological*	Neuropathy
	Carpal tunnel syndrome
– *Serology*	Antinuclear antibodies
	SSc selective autoantibodies (anticentromere, antitopoisomerase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III)

A patient, aged less than 16 years, shall be classified as having juvenile systemic sclerosis if the one major and at least two of the 20 minor criteria are present. This set of classification criteria has a sensitivity of 90%, a specificity of 96%, and kappa statistic value of 0.86

most frequent symptom, being present in 40% of cases (Fig. 162.1). As expected, the association of RP and skin changes, eventually with some signs of internal organ involvement, are the key diagnostic features.

During the overall course of the disease, RP and skin induration are far the most frequent symptoms (84%), followed by the respiratory involvement with pulmonary fibrosis and hypertension, gastrointestinal symptoms (malabsorption and gastroesophageal reflux), arthritis, and cardiac involvement (arrhythmia, heart failure). Rarely reported are scleroderma renal crisis, renal failure, and central nervous system involvement.

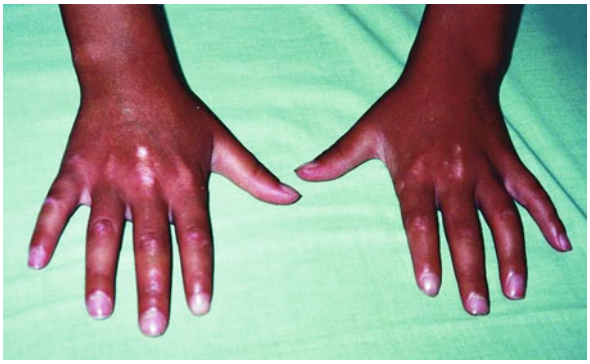

Figure 162.1
Sclerodactyly and flexion contracture of the fingers in a 10-year-old Hispanic girl with systemic sclerosis

Distinctive Features from the Adult Form

In general, a comparison with adult series is difficult because in children the limited cutaneous form, which is the far most frequent in adults, is rare. Children, at the time of diagnosis, show a significantly less frequent visceral involvement compared to adults. The exception is for the prevalence of arthritis seen early in JSSc. Differences with adults become less evident during the follow-up with the exception of interstitial lung involvement, gastroesophageal dysmotility, renal involvement, arterial hypertension which are significantly much more common in adults. Other differences during the course of the disease include the prevalence of arthritis and myositis, which are slightly more common in children than adults; while Raynaud's phenomenon and skin sclerosis are fairly less frequent in the pediatric age.

Similarly to adults, children with JSSc are commonly found to have antinuclear antibodies (ANA) with a frequency of 81–97%. Antitopoisomerase I autoantibodies are present in 28–34% of patients while the prevalence of anticentromere antibodies is lower in children (7–8%) as compared to adults (21–23%). The frequency of occurrence of rheumatoid factor (RF) and antiphospholipid antibodies (APL) is similar in adults and children with SSc.

Treatment

The pharmacologic management of patients with JSSc is challenging since no drug has been shown to be of unequivocal benefit in either children or adults with systemic sclerosis.

Recently, an EULAR task force, including pediatric rheumatologists, has proposed some recommendations for the management of SSc.

For Raynaud phenomenon, calcium channel blockers (CCB), oral nifedipine or nicardipine, should be considered as first-line therapy, and iloprost, or other available intravenously delivered prostanoids, would be used for severe SSc-related RP and digital ulcers. In fact, a recent study in children with JSSc and other connective tissue diseases reported that intermittent infusions of iloprost were safe and effective in treatment of refractory RP and ischemic digits.

For the treatment of interstitial lung disease, cyclophosphamide should be considered. According to the experience in juvenile SLE, cyclophosphamide should be administered as i.v. pulse therapy at a dosage of 0.5–1 g/m^2 every 4 weeks for at least 6 months. To prevent cystitis, adequate hydration and frequent voiding must be emphasized. Indeed, prophylactic MESNA should be considered to minimize contact of acrolein with the bladder mucosa.

Glucocorticoids, preferably prednisone at a dosage of 0.3–0.5 mg/kg per day, should be reserved for the treatment of myositis, arthritis, and tenosynovitis. Since several studies suggest that steroids are associated with a higher risk of scleroderma renal crisis patients should be carefully monitored for blood pressure and renal function.

Methotrexate, which is widely used for the treatment of many rheumatic conditions in children, has been shown to improve skin score in early diffuse SSc in adults. Accordingly, methotrexate could be the treatment of choice for the skin manifestations also for children with JSSc, especially in the early phase. Angiotensin-converting enzyme (ACE) inhibitors (e.g., captopril, losartan) are unanimously considered effective for the long-term control of blood pressure and stabilization of renal function of scleroderma renal crisis. Symptomatic treatments are essentially based on the principle of good clinical practice and include the use of proton pump inhibitors, such as omeprazole and lansoprazole, for prevention of gastroesophageal reflux disease and esophageal ulcers; the use of prokinetic drugs, such as domperidone, for the management of symptomatic motility disturbances; and rotating antibiotics, such as metronidazole, ciprofloxacin, and doxycycline, to treat malabsorption due to bacterial overgrowth.

As far as new experimental drugs (i.e., bosentan, sitaxsentan, and sildenafil for pulmonary arterial hypertension and digital ulcers), there is not enough experience, at present, to recommend their use.

Prognosis

The ultimate prognosis of the child with JSSc depends primarily on the extent of visceral involvement. Skin tightness and joint contractures inevitably lead to severe disability in some patients. Progressive gastrointestinal involvement is typical, however, starting with the esophagus and proceeding distally. Although the disease may stabilize in some patients for long periods, gastrointestinal complications and inanition may become severe. Cardiac arrhythmias may result from myocardial fibrosis and congestive heart failure is often a terminal event. Pulmonary interstitial disease and vascular lesions are probably universal, even if not clinically evident. Renal failure or acute hypertensive encephalopathy supervenes as a potentially fatal outcome in a few children and this event seems more likely to occur early in the course of the disease.

Recent studies showed that the prognosis of SSc in children appears better than in adults. The survival of childhood onset SSc at 5, 10, 15, and 20 years after diagnosis resulted to be 89%, 80–87.4%, 74–87.4%, and 69–82.5%, respectively, so significantly higher than in adult onset disease.

The commonest causes of death in children are related to the involvement of cardiac, renal, and pulmonary systems. Indeed, cardiomyopathy is a leading cause of early death, especially in children. This complication is rare and usually associated with diffuse cutaneous disease and features of polymyositis. An aggressive immunosuppressive treatment has been shown to be effective on muscle, skin, and lung involvement but does not impair progression of myocardial dysfunction.

In children with poor prognosis, diagnosis is made earlier as probably clinical manifestations are clear since the onset of the disease and severe enough to lead rapidly to death. This is confirmed by the fact that most of the deaths occurs in the first 5 years after diagnosis. Therefore, in children, SSc may have two possible evolutions: few children have a rapid development of internal organ failure leading to severe disability and eventually to death, while other patients experience a slow insidious course of the disease with lower mortality and disability.

Juvenile Localized Scleroderma

Definition/Classification

Juvenile localized scleroderma (JLS), also known as morphea, comprises a group of conditions in which the

process of fibrosis involves essentially the skin and subcutaneous tissues. They may range from very small plaques to extensive indurate lesions which cause significant functional and cosmetic deformity.

The most widely used classification divides JLS into five general types: plaque morphea, generalized morphea, bullous morphea, linear scleroderma, and deep morphea. Some conditions, such as atrophoderma of Pasini Pierini, eosinophilic fasciitis or lichen sclerosus et atrophicus, are sometimes classified among the subtypes of JLS but this aspect is still controversial. This classification does not include the mixed forms of JLS where different types of lesions occur in the same individual. This subtype is more common than previously recognized, accounting for 15% of the whole group.

A proposal for a new classification includes five subtypes: circumscribed morphea (CM), linear scleroderma, generalized morphea (GM), pansclerotic morphea, and the new mixed subtype where a combination of two or more of the previous subtypes is present.

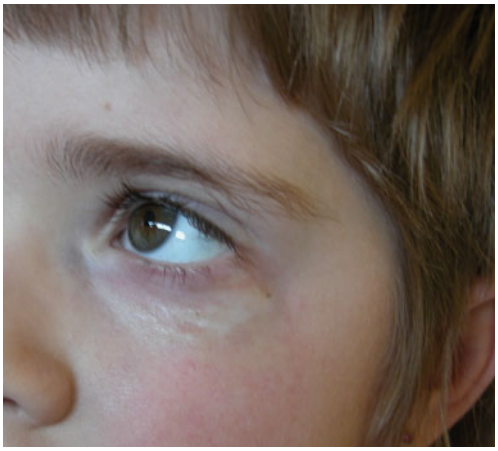

Figure 162.2
Circumscribed morphea of the lower left eyelid, characterized by an area of induration with waxy consistence and ivory color, surrounded by an inflammatory edge

Epidemiology

Although JLS is relatively uncommon, it is far more common than systemic sclerosis in childhood, by a ratio of at least 10:1. There is a mild female predilection with the female to male ratio being 2.4:1. The mean age at disease onset is 7.3 years and a few cases with onset at birth, so-called congenital localized scleroderma, have been also described.

Clinical Manifestations

Circumscribed morphea (CM) is characterized by oval or round circumscribed areas of induration surrounded by a violaceous halo (*Fig. 162.2*). It is confined to the dermis with only occasional involvement of the superficial panniculus.

When there are four or more individual plaques larger than 3 cm and involving at least two out of seven anatomic sites (head-neck, right upper extremity, left upper extremity, right lower extremity, left lower extremity, anterior trunk, posterior trunk) we have the so called *generalized morphea* (GM) (*Fig. 162.3*).

Linear scleroderma, the most common subtype in children and adolescents, is characterized by one or more linear streaks that can extend through the dermis, subcutaneous tissue, and muscle to the underlying bone,

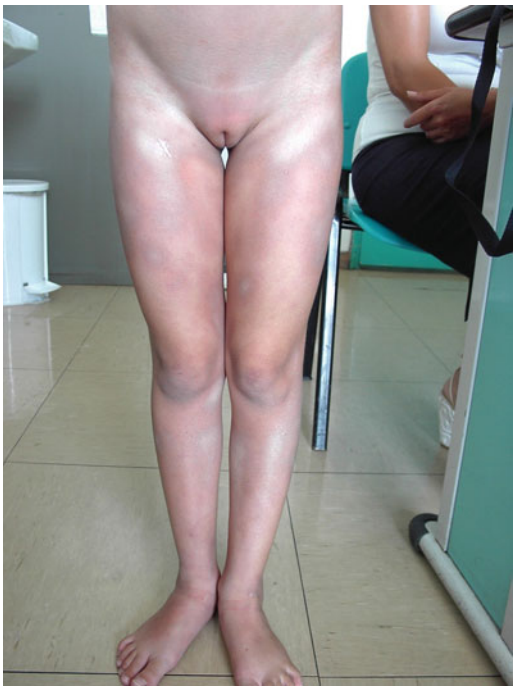

Figure 162.3
Generalized morphea involving, symmetrically, the lower limbs in an 8-year-old girl. Note the bluish halo of the active lesions, named lilac ring

causing significant deformities (Fig. 162.4). The upper or lower extremities can be affected but also the face or scalp, as in the *en coup de sabre* variety (ECDS). The Parry Romberg syndrome (PRS), characterized by hemifacial atrophy is considered the severe end of the spectrum of ECDS and for this reason is included in subtype of linear scleroderma. Evidence for this close relationship is the presence of associated disorders, including seizures, CNS abnormalities, and dental and ocular abnormalities, reported with similar prevalence in both conditions.

Pansclerotic morphea, an extremely rare but severe subtype, is characterized by generalized full-thickness involvement of the skin of the trunk, extremities, face, and scalp, with sparing of the fingertips and toes. It is more common in children than adults. Recent reports raised the attention on the possible evolution of chronic ulcers, frequently complicating pansclerotic morphea, to squamous cell carcinoma, a threatening complication already reported in LS.

Conversely to what has been reported for many years, JLS is not exclusively confined to the skin but can present many extracutaneous features. A recent multinational study reported that almost one fourth of the patients present extra-cutaneous manifestations. The overall distribution of these manifestations includes arthritis 19%, neurological findings 4%, associated autoimmune conditions 3%, vascular changes (i.e., Raynaud's phenomenon) 2%, and ocular or gastrointestinal abnormalities 2%.

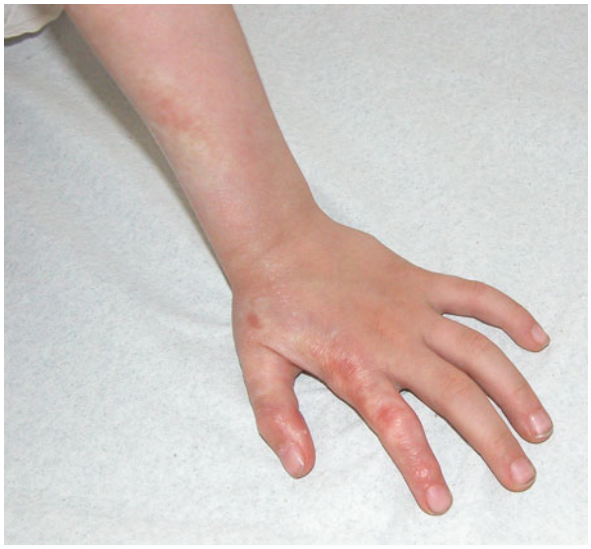

Figure 162.4
Linear scleroderma of the right upper limb involving the forearm and the first and second fingers

Articular involvement is the most frequent finding, especially in linear scleroderma. Children who develop arthritis often have a positive rheumatoid factor (RF), and sometimes an elevated erythrocyte sedimentation rate (ESR) and circulating autoantibodies. The most frequent neurological conditions are seizures and headaches, although behavioral changes and learning disabilities have also been described. Abnormalities on magnetic resonance imaging (MRI), such as calcifications, white matter changes, vascular malformations, and vasculitis, also have been reported.

Gastroesophageal reflux (GER) is the only gastrointestinal complication reported so far in JLS.

Autoantibodies

Antinuclear antibodies (ANA) are present in more than 40% of patients with JLS. This frequency is lower than in adult with LS but is higher than in normal population. In children there is no correlation between the presence of ANA and a particular subtype or disease course.

Of interest, antitopoisomerase I antibodies (anti-Scl 70), a marker of SSc in adults, were found to be positive in 2–3% of children with JLS but not in adults with LS. Conversely, anticentromere antibodies (ACA) were found in 12% of adults with LS but only in 1.7% of children. Whether these antibodies are markers that reflect the immunological component of the disease process or can have a prognostic significance is unclear. It should be noted that none of SCL-70-or ACA-positive patients in a series of 750 JLS patients presented signs or symptoms of internal organ involvement after a mean follow-up of 3.4 years.

Rheumatoid factor (RF) has been detected, at low titer, in 16% of the patients with JLS, and significantly correlated with the presence of arthritis.

One of the major autoantigens for ANA in JLS is nuclear histone. Anti-histone antibodies (AHA) have been detected in 47% of patients with JLS with a different prevalence in the various subtypes, higher in GM, lower in circumscribed morphea.

Diagnosis and Disease Assessment

The management of JLS is challenging and the detection of disease activity and progression remains a fundamental

problem. Clinical examination is subjective – classical skin scoring methods utilized in the assessment of systemic sclerosis cannot be applied. Among the new tools which have been proposed for the assessment of the skin lesions, infrared thermography (IRT), computerized skin score (CSS), ultrasound (US), and magnetic resonance imaging (MRI) are those most frequently used.

Infrared thermography (IRT) is able to detect areas of increased temperature caused by the inflammatory process, revealing, in this way, active lesions. This technique has shown to have a very high reproducibility but yields false-positive results in the assessment of old lesions characterized by marked atrophy of the skin and subcutaneous tissues. In these cases, an accurate clinical examination can help differentiate these lesions from the active ones.

The computerized skin score (CSS) consists in the demarcation of hyperemic and indurate borders of the lesions on an adhesive transparent film with different colors. The film, transferred over a cardboard, is scanned and recorded in a computer. Calculation of the affected area is performed by computer software.

Ultrasonography (USG) is another technique that has been proposed for monitoring JLS. USG can detect several abnormalities such as increased blood flow, increased echogenicity due to fibrosis, and loss of subcutaneous fat. The first two parameters appear to be signs of active lesions, which disappear in the remission phase. Loss of subcutaneous tissue was found in both active and stable patients. The two main limits of USG are represented by its operator-dependent value and the lack of validation as outcome measure in prospective studies.

MRI is also an important tool in the clinical management of JLS. MRI is clearly most useful when CNS involvement is suspected but is also able to demonstrate the true depth of soft tissue lesions and the degree to which different tissues are involved in other sites.

In comparison to USG, MRI has two main disadvantages: the need for sedation in younger patients and the presence of possible artifacts.

Treatment

Over the years, many treatments have tried for localized scleroderma.

Circumscribed morphea generally is of cosmetic concern only, and therefore systemic treatments with potentially significant toxicity are not justified. In general, these lesions will spontaneously remit with residual pigmentation as the only abnormality. Therefore, treatment should

Table 162.2
Treatment with phototherapy in localized scleroderma

Author	Treatment	Regimen	No. patients (children)	Follow-up	Result	Assessment
Kersher	UVA1	UVA1 20 J/cm^2 for 12 weeks (total number of treatments: 30; cumulative UVA1 dose: 600 J/cm^2	20 (0)	12 weeks	Effective (90%)	Clinical judgment, 20 Mhz USG, histopathology
Kreuter	LdUVA1 + Vit D	UVA1 40 sessions in 10 weeks, Cumulative dose 800 J\cm^2) + calcipotriol ointment 0.005% twice daily for 10 weeks	19 (19)	10 weeks	Effective (100%)	Clinical judgment, 20 Mhz USG
Gruss	UVA1	UVA1 20 J/cm^2, 4 times/week for 6 weeks, once/week for 6 weeks	3 (0)	12 weeks	Effective (100%)	Clinical judgment, photos
De Rie	UVA1	UVA1 = 48 J/cm^2 4 times/week for 5 weeks	8 (0)	12 weeks	Effective (100%)	mRodnan skin score, cutometer, histopathology
El Mofty	UVA	BB-UVA = 20 J/cm^2 or BB-UVA = 10 J/cm^2, 3 times/week	21 (10)	7 weeks	Effective (86%)	Clinical judgment
Kreuter	UVA1, UVB	LdUVA1 = 20 J/cm^2, MdUVA1 = 50 J/cm^2, NB-UVB 0.1–0.2 J/cm^2 5 times/week	64 (na)	8 weeks	Effective (97%)	MSS, VAS, histopath, 20-Mhz USG

UVA ultraviolet A, *LdUVA* low dose UVA, *BB-UVA* broad band UVA, *USG* ultrasonography

Table 162.3
Methotrexate treatment in juvenile localized scleroderma

Author (year)	Study	Regimen	No. patients	Follow up (Months)	Result	Assessment
Uziel (2000)	Retrospective	MTX 0.3–0.6 mg/kg/week os or sc + MPDN 30 mg/kg/day pulse for 3 days/ month for 3 months	10	2–7	Effective (90%)	Clinical judgement
Fitch (2006)	Retrospective	MTX 0.4–1.0 mg/kg/week os or sc ± PDN 1 mg/kg/day or every other day for 3–6 months	17	6–60	Effective (94%)	Clinical judgement, family telephone questionnaire
Wiebel (2006)	Retrospective	MTX 10 mg/m^2/week ± PDN 1 mg/kg/day or every other day for 3–6 months	34	24	Effective (74%)	Clinical judgement, thermography
Zulian (2011)	Double-blind randomized controlled trial	MTX 15 mg/m^2/week for 12 months + PDN 1 mg/kg/day for 3 months *versus* PLACEBO for 12 months + PDN 1 mg/kg/day for 3 months	70	12	Effective (MTX 67%) (PLAC 29%)	Clinical judgement, thermography, computerized skin score

MTX methotrexate, *USG* ultrasonography

be directed mainly at topical therapies such as moisturizing agents, topical glucocorticoids, or calcipotriene.

Phototherapy with ultraviolet (UV) represents another possible therapeutic choice for localized scleroderma. Treatment with UVA1 at low, medium, and high doses, with or without psoralens (PUVA) all seem to be effective clinically, although high doses seem somewhat better. This approach seems to be much more effective for localized or superficial lesions than for the subtypes with deeper involvement such as linear or generalized scleroderma (◉ *Table 162.2*).

Since the rate of relapse after UV phototherapy discontinuation is not known, the need for prolonged maintenance therapy, leading to a high cumulative dosage of irradiation, and the increased risk for potential long-term effects such as skin aging and carcinogenesis are clear limitations for its use in the pediatric age group.

When there is a significant risk for disability, such as in linear and deep subtypes, systemic treatment methotrexate (MTX) in combination with corticosteroids should be considered (◉ *Table 162.3*). The treatment protocol usually consists in a combination of oral prednisone (0.5–1 mg/kg/day) or intravenous methylprednisolone (20–30 mg/kg/day for 3 days) and MTX (10–15 mg/m^2/week). Most patients show a response within 2–4 months and the side effects are usually mild and associated more with corticosteroid use rather than with the MTX treatment. Only one study has recently proven MTX efficacy and safety in a double-blinded randomized controlled trial (◉ *Table 162.3*).

Prognosis

Information on the long-term outcome of children with JLS is very less and based on small series of patients. However, it is common experience that adults with childhood-onset localized scleroderma suffer from long-term disease sequelae that significantly impact quality of life, including permanent functional and cosmetic impairment. In addition, some continue to have episodes of active disease throughout life.

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163 Sjogren Syndrome, Raynaud's Phenomenon, Overlap Syndromes

Fabrizio de Benedetti

Sjogren Syndrome

Definition/Classification

Sjogren syndrome (SS) is a chronic autoimmune disease, of unknown etiology, whose main characteristic is lymphocytic infiltration of exocrine glands. SS may occur as an isolated disorder (primary) or, more commonly, in association with systemic lupus erythematosus or other connective tissue diseases. SS is characterized by a wide clinical spectrum ranging from isolated involvement of salivary and lacrimal glands to a systemic disease that may involve lungs, kidneys, muscles, and the central nervous system.

Epidemiology

Primary SS appears to be very rare in children, while secondary SS is more common. SS is more frequent in females and usually occurs in adolescence, although it has been observed in children as young as 5 years.

Pathology

The common finding in affected organs is lymphocytic infiltration. In salivary glands, infiltrating lymphocytes progressively replace the salivary epithelium. Germinal centers formation may occur. A typical finding is the proliferation of ductal lining cells leading to the formation of epimyoepithelial islands, with keratin-containing epithelial cells. Labial (usually lower lip) salivary gland biopsy is a practical and easy way to access the main target tissue of SS. Focal aggregates adjacent to ducts and acini are typical. Epimyoepithelial islands, which are a characteristic feature in major salivary glands, are very uncommon in labial salivary glands.

Clinical Manifestations

Differently from adults, recurrent parotid swelling is the most frequent symptom at onset, occurring in 70–90% of children with SS. It is more often painless. At presentation, xerostomia and xerophthalmia are relatively rare in children, but occur in up to 50% during the course of the disease. As a consequence of saliva deficiency, patients complain of difficulties in chewing and in initiating swallowing, burning sensation, abnormalities of taste, and dental caries. The oral mucosa may appear dry, erythematous, and sticky. Infection with Candida may be observed. Decreased tear secretion progressively damages the conjunctival and chorneal epithelia causing eye irritation (burning, foreign body sensation, and photophobia). Dryness of other mucosae may occur. Extraglandular manifestations appear to be rare at onset in children. Fever, arthritis and arthralgia, and fatigue are the most common ones both at the onset and during the course. Involvement of the lungs (with interstitial disease), kidneys (interstitial nephritis, renal tubular acidosis), and the central nervous system is relatively uncommon, but may represent significant challenges. Vasculitic and hematological (thrombocytopenia) features have also been described.

Diagnosis and Differential Diagnosis

The disease course in children may be very insidious, with a long time between initial symptoms and development of full-blown sicca syndrome. As a consequence, diagnostic criteria for adult SS are not sensitive enough in children. As mentioned above, recurrent parotid swelling, which is not included in adult criteria, is by far the most frequent presentation in children.

Polyclonal hypergammaglobulinemia, rheumatoid factor at high-titer antinuclear antibodies, and anti-Ro/SSA and anti-La/SSB antibodies are present in the large

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majority of patients. Increased ESR is common. Leukopenia, anemia, and thrombocytopenia may also be observed. The Shirmer's test is used to evaluate tear's secretion (<5 mm wetting of a filter paper strip in 5 min is considered positive). Traditional radiocontrast sialography provides evidence of ectasia of the salivary ducts. Recent data, yet to be confirmed in children, showed that ultrasonography revealed parenchymal inhomogeneity in major glands and decreased echogenicity and volume of submandibular glands in patients with SS. Demonstration of periductal and/or periacinal lymphocytic infiltrates in the minor salivary glands of the lower lip is the best single criterion for establishing a definitive diagnosis. Differential diagnosis includes juvenile recurrent parotitis, which is characterized by intermittent swelling of one or both parotid glands, associated with fever, pain, and skin erythema. Autoantibodies and lymphocytic infiltration are absent. It is usually responsive to antibiotics. Diffuse lymphocytosis syndrome, a well-known entity in HIV infected children, may cause parotid enlargement. HCV infection may be associated with chronic sialadenitis. Malignancy and sarcoidosis should also be considered in the diagnosis.

Treatment and Prognosis

The outcome of children with SS is usually good. However, since SS is potentially a multisystem disease, patients with SS should be followed regularly. Treatment of symptoms secondary to xerostomia is based on the use of sugar-free lemon drops or chewing gum to stimulate salivation. Frequent ingestion of fluid is often the best solution. Careful oral hygiene is important to prevent dental disease. Xerophthalmia is treated with artificial tears (as frequently as every 30 min); attention to environmental humidity is also important. Oral pilocarpine has been suggested for sicca syndrome (both eye and oral). Systemic and organ manifestations are managed usually with corticosteroids and immunosuppressants. Hydroxychloroquine has been reported to be useful in the long-term treatment.

Raynaud's Phenomenon

Definition

The characteristic triphasic color change sequence (blanching, cyanosis, erythema) originally described by Raynaud in 1862 is still the definition of Raynaud's phenomenon. The term "primary Raynaud's phenomenon" (RP) is applied to patients in which no underlying disorder can be identified. In contrast to adults, in children primary RP is rather rare (probably less than 10%). Secondary RP in children is usually associated with autoimmune connective tissue diseases. The association with other underlying diseases that have been reported in adults (i.e., mechanical obstruction, polycythemia, cryoglobulinemia) is rare, if not exceptional in children.

Clinical Manifestations

RP is usually suspected in a child who presents with the characteristic triphasic color change of distal body parts on exposure to cold or stress: white to blue to red. The blanching phase is clearly demarcated and uniformly white. It begins at the distal end of digits. More often ends abruptly at the distal interphalangeal joints, but it may involve the whole digit up to the metacarpophalangeal joints. RP invariably involves fingers, usually more than one, and the thumb is usually spared. Toes, and more rarely, ears, nose tip, and lips may be involved. Paresthesias, numbness, or pain (particularly during the red phase) may accompany the changes in color.

Diagnosis and Differential Diagnosis

The diagnosis of RP is based on the presence of the triphasic color changes. Isolated RP may be the first sign of systemic scleroderma, and in some children may precede other manifestations by years. The presence of positive antinuclear antibody, nailfold capillary abnormalities, or, more rarely, esophageal dismobility, is a hint that the child may evolve to scleroderma. RP must be distinguished from normal vascular instability which is rather common particularly in adolescents, more often girls. The skin becomes reddish, but the triphasis color changes are not present and nailfold capillaroscopy is normal. Acrocyanosis should also be considered: it is a rare vasospastic disorder characterized by bluish color and coldness of the hands (not limited to the distal part of the fingers), often associated with excessive perspiration and edema. Minor abnormalities in nailfold capillaries have been described (dilated loops, decrease in number).

Treatment

Precipitating circumstances, such as exposure to cold and stress, should be avoided as much as possible. A number of

drugs have been used for the specific treatment of RP, but they have not been specifically investigated in children. Nifedipine should probably be considered the drug of choice (starting dose 0.2 mg/Kg at bedtime to avoid hypotension and up to the same dose for 2–4 times per day). Intravenous prostanoids and, particularly, iloprost are efficacious in RP and healing digital ulcers, but the experience in children is very limited. Other vasodilators, including ACE inhibitors and bosentan, have not shown significant benefit in adult trials.

Overlap Syndromes

Definition

Some children present with clinical and laboratory features that are characteristics of the major classic rheumatic diseases, such as juvenile idiopathic arthritis (JIA), systemic lupus erythematosus (SLE), juvenile dermatomyositis (JDM), and systemic scleroderma (SS). The terms "overlap syndrome" and "undifferentiated CTD" are used to define these children. Based on the presence of diagnostic criteria and characteristic serologic features, the best defined entity is mixed connective tissue disease (MCTD). MCTD is defined by the presence of features of SLE, JIA, JDM, and SS, associated with high-titer antinuclear antibody (speckled pattern) and with autoantibodies directed against one of the extractable nuclear antigens, namely U1RNP.

Epidemiology

MCTD is very rare representing less than 1% of CTDs in children. It is more common in adolescence with a 5:1 female-to-male ratio. Young children affected with MCTD have been reported

Clinical Manifestations

Most often, the initial presentation is characterized by edema and swelling of the hands, Raynaud's phenomenon, and arthralgias and/or polyarthritis. The subsequent course is defined by which component of the overlap syndrome plays the major role. Polyarthritis is very common; it may be erosive or nonerosive. Joint contractures may develop and skin involvement may contribute. Indeed, scleroderma-like skin disease is frequent and may become the prominent feature in several patients. Raynaud's phenomenon usually persists throughout the course of the disease. Pulmonary involvement is rather common and may progress with time to overt interstitial lung disease. Also esophageal manifestations of scleroderma, such as reflux and dysphagia, develop rather commonly. Renal disease occurs in less than one fourth of the patients; it is usually less severe than in SLE. Other manifestations may occur: skin signs of JDM such as heliotropic rash and Gottron's sign; myositis is frequent but rarely severe. Serositis are occasional.

Diagnosis

The diagnosis is based on the association of signs and symptoms of various CTDs with the high-titer ANA with speckled pattern and autoantibodies to U1RNP. Other ANA specificities are usually not present at high titer. Rheumatoid factor is often present. Several sets of criteria for MCTD have been developed in adults, but have not been validated in children. The most frequently used criteria in childhood are the Kasukawa's criteria (*Table 163.1*).

Treatment and Prognosis

There is no specific treatment for MCTD. Therapy is aimed at addressing the predominant problem of a given child, according to the principles of the treatment of each CTDs. The long-term outcome is variable and unpredictable, although two third of the patients have a favorable outcome. Significant morbidity and mortality are more often associated with pulmonary involvement. Deaths associated with myocarditis and renal involvement have also been reported.

Table 163.1
Diagnostic criteria for MCTD (Kasukawa's criteria)

I. Raynaud's phenomenon or swollen finger or hands
II. Anti-RNP antibody positivity
III. At least one abnormal finding from two or more of the following categories
1. Signs or symptoms of SLE (polyarthritis, facial rash, serositis, lymphadenopathy, leukopenia, thrombocytopenia)
2. Signs or symptoms of scleroderma (sclerodactyly, pulmonary fibrosis, vital capacity <80%, carbon monoxide diffusion <70%, decreased esophageal motility)
3. Signs or symptoms of dermatomyositis (muscle weakness, elevated creatine kinase, EMG abnormalities)

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164 Henoch–Schöenlein Purpura

Nicolino Ruperto

Definition/Classification

Henoch–Schönlein purpura (HSP) is an acute small-vessel leucocytoclastic vasculitis which was first reported in the nineteenth century by Heberden and later by Schönlein and Henoch who described the typical rash, joint manifestation, and gastrointestinal and renal involvement.

Etiology

The disease presents in most patients from autumn to spring often following an infection. A wide variety of pathogens, drugs, and other environmental exposures have been associated with HSP. Antistreptolysin O titers are raised in 20–50% of patients, but most cases have no direct link to streptococcal infection.

Epidemiology

Henoch–Schönlein purpura is the most frequent systemic vasculitis of childhood with an estimated annual incidence of 20.4 per 100,000 for all children, and 22.1 per 100,000 in children younger than age 14. The mean reported age of onset is 6.4 years. Black children seem to have a significantly lower annual incidence of HSP than white or Asian children. The reported boys to girls sex ratio is 1.2:1. It is much more frequent in children than in adults.

Pathogenesis

The cause of HSP is unknown, but it is likely that IgA has a fundamental role in the pathogenesis of the disease. Skin or renal biopsies demonstrate the deposition of IgA (IgA1) in the wall of skin capillaries and in the glomeruli. Diminished glycosylation of the hinge region of IgA1 has been reported in patients with HSP and IgA1 molecules with diminished hinge-region glycosylation are prone to aggregate into macromolecular complexes that can activate the alternative pathway of complement.

In regard to host susceptibility, several genetic polymorphisms relating to HSP and in particular to severity and/or risk of renal involvement have been described.

Clinical Manifestations

The onset is usually that of an acute purpura associated with other signs and symptoms with malaise and fever present in about one third of the children.

Purpura is present to different degree in all children with most of them typically showing the characteristic palpable purpura, 2–10 mm in diameter, commonly in crops, with lower limb predominance (*Fig. 164.1*). The lesion usually appears on the lower extremities and buttocks and in the region of frictions (e.g., socks or slip). The lesions begin as erythematous maculopapules that later became petechial or purpuric. Similar to ecchymoses, they change in color from red to purple and then vanish. Damage to vessels can also result in local angioedema.

Arthritis occurs in most cases, is painful, mainly affects the large joints of the lower limbs, and disappears spontaneously after few days.

Diffuse abdominal colicky pain with acute onset is present in the majority of HSP children. Many patients have occult heme-positive stools, but massive hemorrhage only occurs occasionally. Intussusception (usually ileoileal) is a severe but rare complication. Pancreatitis, hydrops of the gallbladder, and protein-losing enteropathy have been occasionally reported. Sometimes, gastrointestinal complaints can precede the appearance of the classic purpuric lesions.

Renal involvement is reported in around 35% of children and may manifest as proteinuria and/or hematuria, nephritis, nephrosis, or acute renal failure. In most cases, renal involvement is mild (microscopic hematuria with or without low-grade proteinuria). More rarely, renal involvement is severe and can progress to chronic renal failure. Renal manifestations usually occur within 4 weeks from disease onset. Urinalysis should be done each week while the disease is active, then each month for 3 months

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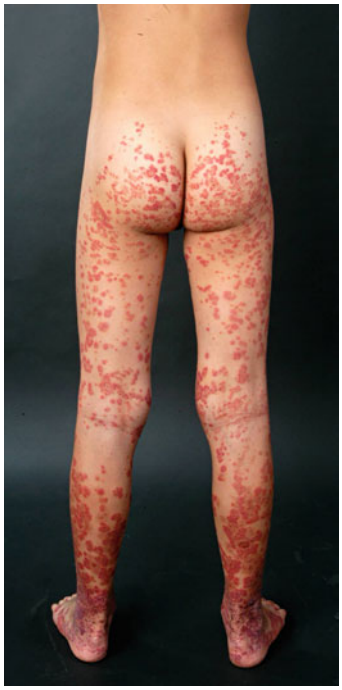

Figure 164.1
The figure showed the characteristics palpable purpura, 2–10 mm in diameter, commonly in crops, with lower limb predominance. The lesion usually appears on the lower extremities and buttocks and in the region of frictions (e.g., socks or slip)

thereafter. If all analyses are normal, nephritis is unlikely to occur. An uncommon manifestation is ureteritis which can cause obstruction and renal colic.

Other less common complications include central nervous system involvement, orchitis, epididymitis, carditis, pulmonary hemorrhages, neuropathies, and ocular involvement.

Laboratory findings are unspecific. Erythrocyte sedimentation rate as well as acute phase reactants may be normal or elevated. Serum IgA are elevated in about half of patients. Other laboratory studies are useful only to exclude other forms of vasculitis that can mimic HSP.

Diagnosis

Diagnosis is usually established on the presence of recurrent crops of palpable purpuric lesions predominantly affecting the skin of lower limbs and buttocks often associated with arthritis/arthralgia, colicky abdominal pain, and abnormalities in the urinalysis. In doubtful cases, a punch skin biopsy will show leukocytoclastic vasculitis with IgA and C3 deposition.

Acute hemorrhagic edema is a benign form of leukocytoclastic vasculitis that can be confused with HSP. It is characterized by the triad of fever, purpura, and edema, and affects children of less than 2 years of age. Purpuric lesions, usually larger than those seen in HSP, are localized on the face and extremities, while the trunk is spared. Edema, which is nonpitting, usually also affects the face and the limbs. It is a benign and self-limiting disease that usually resolves spontaneously without sequelae.

Treatment

Most patients require only supportive treatment. Nonsteroidal anti-inflammatory drugs (NSAIDs) are indicated to control joint pain. The efficacy of corticosteroid therapy is controversial. However, in general, prednisone is used in case of severe complications and its administration is often associated with prompt improvement of severe abdominal pain. There is no evidence that corticosteroid therapy is effective in treating the purpura, shortening the duration of the disease, or preventing recurrences or the development of nephritis.

Similarly, there is a lack of randomized controlled trial to establish the benefit of treatment in case of severe renal involvement. Uncontrolled studies suggest the potential efficacy of high-dose corticosteroids associated with cyclophosphamide or azathioprine in patients with severe HSP nephritis (nephrotic syndrome, diminished renal function, and diffuse extra-capillary nephritis on renal biopsy). Therefore, it is acknowledged that, even in the absence of controlled evidence, early aggressive therapy is warranted in patients with severe nephritis.

Prognosis

In the vast majority of cases, HSP is a self-remitting disease that disappears in few days or weeks. Although symptoms might recur, they generally totally disappear within 4–6 months. Prognosis mainly depends on the extent and severity of renal involvement. Patients with nephritis may show persistent urinary abnormalities for months or even years, but only 1–3% of patients are at risk to progress to end-stage renal disease. At renal biopsy, the presence of crescent formation in more than 50% of the glomeruli is associated with a poor prognosis.

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165 Kawasaki Disease

Rae S. M. Yeung

Disease Definition

Kawasaki Disease (KD) is one of the most common causes of vasculitis affecting children. Although the inflammatory response is found in medium and small vessels throughout the body, the most common site of damage is the coronary arteries, making KD the leading cause of acquired heart disease in children from the developed world. KD continues to be a diagnostic challenge. There is no single diagnostic test or unique clinical finding to distinguish KD from other acute febrile exanthems of childhood. Although called a disease, KD is truly a syndrome complex characterized by multi-system inflammation. KD presents clinically as prolonged fever, usually greater than 5 days in duration, a polymorphous skin rash, nonexudative bilateral conjunctival injection, oral mucosal inflammation with erythema of the lips and a strawberry tongue, extremity changes which include redness of the palms and soles and swelling of the dorsum of the hands and feet, as well as cervical lymphadenopathy, typically unilateral and greater than 1.5 cm in diameter. Presence of fever plus at least four out of five of these principal features constitutes the diagnosis of typical KD (◉ *Table 165.1*). The absence of a specific diagnostic test for the disease continues to hinder identification of affected children and a lack of predictive markers of this clinically heterogeneous clinical syndrome is an obstacle to the improvement of therapy for affected children.

Epidemiology

The most common age of occurrence is between 12 months and 5 years although younger children and adults can be affected. Since the initial clinical descriptions in Japan and Hawaii, the number of cases of KD has increased dramatically and is currently recognized worldwide. KD is seen in all ethnic groups and in all regions of the world, but the incidence of disease varies dramatically from region to region and between different ethnic groups suggesting a major role for genetics in KD risk and outcome. The annual incidence, reported as number per 1,000,000 children under 5 years of age, ranges from 5 in Denmark, 8 in New Zealand, 26 in Canada, 39 in Hong Kong, 55 in China, 105 in Korea to over 180 in Japan. Siblings of affected children are at tenfold higher risk for KD compared to the general population, and incidence of KD is twofold higher than normal in children of affected individuals.

In Asia and North America, KD is more common during the winter and early spring months and boys outnumber girls by 1.5–1.7 to 1 with greater than three quarters of affected children under the age of 5. The case fatality rate of KD in Japan is about 0.08%. This number appears to be decreasing in the most recent nationwide surveys done in countries that have active surveillance programs for KD. Virtually all deaths of patients with KD result from its cardiac sequelae. The peak mortality has been reported to occur between 15 and 45 days after the onset of fever. During this subacute phase of illness, inflammation continues and is coupled with marked elevation in the platelet count and a hypercoagulable state. Sudden death from myocardial infarctions may also occur years after the acute KD episode in children who had coronary artery aneurysms and stenosis.

Etiology

Despite numerous studies, the etiology of KD remains elusive. KD has been linked with many different etiologic agents ranging from bacteria such as *Staphylococcus*, *Streptococcus*, *Proprionibacterium*, and *Chalmydia* to viruses such as Epstein–Barr virus, parvovirus, coronavirus, and retroviruses, but no one causative agent has been consistently demonstrated. KD fits nicely in the spectrum between an infectious disease, an inflammatory syndrome, and a true autoimmune disease, with an infectious trigger leading to a prolonged self-directed immune response in a genetically susceptible host. The etiology debate has centered around the mechanism of immune activation: conventional antigen versus superantigen. Evidence supporting both hypotheses continues to accumulate. Some investigators have focused their work on identifying

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Table 165.1
Diagnostic features of KD

Prolonged fever (at least 5 days in duration) plus the presence of at least four of the following five principal features:
1. Polymorphous skin rash
2. Bilateral nonexudative conjunctival injection
3. Oral–mucosal changes including:
• Erythema
• Cracked lips
• Strawberry tongue
• Injection of the oral and pharyngeal mucosa
4. Extremity changes including:
• Erythema of the palms and/or soles
• Swelling of the hands and/or feet
• Periungual peeling of the fingers and/or toes in the subacute phase
5. Cervical lymphadenopathy (>1.5 cm in diameter), usually unilateral

one specific pathogen or family of pathogens responsible for disease. One group has identified oligoclonal IgA antibodies present in arterial tissue from fatal cases of KD. Recent interest and debate has centered on a novel human coronavirus found by a group of investigators in the respiratory secretions of some children with KD. Others investigators have not been able to confirm these data, echoing the outbreak-dependent nature of this syndrome.

The longer the search for a single infectious agent, the longer the list of diverse infectious organisms found. The presence of a shared property, common to multiple infectious agents, resulting in the same pathogenic process leading to the clinical syndrome of KD is another explanation. One such common feature of many infectious organisms is the presence of superantigenic activity. Superantigens are a group of proteins which share the ability to stimulate a large proportion of T cells (up to 30% of the T cell repertoire compared to one in a million T cells for conventional antigens) by binding to a portion of the T-cell receptor β chain (TCRVβ) in association with the major histocompatibility complex (MHC) class II molecules with no requirement for antigen processing. Superantigens have been identified in a variety of microorganisms including bacteria (*Staphylococci*, *Streptococci*, *Mycobacterium*, *Mycoplasma*, *Yersinia*), and viruses (rabies, EBV). Evidence from a number of KD outbreaks point to the classic footprint for superantigens specifically TCRVβ skewing in the peripheral blood and in affected cardiac tissue.

Although the debate continues regarding the mechanism of initial immune activation, the more likely scenario is that there is cooperation between different mechanisms and a final common pathway of immune activation responsible for this clinical syndrome. One of the unifying features of KD is a prolonged inflammatory response. It is possible that in many cases the infectious trigger, which started the inflammatory process, has been eliminated, and in those children who develop KD the persistent inflammatory response has become the problem. Containing the inflammatory response is one of the objectives of therapy in acute KD. Inflammation in itself is not worrisome, but prolonged inflammation leads to activation of downstream effectors, which can lead to coronary artery damage.

Pathogenesis

Systemic inflammation is the most striking finding in KD. This is evidenced clinically and biochemically during the acute phase of illness. Like other syndromes characterized by systemic inflammation, TNF-α is markedly elevated in children during the acute phase of KD. TNF-α is a pleiotropic cytokine critical in the regulation of immune cells and plays a critical role in inflammation. The link between the systemic immune response seen in the acute phase of KD and subsequent damage to the coronary arteries is not clearly understood. There is now emerging evidence that TNF-α is critical in the pathogenesis of KD, specifically at the level of the target tissue- the coronary artery. Key downstream effects of TNF-α signaling include leukocyte recruitment to the coronary artery and up-regulation of matrix degrading enzymes and pro-inflammatory cytokines. TNF-α up-regulates expression and activity of many members of the matrix metalloproteinase (MMP) family of enzymes. MMPs are a family of zinc-dependent matrix-degrading proteases that share the ability to degrade molecules of the extracellular matrix. Elastin is an important extracellular matrix component in arterial vessel walls. Breakdown of elastin leads to the loss of structural integrity of the vessel wall and ballooning, the hallmark of aneurysm formation. MMPs play an important role in the degradation of elastin leading to aneurysm formation. Two MMPs in particular, MMP-2 and MMP-9, have been localized to areas of inflammation and internal elastic lamina degradation in aneurysms. In fatal cases of human KD, MMP-9 was expressed in coronary artery aneurysms but not in non-KD control coronary vessels suggesting a role in the development of aneurysms.

Clinical Manifestations

KD has many features suggestive of an infectious trigger. The illness is endemic with seasonal fluctuations and is punctuated with epidemic outbreaks. Many of the clinical features of KD are outbreak dependent with a different spectrum of clinical findings found from one mini outbreak to another, and cases having similar clinical phenotypes clustering temporally. KD can be divided into three phases: acute, subacute, and convalescent. The acute phase is characterized by a multi-system vasculitis, evidenced by the classic signs of inflammation including redness, heat, and swelling. The five principal features plus fever are the distinctive inflammatory changes seen in this illness. There are many associated clinical features, all attributed to the underlying vasculitis. The effects of KD on multiple systems of the body are well recognized. These include: aseptic meningitis, anterior uveitis, myositis, and hydrops of the gall bladder. The pattern of manifestations of many of these associated features has evolved over the past 2 decades mainly due to the changing pattern of clinical treatment. Arthritis can also be a common finding in KD, seen in 7% of children at diagnosis of KD. Which compares favorably to a much higher incidence in the pre-intravenous immunoglobulin (IVIG) treatment era. The arthritis of acute KD is effusive and often noted to be intensely painful, affecting ambulation in many instances. A predominance of large joints are affected regardless of the pattern of joint involvement. The clinical course of symptomatic arthritis is short-lived in the majority of affected children. Most affected children have a dramatic and rapid resolution of their arthritis following combined treatment with IVIG and high dose aspirin, regardless of the number of joints involved or distribution of disease. Despite evidence of increased systemic inflammation in children with arthritis, their response to treatment and coronary outcome are unchanged compared to children without arthritis.

The subacute phase of illness is characterized by resolution of fever, as well as the associated systemic symptoms associated with inflammation. There is often a classic peeling of the skin starting at the periungual region of the fingers and toes. During this phase, coronary artery lesions are most commonly detected. Despite early treatment with high dose IVIG and aspirin, aneurysms continue to develop in approximately 5% of children who are appropriately treated. When adjusted for body surface area, this number increases to 20–30% of affected children who develop coronary artery lesions (CAL). KD is now recognized as the number one cause of acquired heart disease in children in the developed world.

There has been increasing recognition of typical KD (see *Table 165.2* – differential diagnosis). The challenge clinically is recognition of children who present with incomplete or atypical disease. Incomplete KD is the more appropriate term as these children do not present with atypical features but rather they simply do not present with the full clinical picture typical of the disease and have fever with less than four out of five of the principal clinical features of KD. The diagnosis of KD is strictly based on clinical criteria. Having said this, many physicians and experts in the area have recognized that there are supportive criteria which aid in the identification of this group of children at increased risk for development of CAL. The American Heart Association (AHA) has proposed an algorithm to aid in the evaluation and management of children who do not fulfill full diagnostic criteria for KD (*Fig. 165.1*). The proposed supportive criteria include laboratory findings which reflect the underlying multi-system inflammation. These include elevated C-reactive protein (CRP), raised erythrocyte sedimentation rate (ESR), hypoalbuminemia, anemia, elevated serum transaminases, thrombocytosis, and leukocytosis (*Table 165.3*). Incomplete KD presents clinicians with the challenge of correctly identifying and treating patients to prevent the development of coronary artery lesions. The studies investigating the contribution of clinical phenotype to coronary outcome have identified duration of

Table 165.2
Differential diagnosis of KD

• *Staphylococcal* and *Streptococcal* disease
–Scarlet fever
–*Staphylococcal* scalded skin syndrome
–Toxic shock syndrome
• Viral infections
–Measles
–Adenovirus
–Enterovirus
–Epstein–Barr virus
• Cervical adenitis
• Drug hypersensitivity reactions
• Stevens–Johnson syndrome
• Rocky Mountain spotted fever
• Leptospirosis
• Systemic onset juvenile idiopathic arthritis
• Mercury hypersensitivity reaction (acrodynia)

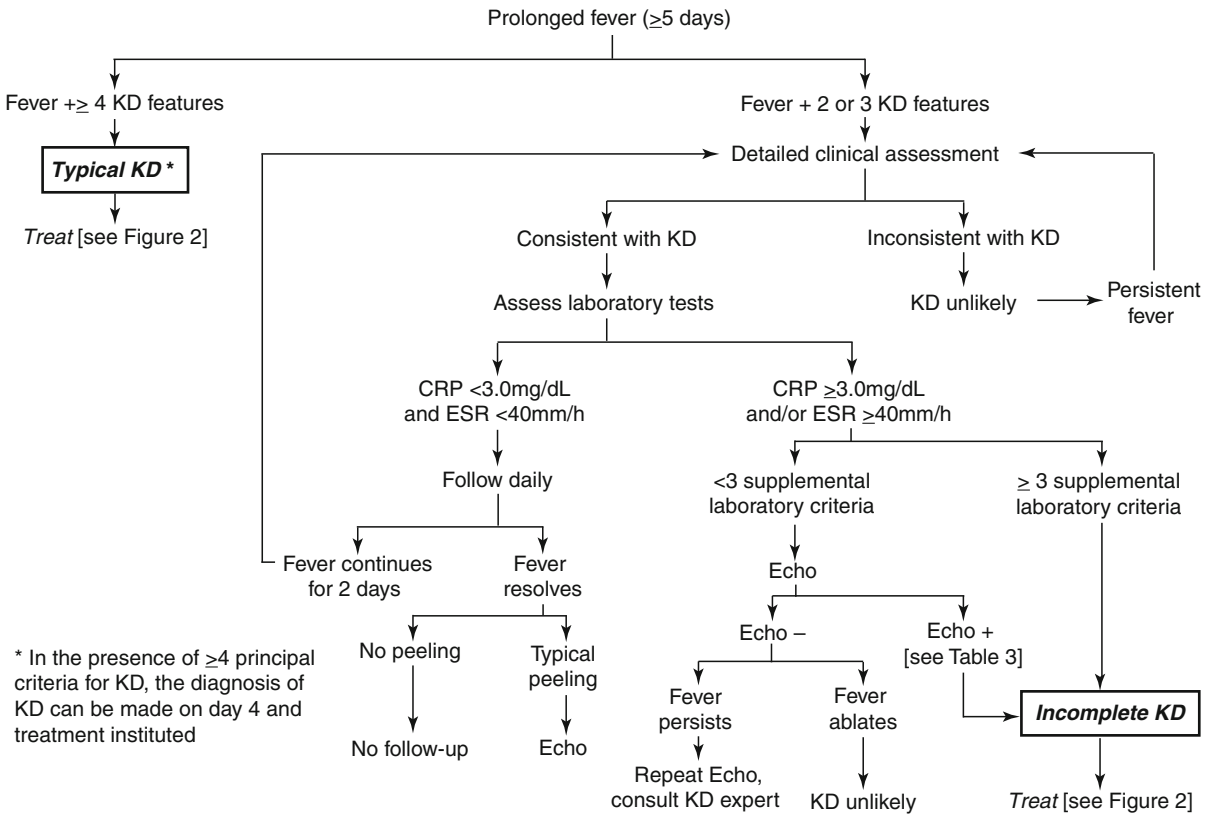

Figure 165.1
Proposed algorithm from the American Heart Association for the evaluation of a child with suspected Kawasaki disease (Adapted from Newburger 2004)

Table 165.3
Supplemental laboratory criteria in the evaluation of suspected incomplete KD[a]

1.	Hypoalbuminemia (Albumin ≤ 3.0 g/dL)
2.	Anemia for age
3.	Liver inflammation (elevated alanine aminotransferase)
4.	Thrombocytosis (platelets ≥ 450,000/mm after day 7)
5.	White blood cell count ≥ 15 000/mm
6.	Sterile pyuria (urine ≥ 10 white blood cells/high-power field)

[a]AHA algorithm 2004

fever as the most powerful predictor of poor coronary outcome. Duration of fever may be an indirect measure of the severity of the underlying vasculitis. Other surrogate markers of inflammation include the platelet count, serum albumin level, and failure to respond to IVIG therapy, all of which are related to fever duration. These clinical and laboratory features have all been identified as high-risk factors for development of coronary artery aneurysms.

The take home message for the evaluation and management of the child with suspected KD is a high index of suspicion for KD in children presenting with prolonged fever. Every young child with prolonged fever and signs or symptoms consistent with KD, with no other disease accounting for these clinical findings, needs close clinical follow-up and appropriate laboratory investigations (*Fig. 165.1*). The AHA algorithm aims to improve identification of at risk children and to initiate appropriate treatment in affected children.

Pathology

The basic pathologic lesion in KD is a necrotizing vasculitis with fibrinoid necrosis of medium-sized muscular arteries (predominantly coronary arteries), but venous involvement is also documented. The initial lesion begins

in the microcirculation in the adventitia. Inflammatory cells are detected by 7–9 days after fever onset with neutrophils rapidly giving way to lymphocytes and large mononuclear cells. Destruction of the external elastic lamina and all layers of the artery accompany this cellular infiltrate resulting in aneurysm formation.

Coronary Artery Lesions

The major long-term sequelae of KD is damage to the coronary vasculature; thus, cardiac imaging is an integral component of the management of children with KD. Two-dimensional echocardiography is the imaging modality of choice due to the noninvasive nature and the high sensitivity and specificity for detection of abnormalities in the proximal segments of the coronary arteries. Echocardiographic evaluation of the coronary anatomy should include assessment of the internal coronary artery diameters. The numbers and locations of aneurysms and the absence or presence of intraluminal thrombus should also be assessed. The criteria used to define coronary artery abnormalities in KD were first proposed by the Japanese Ministry of Health in 1984. These criteria were applicable to either angiographic or echocardiographic measurements, and defined coronary arteries as abnormal if the internal lumen diameter is greater than 3.0 mm in children less than 5 years of age or greater than 4.0 mm in children above 5 years of age, if the internal diameter of a segment measures at least 1.5 times that of an adjacent segment, or if the coronary artery lumen is clearly irregular (◉ *Table 165.4*). The AHA classified aneurysms as small (<5 mm), medium (5–8 mm), or giant (>8 mm). Coronary artery dimensions in normal children increase linearly with body size, as measured by body surface area (BSA). Thus more recently, investigators have recognized the need to correct for BSA and have classified coronary artery lesions as measurements greater than 2.5 standard deviations above the expected mean. Using this corrected BSA definition (Z-scores), there is approximately a 20% incidence of CALs despite appropriate treatment. Although the coronary anatomy is the focus of the attention in KD, cardiac function should be included in the imaging evaluation, as depressed ventricular contractility is common early in acute KD and histologic studies suggests the myocarditis is universal during the acute phase.

Although imaging protocols may vary, most agree that in uncomplicated cases, echocardiographic evaluations are needed at time of diagnosis and in the subacute phase (6–8 weeks). Additional echos between these time points may be needed to guide management of high-risk patients. Some advocate repeat imaging 6 months to 1 year post acute KD, but recent studies have suggested that normal coronary outcome at the subacute echo is unlikely to change at 1 year. There remain limitations to echocardiography, including detection of thrombi and coronary artery stenosis. In addition, the visualization of coronary arteries becomes more difficult as a child grows and body size increases. Angiography, intravascular ultrasound, transesophageal echocardiography, magnetic resonance angiography, and ultrafast computed tomography may be of benefit in the management of certain cases.

The initial size of the aneurysm is an important contributor to the likelihood of resolution/regression of that lesion, with smaller aneurysm more likely to regress. Coronary aneurysms that do not regress may progress to stenosis or occlusion or abnormal tortuosity or show continued aneurysmal morphology. Aneurysmal dilatation can also progress to rupture, but fortunately is extremely rare in KD.

◘ Table 165.4
Echocardiographic results (Echo +) supportive of KD diagnosis[a]

Any of the following three conditions:
1. BSA normalized z-score of ≥ 2.5 for the LAD or RCA
2. Japanese Ministry of Health definitions of coronary artery aneurysm which include:
• Coronary artery internal diameter > 4 mm in those ≥ 5 years old
• Coronary artery internal diameter > 3 mm in those < 5 years old
• Coronary artery internal diameter ≥ 1.5 times that of the adjacent segment
• Coronary artery lumen is clearly irregular
3. ≥3 other suggestive features including:
• Perivascular brightness
• Lack of tapering
• Decreased LV function
• Mitral regurgitation
• Pericardial effusion
• z-scores in LAD or RCA of 2–2.5

[a]AHA guidelines 2004

Treatment of Acute KD

IVIG

High dose IVIG is the accepted therapy in acute KD. Its efficacy in reducing the prevalence of coronary artery

lesions is well documented. Many different doses and administration schedules have been used in North America, Europe, and Japan. The general consensus is that higher doses given in a single infusion have the greatest efficacy. Several meta-analysis have confirmed this dose effect. Dose comparison studies showed a significant reduction of aneurysms with increasing dose, with those receiving 2 g/kg in a single dose showing both a reduction in the number of aneurysms as well as a reduction in the duration of fever compared to those receiving lower doses. Different predictive instruments have been developed to model risk for poor coronary outcome. In Japan, the Harada score was developed to aid in the rational allocation of a limited IVIG supply to those at highest risk for aneurysm formation. In addition to the clinical factors already described, male sex and the very young (<12 months old) were added as demographic features of those at risk.

The AHA recommends that IVIG be administered in a single infusion at a dose of 2 g/kg. Most infusion protocols start with a very slow rate with stepwise increases in infusion rate. The total duration of the IVIG infusion is typically 8–12 h depending on the concentration of IVIG. Multi-system inflammation involving the heart can potentially compromise the heart's ability to handle the fluid challenge associated with the IVIG infusion, thus necessitating the long duration of infusion. IVIG therapy should be instituted during the acute phase of illness, typically within the first 10 days of fever, but IVIG treatment is indicated anytime during the acute phase of illness even in those presenting after day 10 of illness. Early treatment with IVIG before day 5 of illness does not affect coronary outcome, but may increase the need for IVIG retreatment. This observation may be biased for a more severe phenotype in those treated early. When analyzed separately, those treated early ($\leq$ 4 days of fever) had higher risk scores than those treated later suggesting that those treated early in their disease course had more dramatic clinical features implying more intense inflammation and severe vasculitis.

IVIG is made from pooled donor plasma. As such, manufacturing and product differences are present. There are ongoing and conflicting investigations into potential differences in efficacy and side-effect profile between different IVIG preparations. Nonetheless, prescribing practices vary from institution to institution and the use of many different products and concentrations (5% or 10% solutions) of IVIG are employed in the acute therapy of KD and may be dictated by product availability. Although the mechanism of action of IVIG in the treatment of KD is not clearly understood, IVIG does have general immunomodulatory effects. Possible mechanisms of action include general immunosuppression via the modulation of pro-inflammatory cytokine production, and regulation of expression and function of Fc receptors, inhibiting activation of complement, neutralization of bacterial superantigens or other infectious agents, anti-idiotypic antibody effects, and effects on the activation, differentiation, and effector functions of both T cells and B cells and other antigen presenting cells.

Due to the protective effects of receiving pooled immunoglobulin and the general immunomodulatory effects, immunizations may not generate an effective or protective immune response for months after IVIG administration. Although harmless to receive immunizations, both live or killed vaccines, they may not be effective and the child may need to be re-immunized 9–11 months after IVIG administration if there is an inadequate immune response. Typically, live vaccinations are deferred for 9–11 months after a child receives high dose IVIG unless the risk of infectious exposure is high.

Aspirin

A widely debated issue in the acute therapy of KD is the dose of aspirin – high versus low dose. At high doses, aspirin has important anti-inflammatory properties and at low doses, it has anti-platelet activity. At high doses, salicylates inhibit the activity of IKK, thereby preventing NF-κB nuclear translocation. At lower doses, salicylates inhibit the cyclooxygenase enzymes leading to a reduction in prostaglandin and thromboxane synthesis. Despite high dose aspirin having an additional mechanism of immunomodulation compared to low dose aspirin, with inhibition of nuclear translocation of NFκB affecting transcriptional regulation of important pro-inflammatory cytokines as well as inhibition of TNFα signal transduction, administration of aspirin during the acute phase of KD does not appear to alter coronary outcome. During the acute phase of KD, the anti-inflammatory dose of aspirin, 80–100 mg/kg/day given in four divided doses, is typically prescribed in North America. Circulating total salicylate levels have been shown to vary tremendously despite consistent oral dosing at 80–100 mg/kg/day, with serum concentrations ranging from 0.1–0.25 mg/mL.

The duration of high dose aspirin therapy varies from institution to institution. Many centers reduce the aspirin dose to anti-platelet levels (3–5 mg/kg/day) after the affected child has been afebrile for 24–72 h. Others continue anti-inflammatory doses of aspirin until day 14 of illness or longer. In Japan, the dose of aspirin used is lower

(20 mg/kg) and may reflect the different pharmacokinetics of aspirin metabolism in the Oriental population. A Cochrane review of aspirin in the therapeutic management of acute phase of KD concluded that there is insufficient evidence to support or refute the use of aspirin as part of the treatment regimen due to lack of good quality randomized clinical trials. Low dose aspirin is administered for its anti-platelet effect and typically continued until the child shows no evidence of coronary artery damage at 6–8 weeks after fever onset and laboratory measures of inflammation have returned to normal. Children with coronary artery lesions may continue aspirin or other anti-platelet agents indefinitely.

Refractory Disease

One of the major challenges in the current management of KD is the treatment of patients who fail to respond to initial therapy with IVIG. Ten to twenty percent of children will not respond to a single dose of IVIG. The definition of refractory disease or treatment failure varies, but in general is defined as persistent or recrudescent fever $\geq$ 36 h after initial IVIG therapy. Persistent fever is more common than recrudescent fever. Although debate continues regarding the optimal therapy for refractory disease, most investigators agree on a second dose of IVIG. The second dose of IVIG continues to be high dose therapy at 2 g/kg. Treatment of this subgroup of patients with refractory KD has included additional IVIG, corticosteroids, and much less commonly various immunosuppressive agents including cyclophosphamide and cyclosporin, as well as plasma exchange, inhibition of elastase activity (ulinastatin), and more recently the biologic therapy against tumor necrosis factor-alpha (*Fig. 165.2*). The goal of all these therapies is to ameliorate the immune response thus decreasing the chance of ongoing inflammation and damage to the coronary arteries. The order of these therapeutic interventions continues to be controversial.

Although steroids are efficacious and widely used in other forms of vasculitis, their use in KD is very limited.

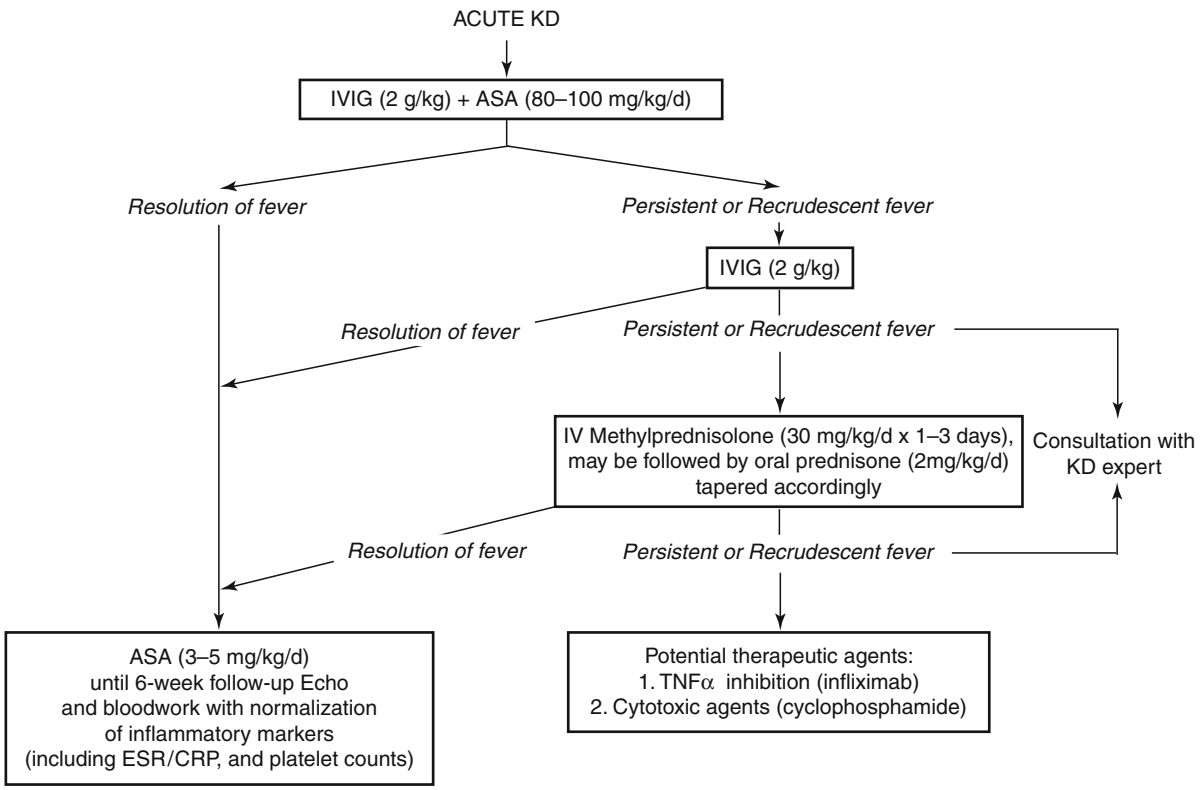

Figure 165.2
Proposed algorithm for the management of acute Kawasaki disease

Use of steroids in acute KD has been controversial, but more recent studies have shown their usefulness in both the acute phase as well as in refractory disease. KD refractory to IVIG was the most common indication for corticosteroid use in patients with KD, and this treatment was found to be effective, with rapid resolution of fever in the majority of patients. The most common dosing regimen of steroids is high dose pulse steroids given as intravenous methylprednisolone 30 mg/kg up to a maximum of 1 g. This is given once per day over 1–3 days. Dosing regimens vary from center to center and little evidence is available to support the dose or schedule of steroid administration. At our institution, high dose IV dosing may be followed by oral prednisone at 2 mg/kg/day which is then rapidly tapered to 0 over the course of 1 to 2 weeks unless resistant fever or fever recrudescence requires a longer taper or alternate therapy (◉ *Fig. 165.2*).

Therapeutic Options in Children with Coronary Artery Aneurysms

No prospective studies are available to guide treatment decisions in children with coronary artery lesions, thus recommendations are based on knowledge of the pathophysiology and lessons learned from adults with coronary disease. The basis of these therapeutic guidelines is prevention of thrombosis, and specific management is dependent on the extent and severity of coronary artery disease. As such, anti-platelet therapy alone or in combination with anti-coagulation is an integral component of the management plan. Thrombocytosis together with platelet activation is a key finding in KD, thus necessitating the use of anti-platelet agents. Low dose aspirin is used even in those with no evidence of coronary damage until the 6-week follow-up echocardiogram and may be continued indefinitely in those with coronary artery damage. In the presence of more severe coronary disease, the addition of another anti-platelet agent targeting non-ASA-dependent pathways of platelet activation (dipyridamole and clopidogrel) may be included. In the presence of large or giant aneurysms, which pose a significant thrombotic risk, anti-coagulation is added. In the acute phase, the usual choice is heparin. Long-term anti-coagulation can be achieved by either warfarin or low-molecular weight heparin in combination with an anti-platelet agent. Little data is available to guide interventions in the presence of intravascular thrombi, but recent trials have targeted the platelet glycoprotein IIb/IIIa receptor involved in the final common pathway of platelet aggregation. Abciximab, a platelet glycoprotein IIb/IIIa receptor inhibitor, has been used acutely in children with intraluminal thrombus to reestablish vessel patency and salvage the myocardium.

Conclusion

In summary, KD is an important cause of acquired heart disease in childhood. There is increasing recognition of typical KD. The challenge clinically is recognition of children who present with an incomplete clinical presentation. A high index of suspicion in every child with prolonged fever and signs or symptoms consistent with KD, coupled with close clinical follow-up and appropriate laboratory investigations and imaging is warranted. Prolonged inflammation leading to coronary artery damage is the underlying pathology in KD. Early identification and treatment of affected children to suppress the inflammatory response is one of the objectives of therapy. High dose IVIG together with aspirin is the mainstay of therapy in acute KD. Disease modeling continues to be imperfect and future studies will need to identify novel biomarkers to enhance the traditional clinical and laboratory measures of inflammation. The ultimate goal for identification of this high-risk phenotype is to guide clinical decisions involving use of therapeutic interventions to improve coronary outcome in affected children.

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166 Childhood Polyarteritis Nodosa

Fatih Ozaltin · Seza Ozen

Definition/Classification

Polyarteritis nodosa (PAN) is a clinical syndrome with a wide variety of signs and symptoms, which are caused by fibrinoid necrosis of small and/or medium-sized arteries. Two disease entities are defined: classical PAN and cutaneous PAN. Microscopic PAN will be discussed in another section. Patients are often classified as PAN based on existing criteria. The recent EULAR/PRINTO/PRES (Ankara) criteria propose the need for a biopsy showing characteristic histological features of PAN or angiography reflecting the mid-size arteritis, as mandatory criteria for the classification of a child as PAN (*Table 166.1*).

Epidemiology

PAN is a rare disease in both children and adults. The disease is seen worldwide. In a large international multicenter study, where 110 patients with PAN were included, it has been reported that mean age at diagnosis was 9.05 ± 3.57 years and that the girl to boy ratio was 56:54.

Etiology, Pathogenesis, and Genetic Background

In most cases, the etiology remains unknown; however, infectious agents have been considered as etiologic or contributing factors. A relationship between hepatitis B infection and PAN has been well described and probably represents an immune complex disease. Streptococcal infections could also be a contributing factor especially in patients with cutaneous PAN.

There is no substantial evidence on genetic predisposition for PAN. Familial occurrence is rare. Recent studies have suggested that PAN is more frequent in patients with familial Mediterranean fever (FMF). It has been suggested that mutations in the gene for FMF provide a susceptibility factor for the development of PAN by forming a proinflammatory state.

Clinical Manifestations

PAN is typically a multisystem disease resulting from vascular inflammation predominantly in skin, abdominal viscera, kidneys, central nervous system (CNS), and muscles. Symptoms may be subtle. However, PAN should be considered in any child with unexplained fever, palpable purpura, myalgia, arthritis, mononeuritis multiplex, or unexplained pulmonary, cardiovascular, or renal disease. Children usually have constitutional symptoms such as fever, malaise, and weight loss. Skin lesions include petechia/purpura, splinter hemorrhages, infarction and ulceration, papules, livedo reticularis, and painful nodules.

Nonspecific abdominal pain occurs in two thirds of patients, usually due to mesenteric and other ischemia caused by vasculitis. Infarction of the gut, gallbladder, or pancreas may develop. Aneurysms of abdominal mid-size arteries have been reported.

Renal involvement (proteinuria, hypertension) has been reported as 45–80%. Renal involvement is classically limited up to the level of spiral arteries, and glomerulonephritis is not seen in this type of PAN.

Clinical findings regarding central nervous system involvement may vary from organic brain syndrome to seizures and hemiparesis. Sensorimotor peripheral neuropathy (mononeuritis multiplex) is quite characteristic.

Cardiovascular involvement including mitral and/or tricuspid valve regurgitation, and impaired left ventricular function may rarely occur.

Testicular or epididymal swelling and tenderness are again rare but important findings for diagnosis in males.

Laboratory Findings

Mild anemia, leukocytosis, thrombocytosis, and elevated acute phase reactants are characteristic features. Autoantibodies are negative and ANCA is frequently negative in this type of PAN.

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Table 166.1
Classification of PAN (Ozen et al. (2010))

Typical histopathology or angiographic abnormality (mandatory) plus one out of five of the following criteria:
1. Skin involvement
2. Myalgia or muscle tenderness
3. Hypertension
4. Peripheral neuropathy
5. Renal involvement

Treatment

Corticosteroids and cyclophosphamide are the mainstay of treatment of systemic necrotizing vasculitides. Oral or intravenous cyclophosphamide is indicated in severe organ involvement. The cumulative dose of cyclophosphamide is a major concern. A number of large studies have shown that a cumulative dose up to 200–250 mg/kg is safe in terms of gonadal toxicity. Azathioprine is used for maintenance treatment.

Prognosis

The prognosis of childhood PAN was guarded in initial series. However, with the judicious use of immunosuppresants, the prognosis, even in children with definite systemic involvement, is better than adults, with reported survival rates.

Cutaneous PAN

Cutaneous PAN (CutPAN) is designated for polyarteritis nodosa limited fundamentally to the skin. It has been described as a distinct clinical entity with benign but relapsing course without systemic involvement. However, there has been much debate on whether or not it can progress to systemic form.

A history of a preceding upper respiratory tract infection, often with streptococcus, is usually present. CutPAN is characterized by purpura, multiple painful subcutaneous nodules, livedo reticularis, and sometimes nonspecific musculoskeletal findings such as myalgia and arthralgia. Constitutional symptoms are not expected to be present and the acute phase reactants are often normal. Nonsteroid antiinflammatory drugs are used in most cases. CutPAN usually responds to short courses of prednisone (0.5–1 mg/kg/day) therapy. Prolonged course and relapses are frequent. Penicillin prophylaxis may be needed if streptococcal infection is implicated as triggering agent. Prognosis is generally good; however, relapses and the chronic course are of concern.

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167 Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Small-Vessel Vasculitides

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Definition

The antineutrophil cytoplasmic antibody (ANCA)-associated small-vessel vasculitides (AAV) comprise a group of disorders characterized by necrotizing vasculitis with a paucity of immune deposits associated with antibodies against cytoplasmic constituents of neutrophils, particularly proteinase 3 (PR3) and myeloperoxidase (MPO). In this group, three major clinical entities are present: *Wegener's granulomatosis* (*WG*), *Churg–Strauss syndrome* (*CSS*), and *microscopic polyangiitis* (*MPA*). It should be emphasized that most but not all patients show a positive ANCA by serology.

Wegener's Grantulomatosis

Wegener's granulomatosis (WG) is a necrotizing vasculitis affecting small to medium-sized vessels. The disease is characterized by granulomatous inflammation involving respiratory tracts, including sinuses, nasal passages, pharynx, and lungs, and pauci-immune necrotizing crescentic glomerulonephritis, and in most patients the presence of ANCA.

Epidemiology

WG is rare in childhood. This has resulted in descriptions in the pediatric population that have been based on smaller numbers of patients, most often in the form of case reports, case series, and literature reviews. The two largest single-center pediatric series to date have reported on a combined total of only 40 patients. In a recent report of 60 patients, the mean age of diagnosis was 11.7 years.

Etiology and Pathogenesis

The etiology of WG remains unknown. Both genetic and environmental factors seem to be involved. Familial occurrence is extremely rare. Use of cocaine and exposure to silica have been indicated as environmental factors. As carriage of *Staphylococcus aureus* is strongly associated with PR3–ANCA positive Wegener's granulomatosis, the bacterium might be involved in the PR3-specific autoimmune response. However, it has not been possible yet to produce the disease associated with PR3 ANCA in animals.

Pathology

The characteristic pathologic finding is granulomatous involvement in arteries. Kidney biopsy is indicated in children with kidney involvement. Characteristic finding is pauci-immune necrotizing crescentic glomerulonephritis (◉ *Fig. 167.1*). Granuloma formation is rarely observed in kidney tissue unlike to the lung or sinus biopsy.

Clinical Manifestations

Clinical manifestations are nonspecific and virtually any organ can be involved. However, presenting and diagnostic symptoms are usually confined to the respiratory tract and the kidneys. The classical triad of the disease is paranasal sinus involvement, pulmonary infiltration, and kidney involvement (◉ *Table 167.1*). Constitutional symptoms, including fever, malaise, and weight loss, are common at presentation. In different pediatric series, upper respiratory tract involvement (sinusitis, epistaxis, otitis media, etc.) has been reported in 84–100% of the patients, while lower respiratory tract involvement in 80–87%. Since subglottic stenosis is common in the pediatric practice, the presence of upper airway involvement (subglottic, tracheal, and endobronchial stenosis) has been added as a criterion to the revised classification criteria in childhood WG.

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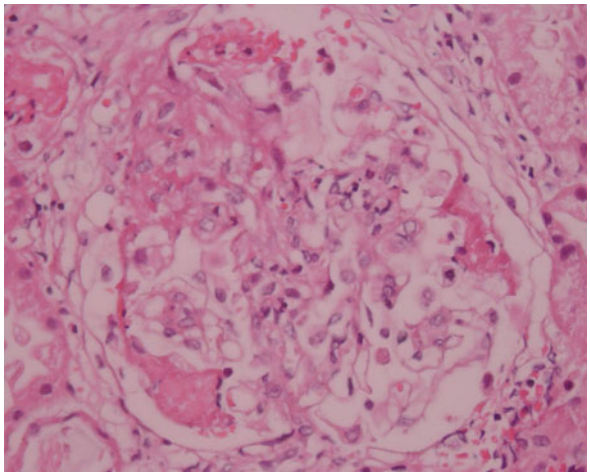

Figure 167.1
Necrotizing crescentic glomerulonephritis in a child with ANCA-associated vasculitis

Renal involvement, which is characterized by necrotizing pauci-immune glomerulonephritis in biopsy, is frequently seen and often causes renal failure requiring dialysis. Skin lesions including purpura and panniculitis/nodules may be seen in one third of the patients. Conjunctivitis, scleritis, and proptosis have also been reported as frequent symptoms at onset or during the course of the disease. Arthritis/arthralgia, hypertension, gastrointestinal involvement venous thrombotic events and CNS involvement occur less frequently. The disease may also present in a limited form.

Diagnosis and Laboratory Findings

Many of the "classic" features of the disease may be lacking early in the course. Although diagnostic criteria do not exist, for diagnosis the child should have (1) small-vessel vasculitis; (2) granulomatous inflammation of the airways; (3) nodules, infiltrations on chest radiographs; and (4) renal involvement. According to recently proposed classification criteria, three out of six criteria should be present for WG (*Table 167.1*).

There is usually mild anemia and thrombocytosis. Marked elevation of acute phase reactants are usually present. Urinalysis may show microscopic hematuria, proteinuria, and casts in case of renal involvement. Renal impairment may be present.

ANCA is highly associated with WG (*Table 167.1*). ANCA may be either cytoplasmic (c-ANCA), which is related to proteinase 3 (PR3) or more rarely related to myeloperoxidase (MPO). Sensitivities of PR3-ANCA and MPO-ANCA for WG are 70–80% and 10%, respectively. A few patients with WG are ANCA-negative.

Table 167.1
EULAR/PRINTO/PRES (Ankara, 2008) classification criteria for Wegener's granulomatosis (From Ozen et al. (2010))

Three of the following six should be present:
1. Abnormal urinalysis[a]
2. Granulomatous inflammation on biopsy
3. Nasal and/or sinus and/or oral inflammation
4. Subglottic, tracheal, or endobronchial stenosis
5. Abnormal chest X-ray or computed tomography
6. Any ANCA positivity

[a] If kidney biopsy is performed, it characteristically shows necrotizing pauci-immune glomerulonephritis

Radiologic Findings

Chest radiographs or CT are abnormal in up to two thirds of the patients and include nodules, cavitation and infiltrates, and pleural effusions. Sinus radiographs will reflect the sinusal involvement.

Treatment

Since there are few data relating to treatment of children with WG evidence-based treatment, recommendations come from studies performed in adult population.

Localized disease defined by the European Vasculitis Study (EUVAS) group refers to patients with symptoms restricted to the upper and/or lower airways, without constitutional symptoms or systemic vasculitis. In this group, Methotrexate may be used to induce remission.

EUVAS approaches the treatment of (systemic) WG and MPA in a similar fashion, and thus the treatment of these two diseases will be reviewed together. Conventional treatment is to induce remission with cyclophosphamide and corticosteroids in these two ANCA-associated vasculitides, WG, or MPA. Patients should be started with oral prednisone plus pulse intravenous cyclophosphamide or oral cyclophosphamide to induce remission. In this study of adults, prednisone was tapered to 10 mg by 6 months. Cyclophosphamide doses should be adjusted to age, renal function (level of evidence 1b; recommendation A).

In the CYCAZAREM study, azathioprine has proven to be effective for maintenance therapy after 3–6 months of remission induction therapy with prednisolone and oral cyclophosphamide. Leflunomide, methotrexate, and

mycophenolate mofetil may be alternative therapies to maintain remission.

In severe renal vasculitis and immediately life-threatening disease, plasma exchange should be started to improve renal prognosis (level of evidence 1b; recommendation A). In refractory disease, there are no randomized trials providing evidence for the best therapy. Rituximab has been proven to be effective in recent trials of ANCA-associated vasculitides in adults.

Prognosis

The use of immunosuppressives has resulted in much lower mortality rates than those published in early studies of WG. Lack of ear, nose, and throat involvement has also been shown to be a significant indicator of increased risk of mortality. Treatment may result in significant morbidity and mortality.

Churg–Strauss Syndrome (Allergic Granulomatosis)

Churg–Strauss syndrome (CSS) is a disease characterized by pulmonary and systemic small-vessel necrotizing vasculitis, vascular and/or extravascular granulomas, eosinophilia and tissue infiltration by eosinophils, occurring in individuals with asthma, and often allergic rhinitis or sinusal polyposis. Asthma and severe eosinophilia in combination with vasculitic organ manifestations are key features of this unique disease.

Epidemiology

Reports of CSS occurring in children are limited and generally consist of single case reports. In a recent systematic review, where 33 children with CSS have been included, mean age at onset has been found as 12 years with a male-to-female ratio of 0.74.

Etiology and Pathogenesis

Etiology and pathogenesis remain unknown. Inhaled allergens, infections, drugs have been implicated as triggers. A possible contribution of leukotriene receptor antagonists to the development of CSS has been suggested.

The pathogenic role of anti-MPO autoantibodies is now well established both in vitro and in vivo. However, the mechanisms leading to vasculitis in CSS are yet to be elucidated, particularly in ANCA-negative patients.

Pathology

Histological signs of CSS include eosinophilia, vasculitis, or granuloma. Small-vessel vasculitis is found in most of the patients, extravascular eosinophils are histologically evident in 80% of the patients, while granulomas are seen in 45% of them.

Clinical Manifestations

History of asthma has been reported in 91% of the patients while sinusitis in 77% at the time of clinical presentation. Pulmonary infiltrates are also a common finding (85%), whereas pleural effusions are rarely seen (12%). Other organs such as the skin (66%), peripheral nerves (39%), and the gastrointestinal tract (40%) are also involved. Renal and musculoskeletal symptoms occur rarely. Cardiac involvement is frequently seen and is characterized by granulomatous pericardial disease (27%) and eosinophilic cardiomyopathy (42%). Severe mitral valve regurgitation has also been reported. Other organs are rarely affected.

Diagnosis

According to the American College of Rheumatology criteria for classification of the CSS, a patient is considered to have CSS in the presence of at least four of the following criteria with a sensitivity of 85% and a specificity of 99.7%: (1) asthma, (2) eosinophilia, (3) history of allergy, (4) mono/polyneuropathy, (5) pulmonary infiltrates, (6) paranasal sinus abnormality, (7) extravascular eosinophils in biopsy.

Laboratory Findings and Pathology

The most striking laboratory features are significant eosinophilia ($\geq$10% of the peripheral leukocytes) and elevation of serum IgE level. Acute phase reactants are increased in active disease. ANCA positivity is not a consistent finding however the usual association is with MPO-ANCA.

Chest X-Ray may reveal diffuse pulmonary infiltrates with impaired pulmonary function tests.

Treatment and Prognosis

Strict and aggressive therapy is indicated in patients with CSS. Most children respond well to initial steroid therapy. However, those patients with vital organ involvement immunosuppressive agents such as cyclophosphamide, azathioprine, or metotrexate are often needed.

Mortality is significantly higher (19%) in children than adults (5%). This is partly explained by the more severe cardiac involvement, which has major impact on mortality.

Microscopic Polyangiitis

Microscopic polyangiitis (MPA) is defined as non-granulomatous small-vessel vasculitis with few or no immune deposits affecting small vessels. Necrotizing glomerulonephritis is very common and necrotizing arteries of medium-sized arteries may also be present. Pulmonary capillaritis without upper respiratory tract involvement often accompanies to glomerulonephritis. It can mimic classical PAN histologically, as both diseases produce necrotizing arteritis. The key distinction between them is in the involved vessel size since MPA is predominantly small-vessel vasculitis, while PAN is confined to mid-sized arteries. In addition, MPA is often associated with a high titer of MPO-ANCA.

Epidemiology

Microscopic polyangiitis is rare in children. The annual prevalence of MPA has been reported as 25.1 per million adults in France. In two pediatric series, the mean age at diagnosis was 12 years.

Etiology, Pathogenesis and Genetic Background

Infections may have an initiating role, although a specific antigen has not been indicated. MPO-ANCA has been implicated in the pathogenesis. There are several in vitro data supporting the observation that ANCA are capable of endothelial damage. In two elegant animal models, anti-MPO antibodies in mice and in rats induced necrotizing and crescentic glomerulonephritis with widespread vasculitis in the lung and other organ systems.

Genetic factors may be operative in the pathogenesis. MPO levels are influenced by two single nucleotide polymorphisms in the gene, MPO463 and MPO129. The MPO 463 polymorphism has been associated with an increased risk of development of MPO-ANCA associated disease.

Clinical Manifestations

The constitutional features of MPA are similar to those of classical PAN. However, the predominant feature is progressive (often rapidly) glomerulonephritis with or without pulmonary involvement. It is one of the leading causes of pulmonary-renal disease in children. Renal disease manifests as nephritis and renal functions may be acutely impaired. Myalgia, skin lesions, joint disease, gastrointestinal symptoms, and central and peripheral nervous system involvement have all been defined in MPA. In some series, end stage renal disease has been reported as high as 40%.

Diagnosis and Laboratory Findings

Diagnosis depends on characteristic renal biopsy findings in the presence of typical clinical manifestations and a positive p-ANCA staining with high MPO-ANCA level by ELISA. Classical PAN, Henoch Schonlein purpura, Wegener's granulomatosis, Churg–Strauss syndrome, and systemic lupus erythematosus should be considered in differential diagnosis.

Leukocytosis, thrombocytosis, and elevation of erythrocyte sedimentation rate and C-reactive protein level are consistently present. Urinalysis shows proteinuria and hematuria. Renal functions may be impaired.

MPO-ANCA is important in diagnosis and follow-up of the disease. In childhood, those patients with necrotizing glomerulonephritis and pulmonary involvement seem to have the highest MPO-ANCA levels.

Treatment and Prognosis

Guidelines for treatment of Wegener's Granulomatosis (WG) are applicable for MPA as well.

Five-year survival rates vary between 45% and 74% in different adult series. Renal involvement is a significant factor in predicting poor prognosis, either in the form of proteinuria (>1 g/day) or raised creatinine levels. Overall relapses seem to be less frequent as compared to WG.

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168 Takayasu Arteritis

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Definition

Takayasu arteritis (TA) is a chronic, idiopathic vasculitis of the large arteries. It primarily affects the aorta, its proximal branches, and occasionally the pulmonary arteries, which result in luminal stenosis, occlusion, or aneurysms.

Epidemiology

In children, the mean age of onset is 12 years. The female: male ratio is about 2:1. There are geographic variations in the presentation of TA. While obstructive lesions are frequent in the United States, Europe, and Japan, aneurysms are more common in Africa and India.

Etiology, Pathogenesis, and Genetic Background

Although many studies have proposed microorganisms such as bacteria and viruses as causative agents in TA, no specific infectious agents have been confirmed so far.

Circulating antiaortic endothelial cell antibodies (AAECAs), increased expression of E-selectin and vascular cell adhesion molecule-1, and increased production of interleukin (IL)-4, IL-6, and IL-8 have been reported in patients with TA.

Rare familial cases may suggest the role of genetic factors. Genes of certain activation molecules are upregulated in patients with TA.

Clinical Manifestations

Clinical manifestations are symptoms secondary to ischemia of organs supplied by stenotic vessels and constitutional symptoms such as fever, weight loss. The ischemic symptoms include stroke, visual aberration, angina, and renovascular hypertension, and claudication of extremities. Hypertension is one of the most frequent presenting symptoms in childhood. Headache is also a frequent complaint. Absent pulses and bruits over the stenotic vessel may be detected. Classically, TA follows a number of courses. The monophasic course is limited to 20% of cases. Some patients exhibit progressive or relapsing/remitting course.

Diagnosis and Laboratory Findings

To demonstrate angiographic abnormalitie(s) is mandatory for the diagnosis. Recent proposed classification criteria for TA is given in *Table 168.1*.

Acute phase reactants are elevated in about 2/3 of the patients. Autoantibodies, rhematoid factor, and ANCA are negative; however, anti-endothelial antibodies are frequently present. Electrocardiography may show findings of left ventricular hypertrophy suggesting chronic hypertension.

Radiologic Findings

Since TA involves aorta and its main branches, MR angiogram will be adequate to show the vascular lesions (*Fig. 168.1*). PET scan can be performed in selected cases, especially for differential diagnosis; however, the high cost is of concern.

Four types of involvement have been described in angiography. These include (1) aortic arch only; aortic arch and descending thoracic aorta; aortic arch, thoracic and abdominal aorta; aortic arch and abdominal aorta, (2) descending thoracic aorta only; descending thoracic and abdominal aorta, (3) diffuse aortic involvement, and (4) diffuse aortic and pulmonary artery involvement.

Treatment

Corticosteroids, methotrexate (MTX), azathioprine, mycophenolate mofetil, and cyclophosphamide (CYC) have all been used in the treatment of TA. A high (50%)

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Table 168.1
Classification criteria for Takayasu Arteritis, Ankara 2008 (Ozen S, Pistorio A, Iusan SM et al. (2010) The EULAR/PRINTO/PRES criteria for Henoch-Schönlein Purpura, Wegener Granulomatosis, Takayasu Arteritis and Childhood Polyarteritis Nodosa: ANKARA, 2008. Ann Rheum Dis 69:798–806)

Angiographic abnormalities (mandatory criterion) and 1 out of 5 of the following criteria:
1. Pulse deficit or claudication
2. Four limbs blood pressure discrepancy
3. Bruits
4. Hypertension
5. Increased acute phase reactants

relapse rate is observed in adults treated with corticosteroids only. There is no consensus on follow-up and no A-level evidence-based data on the treatment of childhood patients. In a recent study, patients were allocated to receive (1) oral steroids and MTX if they had disease limited to one side of the diaphragm only, and without pulmonary disease; and (2) oral steroids and oral CYC followed by oral MTX as above if the disease was more widespread. This single-center experience suggests that cyclophosphamide and corticosteroid induction followed by methotrexate is an effective and safe treatment for childhood TA and may prevent relapses. Angiotensin-converting enzyme inhibitors and angiotensin1 receptor blockers should be avoided in the presence of renal artery involvement. In resistant cases, anti-TNF treatment has been successful in case series.

Angioplasty or bypass grafting can successfully be performed when needed. However, this procedure should be done when the patient is in remission.

Prognosis

There is an absence of prospective and randomized controlled trial data in TA in childhood. However, from adult studies, it is estimated that TA has an overall 10-year survival rate of approximately 90%. This rate is reduced by the presence of complications. Optimal management of these factors could reduce the mortality.

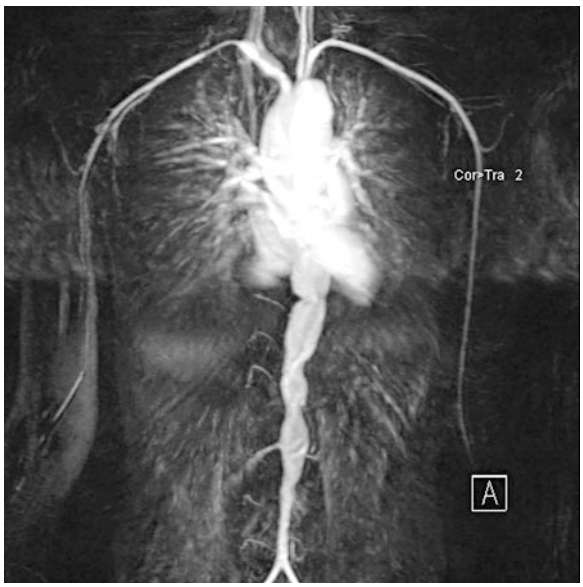

Figure 168.1
Stenosis in right subclavian artery and aneurysmal and stenotic segments in the abdominal aorta (With the courtesy of Dr. Tuncay Hazrolan)

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169 Other Forms of Vasculitis

Fatih Ozaltin · Seza Ozen

Hypocomplementemic Urticarial Vasculitis Syndrome

Definition

Hypocomplementemic urticarial vasculitis syndrome (HUVS) is a rare vasculitic disorder characterized by recurrent attacks of erythematous, urticarial, and hemorrhagic skin lesions associated with arthritis and sometimes abdominal distress. HUVS can also be distinguished by the presence of angioedema, urticaria, uveitis, and chronic obstructive pulmonary disease.

Etiology and Pathogenesis

Exact etiology of the diseases is unknown. HUVS is an immune complex disease characterized by the presence of anti-C1q antibodies at a high titer in all patients. Anti-C1q is thought to contribute to the formation of circulating or locally formed immune complexes. Furthermore anti-C1q may be pathogenic by disturbing the clearance of apoptotic cells, resulting in induction of autoimmunity or aggravating the autoimmune inflammatory state.

Clinical Manifestations, Laboratory Findings, and Pathology

Although rare, HUVS must be considered in the differential diagnosis for all patients with urticarial rash (*Fig. 169.1*). Renal disease affects up to 50% of patients and usually occurs within 4 years of onset of the rash. The laboratory hallmark of HUVS is hypocomplementemia involving the early components of the classical complement pathway. Urinalysis may be normal or can demonstrate hematuria and/or proteinuria.

The skin biopsy shows leukocytoclastic vasculitis whereas the kidney involvement may vary from crescentic glomerulonephritis to membranoproliferative or membranous lesions.

Differential Diagnosis

Systemic lupus erythematosus (SLE), cryopyrin associated periodic fever syndromes and other hypocomplementemic diseases should be considered in the differential diagnosis. A certain portion of the patients may progress to SLE as well.

Treatment and Prognosis

No specific therapy is currently available for HUVS. Skin lesions appear to be poorly responsive to antihistamines. Prednisone, hydroxychloroquine, or dapsone has been used successfully in anectodal reports. Pulmonary disease associated with HUVS can be life threatening, and no therapies have been shown to be consistently effective. Some patients with progressive renal deterioration have responded to high-dose prednisone, with or without cyclophosphamide. Prognosis depends on the extent of systemic involvement.

Cogan Syndrome

Definition

Cogan syndrome (CS) is a systemic vasculitis characterized by sensory neural hearing loss and nonsyphilitic interstitial keratitis.

Etiology and Pathogenesis

Etiology and pathogenesis remain unknown although association with some particular infections has been suggested. Organ-specific autoimmune processes have been implicated.

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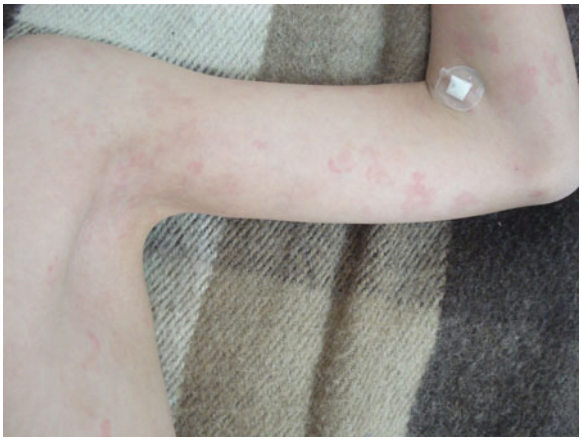

Figure 169.1
Typical urticarial lesions in hypocomplementic urticarial vasculitis in a girl

Clinical Manifestations and Laboratory Findings

Clinical manifestations include inflammatory eye disease (i.e., interstitial keratitis, conjunctivitis, scleritis, retinitis, retinal vasculitis) and vestibuloauditory dysfunction. Systemic vasculitis affecting aorta or small-/medium-sized arteries and aortic valve insufficiency and constitutional symptoms may be observed. Acute phase reactants are elevated and antinuclear antibody may be positive.

Differential Diagnosis

In differential diagnosis, one should consider Takayasu arteritis, Wegener's granulomatosis, and polyarteritis nodosa.

Treatment and Prognosis

Early diagnosis and treatment are mandatory to avoid ophthalmologic and otologic sequelae. A combination of corticosteroids and corticosteroid-sparing immunosuppressive drugs such as cyclophosphamide and methotrexate have been advocated. Disease course may be characterized by flares and remissions over years. A significant proportion of the patients become deaf.

Central Nervous System Vasculitis

Definition

Primary vasculitis (or angiitis) of the central nervous system (CNS) is inflammatory vasculitis affecting the CNS vessels alone. Diagnostic criteria have been suggested for adults including (1) a newly acquired neurologic deficit, (2) angiographic and or histologic features of CNS vasculitis, and (3) no evidence of systemic condition. CNS vasculitis can also be secondary to a number of infectious diseases or systemic lupus erythematosis.

Etiology and specific pathogenesis of the primary CNS vasculitis are unclear.

Clinical Manifestation, Laboratory Findings, and Pathology

Headache, transient ischemic attacks, paresis and plegia, seizures, encephalopathy, and neurocognitive impairment may all occur. The diagnosis may be considered in any child with sudden onset neurologic deficit.

Acute phase reactants and cerebrospinal fluid examination may be completely normal. There may be an increased protein and mild pleocytosis in the cerebrospinal fluid. An angiography is indicated for the assessment of CNS vasculitis. In large/medium vessel vasculitis, a magnetic resonance (MR) angiography may suffice. However, for small-vessel involvement a conventional angiogram has higher sensitivity and should be considered in the presence of typical MR changes. Angiography may be negative in small-vessel CNS vasculitis where only a brain biopsy will provide the definite diagnosis.

The histopathology reveals infiltration of mainly mononuclear cells around the vessel and sometimes granuloma formation.

Differential Diagnosis

Differential diagnosis includes systemic rheumatological diseases with CNS involvement including: SLE, Behcet's disease, polyarteritis nodosa, Kawasaki disease, Henoch–Schonlein purpura, and ANCA-associated vasculitides. Bacterial infections due to streptococcus, mycobacteria; viral infecations such as *Varicella zoster*, *Ebstein-Barr virus*; spirochetal infections such as *Borelia burgdorferi* and fungal infections such as aspergillus should also be considered. Finally, the differential diagnosis also includes neoplasms of the brain.

Treatment and Prognosis

There are no established treatment protocols but it is suggested to treat children with CNS vasculitis with corticosteroids and cyclophosphamide. Long-term follow-up is necessary to define the neurological, cognitive, and behavioral outcome. Distal artery involvement is associated with poorer outcome. Permanent neurologic deficit may occur.

Hypersensitivity Vasculitis

Definition, Etiology, and Pathogenesis

Hypersensitivity vasculitis (HV) is an inflammatory vascular disease characterized by prominent skin involvement with the existence of a trigger (usually a drug or vaccine). ACR defines HV as palpable purpura, precipitated by a medication or other agent with characteristic biopsy. It has been described after treatment with heterologous antiserum.

Pathology

Pathology is characterized by the perivascular or extravascular infiltration of the small vessels with polymorphonuclear leukocytes and the presence of leukocytoclasia.

Clinical Manifestations and Laboratory Findings

Skin lesions (i.e., purpura, urticaria, and palpable nodules) are predominantly located on the legs, although the upper limbs and trunk may also be affected. Generally the disease lasts few weeks with a self-limiting course. Relapsing and chronic course has been defined.

Leukocytosis usually occurs and is sometimes accompanied by eosinophilia and circulating immune complexes. The erythrocyte sedimentation rate is often normal.

Differential Diagnosis

Other causes of leukocytoclastic vasculitis should be considered in the differential diagnosis.

Treatment

Management is usually symptomatic consisting of antihistamines and NSAIDs. If systemic symptoms are present, corticosteroid therapy is indicated.

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170 The Autoinflammatory Diseases

Marco Gattorno

Introduction

Under the term of autoinflammatory diseases are gathered a number of inherited disorders secondary to mutations of genes coding for proteins that play a pivotal role in the regulation of the inflammatory response. Most of these disorders have generally an early onset, ranging from the first hours to the first decade of life. The clinical spectrum of these disorders is extremely variable (*Table 170.1*).

Some of them are characterized by recurrent flares of systemic inflammation presenting as sudden fever episodes associated with a dramatic elevation of acute phase reactants, and with a number of clinical manifestations, such as rash, serositis (peritonitis, pleuritis), lymphadenopathy, arthritis. Disease flares are usually separated by symptom-free intervals of variable duration, characterized by a complete well-being, normal growth, and complete normalization of acute phase reactants. Familial Mediterranean Fever (FMF), Mevalonate kinase deficiency (MKD), and tumor necrosis factor (TNF)-receptor-associated periodic syndrome (TRAPS) are the three monogenic disorders gathered under the term of *Periodic fevers.*

In other disorders, systemic inflammation is dominated by a characteristic urticarial rash associated with a number of other clinical manifestations. Familial Cold Autoinflammatory Syndrome (FCAS), Muckle–Wells Syndrome (MWS), and Chronic Infantile Neurological Cutaneous and Articular Syndrome (CINCA) represent the clinical spectrum associated to different mutations of a gene named *NALP3* (or *CIAS1*, cold-induced autoinflammatory syndrome 1) coding for a protein called Cryopyrin. These three disorders are also gathered under the term of Cryopyrinopathies or Cryopyrin-related periodic syndromes (CAPS). Mutations of another member of the NALP family, the *NALP12* gene, have been recently associated with a new autoinflammatory disease.

Other diseases are characterized by typical granulomatous formations (*Granulomatous disorders*). Blau's syndrome is characterized by noncaseating granulomatous inflammation affecting the joint, skin, and uveal tract and is associated with mutations of the *CARD15* (or *NOD2*) gene.

A further group of diseases are dominated by the presence of sterile pyogen abscesses affecting skin, joints, and bones (*Pyogenic disorders*). These include the Pyogenic Sterile Arthritis, Pyoderma Gangrenosum and Acne (PAPA) syndrome secondary to mutations of the CD2-binding protein 1 (*CD2BP1*) gene, and the Majeed syndrome, characterized by chronic recurrent multifocal osteomyelitis, congenital dyserythropoietic anemia, and neutrophilic dermatosis caused by mutations of the *LPIN2* gene. Finally, a recently identified autosomal recessive autoinflammatory syndrome, due to the deficiency of the interleukin-1-receptor antagonist (DIRA), is characterized by a neonatal-onset multifocal osteomyelitis, periostitis, and skin pustulosis.

The Cryopyrinopathies

FCAS, MWS, and CINCA are autosomal-dominant disorders related to different mutations of a single gene: *NALP-3* (or *CIAS1* or *PYPAF1*), encoding a protein called cryopyrin. So far, more than 80 different missense mutations have been described (http://fmf.igh.cnrs.fr/infevers/). However, 30% to 40% of patients with a phenotype consistent with a cryopyrinopathy do not display any mutation of the *NALP3* gene.

Pathogenesis

Interleukin-1β (IL-1β) is one of the major proinflammatory cytokines. Unlike most cytokines, IL-1β lacks a secretory signal peptide and is externalized by monocytic cells through a nonclassical pathway, arranged in two steps, as shown in *Fig. 170.1* (ref). A crucial role in IL-1β processing is played by the Inflammasome, a multi-protein complex responsible for activation of the IL-1 converting enzyme (ICE) (or Caspase-1). NALP3 is a key protein of the Inflammasome that, in the presence of adequate stimuli, oligomerizes becoming available for the binding of the adaptor protein ASC (Apoptosis associated Speck-like protein containing

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Table 170.1
The autoinflammatory diseases

	Diseases	Gene chromosome	Protein	Transmission	Clinical features
Periodic/ recurrent fevers	Familial Mediterranean fever	*MEVF* 16p13.3	Pyrin	AR	Short duration of fever episodes: 24–48 h
					Abdominal and chest pain. Erysipelas-like erythema
					High incidence of renal amyloidosis in untreated patients
					Good response to Colchicine
					Possible response to IL-1 blockade
	Mevalonate kinase deficiency	*MVK* 12q24	Mevalonate kinase	AR	Early onset (usually <12 months)
					Mean duration of fever episodes: 4–5 days
					Poor conditions during fever episodes. Abdominal pain, vomiting, and diarrhea. Splenomegaly
					Good response to steroids. High rate of self-resolution during adulthood. Amyloidosis is rare
	TNF-receptor-associated periodic syndrome	*TNFRSF1A* 12p13	p55 TNF receptor	AD	Prolonged fever episodes: 1–3 weeks
					Periorbital edema, monocytic fasciitis
					Incidence of renal amyloidosis: 15–25%
					Response to TNF- and IL-1 blockade
NALPs-related diseases	FCAS, MWS, CINCA	*CIAS1/NALP3* 1q44	Cryopyrin	AD	FCAS: rash, fever, and arthralgia after cold exposure
					MWS: recurrent or sub-chronic urticaria-like lesions, sensorineural hearing loss, amyloidosis
					CINCA: as above + mental retardation, chronic aseptic meningitis, and bone deformities
					Good response to IL-1 blockade
	NALP12-associated periodic fever	*NALP12 19p13*	NALP12	AD	Periodic fever after cold exposure, hearing loss
Granulomatous disorders	Blau's syndrome	*CARD15/ NOD2* 16q12	CARD15	AD	Early onset (<5 years)
					Polyarticular granulomatous arthritis, uveitis, skin rash
					Good response to anti-TNF monoclonal antibodies
Pyogenic disorders	PAPA syndrome	*PSTPIP1* 15q24–q25.1	PSTPIP1	AD	Pyogenic sterile arthritis, pyogenic gangrenosum, Cystic acne. Good response to IL-1 blockade
	Majeed's syndrome	*LPIN2* 18p	LPIN2	AR	Multifocal osteomyelitis, congenital dyserythropoietic anemia, inflammatory dermatosis
	DIRA	*IL1RN* 2q	IL1 receptor antagonist	AR	Neonatal-onset multifocal osteomyelitis, periostitis, and pustulosis. Dramatic response to Anakinra

FCAS familiar cold autoinflammatory syndrome, *MWS* Muckle–Wells syndrome, *CINCA* chronic infantile neurological cutaneous and articular syndrome, *PAPA* pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome, *CRMO* chronic recurrent multifocal osteomyelitis, *DIRA* deficiency of the interleukin-1-receptor antagonist, *AR* autosomal recessive, *AD* autosomal dominant

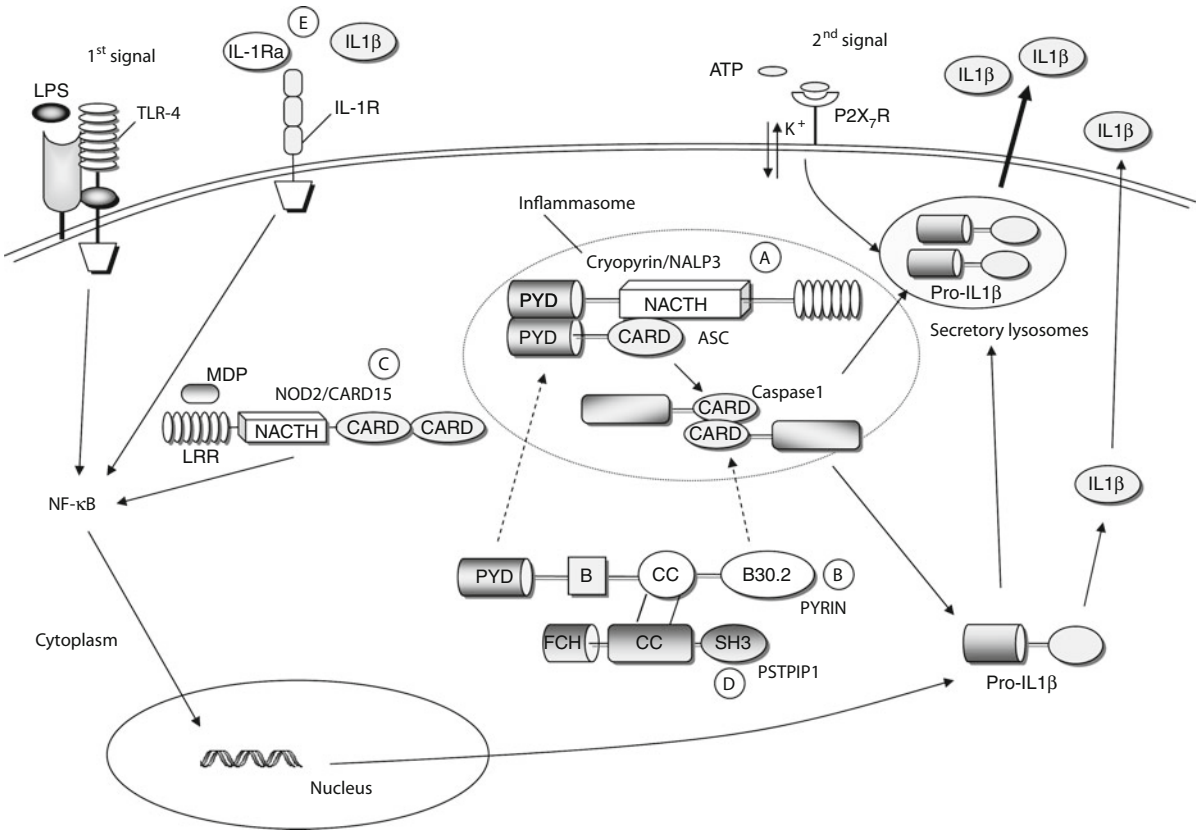

Figure 170.1

Schematic representation of the functional role of genes involved in autoinflammatory diseases in the control of NF-kB activation and IL1β secretion. (a) Role of Cryopyrin (NALP3) in the activation of Inflammasome and induction of IL-1β secretion. Toll-like receptor ligands, such as LPS, are the first signal for gene expression and synthesis of the inactive IL-1βprecursor (pro-IL-1β). A second stimulus, such as exogenous ATP, strongly enhances proteolytic maturation and secretion of IL-1β. After stimulation, NALP3 oligomerizes becoming available for the binding of the adaptor protein ASC (Apoptosis associated Speck-like protein containing a CARD). This association activates directly two molecules of Caspase-1 which, in turn converts pro-IL-1β to the mature, active 17 kDa form. (b) Role of Pyrin in the regulation of Inflammasome activation. Marenostrin/pyrin modulates the inflammasome by interacting with both ASC and Caspase-1 with the pyrin and SPRY domains, respectively (see also text). (c) CARD15/NOD2 is an intracellular sensor for pathogen-associated molecular patterns, such as MDP (muramyl dipeptide). After stimulation NOD2/CARD15 is able to induce both NF-κB activation and the release of bioactive IL-1β in a Caspase 1 dependent-manner. (d) PSTPIP1 binds to pyrin. Disease-associated mutations in PSTPIP1 enhance pyrin binding forming a trimolecular complex with ASC. (e) The binding of IL-1β with type I IL-1 receptor (IL-1R1) lead to a proinflammatory response via the activation of NF-kB pathway. The IL-1 receptor antagonist (IL-1ra) acts as a natural inhibitor of IL-1β activity by competing for binding to IL-1R1

a CARD). This association activates directly two molecules of Caspase-1 which, in turn converts pro-IL-1β to the mature, active 17 kDa form (*Fig. 170.1*). Mutations in the *cryopyrin* gene in humans are associated with its gain of function that lead to an excessive production of IL-1β even in absence of a second signal, such as extracellular ATP.

Clinical Picture

FCAS is characterized by urticarial rash and fever spikes of short duration (usually <24 h) induced by cold exposition. Arthralgia and conjunctivitis are also common. Muckle–Wells syndrome is characterized by recurrent episodes of urticaria and fever that may develop in the early

infancy. The fever episodes can be associated with arthralgia, conjunctivitis, and drowsiness and are not strictly evoked by cold exposure. Acute phase reactants are elevated during fever episodes and may persist slightly increased also during free intervals. During the course of the disease, neurosensorial deafness may develop. Amyloid A (AA) amyloidosis is a complication of the late stage of the disease.

CINCA represents the more severe phenotype associated with mutations of *NALP3* gene. An urticaria-like rash may develop during the first weeks of life (Fig. 170.2a). Many affected individuals present typical "facies" characterized by frontal bossing, saddle back nose, and midface hypoplasia, causing a sibling-like resemblance (Fig. 170.2b). Bone involvement is another characteristic hallmark of the disease. The most characteristic features are represented by bony overgrowth that predominantly involves the knees (including the patella) and the distal extremities of hands and feet. A chronic inflammatory polyarthritis may be also present, sometime leading to bone erosions. Central nervous system (CNS) manifestations include chronic aseptic meningitis, increased intracranial pressure, cerebral atrophy, ventriculomegaly (Fig. 170.2c), sensorineural hearing loss, and chronic papilledema, with associated optic-nerve atrophy and loss of vision. Mental retardation and seizures have also been reported. Patients display a persistent elevation of acute phase reactants, leukocytosis, and chronic anemia.

Treatment

The pivotal role of Cryopyrin in the control of Caspase 1 activation and the massive secretion of active IL-1β observed in cryopyrin-mutated individuals, suggested that anti-IL-1 treatment could represent an effective therapy. Initial isolated case reports suggested that the recombinant IL-1 receptor antagonist (Anakinra) has a dramatic effect on the control of rash and constitutional symptoms in FCAS and Muckle–Wells patients. These findings have been confirmed in different studies on CINCA patients.

Anakinra is given at a starting dosage of 1 mg/kg/day s.c. Soon after the first injections, patients displayed a prompt normalization of acute phase reactants with a dramatic improvement of urticarial rash, arthritis, headache, and fever with a complete resolution within 1 week from the beginning of the treatment. Improvement of hearing loss after Anakinra treatment has been described in up to 30% of CINCA patients. Recently, the use of other IL-1 blockers characterized by a longer half-life, such as IL-1 trap (Rilonacept) and IL-1 monoclonal antibody (Canakinumab), has shown the same preliminary excellent results at least in FCAS and MWS patients.

NALP12-Associated Periodic Fever Syndrome

This new disorder was firstly described in two families originating from Guadeloupe presenting a clinical phenotype characterized by recurrent fever episodes associated with arthralgias, myalgias, and abdominal pain. A particular sensitivity to cold as a trigger factor for the clinical manifestations has been reported in most of the cases so far described. Urticarial rash, recurrent oral ulcers, and neuronal hearing loss have been also reported. Little information is so far available on the response to treatment.

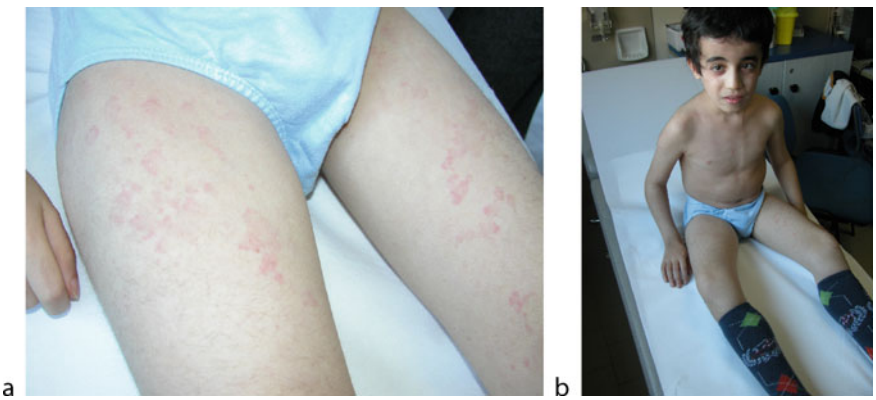

Figure 170.2
Clinical manifestations in CINCA patients: (a) urticarial rash; (b) typical facies characterized by frontal bossing and midface hypoplasia

The NALP12 protein has been identified as an important regulator of the inflammatory response, in particular, it acts as a negative regulator by suppressing both canonical and noncanonical NF-kB activation and subsequent production of proinflammatory cytokines and chemokines.

Mutations in *NALP12* gene have been associated with a defective regulatory function of the protein. However, further studies are needed to better clarify the actual pathogenic impact of mutations of this protein in affected patients.

The Periodic Fevers

Familial Mediterranean Fever (FMF)

Familial Mediterranean fever is the most frequent among hereditary recurrent inflammatory disorders. This disease mainly affects populations originating from the eastern part of the Mediterranean basin: Armenians, Turks, Non-Ashkenazi and other Jews, Arabs. A much lower prevalence is observed in Greece, Southern Italy, and even in Japan. Among Armenians, non-Ashkenazi Jews, and Turks, the frequency of heterozygotes in the general population is greater than one fifth. In 1997, the gene associated with FMF was cloned by two parallel International consortia and called *MEFV* (for MEditerranean FeVer) coding for a protein called pyrin or marenostrin. To date, more than 70 MEFV mutations have been recorded (http://fmf.igh.cnrs.fr/infevers/). In the ethnic groups in which FMF is endemic, 80–90% of the mutations are localized in exon 10. In particular, five founder molecular alterations, V726A, M694V, M694I, M608I in exon 10, and E148Q in exon 2, account for 70–80% of cases.

Pathogenesis

The Pyrin protein is made by a number domains that play an important role in its function. The pyrin domain is a specific domain of 90 amino acids located in the N-terminal region and is able in interact with the ASC protein involved in the Inflammasome by homotypic pyrin domain binding. A second pivotal domain is called B30.2 (or SPRY) and is located in the C-terminal region of the protein, where the most frequent mutations associated with FMF are located. The B30.2 interacts directly with Caspase-1 modulating the IL-1β production. Recent works suggest that marenostrin/pyrin modulates the inflammasome by interacting with both ASC and Caspase-1 with the pyrin and SPRY domains (*Fig. 170.1b*).

Clinical Picture

Even if a disease onset in adulthood can be observed, most patients begin to suffer of fever attacks since during childhood. Fever episodes have a short duration (1–3 days) and often associated with acute inflammation of the serosa with severe abdominal pain due to aseptic peritonitis and/or chest pain due to pleuritic involvement. Joint involvement is frequent and characterized by an asymmetrical and nondestructive oligo- or mono-arthritis, that most commonly involves hip, knee, or ankle. An erysipelas-like erythema on the lower part of the legs (ankle and the dorsum of the foot) is not frequent, but is highly suggestive for the disease. Myalgia may be observed during fever episodes. Neutrophilia and elevated erythrocyte sedimentation rate are typically associated with fever attacks.

Amyloid A (AA) type amyloidosis is the most severe long-term complication of FMF. The most common clinical manifestation of amyloidosis is the development of proteinuria and may lead to renal failure. Renal involvement is usually observed after a variable time from disease onset (phenotype-I). In some rare patients (less than 1%), renal amyloidosis may represent the first manifestation of the diseases (phenotype-II).

Treatment

Colchicine is the treatment of choice for FMF. The adult dose is 1 mg/day and, in nonresponsive patients, it can be increased to 2 mg. In children, the starting dose should be $\leq$0.5 mg/day for children below 5 years of age, 1 mg/day (5–10 years) and 1.5 mg/day (>10 years). Dosage can be increased in a stepwise fashion up to a maximum of 2 mg/day. The use of colchicine has dramatically reduced the incidence of amyloidosis. However, poor compliance to treatment (mainly due to gastrointestinal side effects, such as nausea and diarrhea) is one of the major causes of treatment failure.

Periodic Fever Associated with Mevalonate Kinase Deficiency

Periodic fever associated with mevalonate kinase deficiency (MKD) was originally identified in 1984 in six patients of Dutch ancestry with a long history of recurrent attacks of fever of unknown cause and a high serum IgD level. High IgD plasma levels have been used as a diagnostic hallmark until mutations in the mevalonate kinase (*MVK*) gene, encoded on chromosome 12q24, were

identified as the cause of the disease. The complete deficiency of this enzyme causes a distinct syndrome called mevalonic aciduria (MA), which is clinically characterized by severe mental retardation, ataxia, failure to thrive, myopathy, and cataracts; notably, these patients also suffer from recurrent fever attacks.

Pathogenesis

MVK is an essential enzyme in the isoprenoid biosynthesis pathway which produces several biomolecules involved in different cellular processes. Although the dysregulation of this biochemical pathway seems to play a pivotal role in the developing of fever, at present the pathogenetic mechanisms leading to the autoinflammatory disease remain still poorly understood. Cells from patients with the MKD phenotype still contain residual MVK enzyme activities (from 1% to 8% of the activities of control cells), while in cells from patients with the MA phenotype the MVK enzyme activity is below the detection level (approximately 0.1% of normal individuals). Recent in vitro studies have shown that shortage of non-sterol isoprenoid end products, mainly the geranylgeranyl groups, lead to an increased activation of Caspase 1 in circulating monocytes with a consequent hypersecretion of the 17 kDa active form of IL-1β.

Clinical Picture

Disease onset occurs very early in life. Fever attacks have an abrupt onset and last 4–6 days. Severe abdominal pain often accompanied by vomiting and/or diarrhea is frequently associated with fever attacks. Cervical lymphadenopathy is common. Splenomegaly is observed during fever attacks in about half of patients. Mucocutaneous manifestations are frequent and include erythematous macules, urticaria-like lesions and, less commonly, oral aphthous lesions. Articular involvement occurs in the majority of patients as arthralgia or as an oligoarticular arthritis.

The symptoms of MKD persist for years, but usually tend to become less prominent with time. However, in some patients, the disease may progress toward adulthood. Even if amyloidosis was not considered as a possible long-term complication of MKD, it has been recently described in rare patients.

Increased plasma levels of IgD (>100 UI/ml) during fever episodes and in basal conditions have been considered in the past as a hallmark of the disease. However, the specificity of this finding is low. An increased urine excretion of mevalonic acid is observed during fever spikes and decreased MVK activity may also orientate toward the diagnosis.

Treatment

Fever attacks usually respond dramatically to the administration of steroids (prednisone: 1 mg/kg/day in a single dose). However, due to the high frequency of the fever episodes, some patients may need almost continuous treatment. The use of biologic treatments is largely anecdotal and sometimes controversial. Anti-TNF therapy has been found to reduce the frequency and intensity of fever attacks in some patients, but not in others. Recently, the use of the IL-1 receptor antagonist (Anakinra) was found to be effective in sporadic patients.

The TNF-Receptor-Associated Periodic Syndrome (TRAPS)

The name TRAPS refers to the protein affected by the mutation in this disease: TNF receptor superfamily type 1A (*TNFRSF1A*). Even though TRAPS has been initially described in subjects of Nordic origin, as emphasized by the name of Familial Hibernian Fever, mutations in *TNFRSF1A* have now been found in many populations, including Black Americans, Japanese, and also along the Mediterranean basin.

Pathogenesis

In most of the patients, plasma concentrations of the soluble form of the receptor are low or paradoxically normal during attacks. This suggests a quantitative or qualitative abnormality of the soluble form of the receptor. In fact, the shedding of free TNFRs from the membrane produces a pool of soluble receptors that may scavenge circulating TNF by competing with membrane bound receptors (*Fig. 170.3*). This latter phenomenon represents an important strategy for the regulation of the effect of circulating free TNF during acute inflammation. At variance with the other, p75 receptor, p55 TNFR is also able to induce cell apoptosis, via activation of the caspases cascade trough the induction of the so-called Complex II (*Fig. 170.3*). It has been shown that neutrophils from TRAPS display a clear defect in the activation of Complex II and, therefore, a resistance of TNF-induced

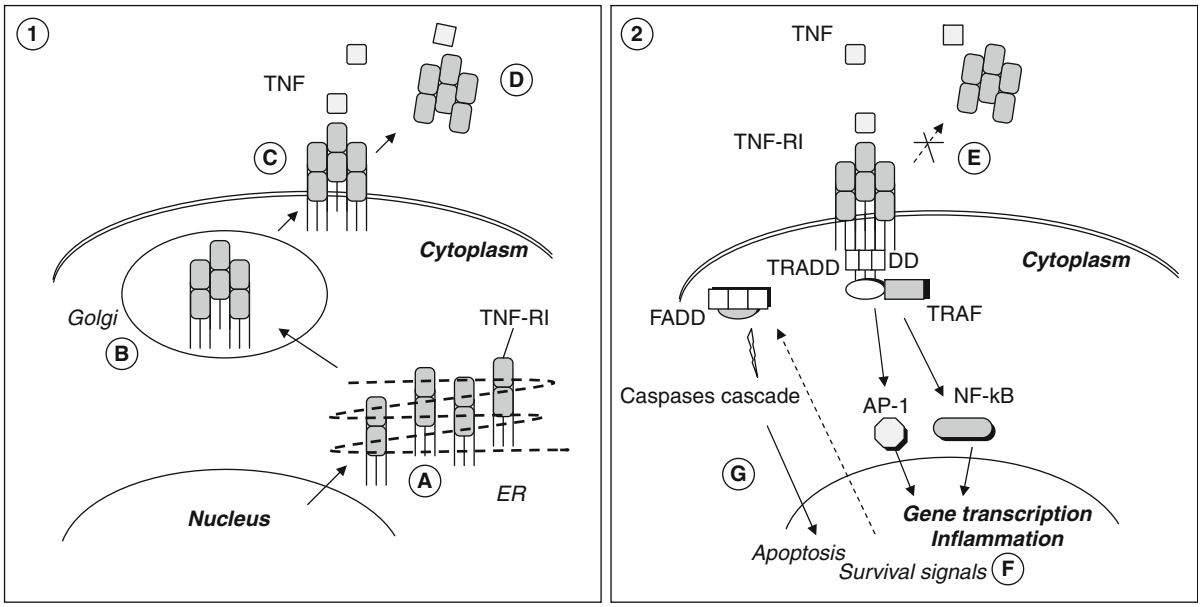

Figure 170.3

Physiopathology of TRAPS syndrome Panel (1). The TNFR1 molecules are transported from endoplamic reticulum (ER) (a) to the Golgi, where they are pooled, (b) before going on to the surface as a trimer (c). When TNF binds to the cell surface TNFR1 trimer, intracellular signalling results in NF-κB activation (Complex I). A defect of trafficking of mutated TNFR1 has been postulated. Upon activation, cell surface receptors are cleaved off by metalloproteinase to buffer the circulating TNF (d). Panel (2) Some TNFRSF1A mutations may interfere with the process of shedding, leading to a lack of appropriate TNF inhibition and therefore to uncontrolled inflammation (e). TNFRSF1A is also able to induce cell apoptosis, via activation of the caspases cascade (Complex II). During cell activation, Complex II is inhibited by the expression of anti-apoptotic factors produced through the activation of the NF-kB pathway (f). When the NF-κB activity subsides, the pro-apoptotic signals inducible by the intracellular p55 TNFR complex lead to cell death (g). Neutrophils from TRAPS display a clear defect in the activation of Complex II and, therefore a resistance of TNF-induced apoptosis

apoptosis. This defect may represent an additional mechanism explaining the sustained activation of inflammatory cells during fever episodes. Additional insights came from the study of transfected cells with the mutant form of the TNFRI protein, showing a defect of trafficking of the mutated TNFRI to the cell membrane with an accumulation of the protein in the endoplasmic reticulum (*Fig. 170.3*). The possible pathogenic consequences of ER retention of mutated TNFR1 are matter of intensive investigations by several groups.

Clinical Picture

TRAPS attacks last longer than in FMF, generally more than 5 days and up to 3 weeks, even though attacks shorter than 5 days have been reported. Abdominal pain can simulate a surgical event. Skin manifestations are present in more than three fourths of the cases. A wide spectrum of rashes can be observed: urticaria-like, plaques, and patches. The most distinctive lesion is an erythematous, swollen, warm, and tender plaque of various sizes with hazy edges (*Fig. 170.4*). It rather involves the upper and lower limbs, but can be observed at the chest. Usually, the rash has a migratory course from the root to the extremity of the limbs. This pseudo-cellulitis is often accompanied by painful myalgias and constitutes the other most distinctive manifestation of TRAPS attacks. Thoracic, scrotal pain, arthritis, orbital edema, and conjunctivitis are also observed in TRAPS attacks.

Treatment

Corticosteroids, when given at the onset of an attack, can attenuate the length and the severity of it. In the most

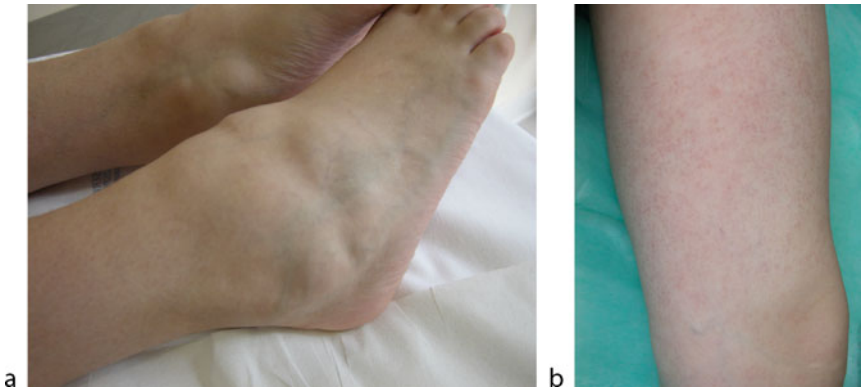

Figure 170.4
Clinical manifestations in a Blau's patient. Typical "boggy" synovitis (a) and tan-colored, scaly, ichthyosiform rash (b) in a 5-year-old girl

severe forms of the disease, clinical signs of inflammation are almost permanent and require daily use of corticosteroids, and may lead to dependency, requiring the use of other anti-inflammatory drugs. TNF inhibitors seem designed as treatment of TRAPS. Etanercept and other TNF inhibitors have provided various degrees of clinical improvement and allowed to spare steroids. Notably, a paradoxal reaction with exacerbation of the inflammatory signs has been observed after the administration of anti-TNF monoclonal antibody (Infliximab) in some TRAPS patients. A persistent response to IL-1 blockade (Anakinra) has also been recently observed.

The PFAPA (Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis) Syndrome

PFAPA was first described by Marshall et al. in 1987. The disease usually develops before 5 years of age. It is characterized by fever spikes of abrupt onset lasting 3–6 days; fever recurs regularly (sometime with a clockwise periodicity) every 2–6 weeks. Children with PFAPA syndrome appear often in good conditions also during the fever spikes. The aphthous lesions observed in PFAPA are small and localized to labial gingival and are rapidly self-remitting. Cervical lymph node enlargement is frequent (and may be relevant); enlarged lymph nodes are tender and normalize with the resolution of the fever attack. Typically, fever attacks dramatically respond to a single dose of steroids (betamethasone: 0.1 mg/kg). The disease has a benign course and tends to spontaneously remit with time. Although some anecdotal familial cases of PFAPA have been reported, no documented genetic basis has been so far identified.

Granulomatous Disorders

Blau Syndrome

Blau syndrome (see also ❯ Chap. 172, "Sarcoidosis"), or familial juvenile systemic granulomatosis, is an autosomal-dominant disease characterized by a noncaseating granulomatous inflammation affecting the joint, the skin, and the uveal tract (the triad of arthritis, dermatitis, and uveitis). The gene responsible for Blau syndrome, *NOD2/CARD15*, encodes a protein containing a NACHT domain. NOD2/CARD15 recognizes muramyl dipeptide (MDP), the minimal motif of peptidoglycan of both Gram-positive and Gram-negative bacteria. After stimulation with MDP, NOD2/CARD15 is able to induce both NF-kB activation and the release of bioactive IL-1β in a Caspase 1 dependent-manner (❯ *Fig. 170.4*). Notably, mutations of the LRR domain of the same gene are associated with another chronic granulomatous disease, such as Crohn's Disease.

Disease onset is usually observed during the first years of life. A symmetrical polyarticular arthritis with a typical pattern of boggy synovitis is the typical joint manifestation. A typical tan-colored, scaly, ichthyosiform rash is seen in almost 90% of the affected individuals (❯ *Fig. 170.4*). Eye involvement is characterized by intermediate uveitis or panuveitis. Fifty percent of the patients with ocular involvement develop cataracts, and approximately one third may undergo into secondary glaucoma.

Patients are treated with oral steroids and immunosuppressive drugs (methotrexate, cyclosporin A) with variable results. Recent anecdotal reports suggest a beneficial effect of anti-TNF (Infliximab) and anti-IL-1 treatment.

Pyogenic Disorders

PAPA Syndrome

Pyogenic Sterile Arthritis, Pyoderma Gangrenosum, and Acne syndrome (PAPA, MIM 604416) is a disorder caused by mutations of gene coding for the CD2-binding protein 1 (*CD2BP1*), or *PSTPIP1*. PSTPIP1 protein has been shown to bind pyrin (Fig. 170.1), and it is postulated that the increased pyrin binding seen with the PAPA mutations may alter inflammatory susceptibility. The manifestations of this disorder are pyogenic gangrenosum, cystic acne, and pyogenic sterile arthritis which represents the most common symptom of the disease. An oligoarticular arthritis has its onset in early childhood and is characterized by recurring inflammatory episodes that resembles septic arthritis leading to accumulation of sterile pyogenic, neutrophil-rich material within the affected joints, which ultimately results in significant synovial and cartilage destruction. Dermatologic manifestations are also episodic and recurrent and are characterized by debilitating, aggressive, ulcerative skin lesions, usually of the lower extremities, undistinguishable from pyogenic gangrenosum. Sterile abscesses at injection sites may also be observed. PAPA syndrome has been reported to be generally responsive to oral glucocorticoids. Anecdotal reports have shown the possible efficacy of anti-TNF and anti-IL-1 treatment.

The Majeed's Syndrome

In 1989, three related Arab children presenting an association of chronic recurrent multifocal osteomyelitis (CRMO), congenital dyserythropoietic anemia, and inflammatory dermatosis were described by Majeed and coworkers.

Unlike isolated CRMO, bone manifestations has an earlier age at onset, more frequent episodes, shorter and less frequent remissions, and is probably lifelong. Congenital dyserythropoietic anemia is characterized by microcytosis both peripherally and in the bone marrow, which may need repeated blood transfusions. Inflammatory dermatosis may vary from a Sweet syndrome to chronic pustulosis. In 2005, a linkage analysis was performed on two Jordan families allowing the identification of the *LPIN2* gene mapped on chromosome 18p.

DIRA (Deficiency of the Interleukin-1-Receptor Antagonist)

DIRA is a recently identified autosomal recessive autoinflammatory syndrome, due to the deficiency of the interleukin-1-receptor antagonist secondary to truncating mutations of the *IL1RN* gene. As a result of these mutations, no interleukin-1-receptor antagonist protein is secreted, which inhibits the proinflammatory cytokines interleukin-1 and interleukin-1β. The disease begins around birth with multifocal osteomyelitis, periostitis, and pustulosis. Persistent elevation of acute phase reactants (ESR and CRP) is observed since birth. The skin manifestations range from groupings of small pustules to a generalized pustulosis. The bone manifestations include osteolytic lesion with a sclerotic rim, epiphyseal ballooning of multiple distal and proximal long bones, widening of ribs and clavicles, heterotopic ossification or periosteal cloaking of the proximal femoral metaphysis, and periosteal elevation of the diaphysis. The patients show a dramatic response to the substitutive treatment with recombinant IL-1 receptor antagonist (Anakinra).

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171 Behçet's Disease

Isabelle Koné-Paut · Tu-Anh Tran

Definition, Classification

Behçet's disease (BD) is a multisystem recurrent inflammatory disorder usually grouped into vasculitic syndromes, and initially reported in 1931 by Adamantiades in the French literature as one case of relapsing hypopion, then by Huluci Behçet in 1937 under the association of bipolar aphthous lesions plus uveitis. Involvement of medium- and great-sized vessels leads to serious neurological and ocular damage and also to patient's death by pulmonary or cardiac complications. BD encompasses a number of clinical manifestations classically distinguished between major and minor in accordance to their severity and frequency (*Table 171.1*). Most of them are self-limited, but some of them like genital ulcers and eye lesions may cause permanent tissue damage. Most commonly used diagnostic criteria have been proposed by an International Study Group in 1990, but they are not applicable for every patient especially pediatric ones.

Etiology/Pathogenesis

BD appears as a polyfactorial disease where the participation of the innate immunity, environmental factors, as well as inflammatory responses abnormalities could play a pivotal role. Ubiquitous microbial pathogen and heat-shock proteins may stimulate the innate immune system of BD patients through Toll-like receptors, especially TLR2 and TLR4. The involvement of pathogens in individuals with genetic susceptibility is widely believed in BD, especially in those carrying the HLAB51 tissue antigen. The association of the HLAB51 with BD reaches 40–80%, in countries where the disease is prevalent. The genetic hypothesis is for a long time suspected because of the peculiar geographic distribution of BD and the occurrence of familial cases (2–10%), and increased in pediatric BD. Several susceptibility loci were identified by genome-wide studies in BD multicase Turkish families. Several autoinflammatory genes could also influence the phenotype of BD.

Epidemiology

BD is reported elsewhere; however most cases cluster from Japan to Mediterranean basin along the former Silk Route. The usual age for the disease is 30–40 years but the disease may start and may be completed before the age of 16 years. BD affects more frequently males in Mediterranean countries but more frequently females in Japan and Korea.

Pathology

BD lesions evidence a mixed immunologic pattern, that is, increased and deregulated nonspecific inflammatory responses with organ mononuclear cell infiltration suggesting an autoinflammatory mechanism as well as specific antigen-driven responses with oligoclonal T-cells expansion running in parallel with disease exacerbation which more likely is associated with autoimmune mechanisms. Activated mononuclear cells secrete pro-inflammatory cytokines: IL-1, IL-6, TNF-α, GMCSF, and IL-8 activating and attracting granulocytes in skin lesions. Neutrophils express activation receptors, adhesion molecules, and chimiokines receptors (CXCR2) producing an excess of free radicals and having increased phagocytosis. T lymphocytes from BD patients secrete TH1-polarized cytokines spontaneously. Activated NK cells, CD8+ lymphocytes, and $\gamma\delta$ T are increased in patient's sera but also infiltrate the inflamed sites. Circulating endothelial cells and elevated markers of endothelial activation reflect vascular injury, also one major trait of BD. Both endothelial alteration and hypercoagubility state contribute to vasculitis and vascular occlusion

Clinical Manifestations

Recurrent oral aphthosis (ROA) is the initial manifestation of 70–90% of pediatric BD. Lesions may involve any part of the oral mucosa including lips and usually disappear without scarring. Genital lesions are generally painful, and located on the vulva or scrotum. Other locations

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Table 171.1
Major and minor symptoms of Behçet's disease, frequency, from Barnes (1999)

Major		Minor	
Oral ulceration – recurrent	(97–98)	Arthritis and arthralgia	(45–50)
Genital ulceration	(80–90)	Neurological lesions	(5–25)
Inflammatory eye disease	(50)	Vasculitis	(25)
Iritis ± hypopyon		Aneurysm formation	
Retinal vasculitis		Arterial/venous thrombosis	
Skin lesions	(80)	Gastrointestinal lesions	(0–25)
Erythema nodosum	(45)	Cardiovascular lesions	
Folliculitis/acne	(70)	Pleuropulmonary lesions	
Pathergy test		Epididymitis	(8)

on penis and in the perianal area occur more likely in childhood than in adult BD. The presence of scar is remarkable and is a useful clue for eventual retrospective evaluation. Other causes of ROA are common in childhood and must be ruled out as possible. Children with ROA alone that increases in severity with time justify careful follow-up, while other BD symptoms may appear secondarily. Acneform, folliculitis-like, and papulopustular lesions onto the lower extremities are the most common skin lesions often occurring in combination. Sweet's syndrome like lesions, pyoderma gangrenosum, and necroziting vasculitis are more exceptional. The hyperreactivity of skin to intracutaneous injection or needle prick, known as pathergy, considered as a key feature BD, is less commonly observed in pediatric BD than adult BD. Posterior or total uveitis, frequently bilateral accompanied with retinal vasculitis, macular edema, and papillitis are the most typical of BD. The course may be very severe, especially in male patients, with definite impairment of visual acuity secondary to optic atrophy. Anterior uveitis with hypopion is classical but rarely observed. Neuro-BD includes encephalomyelitis, aseptic meningitis, benign intracranial hypertension, and organic psychiatric disturbances. Cerebellar signs, pyramidal and extrapyramidal syndrome, spinal cord involvement, pseudobulbar syndrome, and epilepsy reveal encephalomyelitis. These features are not specific and look like multiple sclerosis especially if they are the first manifestation of BD (5% of cases). Joint problems in BD are usually minor, limited to few joints (knees, ankles, elbows, and wrists), and run acute and recurrent course. Venous thrombosis is a predominant feature of BD even if not part of the international criteria. Involvement of the lower extremities: tibial, femoral, and iliac vessels are the most common. Vasculitis of pulmonary arteries leads to aneurysm and thrombus formation and frequently to the patient death.

Diagnosis, International Criteria

In the absence of pathognomonic feature, the diagnosis is made according to the international criteria (Lancet 1990). Recurrent oral ulceration (at least three times a year and observed by a physician) is mandatory. This criterion must be associated with two signs among genital ulceration, skin lesions – erythema nodosum, papulopustular lesions, pseudo folliculitis, eye lesions – posterior or total uveitis, retinal vasculitis, and positive pathergy test (pustula with surrounding erythema at 24–48 h following intradermal 24-gauge needle prick or saline injection).

Treatment

Steroids and immunosuppressive drugs are still currently used for treatment of serious manifestations. Azathioprine is convenient for use in children with good tolerance. A daily dose of 2 mg/kg is effective to control and prevent eye disease, genital ulcers, and thrombophlebitis. Severe aphthosis may be responsive to thalidomide but side effects are frequent as well as the development of polyneuropathy. Daily colchicine (1–2 mg/day) is commonly used as disease-modifying drug; however only two placebo-controlled studies have shown its efficacy in preventing oro/genital ulcers, skins lesions, and arthritis. Interferon α may improve steroid-dependant uveitis with few experience in children. They also control mucous and

papulopustular lesions. More specifically targeted biologic therapies against TNF and IL-1 will progressively overstep immunosuppressive treatments. Treatment of thromboses with anticoagulants is controversial, while BD-thrombus is adherent with no risk for embolism. Moreover, the use of anticoagulants could favor bleeding into vascular aneurysm.

Prognosis

The disease course is unpredictable but more severe in males than females. The eye and brain involvement are responsible for chronic morbidity and severe disability (blindness, dementia, and pseudobulbar syndrome). The mortality is related to vascular complications.

Prevention

Daily colchicine may prevent mucous/skin lesions and eye disease and low dose aspirin may prevent BD thromboses.

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172 Sarcoidosis

Carlos D. Rose · Carine H. Wouters

Definition and Classification

The term Pediatric Sarcoidosis encompasses a spectrum of granulomatous inflammatory conditions of childhood of which the pathologic hallmark is the presence of non-caseating epithelioid and giant cell granulomas in a variety of tissues and organ systems.

Blau Syndrome (BS) and *Early Onset Sarcoidosis* (EOS) constitute, respectively, the familial and sporadic forms of a pediatric autoinflammatory disease characterized by a clinical triad of polyarthritis, uveitis, rash, and a unique association with mutations of the *NOD2* gene. The term *Pediatric Granulomatous Arthritis* (PGA) has been proposed to refer to both.

A large number of children with sarcoidosis are *NOD2* mutation negative and tend to exhibit systemic and visceral manifestations at presentation. Within this group, a distinct entity named *Infantile Onset Panniculitis with Uveitis and Systemic Granulomatosis* has been identified recently.

The adult form of sarcoidosis, characterized mainly by pulmonary involvement and hilar adenopathy, can rarely be seen at the pediatric age, especially in older children; for this subset the authors have proposed the term "*Childhood Onset Adult Sarcoidosis*."

Etiopathogenesis

BS and EOS are part of the hereditary autoinflammatory diseases, characterized by an autosomal dominant inheritance pattern, and strongly associated with mutations in the central NOD/NACHT domain of the *NOD2* protein. These mutations are not found, however, in other forms of pediatric sarcoidosis which display a more heterogeneous phenotype, nor are they found in adult sarcoidosis.

The NOD2 protein is a member of a family of NOD-like receptor cytosolic proteins comprising different functional domains and implicated in pathways of inflammation and apoptosis. The two amino-terminal CARD domains of NOD2 have a role in the mediation of NF-κB activation and secretion of pro-inflammatory cytokines. The central NOD domain mediates self-oligomerisation of NOD2 proteins and activation of downstream effector molecules. The LRR region is important in the "sensing" of molecular motifs specific to pathogens, such as lipopolysaccharide.

The pathologic hallmark of sarcoidosis is the presence of non-caseating epithelioid granulomas in affected tissues/organs. The granulomas consist of a central cluster of monocytes/macrophages, epithelioid cells, and multinucleated giant cells, surrounded by a corona of lymphocytes.

Epidemiology

An overall incidence of sarcoidosis in children of 0.29/100,000/year, ranging from 0.06/100,000/year for children below 5 years to 1.02/100.000/year for children 14–15 years, has been estimated.

Clinical Manifestations

Sarcoidosis Associated with *NOD2* Mutation (BS/EOS)

BS/EOS most often presents during the first years of life with a characteristic tan-colored, scaly, fine papular rash. A symmetrical polyarthritis involving large and small joints with exuberant "boggy" synovial and tenosynovial swelling and relatively preserved range of motion is typical; clinodactyly results from contractures of the flexor tendons of the digits. Ocular involvement consists of an insidious granulomatous iridocyclitis and posterior uveitis and can evolve into a severe destructive panuveitis see (*Fig. 172.1*).

More recently, a myriad of clinical manifestations beyond the clinical triad, including prolonged fever, granulomatous and interstitial nephritis, vasculitis, severe hypertension, interstitial pneumonitis, peripheral and mediastinal lymphadenitis, pericarditis, cranial neuropathy, and parotitis have been documented.

Sarcoidosis Without *NOD2* Mutation

Sarcoidosis with wild-type *NOD2* constitutes a heterogeneous group of granulomatous inflammatory disorders, in which some distinct subsets can be identified.

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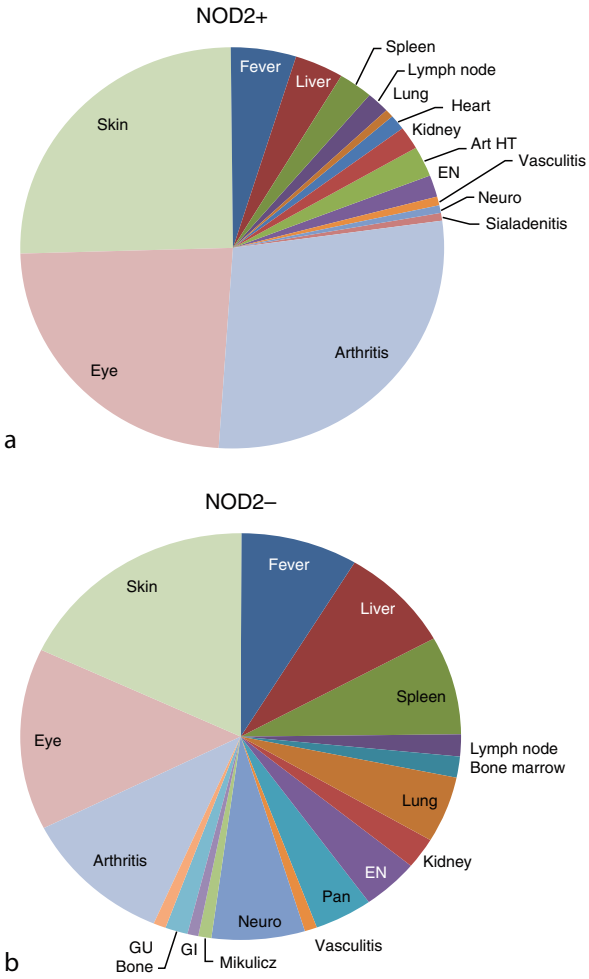

Figure 172.1
Cumulative clinical manifestations in 75 patients with pediatric sarcoidosis recruited through the International PGA Registry. (a) The large majority of patients with *NOD2* associated sarcoidosis display a clinical triad with skin, joint, and eye involvement, although incomplete forms and extended manifestations exist. (b) A large heterogeneity of clinical manifestations is typical of sarcoidosis with wild-type *NOD2*

Infantile onset Panniculitis with Systemic Granulomatosis is characterized by severe systemic inflammation with lobular panniculitis from infancy, progressive widespread granulomatous infiltration affecting joints, eyes, internal organs and central nervous system, and a potentially fatal course.

A review of published clinical manifestations of *Childhood onset Adult Sarcoidosis* reveals a relatively high frequency of systemic features (malaise, fever, weight loss), lung involvement, hilar and peripheral lymphadenopathies at presentation compared to adults. Hepatomegaly and splenomegaly are often seen; mild elevation of liver enzymes is common. Cutaneous manifestations include erythema nodosum, erythematous macules, papules, and plaques (Fig. 172.2) left. Uveitis is the most common ocular manifestation. Neurological manifestations mostly indicate central nervous system involvement (seizures, hypothalamic dysfunction). Renal involvement, mainly a tubulo-interstitial nephritis, most commonly manifests with decreased creatinine clearance and hypercalciuria. Some particular presentations rarely observed in older children include Löfgren's syndrome (arthritis, erythema nodosum and hilar adenopathy) and Mickulicz syndrome (parotid and lacrimal gland involvement) (Fig. 172.2) right.

Diagnosis

There is no laboratory test diagnostic of sarcoidosis. The ESR and acute phase reactants may reflect disease activity. Peripheral blood cell counts may show mild anemia, leucopenia, or lymphopenia. Hypergammaglobulinemia is often present, but autoantibodies are absent. Elevation of angiotensin converting enzyme (ACE) is not consistent and the value of serum ACE levels in sarcoidosis remains controversial. Hypercalciuria and hypercalcemia can lead to nephrocalcinosis and nephrolithiasis.

The diagnosis is confirmed by the finding of characteristic non-caseating epithelioid and giant cell granulomas which can be documented in biopsies of any involved organ/tissue.

The frequencies of *NOD2* mutation among sarcoidosis patients exhibiting the clinical triad of dermatitis, arthritis, and uveitis vary between 50% and 98%.

Differential Diagnosis

The diagnosis of sarcoidosis in a child requires the exclusion of other causes of granulomatous inflammation including primarily chronic infections by mycobacteria and fungi, but equally primary immunodeficiency disorders (Chronic Granulomatous Disease, Common Variable Immune Deficiency), and systemic inflammatory diseases such as granulomatous vasculitides (Wegener's Granulomatosis, Churg-Strauss syndrome) and Crohn's disease.

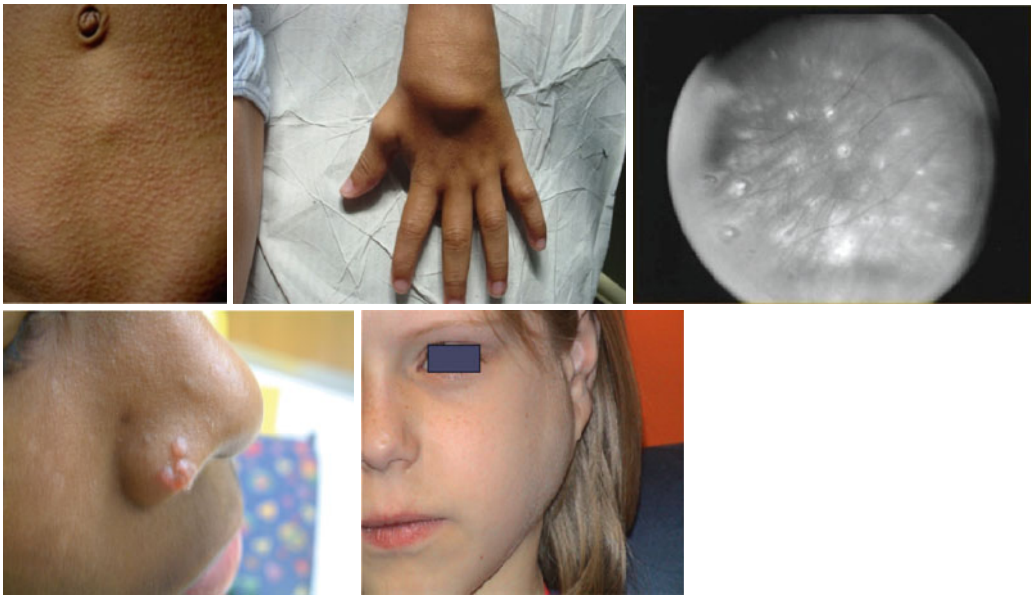

Figure 172.2
***Upper row*: clinical triad typical of *NOD2* associated Pediatric Saroidosis. *Left*: Fine maculopapular erythematous/tan eruption. *Middle*: Typical "boggy" synovitis with cyst-like synovial swelling. *Right*: Multifocal choroiditis characteristic of granulomatous panuveitis. *Lower row*: Pediatric sarcoidosis with wild-type *NOD2*. *Left*: Typical maculopapular lesion consisting of multiple non-caseating granulomas on nose. *Right*: Mikulicz syndrome with parotid and lacrimal gland involvement in a girl presenting with sicca symptoms**

Treatment

Evidence-based data on the optimal treatment of pediatric sarcoidosis are scarce. Moderate to low-dose daily corticosteroid therapy is effective to control uveitis and joint disease. Methotrexate at a dosage of 10–15 mg/m^2 once weekly was found to be effective in suppressing disease activity and allowing corticosteroid tapering. Anti-TNF monoclonal antibody agents (Infliximab, Adalimumab) may constitute a major therapeutic advance in the treatment of arthritis and visceral manifestations of pediatric sarcoidosis; the effect on uveitis activity is less convincing. Experience with IL-1 antagonists is minimal and associated with variable results.

Prognosis

There are limited data on the outcome of *NOD2* mutation-associated sarcoidosis in children. Ocular disease can be relentless and causes visual loss in more than one third of patients. Dissemination of granulomatous inflammation and vital organ involvement can occur at a later stage, indicating the necessity of thorough systemic surveillance throughout the disease course.

The outcome of pediatric sarcoidosis forms with wild-type *NOD2* is variable. The large majority of patients with adult-type sarcoidosis enter into remission within 2–5 years after disease onset. Conversely, chronic inflammation and organ damage involving lung, eye, CNS, and/or kidney have been noted in up to one fifth of patients. The outcome is worse in patients with severe lung/organ involvement at presentation, in case of multiorgan involvement, CNS, or eye disease.

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173 Amyloidosis

Tekin Akpolat · Seza Ozen

The amyloidoses constitute a group of diseases characterized by extracellular tissue deposition of fibrils composed of low molecular weight subunits of a variety of proteins. At least 25 different precursors of amyloid fibrils are now known. In pediatrics, the most common form of amyloidosis is reactive AA amyloidosis due to chronic inflammatory diseases and will be the subject of this chapter. AA amyloidosis was described secondary to chronic infections as well, in the early twentieth century. AL amyloidosis, which is seen generally in the elderly, is the most common type of amyloidosis in the developed countries today. Other forms of amyloidosis such as AFib, AL, and ACys have rarely been reported in children.

AA Type Amyloidosis

Familial Mediterranean fever (FMF) and juvenile rheumatoid arthritis are the two most common causes of AA type amyloidosis in the childhood. Recent developments in the diagnosis and treatment of these two diseases have led to a decrease of AA type amyloidosis. Sickle cell anemia, chronic granulomatous disease associated aspergillosis, Hodgkin's disease, and Behçet disease are other diseases that have been associated with AA type of amyloidosis in children in the medical literature.

Pathogenesis

The pathogenesis of amyloidosis depends on the underlying cause and the type of fibrils deposited. In the case of reactive (secondary) amyloidosis, serum amyloid A (SAA) which is the precursor protein for the AA fibrils is an acute phase reactant. Classically, secondary or reactive amyloidosis was associated with any chronic inflammatory disease. The persistence of inflammation subsequently is thought to result in the deposition of AA fibrils. In recent years it has become clear that secondary amyloidosis is mainly the complication of autoinflammatory diseases which is a new chapter in medicine that flourished with the definition of the gene for FMF. The most important complication of inadequately treated monogenic autoinflammatory diseases is the development of secondary amyloidosis. In the case of FMF, the contribution of genetic modifiers such as SAA genotype or M694V mutation and environmental factors (e.g., country) have also been implicated in the pathogenesis.

Clinical Manifestations

The child will often have a medical history covering the features of the autoinflammatory disease that is the primary cause of reactive amyloidosis. The reader is referred to the chapter on autoinflammatory diseases for the review of clinical features of these diseases. Secondary amyloidosis can be seen in autoinflammatory diseases that do not have a monogenic inheritance such as Behçet disease and inadequately treated systemic juvenile idiopathic arthritis (JIA) as well. The clinical manifestations of amyloidosis vary widely and depend on the involved organ(s) and the amount of amyloid fibrils deposited. Amyloid fibrils are most commonly deposited in kidneys, but may also attack the heart, peripheral nerves, thyroid, gastrointestinal system, and bone marrow. Although more than one organ is affected generally, localized forms also can occur.

Proteinuria, nephrotic syndrome, and progressive kidney failure are the main presenting features of AA amyloidosis. Involvement of heart and kidneys are the most important predictors affecting survival. On the other had gastrointestinal amyloidosis may also have devastating complications.

Diagnosis

Amyloidosis should be suspected typically in a patient who presents with proteinuria and who has one of the autoinflammatory syndromes. However, organs other than kidney may be affected as well. In fact in patients who are candidates for this complication, amyloidosis should also be considered in the differential diagnosis of cardiomyopathy, peripheral neuropathy, hepatomegaly, or in the presence of symptoms related to gastrointestinal tract.

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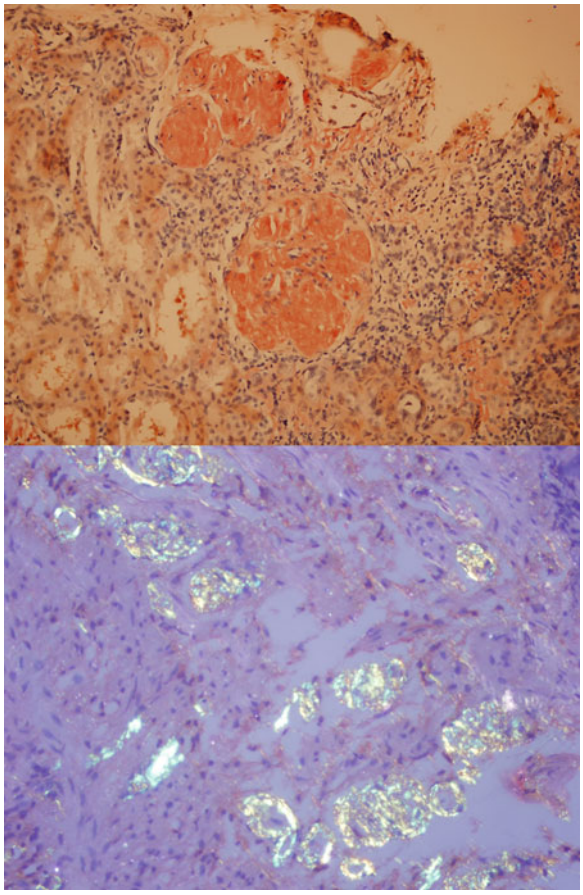

Figure 173.1
Congo red staining on kidney (*upper*, light microscopy, ×200) and rectum (*lower*, polarized light, ×400) biopsies

The diagnosis of amyloidosis is based on the demonstration of amyloid fibrils in the biopsy of the involved tissue (*Fig. 173.1*). Rectal or abdominal fat biopsies may also reveal amyloid deposition. The deposited amyloid fibrils are extracellular, eosinophilic, and metachromatic on light microscopy. Congo red staining is necessary for diagnosis. Amyloid fibrils appear faintly on Congo red staining and show the characteristic apple-green birefringence under polarized light. Specific investigation is needed for detection of types of amyloid fibrils.

Treatment

Specific treatment of the underlying disorder, aiming to suppress the inflammatory activity is the major strategy. Colchicine suppresses the inflammatory activity, decreases the severity and frequency of attacks, and prevents amyloidosis in patients with FMF. Clinical remission may occur at the stage of proteinuria in a few number of FMF patients after colchicine treatment. In the other autoinflammatory syndromes, specific therapy for the suppression of inflammation is often achieved with anti-IL-1 treatment. Biologic treatment such as anti-TNF, anti-IL-1 therapy may have a beneficial effect on amyloidosis per se. However, many patients continue to progress to end-stage renal failure, albeit with a longer renal survival, even with these agents. New treatment options directed to affect the amyloid structure or to prevent fibrillogenesis or to weaken their structural stability are being investigated.

Symptomatic Treatment is Required for Affected Organs

Once end-stage renal failure develops, renal replacement therapy is required. Renal transplantation is one of the options, but the decision should be based on other involved organs, especially the heart. New agents are needed to change the poor outcome of patients with amyloidosis and trials are under way. Since there is no excellent therapy for amyloidosis, the physician should concentrate on the prevention of the disease.

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Oral and Craniofacial Disorders

J. Burton Douglass

174 The Oral Cavity

J. Burton Douglass · Christer Ullbro

The primary function of the oral cavity, as part of the gastrointestinal tract, is to start the digestion process by mastication and the breakdown of carbohydrates through enzymes in the saliva. These functions require a well-functioning oral cavity with healthy teeth, intact and healthy oral mucosa, and normal salivary production. Several diseases and medical conditions threaten the preservation of the health of the oral cavity. On the other hand, bad oral conditions might be a complicating factor to, and a diagnostic aid for, several diseases.

The Teeth

Development

All teeth develop from a band of ectodermal tissue, the dental lamina, formed from the oral epithelium and mesodermal connective tissue. The formation of the lamina starts around the fifth week of intrauterine life. The lamina will develop a number of swellings. They will gradually develop into germs for the deciduous teeth. The permanent teeth will later develop from the same dental lamina.

The tooth germ consists of the enamel organ, derived from the ectoderm, which produces the enamel. It also consists of the dental papilla and the dental sac, derived from the mesenchyme, producing dentine, pulp, and the cementum on the root. The mineralization of the tooth germ is a two-step procedure, in which the initial mineralization provides one third of the minerals and the second mineralization provides the remaining two thirds. The initial mineralization takes place when the tooth is forming, while the second mineralization takes place from the time when the formation of the crown is finished and up to 1 year prior to eruption.

During the time of development, there are many disorders that may interfere with different stages of the tooth formation. The tooth's developmental stage at the time of disturbance will affect the type of defect that will emerge more than the nature of the disorder. Disturbances range from the total destruction of the tooth bud (due to infection or radiation in an early stage of tooth development) to a mild disturbance of the mineralization of enamel (due to trauma or infection late during the secondary mineralization). The enamel will not be changed once it has been formed. It is, therefore, possible to estimate when the disorder happened through the nature and the location of the disturbance.

The *enamel* may develop *hypoplasia* if an early disorder interferes with the formation of the enamel matrix, or *hypomineralization* if the disorder affects the secondary mineralization. The etiology varies and includes genetic as well as acquired and idiopathic factors (*Table 174.1*).

The *dentin* can be affected by *dentinogenesis imperfecta*, a hereditary disorder in which the dentin is composed of irregular tubules, often with large areas of poorly calcified matrix. Both the primary and the permanent dentitions are affected. The teeth have a gray-yellow to yellow-brown appearance. The enamel is normal but as the dentin is soft, the enamel will often be lost due to stress fractures. Dental radiographs on affected teeth show pulp obliteration and short, blunted roots. Dentinogenesis imperfecta is a specific condition or a clinical feature of *osteogenesis imperfecta type III* and *IV*.

The dentin also shows deficiencies with poorly mineralized hard tissue and porosities in *vitamin D-resistant rickets*. Dental abnormalities include normal but thin enamel, interglobular dentin, and enlarged pulp chambers where the pulp horns reach to or beyond the dentoenamel junction. Clinically healthy teeth might show abscesses emerging from pulpal infection, caused by bacteria penetrating to the pulp through cracks in the enamel and the poorly formed dentin (*Fig. 174.1*).

Dentin dysplasia is a rare hereditary anomaly. The dentin is atypical with pulpal obliteration, defective root formation, and a tendency for periapical infection. Both the primary and the permanent dentitions are affected. The enamel is normal.

Shell teeth is a condition where the enamel is of normal thickness but the dentin is thin, giving the appearance of a thin shell of hard tissue surrounding a large pulp chamber and large pulp canals. Shell teeth are sometimes seen as the result of early childhood osteomyelitis or radiation therapy.

Both *enamel* and *dentin* are affected in *odontodysplasia*, a developmental anomaly involving

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Table 174.1
Developmental defects in the enamel

Etiology	Hypomineralization	Hypoplasia
Genetic	Amelogenesis imperfecta	Amelogenesis imperfecta
	Epidermolysis bullosa	Epidermolysis bullosa
Acquired	Trauma	Trauma
	Fluorosis	Perinatal hypoxia
	Local infection	Vitamin D deficiency
	Renal diseases	Renal diseases
	Hypoparathyroidism	Rickets
	Radiation	
	Chemotherapy	
Idiopathic	Odontodysplasia	Odontodysplasia

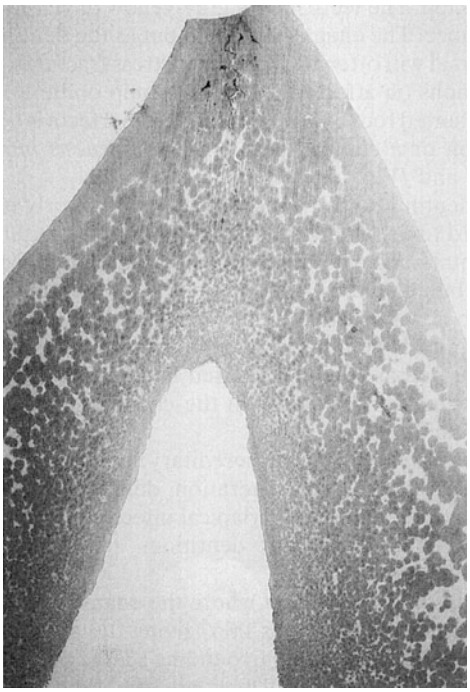


Figure 174.1
Poorly formed dentin in a primary cuspid from a 6-year-old boy with vitamin D-resistant rickets

both mesodermal and ectodermal components in a group of teeth. The affected teeth are discolored, hypoplastic, and hypomineralized. The teeth are smaller with short roots, open apices, and wide pulp chambers. They often fail to erupt completely. The anomaly affects the primary as well as the permanent dentition. The condition is unilateral and, generally, only affects one arch. The term *ghost teeth* has been used for teeth with this condition. The etiology is unknown.

The *cement* is affected in *hypophosphatasia*. In this condition, hypoplasis or aplasia of the cementum causes premature loss of primary and sometimes permanent teeth. In *cleidocranial dysostosis*, there is no deposition of cellular cement. It has been suggested that the cement is deficient in *juvenile periodontitis* and that the premature tooth loss in this disease might be the result of this defect.

Chemotherapy and *radiation* used in pediatric oncology patients often cause dental developmental anomalies. Defects noted include tooth and root agenesis, root thinning and shortening, and enamel defects. Odontogenic cell sensitivity is dependent on the position on the cell cycle and the mitotic activity of the developing tooth at the time of chemoradiation therapy.

Eruption

The eruption of the *primary dentition* usually starts with the eruption of the lower incisors, at the age of 6–8 months. The primary dentition is fully erupted by the age of 3. The approximate number of teeth erupted at different ages is given in *Table 174.2*. The eruption time for primary teeth has a wide normal range.

Premature eruption of primary teeth is uncommon, but might happen with *natal* or *neonatal teeth*. It might cause soft tissue ulceration or interfere with feeding. Due to poor root formation there is also a risk of inhalation of the tooth. Natal or neonatal teeth are in most cases extracted to avoid these complications. Premature eruption of primary molars might occur in Letterer-Siwe disease or other histiocytoses, Ellis-van Creveld syndrome, hyperplasia of the adrenal cortex, diabetes mellitus, and hemifacial hyperplasia.

Delayed eruption of primary teeth may be the result of lack of space, fibrous gingiva, or other local factors disturbing the eruption. Children with obvious delayed or premature eruption should be dentally and medically investigated.

The eruption of the *permanent dentition* starts with the eruption of the central mandibular incisor at the age of 6–7 years and ends with the eruption of the second permanent molar at the age of 12–14 years (with the exception of the third molars). Eruption time for permanent

Table 174.2
Eruption of primary teeth

Age (mo)	Total number of erupted teeth	Latest erupted teeth
8	2	Lower central incisors
10	4	Upper central incisors
13	8	Lateral incisors
16	12	First molars
20	16	Cuspids
30	20	Second molars

Table 174.3
Eruption disturbances in the permanent dentition

Premature eruption	Delayed eruption
Histiocytosis X	Amelogenesis imperfecta
Hyperthyroidism	Cleidocranial dysostosis
Hyperpituitarism	Hypopituitarism
Hypophosphatasia	Hypothyroidism
Turner syndrome	Hypoparathyroidism
Loss of primary teeth in early age	Hypovitaminosis
	Lack of space
	Malnutrition
	Fibrotic mucosa

teeth has a wide normal range. Systemic, inherited, or local factors may cause anomalies in the eruption of teeth (*Table 174.3*).

An *eruption cyst* is a follicular cyst sometimes seen in connection with normal tooth eruption. If there is bleeding in the cyst it is classified as *eruption hematoma*. Usually there is a small, smooth swelling in the soft tissue at the site for tooth eruption. If treatment is needed, puncturing of the cyst is usually the treatment of choice.

Age Determination

Developing teeth can be used as indicators of chronologic age, and have been regarded as superior to other developing organs or structures for age determination of children with unknown birth dates. Different methods, based on comparison of radiographic development of teeth, are used.

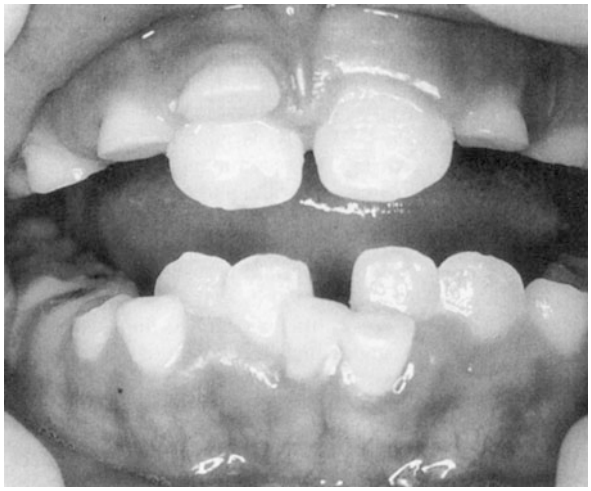


Figure 174.2
Lingual eruption of permanent incisors with persisting primary mandibulary and maxillary incisors

Exfoliation

The reason for normal exfoliation of the primary tooth is the resorption of the root. Resorption is slow up until 1 year prior to exfoliation, when the process is accelerated. The resorption is thought to be initiated by the pressure of the erupting permanent tooth and is caused by osteoclasts resorbing the root and surrounding tooth structure.

The shedding of the primary tooth is usually bloodless, through proliferation of the gingival epithelium below the exfoliating tooth. The permanent tooth will normally erupt without rupture of the soft tissue.

The permanent successor may sometimes have a position that allows the permanent tooth to erupt without any, or only partial, resorption of the primary tooth in the area. This is especially common in the mandibular incisor region (*Fig. 174.2*). The treatment is extraction of the primary tooth.

Premature exfoliation may be seen in patients with hypophosphatasia, acatalasia, Papillon-Lefèvre syndrome, and prepubertal periodontitis. It can also be seen in patients with acute leukemia, neutropenia, Chédiak-Higashi syndrome, and acrodynia.

Divergence in Number

Hypo- and hyperdontia in the *primary dentition* are usually found in the incisor region. None of these numerical variations will normally need any treatment. The prevalence of hypodontia is 1–7 per 1,000 and can be seen in children with ectodermal dysplasia, Down syndrome, and cleft lip and palate.

Hyperdontia has a prevalence of 3–6 per 1,000 and can be seen in children with cleidocranial dysostosis.

Numerical variations in the primary dentition should always be investigated by radiographic examination. With hypodontia in the primary dentition, there is a 75% risk that the corresponding tooth in the permanent dentition will be missing. In hyperdontia there is a 25% risk that there will be an extra tooth in the permanent dentition.

Hypodontia in the *permanent dentition* is not uncommon in healthy individuals. The lower second premolar is missing in about 3%, and the upper second premolar and lateral incisor in about 1.5% of the population. Severe hypodontia may be seen in *hypohidrotic ectodermal dysplasia*, *orofacial-digital syndrome*, *Ellis-van Creveld syndrome*, and *cleidocranial dysostosis*. Anodontia, complete absence of primary and permanent teeth, is a rare condition usually associated with a systemic disorder.

Hyperdontia is usually seen as an upper, midline supernumerary tooth (mesiodens) and has a prevalence of 1–36 per 1,000. Supernumeraries are often seen in *cleft-palate syndrome*, *cleidocranial dysostosis*, and *orofacial-digital syndrome*. Supernumeraries affecting eruption of permanent teeth should be surgically removed.

Divergence in Shape

Variation of tooth shape is predominantly determined by genetic factors. It is uncommon in the primary dentition, except for double formation. This formation can be due to a fusion of two or more teeth or a division of a single tooth germ.

In the permanent dentition, variation in shape is most often seen on third molars and upper lateral incisors. The most common malformation is invaginated odontome. This occurs mostly in the upper lateral incisor.

Local macrodontia can be seen in hemifacial hypertrophy. Other disorders affecting tooth morphology are trauma, radiation, and chemotherapy during the time for tooth development. Microdontia can be seen in pituitary dwarfism.

Discoloration

Primary teeth are naturally whiter than permanent teeth. Depending on the thickness of the enamel and dentin, the natural color of permanent teeth might differ. Extrinsic discoloration with staining from food, drinks, or medication may affect the teeth. Intrinsic discoloration is often the result of hypomineralization (e.g., fluorosis), medication (tetracycline), or the incorporation of different metabolites (porphyria, cholestasis). Extrinsic discoloration can easily be removed with professional tooth cleaning. Intrinsic discoloration can sometimes be affected by bleaching of the enamel, but the result of such a treatment is unpredictable.

Dental Caries

Dental caries is the most common disorder of the dental hard tissue. Although the prevalence of caries among children has decreased in most Western countries, epidemiologic studies have shown that dental caries is still a considerable problem in the Middle East, with high incidence of dental decay at a young age.

Dental caries is a demineralization and disintegration of the dental hard tissue. Caries is caused by acids produced from bacterial fermentation of carbohydrates, preferably sugar. A normal salivary production is important to alter the effect of the acid achieved through the saliva's diluting and buffering capacity.

The keys to avoid dental caries are to reduce the number of cariogenic bacteria in the mouth, to reduce the amount of fermentable carbohydrates consumed, and to increase the resistance of the tooth surface with frequent supply of fluoride.

The cariogenic bacteria, *Streptococcus mutans* and lactobacilli, are reduced by proper oral hygiene. Basic oral hygiene is performed by mechanical cleaning, which should be initiated as soon as the first primary tooth erupts. Children with severe caries problems and conditions making cleaning difficult may benefit from chemical cleaning with chlorhexidine. The numbers of cariogenic bacteria will also be reduced by decreasing the amount and the frequency of sugar intake. A well-balanced diet, with not more than five to six intakes per day, is a good basis for maintained dental health. The protective action of fluoride against the development of caries is well established. The fluoride will be present in the fluid interacting with the enamel, thereby increasing the resistance to acid. Fluoridation of the water supply, naturally or artificially, is an effective means of preventing dental caries.

The recommended dose is 1 ppm. Most toothpastes contain fluoride, and cleaning two times daily will provide a basic fluoride protection. More intensified fluoride treatment by means of fluoride tablets, varnishes, or topical solutions should be used as per individual needs.

Young children with short exposure to fluoride, inefficient oral hygiene, and a high frequency of sugar intake through a feeding bottle or on a pacifier have a high risk of developing rampant caries, usually affecting the upper incisors and primary molars (nursing bottle caries).

Children treated with radiation to the head and neck region because of malignant neoplasms or with total body radiation prior to bone marrow transplantation will have a reduced salivary secretion. It has been shown that the buffer capacity of the saliva is reduced in children treated for malignancies. With reduction of salivary flow, there will be an increase of the *Streptococcus mutans* and an increased risk of developing caries. Fluoride and chlorhexidine are efficient in preventing decay and should be used, together with other preventive measures, for children treated with radiation and chemotherapy.

Dental decay in primary and permanent teeth should be removed to prevent the decay from causing complications in the form of pulp infections or abscesses with infections in surrounding bone tissue and, ultimately, loss of teeth. It is important to retain primary molars to obtain a functional occlusion. The fact that primary teeth will be shed and replaced with permanent teeth does not justify not treating decay, even in young children. Regular annual visits to the dentist from the age of 3 are important in making the patient and the family dentally aware.

Trauma

Trauma is a common reason for dental injuries in young children. Epidemiologic studies have shown that one fourth of all children have had traumatic injuries to their permanent teeth and one fifth of the children under the age of 7 have had injuries to their primary teeth. All children with trauma to their teeth should be examined by a dentist. Prompt and correct treatment of the injury will reduce the number of complications and improve the prognosis for the traumatized tooth.

Trauma to the oral tissues in the form of tooth fractures, soft tissue lacerations, bruises, and bone fractures are common symptoms of physically abused children. Studies have revealed that 50% of physically abused children suffer from trauma to the head and neighboring areas.

Gingiva

The gingiva, together with alveolar bone and the periodontal ligament, form the periodontium. Several diseases and medical conditions involve the gingiva and the periodontium. The role of dental bacteria, accumulated on the teeth (plaque), as a factor in the development of gingivitis and periodontitis has been clearly recognized. The inflammatory response of the gingiva usually reflects the amount of dental plaque accumulated on the teeth, but can also be influenced by the state of general health.

Gingivitis

Gingivitis is a nonspecific term used to indicate an inflammatory condition of the gingiva, regardless of the etiology. Plaque-associated gingivitis is an inflammation, with redness, swelling, and bleeding. It includes the interdental as well as the marginal gingiva. The inflammation can be controlled or prevented by removal of, or inhibiting, the plaque accumulation.

In cases where the inflammatory response does not correspond to the level of plaque accumulation or to improved oral hygiene, other conditions should be considered. Examples of such conditions are acute leukemia, diabetes mellitus, neutropenia, thrombocytopenia, and hormonal changes associated with puberty.

Gingivitis, as such, is a harmless disease and will most likely not proceed into periodontitis, except in specific cases where the immunologic defense system is weakened or the microorganisms of the plaque are aggressive. Dental plaque consists normally of gram-positive bacteria, but the amount of gram-negative bacteria increases in aging plaque. Two-week-old plaque consists of up to 50% gram-negative bacteria. The plaque initially accumulates above the gingival margin but, if not removed, will accumulate in the periodontal pocket. The aging plaque consists of more than 300 different species, among them bacteria with considerable pathogenic potential.

Mouth breathing, due to deficient lip closure or impaired ability to breathe through the nose, may cause frequent drying out of the gingiva in upper anterior areas. This is thought to cause vasoconstriction and decreased resistance to microbial attack.

Acute necrotizing gingivitis (ANG) is a rare periodontal condition primarily seen in young adults and adolescents. It rarely affects healthy children in developed countries, but can frequently be seen among malnourished children in developing countries. It is also seen as a frequent symptom among young human immunodeficiency syndrome

(HIV)-infected adults. The disease is characterized by a necrosis at the top of the interdental papilla that later spreads along the marginal gingiva. The lesions are covered with a grayish yellow membrane which, when removed, exposes a bleeding surface. Patients usually exhibit severe pain and a characteristic oral fetor and may also suffer from regional lymphadenopathy, increased salivation, and elevated temperature. The exact etiology of ANG is unknown but affected sites usually harbor high levels of spirochetes and *Prevotella intermedia*. Local treatment, by removal of plaque, will usually produce rapid healing. In cases with severe gingival necrosis, antibiotics should be used.

Acute streptococcal gingivostomatitis is caused by streptococci and is usually preceded by tonsillitis. The gingiva becomes inflamed, red, and swollen, with an increased tendency to bleed. The submandibular lymph nodes are sometimes enlarged and tender.

Herpetic gingivostomatitis is an acute gingivitis normally caused by herpes simplex virus type 1. In recent years, type 2 virus has been increasingly found in oral infections. The disease is usually seen in children between the ages of 2 and 4 years. Often, the symptoms proceed unnoticed and subclinically but occasionally the disease manifests clinically and is characterized by a sudden onset of fever, general malaise, regional lymphadenopathy, crusts on the lips, oral lesions with acute gingivitis, and small vesicles in the and swollen and often covered by a serofibrinous exudate. This disease is not associated with destruction of the gingiva, and the oral lesions will usually heal in 10–14 days. Treatment is medication against fever and sufficient hydration. Topical anesthetics may be used if the lesions are too painful to permit eating. Antibacterial mouthwashes may be used to reduce secondary infection. In immunologically compromised patients, systemic antiviral treatment may be necessary.

Gingival hyperplasia may be caused by the use of antiepileptic drugs, or it may be inherited as an autosomal dominant trait. In the inherited type, the gingiva usually enlarges in infancy. The teeth are usually covered by thick, firm to soft, pink or red gingiva. Surgical intervention may sometimes be necessary to ensure the eruption of primary molars and permanent teeth, and also for cosmetic purposes and the enhancement of oral hygiene.

Medication with antiepileptic drugs of phenytoin type produces gingival hyperplasia in approximately 50% of patients. The drug induces an increased synthesis or retarded breakdown in drug-sensitive fibroblasts. In areas with chronic irritation, for example in areas with gingivitis, there will be subepithelial fibrosis. Poor oral hygiene with marginal plaque accumulation is a factor favoring gingival enlargement in patients treated with drugs of this type.

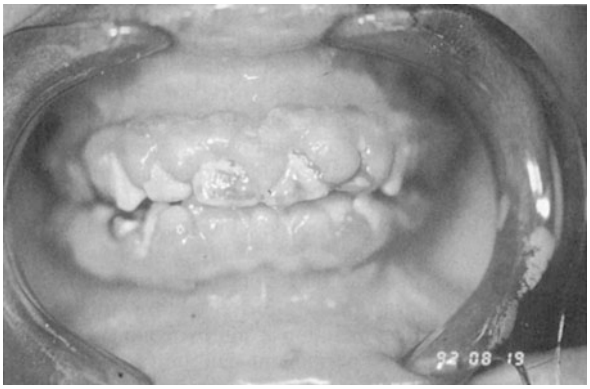


Figure 174.3
Gingival overgrowth on a renal transplant patient on cyclosporine medication (see Color, Figure 175-3)

Cyclosporine induced gingival overgrowth is frequently seen in patients taking cyclosporine after organ transplantation (*Fig. 174.3*). Studies have shown that there is no correlation between blood levels, or oral dosage of the drug, and the occurrence or severity of gingival overgrowth. An oral hygiene regimen initiated after the treatment with cyclosporine has been induced will reduce the gingival inflammation, but not the overgrowth. The gingival changes occur most rapidly during the first 2–6 months, reaching a plateau at about 12 months. Treatment of gingival overgrowth will be surgical reduction of the gingiva for cosmetic or functional purposes.

Periodontitis

Periodontitis is a chronic inflammatory condition preceded by gingivitis. It culminates in the loss of tooth attachment and even loss of the tooth. Periodontitis is rare in healthy children. The incidence increases during adolescence and among children with impaired immune systems.

The organism in the subgingival plaque, consisting mostly of anaerobic and motile bacteria, will destroy the periodontal tissue through the release of toxins, enzymes, and other harmful substances. The immunologic answer to this attack will contribute to the destruction of the connective tissue. The final result is the loss of the tooth due to lack of periodontal support. The periodontal destruction is initiated by bacterial mechanisms. Both the humoral and the cellular immune systems will participate in the defense toward the bacterial antigens.

Periodontal destruction might be severe due to disturbances in these systems (e.g., neutropenia or acute forms of leukemia).

Prepubertal Periodontitis

This is a rare condition affecting the primary dentition in young children. There is one generalized and one localized form of the disease, probably with a genetic basis. *The generalized form shows* acute inflammation and gingival hyperplasia with rapid destruction of the alveolar bone. Children with this condition have functional defects in neutrophils and monocytes, and are frequently affected by other infections (e.g., respiratory infections and otitis media). The permanent dentition may or may not be affected. In the *localized form*, the inflammation is mild and the bone loss is less rapid, affecting only a few teeth. In this form, there is no functional defect of the neutrophils or monocytes. Diseases in which prepubertal periodontitis has been reported include acrodynia, Chédiak-Higashi syndrome, cyclic neutropenia, Ehlers-Danlos syndrome, histiocytosis X, hypophosphatasia, lazy leukocyte syndrome, leukemia, neutropenia, Papillon-Lefèvre syndrome, and scleroderma.

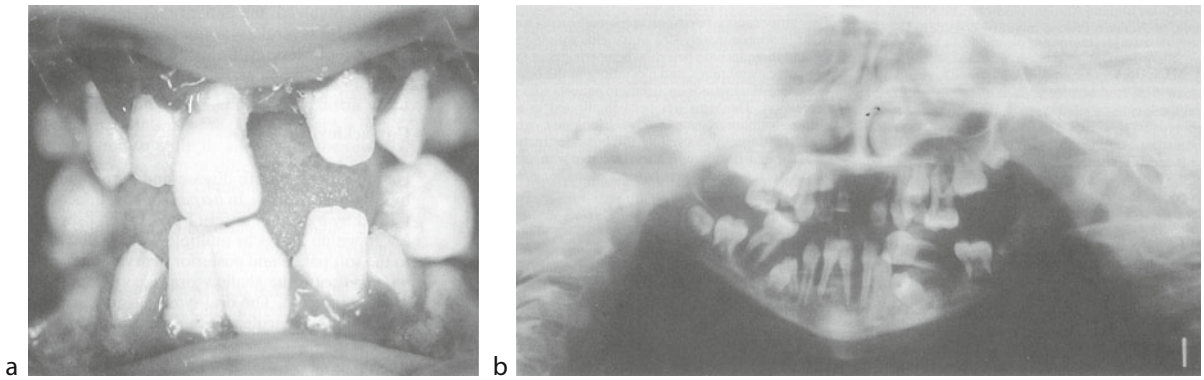
Juvenile Periodontitis

Juvenile periodontitis affects less than 1% of all teenagers. It has its onset around puberty and there is a familial distribution. The oral tissue appears normal, but usually bleeds severely on gentle touch. Radiographic and clinical examinations show deep pockets with severe bone loss, predominantly around first permanent molars and incisors. The amount of plaque does not correspond to the degree of periodontal destruction. Functional defects in neutrophils or monocytes, local disturbances in the root cement, and the presence of *Actinobacillus actinomycetem comitans*, possibly together with Bacteroides-like species, have been discussed as possible factors causing the disease.

Treatment of periodontal lesions in the primary dentition is usually extraction of affected teeth, with the goal being to prevent the infection from involving the permanent dentition. In the permanent dentition the treatment includes professional tooth cleaning and periodontal treatment, sometimes including surgical intervention. If bacteria samples show involvement of specific bacteria involved in periodontitis, treatment with broad-spectrum antibiotics may be justified. It is important to use the antibiotics for a period of at least 3 months because the periodontal bone is affected.

Papillon-Lefèvre Syndrome

Papillon-Lefèvre syndrome is an autosomal recessive disease characterized by palmar-plantar hyperkeratosis and severe periodontal destruction (◉ *Fig. 174.4*). The cutaneous lesions of the palms and soles are usually manifested during the first year of life. The oral symptoms start immediately upon eruption of the primary teeth and cease after the premature loss of the first dentition, only to start again after eruption of the permanent teeth. Patients with Papillon-Lefèvre syndrome are in most cases edentulous in the early teens.



◉ Figure 174.4
(a) Patient with Papillon-Lefèvre syndrome. (b) Radiograph from the same girl showing total bone loss around molars and incisors in the mandible

The treatment is a combination of measures to improve the oral hygiene and to extract teeth with periodontal disease before the loss of alveolar bone is extensive. In the event of gingival infection and the presence of gram-negative anaerobic bacteria, the use of antibiotics has been successful in preventing destructive periodontal infection.

There are reports that treatment with retinoids reduces the periodontal breakdown. Long-term follow-up of this treatment does not support this opinion. Studies to find the etiology behind the severe periodontitis and the optimal treatment for affected children are ongoing.

Hypophosphatasia

Hypophosphatasia is an autosomal recessive disorder defined by low serum alkaline phosphatase activity. Children with this disorder may show skeletal abnormalities (that resemble rickets) and loss of alveolar bone on radiographs. Loosening and premature exfoliation of primary teeth without evidence of any gingival or periodontal infection are classic features of hypophosphatasia. Histology of exfoliated primary teeth exhibits aplasia and hypoplasia of root cementum, large pulp chambers, and interglobular dentin formation. Supplements of vitamin D, phosphate, or a combination of vitamin D and fluoride are used as treatment for bone abnormalities. None of these approaches have been shown to be consistently successful.

Histiocytosis X

Histiocytosis X is a group of diseases with varied clinical manifestations, but sharing the common histologic feature of an infiltrating histocytosis. *Letterer-Siwe disease* occurs in infants with oral ulcerations, gingival hyperplasia, and diffuse bony destructions of the jaw. *Hand-Schüller-Christian disease* occurs mainly in young children diagnosed with multifocal bone defects and sometimes progressive loosening of teeth. *Eosinophilic granuloma* is a unifocal cystic lesion in bone, most often in the mandible. Patients with histiocytosis X are treated with corticosteroids, radiation, and chemotherapy.

Primary Hyperoxaluria

Dental and periodontal findings in primary hyperoxaluria include extensive infiltration of oxalate crystals in the pulp of developing teeth, in the marrow spaces of the alveolar bone, in the gingival corium, and in the periodontal ligament. Crystalline calcium oxalate deposits within the periodontal ligament provoke a granulomatous foreign-body reaction that results in external root resorption, pulp exposure, and tooth mobility.

Pigmentation of the Gingiva

All people except albinos have a certain degree of melanin pigmentation, distributed throughout the epidermis of the skin. There is a great variation in the degree of pigmentation of the skin and of the mucosa between races and also between individuals of the same race. Light-skinned individuals normally have a relatively even coloration throughout the oral cavity, while dark-skinned people frequently have macules of pigmentation of various configuration and sizes on their oral mucosa. The gingiva are frequent sites of this pigmentation (*Fig. 174.5*).

If the pigmentation has a sudden onset, differential diagnosis including melanoma, junctional nevus, hemosiderin deposition after trauma, Albright syndrome, Peutz-Jeghers syndrome, or Addison disease might be considered.

Oral Mucosa

The oral mucosa has a special appearance and is of three different types. The keratoid fixed mucosa covers the hard palate and the alveolar process. The keratoid movable

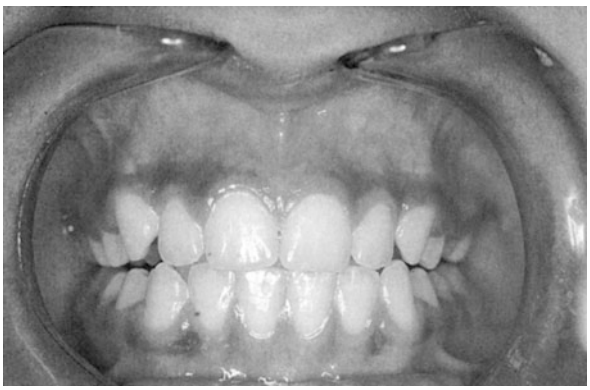


Figure 174.5
Pigmentation of the gingiva on an 8-year-old girl (see color Figure 175-5)

mucosa is located inside the lips and cheeks, soft palate, floor of the mouth, and bottom of the tongue. Specialized mucosa covers the tongue.

Herpes Labialis

Studies have shown that 40–90% of individuals have antibodies to herpes simplex virus type 1. Many only suffer infection subclinically. In individuals with low antibody titer, reinfection in the oral mucosa is possible. Recurrent herpes simplex infections develop in about 30–40% of patients who have had primary herpetic stomatitis. The disorder originates from reactivation of the virus, which remains latent in the nerve tissue in between periods of excitation. Recurrent infection usually appears as small vesicles around the mucocutaneous junction of the lips, often called herpes labialis, while recurrent intraoral herpetic infections are rare. Use of systemic acyclovir is useful in many patients who suffer frequent recurrences of either herpes labialis or intraoral lesions.

Varicella-Zoster Virus

Varicella-zoster virus causes chickenpox and herpes zoster. Oral symptoms in *chickenpox* are vesicles in the palate and throat, sometimes preceding the onset of the typical skin rash. The *herpes zoster* infection is a reactivation of these viruses persisting permanently in the sensory nerves or root ganglia. The reinfection is usually unilateral, appearing in the distribution of the corresponding nerve. If the maxillary or mandibular division of the trigeminal nerve is involved, the patient may experience toothache-like pain for several days prior to onset of more characteristic cutaneous lesions. Relief of pain can be accomplished with the use of analgesics and systemic acyclovir therapy.

Coxsackievirus

Hand-foot-and-mouth disease and herpangina are caused by Coxsackievirus A. In *herpangina* the infection is characterized by a sudden onset of pyrexia and sore throat, followed within 2 days by multiple vesicles that are restricted to the soft palate and posterior pharynx. In *hand-foot-and-mouth disease* the shallow oral ulcers are usually spread over the mucosa. The oral symptoms are accompanied by erythematous macules on the hands and feet.

Epstein-Barr Virus

This virus causes *infectious mononucleosis*. Oral lesions occur in approximately 30% of patients with mononucleosis, and these include petechial hemorrhages in the palate, exudative membranes, and ulcerations in the oral mucosa.

Epstein-Barr virus is oncogenic in patients with immunodepression. The virus has been implicated in a type of diffuse lymphosarcoma, *Burkitt lymphoma*, which may present intraorally as swelling and bone destruction of the jaws. Epstein-Barr virus is also associated with *hairy leukoplakia*, seen on the lateral borders of the tongue in HIV-infected persons.

Cytomegalovirus

Cytomegalovirus can cause sialadenitis with salivary gland swelling. This condition is uncommon and is limited to immunosuppressed patients or newborns.

Bacterial Infections

Scarlet fever is caused by an infection of streptococci. Oral symptoms include a congested oral mucosa and a tongue coated with red, protruding papillae (strawberry tongue) or bright red, swollen, hyperemic papillae (raspberry tongue).

Primary tuberculous infections are rarely manifested by oral signs and symptoms. However, with advanced pulmonary tuberculosis, painful intraoral ulcers can be seen. The most common place is the dorsum of the tongue, and the shape is irregular with overhanging edges.

Actinomycosis is a chronic suppurative and granulomatous disease caused by *Actinomyces israelii*. Other actinomycetes may contribute. The actinomyces gain entrance to the soft tissues through open necrotic pulps, radicular cysts, wounds, or impacted teeth. The infection is usually localized in the submandibular area, around the jaw angle, and is spread, forming abscesses and sinuses with subsequent fibrosis. Treatment is usually excision and, due to a strong tendency to relapse, prolonged antibiotic therapy for 4–6 weeks.

Fungal Infection

Oral candidiasis is an infection caused by *Candida albicans*, a microorganism normally found in the oral

flora in 30–50% of the population. A local or systemic disturbance of the resistance mechanisms or the environment is necessary if the organism is to multiply and invade the mucosa. Oral candidiasis may be seen in different clinical forms.

Acute pseudomembranous candidiasis (thrush) is the most common fungal infection in children. It is seen as raised, pearly white patches covering the tongue, cheek, or soft palate. It can be rubbed off, leaving an erythematous surface.

Acute atrophic candidiasis is seen as red, painful, edematous mucosa. *Chronic atrophic candidiasis* is seen in angular chelitis in children.

Mucocutaneous candidiasis can be seen in children with hypoparathyroidism or Addison disease, in children taking long-term broad-spectrum antibiotics, and in children with iron deficiency and diseases or medical treatment associated with immunodeficiency. The oral changes are similar to those seen in acute pseudomembranous candidosis. The nails and skin may also be affected. Children with congenital immunoglobulin A (IgA) deficiency or cellular immunodeficiency reveal increased prevalence of fungal infections.

Median rhomboid glossitis is sometimes regarded as a chronic candida infection. It usually presents as a rhomboid patch without papillae on the dorsum of the tongue. Histologically, there is a lack of filiform papillae, and varying degrees of hyperkeratosis in which fungal hyphae is demonstrated. Treatment with antifungal agents can be successful. Spontaneous regression may also be seen of this innocent lesion.

HIV infection in children is characterized by oral candidiasis. This is usually manifested as pseudomembranous *Candida* infections, but gingivitis and angular cheilitis, superinfected with *Candida*, is not uncommon.

Treatment of Oral Candidiasis

Good oral hygiene is an important part of managing oral candidiasis, along with the support of chemical agents such as chlorhexidine. Local and systemic predisposing factors should also be addressed. If a specimen from the mucosa or clinical signs confirms candidiasis, treatment with topical antifungal drugs such as nystatin lozenges or amphotericin B lozenges are the first drugs of choice. The lozenges should dissolve slowly in the mouth, four times daily for at least 4 weeks. If lozenges are difficult for the patient to use, nystatin mixture is available. In severe cases of oral candidiasis, ketoconazole, fluconazole, or clotrimazole have been shown to be efficient.

Aphthous Ulcer

Aphthous ulcer is probably caused by an immunologic reaction causing deterioration of the epithelium. The ulcers are oval and have a crateriform base with elevated, reddened margins. The central part of the ulcer is covered with a gray-yellow coating. These painful ulcers are usually situated on the tongue and the buccal and lingual mucosa. The ulcers will heal without any scar formation. Antibacterial mouth rinses might be used to reduce secondary infection. Patients with Crohn disease sometimes reveal ulcerated oral lesions with a clinical appearance similar to aphtous ulcer.

Periadenitis mucosa necrotica recurrens or Sutton aphthae is a severe form of recurrent aphthous ulcers. These ulcers are deeply extended and extremely painful. They usually heal slowly and with scar formation. Topical treatment with corticosteroids, ointment or spray, is sometimes efficient. Rinsing with a solution of chlortetracycline three times a day for 4 days has shown to be efficient in 50–75% of patients.

Erythema Multiforme

Erythema multiforme is a dermatologic disease of unknown etiology. The skin reacts with asymptomatic erythematous macules or papules. The oral lesions can involve the mucosa anywhere in the mouth. Most commonly the lips are affected, with vesicles or bullae rapidly bursting into ulcers. The oral findings might be the only symptoms of the disease. The lesions usually heal in 2 weeks, but recurrent attacks are common. Treatment is mainly with corticosteroids and sometimes with antibiotics to prevent secondary infection. In mild cases, topical anesthesia may be the only treatment needed.

Epidermolysis Bullosa

Epidermolysis bullosa is a diverse group of disorders, with blister formation as a common feature. Tissue separation occurs at variable depths in the skin and/or mucosa depending on the specific type of epidermolysis bullosa. The disorder may involve the eyes, teeth, oral mucosa,

esophagus, intestinal tract, anus, genitourinary tract, and musculo-skeletal system.

The character and extent of oral involvement vary greatly from one type to the other. In the milder forms, the oral mucosa may suffer only occasional blistering, with vesicles that heal rapidly without scarring. In more severe cases, the entire mucosa is affected with severe intraoral blistering with subsequent scar formation, microstomia, obliteration of the oral vestibula, and ankyloglossia. Depending on the type of epidermolysis bullosa, the dentition may be severely affected by enamel defects similar to defects appearing in amelogenesis imperfecta.

Children with epidermolysis bullosa have an extremely cariogenic diet and have difficulty performing routine dental prophylaxis. Preventing dental caries is therefore challenging. Oral hygiene instructions using a soft-bristled, small-headed toothbrush and administration of fluoride are important. Routine dental treatment with local anesthesia is possible in patients with minimal soft tissue involvement or limited treatment needs. Individuals with severe soft tissue involvement, requiring multiple restorative and surgical procedures, are best managed with general anesthesia, often with a modified anesthesiologic approach.

Lichen Planus

Lichen planus is a chronic, inflammatory condition with unknown etiology involving the skin and the oral mucosa. Children are occasionally affected. Oral lesions usually are found on the posterior part of the buccal mucosa, but can also be seen on the tongue or anywhere in the mucosa.

Oral lichen planus exhibits six different clinical appearances: three white (papular, reticular, plaque-like) and three red (atrophic, ulcerative, and bullous). The red lesions are sometimes painful and often infected with *Candida albicans*. All red lesions should be treated by the elimination of trauma, antifungal therapy, and usually corticosteroids for anti-inflammatory treatment. Surgical excision or cryosurgery may be used for ulcerations if pharmacologic treatment is ineffective.

Leukoplakia

Leukoplakia or hyperkeratotic lesions are rare in children. They are often the result of long-standing trauma to the mucosa from dental appliances or as a result of the use of snuff. Most of these changes are reversible after elimination of the trauma. If they persist, they have to be observed because of their precancerous potential.

Oral Mucosa Manifestations of Systemic Diseases

Crohn Disease

Crohn disease is a chronic relapsing inflammatory granulomatous disorder of unknown etiology. The disorder may affect the gut, from the mouth to the anus. In the mouth, the gingiva in the vestibulum may demonstrate linear, hyperplastic folds, occasionally ulcerated.

Kawasaki Syndrome

Kawasaki syndrome usually occurs in children under the age of 5 years. The etiology is unknown. Oral manifestations, occurring within 1–3 days of onset of the disease, consist of erythema, fissuring and crusting of the lips, oropharyngeal erythema, and increased prominence of the lingual papilla ("strawberry" tongue). Other symptoms are fever, generalized nonvesicular rash, swelling and erythema of the hands and feet, and cervical lymphadenopathy. The overall prognosis is good, but cardiac disorders can arise.

Lupus Erythematosus

Lupus erythematosus is a chronic autoimmune disorder of unknown etiology. It is usually divided into chronic discoid lupus erythematosus and the acute systemic type. Oral lesions occur in patients with the discoid and also in patients with the systemic type of the disease. Oral discoid lesions are often found on the buccal mucosa, gingiva, and vermilion border. A typical lesion presents with a central erythematous lesion and peripheral radiating striae. In systemic lupus erythematosus discoid lesions, erythematous lesions and, rarely, ulcerations have been described. In severe cases, oral mucositis superinfected with *Candida albicans* can be seen. Systemic corticosteroids and immuno-suppressants are the treatments of choice for systemic lupus erythematosus. Oral lesions may be treated with topical steroids combined with antifungal treatment if necessary.

The Tongue

Several diseases and disorders affect the tongue with lesions in the mucosa. Some changes in the texture are, however, normal anatomic features. An example is anomalous thyroid tissue in the tongue, usually located around the foramen cecum.

Geographic tongue is a benign, inflammatory condition characterized by round areas with atrophy of papilla filiformis. The lesions are red areas with irregular circinate patterns on the tongue. The areas are outlined by a thin white or yellowish line (*Fig. 174.6*). The pattern and the locality of the red areas may change from time to time. Histologically, the lesions resemble those seen in psoriasis and have been suggested as oral manifestations of psoriasis. Most lesions are asymptomatic, but some patients may complain of soreness or a burning sensation. Treatment with etching solution has been reported to be effective.

Scarlet fever may be diagnosed early in the course through its oral manifestations. The tongue is heavily coated and grayish, and becomes fiery red with large fungiform papillae. This is called "raspberry tongue." By the fourth to fifth day, there is a complete desquamation of the tongue with multiple papillary elevations, sometimes called "strawberry tongue."

Hairy leukoplakia is a lesion usually seen in people with late-stage HIV or acquired immunodeficiency syndrome (AIDS). The lesion is a white patch, usually on the lateral margin of the tongue. The surface is irregular and may show corrugations or flat papules. The lesion is usually asymptomatic, but may be painful if superinfected with *Candida*. Immunohistochemical studies have demonstrated the presence of Epstein-Barr virus in the nuclei of epithelium from hairy leukoplakia.

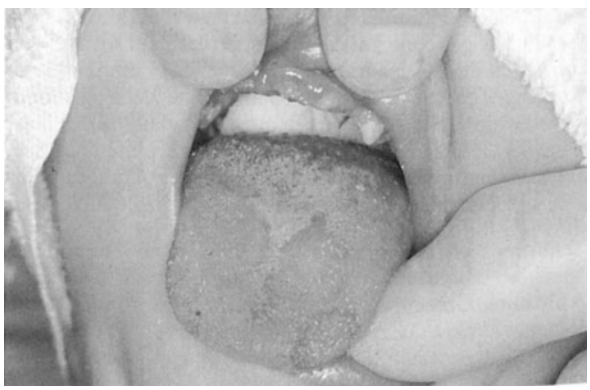


Figure 174.6
Geographic tongue on a young patient (see color Figure 175-6)

Salivary Glands

Xerostomia is a condition usually seen in children with fever, but is also a complication of drugs with anticholinergic activity. It is also found in chronic graft-versus-host disease, rheumatoid disorders affecting the salivary glands, and after high-dose irradiation involving the salivary glands.

Mumps is a viral disease affecting the parotid glands with painful swelling of one or both glands. The swelling usually appears between the posterior border of the mandible and the mastoid and then extends downward and forward. The swelling usually disappears after 3–7 days.

Recurrent parotitis is a recurrent, idiopathic swelling of the parotid gland of otherwise healthy children. One or both parotid glands are involved. The swelling might appear several times every year and will usually last for 2–3 weeks. Sialography will often reveal sialectasis in both glands, even though each episode of infection tends to affect only one side. It is generally accepted that recurrent parotitis resolves around puberty and that sialographic features can return to normal as the patient becomes older. Treatment options are to provide antibiotic therapy when each episode occurs or to provide long-term prophylactic antibiotics.

Suppurative parotitis is a swelling, usually unilateral, that is caused by *Staphylococcus aureus*. The swelling is followed by pain and fever and, once treated with antibiotics, is not recurrent.

Mucocele is a soft, painless, fluctuant, well-defined swelling often with a bluish color. The mucocele usually originates from the small salivary glands in the oral cavity. The cause for the mucocele is trauma, causing mucous to extravasate into the tissue and eventually be enclosed with granulation tissue. It might also be caused by an obstruction of the excretory duct creating a mucous retention cyst. Treatment for mucoceles is surgical removal.

Ranula is the term for a mucocele localized in the floor of the mouth. It may originate from minor salivary glands, in which case it is located superficially. If it originates from one of the sublingual glands, it is larger and more deeply located. Most sublingual mucoceles are extravasation cysts. Marsupialization with packing is the treatment of choice.

Salivary calculus may develop in any of the salivary glands and produce transient episodes of gland swelling, particularly at mealtimes. Approximately 20% of salivary calculi are radiopaque. If not detected in routine radiographs, salivary calculus should be apparent on sialographic views. The treatment is surgical removal.

Tumors seen in the salivary glands of children are usually of the vascular type. Both minor and major glands may be affected, and the palate is the most frequent involved site.

Pleomorphic salivary adenoma accounts for the majority of tumors in the parotid gland. In the submandibular gland, a high proportion of lesions are either *adenoid cystic carcinoma*, *mucoepidermoid tumor*, or *adenocarcinoma*. Neoplasms of the sublingual salivary gland are virtually all malignant, while in the minor salivary glands, around 50% of lesions are malignant.

Cysts

Most of the cysts in the mouth are of epithelial origin.

Odontogenic Development Cyst

Follicular cysts develop around the crown of an unerupted tooth. The cyst is developed by fluid accumulation in the dental follicle. Treatment is enucleation or occasionally marsupialization.

Primordial cysts and *keratocysts* are thought to develop from the dental lamina, or the tooth germ, before mineralization starts. The epithelium of the cyst is often keratinized. These cysts are often found in the lower jaw, and may reach considerable size without causing any pain or swelling of the jaw. The treatment is enucleation, and the surgery must be done with good margin to avoid recurrence. Keratocysts are one of the diagnostic features seen in the basal cell nevus syndrome.

Gingival cysts of the newborn occur with high frequency up to the age of 3 months. These cysts are called *Bohn nodules* when they are located on the buccal or lingual side of the alveolar ridge and *Epstein pearls* when they are located at the midpalatine raphe, the borderline between the hard and the soft palate. The cysts are whitish and 2–3 mm, and will quickly disintegrate. They develop from epithelial remnants of the dental lamina or epithelial inclusions at fusion lines. No treatment is necessary.

Lateral periodontal cysts arise in the periodontal ligament of a vital tooth. The cyst often develops in the lower jaw in combination with erupting molars. The mechanism by which the cyst arises is thought to be from a follicular cyst that is displaced laterally as the tooth erupts. Symptoms are often swelling of the jaw and pain, due to secondary infection. Treatment is surgical enucleation.

Odontogenic Inflammatory Cyst

Radicular cysts are caused by an inflammatory process from a nonvital tooth and develop from epithelial remnants in the periodontium. These cysts are often asymptomatic and grow slowly. They appear radiographically as round or ovoid radiolucencies around the tooth apex. They are treated by enucleation, and the nonvital tooth is extracted or treated endodontically.

Developmental Nonodontogenic Cysts

Nasopalatine duct cysts and globulomaxillary cysts are developed from epithelial remnants in the fusion lines of the embryonic process. The nasopalatine duct cyst is situated in the midline, and the globulomaxillary cyst is between the upper lateral incisor and the maxillary canine. The treatment is surgical excision.

Nonepithelial Cysts

Simple bone cysts are also called hemorrhagic or traumatic cysts. The etiology is unknown, and the cyst is without epithelial lining. It is most commonly found in the lower jaw, and does not involve the teeth in the area. The cyst is usually asymptomatic. Surgical curettage is recommended, but spontaneous healing has been reported.

Odontogenic Tumors

Ameloblastoma is a slowly growing, destructive tumor that is asymptomatic at its early stage. Most of these tumors are located in the molar area of the lower jaw. Radiographically, they resemble expanding uni- or multilocular cysts. Histologically, there is a fibrous stroma with proliferating odontogenic epithelium. Treatment is excision with good margin, as these tumors have a strong tendency to recur.

Adenoameloblastoma is surrounded by a capsule and is usually located in the anterior region of the maxilla.

Ameloblastic odontoma is a tumor consisting of both ameloblastic tissue and mineralized dental tissue. The tumor is encapsulated, and the treatment is excision.

Ameloblastic fibroma is a rare, benign, and slowly expanding tumor. It is predominantly found in children in the maxilla. The tumor is encapsulated and can easily be removed surgically. There is no risk of recurrence.

Odontoma is a tumor that contains both enamel and dentin. Most odontomas are found in the mandible, and they are often asymptomatic.

Odontogenic myxoma is a benign, locally aggressive, nonmetastasizing neoplasm arising from the primitive mesenchymal structure of a developing tooth. The tumor is often clinically asymptomatic. The main symptom is usually bone expansion, but mobility and displacement of teeth may also occur. Radiographically, the tumor usually appears as a multilocular radiolucent lesion. Treatment is surgical resection, but the recurrence rate is high.

Nonodontogenic Lesions

Central giant cell tumor is a benign tumor consisting of osteoclast-like giant cells. Symptoms are swelling and expansion of the cortical plate of the jaw, together with tooth mobility. The tumor has the capacity to destroy bone. The tumor appears as a radiolucency on the radiograph, revealing resorption and tooth displacement. Giant cell tumors are often associated with *hyperparathyroidism.*

Fibrous dysplasia is a condition with a painless bony swelling during childhood. The lesion consists of proliferating fibrous tissue, replacing bone. The tissue contains foci of giant cells and may involve multiple bones or a single bone. It is a self-limiting disease, and the lesions become inactive over the years. Surgical treatment is necessary only when the swelling is disfiguring or interferes with function.

Eosinophilic granuloma is a lesion that is primarily an inflammatory reaction involving the reticuloendothelial structures of bone. The lesions are clinically without symptoms but pain, swelling, and tenderness may occur. The lesions are destructive and are well demarcated. The area destroyed by the lesion is replaced by soft tissue. The treatment is curettage and sometimes radiation. The prognosis of most cases is good.

Osteomyelitis is an inflammation of bone marrow and can present in acute or chronic forms. *Acute suppurative osteomyelitis* of the jaw is most often due to the spread of infection into the medullary space after a periapical tooth abscess. The infection presents with pain, swelling, and pus formation. Cortical expansion and bony swelling occur due to appositional bone growth in the periosteum. Radiographs reveal radiolucent bone areas due to necrotic and sclerotic conditions. Long-term antibiotic treatments, sometimes together with surgical intervention, have been shown to be successful in some cases, but recurrences are frequent. Short-term treatment with corticosteroids, at the time of recurrence, has also been shown to be successful.

Soft Tissue Tumors

Hemangiomas are hamartomas and often congenital. Most hemangiomas are present at birth or arise at an early age. Hemangiomas frequently occur in the head and neck region in children, with lips, tongue, buccal mucosa, and palate as common sites of location. Many congenital hemangiomas undergo spontaneous regression at a relatively early age. Cases that do not show remission have been treated in a variety of ways, including surgery, radiation therapy, sclerosing agents, or cryotherapy. Hemangiomas do not become malignant or recur after adequate removal or destruction.

Lymphangiomas are most often seen in the tongue, but are occasionally found on the lips, gingiva, and buccal mucosa. Most cases are present at birth. If the tongue is affected, considerable enlargement may occur. Spontaneous regression of lymphangioma is rare. Surgical excision is the treatment of choice in cases with functional or extensive disturbances. Lesions show a tendency to recur after removal.

Cystic lymphangioma (hygroma) occurs as a large, deep, diffuse swelling. It is usually located in the neck but can also be found in the mouth (◉ *Fig. 174.7*).

Neurofibromatoma is a benign tumor originating from nerve tissue. The tongue is the most common site in the

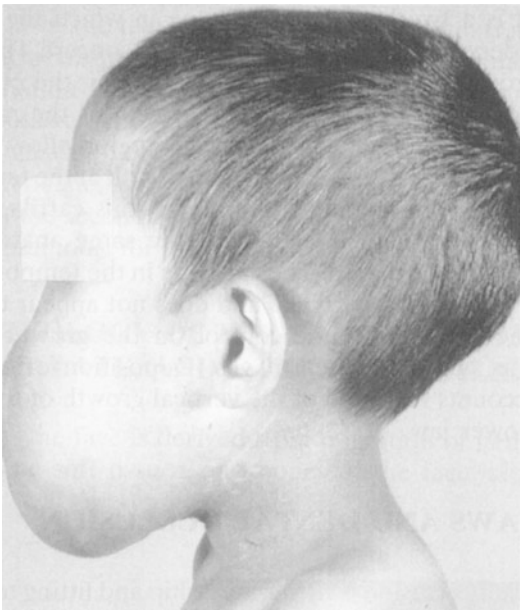


Figure 174.7
Disfiguration of the mandible due to a cystic hygroma on a 6-year-old boy

oral tissue but other locations in the mouth and the pharyngomaxillary space may be involved. Intrabony mandibular neurofibromas have been reported.

Malignant Tumors

Malignant lymphomas are classified into Hodgkin and non-Hodgkin lymphomas. Hodgkin disease frequently affects the lymph nodes in the neck; this is often the presenting symptom. The lymphoid tissue in the oral cavity and the soft tissue of the mouth and jaws may be involved later. *Burkitt lymphoma* is an undifferentiated non-Hodgkin lymphoma. It is worldwide in distribution and occurs mainly in children between 2 and 14 years of age. It has the highest proliferation rate of any human neoplasm, and when the tumor involves jaw lesions it can cause toothache, tooth mobility, and displacement, as well as intraoral and extraoral swelling.

Rhabdomyosarcoma is a malignant tumor originating from striated muscle masses. The lesions are often located on the tongue or soft palate.

Craniofacial Growth and Development

The bony growth and development of the head is best described by dividing the complex into four different areas: the cranial vault, the cranial base, the nasomaxillary complex, and the mandible. Basically, the head matures from the top down (i.e., the cranial vault attains its adult growth, then the base, the nasomaxillary complex, and finally the mandible). There are exceptions in this scheme, but overall it assists in understanding how the head grows and develops and is critical to understanding the morphogenesis of some craniofacial anomalies.

Some basic concepts pertaining to growth of the craniofacial skeleton are essential in the understanding of the development of the head. Bone growth can occur by deposition of new bone on a surface (e.g., the periosteal surface of the posterior ramus of the mandible) and concomitant resorption on the endosteal surface. This produces bone growth known as drift. The apposition of new bone and resorption of preexisting bone is called remodeling and is a fundamental bony growth process. As a result of growth, the bones of the face are relocated relative to each other. This is known as displacement or translation of the bones. Primary displacement occurs when the bones move in response to direct forces and secondary displacement occurs when the bones are repositioned by the growth of adjacent bones. For example, the maxilla grows downward and forward partially in response to growth of soft tissues in the midface (primary displacement). The maxilla is also affected by the expansion of the cranial vault and the growth of the cranial base. As these structures grow, the maxilla is translated in space relative to its preexisting position (secondary displacement).

There are 32 bones in the skull. Some of the bones have cartilage precursors (endochondral bones); others have connective tissues precursors (membranous bones). Some bones develop from both membranous and endochondral sites. The overall mechanisms controlling the growth of the bones in the head are unknown. Genetic control is the most powerful, but how the genetic control is expressed and how other factors (i.e., the environment) affect normal growth and development is only partially known or theorized.

There are three major theories that attempt to explain the bony growth and development of the head. The first states that the bones, like many other tissues and organs, are the primary determinants of their own growth and development. The second theory states that cartilage is the primary determinant of growth and that bone responds secondarily and passively to the growth of these structures. The third theory holds that all skeletal growth is a result of the bones being imbedded in a soft tissue functional matrix and it is the growth of the soft tissues that determine the growth and development of the bones and cartilages. The major difference in these theories is the location where the genetic control is expressed: directly at the level of the bone (therefore, the periosteum), directly on the cartilage (therefore, bone responds secondarily, an example of epigenetic control), or housed in the investing soft tissues (epigenetic control). The more growth is controlled indirectly, the greater the opportunity for environmental influences to affect it. The exact mechanisms are not known, but the face appears to grow in response to the growth of the cartilages and the investing soft tissues (i.e., combination of the second and third theories of growth).

For example, the cranial base is essentially endochondral bone, and the growth control for these structures appears to reside in the endochondral cartilages. Therefore, these cartilages are growth centers. That is, they have intrinsic forces responsible for the growth of the bone. Remodeling at the posterior ramus of the mandible accounts for a tremendous amount of the overall growth of this bone, but this area grows not in response to an expanding cartilage but passively in response to other forces, probably the development of the muscles of mastication (the pterygoids, masseter, and temporalis).

This passive growth in the area makes the posterior ramus a growth site. All growth centers are growth sites, but not all sites are growth centers. The growth of the orbit is an example of another response of the facial bones to extrinsic forces. As the globe expands and develops, the bony socket surrounding the eye develops in response to this soft tissue growth.

The Cranial Vault

The cranial vault is composed of a series of flat membranous bones interconnected in the fetus and infant by connective tissue sutures and six "soft spots," the fontanelles. The bones of the vault grow in response to the rapidly expanding infant brain. This growth of bone in response to growth of soft tissue is an excellent example of growth controlled by the soft tissue functional matrix. The brain case is approximately 65% complete at birth and is 90% complete by age 5. Premature closure of one or more sutures is called craniosynostosis. This can lead to a number of developmental complications, including mental retardation, abnormal facies, and lopsidedness of the skull (e.g., plagiocephaly).

Cranial Base

The cranial base grows as a result of remodeling and endochondral growth. The posterior cranial base continues to grow interstitially at the speno-occipital synchondrosis until approximately age 20, having started the fusion process in the early teens. This growth contributes to the posterior lengthening of the maxilla. This is important for the late eruption of the third molars and aids in the growth of the nasopharynx. The other cranial base synchondroses fuse considerably earlier, and much of the apparent increase in length of the anterior cranial base is remodeling and expansion of the frontonasal sinuses. The cranial base cartilages have traditionally been thought to be growth centers and as such they house the genetic control for the growth of the cranial base. Growth of the cranial base – by secondary displacement – affects the downward and forward movement of the middle and lower face.

Nasomaxillary Complex

The maxilla grows downward and forward by primary displacement from growth at the sutures, by surface remodeling, by expansion of the nasal airway, and by secondary displacement from growth of the brain and the cranial base. In many craniofacial anomalies the cranial vault and cranial base are malformed, and as a partial consequence of this, maxillary hypoplasia is seen (because of lack of secondary displacement). The role of the nasal cartilage in "pulling" the maxilla is not completely known, but it appears to play a role in the forward development of the complex. The investing soft tissues of the face play a role in the development of the bony midface. The maxilla appears to grow in response to other forces, as it has no cartilages directly affecting it. The tongue plays a role in molding the maxilla and alveolus in the early development years. Abnormal tongue position (e.g., glossoptosis) can contribute to abnormal maxillary dental arch form (a narrow V-shaped palate).

Mandible

The mandible develops as a single bone, unique in the skeleton because of its horseshoe-shaped anatomy and because it is a two-hinged single bone in which the hinges work independently of each other but in concert. The mandible grows primarily at the posterior rami, the coronoid processes, and the condyles. The growth at the ramus is membranous, and the changes in this region allow for the eruption of the posterior teeth. The growth at the temporomandibular joint is endochondral, but this cartilage does not behave like, nor does it have the same anatomy as, other skeletal cartilages. The cartilage in the temporomandibular joint is fibrocartilage and does not appear to exert the same type of genetic control on the growth of the mandible as do other cartilages. Deposition of alveolar bone accounts for some of the vertical growth of the body of the lower jaw.

The Jaws and Dental Occlusion

The dental occlusion is the relationship and fitting together of the maxillary teeth with the mandibular teeth and therefore is the interface of the independent, movable lower jaw with the upper jaw that is fixed to the skull. The development of the occlusion accounts for the vertical alveolar growth of the jaws. The teeth and their position relative to each other and subsequently the position of the jaws play three major roles in the growth and development of the child:

1. They are essential in the change from a soft to a hard diet, and after a more diverse diet is achieved, the teeth

have a major role in *digestion*, namely, *mastication* of food.
2. The teeth are essential in *proper speech development.*
3. The appearance and position of the teeth – especially in combination with functioning, normal muscles of facial expression – have a role in the development of the child's *positive self-image.*

In order for the lower face to function properly and to be pleasing esthetically, the jaws must have a reasonable relationship to each other in all three planes of space (sagittal, vertical, and transverse). In the sagittal plane, three basic types of jaw relationship exist. An orthognathic relationship implies that the jaws are well related. Prognathism implies that the lower jaw is anterior to the upper jaw. Retrognathia implies that the lower jaw is posterior or behind the upper jaw. This is implied because jaw relationship is a function of the position of both jaws; consequently, what on first observation may appear to be a mandibular prognathism may in fact be a maxillary retrusion. The vertical plane of space can again yield three basic types of jaw relationship: normal, apertognathia, and closed bite. Normal is self-explanatory; apertognathia is commonly called open bite. In open bite, the anterior teeth are disarticulated vertically; persons with apertognathia often have long, narrow, tapering faces, and the lips are open at rest. In closed bite or deep bite, the upper incisors cover the lower incisors vertically, and persons with this type of skeletal and dental relationship typically have short, square faces, and often have excessive lower lip curl. In the transverse plane, most of the problems reside in the maxilla, and are expressed by unilateral or bilateral dental crossbites. There are a myriad of combinations of relationships of the jaws, the teeth, and the planes of space. It is normal for the newborn and infant to present with mandibular retrognathia. However, if a newborn is examined and shows an excessive degree of retrognathia (i.e., micrognathia or brachygnathia), the palate should be thoroughly examined for cleft palate, as children born with micrognathia can have cleft of the secondary palate and glossoptosis. This triad is pathognomonic for the Robin sequence.

Embryology of the Face, Cleft Lip and Palate, and Other Anomalies

Most of the face is derived from migration of neural crest cells. The soft tissues, and bones of the face, along with the teeth, are derivatives of this tissue, and disturbances with the migration of the cells can account for some of the phenotypes observed in many craniofacial anomalies. The migration is completed by the fourth week of intrauterine life. The face then develops from the fusion of various processes. Interference with this fusion accounts for a variety of the facial clefts. Clefting of the lip and/or palate is a common congenital deformity, but club foot and syndactyly are the most common. Cleft lip and/or palate is, by far, the most common craniofacial deformity (*Fig. 174.8*).

At approximately the fourth week, the neural crest cells give rise to the facial processes: the frontonasal, maxillary, and mandibular processes. The maxillary and mandibular are both derived from the first branchial arch, the skeleton of this arch being the Meckel cartilage. The bilateral frontonasal processes give rise (at approximately 31 days) to lateral and medial nasal processes and an intervening nasal pit. At approximately 36 days in the human, the median nasal, lateral nasal, and maxillary processes fuse to form the upper lip and primary palate.

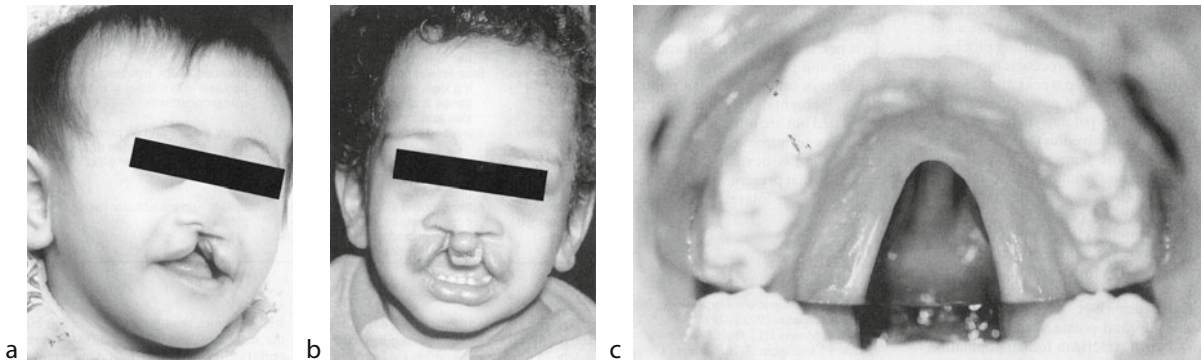


Figure 174.8
(a) Unrepaired unilateral cleft lip. (b) Unrepaired bilateral cleft lip. (c) Unrepaired cleft palate

The maxillary and mandibular processes fuse at the corners and establish the width of the mouth. The depression between the fusing processes of the upper face and the mandibular process is the stomodeum or the primitive oral cavity. Two weeks after closure of the primary palate, the secondary palate closes. This occurs by the elevation of the palatal shelves. Consequently, clefting of the lip (and alveolus) and clefting of the secondary palate are not the same embryologic phenomenon. Clefting of the lip and primary palate can lead to the subsequent clefting of the secondary palate, but not vice versa. Approximately 60% of people born with cleft lip also have cleft palate. Isolated cleft palate occurs well after lip closure and in many cases represents a mechanical deformation rather than a true malformation (i.e., the tongue prevents the shelves from closing properly and, therefore, inhibits proper fusion).

The incidence of cleft lip and palate varies, from 2.79 per 1,000 reported in a North American Indian population to 0.24 per 1,000 in an African-American population. In a study of more than 400,000 Caucasian births in England, the incidence was 0.95 per 1,000. There are conflicting reports from the Middle East. One report from Saudi Arabia puts the incidence at 2.19 per 1,000, while another report from Saudi Arabia places the incidence at 0.3 per 1,000. A report from Kuwait places the incidence at 1.48 clefts per 1,000 live births. It appears that the incidence of cleft lip and palate in Arab populations is consistent with that seen in other Caucasian populations.

Developmental disturbances of the face and mouth can be isolated but are often associated with other organ system anomalies (syndromes). The list of these problems is exhaustive and is beyond the scope of this chapter.

Table 174.4
Some anomalies that have orofacial components

Diagnosis	General findings	Orofacial findings	Etiology and frequency
Achondroplasia	Generalized skeletal dysplasia with short stature	Facial dysmorphism	Autosomal dominant
Apert syndrome	Acrocephaly, hypertelorism with exophthalmos, syndactyly of the fingers, antimongoloid slant of the palpebral fissures, low-set ears	Maxillary hypoplasia, often cleft palate	Autosomal dominant
Cleidocranial dysostosis (dysplasia)	Upper thorax narrow with a hypo or dysplasia of the clavicles, large, broad, short cranium	Delayed dental development	Autosomal dominant
Crouzon syndrome	Oxycephaly (turricephaly), exophthalmos, hypertelorism	Maxillary hypoplasia, malocclusion	Autosomal dominant
Cutis laxa, recessive type II	Loose skin, dislocated hips	Maxillary hypoplasias, relative prognathism, dental crowding	Autosomal recessive
Hemifacial microsomia (Goldenhar syndrome, oculoauriculovertebral spectrum)	Marked facial asymmetry with underdeveloped mandible on the affected side, microtia or ear tags, deviated chin	Canted occlusal plane, malocclusion	Sporadic occurrence
Osteogenesis imperfecta (generalization of all types)	Blue sclera, bone fragility, hearing loss, deformities of long bones and spine, hearing loss and joint hyperflexibility	Opalescent teeth, maxillary hypoplasia with relative mandibular prognathism	Autosomal dominant
Osteopetrosis (Albers-Schönberg disease)	Increased bone density	Primary molars and all permanent teeth are distorted and remain, or partially erupted	Autosomal dominant
Robin sequence	Cleft palate, micrognathia, glossoptosis	See general findings	Sporadic occurrence
Treacher-Collins syndrome (mandibulofacial dysostosis)	Antimongoloid slant of the palpebral fissures, malar hypoplasia, microtia with frequent conductive hearing loss	Maxillary and mandibular hypoplasia	Autosomal dominant

Some anomalies that present with orofacial disturbances that may be of particular interest are presented in *Table 174.4*.

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Gastrointestinal and Liver Disorders

Hisham M. Nazer

175 Major Symptoms and Signs of Gastrointestinal Disorders

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Introduction

This chapter is intended to address in some details the major symptoms and signs of gastrointestinal, as well as, some other hepatic disorders.

The chapter is a new addition to second edition of ***"Textbook of Clinical Pediatrics"*** to enrich the knowledge and modify the clinical approach in dealing with such a wide spectrum of clinical manifestations with practical approach and clinical applications of varied spectrum of symptoms and signs pertinent to gastrointestinal and liver disorders.

The chapter is to be looked as complementary to other chapters covering various relevant symptoms and signs with practical clinical application. It does reflects real recognition for the needs of such added information to the classically set and written chapters.

This chapter will focus on four major topics:

1- Dysphagia	2- Diarrhea
3- Constipation	4- Abdominal pain

Other chapters of relevance to cover the remaining varied spectrum of gastrointestinal and hepatic disorders that the reader is advised to refer to for completion include:

1. Approach to a child with failure to thrive (Chap. 183, "Approach to a Child with Failure to Thrive")
2. Approach to a child with malabsorption (Chap. 184, "Approach to a Child with Malabsorption")
3. Cyclical vomiting syndrome (Chap. 176, "Cyclical Vomiting Syndrome")
4. Functional gastrointestinal disorders (Chap. 185, "Functional Gastrointestinal Disorders")
5. Intractable diarrhea of infancy (Chap. 188, "Intractable Diarrhea of Infancy")
6. Chronic diarrhea (Chap. 190, "Chronic Diarrhea")
7. Practical approach to children with hepatobiliary disorders (Chap. 203, "Practical Approach to a Child with Hepatobiliary Disorder")
8. Cirrhosis and Ascites (Chap. 212, "Cirrhosis and Ascites")

Dysphagia

Dysphagia is the medical term for the symptom of difficulty in swallowing. It is derived from the Greek *dys* meaning bad or disordered, and *phago* meaning "eat". It is a sensation that suggests difficulty in the passage of solids and/or liquids from the mouth to the stomach. http://en.wikipedia.org/wiki/Dysphagia - cite_note-isbn0721600107-9#cite_note-isbn0721600107-9

Dysphagia is distinguished from other symptoms including odynophagia, which is defined as painful swallowing, and phagophobia which is a psychogenic dysphagia.

Dysphagia either refers to the difficulty with initiating a swallow (usually referred to as oropharyngeal dysphagia) or the sensation that foods and or liquids are somehow hindered in their passage from the mouth to the stomach (usually referred to as esophageal dysphagia). Dysphagia therefore is the "perception" that there is an impediment to the normal passage of swallowed material.

There are two main types of dysphagia, each categorized by the part of the body that is affected. The two types have different symptoms.

Oropharyngeal Dysphagia

Oropharyngeal Dysphagia is a swallowing problem that originates from a problem or abnormality affecting the throat or mouth. The process of moving a food bolus, in particular liquids, from the mouth to the esophagus, while coming in close proximity to the airway, requires a fine coordination of events happening at a very rapid rate.

Some signs and symptoms of oropharyngeal dysphagia include difficulty controlling food in the mouth, inability to control food or saliva in the mouth, difficulty initiating a swallow, coughing, choking, frequent pneumonia, unexplained weight loss, gurgly or wet voice after swallowing, nasal regurgitation, and dysphagia which are usually related to a disruption of this phase of swallowing

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that be caused by either structural defects or more commonly neuromuscular dysfunction. Both sensory and motor injury may result in an inability to accomplish the transfer of a bolus of food or liquids from the mouth to the esophagus.

Structural abnormalities that may be encountered in the hypopharynx include: hypopharyngeal diverticulum (Zenker diverticulum), head and neck tumors, irradiation, or postcricoid webs.

Causes

- Myasthenia gravis
- Bell's palsy
- Bulbar palsy and pseudobulbar palsy
- Xerostomia
- Radiation
- Neck malignancies
- Neurotoxins (e.g., snake venom)
- Eosinophilic esophagitis
- Poliomyelitis
- Tardive dyskinesia

In these settings, patients may note that a solid bolus presents difficulty leaving the mouth and entering the tubular esophagus. The actual site of obstruction is always at or below the level at which the level of obstruction is perceived. This may occur as a result of poor motor control of the tongue, jaw, or other oral structures or may be due to an abnormality of the swallowing reflex.

Some patients have limited awareness of their dysphagia, so lack of the symptom does not exclude an underlying disease. When dysphagia goes undiagnosed or untreated, patients are at a high risk of aspiration and subsequent aspiration pneumonia. Some patients present with "*silent aspiration*" and do not cough or show outward signs of aspiration. Dysphagia within 1 s after swallowing suggests oropharyngeal dysphagia.

Signs and symptoms may include:

Low interest in feeding or meals
Tension in the body while feeding
Refusal to eat foods that have certain textures
Lengthy feeding or eating times (30 min or longer)
Food or liquid leaking from the mouth
Coughing or gagging when eating or nursing
Spitting up or vomiting during feeding
Poor weight gain

Inspection of oral cavity should alert for oral ulceration, masses, and lesions.

Neurologic testing of the cranial nerves involved in swallowing, both sensory and motor

Skin exams for scleroderma, and limbs for neuromuscular disorders

Esophageal Dysphagia

Once the food bolus enters the esophagus, passage may be hindered by structural abnormalities or alterations in esophageal motility. These alterations range from congenital abnormalities to acquired conditions.

Solid food dysphagia is the hallmark symptom of esophageal dysphagia, although both solid and liquid dysphagia are typically encountered in achalasia.

The most common symptom of esophageal dysphagia is the inability to swallow solid food, which the patient will describe as "becoming stuck" or "held up" before it either passes into the stomach or is regurgitated.

Esophageal dysphagia may be caused by two general mechanisms:

1. Structural or mechanical process impairing movement of a food bolus through the lumen, including structural abnormalities in the esophagus or extrinsically impinging upon the esophagus
2. Functional disorder

Etiologies may be differentiated by several historical points:

1. Solid versus liquid dysphagia: Dysphagia to solids alone suggests a mechanical or structural abnormalities, while dysphagia to both solids and liquids suggests a neuromuscular disorder.
2. Intermittent versus progressive symptoms: Intermittent dysphagia suggests a fixed esophageal ring or web which has not changed in size. In contrast, progressive one suggests a peptic stricture or achalasia.
3. Associated symptoms: History of heartburn or acid reflux suggests a peptic stricture. Chest pain with intermittent dysphagia indicates diffuse esophageal spasm.

Achalasia is a major exception to usual pattern of dysphagia in that swallowing of fluid tends to cause more difficulty than swallowing solids. In achalasia, there is idiopathic destruction of parasympathetic ganglia of the auerbach submucosal plexus of the entire esophagus, which results in functional narrowing of the lower esophagus, and peristaltic failure throughout its length

Signs and symptoms of esophageal dysphagia may include:

- Trouble in swallowing
- Constant feeling of a lump in the throat
- Pain with swallowing
- Drooling
- Coughing or choking with eating or drinking
- Recurrent pneumonia
- Nasal sounding voice
- Sensation of food sticking in the chest
- Weight loss
- Signs of malnutrition and dehydration
- Taking a long time to chew food
- Moving the head or neck in a strange motion while swallowing

Causes

- ***Functional causes include***
  - Achalasia
  - Myasthenia gravis
  - Bulbar or pseudobulbar palsy
- ***Mechanical causes include***
  - Peptic esophagitis
  - Carcinoma of the esophagus or gastric cardia
  - External compression of the esophagus, such as obstruction by lymph node and left atrial dilatation in mitral stenosis
  - Candida esophagitis
  - Pharyngeal pouch
  - Esophageal web
  - Esophageal leiomyoma
  - Systemic sclerosis
- ***Others***
  - Muscle disorders (dermatomyositis, myotonic dystrophy)
  - Nervous system problems
  - Obstructive lesions in the throat or esophagus, such as tumors
  - Vitamin B12 deficiency
  - Head injury, stroke
  - Cerebral palsy
  - Huntington's disease
  - Myasthenia gravis
  - Amyotrophic lateral sclerosis
  - Scleroderma
  - Infection with herpes simplex virus or yeast
  - Narrowing of the esophagus after infection or irritation
  - Injury to the swallowing muscles from chemotherapy and radiation for cancer

Differential Diagnoses of Dysphagia in Pediatric Patients

Congenital Anomalies

- Prematurity
- Nasal and nasopharyngeal
- Nasal and sinus infections
- Septal deflections
- Tumors
- Defects of lips and alveolar processes
- Hypopharyngeal stenosis and webs
- Craniofacial syndromes (e.g., Pierre Robin, Crouzon, Treacher Collins)
- Laryngeal stenosis, cleft, paralysis, and webs
- Laryngomalacia, laryngotracheoesophageal cleft
- Tracheoesophageal fistula/esophageal atresia
- Esophageal strictures and webs
- Vascular anomalies:
- Aberrant right subclavian artery (dysphagia lusorum)
- Double aortic arch, right aortic arch with left ligamentum

Acquired Anatomic Defects

- Trauma
- Intubation and endoscopy
- Central nervous system disease, anomalies, infections, hypoxia
- Head trauma
- Peripheral nervous system disease
- Neuromuscular disease
- Myotonic muscular dystrophy
- Myasthenia gravis
- Guillain–Barré syndrome
- Poliomyelitis (bulbar paralysis)

Diagnostic Tests

- Nasopharyngoscopy
- Blood tests – to check for infection and thyroid function

- Esophagram with barium swallow – is favored as the initial step because it provides information about both the structural lesions as (web, strictures, rings, or neoplasm) and esophageal motility
- Endoscopy – to assess for strictures, web, and ring, but poor for motility assessment
- Videoradiographic studies
- Ultrasound
- Manometry – for achalasia and motility study
- pH studies for gastroesophageal reflux disease
- CT scan – for neck and chest
- Chest X-ray

Treatment of Dysphagia

Symptomatic

A thorough investigation of dysphagia reveals a diagnosis in a large proportion of cases, and therapy is directed at the specific diagnosis. In some instances, empiric interventions are employed for both diagnosis and treatment. Corrective swallowing strategies and dietary manipulations are the principal empiric interventions, aimed at reducing aspiration risk and avoiding nonoral feeding. Balloon catheter or Savary dilation of the cricopharyngeus has been reported for patients with primary cricopharyngeal dysfunction, with good success.

For esophageal dysphagia, empiric strategies include dilation, antireflux therapy, and treatments aimed at sensorimotor dysfunction. Although the risk of perforation or significant bleeding approximates 1% when standard dilation is performed for a variety of benign indications, Antireflux therapy is offered to many patients with esophageal dysphagia, but a real estimate of its efficacy is unknown. Esophageal *prokinetics*, such as the 5-HT_4 agonist cisapride, increase midesophageal contraction pressures and could conceivably benefit patients with unexplained esophageal dysphagia.

Glucagon inhibits LES contraction and has been used acutely in patients with idiopathic food bolus impactions. The limited benefits of this approach may be related to the negative effects of glucagon on esophageal body motility. *Smooth muscle relaxants*, such as nitrates, calcium channel blockers, and peppermint oil, effectively decrease LES pressure or reduce distal esophageal contraction amplitudes and improve transit symptoms in achalasia. These agents have been tried in patients with spastic disorders with limited benefit.

Symptoms

Symptoms include:

- Trouble swallowing
- Constant feeling of a lump in the throat
- Pain with swallowing
- Drooling
- Coughing or choking with eating or drinking
- Recurrent pneumonia
- Nasal sounding voice
- Sensation of food sticking in the chest
- Weight loss

Diagnosis

The doctor will ask about your symptoms and medical history, and perform a physical exam. The exam will focus on the nervous system. The doctor will also watch you chewing and swallowing.

Tests may include:

- Nasopharyngoscopy – using a scope to view the throat
- Blood tests – to check for infection and thyroid function
- Esophagram with Barium Swallow – X-ray test of the esophagus
- Endoscopy – a thin, lighted tube inserted down the throat to examine the esophagus
- Videoradiographic studies – X-rays during which swallowing is filmed on video
- Ultrasound – a test that uses sound waves to examine structures inside the body
- Manometry – tests the amount of pressure generated in various parts of the esophagus
- pH studies – tests the degree of acidity in the esophagus
- CT scan – a type of X-ray that uses computers to make pictures of the neck and chest
- Chest X-ray – to check for pneumonia

Swallowing Techniques and Exercises

A speech-language pathologist can teach

- Techniques to help you swallow more easily
- Exercises that strengthen the muscles needed for swallowing

Diet Changes

In severe cases, high-nutrition liquid drinks and thickener powder may be added. If a problem persists with feeding liquids, gastric tube will be placed.

Surgery

In severe cases, surgery may be needed to:

- Release an overly tight muscle
- Remove a stricture or web that is blocking the esophagus
- Place a stent to hold the esophagus open
- Place a gastric feeding tube

Diarrhea in Children

Definition

Diarrhea implies an increase in stool volume and diminished stool consistency. It is a common cause of death in *developing countries* and the second most common cause of infant deaths worldwide. The loss of fluids through diarrhea can cause dehydration and electrolyte imbalances. It has been defined in infants and young children as daily stools with a volume greater than 10 ml/kg and in older children as daily stools with a weight greater than 200 g. This situation typically implies an increased frequency of bowel movements, which can range from 4 to 5 times to more than 20 times per day.

Diarrheal episodes are classically distinguished into acute and chronic based on their duration. *Acute diarrhea* is thus defined as an episode that has an acute onset and lasts no longer than 14 days*; chronic or persistent diarrhea* is defined as an episode that lasts longer than 14 days. The distinction often has a different set of causes, presentation, complications, management, and a different prognosis.

Pathophysiology of Diarrhea

Normally, the small intestine and colon absorb 99% of both oral intake and endogenous secretions from the salivary glands, stomach, liver, and pancreas. Diarrhea results from a disruption of this normal mechanism and as a result, the net absorptive status of water and electrolytes will be disturbed, resulting in excess losses and dehydration. The small intestine is the prime absorptive surface and the colon then absorbs additional fluid, transforming a relatively liquid fecal stream in the caecum to well-formed solid stool in the rectosigmoid part. Either a decrease in absorption or an increase in secretion leads to additional fluid within the lumen and diarrhea.

Diarrheal illnesses may be classified as follows:

- Osmotic, due to an increase in the osmotic load presented to the intestinal lumen, either through excessive intake or diminished absorption
- Secretory, when increased secretory activity occurs
- Inflammatory (or mucosal), when the mucosal lining of the intestine is inflamed
- Motile, caused by intestinal motility disorders

In osmotic diarrhea, stool output is proportional to the intake of the unabsorbable substrate; osmotically active substance (e.g., magnesium ion, lactulose) that osmotically retains fluid within the lumen, thereby reducing water absorption. Diarrheal stools promptly regress with discontinuation of the offending nutrient, and the stool ion gap is high, exceeding 100 mOsm/kg. Because neither the small intestine nor colon can maintain an osmotic gradient, unabsorbed ions remaining in the intestinal lumen obligate retention of water to maintain an intraluminal osmolality equal to that of body fluids (about 290 mOsm/kg). The most common cause is related to poorly absorbed sugar and the most common clinical syndrome related to excess sugar malabsorption is of disaccharidase enzyme deficiency such as *lactase deficiency,* which accounts for lactose intolerance. javascript:top.left.goRef('r_chap09.htm','r11')

Lactase is present in the brush border of the small intestine and if the enzyme level transiently or permanently disappears, then lactose malabsorption forms and diarrhea develops. Congenital deficiency of lactase is quite rare and seems to be due to a mutation in a gene distinct from that for lactase-phlorizin hydrolase. Other disaccharidase enzyme deficiency is quiet rare.

The essential characteristic of osmotic diarrhea is that it disappears with fasting or cessation of ingestion of the offending substance. This characteristic has been used clinically to differentiate other causes of diarrhea. Electrolyte absorption is not impaired and low in the stool.

In secretory diarrhea, the driving force for this type of diarrhea is always either net secretion of chloride or bicarbonate or inhibition of net sodium absorption. There is little-to-no structural damage. The epithelial cells' ion transport processes are turned into a state of active secretion.

The most common cause of acute-onset secretory diarrhea is a bacterial infection of the gut. They may trigger release of cytokines attracting inflammatory cells, which, in turn, contribute to the activated secretion by

inducing the release of agents such as prostaglandins or platelet-activating factor.

Features of secretory diarrhea include that the intestinal fluid secretion is isotonic, continues even when there is no oral food intake, a lack of response to fasting, and a normal stool ion gap (i.e., 100 mOsm/kg or less), indicating that nutrient absorption is intact.

The absence or disruption of a specific absorptive pathway may cause diarrhea. For example, there are congenital syndromes due to absence of a specific transport molecule, such as *congenital chloridorrhea* and *congenital sodium diarrhea*.

In chloridorrhea, cl-HCO3 exchange in the ileum and colon is defective, transforming chloride into a poorly absorbed ion. Diarrhea due to chloridorrhea can be reduced by limiting chloride intake or inhibiting chloride secretion by reducing gastric acid secretion with a proton-pump inhibitor.

In inflammatory diarrhea, there is damage to the mucosal lining or brush border, which leads to a passive loss of protein-rich fluids, and a decreased ability to absorb these lost fluids. It can be caused by bacterial infections, viral infections, parasitic infections, or autoimmune problems such as inflammatory bowel diseases. Some of these are usually temporary, because over time the intestine may improve its capacity for absorption by the process of *adaptation.*

In motility-related diarrhea, diarrhea is caused by the rapid movement of food through the intestines (hypermotility). For fluid and electrolyte absorption to be complete, the contact time between luminal contents and the epithelium must be sufficient to permit absorption. There is not enough time for sufficient nutrients and water to be absorbed.

This can be due to a vagotomy, diabetic neuropathy, or hyperthyroidism that can produce hypermotility and lead to pseudodiarrhea and occasionally real diarrhea. Diarrhea can be treated with antimotility agents. Hypermotility can be observed in people who have had portions of their bowel removed, allowing less total time for absorption of nutrients.

Common Causes of Chronic Diarrhea

- **Infectious diseases.** There are a few infectious diseases that can cause chronic diarrhea. Although most bacteria causing diarrhea are cleared spontaneously within 4 weeks, some organisms, such as *Aeromonas* and *Pleisiomonas*, and *Giardia lamblia*, may cause chronic diarrhea. Patients with AIDS often have chronic infections of their intestines that cause diarrhea.
- **Postinfectious.** Following acute viral, bacterial, or parasitic infections, some children develop chronic diarrhea. The cause of this type of diarrhea is not clear, but some of the individuals have bacterial overgrowth of the small intestine. This condition also is referred to as postinfectious diarrhea.
- **Bacterial overgrowth of the small intestine.** Because of small intestinal problems, normal colonic bacteria may spread from the colon and into the small intestine. The diarrhea is presumably due to toxins, as well as fatty diarrhea, due to bile salt deconjugation.
- **Inflammatory bowel disease (IBD).** Crohn's disease and ulcerative colitis, diseases causing inflammation of the small intestine and/or colon, commonly cause chronic diarrhea. Stools are characterized by the presence of mucus and pus and are usually associated with ulceration of the mucosa.
- **Carbohydrate (sugar) malabsorption.** Carbohydrate or sugar malabsorption due to deficiency in diasaccharidase enzymes will result in malabsorption of sugar as with lactase deficiency in which milk products containing lactose, leading to diarrhea. The undigested lactose reaches the colon and pulls water (by osmosis) into the colon. This leads to diarrhea. Although lactose is the most common form of sugar malabsorption, other sugars in the diet also may cause diarrhea, including fructose and sorbitol.
- **Fat malabsorption.** Fat malabsorption may occur because of reduced pancreatic secretions that are necessary for normal digestion of fat (e.g., pancreatitis) or by diseases of the lining of the small intestine that prevent the absorption of digested fat (e.g., celiac disease). Passage through the small intestine and colon also may be more rapid when there is malabsorption of fat.
- **Irritable bowel syndrome.** The irritable bowel syndrome (IBS) is a functional cause of diarrhea or constipation. Inflammation does not typically exist in the affected bowel. It may be caused by several different underlying problems, but it is believed that the most common cause is rapid passage of the intestinal contents through the colon.
- **Endocrine diseases.** Several endocrine diseases (imbalances of hormones) may cause diarrhea, for example, (hyperthyroidism) and (Addison's disease).
- **Laxative abuse.** Can be an occasional cause of chronic diarrhea.

Clinical Presentation

History

- *Acute diarrhea* is a benign, self-limited condition, subsiding within a few days. The clinical presentation and course of illness depend on the etiology of the diarrhea; for example, rotavirus is more commonly associated with vomiting, dehydration, and diarrhea. Diet history should include the amount and type of fluids, solid foods, and formula ingested. The volume intake and hydration status determine the amount of fluids that is lost.
- The proper amount of fluid for most young children is around 100 ml/kg/day. Fluid intake that exceeds this amount may result in looser stools. Fat intake of less than 3 g/kg/day may contribute to toddler's diarrhea, especially in the setting of excessive free fluid and carbohydrate intake (e.g., as occurs with large amounts of fruit juice intake). Apple and pear juice contain a high fructose-to-glucose ratio, and consumption of these juices can result in fructose malabsorption and diarrhea.

Stool Characteristics

- Patients with toddler's diarrhea often have loose stools with undigested food particles.
- Frequent loose watery stools may indicate carbohydrate intolerance.
- Pasty or loose foul-smelling stools indicate fat malabsorption. This symptom is commonly seen in *Giardia* infections, enterokinase deficiency, hepatic and pancreatic dysfunctions, and protein sensitivity syndromes.
- Bloody stools are seen in patients with protein sensitivity but not in disaccharidase and pancreatic enzyme deficiencies or in patients with giardiasis.

Other Symptoms

- Systemic symptoms, including weakness, fatigue, and failure to thrive, are systemic consequences of chronically poor nutrient absorption. Malabsorption of carbohydrates, fats, or proteins can cause failure to thrive.
- Flatulence associated with foul-smelling stools that float suggests fat malabsorption, which can be observed with infection with *Giardia lamblia*.
- Stool characteristics such as consistency, color, volume, and frequency can be helpful in determining whether the source is from the small or large bowel.
- Food history can be helpful.
  - Ingestion of contaminated food is a common cause.
  - Organisms that cause food poisoning include the following:
    - Dairy food – *Salmonella* species
    - Eggs – *Salmonella* species
    - Meats – *C. perfringens* and *Aeromonas, Campylobacter*, and *Salmonella*
    - Ground beef – Enterohemorrhagic *E. coli*
    - Poultry – *Campylobacter* species
    - Vegetables – *Aeromonas* species and *C. perfringens*
- Water exposure can contribute to diarrhea.
  - Swimming pools have been associated with outbreaks of infection with *Shigella* species; *Aeromonas* organisms are associated with exposure to the marine environment.
- *Giardia, Cryptosporidium,* and *Entamoeba* organisms are resistant to water chlorination; therefore, exposure to contaminated water should raise index of suspicion for these parasites.
- A history of camping suggests exposure to water sources contaminated with *Giardia* organisms.

Physical Examination

- Dehydration
  - Dehydration is the principal cause of morbidity and mortality
  - Signs, symptoms, and severity
  - Lethargy, level of consciousness, sunken anterior fontanel, dry mucous membranes, sunken eyes, lack of tears, poor skin turgor, and delayed capillary refill are signs of dehydration
- Failure to thrive and malnutrition
  - Reduced muscle and fat mass or peripheral edema secondary to carbohydrate, fat, and/or protein malabsorption.

    Giardia organisms can cause intermittent diarrhea and fat malabsorption.
- Abdominal pain
  - Nonspecific abdominal pain and cramping are common with some organisms.
  - Pain usually does not increase with palpation.

Laboratory Studies

- In patients with diarrhea, a stool pH level of 5.5 or less or presence of reducing substances indicates carbohydrate malabsorption, which is usually secondary to viral illness and transient in nature.

- Enteroinvasive infections of the large bowel cause leukocytes. Absence of fecal leukocytes does not eliminate the possibility of enteroinvasive organisms. However, presence of fecal leukocytes eliminates consideration of enterotoxigenic *E. coli, Vibrio* species, and viruses.
- Exudates found in stool highly suggest colitis. Colitis can be infectious, allergic, or part of inflammatory bowel disease.
- Always culture stool for *Salmonella, Shigella,* and *Campylobacter* organisms and *Y. enterocolitica* in the presence of clinical signs of colitis or if fecal leucocytes are found.
- Look for *C. difficile* in persons with episodes of diarrhea characterized by colitis and/or blood in the stools. *C. difficile* may also occur without a history of antibiotic use.
- Bloody diarrhea with a history of ground beef ingestion must raise suspicion for enterohemorrhagic *E. coli.* If *E. coli* is found in the stool, determine if the type of *E. coli* is O157:H7.
- Rotavirus antigen can be identified by enzyme immunoassay and latex agglutination assay of the stool.
- Adenovirus antigens can be detected by enzyme immunoassay. Only serotypes 40 and 41 are able to induce diarrhea.
- Examination of stools for ova and parasites is best for finding parasites. Perform stool examination every 3 days or every other day.
- The leukocyte count is usually not elevated in viral-mediated and toxin-mediated diarrhea. Leukocytosis is often but not constantly observed with enteroinvasive bacteria. *Shigella* organisms cause a marked bandemia with a variable total white blood cell count.
- At times, a protein-losing enteropathy can be found in patients with extensive inflammation in the course of enteroinvasive intestinal infections (e.g., *Salmonella* species, enteroinvasive *E. coli*). In these circumstances, low serum albumin levels and high fecal alpha-1-antitrypsin levels can be found.

Procedures

Endoscopy for intestinal biopsies for others ill-defined causes as: celiac disease, enzyme assays, duodenal aspirates for Giardia, inflammatory bowel disease, congenital lymphangiectasia, and other rare conditions.

Management

- In many cases of diarrhea, replacing lost fluid and salts is the only treatment needed. It should be started as soon as possible mainly in infants before it progresses to dehydration that warrants hospitalization. This is usually by mouth – oral rehydration therapy – or, in severe cases, intravenously.
- Research does not support the limiting of milk to children as no effect on duration of diarrhea. Certain food and drinks are better to be avoided during the course of the illness that may increase the intestinal load and worsen the diarrhea. Examples of these foods are: whole grain breads and cereals, fresh or frozen fruits (except banana), dried fruits, fruit juices with pulp and prune juice, fatty foods, rich desserts, spicy foods and fried foods.
- However, certain foods are encouraged during the course of the disease to be consumed that will lower the frequency and volume of stool as: bananas, applesauce, boiled white rice, potatoes (without skin; mashed or baked), and plain pasta.
- The use of probiotics in treating diarrhea showed some effectiveness. The probiotic lactobacillus can help prevent antibiotic-associated diarrhea and in those who had lactose intolerance, taking digestive enzymes containing lactase when consuming dairy products has helped in alleviating sign and symptoms of lactose intolerance and diarrhea-related symptoms.

Medications

Medications may be beneficial; however, you need to be cautious when prescribed or it could be contraindicated in certain situations and would worsen the diarrhea or mask the underlying disease.

- Antibiotics: While antibiotics are beneficial in certain type of acute diarrhea, they are usually not used in most of them. There are concerns that antibiotic may increase the risk of hemolytic uremic syndrome in people infected with Escherichia coli O157:H7. However, some bacteria are developing antibiotic resistance, particularly *Shigella.*
- Antimotility agents: Antimotility agents like loperamide are effective at reducing the duration of diarrhea.

- Bismuth compounds: While bismuth compounds (Pepto-Bismol) decreased the number of bowel movements in those with travelers' diarrhea, it does not decrease the length of illness.
- Codeine phosphate: Codeine phosphate is used in the treatment of diarrhea to slow down the peristalsis and the passage of fecal material through the bowels, which gives a firmer stool, and also means that feces is passed less frequently.

Abdominal Pain

Abdominal pain is a common pediatric problem seen frequently in the outpatient clinics and emergency departments. It constitutes around 5% of the unscheduled visits and presents as an acute or chronic abdominal pain. It can be such a difficult problem to resolve especially in the young infant. Involvement of most, if not all systems of the body, may be associated with abdominal pain as part of its clinical presentation. The viscera are full of pain receptors. Two types and locations of pain receptors in the bowel have been identified. The first type is located in the serosa and the submucosa of the intestine and responsible for painful stimuli caused by distention, torsion, compression, and traction. The second type of receptors located on the surface of the mucosa induce pain through chemical stimuli of histamine, bradykinin, prostaglandins, and serotonin released in response to inflammation and ischemia. Pain arising from the bowel is usually felt in the midline because of the bilateral innervations, while pain arising from solid organs like liver, kidneys, ureter, ovaries, etc., usually lateralizes because they are unilaterally innervated. The central, peripheral, sympathetic, and parasympathetic innervations of the gastrointestinal tract make the intestine a very sensitive organ to many of the hormones released in the body that can easily be provoked by psychological stresses. Hence, it acts like a mirror to our psychological and emotional states. In this chapter, abdominal pain will be addressed as a problem rather than specific etiologies.

Epidemiology

Up to 17% of the schoolchildren complain of abdominal pain at some time of their life. The prevalence of acute abdominal pain in childhood is around 5.1%. Upper respiratory tract infections and gastroenteritis account for 35% and 11% of causes of acute abdominal pain, respectively. Approximately 1% of children with abdominal pain require surgical intervention. It is the acute pain that usually warrants quick comprehensive coverage of history, physical examination, and investigations to reach the diagnosis as soon as possible and to save the child from the risk of delayed diagnosis and improper management. The incidence of chronic abdominal pain is around 15%. Functional or nonorganic causes of chronic abdominal pain account for more than 90% of the chronic abdominal pain in the pediatric age group. Chronic abdominal pain is more common in girls than boys with two peaks: an early one from 4 to 6 years and a later one at early adolescence life.

Acute Abdominal Pain

Acute abdominal pain is a frequent, nonspecific, symptom for many of the childhood viral illnesses like upper respiratory tract infection, gastroenteritis, constipation, in addition to nonorganic conditions. Nonsurgical but serious diseases can present with abdominal pain and need immediate attention and intervention like diabetic ketoacidosis (DKA), peritonitis, bacterial gastroenteritis, pneumonia, and urinary tract infections (UTI). Life-threatening conditions like upper respiratory tract infection cause diffuse abdominal pain secondary to mesenteric lymphadenitis. Diffuse pain is also found in gastroenteritis. Pain at the epigastria is usually due to gastritis, peptic ulcer disease, and pancreatitis, while pain at the right upper abdomen is due to hepatitis and cholecystitis. Pain at the umbilicus that migrates to right lower quadrant is typical for appendicitis. Epigastric pain that refers to the back is characteristic of pancreatitis. Intermittent colic with intervals of well-being is characteristic of intussusceptions. Pain associated with peritonitis is aggravated by movement. History of trauma raises the possibility of solid organ injury, while past history of surgery is usually associated with adhesions and bowel obstruction. History should include bowel habit to rule out constipation. History of abdominal pain in adolescent girls should include regularity of the menstrual periods and sexual activity to include or exclude the possibility of pelvic inflammatory disease and ectopic pregnancy. Pain precipitated by hunger is associated with peptic ulcer which is not common in children. Family history of peptic ulcer is positive in about 70% of children with peptic ulcer disease. Associated symptoms with abdominal pain give additional clues toward the diagnosis. Fever is a sign of infections as with gastroenteritis, pharyngitis, urinary tract infections, peritonitis, and occasionally appendicitis. Pneumonia is also recognized cause of abdominal pain

usually associated with cough and fever. Vomiting is a nonspecific but frequent association of acute abdomen. Abdominal pain and vomiting are common initial presentation of gastroenteritis; on the other hand, they can also be signs of intestinal obstruction secondary to volvulus, adhesions, malrotation, and intussusception. Bilious vomiting indicates obstruction below the ampulla of Vater and should be taken seriously. Nausea and vomiting are among the common symptoms of appendicitis. Vomiting and abdominal pain is a common presentation of DKA. Diarrhea is a manifestation of gastroenteritis but also an uncommon manifestation of UTI, pneumonia, and appendicitis. Bloody diarrhea and abdominal pain should raise the suspicions of hemorrhagic colitis, hemolytic uremic syndrome, intussusception, and inflammatory bowel disease. Hemolytic anemia and recurrent bouts of hemolysis induce gall stone formation leading to abdominal pain secondary to cholecystitis, common bile duct obstruction, or pancreatitis. In the neonates, feeding history, amount, and frequency can be diagnostic of GER, colic, and/or cow's milk allergy. Constipation in neonates can be a manifestation of Hirschsprung's disease which per se can cause abdominal pain or secondary to its serious complication of enterocolitis.

The physical examination of a child with abdominal pain should be thorough and may have to be repeated more than once. An ill-looking child with abdominal pain should be carefully evaluated for peritonitis or perforated appendix. Poor perfusion and signs of hypovolemia result from trauma (solid organ injury) and sepsis secondary to perforated appendix or peritonitis. A common presentation of diabetic ketoacidosis is deep breathing (Kussmaul breathing), abdominal pain, and decreased level of consciousness. Congested and inflamed large tonsils covered with exudates support the diagnosis of streptococcal infection. Chest crepitations and decreased air entry to parts of the lung points toward pneumonia. A soft abdomen in a comfortable well-looking child is unlikely to be seen in serious illnesses or acute abdomen. Abdominal distention is commonly due to gas, stool, organomegaly, bowel obstruction, or the presence of a mass. The child can be asked to use his or her finger to point to the site of the pain. Children with acute abdomen usually have tenderness and sometimes guarding. Consistent tenderness at the same site and abdominal guarding are signs of intra-abdominal inflammation or inflamed peritoneum. Organomegaly in a child with abdominal trauma can be due to hemorrhage in the solid organ that warrants prompt action toward stabilizing the patient with possible surgical intervention. Tenderness on percussion indicates inflamed peritoneum as seen in acute appendicitis. Bowel sounds are exaggerated in gastroenteritis as well as in intestinal obstruction. In male patients, examination of the scrotum is essential. A swollen tender scrotum is a sign of testicular torsion. Rectal examination is uncomfortable for young children. Recent studies showed that rectal exam is of little help even in case of appendicitis. Although historically seen as an important item in assessing abdominal pain, if it is to be done, it should be done by pediatric gastroenterologists or pediatric surgeons. Abdominal pain and typical purpuric rash over the lower limp extensor surfaces is likely caused by intestinal submucosal hemorrhage associated with Henoch–Schonlein purpura. Important causes of acute abdominal pain in childhood are summarized in *Table 175.1*.

Investigation

The investigations required in most cases after completing history and thorough examination are usually limited. According to the specific suspected entity/entities, laboratory tests should be directed. The habit of ordering a set battery of investigations for every patient with acute abdominal pain is a malpractice and should be avoided. High WBC is an acute phase reactant of infections particularly bacterial. High WBC among other criteria is a supportive evidence of appendicitis although normal

Table 175.1
Causes of acute abdominal pain in childhood

– Infantile colic	– Mesenteric lymphadenitis
– Volvulus	– Henoch–Scholein purpura
– Appendicitis	– Pyelonephritis
– Gastroenteritis	– Diabetic ketoacidosis
– Constipation	– Inflammatory bowel disease
– Urinary tract infection	– Peptic ulcer disease
– Dietary protein allergy	– Cholecystitis
– Viral illness	– Urolithiasis
– Foreign body ingestion	– Adhesions
– Trauma	– Incarcerated hernia
– Renal colic	– Tumors
– Pneumonia	– Hemolytic uremic syndrome
– Pancreatitis	– Meckel's diverticulum
– Poisons	– Hepatitis
– Porphyria	– Child abuse
– Sickle cell crisis	– Intussusception
– Testicular torsion	

WBC does not rule out appendicitis. Blood chemistry, random blood sugar, and blood gases are important when DKA is suspected. Urine dipstick can be an indicator for the presence of WBC, nitrate, ketones, and sugar and is valuable in the diagnosis of dehydration, UTI, and DKA. Serum amylase and lipase are usually elevated in case of pancreatitis. Throat swab and culture should be ordered when streptococcal infection is suspected. Barium contrast studies may be also helpful in identifying the cause of abdominal pain, especially when it is vague and nonspecific (*Fig. 175.1*). Abdominal ultrasonography may confirm the presence of gallstones in the gall bladder (*Fig. 175.2*) or the biliary ducts. Cholestatic liver disease is associated with bile plug and bile sludge formation in the biliary duct with increased incidence of stone formation. Hepatic ultrasonography may also identify other causes of chronic vague abdominal pain as in hydatid disease (*Fig. 175.3*) The treatment of abdominal pain due to hepatobiliary disorders depends mainly on treatment of the underlying cause.

Abdominal ultrasound is very useful to assess organomegaly, stones, cyst, and abscess formation. Moreover, it can be diagnostic for intussusceptions and occasionally appendicitis. Plain abdominal X-ray is helpful in the diagnosis of intestinal obstruction and perforation by showing air-fluid levels or free air in the peritoneum. Upper GI contrast X-ray series can be used to diagnose obstruction in case of volvulus, and barium enema as a diagnostic and sometimes therapeutic in suspected intussusceptions. Contrast computed tomography has been utilized in the diagnosis of appendicitis with high sensitivity and specificity as well as in the confirmation of pancreatitis. In some instances, magnetic resonance cholangio pancreatography (MRCP) examination may be required.

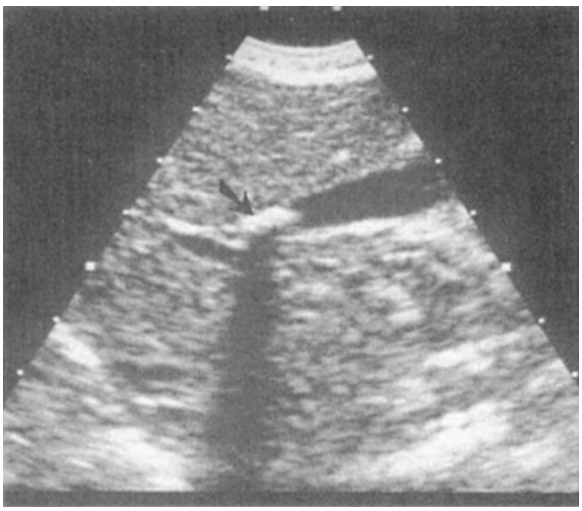

Figure 175.2
Cholelithiasis: abdominal sonography in an 11-month-old male infant with abdominal pain, renal tubular acidosis, and gallbladder stone (*arrow*)

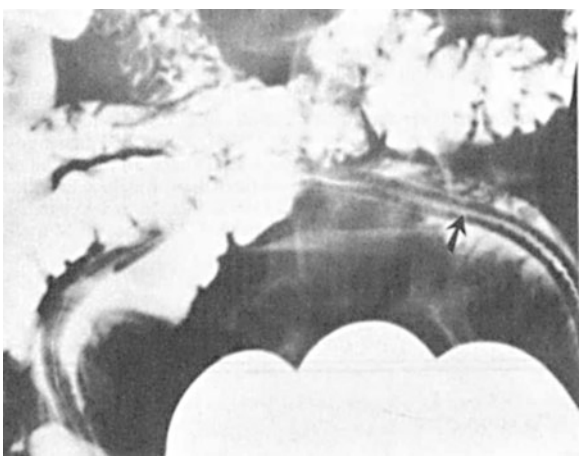

Figure 175.1
Barium contrast study in 10-year-old boy with vague abdominal pain. The follow-up study has revealed an elongated defect of *Ascaris* worm (*arrow*) in the contrast

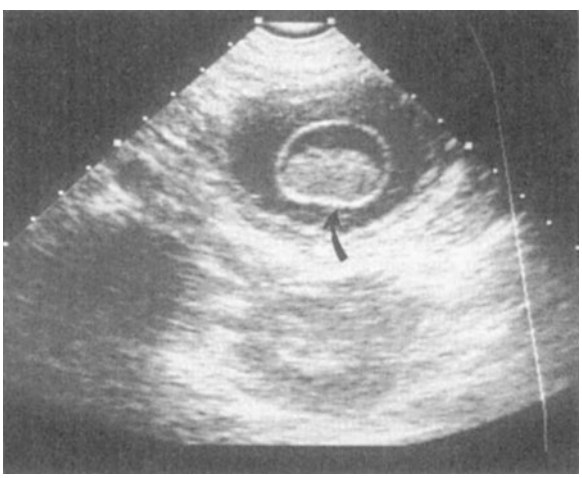

Figure 175.3
Hydatid cyst: abdominal sonography in a 12-year-old girl with vague abdominal pain. Note the round mass (hydatid cyst) in the left lobe of the liver *(arrow)*

Management

Once the diagnosis is reached, proper treatment can be instituted. Appropriate resuscitation measures while maintaining homeostasis should be applied to any patient who is morbid, ill looking with signs of hypovolemia and pending shock. While obtaining history, a good intravenous line should be established and, if needed, blood for cross-match and transfusion should be sent to the laboratory. Child trauma management is a team task of nurses, pediatricians, and surgeons. Traditionally, analgesia is contraindicated for patients with acute abdomen, but this concept seems to be changing. A double-blind study concluded that intravenous morphine provides significant pain reduction to children with acute abdominal pain without adversely affecting the examination. Moreover, morphine does not affect significantly the ability to identify children with surgical conditions.

Chronic "Recurrent" Abdominal Pain (RAP)

Chronic abdominal pain and recurrent abdominal pain (RAP) are two terms used interchangeably. Recurrent abdominal pain is defined as at least three episodes of abdominal pain, over a period of 3 months, severe enough to interfere with activity. Pain lasting more than 1 month is considered chronic. Recurrent abdominal pain is one of the most frequent complaints in the childhood and the most common episodic pain in pediatric age group. The incidence of childhood RAP has been found to be up to 15% and the prevalence between 4% and 12% in children aged 2–6 years. Girls are affected more than boys. The peak incidence of RAP is 5–6 years for boys and girls, and second peak for girls is, in early adolescence, 9–10 years of age. There are two categories of RAP: organic and functional (nonorganic) causes (Table 175.2). The list is incomplete but is intended to give some guidance on the spectrum of causes of RAP in childhood. The clinical details of these conditions are discussed in their relevant chapters. However, the nonorganic RAP is the most common as it accounts for more than 90% of the cases.

Functional (Nonorganic) Abdominal Pain

Functional disorders are those without any evidence of organ pathology. Children with nonorganic RAP have lower pain threshold than their peers particularly gastrointestinal pain. The child stresses and worries start to be projected and expressed through the digestive system in the form of abdominal pain. Hence, psychosocial evaluation and verifying family dynamics are essential for the diagnosis, treatment, and counseling.

Table 175.2
Alarming symptoms and signs in chronic "recurrent" abdominal pain

Symptoms	Signs
– Young age < 5 years	– Flank tenderness
– Constant site of pain	– Organomegaly
– Pain awaking child while asleep	– Abdominal mass
– Vomiting and/or diarrhea	– Anal fissures and ulceration
– Blood in stool or urine	– Anal skin tags
– Fever	– Oral ulcers
– Weight loss	– Joint swelling and redness
– Failure to thrive	– Anemia
– Delayed puberty	– High ESR
– Dysphagia	– Abnormal liver function test
– Respiratory symptoms	– High urine WBC or bacteria
– Arthralgia	
– Hematuria, dysuria	

Clinical Evaluation

Until recently, nonorganic RAP was collectively called functional abdominal pain. Rome group came up with Rome I and II criteria that shaped the diagnosis, but it was adult oriented. Rome III criteria described four different presentations of childhood functional RAP which started to be adopted by pediatricians and pediatric gastroenterologists. The four recognizable types of functional RAP are:

1. Functional dyspepsia: The pain is felt mostly in the upper abdomen. The pain is peptic ulcer–like in its location and is associated with symptoms of recurring nausea and vomiting. Additional symptoms are dysmotility or delayed gastric emptying causing bloating and upper abdomen fullness.
2. Irritable bowel syndrome (IBS): The pain is in the lower abdomen or takes the course of the colon. Some of the patients have rectal pain or spasms. Like adult IBS, the child often has alternating bowel habit of diarrhea and constipation.

3. Abdominal migraine: This is a rare type of RAP. It is characterized by episodic bouts of severe non-colicky abdominal pain that lasts for hours and is associated with pallor, nausea, and vomiting. Family history of migraine is commonly positive.
4. Functional abdominal pain: When the pain does not fit the above categories and no organic cause is found, the diagnosis of functional abdominal pain comes to play.

Although there are four different types of nonorganic chronic recurrent abdominal pain, yet all are precipitated by either anxiety or depression. The anxiety and depression are secondary to psychosocial or family dynamic disturbances.

Four circles need to be explored for children when functional RAP is suspected (Fig. 175.4). These are the family and the child personality, the schooling, peers, and physical or sexual abuse.

The fist circle is the child personality and family dynamics. A chaotic family, parental dispute and fights, abusive parents, and a passive dependent personality all can lead to stressful environment for the child and eventually appear in the form of abdominal pain. Similarly, hospitalization, loss of a family member, or even moving to another neighborhood can be stressful for the child.

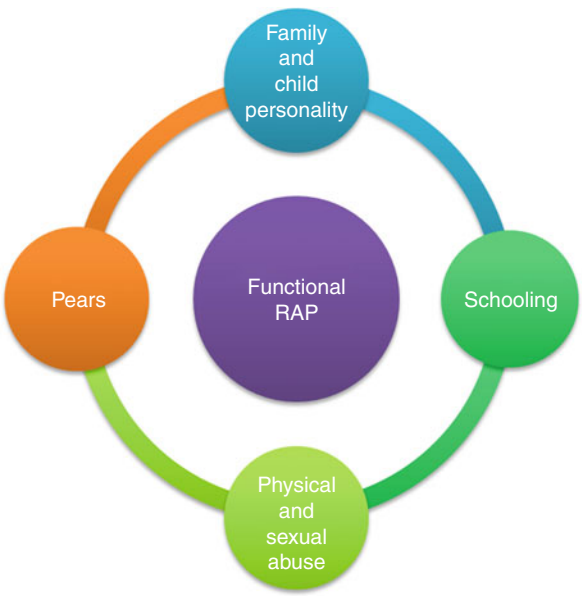

Figure 175.4
Functional RAP in childhood: recognized four interrelated circles

The second circle is schooling and, in particular, school performance. Poor school performance can lead to depression; on the other hand, the perfectionist, competitive, and excellent students are prone to develop anxiety. Both depression and anxiety can lead to RAP.

The third circle is the peers, and bullying has been reported to be a major cause of RAP.

The fourth and last circle is the area of child abuse, in particular, sexual abuse which is an area of marked stress, anxiety, and/or depression. The treating physician needs to explore all the four circles carefully and tactfully. The child and the parents need to be interviewed together and sometimes separately as some important information may not be obtained in the presence of the parents.

History and interviews may be done over two or three sessions. Repeated visits promote the child–physician trust and help the child to volunteer difficult and sensitive information. In most of patients, functional RAP is associated with other symptoms like headache, bone or muscle pain, commonly leg pain, and varied spectrum of psychosomatic manifestations.

The physical examination of a child with functional RAP should be thorough to assure no organic pathology is present. The child growth has to be plotted to make sure he or she is growing normal. Similarly, sexual growth and the Tanner stage are to be determined. Typically, abdominal examination frequently shows inconsistent and changing pain location. Tenderness may be found but may disappear when the child is distracted. The pain is usually localized at or around the umbilicus and is not related to meals. The abdomen is otherwise soft, with no guarding or organomegaly. The rest of the body exam is usually unremarkable.

Organic Chronic Abdominal Pain

The organic causes of chronic recurrent abdominal pain constitute less than 10%. Certain signs and symptoms (red flags) associated with chronic abdominal pain should be alarming for possible organic etiology (Table 175.3). In such situations, the child deserves attention and proper investigations. Pain that awakens the child from sleep is unlikely to be functional and could be secondary to inflammatory bowel disease (IBD) or peptic ulcer disease. Family history of IBD and peptic ulcer disease raises such possibility even further. History of recurrent mouth ulcers, weight loss, joints pain, and hematochezia are manifestations of Crohn's disease. Respiratory symptoms, dysphasia, and chronic abdominal pain are found in gastroesophageal reflux or chest infection. Dysuria is

Table 175.3
Organic causes of chronic "recurrent" abdominal pain

– Constipation	– Heavy metal poisoning (Lead. . .)
– Urinary tract infection	– Familial mediterranian fever (FMF)
– Hiatal hernia	– Pelvic inflammatory disease
– Lactose intolerance	– Tumors (ovarian, etc.)
– Gastritis	– Tuberculosis
– Parasitic infestations	– Dysmenorrhea
– Intestinal malrotation	– Nephrolithiasis
– Subacute intestinal obstruction	– Porphyria
– Hernia	– Hydronephrosis
– Cholecystitis and cholelithiasis	– Cystic fibrosis
– Cholydocal cyst	– Pancreatitis
– Celiac disease	– Peptic ulcer disease
– Eosinophilic gastroenteritis	– Meckel's diverticulum
– Inflammatory bowel disease	

a sign of urinary tract infection. Vomiting after meals and family history of pancreatitis are a call to pursue the diagnosis of pancreatitis, particularly hereditary pancreatitis, while vomiting blood could be due to peptic ulcer or esophagitis. Bilious vomiting is a sign of bowel obstruction below the ampulla of Vater and can be intermittent as in intestinal malrotation, superior mesenteric artery syndrome (SMS), and intussusception. Fever is always a sign of organic disorders either an infection or chronic diseases like juvenile rheumatic arthritis. Chronic diarrhea and weight loss might be secondary to celiac disease or cystic fibrosis. Tenderness that is severe and persistent in the same location should be considered organic until proven otherwise as well as organomegaly and masses. Familial Mediterranean fever (FMF) is a rare autosomal recessive disease that presents with recurrent episodes of severe abdominal pain.

Investigations

In the era of evidence-based medical practice, ordering full investigation to rule out everything is not acceptable and is a waste of resources. Thorough history, clear psychosocial stressful event, normal growth, physical examination, and no alarming signs or symptoms should be sufficient to diagnose functional abdominal pain; hence, no additional investigations are needed. Occasionally, anxious parents are not convinced of the diagnosis of functional disorders. In such situation, basic laboratory workup of CBC, ESR stool, and urinalysis can be assuring and convincing.

When alarming sign or symptoms are found in history or physical examination, proper investigations should be done. Full chemistry, liver function test, lipase and amylase can be done in case of possible hepatobiliary and pancreatic disorders, and urinalysis and culture when UTI is suspected. A urea breath test or stool antigen is done to rule in or out *Helicobacter pylori* infection for patients with peptic disease. Although *Helicobacter pylori*, per se, as a cause for functional RAP have been postulated by some studies; yet, the general consensus is that there is no relation between *H. pylori* infection and functional abdominal pain. Abdominal ultrasound can help to show abnormal pancreas, cysts, gall bladder, and urinary tract stones. Endoscopy is the proper tool for investigating peptic diseases, IBD, and obtaining biopsy for celiac disease.

Management

Once a specific diagnosis is reached, appropriate treatment should be instituted accordingly. Nonorganic, functional RAP in childhood is a cry for help, and the child is usually under psychological pressure. It is important to make sure that the parents are aware of the fact that the pain is real and the child is not malingering. The pediatrician should explore the four circles, explained earlier, and look for the triggering situation. The child should be referred to the psychologist for counseling to resolve the problem and /or provide the child with strategies to cope with his or her stresses. A one-to-one, family, or group therapy may be needed and beneficial. Additionally, relaxation techniques can help the child to release the pressure. Psychologist, social services, and child abuse team need to be involved in case of child abuse. If schooling is the problem, the pediatrician, as the child advocate, may communicate with the school principal or the child teacher and explain the child's problem as well as suggesting solutions. Alternative therapy and dietary manipulation has been suggested and used with some help. Peppermint oil, high-fiber, low-lactose, and low-oxalate diet has been used in children with abdominal migraine, and some cases provided relief. The most important factor that helps the treatment of functional RAP is the insight of the child and the parent of the problem and its causes. The family should be patient as it takes time for the therapy to give effect, and their cooperation is essential.

Constipation

Definition

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) defined constipation as delay or difficulty in defecation for 2 or more weeks. Constipation is also defined as a stool frequency of less than three times per week, hard painful defecation, or palpable abdominal or rectal mass on examination. Constipation definitions can be summarized as the change from the normal habit of stool frequency and/or consistency.

Etiology

According to the etiology, constipation can be classified into two categories: functional and organic. The functional type is also called idiopathic as there is no identified pathology and/or organic etiology. In the organic type, constipation is part of the symptoms of an underlying pathology or diseases like Hirshsprun's disease, hypothyroidism, etc.

Epidemiology

Constipation is a common problem in childhood with prevalence that ranges from 0.3% to 30%. It constitutes up to 3% of the general pediatrics visits and 25% of the pediatric gastroenterology consultations. Constipation is four times higher in monozygotic twins than in the dizygotic ones and 6–12 times higher when parents have constipation. There is no gender difference in the prevalence of constipation. Constipated children have higher rate of functional urinary incontinence than nonconstipated. The most common cause of constipation is the functional, while organic causes constitute a small percentage of the causes. The incidence of encopresis and fecal soiling (involuntary passage of stool) in children less than 7 years of age is 1–3%.

Pathogenesis

The child who is engaged in playing or activities of interest will not respond to the urge of defecation. He or she will resist the urge until it resolves. As the child keeps resisting defecation, stool accumulates, the rectum will dilate, and eventually the child will lose the feeling of the stool in the rectum. The rectum is efficient in absorbing the stool fluids turning the stool into a hard bulk that is difficult to pass. Passing hard stool causes anal fissures resulting in considerable pain on defecation. Children respond to fissures pain by stopping defecation to avoid the unpleasant feeling, hence worsening constipation. Similarly, the stubborn and defiant toddlers react to parental pressure and forceful toilet training by avoiding bowel movements with consequent accumulation of hard stool in the rectum and finally constipation. Rectal dilatation and spontaneous relaxation of anal sphincter will allow the soft stool to seep around the hard stool causing fecal soiling, i.e., encopresis. Encopresis is a term used for involuntary passage of stool "fecal soiling" in children who have usually already been toilet trained. Other situations and events that can cause stool withholding and functional constipation are: unavailability of toilets, dirty school toilets, change of environment, intercurrent illness, psychosocial stresses due to parental fights or loss of one of the parents, schooling or peer problems, and finally, physical or sexual abuse.

In case of secondary or organic causes, constipation will be part of the symptoms of the causative disease

Clinical Manifestations

Constipation in newborns and infants should be alarming to rule out pathologies like anal atresia and Hirschsprung's disease. Constipation is more common in babies who are formula fed and frequently starts toward the end of the first month of life. Cow's milk allergy (CMA) has been found to cause constipation, and infants may improve when taken off cow's milk. Positive allergy and immunological studies were found in constipated children secondary to CMA. Although newborns have frequent bowel movement, constipation in exclusively breast-fed babies is normal, harmless and affected babies show no discomfort, feeding well and thriving. It is normal for exclusively breast-fed babies to go for several days to a week without a bowel movement. Older children with constipation may complain of abdominal pain, decreased appetite, and urinary frequency secondary to pressure by the full rectum on the bladder. Painful defecation and anal itching are signs of anal fissure. The time when the child tries to avoid defecation in an attempt to withhold stool, he or she will stand on toes, cross legs, contract the anus and the gluteal muscles, and start rocking back and forth until defecation urge resolves. This action is usually performed while hiding behind furniture or in a corner. The position and facial features adopted by the child can be mistaken for seizure disorder. Chronic dilatation of the rectum with large and hard stool

makes the anus dilated with decreased sensation. The soft and liquid stool can pass around the hard stool down the underwear causing fecal soiling (encopresis). Delayed walking may be a sign of spinal cord abnormalities like tethered cord that can present with constipation. Constipation rarely can be secondary to diabetes insipidus (DI) where the rectum absorbs the stool fluids, resulting in constipation. History should include inquiry about polydipsia, polyurea, and signs of hypothyroidism.

Physical examination of children with functional constipation is generally unremarkable. Stool mass occasionally can be felt on abdominal examination. Anus should be examined, under good and bright light, for fissures, signs of abuse, and anal position. Ectopic anus is usually displaced interiorly and associated with constipation. Rectal examination is important to assess the tone of anal sphincter and stool in the rectum. In some children, the anus is dilated and stool can be visualized without the need for rectal examination. In Hirschsprung's disease, the anal sphincter is very tight and the rectum is empty contrary to functional constipation. The back of the child should be inspected for the presence of hair tuft and/or lumbosacral deformity which can be associated with tethered cord. For the children with chronic and refractory constipation, neurological assessment of the lower limbs reflexes and anal wink needs to be part of the physical examination. Short stature and course facial features can be signs of hypothyroidism with resulting constipation.

Diagnosis

Functional constipation in a healthy child with normal growth and physical exam requires no investigations. Plane abdominal radiography can be done when it is difficult to assess fecal content of the colon or in case of child's refusal of rectal exam. Investigations are reserved to rule in or out suspected diseases or pathologies causing the constipation. When Hirschsprung's disease is suspected, rectal manometry, rectal biopsy, and rarely barium enema are required for confirmation. Blood work is reserved to investigate hypothyroidism, hypercalcemia, diabetes insipidus, and cow's milk allergy. MRI is a valuable tool to investigate spinal cord dysraphism like spina bifida, lipoma, and tethered cord.

Treatment

Specific organic causes of constipation require specific management according to the etiology. For functional constipation, the following are the steps of management.

Education

The first step in the treatment of constipation is good explanation and education of the parents and older patients. Education gives good insight and magnitude of the problem and helps in achieving therapeutic goals. The use of drawings and illustrations gives visual clarification and supports in understanding the problem and the rationale behind long-term treatment. The purpose of long-term treatment of chronic constipation is to get the dilated colon and rectum return to the normal caliber. The steps of the treatment should be written on a paper and handed to the patient and family.

Disimpaction

Newborns and infants do not need disimpaction, and at most need stool softeners such as lactulose. In older children for maintenance therapy to work it is important to clear the hard stool occupying the colon and rectum. Disimpaction can be done rectally or orally. Rectal disimpaction is done by one or two phosphate enema which is widely used and is effective. Repeated phosphate enemas carry the risk of electrolyte disturbance particularly infants and young children. Glycerin suppository can be used, and it is a safe one. Agents used for oral disimpaction are: (1) Mineral oil (liquid paraffin oil) at 15–30 ml/year up to 240 ml daily until disimpaction is achieved but should not be used for young children because of risk of aspiration and lipoid pneumonia. (2) Polyethylene glycol (PEG) at dose of 1.5 g/k/day for 3 days. (3) Senna and bisacodyl in appropriate dosage also can be used.

Maintenance Therapy

The goal of the maintenance therapy is to have at least one to two bowel movements a day. In chronic constipation, treatment should continue for at least 3–6 months to allow the colon to return to normal caliber and withdrawal of medication should be slow. The once-a-day-treatment regime should be the target to ensure compliance. Treatment may be frequent initially to ensure good effect but eventually to come to once a day. Choices of maintenance therapy are: (1) Lactulose 1–3 ml/kg/day initially twice daily then once a day. The dose can be increased or decreased according to the response with the aim of soft bowel movement daily. (2) PEG 1 gm/kg/day dissolved in water or juice. The pediatric PEG 3350 contains minimal electrolytes to

avoid sodium overload, and it is more palatable for kids. (3) Mineral oil (liquid paraffin oil) at a dose of 1–3 ml/kg/day, best to be given 2–3 h after meals to avoid malabsorption of fat-soluble vitamins. Mineral oil still holds as one of the good and effective stool softeners but should not be used in infants. Other maintenance medications less used are Magnesium hydroxide/citrate and sorbitol.

The maintenance therapy can be given at bedtime, while, during daytime, high-fiber diet, natural stool laxatives like prune juice, and hydration should be encouraged.

Treatment of anal fissure helps resolve the pain and allows easier defecation and toilet training. Anal fissure can be treated by sitz baths and frequent application of petroleum gel or 0.2% nitroglycerin cream.

Behavioral Modification

Toilet training is an important part of treatment. The child should have regular toilet time. He or she should take enough time especially after meals. The use of rewards and calendar with stickers will enforce good and regular toilet habit. Psychologist's help may be needed to prepare the child for the behavioral modification. Sitting on the toilet regularly and having a bowel movement twice or at least once daily is the target of the management.

Failure of therapy and/or the possibility of organic causes should be an indication for referral to pediatric gastroenterologist for further workup and management.

Prognosis

Response to therapy is good initially; however, there is high rate of relapse particularly in chronic constipation. Long-term maintenance therapy is important for good outcome. Maintenance therapy may need to continue for 6 months to 1 year coupled with slow withdrawals of stool softeners. Failure of treatment despite good stool softener dosage and therapy adherence is an indication for possible nonfunctional (organic) cause for which the child should be well investigated. It has been found that one-fourth of children with functional constipation continued to experience symptoms at adult age particularly when constipation starts at older age and there is a delay in seeking medical treatment. Studies have found a statistical link between constipation and colon cancer among middle-aged adults.

Prevention

Early treatment of anal fissures and constipation prevents progression to chronic constipation and fecal soiling. Healthy dietary habits and natural dietary fibers are important for good bowel function and prevention of constipation. Hydration and exercise are supportive factors in preventing constipation.

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176 Cyclical Vomiting Syndrome

Sonny K. F. Chong · Dinesh Banur

Historical Perspective

Samuel Jones Gee (1839–1911) a physician at St Bartholomew's Hospital, London first described in 1882 a group of children with a poorly understood condition, in the hospital reports:

- These cases seem to be all of the same kind, their characteristics being fits of vomiting which occur after intervals of uncertain length. . ..free from signs of disease. The vomiting continues for a few hours or a few days. . .. Patients are left exhausted

The periodic disorders in children were first published in the British Journal of Children's diseases in 1933 by Willye WB and Schlesinger D. They described 80 cases, in a detailed study of children with nervous instability and a relationship between migranous attacks and epilepsy. JJ Kempton further described the *Periodic Syndrome* in 1956 in the British Medical Journal. Five main symptoms were discussed – *pallor, headache, abdominal pain, vomiting, and pyrexia.*

Any combination of these, in any order, make up this periodic illness, with intervals of certain regularity or sometimes with irregular intervals.

Definition

The most recent revised diagnostic criteria of CVS (cyclic vomiting syndrome) in both children and adults is best described by Rome III criteria (2006)

- Stereotypical episodes of vomiting regarding onset (acute) and duration (<1 week)
- Three or more discrete episodes in the prior year
- Absence of nausea and vomiting in between episodes
- No metabolic, gastrointestinal, or CNS structural disorders
- Supportive criteria: Past or family history of migraine

Clinical Features

CVS was initially thought to be rare, but now it is seen relatively common in pediatric populations. Abu Arafeh and Russell's study (1995) of schoolchildren in Scotland found that 1.9% fulfilled the diagnostic criteria for CVS. Chong and Bartlett carried out a CVS Audit in the UK (2003) and found a higher proportion of female to male (ratio 2:1), with a mean age of onset of 6.5 years and age at diagnosis of 9 years, although other studies have reported much younger or older ages of onset.

Although there are a large number of differential diagnoses, CVS is characterized by stereotypic, self-limiting episodes of intractable nausea and vomiting which is seen in childhood and less frequently in adults. The child is free from symptoms between episodes which can last from weeks to months. There may be associated symptoms of lethargy, pallor, pyrexia, headache, abdominal pain, and excess salivation. Physical examination is usually normal.

Typical attack of CVS progress through four phases:

Phase 1 – No symptoms. Trigger factors have been reported in 73% of the children during this period. Infection 41%, stress 34%, diet 26%, motion 9%, menses 13%.

Phase 2 – Prodrome characterized by nausea (93%), disturbed gastric antral myoelectric activity, and associated autonomic components (salivation, tachycardia, vasoconstriction).

Phase 3 – Episodes are frequently characterized by retching, vomiting (94%) usually in the morning; nausea, tiredness (91%) (at times so severe that it can result in a "conscious coma"); vomiting bile (88.7%), abdominal pain (67%), fever (37%), headache (36%), prostration, encephalopathy, posturing dystonia, hypertension, retention of urine.

Phase 4 – Recovery. Each episode lasts for few hours to few days.

The average number of episodes reported varies from 8 to 12 per year. Over 60% had onset of an episode in the early morning and over 10% in the evenings.

A very high percentage, over 65%, have a family history of migraine in first-degree relatives in the national UK audit of Bartlett and Chong, with a family history of CVS in 11% of children.

In summary, it is important to establish in the diagnosis that the episodes are discrete (93% have this), that the

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patient is well in between episodes (64%), the episodes are stereotypical (98%), and the family has a history of migraine (66%).

Pathophysiology

The etiology and pathogenesis of CVS remains elusive. Several hypotheses in vogue include a disorder of the brain-gut axis, migraine variant, corticotrophin-releasing factor in excess in response to stress which induces a hypercortisolemia resulting in inhibition of GTP cyclohydrolase and reduction in BH4 and Nitric oxide. This could result in hypertension in severe case as seen in Sato's syndrome. Autonomic dysfunction, gastric dysmotility, and a mitochodriopathy has also been hypothesized, with mitochondrial energy depletion due to a mitochondrial mutation has been suggested. Genetic association including A3243G mitochondrial DNA mutation have been seen in some cases with a resultant metabolic encephalopathy occurring as a result of hyperphenylalaninaemia, reduced dopamine, and serotonin turnover.

Recent advances in the understanding of the electric rhythms of the stomach, which control gastric motility and emptying, have been made with the mapping of the stomach. Preliminary studies have shown more detailed electrical differences between different regions of the stomach. This has lead to the use of gastric electrical stimulation devices in treating nausea and vomiting in adults and new targets for therapy.

Making the Diagnosis

Diagnosis requires taking an accurate clinical history, identifying key clinical features, and excluding other disorders. It is important to differentiate between chronic and cyclical vomiting. Chronic vomiting persists regularly with vomiting for a short time every day. Cyclical vomiting occurs on a regular pattern with intense vomiting for a few days and then a gap of several weeks.

Essential features are recurrent episodes of severe vomiting lasting hours to days, separated by symptom-free periods in the absence of any identified pathology. Supportive features include a clear pattern with regard to onset, frequency, intensity, and duration of self-limiting episodes.

A history of associated signs and symptoms such as fever, pallor, social withdrawal, abdominal pain, and migraine-like symptoms (headache, photophobia, phonophobia) may be seen and help to clinch the diagnosis. Nevertheless, it is important to exclude meningitis.

Triggering Factors

It is important to identify triggering factors. The most common are unpleasant emotional factors. Factors reported to trigger an episode included 41% infection, 34% psychological, 26% dietary, 18% exhaustion, 13% menses, 13% atopic, and 9% motion. Some reported foods that may trigger an episode include tomatoes, chocolate, cola, caffeine, artificial sweeteners, soy foodstuffs, dairy products, nuts, and eggs.

Investigations

- Urine MC&S
- FBC, liver function test, Ca, Lipase, amylase
- Urine for metabolic screen to exclude mitochondriopathy and fatty acid oxidation defects
- Radiological investigations include abdominal ultrasound, barium meal, and follow through to exclude life-threatening conditions such as small bowel obstruction and malrotation
- Sinus X-rays and renal ultrasound scan
- CT or MRI if raised intracranial pressure is suspected
- EEG to rule out abdominal epilepsy, which is rare
- Vestibular function test and autonomic nervous function testing (tilt testing and R-R interval on ECG)

Differential Diagnoses

- Malrotation with volvulus (or intermittent small bowel obstruction)
- Gastroesophageal reflux disease (chronic esophagitis)
- Renal disease
- Raised intracranial pressure (brain tumor)
- Chronic sinusitis
- Chronic pancreatitis (hereditary pancreatitis)
- Addison's disease
- Disorders of fatty acid oxidation
- Urea cycle defects
- Abdominal migraine/epilepsy

There are some *GI etiologies* that have a similar pattern to CVS and have to be checked for and ruled out, before the confirmed diagnosis of CVS. These are anatomic – malrotation, dysmotility of the GI tract – gastric dysrhythmia, mucosal injury, infections, or chronic appendicitis, gall bladder and pancreatic disease.

Non-GI etiologies that also mirror CVS are neurological conditions – migraine, epilepsy, neoplasm, metabolic,

endocrine, e.g., Addison's disease, renal conditions – acute hydronephrosis due to pelvi-ureteric junction stricture (Dietls crisis), kidney stones, and psychological – stress, parental anxiety, and Munchausen by proxy.

General therapy includes:

Supportive measures – IV fluids, analgesia, and sedation
Prophylactic treatment for patients with episodes more than once a month
Abortive treatment for patients with episodes of less than once a month
Identification and avoidance of triggers
Parental support – CVSA support group

Management involves identifying the stage of cyclical vomiting and initiating appropriate treatment. It is obviously best to abort the episode whenever possible or to start prophylactic treatment soon afterward. Some of the strategies used as abortive treatments for patients as an episode begins include antimigraine drugs – sumatriptan or ketorolac inhibitor, and antiemetic drugs – ondansetron, lorazepam, stemetil, and chlorpromazine.

1. To identify and treat any triggering factors
   - Antimigraine prophalaxis
   - Prophylaxis for motion sickness
   - Hormone preparation or low-dose fluoxetine for menses triggered CVS
   - Anticonvulsants

   Prophylactic therapy reduces the number and severity of attacks, and is most appropriate for patients who have frequent attacks of more than three to four episodes per year or of long duration. There is no definitive prophylaxis, but several classes of drug work with varying degrees of success.
2. Treatment of well-defined prodrome
   - Prochlorperazine (Buccastem) 3 mg sublingual 6–8 hourly before full-blown episode begins.
   - Intravenous 5–HT3 antagonist, Ondansetron 0.1–0.2 mg/kg/dose, 8 hourly, maximum 8 mg (rectal administration may be appropriate), or Granisetron 20 mcg/kg up to 1 mg can be used alone or in combination.
   - Lorazepam 0.05 mg/kg IV given with Ondansetron is both an anxiolytic and antemetic.
   - If the above fails, Ondansetron plus Aprepitant can be used. Low or a test dose of Aprepitant should be tried initially using 80 mg every other day as bradycardia and hyperglycemia are infrequent possible side effects.
   - If the above fails, rarely Dexamethasone could be given in addition to the above.

   If a patient can recognize symptoms of a forthcoming attack and can retain oral medication, an attack can be aborted. Some patients experience anticipatory nausea and vomiting as a prodromal anxiety or abdominal pain, which can be treated with an anxiolytic or pain relief.
3. Treatment of established emetic phase
   - Antiemesis with Ondansetron 0.1–0.2 mg/Kg/dose, maximum 8 mg, 8–12 hourly
   - Anxiolysis with Lorazepam (as above)
   - IV fluids and electrolyte balance
   - IM Chlorpromazine, 1 mg/kg, maximum dose of 40 mg for children <5 years and 75 mg for 6–12 years
   - Blood pressure control with IV labetolol or clonidine in CVS with hypertension (Sato's syndrome)

   Start antiemetics (e.g., IV Ondansetron, Granisetron) early and introduce benzodiazepines such as Lorazepam, which have antiemetic, anxiolytic, and sedating actions, as antiemetics alone may not relieve nausea and vomiting.

Prophylaxis or Long-Term Treatment

There are a wide range of treatments for CVS but no large-scale trials have been performed. Treatment remains empirical, and on a patient-by-patient basis. There is an increasingly extensive body of clinical experience in treating CVS leading to a developing consensus view of treatment protocols.

The use of antimigraine prophylaxis should be started as soon as the abortive treatment has controlled symptoms acutely. The following medications below are used in the following order in our unit at Queen Mary's Hospital for children, Carshalton, Surrey.

A metabolic cocktail of carnitine, and coenzyme Q, and Riboflavin are considered in younger children less than 4 years of age if the CVS is resistant to the above standard treatment.

Propranolol 1–3 mg/kg/day in three divided doses (not to be used in asthma patients)
Cryproheptadine 0.3 mg/kg/day in three divided doses
Amytriptyline 25–50 mg/day, starting with 10 mg daily and increase slowly (0.5–1 mg/kg/day)
Pizotifen 500 μg bd, increasing to 1.5 mg daily
Metabolic cocktail – carnitine 500 mg bd and Coenzyme Q10 30 mg daily. (In older children, dose can be increased carnitine 50–100 mg/kg/day in 2 divided doses Coenzyme Q10 10 mg/kg/day in 2 divided doses)

Complications

Prolonged vomiting can cause dehydration, electrolyte imbalance, ketosis, gastritis, esophagitis, dental disease, poor growth, and psychosocial problems. IV infusion of saline or glucose solution with additional potassium, combined with ranitidine, can help prevent most of these complications. However, caution is needed because the syndrome of inappropriate antidiuretic hormone (SIADH) has been noted in some patients, in whom fluids should be limited.

Continuing with intravenous or oral sedation until an episode has resolved may be necessary for 48–72 h or until the episodes of CVS has run its course.

Psychiatric assessment and counseling is important in the further management of the CVS child. Stress management is important for those with stress as a trigger. These episodes can be aborted or shortened with early management.

Complications such as dehydration, electrolyte disturbances, and peptic oesophagitis, can prolong recovery time, but this can be lessened or avoided if IV fluids and H2-receptor antagonists such as ranitidine are used early.

Occasionally, upper GI endoscopy may be necessary to exclude severe gastroesophageal reflux disease or peptic ulcer diathesis, *H pylori* gastritis, or eosinophilic esophagitis which has been shown to masquerade as CVS.

Prognosis

Prognosis is generally good to be guarded as the episodes improve or become less frequent, or cease as children grow older. In long-term studies, Hammond (1974) found an increased likelihood of migraine and psychological difficulties in those diagnosed with severe cyclical vomiting presenting in childhood [3]. In addition, in a study of adults diagnosed with CVS in childhood, Dignan et al. (2001) found 31% continued to experience attacks as teenagers. This suggests that CVS develops into migraine at a later stage in some patients. It should not be viewed simply as a pediatric illness that resolves with the onset of puberty.

Links to Other Conditions

The belief that CVS is psychosomatic is not widely accepted, but many accept it may be triggered by psychological stress. Although psychiatric or psychological disorders may need to be suspected or implicated in children with CVS, more frequently than not, the psychological stressors are secondary. Nevertheless, it is important to exclude an organic pathology first, before counseling is considered.

Current research focuses on the hypothesis that CVS is a disorder of the brain-gut axis that is triggered by physiological or behavioral reactions. An exaggeration of our normal emetic reflex might be one such dysfunction.

CVS, *migraine headache, and abdominal migraine* were described as "manifestations of the migraine diasthesis" as they are "functional, self-limited episodic disorders" that all have symptom-free intervals.

In all three disorders, patients might complain of nausea, vomiting, abdominal pain, headache, photophobia, and phonophobia. The similar features of CVS and migraine, coupled with the widely held belief that these conditions are associated, led to the proposal that antimigraine therapy should be used for managing CVS.

One study found that 91% and 83% of patients given prophylactic Amitriptyline or Cyproheptadine, respectively, had a partial or complete response to therapy. Sumatriptan was effective for aborting episodes. A trial of L-carnitine prophylaxis has recently been shown to reduce frequency of attacks.

Another study investigating gut electrical activity (cutaneous electrogastrogram) found half of CVS patients had accelerated gastric rhythms following food, and during episodes of CVS, but no significant abnormalities in controls. Some suggest abnormal gastric myoelectric activity or dysrhythmias might be responsible for feelings of nausea and vomiting. Vomiting is a nonspecific yet common clinical feature of many inherited metabolic disorders. It has been suggested that mutations or rearrangement in mitochondrial DNA are responsible for metabolic disorders, which can in turn lead to cyclical vomiting.

Conclusion

CVS is a disease of severe episodic vomiting, sudden in onset and associated with continuous nausea and lethargy. The symptoms often start in childhood and can continue on to early adulthood, but adult onset is also possible. CVS is often missed in the early stages of the disease. CVS is more commonly seen in girls than in boys in the UK. A family history of migraine is present in a significant number of first-degree relatives. Contrary to other studies, more than one-third of patients were not symptom free between episodes, suggesting a different etiology.

The condition is frequently missed or undiagnosed until late in the illness, but this is gradually changing as awareness increases.

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177 The Esophagus

Mark A. Gilger · Hisham M. Nazer

Achalasia

Achalasia is a motor disorder of the esophagus characterized by functional obstruction, aperistalsis, and incomplete relaxation of the lower esophageal sphincter in response to swallowing and increased lower esophageal sphincter (LES) pressure. The disease manifests itself usually in late childhood and early adult life. However, achalasia has been recognized in all ages including infancy.

Esophageal achalasia is a well-known pathology described in families with more than one affected siblings. The exact cause of achalasia remains unknown. Genetic factors were suggested to play a role in the pathogenesis, and some authors considered it an autosomal recessive character. Other report suggested that the defect could be neurogenic, myogenic, or hormonal in origin.

Clinical Features

Difficulty in swallowing, dysphagia, and regurgitation of retained food in the esophagus during or after meal are the main complaints. Achalasia is usually presented with dysphagia (usually to solids) and vomiting. Affected patients are therefore slow eaters and slow swallowers. Vomiting of food remnants with inability to eat and failure to thrive are other well-recognized findings. Aspiration pneumonia, regurgitation, respiratory difficulties, choking, and sudden death have also been reported in achalasia.

The onset is insidious with fluctuation of symptoms especially during the early stages of the disease. At a later age, the child may complain of a choking sensation of food sticking in the region of the lower sternum. The child will at a later stage get the habits of drinking water or adopting certain maneuvers to facilitate the passage of food bolus and ease his symptoms. Vomiting which may occur hours after meal is usually associated with the presence of undigested food eaten several hours ago. Aspiration pneumonia and repeated chest infections may complicate recurrent episodes of vomiting. Later recognized complications include malnutrition and failure to thrive.

Diagnosis

Clinical history contributes greatly to the suspicion of achalasia in an index case. Plain chest radiograph may show dilated food-filled esophagus with an air-fluid level. Radiologic signs of recurrent aspiration pneumonia further support the diagnosis, which is usually confirmed on barium swallow and fluoroscopy. The esophagus is dilated and sometimes tortuous, with absence of stripping waves, uncoordinated contraction, and obstruction at the gastroesophageal junction with prolonged retention of the barium in the esophagus (*Fig. 177.1*). The classic *rat-tail* deformity of funneling and narrowing of the distal esophagus is a result of failure of relaxation of the lower esophageal sphincter (LES). Manometric intraluminal pressure studies, when available, should be performed to confirm the diagnosis. Esophagoscopy is performed to exclude any other associated anomalies.

Differential Diagnosis

It is important to distinguish achalasia from other causes of esophageal dysphagia especially esophageal stenosis and partial thoracic stomach. Recurrent or chronic pulmonary infections may dominate the clinical picture to the extent that esophageal dysfunction may be overlooked. Achalasia should therefore be included in the differential diagnosis of a child with recurrent respiratory infections.

Treatment

There is no specific medication that ensures recovery. Pneumatic dilatation is performed to disrupt the muscle fibers of the LES. Pneumatic as well as hydrostatic dilatation have proved ineffective except in mild cases. Relief of symptoms is usually temporary.

Anticholinergic drugs have been found to be of no value though some studies have shown that nifedipine therapy does decrease the lower esophageal pressure and improve esophageal emptying. However, such studies in

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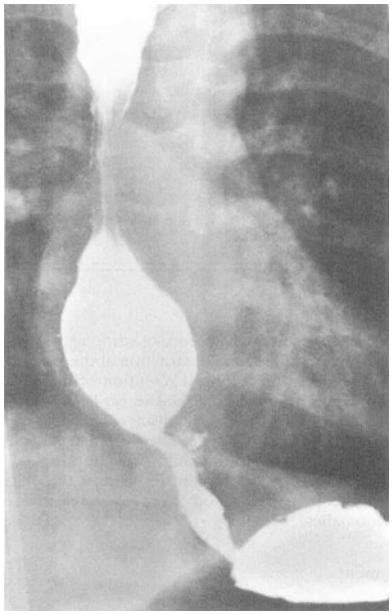

Figure 177.1
Achalasia of the esophagus. Esophagogram in a 3-year-old boy with a history of difficulty in swallowing. Notice the narrowing of the distal esophagus with prestenotic dilatation (Courtesy: Dr. Hisham Nazer)

children are rather limited and mostly resorted to in patients with whom pneumatic dilatation or myotomy is contraindicated to achieve some weight gain before more aggressive therapy is resorted to.

The results of pneumatic dilatation in children have been variable and are difficult to compare because of different techniques used. Recognized complications include bleeding and gastroesophageal reflux. If pneumatic dilatation fails to relieve symptoms, surgical approach in resorted to.

Surgery is resorted to rather early for those babies with severe achalasia, evidence of malnutrition, and lack of response to medications or dilatations. Modified Heller esophago-myotomy via a laparoscopic approach is the operation of choice. The results of myotomy have been quite satisfactory. Studies have concluded that the laparoscopic extended Heller myotomy with fundoplication is a safe and effective method for the treatment for achalasia in the pediatric population even in advanced cases.

Recognized complications of surgical procedures include gastroesophageal reflux, dysphagia, mediastinitis, and recurrence of symptoms. Diet has no role in the primary treatment of the disease. Elevation of the head of the bed helps prevent nocturnal regurgitation.

Esophageal Atresia

This congenital anomaly of the esophagus with or without a fistula to the trachea is discussed in a separate chapter on gastro-surgical emergencies of the newborn.

Esophagitis

Esophagitis is a common problem associated with gastroesophageal reflux disease (GERD). Esophagitis is attributed to abnormal acid secretion. However, recent reports have revealed that reflux esophagitis is not associated with increased acid secretion.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EE) is an inflammatory gastrointestinal disorder that is increasingly diagnosed in pediatric patients. It is a chronic and relapsing condition associated with atopy and infiltration of the esophageal mucosa by eosinophils typically in a density exceeding 15 per high power field, where gastroesophageal reflux disease has been ruled out by negative pH probe study or clinical failure of a proton pump inhibitor trial. Eosinophilic esophagitis (EE) is a disease based on a clinicopathologic diagnosis that involves a localized eosinophilic inflammation of the esophagus. The systematic exclusion of gastroesophageal reflux disease is critical.

Eosinophilic esophagitis (EE) is a condition of esophageal inflammation that occurs in the absence of acidification and is characterized by mucosal eosinophilia and epithelial proliferative changes. Depending on the patient's age, EE may present as a feeding disorder, vomiting, abdominal pain, dysphagia, or food impaction. EE progresses in some individuals to esophageal fibrosis and then presumably to irreversible esophageal dysfunction. The specific mechanism of fibrosis in EE remains unknown, but it may be related to multiple potentially fibrogenic products secreted by eosinophils.

EE in adults typically presents with dysphagia and esophageal food impaction in an episodic manner. The pediatric presentation however varies, and it can mimic other conditions such as gastroesophageal reflux disease. As patients get older, EE manifests as abdominal pain and subsequently may present with dysphagia and food impactions.

Presenting symptoms include vomiting, chest or epigastric pain, and dysphagia with occasional food impaction or strictures. Most patients are males with atopy

associated with food allergens, peripheral esoinophilia, and elevatged immunoglobulin IgE levels.

Endoscopically the esophagus presents a granular furrowed or ring appearance. Esophageal biopsies reveal eosinophilia on histopathology.

Treatment

Elimination diet is prescribed for patients with EE and proven allergens. Inhaled and systemic corticosteroids have also been used successfully for nonallergic or nonresponders to elimination diet. . . .

EE, like most allergic diseases, responds to glucocorticoids. Systemic steroids have proved an efficacious short-term option for the disease. Equally effective are glucocorticoids formulated for inhalation, and fluticasone propionate, which when swallowed from a metered-dose inhaler is as effective as prednisolone.

More recently therapy under investigation and assessment among affected children include leukotriene inhibitors (Montelukast) and anti-interleukin 5 (anti-IL-5) antibody (Mepolizumab). If left untreated, patients with EE may progress to develop stricture formation.

Montelukast has minimal risk of adverse reactions compared with steroid therapy and may offer clinical relief in a small subset of children with eosinophilic esophagitis.

Reslizumab is a humanized monoclonal antibody with potent IL-5 neutralizing effects that represents a potential treatment for eosinophilic diseases. Although the exact mechanism of EE is unknown, food allergens are thought to have an important role. Effective treatment options include dietary restrictions and various steroid formulations.

EE should be considered in the course of evaluating pediatric patients with chronic gastrointestinal symptoms particularly in young white male patients with atopy. Esophageal subepithelial fibrosis is prevalent among children with EE and is considered as a specific marker for the disease. Eosinophilic esophagitis (EE) is caused by immunologic reactions to ingested/inhaled allergens.

Oral viscous budesonide (OVB) is an effective treatment of pan-esophageal disease in children with EE. OVB improves symptoms, endoscopic and histologic features. However, Proton pump inhibitor single therapy did not significantly improve esophageal eosinophilia or symptoms of EE.

Barrett Esophagus

Barrett esophagus (BE) is an acquired defect, the result of chronic mucosal injury, usually from acid reflux, but also possibly from bile, alkali, and other physiochemical causes. GERD is an accepted risk factor for the development of Barrett Esophagus BE occurs in about 10% of patients with GERD, which implies that other factors, genetic or environmental, play an undetermined role. Familial BE has also been reported.

Barrett esophagus is defined as an extension of columnar epithelium into the esophagus and/or as the presence of islets of columnar mucosa in the distal esophagus. BE is a rare condition in the pediatric age group and is known to be associated with reduced lower esophageal sphincter pressure and abnormal esophageal peristalsis. It is frequently associated with hiatal hernia.

Barrett patients have also defective esophageal acid clearance as demonstrated during 24 h pH monitoring. The severity of the disease is correlated with reduced lower esophageal pressure.

Clinical Features

Patients with BE present with a history of regurgitation, epigastric pain, and abdominal pain. Dysphagia (especially to solid), esophagitis, and ulceration are also recognized features.

BE is grossly apparent at endoscopy as velvety red tongues extending up the esophagus from the proximal gastric fold at the gastroesophageal junction. There may be islands of residual white squamous mucosa within an area of Barrett esophagus. There is definite recognized increased risk of adenocarcinoma of the esophagus up to around 100 folds in patients with BE. Other recognized endoscopic findings include ulceration and nodularity or friability. However, the endoscopic appearance of BE in childhood may not be classic.

The diagnosis is confirmed by histology of the lower esophagus being lined with columnar epithelium instead of squamous epithelium. Barrett esophagus is associated with esophagitis, ulceration, and stricture formation. Symptoms usually subside on completion of therapy for gastroesophageal reflux. Surgery is occasionally indicated in the course of therapy to improve outcome.

Corrosive Esophageal Injury

Background

Ingestion of caustic materials remains a concern in children, although severe injury is uncommon. In 2004, the US Toxic Exposure Surveillance System of the American Association

of Poison Control Centers reported 2,438,644 poison exposures for children under age 6. About 10% (124,962) were exposures to cleaning substances. The majority of caustic ingestions occur in children under 6 years and most are minor, only rarely leading to serious caustic injury.

Historically, severe caustic burns in children were increasing during the late 1960s correlated with the commercial availability of highly concentrated (>30%) alkaline liquid drain cleaners. Recognition of this led to legislation in the USA entitled the *Poison Prevention Packaging Act of 1970.* This required child-resistant containers and limited concentrations of caustic material to 10% for hazardous substances routinely stored at home, such as bleach and cleansers. This law has contributed to a decrease in serious caustic injuries in young children, and deaths due to ingestion are now very rare (.011% of all ingestions). Unfortunately, severe caustic ingestions have not stopped as accessibility to industrial-strength caustic agents remains a risk for serious burn injuries in children.

When pediatric ingestions do occur, they are usually minor, being limited to "lick or taste" scenarios. In contrast, ingestions by adolescents and adults are frequently intentional (suicide attempts) with larger volume ingested and greater potential for serious injury.

Corrosive Agents

Alkalis are odorless, colorless substances that are frequent causes of caustic ingestion. Cleaning products, such as oven cleaners and drain cleaners often contain lye, which is a strong alkali such as sodium or potassium hydroxide. Bleaches are the most commonly ingested alkali, but are weak alkali and tend to have a benign clinical course. Acids are generally bitter tasting and subsequently are much less commonly ingested. These include products such as toilet bowel cleaners (sodium bisulfate, sulfuric acid, and hydrochloric acid); metal cleaners (hydrochloric acid); battery fluids (sulfuric acid); and swimming pool products (hydrochloric acid). Acids account for only about 10% of ingestions seen in children.

Pathogenesis

The extent and severity of the corrosive injury is determined by the form (liquid vs. solid), concentration, and amount of material ingested. Lye-containing products are the most common cause of serious burns and strictures following caustic ingestion in children and can injure the esophagus, stomach, and duodenum. Ingestion of alkali causes liquefaction necrosis, which results in rapid destruction of the superficial mucosa, allowing deeper invasion of the caustic substance.

Sites of injury in the esophagus are initially red, progressing to brown within 30 min due to tissue necrosis. Within 24 h shallow ulceration appears, followed by sloughing of the necrotic layer within 2–4 days after ingestion. Tissue repair occurs 1–3 weeks after the initial injury, at which time the esophageal wall is at its weakest. This is important when considering the timing of diagnostic evaluation such as upper endoscopy. Stricture formation is seen 3–6 weeks after ingestion, depending on the extent of the initial lesion.

Acid ingestions result in coagulation necrosis in which a coagulum forms a tissue barrier over the surface mucosa, limiting deeper absorption of the corrosive substance. Acid ingestions are more commonly associated with gastric injury including perforation, stricture, pyloric stenosis, and gastric outlet obstruction.

Solid caustic agents in the form of granules, pellets, and powers tend to adhere to the oral mucosa causing immediate pain and are often expectorated, limiting burn injury to the oropharynx and upper esophagus. Historically, only 10–15% of patients with granular lye ingestions sustain serious injury.

Clinical Presentation

Symptoms such as drooling, dysphagia, vomiting, abdominal pain, and hoarseness indicate the presence of a significant caustic ingestion. These symptoms, however, cannot adequately predict the presence or severity of esophageal mucosal damage. Indeed, the absence of oropharyngeal lesions does not exclude the presence of gastroesophageal injury. A review of nine studies that included 489 patients with caustic ingestions showed that 76% of patients sustained oral burns and 63% incurred esophageal injury. In those patients with oral burns, 54% had concomitant esophageal burns, whereas 45% of patients without oral burns sustained esophageal injury.

Notification of the Poison Control Center is always recommended when evaluating a child with a history of exposure to a caustic substance. The Poison Control Center staff can help identify and categorize the ingested substance and make specific treatment recommendations.

Evaluation

Although a detailed history is helpful, most pediatric ingestions are accidental and occur during times when

a child is unsupervised. The physical examination should include a close inspection of the cheeks, lips, buccal mucosa, and posterior pharynx. Auscultation of the chest can identify evidence of bronchospasm or stridor, suggesting airway involvement. The family should be instructed to bring the container of the ingested material to the hospital to aid in identifying the ingested substance.

After the patient is stabilized, chest and abdominal radiographs should be obtained to assess for free air, suggesting possible perforation. If the findings are equivocal, a CT scan with oral, water-soluble contrast can assist in determining early perforation and need for surgical exploration. Barium studies are useful for verifying perforation and detecting stricture formation 3–6 weeks after ingestion, but are not recommended in the acute burn injury. Corrosive esophagitis is associated with irregular esophageal narrowing and stricture formation, which may be well demonstrated on barium contrast studies (◗ *Figs. 177.2* and ◗ *177.3*).

Endoscopy is the most effective and reliable method to determine the location, extent, and severity of gastroesophageal injury. The timing of the endoscopy is important. Endoscopy should be performed between 6 and 48 h after ingestion, as too early endoscopy (<6 h after the ingestion) may underestimate the extent of injury and late endoscopy (5–15 days after the ingestion) may predispose to perforation. Caustic injuries are graded similarly to skin burns (◗ *Table 177.1*).

Treatment

If the history and physical examination are consistent with an accidental ingestion of a small amount of dilute acid or base and the patient is asymptomatic after observation and able to drink fluids, then the patient can be sent home without an endoscopic evaluation and with instructions to return if symptoms develop. If respiratory symptoms are present, laryngoscopy should be performed to evaluate the presence of an upper airway injury. Intentional vomiting should be avoided to prevent further injury of the esophagus and upper airway.

Administration of a mild acid or base as a neutralizing solution, such as vinegar or bicarbonate, is not recommended because an exothermic chemical reaction may cause thermal injury at the site of mucosal damage. Likewise, the administration of oral fluid (even water) to a child with symptomatic gastroesophageal injury is not

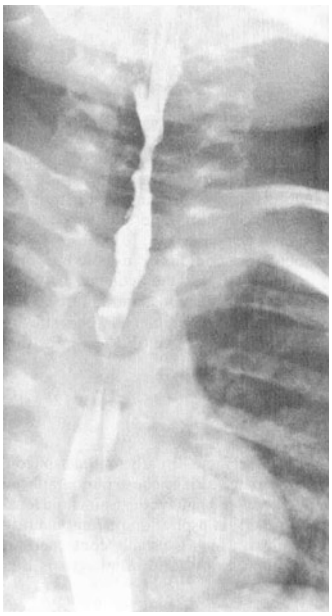

Figure 177.2
Esophageal stricture in a 2-year-old boy as a result of corrosive ingestion 2 months previously. Esophagogram reveals long stricture in the proximal esophagus (Courtesy: Dr. Hisham Nazer)

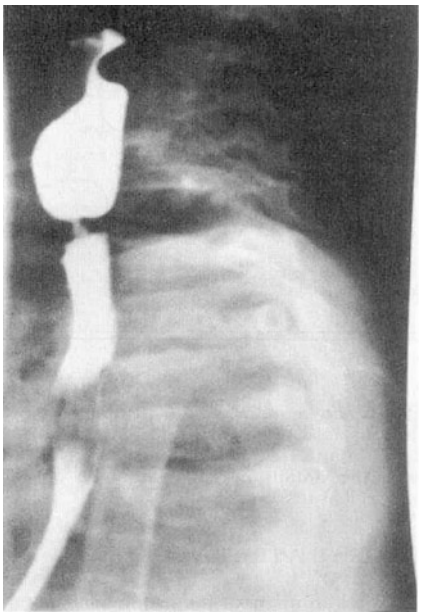

Figure 177.3
Esophageal stricture after acid ingestion. Esophagogram reveals a well-defined narrow stricture in the proximal esophagus with prestenotic dilatation. (Courtesy: Dr. Hisham Nazer)

Table 177.1
Caustic esophageal injury in children

Injury	Type	Endosopic findings	Outcome
Grade 0	Normal	Normal Mucosa	Normal/No Sequelae
Grade 1	First Degree Burn	Superficial Erythema & Edema	Normal/No Sequelae
Grade 2A	Second Degree Burn	Bleeding, erosions, blisters and exudates of mucosa/submucosa	Normal/No Sequelae
Grade 2B	Second Degree Burn	Circumferential Burn	Stricture likely
Grade 3	Third Degree Burn	Full thickness burn with deep ulcers, eschar, necrosis	Stricture + possible perforation

recommended as it may predispose the child to vomit and increase the risk of aspiration.

Children with grade 1 or 2A burns (*Table 177.1*) may be started on clear liquids after 24 h of observation and may be discharged home when tolerating a regular diet without difficulty. Children with grade 2B or grade 3 lesions experience the highest risk of complications and should have a nasogastric tube placed under direct visualization (during endoscopy) to provide nutritional supplementation and prevent complete obstruction of the lumen.

Those children with evidence of extensive transmural necrosis may benefit from early surgical exploration with gastrostomy, intraluminal esophageal stent placement, and radical resection if serosal discoloration of the stomach is present. Children with severe esophageal injury may eventually require colonic interposition surgery.

Treatment to prevent stricture formation is controversial. Systemic corticosteroids have been used since animal studies showed that cortisone prevents stricture formation. Studies in children and adults, however, have not demonstrated such favorable results. Conversely, if corticosteroids are used, a broad spectrum antibiotic should be used simultaneously to prevent local infection. It has been suggested that the depth and severity of the initial burn, rather than the treatment, may be the most important factors in determining risk of stricture formation.

Complications

Early complications of caustic injury are more often seen in children with severe injury and include perforation, mediastinitis, peritonitis, pneumonia, tracheoesophageal fistula, bleeding, sepsis, and even death.

Esophageal stricture formation is the most common late complication of caustic ingestion and can be diagnosed as early as 3 weeks following ingestion. After an esophageal stricture is found, conservative therapy with esophageal dilation is begun to maintain the child's ability to swallow. Gastric ulceration, perforation, and pyloric stenosis with distal outlet obstruction also can occur with alkaline ingestions but are seen more commonly after severe acid ingestions. It has been estimated that lye ingestion patients have a markedly increased risk of esophageal squamous cell carcinoma, with an average onset over 45 years following the initial injury, and hence routine endoscopic screening is recommended later in life.

Foreign Body Ingestion in Children

Foreign body ingestion is primarily a pediatric problem. In the year 2000, there were more than 107,000 cases of foreign body ingestion reported by the American Association of Poison Control Centers and 80% occurred in children. Most ingestions occur in young children 6 months to 3 years of age. The vast majority of ingested foreign bodies pass spontaneously and are symptom-free; however, about 10–20% require endoscopic removal and less than 1% require surgical intervention. Fortunately, mortality from foreign body ingestion is rare.

Coins are the most common gastrointestinal foreign bodies in children. However, young children ingest just about anything, including toys, magnets, batteries, pins, screws, marbles, and bones (*Fig. 177.4*). Multiple foreign body ingestion usually occurs in children with developmental delay. Most ingestions in young children are accidental, as compared to adolescents and adults where ingestions are often intentional.

Clinical Features

Most foreign body ingestions are asymptomatic and often observed by family members. Even in the emergency room

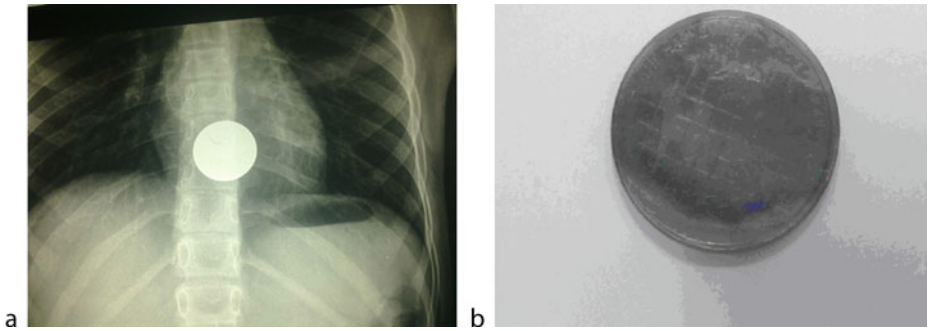

Figure 177.4
(a) Antero-posterior Plain X-ray Chest showing foreign body in the esophagus. (b) Endoscopic removal of the object (Coin) (Courtesy Dr. Hisham Nazer)

setting, only half of children with an ingested foreign body displayed symptoms at the time of the ingestion. Symptoms usually occur related to the location of the foreign body. For example, older children note the sensation of something "stuck" in the throat, suggesting an upper esophageal foreign body. A common symptom is refusal of feeds in infants and toddlers. Drooling suggests a complete esophageal obstruction. If the foreign body has remained in place greater than 24 h, symptoms of respiratory compromise may occur such as wheezing, stridor, or choking.

Foreign bodies tend to stick in areas of anatomic or physiologic narrowing. In the esophagus, these include the upper esophageal sphincter, the aortic arch impingement, and the lower esophageal sphincter. If a foreign body or food bolus lodges in the mid esophagus, esophageal pathology such as a stricture or esophagitis should be suspected. Children with previous esophageal surgery, such as tracheoesophageal fistula repair, are at high risk for foreign body obstruction.

Management

History and Physical Examination

Every child with suspected foreign body ingestion must undergo an initial evaluation of the airway and breathing, making special note of the neck exam for swelling, erythema, or crepitus. Crepitus suggests free mediastinal air from esophageal perforation. Chest exam should focus on inspiratory stridor and expiratory wheezing. For example, wheezing may indicate tracheal compression do to a lodged esophageal foreign body. Examination of the abdomen may indicate small bowel obstruction or perforation. Neck crepitus and possible small bowel obstruction require immediate surgical consultation and abdominal imaging should be obtained.

Diagnostic Examination

The initial diagnostic test should be radiographs (anteroposterior and lateral) of the neck, chest, and abdomen. Coins or disk batteries usually orient in the coronal plane and appear as a round object on an anteroposterior radiograph (*Fig. 177.4a*). Objects lodged in the trachea tend to orient in the saggital plane and are best seen in lateral projection. The lateral projection radiograph may help to identify the object or establish if more than one foreign body is present.

Some objects, such as toys made of plastic or wood, are not visible on plain radiographs. For example, Arana et al. in a study of 325 children found only about two thirds of the ingested objects were radiopaque. When the foreign body is not detected on plain film and a radiolucent foreign body is suspected, computed tomography is useful.

In general, gastrointestinal contrast studies should be avoided as the contrast material may obscure visualization on subsequent endoscopy. In addition, aspiration has been reported after oral contrast administration in cases of unsuspected high esophageal obstruction.

Management

Rapid Intervention

If any of the following warning signs are present, urgent endoscopic intervention is required.

Long (>5 cm) or sharp objects in the esophagus or stomach
Button battery (ies) in the esophagus
Multiple batteries in the esophagus or stomach
Signs of airway compromise
Drooling (patient cannot swallow secretions)
Evidence of intestinal obstruction or infection (fever, abdominal pain, or vomiting)

Routine Intervention

In the asymptomatic patient, most esophageal foreign bodies can be observed for 12–24 h, as spontaneous passage may occur. For example, coins lodged in the esophagus passed spontaneously into the stomach in about one third of asymptomatic children without warning signs.

Esophageal foreign bodies lodged for an unknown duration (or greater that 24 h) should be removed. Failure to spontaneously pass suggests possible esophageal pathology (e.g., stricture, abnormal motility). In addition, delayed passage of the foreign body may predispose to complications such as transmural erosion, perforation, and fistulae formation. In several case series, duration of lodgement for more than 24 h was the strongest predictor of complications.

Coins that reach the stomach can be observed and most will pass within 1–4 weeks. Practitioners can check the location of the coin with a plain radiograph about once a week. Coins that do not pass by 4 weeks should be removed endoscopically. If the child develops signs or symptoms of obstruction, such as abdominal pain, vomiting, or fever, the child should be reevaluated.

Techniques of Foreign Body Removal

The method of removal of an esophageal or gastric foreign body depends upon the expertise and experience of the practitioner. Many techniques exist, including rigid and flexible endoscopy, bougienage, Foley catheter, and the "penny pincher" technique.

Flexible Endoscopy

Flexible endoscopy is generally accepted as the preferred method in most circumstances because it allows the operator to directly visualize the foreign body and gastrointestinal tract. The endoscopist should have a variety of instruments to grasp the foreign body. Specific instruments such as the rat-tooth and alligator forceps, polyp snare, retrieval net, and helical baskets should be available. Removal of a sharp or pointed object generally requires a foreign body protector hood or overtube to avoid injury.

Rigid Endoscopy

Rigid endoscopy is a surgical technique using a rigid, channeled device that is introduced into the esophagus under general anesthesia. It is useful for objects in the proximal esophagus. The technique requires considerable skill and may cause complications such as esophageal abrasion and perforation.

Magill Forceps

Magill forceps are useful to remove foreign bodies in the oropharynx or uppermost esophagus. In cases done under general anesthesia, the anesthesiologist often can remove the object in the upper esophageal sphincter at the time of tracheal intubation, without the need for intubation. Most cases, however, require intubation and a laryngoscope is used to visualize the foreign body and remove it.

Alternative Approaches

Bougienage (passage of a dilator) has been used by some to push esophageal objects into the stomach. This approach is generally not recommended as it does not allow visualization of the esophagus and does not remove the foreign object. It may have a limited role in selected patients with witnessed, short-term (less than 24 h) coin ingestion. The Foley catheter technique has also been advocated. This approach does not permit visualization of the esophagus and carries the risk of balloon inflation below an unsuspected stricture and subsequent esophageal perforation as well as the potential of causing aspiration of the foreign body if it is inadvertently dragged into the trachea. Another published approach is the penny pincher technique in which an endoscopic grasping forceps is inserted through a nasogastric tube, under fluoroscopic guidance (usually without anesthesia or endotracheal intubation). This approach is an improvement over the Foley catheter method because it permits direct control of the object, but does not allow inspection of the esophagus. This method requires considerable experience and operator time.

Special Circumstances

Disk Batteries

Button batteries in the esophagus are an emergency and must be urgently removed. The esophagus is flat and a lodged disk battery will conduct electricity between the anode and cathode (positive and negative poles), which can result in liquefaction necrosis and perforation. Retained batteries can also leak caustic material (e.g., mercury, silver, lithium and sodium, or potassium hydroxide) causing additional mucosal injury. Disk batteries generally pass uneventfully from the stomach. However, because of the potential for leakage and toxicity, batteries should be removed if they are within reach of the endoscope.

Sharp or Pointed Objects

Sharp or pointed objects lodged in the esophagus are a medical emergency and require urgent removal. Many sharp or pointed objects (e.g., straight pins, needles) are not readily visible by X-ray; hence, if there is high suspicion of ingestion, endoscopy should be performed. The risk of mucosal injury during removal of a sharp object can be reduced by using a protector hood on the end of the endoscope or an overtube. If the object is in the stomach or proximal duodenum, it should also be removed promptly, using a flexible endoscope. If the object has passed the stomach and the patient is asymptomatic, it should be followed with serial radiographs. Surgical intervention should be considered for objects that fail to progress for 3 days or if symptoms occur.

Food Impaction

Impacted food bolus is the most common esophageal foreign body in adults, but is unusual in children. This usually occurs while eating. Children who do present with a food impaction suggests underlying esophageal pathology (strictures, achalasia, esophagitis, or esophageal motility disorders). As mentioned, children who are in acute distress or drooling require urgent removal of the impaction. Proteolytic enzymes, such as papain, are not recommended because their use may cause erosion and perforation. The use of glucagon to promote spontaneous passage of an impacted food bolus by relaxing the esophagus can be tried if the patient is stable as it appears generally safe, but it may not be effective and should not delay endoscopic removal.

Magnets

A solitary, smooth ingested magnet is of little risk, but two or more magnets may attract across layers of bowel leading to injury such as fistula, volvulus, perforation, or obstruction. As such, it is important to determine the location and number of magnets as ingestion of multiple magnets requires removal.

Long Objects

Objects longer than 5 cm generally do not pass the stomach and should be removed.

Summary

Many children with esophageal foreign bodies are asymptomatic and the objects pass uneventfully. When symptoms occur, such as a sensation of something stuck in the chest, feeding refusal, drooling, or respiratory symptoms, intervention and foreign body removal are indicated. Flexible endoscopy is the preferred approach in most cases. Objects that have passed beyond the stomach usually pass without complications.

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178 Gastroesophageal Reflux Disease

Mohammad I. El Mouzan

Gastroesophageal reflux disease (GERD) is a common cause of morbidity worldwide. The estimated incidence of 1 in 300 live births and 60% preponderance have been reported. This incidence however is increased in certain conditions such as cerebral palsy, mental retardation, and operated tracheoesophageal fistula.

Pathogenesis

Although the mechanism of GERD remains unclear, several anatomic and functional factors prevent reflux. The phrenoesophageal ligament, the acute esophageal angle, and the lower esophageal sphincter (LES) are the most important "antireflux barriers."

Dysfunction of the LES resulting in inappropriate relaxation of the sphincter in response to increased intra-abdominal pressure (associated with physiologic activity such as crying, cough, sneezing, defecation, etc.) is the commonest mechanism. Other forms of LES dysfunctions such as spontaneous intermittent relaxation or continuous reduction in basal pressure are less common. Reflux of gastric content in the esophagus causes most of the symptoms such as regurgitation and vomiting, chronic bronchitis, recurrent aspiration pneumonia, apnea and bradycardia, and bronchospasm. Failure to thrive results from loss of calories, and esophagitis results from the effects of gastric contents (mostly acid) on the esophageal mucosa. In addition, certain manifestations such as stridor, bronchospasm, and apnea may be related to the presence of acid in the esophagus through a reflex mechanism without aspiration.

Clinical Presentation

Gastroesophageal reflux is a normal phenomenon both in children and adults. The distinction between physiologic reflux and disease (GERD) is a matter of quantity. Regurgitation and vomiting are the commonest manifestations in infants and resolve spontaneously. A minority of infants however develop GERD with recurrent vomiting, hematemesis, odynophagea (pain on swallowing), dysphagea, irritability resembling infant colics, arching of the back during feeding, and failure to thrive. In addition, GERD has been implicated as one of the causes of chronic respiratory diseases such as recurrent bronchospasm, stridor, chronic cough, and recurrent pneumonia. In infants, GERD has been associated with apparent life-threatening events (ALTE). In older children, GERD presents most commonly with recurrent vomiting, hematemesis, heartburns, and dysphagea. Rarely, stereotypical stretching and arching of the back (Sandifer syndrome) is caused by esophageal pain may be confused with seizures or dystonia. Chronic untreated peptic esophagitis leads to chronic blood loss with iron deficiency anemia, esophageal stricture, and replacement of the normal esophageal mucosa of the distal esophagus with a potentially malignant metaplastic epithelium called Barrett's mucosa. Finally GERD has been linked to chronic laryngitis, sinusitis, and otitis media.

Diagnostic Methods

There is no test that can distinguish physiologic reflux from GERD. In infants with uncomplicated reflux (vomiting and regurgitation only), history and physical examination are usually sufficient for the diagnosis of reflux. In complicated cases, however, usually more than one investigation is needed.

Barium Meal

Barium meal (and not swallow) is usually the first investigation. It is inexpensive, readily available, and allows identification of structural anomalies such as hiatal hernia, esophageal stricture, gastric volvulus, malrotation, and pyloric stenosis. However, low sensitivity (31–86%) and specificity (21–86%) suggest high false-negative and false-positive results, indicating that barium meal alone should not be used to diagnose or exclude reflux.

Esophageal pH Monitoring

This test, also called pH probe, detects acid reflux in the lower esophagus. A probe placed in the lower esophagus

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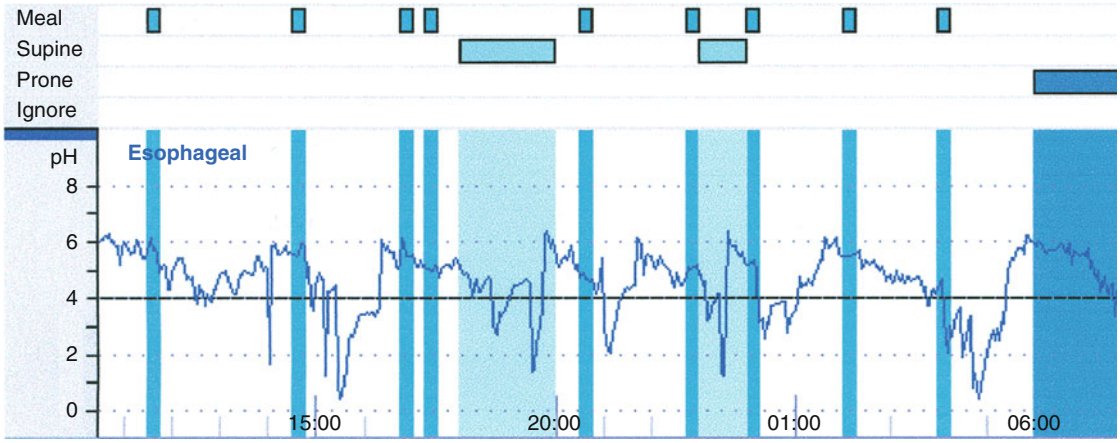
Study summary



Analysis results – esophageal

Acid period table

	Total	Upright	Supine	Prone	Meal	Postpr
Duration of Period	24:00	19:00	03:00	02:00	02:15	14:44
Number of refluxes	115	72	38	5	6	92
Number of long refluxes	9	7	2	0	2	8
Duration of longest reflux (min)	47	47	12	1	47	47
Time pH < 4 (min)	253	218	33	1	9	199
Percent time pH < 4 (%)	17.6	19.1	18.6	1.1	6.9	22.5

Figure 178.1
A 24-h esophageal pH monitoring in an infant. Abnormal study with an abnormal percent time pH < 4 score of 17.6%. On follow-up, the patient developed peptic esophagitis grade III

through the nose measures the pH which is transmitted to a recorder. More recently, a wireless capsule, attached to the esophageal mucosa, transmits pH to the recorder eliminating the nasoesophageal tube and discomfort. The recording lasts for about 24 h during which the patient performs his usual activities. Data collected during this period is analyzed by computer and results are expressed in a graph and table. Parameters include number of reflux episodes, number of prolonged episodes, duration of the longest reflux episode, and percentage of time pH was less than 4. The latter is called the reflux index. Advantages include ability to quantify reflux, allowing the distinction between physiologic and pathologic reflux (GERD). Another important advantage is to clarify the relation between reflux episodes and symptoms by calculating the symptom index score (the number of symptoms occurring during reflux episodes). A causal relationship is suggested when the score is more than 0.50. However, esophageal pH studies do not detect nonacid reflux which occurs in the postprandial period which may cause chronic respiratory disease (*Fig. 178.1*).

The Multichannel Intraluminal Impedance

This recently described technique measures the conductance potential (electrical impedance) of refluxed material and identifies its physical characteristics (liquid, gas, or mixed). It is combined with pH monitoring in the same probe to determine whether these reflux episodes are acid or nonacid. Studies have shown that combined impedance with pH identified more reflux episodes with better identification of weakly acid GERD not detectable by

conventional pH probe alone and yet responsible of symptoms of GERD. At present, the main disadvantages of this technique are lack of normal values for nonacid episodes, poor reproducibility, and high cost.

Endoscopy and Biopsy

Visualization of the esophageal mucosa detects signs of inflammation which is confirmed by histopathology. Thus, this procedure is important in the detection of peptic esophagitis, a complication of GERD and not a diagnostic test of GERD per se. The degree and extent of esophageal lesions (erythema, erosions, and ulcerations) have been used in the grading of esophagitis. Endoscopy and biopsy also detect strictures and Barrett's esophagus. Endoscopy and biopsy also help in the differential diagnosis of peptic esophagitis which include Crohn's disease, webs, and eosinophilic or infectious esophagitis. Because of poor correlation between endoscopic appearance and histology, biopsy is commonly recommended whenever endoscopy is performed.

Scintigraphy

This technique is performed by oral ingestion or instillation of technetium-labeled formula or food into the stomach. The areas of interest, the stomach, esophagus, and lungs, are scanned by a gamma camera for evidence of reflux and aspiration. Main advantages are the ability to demonstrate reflux of nonacidic gastric contents and study of gastric emptying, which may be delayed in children with GERD. Disadvantages include lack of standardization, high cost in terms of equipments, and expertise.

Other Techniques

Ultrasonography: Monitoring of the gastroesophageal region after a meal for reflux has been introduced as a noninvasive technique for the identification of reflux. However, the test requires dedication and expertise which are not commonly available. Therefore, although attractive, this test is not widely performed. *Esophageal manometry*: Manometry is not a diagnostic test for reflux per se. It is frequently performed in adults to detect motility disorders associated with GERD, but rarely indicated in children. *The Bilitec 2000*: This is a fiber optic spectrophotometric probe that detects bilirubin in the refluxate, which may be helpful in the diagnosis of nonacid reflux caused by duodenogastric reflux disease.

Therapeutic Measures

Three modalities are described: medical therapy consisting of dietary, positional, and drug therapies. Nonresponse to an adequate trial of medical therapy or dependence on drug therapy is an indication for surgery. However, endoscopic methods may be considered as an alternative to surgery.

Dietary Measures: Thickening of infant feeds is widely used. Milk-thickening agents decrease the number of episodes of vomiting but do not improve reflux index scores. Thickening may be achieved with the addition of rice cereal to formula or addition of thickening agents to formula. The advantage of thickening with rice cereals is the increase of caloric intake. Newer formulas that contain carob flour or locust bean gum as thickening agents are now available. These formulas have been reported to decrease vomiting and esophageal acid exposure when compared with unthickened formulas and formula thickened with rice cereal.

The usefulness of small volume and more frequent feeds remains controversial.

For older children and adolescents, dietary advice includes cessation of smoking and avoidance of spicy food, chocolate, and caffeine. In overweight and obese patients, weight reduction was associated with improvement of reflux.

Postural therapy: The recommended positioning of infants with GERD has evolved over the last two decades. The prone positioning recommended in the past for the treatment and prevention of GER in infants is now changed to supine positioning. This change in recommendation was based on the recognition that prone positioning was associated with a higher rate of sudden infant death syndrome (SIDS) and on the reduction in SIDS rate and mortality in infants in the non-prone position compared to those in the prone position. Older children and adolescents may benefit from elevation of the head of the bed.

Drug Therapy

Prokinetic therapy: Prokinetic therapy enhances esophageal peristalsis and accelerates gastric emptying. Bethanecol, metoclopramide, domperidone, and cisapride have been used with controversial or marginal effectiveness. Cisapride, widely used in the past, has been withdrawn from the market because of serious cardiac side effects. At present, although domperidone and metoclopramide are used on empirical basis, no prokinetic agent can be recommended on scientific grounds.

Acid-controlling drugs: A wide range of acid-controlling agents is available. *Antacids* neutralize gastric acidity. However, in order to be effective, large doses must be given frequently. *Antihistamine-2 receptor antagonists* (*H-2 blockers*) decrease acid secretion by inhibiting the histamine-2 receptors on the gastric parietal cell. Representatives of this category include cimetidine, ranitidine, and famotidine. Ranitidine is probably the most commonly used in children. *Proton pump inhibitors* (*PPI*) are the most potent acid suppressors. They deactivate the H^+, K^+ – ATPase pumps so that virtually no acid is pumped in the gastric lumen. Optimal effectiveness is achieved when the PPI is administered one-half hour before meals so that peak plasma concentrations coincide with the mealtime. The main indication is the treatment of esophagitis. However, since these agents reduce esophageal acid exposure, they may be useful in the treatment of GER-related respiratory disorders.

Surface Agents (Sucralfate) are represented by sodium alginate forms a surface gel that decreases the regurgitation of gastric contents into the esophagus and protects the esophageal mucosa. Sucralfate gel acts by adhering to peptic lesions and protects the esophageal mucosal surface. Information on the doses and side effects are available in the references given at the end of the article.

Surgical therapy: Although many surgical techniques have been described, Nissen fundoplication is the most commonly used. Surgery is indicated in children unresponsive to an adequate trial of medical therapy. Laparoscopic fundoplication is currently more frequently performed than the open technique. The success rate varies with the degree of selection of cases and the experience of the centers but usually reaches 90%.

Endoscopic therapy: Endoscopic therapeutic techniques have been described recently: endoscopic polymer implantation, delivery of radiofrequency to the cardia (Stretta system), and endoscopic gastroplication (EndoCinch system).The latter appears to be the most popular and has been reported to be safe and effective in adults. Experience in children is limited but encouraging and may become an alternative to surgery in children dependent on antireflux medications.

Approach to the Diagnosis and Therapy

It is well recognized that the majority of uncomplicated GER in infants, the so-called "happy spitters," are self-limited and therefore do not require investigation or medications and supportive measures such as thickening of feeds, and supine positioning may be helpful. An overlap of symptoms between GER and cow's milk protein allergy has been reported, and a trial of hypoallergenic formula for 1–2 weeks may be considered. Regular follow-up is recommended to document recovery or persistence of symptoms and complications. Complicated GERD presenting with recurrent vomiting, weight loss or poor weight gain, irritability in infants, heartburn, chest pain, hematemesis, dysphagia or feeding refusal, apnea or ALTE, wheezing, stridor, hoarseness, cough, abnormal neck posturing (Sandifer syndrome), all require consultation with pediatric gastroenterologist for further evaluation and investigations. An adequate trial (at least 2 months duration) of medical therapy is recommended as soon as the diagnosis of GERD is established. Nonresponse to medical therapy is an indication for surgery.

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179 The Stomach

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The gastric wall is composed of three layers: the mucosa, the muscularis mucosae, and the serosa. The gastric mucosa is lined by a single layer of mucus-secreting columnar epithelium punctuated by pits where the gastric glands are situated. The stomach can be divided histologically into three areas according to the predominant gland type: cardiac, fundus or oxyntic, and antral.

The cardiac region is the area just distal to the gastro-esophageal junction; it contains mainly mucus-secreting glands and endocrine cells. The fundus/oxyntic region extends from the cardia to the dome-shaped fundus and the body of the stomach to the level of the incisura angularis. It contains parietal cells that secrete HCL and intrinsic factor, chief cells that secrete pepsinogen, G cells that secrete gastrin, and enterochromaffin cells that secrete histamine and serotonin.

The antral/pyloric region is located distal to the incisura angularis, and contains D cells that secrete somatostatin, G cells, and enterochromaffin cells.

Gastropathies, Gastritis and Peptic Ulcer Diseases

Gastritis is defined as inflammation of the gastric mucosa. The lesion is usually superficial, though cases may be associated with deeper involvement of the gastric mucosa. There is partial or complete loss of the gastric gland cells. This entity of gastritis is referred to as *nonerosive gastritis*. There may also be some intestinal metaplasia with replacement of the gastric mucosa by an intestinal mucosa. An immunologic mechanism may play a role. Affected patients are prone to suffer from pernicious anemia that requires treatment with intramuscular vitamin B12 injection.

Gastritis may, however, be severe enough to progress into severe erosions and hemorrhages (*erosive gastritis*). The lesion may progress even deeper to the submucosa and muscularis mucosa with secondary ulceration. The mucosal barrier of the stomach is disrupted secondary to decreased mucosal blood flow.

Pathophysiology

Normally, the gastric mucosa is protected from acid and pepsin attack by a viscous gel layer formed of mucus, phospholipids, and bicarbonate which are secreted by the gastric epithelial cells under prostaglandin stimulation. Peptic disease results from an imbalance between the gastric mucosal aggressive and protective mechanisms.

Gastritis and ulcers are classified as *primary or secondary* based on the underlying etiology. *Primary ulcers* are usually chronic, duodenal, and in the majority of cases caused by infection with *Helicobacter pylori*, whereas *secondary ulcers* are usually acute and gastric. Secondary gastritis and ulceration occur in association with severe stress such as systemic illnesses, burns, and head injuries. They may also be induced by the ingestion of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs).

Peptic disorders are far less prevalent in the pediatric age group than in adults, accounting for only about 10–20% of cases of abdominal pain seen in outpatient gastroenterology clinic settings.

Clinical Presentation

In children, the symptoms caused by gastritis and gastric ulcers are highly variable. Young children with peptic disorders may present with irritability, vomiting, and poor appetite. Older children may present with epigastric pain, nausea, early satiety, vomiting, anemia, and weight loss. Epigastric tenderness may be elicited on physical examination.

Gastritis and gastropathies are classified by their endoscopic appearance into *erosive and hemorrhagic* or *nonerosive* types (Table 179.1) based on the most common presenting picture.

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Table 179.1
Classification of gastritis and gastropathy in children

Erosive and/or hemorrhagic gastritis or gastropathy	Nonerosive gastritis or gastropathy
Stress gastropathy	Nonspecific gastritis
	Helicobacter pylori gastritis
Neonatal gastropathy	Crohn's gastritis
Traumatic gastropathy	Allergic gastritis
Aspirin and other nonsteroidal anti-inflammatory drugs	Proton pump inhibitor gastropathy
Portal hypertensive gastropathy	Gastritis of chronic granulomatous disease
Uremic gastropathy	Cytomegalovirus gastritis
Chronic varioliform gastritis	Eosinophilic gastritis
Bile gastropathy	Collagenous gastritis
Henoch–Schönlein gastropathy	Graft-versus-host disease
Corrosive gastropathy	Ménétrier's disease
Exercise-induced gastropathy or gastritis	Pernicious anemia
Radiation gastropathy	Gastritis with autoimmune disease

Note: Although some disorders can present with either erosive or nonerosive picture, each is classified by its most common presentation

Nonerosive Gastritis or Gastropathy

Helicobacter pylori Gastritis

Helicobacter (Campylobacter) pylori are spirochetal-like organisms that were isolated in 1982 from gastric biopsies of adults. *H. pylori* is a gram-negative, flagellated microorganism, that can colonize the gastric epithelium, causing chronic gastritis. Infection with *H. pylori* is strongly associated with duodenal and gastric ulcers, and has been implicated in the etiology of gastric cancer.

H. pylori can be transmitted from person to person via oral–oral and fecal–oral routes. Overcrowded conditions and poor socioeconomic status are risk factors for acquiring the infection.

H. pylori infection is rare in young infants, and its prevalence rises with age. In developing countries, infection occurs at a much earlier age, usually in the first 2 years of age affecting about 40% of children and more than 80% of adults. In developed countries, colonization in childhood is uncommon, and only 40% of adults are infected.

Pathophysiology

H. pylori is capable of withstanding the gastric pH in part due to its ability to secrete urease which hydrolyzes urea into CO_2 and ammonia. Ammonia neutralizes the acid environment in the stomach. In addition, the bacteria posses several flagellae that enable it to penetrate the gastric mucus layer and attach to the gastric epithelium. Production of toxins and bacterial enzymes contributes to epithelial damage.

H. pylori adheres only to gastric epithelium and it is found on the gastric mucosa of almost 90% of children with duodenal ulcers. The mechanisms by which gastric antral colonization with *H. pylori* leads to duodenal ulceration is unclear. Duodenal gastric metaplasia appears to be a risk factor with *H. pylori* colonizing the metaplastic epithelium. Additionally, *H. pylori* induces increased basal and peak acid output contributing to duodenal ulceration.

Although *H. pylori* infection induces a systemic antibody response, this response is incapable of eradicating the bacteria. Up to 15% of patients infected with *H. pylori* develop peptic ulcer disease, and a further 1% may develop gastric cancer.

Clinical Manifestations

Infection with *H. pylori* usually causes asymptomatic chronic gastritis. When symptomatic, patients typically present with epigastric abdominal pain and vomiting. The pain often occurs after meals, but it can also occur early in the morning. Younger children may present with irritability and decreased appetite. Less-frequent presenting symptoms include chest pain, heartburn, nausea, anorexia, or gastrointestinal bleeding.

Chronic iron deficiency anemia has been documented in children with gastritis or ulceration and may be painless.

H. pylori infection also appears to be associated with an increased risk of carcinoma of the stomach especially in those infected as children.

The relationship of chronic *H. pylori*-associated gastritis to symptoms is still controversial. Reports have also indicated that after eradication of *H. pylori*, symptoms resolved only in those patients who had duodenal ulcer disease associated with *H. pylori* gastritis.

Diagnosis

H. pylori infection can be detected by noninvasive and invasive tests.

Noninvasive tests include stool testing for *H. pylori* antigens, urea breath test, and serology.

Stool *H. pylori* antigen test has a sensitivity of 98%, and specificity of 99%. Urea breath test is performed by ingesting a test meal that contains urea labeled with carbon-13 (13C). *H. pylori* urease activity hydrolyses the urea releasing labeled carbon dioxide, which can be detected in the breath. The test is more than 90% sensitive and specific.

Invasive testing is achieved by performing an endoscopic examination. The presence of *H. pylori* correlates better with the histologic rather than with endoscopic finding. Most children with *H. pylori* infection exhibit a nodular pattern in the gastric antrum secondary to lymphoid hyperplasia that can be seen at endoscopy. *H. pylori* can be detected using a rapid urease test by placing a gastric mucosal biopsy in a media containing urea and a pH color indicator; the bacteria cleaves the urea-liberating ammonia, causing a rise in the pH and changing the color of the media from yellow to pink. Microscopic examination of gastric mucosal biopsies identifies the inflammation and the *H. pylori* organisms in the gastric tissue. Tissue culture to detect antibiotic susceptibility patterns can also be performed for patients with refractory disease.

Treatment

H. pylori eradication can be achieved by using a triple therapy consisting of a proton pump inhibitor combined with two antibiotics for 2 weeks. Amoxicillin and clarithromycin are recommended. In persons allergic to penicillin, substitution of amoxicillin by metronidazole should be done. Once the condition is stabilized, it is important to continue therapy with antacids or H2 blockers for a period of up to 2 months.

Patients treated for *H. pylori* should have a noninvasive test (breath test or stool antigen test) 4–6 weeks after treatment to confirm eradication if they remain symptomatic. Patients with ulcer should have a repeat endoscopy 4–6 weeks after therapy to monitor ulcer healing.

More details regarding *H. pylori* gastritis and peptic ulcer disease are covered in the Chap. 181, "Peptic Ulcer Disease."

Inflammatory Bowel Disease

Gastroduodenal involvement is common in Crohn's disease, and is usually associated with distal intestinal involvement. Patients may be asymptomatic, or they may complain of abdominal pain, nausea, or vomiting. Patients may also present with delayed gastric emptying, hematemesis, and melena.

Diagnosis is achieved by histological examination of the gastric mucosa, which may reveal focal chronic active inflammation and noncaseating granulomas.

Allergic and Eosinophilic Gastritis

Eosinophilic gastroenteropathy (EG) is a chronic relapsing disease of unknown etiology, thought to be related to food or environmental allergy, characterized by dense eosinophilic infiltration of parts of the gastrointestinal tract.

EG can present at any age from infancy to adulthood, and can occur in all races, with a slightly higher incidence in males. A personal or family history of allergy or atopy is present in many cases.

The manifestations of the disease vary according to the region and the layer(s) of the gastrointestinal tract involved. In eosinophilic gastritis, the eosinophilic infiltration is limited to the stomach, and can involve the gastric mucosa, the muscularis, or the serosa. Patients with mucosal involvement may present with abdominal pain, vomiting, weight loss, or edema as a result of protein-losing enteropathy. Patients with muscularis disease present with signs of gastrointestinal tract obstruction, while serosal involvement produce eosinophilic ascites, and patients may present with symptoms of peritonitis. Peripheral eosinophilia and an elevated total and food-specific IgE levels may be seen.

Diagnosis

The diagnosis of eosinophilic gastroenteropathy is confirmed by identifying a dense eosinophilic inflammation

in the gastric tissues in the absence of parasitic infection or other causes of intestinal eosinophilia.

Treatment

Although food hypersensitivity plays a major role in eosinophilic gastroenteropathy, no food allergy test (skin, patch, allergen-specific IgE) has been shown to effectively identify culprit foods leading to clinical or tissue eosinophilia improvement. Thus at present there is no evidence base to support routine food allergy testing of eosinophilic gastropathy patients. An empiric elimination diet with the patient avoiding possible culprit allergens (including soy, wheat, corn, egg, milk, peanut, and seafood) may regress the eosinophilic infiltration and alleviate the symptoms. In patients who do not respond to elimination diets, elemental diet may be effective. If symptoms persist despite dietary manipulation, corticosteroids can be used for a short duration to suppress the inflammation. Unfortunately, many patients relapse and may need to be retreated.

Cromolyn sodium, a mast cell stabilizer, may also be used alone or in combination with steroids. Montelukast, a leukotriene receptor antagonist may also be effective. Surgical intervention is rarely required for patients with obstructive symptoms.

Hypertrophic Gastritis (Ménétrier's Disease)

Ménétrier's disease is a disease of unknown etiology, thought to be associated with acute CMV infection. It is characterized by thickening of the gastric mucosal folds associated with protein loss across the abnormal mucosa. Ménétrier's disease can present at any age. The mean age of onset in children is 4.7 years. Patients may present with abdominal pain, anorexia, vomiting, edema, and hypoproteinemia. The diagnosis is confirmed by endoscopy and histological examination of gastric mucosal biopsies. The course in children is self-limited.

Pernicious Anemia

Patients with pernicious anemia have antibodies directed against the gastric parietal cells causing diffuse atrophic gastritis of the gastric body with consequent loss of acid and intrinsic factor secretion. Achlorhydria, and megaloblastic anemia due to vitamin B-12 deficiency result.

At endoscopy, the gastric body appears thin and blood vessels are sometimes visible through the mucosa. Histological examination shows severe atrophic gastritis with absence of parietal cells. Adenocarcinoma may occur.

Other causes of nonerosive gastritis or gastropathy are listed in *Table 179.1*.

Erosive and/or Hemorrhagic Gastritis or Gastropathy

Stress Gastritis

Stress-induced gastric erosions usually occur within 24 h of the onset of a major illness such as shock, sepsis, burns, head injury, and major surgery. The stressor causes a reduction of the gastric mucosal blood flow resulting in ischemia with subsequent gastric erosions and ulcerations. Stress erosions are typically asymptomatic, multiple, and superficial; however, when they are symptomatic, they usually cause overt upper GI hemorrhage, and may lead to perforation. Stress ulcers associated with burns are also known as Curling's ulcers, while those associated with increased intracranial pressure are known as Cushing's ulcers.

Aspirin and Other Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are common causes of gastric mucosal injury. They may cause superficial petechiae, erosions, gastritis, or gastric ulcers. NSAIDs cause damage to the gastric mucosa directly as well as systematically through inhibiting cyclooxygenase 1 (COX-1) which reduces gastric mucosal prostaglandin synthesis, thereby inhibiting epithelial proliferation and mucosal bicarbonate and mucus secretion. The risk of injury is dose dependent.

NSAIDs should be discontinued or at least the dose should be decreased. A proton pump inhibitor or a prostaglandin E analog such as misoprostol may be used as prophylactic therapy. Patients with active ulcer who need to continue NSAIDs should be treated with a proton pump inhibitor. Alternatively, selective COX-2 inhibitors may be used.

Other drugs that can cause erosive and hemorrhagic gastropathies include valproic acid, dexamethasone, iron, and potassium chloride.

Chronic Erosive Gastritis

Also known as chronic varioliform gastritis, chronic erosive gastritis is an uncommon disorder of unknown etiology characterized by thickened gastric mucosal folds

associated with dense lymphocytic infiltration. Patients may present with upper GI symptoms associated with anemia or protein-losing enteropathy.

Bezoars

Bezoars are collections of indigestible material that accumulate, coalesce, and get retained within the gastrointestinal tract, most frequently the stomach. In rare instances, the impaction advances by long strands of twisted hair into the intestine, a condition recognized as "the Rapunzel syndrome." Bezoars are usually seen in emotionally disturbed and depressed patients as well as in mentally handicapped children. They can also develop in patients with gastric dysmotility, and in patients with surgically altered gastric anatomy

Bezoars can be classified according to their composition. The major types are phytobezoars, composed of vegetable matter; trichobezoars, composed of hair; pharmacobezoars, consisting of medications; and lactobezoars, formed from milk curds.

Phytobezoars are the most frequently observed type of bezoars, accounting for 40% of reported cases. They are composed of aggregations of indigestible food fibers such as cellulose, hemicellulose, lignins, and tannin, most commonly from pulpy fruits, seeds, roots, or leaves. Predisposing factors to phytobezoar formation include poor mastication, excessive intake of fiber, histamine H2 receptor antagonists, and gastroparesis. Phytobezoars are usually found in the stomach, but may also occur in the small intestine and colon.

Trichobezoars (hairball) are mostly seen in young children who practice the habit of eating their own hair or fibers from blankets and rugs. The condition is slowly progressive until it presents with abdominal discomfort, pain, vomiting, and constipation together with evidence of emotional disturbances or mental handicap.

Examination reveals a hard tumor palpated in the left hypochondrium.

The diagnosis is considered by the history of the child's habit and is later supported by barium meal, which shows a filling defect in the stomach. The borders and configuration of the bezoar are highlighted after the passage of barium from the stomach. Ultrasonography, computed tomography, and gastroscopy with biopsy are helpful in supporting the diagnosis of trichobezoars.

Treatment is by surgical removal of the mass. Psychiatric follow-up is essential to diminish the frequency of recurrence. Occasionally, an attempt is made to endoscopically remove the hairball. Gastric perforation is a recognized complication of trichobezoar.

Lactobezoars are concretions of casein, fat, and calcium, and occur most commonly in premature low-birth-weight infants. They have also been reported in full-term, and exclusively breast-fed infants. Factors implicated in lactobezoar formation include formulas with a high casein content, high-caloric density formulas, early and rapid feeding advancement in small infants, thickening agents, and immature gastric motility.

Cement bezoars: several cases of cement bezoars have been reported in children. Cement solidifies after various lengths of time depending on their type. Solidified concretions require surgical removal.

Clinical Presentation

Lactobezoars in the newborns present with feeding intolerance, and infants may develop abdominal distension and vomiting. Physical examination often discloses a palpable mid-abdominal mass.

Trichobezoars form over long periods, and may cause subtle signs of abdominal discomfort, early satiety, or nausea. These bezoars can grow to substantial size and cause pressure necrosis and ulceration of the gastric mucosa, causing gastrointestinal bleeding, melena or guaiac-positive stools, and iron deficiency anemia. They may also cause gastric perforation.

Patients with *Rapunzel syndrome* may present with partial or complete intestinal obstruction, and depending on the size and extent of the "tail" may cause obstructive jaundice, pancreatitis, and protein-losing enteropathy.

Phytobezoars are formed much more rapidly than trichobezoars. Symptoms include nausea, vomiting, and signs of gastric outlet obstruction. Gastric perforation is rare.

The physical examination is unremarkable in most patients with gastric bezoars. Occasionally, abdominal distension or a palpable left upper quadrant abdominal mass may be detected. Crepitus caused by putrefaction and bacterial growth may sometimes be elicited.

Severe halitosis may be present due to the putrefying material in the stomach. Patients with trichotillomania may have patchy areas of alopecia.

Diagnosis

Plain radiographs may demonstrate an air shadow or a mottled-appearing mass in the stomach. Barium studies are much more likely to demonstrate a bezoar;

trichobezoars absorb barium and have a mottled appearance, whereas phytobezoars are typically impermeable to barium and appear as filling defects.

Ultrasound or CT scan may also be used and show the bezoar as a mass or a filling defect. However, radiographic studies identify only one fourth of bezoars; moreover, the use of barium may change the acid environment surrounding enteric-coated pharmacobezoar aggregations, leading to absorption of the medication.

Endoscopy is the diagnostic modality of choice allowing direct visualization of the bezoar, biopsy, and therapeutic intervention.

Management

Management of bezoars depends on their composition, size, and/or associated complications.

Lactobezoars almost always resolve in response to withholding feedings for a couple of days while maintaining the infant on intravenous fluids.

Small bezoars may be managed conservatively with a clear-liquid diet and a prokinetic agent such as metoclopramide. Nasogastric lavage may effectively dissolve small phytobezoars.

Chemical dissolution may be used to dissolve phytobezoars, and can be achieved using any of the following agents:

1. Cellulase: can be used to degrade the cellulose and hemicellulose found in phytobezoars. No adverse effects have been reported with the use of cellulase.
2. Papain: papain used in meat tenderizers can be given to dissolve bezoars; however, adverse effects including gastric ulcer and esophageal perforation have been reported.
3. Acetylcysteine: because many phytobezoars contain mucus, acetylcysteine solution can be used to chemically fragment phytobezoars.
4. Coca-Cola: oral, nasogastric, and endoscopic injection of Coca-Cola can be used to dissolve phytobezoars. The mechanism of Coca-Cola's action may be related to its low pH, high sodium bicarbonate content, and the presence of CO_2 bubbles.

    Endoscopy: most bezoars can be fragmented into small pieces endoscopically, and either removed or allowed to pass through the GI tract.

Trichobezoars are not amenable to chemical dissolution, and are more difficult to remove endoscopically, and may require surgical removal. Surgical removal of bezoars can also be done in patients who fail medical therapy or who have complications such as obstruction or significant bleeding. A small gastrostomy can be done through which gastric bezoars can be removed.

Prevention

Recurrence of bezoars is common unless the underlying predisposing conditions are treated. Patients should also be encouraged to chew food carefully, increase the amount of water intake, avoid the offending foods (i.e., persimmon, raw citrus fruit, and high-fiber food), and to seek psychiatric evaluation if needed (for trichobezoars).

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180 Infantile Hypertrophic Pyloric Stenosis

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Epidemiology

Infantile hypertrophic pyloric stenosis (IHPS) is a functional gastric outlet obstruction secondary to hyperplasia and hypertrophy of the muscular layers of the pylorus. IHPS is recognized as one of the most common surgical conditions in young infants. IHPS is more common in whites than Hispanics, blacks, or Asians. The incidence is 2.4 per 1,000 live births in whites, 1.8 in Hispanics, 0.7 in blacks, and 0.6 in Asians. The male/female ratio is about 4:1.

Pathogenesis

The exact nature of the pathogenic process in IHPS remains uncertain. The etiology is probably multifactorial, with both genetic and environmental factors contributing. No special pattern of inheritance has been identified in IHPS, but a familial incidence is recognized.

IHPS has been reported both in nonidentical male triplets as well as in identical male triplets in a family with no previous history of pyloric stenosis. Such observation supports the view that IHPS is the result of a single main dominant gene with multifactorial background working together. IHPS has been associated with other conditions such as trisomy 18, Turner syndrome, phenylketonuria, and maternal myasthenia gravis.

Associated anomalies have been described in up to 33% of cases of IHPS. The condition has mostly been referred to as a congenital disorder, though IHPS is almost unknown in stillbirths. There is an increasing recognition that IHPS is an acquired and not a congenital disorder. The pyloric muscle measurements at birth are reported within the normal range and subsequently hypertrophies resulting in gastric outlet obstruction.

Clinical Manifestations

IHPS classically presents with projectile nonbilious vomiting in the second or third week after birth. Most are symptomatic within the first 2 months of age. Vomiting, which may be intermittent, occurs usually during or shortly after feeding. The vomiting is typically projectile, with gastric contents expelled sometimes for a distance of several feet. The vomiting may occasionally be blood-tinged. The baby initially remains hungry and sucking vigorously after the episode of vomiting. However, if symptoms persist, the baby will be at risk of developing dehydration and hypochloremic alkalosis with failure to thrive. Infants may also develop hypokalemia.

Physical Examination

On examination, visible waves of peristalsis moving from the left hypochondrium downward and to the right are noted. The skin will lose its normal elasticity and subcutaneous tissue. A palpable tumor is usually felt in the right hypochondrium in between the liver and the rectus abdominis muscle. The examination of the pyloric mass is performed while the baby is being fed, lying on his or her back or in the decubitus position. The latter position has been recognized for many years as a useful method for detecting the olive of IHPS. However, the position that seems to be mostly adopted quite satisfactorily is that while the baby is resting on his or her back fed by the mother or the nurse. This will allow observing the baby, the peristaltic waves, and gentle palpation of the tumor with the tip of middle finger of the left hand. The tumor has no fixed consistency and is usually felt to contract and relax under the examining finger. Palpation of the tumor, which requires patience and experience, is positive in over 80% of cases.

The tumor (mass) is usually firm, smooth, nontender, and the size of an olive. It is best felt after vomiting at the end of or during feeding.

Other associated features include constipation, hyponatremia, hypochloremia, and alkalosis, usually precipitated by repeated vomiting. Few patients develop transient jaundice, which resolves after surgery.

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Diagnosis

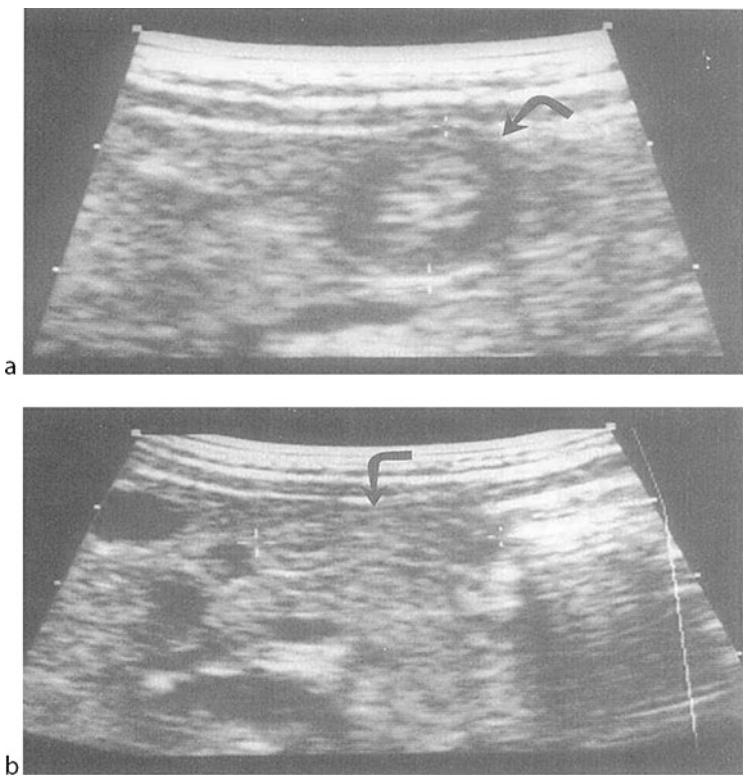
The diagnosis is easily made if the presenting clinical features are typical with projectile vomiting, visible peristalsis, and a palpable pyloric tumor. The loss of hydrogen ions in the vomitus results in metabolic alkalosis with alkaline urine. Secondary hyperaldosteronism leads to retention of sodium and water with excess urinary secretion of potassium. There is usually no need for radiologic investigations once the pyloric tumor is felt on examination. Erect abdominal radiography may show a dilated stomach filled with fluid. Ultrasound examination is considered the diagnostic standard radiologic test to show the elongated hypertrophied pyloric muscle, which is seen as an unechoic mass with strong central echoes (◉ *Fig. 180.1*). The degree of the pyloric hypertrophy tends to be greater the longer the history of the vomiting. It is possible through an ultrasound examination to identify the size of the pyloric mass. The antral region is elongated and thickened to twice its normal size.

Barium studies may have to be performed in a particular case due to lack of supportive findings at examination or through ultrasound examination. The series usually show delayed emptying of the stomach with the demonstration of elongated and narrowed pyloric canal, the *string sign* (◉ *Fig. 180.2*). The barium studies may sometimes show an umbrella-shaped duodenal cap stretched over the pylorus.

Management

Infants with suspected IHPS should be admitted. It is important to have a baseline evaluation of the acid–base status and plasma electrolytes concentration on admission and to correct any present imbalance or fluid deficiency.

The standard surgical procedure for IHPS is pyloromyotomy with an excellent outcome. The Ramstedt pyloromyotomy remains the standard procedure of choice with minimal complications. The usual approach is via



◘ Figure 180.1
(a) Ultrasound scan: hypertrophic pyloric muscle with the characteristic "target sign" of the hypertrophied pyloric muscle (*curved arrow*). (b) Ultrasound, transverse scan, shows elongation of the hypertrophied pyloric muscle (*curved arrow*)

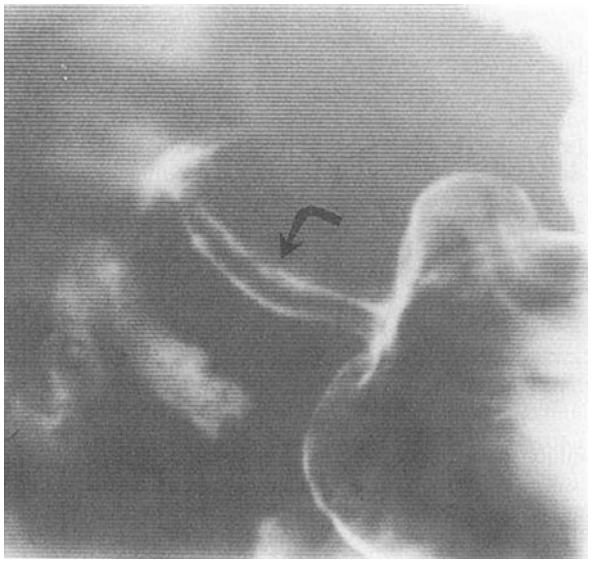


Figure 180.2
Barium meal showing the typically elongated and narrowed pylorus (*curved arrow*) in a 2-month-old infant with IHPS

a right upper quadrant transverse incision that splits the rectus muscle and fascia. Other procedures have been used including: laparoscopic pyloromyotomy, endoscopic pyloromyotomy, and endoscopic balloon dilatation after failed pyloromyotomy. A supraumbilical curvilinear approach has also been used.

Early feeding after surgery is generally recommended. Most patients would have returned to their normal feeding regimen by the second day. Breast-fed infants are usually fed in the first postoperative day. The amounts and duration of feeds are increased gradually. Vomiting will cease after surgery in the majority of cases. Postoperative complications are few. Vomiting may persist for some days after surgery due to pyloric edema, gastroparesis, or pylorospasm. However, if vomiting continues toward the second week, this could well indicate incomplete pyloromyotomy or infection. If symptoms persist for more than 3 weeks after surgery, a second pyloromyotomy is required. Recently, endoscopic balloon dilatation of IHPS after failed pyloromyotomy has been resorted to more often than before.

Nonoperative medical management remains a potential possibility in the management of IHPS. Some patients have responded to oral atropine treatment, especially if it was preceded by intravenous atropine administration until vomiting episodes subside. Further studies are warranted to evaluate the outcome and costs of intravenous atropine medical treatment compared to the standard surgical approach with pyloromyotomy in the management of IHPS.

Prognosis

Resulting mortality and morbidity from IHPS or related complications is extremely low. Very rarely mortality may result from delayed diagnosis and resulting dehydration and shock.

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181 Peptic Ulcer Disease

Mohamed A. El Guindi · Hisham M. Nazer

Peptic ulcer disease (PUD) remains an important clinical problem in medical practice especially among adult population, largely because of the increasingly widespread use of nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin. With advances in fiberoptic endoscopy, there is an increasing awareness that peptic ulcers do occur among infants, children, and adolescents.

Therefore, PUD is diagnosed nowadays with increasing frequency in children. PUD represents a group of disorders associated with ulceration of the gastric and/or duodenal mucosa. The easy application or endoscopy in the pediatric age group and more so in young infants made it possible to confirm such diagnosis of PUD. Males tend to develop duodenal ulcers earlier and commoner than females; however, gastric ulcers occur at the same frequency in males and females. There is also a positive family history of PUD in up to 50% of cases of duodenal ulcer in children.

The prognosis has also improved among affected children due to the availability of effective medications. Duodenal or gastric ulcers represent ulceration of the mucosa that may also extend to affect the submucosa and the muscularis mucosa. PUD in children is classically divided into primary with no known underlying cause and secondary due to varied causes such as stress, diet, infection, burns, ingestion of drugs (aspirin, nonsteroidal anti-inflammatory drugs, corticosteroids), and smoking.

The lesion of peptic ulcer disease (PUD) is mainly caused by a disruption in the mucosa of the stomach or duodenum. An ulcer is characterized by its penetration through the muscularis mucosa or the muscular coating of the gastric or duodenal wall, which is not the case in the superficial gastric erosion. Many differences are noted between children and adults with peptic ulcer disease, especially in clinical presentation, in the prevalence rates of different types of ulcer disease and complications.

As peptic ulcer disease in children is the result of an imbalance between mucosal defensive and aggressive factors, a short account will be given on the stomach anatomy, the epithelial cells, and the innervations before discussing the peptic ulcer disease.

Anatomy of the Stomach

The stomach is a muscular sac that is having a greater and lesser curvature. It connects between the esophagus (by the lower esophageal sphincter) and the duodenum (by the pylorus) (◉ *Fig. 181.1*). The wall of the stomach contains thick vascular folds known as rugae, and at a microscopic level, the surface epithelium can be seen to be invaginated with a series of gastric pits. Each pit opens to a handful of blind-ended gastric glands.

The stomach can also be divided into three major regions by both structure and function.

Structurally: There are the cardia, body, and pylorus.

Most proximally after the esophageal sphincter, the cardia represents approximately 5% of the gastric surface area. It represents a transitional zone where the stratified squamous epithelium of the esophagus gives way to the columnar epithelium that lines the remainder of the stomach and intestinal tract and this is called the *Z-line*.

Next is the fundus or body of the stomach which contains approximately 75% of the gastric glands, and in this region the so-called oxyntic glands consist of specialized cell types (mentioned later) from which arise the characteristic secretions of the stomach.

Finally, the antrum of the stomach just before the pylorus, and is responsible for the secretion of gastrin, the primary regulator of postprandial gastric secretion.

Gastric Cell Types

Functionally: The oxyntic or parietal glands found in the gastric body contain a variety of specific cell types, the parietal, the chief, the endocrine, and the mucus cells. The most important are probably the parietal cells, which are specialized to secrete acid and intrinsic factor.

The parietal cells are remarkable for their secretory capacity and energetic requirements. The capacity for acid secretion in a given individual is directly dependent on the mass of parietal cells. Parietal cell mass is related to body weight, and declines somewhat with age.

More basally in the gland, there are chief cells, which store pepsinogen in apical granules that can release their

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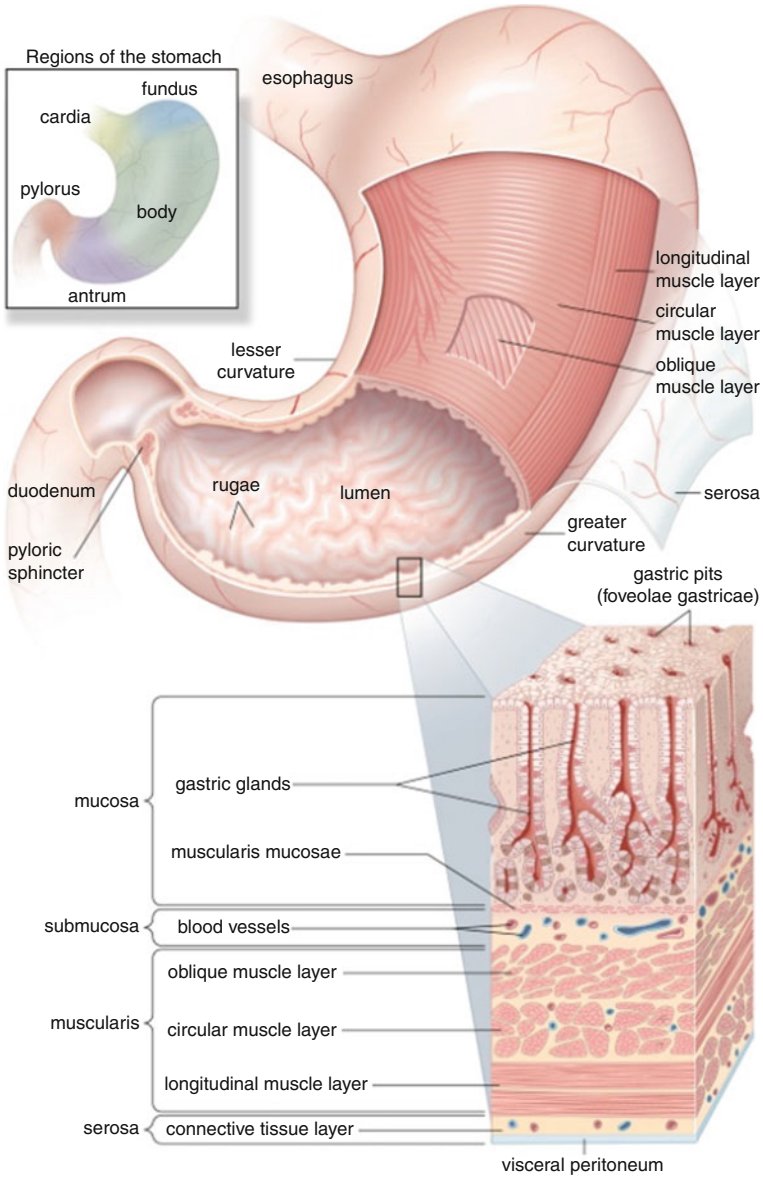


Figure 181.1
A diagram of the stomach structure and stomach wall http://www.britannica.com/EBchecked/topic-art/275485/68634/Structures-of-the-human-stomach-The-stomach-has-three-layer

contents via a process of exocytosis. The glands also contain endocrine cells that are responsible for releasing products that regulate gastric function, particularly the enterochromaffin-like, *or ECL*, cells, that synthesize histamine via the action of the enzyme histidine decarboxylase on the amino acid, histidine.

Toward the top of the gland where it joins with the gastric pit, and moving out onto the gastric surface, the gland contains surface mucous cells that secrete mucus, as their name implies. In the isthmus and neck region of the gland lie the mucus neck cells, which are the precursors for all of the other differentiated cell types in the gland. The anchored stem cells give rise to daughter cells, which migrate downward to become parietal, chief, or endocrine cells, or upward to become surface mucous cells. The surface mucous cells turn over every 1–3 days in adult humans.

In the antral mucosa, the glands do not contain parietal or chief cells, but mainly contains both mucus-secreting cells and enteroendocrine cells that regulate gastric function. Particularly, the glands contain G cells, which synthesize and release gastrin across their basolateral poles, and which have an open morphology implying functionally significant communication with the gastric lumen. Endocrine cells are present, exemplified by D cells, which secrete somatostatin.

Innervation

Nerves carried through the parasympathetic vagus nerve, with both efferent and afferent pathways, richly innervate the stomach. Vagal afferents convey information from the dorsal vagal complex, which is integrated with that coming from higher centers, such as the hypothalamus, to set the overall level of secretory function at any given moment. Visceral inputs also contribute to gastric regulation. Notably, the output of taste receptors travels to a brain region called the nucleus tractus solitarius, where this information is again translated into signals that regulate secretion and other gastric functions.

A more modest amount of sympathetic innervation is also seen, and activation of sympathetic nerves tends to oppose the actions of the parasympathetic limb. Finally, the enteric nerve plexuses that are seen throughout the gastrointestinal tract encircle the walls of the stomach. These allow for some degree of autonomous function, in addition to transmitting effects of central input.

Peptic Ulcer Disease

Primary peptic ulcers are still relatively uncommon in children and account for roughly 1 in 2,500 pediatric hospital admissions. Peptic ulcers can be either primary or secondary. Primary ulcers are more common in adolescents than in children and tend to recur after initial healing. Although affected children are thought to have high acid secretion, this has not been proven. Many of the primary ulcers seen in teenagers are now thought to be associated with gram-negative, spiral-shaped organisms recognized nowadays as *Helicobacter pylori*.

Genetic influences play a role because there is usually a family history of duodenal ulcers among first-degree relatives. The risk of ulcer is increased among siblings of affected parents, among monozygotic and dizygotic twins, and in individuals with the O blood group and HLA-B5 phenotype. The excess in acid output does not necessarily correlate with the severity of the disease. Moreover, PUD affects children with emotional problems more than their counterpart. The likely primary ulcers in young children are gastric, and in older children (>10 years) are likely to be duodenal.

Secondary peptic ulcers, usually silent, account for the overwhelming majority of ulcers that occur in young children in association with either systemic illnesses or drugs. Secondary peptic ulcers are seen in head trauma, severe burns, and with use of corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs).

Demographic Studies

In the United States, the prevalence of *H. pylori* infection is higher in blacks and Hispanics than in whites not of Hispanic origin.

The male-to-female ratio for all childhood peptic ulcer disease is 1.5:1. The incidence of primary peptic ulcer disease is twofold to threefold higher in boys than in girls; however, no sex difference in the incidence of primary peptic ulcer disease has been noted in infants or young children.

Primary peptic ulcer disease is uncommon in infants and in children younger than 10 years. The prevalence of primary peptic ulcer disease increases during adolescence. Secondary peptic ulcer disease can affect patients of all ages, but its prevalence is increased in patients younger than 6 years.

Frequency

The prevalence of *H. pylori* infection in developing countries is as high as 50–100%. The prevalence of peptic ulcer disease is increasing in developing countries. In a retrospective review of 112 Taiwanese children undergoing upper GI endoscopy for upper GI bleeding, gastric ulcer was confirmed in 10% and duodenal ulcer was confirmed in 15%.

Pathophysiology

Peptic ulcer disease in children is the result of an imbalance between mucosal defensive and aggressive factors. The aggressive factors consist of peptic activity that originates from enzymes within the gastric mucosa known as pepsinogen I and II. Pepsinogen I is the major pepsinogen produced by the chief and mucus neck cells of the gastric

fundus and body. The pepsinogen I level is therefore high in duodenal ulcer and gastrinoma.

Pepsinogen II is produced in the antrum, pylorus, and Brunner glands of the duodenum. It is elevated in antral gastritis. All agents that stimulate acid secretion result also in stimulation of pepsin secretion. A physiochemical defense barrier provides cytoprotection of the gastric mucosa. This barrier consists of water-insoluble gastric mucus, gastrically produced bicarbonate, an unstirred water layer, phospholipids, rapid shedding of cells resulting from epidermal growth factor, normal mucosal blood flow, prostaglandin-stimulated bicarbonate, mucus production, and inhibited acid secretion.

The aggressive factors which causes mucosal inflammation and ulceration include endogenous factors, such as gastric acidity (approximates adult values by age 3–4 years), acid-dependent pepsin and mucosal ischemia, and exogenous factors, such as drugs (e.g., NSAIDs, aspirin, corticosteroids), alcohol, cigarette smoking, corrosive chemicals (e.g., lye), and emotional stress.

Causes of patients stress include severe injuries, burns, sepsis, cardiac or respiratory failure, or any other critical systemic illnesses. Other factors that can cause ulcerations include ischemia, increased gastric acid and pepsin production, higher levels of steroids, and decreased prostaglandins and mucus production. Important mediators of mucosal inflammation and resultant ulceration include oxygen free radicals, lymphokines, platelet-activating factors, tumor necrosis factor, leukotrienes, and monokines.

Peptic ulcer disease can be divided into two major categories as mentioned earlier, primary and secondary.

Primary Peptic Ulcer

The primary category includes those few chronic disorders mainly due to *H. Pylori*. Secondary ulceration, which may be gastric or duodenal, occurs in association with acute severe stress.

The gram-negative spirochete, *H. pylori*, was first linked to gastritis in 1983. Since then, further study of *H. pylori* has revealed that it is a major part of the triad, which includes acid and pepsin, and impaired duodenal bicarbonate secretion causing the primary peptic ulcer disease. The unique microbiologic characteristics of this organism, such as the urease catalase, vacuolating cytotoxin, and lipopolysaccharide production, which alkalinize its microenvironment and survive for years in the severe acidic environment of the stomach, leading to inflammation and ulceration.

H. pylori infection in areas of gastric metaplasia induces duodenitis and enhances the susceptibility to acid injury, thereby predisposing to duodenal ulcers. One study that followed 181 patients with endoscopy-negative, nonulcer dyspepsia found that duodenal colonization by *H. pylori* was a highly significant predictor of subsequent development of duodenal ulcers.

The Zollinger–Ellison syndrome (ZES) is a rare disorder that can cause gastric or duodenal ulcers (◉ *Fig. 181.2*) from excessive acid secretion. Consider ZES if a patient has severe peptic ulceration, kidney stones, watery diarrhea, or malabsorption. ZES can also be associated with multiple endocrine neoplasias type I, which occurs earlier than isolated ZES. In addition to the typical pancreatic gastrinomas, ZES has been reported in children with solitary extrapancreatic gastrinomas in the stomach, liver, and kidney. Compared with adult disease, malignant gastrinomas in children are slow growing. Patients with ZES usually have fasting serum gastrin levels of more than 200 pg/mL and basal gastric acid hypersecretion at more than 15 mEq/h. Protein pump inhibitor therapy should be discontinued at least 2 weeks before the gastrin level is measured.

Secondary Peptic Ulcer

PUD may develop secondary to a variety of disorders. Secondary ulcers are often silent and may be diagnosed

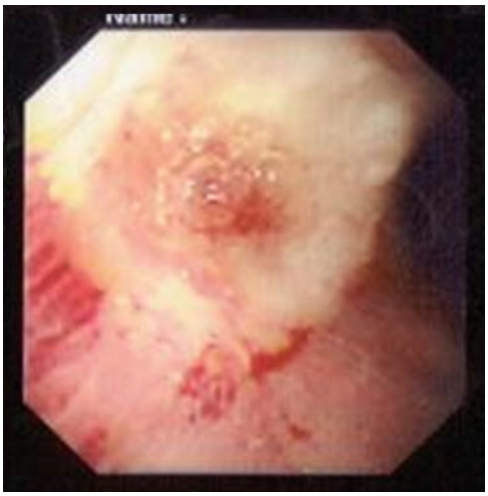


Figure 181.2
Endoscopic view of a peptic ulcer in a young infant with Zollinger–Ellison syndrome (Dr. Hisham Nazer)

at endoscopy for other symptoms or due to acute presentation with complications such as bleeding and shock. Patients with cystic fibrosis are prone to develop duodenal ulcers because their pancreatic secretion is deficient in bicarbonate. Other recognized causes that may result in the development of ulcers include drugs (corticosteroids, nonsteroidal anti-inflammatory drugs, tolazoline), cigarette smoking, and stress. Increased incidence of PUD is also recognized as a result of many clinical conditions such as cirrhosis of the liver. Hypergastrinemia, polycythemia vera, Crohn's disease, diabetes mellitus, and chronic pancreatitis.

Children with secondary gastric or duodenal PUD do not commonly suffer from recurrent disease. In severely ill children with secondary duodenal ulcer, there is a high complication rate, particularly from bowel perforation.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with the development of secondary ulcers. Gastric erosions and peptic ulcers have been reported in association with aspirin, indomethacin, naproxen, and many other such medications. Aspirin inhibits the production of protective prostaglandins and increases the production of inflammatory mediators. NSAIDs have both local and systemic effects on the gastric mucosa. Treatment includes the administration of antacids alone or in combination with H2-receptor antagonists. The causative agent should also, when possible be stopped and replaced by a less irritating agent.

Stress-related ulcers are seen usually in life-threatening illnesses, intracranial lesions, severe dehydration, burns, vasculitis, or renal failure. Stress-related ulcers account for 80% of secondary peptic ulceration seen in infants and children. They result from ischemia, disruption of the mucosal barrier, and increased gastric acid. Prevention is an important step in the management of such ulcers. However, H2 antagonists are used as therapeutic measures as well as prophylaxis in those patients prone to develop stress-related ulcers. Sucralfate has also been used with good results.

Clinical Presentations

PUD in childhood has a variable and often nonspecific clinical presentation that varies with age. The well-recognized manifestations of recurrent epigastric abdominal pain, vomiting, hematemesis, and melena are not usually present in young infants or neonates with PUD. There is usually a family history of such disorders.

In the pediatric age group, abdominal pain related to meals is the most common presenting symptom of peptic ulcer disease. Nevertheless, peptic disorders (oesophagitis, gastritis, gastropathy and duodenitis), account for fewer than 5% of children presenting with abdominal pain, even in a subspeciality practice.

Other presenting symptoms include anorexia, nausea, vomiting, fullness, and anemia. Gastrointestinal bleeding may occur with the epigastric pain or with other symptoms, but painless bleeding may be the only manifestation of ulcer disease.

Up to 25% of children with duodenal ulcers have this "silent" presentation, approximately 25% presenting with bleeding and antecedent pain, and the rest with abdominal pain or recurrent vomiting.

On physical examination, epigastric tenderness is an unreliable sign of gastritis or ulcer disease.

It is only with a high index of suspicion that PUD in young infants and neonates may be diagnosed early to avoid late presentation with its serious sequel.

Complications

Since the introduction of H2 receptor antagonist and proton pump inhibitor, and with the recognition and treatment of *H. pylori*, the incidence of bleeding, perforation, and gastric outflow obstruction has dramatically decreased.

Severe GI bleeding is one of the most common complications of ulcer disease in neonates occurring in both primary and secondary peptic ulcer disease. GI blood loss may be acute and catastrophic, particularly in neonates or in children with a critical medical illness or traumatic injuries, or it may have a slow and chronic course, without posing a serious threat to life.

Perforation of an ulcer is the second main complication in early infancy and is often preceded by or associated with GI hemorrhage.

Children with primary gastritis or duodenal ulcer disease have low mortality rates. The highest mortality rates are found in young infants with secondary stress ulcers, who may present acutely with life-threatening GI hemorrhage or intestinal perforation. Mortality rates from perforated peptic ulcers in adolescent are 3.8%.

Management

Diagnosis

The diagnosis of PUD is highly suspected by the associated clinical features or epigastric pain, sometimes related to

meals, but occasionally as a result of acute presentation with a recognized complication as bleeding and shock. Family history as well as drug history or other relevant information add further to support the diagnosis of PUD. However, PUD should be differentiated from other conditions associated with abdominal pain such as esophagitis, cholecystitis, pancreatitis, pyelonephritis, and giardiasis.

Any child with recurrent vomiting and chronic abdominal pain (more than a month) should be investigated to rule out the presence of PUD. Examination may reveal epigastric abdominal pain.

Stool is occasionally positive for blood (guaiac-positive). Endoscopy has made the diagnosis of PUD possible with the least effort and with a high rate of accuracy. Endoscopy is superior to radiologic examination which is unable to reveal small superficial ulcers. Contrast studies may fail to show ulcers in up to one third of cases. Endoscopy was reported to be diagnostic of ulcers in around 90% of cases while reports have indicated that radiology may miss up to 50% of cases.

Single-contrast barium meals may reveal the presence of peptic ulcer, but its contribution to confirmed diagnosis is far less than that provided by endoscopy (◉ *Fig. 181.3*). However, the role of radiology should not be underestimated in the detection of any other associated gastrointestinal anomalies that might have predisposed to some of the clinical manifestations such as hiatal hernia, malrotation, and duodenal bands. In elder children, the diagnostic yield of radiology in PUD may be improved up to 90% by the application of air-contrast study.

Upper gastrointestinal endoscopy is the current diagnostic tool and will reveal the presence of ulcers as circumscribed mucosal defects that extend beyond the muscularis mucosa with a diameter of 5 mm or more (◉ *Fig. 181.4*). Smaller and more superficial lesions (erosions) that disrupt the epithelium may also be detected on endoscopy.

Endoscopic biopsies remain the most accurate means of diagnosis. *H. pylori* has been identified in cultures from antral and/or duodenal tissue in up to 80% of children with duodenal ulcer and antritis. Several kits for rapid diagnosis of *H. pylori* are available based on the use of urea-impregnated agar. Means of diagnosis of *H. pylori* infection include culture, rapid urease test, C-urea breath testing, and serologic assay. The C-urea breath test has been shown to be highly sensitive and specific in diagnosing *H. pylori* infection in children.

Screening for the serum IgG antibody to *H. pylori* is a practical method for diagnosing *H. pylori* infection in children. Serial measurement of the *H. pylori* IgG antibody is also useful in monitoring treatment of *H. pylori*.

Breath testing is now considered to be the best non-invasive assay for evaluating successful eradication of *H. pylori*. The accuracy of the C-urea breath test in diagnosing *H. pylori* has been recently demonstrated by Delvin et al. If endoscopy is performed on a child with abdominal pain and PUD, biopsies of normal-appearing

Figure 181.3
Barium meal and follow-up in 9-year-old boy reveal an active ulcer in duodenal cap (*arrow*)

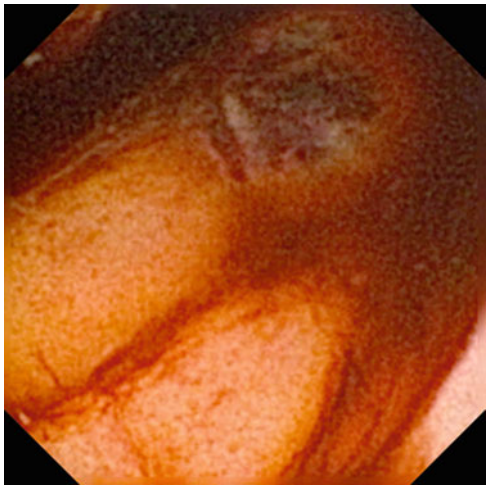


Figure 181.4
Peptic ulcer as seen by endoscopy in a 9-year-old girl (Mohamed El Guindi 2009)

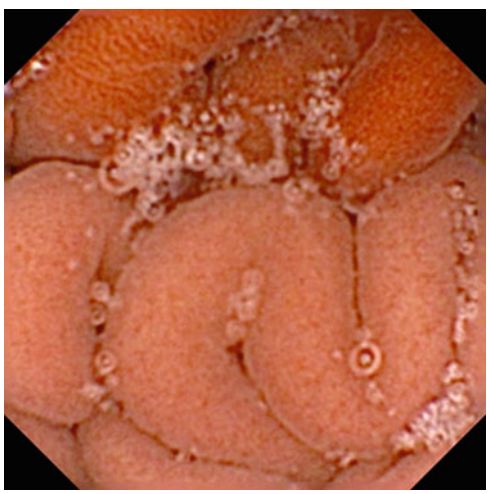
areas of gastric antrum should be stained for *H. pylori* and a biopsy urease test should be done. The increasing recognition of the association of PUD, gastritis, and *H. pylori* colonization of the gastric mucosa has resulted in the availability of more tests to diagnose *H. pylori* PUD related in children. The use of an enzyme-linked immunosorbent assay (ELISA) to test for serum *H. pylori* antibodies has provided clinicians with a simple, reliable, and noninvasive tool to diagnose *H. pylori* infection. An ELISA test may also be used in seroepidemiologic surveys. A recent report on the evaluation of the ELISA test in the diagnosis of *H. pylori* infection was published by de Oliveira et al. in 1999.

The absence of endoscopic abnormalities in some 50% of children with *H. pylori* infection, and the patchy nature of the infection and of gastric mucosa-associated lymphoid tumor (MALT) lymphomas, emphasizes the need to take biopsies from the gastric antrum, body, and cardia as an integral part of diagnostic endoscopy.

Capsule endoscopy is the breakthrough for children refusing to undergo endoscopy and can reveal with accuracy the peptic ulcers (◉ *Fig. 181.5*)

Medical Therapy

All current recommendations support eradication therapy in all children with symptomatic peptic ulcers and proven *H. pylori* infection. The benefits of eradication therapy in children without ulcers or asymptomatic who have gastritis alone are uncertain. Eradication therapy has also been suggested for children with MALT lymphoma, atrophic gastritis, and *H. pylori* with a family history of gastric adenocarcinoma. Eradication therapy could be considered as an option in children with *H. pylori* infection who also have refractory iron-deficiency anemia or autoimmune thrombocytopenic purpura because complete or partial responses are seen in approximately one half of cases.



◘ Figure 181.5
Gastritis and early ulceration as seen by capsule endoscopy in a 12-year-old boy (Mohamed El Guindi 2009)

Drugs used to treat *H. pylori* peptic ulcers are mainly antibiotics, H2 blockers, and proton pump inhibitors.
Antibiotics include metronidazole, clarithromycin, and amoxicillin.
H2 blockers include cimetidine, ranitidine, famotidine, and nizatidine.
Proton pump inhibitors include omeprazole, lansoprazole, rabeprazole, esomeprazole, and pantoprozole.

Several combinations of the above therapeutic agents are recommended. The best success rates are achieved with triple therapy, combining proton pump inhibitors such as omeprazole with two antibiotics (clarithromycin and amoxicillin or metronidazole) for 1–2 weeks: The scheme proton pump inhibitor/amoxicillin/clarithromycin (PPI/AC) is still the first-line treatment for *H. pylori* infections despite evidence suggesting its failure in up to 20–30% of patients.

13C Breath Test is reliable in confirming successful eradication of *H. pylori* infection and should be performed if available at least 4 weeks after completion of therapy. In case of acquired resistance to clarithromycin (up to 45% of *H. pylori* isolates in children) and, to a lesser extent, resistance to metronidazole, an alternative triple-therapy regimen should be used, substituting one or both of the antibiotics. Metronidazole dose of 20 mg/kg/day (maximum 200 mg three times a day) and clarithromycin at a dose of 15 mg/kg/day, maximum 250 mg twice a day are used in children.

Efficacy was determined by negative urease test and absence of *H. pylori* on gastric biopsy samples 12 weeks after the end of treatment.

Acid-suppressing medications, such as H2 blockers, proton pump inhibitors, and mucosal protectants (e.g., sucralfate) are also used in cases of primary and secondary peptic ulcers. Offending substances (e.g., aspirin, NSAIDs, corticosteroids, nicotine, alcohol) should be stopped.

Surgical Therapy

Operation is indicated when blood loss approaches half the blood volume in 8 h or 1 blood volume in 24 h.

With fluid resuscitation and blood transfusions, monitoring for signs of continuous bleeding or hypovolemia is essential. If the rate of bleeding allows the stomach to be lavaged for endoscopy, endoscopic cautery or injection of sclerosants or vasoconstrictors may control the bleeding and prevent further bleeding episodes. If failed, simple oversewing of the ulcer followed by medical therapy is sufficient treatment; resection is seldom required.

Cases of Zollinger–Ellison syndrome can be cured when the gastrinoma is removed. Even with incomplete removal, the use of proton pump inhibitors controls the disease.

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182 Intestine: Normal Development, Structure and Function

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Introduction

The small and large intestine occupies most of the abdominal cavity and is responsible for digestion, secretion, and absorption of nutrients, including fluid and electrolyte transport, excretion, physical and immunological defense mechanism. The mucosal surface of the small intestine is anatomically and physiologically designed to provide extensive surface area for nutrient absorption. This remarkable adaptation also provides massive interface for possible antigenic interaction with the environment. This interface is modulated via the immuno-endocrine system and the enteric nervous system.

This chapter focuses on embryology, anatomy, and physiology of small and large intestine.

Embryology

The primitive gut is recognizable by the fourth week of gestation and is composed of foregut, midgut, and hindgut. The foregut gives rise to the upper gastrointestinal tract including esophagus, stomach, and duodenum up to the insertion of the common bile duct. The midgut gives rise to the rest of the small bowel and large bowel up to the mid-transverse colon. The hindgut forms the remainder of the colon and upper anal canal. The rapid growth of the midgut causes it to protrude out of the abdominal cavity through the umbilical ring during fetal development. The midgut subsequently returns to the peritoneal cavity and rotates counterclockwise until the cecum lies in the right lower quadrant. The process is normally complete by the eighth week of gestation. The contraction of the muscles in the bowel wall is regulated by the enteric nervous system under the influence of the paracrine system. The enteric nervous system is derived from the neural crest cells that migrate in a cranial to caudal fashion. Migration of the neural crest tissue is complete by the 24th week of gestation. Interruption of the migration results in Hirschsprung disease. Normal fasting upper gastrointestinal motility is characterized by a triphasic pattern known as the migrating motor complex. Migrating motor complex occurs less often in neonates and they have more nonmigrating phasic activity. This leads to ineffective propulsion particularly in premature infants. Motility in the fed state consists of a series of ring contractions that spreads caudally.

Small Intestine

The small intestine is a convoluted tubular organ, extending from the pylorus to the ileocecal valve. The average length of the small intestine is between 250 and 300 cm in the term newborn, increasing to as much as 600–800 cm in the adult. The caliber of the small intestine gradually diminishes from its origin to its terminal end.

The duodenum is derived from the distal foregut during embryologic development. It is partly retroperitoneal. The duodenum is arbitrarily divided into four portions. The fourth portion makes a ventral turn to unite with the jejunum at DJ flexure. The biliary and pancreatic ducts drain into the second portion of duodenum at the ampulla of Vater. In 5–10% of individuals, an accessory pancreatic duct also enters 1–2 cm proximal to the ampulla of Vater as the duct of Santorini.

The duodenum receives its arterial supply from the right gastric, supra-duodenal, right gastro epiploic, superior and inferior pancreaticoduodenal arteries. The jejunal and ileal branches of superior mesenteric arteries form an arterial arcade that comes through the mesentery to supply the ileum and jejunum. The main venous drainage is superior mesenteric and portal veins. Lymphatic drainage is to the thoracic duct via the para-aortic lymph nodes. The terminal ileum lymphatic drainage is to the ileocolic lymph nodes.

The jejunum and ileum are derived from the endodermal midgut. There is no distinct demarcation between them although the proximal jejunum is thicker and more vascular than the ileum. The luminal diameter is greatest

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in the jejunum reducing in caliber distally in the ileum. Lastly, the plicae circularis (Kerck rings on endoscopy) which are more prominent in the distal duodenum and jejunum also decrease in number progressively in the ileum. The small intestine is a lymphoid organ. The Payer's patches are lymphoid aggregates located along the ante-mesenteric border in the most abundant region of mid to terminal ileum.

The junction of the small intestine with the large intestine is referred to as the ileocecal valve because the end of the terminal ileum is wedged into the wall of the cecum and functions like a flutter valve. The ileocecal valve is open when a peristaltic valve is strong enough to overcome the resistance of the valve that arrives at the terminal ileum. Overdistension or peristaltic contraction of cecum causes reflex contraction of ileocecal valve thus acting as protective mechanism to prevent bacterial influx into ileum. Therefore during colonoscopy, intubation of the terminal ileum may be difficult if the cecum is over distended with air.

The jejunum and ileum with the exception of the terminal ileum are loosely suspended from the posterior abdominal wall by the mesentery, thereby enabling each coil of small intestine to accommodate easily to changes in form and position with propulsive peristaltic movements. The mesentery is attached to the posterior abdominal wall extending from the left side of the body of the lumbar vertebrae to the right sacro iliac joint.

Intestinal Structure and Cellular Morphology

The small intestine is made up of four layers from outside inwardly. These consist of serosa, muscularis propria, submucosa, and mucosa. The mucosa is subdivided into muscularis mucosa and lamina propria and epithelial cell layer.

There are two major ganglionated enteric nervous system plexi embedded within the wall of the intestines. The submucosal (Meissner's) plexus and the myenteric (Auerbach's) plexus. The myenteric plexus is located in the plane between longitudinal and circular layers of the muscularis. The submucosal and myenteric plexus are extensively interconnected by nerve bundles. Interstitial cells of Cajal, present within the myenteric plexus at the interface between circular muscle and submucosa are now recognized as pacemakers of intestinal contractile activity which regulate intestinal tone and motility. Brunner's glands are located almost exclusively in the submucosa of the duodenum. They secrete a layer of mucus that lubricates the mucosal lining of the proximal intestinal tract.

The luminal surface of small intestine is covered by millions of tiny hair-like, highly vascularized structures called villi which are covered by mature absorptive enterocytes. The crypt of Lieberkühn surround the base of the villi and are lined by less mature epithelial cells. The luminal surface is studded with densely packed finger-like cylindrical projections termed microvilli. The apical surfaces of the intestinal epithelial cells carry multiple brush border transporters that couple ionic influxes or exchange one ion for another. Contiguous enterocytes are tightly opposed at their apico-lateral poles by the formation of junctional complexes. Tight junction is leakier and has a low resistance in the proximal intestine where absorption is more efficient, and tighter with a higher resistance in the ileum and large intestine. Goblet cells are mucin-producing cells scattered among other cells of the intestinal villi. The mucin provides a protective lubricant barrier against shearing stress and shields the intestinal mucosa from peptic digestion and chemical damage.

The gastrointestinal tract is a lymphoid organ and the lymphoid tissues are collectively called gut-associated lymphoid tissue or GALT. Payer's patches are lymphoid tissues present mainly in ileum. The epithelial cells overlying the Peyer's patches are columnar epithelial cells, Paneth cells, and structurally distinct membranous cells (M cells). M cells are responsible for transepithelial transport, delivering foreign antigens and microorganisms to the mucosal lymphoid tissue for recognition and handling, an attribute currently being exploited in vaccine production.

The growth and integrity of the intestinal mucosa are maintained under the influence of digested food and several luminal factors such as autocrine, endocrine, and paracrine secretion from surrounding cells. Thus, enteral nutrition is essential for the well-being of intestinal mucosa. It is now evident that glucagon-like peptides secreted from entero-endocrine cells play a major cytoprotective and reparative role in the survival and proliferation of the intestinal mucosa. The glucagon-like peptides, GLP1, and GLP-2 are released from entero-endocrine cells in response to nutrient ingestion. GLP-1 enhances glucose-stimulated insulin secretion, gastric emptying and feeding. It also has proliferative and anti-apoptotic effects on pancreatic B cells. GLP-2 stimulates proliferation and inhibits apoptosis in intestinal crypts. GLP-2 also regulates intestinal glucose transport and glucose transporter (GLVT) 2 expression as well as food intake and gastric acid secretion, gastric motility, and intestinal barrier function. GLP-2 also enhances nutrient absorption and gut adaptation in rodents or human with short gut syndrome.

Physiology of Absorption and Secretion

Absorption and secretion are the main functions of the intestine. Both the small intestine and large intestine absorb and secrete fluid and electrolytes whereas only the small intestine absorbs nutrients. Only during the neonatal period does significant absorption of nutrients takes place in the large intestine. After that, intestinal absorption occurs exclusively in the small intestine. Fluid secretion may be considered an adaptive mechanism used by the intestinal tract to protect itself from bacteria and bacterial toxins.

The small intestine absorbs net amounts of water, Na^+, Cl^-, K^+ and secretes HCO_3 whereas the colon absorbs net amounts of water, Na^+, and Cl^- and secretes both K^+ and HCO_3^-. Solvent drag is the process by which dissolved solute is swept along by bulk movement of the solvent. Solvent drag accounts for significant fraction of Na^+ and urea absorbed in human jejunum. Solvent drag occurs through a paracellular route and depends on the permeability properties of tight junctions. Na/Glucose and Na/Amino acid cotransport in the small intestine is the major mechanism for post-prandial sodium absorption. Electroneutral Na-H Exchange in the duodenum and jejunum is responsible for sodium absorption that is stimulated by luminal alkalinity. Parallel Na-H and Cl-HCO_3 exchange in the ileum and proximal part of the colon is the primary mechanism of Na^+ absorption during the interdigestive period. Epithelial Na^+ channels are the primary mechanisms of electrogenic Na^+ absorption in the distal part of the colon.

The intestines absorb and secrete solutes by both active and passive mechanisms. K^+ absorption in the small intestine occurs probably through solvent drag. Passive K^+ secretion is the primary mechanism of net colonic secretion. Active K^+ secretion is also present throughout the large intestine and is induced both by aldosterone and by cAMP. Voltage-dependent Cl^- absorption represents coupling of Cl^- absorption to electrogenic Na^+ absorption in both the small intestine and the large intestine.

The overall electroneutral NaCl absorptive process is regulated by both cAMP and cGMP as well as by intracellular Ca2+. Increase in each of these messengers decreases NaCl absorption as in acute diarrhea where *E. coli* enterotoxin activates adenylcylase, increases cAMP which decreases NaCl absorption, and stimulates active Cl^- secretion. This toxin does not affect nutrient coupled Na+ absorption. By using this process, oral rehydration solution which contains glucose, Na^+, Cl^-, HCO_3 is extremely effective in enhancing fluid and electrolyte absorption in secretory diarrhea. The congenital absence of an apical Cl-HCO3 exchanger is an autosomal recessive disorder congenital chloridorrhea which is an autosomal recessive mutation on chromosome 7.

Digestive Process in the Intestine

Luminal Digestion

The majority of starch digestion occurs in the duodenum through the effect of pancreatic amylase. α amylase is an endoenzyme that cleaves the alpha 1,4 internal links leaving oligosaccharides maltose and maltriose. Since α amylase does not cleave α 1,6 or adjacent alpha 1,4 bonds, digestion of amylopectin also leaves branched oligosaccharides termed α limit dextrins. Amylase activity produces only small amounts of free glucose molecules. Therefore, only severe pancreatic insufficiency that leaves less than 10% normal amylase levels affect starch breakdown.

Brush Border Digestion

Only monosaccharides can be absorbed across the enterocyte membrane. Therefore, further digestion of the luminal products of starch and ingested disaccharides takes place at the brush border by different hydrolases like maltase, isomaltase, and sucrase. Lactase breaks down lactose into glucose and galactose. The human lactose gene is located on the long arm of chromosome 2. Lactose digestion in the premature neonate maybe incomplete in the small intestine but partially salvaged through colonic fermentation. Lactase level declines from peak at birth to less than 10% of the preweaning infantile level in childhood as dietary consumption falls. With the exception of lactase where enzyme activity is the rate-limiting step for digestion, brush border hydrolases are inducible by the presence of substrate.

Transport After Digestion

Monosaccharides cross the enterocyte apical membrane via carrier-mediated transport since their size is too large to allow for significant passive diffusion. For glucose and galactose, cotransport with sodium down a sodium gradient takes place. Fructose is transported through facilitated diffusion. All monosaccharides exit the enterocyte by facilitated diffusion across the basolateral membrane into portal circulation. Approximately 10% of ingested starch is not digested in the small intestine and is called digestion resistant starch.

Protein Digestion

The main protein digestion site is the proximal small intestine upon exposure to the pancreatic fluid. Pancreatic proteases are secreted as proenzymes. Although the mediators of pancreatic stimulation are incompletely understood, the cholinergic intestinal system appears to have greater influence than cholecystokinin for pancreozymes while secretin mainly promotes bicarbonate flow. Absorption of aminoacids is maximal in the proximal intestine and occurs by active diffusion aided by Na^+ cotransport.

Fat Digestion

Bile acids and biliary phospholipids further stabilize the lipids presented to pancreatic lipase in the duodenum. Ileal bile acid absorption involves Na^+ cotransport down a gradient secured by the basolateral membrane Na^+, K^+ ATPase. Bacterial enzymatic action in the terminal ileum leads to deconjugation of bile acids that escape ileal absorption.

The next step is transport of the hydrophobic digestion products, carried in water-stable micelles from small intestine lumen into brush border membrane. Monoglycerides, fatty acids, cholesterol, and lyophospholipids can pass through the enterocyte membrane by passive diffusion. Once in the enterocyte, triglycerides are resynthesized from 2-mono acyl glycerol and fatty acid as a result of two processes, namely, monoglyceride acylation and phosphatidic pathway. Chylomicrons are made only in the intestinal cells while VLDLs are also synthesized in the liver. Chylomicrons and VLDL exit the enterocytes into the lacteal system. Medium chain triglycerides move directly into the portal system.

Vitamin B_{12} is absorbed in the terminal ileum and therefore children with distal bowel resection may need lifelong supplementation. Vitamin C is absorbed from proximal small intestine. Absorption of Vitamin D occurs mainly in the upper and mid small intestine. Vitamin A, E, and K also absorbed in small intestine. Iron and calcium is absorbed actively from the duodenum. Zinc, copper

Anatomy of Large Intestine

The large intestine consists of the following segments: (1) cecum and vermiform appendix; (2) colon which is composed of four sections – ascending, transverse, descending, and sigmoid colon; (3) rectum; and (4) anal canal. The colon is approximately 60 cm long in the newborn, increasing to approximately 150 cm in the adult.

The colon is easily distinguished from the small intestine by several features, namely, it is larger in caliber and mostly fixed in position. Its outer longitudinal muscular layer is made of three distinct longitudinal bands or taenia coli extending from cecum to the rectum. It has a characterized sacculated and puckered appearance due to outpouchings (termed haustra) of its walls between the longitudinal bands. Fatty projections of the mesentery and the serosa are found scattered over the free surface of the entire length of the colon with the exception of the cecum, vermiform appendix, and rectum. The luminal surface is interrupted by intermittent irregular folds called plicae semilunares.

Originating from the midgut, the proximal colon, cecum, ascending colon, and proximal two thirds of the transverse colon all derive the blood supply from the superior mesenteric artery. The inferior mesenteric artery supplies the remaining one third of the transverse colon, descending colon, sigmoid colon, and rectum. In addition, the rectum and anal canal also receive blood supply from internal iliac and median sacral arteries. The superior and inferior mesenteric veins drain the same regions of the large intestine supplied by the corresponding arteries.

With the exception of the lower half of the anal canal the large intestine derives its nervous supply from parasympathetic and sympathetic systems. The nerve distribution pattern closely mimics the arterial supply. The proximal colon receives its sympathetic neuronal innervation from celiac and superior mesenteric ganglia, whereas the parasympathetic supply is from the vagus nerve. The distal colon receives its sympathetic nerve supply via branches from lumbar segments of the sympathetic trunk and the parasympathetic nerves originate from the pelvic splanchnic nerves. The lymphatic drainage courses through the mesentery close to the arterial and venous supplies. The lymph from the colon drains into the preaortic nodes. The lymph from the rectum and anal canal drains to the inferior mesenteric and iliac nodes via the perirectal nodes.

The cecum commences as a pouch cul-de-sac in the right iliac fossa and continues superiorly with the ascending colon. The ileocecal valve opens into the posteriomedial wall of the cecum. The appendiceal orifice lies 2.5 cm inferior to the ileocecal valve. Vermiform appendix describes the worm-like elongated shape of the appendix. The appendix may vary in position either present below the distal cecal pouch or behind the cecum posterior to the ileum in a retroperitoneal location. The

appendix once regarded as a vestigial organ, is now recognized as an important component of mucosal immune system, particularly B lymphocyte-mediated immune response and extrathymically derived T lymphocytes.

The ascending colon originates at the level of ileocecal valve and ascends to the posterior surface of the liver where it angulates to form the hepatic flexure. It measures 20 cm in adults. The ascending colon merges from its retroperitoneal position anteriorly and medially to become the transverse colon which is approximately 40–50 cm. It is fully enveloped by mesentery (transverse mesocolon) and curves acutely on itself to form the splenic flexure. A thickened reflection of the peritoneum called phrenico-colic ligament suspends the splenic flexure higher than the hepatic flexure. The descending colon emerges from the splenic flexure continuing downward and posteriorly to join the sigmoid colon at the pelvic brim. The rectum extends from the sigmoid colon at the level of the third sacral vertebra following the sacral curvature to the anal canal distally. The anal canal begins where the distal end of the rectal ampulla narrows and passes inferiorly and outward to the anal opening. The anal canal is 2 cm long in the infant increasing to 4.5 cm in the adult. The anorectal junction is situated within the pelvic diaphragm which is made up of levator ani and coccygeus muscle. The segment of the levator ani sling that encircles the anorectal junction is termed the puborectalis muscle. The contraction of this muscle pulls the rectum forward to retain stool and relaxation straightens the anal canal allowing defecation. Commencing at the anorectal junction the circular muscle layer of the large intestine thickens to become the internal anal sphincter which is made up of smooth muscle fibers and surrounds the upper three-quarters of the anal canal. The external anal sphincter is made up of striated muscle. The luminal surface of the anal canal is thrown into longitudinal folds termed anal columns. These columns converge distally to form small crescenteric folds of tissue termed anal valves at the pectinate line. Beyond the pectinate line, the epithelial cell layer of the anal canal transitions from cuboid to stratified squamous epithelium.

Cellular Morphology

The walls of the large intestine are made up of four layers: serosa or adventitia, muscularis mucosa, submucosa, and mucosa. The mucosa has three layers namely epithelial cell layer, lamina propria, and muscularis mucosa. The muscularis mucosa consists of outer longitudinal and inner circular muscle layers. The outer longitudinal layer is thickened to form three prominent muscle bands called taenia coli. In between the muscular folds is the Auerbach's plexus.

Function of Large Intestine

The primary function of the large intestine is water and electrolyte absorption via the mechanisms described previously. The major short-chain fatty acid (SCFA) butyrate is produced in the colonic lumen by bacterial fermentation of dietary fiber. The SCFAs absorbed by the colon contribute only about 7% of the overall body energy requirements with slightly higher amount being contributed during infancy. However, the colonic epithelium depends on luminal SCFAs for their energy supply as evidenced by the development of diversion colitis after the surgical diversion of fecal stream with the resolution of colitis with colonic instillation of n-butyric acid. Thus, butyrate serves as primary energy source for the colonocytes and also ameliorates mucosal inflammation and promotes epithelial barrier function. Disturbed energy homeostasis seen in inflamed mucosa of inflammatory bowel disease patients has been attributed to impaired absorption of butyrate.

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183 Approach to a Child with Failure to Thrive

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Introduction

Failure to thrive is a general descriptive term, which encompasses a multitude of diagnoses sharing the ultimate consequence of inadequate growth in early childhood. There is no consensus on the anthropometric measurements in defining failure to thrive. Most textbooks define failure to thrive as height or weight less than the third to fifth percentiles for age. Others define height or weight measurements that have decelerated by two major percentile lines on the standard growth charts of the National Center for Health Statistics (NCHS). When evaluating a child's growth, it should be emphasized that growth charts are far more important than assessing growth parameters at one point in time. Growth trends provide valuable insight on the growth pattern in terms of dietary milestones in relation to changes in the dietary history and the development of an organic disease.

Etiology

It may well be very convenient to simply divide failure to thrive into two categories: organic versus nonorganic failure to thrive; however, this over-simplification does not underline the unified etiology behind failure to thrive, that is, malnutrition, be it involving increased caloric requirements as in the case of a chronic inflammatory process or organ failure or malignancy, versus suboptimal intake of calories related to inadequate bonding, neglect or emotional deprivation and poverty. Malnutrition carries inevitable consequences of immunocompromise, poor growth, and negative effects on cognitive and learning skills. It is very sad that failure to thrive often times is a consequence of national level poor economy and scarce resources in the society.

History

The child's perinatal history is the first step in discerning the etiology behind failure to thrive, which is, often times multifactorial, involving suboptimal intake of calories in the setting of psychosocial dysfunction with or without organic disease.

History of intrauterine exposure to cigarettes, alcohol or other teratogens, recreational drugs, or maternal peripartum infections may give the answer to the etiology of failure to thrive. The early identification of fetal alcohol spectrum disorder and its concomitant post-neonatal medical and psychosocial factors may improve the prognosis by early neurodevelopmental, psychosocial, and nutritional interventions.

The inadequacy of birth weight in relation to gestational age may shed some light on prenatal causes that may involve congenital infections, chromosomal abnormalities, a genetic disease, or an ongoing high risk-taking behavior by the mother.

Prematurely born infants should have their growth parameters plotted, corrected for gestational age, up to their 24th month of life, nevertheless bearing in mind that very low birth premiees may well remain smaller than their chronological peers until 36 months of life.

The birth weight, birth length, and birth head circumference will identify intrauterine growth retardation (IUGR) which may have prognostic implications on the infant's growth pattern. Asymmetrical IUGR – with the birth weight disproportionately more affected than birth length and head circumference – carries a better prognosis than symmetrical IUGR in terms of postnatal growth with the provision of intensive nutritional rehabilitation and environmental intervention. Symmetric IUGR carries poor prognosis for growth and development, often times related to a genetic disorder, an intrauterine infection, and/or teratogen or illicit drug exposure in utero.

The growth charts of appropriate for gestational age (AGA) babies who have demonstrated deceleration of growth beyond early infancy should be analyzed in the context of a detailed dietary history. The milestones in the child's history, including developmental milestones, onset of new symptoms, and introduction of potentially allergenic or toxic foods, can be linked into a temporal relationship. Infants with metabolic disorders may

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demonstrate symptoms related to the introduction of potentially toxic diets like fructosemia, phenylketonuria, or much earlier galactosemia; infants with fatty acid oxidation defects may develop clue symptoms as their sleep pattern changes to longer duration fasting. The onset of symptoms after the introduction of gluten in the cereal may give a clue to the diagnosis of Celiac disease.

A detailed review of systems may reveal clues to chronic childhood illnesses, which universally cause growth failure. Increased caloric requirements in the setting of a hyper-catabolic state, suboptimal intake of calories are all complexed into an unfavorable psychosocial milieu, all factors in favor for inadequate nutrition. A detailed diet diary and 3-day calorie count is of paramount importance.

Specific inquiries in the dietary history should include the amount of juice consumed by the child, soda and carbonated beverages, as well as diluting formulas in the face of financial struggles.

Adequate weight gain during hospitalization may not necessarily be a clue to nonorganic failure to thrive. All children will show weight gain with appropriate high calorie nutritional rehabilitation; in fact, children with depression or affective behavioral and feeding disorders may deteriorate when hospitalized without attention to their disordered psyche.

Occult organic disorders should be explored including renal tubular acidosis, dysfunctional oral motor development, and immunodeficiency; by contrast, overdiagnosing eosinophilic gastroenteropathy and food allergies may contribute to failure to thrive by means of restricting their dietary choices and thus caloric intake unnecessarily.

The child's clinical examination should explore clues for eating disorders, with specific inquiries about self-esteem, body image distortion, and ideal weight obsessions. Binge eating, experimentation with laxatives and diuretics, or inducing vomiting behaviors should also be explored.

Parents' heights should be noted in addition to their puberty onset and any history of constitutional delay.

The family history needs to explore chronic illnesses such as cystic fibrosis, autoimmune diseases such as Crohn's disease and insulin-dependent diabetes, metabolic disorders in the setting of consanguinity or sudden infant deaths.

The social history should explore the caregiver's competency, substance use or other high risk-taking behaviors, and psychosocial dysfunction.

Immigrant children or those living in homeless shelters should be evaluated for treatable conditions of malnutrition like giardiasis.

The clinical examination should also explore secondary complications of malnutrition such as impaired cognitive and learning skills, relative immunodeficiency, pica, lead toxicity, and psychosocial retardation, all of which feed into a vicious cycle of more malnutrition and growth failure.

Physical Examination

Thorough clinical evaluation aims at identifying chronic disease, be it a chronic inflammatory process, a malabsorption or a neoplastic process, recognizing genetic syndromes or dysmorphic features as well as identifying the deleterious secondary effects of malnutrition that are feeding into the vicious circle of undernutrition, apathy, and poor cognition.

Signs of systemic illnesses with detailed physical examination to all organ systems, including digital clubbing, cardiac, pulmonary, and abdominal examination, extra-intestinal manifestations, or any features of a systemic, autoimmune inflammatory process, organomegaly, or lymphadenopathy should be sought.

Signs of abuse, neglect, or deprivation should be sought, such as bruises, burns, scars, retinal hemorrhages, genital trauma, hygiene, level of activity, affect, psyche, and adequacy of bonding with the caregiver.

Signs of vitamin and trace element deficiencies should be carefully looked for, such as cheilosis, glossitis, perioral, perianal disease, dental enamel defects, rachitic rosary, brittleness, and pluckability of the hair.

Signs of developmental and cognitive delays should be explored, such as hypotonia, occipital alopecia, and delayed fontanelle closure.

Careful examination of dysmorphic features, eyes, palpebral fissures, philtrum, or any other facial dysmorphism should be done.

Features of immunodeficiency such as skin rashes, skin infections, or draining ears should be explored.

In a patient with body image distortion, disturbed perception of body image, and poor self-esteem, specific attention should be made to clinical signs of self-induced vomiting, like dental enamel erosions, abrasions to the knuckles of the metacarpophalangeal joints, or enlargement of the salivary glands as a result of continued self-induced vomiting.

Laboratory Evaluation

The laboratory evaluation should aim at exploring clues provided in the history and physical examination.

Simple, noninvasive tests, with low risk and high yield, can rule in or rule out organic conditions leading to failure to thrive that is coupled with inadequate nutrition.

Complete blood count, basic metabolic panel including serum electrolytes, bicarbonate, blood urea nitrogen, serum creatinine, lead level, urine analysis, PPD testing, sweat chloride, and pancreatic fecal elastase are easy tests to obtain.

Iron studies, fat-soluble vitamin levels, trace element concentrations, and prealbumin levels can give information to the degree of undernutrition.

Calcium, phosphorus, and alkaline phosphatase may lead to the diagnosis of rickets.

Tissue transglutaminase and quantitative IgA may lead to an endoscopic diagnosis of celiac disease with small intestinal histopathology.

An endocrine workup may be necessary when clinically indicated, such as in clinical feature of thyroid dysfunction. Radiologic bone age can help differentiate constitutional growth delay from endocrine causes of short stature.

HIV testing, in the suggestive clinical setting should also be considered.

Skin patch testing, radio-allergo-sorbent testing along with peripheral eosinophil counts and serum IgE levels may be indicated in the case of severe atopic dermatitis, urticaria, or rash.

In patients with self-induced vomiting, it is not uncommon to find characteristic features of hypokalemic, hypochloremic metabolic alkalosis.

Medical Management

After an initial assessment and hospitalization that has included a detailed dietary history, caloric counts, monitoring of the child's behavior during feeding sessions, a social work evaluation to the home environment, and assessing the caregiver's competence in providing a positive nurturing environment, the child with failure to thrive will need close monitoring with frequent clinic visits and weight checks at regular intervals.

Identifying and properly managing chronic illnesses should be initiated along with high calorie nutritional rehabilitation program. Immunizations should be updated and must include influenza, as malnutrition makes these children relatively immune deficient.

Patients with poor oral motor skills, uncoordinated swallowing or other mechanical feeding difficulties, and behavioral feeding problems should be properly referred for occupational and speech therapy as indicated. In the meantime, as the malnourished child is not taking the high calorie nutritional supplementation orally, the parents are encouraged to accept an alternative method, tube enteral feeding; this, in particular, applies to those chronic silent aspirators with abnormal swallow studies and at high risk for aspiration pneumonias.

Furthermore, the nutritional value of the items listed in a 3-day diet diary should be assessed, as well as proper counseling and education the primary caregiver, and in particular those with strict dietary beliefs or unusual dietary practices or misconceptions.

Nutritional Evaluation

Careful assessment of the child's nutritional status is of paramount importance in planning nutritional rehabilitation, following the effectiveness of re-nourishment, as well as predicting the outcome in terms of developmental potential.

Anthropometric measurements should be taken at baseline as well as at regular intervals along with serial weights and other growth parameters.

Growth parameters should be standardized to minimize subjective variables, using the same scale, in the same setting, preferably by the same health-care provider, and weighed in underwear only.

The National Center for Health Statistics (NCHS) growth charts serve as a standardized tool for realizing the severity as well as the chronicity of malnutrition. There is international consensus that these growth charts should be utilized for children irrespective of their racial or ethnic background.

Looking carefully at a child's weight for age, the clinician can understand the chronicity of malnutrition, the gradual onset, its temporal link to a sub-acute illness/insult, versus a dietary change, versus a major illness. Weight for age has invaluable importance in predicting a mortality outcome.

Looking at a child's standing height (or length) for age, the clinician can predict a genetic, an endocrine, a constitutional delay, or, a long-standing state of undernutrition.

Looking at a child's weight for height, the clinician can predict that the child is failing to thrive due to a fairly recent insult that has required increased caloric requirements, and these have not been met, usually for a variety of mechanisms and confounding factors.

A child with all depressed weight for age, height for age, as well as weight for height has a chronic illness that has long affected the growth parameters, and this state of

chronicity has been complexed with an additional fairly recent state of undernourishment/malnutrition.

Nutritional rehabilitation aims at providing higher calories than children of the same chronological age, to allow for catch-up growth. The aim is to demonstrate a rate of weight gain that is at least twice the median weight gain average for the specific age to allow for catch-up growth and replenish the deficits. The projected weight and caloric goals should be continuously revised as the child's nutritional rehabilitation is monitored.

The caloric goals, the recommended daily allowances of nutrients and other elements, all exceed those age-specific values in a failing to thrive undernourished child, and all are calculated in reference to the ideal weight for chronological age and height.

The trace elements, vitamins, micronutrients should all be taken into account when replenishing the stores and re-nourishment.

Care should be taken to reach caloric goals gradually and over a period of weeks in order to prevent "refeeding syndrome" and its potentially lethal metabolic consequences and electrolyte derangements that may cause circulatory decompensation, cardiac arrhythmias and death; the risk of refeeding syndrome is highest in the first 72 h, during which time, the patient's serum electrolytes should be closely monitored. It is thus the term "re-nourishment" in nutritional rehabilitation as opposed to refeeding is advised.

Special emphasis on high caloric density supplements should be advised in addition to special recipes of high calorie food choices and preparation that are provided by the experienced registered dietician in the team.

Furthermore, nocturnal nasogastric tube feeds can provide 60–100% of the recommended calories for catch-up growth, while allowing the child to eat during the day at their own pace, thus relieving the pressures off of the caregiver's shoulders to meet the caloric goals prescribed.

Continued monitoring to the adequacy of growth should be followed through at least 4–9 months to replenish the stores and allow for catch-up growth; the growth measurements can be followed less often than weekly after multiple weight checks have confirmed at least twice the amount of weight gain recommended for that age (average weight gain in grams per day in the interval).

Psychosocial Aspect

Chronic undernutrition, and depending on the severity and chronicity, has deleterious effects on the sound development of the malnourished child; this includes cognitive development, psychosocial interaction, and learning skills, thus negatively affecting the child's learning potential.

It is well known that nutritional deficiencies impair learning abilities; furthermore, a dysfunctional home milieu, an incapable caregiver, and poor educational opportunities all play a role in a negative cognitive and developmental potential.

Often times developmental testing provides suboptimal and far from accurate results in assessing the child's cognitive and developmental potential as social withdrawal and apathetic response to stimulation and prolonged deprivation. It is therefore crucial after re-nourishment therapy has been initiated and established to have these tests repeated for better prediction of the child's intellectual potential.

Children with malnutrition/undernutrition should receive special attention to their current developmental status, and developmental delays should be addressed and explored and stimulated.

Psychosocial and emotional development, social interactions, response, affect are potentially impaired in the malnourished child and should be properly addressed as well.

An official consult to the social worker in assessing the social situation may unmask psychosocial dysfunction, abuse, violence, and mental illnesses that may render the home situation and/or caregiver a home environment not in the child's best interest to be in.

Intervention

A multidisciplinary approach in evaluating and treating the child with failure to thrive insures the best outcome, as the child's nutritional status, psychosocial development, cognitive and learning skills, and social environment all are properly addressed and appropriately managed.

The team approach involves the pediatrician, the certified dietician, the social worker, the psychologist, the developmental specialist, and other specialists depending on any chronic illnesses.

Regular home visits should be part of the follow-up in addition to clinic visits and weight checks and case conferences. Assessing the home conditions, family resources, financial struggles, and appropriate referrals are made.

Parent training, counseling and education, patient referral for appropriate developmental evaluation, and treatment for early intervention are mandatory for the best outcomes; that includes mental health intervention, and proper management and modification of behavioral feeding issues.

Summary

Failure to thrive is a complex, chronic, and often challenging condition that involves multiple facets leading to this clinical picture. Every aspect needs to be properly addressed, evaluated, and corrected to achieve best outcomes. Chronic organic conditions, nutritional deprivation, social milieu, psycho-emotional deprivation, and secondary cognitive and developmental deficits should all be managed. A multidisciplinary approach insures the most favorable outcomes.

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184 Approach to a Child with Malabsorption

Mohammad El Baba

Malabsorption refers to conditions arising from abnormalities in digestion and absorption of nutrients during their passage through the gastrointestinal tract. It can result from defects in any of the three phases of digestion and absorption:

1. Defects in intraluminal hydrolysis of nutrient
2. Defects in mucosal absorption
3. Vascular and lymphatic defects affecting transport of nutrients

Some disorders are more generalized and affect the absorption of many nutrients, vitamins, and minerals; others are more selective and involve specific nutrients.

Etiology and Pathophysiology

Malabsorption can be caused by many diseases affecting the small intestine (*Table 184.1*) and pancreas (*Table 184.2*). It also can be caused by diseases of the liver and biliary system such as cholestatic liver diseases, cirrhosis, portal hypertension, and inborn errors of bile acid biosynthesis.

Lymphatic and vascular disorders causing malabsorption are shown in (*Table 184.3*).

Carbohydrates

Starch is hydrolyzed into oligosaccharides by the action of both the pancreatic and salivary amylase. Brush border oligosaccharidases and disacharidases are responsible for further digestion of starch derivatives and digestion of dietary disaccharides (lactose and sucrose). The derived monosaccharides, glucose, galactose, and fructose, are absorbed by carrier-mediated transport systems located in the brush border membrane of small intestine. The active transport of glucose and galactose absorption is achieved by the sodium-dependent glucose cotransporter (SGLT1). Fructose is transported by facilitated diffusion from the intestinal lumen into the enterocytes.

Deficiency of one or more of the brush border disacharidases or oligosaccharidases may cause diarrhea, bloating, and flatulence after ingestion of sugar. The symptoms are due to colonic bacterial fermentation of unabsorbed carbohydrates into CO_2, hydrogen, methane, and short-chain fatty acids.

Glucose-galactose malabsorption, caused by mutations in the SGLT1 gene, is characterized by severe diarrhea in the neonatal period and after the newborn's ingestion of breast milk or regular infant formula. Since fructose is not well absorbed as glucose, ingestion of large amount of dietary fructose can cause diarrhea, increased flatulence, and abdominal cramping.

Diffuse mucosal diseases are commonly associated with carbohydrate malabsorption. Celiac disease, Crohn's disease, and short bowel syndrome are common causes of acquired carbohydrate malabsorption in children. Post enteritis syndrome is usually associated with transient carbohydrate malabsorption and lactose intolerance especially in infants and young children.

Fats

Ingested fats are emulsified in the small intestine by the action of bile salts, phospholipids, and monoglycerides. Pancreatic lipase hydrolyzes the emulsified fat into fatty acids and monoglycerides which combine with bile salts to form micelles. Micellar formation further solubilizes the fatty acids and other lipolysis products and provides a mechanism for their transport to the enterocytes.

Absorbed fatty acids are reesterified to triglycerides in the enterocytes and combine with protein, cholesterol, and phospholipid to form chylomicrons. The chylomicrons then leave the enterocytes to enter the lymphatics. Medium-chain triglycerides are water-soluble and absorbed directly into the portal blood.

A decrease in luminal bile concentration can impair lipid intestinal absorption. This can result from obstruction of bile flow as in congenital biliary atresia, or interruption of the enterohepatic circulation of bile acids.

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Table 184.1
Intestinal diseases causing malabsorption

1. Congenital mucosal defects
(a) Microvillus inclusion disease
(b) Tufting enteropathy (intestinal epithelia dysplasia)
(c) Carbohydrate transport defects:
(i) Glucose-galactose malabsorption
(ii) Sucrase-isomaltase deficiency
(iii) Congenital lactase deficiency
(d) Amino acids transport defects:
(i) Neutral amino acids defect (Hartnup disease)
(ii) Dibasic amino acids defects (Lysinuric protein intolerance)
(iii) Tryptophan absorption defect (Blue diaper syndrome)
(iv) Methionine absorption defect (Oasthouse syndrome)
(e) Lipid transport defects
(i) Abetalipoproteinemia
(ii) Familial hypobetalipoproteinemia (homozygous)
(iii) Chylomicron retention disease
(iv) Wolman's disease
(f) Other defects
(i) Congenital chloride diarrhea
(ii) Congenital sodium absorption diarrhea
(iii) Acrodermatitis enteropathica
(iv) Enterokinase deficiency
(v) Congenital bile acid malabsorption
(vi) Congenital disorders of glycosylation
2. Intestinal infections
(a) Parasitic infections
(b) Infections in acquired immune deficiency syndrome (AIDS): Cryptosporidiosis, microsporidiosis, *Mycobacterium-avium* complex infection, cytomegalovirus infection
(c) Bacterial overgrowth
(d) Postinfectious enteropathy
(e) Intestinal tuberculosis
(f) Whipple's disease
3. Immune disorders
(a) Primary Immune disorders
(i) Common variable immunodeficiency
(ii) Selective IgA deficiency
(iii) Agammaglobulinemia, X-linked or autosomal recessive
(iv) Hyper IgM syndrome
(v) Severe combined immunodeficiency
(vi) Immune dysregulation, polyendocrinopathy, enteropathy (IPEX) syndrome
(vii) Chronic granulomatous disease (CGD)
(viii) Wiscott–Aldrich syndrome
(ix) Hermansky–Pudlak syndrome
(b) Acquired immune deficiency
(i) HIV infection
(ii) Immunosuppressive therapy
4. Mucosal inflammatory disorders
(a) Crohn's disease
(b) Eosinophlic gastroenteritis
5. Food-induced enteropathy:
(a) Eosinophilic gastroenteritis.
(b) Celiac disease
6. Others
(a) Acquired primary lactase deficiency (adult-type hypolactasia)
(b) Autoimmune enteropathy
(c) Small intestinal resection
(d) Congenital short bowel
(e) Radiation enteritis
(f) Graft-versus-host disease
(g) Chronic malnutrition

Table 184.2
Pancreatic diseases causing malabsorption

1. Pancreatic insufficiency
(a) Cystic fibrosis
(b) Shwachman–Diamond syndrome
(c) Pearson's syndrome
(d) Johanson–Blizzard syndrome
(e) Chronic pancreatitis
2. Congenital pancreatic enzyme deficiency (lipase, colipase, or trypsinogen deficiency)

Decreased hydrolysis of dietary fat results from impaired pancreatic lipase and colipase secretion as a result of exocrine pancreatic dysfunction. Cystic fibrosis and chronic pancreatitis are common causes of pancreatic insufficiency in children. Congenital deficiency of lipase or colipase is extremely rare. Impairment of lymphatic transport of chylomicrons is another cause of malabsorption of dietary fat. Decreased lymphatic transport is seen

Table 184.3
Lymphatic and vascular disorders causing malabsorption

1. Primary intestinal lymphangiectasia
2. Secondary intestinal lymphangiectasia
(a) Cardiovascular disorders
(i) Fontan procedure
(ii) Congestive heart failure
(iii) Restrictive pericarditis
(b) Thoracic duct trauma or obstruction
(c) Portal hypertension
(d) Mesenteric lymph node disorders
(i) Lymphoma
(ii) Radiation
(iii) Mesenteric tuberculosis

in patients with primary lymphangectasisa or secondary lymphatic obstruction.

Unabsorbed fats trap fat-soluble vitamins and interfere with their absorption leading to deficiencies. Small intestinal bacterial overgrowth results in deconjugation of bile acids and leads to malabsorption of fat and fat-soluble vitamins.

Proteins

Gastric pepsin hydrolyzes protein into polypeptides of variable sizes. Polypeptides are further digested in the small intestine by the pancreatic proteolytic enzymes. Enterokinase, a brush border enzyme, is required to activate trypsinogen into trypsin. Trypsin converts chymotrypsinogens into chymotrypsins and other proenzymes into active enzymes. Active proteolytic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids. The digestion of peptides into amino acids can occur in the intestinal lumen, the brush border, or the cytoplasm of the mucosal cells.

Generalized mucosal diseases such as celiac disease, or reduction of intestinal absorptive surface as in short bowel syndrome, can result in malabsorption of oligopeptides and amino acids. Selective disorders of malabsorption of amino acids are rare and result of defects of amino acid transporters as in Hartnup disease and lysinuric protein intolerance.

Protein-losing enteropathy is a distinct clinical condition which results from excessive loss of serum protein into the gastrointestinal tract and should be differentiated from protein maldigestion or malabsorption.

Clinical Evaluation

Features of malabsorprtion are very variable and depend on etiology and extent of gastrointestinal defect, age of presentation, and other comorbidities. The evaluation of a child for malabsorption should include: confirming the presence of malabsorption, identifying the cause, treating underlying condition, and correcting nutritional deficiencies.

Malabsorption is usually suspected based on clinical history, physical findings, and routine laboratory findings. Symptoms and signs are either secondary to the presence of malabsorbed material in the gastrointestinal tract or related to specific nutrient deficiency. They can be divided into gastrointestinal and extragastrointestinal manifestations:

Gastrointestinal Symptoms and Signs

- *Diarrhea*: Diarrhea is one of the commonest symptoms of malabsorption. Characters and number of stools may be a useful differentiating symptom.
  - Explosive watery stools in the first week of life and after the institution of regular formula are very suggestive of congenital glucose-galactose malabsorption or congenital lactase deficiency. Skin irritation and erythema in the perianal area are characteristic of acidic stools seen in carbohydrate malabsorption.
  - Bulky, greasy, and foul-smelling stools indicate fat malabsorption as in pancreatic insufficiency.
  - Nocturnal diarrhea or diarrhea that does not respond to fasting indicate secretory diarrhea as in toxigenic *Escherichia coli* enterocolitis and in congenital mucosal defects.
  - Bloody stool is a sign of inflammatory process as in inflammatory bowel disease or eosinophilic enterocolitis.
  - Floating of stool can be due to a high stool-fat content, but it also can be caused by high gas content as in carbohydrate malabsorption. Loose stools with undigested food particles are common findings in chronic nonspecific diarrhea of toddlers and not a sign of malabsorption.
- *Abdominal distension and flatulence*: from bacterial fermentation of malabsorbed carbohydrates in colon and in small intestinal bacterial overgrowth.
- *Abdominal pain*: from intestinal distension or inflammation.
- *Edema* of the legs, puffiness and ascites: in protein loss or malabsorption.

Extragastrointestinal Symptoms and Signs

- Failure to thrive and growth retardation: secondary to nutrient malabsorption
- Anorexia and food refusal as in mucosal inflammation
- Weakness, fatigue, and irritability: secondary to poor nutrition or anemia
- Delayed puberty and amenorrhea: in protein-caloric malnutrition
- Bleeding tendencies: in vitamin K deficiency
- Pallor and anemia (iron, folate, or vitamin B12 deficiency)
- Neurologic symptoms and ataxia: vitamin E, vitamin B12, or folate deficiency
- Frontal bossing, widening of wrists, bowed legs, bone pain: vitamin D deficiency
- Acrodermaitis: zinc deficiency
- Cheilitis and glossitis: vitamin B complex deficiency

Useful Clues in the History

- Detailed diet history: diluted formula, high intake of fructose or sorbitol, inadequate caloric intake
- Relation of symptoms to newly introduced food
- History of food allergies
- History of previous gastrointestinal surgeries. History of cardiac surgery
- History of parental consanguinity
- Family history of malabsorption syndromes (celiac disease, congenital mucosal structural defects or transport defects)
- Extraintestinal symptoms suggestive of inflammatory bowel disease or immune deficiency

Diagnostic Approach

Screening Tests for Malabsorption

- Complete blood cell count:
  - Hemoglobin
  - Red blood cell indices: to identify nutritional deficiencies of iron, folate, or vitamin B12, or with anemia of chronic disease
  - Lymphocyte count: low in lymphangectasia
  - Low CD4 count in HIV infection
  - Eosinophils: could see peripheral eosinophilia in allergic conditions
  - Acanthocytes in abetalipoproteinemia
  - Platelets: increased in inflammatory diseases
- C-reactive protein and erythrocyte sedimentation rate: as markers of inflammation
- Low total serum protein and albumin: secondary to protein loss, malabsorption, or inadequate intake
- Prealbumin (Transthyretin): a marker of acute malnutrition (shorter half-life than albumen) and to assess efficacy of nutritional therapy
- Serum iron, ferritin, and iron binding capacity in iron deficiency anemia
- Fat-soluble vitamins (vitamins A, E, and 25-hydroxyvitamin D): in malbsorption syndromes
- Prothrombin times (vitamin K)
- Vitamin B12 level
- Zinc level
- Liver biochemical tests
- Immunoglobulins: immunodeficiency syndromes, IgA deficiency
- Stool tests:
  - Stool pH: low in carbohydrate malabsorption.
  - Reducing substances: suggest carbohydrate malabsorption (glucose, lactose, and fructose).
  - Stool electrolytes (in watery stools) to differentiate secretory from osmotic diarrhea.
  - Fecal occult blood and leukocytes: indicate inflammatory process.
  - Fecal fat (qualitative or quantitative): gives diagnostic clues for fat malabsorption. A 72-h quantitative fecal fat analysis is considered the gold standard for fecal fat analysis. However, this study has several limitations and difficult to perform especially in young children. Acid steatocrit is an alternative and simpler test to perform but has limited applicability in patient with mild steatorrhea.
  - Stool ova and parasites: several studies may be needed to detect Giardia lamblia.

Specific Studies

Sequence of tests to establish the cause of malabsorption is guided by the child's history and results of previous screening tests. Stepwise approach starting with noninvasive tests should be performed initially.

- Serologic studies for Celiac disease: endomysial and tissue transglutaminase antibodies.
- Carbohydrate malabsorption:

  - Lactose malbsorption: lactose breath hydrogen testing. An increase in breath hydrogen concentration of greater than 20 ppm over baseline after ingestion of lactose is considered positive. Early increase within the first 30 min has to be disregarded because it may reflect fermentation of lactose by oral bacterial flora.
  - Fuctose malabsorption: fructose breath hydrogen testing.
- Pancreatic insufficiency: fecal elastase or chymotrypsin. Both are reduced in exocrine pancreatic insufficiency but have variable sensitivity and specificity.
- Protein malabsorption: enteral protein loss could be demonstrated by measuring stool alpha-1 antitrypsin and alpha-1 antitrypsin clearance.
- Small intestinal bacterial overgrowth: by glucose or lactulose breath hydrogen testing.

Imaging Studies

- Upper gastrointestinal series with small intestine follow-through: not routinely used as the radiologic findings in malabsorption are not specific. It can be helpful to identify intestinal abnormalities that can predispose to bacterial overgrowth. It is also a useful technique in evaluating the small bowel for strictures and fistulas in Crohn's disease.
- Abdominal Computed Tomography(CT): This study can be useful in selected cases to detect focal small intestinal lesions such as strictures and abscess formation in Crohn's disease. However, much attention has been pain recently to the potential risks of irradiation to children from CT and fluoroscopy.
- Magnetic resonance imaging (MRI): This study is increasingly being offered to children with suspected small and bowel large diseases because of decreased risk of irradiation.
- Abdominal ultrasound: Abdominal ultrasonography can be useful in detecting bowel wall thickening as in active Crohn's disease. It can also detect complications such as abscesses and fistulas. However, the findings are usually nonspecific and interpretation of the images are operator dependent. It is a valuable and noninvasive toll to evaluate children with chronic pancreatitis and biliary disorders.
- Endoscopic ultrasonography (EUS): The role of EUS is well established in adult gastrointestinal and pancreatobiliary diseases, but the reported experience of its usefulness in children is limited.

Endoscopic Examination

- Endoscopic appearance can provide clues to some underlying disorders. Reduced number of duodenal folds and scalloping are very suggestive of villous atrophy in celiac disease, although may be seen in other disorders such as eosinophilic gastroenteritis and chronic giardiasis. Mucosal aphtous ulceration and strictures suggest Crohn's disease.
- Histology: Findings on mucosal biopsies can be very useful and diagnostic of many malabsorption syndromes.
  - Celiac disease: Villous atrophy and increased intraepithelial lymphocyte are very suggestive of celiac disease. However, definite diagnosis of celiac disease cannot be established by mucosal biopsy alone.
  - Eosinophilic gastroenteritis: Main feature is eosinophilic infiltration of mucosa.
  - Crohn's disease: Patchy inflammation and granulomas.
  - Abetalipoproteinemia: Lipid accumulation and vacuolization of enterocytes.
  - Lymphangectasia: Dilated lymph vessels.
  - Microvillous inclusion disease: Lack of microvilli and presence of secretory granules and inclusion bodies.
  - Infectious:
    - Giardiasis: Parasites may be seen on histologic examination.
    - *Mycobacterium-avium* complex infection: Acid-fast bacilli.
- Duodenal aspiration: Fluid collected from distal part of duodenum can be examined to look for *Giardia lamblia*. It can also be cultured to detect small intestinal bacterial overgrowth.
- Pancreatic stimulation tests: By either secretin, or cholecystokinin stimulation tests. The tests require duodenal intubation to collect serial pancreatic juice samples after stimulation.

Approach to Management

Management should include treatment of the underlying condition if possible, and correction of all nutritional deficiencies.

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185 Functional Gastrointestinal Disorders

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Introduction

While gastrointestinal symptoms of abdominal pain, nausea and vomiting, bloating, diarrhea, and constipation due to organic causes can be identified by various investigations, functional gastrointestinal disorders (FGID), on the other hand, are multi-symptomatic conditions that have no underlying mucosal or structural abnormalities. They are diagnosed based on a collection of symptom complexes. Functional Gastrointestinal disorders (FGIDs) are quite common in children. The exact cause remains unknown; however, it has usually been referred to as multifactorial. Noninfectious causes affecting the gastrointestinal tract early in life, such as cow's milk allergy (CMA), can predispose to the development of FGID later in childhood.

There are three common concepts for FGID: (1) no known structural cause, (2) no symptoms due to stress disorders, or (3) due to a motility disorder.

Although FGID have a great impact on patient morbidity and time off work, some physicians deny or belittle their existence, while other physicians exhibit negative attitude toward such patients.

Over the past 2 decades, researchers have started to unravel the underlying mechanisms behind these conditions. For example, impaired gastrointestinal motility and intestinal secretion, along with enhanced visceral sensitivity, have been shown to be key abnormalities associated with the characteristic symptoms of abdominal pain and altered bowel habits as experienced by patients with irritable bowel syndrome.

Gastrointestinal motility disorders that are due to altered physiological factors lead to altered physiological function. In recent years, these factors stem from the brain-gut axis interaction and dysfunction. Gastrointestinal motility can be measured and abnormal patterns can be identified using tests for different part of the gastrointestinal tract which provide information to help with diagnosis and treatment.

Psychosocial factors, through the brain-gut axis, affect the physiologic function of the gut, which in turn alters motility and sensation, modulating inflammation, which may be caused by or associated with altered bacterial flora. These have impact or lead to FGID. Early in life, genetic factors may affect one's psychological development in developing coping skills as well as susceptibility to gut dysfunction-abnormal motility, altered mucosal immunity, or visceral hypersensitivity. In addition, environmental factors such as child and sexual abuse, loss due to death/bereavement/cancer phobia may affect the psychological development and the interaction of the brain-gut axis.

Over the last decade, gut receptor-active agents have been recognized. These include 5-HT agonists and antagonists, and other newer agents, have been used to treat FGID. Other, more centrally acting agents have been used for treating stress-mediated effects of CNS modulation of the gut.

Within the gut, motility assessment advances, test for visceral hypersensitivity, mucosal immunology, alteration of the gut bacterial flora, and other tests have been used to allow us to quantify the association between motility disorders and FGID.

Rome and FGID

Over the last 17 years, FGID have been studied by nonprofit organizations that formed the Rome Foundation who aimed at providing support for activities to create scientific data to assist in the diagnosis and treatment of FGID.

The Rome II criteria developed structured, symptom-based classification for many FGID. Those criteria are not explained by other pathologically based disorders. This has been revised in the Rome III criteria (28 adult and 17 pediatric FGID). The pediatric gastrointestinal symptoms Rome III version criteria for the diagnosis of FGIDs include those of irritable bowel syndrome, functional dyspepsia, and functional abdominal pain.

Cow's milk allergy constitutes a risk factor for the development of FGIDs in children. Rome III criteria were able to diagnose FGIDs more comprehensively than Rome II.

The Pediatric system is classified first by age range (*category G for neonate/toddler, category H for child/adolescent*) and then by symptom pattern or area of symptom location.

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The symptoms of FGID in children less than 5 years depend on maturational factors in anatomy, gastrointestinal physiology, and intellectual and affective functioning.

G. Functional disorders: neonates and toddlers	
G1	Infant regurgitation
G2	Infant rumination syndrome
G3	Cyclic vomiting syndrome
G4	Infant colic
G5	Functional diarrhea
G6	Infant dyschezia
G7	Functional constipation
H. Functional disorders: children and adolescents	
H1. Vomiting and aerophagia	
H1a	Adolescent rumination syndrome
H1b	Cyclic vomiting syndrome
H1c	Aerophagia
H2. Abdominal pain-related functional gastrointestinal disorders	
H2a	Functional dyspepsia
H2b	Irritable bowel syndrome
H2c	Abdominal migraine
H2d	Childhood functional abdominal pain
H2d1	Childhood functional abdominal pain syndrome
H3. Constipation and incontinence	
H3a	Functional constipation
H3b	Non-retentive fecal disorders (incontinence)

Understanding *the adult FGID* is very important in management of *Pediatric FGID. In the adults, the FGID are classified into six major domains; category A to F* (from esophagus to ano-rectum).

Each category site contains several disorders with specific clinical features. For example, the FGID for category C includes IBS (C1), functional bloating (C2), functional constipation (C3), and functional diarrhea (C4), which anatomically is attributed to the small bowel, colon, and rectum. Symptoms may overlap across these disorders, and each of these disorders has a different diagnostic and treatment approach.

Red Flags

The Rome III innovations include alarm symptoms to help alert physicians to possible structural disorders that might require further investigation. There are separate questionnaires for adolescents and parents of children and toddlers. There is also a psychosocial module to help identifying psychosocial difficulties that might require mental health referral.

The following are considered to be the alarm symptoms which might require further testing to rule out structural disease: blood in stools, black stools, vomited blood, fever, loss of weight, anemia. Also, positive family history of gastrointestinal disease such as ulcerative colitis, Crohn's disease, celiac disease, persistent right upper or right lower quadrant pain, dysphagia, persistent vomiting, pain that wakes the child from sleep, arthritis, and delayed puberty are generally absent in FGID.

The physician should ensure that there is evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explains the patient's symptoms. This might indicate the need for other investigations to rule out such conditions. The clinical diagnosis will depend on the judicious exclusion of other diseases. There are also some tests used to diagnose motility disorders and other FGID which might be used as well.

Psychological Alarm Questionnaire

Included in the Rome III guidance are screening questions which will help to identify psychological problems commonly faced by patients with FGID. The physician should acknowledge, discuss with the patient, and agree on the appropriate action, which might include referral to a mental health specialist and or initiate pharmacotherapy.

Those questions explore how the patient feels regarding anxiety, depression, suicidal ideas, and impaired coping. The patient may chose to answer either not at all, or occasionally, or most of the time. If the answer was most of the time for any of the former condition, this is considered as a red flag, which the physician has to address or refer to the child psychiatrist even prior to treatment of the FGID (or simultaneously with treatment).

The psychological alarm questionnaire has a question for abuse (emotional, physical, or sexual) with a red flag situation to consider early referral to a mental health professional provided the patient agrees.

The Enteric Nervous System (ENS)

Abdominal pain and disordered gastrointestinal function (the interaction between the brain, the spinal cord, and the gut) can be understood by studying ENS neurobiology with respect to visceral sensation and its modulation by inflammation and stresses.

The brain-gut axis allows bidirectional input and links emotional and cognitive centers of the brain with peripheral functioning of the GI tract and vice versa. Extrinsic information (vision, smell, etc.) or enteroceptive information (emotion, thought) has the capability to affect GI sensation, motility, secretion, and inflammation. Visceral afferent communications to the brain can affect central pain perception, mood, and behavior.

Increased motor and sensory reactivity to environmental stimuli leads to greater gut physiological reactivity to stress or to its neurochemical mediators.

Genetic factors may predispose some individuals to develop FGID, whereas in others, environmental factors contribute to the expression of these conditions. Psychological factors are not required for the diagnosis of FGID, but they modulate the patient's behavior and experience, and ultimately, the clinical outcome.

Three general observations were noted:

- Psychological stress exacerbates GI symptoms.
- Psychological factors modify illness behavior.
- FGIDs can have psychological consequence (like any other chronic illness).

GI Motility and FGID

The esophagus is capable of peristalsis during the first trimester. However, complex pattern of esophageal motility are clearly detected during the second trimester.

At birth, the motility of the esophagus functionally consists of three regions: the upper esophageal sphincter, body of the esophagus, and the lower esophageal sphincter.

The upper esophageal sphincter. It is physiologically defined as a zone of high intraluminal pressure lying between the pharynx and the cervical esophagus. Its main functions are to provide physical barrier of the proximal gastrointestinal tract against pharyngeal and laryngeal reflux during esophageal peristalsis, and to avoid the entry of air into the digestive tract during inspiration. It relaxes transiently during swallowing to allow the entry of the food bolus into the esophagus and during vomiting to allow the expelling of the gastric contents.

Esophageal body. Three segments can be identified: cervical, thoracic, and abdominal.

The wall of the esophageal body is composed of the mucosa, submucosa, and muscularis propria (which is composed of an outer longitudinal muscle layer and an inner circular muscle layer). In adults, the proximal 4–5 cm of esophageal muscularis propria is composed of skeletal muscle fibers. The mid-third of the esophagus consists of both skeletal and smooth muscles. The distal 10–14 cm consists entirely of smooth muscle fibers.

At rest, the musculature of the esophageal body does not exhibit rhythmic or tonic contraction. Primary peristalsis is defined as a reflex esophageal peristaltic contraction wave initiated by swallowing. It results from a sequential contraction of the esophageal muscle layers moving down the entire length of the esophagus, appearing shortly after the pharyngeal contraction traverses the upper esophageal sphincter.

The efficacy of esophageal emptying is strongly related to the peristaltic amplitude.

Lower esophageal sphincter (LES). The LOS is the high-pressure zone localized at the esophagogastric junction, which regulate the flow of contents between the esophagus and the stomach. The intrinsic smooth muscle fibers of the distal esophagus and the extrinsic skeletal muscle of the crural diaphragm function as a well coordinated and efficient functional unit of the sphincteric mechanism at the esophagogastric junction. The lower esophageal junction is tonically contracted at rest to produce a roughly concentric occlusion. The resting tone of the LOS is determined by excitatory cholinergic neurons and the myogenic properties of the smooth muscle fibers (independent of neural influences and may be produced with ionic movement).

LES pressure is increased by hormones such as gastrin, motilin, and substance P and neural agents such as the cholinergic agonist serotonin, whereas secretin, glucagon, VIP, and the cholinergic antagonist nitric oxide tend to decrease LES. Proteins tend to increase the LES pressure while fat, ethanol, and peppermint tend to decrease the LES pressure. In children, LES pressure ranges between 10 and 40 mmHg. LES pressures of 5 mmHg above intragastric pressure are sufficient to maintain esophagogastric competence.

Gastric Motility

The stomach is functionally divided into two regions: the proximal stomach including the fundus and the proximal one third of the body, and the distal stomach composed of the distal body and antrum.

The proximal stomach is characterized by properties that enable accommodation of larger volumes of food without a great increase in luminal pressure. Eventually, as food accumulates, the pressure in the fundus increases, resulting in a sustained contraction which propels the gastric contents toward the antrum. The distal portion is

electrically active and able to generate contractions that facilitate the mixing of food and passage of chime to the duodenum.

The stomach pacemaker, located in the corpus along the greater curvature near to the proximal one third of the corpus, generates regular electrical slow waves of depolarization at approximately three cycles per minute (cpm) that spread away, circumferentially and distally toward the pylorus. This frequency varies to between 8 and 11 cpm in the small bowel (explaining the difference in the rate of contractions among regions).

The Interstitial Cells of Cajal (*ICC*) are a group of mesenchymal cells distributed throughout the longitudinal and circular muscle layers of the gastrointestinal tract in close contact with smooth muscle cells. They are considered the gut pacemakers and the mediators of neurotransmission. They initiate and actively propagate electric rhythmic activity between nerves and smooth muscles resulting in gut contraction. They are present in the myenteric plexus of the stomach, small intestine, and colon and are responsible for generating electrical slow waves.

Electrogastrography refers to the methods of recording electrogastrograms (EGGs). EGG rhythms reflect the gastric pacesetter potentials or slow wave of the stomach. Pacesetter potentials are crucial electrical depolarization and repolarization waves because they control the timing and propagation velocity of gastric peristaltic contractions.

Thus, the 3-cpm EGG signals are noninvasive recordings of the electrical activity in health. Gastric dysrhythmias are abnormalities of gastric myoelectrical activity. These can be recorded in the EGG signal. Abnormally fast rhythms are called *tachygastrias*, and abnormally slow rhythms are called *bradygastrias*.

Gastric dysrhythmias are frequently present in patients with functional dyspepsia, unexplained nausea, diabetic, idiopathic, and postsurgical gastroparesis. Furthermore, correction of the gastric dysrhythmias with drug therapies or electrical stimulation is associated with improvement in nausea and vomiting.

Bradygastric activity of the stomach predict disgust sensitivity and perceived disgust intensity. The results suggest that feeling of disgust may be specifically related to increased bradygastria, which may represent a prodromal sign of vomiting.

Intestinal Motility

The motility of the small and large intestine is a function of the intestinal smooth muscle, which is controlled by the enteric nervous system (*ENS*) and the interstitial cells of Cajal (*ICC*). Gastrointestinal motility is modulated by the extrinsic input from the autonomic and central nervous system, from gastrointestinal hormones, and the immune system.

Throughout the intestine, *three layers* of muscle contract in a coordinated fashion:

- *The muscularis mucosa*, a thin layer that lies beneath the villi
- *The circular muscle*, which lies outside of the muscularis mucosa and serves as a pacemaker for gut muscle contraction
- *The longitudinal muscle*, the outermost layer of the three muscles

These muscles have oscillatory membrane potentials and their contraction rate is reflective of the electrical slow waves. The slow wave has a different frequency at each level of the gut (9–11/min in the duodenum, 8–10/min in the jejunum, and so forth).

Evaluation of Motility Disorders

The number of diagnostic tests available to evaluate gastric motor functions is steadily increasing. A combination of several testing modalities is often required in the evaluation of the child with suspected gastric dysfunction.

Radiology. The study usually begins with radiologic contrast studies to provide essential information on anatomical abnormalities (malrotation or a superior mesenteric artery that compresses the small bowel) which may result in small intestine dysmotility. However, barium studies are unsuitable to diagnose a specific motility disorder and are unreliable to assess transit time.

Scintigraphy. It is considered the reference standard for measuring gastric emptying. It is minimally invasive, requires relatively low levels of exposure to radiation. In this test, a liquid or solid food is labeled with a nucleotide, the labeled meal is tracked as it passes through the stomach using a gamma camera.

Antroduodenal manometry. It provides direct information on the amplitude, duration, frequency, and direction of propagation of gastrointestinal contractions. It is an essential aid in determining the presence of a motility disorder in patients with suspected enteric neuromuscular disorders.

Other tests. Gastric emptying can also be measured by ultrasonography, magnetic resonance imaging, single-photon emission computed tomography (*SPECT*), external EGG, water load test, breath test using C-octanoate.

Functional Dysmotility of the Foregut

Primary motility disorders of the foregut are rare. They may result in accelerated or delayed transit. Delayed transit may involve the stomach only (gastroparesis) or be part of a generalized gastrointestinal disorder (intestinal pseudo-obstruction).

They mainly present with a combination of symptoms including *nausea, vomiting, abdominal distention, abdominal pain, and weight loss.*

Gastroparesis

Gastroparesis is a chronic disorder caused by stomach pump failure and characterized by delay in gastric emptying of a meal in the absence of a mechanical gastric obstruction, profound nausea, vomiting, and epigastric pain.

Gastroparesis is a disorder characterized by an abnormality in the gastric myoelectrical activity, which may result in delayed gastric emptying and gastric dysmotility. Vomiting is characterized by being postprandial after meal ingestion and containing undigested food from previous meals. Gastroparesis may result from degenerative processes that affect gastric enteric neurons, smooth muscle, and Interstitial Cells of Cajal (ICC).

Gastroparesis can be found in preterm infants with immaturity of the gastrointestinal tract and in dietary proteins allergy. In allergic infants, cow milk provokes gastrointestinal dysmotility that results in delayed gastric emptying, exacerbating gastroesophageal reflux, and inducing vomiting. Using hydrolyzed formula leads to clinical improvement and acceleration of gastric emptying.

Due to the numerous potential etiologies and the highly variable clinical manifestations, the management of gastroparesis is particularly challenging.

The true prevelance of gastroparesis is unknown.

Children with CNS disorders frequently develop abnormal gastric motility and gastroesophageal reflux due to abnormal modulation of the enteric nervous system. Physical and emotional stress has been shown to be associated with delayed gastric emptying.

Patients with symptoms suggestive of gastroparesis can be studied with various techniques to confirm delayed emptying of the stomach.

Diagnosis is usually made using an isotope-labeled test meal (Isotopic gastric scintigraphy).

Diagnosis of gastroparesis is based on the presence of symptoms such as nausea, vomiting, and postprandial abdominal fullness and on an objectively determined delay in gastric emptying. Gastric emptying can be assessed by scintigraphy and stable isotope breath tests.

Treatment options remain limited despite the disabling nature of the disorder. Treatment is incremental and includes education, dietary support, and prokinetic and antiemetic agents. There are no adequately powered controlled trials to support a particular drug regimen.

Therapies for gastroparesis include dietary modifications, behavioral changes, prokinetic drugs and, in the most severe cases, gastric electrical stimulation (gastric pacing) and surgery. Other interventions to ensure adequate nutrient intake include nasoduodenal feeding, percutaneous gastrostomy, or jejunostomy.

Dietary modifications appear more suitable than pharmacological treatment in resolving symptoms since side effects of suggested drugs have been described and recent studies indicated that appropriate dietary modification offer better results than suggested medication in resolving crises. In intractable gastroparesis, gastric neurostimulation appears to offer some benefit.

Electrogastrographic and gastric emptying tests. Patients with gastric dysrhythmias and upper GI symptoms may or may not have delayed gastric emptying. Similarly, patients with atrial fibrillation with palpitations and chest discomfort may or may not have impaired cardiac output. Patients with bradygastrias have normal or near-normal gastric emptying rates, whereas patients with tachygastrias have poorer gastric emptying. Patients with dyspepsia symptoms can be further categorized on pathophysiological basis by combining the EGG and gastric emptying studies (see diagram) *Fig. 185.1*.

Infantile Colic

Infantile colic has been defined as a condition characterized by paroxysmal episodes of unexplained full force crying for at least 3 days a week and continuing for 1 week or more in a thriving well-nourished infant.

The disorder occurs more likely in the evening, without identifiable causes and resolves spontaneously by the fourth month of life.

Infantile colic is a widespread clinical condition in the first 3 months of life which is easily recognized, but incompletely understood and difficult to solve. The available evidence suggests that infantile colic might have several independent causes. Medical hypotheses include food hypersensitivity or allergy, immaturity of the gut function, and dysmotility. The behavioral hypotheses include inadequate maternal–infant interaction, anxiety in the mother, and difficult infant temperament. Other

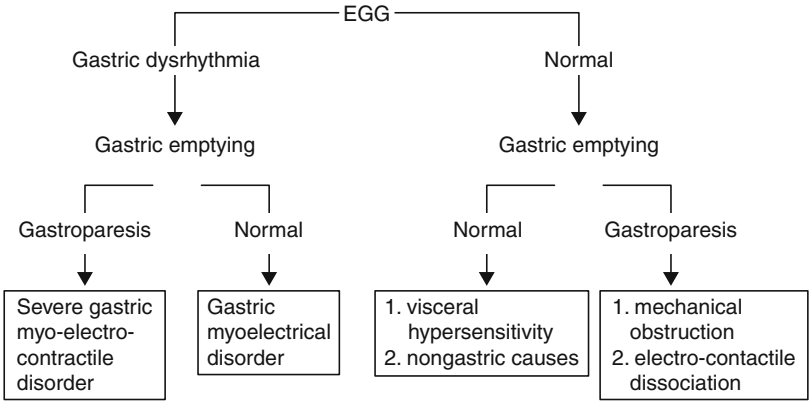

Figure 185.1
Results of Electrogastrogram (EGG) and gastric emptying in patients with dysmotility-like dyspepsia or unexplained nausea and vomiting

recent hypothesis, such as hormone alteration, maternal smoking and alteration in the gut microflora need further confirmation. A safe approach should be adopted which is proportional to the intensity of the infantile colic.

In a small subset of infants with colicky behavior, a specific medical disorder such as GERD or milk protein allergy may be identified.

The most important factors in appropriate intervention are physicians receptivity and sensitivity toward the stressed mother, together with an interested and practical approach to providing adequate support while delineating the individual stress acting on both mother and baby. The several factors involved in the pathogenesis make the management of infants with colic difficult.

Rumination Syndrome

This is a functional gastrointestinal disorder characterized by effortless repetitive regurgitation of undigested food from the stomach into the oropharynx. The food is then partially or completely rechewed, re-swallowed, or rejected.

Postprandial impedance manometry monitoring improves diagnosis of rumination because it allows distinction between rumination and postprandial belching and regurgitation. During rumination, esophageal liquid retrograde flow is first driven by an early small rise in intragastric pressure preceding the peak pressure observed during straining.

Infant rumination syndrome has an onset between 3 and 8 months, not associated with signs of nausea or distress. It constitutes a form of self stimulation, and has been linked to social deprivation. Bonding problems with the mother are frequently described. Adolescent rumination syndrome occurs without retching or nausea. It is immediately preceded by a sensation of belching.

When compared to idiopathic gastroparesis, regurgitation usually occurs during or within minutes from meal ingestion, and in contrast to gastroesophageal reflux disease, it is generally not associated with heartburn, discomfort, or esophagitis.

Rumination syndrome is reported among adolescents and adults of normal intelligence, even though it was initially considered only in infants and mentally retarded individuals. Reassurance and behavioral therapy is the mainstay of treatment with favorable results.

Functional Dyspepsia

Functional dyspepsia (FD) represents a group of gastrointestinal disorders, with patients who experience chronic nausea, postprandial bloating, and epigastric pain centered in the upper abdomen that is not relieved by bowel opening; it is not associated with constipation or diarrhea. Dyspepsia is a highly prevalent condition characterized by symptoms originating in the gastroduodenal region without underlying organic disorder.

While delayed gastric emptying is found in 40% of the patients with functional dyspepsia, other studies have shown accelerated emptying in a subgroup of patients. The possible role of Helicobacter pylori in functional dyspepsia remains controversial.

The 2006 Rome III criteria defined FD and its subgroups, postprandial distress syndrome (PDS), and epigastric pain syndrome (EPS). FD is a very common condition with a high prevalence throughout the world, adversely affecting the quality of life of patients.

Functional dyspepsia in childhood is commonly triggered by food allergen in sensitized individuals. Early onset neuroimmune interactions induced by cow's milk in the gastric mucosa of atopic children are associated with rapid disturbance of gastric myoelectrical activity and dyspeptic symptoms.

Mast cell density is associated with delayed gastric emptying and preprandial dysrhythmia, suggesting that there may be an interaction between antral inflammation and gastric electormechanical dysfunction in the pathophysiology of pediatric functional dyspepsia.

Functional gastrointestinal disorders as functional (or non-ulcer) dyspepsia are characterized by broad spectrum of symptoms referred to the upper abdomen without a detectable cause utilizing routine diagnostic measures. In recent years, placebo-controlled studies have demonstrated superiority of a commercial multicomponent herbal preparation, STW 5, with the trade name of "Iberogast," for the treatment of patients with functional dyspepsia and IBS. This phytopharmacon is a combination of nine plant extracts, each with a number of different active constituents.

Treatment is complex and challenging, as there is insufficient evidence to recommend the use of commonly employed drugs in the management of dyspepsia. Avoidance of nonsteroidal anti-inflammatory agents, spicy and fatty food, and caffeinated and carbonated beverages is generally recommended.

Antisecretory agents (H2 blockers or proton pump inhibitors) are often offered for pain predominant symptoms and prokinetics (metoclopramide, erythromycin, and domperidone) for symptoms associated with bloating and early satiety.

Treatment modalities include helicobacter pylori eradication therapy, tricyclic antidepressants, and psychological therapies.

Intestinal Functional Dysmotility

Irritable Bowel Syndrome (IBS)

In children old enough to provide accurate pain history, IBS is defined as chronic or recurrent abdominal pain, altered bowel habits, and bloating. It is recognized by having at least 12 weeks, which need not be consecutive, of:

1. Abdominal pain that has two or more of the following:
   (a) Improve with defecation
   (b) Onset associated with a change in the frequency of stool
   (c) Onset associated with the change in form (appearance) of stool
2. There is no evidence of an inflammatory, anatomic, metabolic, or neoplastic process to explain the symptoms.

Other features to support the diagnosis of IBS are:

1. Abnormal stool frequency (4 or more stools/day or fewer than 2 stools/week)
2. Abnormal stool form (lumpy/hard or loose/watery stools)
3. Straining, urgency, or a feeling of incomplete evacuation
4. Passage of mucus in the stools
5. Bloating or feeling of abdominal distention

IBS is a multifactorial lower functional gastrointestinal disorder involving disturbances of the brain-gut axis. Numerous studies have found an increased prevalence of abnormal psychiatric disorders, including anxiety, depression, personality disorders.

IBS is not a life-threatening condition, but it can have a serious impact on a patient's daily activities, quality of life and school performance.

Physical examination is generally unremarkable; however, the child may appear tense and anxious with occasional abdominal tenderness.

The diagnosis of IBS requires the identification of the symptoms characteristic of IBS and the exclusion of other clinical conditions of similar clinical presentation. There are no specific laboratory markers for the diagnosis of IBS.

Plain abdominal radiography is recommended during an episode of pain to exclude intermittent obstruction. In some patients, upper gastrointestinal study with small bowel follow through proves useful if a suspicion of Crohn disease or celiac disease does exist. Gastrointestinal manometry can identify patients with suspected intestinal pseudo-obstruction or gastroparesis.

IBS is a chronic illness and has no cure; however, medications targeting associated chronic constipation or diarrhea may result in some relief. Pretreatment with anticholinergic medication in IBS was shown to reduce meal-stimulated pain and diarrhea. Some patients with IBS may benefit from pharmacotherapy and behavioral

treatment. A high-fiber diet is useful in patients with IBS and constipation.

Abdominal Migraine

Abdominal migraine, cyclic vomiting syndrome (CVS), and migraine headache comprise a continuum of a single disorder often progressing from one clinical entity to another.

The diagnostic criteria for abdominal migraine must include all the following:

1. Paroxysmal episodes of intense, acute periumbilical pain that lasts for 1 h or more, with intervening symptom-free intervals lasting weeks to months
2. The pain interferes with normal activity
3. No evidence of an inflammatory, anatomic, metabolic, or neoplastic disease
4. Two or more of these features:
   (a) Headache
   (b) Photophobia
   (c) Pallor
   (d) Anorexia
   (e) Nausea
   (f) Vomiting

Functional Abdominal Pain Syndrome (FAPS)

Rome III (*adult criteria*) states that FAPS represents a pain syndrome attributed to the abdomen that is poorly related to gut function. FAPS is associated with some loss of daily activities, and should have been present for at least 6 months. The pain is constant, nearly constant, or at least frequently recurring. The principal criterion differentiating FAPS from other functional gastrointestinal disorders, such as IBS and functional dyspepsia, is the lack of symptom relationship to food intake or defecation.

The diagnostic criteria for Childhood (4–18 years old): Functional Abdominal Pain is the occurrence at least once per week for at least 2 months of episodic or continuous abdominal pain with insufficient criteria for other FGIDs, and no evidence of an inflammatory, anatomic, metabolic, or neoplastic disease that explains the symptoms.

Childhood Functional Abdominal Pain Syndrome must include childhood functional abdominal pain at least in 25% of the time and one or more of the following:

1. Some loss of daily function
2. Additional somatic symptoms such as headache, limb pain, or difficulty in sleeping

These criteria must be fulfilled at least once per week for at least 2 months.

Constipation and Incontinence

Gastrointestinal motility disorders and chronic constipation are common pediatric problems frequently encountered in the daily practice of pediatricians and pediatric surgeons.

The term "*functional constipation*" describes all children in whom constipation does not have an organic etiology. Because functional constipation and fecal retention often overlap, the two disorders were merged into one category.

Immaturity of the enteric nervous system, but also ganglioneuromatosis, can be the underlying cause of chronic constipation.

The number of affected patients with functional constipation 4 years or younger is much higher than patients older than 4 years.

Emergency department physicians and community pediatricians have an important role in the diagnosis and management of functional constipation despite its relatively low incidence.

Chronic constipation may be caused by myopathy.

For diagnosing functional constipation in infants and toddlers (less than 4 years), there must be at least two of the following criteria (observed for at least 1 month):

1. Two or fewer defecation per week
2. At least one episode per week of incontinence after the acquisition of toileting skills
3. History of excessive stool retention
4. History of painful or hard bowel movements
5. Presence of a large fecal mass in the rectum
6. History of large diameter stools that may obstruct the toilet

Accompanying symptoms may include irritability, decreased appetite, and/or early satiety. The accompanying symptoms disappear immediately following passage of a large stool.

Functional constipation in child/adolescent is similar to the above in addition to the presence of withholding behavior (retentive posturing or excessive volitional stool retention). The criteria must be fulfilled at least once per week for at least 2 months.

Non-retentative fecal incontinence represents the repeated, inappropriate passage of stool into a place other than the toilet in a child older than 4 years with no evidence of fecal retention. In these children, incontinence

is diurnal, and no fecal mass is found on rectal examination. An abdominal radiograph may show occult fecal retention because of incomplete passage of stool.

Macrogol 4,000 is one of the new generation's osmotic laxatives. It is constituted by a heavy molecular weight polymer without additional salts. In most patients, Macrogol 4,000 shows its efficacy in 48 h from the beginning of therapy.

Functional Diarrhea

The diagnosis of functional disease in patients with chronic watery diarrhea should be performed with caution since in most cases there is an organic cause that justifies diarrhea.

Functional abdominal bloating is a functional bowel disorder dominated by a feeling of abdominal fullness without sufficient criteria for another functional gastrointestinal disorder. Gas-related complaints (i.e., passage of flatus), which are present in a subgroup of these patients, might be associated with carbohydrate malabsorption.

The presence of malabsorption is assessed by means of hydrogen breath test.

Sugar malabsorption and intolerance seem to be frequent in patients with functional abdominal bloating and gas-related complaints. A sugar-free diet might be a long-term effective therapy in a high percentage of patients.

Recently, the use of probiotics in the treatment of diarrhea has been encouraged. The medication can help prevent further antibiotic associated diarrhea.

(N.B. More details on this subject are covered in the chapters on gut motility disorders, intractable diarrhea, and major symptoms and signs of gastrointestinal disorders.)

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186 Gut Motility Problem

Abdel-Hai Hammo · Hisham M. Nazer

Introduction

The human small bowel and colon display widely divergent patterns of absorption, motility, and transit. Propulsive, peristaltic motility can move contents over long distances of the small intestine very rapidly, with efficiency approaching that of the esophagus. The small intestine functions to facilitate emptying from the stomach, the mixing of chyme with digestive enzymes and bile, and ultimately delivery of residue to the colon. The ileum possesses a specialized type of contraction (giant migrating contraction) that sweeps unabsorbed residue to the colon and is analogous to the high-amplitude colonic contractions. Intermittent emptying ensures that enough time is available for salvage of the remaining nutrients in the small intestine. The small intestine and colon also set up feedback inhibitory reflexes (e.g., ileal brake) that retard proximal motor functions such as gastric emptying.

Gastrointestinal motility involves a complex processes in which parts of the stomach relax to accept food from the esophagus, whereas other parts deliver chyme to the small bowel at a rate optimal for digestion and absorption. Before delivery to the small intestine, the stomach stores, mixes, grinds, and sorts food substances into liquid and solid components that are processed and cleared by different mechanisms.

The colon receives liquid stool from the small intestine and slowly transports it to the rectum. During this journey, which usually takes 24 h, water is absorbed from the liquid stool, and a semisolid product is presented to the rectum. Rectal motility differs from colonic motility in that it remains stationary and allows the stool to remain there until a socially acceptable time, when a massive contraction (mass peristalsis) pushes the stool out and completely empties the rectum. Smooth muscle and enteric nerves together with interstitial cells of Cajal (ICC) form complex control systems.

Networks of interstitial cells of Cajal embedded in the musculature of the gastrointestinal tract are involved in the generation of electrical pacemaker activity for gastrointestinal motility. This pacemaker activity manifests itself as rhythmic slow waves in membrane potential, and controls the frequency and propagation characteristics of gut contractile activity. Identification of the pacemaker of gut motility will aid in the elucidation of the pathophysiology of intestinal motor disorders, and provide a target cell for pharmacological treatment.

The principal components of the enteric nervous system are two networks or plexuses of neurons, both of which are embedded in the wall of the digestive tract and extend from esophagus to anus:

- The *myenteric plexus* is located between the longitudinal and circular layers of muscle in the tunica muscularis and, appropriately, exerts control primarily over digestive tract motility.
- The *submucous plexus*, as its name implies, is buried in the submucosa. Its principal role is in sensing the environment within the lumen, regulating gastrointestinal blood flow and controlling epithelial cell function. In regions where these functions are minimal, such as the esophagus, the submucous plexus is sparse and may actually be missing in sections.

In addition to the two major enteric nerve plexuses, there are minor plexuses beneath the serosa, within the circular smooth muscle and in the mucosa.

Within the enteric plexuses are three types of neurons, most of which are multipolar:

- *Sensory neurons* receive information from sensory receptors in the mucosa and muscle. At least five different sensory receptors have been identified in the mucosa, which respond to mechanical, thermal, osmotic, and chemical stimuli.

  Chemoreceptors sensitive to acid, glucose, and amino acids have been demonstrated which, in essence, allow "tasting" of luminal contents. Sensory receptors in muscle respond to stretch and tension. Collectively, enteric sensory neurons compile a comprehensive battery of information on gut contents and the state of the gastrointestinal wall.
- *Motor neurons* within the enteric plexuses control gastrointestinal motility and secretion, and possibly absorption. In performing these functions, motor neurons act directly on a large number of effector cells, including smooth muscle, secretory cells (chief,

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parietal, mucous, enterocytes, pancreatic exocrine cells), and gastrointestinal endocrine cells.
- *Interneurons* are largely responsible for integrating information from sensory neurons and providing it to ("programming") enteric motor neurons.

Enteric neurons secrete an intimidating array of neurotransmitters. One major neurotransmitter produced by enteric neurons is acetylcholine. In general, neurons that secrete acetylcholine are excitatory, stimulating smooth muscle contraction, increases in intestinal secretions, release of enteric hormones and dilation of blood vessels. Norepinephrine is also used extensively for neurotransmission in the gastrointestinal tract, but it derives from extrinsic sympathetic neurons; the effect of norepinephrine is almost always inhibitory and opposite to that of acetylcholine.

Two fundamental patterns of motility are conducted by the digestive tube: propulsion, where food must be propelled along the length of the digestive tube for absorption through peristaltic waves and mixing of the ingested materials that simply propelled through the digestive tube. Congenital and acquired derangements in the structure or function of the enteric nervous system are well recognized as causes of digestive tract disease. Examples include small intestinal motility disorders, gastric outlet obstructions, and megacolon.

Normal and Disordered Motility

Gastrointestinal contractions can be broadly divided into three basic types: phasic, tonic, and ultrapropulsive contractions.

Phasic contractions are relatively brief and may be propagated or nonpropagated. Nonpropagated phasic contractions serve to mix the intestinal contents, allowing maximum exposure of the mucosa to luminal contents.

Tonic contractions are prolonged contractions lasting minutes to hours. The gastric fundus and colon exhibit tonic contractions to promote gradual transfer of luminal contents from areas of higher to lower intraluminal pressure.

Ultrapropulsive contractions consist of giant migrating contractions in the antegrade and retrograde direction to move the luminal contents rapidly over relatively large distances.

Intestinal motility disorders apply to abnormal intestinal contractions, such as spasms and intestinal paralysis. This phrase is used to describe a variety of disorders in which the gut has lost its ability to coordinate muscular activity because of endogenous or exogenous causes. GI motility and functional bowel disorders, such achalasia, gastroesophageal reflux disease, gastroparesis, functional dyspepsia, irritable bowel syndrome, colonic inertia, pelvic floor dyssynergia, constipation, and fecal incontinence, comprise high percentage of GI problems for which patients seek health-care advice and management. GI motility disorders affect patients by not only causing symptoms and posing a heavy burden of illness but cause decreased quality of life with decreased work productivity.

Examples of gastrointestinal motility disorders in kids and teens include: Chronic intestinal pseudo-obstruction, Gastroesophageal reflux (GER), Gastroesophageal reflux disease (GERD), Hirschsprung's disease, Constipation, Diarrhea, and Intestinal neuronal dysplasia (IND).

Gastrointestinal motility is defined by the movements of the digestive system, and the transit of the contents within it. When nerves or muscles in any portion of the digestive tract do not function in a strong coordinated fashion, a person develops symptoms related to motility problems. These symptoms may include:

- Heartburn
- Dysphagia
- Abdominal distention and pain
- Nausea
- Vomiting
- Constipation
- Diarrhea

Examples of functional GI and/or motility disorders include:

- Chronic abdominal pain
- Constipation
- Cyclic vomiting syndrome
- Diarrhea
- Dyspepsia
- Encopresis (fecal soiling)
- Functional fecal retention
- Gastroesophageal reflux (GER)
- Gastroesophageal reflux disease (GERD)
- Gastroparesis
- Hirschsprung's disease
- Incontinence
- Intestinal pseudo-obstruction
- Irritable bowel syndrome (IBS)

Dysmotility of the Small Intestine and Colon

The prevalence of small intestinal dysmotility varies according to the underlying disease, and it seems to be less frequent than esophageal, gastric, or colonic dysmotility.

1. *Primary dysmotilities are rare compared with secondary dysmotilities.* They may be familial or sporadic.
   - Familial visceral myopathies
   - Congenital neuropathic motility disorders
     - *Disorders of colonization* by migrating neural crest derived neurons, as in Hirschsprung disease
     - *Disorders of differentiation* of enteric nerves, as in intestinal ganglioneuromatosis
     - *Disorders of survival or maintenance of enteric nerves*, as in hypoganglionosis and possibly congenital achalasia
   - *Childhood visceral myopathies*
2. *Secondary Causes of Small Intestinal Dysmotility*
   - Diabetes mellitus
   - Thyroid and parathyroid disease: Hyperthyroidism, Hpothyroidism, and *Hypoparathyroidis*
   - Celiac disease
   - Anorexia nervosa and bulimia
   - Drug-induced changes in small intestinal motility

Clinical Manifestations

Severe dysmotility of the esophagus, colon, and even the stomach occur much more frequently than dysmotility of the small intestine. Isolated severe small intestinal dysmotility is very unusual. Small intestinal dysmotility is generally associated with dysmotility in other parts of the digestive tract. With a few exceptions, most patients with small intestinal dysmotility have similar clinical manifestations regardless of the underlying causes. The spectrum of clinical manifestations varies widely. At one end, the patient may be asymptomatic, and at the other, the patient may have recurrent symptoms and signs of small intestinal obstruction, termed *chronic small intestinal pseudo-obstruction.*
The patient may have recurrent symptoms of:

1. Postprandial cramping.
2. Periumbilical and epigastric abdominal pain.
3. Abdominal bloating.
4. Easy satiety.
5. Anorexia, weight loss.
6. Nausea and vomiting.
7. Diarrhea can occur in patients with bacterial overgrowth and malabsorption.
8. In severe cases, chronic intestinal pseudo-obstruction syndrome can occur.

The findings on physical examination vary according to the severity of the symptoms. Patients may be cachectic and malnourished because they are unable to take in adequate nutrients, or they may have malabsorption as a consequence of bacterial overgrowth in the small intestine. The abdomen may be distended and mildly tender. The bowel sounds are inactive and infrequent in patients with smooth muscle dysfunction, but they are hyperactive and high-pitched in those with myenteric plexus dysfunction. Borborygmi may be detected in some cases.

In less symptomatic patients, the abdominal examination findings may be normal. In those with chronic intestinal pseudo-obstruction, during an obstructive episode, the abdominal examination findings may be indistinguishable from those of true mechanical obstruction.

Extraintestinal manifestations may be detected in some patients, depending on the underlying disease. Megacystis and megaureter are common in type I familial and childhood visceral mypopathies and may be associated with urinary retention and infection.

Mydriasis, ptosis, and external ophthalmoplegia may be seen in certain forms of familial visceral myopathy, and ataxia, dysautonomia, and neurological symptoms in some forms of visceral neuropathy.

Diagnostic Studies

1. Blood Studies
   (a) Blood Tests: CBC for macrocytosis, anemia, and malnutrition
   (b) Thyroid function tests: T4, TSH
   (c) Blood glucose for diabetes
   (d) Chemistry for malabsorption
   (e) Liver and muscle enzymes and isoenzymes for muscular dystrophy
2. Radiologic Studies
   (a) KUB: gaseous distension. Dilated loops and other anomalies
   (b) Enteroclysis
   (c) Barium enema and intravenous pyelography
3. Whole-gut transit with radiopaque markers
4. Radioactive isotope transit by scintigraphy
5. Small Intestinal Manometry
6. Colonic Manometry

Treatment

Drug Therapy

Drugs that stimulate intestinal motility in normal subjects (e.g., bethanechol, neostigmine, metoclopramide,

erythromycin, tegaserod, prucalopride) have no beneficial effects in patients with small intestinal dysmotility. No information is available on the use of domperidone for small bowel dysmotility. Octreotide, and somatostatin analog, stimulated intestinal motility, possibly reduced bacterial overgrowth, and relieved abdominal symptoms.

Symptomatic and Supportive Treatment

Abdominal pain, bloating, nausea, and vomiting in patients with small intestinal dysmotility are often related to eating. Most of these symptoms can be minimized by manipulating the size, nature, and frequency of meals. When patients still feel full several hours after the first meal, it is important that they do not force themselves to eat subsequent meals to avoid aggravating their symptoms and that they restrict their oral intake to fluids for the rest of the day. In patients with chronic intestinal pseudo-obstruction, recurrent symptoms and signs of intestinal pseudo-obstruction may occur despite those measures.

Medical and Nutritional Approaches

In these situations, nasogastric suction and intravenous fluids are needed when obstructive symptoms develop. When obstructive symptoms and pain persist or occur several times a week despite dietary manipulation, long-term parenteral nutrition is the only treatment that will relieve symptoms and improve nutrition.

Constipation is common in patients who also have colonic involvement. It is important to make certain that the patient has a good bowel movement at least once every few days because constipation tends to increase the symptoms of intestinal dysmotility. Enemas, milk of magnesia, and other laxatives are to be used to relieve the discomfort and constipation.

Those with severe small intestinal dysmotility should avoid bulk-forming laxatives because they increase the load on an inefficient intestine and exacerbate symptoms.

Surgical Treatment

Patients with dysmotility limited to short segments of the small intestine, such as those with megaduodenum, have a better prognosis than those with dysmotility throughout the length of the bowel because the dysfunctional segment can be resected or bypassed.

Venting decompression by percutaneous jejunostomy or minilaparotomy or laparoscopy relieves symptoms and reduces the rate of hospitalization for recurrent exacerbations of pseudo-obstruction.

Any unnecessary surgery should be avoided in these cases because it can create adhesions and additional difficulties.

Complications

- Complications of intestinal motility disorders vary greatly depending on the type of disorder considered.
- Intestinal pseudo-obstruction is often associated with a high morbidity and mortality, depending on associated anomalies.
- Constipation may have a severe complication, impaction.
- Fecal incontinence may cause psychological problems in affected children and have major impact on daily activity and school performance.

Intestinal Pseudo-obstruction

Chronic intestinal pseudo-obstruction is a severe disorder characterized by disabling and potentially life-threatening condition over time.

This condition is characterized by sporadic intestinal obstruction secondary to ileus. There are signs and symptoms of intestinal obstruction but without anatomic or histologic abnormality. It may mimic Hirschsprung disease. The definitive cause of intestinal pseudo-obstruction remains unknown.

The effect of this condition is evident in utero, with fetal abdominal distention and maternal polyhydramnios. After birth, there is failure to pass meconium with repeated vomiting. The condition may be associated with urinary stasis and retention. The condition has to be differentiated from other causes of intestinal obstruction.

Intestinal pseudo-obstruction is defined as a chronic condition, often unrecognized, that represents disorders of the enteric nervous system or the smooth muscle. The disease continues to progress with no definite response to medical therapy. Clinical features are nonspecific and include vomiting in an infant with abdominal pain and distention.

The diagnosis is based on the evidence of recognized typical clinical features, radiological evidence of distended bowel loops with air-fluid levels, and the exclusion of any organic cause for intestinal obstruction. However, because

of lack of high index of suspicion, the diagnosis is often delayed for years resulting in worsening the overall clinical outcome making the prognosis fairly poor.

Barium contrast studies reveal dilated hypomotile intestine with no evidence of mechanical obstruction. Full-thickness intestinal biopsies are helpful in identifying the abnormalities as neuronal or muscular.

Surgical measures are needed in case of urinary tract involvement. Medical therapies have been used, but results were suboptimal.

The majority of patients require parenteral nutrition and if this fails, small bowel transplantation with its guarded prognosis remains the only therapeutic option.

Megacystis-Microcolon-Intestinal Hypoperistalsis Syndrome

Megacystis-microcolon-intestinal hypoperistalsis syndrome (MMIHS) is a rare congenital, fatal autosomal recessive disorder of unknown etiology that was first described in 1976 by Berdon et al. in a live newborn girl.

MMIHS was originally thought to affect only females, but later on, it was reported to also affect males with a reported female-to-male ratio of 3:1. The condition is characterized by abdominal distention secondary to a distended nonobstructed bladder, microcolon, and normal ganglion cell distribution in the intestine.

The exact etiology of this syndrome remains unknown. The pathophysiology and site of the neuromuscular function disturbances in the gut and bladder are as yet unclear.

The condition may be suspected prenatally with the presence of prominent renal pelvis and bilateral hydronephrosis. It is important that MMIHS be differentiated in utero from posterior urethral obstruction due to urethral atresia or posterior urethral valve. In utero decompression by percutaneous catheter drainage under sonographic guidance may be considered.

MMIHS is a rare cause of functional gastrointestinal and genitourinary obstruction in the newborns of unknown pathogenesis whose genes map to 15q24. MMIHS is well recognized for being the most severe form of functional intestinal obstruction in the newborn.

No specific mechanical obstruction is demonstrated in either the genitourinary or gastrointestinal system.

Clinical Features

MMIHS is a recognized cause of intestinal obstruction in the newborn. The clinical manifestations are similar in broad terms to those of functional intestinal obstruction due to other causes with abdominal distention, vomiting, and delayed or absent bowel movements. The abdominal distention results primarily from distention of the urinary bladder.

MMIHS is a rare cause of functional gastrointestinal and genitourinary obstruction in the newborns. Prenatal diagnosis is warranted for optimal prenatal counseling and postnatal treatment.

MMIHS is associated with both polyhydramnios and oligohydramnios. The clinical manifestation may vary accordingly with predominance of renal failure in cases associated with oligohydramnios.

The patient may also present with lax abdominal musculature, incomplete intestinal rotation, and bilious vomiting. The signs and symptoms of MMIHS vary with each individual patient, presenting a spectrum of severity.

Diagnosis

Diagnosis of MMIHS is possible during antenatal routine visits. Bladder dilatation on fetal ultrasound is a reliable sign for prenatal diagnosis prior to 25 weeks' gestation.

The diagnosis is suggested by radiographic evaluation and detection of an enlarged bladder and bilateral hydronephrosis, hydroureter, and microcolon. Barium enema examination will demonstrate the thin-walled, unused, and displaced microcolon (*Fig. 186.1*).

The cecum is located in the left upper quadrant, suggestive of malrotation. In view of the poor intestinal motility, the contrast material will remain in the bowel for an extended period of lime. Voiding cystourethrogram demonstrates massively distended urinary bladder (*Fig. 186.2*). It may also reveal an associated vesicouretric reflux.

The clinical, radiologic, and surgical findings are relatively constant and characteristic enough to allow prompt diagnosis. MRI is safe, accurate, and can be used for early prenatal diagnosis.

The most frequent findings are massively distended urinary bladder and microcolon with normal neuronal innervation. Electron microscopy of bowel and bladder shows vascular degenerative changes in the smooth muscle cells with abundant amounts of connective tissue between muscle cells.

The diagnosis of MMIHS is highly considered by antenatal detection of enlarged bladder in the second trimester and polyhydramnios in the third trimester.

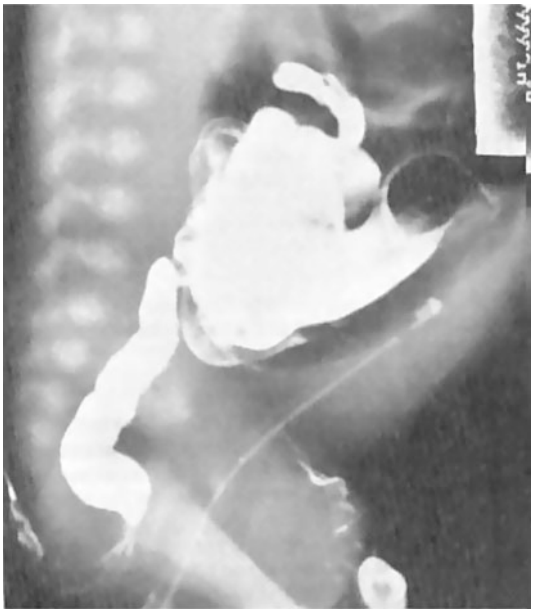

Figure 186.1
Barium enema reveals microcolon in a newborn with megacystis-microcolon-intestinal hypoperistalsis syndrome

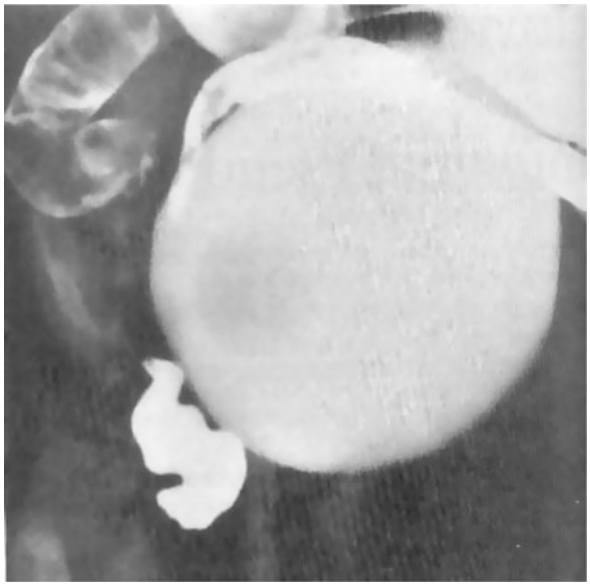

Figure 186.2
Voiding cystourethrogram in a baby with MMIHS at 4 weeks of age demonstrates massively distended bladder

Rectal biopsy is usually obtained to rule out Hirschsprung disease. Ganglion cells have also been present in all reported cases, frequently with areas of hypoganglionosis.

Figure 186.3
Histologic findings in a biopsy from ileum of a baby with MMIHS showing prominent ganglia cell groups in the submucosa (*small arrow*) and in the myenteric plexus (*large arrow*). Hematoxylin and eosin, ×100

Management

Although the urinary tract distention appears to resolve once open drainage has been established, the gastrointestinal tract does not function properly despite the use of various surgical and pharmacologic maneuvers.

Improvement of the nutritional status of affected infants with total parenteral nutrition and effective management of sepsis will ensure a better survival of patients with MMIHS.

A number of prokinetic drugs and gastrointestinal hormones have been tried without a real success (*Fig. 186.3*).

MMIHS is generally incompatible with long-term survival, and death usually occurs in infancy. Intrauterine death has also been reported. Out of the 59 cases reported with MMIHS by the year 1992, 51 (86.4%) died. There is no cure for the disease; however, with increasing recognition of more survivals of patients with MMIHS, it is anticipated that affected patients will gain the benefits of various forms of intestinal diversions and bladder decompression to allow the dilated upper urinary tracts to recover. Young and associate reported one girl with MMIHS still living at age 14 years.

Despite surgical intervention, management generally has been unsuccessful and nutrition must be maintained in most cases by total parenteral nutrition. Recently favorable reports highlighted the favorable outcome in MMIHS combined living–related segmental liver and bowel transplantation.

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187 Acute Gastroenteritis in Infants and Children

Asaad M. A. Abdullah Assiri

Definition

Acute gastroenteritis is generally defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency of evacuations (typically $\geq$3 in 24 h), with or without fever or vomiting. Diarrhea typically lasts less than 7 days and not longer than 14 days. However, a change in stool consistency vs. pervious stool consistency is more indicative of diarrhea than stool number, particularly in the first months of life.

Epidemiology and Incidence

In developing countries, acute gastroenteritis is a common cause of death in children under 5 years of age and that is caused by a wide variety of pathogens. In developed countries death from acute gastroenteritis is less common. Most of acute gastroenteritis is caused by viruses like rotaviruses, calciviruses, astroviruses, and adenoviruses; viral gastroenteritis affects children with two epidemiological patterns. In endemic area it affects children at all ages. Rotavirus is the leading cause of severe diarrheal disease in infants and young children worldwide. About 600,000 children die every year from rotavirus, with more than 80% of all rotavirus-related deaths occurring in resource-poor countries in south Asia and sub-Saharan Africa. Rotavirus-related deaths represent approximately 5% of all deaths in children younger than 5 years of age worldwide. Acute gastroenteritis secondary to rotavirus is severe in infants less than 6 months of age. It has been estimated that 500 million episodes of diarrhea per year occur among infants in Asia, Africa, and Latin America with more than five million deaths.

Risk Factors

Diarrhea-causing pathogens are usually transmitted through the fecal–oral route. Risk factors for this type of transmission include improper disposal of feces and lack of proper hand washing following defecation and feces contact before handling food. Other risk factors include improper food hygiene, inadequate food refrigeration, food exposure to flies, and consumption of contaminated water. Multiple host factors that determine the level of illness once exposure to infectious agents has occurred include age, personal hygiene, gastric acidity and other barriers, intestinal motility, enteric microflora, immunity, and intestinal receptors.

Pathology

Some infectious agents cause mucosal inflammation, which may be mild or severe. Bacteria such as enteroadherent or enteropathogenic *Escherichia coli* and viruses such as rotaviruses and Norwalk agent can cause minimal to moderate inflammation. Bacteria that destroy enterocytes such as *Shigella*, enteroinvasive *E. coli*, the parasite *Entamoeba histolytica*, and bacteria that penetrate the mucosa such as *Salmonella*, *Campylobacter jejuni*, and *Yersinia enterocolitica* result in moderate to severe inflammation with or without ulceration. Ingestion of preformed toxin produced by bacteria such as *Bacillus cereus*, *Staphylococcus aureus*, and *Clostridium perfringens* can result in acute jejunitis.

Causes of Acute Gastroenteritis

Acute gastroenteritis is either caused by viruses like rotaviruses, novoviruses (Norwalk like viruses), enteric adenoviruses, caliciviruses, enteroviruses, or bacteria like *E. coli*, non-typhoid *Salmonella* spp., *C. jejuni*, *Shigella* spp., *Y. enterocolitica*, and *Vibrio cholerae*; other pathogens that cause acute gastroenteritis in children are protozoa like *Giardia lamblia*, cryptosporidium, and *E. histolytica*.

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Causes of Acute Gastroenteritis in Children
Viruses (about 70%) • Rotaviruses • Noroviruses (Norwalk-like viruses) • Enteric adenoviruses • Caliciviruses • Astroviruses • Enteroviruses
Bacteria (10–20%) • *C. jejuni* • Non-typhoid *Salmonella* spp. • Enteropathogenenic *E. coli* • *Shigella* spp. • *Y. enterocolitica* • Shiga toxin producing *E. coli* • *Salmonella typhi* and *Salmonella paratyphi* • *V. cholerae*
Protozoa (<10%) • *Cryptosporidium* • *G. lamblia* • *E. histolytica*

Pathophysiology

Pathogens produce diarrhea by three basic mechanisms:

(1) Enterotoxins that induce active intestinal secretion (*V. cholerae*, *S. aureus*, *B. cereus*, *Clostridium botulinum*, and rotavirus)
(2) Cytotoxic mediators (most bacteria, parasites)
(3) Invasins promoting endocytosis, with subsequent tissue invasion and mucosal injury [*Shigella*, *Salmonella*, enteroinvasive *E. coli* (EIEC)]

In addition to direct effects by microorganisms and their products, enteropathogens induce intestinal damage indirectly via the mucosal inflammatory response, which involves secretion of various powerful mediators of secretion and apoptosis.

On the basis of these three mechanisms, acute infections present as watery, noninflammatory diarrheal syndromes or inflammatory diarrheal syndromes. The majority of watery, noninflammatory diarrhea cases are self-limited diseases characterized by low-grade fever, nausea, vomiting, large-volume diarrhea, and the absence of blood and leukocytes in the stools. This presentation is typically reported in patients infected with enterotoxigenic *E. coli*, *V. cholerae*, clostridial and staphylococcal food poisoning, rotavirus, Norwalk virus agent, *G. lamblia*, and *Cryptosporidium*. On the other hand, the inflammatory diarrheal syndrome is characterized by frequent, small-volume stools that may contain blood and leukocytes, tenesmus, fever, and severe abdominal pain. The most common microorganisms causing this syndrome include *Salmonella*, *Shigella*, *Campylobacter*, enterohemorrhagic *E. coli*, *Clostridium difficile*, *E. histolytica*, and *Yersinia*.

Mechanisms of Acute Gastroenteritis

The majority of bacterial pathogens secretes enterotoxins that selectively activate enterocyte intracellular signal transduction and also affect cytoskeletal rearrangements with subsequent changes in water and electrolyte fluxes across enterocytes upregulations of these mechanism results in inhibition of NaCl paired transport and increased efflux of chloride resulting in secretion and loss of water into the intestinal lumen.

Enterotoxigenic *E. coli* (ETEC) colonizes and attaches its fimbriae to the small bowel enterocyte and leads to hypersecretion of fluids and electrolytes into the small intestine. Both ETEC and *V. cholerae* toxin activate adenyl cyclase and lead to an increase in intracellular cyclic guanosine monophosphate (CGMP).

Non-typhoid salmonella mainly invades the distal ileum and produces toxigenic diarrhea as well as inflammation of the intestine. *Shigella* toxin has both secretory and cytotoxic effects. It invades the colonic mucosa and causes superficial ulceration and increases motility of the large bowel.

Another important pathogen that causes diarrhea is *G. lamblia*, which attaches itself to the small bowel mucosa. *E. histolytica* causes diarrhea through invasion of colonic mucosa.

Viral Gastroenteritis

Viral Pathogens

The viral pathogens that cause acute gastroenteritis represent four distinct viral families. Rotaviruses are members of the family Reoviridae and have a segmented, double-stranded RNA genome enclosed in a triple-layered capsid. Noroviruses and sapoviruses constitute two genera of the family Caliciviridae, with a positive-sense RNA genome inside a capsid composed of a single structural protein. Astroviruses, of the family Astroviridae, are also non-enveloped viruses with a positive-sense RNA genome, but their capsid is composed of several structural protein subunits. Enteric adenoviruses represent a unique

subgroup of the family Adenoviridae and have a double-stranded DNA genome. Each of these viruses also can be distinguished by electron microscopy by their characteristic morphologic features.

Rotavirus

Rotaviruses are 70-nm icosahedral viruses that belong to the family Reoviridae. Seven rotavirus serogroups (serogroups A to G) are described. Most human pathogens belong to groups A, B, and C. Group A rotaviruses are the most important cause of acute diarrhea.

The virus infects the mature villus epithelial cells of the small intestine. Dehydration and electrolyte disturbances are the major sequelae of rotavirus infection and occur most often in the young children. Rotavirus infection is usually localized to the small intestine; however, recent studies reported antigenemia or viremia in children with rotavirus diarrhea. Rarely, rotavirus may involve the extraintestinal sites, including the respiratory tract, liver, kidney, lymph nodes, and central nervous system.

Group A rotaviruses are the most important cause of severe dehydrating diarrhea in infants and children. On a global scale, it is estimated that there are 125 million cases of rotavirus diarrhea, including eight million cases of severe diarrhea and 600,000 deaths.

Children between the ages of 3 months and 3 years are most susceptible to infection. Because immunity to reinfection is not complete, rotavirus disease can also occur in otherwise healthy adolescent, as well as in children who are immunosuppressed.

Infection is transmitted primarily through the fecal–oral route in a highly efficient manner that owes to the large amount of viruses shed in feces. Food and waterborne transmission is not common, but has also been reported. The incubation period ranges from 1 to 3 days and is followed by the abrupt onset of fever, malaise, vomiting, and watery diarrhea. Duration of illness varies from 3 to 8 days. Severely immunocompromised children may have a protracted course. Dehydration, with associated mild elevation of blood urea nitrogen (BUN) and metabolic acidosis, occur most often in young children. Dehydration and electrolyte disturbances are the major sequelae of rotavirus infection and occur most often in the young children.

If specific diagnosis of rotavirus infection is needed, enzyme immunoassays, with >90% sensitivity and specificity, are commercially available. Other diagnostic methods, including immune electron microscopy, nucleic acid hybridization with or without reverse transcriptase and polymerase chain reaction (RT-PCR), RNA electrophoresis, and cell culture isolation, are not as widely available.

Noroviruses

Norovirus is the new name for a genus of the family Caliciviridae that includes a genetically diverse, but related, group of non-enveloped, single-stranded RNA viruses that are a major cause of acute gastroenteritis in humans.

Typically, after an incubation period of 12–48 h, children will experience the acute onset of nausea, vomiting, less diarrhea, and low-grade fever. The symptoms last for 12–60 h, after which there is complete resolution of the illness.

The most widely used assay at present for diagnosing norovirus infection is RT-PCR, which can detect 10^2 to 10^4 viral particles/mL of stool.

Sapovirus

Sapporo virus, a calicivirus with classic morphology, is the prototype of the newly named genus *Sapovirus*.

Sero-prevalence studies indicate that nearly all children have acquired Sapovirus antibodies by the age of 12 years, and these antibodies seem to confer long-term resistance to reinfection. Infection is most likely transmitted through the fecal–oral route. Oysters and cold foods have also been implicated as vectors of transmission. Following an incubation period of 24–72 h, children develop vomiting and diarrhea acutely, with associated fever and respiratory symptoms.

The symptoms, which resemble those of a mild rotavirus infection, last for 24–48 h. The infection can be diagnosed by direct electron microscopy, given the large quantities of viruses shed in feces and their distinctive appearance.

Astroviruses

Human astroviruses primarily cause acute gastroenteritis in children, who are immunocompromised (HIV-infected children and bone marrow transplant recipients). Astrovirus antibodies are acquired early in childhood, with antibody prevalence rates in the range of 70% by school age. A typical case of astrovirus gastroenteritis in an immunocompetent child consists of a mild, watery

diarrhea, vomiting, fever, and abdominal pain, which begin after an incubation period of 1–4 days. The symptoms last 2–3 days. In some immunocompromised children, protracted and severe illness may occur.

Because astroviruses are shed in large quantities during infection and because at least 10% of the viruses display a distinctive surface star, diagnosis can be made by direct electron microscopy.

Enteric Adenovirus

Enteric adenovirus infections have a worldwide distribution, primarily infecting children under the age of 2 years.

After an incubation period of about 7 days, children develop watery diarrhea and less commonly vomiting. Respiratory symptoms and low-grade fever may also develop during the course of illness. Infection can range from mild to severe, but the majority of cases are mild. Viral shedding in stool lasts for up to 2 weeks, substantially longer than for rotavirus. The clinical course may be complicated by prolonged lactose intolerance and malabsorption. The preferred method to detect the presence of enteric adenovirus in stool is the enzyme immunoassay.

Bacterial Gastroenteritis

Bacterial Infections

Salmonellosis

The most common form of salmonellosis is acute gastroenteritis, because the organisms are frequently ingested in foods that have been contaminated by animal feces or by human carriers. The syndrome has often been referred to as salmonella food poisoning. The incubation period varies from 18 to 36 h, although it may be as short as 8 h or as long as 3 days. The first symptoms are nausea and vomiting; abdominal pain is frequent and may be very mild or severe. Fever may be absent, or of low or high degree. Chills occasionally occur. There may be only mild diarrhea; in severe cases the diarrhea is often profuse and bloody. In very young children the disease may cause severe watery diarrhea. Symptoms are present for 3–4 days on the average, although they may last only a day or persist for weeks. Rarely children may develop chronic diarrhea which is marked by remissions and exacerbations of marked diarrhea, fever, and abdominal pain. The white cell count is usually normal, but it might be elevated. Blood cultures are rarely positive; the stool may contain blood and leukocytes if the diarrhea is severe. Septic complications are uncommon except in young children. The carrier state appears in some instances without relation to the severity of the acute episode, and in 10–20% of the cases salmonellae may be excreted for weeks or months after acute gastroenteritis. Acute gastroenteritis with a fatal outcome is most frequent in small infant with impaired immunological defenses.

Shigellosis

The infection is restricted to the large bowel. In some patients the lesions may involve the terminal ileum, but with less inflammation than in the colon.

The incubation period of shigellosis is usually 2–4 days, but it may be as long as a week. Commonly acute gastroenteritis secondary to shigellosis is mild; the classic manifestations of bloody diarrhea, high fever, abdominal pain, and leukocytosis are lacking in the majority of infants and children. In some, the disease is moderately severe, with an abrupt onset, high fever, abdominal pain, vomiting, and frequent, loose, watery stools; in a small group of children, the symptoms are severe and complicated with marked dehydration and shock from loss of fluids and electrolytes. The absorption of large amounts of shigella toxins is thought to play a role in the severe cases.

Yersinia

Y. enterocolitica infection (as its name indicates) is characterized by an enterocolitis, similar to that caused by *Salmonella*, *Shigella*, *Campylobacter*, and invasive *E. coli*. The diarrhea may be mild and self-limiting or it may be severe, with high fever (39°C or greater), vomiting, abdominal pain, and, infrequently, blood in the stools. The organisms may invade the mesenteric lymph nodes, mimicking an acute appendicitis in older children.

C. jejuni

Overall, the clinical picture of *C. jejuni* gastroenteritis in infant and children is characterized by diarrhea which is usually present at the onset of fever and abdominal pain; the diarrhea is watery, profuse, and foul smelling. After 1–3 days of diarrhea, many children have blood-streaked stools. The abdominal pain is periumbilical and colicky and may precede other symptoms. The pain may simulate that experienced with acute appendicitis, mesenteric

adenitis, intussusceptions, or visceral perforation. Vomiting is present in less than 30% of cases, and dehydration is unusual. Fever is variable, usually present, and of low grade; it may be present initially. Bacteremia is rare. The diarrhea usually lasts only 3–5 days.

E. coli

E. coli are gram-negative, lactose-fermenting motile bacilli of the family Enterobacteriaceae. Currently, 171 somatic (O) and 56 flagellar (H) antigens are recognized. Six distinct categories of *E. coli* are currently considered enteric pathogens: enteropathogenic *E. coli* (EPEC), enterotoxigenic *E. coli* (ETEC), enteroinvasive *E. coli* (EIEC), enterohemorrhagic *E. coli* (EHEC), diffusely adherent *E. coli* (DAEC), and enteroaggregative *E. coli* (EAggEC).

The diagnosis of diarrheagenic *E. coli* relies on isolation from stool and subsequent differentiation from commensal *E. coli* either by using genetic probes or by phenotypic assays. With the exception of *E. coli* O157:H7, assays for detection are not routinely available in clinical laboratories.

Enteropathogenic E. coli: (EPEC)

This was the first group of *E. coli* species shown to be pathogens for humans and has been responsible for devastating outbreaks of nosocomial neonatal diarrhea and infantile diarrhea in virtually every corner of the globe. Species of EPEC are distinguished from other *E. coli* species by their ability to induce a characteristic attaching and effacing lesion in the small intestinal enterocytes and by their inability to produce Shiga toxins.

Clinical Manifestations

The infective dose for EPEC is high ($\approx 10^9$ colony-forming units). EPEC causes a self-limited watery diarrhea with a short incubation period (6–48 h). There may be associated fever, abdominal cramps, and vomiting, and EPEC is a leading cause of persistent diarrhea (lasting 14 days or longer) in children.

Enterotoxigenic E. coli: (ETEC)

Species of ETEC are an important cause of diarrheal disease in humans and animals worldwide. Their pathogenicity is related to the elaboration of one or more enterotoxins that are either heat stable (ST) or heat labile (LT) without invading or damaging intestinal epithelial cells.

Clinical Manifestations

Like EPEC, ETEC requires a relatively high inoculum and a short incubation period (14–30 h). The cardinal symptom is watery diarrhea, sometimes with associated fever, abdominal pain, and vomiting. In its most severe form, ETEC can cause cholera-like diarrhea, even in adolescents. The illness is typically self-limited, lasting for less than 5 days, with few cases persisting beyond 3 weeks. Infection with ETEC has also been associated with short- and long-term adverse nutritional consequences in infants and children.

Enteroinvasive E. coli: (EIEC)

Presenting with bloody mucosy diarrhea associated with fever and abdominal pain, it also causes hemorrhagic colitis.

This group consists of invasive *E. coli* species that are generally, biochemically, and clinically nearly identical to *Shigella*.

Clinical Manifestations

Like *Shigella*, EIEC can produce dysentery, but watery diarrhea is more common.

Enterohemorrhagic E. coli: (EHEC)

These *E. coli* species produce either one or both phage-encoded potent cytotoxins termed Shiga-like toxin (SLT) I (which is neutralized by antisera to Shiga toxin produced by *Shigella dysenteriae* type I) or SLT II (which is not neutralized) and can cause diarrhea or Hemolytic Uremic Syndrome (HUS). *E. coli* O157:H7 is the prototypic (but not the exclusive) EHEC serotype because it is the predominant SLT-producing *E. coli*.

Clinical Manifestations

Illness with EHEC follows 3–9 days after ingestion of as few as 100 organisms. Colicky abdominal pain and

nonbloody diarrhea are the first symptoms, sometimes associated with vomiting. By the second or third day of illness, diarrhea becomes bloody in approximately 90% of cases, and abdominal pain worsens. Bloody diarrhea lasts between 1 and 22 days (median 4 days). Unlike other infectious causes of blood diarrhea, fever is usually absent or remains low grade. Younger children appear to excrete the organisms longer (median 3 weeks) than older children.

Intestinal complications include rectal prolapsed, appendicitis, intussusceptions, and pseudomembranous colitis. Extraintestinal complications are rare.

The most frightening complication of EHEC infection is HUS. It is usually diagnosed 2–14 days after the onset of diarrhea. Risk factors include young and old age, bloody diarrhea, fever, an elevated leukocyte count, and treatment with anti-motility agents. Two-thirds of children who develop HUS are no longer excreting the organism at presentation.

Diffusely Adhering E. coli: (DAEC)

DAEC was considered a nonpathogenic *E. coli* because early studies failed to find an association between this microorganism and diarrheal disease. However, studies performed during the past 15 years have demonstrated such an association, particularly in children older than 2 years of age.

Clinical Manifestation, Diagnosis

The gastrointestinal symptoms that characterize DAEC infection are practically indistinguishable from those caused by ETEC, with self-limiting watery diarrhea rarely associated with vomiting and abdominal pain. The diagnosis is mainly based on DNA probe technique and on the pattern of adherence of the microorganism on Hep-2 cells.

Enteroaggregative *E. coli*: (EAggEC)

EAggEC are diarrheagenic *E. coli* defined by a characteristic aggregating pattern of adherence to Hep-2 cells and the intestinal mucosa. They have been particularly associated with cases of persistent diarrhea. It has been hypothesized that the aggregating pattern of adherence may be a result of nonspecific, possibly hydrophobic, interaction; therefore, not all organisms meeting the definition of EAggEC may be pathogenic in humans.

Clinical Manifestations

Typically, illness is manifested by a watery, mucoid, secretory diarrheal illness with low-grade fever and little or no vomiting. However, in epidemiologic studies, grossly bloody stools have been reported in up to one-third of patients with EAggEC diarrhea.

Diagnosis and Treatment

Colonization of EAggEC is detected by the isolation of *E. coli* from the stools of patients and the demonstration of the aggregative in the hep-2 assay. Implication of EAggEC as the cause of the patient's disease must be done cautiously, given the high rate of asymptomatic colonization in many populations. If no other organism is implicated in the patient's illness and EAggEC is isolated repeatedly, then EAggEC should be considered a potential cause of the patient's illness. A DNA fragment probe has proven highly specific in the detection of EAggAC strains. A PCR assay using primers derived from the aggregative probe sequence shows similar sensitivity and specificity.

Cholera

The incubation period is between 18 and 120 h. Acute watery diarrhea with no abdominal pain and no fever, the stool looks like rice water, infants and children will develop moderate to severe dehydration with electrolyte imbalance within few hours. The condition might be associated with hypovolemic shock, hypoglycemia, and convulsion. Children, if untreated, may die within few hours of the onset of the disease.

The disease may be associated with acute tubular necrosis, hypokalemia and arrhythmia or hypoglycemic is one of the most common serious complication of cholera.

Aeromonas

Aeromonads are gram-negative facultative anaerobic, motile bacilli. Although their association with gastroenteritis is still somewhat controversial, experimental, clinical, and epidemiologic data continue to support evidence that at least certain strains are involved in diarrheal disease. The highest attack rate appears to be in young children, particularly those under 3 years of age. Aeromonas infections occur more frequently during the warm months.

Acute secretory diarrhea is the most commonly reported, with as many as 20 bowel movements a day. Abdominal pain, fever, nausea, and vomiting are common associated symptoms. Although the infection is usually self-limited (<7 days in duration), dehydration or persistent diarrhea may occur in one-third of the cases. The most common *Aeromonas* species isolated in these cases is *Aeromonas caviae*. Some children with this infection experience abdominal complications secondary to their diarrheal episodes, including failure to thrive, gram-negative sepsis, and HUS.

Plesiomonas

Plesiomonas, originally assigned to the family Vibrionaceae but more recently reassigned to enterobacteriaceae, are gram-negative, facultative anaerobic, motile primarily freshwater organisms, with isolation rates increasing during the warm months. Fish and shellfish, especially if associated with mud or sediment, frequently harbor plesiomonads. However, the microorganism can also be isolated from the feces of asymptomatic animals, including cats and dogs.

Typical symptoms of *Plesiomonas shigelloides* infection include secretory or a colitis/proctitis type of diarrhea (one-third of patients experience frank bloody diarrhea), abdominal pain, nausea, vomiting, and fever. Fatal outcomes of severe gastrointestinal infections without apparent dissemination by *Plesiomonas* have also been described.

Parasitic Gastroenteritis

Giardiasis

Giardia is transmitted via ingesting infective cysts in food and more commonly water, which includes water from swimming pools and direct person to person contact. After ingestion, the parasite inhabits the upper small intestine. Incubation period varies from 5 to 20 days. The parasite adheres to the enterocyte by its ventral sucker. *G. lamblia* multiplies in the small bowel and adhere to the mucosa. It is associated with acute diarrhea, bulky and offensive stool, abdominal distention, and abdominal pain. Chronic giardiasis may be associated with weight loss and malabsorption.

The diagnosis is usually made by demonstrating the trophozoites in fresh stool or small bowel aspirate or demonstration of the cyst in stool or by detecting the antigen in the stool by ELISA. Three stool samples need to be tested before *Giardia* is excluded.

The infection can remain asymptomatic or may present as an acute infection, recurrent or chronic disease. The various manifestations include watery diarrhea, anorexia, nausea, bloating, malaise, abdominal discomfort or pain and in heavy infections, failure to thrive as the organism coats the intestine leading to malabsorption.

Cryptosporidium

Cryptosporidium is a coccidian parasite that infects man, cattle, sheep, dogs, and chickens; it causes severe illness in infants and children with immunodeficiency. Immunocompetent children usually develop a short diarrheal illness that is self-limited. Children with defective cellular immunity or AIDS develop severe protracted diarrhea. The diagnosis of cryptosporidiosis is made by finding the pink-staining oocysts in fecal smear. Cryptosporidium is clinically the most important spore-forming intestinal protozoa. Infection occurs with ingestion of the oocysts.

The incubation period is estimated as 5–7 days and also it might range up to 14 days. The protozoa attaches to the enterocyte resulting in fluid loss and malabsorption. In otherwise healthy individuals, the disease may be asymptomatic or may result in a self-limiting watery diarrhea that could be severe and may be accompanied by abdominal pain, nausea, and vomiting. Some children may have a viral flu like syndrome while others could manifest lactose intolerance. The infection lasts about 7–14 days. Though the clinical disease may last only 2 weeks, lethargy and weakness can persist for a month. In addition, the child may continue to discharge oocysts for several more weeks. The diagnosis is made by finding small oocysts in the stool.

Isospora

Isospora belli is similar to *Cryptosporidium* in most aspects including the type of clinical diseases; it causes eosinophilia which has been reported more commonly.

Entamoeba histolytica

The majority of infection with *E. histolytica* causes no symptoms. *E. histolytica* cause mild diarrhea to severe bloody diarrhea, secondary to amoebic colitis with fever and abdominal pain. Amoebic liver abscess is the most

common extra intestinal form of invasive amebiasis. The diagnosis is made by finding the trophozites in fresh stool specimen.

C. difficile and Antibiotic-Associated Colitis

C. difficile causes pseudomembranous colitis, which usually follows ingestion of ampicillin, amoxicillin, clindamycin, and lincomycin. The colitis is mediated by *C. difficile* toxin. Commonly it presents with watery diarrhea, fever, and abdominal cramps. The diagnosis is made by colonoscopy, which shows punctuated, raised, yellowish white plagues with normal skip areas. The diagnosis also depends on demonstration of *C. difficile* toxin in stool and isolation of *C. difficile* from stool.

Fungal Infections

A healthy child with intact host defense mechanisms is generally not considered susceptible to fungal infections of the digestive tract. As immunosuppressive therapies become more aggressive and myelotoxic regimens more effective, opportunities increase for fungi to invade and establish themselves in humans. Patients disabled from chronic malnutrition and those exposed to intense antimicrobial infection are also susceptible to these organisms. HIV infection and AIDS have produced a group of chronically immunosuppressed children susceptible to a wide range of organisms, including fungi. The digestive tract is not a preferred site of infection in cases of disseminated fungal infection, but certain species are capable of infecting the esophagus, the stomach, or the intestine.

Candidiasis

Candida species are oval cells (4–6 μm in size) that produce by budding. There are at least 80 species, of which 8, including *Candida albicans*, are of GI significance. In disseminated candidiasis, there is widespread involvement of several organs. The major risk factor leading to this serious problem is neutropenia. The liver may be involved in addition to the heart, brain, kidney, lung, spleen, and eye.

Candida infection has been associated with acute watery diarrhea in newborn infants, although its causative role has not been definitely established. *C. albicans* can invade the small bowel and large intestine in terminally ill children.

Aspergillosis

Most cases of invasive *Aspergillus* infection are seen in severely immunocompromised children. In about 20% of such cases of invasive infection, the small and large intestines are involved, in addition to the esophagus and stomach.

Food Poisoning

Food poisoning is acute onset of vomiting and or diarrhea after eating a meal. It affects more than one member of a family. Food poisoning may be caused by pre-existing enterotoxins like *S. aureus* or *B. cereus* in which the incubation period is less than 6 h. Vomiting is the predominant picture of the illness. In contrast, food poisoning secondary to *C. perfringens* is characterized by an incubation period of 8–12 h; the diarrhea is severe but brief (less than 3 days) and it is accompanied with abdominal pain. Another cause of food poisoning is salmonella, in which the incubation period is 12–48 h and it presents with diarrhea, vomiting, and abdominal pain. Vomiting and diarrhea that are associated with neurological manifestations indicate botulism as a cause of food poisoning.

Food poisoning is an acute illness that develops from less than 1 h to 15 or more hours after the ingestion of food contaminated with bacterial, viral, or parasitic pathogens or toxins (biological or chemical).

C. perfringens

This form of food poisoning is caused by a heat-labile, 35 kDa enterotoxin produced by *C. perfringens* type A. The enterotoxin is structural protein of the spore coat and is produced during sporulation. The *C. perfringens* enterotoxin has greatest activity in the ileum and can inhibit glucose transport, damage intestinal epithelial cells, and induce protein loss.

The typical episode of food poisoning by *C. perfringens* is characterized by watery diarrhea and severe crampy abdominal pain that develop 8–24 h after the suspect meal. Vomiting is usually not a prominent symptom. The illness usually resolves within 24–36 h after onset, with no sequelae.

S. aureus

S. aureus food poisoning is associated with coagulase-positive strains that elaborate heat-resistant enterotoxins

A, B, C1, C2, C3, D, and/or E. Most outbreaks are caused by strains that produce enterotoxin A alone or together with enterotoxin D.

Staphylococci grow well in foods that have a high salt (e.g., canned meats) or sugar/protein (e.g., custards and creams) content and can be passed to prepared food by food handlers who carry toxin producing *S. aureus.*

After a short incubation period (1–6 h), affected children develop nausea, vomiting, and diarrhea. Profuse vomiting may result in dehydration and metabolic alkalosis. Despite a stormy acute course, the illness resolves completely in 24–48 h.

B. cereus

B. cereus, an aerobic, spore-forming, gram-positive rod is found in soil and water globally, in most raw foods, and in human carriers (10–40%). The spores are heat-resistant. *B. cereus* is associated with two distinct toxin-mediated types of food poisoning: the emetic syndrome, which has a short incubation period (range 1–6 h), and the diarrheal syndrome, which has a longer incubation period (range 8–16 h). The type of toxin elaborated depends on the type of food contaminated with *B. cereus*, rather than the strain of the organism.

Differential Diagnosis of Infantile Gastroenteritis

The differential diagnosis of acute vomiting and diarrhea includes medical condition like infections which include upper respiratory tract infections and urinary tract infections, cow's milk protein intolerance which can be diagnosed by short-term dietary elimination, and hemolytic uremic syndrome.

Other major differential diagnoses are surgical conditions like pyloric stenosis, which affect children from 2 to 8 weeks and characterized by projectile vomiting, pyloric tumor, which can be felt after the test feeding, and intussusceptions, which are characterized by colicky abdominal pain, sausage-shaped mass in abdomen, red currant jelly stool, and atypical or minimal physical signs in most patients.

Clinical Characteristics

Viral infections cause low grade fever and watery diarrhea without blood. Rotavirus infection occurs throughout the year. The peak age for infection is between 6 months and 2 years, the mode of spread is by the fecal–oral or respiratory route.

Children with bacterial gastroenteritis are more likely to have high fever and may have blood and white blood cells in the stool. Infection with Shiga toxin producing *E. coli* or *S. dysenteriae* may cause hemorrhagic colitis (with severe bloody diarrhea), which might be complicated by hemolytic uremic syndrome. This syndrome is characterized by acute onset of microangiopathic hemolytic anemia, thrombocytopenia, acute renal impairment, and multisystem involvement.

V. cholerae toxin causes chloride and water secretion from the small bowel but does not damage the intestinal mucosa; it results in "rice water" stools that have a high sodium content but do not contain blood or white blood cells.

Ingestion of food containing toxins produced by bacterial contaminants (for example, *S. aureus* in ice cream or *B. cereus* in reheated rice) causes acute onset of vomiting or diarrhea shortly after ingestion of the contaminated food.

Diagnosis can be made clinically. Information should be sought about recent contact with children with gastroenteritis, nature and frequency of stool and vomitus, fluid intake and urine output, and travel and use of antibiotics and other drugs that may cause diarrhea. Chronic constipation is common in children, and overflow fecal incontinence may present as spurious diarrhea. Diarrhea and vomiting are nonspecific symptoms in young children, and the diagnosis of gastroenteritis should be questioned in children with high fever, prolonged symptoms, and suspected surgical cause (such as severe abdominal pain, bilious vomiting, and abdominal mass). Children with diabetic ketoacidosis and inborn errors of metabolism may present with vomiting.

Laboratory Evaluation

A gross examination of the stool specimen should be routine on all patients with diarrhea. Stool that is watery and without mucus or blood is usually caused by an enterotoxin or a virus. Stools with blood or mucus suggest a cytotoxin-mediated or enteroinvasive mucosal inflammatory process. When present, blood is usually mixed evenly into the stool except in the case of *E. histolytica*, in which blood is often on the surface of the stool. Stools that are particularly foul smelling are consistent with Salmonella and other bacteria as well as

Giardia, *Cryptosporidium*, and *Strongyloides*. Stools with little odor suggest an enterotoxin such as cholera toxin or *E. coli*; stool should also be examined for ova, parasites, PH, and reducing substance.

Microscopic examination of stool specimens for evidence of fecal leukocytes indicate that the patient has colitis. If the fecal leukocyte is positive, it is likely that the patient has *Shigella*, *Salmonella*, *Campylobacter*, invasive *E. coli*, and *C. difficile*. Fecal leukocytes are generally not present in stools from patients with diarrhea secondary to viruses. The fecal leukocyte examination is performed by mixing fresh mucus from stool with methylene blue and observing the fresh or dried preparation microscopically. When stool culture is indicated, the specimen should be inoculated onto culture plate media adequate to isolate *E. coli*, *Shigella*, *Salmonella*, and *Campylobacter*. Rotavirus as well as other viruses as astrovirus, calicivirus has been identified by the examination of stool specimens for 70-nm particles by electron microscopy. Commercially available enzyme immunoassay and latex agglutination kits are available to detect rotavirus antigen in stool specimens. Other test that should be done is BUN Creatinine electrolytes urine analyses and urine culture; if fever persists, blood culture should also be done.

Assessment of Dehydration

It is important to assess hydration in gastroenteritis as it determines the immediate management of this condition. Assessment of dehydration is shown in ● *Table 187.1*.

Fluid Therapy in Dehydration

Children with no dehydration or mild dehydration can usually be managed at home, although children with high risk for complications or who cannot be adequately cared for at home should be considered for admission. Children with mild–moderate dehydration who do not tolerate oral fluids should be admitted for observation. Oral rehydration solutions are preferable to other clear fluids for preventing and treating dehydration. Fluids high in sugar (such as cola, apple juice, and sports drinks, which contain $\leq$20 mmol/L sodium and have a high osmolality of 350–750 mOsm/L) may exacerbate diarrhea and should be avoided. Breastfeeding should be continued during acute gastroenteritis and supplemented with an oral rehydration solution if needed.

Although most children with dehydration drink readily, some refuse rehydration solutions because they dislike

Table 187.1
Assessment and management of dehydration

Dehydration(% weight loss)	Clinical signs	Pinch test*	Management
No dehydration	None	Normal (skin fold retracts immediately)	Most can be managed at home; encourage normal diet and fluids (continue breast milk); consider admission if high risk of dehydration (very young, diagnosis in doubt, large losses)
Some dehydration: includes previous categories of mild (5%) and moderate (6–9%) dehydration	Two or more of restlessness or irritability, sunken eyes, thirst (eagerness to drink)	Slow (skin fold visible <2 s)	Some can be managed at home with oral rehydration therapy; some need to be observed and, if therapy is not tolerated or large ongoing losses occur, may need nasogastric or intravenous fluids over 4–6 h; normal diet when tolerated
Severe dehydration (>10%) with or without shock	Two or more of abnormally sleepy or lethargic, sunken eyes, drinking poorly or not at all	Very slow (skin fold visible >2 s)	Check acid base status, urea, electrolytes before intravenous fluids; if shock is present, first resuscitate with intravenous bolus; rehydrate intravenously (enteral fluids have been used) over 4–6 h with regular clinical and biochemical review.

Calculation of ORS maintenance fluid requirements
100 mL per kg per 24 h for the first 10 kg of body weight
Added to: 50 mL/kg/day for the next 10 kg of body weight
Added to: 20 mL/kg/day for remaining kg of body weight

the taste, feel nauseated, or have profuse vomiting. Older children may be afraid of vomiting and parents may perceive that fluids are the cause of vomiting. Alternatively, fluids may be given intravenously. Enteral (oral or nasogastric) and intravenous fluids are equally safe and effective for mild–moderate dehydration, and rehydration can usually be achieved in 4–6 h. The obvious major risk in acute diarrhea is the loss of water and electrolytes with consequent dehydration and possibly even loss of Na homeostasis. Rehydration or maintenance of hydration is therefore the cornerstone of treatment. Until the mid-1960s, this was accomplished almost exclusively via the intravenous route. Subsequently, the expanded understanding of the pathophysiologic events in intestinal transport processes allowed a dramatic change of approach. In fact, it became apparent that enterotoxigenic bacteria such as *V. cholerae* or ETEC leave intact small intestinal mucosal morphology and absorptive functions.

Numerous studies, analyzed in a recent meta-analysis published in the Cochrane Library, had shown convincingly that ORT could safely be used to rehydrate children both in developed and developing countries, with fewer than 5% of children failing ORT and requiring intravenous fluids regardless of the etiology of acute diarrhea. ORSs have proved both safe and effective worldwide in hospital settings and also in the home to prevent dehydration. For about 3 decades, the WHO has recommended a standard formulation of glucose-based ORS with 90 mmol/L of sodium and 111 mmol/L of glucose, with a total osmolarity of 311 mmol/L. However, many in vitro and in vivo studies during the late 1980s and 1990s had consistently shown that lower concentrations of sodium and glucose enhance solute-induced water absorption and might therefore be superior to the solution with a higher osmolarity.

Reduced-osmolarity solutions have concentrations of glucose and Na inferior to those in the traditional WHO solution: glucose ranges between 75 and 100 and Na between 60 and 75 mmol/L; so osmolarity is maintained at 225–260 mOsm/L, and the ratio between glucose and Na close to 1:1. Hypo-osmolar ORSs appear to have the additional advantage of allowing a reduced stool output while being just as effective in obtaining and maintaining rehydration and can be safely given throughout the duration of diarrhea, as shown in both developed and in developing countries. Indeed, in 2002, a large meta-analysis of all published controlled trials comparing low-osmolarity solutions with standard WHO formulas appearing in the Cochrane Library concluded that in children hospitalized for diarrhea, reduced-osmolarity ORS compared to WHO standard ORS is associated with fewer unscheduled intravenous fluid infusions, lower stool volume, and less vomiting, without additional risks of hyponatremia. More recently, evidence has been provided that hypo-osmolar ORS can be used safely and effectively even in newborns and infants.

Accepting all the evidence accumulated until then, in 2002 the WHO announced the adoption of a new ORS formulation consistent with these recommendations, with 75 meq/L sodium, 75 mmol/L glucose, and a total osmolarity of 245 mOsm/L. This hypotonic WHO-ORS is also recommended for use in adults and children with cholera, a condition characterized as we have seen by a marked high stool Na, but further studies are underway to confirm the safety of this indication. A large meta-analysis published in the Cochrane Library confirmed the safety, efficacy, and clinical superiority of low-osmolality ORS.

In constant search of a "super-ORS" that would not only be efficacious for rehydration but also could result in a substantial improvement in reducing the stool volume, in recent years the possibility has been advanced that adding to ORS starches resistant to small intestinal hydrolysis by amylase, could be beneficial by allowing an added stimulus to colonic water absorption due to release of fatty acids by the fermenting microflora. This concept was originally tested in adolescents and adults with cholera, where the solution was found able to reduce fecal fluid loss and to shorten the duration of diarrhea. Subsequently, ORSs with amylase-resistant starches have been tried in children, with conflicting results of interest; initial evidence from the laboratory animal seems to suggest that such solutions may prove even more beneficial if associated with a low-osmolarity ORS.

In summary, ORT with a glucose-based ORS must be viewed as by far the safest, most physiologic, and most effective way to provide rehydration and maintain hydration in children with acute diarrhea worldwide, as recommended by the WHO.

Children with shock require intravenous resuscitation before rehydration.

Children who have mild–moderate dehydration secondary to acute gastroenteritis should have their deficit estimated (3–8%) and replaced with ORS (30–80 m/kg) given "little and often" over 3–4 h, whenever this is practically possible.

Regularly assess the success of rehydration (for example, two hourly). If no improvement in clinical signs of dehydration or worsening signs, consider nasogastric tube or intravenous infusion. The child who was not dehydrated and the child who is no longer dehydrated following rehydration should be allowed free fluids, and be encouraged to drink more than usual.

To prevent primary dehydration or recurrence of dehydration, allow unrestricted fluids (for example, milk or water). Ensure that at least maintenance fluids are taken for assessment, and management of dehydration is shown in Table 187.1.

The most common adverse effect of intravenous cannulation is infiltration at the cannula site, but infection, pain, bleeding, and physical and emotional trauma may also occur. Intravenous therapy is more expensive than oral rehydration therapy and requires hospital admission. Iatrogenic complications – especially electrolyte disturbance due to inappropriate composition, rate of administration, or volume of intravenous fluids – may lead to complications, including hyponatremia with brain injury or death. If rapid intravenous rehydration is used, careful supervision is needed to avoid fluid overload and electrolyte imbalance.

The child who was not dehydrated and the child who is no longer dehydrated following rehydration should be allowed free fluids, and be encouraged to drink more than usual.

Feeding During Acute Gastroenteritis

Carbohydrate (particularly lactose) intolerance is a common complication of viral gastroenteritis as a result of damage to and loss of mature enterocytes containing lactase. Lactose intolerance is usually mild and self-limited and does not require treatment. If lactose intolerance persists, a lactose-free formula is recommended for 4–6 weeks. The damaged gut is more permeable to foreign antigens and intolerance to food proteins (β lactoglobulin in cow's milk and other proteins) is occasionally seen after gastroenteritis; it can be managed by a period of dietary exclusion. Feeding during acute gastroenteritis is shown in Table 187.2.

Table 187.2
Feeding during acute gastroenteritis

Breast fed	Continue breast feeding throughout rehydration and maintenance phases
Formula fed	Restart feed at full strength as soon as rehydration is complete (ideally 4 h)
Weaned children	Child's normal fluids and solids following rehydration. Avoid fatty foods or foods high in simple sugars.

Refeeding Following Rehydration

Good evidence exists to show that children who are breast fed should continue breast feeding throughout the rehydration and maintenance phases of their therapy. In so doing they reduce the risk of dehydration, pass smaller volumes of stool, and recover quicker.

Medication Used for Acute Gastroenteritis

There is evidence from several randomized controlled trials that antidiarrheal and anti-motility agents are not clinically beneficial in the management of acute childhood gastroenteritis, and their side effect is unacceptable. Oral zinc given at the onset of symptoms decreases the duration and severity of acute diarrhea and is recommended by the WHO. Vitamin A does not influence the course of acute gastroenteritis. A guide to a drug treatment of acute gastroenteritis is shown in Table 187.3.

Criteria for Admission of Children with Acute Gastroenteritis

Children presenting with acute gastroenteritis who are severely dehydrated should be admitted to hospital.

Those children with mild–moderate dehydration should be observed in a hospital pediatric emergency room for a period of at least 6 h to ensure successful rehydration (3–4 h) and maintenance of hydration (2–3 h).

Those children at high risk of dehydration on the basis of young age (infants <6 months with high frequency of watery stools more than eight per 24 h) or those who vomit more than four times per 24 h should be observed in a hospital pediatric emergency room for at least 4–6 h to ensure adequate maintenance of hydration.

Table 187.3
Guide to a drug treatment in acute gastroenteritis

Antidiarrheal	Infants and children should not be treated with antidiarrheal agents
Antibiotics	Patients with invasive *S. typhi*, *Shigella*, amebiasis, *Isospora*, and giardiasis should be treated with antibiotics. Consider in infants <6 months with either salmonella infections or those who are systematically unwell, and the immunocompromised.

Those children whose parents or carers are thought to be unable to successfully manage the child's condition at home should be admitted to hospital.

Clinicians often overestimate the extent of dehydration. Documented recent weight loss is a good indicator of the degree of dehydration, but this information is rarely available.

Prevention of Acute Gastroenteritis

Breast feeding, cup and spoon feeding, hygienic preparation of feeds, including hand washing is a major factor in reducing contamination, measles vaccine, cholera vaccine, enterotoxigenic *E. coli* vaccine, and rotavirus vaccine.

Rotavirus vaccines have been developed using a "Jennerian" approach. Strains of bovine and simian rotaviruses that are naturally attenuated for humans have been assessed and found to confer immunity that is serotype-specific in a varying proportion of recipients.

The spectrum of protection has been widened by developing reassortants in which the bovine or simian gene coding for VP7 (the major outer capsid protein) has been replaced by the corresponding gene from human VP7 types 1, 2, 3, or 4. Once the protective antigens (s) are identified it may be possible to develop subunit vaccines that eliminate side effects sometimes observed with live vaccine candidates.

Passive prophylaxis has been tried in special situations. Human gamma globulin, given by mouth to newborn premature infants, has been shown to delay onset of excretion and to decrease the severity of rotavirus disease. Addition of bovine milk rotavirus antibody to formula given to infants protected them against symptomatic infection.

Cholera Vaccine

The parenteral killed vaccines in current use have limited efficacy (approximately 50%) and duration (6–12 months or less). Also, they require multiple doses and are poorly immunogenic in young children. Much of the current research is focused on the development of an oral vaccine with both bacterial cell wall and toxin epitopes, based on evidence that there is a strong correlation between protection against experimental cholera and intestinal anti-cholera toxin secretory IgA levels rather than serum antibodies and that antibacterial and antitoxic effects appear to be important for protective efficacy.

Prevention of Food Poisoning

Prevention of foodborne infections begins with good hand washing and safe practices for food preparation. Public education about the risks associated with eating certain foods and transmission of viruses is essential.

Improved methods to decontaminate food or for rapid detection of gastroenteric viruses in food should also be helpful.

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188 Intractable Diarrhea of Infancy

Ian R. Sanderson · John A. Walker-Smith

Intractable diarrhea, first described by Avery et al. in 1968, is recognized as prolonged severe diarrhea, associated with malnutrition, not easily dealt with, despite extreme hospital therapy.

The syndrome has the following features:

- Diarrhea of more than 2 weeks duration.
- Age, less than 3 months.
- Three or more stool cultures negative for bacterial pathogens.
- Managed with intravenous fluids.
- Despite hospital management, diarrhea was persistent and intractable.
- There was a high mortality at the time.

Three clinical variants of the syndrome may be recognized:

1. Chronic diarrhea persisting despite intravenous fluid and nil by mouth. This is very likely to be secretory diarrhea.
2. Chronic diarrhea that disappears on intravenous fluids and nil by mouths, only to recur whenever oral feeding is resumed. This is likely to be osmotic diarrhea, and associated with small intestinal enteropathy. Although, in some patients, it is clear that both secretory and osmotic diarrhea are present.
3. Chronic diarrhea that has been managed by a variety of elimination diets but still persists; again this is likely to be associated with small intestinal enteropathy.

Intractable diarrhea of infancy is therefore a heterogeneous syndrome with a number of causes. This heterogeneity is clear from Avery's original report. Eight children, six of whom died, had idiopathic conditions which Avery et al. termed "nonspecific enterocolitis" as both small and large intestinal abnormalities were found; four of these cases were diagnosed on admission as gastroenteritis. However, although the authors listed small intestinal biopsy as a diagnostic test, it was just recommended as a means to confirm or exclude celiac disease. It was only autopsy material which was available for study of small intestinal mucosal morphology.

Shwachman et al. were the first to perform small intestinal mucosal biopsies on 5 such patients, which they later extended to 11 cases. They performed light microscopy and assayed disaccharidase levels and found a moderately severe to mild lesion in nine cases. Their studies were only possible because the children had been kept alive by parenteral nutrition.

It is this development of parental nutrition as a practical option for infants in the early 1970s that transformed the scene and enabled infants, who otherwise would have died, to survive. As a result, it became possible to perform investigations to determine the cause of their intractable diarrhea.

Diagnosis

A full diagnostic workup of these children requires morphological and functional assessment of both the small and large intestinal mucosa, including small intestinal biopsy and colonoscopy with multiple colonic biopsies.

It is now clear that not only is proximal small intestinal biopsy important, but that the development of safe and effective total colonoscopy in infancy has been another major advance which has lead to increased understanding of the intractable diarrhea syndrome.

Functional assessment is more difficult. Testing of stools for excess stool-reducing substances is a practical and simple test for diagnosis of sugar intolerance. Serial estimation of intestinal permeability is a practical opinion. However, this gives very little additional diagnostic information.

The extensive diagnostic approach for children with intractable diarrhea has led to the recognition of specific disease entities and at times, specific therapy resulting in effective treatment and so, elimination of the intractable diarrhea as a symptom complex in many cases. Over the past few years, molecular techniques have enabled scientists to define the exact gene defects causing some of these conditions.

It must be remembered that failure to make a specific diagnosis in children may be due to diagnostic inadequacy, which in turn may be due to lack of the existence of a clinical entity or lack of availability of particular diagnostic techniques. For example, undiagnosed celiac disease can go on to intractable diarrhea. This has clearly

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been shown in India where only in recent years has it been appreciated that celiac disease in Northern India is an important cause of intractable diarrhea.

Within the broader syndrome of intractable diarrhea is the syndrome known as malnutrition in chronic diet-associated infantile diarrhea (McDAID). The features of this syndrome include: diarrhea of more than 2 weeks duration, malabsorption, and intestinal malfunction, which is further aggravated when food and/or specific dietary products are fed. Fasting usually brings about improvement in the diarrhea, but may lead to considerable nutrition deterioration. These diet-associated problems have dramatically decreased in the developed world. This relates to a decline in gastroenteritis and the recognition of temporary cow's milk protein intolerance occurring as a sequel. Thus, in the past, undiagnosed lactose intolerance and cow's milk sensitive enteropathy were important causes of intractable diarrhea.

In summary, many of the infants who present with intractable diarrhea in fact eventually prove to have a diagnosable condition, i.e., have a specific diagnosis sometimes with specific therapy, sometimes without. Despite advances of the past few years, there remains an important group in whom no primary cause can be determined.

Categories of Intractable Diarrhea

It is now possible, after extensive diagnosis, to divide intractable diarrhea syndrome into four categories:

1. Failure to make a diagnosis of any kind
2. Specific diagnosis but no therapy
3. Specific diagnosis but therapy of variable efficacy
4. No specific or only partial diagnosis

There are now fewer and fewer patients who fit into category 1 and this will not be discussed here.

Specific Diagnosis but No Therapy

Two examples of this are microvillous atrophy and congenital enterocyte heparan sulfate deficiency.

Microvillous Atrophy

Davidson et al. (1978) in Canada described five infants with severe diarrhea and failure to thrive from birth, leading to death in four cases. All infants had small intestinal villous atrophy, without crypt hypertrophy, i.e., hypoplastic villous atrophy. There was a familial history in four cases and the term familial enteropathy was used to describe this syndrome. Electron microscopy of three of the children showed striking ultrastructural changes in one. Involutions of the apical membrane of some surface epithelial cells were seen containing microvilli, and secretory granules accumulated in upper crypt cells. Light microscopy of small intestinal biopsy for infants with congenital microvillous atrophy demonstrated villous atrophy without crypt hypertophy. Schmitz et al. (1982) called this syndrome *congenital microvillous atrophy*. But more recently this entity has been termed *microvillus inclusion disease*. Late-onset cases have also been described where the child was well for the first weeks of life, and then developed the condition. The specific diagnostic features and clinicopathological spectrum of microvillous atrophy have been reviewed by Phillips and Schmitz. The familial nature of the condition has enabled molecular genetics to be performed. The gene was identified on Chromosome 18, and informative families demonstrated that it was due to a defect in a cytoskeletal element MYO5B. Interestingly, this myosin binds to another protein RAB 8. Deleting RAB 8, from enterocyte lines, had shown a lesion similar to that seen in children with microvillous atrophy. It is not yet clear if the late-onset disease is due to a distinct genetic defect from the congenital type.

Tufting Enteropathy

Congenital tufting enteropathy (CTE) is a rare autosomal recessive diarrheal disorder presenting in the neonatal period. It is characterized by intestinal epithelial cell dysplasia leading to severe malabsorption and significant morbidity and mortality. SNP Homozygosity mapping identified in an information family a unique 6.5-Mbp haplotype of homozygous SNPs on chromosome 2p21 where approximately 40 genes are located. Direct sequencing identified the gene epithelial cell adhesion molecule (EpCAM).

Congenital Enterocyte Heparan Sulfate Deficiency

A new cause of intractable diarrhea syndrome of infancy, associated with histologically normal small intestinal mucosa by conventional assessment, has been described by Murch et al. This syndrome begins in the first days of life and is characterized by chronic diarrhea associated

with profound hypoproteinemia. The diarrhea is secretory in character and there is severe protein-losing enteropathy. The small intestinal mucosa is normal on light microscopy, although there is some minor thickening of the subepithelial basement membrane with increased fibrillar collagen on electron microscopy. However, there is almost complete absence of *epithelial glycosaminoglycans*. There is in particular a gross reduction of sulfated glycosaminoglycans (heparan sulfate) in the basolateral membrane, lining the lateral intercellular spaces. As glycosaminoglycans play a major role in retaining circulating proteins within the vasculature, it has been proposed that this loss is responsible for the severe enteric protein loss and secretory diarrhea in these infants. These infants have been thus described as suffering from "minimal-change" enteropathy, analogous to lesions in the glomerulus of the kidney in patients with nephrotic syndrome. So far there is no effective therapy.

Specific Diagnosis but Therapy of Variable Efficacy

The best example of this is *autoimmune enteropathy*. This syndrome describes children with intractable diarrhea and small intestinal enteropathy who possess an antibody against their intestinal epithelium and thus appear to have an *autoimmune enteropathy*. These children represent a very difficult management problem with a high mortality. They have a characteristic clinical syndrome which may be associated with other autoimmune phenomena, e.g., diabetes mellitus associated with islet cell antibody. This syndrome has now been seen in a number of countries. However, its relative frequency is not yet clear. In a highly selected group of 25 infants with intractable diarrhea, 14 in fact had evidence of this syndrome. Cyclosporin can be effective in the management of such children.

In 2001 with the discovery of disease-causing mutations of the FOXP3 gene, located on the X chromosome, a major breakthrough in the understanding of the pathophysiology of autoimmune enteropathies was made. A great variety of different forms of AIE exist with some of them FOXP3-dependent, others FOXP3-independent. A genetic approach, combined to immunological evaluations (as discussed below), can distinguish several forms of autoimmune enteropathy, as recently proposed:

1. A systemic X-linked form associated to different endocrinopathies, hematological symptoms and severe eczematic skin disease, now well characterized as immune dysregulation, polyendocrinopathy, autoimmune enteropathy X-linked (IPEX) syndrome
2. An IPEX-like form a priori FOXP3-independent occurring in both boys and girls
3. A predominantly or isolated gastrointestinal form with typical anti-enterocyte antibodies also occurring in both boys and girls

Another example is congenital secretory diarrhea due to defective jejunl brush border Na/H exchange.

Small Intestinal Enteropathy of Unknown Origin

Small intestinal enteropathy of unknown origin can be a very severe disorder. It is possible that it is a variant of autoimmune enteropathy. These children with intractable diarrhea with an enteropathy of unknown origin may have an immunological pathogenesis, as there are increased numbers of inflammatory cells in the lamina propria. They need to be distinguished from children with autoimmune enteropathy. In an ESPGAN study group of 13 non-autoimmune and 18 autoimmune children with small intestinal enteropathy, these two groups were compared in relation to age and onset of diarrhea. They were all 12 months or under. There was a higher mortality in the autoimmune group. Such children may be totally dependent on home parenteral nutrition and they provide a very great challenge at present for both diagnosis and management.

Intractable Enterocolitis

Intractable ulcerating enterocolitis of infancy is a disorder of unknown origin. This disorder is now often reported in communities with a high degree of consanguinity. It typically presents in infancy. It may sometimes resemble Crohn's disease. The children often require subtotal colectomy for severe colitis. The long-term progress may be quite good. This has been improved by the use of bone marrow transplant. The underlying disorder may include defects in the IL-10 and its signaling pathways, but this is an area of investigation.

Conclusion

As more causes of intractable diarrhea are recognized with better diagnostic techniques, the residuum of cases where the diagnosis is incomplete and therapy unsatisfactory

continues to decline. These cases, however, remain as one of the most difficult problems faced by pediatric gastroenterologists for whom they provide a continuing challenge.

However, the diagnostic advances over the past 40 years, whereby it has become safe and effective to biopsy both the small and large intestine of infants, have led to the notable advances in our ability both to make diagnosis and also to understand pathogenesis. These advances too have in part only been possible because highly effective parenteral nutrition is now able to keep these babies alive. In previous years they would have died.

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189 Congenital Chloride Diarrhea

Hisham M. Nazer

Congenital chloride diarrhea (CCD) is a rare autosomal recessive disorder of chloride transport caused by mutations in the down-regulated in adenoma gene, characterized by lifelong watery diarrhea with high fecal chloride concentration. CCD was first described in simultaneous publications by Gamble et al. and by Darrow in 1945, who coined the term "congenital alkalosis with diarrhea."

Though more than one third of reported cases come from Finland, CCD has also been reported from several countries in Europe, America, and the Arabian Peninsula. As in Finland, a major founder effect was observed in Arab patients in whom 94% of the CCD-associated chromosomes carried a nonsense mutation, G187X, which occurred in either a conserved ancestral haplotype or its derivative. The frequency of CCD in Finland is approximately 1 in 43,000 newborns. Three regions were reported to have high incidence: Finland, Poland, and Arab counties in the Gulf Region with supportive evidence from Kuwait and Saudi Arabia.

Pathogenesis

Intrauterine diarrhea predisposes to polyhydramnios, prematurity, and lack of meconium passage. Hyperbilirubinemia is partially caused by the hypovolemia and acidosis in premature infants with CCD.

The basic defect in CCD is impaired active chloride transport in the distal ileum and colon. Perfusion studies have established the absence of active chloride-bicarbonate exchange in the ileum and colon as the primary defect in CCD. The defective Cl^- absorption leads to osmotic diarrhea and hypovolemia. Normally, the chloride is actively coupled in the ileum to bicarbonate. The resultant excess of intraluminal chloride obligates further loss of the positive ions Na^+ K^+, and H^+, while retaining bicarbonate in the serum. Metabolic alkalosis is therefore a recognized biochemical association of CCD. Sodium ion absorption is also impaired when the luminal content is acidic. Moreover, the excess of electrolytes in the gut will retain more water, resulting in severe watery diarrhea and hypovolemia if it is not adequately replaced.

Other recognized laboratory findings in CCD include increased renin and aldosterone levels. The kidney is also involved, which makes CCD a disorder of shared interest between the gastroenterologist and the nephrologist. Recognized renal lesions in congenital chloride diarrhea include juxtaglomerular hyperplasia, hyalinized glomeruli, calcium deposits, and vascular changes resembling those seen in hypertensive disease.

Clinical Features

Congenital chloride diarrhea may be considered during antenatal routine checkup with the finding of polyhydramnios and fluid-filled distended loops of the bowel of the fetus. This combination may result in the baby being delivered prematurely. There is usually no passage of meconium. The infant presents with unremitting watery diarrhea with chloride content of greater than 90 mmol/L. The baby tends to pass a severe watery diarrhea that simulates urine, resulting in rapid weight loss. Some newborns develop jaundice, possibly due to hypovolemia and prematurity. Celiac disease was reported in a girl with CCD.

The disease is therefore characterized by long-standing watery diarrhea, acid stool, metabolic alkalosis, and a high stool chloride concentration, usually exceeding that of the serum chloride. Affected infants present also with abdominal distention and failure to thrive. Children who continue to show growth retardation are usually diagnosed late. If the condition is not properly managed, the baby might suffer the sequelae of severe hypovolemia, electrolyte disturbances with metabolic alkalosis, and presents with evidence of renal impairment and psychomotor retardation. Renal involvement may result in nephrocalcinosis with echogenic kidneys on ultrasonography. Hyperaldosteronism results in hypokalemic alkalosis, which predisposes to nephrocalcinosis. CCD which was considered as a purely pediatric disease has recently been reported to affect adults.

Diagnosis

The diagnosis may be highly suspected from the antenatal period. A history of polyhydramnios and a lack of meconium at birth, together with abdominal distention and

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watery diarrhea are strongly suggestive of CCD. The condition may mimic low intestinal obstruction on ultrasound examination after 30 weeks of gestation.

Congenital sodium secretory diarrhea: Another congenital condition is also recognized to result in intrauterine intestinal secretion due to defect of sodium transport. This condition is also associated with polyhydramnios, which becomes evident toward the end of the second trimester. Ultrasound scan of the mother's abdomen shows an enlarged fetal abdomen containing distended loops of fluid-filled bowel.

Amniotic fluid α-fetoprotein and bilirubin are reported to be abnormally high from around the 29th week of gestation in affected pregnancies with CCD.

The diagnosis is further supported by the laboratory findings of hypokalemia, hyponatremia, hypochloremia, and metabolic alkalosis. Serum sodium may be normal in some patients due to secondary hyperaldosteronism. Hyperuricemia occurs in some patients. Angiotensin II is known to reduce the clearance of urate. The diagnosis is often delayed in the newborn infant, as the diarrheal fluid is frequently mistaken for urine. Abdominal ultrasonography reveals dilated bowel loops with an abnormal echogenic pattern of kidneys (◉ *Figs. 189.1* and ◉ *189.2*).

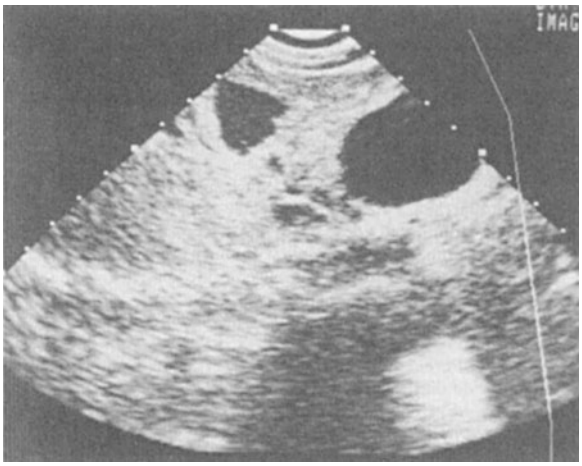
Diagnosis is usually confirmed by the presence of high levels of electrolytes in the stool, with stool chloride concentration of over 90 mmol/L in excess of the sum of sodium and potassium concentration. Lower fecal chloride content has been reported in CCD among affected infants with severe dehydration and electrolyte depiction as well as among newborns. In severe cases that suffered the consequences of delayed diagnosis with severe extracellular fluid depletion, the infant may present with the passage of formed stools or even constipation, which might lead to a serious diagnostic dilemma.

Differential Diagnosis

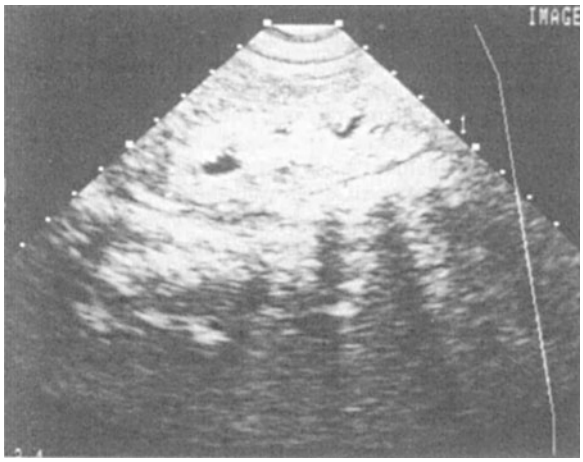
Congenital chloride diarrhea should be differentiated from other conditions associated with antenatal dilated bowel such as cystic fibrosis and intestinal obstruction. CCD should be differentiated from Bartter syndrome, in which there is also hypochloremia with hypokalemic alkalosis, hyperreninemia, and secondary hyperaldosteronism. Diarrhea is not a feature of Bartter syndrome. Moreover, untreated patients with CCD have low or undetectable chloride in their urine, while Bartter syndrome is characterized by high urinary chloride excretion due to impaired chloride reabsorption by the renal tubules.

CCD should also be differentiated from other conditions associated with metabolic alkalosis in infancy such as pyloric stenosis, potassium-losing nephropathies, dietary chloride deficiency, and cystic fibrosis.

Early diagnosis and proper management are essential prerequisites to improve the prognosis of CCD especially among affected infants in the developing world where a high rate of consanguineous marriages prevail. In a multinational



◉ Figure 189.1
Ultrasound of the abdomen showing dilated loops of the intestine in a patient with CCD



◉ Figure 189.2
Ultrasound of the kidneys in a patient with CCD showing increased echogenicity with nephrocalcinosis

study, parental consanguinity was known in all Saudi Arabian and Kuwaiti CCD families included in the study.

Treatment

Early diagnosis and initiation of treatment with replacement of electrolytes and correction of the associated hypovolemia are the essential steps in management of CCD to rescue the patients of its potential renal and central nervous system complications. It is important to stress to the parents that their child's diarrhea is expected to persist in spite of their adherence to therapy, but that the treatment is likely to prevent complication and ensure a better weight gain. Initially, the baby may require intravenous replacement of fluid and electrolyte loss followed later by oral supplement of chloride with sodium and potassium salts.

The treatment should be monitored regularly, especially in the early stage after diagnosis, by serum and urine electrolytes. With the electrolyte supplement the urine, which initially lacks electrolytes, will reveal the presence of some electrolyte excretion after a satisfactory compensation of the electrolyte loss in the stools. The dose is titrated to ensure a urinary chloride concentration in excess of 30 mmol/L. Chloriduria is a convenient indicator of the normality of the extracellular fluid volume and adequacy of the oral replacement of the chloride. With early diagnosis and appropriate therapy, children with CCD achieve adequate growth and development. Though this therapy does not abolish the diarrhea, most children will become toilet trained at a normal age and will lead a normal life with no impairment of social activity.

Prostaglandin synthetase inhibitors like indomethacin and ketoprofen have been tried in the therapy of patients with CCD. Although they tend to improve the electrolyte abnormalities and normalize plasma renin and aldosterone, the efficacy of prostaglandin synthetase inhibitors in the treatment of CCD remains debatable, and their use has not replaced the standard therapy with sodium and potassium chloride solutions.

The Gene for CCD

Recent research with the use of linkage analysis has provided strong evidence that the gene responsible for CCD maps close to but is distinct from the gene for cystic fibrosis transmembrane regulator (CFTR). Further reports have been published to support the gene location in CCD on chromosome 7. There are at least eight Cl^-/$HCO3^-$ exchange protein genes and highly homologous genes from different species encoding exchange proteins in human, mouse, rat, and chicken. More recently, it was demonstrated that mutations of the intestinal anion transport molecule down-regulated in adenoma (DRA) gene cause CCD.

The condition is recognized nowadays to result from mutations in the intestinal $Cl(^-)HCO(3)(^-)$exchange (SLC26A3) which results in sodium chloride and fluid depletion leading to hypochloremic and hypokalemic metabolic alkalosis. Mutations in SLC26A3 (solute carrier 26 family member 3), which functions as a coupled Cl^-/HCO_3 exchanger, cause CCD. Currently there are over 30 mutations in SLC26A3 linked to CCD.

The most frequent Saudi Arabian and Kuwaiti mutation was a G→T transversion at nucleotide position 559. The predicted amino acids change was a substitution of glycine by the termination codon at 187(G187X). This mutation was found in all Saudi Arabian patients and all but one of the Kuwaiti CCD–associated chromosomes included in a major multinational study.

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190 Chronic Diarrhea

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Diarrhea is a recognized manifestation of a variety of gastrointestinal diseases. While the majority of diarrheal episodes last less than 2 weeks and are self-limited, a smaller proportion of diarrheal illnesses persists for more than 2 weeks, substantially impacting the quality of life and the overall health of the individual; not only because of the inconvenience of persistent diarrhea, but also because of the risk of malnutrition and even death.

Definition

Diarrhea is defined as frequent passage of loose stools. Diarrhea occurs when the stool volume exceeds the normal value of approximately 10 g/kg/day in infants and toddlers, and 200 g/day in older children and adults. This is typically manifested as loose or watery stools occurring at least three times a day. However, since the absolute limits of normal bowel movements is difficult to define, with normal bowel movements ranging from three times/week to three times/day, any deviation from the child's usual pattern should raise concern (particularly if passage of blood or mucus, or dehydration occurs), regardless of the actual number of bowel movements or their water content.

Diarrheal episodes are classically divided into acute and chronic based on their duration. The WHO defines acute diarrhea as less than 14 days in duration and persistent diarrhea episodes as 14 days or longer in duration. Such a distinction can help in forming a differential diagnosis, and thus impact management, as well as prognosis. Acute diarrhea lasts no longer than 14 days, is often infectious in etiology (bacterial, viral, or parasitic infections), and is usually self-limited. Chronic diarrhea refers to the persistence of loose stools (with or without an increase in stool frequency) for at least 14 days.

Chronic diarrhea may occur in many conditions, including a variety of infectious and immunologic states, as well as several congenital syndromes. Reports have indicated that between 5% and 18% of all diarrheal episodes are categorized as persistent diarrhea; however the exact cutoff point between acute and chronic diarrhea and persistent diarrhea is arbitrary.

Etiology

Many gastrointestinal and systemic diseases present with diarrhea. In children, the differential diagnosis may be age specific; however, a number of diseases may occur at any age (*Table 190.1*).

Furthermore, the etiology of chronic diarrhea differs between developing and developed countries. In developing countries, most cases of persistent diarrhea are caused by recurrent bouts of enteric infections leading to chronic enteropathy and diminished digestive and absorptive capacity. Poor caloric and protein intake, dietary deficiency of micronutrients such as zinc and vitamin A, and/or immunodeficiency, further contribute to the development of chronic enteropathy and persistent diarrhea.

In developed countries, the causes of chronic diarrhea in children range from dietary factors (e.g., excessive consumption of juice), to diseases causing maldigestion or malabsorption (e.g., celiac disease and other food allergies), to enteric infections (particularly in immunocompromised patients).

Prevalence and Morbidity

Persistent diarrhea occurs in up to 3–5% of the infant population worldwide. The prevalence is substantially higher in developing countries compared to developed countries. Although less than 10% of diarrheal episodes become persistent, persistent diarrhea accounts for more than half of diarrheal deaths, and 30–50% of deaths overall among children younger than 5 years of age in the developing world.

Pathophysiology

The intestine is the major site of gastrointestinal fluid absorption and secretion. It is lined by a single layer of polarized epithelial cells that are joined together by tight junctions. These cells maintain concentration gradients through specialized channels and ion pumps located in their apical and basolateral membranes, and thus regulate

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Table 190.1
Main causes of chronic diarrhea according to the age of onset

0–30 days	1–36 months	3–18 years
Abetalipoproteinemia	Acrodermatitis enteropathica	Antibiotic-associated C. difficle colitis
Autoimmune enteropathy	Antibiotic-associated C. difficle colitis	Celiac disease
Congenital chloride diarrhea	Autoimmune enteropathy	Congenital sucrase-isomaltase deficiency
Congenital enterokinase deficiency	Celiac disease	Eosinophilic gastroenteritis
Glucose–galactose malabsorption	Chronic infection by *G. lambilia*	Fruit juices, sorbitol, carbonated beverages
Congenital lactase deficiency	Chronic nonspecific diarrhea	*G. lambilia*
Congenital lymphangectasia	Sucrase-isomaltase deficiency	Infectious gastroenteritis
Congenital sodium diarrhea	Cystic fibrosisEosinophilic gastroenteritis	Inflammatory bowel disease
Cow's milk protein/soy allergy	Infectious gastroenteritis	Irritable bowel syndrome
Hirschsprung's enterocolitis	Postinfectious enteropathy	Lactose intolerance
Microvillus inclusion disease	Shwachman–Diamond Syndrome	Laxative abuse
Postinfectious enteritis		Postinfectious enteropathy
Primary bile acid malabsorption		

ion and water fluxes. The epithelial cells located on the villi are responsible for absorption, while the cells located in the crypts are responsible for secretion.

Sodium transport occurs across the brush border membrane through several mechanisms including passive diffusion, special sodium channels, and chloride-linked protein carriers. A sodium gradient is maintained by a Na^+,K^+, -ATPase pump located at the basolateral membrane.

In contrast to sodium, chloride may be actively secreted into the intestinal lumen and acts as a powerful stimulant for fluid secretion. Chloride secretion may occur in response to changes in the intracellular gradient or messenger pathways. Water absorption for the most part occurs freely in the intestine in response to the osmotic gradient created by Na^+ transport from the lumen across the apical membrane of the enterocytes. Na^+ transport across the enterocytes occur through three major pathways:

1. Selective Na^+ channels
2. Sodium chloride-coupled pathway
3. Cotransport of Na^+ with glucose, galactose, or amino acids

Several other factors play a role in altering the volume of the stools including fluids and electrolytes, dietary factors, gut flora, and various gastrointestinal hormones.

Intestinal secretion is activated by an increase in intracellular level of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), and Ca^{++}. These mediators increase the secretion of Cl^-, and consequently sodium and water.

In normal conditions, the secretory process is balanced by fluid absorption. Diarrhea occurs when there is an imbalance between those two processes, leading to incomplete absorption of water. This occurs through two basic pathologic mechanisms: secretory or osmotic.

As stool leaves the colon, the fecal osmolality is equal to that of the serum (290 mOsm/kg). Under normal circumstances, the major osmoles in the stool are Na^+, K^+, Cl^-, and $HCO_3{}^+$. The stool osmolality may be estimated by multiplying the stool $(Na+K)\times 2$. The osmotic gap is the difference between the measured osmolality of the stool electrolytes and the total osmolality of the stool (which is approximately 290 mOsm/kg).

$$\text{Stool osmolal gap} = 290 - (2 \times (\text{Na} + \text{K}))$$

Normal stool osmotic gap is <50. An increased osmotic gap indicates the presence of unmeasured substances in the stool (osmotic diarrhea).

Osmotic diarrhea occurs when poorly absorbed osmotically active solutes are present in the gut lumen. These solutes provide an osmotic gradient that draws water into the intestinal lumen. The most common cause of osmotic diarrhea is carbohydrate malabsorption; the classic example is lactose intolerance. In this state, ingested lactose cannot be digested in the small intestine due to deficiency of lactase enzyme and reach the colon intact causing an osmotic load that attracts water and electrolytes into the bowel. The colonic bacteria ferment the unabsorbed sugar into free fatty acids which is absorbed by the colon.

The essential characteristic of osmotic diarrhea is that the stool output is proportional to the intake of the unabsorbable substrate, and the diarrhea disappears with fasting or cessation of ingestion of the offending substance. The stool osmolality is increased, and the osmolal gap is >125. In osmotic diarrhea secondary to carbohydrate malabsorption the stool pH is low (due to the presence of short-chain organic acids produced by bacterial fermentation of the unabsorbed sugar), and the stool may be positive for reducing substances (reducing sugars are glucose, lactose, galactose, maltose, and fructose). Sucrose is not a reducing sugar (Table 190.2).

Secretory diarrhea occurs secondary to upregulation of the mechanisms involved in the active secretion of intestinal fluids, resulting in large fluxes of water and electrolytes into the small intestine. Intestinal fluid secretion results predominantly from the active secretion of Cl^- through the cystic fibrosis transmembrane regulator (CFTR) channel. Activation of the CFTR may occur secondary to increase in intracellular cAMP, cGMP, Ca^{2+}, resulting in Cl^- secretion into the intestinal lumen. Na^+ and water are secreted with Cl^-, maintaining electrogenicity and osmotic balance.

The most common cause for secretory diarrhea is infection. Enterotoxins from a host of infectious agents bind to specific receptors on the enterocytes, a fragment of the toxin then enters the cell and activates either adenylate cyclase (resulting in an increase in intracellular cAMP; e.g., cholera toxin, heat-labile *Escherichia coli* toxin, Salmonella, Campylobacter, Sheila toxins); or guanylate cyclase (resulting in an increase in intracellular cGMP; e.g., heat-stable *E. coli* toxin, *Yersinia* enterotoxin); or Ca^{2+} (e.g., *Clostridium difficile*, *Cryptosporidium*), and stimulate Cl^- secretion. Cl^- secretion can also be activated by several endogenous secretagogues, infiltrating inflammatory cells, and stimulation of the subepithelial neurons that terminate in the basolateral membrane. Secretory diarrhea is characterized by high-volume, extremely watery stools. Stool analysis reveals high sodium and chloride content (>70 meq/L), and a stool osmolal gap less than 50 mOsm/kg. Fecal pH is normal, and the stool is negative for reducing substances. Secretory diarrhea continues with fasting. Congenital defects of chloride transport such as *congenital chloridorrhea* also produce secretory diarrhea.

Diarrhea can be further classified according to the stool characteristics into watery, fatty, or inflammatory. Watery diarrhea implies a defect primarily in water absorption, and as discussed earlier, can either be secretory or osmotic. Fatty diarrhea implies a defect in fat absorption. Inflammatory diarrhea characterized by the present of mucus and pus in the stools, imply an infectious or inflammatory etiology.

Causes of Chronic Diarrhea

Infections

Chronic diarrhea may be associated with intestinal or extraintestinal infections. In developing countries, chronic diarrhea usually results from recurrent enteric infections, often with multiple pathogens, leading to destruction of the intestinal mucosa, with no sufficient time between infections to allow healing. This leads to chronic enteropathy which causes malabsorption, and can result in malnutrition if caloric intake is not sufficient. Malnutrition further contributes to the prolongation of diarrheal episodes by impairing both the immune system and tissue healing.

The most common causes of infectious persistent diarrhea are bacterial microorganisms (enteroadherent *E. coli*, enteropathogenic *E. coli*, *Shigella*, *Cryptosporidium*, and *Cyclospora*). Intestinal parasites can also cause persistent diarrhea, while viruses typically cause acute diarrhea, though prolonged symptoms may occur due to postinfectious enteritis. Rotavirus, cytomegalovirus, Torovirus, and astrovirus have been associated with chronic diarrhea.

Table 190.2
Osmotic versus secretory diarrhea

	Osmotic diarrhea	Secretory diarrhea
Volume of stool	Large	Very large
Response to fasting	Diarrhea stops	Diarrhea continues
Reducing substances	+	–
Fecal pH	<5	>6
Stool osmolality	Normal to increased	Normal
Stool ion gap	>125	<50

Rotavirus: Rotavirus usually causes severe acute watery diarrhea in young children, but may also cause chronic diarrhea in both immunodeficient and immunocompetent hosts.

Yersinia enterocolitica: *Y. enterolitica* is associated with diarrhea, mesenteric adenitis, and terminal ileitis mimicking IBD. Symptoms usually resolve in 5–14 days, but may persist for several months.

C. difficile: *C. difficile* is the most common infectious etiology of antibiotic-associated diarrhea (AAD) accounting for 20% of cases. AAD manifests with variable degrees of severity, ranging from acute mild watery diarrhea to persistent bloody diarrhea and fulminant hemorrhagic colitis. The usual presentation of AAD in children is an acute onset of profuse watery diarrhea, often associated with blood, which begins during the first 5–10 days of antibiotic therapy, but may develop up to 10 weeks after the completion of the antibiotic therapy. The diarrhea is usually associated with abdominal pain, nausea, and vomiting. Low-grade fever and leukocytosis may occur. In uncomplicated cases, the symptoms resolve shortly after stopping the antibiotics. Metronidazole may be used in the presence of fever, colic, leukocytosis, or pseudomembranous colitis. Vancomycin can be used for severe recurrent cases.

Giardia lambilia is the most common cause of intestinal protozoal infection worldwide. The majority of the infections are asymptomatic. Infection occurs by the ingestion of the water-borne cysts; as little as 10–100 cysts can cause infection. Once the cysts reach the upper small intestine, they divide into four trophozites, which colonize the lumen of the duodenum and jejunum. In the small intestine, the trophozites adhere to the enterocytes, causing local effacement of the microvilli which can cause malabsorption. The most common clinical manifestation is diarrhea. Weight loss, crampy abdominal pain, steatorrhea, malabsorption, and failure to thrive may occur.

The diagnosis can be made by identifying the cysts, or antigen in stools, or by identifying the protozoa in a duodenal aspirate or biopsy. Microscopic examination of a single stool specimen is approximately 70% sensitive. Sensitivity increases to 85% when three stool specimens collected on separate days are examined.

Treatment is with metronidazole. Some apparent clinical treatment failures are due to lactose intolerance, which can persist for weeks after successful treatment.

Entamoeba histolytica: *E. histolytica* is transmitted primarily through fecal–oral route via ingestion of the cysts of the protozoan. The cysts can be found in fecally contaminated food and water supplies, and on contaminated hands of food handlers. The cysts remain viable in the environment for weeks to months, and ingestion of a single cyst is sufficient to cause disease. Excystation occurs in the terminal ileum or colon, forming trophozoites. The trophozoites can invade and penetrate the colonic mucosa, leading to tissue destruction and bloody diarrhea (dysentery). Chronic nondysenteric syndrome of diarrhea, weight loss, and abdominal pain, which can last for years, can occur. The trophozoites can also spread hematogenously via the portal circulation to the liver, lungs, heart, and brain.

The best method to diagnose *E. histolytica* is by fecal antigen detection assay, as stool microscopy cannot differentiate between *E. histolytica* and *Entamoeba dispar* or *Entamoeba moshkovskii* which are more common than *E. histolytica* but are nonpathogenic. A minimum of three specimens (85–95% sensitivity), collected on separate days, should be evaluated since shedding of organisms vary from day to day. Antibody measurements (detect *E. histolytica* but not *E. dispar*) can also be used but they remain positive for years.

Treatment is by metronidazole orally (children: 35–50 mg/kg/day in three divided doses for 7–10 days, adults: 500–750 mg/kg/day three times daily for 7–10 days). Following treatment for invasive amebiasis, treatment with a luminal agent (paromomycin, diiodohydroxyquin, diloxanide furoate) may be required to eliminate intraluminal cysts. Follow-up stool examinations are required.

Asymptomatic carriers should also be treated with metronidazole because of the risk of developing an invasive disease, and to prevent shedding of the cysts.

Cryptosporidium: It is a protozoan which causes a self-limited watery diarrhea in normal children, but can cause prolonged diarrhea in immunocompromised patients. Infection occurs by ingesting the cysts from infected feces. The trophozoite divides in the jejunal mucosa and attaches to the intestinal brush border, destroying the microvilli reducing the intestinal absorptive capacity, and producing watery diarrhea and malabsorption. Diagnosis is by stool examination, or by intestinal mucosal biopsy. Patients can be treated with nitazoxanide, or paromomycin, or azithromycin.

Small bowel bacterial overgrowth (*SBBO)*: SBBO is defined as proliferation of bacteria in the upper gastrointestinal tract (stomach, duodenum, and jejunum). In healthy children, the upper small intestinal tract is relatively sterile due to a number of factors including gastric acidity, immunologic factors, and secretory and motility mechanisms. When a disease or therapy interferes with these protective mechanisms, bacteria can proliferate and damage the small intestinal mucosa causing carbohydrate and protein malabsorption. Fat malabsorption can also occur due to bacterial deconjugation of bile acids.

Anaerobic bacteria compete for vitamin B12 uptake, which can result in macrocytic anemia (on the other hand, folate which can be synthesized by luminal bacteria is rarely deficient).

Conditions that predispose to bacterial overgrowth include hypochlorhydria (e.g., acid-secretion blocker medications), motility disorders (e.g., chronic intestinal pseudo-obstruction, scleroderma), and anatomic problems (gastrocolic or enterocolic fistulas).

Although empiric treatment with broad spectrum antibiotics can be tried when the suspicion of SBBO is high, the gold-standard test for diagnosing SBBO is culture of the jejunal aspirate. Glucose breath hydrogen test can also be used to diagnose SBBO. Empiric treatment can be achieved with Rifaximin (800–1,200 mg/day). Other antibiotics that can be used include amoxicillin-clavulanate plus metronidazole, metronidazole combined with a cephalosporin or trimethoprim-sulfamethoxazole, or oral gentamicin. Antibiotic treatment is given for 7–10 days, though some patients require prolonged treatment. Recurrence is common, and retreatment may be needed.

HIV disease: Persistent diarrhea resulting from immunodeficiency, enteric infections, malnutrition, and medications frequently occur in patients with HIV. The infectious pathogens associated with diarrheal diseases in HIV infection may vary with the degree of immunocompromise in the host. Patients with CD4 cell counts <100 cells/microL are at risk for opportunistic infections which are typically chronic, such as Cryptosporidium, Mycobacterium avium complex (MAC), CMV, Isospora, or Microsporidium.

Villous Atrophy

Many pathologic conditions may cause damage to the intestinal mucosa leading to maldigestion/malabsorption and diarrhea. The most common cause is postinfectious enteritis.

Postinfectious enteritis: Postinfectious enteritis is a relatively common complication of acute viral and bacterial infections. Patient presents with a prolonged course of loose diarrhea after an infectious illness had resolved. The etiology is multifactorial and includes acquired lactase deficiency and protein-losing enteropathy that occur secondary to intestinal mucosal injury.

Mild cases can be diagnosed by history alone, while severe, very prolonged diarrhea or weight loss may warrant further investigations. Lactase deficiency can be diagnosed by a hydrogen breath test. Other tests for malabsorption may also be abnormal depending on the extent of the mucosal injury. A small bowel biopsy may be indicated in severe cases for definitive diagnosis.

Mild cases usually respond to a lactose-free diet. Patients with severe cases may require elemental formulas.

Protein-induced proctitis/proctocolitis: It is found almost exclusively in infants. It can occur in both breastfed infants, and infants receiving standard cow's milk or soy-based formulas. Infants usually present by 6 months of age (mean age of presentation is 2 months) with blood-streaked, mucusy, loose stools. Some infants may have increased frequency of bowel movements, but frank diarrhea is not typical. Diagnosis is usually made based on the clinical presentation and the resolution of symptoms upon withdrawal of the offending allergen from the diet.

Dietary protein-induced enteropathy: It occurs in infants with hypersensitivity to cow's milk protein. Food antigens implicated in cow's milk allergy are casein, whey proteins, β-lactoglobulin, and α-lactalbumin. It can also occur secondary to hypersensitivity to other foods, including soy, eggs, rice, poultry, fish or shellfish, as well as following an episode of gastroenteritis. Ingestion of the offending protein causes destruction of the small intestinal villi, causing malabsorption. Infants develop diarrhea, vomiting, failure to thrive, and hypoproteinemia. Intestinal protein and blood loss may occur and stool tests positive for an acidic pH with reducing substances, fecal leukocytes, and blood.

Diagnosis is based on the clinical features, response to allergen elimination, and endoscopy with biopsy.

It is managed by eliminating the causal food from maternal diet in breastfed infants, and substituting cow's milk or soy-based formulas with an extensively hydrolyzed cow's milk formula. Some infants may be sensitive to the residual peptides in extensively hydrolyzed cow's milk formulas and require an amino-based formula. The condition generally resolves after 1–2 years.

Gastrointestinal symptoms may occur along with respiratory and skin manifestations as well. Detection of antigen-specific IgE, either by blood tests (radioallergosorbent test [RAST]) or skin tests, supports the clinical diagnosis. Total IgE determinations and eosinophil counts do not reliably correlate with immediate hypersensitivity responses to foods. Skin testing is done with the puncture or prick method, a drop of food extract placed on the skin.

Food hypersensitivity responses are unusual with a negative skin test, but positive tests carry only a 20–30% chance of predicting a positive food challenge. The RAST and the enzyme-linked immunosorbent assay, (ELISA) are useful for in vitro determination of IgE to antigens. The RAST is the most commonly used in vitro test and is useful particularly when skin tests may be hazardous. Elimination of the offending food is the treatment of choice.

Food protein-induced enterocolitis syndrome (*FPIES*): It most often develops in response to dietary cow's milk protein or soy. Typically, it presents in infants less than 9 months old, with a higher incidence between 1 week and 3 months of age. Patients present with chronic vomiting, diarrhea, malabsorption, or melena. Failure to thrive, anemia, and hypoproteinemia may develop. FPIES may also present acutely if cow's milk protein was previously eliminated from the diet and subsequently re-ingested. In these cases, patients may present with severe vomiting and diarrhea within 2–4 h of ingesting the offending allergen, progressing to profound dehydration, lethargy, and sometimes shock.

Standard skin prick testing and food-specific IgE assays are not helpful in the diagnosis of cow's milk protein allergy, and the diagnosis is based on the clinical features, response to allergen elimination, and endoscopy with biopsies. Symptoms resolve upon elimination of the offending food.

Eosinophilic gastroenteritis is a disorder of unknown etiology, thought to be related to environmental or dietary allergens. It is characterized by eosinophilic infiltration of one or more areas of the gastrointestinal tract, usually the stomach and the small intestine. The disease can affect patients at any age, and usually presents with abdominal pain, nausea, vomiting, and diarrhea.

The clinical features are related to the anatomical location of the eosinophilic infiltration within the gastrointestinal tract and the layer(s) of the bowel wall involved mucosa, muscle, and subserosa. Patients with diffuse small bowel disease may develop malabsorption, protein-losing enteropathy, and failure to thrive. Patients with eosinophilic infiltration of the muscle layer of the gastrointestinal tract may present with symptoms of obstruction (e.g., nausea, vomiting, abdominal distention), while patients with subserosal involvement may present with ascites. Peripheral eosinophilia may be present. Skin prick/patch tests can help identify the culprit allergen.

Management is by dietary exclusion of offending food and/or steroids and immunosuppression.

Celiac disease (*gluten-sensitive enteropathy*): Celiac disease is an immune-mediated inflammation of the small intestine caused by sensitivity to gluten (found in wheat, rye, and barley) in genetically susceptible individuals. The disorder occurs in 0.5–1% of the general population in most countries. It may be asymptomatic, or may present with a variety of gastrointestinal and non-gastrointestinal manifestations, presenting either in childhood or adult life.

Celiac disease often presents during late infancy or early childhood with chronic diarrhea, with or without malnutrition. Stools are typically bulky, foul smelling, and may be floating steatorrhea; alternatively, it may be watery, and in some patients manifested as frequent passage of normal soft stools. The stools may also be bulky but infrequent, and some patients even present with constipation. Patients may also have abdominal distension, anorexia, weight loss, muscle wasting, and hypotonia. Non-gastrointestinal manifestations include irritability, mouth ulcers, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, fatigue, delayed puberty, iron-deficiency anemia resistant to oral iron supplements, hepatitis, arthritis, and infertility.

Celiac disease is associated with IgA deficiency, Type I diabetes, autoimmune thyroiditis, Down syndrome, Turner's syndrome, and William's syndrome. Screening for celiac disease is best done using serum tTG IgA. Recently, saliva tTG IgA has showed promising results as a screening test for celiac disease. The disease should be confirmed by intestinal biopsy.

Treatment is by a lifelong adherence to a gluten-free diet.

Microvillous inclusion disease (*microvillous atrophy*): is an inherited abnormality of the intestinal mucosal structure characterized by hypoplastic atrophy of the intestinal villi that can be identified on light microscopic examination of small intestinal biopsies. Further confirmation is made through electron microscopic examination. Affected individuals present with severe secretory diarrhea within days of birth. Patients may pass over 250–300 mL/kg/day of stool containing electrolyte concentrations similar to those seen in small intestinal fluid. Intestinal transplantation is the only definitive treatment.

Intestinal epithelial dysplasia (*Tufting enteropathy*): Its presentation is very much similar to microvillous atrophy.

Enterocyte heparan sulfate deficiency: similar presentation to microvillous atrophy.

Inborn Errors of Electrolyte Transport

Congenital sodium diarrhea: Congenital sodium diarrhea is an inherited defect in the Na^+/H^+ exchanger in the jejunal brush-border membrane, causing high stool Na^+ concentration, often more than 100 mmol/L. Patients present in utero with maternal polyhydrominous. Prenatal ultrasound shows a distended fetal abdomen with fluid-filled loops of bowel. Abdominal distension at birth may be marked, and can be misdiagnosed as intestinal obstruction. Profuse watery, secretory diarrhea is present from birth. Patients develop metabolic acidosis, and have increased serum aldosterone and renin activity. Normal colonic salvage of sodium can subsequently mask net intestinal secretion, and the diarrhea resolves during the

first year of life. The prognosis is generally good provided fluid and electrolyte losses are replaced in the first few months of life.

Congenital chloride diarrhea: It is the only type of diarrhea that causes metabolic alkalosis rather than acidosis. Affected babies are clinically indistinguishable from patients with congenital sodium diarrhea. Abdominal distension at birth may be marked, and can be misdiagnosed as intestinal obstruction. Stool may be so profuse and watery that it is mistaken for urine. Stool chloride concentration is greater than the sum of sodium and potassium (>90 mmol/L). The prognosis is good if it was early diagnosed and properly managed.

Acrodermatitis enteropathica: A recessively inherited defect in the intestinal absorption of zinc. Zinc deficiency becomes apparent in the first few months of life, manifesting by characteristic symmetrical, scaling erythematous skin lesions around the mouth, perianal area, and elbows. Patients also develop diarrhea, alopecia, and failure to thrive.

Plasma zinc is low as is alkaline phosphatase activity. If untreated, the disease is usually fatal. Lifelong treatment with oral zinc (30–45 mg elemental zinc per day) is curative.

Carbohydrate Intolerance

Carbohydrate intolerance results from the inability to digest certain carbohydrates due to deficiency of one or more of the intestinal disaccharidase enzymes. Disaccharidases, located in the brush border of the small-intestines' enterocytes, split disaccharides into monosaccharides to be absorbed (lactose is split into glucose and galactose, maltose into glucose and glucose, sucrose into glucose and fructose). Undigested disaccharides cause an osmotic load that attracts water and electrolytes into the bowel, causing watery diarrhea. Colonic bacteria ferment the carbohydrates in the colon-producing gases (H_2, CO_2, and methane), resulting in excessive flatus, bloating, distention, and abdominal pain.

Disaccharidase deficiencies can be congenital, late-onset (primary), or secondary. Congenital deficiencies are rare.

Late-onset lactase deficiency (*primary adult hypolactasia*): The most common form of carbohydrate intolerance is late-onset lactase deficiency. Lactase levels are high in neonates, permitting digestion of milk; however, in most ethnic groups, the levels decrease later on in life, rendering older children and adults unable to digest significant amounts of lactose. The decline in lactase activity level is genetically regulated, with the majority of the world's population developing low intestinal lactase levels during mid-childhood (approximately at age 5 years). Lactose that is not absorbed by the small intestine is passed rapidly into the colon, where it is converted by the bacterial flora to short-chain fatty acids and hydrogen gas. The short-chain fatty acids are absorbed by the colonic mucosa, thereby salvaging the malabsorbed lactose for energy utilization. The production of hydrogen by colonic bacteria serves as the basis for the lactose breath hydrogen test used to diagnose lactose maldigestion.

Secondary lactase deficiency: It occurs in conditions that damage the small-bowel mucosa (e.g., celiac disease, acute intestinal infections) due to loss of the brush border lactase enzyme. The deficiency of the lactase enzyme in this case is transient, and the enzyme activity normalizes following the recovery from the underlying disease. In infants, temporary secondary disaccharidase deficiency may complicate enteric infections resulting in prolongation of diarrhea, which may be severe enough to purge other nutrients before they can be absorbed. On biopsy, the intestinal mucosa appears abnormal with varying degrees of villous atrophy, and lactase enzyme activity is reduced concomitantly with other disaccharidases.

The diagnosis of carbohydrate intolerance is suggested if the stool is acidic (pH < 6), and positive for reducing sugars. Diagnosis can also be done by stool sugar chromatography. Lactose intolerance can be confirmed by H_2 breath test.

Management of disaccharidase deficiency consists of dietary restriction of the carbohydrates that cannot be absorbed. However, because the degree of lactose malabsorption varies greatly in patients with lactose intolerance, many patients can ingest up to 12 oz (18 g of lactose) of milk daily without symptoms. Yogurt is usually tolerated because it contains an appreciable amount of lactase produced by intrinsic Lactobacilli. Commercially prepared predigested milk (i.e., pretreated by the addition of lactase) can be used. Lactase drops and pills are also available.

Sucrase-isomaltase deficiency: can be congenital (CSID), or acquired.

CSID is an autosomal recessive inherited disorder characterized by the absence of intestinal sucrase, with varying degrees of isomaltase activity. The exact incidence of this condition is unknown. A high incidence has been observed in the Eskimo population of Greenland, where it has been reported in 10% of the population. Heterozygote carriers occur in 1 in 50 persons, and have a lower than normal sucrase activity. Symptoms will not appear until sucrose is introduced into the child's diet, and the severity of the symptoms depends on the residual enzyme activity, the amount of sucrose ingested, the rate of gastric emptying, the colonic bacteria, and the absorptive capacity of the colon. Infants usually present with severe watery diarrhea

associated with poor weight gain. Older children and adults may have less severe symptoms of an osmotic-fermentative diarrhea following ingestion of disaccharides and oligosaccharides. They may present with a picture identical to a diarrhea-predominant irritable bowel syndrome, with flatulence, especially at the end of the day, and episodic diarrhea associated with large sucrose intake.

The condition may also present with incontinence and intermittent watery diarrhea, or incontinence and intermittent abdominal distention in the older child. Stools are usually acidic and positive for reducing substances. The diagnosis can be confirmed by a sucrose breath test. An enzyme assay of the small intestinal mucosa will demonstrate the characteristic sucrase-isomaltase deficiency in morphologically normal mucosa. Affected children usually respond to a sucrose free diet within 24 h. Sacrosidase (Sucraid) supplement can be taken with each meal and snack.

Colonic adaptation to fermentation may result in spontaneous improvement.

Inflammatory Bowel Diseases Including Crohn's Disease, Ulcerative Colitis, and Indeterminate Colitis

Diarrhea associated with abdominal cramps, weight loss, and the presence of blood in the stools raises suspicion for *inflammatory bowel disease*. Although the incidence of *inflammatory bowel disease* is lower in young children, well-documented cases of *Crohn* and *ulcerative colitis* have been seen in children between 2 and 4 years of age.

Crohn's disease (*CD*): CD is an idiopathic chronic inflammatory disease that can affect any part of the gastrointestinal tract, from mouth to anus, with the terminal ileum being most frequently affected. CD of the gastrointestinal tract is characterized by "skipping" lesions, with inflamed areas interspersed with normally appearing mucosa. The rectum is usually, but not always, spared in CD. *Crohn disease* is characterized by transmural inflammation, anywhere in the gastrointestinal tract, with fissures, cobble-stone appearance, and skip areas. The inflammation can affect all layers of the bowel wall, and may lead to perforation, abscess, and fistula formation. Patients frequently present with chronic diarrhea that is usually not grossly bloody, and abdominal pain that is frequently located in the right lower quadrant. Growth retardation is common. Intestinal biopsy may detect noncaseating granulomas.

Pharmacologic treatment, during an acute exacerbation, includes the use of methylprednisolone at 1–2 mg/kg/day, tapered slowly over 4–6 weeks, depending on response. Sulfasalazine and meselamine are used to induce remission.

Ulcerative colitis (UC): UC virtually always involves the rectum, and the inflammation may extend proximally in a continuous manner to variable lengths of the colon though a backwash ileitis may occur in the presence of severe cecal disease. Patients with UC typically present with bloody diarrhea, associated with abdominal pain that is relieved by bowel movement.

Autoimmune enteropathy: Presents with severe, persistent, secretory diarrhea caused by circulating anti-enterocyte and/or anticolonocyte antibodies. The severity of the enteropathy is highly variable. Some patients respond to dietary manipulation, but most require immunosuppression, to which not all respond. In these, the outcome is often fatal.

Pancreatic Diseases

Pancreatic diseases include conditions associated with a total pancreatic insufficiency, such as cystic fibrosis and Shwachman–Diamond syndrome, or with selective enzyme deficiency, such as congenital lipase deficiency.

Cystic fibrosis (*CF*): *CF* is the most common cause of exocrine pancreatic disease in white Caucasian children, occurring in 1 per 2,500 live births. The disease is caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene located on the long arm of chromosome 7. There are over 640 well-recognized mutations, the commonest being ΔF508 mutation. These mutations lead to impaired chloride transport in epithelial tissues, and inspissation of secretions and obstruction in the respiratory tract, pancreatic ducts, biliary tree, and intestines, as well as impaired chloride reabsorption from sweat duct which result in the characteristic high sweat chloride. Clinical signs of pancreatic insufficiency develop when less than 10% of normal pancreatic enzyme activity is present in the duodenum.

Most patients with *CF* (80–90%) have pancreatic insufficiency. In pancreatic insufficient patients, *CF* usually presents before 6 months of age with malnutrition and failure to thrive. Hypoalbuminemia and edema may also occur. Patients may also present with chronic diarrhea; with bulky, loose, foul, oily or watery bowel movements, and are at risk of fat-soluble vitamins deficiency (vitamins A, D, E, K).

Diagnosis is by a sweat chloride test (chloride level equal or more than 60 is diagnostic). Intermediate results of sweat testing (30–59 mmol/L in infants younger than

6 months, and 40–59 mmol/L for older children), should be clarified by DNA analysis using a CFTR multimutation method, and the sweat test should be repeated.

Shwachman–Diamond Syndrome (*SDS*): SDS is a rare autosomal recessive disorder characterized by exocrine pancreatic insufficiency, ineffective hematopoiesis, and skeletal abnormalities. After cystic fibrosis, SDS is the second most common cause of pancreatic insufficiency in childhood. Patients with SDS have exocrine pancreatic insufficiency as a result of failure of the pancreatic acinar cells to develop in utero and their replacement with fatty tissue. Pancreatic endocrine functions generally remain intact. Patients typically present in early infancy with malabsorption, steatorrhea, failure to thrive, and deficiencies of fat-soluble vitamins A, D, E, and K. They may have fatty stools but this tends to improve with age. Recurrent bacterial infections are common because of a neutropenia/neutrophil migration defect.

Evaluation may include a CBC (which may reveal neutropenia, anemia, or thrombocytopenia), but since neutropenia may be intermittent, CBC counts may need to be repeated biweekly over a 3-week period to document neutropenia. Fetal hemoglobin is elevated in approximately 80% of the patients. Neutrophil function studies may reveal neutrophil migration defect. Low serum pancreatic trypsinogen and low isoamylase levels are helpful markers for pancreatic insufficiency depending on the age of the patient. Fecal fat loss varies from 3% to 60%, and tends to decrease with age, so absence of steatorrhea in a 72-h fecal fat measurement test does not exclude the diagnosis of SDS. Pancreatic insufficiency can be diagnosed by the absence or decrease of pancreatic enzymes after stimulation with intravenous secretin and cholecystokinin.

For unknown reasons, pancreatic lipase secretion increases with age, often resulting in normal fat absorption. Approximately 50% of patients with SDS become pancreatically sufficient later in childhood.

Bile Acid Deficiency

Bile acids play an important role in micelle formation and fat absorption. Deficiency can occur in cirrhosis and chronic cholestatic liver diseases (e.g., biliary atresia, primary biliary cirrhosis), diseases affecting the terminal ileum (where bile acid absorption takes place), and following extensive resection of the terminal ileum. Bile acid can also be deconjugated by bacteria in patients with small bowel bacterial overgrowth.

Deconjugation of bile acids renders free bile acids amenable for absorption, thus lowering the luminal bile acid available for micelle formation and fat absorption, leading to steatorrhea. Additionally, free fatty acids may cause damage to the mucosa and further contribute to malabsorption.

Motility Disorders

Functional diarrhea (also known as chronic nonspecific diarrhea of childhood, or *toddler's diarrhea)*: Toddler diarrhea is the most common cause of chronic diarrhea in otherwise well children referred to pediatricians in the developed world. It is a benign disorder characterized by daily passage of three or more large, unformed stools foul-smelling, mushy stools containing undigested food, with onset between 6 and 36 months of age. It is characterized by normal growth unless the child has been placed on a hypocalorie diet to relieve symptoms. It may result from dietary factors such as excessive fiber and low fat intake, ingestion of large amounts of osmotically active carbohydrates such as fruit juice, carbonated beverages, sorbitol.

Children with functional diarrhea usually pass stools only during waking hours. Early morning stools typically are large and semi-formed, then stools become progressively looser as the day progresses. There are periods of relatively normal stools or even constipation between the bouts of diarrhea. Virtually all children develop normal bowel patterns by 4 years of age. Apart from restricting fruit juices and carbonated beverages and increasing dietary fat to 30–50% of total calories, no other intervention is necessary. Response to the dietary intervention supports the diagnosis.

Fecal impaction and overflow incontinence: Chronic constipation often presents with the complaint of diarrhea. This results from seepage of loose stools around a hardened fecal matter in the rectum. The rectum becomes chronically dilated, and the child may lose the sensation of rectal fullness and the need to defecate. Soiling of the child's underwear occurs, which the parent may perceive as the loose stool and loss of control of diarrhea.

Irritable bowel syndrome (*IBS*): The typical presentation of IBS is that of multiple bouts of diarrhea alternating with constipation, associated with lower abdominal pain and flatulence. There is no weight loss, and the stool is negative for blood. Physical examination is normal. Some patients respond to fiber intake, others to elimination of suspected offending food. Antispasmodics, loperamide, and anticholinergics can be given.

Other Causes

Drugs: Many drugs can cause diarrhea. Identification of drugs as the cause of diarrhea depends on recognition of

the coincidence of the initiation of drug ingestion with the onset of diarrhea.

Lymphangectasia: Intestinal lymphangectasia is characterized by the formation of dilated lymphatic channels in the small intestine. These dilated lacteals result in poor lymphatic drainage which results in increased intestinal lymphatic pressure and leakage of protein, lymphocyte, and chylomicron-rich lymph into the intestinal lumen. Lymphangectasia may be congenital, or it can occur secondary to disorders that interfere with intestinal lymphatic drainage (e.g., constrictive pericarditis, patients with cavopulmonary anastomosis (Fontan), retroperitoneal tumors that compress the lymphatic drainage). Patients may present at any age, with diarrhea, vomiting, growth retardation, peripheral edema, or lymphopenia.

A number of congenital diseases are associated with lymphangectasia, including autoimmune polyglandular disease type 1, Noonan's syndrome, and aplasia cutis congenita.

Diagnosis can be established by measuring the fecal concentration of alpha1-antitrypsin. Alpha1-antitrypsin is a protease inhibitor that is present in the serum and not present in diet. Therefore, its presence in the stool indicates a protein-losing enteropathy. Mucosal biopsies show dilated lymphatic channels.

Since intestinal lymph flow varies with meal composition, dietary manipulation can provide symptomatic improvement. A low fat diet can reduce protein loss. Medium-chain triglycerides (MCT) are transported in portal blood and do not increase lymph flow, and can be used in the diet.

Prognosis is good, and spontaneous remission may occur.

Neuroendocrine tumors: Neuroendocrine tumors affecting the gastrointestinal tract are rare in children, and usually cause secretory diarrhea.

Gastrinoma (*Zollinger–Ellison syndrome*): Gastrinomas arise from enteroendocrine cells, located mainly in the pancreas and the small intestine, and result in unregulated gastrin secretion which in turn causes hypersecretion of gastric acid, and consequent peptic ulcers and chronic diarrhea. Diarrhea occurs because of the high volume of the gastric acid secreted, which exceeds the neutralizing capacity of the pancreatic bicarbonate, resulting in inactivation of the pancreatic enzymes, and interfering with the emulsification of fat by bile acids. The acid also damages the intestinal mucosa, causing malabsorption.

Less than 5% of patients with ZES present during adolescence. The disorder may be suspected in patients with multiple or refractory ulcers, or ulcers located distal to the duodenum and/or a secretory diarrhea and fat malabsorption. Fasting serum gastrin levels are usually elevated five- to tenfold.

VIPomas: Unregulated hypersecretion of vasoactive intestinal polypeptide (VIP) causes watery diarrhea, hypokalemia, and achlorhydria. VIPomas are very rare in children, but may occur as ganglioneuromas and ganglioneuroblastomas.

Diagnosis

History and Physical Examination

A detailed history and physical examination can often provide clues to the diagnosis, and point toward appropriate investigations. Neonatal onset of watery diarrhea suggests a congenital disorder (e.g., congenital chloride diarrhea, congenital sodium diarrhea, Tufting enteropathy). Steatorrhea and recurrent respiratory infections suggest cystic fibrosis. A history of excessive ingestion of carbonated drinks or fruit juices with normal growth parameters suggest chronic nonspecific diarrhea. Stools that become looser as the day progresses are typical of functional diarrhea. Small-volume fecal incontinence occurs with constipation and fecal impaction. An irritable child with failure to thrive, abdominal distention, and foul-smelling diarrhea may have celiac disease.

Diarrhea of abrupt onset suggests an infectious etiology. Diarrhea that develops during or within 6–8 weeks of antibiotic therapy suggests antibiotic-associated diarrhea. Stools that contain blood or pus suggest inflammation, which can be caused by dietary protein intolerance (common in infants), inflammatory bowel disease, or rarely chronic enteric infections. Passage of diarrheal stools at night raises the suspicion of an organic etiology.

A family history can suggest inherited disorders as celiac disease, cystic fibrosis, and inflammatory bowel disease. It is important to remember that as important a positive family history is, a negative family history does not rule out the possibility of an inherited disorder.

On physical examination, dry, brittle hair may suggest fat malabsorption. Pale mucous membranes are seen in anemia, and may suggest blood loss or iron or vitamin B12 malabsorption. Dental hypoplasia may be seen in patients with celiac disease or Shwachman–Diamond syndrome. Clubbing of the fingers suggests a chronic disease like cystic fibrosis or IBD. Muscle wasting may be noted on the proximal limbs, and suggest malnutrition or chronic malabsorption. Edema may be noted on extremities, and suggest protein-losing enteropathy. Bony defects suggest Shwachman–Diamond syndrome.

Abdominal examination may reveal abdominal distension that can be seen in celiac disease and carbohydrate malabsorption. A tender abdomen may suggest enterocolitis. Signs of severe perianal erythema point toward carbohydrate malabsorption. Rectal examination may reveal skin tags, fissures, or fistulas that occur in inflammatory bowel disease. Soiling may be noted on the underwear, and fecal impaction may be noted on rectal examination, suggesting overflow incontinence.

Laboratory evaluation: Because the etiology of chronic diarrhea differs between developed and developing countries, and in situations where limited resources exist in developing countries, the diagnostic approach varies according to the situation.

In the developing countries, the predominant cause of chronic diarrhea is persistent infectious gastroenteritis, and because the diagnostic resources are often limited, an algorithmic approach to diagnosis and management is practical and usually effective.

Infectious diarrhea can be classified based on the appearance of the stools into watery or bloody. Most cases of persistent watery diarrhea in children in developing countries improve with improving the nutritious status and reducing the likelihood of reinfection, and require no further workup or medications. If watery diarrhea persists, stool microscopy can be performed to detect trophozoites or cysts.

Bloody diarrhea in most cases is caused by Shigella spp (45–67%), or Campylobacter (35–37%). If available, bloody diarrhea should be tested by stool microscopic examination, and treatment based on local resistance patterns should be started empirically. If no improvement is seen within 2 days, treatment should be changed to another agent known to be effective against local strains.

E. histolytica is the most important nonbacterial pathogen in bloody diarrhea, but is responsible for less than 3% of the episodes. Empiric treatment of intestinal parasites is not recommended, except for persistent bloody diarrhea in a patient who has failed trials of two different antimicrobials known to be effective against local strains of *Shigella*. In this case, the patient can be treated empirically for amebiasis.

Comorbid conditions that may be the underlying cause of the malnutrition, such as cystic fibrosis, congenital heart disease, HIV disease, and tuberculosis, should also be looked for and addressed. All children should also be evaluated (and treated) for associated nonintestinal infections, including pneumonia, urinary tract infections, sepsis, and otitis media.

In developed countries, given the high prevalence of celiac disease and the availability of noninvasive, sensitive, and specific testing, most if not all children with chronic diarrhea should be screened for celiac disease. Serum testing for anti-tissue transglutaminase antibodies (tTG) is recommended. Testing serum immunoglobulin A (IgA) levels at the same time is suggested to avoid the possibility of a false-negative result in patients deficient in IgA (IgA deficiency is 10–15 times more common in patients with celiac disease than in healthy subjects).

Categorizing the stool type into watery, inflammatory, or fatty can help narrow the diagnostic possibilities.

In patients with watery diarrhea, assessing the effects of fasting on stool output can help distinguish between secretory and osmotic diarrhea, as fasting is associated with decreased stool volume in osmotic but not secretory diarrhea. Further distinguishing between osmotic and secretory types of watery diarrhea can be done by measuring fecal electrolytes, pH, reducing substances, and calculating the osmotic gap (*Table 190.2*). In children with secretory diarrhea, an infectious etiology should be suspected and evaluated.

Pure secretory diarrhea occurs in some congenital diarrheas, and should be evaluated according to likely etiologies. Patients suspected of hyperthyroidism should have TSH measured. Antienterocyte anticolonocyte antibodies should be done in patients suspected of autoimmune enteropathy.

The presence of reducing substances in the stool or low fecal pH (<6) suggest carbohydrate malabsorption. Patients suspected of lactose intolerance can undergo a hydrogen breath test (H_2 breath test).

In patients suspected of factitious diarrhea, stools should be checked for phenolphthalein, magnesium, sulfate, and phosphate to determine whether the diarrhea is secondary to laxative abuse.

Empiric treatment with broad spectrum antibiotics can also be done.

In patients with gross or occult blood, fecal leukocytes, or fecal calprotectin (a protein found in leukocytes), an inflammatory etiology of the diarrhea should be suspected and evaluated. A stool examination should be performed to exclude infection. If this is negative, the patient must be evaluated for inflammatory bowel disease; a complete blood count (may depict anemia, or thrombocytosis), and an increased erythrocyte sedimentation rate and/or C-reactive protein level, although not specific for IBD, suggest an inflammatory process. Further evaluation include small bowel contrast radiographs or CT scan (which can reveal mucosal thickening, strictures, fistulas) and upper endoscopy and colonoscopy with biopsies.

In patients with fatty diarrhea, fat malabsorption should be investigated. Celiac disease should be tested, and if excluded the patient should be tested for pancreatic

exocrine insufficiency. Cystic fibrosis can be tested by a sweat test and genetic screening. A secretin test can be done to evaluate pancreatic insufficiency.

Munchausen's syndrome by proxy: Measurement of stool electrolytes, osmolality, and magnesium content should be performed in any case of unexplained chronic diarrhea to evaluate for Munchausen's syndrome by proxy. Low stool electrolytes and osmolality suggests the addition of water to the stool. If magnesium concentration in the stool exceeds that in the plasma, it indicates cathartic administration. Stools should also be tested for phenolphthalein cathartics, emetine, and bisacodyl and its metabolites. A negative study may have to be repeated since children may ingest the laxatives intermittently.

Laboratory Evaluation of the Nutritional Status in Children with Chronic Diarrhea

CBC and red blood cell indices: Identify children with anemia. A microcytic, hypochromic anemia suggests iron deficiency which can occur in malabsorptive conditions such as celiac, or chronic blood loss, such as cow's milk allergy or ulcerative colitis. Serum ferritin level should be checked (may be falsely elevated in inflammatory conditions since ferritin is an acute-phase reactant). A macrocytic anemia suggests folate, or vitamin B12 deficiency (e.g., Crohn's disease of the distal ileum). The levels of these vitamins can be measured in the blood.

Prealbumin and albumin levels are good indicators of short- and long-term dietary intake, respectively. Prealbumin has a short half-life (approximately 2 days); thus it falls rapidly with poor dietary intake, and rises to normal values within 10 days of initiation of adequate nutritional treatment. Therefore, prealbumin can be used as a marker of acute malnutrition, and as a predictor of adequate nutritional therapy.

Albumin has a longer half-life (14–20 days), reflecting dietary intake during the preceding 3 weeks, and serves as a marker of chronic malnutrition (e.g., Crohn's), and as an indicator of the adequacy of long-term dietary intake.

Vitamins: The assessment of specific vitamin deficiencies may be necessary in children with chronic diseases associated with malabsorption or inflammation. Serum concentrations of vitamin A, E, and 25-hydroxy vitamin D can be measured directly. Vitamin K can be assessed by measuring prothrombin time.

Deficiency of water-soluble vitamins is less common, and levels should only be measured when clinically indicated.

Minerals: Zinc and magnesium deficiency may occur in patients with chronic diarrhea. Bone density studies may be indicated in children at risk for osteopenia (e.g., IBD, celiac disease).

Zinc therapy has proven its efficacy in reducing the severity and duration and mortality from diarrheal disease.

Treatment

The most important step in managing a child with chronic diarrhea is to assess and stabilize the hydration and nutritional status. Children with severe malnutrition should be treated in an inpatient setting. Hypokalemia and hypophosphatemia caused by intracellular ion shifts may occur during the early refeeding period, and can cause serious arrhythmias; therefore, serum potassium and phosphorous concentrations should be carefully monitored early in the course of nutritional rehabilitation of severely malnourished children. In most cases, breast feeding should be continued.

Children with moderate malnutrition, and those with dehydration, systemic infections, or infants less than 4 months of age, should be treated in an inpatient setting if possible. Malnutrition complicates the course of most cases of persistent diarrhea in developing countries, and is the primary target for treatment. Dietary therapy should aim at providing 150 Cal/kg/day. Deficiencies of vitamin A, zinc, folic acid, copper, and selenium are common in malnourished children, and should be supplemented. The WHO recommends zinc supplementation for children with diarrhea in developing countries at a dose of 10 mg/day for infants up to 6 months of age, and 20 mg/day for older infants and children, for 14 days. The WHO also recommends providing at least two times the recommended daily allowance (RDA) for folate, vitamin A, iron, copper, and magnesium, for 2 weeks.

Further treatment depends on the specific etiology of the chronic diarrhea.

Prognosis

Prognosis in chronic diarrhea depends on the etiology and the degree of dehydration/malabsorption and associated comorbidities.

Prevention

Control of sanitary conditions decreases the risk of infectious diarrhea. Breastfeeding, especially exclusive breastfeeding, protects against exposure, furthermore, breast milk contains lactoferrin, lysozyme, and oligosaccharides against enteropathogens, as well as antibodies which have a protective effect. In developing countries, breastfeeding to 2 years of age is recommended by the World Health Organization (WHO) and other agencies.

Treating cyst carriers can prevent shedding and spreading of *E. histolytica*.

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191 Gastrointestinal Food Allergy in Infancy and Early Childhood

Ian R. Sanderson · John A. Walker-Smith

The term "food idiosyncrasy" has been used in the sense of a non-immunological abnormal response to food. There is, however, increasing evidence that dietary protein intolerance may be mediated by an allergic reaction or reactions affecting the gastrointestinal tract. It is those syndromes of dietary protein intolerance occurring in infancy and childhood that have an immunological pathogenesis which are the subject of this chapter.

Intolerance to various food may be due to a variety of causes; for example, a congenital enzyme defect such as sucrase-isomaltase deficiency, an acquired digestive enzyme defect such as lactase deficiency secondary to small intestinal mucosal damage, or may be immunological in origin.

Definitions

Gastrointestinal food allergies may be defined as clinical syndromes that are characterized by the onset of gastrointestinal symptoms following food ingestion where the underlying mechanism is an immunologically mediated reaction within the gastrointestinal tract.

A food-sensitive enteropathy is a disorder characterized by an abnormal small intestinal mucosa while having the offending food in the diet; the abnormality is reversed by an elimination diet only to recur once more on challenge with the relevant food. It may be permanent as it occurs in celiac disease. It may however be temporary, and such disorders are generally confined to infancy and early childhood.

Food-induced colitis is a disorder where ingestion of food produces a colitis which is reversed by an elimination diet and which relapses on challenge.

Clinical Spectrum

There is no consistent association between a particular food and any specific syndrome. Clinical intolerance to a variety of food proteins has been described. The most common variety of food protein intolerance described are those to cows' milk, cereals, soy protein, eggs, and fish and intolerance to tomatoes, oranges, bananas, meat, nuts, and chocolates.

Gastrointestinal reactions to food in children with food allergy may be divided into those that manifest quickly, i.e., within minutes to an hour of food ingestion, and those in which the onset is slow, taking hours or days after food ingestion. Both types of reaction may occur individually or together in different children. Yet there are clear immunological differences between these groups. For example, it has been shown by Fallstrom et al. (1986) that children with slow onset reactions to cows' milk feedings have significantly elevated titers of IgG antibodies against both native and digested beta-lactoglobulin, when compared with both controls and those children who develop symptoms quickly after milk ingestion. These children also tend to have higher levels of IgA antibody to both native and processed milk.

Elevated titers of IgE antibodies to cows' milk protein are typical of quick reactors. However, IgE is also elevated in some children with slow onset reactions with enteropathy. Such elevated titers can on occasion be found in milk-tolerant, atopic children. These gastrointestinal food syndromes of early childhood appear to be temporary in duration, although it does seem possible – as in the case of cows' milk protein intolerance – that gastrointestinal syndromes may be replaced with the passage of time by syndromes involving other systems.

Quick Onset Syndromes

The children with quick onset syndrome often have an individual and family history of atopy, peripheral eosinophilia, elevated total serum IgE levels, and positive RAST and skin prick tests to specific foods.

Little information is available concerning small intestinal mucosa in these quick onset syndromes as children with these disorders are not usually biopsied. Theoretically, from animal studies the small intestinal mucosa may be normal.

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When there is intolerance to a number of foods, diets involving the elimination of a number of foods may be impractical or ineffective on their own. However, the addition of disodium cromoglycate may be effective. Curiously, if oral disodium cromoglycate alleviates symptoms these may not relapse when the drug is discontinued.

These patients need to be distinguished from cases of eosinophilic gastroenteritis.

Eosinophilic gastroenteritis is a disorder characterized by gastrointestinal thickening with edema and dense infiltration of eosinophils. It usually affects the gastric antrum and proximal small intestine. It is usually a disorder of young adults but may occur in children. Clinically it is characterized by protein-losing enteropathy and peripheral eosinophilia. IgE levels may be elevated and some patients have been reported to respond to a cows' milk-free diet. Although most patients are not responsive to diet manipulation, some do respond to disodium cromoglycate.

Slow Onset Syndromes

Slow onset syndromes usually present as a gastrointestinal problem to pediatric or pediatric gastroenterology clinics. Affected children may often have failure to thrive. In these cases there is often no clear history of food ingestion being related to the onset of symptoms. Diagnosis may be difficult. Accurate diagnosis requires further investigations of gastrointestinal and immunological functions.

Once the initial investigations have been performed, dietary elimination and challenge continue to have an important diagnostic role. This approach is of best value when such elimination and challenge is related to gastrointestinal structure and function, i.e., serial observations. At present, there are no simple laboratory tests available for routine diagnostic screening of children with these slow onset gastrointestinal symptoms. In individual patients cows' milk antibody estimation is not diagnostically useful. In children, such problems often overlap with gastrointestinal infection thus making diagnosis difficult. Full microbiological study of the stools is needed, i.e., stool virology, as well as stool bacterial culture, because infection of the gastrointestinal tract can be easily overlooked in children presenting these symptoms.

Transient Food-Sensitive Enteropathies

Changes in the structure of the small intestinal mucosa in response to the ingestion of particular foods provide clear objective evidence of food-sensitive disorders affecting the small intestinal mucosa. This approach of using serial small intestinal mucosal biopsies related to dietary elimination and challenge was first used for the diagnosis of celiac disease in the Interlaken or European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) Diagnostic Criteria. In recent years the use of a small biopsy capsule has been replaced by endoscopy and biopsy. Celiac disease is a state of permanent food sensitivity, but there also exists a group of temporary food-sensitive enteropathies, presenting in infancy. Indeed a number of foods apart from gluten have now been shown to produce food-sensitive enteropathies in infancy. These include cows' milk protein, soy protein, eggs, chicken, ground rice, and fish.

Pathology

Most information available concerns cows' milk–sensitive enteropathy and is based upon small intestinal mucosal biopsy. What evidence there is for other food-sensitive enteropathies suggests that the pathology is essentially similar. The characteristic feature is small intestinal mucosal damage of variable extent and severity. The lesion is often patchy. Within one biopsy there may be a wide range of morphological appearances from normal to severe abnormality. Indeed a single normal small intestinal mucosal biopsy does not exclude this diagnosis.

The changes are nonspecific and can only be established to be induced by cows' milk by means of serial small intestinal biopsies taken first at the time of initial diagnosis on a cows' milk containing diet; second after clinical remission on a cows' milk-free diet; and third after a clinical relapse after a return to a cows' milk containing diet, i.e., a cows' milk challenge. Despite their nonspecific nature, when these biopsy changes are found in children with the typical clinical features, i.e., chronic diarrhea and failure to thrive and other causes such as giardiasis have been excluded, their presence is an indication for a therapeutic trial with a cows' milk-free diet. When there is a rapid clinical response to such a diet, from a practical view-point the diagnosis can only be said to have been established when this is followed by a clinical and histological relapse following cows' milk challenge.

The histological changes found in cows' milk–sensitive enteropathy are indistinguishable from those found in post-enteritis enteropathy. As the two disorders overlap it may not be possible to distinguish them without an early cows' milk challenge. This in practice may not be practical as it may not be seen to be a helpful aid to

management, and early cows' milk challenge carries the risk of a severe relapse.

The classical lesion found in the small intestinal mucosa is villous atrophy of variable severity. It is usually less severe than that found in celiac disease. A flat mucosa is quite uncommon. The mucosa is typically thin. While there may be some lengthening of the crypts the most characteristic feature is shortening of the villi, the epithelial abnormality is less severe than in celiac disease. However, functional damage to the enterocyte is usually present.

There may be an elevation of the intraepithelial lymphocyte count. This is not usually as high as in celiac disease. Gamma/delta T cells density is increased in the intraepithelial lymphocyte population of patients with celiac disease.

There is increased DR^+ $CD4^+$ cells in the lamina propria in children with CMSE and increased intraepithelial $CD8^+$ cells. This suggests that a cell-mediated reaction is the basis of the abnormality. In addition, T cell in the duodenal mucosa produced less TGF-beta in children with food allergy suggesting a loss of the ability to downregulate immune responses. This is important because Peyer's Patch T cells in humans have been shown to be sensitized to dietary antigen, and display TH1 phenotypes.

However, the involvement of IgE in the immunological response of the lamina propria to cows' milk challenge in children with cows' milk–sensitive enteropathy has also been described. Furthermore, infiltration of both eosinophils and mast cells occur in cows' milk–sensitive enteropathy. After a relatively short period on a cows' milk-free diet all these changes either heal completely or significantly improve on a cows' milk-free diet.

Pathogenesis

In order to explore the pathogenic role of allergic reactions in gastrointestinal allergy, Type I, Type III, and Type IV reactions have been induced in experimental animals.

Type I or immediate reaginic allergic reaction results in the development within 5 or 10 min of microscopic edema, mucus secretion, and increased blood flow. Histologically, the mucosa may be entirely normal or just show some edema of the lamina propria and small subepithelial blebs.

In a study of intraluminal antigen challenge of actively or passively immunized pigs to produce a type III or immune complex allergic reaction, a massive influx of polymorphs to the mucosa was shown but without morphological damage.

A variety of type IV, local cell-mediated reactions in the mucosa have been produced in animals. The earliest changes in these cell-mediated reactions are infiltration of lymphocytes into the lamina propria and the epithelium. The crypts lengthen (i.e., become hypertrophied) and crypt cell production rate is increased. Villi are shortened. These changes are mediated by lymphokines secreted by activated T cells. So it could be hypothesized in gastrointestinal food allergy, where there is a cell-mediated reaction, that lymphocytes in the small intestinal mucosa lamina propria, which have been sensitized to dietary antigen, interact with food antigens that enter the mucosa from the gut lumen. This leads to activation of T lymphocytes leading to crypt hypertrophy and reduction in villous height. Whether an IgE-mediated reaction plays any part such as triggering the reaction remains unclear.

The evidence that the small intestinal enteropathy, reported in children with gastrointestinal food allergy, is directly related to the ingestion of a particular food is based upon serial small intestinal biopsy studies related to dietary elimination and challenge. The enteropathy is not usually severe as that seen in celiac disease, although a flat mucosa may occasionally be seen.

The underlying causes of temporary food intolerance, in some children following an acute episode of gastroenteritis, probably relate to a transient sensitization of the child to dietary antigens, which may be a result of a breach of the mucosal barrier. The precise mechanisms that cause the enteropathy are unclear. For the reactions to occur the offending food antigen must enter the mucosa in appropriate amounts to cause sensitization. Post-enteritis food-sensitive enteropathies may result from excess local food antigen entry in susceptible individuals following gut damage induced by viral or bacterial pathogens.

There are probably two syndromes, a primary disorder of immunological origin and a secondary disorder, a sequel of mucosal damage. Abnormal handling of dietary antigens across the intestinal mucosa probably occurs in infants with gastrointestinal food allergy. This may be related to a temporary immunodeficiency state such as transient IgA deficiency or to nonspecific small intestinal mucosal damage from any cause permitting excess antigen entry. The pathogenetic role of circulating antibodies to cows' milk remains to be established.

Involvement of systemic immunity, and the local immune system, could explain the transient nature of the illness. The illness could disappear after a period on a milk-free diet when the small intestinal mucosa local immune system was mature enough to prevent much antigen getting through. The role of cell-mediated immunity would come into play in the case of those children who mounted a cell-mediated reaction in the small intestinal mucosa.

Genetic Factors

Although an atopic family history is often very common, no definite genetic factor has been identified. Boys and girls appear to be equally affected. A genetic variation in the control of antigen absorption by the gut has been shown in animals. If this is so in humans, certain individuals may be more predisposed to develop dietary protein intolerance than others.

Food-Sensitive Colitis

Rectal loss of fresh blood that responded to cows' milk withdrawal is well recognized. The advent of safe colonoscopy and multiple mucosal biopsy even in early infancy has clearly established food-sensitive or allergic colitis as an important cause of chronic bloody diarrhea in infancy. Colonoscopically, there is patchy erythema of the mucosa and petechiae and there may be aphthoid ulceration. Histopathologically, edema and infiltration with eosinophils have been reported although others describe a histopathological appearance not dissimilar to ulcerative colitis with an inflammatory infiltrate; however, both changes disappear on a cows' milk-free diet only to reoccur on early challenge. Even breast-fed infants whose mothers drink much cows' milk may develop cows' milk colitis. β-Lactoglobulin has been demonstrated in the breast milk of lactating mothers although the amounts are very small. This disorder needs to be distinguished from ulcerative colitis and Crohn's colitis. The diagnosis rests upon endoscopy and the histopathology demonstrated by mucosal biopsy and the subsequent clinical course, including resolution of symptoms with cows' milk elimination. In food-sensitive colitis, there may be a dense infiltration of eosinophils in the mucosa and the lesion resolves on food elimination pari passu with clinical remission.

It is now clearly established that a variety of foods, but particularly cows' milk, may be associated with food allergy in early childhood causing structural and functional damage to the intestinal mucosa both large and small. Temporary elimination of the offending food is recommended.

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192 Probiotics in Gastrointestinal Disorders

Aziz Koleilat

Introduction

Probiotic is currently defined as a live microbial food supplement with a proven beneficial effect on human health. Probiotics are live microorganisms that occur naturally in the human digestive system. They consist of yeast or bacteria, especially lactic acid bacteria, and are available as capsules, powder, fermented milks, or yoghurts. Most probiotics are bacteria, which are small, single-celled organisms, normal inhabitants of microflora that may confer several benefits, including prevention against intestinal inflammation. Bacteria are categorized by scientists with genus, species, and strain names. Probiotics exhibit strain-specific differences in their resistance to acid and bile, ability to colonize the gastrointestinal tract, clinical efficacy, and benefits to the health of the host.

Health benefits attributed to probiotics have been described for decades. They include the treatment and the prevention of gastrointestinal diseases, vaginal and urinary infections, as well as allergies.

Mechanisms of Action of Probiotic Bacteria

Human beings, like all animals, play host to many types and high numbers of microbes on our skin, mouths, in women's vaginal tracts, and all the way throughout gastrointestinal tract. In fact, it has been estimated that there are more microbes associated with the human body (about 10^{14}, or 100,000,000,000,000 bacterial cells) than there are human cells in it (about 10^{13}). In addition to this very large number of bacteria, there is also a very large diversity of bacteria. It has been estimated that more than 400 different species, or types, of bacteria make their homes on humans.

Taking this into consideration, it is not surprising that microbes have been found to play an important role in human health. Most of these bacteria are not harmful, and in fact contribute positively to normal human growth and development. But some of these bacteria can have negative influences. It is therefore important that the balance of microbes be maintained to favor the beneficial bacteria over the potentially harmful ones as is necessary for digestive and immune health.

To understand how probiotics work, it is important to understand a little about the microbiology and physiology of the human gastrointestinal tract. Probiotic bacteria are normal inhabitants of microflora and may confer several benefits, including prevention against intestinal inflammation. However, the exact mode of action of probiotics is still largely unknown. The first line of defense against the entry of pathogen is represented by the gut membrane barrier and probiotics may prevent pathogen-induced membrane damage by inhibiting pathogen adhesion and maintaining the correct organization of the tight junction and cytoskeleton proteins.

The origin of microbiota and its development depends on genetics, mode of delivery, early feeding strategies, and the hygienic conditions around the child. In diseases with a defective mucosal barrier, probiotics have been documented to decrease intestinal permeability. Mucus production increases in response to certain probiotics, and cytokine-induced apoptosis of enterocytes may be prevented. Complex interactions between the probiotic microorganism and the host may turn out to be more important than the more simple interactions that have been demonstrated with other bacteria.

It is probable that probiotics do not exert their effects by one single mechanism. However, which of the putative modes of action that is relevant when treating a specific disease is still unsettled.

Due to the incomplete understanding of how probiotics work, in vitro methods are not useful tools for evaluation of probiotics and randomized clinical trials have to be performed to test the probiotic abilities of each specific strain for each specific condition. However, this is a very tedious task to handle in a systematic way. Although the number of bacterial species with theoretical probiotic potentials is limited, the number of specific bacterial strains within each species is countless. For the time being, data obtained from in vitro studies and animal models has to be relied on, and carefully designed randomized clinical trials have to be

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carried on. The native microbiota of an infant gastrointestinal tract is modulated through contact and interaction with the microbiota of the parents and the infant's immediate environment. Modifying this exposure can take place by probiotic bacteria when breastfeeding is not possible. Thus, incorporating specific probiotics may form a beneficial possibility for future infants feeding purposes.

Many probiotics have documented strain-specific health-promoting effects, and most of the effects have been demonstrated in infants and children.

Molecular and cellular mechanisms of probiotics in therapy are mainly manifested as:

- Restoration of microbiologic balance in the intestine
- Competition with pathogenic bacteria for specific binding sites on intestinal epithelial cells
- Protective functions through modulation of immune activity and epithelial function in both the large and small intestine
- Demonstration of enhanced phosphorylation of actinin and occludin in the tight junction region of epithelial cells
- Maintenance of barrier function by preventing cytokine-induced apoptosis in intestinal epithelial cell models through the inhibition of tumor necrosis factor
- Epithelial cell response to whole bacteria and bacterial components in a differential manner, releasing interleukin-8 in response to pathogenic bacteria such as *E. coli* but not to probiotic strains

The Effects of Probiotics in Various Disorders

Inflammatory Bowel Disease (IBD)

The first evidence for the use of probiotics in IBD in humans comes from pouchitis patients. Pouchitis is a complication after ileal–anal pouch anastomosis in ulcerative colitis (UC) patients. Therapeutic strategies are designed to intervene in these abnormal host microbial communications. A novel approach in the last decade has been to use other bacteria or selective foods to induce beneficial bacteria to normalize inflammation. No superiority of any probiotic was clearly evident, but a multiagent mixture, VSL3# maybe better suited in ulcerative colitis while the probiotic *Lactobacillus rhamnosus GG* appears less useful in other IBD, especially Crohn's disease (CD). The number of studies published with Crohn's disease patient is limited and results are conflicting.

Acute Infectious Diarrhea

Many studies have been performed on the effect of probiotics in acute diarrhea. Gastrointestinal infections are characterized by acute diarrhea. Administration of probiotics in combination or not with an antibiotherapy has shown to decrease the duration and the frequency of diarrhea.

Probiotics may be an effective adjunct to the management, *Lactobacillus GG Saccharomyces boulardii* in appropriate doses is mostly used.

Clostridium difficile Diarrhea

The efficacy of probiotics in *Clostridium difficile* diarrhea has been reviewed. *S. boulardii* and *L. plantarum* 299v were able to prevent disease recurrence in individuals who have more than one *Clostridium difficile* sequential infection, but did not have a beneficial effect on the first *Clostridium difficile* infection.

Antibiotic-Associated Diarrhea

Antibiotic-associated diarrhea is caused by a disturbance of the intestinal microbiota, direct tissue damage, or modulation of the immune system. Probiotics administered as yoghurt prevented antibiotic-induced changes in *Bacteroides fragilis* microflora cultured from human feces. In addition, *L. plantarum* 299v diminished antibiotic-induced overgrowth of *Candida albicans.*

Radiation-Induced Diarrhea

VSL#3 is a high-potency probiotic preparation that contains eight different probiotics. Significant reduction of radiation-induced diarrhea was seen in a clinical trial in patients undergoing pelvic radiation. Furthermore, patients treated with placebo had more severe radiation injury and higher mean daily number of bowel motions.

Irritable Bowel Syndrome (IBS)

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder, characterized by symptoms such as abdominal pain, bloating, diarrhea, or constipation. Growing evidence suggests a potential role of intestinal microbiota in IBS pathophysiology and symptom generation in IBS patients. Initial evidence indicated the presence of increased amounts of bacteria in the upper small

intestine of IBS patients, a condition known as small intestinal bacterial overgrowth. Studies in IBS patients have attempted to target changes in intestinal microflora with different therapeutic approaches, such as the use of probiotics. Overall, results obtained in probiotics clinical trials suggest some beneficial effects over placebo in the relief of IBS symptoms. However, the number of dropouts in these studies was high and the role of concurrent medication and diet were not always taken into consideration.

Acute Pancreatitis

Infection of pancreatic necrosis is the major cause of death in acute pancreatitis. Microbial antibiotic resistance has become a worldwide problem due to excessive use. Several trials with enteral probiotics have shown a significant reduction of infectious complications in acute pancreatitis. It has been suggested that multi-species probiotics are more effective, because effects are strain specific.

Chronic Liver Diseases

Chronic liver diseases such as alcoholic hepatitis and cirrhosis are at risk of developing ascites and spontaneous bacterial peritonitis. Malondialdehyde and 4-hydroxynonenal (markers of lipid peroxidation) improved significantly in alcoholic liver cirrhosis patients while TNF-α, IL-6, and IL-10 improved significantly in chronic hepatitis C patients.

Helicobacter pylori Infection

Several clinical trials have suggested a role of probiotics in the treatment and prevention of *Helicobacter pylori* infection through both a probiotic-induced inhibition of *H. pylori* growth and adhesion to epithelial cells and an effect on the host immune system. Once again, probiotic species specificity is necessary for the therapeutic effect.

Postoperative Complications After Intestinal Surgery

Liver transplant recipients receiving fiber-containing enteral formula plus living *L. plantarum* 299v developed fewer bacterial infections than those receiving standard enteral formula. A larger prospective randomized trial showed that the incidence of bacterial infections after liver, gastric, or pancreatic resections was lower in the probiotic group.

Necrotizing Enterocolitis (NEC)

Probiotics could inhibit or reduce inflammatory signaling in the intestinal cells by inhibition of NF-Kb cascade or pathway, by inducing interleukin 10.

Probiotics might reduce the risk of necrotizing enterocolitis (NEC); however, the short-term and long-term safety of probiotics needs to be assessed and studied further in large trials.

Other Conditions

The potential role of probiotics in the prevention and treatment of lowering cholesterol levels, constipation, and cancer should be evaluated.

The Reasonable Move Toward the Use of Probiotics

Probiotics such as *Lactobacillus* species have been theorized to improve the balance of gastrointestinal tract flora and immune function within the gut. Through biopsies of the gastrointestinal tract, researchers have shown that probiotic bacteria can colonize and grow within the gut following oral administration. Moreover, in children with diarrhea due to rotavirus, *Lactobacillus* administration has been demonstrated to improve IgA humoral immunity compared with controls.

In addition, several clinical trials have provided evidence of probiotic effectiveness for the treatment and prevention of acute diarrhea and antibiotics-induced diarrhea as well as for the prevention of cow's milk-induced food allergy in infants and young children. Probiotics are also effective for the prevention of traveler's diarrhea.

Live probiotic bacteria and dietary prebiotics oligosaccharides are being used in infancy increasingly and they seem to be safe and increase resistance to respiratory infection during the first 2 years of life. They are beneficial to the gastrointestinal health of infants, and infants fed formulas containing probiotics or synbiotics proved to be safe and tolerable.

Conclusion

Probiotic bacteria are used to treat or prevent a broad range of human diseases. The intestinal microbiota is a very complex ecosystem, which has several important functions for the host. The efficacy of probiotics is

currently well documented with regard to the improvement of gastrointestinal functions.

Probiotics are normal living bacteria that give benefit if given in adequate and specified amount on the intestinal mucosal membranes. It plays an important role in the defense against potential pathogens, inflammation, and infection.

It stimulates the infant's immune system to respond with specific immunological tolerance, avoiding the development of allergic, inflammatory, and autoimmune diseases.

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193 Protein-Losing Enteropathy

Hisham M. Nazer

Protein-losing enteropathies (PLEs) comprise a group of disorders associated with the loss of abnormal amount of protein into the gastrointestinal tract due to impaired integrity of the mucosa either due to systemic disorders or primary gastrointestinal disorders.

Protein-losing gastroenteropathy (PLGE) includes a large group of diseases characterized by enteric loss of plasma protein in abnormal amounts.

In most instances, PLGE is caused by enhanced mucosal permeability to proteins consequent to cell damage, mucosal erosions or ulcerations, and lymphatic obstruction.

The condition may be short-lived, as in the case of postgastroenteritis, or chronic, as in intestinal lymphangiectasia (IL) and celiac disease. The clinical presentation is highly variable depending on the underlying cause. The diagnosis should be suspected by the presence of hypoalbuminemia presenting usually with edema but without albuminuria. Other causes of hypoproteinemia should be considered. This may be due to either protein loss from intestinal lymphatics or due to loss of protein through an abnormally inflamed mucosal surface.

PLE is commonly diagnosed with radiotracer scintigraphy. MRI is recognized as a useful tool in diagnosis of primary PLE.

Management of PLE should also include dealing with the underlying cause (e.g., celiac disease or inflammatory bowel disease). Some of the recognized clinical conditions associated with PLE are listed in *Table 193.1*. These disorders are usually associated with either blockage of lymphatics or with abnormal mucosal permeability to protein.

Treatment is usually based on providing patient with high protein, low fat with medium chain triglycerides diet, fat-soluble vitamins, as well trying to treat the underlying cause. It is important to emphasize that PLE may complicate some cardiac disorders that result in protein loss through the gastrointestinal tract.

Prognosis: depends upon the severity and treatment options of the underlying disease.

Intestinal Lymphangiectasia

Intestinal lymphangiectasia (IL) is a rare disorder of the lymphatic system, inherited in an autosomal recessive manner characterized by the presence of PLE and dilatation of the small intestinal lymphatics. IL is the main cause of PLE in children. The disorder was originally described by Waldmann et al. (1961). IL may be primary or secondary to some other disorders as in constrictive pericarditis. IL is a potentially fatal disorder if not recognized early and treated properly.

Intestinal lymphangiectasia is characterized by obstruction of lymph drainage from the small intestine and dilated lacteal vessels that distort the villous architecture. It has been described prenatally and in preterm as well as full-term infants' siblings. IL is characterized by lymphopenia, peripheral edema and hypoalbuminemia, thickening of the small bowel wall, PLE, ascites, and pleural effusion.

Once suspected, the diagnosis is usually confirmed by increased fecal concentration of alpha-1-antitrypsin. The underlying cause may be further identified through stool cultures, cardiac screening, serology, or further radiological imaging.

Waldmann Disease is a rare digestive disorder characterized by abnormal dilatation of lymph vessels supplying the Lamina Propria of the small intestine. The main symptoms are abdominal discomfort and swelling of the limbs. The disorder may be congenital, present at birth, or acquired later on in life with abdominal discomfort and swelling of the limbs.

Pathogenesis

Primary IL (PIL) is a rare disorder characterized by dilated intestinal lacteals resulting in lymph leakage into the small bowel lumen and responsible for protein losing enteropathy leading to lymphopenia, hypoalbuminemia, and hypogammaglobulinemia. PIL is caused by a generalized disturbance of the lymphatic system that is probably congenital. The abnormal lymph vessels are located primarily at the level of the small intestine. IL may be generalized or localized depending on the site of blockage of mesenteric lymphatic drainage.

Lymphatic vessel obstruction and elevated intestinal lymphatic pressure results in lymphatic leakage into the intestinal lumen, thus resulting in malabsorption and

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Table 193.1
Clinical conditions associated with protein-losing enteropathy

Constrictive pericarditis	Congenital heart disease
Nephrosis	Tuberculous adenitis
Tumors	Inflammatory bowel disease
Polyposis	Celiac disease
Gastroenteritis	Hirschsprung disease
Mènètrier disease	Allergic gastroenteropathies
Kwashiorkor	Cystic fibrosis
Autoimmune enteropathy	Parasitic infection
Immunodeficiency states	Tropical sprue

PLE. The exact mechanism of protein loss in the gut is not fully understood. Edema develops due to increased protein loss in the intestine. Lymphopenia is a recognized sequel due to the sequestration of lymphocytes in the intestine.

The main symptoms are predominantly bilateral lower limb edema; edema may be moderate to severe with anasarca and include pleural effusion, pericarditis, or chylous ascites, fatigue, abdominal pain, weight loss, inability to gain weight, moderate diarrhea, and fat-soluble vitamin deficiencies due to malabsorption may be present.

IL is a well-recognized complication of the Fontan procedure occurring in up to 24% of patients. Standard medical and cardiac surgical interventions are generally ineffective and the condition is potentially fatal.

Clinical Features

Intestinal lymphangiectasia is characterized by generalized disorders of the lymphatic channels with dilatation of the lymphatic vessels of the intestinal mucosa. There is also obstruction to the lymphatic drainage, which results in dilated intestinal lacteals.

Intestinal lymphangiectasia in the pediatric age group has a wide spectrum of clinical and laboratory manifestations determined by the anatomic location and extent of lymphatic anomaly. Some patients are mildly affected, while others may remain asymptomatic. There is no sex predominance in this disorder.

Symptoms include diarrhea, nausea, vomiting, fatty stools and abdominal pain, edema, low protein levels and low albumin levels. Peripheral edema is the most common complaint. The edema may be asymmetric.

The clinical presentations and radiologic findings of IL may mimic other gastrointestinal disorders, thus contributing to its delayed diagnosis. Nazer et al. (1991) reported three patients with IL who were previously considered to have celiac disease.

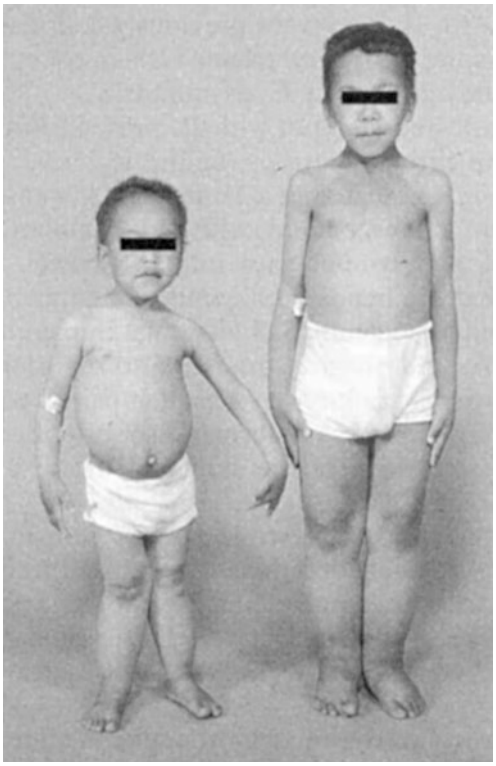


Figure 193.1
Two siblings with protein-losing enteropathy due to primary intestinal lymphangiectasia. Note the marked generalized edema in both siblings

Most affected children with IL present during their infancy with chronic diarrhea, failure to thrive, generalized edema (*Fig. 193.1*), steatorrhea, tetany, and increased susceptibility to infections. Patients with IL lose albumin, immunoglobulins, and lymphocytes into the bowel.

Laboratory findings include hypoalbuminemia, lymphopenia, hypocalcemia, and hypogammaglobulinemia. Impaired neutrophil chemotaxis and phagocytosis were also reported in IL. Affected patients are known to have impaired cell-mediated immunity. Affected patients may also suffer from recurrent bacterial infections of the skin, respiratory and urinary tracts.

Intestinal lymphangiectasia may present in association with other clinical conditions. Recognized associations include those with lymphedema, Zellweger syndrome, congenital hepatic fibrosis, and intussusception where IL acted as a lead point for intussusception.

Diagnosis

Intestinal lymphangiectasia is characterized by dilated lymphatic channels in the mucosa, submucosa, and serosa as well as the mesentery or the intestine. Most cases are diagnosed during childhood. Diagnosis of IL requires a high index of suspicion in a child with chronic diarrhea, failure to thrive, hypoalbuminemia, edema, and no albuminuria. Serum calcium is frequently reduced and stool fat content is usually elevated. Lymphopenia is usually present. Serum levels of IgG, IgA, and IgM are usually reduced.

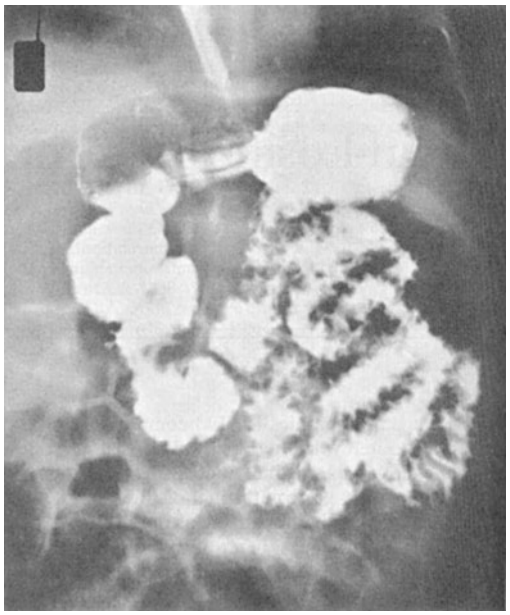
Small bowel follow through is often the initial examination performed. Typical findings include small bowel dilatation, diffusely thickened, coarse, mucosal folds, as well as haziness of the barium due to increased secretions (◉ *Fig. 193.2*).

CT and MRI can play an important role in suggesting the diagnosis and discriminating many secondary forms of IL. MRI can also provide information on the characteristics of fluid content in the small bowel because of the high concentration of protein and/or lipid. The absence of ionizing radiation makes MRI more suitable than CT in the follow up of patients with IL.

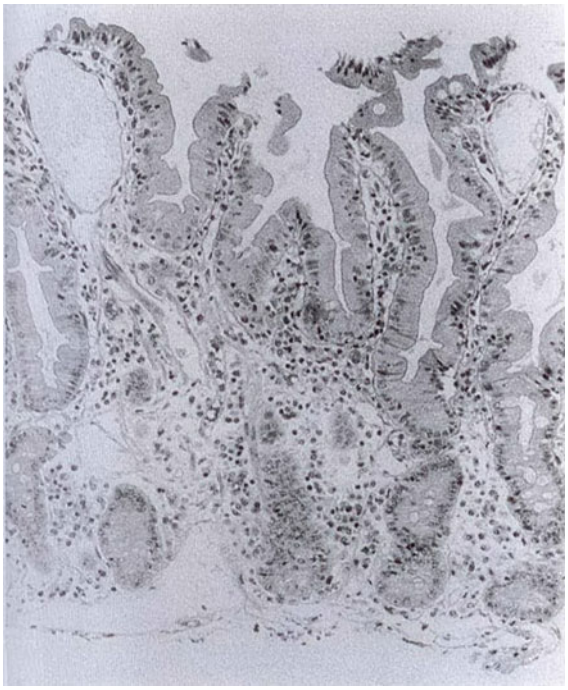
The diagnosis of PIL is that of exclusion, taking into account the wide variety of pathologic conditions that may be associated with intestinal lymphangiectasia, including Crohn disease, Whipple disease, Celiac disease, sarcoidosis, amyloidosis, tuberculosis, lymphoma, Budd–Chiari syndrome, systemic lupus erythematosus, chronic congestive heart failure, and constrictive pericarditis. The diagnosis may be supported by the demonstration of abnormal radioisotope protein loss through the gut.

Small bowel biopsy is still necessary to make the definitive diagnosis. Pathological findings vary from a normal appearance to severe changes. Findings at pathology include a dilatation of the lymphatics in the mucosa and submucosa of the small bowel with resultant bowel wall thickening due to edema and congestion (◉ *Fig. 193.3*). The disease may be patchy, which may result in the biopsy showing normal histologic findings and may have to be repeated if histologic diagnosis is to be established.

In view of the potential failure or blind small bowel biopsies in confirming the diagnosis of IL in some cases, endoscopically directed duodenal biopsies are preferred diagnostic measures. The intestinal changes are more likely to be demonstrated if the child was offered fatty



◘ Figure 193.2
Barium meal and follow-through in a child with intestinal lymphangiectasia. Note the thick irregular mucosal folds in the jejunum



◘ Figure 193.3
Small-intestinal biopsy specimen in a patient with intestinal lymphangiectasia. Note the dilated lymphatic lacteals in the affected villi

meals prior to endoscopy. The biopsies should be taken from the endoscopically abnormal mucosa at the sites of the dilated lacteals. The endoscopic appearance in IL is characterized by plaque-like white lesions overlying the mucosal folds. Biopsies should be obtained from those sites. Villous atrophy and cellular infiltration are absent.

The presence of alpha-1-antitrypsin in the stool is an important diagnostic clue because it is not normally absorbed or secreted into the bowel.

Lymphangiogram may be required to establish the diagnosis. The dye that is injected into the lymphatics of the leg is shown within the small intestinal lumen.

Some authors reserve the investigations of labeled protein excretion, being nonspecific, and the intestinal biopsy, which may miss the lesion, to those patients who do not show the well-recognized clinical findings of IL.

Treatment

Early diagnosis and treatment of IL is of great importance for diet therapy to be effective.

There is no definite cure for lymphangiectasia. Treatment is focused on control of complications, through dietary habits and possible drug therapy for various symptoms. In case of secondary lymphangiectasia, treatment also focuses on the underlying cause.

The treatment is essentially based on limiting the amount of long-chain fat in the diet. This will result in the reduction of the pressure within the dilated lacteals as long-chain fat is absorbed through the intestinal lymphatics. A low-fat diet is recommended for patients with IL. The diet is supplemented by medium-chain triglycerides, which are absorbed through the portal system and not through the lymphatics. In affected young babies, medium-chain triglycerides-based milk is administered. This dietary regimen usually results in clinical remission and cessation of symptoms. In most patients with primary IL, the underlying lymphatic defect and thus the need for dietary treatment appears to be permanent. Water-soluble vitamins and calcium supplements are needed.

Corticosteroid administration should be avoided. Some children who do not adhere to their diet or suffer from severe disease may at times require albumin transfusions. The parents should be advised that this dietary management may well be a lifelong measure that they should adhere to.

Octreotide, in combination with a low-fat diet, has been suggested as a medical treatment option in refractory cases of primary IL. Studies have shown that octrotides, 15–20 μg per body weight two times daily subcutaneously, may help to maintain serum albumin levels, improve clinical findings, and decrease the requirement of albumen infusion in refractory cases of primary IL.

Surgical resection of localized affected loops is rarely resorted to due to the difficulties in localizing the only affected segment and the uncertainty of its outcome. Surgical bowel resection is useful in the rare cases in which IL is segmental or localized.

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194 Celiac Disease

Hisham M. Nazer · Mohamed Rawashdeh

Celiac disease (CD) is an immune-mediated enteropathy affecting the proximal small intestinal mucosa resulting in a permanent intolerance to dietary gluten in susceptible children. CD is characterized by an abnormal small intestinal mucosa leading to malabsorption and associated hematologic and clinical abnormalities.CD is one of the most frequent genetically based diseases of mankind.

Historical Background

The word *celiac* was first used in the second century BC by Cato. Aretaeus, the Cappadocian in the first century AD used the phrase the *celiac diathesis* to describe a condition characterized by the passage of undigested food accompanied by severe emaciation. In 1888 Gee, at St. Bartholomew's Hospital, London, published a paper on *the celiac affection*, describing it as "chronic indigestion," which is commonest in patients between 1 and 5 years of age. This was subsequently followed by the recognition that celiac disease is a lifetime disorder and may affect adults.

Dr. W. K. Dicke in Leiden, Holland, in 1950 was the first to observe that celiac children had improved on a gluten-free diet, as was the case under the appalling conditions of World War II famine, but had relapsed after bread and biscuits were flown to them from Sweden. In 1957, Sakula and Shiner in London demonstrated an abnormal jejunal mucosa in celiac children obtained through laparotomy. In 1969, the European Society of Pediatric Gastroenterology and Nutrition (ESPGAN) established the diagnostic criteria for celiac disease. Such criteria have been subsequently revised and so were the criteria set by the North American Society for PGHCN. The main objectives of such criteria were to ensure a definitive diagnosis from the start supported by well-recognized changes on small intestinal biopsies in the hope that such approach could well minimize the numbers of endoscopies and biopsies the child was supposed to have according to the initial criteria. The objective of such criteria was to make sure the diagnosis is definite especially as it is well known at present that CD is a diagnosis for life.

Incidence and Genetic Factors

Celiac disease is considered as one of the most important, genetically based, disease of the small intestine in childhood. The clinical classification of CD can be divided into *classic CD* (with the typical presentation and supportive histological changes on small intestinal biopsy) and other forms as follows:

Silent CD: patients who are asymptomatic but with a flat mucosa that reverts to normal after introduction of a gluten-free diet.

Potential CD: patients with positive serology and HLA DQ2 /DQ8 but normal or mildly abnormal small bowel histology.

Latent CD: patients with a normal jejunal biopsy when on a normal diet and that at some other time the biopsy has been flat and recovered on a gluten-free diet.

Atypical CD: patients with unusual gastrointestinal or extra-intestinal manifestations but with definite small bowel histology.

Celiac disease has a worldwide distribution, with a high prevalence in northwestern Europe. CD remains underdiagnosed with not more than 20% of patients identified. The incidence varies in different countries and at different times in the same country. For example, the incidence reported in Ireland between 1960 and 1974 was 1 in 300, but this has decreased to 1 in 1,376 in 1981. In Sweden, the incidence was 1 in 6,500 in 1968; this has increased to 1 in 285 in 1992. Accurate figures are not available for the USA or Canada, but a recent study based on the presence of serum endomysial antibodies suggests an incidence of 1 in 7,750 in the New York area.

The occurrence of celiac disease in Arab children has been the subject of only a few reports. In a survey of 34 celiac children between 1991 and 1994 in northern Jordan, the incidence was found to be 1 in 2,800 live births. This incidence is comparable to that of Europe and higher than that of the USA. The disease is certainly very uncommon in blacks living in North America, South Africa, or Britain.

Family studies have established that susceptibility to celiac disease is genetically determined. CD has a strong hereditary component; the reported prevalence of CD in

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first-degree relatives is approximately 10%. Fourteen percent of all jejunal biopsies of first-degree relatives of celiacs have been found to be flat, while monozygotic twins display a 70–100% concordance for the disease. This genetic influence has been mapped at least in part to the short arm of chromosome 6, and in particular to the region encoding the class II human leukocyte antigen. Initially, the disease was found to be associated with HLA class I alleles HLA-A1 and B8. More recently, closer associations have been described with HLA class II alleles DR3 and DQ2. These associations are insufficient, however, to be useful in the screening for celiac disease, in which multiple genes are probably involved. Genes encoding HLA DQ2 or DQ8 are found in the vast majority of patients with CD and testing for their presence can be useful for the diagnosis of CD.

Pathogenesis and Pathophysiology

Celiac disease is induced by the introduction of gluten to the diet of susceptible patients. Gluten is the protein found in wheat, barley, oats, and rye. Gluten from wheat and rye is toxic to all celiacs, while the toxicity of gluten from barley and oats is less established. Gluten is a large complex molecule that has four heterogenous classes of protein: gliadins, glutenins, albumins, and globulins. Gliadin has been recognized to be the toxic molecule. It has also been classified into four parts of protein called α, β, γ, and ω. α-Gliadin is the most toxic part to patients with celiac disease.

The mechanism by which mucosal damage occurs is not known. It was proposed that a protease or peptidase deficiency in the mucosa of the small intestine results in accumulation of gluten or its partially digested products that are toxic to the small intestinal mucosa. There is, however, increasing evidence favoring all immunologic abnormality as the cause for celiac disease. This is evident from an increase in local and systemic production of immunoglobulin (Ig) A and IgG antigliadin antibodies accompanied by autoantibodies (antireticulin and antiendomysial) against structural proteins of the small intestinal mucosa, leading to autodestruction. These antibodies are used in screening for celiac disease. Many diseases have been recognized to occur concomitantly with celiac disease. Many of these have an autoimmune basis, such as type I diabetes mellitus, IgA nephropathy, hyperparathyroidism, chronic active hepatitis, and juvenile rheumatoid arthritis. A higher incidence of celiac disease has been shown to occur in children with IgA deficiency.

Changes in the immune status occur in celiac disease, involving both cellular and humoral antibodies. Increased intraepithelial lymphocyte counts is a recognized finding in the intestinal mucosa of children with celiac disease. Recent studies have indicated that a defect in gluten-specific suppressor T cells precipitates celiac disease in genetically predisposed individuals. *In vitro* studies have indicated that crypt hyperplasia and villous atrophy may be the result of activation of lamina propria T cells.

Intestinal biopsy is essential for the diagnosis of celiac disease. Since 1960 biopsies were obtained using a Crosby capsule from the mucosa at the angle of Treitz. At present, intestinal biopsies are more often obtained through a fiberoptic endoscope from the first, second, and third part of the duodenum. The proximal small intestinal mucosa is abnormal, whereas the distal mucosa is usually normal, indicating that a noxious agent in the diet becomes completely hydrolyzed before it reaches the ileum.

Examination of small intestinal biopsies under the dissecting microscope allows rapid diagnosis of a flat or convoluted mucosa described in celiac disease compared to the fingers and leaves appearance in normal subjects (*Figs. 194.1a* and *194.2a*).

On conventional histologic examination, the characteristic though nonspecific changes include (a) partial to total villous atrophy, (b) absence of identifiable brush border, (c) crypts hyperplasia, (d) increased mitotic index in the crypts, (e) increased intraepithelial lymphocytes, and (f) increased plasma cells in the lamina propria (*Fig. 194.2b*). However, flat small intestinal mucosa with atrophied villi is not pathognomonic of celiac disease and may be seen in other conditions. Causes of flattening of small intestinal mucosa in childhood are listed below.

- Celiac disease
- Transient gluten intolerance
- Cow's milk protein intolerance
- Soy protein intolerance
- Gastroenteritis and postenteritis syndrome
- Giardiasis
- Protein energy malnutrition
- Intractable diarrhea of infancy
- Immunodeficiency
- Bacterial overgrowth

Clinical Features

Celiac disease was recognized as a disease with quite uniform clinical presentation with chronic diarrhea, abdominal distention, and weight loss or poor weight gain. Nowadays, CD is considered a disease with a wide clinical

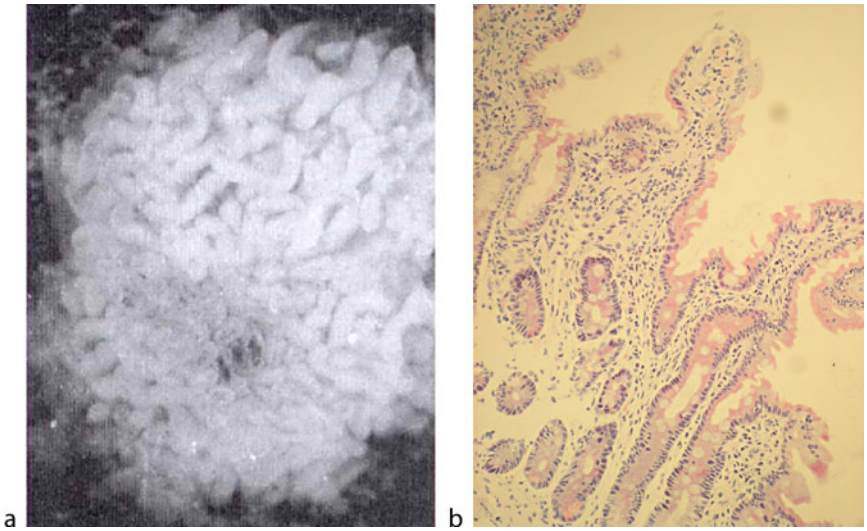

Figure 194.1
(a) Dissecting microscope appearance: normal small intestinal mucosa with leaf-like and tongue-like villi. (b) Histology: small intestinal mucosal biopsy with normal-looking villi

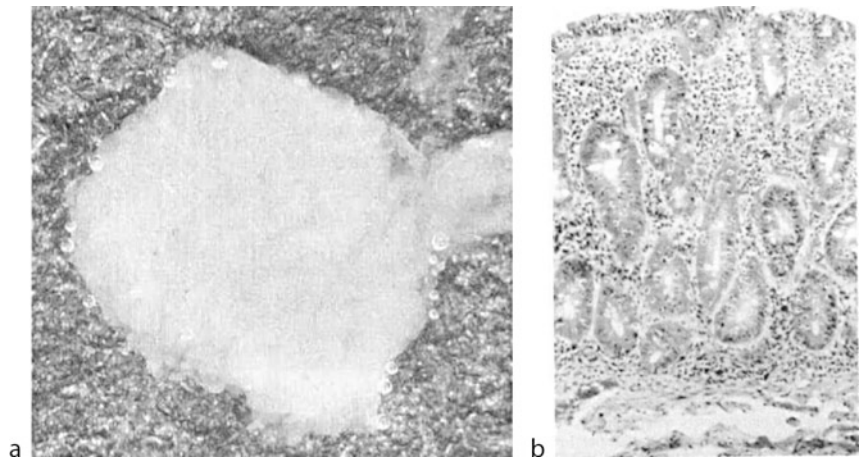

Figure 194.2
(a) Dissecting microscope appearance of abnormal flat jejunal mucosal biopsy. (b) Histologic appearance of small intestinal mucosa (Taken from a child with celiac disease showing subtotal villous atrophy and crypt hyperplasia)

spectrum of intestinal as well as extra-intestinal presentation. Symptoms tend to occur weeks or months after the introduction of gluten-containing diet.

The age of onset of celiac disease is variable. Most cases are diagnosed in the second year of life. There is usually latent interval of variable duration between the introduction of gluten into the diet and the development of symptoms. This may take weeks, months, or even years. In the last few years, a new terminology was introduced within the more comprehensive definition of celiac disease because the numbers detected by screening are five or six times greater than those who received a clinical diagnosis The classic syndrome of chronic diarrhea, anorexia, failure to thrive, muscle wasting, and abdominal distention are most often encountered in young children (*Fig. 194.3*). In a retrospective study of 19 Saudi-Arab celiac children, the mean age of

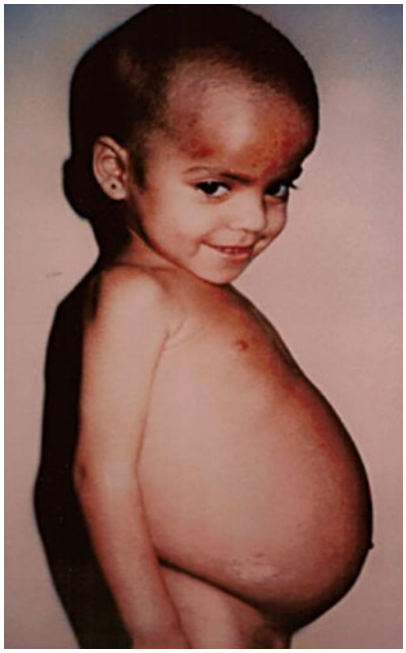

Figure 194.3
A child with active celiac disease: Note the marked abdominal distention

onset was 24 months. CD is no longer a disease of childhood and it could affect adults (Adult CD).

In a study of 34 Jordanian children with celiac disease, the mean age at presentation was 55 months. This rather late presentation may be related to the high prevalence of prolonged breast-feeding in Jordan, where 61% of mothers would still breast-feed at 15 months. Episodes of diarrhea may alternate with constipation, which occurs mainly in children who have anorexia and are generally hypotonic. The colon may be dilated, giving a clinical pattern that may be confused with Hirschsprung disease. Isolated short stature was the second most common presenting symptom.

Gastrointestinal complaints are often revealed only on direct questioning. In these children, there is often little to find on physical examination apart from shortness of stature. Celiac disease is estimated to cause 8–20% of cases of short stature in children.

At diagnosis, anemia, failure to thrive, short stature, and abdominal distention are commonly seen. Height and weight are usually below the 10th percentile, but can also be below 3% for age. However, with increasing new clinical patterns of CD experienced recently, some patients with confirmed CD may have normal weight for age and occasionally may be overweight. Such new trends pose more challenge to consider the diagnosis of CD in a wider spectrum of clinical feature much more than the classically recognized picture known for years. Other recognized rare associations of CD include some neurological disorders such as epilepsy with intracranial calcification seen on computed tomographic scan.

Bleeding disorders related to vitamin K deficiency have also been described. Skin manifestations such as dermatitis herpetiformis have been associated with celiac disease and subsided once a gluten-free diet is introduced. Recent report from Egypt has indicated the high prevelance of CD among Egyptian children with autoimmune hepatitis for which reason a recommendation was made to screen patients with autoimmune hepatitis for CD irrespective of presence or absence of gastrointestinal manifestations. CD is therefore looked at nowadays as a disorder associated with multisystem involvement.

Investigations

Iron deficiency anemia is more common, though less pathognomonic than megaloblastic anemia caused by folate deficiency. Low serum albumin and globulins may result from poor intake, malabsorption, and protein-losing enteropathy. Significant steatorrhea (>10% of fat intake) is found in the majority or cases.

Different screening tests were designed to avoid the conventional repeated jejunal biopsies. The sensitivity of IgG antigliadin antibodies reaches 100%; on the other hand; they are detected in 22% of patients with other gastrointestinal disorders. The IgA antigliadin antibodies are less sensitive (90%), but more specific (97%). Antiendomysium antibodies are most useful antibodies to look for in the screening for celiac disease, with a sensitivity and specificity approaching 100% in untreated celiac disease. Duodenal juice should be obtained and examined immediately for the presence of *Giardia* and sent also for culture if bacterial overgrowth is suspected.

IgA testing is recommended in children with suspected CD; if IgA deficiency is found, a duodenal biopsy or CD serology should be performed.

Diagnosis

The diagnosis of celiac disease is based on the presence of an abnormal small intestinal mucosa using the technique of small intestinal biopsy. Long-term treatment with a gluten-free diet should never be instituted without this evidence, especially in the developing world, where wheat

bread is the staple food. Celiac disease may exist latent in patients having normal mucosa when eating a gluten-containing normal diet.

When celiac disease is suspected, initial testing for serum immunoglobulin A (IgA), tissue transglutaminase (tTG) antibodies is useful because it offers adequate sensitivity and specificity for the diagnosis. A positive IgA tTG should prompt small bowel biopsy to confirm the diagnosis. Failure to diagnose CD can lead to significant long-term sequel.

Inspite of the well-recognized progress in serologic and genetic testing for CD, the definite diagnosis of CD upon which the decision to start gluten-free diet can only be made at the present by small intestinal biopsy and classical histology.

To establish the diagnosis, three jejunal biopsies and a gluten challenge were needed. These diagnostic criteria have been recently revised. Repeated biopsies and gluten challenge are indicated only when there is a doubt about the original diagnosis from the jejunal biopsy and if the child was less than 2 years of age at the time of diagnosis, where cow's milk protein intolerance and transient gluten intolerance may resemble celiac disease. Confirmation of the diagnosis is not needed if the initial diagnosis is based first on the appearance of flat mucosa while the patient is eating adequate amount of gluten.

The detection of circulating antibodies (lgA antigliadin, antireticulin, and antiendomysium) at diagnosis and their disappearance on a gluten-free diet supports the diagnosis. It is highly recommended that at least four biopsy samples should be obtained from the duodenum including the bulb because mucosal changes in celiac disease may be patchy.

The diagnosis is occasionally made difficult when a patient is suspected to have CD, has a negative anti-endomysial antibodies with a borderline histology.

Gluten challenge is usually performed 2–4 years after exclusion and preferably just before school entry. The gluten challenge is performed by adding to the diet 5–10 g/day of powdered gluten, or by allowing the child to gradually resume a normal diet. If significant symptoms occur, then a further biopsy is performed after a week following the return of symptoms. If the mucosa is abnormal, then the diagnosis has been established. If symptoms do not develop, a biopsy is done after 2 years of exposure to gluten. Such a practice is not universally agreed on as the recent trend is to make sure the diagnosis is confirmed at initial presentation without having to subject the child to a period of relapse in the course of trying to confirm the diagnosis. It is only in the situations stated above that the treating physician may be obliged to repeat the biopsies.

The diagnosis of CD is considered definitive when there is complete symptom resolution after treatment with a strict GFD in a previously symptomatic individual with characteristic histological changes on small intestinal biopsy. Genetic testing (HLA-DQ2 & HLA-DQ8) proved to be useful in the diagnosis of CD especially when the small intestinal biopsies and/or serology were inconclusive.

Treatment

A gluten-free diet produces dramatic and rapid clinical response in affected children with celiac disease. All foods containing wheat or rye should be excluded from the diet. Oats and barley are better avoided. Corn, rice, and potato flour are safe. Patients and parents should receive full instructions from the hospital dietitian or doctor and labels of commercially prepared food should be carefully checked. It may be advisable to exclude lactose for 1–2 weeks due to secondary lactase deficiency and to supplement the child with calcium, folate, and vitamins for 2 months Treatment with a gluten-free diet is expected to result in full clinical and mucosal recovery, and subsequent gluten challenge provokes a clinical and mucosal relapse.

There is at present some controversy on whether oat should be considered as part of a gluten free diet. There is no universal agreement on this issue at present as there are some patients who seem to tolerate oat and others who do not. As there are reports of intestinal damage following oat consumption, it may better to keep the child off oat at least for the initial stage of treatment until fully stabilized and then gradual challenge, with close observation and proper assessment, may be attempted.

A lifelong gluten-free diet is mandatory to prevent relapses of the disease, to attain growth potentials, and to prevent the development of malignant diseases like lymphomas as a complication of celiac disease. Treatment requires regular assessment by a medical specialist and an expert dietician, along with education and access to a support group in order to maximize the clinical outcome.

Celiac crisis with severe diarrhea and weight loss is often accompanied by acidosis, hypokalemia, and prolonged prothrombin time. Treatment includes intravenous replacement therapy, a gluten-free diet, and corticosteroids. Within 1 week of gluten restriction, behavioral disorders and appetite improve dramatically. This is followed by stools returning to normal and abdominal distention subsiding. Normal villous architecture is restored within a few months to 1 year. IgA antigliadin antibodies levels fall to

normal within 2–3 months. A small percentage of patients with CD may not improve on GFD as expected. Such patients often have severely damaged intestine that cannot heal even after they eliminate gluten from their diet. Therefore, those patients need to receive intravenous nutrition supplement and lactose-free milk formula.

Future Directions

Screening of high-risk groups and patients with the common symptoms of short stature, irritable bowel syndrome, iron-deficiency anemia, and unexplained arthritis.

One-time screening may be insufficient to detect all those who will develop CD.HLA-related genetic risk has been evaluated and revealed that future siblings of children with celiac disease are at increased risk to develop celiac disease.

The gold standard for diagnosis remains histological confirmation of small intestinal biopsies although serology remains useful for screening purposes. There is an increasing recognition that antigliadin antibody testing is no longer considered as part of the diagnostic strategy.

More efforts should be made to improve the accuracy of CD diagnosis and thus limit the number of patients with unresolved diagnostic dilemma. Researches into the use of genetic and serological markers for the diagnosis of CD should be encouraged to help ease the diagnostic difficulties that do arise in certain cases and to help the family in accepting this lifelong diagnosis with an easy long-term management.

Much research remains to be done to further refine our understanding of CD and to devise more effective strategies for treatment, compliance, and prevention of long-term complications.

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195 Inflammatory Bowel Disease

Fayez K. Ghishan

Definition

Inflammatory bowel disease (IBD) refers to chronic inflammatory disorders of the gastrointestinal tract. The main diseases involved in these pathologic processes are Crohn's disease (CD) and ulcerative colitis (UC). The two diseases are different but appear to share some common clinical and pathogenetic features. The inflammation in CD extends throughout the thickness of the bowel wall from the mucosa to the serosa, whereas in ulcerative colitis the inflammation is confined to the mucosa and submucosa. Although the majority of CD cases involve the ileocolic segment of the gastrointestinal tract, it can affect any region of the gut. In contrast, ulcerative colitis is confined to the colon and always involves the rectum. The clinical, endoscopic, radiologic, and histologic features may distinguish between the two diseases in 85% of patients, another 15% will suffer from indeterminate colitis (IC). The diseases also appear to share some common immunopathogenetic factors. Epidemiological studies suggest that 70–80% of families with members affected by CD, have greater risk of developing CD than UC. The remaining 20% of multiply affected families are mixed (i.e., one member will have CD, whereas others will have UC).

Etiology/Pathogenesis

Recent advances in IBD research suggest a major role for genetic/environmental factors involving the innate and adaptive immunity resulting in dysregulated immune response to commensal bacteria in the intestinal tract.

Genetic Factors

The hypothesis of genetic susceptibility is supported by the higher frequency of IBD in first-degree relatives compared to the general population. Similarly, identical twins have a greater tendency to develop IBD than do fraternal twins. Moreover, Jewish populations seem to be at more risk. An association between different HLA types and susceptibility to IBD has also been proposed. Genome-wide association studies in families with CD compared to controls have shown that more than 40 genes are involved in patients with CD. Alterations in genes of the innate immune system, such as NOD2 (which encodes nucleotide-binding oligomerization domain protein 2; also known as CARD15), ATGI6L1 (which encodes autophagy related 16-like protein 1), and IRGM (which encodes immunity-related GTPase family M) are specific for patients with CD, whereas genes in the IL-23 pathway including IL23R (which encodes a critical subunit for IL-23 receptor), IL12B (which encodes the P40 subunit of IL-R and IL-23), and STAT3 (which encodes signal transducter and activator of transcription 3), have been shown in both CD and UC.

Immunological Factors

Accumulating evidence suggests that dysregulation of the normally controlled immunoresponse to commensal bacteria in a genetically susceptible host derives the development of IBD. Evidence for this concept comes from animal models of IBD, in which spontaneous chronic ileitis/colitis seems to be dependent in the presence of commensal luminal flora. In addition, enteric flora of IBD patients have been found to be more commonly associated with strains of *Escherichia coli* that adhere to the epithelium. Furthermore, empirically antibiotic therapy in patients with CD has beneficial effects.

Epithelial Barrier Function

The epithelial lining of the intestinal tract provide a barrier against luminal bacteria and environmental agents including food antigens. Earlier studies have shown abnormal intestinal permeability in first-degree relatives of CD patients. Expression analysis of biopsies from patients with IBD reveal downregulation of junctional complexes involved in the integrity of the epithelial lining such as E-cadherin and β-catenin. In addition to the columnar

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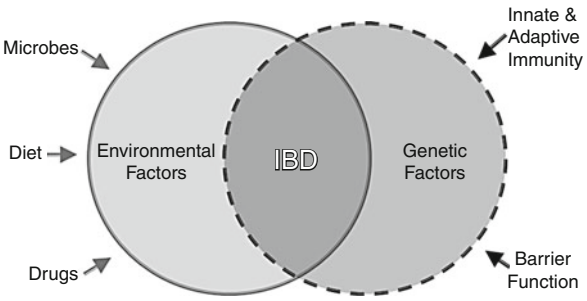

Figure 195.1
Pathogenesis of IBD

epithelial cells, paneth cells in the base of the crypts secrete α-defensins against microbes and their downregulation may contribute to the pathogenesis of IBD. Goblet cells which secrete trefoil peptides and mucus are also involved in the defense of the epithelial barrier, and indeed $Muc2^{-}/^{-}$ mice deficient in goblet cells develop spontaneous colitis. *Figure 195.1* depicts the pathogenesis of IBD.

Clinical Epidemiology of IBD

Incidence (frequency of new case over a certain time) and prevalence (total number of cases of a disease in the population at a given time) of IBD are beginning to stabilize in the Western world. However, they continue to rise in low incidence areas such as the Middle East and much of the developing world. In addition, racial and ethic differences seem to be narrowing. In the USA, 1.4 million people are affected by IBD and 2.2 million in Europe. In North America, the incidence rates for IBD range from 2.2 to 14.3 cases per 100,000 person-years for UC and from 3.1 to 14.6 cases per 100,000 person-years for CD. The peak incidence of IBD is between the ages of 15–25 years. Males and females are equally affected. *Table 195.1* depicts age distribution of IBD patients based on a composite of several studies.

Ulcerative Colitis

Ulcerative colitis (UC) is an idiopathic chronic inflammatory process confined to the colon with occasional cases of backwash ileitis. In almost all cases, the rectum is involved with varying degrees of proximal extension. Disease localized to only the rectosigmoid occurs in 15% of patients, disease extending to the left colon occurs in 22% of patients, while pancolitis occurs in 62% of pediatric patients. Involvement is usually continuous without the skip lesions characteristic of CD.

The clinical spectrum of the disease is wide and depends on the severity, extent, and the duration of the disease.

Table 195.1
Inflammatory bowel disease age of onset[a]

Age	Percentage of patients
0–5	1–3
6–10	5–10
11–15	30–35
16–20	50–60

[a]Composite of several studies

Clinical Manifestations

Intestinal Manifestations

Diarrhea with or without abdominal pain is the main complaint in most children. The stools may contain mucus and gross or occult blood. Nocturnal diarrhea should alert the physician to an organic disease. Abdominal pain in UC is less severe and frequent than in CD. The pain is usually colicky, is worse with food intake, and may precede bowel movements. Tenesmus can be severe and cumbersome. The sense of urgency and lower abdominal cramps are not relieved with defecation.

In acute exacerbations, anorexia can be severe. Lack of appetite can be related to a depressed mood or fear of abdominal pain brought about by food intake. Nausea and vomiting are uncommon. Their presence may indicate the development of toxic megacolon, intestinal perforation, or misdiagnosis of CD. Sixty percent of pediatric patients generally present with moderate to severe disease.

The most extreme presentation of the disease is the development of toxic megacolon. Toxic megacolon is a severe and life-threatening complication of the disease, occurring in 2–4% of children with UC. Patients develop severe bloody diarrhea, constant abdominal pain with distention, fever, pallor, and tachycardia. Abdominal x-rays show a distended colon with a diameter that exceeds 6 cm. Intestinal perforation and sepsis are the major complications.

Unlike CD, intestinal strictures and perianal lesions are uncommon in UC.

Extraintestinal Manifestations

Systemic manifestations are common in children and may wax and wane with disease activity.

Growth Failure and Delayed Puberty

Growth retardation is less severe and less frequent in UC (19%) than in CD (56%). It is related mainly to reduced food intake and increased loss of nutrients.

Musculoskeletal Lesions

Arthralgias are common in UC children, found in 24% of patients. On the other hand, arthritis is less common. Ten percent of children with ulcerative colitis have a migratory, asymmetric arthritis affecting the large joints of the lower extremities. Joint deformity is rare, and flare-ups usually indicate active colonic involvement. Ankylosing spondylitis, on the other hand, occurs in 6% of patients but the spinal disease progresses independent of colonic activity.

Ocular Lesions

There is a wide range of ocular manifestations in UC but these are not usually seen in children. Among the lesions described are uveitis, episcleritis, cataracts, and keratopathy.

Dermatologic Lesions

Erythema nodosum is seen in less than 5% of patients. Pyoderma gangrenosum rarely occurs in children. Oral aphthous ulcers occur in 2% of patients. The presence of any of these lesions is indicative of increased colonic activity, and the lesions resolve with treatment of colonic disease.

Liver Lesions

Fatty infiltration of the liver is the most common hepatic lesion and probably reflects chronic malnutrition. It is usually reversible. Pericholangitis, sclerosing cholangitis, and chronic hepatitis have been described in children, although less commonly than in adults. These diseases may predate the onset of ulcerative colitis and bear no relationship to colonic disease activity.

Hematological Findings

Iron deficiency anemia is common in children and is usually related to blood loss and nutritional deficiency. Patients on sulfasalazine may have macrocytic anemia due to folate malabsorption.

Renal Findings

Approximately 5% of patients with UC have renal calculi composed of calcium oxalate or uric acid. These are thought to be caused by chronic dehydration, decreased water absorption, and infections.

Fever

A history of fever is reported in up to 40% of patients at initial presentation.

Diagnostic Evaluation

Laboratory Tests

Stool examination usually reveals the presence of blood and leukocytes. With bloody diarrhea and fever, it is essential to obtain appropriate studies to rule out infectious agents such as *Salmonella*, *Shigella*, *Yersinia enterocolitica*, *Campylobacter jejuni*, *E. coli*, *Clostridia difficile*, and amoeba.

The erythrocyte sedimentation rate and c-reactive protein (CRP) are elevated during active disease. Hypoalbuminemia is more commonly seen in advanced UC and correlates with the severity of colonic mucosal lesions. Stool lactoferrin and calprotectin are elevated during active disease. Microcytic anemia and leucocytosis are common.

Serological Markers

The dysregulated immune response in IBD patients leads to the development of circulating antibodies in the serum of those patients. The antibodies are directed against multiple targets including autoantigens and bacterial antigens. The autoantigens include perinuclear anti-neutrophil cytosplasmic antibodies (PANCA) and antipancreas antibodies. The antibodies against microbial antigen include anti-sacchromyces cerevisial antibodies (ASCA),

Table 195.2
Serological markers in IBD

	Crohn's (%)	UC (%)	Healthy (%)
PANCA	10	50–60	0.5–1
ASCA	50–60	10	0.5–1
AntiOmpC	50–60	10	0.5–1
Antil2	50–60	10	0.5–1
AntiCBirl	50–60	10	0.5–1

anti-OmpC (outer membrane porin C antibodies), anti-CBirl (antibodies against pseudomonas fluorescens). *Table 195.2* shows the incidence of these antibodies in UC, CD, and healthy controls. In general, PANCA is positive in UC, whereas antimicrobial antibodies are positive in CD.

Endoscopic Studies

Endoscopic studies are the most reliable means for evaluating IBD. The findings on endoscopy are extremely variable. In the early stages, the mucosa is erythematous and edematous with loss of the normal vascular pattern. As the disease progresses, granularity and friability are noted with subsequent development of frank ulcerations surrounded by hyperemic, edematous, and friable mucosa. Pseudopolyps are sometimes noted. However, it is important to note that in the early stages, the mucosa may appear grossly normal. Therefore, obtaining mucosal biopsies is essential if clinical suspicion is strong.

Histologic Evaluation

The most commonly recognized histologic findings in UC are mucosal ulcerations, lymphocyte and plasma cell infiltrates in the lamina propria, crypt abscesses, and the absence of goblet cells. Although these findings are very suggestive of UC, they are not pathognomonic since similar findings can be seen in other pathologic conditions such as infectious colitis. Photomicrographs of mild, moderate, and severe ulcerative colitis are shown in *Figs. 195.2a–c*, respectively.

Radiological Evaluation

Radiological studies compliment endoscopy by evaluating the severity and extent of the disease. Plain films of the abdomen are valuable to evaluate the degree of bowel dilatation and to look for perforation in fulminant disease. Air contrast enemas are no longer utilized, rather CT scans with oral and IV contrast are preferred. Barium studies should be avoided in acutely ill children since they may precipitate a fulminant colitis with incipient toxic megacolon. In the early stages of the disease, findings are nonspecific and can be normal. As the disease progresses, there is usually loss of haustration, superficial ulceration, and thickening of the bowel wall. In more advanced disease, there is complete loss of haustration, narrowing, and shortening of the colon giving the *classically* narrowed and shortened "lead-pipe" appearance.

Differential Diagnosis

Several conditions can mimic UC. The clinical presentation and diagnostic evaluation should help establish an accurate diagnosis in most cases. Infectious colitis, caused by such agents as shigellosis, salmonellosis, yersiniosis, and clostridia difficile should be considered. Stool cultures are therefore necessary. Parasitic infestations, such as amebic colitis and schistosomiasis must also be considered. The diagnosis is established by the finding of parasites in the stool or on histological examination. CD has clinical and histological features that overlap with ulcerative colitis. Indeed, in about 15–20% of the patients, distinction between UC and CD cannot be made. In infancy, cow's milk allergy may present with bloody stools. Distinctive features are a history of allergy in the child or family, eosinophilia, high serum IgE levels, and a high number of eosinophils in the lamina propria. Connective tissue diseases, such as scleroderma and systemic lupus, may mimic some of the clinical features of UC. Such disorders are characterized by systemic manifestations with suggestive laboratory findings that may aid in the differential diagnosis.

Complications

Risk of Cancer

The risk for developing colonic adenocarcinoma in ulcerative colitis is a major concern, especially in patients in whom the disease starts in early childhood. It is estimated that the yearly risk of cancer is about 0.5–1% after 10 years of the disease. Surveillance at regular intervals is strongly recommended. The youngest patient reported to have colon cancer was 16 years old. In patients who have had

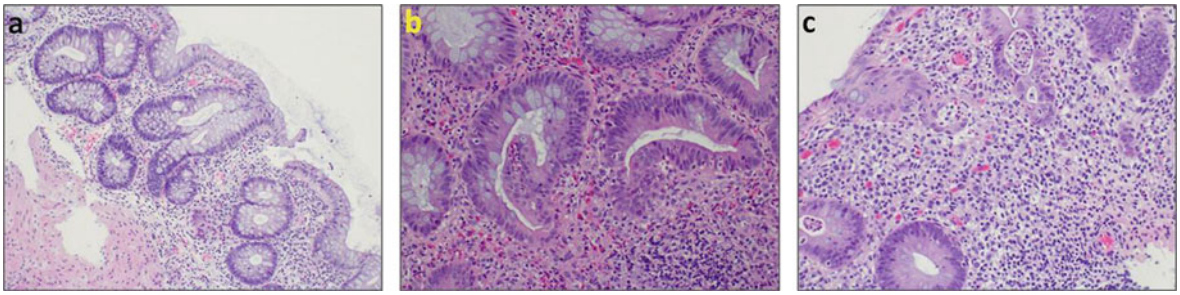

Figure 195.2

(a) Ulcerative colitis, mildly active. Rectal mucosa with crypt distortion, increased chronic inflammation and mild acute inflammation (magnification 100×). (b) Ulcerative colitis, moderately active. Colon mucosa with architectural distortion, increased chronic inflammation, cryptitis, and an early crypt abscess (magnification 200×). (c) Ulcerative colitis, marked activity. Colon mucosa with architectural distortion, increased chronic inflammation, cryptitis, and scattered crypt abscesses (Courtesy of Judith Pugh, M.D., Pediatric Pathologist, University of Arizona)

the disease for more than 10 years, an annual colonoscopy is generally recommended to evaluate for histological dysplasia.

Treatment

The approach to each patient is individualized and is based on the severity and the extent of the disease. First-line therapy for patients with mild to moderate disease is 5-amino salicylic acid (Mesalamine), which includes oral and rectal Mesalamine formulations and oral pro-drugs such as sulfasalazine (5-aminosalycilic acid linked to sulfapyridine), olasalazine (5-aminosalycilic acid dimmer), and balasalazide (5-aminosalycilic acid linked to 4-aminobenzoyl-beta alanine). Dosages vary depending on age, but in older patients, a dose between 2.4 and 4.8 g/day is needed to induce remission. For patients with left-sided colitis, topical 5-aminosalycilic acid alone or in combination with oral 5-aminosalycilic acid is needed to induce remission. For patients with Proctitis, suppositories of 5-aminosalycilic acid (Canasa®) may suffice, whereas enemas (Ruwasa®) will be needed for distal colitis. Mesalamine compounds should be used for maintenance therapy. Patients with moderate to severe disease, who fail Mesalamine, should be treated with steroids, plus azathioprine (2.5 mg/kg) or 6-mercaptupurine (1–1.5 mg/kg). Steroids are used to induce remission, whereas azathioprine or 6MP are used for maintenance. Patients who are unresponsive to conventional therapy may need infliximab at a dose of 5 mg/kg at 0, 2 and 6 weeks followed by maintenance therapy every 8 weeks. Other therapeutic modalities for patients who are refractory include cyclosporine and tacrolimus. Colectomy should be considered when all medical therapies are not effective. *Table 195.3* shows all masalamine compounds and their site of action.

Sulfasalazine

Sulfasalazine is effective in cases with mild to moderate disease activity and as a prophylactic agent to prevent relapses. Sulfasalazine is a compound drug that, when taken orally, is split by the colonic flora to sulfapyridine and 5-aminosalicylic acid (5-ASA). The latter is poorly absorbed and is the active anti-inflammatory agent that acts by inhibiting local prostaglandin and leukotriene synthesis. Side effects are common and are thought to be caused by the rapidly absorbable sulfapyridine moiety. These include anorexia, nausea, vomiting, and a serum sickness-like reaction. Anemia may also occur from either hemolysis or folic acid deficiency due to interference with folate absorption. Rarely, some patients may develop fever, vomiting, and bloody diarrhea.

Due to the high risk of adverse reactions, it is important to start with a low dose of 0.25–0.5 g daily and to increase the dose over 1–2 weeks to 2–3 g daily. Blood counts and red blood cell indices should be checked regularly. Folic acid supplementation is recommended to prevent macrocytic anemia.

Long-term therapy after controlling the acute episode is recommended in an effort to prevent relapses.

Aminosalicylates

Various new drugs have been developed that allow the delivery of 5-ASA without much of the systemic side

Table 195.3
5-Aminosalicylic acid preparations

Generic name	Trade name	Mechanism	Delivery site
Sulfasalazine	Azulfidine®	5-ASA-sulfapyridine coupling	Colon
Olasalazine	Dipentum®	5-ASA-5-ASA coupling	Colon
Mesalamine	Azacol®	pH-dependent capsule	Distal ileum
Mesalamine	Pentasa®	Time-release capsule	Jejunum, ileum, colon
Mesalamine	Lialda®	pH release with hydrophilic and hydrolipophilic coats	Colon

effects associated with sulfapyridine. 5-ASA, when not coupled to sulfapyridine, is easily absorbed by the stomach. In order to allow for delivery of 5-ASA to the colon, various mechanisms have been developed. These include drugs in which 5-ASA is linked to a new carrier moiety that is cleaved by colonic bacteria. Other drugs have been formulated in which 5-ASA is encapsulated by a time-release or pH-dependent coating (*Table 195.3*). (Lialda®) is another compound which utilizes a pH release mechanism with hydrophilic and lipophilic coats. These developments have also enabled the delivery of the drug to more proximal portions of the intestinal tract.

Topical delivery is in the form of 5-ASA enemas or suppositories have also been developed. These have been efficacious in treating active distal colonic and rectal disease, as well as preventing their relapse.

Corticosteroids

The efficacy of corticosteroids in UC is well established. These can be given orally, intravenously or rectally, depending on the severity and the extent of the disease. Patients with mild disease may respond to 5-ASA alone. However, patients with moderate and severe disease will require steroids.

Parenteral administration is reserved for severe and fulminant disease. It is given in the form of either hydrocortisone, 10 mg/kg/daily; or methylprednisolone, 2 mg/kg/daily. With the improvement in bloody diarrhea and appetite, therapy should be switched to oral prednisone, 1–2 mg/kg/daily in two divided doses. Treatment should be continued for 6–8 weeks followed by gradual weaning over a period of several weeks. In patients who relapse after cessation of therapy or in those with chronic smoldering disease, a low maintenance dose of 5–15 mg every other day may be required. In contrast to 5-ASA preparations, corticosteroids alone do not appear to maintain remission.

Local administration of corticosteroids in the form of retention enemas or foam is especially useful in patients with left sided and proctosigmoidal colitis.

Immunosuppressive Therapy

Azathioprine and 6-mercaptopurine have been used as corticosteroid-sparing agents in patients with chronic active UC, who fail to respond to conventional therapy. Oral cyclosporin A has shown some short-term efficacy in patients with fulminant ulcerative colitis in that it allows short-term improvement. This permits avoiding a precipitous colectomy. Cyclosporin A does not appear to result in long-term remission.

Total Parenteral Nutrition (TPN)

The efficacy of hyperalimentation and total bowel rest is well established in CD, but is not as promising in UC. Patients with moderate and severe colitis with anorexia, hypoalbuminemia, and malnutrition, generally will require nutritional rehabilitation in the form of parenteral and/or enteral alimentation.

Surgical Therapy

Unlike CD, surgery is curative in ulcerative colitis. Emergency surgery is life saving in severe fulminant colitis with or without toxic megacolon that fails to respond to adequate medical therapy, and in patients with evidence of perforation or peritonitis. Elective surgery is indicated in chronic smoldering and incapacitating colitis that fails to respond to adequate medical therapy, in patients with long-standing colitis with dysplastic changes, and in patients with delayed puberty and severe growth retardation before epiphyseal closure occurs.

Several surgical options exist, including a proctocolectomy with an ileostomy, a colectomy with an ileorectal anastomosis, and a colectomy with a mucosal proctectomy and an ileoanal anastomosis. The latter procedure is now the most popular as it preserves continence with a diminished risk of relapse.

Crohn's Disease

Crohn's disease (CD) is a chronic inflammatory disease which may affect any part of the gastrointestinal tract from mouth to anus. The disease involves the full thickness of the bowel and is characterized by the presence of granulomas. The involvement is generally discontinuous and most commonly involves the terminal ileum.

Intestinal Manifestations

Signs and symptoms of CD are variable and depend on duration and extent of the disease, and the portion of the GI tract involved.

In children, the disease is limited to the terminal ileum in 26% of patients while extensive small bowel disease is seen in 10% of patients. The disease is limited to the colon in 3% of patients and involves the ileum and proximal colon in 61% of cases.

Abdominal pain can be mild or severe, mimicking an acute abdomen. Most commonly, the pain is cramping, constant, and tends to localize to the right lower quadrant. In some patients with ileal involvement, a tender mass can be felt in the right lower quadrant. This mass represents thickened and matted loops of bowel. The pain is triggered by meals and patients tend to avoid eating in fear of pain. Epigastric pain is seen in patients with gastroduodenal involvement, whereas dysphagia and odynophagia are seen in patients with esophageal involvement.

Diarrhea is less common in CD than in UC, especially in patients with no colonic involvement. Patients with colonic or rectosigmoid disease can have severe and massive bloody diarrhea. Patients with ileal disease and strictures can present with constipation. Steatorrhea is seen in 25% of patients. This may be due to extensive small bowel disease or to bacterial overgrowth due to partial obstruction or ileocolonic fistulae.

Anorexia, nausea, and vomiting can represent a substantial problem in children with CD, leading to a reduced caloric intake and increased nutritional losses. This contributes significantly to the malnutrition and growth retardation frequently encountered in children with CD.

Perianal disease is one of the hallmarks of CD. Perirectal skin tags, fistulas, and fissures are commonly seen. Fistulas are more commonly external and communicate with the perianal area. Internal fistulas are less common and can be ileoileal, ileocolic or communicate with the bladder, vagina, or bone.

Extraintestinal Manifestations

Growth retardation and malnutrition are extremely common in CD with the majority of children below the fifth percentile for weight and at least 30% of patients below the fifth percentile for height. Reduced caloric intake is the single most important element in growth failure. Enteric protein loss and malabsorption are important contributing factors.

Mucocutaneous Lesions

Aphthous stomatitis is common in patients with CD, particularly during active bowel disease. Erythema nodosum, pyoderma gangerenosum, and epidermolysis bullosa are less commonly seen.

Genitourinary Lesions

Hyperoxaluria and renal stones are common in CD with ileal disease due to bile acid loss, resulting in fat malabsorption that binds calcium leaving oxalate to be absorbed in the colon. Enterovesical fistulas or ureteral obstruction by an inflammatory mass are other renal manifestations.

Musculoskeletal Lesions

Arthralgias and arthritis are observed in 15% of children with CD. Arthritis is usually mild, migrating and nondeforming, and involves any joint, particularly the large joints of the legs. It is more commonly seen with colonic involvement. Ankylosing spondylitis (AS) is rarely seen. The activity of peripheral joint disease follows intestinal disease activity, while progression of AS is independent of bowel disease. Clubbing of the fingers is seen in up to 25% of the patients, particularly when the small bowel is affected. Osteopenia has been reported in 31–59% of adult IBD patients with overall risk for fracture in about 40%. The pathogenesis of decreased bone mineralization is related to TNF-α (tumor necrosis factor-α), which downregulates genes involved in bone formation.

Ocular Lesions

Up to 10% of patients have ocular lesions including iritis, episceleritis, and uveitis. Cataracts may be seen with prolonged corticosteroid therapy.

Heptobiliary Manifestations

Abnormalities of the biliary system and liver include pericholangitis, sclerosing cholangitis, fatty liver, chronic hepatitis, hepatic granulomas or abscesses, cholelithiasis, and granulomatous or acalculus cholecystitis.

Fever

Fever occurs in up to 50% of patients. It may be low grade or spiking.

Laboratory Findings

Laboratory findings are nonspecific. The sedimentation rate and c-reactive proteins are usually elevated. A microcytic, hypochromic anemia is common and results from blood loss, reduced intake, and chronic illness. Macrocytic anemia is less common and results from vitamin B12 and/or folate deficiency due to severe ileal disease and/or sulfasalazaline therapy.

Hypoalbuminemia is seen in 50–60% of patients due to malnutrition and protein losses in the stool. Examination of the stool may reveal leukocytes and blood in patients with colonic involvement, as well as increased stool fat in patients with steatorrhea. Stool lactoferrin and calprotectin are elevated with active disease. Urinalysis may reveal evidence of pyuria in patients with an enterovesical fistula.

Radiologic Evaluation

A plain abdominal radiograph may reveal evidence of partial obstruction of the small bowel due to narrowed intestinal segments. An upper gastrointestinal series with small bowel follow through is essential when evaluating for CD because the small bowel is involved in 80% of cases. *Figure 195.3* shows an upper GI series of Crohn's disease of the terminal ileum. Irregular nodular lesions (cobblestoning), thickened bowel loops, stenotic areas (string sign) are seen. Deep ulcers and fistulas may be identified by this technique. Ultrasonography may reveal bowel wall edema, as well as extramural extension of inflammation in the form of a phlegmon or an abscess. Computerized tomography and magnetic resonance imaging utilizing enterography is helpful in defining gastrointestinal involvement as well as delineating extramural extension by fistulization. Capsule endoscopy is gaining wide acceptance to visualize small bowel lesions.

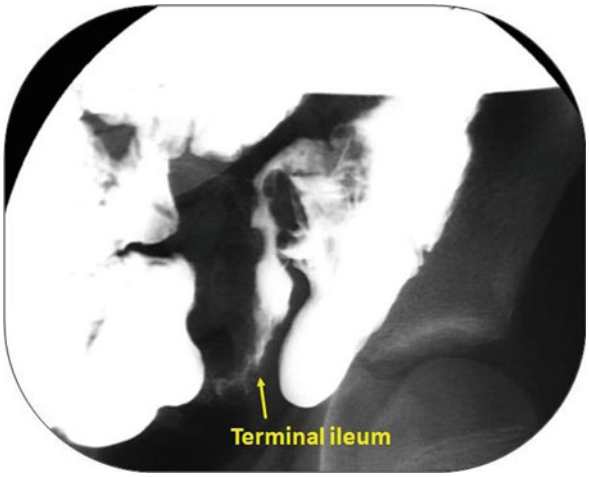

Figure 195.3
Crohn's of the terminal ileum is often first identified on upper GI with small bowel radiograph, which shows ileal stenosis and separation of bowel loops

Endoscopic Evaluation

A colonoscopy is essential in evaluating patients with suspected CD. The presence of a normal rectum and sigmoid colon virtually excludes a diagnosis of ulcerative colitis in a patient with persistent bloody diarrhea. Moreover, the finding of focal or segmental involvement of the colon with intervening areas of histologically normal mucosa is highly suggestive of CD. The involved segments may be edematous and erythematous, may have small aphthous lesions, or may appear to have deep, serpiginous, linear ulcerations with normal appearing mucosa surrounding the ulcer. This normal mucosa is responsible for the "cobblestone" appearance of the lumen in CD. The ability to perform a biopsy of the terminal ileum during colonoscopy greatly increases the sensitivity of this evaluation.

Serological Markers

Antibodies against microbial agents and *Saccharomyces cerevisiae* are seen in 60% of patients with CD (see *Table 195.2*).

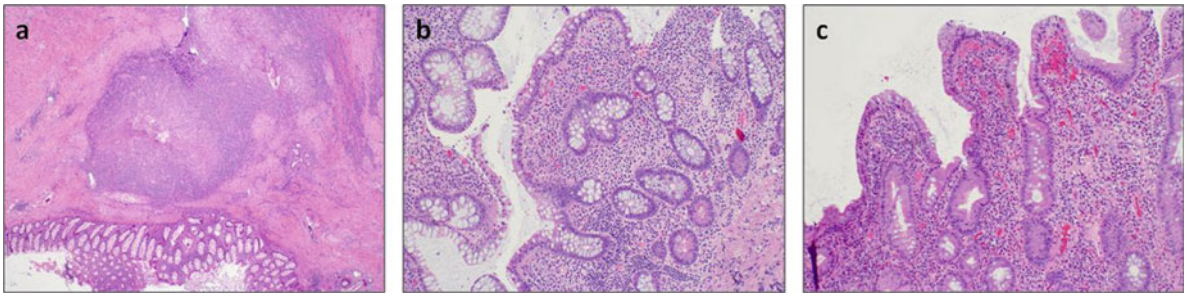

Figure 195.4
(a) Crohn's disease. Terminal ileum with transmural inflammation and prominent lymphoid aggregates within the submucosa and muscularis propria (200× magnification). (b) Crohn's. Terminal ileum with loss of villous architecture, crypt distortion and mild acute and increased chronic inflammation (magnification 100×). (c) Crohn's disease. Terminal ileum with loss of villous architecture, crypt distortion, and marked acute and chronic inflammation (magnification 100×) (Courtesy of Judith Pugh, M.D., Pediatric Pathologist, University of Arizona)

Histology

The earliest lesion of CD is the aphthous ulcer. As the disease progresses, aphthous ulcers become large and coalesce to form longitudinal and transverse linear ulcers. Fissures develop from the base of the ulcers and extend all the way to the serosa. *Figures 195.4a–c* show photomicrographs of mild, moderate, and severe CD of the ileum.

Transmural inflammation is a histologic hallmark of CD. Lymphoid aggregates in the submucosa, and occasionally the muscularis, are common. Noncaseating granulomas are found in most surgical specimens but may be missed on biopsy specimens obtained endoscopically because granulomas are typically submucosal rather than mucosal. Therefore, the presence of granulomas is helpful in distinguishing CD from ulcerative colitis, but the absence of granulomas is not helpful.

Treatment

CD is a chronic debilitating disease. There is no curative medical or surgical treatment available yet. Therapy, in general, is directed toward controlling acute relapses, maintaining remission, improving growth via adequate nutrition, and preventing complications.

Nutritional Support

Several studies have conclusively shown that bowel rest and enteral or parenteral nutrition in children with CD have a substantial positive impact on the disease. In addition to reversing malnutrition and improving growth, it is reported to induce remission in acute episodes and to promote fistula closure.

In active disease, it is often helpful to adhere to a low residue, low lactose diet. This will minimize the postprandial abdominal cramps and promote healing. The diet should be high in protein, calories, folic acid, trace minerals, and vitamins. With extensive ileal disease or after extensive ileal resection, intramuscular vitamin B12 should be provided.

In patients with significant steatorrhea leading to loss of trace minerals and fat-soluble vitamins, a modest restriction of fat intake is recommended. Supplemention with medium chain triglycerides (MCT) may be necessary. It is essential to avoid unnecessary and prolonged fat restriction since this may contribute further to malnutrition.

In more severe disease, where a single modification of the diet is not adequate, an enteral elemental diet or parenteral nutrition is mandatory. Continuous enteral alimentation without drugs has been shown to be effective in inducing remission, and in healing some fistulas. Patients with less acute disease may tolerate supplementation with low residue elemental formulas.

In severely ill patients who are unable to tolerate oral intake and in patients who are candidates for surgical intervention, total parenteral nutrition (TPN) has proven to be effective in the management of this disease.

Sulfasalazine and 5-Aminosalicylic Compounds

Sulfasalazine drug appears to be most effective in patients with colonic involvement; however, it is also reported to

be of benefit in patients with ileal disease only. Newer 5-aminosalicylic preparations allow delivery of 5-ASA to the small intestine (Table 195.3). Some studies have reported measured success in treating ileal and colonic disease. These medications have shown some efficacy in preventing relapses in patients with inactive CD and in those patients who had undergone bowel resection.

Corticosteroids

The majority of children with CD will require prednisone. Prednisone is effective in inducing remission and controlling extraintestinal manifestation. The dose is 1–2 mg/kg/daily for 6–8 weeks followed by gradual weaning. Some patients who relapse after discontinuation of steroids may require a maintenance dose administered daily or every other day. Budesonide (Enterocort) combines potent anti-inflammatory activity with rapid first-pass hepatic catabolism to minimize systemic side effects, which has shown promising results in CD patients with terminal ileum involvement.

Immunosuppressive Therapy

Azathioprine or 6-mercaptopurine (6MP) are usually used to maintain remission in patients with CD and those who require steroids to maintain a remission. Before starting those medications, measurements of the enzyme thioprine methyltransferase (TPMT) is important, as severe deficiency of this enzyme can lead to high levels of 6-thioguanine (6TG), which can cause severe bone marrow toxicity. 6TG is the active metabolite responsible for the immunosuppressive activity of Azathioprine and 6MP. Response is usually seen in 10–12 weeks of the initiation of these drugs. Studies have not shown cyclosporine to be significantly effective in CD.

Surgical Therapy

The role of surgery in CD is less defined than in UC and is used mainly to manage complications. It is indicated in patients with intractable and invalidating disease with or without growth failure; in patients with acute or subacute intestinal obstruction who fail to respond to medical therapy; in patients with intractable intra-abdominal abscesses and/or internal fistulae; in patients with severe hemorrhage or perforation; and in prepubertal patients with growth failure.

Antibiotics and Probiotics

Several antibiotics have shown therapeutic efficacy in patients with CD. Metronidazole, ciprofloxacin, and rifaximin are generally utilized, especially in patients with perianal diseases. The use of probiotics has been shown to be effective in pouchitis; however, their role in IBD patients remains to be determined.

Biologics

The introduction of monoclonal antibiotics against TNF-α has revolutionized the treatment of IBD patients. Table 195.4 depicts the available biologic therapies for the treatment of CD. Only infliximab is approved for the treatment of UC.

Infliximab (*Remicade®*), a chimeric monoclonal antibody is given as an IV infusion at a dose of 5–10 mg/kg at 0, 2, and 6 weeks as induction therapy; and then every 8 weeks as maintenance therapy.

Adalimumab (*Humira®*), a fully human antibody is given subcutaneously (S.C.) at a dose of 160 mg as induction therapy followed by 80 mg 2 weeks later and then 40 mg every other week for maintenance.

Certolizumab pegol (*CIMZIA®*) is a pegylated Fab fragment (the component that binds TNF-α) is also given as SC injection. The dose for adult patients is 400 mg at 0, 2, and 4 weeks as induction and then every 4 weeks as maintenance.

The use of biologic therapy has been shown to be highly effective in inducing remission in adult and pediatric patients. Up to 50–80 % of patients show a decrease in Crohn's disease activity index and endoscopic healing. Most recent studies suggest that the combination of monoclonal antibodies and immunosuppressive drugs (Azithioprine or 6MP) is more effective than monotherapy alone. However, the risk of complications is higher.

Table 195.4
Biologic therapy for Crohn's disease

• Anti-TNF agents
– Infliximab (remicade®) – chimeric mab
– Adalimumab (Humira®) – humanized mab
– Certolizumab pegol (Cimza®) – pegylated Fab fragment of humanized mab
• Anti-integrin agents
– Natalizumab (Tysabri®)
• Granulocyte-macrophage colony stimulating factor
– Sargramostim (Leukine®)

For patients unresponsive to anti-TNF-α's, Natalizumab (α-4-integrin inhibitor) is approved for patients with CD. Side effects of biologic therapy include development of serious infections such as tuberculosis and fungal infections, hypersensitivity reaction secondary to the development of autoantibodies, headaches, rash, demyelinating disorders, pancytopenia, hepatomas, and T-cell lymphoma.

Of all these complications, the most serious is the development of hepatosplenic T-cell lymphoma (HSTCL). This is certainly rare, however it is often fatal. Signs and symptoms associated with this type of lymphoma include fever, fatigue, anemia, leucopenia, hepatosplenomegaly, and abnormal liver function tests. HSTCL is seen more commonly in young male patients who were treated with biologic therapy and Azathioprine or 6MP.

Prognosis

Crohn's disease is a chronic and disabling disease. Newer therapeutic biological agents have improved the quality of life of patients; however, many patients will have ongoing smoldering disease with acute exacerbations. Biological agents can induce remission for extended periods of time.

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196 Short Bowel Syndrome

Ruba A. Abdelhadi · Hisham M. Nazer

Short bowel syndrome (SBS) is a condition characterized by malabsorption, diarrhea, steatorrhea, fluid and electrolyte disturbances, and malnutrition. It is a clinical state of small intestinal failure that occurs following extensive bowel resection, with deleterious metabolic and nutritional consequences.

A full-term newborn has an average of 250 cm of small bowel and 50 cm of colon with maximal increase in length in the first year of life. The small-bowel length doubles during the last trimester of gestation; this implicates a worse prognosis on the short-bowel remnant of a preterm infant. An adult has 600 cm of small bowel and 150 cm of colon; consequently, infants and young children's outcome on the long run is more favorable than adults, since they have the advantage of potential intestinal growth after intestinal resection.

Among the factors predicting the development of short bowel syndrome (SBS) are the premorbid length of small bowel, its functionality and adequacy of perfusion, the cause of the surgical resection, the site of resection, patient age at time of surgery, the remaining length of small bowel and colon, and the presence or absence of the ileocecal valve. The loss of the ileocecal valve creates favorable conditions for bacterial overgrowth and decreases the transit time of the small intestine.

Intestinal adaptation is a long process that involves multiple compensatory changes that involve all layers of the bowel wall, leading to dilatation, lengthening, and thickening of the small bowel. The degree of adaptational changes including epithelial hyperplasia and increase in mucosal mass and surface area is influenced by the amount of resected bowel. It is of vital importance to provide nutritional support through various therapeutic measures, including parenteral nutrition. With major strides in the development and progress of enteral and parenteral nutrition, the long-term outcome of children with SBS has much improved. Patients are now able to grow during the intestinal adaptation phase of the remaining small bowel.

Causes of SBS

- Intestinal resection in severe Crohn's disease that has failed medical treatment and resulted in stricturing or fistulizing disease
- Necrotizing enterocolitis that has failed conservative management and required intestinal resection
- Midgut volvulus resulting in intestinal ischemia
- Long segment Hirschsprung disease
- Abdominal wall defects, omphalocele, gastroschisis
- Intestinal atresias, congenital short intestine
- Intestinal angiomas requiring extensive small-bowel resection
- Complicated intussusception that has failed conservative reduction
- Arterial and venous thrombosis resulting in ischemia
- Post-trauma resection
- Severe motility disorders
- Functional intestinal failure associated with cloacal exstrophy
- Functional short bowel syndrome secondary to radiation enteritis

Expected Consequences of Intestinal Resection

As a consequence to intestinal resection, recognized associated presentations include severe diarrhea and failure to thrive. Factors influencing patient outcome include the age and indication for surgery, the extent of resection, the portion resected, and the functional integrity of the remaining small bowel. The site and length of the small bowel resected influence the degree of functional impairment. The age of the infant or child and the clinical condition that led to the resection influence the potential for the remaining intestine to adapt.

In short resection, there is more than 100–150 cm remaining small intestine according to the measured length of the small intestine along the anti-mesenteric border; in

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large resection, there is 40–100 cm remaining, and in massive resection there is less than 40 cm remaining.

The reduction of the absorptive surface area and bacterial overgrowth lead to malabsorption, vitamin and mineral deficiencies, significant water and electrolyte losses with the disrupted enterohepatic cycle resulting in hyperoxaluria. There is gastric acid hypersecretion and pancreatic insufficiency. The need for long-term parenteral nutrition leads to cholestatic liver disease, biliary lithiasis, and bone disease.

Jejunal Resection

The degree of nutrient and electrolyte malabsorption is a reflection to the extent of jejunal resection resulting in severe diarrhea, vitamin and trace element deficiencies.

Ileal Resection

While the ileum has the potential to adapt after jejunal resection and compensate with macronutrient absorption, the reverse is not true: jejunal adaptation cannot compensate for ileal resection, as the terminal ileum has the exclusive capacity to reabsorb bile salts and vitamin B12. Patients with ileal resection are especially at risk for micronutrient deficiencies; bacterial overgrowth further exacerbates vitamin B_{12} malabsorption. These patients require biochemical screening for micronutrient deficiencies.

Terminal ileal resection with subsequent bile salts malabsorption results in lipid malabsorption, steatorrhea, and fat-soluble vitamin deficiency. Lipid malabsorption with hyperoxaluria predisposes for nephrolithiasis. Bile salt malabsorption and the disruption of the enteroheptic circulation predisposes for gall stones. Colonic mucosal damage from bile salts excess and unabsorbed and hydroxylated fatty acids results in secretory diarrhea.

Ileocecal Valve Resection

With the resection of the ileocecal valve, there is marked decrease in transit time; bacterial overgrowth further potentiates nutrient malabsorption and contributes to colonic mucosal injury by dehydroxylating the bile salts. Bacterial overgrowth also has a negative impact on the normal motility of the remaining gut. Ileocecal valve resection predisposes the infants to bacterial translocation and subsequent sepsis.

Clinical Manifestations

The clinical features of SBS are very much influenced by the primary clinical condition together with associated subsequent complications. Diarrhea, weight loss, abdominal distension, and malnutrition are the most important clinical features of SBS. Ileal resection disrupts the enterohepatic circulation of bile salts and causes depletion of the bile salts pool leading to fat malabsorption.

The clinical course of SBS has been divided into three stages:

Stage 1: This constitutes the initial phase after small-bowel resection, characterized by massive diarrhea with excess loss of fluid and electrolytes. Feeding in this stage is limited to total parenteral nutrition (TPN) for a variable duration of several weeks to a few months; enteral feeding is minimal but advisable as soon as the postoperative condition allows. The mainstay of medical management in this stage involves replenishing the intestinal losses and assessing the potential for reducing them.

Stage 2: This is mainly the phase of progressive adaptation that enables the infant to tolerate some enteral feeds initially through continuous drip infusion but later on by bolus and oral feeding. This stage may suffer a few relapses requiring the return to Stage 1. In general, this stage may last for up to a year but occasionally longer. In an attempt to reach the maximum adaptation potential, cautious advances in enteral feeding are coupled with gradual cycling of TPN.

Stage 3: This is defined as the stage of maximum adaptation with the possibility to tolerate full enteral nutrition without having to require cyclic or home TPN.

Intestinal Adaptation

Intestinal adaptation is a gradual and slow physiologic process that allows the remaining small bowel to assume functional and histological compensatory changes that may accommodate the massive loss of absorptive surface and allow eventual weaning from parenteral nutrition.

Multiple humoral endogenous factors are involved in promoting successful intestinal adaptation. These include insulin-like growth factor (IGF), growth hormone (GH), enterogulcagon, and neurotensin. *Insulin-like Growth Factor* 1 (IGF-1) is produced by the ileum and plays a role in tissue proliferation. The result is multiple functional and histological changes that include mucosal

hyperplasia, lengthening of the villi, deepening of the crypts, increased rate of enterocyte proliferation, and increased number of enterocytes per small-bowel length. Glucagon-like peptide 2 (GLP-2) has shown promising results in promoting intestinal adaptation following ileal resection. Recent studies have demonstrated that subcutaneous injections of GLP-2 had a positive effect on the lengthening of jejunal villi and deepening of the crypts and increasing fluid absorption. GLP-2 may be the medical option for patients with ileal resection and loss of the GLP-2 producing ileum. Exogenous treatment with GH and glutamine supplementation has a positive effect on growth parameters and promotes intestinal adaptation.

It cannot be over-emphasized that small trophic enteral feedings play a vital role in promoting and facilitating intestinal adaptation, healing, and resumption of the absorptive potential of the remaining small bowel by stimulating the secretion of cholecystokinin, neurotensin and gastrin, in addition to enteroglucagon, which plays a role in augmenting the remaining intestine's absorptive potential via stimulating cell turnover and improving motility. Glutamine must be included in parenteral nutrition as it plays a vital role in enterocyte metabolism.

Enteral glutamine supplementation is well tolerated but does not seem to influence the duration of parenteral nutrition or show demonstrable effect on intestinal absorptive or barrier function. Dietary fibers included in enteral or parenteral nutrition undergo fermentation and produce short-chain fatty acids which provide nutrition to the enterocytes and promote adaptation.

Medical Management of Short-Bowel Syndrome

Management of extreme SBS has changed dramatically over the past decade with satisfactory improvement in survival and quality of life in patients with short bowel syndrome. Infants with as little as 20–30 cm of the small bowel are expected to survive well with the support of specialized enteral and parenteral nutrition. Parenteral nutrition is essential in the initial management to stabilize fluid, electrolyte, and nutritional balance. This therapy is planned as a long-term one administered through a permanent central line. It is only rarely that infants with SBS can survive without parenteral nutrition.

In the early stages of adaptation, patients with a short jejunal remnant may not be able to digest and absorb polymeric feeds or those with long-chain triglycerides (LCT). Therefore, continuous infusion of dilute elemental diet is initiated. During the early phase of management of SBS, regular and close supervision of the fluid and electrolyte balance are essential with proper monitoring of nutrient supplement and early awareness of the potential hepatobiliary complications of TPN. The biochemical abnormalities of cholestasis are reversible provided that TPN is discontinued at an early stage. As the techniques of TPN therapy improve and knowledge expands, such therapy is more effective with fewer complications.

Enteral nutrition is introduced once the baby settles on the initial phase of management with TPN. The present trend toward earlier introduction of enteral feedings has very much reduced the risk of TPN-related cholestasis. It is advisable to commence enteral nutrition as continuous enteral infusion through a nasogastric tube or gastrostomy feeds. The baby may require months or years prior to being able to tolerate an adequate amount of enteral feeds to ensure satisfactory progress. This period is very much influenced by the length of the remaining bowel and by the central line-related complications as well as by the baby's tolerance to the gradual increase in his enteral intake. Various formulas are used with variable rates of success for enteral nutrition such as protein hydrolysates, essential amino acids, Neocate and Alimentum. To ensure optimal intestinal adaptation, the enteral supplement should contain fat. Medium-chain triglycerides (MCTs) are more readily absorbed, especially in the absence of bile acids. Nevertheless, long chain triglycerides seem to have a better trophic effect than MCTs in further potentiating better intestinal adaptation; LCTs also are a source of linoleic and linolenic acid. It is advisable in such situations to add cholestyramine, a bile acid-binding resin, to reduce the osmotic diarrhea.

Expressed breast milk that is delivered enterally and gradually by small trophic feeding volumes has unique and invaluable benefits to the infant with short bowel syndrome; a multitude of bioactive constituents influence the infant's intestinal microflora with positive effects on the gut function and development. Mucins and oligosaccharides help eliminate viruses and bacteria from the body; lactoferrin makes iron unavailable to pathogenic bacteria, and interferon and fibronectin have antiviral activities. Furthermore, the high secretory Immunoglobulin A (sIgA) content is specifically tailored to the neonate's needs with the maternal antigenic specificity that is directed against the same antigens in the neonate. Other bioactive substances and growth modulators seem to enhance the maturation of the neonate's gut by stimulating small intestinal cell proliferation; these include interleukins, insulin-like growth factor (IGF), epidermal growth factor (EGF), transforming growth factors (TGFs)–alpha and beta.

During the phase of continuous enteral feeding, gradual increase in concentration is dictated per digestive tolerance; it is essential to monitor the stool output and reducing substances in that regard. Semi-elemental diets contain medium chain and long chain triglycerides; the low osmolality of oligosaccharides makes them better tolerated in view of the relative disaccharidase deficiency. Protein hydrolysates in the form of lactalbumin are better absorbed than casein.

Broad-spectrum antibiotics are needed in case of bacterial overgrowth, especially in those who have had the ileocecal valve resected. It is advisable to combine therapy with antibiotics such as clindamycin or metronidazole. Occasionally, surgery is required to reduce the problems of bacterial overgrowth and its associated complications.

Every effort should be exercised to minimize TPN-related liver injury by prevention of hyperglycemia, TPN cycling, use of ursodeoxycholic acid, provision of essential fatty acids, and decreasing the likelihood of developing hyperinsulinism and its negative consequences of hepatic steatosis. Equally important is the prevention and treatment of bacterial overgrowth. In a recent study published in August 2009, Puder et al. concluded that parenteral fish oil-based lipid emulsion improves the outcome of parenteral nutrition-associated liver injury.

Cholestyramine may improve diarrhea by binding bile acids but may contribute to fat-soluble vitamin malabsorption and deficiency. Octreotide slows intestinal transit time but has a negative effect on the splanchnic circulation and potential intestinal adaptation. Loperamide may be useful in reducing fluid losses and decreasing intestinal transit time, but carries the risk of promoting bacterial overgrowth in the setting of intestinal dysmotility.

Measurement of serum citrulline levels—an intestine-synthesized amino acid, is a useful test that predicts enteral tolerance and TPN independence. Serum citrulline level correlates linearly with the percentage of enteral calories tolerated as well as remaining bowel length. A serum citrulline level above 19 μmol/L has 94% sensitivity and 67% specificity for TPN independence.

Surgical Management of Short Bowel Syndrome

The noticeable progress in the nonsurgical management of patients with SBS has resulted in fewer patients requiring surgical procedures to increase the intestinal transit time and maximize the absorptive potential of the remaining intestine. Multiple surgical procedures have evolved to address SBS functional and anatomic abnormalities, although the overall impact of such procedures has yet to be fully evaluated. Bianchi intestinal lengthening surgery may be encouraging. This surgery is indicated in severe SBS without expectation of further intestinal growth. It is important to introduce enteral feeds as soon as possible to promote gut adaptation. Longitudinal intestinal lengthening and tailoring (LILT) procedure facilitates TPN independence.

Intestinal lengthening and tapering to dilated bowel segments have to be applied cautiously, as the viability of the intestinal segments as well as the function and long-term patency may be at risk. Colonic segment interposition surgeries have shown poor outcome. It must also be emphasized that such procedures (e.g., colonic interposition, reversed small-bowel segment to create retrograde peristalsis) are not without complications such as bacterial overgrowth; so far clinical results have been conflicting.

The serial transverse enteroplasty (STEP) lengthening procedure was developed by the pediatric surgeons at Children's Hospital Boston, to maximize enteral nutrition tolerance and TPN independence. In this procedure, special devices are used to simultaneously cut and staple the bowel in a direction parallel to the direction of the blood supply, which travels from the mesentery and traverses the bowel perpendicular to its long axis.

Home parenteral nutrition has proved to be beneficial for all parties involved in the care of a child with SBS. It may take weeks or months at home before the child should be able to depend in its nutrition supplement mainly on enteral feeds, subsequent to which the parenteral nutrition will be discontinued.

Intestinal Transplant

Today's management of patients with SBS highlights more the importance of intestinal adaptation and delaying surgical intervention for at least a year to verify that the child is not making noticeable progress on a parenteral or enteral regimen.

In some patients with increased rate of central line-related sepsis or TPN-related cholestasis, surgical intervention may be considered. However, it has become clear that there are major difficulties associated with small-bowel transplantation because of the presence of substantial lymphoid tissue. During the first years of attempts to transplant patients with SBS, all recipients died due to technical failure, rejection, suspected graft-versus-host disease, or systemic sepsis. Such results have prompted more work to improve the already existing regimens of enteral and parenteral nutrition in SBS.

The first long-term successful small-bowel transplantation was performed in 1988 using a two-step technique and

a living-related donor. Subsequently, more reports of successful intestinal transplantation in children have been published. Simultaneous bowel–liver transplantation was found to reduce the risk of intestinal rejection. In 1990, Grant et al. reported the first successful small bowel–liver transplantation.

It must be emphasized that in spite of the encouraging results of small-bowel transplantation over the past several years, such procedures as well as that with simultaneous liver transplantation should only be offered to a minor proportion of affected patients with SBS with severe complications on nonsurgical measures.

Complications

The noticeable improved survival of infants with SBS with the application of TPN has left the affected babies with two major causes of mortalities: TPN-related cholestasis and central line-related sepsis.

TPN-related cholestatic liver disease is one of the major complications of parenteral nutrition. TPN cholestasis remains a major cause of morbidity and mortality, with an incidence that has been reported to vary from 7.4% to 33%. The disease is progressive with a characteristic sequential pattern of histological liver damage. The biochemical indices of liver function do not necessarily correlate with liver histology as severe liver injury can occur in the presence of normal liver enzymes; as such, TPN-related cholestasis should be confirmed histologically. The recognized histological pattern in TPN-related cholestasis includes biliary stasis, portal tract inflammation, bile duct proliferation, and portal fibrosis.

TPN-related cholestasis may be predisposed by – or at least contributed by – lack of enteral feeding. Recent reviews recommended early introduction of partial enteral feeding to preserve liver function. Bacterial overgrowth contributes to liver damage and further potentiates hepatotoxicity by facilitating bile acids' reabsorption by deconjugation.

In addition to contributing to TPN-related cholestasis, *bacterial overgrowth* also causes mucosal injury and worsens the malabsorption state related to short bowel and the compromised absorptive surface area and dysfunction. It also predisposes to sepsis by bacterial translocation. Major contributing factors to bacterial overgrowth include bowel dilatation, dysmotility, and stasis, as well as loss of the ileocecal valve. The clinical suspicion of bacterial overgrowth is supported by abnormal breath hydrogen testing in age-appropriate patients or duodenal aspirates and stool studies. Treatment with clindamycin and metronidazole combination is indicated in such clinical setting.

Furthermore, lactobacilli and other bacteria cause *lactic acidosis* by fermenting the non-absorbed carbohydrates. Patients may develop neurological manifestations and episodes of encephalopathy along with high anion gap metabolic acidosis. This is also contributed to by liver dysfunction and thiamine deficiency. Treatment with neomycin, metronidazole, and vancomycin is indicated. Probiotics may be of benefit to repopulate the small intestinal flora. However, Probiotics themselves can contribute to lactic acidosis as evidenced by a case report published by Ku et al. in 2006. On the long term, metabolic acidosis is a potential complication in children with SBS and can lead to growth failure and contribute to failure to thrive.

Loss of the terminal ileum predisposes to *vitamin B12 and fat-soluble vitamins deficiencies.* These patients should receive vitamin B12 and ADEK vitamins supplementation, and get vitamins B12, A, E, 25-hydroxyD checked regularly in addition to PT. Children who have undergone ileal resection are at an increased risk of developing *calcium oxalate nephrolithiasis* as a consequence to hyperoxaluria. These children should have renal sonograms once or twice a year; they should be on a low-oxalate, low LCT diet, and receive calcium supplementation.

Outcome

The survival and prognosis of infants with SBS has improved since the application of long-term TPN. The majority of infants and children now survive after extensive small-bowel resection. Cholestasis and age-adjusted small-bowel length are the major predictors of mortality in pediatric SBS. Prognosis is more favorable when the ileocecal valve is preserved, and directly related to the length, functionality, and adaptability of the remainder of the small bowel and subsequently the shorter duration of PN requirement. Close monitoring of growth velocity and weight gain is of paramount importance. A nutritionist's input is invaluable as a member of a multidisciplinary team approach, which allows fostering the coordination of surgical, medical, and nutritional management to improve survival. Intestinal transplantation option is reserved to those patients with complete PN dependence and extreme short bowel.

Summary

Early and careful introduction of enteral feeding has the strongest impact on intestinal adaptation, prognosis, and eventual outcome. Cholestatic liver disease remains the

leading cause of morbidity in SBS patients with failure of intestinal adaptation and TPN dependence. Intestinal and liver transplantation is reserved to those patients with extreme short bowel, failure of intestinal adaptation, parenteral nutrition dependence, TPN cholestasis, and end-stage liver disease.

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197 Intestine Transplantation in Children

Jorge D. Reyes

Background

Intestinal transplantation has made dynamic progress in the last 20 years, benefiting from important developments in preservation technology, surgical technique, improved perioperative care, and innovative immunosuppressive strategies. It is now recognized as an established modality of care for patients suffering from failure of their intestinal function and requiring Total Parenteral Nutrition (TPN). The dramatically improved outcomes for intestinal transplantation over the last decade have allowed more patients to benefit from this therapy. More importantly, however, an important component of the legacy of intestinal transplantation has been the development of intestinal failure management which has opened a focus of multidisciplinary care to this field. This chapter is intended to review the various components of this field and address the challenges which remain to further progress, which include improvements in intestinal adaptation and prevention of TPN-associated liver disease, enhancing access to organs and transplantation, and decreasing waiting list mortality. Understanding long-term function of the intestinal graft and nutritional outcomes will further help define the optimal timing and role of intestinal and multivisceral transplantation in patients with intestinal failure.

Management of the Intestinal Failure Syndrome

Intestinal failure is defined as the anatomic or functional loss of the ability of the intestine to provide for normal absorption of nutrients and fluid. Patients suffering diseases which result in intestinal failure are managed by administration of total parenteral nutrition (TPN) through catheter placed in a central venous position, usually through access of the Internal Jugular, Subclavian, or Iliac veins. Such acute care management is variable in duration and depends on the adaptive capacity of the remaining intestine. The development of multidisciplinary team management and formation of intestinal rehabilitation programs has resulted in improved long-term outcomes in TPN-dependent patients. There remain, however, a subset of patients who develop irreversible intestinal failure and a syndrome of satellite complications when left on TPN, and where intestinal transplantation may be lifesaving.

A comprehensive assessment includes understanding the etiology/cause of intestinal failure, disease history and surgical procedures, epidemiology of infections, number and location of previous venous catheters, patency of central veins, nutritional history which includes TPN care and enteral feeding. Further assessment often includes radiographic studies of upper and lower gastrointestinal tract using contrast enhanced small bowel follow-through's, contrast enema's, Doppler ultrasound studies of the liver, vena cava, and central veins. A liver biopsy may be indicated if there is evidence of liver dysfunction or portal hypertension.

Management of intestinal failure is focused on enhancement of gut adaptation and preventing/improving the satellite complications of liver dysfunction and infections. To this end, various surgical (non-transplant) procedures that have developed which provide for improved adaptation, the most recent and successful of which has been the serial transverse enteroplasty (STEP). In cases of extreme short gut (loss of the entire small bowel and much of the colon) or severe dysfunction, intestinal failure may be considered irreversible; some patients may be managed with long-term TPN, achieving or maintaining growth and development in children and adults. However, the development of complications of TPN management may limit this form of care.

The development of TPN-associated liver disease has by far been the most critical challenge in this patient population. The 1-year mortality with such complication in patients who are not able to wean off TPN or receive an intestine transplant exceeds 70%. The development of cholestasis may be relatively early in small infants, as compared to adults, so consequently the efforts in prevention, management, and evolution may vary. A general approach to this problem has been the treatment of sepsis, minimizing bacterial overgrowth in the bowel, optimizing enteral nutritional supplementation, interval cycling TPN (to more off time from this therapy), and preventing over feeding.

The role of cholecystectomy in the management of this complication is controversial, as has been the manipulations of the various TPN components; however, excessive glucose and improper ratios of glucose to amino acid have

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been associated with hepatic steatosis and consequent steato-hepatitis. The manipulation of the lipid component of TPN has led some to advocate for the removal of soy-based lipid solutions and their substitution with Omegaven (a fish-oil based, intravenous lipid solution rich in omega-3 fatty acids); the apparent clinical and laboratory improvement in liver function has had an important impact in the progression to worsening liver failure in this patient population.

Catheter-associated sepsis has been the next most common and severe TPN-associated complication, resulting in life-threatening instabilities and need for intensive care unit management, renal failure, and death; it often results in thrombosis and loss of venous access, and may necessitate removal of the venous catheter, thought infants with limited venous access may require preservation of an infected line.

Patients with intestinal failure behave with relative susceptibility to infections, both through the gastrointestinal translocation of bacteria (in a setting of gut dysfunction, bacterial overgrowth, liver dysfunction, and portal hypertension) with sepsis and with community acquired infections.

Indications for Transplant

Intestinal transplantation was approved by the Center for Medicare and Medicaid Services in October of 2000 as a standard of care for patients with irreversible intestinal failure who could no longer be maintained with TPN; this includes isolated intestinal, combined liver-intestine, and multivisceral transplant operations. The limitations of TPN therapy include the aforementioned complications, those who cannot tolerate quality of life limitations associated with TPN therapy, or who must undergo native bowel resection for potentially life-limiting indications or tumors. Causes of intestinal failure are categorized into those entities most commonly found in children or adults and which result in loss of bowel length or function; these include diseases such as necrotizing enterocolitis, volvulus, and mesenteric thrombosis, motility dysfunction such as Crohn's disease, or acquired disorders such as radiation enteritis (*Table 197.1*).

With the development of specialized intestine rehabilitation centers (which include transplant care) overall improved outcomes in these patients have been observed, many of whom have not required transplantation. In a recent consensus panel on intestinal failure management, the following recommendations regarding criteria for consultation for intestine transplant evaluation were endorsed: (1) extreme short gut from massive bowel resection; (2) severely diseased bowel and unacceptable morbidity; (3) uncertain prognostic course; (4) microvillous inclusion disease or intestinal epithelial dysplasia; (5) unresolved clinical jaundice (>6 g/dl); (6) thrombosis of >50% of central veins; (7) the request of the patient or family.

Table 197.1
Indications for intestine transplantation

Children	Adults
Volvulus	Superior mesenteric artery thrombosis
Gastroschesis	Crohn's disease/IBD
Necrotizing enterocolitis	Desmoid tumor
Pseudo-obstruction	Volvulus
Microvillus inclusion disease	Trauma
Intestinal polyposis	Familial polyposis
Hirschsprung's disease	Gastrinoma
Trauma	Budd–Chiari disease
	Intestinal adhesions
	Pseudo-obstruction
	Radiation enteritis

The type of intestinal graft required in a patient with intestinal failure is based on the comprehensive evaluation of the function and anatomy of the remaining bowel and other abdominal organs (liver and pancreas). Intestinal grafts may be of the following general types: isolated intestine, combined liver and intestine (which includes the duodenum and pancreas), and multivisceral graft which includes the liver, stomach, duodenum, pancreas, and small bowel (the modified multivisceral graft excludes the liver); some transplant centers may include allograft colon with these variants. The determination of what would constitute a "multivisceral transplant," however, hinges on the need to "replace" the entire native gastrointestinal tract (resection of same). Important factors in determining whether to replace the liver in patients with intestinal failure is the severity of liver dysfunction and the structural consequences of end stage disease, cirrhosis, and portal hypertension. Some patients with liver fibroses, mild portal hypertension, and normal liver function should be cautiously considered for isolated intestinal transplant.

Evaluation for Transplant

Most patients with intestinal failure are suffering from dramatic complications of their disease and require an inpatient evaluation and management. After initial

assessment of disease, status of nutritional care, and management of complications, the goal of the multidisciplinary team is to determine a need for transplantation and what graft type would be most suitable, weigh in alternatives to transplant, consider potential contraindications, and provide education regarding the transplant experience.

Transplantation Operations

The procurement of intestinal grafts follows the same principles of core cooling and perfusion with preservation solutions as described with other organs; the evolution of these techniques has been one of the most important contributions to the field. The implantation of these grafts follows the principles of arterializations (generally through donor vascular conduits anastomosed to the aorta) and venous outflow to vena cava (or the liver in select isolated intestine recipients). Intestinal continuity follows standard general surgical procedures, establishing proximal (always) and distal (if feasible) continuity, with placement of an allograft decompressing ileostomy. Gastric and intestinal feeding tubes are very important procedural adjuncts which, though not essential to the implantation operation, are essential to optimum postoperative care.

Isolated Intestine

With the isolated intestinal graft (jejunum and ileum), the donor superior mesenteric vessels may be anastomosed directly to the recipient's superior mesenteric artery and vein (portal drainage; this may also be achieved through a donor vascular conduit to native portal vein); however, usually these are anastomosed to interposition vascular conduits attached to the recipient infrarenal aorta and inferior vena cava (systemic drainage).

The intestinal continuity is established proximally to native duodenum or jejunum, and distally to residual ileum or colon (if feasible); a temporary end ileostomy (or loop ileostomy) allows access to the allograft intestine for endoscopic surveillance and biopsies.

Liver and Intestine

In this operation, the recipient liver is removed with preservation of the native retro-hepatic vena cava, preserving the recipient foregut (stomach, pancreas, and duodenum): the venous outflow to these organs is maintained with a permanent end-to-side portocaval shunt. Arterial inflow is achieved using a donor arterial interposition conduit to the recipient infrarenal aorta. The venous outflow is achieved through the donor hepatic veins anastomosed to the confluence of the recipient hepatic veins and vena cava. Intestinal continuity is reestablished in a similar fashion as in an isolated intestinal transplant, with the placement of feeding tubes and ileostomy.

Multivisceral

The crux of the multivisceral operation is removal with replacement of the entire gastrointestinal tract of the recipient (stomach, duodenum, pancreas, liver, and remaining small bowel) and liver, preserving the inferior vena. Vascular inflow is through a donor vascular conduit which now includes celiac inflow to the allograft stomach, and the vascular outflow is identical to liver-intestine transplant. Intestinal continuity is established proximally with the native gastric stump to donor stomach anastomosis, and the distally as in previously described intestinal transplants. A pyloroplasty is routinely performed after reperfusion, as is the allograft ileostomy and placement of feeding tubes.

In a "modified" version of the multivisceral operation, the native recipient liver is preserved along with its vasculature and extrahepatic biliary system, with removal of the native gastrointestinal tract. This procedure requires reconstitution of the biliary tract either with a recipient duct-to-donor Roux-en-Y choledochojejunostomy or a recipient duct-to-donor duct anastomosis; also, the intestinal allograft venous drainage of superior mesenteric vein is anastomosed to the recipient's portal vein.

Immunosuppression

Tacrolimus (Prograf, Astellas, Tokyo, Japan), in conjunction with other medications, has been the cornerstone of immunosuppressive therapy for over 20 years. The field of immunosuppressive management has hinged on prevention of rejection, so common with intestinal transplantation, and initially was fraught with toxicity and infectious complication of this management which included viral, fungal, and bacterial infections, as well as renal failure as the most common complications. Consequently, other drug therapies and immunosuppressive strategies have included IL-2 antibody inhibitors, and the addition of drugs such as cyclophosphamide, azathioprine, mycophenolate mofetil, and rapamycin. Treatment of the donor prior to organ retrieval

with antilymphocyte antibody preparations has also been used with the intent of preventing graft-versus-host disease from the transfer of donor passenger cells with the graft.

Recently, two classes of immunomodulatory drugs have been introduced and associated with improved outcomes and are based on depleting antilymphocyte antibody therapies and include: rabbit anti-thymocyte globulin (rATH, Thymoglobulin, Genzyme Corp., Cambridge, MA) and alemtuzumab (Campath-1 H, Genzyme Corp., Cambridge, MA). Immunosuppression for intestinal and multivisceral transplantation now involves perioperative antibody induction in 60% of cases.

Immunologic Monitoring

Routine allograft ileoscopy and biopsy remains the gold standard of graft monitorization and is performed with varying frequency and when clinically indicated. Noninvasive serologic, proteomic, or genomic markers, as well as the assessment of preformed antibody and de novo anti-donor-specific antibody may identify patients who are at risk of rejection or who may benefit from decreased levels of immunosuppression. The detection of circulating donor cells in the recipient peripheral blood may be serially evaluated by either flow cytometry or PCR; however, the clinical significance of this finding is uncertain. There are reports of the use of fecal calprotectin or serum citrulline as noninvasive biochemical markers of allograft rejection.

Infection Control

The routine use of broad-spectrum antibiotics and antiviral prophylaxis post transplant is important and, though it follow similar guidelines as with other types of organ transplants, there are specific indicators which merit discussion. A thorough history of previous infections prior to transplant (particularly fungal) should guide with the administration of appropriate specific antibiotics, and also a focus on possible specific immune deficiencies. Oral nonabsorbable antibiotics to achieve selective bowel decontamination is performed routinely, though the significance of this management is controversial.

Viral infections can cause significant morbidity with common pathogens including CMV, EBV, herpes simplex virus (HSV), adenovirus, and influenza viruses. Advances in viral monitorization, prophylaxis, and preemptive therapy have significantly decreased morbidity associated with EBV, CMV. EBV/CMV prophylaxis includes a 2-week course of intravenous ganciclovir with concomitant administration of cytomegalovirus-specific hyperimmune globulin (Cytogam).

Nutritional Support

Standard TPN is administered routinely in the postoperative period; however, tapering is aggressively performed as enteral feeding is advanced. Selection of feeding formula usually follows an initial use of isotonic solutions and are changed based on age group and clinical assessment of intestinal allograft function. Because many intestinal failure patients have an oral aversion, tube feeding is usually required.

Assessment of the Intestinal Allograft

Endoscopic evaluations are performed are performed regularly and when clinically indicated based on changes in stomal output or aspect of the allograft stoma itself such as edema, cyanosis, or congestion. These changes, however, are not specific to rejection and may reflect infection or dysfunction of the graft (absorption or motility).

Management of Allograft Rejection

Acute cellular rejection has been previously reported in 70–90% of intestinal allograft recipients; however, recent improvements in immunosuppressive strategy have resulted in reduction of rejection rates to 30–40%.

Endoscopic evaluation may demonstrate normal mucosa despite histologic mild to moderate grades of acute cellular rejection; moderate to severe rejection of the intestinal allograft is reflected in mucosal inflammation with erythema and friability, and may progress to sloughing of the mucosa with the formation of ulcers. Histologically, mononuclear cell infiltrates and intestinal crypt apoptosis with regeneration are the hallmark signs of intestinal allograft rejection that establish the diagnosis.

Treatment of acute cellular rejection is based on intravenous steroids and optimization of Tacrolimus levels. Antilymphocyte antibodies for steroid-resistant rejection includes anti-thymocyte globulin (rATG, rabbit-derived, Thymoglobulin). Addition of a third agent such as mycophenolate mofetil (MMF, CellCept, Roche) or sirolimus (Rapamune) may be indicated if rejection is refractory or recurrent.

Chronic rejection has been observed in 10–15% of intestinal allografts, and occurs more commonly in

isolated intestinal transplantation. The most common clinical presentation of chronic rejection is graft dysfunction with dysmotility and also structural changes of strictures and dilations, with intestinal allograft obstruction and gastrointestinal bleeding. The histologic changes are nonspecific and characterized by villous blunting, focal ulcerations, epithelial metaplasia, and scant cellular infiltrates on endoscopic mucosal biopsies; full-thickness samples will demonstrate obliterative thickening of intestinal arterioles.

Posttransplant Lymphoproliferative Disorder

Posttransplant infection with EBV may result in a spectrum of diseases from mononucleosis syndromes and plasma cell hyperplasia to neoplastic PTLD (lymphoma). Significant risk factors include the type of induction/immunosuppressive regimen used and EBV serology status prior to transplant. The historically high incidence of rejection with intestinal transplantation warranted higher levels of immunosuppression in this recipient population; however, the complications of infection, toxicity, and PTLD made this strategy untenable for long-term success. The monitoring of EBV viral load in the peripheral blood allowed for early detection and management of EBV; however, it was with the present strategy of antilymphocyte antibody induction and minimization of Tacrolimus levels that there has been a true decrease in the incidence of acute rejection/need to treat rejection, with improvement in the incidence of EBV disease.

Treatment of PTLD involves minimization of immunosuppression, and possible discontinuation. Unresponsiveness to this strategy may warrant treatment with a monoclonal antibody (rituximab) if the lesions are shown to be CD20 positive. PTLD refractory to this may require low-dose cytotoxic chemotherapy.

Graft-Versus-Host Disease

Graft-versus-host disease (GVHD) results from immunocompetent donor T cells causing attacking recipient tissues after transplantation, the incidence after intestinal transplantation ranging from 5% to 10%. Major targets of GVHD are epithelial cells of skin, intestine, and liver. Clinical presentation may include fever, rash on the upper torso, neck, or palms of hands and feet, and which may evolve to form blisters or more diffuse erythema. Other signs and symptoms include oral lesions, diarrhea, native intestinal ulceration, native liver dysfunction, and peripeheral lymphadenopathy, and bone marrow suppression with pancytopenia.

The diagnosis of GVHD is based on the clinical presentation and histological confirmation. Corticosteroids are the first-line therapy to control epithelial damage caused by GVHD, and are effective in most cases. Concomitant with this, reduction of calcineurin-based immunosuppression may be necessary and desirable.

Outcomes

Patient and Graft Survival

Over the last decade, significant improvement in early and late patient and graft survival has been achieved, with 1-year patient and graft survival reaching 89.3% and 78.9% for intestine-only recipients and 71.5% and 69.0% for liver-intestine recipients, survivals comparable to those following pancreas, lung, and liver transplantation. Contributing factors to this include the increasing experience with this patient population, and advances in immunosuppressive management.

Summary

Improvements in outcomes after intestinal transplantation have been achieved through advances in multidisciplinary care of intestinal failure, surgical technique, innovative immunosuppressive strategies, and an improved understanding of intestinal transplantation immunology. These accomplishments, however, are overshadowed by the still high waiting list mortality, particularly for infants and adults who have concomitant liver failure. Long-term data on nutritional and functional outcomes and quality of life are necessary to further assess the role of intestinal transplantation in patients with intestinal failure.

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198 The Pancreas

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The pancreas is an elongated retroperitoneal gland in the upper abdomen that has both an exocrine and an endocrine component. The pancreas is divided into three parts: the head, the body, and the tail. The head lies in the C-shaped region of the duodenum, while the body and tail extend from the C-loop of the duodenum across the midline of the body toward the spleen. Pancreatic secretion empties through the pancreatic duct which merges with the common bile ducts into the duodenum via the ampulla of Vater.

In this chapter, the embryology, histology, ultrastructure, and development of the functions of the pancreas have been reviewed. In addition, the physiology of the pancreas, congenital diseases of the exocrine pancreas, and the evaluation of pancreatic function will be discussed. A detailed review of acute and chronic pancreatitis will also be provided.

Embryology

By the fifth week of gestation, the pancreas arises as two outpouchings from the junction of the foregut and midgut. The large dorsal bud enlarges rapidly and contributes to most of the pancreas. The small ventral bud contributes to the uncinate process and the inferior part of the head of the pancreas. The ventral bud, connected to the bile duct, rotates with the duodenum and fuses with the dorsal bud. By the seventh week of gestation, as the two buds join, the ventral duct fuses with the dorsal duct to form the main pancreatic duct (duct of Wirsung). This duct communicates with the common bile duct before entering the duodenum via the ampulla of Vater. The proximal portion of the dorsal duct forms the accessory duct of Santorini, which opens separately above the main papilla. Developmental deviation from these steps may result in clinically significant anomalies as will be discussed later. The pancreatic acini and the islets of Langerhans start developing during the third month of gestation.

Histology and Ultrastructure

The pancreas is composed of the exocrine system involved in digestion, and the endocrine system involved in secretion of hormones such as insulin and glucagon. Histologically, the exocrine system consists of lobules composed of numerous acini lined with epithelial cells which contain zymogen granules. Each acinar gland is drained by a small ductule connected to larger ducts which in turn connect to the major pancreatic duct. The zymogen granules are secretory vesicles that release trypsinogen, chymotrypsinogen, procarboxypeptidase, amylase, and lipase for the purpose of food digestion.

The endocrine system consists of the islets of Langerhans, which are interspersed among the acinar glands. Three major cell types are recognized in these islets: Alpha cells produce glucagon, β-cells produce insulin, and γ-cells produce somatostatin.

Physiology of the Pancreas

The acinar cells secrete the enzymes responsible for the degradation of food, while the epithelial cells lining the pancreatic ducts secrete fluid and bicarbonate that render the duodenal lumen pH alkaline. This provides the optimal milieu for enzymatic activity.

Pancreatic exocrine secretions are under neural and hormonal control. The neural phase is mediated by vagal stimulation and results in the mobilization of enzymes from the acinar cells to the ducts. The hormonal phase is triggered by the passage of the acidic gastric contents into the duodenal lumen and results in the release of secretin from the duodenal mucosa. Secretin stimulates the secretion of bicarbonate and fluids. The hydrolytic products of proteins and fat stimulate the release of cholecystokinin (pancreozymin), bombesin, and neurotensin. These, in turn, stimulate the release of the pancreatic enzymes trypsinogen, chymotrypsinogen, procarboxypeptidase, amylase, colipase, and lipase.

The proteolytic enzymes (trypsinogen, chymotrypsinogen, and procarboxypeptidase) are released in their inactive form in order to protect the pancreas from autodigestion. Enterokinase, an intestinal brush border endopeptidase, activates trypsinogen to trypsin. Trypsin, in turn, activates chymotrypsinogen to chymotrypsin and procarboxypeptidase to carboxypeptidase. These

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pancreatic enzymes are thus activated in the intestine where the digestive process takes place. Endopeptidases (trypsin, chymotrypsin, and elastase) cleave internal bonds within protein chains. Exopeptidases (carboxypeptidase A and B) cleave the bond adjacent to either the amino or carboxyl terminus. Pancreatic lipase is the principal enzyme needed for the hydrolysis of dietary triglycerides. Colipase is a pancreatic enzyme required to prevent the inactivation of lipase by bile salts. Amylase functions to hydrolyze starches into glucose oligomers and α-limit dextrins.

Development of Pancreatic Function

Studies in human fetuses have shown that zymogen granules are first detectable at a fetal length of 14 cm. The number and electron density of these zymogen granules increase as the fetus grows in length. Enzyme measurement of trypsin, chymotrypsin, lipase, and phospholipase are detected at about the same length, increasing slowly until the fetus reaches 40 cm in length. This is followed by a dramatic increase in enzyme activity. Amylase is absent in all fetuses.

In human infants between the ages of 1 day and 1 month, considerable amounts of proteases are found in duodenal fluids. The activity of carboxypeptidase B represents 10–25%, chymotrypsin 50–60%, and trypsin about 90–100%, respectively, of the activity levels found in children at the age of 2 years and older. Basal concentrations of lipase are barely detectable, and those of amylase are totally absent. Moreover, newborns are not responsive to pancreaozymin stimulation at 1 month of age, with only a minimal increase in the output of chymotrypsin. Similarly, the response to secretin stimulation is minimal. A pronounced response is not seen until 2 years of age for both pancreozymin and secretin.

These findings clearly indicate that the infant's digestive capacity of fat and starch are less mature than those for proteins. Although lingual and breast milk lipase may compensate for the low levels of pancreatic lipase, low pancreatic-lipase levels may explain some of the transient malabsorption reported in infancy.

Anomalies of the Pancreas

Pancreas Divisum

Typically, anomalies of the pancreas represent failure of rotation or fusion, or both. Pancreas divisum results from the failure of the ventral and dorsal pancreas to fuse, resulting in separate drainage systems for each bud. As a result, the majority of the exocrine pancreatic flow arising from the dorsal bud is drained by the smaller accessory duct of Santorini and the smaller accessory papilla. This is felt to represent an area of relative stenosis, potentially explaining the association of this anomaly with chronic pancreatitis in some clinical series. Other series, however, have failed to demonstrate a similar association.

In the clinical setting of recurrent pancreatitis, endoscopic and surgical approaches have been used for treatment of this anomaly, including sphincterotomy, stent placement, and pancreaticoduodenectomy. Pancreas divisum detected incidentally in the absence of pancreatitis should be treated expectantly.

Annular Pancreas

Annular pancreas results from a histologically normal pancreas partly or completely encircling the second part of the duodenum distal to the ampulla of Vater. The formation of the annulus is believed to result from the failure of the tip of the ventral pancreas to rotate completely to the right and posteriorly with the duodenum.

Annular pancreas is frequently associated with Down's syndrome, intestinal malrotation, tracheoesophageal fistulas, and congenital heart disease, especially tetralogy of Fallot.

In patients with a complete annular pancreas resulting in duodenal obstruction, presentation is usually in early infancy with bilious vomiting, abdominal distention, and a double bubble sign on plain abdominal films representing duodenal obstruction. If the annulus is incomplete, the patient may be asymptomatic or present later in life with intermittent abdominal pain or discomfort, epigastric fullness, nausea, and vomiting. Rarely, the annulus may compress the common bile duct or the pancreatic duct causing jaundice and/or pancreatitis.

In complete obstruction and in symptomatic patients, surgical intervention with a duodenostomy or duodenojejunostomy is the therapeutic procedures of choice.

Ectopic Pancreas

This is a relatively common developmental anomaly with an estimated incidence of 15%. The ectopic pancreas is found most commonly in the prepyloric region of the stomach, duodenum, and jejunum.

The composition of the ectopic pancreas is variable. It may show normal pancreatic tissue with acini, islets, and ducts, or it may be rudimentary, consisting only of a few ducts and acini. At endoscopy, the ectopic pancreas appears as a firm yellow nodule 0.5–4 cm in diameter with an umblicated center.

Most patients are asymptomatic. However, it has been postulated that ectopic secretions may produce inflammation, spasm in the gut, and pain. Hemorrhagic ulceration and pyloric obstruction have been reported. The nodules may also act as a lead point for intussuscetion. In symptomatic patients, treatment is with simple surgical excision.

Evaluation of Pancreatic Function and Pancreatic Disease

Despite the large array of available tests for evaluating pancreatic function, the definitive diagnosis of pancreatic disorders is often difficult. This is particularly so because the pancreas has significant functional reserves. For example, it is estimated that loss of 99% of lipase and colipase activity is required before steatorrhea is observed. More sensitive tests are required to detect impairment, resulting in less than 98% loss of enzyme secretory capacity. It is therefore important to appreciate the capabilities and limitations of available tests.

Tests for Pancreatic Insufficiency

Stool examination for fat: A simple screening test for the presence of pancreatic insufficiency is examination of a stool smear, preferably stained with Sudan III, under a light microscope. This allows detection of undigested and neutral fat. This test is not reliable in mild steatorrhea. However, it serves as a crude test to identify patients who may need more accurate quantification of fat stool losses.

72-four stool fat: The 72-h stool fat quantification represents a very reliable diagnostic test for steatorrhea. The pediatric patient is instructed to take at least 3 g/kg/day of dietary fat. Intake is documented and stools are collected over a 72-h period. Stool fat is then extracted. Excretion of more than 10% of ingested fat is abnormal in children older than 6 months, while excretion of more than 15% would be abnormal in infants less than 6 months of age.

Oral tolerance tests: This test consists of giving individuals a standard amount of fat (50 g), then measuring their serum triglycerides and chylomicron levels at different time points (0, 2, 3, 5 h). Values are then compared to controls. To determine if an abnormality is a result of pancreatic disease, the test is repeated after the enteral administration of pancreatic enzymes.

Steatocrit: This novel concept of measuring stool fat has recently been proposed and requires further substantiation. In this test, a homogenized sample of stool is centrifuged at 15,000 rpm for 15 min in a hematocrit tube. Lipids separate to the top and are quantitated in a fashion similar to a hematocrit.

Measurement of trypsin and chymotrypsin activity in stool: Measurements of trypsin and chymotrypsin activity in stool are widely used to evaluate pancreatic exocrine function. A recently introduced photometric assay for chymotrypsin has improved the reliability of this method, with measurements correlating well with data for chymotrypsin from stimulated duodenal output. However, the sensitivity of this test is affected by bacterial proteases that may lead to the breakdown of trypsin and to a lesser extent, chymotrypsin.

Bentiromide: Bentiromide is a nonabsorbable synthetic peptide, which is cleaved in the upper small intestine by chymotrypsin to yield the rapidly absorbable compound, para-aminobenzoic acid (PABA). Assuming intestinal mucosal integrity, serum PABA levels would then reflect pancreatic exocrine function. Urine PABA levels can also be measured but rely on normal hepatic, renal, and intestinal function. Different modifications on this test have been introduced to improve its sensitivity.

Fluorescein dilaurate test: The principal behind this test is similar to that of Bentiromide. Fluorescein dilaurate is orally administered and is then subject to hydrolysis by pancreatic cholesterol ester hydrolase to yield water soluble Fluorescein. Fluorescein is rapidly absorbed by the intestine, conjugated in the liver and excreted by the kidney as Fluorescein diglucoronide. Either urine collected over a 10-h period or a serum sample collected at 4–5 h is assayed for Fluorescein diglucoronide. These levels would then indirectly reflect pancreatic exocrine function. Different modifications of this test have been introduced to improve its sensitivity and to eliminate any possible effects of the intestine, liver, and kidney on this assay.

Isotope-labeled breath test: The use of stable isotopes to label ingested triglycerides is gaining momentum. In this test, triglycerides are radiolabeled with ^{13}C, and labeled CO_2 excreted in breath is then measured. The appearance of ^{13}C in the breath is reflective of intraluminal digestion of lipids. This test may eventually be used as a screening test for steatorrhea to replace the 72-h fecal fat test. Specificity for pancreatic disease may be improved by

repeating the assay after enteral administration of pancreatic enzymes.

Measurement of serum pancreatic enzymes: Serum pancreatic enzyme determinations can be specific tests for pancreatic insufficiency in the absence of acute pancreatitis, ductal obstruction, or renal insufficiency. Serum determinations for amylase and lipase are unreliable during early infancy because these enzymes do not reach mature levels until 3–6 months of age. Trypsinogen is the serum pancreatic enzyme of choice for pancreatic exocrine function testing.

Pancreatic stimulation tests: The tests discussed thus far are only able to detect severe cases of exocrine pancreatic insufficiency, where the pancreas has little functional reserve. Assessment of pancreatic reserve in patients without overt malabsorption is achieved through direct stimulation tests. These techniques are valuable in determining pancreatic function in those patients with greater than 2% functional residual capacity. Here the pancreas is stimulated pharmacologically or nutritionally, and pancreatic secretions are collected and analyzed for output of ions, water, and enzymes. This technique involves intubating the duodenum with a double lumen tube. After the collection of baseline duodenal fluids, secretin and panceozymin are infused intravenously, followed by the collection of duodenal fluids at specific intervals. The fluid volume, fluid pH, and HCO_3 and electrolyte concentrations are determined. The fluid is also assayed for activity of trypsin, lipase, and colipase.

Nutrient stimulation tests: This test follows the same principal as pharmacologic tests but utilizes physiologic stimulation of the pancreas via the intraluminal infusion of nutrients. These tests have several disadvantages, including contamination by gastric secretions, and interference of nutrient substances with accurate enzymatic determinations.

Biochemical Tests for Pancreatitis

Serum amylase: Measuring serum amylase level is one of the most commonly used biochemical tests in the diagnosis of pancreatitis. Serum amylase levels increase within 3 h of pancreatic inflammation and may persist for 2–4 days. There is no correlation between the degree of serum elevation of amylase, or other pancreatic enzymes, and the severity of pancreatitis. However, hyperamylasemia may be in association with impaired renal function, in patients with perforated gastric or duodenal ulcers, postabdominal surgery, alcohol poisoning, pancreatic duct obstruction, and salivary-glands inflammation. On the other hand, normal amylase level may be seen in 20% of patients with acute pancreatitis.

The measurement of serum pancreatic isoamylase in the diagnosis of pancreatitis is a more useful test as it may help delineate the source of amylase.

Traditionally, measurement of urinary amylase clearance has been advocated because renal tubular reabsorption of amylase is decreased in pancreatitis. However, it does not provide any advantage over measurement of total serum amylase, except in the setting of macroamylasemia, which is a benign condition seen in 1% of healthy individuals. In the latter condition, serum amylase is conjugated with IgM and, therefore, cannot be excreted through the kidney. Urine amylase clearance would be normal in macroamylasemia.

Serum lipase: Increased serum lipase level is more specific for acute pancreatitis than serum amylase, and the specificity increases when the serum level increases by threefold. Similar to amylase, lipase can come from different sources such as lingual, gastric and breast milk. However, studies in animals have shown that serum lipase is mainly pancreatic in origin. The reabsorbtion of cleared lipase by kidney tubules may keep serum levels elevated as long as 14 days. There is no other source for serum lipase, except the pancreas.

Serum cationic trypsinogen: Serum cationic trypsinogen has been used as a sensitive diagnostic screening test, especially in newborns. Infants with cystic fibrosis usually have manifold elevation in serum trypsinogen level. These values usually decline during the first 7 years in patients with pancreatic insufficiency.

Other tests: Several other tests have been evaluated for the diagnosis of acute pancreatitis. However, none has been proven superior to amylase and lipase. In adults, several tests have shown to be useful in predicting severity, including C-reactive protein, phospholipase A, interlukin 6, SPINK-1, Trypsinogen activator Peptide (TAP), and TNF α receptor. Trypsinogen 2 has been shown to be useful in diagnosing pancreatitis secondary to ERCP.

Radiological Evaluation of the Pancreas

Plain radiography: Plain abdominal films in chronic pancreatitis may show calcification of the pancreas. In acute pancreatitis, radiographs may show generalized ileus or a localized "sentinel loop," which is a loop of dilated jejunum in the midepigastrium or left upper quadrant adjacent to the pancreas. Radiographs may show the "colon cut-off sign" which represents distention of the transverse colon with collapse of the descending colon.

Barium studies: Barium studies of the gastrointestinal tract may show esophageal varices due to splenic vein thrombosis and portal hypertension. An extrinsic mass effect on the stomach and duodenum from an inflamed and swollen pancreas or from a pseudocyst can be seen in some patients. Duodenal loop changes consisting of mucosal edema, distention, and air-fluid levels are frequently seen. Other signs include inverted "3" sign (Frostberg sign) which can be seen in the middle of the duodenum with the middle apex of the "3" representing the origin of the pancreatic duct and curves resulting from the swollen pancreatic head. Another sign is the Poppel sign, defining widening of the duodenal loop with prominent duodenal mucosal folds and the sphincter of Oddi.

Ultrasonography: Abdominal ultrasonograms provide good visualization of the pancreas as well as associated organs such as the hepatobiliary system. In acute pancreatitis, ultrasonography may reveal increase in the size and/or reduced echogenicity of the pancreas compared with that of the liver. Other findings may poorly define borders, dilated pancreatic ducts, and pseudocyst. Ultrasonography has several advantages such as simplicity, lack of radiation, and wide availability. Drainage of pseudocysts can be also done with ultrasonography guidance. Disadvantages of ultrasonography include poor imaging due to overlying gas obscuring the pancreas and the fact that it is operator-dependent. In chronic pancreatitis, in addition to the findings seen in acute conditions, ductal dilatation and accentuated echoes due to calcification are frequently observed. Ultrasonography is also a very useful tool in detecting and following up on pseudocysts.

Computerized tomography: Computerized axial tomography (CT scans) can detect calcification and calculi not evident by other radiologic modalities. Findings on CT scans include diffuse enlargement in patients with acute pancreatitis, hemorrhagic necrosis, and traumatic damage. It can also distinguish between pseudocysts and phlegmons. Therefore, when an ultrasound is inconclusive, CT scans could contribute to the diagnostic evaluation of pancreatic disorders and their complications. The drawback of the use of CT in children with pancreatitis is the need for sedation. A normal CT does not rule pancreatitis as 20% of patients with acute pancreatitis have normal CT.

Magnetic resonance cholangiopancreatography (MRCP): Advances in magnetic resonance technology has allowed the development of MRCP which is an excellent modality for obtaining images of the pancreaticobiliary tree. This imaging technique poses several advantages, including lack of radiation and lower complication rate compared to ERCP. The main disadvantage is poor ability to diagnose peripheral biliary tree in children. Most centers, including ours, have been relying on this imaging modality to diagnose structural abnormalities of the pancreaticobiliary tree in children. The use of MRCP has replaced ERCP as a diagnostic modality limiting the use of ERCP in cases in which MRCP has been inconclusive or when therapeutic intervention is needed, such as stone removal, or when papilotomy or stent placement are needed.

Endoscopic retrograde cholangiopancreaticography (ERCP): This technique involves endoscopic intubation of the pancreatic and biliary ducts. Despite the lack of experience in performing ERCP in children, it may provide very valuable information in patients with chronic pancreatitis. It allows identification of partial or complete obstruction of the intrapancreatic portion of the common bile duct. It also detects areas of narrowing, dilation, and tortuosity, or the presence of intraductal stones. Pancreas divisum can also be identified. Other diagnostic evaluations include measurement of sphincteric and ductal pressures. Therapeutic interventions such as dilatation and sphincterroplasty can also be performed in addition to stone removal and pseudocyst drainage. ERCP can also provide guidance prior to surgical intervention. However, the procedure is technically difficult in small children. Complications of ERCP are not different from those in adults and include pancreatitis, pain-requiring analgesia, perforation, ileus, and fever.

Congenital Diseases of the Exocrine Pancreas

Shwachman–Diamond Syndrome

Shwachman–Diamond Syndrome (SDS) is an autosomal recessive disorder characterized by pancreatic exocrine dysfunction, bone marrow failure, skeletal abnormalities, and leukemia predisposition. Mutations in Shwachman–Bodian–Diamond Syndrome (SBDS) gene located on chromosome 7 account for 90% of patients. The gene product is a protein likely involved in accelerated apoptosis.

The hallmark of this disease is the association of exocrine pancreatic insufficiency, bone marrow hypoplasia, and bony changes. Several other features have been also reported (*Table 198.1*).

Exocrine Pancreatic Insufficiency

Most patients present with steatorrhea in the first year of life. However, residual pancreatic function may allow

Table 198.1
Feature of Shwachman–Diamond Syndrome

Exocrine pancreatic insufficiency	Recurrent infections
Short stature	Renal tubular defects
Bone marrow hypoplasia	Fatty liver
Skeletal abnormalities	Dental effects
Hirschsprung disease	Ichthyosis
Impaired neutrophil functions	Diabetes mellitus
Endocardial fibrosis	

some patients to go unnoticed for several years. Exocrine function is abnormal with lipase being more severely depressed than other enzymes.

The pancreas appears grossly lipomatous. Histologically, the acinar glands are scarce or absent and are replaced entirely by fatty tissue. The islets of Langerhans appear intact.

Bone Marrow Hypoplasia

Bone marrow abnormalities may occur in one or all three blood lines. Neutropenia can be recognized in up to 95% of the patients, thrombocytopenia in 70%, and anemia in 50%. Neutropenia is usually cyclic with some patients mounting leucocytosis in response to infection. In vitro studies show impaired neutrophil mobility and chemotaxis. Bone marrow aspirates reveal hypocellularity and maturational arrest. Otitis media, sinusitis, osteomyelitis, and skin infections may be seen. However, overwhelming sepsis is usually the leading cause of death in this disorder.

Skeletal Abnormalities

Metaphyseal dysostosis in the femur, tibia, and ribs is recognized in about 10–15% of patients. The hip is the most frequently affected site thus adversely affecting the child's gait. The pathogenesis of these bony lesions is poorly understood. Spontaneous and complete resolution of these lesions after puberty has been reported in some patients. Early features include thoracic dystrophy manifesting as short ribs with flared anterior end "cup deformities" which may result in narrowing of the thoracic cage, causing respiratory distress. Clinodactly of the fifth finger is a frequent finding seen in up to 50% of affected individuals. However, the most frequent radiologic abnormality is delayed bone age.

Growth Retardation

Growth retardation is characteristic of this disease. While pancreatic enzyme replacement may improve weight gain, linear growth is usually not ameliorated. The severity of skeletal abnormalities also does not correlate with the retardation of height. Intrauterine growth retardation may occur, but in most patients, growth retardation manifests in the first year of life.

Diagnosis

SDS should be considered in any patient with malabsorbtion, hematologic or skeletal abnormalities, and negative sweat chloride test. Evaluation of pancreatic function by the pancreozymin-secretin stimulation test is the most sensitive test in evaluating pancreatic function. Patients with SDS characteristically show normal or slightly low bicarbonate levels with depressed or absent pancreatic enzymes. Blood counts reveal variable neutropenia, thrombocytopenia, and anemia. Bone marrow aspiration may show hypocellularity. Abdominal ultrasonography may reveal normal pancreatic size with fatty tissue infiltration. Bony films show the characteristic of metaphyseal dysostosis.

Treatment

Pancreatic enzyme replacement is usually effective in controlling steatorrhea and improving weight gain. However, it rarely influences linear growth. Pancreatic enzyme supplementation may be eventually discontinued because most patients achieve normal fat absorption with age. Fat-soluble vitamins supplementation is usually recommended. Patients with neutropenia require no treatment when asymptomatic. However, these patients should be treated

as immunosuppressed individuals when presenting with fever, and appropriate antibiotic therapy and cultures are indicated. Cyclosporin A has been found to be efficacious in treating aplastic anemia associated with this disorder.

Johanson–Blizzard Syndrome

Johanson–blizzard syndrome is an extremely rare ectodermal dysplastic disorder characterized by microcephaly, aplasia or hypoplasia of alae nasi, midline scalp defects, abnormal hair pattern, absence of permanent teeth, growth retardation, mental retardation, hypothyroidism, exocrine pancreatic insufficiency, Café au lait spots, genitourinary anomalies, congenital heart defects, thyroid dysfunction, imperforate or anteriorly displaced anus, and congenital deafness. This condition results from an autosomal recessive disorder. The molecular basis of this disorder has been recently defined as mutations in the ubiquitin protein ligase E3 component n-recogenin1 gene (UBRI) located on chromosome 15q.

Isolated Enzyme Deficiencies

Enterokinase deficiency: Enterokinase, an enzyme secreted by duodenal mucosa, is responsible for activating trypsinogen to trypsin. Accordingly, enterokinase deficiency results in trypsin, chymotrypsin, and procarboxypeptidase deficiency. Patients present early in life with diarrhea, anemia, hypoproteinemia, and failure to thrive.

Treatment with exogenous enterokinase is highly effective in controlling symptoms and improving growth.

Trypsinogen deficiency: Trypsinogen is activated by intestinal enterokinase into trypsin, which in turn activates chymotrypsinogen and procarboxypeptidase into their active form. Therefore, trypsinogen deficiency results in protein malabsorption. The clinical manifestations of this disease are indistinguishable from enterokinase deficiency. Treatment requires pancreatic enzyme replacement and providing formulas composed of protein hydrolysate.

Lipase and colipase deficiency: Lipase and its cofactor, colipase deficiencies are rare but well-recognized causes of steatorrhea and failure to thrive. Treatment with pancreatic enzymes and a low fat diet are effective means of controlling symptoms.

Acute Pancreatitis in Childhood

Acute pancreatitis refers to acute pancreatic inflammation with return of pancreatic morphology and function to normal between attacks. Hemorrhagic or necrotizing pancreatitis refer to severe disease with extensive pancreatic necrosis associated with life-threatening systemic manifestations.

Previously considered to be uncommon in the pediatric age group, acute pancreatitis has been recognized more frequently in recent years. The disease carries with it a high rate of morbidity and mortality. The disorder should be considered in children with abdominal pain and elevated pancreatic enzymes. Lack of awareness and a delay in diagnosis may contribute to these high rates. It is therefore essential to keep a high index of suspicion to allow the early diagnosis and management of acute pancreatitis.

Etiology

While alcoholism and biliary tract disease are the most common causes of pancreatitis in adults, drugs, abdominal trauma, and multisystem disease are recognized to be the major offenders in children. *Table 198.2* depicts the major causes of pancreatitis in childhood.

Trauma could be blunt, penetrating, or postsurgical. Some children may present immediately after the trauma with abdominal pain and vomiting, but in most cases, the presentation is delayed days to weeks, which makes the causal relationship between the trauma and pancreatitis uncertain. Child abuse is increasingly recognized as a cause of pancreatitis in toddlers and infants.

Many drugs are known to induce pancreatitis in all age groups. Corticosteroid-induced pancreatitis is known to be associated with a high mortality rate, probably related to the underlying disease process for which the steroids were given. Valporic acid has been strongly linked to acute pancreatitis, although the process is reversible upon withdrawal of the drug. With aggressive therapies that increase survival of children with malignancies, an increasing number of cases of pancreatitis induced by chemotherapeutic agents have been recognized.

Although mumps virus is the most frequent viral infection thought to be responsible for pancreatitis, several other viruses have been recently recognized as causative agents. These include coxsackie B_5 virus, EB virus, adenovirus, reovirus, and Hepatitis A and Hepatitis B viruses. Most viral-induced pancreatitis are of the interstitial variety that usually run a milder course than hemorrhagic pancreatitis.

Several metabolic disorders have been associated with acute pancreatitis, including hyperlipoproteinemia type I, IV, and V, hyperparathyroidism, diabetes mellitus, and cystic fibrosis. Recently, refeeding pancreatitis in

Table 198.2
Causes of acute pancreatitis in children

1. *Trauma* – blunt or penetrating
2. *Drugs and toxins* (a) *Anti-inflammatory agents*: Corticosteroids, salicyclates, and indomethacin (b) *Chemotherapeutic agents*: L-Asparaginase, 6-mercaptopurine, and azathioprine (Imuran) (c) *Diuretics*: Furosemide, chlorothiazides, and ethycrynic acids (d) *Anticonvulsants*: Valporic acid and dilantin (e) *Antibiotics*: Tetracycline and sulphonamide (f) *Anticoagulants* (g) *Alcohol* (h) *Venom of Scorpions* (i) *Organophosphates*
3. *Infection* – Mumps, rubella, hepatitis A and B, coxsacki B, mycoplasma pneumonia, and bacterial sepsis
4. *Parasites* – Ascaris and hydatid cysts
5. *Anatomic anomalies* – Choledochal cyst, annular pancreas, anomalous insertion of common bile duct, pancreas divisum, and stenosis of ampulla of vater
6. *Metabolic and nutritional disorders* – Hypercalcemia, hyperlipoproteinemia Type 1, IV & V, Diabetes mellitus, cystic fibrosis, high concentrations of intralipids, and refeeding of malnourished children
7. *Vascular diseases* – Systemic lupus erythematosis, hemolytic uremic syndrome, and Henoch–Schönlein purpura
8. *Biliary diseases* – Gall stones, choledochal cyst, and biliary tree anamolies
9. *Hereditary*
10. *Shock*
11. *Idiopathic* (25%)

malnourished children and pancreatitis associated with high concentrations of lipid emulsions have been recognized with increasing frequency. Patients with 3-hydroxy-3 methyl glutaryl-coenzyme A lyase (HMG-CoA lyase) deficiency who present with recurrent pancreatitis are successfully managed with a low leucine diet. Patients with HMG-CoA lyase deficiency usually present with a clinical picture indistinguishable from Reye's syndrome, which has also been shown to be associated with pancreatitis.

Anatomic malformations are frequently encountered in patients with recurrent, relapsing pancreatitis. One common example is stenosis of the ampulla of Vater, which is amenable to sphincteroplasty in most cases. Other conditions include an annular pancreas, choledochal cysts, and anomalous insertions of the common bile duct.

Biliary disorders as a cause of pancreatitis are encountered much less frequently in children than in adults. However, a high index of suspicion is essential in high-risk groups, such as patients with hemolytic anemia who are susceptible to cholelithiasis and subsequent pancreatitis.

Pathophysiology

As mentioned earlier, pancreatitis has a variable etiology. However, the fundamental event that leads to the pathology in pancreatitis is the activation of pancreatic zymogen and initiation of enzymatic autodigestion of the pancreas. The mechanism by which these zymogens are activated within the pancreas is as yet not completely clear.

Studies in experimental animals have shown that the retrograde injection of activated proteolytic enzymes (trypsin, chymotrypsin, and elastase) in small amounts results in interstitial edema and, in larger doses, leads to extensive vascular damage, edema, and hemorrhage. Kallikrein, also activated by trypsin, liberates bradykinin and kallidin, both of which induce vasodilation and increase vascular permeability, ultimately leading to hypotension.

Phospholipase A contributes to the pathogenesis of pancreatitis in several ways. Studies in rats have shown that the injection of phospholipase A into the pancreatic duct results in severe pancreatic parenchymal necrosis indistinguishable from that seen in human pancreatitis. The lecithin of pulmonary surfactant can be a target for phospholipase A and may contribute to the adult-type acute respiratory distress syndrome encountered in severe cases of acute pancreatitis. Phospholipase A can also release histamine from mast cells and potentiate the refractory hypotension seen in acute pancreatitis.

Lipase, which is present in the pancreas in the active form, results in parapancreatic and peritoneal fat necrosis when released from the pancreas. Circulating lipase may lead to fat necrosis in skin, bone, and joints. Medullary fat necrosis may result in pulmonary or cerebral fat embolization with a catastrophic outcome.

Refractory hypotension and respiratory failure are the leading causes of death in severe pancreatitis.

Many factors may contribute to the hypotension, sometimes seen in acute pancreatitis. Recognized entities include the acute loss of plasma and blood into the peritoneum caused by disruption of the blood vessel integrity and by increased permeability and vasodilatation, resulting from kallikrein and histamine release.

Respiratory compromise ranges from mild hypoxia to full blown respiratory distress syndrome. Many factors are implicated in its pathogenesis, including pleural effusions, fat embolization, pseudocyst formation, and surfactant destruction by phospholipase A.

Hypocalcemia seen in acute pancreatitis is thought to result from the binding of calcium with fatty acids in the areas of fat necrosis.

Clinical Manifestations

Abdominal pain, nausea, and vomiting are the most common presenting symptoms of acute pancreatitis. Abdominal pain is usually constant and severe but may be mild and intermittent. Pain is usually localized to the epigastric region and may spread to the back, although some children may localize the pain to the periumbilical region or the right upper quadrant. The pain is aggravated by oral intake and not relieved by vomiting. The child may lie on his or her side and assume the knee-chest position. Other symptoms may include anorexia, nausea, and vomiting which may be bilious.

The physical exam may reveal a low-grade fever, tachycardia, and hypotension. The patient may be dyspneic with decreased breath sounds due to the presence of a pleural effusion. The abdomen is usually tender with some guarding, especially in the epigastric region. Bowel sounds may be normal, hypoactive, or completely absent in patients with advanced paralytic ileus. Subcutaneous fat necrosis may result in bluish discoloration of the skin in the flanks (Turner's sign) and the periumbilical area (Cullen's sign). Other manifestations include hematemesis, melena, abdominal mass, and coma.

Diagnosis and Laboratory Data

The diagnosis of acute pancreatitis rests on compilation of clinical features, laboratory findings, and imaging techniques. Careful medical history is mandatory with special emphasis on family history and history of trauma in order to define the cause of pancreatitis.

Pancreatic enzyme levels: The most common laboratory changes are elevated serum lipase, amylase, and trypsin levels, as well as an elevated renal amylase/creatinine clearance ratio (above 4 is abnormal). Keeping in mind the several clinical entities that may result in similar chemical derangements and correlating these data with the clinical findings and radiological studies is the correct approach to reaching an early diagnosis of this catastrophic disease. Although measuring serum lipase level is the most commonly used test in the diagnosis of pancreatitis, 35% of cases of acute pancreatitis may be missed if serum amylase is the only test done.

Hypocalcemia: Hypocalcemia is usually seen in severe cases of acute pancreatitis and correlates with a poor prognosis.

Hyperglycemia: Hyperglycemia is frequently encountered in acute pancreatitis. This complication is believed to result from an insult to β cells in the islets of Langerhans. However, plasma cortisolglucagon and growth hormone may also play a role. Glucose intolerance is usually transient; however, lifelong diabetes mellitus has resulted from viral infections of the pancreas, especially mumps and coxsackie virus.

Hyperlipidemia: Hyperlipidemia not only induces pancreatitis but may also result from the metabolic derangements induced by acute pancreatitis.

Hypoalbuminemia: Hypolbuminemia may be seen in patients with acute pancreatitis as albumin is an acute phase reactant and may be also seen secondary to expansion of the intravascular compartment with fluids.

Hematologic disturbances: Mild leukocytosis with left shift and hemoconcentration may be seen in some patients. Rapid decline in hematocrit indicates hemorrhagic pancreatitis.

Plain abdominal films should be done in patients with acute abdomen in order to exclude other abdominal disorders. As mentioned earlier, plain films may provide helpful information and characteristic signs that can help establishing the diagnosis (see Evaluation of Pancreatic Function and Pancreatic Disease).

Chest film should be obtained to rule out diaphragmatic or pulmonary involvement such as pleural effusion or adult respiratory distress syndrome (ARDS).

Abdominal ultrasounds, or CT scans, may reveal an enlarged and edematous pancreas with reduced echogenicity. It may also show a pseudocyst in the vicinity of the pancreas.

Complications of Acute Pancreatitis

Pseudocysts is a common complication following acute pancreatitis and may develop in 16–50% of the patients. The lining of the pseudocyst is composed of fibrous or granulation tissue without an epithelial component. It is fluid filled with pancreatic juice, blood, and tissue debris. It may develop in the course of the acute attack or many weeks later. In contrast to pseudocysts associated with chronic pancreatitis in patients with acute pancreatitis, psudocysts do not communicate with pancreas. The presentation is usually that of a prolonged course of acute pancreatitis with persistent nausea and

vomiting, and prolonged elevation of serum amylase and lipase. Ultrasounds or CT scans are diagnostic. Small pseudocysts will most likely resolve spontaneously. However, large cyst, those that last more than 6 weeks, and those with abscess formation require immediate drainage. Ruptured cysts may cause severe and life-threatening chemical peritonitis.

Other complications such as respiratory, renal and hepatic failure, and refractory hypotension correlate with severe disease and a grave outcome.

There is no available data regarding mortality rate following acute pancreatitis in children. In adults, mortality rate is usually 9% per attach. On the other hand, the mortality rate following hemorrhagic and necrotic pancreatitis ranges between 15% and 50%.

Treatment

Treatment of acute pancreatitis is primarily supportive. The treatment should be directed toward the cause whenever identified. Other than avoiding the precipitating factors, maintaining intravascular volume, the mainstays of therapy are minimizing the stimulation of pancreatic exocrine secretions and pain management.

Almost all patients will have some degree of dehydration due to decreased intake, vomiting, leakage of intravascular fluids to the peritoneum, or hemorrhage. Based on the degree of dehydration, patient will require replacement of deficits, ongoing losses, and maintenance fluids. Caution should be applied in order to avoid fluid overload, which may result in pulmonary edema and congestive heart failure commonly seen 3–7 days from the onset of pancreatitis. Potassium should not be added to intravenous fluids before establishing acceptable urine output as renal failure may be seen in 2% to 17% of patients with acute pancreatitis. Monitoring electrolytes, including calcium and magnesium, is mandatory. If shock and hemorrhage are present, fresh frozen plasma or blood may be required. Treatment with intravenous pressor agents may be needed if these measures have failed in improving blood pressure. H2 blocker or proton pump inhibitors may help reduce duodenal acidity and prevent gastritis and ulcer formation.

Complete bowel rest and employing gastric suction will reduce the dietary and hormonal stimulation of the pancreas. Oral feedings should not be resumed until pain and ileus have resolved and amylase normalized. When oral feedings are resumed, carbohydrates should be introduced first, avoiding fats and proteins in order to decrease pancreatic stimulation. If the patient requires prolonged therapy, total parenteral nutrition is in order. In the past, anticholinergic drugs were frequently used to suppress the neural stimulation of pancreatic secretions. However, controlled studies have failed to prove their efficiency.

Adequate pain relief is essential. This can be accomplished with meperidine. Opiates should be avoided because they may cause spasm of the sphincter of Oddi. Persistence of pain beyond 2 weeks may indicate the development of pseudocyst, and ultrasound is usually recommended every few days to detect to monitor for this complication.

Prophylactic antibiotics are not recommended since studies have failed to substantiate their efficacy in preventing secondary infection.

Many patients with pancreatitis may have some degree of hypoxia which requires oxygen administration. With respiratory failure, ventilatory support may also be required. Thoracentesis may help in relieving the respiratory compromise resulting from pleural effusions.

Surgical intervention is usually reserved for treatment of complications of the disease or for the correction of underlying anomalies.

Chronic Pancreatitis

Chronic pancreatitis is a chronic inflammatory process with progressive and permanent damage to the structure and function of the pancreas. The disease is uncommon in childhood; however, it is encountered frequently enough to require a high index of suspicion.

Etiology of Chronic Pancreatitis

There are numerous causes of chronic pancreatitis. Hereditary or familial pancreatitis is an autosomal-dominant disease with incomplete penetrance, recognized mainly among whites in Europe and North America, and among Chinese children. The onset of this disease is usually in the second decade of life. Several mutations have been described such as mutations in the cationic trypsinogen (PRSS1) gene. In addition, mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) and the serine protease inhibitor Kazal type 1 (SPINK1) genes are also associated with pancreatitis.

Juvenile tropical pancreatitis inflicts young people in the tropics, where low protein staples are commonly consumed. The largest series has been reported from the southern Indian state of Kerala. It is also recognized in Zaire, Nigeria, Uganda, South Africa, and Malaysia.

The disease has been strongly linked to protein calorie malnutrition, although conclusive data is lacking.

Chronic pancreatitis may also result from obstructive processes usually arising from congenital anomalies. These include stenosis of the papilla of Vater, choledochal cysts, an annular pancreas, and pancreas divisum.

Chronic pancreatitis also arises from systemic and metabolic disorders, including hypercalcemia, hyperparathyroidism, hyperlipidemias, alpha-1-antitrypsin deficiency, cystic fibrosis, and inflammatory bowel disease.

Biliary disorders such as cholecystitis, cholelithiasis, and sclerosing cholangitis may also lead to chronic pancreatitis.

Chronic pancreatitis also results from extensive necrosis and fibrosis following an episode of acute pancreatitis.

Idiopathic chronic pancreatitis requires the exclusion of recognizable causes.

Clinical Presentation

The most common initial presentation of chronic pancreatitis is a clinical picture suggestive of repeated episodes of acute pancreatitis. Approximately one-half of patients present initially with episodes of acute pancreatitis. The other half will present with insidious pain, and a small percentage of patients will have no pain at all. Therefore, the majority of children with chronic pancreatitis have either intermittent or chronic abdominal pain lasting for weeks. The pain is localized to the epigastrium, the upper abdominal quadrants, the back, or occasionally the periumbilical area. As the disease progresses, the pain may diminish. Patients with chronic pancreatitis usually present between 10 and 12 years of age. By the age of 20 years, 75% of the patients are symptomatic. Males and females are equally affected. The diagnosis of chronic pancreatitis should be considered in patients presenting with obstructive jaundice, malabsorption, and diabetes.

Some patients may present with obstructive jaundice, with or without abdominal pain, secondary to narrowing of the distal common bile duct due to extensive fibrosis.

Exocrine insufficiency with steatorrhea and failure to thrive can be the presenting symptom in up to 20% of patients. Pancreatic exocrine failure could result from destruction of more than 98% of pancreatic acini or from obstruction of pancreatic ducts.

Glucose intolerance with hyperglycemia and glucosuria are common in the early stages of the disease. As the disease progresses, lifelong diabetes mellitus may develop, particularly in calcifying pancreatitis and tropical pancreatitis.

There have been numerous reports of pancreatic malignancies in some etiologic subgroups of patients with chronic pancreatitis. Nonpancreatic malignancies are also reported in patients with familial pancreatitis.

Splenic vein thrombosis has been reported in chronic pancreatitis secondary to perivenous inflammation. Gastric varices secondary to splenic vein thrombosis is a common finding in patients.

Diagnosis

(See ❯ Evaluation of Pancreatic Function and Disease)

The same diagnostic tests used in acute pancreatitis also apply to chronic pancreatitis. However, it is important to recognize that serum amylase and lipase may be normal or decreased in advanced cases due to pancreatic insufficiency. Pancreatic function evaluation with pancreozymin-secretin stimulation is a very valuable tool in assessing the degree of compromise in pancreatic exocrine function. Malabsorbtion may cause fat-soluble vitamin deficiency. Serum vitamin D and vitamin E carotene level and essential fatty acids may be decreased with prolongation of prothrombin time. Endoscopic retrograde cholangiopancreatography (ERCP) is the most sensitive diagnostic test in chronic pancreatitis. However, normal studies do not exclude the existence of pancreatitis.

Therapy for Chronic Pancreatitis

In the management of acute episodes of chronic pancreatitis, the same measures taken in acute pancreatitis are applied.

Management of malabsorption is also important. Fat intake should be limited while providing adequate protein and calories for growth. Use of medium chain fatty acids for improved absorption may be required. Continuous nasogastric alimentation with elemental formulas may be necessary in some patients. Pancreatic enzyme supplementation will also result in improvement of steatorrhea. Since lipase is inactivated in acidic pHs, gastric acid blockade with H_2-blockers or proton pump inhibitors can lead to increased bioavailability of pancreatic enzyme supplements. Patients may need insulin therapy with the development of diabetes mellitus.

Management of pseudocysts requires surgical internal or external drainage. Surgical therapy or ERCP-directed therapy is indicated for patients with intractable pain and for patients with obstruction of the common duct. ERCP can drain pseudocysts and allow removal of intraductal stones, placement of drains and stents, in addition to performing sphincterotomy. For definitive drainage of

the pancreas, a pancreaticojejunostomy may be required. In some patients, a partial or subtotal pancreatectomy may be required. With complete common bile duct obstruction, a choledochojejunostomy may be indicated. Pancreatic transplantation has recently become available, but experience in children is limited.

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199 Gastrointestinal Bleeding

Mark A. Gilger · Hisham M. Nazer

Introduction

Gastrointestinal bleeding in infants and children is a potentially life-threatening problem that can be quite alarming for the child and his family. The cause, however, is usually benign; however, the differential diagnosis is so extensive and does vary with age. The approach to diagnosis and management of gastrointestinal bleeding by the physician should be calm and expeditious to help allay the fears of the patients and the family and to reduce any likely associated morbidity. This chapter is intended to review the spectrum of GI bleeding in infants and children and to discuss means of investigations and therapy (*Fig. 199.1*).

Initial evaluation should aim at confirming that the child has definitely an upper or lower gastrointestinal bleeding. Detailed history is a very important first step in the evaluation of a child with gastrointestinal bleeding. There is a tendency to overestimate the amount of blood loss; therefore, a detailed history is a very important first step in patients' evaluation. Identification of heme products is based on the interaction of peroxidase activity found in the hemoglobin and various reagents. Food-coloring agents added to cereals, drinks, and medications could result in discoloration of the stools. Vegetables, iron-fortified cereals, ketchup, and gelatin deserts are also some other examples to be considered in the initial evaluation to confirm that the child has really had upper or lower gastrointestinal bleeding. Guaiac-based tests are most reliable, but still have a false-positive rate of 1–2%. Hemoglobin in red meat will also result in a false-positive test. None of the available tests for occult blood are 100% specific.

A normal physical examination is not uncommon in patients with GI bleeding. It is important to document the vital signs of the child on admission as part of the initial evaluation. A comprehensive checkup on abdominal distention, masses, hepatosplenomegaly, rectal prolapse, and anal fissure should be also made.

The child should be admitted to prevent any potential subsequent complications and to manage early any potential further bleeding. The site and cause of bleeding should be determined as soon as possible.

Hemorrhagic disease of the newborn is due to vitamin K deficiency and responds fairly well to vitamin K injection. In up to 50% of cases, the actual cause of bleeding is not defined in the neonate whose general condition remains good and fairly stable. Gastrointestinal bleeding beyond the neonatal period is usually due to esophagitis, gastritis, or peptic ulcers. Other important cause to be considered is Mallory–Weiss Syndrome especially in young infant with hematemesis or melena and a history of paroxysmal cough or vomiting resulting in longitudinal mucosal laceration at the gastroesophageal junction.

Helicobater pylori should also be considered as an important cause of GI bleeding. The recurrence of the infection and GI bleeding can be prevented with eradication of *H. pylori.*

Endoscopy is the investigation of choice. Diagnostic endoscopy may have to be performed in the first hours following admission. Other investigations of importance in infants and children with gastrointestinal bleeding include Meckel's scan, red blood cells scan, angiography, and contrast barium studies.

Pathophysiology

When a child bleeds, a number of homeostatic mechanisms interact. These include an increase in the sympathetic activity, with catecholamine and release of adrenocorticotropic hormone, antidiuretic hormone, aldosterone, glucocorticoids, and prostaglandins. The rapidity of blood loss may be a more important factor than the volume that is lost. As much as 15% of our blood volume can be lost slowly without any hemodynamic response. The venous bed normally contains a substantial volume of blood that can easily compensate for minor losses to prevent any changes in cardiac output and oxygen consumption. Blood flow to the brain and heart is maintained. A very narrow pulse pressure may be a valuable warning of impending vascular collapse as compensatory vasoconstriction is exhausted. Patients may experience shock with as little as 10% volume loss if bleeding is extremely rapid.

When the blood loss exceeds 15% of the blood volume, compensatory mechanisms are no longer adequate. Cardiac output is maintained by sympathetic stimulation

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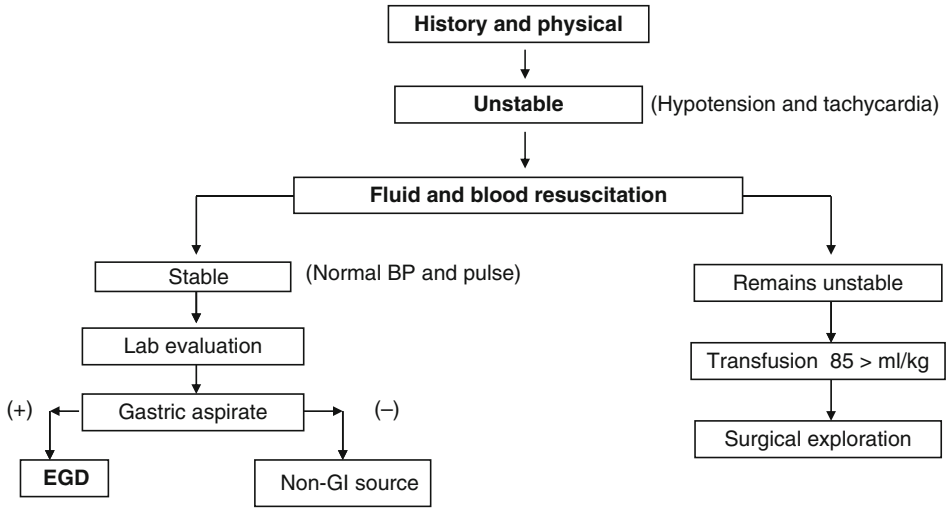

*Adapted from: Walker's Pediatric Gastrointestinal Disease 5th Edition, Section 6 Diagnosis of Gastrointestinal Disorders: Gastrointestinal Endoscopy Chapter 46.2b Upper Gastrointestinal Bleeding. Gilger MA and Whitfield KL

Figure 199.1
Approach to GI bleeding in children

resulting in increased heart rate. Peripheral vasoconstriction and increased secretion of aldosterone and antidiuretic hormone also assist in maintaining blood volume. Oxygen consumption as well as blood lactate levels increase in response to tissue hypoxia, hyperventilation, and respiratory alkalosis before significant metabolic acidosis presents.

In case of severe blood loss greater than 30% of the circulatory blood volume, hypotension is invariably present together with decreased cardiac output, tissue damage, cardiac infarction, and metabolic acidosis. Acute renal failure may develop, determined by the degree of vasoconstriction and duration of hypotensive episodes. Hepatic ischemia can lead to tremendous elevation in transaminases and bilirubin. Sepsis may develop as a result of impaired organ function or depressed immune status. Both acidosis and sympathetic activity may increase the degree of myocardial damage during shock.

Table 199.1
Causes of upper gastrointestinal bleeding in children

In neonates
Swallowed blood: during birth, epistaxis
Hemorrhagic disease of the newborn
Stress ulcer, esophagitis
Foreign body irritation, trauma
Duplication cyst
In older children
Esophagitis, peptic ulcer disease, gastric erosions
Esophageal varices, portal hypertension
Mallory–Weiss syndrome
Pyloric stenosis
Blood dyscrasia: thrombocytopenic purpura, von Willebrand disease, leukemia
Tumor, vascular anomalies
Epistaxis, foreign body
Duplication cyst, acute poisoning

Upper Gastrointestinal Bleeding

Upper gastrointestinal bleeding is a relatively common problem and is occasionally a life-threatening emergency in infants and young children. Causes of upper gastrointestinal bleeding in children are summarized in *Table 199.1*. Hematemesis imply bleeding proximal to the ligament of Treitz. The vomiting may be bright red or coffee ground in appearance if it has been altered by the gastric acid. Blood from the upper gastrointestinal tract may appear per rectum as black or tarry in color, *melena*.

The odor of melena is quite distinct. In Melena, the lesion is usually proximal to the ascending colon.

The following points are important to consider in the overall management of a child with upper gastrointestinal bleeding:

1. Most children stop bleeding prior to or early in their hospital course.
2. Localization of the bleeding site can be established in more than 90% of cases.
3. Flexible fiber-optic endoscopy is the investigation of choice for upper gastrointestinal bleeding.
4. Erect and supine (or lateral decubitus) plain films are useful investigations to exclude bowel obstruction and free intra-abdominal gas. Barium examination of the upper gastrointestinal tract has little to offer in the initial evaluation of the actively bleeding child.
5. Nearly 20% of patients with varices who bleed do so from sources other than varices.
6. Avoid overtransfusion, especially in case of esophageal varices.
7. In suspected hepatic encephalopathy, sedation, if any, should be minimal.

History

Parents tend to overestimate the amount of blood lost by hematemesis and even more so the amount of bleeding per rectum. Confirm that the child has in fact had a bleeding. Detailed history taking is a very important first step in the evaluation of a child with gastrointestinal bleeding. One must inquire about possible cough or epistaxis and the duration of the vomiting before the blood appeared. Projectile vomiting in young infants points to pyloric stenosis with secondary gastroesophageal reflux and esophagitis. Vomiting of coffee ground-like material does not necessarily signify a specific quantity of blood, nor does vomiting of bright red blood mean that major bleeding is taking place. It is important to note that as much as 20% of upper gastrointestinal tract bleeding occurs without hematemesis.

Passage of bright red blood on the toilet paper or in the toilet bowl or on the surface of the stool suggests anorectal pathology, as in the case of anal fissure, proctitis, or polyposis.

Other points of importance in the history include inquiry about associated findings or complaints such as fever, postprandial pain, colic pain, anorectal pain, history of drug ingestion, or similar disorders in the family. Special enquiry should be made concerning the child's ingestion of nonsteroidal anti-inflammatory drugs prior to admission.

Physical Examination

A normal physical examination is not uncommon in patients with gastrointestinal bleeding. It is important to document the vital signs of the child on admission and initial evaluation. The skin should be examined for ecchymosis, purpura, petechia, rashes, jaundice, and pigmentation. The skin is further evaluated for signs of collagen vascular disorders or infections.

Examination should also include assessment of lymph nodes. The mucous membrane is also inspected for signs of hemorrhage from the nose, nasopharynx, and mouth. Examination should also include checking for abdominal distention, masses, hepatosplenomegaly, anal fissure, and rectal prolapse.

General Management

The child should be admitted to prevent any potential subsequent complications and to manage any further bleeding. There is also a potential risk of hypotension, impairment of hepatic perfusion, with deterioration of liver functions resulting in the appearance: of further evidence of hepatic involvement with jaundice, ascites, and encephalopathy.

The doctor should determine the cause and locate the site of the bleeding as soon as possible. History and physical examination should provide detailed answers to the following questions: Is it really blood? How much blood is lost and its effect on the child? Is the child still bleeding?

On admission, the child should have a baseline laboratory assessment with full blood count and differential, liver function tests, and renal function rests. At least a unit of whole blood should always be kept available in the blood bank. In case of bleeding varices in an older child, 3–4 units of blood should be kept on standby. The intravenous infusion line should be secured, whether peripheral or central. Serial evaluations of vital signs, urinary output, and hematocrit are critical. Nasogastric tube insertion may provide important diagnostic information. It is a useful adjunct for monitoring bleeding. The size of the nasogastric tube depends on the size of the patient. The smaller bore lubes may be adequate for assessing bleeding but not for removing large clots. The larger bore nasogastric tubes may cause trauma to the gastric mucosa. Gastric lavage with the nasogastric tube helps the endoscopist to obtain a clear view of the bleeding site. The presence or potential presence of esophageal varices should in no way preclude the use of a tube.

The presence of bright red blood is a marker of active bleeding. Avoid overtransfusion especially in patients with esophageal varices.

Water is found to be as efficacious as saline to lavage the stomach. Tap water would appear to be a suitable solution for gastric lavage because of its low cost and its temperature. All patients in whom the level of gastrointestinal bleeding is not obvious should have a nasogastric tube passed and their stomach aspirated, especially if there was no previous history of gastrointestinal bleeding.

In severe cases and in those patients requiring intensive care nursing, endotracheal intubation is required to protect the airway and prevent aspiration. It is important to notify, in advance, the intensive care unit staff of any potential admission or referral. Emergency drugs like vasopressin and ranitidine should be made available as well as a Sengstaken-Blakemore tube if the unit staff are familiar with its application and complications.

Intravenous vasopressin has been used to control gastrointestinal bleeding. Vasopressin in a dose not exceeding 0.01 U/kg/min intravenously is recommended. Higher doses were reported to be associated with complications without improving the control of hemorrhage. Tuggle et al. recommend starting vasopressin at 0.002–0.005 U/kg/min, which would allow increasing the dose of vasopressin before the risk of complications increases.

Urine output should be measured carefully. Foley catheterization of the bladder may be required. In massive bleeding, replacement fluid should contain whole blood. The patient's vital signs give some indication of blood volume to be replaced. The hemoglobin and hematocrit are not accurate reflections of blood volume during an acute hemorrhage. The usual goal of transfusion is to restore an adequate circulatory volume to allow tissue perfusion. A hemoglobin level of 10 g/dL or a hematocrit of 30% is adequate. Monitoring of blood gases is important, especially in those patients who have had severe bleeding with poor tissue perfusion. All patients with massive bleeding should receive oxygen.

Diagnostic endoscopy and injection sclerotherapy may have to be performed in the first hours following admission, especially in patients known to have esophageal varices or if the bleeding recurs. It is essential to confirm the presence of varices, to ascertain the cause of bleeding, and to determine the sites of ulceration and erosions. Coagulation disorders and hemodynamic instability must be corrected before performing any endoscopic procedure. Variceal banding with a well-set elastic band to an esophageal varix through the endoscope may have to be performed soon after admission. The varix is sucked into the device and a band of fired to ligate the varix. Multiband set does allow the application of several bands without the need for reloading.

Upper gastrointestinal endoscopy should not be performed in an uncooperative patient. The most common reason for inadequate examination is inadequate sedation. Shock, perforated hollow viscus, and cervical spine injury are contraindications to upper gastrointestinal endoscopy. In a small percentage of patients in whom endoscopy and barium studies have failed to determine the source of bleeding or when bleeding is massive, arteriography should be performed. This examination of the superior and inferior mesenteric arteries and the celiac axis may reveal some common causes of bleeding as well as unusual causes such as hepatic artery aneurysm, gastropancreatic duplication, and arteriovenous malformations.

Upper Gastrointestinal Bleeding in the Neonate

Most neonates who bleed do so within 48 h of birth. The bleeding usually stops within the next 24 h and rarely recurs. Most bleeding in the first month of life does not require surgery. Major bleeding in the neonatal period may be the result of hemorrhagic gastritis or stress ulcers caused by perinatal insult of hypoxia, sepsis, or lesions of the central nervous system.

The common causes of upper gastrointestinal bleeding in the neonates include the following

Hemorrhagic Disease of the Newborn

This is due to vitamin K deficiency, resulting in generalized bleeding that may be massive. It is usually treated with 1 mg of vitamin K intramuscularly followed by 1 mg of vitamin K each day for 5 days.

Swallowed Maternal Blood

One of the most common causes of hematemesis or melena in the neonate is swallowed maternal blood during delivery or during breast-feeding if the mother has cracked nipples. The Apt test may have to be used at bedside to differentiate fetal from maternal blood based on the fact that fetal hemoglobin is more resistant to alkali denaturation than adult hemoglobin.

Cow's Milk Protein Allergy

This should also be considered and confirmed by the presence of high serum milk antibodies and endoscopic and histologic changes of the intestinal mucosa. Other causes of bleeding in the neonates, though rare, include duplication cysts of the intestine, midgut volvulus, peptic ulcer disease, and esophageal varices.

In up to 50% of cases, the actual cause of bleeding is not defined in the neonate, whose general condition remains good and fairly stable.

Upper Gastrointestinal Bleeding in Infancy and Childhood

Gastrointestinal bleeding beyond the neonatal period is usually due to esophagitis, gastritis, or peptic ulcers. Other causes to be considered include Mallory–Weiss syndrome and swallowed foreign body. Zollinger Ellison syndrome is a well-recognized condition affecting young infants associated with peptic ulcer–like disease.

Zollinger Ellison syndrome is typically caused by a gastrin-secreting tumor, usually located in the pancreas, occasionally in the duodenum, lymph nodes. Rare locations in children include the liver, kidney, and heart. Peptic ulcer disease is a recognized presentation of ZES with the presence of single or multiple ulcers in the first part of the duodenum. The diagnosis is considered even further if peptic ulcers were found in the second or third part of the duodenum or in the jejunum The associated peptic ulcers in this condition are usually big and about 2 cm in diameter or more and are seen in multiple sites.

The diagnosis of ZES is considered when plasma gastrin is >1,000 pg/ml, basal acid output is >15 meq/h, or when associated with a pH 2. Secretin stimulation test is considered as the most important diagnostic test for ZES. Eighteen to twenty-five percent of patients do not have ulcers at diagnosis.

The treatment is directed toward controlling gastric acid hypersecretion, and localization of the tumor and its metastasis. Associated peptic ulcers are known for being resistant to conventionl therapy.

Mallory–Weiss Syndrome

Mallory–Weiss syndrome is a condition associated with upper gastrointestinal bleeding due to longitudinal mucosal laceration at the esophagogastric junction (*Fig. 199.2*). The bleeding in Mallory–Weiss syndrome is due to a tear precipitated by forceful vomiting, repeated retching, cough, trauma, or even straining at stool resulting in a rise in intragastric pressure and presenting usually as hematemesis or less commonly as melena.

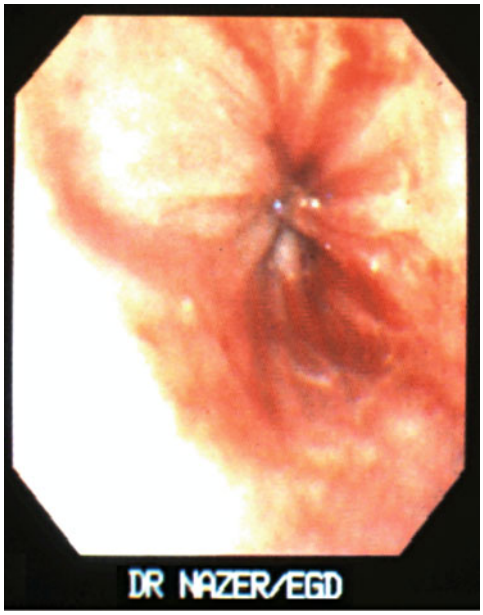

Figure 199.2
Mallory–Weiss syndrome: endoscopic appearance of Mallory–Weiss tears in young infant with upper gastrointestinal bleeding

The patient may have two to three forceful emeses without blood followed by massive hematemesis. Mallory–Weiss tears have been reported in children as young as 16 weeks of age; bleeding usually stops spontaneously and surgery is rarely indicated. The tear may sometimes result in severe upper gastrointestinal bleeding that warrants immediate attention and intensive care management.

Diagnosis is confirmed endoscopically. Ninety percent of the tears are in the stomach at or near the gastroesophageal junction. In only 10%, the rears involve the esophagus. Treatment is conservative, as the bleeding usually stops on its own. The patient should receive no feeds or fluid by mouth. He or she should be given H2-blockers or antacids or both for a period of at least 48–72 h before the nasogastric tube is withdrawn. Feeding can be commenced 24 h after withdrawing the nasogastric tube and with no evidence of recurrent bleeding.

Esophageal Varices

Variceal bleeding is usually painless but profuse. Endoscopy enables detection of the bleeding site in about 90%

of cases. Variceal bleeding may be the initial presentation of portal hypertension as in congenital hepatic fibrosis. Esophageal varices is discussed in a separate chapter together with portal hypertension.

Other causes to consider in the evaluation of an elder child with upper gastrointestinal bleeding include hemolytic uremic syndrome and Henoch–Schönlein purpura.

Diagnostic Techniques

After stabilizing the patient's vital signs, nasogastric aspiration is the second recognized step in the management to identify the severity and continuity of the bleeding.

Endoscopy

Upper gastrointestinal endoscopy is the diagnostic technique of choice in evaluating the upper gastrointestinal bleeder. It is extremely accurate in establishing the diagnosis in over 90% of patients compared to not more than 60% using upper gastrointestinal barium study. Barium contrast studies will not identify some conditions such as esophagitis, gastritis, and Mallory–Weiss tear. Therefore, barium studies should not be used as the first diagnostic modality for upper gastrointestinal bleeding if flexible fiber-optic endoscopy is available. However, it must be accepted that although emergency endoscopy is the most effective diagnostic procedure, it has no relevant influence on mortality if endoscopic hemostatic procedure is not employed simultaneously. Furthermore, the diagnostic yield of endoscopy performed 12–24 h after admission is no less than that performed immediately on admission. Current studies have not confirmed that early diagnosis improves mortality and morbidity associated with upper gastrointestinal bleeding.

Meckel Diverticulum Scan

Technetium-99m pertechnetate is concentrated in the gastric mucosa as well as in the ectopic gastric mucosa of a Meckel diverticulum, which is usually responsible for associated gastrointestinal bleeding.

Red Blood Cells Scan

This test offers a definite advantage for intermittent bleeds. The scans are done at intervals of 5–15 min for 1–3 h. The tagged red blood cells scan may not be positive until 4–6 h after injection or even after 12–24 h. The exact site of bleeding cannot be ascertained as accurately as with angiography.

Arteriography

Arteriography may be used in critically ill patients. The patient must be bleeding approximately 0.5–2 ml/min before the study is expected to be positive. The study should include injection of superior and inferior mesenteric arteries and celiac axis. Angiography should be considered when medical measures employed in the control of the bleeding gastrointestinal lesion have been unsuccessful. Embolic therapy may be performed through the angiographic catheter in an attempt to stop the bleeding and avoid surgery.

Contrast Barium Studies

Contrast upper gastrointestinal barium studies are not routinely resorted to in the workup of gastrointestinal bleeding as was the case a few decades ago. Such contrast studies rank last in the diagnostic workup list in upper gastrointestinal bleeding.

Endoscopic Approach to Upper Gastrointestinal Bleeding in Children

Upper gastrointestinal (UGI) bleeding is unusual in children. Data from the Pediatric Endoscopy Database System–Clinical Outcomes Research Initiative (PEDS-CORI) indicates that hematemesis accounts for only about 5% (327 of 6,337) of indications for upper endoscopy in children. In general, UGI bleeding is rarely life threatening and usually stops. UGI bleeding is considerably more common in critically ill children with an incidence ranging from 6% to 25%. However, even in this critically ill population, life-threatening UGI bleeding was rare, found in only 0.4% of children. Although the causes of UGI bleeding have remained unchanged, the treatment, such as the use endoscopic therapy, has evolved.

Initial Assessment and Intervention

As a rule, UGI bleeding always warrants further investigation. Prior to considering endoscopy, any child with gastrointestinal bleeding must have a brief history followed by a quick assessment of the physical status, especially the

vital signs and level of consciousness. If the bleeding is severe, therapy should begin before the location of the bleeding can be ascertained. For example, significant gastrointestinal bleeding will be manifested by tachycardia, followed by hypotension, an ominous signal of impending cardiovascular collapse. Immediate therapy is aimed at correction of volume loss and anemia, which should include aggressive fluid and blood resuscitation.

If the patient remains unstable after transfusion of 85 ml/kg or greater of blood, emergency exploratory surgery is indicated. Surgical consultation is mandatory in any case of severe UGI bleeding. Varices, ulcers penetrating into an artery, or tears into arterial vasculature must be considered.

Laboratory evaluation should include a complete blood count with platelets and reticulocyte count, prothrombin time and partial thromboplastin time, and a blood type and cross match. Assessment of liver function (alanine aminotransferase, aspartate aminotransferase, and albumin) may prove useful in that elevated transaminases and a low albumin or an elevated protime can be an indication of chronic liver disease. Assessment of kidney function (blood urea nitrogen (BUN) and creatinine) is also recommended as an elevated BUN (azotemia) may indicate UGI bleeding which may result from intestinal absorption of the blood and hypovolemia.

Endoscopy

Esophagogastroduodenoscopy (EGD) is the preferred approach to assess the UGI tract for bleeding. EGD is indicated for acute UGI bleeding requiring transfusion or unexplained recurrent bleeding and it determines the source of the bleeding in 90% of cases. EGD is particularly useful in the diagnosis of mucosal lesions such as gastritis, esophagitis, peptic ulcers, and Mallory–Weiss tears. Most UGI bleeding in children stops spontaneously; thus, emergency endoscopy is indicated only when the findings will influence clinical decision, such as the need for medical or surgical therapy. EGD is contraindicated if the patient is clinically unstable.

Endoscopic Therapy

Many endoscopic therapies are now available for the treatment of UGI bleeding. These include electrocoagulation (bipolar electocoagulation [BICAP], heater probe, and monopolar probe), laser photocoagulation, argon plasma coagulation, injection of epinephrine and sclerosants, band ligation, and mechanical clipping. There is little published experience with these techniques in children; hence, which approach is best in children remains unknown. Perhaps the most widely used approach is injection therapy followed by BICAP. This approach is appealing because it is simple, inexpensive, and uses a sclerotherapy needle, all of which are familiar to the pediatric endoscopist. Although no data exist, the combination of 1:10,000 epinephrine injection followed by bipolar electrocoagulation is likely the most commonly performed endoscopic treatment of UGI bleeding in children.

Thermal coagulation of a bleeding ulcer using a heater probe has been reported to be safe in neonates. The argon plasma coagulator is useful as it fits through small pediatric endoscopes and has a controlled depth of penetration. Unfortunately, it remains expensive. Laser therapy is commonly applied in adults, but there is a significant learning curve and high potential for full-thickness wall injury and is even more expensive that argon plasma coagulation.

Endoscopic treatment of esophageal varices includes either injection sclerotherapy or variceal banding. Sclerotherapy has been used for the treatment of variceal hemorrhage in children since 1959. Control of bleeding is achieved in over 90% of cases and varices are eradicated in over 80% of cases. Complications after sclerotherapy are common, such as strictures, recurrence of the varices, and recurrent bleeding. Variceal banding was introduced in 1989 as an adaptation of the treatment for hemorrhoids. Meta-analysis studies in adult patients demonstrate no difference between sclerotherapy and banding in the control of bleeding or mortality. There are no comparative studies between sclerotherapy and banding in children, but some studies suggest that banding may be the preferred method in children. Banding appears to be better tolerated in children compared with sclerotherapy, causing less retrosternal pain and no fever. Unfortunately, banding devices remain too large for use in infants and small children. Although variceal banding is effective in controlling bleeding, rebleeding occurs in up to 80% of patients.

Endoscopic treatment of gastric varices remains controversial. Endoscopic visualization during UGI bleeding is imperative but often difficult. Studies indicate that the prokinetic erythromycin given prior to EGD is effective in clearing the gastric lumen, providing better visualization of the mucosa during endoscopy.

Lower Gastrointestinal Bleeding

Rectal bleeding is an alarming symptom in children but is usually not life threatening. Bleeding per rectum can be bright red (hemotochezia) or tarry black and sticky with

a characteristic smell (melena). Hemotochezia usually results from lesions in the colon or terminal ileum, while melena is typical of sources above the ligament of Treitz.

Melena is defined as the passage of black tarry stools due to the presence of digested blood. The stool is shiny, sticky, and virtually always extremely foul smelling.

Hematochezia is the passage of bright red or maroon blood from the rectum. This may be pure blood, bloody diarrhea, or blood mixed with the stool. The site of the bleeding is usually in the left colon and primarily in the anorectal region.

Recognized causes of lower GI bleeding in young infant include anal fissures, cow's milk protein intolerance, necrotizing enterocolitis, gastritis and peptic ulcer disease, Meckel's diverticulum, gastrointestinal polyps, intestinal duplication, and intussusception. Meckel's diverticula and intestinal duplications may cause gastrointestinal bleeding in almost any age group and require a high index of suspicion for diagnosis. Bleeding usually is painless but may be massive. The advent of technetium (Tc) 99m pertechnetate radionuclide scanning has greatly facilitated the diagnosis. A positive scan requires the presence of ectopic gastric mucosa, which may be identified in both Meckel's diverticula and intestinal duplications The significance of ectopic gastric mucosa is that it contains acid-secreting parietal cells, which may cause ulceration and bleeding. After initial fluid resuscitation, bleeding from Meckel's diverticula and intestinal duplications require surgical intervention.

Causes of lower gastrointestinal tract bleeding are summarized in *Table 199.2*.

Table 199.2
Causes of lower gastrointestinal tract bleeding in childhood

In neonates
Anal fissure
Duplication of bowel
Arteriovenous malformation
Necrotizing enterocolitis
Peptic ulcer
Milk allergy
Intussusception
Tumor
Ischemic colitis
Midgut volvulus
In the older child
Anal fissure
Peptic ulcer
Enterocolitis: infective, allergic
Pseudomembranous colitis
Meckel diverticulum
Henoch–Schönlein purpura
Autoimmune disorders
Arteriovenous malformation
Foreign body intussusception
Antibiotics
Inflammatory bowel disease
Ischemic colitis
Polyps
Infection
Hemolytic uremic syndrome
Duplication cyst
Trauma

Rectal Bleeding in the Neonate

The most common cause for rectal bleeding in the neonate may also be swallowed maternal blood. Necrotizing enterocolitis in the preterm or the stressed term infant and enterocolitis secondary to Hirschsprung disease may frequently cause occult to moderate bleeding per rectum.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common serious gastrointestinal disorder encountered in neonatal intensive care units. NEC is a major cause of morbidity and mortality in the newborn, particularly the preterm infant. The incidence is inversely proportional to birth weight and degree of maturity.

NEC should be suspected in any infant, especially if premature and stressed, who develop abdominal distention, decreased gastric emptying, apnea or bradycardia, and heme-positive stools. There is also abdominal wall discoloration with visible bowel loops. NEC may result in moderate rectal bleeding that is maroon to bright red in color and tissue may be present. NEC varies widely in severity and rate of progression. Although NEC can be suspected on clinical grounds, confirmation usually requires the demonstration of characteristic and radiologic findings that include pneumatosis intestinalis (intramural air) in up to 90% of cases and portal air (*Fig. 199.3*). Perforation is the most common and urgent early complication. Late complications include

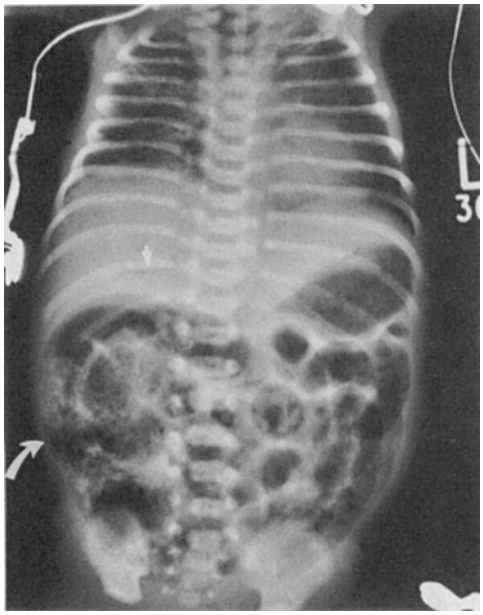

Figure 199.3
Necrotizing enterocolitis: abdominal radiograph of a preterm infant with abdominal distention showing dilated bowel loops with intramural gas; pneumatosis intestinalis (*curved arrow*) and portal vein gas (*straight arrow*)

intestinal stricture and short-bowel syndrome. Other radiologic findings include small bowel dilatation, ileus, and ascites. Diagnosis is also confirmed at surgery and histologic examination of the intestine if the radiologic features are not conclusive.

Treatment consists of nasogastric decompression, withholding enteral feeding, intravenous antibiotics, and close radiologic and clinical monitoring to diagnose perforation. Surgery is performed on those with perforation or in whom supportive therapy proves ineffective. Some complicated cases with gangrene warrant resection of good length of the bowel, resulting in short-bowel syndrome with its associated serious complications. For more information about NEC in the newborn, see section "Neonatology."

Anal Fissure

This is a relatively common neonatal condition associated with lower gastrointestinal bleeding. Most anal fissures occur in the sagittal plane secondary to constipation. Anal fissure may also be seen in late childhood associated with other disorders such as Crohn disease. Perianal fissures are the most common cause of mild bright red rectal bleeding in children. Blood tends to streak the stool and may be mixed with flecks or mucus. The fissures may be apparent by gently spreading the buttocks. Rectal fissures can be felt by digital palpation with a well-lubricated glove. Most anal fissures heal spontaneously. Healing may be facilitated by anal dilatation by the mother's own lubricated finger twice daily for 7–10 days. In the presence of constipation, a mild stool softener such as natured bran may be useful, If symptoms persist in spite of all conservative measures, surgical management such as stretching of the anus with excision of the fissure may be required.

Rectal prolapse is also a recognized cause of bleeding per rectum. This condition is usually associated with constipation. Other causes to be ruled out include cystic fibrosis and parasitic infestations.

Rectal Bleeding in the Elder Child

There is some overlap in the conditions associated with hematemesis and melena. It is quite possible for one condition to be presented as upper or lower gastrointestinal bleeding or both. Detailed history and thorough physical examination assist in making the likely diagnosis. Some of the relatively common causes of rectal bleeding beyond the neonatal age group include the following.

Meckel's Diverticulum

This diverticulum is a remnant of the omphalomesenteric duct, which connects the yolk sac to the intestine. It occurs in about 2% of the population. It is found on the antimesenteric border of the ileum, usually within a foot of the ileocecal valve. Meckel diverticulum is the most common cause of severe lower gastrointestinal bleeding at all age groups. The bleeding is usually painless and typically maroon colored alternating with bright red–colored bleeding per rectum. Other associated complications include inflammation, intussusception, ulceration, and obstruction. About 4% of patients with Meckel diverticulum will develop complications, most of them in the first 2 years of life.

The diagnosis is made on clinical grounds and supported by positive technetium-99m scan. A negative scan does not rule out the diagnosis. False-negative or false-positive results occur in about 15% of cases.

The sudden onset of melena with bilious vomiting in an apparently healthy child should suggest malrotation or midgut volvulus. Barium enema should be performed

immediately if such diagnoses are suspected to confirm the malrotation and to ensure emergency laparotomy if the diagnosis is confirmed.

Duplication

Duplication has been attributed to a failure of recanalization after the solid stage of intestinal development. Gastric duplication is usually cystic or tubular structure that usually occurs within the wall of the stomach. Intestinal duplications share a common wall and blood supply with native bowel. Diagnosis is confirmed by Tc-99M radionuclide scan. Approximately two thirds of all intestinal duplications are discovered within the first 2 years of life.

Duplications may be classified into three categories:

- Localized duplications, duplications associated with spinal cord defects, and vertebral malformation duplications of the colon.
- Communicating duplications may cause gastric ulceration and be associated with hematemesis or melena that may result in significant morbidity and mortality if left untreated. The most common clinical manifestations are associated with partial or complete gastric outlet obstruction. The treatment is surgical resection and management of associated defects.

Gastrointestinal Polyps

Single and multiple colonic polyps are recognized causes of rectal bleeding. Painless intermittent fresh rectal bleeding is likely to be due to polyps in the large bowel.

Although polyps may undergo autoamputation, profuse bleeding or malignancy remains a potential complication. Fiber-optic colonoscopy is the best way to diagnose polyps and permits immediate painless removal under mild sedation by snare polypectomy.

Colonic polyps also include those associated with familial syndromes such as in Peutz-Jeghers syndrome in which the polyps are hamartomas with rare incidence of malignant transformation.

Gastrointestinal polyps are divided into the following main types.

Juvenile Polyps

The juvenile polyps are benign lesions of the colon associated with few problems and tend to undergo autoamputation. They are the commonest form of intestinal polyposis in childhood (>90%). Juvenile polyps are most commonly seen in early childhood and are rarely encountered after the age of 16 years. Juvenile polyps are hamartomas, usually solitary and located in the rectum or sigmoid colon. They appear as smooth red or brown, round or ovoid, cyst-like projections into the intestinal lumen. Painless rectal bleeding is invariably the presenting symptom. Intussusception is not a common complication, but low-lying polyps tend to prolapse. Juvenile polyps can be easily visualized in most cases through the sigmoidoscope. A barium enema and air-contrast study may detect solitary polyps in the anorectal region (*Fig. 199.4a*) or higher up in the colon. Diagnosis is confirmed on histology.

Treatment is primarily conservative and supportive. If symptoms persist after I year, snare polypectomy is performed (*Fig. 199.4b*). Once removed, a simple juvenile polyp does not recur. Juvenile (retention) polyps are generally hamartomas with link malignant potential. Colorectal carcinoma is a rare complication with either single or multiple juvenile polyps. Patients with multiple juvenile polyps and a positive family history should undergo surveillance for colorectal carcinoma.

Juvenile Polyposis

This is a rare condition of familial polyposis predominantly in the colon. The polyps may be segmental or diffuse and extend through the colon with age. There is now little doubt that juvenile polyposis is a premalignant condition.

Generalized Juvenile Gastrointestinal Polyposis

This is a serious and fatal disease of infancy. The polyps extend from the stomach through the small intestine, colon, and rectum. Recognized clinical manifestations include rectal prolapse, gastrointestinal hemorrhage, and intussusception.

The diagnosis is suspected by a positive family history. Sigmoidoscopy shows numerous rectal and sigmoid polyps. Rectal polyps are removed to prevent prolapse. The treatment is basically conservative. The disease carries a high mortality rate.

Familial Polyposis Coli

This disease, inherited as an autosomal dominant trait, carries with it the formidable risk of carcinoma. Colectomy is the treatment of choice as soon as diagnosis is made. The polyps occur mostly in the sigmoid colon but

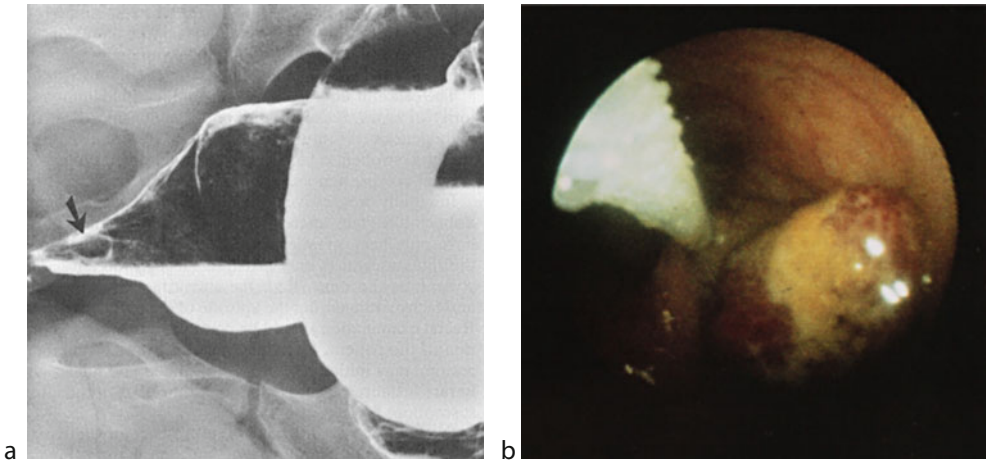

Figure 199.4
Juvenile rectal polyp. (a) Barium enema with air contrast (anteroposterior decubitus) showing solitary polyp in the anal canal of a 4-year-old girl with intermittent rectal bleeding. (b) Snare polypectomy of a solitary juvenile polyp

may extend through the entire colon and rectum. The number of the polyps is variable, from only a few to thousands. Although the disease is usually recognized in late childhood and adolescence, it has been reported in young infants. Clinical features include bloody diarrhea, abdominal pain, and weight loss.

Diagnosis is made through sigmoidoscopy, which reveals the numerous polyps in the rectum and sigmoid colon. Air-contrast enemas are particularly helpful in demonstrating multiple polyps. The accepted treatment for familial polyposis coli is proctocolectomy and ileostomy. All siblings of affected patients should be screened by sigmoidoscopy and radiology.

Gardner Syndrome

This is a familial disorder of diffuse adenomatous polyps as seen in familial polyposis coli together with soft tissue tumors and osteomas of the skull, mandible, and long bones.

Peutz-Jeghers Syndrome

This syndrome consists of multiple polyposis of the gastrointestinal tract associated with melanotic spots of the buccal mucosa, lips, and skin. Inheritance is through a dominant gene of high penetrance. The polyps, which are hamartomas, usually extend from the stomach to the rectum. The polyps are not present at birth but develop later with age. The polyps are subject to intussusception, torsion with infarction, and hemorrhage. Melena occurs in about one third of patients. Rectal prolapse is not unusual. The typical mucosal pigmentation is the prerequisite for the diagnosis. Asymptomatic polyps need not be treated. Surgical resection is required in case of intussusception or obstruction.

Intussusception

Intussusception is defined as the invagination of a segment of the intestine within the lumen or the adjoining segment. Intussusceptions are most often ileocolic and ileoileocolic. Other areas of the gut including the appendix may also be involved. Intussusception is a well-recognized surgical emergency in infants and children. It is a common cause of both intestinal obstruction and strangulation as well as a cause of bleeding per rectum. Therefore, once intussusception is diagnosed, appropriate management should immediately follow. The incidence of intussusception ranges between 1 and 4 per 1,000 live births. Intussusception is more common in males than in females. The condition is seen mostly in young infants (6–10 months of age) who present with severe abdominal pain associated with flexion of knees and hips.

The child looks normal in between the episodes of pain. Abdominal examination may also be normal at this stage. A palpable "sausage-shaped" mass in the right upper and middle abdomen is recognized on clinical examination. The passage of "currant jelly" stools or its detection on rectal examination is not essential for the

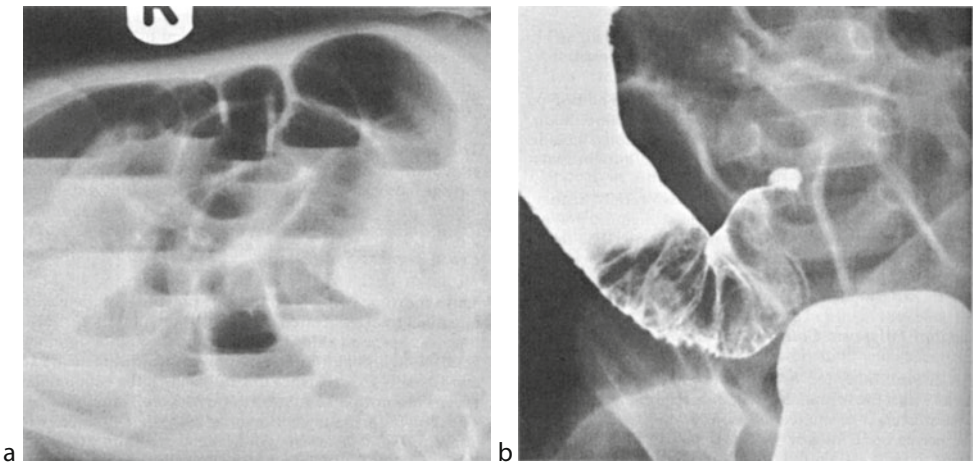

Figure 199.5
Ileo-colic intussusception in a 9-month-old female infant. (a) Abdominal radiograph (anteroposterior decubitus): features of intestinal obstruction with multiple fluid levels in the small bowel. (b) Barium enema: filling defect in cecum and ascending colon with "coil-spring" appearance

diagnosis when other clinical features and radiologic findings are very much supportive of the diagnosis.

However, intussusception is almost always accompanied by rectal bleeding, especially in young infants. The condition is uncommon in babies under 4 months of age.

The clinical picture is generally different among babies with intussusception aged less than 4 months than those aged 4 months or more. Affected babies with intussusception in the younger age group (<4 months) have less painful episodes, more vomiting, and rectal bleeding. Their response to hydrostatic reduction is also less than that of the elder age group. Vomiting, which is a common symptom of intussusception, may become bile-stained.

The cause of intussusception is not identified in the majority of cases. Some conditions to be considered in the pathogenesis of intussusception are Henoch–Schönlein purpura, swollen Peyer patches, Meckel diverticulum, intestinal polyps, tumors, and hemangioma.

In rapidly progressive cases, the infant may present with a shock-like state where the classic clinical features could have only been manifested at home. On rare occasions, the intussusception may prolapse through the anus. The patient may become pale at the initial stage, with sweating and tachycardia during the episode of the abdominal pain. Rectal examination should be performed at initial evaluation of the patient. Examination, which reveals an empty rectum, may initiate the passage of blood and mucus and in rare instances enable palpation of the apex of the intussusception.

Diagnosis is not difficult in the presence of the typical clinical presentation and radiologic confirmation (*Fig. 199.5*). A barium enema may show the "coiled-spring sign" at the site of the intussusception; however, ileoileal intussusception is not usually demonstrated by barium enema. The usual site of intussusception is in the region of ileocecal valves.

The application of air-contrast enema has contributed favorably to the diagnosis and management of intussusception. Ultrasound examination is resorted to more often nowadays early following admission of a child with suspected intussusceptions, and in positive findings, it could well save affected child the needs for subsequent radiation. The well-recognized ultrasound findings in intussuception may be so typical and supportive to the diagnosis to warrant considering the child for surgery with no further delay.

Once the diagnosis of intussusception is made, there is hardly any time for observation. Reduction may first be attempted by hydrostatic or pneumatic pressure under fluoroscopy, provided the surgeon and the operating theater staff were already informed of the plan and the possibility of surgery should the nonsurgical reduction fail. The prognosis in intussusception is very much related to the time interval between clinical manifestations and successful reduction, whether through hydrostatic pressure or surgical measures.

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200 Gastrointestinal Tumors

Issam M. Halabi

Gastrointestinal tumors are less common in children compared to adults. Furthermore, the presentation can mimic common gastrointestinal disorders. Therefore, a high index of suspicion is needed to detect these tumors in children.

Luminal Gastrointestinal Tumors

These tumors constitute about 5% of all childhood tumors. Presentation is variable and relatively nonspecific. The symptoms and signs include abdominal pain, abdominal distension, vomiting, palpable mass, anemia, GI bleeding, or weight loss. They can also be found in the course of surgery for intussusceptions, bowel obstruction, or perforation as well as the incidental finding during a surgical or radiological procedure for other reasons. Definitive diagnosis usually requires a biopsy for histopathological examination and possibly immunotyping and cytogenetics, depending on the tumor.

Luminal tumors are divided according to their cells of origin: lymphoid, epithelial, or mesenchymal. Lymphoid tumors are the most common. Any of these types can be benign or malignant. In the following sections, the types, diagnosis, treatment, and prognosis of the more common tumors will be discussed.

Lymphoid Tumors

The gastrointestinal tract is rich in lymphoid tissue, particularly the ileum. This represents an adaptation for response to antigens.

Lymphonodular Hyperplasia

Lymphonodular hyperplasia (LNH) is a benign condition that is common in early childhood and adolescence parallel to the lymphoid tissue growth. It is more common in males. It can present with diarrhea, rectal bleeding, abdominal pain, or intussusceptions. Endoscopically nodular and frequently umbilicated mucosal lesions are seen in small and large intestines. Reactive hyperplasia and prominent germinal cells are seen on histology. No specific therapy is required and prognosis is excellent.

Lymphoma

The gastrointestinal tract is second to nodal tissue for the incidence of lymphomas. It represents 15% of all small bowel malignancies. The vast majority are non-Hodgkin. The most common site (40–50%) is terminal ileum, cecum, and appendix. This is contrary to adult data showing stomach as the most common site. Lymphomas secondary to celiac disease are exception to this rule with the jujenum being the most common location.

Lymphomas present most commonly with abdominal mass or intussusceptions. Diagnosis usually requires surgical resection. Endoscopic biopsy is inadequate since lesions may involve deeper layers than mucosa or submucosa. If suspected, tumor distribution should be determined using abdominal CT, bone scan, lumbar puncture, and bone marrow aspirate. Certainly, consultation with an oncologist is needed.

The histological appearance is characterized by "starry-sky" appearance. This image is created by sheets of mitotically active cells with scanty cytoplasm and round to oval nuclei with small nucleoli.

Treatment is mainly chemotherapy with radiotherapy as an augmentation. Surgical resection is only helpful in focal disease. Prognosis depends on several factors, with staging being the most important. Resectability also is a favorable factor.

Epithelial Neoplasm

Tumors of epithelial origin are either carcinoma or carcinoid with the latter being uncommon in childhood.

Carcinoma of the Colon

Despite infrequency of colorectal cancer in children compared to adults, it remains the most common primary

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solid malignancy of the GI tract in this age group. It is reported in less than 0.1 cases per million children less than 20 years of age.

Colorectal cancer can be sporadic or familial with 70–80% of cases belonging to the former. It is widely believed that that environmental factor play significant role in the etiology. This belief is based on the higher incidence seen in the Western world with high-fat/low-fiber diet as a variable.

Besides the sporadic type, a familial type with autosomal dominant pattern was also described in the absence of polyposis or ulcerative colitis. There are two patterns recognized. Lynch 1 syndrome with no associated extracolonic carcinoma while in Lynch syndrome 2 such an association with carcinoma of genital tract, breast, and pancreas is seen.

The clinical presentation is vague abdominal pain in 95% of cases, altered bowel habits in 17–32%, and rectal bleeding in 14–23%. Abdominal mass is appreciated in 59%, abdominal distension in 48%, and anemia in 25%. Diagnosis needs high index of suspicion. Any suspected mass on CT or MRI should be followed by lapratomy and surgical resection. Pathology is needed for diagnosis. Surgical resection is the mainstay of treatment. Staging is necessary by bone scan and chest CT.

The genetic basis for colorectal carcinoma is the mutational inactivation of the APC gene in the colonic epithelial cells.

Carcinoids

These tumors originate from differentiated endocrine cells; therefore, they may secrete GI peptides and hormones including serotonin, 5-hydroxytryptophan, histamine, prostaglandins, catecholeamines, and bradykinins. Metastasis to the liver can happen. Most common site is the appendix. Although most of these tumors are asymptomatic in adults, children can present with appendicitis.

Symptoms related to secreted substances include diarrhea, bronchoconstriction, edema, and flushing. Diagnosis can be established on surgical resection. Some patients have high urine level of 5-HIAA a serotonin metabolite. Histological appearance is remarkable for islands of tumor cells with granular cytoplasm and round nuclei with chromatin seen within.

Treatment is by resection. However, if metastasis has taken place, symptomatic relief should be sought by somatostatin analogues. Chemotherapy is needed sometimes. Prognosis depends on the presence of metastasis. In this regard, appendiceal tumors have much lower chance of metastasis (4%) compared to intestinal (55–70%).

Neoplasm of the Liver

Represent 1–4% of pediatric solid tumors. Metastatic tumors are more common. The vast majority 80% of primary tumors are seen in children before the second birthday with hepatoblastoma and infantile hemangioendothelioma the two most common.

Hepatoblastoma

Hepatoblastoma (HB) is the most common pediatric liver malignancy. It represents 43% of all pediatric primary hepatic tumors. Male to female ratio is 2:1. It occurs in association with a number of familial cancer syndromes. Beckwith–Wiedemann syndrome and familial adenomatous polyposis are clear examples. Non-tender abdominal mass is the most common presentation. Anorexia, weight loss, nausea, vomiting, and abdominal pain are less common.

Diagnosis is established by histology. Because these tumors originate from undifferentiated cells pathologically, they are characterized by fetal and embryonal hepatocytes. However, alpha fetoprotein (AFP) is elevated in 90% of patients. It has diagnostic, prognostic, and monitoring indication. It correlates with the size of the tumor and metastasis. It drops with treatment and resurges with recurrence. Hypercalcemia and hyperlipidemia are also seen. Imaging is helpful in suggesting the diagnosis. Ultrasound is a good initial test but inadequate particularly for the extent of the tumor and the detection of small-size tumors. CT or MRI with contrast can show right lobe mass with calcification found in 50%. Surgical resection is the treatment for early stage tumors. It should be preceded by chemotherapy for advanced stages.

Infantile Hemangioendothelioma

Hemangioendothelioma is a benign vascular tumor. It is most commonly seen in the first 6 months of life. One third of these cases are seen in the first month of life. A distinction should be made between these tumors and their counterparts in adults with malignant potential.

Anemia is the most common presentation (50%) and congestive heart failure can develop in 10–15% of cases. Abdominal distension is common. Less common signs include jaundice, thrombocytopenia, failure to thrive, fever, and intrahepatic hemorrhage.

Diagnosis is suspected with ultrasound. Ultrasound shows lesions of different echogenecity depending on the

vascularity. CT and MRI are diagnostic in defining the extent of lesions. Histology is not necessary for diagnosis. It shows ecstatic vascular spaces lined by endothelial cells and contains erythrocytes.

Treatment strategies are directed toward tumor regression. Resection is indicated if heart failure is associated. Embolization can also be considered. Diuretics, alpha interferon, and steroids have been used in hemodynamically stable patients. Prognosis is excellent.

Hamartomas

Hamartomas are rare benign fluid-filled tumors as visualized on US, CT, and MRI. They are seen usually in the first 2 years of life. Resection is the treatment of choice.

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201 Capsule Endoscopy in Childhood

Issam M. Halabi

Introduction

Video capsule endoscopy (VCE) helps close the gap in the evaluation of the small bowel, which has been regarded as the "black box" of endoscopy. The invention of the PillCam SB capsule endoscope, a small, ingestible camera, established a minimally invasive method for imaging the gastrointestinal (GI) tract in its natural physiological state. A second version, the PillCam ESO capsule endoscope, was subsequently developed for imaging of the esophagus.

The disposable PillCam capsule endoscope glides through the digestive system and takes high-quality color pictures of the inner GI tract. The pictures are immediately transmitted by radio via antennas attached to the patient's abdomen to an external, belt-worn data recorder. The data recorder picks up the images, allows for immediate real-time viewing of the captured images, and stores them for later review.

The pictures may be viewed in a real-time by connecting the data to RAPID Access, a special system for display of real-time pictures captured by the PillCam capsule (*Fig. 201.1*). Otherwise, the patient is free to move around, wearing the data recorder.

When the test is done, the antennas and data recorder are removed from the patient and the pictures are downloaded from the data recorder to a computer workstation featuring the RAPID application. This process automatically prepares a RAPID video movie from the captured pictures for diagnostic review and evaluation. The capsule continues to pass through the digestive system until it is excreted naturally.

Once the RAPID video is ready in the RAPID Workstation, it can be viewed either on the RAPID Workstation or transferred to and viewed on any computer installed with the RAPID Reader application, which is a read-only application for RAPID videos.

The main components of the given diagnostic system are:

1. PillCam capsule endoscope
2. Data Recorder
3. RAPID Workstation with RAPID Application
4. RAPID Reader Application

Capsule endoscopy does not need any sedation to perform. There is no loss of work since the patient can conduct usual daily activities during the recording process. There is no insufflation or forcing instruments through the GI tract that diminishes the likelihood of perforation. The capsule passes through by virtue of peristaltic propulsion.

PillCam incorporates a small video camera complete with light emitting diode (LED)-based illumination, optics, wireless radio transmitter, all encapsulated in a biocompatible and inert plastic casing (*Fig. 201.2*). The capsule is 26 mm long and 11 mm in diameter. Pictures are taken and transmitted at a rate of two per second. This means that an 8-h recording by which time the capsule reaches the cecum, a total of 56,700 images are produced. It is activated when taken out of its holder. The holder keeps the capsule from activation by a magnet incorporated.

Procedure

The capsule endoscopy procedure involves ingesting the capsule endoscope, collecting the captured pictures in belt-worn Data Recorder, returning the Data Recorder to the physician, and downloading the accumulated data to the RAPID Workstation and viewing the RAPID Video. The patients are asked to fast for eight hours prior to the ingestion. Ordering GI prep is controversial among gastroenterologists.

Indications

According to 2005 ICCE Consensus, the indications for this study include:

1. Obscure GI bleeding
2. Crohn's disease
3. Polyposis syndrome
4. Small intestinal tumor

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Figure 201.1
Illustration of the relative size of ingested capsule

Obscure GI Bleeding

Defined as GI bleeding with negative EGD and Colonoscopy. The source is most likely small intestines. It can present with iron deficiency anemia, melena, or guaiac positive stools. In published meta-analysis, VCE has been shown to have superior diagnostic yield compared with small bowel follow through (SBFT) and push enteroscopy.

Crohn's Disease

VCE is superior to SB barium evaluations and colonoscopy with ileoscopy in the diagnosis of Crohn's disease. This is particularly obvious when upper studies show "indeterminate colitis." Detection of small bowel (SB) lesions settles the diagnosis. In addition VCE helps in determining the extent of the disease in those patients with established diagnosis.

Polyposis Syndrome

VCE can detect SB involvement in familial adenomatous polyposis (FAP) and Peutz–Jeghers syndrome. It is superior to more conventional methods including SBFT.

Small Intestinal Tumors

VCE is considered first-tier imaging modality for the small intestine based upon the literature and data presented to the US Food and Drug Administration. Earlier detection of such lesions improves the outcome and enables earlier intervention.

Complications

To date a total 750,000 procedures have been performed. Capsule retention in the SB is the most common serious complication. It happens in about 1% of ingestions. It is more likely to happen in patients with Crohn's disease. Retention of the capsule would warrant surgical extraction. However this does not have to be done urgently since the risk of perforation is minimal. Using an Agile patency capsule will minimize the potential of retention (see following section).

Other less likely complications include tracheal aspiration of the capsule.

Contraindication

Implanted cardiac devices (pacemakers and defibrillators) are absolute contraindications. Intestinal strictures are relative contraindications because of retention risk. VCE can still be performed provided that the stricture is not significant enough to prevent the passage of the capsule. To aid in that determination Agile patency capsule is performed prior to VCE (see following section). Another contraindication is swallowing disorders for aspiration risk. This can be overcome by introducing the capsule through EGD.

Patency Capsule

Capsule retention is the most common serious complication of VCE, as discussed previously. This usually occurs in the setting of undiagnosed SB stricture. Crohn's disease, abdominal radiation or surgery history, NSAID use, or obstructive symptoms may warrant confirmation of SB luminal patency prior to VCE. Barium studies of the SB are helpful for significant strictures, but are of limited utility in the detection of mild to moderate luminal narrowing, which may cause capsule retention.

The patency capsule consists of a radiofrequency tag within a lactose composition that dissolves after

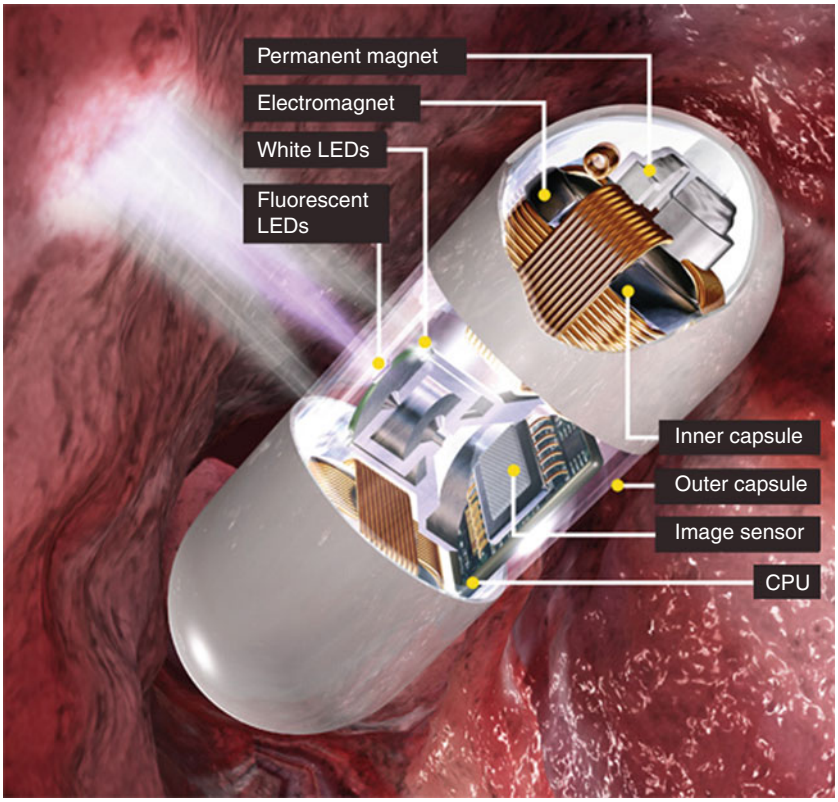

Figure 201.2
Longitudinal section of the capsule illustrating different components

approximately 30 h if retained in the luminal tract. The persistence of the patency capsule and tag is detected by a handheld scanner in the office or endoscopy setting. This capsule does not produce images. In contrast to VCE, the risk of acute intestinal obstruction with the patency capsule is finite.

Procedure Details

The exam begins between 7 and 8 a.m. with capsule ingestion, following 12 h of fasting. It ends the same day at 4 p.m. with the patient being disengaged from the data recorder. Initially, the 8-lead sensor array is fixed to the patient's abdomen. The capsule is activated by removal of the magnet, followed by confirmation of signal transmission to the data recorder. During the day-long procedure, patients may return, work, or engage in other activities. They may drink water 2 h after ingestion. They may then take their medications and eat a light lunch 4 h after ingestion. Patients should exercise care with the sensor array when changing clothes or in the bathroom. A study is considered complete when on VCE recording review the capsule reaches the cecum before the end of recording. In this case no radiologic confirmation of passage is needed. Otherwise a plain film should be checked in 2 weeks.

Bowel prep may improve the quality of visualization of the SB with VCE, but the recommendations are in evolution. Optimal prep type, dosage, and timing remain to be defined.

Conclusion

In summary, capsule endoscopy is a safe, well-tolerated exam, which provides for unique visualization of the small intestine. Small bowel indications are expanding beyond the current focus on OGIB and CD. The growing literature and extensive international experience underscore the diminishing numbers of contraindications, particularly in carefully selected patients. The development of the patency capsule significantly decreases the complications.

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202 The Liver and Biliary System

Bernadette Vitola · Jorge A. Bezerra

Embryogenesis and Anatomy

The liver is a cellular organ that executes vital cellular functions and communicates with the remainder of the digestive system by a series of ductular and vascular structures essential for normal metabolic and excretory pathways. Its developmental landmarks begin in early embryogenesis, when the liver begins as a thickening of endothelial cells that proliferate and invade the neighboring mesoderm of the septum transversum. This is followed by a series of steps involving cellular proliferation, migration, and differentiation to give rise to the hepatic parenchyma and additional morphogenic changes to form the bile ducts. These processes occur in an orderly fashion during embryogenesis and establish structural and functional features that are well recognized in the mature liver (*Table 202.1*).

The Liver

The first identifiable structure indicating the developing liver appears in the ventral part of the foregut at about 4 weeks of gestation, just cranial to its opening into the yolk sac. At this stage, the cellular plate projects ventrally and lies closely to the endothelial lining of the heart in the transverse septum. Soon thereafter, this plate forms the hepatic diverticulum, and subsequently a (cystic) diverticulum develops caudally (*Fig. 202.1a*). The cells from the hepatic diverticulum advance into the splanchnic mesoderm of the transverse septum, between the heart and the midgut, and form cellular masses that intermingle with the epithelium-lined spaces, which arise from closed vesicles (vitelline veins). These invading cells, also known as hepatoblasts, unite and form hepatic cords, anastomosing around these vesicles to form the configuration of parenchyma and sinusoids. This "*primordial parenchyma*" is at first three to five cells thick, but later is reduced to a single-cell layer due to growth of the blood vessels. The proximity of two or more adjacent hepatocytes forms *biliary canaliculi*, which lose continuity with the perisinusoidal space (of Disse) by the formation of junctional complexes. Lastly, these canaliculi are connected with the developing interlobular bile ducts in the portal areas by short intercalated ductules (or *canals of Hering*). Together, the proliferation of endoderm-derived epithelial cells and the expansion of hematopoietic mesenchymal cells establish a configuration of a solid organ that begins to bulge out of the transverse septum, and later becomes an intra-abdominal organ lying within the mesentery.

The Biliary System

The biliary ductular system develops from the hepatic and cystic diverticula (*Fig. 202.1a*). The intrahepatic bile ducts derive from hepatoblasts, bipotential endodermal cells capable of differentiation into hepatocytes or bile duct cells. Hepatoblasts adjacent to mesenchyme around the largest hilar portal vein branches shift their phenotype toward bile duct-type cells. These cells form a layer that surrounds the portal vein branches and become the ductal plate. Soon, the ductal plate acquires a second cell layer and a progressive remodeling occurs, first with tubular dilatation of the slit-like lumen within the double-layered plate, and subsequently with disappearance of most of the nontubular portions of the ductal plate. The remaining structure is the *bile duct*, which is further separated from hepatoblasts by expansion of the mesenchyme and formation of the portal space. These morphogenic steps also occur toward the periphery, around smaller portal vein branches. Toward the hilum, the ducts enlarge by merging with neighboring ducts, finally uniting with extrahepatic ducts.

The extrahepatic ducts derive from the cystic diverticulum, which becomes solid due to the migration of endodermal cells into the original lumen. By the end of the first trimester, the lumen is reestablished and the bile duct is formed by recanalization of the stalk that connects the hepatic and cystic ducts to the duodenum. This establishes a continuous ductular unit that extends from the biliary canaliculi to the most terminal end of the extrahepatic bile duct as it enters the duodenum (*Fig. 202.1b*).

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Table 202.1
Developmental landmarks during embryogenesis of the human liver

Embryonic age	Developmental landmark
3–4 weeks	Formation of hepatic diverticulum
	Hepatic diverticulum projects as an epithelial plug into the septum transversum
5 weeks	Hepatic parenchyma can be seen
	Primordial hepatocytes are identified as large polygonal cells
6 weeks	Formation of bile duct-type cells (begins closer to hilum)
	Formation of ductal plate
	Primitive gallbladder and common bile ducts are solid cords of epithelial cells directly underneath the developing liver
	Bile canaliculus is present
7–9 weeks	Hepatocytes acquire apical-basal polarity
	Lumen in the common bile duct
	Lumen in the hepatic duct
	Lumen in the gallbladder and cystic duct
10 weeks	Hepatoblasts close to portal space (but not involved in ductal plate formation) lose cytokeratin 19 and retain 8 and 18
12 weeks	Glycogen granules are seen in hepatocytes
16 weeks	Bile secretion begins
20 weeks	Cytokeratin 7 appears in cells of developing ducts

Vascular Structures and Ligaments

The developing liver incorporates the omphalomesenteric and umbilical veins. The inferior segments of the omphalomesenteric (vitelline) veins feed the sinusoidal plexus and later become *the portal vein*, while the superior segments form the hepatic veins, which receive the sinusoidal blood and drain it into the sinus venosus (suprahepatic inferior vena cava). The placental blood flows through the umbilical veins, which send branches to the liver; part of the left umbilical vein becomes *the ductus venosum*, which shunts placenta-derived arterial blood from the umbilical vein to the inferior vena cava. After birth, the obliterated pre-hepatic segments of the umbilical veins atrophy become *the round ligament of the liver*, while the ductus venosus becomes the ligamentum venosum. The residual transverse septum forms *the falciform ligament*, hepatic capsule, and mesothelium. Later, the mesothelium becomes the visceral peritoneum, which will cover the entire liver, except for the bare area of the liver, where it maintains original contact with the transverse septum. Finally, by 6 weeks of human gestation, the liver appears bilobed and branches of the hepatic and portal veins are evident.

Cellular Composition

Microscopically, the developing liver is populated by endodermal cells (*hepatocytes and bile duct cells*) and mesenchymal cells (sinusoid endothelial, stellate and Kupffer cells, and lymphocytes). The existence of a pluripotent (stem) cell in the adult liver, which is able to give rise to hepatocytes or bile duct cells, has been suggested to reside in the periportal space, at the junction between hepatocytes and the small ductules of the biliary tree. Together, cords of hepatocytes maintain close proximity with neighboring sinusoidal endothelial, stellate, and Kupffer cells; they assume a typical architectural frame, which links the central vein to the portal space and form the liver acinus. Hepatocytes are grouped into concentric zones surrounding the terminal afferent vessels in the portal space: cells proximal to these vessels comprise *zone 1, followed by zone 2, and then zone 3*, which contains hepatocytes more proximal to the central vein. In this organization, *zone 1 cells* are exposed to high nutrient and oxygen content, whereas those of *zone 3* receive blood of considerably less oxygen content and are possibly more susceptible to vascular and toxic forms of liver injury. The directional blood flow from zones 1–3 is important for the development of functional differences among hepatocytes according to their placement along the liver acinus.

Anatomy and Geography

The liver is held in place below the diaphragm in the right upper quadrant of the abdomen by the falciform, coronary, triangular, and hepatoduodenal ligaments. The location of the *falciform ligament* divides the liver into the right and left lobes, with the right lobe typically being larger than the left lobe. The liver can be further divided into eight segments based on the distribution of blood vessels and bile ducts.

The biliary system drainage begins with canaliculi, formed by canalicular domains of adjacent hepatocytes, which evolve into intrahepatic bile ducts that drain bile by maintaining continuity with extrahepatic bile ducts.

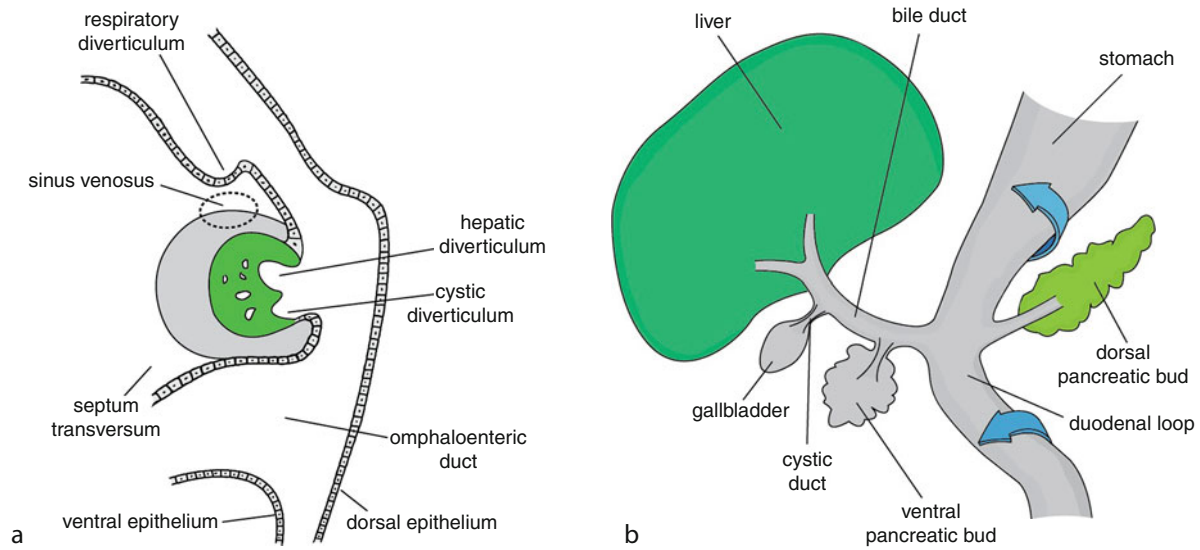

Figure 202.1

(a) Development of the liver and biliary system from the embryonic endoderm. The figure depicts a medium section of the developing embryo at 4.5 weeks of gestation, a time when the hepatic and dystic diverticula can be seen in relation to the respiratory diverticulum and septum transversum. (b) Development of the extrahepatic biliary system. At 6 weeks of gestation, the extrahepatic ductal system has continuity with intrahepatic ducts, the pancreatic exocrine ductal system, and with the developing duodenum

The gallbladder stores bile excreted from the liver until it is needed for a meal.

The primary blood supply to the liver is *the portal vein*, which is formed by the union of the splenic and mesenteric veins. *The common hepatic artery* also supplies blood to the liver, especially the bile ducts. Both the portal vein and hepatic artery divide into right and left branches to supply the lobes of the liver.

Functions

Metabolic Function

Carbohydrate Metabolism

One of the most important functions of the liver is to maintain appropriate serum glucose values, which it does by converting ingested fructose and galactose to fuel-ready glucose or trioses, storing glucose excess as glycogen, and by a combination of glycogenolysis (timely breakdown of glycogen) and gluconeogenesis (formation of glucose by amino acids and fatty acids). The formation of glycogen from glucose and the enzyme-dependent breakdown of glycogen to release glucose are regulated by enzymes that are functional prior to birth. This enables the fetal liver to efficiently store enough glycogen to prepare for the energy needs of birth. By the third postnatal week, glycogen stores reach sufficient levels in most full-term newborns. Therefore, neonates are dependent on external source of nutrients (via frequent feeding) to maintain adequate serum glucose after the initial glycogen stores are depleted immediately after birth.

Protein Metabolism

Amino acids are a major source of energy utilization in the fetus providing up to 40% of fetal energy needs. The liver uses deamination and transamination of amino acids to remove the nitrogen portion of the protein, with the remaining protein to be converted to lipid or carbohydrate for further metabolism. Excessive nitrogen is prevented by metabolism of ammonia to urea, which is the major source of clearance of urea. The liver is also able to synthesize nonessential amino acids from uptake of free amino acids.

Lipid Metabolism

The liver plays a central role in how the body handles lipids, including bile acid-driven digestion and absorption,

packaging into lipoproteins, esterification, and storage. When the supply of glucose is limited, the liver utilizes ketones produced from fatty acid oxidation to provide an energy source for gluconeogenesis. This represents a major source of calories in early infancy given the high-fat, low carbohydrate diet in this age group. The liver also esterifies glycerol to form triglyceride as a mechanism to store fat when glucose is in abundance.

Metabolic Defects and Clinical Syndromes

Defects in any of the enzymatic steps involved in carbohydrate, protein, and lipid metabolism can result in severe liver and/or extrahepatic disease. For carbohydrates, the excessive storage of normal substrates (example: glycogen) or the production of metabolic precursors that are toxic to hepatocytes (example: galactose-1-P) can manifest as hepatomegaly with hypoglycemia or liver failure (◉ *Table 202.2*), respectively. Liver failure in young infants can also result from the inability to complete final steps in the degradation of tyrosine in infants with *hereditary tyrosinemia*. In older infants, the disease may present with rickets and hepatocellular carcinoma as clinical manifestations of the underlying chronic exposure to abnormal metabolytes. Interestingly, liver function and anatomy are normal in children who are unable to metabolize ammonia due to main enzymatic defects in the urea cycle, but the abnormal accumulation of ammonia is toxic to the central nervous system with high mortality or devastating neurologic sequelae (◉ *Table 202.2*).

Disorders of fatty acid oxidation present with muscle weakness and lethargy, often precipitated by prolonged fasting or stress; cardiomyopathy and coma can be severe manifestations. Laboratory studies show hypoketotic hypoglycemia and variable degrees of liver dysfunction. Fatty acids, substantial sources of reserve energy, are utilized during periods of prolonged fasting since hepatic glycogen stores are depleted within a few hours of no caloric intake. Similar symptoms may also be present in children with mitochondrial dysfunction, which leads to primary energy failure (unavailability of ATP) and secondary disruption of fatty acid oxidation (◉ *Table 202.2*).

Table 202.2
Examples of liver-based metabolic defects that result in significant hepatic and/or extrahepatic clinical syndromes

Substrate or organelle	Disease	Key clinical features
Glucose	Glycogen storage disease	Hepatomegaly, hypoglycemia
Galactose	Galactosemia	Hypoglycemia, neonatal liver failure, sepsis
Fructose	Fructosemia	Vomiting, lethargy, hypoglycemia, liver failure
Tyrosine	Hereditary tyrosinemia	Acute form: Coagulopathy, liver failure
		Chronic form: Coagulopathy, liver tumor, rickets
Ammonia	Urea cycle disorders	Vomiting, seizures, coma
Fatty acid	Fatty acid oxidation defects	Lethargy, muscle weakness, cardiomyopathy, hepatomegaly, hypoketotic hypoglycemia
Carnitine	Carnitine deficiency	Lethargy, vomiting, cardiomyopathy, muscle weakness, hypoglycemia
Bile acids	Bile acid defects	Jaundice, malnutrition, coagulopathy, rickets
Mitochondria	Mitochondriopathies	Metabolic acidosis, nausea, vomiting, hypotonia, seizure, cardiomyopathy, liver failure

Synthetic Function

The liver is central to the synthesis of a wide range of soluble factors and hormones, besides the production of albumin, clotting factors, carrier proteins, complement, and lipoproteins. Albumin is commonly low when children have decreased liver synthetic function, but it is not a reliable marker of recent changes in synthetic function because it has a long serum half-life and its production is usually preserved until the liver injury is widespread and advanced. A more timely evaluation of hepatic function is best obtained by prothrombin time, whose assay takes into account the presence of clotting factors that are synthesized in the liver and have a short half-life. Thus, measuring the prothrombin time or the

levels of vitamin K-dependent factors II, V, VII, X, especially after the parenteral administration of vitamin K, gives a very reliable indication of the extent of liver cell loss and the potential for recovery.

Excretion

The liver excretes a variety of substances into bile, *including bilirubin, bile acids*, and xenobiotics. Bilirubin is a lipid-soluble byproduct of hemoglobin breakdown. It circulates in blood bound to albumin and is actively taken up by hepatocytes, where it is conjugated to glucuronic acid and transported to the canaliculi as conjugated bilirubin for final excretion into bile. A similar parallel process involves the *synthesis of bile acids from cholesterol*, followed by conjugation with glycine or taurine for excretion, transport by canalicular proteins, and final excretion as part of bile into the duodenum. The synthesis and delivery of bile acids into the gut are the most important means for the body to excrete cholesterol. Further, an adequate intraluminal concentration of bile acids is critical for the efficient absorption of fat and fat-soluble vitamins. Thus, impairment in formation and excretion of bile acids results in decreased cholesterol output and impaired absorption of lipids and lipid-soluble vitamins. Bilirubin, the colored pigment in bile, is responsible for the typical color of stools. When it is absent, stools become white, gray or pale yellow (acholic stools), which is often seen in young infants with impaired bile formation and/or secretion because of hepatocellular injury (e.g., viral hepatitis) or obstruction of extrahepatic bile ducts (e.g., biliary atresia).

Biochemical Evaluation of Liver Disease

Markers of Liver Injury or Impaired Bile Excretion

Acute hepatocellular injury typically results in elevation of the aminotransferases: aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Although these enzymes are also expressed in extrahepatic organs (e.g., erythrocytes and muscle), their primary source is the hepatocyte. Regardless of the type of liver injury, such as viral infection, metabolic defects, autoimmune disease, or drug toxicity, a rise of AST and ALT is a good marker of hepatocyte injury. Generally, ALT rises more or at the same level of AST; however, acute ischemia and alcohol toxicity are more associated with higher levels of AST. If the acute liver injury is widespread, serum AST and ALT may rise >100-fold above baseline; with persistent injury, a sudden drop in the level of the enzymes may indicate liver failure. In contrast, the degree of elevation of aminotransferases in chronic hepatocellular injury is more modest, often ranging from two- to tenfold above normal. This is typically seen in chronic viral hepatitis, syndromes of intrahepatic cholestasis, autoimmune hepatitis, biliary atresia, and some metabolic diseases.

A rise in bilirubin is a common hallmark of biliary injury or abnormal bilirubin transport at the level of hepatocyte canaliculi. Jaundice is the typical manifestation of hyperbilirubinemia; pruritus may also be present. Elevation of unconjugated bilirubin can be caused by hemolytic diseases or genetic abnormalities that decrease the function of UDP-glucuronosyltransferase, the enzyme that conjugates newly formed bilirubin before transport into bile. In both settings, there is no intrinsic hepatocellular injury. In contrast, a rise in conjugated bilirubin is a hallmark of liver disease. Although most liver diseases display variable elevations of conjugated bilirubin sometime during progression of the disease, a rise in conjugated bilirubin disproportionate to more modest elevations in AST and ALT point to cholestatic liver disease, such as biliary atresia, syndromes of intrahepatic cholestasis, and obstruction of extrahepatic bile ducts. Elevated bilirubin can also be detected in the urine, which sometimes is the first indication of liver disease when a urinalysis is obtained during a health screen or as part of an evaluation of an acute illness.

Two other enzymes may also increase in cholestasis: alkaline phosphatase and γ-glutamyl transpeptidase (GGT). High levels of serum alkaline phosphatase and GGT are seen with biliary obstruction (e.g., cholelithiasis and biliary atresia) or injury of biliary canaliculi and bile ducts (e.g., intrahepatic cholestatic syndromes and sclerosing cholangitis). Alkaline phosphatase is also found in a variety of tissues including bone, enterocytes, and kidney. Therefore, in growing children, alkaline phosphatase may be elevated from bone growth. Unlike alkaline phosphatase, GGT does not increase with bone growth and is somewhat more specific to biliary duct disease; however, it often increases transiently upon exposure to common drugs and toxins. In newborns, GGT is typically elevated with peak concentrations in the first 2 weeks of life. In patients with intrahepatic cholestasis, GGT concentrations may enable the differentiation between these specific syndromes. Among these syndromes, deficiency of the canalicular transporters familial intrahepatic cholestasis-1 (FIC1) or bile salt export pump (BSEP) have normal or low serum GGT despite high levels of conjugated bilirubin,

Table 202.3
Relationship between serum markers of cholestasis and clinical syndromes with functional or anatomical impairment of bile flow

	UB	CB	GGT	AP	Bile acids	Cholesterol
Physiologic jaundice	High	Normal	Normal	Normal	Normal	Normal
Breast milk jaundice	High	Normal	Normal	Normal	Normal	Normal
Biliary atresia	Variable	High	High	High	High	Normal
Alagille syndrome	Normal	High	High	Normal	High	High
PFIC types 1 or 2	Normal	High	Normal	Normal	High	Normal
PFIC type 3	Normal	High	High	Normal	High	Normal
Obstructive cholelithiasis	Normal	High	High	High	Variable	Normal
Choledocal cyst	Normal	High	High	High	High	Normal

UB unconjugated bilirubin, *CB* conjugated bilirubin, *GGT* γ-glutamyl transpeptidase, *AP* alkaline phosphatase, *PFIC* progressive familial intrahepatic cholestasis

whereas defects in MDR3, a phospholipid flippase, results in high levels of GGT (Table 202.3). Another marker of cholestasis is the increased concentration of serum bile acids. A rise in serum bile acids (before feeds in young infants or after an overnight fast in older children) indicates abnormal canalicular function or impaired excretion by bile ducts. Increases in serum bile acids and/or the presence of xanthomas may be the only clinical manifestation of cholestasis (Table 202.3), thus comprising the clinical signs of "anicteric cholestasis."

Laboratory evaluation of synthetic function includes prothrombin time (PT)/international normalized ratio (INR), albumin, and vitamin K-dependent factor levels (factors II, V, VII, X). Typically, impairment of liver synthetic function results in coagulopathy with an elevated PT and INR and variable decreases in albumin and factor levels. The clinical consequences of decreased synthetic function can be mild, as in easy bruising, epistaxis, and small hematomas, or more severe with gastrointestinal and intracranial bleeding.

Other Laboratory Tests

A variety of other laboratory tests are used to diagnose specific hepatic disorders. For example, in the evaluation of disorders of protein metabolism, serum and urine amino acid profiles are important diagnostic tools for urea cycle defects and amino acidopathies. Familial hyperlipidemias can be characterized by serum lipid profile, in which the determination of high, low, and very low-density lipoproteins, cholesterol and triglycerides enables subtyping and treatment with lipid-lowering agents. Finally, the evaluation of children with *syndromes of energy failure* involves a combination of routine and specialized metabolic tests. These syndromes usually present with altered mentation (changes in behavior, somnolence, coma), sepsis-like illnesses, seizures or sudden cardiac arrest during febrile illnesses or prolonged fasting. Very useful routine tests include serum bicarbonate, glucose, and ammonia, coupled with the concentration of lactate and pyruvate, plasma acyl-carnitine profile and urine organic acids. These tests are critical for the evaluation of infants and children suspected of having disorders of mitochondrial function, fatty acid oxidation, and carnitine metabolism.

The type and titer of circulating antibodies and the detection of viral DNA or RNA by reverse transcription-polymerase chain reaction can be used individually and in combination with other tests to diagnose viral hepatitides and other viral infections of the liver. The presence and high titers of autoantibodies (e.g., anti-nuclear, anti-smooth muscle, anti-liver/kidney/microsome), total immunoglobulin levels, and abnormal gamma-tracing in electrophoresis of serum proteins are helpful in establishing autoimmune liver disease. Lastly, a serum level of alpha-fetoprotein, a protein that is normally expressed during embryogenesis, is used to screen for liver cancer in patients with chronic liver disease.

Imaging Techniques to Evaluate the Liver

Ultrasound

Ultrasound can evaluate the texture and shape of the liver, the gallbladder, and extrahepatic bile ducts. It provides very useful information about intrahepatic, gallbladder or

ductal gallstones, the presence of choledochal cysts, and dilatation of bile ducts. The benign nature of sound waves enables the performance of the test during gestation, and can diagnose cystic malformations in the liver and porta hepatis. The use of ultrasound has become widespread in pediatric hepatology, and is often the first test to evaluate the anatomy of the liver and biliary system in children with abnormal liver function tests. Specific signals can point to the presence of fatty liver or hepatic inflammation.

The addition of doppler-based imaging provides insight into the arterial and venous blood flow to the liver, and reliably assesses the status of the portal blood flow, including patency and the existence of portal hypertension by the presence of excessive collateral vessels and/or abnormal direction of venous blood flow away from the liver. The detection of arterial flow in cystic lesions is indicative of vascular malformations. Ultrasound and doppler are routinely used in interventional radiology to direct biopsies to specific anatomic location (as in the evaluation of liver mass or cysts). Ultrasound is also useful in confirming the presence of ascites, detecting small amounts of ascitic fluid that moves freely in the abdominal cavity, or fluid that is loculated within a specific location as seen when the ascitic fluid is infected in children with recurrent bouts of spontaneous bacterial peritonitis in the setting of chronic liver disease.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI)

CT and MRI provide more detailed evaluation of intrahepatic lesions when compared with ultrasound. Administration of intravenous contrast is particularly useful to define vascular patency and anatomy, as well as the relationship between blood supply and intrahepatic lesions. CT provides great anatomical detail of lesions within individual anatomical domains, which is very useful in assessing the feasibility of surgical approaches to remove masses or cystic lesions (*Fig. 202.2*). CT images can be obtained very quickly, thereby making this technique useful in infants and young children who require immobilization or sedation for more prolonged imaging that is required for MRI. The primary concern with CT is the patient's exposure to ionizing radiation. To minimize this exposure, ultrasound should be used preferentially as a follow-up study of lesions detected by CT scan.

MRI provides great anatomical details of the liver, biliary system, and blood vessels. One superior feature of MRI is the ability to change the contrast of the image,

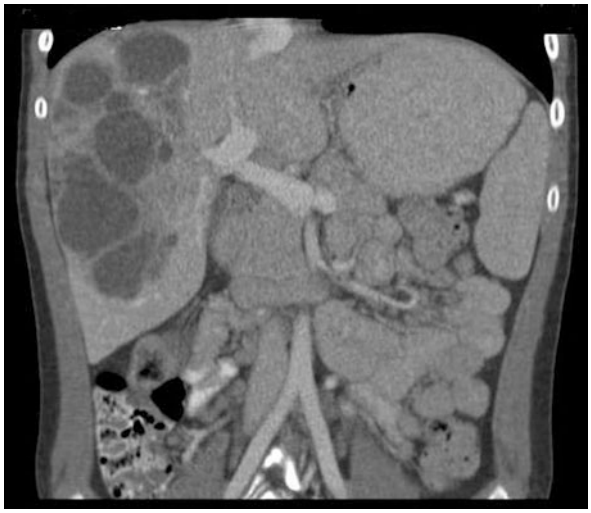

Figure 202.2
Computerized tomography of a 7-year-old boy with hepatomegaly showing multiple cysts in the right liver lobe. Right hepatectomy was performed and the histopathology was consistent with hamartoma

which can generate very useful information regarding fat accumulation in the liver. An improvement in the technique offers a noninvasive alternative to diagnostic endoscopic retrograde cholangiopancreatography (ERCP) when evaluating diseases of the biliary tract, known as magnetic resonance cholangiopancreatography (MRCP). The technique is performed with the use of heavily T2-weighted sequences to visualize fluid-containing bile ducts as anatomically distinct high-signal-intensity structures. Despite the noninvasive advantages over endoscopic cholangiography, MRCP is limited in the evaluation of bile duct diseases in infants and young children, although advances in the field are likely to facilitate the performance and accuracy of this imaging technique in this patient population in the future.

Cholangiography

ERCP allows direct visualization of the biliary tract by the injection of contrast through the ampulla of Vater during endoscopy. Images obtained with ERCP provide very detailed information about the intra- and extrahepatic bile ducts. ERCP also permits intervention for stone removal, ductal strictures, or obstructions. When performed by experienced endocopists, ERCP is very useful in the evaluation of hepatobiliary diseases in all age groups. A technique that also requires sedation/anesthesia is percutaneous

transhepatic cholangiography (PTC); it is often under the domain of interventional radiologists. PTC is used when ERCP expertise is not readily available, and it is commonly used in the evaluation of biliary lesions following liver transplantation. When evaluating infants for extrahepatic biliary diseases, of which the most common is biliary atresia, *intraoperative cholangiogram* remains the most direct modality to evaluate patency and anatomy of bile ducts.

Hepatobiliary Scintigraphy

Scintigraphy uses technetium-labeled iminodiacetic acid to assess hepatocellular uptake (function) and patency of the biliary tract by documenting the production and flow of bile from the liver to the small intestine. Following administration of the labeled agent, sequential images of the liver, biliary tract, and intestine are obtained. Computer acquisition and analysis enable the visualization of uptake by the liver and whether bile ducts are patent, as demonstrated by enhancement of the small intestine. To improve uptake and excretion, children may be given doses of phenobarbital. While this technique has high sensitivity in detecting biliary atresia by demonstration of optimal liver uptake but no excretion, it may lead to false-positive results since poor excretion may also be seen in other liver disease. Further, the time required for preparation of the patient and the need for delayed images may limit the usefulness of hepatobiliary scintigraphy in the diagnosis of biliary atresia, in which the timely diagnosis and treatment with hepatoportoenterostomy are key to improve long-term outcome. Hepatobiliary scintigraphy is very useful in demonstrating biliary leaks, as in spontaneous perforation of the gallbladder in infants or in complications of biliary surgery.

Microscopic Evaluation of the Liver

There are two purposes for performing a *liver biopsy:* diagnosis of liver disease and monitoring of chronic liver disease. For diagnosis, obtaining liver tissue is useful for a number of reasons. The histologic appearance alone of certain diseases is highly suggestive of the diagnosis. For example, livers of infants with biliary atresia have expanded portal tracts, portal edema, bile duct proliferation, and bile plugs (*Fig. 202.3a*). In congenital hepatic fibrosis, the portal tract is expanded by dense collagen deposition and the bile ducts display features typical of ductal plate malformation, in which bile duct profiles surround the edges of portal tracts (as well as within the portal space). Examination of the lobular domains can show panlobular injury to hepatocytes, or the typical centrilobular injury induced by acetaminophen toxicity. Giant cell transformation of hepatocytes is a frequent feature of injury to the neonatal liver, especially in inborn errors of bile acid metabolism. An assessment of the presence, type, and location of inflammatory cells is very important in the evaluation of elevated liver enzymes secondary to viral infection or autoimmune liver disease (*Fig. 202.3c*).

Fragments of liver biopsies can be used for quantitative analysis of a variety of substances (iron, copper, glycogen, lipid) and for assays of specific enzyme activity, such as the activity of glucose-6-phosphatase to determine the type of glycogen storage disease. In patients with chronic liver disease, biopsy can provide information regarding the status of the liver, as demonstrated by excessive collagen deposition visualized by trichrome staining in liver biopsies of children with cirrhosis (*Fig. 202.3b*). Liver biopsies can also be very useful in assessing the efficacy of therapy, such as in children on corticosteroid

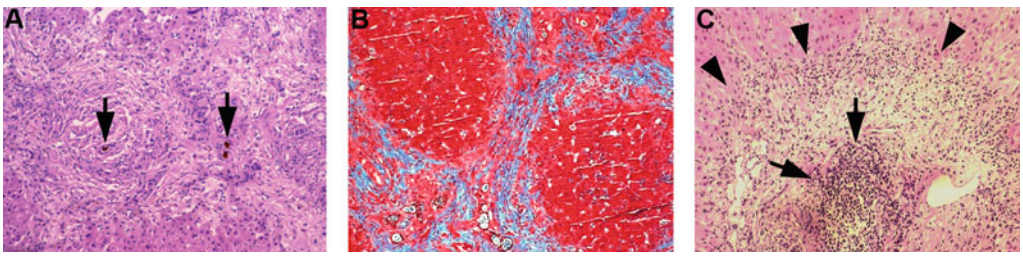

Figure 202.3

(a) shows hematoxylin/eosin staining of a liver section depicting an expanded portal tract with proliferation of bile ducts, some of which contain bile plugs (*arrows*). In (b), trichrome stain shows increased collagen deposition of expanded portal tracts, encasing hepatocytes and forming micronodules. (c) shows hematoxylin/eosin staining of a liver section from a child with autoimmune hepatitis, in which there is dense inflammation within the portal tract (*arrows*) and along the limiting plate (*arrow heads*).

treatment for autoimmune hepatitis or in older children and adolescents on iron-chelating agents for hemolytic disorders.

Percutaneous liver biopsy is usually a safe and relatively straightforward procedure when performed by a skilled hepatologist. In specific instances where the anatomy is modified, as in segmental liver transplantation, or when there are concerns for abnormal blood flow, liver biopsy is best performed under ultrasound guidance. The primary risk is bleeding since the liver is a highly vascular organ. Thus, it is important to assess the bleeding risk prior to performing a liver biopsy. Patients who are thrombocytopenic or coagulopathic need these issues to be addressed with the administration of blood products prior to and/or during the procedure; otherwise, percutaneous biopsies are contraindicated and a surgical approach must be considered.

Although most liver biopsies are obtained for evaluation by light microscopy, there are additional types of evaluation that can be invaluable. Immunostaining can be applied to detect abnormal accumulation of alpha-1-antitrypsin, to identify markers of neoplastic cells within the hepatic lobule, or to detect the abnormal expression or absence of specific molecules. When there is concern for a viral infection (e.g., cytomegalovirus and Epstein-Barr virus), in situ hybridization may be utilized to confirm the presence of viral particles. In situ hybridization utilizes a labeled DNA or RNA probe to bind to viral mRNA in the liver tissue.

Liver biopsies can also be used for electron microscopy to establish the diagnosis of diseases that involve malformation or injury of specific cellular organelles or the cytoplasmic accumulation of substrates. For example, livers of children with mitochondrial disorders may demonstrate large numbers of disorganized mitochondria with shortened, fragmented, or absent cristae. The cytoplasm may show accumulation of glycogen or other substrates in storage diseases, or may uncover virus particles. The ultrastructural visualization of the canalicular lumen may reveal the presence of granular bile, which is typical in children with an inherited syndrome of progressive familial intrahepatic cholestasis type 1 (*Table 202.3*).

Clinical Manifestation of Liver Disease

Jaundice

Jaundice is the physical manifestation of hyperbilirubinemia, either conjugated or unconjugated. Total serum bilirubin needs to be 2–3 mg/dL before jaundice can be noted on sclera or skin. Unconjugated bilirubin is common in healthy neonates owing to a developmental delay in conjugation of bilirubin with glucuronic acid within hepatocytes, and in breastfed infants. Unconjugated bilirubin also increases with hemolysis, genetic defects that impair hepatic conjugation (as in *Gilbert and Crigler-Najjar syndromes*), or increased enterohepatic circulation. Although jaundice is common in newborns, the presence of jaundice beyond the second week of life requires fractionation of serum bilirubin even if the infant is breastfed, so that further investigation can be pursued if there is a concomitant rise in conjugated bilirubin. Such an increase in conjugated bilirubin should immediately raise concerns for liver disease, especially if the conjugated fraction represents >20% of total bilirubin. Jaundice owing to conjugated hyperbilirubinemia can be caused by a specific defect in the transport of conjugated bilirubin into bile (e.g., *Dubin–Johnson syndrome*). More commonly, however, it can be a manifestation of a systemic disease that indirectly affects the hepatobiliary system, as is seen in septicemia, or represents the first sign of primary disease of the liver or the biliary tract, as in biliary atresia.

Hepatomegaly

Liver size can be assessed by palpation below the costal margin and by percussion of the liver span. For children with diffuse storage of substances (e.g., glycogen) in hepatocytes, hepatomegaly is easily detected by the palpation of the liver edge well below the right costal margin. An abnormally long end of the right lobe may be present in normal children *(Riedel's lobe)*, but the presence of a firm liver edge below the xyphoid process can be seen in children with advanced fibrosis and hypertrophy of the left lobe. Ultrasound is useful in assessing the size and consistency of the liver. Generally, hepatomegaly can result from storage of glycogen, lipid, mucopolysaccharides and other substances, from infiltration of inflammatory or neoplastic cells, or from venous obstruction.

Ascites

Ascites, an accumulation of fluid in the peritoneal cavity, is a common manifestation of advanced liver disease. Ascites results from portal hypertension accompanied by hypoalbuminemia (secondary to impaired liver synthetic function) and inappropriate sodium and water excretion (secondary to an imbalance of the rennin-angiotensin system). Accumulated fluid can become secondarily infected from translocation of gastrointestinal pathogens in a condition known as spontaneous bacterial peritonitis.

Ascites is usually managed by sodium restriction and diuretics, primarily spironolactone and furosemide. With progression of liver disease, ascites becomes difficult to manage with standard medical therapy; the child may develop hyponatremia and may not tolerate feedings or meals owing to compression of the gastrointestinal tract. It may become necessary to perform paracentesis to remove ascitic fluid if the child develops respiratory distress and has no response to diuretic therapy.

Portal Hypertension

The excessive deposition of collagen and other matrix fibers in the portal space and along the sinusoids impairs portal blood flow and raises intravascular portal pressure. As the pressure rises, collateral channels develop, the umbilical vein becomes recanalized, and portal venous flow may be reversed. Venous collaterals can form almost anywhere in the abdomen, but those in the esophagus and stomach have greater clinical significance because they form varices and can be the source of gastrointestinal bleeding. Within the abdominal wall, collaterals can be seen arising from the paraumbilical veins, which are referred to as *caput medusae* due to their tortuous appearance. In addition, increased portal pressure leads to splenomegaly and *hypersplenism* resulting in pancytopenias.

Bleeding/Bruising

Easy bruising and epistaxis can be presenting features of impaired protein synthesis, which decreases the levels of clotting factors. In children with advanced liver disease, the combination of coagulopathy and thrombocytopenia increases the risk of severe gastrointestinal bleeding. Any child with brisk variceal hemorrhage, hematemesis, or hematochezia should be promptly evaluated, receive blood products as needed, and admitted to a specialized service. If red blood cells are administered, they should correct hemoglobin levels to 8–9 g/dL to avoid over-filling of vascular beds, which may increase intravascular pressure and precipitate new episodes of variceal hemorrhage. Specific treatment of variceal hemorrhage may be performed with banding or sclerotherapy by an experienced endoscopist.

Encephalopathy

Hepatic encephalopathy is a manifestation of advanced liver disease.

It is divided into four stages based on clinical manifestations:

The first stage is associated with day–night sleep disturbance and impaired mentation. Without treatment, the child evolves into *the second stage* with lethargy, confusion, and asterixis, and *the third stage is* characterized by an arousable stupor; *the fourth stage* manifests as coma. It is not uncommon for a patient to move between stages rapidly.

The pathogenesis of hepatic encephalopathy is not clear. However, it is associated with impaired clearance of metabolic products, which may be toxic to the central nervous system. Serum ammonia is often used as a marker of encephalopathy, but the serum concentration does not correlate well with the stages of encephalopathy. Although protein intake is often restricted to reduce ammonia production, children still need to maintain adequate caloric intake to prevent further deterioration of malnutrition and decreased muscle mass. *Lactulose*, a non-digestible disaccharide, is frequently given to induce ammonia loss in the stools and decrease serum ammonia. Children with encephalopathy must be evaluated for liver transplantation.

Hepatopulmonary Syndrome

Hepatopulmonary syndrome occurs in children with portal hypertension, most commonly associated with chronic liver disease. It is characterized by an intrapulmonic shunt and manifests as hypoxemia. Although the pathogenesis of hepatopulmonary syndrome is not well understood, it probably relates to the uncontrolled exposure to vasoactive substances that are not properly processed by the liver. Symptoms include exercise intolerance, digital clubbing, and dyspnea. Screening for hepatopulmonary syndrome can be performed by quantification of oxygen saturation by pulse oxymetry; arterial gasometry and bubble echocardiography demonstrate shunting more precisely. Hepatopulmonary syndrome can be reversed in children after transplantation.

Malnutrition

Malnutrition is highly prevalent in children with chronic liver disease and is a known risk factor for adverse outcomes after transplant. The factors leading to malnutrition include decreased intake, poor digestion, and impaired absorption. Fat malabsorption is present even in early phases of disease due to a decrease in the

intraluminal concentration of bile acids. Even when caloric intake is optimized, children with chronic liver disease exhibit resistance to growth hormone with low levels of insulin growth factor-1.

It is not unusual to supplement the child's diet with continuous enteral feedings, often as overnight infusions, in an attempt to meet a child's daily energy requirements for growth. The use of formulas that contain medium-chain triglycerides improves absorption as they do not require bile acids for digestion and absorption. Parenteral nutrition may be considered for those children who do not tolerate enteral feedings, but it brings new risks of infections related to the presence of indwelling catheters.

In addition to general nutrition support, children with chronic liver disease are at high risk of fat-soluble vitamin deficiency. Supplementation with vitamins A, D, E, and K is almost universally indicated given the high frequency of fat-soluble vitamin deficiency. Vitamin A, D, E, and K deficiency occurs in approximately 30%, 70%, 5%, and 70% of children with liver disease, respectively. It is important to follow the levels of these vitamins because fat-soluble vitamin deficiency is still common despite supplementation. If deficiency develops, children may present with coagulopathy (vitamin K deficiency), peripheral neuropathy and cerebellar ataxia (vitamin E deficiency), eye dryness, corneal damage and night blindness (vitamin A deficiency), and osteomalacia and rickets (vitamin D deficiency). Therefore, supplementation of all vitamins should be common practice to prevent morbidity associated with chronic liver disease in children.

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203 Practical Approach to a Child with Hepatobiliary Disorder

H. Hesham A-Kader

The practical approach to a child suspected to have hepatobiliary disorder should entail detailed history, careful physical examination, and judicious selection of biochemical tests and imaging techniques.

When evaluating a patient with possible hepatobiliary disorder the goal is to determine whether or not the patient has hepatobiliary disorder and if he does how severe is it. The priority should be focused on the disorders for which an early recognition and intervention can prevent long term sequelae and prevent vertical and horizontal transmission. These goals should be achieved in the most cost-efficient and noninvasive manner without subjecting the child to unnecessary tests or invasive procedures unless indicated.

For example, during the neonatal period the initial evaluation of a newborn with cholestasis should initially focus on the exclusion of manageable metabolic diseases such as tyrosinemia and galactosemia, treatable infections such as *E. coli*, and surgically correctable disorders such as biliary atresia and choledochal cyst. The prompt diagnosis and immediate intervention for these disorders is of paramount importance to prevent damage to liver and other organs.

Therefore, the selective choice of currently available diagnostic tools commonly used in daily practice requires understanding of their justification, implications, as well as limitations.

History

Age is an important factor in reaching the diagnosis of a child suspected to have a hepatobiliary disorder. Inborn errors of metabolism and disorders of biliary tract development are commonly seen early in life. It is uncommon to diagnose Wilson's disease before the age of 4 years. Autoimmune hepatitis is more commonly seen in teenagers and Reye syndrome is usually diagnosed in the 4–8 year range. The sex of the patient should be recorded. Autoimmune hepatitis and cholecystitis are more commonly diagnosed in girls while Indian childhood cirrhosis is more often seen in boys.

Information regarding the ethnic background of the child should be obtained. Hepatitis B is common in people from Southeast Asia and Eastern Europe. Portal vein thrombosis is common among Egyptian children while veno-occlusive is common in Jamaica. Cystic fibrosis is the most common genetic disease in Caucasians affecting 1 of 2,000 individuals.

History of drug intake is also very important. Several drugs and excessive vitamin intake, such as vitamin A, can be hepatotoxic. (A detailed description of drugs and hepatotoxicity will be covered in the section on Drug Induced Liver Injury.) Similarly toxins exposure can result in hepatotoxicity. An example is aflatoxin from toxigenic strains of *Aspergillus flavus* which occurs commonly in parts of Asia and Africa. Aflatoxin may play a role in the pathogenesis of Reye syndrome. Similarly bush tea has been linked to the development of veno-occlusive disease.

Physical Examination

Careful physical examination is an integral part of the diagnostic process of hepatobiliary disorder in the pediatric age group. Physical examination is never complete without assessment of vital signs (temperature, pulse, blood pressure, and respiratory rate). Patients with liver cirrhosis may develop hyperdynamic circulation due to arteriovenous shunts manifesting with rapid high-volume pulse, increased pulse pressure, and ejection systolic murmur.

Weight, height, and head circumference need to be assessed at the time of presentation and during every visit and plotted on the growth charts. Patients with hepatobiliary disorder commonly present with failure to thrive. Growth retardation is more profound if the hepatic dysfunction results from an inborn error of metabolism. Intrauterine infection such as rubella, cytomegalovirus, and toxoplasmosis may be associated with microcephaly. On the other hand hydrocephalus may be a feature of syphilis or toxoplasmosis.

Examination of the abdomen begins with careful inspection. Abdominal distension may be seen in patients

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with hepatosplenomegaly and ascites. Patients with portal hypertension may have dilated veins in the epigastrium and flanks or caput medusae radiating from the umbilicus. Palpation of the abdomen requires patience and expertise as children usually cry during examination tensing their abdomen. Distracting the child by conversation or with a colorful stethoscope may facilitate the examination process. In some cases asking the mother to keep the patient on the mother's lap may comfort the child. The lower liver edge may be palpable in normal infants and children. The lower lobe may be felt up to 3.5 cm below the costal margin in the first 6 months of life, up to 3 cm in the first 4 years and 2 cm in children between 4 and 10 years old. Since lung inflation can push the liver down the liver span as measured between the upper border determined by percussion and the lower border detected by palpation provides a more accurate measure of the liver size. Lawson et al. measured the liver span in 350 infants and children by percussion of the upper and lower borders in the midclavicular line. Mean liver span ranged from 1.9 cm at 1 week of age to 7.7 cm in males and 6.3 cm in females at 20 years of age and was found to be related to age in a curvilinear manner.

Age and sex were found to be the main factors influencing liver size. Although height and weight correlated with liver span they did not add substantially to the correlation using age and sex.

Normal livers usually have a smooth round edge. Cirrhotic liver usually have a sharp irregular border. Patients with acute hepatitis may experience tenderness to palpation or percussion. Palpation of the abdomen may reveal anatomical abnormalities such as central liver in patients with polysplenia, laevo-position of the liver or a Reidel's lobe projecting inferiorly from the right hepatic lobe.

The spleen is usually felt on the left. However, palpation for the spleen should begin from the right iliac as very large spleens can cross the midline and felt on the right side. The spleen is usually not palpable unless it is at least three times the normal size. The spleen size should be recorded in centimeters measured in its long axis. If the spleen is not felt the Short's maneuver can be used. With patient being asked to lie on the right side, the examiner places the left hand on the lower left ribs in the midscapular line pushing the spleen forward while palpating for the spleen with the other hand.

Patients with suspected liver disease should be evaluated for the presence of ascites. Generally there are two methods to detect free fluid in the peritoneal cavity: A fluid wave may be elicited with the patient in the supine position and an observer placing his hand on the midline of the abdominal wall while the examiner is placing one palm on one side of the abdomen and tapping on the opposite flank with the fingers of the other hand. In the presence of free fluid a fluid wave can be felt. Another method is to ask the patient to lie in the supine position and the examiner's finger is placed on one flank parallel to the midline and percusses on a dull area. The patient is asked to lie on the opposite side while keeping the finger on the same place. After allowing the fluid to settle repercussion will give a tympanic note. Small amounts of fluid may be detected by placing the patient in knee-chest position while percussing the periumbilical area. This area should not be dull under normal circumstances.

Clinical Features

Unlike adults, symptoms of liver disease can be subtle in children and the majority of patients with infectious hepatitis are asymptomatic. Among the common signs and symptoms of hepatic dysfunction in children are:

Symptoms

Abdominal pain in the right upper quadrant	Fever
Malaise	Nausea
Vomiting	Pruritus
Bleeding	Irritability
Mental changes	

Signs

Jaundice	Dark urine
Pale stools	Anemia
Abdominal distension	Hepatomegaly
Splenomegaly	Ascites
Clubbing	Failure to thrive
Xanthomas	Ecchymosis
Palmer erythema	Edema
Altered skin pigmentations	

Biochemical Tests

Unfortunately the currently available liver function tests do not actually quantitate liver function but merely indicate the presence or absence of hepatic dysfunction.

In addition they do not assess severity, predict prognosis, or monitor disease activity as they often stay normal despite progression of the disease. The presence of one abnormal test should be considered in the context of the whole clinical presentation.

Transaminases

Aminotransferases (transaminases) are intracellular enzymes frequently measured as indicators of hepatocellular necrosis. Aspartate aminotransferase (AST, formerly serum glutamic oxaloacetic transaminase) and Aspartate aminotransferase (ALT, formerly serum glutamic pyruvic transaminase) catalyze the transfer of α-amino groups of aspartate and alanine, respectively, to the α–keto group of ketoglutaric acid.

ALT is primarily localized in the liver while AST is found in many tissues including liver, kidney, muscle, heart, and brain. Another difference between AST and ALT is the fact that ALT is a cytosolic enzyme while AST is present in the cytosol as well as the mitochondria.

Mild to moderate rise in transaminases is usually seen in patients with chronic viral hepatitis and cholestatic disease. On the other hand marked elevation is observed in acute viral hepatitis, following ischemia, and in patients with drug and toxin-induced hepatitis. The decline of the transaminases is seen with improvement but can be observed in patients with massive hepatic necrosis. Rise of serum bilirubin and worsening coagulopathy can help differentiating between the two conditions.

AST/ALT ratio can provide diagnostic information. Patients with alcoholic liver disease usually have a ratio of two or more because alcohol is a mitochondrial toxin. It should be noted that a decline of the ratio is seen with the development of cirrhosis. On the other hand ALT is usually higher than AST in patients with nonalcoholic fatty liver disease.

Serum transaminases levels should be cautiously interpreted in patients undergoing hemodialysis which can decrease the normal upper limits of these enzymes considerably.

Alkaline Phosphatase

Alkaline phosphatase (ALP) is a group of isoenzymes which catalyze the hydrolysis of phosphate esters at an alkaline pH. The enzymes are widely distributed in different tissues including liver, bone, kidney, intestine, and placenta. Therefore, elevation of ALP can be seen in multiple disorders in the absence of liver involvement. Mild elevation of ALP is seen in infiltrative hepatic diseases while marked elevation suggests the presence of extrahepatic biliary obstruction such as biliary atresia, choledochal cyst, and sclerosing cholangitis. Unfortunately the degree of elevation cannot differentiate between extra and intrahepatic obstruction. Actively growing children and adolescents may have increased serum level of ALP up to threefold and high ALP may be seen also as a familial trait.

Depressed serum ALP levels may be associated with congenital hypophosphatasia, hypothyroidism, pernicious anemia, and zinc deficiency. Patients with fulminant Wilson's disease complicated with hemolysis may have undetectable serum ALP levels possibly due to replacement of the cofactor zinc by copper leading to inactivation of ALP.

Gamma-Glutamyl Transpeptidase

Gamma-glutamyl transpeptidase (γ-GT) has been localized to the entire hepatobiliary tree with the greatest concentration in the epithelial cells lining the biliary ductules. Similar to ALP, γ-GT is widely distributed in different tissues including heart, kidney, brain, spleen, pancreas, and seminal vesicles. Elevated serum levels have been associated with an array of disorders such as pancreatitis, myocardial infarction, and renal failure. However, γ-GT is not found in bone and can help exclude bone disease as the source of elevated ALP.

Elevated γ-GT levels may be seen due to enzyme induction by alcohol and phenytoin. Normal levels can be seen in some forms of familial intrahepatic cholestasis. γ-GT normal levels are sex and age-related with levels higher in men. Neonates may have values five to eight times greater than adults with gradual decline during infancy.

5′-Nucleotidase

5′-Nucleotidase catalyzes the hydrolysis of nucleotides by releasing inorganic phosphate from the 5′-position of the pentose ring. 5′-Nucleotidase is present in the liver, intestine, brain, heart, and blood vessels. Despite the wide distribution of 5′-Nucleotidase elevated serum levels are usually from hepatic origin due to the unique detergent effect of bile salts on plasma membrane. Therefore measuring 5′-Nucleotidase can help distinguishing between hepatic and non-hepatic causes of raised serum ALP levels. Unfortunately measuring 5′-Nucleotidase is technically difficult.

Albumin

Albumin is made by the liver and is commonly used to measure hepatic synthetic function. Patients with liver disease may have low serum albumin levels due to decreased synthesis, increased degradation, or increased volume of distribution such as in the case of ascites. However, the long half-life of albumin (20 days) makes it an unreliable measure of recent hepatic function in patients with acute liver disease. Prealbumin may serve as a better index of recent hepatic protein synthesis due to its short half-life (1.9 days). Albumin is an acute phase reactant and serum levels may be also decreased in patients with non-hepatic disorders such as nephrotic syndrome, malnutrition, and protein-losing enteropathy. Hypergammaglobulinemia may lead to feedback inhibition of albumin synthesis by increasing the contribution of serum immunoglobulins to the plasma oncotic pressure.

Prothrombin Time and Coagulation Factors

The liver synthesizes all clotting factors with the exception of factor VIII which is made by the reticuloendothelial system. Prothrombin time evaluates the extrinsic coagulation pathway by measuring the rate of conversion of prothrombin to thrombin in the presence of thromboplastin and Ca^{2+} ions. Although the International Randomized ratio has been widely used it does not offer an advantage over prothrombin time in the evaluation of patients with liver disease.

With the deterioration of hepatic function the ability of the liver to synthesize the clotting factors declines and prolongation of prothrombin time is seen. Prolongation of 2 or more seconds poses risk for bleeding while prolongation of 3 or more seconds is a contraindication for invasive procedures such as liver biopsy.

Certain coagulation factors (II, VII, IX and X) are vitamin K-dependent. Vitamin K deficiency commonly seen in patients with cholestasis and steatorrhea can result in prolongation of prothrombin time. Parenteral injection of vitamin K usually results in at least 30% improvement in 24 h. Prolongation of prothrombin time can be also seen in association with congenital coagulation factors deficiency, consumptive coagulopathy, and the ingestion of drugs antagonizing the prothrombin complex such as bishydroxycoumarin derivatives.

Measuring clotting factors with short half-life can be used as a prognostic index in patients with acute liver failure. Although factor VII has the shortest half-life factor V is usually utilized since it is not vitamin K-dependent.

Des-γ-carboxy prothrombin is elevated in patients with cirrhosis due to defective γ-carboxylation of prothrombin which results in failure to bind calcium ions and functional impairment. Elevation of elevation of des-γ-carboxy prothrombin is also seen in patients with hepatocellular carcinoma and can be used as a complementary test to the measurement of alpha fetoprotein. Elevated serum level of Des-γ-carboxy prothrombin in liver donors has also been suggested as an indication for possible graft dysfunction in potential recipients.

Ammonia

Most centers no longer depend on ammonia level as an index for hepatic function for several reasons. Unless the sample is properly handled the ammonia level can be falsely raised. Samples should be run immediately or placed on ice. Following venipuncture ammonia levels can rise secondary to the action of the adenylic deaminase enzyme in the erythrocytes. Hemolysis can also increase ammonia levels since the majority of blood ammonia resides within the erythrocytes. The technique of obtaining blood samples in newborns by heel stick is commonly associated with hemolysis and falsely elevated ammonia, LDH, and AST.

On the other hand the elevation of ammonia levels do not correlate with the staging of portosystemic encephalopathy [PSE], normal levels do not rule out the diagnosis of PSE and raised values do not indicate the presence of PSE since it can be elevated in patients with urea cycle defects.

In most cases the diagnosis of PSE does not rely on determining ammonia level and is usually made clinically and measuring ammonia does not change management.

Imaging Studies

Plain Radiography and Barium Studies of the Upper Gastrointestinal System

Plain abdominal radiographs can provide helpful diagnostic information regarding the size of liver and spleen and the presence of ascites. More important, it can detect calcified lesions particularly gall stones, hepatic tumors, and granulomas.

Gas in the portal circulation can be seen in patients with itra-abdominal sepsis, ischemia, and perforated ulcers. Biliary gas may be seen following biliary surgery due to abnormal communication between the gut and biliary system.

Chest X-ray may show evidence of congenital heart disease or butterfly vertebrae commonly associated with Alagille syndrome. Wrist and knee X-rays may demonstrate the presence of osteopenia or rickets and can help determine bone age.

Although barium swallow may show large esophageal varices, it is much less sensitive than endoscopy.

Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP is a useful procedure with several diagnostic and therapeutic advantages. During the procedure the scope is introduced into the duodenum where the ampulla of Vater is identified and both biliary and pancreatic ducts can be cannulated and contrast material injected. The procedure has a definite value in the assessment of patients with extrahepatic biliary disease as well as patients with chronic and recurrent pancreatitis.

Although ERCP can help differentiate neonatal hepatitis from extrahepatic biliary atresia in patients with neonatal jaundice, the procedure is technically difficult in infancy and the development of smaller scopes is needed.

Therapeutic benefits of ERCP include placement of biliary stent, removal of biliary stones, and sphincterotomy. However these procedures are uncommonly needed in the pediatric age group.

Ultrasound

The development of Doppler Ultrasonography has been a major advance in the investigation of liver disease in children and adults. Ultrasonic examination can provide helpful information regarding the presence of gall stones and the size of spleen, pancreas, kidney, and gall bladder. However, it is imprecise in estimating the size of the liver. The detection of gall bladder makes the diagnosis of extrahepatic biliary atresia less likely. It can identify tumors, cysts, abscesses, and hemangiomas. It also helps in ultrasound-marked and guided liver biopsies especially when targeting a specific lesion. Extrahepatic bile ducts can be easily identified in most cases but intrahepatic ducts can rarely be seen except when dilated.

Portal hypertension is suggested by the presence of ascites, splenomegaly, gastric, and splenic varices. In patients with cirrhosis reversal of flow in the portal vein, increased pulsatility in the hepatic artery and, in advanced cases, reversal of flow during diastole may be seen.

Color-flow Doppler is extremely valuable pre- and post liver transplant for the evaluation of the patency of portal vein, hepatic veins and artery, and splenic vessels.

Computed Tomography (CT)

CT can help identify and perform biopsy on hepatic tumor and other space-occupying lesions. The use of oral contrast defines the bowel lumen while intravascular contrast enhances blood vessels and tissues. The introduction of spiral CT has been a major advancement allowing a faster collection of CT data than conventional scanners and permitting the scan of the entire liver at the peak enhancement of the contrast. CT of the brain can help detect cerebral edema in patients with acute liver failure as well as cerebral atrophy in children with metabolic disorders. CT angiography can provide noninvasive evaluation of the vascular structures.

CT has several advantages over ultrasonography. It is not operator-dependent, not affected by gas or obesity, and provides more global examination of the abdomen and pelvis. However, it is more expensive, requires general anesthesia in infants and small children, and involves radiation exposure.

Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is done by placing the patient in a uniform magnetic field and the images are obtained by applying and sampling of repetitive radiofrequency waves.

The technique of MRI has greatly improved recently and has replaced angiography in the diagnosis and staging of hepatic tumors. With the development of new software, three-dimensional images of the biliary system can be obtained (magnetic resonance cholangiography (MRC)) without the need to inject contrast material.

Currently with faster scans and new software noninvasive angiography (MRA) can provide very helpful information regarding portal venous hemodynamics such as direction and flow speed, anatomy, and patency.

MRI can also provide important information regarding consistency and storage of heavy metals in the liver and brain such as iron in patients with hemochromatosis and copper in patients in Wilson's disease.

The biliary and pancreatic ducts can be visualized in a noninvasive manner using MRCP which is an imaging technique that uses magnetic resonance imaging. MRCP is a much less invasive investigation when compared to

endoscopic retrograde cholangiopancreatography (ERCP) in the diagnosis of biliary and pancreatic pathologies. Therefore MRCP is currently used with increasing rate as an alternative to ERCP. In addition to imaging the biliary system in detail, MRCP has the advantage of imaging the surrounding tissues. In a recent study the diagnostic accuracy of MRCP with a heavily T2-weighted TSE MR sequence compared favorably with ERCP in various hepatobiliary disorders (Hekimoglu et al.).

Quantitative Liver Function Tests

Since most available liver function tests do not quantitate hepatic function and usually fail to provide prognostic information in patients with acute and chronic liver disease there is a pressing need for newly developed liver function tests especially in the era of liver transplantation.

Several quantitative liver function tests have been developed based on the ability of the liver to clear a substance from the blood.

Indocyanine green (ICG) is removed by the hepatocytes following intravenous injection. The administration of low doses can be used to measure hepatic blood flow. On the other hand, administration of higher doses can lead to uptake saturation and therefore can be used to measure hepatic function.

Aminopyrine breath test has been used to provide prognostic information in patients with chronic liver disease. However the test requires the administration of a radioisotope which limits its usefulness in children.

Serial measurement of galactose elimination capacity (GEC) by the 14C-galactose breath test can provide prognostic information regarding mortality in patients with chronic liver disease. However, similar to aminopyrine test, it requires radioisotope administration, and the ability of some tumors to metabolize galactose has limited its usefulness to measure hepatic residual function prior to tumor resection.

Caffeine breath test has been also investigated as a simple noninvasive way to measure hepatic function which does not require the administration of radioisotopes. Hoverer, the test fails to provide useful information in patients with mild liver disease. The common exposure to caffeine and the long half-life have limited the application of this test.

Lidocaine is metabolized by cytochrome p450 into monoethylglycinexylidide (MEGX). The measurement of MEGX is a simple, fast, and safe way to measure hepatic function. Measuring MEGX does not need sophisticated equipment and results can be rapidly obtained within minutes. MEGX levels have been shown to correlate with lack of serious complications in patients with liver cirrhosis. MEGX has also been shown to provide prognostic information regarding primary malfunction in liver transplant.

Liver Biopsy

Liver biopsy is a very valuable tool in the assessment of children with hepatic dysfunction. The morphological features seen in liver biopsy combined with the clinical manifestations can help to establish the diagnosis, assess severity, monitor response to treatment and follow progress of the disease. In addition liver biopsy can provide tissue for enzyme analysis in patients suspected to have inborn errors and to assess stored materials such as iron and copper. Although percutaneous liver biopsy is the most commonly used technique for collecting a liver sample other techniques include transvenous, laparoscopic, and open surgical biopsy.

Percutaneous liver biopsy may be performed via an anterior abdominal, right lateral abdominal, or right lateral intercostal (usually the tenth intercostal space) approach. The site for the procedure is usually chosen by physical examination or with an ultrasound. A percutaneous image-guided liver biopsy is similar to the one described above except that the needle is guided by CT scan or ultrasound images. In young infants (below the age of 6 months) percutaneous liver biopsy can be performed with a local anesthetic (lidocaine 1%); however, in older infant and young children a brief general anesthesia is preferred in order to guarantee compliance.

Following the procedure the patient is usually asked to lie on the right side for 4 h during which the vital signs are frequently monitored. Arguments against liver biopsy include cost, sampling error, variability of pathological interpretation, the lack of effective therapy for many disorders, morbidity, and mortality. The procedure is usually safe in expert hands. Complications of percutaneous liver biopsy include local pain, pleura pain, infection pneumothorax, peritonitis, hemorrhage, hematoma, hemobilia, arteriovenous fistula, and death.

Contraindications include coagulopathy, thrombocytopenia, suspicion of cystic, vascular or infectious lesions in the path of the needle, and extensive ascites. If fresh frozen plasma and platelet transfusion fail to correct the coagulopathy and thrombocytopenia, the most reasonable approach is to do a laparoscopic liver biopsy which is usually done in order to obtain a tissue sample from

a specific area(s) of the liver or when the risk of spreading cancer or infection exists.

Another option is performing transjugular liver biopsy which is done by a catheter passed through the internal jugular vein into the right hepatic lobe and then cannulating the hepatic vein. In addition to obtaining liver tissue this technique can measure intracardiac and hepatic vein pressure.

Open surgery liver biopsies are rarely performed nowadays unless they are part of another surgical procedure. During open surgery the liver tissue sample may be obtained by surgical excision or by using a biopsy needle.

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204 Disorders of the Gallbladder and the Biliary System

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Introduction

Although gallbladder and biliary tract diseases are relatively uncommon in infants and children, pediatric patients comprise a relatively big number of cholecystectomies, with a rising rate in recent years. Pediatric gallbladder stones (cholelithiasis) and bile duct stones (choledocolithiasis) are most commonly associated with hemolytic diseases or hemoglobinopathies; however, other risk factors are recognized. Extended administration of total parenteral nutrition (TPN) support and prolonged survival after extensive bowel resection increase the risk of gallbladder disease, a cause that will likely continue to increase as survival rates improve in extremely low birth weight infants. In addition, as childhood obesity reaches near-epidemic proportions in many Western countries, gallbladder disease related to dietary factors is increasing.

Gallbladder and biliary tract diseases should be in the differential diagnosis of any pediatric patient who presents with right upper quadrant pain, jaundice, or unremitting dyspepsia with normal endoscopic gastric findings. Asymptomatic gallstones and symptomatic pigment gallstones in children are common indications for surgery. Noncalcified gallstones due to long-term cholestasis or TPN may respond to medical therapy with choleretics such as ursodeoxycholic acid (UDCA). Aside from gallstones, the pediatric population can experience anatomical abnormalities including hydrops of the gallbladder, extrahepatic biliary atresia (EHBA), and choledochal cysts discussed below. Other anomalies as intrahepatic biliary hypoplasia, Caroli disease, perforations, and biliary dyskinesia are beyond the scope of this chapter.

Hypdrops of the Gallbladder

Hydrops, or mucocele, describe an overdistended gallbladder filled with mucoid or clear, watery content. It is rarely seen in childhood and characterized by massive acalculous distention of the gallbladder.

Causes

Hydrops can result from various causes including complicated gallstone disease. Gallbladder dilatation is largely due to atony or failure of muscular contractions. Children with acute hydrops may have salmonellosis or *Enterococcus* sepsis. Other conditions associated with hydrops are mesenteric adenitis, staphylococcal infection, Henoch–Schönlein purpura, sepsis, prolonged fasting, sickle cell crises, thalassemia, ascariasis, Kawasaki disease, viral hepatitis, threadworm infestation, necrotizing enterocolitis, and typhoid fever.

Diagnosis

The most consistent clinical features are fever, nausea, vomiting, and abdominal pain. Diagnosis is often easy by abdominal ultrasonography (US), as in *Fig. 204.1*.

Since the clinical picture may mimic common surgical conditions of childhood such as appendicitis, intussusception, or volvulus, early diagnosis is important.

Treatment

The treatment of hydrops of the gallbladder varies depending on the etiology and the clinical presentation. Most cases are self-limited, and the gallbladder may spontaneously decompress with the treatment of the underlying systemic disease within approximately 2 weeks. Associated cholelithiasis, complications as gallbladder perforation, and deterioration of abdominal signs are indications for surgical exploration.

Extrahepatic Biliary Atresia

EHBA is one of the most challenging conditions in pediatric hepatology practice. It is characterized by complete obliteration or partial discontinuity of the biliary system outside the liver, resulting in obstruction to the bile flow.

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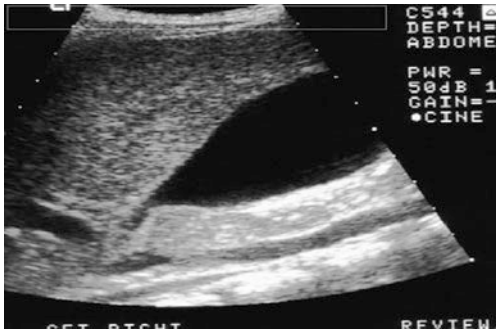

Figure 204.1
Ultra sonogram of the right upper quadrant shows hydrops of the gallbladder. Note the size of the gallbladder compared with that of the inferior vena cava (Courtesy of Dr. S. Methratta, UMDNJ-New Jersey Medical School)

Infants with EHBA can be subdivided into two distinct groups:

1. Patients with isolated biliary atresia (postnatal form), which accounts for 65–90% of cases
2. Patients with associated situs inversus or polysplenia/asplenia syndrome with or without other congenital anomalies (fetal/embryonic form), comprising 10–35% of cases

The pathology of the extrahepatic biliary system varies widely in these patients. Based on the predominant site of atresia, EHBA is classified into three classic types:

- Type I involves obliteration of the common bile duct; the proximal ducts are patent, therefore called *common bile duct type.*
- Type II is characterized by atresia of the hepatic duct, with cystic strictures found in the porta hepatis, called *common hepatic duct type.*
- Type III (>90% of patients) involves atresia of the right and left hepatic ducts to the level of the porta hepatis and called *porta hepatis type.*

These variants should not be confused with intrahepatic biliary hypoplasia, which comprises a group of distinct and surgically non-correctable disorders characterized by diminution in size and/or number (paucity) of the interlobular bile ducts.

Causes

EHBA is rarely seen in stillborn or in premature infants, which supports a rather late gestational insult. By contrast, infants with idiopathic neonatal giant cell hepatitis, which is the major differential diagnosis of EHBA, might be preterm, small for gestational age, or both.

- Infectious agents

  No single agent has been identified as causative for EHBA, although the role of infecting organisms has been the most extensively studied.

  Fischler et al. (1998) reported cytomegalovirus (CMV) infection in almost 25% of affected infants in one study based on immunoglobulin M (IgM) serology. Interestingly, an even higher frequency of CMV infection has been found by Chang et al. (1992), in patients with idiopathic neonatal giant cell hepatitis, lending support to the concept that both disorders might be the extreme ends of the same pathological spectrum, originally described by Landing (1974) as the infantile obstructive cholangiopathy.

  Investigations of reovirus type 3 have yielded conflicting results. Wilson et al. (1994), noted in one study that the virus damages the bile ducts and hepatocytes in weanling mice, whereas another study by Steele et al. (1995), failed to demonstrate evidence of infection in infants with cholestasis.
- Genetic factors

  The existence of the fetal/perinatal form of EHBA, frequently associated with other gastrointestinal and cardiac anomalies, suggests the possibility of a disorder in ontogenesis. Studies have identified specific genetic mutations in mice with visceral heterotaxy and cardiac anomalies, defects similar to those found in conjunction with the fetal/perinatal form of biliary atresia.

Diagnosis

Any cholestatic young infant with persistently acholic or clay-colored stools must raise the suspicion of EHBA which has to be diagnosed as soon as possible. Diagnosis largely depends on abdominal ultrsonographic findings after 2–4 h fast, percutaneous liver biopsy and laparoscopic or intraoperatve cholangiography. The role of technetium^{99m} labeled hepatic imino-diacetic acid (HIDA) radionuclide scans in diagnosis of EHBA and its differentiation from idiopathic neonatal giant cell hepatitis has decreased in the past few years due to the time consumed in preparations for HIDA scan and the technical limitations of the procedure.

Treatment

Apart from vitamin K_1 administration to prevent unexpected bleeding, no primary medical treatment is relevant in the management of EHBA. Surgical intervention is the only mechanism available for a definitive diagnosis by intraoperative cholangiography and therapy by Kasai porto-enterostomy.

- Practice guidelines for the evaluation of a patient for liver transplantation set by the American Association for the Study of Liver Diseases (AASLD) have defined factors that predict improved long-term outcome after Kasai porto-enterostomy including:
  - Young age less than 10 weeks (in other reports, 8 weeks only) at operation
  - Preoperative histology and ductal remnant size
  - Presence of bile in hepatic lobular zone 1
  - Absence of portal hypertension, cirrhosis, and associated anomalies
  - Experience of the surgical team
  - Postoperative clearing of jaundice

Choledocal Cysts

Choledochal cysts are congenital anomalies of the bile ducts consisting of cystic dilatations of the extrahepatic biliary tree, intrahepatic biliary radicles, or both. Alonso-Lej et al. provided the first systematic description of choledochal cysts, based on the clinical and anatomic findings. They classified choledochal cysts into three types and outlined therapeutic strategies for each. The classification system was further refined by Todani and colleagues, and currently includes five major types:

- Type I choledochal cysts – These are the most common, representing 80–90% of the lesions. Type I cysts are dilatations of the entire common hepatic and common bile ducts or of segments of each. They can be saccular or fusiform.
- Type II choledochal cysts – These are relatively isolated protrusions or diverticula that project from the common bile duct wall. They may be either sessile or connected to the common bile duct by a narrow stalk.
- Type III choledochal cysts – Also called choledochoceles, these are found in the intraduodenal portion of the common bile duct.
- Type IV cysts – These are further subclassified into:
  - Type IV-A cysts – These are characterized by multiple dilatations of the intrahepatic and extrahepatic biliary tree. Most frequently, a large, solitary cyst of the extrahepatic duct is accompanied by multiple cysts of the intrahepatic ducts.
  - Type IV-B choledochal cysts – These consist of multiple dilatations that involve only the extrahepatic bile duct.
- Type V choledochal cysts – These are defined by dilatation of the intrahepatic biliary radicles. Often, numerous cysts are present with interposed strictures that predispose the patient to intrahepatic stone formation, obstruction, and cholangitis. The cysts are typically found in both hepatic lobes. Occasionally, unilobar disease is found and most frequently involves the left lobe.

Diagnosis

The clinical history and presentation of a patient with a choledochal cyst varies with the patient's age. Overt, dramatic signs and symptoms are more common in infancy, whereas manifestations are more subtle and protean in adulthood. Infants frequently come to clinical attention with jaundice and the passage of acholic stools. If this presentation occurs in early infancy, EHBA must be excluded. Infants with choledochal cysts can have a palpable mass in the right upper abdominal quadrant; this may be accompanied by hepatomegaly. US is the best initial study. In neonates, it may be the only test needed. US can demonstrate changes in the bile ducts as well as in the liver. Endoscopic retrograde cholangiopancreatography (ERCP) was, until recently, the standard diagnostic study. In expert hands, ERCP can be performed with a high rate of success, even in small infants clearly showing the anatomy of the pancreatico-biliary junction. Magnetic resonance cholangiopancreatography (MRCP) has largely supplanted ERCP as the standard diagnostic test of choice for choledochal cysts because it offers high resolution and detailed images of relevant anatomy, is noninvasive, and does not result in complications such as post-procedure pancreatitis. MRCP detects most choledochal cysts with sensitivities from 90% to 100% and specificities from 73% to 100%, with the exception of small choledochoceles and minor ductal anomalies. MRCP has been shown to be effective not only in neonates and children, but even in fetuses.

Children in whom the condition is diagnosed after infancy present with a different constellation of symptoms and signs, including intermittent bouts of biliary obstructive symptoms or recurrent episodes of acute pancreatitis. Children in whom biliary obstruction is present have jaundice and may also have a palpable mass in the right upper quadrant. The correct diagnosis is occasionally more difficult in children with pancreatitis. Often, the only clinical symptoms are intermittent attacks of colicky abdominal pain. Eventually, an analysis of biochemical laboratory values reveals elevations in serum amylase and lipase levels. This leads to the proper diagnostic imaging workup.

Treatment

Total excision of the cyst in types I, II, and IV followed by reconstruction of the biliary tree with hepatico-jejunostomy in a Roux-en-Y fashion has been widely accepted as the procedure of choice in treating choledochal cysts, and has been found to be superior to hepatico-duodenostomy. This procedure involves excision of the distal common bile duct (CBD). Consequently, it blocks the reflux of pancreatic enzymes into the biliary tract decreasing the incidence of carcinoma of the bile duct. With type III choledochal cysts, the general approach is one of lateral duodenotomy with unroofing of the choledochocele to drain the bile duct and pancreatic duct directly into the duodenum. The two ductal openings should be carefully examined to determine whether ductoplasty is required.

Complications after surgery have been mainly observed with types I, IV, and V choledochal cysts. They are much less common in excisional procedures. The overall morbidity rate is less than 10%. Mortality and repeat surgery rates are low after excision, compared with those associated with internal drainage operations. The complications include cholangitis, biliary stone formation, anastomotic stricture, residual debris in the intrahepatic bile ducts, intrahepatic bile duct dilatation, and malignant transformation.

Cholelithiasis and Choledocolithiasis

Cholelithiasis is uncommon in otherwise healthy children and usually occurs in patients who have predisposing factors such as hemolytic disease, hepatobiliary disease, obesity, prolonged TPN, abdominal surgery, trauma, sepsis, impaired immune system, and spinal injury. Adolescents exposed to hepatitis C virus (HCV) infection and teen age pregnancy have an increased incidence of gallstones. Less-prominent risk factors identified to increase the incidence of gallstones include acute renal failure, prolonged fasting, low-calorie diets, and rapid weight loss. Biliary pseudolithiasis, or reversible cholelithiasis, has been identified with the use of certain medications, primarily ceftriaxone. Gallstones are a frequent complication in children with hemoglobinopathies because of the recurrent episodes of hemolysis leading to increased bilirubin excretion and pigment gallstones formation. The incidence of gallstones in children with sickle cell disease (SCD) has increased over the past few years due to both the regular use of the noninvasive detection technique (US versus cholecystography) and the longer survival of these patients. The frequency of cholelithiasis in children with SCD is almost double that of the general population. The development of pigment gallstones in patients with SCD is age dependent: 15% under 10 years of age, 22% between 10 and 14 years of age, and 36% between 15 and 18 years of age, with a reported prevalence of 50% by the age of 22.

Diagnosis

Gallstones in children with hemoglobinopathies are most commonly an incidental finding, but should be strongly suspected in the workup of nonspecific intermittent abdominal pain with risk factors. Murphy sign is the expiratory arrest with palpation in the right upper abdominal quadrant, and it is almost always pathognomonic. US is the study of choice in patients with uncomplicated cholelithiasis (*Fig. 204.2*). It can be used to identify the location of the stone, gallbladder wall thickening, the presence of gallbladder sludge, and peri-cholecystic fluid.

Gallstones are typically classified as cholesterol, black pigment, and brown pigment stones. Typically, only one type of stone forms at a given time. The distribution of gallstone types in children differs from the adult population with cholesterol stones being the most common type of stone in adults, and black pigment stones being the most common type in children. Cholesterol stones are formed from cholesterol supersaturation of bile and are composed of 70–100% cholesterol with an admixture of protein, bilirubin, and carbonate. These account for most gallstones in adults, but comprise only about 21% of stones in children. Black pigment stones comprise 48% of gallstones in children. They are formed when bile becomes supersaturated with the calcium salt of unconjugated bilirubin (calcium bilirubinate). Black

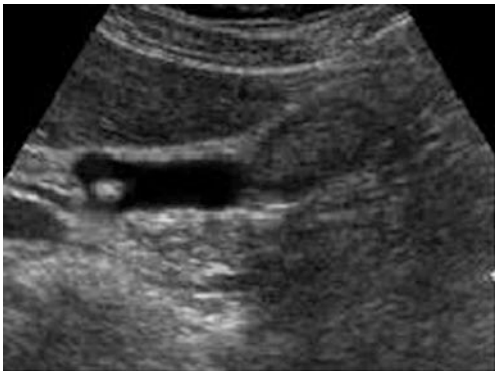

Figure 204.2
Choledocholithiasis: A Common bile duct stone. The sensitivity of transabdominal US for choledocholithiasis is approximately 75% in the presence of dilated ducts and 50% for nondilated ducts (Image courtesy of DT Schwartz)

pigment stones are commonly formed in hemolytic disorders, and can also develop with TPN. Brown pigment stones are rare, accounting for only 3% of gallstones in children, and form in the presence of biliary stasis and bacterial infection. They are composed of calcium bilirubinate and the calcium salts of fatty acids, and occur more often in the bile ducts than in the gallbladder. Calcium carbonate stones, which are rare in adults, are more common in children and account for 24% of stones in children. The remaining portion of gallstones in children is protein-dominant stones, which comprise about 5%. The incidence of gallstones among boys and girls is almost equal, with a slightly high incidence among boys.

Treatment

Treatment for simple cholelithiasis is symptomatic. Surgical removal of asymptomatic gallstones is currently not the standard practice. Expectant management with periodic clinical and US surveillance is appropriate for asymptomatic cholelithiasis. Elective cholecystectomy is the treatment of choice for symptomatic cholelithiasis. Twenty years after its first introduction, laparoscopic chloecystectomy has been confirmed to be a safe and efficacious treatment for pediatric cholelithiasis. In uncomplicated cholelithiasis with biliary colic, medical management may be a useful alternative to cholecystectomy in selected patients, particularly in patients with high surgical risk. Medical treatment, beyond pain control, however, is not initiated in the emergency department, and patients should be referred to their primary care provider for further medical management. Laparoscopic cholecystectomy has also been demonstrated to be both safe and effective in SCD patients. In addition, because gallbladder sludge is frequently documented in patients with SCD and most patients with SCD who have biliary sludge go on to develop gallstones, elective cholecystectomy has been recommended with evidence of biliary sludge, with or without stones. Surgical complications of laparoscopic cholecystectomy include CBD injury, bile leaks, as well as complications of hemolytic disease in those at risk.

Medical management of gallstones used alone or in combination includes the following: oral bile salt therapy (UDCA and chenodeoxycholic acid), contact dissolution, and extracorporeal shockwave lithotripsy. Medical management is more efficacious in patients with small stones (<1 cm), high cholesterol content, and good gallbladder function.

Primary Sclerosing Cholangitis

Primary sclerosing cholangitis (PSC) is a chronic cholestatic disease of unknown etiology that is characterized by inflammation and fibrosis of the intra- and/or extrahepatic bile ducts. Despite its importance, there have been few advances in understanding the pathogenesis of PSC. Furthermore, there are uncertainties regarding optimal means of diagnosis, monitoring, and therapy. Greater use of ERCP led to the identification of many cases, suggesting a higher incidence of PSC in childhood than would appear from the pediatric literature.

Causes

The mechanism(s) responsible for the development of PSC are still largely unknown. Immunologically mediated damage to the biliary tree remains the most likely etiology. The relationship between PSC and inflammatory bowel disease (IBD) offers several clues. The biliary injury may be initiated by an immune-mediated destruction of the hepatobiliary tract that is perhaps caused by transient infection or the absorption of bacterial by-products in genetically predisposed individuals with colonic disease. In children, PSC is commonly associated with markers suggestive of an autoimmune process. Some patients have elevated levels of circulating immune complexes, immunoglobulins, and/or non-organ-specific autoantibodies. Clinical and histologic overlap with autoimmune hepatitis (i.e., overlap syndrome) may be observed. While often associated with non-organ-specific

autoantibodies and closely linked to IBD, PSC is not a typical autoimmune disease and responds poorly, if at all, to standard immune suppressive therapy.

Diagnosis

The clinical presentation in children with PSC varies widely, and frequently lacks the obvious features of cholestasis. Patients may be asymptomatic with hepatomegaly or elevated biochemical liver function test (LFT) results, prompting further workup for PSC. Patients may also present with fatigue, pruritus, fever of unknown origin, intermittent jaundice, or weight loss. Some patients present with manifestations of chronic liver disease and cirrhosis. The onset and progression tend to be insidious. The modes of presentation include the following:

- Asymptomatic patients present with incidental finding of hepatomegaly on examination or abnormal LFT results.
- Symptomatic patients may present with nonspecific complaints, including fatigue, pruritis, abdominal pain, fevers, weight loss, and intermittent jaundice.
- Complications of prolonged cholestasis including pruritis, cholangitis, and malabsorption of fat/fat-soluble vitamins.
- Patients with cirrhosis present with complications of portal hypertension including splenomegaly, ascites, and variceal bleeding.

The overall diagnostic accuracy of MRCP in patients with PSC is 90%, compared to 97% for ERCP or percutaneous transhepatic cholangiography (PTC). The advantages of MRCP include less risk for complications as compared with ERCP as well as visualizing bile ducts proximal to obstructed areas.

Treatment

PSC is a rare, but important, cause of chronic liver disease. The chronic inflammation and obliterative fibrosis of the biliary tree leads to bile stasis, hepatic fibrosis, and ultimately to cirrhosis, end-stage liver disease, and need for orthotopic liver transplantation (OLTx). PSC can lead to cholangiocarcinoma, a highly malignant tumor, in adulthood. Treatment of patients with PSC should be directed at managing each of the following:

- Chronic cholestasis with pruritis and fat malabsorption
- Cirrhosis and portal hypertension
- Ductular complications, such as dominant strictures, cholelithiasis, and ascending bacterial cholangitis
- Other associated diseases such as IBD or other autoimmune diseases

Recent meta-analysis of many studies found that UDCA can improve liver biochemistry, and there is a trend toward improvement in liver histology and cholangiography, but does not improve survival and was associated with higher rates of serious adverse events.

Dominant strictures of the extrahepatic biliary tree, most often at the bifurcation of the hepatic ducts, are major problems for patients with PSC. They can be treated by transhepatic or endoscopic balloon dilatation that has been shown to be useful in children. Short-term stenting of strictures has also demonstrated clinical improvement of symptomatic strictures. Surgical, endoscopic, and interventional radiologic procedures to relieve symptomatic dominant strictures have been demonstrated to prolong survival time of the native liver in patients with PSC. None of these interventions have altered the ultimate rate of progression of PSC to end-stage liver disease. Bacterial cholangitis, which can occur spontaneously, is more common after endoscopic or surgical manipulation of the biliary tree. Episodes of cholangitis require prompt antibiotic therapy.

OLTx has been proven successful in treating children with PSC. Data from numerous liver transplant centers demonstrate excellent long-term patient and graft survival in end-stage PSC with actuarial patient survival rates at 1 and 5 years after OLTx greater than and approximately equal to 90%, respectively.

Progressive Familial Intrahepatic Cholestasis

Progressive familial intrahepatic cholestasis (PFIC) is a genetically determined group of autosomal-recessive disorders. Consanguinity is a major risk factor. The condition is clinically characterized by hepatocellular cholestasis and normal or low serum levels of gamma glutamyl transpeptidase (GGT) activity. It was initially described in the ethnic Amish descendants of Jacob Byler, so the condition was originally named Byler disease. Subsequently, numerous phenotypically similar non-Amish patients were reported, and the term "Byler syndrome" was used to describe these patients' condition. These terms now have been superseded by the term "PFIC."

PFIC is considered as a chronic cholestasis syndrome that begins in infancy and usually progresses to cirrhosis

within the first decade of life. The average age at onset is 3 months, although some patients do not develop apparent cholestasis until later, even as late as adolescence. PFIC can progress rapidly and cause cirrhosis during infancy or may progress relatively slowly with minimal scarring well into adolescence. Few patients have survived into the third decade of life without treatment.

Causes

At present, specific gene defects have been identified for two subtypes of low-GGT types: PFIC-1 (the former Byler disease) and PFIC-2. Despite their genetic distinctiveness, PFIC-1 and PFIC-2 have few clinical differences, and both are caused by the absence of a gene product function for canalicular export and bile formation.

Patients with PFIC but with high serum GGT have a condition termed high-GGT PFIC. These patients manifest severe progressive intrahepatic cholestasis in the first year and progress toward hepatic failure in the first few years of life. Liver biopsy results reveal expanded portal areas with proliferation of interlobular bile ducts plugged with bile sludge. Several clinical differences have been reported between patients with PFIC-2 and patients with PFIC-1, although the distinction remains in question. Clinically, patients with PFIC-2 seem to lack the relapsing course seen in the early stages of PFIC-1 and, instead, have a more rapidly progressive course to fibrosis. Light microscopy and transmission electron microscopy demonstrate that liver tissue from patients with PFIC-1 has coarse granular bile and bland canalicular cholestasis, whereas patients with PFIC-2 have amorphous or finely filamentous bile and neonatal hepatitis.

Patients with PFIC-1 are more likely to have associated watery diarrhea, some of which are severe. This secretory diarrhea may persist or even increase after OLTx, and may reflect an important role for FIC-1 in the intestine, where it is expressed in quantity.

Diagnosis

The disease typically does not respond to any form of medical therapy. Some have reported success in treating patients having low-GGT PFIC with UDCA (20–30 mg/kg/day), which may be tried as an initial treatment. Surgical therapy that diverts bile salts from the enterohepatic recirculation arrests the progression of disease and relieves pruritus in most patients with low-GGT PFIC. The most common procedure, partial cutaneous biliary diversion, diverts gallbladder bile to a cutaneous stoma. Patients typically drain 30–120 mL of bile per day, which is discarded. A variation on this procedure is the limited ileal diversion, in which the distal 20–25% of the ileum is removed from the intestinal mainstream and made into a self-emptying blind loop.

UDCA therapy should be initiated in all patients to prevent liver damage. In some PFIC-1 or PFIC-2 patients, biliary diversion can also relieve pruritus and slow disease progression. However, most PFIC patients are ultimately candidates for OLTx. Monitoring for hepatocellular carcinoma, especially in PFIC-2 patients, should be offered from the first year of life. Hepatocyte transplantation, gene therapy, or specific targeted pharmacotherapy may represent alternative treatments in the future.

OLTx is indicated in patients with decompensated cirrhosis or with a failed diversion with debilitating pruritus. Survival rates after OLTx are excellent. OLTx is the only effective treatment of high-GGT PFIC.

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205 Neonatal Cholestasis

Ronen Arnon · Fredrick J. Suchy

Cholestasis, associated clinically with conjugated hyperbilirubinemia, may be defined as a decrease in bile flow due to impaired secretion by hepatocytes or to obstruction of bile flow through the intra- or extrahepatic bile ducts. The consequences of chronic cholestasis are related to the retention of potentially noxious substances that are normally excreted into bile including bilirubin, bile acids, copper, and lipids and to a deficiency of micelle-forming bile acids within the intestinal lumen that are essential for dietary lipid and fat-soluble vitamin absorption. Damage to the liver may be progressive from the underlying disease and from secondary effects of cholestasis. Owing to an immaturity of hepatobiliary function, the number of distinct disorders presenting with cholestatic jaundice may be greater during the neonatal period than at any other time of life. The myriad conditions, manifesting as neonatal cholestasis, are shown in *Table 205.1*. These diseases reflect the unusual susceptibility of the neonatal liver and biliary tract to many bacterial and viral infections and the initial presentation of many inborn errors of metabolism and structural abnormalities.

The overall incidence of neonatal liver disease manifesting clinical or biochemical evidence of cholestasis is approximately 1 in 2,500 live births. Idiopathic neonatal hepatitis, an anachronistic term, has been reported to have an incidence of 1 in 4,800–9,000 live births. However, reliable figures do not exist regarding the current incidence because newer and more accurate diagnostic methods have decreased markedly the number of infants previously labeled as having idiopathic neonatal hepatitis. The incidence of biliary atresia ranges from 1 in 8,000 to 21,000 live births according to reports from several centers around the world.

Figure 205.1 shows an estimate of the relative frequency of the most important disorders producing cholestatic liver disease. Biliary atresia is the most common disease and consistently has accounted for one third of all cases in multiple reports over several decades. Various forms of inherited cholestasis may occur in 10–20% of cases. Approximately 10% are caused by alpha1-antitrypsin deficiency. Other inborn errors of metabolism comprise about 20% of all cases.

Congenital infections, including those caused by so-called TORCH agents, account for about 5% of cases. In contrast to reports as late as 10 years ago, in which idiopathic neonatal hepatitis accounted for almost one third of the cases, improved diagnostic methods has decreased this category to no more than 10–15% of cholestatic infants.

Cholestatic jaundice may present in the first weeks of life as part of a severe acute illness with impairment of other liver functions or as an isolated finding. The possibility of cholestatic liver disease should be considered in any infant who is jaundiced beyond 14 days of age. Acholic stools may also occur in severe liver dysfunction and with biliary obstruction, but stools may be only lightly pigmented or intermittently pigmented with partial or evolving obstruction. The urine is usually dark. Bleeding secondary to vitamin K deficiency may be a presenting feature of cholestasis.

In cholestatic infants, there are usually few clues regarding the etiology of the disorder. Maternal illness during pregnancy, low birth weight, or microcephaly may suggest hepatitis from a congenital infection. Metabolic disturbances, particularly hypoglycemia, may be a feature of liver failure or an endocrinopathy such as panhypopituitarism. Extrahepatic anomalies, including dysmorphic facies, should prompt evaluation of the biliary system.

Evaluation

Urgent evaluation of the cholestatic infant is critical to treatment of life-threatening metabolic or infective liver diseases and for the surgical management of biliary anomalies. The general features of the many cholestatic liver diseases of the neonate are similar, and it remains one of the most difficult pediatric problems to differentiate severe intrahepatic from extrahepatic cholestasis.

The approach to the evaluation of the infant with cholestatic liver disease is outlined in *Fig. 205.2*.

The most important initial test should be the measurement of a serum conjugated bilirubin level to establish that liver disease is present. The conjugated fraction of serum bilirubin should be no higher than 15% of the total serum

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Table 205.1
Differential diagnosis of neonatal cholestasis

Neonatal hepatitis
Idiopathic
Viral Cytomegalovirus Herpes (simplex, zoster, human type 6) Rubella Reovirus type 3 Adenovirus Enteroviruses Parvovirus B19 Hepatitis B Human immunodeficiency virus
Bacterial and parasitic Bacterial sepsis Urinary tract infection Syphilis Listeriosis Tuberculosis Toxoplasmosis
Bile duct obstruction
Cholangiopathies Biliary atresia Choledochal cyst Non syndromatic paucity of interlobular Bile ducts Alagille syndrome Neonatal sclerosing cholangitis Spontaneous perforation of common bile ducts Caroli's disease Congenital hepatic fibrosis
Chromosomal disorder Autosomal trisomies Turner syndrome
Cardiovascular disorders Shock/hypoperfusion Congestive heart failure
Cholestatic syndromes Progressive familial intrahepatic cholestasis type 1 (Byler's disease), types 2 and 3 Benign recurrent cholestasis Hereditary cholestasis with lymphedema North American Indian cholestasis
Metabolic disorders Alpha 1-antitrypsin deficiency Cystic fibrosis Neonatal iron storage disease
Amino acid disorders Tyrosinemia
Lipids Nieman–Pick type C Gaucher disease Wolman's disease
Urea cycle disorders Arginase deficiency
Carbohydrate disorders Galactosemia Fructosemia
Mitochondrial disorders Beta oxidation defects Respiratory chain defects
Bile acid synthetic defects
Peroxisomal defects Zellweger syndrome
Endocrinopathies Hypopituitarism(septo-optic dysplasia) Hypothyroidism
Toxic Drugs Parenteral nutrition
Miscellaneous associations Inspissated bile/mucous plug Cholelithiasis Tumor/masses (intrinsic and extrinsic) Histiocytosis X Neonatal leukemia

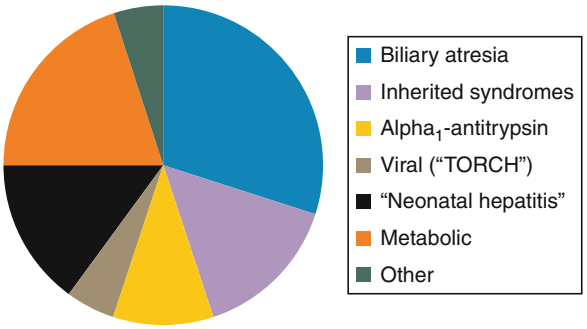

Figure 205.1
Estimated incidence of important disorders producing cholestatic liver disease

bilirubin concentration. Standard liver biochemical tests usually show variable elevations of aminotransferase levels, serum alkaline phosphatase, gamma-glutamyl transferase (GGT), and serum lipids. These tests along with others of

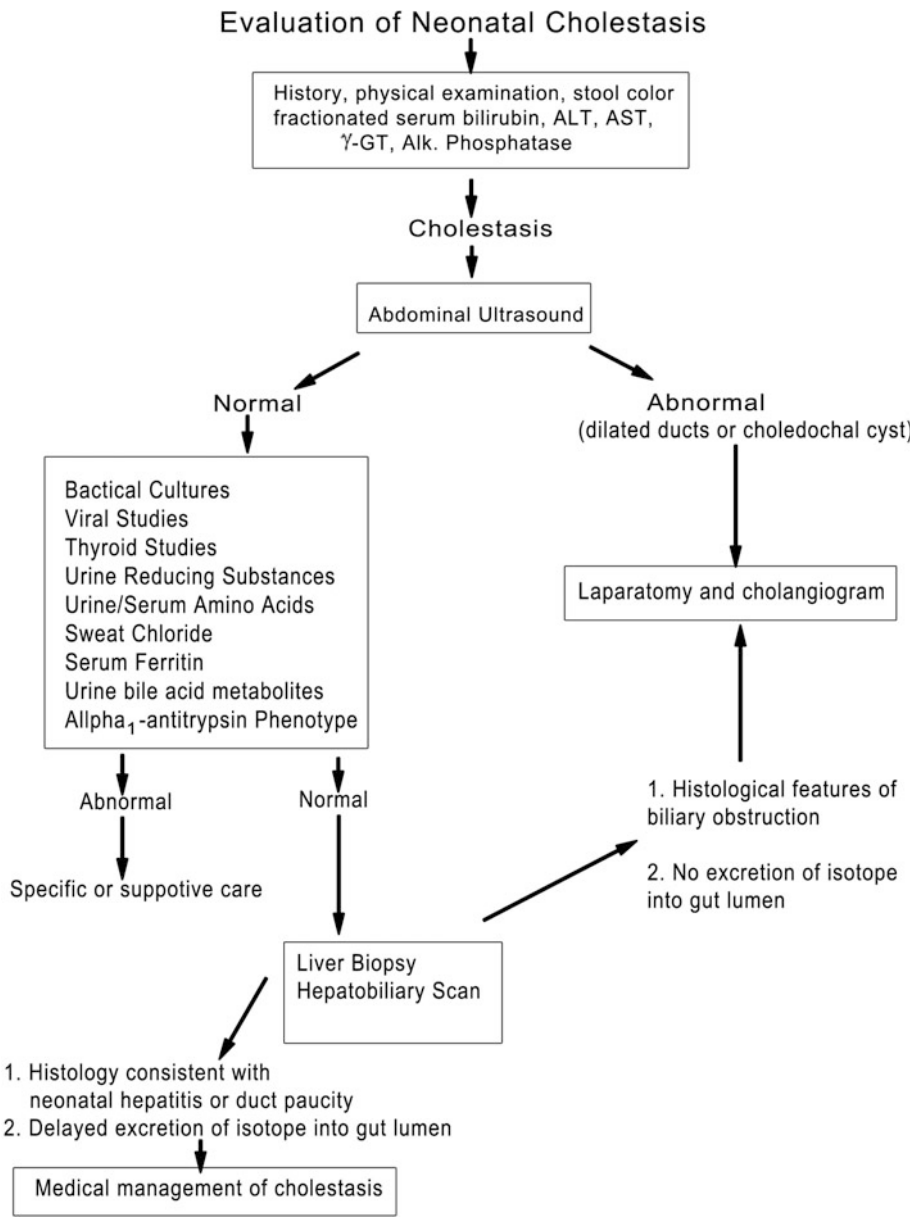

Figure 205.2
Flow diagram for the evaluation of neonatal cholestasis

hepatic function such as blood glucose and ammonia levels and coagulation studies may provide insight into the severity of the liver dysfunction but are not specific.

Numerous routine and specialized biochemical tests and imaging procedures have been used to help distinguish between infants with intra- and extrahepatic cholestasis and, thus, avoid unnecessary surgical exploration. Unfortunately, no single test has proven to be of satisfactory discriminatory value, since at least 10% of infants with intrahepatic cholestasis will have sufficient bile secretory failure so as to have diagnostic tests that overlap with biliary atresia.

Ultrasonography can be used to assess the size and composition of the liver and can usually define the

presence and size of the gallbladder, detect stones and sludge in the bile ducts and gallbladder, and demonstrate cystic or obstructive dilatation of the biliary system. Extrahepatic anomalies may also be identified.

Hepatobiliary scintigraphic imaging with agents such as the technetium-99 m iminodiacetic acid derivatives has been used to differentiate biliary atresia from other causes of neonatal jaundice. A 5-day period of pretreatment with phenobarbital is required to maximize bile secretion and visualization of the biliary tract. In patients with biliary atresia, hepatic uptake of the isotope occurs rapidly because liver function is usually preserved early in the disease but excretion into the intestine is absent even on scanning 24 h later. In contrast, uptake is poor in cases of neonatal hepatitis, but excretion of bile into the intestine should eventually be detected. In practice, the distinction between severe hepatocellular disease and biliary obstruction may not be reliably made using this technique.

Percutaneous transhepatic cholangiopancreatography (PTC) or endoscopic retrograde cholangiopancreatography (ERCP) may be of value in visualizing the biliary tract in selected patients.

Magnetic resonance cholangiopancreatography (MRCP) is being performed more frequently in cholestatic infants. The instrumentation and software have improved significantly to allow the imaging of a normal biliary tree in infants. In several small studies, patent extrahepatic bile ducts and a gallbladder could not be demonstrated in infants who had biliary atresia. Further studies are required before MRCP evaluation of the cholestatic infant can be considered reliable.

The percutaneous liver biopsy remains particularly valuable in the evaluation of the cholestatic patient and can be performed in even the smallest infants employing only sedation and local anesthesia. A diagnosis of biliary atresia can be successfully made on the basis of clinical and histological criteria in 90–95% of patients. In the small number of cases where doubt about the diagnosis persists, the patency of the biliary tree can be directly examined at the time of a mini laparotomy and operative cholangiogram. Liver tissue may also be used for ultrastructural analysis and enzymatic assays, and can be cultured for infectious agents.

Disorders of the Bile Ducts

Biliary Atresia

Biliary atresia is a cholestatic disorder presenting in infancy caused by a complete obstruction of bile flow due to destruction or absence of all or part of the extrahepatic bile ducts. The disorder occurs worldwide, affecting an estimated 12,000–18,000 live birth. It is the single most frequent cause of death from liver disease and of referral for liver transplantation (up to 50% of all cases) in children. In most large series, it accounts for approximately one third of the cases of neonatal cholestatic jaundice.

There are two different forms of biliary atresia: (1) fetal or embryonic form and (2) peri or postnatal form.

In the fetal form (10–20% of all patients), cholestasis is present from birth with no jaundice free interval, bile duct remnant may not be detectable in the hepatic hilum. There are associated anomalies in 10–20% of patients such as the splenic malformation syndrome. Associated findings may include cardiovascular defects, asplenia, abdominal situs inversus, intestinal malrotation or atresia, and positional anomalies of the portal vein and the hepatic artery. The fetal form of biliary atresia may represent defective embryogenesis. The postnatal form, in which there are no associated congenital anomalies, may be the result of an acquired obliteration. There is no difference in the histologic features of the liver between infants with and without congenital anomalies.

The etiology of biliary atresia is unknown. Viral, toxic, and developmental causes have been proposed but not proven. The disease is not inherited. Familial cases have been reported rarely but in most a detailed histologic description of the extrahepatic biliary tree was not provided to convincingly exclude narrowing or "hypoplasia" of the common duct due to severe intrahepatic cholestasis.

Numerous mechanisms have been proposed to account for the progressive obliteration of the extrahepatic biliary tree. There is little support for an ischemic or toxic origin of extrahepatic bile duct injury. No abnormal toxic bile acid metabolite specific for the disorder has been identified. Congenital infections with cytomegalovirus, Epstein–Barr virus, or rubella virus have been occasionally found, but the presence of these common agents may be coincidental. A possible role for *reovirus type 3* has been proposed based on serologic evaluation of patients and controls. Further evidence that reovirus type 3 may cause some cases of biliary atresia has come from immunolocalization of reovirus 3 antigens in a bile duct remnant of a patient with biliary atresia and by the apparent ability of reovirus 3 to produce extrahepatic biliary atresia in an infant rhesus monkey. However, these serologic data have not been confirmed by other workers.

Biliary atresia may be a result of a "multiple hit" phenomenon. A viral or toxic insult to the biliary epithelium leads to newly expressed antigens on the surface of the bile duct epithelia. Recent studies from a mouse model

of biliary atresia and microarray analysis of liver tissue from affected infants with the perinatal form of the disease further suggest that immune dysregulation is central to the pathogenesis of the disorder. It remains unknown whether this immune response is induced by a viral infection or reflects a genetically programmed response to an infectious or environmental exposure. In a microarray analysis of liver tissue from infants with a so-called embryonic form of biliary atresia in which extrahepatic malformations and early onset of cholestatic jaundice occur, a unique pattern of expression of genes involved in chromatin integrity/function and overexpression of five imprinted genes (Igf2, Peg3, Peg10, Meg3, and IPW) was found, implying a failure to downregulate embryonic gene programs that influence the development of the liver and other organs.

Histopathologic findings early in the course of the biliary atresia generally show good preservation of the hepatic architecture with a variable degree of bile ductular proliferation, canalicular and cellular bile stasis (*Fig. 205.3*), portal tract fibrosis, inflammation, and edema. The presence of bile plugs in portal triads is an important feature of large duct obstruction. Bile ductules show variable injury to the biliary epithelium including swelling, vacuolization, and even sloughing of cells into the lumen. Giant cell transformation of hepatocytes may also be present to a degree more commonly seen in neonatal hepatitis. Intrahepatic bile ductules may occasionally assume a ductal plate configuration, suggesting that the disease process has interfered with the developmental process of ductular remodeling. Biliary cirrhosis may be present initially or can rapidly evolve over the first months of life with or without the successful restoration of bile flow. Complete fibrous obliteration of at least a portion of the extrahepatic bile ducts is a constant feature. Other segments of the biliary tree may demonstrate lumina with variable degeneration of bile duct epithetial cells, inflammation, and fibrosis in the periductular tissues. A useful classification of the anatomic variants is based on the predominant site of the atresia:

Type I atresia: Involves obliteration of the common bile duct but the proximal ducts are patent.

Type II atresia: The hepatic duct is obstructed, but cystically dilated bile ducts are found at the porta hepatis. In type IIa the cystic and common ducts are patent, while in type IIb these structures are also obliterated.

These forms of biliary atresia have been referred to as "surgically correctable" but, unfortunately, comprise less than 10% of all patients with the disorder.

Type III atresia: Type III atresia (present in 90% or more of patients) involves obstruction of ducts at or above the porta hepatis. The entire perihilar area is encased in a cone of dense fibrous tissue. The gallbladder is involved to some extent in approximately 80% of patients. The type III variant has been referred to as "noncorrectable" in that there are no patent hepatic or dilated hilar ducts that can be used for a simple biliary-enteric anastomosis.

Most infants with biliary atresia appear healthy at birth and are of normal birth weight. Female infants are affected more commonly than males. Jaundice may be observed by the parents or the physician after the period of physiologic hyperbilirubinemia. The possibility of liver or biliary tract disease must be considered in any neonate jaundiced beyond 14 days of age. Stools of a patient with complete biliary obstruction are acholic; however, early in the course with incomplete or evolving atresia, stools may appear normally pigmented or only intermittently pigmented. Moderate hepatomegaly with a firm liver edge is commonly observed. The spleen is usually not enlarged early in the course but will become enlarged as portal hypertension develops. Bleeding due to vitamin K deficiency may be a presenting feature. Ascites and edema are not initially present.

Laboratory studies initially show a variable elevation of serum bilirubin levels, often between 6 and 12 mg/dL, with at least 50% of the total conjugated. Serum aminotransferase, gamma-glutamyltransferase, and alkaline phosphatase levels are moderately elevated. Various laboratory tests, imaging methods, and biopsy samples have been suggested in attempts to establish the diagnosis of

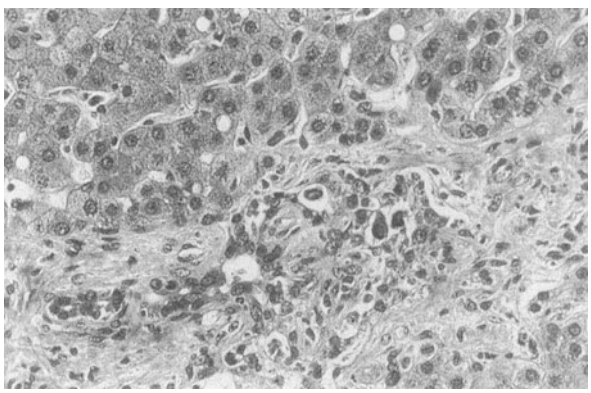

Figure 205.3
Liver biopsy from patient with biliary atresia showing portal fibrosis and bile plugs in bile ducts

biliary atresia and to differentiate it from various forms of intrahepatic cholestasis.

The most reliable information is obtained by liver histopathology followed by intraoperative cholangiography. Exploratory laparotomy and operative cholangiography are necessary to document the site of obstruction and properly direct attempts at surgical treatment of biliary atresia. Patent proximal portions of the bile ducts or cystic structures in the porta hepatis allow a conventional anastomosis with a segment of bowel in approximately 10% of patients. The most common operative approach in cases with obliteration of the proximal extrahepatic biliary tree requires the hepatoportoenterostomy or Kasai procedure. The fibrous extrahepatic biliary tree is resected with the dissection carefully progressing backward and laterally to include a fibrous cone of tissue in the area of the porta hepatis. The fibrous tissue is transected flush with the liver surface to expose an area that may contain residual, microscopic bile ducts. The operation is then completed by the anastomosis of a Roux-en-Y loop of jejunum around the bare edge of the transected tissue to provide a conduit for biliary drainage. Multiple attempts at reexploration and revision of nonfunctional conduits should be avoided.

A number of factors have been identified that contribute to the success of hepatic portoenterostomy. First, the age at which the operation is performed has been found to be most critical. Bile flow has been reestablished in several recent series in 80–90% of infants who were referred for surgery within 60 days after birth. Predictors of a bad outcome have been of Caucasian race, with an operative age greater than 60 days, the presence of cirrhosis on initial biopsy, totally non-patent extrahepatic ducts, and absent ducts at the level of transection in the liver hilus.

The prognosis of untreated biliary atresia is extremely poor, with death from liver failure usually occurring within 2 years. Children with biliary atresia derive long-term benefit from the hepatic portoenterostomy procedure even though in most cases the operation is not curative. Progressive biliary cirrhosis may eventually result in death from hepatic failure or need for liver transplantation despite an apparent successful relief of biliary obstruction. The overall management of extrahepatic biliary atresia in the era of liver transplantation is illustrated in Fig. 205.4.

Liver transplantation is frequently required in children whose operation is not successful in restoring bile flow, who are referred late (probably at 120 days of age or later), and who eventually develop progressive hepatocellular decompensation, recurrent cholangitis, refractory growth failure with hepatic synthetic dysfunction, coagulopathy or intractable portal hypertension with recurrent variceal bleeding, ascites, and hypersplenism. With the use of reduced size allografts and living-related donors, rates of survival at 1 year have exceeded 90% in most centers.

Spontaneous Perforation of the Common Bile Duct

Spontaneous perforation of the common bile duct is a rare disorder of the infant presenting with cholestatic jaundice.

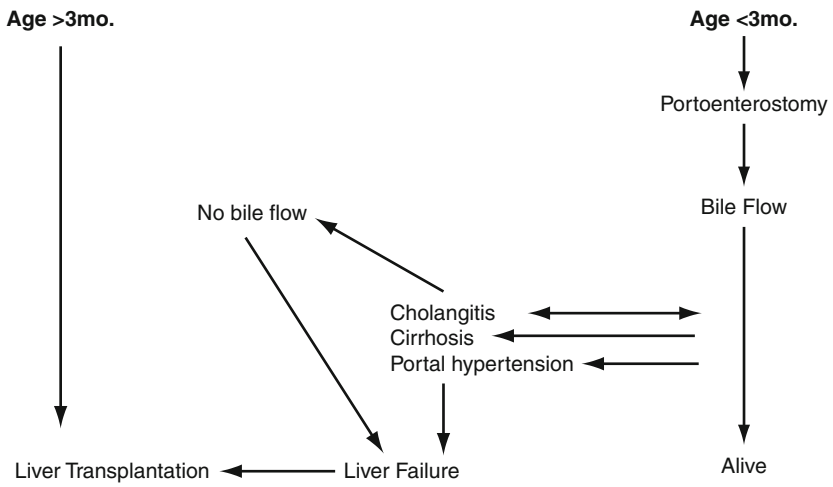

Figure 205.4
Flow diagram for the management of biliary atresia in the era of liver transplantation

The cause is unknown, but in some cases there may be obstruction at the distal end of the common bile duct secondary to stenosis or inspissated bile. Congenital weakness in duct wall or inflammation from infection at the site of the perforation may be causal.

Clinical signs of irritability, jaundice, acholic stools, dark urine, and ascites typically occur during the first months of life. Progressive abdominal distension is a regular feature. Bile staining of fluid within umbilical or inguinal hernias may be observed. The diagnosis is suggested by the relatively mild elevation of aminotransferase levels in association with acholic stools.

Ultrasonography reveals ascites or loculated fluid in the right upper quadrant. Hepatobiliary scintigraphy may demonstrate the free accumulation of isotope within the peritoneal cavity. Abdominal paracentesis reveals clear bile-stained ascitic liquid which is usually sterile.

Operative cholangiography is required to demonstrate the site of the perforation, which usually occurs at the junction of the cystic and common ducts. Surgical treatment may involve simple drainage of the bilious ascites and repair of the site of the perforation, but with an obstruction of the common bile duct, drainage via a cholecystojejunostomy may be required.

Spontaneous posterior perforation of the biliary tract and portal vein thrombosis in infancy has been reported, presumably due to their intimate anatomical relation.

Bile Plug Syndrome

A plug of thick, inspissated bile and mucus may obstruct the common bile duct. The condition occurs particularly in sick premature infants who cannot be fed and require prolonged parenteral nutrition. Otherwise healthy infants have been affected. Bile stasis, prolonged fasting, infection, and an increased bilirubin load may contribute to the pathogenesis. Bile plug syndrome is associated with other etiologic factors such as cystic fibrosis, severe erythroblastosis fetalis, and altered biliary dynamics with total parenteral nutrition. The "inspissated bile syndrome" associated with massive hemolysis may have been a variant but is now infrequent with current measures to prevent and treat blood group incompatibilities.

The differential diagnosis of inspissated bile syndrome in the neonatal period includes biliary atresia.

Abdominal US may reveal dilated intra- and extrahepatic bile ducts secondary to impacted inspissated bile in the distal common bile duct. *Magnetic resonance cholangiography* has been shown to be useful in the evaluation of bile plug syndrome in children.

Percutaneous transhepatic cholangiography (PTC) may be diagnostic and occasionally can be therapeutic after flushing the biliary tree via small catheter. It may be a difficult procedure because of the small size of the intrahepatic ducts and the need to obtain a sufficient flushing pressure.

Exploratory laparotomy and operative cholangiography may be required for diagnosis and treatment. Recently, laparoscopic-aided cholecystostomy as a treatment of inspissated bile syndrome has been described. The use of ursodeoxycholic acid (UDCA) 20 mg/kg/day may help to avoid the need for surgery.

Neonatal Sclerosing Cholangitis

An idiopathic form of primary sclerosing cholangitis may present in the neonate. Immunodeficiency states and histiocytosis *X* should be considered in the differential diagnosis. The presenting features of cholestatic jaundice and acholic stools within the first weeks of life may mimic biliary atresia. Liver histology findings in infancy suggest bile duct obstruction. Percutaneous cholecystography reveals a patent biliary system with rarefaction of segmental branches, stenosis, and focal dilatation of the intrahepatic bile ducts. The extrahepatic bile ducts are often involved. Although jaundice may subside, liver disease is usually progressive with evolution to biliary cirrhosis and portal hypertension.

Neonatal sclerosing cholangitis has been reported in association with Kabuki syndrome (involving facial dysmorphism, mental retardation, growth deficiency, skeletal abnormalities, and congenital heart defects) and neonatal ichthyosis – sclerosing cholangitis (NISCH) syndrome. The latter is a disease of tight junctions which result from Claudin-1 gene mutations.

In contrast to sclerosing cholangitis of the adult and older child, intestinal disease has not been detected in these patients.

Children with neonatal sclerosing cholangitis have been treated with UDCA with variable results. Patients with recurrent cholangitis and progressive liver disease may require liver transplantation.

Choledochal Cysts

Choledochal cysts are congenital anomalies of the biliary tract characterized by cystic dilatation of the extrahepatic and intrahepatic bile ducts. The cysts occur in an

incidence of 1 in 13,000–1 in 15,000 in Western countries and as high as 1 in 1,000 in Japan. They are not familial; females are more commonly affected (3–4:1). A choledochal cyst may be detected at any age and in any portion of the bile duct. Cysts can be present in up to 2% of infants with obstructive jaundice and 18% of the patients with choledochal cyst are diagnosed before 1 year. Cases have been described in utero and are an important, treatable cause of obstructive cholestasis in the neonate. In certain patients, choledochal cyst is associated with other anomalies of the biliary tree and with polycystic and hypoplastic kidneys.

Segmental or diffuse fusiform dilatation of the common bile duct (*type I cysts*) accounts for 80–90% of the cases. *Type II cysts* consist of a true choledochal diverticulum. A dilatation of the intraduodenal portion of the common bile duct, or a so-called choledochocele (*type III*), may be a variant of this condition. *Type IV cysts* may be subdivided into type IVa, multiple intrahepatic and extrahepatic cysts, and type IVb, multiple extrahepatic cysts. The type lVb variant is either uncommon or may overlap with type I. *Type V cysts* (*Caroli disease*) consists of single or multiple dilatations of the intrahepatic ducal system, probably should not be considered a choledochal cyst.

The etiology of choledochal cysts has not been established. Congenital weakness of the bile duct wall, a primary abnormality of epithelial proliferation during embryologic ductal development, and congenital obstruction have been suggested.

The infantile presentation of a choledochal cyst must be distinguished from the other forms of hepatobiliary disease of the neonate, particularly biliary atresia. Patients often present during the first months of life with cholestatic jaundice and acholic stools. Vomiting, irritability, and failure to thrive may occur. At this time hepatomegaly is present, but less than half the patients may have a palpable abdominal mass. Progressive hepatic injury can occur during the first months of life as a result of biliary obstruction. Prolonged obstruction results in biliary cirrhosis. Portal hypertension and ascites may be present. Recurrent pancreatitis is an unusual complication of this malformation. Spontaneous perforation of a choledochal cyst in infancy can cause biliary peritonitis.

The diagnosis of a choledochal cyst is best established by MRCP (magnetic resonance cholangiopancreatography) or by ultrasonography, which may also demonstrate the presence of a choledochal cyst in the fetus. Pediatric surgeons rely on an operative cholangiogram to confirm the diagnosis of a choledochal cyst and define the extent of intra- and extrahepatic disease.

Surgical excision of the cyst and reconstruction of the extrahepatic biliary tree to jejunal Roux-en-Y loop is the preferred method of treatment. Excision of the cyst reduces bile stasis and the risk for cholangitis and malignancy (adenocarcinoma or cholangiocarcinoma) within the cyst wall. Recently, laparoscopic resection of choledocal cyst and Roux-en-Y hepaticojejunostomy was reported in children. Preoperative pancreatitis may cause increased technical difficulty, necessitating a conversion to laparotomy. If segmental intrahepatic cystic disease with area of stenosis (Caroli's disease) is present, cyst excision and hepatic lobectomy is indicated. If the intrahepatic disease is diffuse and involves all hepatic lobes, and successful decompressive drainage is not possible, liver transplantation may be indicated.

Paucity of the Interlobular Bile Ducts

A paucity of interlobular bile ducts can occur as an isolated and unexplained finding in infants with idiopathic cholestasis. Bile duct injury and loss seem to be prototypic response to neonatal liver disease, and may be observed in congenital infections with rubella and cytomegalovirus and in metabolic disorders such as α1-antitrypsin deficiency and inborn errors of bile acid metabolism. Paucity of interlobular bile ducts can be defined as the ratio of the number of interlobular bile ducts to the number of portal tracts of less than 0.4 on a liver biopsy with at least ten portal tracts. The prognosis is highly variable. Severe cholestasis may develop early in infancy and may be associated with progressive liver disease.

Alagille Syndrome (Syndromic Paucity of Interlobular Bile Ducts)

Syndromic paucity of interlobular bile ducts (*Alagille syndrome, or arteriohepatic dysplasia*) is the most common form of familial intrahepatic cholestasis. This disorder is characterized by chronic cholestasis, a decreased number of interlobular bile ducts, and a variety of other congenital malformations.

The disorder is inherited as an autosomal-dominant trait with incomplete penetrance and variable expressivity. Mutations in the jagged 1 (JAG1) gene have been identified in approximately 94% of affected patients. JAG1 encodes a ligand in the Notch signaling pathway that is involved in cell fate determination during development. Mutations in the gene encoding for the NOTCH2 receptor have recently been found in patients with Alagille syndrome who were negative for JAG1 mutations.

Chronic cholestasis of varying severity affects 95% of patients, and may be observed during the neonatal period. Intense pruritus may be present by 6 months of age. The liver and spleen are often enlarged. During the first years of life, xanthomata appear on the extensor surfaces of the fingers and in the creases of the palms and popliteal areas. Dysmorphic facies are usually recognized during infancy and become more characteristic with age. The forehead is typically broad, the eyes are deeply set and widely spaced, and the chin somewhat small and pointed, imparting a triangular appearance to the face. The malar eminence is flattened and the ears are prominent (*Fig. 205.5*).

Extrahepatic anomalies have been described with this syndrome, but there is considerable variability in phenotypic expression. In a 1999 series of 92 patients, cholestasis occurred in 96%, cardiac murmur in 97%, butterfly vertebrae in 51%, posterior embryotoxon in 78%, and characteristic facies in 96% of patients. Short stature is a regular feature but is only partially attributed to the severity of chronic cholestasis. Mild-to-moderate mental retardation affects 15–20% of patients. Congenital heart disease occurs in most patients, and peripheral pulmonic stenosis is observed in approximately 90%. Systemic vascular malformations also may be present. Osseous abnormalities include a decreased bone age, variable shortening of the distal phalanges, and vertebral arch defects (e.g., butterfly vertebrae, hemivertebrae, and a decrease in the interpedicular distance). Eye anomalies include posterior embryotoxon (mesodermal dysgenesis of the iris and cornea), retinal pigmentation, and iris strands. Renal abnormalities and hypogonadism may be present.

An elevation of total serum bilirubin levels (usually 2–8 mg/dL) is found during infancy and intermittently later in life. Approximately 50% of the total serum bilirubin is conjugated. Serum alkaline phosphatase, gamma-glutamyl transpeptidase, 5′ nucleotidase, and bile acid levels may be extremely high. Serum aminotransferase levels are mildly to moderately increased. Serum cholesterol levels may be 200 mg/dL or higher. Serum triglyceride concentrations may range from 500 to 1,000 mg/dL.

On liver biopsy, the cardinal feature of this disorder is a paucity of interlobular bile ducts (*Fig. 205.6*). The number of interlobular bile ducts may not be decreased on initial liver biopsy, but there may be evidence of bile duct injury. The histologic features during the first months of life may overlap with those of neonatal hepatitis with ballooning of hepatocytes, variable cholestasis, portal inflammation, and giant cell transformation. Serial biopsies of an individual patient may initially show bile duct proliferation, followed later in life by a paucity of bile ducts. Paucity of interlobular bile ducts is usually apparent after 3 months. There may also be mild periportal fibrosis, but progression to cirrhosis is uncommon. The extrahepatic bile ducts are patent but usually narrowed or hypoplastic.

The mechanisms involved in the pathogenesis of bile duct paucity and cholestasis are not settled. It is also unknown how the bile duct abnormalities relate to the

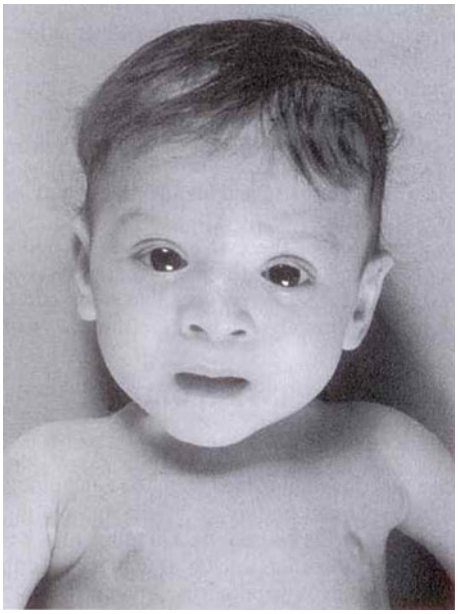

Figure 205.5
Child with Alagille syndrome (Courtesy of Prof. Hisham Nazer, Amman, Jordan)

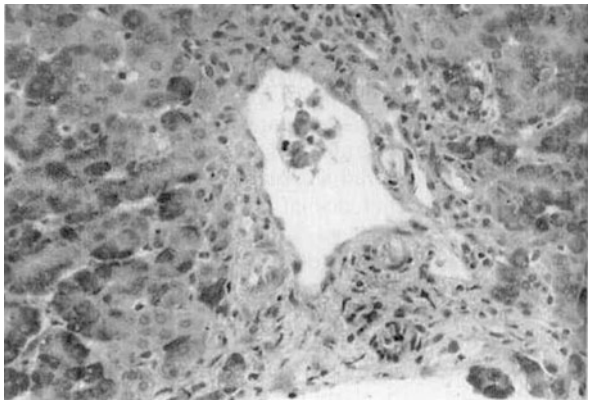

Figure 205.6
Liver biopsy from a child with paucity of interlobular bile ducts (Courtesy of Prof. Hisham Nazer, Amman, Jordan)

congenital anomalies found in other organ systems. The strong jagged 1 expression during human embryogenesis, both in the vascular system and in other mesenchymal and epithelial tissues, suggests that abnormal angiogenesis may be a key factor in the pathogenesis of Alagille syndrome. Although a vascular basis for the anomalies in Alagille syndrome seems possible, the precise mechanisms leading to bile duct paucity remain unknown. Notch signaling has an important role in the differentiation of biliary epithelial cells and is essential for their tubular formation during intrahepatic bile ducts development. There is recent evidence that a lack of branching and elongation of bile ducts during postnatal liver growth contributes to peripheral bile duct paucity and cholestasis.

The clinical course of Alagille syndrome is marked by varying degrees of cholestasis that may be exacerbated by intercurrent viral infections. Neonatal cholestatic jaundice has been associated with poorer survival with native liver. Significant morbidity may result from pruritus, cutaneous xanthomata, and neuromuscular symptoms related to vitamin E deficiency. Treatment involves the provision of good nutrition including prevention or correction of fat-soluble vitamin deficiencies. Symptomatic measures to relieve pruritus are variably successful. Partial external biliary diversion may be effective for treating severe pruritus and hypercholesterolemia in Alagille patients without cirrhosis who did not respond to medical therapy. The factors contributing significantly to the mortality are hepatic disease or complications of liver transplantation (25%), complex congenital heart disease (15%), and intracranial hemorrhage (25%). Hepatocelluar carcinoma may occur. Survival and candidacy for liver transplantation may be limited by the severity of associated cardiovascular anomalies. The 20-year predicted life expectancy is approximately 75% for all patients, approximately 80% for those not requiring liver transplantation, and approximately 60% for those who require liver transplantation. In patients requiring liver transplantation, a higher than expected mortality rate can be attributed to cardiac disease or a previous Kasai procedure.

Cystic Fibrosis

Patients with cystic fibrosis may rarely present in the neonatal period with cholestatic jaundice and acholic stools. It may be associated with meconium ileus. Clinical features may mimic extrahepatic biliary atresia. Cholestasis may develop as a result of inspissated bile in the biliary tree.

Intraheptic Cholestasis

Neonatal Hepatitis

Neonatal hepatitis refers to a hepatocellular process characterized by swelling and multinucleated giant cell transformation of hepatocytes and variable cholestasis, inflammation, necrosis, and fibrosis. This process should be considered a pattern of injury typical of the neonatal liver rather than a specific diagnosis. In many series of infants with cholestatic jaundice, at least one third of the patients fell into the category of so-called idiopathic neonatal hepatitis. The relative incidence of the disorder in early reports varied from 1 in 2,500 to 1 in 8,000 live births. A familial form affects 10–15% of patients suggesting causation by an underlying immunologic defect or inborn error of metabolism. At present, the incidence of idiopathic neonatal hepatitis is likely to be much lower because advances in virology and application of novel biochemical and molecular methods more commonly lead to a precise diagnosis. For example, perinatal infection with parvovirus B19 and human herpesvirus-6 has been associated with neonatal hepatitis. Other important associations include neonatal lupus erythematosus, α1 antitrypsin deficiency, and inborn errors of bile acid metabolism.

The clinical presentation and course are highly variable. However, the infant is often born prematurely or is of low birth weight. Cholestatic liver disease may be noticed during the first week or life or escape recognition until 1–2 months of age. A third of infants may fail to thrive. Cholestatic jaundice and acholic stools may suggest biliary obstruction. Hepatosplenomegaly is usually present. A hemorrhagic diathesis may result from deficiency of coagulation factors and from thrombocytopenia. Congenital malformations are found less commonly than with the cholangiopathies, but microcephaly and chorioretinitis strongly suggest intrauterine infection with rubella or cytomegalovirus. A fulminant course, reflecting massive necrosis of hepatocytes, can occur with herpes simplex and enteroviral infections or with inborn errors of metabolism such as neonatal iron storage disease or tyrosinemia.

Standard liver biochemical tests are variably abnormal. Total and conjugated serum bilirubin levels are elevated. Serum aminotransferases are moderately elevated, but markedly abnormal levels may be found with significant necrosis. Alkaline phosphatase, 5′-nucleotidase, and γ-glutamyltransferase levels are raised but usually to a degree less than in biliary obstruction.

Liver biopsy is valuable in defining alterations of the hepatic parenchyma in neonatal hepatitis that in most

cases can help differentiate the process from biliary atresia. The lobular architecture may be severely disturbed with variable swelling, degeneration, and necrosis of hepatocytes and extramedullary hematopoiesis. Multinucleated giant cells, thought to be formed by fusion of hepatocytes, may be prominent throughout the lobule (*Fig. 205.7*). Hepatocellular and canalicular bile stasis are regular features, but ductular bile plugs and proliferation should be negligible. Periportal and lobular fibrosis may be present. Pseudoacinar arrangement of hepatocytes and steatosis should suggest a metabolic cause for the liver disease.

There is no specific treatment for neonatal hepatitis. Efforts should be directed toward correction and prevention of fat-soluble vitamin deficiencies and provision of a formula containing high medium-chain triglycerides (MCTs).

The prognosis of idiopathic neonatal hepatitis is highly variable. Approximately 60% of patients with the sporadic form recover completely, one third die from rapidly progressive disease, and about 10% develop chronic liver disease.

α1-Antitrypsin Deficiency

α1-Antitrypsin, a 50-kDa glycoprotein synthesized predominantly in the liver, is the major serum protease inhibitor and acts to inhibit a broad range of proteolytic enzymes, particularly neutrophil elastase. The protease inhibitor occurs in over 75 variants, known Pi phenotypes, which are inherited as codominant alleles.

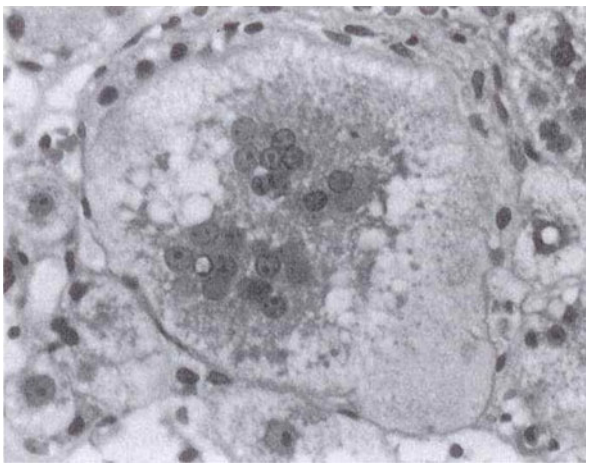

Figure 205.7
Liver biopsy from patient with idiopathic neonatal hepatitis showing multinucleated giant cell

The normal phenotype, determined by protein electrophoresis, is designated MM. Patients with a homozygous deficiency state or ZZ phenotype have low serum α1 antitrypsin levels, usually 10–15% of normal values. The incidence of the PiZZ phenotype is 1 in 2,000–1 in 4,000. The deficiency state can be associated with progressive liver disease in infants children and adults. Heterozygotes with the SZ and MZ phenotypes have a less-severe reduction in serum α1-antitrypsin concentration. The role of α1-antitrypsin heterozygosity as a modifier for other liver diseases remains unsettled.

Approximately 10–15% of patients with the P1ZZ phenotype develop cholestasis in the newborn period. Hepatomegaly and acholic stools are typical in these patients. Patients may rarely present with ascites or bleeding. Although asymptomatic, another 40–50% of infants may have abnormal liver biochemical tests in the first months of life. The diagnosis should be made by determination of the α1-antitrypsin phenotype. Measurement of α1-antitrypsin levels alone is not reliable, since the protein is an acute phase reactant.

Liver biopsy in the neonate often shows giant cell hepatitis. Bile ductular proliferation may be variably observed; paucity of bile ducts may be found later. The presence of periodic acid-Schiff-positive diastase-resistant inclusions within hepatocytes, representing the abnormal α1 antitrypsin, is a characteristic feature but is not usually prominent before 4 months of age. A variable degree of fibrosis may be present. Cirrhosis has been reported in the neonate.

The pathophysiology of liver disease in α1-antitrypsin deficiency is not entirely clear, particularly as to why only 10–15% of neonates manifest liver disease. The PiZZ defect, caused by the substitution of a lysine for a glutamate at position 342, leads to misfolding of the protein and its retention in the endoplasmic reticulum. Studies in transgenic animals expressing the abnormal human protein support the notion that the retained α1-antitrypsin is toxic to the liver. The mutant α1-antitrypsin molecule polymerizes in the ER by a novel loop-sheet insertion mechanism. The intracellular accumulation of the mutant Z protein in the liver leads to the activation of autophagy, mitochondrial injury, and caspase activation, which causes progressive liver damage. The subpopulation of α1-antitrypsin-deficient individuals who develop liver disease may have another trait that reduces the efficiency with which the mutant α1-antitrypsin protein is degraded in the endoplasmic reticulum.

The course of patients with neonatal liver disease related to α1-antitrypsin deficiency is variable. Rare patients presenting with cirrhosis may deteriorate rapidly within the first months of life. However, in most patients, the jaundice clears by 4 months of age. Nearly equal proportions of patients will manifest one of the following outcomes:

Continued liver dysfunction with progression to cirrhosis and end-stage liver disease by age 10 years, persistent liver test abnormalities with slow progression to cirrhosis in adolescence or later, mild liver test abnormalities and minimal fibrosis with survival into adulthood, and apparent complete resolution of hepatic disease. Hepatocellular carcinoma may occur in these patients. There is no specific treatment for α1-antitrypsin deficiency. Liver transplantation is curative for patients progressing to end-stage liver disease; the recipient assumes the Pi type of the donor organ.

Progressive Familial Intrahepatic Cholestasis

The group of inherited disorders of bile formation, known as progressive "familial intrahepatic cholestasis" (PFIC) often present in infancy and are associated with progression at a variable rate to end-stage liver disease. Mutations in several genes encoding transport proteins located on the liver canalicular membrane have been defined.

PFIC1 (also called *Byler disease*) is characterized by unremitting cholestasis with pruritus and jaundice that usually starts before the age of 1 year. Progression to cirrhosis and liver failure occur at a variable rate. Diarrhea, malabsorption with fat-soluble vitamin deficiencies, and failure to thrive are common. Intractable pruritus, often out of proportion to the level of jaundice, is the dominant feature of cholestasis. Serum γ-glutamyl transpeptidase activity and cholesterol concentrations are paradoxically normal. The serum bile acid concentration is markedly elevated. Liver biopsy shows hepatocellular and canalicular cholestasis early in the course of the disease.

Cirrhosis eventually occurs. Electron microscopy shows distended bile canaliculi with effaced microvilli that contain unusually coarse and granular bile (so-called Byler's bile). Patients with PFIC1 have mutations in the gene FIC1 that encodes for ATP8B1, a P-type ATPase localized to the liver canalicular and cholangiocyte apical membranes. ATP8B1 is thought to maintain asymmetry of aminophospholipids in lipid bilayers, and may play a role in regulating important lipid-dependent signaling pathways and the activity of membrane receptors and transport proteins. The loss of canalicular phospholipid membrane asymmetry in PFIC1 also renders the canalicular membrane less resistant to the damaging effects of hydrophobic bile salts. The FIC1 gene is also expressed in other organs including the lungs, small intestine, pancreas, and kidneys. This may account for some of the extrahepatic symptoms in PFIC1. Biliary diversion or ileal bypass are used often to treat pruritus and slow the progression of liver damage by depletion of hydrophobic bile acids. Liver transplantation may be required in some patients. Owing to the extrahepatic expression of FIC1, patients may still suffer from growth failure, malabsorption, and pancreatitis after an otherwise successful liver transplant.

Benign recurrent intrahepatic cholestasis type 1(BRIC1) is also caused by FIC1 mutations. Attacks of jaundice and pruritus occur separated by symptom-free intervals. The age of presentation ranges from 1 to 50 years but usually before the age of 20 years. Episodes begin with 2–4 weeks of malaise, anorexia, and pruritus, followed by an icteric phase that may last from 1 to 18 months. Progression to cirrhosis and long-term complications of chronic liver disease do not occur.

PFIC2

Patients with PFIC2 usually present in the neonatal period with a giant cell hepatitis and severe cholestasis. Pruritus is the dominant feature of the disorder in most patients. Patients with PFIC2 have low serum γGT and normal or near-normal serum cholesterol levels. In contrast to patients with PFIC-1, serum aminotransferase levels are usually elevated to at least five times normal values. A rapid progression to cirrhosis is seen without therapy. Patients with PFIC2 are at risk for developing hepatocellular carcinoma and cholangiocarcinoma. PFIC2 is caused by mutations in ABCB11 which encodes for the bile salt export pump (BSEP), the predominant transporter for bile acids on the liver canalicular membrane. Progressive liver damages result from bile secretory failure with retention bile salts and other biliary constituents in the hepatocyte. Liver morphology in PFIC2 shows a neonatal hepatitis with giant cell transformation of hepatocytes and lobular cholestasis that may persist beyond infancy. Electron microscopy demonstrates effaced microvilli and dilated bile canaliculi that contain finely granular or filamentous bile. Patients demonstrating the phenotype of BRIC have recently been described with mutations in ABCB11. These patients have recurrent episodes of cholestasis and are clinically healthy and biochemically normal between attacks. The age of onset and total number of recurrent episodes are variable.

Several patients have been reported who developed permanent cholestasis as adults after initial periods of recurrent attacks as children. Biliary diversion and ileal exclusion have been done to treat intractable pruritus and progression of liver disease. A risk for liver cancer may still exist. Liver transplantation may be required, but extrahepatic complications seen in PFIC1 patients post-transplant do not occur.

PFIC3

The age of onset of PFIC3 with jaundice, hepatomegaly, and acholic stools can range from 1 month to over 20 years (mean age ~3.5 years). The disorder is caused by mutations in the ABCB4 (MDR3) gene which encodes a transporter required for biliary phosphatidylcholine secretion. The formation of mixed micelles with phosphatidylcholine, cholesterol, and bile salts is needed to protect the canalicular and cholangiocyte membranes from damaging effects of bile acids. Pruritus is less severe than in the other types of PFIC. Growth failure may occur as the disease progresses. Evolution occurs slowly to biliary cirrhosis with or without overt cholestatic jaundice. Portal hypertension may occur early in childhood, or can be a presenting feature in adolescents and young adults. In contrast to the other forms of PFIC, the serum concentration of γ-glutamyltranspeptidase is elevated in PFIC3, often over ten times the normal value. The serum aminotransferases, conjugated bilirubin, and alkaline phosphatase are variably elevated. The serum cholesterol concentration is usually normal. Biliary phospholipids are markedly reduced.

Liver biopsy shows bile ductular proliferation, mixed inflammatory infiltrates, and eventually periductal sclerosis affecting the interlobular bile ducts. Biliary cirrhosis may occur in older children. Treatment with ursodeoxycholic acid (UCDA) appears to be of value in patients with milder MDR3 missense mutations and residual biliary phospholipid secretion. Enrichment of bile with this hydrophilic bile acid reduces cytotoxic injury to hepatocytes and bile ducts and stimulates bile flow. Other patients progress to end-stage liver disease at a variable rate and require liver transplantation.

Inborn Errors of Bile Acid Metabolism

Nine inborn errors of bile acid metabolism have been described that have different clinical phenotypes. Defects in modification of steroid ring of cholesterol are most likely to produce severe cholestasis and liver disease, whereas defects in side chain modification lead to neurological dysfunction, fat-soluble vitamin malabsorption, and milder liver disease (Table 205.2).

Primary defects in enzymes mediating bile acid biosynthesis may present with cholestasis and sometimes liver failure in the neonate.

An enzymatic block in bile acid synthesis leads to a lack of primary bile acids critical for generating bile flow and the concomitant accumulation of unusual toxic bile acids and metabolites in the hepatocyte. However, in contrast to other cholestatic disorders, impaired synthesis of bile salts is not associated with either pruritus or elevated serum bile salt concentrations because the normal end products are not synthesized. Indeed, measurement of serum bile acid concentrations by standard clinical assays shows paradoxically low to absent primary serum bile acids in the face of severe cholestasis. The serum γ-glutamyl transpepsidase concentration is often normal. A high index of suspicion for these disorders needs to be maintained because their features are variable. The possibility of a primary abnormality in bile acid biosynthesis should be entertained in any child with chronic cholestasis or hepatitis of obscure etiology. Screening for these defects requires specialized testing by liquid secondary ionization mass spectrometry of urine. Additional information is derived from gas chromatography–mass spectrometry of urine, serum, and bile. Genetic diagnosis of some disorders is available.

Prompt diagnosis of an inborn error of bile acid metabolism is essential because several of these disorders can be treated with oral bile acid replacement. Treatment with the primary bile acid, cholic acid, has been particularly successful in patients with the more common defects,

Table 205.2
Inborn errors in bile acid metabolism associated with neonatal cholestasis

Enzyme defect	Phenotype
3β-hydroxy C_{27} steroid oxireductase	Severe, progressive cholestasis.
Δ*-3-oxosteroid 5β reductase	Severe, progressive cholestasis, liver failure
Sterol 27-hydroxylase	CTX, neonatal cholestasis
Oxy 7α-hydroxylase	Hyperoxysterolemia, neonatal liver failure
2-methyl-CoA-racemase	Adult sensorimotor neuropathy, neonatal liver disease

3β-hydroxy-C27-steroid oxidoreductase deficiency and Δ4-3-oxosteroid 5β-reductase deficiency. Cholic acid provides the primary bile acid required to generate bile flow and to downregulate the production of toxic bile acid precursors by feedback inhibition at the level of the rate limiting enzyme 7α-hydroxylase. Ursodeoxycholic acid that is commonly used in other forms of cholestasis is ineffective because it does not inhibit bile acid synthesis. Therapy must be continued life long.

Medical Management of Chronic Cholestasis

In the infant with chronic, and sometimes progressive, cholestatic liver disease, efforts should be directed toward promoting growth and development and minimizing discomfort.

As a result of impaired intraluminal long-chain triglyceride lipolysis, solubilization and absorption leading to steatorrhea, failure to thrive is common in children with cholestasis. Medium-chain triglycerides (MCTs) do not require prior bile salt solubilization for their absorption, and thus can provide needed calories when administered in one of several commercial formulas or as an oil supplement. However, it is important to recognize that essential fatty acid deficiency can develop if MCT is the only source of dietary fat.

Fat-soluble vitamin deficiencies can result in significant morbidity, and might largely be prevented in the cholestatic child. Metabolic bone disease, manifesting as rickets and pathologic fractures, can occur from vitamin D deficiency.

Vitamin D supplementation as D2 (5,000 IU/day) may be required. In patients with severe cholestasis, supplementation with 1,25 (OH) 2 (Calcitriol) at a dosage of 0.05–0.2 microgram/kg/day should be administered. This requires monitoring (including 1,25 (OH) 2 levels) because there is no physiologic regulation of this compound. Supplements of elemental calcium (50–100 mg/kg/day) and phosphorous (25–50 mg/kg/day) may also be required.

Vitamin A deficiency may manifest as xerophthalmia, night blindness, and thickened skin. Oral supplements of 5,000–25,000 IU/day should be administered.

Coagulopathy related to vitamin K deficiency may be treated with an oral water-soluble supplement twice weekly (2.5–5 mg) up to a daily dose of as much as 5 mg. Intramuscular injections of vitamin K may be required in children with advanced liver disease.

A degenerative neuromuscular syndrome characterized by areflexia, ophthalmoplegia, cerebellar ataxia, peripheral neuropathy, and posterior column dysfunction occurs in children with chronic deficiency of vitamin E. Onset can be observed within the first 2 years of life. Since serum vitamin E levels may be spuriously elevated in the presence of hyperlipidemia, the serum vitamin E/total serum lipids ratio (deficiency in a child <12 years old indicated by a ratio <0.6) is used in monitoring the vitamin E status. Since the infant may fail to respond to even massive doses of standard vitamin E preparations (up to 150–200 IU/kg/day), therapy with a water-soluble form of vitamin E, D-alpha-tocopheryl polyethylene glycol-1000 succinate (TPGS) (15–25 IU/kg/day) should be initiated. The polyethylene glycol-1000 in this preparation will also promote the absorption of other fat-soluble vitamins if administered at the same time. Significant discomfort may be a consequence of xanthomas and pruritus. Pruritis may be observed by 3 months of age. Regression of the symptoms may follow efforts to increase the conversion of cholesterol to bile acids, reducing the regurgitation of biliary constituents into the systemic circulation, and enhancing the elimination of bile acids, cholesterol, and putative pruritogenic substances. The success of most therapies depends on the presence of patent bile ducts, which allow bile acids and other biliary constituents to reach the gut lumen.

The nonabsorbable anion-exchange resin, cholestyramine, may be used to bind bile acids, cholesterol, and presumably other potentially toxic agents in the intestinal lumen. The agent is often effective in lowering serum lipid levels and in binding of substances involved in the pathogenesis of pruritus. A dose of 0.25–0.5 g/kg/day is given before breakfast or in divided doses before meals for relief of severe pruritus and xanthomas. However, cholestyramine is relatively unpalatable and may cause intestinal obstruction from inspissation of the drug and a hyperchloremic acidosis. The antibiotic rifampicin (10 mg/kg/day, 300 mg maximum), through undefined mechanisms and the choleretic bile acid ursodeoxycholic acid (10–20 mg/kg/day), may be used for the treatment of pruritis. Biliary diversion has been used as a successful alternative to relieve intractable pruritus in some patients with intrahepatic cholestasis.

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206 Alpha-1 Antitrypsin Deficiency

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Alpha-1 antitrypsin (α_1-AT) deficiency is the most common genetic cause of liver disease. The inheritance of α_1-AT deficiency follows an autosomal recessive pattern. It affects 1–1,600 to 2,000 live births in North Americans and the European population, respectively, but is less common in other ethnic groups.

α_1-AT is a glycoprotein synthesized primarily in the liver and to a lesser extent by other tissues, including macrophages, renal tubular, and small intestinal epithelial cells. It functions as a serine protease inhibitor with its main target being leukocyte elastase. The most common form of the disease, P_iZZ, results in the production of abnormal α_1-AT. Only a small proportion of patients with α_1-AT deficiency will develop clinically significant liver disease but it is the main cause of emphysema in adults. In addition to lung and liver disease, several disorders have been reported in association with α_1-AT deficiency including systemic vasculitis, interstitial fibrosis in patients with rheumatoid arthritis, relapsing panniculitis, multiple sclerosis, peripheral neuropathy, and intracranial aneurysms.

Classification of Human α_1-AT Variants

The gene encoding for α_1-AT has been localized to the q 31–32.2 locus on the long arm of chromosome 14. This locus is termed P_i (protease inhibitor). At least 75 genetic structural variants of α_1-AT have been identified based on their different mobilities on acid starch gels. The variants are assigned a letter using alphabetical order from high to low migration rates. For example, the most common normal α_1-antitrypsin haplotype are members of the M family because these variants migrate to the M isoelectric point. On the other hand, patients with the most common severe deficiency have an α_1-AT variant that slowly migrates to the Z isoelectric point.

Variants of α_1-AT associated with serum concentrations and functional activity in the normal range are classified as normal allelic variants, and include M_1, M_2, M_3, and X. Variants of α_1-AT associated with a reduction in serum concentration or functional activity of α_1-AT are classified as deficiency variants and include S, M_{Duarte}, and Z. Thus, patients with liver disease usually have the P_iZZ phenotype in which the abnormal α_1-AT is synthesized in hepatocytes but not secreted at a normal rate. Clinically important phenotypes include P_iMM, P_iMZ, P_iMS, P_iSZ, and P_iZZ – these correlate with total serum α_1-AT concentrations of 100%, 60%, 45%, less than 40%, and 15% of normal, respectively. Significant hepatic and pulmonary disease is usually associated with serum α_1-AT concentrations less than 40%. Variants of α_1-AT in which α_1-AT is absent from the serum are classified as null allelic variants and include $Null_{Granite\ Falls}$ and $Null_{Hong\ Kong}$. These variants, when inherited with other null variants or with deficiency variants, are associated with the development of emphysema but not liver disease.

Pathogenesis

α_1-AT functions as a serine protease inhibitor (serpin), and its predominant inhibitor is neutrophil elastase. Similar to other proteins in the serpin family of protease inhibitors, α_1-AT undergoes conformational change after encountering elastase which cleaves the reactive center of α_1-AT allowing marked structural change in α_1-AT, which irreversibly destroys its structural integrity promoting its degradation.

The most common α_1-AT mutant molecule, PiZ, results from a single amino acid substitution of lysine for glutamate at position 342 in the coding sequence. The mutation promotes spontaneous polymerization in the hepatocyte through insertion of the reactive center of one protein into the β-sheet of another, known as "loop-sheet" insertion and therefore polymers of α_1-AT protein are retained in the endoplasmic reticulum of the hepatocyte due to failure of the secretory process.

Not all patients with PiZZ patients develop liver disease, which suggests that other factors are involved in the pathogenesis of the disorder. One possible mechanism is that susceptible individuals may have delayed intracellular degradation of the mutant protein, rather than its accumulation in the endoplasmic reticulum. It has been suggested that delay in degradation of the mutant protein may result of abnormalities in calnexin, a protein that interacts with the mutant α_1-AT protein in the endoplasmic reticulum.

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While liver injury results from retained alpha α_1-AT glycoprotein in the endoplasmic reticulum, the mechanisms of lung injury are different. Lung damage occurs as a result of uninhibited proteolytic changes of the connective tissue secondary to low concentration of circulating alpha 1-antitrypsin.

Clinical Manifestations

One of the intriguing facts about this disease is the variable presentation and significant variation in outcome even in members of the same family. These observations are true for both P_iZZ disease and disease caused by other variants.

Hepatic Disease in Infancy and Childhood

A picture regarding the varied natural history of P_iZZ disease in infancy and early childhood was first provided by landmark studies in Swedish infants. One hundred and twenty two children with P_iZZ α_1-AT deficiency and 48 with P_iSZ α_1-AT deficiency were identified and followed prospectively till the age of 8 years. Fourteen patients (12%) of infants with the P_iZZ phenotype presented with neonatal jaundice. Seven percent had clinical evidence of liver disease in infancy but by 6 months of age they had clinically recovered. The remaining P_iZZ infants were initially clinically normal, but 47% had elevated liver enzymes at 3 months of age. Thus, 64% of P_iZZ infants were found to have clinical or laboratory evidence of hepatic disease. The outcome for children with liver disease is variable. Around 25% will persist in having abnormal liver function tests and may develop cirrhosis rapidly and die from hepatic complications. Approximately 25% will have minimal liver abnormalities, but will have slow progression to cirrhosis. Another 25% will have minimal liver dysfunction and fibrosis, and will live to adulthood. Another 25% will recover from the initial insult and return to normal liver function.

Occasionally, chronic liver disease or cirrhosis can be identified in older children without a history of neonatal liver disease. As many as 50% of the children presenting with cirrhosis due to α_1-AT deficiency have no antecedent history of neonatal disease. Hepatomegaly is a common presenting finding while splenomegaly is usually seen in those presenting with decompensated advanced cirrhosis. Some patients may also present with vitamin K deficiency manifesting as coagulopathy especially in patients who did not receive vitamin K injection at birth and breast-fed babies. Coagulopathy may result in umbilical bleeding and bruising in the first few days of life or may present later with intraventricular hemorrhage.

Hepatic disease in α_1-AT deficiency is more commonly seen in children than in adults. In adults, premature pulmonary emphysema is the most common presentation. Pulmonary emphysema in α_1-AT deficiency is essentially an adult disease. There is evidence of hyperactive airway disease in 3–8% of children with α_1-AT disease. However, several cases of chronic hepatic disease and cirrhosis in the presence and absence of emphysema have been reported in adults with α_1-AT deficiency. Hepatocellular and cholangiocellular carcinomas are strongly linked to α_1-AT deficiency in adult patients. Thus, similar to tyrosinemia, α_1-AT deficiency can be viewed as a potentially premalignant metabolic liver disease.

Diagnosis of Liver Disease in α_1-AT Deficiency

The diagnosis of α_1-AT deficiency is suggested by low-level α_1-AT serum level. However, one should bear in mind that α_1-AT is an acute phase reactant and can be falsely elevated in association with inflammatory processes or decreased in patients with protein-losing enteropathy. The diagnosis is usually established by α_1-AT phenotype determination using isoelectric focusing or agarose electrophoresis at acid pH.

It is also now possible to detect specific α_1-AT variants by amplification of genomic DNA using polymerase chain reaction techniques.

The diagnosis is also suspected from the characteristic periodic acid-Schiff (PAS) positive, diastase-resistant globules found on histologic sections, in the endoplasmic reticulum of hepatocytes.

Biochemical abnormalities demonstrate hepatocellular and obstructive patterns with elevation of aminotransferases, alkaline phosphatase, and bilirubin. Hepatobiliary scintigraphy may show decreased excretion of the dye into the intestine. Patients may also show signs of coagulopathy secondary to vitamin K deficiency resulting from malabsorption due to cholestasis or due to impaired hepatic synthetic function in subjects with advanced disease.

Antenatal diagnosis is feasible by chronic villous sampling using synthetic oligonucleotide probes specific for the M and Z genes or by restriction fragment length polymorphism.

Histopathologic Findings

Patients with α_1-AT deficiency characteristically show diastase-resistant, periodic acid-Schiff (PAS)-positive

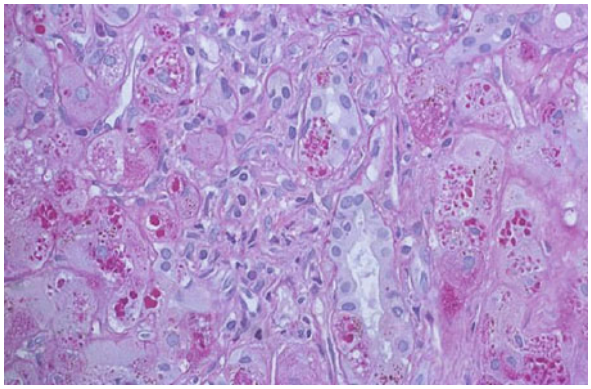

Figure 206.1
Characteristic diastase-resistant, periodic acid-Schiff (PAS)-positive globules in the cytoplasm of the hepatocytes in a patient with alpha-1-antitrypsin deficiency

globules in the cytoplasm of periportal hepatocytes (*Fig. 206.1*). These globules are found in P_iZZ patients but have been recognized in heterozygote variants as well as in patients without Z allele because of M variant associated with accumulation of hepatocellular α_1-AT. These globules have been shown by immunoperoxidase technique, to be misfolded alpha-1-antitrypsin. These inclusion bodies should be differentiated from the similar centrilobular globules seen as a result of sinusoidal congestion and anoxia.

In addition to the characteristic globules, newborns commonly show cholestasis with portal tract expansion by fibrous tissue, marked biliary duct proliferation, and very few inflammatory cells. Intrahepatic biliary hypoplasia has been seen in some patients, while classic giant cell neonatal hepatitis has been recognized in others.

Micronodular or macronodular cirrhosis is seen in older children and adults, although well-established cirrhosis has been documented in some newborns.

Therapy

Patients with α_1-AT deficiency should refrain from smoking and avoid secondary smoke in order to slow the progression of lung emphysema.

Children with cholestatic liver disease should be supplemented with fat-soluble vitamins and treated for pruritus and ascites with diuretics and paracentesis as indicated.

Pharmacologic therapy with stanzol and danazol, drugs effective in other serine proteinase inhibitor deficiencies, has failed to show substantial improvement in α_1-AT serum levels.

Patients with progressive emphysema have been treated with infusions of purified plasma α_1-AT in limited clinical trials, a process known as augmentation therapy. This therapeutic modality has been associated with elevation of serum levels of alpha 1-antitrypsin in the absence of significant decrease of FEV1 (forced expiratory volume in 1 s). This form of therapy is not being considered for patients with liver disease because deficient serum levels of α_1-AT are not thought to be the cause of liver disease (see "Pathogenesis").

Gene augmentation has been conducted in animal models using adenovirus-associated, recombinant gene therapy and demonstrated successful gene transfer to peripheral skeletal muscle with elevation of serum alpha 1-antitrypsin concentration. However, concomitant expressions of the mutant allele would restrict benefit from this form of therapy to patients with emphysema.

In patients with end-stage liver disease, liver transplantation may be the only left consideration. Although α_1-AT deficiency is a rare indication for liver transplantation among adults in pediatric patients, liver transplantation for metabolic liver disease is second only to biliary atresia as the most common indication for transplant. α_1-AT deficiency is the primary metabolic liver disease leading to a transplant in the pediatric age group. The outcome of liver transplantation is excellent in children with α_1-AT deficiency, with 3-year survival rates approaching 85%. Without transplantation poor prognostic variables include jaundice lasting more than 6 weeks, higher aminotransferases at presentation, and severe bile duct proliferation and stage of fibrosis on liver biopsy. Transplant recipients acquire the donor phenotype and have normalization of alpha 1-antitrypsin levels. However, the effect of liver transplantation on the lung disease is not known.

Few patients with metabolic defects of liver function have been treated with hepatocyte transplantation including patients with urea cycle disorders, ornithine transcarbamylase deficiency, Crigler–Najjar syndrome, and α_1-AT deficiency. Hepatocyte transplantation at the time being is still considered an experimental procedure but may prove to be an effective therapeutic modality in the future for the treatment of patients with metabolic liver disease or as a bridge for those waiting for liver transplantation.

Future therapeutic strategies may include the development of chemical chaperones, aiming at blocking the aberrant β-stand linkage with competing peptides and targeting small molecules to an allosteric cavity. None has yet been shown to be effective in humans.

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207 Inherited Deficient Conjugation of Bilirubin

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Hyperbilirubinemia results from three major mechanisms: excessive bilirubin production (e.g., hemolysis), impaired hepatic handling of bilirubin (e.g., inherited disorders and hepatitis), or defective biliary outflow (e.g., intrahepatic or extrahepatic biliary obstruction). Unconjugated hyperbilirubinemia may present as an isolated finding in the newborn infant without evidence of overt hemolysis or structural liver disease. This chapter focuses on genetic disorders associated with unconjugated hyperbilirubinemia in childhood. Other conditions associated with hemolysis in the newborn or later childhood are discussed elsewhere. It is not uncommon to have an isolated unconjugated hyperbilirubinemia in symptom-free individuals. There is no generally agreed-upon approach to the evaluation of such affected children. The child is considered to have unconjugated hyperbilirubinemia if the direct-reacting bilirubin comprises less than 15–20% of the total serum bilirubin.

Unconjugated hyperbilirubinemia is characterized by the absence of bile in the urine. The total serum bilirubin in normal infants is usually less than 1.5 mg/dL (25 μmol/L), with the conjugated or direct reacting portion less than 0.5 mg/dL (7 μmol/L). The plasma concentration of unconjugated bilirubin reflects a balance between bilirubin production and hepatic bilirubin clearance. Jaundice appears in children and adults when the serum bilirubin concentration exceeds 2 mg/dL (34 μmol/L).

Neonatal hyperbilirubinemia including physiologic and pathologic neonatal jaundice as well as hemolytic conditions are discussed in other sections. In this section, two genetically inherited disorders presenting with unconjugated hyperbilirubinemia will be discussed: Crigler–Najjar syndrome (CNS) ((a) Type I glucuronyl transferase deficiency, (b) Type II glucuronyl transferase deficiency) and Gilbert syndrome.

Crigler–Najjar Syndrome

Crigler–Najjar (CN) syndrome is a well-recognized congenital familial nonhemolytic jaundice associated with high level of unconjugated bilirubin due to deficiency or almost complete absence of the hepatic microsomal bilirubin uridine 5-diphosphate glucuronosyltransferase (UDPG-T) activity. Bilirubin UDPG-T is a membrane-bound enzyme system concentrated in the lipid bilayer of the endoplasmic reticulum in hepatocytes and cells of the intestine, kidneys, and other tissues.

Crigler–Najjar syndrome (CNS) results from a mutation in one of the five exons of the gene coding for the enzyme bilirubin-UDP-glucuronosyl transferase by exon 1*1 and exons 2–5 of the UDP-glucuronosyl transferase 1 locus, the bilirubin glucuronidating isoform of UDP-glucuronosyltransferase.

This syndrome was first recognized by Crigler and Najjar (1952) in their report of six infants of three related families with severe unconjugated nonhemolytic jaundice. Arias et al. subdivided the disease into two types (1 and 2) based on the responsiveness of serum bilirubin to phenobarbital therapy. However, the clinical differentiation of both types can be difficult, especially in early infancy. It has even been suggested that both types are merely different expressions of one disease.

Crigler–Najjar Syndrome Type1

Definition and etiology: This type constitutes the more serious form of CN syndrome, with severe jaundice in the first few days of life and potential risk of developing kernicterus in early infancy. The mode of inheritance of this type of CN syndrome with almost complete absence of UDPG-T activity in the liver is in an autosomal recessive fashion. Heterozygotes are phenotypically normal with normal serum bilirubin.

Reports have suggested a considerable heterogeneity with regard to the expression of UDPG-T isoenzymes among CN type 1 patients. Bilirubin UDPG-T activity arises from a gene complex of unusual structure located on human chromosome 2. Affected patients with this type of CN syndrome do not respond to phenobarbital therapy

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and may require repeated exchange transfusions followed by long-term phototherapy to prevent the development of neurologic complications.

Clinical Manifestations

In spite of the severe jaundice with very high levels of serum unconjugated bilirubin, there is no evidence of hemolysis or liver disease. The newborn usually appears normal at birth apart from jaundice, which progresses rapidly to reach a high level that warrants exchange transfusion in spite of phototherapy. The serum bilirubin is recognized in this group of patients to reach a very high level by the end of the first week, reaching as high as 45 mg/dL (765 μmol/L) or even higher.

Kernicterus is a neurologic syndrome resulting from the deposition of unconjugated bilirubin in the basal ganglia and brainstem nuclei. It is an almost universal complication of CN type 1 and is first noted in the early neonatal period. Initial symptoms include lethargy, poor sucking, and loss of Moro reflex. Infants then develop respiratory distress, diminished tendon reflexes, opisthotonos, convulsions, and spasms.

Treatment with exchange transfusions and phototherapy should be intensified at the early stage to ensure a relatively safe level of unconjugated bilirubin to prevent the development of kernicterus. There is usually a family history of consanguinity or similarly affected siblings.

Diagnosis

The diagnosis is usually suspected in view of the family history, severe jaundice with absence of hemolysis, or evidence of liver disease. History of exchange transfusions in the index case and/or other siblings adds further to the consideration of such diagnosis. Liver function tests are usually normal.

Persistence of unconjugated hyperbilirubinemia at a level higher than 20 mg/dL, (340 μmol/L) after the first week of life in the absence of hemolysis or evidence of liver disease should suggest the diagnosis. Bilirubin concentration in the bile is less than 10 mg/dL (normal concentration 50–100 mg/dL) and there is no bilirubin glucuronide. Parents of affected children have normal serum bilirubin concentrations, but have partial defects in conjugation detected when glucuronide formation is measured.

The diagnosis is confirmed by percutaneous liver biopsy, which reveals normal histology apart from occasional bile plugs in the bile canaliculi (*Fig. 207.1*). Intrahepatic cholestasis may be detected in some cases, which could account for the occasional slight elevation in liver enzymes. The measurement of hepatic glucuronyl transferase activity in the liver specimen establishes the diagnosis. DNA diagnosis is also available.

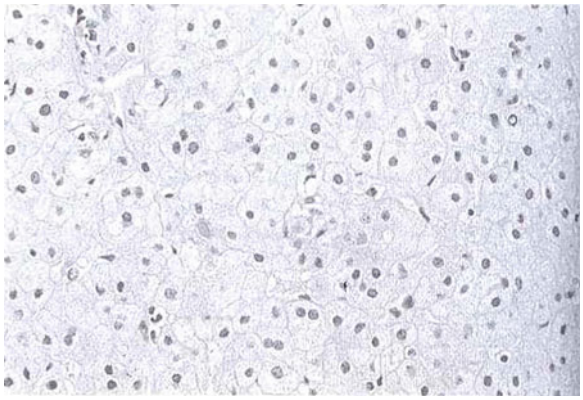

Figure 207.1
Percutaneous liver biopsy (hematoxylin and eosin) from an infant with Crigler–Najjar syndrome type 1; the liver histology is normal without fibrosis but with only few bile plugs

Treatment

Affected patients with CN syndrome type 1 do not respond to phenobarbital therapy. They require repeated exchange transfusions followed by long-term phototherapy to prevent the development of neurologic complications. It is crucial that infants are recognized and treated promptly to prevent neurological sequelae which if untreated are lethal. Exchange transfusions may be required in the neonate with CN syndrome type 1 to ensure a safe level of unconjugated bilirubin (<20 mg/dL) in spite of continuing phototherapy for up to 18 h/day. Later on, the child may settle on fewer hours of phototherapy, especially as the child grows older and cannot accept as many hours of phototherapy. Double phototherapy may be required to achieve this with allowances for fewer hours of phototherapy. It is important to recognize the adverse side effects of long-term phototherapy such as impaired weight gain, developmental delay, and possible psychological disturbances.

Oral cholestyramine may be added to therapy to bind the bilirubin in the gut. Other adjunct therapy

includes calcium phosphate and agar. These agents bind photobilirubin products and interfere with the enterohepatic bilirubin circulation.

Liver transplantation is the only guaranteed form of therapy to save the child the risk of kernicterus. As phototherapy becomes less effective and practical with age, liver transplantation is expected to be performed on young patients with CN syndrome type 1 prior to the development of neurologic manifestations. Despite long-term phototherapy, adolescents and adults with CN syndrome type 1 almost invariably develop some neurologic damage secondary to chronic unconjugated hyperbilirubinemia.

Orthotropic liver transplantation has been performed on patients with CN syndrome type 1 since 1980. It has proved its efficacy in curing such patients and improving their lifestyle with an excellent survival rate. Auxillary partial orthotopic liver transplantation has proved to be technically feasible and it does provide adequate hepatocyte mass to correct the underlying metabolic abnormality in CN syndrome. Since the application of living-related liver transplantation, patients with CN syndrome are saved the long delay of waiting for transplantation. In addition, with increasing demands for liver grafts, affected patients have also benefited from split liver transplantation and also from orthotropic auxiliary liver transplantation by leaving the recipient right lobe in place. This latter approach could be repeated if necessary without the risk of whole-liver replacement. It also ensures less dependence on the graft function should the graft fail.

Hepatocyte transplantation is a promising treatment for several liver diseases and can also be used as a "bridge" to liver transplantation in cases of liver failure.

Over the last decades ex vivo and in vivo gene therapy using viral and nonviral vectors has been used to correct hyperbilirubinemia in Gunn rats, the relevant animal model for CN syndrome. Several of these approaches resulted in long-term correction of serum bilirubin levels in this animal model. Future directions aim to translate this model into human clinical trials.

Crigler–Najjar Syndrome Type 2

This is a milder form of CN syndrome. CNS type 2 is caused by a single base pair mutation leading to a decreased but not totally absent enzyme activity. In these patients, the enzyme remains responsive to phenobarbital induction therapy and their bile contains low amounts of bilirubin mono- and diglucuronides. Serum unconjugated bilirubin does not usually exceed 20 mg/dL (340 μmol/L) and responds satisfactorily to phenobarbital therapy. The inheritance of CN syndrome type 2 is still unclear. Both autosomal dominant transmission with variable penetrance and autosomal recessive transmission have been reported. Hepatic UDPG-T activity is usually deficient but not absent. The majority of patients survive into adulthood.

Clinical Features

The baby is normal at birth with no evidence of liver disease. Jaundice develops later in early infancy but it is usually mild. However, kernicterus has been reported in CN syndrome type 2.

Diagnosis

A positive family history supports further the clinical suspicion of this entity. A provisional diagnosis is made on the presence of unconjugated hyperbilirubinemia, and family history with no evidence of hemolysis or liver disease. Liver function tests are usually normal.

The diagnosis is confirmed by enzymatic assay on liver tissue obtained through a percutaneous liver biopsy. Hepatic UDPG-T activity is diminished but not absent. Liver histology is also normal.

The satisfactory response to phenobarbital therapy supports further the diagnosis.

Treatment

Phenobarbitone 5–10 mg/kg body weight per day results in a satisfactory reduction of the elevated serum unconjugated bilirubin. It is only rarely that patients with confirmed CN syndrome type 2 require exchange transfusions or long-term phototherapy.

Treatment of patients with CN syndrome is not limited to phototherapy and/or phenobarbital therapy. Other recognized therapies include plasmapheresis, hemoperfusion, cholestyramine, and oral agar. Sn-protoporphyrin, a heme oxygenase inhibitor, is considered to prevent the increase in serum bilirubin level. This medication and more recently, tin-mesoporphyrin are recognized modes of therapy adjuvant to phototherapy in the management of patients with CN syndrome type 1 to prevent heme catabolic breakdown to bilirubin.

Genetic Research

The application of the newly developed intragenic polymorphic probes may prove useful in carrier detection and prenatal/presymptomatic diagnosis.

Should enzyme replacement therapy become available, patients with CN syndrome may be cured early in life without liver transplantation.

Gilbert Syndrome

Gilbert syndrome is characterized by a mild form of unconjugated hyperbilirubinemia with serum bilirubin rarely reaching a level higher than 5 mg/dL (85 μmol/L). The familial nature of this disorder was first recognized by Gilbert and Lereboullet in 1901. There is usually no evidence of hemolysis or liver disease. The condition is often but not always familial. Liver function tests are also normal. Liver biopsy will only be necessary if additional abnormalities of liver function tests are found. There may be impaired hepatic uptake of bilirubin.

The mode of inheritance is autosomal dominant with incomplete expression. The condition may result from a reduction in hepatic bilirubin clearance to about one third of the normal value. The percentage of bilirubin disconjugates in bile is reduced.

Clinical Features

Affected patients with Gilbert syndrome may present with vague abdominal symptoms of pain and discomfort in association with mild fluctuating jaundice. It may also be associated with asthenia, dyspepsia, and lethargy. There is no real explanation to account for such varied symptoms in this disorder.

Diagnosis

A history of mild fluctuating jaundice with elevated level of serum unconjugated bilirubin together with the absence of hemolysis or evidence of liver disease should alert the physician to such diagnosis. This is further supported by normal liver function rests. The diagnosis is confined by the documentation of deficient enzymatic assay of UDPG-T activity on percutaneous liver biopsy.

Treatment

Gilbert syndrome is a mild benign condition of fluctuating jaundice. There is no morbidity directly related to this disorder. The condition is recognized to respond fairly well to phenobarbital therapy in a dose of 5–10 mg/kg of body weight per day.

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208 Congenital Hepatic Fibrosis

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Congenital hepatic fibrosis (CHF) is a rare hereditary disorder characterized by hepatic fibrosis, intrahepatic portal hypertension, esophageal varices, and well-defined histologic changes on liver biopsy. CHF is also associated with cholangitis and impairment of renal functions, usually due to an autosomal recessive polycystic kidney disease (ARPKD), which is described more frequently in neonates and infants and characterized by cystic and tubular dilatation affecting both cortical and medullary portions of the kidney.

CHF has also been reported in association with autosomal dominant polycystic kidney disease (ADPKD). The disease is reportedly inherited in an autosomal recessive fashion. However, about 50% of cases occur sporadically. CHF is known to occur in association with a range of both inherited and noninherited disorders with multi-organ involvement as a result of ductal plate malformation. CHF has been reported also in association with other conditions as choledochal cyst and nephrolithiasis.

Cystic disease of the liver and kidney has been recognized for centuries. The term "congenital hepatic fibrosis" with its varied clinical presentation was first recognized in 1960 (Dobbs RH) and described further in 1961 by Kerr et al.

Clinical Manifestations

The first clinical manifestations in most patients with CHF are signs and symptoms related to portal hypertension especially splenomegaly, and varices, often with gastrointestinal bleeding. Most affected neonates and young infants with predominant kidney disease die of renal failure within the first year of life. When hepatic lesions dominate the clinical expression of the disease, the affected child may remain asymptomatic with hepatomegaly involving especially the left lobe. The hepatic disease progresses to develop portal hypertension associated with splenomegaly and esophageal varices. Portal hypertension in CHF has been attributed to the hypoplasia or compression of the portal vein radicles in the fibrous bands. Abdominal pain is rare, but when present, it is usually localized to the right upper quadrant. Some patients may remain asymptomatic until late childhood or even adulthood.

Coexisting renal lesions may also remain asymptomatic until early adulthood. The typical lesions of congenital hepatic fibrosis have also been reported in adults with the autosomal dominant form of polycystic kidney disease.

The majority of fibropolycystic hepatic disorders are thought to result from the same embryonic defect, the so-called ductal plate malformation. Associated conditions include choledochal cysts, medullary sponge kidney, ARPKD and ADPKD, and cholangiocarcinoma.

On physical examination, the liver is firm on palpation with a smooth or finely nodular surface. The liver edge is sometimes irregular, suggesting cirrhosis.

Diagnosis

Congenital hepatic fibrosis is a rare autosomal recessive disorder that is diagnosed essentially by finding a firm liver with rather classic histologic changes in a good size liver biopsy. Microscopically, *ductal plate malformation* (DPM) is always found, and the involved bile ducts are in communication with the rest of the biliary system.

The diagnosis of CHF is dependent on histologic findings of liver biopsy preferably obtained through minilaparotomy. Percutaneous liver biopsy is not recommended because the pathologic lesions may not be uniform throughout the liver. Liver biopsy reveals a variable degree of periportal fibrosis and irregularly shaped proliferating bile ducts lined by normal cuboidal epithelium. Unlike cirrhosis, hepatic lobules are usually normal with normal hepatocyte morphology. Liver biopsy is essential in confirming the diagnosis of CHF and differentiating it from similar clinical conditions as idiopathic portal hypertension and early liver cirrhosis.

The liver histology is not uniform and does shows extensive hepatic fibrosis. The widened fibrous bands in the portal tract contain increased number of ectatic and dysplastic branches of the interlobular bile ducts. The irregularly shaped proliferating bile ducts are lined by normal cuboidal epithelium. The hepatic lobules are usually normal (*Fig. 208.1*). Cholestasis is rarely observed except when associated with cholangitis.

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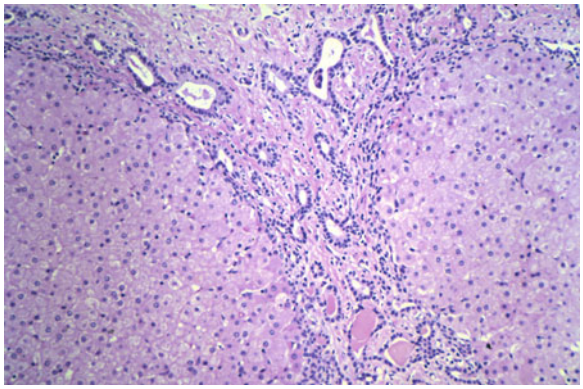

Figure 208.1
Liver biopsy in congenital hepatic fibrosis (hematoxylin and eosin) shows widened portal tract with bands of fibrous tissue that separate areas of normal hepatic parenchyma. Within the fibrous bands are multiple irregularly shaped, narrow, and elongated spaces lined with bile duct epithelial cells

The typical histopathologic changes in CHF are quite distinct from those with cirrhosis. Other findings include portal vein branch hypoplasia, degeneration of the bile duct epithelium, and mild cholestasis.

Liver function tests are usually normal, although serum alkaline phosphatase or y-glutamyl transpeptidase (GGT) may be elevated. Serum bilirubin, albumin, and prothrombin time are usually normal. Hypersplenism is manifested by thrombocytopenia and leukopenia.

In the presence of renal involvement, there is elevation of serum urea and creatinine. The intravenous pyelogram may be abnormal, showing alternation of radiodense and radiolucent streaks radiating from the medulla to the cortex.

Splenoportography may show an abnormality of the intrahepatic portal venous system characterized by duplication of the venous channels. Angiography further illustrates the details of the vascular anatomy, patency, as well as the extent of the variceal formation (*Fig. 208.2*).

Diagnosis is further supported by the recognized changes on ultrasonography or computed tomographic scan of the abdomen. Sonographic evaluation should include Doppler flow studies of the portal vasculature. Portal vein morphology should be evaluated in all patients with CHF since portal vein involvement may well result in more severe and complicated portal hypertension.

Ultrasonography is generally regarded as the first-line modality in the diagnostic process with its high utility, lack of radiation exposure, and its capability of detecting the parenchymal heterogenicity and the associated kidney abnormalities that strengthens its role in the diagnosis. Characteristic imaging findings are generally present and in progress so that they may well prove by time their efficacy to give as accurate a diagnosis as liver biopsy and thus save the affected child the risk of liver biopsy.

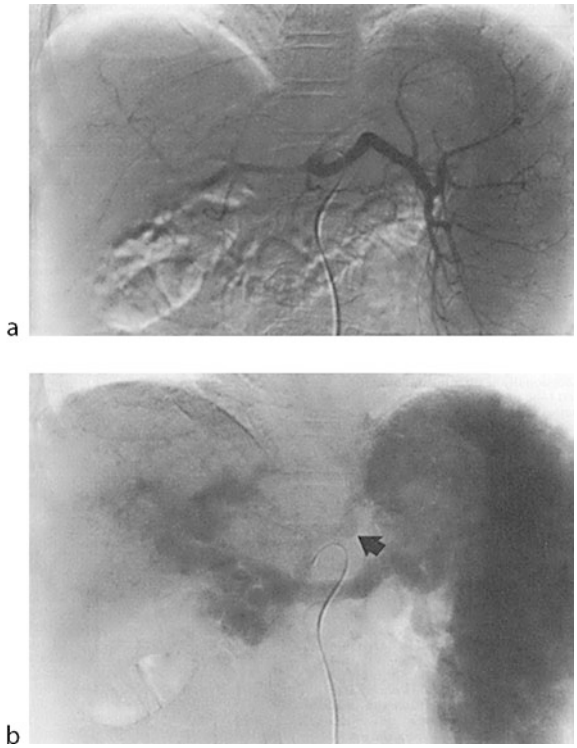

Figure 208.2
Celiacography in a 12-year-old with congenital hepatic fibrosis associated with portal hypertension, splenomegaly, and esophageal varices. (a) Arterial phase shows narrow intrahepatic arteries (b) Venous phase shows tortuous veins within porta hepatis and dilated coronal veins (*arrow*) with esophageal varices

Clinical Course and Management

Congenital hepatic fibrosis is an infrequent cause of recurrent cholangitis. The disease might manifest in early infancy, late childhood, or in adulthood. The condition progresses to portal hypertension with the potential possibility for recurrent hemorrhages due to the development of esophageal varices. The course of the disease is largely

influenced by the recurrent episodes of gastrointestinal bleeding that are often well tolerated by the patient and are not usually followed by hepatic encephalopathy.

Portal hypertension is a common and serious sequela of CHF, the cause of which is suggested to be secondary to presinusoidal block. It has been reported that cavernous transformation of the portal vein, a congenital component of CHF, is an important causative factor of portal hypertension in affected patients.

Four clinical forms of CHF are recognized:

1. Portal hypertensive form: This is the most common type with periportal fibrosis and features of portal hypertension as described earlier.
2. Cholangitic form: This is manifested with cholestasis and recurrent cholangitis. It may be associated with Caroli syndrome.
3. Mixed form: This is characterized by both portal hypertension and cholangitic symptoms.
4. Latent form: This is recognized late in life and may even be diagnosed at autopsy.

CHF was recognized to be associated with varied clinical conditions far more than just renal anomalies such as infantile polycystic disease of the kidneys. Portal hypertension with congenital hepatic fibrosis may be the initial manifestation of ARPKD or ADPKD. Other associations include: gluten-sensitive enteropathy, congenital heart disease, pulmonary hypertension, intestinal lymphangiectasia, tuberous sclerosis, Caroli disease, pulmonary fibrosis, pancreatic fibrosis, and secretory diarrhea. CHF occurs in association with a range of both inherited and noninherited disorders, with multigorgan involvement. The exact correlation between those conditions and CHF warrants further appraisal.

It is important to recognize the presence of cholangitis and prevent its recurrence by appropriate surgical procedure. Transhepatic cholangiography is a safe and direct means of identifying this entity.

Treatment

There is no definitive treatment that could stop or reverse the pathological process in CHF. Antibiotics are prescribed in the presence of cholangitis. The role of antifibrotic therapy has shown some promising results in animal studies but not in human.

Early surgery with portacaval anastomoses may be required if repeated endoscopic sclerotherapy or variceal banding could not arrest the variceal bleeding. The incidence of hepatic encephalopathy post shunt surgery is low. Cholangiocarcinoma and amyloidosis have been reported as late squeal of CHF.

Liver transplantation is also considered in the management of CHF complicated by recurrent cholangitis or failure to respond to various medical and surgical therapeutic modalities with progressive hepatic dysfunction.

Prognosis

The majority of patients do well. The prognosis in CHF is expected to be good if bleeding from varices can be controlled. However renal failure limits the survival in those patients with renal involvement.

Caroli Disease

This disease was originally described by Jacques Caroli. It is characterized by nonobstructive saccular or fusiform dilatation of the intrahepatic bile ducts. The dilatations may involve a part or the whole of the liver. Though renal involvement has been described in Caroli disease as in congenital hepatic fibrosis, there is no associated hepatic fibrosis and portal hypertension.

There are two types of Caroli disease:

1. The rare variety (pure form) originally described by Caroli and characterized by segmental saccular and communicating intrahepatic bile duct ectasia, frequently associated with cholangitis and stone formation but without fibrosis. Recognized and fatal associated complications include cholangiocarcinoma, septicemia, and hepatic abscesses.
2. The more common variety, which is associated with congenital hepatic fibrosis. This entity is now referred to as Caroli syndrome. Bile duct dilatation is less prominent. Associated complications include esophageal varices, portal hypertension, and liver failure.

The disease is occasionally segmental and limited to one lobe, usually the left lobe of the liver. The renal abnormality in Caroli disease occurs in up to 25% of cases and includes both cortical cysts and features of medullary sponge kidneys. Caroli disease is sporadic, whereas Caroli syndrome is generally inherited in an autosomal recessive manner.

Therapy in Caroli disease is similar to that for CHF. However, Caroli disease may only require antibiotic therapy to combat the risk of cholangitis and in severe cases lobectomy of the affected lobe may have to be performed.

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209 Metabolic Liver Disease

Fayez K. Ghishan

This chapter will deal with some of the more common inborn errors of metabolism that lead to hepatic dysfunction. This includes three inborn errors of carbohydrate metabolism: Galactosemia, hereditary fructose intolerance, and glycogen storage disease types I, III, and IV and VI. Tyrosinemia, a disorder of amino acid metabolism will also be reviewed.

Galactosemia

Galactose is the end product of hydrolysis of lactose. Galactosemia is a rare inherited defect in galactose metabolism transmitted by autosomal recessive inheritance. Three distinct disorders of galactose metabolism and several variant forms have been identified. These disorders are expressed as a cellular deficiency of one of the three enzymes in the metabolic pathway through which galactose is converted to glucose: galactose-1-phosphate uridyl transferase, galactokinase, and uridine diphosphate (UDP) galactose-4-epimerase. Each enzymatic defect results in a distinctive clinical presentation. Thus, the disease is now classified in terms of transferase deficiency Galactosemia, galactokinase deficiency Galactosemia, and epimerase deficiency Galactosemia.

Physiology of Galactose Metabolism

Galactose is a monosaccharide that is derived from the hydrolysis of lactose, the major sugar in breast milk and dairy products. Lactose is hydrolysed into glucose and galactose by the disaccharidase, lactase, present on the brush border membrane of enterocytes. Galactose is transported across the brush border membrane of enterocytes by means of the Na^+-dependent glucose-galactose transporter. Galactose is metabolized to glucose in a series of reactions as depicted in (*Fig. 209.1*).

Transferase Deficiency Galactosemia (Classic Galactosemia)

Molecular Basis of Disease

Transferase deficiency Galactosemia is an inborn error of metabolism resulting from deficiency of the human galactose-1-phosphate uridyl transferase enzyme. The cDNA that encodes the human transferase enzyme is 1,295 bases in length and encodes a 43,000 molecular weight protein. Most individuals with transferase deficiency have missense mutations, resulting in low or undetectable enzymatic activity. The most common transferase mutation identified in caucasean populations is an arginine for glutamine substitution at position 188 (Q188R), accounting for 60% of transferase deficiency mutations. S135L mutation (substitution of leucine for serine) is common in African-American patients. Several other mutations have been described suggesting that the variability in clinical outcome is a result of different mutations at the molecular level.

Multiple variants of transferase deficiency have become apparent since the advent of genetic screening for the disease. Three common homozygotic types exist:

1. Classic Galactosemia is autosomal recessive, and transferase activity is absent in red cells, hepatocytes, and presumably in other tissues. Asymptomatic heterozygotic carriers, on the other hand, exhibit 50% enzyme activity. The incidence of classic Galactosemia in the United States has been estimated to be 1 in 63,000 births.
2. The most frequently detected abnormality in neonatal screening is the compound heterozygous state consisting of allelic genes for classic Galactosemia and the Duarte variant (N314D substitution of aspartic acid for aspargine); presence of the Duarte variant is quite common affecting up to 15% of the general United States population.
3. The Negro variant has complete absence of transferase activity in erythrocytes, whereas the liver and intestine exhibit 10% of normal activity. Clinical manifestations of the Duarte and Negro variants range from complete lack of symptoms to symptoms similar to classic Galactosemia.

Recently, several heterozygotic forms of Galactosemia have been identified, including the Indiana, Rennes, Los Angeles, Chicago, and West German variants.

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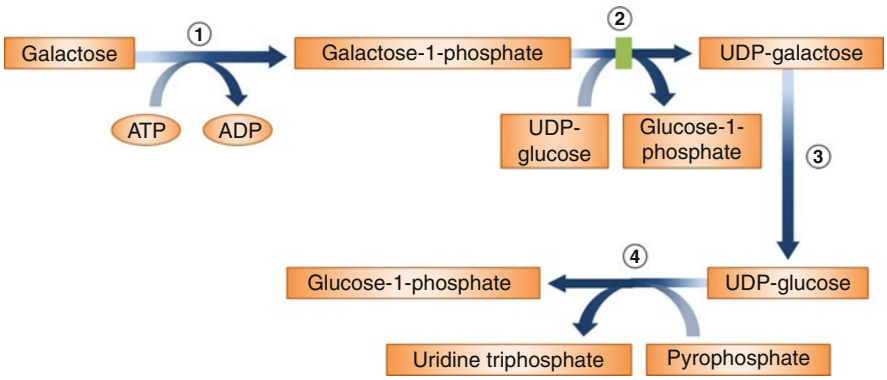


Figure 209.1
Reactions in the conversion of galactose to glucose. (1) galactokinase; (2) galactose-1-phosphate uridyltransferase; (3) uridine diphosphate (UDP) galactose-4-epimerase; 4, UDP-glucose pyrophosphorylase. (Modified Fig. 69.3, Ghishan, 2006)

Clinical Manifestations

The clinical presentation of classic transferase deficiency Galactosemia varies in severity from an acute fulminant illness characterized by abdominal distention, vomiting, diarrhea, anorexia, and hypoglycemia following the first milk feeding to a subacute illness beginning within the first few days of life. Failure to thrive is the most common presenting symptom and occurs in almost all patients. Vomiting and diarrhea may occur in 95% of patients. Jaundice and hepatomegaly develop almost as frequently after the first week of life. Severe hemolysis may accentuate jaundice due to intrinsic liver disease. Prolonged conjugated hyperbilirubinemia is a common presenting symptom in infants with this form of Galactosemia. Therefore, urine screening tests for reducing sugars should be performed in all infants presenting with jaundice. Ascites may develop within 2–5 weeks after birth as a result of continued galactose ingestion and has been present in most infants who succumb to the disease.

Cataracts may develop early within the postnatal period, or they may be present at birth if the mother ingested generous amounts of dairy products in late pregnancy. These punctuate lesions may be so small that slit-lamp examination is required for visualization.

Signs of increased intracranial pressure and cerebral edema have also been observed as presenting features in transferase deficiency Galactosemia.

Escherichia coli sepsis at about 7–14 days of age occurs with a higher frequency in patients with classic Galactosemia compared to controls. It appears to be directly associated with continued galactose ingestion and subsequent inhibition of leukocyte bactericidal activity. As a result of these important clinical observations, neonates diagnosed with Galactosemia or *E. coli* sepsis should undergo further evaluation to rule out the alternate condition.

Mild symptoms of vomiting and diarrhea may be the only presenting symptom in infants with mild forms of the disease.

Lactose-free formulas have been increasingly accessible, and feeding trials with these products are often used in infants with recurrent vomiting and growth failure early in life. Since these are the most common presenting symptoms of Galactosemia, a child with the disorder may display improvement in symptoms without recognition of the underlying defect. In such cases, Galactosemia may remain undetected through the first several months of life until motor retardation, hepatomegaly, or cataracts develop.

Renal tubular acidosis with proteinuria, amino aciduria, glucosuria, phosphaturia, and bicarbonaturia may occur in some patients as part of other systemic manifestations.

Biochemical Basis of Disease

The metabolic defect in transferase deficiency (*Fig. 209.1*) results in toxic insults in galactosemic patients, primarily due to the accumulation of two metabolites: Galactose-1-phosphate, the metabolite which accumulates prior to the metabolic block, and galacticol, the product of an alternate pathway for galactose metabolism. Various organs are influenced differently by these two compounds.

Liver The cause of hepatic toxicity in transferase Galactosemia has not been fully elucidated. In affected persons, galactose ingestion results in elevated levels of galactose-1-phosphate, galacticol, and galactonate in the liver.

However, other findings suggest that one or more additional metabolites act singly or together to produce liver damage. For example, humans with galactokinase deficiency accumulate large amounts of galacticol but develop no liver damage. Moreover, evidence from rat models suggests that hepatic accumulation of galactose-1-phosphate does not result in liver damage.

Kidney The renal tubular dysfunction seen in transferase deficiency appears to result primarily from accumulation of galactose-1-phosphate in these tissues. Evidence for this arises from the observation that patients with galactokinase deficiency who characteristically excrete large amounts of galacticol do not develop renal impairment.

Lenticular Changes Changes in the lens seem to result primarily from galacticol accumulation in the lens. Poor diffusion of galacticol from lens tissue and subsequent increased osmotic pressure result in water accumulation and eventually to cataract formation.

Brain Neurotoxicity in Galactosemia has been attributed to changes in osmolality of brain tissue, abnormal synthesis of glycolipids, and inhibition of glucose uptake by the central nervous system due to elevated serum galactose levels.

Intestine Gastrointestinal symptoms such as vomiting and diarrhea following galactose ingestion are hypothesized to be secondary to effects on the central nervous system. This is suggested partly by the fact that galactose transport appears to remain normal in deficient patients.

Gonads Most galactosemic females have ovarian failure characterized by hypergonadotropic hypogonadism. This process appears to start postnatally, and appears to be related to galactose-1-phosphate toxicity. Interestingly, males do not appear to have gonadal atrophy.

Red Blood Cells Toxicity Toxicity to red blood cells in transferase deficiency appears to be secondary to galactose-1-phosphate toxicity.

Liver Histopathology in Galactosemia

The initial hepatic changes consist of cholestasis and extensive fatty infiltration. Bile duct proliferation and pseudoglandular proliferation of hepatic plates could occur very early in the course of the disease. With continuing hepatic damage, extensive fibrosis and progressive regenerative nodules replace the normal liver parenchyma and cirrhosis ensues.

Laboratory Findings and Diagnostic Studies

Aberrant laboratory findings in Galactosemia vary but may include elevations in blood and urinary galactose levels, hypercholeremic acidosis, hypoglycemia (occasionally severe and prolonged in nature), abnormal liver function tests, albuminuria, and amino aciduria.

Galactosuria with resulting positive urinary reducing substances occurs only intermittently during periods of substantial food intake and completely resolves within 3 days of intravenous feeding. Thus, diagnosis of Galactosemia may be overlooked if a urine test for reducing sugar is timed inappropriately. Typically, patients have a positive urine reducing substance by the clinitest (Benedict test) and a negative clinistex (glucose oxidase test) indicating a reducing sugar in the urine other than glucose. In contrast, the presence of urinary reducing sugars does not confirm the diagnosis since other conditions that impair blood galactose clearance such as severe liver disease may lead to galactosuria. In the first 2 weeks of life, some normal infants may excrete galactose in their urine. Moreover, fructosuria and lactosuria due to the absorption of intact lactose in patients with intestinal lactase deficiency also result in positive urinary sugars; the specific sugar may be identified by paper or gas-liquid chromatography. More recently, screening for galactosuria has been simplified by the availability of paper impregnated with galactose oxidase. Nevertheless, galactose restriction should be promptly instituted if no other dietary carbohydrate is identified as even limited exposure to a large quantity of galactose may produce brain injury from prolonged hypoglycemia.

Confirmation of the diagnosis should be made through direct measurement of transferase activity. This is based on quantitation of UDP-glucose before and after incubation of galactose-1-phosphate using added red-cell hemolysate as the enzyme source. Homozygous patients exhibit complete absence of enzyme activity. Heterozygous carriers typically display intermediate levels of enzyme activity. Multiple variants of Galactosemia have been identified and are more prevalent than classic (complete) transferase deficiency Galactosemia. Therefore, infants with 50% enzyme activity should undergo further tests to identify a specific variant of the disease. This may be achieved by starch gel electrophoresis of red blood cells to determine differing transferase mobilities.

Cloning of the cDNA encoding for the transferase enzyme as well as the observation that most galactosemic patients have a missense mutation allowed introduction of rapid molecular techniques for analysis of common mutations such as Q188R.

Treatment

Elimination of dietary galactose is the only available approach to treatment of transferase deficiency. Traditionally, patient management has focused on the elimination of milk and dairy products. In infants, this involves use of soy formulas. The use of soy preparations has been questioned in the past because of the presence of galactose in oligosaccharides such as raffinose. However, evidence has accumulated that galactose absorption does not occur from these products. Careful attention to elimination of galactose should be given throughout progression to solid foods because of the frequent unsuspected use of dairy products in food preparation. Absorbable galactose is also found in grains, fruits, and vegetables. Therapeutic nutritional regimens now account for this finding, although the actual impact of eliminating this dietary source of galactose awaits further clinical investigation.

Most patients experience an improved tolerance to galactose around puberty, postulated to be due to the development of an alternate pathway of galactose metabolism. Therefore, in older patients, liberalization of the diet to include limited quantities of foods containing dairy products should be considered to minimize the psychological effect of lifelong stringent restrictions. However, milk restriction should be maintained. Compliance with therapy may be followed by monitoring galactose-1-phosphate content of erythrocytes which should be maintained below 4 mg/g hemoglobin. Pregnant women with galactosemic children are advised to eliminate galactose from their diet in subsequent pregnancies.

Subsequent Course and Prognosis

All acute manifestations of galactose toxicity show marked improvement by the end of 1 week of dietary elimination. Nausea and vomiting abate, hepatic function returns to normal, acute central nervous system changes as shown by CT scan improve, and catch up growth ensues.

Cataracts regress substantially with elimination of dietary galactose. Residual and ongoing central nervous damage sometimes continues even in patients maintained on appropriate restriction of galactose from their diet. This is usually manifested by lower IQ values compared to the normal population.

As previously mentioned, a high incidence of hypergonadotropic ovarian failure is seen in female patients. This is usually irreversible when it occurs. It has been proposed that this phenomenon occurs despite adequate dietary control. However, other findings suggest that ovarian failure develops as a result of ongoing galactose exposure.

Galactokinase Deficiency Galactosemia

Galactokinase deficiency is a rare autosomal recessive disease characterized by cataract formation very early in life. Its incidence is one per 100,000 births. Due to lack of galactokinase, galactose is metabolized via the alternate pathway (*Fig. 209.1*) with production of galacticol. Galacticol accumulates in the lens and results in cataracts. There are no other systemic manifestations presumably due to the lack of galactose-1-phosphate accumulation. However, pseudotumor cerebri has been reported in some patients. Treatment of this defect requires lifelong restriction of galactose intake. Fetal cataract formation may even result from maternal galactokinase deficiency.

Uridine Diphosphate Galactose-4 Epimerase Deficiency Galactosemia

UDP galactose epimerase catalyzes the third reaction in galactose metabolism. Epimerase deficiency is apparently caused by diminished stability of the enzyme, leading to an inadequate reserve in such cells as erythrocytes in which turnover is slow or absent. Incidence of epimerase deficiency has been reported as one per 46,000 in Switzerland. This form was discovered incidentally through screening for Galactosemia. The diagnosis is suspected in persons having low galactose-1-phosphate levels despite normal erythrocyte transferase activity.

Initially, epimerase deficiency was considered a benign condition due to the lack of symptoms in affected persons and limitation of the deficiency to erythrocytes and leukocytes. Recently, however, cases of generalized epimerase deficiency have been reported, and affected patients exhibit symptoms identical to those of the classic form of the disease. With UDP-4-epimerase deficiency, in contrast to transferase deficiency, treatment may mandate inclusion of small quantities of dietary galactose because no galactose is synthesized endogenously to meet body requirements. Frequent monitoring of erythrocyte galactose-1-phosphate levels is required to determine the optimal level of dietary restriction.

Disorders of Fructose Metabolism

The monosaccharide fructose is an important source of carbohydrates in the human diet. Free fructose is found in fruits and honey. Another major source of fructose is the disaccharide sucrose which is hydrolyzed into

fructose and glucose through the action of sucrase at the brush border membrane of enterocytes. Fructose metabolism takes place mainly in the liver (75%) and to a lesser extent in the intestine and kidney (25%). Therefore, it is not surprising that disorders of fructose metabolism manifest mainly as dysfunction of these organs. Three enzymopathies are recognized in fructose metabolism: fructokinase, fructose-1-phosphate aldolase, and fructose 1-6-diphosphatase deficiencies. A fourth potential defect characterized by incomplete fructose absorption has been reported in children with unexplained abdominal pain, but the underlying defect has not been elucidated.

Essential or Benign Fructosuria (Hepatic Fructokinase Deficiency)

Benign fructosuria is a rare disorder inherited as an autosomal recessive gene. It results from a deficiency of fructokinase, the first enzyme in the metabolic pathway of fructose (◉ *Figs. 209.2* and ◉ *209.3*).

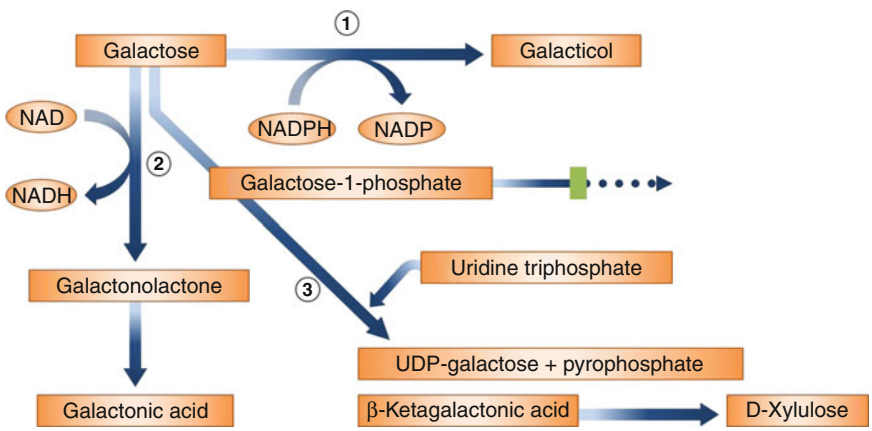
In the absence of fructokinase, the body utilizes a minor pathway for fructose metabolism catalyzed by the enzyme hexokinase in muscle and adipose tissue. In addition, there is no accumulation of the toxic metabolite, fructose-1-phosphate, which is believed to be the main offender in hereditary fructose intolerance. Hence, apart from the fructosemia and fructosuria upon consuming large quantities of fructose, patients are healthy and free of symptoms. Diagnosis is usually made incidentally by the finding of a positive reducing substance and verified by the identification of fructose by thin layer or paper chromatography. Confirmation of the diagnosis is made by enzyme assay in a liver biopsy specimen. However, this is not always necessary as the disorder is benign.

Hereditary Fructose Intolerance (HFI)

Hereditary fructose intolerance is a rare disease seen mainly in Europe and North America. It is inherited as an autosomal recessive gene with an estimated incidence of 1 in 20,000.

This disorder is caused by the catalytic deficiency of aldolase B normally found in the liver, kidney, and small intestine. The activity of tissue aldolase B is reduced to less than 15% of normal values. The enzymatic activities of aldolase A, found in muscle, and aldolase C, found in the brain, are normal.

The aldolase B gene has been sequenced and mapped to human chromosome 9 q 13 → q 32. Several missense mutations in this gene sequence resulting in different abnormal products have been identified. These include a mutation resulting in a proline residue substituting for an alanine at position 149 (A149P), a mutation resulting in alanine being replaced by aspartic acid at position 174 (A174D), and a mutation resulting in aspargine being replaced by lysine at position 334 (N 334 L). Testing for these mutations by DNA amplification using polymerase chain reaction technology with a limited panel of allele-specific oligonucleotides identifies more than 95% of patients with HFI.



◘ Figure 209.2
Alternate pathways of galactose metabolism. (1) aldose reductase or L-hexonate dehydrogenase; (2) galactose dehydrogenase; (3) uridine diphosphate galactose pyrophosphorylase. (Modified Fig. 69.4, Ghishan, 2006)

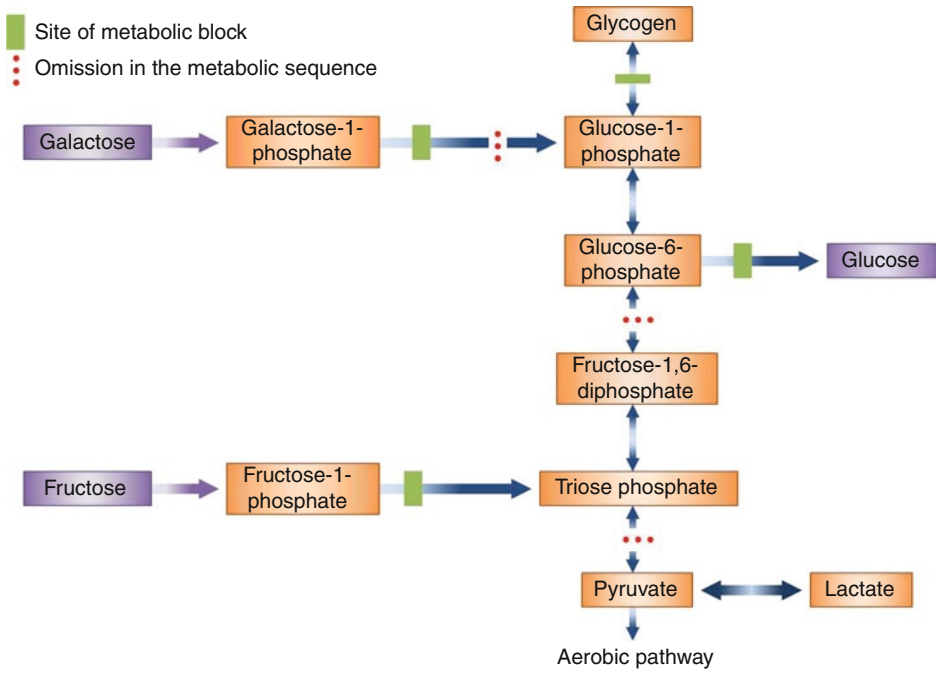


Figure 209.3

Metabolic relationship between disorders in glycogen, galactose, glucose, and fructose metabolism. Solid rectangle indicates site of metabolic block indicates omission in the metabolic sequence. (Modified Fig. 69.1, Ghishan, 2006)

Pathophysiology

Deficiency of fructose-1-phosphate aldolase results in the accumulation of fructose-1-phosphate, a known toxic metabolite, in the liver, intestine, and kidney cortex. Some of the toxic effects of fructose-1-phosphate are the result of ATP depletion as a result of continuous utilization by the fructokinase reaction. The loss of hepatic ATP results in inhibition of protein synthesis, liver failure, and subsequent hyperaminoacidemia. Hemorrhage results from decreased synthesis of coagulation factors as a result of protein synthesis inhibition in the liver.

Renal tubular dysfunction is believed to result from ATP degradation in the kidney.

Fructose-1-phosphate also inhibits glycogenolysis and gluconeogenesis at the level of fructose-1-diphosphate inducing severe hypoglycemic episodes.

Metabolic acidosis results from lactic acidosis and renal tubular acidosis. Hyperuricemia results from purine degradation induced by both ATP depletion and phosphate sequestration (in the form of fructose-1-phosphate).

Clinical Manifestation

Newborns are asymptomatic as long as they are on breast milk or formulas lacking sucrose. Acute symptoms develop as soon as formulas or solid food containing fructose or sucrose are introduced. The reaction to fructose introduction is most prompt and dramatic in newborns and infants and can be fatal. Acute symptoms include nausea, vomiting, and refusal to eat. Hypoglycemic episodes result in sweating, trembling, convulsions, lethargy, and coma. If exposure to fructose continues, the clinical picture may progress rapidly to hemorrhage, acute hepatic failure, coma, and death.

If the patient escapes the acute episode or in infants whose exposure to fructose is delayed long enough for them to develop an aversion to sweets, the disease may go undiagnosed for a long time. Chronic exposure to small quantities of fructose results in severe failure to thrive, gastrointestinal symptoms that include nausea, vomiting, diarrhea, and poor feeding. Hepatic dysfunction is also noted, manifesting as jaundice, hepatomegaly, ascites, and hemorrhage resulting from deficiency of hepatic coagulation factors. Hypoglycemic episodes result in drowziness, tremors, and convulsions.

Laboratory Data and Diagnosis

Fructosemia, fructosuria, hypoglycemia, hypophosphatemia, hypermagnesemia, hyperuricemia, and lactic acidosis are the major biochemical changes.

Liver dysfunction manifests as hyperbilirubinemia, hypoalbuminemia, increased transaminases, prolonged prothrombin time, and partial thromboplastin time, as well as increased plasma levels of the amino acids, methionine, and tyrosine.

Disturbed proximal renal tubular function, manifesting as proteinuria, amino aciduria, phosphaturia, and bicarbonaturia, is a common finding. Suspicion is fostered by the presence of reducing sugars in the urine. Traditionally, definitive diagnosis requires an enzyme assay in liver or intestinal biopsy specimens as this enzyme is not normally found in the circulation. A liver biopsy is preferred as this allows assessment of liver tissue damage. Currently, more than 95% of HFI cases can be diagnosed through amplification of DNA with a limited number of allele-specific oligonucleotide probes circumventing the need for a tissue biopsy.

Histologically, liver tissue shows diffuse fatty infiltration of hepatic cells, scattered necrosis of hepatocytes, biliary duct proliferation, and periportal, as well as intralobular, fibrosis. In more advanced cases, hepatic cirrhosis may ensue.

Treatment and Prognosis

Prompt and permanent elimination of fructose, sucrose, and sorbitol (converted to fructose) results in substantial and rapid improvement of gastrointestinal symptoms.

Hepatic changes regress rapidly, with return of hepatic enzymes, bilirubin, and coagulation factors to normal levels. However, some degree of hepatomegaly and steatosis may persist for a long time.

Despite the recurrent episodes of hypoglycemia, intellectual development seems to proceed normally with maintenance of a fructose-free diet.

Fructose-1,6-Diphosphatase Deficiency

Fructose-1,6-Diphosphatase deficiency is a rare disorder believed to be inherited as an autosomal recessive gene. Fructose-1,6-diphosphatase is a key enzyme in gluconeogenesis from lactate, glycerol, and amino acids. In patients with fructose-1,6-diphosphatase deficiency, fasting results in glycogenolysis and glucose release. However, after depletion of hepatic glycogen stores the liver is no longer capable of providing glucose through gluconeogenesis. Therefore, fasting is a major trigger of severe episodes of hypoglycemia and acidosis, especially in the newborn who has limited hepatic glycogen stores.

Similar episodes also result from fructose ingestion or acute febrile illnesses. Patients usually present with signs and symptoms of hypoglycemia and acidosis. Hepatomegaly is usually moderate. Liver histology characteristically shows fatty infiltration of the liver. The derangements in liver function tests are less drastic than in hereditary fructose intolerance. Diagnosis is confirmed by enzyme assay in a liver biopsy specimen. The gene (FBP-1) has been localized to chromosome qq22.2–q22.3 and several mutations have been described in the gene which leads to a decreased activity of fructose-1,6-diphosphatase enzyme. Treatment consists of management of hypoglycemic and acidosis episodes with intravenous glucose and bicarbonate infusions. Long-term management includes complete avoidance of fructose, sucrose, and sorbitol, avoidance of fasting, and following a diet which is low in fat, high in carbohydrate, and moderate in protein.

Glycogen Storage Diseases with Hepatic Manifestations

Glycogen, a polysaccharide, is the primary carbohydrate storage compound in animals. It is present in all animal cells but is particularly abundant in liver and muscle tissue. It undergoes depolymerization through phosphorylsis and hydrolysis to release free glucose when needed to sustain cellular processes, and to maintain normal blood glucose concentrations during fasting. The formation and degradation of glycogen are highly regulated processes involving at least eight enzymes. Deficiencies of these enzymes have been identified in humans and result in 12 recognized forms of glycogen storage disease (GSD). The following discussion will be limited to types I, III, IV, and VI, because the clinical expression of these forms of GSD primarily involves the liver. In type I, the accumulating glycogen is structurally normal, while in types III, IV, and VI it is structurally abnormal.

Physiology and Biochemistry of Glycogen Metabolism

Glycogen is a polymer of glucose units linked between the C_1 of one D-glucopyranosyl residue and the hydroxyl group at C_4 of the adjacent residue (1,4 linkage). Short chains of glucose residues linked through the hydroxyl groups at C_6 of some of the residues (α-1,6 linkage) represent 7–8% of glucose found in glycogen. The role of glycogen in the liver is to provide glucose to the blood for various organs. At times of stress or when blood glucose levels fall, the liver rapidly releases glucose into the blood stream, and blood carries it to organs such as the brain which cannot synthesize glucose. Glycogen in muscle serves as a reserve of glycolytic fuel to be used locally when oxygen or glucose availability declines. *Figure 209.4* depicts the sequence of reactions involved in glycogen synthesis and degradation.

Type I Glycogen Storage Disease (GSD) (Glucose-6-phosphatase Deficiency, Von Gierke's Disease)

This is the most recognized form of glycogen storage disease. The disease is autosomal recessive and has two major subtypes. GSD type1a is caused by deficiency of glucose-6-phosphatase (G6Pase) in the liver, kidneys, and intestine. GSD type1b is caused by a deficiency in the glucose-6-phosphate transporter (G6PT). Together, G6Pase and G6PT are functionally linked and are responsible for the formation of the majority of glucose from glycogenolysis and gluconeogenesis. GTPase is present in the liver, kidney, and intestinal mucosa, whereas G6PT is expressed ubiquitously. Therefore, a mutation in either enzyme results in a common metabolic phenotype of disturbed glucose homeostasis (*Fig. 209.5*). Recently, a second

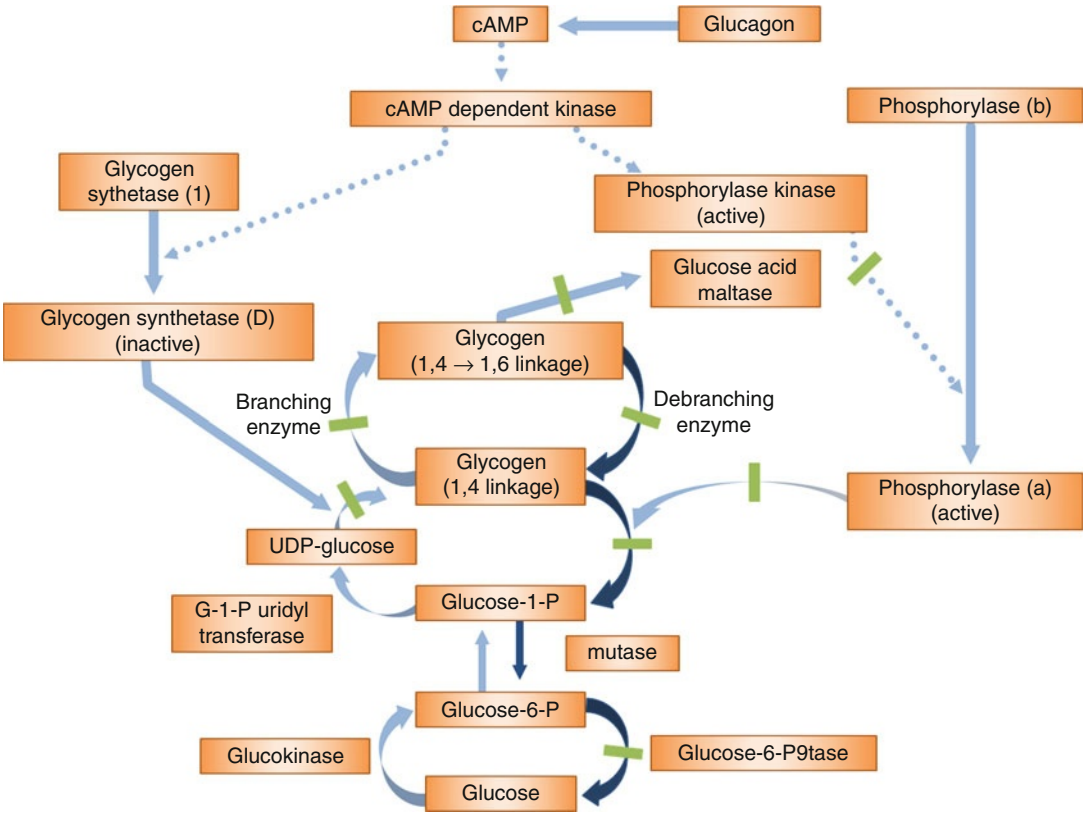


Figure 209.4

Pathway for glycogen synthesis and degradation to glucose. *Broken lines* indicate enzymic activation after glucagon simulation, *heavy arrows* indicate glycogen degradation from glucagon infusion; and *hatched boxes* indicate points in the metabolic sequence where enzymic defects have been identified. (Modified Fig. 69.5, Ghishan FK (2006) Inborn errors of metabolism that lead to permanent liver injury. In: Boyer T, Zakim D (eds) Hepatology: a textbook of liver disease. Elsevier, Canada)

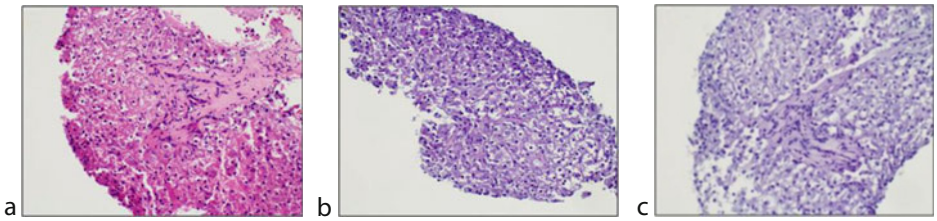


Figure 209.5
Histological photomicrograph of liver biopsy of a patient with glycogen storage disease type 1a. (a) Sections of liver including portal area, hematoxylin, and eosin stain showing increased glycogen deposition in hepatocytes (200 × magnification); (b) Sections of liver with PAS stain showing PAS stain of glycogen (200 × magnification); (c) Section of liver with PAS stain after diastase treatment showing decrease in glycogen (200 × magnification)

G6Pase has been described and designated G6Paseβ, which is ubiquitously expressed and forms functional unit with G6PT as well in nongluconeogenic tissues including neutrophils.

Classification of Type I Glycogen Storage Disease

Two forms of the disease are recognized:

1. Patients with type Ia GSD have complete absence of glucose-6-phosphatase activity.
2. 2-Type Ib has a clinical picture similar to type Ia. However, in these patients the activity of glucose-6-phosphatase in fully disrupted microsomes is completely normal, whereas the activity in intact microsomes and in vivo is abnormal. These patients have a defect in the endoplasmic reticulum–bound glucose-6-phosphate transporter and classically have neutropenia.

Molecular Basis of Glycogen Storage Disease Type Ia

The gene encoding for the enzyme glucose-6-phosphatase has been cloned. So far, 76 mutations in the glucose-6-phosphatase gene have been identified resulting in greatly reduced enzymatic activity of glucose-6-phosphatase. The most common mutations in Caucasian populations are a cystine substitution for arginine at position 83 (R83C) and unspecified amino acid for glutamine (Q347X). In the Arab world, 50% of the alleles analyzed are V166G (glutamine substitution for valine) which appear to be unique in ethnic Arabs. Sixty-nine mutations have been described in the G6PT gene and are responsible for GSD type1b. These include 28 missense mutations, 10 nonsense, 17 insertion/deletion, and 14 splicing mutations. Similar to Typ1a mutations in type1b shows ethnic variability.

Clinical Presentation

The expression of clinical and biochemical symptoms of type I GSD varies considerably among patients. Some persons require frequent hospitalizations because of marked metabolic abnormalities. Others experience only mild symptoms and slightly delayed growth.

Children with the full spectrum of this disorder characteristically have proportionate short stature, massive hepatomegaly leading to a protuberant abdomen, renal enlargement, hypoglycemic episodes, lactic acidosis, hyperuricemia, hyperlipidemia, xanthomas, and a bleeding tendency.

Hypoglycemia Hypoglycemic episodes are one of the most striking and detrimental factors in type I GSD. Glucose-6-phosphatase deficiency results in impairment of glucose release resulting in hypoglycemic episodes that may follow a short period of fasting. Except in severe cases, hypoglycemia may not become apparent in the first several weeks of life when the infant feeds every 2–3 h. However, septicemia may lead to earlier recognition of this symptom, particularly in patients with type Ib GSD. Convulsions associated with hypoglycemia can occur in patients without symptoms. Metabolic acidosis due to hypoglycemia may cause weakness, malaise, headache, an increased respiratory rate, and fruity breath; a few patients experience recurrent fevers with these symptoms. In other patients, profound hypoglycemia can occur without symptoms. It is believed that these asymptomatic patients utilize β-hydroxybutyrate and acetoacetate in lieu of glucose as the primary fuel of the brain.

Growth Failure Growth failure can be profound. The exact mechanism behind this is not completely clear, although chronic acidosis and hypoinsulinemia associated with hypoglycemia are believed to be the major

contributing factors to growth impairment. Correction of hypoglycemia and metabolic acidosis results in improved growth.

Lactic Acidosis Lactic acidosis is one of the major features of glycogen storage disease type I. Blood lactate levels in these patients are generally four to eight times the normal values. Hypoglycemia results in decreased insulin and increased glucagon which promotes glycogenolysis. Glycogen degradation proceeds normally until the last step in which glucose release from glucose-6-phosphate is impaired because of glucose-6-phosphate deficiency. The accumulated glucose-6-phosphate is diverted into the glycolytic pathway resulting in increased lactate production.

Hyperlipidemia Hyperlipidemia is a striking abnormality in patients with type I GSD. Serum levels of triglycerides may reach 4,000–6,000 mg/dl, and cholesterol elevation to levels of 400–600 mg/dl is common. The mechanisms underlying hyperlipidemia relate to the increased products of glycolytic pathways such as NADH, NADPH, glycerol-3-phosphate, and acetyl coenzyme A. These compounds are essential for fatty acid and cholesterol synthesis. They are synthesized abundantly in patients with GSD type I as a result of the block in the glycolytic and gluconeogenic pathways. Moreover, elevation of free fatty acids occurs in the serum secondary to hypoglycemia. Although controlling hypoglycemia with frequent and nocturnal intragastric feeding seems to promote growth and controls acute metabolic disturbances, its influence on hyperlipidemia has been variable. The exact mechanism behind this variable response is not well known.

Hyperuricemia Hyperuricemia appears in early infancy, but gouty complications such as arthritis or nephropathy rarely develop before puberty. It has been suggested that because of glucose-6-phosphatase deficiency, the rate of purine synthesis increases due to increased availability of the purine precursors, glutamine, and ribose-5-phosphate. In addition, the trapping of phosphate in glucose-6-phosphate and lowering of ATP levels promotes degradation of preformed purines to xanthine and uric acid.

Bleeding Tendency The presence of bleeding tendency is well recognized in type I GSD. Abnormalities in platelet aggregation and adhesiveness have been described in these patients. These abnormalities are thought to be the result of impairment of the ability of platelet membranes to release ADP secondary to changes in membrane fluidity. Presence of xanthomas, which usually appear during puberty, also contributes to frequent nosebleeds in patients with type I GSD.

Neutropenia Neutropenia has been documented in most patients with type Ib GSD. The degree of neutropenia varies among such patients, especially during periods of infection. The functional impairment is related to impaired glucose production by neutrophils resulting in endoplasmic stress and increased apoptosis.

Liver Manifestations Hepatic adenomas are frequently found in patients with type I GSD, usually during the second decade of life. However, these have been detected as early as 3 years of age. Malignant transformation has been reported in a large number of adult patients. Controlling the metabolic disturbances through dietary therapy may retard the growth of these adenomas or may result in the regression of existing adenomas. However, adenomas are even reported in patients who are under tight metabolic control. On the other hand, liver abnormalities usually include only slight elevations in serum transaminase which improve quickly with stabilization of blood glucose between 70 and 110 mg/dl. Type I GSD does not lead to hepatic cirrhosis or liver failure.

Renal Disease Although renal enlargement is a frequent finding in type I GSD, significant renal disease has not been recognized in the early stages of the disease. Patients with renal involvement usually present with persistent proteinuria and hematuria. The predominant histologic findings in kidney biopsies are focal segmental glomerulosclerosis and glomerular basement membrane abnormalities that include thickening of the membrane and glycogen deposition. Moreover, those who survive beyond puberty may develop progressive nephropathy and gouty complications due to uncontrolled hyperuricemia.

Diagnosis

The diagnosis of type I GSD is suspected in patients with the above presentation. The need for accurate diagnosis of type I GSD has become critical since the development of an effective approach to treatment. Traditionally, direct assay of hepatic enzyme activity of glucose-6-phosphate in a fresh liver biopsy is utilized.

The diagnosis is also suspected from the microscopic examination of the biopsy which characteristically shows striking steatosis and high glycogen content in hepatic cells. Usually there is no fibrosis or cirrhosis. Adenomatous changes may also be seen very early in the course of the disease. Mutations in the gene encoding for

the glucose-6-phosphatase enzyme is becoming the standard mode of making a diagnosis.

Treatment

The pioneering work of Folkman and associates led to the development of current treatment strategies for patients with type I GSD. Through the use of total parenteral nutrition, these researchers were able to effect dramatic improvement in most biochemical abnormalities associated with the disease. Other researchers have subsequently shown equally positive results with continuous nasogastric infusion of nutrients. This has led to the speculation that when blood glucose levels fall below 70–90 mg/dl, compensatory mechanisms result in the breakdown of glycogen to glucose-6-phosphate. Thus, any treatment that maintains blood glucose levels above the critical level reduces the stimulus for glycogenolysis and the subsequent accumulation of abnormal metabolites. Parenteral and entered nutrition produce the desired effect by providing a continuous source of glucose, but are impractical for long-term use. Thus, a more feasible approach has been devised using frequent daytime feedings of a high-starch diet in combination with a continuous nocturnal enteral infusion. Raw cornstarch, which undergoes slow degradation to glucose by α-amylase, has been shown to be effective in maintaining glucose levels during the daytime. A dose of 2 g/kg of raw cornstarch every 6 h has provided a suitable alternative to nighttime infusions in some patients.

More aggressive approaches have been used in the treatment of patients with type I GSD, including liver transplantation and gene therapy. Renal complications have been recognized and their management includes alkalinization of urine with citrate for prevention of urolithiasis and nephrocalcinosis and angiotensin converting enzyme inhibitors for persistent microalbuminemia.

Recommendations for treatment of type Ib GSD patients are identical to those for type Ia. Similar results may be expected with the exception of lack of improvement of the neutropenia that accompanies this form of the disease. Prophylactic antibiotics may reduce the incidence of infections.

Prognosis

The use of current treatment strategies has significantly altered the clinical course and prognosis of patients with type I GSD. Life expectancy now extends beyond the third decade. Prior to the mid-1970s, patients required frequent hospitalizations due to hypoglycemia, fever, and acidosis. Current treatment has been successfully used in a group of patients who have experienced near normal growth and have remained relatively symptom free for 10 years. Furthermore, the tendency to develop hypoglycemia seems to mitigate as patients reach adulthood. Complete resolution of adenomas has been documented as a result of this therapy. On the other hand, suboptimal treatment will continue to result in the consequences of poor metabolic control and development of hepatic adenomas which can progress to hepatocellular carcinomas. Unfortunately, adenomas have been reported in patients who are under good control. Therefore, careful follow-ups and monitoring are essential.

Type III Glycogen Storage Disease (Amylo-1,6-Glucosidase Deficiency, Debrancher Deficiency, Forbes Disease)

This is an autosomal recessive disease resulting from debrancher enzyme deficiency most commonly found in Jewish communities of North African descent. Under normal conditions debrancher enzyme coupled with phosphorylase and phosphorylase kinase allows the release of glucose from 1,6 glucosyl linkages. However, the absence of the debrancher enzyme interferes with the release of glucose from 1,6 glucosyl linkages. This results in the accumulation of abnormal glycogen molecules that have an excessive number of shorter outer branch points (1,6 linkages), similar to the structure of limit dextrins.

Debranching enzyme contains two catalytic activities on a single 160-kd polypeptide chain; oligo-1,4-1,4-glucantransferase and amylo-1,6-glucosidase. Complete absence of enzyme activity has been designated GSD IIIa. Absence of debrancher enzyme in only the liver or only the kidney has been designated GSD IIIb and GSD IIIc, respectively. Some patients have isolated oligo-1,6-1,4 glucantransferase deficiency with retention of glucosidase activity (GSD IIId).

Clinical Presentation

The clinical manifestations of patients with type III GSD result directly from its effects on hepatic and muscle tissue, although amylo-1,6-glucosidase activity is generalized to most cell types.

In infancy and childhood type III and type I GSD are not readily distinguishable by physical examination alone, primarily because hepatic manifestations predominate in this age group. Growth failure and hepatomegaly may be striking early in life. Hepatic fibrosis may lead to the development of splenomegaly in some children by the time they are 4–6 years of age. However, a decrease in liver size has been noted to occur in some patients around

puberty. Nevertheless, hepatic fibrosis has progressed to cirrhosis and liver failure in a few patients with type III GSD who have concomitant phosphorylase or phosphorylase kinase deficiencies. Moderate elevations in serum transaminase levels (300–600 IU) are consistently seen in almost all patients. Hypoglycemic episodes in type III GSD are milder than in type I and occur mainly with prolonged fasting. This results from the release of glucose from 1,4 glucosyl linkages and through gluconeogenesis, which is not impaired in type III GSD. Unlike type I GSD, serum levels of uric acid and lactic acid are usually normal.

Onset of muscular symptoms usually occurs in adulthood and is primarily manifested as muscle weakness and muscle wasting.

Renal enlargement is not seen in type I GSD. Glycogen accumulation in the heart may produce cardiomegaly and nonspecific electrocardiographic changes.

Histopathologic Features

The appearance of the liver in type III GSD is remarkable for the presence of fibrous septa and paucity of fat, unlike type I GSD in which there is striking steatosis with no fibrosis. Evidence of cirrhosis is present in some patients with concomitant phosphorylase or phosphorylase kinase deficiencies. Glycogen content of hepatic tissue is also abnormally high.

Diagnosis

The diagnosis is suspected based on distinguishing clinical and laboratory features. The presence of elevated creatine kinase supports the diagnosis. While various sugar tolerance tests have been traditionally used to confirm the diagnosis, these have shown inconsistent results. Direct measurement of amylo-1,6-glucosidase activity in liver and muscle samples and concomitant examination for abnormal glycogen structures should be relied on for the definitive diagnosis. Means of prenatal diagnosis are also now available via enzyme analysis in amniotic fluid cells. The gene encoding the debrancher enzyme was cloned and mapped to chromosome lp21. Mutations in exon 3 of the gene were found in the majority of the patients with GSD3b. So far 31 mutations have been identified.

Treatment

Dietary regimens similar to, but less stringent than, those for patients with type I GSD have been used in the management of debranching enzyme deficiency. Improvement of liver transaminases, liver size, and growth has been demonstrated following a high-starch diet containing only the recommended dietary allowance (RDA) for protein. For the most part, treatment of type III GSD remains investigative and should be reserved for patients with progressive muscle disease or hepatic fibrosis.

Type IV Glycogenesis, Amylopectinosis Amylo-1,4-1,6-Transglucosidase (Brancher) Enzyme Deficiency

This is a rare inborn error of glycogen metabolism that results from brancher enzyme deficiency. Only about 20 cases have been documented in the literature. The disease is inherited as an autosomal recessive gene. Absence of brancher enzyme activity results in the accumulation of an abnormal glycogen molecule that has a long outer chain and fewer than normal number of branch points. This abnormal glycogen molecule resembling amylopectin may accumulate in the liver, cardiac muscles, and the nervous system, with subsequent dysfunction of these organs.

Clinical Presentation

The disease usually presents in early infancy with failure to thrive, hepatosplenomegaly, progressive cirrhosis, and hepatic failure. Most children die in the first 2 years of life. Recently, several variants of the disease have been reported with presentations including cardiomyopathy, arthrogryposis, and hydrops fetalis. Fasting-induced hypoglycemia has been reported in two infants. The heart can be enlarged with nonspecific electrocardiographic changes. Some children may show significant hypotonia and muscular atrophy. A less severe form of type IV glycogen storage disease with a mild course presenting at 2 years of age has been described. Serum transaminase levels are characteristically elevated in this form of glycogenesis.

Diagnosis

Definitive diagnosis is by enzyme assay in hepatic tissue and in skin fibroblasts. Identification of the characteristic abnormal glycogen in liver tissue, either ultrastructurally or histochemically, also points to the diagnosis. Prenatal diagnosis is possible by enzyme analysis of cultured amniotic fluid cells. The gene is located on chromosome 3p14. Mutations in the gene have been reported.

Treatment

Controlling fasting-induced hypoglycemia resulted in some improvement in liver dysfunction and reduction of the hepatosplenomegaly in two infants. The only available

definitive treatment for the fatal form of the disease is liver transplantation. However due to the accumulation of the abnormal polysaccharide in muscle and nervous system, the long-term effect of liver transplantation on these organs is uncertain.

Type VI Glycogenesis (Liver Phosphorylase Deficiency)

This is a rare inborn error of glycogen metabolism that results from hepatic phosphorylase deficiency. The disease is inherited as an autosomal recessive gene. Affected children are usually asymptomatic except for massive hepatomegaly. Hypoglycemia after prolonged fasting is rare. Glucagon tolerance tests reveal a flat curve. Diagnosis is by demonstrating low hepatic levels of phosphorylase.

Hereditary Tyrosinemia Type I

Hereditary tyrosinemia type I is a disorder of tyrosine metabolism which is strongly linked to deficiency of the enzyme, furmarylacetoacetate hydrolase (FAH). This enzyme is normally found mainly in the liver and kidneys. It is inherited as an autosomal recessive gene with a very high prevalence (1/700) in the Quebec province of Canada and in Scandinavian countries.

It is characterized by progressive hepatic fibrosis leading to cirrhosis, hepatomas, proximal renal tubular dysfunction, and hypophosphatemic rickets.

Pathophysiology

The cause of hereditary tyrosinemia is a reduction in the activity of fumarylacetoactate hydrolase (FAH), the final enzyme in tyrosine degradation. Absent to low activity of the enzyme p-hydroxyphenylpyruvate dioxygenase in liver tissue is also recognized but this enzyme deficiency has been shown to be secondary to the disease rather than the primary cause of hereditary tyrosinemia. FAH is a 419 amino acid protein found in the liver, kidney, lymphocytes, erythrocytes, and fibroblasts. A human liver FAH cDNA has been sequenced and the human gene has been localized to chromosome 15q23 → q25.

The deficiency of the enzyme FAH results in the accumulation of fumaryl and maleylacetoacetate. These compounds are metabolized to succinylacetone (SA) and succinyl acetoacetate (SAA) which are elevated in the serum and urine of patients with hereditary tyrosinemia type I and absent in other forms of disorders of tyrosine metabolism. Therefore, succinylacetone and succinylacetoacetate are virtually diagnostic of hereditary tyrosinemia type I when combined with assays of hepatic tissue for FAH. Succinylacetone has been used for neonatal screening in areas with a high prevalence of the disease.

Succinylacetone (SA) is a potent inhibitor of delta-aminolevulinate dehydratase (porphobilinogen synthetase) and leads to increased serum levels and urinary excretion of delta-aminolevulinic acid. The latter is believed to be responsible for the neurologic symptoms resembling acute intermittent porphyria. SA is also believed to be toxic to the proximal renal tubules leading to pronounced tubular dysfunction manifesting as renal tubular acidosis and rickets. Other causes of rickets include impaired hepatic and renal hydroxylation of vitamin D. SA inhibits several enzymes of tyrosine metabolism and results in a reduction of glutathione levels. The significance of this observation is not known, but free sulfahydryl groups play a role in protection from free radicals.

Genetics and Screening

Tyrosinemia is inherited as an autosomal recessive trait. Heterozygotes are asymptomatic because they possess 50% of normal enzymatic activity leading to normal levels of tyrosine-related metabolites.

A human liver FAH cDNA has recently been sequenced and the human gene localized to 15q23 → q25. The gene contains 14 exons and spans approximately 35 kilobases of DNA. The disease in Quebec families has been found to be caused by a guanine to adenine change in the splicer-donor sequence of intron 12 of the gene leading to aberrant splicing and an inactive product. In Northern Europeans, multiple missense and complex splicing defects have been detected. Once the major mutations have been identified, use of allele-specific oligonucleotides will become established as a diagnostic and screening test for this disorder.

Clinical Manifestations

Tyrosinemia should be suspected in a child or infant with unexplained hepatocellular necrosis, cirrhosis, or decreased hepatic synthetic function for which a cause is not immediately evident. Rickets, characteristic renal or

neurologic findings, especially if associated with abnormal hepatic function, should raise suspicion of this disease.

Two forms of the disease have been recognized, *acute and chronic:*

In the *acute* form, the enzyme deficiency is more profound. Patients may present in the neonatal period or early infancy with fulminant hepatic failure, renal dysfunction, and disseminated intravascular coagulation. A large proportion of patients have a fatal outcome. In others, the presentation can be less dramatic with failure to thrive, vomiting, and diarrhea. These patients die within a few months from liver failure.

In the *chronic* form, the enzyme deficiency is believed to be less severe than in the acute form. Patients present with failure to thrive, hypophosphatemic vitamin D-resistant rickets, hepatomegaly, and progressive hepatic failure. Some patients may present with severe attacks of abdominal pain resembling those of acute intermittent porphyria. Other patients may have acute episodes of lower extremity pain followed by transient paralysis. Up to 37% of the patients develop hepatomas with some risk of malignant transformation.

Laboratory Findings and Diagnosis

Liver function tests reveal hypoproteinemia, deficient vitamin K-dependent coagulation factors, and moderate elevation of transaminases and bilirubin. Alpha-fetoprotein is characteristically elevated in the presence or absence of hepatomas.

Phosphaturia, glucosuria, and generalized amino aciduria are common findings. Urinary excretion of delta-aminolevulinic acid, succinylacetone, and succinylacetoacetate are pathognomonic of type I hereditary tyrosinemia. Elevated serum levels of succinylactone detected using blood samples dried on a filter paper are very specific and serve as a reliable neonatal screen. Serum levels of tyrosine, methionine, and phenylalanine are usually increased but these are nonspecific findings as they may occur with any form of liver failure. The diagnosis is confirmed by enzyme assay for FAH in hepatic tissues, and more recently, on lymphocytes and fibroblasts.

Prenatal diagnosis can be achieved by FAH assay in cultured amniotic fluid cells or chorionic villus cells, as well as measuring succinylacetone in amniotic fluid.

Histopathology

The liver shows fatty metamorphosis, inflammatory cell infiltrate with lymphocytes and plasma cells, extensive fibrosis, and nodular regeneration. Hepatomas are frequently seen in advanced cases.

The kidneys are usually enlarged with tubular epithelium degeneration, as well as evidence of glomerulosclerosis. The pancreas shows diffuse hyperplasia of the islets of Langerhans although most patients have normal blood glucose levels.

Treatment

Dietary restriction of tyrosine and its precursor phenylalanine has been the standard treatment of type I hereditary tyrosinemia although the long-term outcome of this approach has not been formally documented. This dietary regimen has a substantial beneficial effect on renal function with reduction in renal loss of phosphate, glucose, and amino acids. However, the effect of this diet on hepatic dysfunction is uncertain. Limited amounts of tyrosine and phenylalanine are reintroduced as the patient's clinical status improves to allow adequate growth. Control of infections, fasting, and other stressors that liberate amino acids through catabolism should be dealt with appropriately by treating the underlying condition and by providing sufficient calories for tissue repair during catabolic states. The use of 2 - (nitro-4-trifluoromethylbenzoyl) - 1–3 - cyclohexanedione (NTBC) which inhibits the enzyme 4-hydroxyphenylpyruvate oxidase has resulted in improvement in clinical and biochemical parameters in a large study involving 207 patients. Children treated before 6 months of age have a 10-year survival rate of 85%. This treatment reduced the need for liver transplantation. Side effects of NTBC include thrombocytopenia, leukpenia, and cutaneous disorders. Liver transplantation remains a life-saving treatment modality in patients with late diagnosis and failure to respond to NTBC. In patients with advanced renal disease a liver-kidney transplant may provide a solution to failure of both organs.

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210 Wilson Disease

Hisham M. Nazer

Wilson disease (WD) is a disorder of copper transport caused by mutation within the ATP7B gene. WD is an autosomal recessive inborn error of metabolism in which there is an excessive deposition of copper in many tissues, especially the liver, brain, cornea, bones, and kidneys, resulting in a variable spectrum of clinical presentation, the exact of mechanism for which is not well known.

Wilson disease, previously called hepatolenticular degeneration, was first described in 1912 by the American neurologist Samuel Alexander Kinnear Wilson, who was working in England at the time. Wilson recognized the disease as being familial and associated with cirrhosis and progressive lethal neurologic disorder together with degeneration of the lens of the eye. Although the neurologic features were dominant in Wilson's original report, it is the liver that is the site of the biochemical abnormality and also the organ most frequently damaged by the excessive deposition of copper.

The disease is also associated with the presence of corneal rings previously recognized by Kayser and Fleischer in 1902–1903. Walsh introduced the chelating agent penicillamine as the medical therapeutic agent in WD. This treatment resulted in a radical change in the prognosis of the disease, especially when introduced at an early stage. Without treatment, there is usually progressive damage to the liver and the brain, with a fatal outcome.

WD is a rare disorder, with an incidence of 15–30 affected individual per one million population. WD is still considered as probably the most frequent cause of chronic genetic liver disease in the pediatric age group.

Pathogenesis

The basic defect in WD is not known, but the sequel of the disease seems to be caused by the accumulation of copper in various organs, especially the liver. Copper is not incorporated into its carrier protein ceruloplasmin within the liver. There is some evidence that the excretion of copper via the bile is disturbed in WD.

It has been established that the disease results from failure of the biliary copper excretion, with accumulation of the metal in various organs leading to hepatic cirrhosis and brain damage. Copper incorporation into ceruloplasmin is also impaired. There is accumulating evidence to dispute the longstanding recognition that ceruloplasmin has a primary role in the pathogenesis of WD. Moreover, the gene for ceruloplasmin is localized to chromosome 3, while that of WD is localized on chromosome 13.

GP73, a Golgi membrane protein is expressed in hepatocytes in response to acute or chronic liver disease. Increased hepatocyte GP73 expression is more commonly a feature of hepatic than neurologic WD.

Liver damage results from massive accumulation of copper in the tissue. Brain damage subsequently develops when the cerebral copper-binding proteins are saturated.

Clinical Features

Wilson disease has varied clinical manifestations. It may mimic most if not all forms of liver disease, but it is also associated with highly variable neurological symptoms with basal ganglia and cerebellar manifestation. Some patients with hepatic manifestations present with clinical features similar to those of autoimmune hepatitis. Unexplained hepatomegaly, progressive liver disease, behavioral or neurologic abnormalities, and hemolytic anemia are the most common presenting features in WD.

Occasionally, the incidental finding of Kayser–Fleischer (K-F) rings or of renal tubular acidosis leads to the diagnosis of WD.

A number of reports have emphasized the difficulty of differentiating chronic active hepatitis from WD. As the management is different, it is extremely important to make this distinction in all young patients with such histologic features. Liver copper concentration is found to be a useful test in enabling the clinician to differentiate chronic active hepatitis from WD.

Initial symptoms in WD are frequently nonspecific and delay in diagnosis and institution of penicillamine therapy is all too common. This is particularly important, as once signs of hepatic failure develop, the response to medical therapy is often disappointing. Nazer et al.

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introduced a prognostic score based on the severity of the abnormalities of serum aspartate aminotransferase, bilirubin, and prothrombin time on admission. Such a score facilitated separation of fatal and nonfatal cases in a series of 27 patients. Cases with indices in the fatal category may do well after emergency liver transplantation.

WD is unlikely to manifest clinically before the age of 4 years and may remain latent until the fifth decade. It is likely to produce signs and symptoms of hepatic involvement, and then at a later age, the neurologic manifestations appear if the disease continues to progress. The younger the patient, the more likely the presentation of WD is that of predominant hepatic manifestations. The variable presentation of WD raises the possibility that there could be a genetic basis for such varied manifestations and that some form of mutation may influence the severity of the disease with its multisystem involvement.

The varied clinical manifestations may be outlined as follows.

Hepatobiliary Manifestations

Asymptomatic hepatomegaly with or without splenomegaly and jaundice are well-recognized manifestations of WD. The disease is also characterized by chronic aggressive hepatitis with evidence of progressive hepatic insufficiency, and portal hypertension with its associated complications such as ascites and gastroesophageal varices. Hepatic cirrhosis may be well compensated with normal liver function tests for quite some time. Later in the course of the disease, the child may suffer from rapidly progressive jaundice, coagulopathy, fulminant hepatic failure, and encephalopathy. The disease may progress rapidly with fatal outcome within months to a few years without a definite diagnosis made. Fulminant hepatic failure secondary to WD is usually associated with intravascular, Coombs-negative hemolytic anemia, and low-serum alkaline phosphatase and aminotransferase levels. The prevalence of fulminant hepatic failure in WD is unknown.

The evidence of hepatoma complicating cirrhosis appears to be lower than in other types of cirrhosis. Moreover, it has been postulated that the high tissue copper might protect against tumor formation.

Neurologic Manifestations

Neurologic abnormalities usually develop at a later age than that of hepatic manifestations. They may result directly from deposition of copper in the brain, indirectly as an encephalopathy complicating progressive liver disease, or as a combination of both. The neurologic manifestations of WD result primarily from the anatomic disruption of the basal ganglia, cerebellum, and brain stem. The putamen is most severely affected with diffuse symmetric softening, atrophy, and cavitation.

Early diagnosis and subsequent initiation of adequate chelating therapy can reduce neurologic disturbances or prevent their development. Early manifestations include tremors, dysarthria, ataxia, grimacing, and incoordination. Late manifestations include dystonia, spasticity, and rigidity.

Computed tomographic (CT) scan can demonstrate brain involvement in WD and has been used to follow the effects of therapy. Comparative studies have shown superiority of magnetic resonance imaging (MRI) over CT scan, and the efficacy of MRI has been well documented.

Ophthalmic Manifestations

K–F rings consist of electron dense granules containing both copper and sulfur. They are usually bilateral, green, yellow, or brown-green rings located at the periphery of the cornea on the posterior surface close to the limbus (*Fig. 210.1*). These rings are very important findings in WD as they are present in most if not all cases of WD with neurologic presentation. The rings vary from full to incomplete circles with deposits seen in the superior and inferior poles of the cornea. The rings may be seen by naked eyes but, in most cases, they are only visible on slit-lamp examination.

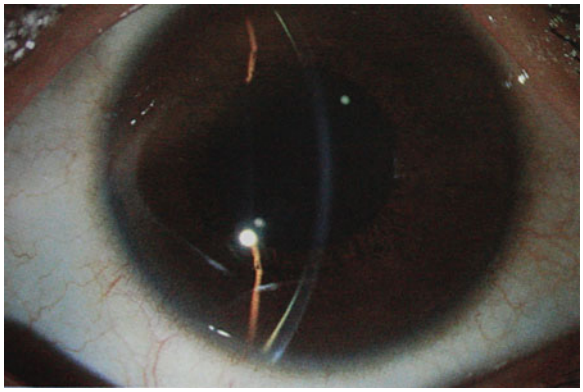

Figure 210.1
Kayser–Fleischer ring in a patient with Wilson disease (slit-lamp examination)

K-F rings have a variable appearance in different patients. The development of the rings usually occurs after the age of 4 years. With chelating therapy, there is reduction in the deposits, although complete disappearance is not guaranteed in spite of adequate therapy and satisfactory compliance on the part of the patient.

It is important to recognize that K-F rings, which are considered to be diagnostic of WD in patients with neurologic presentation, are frequently absent in young patients with hepatic manifestations. They may also be absent in patients with neurologic manifestations of WD and present in conditions other than WD. Some of the conditions associated with K-F-like rings include primary biliary cirrhosis, chronic active hepatitis, cholestasis syndromes, and multiple myeloma.

Sunflower cataracts due to copper deposition in association with K-F rings have also been reported in WD. They do not impair vision. Sunflower cataracts are also seen through slit-lamp examination in about 10% of patients with WD. They are usually located beneath the anterior and posterior lenticular capsules.

Hematologic Manifestations

These include nonspherocytic, Coombs-negative intravascular hemolysis. Acute hemolysis may be the first indication of the disease in about 10% of cases. Fulminant hepatitis in WD is usually associated with severe hemolysis.

Psychiatric Manifestations

These are comprised of behavioral, affective, psychotic, and neurotic disorders. Symptoms may be vague and nonspecific, such as fatigue, anorexia, and mood disturbances. Other recognized manifestations include deterioration in the patient's performance at work or at school.

Renal Manifestations

Renal manifestations include proximal or distal renal tubular acidosis, microscopic hematuria, proteinuria, aminoaciduria, and reduction in glomerular filtration rate. Other features of renal lesions include hypercalciuria, uricosuria, and renal tubular acidosis. Renal damage may result from copper deposition in the renal tubules. The phosphaturia may result in hypophosphatemia and bone disease. The disease may present with features of renal rickets and Fanconi syndrome (generalized aminoaciduria, glucosuria, uricosuria. hypercalciuria, hyperphosphaturia, and reduced specific gravity).

Rheumatologic Manifestation

Osteomalacia, rickets, osteoporosis, localized bone demineralization, and spontaneous fractures

Other Miscellaneous Manifestations

These include congestive heart failure, cardiac arrhythmia, cardiomyopathy, acanthosis nigricans, gynecomastia, glucose intolerance, parathyroid insufficiency, amenorrhea, and hepatocellular careinoma.

Diagnosis

Wilson's disease is rare and has no specific early manifestation; thus, clinicians may not suspect it, and clinical signs tend to be overlooked causing delay in diagnosis.

Wilson disease may have many clinical presentations. Early diagnosis is difficult unless a high index of suspicion is maintained. The availability of an effective treatment makes it prudent to diagnose WD early enough to prevent irreversible damage to vital organs such as the liver and the brain. It is even essential to try and diagnose WD in the asymptomatic stage by screening siblings of affected patients.

In view of the variable clinical manifestations of WD, the diagnosis should be considered virtually in any child with hepatic disorder presenting in early childhood, especially if it is associated with neurologic abnormalities, renal or bone disease, hemolytic anemia, or deteriorating school performance. The presence of bilateral K-F rings supports the diagnosis, though their absence in children with hepatic manifestations or with hemolytic anemia does not rule out the diagnosis. Multiple laboratory studies are usually needed to confirm the diagnosis of WD.

The diagnosis of WD might pose some challenge to the clinician as not only the classic triad of K-F rings, hepatic cirrhosis, and neurologic disorders may be absent, but serum ceruloplasmin may also be normal.

Most patients with WD (>90%) show low levels of serum ceruloplasmin, whether measured by enzymatic activity or immunochemical methods. Normal levels are seen in about 5–10% of cases. Serum copper concentration is also low, but the free (nonceruloplasmin bound) copper concentration is elevated. Rarely, serum copper concentration may be normal in WD or even above normal.

Peripheral blood examination may show features of hemolytic anemia or hypersplenism. Failure to consider diagnosis early results in unnecessary morbidity and mortality.

Liver enzymes are usually only moderately elevated, whereas the bilirubin level is markedly raised.Such findings should alert the clinician to the possibility of WD, especially in an affected child with hepatic failure.

Ceruloplasmin is a blue α2-glycoprotein. The gene for ceruloplasmin is now mapped to chromosome 3. WD is associated with a low serum ceruloplasmin (normal levels, 20–40 mg/dL). A low serum ceruloplasmin is not diagnostic of WD as it may be found in other conditions such as in normal neonates, chronic active hepatitis, intestinal malabsorption, protein calorie malnutrition, protein-losing enteropathy, nephrotic syndrome, and fulminant hepatic failure. Ten to twenty percent of heterozygotes for WD also have low serum ceruloplasmin. Ceruloplasmin concentration is the most useful adjunct to clinical information for differentiating WD and chronic active hepatitis. Serum ceruloplasmin itself does not distinguish between chronic active hepatitis and WD.

Elevated urinary and hepatic copper have also been reported in patients with chronic active hepatitis. High urinary copper excretion of 25 mmol of Cu or more over 24 h is considered diagnostic of WD. However, urinary copper excretion is increased in patients with cholestasis, hepatitis, and cirrhosis. Estimation of 24-h urinary copper excretion is performed first as a baseline and second after challenge with penicillamine. Though the urinary copper excretion is increased, the positive copper balance persists.

When serum ceruloplasmin and urinary copper are equivocal, determination of the liver copper will usually enable the diagnosis to be confirmed.

The discriminatory value of hepatic copper concentration makes this test the most reliable test for differentiating chronic active hepatitis and WD in children and adolescents.

Liver copper concentration remains the most important laboratory information on which the diagnosis of WD may be based, supported by consistent clinical features. In homozygous WD, copper concentrations are usually more than 250 μg/g dry liver tissue.

Recent reports have also indicated that high liver copper concentration is not specific for WD as the copper deposition in the liver parenchyma may be inhomogenous. Increased liver copper concentration is seen in all chronic cholestasis and in chronic active hepatitis.

Clinicians should recognize that there are problems in the estimation of hepatic copper concentration. Furthermore, such investigation may not be possible in advanced hepatic involvement in WD with severe coagulopathy, so the diagnosis may have to be established without such investigation.

Occasionally, the tissue copper concentration is inconclusive in confirming the diagnosis, in which case it might be necessary to perform *radioactive copper studies* to establish the diagnosis. Patients with WD fail to incorporate radioactive copper into the newly synthesized ceruloplasmin. In patients with equivocal copper studies and in whom liver biopsy is contraindicated, the rate of copper incorporation into ceruloplasmin may be helpful in the diagnosis. Patients with WD do not show a normal secondary rise in plasma radioactivity or incorporation of radioactive copper into ceruloplasmin even in patients with normal ceruloplasmin levels.

Establishing the diagnosis of *fulminant Wilson disease* can be difficult, especially in situations where the clinical features and laboratory data are neither specific nor diagnostic. Recent reports highlight the use of diagnostic criteria for the diagnosis of acute liver failure (ALF) in WD; however, the value of slit-lamp examination for the presence of K-F rings and liver biopsy for the determination of hepatic copper concentration still remain important for the diagnosis of ALF due to WD.

Laboratory investigations may confirm the existence of renal involvement by the presence of hematuria, proteinuria, aminoaciduria, phosphaturia, and defective acidification of the urine.

Recent reports indicate that CT scan changes may lack correlation with neurologic status and may even worsen despite clinical improvement. CT scan changes may reveal dilated ventricles together with abnormalities in lenticular, thalamic, caudate, and dentate nuclei even in the absence of neurologic manifestations. MRI has contributed to early detection of cerebral lesions in WD. Aisen et al. were the first to report MRI changes of partial necrosis in the basal ganglia in patients with WD. The changes are usually more evident on MRI than on CT scan, especially those in the brain stem. As with CT scan, there is no definite correlation between MRI changes and clinical features (i.e., MRI may be normal in patients with neurologic manifestations or abnormal in those with the hepatic form of the disease).

Hepatic Pathology

The diagnosis of WD is rather incomplete without the evaluation of liver histology by percutaneous or wedge liver biopsy, and histochemical staining for excess copper and liver copper concentration. Hepatic pathology in WD is characterized by marked fatty infiltration of the

hepatocytes associated often with prominent glycogen nuclei. There are also Kupffer cell hypertrophy, hepatocellular necrosis, and fibrosis. The liver may be enlarged, but in more advanced cases, it is normal in size or even shrunken due to multilobular cirrhosis with nodules showing variable amounts of stainable copper (◉ *Fig. 210.2*). Orcein staining and rubeanic acid staining are usually negative in early WD. Later in the course of the disease, the histochemical staining for excess copper is usually positive. The rhodanine stain seems to provide reproducible and satisfactory results in demonstrating excess tissue copper in liver biopsies from patients with WD (◉ *Fig. 210.3*).

Histologic changes consistent with chronic active hepatitis, subacute hepatitis, or postnecrotic cirrhosis may be seen in WD, which contribute further to the diagnostic dilemma occasionally experienced in new cases of WD. Mallory cytoplasmic hyaline bodies are also seen in liver biopsy from patients with WD. With the progress of the disease, the child may manifest features of hypersplenism and portal hypertension.

Electron microscopic examination contributes further to the diagnosis by the presence of abnormalities in the mitochondria in the form of dilatation of the tips of the cristae with abnormal morphology and condensation of dense bodies.

The cerebral changes are seen mostly in the corpus striatum and to a lesser extent in the cerebellum, cortex, and thalamus. The changes include decrease in the number of neurons and in the myelinated nerve fibers with increased astrocytosis.

Presymptomatic Wilson Disease

Once the diagnosis of WD has been established in a patient, it is mandatory that all siblings be screened since there is a one-in-four chance of them having the disease. It is also advisable to screen any blood relative for the presence of WD.

Diagnosis of asymptomatic patients is important so that treatment can be initiated and neurologic and hepatic damage can be avoided.

Even with extensive biochemical testing, it is not always possible to distinguish heterozygous WD from affected homozygous.

In normal newborn, the biochemical copper profile mimics that seen in WD; therefore, screening affected siblings should not be performed on those below the age of 3 years. Treatment of the asymptomatic homozygous will prevent the evolution of the disease manifestations.

Screening should include serum ceruloplasmin, 24-h urinary copper excretion, slit-lamp examination, and standard tests of liver function. K–F rings should also be looked for. Urinary copper excretion greater than 40 μg/24 h is suggestive of WD in Asymptomatic children, whereas penicillamine challenge does not have a diagnostic role in this group of patients.

If the results are abnormal or equivocal, a liver biopsy for histologic examination and determination of copper content should be performed.

DNA markers may nowadays contribute to the diagnosis of presymptomatic WD. The use of molecular genetics for screening siblings plays a role in the diagnosis

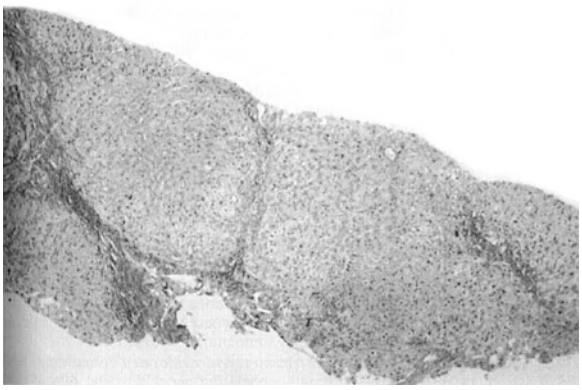

Figure 210.2
Percutaneous liver biopsy from a child with Wilson disease and predominant hepatic manifestation. Note the severity of hepatic involvement with nodular cirrhosis (hernatoxylin and eosin)

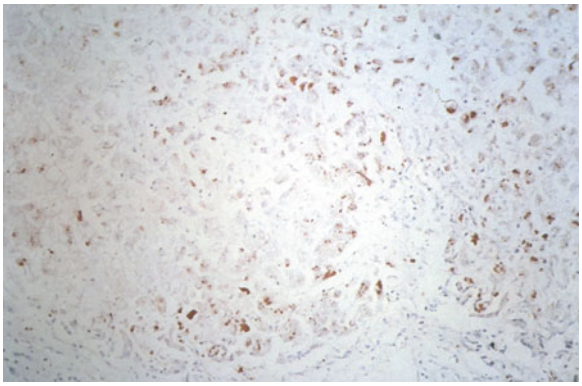

Figure 210.3
Percutaneous liver biopsy from a child with Wilson disease and advanced hepatic involvement. Note the extensive tissue copper deposition (rhodanine stain)

of presymptomatic patients. A probe from the linked retinoblastoma (RB) gene can be very helpful in problem cases. The quantitative determination of liver copper concentration remains the definitive diagnostic criterion.

Treatment

The availability of an effective treatment makes it important to diagnose WD before overt clinical manifestations appear. Early diagnosis and therapy could prevent irreversible tissue damage. Screening of sibs is vitally important. Untreated WD is invariably fatal.

D-*penicillamine*, a metabolite of penicillin, is currently the drug of choice. Penicillamine functions as a chelating agent with its free sulfhydryl group excreted in the urine intact. Penicillamine interferes with collagen cross-linking and acts also as an immunosuppressant.

Treatment with D-penicillamine is started with a dose of 15–20 mg/kg/day divided into four daily doses half an hour before meals and before retiring. If there is no response within 4–6 months, the dose should be increased up to 1.5 g/day. Only rarely is a higher dose than this required. Pyridoxine (5–10 mg/day) should also be given to compensate for the weak antipyridoxine effect of D-penicillamine. Liver functions slowly improve. The dose of penicillamine may be reduced once symptoms are controlled. A useful indicator of successful decoppering is the fall in the plasma nonceruloplasmin copper (the difference between the total serum copper and the ceruloplasmin copper) to virtually zero.

Approximately 30% of patients have some side effects to penicillamine therapy. It is not effective in patients with acute liver failure, which signifies once more the importance of early diagnosis and initiation of therapy before it is too late. It is important to recognize that though penicillamine remains the first line of therapy, neurologic status may worsen at the initiation of therapy.

Recognized side effects of penicillamine include bone marrow suppression, proteinuria, nephrotic syndrome, systemic lupus erythematosus, Goodpasture syndrome, aphthous ulceration, arthralgia, and loss of the sense of taste. In view of the relatively high frequency of side effects, white blood cells and platelet counts should be checked twice weekly for the first 6–8 weeks of treatment then at monthly intervals for the first 4 months.

Neurologic abnormalities may be reversible if therapy is commenced early. However, it has also been emphasized that neurologic disturbances may progress or even appear de novo during D-penicillamine therapy. If left untreated, WD progresses to hepatic failure or severe neurological disability and death. While those adequately treated are expected to have normal life span.

Treatment with penicillamine should continue during pregnancy. However, the teratogenic effects of the drug and its effect on the newborn need to be considered. The dose of penicillamine is best reduced to about 1 g daily during pregnancy.

Triethlyene tetramine hydrochloride (Trientine) is an effective alternative chelating agent introduced by Walshe as an alternative copper-chelating agent for WD patients with D-penicillamine-induced side effects such as neutropenia, thrombocytopenia, and nephrosis. Trientine is a less potent chelating agent than penicillamine. Copper is chelated by forming a stable complex with the four constituent nitrogens. Trientine increases urinary copper excretion and may interfere with intestinal absorption of copper. Trientine has one advantage over penicillamine in that treated patients are not at risk of rapid clinical deterioration on discontinuation of therapy. In contrast to penicillamine, trientine therapy results in an elevated serum free Cu concentration. Initially, 0.5 g of trientine should be given daily for children less than 10 years old and 1 g to older patients, taken in divided doses at least 1 h before or 2 h after meals. Dosage is increased only if the clinical response is inadequate after 6 months of treatment or if the concentration of free serum copper remains persistently above 20 μg/dL.

In a recent report by Dahlman et al., long-term treatment with trientine was evaluated in 19 patients with WD. The authors concluded that in spite of reported serious colitis in two patients and duodenitis in one patient, therapy with trientine remains a drug of first choice in parallel with penicillamine in patients with WD. Lupus nephritis has also been reported in patients receiving trientine therapy. Trientine chelates dietary iron and may result in iron deficiency. Recent study from King's college Hospital, London, has indicated that trientine is as efficacious as penicillamine with possibly lower side effect.

Zinc sulfate or acetate is also implicated in the medical management of WD. The postulated mechanism of zinc is that excess zinc induces metallothionein in enterocytes, which have greater affinity for copper than zinc. The average dose of zinc sulfate is about 150 mg orally three times daily. Once bound, the copper is not absorbed but is lost in the feces as enterocytes are shed in normal turnover. Recognized side effects of zinc therapy include gastritis and microcytic anemia by interference

with iron utilization. More patients, especially new cases, are currently placed on zinc therapy.

Reports have indicated that oral zinc used as the initial treatment for WD can control the illness effectively and prevents its progress, provided it is given early in the course of the disease. Recent reports have also indicated the efficacy and safety of zinc acetate for the prophylactic treatment of presymptomatic WD patients.

The treatment is nontoxic and does not carry the risk of worsening the neurologic manifestations recognized with D-penicillamine therapy. Zinc therapy is also recommended for WD mothers during pregnancy.

In view of the recognized deteriorating neurologic manifestations in some WD patients following the initiation of D-penicillamine therapy, Brewer et al. introduced a new drug, ammonium tetrathiomolybdate, which might save patients of that potential complication. *Tetrathiomolybdate* functions as an immediate blocker of copper absorption as well as forming complexes with copper in the blood, rendering the copper nontoxic. The authors concluded from their study on five WD patients with acute neurologic symptoms that ammonium tetrathiomolybdate is an effective therapy with a favorable outcome. The drug in bulk form stored under anaerobic conditions at room temperature is adequately stable. Other study has indicated that Tetrathiomolybdate is a better choice than trientine for patients with neurological WD. More studies are needed to confirm the superiority of tetrathiomolybdate over other available chelating agents.

It has been reported that histopathological correlations with treatment should better be made through liver biopsy with hepatic copper quantification every 3 years.

Symptomatic treatment may be required for ascites and edema. Spironolactone together with a potent loop diuretic may considerably improve the patient's well-being.

A low-copper diet is required, though the issue of compliance is often in question. The child is advised to stay away from food with a high copper content such as nuts, chocolates, mushrooms, liver, and fish.

Death may occur as a result of fulminant hepatitis or bleeding esophageal varices. Other recognized causes of death include central nervous system disease or as a sequela to other system involvement or to surgical intervention.

Recent Advances

In 1985, the WD gene was localized to chromosome 13, also the site for the retinoblastoma protein gene. In the meantime, the gene for Menkes disease was cloned. The gene for Menkes disease is technically named ATP7A but conventionally called MNK.

The identification of the WD gene on chromosome 13 constitutes a stimulating factor to the ongoing research on WD. In 1993, the gene was identified. The gene, technically called *ATP7B* but conventionally called *WND*, codes for an enzyme that is a P-type ATPase, which has six copper-binding sites and acts as a copper transporter.

Mutations may account for some of the varied clinical manifestations of WD.

The Long-Evans cinnamon (LEC) rat is a highly inbred strain of rat that develops hepatic disease similar to WD due to copper deposition in the liver. The LEC rat is recognized as the animal model in the research on WD, though it does not develop the neurologic abnormalities.

The gene (ATP7B) for WD is localized to chromosome 13 at location 13q14. The WD gene has 57% homology with the copper-binding domain or Menkes disease, whose gene is ATP7A. The encoded protein for transporting copper is P-type ATPase.

Mutation analysis is a future prospect for diagnosis, DNA linkage studies have been shown to aid in identifying affected sibs of index cases or for prenatal diagnosis. However, the increasing number of mutations raises some difficulty if there is not already a well-authenticated case in the family.

Haplotype analysis offers an alternative approach. It may enhance identification of currently unrecognized mutations in WD.

WD is recognized to pose a diagnostic challenge, especially when the important diagnostic criteria do not all support the diagnosis. With the identification of the gene locus of WD, DNA markers can be used to discriminate between presymptomatic patients and nonaffected individuals when biochemical results are equivocal.

Yuzbasiyan-Gurkan et al., in their study on the use of molecular genetics for screening siblings of affected patients for WD, have concluded that a probe from the linked retinoblastoma gene can be very helpful in problem cases.

Walshe and Yealland reviewed 189 patients with neurologic signs and symptoms referred to the WD clinic over 30 years. The review concluded that the referral diagnosis was correct in only 72% of cases.

It is hoped that with the available knowledge of WD genetic methods for diagnosis, an effective genetic treatment will be available in the near future.

Liver Transplantation

Liver transplantation is performed more often than previously on patients with progressive hepatic involvement and those with fulminant hepatitis. It is also performed in young cirrhotic patients with laboratory findings of severe hepatic compensation with lack of response after a few months of medical therapy. Liver transplantation is also indicated in progressive hepatic insufficiency and hemolysis, especially that following discontinuation of penicillamine.

Orthotopic liver transplantation is now accepted as the only effective treatment of WD presenting with fulminant hepatic failure and end-stage chronic liver disease that have not responded to medical therapy. Early referral of such patients for liver transplantation ensures a better outcome. However, based on recent reports, the need for liver transplantation in acute liver failure in WD should be evaluated carefully as the prognosis is not necessarily fatal. Some affected children have survived without having to have liver transplantation. The role of liver transplantation in the management of WD with neurologic manifestations in the absence of hepatic insufficiency remains rather uncertain. Some reports have indicated that neurologic and psychiatric symptoms due to WD have improved after liver transplantation.

Liver transplantation corrects completely the biochemical abnormality and reverses many of the clinical features of WD, although lifelong immunosuppression is required in most cases. After transplant, patients do not require penicillamine.

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211 Noninvasive Diagnosis of Liver Fibrosis

Mortada El-Shabrawi · Fetouh Hassanin

Introduction

Hepatic fibrosis is an important consequence of inflammatory disorders affecting the liver, that might ultimately progresses to cirrhosis. Several methods for the detection and monitoring of hepatic fibrosis have been proposed, particularly in chronic hepatitis C virus (HCV) infection, alcoholic liver disease, nonalcoholic fatty liver disease (NAFLD) and during methotrexate therapy, in all of which progressive fibrosis can develop over a number of years in a minority of patients. Establishing the presence of fibrosis or cirrhosis in patients with chronic liver disease is important for assessment of prognosis and for evidence of progressive disease. Liver biopsy currently remains the gold standard to assess fibrosis. However, it has several limitations ranging from manpower issues and cost, to risk of patient injury, mortality and morbidity, as well as inter- and intra-observer variability and sampling variation. Liver biopsy is also a relatively costly and invasive procedure, associated with pain and discomfort, which render it not well accepted by patients, especially when it has to be occasionally repeated. Infrequent but serious complications such as profuse bleeding may occur. Even when an experienced physician performs liver biopsy and an expert pathologist reads and interprets the findings, up to a 20% error rate in disease staging has been reported. Regev and colleagues found a difference of at least one fibrosis stage between the right and left lobes in 33% of 124 patients, whereas Siddique and colleagues observed a difference of at least one fibrosis stage between two specimens of at least 15 mm taken at the same puncture site in 45% of patients. In addition, Colloredo and colleagues reported a tendency to underscore fibrosis as the size of the biopsy sample diminished. All the previous observations and findings prompted an active search over the past few years for a noninvasive method(s) to diagnose liver fibrosis that might supplement or probably replace liver biopsy.

Ideally, a noninvasive marker of liver fibrosis should be liver-specific, easy to perform, reliable, and inexpensive. It should be also accurate not only for the grading of fibrosis, but also for the monitoring of disease progression and the efficacy of therapy. Various direct and indirect serum biochemical markers as well as imaging modalities have been proposed as noninvasive diagnostic markers of liver fibrosis. To date, almost all the data regarding the use of noninvasive markers of fibrosis have originally been generated in patients with chronic HCV infection. Several markers of liver fibrosis have been proposed and actively investigated in immune-competent patients with chronic HCV infection. These data are being extended to other chronic liver diseases.

Serum Biochemical Markers

Direct markers of fibrosis refer to the measurement of specific substances involved in liver fibrosis generation and modeling. They are expensive and not easily available in all laboratories. Indirect markers have gained popularity as they could provide clinical useful information utilizing readily available clinical parameters. Several laboratory noninvasive liver fibrosis tests (NILFT) have been developed to assess liver fibrosis, including a combination of prothrombin time (PT), gamma glutamyl transpeptidase (GGT), apolipoprotein A1 (Apo-A1) and alpha-2 macroglobulin (α-2 M) levels called the PGA and PGAA index, serum hyaluronic acid (HA) levels, PT alone and the aspartate aminotransferase (ASAT) to platelet ratio index (APRI).

Aspartate Aminotransferase to Platelet Ratio Index (APRI) Test

APRI was the most promising of the NILFT that have been recently studied. It is a simple tool based on AST measurement and platelet count. Progression of liver fibrosis may reduce AST clearance, leading to increase in its serum levels; in addition, liver disease may be associated with mitochondrial injury, resulting in further AST release from the hepatocytes. The platelet count decreases, in inverse proportion to progressive liver fibrosis, due to worsening of portal hypertension with consequent increased platelet

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sequestration and destruction in an enlarging spleen. Interestingly, the diagnostic value of APRI was found to be influenced by sex; APRI was found much more sensitive in female (91%) than in male (60%) patients. A possible explanation relates to the correction, required by the formula by which APRI is calculated, for AST upper normal limit. Mean aminotransferase values are higher in men than in women, in relation to confounding factors such as body mass index (BMI), alcohol consumption, and lipid metabolism profiles. Accelerated liver fibrosis progression due to recurrent HCV is more frequently observed in female than in male liver transplant recipient. This finding is confirmed by some researchers who found that significant liver fibrosis (Ishak staging score >2) was observed more frequently among female recipients. This is another factor suggesting that the diagnostic value of APRI would be better in women, as where the prevalence of the condition to be identified is supposedly high, the positive predictive value of the test is increased. Among NILFT, APRI has the highest diagnostic value in discriminating liver transplanted patients with progression to significant liver fibrosis, although its accuracy is influenced by recipient sex. APRI was recommended by some researchers as the most accurate simple marker for predicting significant hepatic fibrosis in various etiologies of chronic liver diseases, especially in chronic hepatitis B, though APRI and the platelet count were also good indirect markers. Concerns were also raised regarding the impact of serum lipid abnormalities and modifications induced by cholesterol altering medications.

Patients with and without significant fibrosis could be excluded with negative and positive predictive values of 86% and 88%, respectively. This test is very simple, but is subject to issues related to the reproducibility of AST measurement and platelet count.

FibroTest (FT)

The limitations of single parameters to assess liver fibrosis have led to the development of algorithms or indices combining the results of panels of markers that substantially improve diagnostic accuracy. Imbert-Bismut and colleagues were the first to propose an index based on a mathematical formula combining five variables: total bilirubin, GGT, haptoglobin, α-2 M, and Apo-A1. The results of this test, known as the FibroTest (BioPredictive; Paris, France), are scored from 0 to 1. In the initial report, a score <0.1 allowed for the exclusion of significant fibrosis (METAVIR score F2 or greater), with a 100% negative predictive value, whereas a score >0.6 allowed for the diagnosis of significant fibrosis, with a 90% positive predictive value, using liver biopsy as the reference. Overall, liver biopsy could have been avoided in 46% of the patients on the basis of these study findings. FibroTest has been extensively evaluated by the developers and other groups. El-Shabrawi and his colleagues found a significant linear trend and correlation between FT-related fibrosis and fibrosis stage by METAVIR scoring on histopathological examination of biopsies from children with chronic HCV infection. The FT area under the receiver operating characteristic curve (AUROC) was found to be 0.97, which could diagnose patients with mild stage of fibrosis, thus discriminating them from those with no (or minimal) fibrosis. This test is now licensed in several European countries as well as in the United States. When using FT in clinical practice, the interpretation of the findings should take into account each of the five components individually so as to avoid false-positive results related to hemolysis (decrease in haptoglobin), Gilbert syndrome (increase in bilirubin), or false-negative results related to inflammation (increase in haptoglobin or in α-2 M levels).

Forns' Index

Forns and colleagues reported a fibrosis index based on age, platelet count, GGT, and cholesterol levels. The lower cut-off value (4.2) had a 96% negative predictive value for excluding significant fibrosis, whereas the upper cut-off value (6.9) had a 66% positive predictive value for diagnosing significant fibrosis. This test was shown to be useful in excluding patients with minimal fibrosis, but was of limited utility in identifying patients with more advanced fibrosis.

Other Biochemical Markers

Several other indices have been developed including FibroSpect (Prometheus Laboratories Inc.; San Diego, California), the Sud score, Leroy's score, and the European Liver Fibrosis (ELF) Study score.

Although the diagnostic performance of these indices is generally good, with areas under the ROC curves ranging from 0.77 to 0.88, more than half of patients are not appropriately classified relative to findings on liver biopsy. Another limitation of these markers is that none is liver-specific and they may be influenced by changes in their clearance and excretion. Additionally, in clinical practice, the reproducibility in the measurement of some parameters, such as AST levels or platelet count, is questionable.

Imaging Modalities

Two noninvasive imaging techniques to assess hepatic fibrosis have been studied. The first is ultrasound elastography and the second is magnetic resonance elastography (MRE), both rely on assessment of the effect of liver stiffness (fibrosis) on the velocity of transmission of a shear wave through the parenchyma of the liver to determine hepatic stiffness. Both techniques are similar in assessment of fibrosis, although it has been suggested that MRE may have less variability with repetitive imaging than ultrasound. Acquisition time is similar for both techniques.

Ultrasound Elastography

Ultrasound elastography, commercially known as the FibroScan®, uses a modified ultrasound probe to measure the velocity of a shear wave created by a vibratory source. Estimates of stiffness of the liver by ultrasound correlate with fibrosis stage. Ultrasound elastography can be performed in approximately 95% of patients, although older patients and patients who are obese can be more difficult to study. With ultrasound elastography, a transducer probe is mounted on the axis of a vibrator. Vibrations of mild amplitude and low frequency are transmitted inducing an elastic shear wave that propagates through the underlying tissues. Pulse-echo ultrasound acquisitions are then used to follow the propagation of the shear wave and measure its velocity, which is directly related to tissue stiffness (the elastic modulus): the stiffer the tissue, the faster the shear wave propagates. Transient elastography measures liver stiffness in a volume that approximates a cylinder 1 centimeter (cm) wide and 4 cm long, with a measurement depth between 25 millimeter (mm) and 65 mm below the skin surface. This volume is at least 100 times larger than a biopsy sample and is therefore far more representative of the hepatic parenchyma. Transient elastography is painless, rapid (takes less than 5 min), and easy to perform at the bedside or in the outpatient clinic. The results are immediately available and independent from the operator. Transient elastography has been shown to be reliable in the assessment of liver fibrosis in patients with chronic HCV infection. Transient elastography has its own limitations. Measurement of liver stiffness can be difficult in obese patients and impossible in patients who have ascites. Ultrasound elastography does not distinguish patients with no fibrosis from patients with minimal fibrosis. Ascites can interfere with the generation of a shear wave through the liver.

Ultrasound elastography is strongly correlated with advanced fibrosis in patients with chronic hepatitis, and values above 12.5 kilo Pascal (kPa) are indicative of cirrhosis. This technique works best for separating patients with minimal or no fibrosis from those with significant fibrosis. A linear correlation with increasing fibrosis has not been demonstrated, and 15% discordance between elastography scores and histologic fibrosis has been observed. Advanced fibrosis may be underestimated and patients with macronodular cirrhosis may be classified as noncirrhotic. Fibrosis may be overestimated in patients with extrahepatic cholestasis or acute hepatocellular injury due to the effects of these conditions on liver stiffness.

The use of the ultrasound elastography for the noninvasive diagnosis of liver fibrosis has been widely validated in patients with HCV infection, with a significant correlation between liver stiffness and grades of portal and periportal fibrosis, fibrosis area, chronic HBV infection, HIV–HCV coinfection, cholestatic intrahepatic diseases, and the diagnosis of cirrhosis. Foucher and colleagues assessed the accuracy of FibroScan® for the detection of cirrhosis in 711 patients with chronic liver disease. Liver stiffness was significantly correlated with clinical, biological, and morphological parameters of liver disease and came to the conclusion that FibroScan® is a promising noninvasive method for detection of cirrhosis in patients with chronic liver disease. They noted that its use for the follow-up and management of these patients could be of great interest and should be further evaluated.

Corpechot and associates assessed the diagnostic performance of liver stiffness measurement for the determination of fibrosis stage in chronic cholestatic diseases. The authors concluded that FibroScan® is a promising tool to assess antifibrotic therapies in primary biliary cirrhosis (PBC) or primary sclerosing cholangitis (PSC). The Canadian Agency for Drugs and Technologies in Health (CADTH) performed an evaluation on FibroScan® for noninvasive assessment of liver fibrosis. It stated that the diagnostic performance of FibroScan® is good for identifying severe fibrosis or cirrhosis, but it is less accurate for milder presentations. CADTH concluded that additional studies are necessary to evaluate the comparative cost-effectiveness of different methods of assessing liver fibrosis. de Franchis et al., stated that transient elastography (Fibroscan) reproducibility needs to be further validated. Furthermore, Berrutti et al. suggested that the exact role of FibroScan® needs to be defined. de Lédinghen et al., assessed the feasibility of liver stiffness measurement and compared FibroScan®, FibroTest, and APRI with liver biopsy for the diagnosis of cirrhosis in children with chronic liver diseases. They stated that a specific probe dedicated

to children and slender patients has thus been developed and is currently under evaluation. Therefore, a FibroScan® equipped with this specific probe could become a useful tool for the management of chronic liver diseases in children. Shaheen et al., stated that in adults FibroTest and FibroScan® have excellent utility for the identification of HCV-related fibrosis/cirrhosis, but lesser accuracy for earlier stages. They noted that refinements are necessary before these tests can replace liver biopsy. Sagir et al. noted that inspite that FibroScan® frequently yields pathologically high values in patients with acute liver damage and is unsuitable for detecting cirrhosis/fibrosis in these patients. Han and Yoon noted that based on accumulating clinical data, clinical applications of elastography will increase in the near future. Sporea and colleagues stated that despite the fact that FibroScan® is not a perfect test, in a few years, most authorities in the field will consider it to be useful and necessary for the evaluation of chronic hepatopathies. Castera and associates stated that combining transient elastography with serum markers increases diagnostic accuracy and as a result, liver biopsy could be avoided for initial assessment in most patients with chronic hepatitis C. They strongly recommended constucting guidelines for the use of elastography in clinical practice. In a meta-analysis, Friedrich-Rust et al. concluded that transient elastography can be performed with excellent diagnostic accuracy and independent of the underlying liver disease for the diagnosis of cirrhosis. However, for the diagnosis of significant fibrosis, a high variation was found dependent on the underlying liver disease. Abenavoli et al. noted that currently most of the studies that were done for evaluating the effectiveness of transient elastography are used for patients infected with HCV. They suggested that its application must also be studied in the monitoring of patients suffering from other chronic liver diseases with possible fibrosis.

Magnetic Resonance Elastography (MRE)

Magnetic resonance plays an increasingly important role in assessment of patients with chronic liver disease because of the lack of ionizing radiation and the possibility of performing multiparametric imaging. Many researchers are prefering and encouraging the use of MRE as it can enable a safe, prompt, and accurate diagnosis of liver fibrosis and help the physician proceed with the most appropriate treatment plans. MRE may soon be established as the only technique able to stage fibrosis or diagnose mild disease.

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212 Cirrhosis and Ascites

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Cirrhosis

The World Health Organization defined cirrhosis as a diffuse liver process characterized by fibrosis and the conversion of normal liver architecture into structurally abnormal nodules. Cirrhosis is a recognized end-stage irreversible pathologic condition of chronic liver disease. The hepatocytes show considerable pleomorphism, with some cells appearing normal while others grossly abnormal.

Clinically, some affected patients with cirrhosis may remain asymptomatic for years (compensated cirrhosis), while others present with features of hepatocellular failure (decompensated cirrhosis). The normal anatomic relationship of the portal tract and hepatic veins is completely disrupted. Moreover, the normal flow pattern of blood from the portal tracts via the sinusoids to the central veins is impeded. In view of the presence of irreversible distortion of intrahepatic vascular and biliary structures, further liver cell damage and lobular collapse develop. There are many classifications for cirrhosis depending on the etiology, pathogenesis, clinical status, stage of development, and amount of hepatocellular necrosis. Some affected patients continue to have reasonably normal biochemical data (inactive cirrhosis), while others are seen with abnormal biochemical laboratory data (active cirrhosis).

Pathologically, cirrhosis is classified into micronodular cirrhosis with small nodules surrounded by bands of fibrous tissue (*Fig. 212.1*) as in extrahepatic biliary atresia, and macronodular cirrhosis with larger nodules and broader fibrous septa as in Wilson disease, or mixed with features of both micronodular and macronodular cirrhosis (incomplete septal cirrhosis). The histologic hallmarks of cirrhosis are increased liver fibrosis, collapse of normal lobular architecture, and the formation of regenerative nodules. Some children with chronic bile duct obstruction progress to develop fibrosis within the portal tracts extending into the parenchyma (biliary cirrhosis).

Postnecrotic cirrhosis due to chronic or recurrent cell destruction is characterized by piecemeal necrosis, bridging fibrosis, and regenerative nodules. This may be seen as a sequela to neonatal hepatitis or chronic active hepatitis.

Pathogenesis

Various hypotheses have been put forward to explain why livers of affected patients respond to varied forms of insults with the development of hepatocellular injuries, regenerative nodules, and prominent fibrous tissue formation. An important factor in the pathogenesis is the abnormal accumulation of extracellular matrix components, collagens, Iaminin, and fibronectins.

Hepatocyte injury causes cell death (necrosis), followed by scar formation (fibrosis), and in some cases, nodule formation (cellular regeneration). The reduction in the amount of viable hepatic tissue leads to compensatory growth and regenerative nodule formation as the cells replicate within a restrictive connective tissue framework. The hepatic nodules compress the hepatic arterial and venous blood flow further impeding the hepatic blood flow. The cycle of necrosis, fibrosis, and nodule formation results in cirrhosis.

Hepatocellular injury can result from various insults, including infections, hepatotoxic compounds, immune-mediated cytotoxicity, ischemia, and biliary obstruction.

The extracellular matrix is vital to the survival and proper function of hepatocytes. In cirrhosis, the extracellular matrix is altered qualitatively and quantitatively. Biochemical assays for enzymes and metabolites associated with fibrogenesis have been developed. Factors controlling connective tissue synthesis and degradation remain poorly understood. Pericellular fibrosis may also interfere with the nutrition of the hepatocytes. Lymphocytes activated either as an integral part of the liver-damaging process or activated in response to liver injury produce lymphokines, which induce fibroblast migration and proliferation. The factors that control hepatic regeneration are also poorly understood.

Many hormones are known to influence the process of hepatic regeneration including insulin, glucagon, adrenocorticotropic hormone, vasopressin, estrogen, and growth hormone. Hepatocyte growth factors and fibroblast growth factors are also involved in hepatic embryogenesis and regeneration. Interleukin-6 also plays a role in hepatocyte proliferation.

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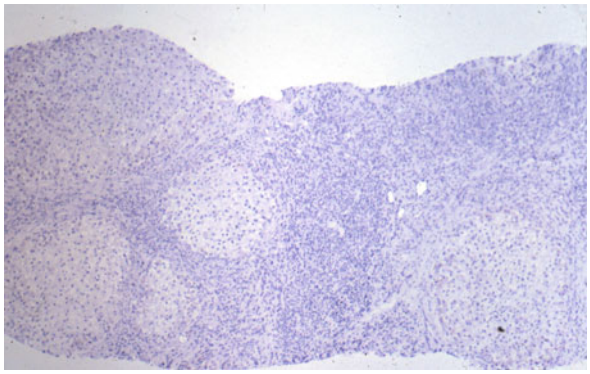

Figure 212.1
Percutaneous liver biopsy. Microscopic findings of nodular cirrhosis with marked fibrosis and distortion of the hepatic architecture

Etiology

Cirrhosis in children may result from metabolic disorders, infectious diseases, inflammatory diseases, biliary abnormalities, toxins, and vascular diseases (*Table 212.1*).

Clinical Features

Cirrhosis in children is often compensated, presenting as asymptomatic hepatosplenomegaly, splenomegaly, or any other stigmata of chronic liver disease. Cirrhosis may be discovered incidentally by abnormal laboratory tests. Alternatively, patients may present with decompensated cirrhosis; with signs related to decreased hepatic synthetic function (e.g., coagulopathy, fat-soluble vitamin deficiency), or decreased detoxification abilities of the liver (e.g., hepatic encephalopathy), or portal hypertension (e.g., variceal bleeding, hypersplenism, ascites).

Moreover, patients with cirrhosis usually present with features of the primary disease, chronic hepatocellular failure, together with those of subsequent complications such as portal hypertension. There is also evidence of malabsorption, failure to thrive, and malnutrition.

Some patients may complain of abdominal pain, which may be due to peptic ulcer disease, gastritis, gallstones, or gastroesophageal reflux. Patients may also present with evidence of florid rickets (*Fig. 212.2*) or

Table 212.1
Causes of hepatic cirrhosis in children

Genetic/metabolic disorders
Alpha-1-antitrypsin deficiency
Cystic fibrosis
Fructosemia
Galactosemia
Gaucher disease
Glycogen storage diseases, types III and IV
Hemochromatosis
Histiocytosis X
Niemann-Pick disease
Tyrosinemia
Wilson disease
Wolman disease
Toxins
The yellow death-cap mushroom (*Amanita phalloides*)
Organic solvents
Hepatotoxic drugs (e.g., methotrexate, amiodarone)
Nutritional disorders
Hypervitaminosis A
Total parenteral nutrition
Malnutrition
Infectious diseases
Ascending cholangitis
Cytomegalovirus
Chronic hepatitis B,C
Herpes simplex virus
Congenital rubella
Biliary malformations
Biliary atresia
Caroli disease
Choledochal cyst
Alagille syndrome
Nonsyndromic paucity of bile ducts
Vascular diseases
Budd–Chiari syndrome
Congestive heart failure
Veno-occlusive liver disease
Venocaval web
Others
Neonatal hepatitis

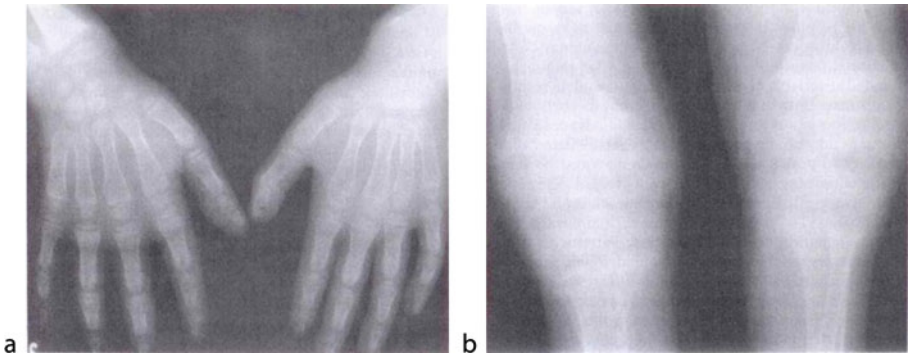

Figure 212.2
Plain radiograph in a child with cirrhosis showing features of florid rickets with poor mineralization of the bones and widening and fraying of the metaphysis of both wrists (a) and knee joints (b)

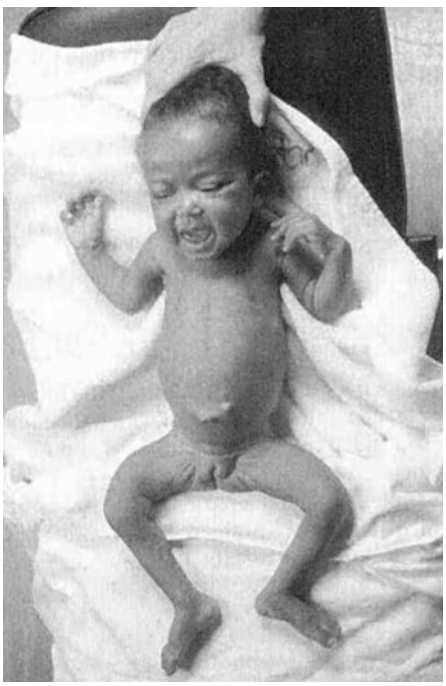

Figure 212.3
A young infant with cirrhosis and deformed right thigh as a result of pathologic fracture of the right femur secondary to florid rickets

even an associated pathologic fracture (*Fig. 212.3*). This is important to note at the time of examination and initial evaluation and to inform the parents of its presence.

Other recognized features include jaundice, spider hemangiomata, palmar erythema, and clubbing of fingers and toes.

In advanced liver disease, there are features of hyperdynamic circulation with increased cardiac output and decreased vascular resistance.

Hypoxemia, largely due to intrapulmonary shunting, is a relatively common complication of cirrhosis. Later on, peripheral edema, ascites, and hepatoencephalopathy develop. Spontaneous bruising, epistaxis, and septicemia are often indicative of serious outcome and grave prognosis.

Physical Examination: physical examination in patients with cirrhosis may reveal the following:

Jaundice, a yellow discoloration of the skin and mucus membranes secondary to increased serum bilirubin. Jaundice is usually not clinically detectable until the bilirubin is greater than 2–3 mg/dL.

Pruritus is intense generalized itching, possibly related to endogenous opioids, may be the sole presenting symptom of cirrhosis. The degree of pruritus is not directly related to the degree of hyperbilirubinemia.

Xanthomas are deposits of lipids in the dermis and subcutaneous tissue as a result of marked elevation of serum cholesterol due to chronic cholestasis. They are usually located over the extensor surfaces of the extremities.

Spider angiomata (also known as spider telangiectasias) are vascular lesions consisting of a central pulsating arteriole from which many smaller vessels radiate. Spider angiomata are most commonly located on the trunk, face, and upper limbs, and are believed to result from

alterations in sex hormone metabolism associated with an increase in the estradiol/free testosterone ratio.

Spider angiomata are not specific for cirrhosis and may be seen in otherwise healthy individuals as well as during pregnancy and in patients with severe malnutrition. The number and size of spider angiomata correlate with the severity of liver disease. Patients with numerous and large spider angiomata may be at increased risk for variceal hemorrhage.

Palmar erythema, most noticeable on the thenar and hypothenar eminences and on the tips of the fingers, is also believed to be caused by altered sex hormone metabolism and vasodilation with increased blood flow. Palmar erythema however is not specific for cirrhosis and can be seen in association with pregnancy, rheumatoid arthritis, hyperthyroidism, and hematological malignancies.

Nail changes, paired horizontal white bands separated by normal color nail plate (Muehrcke's nails), or whitish discoloration of the proximal two-thirds of the nail plate with the distal one-third being red (Terry's nails) can be seen in patients with cirrhosis. The exact pathogenesis for these nail changes is unknown but believed to be caused by hypoalbuminemia. Clubbing and hypertrophic osteoarthropathy may also be seen in patients with cirrhosis though none of these nail features is specific for liver disease.

Gynecomastia is a benign proliferation of the glandular tissue of the male breast possibly caused by enhanced aromatization of androstenedione to estrone, and increased conversion of estrone to estradiol. Gynecomastia can be seen in a variety of conditions other than cirrhosis.

Caput medusae is the term used to describe the prominent abdominal wall veins that occur secondary to shunting of the blood from the portal venous system into the umbilical vein and ultimately to the abdominal wall veins. A venous hum may be auscultated. Dilated abdominal veins can also be seen in other diseases (e.g., inferior vena cava syndrome, superior vena cava syndrome).

Ascites is the pathologic accumulation of fluid in the peritoneal cavity, and in cirrhosis ascites is a sign of decompensated hepatic cirrhosis. (Further details on ascites will be presented later in this chapter).

Hepatomegaly may be detected on physical examination by assessing the hepatic span. The cirrhotic liver may be enlarged with a firm nodular consistency, or normal sized, or it may be small and shrunken.

Splenomegaly is common and is believed to be caused by congestion of the red pulp as a result of portal hypertension. However, splenic size does not correlate well with portal pressures, suggesting that other factors may be involved.

Fetor hepaticus is a sweet, pungent smell to the breath, caused by increased concentrations of dimethylsulfide that occur in cirrhosis secondary to severe portal-systemic shunting.

Encephalopathy, secondary to accumulation of ammonia, aromatic amino acids, gamma aminobutyric acid, and other substances that are normally removed by the hepatic cells, may occur with the loss of functioning liver parenchyma. Patients may present with altered mental status, neuromuscular dysfunction, or change in the level of consciousness.

Asterixis is bilateral, asynchronous flapping of outstretched, dorsiflexed hands, and can be seen in patients with hepatic encephalopathy. Astrexis is potentially reversible, and may also be seen in patients with uremia and severe heart failure.

Variceal bleeding, portal hypertension results in portosystemic blood shunting, leading to the formation of esophageal, gastric, and rectal varices. Those varices can rupture causing profuse gastrointestinal bleeding.

Hepatorenal syndrome refers to the development of renal failure in a patient who has advanced liver disease. The pathophysiology is poorly defined and may be related to reduced renal blood flow and altered hormonal metabolism. The urinary sodium concentration is low, and the sedimentation is normal. Serum creatinine is increased. The diagnosis is achieved after excluding other causes of renal failure. Kidney function usually improves after liver transplantation.

Hepatopulmonary syndrome patients develop intrapulmonary arteriovenous shunts with resultant hypoxemia and cyanosis. The diagnosis is established by ruling out an underlying cardiac defect.

Diagnosis

Diagnosis may be easy if the liver is enlarged, hard, and irregular. Laboratory investigations indicate varying degrees of hepatic dysfunction. Protein electrophoresis may reveal hypoalbuminemia with normal or increased gammaglobulins. Serum complement component C3 may be decreased, while serum alkaline phosphatase is often elevated. The prothrombin time is frequently prolonged. Serum transaminases may be normal or increased.

Aminotransferase: The intracellular hepatic transaminases, aspartate aminotransferase (AST), and alanine

aminotransferase (ALT) are sensitive indicators of hepatocellular injury. AST elevation is not specific for liver disease. ALT, however, is more specific.

Markedly elevated aminotransferase levels occur with acute hepatocellular injury, such as acute viral hepatitis, hypoxia, or toxic injury. In chronic liver disease, the levels are usually mildly to moderately elevated. Normal aminotransferase levels do not rule out cirrhosis.

Alkaline phosphatase (ALP): ALP is often elevated.

Gamma-glutamyl transpeptidase (GGT): GGT levels often correlate with the level of alkaline phosphatase.

Bilirubin: Bilirubin level may be normal in compensated cirrhosis, but rise as the cirrhosis progresses.

Albumin: Albumin is synthesized exclusively in the liver, and its level falls with the loss of hepatic parenchyma. Thus, serum albumin can be used to assess the liver synthetic ability and grade the severity of cirrhosis. Hypoalbuminemia is not specific to liver disease and may be seen in nephrotic syndrome, protein-losing enteropathy, and malnutrition.

Prothrombin time (PT): Loss of the hepatic parenchyma in cirrhosis causes decline in the liver's synthetic ability and may result in deficiency of the clotting factors that are synthesized by the liver (all coagulation factors except factor VIII). This results in prolongation of PT.

The liver also synthesizes inhibitors of coagulation including protein C and S, plasminogen, and antithrombin III.

Hematologic abnormalities include thrombocytopenia, which results from platelets sequestration in the enlarged spleen. Anemia may result from gastrointestinal blood loss, hypersplenism, bone marrow suppression or inflammation (anemia of chronic disease). Leukopenia and neutropenia may occur secondary to hypersplenism with splenic margination.

Testing for specific diseases guided by the available information from the history, physical examination, laboratory and radiologic tests, should be performed (◉ *Table 212.2*).

Table 212.2
Investigation of chronic liver disease in children

General	Specific
Bilirubin	*Infections*
AST, ALT	HBV: HBsAg, HBeAg, HBe antibody, HBV DNA
ALP, GGT	
Albumin	HCV: HCV Ab, HCV RNA
Prothrombin time (PT)	CMV: CMV serology, urine for CMV antigen
Cholesterol	
Complete blood count	EBV: EBV serology, heterophile
Urea and creatinine	Wilson's disease: serum copper, serum ceruloplasmin, 24-h urine collection for copper, slit-lamp examination, liver copper concentration
Ammonia	
Alpha-fetoprotein	
Chest X-ray	Autoimmune chronic active hepatitis: ESR, ANA, anti-smooth muscle antibody, antimitochondrial antibody, anti-liver-kidney microsomal antibody
Hepatobiliary and renal ultrasound	Glycogen storage disease: lactic acid, fasting blood sugar, uric acid, liver and muscle tissue enzyme level
Electrocardiogram	Galactosemia: urinary non-glucose reducing sugar, red blood cell galactose-1-phosphate uridyl transferase level
Electroencephalogram	Tyrosinemia: serum amino acid levels, urine organic acids
Upper endoscopy	Alpha-1 antitrypsin deficiency: serum alpha 1-antitrypsin level, Pi type
Liver biopsy	Hemochromatosis: serum iron, TIBC, ferritin
	Cystic fibrosis: sweat chloride test, genotype analysis
	Toxic ingestion: toxic screen, serum acetaminophen level

Radiographic Findings

Although radiographic findings can occasionally suggest the presence of cirrhosis, they are not adequately sensitive or specific for use as a primary diagnostic modality. The major utility of radiography is in the evaluation of the presence of complications in cirrhotic patients.

Ultrasonography: An abdominal ultrasound can reveal the presence of ascites, splenomegaly, portal vein thrombosis, or cystic malformations, and should be routinely obtained. An increased diameter of the portal vein and the presence of collateral veins suggest portal hypertension.

Ultrasonography may also be used as a screening test for hepatocellular carcinoma.

A barium meal may show esophageal varices (◉ *Fig. 212.4*) and peptic ulceration. Flexible fiberoptic endoscopy is performed to confirm varices, assess its severity, and identify the site of bleeding.

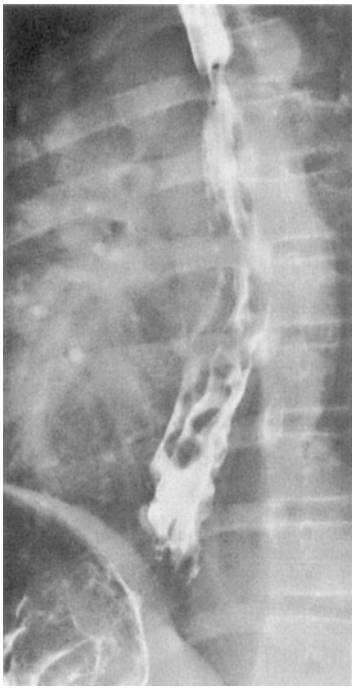

Figure 212.4
Barium study (esophagogram) showing longitudinal mucosal defects in the distal half of the esophagus: Esophageal Varices

CT scanning provides similar information to ultrasonography, and is not routinely used in the diagnosis and evaluation of cirrhosis.

Magnetic resonance imaging provides similar information to ultrasonography, and is not routinely used in the diagnosis and evaluation of cirrhosis.

MRI may reveal iron overload and provide an estimate of the hepatic iron concentration in patients with hemochromatosis.

MR angiography can be used to diagnose portal vein thrombosis and is more sensitive than ultrasonography.

Biliary scintiscan may be obtained in infants suspected of biliary atresia.

Liver Biopsy

The gold standard for diagnosis of cirrhosis is by histological examination of the hepatic tissue. A liver biopsy can be obtained either by a percutaneous, transjugular, laparoscopic, or radiographically guided fine-needle approach. The severity and sometimes the etiology of cirrhosis can be suggested by the histological examination of a liver biopsy (e.g., hemochromatosis, Wilson's disease, and alpha-1 antitrypsin deficiency).

Management

Management of cirrhotic patients is very much oriented toward prevention and treatment of life-threatening complications such as portal hypertension, gastrointestinal hemorrhage, hypersplenism, and hepatic encephalopathy. Increased awareness of the possible etiologic factors and initiation of appropriate therapy in the course of the disease influence the outcome of management of relevant conditions associated with cirrhosis. Careful monitoring of the hepatic status with periodic physical examinations and liver function tests are essential steps in the management.

Special emphasis should also be put on the dietary regimen of the patients to ensure adequate nutrition and optimal growth. The caloric intake may be increased with the supplement of glucose polymers and medium-chain triglycerides.

Caloric supplementation to achieve 120–130% RDI should be instituted, providing 3–4 g/kg/day of protein. This can be achieved by nocturnal enteral nutrition.

Parenteral vitamin K (2.5–5 mg/day) should be given to any patient with prolonged PT. Fresh frozen plasma infusions and cryoglobulin and/or platelet transfusions should be reserved for bleeding episodes and for patients undergoing invasive procedures such as liver biopsy.

Vitamin D (50 ng/kg), vitamin E (50–400 IU/day), and vitamin A (5,000–10,000 IU/day) should be supplemented.

Zinc deficiency commonly occurs in patients with cirrhosis, and zinc supplementation may stimulate appetite. Zinc is also effective in treating muscle cramps and may be used as an adjunctive therapy for hepatic encephalopathy.

Patients with cirrhosis, especially those with biliary cirrhosis, may also suffer from intractable pruritus that fails to respond to various medical therapeutic modalities. Cholestyramine, phenobarbitone, and/or rifampicin have been tried in this regard with variable degrees of response. Cholestyramine in a dose of 4 g given with meals two to three times daily is recommended for children with cirrhosis not only to relieve pruritus but also to improve liver function in patients with postnecrotic cirrhosis.

Spontaneous bacterial peritonitis is best treated as dictated by bacteriology. Early institution of therapy with a third-generation cephalosporin (such as cefotaxime

or ceftriaxone) is recommended. Prophylactic treatment for recurrent cases can be achieved by oral cotrimoxazole, ciprofloxacin, or norfloxicin.

Hepatic encephalopathy can be managed by avoiding triggering factors like fasting, sedatives, and by reducing the intestinal nitrogen load.

Since protein restriction in children may result in growth failure, dietary and/or intravenous protein restriction to 1–2 g/kg should be used only in acute or very symptomatic patients. The protein should be reintroduced as the encephalopathy subsides.

Administration of neomycin with or without lactulose can reduce intestinal bacterial flora, thus reducing the amount of bacterial urease and ammonia formation. Lactulose, an unabsorbable sugar, is metabolized by colonic bacteria producing lactic acid, which results in a drop in pH in the colon and a reduction in ammonia reabsorption.

In cases where an acute encephalopathy is precipitated by gastrointestinal bleeding, a reduction in the intestinal protein load can be achieved by enemas.

Monitoring Patients with Cirrhosis

Routine monitoring with complete blood count, renal and liver chemistries, and prothrombin time should be performed (e.g., q3–4 months in stable patients).

Diagnostic endoscopy to determine if the patient has asymptomatic esophageal varices may be done. Patients with varices may be started on a nonselective beta-blocker (e.g., propranolol, nadolol), titrating the dose to achieve a 25% reduction in heart rate.

Patients should be monitored for the development of hepatocellular carcinoma by abdominal sonography and alpha-fetoprotein testing every 1–2 years.

Ascites

Ascites is an accumulation of fluid, usually serous, in the peritoneal cavity. The causes of ascites are not limited to gastrointestinal conditions, but may occur in diseases affecting other systems such as the renal and the cardiac systems. Other recognized causes of ascites include peritonitis, especially tuberculous peritonitis, rheumatic peritonitis, and tumors. The emphasis in this chapter is on ascites that develop as a result of gastrointestinal and hepatic disorders. Progressive liver diseases leading to cirrhosis and portal hypertension are usually associated with ascites.

Pathogenesis

The exact mechanism leading to ascites in liver disease is not fully understood. Certain recognized factors and pathogeneses could well contribute to the formation of ascites in gastrointestinal and hepatic disorders. The accumulation of ascites represents a breakdown of intravascular volume homeostasis. It has been recognized that the renin-aldosterone-angiotensin system, sympathetic nervous system activity, and arginine vasopressin release are the main regulators of the plasma volume.

Hypoalbuminemia

This is a well-recognized condition associated with ascites. Hypoalbuminemia can occur in gastrointestinal and hepatic disorders, as well as in renal and cardiac diseases. Fluid is accumulated in the peritoneal cavity due to reduced oncotic pressure of the plasma. Albumin may be lost through the gut due to any of the recognized conditions associated with protein-losing enteropathy or in urine as in nephrotic syndrome. In the developing countries, dietary causes associated with protein caloric malnutrition, such as in kwashiorkor, should also be considered. With the progress of liver disease, there will be reduction in albumin synthesis, which results in reduction of the intracapillary oncotic pressure with extravasations of fluid into the peritoneal cavity resulting in ascites formation.

Disturbances in Water and Electrolytes Distribution

Chronic liver disease is a recognized cause of increased production of aldosterone plasma renin, as well as antidiuretic hormone, resulting in further sodium and water retention. Capillary hydrostatic pressure and plasma colloid osmotic pressure are involved in controlling fluid movement between blood and tissue.

Increased hydrostatic pressure in hepatic sinusoids such as in hepatic vein obstruction (Budd–Chiari syndrome) results in severe ascites with respiratory distress. This mechanism in the formation of ascites constitutes the basis of the *underfilling hypothesis* in which increased sinusoidal pressure is claimed to contribute to fluid retention and ascites formation.

The underfilling hypothesis suggests that ascites due to portal hypertension and inappropriate sequestration of

fluid within the splanchnic vascular bed results in a decrease in effective circulating blood volume and renal perfusion, which in turn causes increase in plasma rennin and aldosterone, resulting in sodium and water retention. This hypothesis could not explain all points regarding the pathogenesis of ascites.

The overfill hypothesis suggests that the primary abnormality is inappropriate renal retention of sodium and water in the absence of volume depletion, leading to increased blood volume. The increased blood volume in combination with portal hypertension results in ascites. This theory was developed in accordance with the observation that patients with cirrhosis have an intravascular hypervolemia rather than hypovolemia.

The peripheral arterial vasodilation hypothesis is the most widely accepted theory of ascites formation, and suggests that portal hypertension leads to increased production of vasodilators, mainly nitric oxide, leading to arterial vasodilation, which causes decreased effective blood volume. As the disease progresses, activation of vasoconstrictor and antinaturetic factors occurs, resulting in sodium and water retention.

Spontaneous bacterial peritonitis is a potentially fatal complication of ascites in children. It should be suspected in patients with ascites, fever, abdominal pain, or neutrophilia. Occasionally, patients present only with fever. The diagnosis is achieved by abdominal paracentesis, which is characterized by a cloudy fluid with a neutrophil count of >250/mm, and a protein concentration <20 g/l. Spontaneous bacterial peritonitis is usually caused by a single species, often enteric bacteria such as *Klebsiella* spp., *E. coli*, or enterococcus. Infection with *streptoccocus pneumoniae* may also occur.

Clinical Features

The child with ascites due to gastrointestinal or hepatic disorders should be evaluated at the time of examination together with the other associated manifestations secondary to the underlying disease. The onset of ascites may be slow and insidious, or sudden with rapid increase in abdominal girth such as in cases of hemorrhage, sepsis, or acute portal vein thrombosis.

The clinical features of ascites do not differ greatly from those due to other recognized causes such as in cardiac and renal disorders. Inappropriate weight gain may be the first clinical feature of ascites formation. The abdomen is distended at variable degrees, which might result in respiratory distress. Intra-abdominal organs may be ballotable, as ascites formation continues, although in advanced cases the organs may not be palpable at all. Visible dilated veins secondary to portosystemic collaterals may also be seen. The umbilicus may be flattened or even everted. The abdomen may appear shiny with severe distention and sometimes associated with umbilical, inguinal, or femoral hernia (Fig. 212.5).

Palpation, which may be associated with some discomfort, reveals fluctuation of the fluid. Percussion over the umbilical area may be resonant, but increased tone of dullness will be noted as the percussion proceeds toward the flanks. Shifting dullness is detected with changing the position of the patient. When the fluid collection in the peritoneal cavity is massive, the examiner is able to detect transmitting thrill by placing an assistant hand firmly over the midline and tapping on one side with one hand with the other hand receiving the impulse on the other side.

Other associated features of the primary liver or gastrointestinal disorders such as muscle wasting, jaundice, clubbing, or hepatosplemegaly should be looked for in the overall evaluation of the child with ascites. Edema is precipitated by hypoproteinemia or venous obstruction. Examination should also include the chest to rule out associated pleural effusion or pneumonia. It should also

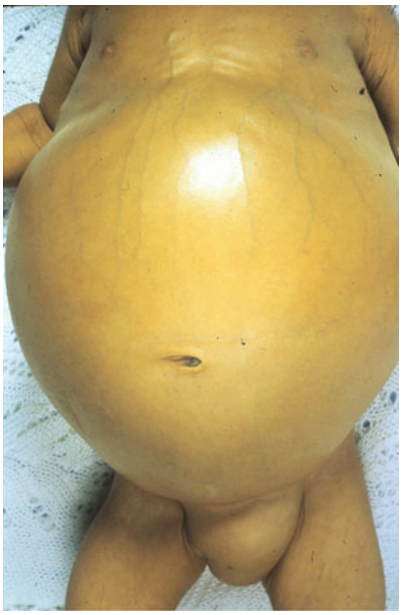

Figure 212.5
A young infant with neonatal hepatitis syndrome showing tense ascites, flat or everted umbilicus, and left inguinal hernia

ensure exclusion of other conditions associated with abdominal distention such as bladder distention, obesity, fecal distention, tumor masses, or gaseous distention of the gut.

Diagnosis

Ascites is a clinical condition, the diagnosis of which requires only a few diagnostic measures beyond a thorough clinical examination. Usually, the clinical features stated above are sufficient to diagnose the patient as having ascites. Ultrasound examination performed as part of the investigation of affected patients with liver disorder may reveal the presence of ascites at its early stage. Computed tomography is not performed routinely in the diagnosis of ascites. Its application or that of magnetic resonance imaging is mainly confined to identifying the cause or assessing the progress of the disease.

Diagnostic tapping of ascites is indicated in progressive liver disease, where there is a recognized risk of developing spontaneous bacterial peritonitis and to decide appropriately on therapy. The fluid is examined for cytology, protein content, leukocyte count, amylase, and culture as well as being examined for its color and consistency. Sterile ascitic fluid is usually clear and straw-colored but may sometimes be bile-stained with a protein content of less than 2.0 g/dL. Concentrations higher than 2.0 g/dL are consistent with infection or obstruction of hepatic vein (Budd–Chiari syndrome).

Spontaneous bacterial peritonitis may develop in the absence of localized intra-abdominal sepsis. It is associated with abdominal pain, tenderness, and fever. Abdominal ultrasound is indicated in the course of management to assess progress of the disease and rule out the development of abscess formation.

Management

Management of ascites should be part of the overall management of the primary liver or gastrointestinal disease. Management of ascites due to other causes is covered in the appropriate chapter. The outcome of the management is very much influenced by the status of the primary disease to the extent that occasionally treatment of the underlying cause may result in resolution of ascites, as in the case of ascites due to peritonitis. Evaluation of serum electrolytes, albumin, total protein, urea nitrogen, creatinine, and urine volume should be performed quite regularly, maybe daily in some cases.

Sodium intake is limited to 1–2 mEq/kg/day. In practice, a very low sodium intake is not always acceptable by the affected child as compared to the adult. Moreover, water restriction is only enforced in cases of hyponatremia.

In end-stage liver disease with ascites, the optimum therapy is liver transplantation, short of which the management is mainly to relieve the patient's distress and minimize the risk of associated complications. In spite of the above, the physician while managing a patient with ascites and severe abdominal distention is obliged to try and alleviate the symptoms by applying certain therapeutic modalities as follows:

Diuretics

Aldosterone antagonists, thiazides, and loop diuretics are the most commonly used diuretics in children with ascites to achieve a negative fluid balance. An aldosterone antagonist (spironolactone) is usually prescribed for patients with ascites and liver disorders. It has the advantage of a potassium-sparing effect, which is useful for such patients known already to be prone to potassium depletion. The required dose varies with the severity of the condition and the associated side effects of therapy, especially hyponatremia. The average dose is about 3 mg/kg/day in two to three divided doses. The physician should allow a few days for the drug to show its effect on ascites before resorting to increasing the dose if the patient's condition permits. However, the dose may still have to be increased to achieve negative fluid balance.

In cases of severe ascites where spironolactone administration is not effective, addition of thiazide diuretics or loop diuretics (furosemide) is advisable, provided the patient is receiving satisfactory evaluation, especially for any potential electrolytes disturbances such as hypokalemia, which is known to aggravate hepatic coma. Potassium supplement may be necessary in some cases.

Moreover, it has been recognized that furosemide increases ammonia production, which could contribute to the development of hepatic encephalopathy. The starting dose of furosemide in infants and young children is 1 mg/kg/day increased gradually up to 5 mg/kg/day.

Thiazide diuretics have also been used with spironolactone in children with ascites. The usual starting dose of hydrochlorothiazide in children is 2 mg/kg/day. Triamterene may be prescribed to enhance potassium retention. In case of associated renal failure, diuretic therapy ought to be stopped.

If the above measures are inadequate in alleviating the child's symptoms, salt-free albumin transfusion in a dose up to 1 g/kg is required to be infused over a few hours with simultaneous furosemide infusion.

Abdominal Paracentesis

Abdominal paracentesis to drain a large volume of the ascitic fluid is occasionally required in the treatment of tense ascites refractory to the above-mentioned therapeutic measures. Studies have demonstrated that large-volume paracentesis when combined with intravenous infusion of albumin can be safely performed on children with massive ascites and respiratory distress. However, because of the availability of fairly effective drug therapies in most cases of childhood ascites with early recognition and management, the need for total paracentesis or even large volume is rarely necessary nowadays except perhaps in those with respiratory compromise.

Surgery

In refractory ascites, peritoneovenous shunt (LeVeen shunt) is performed. The excess fluid is drained extraperitoneally into the internal jugular vein, resulting in rapid resolution of ascites. The use of this device is not without major complications such as coagulopathy and infections. Long-term prognosis after such an operation remains very much determined by the underlying disease contributing to ascites formation.

Chylous Ascites

This is a congenital or acquired condition with accumulation of chylomicron-rich lymphatic fluid within the peritoneal cavity, resulting from obstruction or disruption of abdominal lymphatic channels.

Chylous ascites may he precipitated by trauma, neoplasms, or obstruction to the abdominal portion of the thoracic duct. The condition may also be associated with accumulation of the chyle in the thorax (chylothorax). Diagnostic aspiration of the fluid is needed to establish the milky appearance of the ascitic fluid with an increase in its fat content.

The incidence of spontaneous chylous ascites in patients with chronic liver disease is estimated to be 0.5–1%, and results from rupture of the serosal lymphatic channels secondary to portal hypertension. It is generally believed that the incidence has increased due to the longer survival of patients with cancer and more aggressive abdominal and cardiothoracic interventions.

The most common causes of chylous ascites in developed world are abdominal malignancy and cirrhosis, in contrast to infectious etiologies in the developing world.

Other causes include congenital, inflammatory, traumatic, postoperative, and miscellaneous disorders. Peritoneal tuberculosis and filariasis are the common infectious causes of chylous ascites.

Congenital lymphatic abnormalities are more common in the pediatric age group.

Chylous ascites can occur early after abdominal surgery due to disruption of the lymphatic vessels or late due to adhesions or extrinsic compression of the lymphatic vessels.

Chylous ascites is a rare complication following liver transplantation.

The diagnosis of chylous ascites is made by paracentesis, which shows a milky ascetic fluid with a specific gravity of 1.010–1.054 and total fat content of 4–40 g/l. Triglyceride level is greater than 110 mg/dl, and the cholesterol level is usually low. Lymphangiography is the gold standard in defining cases of obstruction and to identify leak sites, but it is associated with several complications such as tissue necrosis, fat embolism and hypersensitivity related to the volume and type of contrast used. Palmitic acid, a long-chain fatty acid which enters directly into the intestinal lymph trunk after absorption, has been used labeled with 13C, to detect chyle leaking from the intestinal lymphatic system, to help determine the site of leakage and the degree of obstruction. It can be used in patients who had negative results with isotope examination and lymphangiography.

Management is primarily medical with a high-protein diet and medium-chain triglyceride-based low-fat diet to ensure its absorption through the portal circulation and not the systemic circulation. Treatment with high-protein diet and low fat diet with mCT reduces the production and flow of chyle. Dietary restriction of long-chain triglycerides (LCT) avoid their conversion into monoglycerides and free fatty acids (FFA), which are transported as chylomicrons to the intestinal lymph ducts. As with other forms of ascites, the indication for paracentesis is basically limited to those patients with massive ascites and respiratory distress.

Somatostatin and total parenteral nutrition are an effective option for the treatment of chylous ascites after living donor liver transplantation.

In patient with cirrhosis and chylous ascites refractory to medical therapy insertion of transjugular intraheptic portosystemic shunt (TIPS) may be effective in reducing ascites significantly by decreasing portal pressure.

Fibrin glue application on absorbable mesh after dissection of the leakage zone is easy, safe, and effective. It is recommended that surgery with glue application to be repeated until control of ascites is achieved. Furthermore, fibrin glue application has been recommended as a preventive measure against postoperative chylous ascites. Laparoscopic surgery, instead of open surgery, has been recommended as a treatment of choice for intractable chylous ascites. Intractable chylous ascites may also respond better to combination of octreotide and total parenteral nutrition.

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213 Budd–Chiari Syndrome

Hisham M. Nazer

Definition

Budd–Chiari Syndrome (BCS) is a rare disorder characterized by venous outflow obstruction either at hepatic veins or inferior vena cava associated with blood clots that completely or partially block the hepatic vein anywhere between the efferent hepatic vein and the entry of the inferior vena cava to the right atrium. BCS is rarely associated with portal vein thrombosis.

Etiology

Hepatic vein occlusion may result from various clinical conditions such as polycythemia, leukemia, neoplasms (e.g., hepatoma and hypernephroma), systemic lupus erythematosus, infections, membranous obstruction of the inferior vena cava, and trauma. However, no definite cause can be found even at autopsy in a majority of cases. The obstruction to the hepatic vein may also be caused either by compression from outside or by invasion by tumor or thrombi.

Other recognized causes of BCS include thrombophilic conditions, chronic inflammatory disease like Behcets syndrome, inflammatory bowel disease, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinemia, veno-occlusive disease, and hypereosinophilic syndrome. Other inherited and hypercoagulable states may also predispose to thrombosis (protein C or S deficiency, antithrombin III deficiency, etc.). A similar picture of BCS has been observed in association with primary pulmonary hypertension, constrictive pericarditis, and right atrial myxoma.

Hepatic vein thrombosis has also been reported in neonates with gastroschisis or large omphalocele after surgical repair and in older children following some herbal ingestion. Enlargement of the caudate lobe is a recognized potential cause of obstruction to the inferior vena cava or hepatic veins.

Pathology

The histopathologic changes of the liver in BCS are affected by the time interval between the onset of symptoms and the time of the biopsy. Early in the disease, the changes are usually those of severe central venous congestion, centrilobular hemorrhage, and necrosis. Later on, the hepatic cells in the central zones may resemble ghost cells, and thrombi may be found in some of the larger hepatic veins. The thrombus may contain malignant cells or inflammatory cells.

The primary lesion shows intimal thickening and fibrous obliteration of the ostium of the major hepatic veins or intrahepatic portion of the inferior vena cava.

The liver is enlarged and smooth. BCS is associated with progressive liver disease leading to cirrhosis. There is a marked central venous congestion with hepatocellular necrosis with endothelial thickening and fibroblastic proliferation.

Clinical Manifestations

The clinical presentation is highly variable and may be categorized as acute, and perhaps fulminant hepatic failure, as subacute without evidence of cirrhosis, or as chronic with evidence of portal hypertension and cirrhosis.

The most common features in BCS include abdominal distention with pain, marked hepatomegaly, and ascites. Other recognized features of BCS include nausea, vomiting, diarrhea, edema of the legs and those of portal hypertension as esophageal varices, massive hemorrhage, splenomegaly, mild jaundice, and distended abdominal veins. In progressive condition, hepatic failure may develop with a fatal outcome.

Diagnosis

BCS is characterized by venous outflow obstruction either at hepatic veins or inferior vena cava. The diagnosis of BCS is highly suspected in the presence of the above-mentioned clinical manifestations. The goal of the initial evaluation of a patient with suspected BCS is to determine the cause and level of obstruction.

Liver function tests reveal mild elevations of serum bilirubin, alkaline phosphatase, aspartate transaminase, low albumin, and prolongation of the prothrombin time.

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Computed tomography or magnetic resonance imaging with contrast demonstrates no visualization of the hepatic veins. Liver scintigraphy reveals diminished uptake in the right and left lobe and increased uptakes in the caudate lobe since it drains directly into the inferior vena cava.

Hepatic vein catheterization with pressure measurement and hepatic venography contribute further to the diagnosis. Wedged hepatic vein pressures and venograms from the wedged position are helpful. These are not possible if the obstruction is in the hepatic portion of the inferior vena cava. Saphenous or femoral vein studies may show complete obstruction of the vena cava.

Occasionally, obstruction of the infra diaphragmatic portion of the inferior vena cava may result from massive ascites precipitating increased intra-abdominal pressure.

Open liver biopsy is recommended to confirm the diagnosis. There has been some concern about the percutaneous liver biopsy because of potential increased risk of bleeding due to elevated intrahepatic venous pressure and liver engorgement. Histologic findings include sinusoidal dilatation with centrilobular congestion and minimal inflammation.

Management

Management of BCS depends on the underlying cause, anatomic location, the extent of the thrombotic process, and the functional capacity of the liver. It can be divided into medical, radiological, and surgical.

Medical treatment, including anticoagulation and thrombolysis, starts at the time of diagnosis initially with low-molecular heparin and switching to oral agents after an average period of 2 weeks.

The use of warfarin for anticoagulation proved to be simple, safe, and feasible for BCS with chronic IVC thrombosis.

Spontaneous fibrinolysis of IVC thrombus occurs within 1 year in the majority of the patients treated with warfarin.

Major bleeding is common in BCS patients receiving anticoagulant therapy. Invasive procedures and portal hypertension are major factors while excess anticoagulation plays a contributory role.

Radiological therapeutic intervention is feasible and safe in children with BCS. Radiological intervention in the form of balloon angioplasty or transjugular intrahepatic portosystemic shunt (TIPS) gives good results in a subgroup of BCS patients. Complete disappearance of the thrombosis may be successfully achieved with balloon dilatation.

Pulmonary embolism is one of the major complications after percutaneous balloon angioplasty for BCS. Pretreatment with warfarin may prevent such complication.

Transjugular intrahepatic portosystemic shunt (TIPS) is a minimally invasive vascular and interventional radiological procedure. TIPS could be regarded as a definitive treatment option in BCS.

TIPS seems to have replaced surgical shunting as the most common invasive therapeutic procedure. The overall results of stenting/TIPS are better than angioplasty and surgical intervention including orthotopic liver transplantation.

Surgical: Various surgical procedures have been suggested and implemented in cases of BCS with variable degrees of success. Failure to relieve the obstruction through various surgical modalities may result in hepatic failure and death.

Portacaval shunt (side-to-side anastomosis) is the operation of choice in most cases; however, mesocaval shunt provides good results in selected cases. Orthotopic liver transplantation (OLT) should be limited to patients who cannot be managed by TIPS.

The prognosis in some cases of BCS with progressive liver disease has been very much improved with liver transplantation. Liver transplantation can be an effective treatment, particularly for people with severe liver failure and those with deteriorating liver function and complications.

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214 Portal Hypertension and Esophageal Varices

Mohamed A. El Guindi · Hisham M. Nazer

Over the past several years, there has been a noticeable progress in the field of portal hypertension especially in its management. Such progress has also benefitted the overall management of esophageal varices especially during its episodes of hemorrhage. The implementation of beta-blockers in the overall management of esophageal varices variceal and the establishment of endoscopic variceal band ligation in the management of acute variceal bleeding have become the mainstays of clinical management of children with portal hypertension.

Embryologically, the portal system in also unique, as it develops from the extra-embryonic vitelline and umbilical veins draining from the yolk sac and the placenta, in contrast to the systemic which develop from the intraembryonic anterior and posterior cardinal veins. Thus, any umbilical infection or intervention could affect the portal venous system. The portal vein is formed by the uniting of the splenic vein with the superior mesenteric vein which occurs mostly in the retroperitoneal area of the pancreas. It is the main transporter of blood from the gastrointestinal tract and the spleen to the liver.

The liver has a unique blood supply consisted of two afferent vessels, a portal vein and a hepatic artery, and an efferent vessel the hepatic vein. Then portal vein represents the main blood supply to the liver around 70% leaving the other 30% to the hepatic artery. Thus, any burden on the portal vein would have its impact on the liver blood supply and any burden on the liver would have its impact on the portal pressure. Another unique feature is that the portal venous system is the only venous system in our body, which begins with capillaries and ends with capillaries. The intrahepatic branches of the portal vein terminate in small vessels forming the hepatic sinusoids.

Definition

Portal hypertension (PH) or, more strictly, portal venous hypertension, is defined as an increase in the intravascular pressure within the portal vein of over 11–12 mm of mercury as measured directly or a splenic pulp pressure of over 16 mm of mercury. The rise in portal pressure is not simply a consequence of an increase in systemic venous pressure, but it is intrinsically part of an increase in the pressure gradient between the portal venous inflow to the liver and its hepatic venous outflow.

A rise in the portal pressure leads to splenomegaly and the development of natural portosystemic shunts at the following sites:

- Gastresophageal varices at the lower end of the oeophagus and cardia through the gastroesophageal veins
- Fundal varices at the fundal area of the stomach below the cardia and to a lesser extent the body of the stomach and the duodenum through the gastric veins
- Anal hemorrhoids at the anal canal via the hemorrhoidal veins
- In the falciform ligament via the umbilical veins
- In the abdominal wall and retroperitoneum

In pediatric age group, esophageal varices are the most likely cause for large gastrointestinal bleeding. Variceal bleeding is associated with a mortality rate of around 7% in children with portal vein obstruction due to the massive bleeding and most probably the presence of fundal varices.

Portal hypertension is usually due to an extrahepatic or intrahepatic portal venous obstruction. Umbilical vein catheterization especially when it is associated with complications as obstruction or infection has been recognized as predisposing cause. Other associated causes include hepatic vein thrombosis (Budd–Chiari syndrome), portal vein thrombosis, schistosomiasis pancreatitis, hepatoveno-occlusive disease, tumors, and cirrhosis. Other well-recognized progressive liver disorders associated with portal hypertension include tyrosinemia, biliary atresia, α1-antitrypsin deficiency, cystic fibrosis, Wilson's disease, congenital hepatic fibrosis, and chronic active hepatitis. Those liver disorders have been covered in details elsewhere in this section.

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Classification

The causes of portal hypertension are classified into (1) posthepatic, (2) prehepatic, and (3) intrahepatic causes.

The intrahepatic causes can be further subdivided into presinusoidal, parasinusoidal, and postsinusoidal causes.

The major causes of posthepatic causes of PH are right-sided heart failure, constrictive pericarditis, and Budd–Chiari syndrome (BCS).

The prehepatic causes of PH include portal vein thrombosis (PVT) and portal compression or occlusion by biliary and pancreatic neoplasms and metastases.

PH may be caused by an increase in flow secondary to arterioportal fistula, pancreatic arteriovenous malformations, and massive splenomegaly. The most common intrahepatic cause is cirrhosis. The common feature of all the causes is an increase in resistance to portal venous flow, although in a few cases, increased inflow into the portal venous system is present.

The basis of PH in patients with cirrhosis is an increase in resistance to portal venous flow at the level of the sinusoids as a result of the perisinusoidal deposition of collagen leading to fibrosis and narrowing and compression of the central veins. Augmentation of such compression is due to the excessive regenerative nodule. Arteriovenous anastomosis in a fibrous scar would further increase the portal venous pressure.

The commonest cause of cirrhosis in neonates is biliary atresia. Besides this cause alpha-1- antitrypsin deficiency and metabolic liver diseases are the commonest medical conditions leading up to cirrhosis of the liver. Many of these patients have the stigmata of their underlying disease and the diagnosis of portal hypertension is not difficult.

The diagnosis may not be as clear in children with prehepatic PH. Portal vein thrombosis (pre-hepatic PH) may present within the first 5 years of life as a major hematemesis with only splenomegaly and a reduced platelet count as clues to the diagnosis. Many affected patients have no documented cause for their portal hypertension. However, at times, a history of umbilical vein canulation, abdominal infection, trauma, or pancreatitis may be responsible for the portal thrombosis. The liver size and function tests in such patients are essentially normal. A confirmation of portal vein occlusion will rely on Doppler and ultrasound demonstration of collateral venous channels in the porta hepatis replacing the occluded portal vein. Half of these patients have a history of umbilical vein catheterization or abdominal sepsis in the neonatal period, while the other half appears to be congenital in origin.

Congenital hepatic fibrosis may also present with the same picture of acute hematemesis and normal liver function tests but the difference would be in the clinical features which will include hepatomegaly. A liver biopsy shows bands of fibrous tissue joining the portal tracts and this condition may be associated with polycystic disease and other renal disorders.

Several studies have shown an idiopathic non-cirrhotic subendothelial thickening of intrahepatic branches of the portal vein causing presinusoidal obstruction to portal blood flow within the liver leading to the formation of collateral venous channels in the porta hepatis thus being named hepatoportal sclerosis.

Several studies in the Middle East and Asia have discussed a post-sinusoidal PH named veno-occlusive disease. This disease is claimed to be due to bush tea and herbs but no definite etiology has been definitely outlined. This can be of acute, subacute, or chronic onset of the disease leading to congestive hepatomegaly with ascites.

Suprahepatic obstruction caused by either an occlusion or a web in the inferior vena cava above the entrance of the hepatic veins or thrombotic occlusion of the hepatic veins (Budd-Chiari syndrome) is extremely rare in childhood. The clinical features may be mimicked by constrictive pericarditis but echocardiography and venography should make the diagnosis clear.

Clinical Features

The clinical features of PH depend, in general, on the etiology.

In portal venous occlusion: The presentation is usually in younger children (5 years) with acute episode of upper or lower gastrointestinal bleeding. This may or may not be accompanied by splenic enlargement depending on the blood loss due to the hematemesis or malena and the site of occlusion. The accompanying anorectal varices and hemorrhoids are present in more than half of patients with portal venous occlusion.

In older children suffering from chronic liver disease, *the intrahepatic PH* is presented mainly with abdominal distension due to hepatomegaly, splenomegaly, and/or ascites. Once hematemesis is present in those patients, encephalopathy together with the abdominal distension due to ascites may complicate the condition. Growth retardation is a well-recognized complication of cirrhosis and portal hypertension. In patients with post-sinusoidal and post-hepatic PH Budd–Chiari syndrome, intractable ascites with hepatomegaly is the usual initial presentation.

Investigations

Blood Investigations

Anemia and reduced WBC and platelet count are signs of hypersplenism. A bone marrow hyperactivity will differentiate hypersplenism from bone marrow depression. Plasma concentrations of procoagulant and anticoagulant proteins may be reduced in portal venous thrombosis or Budd–Chiari syndrome. Biochemical liver function tests are abnormal in cirrhosis, but are rarely deranged in portal venous occlusion. Serum albumin levels are depleted in acute variceal bleeding as well as in cirrhosis.

Ultrasound and Doppler Scan of Abdomen

Abdominal ultrasonography is used to identify hepatomegaly, cirrhosis, fibrosis (recently by fibroscan), large collateral veins, portal cavernoma, and splenomegaly. Ascites can be definitely identified and quantified by ultrasonography. Doppler studies provide the information about the direction, velocity, and waveform characteristics of vessels including portal blood flow.

In cirrhosis of liver, the maximum velocity of the blood flow in the main portal trunk is correlated to the portal pressure and inversely correlated with the severity of the liver disease. Budd–Chiari syndrome is diagnosed conclusively with Doppler sonography of the hepatic veins and the inferior vena cava.

Upper and Lower Gastrointestinal Endoscopy

This procedure is the cornerstone in the diagnosis and treatment of varices of the esophagus, stomach, the proximal duodenum, and the ano-rectal area. Several trials has been undergone to use noninvasive parameters for diagnosis of large esophageal varices of chronic liver diaseases, but all were not as accurate as endoscopy. In children, for safer and easier endoscopic procedure, the use of anesthesia or sedation is recommended.

Various grading systems are used in the assessment of esophageal varices in adults and adopted in children (*Fig. 214.1*).

Grade I: small varices which are bluish with a relatively thick mucosal covering

Grade II: larger ones may have signs of recent or impending bleed like "cherry red spots" leading next to

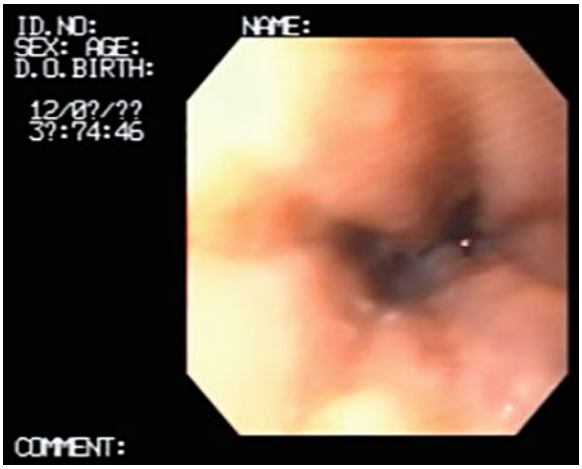

Figure 214.1
Esophageal varices grade II (Mohamed El Guindi 2010)

Grade III: confluent varices covering the whole circumference of the esophagus

Portal congestive gastropathy is characterized by mucosal hyperaemia with dilated submucosal veins.

Fundal varices are present just below the cardia and are isolated and should be differentiated from esophageal varices extended into the stomach due to difference in treatment.

Recently, capsule endoscopy is a useful diagnostic tool for all forms of varices especially the duodenal varices out of reach of upper endoscopy or in cases after devascularization and formation of intestinal varices.

CT Angiography and MRI Scan

The evolutionary modalities of multislice CT and MRI have replaced many of the conventional procedures. The above modalities are increasingly used in the diagnosis of Budd–Chiari syndrome and to identify liver lesions associated with portal hypertension like focal nodular regenerative hyperplasia. MR angiography is recently used as a noninvasive alternative to conventional angiography to delineate porto-mesenteric venous anatomy.

Inferior vena cavography with pressure measurements is valuable in patients with Budd–Chiari syndrome in whom hepatic venography can be used to assess hepatic venous patency. Balloon dilatation can be undertaken of inferior vena caval membrane or short segment narrowing of the hepatic veins, which can prove therapeutic.

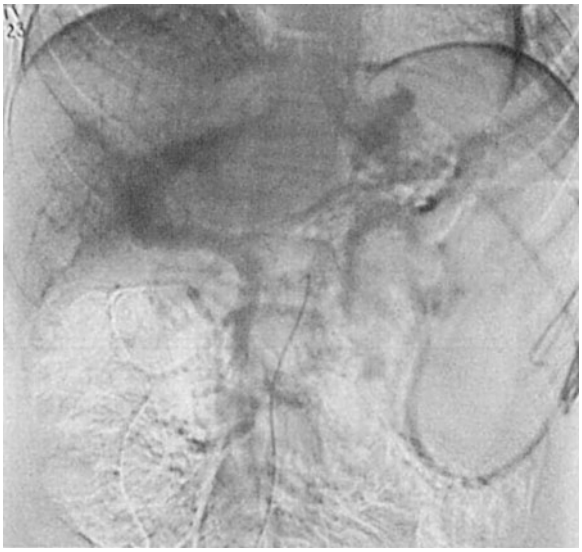

Figure 214.2
Superior mesenteric angiogram in a 13-year-old girl with hematemesis. There is patency of the mesenteric-portal varices. Retrograde flow to the splenic Collaterals and esophageal varices with irregular intrahepatic branches (Nazer)

Superior mesenteric angiogram is also performed to assess the size and patency of the superior mesenteric, splenic, and portal veins and to identify bleeding site (*Fig. 214.2*).

Treatment

As previously stated, the main aim of therapy is to promptly treat the serious complication of hematemesis and massive blood loss. Recent reports indicate that esophageal varices in childhood are well controlled with either injection sclerotherapy or banding and if this fails, portosystemic shunting would be the answer. Patients with portal vein obstruction and normal liver histology can be expected to live normal lives providing the esophageal varices are under control.

Medical Treatment of Variceal Bleeding

The cornerstone in treatment of acute variceal bleeding is endoscopic sclerotherapy or banding, therefore in areas where PH are prevalent, skilled and well-equipped endoscopic centers should be within accessible distances to improve morbidity and mortality outcomes. A delay in immediate management could prove fatal for a child.

Immediate medical measures include blood transfusion and the intravenous infusion of vasopressin (0.2–0.4 units/1.73 m/min) which may arrest the bleeding. Vasopressin has been used for decades in controlling gastrointestinal hemorrhage through its effect on blood flow and pressure through the portal circulation. It lowers the portal blood pressure by about 25–50% through splanchnic arteriolar vasoconstriction Vasopressin is a peptide produced by the posterior pituitary gland. It regulates the permeability of the collecting tubules of the kidney to water.

Vasopressin or its precursor, glyopressin may be used to reduce the portal venous pressure. These agents have tolerable side effects related to systemic vasoconstriction like headache, nausea, and abdominal cramps.

Somatostatin reduces splanchnic blood flow and portal pressure with minimal side effects, but it has a short half-life of less than 3 min. Octreotide, a long-acting analog of somatostatin, has a plasma half-life of more than 1 h and proved its safety and low side-effect profile thus encouraging its use in cases of acute variceal bleeding.

The use of Sengstaken-Blakemore (S-B tube) compression balloon has been minimized after the experience with endoscopes; however, it may still prove to be life-saving when there is a failure of visualization of the varices due to overwhelming hemorrhage.The risks involved in the usage of such instrument cannot be overemphasized. Correct placement of the gastric balloon must be checked with X-ray control in order to avoid the inflation within the lumen of the esophagus.

After stabilizing the child, continued bleeding should be controlled with injection sclerotherapy or by band ligation using the pediatric video endoscopes. General anesthesia should be advocated in all cases.

Endoscopic Intervention of Variceal Bleeding

Injection Sclerotherapy

Injection sclerotherapy was suggested for the treatment of esophageal varices in children because of failures and complications of primary surgery. Portosystemic shunt thrombosis and rebleeding, the hazards of splenectomy in children and long-term risks of encephalopathy all encouraged an alternative therapy.

Controlled trials in adult patients confirmed that early endoscopic sclerotherapy after the onset of bleeding significantly reduced the risk of rebleeding and may prolong survival in the cirrhotic. Injections are performed through

a flexible upper GI endoscope under general anesthesia. Intravenous sedation has been used occasionally in older children. A variety of sclerosants are available for esophageal varices including ethanolamine oleate, sodium tetradecyl sulpfate, sodium morrhuate, phenol in almond oil, and polidocanol (Fig. 214.3).

For gastric varices, intravariceal injection of *histoacryl and lipiodol* is the standard measure (Fig. 214.4). The recent results showed well-tolerated histoacryl with minimal complications. It is a life-saving procedure as the hemorrhage due the fundal varices is always life-threatening.

For esophageal varices, the injections are given either intra or para-variceal and are mostly given into the cardia and lower 3 cm of the esophagus. A maximum of 3 mL is injected into each varix to a maximum of 5–20 mL per session depending on the age and the size of the patient. A nasogastric tube is inserted in small infants to control the degree of gastric distension. The initial three injections are given at weekly intervals and subsequent treatments on a monthly basis until the varices are obliterated.

Mild symptoms of retrosternal discomfort and a transient fever are common after endoscopic sclerotherapy. The variceal hemorrhage may recur, particularly between the first two or three treatments, and esophageal ulceration may be followed by stricture formation and dysphagia. Rare serious complications have included broncho-esophageal fistula, chylothorax, and pericarditis. One case of paraplegia has been reported from injection of segmental spinal vessels.

An analysis of seven reports published since 1984 of the results of sclerotherapy in 248 children shows a mortality rate of 3% and a rebleed rate of 12%. The rebleed rate in a series of seven reports of surgery for portal hypertension (1980–1986) was 14%.

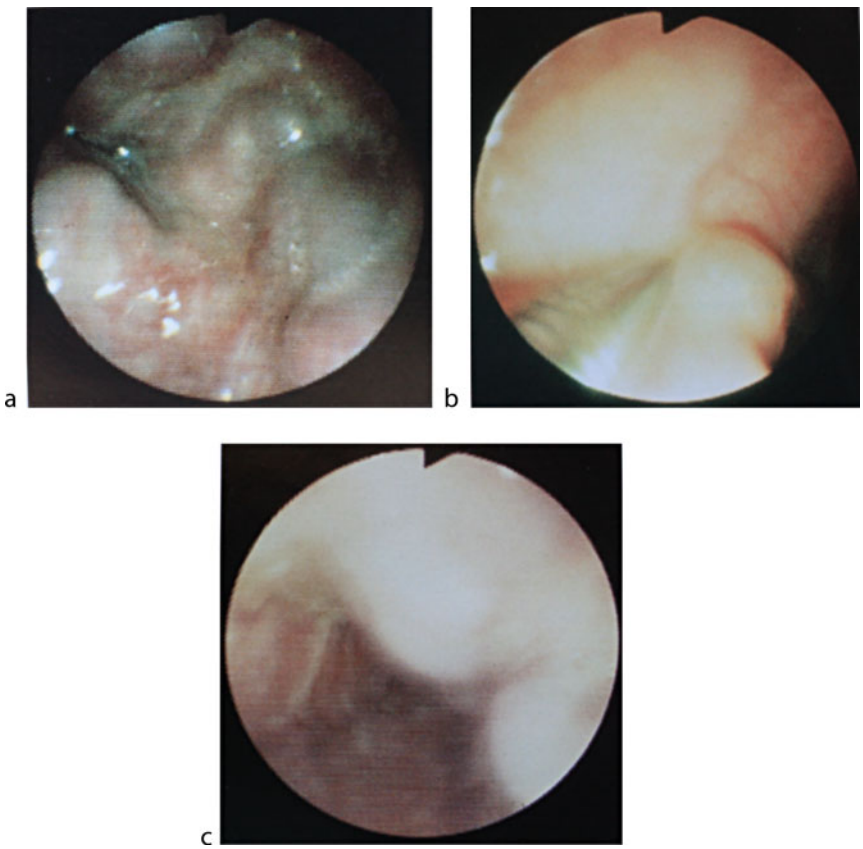

Figure 214.3

Endoscopic variceal sclerotherapy. (a) Endoscopic view of esophageal varices (b) Endoscopic sclerotherapy: note the blanching at the site of injection with polidocanol (c) Endoscopic view of postsclerotherapy. Note complete blanching at the site of the sclerosed varices (Nazer)

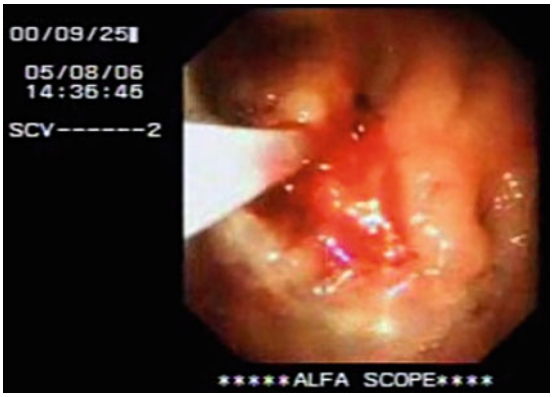

Figure 214.4
Gastric fundal varices with histoacryl injection (Mohamed El Guindi 2010)

Variceal Banding

The application of an elastic band to an esophageal varix is done through upper gastrointestinal endoscopes (*Fig. 214.5*). A device is loaded with multiple bands and then applied to the endoscope tip. The varix is sucked into the device and a band is fired to ligate the varix. Several bands can be are applied to a single varix and to all varices in each session. Multiband devices allow the application of several bands without the need for reloading. The strangulated ligated varix will be thrombosed and sloughed. Treatment is performed initially at 1–2 weekly intervals, extending to monthly intervals once the larger varices are treated. The incidence of esophageal stricture and systemic side effects is lower with this treatment modality. All reports showed superior results of banding versus injection regarding the numbers of sessions needed for obliteration and complications.

Partial Splenic Embolization (PSE)

Hypersplenism is one of the major complications of portal hypertension. Splenectomy had been the treatment of choice for severe hypersplenism owing to portal hypertension, but because of the risk of overwhelming sepsis after splenectomy, partial splenic embolization (PSE) has been used widely in patients with severe hypersplenism especially in small children. PSE proved to be a safe and effective procedure. Hematologic indices improve in all patients after PSE, and its long-term efficacy is shown in 70% of the survivors.

Transjugular Intrahepatic Portosystemic Shunt (TIPS)

Transjugular intrahepatic portosystemic shunt (TIPS) is considered a valid therapeutic option for the treatment of portal hypertension and its complications. This intervention includes the insertion of an expandable metallic stent connecting the hepatic to the portal vein through the percutaneous tranjugular route. Under fluoroscopic imaging, the procedure involves needle advancement over a guide wire into the hepatic vein and thence to the portal vein. A balloon catheter is subsequently inflated to dilate the intrahepatic tract and the stent is deployed.

The indications of TIPS in children include uncontrolled variceal bleeding especially the ones awaiting liver transplantation, thus working as a bridge procedure. Some patients of Budd–Chiari syndrome or intractable ascites may also benefit by this procedure. Portal vein thrombosis, bacterial sepsis, and coagulopathy are contraindications to TIPS.

TIPS, if correctly placed, has no adverse effect on the transplant operation. Close communication with the interventional radiologists who place TIPS is important in the overall management strategy. The concept that TIPS placed prior to transplant to relieve the portal hypertension would make transplant technically easier has not been well supported by data. TIPS is a nonsurgical means of diverting blood from the portal circulation through the hepatic parenchyma to the systemic circulation, thereby creating a portosystemic shunt. Where successful, this results in immediate decompression of the portal circulation and elimination of portal hypertension.

Surgery – Portosystemic Shunts

Endoscopic sclerotherapy with banding is an effective treatment modality of bleeding esophageal varices in most of children with reasonable liver function. However, a further step to TIPS, surgical intervention is indicated for the following cases:

- Uncontrolled bleeding from the not responding esophageal varices
- Bleeding gastric or ectopic varices not responding to endoscopic treatment
- Hypersplenism or massive symptomatic splenomegaly
- Lack of access to endoscopic treatment
- Symptomatic biliary obstruction due to choledochal varices
- Selected patients with Budd–Chiari syndrome

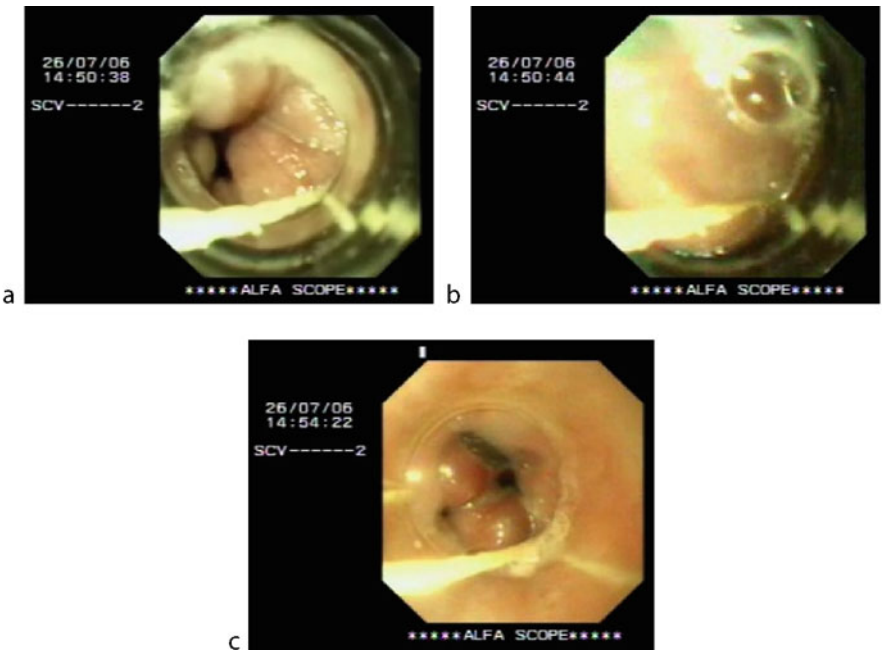

Figure 214.5
Band ligation of gastric varices as seen through a banding device before and after sucking of the varix and then the band applied (Mohamed El Guindi 2010)

The great variety of surgical procedures advocated for the management of portal hypertension was reflected in several studies due to the wide range of the pathology of the portal venous system and the preferences and experience of individual surgeons. Thirty different operations have been mentioned, which included a range of portosystemic shunts and various devascularization techniques.

The construction of a shunt between the superior mesenteric vein and the inferior vena cava using a segment of the internal jugular vein bypassing the liver seems to offer the best combination of long-term patency and the lowest incidence of rebleeding.

The complications of portosystemic shunting are not only concerned with rebleeding, which is minimal, but to more serious ones including deterioration of liver function and hepatic encephalopathy particularly in children with advanced cirrhosis.

Portosystemic shunt surgery should be regarded as a complementary therapy to endoscopic treatment. Porto-mesenteric venous anatomy does not permit successful shunt surgery in every child, and shunt thrombosis has been recorded with all types of shunts especially in smaller children.

The introduction of the mesoportal bypass or mesenterico-left portal (Rex) shunt is likely to broaden the indications once more for shunt surgery as the primary treatment for children with portal venous occlusion. This shunt utilizes an interposition graft between the superior mesenteric vein and the intrahepatic portion of the left portal vein, which is identified in the Rex recessus adjacent to the falciform ligament thus bypassing the thrombosed portal vein. By restoring hepatic portal blood flow and correcting portal hypertension, this technique is more physiological and obviates the potential disadvantages of the portosystemic shunts with close to cure after 5 years follow-up.

A percentage of these patients are not suitable for any form of shunt surgery due to advanced thrombosis and massive collaterals thus leading to some type of devascularization specially the esophageo-gastric devascularization. Most of the cases showed low incidence of rebleeding.

Liver Transplantation (LT)

Liver transplantation is the procedure of choice for patients with complications of portal hypertension associated with end-stage liver disease. This procedure is done using living related LT or cadaveric LT. Most countries are

using both procedures but in some countries living related LT is the only one used where segments of the liver are donated from a relative. The 5 years survival is relatively high reaching 70–80%.

Differential Diagnosis

The major differential diagnosis would be mainly related to those of hematemesis and melena.

In the esophagus the most common differential diagnosis to varices are reflux esophagitis, the Mallory–Weiss syndrome, and corrosive esophagitis should not be forgotten together with foreign bodies or irritants such as lye especially in children. Barrett esophagitis and ulcers caused by ectopic gastric mucosa are rare causes of hematemesis. Aortic aneurysms, mediastinal tumors, and carcinomas of the lung may ulcerate through the esophagus and bleed although these causes are very rare in children.

In the stomach, inflammation, especially gastritis and ulcers, is a prominent cause. Aspirin or NSAID, however, is often the cause and should be differentiated from varices of the cardia of the stomach. Carcinomas and hereditary telangiectasis are less common causes.

Duodenal ulcers are usually the cause of bleeding from the duodenum, but occasionally regional ileitis may be involved. Ulceration of gallstones through the gallbladder and duodenal wall is another rare cause of bleeding from this site. The pancreas can occasionally cause gross hematemesis during acute hemorrhagic pancreatitis into the duct and the duodenum.

Trauma is an important cause of bleeding from all the aforementioned sites, especially following intubation or surgery.

Blood dyscrasias associated with coagulation disorders should always be considered immediately whenever a focal cause of hematemesis cannot be found, especially if bleeding is massive.

Prevention

The best way to prevent portal hypertension and esophageal varices is to reduce the risk of cirrhosis. It is not always possible to prevent esophageal varices in children with liver disease or portal hypertension. Treating the underlying problem such as chronic hepatitis, iron overload, or exposure to toxic chemicals and drugs is of primary importance. Equally important is the use of beta-blockers and other medications to prevent increased blood pressure in the portal vein and eventually ruptured varices.

Prevention of rebleeding of varices should be achieved through scheduling repeated endoscopic sessions for variceal injections and/or band ligation until the varices is obliterated. Other surgical interventions mentioned earlier such as TIPS and devascularization should be resorted to prevent uncontrolled bleeding.

Diuretics may be necessary to suppress ascites. Salt restriction is often necessary, as cirrhosis leads to accumulation of salt (sodium retention).

Growth failure in cases of liver diseases in children is prevented through healthy nutrition and close follow-up.

Prognosis

This depends on the prognosis of the underlying disease, and on the outcome of any complications such as variceal bleeding. The Pediatric End-Stage Liver Disease [PELD] model is the best overall model for prioritization of pediatric patients for liver transplantation.

The Child–Pugh classification system indicates prognosis of cirrhosis in adults and can be extrapolated in children. It includes five parameters (serum albumin, total serum bilirubin, international normalized ratio (INR), ascites, and encephalopathy). Serum albumin is given a score of 1 if >35 g/l, 2 if 28–35 g/l, and 3 if <28 g/l. Total serum albumin is given a score of 1 if <34 μmol/l (<2 mg/dl), 2 if 34–50 μmol/l (2–3 mg/dl), and 3 if >50 μmol/l (>3 mg/dl). INR is given a score of 1 if <1.7, 2 if 1.7–2.2, and 3 if >2.2. Ascite is given a score of 1 if absent, 2 if it controlled medically, and 3 if poorly controlled. As for encephalopathy, it is given a score of 1 if absent, 2 if it controlled medically, and 3 if poorly controlled.

A score of 5–6 is class A predicts life expectancy of 15–20 years; a score of 7–9 is class B predicts life expectancy of 4–14 years; and a score of 10–15 is class C predicts life expectancy of 1–3 years. This aligns with a perioperative mortality for abdominal surgery of 10%, 30%, and 80% respectively.

Survival rates according to Child–Pugh class are 1 year survival in class A is 100%; class B 81%; class C 45%.

As mentioned earlier, almost 90% of patients with cirrhosis develop varices, but only 30% of varices bleed. The first episode of variceal hemorrhage is estimated to carry a mortality rate of 30–50%. At least 50% of people who survive bleeding esophageal varices are at risk of more bleeding during the next 1–2 years. The risk can be reduced by endoscopic and drug treatments.

TIPS does not necessarily improve survival. A TIPS risk score has been devised to help predict prognosis after the procedure.

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215 Chronic Hepatitis in Childhood

H. Hesham A-Kader · Fayez K. Ghishan

Chronic hepatitis refers to an ongoing inflammatory process within the liver. This inflammation is reflected by clinical signs and symptoms of hepatitis, abnormally high serum levels of liver enzymes, or by a spectrum of pathological and histological changes. The evolution of these inflammatory changes is variable, whereby the inflammation may subside, may persist unchanged, or may progress to more severe disease and possibly cirrhosis.

The definition of chronicity with respect to hepatitis in childhood does not follow the same criteria used in adults. International criteria used to define chronic hepatitis in adults demand evidence of continued hepatic inflammatory activity for a period exceeding 6 months. Most pediatric hepatologists, however, consider 3 months of persistent inflammation as an adequate time frame to exclude an acute hepatic inflammatory insult. At that point, the diagnosis is confirmed by obtaining a liver biopsy. This more aggressive approach enables early diagnosis of treatable conditions such as autoimmune hepatitis in a timely fashion. If the patient initially presents with signs and symptoms suggestive of chronicity then a liver biopsy should be obtained without further delay.

Etiology

There are various conditions that lead to chronic hepatitis including infections, metabolic, autoimmune and toxic causes (*Table 215.1*).

With the discovery of specific markers for hepatitis viruses B and C it has become apparent that approximately 70% of all cases of chronic hepatitis in adults have a viral origin. Although definitive data from children are not available, it is reasonable to expect that genetic and autoimmune causes also play a significant role in younger patients.

Evaluation

Evaluation of a child suspected to have chronic hepatitis may represent a challenge as the condition may result from a long list of possible etiologies and can present with a wide variety of symptoms and signs. The evaluation includes clinical assessment, serologic testing in addition to imaging, and histopathologic examination. The goals of evaluation should include confirming the diagnosis, grading and staging the disease, and the detection of the associated conditions and complications.

Clinical Presentation

Some patients with hepatitis are asymptomatic and the condition can be accidentally discovered following routine laboratory testing, during the evaluation of unrelated illness, or as a result of screening individuals at risk such as family members of patients with chronic hepatitis B and C, transfusion recipients, patients with inflammatory bowel disease, and those receiving drugs known to cause hepatotoxicity such as methotrexate.

On the other hand some children will present with the typical clinical features of hepatitis such as right upper quadrant pain, jaundice, and malaise. Patients with end-stage liver disease may present with symptoms and signs of cirrhosis, portal hypertension, and liver failure including ascites, gastrointestinal bleeding, and cachexia.

Patients suspected to have chronic hepatitis should undergo a detailed history intake including medication use, drug abuse, family history of congenital and acquired liver disease as well as history of prior surgery and blood or blood products transfusion. A thorough physical examination is mandatory looking for icterus, petechiae, ecchymosis, popular erythema, acanthosis nigricans, spider angiomas, clubbing, muscle wasting, ascites, hepatosplenomegaly, edema in addition to the assessment of mental status.

Laboratory Testing and Imaging

Following history intake and physical examination, the physician should be able to *formulate* an idea about which laboratory tests are needed in the evaluation process. Several imaging modalities are now available and can be helpful in the evaluation of children with chronic

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Table 215.1
Classification of chronic hepatitis

Etiology	Viral (B/C/D)
	Autoimmune
	Drug-induced
	Metabolic: α-l-antitrypsin deficiency, Wilson's disease, Nonalcoholic fatty liver disease (NAFLD), cystic fibrosis.
Histology grade	Mild
	Moderate
	Severe
Histology stage	No fibrosis
	Mild fibrosis
	Moderate fibrosis
	Bridging fibrosis
	Cirrhosis

hepatitis. The role of different imaging techniques will be discussed separately during the review of common causes of chronic hepatitis in children.

Histology

Although liver biopsy is not usually indicated in patients with acute hepatitis, it can provide critical information in the evaluation of children with chronic hepatitis, including confirming the diagnosis in addition to the grading and staging of hepatic inflammation and fibrosis. The role of an experienced hepatic pathologist familiar with pediatric liver disease cannot be over stressed.

Chronic Hepatitis B

Etiology

Hepatitis B virus (HBV) is a member of Hepadnaviridae family of DNA viruses. The intact virion is double-shelled, with an outer component designated as the HBV surface Ag (HBsAg) and the inner component designated as the HBV core antigen (HBcAg). The HBV core Ag or nucleocapsid houses the genome of HBV in the form of partially double stranded DNA, along with DNA polymerase and the HBeAg. The genomic DNA of HBV consists of four open reading frames corresponding to four gene products: The S gene and the pre-S gene encode for the HBsAg, the C gene encodes for the viral nucleocapsid HBeAg as well as for the HBcAg, the P gene encodes for DNA polymerase, and the X gene encodes for a protein (HBxAg). The HBxAg contains an enhancer/promoter complex with transcriptional transactivity function that is thought to play a role in the promotion of hepatocellular carcinoma.

HBV exhibits trophism for liver cells and replicates freely within hepatocytes producing an excess of HBsAg found in the serum of acutely or chronically infected patients. Immunity to HBV is mediated through virus-neutralizing antibodies directed against the HBsAg (anti-HBs). The appearance of these antibodies signifies recovery from Hepatitis B and subsequent immunity to HBV infection. During acute infections, IgM antibody to the core antigen appears during the onset of clinical symptoms indicating persistent viral replication. IgG antibody to the core Ag appears at the onset of symptoms and may persist for years if viral replication continues. The presence of HBeAg or HBV-DNA in serum correlates with ongoing viral replication and the complete viral particles in the circulation and thus, reflects HBV infectivity or the potential for transmission of HBV. The presence of antibodies directed against HBeAg (anti-HBe) usually correlates with the clearance of HBeAg from the circulation. However, some HBsAg- and anti-HBe-positive patients exhibit ongoing viral infection as evidenced by HBV DNA seropositivity and HBeAg in liver.

Pathogenesis

HBV is not itself directly cytopathic to hepatocytes. The evidence for this comes from the observation that during the long latency period between infection and hepatic disease, active viral replication occurs without liver damage. Injury is mediated through the patient's immune system. In the majority of patients, all infected hepatocytes are destroyed by primed cytotoxic lymphocytes. An overly aggressive immune response can result in fulminant hepatitis. In the chronic state, the immune system destroys only a portion of infected liver cells. The HBV virus, therefore, may survive to replicate and infect other hepatocytes. The mechanism behind this variable immune response has not been completely elucidated.

One proposed theory explaining how the immune system attacks infected hepatocytes may also explain the reason behind the effectiveness of alpha interferon therapy in some patients. In patients with HBV in active replication as evidenced by the presence of HBeAg in the circulation, a component of the replicating virus, either the core antigen or the e antigen, migrates to the cell surface

where it presents a target for primed cytotoxic lymphocytes. In a successful immune response, the hepatocyte is stimulated by intracellular interferon to produce an HLA class I surface antigen that serves as a second target for the lymphocyte. T-cell release of lymphotoxin and subsequent cell lysis is possible only when both antigens are present. Patients with chronic Hepatitis B may have diminished production of HLA Class I surface antigens as a result of inadequate interferon production. This theory explains why some patients with chronic active hepatitis respond to interferon therapy.

Epidemiology and Risk Factors for Chronicity

Transmission of HBV typically occurs through the parenteral route, primarily through the exchange of blood or other body fluids (excluding stool).

HBV infection incidence and prevalence vary with geographic areas. In North America and Europe the prevalence is less than 1%. On the other hand, HBV infection is highly endemic in Southeast Asia and parts of Africa (up to 15–20% of the general population).

In the Middle East and the Arab world, the prevalence of Hepatitis B in children varies with different countries, and within different regions of the same country. In 1990, 6.7% of Saudi Arabian children were HBsAg positive, a rate similar to adults, with the highest prevalence being among urban dwellers. The peak prevalence (9.7%) was among the 1 year age group. Significantly the degree of infectivity as reflected by a positive HBeAg was 17.9%. In Jordan, a study conducted in 1985 demonstrated that Hepatitis B was highly endemic, with a prevalence of HBsAg of approximately 10% among children. A WHO collaborative study published in 1980 demonstrated HBsAg age specific prevalence of 23% in Egyptian children aged less than four, with the prevalence decreasing to 3.7% by late adolescence.

Perinatal Transmission

In some areas of hyperendemicity such as the Far East, perinatally acquired disease is the major vehicle for transmitting the disease and perpetuating the chronic carrier state. The offspring of all HBsAg positive mothers are at risk but infection is most frequently noted when the mother is a chronic HBV carrier, has acute disease in the third trimester, or is HBeAg or HBV DNA polymerase positive. If the mother is HBeAg seropositive, the risk of transmission without treatment of the neonate is 90%. If the mother is seronegative for HBeAg, the risk of transmission is around 20%.

While there is some evidence to indicate that Hepatitis B is endemic in the Arab world, horizontal transmission plays a more significant role than vertical transmission in propagating the disease. In Egypt vertical transmission occurred in only 1.7% of births to HBsAg positive mothers, while 17.2% of children born to Hepatitis BsAg negative mothers acquired Hepatitis B in childhood. Similar trends demonstrating a low contribution by vertical transmission to the pool of HBV carriers has been demonstrated in Jordan, Egypt, Saudi Arabia, Kuwait, and Yemen. This has been partly attributed to a low level of HBsAg and HBeAg seropositivity in the child-bearing age group of females.

Infants who acquire HBV infections through vertical transmission from HBsAg positive mothers usually do not exhibit serologic evidence of infection until they are 1–3 months old. This implicates ingestion of maternal blood during birth as the route of transmission. Rarely, transmission occurs in utero via a maternal-fetal transplacental leak.

The significance of acquiring Hepatitis B perinatally or early in life lies in the significantly higher risk of developing a chronic infection. More than 90% of infants infected in the perinatal period will develop chronic HB infection, as will 25–50% of children infected before the age of 5 years. This is in contrast to patients who acquire the infection in adulthood, where only 6–10% will continue to be chronically infected. The frequent development of the chronic carrier state after acquiring HBV infection perinatally has been attributed to the immaturity of the newborns' immune system.

Chronic disease is unusual in patients with acute icteric hepatitis B, and the majority of cases of chronic hepatitis will not experience an episode of clinically apparent icterus, thus suggesting that clearance of HBV infection requires a hepatitis illness.

Chronic disease is also more common in immunocompromised patients, especially those patients with T-cell dysfunction. Children with Down's syndrome, leukemia, or leprosy are also at greater risk for chronicity. As mentioned previously, the age at the time of initial infection seems to be essential. Eighty percent of those infected prior to 1 year of age develop chronic infection. This figure decreases to 40% between 1 and 10 years of age, and is less than 10% in adults.

It is also believed that administering corticosteroids during the acute state increases the risk of persistent infection.

Diagnosis of Chronic Hepatitis B and Laboratory Data

The diagnosis of chronic hepatitis B is suspected in patients who are HBsAg seropositive in the absence of anti-HBs, particularly if this picture persists for more than 6 months. Infection is confirmed with the evidence of ongoing viral replication through the presence of either HBeAg or HBV-DNA in serum or HBcAg in liver tissue. HBeAg may be absent in patients with mutant HBV that does not synthesize HBeAg.

Serum aminotransferase levels and bilirubin are moderately elevated. Prolonged prothrombin time and low albumin may be seen in advanced cases.

There are eight different HBV genotypes with geographic propensity. Types B and C are common in Asia, types A and D in Europe, type E in west Africa, types F and H in South America, and type G in France. Compared to type A, type D is associated with a more severe disease. Similarly type C is more aggressive than type B leading to cirrhosis and hepatocellular carcinoma.

Natural History

HBV infection in children is characterized by high rate of chronicity especially in newborns with approximately 90% of perinatally infected babies developing chronic disease compared to 25% in children between 1 and 4 years and 1–5% in adolescents. The high rate of chronicity at early age may be explained by immaturity of the immune system.

Long-term studies have shown that 50% of children have seroconversion of HBeAg to HBeAb within 5 years and 70% cleared the infection in 10 years with spontaneous clearance of HBsAg at 0.5% per year. Patients with high ALT and later acquisition of the infection seem to have the best seroconversion rate.

Children usually develop a less severe liver disease compared to adults. Cirrhosis is rarely seen during childhood and is more commonly found in patients with perinatal or early postnatal infection. On the other hand, hepatocellular carcinoma, though rare, have been reported in children under the age of 10 years

Prevention and Immunization

Prevention remains the cornerstone of the management of this disease. The first HBV vaccine was a plasma-derived HBsAg subunit vaccine, prepared from plasma of chronic HBsAg carriers. Extensive studies and worldwide use of this vaccine proved its safety and efficacy. Immune response occurred in up to 90% of the healthy individuals and in 50% of immunocompromised patients.

The nucleotide sequence of HBV genome that codes for HBsAg has been isolated and inserted into yeast, thus producing large amounts of HBsAg using recombinant DNA technology. These recombinant vaccines have proven to be as safe and effective as the plasma vaccine.

Based on the epidemiology of the disease, different immunization programs have been tried in different parts of the world. In Taiwan, where perinatal exposure is the main vehicle for infection, immunization starts in early infancy and childhood. In the USA, where the disease is acquired later in life, immunization was recommended for high-risk groups only, which includes homosexuals, IV drug abusers, health care workers, and infants of HBsAg positive mothers. However, failure of this strategy in reducing the incidence of the disease has led to the recent recommendation of universal immunization of all infants and children by the age of 11 years regardless of their maternal HBsAg status. Immunization of adolescents and adults in high-risk groups is also recommended.

Pre-Exposure Prophylaxis

For high-risk groups and partners of infected people, testing for anti-HBs before immunization is recommended. If the level of anti-HBs is more than 10 RU by RIA or positive by ELISA, this would indicate previous exposure and immunity. If anti-HBs is less than 10 RU or negative by ELISA, anti-HBc needs to be checked. If positive, the patient is immune to the disease or has the disease. If negative, the person needs to be immunized.

Post-exposure Prophylaxis

This approach is recommended for (1) newborns with perinatal exposure to a known HBsAg carrier mother; (2) accidental exposure to HBsAg positive contaminated blood, whether mucosal, ocular, or percutaneous; and (3) sexual exposure to a chronic HBsAg carrier.

Hepatitis B immunoglobulin (HBIG) 0.5 ml IM should be given within 12 h after exposure followed by HB vaccine given at a different site. Two more HB vaccine doses should be given at 1 month and at 6 months after the first dose.

When used as a sole agent, HBIG has a protective effect on newborns of 75%. Combined with HB vaccine, the protection approaches 95%. Since 5% of perinatal infections are thought to be acquired in utero, further reduction of perinatal transmission may not be possible.

Protective levels of HBsAg develop in 90% of healthy adults given the Hepatitis B vaccine, and the efficacy in healthy children and newborns appears to be even higher. Several investigators, however, have reported the detection of antibody escape mutants in children vaccinated against hepatitis B. These mutations are usually found in the S gene or associated with alteration in the antigenicity of a component of HBsAg resulting in the inability to raise protective antibodies to the vaccine.

Clinical Manifestations

As mentioned before, the presentation of chronic hepatitis B can be extremely variable. Prolonged jaundice after an acute hepatitis, neonatal cholestasis, liver cirrhosis with portal hypertension or mild fatigue are a few of the wide spectrum of clinical manifestations.

Hepatocellular carcinoma is well documented in adults, but is extremely rare during childhood. However, children who are suffering from chronic hepatitis B are at a high risk to develop hepatocellular carcinoma in their adult years.

Histology

Liver tissue may show inflammatory cell infiltrates of the portal triad, mainly by plasma cells and lymphocytes, piecemeal necrosis, and bridging necrosis in more severe cases. HB particles can be occasionally identified in liver cell by the ground glass appearance of the cytoplasm and confirmed by Shikata's orcein staining.

Complications of HBV – Chronic Hepatitis

Cirrhosis

Adult studies have shown that the risk of cirrhosis is significant, especially in the presence of bridging necrosis. Cirrhosis in HBsAg positive infants and children was thought to be a rare occurrence. However, it has been frequently reported in Taiwanese children and is particularly common among infants and children who acquired the disease perinatally.

Hepatocellular Carcinoma

Hepatocellular carcinoma is one of the ten most common cancers worldwide, and is one of the most common cancers in some parts of Southeast Asia where the hepatitis BsAg carrier rate is approximately 20% of the population. The molecular mechanism behind carcinoma induction in HBsAg positive patients is not completely clear. However, it is thought that integration of HBV into the genome of the host precedes hepatic oncogenesis. Recent evidence points to a possible role for the HBV-X gene as a promoter in those patients who develop cancer.

Polyarteritis Nodosa

Glomerulonephritis and papular acrodermatitis have been reported in adult patients.

Management of Chronic Hepatitis B

The optimum goals of treating patients with chronic hepatitis B are to decrease viral replication in addition to normalization of liver enzymes and histology. Unfortunately these goals are not easily attainable in all patients with currently available medications. There are currently seven approved medications for the treatment of hepatitis B in adults in the USA including IFN-α, Lamivudine, Adefovir Diprovoxil (ADV), Entecavir, Telbivudine, and Tenofovir. However, only three medications are approved for treating children, which are IFN-α, Lamivudine, and Adefovir.

Children should be considered for treatment if they are in the immuno-reactive phase with ALT levels at least twice the normal levels and have serologic evidence of chronicity as shown by positive HBeAg and/or HBV DNA on two samples 6 months apart.

Liver biopsy is usually recommended prior to initiating therapy in order to grade inflammation and stage fibrosis.

IFN-α is the only approved therapy for hepatitis B in Europe. Typical dosing is 6 MU/m^2 with maximum dose of 10 MU/m^2 per dose thrice weekly subcutaneous injection for 16–24 weeks. Children with high ALT and later acquisition of the virus are more likely to respond to therapy. Side effects of IFN-α are similar to those in adults including flu-like symptoms, bone marrow suppression, irritability, alopecia, nausea, vomiting, diarrhea, hypothyroidism, exacerbation of depression, and suicide ideation.

In general, seroconversion of HbeAg and DNA ranges between 26% and 60% as shown in multiple studies. Studies of pretreatment with prednisone have shown conflicting

results and currently, therefore, pretreatment with prednisone is not a standard therapy. On the other hand patients with genotypes A and B appear to respond better to therapy compared to those with genotypes C and D.

In general although spontaneous HbeAg seroconversion can happen in many patients, treatment with IFN-α accelerates the seroconversion especially in children with high ALT. Whether or not the acceleration of seroconversion by 12–36 months can help prevent long-term damage to the liver has yet to be studied.

Lamivudine is a nucleoside analogue that can be taken orally. Children who received lamivudine (3 mg/Kg) for 52 weeks had a higher virologic response compared to those who received placebo (23% vs. 13%). The response was associated with the normalization of ALT and suppression of HBV DNA. Lamivudine is usually well-tolerated without adverse effects. However, the long-term use of lamivudine can be associated with the development of viral resistance. The most common HBV mutation that leads to resistance is a codon change at site 552 in the C domain of the YMDD motif of the HBV polymerase gene (methionine to valine or isoleucine) and therefore, called the YMDD mutation. The duration of lamivudine therapy is yet to be determined but has to continue for 12 months and at least 6 months following HBVeAg seroconversion.

Lamivudine may be also helpful in patients with fulminant hepatic failure due to exacerbation of chronic hepatitis B infection. Twenty-four patients with chronic hepatitis B and fulminant hepatic failure responded to lamivudine therapy without the need for transplantation.

Adefovir dipivoxil has been used successfully in adults with chronic HBV infection for years both as first-line therapy as well as in patients with lamivudine resistance. Studies in adults have shown twice the HBeAg seroconversion rate in patients treated with adefovir compared to those who received placebo (12% vs. 6%) in addition to normalization of ALT and decreased HBV DNA. The usual adult dose is 10 mg per day as higher doses were associated with nephrotoxicity and failed to demonstrate better efficacy.

A multi-center study by Jonas et al. in children with chronic hepatitis B in various age groups found that the use of adefovir is safe and that 48 weeks of therapy was superior to placebo in HBeAg positive adolescents. However, the study did not demonstrate efficacy in children under the age of 12 years.

The disappointing results of monotherapy in patients with chronic HBV infection have led to multiple trials examining the effects of combining medications either simultaneously or sequentially with mixed results.

In a promising study, 23 children with perinatal-acquired HBV infection were treated for 8 weeks with lamivudine followed by IFN-α combined with lamivudine for 10 months. HbeAg seroconversion was seen in 22% of the patients. In addition 78% became HBV DNA negative and 17% lost HBsAg and became HBsAb positive. None of the patients developed YMDD mutation and all maintained their seroconversion when followed up for at least 3 years.

In summary, chronic HBV infection is a major cause of liver disease in children worldwide. Children are more likely to develop chronic HBV infection as they demonstrate greater immunotolerance to the virus, and response to therapy in children remains disappointing. Only three medications have been approved for treatment of children with chronic HBV infection. IFN-α has been shown to be the most effective so far with approximately 30% HBeAg seroconversion and 10% HBsAg seroconversion. IFN-α is more effective in patients with ALT at least twice the upper normal limit and in children with later-acquired infection. However, IFN-α is associated with a long list of side effects. Moreover, long-term follow studies have suggested that IFN-α simply accelerates a spontaneous event. Lamivudine's virologic response is not much different from IFN-α in terms of HbeAg seroconversion, however, it has a lower HBsAg seroconversion (2–3%). Advantages of lamivudine include easy administration and better safety profile but it has high rates of drug resistance. Although adefovir has been shown to be safe in children, its efficacy is limited to children above the age of 12 years. Adefovir's efficacy is also lower than lamivudine (16% HBeAg seroconversion; <1% HBsAg seroconversion).

In the future, therapies approved in adults such as entecavir and tenofovir may prove to be effective in children, and combination therapy may be another available option in the pediatric age group. The search for a perfect therapy for children with chronic HBV infection continues and careful observation for these patients while awaiting such therapy is not unreasonable.

Chronic Hepatitis C

A third form of infectious hepatitis not caused by hepatitis A or B has been termed as non-A, non-B hepatitis (NANB). The long-suspected virus is currently known as the hepatitis C virus (HCV), an RNA virus cloned in 1989. The virus is composed of 9,400 nucleotides encoding a 3,010–3,033 amino acid sequence, which is further cleaved into distinct polypeptides during or after translation to yield different viral proteins. The envelope and nucleocapsid proteins are encoded at the 5′ end of the open reading

frame, while nonstructural proteins are downstream. Because of nucleotide sequence diversity, six major genotypes of Hepatitis C with different component subtypes based on nucleotide homology have been identified. Genotype information can provide useful information regarding prognosis and response to therapy. For example, type I has been shown to be resistant to anti-viral therapy. Geographical differences in the prevalence of these types have been reported. For example, while types 1 (a and b) and 2 are more prevalent in North America, genotype 4 appears to predominate in patients from the Middle East.

The E_1, E_2 regions of the open reading frame have hypervariable regions. Their variability is postulated to play a role in the persistence of infection.

Epidemiology and Transmission

The distribution of HCV is worldwide similar to HAV and HBV. Twenty-eight thousand new cases of HCV happen in the USA each year. However the proportion of pediatric cases is not known. The prevalence of HCV infection in the USA is approximately 1.8%, which represents approximately 3.9 million people. The seroprevalence is 0.2% among children below the age of 12 years and 0.4% in children between 12 and 19 years.

Studies in children without identifiable risks have shown seroprevalence rates ranging from 0% in Japan and Taiwan, 0.4% in Italy, 0.9% in Saudi, and 14% in Cameroon. On the other hand, the prevalence of HCV in patients with NANB is much higher in patients with identifiable risk factors such as thalessemia (60–65%), hemophilia (59–95%), and leukemia (52–72%).

Although HCV infection is much less common than HAV and HBV, the propensity of HCV infection to chronicity has resulted in HCV responsible for 63% of chronic hepatitis and 35% of all cases of chronic liver disease and cirrhosis.

The typical mode of transmission of HCV is parenteral. Transmission may be divided to percutaneous (Blood transfusion, intravenous drug abuse) and non-percutaneous (intrafamilial and sexual).

Traditionally the transmission of HCV has been attributed to the transfusion of infected blood as well as blood products. However, this route of transmission has declined tremendously following the advent of screening for HCV antibodies after 1991. Similarly blood products are now much safer thanks to the improvement of inactivation procedures.

On the other hand there has been a progressive increase in the number of cases attributable to intravenous drug abuse, which may be as high as 60% of new cases. This may be explained by the declining risk of transmission with blood and blood products and the increased frequency of drug abuse.

Other percutaneous transmission modes include accidental needle stick that carries a risk of 10% and usually results in a symptomatic disease. Tattooing has become very popular among adolescents and has been associated with the transmission of HCV.

The risk of transmitting HCV by sexual contact is not well defined. Although accumulated epidemiologic evidence indicates that HCV can by transmitted by sexual contact, this mode of transmission is much less efficient than other sexually transmitted viruses such as HBV and HIV. Individuals engaged in long-term monogamous relationship carry a low risk for transmission of HCV (0 – 0.6% per year), and there is no need to change their regular practice. On the other hand those involved in short-term relationship with multiple partners may experience a higher risk, and barrier or abstinence methods are advised. In general, couples should refrain from sharing tooth brushes, razors, and nail-grooming equipments.

Maternal-infant transmission of HCV infection is comparatively uncommon. The mother to infant transmission is estimated to be 4 – 7% per pregnancy. However, co-infection with Human Immunodeficiency Virus (HIV) will increase such risk by fourfold to fivefold. Transmission happens when HCV RNA is detectable and possibly related to high levels (above 10^6 copies/ml). The time and mode of transmission are not known and therefore, cesarean section should not be recommended in order to prevent the transmission of HCV.

HCV can be detected in breast milk. Nevertheless, breast feeding is not considered a risk factor for the transmission of HCV in the absence of traumatized, cracked, or bleeding nipples. As a matter of fact, several studies have shown that the rate of transmission of HCV is similar in breast-fed and bottle-fed infants. However, breast feeding may pose risk for transmitting HCV during periods of postpartum hepatitis flare up.

Some cases of HCV infection can be attributed to intrafamilial and occupational spread. However, in 35–50% of the cases no source can be identified creating uncertainty regarding the existence of other modes of transmission.

Pathogenesis

The pathogenic mechanisms of HCV are not well understood. The virus is presumed to be directly cytopathic, but

there is some evidence that immune reaction to HCV may also lead to liver damage.

Frequent episodes of hepatitis are observed which may represent re-activation or reinfection. These episodes are postulated to be due to the emergence of mutants of HCV not neutralized by circulating antibodies.

Immune cross-reaction of P450 epitopes and hepatitis C proteins may explain the occurrence of anti-LKM antibodies in some patients.

Clinical Presentation

Hepatitis C causes both *acute* and *chronic* infection, although the rate of chronicity is alarmingly higher than Hepatitis B infection.

In *acute* transfusion-related transmission, the disease is usually mild and often asymptomatic and subclinical. The mean incubation period of hepatitis C is 6–12 weeks, the average time from transfusion to anti-HCV positivity is 8 weeks, and HCV RNA has been detected within 1–3 weeks of transfusion. The acute course of HCV is clinically mild with only 25% of cases having an icteric phase. The peak aminotransferase levels are less than those encountered in acute Hepatitis B. During the early phase, serum aminotransferase levels may fluctuate (multiphasic), may become normal (monophasic), or may plateau. Patients with the single monophasic rise are at the least risk for developing chronic infection.

Chronic HCV infection occurs in 50–75% of patients with HCV post-transfusion or sporadic hepatitis. Aminotransferase levels decline from the peak values of the acute phase to remain two to eight folds above normal. These levels may fluctuate over time, and may even be intermittently normal. Unlike the acute disease, chronic HCV may lead to grave consequences. Persistent HCV infection leads to chronic hepatitis, and cirrhosis develops in 20% of patients within 10 years of acquiring the infection, although the cirrhosis remains indolent and progresses slowly. The disease has also been linked to the development of hepatocellular carcinoma.

Diagnosis

The diagnosis of HCV infection rests on the detection of anti-HCV antibody in the serum of infected individuals, or the detection of HCV RNA in the serum or liver. HCV antigens cannot be detected in the serum due to the low concentration of the virus in the blood.

The detection of antibodies to HCV is an indicator of past or present infection. The methodology used in assaying for HCV antibodies has undergone rapid evolution. The first generation ELISA assay detected antibodies to c100-3, a polypeptide representing part of the HCV genome. This assay, however, lacked sensitivity and specificity. Subsequently, second generation ELISA assays (versus c100-3, c200, c33c) and third generation ELISA assays (versus epitopes from the NS5 region) have greatly improved sensitivity. Although the mean interval from the onset of hepatitis to seroconversion is 8 weeks, some individuals may not seroconvert for up to 1 year. Thus, when using ELISA tests it may be necessary to test sequential samples over a 1 year period to exclude the diagnosis. Moreover, in acute phases that fully recover, there may be considerable delay in the clearance of anti-HCV.

Recombinant immunoblot assay (RIBA) detects recombinant antibodies to structural and nonstructural proteins of HCV coated on nitrocellulose strips. This test has decreased the incidence of false positive results seen with ELISA tests. A positive test for HCV using RIBA 4 not only confirms infection but is an indicator of viremia and infectivity.

A negative anti-HCV does not exclude infection in the early stage or past infection as it may disappear with disease resolution.

Detection of serum HCV RNA using polymerase chain reaction techniques is now the "gold standard" for detection of the disease. This method allows the detection of HCV RNA in almost all of anti-HCV positive patients and also in a proportion of those who are antibody negative, particularly neonates born to anti-HCV-positive mothers. RNA is detected in the serum during the incubation period and can detect as low as 1 – 10 molecules of nucleic acids. The persistence of RNA in the circulation for 6 months indicates chronic infection. Quantification of HCV RNA can help determining response to therapy. Rarely, HCV RNA is absent from the circulation but present in hepatic tissue.

Serum aminotransferase levels rise with the development of symptoms and the appearance of jaundice. The enzymes decline in a rapid monophasic fashion or a multiphasic pattern with fluctuations and more protracted course.

Histological features of HCV infection are similar to those in adults. Mild inflammation and necrosis is usually seen. However, patients may develop fibrosis which progresses with increase in age and infection duration.

Treatment

Studies of treatment for HCV infection in children have used the same drugs and measures of efficacy as in adults

(see section "Evaluation"), but have been limited to relatively small numbers of children.

A meta-analysis of 19 trials of IFN[alpha] for children with HCV infection examined the effect of treatment in 366 children compared with 105 untreated controls. Response to treatment occurred in a mean of 54% (range 0–91%) of patients, with a sustained response in 36% (0–73%). HCV genotype 1 adversely affected the likelihood of response, with a sustained response in 27% of children compared with 70% in those with other genotypes. A small study of pegylated IFN[alpha] as monotherapy for 48 weeks in 14 children achieved an SVR in 43% of children with HCV genotype 1.

Children may benefit from the treatment of HCV infection. Meta-analysis of studies of monotherapy with interferon has shown sustained virologic response (SVR) in 33–45% of chronically infected children, which is significantly higher than adults. The SVR was considerably less in patients with genotype I (26%) compared to other genotypes (70%). The spontaneous clearance rate in untreated children was 5%. Treatment duration ranged from 6 to 18 months. Most studies used a dosage of 3 MU/m^2 via subcutaneous injection three times weekly. The better success rate in children may be explained by the shorter duration of infection and the absence of co-morbd conditions and aggravating factors. The spontaneous clearance rate in untreated children was 5%. Treatment duration ranged from 6 to 18 months. Most studies used a dosage of 3 MU/m^2 via subcutaneous injection three times weekly.

Studies of the use of combination therapy using interferon and ribavirin have shown SVR of 38%. Recently, combination therapy with pegylated interferon and ribavirin has been approved by the FDA in the USA in children 3 years of age and older.

Children seem to tolerate IFNα well. Although interferon therapy can affect weight gain and linear growth, these effects disappear following cessation of therapy. Possible complications following interferon therapy in young children include serious hemangiomas, spastic diplegia, and seizure. On the other hand, ribavirin is usually well tolerated in children. Although dose-dependent hemolytic anemia may be seen, this usually does not result in discontinuation of treatment.

HCV infection is a common indication for transplantation in adult patients. Reinfection following transplant is universal. Although liver transplantation is a rare indication for HCV infection in children, the outcome after transplant is not different with 31% of the patients requiring retransplantation mainly for HCV recurrence. Immunosuppressive therapy decreases the efficacy of HCV treatment and potentiates ribavirin-induced hemolysis. On the other hand, HCV treatment induces acute and chromic rejection in 10–25% of transplanted patients. Pre-emptive treatment of HCV early after transplant is associated with adverse effects in 50% of the patients and results in an SVR of only 10–20% compared to SVR of 25–40% in patients treated after recurrence of HCV following transplantation.

Future Directions

Future therapy may include the use of ribavirin analogues that are liver-specific, minimizing the risk of hemolytic anemia. Fusing albumin with recombinant IFNα-2b is currently under evaluation with the potential of a monthly rather than weekly administration injection which will be much more convenient for patients especially those in the pediatric age group. Other future options may also include protease and polymerase inhibitors and Toll-like receptor agonists which can prevent the activation of inflammatory response initiated by microbe gene and cytokine induction. Gene therapy strategies aiming at rendering hepatocytes resistant to HCV are currently under evaluation in animal models including transfer of IFNα gene and also the integration of antisense DNA/RNA molecule into the host genome. Finally, clinical trials of human monoclonal antibody against HCV are underway.

The development of HCV culture model that is infectious in chimpanzees has raised hopes for an effective vaccine. Data in chimpanzees indicates that the vaccine may prevent the progression to chronic disease. Clinical trials in humans are going through phase I and II presently.

Autoimmune Liver Disease

Autoimmune liver disease encompasses a group of disorders characterized by the presence of circulating antibodies and inflammatory process directed toward the hepatocytes causing autoimmune hepatitis or directed against the biliary tree resulting in sclerosing cholangitis or both (overlap syndrome).

Autoimmune Hepatitis

Autoimmune chronic hepatitis is characterized by features of chronic hepatitis, hypergammaglobulinemia, and the

presence of non-organ–specific autoantibodies as well as liver-specific autoantibodies, in the absence of a known cause of liver disease.

Etiology

The pathogenesis of autoimmune chronic hepatitis has not been completely elucidated. It is postulated that liver damage in patients with autoimmune hepatitis stems from the interaction of helper/inducer T-cell lymphocytes with a self-antigen, the asialoglycoprotein receptor (ASPGR) that is mistakenly recognized as foreign. This initiates a cascade of events leading to the production of cytokines, activation of cytotoxic T-cells, and induction of autoantibody production by B lymphocytes. A genetic background has been suggested due to the high frequency of HLA haplotypes HLA B*/DR3 and allotypes DR3 in addition to the presence of other autoimmune disorders.

Several triggers have been proposed such as viral infection–inducing autoimmune hepatitis. A long list of viruses including Hepatitis A and C, Epstein Barr, and human herpes virus 6 have been suggested as triggering factors for autoimmune hepatitis. It is known that the molecular structure of the HCV polyprotein bears resemblance to a component of cytochrome P450 and therefore, it may trigger the production of liver kidney microsomal (LKM) antibodies. Similarly, an epitope of P450 displays homology with a herpes simplex virus type I (HSV-I) protein, and in adults, increased frequency of HSV-I has been reported.

On the other hand several drugs have been associated with the development of autoantibodies. ANA, SMA, LKM, and anti-liver microsomal antibody have been reported secondary to the use of α-methyldopa, nitrofurantoin, and tienilic acid dihydralazine, respectively. Although the mechanism of drug-induced autoimmune hepatitis is still poorly understood, a possible mechanism might be the production of unstable drug metabolite, which can induce an antibody response followed by combining with cellular component.

Diagnosis

Diagnosis of autoimmune hepatitis rests on clinical picture, histological changes, and the detection of autoantibodies. Liver biopsy of patients with autoimmune hepatitis shows necroinflammatry changes with portal triad dense infiltration with mononuclear inflammatory cells including plasma cells and parenchymal collapse.

Transaminase levels are elevated 2–30-fold. Alkaline phosphatase and gamma-glutamyl transferase are normal or modestly elevated up to twice the normal level. Hyperbilirubinemia is usually present except in those patients presenting insidiously. At presentation, the prothrombin time is usually prolonged 4 s or more. Serum albumin concentrations are usually low. Hypergammaglobulinemia is a characteristic abnormality with levels greater than 2.0 gm/dL. Serum IgG levels are always high, while serum IgM levels are occasionally high, and serum IgA levels are occasionally low. C_3 and C_4 levels may be low.

IgG autoantibodies to internal components of cells are present in almost all patients. However, antibodies may occasionally disappear on immunosuppressive therapy, or infrequently, may appear only after the initiation of immunosuppression. Some clinicians divide autoimmune hepatitis into *different subgroups* based on the type of non-organ–specific autoantibodies detected.

Type I is that associated with smooth muscle antibody (SMA) with or without antinuclear antibody (ANA).

Type II is that associated with anti-liver/kidney (LKM) antibody, which is also designated as endoplasmic reticulum antibody because it is directed against P-450 antigens and other antigens of the monooxygenase system. This type of autoimmune hepatitis has a more severe course with rapid progression to cirrhosis, despite immunosuppressive treatment. Of note is that antibodies to the P-450 component of LKM are commonly found in adult patients with hepatitis C.

Type III characterized by the presence of anti-soluble-liver-antigen antibody (SLA) has been proposed but has not gained universal acceptance as many believe that it is a subset of type I.

These forms of autoimmune hepatitis may be associated with a Coomb's-positive hemolytic anemia, thyroid antibodies, and rheumatoid factor (RF), or parietal cell antibodies. In addition, autoantibodies to liver-specific lipoprotein (LSP) antigen or to one of its components and the asialoglycoprotein receptor (ASGPR) found on hepatocyte membranes may be present. The titers of LSP and ASPGR antibodies frequently correlate with the extent of liver damage and disease activity, respectively.

Clinical Manifestations

Autoimmune hepatitis affects both children and adults with two peaks at 10–20 and 45–70 years of age. Eighty percent of adult patients have type I, while type II is mainly a disease of younger patients especially females.

Patients with autoimmune hepatitis may present acutely with anorexia, malaise, nausea and vomiting, and features suggestive of ongoing hepatitis. Occasionally, the presentation is insidious with nonspecific symptoms. Rarely, the picture may be that of acute liver failure. A group of patients may initially present with manifestations of end-stage liver disease such as jaundice, ascites, and gastrointestinal bleeding. Extrahepatic manifestations such as amenorrhea, acne, arthritis, dermatitis, thyroiditis, or hemolytic anemia may accompany the hepatitis. Some patients may be diagnosed following an incidental finding of elevated serum aminotransferases during routine laboratory testing.

Autoimmune hepatitis may be seen in association with a long list of autoimmune disorders such as celiac disease, inflammatory bowel disease, glomerulonephritis, hemolytic anemia, idiopathic thrombocytopenia, Sjogren syndrome, Grave's disease, and thyroiditis. Manifestations of autoimmune hepatic may precede; accompany, or follow the presentation of these autoimmune disorders. Autoimmune hepatitis may also be seen in 20% of patients with polyglandular syndrome type I (APECED) which is a monogenic disorder with a variable phenotype. About 20% of the cases develop autoimmune hepatitis (AIH) that resembles AIH type 2. This disorder is an autosomal recessive disorder caused by homozygous mutations in the ***AIRE1*** gene and characterized by a variety of organ-specific autoimmune diseases, the most common of which are hypoparathyroidism and primary adrenocortical failure, accompanied by chronic mucocutaneous candidiasis.

Treatment of Autoimmune Hepatitis

Patients with autoimmune hepatitis usually respond to corticosteroids which is the mainstay therapy and should be tried even in patients with fulminant hepatic failure or with cirrhosis.

Predinosolone at a dose of 2 mg/kg/day (maximum 60 mg/day) is usually recommended with gradual tapering after normalization of serum aminotransferases which is usually seen in 80% of the patients within few months. Clinical improvement usually precedes biochemical normalization of liver enzymes. On the other hand histologic resolution may take 3–6 months. A low dose of steroids is usually needed to maintain remission. If maintenance therapy with steroids is associated with side effects the addition of another immunosuppressive agent may allow discontinuation of steroids.

Azathioprine acts by inhibiting maturation of lymphocytes and therefore, may take up to 3 months to be effective. Azathioprine is usually used as a steroid sparing agent in patients requiring long-term steroid therapy or with the appearance of unacceptable steroids side effects. An initial dose of 0.5 mg/kg/day is usually recommended and can be increased to 2 mg/kg/day while monitoring carefully for side effects. Azathioprine may also be used at the start of treatment if relapse is considered likely.

A related Purine analogue, 6 *Mercaptopurine*, can be substituted for Azathioprine in lower doses in patients who fail to respond to Azathioprine. Remission of autoimmune hepatitis can be maintained by Azathioprine alone or in combination with low-dose steroids.

Cyclosporine has been shown to be effective in patients with autoimmune hepatitis who failed therapy with steroids/azathioprine. Cyclosporine has been also tried as monotherapy. In a study that involved 32 patients, treatment of cyclosporine for 6 months was followed successfully by the introduction of low-dose steroids and Azathioprine with withdrawal of cyclosporine. The significant side effects of cyclosporine such as renal toxicity, gingival hyperplasia, and hirsutism have limited its use as a first-line therapeutic agent.

There is little evidence supporting the use of *tacrolimus* in children with autoimmune hepatitis. As in the case of cyclosporine the significant side effects associated with tacrolimus including renal impairment have been reported.

Recently *mycophenolate mofetil (MMF)* has been shown to be a promising therapeutic agent but this needs to be further studied.

There is no consensus regarding the duration of therapy in children with autoimmune hepatitis. In general, treatment is continued for 1–2 years and then discontinued in the absence of biochemical hepatic dysfunction or activity in liver biopsy.

Unfortunately in many patients, the only remaining consideration is orthotopic liver transplantation such as in patients with fulminant hepatic failure, end-stage liver disease, and failed medical therapy and with the appearance of unacceptable side effects. Autoimmune hepatitis recurs in 25% of the patients following liver transplantation, despite aggressive immunosuppressive therapy.

Prognosis

Spontaneous remission is rare. In adults not treated, clinical deterioration is rapid, ultimately leading to cirrhosis and death within 5 years of onset in 50% of cases. With the advent of immunosuppressive therapy, the prognosis has improved; up to 85% of adults respond to treatment with

a subsequent 93% 5-year survival in patients in remission. However, relapse rates after histological cure and discontinuation of therapy remain high, in some series exceeding 85%.

Forty percent of children will have at least one episode of relapse while on therapy for autoimmune hepatitis and many will progress toward cirrhosis. Bad prognostic signs include cirrhosis on initial biopsy, young age on presentation, and HLA B* or DR3 phenotypes. Patients with type I are more likely to maintain remission compared to those with type II.

Autoimmune Sclerosing Cholangitis (ASC)

ASC has the same prevalence as AIH type 1 in childhood. Susceptibility to ASC in children is conferred by the presence of HLA DRB1*1301.

In a prospective study conducted over 16 years, approximately 50% of patients with serological and histological features of autoimmune liver disease presentation had alterations of the bile ducts characteristic of sclerosing cholangitis on cholangiogram. Despite the presence of abnormal cholangiogram, a quarter of children with ASC have no histological features suggesting bile duct involvement. Inflammatory bowel disease was present in about 45% of children with ASC compared to about 20% of those with AIH. At the time of presentation, standard liver function tests did not help in discriminating between AIH and ASC, though the alkaline phosphatase/aspartate aminotransferase ratio was significantly higher in ASC. pANNA were present in 74% of patients with ASC compared to 45% of patients with AIH type 1 and 11% of those with AIH type 2.

ASC in children usually responds to the same immunosuppressive regimens used in patients with AIH. Although steroids and azathioprine are helpful in reducing the parenchymal inflammatory changes, they do not seem to be as effective in controlling the bile duct disease. Based on data from adult studies *ursodeoxycholic acid* is usually added at a dose of 20–30 mg/kg/day, although there is no evidence that it has an effect on the progression of the disorder. Following patients with ASC for 7 years has shown survival in 100% patients, despite the fact that orthotopic liver transplantation was needed in 15% of the patients.

A prospective study done at King's college Hospital has shown that ASC is more common than sclerosing cholangitis lacking autoimmune features as it has been observed in only few children referred over the 16-year-study period. In order to prove that, a prospective study examining bile duct at the time of the initial presentation of AIH is needed.

De Novo AIH Following Liver Transplantation

De novo AIH is characterized by a histological picture of interface hepatitis and multilobular collapse associated with increased IgG levels and positive autoantibodies including ANA, SMA, and classical anti-LKM-1as well as atypical anti-LKM-1, staining the renal tubules but not the liver. Importantly, treatment with prednisolone and azathioprine in parallel to reduction of the calcineurin inhibitor dose is usually effective in de novo AIH as these patients do not usually respond to standard anti-rejection treatment.

Many physicians believe that AIH following transplant is a form of rejection. Another possible theory is an "autoimmune" injury, possibly triggered by drugs. The administration of cyclosporin A or tacrolimus to rodents who received bone marrow may interfere with maturation of T lymphocytes favoring the emergence of autoaggressive T-cell clones. This experience in animals may explain, in part, the development of this disorder in immunosuppressed children after liver transplantation.

Nonalcoholic Fatty Liver Disease in Children

Childhood obesity has grown considerably in the past 2 decades. The percentage of overweight children and adolescents has more than doubled since the early 1970s. According to the Centers for Disease Control, about 15% of children and adolescents are considered overweight. Unfortunately, despite the fact that obesity is an easy medical condition to recognize, it is very difficult to treat.

Chronic liver disease associated with obesity was first reported in the 1970s in obese pregnant women. The histological features were similar to those seen in patients who are heavy alcohol drinkers and hence the disorder was initially called nonalcoholic steatohepatitis (NASH). Currently, a new term "Nonalcoholic Fatty Liver Disease (NAFLD)" is more widely used as it encompasses a spectrum of hepatic pathological changes ranging from fatty liver (steatosis) to cirrhosis. Nonalcoholic steatohepatitis (NASH) is an intermediate form of liver damage that may progress to fibrosis and cirrhosis.

The first report of steatohepatitis in obese children was published in the early 1980s. The authors reported three

American children with steatosis and steatohepatitis. Although NAFLD was considered to be a disease of adults, it has been realized recently that NAFLD can also affect children and is currently the most common hepatic disorder in pediatric hepatology practice.

Pathogenesis

There is lack of complete understanding of the pathogenesis of NAFLD as well as the mechanisms involved in the progression from steatosis to NASH and cirrhosis. The most accepted theory involves a "two hit" process. Disorders of the hepatic uptake, synthesis, degradation, and secretion of free fatty acids will lead to accumulation of lipids in the hepatocytes resulting in macrovesicular steatosis which will prime the liver for a second hit resulting in inflammatory changes and disease progression.

Fat-derived factors such as fatty acids, adiponectin, and tumor necrosis factor (TNF) alpha regulate the inflammatory response and promote NAFLD in patients with metabolic syndrome by modulating the hepatic inflammatory response. *Adiponectin* inhibits fatty acid uptake, stimulates fatty acid oxidation and lipids export, and enhances hepatic insulin sensitivity. On the other hand, TNF recruits inflammatory cells to injured tissues and promotes insulin resistance. Therefore, adiponectin and *TNF alpha* are mutually antagonistic. Patients with metabolic syndrome have cytokine imbalance with increased production of TNF and reduced activity of adiponectin, which may result in increased insulin resistance with fat accumulation, inflammation, and cell necrosis.

Epidemiology

The exact incidence and prevalence of NAFLD are not known due to the lack of accurate noninvasive diagnostic methods. Noninvasive imaging techniques such as ultrasonography can detect fatty changes but they lack sensitivity in patients with mild steatosis and cannot differentiate steatohepatitis from simple steatosis.

The prevalence of NAFLD ranges from 9% to 36.9% worldwide in patients with no known risk factors. In the USA, the percentage of subjects presumed to have NAFLD due to unexplained high liver enzymes has been estimated to be 23% of the population. The prevalence of NAFLD is much higher in subjects with known risk factors such as those with metabolic syndrome. The prevalence of NAFLD in morbidly obese patients undergoing bariatric surgery was reported to be as high as 96%, while the prevalence of NASH in the same group ranges from 12% to 25%.

Although NAFLD has been reported in patients as young as 2 years of age, the majority of pediatric patients are diagnosed during the second decade of life. In the largest pediatric report published so far, 77% of NAFLD patients were males. NAFLD seems to be more common in Hispanics with higher prevalence in non-Hispanic whites compared to non-Hispanic blacks.

Clinical Picture

Most patients with NAFLD are asymptomatic. Common symptoms include mild right upper quadrant abdominal pain, fatigue, and malaise. Patients usually come to medical attention due to abnormal serum aminotransferase level detected during a routine lab or abnormal hepatic imaging performed for different reasons such as abdominal pain or suspected gall stones. The most common physical finding is *Acanthosis Nigricans*, which may be seen at the nape of the neck, axilla, and groins or over the knuckles. Hepatomegaly can be difficult to detect in obese children.

Patients with advanced liver disease may have manifestations of end-stage liver disease such as jaundice, pruritus, ascites, spider angiomatas, splenomegaly, sharp liver border, palmar erythema, or asterixis. Manifestations of metabolic syndrome are seen in most patients including obesity, diabetes, hypertension, and dyslipidemia.

Diagnosis

Liver Biopsy

Liver biopsy is the gold standard for diagnosing NAFLD and the only method that can differentiate steatohepatitis and fibrosis from simple steatosis. Liver biopsy will establish the diagnosis, provide prognostic information, assess severity, and motivate the patient and the family to seek treatment. Although trial of weight loss while monitoring liver enzymes has been suggested, normalization of liver enzymes is not necessarily associated with histological improvement. A reasonable approach for patients suspected to have NAFLD is to measure ALT level and perform liver ultrasound. If one or both tests are abnormal liver biopsy is needed, but if both are normal, risk factors should be corrected if present.

Histological features include macro- and microvesicular steatosis, acute and chronic inflammation, cytologic ballooning, and glycogen nuclei of hepatocytes, perisinusoidal fibrosis and Mallory hyaline bodies (*Figs. 215.1* and *215.2*). The use of serum markers of fibrosis, though promising, needs further validation. The lack of availability of these tests in most labs limits its use in routine clinical practice.

In patients with suspected NAFLD, lab testing should include levels of AST, ALT, total and direct bilirubin, and fasting serum glucose, as well as a lipid panel. Viral, autoimmune hepatitis and metabolic liver diseases, including Wilson's disease, hypothyroidism, and α-antitrypsin deficiency need to be excluded. Patients usually have mild to moderate elevation of serum aminotransferases (mean range, 100–200 IU/L). AST to ALT ratio is usually less than one, but may reverse with development of fibrosis. Liver enzymes may be normal in children with NAFLD, despite the presence of advanced disease. Serum alkaline phosphatase and gamma-glutamyl transpeptidase may also be mildly abnormal. Albumin, bilirubin, and platelet levels are usually normal unless in the presence of cirrhosis. Autoimmune antibodies (antinuclear and anti-smooth-muscle antibody), ferritin, and transferrin may be elevated in some patients with NAFLD. The reason of such elevation is still unknown.

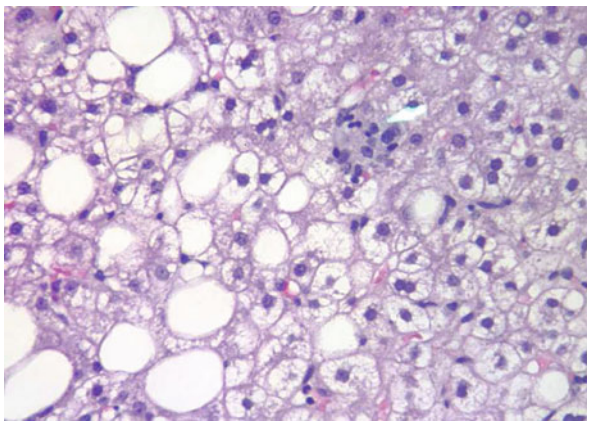

Figure 215.1
Liver biopsy in a patient with nonalcoholic fatty liver disease showing steatosis and lobulitis (*arrow*)

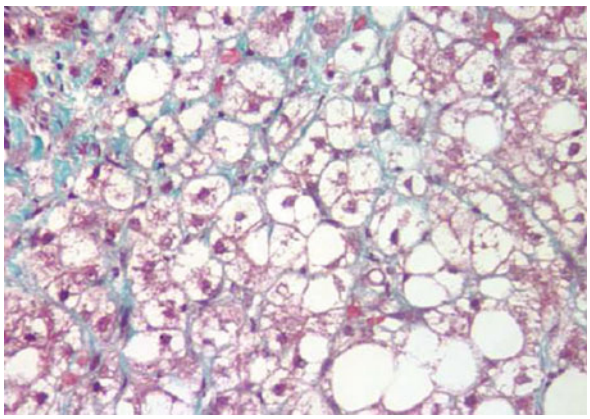

Figure 215.2
Liver biopsy with trichrome stain in a patient with nonalcoholic fatty liver disease showing fibrosis

Radiology

Ultrasonography is the most commonly used radiologic modality in patients suspected to have NAFLD. Ultrasonic examination of fatty liver usually reveals the characteristic picture of "Bright Liver" due to increased echogenicity of the liver. Other features include hepatomegaly, hypoechoic kidney, and decreased visualization of hepatic and portal veins secondary to compression of swollen hepatocytes on their walls. Accumulation of fat may also result in abnormal hepatic vein. Doppler waveform pattern may either be monophasic or biphasic.

Several studies have looked into the sensitivity of ultrasound in detecting steatosis and fibrosis with a wide range of results. The sensitivity of ultrasonography seems to improve with increased hepatic fatty infiltration with a range of 60– 90% in patients with moderate hepatic steatosis. The major limitation of ultrasonography is subjectivity as it is an operator-dependent procedure.

Computed tomography (CT) has been commonly utilized in the evaluation of patients with fatty liver. Disadvantages of CT include limitation of use in patients with hepatic iron overload and radiation exposure.

Different magnetic resonance imaging (MRI) techniques have been used in the evaluation of NAFLD patients. Disadvantages of MRI include limitation of use in patients with hepatic iron overload, and it is contraindicated in patients with implantable devices and pace makers and also in claustrophobics.

In the future, other diagnostic modalities may prove to provide diagnostic information in patients with NAFLD such as contrast-enhanced ultrasonography, localized proton magnetic resonance spectroscopy (MRS), and measuring liver stiffness by fibroscan.

Natural History

It is difficult to determine the natural history of NAFLD in children in the absence of long-term prospective studies. In a recently published report, 18 children were reported to have a follow-up biopsy over an average period of 28 months. No change was seen in eight patients, while seven patients had progression of fibrosis, three patients had regression or disappearance of fibrosis followed by loss of weight. The only patient who progressed from stage I fibrosis to cirrhosis had a significant weight gain over a short period of time.

Hepatocellular carcinoma (HCC) is a known complication of liver cirrhosis and can be seen in patients with NAFLD-associated cirrhosis. Therefore, it is recommended to screen patients with NAFLD who develop cirrhosis for HCC periodically by ultrasound and serum alpha fetoprotein.

Orthotopic liver transplantation has been successfully performed in patients with NAFLD and end-stage liver disease with survival rates not different from results following transplant due to other forms of liver disease. Unfortunately, NAFLD commonly recurs following transplant and can be severe enough to cause failure of the allograft.

Treatment

Weight Loss

Weight reduction leads to loss of adipose tissue and decreases insulin resistance. Exercise improves muscular insulin sensitivity and leads to weight loss. Reduction of body weight through dieting with or without exercise has been shown to improve liver enzymes in children and adults with NAFLD (Some reports have shown histological improvement). It is recommended that weight loss not to exceed 1.6 kg/week as more rapid weight loss may result in portal inflammation and fibrosis.

Antiobesity medications have also been tried with promising results including orlistat (an enteric lipase inhibitor), and sibutramine (a serotonin and norepinephrine reuptake inhibitor). However, the long-term effects of these medications remain to be determined.

Insulin Sensitizers

Insulin sensitizers have been the subject of intensive research efforts.

Thiazolidinediones is a group of drugs known to decrease insulin resistance mainly in adipose tissue by activating the nuclear transcription factor, peroxisome proliferators–activated receptor-γ (PRAPγ) by binding selective ligands. The first drug, troglitazone showed promising therapeutic effects in patients with NAFLD. However, it was withdrawn from the market due to severe idiosyncratic hepatotoxicity. The second generation drugs rosiglitazone and pioglitazone have been shown to improve histological features, liver enzymes, and insulin sensitivity in adult NAFLD patients.

Metformin is an insulin sensitizer that has been studied in children and adults with NAFLD. The use of metformin has been associated with improved insulin sensitivity, liver enzymes, and histological features. Metformin has been also shown to decrease the incidence of diabetes by 31% compared to placebo in a large trial of the Diabetes Prevention Program involving nondiabetics and prediabetics. Taking into consideration that the majority of patients with NAFLD are either diabetics or prediabetics, the use of metformin seems to be a reasonable choice in these patients.

Antioxidants

Antioxidants have been proposed as a possible therapeutic option as oxidative stress has been implicated in the pathogenesis of NAFLD. Therefore, *vitamin E* alone or in combination with other medications or life style modification has been evaluated for the treatment of NAFLD. In a small open-label trial, vitamin E was found to improve liver enzymes in ten children with NAFLD. The enzymes, however, increased following cessation of therapy. In another randomized trial, vitamin E was superior to placebo in a study involving 28 children. Although vitamin E has many advantages including low cost and tolerability, the lack of proved efficacy and the concern about long-term safety do not support its use in patients with NAFLD.

Antihyperlipidemics

Dyslipidemia is common in patients with NAFLD and may promote the progression of steatosis to steatohepatitis. Therefore, treatment with antihyperlipidemics seems like a reasonable option. Several agents have been looked at including statins, gemfibrozil, probucol, and omega3 fatty acids. However, the efficacy of these medications remains uncertain. Antihyperlipidemic agents may have a role in patients with significant dyslipidemia and increased risk for cardiovascular disorders.

Ursodeoxycholic Acid

Ursodeoxycholic acid is a known chloretic, immunomodulator, and cytoprotective agent. An initial report showed promising results in adult patients with NAFLD. However, a large randomized placebo-controlled trial that involved 166 patients with NASH for duration of 2 years could not reproduce similar findings.

The search for an effective therapy for NAFLD continues. Ideally such therapy should be safe, effective, well-tolerated, and of limited duration, and the effects should be sustained following cessation of treatment. For the time being several agents are being evaluated including angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), probiotics, antibiotics, lactulose, and nateglinide (insulin secretagogue). In the absence of a proved effective pharmacologic therapy in children, diet and exercise remain to be the safest approaches.

Surgery

Surgical treatment of obesity should be considered in patients with BMI greater than 40 or in patients with obesity-associated health disorders. However, the safety and effects of this approach has not been examined in children.

Several obesity surgical procedures have been tried including jejunoileal bypass, biliopancreatic diversion, gastroplasty with stapling, and gastric banding. However, the most effective and safest antiobesity surgical procedure is gastric bypass. In the procedure, gastroenterostomy is created dividing the stomach into a small proximal pouch excluding the fundus and the antrum. Gastric bypass is a very effective procedure and 49% of the patients can maintain loss of 50% of their excess weight. The procedure has been successfully performed in patients with cirrhosis and following liver transplant due to recurrent NASH. Marked improvement in steatosis, inflammation, ballooning degeneration, and perisinusoidal fibrosis have been reported following gastric bypass. However, there was little improvement in periportal fibrosis.

However, the anti-obesity procedures can be associated with significant morbidity including pulmonary embolism, sepsis, wound infection, volvulus, nutrient deficiencies, stomal stenosis, dilatation, ulceration, and bleeding. Approximately, one third of the patients develop gall stones within 6 months of the procedure and 10% develop symptoms requiring cholecystectomy. However, the use of UDCA can dramatically decrease the incidence of gall stones development.

Finally the rising incidence of NAFLD, NASH, and cirrhosis emphasizes the need for the development of effective therapeutic modalities. However, our efforts are limited by the lack of complete understanding of the pathogenesis of NAFLD. Increased awareness, prevention, early recognition, and management of obesity in the pediatric age group may prevent the development of NAFLD and its progression to advanced liver disease.

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216 Fulminant Hepatic Failure

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Definition

Fulminant hepatic failure in children is a clinical syndrome that evolves over a period of 8 weeks from the onset of signs and symptoms of liver disease. The clinical manifestations result from massive necrosis or severe functional impairment of hepatocytes. The synthetic, excretory, and detoxifying functions of the liver are all severely impaired, presenting in coagulopathy, jaundice, and hepatic encephalopathy. In children, recognition of hepatic encephalopathy is difficult and subtle and may only be apparent at the terminal stages.

The multinational Pediatric Acute Liver Failure (PALF) Study Group, formed in 2000, defined entry criteria of the study:

1. No evidence of a known chronic liver disease.
2. Hepatic-based coagulopathy not corrected by parenteral administration of vitamin K.
3. Hepatic encephalopathy must be present if the international normalized ratio (INR) is between 1.5 and 1.9.
4. Hepatic encephalopathy not required if INR is greater than or equal to 2.0.

There are a number of limitations to this narrow definition of fulminant hepatic failure, which are particularly highlighted in pediatric patients. For example, infants may present with hepatic failure in the perinatal period associated with the prenatal onset of liver disease, which may even evolve to cirrhosis before birth. This pattern may be observed in neonates with several inborn errors of metabolism including tyrosinemia, neonatal hemochromatosis, and inborn errors of bile acid synthesis. Congenital viral infection may also become manifest as hepatic failure. In some cases of non-A-E hepatitis, the onset of encephalopathy may occur later, often from 8 to 28 weeks after the onset jaundice and have a subfulminant course. In older children, fulminant Wilson disease may also present in children who were previously asymptomatic but have a prior significant preexisting liver disease and have an acute or chronic presentation. The time frame over which loss of hepatic function occurs may also present problems.

Etiology

In developed countries, the etiology of pediatric ALF significantly differs from adults. In adults, drug-induced liver failure (especially acetaminophen overdose) is the leading cause. In children, it accounts for less than 20% of cases. A diagnosis is not established in up to 50% of children. Etiologies are presented in ❯ *Table 216.1*.

Viral hepatitis types A, B, D, or E are a common cause of identifiable fulminant hepatic failure worldwide; however in only 5% of children in North America and the United Kingdom, infections are identified more frequently in infants and immunodeficient patients. The viruses include Herpes simplex, human herpesvirus-6, Parvovirus B19, cytomegalovirus, adenovirus, varicella zoster, enterovirus, and paramyxovirus, while Epstein–Barr virus (EBV) occurred more frequently in older patients. The viral hepatitis often presents as part of a more generalized, severe, systemic illness. The routine immunizations of children for hepatitis A and B may be responsible for the decline in these infections. Hepatitis A virus is a common cause in endemic areas but not in developed countries in the absence of an outbreak. Children with underlying chronic liver disease are more susceptible to develop ALF with HAV infection. Hepatitis B as a cause of ALF is less common in children than in adults and risk factors include older age, genotype D, and infants born to mothers with hepatitis B e antigen negative chronic hepatitis. Hepatitis C virus is a very rare primary cause of ALF. Hepatitis E occurs in endemic areas such as India, Africa, and Mexico. Non-A-E hepatitis (seronegative hepatitis) is the most common cause of ALF in the Western world and accounts for 45% of cases. The diagnosis is one of exclusion in which other causes of ALF are eliminated with appropriate laboratory investigations and clinical examination.

Fulminant hepatic failure may result from some hepatotoxic drugs and chemicals. Risk factors for drug-induced hepatotoxicity are age (very young children or adolescents), abnormal renal function, concurrent use of other hepatotoxic agents, drug interactions, and preexisting liver diseases. Drug-induced hepatotoxicity can be dose-dependent, idiosyncratic, or a synergistic

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Table 216.1
Causes of fulminant liver failure

Infection	
Viral; Hepatitis A, B, C, D, and E	
Non-A-E hepatitis	Herpes simplex, Adenovirus, Varicella, EBV, and CMV
Enterovirus	Septicemia
Drugs	
Dose-dependent; Acetaminophen, Halothane	
Idiosyncratic reaction; Isoniazid, NSAID, Phenytoin, valproate	
Antibiotics (Penicillin, Amoxycillin + Clavulanic acid Erythromycin, Tetracyclines, Sulfonamides, and Quinolones)	
Toxins	
Amanita, herbal medicines, CCl4	
Metabolic	
Wilson's disease	Galactosemia
Tyrosinemia	Hereditary fructose intolerance
Neonatal hemochromatosis	Niemann–Pick disease type C
Mitochondrial cytopathies	Inborn error of fatty acid oxidation
Hereditary fructose intolerance	Congenital disorder of glycosylation
Autoimmune hepatitis	
Vascular/ischemic	
Budd–Chiari syndrome	Acute circulatory or cardiac failure
Cardiomyopathies	Heat stroke
Infiltrative	
Leukemia, lymphoma	Hemophagocytic lymphohistiocytosis

reaction. Acetaminophen-induced liver injury is dose-dependent and may be intentional or a result of "therapeutic misadventure." Recent studies have identified APAP-cysteine protein adducts, which are detected in the plasma of patients with liver injury due to APAP long after the parent compound has been metabolized. Among children with indeterminate ALF, 12.5% had positive APAP-cysteine protein adducts, despite a lack of acetaminophen history. Fasting associated with an extended illness (depleted glutathione stores) and underlying susceptibility (e.g., fatty acid oxidation defect, altered cytochrome P-450 enzymes) are risk factors for APAP ALF. Common drugs that induce an idiosyncratic toxicity include isoniazid, sodium valproate, carbamazepine, penicillin, erythromycin, tetracyclines, sulfonamides, quinolones, amiodarone, and pemoline among others. Toxins that induce ALF include amanita phalloides (mushroom poisoning), herbal medicines, and Carbon tetrachloride (CCl4).

Metabolic causes of ALF are more common in children less than 1 year of age, but may be observed in all age groups. Galactosemia, hereditary tyrosinemia type 1, mitochondrial disorders, fatty acid oxidation disorders, hereditary fructose intolerance, neonatal hemochromatosis, inborn errors of bile acid metabolism, congenital disorder of glycosylation, and other inherited metabolic disorders may all result in hepatic failure. Wilson's disease is currently the most common metabolic disease presenting with ALF in older children and adolescents.

Autoimmune hepatitis can present as ALF, most of these patients being liver/kidney microsome antibody–positive. Nonspecific elevation of autoimmune antibody titers can occur in children with ALF, making the diagnosis difficult.

Fulminant hepatic failure may also be associated with severe birth asphyxia, sepsis, vascular occlusion (Budd–Chiari syndrome and veno-occlusive disease), congestive heart failure, cyanotic congenital heart disease, obstructive lesions of the aorta, circulatory shock, heat stroke, and hemophagocytic lymphohistiocytosis. Celiac disease and sclerosing cholangitis are rare causes of ALF.

Pathogenesis

The pathogenesis of hepatic encephalopathy remains an area of controversy and continued investigation. Increased serum levels of ammonia do not entirely explain altered cerebral function, as ammonia may be normal or only slightly elevated even when patients are deeply comatose. False neurotransmitters, amines, increased γ-aminobutryic acid receptor activity, or increased circulating levels of endogenous benzodiazepine-like substances have all been proposed. Increased absorption of these potential neurotoxins and decreased hepatic clearance may be involved in producing encephalopathy. Impaired regeneration of the liver following massive destruction of liver cells is likely to be a critical determinant. The mechanisms that underlie the poor regenerative response in these cases are not well defined.

Massive destruction of hepatocytes may represent a direct cytotoxic effect of a viral agent or hyperimmune response to viral antigens. Indeed, in over a third patients with hepatitis B-induced hepatic failure, serum may be negative for hepatitis B surface antigen within a few days

of presentation and there is often no detectable hepatitis B DNA in serum. In inborn errors of metabolism, the accumulation of potentially hepatotoxic metabolites may be involved in cellular injury. Oxidative damage may be of importance in disorders such as Wilson disease or neonatal hemochromatosis. Formation of hepatotoxic metabolites that bind to cellular macromolecules is involved in the injury produced by acetaminophen and isoniazid. Depletion of intracellular glutathione, which is essential for detoxification of reactive metabolites, is involved in the pathogenesis of hepatic injury.

Table 216.2
Clinical grades of hepatic encephalopathy

Grade 1	Confused; altered mood or behavior, psychometric defects[a]
Grade 2	Drowsy; inappropriate behavior[a]
Grade 3	Stuporous but speaking and obeying simple commands; inarticulate speech; marked confusion
Grade 4	Coma

[a]In infants, irritability, poor feeding, disturbance of sleep cycle

Pathology

Fulminant hepatic failure is associated with little or no regeneration of hepatocytes. Patchy or confluent, massive necrosis of hepatocytes is commonly found on liver biopsy or explant. Collapse of the reticulin frame work of the liver may occur as a result of multilobular or bridging necrosis. Centrilobular necrosis may be characteristic of certain forms of liver injury, particularly with acetaminophen intoxication or with circulatory shock. Microvascular fatty change of hepatocytes may be the predominant lesion rather than liver cell necrosis. This occurs in defects of the B-oxidation of fatty acids, Reye syndrome, and valproate hepatotoxicity. The absence of cell necrosis in these disorders implies a failure of organelle function. In inborn errors of metabolism such as galactosemia and hereditary fructose intolerance, there may be spotty hepatocyte necrosis combined with microvascular fat accumulation within the hepatocytes. Hepatocyte death may occur predominantly by apoptosis rather than by necrosis in some metabolic disorders. *Liver biopsy* is rarely helpful in ALF and is usually contraindicated because of the presence of coagulopathy.

Clinical Manifestations

The child with fulminant hepatic failure usually has been previously healthy. Progressive jaundice, fetor hepaticus, fever, anorexia, vomiting, and abdominal pain are commonly observed. In patients with severe acute liver there should be careful observation for features of hepatic encephalopathy, which initially may be characterized by minor disturbances of consciousness or motor function (*Table 216.2*). Early stages of encephalopathy may be particularly difficult to detect in infants. Irritability, poor feeding, and a change in sleep rhythm may be the only finding in infants. In older children asterixis may be demonstrated. The patient may become somnolent and confused or combative on arousal and eventually may become responsive only to painful stimuli. Progression can occur over the course of a few days or even weeks to deeper stages of coma in which extensor responses and decorticate posturing appear. The neurologic dysfunction associated with higher grades of coma is thought to be related to the development of cerebral edema, which is related to both cytotoxic and vasogenic factors.

Respiratory rate may be increased early, but respiratory failure may occur in evolution to stage IV coma. A rapid decrease in liver size without clinical improvement is an ominous sign. Bleeding from the gastrointestinal tract and easy bruising, as a result of severe coagulopathy is a common finding. Pruritus, ascites, growth failure, digital clubbing, palmar erythema, cutaneous xanthoma, and prominent abdominal vessels suggest a chronic liver condition.

Laboratory Findings

Serum aminotransferase levels are often markedly elevated. Serum direct and indirect bilirubin levels are variably increased. Although extremely high levels of serum aminotransferase activity are often found, the peak level does not correlate well with the severity of illness. In metabolic disorders, liver failure may be present with only modest elevation in their activity. Serum aminotransferase activities may actually decrease as the patient deteriorates, as the process of liver necrosis has released most of the available sources for the enzymes. A coagulopathy is always present with prolongation of the prothrombin time, which does not improve after the parenteral administration of vitamin K. Hypoglycemia can occur, particularly in infants. A functional form of renal failure – so-called hepatorenal syndrome – can occur in patients with liver failure and correlates with a

very poor outcome. A number of electrolyte disturbances are common, including hypokalemia, hyponatremia, hypophosphatemia, hyperammonemia, metabolic acidosis, and respiratory alkalosis. Renal function may be impaired as a result of tubular injury or hypovolemia. Serum acetaminophen levels after 4 h of ingestion are useful in identifying high-risk patients but are not informative in patients in whom toxicity is secondary to chronic administration. Myelosuppression is associated with non-A-E ALF and nonimmune hemolytic anemia with Wilson's disease. Alpha fetoprotein and selective clotting factors may serve as a marker of liver regeneration.

Treatment

There is no proven therapy that is known to reverse hepatocyte injury or to promote regeneration of hepatocytes. The treatment of fulminant hepatic failure involves primarily supportive care. Patients with fulminant hepatic failure with higher stages of coma should be treated in the setting of an intensive care unit, where monitoring of vital functions is possible. A quiet environment is necessary to avoid increase in intracranial pressure. Caregivers must carefully examine the child multiple times to assess evidence of changing mental status, increased respiratory effort, changing heart rate, or changes in blood pressure that might be signs of infection, increased cerebral edema, bleeding, or electrolyte imbalance. Numerous complications can also be identified and promptly treated (*Table 216.3*). In patients who are significantly disoriented or in coma, endotracheal intubation may be required to prevent aspiration, to reduce cerebral edema by hyperventilation, and to facilitate aspiration of secretions. Cerebral edema is an extremely serious complication that responds poorly to measures usually used to treat this complication in other disorders. Initial treatment would include minimizing excess stimulation, reduction of protein intake, treating suspected sepsis, and removing sedative medications that would affect mental status. The role of hypothermia in clinical practice remains unclear. Hyperventilation may actually worsen oxygen availability to the brain, but osmotic diuresis may be useful in maintaining cerebral perfusion pressure. The placement of an intracranial pressure monitor may be useful in guiding treatment. The gut should be purged with lactulose, a nonabsorbable disaccharide, thought to lower blood ammonia by decreasing microbial ammonia synthesis and trapping ammonia in acid colonic contents. Lactulose is administered in a dose sufficient to produce several acidic loose bowel movements daily. Nonabsorbable antibiotics, as neomycin, may be given to decrease enteric bacteria that produce ammonia. A variety of approaches have been used to assist the liver in removing toxins that may cause encephalopathy. Plasmapheresis or perfusion of the patient's plasma through an ion-exchange resin or a column of charcoal has been used in several studies. In uncontrollable studies, the patients may experience some clinical improvement, but no impact on neurological outcome or ability of the liver to recover spontaneously. Albumin dialysis is suggested in selective patients. Gastrointestinal hemorrhage, infection, sedatives, electrolyte balance, and hypovolemia may precipitate or exacerbate hepatic encephalopathy and should be prevented and aggressively treated.

Mechanical ventilation and the administration of oxygen are often required in more severely affected patients. Input and output should be strictly monitored. Renal dysfunction commonly occurs from dehydration, from acute tubular necrosis, from the initial toxic insult, and from hepatorenal syndrome. Renal replacement therapy with continuous veno-venous hemofiltration or dialysis may be necessary in some cases, but only liver transplantation can reverse HRS. Intravenous fluids should be restricted to between 85% and 90% of maintenance fluids to avoid over hydration. Electrolyte- and glucose-containing solutions should be administered intravenously to maintain urine output, correct electrolyte abnormalities, and prevent hypoglycemia. Hyponatremia is usually dilutional and not a reflection of sodium depletion. Parenteral infusion of calcium, phosphorous, and magnesium is often required.

Table 216.3
Extrahepatic complications of fulminant hepatic failure

Failure (in order of relative frequency)
Hepatic encephalopathy
Complex coagulopathy
Cerebral edema
Cardiovascular abnormalities
Acid–base disturbances
Gastrointestinal bleeding
Electrolyte imbalances
Renal failure
Sepsis
Pulmonary problems
Hypoglycemia
Pancreatitis

Intravenous/subcutaneous or intramuscular vitamin K should be given in an attempt to correct coagulopathy. Disseminated intravascular coagulation may be present in these patients as a result of liver failure as well as from infection. Infusion of FFP, factor concentrates (recombinant factor VII), or platelets may be necessary in the setting of active bleeding or in anticipation of an invasive surgical procedure, rather than treating laboratory abnormalities. Patients can rapidly become fluid overloaded with infusions of large amounts of fresh frozen plasma. Bone marrow suppression may be treated with immunomodulatory medications, steroids, cyclosporine A, antilymphocyte or antithymocyte globulin, as well as hematopoietic stem-cell transplant.

Infection commonly occurs and is often responsible for the demise of these patients. At least 50% of patients experience serious infections, including septicemia, pneumonia, peritonitis, and urinary tract infections. Gram-positive and gram-negative organisms as well as fungal infections can occur. Infection may present subtly, with tachycardia, intestinal bleeding, reduced renal output, or changes in mental status. Fever may not be present. Blood cultures should be obtained daily or with any evidence of clinical deterioration and antibiotics initiated with a clinical concern for sepsis. Prophylactic administration of H2-receptor blockers is usually advised because of the high risk of developing gastrointestinal bleeding. Ascites may be managed by fluid restriction and diuretics, but should be reserved for those patients who experience respiratory compromise or discomfort due to the fluid accumulation. Spironolactone is the drug of choice to initiate therapy, but furosemide may also be required. Overly aggressive diuresis may precipitate hepatorenal syndrome.

Specific therapies for unique causes of ALF are few: NAC for acetaminophen overdose, removal of galactose-containing formula in children with galactosemia, intravenous glucose and avoidance of fasting for children with inherited defects in fatty acid oxidation, and prompt administration of 2-(2-nitro-4-3 trifluoromethylbenzoyl)- 1,3-cyclohexanedione (NTBC) in children with hereditary tyrosinemia type 1. Other therapies in use include activated charcoal and high-dose intravenous penicillin for mushroom poisoning; corticosteroids for autoimmune hepatitis; copper chelation, plasmapheresis, and antioxidant therapy for Wilson disease; lamivudine or entecavir for acute hepatitis B; acyclovir for herpes simplex virus infection; hemodynamic support for shock or ischemic liver injury; decompressive surgery or transjugular intrahepatic portosystemic shunts (TIPS) for acute Budd–Chiari syndrome, corticosteroids, and chemotherapy for hemophagocytic syndrome; and antioxidant cocktail IVIG and double volume exchange transfusion for neonatal hemochromatosis. Currently, the only effective therapy of ALF is liver transplantation.

There are a number of liver assist devices under evaluation: non-cell-based (molecular absorbents recycling system, MARS), cell-based bioartificial liver systems, hepatocyte bioreactor, and stem-cell transplantations. These devices are being used to support patients until regeneration of the patient's liver occurs or to serve as a bridge until a suitable organ donor can be found.

Prognosis

Survival depends on the ability of the liver to recover from the ensuing insult, but it is very difficult to predict the potential for recovery. There is no single criterion that can predict the outcome with absolute certainty and be universally applicable to all patients with ALF with different etiologies. The prognosis varies and depends on the etiology of the hepatic injury, age, and stage of encephalopathy. Survival without liver transplant was highest in the APAP group (94%), while children with non-APAP drug-induced ALF (41%), metabolic disease (44%), or indeterminate ALF (43%) fared less well. In contrast, children with a non-A-E hepatitis or acute Wilson's disease rarely recover without liver transplantation.

Twenty percent of children in the PALF study who never developed encephalopathy either died or underwent liver transplant and those who presented with grade 4 encephalopathy fared better than those who progressed to grade 4. Complications of liver failure including sepsis, hemorrhage, or renal failure increase mortality. An INR <4 was associated with 73% survival versus 16.6% in those with an INR >4. Jaundice for more than 7 days prior to the onset of encephalopathy, alanine aminotransferase $<2{,}384$ IU/L on admission, factor V concentration of $<25\%$ of normal are other predictors of poor outcome. A liver injury unit score based upon total bilirubin, INR, and ammonia at presentation and with "peak" values appears to effectively predict survival without liver transplant; further prospective analysis will be necessary to confirm these findings.

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217 Mitochondrial Hepatopathies and Reye's Syndrome

Roshni Vara · Giorgina Mieli-Vergani

Definition

- *any symptom in any organ or tissue at any age with any mode of inheritance*

Mitochondria are ubiquitous organelles and the main source of the high energy adenosine triphosphate (ATP) required for intracellular processes. ATP is synthesised from oxidative phosphorylation, which takes place via the respiratory chain enzyme complex. The liver is highly dependent upon ATP for its many metabolic functions and, consequently, disorders of mitochondrial function can cause liver disease. Clinical manifestations of mitochondrial hepatopathies vary from mild liver dysfunction, chronic liver disease, fulminant hepatic failure, and end-stage liver disease, which can occur at any age, with or without other organ involvement.

Liver involvement in mitochondrial disorders rarely presents in adulthood but is a common feature of childhood disease, especially in the neonatal period. Mitochondrial hepatopathies can be classified as either primary (or genetic) or secondary when mitochondrial dysfunction occurs as a consequence of an exogenous insult, e.g., highly active anti-retroviral therapy (HAART), non-alcoholic steatohepatitis (NASH), and viral hepatitis (*Table 217.1*).

Mitochondria are unique in possessing two genomes; nuclear and mitochondrial DNA and therefore, mutations in either can lead to phenotypic expression. Whichever organ is affected, the clinical manifestations are heterogeneous despite identical genotype. This chapter will address the clinicopathological features of primary disease and secondary mitochondrial hepatopathy in Reye syndrome.

Epidemiology

Disorders of mitochondrial respiratory chain are thought to affect approximately 1 in 20,000 children. Around 10% of these have liver involvement, half of whom present in the neonatal period. It is likely that this is an underestimate in view of under recognition and difficulties in establishing the diagnosis. Mitochondrial disorders are pan-ethnic and those resulting from autosomal recessive inheritance, i.e., nuclear DNA mutations tend to be more common within consanguineous families.

Pathogenesis and Genetics

Mitochondria are multifunctional, double membrane subcellular organelles; the respiratory chain enzyme complex is embedded in the inner membrane (*Figs. 217.1* and *217.2*). The outer layer is a freely permeable phospholipid bilayer, which allows molecules to pass with ease. The inner membrane structure is complex and includes transport proteins whilst the cristae allow a greater surface area for the inner membrane.

Many oxidative pathways exist within the mitochondria, including β-oxidation for fatty acids, the pyruvate dehydrogenase complex, and the tricarboxylic acid cycle. These reactions generate reduced cofactors (e.g., $FADH_2$, NADH) and coupled with reoxidation via the respiratory chain produces ATP. This process is known as oxidative phosphorylation and is the final stage in aerobic respiration.

The respiratory or electron transport chain is a series of five coupled reactions. Each complex is made up of separate polypeptide subunits. There are also two independent electron carriers, ubiquinone or coenzyme Q and cytochrome c. The reduced cofactors allow electrons to pass into the respiratory chain; complex IV (cytochrome oxidase c) is the last carrier, which reduces oxygen to water. The energy produced by these reactions is sufficient to drive protons across the mitochondrial membrane and, by creating a gradient, powers the linked ATP synthase (complex V) in its phosphorylation of ADP to ATP and net production of energy. For this process to take place, it requires not only the functional integrity of the enzyme complexes but also the presence of other components such as substrate transport proteins.

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Table 217.1
Classification of mitochondrial hepatopathies

Primary	Molecular defect
Respiratory chain defects	
– Single	Complex I deficiency
	Complex III deficiency (*BCSL1*)
– Multiple	Complex IV deficiency (*SCO1*)
	Complex V (*ATP12*)
mtDNA depletion syndrome	*POLG, DGUOK, MPV17*
Aplers–Huttenlocher syndrome	*POLG*
Pearson syndrome	*mtDNA depletion*
Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE)	*TP mutation*
Villous atrophy with hepatic involvement	Complex III deficiency
Navajo neurohepatopathy	*MPV17*
Fatty acid oxidation defects	
Urea cycle disorders	
Secondary	
Reye syndrome	
Hepatic copper overload (Wilson disease)	
Hepatic iron overload	
Drugs/toxins – HAART, valproate, ethanol	
Viral hepatitis	
Cholestasis	
Cirrhosis	

Source: Modified from Treem WR, Sokol RJ (1998) Disorders of the mitochondria. Semin Liver Dis 18:237–253

In disorders of the respiratory chain, liver injury is thought to occur through a variety of pathogenic mechanisms:

1. Generation of reactive oxygen species (ROS) – their accumulation may contribute to liver pathology and the initiation of apoptosis.
2. Failure of ATP production and an energy-deficient state leads to cell death and subsequent fibrosis.
3. Secondary inhibition of pathways, such as β-oxidation of fatty acids, contributes to steatosis in liver and muscle.

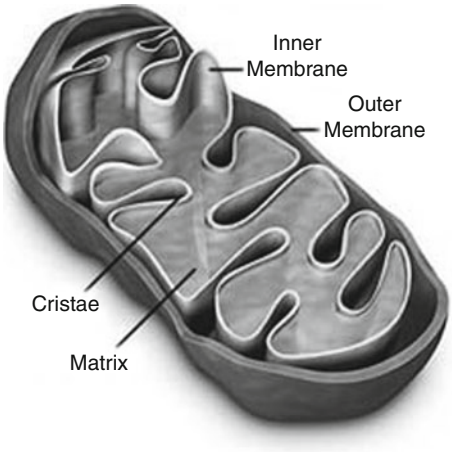

Figure 217.1
Schematic appearance of a mitochondrion (From www.cartage.org.lb)

Mitochondria are unique in possessing their own mitochondrial DNA (mtDNA); this is a circular double stranded molecule, 16,569 base pairs long. It codes for 37 genes, including the 13 polypeptides of complex I, III, and IV, the two ribosomal RNAs, and 22 transfer RNAs of mitochondrial protein synthesis. The proteins responsible for its transcription, translation, and replication are nuclear encoded.

Nuclear genes enocode more than 70 respiratory chain subunits and an array of enzymes and cofactors involved in mtDNA maintenance. These include DNA polymerase γ (POLG), thymidine kinase 2 (TK2), and deoxyguanosine kinase (DGUOK).

Unique to mtDNA is to be exclusively maternally inherited. The genome contains few introns, no protective histones, nor an efficient repair system. These factors, coupled with the increased number of reactive oxygen species mtDNA, increase greatly the potential of the mitochondrion for mutations when compared to nuclear DNA (nDNA).

Each mitochondrion contains two to ten copies of mtDNA; a typical hepatocyte contains approximately 1,000 copies of mtDNA. Normally, all copies of mtDNA in a cell are identical, a phenomenon known as "homoplasmy." A state of heteroplasmy exists when a cell harbours both normal (wild-type) and mutant mtDNA in various amounts as a consequence of random partitioning during cell division. This phenomenon accounts for the wide variation in severity and phenotypic expression of disease. Clinical manifestation of disease is determined by the percentage of mutant mtDNA in a given cell or tissue.

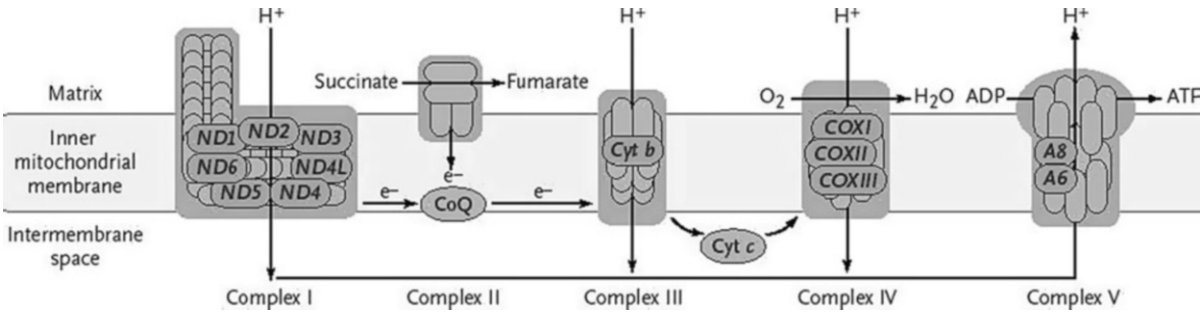

Figure 217.2
The respiratory chain enzyme complex (From DiMauro S, Davidzon G (2005) Mitochondrial DNA and disease. Ann Med 37:222–232)

Children with a defect in oxidative phosphorylation affecting a single respiratory chain complex may have a mutation in a gene encoding a subunit of that complex or in a gene encoding an assembly factor for that complex and therefore a defect in mtDNA or nDNA. Multiple complex deficiencies in children with liver involvement can be due to primary pathogenic point mutations or single deletions of mtDNA, but are more often associated with mitochondrial depletion syndromes (see below).

Mutations in mtDNA explain only about 20% of mitochondrial disorders in children and probably an even smaller percentage of those with liver involvement, despite there being over 200 pathogenic point mutations, deletions, insertions, and rearrangements identified since 1988. Most disorders involving primarily the liver are caused by nDNA mutations and the number of nuclear gene mutations identified is increasing continuously with improved molecular diagnostic techniques. Only mutations associated with liver disease in children are discussed in this chapter (◉ *Table 217.1*).

Single Respiratory Chain Defects

Complex I is the largest subunit with seven of its 43 subunits encoded by mtDNA. Nuclear mutations are probably involved in 95% of all children with complex I deficiency, the first mutations were identified in 1998 in the NDUFS4 and NDUFS8 genes by the group in Nijmegen. Isolated complex I deficiency is relatively frequent in mitochondrial hepatopathies and is associated with Alpers syndrome and a Leigh-like presentation with encephalopathy, hepatomegaly, growth retardation, and anemia.

Complex III is encoded by nDNA, except for one subunit. BCSL1 is an assembly factor for complex III: mutations in this gene have been identified in children with complex III deficiency and features of tubulopathy, encephalopathy, and liver failure and in GRACILE (growth retardation, aminoaciduria, cholestasis, iron overload, lactic acidosis, and early death) syndrome.

Complex IV or cytochrome oxidase (COX) is the terminal enzyme and has 3 out of 13 subunits encoded by mtDNA. Mutations in the nDNA encoded subunits have not yet been identified. SCO1 and SCO2 are proteins thought to be involved in copper delivery for the copper centers of COX. To date, mutations in the *SCO1* gene have been reported in two siblings with COX deficiency, neonatal-onset hepatic failure, and encephalopathy.

Complex V or *ATP synthase*, site of the final step in oxidative phosphorylation, uses the proton gradient across the inner mitochondrial membrane for the production of ATP. nDNA encodes all the subunits. Pathogenic mutations on one gene, *ATP12*, have been reported in two unrelated cases with isolated complex V deficiency, one with a cerebral malformation syndrome and the other with lethal neonatal lactic acidosis.

Multiple Respiratory Chain Defects

Mitochondrial depletion syndromes (*MDS*) are autosomal recessive diseases characterized by a dramatic decrease in mtDNA content leading to disease in the affected organ. These disorders, like all mitochondrial diseases, are extremely heterogeneous and are classified as myopathic, encephalomyopathic, and hepatocerebral. The latter group is associated with mutations in *Twinkle (PEO1), POLG1, DGUOK, and MPV17* genes and, in general, present with neonatal progressive liver failure and neurologic abnormalities.

POLG1 encodes the catalytic subunit of mitochondrial DNA polymerase and is probably the most frequently

involved nuclear gene with three commonly screened mutations. The clinical spectrum ranges from neonatal to adulthood onset, failure to thrive, hypoglycaemia, hypotonia, liver dysfunction (ranging from persistent jaundice to fulminant hepatic failure), and progressive neurological symptoms. A particular form is *Alpers–Huttenlocher syndrome* characterized by infantile onset, variable liver involvement, and intractable seizures.

DGUOK encodes the mitochondrial deoxyguanosine kinase (dGK) which is involved in the initial steps of the mitochondrial nucleoside salvage pathway. More than 80 affected patients from about 50 families have been reported. Characteristic presentation is with neonatal liver failure and variable neurological involvement. The condition is often fatal before 1 year of age.

TRMU nuclear gene encodes for a long protein that participates in the modification of mitochondrial tRNAs and is important for mitochondrial translation. Mutations in this gene have been found in infants presenting with acute liver failure with no evidence of mtDNA depletion and in one case with liver cirrhosis.

MPV17 is an inner mitochondrial protein of unknown role in mitochondrial maintenance. Mutations in the gene were initially identified in patients with neonatal liver failure, hypoglycaemia, failure to thrive, and neurological symptoms. A particular homozygous mutation is associated with *Navajo neurohepatopathy*, prevalent in the Native American Navajo population and manifesting as liver disease and motor neuropathy. Novel mutations are being identified in association with hepatocerebral forms with a variable clinical phenotype.

TYMP encodes thymidine phosphorylase, a multifunctional enzyme playing a role in the nucleoside salvage pathway by catalysing the breakdown of thymidine to be reutilized for mtDNA synthesis. Impaired thymidine metabolism has been demonstrated in patients with *MNGIE*, this progressive neurodegenerative syndrome was first described in 1983 and involves skeletal muscle, peripheral and central nervous systems, the intestinal tract, and liver. It is an autosomal recessive disease with multiple mtDNA deletions and depletion in muscle.

Mitochondrial deletion syndromes are due to large-scale mtDNA rearrangements and defects in nDNA. They are usually sporadic, heteroplasmic, and probably arise de novo during oogenesis or in early development. Pearson, or marrow-pancreas, syndrome is included in this group and is characterized by sideroblastic anaemia in infancy, often associated with pancytopenia, and variable exocrine pancreatic insufficiency, enteropathy, renal tubulopathy and hepatomegaly, or abnormal liver function tests.

Diagnostic Classification

There are as yet no definitive diagnostic criteria for mitochondrial hepatopathies in children, while diagnostic criteria have been proposed for adults with encephalomyopathies in 1996 by Walker et al.

Modified Walker criteria have been proposed for children with neurological disease. In children, the diagnosis of a mitochondrial hepatopathy with or without other organ involvement should be defined as:

1. Clinical, biochemical, and/or histological evidence of liver disease
2. Tissue respiratory chain enzyme deficiency (liver or muscle)
3. And/or identification of a nDNA or mtDNA mutation

The interpretation of respiratory chain enzyme deficiency, however, is sometimes difficult because of inadequacy of the tissue sample size, only moderately reduced activity and the theoretical effect of hepatic failure on enzyme activity. Therefore, diagnosis remains a challenge in clinical practice, with an urgent need for rapid and accurate diagnostic tests. In those cases where genetic mutation analysis can be directed by clinical manifestations and/or specific complex deficiency, recently developed sequencing techniques are proving beneficial. It is now possible to sequence the whole mitochondrial genome, though this is time-consuming and expensive. Oligonucleotide microarray sequencing (Mitochip) is a novel method to identify rapidly targeted gene mutations and a focus of great interest.

Clinical Manifestations

Mitochondrial hepatopathies can manifest at any age:

- Antenatally, e.g., with ascites, polyhydramnios
- Neonatal period with liver failure, often associated with poor feeding, vomiting, lethargy, hypotonia, seizures
- From the neonatal period to adulthood, with liver dysfunction, jaundice, hepatomegaly, chronic liver disease, end-stage liver disease

Initial symptoms of hepatic involvement can be masked by other organ involvement. Elevated transaminase levels, but rarely above 10 times the normal limit, can be the first indication of hepatopathy. In some patients, the liver dysfunction spontaneously resolves or remains stable, but in others there can be rapid progression with cholestasis, coagulopathy, and ascites.

Extrahepatic involvement, in particular of the central nervous system, is common, though infrequently, the liver can be involved in isolation. Liver disease can precede neurological involvement. This is a serious problem for children presenting with acute liver failure, in whom life-saving emergency liver transplantation might be followed by seizures, progressive neurological impairment, and early death. Other organs involved include kidneys (Fanconi-type tubulopathy), bone marrow (pancytopenia), intestine (enteropathy, villous atrophy), and heart (cardiomyopathy, arythmias).

The biochemical parameters listed below can suggest general mitochondrial dysfunction in the presence of liver dysfunction, but they are difficult to interpret/assess in the presence of severe liver failure:

- Hypoglycaemia
- Raised serum lactate
- Serum lactate/pyruvate ratio (>20)
- Raised cerebrospinal fluid lactate
- Raised ketone body ratio (β-hydroxybutyrate: acetoacetate >2.0)
- Raised plasma amino acids (alanine, glutamine)
- Organic acid profile; Kreb cycle intermediates, 3-methylglutaconic acid
- Aminoaciduria
- Raised tubulopathy markers (RBPs, NAGs)

Investigation of a Child with Suspected Mitochondrial Hepatopathy

Clinical history: Clinical suspicion guides formal tests. Physicians should maintain a high index of suspicion when liver disease presents in a consanguineous family, with other organ involvement without a known cause. Documentation of an extensive family history including minor signs in relatives is of paramount importance.

Laboratory tests include those listed above and the following precautions in taking samples should be observed:

- Sampling for lactic acidaemia, which may be present or absent, should be optimal and other conditions causing it, i.e., hypoxia, hypoperfusion, shock, sepsis and cardiac failure, should be excluded.
- Reduced respiratory chain complex activity should be measured in snap frozen tissue (muscle, liver, or skin fibroblasts).
- Leukocyte or tissue sample should be analyzed for mtDNA and nDNA mutations (this can be directed toward specific mutations in light of clinical features and respiratory chain complex(es) deficiency).

Histological features are often variable and nonspecific. Red ragged fibers in muscle biopsies, a common finding in affected adults, is extremely rare in children. Where liver biopsy is not contraindicated by coagulopathy, it may provide additional information with the presence of steatosis (micro- or macrovesicular) as a consequence of defective β-oxidation (Fig. 217.3a). However histological features can range from giant cell hepatitis, cholestasis with bile duct proliferation, to cirrhosis with nodular formation. Electron microscopy depicting megamitochondriae (Fig. 217.3b) are seen but are not as common as previously reported.

Neuroimaging can be useful in identifying features compatible with mitochondrial disease usually with symmetrical basal ganglia and/or brain stem changes. However, it can be normal and in the acute presentation, it may show generalized nonspecific changes.

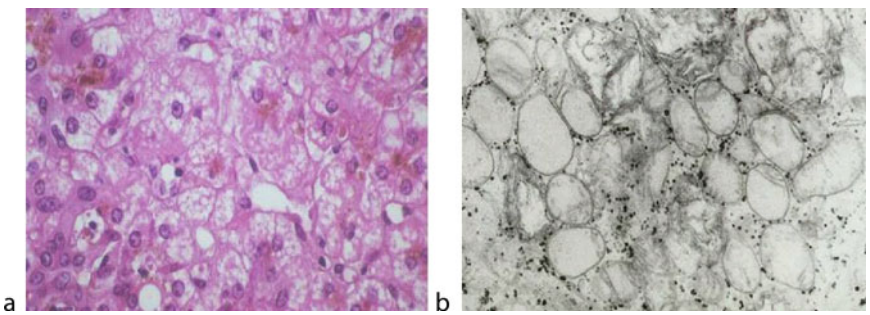

Figure 217.3
Light microscopy and electron microscopy appearance of liver disease in mitochondrial disorders. (a) shows microvesicular steatosis (light microscopy, haematoxylin and eosin); (b) shows abnormal mitochondrial architecture and megamitochondria (electron microscopy) (Pictures courtesy of Professor Bernard Portmann)

Table 217.2
Summary of mitochondrial hepatopathies

Clinical signs/ syndrome	Age at onset	Extrahepatic involvement	Complex deficiency	Molecular defect	Outcome
Neonatal liver failure	First weeks of life	Hypotonia, seizures, lactic acidaemia, hypoglycaemia	Single or multiple	*POLG1, DGUOK, SCO1, MPV17*	Mostly fatal
Acute liver failure	Postnatal–adolescence	Central nervous system or any other organ	Single or multiple; can be isolated to liver	*POLG1, DGUOK TRMU*	Variable
Alpers–Huttenlocher	Infancy–adolescence	Developmental delay, intractable seizures	Usually multiple	*POLG1*	Variable
Pearson	Infancy	Bone marrow, pancreas, gut, kidney	Normal or any	mtDNA rearrangement	Variable
Navajo neurohepatopathy	Infantile, childhood	CNS	All	*MPV17*	Usually fatal in first decade
Other chronic liver disease	Any	Any	Normal or single or all; can be isolated to liver	Not clearly defined	Variable; some survivors after liver transplant

If a mitochondrial hepatopathy is diagnosed, extensive investigation to search for extrahepatic involvement is of paramount importance to guide appropriate management. A summary of characteristics is presented in *Table 217.2*.

Treatment

Presently, there is no satisfactory treatment for mitochondrial disorders. Management remains symptomatic and in the case of mitochondrial hepatopathies is directed by the presence of acute or chronic disease. Medical treatments include the use of various vitamins, cofactors, respiratory substrates, and antioxidant compounds, e.g., thiamine, riboflavin, ubiquinone, though none of them has universally proven effectiveness. Ubiquinone, or coenzyme Q, may be effective in myopathic patients, but there is no reported benefit for cases with liver disease.

Supportive measures include bicarbonate infusions or oral supplementation where acidosis requires correction, carnitine supplementation in patients with secondary carnitine deficiency and fat-soluble vitamins in cases with cholestasis and features of chronic liver disease.

Sodium valproate can induce liver failure in mitochondrial disorders. *Valproate-induced hepatotoxicity* is well described and has been ascribed to alteration of several metabolic pathways including mitochondrial dysfunction. It is advised to avoid sodium valproate in children with cryptogenic liver disease and neurological involvement due to the small but significant risk of inducing acute liver failure.

Liver Transplantation

The decision to perform a liver transplantation involves two main scenarios:

(a) Children presenting with *fulminant hepatic failure* in whom an immediate diagnosis is not possible. Symptoms of mitochondrial disorders or severe liver failure due to different causes are often identical. Enzymatic studies are time-consuming and initial brain imaging may be normal or nonspecific. There are reports of patients transplanted in this situation, with diagnosis of mitochondrial disorder made retrospectively: those with neurological involvement have a poor prognosis.

(b) Children with a *chronic presentation* in whom liver disease progresses to require transplantation. In these cases, extensive investigation to exclude extrahepatic involvement is essential, there are few cases where the defect is isolated to the liver and liver transplantation can be an option. In cases where neurological involvement is thought to be stable and liver disease is progressive, again liver transplantation could be considered, but this needs to be decided in the setting of a multidisciplinary and tertiary referral center.

In conclusion, liver transplantation remains an option for selected cases, but the risk of progressive neurological deterioration and early death highlights the need for extensive investigation and caution when assessing patients.

Longer-term, posttransplant follow up of patients with isolated liver involvement and those with extrahepatic involvement presenting with liver disease is essential.

Prognosis

The prognosis of mitochondrial hepatopathies is variable, but those with an acute and early presentation tend to be fatal, neurological deterioration being often the cause of death. Children with a more chronic presentation can have stable liver and neurological disease and should be monitored with regular outpatient follow up, liver function tests, ultrasound scan, and neurological assessments. A small proportion of these children have progressive liver disease, developing cirrhosis, end-stage liver disease, and even hepatocellular carcinoma.

With the possibility of defining more accurate genotype/phenotype correlations and with more medium- to long-term follow up studies being published, our ability to provide an accurate prognosis is improving.

Genetic Counselling and Future Directions

Genetic counselling of affected families is important however complicated by the involvement of two genomes. Certain clinical phenotypes allow prediction of their mode of inheritance. nDNA mutations identified in the proband provide the possibility of prenatal testing of amniocytes or chorionic villi. In cases of maternal inheritance, the risk is absent for the progeny of an affected male but is high for that of an affected female. Mitochondrial inheritance is hampered by the incomplete knowledge of the exact proportion of mutant mtDNA required to produce a clinical phenotype, making recurrence risk difficult to predict. Available techniques to reduce the risk of recurrence are respiratory chain enzyme-based prenatal testing (if identified in fibroblasts), donor oocytes, preimplantation genetic diagnosis, nuclear and cytoplasmic transfer. It is important to consider each family individually and assess ethical issues appropriately within a multidisciplinary team of specialists.

Reye Syndrome

Reye syndrome is a rare and severe secondary mitochondrial hepatopathy with often, fatal consequences. There is typically a preceding viral illness and/or salycilate use (this is still a debatable association) and an intermediate recovery phase of about 3–5 days with subsequent development of encephalopathy and liver dysfunction. The syndrome was first described by the Australian pathologist R. D. Reye in 1963. The exact cause of 'classical' Reye syndrome is unknown, but most cases occur in the winter months with a peak age of occurrence between 5 and 15 years. Symptoms develop several days following an influenza or varicella infection. The child appears to be recovering but then develops sudden onset intractable vomiting followed by a noninflammatory encephalopathy and liver dysfunction (elevated transaminases rather than bilirubin), hyperammonaemia, mild to moderate coagulopathy, and variable hypoglycaemia. Progression of encephalopathy would lead to cerebral oedema and brainstem herniation. Urgent intervention with metabolic support and control of raised intracranial pressure are the mainstays of treatment until spontaneous recovery occurs or irreversible brain injury develops. The liver makes a full recovery. Mortality is high (40%) and higher in males than females. Abnormal mitochondrial architecture characterizes this disorder with involvement of brain, liver, muscle, and kidney. Liver biopsies are characterized by microvesicular steatosis in the absence of inflammation or necrosis.

Nowadays, many children thought to have had Reye syndrome are subsequently diagnosed with an inherited metabolic disorder, namely fatty acid oxidation effects. The incidence of Reye syndrome has dramatically declined since 1986 in Western countries following restriction of salycilate use in children, though not all agree that this is the only explanation. Some believe that improvement in diagnostic tests for fatty acid oxidation defects and other metabolic diseases also accounts for the decline in its incidence. It is, therefore, imperative to exclude fatty acid oxidation defects and other known metabolic causes in a child with an unexplained encephalopathy and liver dysfunction.

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218 Pyogenic Liver Abscess

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History

Liver abscesses have been recognized since the age of Hippocrates. In 1883, Koch described the amoebae as a cause of liver abscess. In 1938, Ochsner and Debakey published the largest series of pyogenic and amebic liver abscesses in the literature. The complications of liver abscess were not uncommon in that series and reported to result from rupture of the abscess into adjacent organs or body cavities resulting in pleuropulmonary and intra-abdominal complications. Pleuropulmonary complications are the most common and have been reported in 15–20% of early series including pleurisy, pleural effusion, empyema, and broncho-hepatic fistula. Intra-abdominal complications included subphrenic abscess and rupture into the peritoneal cavity, stomach, colon, vena cava, or kidney. A large abscess compressing the inferior vena cava and the hepatic veins may result in Budd-Chiari syndrome. Rupture into the pericardium or brain abscess from hematogenous spread is rare.

Types of Liver Abscesses

There are three major forms of liver abscesses, classified by etiology:

1. Pyogenic abscess, which is most often polymicrobial, and accounts for 80% of hepatic abscess cases in the United States
2. Amebic abscess, due to *Entamoeba histolytica*, accounts for 10% of cases
3. Fungal abscess, most often due to *Candida* species, accounts for less than 10% of cases

Pyogenic liver abscess (PLA) is a potentially life-threatening condition, complicating diverse abdominal pathologies. The global reported incidence for PLA is variable, ranging from 3 to 25 per 100,000 pediatric hospital admissions. PLA is a problem in developing countries. Children with liver abscesses constitute more than 79 per 100,000 pediatric admissions (<12 years old) in tertiary care centers in India. In larger series from developing nations, as Brazil, its frequency is approximately 1 out of 140 admissions. However, in developed countries, it is rare with an incidence of 25 per 100,000 admissions in United States to 11 out of 100,000 admissions in Denmark. It is a cause of significant morbidity and mortality. For unknown reasons, boys are affected by liver abscesses more than girls.

The frequency of individual infective agents as causes of liver abscesses is intimately linked to the demographics of the affected population. In developing countries, parasitic abscesses are most common, including amoebae, *Echinococcus granulosus* (hydatid disease of the liver), as well as protozoa and helminthes. In developed countries, liver abscesses are rare in healthy individuals, with imported infections from overseas visits accounting for the majority of cases. In developing countries, bacterial liver abscesses are more common and are usually seen in the setting of abdominal sepsis, especially the immunocompromised children, such as in diabetes mellitus, human immunodeficiency virus (HIV) infection, chemotherapy/transplant recipients, and in malignancy. Also, it may occur due to trauma or use of endoscopic retrograde cholangio-pancreatography (ERCP) and occasionally cryptogenic in about 15% of cases. Trauma may predispose to liver abscesses both by direct injury to the liver or by providing habitat for proliferation of organisms elsewhere. Child abuse can sometimes be the cause of sepsis and liver abscesses. Most of the liver abscesses in children are pyogenic in nature with amoebic liver abscesses constituting from 21–30% up to 50% of cases.

The most common microorganisms isolated from blood and abscess cultures are as follows: *Escherichia coli* (33%), *Klebsiella pneumoniae* in (18%), *Bacteroides* species (24%), streptococcal species (37%), and microaerophilic streptococci (12%).

Biliary disease accounts for 21–30% of reported cases. Extrahepatic biliary obstruction leading to ascending cholangitis and abscess formation is the most common cause. The infectious process originates within the abdomen and reaches the liver by embolization or seedling of the portal vein. With the liberal use of antibiotics for intra-abdominal infections, portal pyemia is now a less frequent cause of PLA but still accounts for 20% of cases.

Hematogenous infection via the hepatic artery results from seedling of bacteria into the liver in cases of systemic

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bacteremia from bacterial endocarditis, urinary sepsis, or following intravenous drug abuse. Blunt or penetrating trauma and liver necrosis from inadvertent vascular injury during laparoscopic cholecystectomy are recognized causes of PLA. In addition, transarterial embolization and cryoablation of liver masses are now recognized as etiologies of PLA.

Diagnosis

The clinical presentation of liver abscess is insidious. Many patients have symptoms for weeks prior to presentation. Fever and right upper quadrant pain are the most common complaints. Pain is reported in as many as 89–100% of patients and may be associated with pleuritic chest pain or right shoulder pain. Symptoms are often misdiagnosed as acute cholecystitis. Fever occurs in 87–100% of patients and is usually associated with chills and malaise.The most common symptoms and signs of PLA are shown in *Table 218.1*.

Ultrasound examination is the investigation of first choice (*Fig. 218.1*). It is rapid, safe, relatively inexpensive, and accurate in picking a liver lesion. Appearances of an abscess may be a rounded or an oval lesion which is usually hypoechoic, but may have heterogenous echotexture. A solid or heterogenous lesion often evolves into a hypoechoic lesion on subsequent examination. Real-time ultrasonography findings are 80–100% sensitive.

Computed tomography (CT), as in *Figs. 218.2* and *218.3*, is more sensitive in detecting even small abscesses anywhere in the liver; yet it is inconvenient and expensive with risk of contrast reactions being always there. A hypodense lesion with low attenuation areas and an enhancing rim is a classical contrast-enhanced CT image. Small hypoechoic lesions in clusters may suggest the beginning of later process of coalescence into a single large abscess.

CT scanning has become the imaging study of choice for detecting liver lesions. If ambiguity arises in the diagnosis of an occasional patient with conventional imaging, scintigraphy may help. Diagnostic aspiration should

Table 218.1
Symptoms and signs of pyogenic liver abscess

Symptoms	Percentage	Signs	Percentage
Abdominal pain	89–100	Normal findings	38
Fever	87–100	Right upper quadrant tenderness	41–72
Chills	33–88	Hepatomegaly	51–92
Anorexia	38–80	Mass	17–18
Weight loss	25–68	Jaundice	23–43
Cough	11–28	Chest findings	11–48
Pleuritic chest pain	9–24	–	–

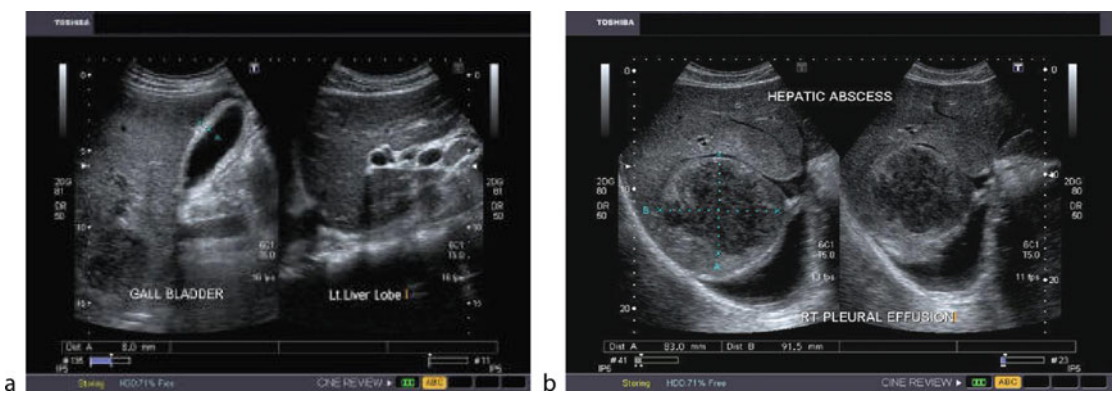

Figure 218.1
(a) Markedly hypoechoic nature of the lesions suggesting further breakdown of the solid liver tissue (liquifactive necrosis). On aspiration, the fluid was typically anchovy sauce-like in appearance. This suggests hepatic amebic abscess at a more advanced stage. The gallbladder shows wall thickening suggesting edema of the wall. (b) This figure shows a small pleural effusion just above the right lobe abscess (reactionary fluid collection due to pleurisy) (Ultrasound images were taken using a Toshiba Xario ultrasound system, courtesy of Gunjan Puri, MD, India)

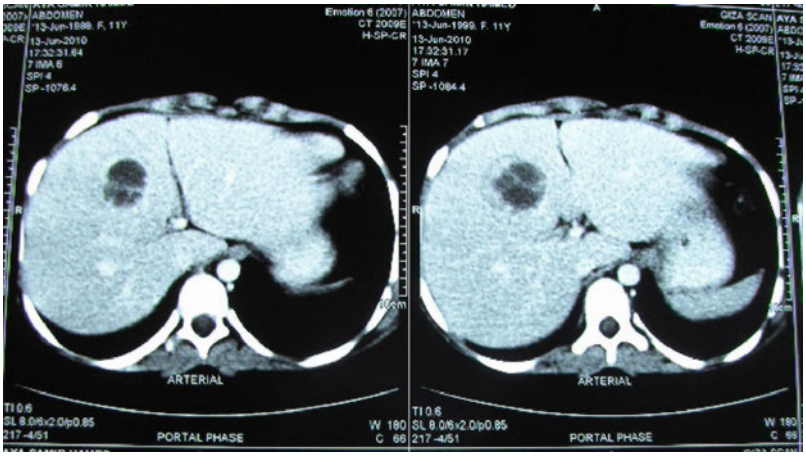

Figure 218.2
CT scan of a 9-year-old girl with pyogenic liver abscess

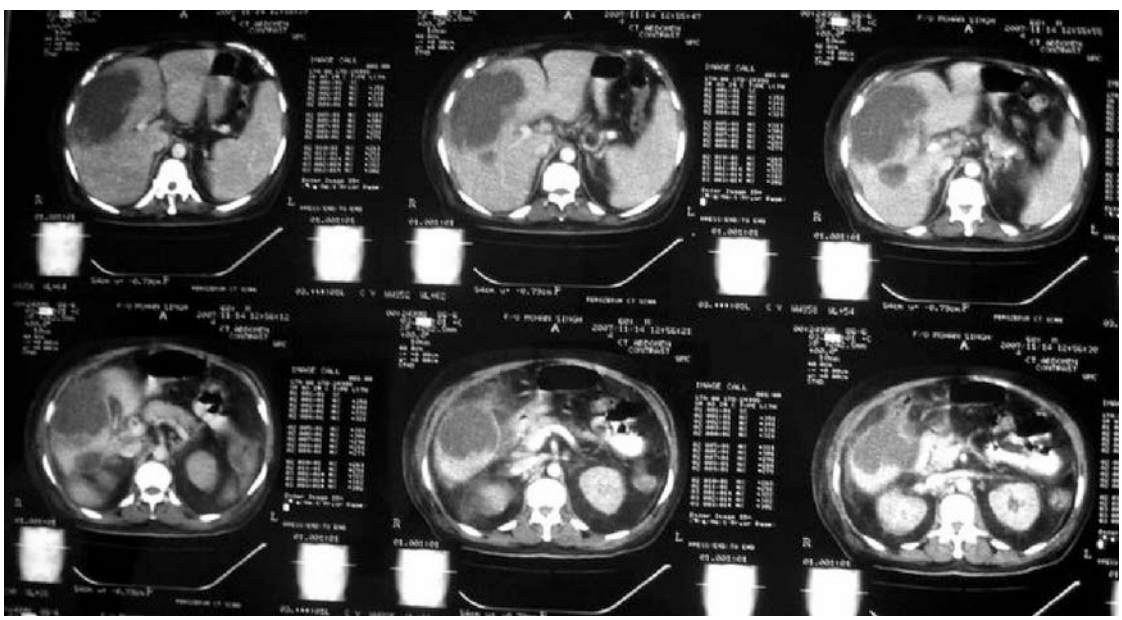

Figure 218.3
CT scan of an amebic liver abscesses involving the right lobe of liver (Courtesy of Vikas Arora, MD, India)

be performed as soon as the diagnosis is made. It can be performed under ultrasonographic (if small or superficial) or CT guidance and is usually followed by placement of a drainage catheter. Multiple abscesses necessitate CT-guided drainage. Once positioned, the catheter should be irrigated with isotonic sodium chloride solution and placed to allow gravity drainage. The drain is removed when the abscess cavity collapses, as confirmed on CT scan images. Presence of ascites and proximity to vital structures are contraindications to percutaneous drainage. Coagulopathy can be corrected with transfusion of fresh frozen plasma prior to drainage.

Treatment

The most dramatic change in the treatment of PLA has been the emergence of CT-guided drainage. Prior to this modality, open surgical drainage was the treatment most often employed, with mortality rates as high as 70%. If the abscess is multiloculated, multiple catheters might be needed to achieve adequate drainage. The current accepted approach includes three steps: initiation of antibiotic therapy, diagnostic aspiration and drainage of the abscess, and, finally, surgical drainage in selected patients.

Antimicrobial agents adminstered should provide adequate coverage against aerobic gram-negative bacilli, microaerophilic streptococci, and anaerobic organisms, including *Bacteroides fragilis*. Usually, a combination of two or more antibiotics is used. Metronidazole and clindamycin have wide anaerobic coverage and provide excellent penetration into the abscess cavity. A third-generation cephalosporin or an aminoglycoside provides excellent coverage against most gram-negative organisms. Fluoroquinolones are an acceptable alternative in patients who are allergic to β-lactams. This modality has been shown to be effective in patients with unilocular abscesses that are less than 3 cm in size.

The success rate of *percutaneous drainage* ranges from 80% to 87%. Percutaneous drainage is considered failed if no improvement occurs, if the condition worsens within 72 h of drainage, or if the abscess recurs despite adequate initial drainage. Percutaneous drainage failure can be treated by either inserting a second catheter or performing open surgical drainage. Surgical drainage is indicated in the following:

- Abscesses larger than 5 cm
- Abscess not amenable to percutaneous drainage secondary to location
- Coexistence of intra-abdominal disease that requires operative management
- Concominant biliary tract disease
- Failure of antibiotic therapy
- Failure of percutaneous aspiration
- Failure of percutaneous drainage

Untreated, PLA is associated with 100% mortality. Early series reported a mortality rate of greater than 80%. With early diagnosis, appropriate drainage, and long-term antibiotic therapy, the prognosis has improved dramatically. Poor prognostic factors are multiplicity of the abscesses, polymicrobial infection, presence of associated malignancy or immunosuppressive disease such as HIV infection, and evidence of systemic sepsis.

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219 Drug-Induced Liver Injury

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Drug-induced liver injury (DILI) is an important cause of liver disease in adults and pediatrics. Although most patients develop mild hepatotoxicity such as hepatitis, cholestasis, or asymptomatic enzyme elevation, some patients may progress to fulminant hepatic failure, which may lead to liver transplantation or death.

Etiology

Hepatotoxicity has been reported with numerous drugs and the number is expected to increase with the development and approval of new medications (*Table 219.1*). Acetaminophen is considered as one of the main drugs causing liver injury. In a study of 348 pediatric patients with acute liver injury, 14% of the cases were due to acetaminophen, while 5% were due to non-acetaminophen drugs, such as antituberculous and antiepileptic drugs. Acetaminophen-induced liver injury usually results from acute or chronic ingestion of high doses, but hepatotoxicity resulting from therapeutic doses has also been reported. Initially, patients develop nonspecific symptoms such as nausea, vomiting, and anorexia. However, if not managed early, patients develop histological and biochemical liver toxicities and other non-hepatic complications such as cerebral edema and multiorgan failure. Overall, patients presenting with acetaminophen-induced liver injury have a better prognosis, compared to patients presenting with liver injury due to non-acetaminophen drugs, especially when the acetaminophen hepatotoxicity is recognized and managed early.

Aspirin-induced liver injury is uncommon, but has been described in children receiving chronic aspirin therapy for juvenile rheumatoid arthritis. Aspirin was associated with an increase in liver transaminases and alkaline phosphatase, and in some patients prolongation of prothrombin time and epistaxis.

Most antimicrobial drugs may cause hepatotoxicity, although the incidence is relatively low. Penicillins and cephalosporins may cause an increase in the liver transaminases, which is usually subclinical and reversible. Drug-induced liver injury has been described with amoxicillin and the incidence increases when amoxicillin is combined with clavulanic acid. Liver injury associated with amoxicillin-clavulanic acid is usually delayed in its onset, with a cholestatic or mixed hepatocellular cholestatic pattern. In most cases, the patient's condition resolves within a few weeks of discontinuing treatment, but progressive hepatotoxicity due to amoxicillin-clavulanic acid therapy has been reported.

All forms of erythromycin are potentially hepatotoxic. The onset of hepatotoxicity is usually delayed. Patients may present with anorexia, nausea, jaundice, abdominal pain, and a mixed hepatocellular cholestatic injury pattern. Complete recovery is typically seen after discontinuation of erythromycin therapy, although cases of severe liver failure have been reported. Azithromycin and clarithromycin are generally associated with fewer side effects, compared to erythromycin. However, cases of abnormal liver function, including hepatitis and cholestatic liver disease have been reported.

Tetracycline antibiotics are associated with a dose-related hepatotoxicity. Liver injury usually appears 4–6 days after initiating therapy and is characterized by nausea, vomiting, abdominal pain, mild jaundice, and increased serum aminotransferases up to 10 times the upper limit of normal.

Trimethoprim-sulfamethoxazole may induce hepatotoxicity. Symptoms are usually apparent within days to 1 month of initiating therapy. Most cases of liver injury involve cholestasis, although cases of hepatocellular hepatitis have also been described with trimethoprim-sulfamethoxazole. Patients may also present with extrahepatic manifestations such as fever, rash, peripheral eosinophilia, and other organ involvement.

Hepatotoxicity has been reported with all antifungal agents, though the incidence varies between the individual drugs. Amphotericin rarely causes severe liver injury, but may result in asymptomatic self-limited hepatitis. Azole antifungal drugs (i.e., ketoconazole, itraconazole, fluconazole, voriconazole, posaconazole) may cause hepatotoxicity, with the highest reported incidence with ketoconazole. Asymptomatic elevations of serum aminotransferases, with or without elevations in bilirubin, have been reported within a few days to a few weeks after initiating azole antifungal therapy. Hepatitis, cholestasis, and fulminant

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Table 219.1
Drugs associated with liver injury

Antipyretics/analgesics	*Antiepileptic drugs*
Acetaminophen	Phenytoin
Aspirin	Phenobarbital
Nonsteroidal antiinflammatory drugs (ibuprofen, naproxen)	Carbamazepine
Antimicrobial drugs	*Chemotherapy medications*
Penicillins and Cephalosporins	6-Mercaptopurine
Macrolides (erythromycin, azithromycin, clarithromycin)	Cisplatin
Sulfa (trimethoprim-sulfamethoxazole)	Decarbazine
Antifungals (azoles, echinocandin)	Cyclophosphamide
Antituberculous (isoniazide, rifampicin, pyrazinamide)	

The table lists commonly used drugs that are associated with liver injury. It does not provide a comprehensive list of drugs that may induce liver injury

hepatic failure have also been described in patients receiving azole therapy. Laboratory abnormalities have been seen in patients treated with the echinocandin antifungal drugs, caspofungin, anidulafungin, and micafungin, and cases of clinically significant hepatic dysfunction, hepatitis, and hepatic failure have been reported.

Hepatotoxicity associated with antituberculous drugs varies depending on the specific drug, presence of other hepatotoxic drugs, and the age of the patient. In one study, the incidence of severe hepatotoxicity, defined as serum tansaminases five times above the upper limit of normal, in pediatric patients was 8%. Age younger than 5 years and the coadministration of pyrazinamide were significant contributions to the development of severe hepatotoxicity. The clinical presentation ranges from asymptomatic elevations of liver enzymes to severe hepatitis or acute liver failure, resulting in death or the need for liver transplantation in some patients.

Subclinical and significant hepatotoxicities have been reported with most antiepileptic drugs, though progression to severe hepatic failure is not common. Elevated transaminases with phenytoin are common, but mostly reversible after discontinuation of therapy. Hepatotoxicity due to phenobarbital and carbamazepine is rare. Cases were associated with a multisystemic drug hypersensitivity syndrome, with the liver involvement predominating. Valproic acid is associated with two types of liver injury: one that is dose-dependent, which develops shortly after starting therapy and liver enzymes improve after reducing the dose. The second type of hepatotoxicity is delayed and is not influenced by the dose.

Various antimetabolites used in the therapy of leukemia and other neoplastic conditions may result in hepatic injury with jaundice, hepatomegaly, dark urine, and elevated liver enzymes. Antineoplastic drugs such as 6-mercaptopurine, cisplatin, decarbazine, and cyclophosphamide are associated with hepatotoxicity. Patients usually present acutely with an enlarged tender liver, ascites, jaundice, and elevated liver enzymes. Liver disease may continue to progress to cirrhosis with hepatic venular sclerosis and sinusoidal fibrosis.

The drugs discussed above are those that are commonly used, which may cause drug-induced liver injury. However, single cases have been reported with many other drugs

Epidemiology

The true incidence of DILI in pediatric patients is unknown. In one study, DILI was reported in about 20% of cases of acute liver failure in children. However, the actual incidence of DILI is thought to be higher than the reported incidence in the literature. In a French prospective study, the incidence of hepatic drug reactions was 16 times more than the number reported in the French Pharmacovigilance system.

Pathogenesis

The exact pathogenesis of drug-related hepatocellular injury is not always identified. Childhood drug hepatotoxicity is generally uncommon compared to that of adult. This may be partly due to the fact that children are usually free of many of the factors like smoking and cardiovascular disorders as hypertension, compared to adults.

The pathogenesis of DILI occurs through direct intrinsic hepatotoxicity or idiosyncratic reactions. Intrinsic hepatotoxins are associated with a dose-dependent predictable liver injury and the latent period between exposure and onset of symptoms is typically short (i.e., hours to days). Serum aminotransferases are typically 8–500 times normal and serum alkaline phosphatase is one to two times the upper limit of normal. The classic example of an intrinsic hepatotoxin is acetaminophen.

Acetaminophen is metabolized by cytochrome P-450 to a reactive metabolite, *N*-acetyl-benzoquinone imine (NAPQI). The NAPQI metabolite is detoxified by

glutathione to form an acetaminophen-glutathione conjugate. At therapeutic doses, there is sufficient glutathione to conjugate acetaminophen. However, toxic doses of acetaminophen deplete the glutathione stores, and the acetaminophen covalently binds to cysteine groups on protein, forming acetaminophen-protein adducts, which are responsible for acetaminophen-induced hepatotoxicity. Several other mechanisms such as superoxide formation and mitochondrial dysfunction may play a role in the pathogenesis of acetaminophen toxicity, but the concept of the reactive metabolite NAPQI is still considered as the primary mechanism. Salicylate-induced hepatic injury is also thought to be dose-dependent, since most cases of liver injury were reported in children receiving chronic therapy for arthritic disorders.

The pathogenesis for most drug-related hepatotoxicity is considered an idiosyncratic reaction. In this type of reaction, the liver injury is unpredictable, is not dose-dependent, and the latent period between exposure to the drug and the sensitivity reaction is variable. The idiosyncratic reaction may be either immunologic/allergic or nonallergic/metabolic. In the immunologic reaction, it is thought to depend upon a complex interaction of the drug and its metabolites with the immune system, which results in hepatocyte necrosis and apoptosis and the release of cytokines that can lead to secondary cell damage or have immune modulating effects.

Clinical Manifestations

The clinical presentation of DILI ranges from asymptomatic enzyme elevations to fulminant hepatic failure, which may be fatal. Symptoms resembling acute viral hepatitis with jaundice, malaise, anorexia, nausea, and abdominal pain are commonly reported in patients with DILI. However, several other clinical presentations have been reported, such as hepatic veno-occlusive disease, cirrhosis, and steatohepatitis.

Based on the laboratory findings, patients may present with hepatocellular, cholestatic, or mixed liver injury. Acute hepatocellular liver injury is defined as an increase in ALT $>$ 2 folds the upper limit of normal (ULN) or an ALT/AP ratio $>$ 5. Patients with hepatocellular liver injury have nonspecific clinical features, and jaundice is not always present. In some patients, findings suggestive of a drug allergy may be present, such as fever, rash, or peripheral eosinophilia. Acute cholestatic injury is defined as an increase in serum AP $>$2-fold the ULN or by an ALT/AP $<$2. Patients with acute cholestasis usually present with jaundice and itching. As for mixed liver injury, the clinical and laboratory findings are intermediate between a hepatocellular and cholestatic pattern. The ALT/AP ratio is between 2 and 5 and drug allergy manifestations are usually present. In the event of mixed liver injury, a drug etiology should be considered, as the mixed liver failure findings are not characteristic of viral hepatitis.

The clinical presentation of patients may also be classified based on the onset of symptoms. The time between the initiation of the drug and the onset of symptoms may be short (i.e., hours to days) as with acetaminophen, intermediate (i.e., within the first 8 weeks) as with phenytoin, or long (i.e., within 1–12 months) as with isoniazid. With some antibiotics, such as amoxicillin/clavulonate and ciprofloxacin, patients may present with symptoms of liver toxicity several weeks after discontinuation of therapy.

Diagnosis

The diagnosis of DILI can be difficult, especially in the presence of other medications and underlying disease states. The patient's initial assessment may include liver function tests, serologies for viral and autoimmune hepatitis, and an abdominal ultrasonography. The diagnosis involves ruling out other potential causes of liver failure and evaluating the clinical features associated with the liver injury. The clinical features of DILI include the patient's clinical presentation, laboratory findings, the time from drug intake/withdrawal and onset of symptoms, and time for symptoms to resolve after removal of the suspected drug. Although variations exist among patients for each drug and the clinical features commonly associated with specific drugs are not consistently seen in all patients, evaluating the clinical presentation of the patient still helps in identifying the most likely culprit, especially when multiple hepatotoxic drugs are present. The findings of the liver biopsy may also aid in the diagnosis of DILI, but in most cases, a liver biopsy is not done.

Rechallenging the patient with the suspected drug may help in confirming the diagnosis of DILI. However, one should weigh the risks and benefits of a rechallenge, especially with drugs that are known to cause hepatocellular damage, as in these cases patients may rapidly progress to fulminant hepatic failure. In addition, failure to demonstrate hepatic injury following a rechallenge may not completely exclude DILI. With certain medications, several weeks of therapy is required before liver damage is detected and in some patients a recurrence of hepatic injury may not occur after one rechallenge dose is given.

Several scales and scoring systems have been developed in an attempt to provide an objective tool for the diagnosis

of DILI and to establish a causal relationship between the offending drug and liver damage. The most common scales are the Rouse Uclaf Causality Assessment Method of the Council of International Organization of Medical Sciences (RUCAM/CIOMS), the Naranjo Probability scale, and the Maria and Victorino (M&V) scale. Compared to the Naranjo and the M&V Scales, the RUCAM/CIOMS scale demonstrated better validity and reproducibility in the assessment of DILI. However, the RUCAM/CIOMS has risk factors (e.g., pregnancy, alcohol consumption, and age >55 years) that are not applicable to pediatric patients, and therefore its use is limited in this patient population.

Treatment

The key to the management of DILI is early recognition and discontinuation of the suspected drug. In most cases, once the culprit drug is discontinued, liver disease improves, although the rate of recovery varies. Cholestatic and mixed liver injuries tend to resolve slower than the hepatocellular reactions and may last for more than a year in some cases. Liver transplantation is considered in patients who progress to fulminant hepatic failure, despite removal of the culprit drug. However, liver transplantation is associated with complications and a risk of death that should be weighed into the clinical decision. In an analysis of the United Network for Organ Sharing database, which included 22 patients less than 18 years old with acute liver failure due to antiepileptics, 73% died within the first year of transplantation.

The use of ursodeoxycholic acid has been suggested for patients with drug-induced cholestatic liver failure. The drug has not been evaluated in this setting, but case reports of patients with drug-induced cholestasis in which ursodeoxycholic acid was administered reported improvement in the clinical and laboratory findings. Therefore, given the relatively safe adverse event profile and the concerns of prolonged cholestasis, it is recommended to consider ursodeoxycholic acid in patients with severe or prolonged drug-induced cholestasis.

The role of corticosteroids in the management of DILI has not been well established. The available evidence is limited to case reports that described improved symptoms after the administration of corticosteroids. Two studies that evaluated the use of corticosteroids in patients with acute liver failure, regardless of the etiology, did not show improved outcomes with steroid therapy. In one of the studies, the subset of patients with DILI that received steroids had a trend toward worse prognosis. The studies had several limitations and did not include pediatric patients, which makes the role of steroids for the management of DILI in pediatric patients unclear. Despite the lack of strong evidence, steroids are generally recommended in patients who develop severe hepatitis associated with jaundice and coagulopathy, along with a clinical picture suggestive of drug allergy (i.e., fever, rash, eosinophilia), and who do not improve following the discontinuation of the suspected medication.

It is unclear if a patient who develops hepatotoxicity due to a specific drug can be safely switched to another drug within the same class, without experiencing a similar adverse reaction. Cross hepatotoxicity has been reported between chemically related drugs. However, there are also cases in which cross hepatotoxicity was not seen when switching from one drug to another within the same class. Due to the lack of sufficient data regarding cross hepatotoxicity, it is advisable to be cautious in patients who develop severe DILI when switching to a drug within the same chemical class.

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220 Pediatric Liver Transplantation

Michael B. Ishitani

Pediatric liver transplantation is a widely accepted therapy for children with end-stage liver disease or liver-based inborn errors of metabolism. This chapter is intended to briefly review the development of this technique and to highlight the indications and contraindications for liver transplantation in children. It also examines some of the new technical advances that have been made over the last decade and resulted in an increase in the pool of available donor organs. The chapter also discusses some of the complications and management issues that occur after liver transplantation, especially those problems unique to children.

History

Liver transplantation in humans was first attempted in 1963 when Thomas Starzl performed a liver transplant in a 3-year-old child. Initial efforts at other centers also failed and it was not until 1967 that Starzl was able to obtain long-term survival of a patient. Mortality in these patients was high due to technical problems with the operation itself and complications of the relatively crude immunosuppressive agents.

The introduction of cyclosporin into clinical use in the late 1970s coupled with advancements in surgical technique led to major improvements in patient survival. By 1983, a National Institutes of Health consensus statement declared that liver transplantation was no longer experimental and was now an accepted form of therapy for end-stage liver disease. Over the last decade, survival rates for children undergoing liver transplantation have improved, with current 1-year survival rates of 89%, 3-year survival rates of 83%, and with many centers reporting greater than 90–95% 1-year survival rates.

In the past, a major problem in pediatric liver transplantation has been obtaining an adequate supply of size-matched cadaveric donors. The majority of children who require liver transplantation weigh less than 20 kg and the potential pool of donor organs is therefore small. Initial reports indicated that mortality rates ranged from 25% to 40% among children who were awaiting a suitable size-matched cadaveric liver. In the mid-1980s, Bismuth and Houssin in France and Broelsch in the United States pioneered the use of reduced size cadaveric grafts for children. Using this technique, an adult cadaveric donor liver could be utilized in a child with nearly equivalent results to a size-matched pediatric cadaveric donor graft. In the 1990s, new technical advances led to the successful use of split-liver grafts, whereby a single liver was divided into two pieces and given to two recipients, and living-related liver transplants, whereby a segment of liver from an adult living donor was removed and transplanted into a child. Some centers are now utilizing donor organs from non-heart-beating donors with some success.

Indications

Children who are referred to a transplant center for evaluation generally have some form of acute or chronic liver failure or a correctable inborn error of metabolism. Clinical presentation is variable, but usually consists of some combination of signs and symptoms, noted in (*Table 220.1*). For children in the United States, the most common etiology of chronic liver failure is cholestatic liver disease due to biliary atresia (*Table 220.2*). Other common etiologies for chronic liver failure in children include neonatal hepatitis, autoimmune hepatitis, and viral hepatitis. Secondary causes of liver failure include cystic fibrosis with minimal pulmonary involvement and Langerhans histiocytosis.

Acute fulminant hepatic failure presents with the sudden onset of encephalopathy, coagulopathy, and jaundice in children with no previous history of liver disease. The most common causes are viral hepatitis (usually non-A, non-B or hepatitis B) or drug-induced liver failure (acetaminophen, valproic acid). Mortality can be very high and early referral is mandatory to maximize the chance for survival.

Certain disorders of metabolism are also successfully treated by liver transplantation. These include common disorders where the liver is injured by the underlying disease process (Wilson's disease, a_1-antitrypsin disease) and uncommon disorders (ornithine transcarbamylase deficiency, tyrosinemia type 1) where the new liver provides a missing enzyme and allows phenotypic normal function.

Experience with liver transplantation in children with unresectable neoplasms is limited, although there is

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Table 220.1
Clinical presentations indicative for liver transplantation

Decreased hepatic synthetic function (hypoalbuminemia, coagulopathy)
Encephalopathy
Intractable pruritus
Complications of portal hypertension (ascites, variceal bleeding, subacute bacterial peritonitis)
Episodes of cholangitis
Bone complications of liver disease (hepatic osteodystrophy)
Pulmonary complications of liver disease (hepatopulmonary syndrome)

Table 220.2
Clinical conditions requiring liver transplantation in children

Primary end-stage progressive liver disease (e.g., biliary atresia, Alagille syndrome)
Secondary progressive liver disease (e.g., a_1-antitrypsin deficiency, Wilson disease)
Acute fulminant hepatic failure (e.g., acetaminophen overdose, non-A, non-B viral hepatitis)
Inborn errors of metabolism that are correctable by liver transplantation for which there are no acceptable alternatives (e.g., ornithine transcarbamylase deficiency)
Neoplasms in which a reasonable chance for cure is present with transplantation (e.g., hepatoblastoma)

a definite improved survival in children with unresectable hepatoblastoma, who have undergone transplantation followed by adjuvant chemotherapy.

Referral to a transplant center should be done as soon as the child has been identified as having a progressive condition that will eventually require transplantation. An early referral allows the greatest flexibility possible for the transplant center to assist in the management of the patient and provide the parents with the best choice of alternatives for treatment that could allow the transplant center the best opportunity to find a suitable donor. In addition, results with liver transplantation are significantly better in patients who undergo early elective procedures as opposed to those who are transplanted in a state of acute hepatic decompensation.

Contraindications

The current contraindications for liver transplantation are those children who have an untreated systemic infection, are infected with the human immunodeficiency virus, have an untreated malignancy outside the confines of the liver, or have a condition with an acceptable alternative therapy. Relative contraindications to liver transplantation include children with poor neurologic, psychosocial, or physical condition prior to transplantation with no expectation for improvement (e.g., cerebral palsy), impairment of other organ systems at the time of transplant that would preclude successful transplantation, or disease that would be expected to recur following transplantation (e.g., hepatocellular carcinoma). These relative contraindications may change over time as either medical progress is made or the condition of the patient improves.

Technical Advances in Pediatric Liver Transplantation

A significant problem facing pediatric liver transplantation in the early 1980s was the scarcity of suitable size-matched cadaveric donors. Biliary atresia is the most common cause of chronic liver failure in children. Unfortunately, these children frequently present during the first or second year of life following a failed Kasai portoenterostomy and almost invariably weigh less than 10 kg. Because of their small size, relatively few size-matched cadaveric donors are available for these patients.

Recent advances in surgical technique with cadaveric reduced-size, split-liver, and living-related segmental liver grafts have allowed the use of small adult livers in small children. As a result, the mortality of children awaiting transplant is now less than 5%.

Reduced-Size Liver Transplantation

The technique of reduced-size liver transplantation was initially suggested and performed by Bismuth and Houssin in 1984. Broelsch popularized the technique in the United States, and it has gained widespread acceptance as a means to increase the number of donor organs available for children. In most cases, an adult donor liver is obtained using standard techniques of multiorgan procurement. An anatomic dissection is then performed on the back-table with the appropriate segment determined by the relative sizes of the donor and recipient.

In general, a left lateral segment graft (segments 2 and 3) is used in a recipient up to eight times smaller than the donor, a left lobe graft (segments 2, 3, and 4) is used in

recipients up to four times smaller than the donor, and a right lobe graft used in recipients up to two times smaller. However, these are estimates, not rigid size determinations, since the anatomy of the donor liver (e.g., long slender left lateral segment) and recipient abdominal cavity can vary significantly (e.g., ascites, hepatomegaly). After preparation of the donor liver, the recipient hepatectomy is done in standard fashion and the reduced-size graft placed in orthotopic position. Care must be taken to place the graft so as not to have it twist upon itself and cause kinking of any vascular or biliary structures.

Overall success with the technique of reduced-size cadaveric grafts approaches that of size-matched cadaveric grafts. However, there does appear to be an increased risk of complications due to bile leakage from the surface of the liver.

A logical extension of this technique is to split the liver into two separate portions and to use the pieces in two different recipients. Results suggest an increase in morbidity with this approach, but recent experience indicates that this approach may be more successful as technical improvements have been made. In many centers, split liver transplantation is now the preferred approach.

Living-Related Liver Grafts

Recently, another approach to increase the availability of donor grafts for children has been to utilize living-related adults to undergo a segmental liver resection to provide a graft for the child. In most cases, consenting adult volunteers undergo a full medical and surgical evaluation. If he/she is deemed a suitable candidate, a left lateral segmentectomy or a left or right lobectomy is performed in the donor. The donor graft is then transplanted into the recipient using standard techniques.

Results with this technique appear good. However, there is a small but real risk for donor morbidity and mortality associated with the living-related donor procedure. At least five donors have died since this technique has been developed and popularized for use in adults and children.

Long-Term Management Issues and Complications after Liver Transplantation

The care of children immediately following liver transplantation is often complex and difficult. However, the overall success rates are high and these children will usually return to relatively normal lives. This portion of the chapter examines some of the many long-term management issues and complications that have to be dealt with as these children grow and develop. The transplant center is designed to address these problems in a timely fashion through a multidisciplinary approach.

Rejection

Rejection of the liver occurs in 40–70% of patients. Rejection usually occurs after the first week following the transplant. The clinical presentation is highly variable but may include fever, chills, tachypnea, abdominal pain, ascites, or a picture resembling sepsis. Hepatic biochemical abnormalities are usually seen, with elevation of alkaline phosphatase, bilirubin, and aminotransferases.

A liver biopsy is generally performed to confirm the diagnosis and an ultrasound done to exclude hepatic artery thrombosis or bile duct stricture as a cause for the abnormalities. Treatment is generally begun with a short course of high-dose corticosteroids and an increase in baseline immunosuppression. If the response is not satisfactory, treatment with OKT3 or thymoglobulin is indicated. These measures are able to reverse rejection in the vast majority of cases.

Growth and Development

Children with end-stage liver disease are often delayed in both growth and development. Following successful liver transplantation, growth and development recover to some degree, though recipient growth rates often do not completely return to normal. Since it is known that corticosteroids retard growth, efforts have been made to wean corticosteroid doses as rapidly as possible. Indeed, with the use of immunosuppressants such as tacrolimus and mycophenolate mofetil, it may be possible to discontinue corticosteroids within the first year after transplantation; nevertheless, the immunosuppressant regimen that best optimizes growth in children has still not been clearly defined.

Hypertension

Hypertension develops in most children following liver transplantation. This is usually a complication of the immunosuppressant regimen. Cyclosporine, tacrolimus, and corticosteroids are all known to predispose to hypertension. As the risk of rejection decreases over time, the dosages of immunosuppression drugs can be decreased

and the antihypertensive regimen can often be modified or discontinued.

Immunizations

The immunization history should be obtained early in the pre-transplant evaluation and a plan developed to ensure that appropriate vaccines are given. In general, response to vaccination is better prior to transplantation and immunosuppression. After transplant, live virus vaccines as a rule should be avoided.

Infection

Infections are common following liver transplantation. While bacteria are still the most common cause of infection, viral and fungal infections are frequent. Cytomegalovirus (CMV) infections characteristically occur 4–8 weeks following transplantation and present with fever, interstitial pneumonia, gastrointestinal bleeding, and graft hepatitis.

Treatment with prophylactic antiviral agents is still controversial; however, once CMV disease has been diagnosed, a course of intravenous ganciclovir is warranted. Infection with the herpes viruses can lead to localized or generalized herpes type 1 infection. Varicella infections can lead to systemic infection or viral reactivation and shingles. Epstein–Barr virus infections can lead to systemic symptoms and have been linked to posttransplant lymphoproliferative disorders and lymphomas. *Pneumocystis carinii* infections are seen in immunosuppressed patients, and most centers employ prophylaxis with trimethoprim–sulfamethoxazole. Prophylaxis for *Candida albicans* fungal infections is also routinely employed with oral nystatin.

Quality of Life

Children with successful liver transplants can achieve an excellent quality of life. With improvements in survival come questions as to the limitations in life they have as they grow and develop.

As children go through adolescence, they ideally develop a sense of self-confidence, independence, and responsibility. Unfortunately, adolescence may also lead to rebellious behavior influenced by a desire to conform with peer behavior and appearance. It is clear that immunosuppressive medications can lead to significant alterations in physical appearance, ranging from hirsutism to cushingoid complications of corticosteroids.

Compliance with medications in adolescent renal transplant patients is recognized to be poor, but information is lacking in adolescent liver transplant patients. Compliance is probably somewhat better, since most patients realize that there is no life-sustaining counterpart to dialysis for patients with liver failure. Nevertheless, noncompliance should be suspected in previously stable adolescents who present with low blood levels of cyclosporine or tacrolimus and liver function abnormalities. A low threshold for investigation must be maintained in order to prevent graft injury and life-threatening rejection.

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Respiratory Disorders

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221 Development of the Lung and Respiratory System

Gabriel G. Haddad

Introduction

By reviewing the development of the respiratory system, this introductory chapter paves the way to the understanding of diseases of the chest in children. It is important to realize that the chest, the lungs, the ribcage, and the respiratory muscles in the newborn are very different from those of the child and from those of the adolescent and young adult. This is the case for both the structural and functional aspects of the development of the respiratory system.

In animals living on land, the gas-exchanging apparatus develops in alveolar (reptiles, amphibian, mammals) or parabronchial (birds) lungs. Gas-exchanging surfaces in lungs depend on two important factors, one is related to a surface-active material, the pulmonary surfactant, which prevents collapse and the other depends on a pump operated by muscles. The function of these respiratory muscles is regulated by a feedback system inclusive of a network of sensors, which relay information from the blood (e.g., gases), the airways (e.g., stretch), and the pump itself to a control center in the brain. The pump can in this manner generate lung ventilation that keeps pace with the metabolic pace of warm-blooded animals and humans.

Early Development: Lung Morphogenesis

In humans, the morphological development of the respiratory system is divided into five periods. The first, or *embryonic period,* begins at approximately 4 weeks of gestation, when the primitive airways appear as an outpouching of the foregut and which divides almost immediately into two main stem bronchial buds. The bronchial buds start to branch, first by monopodal outgrowth (secondary branches grow out of a main branch) and then by asymmetric dichotomy (two secondary branches originate from one main branch). The peribronchial mesenchyme plays an essential role in shaping the lungs during the embryonic period. Close contact between this mesenchyme and the epithelium of the bronchial buds is essential for the continued branching of the airways. The factors that promote bronchial division are not fully identified but steroid-induced secretion of growth factors by the mesenchymal fibroblasts and direct molecular communications between fibroblasts and endodermal cells have been proposed as signaling mechanisms.

Soon after their appearance, the bronchial buds are surrounded by a vascular plexus, which stems from the aorta and drains into the major somatic veins. This vascular plexus connects with the pulmonary artery and veins to complete pulmonary circulation at about the seventh week of gestation but retains some aortic connections that form the bronchial arteries.

Toward the sixth week of gestation, at the beginning of the second or *pseudoglandular period*, the lungs resemble an exocrine gland with a thick stroma with narrow ducts lined by tall epithelial cells. Even at that early stage, the major airways are already in close association with pulmonary arteries and veins. The trachea and the foregut are now separated after the progressive fusion of epithelial ridges growing from the primitive airway. During the pseudoglandular period, the airways continue to branch until the entire conducting airway system is formed, including the primitive bronchioles that eventually give rise to the air-exchanging portions of the lungs. Simultaneously, the pluripotential cells that line the airways differentiate, starting from the trachea and main bronchi, in a process that appears to be under some degree of mesenchymal control. They will form a thinner, pseudostratified epithelium containing ciliated, secretory (Clara), globular, and neuroendocrine cells of neuroectodermal origin. Mucous glands, cartilage, and smooth muscle can be easily distinguished by the 16th week of gestation.

The diaphragm is formed during this period. Its central tendon originates from the transverse septum, a plate of mesodermal tissue located between the pericardium and the stalk of the yolk sac. Its lateral portions are formed by the pleuroperitoneal folds, which grow from the body

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wall until they fuse with the esophageal mesentery and the transverse septum. The fusion eliminates the communication between thorax and abdomen and establishes a barrier to the caudal growth of the lungs. Its failure, usually on the left side, causes the *congenital diaphragmatic hernia of Bochdalek*. This defect, which is the most frequent type of diaphragmatic hernia, allows the abdominal organs to enter the primitive pleural cavity and interferes with airway and pulmonary vascular branching. The result is severe hypoplasia of the lung, particularly on the side of the hernia. Initially membranous, the normal diaphragm is eventually invaded by striated muscle derived from cervical myotomes.

During the third or *canalicular period*, between the 16th and 26–28th week of gestation, epithelial growth predominates. As a result, the bronchial tree develops a more tubular appearance, whereas its distal regions subdivide further to lay the structural foundations of the pulmonary acinus. The epithelial cells in these regions become more cuboidal and start to express some of the antigen markers that characterize cells as *type II pneumocytes*. Some cells become flatter and can be identified as potential type I pneumocytes by the presence of a sparse endoplasmic reticulum and cytoplasmic glycogen. The capillaries contained in the distal bronchial mesenchyme form a denser network and grow closer to the potential air spaces, making a very limited gas exchange possibly by the 22nd week of gestation. This is precisely why a premature at about 24-week gestation has a limited gas-exchange capacity.

Between the 26th and 28th week of gestation, lung morphogenesis enters its *saccular period*, during which the terminal airways continue to widen and form cylindrical structures known as saccules. Initially smooth, the internal surface of the saccules soon develops ridges, which originate as folds of the epithelium and contain a double capillary layer. The distance between the capillaries and the potential air spaces narrows further until eventually only a thin basal membrane separates them. Exactly when the saccular period ends and the alveolar period begins depends on the definition of what constitutes an alveolus. Formation of alveoli before birth is not a requisite for survival, as demonstrated by the observation that in altricial species, such as the rat or the rabbit, alveoli are not present until several days after birth. In the human fetus, the saccular septation initiated with the appearance of the secondary crests continues at a rapid rate so that multifaceted structures analogous to the alveoli of the mature lung can be seen at 32-week gestation. Furthermore, there is substantial evidence that the timing and progression of alveolar septation is under endocrine regulation. Thyroid hormones stimulate septation, whereas glucocorticoids impair it in a fashion that – at least in the rat – can be irrevocable (even though they accelerate the thinning of the alveolar capillary membranes). Alveolarization is also influenced by physical stimuli. Both the stretch by the liquid contained in the fetal lung and the periodic distention provided by the action of the respiratory muscles during fetal breathing, for instance, appear to be necessary for the development of acini. Their absence when the lungs or chest are compressed (as in the case of a diaphragmatic hernia or oligohydramnios) or when fetal breathing is abolished (e.g., by spinal cord lesions) results in pulmonary hypoplasia with reduced numbers of alveoli.

A number of gene families have been identified as being essential for development. The homeo-domain or homeo-box (hox) gene family was discovered first in *Drosophila* and was later shown to be well preserved in mammals and critical mammalian organ development, including that of respiratory system. Hoxa-1,2,3,4,5 and Hoxb-3,4,6,7,8 mRNA transcripts have been identified using molecular biologic techniques in branching regions of the developing mouse lung. These Hox genes were differentially expressed in time and space in early lung development, indicating that they play a role in the differentiation, maturation, and proliferation of various lung cells throughout the various phases of lung development. Furthermore, some of these genes seem to be important in distal versus proximal branching and differentiation. Hoxa-2 seems to be tied to a proximal role, whereas Hoxb-6 is involved in distal airway branching.

A number of other gene families have also been implicated in fetal lung development. For example, GATA-6 is a member of a family of six zinc finger transcription factors and its expression is restricted to the bronchial epithelium. Its importance is demonstrated by the fact that GATA-6 knockout mice die at day ~7. *Foxa2*, which is a downstream target of GATA-6, is a transcription factor which is expressed in the lung epithelium throughout embryonic and into adult life. Null mutations in Foxa2 are also lethal by a couple of days later than for GATA-6. Vitamin A (retinoic acid) is essential for growth, vision, reproduction, and survival. Retinoic acid acts through two groups of receptors: the RAR and the RXR families. Depriving pregnant rats of vitamin A in early fetal life results in animals with lung agenesis. Mutations in both α and β_2 RAR genes produced animals with left lung agenesis or hypoplasia of the lungs. Similar defects are seen in vitamin A-deficient infants. These defects can be are prevented by administration of vitamin A. Fibroblast growth factors and receptors (fgfs and fgfrs), which are

transmembrane receptor tyrosine kinases are expressed in the developing lungs. These are critically important for early branching morphogenesis. Mutations in these receptors lead to trachea with no branching, a striking similarity between mice and Drosophila (mutation in branchless, an FGF ortholog).

Gas Exchange and Adaptation to Air Breathing

The transition from fetal to postnatal gas exchange requires adaptive changes in the lungs. These changes include the (a) production of *surfactant* in the alveoli, (b) the transformation of the lung from a secretory to a *gas-exchanging* organ, and the establishment or parallel *pulmonary and systemic* circulation.

As soon as the newborn takes the first breath, an air–liquid interface is established in the lungs. Unless the surface tension generated at this interface is reduced, the walls of the air spaces would collapse, threatening the stability of lung units. The pulmonary surfactant makes such a reduction in surface tension possible by forming a lipid monolayer at the very surface of the liquid film that lines the air spaces. This surfactant is a heterogeneous mixture of phospholipids and proteins secreted into the saccular or alveolar spaces by the type II pneumocytes. Its presence is first recognized in secretory organelles known as *lamellar bodies* as early as the 24th-week gestation. However, surfactant lipids, of which the most abundant is phosphatidylcholine, are not detectable in the amniotic fluid until the 30th week of gestation, suggesting that there is a chronologic gap between surfactant synthesis and secretion. Labor probably shortens this gap because phospholipids are consistently found in the air spaces of infants born before the 30th week of gestation. Four apoproteins (SP-A, SP-B, SP-C, SP-D) identified in the lung promote the effective reduction of surface tension. Apoproteins also appear to be important for the reuptake and recycling of surfactant products and for the formation of tubular myelin (the structures in which surfactant is stored in the liquid subphase).

Surfactant apoproteins and phospholipids share some, but not all, of their regulatory influences. Glucocorticoids, for instance, increase the synthesis of both apoproteins and lipids; accordingly, their prenatal administration has been used to prevent the respiratory distress syndrome associated with prematurity. Because many actions of the steroids involve direct stimulation of response elements in apoproteins and phospholipid enzyme genes and therefore require messenger RNA production, sufficient time must elapse between steroid administration and birth. Thyroid hormones also enhance the synthesis of phospholipids by a receptor-mediated mechanism, but, unlike the glucocorticoids, have little or no effect on surfactant apoproteins synthesis. Conversely, β-adrenergic agonists and other agents that raise cellular cyclic adenosine monophosphate content increase apoprotein synthesis and phosphadylcholine secretion into the air spaces but have ketosis, and androgens may have negative effects on the production of surfactant proteins and phospholipid, thus explaining the high incidence of respiratory distress syndrome in infants of diabetic mothers and the slight maturational delay of the lungs of male fetuses compared with female fetuses.

Surfactant proteins and lipids also may play an important role in lung immunity, although the molecular details are not known. Surfactant proteins A and D are lectins (bind to carbohydrates) and belong to the collectins family of genes. These proteins, present in the serum and lungs, stimulate phagocytosis and chemotaxis, produce reactive oxygen species, and regulate the production and release of cytokines by immue cells. Alternatively, surfactant lipids can suppress immunity. It is possible that the ratio between surfactant lipids and proteins is important in regulating the immune status of the lungs. This may be critical in premature infants and in newborns who lack surfactant proteins; knockout mice with SP-A deficiency have major problems with infections.

The fetal lung is a secretory organ. Throughout gestation, a Cl^--, K^+-, and H^+-enriched fluid is produced in its peripheral air spaces with the help of a Cl^- pump and channels. The presence of this fluid appears to be important for the development of the acinus because chronic drainage of the trachea in experimental animals results in lung hypoplasia. Fluid secretion, however, is incompatible with air breathing. Therefore, in preparation for birth, lung fluid production decreases slowly at the end of gestation. This decrease, which is accelerated by the beginning of labor, denotes a transformation in the ion transfer activities of the pulmonary epithelium *from Cl^- (and water) secretion to Na^+ (and water) absorption.* In experimental animals, such a transformation can be precipitated by the administration of β-adrenergic agonists at doses that result in serum levels comparable to those found during labor. After birth, the still substantial amount of fluid left in the lungs is absorbed over several hours into the circulation either directly through pulmonary vessels or indirectly through an already very effective lymphatic system. The cellular elements responsible for fluid secretion and absorption in the lungs are not fully identified. It is obvious that a mature alveolar epithelium

is not essential for fluid secretion, which is already taking place before alveoli or even saccules exist.

A number of transporters and channels that have importance on water and solute transport in early life have been cloned and identified in the past decade. Most prominent has been the epithelial sodium channel or ENaC. It is the amiloride-sensitive apical channel that is responsible for sodium and water absorption in the luminal surface of the airways and renal tubular cells. This channel is made up of three types of subunits, α, β, and γ. This channel seems to be critical in early life; knockout mice for this channel develop pulmonary edema and die soon after birth.

At birth, the pulmonary circulation changes from a high resistance to low-resistance system and, as a consequence, pulmonary blood flow become capable of accommodating systemic venous return. The change in resistance is brought about by the combined effects of the mechanical forces applied on the pulmonary vascular walls by the expanding lung tissue and the relaxation of the pulmonary arterial smooth muscle caused by the increased alveolar concentrations of oxygen and probably by endogenous release of vasodilators. The subsequent closure of the foramen ovale and the ductus arteriosus completely separates the pulmonary from the systemic circulation. Arterial oxygen tension then rises sharply and becomes homogeneous throughout the body. Pulmonary vascular resistance continues to decrease gradually during the first few weeks after birth through structural remodeling of the pulmonary vessels.

Postnatal Alveolar and Capillary Development

The postnatal development of the lungs is divided into two phases. During the first phase, which extends to the first 18 months after birth, there is a disproportionate increase in the surface and volume of the compartments involved in gas exchange. Capillary volume increases more rapidly than air space volume, which in turn, increases more rapidly than solid tissue volume. This process is particularly active during early infancy and may reach completion within the first 2 years of life. The configuration of the air spaces becomes progressively more complex, not only because of the development of new septae but also because of the lengthening and folding of the existing alveolar structures. Soon after birth, the double capillary system contained in the alveolar septa of the fetus fuses into one single one. At the same time, new arterial and venous branches develop within the circulatory system of the acinus and muscle starts to appear in the medial layer of the intra-acinar arteries.

During the second phase, all compartments grow more proportionately to each other. Although there new alveoli can still be formed, the majority of the growth occurs through an increase in the volume of existing alveoli. Alveolar and capillary surfaces expand in parallel with somatic growth. As a result, taller individuals tend to have larger lungs. However, the final size of the lungs and, ultimately, the dimensions of the individual constituents of the acinus are also influenced by factors such as the subject's level of activity and prevailing state of oxygenation (altitude), which allow for a better adaptation of lung structure and function. The same factors are probably operative in the compensatory responses to pulmonary disease and injury.

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222 History and Physical Examination

Anthony E. Magit

The initial assessment of the airway begins with a focused history. Information obtained from the history influences decisions regarding the extent of the examination, the need for diagnostic tests, and the urgency of interventions. The history addresses the onset of the airway problem, whether congenital or acquired, as well as the presence of signs or symptoms of an infectious process. A history of airway manipulation, including intubation, can be key factor in the development of an airway problem.

Assessment of a child's airway may start before birth. Critical information regarding the airway may be available prior to a birth as a result of prenatal ultrasound or other imaging modalities. Ultrasound findings suggesting airway obstruction include masses of the head or neck, anatomic abnormalities including micrognathia or retrognathia, as well as a distended pulmonary system suggesting high airway obstruction due to laryngeal or tracheal obstruction. The prenatal evaluation may include ultrasound findings predicting airway obstruction at delivery. Ultrasound abnormalities may influence the decision to obtain other imaging studies, particularly a magnetic resonance imaging (MRI) study.

The degree of airway obstruction predicted to be present at delivery may necessitate creating a specific plan for managing the child's airway at the time of delivery. A means of maintaining fetal circulation while assessing a newborn's airway is the ex utero intrapartum treatment (EXIT) procedure.

The type of airway intervention required to stabilize the airway provides valuable information regarding the level of obstruction. Airway compromise present at birth can result from obstruction from the level of the nose to the lower airway. Bilateral nasal obstruction will cause respiratory distress as a result of newborns being obligate nasal breathers. Relief of airway obstruction with ventilation through a facemask is consistent with obstruction from the nose to the oral cavity. Resolution of airway obstruction following laryngeal intubation with an appropriately sized endotracheal tube suggests that the etiology of the obstruction is from the level of the glottis or superior to the glottis. Airway obstruction resolved with the placement of a smaller than expected endotracheal tube implies glottic or subglottic stenosis.

The timing and quality of airway noises correlates with the site of the airway abnormality. Stertor, the sound associated with disrupted nasal airflow, indicates partial nasal obstruction. Stridor is the term used to describe the high-pitched sound associated with partial airway obstruction below the level of the oropharynx. Stridor is typically tied to a phase of respiration, whether present on inspiration or expiration. Stridor present on inspiration, referred to as inspiratory stridor, is associated with lesions above the vocal folds. Stridor present on expiration, referred to as expiratory stridor, is associated with lesions below the level of the subglottis. Stridor present on inspiration and expiration, referred to as biphasic stridor, typically results from lesions at the level of the glottis or subglottis.

Airway problems developing subsequent to delivery may be anatomic or functional. A non-obstructing mass at birth may increase in size and lead to a compromised airway.

A history of airway manipulation can provide valuable information. Previous intubation, including a brief period of time for a procedure or short-term respiratory management, can be associated with the development of subglottic lesions, including cysts and stenosis. A hoarse or raspy cry may result from vocal fold inflammation as a result of silent or clinically apparent gastroesophageal reflux (GER). Signs and symptoms of GER include agitation during or after feeding as well as arching of the neck during or after feeding.

Coughing while feeding may be an indication of laryngeal penetration or aspiration. Underlying conditions predisposing to laryngeal penetration or aspiration include vocal cord paralysis, vocal cord paresis, laryngeal clefts, and tracheoesophageal fistulae.

Examination of the airway is influenced by the age of the patient and the urgency of the clinical situation. The initial evaluation of the airway consists of assessing for impending airway obstruction and determining the need for acute intervention. Signs of upper airway compromise include suprasternal retractions, abdominal breathing, and worsening stridor. Clinical deterioration of the airway is suggested by hypoxia, tachypnea, and diaphoresis. The clinician must recognize the urgency of the clinical situation and transition from a diagnostic algorithm to an interventional mode to improve the airway.

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Airway assessment involves a systematic review of anatomic sites. The basic elements of an airway assessment are typically a component of any comprehensive physical examination. A detailed evaluation of specific anatomic sites is driven by the patient's condition.

Newborn

The nasal examination begins with a visual inspection of the external nose. A newborn's nose is assessed for symmetry of the dorsum. Significant deformity resulting from intrauterine positioning may result in deviation of the nasal tip and distortion of one or both nares. Anterior rhinoscopy using a handheld otoscope allows for inspection of the anterior nasal cavities posteriorly to the anterior aspect of the middle turbinate. Patency of the nose has traditionally been established by passing catheters through each side of the nose into the nasopharynx. This procedure can be traumatic and falsely indicate that the nose is patent if the catheters curl in the nasopharynx when posterior nasal obstruction exists. A nontraumatic means to determine nasal patency is to place a mirror in front of the nares and observing condensation on the surface of the mirror. This method does not provide information regarding the caliber of the nasal opening; however, it does prove that airflow is present. The addition of a dilute nasal decongestant can facilitate the intranasal examination.

Examination of the oral airway includes the mandible, tongue, oral cavity, and oropharynx. Mandibular position and size directly relates to adequacy of the airway at the level of the oral cavity. An undersized or posteriorly positioned mandible will result in inadequate anterior support of the tongue. The mandible is observed and position is assessed relative to the maxilla. The oral cavity is visualized using a tongue depressor or examiner's finger. The position and size of the tongue is noted with reference to the child's ability to keep the tongue within the oral cavity. A tongue that tends to oppose the palate may be intrinsically large or superiorly displaced by a mass in the floor of the mouth. The tongue should be elevated with a tongue depressor or the examiner's finger and the anterior floor of mouth inspected for masses or fullness.

The palate examination assesses structure and function. Visual examination of the palate involves noting clefts of the hard or soft palate. Digital palpation detects notching of the hard palate or thinning of the midline of the soft palate suggesting a submucosal abnormality. The soft palate is visualized to determine if the uvula is intact or whether there is a bifid uvula or prominent median raphe of the uvula supporting the possibility of an underlying muscular abnormality. Visual inspection of the oral cavity with adequate illumination is critical as digital examination alone is associated with delay in the diagnosis of cleft palate.

The airway below the level of the oropharynx cannot be directly visualized without specialized equipment; however, examination of the neck can provide valuable information regarding the larynx and hypopharynx. Visualization and palpation of the neck can reveal masses that impact upon the airway. A stethoscope can be "marched down" the airway to localize the site of an airway abnormality. The "headless" stethoscope is one in which the head of the stethoscope is removed and the open end of the stethoscope tubing is placed directly on the skin over the airway. The smaller area of the tubing allows for more precise localization of the airway abnormality.

The quality and clarity of the cry provides information regarding involvement of the vocal cords and glottis. Noisy respirations in the absence of an abnormal cry suggest that the airway abnormality spares the vocal cords.

Pediatric Airway

A history of pediatric nasal problems must clearly address the status of the airway. Oftentimes, parents or caregivers will describe a child as being "nasal" when the concern is actually nasal obstruction and "hyponasality." Observing the patient prior to beginning the physical examination can provide critical information. A child with chronic nasal obstruction may exhibit an open mouth breathing posture with audible respiration.

Chronic unilateral nasal drainage is consistent with anatomic obstruction or the presence of a nasal foreign body. Intranasal examination using a handheld otoscope or a headlight and speculum focuses upon the appearance of the mucosa, presence of secretions, or intranasal masses.

Detecting the presence of nasal airflow while a child produces "nonnasal" sounds can grossly assess hypernasality. Standard "nonnasal" sounds are "s" sounds such as "sister." Nasal airflow during the vocalization of these sounds suggests hypernasality due to a structural or functional problem.

In addition to assessing the tongue, floor of mouth, and palate, the oral cavity examination addresses the transition zone from the oral cavity to oropharynx at the level of the tonsillar pillars. Tonsil size and position is usually described on a scale from 1 to 4. The tonsils are assessed with an open mouth and relaxed position. Excessive opening of the mouth can position the tonsils in a more lateral position. The posterior and inferior extent of the tonsils

Table 222.1

Modified mallampati
1. Clearly visible tonsils, tonsillar pillars, and soft palate
2. Only visible uvula, tonsillar pillars, upper tonsil pole
3. Partially visible soft palate
4. Only visible hard palate

may be difficult to assess with a transoral examination. True tonsil size is best assessed by depressing the tongue with this physical examination technique resulting in good correlation between subjective and objective tonsil size.

Another system for describing the appearance of the oral cavity and orophayrnx is the Mallampati classification (*Table 222.1*). This system is primarily used for a preanesthetic airway evaluation of the airway and focuses upon the structures that are identified when the patient's mouth is open.

Phonation tends to improve the view of the oropharynx while a supine position tends to obscure the view of the oral cavity and oropharnx. This should be taken into consideration when having the parent or another adult position the child during the physical examination.

The larynx can be assessed indirectly by examining the neck. The larynx is palpated to determine its midline position or distortion due to masses or trauma. Auscultation over the larynx establishes the presence or absence of stridor due to a partially obstructed airway.

Cough

Evaluating a cough in a child relies heavily upon the history provided by the adults and the child. In the absence of signs or symptoms of an infectious process, a significant concern is the presence of an airway or esophageal foreign body. The importance of a history suggestive of a foreign body is supported by a study by Linegar in which a clinical history consistent with an airway foreign body and a negative history was associated with a positive endoscopy for a foreign body in 45% of cases.

Airway Sounds

Assessing the quality and location of airway noises assists in developing a working diagnosis for a child with a respiratory problem. An important consideration is that the intensity of the sound may not correlate with the severity of the airway situation. History provided by the parent is more likely to correctly identify the origin or location of the airway noise than identify the etiology of the noise. Parents are more likely to misidentify stridor as wheezing and attribute the airway noise to asthma rather than an upper airway problem. Parental report of wheezing correlates with a health professional's report of wheezing in less than 50% of cases.

Older children may be able to provide valuable information regarding their airway. With regard to the frequency and severity of wheezing, school-age children have been reported as being more accurate reporters of their wheezing than their parents.

The type of airway sound provides a clue as to the location of the abnormality. A "monophasic" sound suggests a structural lesion in al large airway while a "polyphonic" wheeze is more likely to be associated with extensive small airway narrowing.

A snore results from increased resistance to airflow in the nasopharynx and oropharynx. Snoring becomes more intense with increased relaxation of the pharyngeal musculature that occurs during the REM (rapid eye movement) phase of sleep.

Stridor

Stridor describes audible air movement due to partial obstruction of the airway. Characteristics of stridor are the timing relative to inspiration and expiration. The examiner notes the severity of obstruction, and the need to establish an acute intervention is determined. Pertinent history is the presence of a coexistent syndrome, chronic cough, growth abnormalities, cutaneous lesions, and neurodevelopmental problems.

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223 Pulmonary Function Testing

Gabriel G. Haddad

Spirometry and Plethysmography

Pulmonary lung function testing has been useful in monitoring and diagnosing pathological processes in the lung. Hence, although pulmonary function testing rarely results in a diagnosis, it is helpful in defining the type of process (obstruction, restriction) and the degree of functional impairment in following the course and treatment of disease, and in estimating the prognosis. Such measurements of respiratory function especially in infants and young children can however be difficult because of lack of cooperation. Whether restrictive or obstructive, most forms of respiratory disease cause alterations in lung volume and its subdivisions and pressure generated.

Restrictive diseases typically decrease total lung capacity (TLC) because of lack of ability to stretch the lungs. TLC includes residual volume and vital capacity (VC). Residual volume is measured indirectly by gas dilution methods or plethysmography. VC is measured by spirometry and can be often used at the bedside to assess progression of disease such as in muscle weakness and neuromuscular disorders. Obstructive diseases produce gas trapping and thus increase residual volume and functional residual capacity or FRC.

Airway obstruction is most frequently evaluated from gas flow measurements of a forced expiratory maneuver. The *peak expiratory flow* is reduced in obstructive disease and there are numerous simple devices that perform this measurement at the bedside. This makes these devices useful for evaluating children with airway obstruction and for monitoring progress rather easily. Peak flow measurements are sometime difficult to evaluate since they require a voluntary effort. In addition, peak flows are not very sensitive as these peak flows may not be altered when the obstruction is mild or even moderate.

Gas flow measurements other than peak flows are also not always easy to perform on young children since they require that the child inhale to TLC and then exhale as fast and as much as possible for several seconds. Cooperation and good muscle strength are therefore necessary for the measurements to be reproducible. The *forced expiratory volume in 1 s* (FEV_1) correlates well with the severity of obstructive diseases. *The maximal mid-expiratory flow rate* ($MMEF_{25–75}$), the average flow during the middle 50% of the forced vital capacity, is more reliable in mild airway obstruction. The construction of flow–volume relationships during the forced vital capacity maneuvers can also be used and is particularly helpful in relating expiratory flows as a function of lung volume.

Spirometry is used to measure VC and its subdivisions and expiratory (or inspiratory) flow rates. A simple manometer can measure the maximal inspiratory and expiratory force a subject generates, normally at least 30 cm H_2O, which is useful in evaluating the neuromuscular component of ventilation. Normal values for pulmonary function tests such as VC, FRC, TLC, and residual volume are obtained from equations based on body height. Caution must be exercised to make sure that the prediction equations from which normative values are obtained are appropriate for the patient in question since often these equations are derived from studies using children that may have different skeletal structures and proportions. Flow rates measured by spirometry usually include the FEV_1 and $MMEF_{25–75}$ but more information can result from a maximal expiratory flow–volume curve where expiratory flow rate is plotted against expired lung volume. Expiratory flow rates at low lung volumes ($<$50% VC) are influenced by small airways than are flow rates at higher lung volumes. The flow rate at 25% VC (V_{25}) is a useful index of small airway function. Low flow rates at high lung volumes associated with normal flow at low lung volumes suggest upper airway obstruction.

Plethysmography is used to measure *airway resistance* (R_{AW}) or, alternatively, the reciprocal of R_{AW}, airway conductance (G_{AW}). Because airway resistance measurements vary with the lung volume at which they are taken, it is convenient to use specific airway resistance, SR_{AW} ($SR_{AW} = R_{AW}$/lung volume), which is nearly constant in subjects older than 6 years of age (normally $<$7 s/cm H_2O). The *diffusing capacity for carbon monoxide* (DLCO) is a measure of oxygen diffusion and is assessed by rebreathing from a container having a known initial concentration of carbon monoxide (CO) or by using a single breath technique. A decrease in DLCO reflects a decrease in effective alveolar-capillary surface area or a decrease in diffusibility of the gas across the

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alveolar-capillary membrane. Primary diffusion abnormalities are unusual in children but this test is most frequently employed in children with cancer exposed to toxic drugs to the lungs or to chest wall radiation. Regional gas exchange can be conveniently estimated with the perfusion–ventilation xenon scan. *Exercise testing* is a more direct approach for detecting diffusion impairment as well as other forms of respiratory disease. This testing involves a variety of measurements, including heart and respiratory rate, minute ventilation, oxygen consumption, carbon dioxide production, and arterial blood gases during incremental exercise loads. This often provides invaluable information about the functional nature of the disease. Often, a simple assessment of the patient's exercise tolerance in conjunction with other, more static forms of respiratory function testing can allow a distinction between respiratory and nonrespiratory (e.g., cardiovascular) disease in children.

The most important limitations of these function tests are related to the fact that most of them require cooperation by the patient. Hence, the interpretation is facilitated if the test conditions and the patient's behavior during the test are known. Infants and young children who cannot or will not cooperate with test procedures can be studied in a limited number of ways, often requiring sedation, which can affect the very measurements that are being made. Flow rates and pressures during tidal breathing, with or without transient interruption of the flow, may be useful to assess some aspects of airway resistance or obstruction and to measure compliance of the lungs and thorax. Expiratory flow rates can be studied in sedated infants with passive compression of the chest and abdomen with a rapidly inflatable jacket. Gas dilution or plethysmographic methods can also be used in sedated infants to measure FRC and R_{AW}.

In summary, pulmonary function tests are useful in (a) monitoring and diagnosing pathological processes such as restrictive and obstructive disease, (b) the degree of functional impairment in lung function, (c) estimating the prognosis, (d) studying the reversibility of disease as in patients with obstructive disease and bronchodilator therapy, (e) in preoperative evaluation, and finally (f) in confirmation of functional impairment in patients having subjective complaints but with a normal physical examination.

Blood Gases

Although in the presence of hypoxemia the color of the skin is changed to that of cyanosis, this usually occurs when hypoxemia is rather severe. This change in color however is often influenced by skin color, perfusion, and blood hemoglobin concentration, and the clinical detection by inspection is an unreliable sign of hypoxemia. Although blood gas analysis does not specify the cause of the condition/disease or the specific nature of the disease, this analysis is a very useful rapid test of pulmonary function as it can give an assessment of the *overall functional state* of the respiratory system. In addition, arterial blood gases can give clues about the *pathogenesis of the disease*. Blood gas exchange is evaluated by the direct measurement of arterial PO_2, PCO_2, and pH. The blood specimen is collected anaerobically in a heparinized syringe. The syringe should be sealed, placed in ice, and carried to the laboratory for immediate analysis. These measurements require arterial puncture and this is one reason why PO_2, by and large, has been well replaced to a great extent by noninvasive monitoring of O_2 saturation.

The age and clinical condition of the patient need to be taken into account when interpreting blood gas tensions. With the exception of neonates, values of arterial PO_2 $<$85 mmHg are usually abnormal for a child breathing room air at sea level. Calculation of the alveolar-arterial oxygen gradient is useful in the analysis of arterial oxygenation, particularly when the patient is not breathing room air or in the presence of hypercapnia. Values of arterial PCO_2 $>$ 45 mmHg usually indicate hypoventilation or a severe ventilation–perfusion (V/Q) mismatch. This is usually associated with a low PO_2 as well when indicative of hypoventilation. A low PO_2 with no change or a decrease in PCO_2 is usually indicative of V/Q mismatch in children.

Sleep Studies

Sleep states have an important influence on respiratory function in children and particularly in the newborn and young infant. The gold standard to assess pulmonary function, especially for obstructive sleep apnea and hypoventilation syndromes, is polysomnography. Such studies are often helpful when abnormalities of central respiratory control, muscular disorders, or respiratory complications from gastroesophageal reflux (GER) are suspected. pH probe studies are indicated and are added to such sleep studies when GER is suspected. In these studies, a pH probe is placed in the esophagus and prolonged (usually over several hours) monitoring is undertaken. These studies, which usually include the simultaneous assessment of ventilatory effort (pressure or volume), airway gas flow, blood gases or O_2 saturation, and sleep state (EEG, EOG, and EMG), are also useful

in the diagnosis and management of disorders of respiratory control and nocturnal hypoxemia and hypercapnia in children with chronic and ill-defined respiratory disease.

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224 Diagnostic Imaging and Procedures

Julie Ryu

Chest Radiographs (CXR)

Chest radiographs are the most commonly performed imaging tests in children. When interpreting a CXR, a systematic approach is often helpful.

1. Lung volume: An overview of lung volume can give clues to the general respiratory state such as hypoventilation (low volumes) or air trapping (increased volumes).
2. Symmetry: Asymmetric lung volumes can indicate either ipsilateral or contralateral lung pathology (pneumothorax, lobar pneumonia, etc.) versus symmetric (general or diffuse processes such as viral infection, muscle weakness, etc.).
3. Airway: Is the trachea midline? The trachea may be shifted toward an area of collapse or away from an area of fluid or air collection. Is the trachea narrowed? Vascular compression or mediastinal masses can impinge on the trachea making the trachea appear narrowed or deviated.
4. Pulmonary vasculature: Are the vessels prominent? Overflow circulation due to left-to-right cardiac shunting can dilate pulmonary vessels. A pruning effect can also be seen in the peripheral vessels due to vascular constriction in conditions such as pulmonary hypertension.
5. Parenchyma: Diffuse opacities? Viral infections, pulmonary edema, or an interstitial process can appear diffusely. Localized? Bacterial infections, fungal infections, and abscesses are often localized to one area or distinct areas.
6. Pleural space: This is a potential space, so anytime it is visible it is abnormal. Pleural fluid should be assessed for loculations by ordering a lateral decubitus film with the suspected side down; if fluid is free flowing, it should spread evenly across the dependent side. If a pneumothorax or hydropneumothorax is suspected and an upright film is not helpful or possible, a lateral decubitus film with the contralateral side down (since air will rise to the highest point) may be useful.

CXRs can be extremely helpful as an initial diagnostic tool, but often additional diagnostic imaging is required to diagnose the condition suspected. Common uses for other diagnostic tools are summarized in ◉ *Table 224.1* and discussed in detail in their respective sections.

Computer Tomography (CT)

Chest CT has significantly improved not only in image quality, but also in the speed of image acquisition making this diagnostic tool much more accessible in pediatrics. In fact, since the advent of helical/spiral CTs, the need for sedation has decreased in patients less than 6 years of age. In addition, motion artifact from respiration has improved due to faster scanning techniques. However, despite the advances in imaging, CT imaging still requires much more radiation than that of CXR; it is equivalent to 25–50 CXRs in a 2-month-old child. Newer CT scanners are able to image thinner lung sections and, therefore, require more passages to image the chest resulting in higher radiation exposure than traditional CTs. Every year, the number of chest CTs ordered has increased, which has raised the concern of the accumulative risk of neoplasms in children over time. While the benefits of a single chest CT may outweigh the overall risk of radiation exposure, it is important to remember that many pediatric patients will require multiple imaging studies over their lifetimes and therefore it is important to use it judiciously and order the most appropriate test. Fortunately, new methods to lower the risk of radiation exposure in children are continually being developed to counteract this problem.

Chest CT is currently the best diagnostic tool to investigate lung parenchyma since it is the only imaging tool that allows for a cross-sectional image of the chest. Chest CT can be helpful in investigating parenchymal disease, and it is particularly helpful when interstitial lung disease is suspected. Increased density in the parenchyma indicates a loss of air in airspaces, which may suggest an infection, mass or fluid collection. When the increased attenuation is less discrete, or "ground glass" in appearance, there is partial airspace filling which may indicate an interstitial process. Since lung volumes change with respiration, it is important to note that some images may appear worse with exhalation. When there are regional differences in density, consider air trapping especially in obstructive lung diseases.

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Table 224.1
General indications

CXR: general initial study
Chest CT without contrast: imaging lung parenchyma or airway
Chest CT with contrast: nodules, cavitary lesions, sequestrations, lymph nodes
MRI/angiogram: vascular lesions, cardiac malformations
Fluoscopy: dynamic airway disorders
Ultrasound: diaphragm motility, asses pleural effusions
Bronchoscopy: visualization of airway, obtain cultures

Chest CT can also be used to identify pathology in the airways. Bronchiectasis, dilation of the bronchus, can readily be identified on CT. In addition, bronchial wall thickness and lumen obstruction can also be visualized.

Chest CT can be used to assess and treat severe pneumonias with empyema. CT-guided procedures can be helpful in the removal of loculated fluid or biopsy a lesion. The addition of intravenous contrast allows for excellent vascular imaging and can identify vascular malformations, sequestrations, and lymphadenopathy. In addition, many centers are able to reconstruct CT images to 3D images making it an excellent tool to assess anatomy.

Magnetic Resonance Imaging (MRI)

Chest MRI is rarely used to assess pediatric lung disorders since it does not image the lung parenchyma well. However, it is an excellent imaging tool to visualize vasculature and does not use any ionizing radiation as does CT and CXR but uses magnetic fields to create an image. While the advantages of MRI consist of no radiation, the time required for imaging is extensive and usually requires sedation. However, newer MR techniques such as helium-enhanced images offer potential alternatives to CT. MR imaging has been limited in the lung because the traditional MR imaging system detects hydrogen protons that are abundant in most organs but are lacking in the aerated lung. With the helium-based system, the patient inhales Helium 3 and the image is taken, detecting the existing hydrogen-based image as well as the inhaled helium. This technology therefore allows for an image that is representative of lung ventilation, much like a nuclear scan but with the resolution of a tradition MRI. While this system is not widely available, it is an example of new imaging systems currently being used to reduce radiation exposure in children with chronic lung disease that require repeated imaging.

Fluoroscopy

Airway fluoroscopy can be a useful tool in detecting airway pathologies. The advantages of airway fluoroscopy are that it requires no sedation, is quick, and can assess airway patency in real time. Thus, it is often used in the diagnosis of laryngo/tracheomalacia since the airway may appear normal on exhalation but narrows on inspiration.

Ultrasonongraphy (US)

Ultrasonography of the chest is a useful diagnostic tool that is not associated with any radiation. It can be used to distinguish chest wall masses from cystic lesion, distinguish fluid collection from pneumonia on a "white out" on CXR, and can be used to follow effusions. In addition, ultrasound can be useful in detecting diaphragm abnormalities. Ultrasound of the diaphragm can measure diaphragm thickness during contraction and therefore may be a good tool to assess patients with diaphragmatic dysfunction.

Bronchoscopy

Flexible bronchoscopy can be used as both a diagnostic as well as a therapeutic tool. In most cases, the use of a flexible bronchoscope is diagnostic. It is often used to collect bronchoalveolar fluid to identify an organism during an infection. Pediatric pulmonologists perform flexible bronchoscopy as opposed to rigid bronchoscopy which is usually performed by an otolaryngologist. The benefit of flexible bronchoscopy is the ability to reach the lower airways and the right upper lobe, which can sometimes be difficult to access with a rigid scope. Therefore, flexible bronchoscopy allows fluid samples to be obtained from a particular segment of the lung. In addition, the risk of pneumothorax and bleeding is much lower than that of a rigid scope due to the inherent flexibility of a flexible bronchoscope.

However, there are limitations to flexible bronchoscopy. The major limiting factors in pediatric flexible bronchoscopy are the size of the scope and the size of the channel. Whereas the bronchoscopes used in the adult population are able to provide excellent images in addition to a number of tools including biopsy clips, lasers, and brushing inserts, most pediatric airways are too small for these bronchoscopes. While there are currently bronchoscopes that range from 2.2 mm outer diameter and larger, the commonly used 3.5 mm bronchoscope typically

has a channel for suction (or biopsy etc.) of about 1.2 mm. While this small channel is adequate for suctioning, it is not a good tool for foreign body removal. Foreign body removal is generally a procedure performed using a rigid bronchoscope, which allows for control of the airway (and not limited to a small channel) as well as better ventilation.

Flexible bronchoscopy is a very good tool to evaluate lower airways and obtain culture specimens or cell scrapings. The procedure is safe and usually a same day procedure. Since bleeding can be a potential risk, platelet count should be at least 20 K and coagulation studies may be indicated. The patient should have nothing to eat for at least 6 h and no liquids at least 2 h prior to the procedure. Anesthesia is used to sedate the patient, and fiber-optic bronchoscope is inserted to the airways either by the nose or through an artificial airway. If inserted to the nose or laryngeal airway mask, the vocal cords can be visualized and inspected for edema or erthyema, which may suggest chronic irritation. Below the vocal cords, the trachea can be assessed for presence of tracheal rings and/or malacia. The carina, bronchi, and general mucosal appearance is noted for any swelling, friability, malacia, and quality of mucous secretions. Saline can be injected into the bronchoscope channel and the fluid sample that is obtained can be analyzed for a number of different studies. Common studies include cell count which may help identify the likelihood of infection (increased neutrophils) or certain disorders such as collagen vascular disease (increased lymphocytes). In addition to the type and number of cells present in a BAL sample, specialized studies can be performed to analyze cell surface markers and detect malignant cells. Macrophages can also be stained for lipid or hemosiderin. Lipid-laden macrophages are often present with chronic microaspiration, and hemosiderin is found in patients with hemoptysis. BAL fluid can also be gram stained, cultured for bacteria, viruses, and fungi. Although cultures can always be sent, if the patient is receiving antibiotics, the probability of identifying a bacterial organism lowers with time. Contraindications for the procedure may include a unstable airway, respiratory failure or a platelet count under 20,000. Risks include bleeding, hypoxia, and infection. Although the risk of a pneumothorax is possible, the possibility is much lower than during rigid bronchoscopy.

While bronchoscopy is a valuable diagnostic tool, new technologies have to be developed to fully utilize this modality. As imaging equipment becomes smaller and the ability to assay bronchoalveolar lavage improves, the utility of bronchoscopy will increase in the pediatric population.

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225 Respiratory Failure

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Definition/Classification

Respiratory failure is defined as failure of gas exchange to meet metabolic demands. In an otherwise healthy child, this is present when there is hypoxemia with measured arterial oxygen level (PaO_2) of less than 60 mmHg or hypercarbia with measured arterial carbon dioxide level ($PaCO_2$) greater than 50 mmHg. Other definitions distinguish between these states as *Type 1* versus *Type 2* or oxygenation versus ventilation respiratory failure. Most authorities agree that acute respiratory failure is that which develops over hours where chronic is reserved for states evolving over days or longer.

Although not all cases of respiratory failure are due to acute lung injury (ALI) or progress to the acute respiratory distress syndrome (ARDS), understanding these terms is important when evaluating respiratory failure. The 1993 American–European Consensus Conference (AECC) provided a new definition of ALI and ARDS as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiological, and physiological abnormalities that cannot be explained by, but may co-exist with, left atrial or pulmonary capillary hypertension." Specifically, both are associated with a pulmonary capillary occlusion pressure of less than 18 mmHg and bilateral infiltrates on chest radiography. ARDS is characterized by more severe hypoxemia, with ALI defined by a $PaO_2/FiO_2 < 300$ and ARDS by a $PaO_2/FiO_2 < 200$, both regardless of positive end-expiratory pressure level.

Etiology

Causes of respiratory failure fall into three large categories: failure of air delivery/release (obstruction), failure of appropriate pulmonary gas exchange, and failure of neuromuscular or central control over respiratory drive. Specific causes of acute and chronic respiratory failure in children differ from those of adults. Common etiologies in acute cases include primarily large and distal airway infections, status asthmaticus, direct lung injury, or acute traumatic or medication-induced loss of central respiratory control. Chronic etiologies include congenital or acquired lung maldevelopment, systemic diseases with progressive pulmonary involvement, complex congenital heart disease, disorders of central nervous system control with loss of airway protective mechanisms, and neuromuscular disorders with respiratory muscle weakness. These states may present with failure within a short period (months of age) or evolve over years.

Epidemiology

True incidence of all-cause pediatric respiratory failure as defined above is not well documented in all countries and varies widely from 9.7 to 77 per 100,000 person-years in the United States and Europe. Pediatric morbidity and mortality from respiratory failure in developed countries is best approximated by international data on ALI and ARDS. Rates reported by the AECC and others vary from 1% to 9%, with population incidence in 100,000 person-years of 2.95–3.4 in Germany, Australia, and New Zealand to as high as 12.8 in areas of the United States and 17.9 in Sweden.

There are few published reports on pediatric respiratory failure from developing countries. Worldwide, pneumonia is the most common risk factor, and toddlers are the most commonly affected age group. The World Health Organization reports that pneumonia is responsible for about 19% of all deaths in children aged less than 5 years, of which more than 70% take place in ten countries in sub-Saharan Africa and south-east Asia.

Pathogenesis

Physiology

The most frequent cause of respiratory failure is hypoxemia due most commonly to three main pathophysiologic derangements: hypoventilation, ventilation/perfusion (V/Q)mismatch, and shunting. The PO_2 of alveolar gas is determined mostly by the balance of oxygen removal from and delivery to the alveoli, and therefore affected primarily by the level of alveolar ventilation. When

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ventilation drops in hypoventilation, oxygen levels fall and carbon dioxide levels rise, leading to a high $PaCO_2$. In contrast to hypoventilation, the $PaCO_2$ in V/Q mismatch is usually normal or low. In V/Q mismatch, areas of poor ventilation (low V) receive continued blood flow (Q), resulting in a low V/Q ratio (less than the normal ratio of 1). At baseline, there is always a small amount of intrapulmonary shunting through bronchial vessels and coronary veins. V/Q ratios vary by lung segment and by lobe, with ratios greater than 1 in the apices. However, increasing perfusion to well-ventilated areas cannot compensate for continued blood flow to poorly ventilated areas, due to limitations of the oxyhemoglobin dissociation curve (*Fig. 225.1*). Oxygen therapy can aid in less severe forms of V/Q mismatch; however, when 30% or more of blood flow is shunted, supplemental oxygen does not correct the hypoxemia. When V/Q reaches zero, a state of intrapulmonary shunting is present, where the perfused lung is not ventilated. In this state, chemoreceptors stimulate an increase in minute ventilation in an attempt to increase oxygen delivery. Pulmonary vasoconstriction causing increased pulmonary vascular resistance also occurs in an attempt to limit blood flow to unventilated alveoli. At the other extreme, when V/Q reaches infinity, ventilated lung is not perfused resulting in alveolar dead space. At baseline, there is always some physiologic dead space due to a combination of normal alveolar dead-space ventilation as well as anatomic dead space caused by air in conducting airways that does not participate in gas exchange. Pathologic increases in alveolar dead space are seen with abnormal pulmonary blood flow resulting in both hypoxemia and hypercarbia.

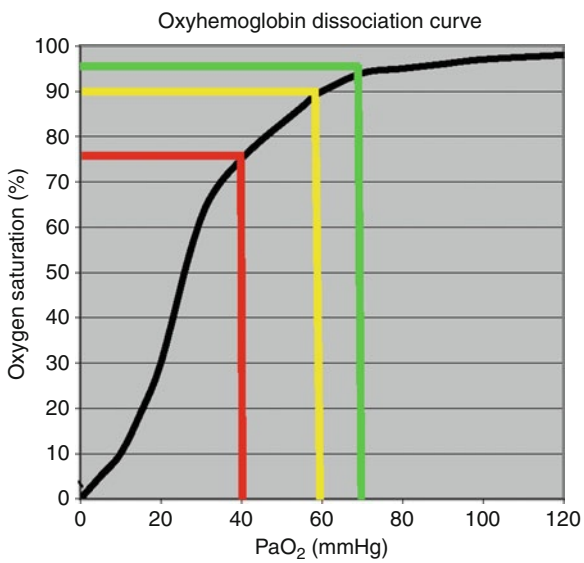

Figure 225.1
Oxyhemoglobin dissociation curve with key points noted: oxygen saturation of 94%–70 mmHg PaO_2 (green); 90%–60 mmHg PaO_2 (yellow); 75%–40 mmHg PaO_2 (red)

Ventilation failure, or failure to exhale gases, is due predominantly to a deficiency of alveolar ventilation with or without excessive production of CO_2. Compared to *Type I* respiratory failure where hypoxemia is accompanied by normal or low $PaCO_2$, *Type II* is characterized by both hypoxemia and hypercarbia. *Type II* can be thought of as excessive respiratory workload that exceeds the patient's gas exchange capacity.

Risk Factors

Children are at greater risk for respiratory failure than adults, with differences in each of the three large etiologic categories previously mentioned. Airway obstruction occurs more readily due to the relatively limited cartilage support of airway, small airway diameter, large tongue, larger and more horizontally placed epiglottis, narrow subglottis, and cephalad position of the larynx. Gas exchange is limited by fewer and smaller alveoli and fewer collateral channels for ventilation between alveoli (pores of Kohn, Lambert channels). Respiratory drive is affected by immature central respiratory control in young infants, underdeveloped respiratory muscles, and a compliant chest wall. Risk of respiratory failure is also dependent on other important components of oxygen delivery, including hemoglobin level and cardiac output.

Genetic risk factor studies have focused on predicting development of ALI and ARDS. The proinflammatory cytokine interleukin-1 (IL-1) induces expression of other cytokines and chemokines involved in the inflammatory response. IL-1 is also involved in the fibroproliferative response in ALI and ARDS. Levels of IL-1ra and IL-1 are increased in bronchoalveolar lavage and pulmonary edema fluid from adult patients with early ALI or ARDS. A genetic polymorphism in the IL-1ra gene is associated with variation in IL-1ra and IL-1 activity. In children with community-acquired pneumonia, absence of an allele at the IL-1 receptor antagonist site has been reported in association development of ALI or ARDS. Other studies of ARDS risk target angiotensin II, which in alveolar epithelial cells stimulates the production of pro-inflammatory mediators and is involved in apoptosis (programmed cell death). A polymorphism in the angiotensin-converting enzyme (ACE) gene has been found, which affects production of

angiotensin II. In animal models of ALI, deficiency of ACE is associated with reduced pulmonary edema formation and leukocyte infiltration.

Pathology

Lung pathology varies with the etiologic agent. In ALI and ARDS, specific histopathological patterns are noted. Diffuse alveolar damage is the most commonly reported pattern seen at autopsy and is defined as interstitial edema, neutrophils in diffuse distribution, alveolar collapse, and hyaline membranes. Pulmonary edema is also frequently noted, evidenced by leakage of plasma proteins and fluid into alveoli. Alveolar hemorrhage or pulmonary emboli are less commonly seen (9% and 5–20% of cases, respectively). Interstitial inflammation with monocytes, lymphocytes, histiocytes, and plasma cells and organizing fibrosis can be seen more often in HIV patients. The extent of all types of inflammation varies based on the production of pro- versus anti-inflammatory cytokines.

Clinical Manifestations

Signs and symptoms of respiratory failure include changes in vital signs, mental status, and oxygenation-ventilation status. Young infants may progress rapidly and have little cardiopulmonary reserve and limited compensatory mechanisms. Children with chronic cardiopulmonary disease who have baseline abnormal ventilation may present insidiously. During acute decompensation, these children may demonstrate only mild alterations of respiration and instead show predominantly behavioral changes. These changes are related to acute plus chronic hypoxia causing sleep fragmentation resulting in irritability, tiredness, morning headaches, and restlessness.

While specific respiratory distress scoring systems have been created for conditions such as asthma and bronchiolitis, general characteristics of respiratory compromise regardless of underlying etiology are noted in *Table 225.1*.

Cardiovascular findings accompanying severe respiratory distress or respiratory failure include tachycardia, poor perfusion, and hyper- or hypotension depending on stage of catecholamine release or depletion. Children with severe asthma may demonstrate pulsus paradoxus. Pulsus paradoxus primarily reflects a decline in left ventricular stroke volume, noted as a decline in systolic and pulse pressures upon inspiration. It may be evident by watching oxygen saturation waveform for changes of 25% or greater during respiration.

Diagnosis

Diagnosis of respiratory failure is based on interpretation of history and physical examination findings and blood gas results. Arterial blood gas (ABG) is preferred whenever reasonable, weighing the benefits of accurate PaO_2 measurement against the invasiveness of testing. While venous blood gas (VBG) measurements of pH, carbon dioxide, and base deficit differ slightly from an arterial sample, VBG has been proven as accurate as ABG where

Table 225.1
Signs and symptoms of severe respiratory distress progressing to respiratory failure (noted with *arrows*)

Parameter	Infant	Child
Respiratory rate	>70 breaths/min → erratic	>50 breaths/min → erratic
Retractions	Subcostal →intercostal; may also have suprasternal	Same as with infant
Respiratory effort	Grunting, head bobbing, nasal flaring → intermittent apnea	May prefer upright sitting position→"tripod" position, breathlessness, unable to speak
Air entry	Significantly decreased →absent especially at bases	Same as with infant
Color	Pallor →acrocyanosis → central cyanosis	Pallor → cyanotic lips and fingertips/toes
Feeding	Poor/no feeding	Signs of dehydration, history of poor intake, and/or vomiting
Mental status	Poor eye contact → lethargic	Tired or anxious→ unable to give expected answers to questions

ventilation failure is of greatest concern. Noninvasive oxygen saturation monitoring results paired with VBG are commonly used to define respiratory failure. ABG is preferably for states of shock, congestive heart failure, and congenital heart diseases.

Determination of *Type I* versus *Type II* respiratory failure aids in placing the event into one of the three large etiologic categories. *Type I* is more commonly associated with failure of gas exchange where obstruction and failure of respiratory drive are typically *Type II*. Calculating the arterial-alveolar (A-a) gradient and assessing response to oxygen therapy can also be diagnostic. The A-a gradient can be calculated using the alveolar gas equation:

$$A\text{-}a \text{ gradient} = P_AO_2 - P_aO_2(\text{arterial}), \text{where}$$
$$PAO_2 = FIO_2(P_B - 47) - 1.2(PaCO_2)$$

P_B = barometric pressure, which at sea level is 760 mmHg, dropping with increases in elevation. If the A-a gradient is elevated above the age-dependent normal range of 5–30 mmHg, then V/Q mismatch is most likely present. However, failure to resolve hypoxemia with 100% oxygen is most often associated with shunting.

Differential Diagnosis

The list of potential etiologic causes of respiratory failure is extensive (◉ *Table 225.2*). Diagnostic studies may be supportive of the etiologic diagnosis or aid in determining the extent or severity of the effects of hypoxemia or hypercarbia.

Chemistry tests	Rising serum lactate is an indicator of significant tissue hypoxia
	Elevated bicarbonate suggests chronic hypercarbia
	Low potassium, calcium, or phosphate can impair muscle function
Hemoglobin	Polycythemia suggests chronic hypoxemia
PaO_2/FiO_2 ratio	Ratio < 200 is correlated with a shunt fraction greater than 20%
Chest radiograph	Focal or diffuse infiltrates suggest pneumonia and/or ARDS
	Bilateral hyperinflation suggests asthma
	Other helpful findings: upper airway narrowing or deviation, lobar collapse, air leak, asymmetric diaphragms, effusions, cardiomegaly, pulmonary edema

Chest CT or MRI with or without angiography may be helpful in defining parenchymal or pleural acute versus chronic disease as well as vasculitis. Pulmonary embolus can usually be defined on CT angiography or V/Q scan.

Table 225.2
Etiologies of respiratory failure (selected examples in parentheses)

Failure of air delivery/release (obstruction)		
Acute infections (croup, retropharyngeal abscess, bacterial supraglottitis, or tracheitis)	*Traumatic injury* (post-extubation, foreign body)	*Congenital airway* (subglottic stenosis/web/cyst, tracheomalacia, craniofacial anomalies, vascular slings)
	Multifactorial (obesity – obstructive)	
Failure of appropriate pulmonary gas exchange		
Acute infections (bronchiolitis, pneumonia, sepsis)	*Traumatic injury* (pulmonary contusion, drowning, inhalation lung injury, pneumothorax)	*Congenital pulmonary* (lung aplasia, congenital cystic adenomatoid malformation, diaphragmatic hernia – pulmonary hypoplasia)
Systemic (lupus, Wegener's granulomatosis, cystic fibrosis, sarcoidosis)	*Multifactorial* (chronic lung disease, asthma, pulmonary embolus, pulmonary edema)	*Cardiovascular* (congestive heart failure, cyanotic heart disease)
Failure of neuromuscular or central control over respiratory drive		
Acute infections (meningitis, meningoencephalitis, CNS abscess, infantile botulism, tetanus, polio)	*Traumatic injury* (accidental or non-accidental CNS hemorrhage, CNS shearing injury, CNS anoxic injury, spinal cord trauma)	*Musculoskeletal* (diaphragmatic hernia-muscular dysfunction, scoliosis)

Table 225.2 (Continued)

Congenital CNS (apnea of prematurity, central hypoventilation syndrome, brainstem malformations, cerebral palsy)	*Multifactorial* (sedating/paralyzing medication overdose, seizures, sleep apnea, obesity-hypoventilation, stroke, electrolyte disturbances, e.g., periodic paralysis)	*Neuromuscular* (muscular dystrophies, e.g., Duchenne, metabolic myopathies, congenital myopathies, e.g., spinal muscular atrophy, neuromuscular junction disorders, e.g., Guillan-Barré)

Other testing should be targeted at the likely underlying etiologic diagnosis in consultation with pediatric subspecialists from pulmonology, rheumatology, cardiology, or neurology.

Treatment

Basic tenants of pediatric advanced life support such as the jointly published 2005 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations and the American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care should be followed to stabilize patients with respiratory failure.

Transfer to an intensive care setting should be considered when:

- More than 50% FiO_2 is needed to maintain an oxygen saturation $\geq$ 92%.
- Evidence of respiratory distress is accompanied by tiring or exhaustion.
- A normal $PaCO_2$ cannot be maintained with available pressure support systems.
- Apnea or irregular respirations are noted.

General treatment includes prone positioning, which increases the functional residual capacity, improving lung compliance and oxygenation. Oxygenation improves within 1–2 h after position change and is usually sustained. Other treatments critical to good outcomes include maintaining adequate perfusion, resolving acidosis, stabilizing electrolytes and glucose, maximizing nutrition, delivering appropriate sedation, and minimizing exertion or energy use.

A simplistic view of treatment that addresses the three main pathophysiologic derangements of respiratory failure includes oxygen for hypoventilation, positive pressure to maximize lung volume for shunting, and one or both of these for ventilation/perfusion (V/Q) mismatch. Oxygen delivery methods in brief include nasal cannula (preferably humidified), high-flow nasal cannula, simple face mask, oxygen box or head helmet, non-re-breather mask, laryngeal mask airway, and endotracheal or nasotracheal intubation (cuffed or uncuffed). Actual FiO_2 delivered should be monitored. Blenders are often used when FiO_2 greater than 50% is required for greater accuracy in oxygen delivery. Response to treatment should be monitored by either calculating the PaO_2/FiO_2 ratio or the oxygenation index (OI) = (Mean airway pressure (MAP) $\times$ FiO_2)/$PaO_2 \times 100\%$.

Treatment for hypercarbia has more recently focused on a permissive approach toward treatment of ALI/ARDS. Adverse effects of acidosis produced by hypercarbia maybe overstated. In fact, mortality may be decreased if permissive hypercarbia in conjunction with pressure-limited reduced tidal volume mechanical ventilation is used. As long as oxygen levels are appropriately maintained, allowance of PCO_2 in the 50 s with pH as low as 7.2 have been accepted by most intensivists, and have been associated with attenuated lung injury in animal models. However, acute rises in PCO_2 or chronic rise to levels of 100 or higher are not typically acceptable. Acute rises in PCO_2 result in intracellular acidosis, pulmonary hypertension, and dysregulation of cerebral blood flow. Monitoring of treatment response should include end-tidal CO_2.

Improvement in ventilation can assist both carbon dioxide removal and oxygen delivery. Simple and effective intervention for patients with partial airway obstruction may include oropharyngeal or nasopharyngeal airways. For other airway and parenchymal disease, delivery of positive pressure is necessary. Delivery of continuous distending pressure via nasal or mask continuous positive airway pressure (CPAP) has been successful in infants with severe respiratory distress from bronchiolitis and apnea. Noninvasive positive pressure ventilation (NPPV) using bilevel positive airway pressure (Bipap) is most often used for children past infancy with poor neuromuscular control but can be used for acute chest syndrome and pneumonia in healthy and immunocompromised patients. Bipap offers different modes beyond the traditional spontaneous modality, such as spontaneous/timed, timed, or pressure control. With the latter, assisted breaths are triggered by and synchronous with the patient, and pressure delivery is limited making this mode a closer parallel to native respiration. However, the risk of iatrogenic barotrauma

resulting in pneumothorax or pneumomediastinum is greater when delivering both inspiratory and expiratory pressure with Bipap as compared to the constant pressure delivered with CPAP. Use of Bipap in ARDS is not recommended, as over 75% of patients ultimately require intubation. Use of NPPV for asthma patients is somewhat controversial. In asthmatics, the risk of barotrauma is nine times higher in those receiving some form of ventilation assistance compared to those treated without this support. However, the risk is the same whether intubated or using NPPV. In children with neuromuscular disorders on home NPPV presenting with acute decompensation, treatment may vary from changing NPPV pressures to intubation. Infants and children receiving any form of pressure support must have continuous oxygen saturation and cardiorespiratory monitoring, CO_2 assessments, and immediate access to experienced providers who can act in response to changes in pressure readings, oxygenation and ventilation, hydration status, and mental status.

For patients requiring intubation, avoidance of ventilator-induced lung injury (VILI) includes use of end-expiratory pressure sufficient to avoid atelectasis yet not cause barotrauma. High-frequency ventilation and liquid ventilation have been used with varied outcomes. High-frequency ventilation is available in three forms: positive-pressure ventilation (HPPV) (rate 60–150/min), jet ventilation (HFJV) (rate 100–600/min), and oscillatory ventilation (HFOV) (rate 180–1,500/min or 3–25 Hz).

HPPV and HFJV promote gas exchange using tidal volumes greater than dead space volume, with passive expiration. In contrast, HFOV uses tidal volumes that are less than dead space and expiration is active. Of the three, HFOV has been used most successfully in both neonatal and old-aged patients. It is being used more often as a lung protective strategy in children with ALI regardless of cause.

Special gases are of great interest, and may be used in both intubated and non-intubated patients. Heliox, a low-density combination helium–oxygen mixture, improves ventilation by improving flow through turbulent airways. Its use in non-intubated bronchiolitis patients has been associated with improved oxygenation, respiratory rate, and retractions; however, its value in intubated patients is less conclusive. The clinical limitation to heliox use is mainly the ability to maintain adequate oxygenation. For patients requiring more than 40% FiO_2 to maintain adequate oxygenation, the 60% helium is of limited benefit in reducing turbulent flow. Inhaled nitric oxide (iNO) dilates the pulmonary vasculature and has been used primarily for pulmonary hypertension. Its use requires monitoring for methemoglobinemia in patients and for toxic NO and nitrogen dioxide gas exposure in personnel. Use of iNO in other disease states has been reported to result in up to 20% improvement in short-term oxygenation but may be associated with decreased survival when given prior to extracorporeal membrane oxygenation (ECMO). ECMO is reserved for the most extremely affected patients, but has been successfully used even in patients who are immunocompromised or have cancer.

Specific treatment for ARDS must address the acute increase and imbalance between both pro-inflammatory and anti-inflammatory cytokines. Steroids have been used in cases where autoimmune diseases or viral infections result in ARDS, with varied outcomes. It is currently unclear if steroids improve acute or chronic pulmonary outcomes in ARDS.

Future considerations target treatment and genetic testing. Expanded assessment is needed of the risks of iNO use, including potential for increased oxygen and nitrogen radical formation which may damage the alveolar epithelium. Inhaled prostacyclins have been shown in adults to decrease intrapulmonary shunts. Surfactant studies to date have been underpowered but metanalysis of the studies combined shows promise with decreased ventilator days reported. Genetic testing for ACE activity may allow for use of ACE inhibitors in select patients.

Prognosis

Prognosis is highly dependent on the cause of the respiratory failure, particularly in immunosuppressed patients. Regardless of underlying chronic disease, the highest mortality rate is seen in children with ARDS, with rates of 30–50% in the United States and as high as 50–65% in developing countries. Most patients with ARDS have multiorgan system involvement and worse Pediatric Risk of Mortality (PRISM) scores. ALI not associated with ARDS carries a mortality rate of 3–35%. For surviving patients, likelihood of long-term lung disease is thought to be related to the underlying etiology; however, few studies of long-term pulmonary function testing have been performed.

Prevention

Prevention is aimed at clinician recognition of signs and symptoms of acute respiratory distress. Clinicians should be knowledgeable regarding patients at risk for progression from acute respiratory distress to respiratory failure. Prompt diagnosis and treatment of the precipitating factors and institution of respiratory support is critical to reduce avoidable acute respiratory decompensation.

Patients with chronic pulmonary disease should have monitoring of pulmonary functions and institution of home NPPV as appropriate.

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226 The Pathophysiology of Cough

Gabriel G. Haddad

Physiology of Cough

Neuroanatomy and Cough Reflex

Cough receptors are fairly widespread in the tracheobronchial tree and in various sites of the respiratory system. However, the density of these receptors is highest in the larynx, trachea, and main bronchi. Receptors are also present in the nose, pharynx, paranasal sinus, ears, pleura, and diaphragm. There are no known cough receptors in the alveoli. Outside the respiratory system, the pericardium contains receptors that are capable of stimulating cough. By far, most cough receptors are of the rapidly adapting or irritant airway receptor types. Such receptors are stimulated by numerous modalities, including mechanical (e.g., touch, deformation, pressure), and chemical (e.g., smoke, ammonia, endogenous chemical mediators, mucus). The afferent fibers travel mostly through the vagus nerve but discharges from the pharyngeal receptors are carried by the IX cranial nerve and those from the nose and paranasal sinuses through the V nerve. The pericardial and diaphragm receptors are carried through the phrenic afferents. Vagal, glossopharyngeal, and trigeminal fibers synapse in the brain stem and in particular in nucleus of the tractus solitarius (TS), a main sensory station.

After making the first synapses in the TS, projections are made on motor neurons in the ventrolateral part of the medulla oblongata, that is, the nucleus retroambiguus and ambiguous. Through vagal efferents, the laryngeal, tracheal, and bronchial muscles are activated during the cough reflex. The phrenic and intercostals motor pools are also recruited to contract the respective muscles and help in building the pulmonary pressures needed. Of clinical interest are patients who have brain stem lesions and fail to have an involuntary type when their airway receptors are stimulated. These patients continue to be able to cough on command, suggesting that they can bypass brain stem nuclei and activate a set of respiratory muscles responsible for a voluntary type of cough.

Characteristics of Cough and Mucus Clearing

The actual mechanical cough is characterized by four specific mechanical phases, each of which is distinct from the others. *First*, cough starts with a very deep and rapid *inspiratory effort*. This has the effect of achieving a more optimal thoracic volume for the subsequent phases of the cough. *Second,* a phase of *compression* immediately follows the end of inspiration. This compression results from the closure of the glottis and activation of the diaphragm and chest wall muscles to compress and splint airways and build abdominal and pleural pressures. The *expression* of cough marks the start of the *third* phase, during which there is a sudden opening of the glottis, high expiratory airflow, and an explosive sound; collapse of some airways also occurs. The *fourth* phase is marked by relaxation of the musculature and reversal of pressures and caliber of airways. Although such a cascade of events occurs in the characteristic cough, each event may not occur in every cough. For example, large inspirations or very high pressures or volumes may not take place at the onset. In addition, body position affects the strength and the efficacy of cough, as the pressures reached are higher in the sitting than in the supine position. Since the role of the cough is to remove or clear the mucus and foreign objects from the airways, it is important to review the factors that render the cough effective. In general, there are various factors that are critical:

1. *Speed of airflow*: There are various speeds of airflow and these have varied effects on mucus movements. With very "slow" airflow, air is so sluggish that it forms a noncontinuous flow without affecting the transport of the mucus toward the mouth. Annular or misty airflows are much higher and continuous flows, reaching a speed of 280 m/s. These flows can be very effective. They may put enough pressure on the mucus to move it on the periciliary fluid. If the airflow is extremely high, such flows may blow the mucus into droplets.
2. *Mucus rheology*: It should be intuitively clear that the more viscous and the less elastic the mucus is, the

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more difficult it is to affect its transport. This is evident when one considers, for instance, the nature of the secretions in cystic fibrosis and chronic obstructive lung disease.

3. *Size of inspiration and expiration*: The higher the volume inspired and the shorter the expiratory phase, the higher the airflow and the higher the probability for the cough to clear secretions.
4. *Pump structure*: Since the strength of cough depends on the structure of the airways and their integrity, pathology in the airway walls may affect the ability of the cough to affect secretion movements: any exaggerated collapse of the airways during expiration should severely limit the forcefulness of the cough (e.g., tracheomalacia in the premature infant). Another good example would be the limited effect of cough in patients with bronchiectasis because of outpouchings in the airways.

From the information above, it can be seen that cough would be very ineffective in cases where the *airflow* is relatively low, such as in obstructive disease of various etiologies and nature, and when the nature of the *mucus* is affected by inflammation, debris, cellular material (DNA), and increased amount of secretion. Cough can also be jeopardized when respiratory *muscles* do not generate the necessary pressures (i.e., weak, paralyzed, fatigued) and when the *airways* cannot be well splinted because of airway wall pathology or extraluminal compression by space-occupying masses. Hence, both pulmonary and extrapulmonary disease can contribute to the inefficiencies of the cough reflex and can therefore potentially exacerbate lung diseases.

Cough and Clinical Conditions

Frequency and Intensity of Cough

The frequency of cough varies considerably from condition to condition and depending on the state of consciousness. First, it is important to realize that there is no correlation between disease severity and frequency of cough. In some studies, the number of coughs per day in patients with upper respiratory tract infections was much higher than the number seen in patients with active tuberculosis. In addition, the frequency of cough depends on the time of day and whether the individual is awake or asleep, with the frequency of cough being higher upon waking up and much lower between 12 midnight and 6 a.m., especially during rapid eye movement sleep. It is not clear also whether the sensitivity to cough increases in patients with increased cough. Adult studies have shown that in patients with productive or dry cough, such as in chronic obstructive lung disease and bronchiectasis, the dose of capsaicin needed to elicit three to five coughs is not increased. More such studies need to be performed to resolve the issue in both adults and children.

Etiology of the Cough

Often the pediatrician or pediatric pulmonologist is faced with questions pertaining to the etiology of cough. Clearly, if the child has an acute episode of an upper respiratory infection and the disease is in the acute stage, there will be little need for investigation. It is only when a condition has moved into a chronic stage that certain testing needs to be done. Chronic cough can be defined as a cough that has lasted 4 weeks or more and has not resolved. Of major importance is the need for asking the right historical questions to delineate the etiology of the disease process. Some of these are: What is the nature of the cough? Is it productive or dry? What does it sound like? What is the cough associated with? What makes it better or worse? What time of the day does it occur? Does it occur during sleep? Is it related to position? Feeding? Exercise? Cold air? Is it seasonal? Is it associated with constitutional symptoms, such as fever, weight loss? Is the cough responsive to medications such as bronchodilators? Steroids? Since the cough reflex is really a manifestation not only of pulmonary disease but also of extrapulmonary conditions, the physical exam should be complete. In particular, a complete chest, lungs, and heart exam should be done. An ear, nose, and throat exam is very important as well to rule out etiologies in these organs that can produce cough. The presence of digital clubbing would indicate chronicity, although this is not pathognomonic to any particular lung disease, and should therefore be checked.

Establishing a Diagnosis

Besides an adequate history and physical examination, some laboratory tests may be essential depending on the disease. For example, depending on the suspected etiology, some or all of the following tests should be entertained: chest x-ray and sinus films, including sinus computerized tomography; sweat chloride test; barium swallow or esophageal pH; immunologic studies; Cilia biopsy for electron microscopy studies and ciliary function (beat frequency) assessment; and pulmonary function tests

(PFTs). PFTs are important as they may give clues about occult reactive airway disease and data on whether the disease pattern is obstructive or restrictive.

One of the most important factors, however, is age. In general, the etiologies of cough may be divided into three *age groups*, based on the causes of chronic cough. For example, congenital anomalies, such as tracheoesophageal fistula, would be important to consider in the first few months of life. Similarly, viral infections, such as respiratory syncytial virus (RSV) and especially Chlamydia, are notorious at this age. In the preschool child, foreign body aspiration and reactive airway disease become important diagnostic possibilities. In the older child and adolescent, psychogenic cough and irritative cough, such as due to smoking should be considered. In addition to these conditions, infections whether viral or bacterial, cystic fibrosis (CF), aspiration syndromes from gastroesophageal reflux (GER) or lack of coordination of pharyngeal muscles, and exposure to smoke should always be entertained. Rarer conditions would include restrictive diseases, pulmonary vascular disease, and tumors. Also of importance, the determination of the etiology for the cough can be aided by association of the cough with other symptoms. Chronic illness with high fevers and repeated lung infections should lead to suspicion of immune disorders. Hemoptysis with cough is often present in CF, tuberculosis, or bronchiectasis. Recurrent episodes of cough and lung infections with ear or sinus infections should point possibly to primary ciliary disease of the airways, such as Kartagener syndrome. In addition, the nature of the cough and the associated breath sounds on chest exam should be illuminating. For example, paroxysmal coughing should point to the etiologic agents of *Chlamydia* or pertussis. Recurrent cough with wheeze should point to the presence of airway obstructive disease.

Complications of Cough

Cough, as a symptom, is an important expression of diseased or abnormal airways. Hence, it is very important to monitor the cough in order to determine the effect of therapy or the natural course of the disease entity itself. In addition, although it is important not to interfere with cough, cough in some instances can be so "abrasive" and severe that complications can result from it. These complications may be relatively benign or really severe. Complications of cough include rupture of small nasal veins or may be so severe to result in loss of consciousness, fractures, rupture, or perforation of the esophagus, bronchus, or bladder; or air in the mediastinum, peritoneum, and pleural space.

Drug Therapy for Cough

It is when cough is severe and complications are occurring from the cough itself that drug therapy is indicated. Various agents have been tried, and some have proven to be effective. Opiods are the longest known antitussive, but their mechanism of action is not well delineated. They are thought to decrease the sensitivity of the cough reflex mainly by a central effect. Antihistaminics are sedatives and can alleviate the cough associated with asthma effectively in a fashion similar to steroids and cromoglycate, although the mechanism of action of these agents is likely to be very different. Administration of local anesthetics through lozenges or sprays to blunt the sensitivity of the reflex has also been used.

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227 Chest Pain

John Moore

Introduction

Because adults presenting with chest pain frequently have serious and life-threatening conditions, parents often bring their child complaining of chest pain to the emergency department or the pediatrician's office for evaluation. It is fortunate, however, that most children with chest pain have a benign condition.

Case #1

A 14-year-old female was brought to the emergency department complaining of left chest pain. She was playing soccer with her team earlier in the day and had the sudden onset of sharp left chest pain after running the field. The pain was aggravated by taking a deep breath. On shallow breathing she had little discomfort. Her examination showed no respiratory distress and her oxygen saturation was 98% in room air. Auscultation of her chest was unremarkable. A chest x-ray was obtained (*Figs. 227.1* and *227.2*). She was found to have a small left apical pneumothorax. She was admitted to the hospital and treated with nasal oxygen.

Case #2

A 10-year-old male was brought to the emergency department complaining of substernal chest pain. It was intermittent, aggravated by exercise and relieved by resting. He denied other symptoms such as palpitations and syncope. Family history was not remarkable for sudden unexplained death, syncope, or heart disease in younger members. His examination showed no distress, normal vital signs, and a grade 2 systolic ejection murmur at the left upper sternal border. His electrocardiogram in the emergency department showed left ventricular hypertrophy (*Fig. 227.3*). Cardiology consultation revealed hypertrophic cardiomyopathy. He was treated with beta blockers and followed by the cardiology service.

Epidemiology

Up to 0.6% of patients evaluated in pediatric outpatient clinics and pediatric emergency departments have a chief complaint of chest pain. The peak age of presentation is between 12 and 14 years old, and there is no sex predilection. The age of presentation is at least partially dependent on communication skills. Very young children or infants, for example, may experience pain but manifest irritability or other less specific complaints. Studies investigating the etiologies of pediatric chest pain in emergency departments and outpatient clinics suffer from lack of consistency in methods of evaluation and diagnostic categories. Nevertheless, existing studies suggest that the large majority of cases are of idiopathic, psychogenic, or musculoskeletal origin, and have a benign prognosis. Pain, caused by diseases of the respiratory system, are less common and may be more significant. Cardiovascular pain is uncommon even in emergency departments of hospitals harboring significant pediatric cardiovascular surgery programs. However, chest pain of cardiovascular origin, as in adult patients, may be caused by serious cardiovascular disease.

Pathogenesis

Chest pain is caused by inflammation, trauma, or ischemia to tissues with sensory nerve fibers in the chest cavity. The lung parenchyma and the visceral pleura of the lung are not innervated. The lung parietal pleura, however, is densely innervated by intercostal and diaphragmatic nerves, which localize pain to the pleura. This type of pain may be identified by deep inspiration but not usually by palpation. In addition, the center part of the diaphragm is innervated by the vagus nerve, and the sensory afferent fibers enter the cervical cord. Thus, pain originating from the adjacent parietal pleura may also be referred to the neck and the shoulder. Other deep viscera in the mediastinum such as the heart, pericardium, aorta, bronchi, and esophagus have sensory innervations carried via the vagus

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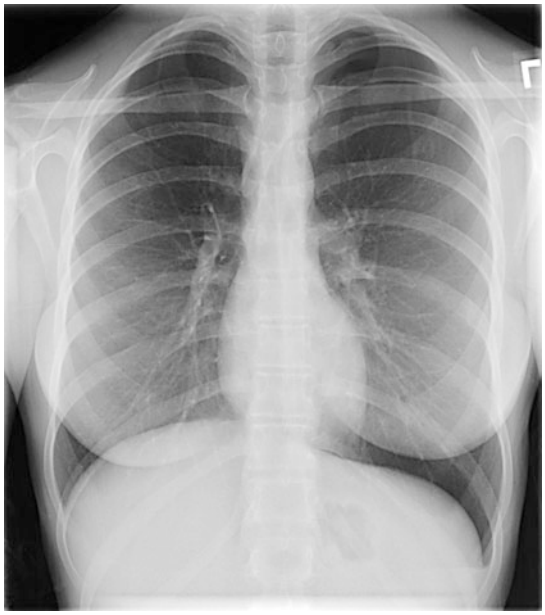

Figure 227.1
Chest x-ray of 14-year-old female with left chest pain

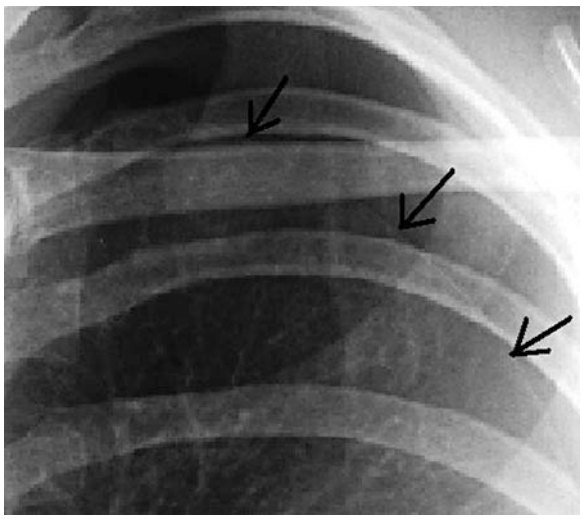

Figure 227.2
Magnified view of the left apical portion of chest x-ray in Fig. 227.1, showing small apical pneumothorax. *Arrows* show edge of visceral pleura

nerve and may have somewhat irregular density and distribution of fibers such that sensation is more diffuse and more difficult for patients to describe and to localize. Skin, subcutaneous tissue, and chest wall structures (bone, muscle, and cartilage) are highly innervated by cutaneous nerves, which allow specific localization of pain to the chest wall.

Pathology and Differential Diagnosis

The differential diagnosis of chest pain in children is extensive because of the numerous chest structures which are vulnerable to pain producing stresses or pathology.

Idiopathic

Idiopathic pain is pain with no identifiable cause and without apparent pathophysiology. It has been common in some pediatric series. Idiopathic pain may be chronic or recurrent. One type of idiopathic pain known as the *precordial catch syndrome* is often classified with chest wall pain. However, because this pain has no accepted source or known pathophysiology, it should be considered to be a type of idiopathic pain. It is usually left-sided and manifested by a "popping" or "ripping" sensation of seconds to minutes duration. Deep breathing typically intensifies this pain.

Musculoskeletal Causes

Musculoskeletal chest pain has multiple causes and is extremely common. Trauma or muscle strain may be related to normal activities of daily living among rapidly growing youths. Breast enlargement or pectus deformities may accentuate these effects. *Slipping rib syndrome* is pain caused by lack of attachment of ribs 8, 9, and/or 10 to the sternum and results in their excess mobility. This causes stretch or irritation of the intercostal nerves. Costochondritis is very common and is caused by inflammation of the costochondral junctions, possibly related to growth, exercise, or trauma. It most commonly involves the second, third, fourth or the fifth costal cartilages. *Tietze's syndrome* may be a specific severe form of costochondritis. It is characterized by nonsuppurative, fusiform, or spindle-shaped swelling often at the right sternoclavicular or second chondrosternal junction. *Hypersensitive xiphoid syndrome*, caused by inflammation of the the xiphoid process, is related to trauma or strain of the abdominal muscles which insert into it. Myositis of the chest wall muscles may be caused by connective tissue disorders or by viral inflammation. *Epidemic pleurodynia* is relatively common and is caused by Coxsackie virus. Shingles is infection by herpes zoster along a dermatome distribution causing severe localized chest pain. Cutaneous vesicles may follow pain by several days. Finally, sickle

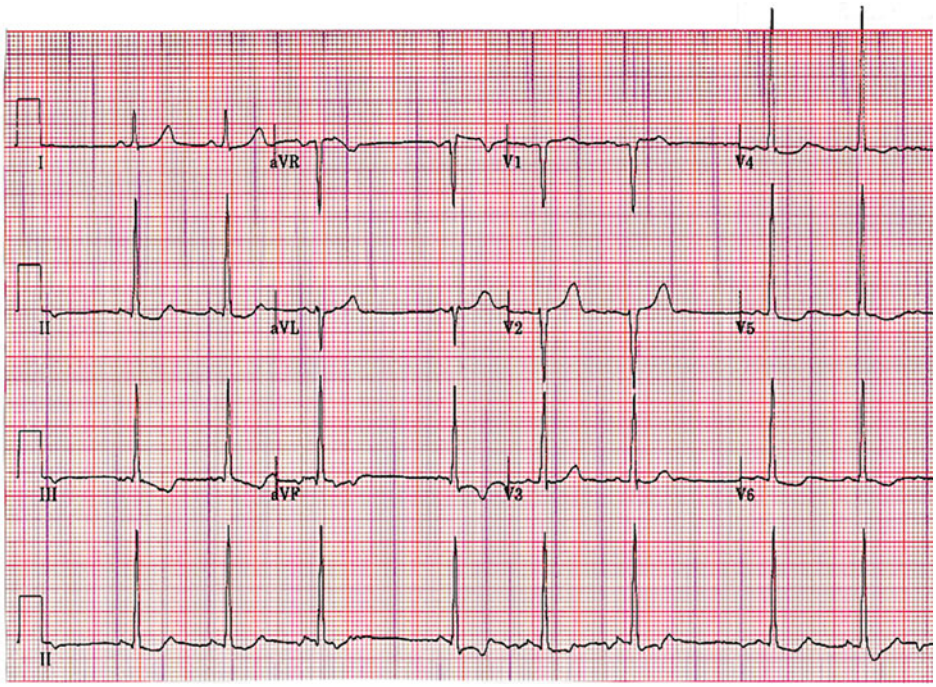

Figure 227.3
Twelve-lead electrocardiogram of 10-year-old male with substernal pain on exertion. The patient has voltage criteria for left ventricular hypertrophy (and premature atrial contractions with block)

cell disease may have numerous presentations including *acute chest syndrome*. The pathophysiology has been attributed to fat embolism, infection, or bony infarction.

Psychogenic Factors

Many children and adolescents under situational stresses or with neurotic disorders report chest pain. There may be specific identifiable stresses or a role model such as a family member or members who died or developed serious illnesses after reporting chest pain. There will often be a discrepancy between objective findings and reported symptoms. There may be primary or secondary gain from the pain, such as missing school. In addition, both hyperventilation syndrome and panic disorder may present with chest pain.

Pulmonary Disorders

Bronchitis, pneumonia, asthma, and cystic fibrosis may all cause chest pain (with accompanying dyspnea or respiratory distress) from muscle strain related to persistent cough or difficulty breathing. Bronchitis may also cause chest pain because of inflammation of the large airways. Inflammation of the parietal pleura may be a consequence of pneumonia or malignancies. Disease of the pleura may also result in pleural effusion, which further aggravates dyspnea and cough. Pneumothorax resulting in chest pain and dyspnea may occur spontaneously, with trauma, or postoperatively. It is specifically associated with Marfan's syndrome and cystic fibrosis. Airway foreign bodies may cause chest pain in younger patients related to cough and dyspnea. Pulmonary embolism, though rare in childhood, causes chest pain, dyspnea, and hemoptysis. Risk factors for thrombus formation and pulmonary embolism include taking oral contraceptives, presence of a central venous catheter, and the postoperative state.

Gastrointestinal Disorders

Esophagitis from gastric acid reflux or infection may cause chest pain. Esophageal spasm may also be a cause. Peptic ulcers and other subphrenic disease processes may also cause epigastric pain, which may be reported as chest pain.

Cardiac Disorders

The least common and perhaps most serious type of chest pain is caused by cardiac disease. There are multiple possible etiologies, but only three major pathophysiologies of cardiac chest pain: myocardial oxygen supply demand mismatch, irritation or inflammation of the pericardium, and dissection of the aorta. Other symptoms such as palpitations (suggesting arrhythmias) may be reported as cardiac pain, and pain may be associated with additional symptoms such as syncope and near-syncope. Several coronary artery diseases may cause myocardial ischemia related to inadequate coronary blood flow: Congenital defects include anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA). Ischemic chest pain occurs first in infants when the pulmonary vascular resistance falls. If this disease is not detected, coronary artery collaterals may develop from the right coronary artery system and ischemic pain may occur later in life during exertion. Coronary artery fistula, another congenital anomaly, may cause pain by coronary artery steal and related localized coronary insufficiency. The most common acquired coronary artery disease is Kawasaki disease. Typical patients are toddlers or young children a small percentage of which develop coronary artery aneurysms. "Atypical" patients may be older children or teenagers. Aneurysms may predispose to coronary insufficiency by thrombus formation or by healing with areas of coronary artery stenosis. Older children and teenagers may also manifest coronary artery–related ischemic chest pain because of Prinzmetal angina (coronary artery spasm), myocardial bridging, coronary ostium stenosis, or abnormal course and origin of the coronary arteries. Coronary artery spasm may also be induced by cocaine abuse, and may rarely be caused by postoperative scarring in patients with previous cardiac surgery involving the coronary arteries or the aortic root (e.g., transposition of the great arteries). Myocardial ischemia and related chest pain may also be caused by other cardiac conditions with normal coronary arteries. These include severe left ventricular outflow tract obstruction from valve or sub-valve aortic stenosis or hypertrophic cardiomyopathy and severely depressed cardiac output related to end-stage dilated cardiomyopathy or acute severe mitral regurgitation. Mitral valve prolapse may also cause "atypical" chest pain. The pathophysiology of this pain is believed to be related to localized papillary muscle ischemia. Irritation or inflammation of the pericardium resulting in chest pain may occur in pericarditis or in myopericarditis. These conditions most often have a viral etiology, but may also be caused by bacterial infections, tuberculosis, collagen vascular diseases, uremia, and Kawasaki disease. Postpericardiectomy syndrome may occur several days or weeks after cardiac or chest surgery, and chest trauma may cause injury and inflammation to the pericardium resulting in pericardial-type pain. Finally, patients with connective tissue disorders, most commonly Marfan's disease, may experience severe chest pain from dissection of the aorta.

Malignancies

Thoracic tumors of various sorts including lymphomas and malignant cardiac tumors may cause chest pain by their mass effects.

Evaluation

Because chest pain may rarely be a prominent symptom of a serious and/or life-threatening disorder in children, chest pain should be approached seriously and should receive a thorough, systematic evaluation. A major purpose of the emergency room or clinic evaluation is to screen for serious or life-threatening disorders. In general, this may be accomplished by a thorough history and physical examination, and a few simple laboratory tests.

Keeping in mind the innervations of chest structures, the differential diagnosis, and the epidemiology of pediatric chest pain, the diagnosis or at least the diagnostic category should be strongly suggested by a detailed history of the present illness, a past medical history, a review of symptoms, and a family history. As in most pediatric evaluations, information should be obtained both from the patient directly and from adult family members or guardians. Details about the pain should be identified: acute or chronic/recurrent, severity, localization, description/character, factors which aggravate or alleviate, duration, and timing. Any associated symptoms and their relationship to the pain should be determined. Use of medications, accidental ingestions, drug abuse, and behavioral or psychiatric conditions should be solicited. History of exposure to infectious diseases, previous medical problems, chronic medical conditions, prior surgeries, and trauma should be ascertained. Family history of chest pain, cardiac diseases, sudden death, chronic pulmonary conditions, lung cancer etc., may be significant from both the pathologic and the behavioral perspectives.

A complete physical examination focusing on the chest should be performed. The physical examination should include vital signs, temperature, and oxygen saturation in room air, as well as examination of the chest wall, lungs,

heart, and abdomen. If the examination is normal or strongly suggests a relatively benign etiology of pain, then laboratory examinations may not be required. However, if there are significant alterations in vital signs or significant abnormalities on examination of specific organ systems, further evaluations and consultations are mandatory to obtain a definitive diagnosis.

Basic laboratory evaluations that may be required are usually suggested by the history and physical examination. One or more of the following tests may be needed or important to confirm the diagnosis and plan the patient's disposition: chest radiograph, electrocardiogram, complete blood count, acute phase reactants, toxic screen, and serum troponin.

Treatment

Whenever possible, a specific diagnosis should be determined. Management of pain should be directed at the cause. For the majority of cases, reassurance and symptomatic treatment with over-the-counter analgesics, heat or cold, and rest is sufficient. Patients suspected of psychopathology should be referred for mental health evaluation. Patients with chest infections may require antibiotics and, if respiratory distress is significant, inpatient care. If significant pulmonary problems, cardiac disorders, malignancies, or severe trauma are suspected, hospital admission, specialty consultation, more extensive testing, intensive care, and appropriate treatment including surgery may be required.

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228 Hemoptysis

Julie Ryu

Definition

Hemoptysis is defined as coughing up blood or expectorating blood from the bronchus, trachea, or lungs. Pulmonary hemorrhages can be either diffuse or focal and be caused by a variety of etiologies. Pulmonary hemosiderosis by definition is the collection of hemosiderin-laden macrophages in the lung and therefore can result from a number of different conditions. While hemoptysis, pulmonary hemorrhage, and pulmonary hemosiderosis are often used interchangeably they have distinct definitions.

The majority of patients who present with hemoptysis are patients with cystic fibrosis. Patients with cystic fibrosis present with acute hemoptysis due to bronchiectasis; however, there are many other etiologies for hemoptysis. According to Coss-Bu et al. who looked at over 228 children presenting with hemoptysis over 65% were patients with cystic fibrosis, 16% had congenital cardiac disease, and remainder had a variety of conditions. While mild hemoptysis is not rare and often of non-pulmonary origin, life-threatening hemoptysis occurs less frequently. Massive hemoptysis is defined as greater than 300 mL of blood/24 h or 100 mL over 3 consecutive days with mortality usually due to asphyxiation.

Pathophysiology

Hemoptysis is a sign of many disease processes which can be categorized into prevalence by age as in *Table 228.1*. In addition to age, the type of bleeding, diffuse or focal, can narrow the possible etiologies for hemoptysis (see *Fig. 228.1*). Focal or localized bleeding can be associated with damage to a specific area of lung parenchyma or a large vessel (pulmonary or bronchial artery or vein). Focal bleeding can occur with any process that disrupts the endothelial integrity of a neighboring large vessel. Any process that damages a large vessel (trauma, AV malformation, foreign body, bronchiectasis, disruption of a aorto-pulmonary collateral artery in children with congenital heart disease, etc.) can result in a sudden massive hemoptysis.

The etiologies for diffuse bleeding are numerous and often more insidious in presentation. This type of bleeding can be divided into five broad categories: (1) Pressure related: cardiac failure, pulmonary edema, pulmonary embolism (acute chest syndrome in sickle-cell disease). (2) Immune related: Goodpasture's disease, Wegener's granulomatosis, systemic lupus erythematosus, Henoch-Schönlein purpura, alveolar capillaritis, Heiner syndrome/cow's milk hyperreactivity. (3) Congential abnormalities: pulmonary capillary hemangiomatosis, lymphangioleiomyomatosis. (4) Diffuse alveolar injury: any diffuse alveolar injury extending to the endothelial cells (often infectious or toxins). (5) Miscellaneous: idiopathic pulmonary hemosiderosis, coagulapathies (associated with immunocompromised patient). Diffuse bleeding is usually associated with capillary damage and therefore likely not to localize to only one area of the lung. This type of bleeding is more likely to be present in both lung fields and hemoptysis may be recurrent or massive depending on the extent of lung damage. Hemoptysis from immune etiologies may not present to medical attention until hemoptysis is significant and can be the initial presentation of a collagen vascular disorder.

Diagnosis

On physical exam, patients who have chronic pulmonary hemorrhage may present with increased work of breathing, cough, pallor, and fatigue. Patchy haziness or "whiteout" of one or more lung lobes may be apparent on chest radiograph. History can be helpful in verifying pulmonary hemorrhage; the patient may describe the blood as bright red and frothy which would be consistent with hemoptysis versus dark red which may suggest hematemesis. Stool guiac testing may be positive during active pulmonary hemorrhage as well as during gastroenteral bleeds and therefore does not rule out hemoptysis since younger patients may swallow sputum rather than expectorate it. A complete blood count may demonstrate a nonspecific microcytic hypochromic anemia in chronic bleeding but if eosinophilla is seen, Heiner/cow's milk hyperreactivity or an immune process should be considered. If eosinophilla

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Table 228.1
Common causes of bleeding by age group

Neonatal period
Hyaline membrane disease
Mechanical ventilation (instrumentation of airways)
Diffuse alveolar injury
Congenital abnormalities
Aspiration
Cardiovascular abnormalities with heart failure (pulmonary edema, pulmonary hypertension)
Sepsis
Infancy
Congenital cysts
Abscess
Hemangiomas
Heiner syndrome/cow milk hyperreactivity
Foreign bodies
Diffuse alveolar injury
Sepsis
Neoplasms
Childhood
Foreign bodies
Abscesses
Sequestrations
Immune-related causes
Endobronchial tuberculosis
Hemangiomas
Fungal or parasitic infections
Diffuse alveolar injury
Neoplasms
Pulmonary embolism (acute chest in sickle-cell disease)
Adolescence
Cardiovascular lesions with pulmonary artery or pulmonary vein obstruction, disruption of aorto-pulmonary artery collateral vessels in congenital heart disease
Bronchiectasis (especially in cystic fibrosis)
Foreign bodies
Immune-related causes
Diffuse alveolar injury
Pulmonary embolism (acute chest in sickle-cell disease)

is detected, an elevated IgE may suggest Heiner syndrome or a hypersensitivity reaction. An immune workup may also be helpful patients with a diffuse bleeding pattern since systemic lupus erythematosus, Wegener's granulomatosis, and Goodpasture's disease can all present with hemoptysis. In addition, urine analysis for hemoglobinuria may uncover underlying nephritis, which is associated with several immune disorders.

Endoscopy and bronchoscopy can be very helpful in determining if the blood is from the GI or respiratory tract. If bronchoscopy is performed, the procedure can be diagnostic as well as therapeutic. Bronchoalveolar lavage can be evaluated for hemosiderin-laden macrophages. Alveolar macrophages can remove freed hemoglobin degradation products from ruptured red blood cells and therefore positive staining for hemosiderin is diagnostic for blood in the airway even if no frank blood is seen during the bronchoscopy. On average, hemosiderin-laden macrophages can be detected within 2–3 days and peaks around 5–6 days after the initial bleed. While flexible bronchoscopy can help localize the source of bleeding, rigid bronchoscopy should be performed if hemoptysis is massive. Rigid bronchoscopy allows for better aeration since ventilation is not through a narrow endotracheal tube but through the rigid bronchoscope. In addition, a rigid scope is preferred when removing large clots is not possible through a flexible scope's suction channel; furthermore, removing large clots can reactivate bleeding necessitating surgical intervention. Thus, bronchoscopy, flexible or rigid, can be diagnostic as well as therapeutic. Ice-cold saline or topical epinephrine (1:10,000 to 1:20,000) may be instilled through the bronchoscope to vasoconstrict vessels. Furthermore, topical thrombin and thrombin/fibrinogen solutions have also been described to abate bleeding. All of these topical solutions may be helpful in the mild to moderate bleeding but often are not sufficient for massive bleeds. Other diagnostic procedures include CT scan to help identify any underlying pulmonary or cardiac cause for bleeding. CT scan with angiography is indicated if bronchiectasis-associated hemoptysis is suspected, especially in patients with cystic fibrosis. An echocardiogram (and/or cardiac catheterization) is indicated in patients with known or suspected of cardiac disease. In all cases, the ultimate goal is to identify the underlying cause of pulmonary hemorrhage as well as to confirm that the hemoptysis is truly pulmonary in origin.

Treatment

In most cases, hemoptysis is usually mild and self-limited. However, in cases of massive or recurrent hemoptysis, the goal is to treat the underlying disease. In the acute response to hemoptysis, the first priority is to assure adequate ventilation and correct any existing coagulopathy. Due to the decreased ventilation capacity from blood in the air space, additional respiratory support may be

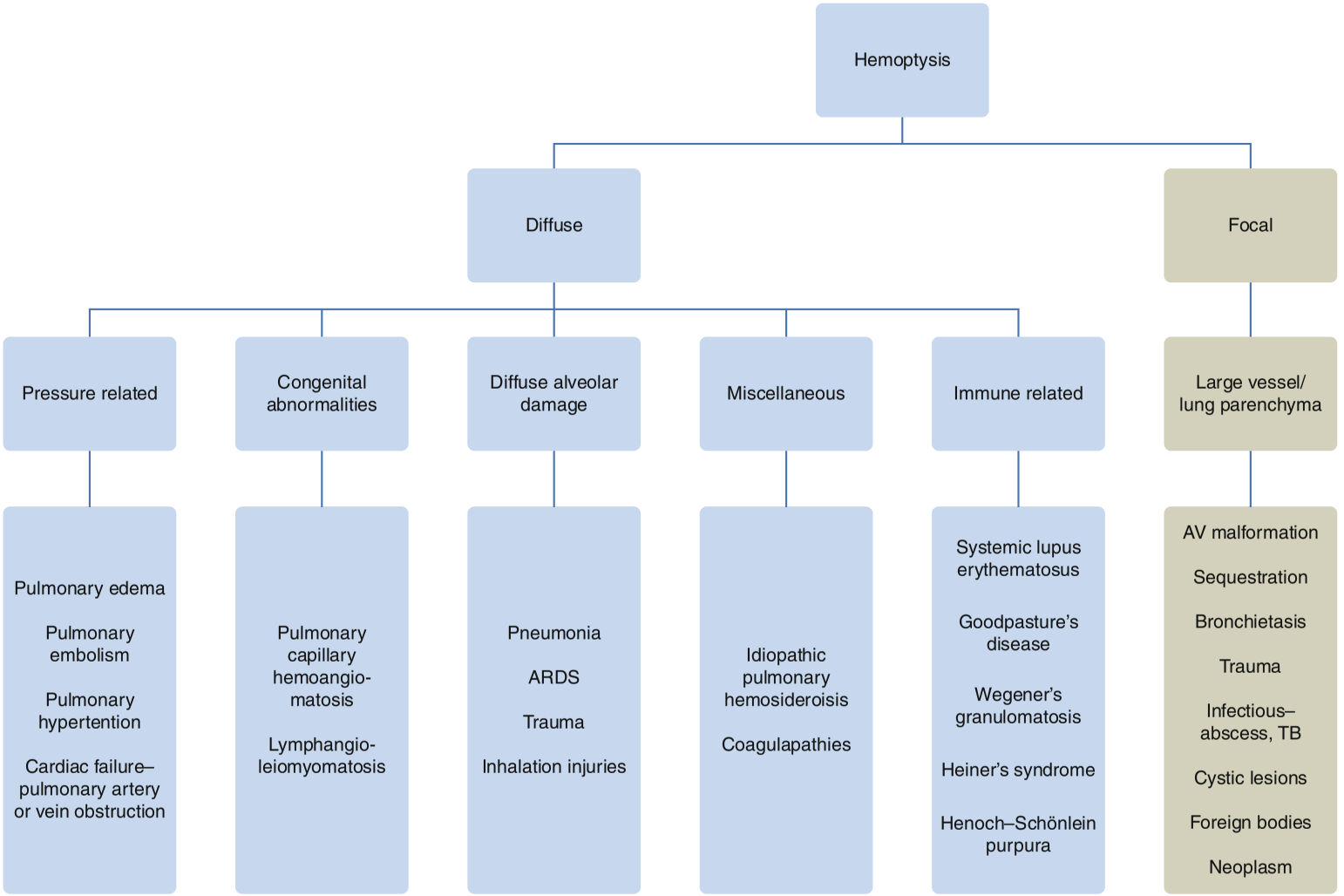

Figure 228.1
Common causes of bleeding by pattern, diffuse or localized

required. Intubation may be necessary to maintain airway patency and in some cases intubation with a double lumen endotracheal tube is required to ventilate the unaffected side of lung. However, many pediatric patients are too small for a double lumen endotracheal tube and some require high-frequency ventilation while others need extreme support such as extracorporeal membrane oxygenation (ECMO). In patients with cystic fibrosis, hemoptysis is not uncommon and is usually associated with bronchiectasis. In bronchiectasis, a bronchus enlarges due to mucous impaction. This impaction causes the adjacent bronchial vessel to stretch and become tortuous making rupture due to strain possible. Embolization of the ruptured bronchial vessel can be performed without impacting the pulmonary circulation. In extreme cases when hemorrhage cannot be controlled, lung resection may be indicated. In patients with systemic-pulmonary collateral vessels due to cardiac disease, cardiac catheterization with embolization/coiling of the ruptured vessel may be required to cease the bleeding. In cases of immune-related hemoptysis or idiopathic hemosiderosis, systemic steroids or immunosuppressive agents may be helpful in treating the underlying disease process.

Prognosis

When hemoptysis is isolated and mild, there are few if any long-term complications. However, patients with recurrent pulmonary hemorrhage or idiopathic pulmonary hemosiderosis can develop progressive pulmonary disease. Prognosis is dependent on quickly stabilizing the acute hemorrhage and treating the underlying disorder.

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229 Pulmonary Edema

David Nathalang · Bradley Peterson

Definition

Pulmonary edema is the abnormal accumulation of fluid within the interstitial tissue and/or within the alveolar air spaces of the lung.

Pathophysiology

Normally, small amounts of intravascular fluid continuously leak out of the pulmonary capillaries into the pulmonary interstitium. This fluid is removed by the lymphatic system preventing the development of pulmonary edema. Pulmonary edema occurs when the lymphatic system and other fluid removal mechanisms become overwhelmed.

Fluid flow across the capillary endothelium into the surrounding interstitium is dependent on a balance between hydrostatic and oncotic pressures on both sides of the endothelium. This is described by Starling's equation for liquid movement: $Q = K_f\ (P_c - P_{is}) - K_d\ (\pi_{pl} - \pi_{is})$, where Q is net fluid movement across a unit surface area of the capillary endothelium, K_f is the capillary filtration coefficient which quantifies the ease of which fluid can pass through the endothelium, P_c and P_{is} represent the hydrostatic pressures in the capillary or interstitial spaces, respectively; K_d is the reflection coefficient which describes the membrane's permeability to proteins, and π_{pl} and π_{is} represent the oncotic pressures in the capillary and interstitial spaces, respectively. According to Starling's equation, an increase in hydrostatic pressure inside the pulmonary vasculature will increase fluid flow across the capillary endothelial layer into the interstitium. With enough fluid accumulation, hydrostatic pressure in the interstitial space will then drive fluid across the alveolar epithelium into the alveolar airspace. Also, changes in capillary filtration allow increased amount of fluid to leak across the capillary endothelium and collect in the interstitial space. Additionally, higher osmotic pressures in the extravascular space compared to the intravascular space, due to protein leakage across the endothelium, can pull fluid across the endothelium into the interstitium.

Multiple mechanisms serve to eliminate abnormal fluid accumulation in both the interstitial space and the alveolus. The lymphatic system returns fluid from the interstitial space to the central venous system and is able to increase fluid removal to a certain degree in the face of increased interstitial fluid deposition. Alveolar fluid collections are managed by sodium channels embedded in the apical surface of the alveolar epithelial cells. Sodium is transported from the alveolar airspace across the alveolar epithelial barrier, and is then actively transported into the interstitium by basolaterally oriented Na-K-ATPase channels. This process creates an osmotic gradient that encourages water flow from the alveolar airspaces back into the interstitium. A variety of factors can stimulate this mechanism, including β_2-adrenergic agonists, α-adrenergic agonists, steroids, certain growth factors (e.g., epidermal growth factor), and thyroid hormones.

Overall pulmonary edema formation will depend on the rate of fluid accumulation compared to the rate of fluid removal. While intrinsic fluid removal mechanisms can increase the rate of fluid removal with increasing accumulation, they can become overwhelmed in the face of rapid, excessive fluid buildup resulting in pulmonary edema. For this reason, acute elevations in left atrial pressure are more likely to lead to pulmonary edema than chronic elevations.

Fluid will initially collect in the perivascular and peribronchial spaces, spread to the interstitium, then accumulate in the intra-alveolar spaces. Fluid that collects in these spaces will lead to the clinical signs and symptoms of pulmonary edema, including tachypnea, dyspnea, wheezing, crackles, and cyanosis.

Etiology

Using Starling's equation, disease processes leading to pulmonary edema can be divided into two major categories: high-pressure pulmonary edema and capillary leak pulmonary edema (*Fig. 229.1*).

High-pressure pulmonary edema occurs secondary to elevated pulmonary capillary hydrostatic pressure (increased P_c). Examples of this can be seen with volume

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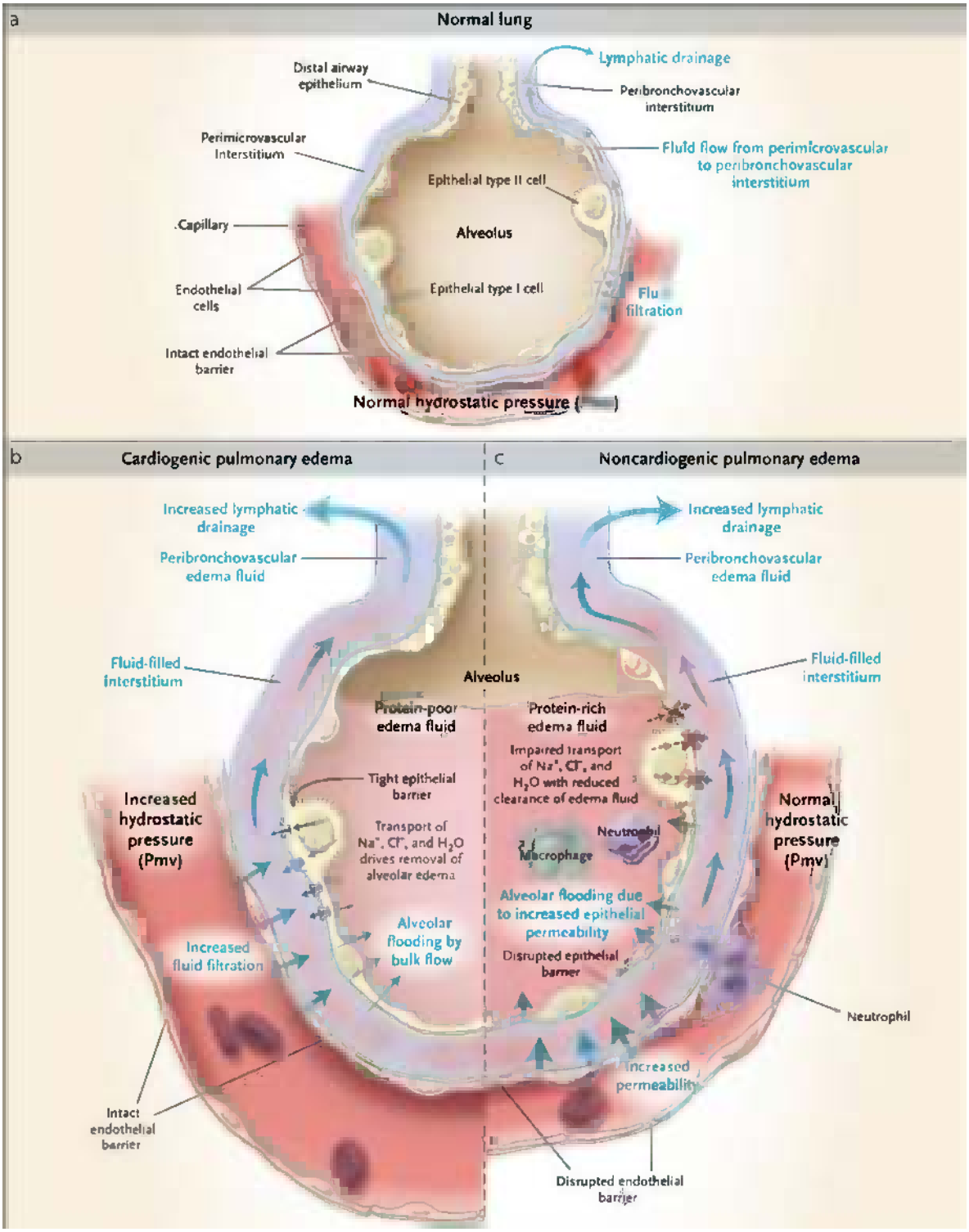

Figure 229.1
Mechanisms of pulmonary edema formation. (Reprinted with permission from Ware LB, Matthay MA (2005) Acute pulmonary edema. N Engl J Med 353:2788–2796)

overload states caused by overly aggressive fluid administration or oliguria due to renal failure. With cardiogenic pulmonary edema, a type of high-pressure pulmonary edema, elevated left atrial pressure secondary to left ventricular failure is transmitted to the pulmonary capillaries causing elevated pulmonary capillary hydrostatic pressure. This phenomenon is usually seen with left atrial pressures of 18 mmHg or higher. Endocarditis, myocarditis, arrhythmias, or any disease process that leads to left ventricular failure can bring about cardiogenic pulmonary edema. This can also occur with a normally contracting heart with an impairment of forward flow, such as aortic stenosis or mitral regurgitation, because of limited cardiac emptying and transmission of pressure to the pulmonary vasculature. Certain types of congential heart disease with large left-to-right shunts (e.g., ventricular septal defects) can cause overcirculation of the pulmonary circuit resulting in increased volume and pressure in the pulmonary capillaries.

In capillary leak pulmonary edema, damage to either the alveolar epithelial cells and/or the capillary endothelium causes an alteration of K_f, K_d, or both, leading to leakage of fluid, protein, and other molecules across the membrane. Additionally, damage to the alveolar epithelium may also impair the intrinsic sodium transport mechanism used for fluid resorption. Bacterial or viral pathogens are common causes of alveolar epithelial damage, and the resultant pulmonary edema can be worse in individuals with preexisting changes to the pulmonary vascular system, such as those seen with chronic lung disease. In addition, some infections stimulate the production of high-protein exudates in the alveolar airspaces leading to increased osmotic pressure in the alveolus and fluid accumulation. In acute lung injury and acute respiratory distress syndrome (ARDS), characterized by rapidly progressive bilateral infiltrates on chest radiography in the face of a pulmonary artery occlusion pressures below 18 mmHg, increased permeability and protein-rich edema fluid are commonly seen in the initial stages. Toxin and smoke inhalation, reactive nitrogen species, reperfusion injury, aspiration, radiation, and vasoactive substances (e.g., histamine) are also known to lead to endothelial or epithelial damage and edema formation. Several possible causes of both high-pressure and capillary leak pulmonary edema can be seen in Table 229.1.

Epidemiology

Edema formation is the result of a primary disease process leading to either high-pressure or capillary leak pulmonary edema. The incidence of pulmonary edema is related to the incidence of the inciting disease process.

Clinical Findings

History and physical findings enable determination of the severity of respiratory compromise and often point to the diagnosis and etiology of pulmonary edema.

Patients may have complaints of dyspnea, orthopnea, or cough. Patients with congenital heart disease may present with vague complaints of poor feeding, poor weight gain, diaphoresis with feeds, or even sudden cyanosis and shock-like symptoms with ductal-dependent lesions. Patients with capillary leak pulmonary edema may present with symptoms related to the initiating disease process, such as fever seen with bacterial pneumonia.

Physical findings will be related to the amount and location of pulmonary edema fluid. In children, cough and tachypnea may be the first signs of respiratory compromise. Wheezing may be noted when fluid accumulates in the peribronchial spaces in the early stages of pulmonary edema. As more fluid collects in the interstitial and intra-alveoli spaces, crackles will become apparent on exam and coughing may produce a frothy edema expectorant. Cyanosis will occur if gas exchange is severely depressed. Enlarged neck veins, hepatomegaly, peripheral edema, and abnormal heart sounds, including murmurs or gallops, may occur, suggesting a cardiogenic cause of edema formation. Abnormal rate or rhythm may occur and be the primary cause of cardiac dysfunction.

Diagnosis

Laboratory Studies

Initial labs should include a blood gas, a complete blood count with differential, C-reactive protein, chemistry panel, and B-type natriuretic peptide (BNP). These tests will help characterize the amount of respiratory distress and differentiate between cardiac, infectious, and other causes of pulmonary edema.

BNP, secreted by the ventricles in the face of increased cardiac pressures, is usually elevated in the presence of congestive heart failure. In adults, levels less than 100 pg/ml have a negative predicative value above 90% for congestive heart failure, while levels above 500 pg/ml have a positive predictive value above 90%. However, BNP levels should not be used as the sole criteria supporting a diagnosis of cardiogenic pulmonary edema, as they may

Table 229.1
Pulmonary edema by mechanism

High-pressure pulmonary edema	Capillary leak pulmonary edema	Mixed, other, or unknown mechanisms
1. Noncardiogenic a. Fluid overload i. Iatrogenic ii. Renal failure b. Increased pulmonary venous vascular resistance i. Pulmonary veno-occlusive disease 2. Cardiogenic a. Left ventricular failure i. Myocardial infarction ii. Cardiomyopathy iii. Endocarditis b. Arrhythmia c. Left-to-right shunt (Systemic to pulmonary shunt) i. Ventricular septal defect ii. Persistant ductal arteriosus d. Obstruction of left-sided emptying i. Aortic stenosis ii. Mitral stenosis e. Impaired left-sided emptying i. Aortic regurgitation ii. Mitral regurgitation f. High systemic vascular resistance	1. Infectious causes (e.g., bacterial or viral pneumonia) 2. Inhaled toxins a. Acid fumes b. Oxides of nitrogen c. High oxygen exposure 3. Circulating toxins a. Endotoxin b. Snake venom 4. Vasoactive substances a. Histamine b. Prostaglandins 5. Disseminated intravascular coagulation 6. Radiation pneumonia 7. Uremia 8. Aspiration pneumonia 9. Near-drowning and drowning 10. Smoke inhalation 11. Reperfusion injury	1. Decreased oncotic pressure 2. Decreased resorption of fluid a. Lymphatic insufficiency 3. High altitude pulmonary edema 4. Negative-pressure pulmonary edema 5. Neurogenic pulmonary edema 6. Re-expansion pulmonary edema 7. Transfusion-related acute lung injury

be elevated with other, noncardiac disease processes, such as sepsis and renal failure. Troponin levels are usually elevated with myocardial ischemia, infarct, or myocarditis, but like BNP levels, can be elevated without cardiac dysfunction.

Imaging

Chest radiography is commonly performed to confirm the diagnosis of pulmonary edema and help determine the cause of pulmonary edema. High-pressure pulmonary edema usually presents with an interstitial pattern of the infiltrates. Cardiomegaly, prominent septal lines, peribronchial cuffing, pleural effusions, and centrally distributed infiltrates are more common with cardiogenic pulmonary edema (*Fig. 229.2*). In contrast, patients with capillary leak pulmonary edema (*Fig. 229.3*) will have infiltrates that are more commonly peripheral in distribution, will present in an alveolar pattern, and will lack the characteristic cardiomegaly seen with cardiogenic causes of edema. Unfortunately, findings of the chest radiograph are mostly nonspecific to the diagnosis of either high-pressure or capillary leak pulmonary edema, as various findings may be seen with both types of pulmonary edema. Moreover, a radiograph may be affected by technique and user error, further decreasing the reliability of the chest radiograph as a means of definitive diagnosis.

Computed tomography can also be used to further visualize the lung affected and help determine the cause of pulmonary edema formation.

Monitoring

Bedside monitoring should include respiratory rate and continuous oxygen saturations, as well as temperature, heart rate, blood pressure, and hourly urine output. In more serious cases, central venous pressure should be measured which would be elevated in the case of cardiac dysfunction, fluid overload, or increased pulmonary artery resistance. If pulmonary artery occlusion pressures are measured, pressures above 18 mmHg are associated

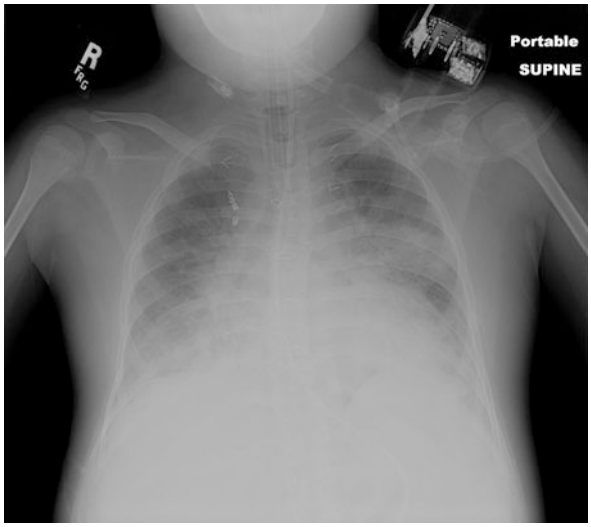

Figure 229.2
Cardiogenic pulmonary edema in a 9-year-old male with heart failure and elevated left ventricular end-diastolic pressure. Note the enlarged heart size and centrally distributed infiltrates

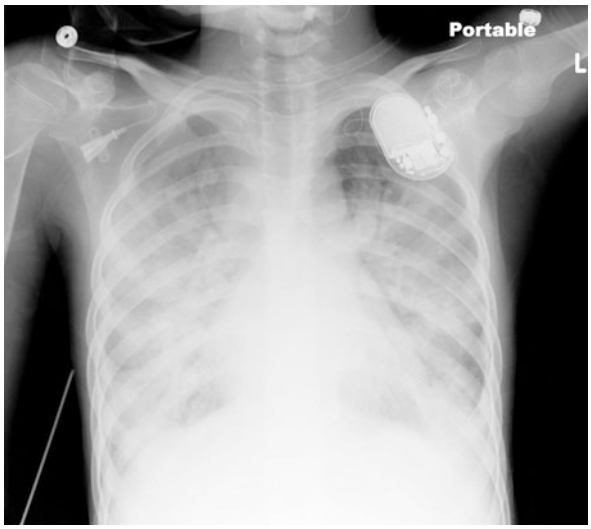

Figure 229.3
Capillary leak pulmonary edema in a 12-year-old male with early ARDS. Note the normal heart size and peripherally distributed infiltrates

with either cardiac dysfunction or volume overload and confirm high capillary hydrostatic pressure as the cause or at least a contributing factor to pulmonary edema formation.

Other bedside studies can be used to further assess the cause of pulmonary edema. Electrocardiography may suggest abnormal cardiac structure, evidence of ischemia and infract, or rhythm abnormalities. Echocardiography can evaluate cardiac function and assess for valvular dysfunction leading to increased left atrial pressures.

Treatment

General Care

Initial treatment of pulmonary edema should focus on improvement of gas exchange and resolution of any initiating disease process. Upright positioning is the easiest of all treatments to improve dyspnea. Diuretics may be used, though careful diuresis should be employed to avoid dehydration or worsening of cardiac output. Supplemental oxygen should be initiated early on in order to offset the effects of hypoxia. However, if 50% supplemental oxygen does not satisfactorily improve an individual's arterial oxygen saturation or respiratory distress then positive pressure ventilation should be employed.

One option for providing positive pressure ventilation is noninvasive ventilation as either continuous positive airway pressure (CPAP) or noninvasive intermittent positive pressure ventilation (NIPPV). CPAP provides a constant level of positive pressure throughout the respiratory cycle, effectively providing peak end-expiratory pressure (PEEP), which prevents alveolar collapse, increases functional residual capacity, and redistributes alveolar fluid. Conversely, NIPPV provides both PEEP and positive pressure during inhalation and supplies a higher level of mean airway pressure, which in turn decreases the work of breathing, increases surface area for gas exchange, and improves oxygenation. Noninvasive ventilation has been shown to improve respiratory status shortly after initiation, decrease the need for intubation, and improve hospital mortality.

Intubation and mechanical ventilation should be considered when there is hypoxia refractory to supplemental oxygen, low levels of positive pressure ventilation, or worsening clinical exam. Ventilator strategies will need to be chosen based upon the patient's disease process, e.g., lung-protective strategies using low stretch ventilation for ARDS, as inappropriate strategies using large tidal volumes have been linked to further alveolar epithelial damage and capillary leak pulmonary edema. In the case of persistent inability to oxygenate, inhaled nitric oxide and extracorporial membrane oxygenation can be considered.

Specific Treatments

Treatments for cardiogenic pulmonary edema target optimization of preload, reduction of afterload, and improvement of cardiac function. These treatments are used concurrently and are titrated to the patient's needs. Loop diuretics, such as furosemide, are commonly used to decrease preload and pulmonary capillary hydrostatic pressure. They may also have the additional effect of directly dilating pulmonary vasculature which would further decrease intravascular hydrostatic pressure. However, diuretics should be used with caution in the face of decreased cardiac output. Afterload reduction may be achieved with a direct vasodilator, such as Nitroprusside, or other medications such as Milrinone and Nesiritide, but should be avoided in hypotensive patients or when dealing with afterload-dependent lesions, such as severe aortic stenosis. Inotropic support with the use of exogenous catecholamines, such as Epinephrine, Norepinephrine, or Dobutamine, not only improves contractility but can also increase myocardial work and oxygen demand. Some medications can treat cardiogenic pulmonary edema in multiple ways. Nesiritide, a recombinant form of beta-natriuretic peptide, can improve diuresis as well as lower afterload. Milrinone, a phosphodiesterase inhibitor, not only causes afterload reduction via vasodilation, but also provides some inotropy without increased risk of tachycardia and arrhythmogenesis. It should be noted that some causes of cardiogenic pulmonary edema will require surgical repair, as in the case of a large ventricular septal defect causing pulmonary overcirculation.

With capillary leak pulmonary edema, treatments are chosen that specifically target the cause of the edema formation. Antibiotics or antivirals should be chosen in the case of infectious etiologies. Supportive therapy and mechanical ventilation will be needed for the treatment of ARDS.

Future Developments

Current research is investigating techniques that will enable the quantification of edema fluid in the lungs. Levosimendan, which increases myocardial troponin calcium binding, may be used to increase cardiac output by improving both systolic and diastolic functions and shows promise in the treatment of cardiogenic pulmonary edema. Methods to increase alveolar fluid resorption are also being investigated. Inhaled β-adrenergic agonist and certain growth factors, such as keratinocyte growth factor, have been shown to increase sodium transport across the alveolar epithelium.

Prognosis

As pulmonary edema is typically seen in conjunction with an inciting disease process, prognosis is mostly related to the severity of the primary disease.

Special Considerations

High Altitude Pulmonary Edema

Noncardiogenic, high-pressure pulmonary edema in a previously healthy individual 2–4 days after rapid ascent above 2,500 m is the hallmark of high altitude pulmonary edema (HAPE). Current theories regarding the pathogenesis of HAPE involve nonhomogenous, exaggerated hypoxic pulmonary vasoconstriction (HPV) and possible epithelial dysfunction. Due to the nonhomogenous nature of HPV seen in HAPE, certain areas of the lung undergo excessive vasoconstriction in response to hypoxia, shifting blood flow to other, less vasoconstricted areas of the lung. This leads to local overperfusion and high-pressure pulmonary edema.

Treatment is relatively conservative, with oxygen and descent being the most supported treatment for the pediatric population. Non-pharmacologic treatments in adults include portable CPAP devices as well as the Gamow bag, though pediatric experience with these treatments is limited. Medical treatments include calcium channel blockers, phosphodiesterase inhibitors, and inhaled β-adrenergic agonist, though literature supporting the use of these therapies for the pediatric population is scarce. Prevention includes gradual ascent, avoidance of strenuous activity, and adequate hydration.

Negative-Pressure Pulmonary Edema

Also known as post-obstructive pulmonary edema, negative-pressure pulmonary edema may occur during an episode of airway obstruction.

Acute airway obstruction with severe respiratory effort leads to dramatically increased negative-intrathoracic pressure during inhalation with resulting pulmonary edema. Increased negative-intrathoracic pressure is also associated with increased venous return, increased

pulmonary blood volume, and increased intravascular hydrostatic pressure which promotes edema formation.

Because symptoms are usually limited to 12–24 h, treatment is supportive. Supplemental oxygen and positive pressure ventilation should be utilized as needed.

Neurogenic Pulmonary Edema

Pulmonary edema has been associated with various types of neurological disease, including head trauma, subarachnoid hemorrhage, meningitis, status epilepticus, and cervical spine injuries.

One theory suggests that a sudden increase in α-adrenergic activity due to the neurological injury leads to systemic vasoconstriction and increased afterload on the left ventricle. Decreased emptying of the left ventricle increases left atrial pressure which is transmitted to the pulmonary capillaries and results in high-pressure pulmonary edema. Rapid increases of pulmonary vascular pressure may also cause fracturing of the vessels leading to capillary leak. Another theory proposes that inflammatory mediators released from damaged neural tissue gain access to the systemic circulation through the disrupted blood-brain barrier. These mediators increase pulmonary capillary endothelial permeability and pulmonary edema results.

The onset of neurogenic pulmonary edema is usually within hours of the initial neurological insult, but can take place days after neurological damage occurs. Edema usually resolves within 72 h, and treatment is supportive.

Re-expansion Pulmonary Edema

Sudden resolution of pneumothorax or rapid evacuation of pleural effusion may also result in pulmonary edema. This can be seen in younger patients or patients with prolonged deflation of the lung, usually of 3 or more days. And while the majority of cases occur in the collapsed lung, re-expansion pulmonary edema can occur in the contralateral lung.

According to one theory, during prolonged deflation of the lung, the capillary endothelium and basement membrane become thickened, hardening the microvasculature and decreasing its flexibility. With sudden re-expansion of the lung, the microvasculature is unable to tolerate sudden expansion of the lung and fractures, leading to leakage of fluid across the membrane. Some research suggests that oxygen free radicals, inflammatory mediators, and migrating neutrophils cause direct alveolar epithelial damage. Surfactant dysfunction may also play a role.

Treatment is again supportive. Prevention of re-expansion pulmonary edema includes limitation of the amount of fluid drained from a pleural effusion and the avoidance of excessive negative intrapleural pressures.

Transfusion-Related Acute Lung Injury

Acute lung injury within 6 h of blood product transfusion without evidence of volume overload or cardiac etiology is the hallmark of transfusion-related acute lung injury (TRALI). Fresh frozen plasma is the most common blood product associated with TRALI, though any type of blood product can be implicated.

It is possible that the interaction of donor antibodies with recipient granulocytes causes the release of various oxidases and inflammatory mediators, leading to an increase in capillary permeability. Other theories include possible proinflammatory mediators that accumulate during blood product storage prior to transfusion which are then released into the recipient. Similarly, the "two-hit" theory states that an initial insult (e.g., surgery, infection, etc.) sensitizes the endothelium, which is further activated by mediators found within the transfused product leading to endothelial damage.

Treatment is supportive with oxygen or positive pressure ventilation. Any remaining blood product should be returned to the blood bank for additional analysis.

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230 Pulmonary Embolism

Julie Ryu

Pulmonary embolisms in children are rare but the incidence increases with age. In 1998, Silverstein et al. published a 25-year-retrospective review that found the incidence of pulmonary embolism in the USA to be 69 per 100,000 individuals. However, they found only four events among patients younger than 15 years during the entire 25-year study period or under 0.3 per 100,000 individuals. While other investigators have also reported an incidence rate under 0.1 per 10,000 pediatric patients annually, these figures are likely underestimated due to the difficulty in diagnosing pulmonary embolism in children. Buck et al. found that even in patients with significant pulmonary embolism only 50% had symptoms associated with pulmonary embolism and only in 14% was the diagnosis even considered.

Pathophysiology

Pulmonary embolism is defined as an obstruction in the pulmonary circulation. The impact of a pulmonary embolus is dependent on the extent of compromise to the pulmonary circulation. In adults, despite changes on ventilation/perfusion (VQ) scans, symptoms of a pulmonary embolus do not become apparent until about 50% of the pulmonary circulation is compromised. In children who develop a pulmonary embolus, the extent of compromise needed to show respiratory distress may be much less due to a child's lower respiratory reserves and likelihood of underlying conditions. While obstruction of the pulmonary circulation is the hallmark of a pulmonary embolism, the characteristics of the embolus itself may vary with different risk factors. Healthy children very rarely develop pulmonary embolisms but certain conditions may predispose a child to develop them. The type of embolus formed will be dependent on the underlying condition or risk factors. The most common type of embolism is a thrombus (blood clot), but other types of emboli include infectious (bacterial or fungi), fat, and air. While it very rare for fat emboli to occur in the healthy child, fat emboli can occur with traumas or orthopedic procedures involving the release of bone marrow from long bones. Air emboli can occur with traumas, insertion of an intravenous line, or during certain surgeries. Small venous air emboli are rarely of significant consequence since most are trapped and resorbed in the lung. Gas emboli associated with decompression sickness from diving, due to nitrogen release from the blood stream from a sudden shift in pressure, can be associated with multiple infarcts to the brain and other vital organs.

Coagulopathies, vasculitides, central venous catheters, cardiac disease, or any endothelial injury are risk factors for pulmonary embolism (see *Table 230.1*). Thus the incidences of pulmonary embolisms will likely increase in premature infants or any population that requires long-term indwelling catheters. Thrombotic emboli can lead to ventilation/perfusion mismatch and ultimately hypoxemia. When the source of thrombi is an infectious growth or clot on an indwelling catheter or prosthetic valve, thrombi can be numerous and obstruct vessels in multiple organs making the diagnosis difficult to make.

Diagnosis

The signs and symptoms of pulmonary embolism in children can be subtle and be confounded by preexisting medical conditions. Some of the more common symptoms are listed in *Table 230.2*. However, signs and symptoms alone cannot confirm the diagnosis of pulmonary embolism. In most cases, symptoms along with the presence of risk factors are needed to increase the likelihood of pulmonary embolism. The leading risk factor for a pulmonary embolism is having a preexisting condition followed by having a central venous catheter. In patients with medical conditions that are associated with coagulopathies, the risk of pulmonary embolism greatly increases. Disorders such as congenital heart disease, sickle cell anemia, collagen vascular disease, presence of lupus anticoagulants, and malignancy are some examples of conditions that increase the probability of developing a pulmonary embolism.

Studies including chest radiograph, arterial blood gas, and echocardiogram are helpful but these studies cannot definitively rule in or rule out pulmonary embolisms. Ventilation/perfusion (V/Q) scans were the most commonly utilized test in the past to assess the probability of a pulmonary embolus; low $\leq$ 10%, intermediate 25%, and

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Table 230.1
Risk factors associated with pulmonary embolism

Indwelling central line
Bone marrow transplant
Infection
Systemic lupus erthematosis
Sickle cell disease
Massive obesity
Cardiac disease
Ventricular-atrial shunts
Intravenous drug use
Oral contraception use
Surgery or trauma involving the long bones or pelvis
Intravenous drug use
Coagulopathies: deficiencies of protein S, C, antithrombin III, or abnormal factor V; presence of antiphospholipid antibody

Table 230.2
Signs and symptoms of pulmonary embolism

Chest pain
Dyspnea
Cough
Hemoptysis
Syncope
Cyanosis
Hypoxia
Fever
Tachypnea
Tachycardia
Accentuated S_2
Fourth heart sound
Rales
Signs of deep vein thrombosis
Abnormal chest radiograph

high $\geq$ 60% probability. While this imaging study is helpful in eliminating the diagnosis if the study is normal, the test is difficult to interpret when abnormal. A V/Q scan in some patients may be inherently difficult to interpret. For example, in children with congenital heart disease, blood flow may not be equally distributed throughout both lung fields at baseline thus making any assessment for a pulmonary embolism difficult to make. Pulmonary angiography is the gold standard in diagnosing a pulmonary embolus with direct visualization of any vascular filling defects. While this test may most accurately demonstrate vascular compromise, it is not available in every institution and can be both difficult to perform and interpret.

Helical (spiral) CT is now the most accessible test and is replacing pulmonary angiography as the method of choice for diagnosing a pulmonary embolism. Spiral CT with contrast can visualize the lung as well as pulmonary vasculature thereby allowing for the detection of any filling defect. In addition, due to the excellent imaging capacity of lung parenchyma, this test can help identify any underlying lung disease. However, spiral CT does have its disadvantages. A spiral CT exposes the child to both radiation and iodinated contrast. New advances in real-time MR angiography may provide alternatives in diagnosing pulmonary embolisms without radiation but currently are not readily available at all institutions.

Treatment

The treatment of pulmonary embolism due to thrombi is anticoagulation and respiratory support as needed. Anticoagulation treatment decreases the risk of further embolic events by preventing the existing thrombus from growing and causing further damage. Once a patient is hemodynamically stable, heparin is administered as a loading dose of 75–100 units/kg iv followed by an infusion rate of 28 U/kg/h iv (<1 year) or 20 units/kg/h (over 1 year of age) to maintain a PTT of 60–85 s. Afterward, oral or subcutaneous anticoagulants are given for 3 months or more depending on the patient's underlying medical condition. Low molecular weight heparin, warfarin, and vitamin k antagonists are just some long-term medications for anticoagulation. With all anticoagulants, the complications include bleeding; therefore, close monitoring of PT/PTT is required. In non-thrombotic emboli, the treatment is supportive. Sickle cell anemia related pulmonary emboli in acute chest syndrome, transfusion and supplemental oxygen or respiratory support are often required. The treatment for septic emboli is to eliminate the infection and potentially remove the infected device or prosthesis. In severe embolic events, thrombolytics or surgical embolectomy may be indicated.

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231 Congenital Anomalies of the Respiratory Tract

Anthony E. Magit

Congenital anomalies of the respiratory tract present difficult and often urgent clinical situations. The increasing use of fetal imaging provides the opportunity to anticipate airway problems prior to delivery and implement complex and frequently lifesaving procedures involving several medical and surgical specialties. This chapter will address specific anomalies with respect to anatomic site.

Nasal Anomalies

Pyriform aperture stenosis presents as unilateral or bilateral anterior nasal obstruction. The obstruction is firm and exists immediately posterior to the nares. The anatomic abnormality causing pyriform aperture stenosis is bony overgrowth of the nasal lateral process of the maxilla. Associated findings with pyriform aperture stenosis include a central incisor and may be considered a form of holoprosencephaly.

Significant respiratory distress results from marked stenosis and establishing an airway may require placement of an oral airway or endotracheal intubation. The definitive diagnosis is made with a computerized axial tomogram (CAT) scan. With noncritical stenosis, the child may be managed expectantly by controlling nasal edema. Definitive management is surgical and involves the submucosal removal of bone with using either a transnasal or sublabial approach. Stenting of the nasal airway for a period of time may be necessary after surgery for pyriform aperture stenosis.

Nasolacrimal duct cysts result from obstruction of the nasolacrimal duct as the duct enters the lateral nasal wall below the attachment of the inferior turbinate. The cysts can be unilateral or bilateral and present as compressible masses attached to the lateral nasal wall. Catheters can be passed beyond the cysts and may confuse the physical examination, as the child will have nasal obstruction despite the catheter placement procedure not being consistent with a fixed nasal obstruction. Confirmation of the suspected diagnosis of a nasolacrimal cyst is achieved with a CAT scan. Management can be via nasolacrimal duct probing by an ophthalmologist or by removal or marsupialization of the cyst by an otolaryngologist. Recurrent cysts are infrequent and stenting of the nasal airway is not necessary.

Choanal stenosis or atresia denotes a compromised nasal opening at the choana, or posterior aspect of the nasal cavity at the point of entry into the nasopharynx. Choanal stenosis may be the diagnosis when the nasal airway is compromised and the only abnormality is an apparently small choana. Choanal atresia describes complete obstruction of the posterior nasal cavity. Choanal atresia can be unilateral or bilateral. The incidence of choanal atresia is between 1/5,000 and 1/9,000 live births. Pure bony atresia accounts for 30% of choanal atresia cases and mixed bony/membranous atresia in the other 70% of patients with choanal atresia.

The preferred imaging study of suspected choanal atresia is a non-contrast CAT scan. An axial view will demonstrate the atresia plate. Preparation for the CAT scan includes instillation of an intranasal decongestant and gentle suctioning of the nasal cavities to remove nasal secretions.

CHARGE association must be considered in patients with choanal atresia as approximately 30% of patients with choanal atresia have CHARGE association.

Bilateral choanal atresia creates an airway emergency in the newborn as newborn infants are considered obligate nasal breathers. Passage of nasal catheters into the nasopharynx will not be successful with choanal atresia. Atresia plates may consist of bone or mucosa. Atresia plates consisting primarily of mucosa, tend to have some abnormalities of bone, either in the form of widening of the posterior nasal septum, the vomer, or with medialization of the lateral aspect of the choana. In premature infants or those with other craniofacial anomalies, placement of a tracheostomy to establish an airway may be indicated prior to surgical repair of the choanal atresia. Surgical repair of choanal atresia can be performed via a transnasal or transpalatal approach as determined by the specific anatomy of the child and the preference of the surgeon. Nasal stents are typically left in place for several weeks following the repair.

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Unilateral choanal atresia resulting in unilateral nasal obstruction is compatible with an adequate airway in a newborn and may not pose an urgent airway situation. Unilateral choanal atresia may not be identified in a newborn infant and only discovered as part of an evaluation for chronic unilateral rhinorrhea. Repair of unilateral choanal atresia can be approached similarly to the management of bilateral choanal atresia.

Astomia and Microstomia

Astomia and microstomia can present in isolation or concurrently with other craniofacial abnormalities. A newborn with other airway abnormalities resulting in respiratory distress makes microstomia more significant when needing to establish an airway. The degree of microstomia may make orotracheal intubation impossible and require either nasotracheal intubation or placement of a tracheostomy. Feeding may be adversely affected my microstomia and alternative approaches for nutrition may be necessary.

Several syndromes are associated with microstomia, including holoprosencephaly, oro-palatal dysplasia, hemifacial microsomia, and Freeman–Sheldon syndrome.

Tongue

The tongue can present as a congenital airway anomaly due to intrinsic hypertrophy or because of the presence of a congenital lesion. Lingual hypertrophy or macroglossia can be associated with an underlying syndrome. Beckwith–Wiedemann syndrome includes macroglossia that is usually symmetric and presents as an enlarged tongue typically extruding from the mouth. Despite macroglossia, patients with Beckwith–Wiedemann may have minimal or nonexistent airway or feeding difficulties. Surgical management of the patient with Beckwith–Wiedemann may be delayed for several years if the patient does not have airway or feeding difficulties. Airway problems become more likely when the base of tongue, rather than the anterior aspect of the tongue, is hypertrophic.

Lesions involving the tongue causing lingual enlargement include vascular and lymphatic malformations. Lymphatic malformations involving the tongue may be detected by fetal ultrasound (*Fig. 231.1*). Lymphatic malformations consist of cystic spaces that are prone to rapid fluctuations in size. Lymphatic malformations involving the tongue are associated with airway obstruction, feeding problems, and bleeding from the mucosal surfaces. The management of lymphatic malformations involving the tongue is extremely challenging and a tracheotomy may be required to secure the airway. Management of the lingual lymphatic malformation may require multiple surgical modalities, including partial glossectomy.

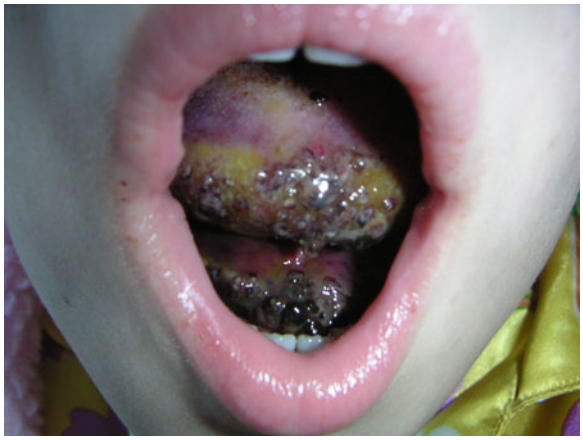

Figure 231.1
Lymphatic malformation involving the tongue and floor of mouth

Macroglossia is found with many other conditions. These include hemihyperplasia, cretinism, Down syndrome, mucopolysaccharidoses, neurofibromatosis, and multiple endocrine neoplasia. Macroglossia associated with these conditions may become more significant as the child grows and with progression of the specific disease process. The airway implications of macroglossia require frequent monitoring, often including polysomnography to assess the degree of airway obstruction.

Lingual thyroid can present as a posterior tongue mass. Lingual thyroid results from failure of complete descent of the thyroid from its fetal position at the foramen cecum of the tongue to the normal location anterior to the trachea. Lingual thyroid is present in 1/200,000 of the general population and 1/6,000 of patients with thyroid disease. Patients with a lingual thyroid can be euthyroid, hypothyroid, or hyperthyroid.

Oral Cavity

Anterior floor of mouth masses can present at birth with airway or feeding difficulties. Midline masses are likely to be epidermoid or dermoid cysts. Masses found in the anterior floor of mouth presenting lateral to the midline are most likely to be mucoceles or ranulas. These cystic lesions are pseudocysts and result from salivary mucin extravasating into surrounding tissue. Ranulas are the

result of leakage from the sublingual glands. Ranulas that extend beyond the mylohyoid muscle and into the neck are referred to as plunging ranulas. The management of ranulas consists of surgical removal of the sublingual gland with aspiration of the pseudocyst. Alternative therapies include injection with sclerosing agents.

Mandible

Median mandibular clefts are rare conditions with less than 70 reported cases.

Anomalies of the mandible may be associated with other craniofacial characteristics or present as an isolated problem. Airway obstruction results from inadequate anterior projection of the mandible due to micrognathia, a small mandible, or from retrognathia, a posteriorly positioned mandible. The result of inadequate anterior projection of the mandible is posterior positioning of the tongue. Micrognathia is one characteristic of patients with Pierre Robin sequence, Treacher Collins syndrome, Nager syndrome, and hemifacial microsomia.

Pierre Robin sequence is an example of micrognathia often resulting in airway problems. The consequence of micrognathia in Pierre Robin sequence is posterior placement of the tongue during gestation resulting in a "u" shape cleft of the palate and airway obstruction and feeding problems after birth. The airway may be managed with positioning of the child in a prone position to minimize the posterior tongue displacement or by placing an orogastric tube to assist in keeping the base of tongue forward. Mandibular growth may eventually lead to a normal mandible. When conservative measures do not provide an acceptable airway, placement of a tracheostomy or mandibular distraction may be required in the newborn period. Approximately 20% of infants with Pierre Robin sequence have significant airway problems, and one report cites a tracheotomy rate of 12% due to airway obstruction.

A technique used to improve mandibular projection with the intent of avoiding a tracheostomy is distraction osteogenesis of the mandible. This approach may have limited value in infants with craniofacial syndromes due to the presence of lower airway problems or temporomandibular joint anomalies.

Larynx

Congenital laryngeal anomalies can present with airway distress as well as feeding difficulties. Laryngeal abnormalities are present in 1/2,000 to 1/10,000 live births. The most common congenital laryngeal anomalies are laryngomalacia, vocal cord paralysis, subglottic stenosis, and laryngeal webs.

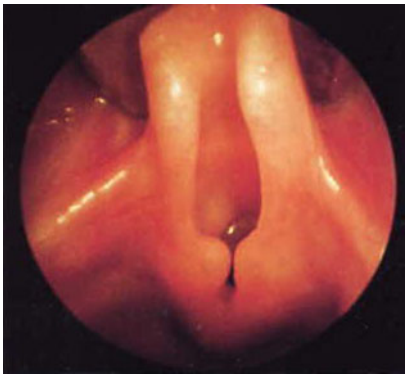

Figure 231.2
Endoscopic view of laryngomalacia with characteristic omega-shaped epiglottis

Laryngomalacia is used to describe the collapse of supraglottic structures upon inspiration. The clinical presentation of laryngomalacia is inspiratory stridor with a "staccato" characteristic (*Fig. 231.2*). Stridor is typically exacerbated with agitation, feeding, and being in a supine position. Placing the infant in a prone position or administering "jaw thrust" may mitigate stridor. In the majority of infants with laryngomalacia, the stridor will become transiently worse over several months with gradual resolution. Laryngomalacia can have various findings on laryngoscopy, including anterior prolapse of the arytenoids on inspiration, shortened aryepiglottic folds pulling the epiglottis posteriorly, as well an omega-shaped epiglottis. Approximately 15% of infants with laryngomalacia have a second airway abnormality, specifically subglottic stenosis, tracheal stenosis, or tracheomalacia.

The diagnosis of laryngomalacia is made with awake flexible laryngoscopy or by laryngoscopy under anesthesia. The decision to proceed with bronchoscopy to evaluate the entire airway is based upon clinical concerns regarding significant airway compromise. Signs of airway problems other than uncomplicated laryngomalacia are cyanosis, poor weight gain, difficulty in feeding, and acute respiratory distress. Uncomplicated laryngomalacia rarely requires surgery. When indicated, surgical procedures to treat laryngomalacia involve cutting the aryepiglottic (AE) folds with or without removing redundant mucosa from the epiglottis or arytenoids. Although aryepiglottoplasty is a relatively simple procedure, patients with hypotonia or underlying neurologic conditions can develop dysphagia

postoperatively and a swallow study may be indicated prior to surgical intervention.

Vocal cord paralysis is the second most common congenital laryngeal anomaly in some series. Vocal cord paralysis is unilateral in 30–62% of cases and bilateral in 48–62% of cases. Congenital, unilateral vocal cord paralysis is usually idiopathic. Newborns with unilateral vocal cord paralysis present with a hoarse or breathy cry. The left vocal cord is more often involved, presumably due to the longer course of the left recurrent laryngeal nerve.

Awake transnasal or transoral flexible laryngoscopy is sufficient to make the diagnosis in most cases. When copious secretions or obstructing supraglottic structures compromise visualization of the glottis, laryngoscopy with general anesthesia may be necessary. A swallow study should be considered after making the diagnosis of vocal cord paralysis to assess for laryngeal penetration or frank aspiration. Most infants with unilateral vocal cord paralysis maintain an adequate airway without surgical intervention. The contralateral, normal vocal cord may compensate adequately and spontaneous movement of the vocal may occur over months or several years.

Bilateral vocal cord paralysis presents with biphasic stridor. Respiratory problems associated with bilateral vocal cord paralysis included tachypnea, oxygen desaturation, and biphasic stridor. The cry tends to be relatively normal as the vocal cords tend to be in a paramedian position with functional opposition of the vocal cords. A swallow study to assess laryngeal penetration or aspiration with feeding should be considered. Bilateral vocal cord paralysis is an indication for imaging the central nervous system. An Arnold–Chiari type II with a myelomeningocele is the most common neurologic finding in children with bilateral vocal cord paralysis.

Interventions required to maintain adequate respiration range from supplemental oxygen to placement of a tracheostomy. Infants managed without a tracheostomy require close observation as the airway may deteriorate with time. Spontaneous vocal cord motion may be detected after months or years, with reported cases of vocal cord motion after 11 years. Reconstructive procedures exist for improving the airway in older children.

Laryngeal webs describe the condition of blunting of the anterior glottis (*Fig. 231.3*). Laryngeal webs present with an impaired cry as a result of abnormal vocal cord vibration. Laryngeal webs may be thin and limited to the level of the glottis, or thick and extend to the anterior subglottis. Webs that are thin can be managed with surgical lysing of the web; although, some degree of blunting may occur as a result of healing. Webs that extend to the subglottis are associated with subglottic stenosis and stridor with respiratory embarrassment more common than with isolated webs. Laryngeal webs with subglottic extension are more likely to be associated with a syndrome and a geneticist should be consulted to assist in establishing the diagnosis of an underlying genetic condition. Webs with subglottic involvement are more difficult to manage and may require extensive laryngeal surgery with the expectation of a less than normal voice.

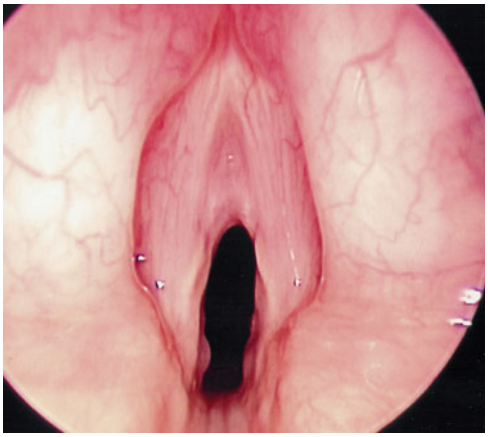

Figure 231.3
Anterior laryngeal web in a patient with DiGeorge syndrome

Laryngeal clefts denote a defect in the posterior larynx between the arytenoids with more severe clefts extending through the cricoid cartilage and into the trachea. Sixty percent of infants with laryngeal clefts have additional airway abnormalities, including tracheoesophageal fistulas and tracheomalacia. Newborns with laryngeal clefts may present with dysphagia or coughing while feeding as a result of liquids being aspirated because of inadequate airway protection. The radiographic finding of a feeding tube displaced anterior toward the trachea suggests the presence of a laryngeal cleft.

A swallow study will establish the diagnosis of aspiration. The initial assessment may consist of awake, flexible laryngoscopy to visualize the larynx; however, direct laryngoscopy under anesthesia is necessary for an adequate examination. The classification scheme for laryngeal clefts is based upon the extent that the cleft extends into the trachea. The Benjamin–Inglis classification system describes type I to IV clefts. This classification system reflects the extent of the cleft, I being above the level of the cricoid IV extending into the trachea.

The initial management of a newborn with a laryngeal cleft may require placement of a gastrostomy tube with or without a tracheostomy. Definitive management involves surgical repair of the cleft. Type I clefts may be managed medically with gastroesophageal reflux treatment and close observation. Type I clefts may be treated endoscopically without the need for a tracheostomy. Clefts involving the cricoid cartilage can be managed in some cases with anti-reflux medication and a feeding tube. Surgical repair of larger clefts are more likely to be managed with an open surgical procedure.

Newborns with congenital subglottic stenosis have stridor of varying degrees related to the extent of the stenosis. The size of the newborn subglottis supports the role that a small degree of edema can impact the airway. One millimeter of edema will reduce the cross-sectional area of the subglottis to 32% of a normal airway.

Biphasic stridor exists due to impaired air movement on inspiration and expiration. The cry is typically normal, as the glottis is not involved. Subglottic stenosis is diagnosed with direct laryngoscopy as awake, flexible laryngoscopy does not provide for sufficient visualization of the subglottis.

Medical management for a noncritical airway includes close monitoring, supplemental oxygen, and empiric management of gastroesophageal reflux if indicated. Surgical interventions for critical subglottic stenosis include tracheostomy or laryngotracheal reconstruction. The type of surgical intervention chosen to manage a critical subglottic stenosis is based upon multiple clinical factors, including the weight of the child, the degree of stenosis, and the presence of pulmonary disease. Congenital subglottic stenosis can resolve spontaneously as the child grows. One approach to managing critical subglottic stenosis is placement of a tracheostomy with close monitoring with the anticipation for eventual removal of the tracheostomy tube after growth of the subglottis. The trend for the past several decades has been early airway reconstruction. Newborns may be managed with laryngotracheal reconstruction rather than a tracheostomy based upon their weight and pulmonary status. Newborns with concurrent medical conditions may require a tracheotomy for a period of time to allow for the management of concurrent medical conditions. The most common medical conditions requiring management are gastroesophageal reflux and primary pulmonary disease.

Subglottic stenosis is more common in specific populations of patients, including patients with Down syndrome. The degree of subglottic stenosis is described either by the percent reduction in the area of the subglottis or by the size of endotracheal tube that can be passed through the subglottis.

Tracheomalacia

Tracheomalacia is a functional disorder with collapse of the trachea with or without involvement of the bronchi. Tracheomalacia tends to be overdiagnosed when the actual airway disorder is more proximal. The cough associated with tracheomalacia is characteristically "vibratory" or "brassy." Patients may have evidence of bacterial bronchitis and pneumonia with radiographic findings including air trapping or radiographic densities.

The disorder may be due to an intrinsic problem with tracheal cartilage or secondary to external compression from aberrant vessels. Some degree of tracheomalacia exists in patients with tracheoesophageal fistulas (TEF) before and after repair. Patients with congenital heart disease and stridor represent of group of patients at risk for tracheomalacia due to vascular anomalies.

The diagnosis of tracheomalacia is made with airway endoscopy or dynamic radiographic imaging. The endoscopist must have experience in recognizing tracheomalacia and not inadvertently stent open the airway with the bronchoscope and therefore lessen the degree of tracheal collapse. Vascular anomalies associated with tracheomalacia are assessed with an esophagram when a vascular ring is suspected or with a contrast CAT scan to provide information regarding vessels anterior and posterior to the trachea. The CAT scan should be done on a spontaneously breathing patient without intubating the trachea as this can compromise the radiographic appearance of the trachea.

Management of tracheomalacia is guided by the severity of the airway obstruction. Mild forms for tracheomalacia may only become symptomatic when the child has an acute illness and medical management can be episodic. Medical management may include supplemental oxygen, bronchodilators, steroids, continuous positive airway pressure (CPAP), bilevel positive pressure (BiPap), or treatment for an acute respiratory illness. Tracheomalacia with sustained symptoms may require chronic CPAP or BiPap during sleep.

Severe forms of tracheomalacia refractory to medical management require more aggressive surgical interventions. The types of surgical interventions include aortopexy to suspend the trachea, tracheotomy to reduce airway resistance, and facilitate mechanical airway support, management of aberrant vessels, and placement of

airway stents. The use of airway stents is controversial and associated with difficult management issues. The majority of cases of tracheomalacia will improve with time; however, the management of the airway can be extremely challenging and require flexibility in changing the treatment strategy when interventions are not successful.

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232 Acute Bronchiolitis

Erin R. Stucky

Definition/Classification

There is no single worldwide accepted definition of bronchiolitis. In general, bronchiolitis is an acute, seasonal respiratory illness most classically associated with crackles, wheezing, respiratory distress, and varying degrees of hypoxia. In the United States, the American Academy of Pediatrics (AAP) definition is typically used, which focuses on presence of wheeze in infants 1 month to 2 years of age. A diagnosis of bronchiolitis should be limited to infants with a first episode of wheezing. Although current accepted definitions allow this diagnosis to be given to infants under age 2, many argue only less than 1-year-olds should be considered. In the United Kingdom, Australia, and New Zealand, the Scottish Intercollegiate Guideline Network (SIGN) recommendations are followed, which focus on presence of crackles in infants under age 1 year. Wheezing infants in these countries are not given the diagnosis of bronchiolitis making true global population comparisons difficult.

Etiology

Viruses, in particular Respiratory Syncytial Virus (RSV), are the predominant cause of bronchiolitis. Viral frequencies vary by age, with RSV most common in less than 1-year-olds and rhinovirus more commonly detected in 1–2-year-olds. Parainfluenza, bocavirus, influenza, adenovirus, and human metapneumovirus are other common encountered pathogens. Almost one quarter of bronchiolitis episodes involve more than one pathogen. Atypical bacteria have been reported, but true incidence is unknown as testing for these pathogens is not typically performed. Up to 40% of tracheal cultures obtained on infants requiring intensive care demonstrate a bacterial pathogen, most often Haemophilus influenza, *Streptococcus pneumoniae*, or *Staphylococcus aureus*.

Epidemiology

Bronchiolitis is the most common discharge diagnosis for infants in the United States, accounting for over 400,000 hospitalizations annually. Despite differences in definition of bronchiolitis between the AAP and the SIGN, some incidence rate comparisons can be made. Rates and causative agents are similar in the United States, United Kingdom, Greece, Portugal, Saudi Arabia, and other parts of the world. Up to 15% of infants will present for care for bronchiolitis in the first year of life, with 1–2% requiring hospitalization. With immunoprophylaxis, admission rates in the United States for preterm infants have decreased by over 75%, and for those with chronic lung disease and congenital heart disease by approximately 40%.

Pathogenesis

The genetics of underlying chronic pulmonary diseases that may first present due to provocation by bronchiolitis are covered in other chapters (Lung Injury in the Premature Infant and BPD; Asthma; Chap. 237, "Cystic Fibrosis"). Important discoveries specific to bronchiolitis suggest a role for both pathogen-specific invasiveness and host immunomodulation. Certain adenovirus and even rhinovirus serotypes have been associated with more significant morbidity in different countries. How this information can be used to adjust treatment is currently undetermined. The central role of the immune response is becoming clearer as susceptibility genes for innate and adaptive immunity and airway remodeling have been reported. Specific single nucleotide polymorphisms (SNPs) have been associated with both increased susceptibility and severity to RSV, with some notably more apparent in preterm infants. Vitamin D metabolites function as immunomodulators, and therefore deficiency of this vitamin is under consideration as a risk factor for poorer clinical outcome. These insights may play a role in future prevention and treatment strategies.

Pathology

Despite being caused by varied pathogens alone or in combination, the impact on the airways is similar.

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Mucus production, bronchospasm, acute inflammation, epithelial necrosis, and mucosal edema are found from the nasal passages to the bronchioles. More severe inflammation and destruction is associated with invasive viral pathogens, co-viral infections, or bacterial superinfections. The cytokine-driven influx of neutrophils combined with the inhibition of neutrophil apoptosis result in high levels of neutrophil elastase and myeloperoxidase enzymes, causing mucus secretion and airway edema. Animal models suggest certain viruses, such as human metapneumovirus and RSV may persist in nerves, available to be triggered in future exacerbations. Though not yet proven in humans, the potential for latent viral reactivation and its relationship to development of chronic lung disease is under consideration.

Clinical Manifestations

Most infants begin this illness with symptoms typical of an upper respiratory infection. Over the subsequent 1–3 days, symptoms evolve to include those of the lower respiratory tract. Common clinical features include wheezing, rales, rhonchi, cough, coryza, tachypnea, cyanosis, fever, and evidence of respiratory distress such as retractions, nasal flaring, grunting, and head bobbing. Young infants are obligate nose-breathers and can demonstrate significant distress from nasal swelling and secretions. Poor oral intake and fussiness are typically seen. Apnea may precede respiratory symptoms, especially in preterm infants. Symptoms may resolve in a few days or persist for 1–2 weeks or even longer in those with underlying pulmonary disease. Progression to respiratory failure occurs in 3–8% of admitted patients.

Diagnosis

The most commonly cited diagnostic and therapeutic guidelines are from the AAP and SIGN. Both state that diagnosis is made clinically using the definitions and signs and symptoms noted above. Routine laboratory testing including complete blood count, chemistries, and viral studies are not recommended. However, there are instances where rapid viral testing may be of value: if antibiotic use in the neonate can be discontinued more rapidly, if coinfection is thought to be prognostic, or if cohorting is necessary in certain medical environments. In addition, community-wide testing of symptomatic infants for RSV at the beginning and end of the average 16-week season can inform local immunoprophylaxis decisions. Test sensitivity is 80–90%, affected by varied methods of specimen collection (nasal wash, scraping, and swabs), transport, and storage.

Chest radiography is often performed yet of unproven value and is not recommended in routine evaluation of patients with mild symptoms. Classic findings are nonspecific but may be supportive of a diagnosis of bronchiolitis and include atelectasis, hyperinflation, and peribronchial cuffing. Radiologist interpretation may use phrases such as "infiltrate versus atelectasis" which is associated with increased antibiotic use that has not been proven to speed recovery or change ultimate clinical outcome.

Differential Diagnosis

A diagnosis of bronchiolitis does not preclude an acute dual infection or first presentation of an underlying chronic disease. Most of the critical history and physical examination elements helpful in determining the severity of disease or eliciting alternate diagnoses have been previously noted in Table 1 of the chapter on Wheezing. Crackles, rather than wheezing, however, may be the primary disease manifestation. Presentation during the respiratory season, state of hydration, perfusion, respiratory effort, and oxygenation status are particularly important components of the global assessment. Fever may be present or absent.

Rates of dual infection for infants less than 60 days of age are low but not insignificant (blood, 1–2%; urine, 2–7%; cerebrospinal fluid, 0–2%). At this time, it is recommended that infants under 28 days of age with fever have traditional "fever without source" testing of blood, urine, and cerebrospinal fluid. For infants 28 to approximately 60 days of age, testing is more controversial, and therefore many of these infants have only blood and urine samples obtained. Tracheal aspirate gram stain and culture for bacterial pathogens should be obtained on appropriate infants. Compared to proven bacterial pneumonia, distinguishing viral pneumonia from bronchiolitis clinically or radiographically is often not possible. For most cases not requiring intensive care, differentiating between these is not relevant for treatment or prognosis.

The clinician must judiciously reassess infants and monitor response to traditional supportive therapies in order to determine if testing or specialty consultation is warranted. Overall, the population prevalence of alternate diagnoses is low but not insignificant (congenital vascular diseases, 1–3%; tracheobronchial anatomic abnormalities, 2–12%). The number of these that are symptomatic in infancy that could present with symptoms characteristic

Table 232.1
Commonly Considered Differential Diagnoses, Testing, and Consultation

Organ System	Comments	Testing/Consultation
Congenital Pulmonary Anatomic/Genetic		
Larygnotracheal cleft Tracheoesophageal fistula (TEF) Tracheal web or ring Tracheal stenosis Tracheomalacia*	• Stridor noted with higher level anomalies • Cough, feeding difficulties with TEF • Tracheomalacia symptoms worse in supine position	• Testing: Chest x-ray, high resolution airway film, direct laryngobronchscopy, barium swallow • Consults: otolaryngology, pulmonology * Tracheomalacia may be primary or secondary; associated cardiovascular anomalies should be considered
Bronchial stenosis Bronchomalacia Bronchial cyst Hemangioma	• Symptoms worse in supine position • Hemangioma symptoms with age	• Testing: Chest x-ray, bronchoscopy, chest CT • Consults: surgery, pulmonology
Diaphragmatic hernia	• Chronic respiratory symptoms	• Testing: Chest x-ray • Consults: surgery, pulmonology
Cystic fibrosis Alpha-1 antitrypsin deficiency	• Recurrent respiratory illnesses • Failure to thrive	• Testing: Chest x-ray, sweat chloride, genetic testing • Consults: pulmonology, gastroenterology and nutrition, endocrinology
Congenital Cardiovascular Anatomic		
Cardiovascular rings, slings (double aortic arch; anomalous left coronary artery; anomalous innominate artery; right aortic arch; anomalous left pulmonary artery; aberrant left subclavian artery) Congenital heart disease with aberrant pulmonary circulation or congestive heart failure (partial or total anomalous venous return)	• Symptoms worse with neck flexion • Noisy breathing since birth • Mild to severe persistent hypoxia • Signs of congestive heart failure • Severe tachypnea	• Testing: Static imaging - Chest x-ray, chest CT or MRI (with or without 3D reconstruction). Dynamic imaging - flexible bronchoscopy, video fluoroscopy (with or without contrast), esophagram, echocardiogram • Consults: cardiology, cardiothoracic surgery, otolaryngology, pulmonology
Multi-factorial		
Chronic lung disease	• Chronic daily symptoms possible • History - preterm or neonatal lung injury	• Testing: Chest x-ray, pulmonary function tests, blood gas analysis • Consults: pulmonology
GERD with aspiration (idiopathic/developmental; neurologic; anatomic/obstructive)	• Cough, feeding difficulties • If associated with hypotonia, may be part of generalized neuromuscular disorder	• Testing: None; may consider swallow study as needed to rule out oromotor dysfunction; consider GERD as manifestation of anatomic abnormalities listed above • Consults: None (idiopathic); others based on underlying condition

of bronchiolitis is unclear. The most significant differential diagnoses and possible testing or consultation are noted in *Table 232.1*. It should be stressed that these diagnoses may be made *in addition* to infectious bronchiolitis. Consultants should be pediatric subspecialists unless emergent access is needed and not available.

Treatment

Hospitalization should be considered for those at higher risk based on age (preterm infants under 35 weeks gestation or any infant less than 3 months), chronic underlying condition, or acute signs of respiratory distress or systemic

instability (lethargy, dehydration). Inpatient treatment is supportive, with enteral nutrition or IV fluids, humidified oxygen, suctioning, and positioning in a level of comfort. An example treatment flow diagram is shown in *Fig. 232.1*. Optimal minimum oxygen saturation levels have not been rigorously tested and in practice vary between 88% and 96% depending on sleep state and elevation relative to sea level. Minimum oxygen saturation levels suggested by national societies are greater than 90% (AAP) or 92% (SIGN) or at the patient's baseline level. Beta-agonist or racemic epinephrine treatments with normal or hypertonic saline are of limited to no value in most infants with no underlying disorder. However, they may be trialed particularly in the emergency department setting, using a respiratory scoring system to assess outcomes. Blood gas testing of infants with worsening respiratory scores may help assess failure of ventilation and guide interventions. Pressure support in the form of high-flow nasal cannula or noninvasive ventilation with nasal continuous positive airway pressure (NCPAP) opens collapsed airways, thus improving ventilation and oxygenation. Apneic patients may also benefit from the stimulation provided by pressure support. Apneic preterms may stabilize with use of stimulant medication as well. Helium–oxygen mixtures with and without NCPAP has been reported to improve respiratory scores and may avert intubation.

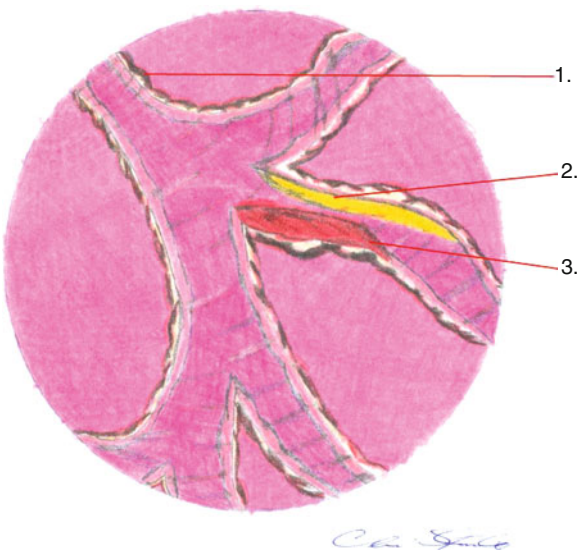

Figure 232.1
Airway involvement in bronchiolitis: (1) bronchoconstriction, (2) mucus production, (3) inflammation

Antibiotics should be reserved for treatment of highly suspected or proven extrapulmonary infections, infants under 28 days with fever at risk for concomitant bacterial infection awaiting bacterial culture results, or those with highly suspected or proven secondary bacterial pulmonary infections based on tracheal aspirate culture. Limited studies suggest the rate of bacterial pulmonary coinfection in intubated patients is as high as 50%. Antiviral therapies, including use of immunoprophylaxis at high levels as a treatment, as well as surfactant therapy have been studied in small populations and may be of benefit for more severely ill or intubated patients.

Treatment typically targets acute symptoms; however, avoidance of longer-term inflammation during lung remodeling may be important in patients with underlying chronic pulmonary disease or at risk for development of asthma. For most patients, steroid use after bronchiolitis does not avert future wheezing episodes. Steroid and leukotriene inhibitors may however be helpful in a subset of atopic patients. Steroids have also been noted to assist those with rhinovirus, although this may be due to the association of underlying risk for asthma with that virus. Use of macrolides for anti-inflammatory effect has also been suggested.

Prognosis

Episodes of bronchiolitis are typically self-limited; however, both acute morbidity and long-term outcomes vary greatly among infants. Complications may be due to the infectious agent, infant's own immune response, consequences of treatment, stress and instability of an underlying condition, or a combination of these factors. Initial oxygen saturation less than 90% and tachypnea (respiratory rate >70) have been associated with more severe disease. Prognosis is typically associated with the underlying state, with various reported odds ratios of intensive-care need highest in infants under 6 weeks (OR 2–4), preterm (OR 4–7), or having chronic pulmonary, cardiac, or immunologic disorders (OR 15–21). Death is rare (<3%) and occurs most often in patients with chronic diseases. Predicting which otherwise health term infant will develop acute respiratory failure is however difficult. For the term otherwise healthy infant with bronchiolitis, outcomes are very good with no demonstrable long-term impact on lung function and no increase in number of future respiratory illnesses. However, some infants who will be ultimately diagnosed with asthma present for the first time with bronchiolitis, particularly those with rhinovirus. Response to trial of beta-agonist

therapy, severity of bronchiolitis presentation (need for admission), atopy, and a family history of asthma or atopy may be clues to future asthma.

Prevention

Avoidance of smoke exposure, breast feeding, and hand washing are suggested methods to prevent both acquisition and spread of viral-induced bronchiolitis. Hospital staff should follow infection control recommendations for droplet precautions which include gown, mask, and glove use. Immunoprophylaxis during the respiratory season (typically November through March in the United States) of at-risk infants should follow national guidelines. Those with chronic cardiopulmonary diseases, immunodeficiency, and premature birth at less than 35 weeks gestation under 6 months postnatal age are typically targeted. The clinician is encouraged to review current guidelines for the most up-to-date information on use. Maternal immunoprophylaxis has been attempted with limited success in research settings but is an important model for disease prevention in the future.

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233 Management of the Wheezing Infant

Erin R. Stucky

Definition/Classification

Wheezing is a common respiratory complaint in childhood, with an estimated 25% of infants having at least one episode of wheezing by age 1 year. Wheezing is defined as a high-pitched somewhat musical sound caused by variable obstruction within the intrathoracic respiratory system, predominantly involving the bronchi and bronchioles. Wheezing can be monophonic – single tone from obstruction of the large caliber airways – or polyphonic with varied pitches from obstruction of airways of differing diameters. It should be distinguished from other sounds such as stertor, stridor, rales, rhonchi, and rubs, each with its own association with specific locations within the respiratory system. Wheezing is continuous throughout a phase of the respiratory cycle, and although it is most associated with expiration, it can be heard on both inspiration and expiration. Although wheezing is commonly associated with primary pulmonary disturbances, influences from outside the pulmonary tree may also cause a change in airway dynamics that result in production of this noise.

Epidemiology

Assessing prevalence of wheezing episodes leading to healthcare visits is difficult given the varied underlying causes of this clinical sign. Available prevalence information is biased due to many reasons such as coupling of "asthma" and "wheezing" search terms, the limited numbers of studies in many countries, inconsistent coding, and infrequent inclusion of the infant age group. However, the data on older children does demonstrate interesting differences and similarities between countries. All countries show graded decreases in prevalence with increasing age from toddler to teen. Reported rates vary significantly between countries from $<2\%$ in Ethiopia to 5–14% in Kenya, with other countries varying from 10% (Mexico, China, Palestine) up to 20% (Finland, Ireland, United States, Israel, United Kingdom, New Zealand, and Fiji) for a similar preteen age group.

Pathogenesis/Genetics

A comprehensive summary of the pathogenesis of wheezing is beyond the scope of this chapter. However, certain findings to date may be of value for the clinician. Low birth weight, prematurity, and respiratory distress syndrome are well known to forecast repeated wheezing within the first year of life. Each of these may be the outcome of an underlying factor that leads to wheezing as well, or may be a state that places the infant at risk for wheezing after birth due to adaptation to the ex utero environment and exposure to therapeutic interventions. Maternal and maternal–fetal factors of high levels of IL-8 in cord blood, maternal eczema, and cesarean section have been independently associated with development of wheezing by age 1. Maternal asthma is a more significant predictor of infant wheeze than the paternal counterpart. Combined, these suggest that both the imbalanced heritability of wheezing potential and the exposure to inflammatory mediators in the immediate newborn period have significant influence on ultimate development of wheezing in the infant.

Pathology

Aberrant airflow through critically narrowed airways is the predominant cause of audible or auscultated wheezing. Changes to the bronchi and bronchioles may be due to a fixed obstruction causing airway compression or due to acute changes such as mucus plugging, airway or interstitial edema, or constriction of bronchial smooth muscle. Each results in variable airflow speed through affected airways. This variability in aerodynamics causes sound to be transmitted, in contrast to normal respirations, which are silent due to simple linear flow with consistent velocity. Infants are at particular risk for airflow obstruction due to simple physics. Airway resistance is inversely related to the radius of the lumen to the fourth power, so even a small decrease in airway diameter in an infant can cause a dramatic increase in resistance. Compliant bronchial cartilage also allows for collapse. In this setting, the next inspiration is begun before full expiration is achieved causing air trapping.

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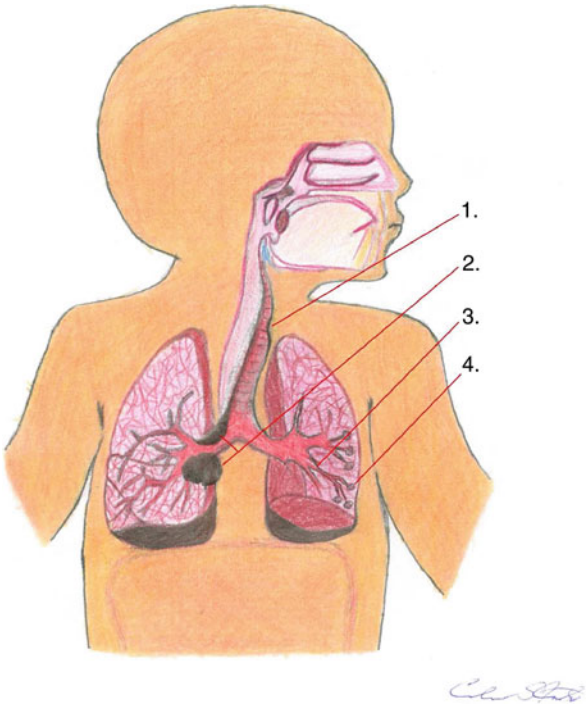

Figure 233.1
Airway involvement in wheezing. *1* intrathoracic tracheal compression, *2* bronchiolar compression, *3* alveolar hyperinflation, *4* intraluminal and external compression

Wheezing may be due to fixed obstruction resulting in turbulence at one or more sites, or may be sporadic, with patchy involvement of the airways in an inconsistent manner. Both may present with exacerbations of varying severity at different times in a given patient. Although commonly perceived as a small airway phenomenon, obstruction of the intrathoracic trachea or bronchi also can result in wheezing. Typically, large airway obstruction does not cause hypoxemia compared to small airway involvement where ventilation–perfusion mismatch results in changes in oxygen delivery to the body. In addition to causes of wheezing directly related to problems of the pulmonary tree, external compression may result in wheezing and other associated respiratory signs and symptoms that may be impossible to distinguish from the former (*Fig. 233.1*).

Clinical Manifestations

Two general patterns of wheezing are commonly noted – episodic and unremitting. Episodic is defined as discrete events lasting 2–4 weeks in duration, between which the child is well. Unremitting or persistent wheezing is characterized by triggered severe episodes between which symptoms associated with exercise, cold air, or emotional outburst (crying or laughing). These two general patterns are more often considered when evaluating wheezing of older infants and addressing the potential diagnosis of asthma.

Isolated wheezing should be distinguished from that associated with other respiratory noises of the upper tract, as the latter may more often involve anomalies of the entire airway. The physical examination should be repeated after a therapeutic intervention, as in cases of severe distress wheezing may not be audible until aeration improves. A thorough history and physical examination should be performed to elicit evidence of severity of respiratory distress, assess the need for urgent basic supportive treatment, and obtain supporting information for a differential diagnosis. Specific elements to consider are noted in *Table 233.1*.

Differential Diagnosis

More commonly considered potential etiologies of wheezing include primary pulmonary, extrapulmonary, and systemic sources, which are noted in *Table 233.2*. The diagnostic approach should take into account the history and physical examination elements as well as age. Although less common, distress due to congenital anatomic malformations present most often in the first few months of life and are critical to not overlook.

Acute, self-limited infectious sources of wheezing in infancy are extremely common. Bronchiolitis and pneumonias are discussed in more detail in other chapters. Infections due to tuberculosis and pertussis are more subacute to chronic in nature. Pertussis typically present with cyanotic episodes and classic repetitive cough or episodes of apnea, with subacute wheezing more often following this initial diagnostic presentation. Infections-associated mediastinal adenopathy may have parenchymal involvement; however, the asymmetry produced by focal compressing adenopathy may be a valuable physical exam finding.

Congenital anatomic/genetic causes may be apparent immediately after birth (tracheal stenosis, some tracheoesophageal fistulas) or present with growth of the infant (hemangiomas) and/or in association with influence or failure of normal physiologic drop in pulmonary vascular resistance (congenital heart diseases, vascular rings/slings). Vascular rings are often associated with "noisy

Table 233.1
Signs and symptoms to elicit from the history and physical examination

History element	Consideration
Symptom detail: progression and/or change in noise pattern, cough/choking, change with position (prone/supine), associations with feeding/febrile illnesses/environmental exposures	• Obstructing growth • Inadequate airway development such as bronchomalacia • GERD with associated aspiration • Acute infectious respiratory illnesses
Birth history: prematurity, intubation, or suctioning at delivery, ventilator assistance	• Underappreciated chronic lung disease • Airway injury • Upper airway obstruction
Family history: asthma, allergy, heritable pulmonary diseases	• Atopic diseases • Genetic disorders such as cystic fibrosis
Past medical and surgical history: past use of/response to bronchodilators, recurrent otitis media or sinusitis, tonsillectomy/ adenoidectomy, admission for ALTE, gastroesophageal reflux disease (GERD), cardiovascular disease, diaphragmatic hernia	• Nasopharyngeal obstruction masquerading as lower tract wheezing • GERD with associated aspiration • Underdeveloped pulmonary system • Aberrant pulmonary vascular flow
Review of systems: appetite, weight gain, stool pattern, emesis, rashes, smoking exposure, maternal (prenatal), and infant pollution/inhalant exposure	• Systemic genetic disorders such as cystic fibrosis • Atopic or irritant-induced symptoms from aeroallergens and pollutants
Physical examination element	**Finding**
General appearance, including facies	• General state • Airway anatomic issues
EENT	• Evidence for atopy • Nasal obstruction/pallor • Oropharyngeal anomalies
Vital signs including weight for height, respiratory rate, pattern, retractions, oxygen saturation	• Failure to thrive • Effort/severity of distress • Cyanosis
Skin	• Vascular malformations • Eczema
Chest wall, cardiopulmonary exam including lung auscultation, cardiac murmurs/rubs/gallops, perfusion, hepatomegaly	• (A)symmetry of wheezing, phase (inspiratory/ expiratory), associated sounds • Deformations of chest wall • Congestive heart failure • Evidence for cardiovascular diseases
Abdominal distention/ scaphoid, bowel sounds, masses	• Abdominal tumor • Evidence for diaphragmatic hernia
Extremities	• Clubbing
Neurologic exam	• Hypotonia/swallowing dysfunction

breathing since birth" and are frequently underlying causes of secondary tracheobronchomalacia.

GERD with aspiration of refluxate is not uncommon, and is most often idiopathic or "developmental" resulting from a combination of effects such as immaturity of lower esophageal sphincter function and the angle of the gastroesophageal junction. Aspiration of oropharyngeal secretions due to poor swallowing coordination may be seen in infants with prolonged periods of feeding disruption (complex congenital heart disease), developmental delays, or global motor control with the latter group often demonstrating aspiration from both above and below.

Although commonly considered to be primary pulmonary disorder, cystic fibrosis is a systemic genetic disorder with varied phenotypes, the most significant presenting early in infancy with recurrent pneumonias and failure to thrive. Newborn screening in many but not all states has been of great value in identifying these children and offering intensive respiratory therapies and nutrition management.

Other primary pulmonary disorders of importance are chronic lung disease and asthma. Chronic lung disease is most often the result of prematurity with most complications seen in the extreme preterm infant. However even a near-term infant may have recurrent wheezing with respiratory infections. Although asthma is not traditionally diagnosed in infancy, those meeting criteria with appropriate elimination of other diagnostic considerations are labeled and treated as asthmatic.

Diagnostic testing is guided by age, history, and physical examination findings. Basic evaluation includes a plain

Table 233.2
Commonly considered etiologies of wheezing in infancy

Primary pulmonary		
Infectious	**Congenital anatomic/genetic**	**Allergic/immunologic**
• Bronchiolitis[a,b] (viral, atypical most common) • Pneumonia[b] (viral, atypical most common) • Pertussis/parapertussis	• Larygnotracheal cleft • Tracheoesophageal fistula • Tracheal web or ring • Tracheal stenosis • Tracheomalacia • Bronchomalacia • Bronchial stenosis • Bronchogenic cyst • Hemangioma	• Asthma[b]
Multifactorial	**Trauma**	**Neoplastic[c]**
• Chronic lung disease[a,b]	• Foreign body • Inhaled irritant	• Hamartoma • Lipoma • Bronchial adenoma
Extrapulmonary		
Infectious	**Congenital anatomic/genetic**	**Neoplastic[c]**
• Compression due to reactive adenopathy (such as in tuberculosis or fungal infections)	• Hemangiomastosis • Diaphragmatic hernia • Cardiovascular rings, slings • Congenital heart disease with aberrant pulmonary circulation or congestive heart failure	Tumor compressing tracheobronchial tree: • Thymic tumors • Teratoma • Hemangioma • Pericardial cyst • Lymphoma • Hernia • Angiomas • Neurogenic tumor
Multifactorial		
• GERD with aspiration[a,b] (idiopathic)		
Systemic		
Allergic/immunologic	**Congenital anatomic/genetic**	**Neoplastic[c]**
• Anaphylaxis	• Hemangiomatosis • Cystic fibrosis • Alpha-1 Antitrypsin deficiency	• Compression due to infiltrative adenopathy, metastases
Multifactorial		
• Aspiration with/without GERD (secondary to swallowing dysfunction/hypotonia, GI obstruction, others)		

[a]Commonly diagnosed at <3 months
[b]Common diagnosed at 3 month to 2 years
[c]Rare causes

posterior–anterior and lateral chest radiograph and oxygen saturation. GERD is a clinical diagnosis, although testing to rule out alternate diagnoses may be indicated. Rapid testing for infectious agents should not preclude further evaluation if warranted by the severity or chronicity of the clinical presentation. Airway compression is assessed with upper GI series or direct laryngobronchoscopy with echocardiogram, contrast 3D chest CT, contrast MRI or angiography often used for confirmation of vascular anomalies. Flexible bronchoscopy is used to diagnose anatomic abnormalities, assess airway injury, or obtain diagnostic biopsies. Genetic testing, bedside swallow study, sweat test, rigid bronchoscopy, and other imaging studies should be performed based on diagnostic considerations.

Treatment, Prognosis, and Prevention

Treatment is targeted to the etiology. For all diagnoses, prevention of further exacerbations and lung damage is paramount. Avoidance of passive smoke exposure and environmental irritants is important for all infants who wheeze. Studies of antihistamine and steroid use to prevent future wheezing events and allow for proper airway remodeling in viral-induced wheezing offer mixed results. As a heterogeneous group, wheezing early in life may not predict future wheeze. Over half of patients with severe early wheeze are symptom-free by age 5.

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234 Acute Upper Airway Obstruction

Anthony E. Magit

Acute airway obstruction can be the result of infection, an acute inflammatory condition, trauma, or a structural abnormality. Every level of the airway is subject to conditions that can result in obstruction, from the nose to the lower airway.

Nose

The newborn infant is considered to be an obligate nasal breather, and respiratory distress at the time of delivery may be due to bilateral nasal obstruction. With the absence of detectable nasal airflow, the placement of an oral airway or laryngeal intubation will bypass the obstruction. The ability of infants to establish nasal breathing when challenged by nasal obstruction has been addressed with a research study. Newborns may exhibit spontaneous oral breathing as well as oral breathing when confronted with nasal obstruction. Oral breathing was detected in 40% of newborns after acute, bilateral nasal occlusion.

A toddler or older child experiencing nasal trauma usually has a transient episode of epistaxis with mild to moderate nasal congestion due to inflammation, secretions, or dried blood. The majority of children with nasal trauma retain some degree of nasal airflow. Acute nasal obstruction due to trauma may be the result of a septal hematoma. Severe nasal obstruction following trauma raises concerns for a septal hematoma that describes a collection of blood located between the septal cartilage and perichondrium. The patient presents with soft tissue occlusion of both nasal vestibules. The distinction between an anterior nasal septal deflection and a septal hematoma is made by failure of transillumination of the septum with a septal deflection. A hematoma prevents transillumination with a light or otoscope and prompts immediate referral for drainage of the hematoma to relieve the obstruction and lessen the likelihood of abscess formation and eventual loss of cartilage and loss of nasal support.

Oral Cavity

Obstruction of the airway at the level of the oral cavity may be due to acute enlargement of the tongue. Trauma to the tongue with hematoma formation can compromise the airway when the base of the tongue is involved. Acute management involves establishing an airway, which may require transoral or transnasal intubation. An emergent tracheostomy may be necessary if the airway cannot be intubated and the patient has signs of respiratory distress. A preexisting lesion that involves the tongue may become infected or experience acute bleeding resulting in an airway emergency. An example of such a lesion is a lymphatic malformation involving the tongue.

Acute problems involving the floor of the mouth have the potential to acutely obstruct the airway. Ludwig's angina is an acute infectious process usually associated with adults who have an aggressive infection of the anterior floor of mouth with a tendency for the tongue to secondarily obstruct the airway. In the majority of situations, the primary infection is dental. Infections involving the anterior floor of mouth in child can have similar clinical presentations with the primary infection resulting from intraoral trauma or infection of a preexisting lesion, including lymphatic malformations and congenital cysts.

Acute inflammation of the anterior floor of mouth from any etiology needs immediate attention as airway obstruction can occur rapidly. The patient should be kept in a closely monitored setting with the necessary resources for intubation or establishment of a surgical airway if the airway becomes compromised.

Tonsil and Adenoid Disease

Most patients with clinically significant tonsil and adenoid hypertrophy have chronic airway problems resulting in obstructive breathing while asleep. Critical obstruction at the level of the pharynx can result from acute increase in the mass of lymphoid tissue as found with infectious adenotonsillitis. An example of this situation is mononucleosis with fulminate lymphoid hyperplasia. Acute management may require intubation and medical management with systemic steroids and the addition of empiric antimicrobial treatment if clinically indicated.

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Peritonsillar abscess describe a collection of purulent material adjacent to the tonsil capsule. The classic triad of a peritonsillar abscess consists of trismus, peritonsillar edema, and deviation of the uvula away from the side of the abscess. Patients commonly present with a muffled or "hot potato" voice. The diagnosis is based upon the clinical examination, and imaging studies are rarely necessary.

Management consists of aspiration of the peritonsillar area. If no fluid is aspirated, then the area is incised and the opening explored with a hemostat. All aspiration attempts and incisions are kept medially to avoid injury to vessels located lateral to the tonsil. Management of a peritonsillar abscess can be done using local anesthesia in a cooperative teenager or preteen. Younger children will require general anesthesia for any aspiration or incision of the peritonsillar area.

Foreign Bodies

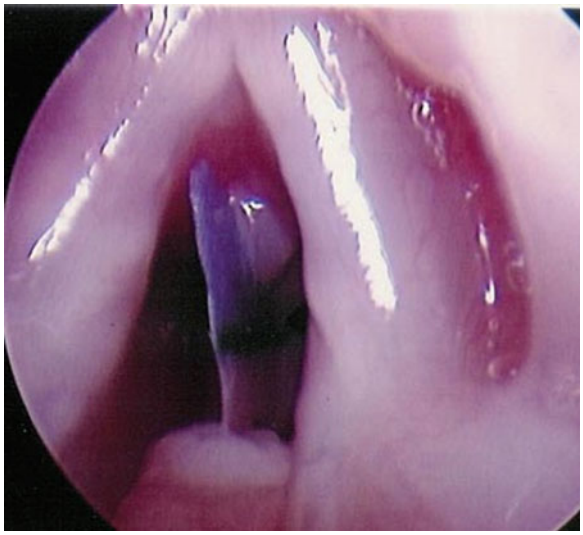
Nasal foreign bodies are unlikely to cause bilateral, complete nasal obstruction. Nasal foreign bodies are associated with unilateral rhinorrhea with decreased nasal airflow. A nasal foreign may result in granulation tissue and scarring if left for a prolonged period of time. Button batteries pose a significant risk of permanent damage to the nose, including a nasal septal perforation, after a brief period of time. Concerns about a button battery in the nose raise the question of whether a radiograph is indicated to assess a nasal foreign body if removal may be delayed.

Oral Cavity and Pharynx

Spherical objects have the potential of obstructing the airway at the level of the oropharynx. Children may present with an inability to manage oral secretions and respiratory distress. A finger sweep performed to remove an oral foreign body not effectively dislodged after striking the back or compressing the chest may result in edema of the epiglottis with exacerbation of the airway situation.

Laryngeal Foreign Bodies

Foreign bodies involving the larynx can cause dysphonia due to involvement with the vocal cords (◉ *Fig. 234.1*). Vocal quality can vary as the foreign body can move with respiration. Despite a period of normal phonation, concern for a laryngeal foreign body should not diminish and a thorough evaluation of the airway is necessary.



◘ Figure 234.1
Foreign body in the glottis with adjacent granulation tissue

Tracheobronchial Foreign Bodies

The acute onset of a cough without an infectious prodrome or subsequent to a choking episode raises the possibility of an airway foreign body. A child with the ability of placing an object in its mouth has the ability to introduce a foreign body into the aerodigestive tract. Older siblings can facilitate younger children having access to potential foreign bodies. A child with a suspected foreign body without evidence of an acutely compromised airway requires thoughtful management with the development of a diagnostic and therapeutic plan. Patients should be maintained in a monitored setting until definitive intervention.

History is the primary reason to proceed with airway endoscopy. One study reported that 45% of children with a history consistent with a foreign body and a negative chest x-ray had a positive endoscopy for a foreign body. Despite false negative chest x-rays, a chest x-ray is indicated as part of the clinical evaluation to provide information regarding the type of foreign body and the degree of pulmonary disease.

One radiographic finding consistent with airway foreign body aspiration is hyperinflation of lung distal to a foreign body. Hyperinflation occurs when air enters the distal airway on inspiration as the airway dilates around the foreign body while air becomes trapped on expiration as the airway collapses around the foreign body. The pathophysiology of air trapping and hyperinflation is an illustration of a "ball valve" effect of a partially occluding foreign body. Atelectasis and complete collapse of lung

distal to a foreign body can occur if the foreign body causes complete occlusion of the airway.

After the acute onset of a coughing or choking episode, the child may appear asymptomatic. One explanation for the absence of signs or symptoms of a foreign body could be that the child displaced the foreign body from the airway. A more concerning scenario is that the foreign body moved to allow sufficient air movement despite remaining in the airway. Despite the absence of persistent signs or symptoms of a foreign body, an endoscopic examination may be warranted if the history of aspiration is convincing.

Specific types of foreign bodies deserve special consideration. Vegetative matter can contain substances that cause significant airway inflammation. Peanuts are an example of a commonly aspirated foreign body. Peanut oil causes airway irritation within a relatively short period of time, and airway endoscopy may reveal mucosal edema and granulation tissue. Another feature of vegetative matter is the tendency to become hydrated secondary to airway secretions and assume a greater mass than when initially aspirated.

Epiglottitis

Inflammation of the larynx and subglottis can cause acute airway obstruction. The epidemiology of acute infectious laryngitis has changed since the introduction of the Haemophilus influenza type B (Hib) vaccine. Acute infection of the epiglottis associated with Haemophilus influenza type B infection has the clinical presentation of drooling, dysphagia, and airway distress. Patients with suspected epiglottis must be kept in a monitored setting and quickly placed in an environment where intubation or a surgical airway can be placed. The radiographic finding associated with epiglottitis is the "thumbprint" sign on a lateral neck x-ray as a result of edema of the epiglottis. The recommended management of a patient with epiglottis is intubation and antimicrobial therapy directed at Haemophilus influenza type B.

The widespread implementation of the Hib vaccine in the early 1990s has dramatically reduced the incidence of infectious epiglottitis. Episodes of epiglottis have declined more than 99%. The cases of H. flu epiglottitis that occur may be secondary to individuals who were either not vaccinated or did not respond to the vaccine.

Noninfectious etiologies of epiglottis include exposure to hot foods or liquids, caustic agents, foreign bodies, smoke inhalation, or angioedema. Most cases of angioedema involving the larynx occur in patients between the ages of 11 and 45 years of age with the first episode occurring in the teenage years.

Croup

Unlike patients with epiglottis, individuals with croup are more likely to have a viral prodrome. Patients with croup present with a "barking" or "seal-like" cough. The radiographic finding associated with croup is a "steeple" sign on an anterior–posterior high kilovolt radiograph of the larynx. The endoscopic appearance of croup is the double vocal cord sign reflecting marked edema of the subglottis. In a child, a relatively small degree of edema can result in clinically significant airway obstruction. One millimeter of mucosal edema in a preschool-aged child will reduce the size of the subglottis by 50%.

Croup is the most common cause of stridor and in some series accounts for 15% of pediatric emergency department visits. Intubation is required in less than 5% of patients with croup and hospital admission ranges from 1.5% to 31% of patients. Approximately 5% of individuals with croup will have more than one episode.

An important element of the medical history is a history of intubation, whether for surgical procedures or for respiratory problems. Airway endoscopy in the acute setting is not usually indicated. Airway endoscopy in the acute setting may be necessary when the patient does not respond to the usual management for croup. Indications for elective airway endoscopy include repeated episodes of croup or croup in the setting of previous intubation. Previous intubations, whether for a brief or a prolonged period of time, can result in subglottic stenosis, subglottic cysts, or other abnormalities.

Medical management of croup consists of systemic steroids and inhaled epinephrine. Patients managed as outpatients should be observed for several hours after receiving epinephrine because of the possibility of rebound edema of the subglottis. The efficacy of cool mist for humidification of the airway has not been confirmed despite its common use.

Acute inflammation of the subglottis referred to as croup is usually caused by parainfluenza with 80% of cases associated with parainfluenza types I, II, or III. Parainfluenza I is associated with 50–80% of patients hospitalized for croup.

Tracheitis

Bacterial tracheitis is usually the result of infection with *Staphylococcus aureus* or *Streptococcus pyogenes*. Bacterial tracheitis does not have specific clinical signs or symptoms to distinguish it from other acute airway infections. The diagnosis of bacterial tracheitis should be considered in

patients who present with the clinical presentation of croup without responding to routine management suggesting a nonviral etiology. Patients with bacterial tracheitis often require intubation in addition to appropriate antimicrobial treatment. The emergence of bacterial tracheitits as the leading cause of life-threatening infection airway infection may parallel the epidemiology of parainfluenza infection and resistant bacterial infections affecting the airway.

Subglottic Hemangioma

Subglottic hemangiomas are a form of vascular malformation that can present as "atypical croup" or as a "croup masquerader." Subglottic hemangiomas are not present at birth and experience growth after 1 or 2 months of life. The natural history of subglottic hemangiomas consists of a period of rapid growth followed by spontaneous resolution. Respiratory distress and eventually airway obstruction result from rapid growth of the hemangioma. Subglottic hemangiomas respond to systemic steroids with involution or cessation of growth while steroids are being administered.

Clinical characteristics that suggest a nonviral etiology of croup include croup in an infant less than 4 months of age and croup presenting in the spring or summer, when parainfluenza infection is rare. A typical history for subglottic hemangioma is a child who is treated with steroids for croup with recurrence of symptoms after completion of steroids. When the response to steroids is slow or met with recurrent symptoms, consideration must be given for a noninfectious etiology of croup and airway endoscopy should be considered. Management of subglottic hemangiomas consists of surgical and medical therapies. Left untreated, subglottic hemangiomas are likely to cause airway obstruction and respiratory distress.

Children with subglottic hemangiomas may also have cutaneous lesions or diffuse involvement of the airway. Patients with cutaneous hemangiomas in the "beard" or cervicofacial region have an approximate 60% chance of having a subglottic hemangioma.

Recurrent Respiratory Papillomatosis

The most common benign neoplasm found in the pediatric larynx is recurrent respiratory papillomatosis (RRP). Patients present with hoarseness that may be associated with respiratory distress. Infants are thought to acquire the disease from mothers infected with human papillomavirus (HPV) during labor and delivery. HPV may not become symptomatic until the child is several years old.

The possibility that a child's hoarseness is due to HPV is an important reason to examine the larynx of a child with hoarseness rather than assume that the hoarseness is due to a less concerning problem such as vocal fold nodules. Multiple strategies exist for managing RRP, including repeated laryngoscopies and debulking procedures. Additionally, adjuvant medical treatments have been utilized extensively with the intent of reducing the number of operative procedures. The epidemiology of RRP is likely to have a marked reduction in incidence with the increasing use of HPV vaccine among adolescent females.

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235 Bronchopulmonary Dysplasia (BPD)

Julie Ryu

Etiology/Epidemiology

Bronchopulmonary dysplasia (BPD) is a chronic lung disorder that can occur in premature infants who require respiratory support early in life. Since the ability to support premature infants has improved over the last few decades, the number of premature babies in the United States has steadily increased since 1990. According to the March of Dimes and the CDC population census, there were approximately 530,000 infants born under 37 weeks gestation or 12.7% of births in the United States in 2006 alone. Despite medical advances, prematurity is still the leading cause of death in the first month of life. Infants, who survive, can develop profound medical and neurocognitive problems that never fully recover. Respiratory distress is often seen in the premature infant since lung development starts in utero but continues into the first few years of life. Infants who require respiratory support such as surfactant, mechanical ventilation, and supplemental oxygen are at risk for developing chronic respiratory problems (such as BPD) beyond the acute respiratory distress events.

Pathology/Pathogenesis

Bronchopulmonary dysplasia is a pulmonary disorder, first described by Northway et al. in 1967. It is a disorder that affects premature infants who have immature lungs that require supplemental oxygen and mechanical ventilation. When BPD was originally described in 1967, this group of patients consisted of infants with severe hyaline membrane disease, prolonged mechanical ventilation with high positive pressure ventilation and high oxygen concentrations. Previously, BPD was defined as having respiratory symptoms requiring oxygen and an abnormal chest radiograph at 36 weeks corrected age (gestational age plus chronological age). On autopsy, these patients had profound lung abnormalities that were evident throughout the lung from trachea to the parenchyma.

Bronchopulmonary dysplasia is a condition that develops after a culmination of chronic injury to the lung with subsequent insufficient healing. Pathology can start at the trachea from injuries from intubation and repeated suctioning resulting in ulcerations, development of granulation tissue, and subglottic stenosis. In addition to the narrowing that might occur, the trachea can also become dilated due to high pressure ventilation. Patients can develop a "floppy" airway (tracheamalacia), or stretched out trachea (tracheomegaly), or both, due to this barotrauma. In addition, stretch-injury can occur beyond the level of the trachea. Due to the uneven distribution of pressure delivered to the lung by mechanical ventilation, compliant areas are ventilated with more volume, while other less-compliant sections are not ventilated; therefore, cystic areas can occur adjacent to atelectatic areas in the same patient. Lung compliance heterogeneity is due to several factors including prematurity, surfactant deficiency, obstruction, and lung remodeling due to repeated lung injury. Surfactant deficiency is a key reason for the heterogeneity seen. Many premature infants are born prior to adequate surfactant levels. Surfactant is secreted by alveolar type II cells which helps reduce surface tension and therefore prevents alveoli collapse on exhalation, but sufficient levels are not produced until around 35 weeks gestation. To overcome this lack of surfactant, infants were mechanically ventilated with high positive pressures to inflate the lungs. In addition to the heterogeneous ventilation, perfusion is also not uniform and does not necessarily correspond to the areas receiving the most oxygen, therefore not correcting the hypoxia but now adding barotrauma and oxidant injury. As a consequence to these stressors, lung epithelia cells become injured starting a cascade of events that may lead to remodeling of the lung. Epithelial and endothelial cell injury can impair cell permeability allowing for increased susceptibility to infections as well pulmonary edema. In response to cell death, the body responds by releasing growth factors, cytokines, and inflammatory cells to remove the injured cells and fight infection. However, since the injury is often more extensive than the body's ability to heal, cells denude off creating an exudative process that further increases an influx of inflammatory cells and further contributing to poor gas exchange by obstructing air flow. Ultimately, as

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the assaults to the lung abate and the body begins to heal, lung remodeling occurs resulting in fibrosis, metaplasia, and bronchial smooth muscle proliferation.

Today, BPD or chronic lung disease (CLD) affects infants born at younger ages, lower supplemental oxygen concentrations, and less barotrauma, thus necessitating a revision of the old definition. Currently, just prior to delivery, pregnant women are given systemic steroids to help accelerate lung maturity and stimulating surfactant production in the fetus. Exogenous surfactant is also now readily available and has dramatically changed the face of BPD. The application of exogenous surfactant has allowed for more uniform lung ventilation with lower positive pressures. In addition, the trend in most centers is toward noninvasive ventilation even in the extremely premature infants to reduce the barotrauma injuries. These infants are now supported with nasal continuous positive airway pressure (NCPAP) and supplemental oxygen. This strategy of ventilation minimizes barotrauma, provides adequate oxygen levels, but does not correct the body's PCO_2, and thus this method of ventilation is often referred to as "permissive hypercapnia." With all the changes in clinical practice and the shift to younger premature infants, the old definition of BPD has become less useful. An infant born at 27 weeks gestation will require oxygen for a month and develop chest radiograph changes but may have a better respiratory status than an infant born at 35 weeks requiring the same support. Therefore a new definition of BPD was required to accommodate the changes in the premature population and the changes in clinical practice since 1967.

In 2001, the National Institute of Health organized workshop to characterize the "new" BPD and have now adjusted the criteria to account for younger premature infants and advances in medical technology. The results of the workshop were published by Jobe et al., and the "new" BPD definition now takes into account gestation age at birth and divides premature infants into two major categories, younger and older than 32 weeks gestation. For infants born before 32 weeks, BPD is assessed at 36 weeks post menstrual age or at discharge to home (whichever comes first) and having required at least 28 days of oxygen since birth. For infants born after 32 weeks, they are assessed at 28–56 days of life or at discharge to home (whichever comes first) and again having required at least 28 days of oxygen since birth. BPD is further categorized in both groups as mild if at time of assessment they are on room air, moderate if they require less than 30% supplemental oxygen, and severe if they need more than 30% oxygen or any invasive or noninvasive mechanical ventilation.

Even though the definition and even the risk factors of BPD have shifted, the molecular pathways involved for both "old" and "new" BPD are still largely unknown. Despite the necessity of these treatment modalities, the combination of immaturity, free radical oxidant injury and barotrauma created by mechanical ventilation still contribute to the development of new and old BPD. And although the histology of new BPD has shifted from the striking fibroproliferative disease of old BPD to one that consists of fewer and more simplified alveoli, the insults associated with new BPD still occur during a critical time in lung development, thus affecting both alveolar and vascular development. Human lung development can be characterized in four stages that begin in the prenatal period but continues well after birth. The final stage of lung development is alveolarization, when alveoli are formed, which begins around the 36 week of gestation and continues to about 2 years of age. Since premature infants by definition are born before 37 weeks gestation, lung injuries prior to term may have a profound impact on lung development, thus explaining why some infants continue to have respiratory problems well beyond the initial insult and into childhood. These alterations in lung development can result in persistent abnormalities in pulmonary mechanics with lower lung compliance and airway obstruction. In fact, Doyle et al. who looked at 147 subjects with a mean age of 18.9 years found that subjects who had BPD as infants had a greater chance of having a decreased forced expired volume in 1 s/forced vital capacity ratio $<75\%$ as compared to non-BPD subjects (42.4% vs. 16.4%), even if lung volumes were not significantly different. Vascular development can also be compromised in the infant with BPD. Vascular cells are very sensitive to inflammation and oxygen levels, and therefore the oxidant injury that occurs during vascular development can increase smooth muscle proliferation and increase pulmonary vascular resistance. Thus infants with BPD are at higher risk for developing left or right ventricular hypertrophy and pulmonary hypertension.

Treatment and Management

Maintaining good oxygen saturations is a key component of the treatment of BPD. Maintaining oxygen saturations above 92% is not only important in respiratory status but also for growth. Supplemental oxygen should be provided not only if the patient's daytime saturation is below 92%, but oxygen saturation may be normal when awake but below 92% when asleep; therefore it is important to assess nighttime oxygen saturations in any child with

persistent respiratory symptoms and/or with poor weight gain. While the optimal oxygen saturation (92–94% vs. >94%) in the infant with BPD is still under debate, below 92% is not recommended.

Infants who require prolonged supplemental oxygen may benefit from diuretic therapy. Diuretics, such as furosemide, have been shown to improve respiratory mechanics independently of their ability to reduce pulmonary edema. However, furosemide has been associated with nephrocalcinosis as well as electrolyte imbalances and, therefore, has limited its uses in the treatment of BPD after hospital discharge. Alternative diuretics such as spironolactone and thiazide are often used in combination to obtain a diuretic effect with less electrolyte disturbances and therefore are often prescribed as an outpatient medication.

Bronchodilators are also often used in infants with BPD and can be helpful during acute wheezing episodes, but it is uncertain if the use of bronchodilators in these patients improves long-term pulmonary function. Systemic corticosteroids, as a treatment for BPD, are controversial and can be associated with numerous adverse effects such as impaired lung growth and neurodevelopmental consequences. However, since some infants with BPD respond to bronchodilators and exhibit symptoms similar to reactive airway disease, this subpopulation may benefit from inhaled corticosteroids.

Since the key treatment for BPD is growth, good nutrition is an essential. It is important to maintain adequate nutrition since most of lung development occurs before age 2. While weight is important, body length is equally if not a better indicator of lung growth. The term infant typically requires 100 kcal/kg/day while infants with BPD may require 140 kcal/kg/day for adequate weight gain. Feeding can be challenging in infants with severe BPD since many will have oral aversion from an immature or inadequate swallowing coordination. In addition, infants with severe BPD may be fluid sensitive and therefore cannot tolerate the volume of feeds that are required to achieve the desired nutritional level.

Furthermore, many infants with BPD suffer from gastroesophageal reflux or have dysphagia which can exacerbate any underlying lung disease by through chronic microaspiration. A diagnosis of reflux can be made clinically and treated with a histamine H2-receptor antagonist, but additional promotility agents may be required in some cases. When aspiration is suspected, a dysphagia study is essential to identify which textures the patient may safely swallow. In severe cases of dysphagia with aspiration, a gastrostomy tube may be necessary to ensure both adequate nutrition and to eliminate the risk of aspiration.

Infants sent home with a diagnosis of BPD often require a readmission to the hospital in the first 2 years of life. Infants with BPD have impaired pulmonary mechanics and low lung reserves, and therefore many require more respiratory support during an upper respiratory infection than their term counterparts. Respiratory Syncytial Virus (RSV) infections can be devastating in these patients, and therefore RSV vaccination is recommended. In addition, influenza vaccinations are recommended annually for the patient as well as his/her caregivers. Hand washing and limited contact with ill individuals are also effective strategies to reduce the probability of respiratory infections.

While many infants with BPD have abnormal chest radiographs on hospital discharge which can consist of hyperinflation, peribronchial cuffing, or patchy interstitial infiltrates, these findings are nonspecific and usually improve with time. Due to the nonspecific findings, routine chest radiograph is not usually recommended when the patient is asymptomatic. Blood work is also not done routinely but may be indicated in patients on diuretics or those whom chronic hypoventilation is suspected. An elevated bicarbonate level may indicate a metabolic compensation for respiratory acidosis and deserves further evaluation. Infants on supplemental oxygen/respiratory support or suspected of chronic hypoventilation, annual echocardiograms may be helpful in monitoring for right ventricular hypertrophy and signs of pulmonary hypertension.

While respiratory symptoms are a key component of BPD, it is a disorder that can result in multiple medical and cognitive problems. These infants often require services including occupational and physical therapy, and are followed by a number of specialists.

Outcomes and Prevention

Infants who do well in the first 2 years of life without recurrent respiratory infections generally do well clinically. However, studies have shown that 25% of adolescents with a history of BPD are more likely to have reduced airway flows, decreased lung compliance, and diminished exercise capacity as compared to age-matched controls without a history of BPD. Therefore it is not surprising that many infants with BPD develop asthma-like symptoms. Further studies are needed since the defining characteristics have changed and older studies may not be representative of the "new" BPD. Despite medical advances, specific medications are not available for infants with BPD, but treatment is supportive and nonspecific. Currently, the emphasis is for the prevention of BPD, and many studies are ongoing looking at new strategies to prevent this disorder. These

strategies include less-invasive ventilation such as permissive hypercapnia, but additional studies are required to assess the long-term consequence of prolonged hypercapnia during lung development. Other studies have stressed the importance of prophylactic rather than rescue surfactant. Antioxidants such as recombinant superoxide dismutase (CuZnSOD) may prevent the oxidant injury that is associated with the development of BDP4). In addition, vitamin A is often given to preterm infants for its nutritional and antioxidant properties. Others are investigating the use of nitric oxide as a tool to prevent pulmonary vascular injury. While these are only a few examples of the modalities currently under investigation, all of these new prevention strategies have been developed to target the pathways believed to be involved in the development of BPD. As the understanding of the pathophysiology of BPD improves, new medications and treatment strategies are emerging demonstrating the importance of further research on this important topic.

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236 Pneumonias

Erin R. Stucky · Meerana Lim

Definition/Classification

Defining pneumonia is particularly difficult in young children in whom other lower respiratory tract infections are common. The World Health Organization (WHO) defines pneumonia clinically, in the following stages: Stage I, fever $\geq$38°C and tachypnea (>50 breaths/min for 2–11 month olds and >40 breaths/min for 1–5 year olds); Stage II, with addition of chest indrawing; and Stage III, with addition of inability to drink and/or central cyanosis. The British Thoracic Society defines community-acquired pneumonia (CAP) as the presence of signs and symptoms of pneumonia in a previously healthy child due to an infection which has been acquired outside hospital. In the developing world, "acute lower respiratory infection" (ALRI) is used, given the limited access to obtaining a chest radiograph (CXR).

Etiology

The etiology of pneumonias in children outside the immediate newborn period varies based on age group, environment, exposures, and underlying comorbid risk factors.

Pneumonia can be caused by microorganisms, irritants, or unknown causes. Infectious etiologies include bacteria, viruses, atypical organisms, fungi, and parasites. The exact infectious etiology of the pneumonia is often not known because this would require an invasive procedure to obtain a specimen for culture. Without a culture, other clinical features and diagnostic study results are used to help make a clinical diagnosis and to guide appropriate therapy. The most commonly reported viral causes are biased due to available testing, but include influenza A or B, rhinovirus, respiratory syncytial virus (RSV), human metapneumovirus (hMPV), and parainfluenza. In the post-pneumococcal vaccine era in the United States, increased rates of invasive pneumococcal pneumonia during the respiratory viral infection season has been reported in association with RSV, influenza, adenovirus and hMPV. Viral causes that are of concern in countries without consistent immunization practices, or in immunocompromised hosts with cancer, primary immunodeficiency, or human immunodeficiency virus (HIV), are varicella and measles.

Epidemiology

According to the WHO, pneumonia is a significant cause of child mortality worldwide, responsible for approximately 2 million deaths each year, of which almost three-quarters are in developing countries. The WHO's Global Burden of Disease Update 2004 reports diarrhea and pneumonia as the leading causes of mortality in children under 5 years of age. In 2008, pneumonia accounted for 14% of deaths in infants less than 28 days of life according to the WHO. In Europe and Australia, incidence is reported at 3.6–6.8% of children less than 5 years of age, with similar hospitalization rates of 41–42%.

Although diagnostic testing is usually limited in practice, studies in the United States and Europe demonstrate that viruses are involved in up to two-thirds of CAP, of which approximately half are mixed viral–bacterial infections. In limited studies in developing countries, rates of the more broadly defined ALRI are reported, with viral causes at approximately 50%, the majority due to RSV. Influenza's impact worldwide varies with the yearly strain antigenic drift, with epidemics and pandemics seen when antigenic shift occurs. New viral etiologies continue to emerge, such as the coronavirus severe acute respiratory distress syndrome (SARS). The clinician must be attentive to outbreaks of respiratory diseases across the globe given the ease with which pathogens travel on human hosts (air travel) and through natural sources (global air streams).

Pathogenesis and Pathology

The most frequent histopathologic findings in major airways with viral pneumonia are congestion, inflammation, necrosis of bronchial epithelium, and hemorrhage. Viral pneumonias affect the lung through direct invasion, causing mucosal inflammation and damaging ciliary clearance allowing secondary bacterial infection to occur more readily.

In severe cases, extensive involvement of the bronchoepithelial cells and mucous glands of trachea, bronchi, and larger bronchioles, and submucosal mononuclear inflammatory infiltrates can be seen. Neutrophilic and monocytic inflammation and extensive secondary

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bacterial pneumonia is reported from autopsies of pediatric influenza patients.

Clinical Manifestations

Typical signs and symptoms include fever, diminished breath sounds, rales, retractions, tachypnea, hypoxemia, and cough. In general, higher fever with a rapid onset is seen in bacterial pneumonia; however, there are many exceptions to this. Viral pneumonia, particularly those caused by influenza, may present with high fevers and chills. *Chlamydia trachomatis* and *Bordetella pertussis* infections are frequently afebrile. A fever many days into a respiratory illness accompanied by worsening symptoms may suggest a secondary bacterial infection after a primary viral illness.

While the characteristic post-tussive inspiratory whoop of whooping cough may help make this diagnosis in school-age children, it is usually not present in very young infants and adults. A productive cough, particularly if associated with large volumes of purulent secretions, is suggestive of a bacterial pneumonia, whereas a dry, nonproductive cough is more likely to be a viral process. In very young children and infants, sputum characterization can be difficult as they are likely to swallow their sputum. If sputum can be expectorated, a culture of the expectorate may be helpful in the diagnosis and treatment of pneumonia.

Poor feeding or poor oral intake is common (~75%), as are vomiting (30–45%), abdominal pain (up to 20%), and dehydration (25%).

Physical Exam

The physical exam for pneumonia may not be as helpful in an infant versus and older child or teenager. The most common findings include fever and tachypnea. Tachypnea has been associated with a sensitivity of 50–85% for diagnosis of lower respiratory tract infection with specificity of 70–97%. In children who have been symptomatic for over 3 days, tachypnea has a sensitivity of 74% and a specificity of 67% for pneumonia confirmed by chest x-ray.

Tachypnea age specific norms recommended for use:

- 60 breaths/min in infants younger than 6 months
- 50 breaths/min in infants 6–11 months old
- 40 breaths/min in children 12–59 months old
- 30 breaths/min in febrile children 5 years of age and older

Decreased breath sounds may occur in the area of a lobar pneumonia. Normal breath sounds may be auscultated in up to 20% of children due to transmission of normal breath sounds across the relatively small thorax; yet they may have complete collapse or consolidation on CXR. Crackles are frequently suggestive of bacterial pneumonia, which are not uncommon in infants with RSV pneumonia. This is the sound of alveoli opening and/or by air bubbling through fluid in the small airways during inspiration. Wheezing may be present; however this sign may be noted in many lower respiratory tract diseases. Dullness to percussion may be heard over an area of focal consolidation. Egophony or increased resonance can be auscultated over an area of consolidation or over a large effusion. The patient is asked to say "e" and what is heard by stethoscope is "a" due to altered transmission of noise through fluid versus air. Chest pain, usually pleuritic, worsened by deep breaths and cough, may also be present.

Diagnosis

Diagnosis of pneumonia in the ambulatory setting is often made clinically, especially where access to radiology services is limited. According to the British Thoracic Society, CXR should not be performed routinely in children with mild uncomplicated acute lower respiratory tract infection. Correlation between clinical assessment of diminished breath sounds and consolidation on CXR is overall poor at only 50–60%.

Neither clinical signs and symptoms nor CXR aid in differentiating between viral and bacterial pneumonias. However, some associations between CXR reports and infectious etiologies may be helpful in treatment decisions. Lobar consolidations are frequently associated with a bacterial pneumonia, whereas a bilateral diffuse interstitial appearance may be more suggestive of Pneumocystis pneumonia, Legionella, or a viral process. Pneumonia caused by Staphylococci in the pediatric population may be associated with pneumatoceles, bronchopleural fistulas, and empyema, although none of these should be considered pathognomonic. Mycoplasma pneumonia usually has a diffuse bilateral interstitial appearance on radiograph, although it can also be seen with lower lobe consolidations and effusions. The preferred imaging is for two views of the chest, frontal (usually posteroanterior), and lateral (to see the retrocardiac area) for initial evaluation. In cases where there is complete opacification of the hemithorax or when there is a complicated pneumonia, computed tomography and/or sonography may also be employed. Recurrent pneumonias and those that are resistant to therapy are candidates for further imaging.

Laboratory testing in ambulatory patients is not routinely indicated, but some studies may be helpful for hospitalized patients (Table 236.1). Lab testing for viruses by real-time (RT) PCR can be valuable in patients at risk for more severe complications of disease who may require more intense monitoring due to underlying cardiac, immune, or chronic pulmonary disorders. Routine laboratory testing for ambulatory children is not indicated. Inappropriate secretion of antidiuretic hormone (SIADH) may be more common than previously thought, found in up to 20% of patients (Table 236.2).

Patients with significant pleural fluid should have specimens sent for gram stain, viral testing, aerobic and anaerobic bacterial culture, with consideration for mycobacteria and fungal cultures at the direction of infectious disease consultation. Sensitivity of latex agglutination studies for *Streptococcus pneumoniae* and *Haemophilus influenzae* type b (Hib) on pleural fluid vary with method and range 77–91%.

For immunocompromised hosts, evaluation for invasive viral infections such as varicella, herpes simplex, and coronavirus should be considered along with parasitic, protozoal, and fungal infections, and in consultation with infectious-disease experts.

Table 236.1
Pneumonia-causing organisms by age

Neonates	Common organisms	Group B streptococcus, gram negative enteric bacteria, cytomegalovirus, *Ureaplasma urealyticum*, *Listeria monocytogenes*, and *Chlamydia trachomatis*
	Less common organisms	*Streptococcus pneumoniae*, group D streptococcus, and anaerobes
Infants	Common organisms	RSV, parainfluenza viruses, influenza viruses, adenoviruses, metapneumovirus, *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*
	Less common organisms	*Bordatella pertussis* and *Pneumocystis jiroveci*
Preschool children	Common organisms	RSV, parainfluenza viruses, influenza viruses, adenoviruses, hMPV, *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Mycoplasma pneumoniae*, and *Mycobacterium tuberculosis*
	Less common organisms	*Chylamydia pneumoniae*
School-age children	Common organisms	*Mycoplasma pneumoniae*, *Chylamydia pneumoniae*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, parainfluenza viruses, influenza viruses, and adenoviruses

Differential Diagnosis

Alternate diagnoses may be both pulmonary and non-pulmonary. For young infants with wheezing and acute respiratory distress, bronchiolitis is the most common diagnosis. Acute respiratory distress may be the result of aspiration of a foreign body, inhalation lung injury, or spontaneous pneumothorax. Non-pulmonary considerations include leukemic infiltrates, congestive heart failure, metabolic acidosis with compensatory tachypnea, asthma, or in appropriate areas malaria. Failure to improve as expected with usual therapy should trigger consideration of both uncommon infectious organisms as well as underlying condition such as HIV or pulmonary anatomic abnormality. Recurrent pneumonia bears a further work-up, depending on the associated signs and symptoms. Underlying diagnoses to consider include: cystic fibrosis, congenital malformations (cystic adenomatoid malformations, pulmonary sequestrations, foregut duplication cysts), immotile cilia syndrome, right middle lobe syndrome, immunodeficiency (congenital or acquired), hemorrhage, vascular malformations, and dysfunctional swallow. In these cases, treatment of the underlying disease is an important part in the prevention of further pneumonias and long-term consequences of recurrent lung infections.

Treatment

Patients not hospitalized should be reevaluated by their primary care practitioner within 24–48 h. Admission should be considered for patients with need for supportive care (oxygen, intravenous hydration, suctioning) or at risk for progression of respiratory disease or potential instability of underlying chronic condition. Specific admission criteria suggested include oxygen saturation less than 92%; respiratory rate >70 breaths/min in infants/50 in

Table 236.2
Commonly performed laboratory testing

Study	Value	Comments
RT-PCR viral (NPA; tracheal)	Influenza treatment can be initiated; discontinuation of antibiotics can be considered	Nasopharyngeal aspirate (NPA) technique influences result; overall sensitivity 80–95%
RT-PCR atypical (NPA; tracheal)	Mycoplasma and Chlamydia pneumonia treatment can be initiated	Not available at many hospital sites
Viral culture (NP, tracheal most common)	Definitive diagnosis of active viral infection	Requires special transport media, processing time, not available at many hospital sites; rarely positive in face of a negative viral PCR
Paired acute and convalescent serology (blood)	Can detect acute infection of some viruses; more reliable result for *M. pneumoniae* than single IgM	Requires blood testing at presentation and at 3 weeks
RT-PCR (blood)	*S. pneumoniae* most often tested	May be negative when paired serology demonstrates acute exposure
C-reactive protein (CRP); Procalcitonin (PCT)	Higher levels seen in typical bacterial infection	Cutoff levels below which typical bacterial disease is not likely to have not been well documented for CRP or PCT
Complete blood count		White blood cell count and band forms do not correlate well with etiology
Electrolytes	For severely dehydrated or ill patients	Hyponatremia, acidosis, and hypoglycemia are not uncommon in severely ill patients
Blood culture	Supportive of more systemic disease	Rarely positive (1–10%); however, it is recommended in any patient with probable bacterial infection

children, grunting or apnea, poor feeding/inability to feed, and concern for caregiver ability to assess respiratory distress. Pulse oximetry should be performed on all hospitalized children.

Antibiotics will be given empirically despite the fact that this approach likely leads to overuse of antibiotics in the general population. Antibiotic choice is typically based on the patient's age and commonly encountered organisms causing infection in that age. It is important to remember that for neonates, early-onset GBS disease is usually severe and almost always includes pneumonia as part of the disease presentation. Treatment of suspected or proven viral pneumonia is typically supportive. Chest physiotherapy (postural drainage, percussion of the chest, or deep breathing exercises) does not affect length of hospital stay, duration of fever, or CXR findings in patients with pneumonia. Sitting upright may help to expand lungs and lessen respiratory symptoms in children with respiratory distress.

For patients with suspected or proven influenza pneumonia, antiviral therapy with oseltamivir is indicated to both treat the patient and to limit spread of the disease. Other pathogen-specific therapies include vitamin A for measles pneumonia, acyclovir for varicella, and ribavirin for SARS and severe RSV. Steroid use is controversial but has been used in severely ill patients in intensive care settings.

Prognosis

Duration of hospital stay is associated with clinical severity rather than etiology. Although acute inflammatory markers (CRP, PCT) are higher in bacterial disease, levels do not correlate with severity of disease.

Follow-up CXR is indicated only for lobar collapse or round pneumonia to document complete resolution and thereby confirm absence of anatomic abnormality or tumor.

Prevention

Primary prevention includes strict infection control measures, immunization, and avoidance of exposures and lung irritants that increase susceptibility to respiratory pathogens. Hand washing and covering the mouth while coughing continue to be significantly effective measures to reduce

spread of disease. Crowding and smoke exposure are associated with increased risk of viral infections, particularly in young infants. Chemoprophylaxis for certain types of pneumonia may be indicated in select populations such as immunocompromised patients, and those with asplenia and certain cardiac disorders. Guidelines for routine vaccination against Hib, *Streptococcus pneumoniae*, and varicella, as well as yearly influenza prevention should be followed. Immunoprophylaxis against RSV should be given to appropriate infants following national guidelines.

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237 Cystic Fibrosis

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Etiology/Epidemiology

Cystic fibrosis (CF) is a genetic disorder that affects multiple organ systems, most notable are the lungs and GI tract. It is known to be caused by mutation of one single gene, known as the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene on chromosome 7, which encodes an ion channel important for chloride and bicarbonate transport across epithelia. Inheritance follows the classical Mendelian autosomal recessive pattern. Therefore, affected patients have mutations in both alleles of the CFTR gene, one inherited from each parent. However, the severity of disease is extremely variable from patient to patient, even among those with identical CFTR mutations. This variation is likely multifactorial, related to differences in compliance to medical regimens, environmental exposures, and the effect of other genes that modify the CF phenotype. The etiology of CF multisystem disease is still not completely understood, but the hallmark of the disease is the production of thick, tenacious secretions, particularly in the airways and GI tract. This is related to imbalance of ion and water transport across these epithelial structures due to CFTR mutations.

First described in the 1930s, CF is a relatively common disease, affecting 30,000 people in the USA and 70,000 worldwide. The carrier frequency is highest in the Caucasian (European descent) population (1 in 30), with the Hispanic population second (1 in 46). It is also found at much lower frequencies, albeit not negligible, in the African population (1 in 65) and Asian populations (1 in 90). The most recent data from the CDC suggests that the incidence of CF is 1 in 2,500–3,500 live births in non-Hispanic whites, and approximately 1 in 3,700 overall.

The earliest presentation of CF is meconium ileus, which can be identified shortly after birth as abdominal distension and lack of passage of meconium in the first days of life. This is the presenting symptom in approximately 15–20% of children with CF. In children without meconium ileus, the most common presenting signs include those of exocrine pancreatic insufficiency (failure to thrive, persistent diarrhea, chronic abdominal pain) and airway inflammation (prolonged cough, recurrent wheezing). The median age of diagnosis based on clinical symptoms (other than meconium ileus) is approximately 14.5 months, often after many other diagnoses have been entertained. The overall median age of diagnosis is 5.3 months, which includes children presenting at birth with meconium ileus, or diagnosed through newborn screening programs, or because of a known family history.

There are now over 1,800 different mutations of CFTR that have been described. By far, the most common mutation in CFTR is a deletion of phenylalanine at position 508 (called delta F508, or ΔF508), which accounts for about two-thirds of the mutations found in CF patients. The other one-third of mutations is comprised of over 1,000 different mutations, all found at much lower frequencies. There are alleles that may be more frequent in certain populations due to founder effect, but none approaches the frequency of ΔF508.

Genetics of CF

Although CF is a disease caused by mutation in a single gene, complexity arises in the vast number of different mutations in the gene that may, or may not, actually cause disease. This is in stark contrast to another monogenic disease, sickle cell anemia, where a single point mutation is the sole variant known to cause the disease.

Strictly speaking, the term "mutation" refers to any change in the nucleotide sequence of a gene. There is no assumption of the functional consequence of the change in sequence, thus mutations may be classified as deleterious, neutral, or even beneficial. The term "polymorphism" refers to variations in gene sequence that have achieved a certain frequency in a population and do not have any overt deleterious consequence. Distinguishing between a disease-causing mutation and a polymorphism has proven to be extremely difficult in CF. Many factors play a role in the manifestation of disease in CF, including the specific organ that is affected (some organs are more affected by certain types of allelic variations), as well as the role of modifier genes on the CF phenotype. This is compounded by the vast array of novel CFTR mutations discovered through genetic sequence analysis, the majority of which have no known or predicted clinical

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consequence. The effects of such phenomena are further discussed in the context of newborn screening for CF.

CFTR mutations can also be classified by the type of defect predicted to occur. In some cases, a missense or frameshift mutation can lead to an early stop codon and defective production of a complete protein product (class I mutation). Mutations that cause defective posttranslational protein trafficking or maturation (class II) or protein regulation (class III) are also predicted to cause disease. In contrast, mutations that affect the conductance function of the protein product (class IV) or that lead to decreased (but not absent) functioning protein product (class V) can have varied degrees of clinical manifestations, including normal sweat chloride and pancreatic sufficiency.

Diagnosis

Newborn Screening

Beginning in 2005, many states in the USA had implemented mandatory newborn screening programs for CF. During 2010, all states and the District of Colombia had mandatory newborn screening programs in place. The push for mandatory screening of all newborns for CF arose from the premise that early intervention, even prior to overt symptoms, can alter the course of the disease in a positive way. The data show that early intervention does improve growth and nutritional parameters, but the effect on respiratory status and progression of lung disease is as yet unproven.

The exact protocol for screening differs slightly from state to state. Generally, screening begins with testing a blood spot for elevated immune reactive trypsinogen (IRT) levels, which has a sensitivity of ~88% and specificity of ~99.5% for detecting cystic fibrosis. If this is positive, then this may be followed by a repeat IRT level, or by DNA testing for CFTR mutations (see Genetic Testing, below). Once an infant is identified as possibly having CF by newborn screening, further confirmatory diagnostic testing and counseling should be done at an accredited CF Center.

Sweat Chloride Test

The most commonly used diagnostic test for CF is the sweat chloride test. This test is based on the fact that the epithelium lining the sweat ducts reabsorbs chloride from the fluid as it travels up the sweat duct to the skin. This chloride reabsorption is dependent on functional CFTR at the apical surface of the epithelial cells. In CF, where there is loss of functional CFTR, the sweat produced by the skin has higher levels of chloride. Typically, patients with CF have sweat chloride levels over 60 mEq/L. However, in infants, levels above 30 mEq/L are considered abnormal.

The sweat chloride test is noninvasive. It involves the application of a tiny, painless electrical current to the skin (usually the forearm) to stimulate sweat production. The test is usually done as an outpatient, and typically can be completed in less than 1 hour. Neonates may not produce enough sweat to be diagnostic, so the earliest recommended age to test if CF is suspected is 2–4 weeks of age. Any infant tested in the first month of life may require a second test later on for confirmation, as the test is less reliable in early infancy.

Genetic Testing

If the sweat chloride test is nondiagnostic, or positive, the next step is often genetic testing to identify specific mutations in the CFTR gene. In the case of a nondiagnostic sweat test, this further testing is done in order to determine if there are two disease-causing mutations present. If this is the case, then the patient meets criteria for a positive diagnosis of CF.

In the case that the diagnosis is made with sweat testing, genetic testing is often pursued because it may give some limited additional prognostic information, but more importantly, new therapies are being developed that are specific to certain mutations or classes of mutations. Thus, in the future, it will become more important to know the genotype of every patient in order to tailor therapy. An additional benefit of genetic testing is the ability to easily screen other family members for known mutations.

There are many different types of genetic tests commercially available. It is important to know the limitations of these different tests in order to interpret the results obtained. If the mutations in a given family are known, then other family members can be screened by looking specifically for these mutations. If there are no known mutations in a family, then a screen using a panel of 20–50 of the most common mutation can be done. The limitation to this is that there are patients for whom the sensitivity of these panels is much lower due to the differences in mutations found in certain ethnic groups compared to non-Hispanic Caucasians. There is also full gene sequencing (exons and splice sites) available to screen more comprehensively for mutations in the CFTR gene. While full gene sequencing can detect ~97–98% of mutations, it will not detect large gross deletions or duplications. If only one mutation is detected with full gene sequencing, the sample can also be screened for large deletions or duplications using different methods.

Nasal or Rectal Potential Difference

This is a functional test for the presence of CFTR, based on the ability of CFTR to regulate the potential difference across epithelial structures. It is not routinely used as a screening test due to the fact that it is somewhat invasive. The test involves one electrode that is placed on the nasal mucosa of the inferior turbinate, and another subcutaneously on the forearm, connected to a voltmeter to measure the potential difference. A potential difference less than −40 mV is considered abnormal.

Special Considerations

According to the CF Foundation, a diagnosis of CF can be made if the patient has suggestive signs and symptoms, *or* a positive family history, *or* a positive newborn screen, *and* evidence of CFTR gene or protein abnormality, i.e., abnormal sweat chloride test, abnormal nasal potential difference, or two CF disease-causing mutations in *trans*.

As newborn screening and gene sequencing have become more routine, a new diagnostic challenge has arisen. This is related to cases where an infant has a positive newborn screen, but normal or borderline sweat chloride level. In these cases, genetic testing is usually performed to determine if there are two disease-causing mutations. However, ambiguity arises when novel mutations, or mutations with unknown clinical consequences, are discovered. In an otherwise asymptomatic infant, making the diagnosis of CF on these grounds has been controversial. In a statement by the CF Foundation in 2009, a new diagnostic entity was proposed to address this issue. For infants who are asymptomatic, have elevated IRT on newborn screening, and have at least one mutation that is not clearly "disease-causing," the term "CF-Related Metabolic Syndrome" (CRMS) has been proposed. There are also proposed guidelines for surveillance and management of these infants, because if signs or symptoms of CF were to develop, they would be given the diagnosis of CF and managed accordingly.

Symptoms/Pathology/Pathogenesis

Lung Disease

Lung disease significantly contributes to the morbidity associated with CF and is the most common cause of mortality. It is for this reason that CF is managed primarily by pediatric pulmonologists, even though many other organ systems are also affected. The hallmark of CF lung disease is thick, tenacious mucus that accumulates in the large, medium, and small airways. This thick, stagnant mucus layer inevitably becomes a nidus for acute bacterial infections and, eventually, chronic bacterial colonization.

In conjunction with persistent bacterial colonization, there is also a chronic inflammatory state mediated primarily by neutrophils in the CF airways. Neutrophils are essential to the lungs' ability to fight infection; however, there is a price paid in host tissue damage. This is especially true in the case of chronic neutrophilic inflammation, in which there is prolonged exposure to released reactive oxygen species and other damaging inflammatory mediators. There still remains a "chicken and egg" question of which arises first, airway bacterial colonization or airway inflammation. Regardless of the inciting factor, it is clear that the ongoing neutrophilic inflammation in the airways over time leads to airway remodeling, fibrosis, bronchiectasis, and, thus, obstructive lung disease.

Onset of respiratory symptoms varies from patient to patient, but can be present early in infancy. Symptoms can include chronic wet cough, prolonged cough after respiratory illnesses, wheezing, dyspnea on exertion, and chest pain or tightness. Over time, patients with CF may experience episodic exacerbations of their lung disease. While the exact etiology of these exacerbations is still not completely understood, they are often precipitated by a concurrent acute respiratory infection (viral, bacterial, or other) or by inadequate airway clearance and adherence to maintenance therapies. Respiratory exacerbations are characterized by increase in cough, change in quality or quantity of mucus production, increased dyspnea (especially with exertion), and usually an associated worsening in airways obstruction (i.e., decreased FEV1 on spirometry). There may or may not be other systemic signs or symptoms such as fever, weight loss, fatigue, and anorexia.

Progression of CF lung disease over time is the rule rather than the exception. The rate of progression varies and is thought to be related to many factors, such as genetics, environmental exposures, nutritional status, and adherence to medical therapies. There have been certain factors that have been shown to be associated with an accelerated rate of decline of lung function. One of these is colonization of the airways with Pseudomonas aeruginosa, particularly the mucoid phenotype. For this reason, routine surveillance cultures are obtained, and measures are taken to eradicate Pseudomonas at each new acquisition to prevent or delay colonization. Methicillin-resistant Staphylococcus aureus (MRSA) colonization is also emerging as a possible factor associated with accelerated decline in lung function,

though this is still under active investigation at this point in time. Another well established factor that contributes to decline in lung function over time is nutritional status. Thus nutritional and growth parameters are carefully monitored, and often aggressive measures are undertaken to correct deficits, such as supplemental feedings with gastrostomy tubes.

Respiratory failure is the most common cause of mortality in CF. Patients with extensive bronchiectasis and fibrosis may become hypoxemic and hypercapneic. In such severe lung disease, other complications may arise, such as hemoptysis (which may be massive) or pneumothorax.

Pancreatic Disease/CFRD

Exocrine pancreatic insufficiency is often the earliest presentation of cystic fibrosis. Patients will usually develop pancreatic insufficiency and chronic malabsoption within the first year of life. Symptoms and signs include chronic abdominal pain and cramping, abdominal distension, diarrhea, steatorrhea, and failure to thrive. Laboratory studies may reveal deficiencies in fat-soluble vitamins.

Exocrine pancreatic insufficiency in CF is a result of production of thick secretions and obstruction of the pancreatic ducts and acini leading to their destruction. Approximately 10–15% of CF patients do not develop pancreatic insufficiency, and this phenotype is usually associated with mutations where there is reduced, but not abolished, CFTR function. There are also certain mutations that are more associated with the predisposition to chronic pancreatitis, or recurrent acute pancreatitis, which then eventually leads to pancreatic insufficiency later in life. The diagnosis of CF should be considered in patients with idiopathic recurrent or chronic pancreatitis, even in the absence of other manifestations of the disease. Interestingly, a significant proportion of patients with idiopathic chronic pancreatitis are carriers of CFTR mutation, suggesting a degree of haplotype insufficiency related to pancreatic disease.

Patients with CF are also at high risk to develop endocrine pancreatic insufficiency, i.e., CF-related diabetes (CFRD). The incidence increases with age, and currently half of CF patients over age 30 have CFRD. The presentation of CFRD increases during times of stress, e.g., respiratory exacerbation, which is the rationale for screening during acute exacerbations in the hospital. The etiology of CFRD is insulin deficiency, not insulin resistance. The pathogenesis is distinct from diabetes mellitus type 1 and 2, and is thought to be related to apoptosis of β-islet cells and defective secretion of insulin from surviving islet cells. Oxidative stress is thought to play a key role in this process, but the exact mechanisms are still elusive. Genetic factors also play a role, including non-CFTR genotypes. Hormonal milieu may also play a role as epidemiologic studies show a higher predisposition to develop CFRD in females as well as increased risk in patients with increased systemic steroid use. Despite the increased incidence of CFRD with increased age, mortality in patient with CFRD is still primarily related to respiratory failure, not cardiovascular disease.

Other Clinical Manifestations of CF

Sinus disease: As part of the respiratory tract, the sinuses are also frequently obstructed with thick mucus and colonized with bacteria. Persistent inflammation can lead to the formation of nasal polyps, which when present should raise consideration of CF. Patients often require surgical intervention for chronic sinusitis symptoms that do not improve with conservative measures.

GI disease: Patients may also have complications of intestinal obstruction due to thick, adherent mucus and fecal material, similar in mechanism to meconium ileus in the newborn, called distal intestinal obstruction syndrome (DIOS).

Less frequently, there can be chronic biliary obstruction leading to the development of cirrhosis of the liver and eventually even liver failure.

Fertility: The development of the vas deferens in males is exquisitely sensitive to CFTR mutation, and the majority of males with CF are azoospermic, and thus infertile. Women with CF can have thick cervical mucus that prevents pregnancy, but this condition can usually be overcome by the use of artificial insemination or in vitro fertilization.

Treatment and Management of Lung Disease

Secretion Clearance

CF lung disease is characterized by the production of thick mucus that is difficult to clear from the airways. The maintenance therapies for CF lung disease have been directed at mobilizing this thick mucus from the airways. This can be accomplished by mechanically assisting clearance of the mucus, via external chest wall percussion/oscillation (manual chest percussion or mechanical external chest wall

oscillation) or oscillating positive expiratory pressure (PEP), using devices such as intrapulmonary percussive ventilation (IPV) or a flutter valve.

In addition to mechanically aiding mucus clearance, there are also therapies that help by making mucus less thick and more easily cleared. One such therapy is inhaled dornase alfa, which acts by breaking down the extracellular DNA, making airway secretions less thick and sticky. Another such therapy is inhaled hypertonic saline, which is thought to act by hydrating airway mucus thus making it less viscous.

Inhaled bronchodilators are also routinely used in conjunction with other airway clearance therapies. The rationale is that when airways are maximally patent, mucus can be more easily cleared. Also, there is some evidence that inhaled bronchodilators may also enhance ciliary function and airway clearance.

Anti-inflammatory Medications

The progressive destruction of the lungs in CF is due to ongoing, relentless neutrophilic inflammation in the airways. Thus, it makes sense that anti-inflammatory therapies have been considered and studied for the treatment of CF. However, studies of the use of corticosteroids have shown modest benefit in lung disease, but with intolerable side effects with long-term use. For this reason, these medications are not routinely used for CF lung disease. High-dose ibuprofen has been shown to improve lung function in children with CF with mild to moderate lung disease. The concerns about side effects have limited widespread use of this therapy.

One medication that has been shown to be helpful in preserving lung function over time via anti-inflammatory effects is the antibiotic azithromycin. The mechanism of action is still not clear, though it is widely thought to be immunomodulatory as opposed to antibacterial. It is well tolerated, and long-term side effects are minimal.

Antibiotics

A hallmark of CF lung disease is chronic airway colonization with bacteria, with Staphylococcus aureus and Pseudomonas aeruginosa being the predominant organisms. There have been aerosolized formulations of antibiotics developed for the chronic treatment and suppression of bacteria in the airways. Only two are currently FDA approved for use in cystic fibrosis: inhaled tobramycin (TOBI) and inhaled aztreonam (Cayston). These are only used for maintenance therapy and not for treatment of acute exacerbations.

Acute pulmonary exacerbations are common in CF and are typically treated with systemic antibiotics. Attempts are made to tailor treatment based on airway culture results. However, data show that there is little correlation between response to antibiotic and susceptibility of cultured organisms. If the symptoms are relatively mild, a course of oral antibiotics could be considered. However, for a severe exacerbation or one that has not responded to an adequate course of oral antibiotics, IV antibiotics are required. It is standard to treat acute exacerbations for 2–3 weeks at a time. Combinations of aminoglycosides, cephalosporins, carbapenems, and extended-spectrum beta-lactams are frequent choices for treatment. Over a lifetime, a CF patient will have been exposed to large amounts of antibiotics, so surveillance for cumulative toxicity is recommended.

Lung Transplant

Progression of CF lung disease in many cases leads to respiratory failure and death. When lung disease is severe, some patients consider the option of a lung transplant. These operations are high risk and only performed at specialized tertiary care centers with specialists trained in post-transplant care. While these operations may provide a prolongation and improved quality of life, it is not a cure for CF. The management of post-transplant patients is beyond the scope of this publication.

Treatment and Management of GI Disease

Pancreatic Enzyme Replacement Therapy

One of the earliest manifestations of CF is pancreatic insufficiency. It is treated with exogenous preparations of pancreatic enzymes that are taken orally with each meal. The dose is titrated to the amount required to prevent malabsoption symptoms such as steatorrhea or abdominal pain and bloating. Typically, doses are not to exceed 2,000 units of lipase/kg/meal, as higher doses can lead to complications such as intestinal strictures. Inadequate dosing may increase the risk of DIOS. The efficacy of the pancreatic enzymes can be enhanced with the concurrent use of gastric acid-lowering medications, such as proton-pump inhibitors. This is because the enzymes work best at a higher pH.

Since patients with CF are at high risk for nutritional failure, due to malabsoption as well as increased metabolic demand, they are also treated with high-calorie, high-protein diets to maintain normal growth parameters. Some patients require supplementation with calorie-dense foods such as shakes, etc., and some even require alternate means of enteral intake, such as a gastrostomy tube for caloric supplementation.

Vitamin Supplementation

The malabsorption of fat also leads to malabsorption of fat-soluble vitamins A, D, E, and K. Despite supplementation with enzymes and vitamins, fat-soluble vitamin deficiency is relatively common. These deficiencies can be seen by laboratory measurement before the onset of clinical signs and symptoms, and so surveillance is recommended as part of routine CF care. Most of these vitamin deficiencies respond to oral supplementation. Dietary modifications may also be utilized as part of the treatment plan.

Gastroesophageal Reflux Disease (GERD)

GERD has been reported in as many as 90% of patients with CF. The majority of these cases are symptomatic and can be difficult to manage. Medical management in the form of proton-pump inhibitors are usually the first line of therapy along with dietary and behavioral modifications as with any patient with GERD. For those with persistent symptoms that are impacting growth or lung function, surgical therapy may be recommended.

Outcomes and Prognosis

The prognosis for a baby born today with CF is better than even a decade ago, and continues to improve every year. The median life expectancy in 2008 was 37.4 years, a number than continues to go up as new therapies emerge. Thus, this statistic would not be applicable to a baby born today with CF, as he or she will likely reap the benefits of new advancements and therapies.

It is often difficult to provide an accurate prognosis for patients with CF, as there is so much variability in the course and severity of disease. With current standards of care, patients with CF are very likely to live well into adulthood and live full and productive lives. Overall, there is every reason for an optimistic outlook for the future of CF patients.

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238 ALTE and Sudden Infant Death Syndrome

Ami Doshi · Erin R. Stucky

Definition

Apparent life-threatening event (ALTE) is defined as "an episode in the first year of life that appears potentially life-threatening to the observer and is characterized by some combination of color change, apnea, alteration in muscle tone, choking or gagging." Although ALTE has been dubbed "near miss sudden infant death syndrome" (SIDS), this is misleading. SIDS is "a sudden death in a child without historical, physical, laboratory, or post-mortem findings that explain the cause of death." ALTE is a witness-defined entity with myriad potential causes, most often benign and nonrecurrent. The relationship of ALTE to SIDS has been questioned in the past, however current literature suggests SIDS in patients with a history of ALTE are most likely to be undiagnosed derangements of metabolism or central respiratory control. ALTE may be accompanied by true apnea (cessation of breathing for $>$20 s) or periodic breathing (three or more pauses of greater than 3 s each with less than 20 s of normal respiration between pauses), thereby making these events pathologic.

Etiology

Multiple underlying causes can result in an ALTE. The common final pathway involves an inability to control respirations, either due to local issues, systemic influences, or both. Airway obstruction may occur from secretions, refluxed material, or impinging mass. Failure of normal breathing patterns may be caused by systemic effects such as seizure, central nervous system respiratory dysfunction, or loss of normal cardiopulmonary circulation. While up to 50% of ALTEs are deemed idiopathic, common discharge diagnoses include gastroesophageal reflux disease (GERD up to 50%), lower respiratory tract infection and seizure (each approximately 10%), with cardiac disease, metabolic disorders, non-accidental trauma, and pertussis being among less common diagnoses.

Epidemiology

The true incidence of ALTE is unknown. Current estimates are based on information limited to infants brought for medical evaluation, and further are more often assessed retrospectively from discharge diagnoses. ALTE is estimated to have an incidence of 0.5–6% in the USA with similar reported rates in Austria and Italy. Median age at presentation is 3 months, although ALTE has been considered for infants up to 1 year of age. Preterm infants are more at risk, with immature control over respiratory drive. SIDS peaks at a similar time (3–5 months) with 90% occurring within 6 months of age. SIDS occurs at an incidence of 0.54 per 1,000 live births in the USA and at a rate of less than 0.2 per 1,000 births in Japan and the Netherlands.

Pathogenesis

Most recent research on the etiopathogenesis of SIDS suggests a role for 5-HTT genotypes; however, a single unifying genetic predisposition, with or without environmental trigger, has not been proven. For the clinician, metabolic diseases (such as medium chain acyl-coA dehydrogenase and very long chain acyl-coA dehydrogenase deficiencies), cardiac conduction disturbances (such as prolonged QT syndrome), and abnormalities of the pons and cerebellum are the diagnostic groups most reported in association with SIDS.

Pathology

Although deemed an abnormal event, ALTE is often due to appropriate reflexive glottic closure to avoid aspiration, or is an understandable result of a systemic stressor or local airway obstruction. True pathology specifically related to ALTE therefore lies in aberrant nervous system respiratory control. Most easily understood are the preterm infants, who have delayed autonomic brainstem maturation and parasympathetic control resulting in variable respiratory and heart rate responses to hypercarbia and hypoxia in

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and out of sleep. Preterm sleep states mature to equal those of terms infants at about 38 weeks postmenstrual age (PMA), with variability noted in some as late as 53 weeks PMA. Reports note SIDS siblings spend less time in quiet sleep while infants born to mothers who smoked during pregnancy have more awake periods and disturbed arousal processes. The relationship between control of sleep state and centrally mediated ALTE and true SIDS is however not yet completely clear.

Pathologic findings on autopsy in SIDS include external findings of frothy, blood-tinged fluid at the nares (in 50%), cyanosis, and anterior hypostatic staining suggesting face-down position. Autopsy also demonstrates pulmonary congestion and edema, thymic petechiae, and persistent hepatic erythropoiesis, all more common in SIDS cases than controls. Additional histologic findings include upper respiratory tract inflammation and focal fibrinoid necrosis of the larynx. Abnormalities of the central nervous system, particularly in the arcuate nucleus and regions of the brainstem, have also been noted on autopsy.

Clinical Manifestations: Symptoms, Signs

In addition to the general features mandated by the definition of ALTE, presentations may include evidence for specific causes as noted in *Table 238.1*.

Diagnosis

ALTE describes a chief complaint rather than a specific diagnosis. As such, no criteria beyond the definition exist for the diagnosis of ALTE itself. Rather, evaluation is directed at determining the underlying cause of the ALTE (see Differential Diagnosis, below). According to the consensus document of the European Society for the Study and Prevention of Infant Death, "there is no standard minimum work-up in the evaluation of an ALTE."

SIDS remains a diagnosis of exclusion, by definition only applicable when thorough review of clinical history, death scene, and clinical autopsy reveal no other diagnosis. In particular, metabolic disease and non-accidental trauma must be considered and ruled out in SIDS patients.

Differential Diagnosis

The differential diagnosis of ALTE is broad, and should be considered in the context of findings from the history and physical examination (*Table 238.2*).

Viral respiratory infections may cause infants to have difficulty managing secretions and may result in obstructive events presenting as ALTE. RSV may cause apnea prior to the onset of typical upper respiratory symptoms. Pertussis can also present as ALTE consisting of apneic or cyanotic episodes, with or without cough.

Apnea is a well-known presentation of seizure in infancy. Seizure accounts for approximately 10% of ALTE in various studies. Other CNS disorders including hemorrhage and hydrocephalus can present as ALTE with apnea, hypotonia, or changes in level of consciousness. Cardiac dysrhythmias, congenital heart disease, and cardiomyopathy may manifest as ALTE characterized by cyanosis, pallor, apnea, or loss of consciousness.

A thorough history and physical examination (*Table 238.1*) critically contributes to the final diagnosis in 70% of ALTE patients. In addition to these elements, these infants should, at a minimum, undergo cardiopulmonary monitoring with event recording and bedside nurse observation and documentation. Testing should be guided by findings from the initial history and physical examination. While most infants with ALTE undergo a variety of common tests, such as complete blood count, basic metabolic panel, urinalysis, and chest x-ray, it has been demonstrated that only 6% of tests performed ultimately contribute to making the diagnosis. As such, testing should be targeted toward a specific working diagnosis. Gastroesophageal reflux can be diagnosed clinically without testing, as recommended by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Upper GI should be reserved for concerns of anatomic anomalies, obstruction, or malrotation. History consistent with seizure or abnormality on neurologic exam should prompt EEG and neuroimaging. Pertussis or rapid viral PCR may help establish diagnosis of infection if positive. Concern for sepsis warrants blood, urine, and spinal fluid culture. Initial cardiac evaluation should include electrocardiogram to evaluate for dysrhythmia or ventricular hypertrophy, chest x-ray, and possibly echocardiogram based on degree of suspicion for structural heart lesion. Social work and child protection team consults, skeletal survey, toxicology labs, and ophthalmologic exam are indicated for concern for non-accidental trauma. Pneumocardiogram can establish central apnea or dysfunction of respiratory control, or aid in further delineation of events noted on the hospital monitor. In several situations, subspecialty consultation prior to ordering studies may be indicated.

Table 238.1

Signs and symptoms to elicit from the history and physical examination

History element	Consideration
Symptom detail: color (cyanosis, pallor, ruddy; peripheral/central), cough/choking, respiratory effort, position and location (prone/supine, crib), associations with feeding/febrile illnesses/environmental exposures, tone and movements during and after event, duration, interventions, recovery time	Perceived severity of event
	Swallowing dysfunction, overfeeding
	Inadequate airway development such as bronchomalacia
	GERD with associated aspiration
	Acute infectious respiratory illnesses
	Seizure
	Disruption of cardiovascular circulation
Birth history: prematurity, poor feeding	Immature respiratory drive
	Global neurologic delay
	Upper airway obstruction
Psychosocial history: family stressors, primary care provider visits, past domestic violence or referral to child protective services, drug abuse (past and current)	Non-accidental trauma
	Neglect
	Exposure to drugs
Family history: cardiac diseases, seizures, heritable disorders, SIDS, fetal demise	Seizure disorder
	Heritable disorders such as prolonged QT syndrome
	Metabolic disorder
Development, medical and surgical history: milestones, previous admission for ALTE and cause, gastroesophageal reflux disease (GERD), cardiac disease, gastrointestinal surgery, CNS disorder	Global neurologic delay
	GERD with associated aspiration
	Systemic-pulmonary vascular shunting, vascular shunt blockage
	Worsening hydrocephalus or ventricular shunt malfunction
	SIDS risk
	GI obstruction
Review of systems: feeding, weight loss, recent illness, smoking exposure, severity of past illnesses, medication use	Metabolic disorder
	Toxic ingestion
Physical examination element	**Finding**
General appearance, including facies	General state
	Airway anatomic issues
EENT	Nasal obstruction
	Oropharyngeal anomalies
Vital signs including weight for height, respiratory rate, pattern, retractions, oxygen saturation	Failure to thrive
	Signs of infection
	Cyanosis
Cardiopulmonary exam including lung auscultation, cardiac murmurs/rhythm, perfusion, hepatomegaly	Congestive heart failure
	Evidence for cardiovascular diseases
Abdominal distention, bowel sounds	Obstruction
Neurologic exam	Hypotonia/swallowing dysfunction
	Increased tone or asymmetric exam

Table 238.2
Differential diagnosis of ALTE

Idiopathic[a]	Infectious	Gastrointestinal
Often diagnosed as "Normal"	Respiratory[a] (RSV, pertussis, others)	GERD[a]
	Meningitis, meningoencephalitis	Gastric volvulus
	Sepsis	Intussusception
Cardiac	**Neurologic**	**Respiratory**
Dysrhythmias (supraventricular tachycardia, Wolf-Parkinson-White, prolonged QT syndrome, post-operative bundle branch blocks, others)	Seizures[a]	Obstructive apnea
Congenital heart disease (critical coarctation, blocked shunts, aortic and pulmonary outflow tract obstructions, others)	Oromotor dysfunction	Breath-holding spells
Cardiac contractility problems (myocarditis, cardiomyopathy)	Congenital brain malformations (Chiari Types II and III, hindbrain and brainstem)	Congenital airway malformations (laryngotracheomalacia, laryngeal clefts, others)
	Hydrocephalus with obstruction	
	Ventricular shunt malfunctions	
	Respiratory control (prematurity, central hypoventilation)	
Trauma, Toxins, Abuse	**Metabolic/Endocrine/Renal**	**Other**
CNS bleed (accidental or non-accidental)	Inborn errors of metabolism (urea cycle defects, galactosemia, fatty acid oxidation disorders, multiple carboxylase deficiency, methylmalonic aciduria, glycogen storage diseases)	Foreign body aspiration
Munchausen by proxy	Electrolyte and mineral disturbances (congenital adrenal hyperplasia, renal tubular acidosis, others)	Electrolyte disturbances, dehydration (due to inappropriate mixing of formula)
Severe Failure to Thrive (due to neglect)	Endocrinopathies (thyroid, parathyroid, others)	Anemia
Ingestions or Exposures (prescribed, over-the-counter cold preparations, accidental ingestions, smoking exposure)		Oncologic central nervous system (CNS) tumors

[a]Most common

Treatment

Although some suggest ALTE patients can be evaluated without hospital admission, current standard practice is to admit all infants for cardiorespiratory monitoring. Observation with monitoring allows for documentation of further events, which may lead to diagnosis. Given the parental anxiety resulting from ALTE, education regarding ALTE, the underlying cause if known, and likelihood of recurrence is critical. Additionally, all parents of infants admitted with ALTE should receive cardiopulmonary resuscitation (CPR) training. Specific treatment should target the underlying diagnosis. Communication and follow-up with the patient's primary care provider after hospital discharge is also central to providing ongoing education and allaying parental anxiety.

Home monitoring of infants with ALTE is controversial. If monitoring is indicated, equipment with an event recorder should be used. Parents should be educated that home monitoring has not been proven to prevent SIDS. Current national guidelines suggest it may be warranted in some ALTE patients who are at high risk for recurrent events. High-risk groups include premature infants at high risk of recurrent apnea, bradycardia or hypoxia,

technologically dependent infants, those with unstable airways, symptomatic chronic lung disease, or rare disorders of breathing regulation. Premature infants should be monitored to 43 weeks post-conceptual age or cessation of severe events.

Prognosis

Prognosis and therefore mortality for ALTE depends on the cause, with highest mortality linked to neurologic (central hypoventilation, seizures) and cardiac (dysrhythmias) causes. There seem to be no long-term effects on development for most patients, with the small number of minor neurologic abnormalities noted in the toddler period resolving by 10-year follow-up.

Recurrence of ALTE is also dependent on the underlying diagnosis. An estimated 10% of ALTE patients will have a recurrent event, with 2.5% readmitted within 30 days of discharge. It has been suggested that a diagnosis of GERD or cardiovascular condition may be a risk factor for readmission with ALTE.

An estimated 1–7% of infants who die of SIDS have a history of ALTE, with higher risk associated with two or more unexplained ALTEs. However, no firm relationship has been established between ALTE and subsequent SIDS. ALTE and SIDS differ in predominant age affected (days to 1 year versus 2–3 months), most common state during the event (awake versus asleep), and peak timing (8 am–8 pm versus midnight–6 am). Also arguing against a relationship between SIDS and ALTE is the absence of a demonstrated decrease in ALTE with interventions to prevent SIDS such as the back-to-sleep campaign.

Prevention

Prevention of ALTE relies on prevention, where possible, of potential causes of ALTE. Proper immunoprophylaxis against respiratory viruses and pertussis which may trigger an ALTE in term or preterm infants should be given. In infants prone to gastroesophageal reflux, small frequent feeds and remaining upright for a period following feeding may prevent related choking episodes presenting as ALTE.

Studies of epidemiological and physiologic risk factors for SIDS have not elucidated predictive characteristics that could be used to screen for high-risk infants. Current national guidelines recommend several interventions that have been targeted at modifiable risk factors. The back-to-sleep campaign has resulted in a decrease in the rate of SIDS but not ALTE, with some concern for increased events in infants with GERD. Avoidance of tobacco smoke exposure, during pregnancy and in infancy, is considered key in prevention of both ALTE and SIDS.

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239 Upper Airway Obstruction and Hypoventilation During Sleep

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Upper Airway Obstruction during sleep and hypoventilation or OSA/H is a common medical problem in adults, and this has now been increasingly recognized in children. It is a disorder of breathing during sleep characterized by prolonged partial upper airway obstruction and/or intermittent complete obstruction (obstructive apnea) that disrupts normal ventilation during sleep and normal sleep patterns. If unrecognized and untreated, it can lead to impaired daytime functioning as well as more serious complications, such as developmental delay, dyslipidemia, insulin resistance, and poor growth. A number of research studies on animal models and children have been very helpful in understanding not only the etiology of this condition but also the repercussions on overall health.

Epidemiology

OSA/H occurs in children of all ages, from newborns to young adults, with estimates of prevalence rates of about 2%. Although this condition spans the whole age spectrum in children, the peak incidence is in the preschool age group (2–5 years), a period when adenotonsillar tissue is the greatest in relationship to airway size. The incidence in males and females is similar in prepubertal children, which is in contrast to OSA/H in adults, where the disorder is more common in males, until about menopause in females, when the incidence increases in women. Among otherwise healthy children, obesity, upper and lower respiratory problems (e.g., chronic rhinitis and asthma), and the African American ethnicity are independent risk factors for OSA/H. For obese children in general, the severity of OSA/H correlates with the severity of obesity. Positive family history of OSA/H in other family member(s) is also a risk factor for OSA/H in childhood.

Etiology

Anatomic factors that increase resistance to airflow predispose to upper airway collapse and OSA/H. The most common anatomic predisposing condition in children is adenotonsillar hypertrophy, and more recently obesity and increasing fat in the pharynx. Many other predisposing nasal, pharyngeal, and craniofacial abnormalities occur less frequently. Even when the structure of the upper airway is normal, if coordinated activation of inspiratory and oropharyngeal dilator muscles does not occur, then children are predisposed to OSA/H. The most common functional process contributing to OSA/H is rapid eye movement (REM) sleep. Apnea frequency, apnea duration, and hypoxemia are almost always more severe during REM sleep as compared with NREM sleep. Childhood conditions associated with either anatomic and/or functional causes of OSA/H include *craniofacial abnormalities* (e.g., Pierre Robin sequence and Crouzon syndrome), genetic syndromes (e.g., hypotonia and short neck in trisomy 21), *skeletal disorders* (e.g., achondroplasia), *storage diseases* (e.g., Hunter syndrome), children with morbid *obesity* or Prader–Willi syndrome, and other *neurologic disorders* (e.g., cerebral palsy). Children with these conditions and diseases should be periodically assessed for the development of signs and symptoms of OSA/H.

Functional Pathogenesis

OSA/H occurs when there is failure to maintain upper airway patency, usually during sleep, which in turn affects blood gas homeostasis. In addition, this affects sleep architecture and results in sleep fragmentation. During inspiration, airflow is not augmented by increased negative pressure downstream, even when inspiratory pressure-generating muscles contract more forcefully. During inspiration, a negative pressure is generated within the pharynx, owing to activation of the diaphragm and intercostals muscles and mucosal adhesion forces. Collapse of the upper airway from the force of this negative pressure is prevented by simultaneous activation of the oropharyngeal dilator muscles such as the genioglossus muscle that protrudes the tongue. OSA/H occurs when an imbalance

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in these forces favors negative oropharyngeal pressures during inspiration. Upper airway muscle tone (oropharyngeal muscle) decreases during sleep, then to a greater degree during REM sleep, thus explaining the increased vulnerability of the upper airway to collapse during this sleep state. In fact, it is the combination of neuromuscular inactivation (or lack of full activation) superimposed on structural narrowing that contributes to the development of OSA/H. For example, the presence of adenotonsillar hypertrophy does not ordinarily cause airflow obstruction during wakefulness. However, decreased airway tone that occurs when a child goes to sleep, superimposed on adenotonsillar hypertrophy, can lead to significant airway obstruction. Conditions that decrease the caliber of the upper airways, such as in micrognathia, retrognathia, macroglossia, fat deposition from morbid obesity or a congenitally small midface or nasopharynx, all narrow the airways. Increased resistance from swollen nasal turbinates or choanal stenosis also predispose to obstruction. This, as well as an increase collapsibility or an alteration in neural control of the upper airway or central ventilatory drive, contribute to the development of obstruction. Episodes of partial or complete airway obstruction result in impaired gas exchange with hypoxemia and hypercapnia. This impaired gas exchange in conjunction with decreased airflow is potent stimuli for increased ventilatory effort and upper airway muscle activity leading to arousal. Arousals may appear in the form of movement or changes in the electroencephalogram (EEG). Following arousal, airflow is restored, blood gases are normalized, and sleep resumes, but the cycle of airway collapse starts again. Compared with adults with OSA/H, fewer cyclic arousals are seen in children in spite of continued hypoventilation and blood gas disturbances throughout the night. This may, in part, explain the relatively low incidence of daytime sleepiness in young children with OSA/H. Another difference from OSA/H in the adults is that there is usually not a complete obstruction in children with OSA/H, although the partial obstruction results in potentially significant blood gas abnormalities. Children with central nervous system abnormalities associated with impaired ventilatory or arousal responses to hypoxemia, hypercapnia, and/or airflow obstruction (e.g., Chiari II malformations) or children with sedative medication or general anesthesia have increased vulnerability to severe OSA/H.

The development of OSA/H can have serious cardiorespiratory and neurobehavioral consequences. Chronic hypoxemia can lead to polycythemia, growth failure, increased pulmonary artery pressure and pulmonary hypertension. Recurrent arousals can lead to sleep fragmentation, loss of normal sleep patterns, and excessive daytime sleepiness. Importantly in children, OSA/H has been associated with daytime sequelae, including inattentiveness and hyperactivity, behavioral problems, and impaired school performance. Indeed, often when the OSA/H is corrected, children hyperactivity is reduced or eliminated and school performance improves.

Clinical Manifestations

A number of common clinical manifestations of OSA/H include snoring and restlessness during sleep with or without frequent awakenings. Children may sleep in unusual positions to help maintain a patent upper airway, for example, with the neck hyperextended. Typically, loud snoring is the symptom that most disturbs and alerts the parents. Mouth breathing is also common among children. However, most children with OSA/H breathe normally while awake.

Habitual snoring, the most common symptom of OSA/H, ranges from 3% to 12% in children. However, it is important to realize that not all habitually snoring children have or are at risk for the development of OSA/H. The spectrum of severity (ranging from snoring to congestive heart failure, which is rare) is related to the degree of upper airway obstruction or presence of hypoxemic episodes. However, because of a more subtle presentation in children than in adults, children often have an unexpected degree of airway obstruction, impairment of gas exchange, and sleep disturbance that is difficult to predict from the clinical history and physical examination alone. Children with the more severe presentation also have noisy, mildly labored awake breathing that clearly worsens with sleep. As described above, parents usually describe the child's sleep as paced with cyclical snoring which becomes louder and louder, followed by silence, a snort, an arousal, and resumption of snoring. When snoring is associated with nocturnal breathing difficulties such as respiratory pauses and snorts and repeated arousals, these symptoms are highly suggestive of OSA/H in children. However, some children with serious OSA/H have minimal noisy breathing, and diagnosis depends on the physician's high index of suspicion.

Some of the less common symptoms include daytime hypersomnolence resulting from sleep fragmentation that occurs with OSA. Poor school performance is increasingly recognized as being associated with OSA/H. There is debate as to whether these neurocognitive deficits are the

result of a poor night's sleep secondary to frequent arousal and hence inability to concentrate in school or the result of hypoxemia that occurs during sleep in these children.

Clinical examination features associated with OSA/H include dysmorphic facies, mouth breathing, hyponasal speech, macroglossia, cleft palate, or enlarged tonsils. A pectus excavatum deformity can develop in long-standing upper airway obstruction. Morbid obesity mechanically loads the chest wall and narrows the upper airway, but OSA/H is not a consistent feature of obesity. Although rare, excessive somnolence in some children can occur during the physical examination, and this requires urgent evaluation.

Diagnosis

The diagnosis is often delayed for several reasons: (a) absence of awake symptoms; (b) a sleep history is not obtained; (c) symptoms of snoring are considered benign or inconsequential; and (d) young children may not generate the loud snoring noises similar to those in the adult. Parental reports of habitual snoring should be investigated. A sleep and breathing history is mandatory for any child with a medical condition that is at risk for OSA/H, especially trisomy 21, craniofacial anomalies, achondroplasia, or other neuromuscular disorders.

OSA/H cannot be diagnosed from clinical history alone. Snoring, reports of difficulty breathing, and enlarged tonsils are not necessarily reliable indicators of the presence or severity of OSA/H in children. Furthermore, the physical examination may be entirely normal and cannot exclude OSA/H when the clinical history suggests otherwise. Pulse oximetry is insensitive because of the shape of the O_2-dissociation curve. An overnight recording of multiple physiologic sensors during sleep (Polysomnography or PSG) is considered the gold standard for the diagnosis of OSA/H. PSG is especially useful in confirming the diagnosis, in determining the severity of OSA/H, and in documenting the efficacy of treatment. PSG in children, especially very young or special needs children, requires skilled, well-trained, child-friendly sleep technicians in family-centered environments. However, PSG may not be required for diagnostic purposes in all patients, especially when the diagnosis is rather clear. For example, PSG may not be necessary when a child has noisy, awake mouth breathing, and tonsils that occlude most of the pharyngeal space; is excessively sleepy; and is observed by skilled personnel to have signs of airway obstruction and hypoxemia. PSG is useful in (a) establishing the diagnosis when the clinical manifestations are not conclusive as above; (b) confirming the presence and severity of airflow obstruction, especially in patients undergoing surgery since prior knowledge of severity can help determine the appropriateness of outpatient surgery versus overnight in-hospital observation; (c) determining the optimal level of CPAP needed to manage OSA/H; and (d) children considered "high risk" such as children with morbid obesity, craniofacial anomalies, and genetic disorders. Laboratory findings may include polycythemia and respiratory acidosis with a metabolic alkalosis, especially in those children when hypoxemia extends to wakefulness. Right ventricular hypertrophy on electrocardiography and dysfunction on echocardiography are seen only in severe OSA/H. A lateral soft tissue radiograph of the neck can identify adenoidal tissue.

Several disorders should be considered in the *differential diagnosis* of OSA/H or may coexist with this problem. Breathing difficulty associated with nocturnal asthma or upper airway obstruction from gastroesophageal reflux may be confused with OSA/H. Stridor caused by anatomic airway problems, such as laryngomalacia, vascular ring, intraluminal masses, and vocal cord dysfunction, should be considered.

Treatment

Adenotonsillectomy is the most common therapy for OSA/H in children with adenotonsillar hypertrophy. However, the treatment for a particular child depends on the underlying abnormalities, the site of obstruction, and the presence or absence of contributing neurologic or functional abnormalities. When adenotonsillar hypertrophy is present, the majority of otherwise healthy children without major risk factors experience resolution or significant improvement after adenotonsillectomy. Children with severe OSA/H who benefit from surgery often demonstrate "catch-up" growth. However, children with underlying problems, such as trisomy 21, craniofacial disorders, and extreme obesity, or who present before 2 years of age are at risk for incomplete resolution of OSA/H after adenotonsillectomy. Even without these risk factors, the parents and physicians of children who have had adenotonsillectomy should be aware that either persistent or recurring symptoms of OSA/H need reevaluation, including reassessment for adenoidal regrowth and possible need for repeat adenoidectomy or other treatments.

Medical management with nasal CPAP is an option in children in whom adenotonsillectomy fails, thus avoiding

the need for tracheostomy. PSG is required to select the appropriate pressure level to relieve obstruction. CPAP should not be the first-line treatment when adenotonsillar hypertrophy is present, and there are no absolute contraindications to surgery. CPAP can be useful in the obese child in whom weight loss is desirable but difficult to achieve. Supplemental oxygen may relieve the hypoxemia associated with OSA/H but is clearly insufficient to address the underlying obstruction and hypoventilation. Treatment of nasal obstruction with topical nasal steroids can reduce snoring and OSA/H severity in some children awaiting surgery. Steroids and antibiotics may be useful adjunct in the acute management of infected pharyngeal tissues that have compromised upper airway patency.

If severe upper airway obstruction is present in both wakefulness and sleep, then tracheostomy is the treatment of choice, particularly when vocal cord dysfunction, impaired swallowing, or absent laryngeal protective reflexes exist. Tracheostomy may be necessary for severe OSA/H complicated by cor pulmonale when CPAP is unsuccessful or not tolerated.

There is increasing pediatric experience with treatment by mandibular distraction osteogenesis as an alternative to long-term tracheostomy. Definitive maxillomandibular reconstructive surgery for children with craniofacial disorders is another therapeutic option but is usually postponed until facial growth is complete. Pediatric experience with uvulopharyngoplasty has been limited to children with muscular hypotonia and oropharyngeal tissue redundancy, but no controlled studies using objective measures of efficacy have been performed.

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240 Primary Ciliary Dyskinesia

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Primary ciliary dyskinesia (PCD) comprises those respiratory disorders having in common the malfunction of airway cilia. The abnormality in PCD results from inherited primary structural defects in the cilia that lead to repeated and chronic lung and sinus infections. The ciliary malfunction in PCD is not a result of acquired repeated pulmonary infections, conditions in which the ciliary abnormalities revert to normal, unlike in PCD. About 50% of patients with PCD have *Kartagener syndrome*: situs inversus, chronic sinusitis and otitis, and airway disease leading to bronchiectasis. Approximately 25% of patients with situs inversus have PCD.

Normal Structure and Function of Cilia

Cilia are finger-like structures that extend from the epithelial membranes into the lumen of airways. They have a diameter of ¼ μ and a length of ~300 μs. On each epithelial cell in the airway, there are about 200 cilia. Each cilium has different parts such as a *trunk*; a *basal body*, where the cilia attach to the cell; and a *crown*, which is a specialized structure presumed to be important in cilia attachment to mucus for its movement. The trunk of each cilium is made of an outer cell membrane and axonemes or cytoskeletal protein structures. The latter form a circular array of nine microtubules in pairs with an additional central pair (9 + 2 structure). Each peripheral pair attaches to the adjacent one via dynein arms. Spokes are also cytoskeletal proteins that join peripheral and central microtubules. Airway cilia are located on cells in the nose, sinuses, ears, and airways. The density of cilia varies with location, with the majority of cells (50–80%) in the large airways having cilia, far fewer cells in the lower airways having cilia, and with no cilia in alveolar cells. The frequency of ciliary beating (*beatquency*) is 1–20 Hz, with the higher beatquency occurring in the larger airways.

In humans, there are at least six types of cilia: airway, ventricular, embryonic, olfactory, photoreceptor, and sperm flagellum. Whereas the embryonic and photoreceptor cilia contain nine microtubular doublets and no central singlets (9 + 0 structure), the other types of cilia share the peripheral structures (nine microtubular doublets) with two central singlets (9 + 2 structure). Although various cilia are present in various parts of the body, their function is related to propelling fluid. For example, airway cilia propel mucus in the airways; ventricular cilia are located on the ependymal lining of the brain ventricles and propel cerebrospinal fluid (CSF). Embryonic cilia are located in the embryonic node and presumed to propel morphogens and establish, at this early stage, a morphogenic gradient that is crucial for the development of embryonic sidedness. Abnormal ciliary function and structure lead to disease conditions: an association between ciliary dyskinesia, hydrocephalus, and mental retardation in four male siblings in a Jordanian family has been reported and might be caused by a mutation that affects pulmonary toilet and fluid movement in the lung and CSF. Abnormal embryonic nodal cilia result in situs inversus.

At the outset of the beating cycle, cilia bend at the base and move backward, perpendicular to the surface. Subsequently, they extend ("slide") while rotating in a forward motion. These movements, which are clockwise three-dimensional rotations, are made possible by adenosine triphosphate (ATP) hydrolysis and the dynein arms, which are ATPases. When visualized under microscopy, airway cilia are seen to coordinate their activity regionally, and *waves of ciliary movements* (many cilia together) occur. How the coordination of ciliary movements is achieved not only within a cell but across cells on the surface is not well understood.

The main function of airway cilia is to transport, through its beating movements, mucus toward the mouth. The effectiveness of this function depends on the beatquency, the composition and thickness of the periciliary fluid and mucous layer above it, and the coordination of ciliary movements. There are a number of neurochemicals that modulate ciliary beating by increasing beatquency, such as β-adrenergic compounds, bradykinins, and serotonin. Alternatively, lowering airway humidity significantly lowers the frequency of ciliary beating. In addition, increasing bacterial loads decreases its beatquency.

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Abnormal Cilia

It is estimated that there are >250 polypeptides in the ciliary structure and primary ciliary dyskinesia is most likely based on the absence of one or several ciliary cytoskeletal proteins that can affect the motion and/or the beatquency of the cilia. The structural abnormalities of these disorders can be observed and detected with electron microscopy. Ciliary ultrastructual changes in PCD include the lack of dynein arms, microtubular transposition, compound cilia, random ciliary orientation, abnormal length of cilia, radial spoke, and nexin link defects. It is important to differentiate transient ciliary defects involving only a subset of cilia (such as acute and chronic respiratory inflammation) from true congenital defects. In classical PCD, there is an *absence of both inner and outer dynein arms*, resulting in a complete dynein arm defect. *Partial dynein arm defects* (in which either inner or outer arms are not visualized) or *defects in central doublets* are generally not associated with situs inversus and appear to occur as isolated genetic abnormalities. *Radial spoke defects* are much more difficult to visualize but are generally considered to be a legitimate entity in this spectrum of ciliary abnormalities. *Random ciliary orientation* is when the sole ultrastructural defect is that the central doublets are arranged in a random orientation. Ciliary motility studies have shown that structural defects and findings may not correlate with function. For example, cilia from patients with Kartagener syndrome are immotile. By contrast, single arm defects may show coordinated movement, although ciliary beatquency will be slower than normal. Random axis orientation of cilia results in uncoordinated random movement.

Genetics

Estimates of PCD prevalence range from 1/15,000 to 1/60,000 live births. It is probably the third most common form of inherited chronic airway disease of Caucasian children, after cystic fibrosis (CF) and genetic immunodeficiency states. Cases have been reported from multiple ethnic and racial groups including populations from Japan, China, and northern Africa. The inheritance pattern of most PCD cases is autosomal recessive, although there are reported cases of autosomal dominant or even X-linked modalities. The prevalence and the pattern of inheritance are most likely not as well appreciated (and underestimated) since only a few mutations have been discovered and there are a great many patients that still belong to an "idiopathic" category of chronic lung disease.

A number of genes have been hypothesized to be at the basis of PCD. *DNAH5* is an axonemal dynein heavy chain gene localized on chromosome 5p (5p14–5p15). This gene is very long (79 exons) and codes for a protein of 4,624 amino acids. It is expressed in lung and kidney and, to a lesser extent, in brain and testis. Several homozygous and heterozygous mutations were found in PCD families. A number of individuals in these families also had situs inversus. *DNAI1*, another gene on chromosome 9 (9p13–21), is highly expressed in trachea and testis and is a long gene, with 20 exons. It encodes for an intermediate chain found in the outer dynein arms. Several other mutations in other PCD families have also been found, such as substitution of conserved bases and deletion of base pairs in exons. A third gene (*DNAH11*), which also encodes a heavy chain dynein in the outer arm, maps to the seventh chromosome (7p21) and has been associated with PCD.

Clinical Manifestations and Diagnosis

Individuals with PCD may start having symptoms in early life. They often have unexplained respiratory distress during the newborn period with nasal congestion, rhinitis, and cough. The disease is so varied that these patients may survive to adulthood without overt chronic sinusitis, ear infections, and airway disease symptoms. The most common complaints and symptoms in children are related to a productive cough, sinusitis, and otitis. A feature that is helpful in differentiating PCD from CF is repeated bouts of acute otitis media. Nasal polyps or clubbing is present in ≈20% of patients. Many children with PCD experience frequent wheezing and have an initial diagnosis of asthma. The hallmark symptom is a chronic, often loose or productive cough. Pneumonia may supervene, and lower respiratory tract disease can progress to weight loss, diminished exercise tolerance, and bronchiectasis. Respiratory failure is uncommon as are lung complications such as pneumothorax and hemoptysis in childhood, but lobar atelectasis occurs frequently. Males are frequently infertile (abnormal sperm flagella) and display absent or poor sperm motility; females are at increased risk for ectopic pregnancy.

PCD should be suspected in children with chronic or recurring upper and lower respiratory tract symptoms, especially in the presence of substantial middle-ear disease. Pulmonary function testing of older children yields a typical obstructive pattern. Radiographic or CT imaging is very useful as it shows often the involvement of the paranasal sinuses. Chest radiographs may demonstrate overinflation, bronchial wall thickening,

and peribronchial infiltrates and often atelectasis and consolidation. Bronchiectasis is a late manifestation and is best detected by CT scanning. The presence of a right-sided heart (situs inversus) in a child with chronic respiratory tract symptoms is virtually diagnostic, but this configuration occurs in only 50% of these patients.

Scrapings or brushings of nasal mucosa can be examined directly by light or, preferably, by phase-contrast microscopy for evidence of motility. In most PCD tissue specimens, little or no ciliary motion is seen. *The gold standard* is documentation of abnormal structural elements, such as missing *dynein* arms or random orientation of cilia in nasal or bronchial biopsies or scrapings on electron microscopic examination. To avoid confusion with acquired ciliary changes, mucosal specimens should be obtained after an acute respiratory tract infection by at least 2–3 weeks since some structural abnormalities are also observed after injury to ciliated epithelial cells by viral infection. Ultrastructural evaluation should be reserved for highly suspicious cases. Of interest is that exhaled nitric oxide (NO) is markedly *decreased* in patients with PCD as compared with patients who do not have PCD, particularly those with cystic fibrosis, idiopathic bronchiectasis, sinusitis alone, and normal controls. A low NO measurement may not be diagnostic, but a high level suggests a disease other than PCD.

Treatment and Prognosis

Therapy is mostly symptomatic. Chest physiotherapy assists the clearance of mucus and antibiotics should be prescribed for evidence of infection of sinuses or lower airways. The choice of antibiotics is best dictated by identification and sensitivity testing of pathogenic organisms. Oral antibiotic administration and bronchodilators can be effective. Children should be examined several times each year and followed by periodic chest radiographs and serial pulmonary function testing. Sinus and middle-ear symptoms refractory to medical therapy deserve consultation with an otolaryngologist. Surgical intervention may be helpful in selected cases. Prevention of lung infection by measles, pertussis, influenza, and, possibly, pneumococcal vaccines is highly desirable. Avoidance of cigarette smoke and other airway irritants is important. Progression of lung disease appears to be much slower for patients with PCD than for those with CF. With proper treatment, disabling lung disease can often be avoided for long periods. A normal life span is possible.

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241 Inhalation Lung Injury

Erin R. Stucky

Definition/Classification

Inhalation lung injury is that induced by inhalation of irritant particles or gases, resulting in airway damage and respiratory compromise. The focus of this chapter is on acute exposure. Although fungi can produce microbial volatile organic compounds (VOC) resulting in irritant symptoms, most effects are due to hypersensitivity pneumonitis from chronic exposure, which is beyond the scope of this chapter.

Etiology

Inhalation lung injury may be caused by small and large particle or gas exposure. Although most exposures are accidental, preteens and teens may purposefully inhale paint, gasoline, and other toxins. The most common pediatric inhalation exposures are chlorine gas (chlorine bleach, industrial accidents, and swimming pools), silica particles, grain and fertilizer dust, hydrocarbons, and wood smoke.

Manufacturing accidents may expose children to elements such as sulfur and chlorine. Copper, zinc, and iron dust on roads from brake wear as well as diesel emissions containing elemental carbon, hydrocarbons, trace metals are causes of chemical pneumonitis noted worldwide. Less common but of great concern are exposures of children to weapons used in warfare such as mustard gas.

Epidemiology

Exposure types vary by development (urban vs rural) and country. Silica particles in cosmetics and cleaning substances combine to represent almost 20% of all poison control calls in the United States. Common urban exposures include smog and lead whereas pesticides and crop particulate dusts are more common in agricultural areas. Wood smoke as well as high viscosity (such as paraffin oil) and low viscosity (such as gasoline) hydrocarbon exposures are seen worldwide. Kerosene lung injury is the most commonly reported hydrocarbon exposure in developing countries. Children may be exposed as a single acute event, or chronically which can lead to different lung pathology.

Pathogenesis

Most acute inhalant injury is due to the inciting agent; however, host response may have an effect on outcome. Atopic children respond to toxic inhalation exposure with increased Immunoglobulin E release, mast cell degranulation, and cytokine-induced inflammation. In animal models, exposure to common gases is associated with increased proinflammatory cytokine, mucus production, and lung airway hyperreactivity. There is some information to suggest that this can be reversed by action of short inhibiting RNAs (siRNAs). Other animal studies are on the protective effect of nitric oxide synthase on acute lung injury. Both of these findings may be models for future research in humans.

Pathology

Water soluble compounds are absorbed by the nasal passages and trachea, where less soluble particles travel to the alveoli and cause distal damage. Particle size is also important in determining the distribution of damage, as small (0.5–3 μm) sized particles travel more readily to the alveoli. For gases, lower viscosity compounds diffuse more widely and cause more damage. Lung injury is the result of recruitment of neutrophils, airway inflammation, mucus production, protein leakage, and macrophage and bronchiolar cell death. Within 24 h, plugs of mucus, fibrin, and cellular debris can obstruct first larger and then smaller airways. Studies from more significant toxins such as mustard gas demonstrate glutathione depletion and free radical generation.

Secondary bacterial pneumonia is not commonly seen in most pathology specimens. It may be seen in up to 90% of smoke inhalation patients, however, usually at 1–2 days after the initial insult. Other abnormalities on biopsy such

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as pulmonary fibrosis, giant cells, and non-necrotizing granuloma formation should raise suspicion of subacute or chronic toxin exposure.

Clinical Manifestations

Signs and symptoms of inhalation injury are both general and source-specific. Symptoms usually present within a few hours but may be delayed up to 3 days postexposure.

Common manifestations include cough, tachypnea, abnormal oxygen saturation (<90%), nasopharyngeal congestion with secretions, and may progress to stridor, rales, wheezing, and more significant upper and lower respiratory distress or failure. Young children may vomit, and often have both ingested and inhaled the irritant. Fever presenting within a few hours is usually secondary to inflammation whereas that developing within several hours to 1–2 days is more likely due to secondary infection. Hypoxemia and pulmonary function may worsen after 24 h as airways fill with debris. Lethargy is more common than irritability for all age groups.

Specific signs may be noted with smoke exposure such as ash and residue on lashes and in nostrils. Hemoptysis is occasionally seen with more caustic basic elements and gases. Older children may also complain of chest pain or headache from carbon monoxide toxicity. Hydrocarbons are often ingested and inhaled, and therefore vomiting and eructation may have an accompanying odor.

Diagnosis

Although there are no specific international guidelines for diagnosis, American and European toxicology associations agree that fever, hypoxemia, interstitial infiltrates on chest imaging, decreased CO-diffusing lung capacity (DLCO), and negative bronchoalveolar lavage (BAL) cultures are the hallmarks of inhalation lung injury. In most cases, DLCO and BAL are not performed, and diagnosis is made based on history of or suspicion for relevant exposure, physical examination, and chest x-ray. Common supportive studies are noted in *Table 241.1*.

Table 241.1
Common findings in inhalation lung injury

Study	Typical finding
Chest x-ray	May be normal initially; bilateral interstitial infiltrates, most often lower lobes; pulmonary edema
Chest CT	As in chest x-ray; diffuse airspace disease
Blood gas	Hypoxemia greater than hypercarbia
Complete blood count	Leukocytosis
Basic chemistries	Metabolic acidosis
Advanced studies	**Utility**
Bronchoscopy with lavage (biopsy in rare cases)	Grading extent of mucosal damage; bacterial cultures to rule out infection; pulmonary toilet (burn patients); biopsy evidence for chronic exposure
Carboxyhemoglobin or rapid CO breath analysis (if available)	Assess for carbon monoxide poisoning

Differential Diagnosis

Children almost always present with a history suggestive of acute inhalant exposure. Differential diagnoses in unclear cases include infectious pneumonias, pulmonary hemorrhage, pulmonary embolism, aspiration pneumonia/pneumonitis, pulmonary contusion, or occasionally systemic cholinergic effects from ingested mushrooms. The time course for evolution of inhalant lung injury may help support this diagnosis. Resolution of symptoms may occur in cases of mild exposure in as little as 8 h. A chest x-ray may demonstrate diminished infiltrates within this time frame in contrast to aspiration and pulmonary hemorrhage that take 24 h or longer to improve. Differential diagnosis of subacute or chronic inhalant lung injury is beyond the capacity of this chapter but in brief includes mycobacteria pneumonia, autoimmune diseases, and other forms of interstitial pneumonia.

Treatment

Patients who are asymptomatic after an exposure still require monitoring for 6–8 h to assure no evolution of symptoms. Both the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists state gastric lavage is contraindicated due to aspiration risk. Immediate care is focused on decontamination and control of the airway (*Table 241.2*). Healthcare workers should wear protective gear to prevent self-contamination. Oxygen should be

Table 241.2
Common therapies for inhalation lung injury

Treatment	Indication
Clothing removal; bathing	Decontamination; repeated washing may be indicated for toxins with potential for significant skin absorption
Oxygen to keep saturation >90%	Hypoxemia
Beta-agonist	Bronchospasm
Steroids (inhaled, systemic)	Controversial; decrease airway and systemic inflammation
Intravenous fluids, nutrition	Hydration to meet increased insensible losses; significant electrolyte imbalance and nutritional deficiencies can be seen in burn victims
Bed rest	Decrease metabolic demand
Antibiotics	Positive BAL bacterial culture; may be used empirically in some severe burn victims

given to maintain normal saturations obtained by an appropriate monitor. Worldwide, access to saturation monitoring is inconsistent, limiting critical use of oxygen therapy.

Nebulized heparin combined with the mucolytic agent N-acetylcysteine has been used in some centers for burn patients to improve pulmonary function and decrease the incidence of re-intubation. Noninvasive positive pressure ventilation or intubation should be provided to support non-cardiogenic pulmonary edema. However, autopsy results suggest pressure may cause mucus to be pushed into the lower airways and delay mucus transport out of the smaller bronchioles, increasing risk of secondary pneumonia.

Routine early antibiotic or steroid use is not recommended for hydrocarbon inhalation exposures. Published data from the United States, France, India, Israel, and other countries, however, suggest the use of antibiotics in up to 40% of these patients. The high rate of pulmonary bacterial superinfection of burn patients mandates prompt treatment covering typical ventilator-associated organisms and nosocomial pathogen.

Antidotes for specific exposures are limited but may include inhaled bicarbonate for chlorine gas exposure and 100% oxygen for carbon monoxide poisoning. These therapies should be managed in consultation with a toxicologist and pulmonologist whenever possible.

Follow-up care for patients requiring more than transient inpatient respiratory support should include chest x-ray to demonstrate resolution of infiltrates and pulmonary function testing at 1 month post insult.

Prognosis

Young children are at greater risk for inhalation lung injury than adults due to the increased respiratory rate and immature lung development and immune systems. Short-term outcomes are worse for patients presenting with significant hypoxemia and in those with underlying pulmonary disease or atopy. Secondary pneumonia is reported to occur in as many as 60% of intubated burn patients and leads to prolonged inpatient stay. Increased morbidity and mortality in smoke inhalation burn victims is associated with greater thermal airway burn and acute respiratory distress syndrome (ARDS).

Wheezing and increased work of breathing with exertion are commonly noted for 1–3 weeks after exposure to most inhalants. Bronchiectasis and chronic lung disease have been reported in children in particular with chlorine and smoke exposure. A concern for the impact of cytokine induction on development of cancers has also been recently raised; however, the impact of inhalant lung injury on development of future cancer is not clear.

Prevention

Toxin avoidance should be part of all well child healthcare visits. Clinicians should ascertain risk of agriculture, manufacturing, airborne pollutant, and roadway exposures and counsel accordingly. Adequate ventilation is necessary when using an enclosed fireplace or kerosene heater. Chemical cleaners, lamp oils, and cosmetics should be kept out of reach of children, preferably in a locked cabinet. Preteens and teens should be educated on inhalant risks.

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242 Pulmonary Complications of Bone Marrow Transplant

Julie Ryu

Pulmonary Complications of Bone Marrow Transplant

As the technology for bone marrow transplant (BMT) improves, the indications for transplant continue to grow beyond the usual realm of oncology. This section will address some of the pulmonary complications that can arise from bone marrow transplant. Although there are now a number of types of bone marrow transplant including autologous, allogeneic, and stem cell varieties, this section will not address the complications that can arise within the subtypes of bone marrow transplant but address the complications that can arise within the respiratory system as a whole. Pulmonary complications can be categorized within the timeline of the BMT, as pre-engraftment and post-engraftment phases.

Pre-engraftment Complications

The pre-engraftment phase is the phase within the first 2 months after BMT. Respiratory complications during this period are usually due to impaired mucosal barrier function created by immunosuppressive and radiation therapy that may have been given prior to BMT to improve engraftment especially in allogeneic bone marrow recipients. *Pulmonary edema* is common, especially soon after BMT, and may be precipitated by a number of factors. In addition to any decreased mucosal barrier function, aggressive hydration, parental nutrition, infection, cardiac dysfunction (from anthracyclines), and impaired renal function may all contribute to the development of pulmonary edema. Pulmonary edema can also facilitate the development of respiratory distress syndrome or a non-infectious idiopathic pneumonia syndrome. *Idiopathic pneumonia syndrome* occurs in about 5–10% of adults undergoing BMT and the diagnosis is made only after bronchoalveolar lavage (BAL) is negative for bacterial, viral, and fungal cultures. This pathologic process can occur as an interstitial pneumonia or of diffuse alveolar injury. The incidence of idiopathic pneumonia is highest around 2 weeks after transplant but can also present after 6–7 weeks. While the causes for idiopathic pneumonia are unknown, they may be related to the preconditioning chemotherapy or an immune response to an allogenic transplant. Treatment for idiopathic pneumonia is supportive.

Another pulmonary complication that can occur during the pre-engraftment phase is a *diffuse pulmonary hemorrhage*. Fortunately, this complication occurs less frequently in children than in adults but is associated with a high mortality rate. These patients are more often recipients of allogeneic BMT and present within the first month after BMT. These patients present with sudden and progressive dyspnea, hypoxia, and crackles. On bronchoalveolar lavage, frank blood can be seen along with neutrophilia on cell count despite being neutropenic on a peripheral complete blood count. Treatment for diffuse alveolar hemorrhage consists of supportive care and systemic steroids.

Pulmonary and hepatic veno-cculusive disease can also present during the pre-engraftment phase. This condition affects children and is associated with intimal fibrosis. While fibrinolytics can be used, the pathophysiology is still unclear and current treatments options may not be effective.

Post-engraftment Complications

Approximately 10–20% of all children who receive BMT develop long-term pulmonary complications. The most common pulmonary complication is chronic lower airway obstruction. *Bronchiolitis obliterans* (BO) is a disorder that presents with dyspnea, cough, and/or exercise intolerance. It is characterized by lower airway constriction that does not respond to bronchodilators. The pathophysiology of this disorder is still unclear but risk factors include chronic graft-versus-host disease, early post-transplant viral infection and advanced age of the

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recipient. BO generally presents about 1–2 years after BMT but can occur as early as 90 days after transplant. While the symptoms are not specific for BO, pulmonary function testing, imaging studies, and/or lung biopsy can make the diagnosis. High resolution CT scans demonstrate a heterogeneous pattern of areas of hyperaeration with bronchial dilation along with areas of hypoaeration with increased density or "mosaic perfusion." On lung biopsy, BO is characterized by bronchial submucosal and peribronchial fibrosis that results in lumen narrowing and obliteration of the bronchioles and small bronchi. Airflow obstruction is seen on pulmonary function testing with a decrease in FEV_1 and FEV_1/FVC ratio. Immunosuppression is the main treatment for BO. Steroids, calcinuerin-inhibitors, azathiprine, and macrolide antibiotics are often used as treatment options to augment immunosuppression but steroids are often ineffective. While BO is generally seen as a steroid non-responsive condition, inhaled steroids may alleviate some symptoms without improving pulmonary function testing. In addition, infliximab, a tumor necrosis factor alpha (TNFa) blocker also shows some promise in slowing the decline in pulmonary function associated with BO.

Restrictive lung disease can also present as a long-term complication of BMT. Unlike the patients with obstructive disease, patients with restrictive disease are usually asymptomatic and are only discovered on routine pulmonary function testing. Some contributing factors include infection and pulmonary veno-occlusive disease. *Pulmonary veno-occlusive disease* usually occurs during the pre-engraftment phase but can extend into the post-engraftment phase and can result in pulmonary hypertension and pulmonary edema which contribute to the restrictive process. The most common cause for restrictive lung disease are cytotoxic drugs and irradiation. The most common offending agents include alkylating agents such as cyclophosphamide, methotrexate, busulfan, and CCNU/BCNU.

Bronchiolitis obliterans with organizing pneumonia (BOOP) is now referred to as *cryptogenic organizing pneumonia* (COP). Unlike BO, COP is a restrictive process that responds to steroid therapy. COP differs from BO in that it is characterized by a mild to moderate inflammatory process with polypoid plugs of loose organizing connective tissue in the alveolar ducts and bronchioles. Imaging studies reveal patchy infiltrates on CXR and a restrictive pattern on pulmonary function testing. Infectious etiologies should be ruled out since they can present similarly to COP.

Table 242.1
Common infectious organisms associated with BMT

Pre-engraftment: Usually not respiratory infections	Post-engraftment
Fungal: *Candida* *Aspergillus*	Fungal: *Aspergillus* *Pneumocystis* pneumonia (PCP) *Mycobacterium tuberculosis*
Bacterial: Gram negative: *Pseudomonas* Gram positive: *Staphylococcus aureus, Streptococcus viridians, Enterococcus*	Bacterial: Similar to pre-engraftment organisms *Legionella*
Viral: Herpes simplex virus	Viral: Cytomegalovirus (CMV) Varicella zoster virus (VZV) Adenovirus Epstein–Barr virus (EBV)

Infections

Bronchoscopy with alveolar lavage can be very helpful in identifying organisms that cause pneumonias post-BMT. The procedure is minimally invasive and can be performed to identify an organism. However, the ability to detect a bacterial organism in a bronchoalveolar lavage (BAL) sample decreases inversely with time on antibiotics. A lavage should be done to differentiate a BOOP from an infectious pneumonia. In addition, a BAL can be helpful in detecting fungal and pneumocystis pneumonias (PCP). See *Table 242.1* for a list of organisms classified into pre- and post-BMT.

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243 Near Drowning and Drowning

Matthew S. Wilder · Erin R. Stucky

Definition/Classification

The nomenclature of drowning has long been a source of debate and confusion. In an attempt to solve this problem, the World Congress on Drowning convened in 2002 and developed guidelines for the definition of drowning. Drowning is defined as "a process resulting in primary respiratory impairment from submersion/immersion in a liquid medium." In addition, terms that have previously been confusing, such as "near drowning," "wet drowning," "dry drowning," and "secondary drowning" should not be used, and the term "drowned" should be reserved for those persons who die from drowning.

Epidemiology

Seventy-five percent of the earth's surface is water, making it one of the most common sources of environmental injury to humans. Consequently drowning has been a cause of unintentional injury and death across all continents, especially in children. Drowning causes substantial morbidity and mortality that varies with location, age group, activity, and type of body of water.

According to the World Health Organization (WHO) Global Burden of Disease estimates that 175,000 children under the age of 20 years died in 2004 worldwide as a result of drowning. Approximately 98% of these deaths occurred in low and middle-income countries. Fatality rates also vary worldwide, from less than 1% in high income European countries to over 10% in low-income countries of the Western Pacific Region including China, Philippines, and Vietnam. In developed countries the age distribution of fatal drowning is bimodal, peaking in toddler and adolescent years. Studies in specific countries reveal that drowning is the leading cause of injury death in children age 1–2 years in the USA and 1–9 years in Bangladesh. Worldwide, the fatality rate for boys is approximately twice that of girls.

In the USA, racial disparities have been noted with higher rates of drowning reported in black male children. Infants are more likely to drown in baths and buckets, 1–4-year-olds in swimming pools, and older children and adolescents in natural bodies of water such as ponds, lakes, rivers, and beaches. Activities associated with teen drowning include boating, swimming, and diving. Alcohol and illicit drug use are also associated with an increased risk of teen drowning.

Pathogenesis

Although there is no direct pathogenetic association with drowning, increased incidence is seen in certain medical conditions. Children with mental or physical handicaps are at increased risk, as they may not adhere to water safety instructions and require extra supervision. The risk for drowning in those with seizure disorders is estimated at 4–14 times that of other children. In contrast to these children where the known underlying state is a precursor to drowning, it is thought that children with certain genetically determined dysrhythmias have their cardiac event subsequent to submersion. Specific channelopathies have been reported in association with submersion-induced syncope or cardiac arrest. Often the drowning event was the first presentation of the underlying prolonged QT abnormality or catecholaminergic polymorphic ventricular tachycardia.

Pathophysiology

The sequence of events that lead to drowning has been well described in both animal models and humans. A drowning episode begins upon submersion/immersion. Initially, there is a period of panic, struggle to stay above water, and voluntary breath-holding. However, hypercarbia and hypoxia eventually drive an involuntary gasp of air. If water is aspirated, laryngospasm may occur, causing further ventilation difficulties but temporarily preventing aspiration. If the victim is not rescued, this phase is followed by a period of involuntary respiratory efforts accompanied by aspiration of water, which may persist for many minutes before respiratory arrest. Convulsions and muscle spasms may occur before eventual cardiac arrest and death (*Fig. 243.1*).

Aspiration of water produces loss of surfactant and lung compliance, inflammation in the lower respiratory tract, non-cardiogenic pulmonary edema, ventilation/perfusion

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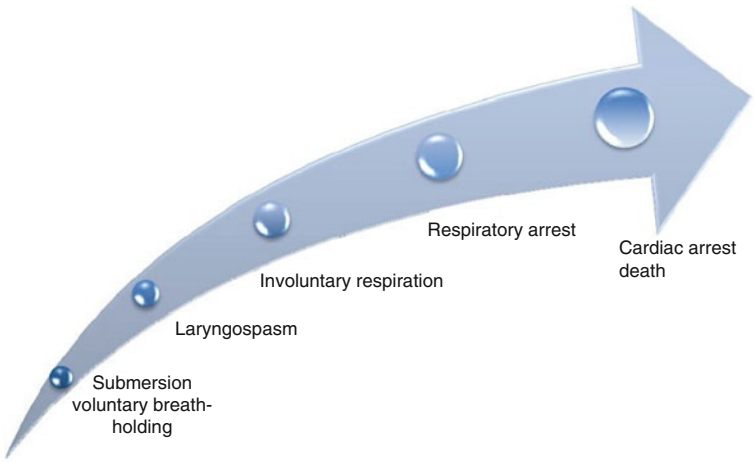

Figure 243.1
Progression of events in drowning

(V/Q) mismatch, intrapulmonary shunting, acute lung injury (ALI), and eventually the acute respiratory distress syndrome (ARDS). This spectrum leads to hypoxic-ischemic insult and end-organ damage. Animal models demonstrate that anoxia in drowning causes an abrupt fall in cardiac function and cardiogenic shock, demonstrated by a rise in pulmonary capillary wedge pressure, central venous pressure, and pulmonary vascular resistance. Hypoxic-ischemic injury, along with hypothermia, can lead to cardiac dysrhythmias including sinus bradycardia and atrial fibrillation, progressing to ventricular fibrillation and asystole. Drowning victims may also develop "cold stress diuresis," leading to hypovolemia. The natriuresis is of tubular origin and may be due to impaired renal autoregulation and/or natriuretic peptide release from hypoxic-ischemic injury.

Clinical Manifestations

Signs and symptoms are predominantly cardiorespiratory and neurologic and vary greatly based on submersion time. Ingestion of water is common, and vomiting usually accompanies rescue.

Respiratory distress may be initially subtle, with elevation of respiratory rate without hypoxemia. Victims of more significant events may present with rales, hypoxemia, and retractions. Pulmonary complications can evolve over a 24–48 h period. Neurologic manifestations vary from fussiness to obtundation. The central nervous system (CNS) is extremely susceptible to hypoxic-ischemic injury in drowning. This can manifest acutely with signs of elevated intracranial pressure.

Hypothermia may further complicate the clinical situation. Conductive and convective heat loss in water cannot be compensated for by thermoregulatory mechanisms. After core body temperature decreases below 35°C, disorientation and lack of muscle strength impair the victim's ability to fight the submersion and self-rescue. While this is more common in colder climates, core body temperatures will be lowered even in warmer water.

Diagnosis

Diagnostic studies focus on defining the extent of the injury. Despite water ingestion, electrolyte abnormalities occur in less than 15% of drowning victims; however metabolic acidosis is common. All patients should have a chest X-ray and oxygen saturation monitoring. A chest radiograph may detect acute changes, usually a pattern of nonspecific, bilateral alveolar infiltrates. Commonly performed studies in most patients requiring rescue include CNS imaging, electrocardiogram (ECG), and blood gas analysis. CT is normal in approximately 80% of patients. If abnormal, however, it can be distinguished from trauma because of lack of hemorrhage and presence of diffuse loss of grey-white matter differentiation, bilateral basal ganglia edema, or infarct.

Differential Diagnosis

Most children arrive at the emergency department with a history of accidental submersion. Drowning as a result of child abuse must also be considered if the history is not

consistent with the injury or plausible based on the age of the child. For teens, toxicology screen and blood alcohol level may be warranted. For any ambulatory patient, an ECG or EEG may be indicated to identify prolonged QT syndrome, other dysrhythmia, or seizure which may have precipitated a fall into water. Cardiac rhythm disturbance after submersion can also occur, and should be considered in patients with an unexpected drowning. Head trauma occurring before or after submersion must be considered for any patient with appropriate history, environmental risk, or bleeding noted on CNS imaging.

Treatment

Immediate treatment goals are to limit hypoxia, cardiovascular compromise, and hypothermia. After initial stabilization, pulmonary, neurologic, and other end-organ sequelae should be addressed.

Prehospital Care

Cardiopulmonary resuscitation (CPR) with cervical spine precautions should be instituted as soon as possible on scene. Even bystander CPR may improve outcome. The coexistence of spinal cord injury is rare but should be suspected, especially in unwitnessed drowning or traumatic drowning such as diving or surfing. After initial stabilization, the victim should be transferred to an emergency medical facility.

Emergency Department (ED) Care

In the emergency department, goals of therapy include continuing resuscitation and performing pulmonary and neurologic assessment. Noninvasive monitoring of vital signs and oxygen saturation are routine. For patients that are awake and alert, monitoring for decompensation may be sufficient. Any patient with a history of submersion greater than 1 min, experienced apnea or cyanosis, or required resuscitation should be admitted to the hospital. For all other patients, if after 6–8 h of observation there have been no symptoms, the chest radiograph is normal, and vital signs and oxygen saturation have been stable, the child may be discharged home. Those with even subtle abnormalities, however, should be admitted for a 24-h period to monitor for progression of symptoms. For patients with serious respiratory distress or failure, more invasive airway management including intubation may be indicated to manage hypoxia and hypercarbia. Fluid status should be assessed and the patient kept euvolemic. For suspected trauma, consultation with a trauma surgeon is indicated. Patients with respiratory distress or impaired neurologic status should be admitted to a pediatric intensive care unit for monitoring and further treatment.

Hospital Care

Specific intensive care management is beyond the scope of this chapter. However, it is important for general clinicians to understand some basic concepts. *Pulmonary* care focuses on keeping patients well oxygenated using supplemental oxygen. The goal for any intubated patient with lung disease, including ALI and ARDS, is to maximize oxygenation and ventilation while minimizing continued injury to the lungs induced by barotrauma and volutrauma. Thus, minimal ventilator settings are preferred. Chest radiography can help visualize improvement or decompensation. However, parameters such as increase or decrease in ventilator support and oxygenation/ventilation analyses are better indicators of clinical change. *Infections* of the lungs due to bacteria or fungi may complicate the clinic picture, but prophylactic antibiotics are not recommended as this may only worsen resistance. *Hemodynamic* instability due to cardiogenic shock and hypovolemia due to renal losses may require careful fluid management and inotropic agents. An echocardiogram to assess cardiac function can guide therapy. *Neurologic injury* due to hypoxic-ischemic brain insult can be compounded by further hypoxia, ischemia, increased intracranial pressure, cerebral edema, and brain metabolic demand. Supplemental oxygen should be used to limit hypoxia. In the 1970s, hyperventilation, hypothermia, and barbiturates were touted as optimal treatment for hypoxic-ischemic injury. However, later studies found that none of these treatments improved outcomes. Goal $PaCO_2$ should be 30–35 mmHg. Re-warming to euthermia remains current practice at most institutions. Induced coma is not recommended unless for seizure activity.

Prognosis

Prognosis is related to the duration of submersion, quality and promptness of resuscitation, and clinical status upon arrival to the ED. Many patients suffering minor events with recovery in the field have no long-term sequelae. Of those surviving, approximately 10% will have severe neurologic sequelae. A longer need for CPR, submersion

time greater than 15–25 min, initial arterial pH less than 7.1, and unconsciousness upon arrival to the ED have each been associated with poorer outcome. Up to 20% of children who arrived to the ED unconscious are discharged with moderate to severe hypoxic-ischemic encephalopathy. Nonreactive pupils on arrival to the ED and severe neurologic deficit (Glasgow Coma Score <5) upon admission to the intensive care unit may be the two best independent clinical predictors of poor neurologic outcome. An abnormal head CT is particularly significant, with an initial abnormal CT associated with mortality and a subsequent abnormal CT at 24–48 h after an initial normal study associated with persistent vegetative state or death in most children.

Prevention

An overwhelming majority of drowning cases worldwide are unintentional and preventable. The WHO 2008 World Report on Child Injury Prevention suggests interventions based on the Haddon Matrix of risk factors applied to childhood drowning: victim and caretaker factors, agent factors, physical environment factors, and socioeconomic factors. Healthcare providers should educate patients and caregivers on the importance of formal swimming instruction and water safety. Studies from the USA, China, and Bangladesh suggest that swimming lessons are protective. In the adolescent population, education on the danger of risk-taking behaviors such as alcohol consumption and swimming should be addressed. Lifeguards/lifesavers and caregiver supervision must be stressed. Personal flotation devices that are approved by a governing body should be used. In addition, access to potential sites of drowning should be limited, including properly locking gates for pools. Finally, governments should have specific campaigns focused on drowning awareness and prevention that take into consideration the regional epidemiology and risk factors.

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244 Neuromuscular Diseases

Paula Costanzo · Sung Min Park

Abbreviations: *BMD*, Becker muscular dystrophy; *DCM*, Dilated cardiomyopathy; *DMD*, Duchenne muscular dystrophy; *IPPB*, Intermittent positive pressure breathing; *IPV*, Intrapulmonary percussive ventilator; *NIV*, Noninvasive ventilation; *NMD*, Neuromuscular disease; *SDB*, Sleep disordered breathing; *SMA*, Spinal muscular atrophy; *SMN*, Survival motor neuron

The diagnosis of neuromuscular disease encompasses several disorders. Many of these diseases have common characteristics and treatment regimens. The identified deficits require similar support and ongoing multidisciplinary intervention. Although the focus of this chapter will be on neuromuscular diseases most commonly seen in pediatrics, the interventions described are used in other disease states with shared symptomology.

Etiology/Epidemiology

Incidence varies depending on disease. Duchenne muscular dystrophy is the most commonly seen muscular dystrophy in pediatrics. The incidence is approximately 1 in 3,000 male births. Becker muscular dystrophy is less common and has a milder more protracted course. BMD and DMD share a common x-linked gene location. DMD presents in early childhood with initial delay and subsequent loss of developmental milestones. Progression in muscle weakness and wasting occur in DMD with most patients becoming wheelchair bound by age 10–12. In DMD, death usually occurs in late teens to early twenties primarily as a result of respiratory insufficiency. Fewer die related due to cardiomyopathy. In BMD, boys may remain ambulatory until adolescence or as early adulthood. Death in BMD is also related to cardiopulmonary dysfunction, in thirties to forties.

Spinal muscular atrophy is a neurodegenerative disease commonly presenting in infancy or early childhood. Transmitted by an autosomal recessive gene and manifested by degeneration of spinal cord motor neurons with extensive muscular atrophy and weakness. It is second in frequency of NMD seen in children. Carrier frequency has been estimated at 1 in 50 to 80, with an incidence of 1 in 6,000 to 10,000 worldwide according to the SMA foundation. There are 4 types of SMA. SMA1 or Werdnig–Hoffmann disease is usually identified in early infancy and is the most aggressive form. Manifestations include severe hypotonic, poor head control, generalized weakness, weak cry and cough, fasciculation of the tongue, absent deep tendon reflexes, difficulty with swallow, feeding and secretion control. Without intervention death usually occurs before age 2. SMA type 2 is identified from ages 6 to 18 months, with loss in developmental milestones. Usually the child is unable to stand without assistance, and becomes wheelchair dependant. In both SMA types 1 and 2, chest x-rays reveal a bell-shaped chest. SMA 3 is a milder form of the disease with survival into adult life. Those not recognized until adulthood are identified as SMA 4.

Pathogenesis/Pathophysiology

DMD and BMD are X-linked recessive disorders caused by mutations in the dystrophin gene on the X chromosome at Xp21. Dystrophin is made up of proteins and complex sugars. In BMD, there is some dystrophin as compared to none in DMD. Lack of dystrophin causes progressive muscle wasting and weakness. Dystrophin is a large gene that bridges the inner surface of the muscle scleroderma. Without dystrophin the muscle scleroderma is less stable.

Muscles undergo repeated cycles of damage/necrosis and regeneration with ultimate inactivation of the regeneration process causing muscle fibrosis. In DMD there is a progressive loss of muscle function. Initial presentation is usually a result of motor delays or an abnormal gait. Normal milestones are usually obtained until the child starts to walk. Progressive muscle weakness is seen affecting the lower extremities before the upper extremities. Other typical findings in DMD include Gower's sign, pseudo hypertrophy of calf muscles, scoliosis, intellectual impairment, progressive cardiomyopathy, and worsening lung function in adolescence. Other NMDs may be more static in nature.

Spinal muscular atrophy is a group of degenerative disorders of the lower motor neurons. SMA is most

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commonly caused by deletion or mutation of the survival motor neuron 1 gene (SMN1), which is located on the 5q13 chromosome. SMN1 is responsible for the production of a protein needed in motor neuron function. Without a working protein, lower motor neurons along the spinal cord degenerate leading to progressive muscular weakness and atrophy. Classification of SMA is based on age on onset, severity of disease, and course of illness. Type one and two are the types seen most often in pediatrics.

Despite varied clinical presentation and genetic characteristics, progression of NMD often necessitates more frequent medical intervention. Although there is no cure for these disorders; and treatment is directed toward maintaining maximum function possible, prompt treatment of intercurrent illness, and maintaining quality of life. Gene analysis has become the primary tool for accurate identification of specific NMD with testing for a mutation, deletion, or duplication within a gene. In DMD, a deletion in the dystrophin gene is not always seen. A muscle biopsy may be needed if gene analysis is not definitive. In SMA, the SMN gene usually shows deletions of exons 7 and 8. Muscle biopsy shows denervation atrophy. Serum CK sometimes used in screening may be normal or elevated in both SMA and DMD.

Management and Treatment

Ongoing management of NMD requires a multidisciplinary approach. Most pediatric facilities have specialty clinics with medical and other specialists available to address current and anticipated needs of these patients. Medication treatment is respiratory based on treatment of symptoms and is mainly for the management of intercurrent respiratory illness. Clinical trials in both SMA and DMD are ongoing as well as gene therapy. There is no definitive treatment at present. In DMD, corticosteroids have shown to be effective in improvement in muscle strength in the short term with a dose of 0.75 mg/kg/day. Improvement in strength was noted within 10 days of onset of steroids and maintained for up to 18 months. There were also indications that steroid therapy was beneficial in preservation of respiratory muscle strength and cough efficiency.

Respiratory Management in NMD

Pulmonary function testing is useful in ascertaining baseline values and identifying decline in lung function. Respiratory muscle weakness influences PFT values. Patients with NMD demonstrate a restrictive pattern when lung volumes are evaluated. Initial worsening in PFTs is expected at the loss of ambulation abilities. American Thoracic Society guidelines for the DMD patient suggest evaluation by a physician specializing in pediatric respiratory care twice yearly after confinement to a wheelchair, fall in vital capacity below 80% predicted, and/or age 12 years. Weak or ineffective cough in NMD contributes to impairment in respiratory tract secretion clearance. This is a concern both in chronic and acute illness states. Inability to clear secretions sufficiently can result in atelectasis or pneumonia. There are manual and mechanical means to facilitate airway clearance. Manual techniques include positioning, chest physiotherapy (CPT), and cough assist maneuvers such as supporting or pushing on the upper abdomen or pushing the knees to the chest in conjunction with the patient's own cough. The mechanical insufflator-exsufflator (cough assist) is a device that assists in clearing retained secretions by delivering gradually increasing pressure to the airway then shifting to negative pressure with high expiratory flow rates that expel secretions in those with ineffective coughs. An oral suction device may be needed to extricate secretions from the mouth. Intrapulmonary percussive ventilation (IPV) helps to clear retained secretions by delivering rapid high flow short bursts of air into the lungs creating occult oscillation of the chest wall. Intermittent positive pressure breathing (IPPB) delivers positive pressure with or without aerosolized medication. IPV and IPPB can be used with a mouthpiece or mask. Other devices may include sSmart or the Thairapy vest which deliver high frequency mechanical oscillations to the chest wall. Inhaled bronchodilators and inhaled steroids may be used in conjunction with these therapies. Systemic steroids may also be used to treat acute respiratory distress or if due to underlying reactive airways disease.

Individuals with neuromuscular disease are at higher risk for sleep disordered breathing. Muscle wasting and weakness including intercostal and diaphragmatic muscles contribute to chronic respiratory insufficiency. Decrease in ventilatory drive and increase in upper airway resistance are seen. Tidal volume is reduced which leads to reduction in oxygenation and increase in CO_2. With progressive NMD, patients may need both day and nighttime ventilatory assistance. Polysomnography (sleep study) can identify appropriate abnormal oxygenation, hypoventilation, and carbon dioxide (CO_2) retention. Degree of pulmonary insufficiency may be identified in the context of a hospital stay when during recovery from a respiratory illness the child is unable to be weaned

successfully from ventilation. NMD patients using NIV are able to avoid some routine hospitalizations. Reduction in hospital stays including intensive care (ICU) admissions can decrease healthcare costs, and keep the patient in their preferred home environment. Caregivers of those with NMD are advised to contact their pulmonologist if they are using NIV more frequently. NMD patients with identified symptoms of SDB (headache, daytime somnolence, fatigue) reported improvement in symptoms following routine use of NIV. BiPAP (bi-level positive airway pressure) is the most frequently used type of NIV in pediatrics. Once initiated annual reevaluation with polysomnography will determine if adjustments in settings are indicated.

Invasive ventilation such as tracheotomy and ventilator support may be used in those patients unable to be successfully treated with other methods of support. Discussions of quality of life should be initiated prior to these measures.

Cardiology Management

Cardiomyopathy and cardiac rhythm disturbances are commonplace in individuals with DMD and BMD. Electrocardiographic abnormalities are seen in 90% of individuals with Duchenne or Becker muscular dystrophy. Dilated cardiomyopathy occurs in up to 90% of DMD patients 18 years or older. DCM is considered responsible for 20% of deaths in DMD. Pathological changes in the heart consist of necrosis, fibrosis, and fatty replacement of the muscle. Symptoms of cardiac dysfunction may be vague. Fatigue, weight loss, gastrointestinal complaints, and sleep disturbances may be signs of cardiac dysfunction. Female carriers are also at risk for cardiomyopathy. Cardiology evaluation is recommended at the time of confirmed diagnosis of DMD and at least biannually, beginning at approximately age 10 years or at the onset of cardiac symptoms. Cardiology input should also be initiated if surgical intervention is needed or with systemic steroid, which may affect blood pressure.

Nutritional Management

Nutritional intervention should include surveillance of appropriate weight gain, body mass index, and assessment of swallow function. Bulbar dysfunction is seen in spinal muscular atrophy. Inability to consume sufficient calories orally is also a common problem in SMA. Recommendations from the Consensus Statement for Standard of Care in Spinal Muscular Atrophy recognized problems of: feeding and swallowing, gastrointestinal dysfunction/dysmotility, growth and undernutrition and overnutrition, and concerns of aspiration in those with chronic respiratory problems. Individuals with DMD may be obese or malnourished. Obesity can put further stress on the respiratory system. Swallow evaluation (dysphasia study) is indicated in those individuals experiencing feeding-related difficulties. Risk of aspiration can be evaluated during this study as well as determination of appropriate consistency of liquids needed for safe oral intake. If aspiration is revealed alternative methods of feeding may be necessary. Percutaneous gastrostomy tube placement is an alternative to if oral feedings are deemed unsafe or inadequate. Some families opt to continue oral feedings even if aspiration risk is determined, if feeding is thought to be enjoyable to the individual. Constipation is a common issue in NMD due to lack of muscle tone. Juices and laxatives as well as a high fiber diet may be used. In addition a bioscopy bisacodyl or other rectal suppository can be effective in stimulating bowel movements.

Orthopedic Management

Surgical intervention for treatment of scoliosis in NMD is considered if spinal curvature is severe enough to cause discomfort or impair lung function. Orthopedic evaluation throughout childhood can help with determination of most appropriate time of surgery to achieve optimum correction. Pulmonary function should be determined prior to surgery. Scoliosis surgery often improves sitting balance, endurance, and appearance. Tendon releases may also be considered in DMD to prolong ambulation. Ongoing evaluation by physical therapists is helpful in evaluation and timeliness of orthotics and wheelchair use. Occupational therapy focuses on activities of daily living and maintaining functional abilities as long as possible.

Immunizations

Routine childhood immunizations are important in maintaining heath and avoiding illness. Annual influenza vaccines should be obtained. Pneumococcal and varicella vaccines should be considered.

Education, Psychosocial, and Palliative Care

Education about the affecting disease should start soon after diagnosis. Families should be referred for genetic

counseling. Expected disease course and outcomes should be discussed. Identification of community organizations, such as the Muscular Dystrophy Association can be offered as a resource to families. Medical social workers are often available in muscle disease specialty clinics. They can assist in guiding difficult discussions aimed at treatment options including surgeries, ventilation, tracheostomy, and quality of life. Anticipatory guidance is important in allowing the patient and family to consider possible choices in treatment of their disease prior to a crisis situation. The goal of palliative care is to maintain quality of life, relieving physical, psychological, emotional, and existential suffering. When available treatments no longer achieve desired outcome, and quality of life is diminished, care is transitioned to end of life or hospice care, with comfort of the patient being the primary goal. Support from medical professionals, family, and others involved in the individuals life help with the transition.

Duchenne muscular dystrophy and spinal muscular atrophy types one and two are the most common neuromuscular diseases seen in pediatrics. Management of neuromuscular disease is directed at maintaining functional abilities, treatment of symptoms, supportive care, and maintaining quality of life. A multidisciplinary approach is important in achieving optimal care. Attention should be focused on medical and psychosocial needs of the patient and family, with identification of the most appropriate intervention for each unique situation.

Cardiology

Mark B. Lewin

245 Fetal Cardiology and Neonatal Transition

Margaret MacMillan Vernon

Knowledge of the fetal, transitional, and neonatal circulations is integral to successful evaluation of the cardiovascular system and understanding the pathophysiology of congenital heart disease (CHD).

Fetal Cardiology

Cardiac Embryology

The cardiovascular system is the first organ system to reach functional maturity in the human embryo. The heart begins as a straight tube, developing by 20 days post conception when the embryo is no longer able to satisfy its nutritional requirements by diffusion alone. The heart tube is oriented in a caudocranial direction with segments which will become, in order, the atria, the left ventricle, the right ventricle, and the truncus arteriosus. The truncus arteriosus is the precursor to the aorta and main pulmonary artery (MPA). The tube elongates and then complex looping and septation follow. By the eighth week post conception, cardiogenesis is essentially complete and ventricular contraction – the fetal heart beat – can be detected by transvaginal ultrasound at that time. *Abnormal looping and incomplete septation form the basis for many forms of congenital heart disease.*

Fetal Circulation

The fetal circulation differs from the postnatal circulation in several ways; nearly all of which are attributable to the fundamental difference in the site of gas exchange (oxygen uptake and carbon dioxide removal) between the fetus and the newborn. In the fetus, both gas exchange and the absorption of nutrients occur in the placenta. In the healthy newborn, gas exchange occurs in the lungs and nutrient absorption occurs in the gastrointestinal tract.

In the fetus, oxygenated blood returns to the body through the umbilical vein having just taken up oxygen in the placenta. As the blood within the umbilical vein approaches the liver, the majority flows through the ductus venosus directly into the inferior vena cava before entering the right atrium where preferential streaming occurs. In the right atrium, blood originally from the ductus venosus flows across the foramen ovale into the left atrium and left ventricle, whereas blood from the abdominal inferior vena cava joins that from the superior vena cava and flows preferentially through the tricuspid valve into the right ventricle.

The blood entering the left ventricle is then pumped across the aortic valve and into the ascending aorta where it supplies the coronary, carotid, and subclavian arteries (and hence the heart, brain, and upper body) with relatively richly oxygenated blood.

Blood entering the right ventricle is then pumped across the pulmonary valve and into the main pulmonary artery. Because the lungs are fluid-filled and offer high resistance to flow, most of the blood passes not to the lungs, but through the ductus arteriosus and into the low-resistance descending aorta. Here it mixes with blood from the ascending aorta before ultimately returning to the placenta for oxygen uptake by way of the two umbilical arteries.

Unique Features of Fetal Circulation

1. In the fetus, oxygen-rich umbilical venous blood and oxygen-poor systemic venous blood mix at several sites before being pumped into the systemic arteries. These in utero *shunts*, including the ductus venousus, foramen ovale, and ductus arteriosus, assure the preferential delivery of oxygen-rich blood to the metabolically active tissues of the heart and brain. Abolished soon after birth, their in utero existence permits fetal survival and even thriving in the presence of complicated congenital heart disease. Postnatally, there is essentially no mixing of the pulmonary venous and systemic venous blood.

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From a hemodynamic standpoint, the widely patent foramen ovale and ductus arteriosus result in equalization of the pressures between the right and left atria and similarly in the right and left ventricles. This is in distinct contrast to postnatal hemodynamics.

2. In general, the oxygen content of the blood in the fetus is considerably lower than that of a neonate or child. Blood in the umbilical vein has the highest concentration of oxygen, about 80%, gradually decreasing by the mixing in of desaturated blood as it courses from the placenta to the organs of the fetus and back to the placenta. The blood returning to the placenta not surprisingly then has the lowest content of oxygen, with a saturation of approximately 58%.

   This difference in oxygen content is due to the relatively poor efficiency of the placenta in comparison to the lungs as an organ of gas exchange. To compensate, fetal blood is composed of a high percentage of fetal hemoglobin which has a substantially higher oxygen affinity and lower p50 (the partial pressure of oxygen at which 50% of it is oxidized). This unique composition facilitates oxygen uptake at the relatively low pO2 levels of the placenta.
3. Cardiac output (CO) is determined by heart rate (HR) and stroke volume (SV): CO = HR × SV. Postnatally, alterations in heart rate as well as stroke volume, via changes in filling pressure (preload), resistance against which the ventricles contract (afterload), and myocardial contractility, allow for significant adjustments (multifold increases) in cardiac output to meet the increased requirements of a physiologic stressor.

   The fetus however, has a limited capacity to adjust cardiac output in response to stress. The fetal myocardium is relatively stiff and as a result an increase in preload does not increase cardiac output significantly and an increase in afterload markedly decreases cardiac output. Thus, the fetus relies on an increase in heart rate almost exclusively as a response to stress.

Indication for *in utero* Evaluation of the Cardiovascular System

As ultrasonographic technology has advanced and experience has been gained, more and more anomalies are being detected *in utero*. Currently, most pregnant women undergo an ultrasonographic evaluation close to midpregnancy. Typically performed between 16 and 22 weeks gestation, this ultrasound includes an assessment of fetal growth as well as an anatomic survey used to screen for major developmental anomalies. As part of this survey, the fetal cardiovascular system is evaluated. The heart is visualized, rate and rhythm noted, and a four-chamber view is obtained. The recognition that adding evaluation of both ventricular outflow tracts can significantly increase the detection of major structural heart disease has led to inclusion of them if technically feasible.

If an abnormality is identified during this screen, or at any point during a pregnancy, a comprehensive *in utero* evaluation of the cardiovascular system is recommended.

While the majority of fetal cardiovascular evaluations are requested for incomplete midtrimester anatomic screens or a suspected abnormality, a variety of maternal or fetal disorders may place a fetus at increased risk for congenital heart disease (*Table 245.1*) and *in utero* evaluation is recommended in these scenarios as well.

Infrequently a rhythm abnormality prompts consultation as well. *In utero* the fetal heart rate varies widely, from as low as 80 beats per minute during periods of rest to 160 beats per minute during periods of activity. Most commonly, the heart rate however is between 120 and 140 beats per minute. Variability is essential and is an indication of fetal well-being. Occasionally a skipped beat, early beat, or series of such will be noted during a routine prenatal evaluation. While frequently benign, their presence often prompts further evaluation for confirmation. Premature atrial contractions which can be either conducted or blocked account for the vast majority of

Table 245.1
Indications for *in utero* evaluation of the cardiovascular system

Maternal indications	Fetal indications
Family history of CHD including prior child or pregnancy with CHD	Abnormal obstetrical screening ultrasound
Maternal Diabetes	Extracardiac abnormality
Exposure to teratogens	Chromosomal abnormality
Exposure to prostaglandin synthetase inhibitors (ibuprofen)	Arrhythmia
Infection (Rubella, Coxsackie, Parvovirus B19)	Hydrops fetalis
Autoimmune dx (Sjogren's, Systemic Lupus Erythematosus (SLE))	Ultrasound screen: Increased first trimester nuchal translucency
Familial inherited disorder (Marfan's, Noonan's)	Multiple gestation and suspicion for twin–twin transfusion syndrome
In vitro fertilization	

such Doppler findings, however occasionally a fetus will be noted to have a persistently fast or slow rhythm. Fetal bradycardia can be seen in association with complex congenital heart disease or maternal antibody–mediated inflammatory disorders such as systemic lupus erythematosus (SLE) or Sjogrens syndrome. Fetal tachycardia can be seen in the setting of a primary rhythm disturbance, most commonly supraventricular tachycardia, or as a consequence of fetal heart failure due to a variety of primary etiologies including fetal anemia or myocarditis.

Following these guidelines, ~5% of pregnancies are referred for a comprehensive *in utero* cardiovascular evaluation and the proportion of congenital heart disease diagnosed prenatally has dramatically improved. Nowadays, reported rates of prenatal diagnosis frequently approach 50% whereas as recently as the early 1990s, the rate of prenatal diagnosis was less than 10% of infants undergoing cardiac surgery in the first month of life. Unfortunately, despite these strides, many babies postnatally diagnosed with congenital heart disease are born with no identified risk factors (including an identified concern at the mid-gestation anatomic screen) and cardiac anomalies continue to be one of the most frequently missed lesions *in utero*.

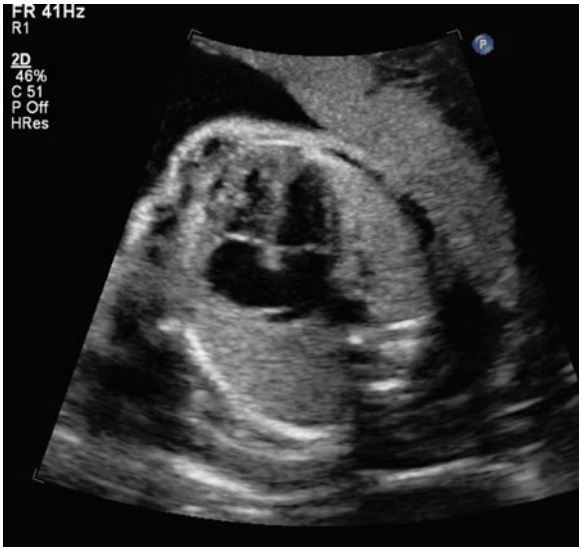

Figure 245.1
Four-chamber view of a normal fetal heart. All four chambers are visible with relative symmetry in size between the ventricles and atria. The right ventricle is identified by the presence of the moderator band and increased myocardial trabeculations in comparison with the left ventricle. A pulmonary vein is seen entering the left atrium from the right lung field. The descending aorta is seen directly behind the left atrium

In utero Evaluation

Echocardiography is the main diagnostic modality used to evaluate the fetal heart. The optimal timing for performance of a comprehensive transabdominal fetal echocardiogram is 18–20 weeks gestation. In select cases earlier, including late in the first trimester, evaluation may be possible. Evaluation late in gestation is often complicated by a more "fixed" fetal position which may limit the available acoustic windows and thus the completeness of the evaluation.

Similar to a pediatric transthoracic echocardiogram, a fetal echocardiogram involves assessing cardiac anatomy in a sequential fashion, obtaining standard views of all cardiac structures. Initial imaging establishes fetal position (vertex, breech, or transverse). Once fetal left and right are established, the fetal abdominal situs is confirmed as well as the position of the heart within the thorax. While uncommon as a whole, congenital heart disease and abnormalities of laterality (heterotaxy syndrome) are commonly found together. The cardiovascular system is then evaluated beginning below the diaphragm in the abdomen and ending at the thoracic inlet as a series of imaging planes. The four-chamber view (◉ *Fig. 245.1*) is the most important in a comprehensive examination of the fetal heart. In this view, cardiac position, size, rate and rhythm, and qualitative contractility can all be assessed. Additionally many congenital heart defects can be detected. After a four-chamber view is obtained, attention turns to visualization of the left and right ventricular outflow tracts and an assessment of ventriculo-arterial concordance (◉ *Fig. 245.2a, b*). Establishing the origin of the main pulmonary artery from the right ventricle and the aorta from the left ventricle is mandatory. The aortic and ductal arches are then evaluated. Finally, the systemic and pulmonary venous return are evaluated.

Structures are evaluated in orthogonal imaging planes in order to form a composite picture of the heart including any identified malformation as the primary goal of fetal echocardiography is to identify any existing abnormality *in utero*. In addition to obtaining clear two-dimensional (2D) pictures of each structure, flow is evaluated with color Doppler and pulse Doppler. Valve regurgitation and/or stenosis can be detected and valve leaflet motion

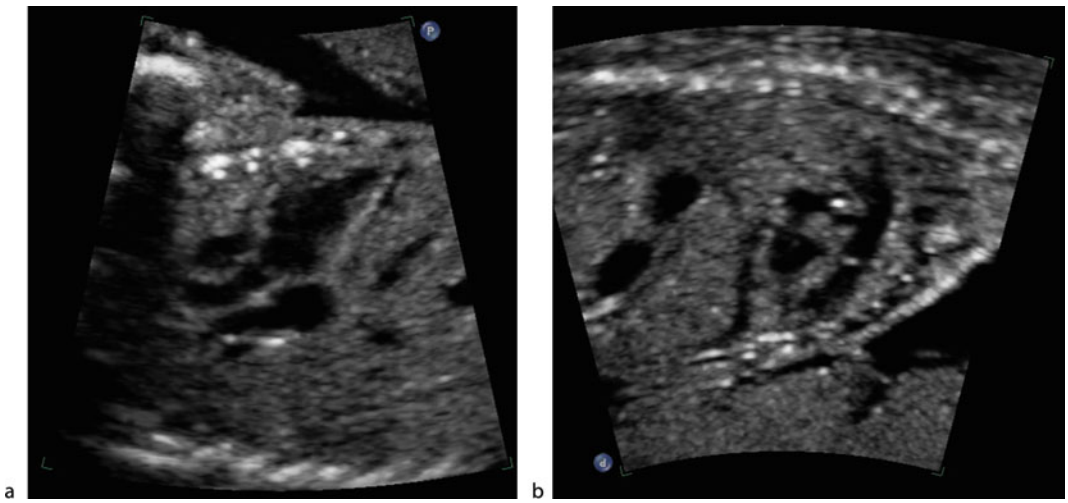

Figure 245.2
(a) The left ventricular outflow tract in a normal fetal heart. The aorta is seen arising from the left ventricle. (b) The right ventricular outflow tract in a normal fetal heart. The main pulmonary artery (MPA) is seen arising from the right ventricle. The right pulmonary artery is seen as the first branch off the MPA which continues as the ductus arteriosus in this image

observed. From 2D images, structures can be measured and compared with established normals for varying gestation ages.

Once a comprehensive assessment of the cardiac anatomy is complete, the heart rate and rhythm are documented (*Fig. 245.3a, b*). The rate and rhythm of the fetal heart are evaluated by mechanical surrogate events, specifically the movement of the atria and ventricles or blood flow across valves. By convention, the heart rate is established by measuring the time between successive aortic Doppler profiles. As a result of the normal orientation of the aortic and mitral valves, a Doppler cursor can be placed just beneath the aortic valve and pick up both aortic outflow and mitral inflow. Measuring the time between the onset of the a wave and the aortic outflow is referred to as the mechanical PR interval and is an accepted mechanical surrogate for the postnatal ECG PR interval, allowing for normal sinus rhythm to be inferred *in utero*.

Prenatal Counseling

If an abnormality is diagnosed *in utero*, counseling includes a discussion of the anatomic malformation and frequently the increased risk for extracardiac anomalies and chromosomal or genetic abnormalities. In addition, treatment options, including surgical strategy, and long-term outcomes are discussed. As part of this initial consultation the options of pregnancy termination and neonatal comfort care are discussed if locally available. Going forward, patients are evaluated serially, often at 6–8 week intervals to assess for fetal well-being, growth, and *in utero* evolution of the lesion. As a pregnancy advances toward full-term, perinatal management plans can be created to smooth the transition to the postnatal time period.

Genetics

Many congenital heart lesions are isolated; however others are frequently associated with a clinical syndrome or identifiable chromosomal abnormality. For decades it has been widely recognized that certain cardiovascular lesions are commonly seen in association with a distinct set of facial features or organ system anomalies.

With each passing year, the ability to ascribe a chromosomal deletion syndrome, microdeletion, and even single gene defect to such clinical observations increases. Identification of these anomalies, from monosomies and trisomies to much smaller chromosomal abnormalities, during the prenatal time period utilizing amniocentesis or chorionic villus sampling is rapidly increasing as well.

Frequently it is the other anomalies (skeletal dysplasias, gastrointestinal abnormalities, brain malformations, etc.)

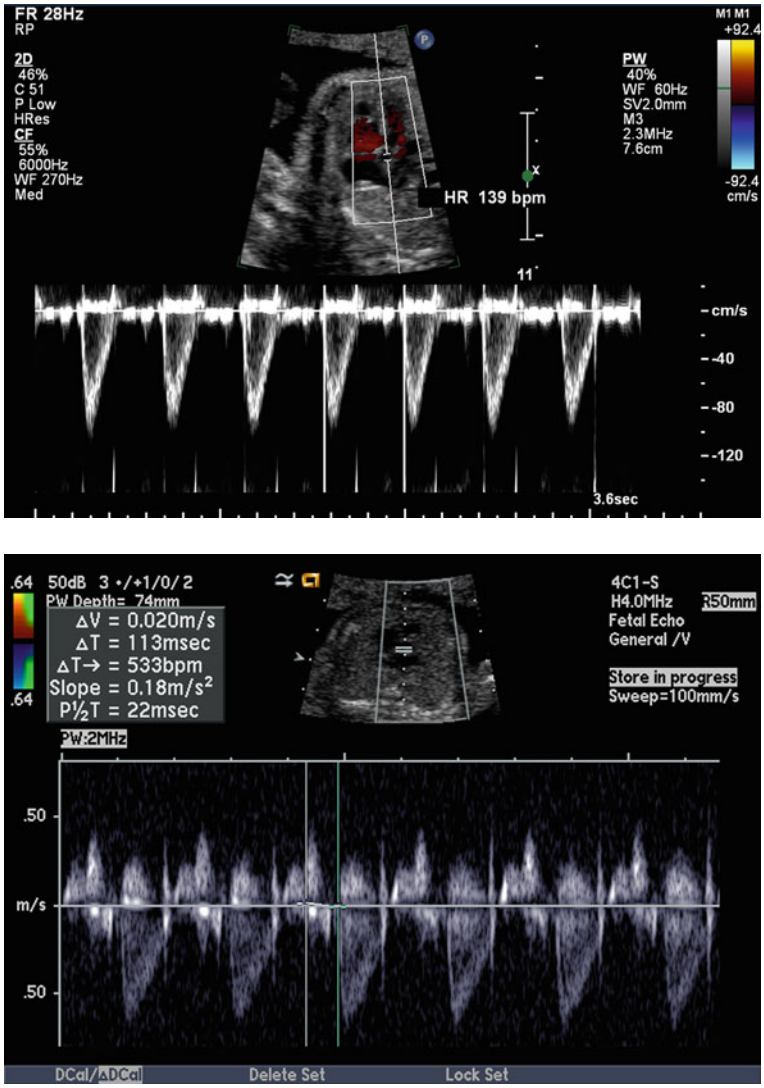

Figure 245.3

(a) The fetal heart rate (HR) is established by this Doppler tracing obtained with the sample volume just distal to the aortic valve. The time between successive beats is recorded and heart rate per minute calculated. (b) The fetal heart rhythm is evaluated by placing the Doppler sample volume just beneath the anterior leaflet of the mitral valve. In this position, Doppler tracings of both the mitral inflow and the aortic outflow are obtained and a mechanical PR interval can be recorded

which are detected first and only after a careful examination is the cardiac anomaly identified. Identification of the cardiac defect may however have a significant impact on the expected clinical course and ultimate outcome. Additionally, identification of a second anomaly greatly increases the chance of an underlying chromosomal anomaly or congenital malformation syndrome.

Neonatal Transition

Normal Events

Following birth, a series of profound changes involving the cardiovascular system occur. These events take place within the first hours to days of life and constitute the transitional circulation.

With the clamping of the umbilical cord, the systemic vascular resistance suddenly increases. At approximately the same time, the first cries of a healthy newborn, announce his or her arrival and signal the initiation of respiration. The lungs now assume their role as the organ of respiration. They expand and oxygen is brought to the alveoli. This results in a dramatic fall in pulmonary vascular resistance (PVR) and pulmonary arterial blood pressure and an increase in pulmonary blood flow. Pulmonary arterial blood pressure, which in the fetus was equivalent with the systemic blood pressure, drops to half of the systemic level within 24 h of birth.

The initial rapid fall in pulmonary vascular resistance is due primarily to the vasodilatory effect of oxygen on the pulmonary vasculature. The physical expansion of the lungs and increased production of vasoactive substances, mainly prostacyclin and endothelium-derived nitric oxide, also contribute to the fall. Subsequently there is a continual slow fall in PVR until adult levels are reached by 6 weeks of life as the medial layer (smooth muscle) of the pulmonary arteries thins. Ultimately, the decrease in pulmonary vascular resistance leads to an eight- to tenfold increase in pulmonary blood flow.

An increase in pulmonary venous return to the left atrium is seen with this increase in pulmonary blood flow. This results in a pressure gradient between the left and right atria and functional closure of the foramen ovale.

Within a few hours of birth, the increase in systemic vascular resistance and drop in PVR leads to a reversal of flow through the ductus arteriosus. *In utero* flow was from right to left (pulmonary artery to aorta) and now flow switches to left to right (from aorta to pulmonary artery). Soon thereafter, normally within 10–15 h of birth, as a result of increased arterial oxygen saturation, the ductus arteriosus closes although permanent closure may not take place for weeks. In addition, the ductus venosus closes as a result of lack of blood return from the placenta.

Anything increasing the PVR or delaying the fall in pulmonary vascular resistance, such as acidosis, hypoxemia, polycythemia, lung disease, or immaturity (such as premature delivery), may interfere or prolong these normal events.

Indications for Cardiovascular Evaluation

Congenital heart disease (CHD) is by definition heart disease present at birth. The majority of congenital heart defects are anatomic abnormalities, such as septal defects, stenosis or atresia of a valve or valves, hypoplasia or absence of a ventricle, or abnormal great arterial connections. Infrequently a newborn is born with an arrhythmia or cardiomyopathy. This is in contrast to adult cardiovascular disease, the majority of which is functional or rhythm-related.

CHD is one of the most serious congenital anomalies, occurring in approximately 1% of newborns. Despite near universal mid-gestation ultrasonographic screening, the majority of congenital heart disease, both subtle and more serious, is diagnosed after birth. While the vast majority of these newborns are hemodynamically stable and require no more than normal newborn care, early recognition of congenital heart disease allows for expeditious identification of those who are at risk for hemodynamic compromise.

The uniqueness of the fetal circulation has great consequences during the transitional period for those with congenital heart disease. It is during this time, that many complex lesions unmask themselves after being tolerated silently *in utero*. The symptoms of cardiovascular disease may be nonspecific, resembling more common scenarios such as neonatal sepsis or respiratory distress syndrome (RDS). When clinical events such as tachypnea, tachycardia, hypoperfusion, persistent cyanosis, or the presence of a murmur suggest an abnormality in the cardiovascular system, evaluation is warranted.

Systemic Hypoperfusion

In the simplest sense, insufficient cardiac output presents as systemic hypoperfusion and ultimately shock. Following delivery, the work of respiration and maintenance of body temperature are both assumed. Abnormalities in myocardial contractility or heart rate may present as hypoperfusion if the cardiac output fails to meet the increasing metabolic demands of the newborn.

In addition, and more frequently, infants with clinically significant aortic arch obstruction present with systemic hypoperfusion and shock following closure of the ductus arteriosus.

In utero, the left ventricle and aortic isthmus see only a small amount (~10%) of the cardiac output. The left heart is therefore developmentally particularly vulnerable. Significant narrowing or coarctation and interruption of the aortic arch together account for a relatively large proportion of congenital heart disease. Both lesions are silently tolerated *in utero* and more commonly diagnosed in the postnatal period rather than prenatally.

Persistent Cyanosis

Central cyanosis, distinguished from acrocyanosis by involvement of the warm mucous membranes, including the tongue and buccal mucosa, is abnormal. A distinctive feature between the two is that central cyanosis generally worsens with activity and increasing cardiac output (crying for instance), whereas acrocyanosis generally improves. Central cyanosis is evident when the content of reduced hemoglobin is greater than 3–5 g/dl.

Because of the low levels of circulating oxygen before birth, newborns with cyanotic congenital heart disease (*Table 245.2*) may be quite active, feeding and appearing comfortable, at oxygen levels which older children would not tolerate (PaO2 20–25 mmHg).

In addition, pulmonary arterial flow *in utero* is reduced compared with that following delivery and expansion of the lungs. Because of the resultant minimal pulmonary venous return *in utero*, anomalies of pulmonary venous return (specifically total anomalous pulmonary venous return) may easily be masked. Total anomalous pulmonary venous return is one of the cyanotic lesions unmasked when effective oxygenation and ventilation fail to improve an affected newborn's visible central cyanosis.

Alternatively, persistent pulmonary hypertension of the newborn (PPHN), occasionally referred to as persistent fetal circulation, results when the PVR fails to fall following the initiation of ventilation. Pulmonary arterial pressure and right ventricular pressure remain elevated as they were *in utero*. In PPHN, blood continues to bypass the lungs by shunting across the foramen ovale and ductus arteriosus resulting in persistent cyanosis. Several factors may disrupt the normal decrease in PVR and increase in pulmonary blood flow; these include apnea and parenchymal lung disease both of which interfere with ventilation. Meconium aspiration and severe respiratory distress syndrome are the major parenchymal lung diseases. Pneumonia and asphyxia can cause PPHN as well.

Table 245.2
The five *T*'s of cyanotic heart disease

*T*etralogy of Fallot
*T*ransposition of the great arteries
*T*runcus arteriosus
*T*otal anomalous pulmonary venous return
*T*ricuspid atresia

Presence of a Murmur

Murmurs are very common in children. CHD is much less common, however the vast majority is diagnosed within the first week of life if not prenatally. Given the increased likelihood of a pathologic etiology, a murmur noted within the first hours or days of life warrants thoughtful investigation.

Significant semilunar valve pathology, such as aortic or pulmonary stenosis (PS), typically presents early as the entire cardiac output is ejected across the narrowed orifice. On the other hand, the murmur of a ventricular septal defect (VSD) may present early or may develop as the pressure gradient between the right and left ventricles evolves as the PVR drops.

A murmur may be normal in the transitional time period. If no other clinical concern exists, close observation may be appropriate. Within the first 24 h following birth, the ductus arteriosus closes as a result of constriction of the ductal smooth muscle. Until complete closure is achieved, a murmur may be noticed. Additionally, *in utero*, the lungs receive a relatively small proportion of the combined ventricular output and therefore the branch pulmonary arteries are relatively small. This is important in the genesis of the normal physiologic pulmonary flow murmur.

Presence of an Extracardiac Anomaly or Chromosomal Abnormality

In addition to evaluating symptomatic newborns presenting with signs suggesting cardiovascular abnormalities or abnormal transition, a comprehensive evaluation of the cardiovascular system including an echocardiogram is indicated in the assessment of a neonate with a presumed chromosomal abnormality, recognized syndrome (*Table 245.3*), or extracardiac malformation with an increased risk of associated CHD (i.e., omphalocele). Additionally, a neonate with a condition which may adversely impact the cardiovascular function (i.e., arteriovenous malformations) warrants evaluation.

Confirmation of the absence of structural heart disease or alternatively the identification of a significant congenital heart defect can be extremely helpful to the team caring for a neonate, particularly one with a recognized extracardiac anomaly. Frequently, outcome may be impacted by the presence of CHD. Detection of CHD allows for development of a comprehensive management strategy.

Table 245.3
Commonly recognized syndromes associated with congenital heart disease (CHD)

Syndrome	Lesion
Trisomy 21	VSD, AVSD
Trisomy 13	VSD, PDA
Trisomy 18	VSD, PDA
45 XO (Turner)	Coarctation of the aorta, AS
DiGeorge	IAA, truncus arteriosus, TOF
Williams	Peripheral PS, supravalvar AS
Noonan	PS, ASD, HCM
VACTERAL	VSD, TOF
Fetal Alcohol	ASD, VSD, TOF
Infant of a diabetic mother	HCM, TGA, VSD
Marfan	MVP, aortic aneurysm

AS aortic stenosis, *ASD* atrial septal defect, *AVSD* atrioventricular septal defect, *HCM* hypertrophic cardiomyopathy, *IAA* interrupted aortic arch, *MVP* mitral valve prolapse, *PDA* patent ductus arteriosus, *PS* pulmonary stenosis, *TGA* transposition of the great arteries, *TOF* tetralogy of Fallot, *VSD* ventricular septal defect

The Premature Neonate

The incidence of persistent patency of the ductus arteriosus increases with decreasing gestational age at birth. In the premature infant where the clinical course falls outside that typically encountered, ensuring the absence of structural heart disease is crucial. Additionally, in the present era, echocardiographic assessment is considered the standard of care before medical treatment of a presumed patent ductus arteriosus (PDA).

Evaluation of the Cardiovascular System

A brief period of observation is essential in developing a general assessment of overall health.

A varying degree of acrocyanosis or blueness of the hands and feet is the rule rather than the exception following delivery. Although the precise etiology is unknown, acrocyanosis is likely secondary to a difference between the cutaneous arterial and venous vessel tone. In a newborn with acrocyanosis, pulse oximetry will be normal as it estimates arterial oxygenation defined as the percentage of hemoglobin molecules bound by oxygen. Frequently obtaining an accurate tracing with corresponding heart rate is challenging. Placing the newborn under a warming light or swaddling him or her with a warm blanket may be very helpful.

A complete set of vital signs should be obtained and recorded for every newborn. The most reproducible set of vital signals are obtained in the resting state.

The heart rate is generally faster in the newborn than during childhood. A normal resting newborn heart rate is usually over 100 beats per minute, typically between 120 and 140 beats per minute.

The respiratory rate should be counted for a full minute as rates may vary considerably. The normal respiratory rate can vary from 45 to 60 breaths per minute. Tachypnea can occur as a consequence of increased pulmonary blood flow and dyspnea, manifest as grunting, flaring of the nostrils, and intercostal, suprasternal, and subcostal retractions, as a consequence of increasing pulmonary congestion.

Every newborn should have a comparison of upper and lower blood pressures on at least one occasion. Because the subclavian arteries may arise aberrantly beyond the site of the ductal ligament, both upper extremities should be measured and compared with the lower-limb pressure. Normal lower-limb systolic blood pressure is 10 mmHg higher that the upper-limb pressure.

Mild arterial desaturation is not unusual in a normal neonate. In an otherwise healthy newborn, this transient mild desaturation is secondary to an intrapulmonary shunt through an as-yet unexpanded portion of the lungs.

Developing an organized routine in the performance of the cardiac examination is necessary so that important points are not missed or neglected. A peacefully resting or sleeping infant is essential to a complete auscultatory examination. One strategy is to concentrate first on the cardiac rhythm, establishing its regularity, before moving to an evaluation of the heart sounds and murmur recognition. Identifying the splitting of the second heart sound, not only implies the presence of two semilunar valves but also their normal anatomic configuration, is quite challenging and moves from an advanced auscultatory skill to an impossible task if the newborn is fussing or crying.

The presence of a murmur in a newborn, while not necessarily pathonomonic for congenital heart disease should increase one's suspicion. Occasionally the closure of the ductus will be audible though this should be a soft, transient murmur (not the machinery type murmur of a persistently patent ductus). Localization of a murmur source may be quite challenging. This is not surprising as the newborn heart is approximately the size of a walnut (2–3 cm in diameter).

In addition to the auscultatory examination, the presence of hepatomegaly and localization of femoral pulses are essential components of a comprehensive cardiovascular examination. Palpation of the liver edge can be aided by allowing the newborn to rest their feet on the examiner's palm and raise their toes 90° (flexing at the hips) to relax the abdominal wall muscles. Examination of the newborn abdomen is particularly important as the size of the liver offers the most reliable indicator of systemic venous congestion.

Identifying the iliac crest and then sliding the tip of the examining finger along the femoral crease often aids in identification of the femoral pulse. While frequently difficult to locate, once located the femoral pulse should be easy to palpate. Both the brachial and femoral pulses should be assessed and compared to each other.

The cardiovascular evaluation includes review of a complete set of vital signs including four extremity blood pressures and pre- and post-ductal saturation and performance of a physical examination. Frequently a chest X-ray, electrocardiogram (ECG), and/or echocardiogram are indicated to complete a comprehensive evaluation.

The normal newborn electrocardiogram (ECG) has more right ventricular force than that of an older child or adult. Newborn infants have right ventricular dominance with a thick right ventricular wall and elevated PVR secondary to a thick medial layer of the pulmonary arterioles. The thick pulmonary arterial smooth muscle gradually becomes thinner and by 6–8 weeks of age the ECG resembles that of an older child.

Echocardiography is the primary imaging modality utilized to evaluate the cardiovascular system. High-resolution images can clearly identify anatomic abnormalities and an assessment of hemodynamics can be made by applying the Doppler principle. Although echocardiography is considered a noninvasive diagnostic test, care must be taken during the performance of the echocardiogram as prolonged environmental exposure and even transducer pressure can lend to instability in vulnerable newborns. A detailed discussion of echocardiography can be found in Chap. "❯ NonInvasive Imaging."

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246 Cardiovascular Genetics

Aaron K. Olson · Jeffrey A. Towbin

The goal of this chapter is to provide a review of the common genetic conditions associated with cardiovascular disease in children. Congenital heart disease can be one of the earliest recognized manifestations of a genetic syndrome. For example, interrupted aortic arch type B is often the presenting finding in patients with 22q11 deletion syndrome. Conversely, the recognition of a genetic syndrome may prompt an evaluation for congenital heart lesions, such as in Down syndrome (DS). Correctly diagnosing a genetic syndrome can provide important benefits such as detection of additional anomalies and assessment of reproductive risk for future pregnancies.

Certain genetic syndromes present with a variety of important cardiovascular complications in childhood such as cardiomyopathy or aortic root dilation. Often, these patients present for evaluation only after another family member is diagnosed. It is important to recognize that the initial cardiac evaluation may be normal, even in patients who will eventually develop serious cardiovascular complications. Therefore, ongoing cardiac evaluations are necessary for this patient population.

This chapter is not meant to be a complete review of every genetic syndrome with pediatric-onset cardiovascular disease. Many comprehensive resources are available including the online sites www.ncbi.nlm.nih.gov/omim (Online Mendelian Inheritance in Man from Johns Hopkins University) and www.genereviews.org (from the University of Washington). Of special note, hypertrophic cardiomyopathy and long QT syndrome will be discussed in other chapters of this section.

Down Syndrome

To most health-care providers, Down syndrome (DS) is the most familiar genetic syndrome associated with congenital heart disease. The vast majority of DS patients have a complete trisomy 21. Rarely, individuals may have a partial trisomy due to a chromosomal translocation or mosaicism. These chromosomal anomalies are readily detectable by karyotype analysis. Depending on age and ethnicity, patients have a typical appearance that includes microbrachycephaly, small facial features, protruding tongue, short upslanting eyes with epicanthal folds, fifth finger clinodactyly, brachydactyly, transverse palmar creases, and sparse hair. Global developmental delay of at least moderate degree is universally present. Other common clinical features include gastrointestinal anomalies, hematologic disorders, endocrine disorders, sleep apnea, and atlantoaxial instability. The reader is encouraged to consult other sources for in-depth information on noncardiac features of DS.

Congenital heart disease is present in about half of live-born DS patients. Of these, approximately 40% will have a complete atrioventricular septal defect (AVSD), which is synonymous with atrioventricular canal defect or endocardial cushion defect. When primum atrial septal defects (ASDs) and transitional AVSDs are included, this number increases to almost 60%. Other commonly encountered forms of CHD include secundum ASDs, perimembranous and muscular ventricular septal defects (VSDs), tetralogy of Fallot (with or without AVSD), and hemodynamically significant patent ductus arteriosus (PDA). In DS patients with congenital heart disease, cardiac treatment does not differ from non-syndromic patients. Commonly encountered problems in DS, which may directly affect the cardiovascular system, include thyroid abnormalities and obstructive sleep apnea. Pulmonary hypertension commonly develops if certain cardiovascular defects are not repaired during the first months of life.

Many patients with Down syndrome are diagnosed prenatally and undergo a screening fetal echocardiogram. A screening echocardiogram should be performed in patients with newly recognized DS at birth, since complete or transitional AVSD may not have a distinctive murmur at this time. A consultation with a pediatric cardiologist should be obtained if any cardiac anomaly is identified. In addition, evidence of pulmonary hypertension should be monitored, particularly in those with late repairs.

Trisomy 18 (Edwards Syndrome)

Trisomy 18 is the second most common autosomal trisomy in live-borns (after trisomy 21) and occurs in

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approximately 1 in 6,000 live births. Trisomy 18 is characterized by multiple congenital anomalies and early death. Like DS, most patients have a nondisjunction. However, unbalanced translocations and mosaicism also occur. Around 80% of live cases are found in females. Males with this trisomy have decreased pre- and postnatal survival. Neonates with trisomy 18 are often small for gestational age. Common physical findings include a prominent occiput, short palpebral fissures with droopy eyelids, micrognathia, external ear abnormalities, clenched fist, underdeveloped thumbs, short sternum, rocker-bottom feet, and redundant skin in the back of the neck. Congenital heart disease is present in between 80% and 100% of these patients. Other less common abnormalities include cleft lip and/or cleft palate and abnormalities of the bowel, kidneys, or brain structure. Patients with the mosaic or translocation forms often have fewer of these features than those with nondisjunction.

The prognosis for patients with trisomy 18 is very poor. Fifty percent die by 6 months of age and 90% die by 1 year of age commonly due to evolving symptoms related to their heart disease. Patients who live beyond infancy have severe developmental delays. Because of these features, parents may elect to terminate a pregnancy with trisomy 18 or provide only comfort care after birth.

As noted above, congenital heart defects frequently occur in these patients. The most common lesions are atrial septal defects, ventricular septal defects, patent ductus arteriosus, and polyvalvular disease. Other lesions that occur less frequently include double outlet right ventricle and hypoplastic left heart syndrome. Due to the poor prognosis, the majority of medical centers do not offer surgery to repair congenital heart defects in this population. If necessary, heart failure is managed medically. However, a few reports have described the experience with performing cardiac surgery for these patients.

Trisomy 13 (Patau Syndrome)

Trisomy 13 (also known as Patau Syndrome) occurs in approximately 1/10,000–1/15,000 newborns. Like the other trisomies, most patients have a nondisjunction, but mosaicism and translocations also occur. Patients with trisomy 13 have multiple malformations and severe developmental delay. The prognosis is extremely poor with an 82% mortality within the first month and 5% survival at 6 months of age. Like trisomy 18, many parents choose to terminate pregnancies affected with this disorder or perform comfort care in live-borns. Common characteristics include orofacial clefting, microphthalmia/anophthalmia, cutis aplasia of the scalp, and postaxial polydactyly of the limbs. Cardiac malformations are present in about 80% of individuals. The most common cardiac lesions in this disorder are atrial septal defects, ventricular septal defects, patent ductus arteriosus, and dextrocardia. Symptoms related to these lesions are a common cause of death in this population. Like trisomy 18, cardiac surgery is not usually offered due to the extremely poor long-term prognosis. However, there are a few sporadic reports of surgery for these patients. Other malformations include holoprosencephaly, omphalocele, genital abnormalities, renal defects, and seizures.

22q11 Deletion Syndrome

22q11 deletion syndrome is also referred to as DiGeorge syndrome, velocardiofacial syndrome, Shprintzen syndrome, cardiac anomaly face syndrome, or Takao syndrome. These syndromes share a common genetic origin, namely a deletion at chromosome 22q11. This abnormality results in a developmental field defect that affects derivatives of the branchial arch/pharyngeal pouch system. 22q11 deletion syndrome is characterized by aplasia or hypoplasia of the thymus, aplasia or hypoplasia of the parathyroid gland, cardiac malformations, and specific facial features. The estimated incidence is 1 per 5,950 live births.

The clinical features of the 22q11 deletion syndrome are highly variable. The most common manifestations include cardiovascular anomalies, palate anomalies, feeding disorders, speech and learning disabilities, renal anomalies, and behavioral disorders. Additional problems include hypocalcemia, immunodeficiency, skeletal abnormalities, and growth hormone deficiency. The typical facial features include tubular nose, hypoplastic alae nasi, bulbous tip nose, low set or dysplastic ears, and myopathic facies. Manifestations that present in the child include hypernasal speech, learning disabilities, behavioral disorders (such as ADHD), and psychiatric disorders (bipolar disorder and/or schizophrenia).

The most commonly encountered cardiovascular defects in this disorder include tetralogy of Fallot (TOF), interrupted aortic arch type B (IAA type B), truncus arteriosus, conoventricular septal defects, and other aortic arch anomalies. The arch anomalies include right aortic arch, cervical location, or abnormal branching patterns. These defects fall into the general category of conotruncal lesions based upon embryological development. As noted,

22q11 deletion syndrome is especially common in patients with IAA type B and is found in between 50% and 89% of patients with this specific lesion. Among patients with TOF, the deletion is more common with absent pulmonary valve syndrome or aortopulmonary collateral vessels. Patients with transposition of the great arteries or double outlet right ventricle rarely have a 22q11 deletion. The early identification of patients with 22q11 deletion is important in order to screen for disorders that may affect the immediate management such as hypocalcemia and immune defects. Patients should be given leukocyte-depleted and CMV-negative blood.

Data supports genetic testing in all infants with IAA type B, truncus arteriosus, TOF with absent pulmonary valve, TOF with aortic arch abnormalities, TOF with aortopulmonary collaterals, perimembranous VSDs with associated arch anomalies, and isolated aortic arch abnormalities. It is unclear whether testing infants with TOF without additional lesions is cost effective. Only about 6% of isolated TOF patients are estimated to have a 22q11 deletion. Therefore, a careful clinical and laboratory evaluation is indicated to identify supportive features prior to performing genetic testing. Genetic testing consists of fluorescent in situ hybridization (FISH) for the 22q11 deletion.

22q11 deletion syndrome is inherited in an autosomal dominant manner from a parent in around 6–28% of cases. The affected parent may not be identified until the diagnosis is made in their child. Importantly, a parent with the deletion has a 50% chance of transmitting this abnormality to their offspring.

Williams–Beuren Syndrome (Williams Syndrome)

Williams syndrome (WS) is an autosomal dominant disorder that occurs in about 1 per 20,000 live births. WS is characterized by specific cardiovascular defects (typically supravalvular aortic and pulmonic stenosis), infantile hypercalcemia, skeletal and renal anomalies, cognitive defects, "social personality," and elfin facies. Unrecognized hypercalcemia is a risk factor for nephrocalcinosis and can lead to renal failure. In the long term, patients are at risk for developing hypertension due to either renal artery stenosis or another yet unidentified mechanism. Approximately 90% of those with a clinical diagnosis are found by FISH analysis to have a microdeletion at chromosome 7q11.23. The clinical phenotype corresponds with deletions or alterations of specific genes within the affected region. For example, cardiovascular manifestations are associated with alterations in the elastin gene.

Because of the clinical variability and the fact that characteristic facial features are not particularly evident in infants, it is appropriate to consider FISH testing for WS in all infants with the characteristic cardiac lesions (discussed below). Most cases arise as de novo mutations.

The most common cardiovascular abnormalities include supravalvular aortic stenosis (SVAS), supravalvular pulmonary stenosis, and peripheral pulmonary stenosis. The degree of cardiovascular involvement varies widely across patients. Pulmonary lesions, especially peripheral pulmonary branch stenosis, typically improve over time and commonly predate the development of SVAS. However, SVAS is often progressive. Significant stenosis in either the pulmonary artery or aorta can cause ventricular hypertrophy and lead to heart failure. Nearly half of WS patients will require cardiac surgery, most commonly for supravalvular aortic stenosis. Current surgical management for supravalvular aortic stenosis typically involves patch augmentation to enlarge the area of narrowing. Sudden death has also been reported in these patients. Many of the deaths are associated with coronary artery stenosis and severe biventricular outflow stenosis. The mechanism of death is believed to be due to myocardial ischemia, decreased cardiac output, or arrhythmias.

Alagille Syndrome

Alagille syndrome is multisystem disorder affecting the liver, heart, eyes, skeletal system, and face. Disease severity can vary greatly between patients and even within families. The primary diagnostic feature is bile duct paucity on liver biopsy. However, this finding may not be present until after the neonatal period. Liver manifestations include chronic cholestasis, minimal liver enzyme elevation, hypercholesterolemia, or rarely liver failure. Butterfly vertebrae are the most common skeletal feature. Ophthalmological findings include posterior embryotoxon. Finally, facial features include a prominent forehead, deep-set eyes with moderate hypertelorism, pointed chin, and saddle or straight nose with a bulbous tip. These features give the face the appearance of an inverted triangle.

Cardiovascular complications are almost universally present, primarily affecting pulmonary circulation. Typical cardiac lesions include peripheral pulmonary artery hypoplasia, tetralogy of Fallot, and pulmonary valve stenosis. Tetralogy of Fallot is found in between 7% and 16% of individuals. Beyond cardiac lesions, neurovascular accidents are common with reported at rates as high as 15% and accounting for 34% of total mortality in one large

study. At this time, presymptomatic screening for CNS vascular abnormalities has not been formally recommended. However, all patients with CNS complaints should undergo vascular imaging studies.

Alagille syndrome should be suspected in any patient with hepatic abnormalities in addition to the typical cardiac lesions. To make the diagnosis, a histological finding of bile duct paucity plus three of the five major clinical criteria are necessary. The major clinical criteria include: cholestasis, cardiac defects, skeletal abnormalities, ophthalmologic abnormalities, and the characteristic facial features. If an affected first-degree relative is identified, the presence of only one feature is necessary to make the diagnosis. Unless they have already been performed, all newly diagnosed individuals should undergo cardiac, hepatic, ophthalmologic, orthopedic, hematologic, and renal evaluations.

The main reason to perform genetic testing is to offer a recurrence risk for families. The two genes have been found in association with Alagille syndrome. The most common mutation is in the *JAG1* gene, which is present in around 90% of clinically identified patients. *NOTCH2* mutations are rarely found in this disorder at less than 1% of patients. Sequence analysis is clinically available for both *JAG1* and *NOTCH2* in the United States. Interestingly, half of mutation-positive relatives of affected individuals in one study did not meet clinical diagnostic criteria.

Alagille syndrome is inherited in an autosomal dominant manner. Approximately 30–50% of individuals have an inherited mutation and about 50–70% have a de novo mutation. Prenatal testing is possible if the *JAG1* disease-causing mutation or deletion is identified in an affected family member. Although testing can determine whether or not the fetus has inherited the *JAG1* disease-causing mutation or deletion, it cannot predict the occurrence or severity of clinical manifestations.

Noonan Syndrome

Noonan syndrome (NS) is characterized by short stature, characteristic facies, and cardiovascular abnormalities. Additional features include a broad neck, chest deformity, cryptorchidism, variable coagulation defects, lymphatic dysplasias, and developmental delays of variable degrees. NS is inherited in an autosomal dominant manner, although most cases are sporadic. The incidence is estimated to be between 1/1,000 and 1/2,500 live births. There are currently four genes known to be associated with NS: *PTPN11, KRAS, SOS,* and *RAF1.*

NS does not have defined diagnostic criteria; therefore, the diagnosis is made by observation of the key clinical features. The cardinal features are: short stature, congenital heart disease, developmental delay of variable degree, broad or webbed neck, chest deformity with a superior pectus carinatum and inferior pectus excavatum, low set nipples, cryptorchidism in males, and characteristic facies. The described facial findings includes hypertelorism, posteriorly rotated and low set ears with fleshy helices, vivid blue or blue green irises, epicanthal folds, and thick or droopy eyelids. Importantly, the facial features are most apparent in the neonate and in middle childhood.

Cardiac involvement is present in 80–90% of patients. The most common cardiac complications are pulmonary valve stenosis and hypertrophic cardiomyopathy. Additional cardiac findings include secundum ASD, AVSD, mitral valve abnormalities, coarctation of the aorta, and tetralogy of Fallot. Pulmonary stenosis is found in about 60% of patients; however fewer than half require intervention. Severe pulmonary stenosis is typically treated with balloon pulmonary valvuloplasty initially, but will often require surgical valvuloplasty or valvectomy. In nonsyndromic patients, isolated pulmonary stenosis is rarely progressive beyond infancy. However, pulmonary stenosis in NS can progress beyond this timeframe. In patients requiring an intervention, lifelong follow-up is necessary especially if significant pulmonary regurgitation develops.

Hypertrophic cardiomyopathy occurs in around 20–30% of patients, sometimes coexisting with structural heart lesions. The course and prognosis for hypertrophic cardiomyopathy in NS is variable and not well understood. The hypertrophic cardiomyopathy may not develop until late in childhood and gradually progress; rarely it is rapidly progressive in infancy. Treatment is similar to other forms of hypertrophic cardiomyopathy and includes the use of β-blockers and surgery for severe outflow tract obstruction. Occasionally, heart failure will not be amenable to medical therapy and heart transplantation is required. The risk of sudden death in this population is unknown with few case reports in the literature. Of note, the largest natural history follow-up study (of 112 patients) did not identify any cases of sudden death.

As mentioned above, NS is a genetically heterogeneous disorder with four genes identified thus far. *PTPN11* is the most commonly affected gene with abnormalities identified in about 50% of NS individuals. *SOS* is the next most commonly affected gene at approximately 13%. *RAF1* mutations are found in 3–17% and KRAS is found in $<$5% of patients. Clinical genetic testing is available in North America. For the recommended genetic testing algorithm, the reader should refer to the NS review at

www.genetests.org. LEOPARD syndrome has significant overlap with NS and shares mutations in *PTPN11* and *RAF1*. LEOPARD syndrome is characterized by lentigines, ECG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormalities of genitalia, growth retardation, and deafness. It is differentiated from NS by the presence of pigmentary findings.

Genotype–phenotype correlations exist within NS. *PTPN11* mutations are more common in patients with pulmonary stenosis, but uncommon in patients with hypertrophic cardiomyopathy. *RAF1* mutations are strongly correlated with hypertrophic cardiomyopathy in NS with around 95% patients developing this complication.

NS is an autosomal dominant disorder. Many affected individuals are found to have a de novo mutation. An affected parent is identified in 30–75% of cases. The risk of having additional offspring with this disorder depends on the genetic status of the parent. Prenatal testing is available if the disease-causing allele has been previously identified in an affected family member.

Holt–Oram Syndrome

Holt–Oram syndrome (HOS) is the most common of the "heart–hand" syndromes. It is characterized by skeletal anomalies of the upper limb, congenital heart disease, and/or cardiac conduction abnormalities. The incidence is 1 per 100,000 live births. Mutations in the *TBX5* gene are found in approximated 75% of affected individuals. The condition shows an autosomal dominant inheritance pattern; however, most cases result due to de novo mutations.

The diagnosis of HOS should be suspected in any patient with an upper limb defect and heart anomalies. It should also be considered in any patient with an apparently isolated septal defect and family history of upper limb abnormalities. All patients with HOS have anomalies involving the preaxial radial ray. Typically, skeletal anomalies include a triphalangeal, hypoplastic, or absent thumb. Importantly, some patients have subclinical skeletal abnormalities (such as to the carpel bone) that can only be picked up radiographically. Anomalies can be present in one or both upper limbs and can be symmetric or asymmetric.

Approximately 75% of patients with HOS have cardiac abnormalities. Secundum ASDs and VSDs are the most common structural heart lesions, but more complex lesions have also been identified. Atrioventricular conduction delays are another important feature that require lifelong surveillance. Sinus bradycardia and first-degree atrioventricular (AV) block represent the initial manifestations. AV block can progress and lead to symptoms such as syncope. Yearly ECG is recommended for all HOS patients as well as 24-h Holter monitor for those with identified conduction abnormalities.

Clinical genetic testing for the *TBX5* is available; however, failure to identify a mutation does not alter management or diagnosis. HOS is inherited in an autosomal dominant manner. Approximately 85% of diagnosed patients have a de novo mutation. Offspring of an affecting individual are at 50% risk of also being affected. Prenatal molecular genetic testing may be performed if the disease-causing mutation has been identified in an affected relative.

Muscular Dystrophy

The muscular dystrophies are a genetically diverse group of disorders that are characterized by progressive muscle weakness. The various forms of muscular dystrophy are classified by their specific gene defect, pattern of skeletal muscle involvement and unique clinical features. In the heart, the primary pathology is that of a cardiomyopathy, although abnormalities of the conduction system can occur. Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) are the largest group of muscular dystrophies that affect the heart. As such, this chapter will primarily focus on these disorders. However, a brief mention of cardiovascular problems in other muscular dystrophies will be included.

The responsible gene for DMB/BMD is called *DMD* and is found on the short arm of the X chromosome. This gene encodes for the protein dystrophin. DMD and BMD are similar disorders that differ in severity due to the amount or quality of the protein from the dystrophin gene. Patients with DMD typically express less that 3% dystrophin on skeletal muscle biopsies. BMD is a more clinically heterogeneous disorder with varying dystrophin expression. Patients with BMD can have mild to severe disabilities depending upon the specific gene mutation. The incidence of DMD is 1 in 3,500 boys while the incidence in BMD in estimated at 1 in 30,000 boys. The condition is X-linked and thereby almost exclusively affects males. However, female carriers can be at risk for muscle disease and cardiomyopathy (discussed below).

Typically, patients with DMD will begin to manifest symptoms of muscle weakness around 3 years old and nearly all are wheelchair dependent by age 12 years. The diaphragm and intercostal muscles are affected leading to poor cough, aspiration, and a predisposition to

pneumonia. DMD patients often require some form of respiratory support. IQ is typically 1 standard deviation below the normal population. Finally, survival can reach into the late teens to early twenties and is primarily determined by cardiopulmonary status.

BMD patients have later-onset skeletal muscle weakness. As such, they are not wheelchair dependent until after age 15 years and may not require one until the third decade of life. The mean age of death in BMD is in the mid-forties.

The diagnosis of DMD and BMD is beyond the scope of this chapter and is covered elsewhere. Briefly, DMD typically presents with muscle weakness starting before age 5 years old whereas BMD presents later. Creatine phosphokinase (CK) levels are typically five (BMD) to ten (DMD) times normal. After an elevated CK is found, molecular genetic analysis of the dystrophin gene should be performed. If no mutation is found, consideration for a skeletal muscle biopsy with western blot and immunohistochemistry studies for dystrophin is warranted.

Dilated cardiomyopathy (DCM) is a common feature to both BMD and DMD. Prior to the development of overt DCM, histological studies have shown cardiac muscle replacement with fat and fibrosis. The fibrosis eventually leads to ventricular dysfunction and dilation. The conduction system can also be affected by fibrosis, potentially leading to arrhythmias.

Owing to the significant physical limitations in DMD, the DCM does not usually present with the typical features of heart failure. Potential signs of heart failure in this population include altered duration and quality of sleep, pronounced fatigue, and unexplained weight loss or gain. Children with BMD have milder skeletal muscle involvement and therefore may present with more typical signs of heart failure such as activity intolerance. The cardiac exam is seldom abnormal even in the face of a significant cardiomyopathy. The incidence of DCM in DMD increases throughout the teenage years, with approximately one-third of individuals being affected by age 14 years, one-half by age 18 years, and essentially all individuals after age 18 years. In patients with BMD, heart failure is a common cause of morbidity and is the most common cause of death.

Arrhythmias and electrocardiographic abnormalities are also common. The classic EKG in older DMD patients consists of tall R waves in the right precordial leads and prominent Q waves in the left precordial and limb leads. Between 30% and 50% of children with DMD have a sinus tachycardia independent of cardiac function. Arrhythmias may eventually arise including ectopic atrial tachycardia, atrial fibrillation, transient second- and third-degree AV block, and ventricular tachycardias. The risk of sudden death due to ventricular fibrillation is increased in those with the presence of multiform premature ventricular contractions and ventricular tachycardia on Holter monitor.

Appropriate management of patients with DMD/BMD can prolong survival and improve quality of life. The predictability in the onset of cardiomyopathy and potential lack of symptoms mandate screening examinations for optimal care. The American Academy of Pediatrics published cardiac screening recommendations. In DMD, complete cardiac evaluation at least every 2 years should begin in early childhood. At approximately age 10 or at the onset of cardiac dysfunction, annual cardiac evaluation is recommended. For BMD, cardiac evaluations should begin at approximately age 10 years or at the onset of cardiac signs and symptoms. Evaluations should continue at least every 2 years as long as cardiac function remains normal.

Echocardiography is the mainstay of cardiac functional evaluation. The commonly used parameters of ventricular function include end-diastolic and end-systolic dimensions, shortening and ejection fractions, and sphericity indices. New functional measures are being developed in echocardiography and applied to muscular dystrophy patients. For example, tissue Doppler-echocardiography can show decreased systolic contraction and diastolic relaxation in DMD patients with an otherwise normal-appearing echocardiogram. It is important to note that acoustic windows are often limited in these patients due to problems such as scoliosis and chest wall adiposity. Therefore, additional assessment tools are necessary.

Cardiac magnetic resonance imaging (MRI) is another modality to evaluate cardiac function. Global and regional ventricular function is easily obtainable even in patients with difficult echocardiographic imaging. Unlike echocardiograms, cardiac fibrosis and novel early functional abnormalities can also be determined by MRI. The role of these newer markers of cardiac dysfunction detected by MRI or tissue Dopper echo in regards to treatment and prevention of DCM in this patient population remains to be established.

The approach to the treatment and prevention of cardiomyopathy in muscular dystrophy patients differs between institutions. There is still a need to establish the functional parameters that best indicate the need for starting treatment as well as long-term therapeutic outcomes. Nevertheless, some consensus has emerged around the findings of Jefferies et al. In this study, therapy was started with an angiotensin-converting enzyme inhibitor

(ACE inhibitor) once the left ventricular ejection fraction dropped below 55% or left ventricular dilation developed (>2 standard deviations from the normal value based upon body surface area). A β-blocker, typically carvedilol or metoprolol, was added if cardiac function did not return to normal values after 3 months of ACE-inhibitor therapy. This treatment algorithm resulted in stable findings in 2/29 patients, improvement in 8/29, and normalization in 19/29 (16 DMD, 3 BMD). In overt heart failure, digitalis and diuretics are added to the above therapies. Cardiac transplantation may be an option for some patients with BMD with limited skeletal muscle involvement.

As noted, arrhythmias are another potential complication. Ventricular tachyarrhythmias are often treated initially with β-blockers, followed by sotalol or flecainide if necessary. Additionally, an automatic implantable cardioverter defibrillator or automated external defibrillator may used to prevent sudden arrhythmic death.

Female carriers of the DMD/BMD are at an increased risk for developing a DCM. A consensus conference estimated that approximately 10% of female carriers will develop heart failure in the absence of skeletal muscle involvement and nearly half will develop preclinical disease. In light of this, the American Academy of Pediatrics established cardiac screening guidelines in 2005. These guidelines state that carriers should be educated as to the risk of developing cardiomyopathy and the signs of heart failure, have a complete cardiac evaluation starting in late adolescence/early adulthood, have follow-up complete cardiac evaluation every 5 years, and, if necessary, be treated similarly as male patients with DMD/BMD. Unfortunately, a recent survey demonstrated that about one-third of carriers have never had any cardiac testing.

As noted above, mutations in the *DMD* gene are associated with DMD and BMD. Commercial genetic testing for this gene is available. Virtually all males with DMD and at least 85% of males with BMD have identifiable *DMD* mutations. DMD/BMD are inherited in an X-linked manner. The risk to siblings of a proband depends on the carrier status of the mother. Carrier females have a 50% chance of transmitting the *DMD* mutation in each pregnancy. Sons who inherit the mutation will be affected, whereas daughters who inherit the mutation are carriers. After the disease-causing mutation is identified in a proband, female siblings and the mother should undergo testing for the same mutation to establish their carrier status and need for ongoing cardiac screenings. Prenatal testing for pregnancies at increased risk is also possible.

Cardiac Involvement in Other Forms of Muscular Dystrophy

The limb-girdle muscular dystrophies (LGMDs) are a genetically and phenotypically diverse group of disorders that are classified into at least separate 13 types. Routine cardiac evaluations are recommended for subtypes LGMD1B, 2E, 2F, and 2I. Cardiac complications include ECG abnormalities, conduction defects, atrial and ventricular arrhythmias, and DCM. Subtypes LGMD2A, 2B, 2G, 2H, 2J, 1A, and 1C do not have described cardiac complications and therefore do not require cardiac surveillance.

Emery–Dreifuss muscular dystrophy (EDMD) has a unique set of clinical features including contractures of the elbow, Achilles tendon, and posterior cervical muscles prior to the development of muscle weakness. Arrhythmias are an important problem in this disorder. Patients may have prolonged PR intervals, atrial fibrillation/flutter, bradyarrhythmias, and tachyarrhythmias. Some patients develop ventricular dilation. Pacemaker therapy may be necessary to treat severe or life-threatening rhythm disorders.

Marfan Syndrome

Marfan syndrome (MFS) is an autosomal dominant, systemic connective tissue disorder that affects 1 per 3,000–5,000 individuals. Multiple organ systems are affected including the eye, skeleton, skin and integument, lung, and cardiovascular system. There is a broad range of clinical severity among patients with MFS. Some patients present with a severe and rapidly progressive form starting at birth, while some are not diagnosed until after an affected offspring is found. The diagnosis of MFS is primarily based upon clinical criteria. Most patients have a mutation of the gene *FBN1*, which encodes for the extracellular matrix protein Fibrillin-1.

Typical eye disorders found in MFS include lens dislocation and myopia. Skeletal system abnormalities are characterized by joint laxity and bone overgrowth. Patients with MFS have long arms and legs compared to their trunk. Overgrowth of the ribs leads to pectus excavatum or carinatum. Scoliosis is also common. The typical facial features include a long and narrow face with deep-set eyes, down slanting palpebral fissures, malar hypoplasia, and a small chin. Patients are at risk for a spontaneous pneumothorax, orthodontia, and stretch marks.

As noted, the diagnosis of MFS is based upon a set of clinical criteria commonly referred to as the Ghent

criteria. Changes to the criteria are under preparation, but were not published at the writing of this chapter. Therefore, the reader should consult the medical literature for the updated diagnostic criteria. Genetic testing for the *FBN1* gene is possible (discussed below) and may help make the diagnosis in some situations. It is important to note that many manifestations are age-dependent, which diminishes the utility of the Ghent criteria in children. Therefore, children with some features of MFS or with a family history require repeat evaluations throughout childhood before the diagnosis of MFS is excluded.

Cardiovascular complications are the most serious aspect of MFS. Prior to effective surgical approaches for aortic root disease, over 90% of deaths in MFS were due to cardiovascular disease. Commonly encountered cardiac abnormalities include proximal ascending aortic dilation, aortic dissection, aortic valve regurgitation, main pulmonary artery dilation, prolapse of the atrioventricular valves, and mitral annular calcification. Aortic root dilation and dissection are the leading cause of morbidity and mortality. Rarely, infants and young children will have severe mitral prolapse and regurgitation leading to heart failure and potentially valve replacement.

Severe aortic root dilation can lead to a life-threatening dissection. Aortic root dilation is progressive in MFS and may not be present during the initial exam. The features associated with the greatest risk of dissection include an aortic root diameter greater than 5.0 cm, rapidly increasing aortic size (>0.5 cm/year), and a family history of early aortic dissection. These high-risk features are readily detectable during a through cardiac evaluation; therefore, surveillance screening is important to prevent catastrophic complications. In the authors' institutions, screening exams with an echocardiogram are typically performed yearly. Patients with rapidly increasing aortic dilation or an absolute aortic root measurement >4 cm require follow-up echocardiograms every 6 months.

Medical treatment is initiated once aortic root dilation is detected (Z score >2 for body surface area). The current standard of practice is to use β-adrenergic blocking agents as initial therapy, most commonly atenolol. The first and largest randomized trial on the use of β-blockers in adults with MFS was reported in the 1990s. Thirty-three treated and 38 similar untreated Marfan patients were enrolled. Patients were followed prospectively for 10.7 years in the treatment group. Medications were titrated to achieve a heart rate of <100 beats/min during submaximal exercise. The rate of growth in the proximal aorta was significantly lower in the treated patients. Overall event-free survival was not different between the groups at the end of the study; however, event rates in the treated group were significantly lower during intermediate years of follow-up. In adults, the β-blocker dose is titrated to achieve a resting heart rate of <60 beats/min assuming no bothersome side effects. Based upon expert recommendation, the dose in children is typically adjusted to maintain the heart rate at 110 beats/min during submaximal exercise.

Recently, molecular studies utilizing a mouse model of MFS have shown that upregulation in transforming growth factor-beta (TGF-β) signaling may account for disease manifestations and progression. TGF-β inhibition through either blocking antibodies or losartan prevented aortic dilation in this mouse model. Limited, nonrandomized clinical data has suggested that losartan may slow the rate of aortic dilation in children, but the patient numbers are too small to judge at present. Currently, a randomized clinical trial comparing β-blockers (atenolol) versus losartan for the treatment of aortic dilation in MFS is being conducted by the Pediatric Heart Network and NIH. It is hoped that this study will provide important therapeutic guidance for the medical management of MFS patients.

Exercise limitations are another important component in preventing catastrophic events in MFS patients. Strenuous static exercise, such as heavy weightlifting, is contraindicated due to the marked increase in aortic wall stress. Contact sports should also be avoided in patients with aortic root dilation. In general, patients with no aortic root dilation can participate in low and moderate static exercise and low dynamic activity. Once the aorta becomes dilated, only low dynamic exercises are recommended. For details about specific exercises, the reader is referred to the *36th Bethesda Conference* document for details.

The timing of aortic root surgery is critically important to prevent morbidity and mortality from acute aortic dissection. Elective replacement carries a lower risk than emergency repair of a dissection. As discussed above, the risk of dissection is proportional to the overall diameter of the ascending aorta. The American Heart Association/American College of Cardiology recommend elective surgery for an aortic root diameter >50 mm, while the European Society of Cardiology recommend surgery at a diameter >45 mm. Patients with a family history of dissection at a smaller aortic root diameter (<50 mm) or with a diameter increase greater than 5 mm/year may be considered for early elective surgery provided that the procedure is performed at a center with established expertise. The optimal timing for elective surgery in children is unknown. Fortunately, aortic dissection is rare in children with MFS under 12 years old. Commonly used surgical indications in children include aneurysms that meet adult criteria for intervention, rapid

enlargement (>10 mm/year), and progressive aortic regurgitation. Surgical intervention in all age groups includes replacement of the aortic root and valve with a valved composite graft or replacement of the root only with a valve-sparing aortic root replacement.

Mitral valve prolapse (MVP) with or without mitral regurgitation (MR) is another important cardiac complication of MFS. In the general population, MVP has an estimated prevalence of between 0.6% and 2.4%. The prevalence is increased in MFS to at least 28%. Children with MFS and MVP typically have only a small amount of MR that does not cause heart failure symptoms. However, the MR can slowly progress over time necessitating follow-up evaluations as part of the routine aortic root screening.

When significant MR is present, left ventricular enlargement and failure can ensue. While uncommon, MVP with severe MR is the leading cause of cardiovascular morbidity and mortality in young children with MFS. Indication for mitral valve repair or replacement in patients with severe MR include: clinical symptoms of heart failure; asymptomatic patients with left ventricular enlargement and/or diminished ejection fraction; new onset atrial fibrillation (presumably due to left atrial enlargement); and pulmonary hypertension.

Children often present for evaluation of MFS based upon a family history of the disease. Therefore, it is important to understand the genetics of this disease. MFS is inherited as an autosomal dominant condition. It is estimated that about 75% of patients have an affected parent and the remaining cases arise from a de novo mutation. *FBN1* is the only known causative gene. Genetic testing is commercially available for *FBN1*. Mutation detection frequency is between 70% and 93%. The diagnosis of MFS remains primarily clinical. However, a positive genetic test can confer the diagnosis in a patient with one major organ system involvement and minor involvement of a second. Genetic testing is also useful for screening presymptomatic individuals (like those sent for evaluation based only upon a positive family history) when the pathological mutation within a family is known. If the patient has the same mutation as the affected relative, then continued cardiovascular monitoring is necessary. However, if they do not have the mutation, then follow-up evaluations are probably not necessary. Prenatal and preimplantation genetic testing is available.

Loeys–Dietz Syndrome

Loeys–Dietz syndrome (LDS) is a recently described connective tissue disease associated with arterial aneurysms and dissections as well as skeletal manifestations. Importantly, aortic dissection can occur at diameters smaller that those observed in MFS.

TGFBR1 and *TGFBR2* are the only genes currently known to be involved in this disorder. These genes code for the transforming growth factor beta-receptors 1 and 2. Unlike MFS, arterial aneurysms and tortuosity are often present at sites distant from the aortic root. Other common manifestations include a bifid uvula or cleft palate, ocular hypertelorism, craniosynostosis, translucent skin, pectus excavatum or carinatum, scoliosis, joint laxity, and arachnodactyly. Females are at risk for uterine rupture during pregnancy.

Specific diagnostic criteria for LDS have not been established. Typically, the diagnosis is rendered when a patient has findings from some of the commonly affected organ systems in addition to identification of a disease-causing mutation on genetic testing. The four main groups of clinical findings are vascular, skeletal, craniofacial, and cutaneous. Vascular findings include aortic root dilation or dissection and distal arterial aneurysms and tortuosity. Skeletal manifestations include pectus excavatum or carinatum, scoliosis, joint laxity, arachnodactyly, and talipes equinovarus. Craniofacial findings include ocular hypertelorism, bifid uvular/cleft palate, and craniosynostosis. Finally, cutaneous features include translucent skin, easy bruising, and dystrophic scars. It has been our practice to perform genetic testing on patients with aortic root dilation who have any features from the other main groups of clinical findings. Some patients with aortic dilation and dissection have mutations in the *TGFBR1/2* genes without other features of LDS. Therefore, consideration should be given for genetic testing in families with multiple members with only aortic or other arterial dilation. Finally, it has also been our practice to consider genetic testing for the *TGFBR1/2* in patient that have had aortic dissections at diameters less than 5 cm, unless another causative condition is identified.

LDS is often divided into two subtypes. Patients with LDS type I (around 75% of LDS patients) do not typically have cutaneous abnormalities. LDS type II constitutes the remaining patients and does not typically have craniofacial findings with the exception of isolated bifid uvula. There is considerable overlap between the subtypes.

The most important complication in LDS is aortic root dilation and dissection. As noted above, dissection can occur at aortic dimensions that are not considered high risk in MFS. Additionally, aortic dissections have been reported in infancy and early childhood. Around half of LDS patients have dilation or tortuosity in the arterial tree away from the aortic root. Notably, these distal

lesions are not detected by echocardiogram. These features differentiate the vascular disease in LDS from MFS. Additional cardiac malformations include patent ductus arteriosus, atrial septal defects, and bicuspid aortic valve.

Most practitioners employ an aggressive screening regiment to monitor aortic and distal aneurysmal growth. Echocardiographic evaluation of the aortic root is recommended every 6 months. Due to the potential for distal aneurysms, imaging of the vascular tree from the head to the pelvis with either an MR or CT angiogram should be performed at diagnosis and at least yearly thereafter.

No therapeutic trials have been published on the prevention of aneurysmal dilation in LDS patients. Medical management is based upon the recommendations for MFS. Most patients are managed with either β-adrenergic blocking agents or losartan. Exercise recommendations are similar to MFS.

Elective aortic root replacement has been utilized in LDS to prevent catastrophic aortic dissection and rupture. Williams and colleagues published their surgical experience with this disorder in 2007 and offered elective surgical guidelines. The reader should consult this manuscript for complete details. Briefly, elective aortic root replacement is recommended when the maximal diameter reaches 4.0 cm in adults or adolescents. In children, elective root replacement is recommended when the aortic root Z-score exceeds 3.0 or the diameter is expanding by greater than 0.5 cm/year. The authors made an effort to delay surgery in children until the aortic annulus exceeded 1.8 cm in order to allow for the placement of graft that would accommodate patient growth. An extensive family history of dissection at a smaller diameter versus no dissection at a larger diameter may allow the clinician to modify these recommendations for select patients. No early surgical deaths were reported in this series. However, some patients died of a dissection prior to undergoing surgery. About one-third of surgical patients required an additional operation during the study period illustrating the importance of lifelong surveillance of the vascular tree.

A recent paper suggested that the risk for dissection may differ between *TGFBR1* and *TGFBR2* mutations. In this study, 30 patients with *TGFBR1* mutations were compared to 77 with *TGFBR2* mutations. The data suggested that patients with *TGFBR2* mutations are more likely to dissect at aortic diameters less that 5.0 cm than those with *TGFBR1* mutations. In fact, no patients with a *TGFBR1* mutation had a dissection at an aortic diameter less than 5 cm in this series. Future elective aortic root replacement recommendation may take this finding into account. However, more studies are necessary to validate this result.

Like MFS, many children present for evaluation based upon a positive family history. LDS is an autosomal dominant condition and offspring have a 50% chance of inheriting this condition from an affected parent. *TGFBR1* and *TGFBR2* are the only known causative genes. Commercial genetic testing is available in North America. It is currently estimated that about 95% of patients with typical findings of LDS have a positive genetic test. *TGFBR2* accounts for about 75% of the causative mutations. Approximately, 75% of probands have LDS as the result of a de novo mutation. However, family members should have screening evaluations with experts in LDS to determine whether they are at risk for the diagnosis.

Turner Syndrome

Turner syndrome (TS) is caused by loss of all or part of one X chromosome in females (45 X or 45X/46XX). The birth incidence is estimated at 1 per 2,000 live births; however many fetuses with this condition are lost during pregnancy. The main features of TS include short stature, early ovarian failure, and congenital heart defects. Lymphatic abnormalities are common in the neonate and lead to neck webbing, protruding ears, loose nuchal skin, low hairline, puffy hands and feet, and deep-set nails. Renal anomalies are often present and all patients should have a screening renal ultrasound. Many patients receive growth hormone therapy to treat the short stature associated with this syndrome. The diagnosis of TS is typically based upon the presence of the above clinical findings with confirmatory karyotype analysis. Because mosaicism is common, an adequate karyotype should include at least 30 cells.

Both congenital and later-onset cardiac defects are found in TS. Left-sided obstructive lesions are the major associated congenital lesions. Bicuspid aortic valve with or without stenosis is present in approximately 15–25% of TS patients. Coarctation of the aorta (∼10%) may cause early hemodynamic impairment potentially necessitating surgery or interventional catheterization. Interestingly, neck webbing is associated with bicuspid aortic valve and coarctation of the aorta in this condition. Mitral valve abnormalities (∼5%) and hypoplastic left heart syndrome (rare) are additional left-sided lesion described in this syndrome. Other congenital heart lesions found in TS include atrial and ventricular septal defects and partial anomalous pulmonary venous connection. Due to the clinically subtle nature of some of these lesions (such as bicuspid aortic valve), a screening echocardiogram should

be performed after the diagnosis of TS is made. Treatment of specific congenital cardiac lesions in TS does not differ from non-syndromic patients.

Aortic dilation, dissection, and rupture are a well-described phenomenon in TS with aortic dilation present in around 30%. Unlike MFS, the most significant dilation usually occurs in the ascending aorta (as opposed to the aortic root in MFS). Most cases of aortic dissection in TS are associated with bicuspid aortic valve, repaired aortic coarctation, or hypertension. However, TS alone is a risk factor for aortic dilation and dissection. TS patients experience aortic dissection at rates greater than the general population and at younger ages (as early as age 25 years). Dissection usually occurs at aortic diameters less than 5.0 cm. The assessment of aortic dilation must take into account the short stature that is a part of TS. One method is to use the aortic size index (ASI). This measurement consists of the ascending aortic diameter (measured either by echocardiogram, MR, or CT angiogram) divided by the body surface area. In a prospective study on aortic dissection in TS, three episodes of dissection occurred in a total of 158 patients monitored for 3 years. The dissections occurred in patients who were in their 40s and had aortic diameters between 3.8 and 4.8 cm. These patients would not have met criteria for elective aortic replacement according to the standards established in MFS. However, all had ASI ratios greater than 2.5 cm/m^2. This represented 33% of all patients with ASI greater than 2.5 cm/m^2 in the study. The authors concluded that evaluation for aortic replacement should occur when the ASI reaches 2.5 cm/m^2. They also recommended aortic measurements every 6–12 months once the ASI reaches 2.0 cm/m^2. It is unknown whether β-blockers or losartan can effectively diminish the rate of aortic dilation in this condition, however they are still commonly used.

Current screening guidelines recommend aortic imaging at least every 5 years and at the onset of hypertension. The majority of women with TS are infertile. However, some may become pregnant with donated oocytes and assisted reproductive technology. Pregnancy is associated with a high risk for dissection; therefore, aortic imaging should be performed prior to and throughout pregnancy.

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247 Murmur Evaluation

Jeffrey A. Conwell

Finding a cardiac murmur during a physical examination can be a source of frustration and anxiety for a pediatric provider. Perhaps even more challenging than correctly identifying the source of a new murmur is explaining the finding to the parents of the patient. A systematic approach to evaluating cardiac murmurs allows the development of tools to help identify pathologic and nonpathologic murmurs and provides a framework for discussing findings with parents to provide reassurance or the need for further evaluation.

Definition

A cardiac murmur is audible turbulent sound waves in the range from 20 to 20,000 Hz that originate from the heart and vascular system. Most murmurs are just the normal sound of blood flowing through the heart and blood vessels, but murmurs may also occur due to structural heart disease such as a ventricular septal defect. Murmurs in a structurally normal heart are often termed as flow, functional, innocent, or benign. Murmurs occurring from a structural heart defect are termed "pathologic" or "organic" and are usually described by the structural defect that they arise from.

Epidemiology

Cardiac murmurs are a common finding during a pediatric cardiac examination with up to 70–80% of children having a murmur at some point in time. The incidence of structural heart disease is less than 1%, so the vast majority of murmurs are normal or innocent murmurs. With such a high incidence of normal murmurs, a pediatric provider is certainly guaranteed to hear a cardiac murmur on a frequent basis.

Evaluation

Once a murmur is heard, a systematic approach is required to adequately evaluate the murmur. The approach should allow the pediatric provider to develop a good differential diagnosis, evaluation, and treatment plan. As in all patient encounters, evaluation should begin with a history and physical examination.

History

A careful history may provide clues that distinguish a murmur related to a structural defect from an innocent murmur. The history should include questions regarding pregnancy and delivery, family history, past medical history, growth and development, as well as cardiovascular symptoms (*Table 247.1*).

The age of a patient when a murmur was first noted may be helpful in developing a differential diagnosis. Murmurs heard immediately after birth and that persist are more likely to be pathologic in nature than those heard first at a few years of age. Murmurs associated with semilunar (aortic or pulmonary valve) valve stenosis are often noted in the immediate newborn period. A ventricular septal defect murmur may be heard in the first few days or weeks of life, but usually not shortly after delivery. A benign vibratory or Still's murmur is frequently first heard at a few years of age.

The general health of the child with suspected structural cardiac disease is important. Growth of the patient should be assessed as the rate of growth may be impacted in patients with pulmonary overcirculation (congestive heart failure) from large left to right shunts. Feeding difficulties are often the first evidence of pulmonary overcirculation and include disinterest in feeding, excessive fatigue, diaphoresis, a change in pattern of respiration, tachypnea, or dyspnea. These findings are exacerbated during feeds, as this is when the baby is "exercising." Babies with pulmonary overcirculation may take frequent breaks while feeding to "catch their breath" as well as become more tachypneic and diaphoretic during feeds. Most infants take a feed within 10–15 min with rare breaks. Babies with congestive heart failure may take 20 min or longer to finish a feed. Inquire about the feeding pattern, including volume, frequency, and duration to complete a feed. Quantifying the total caloric intake is

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Table 247.1
Pediatric cardiac history

Prenatal history	Infection
	Maternal alcohol intake
	Medications or drugs
	Illness
	Weight/prematurity
	Fetal ultrasound or echocardiogram results
Birth and past medical history	Delivery and events surrounding
	Gestational age
	Birth weight
	Sex
	Development
	Cyanosis/hypoxic spells/squatting
	Respiratory symptoms
	Murmur
	Chest pain
	Medications
	Rheumatic fever
	Neurologic
	Long QT
Family history	Inherited disorders
	Congenital heart disease
	Chromosomal abnormalities
	Rheumatic fever
	Hypertension and atherosclerosis
Signs and symptoms	Cyanosis
	Squatting
	Tachypnea
	Dyspnea
	Feeding difficulty
	Failure to thrive
	Sweating and pallor
	Exercise tolerance
	Chest pain
	Palpitations
	Dizziness/lightheadedness

often helpful so also check the calorie content of formula for infants. Occasionally, early developmental milestones can be delayed, especially gross motor milestones.

Inquire about complications during pregnancy and delivery including questions about maternal medications, maternal infections, diabetes, fetal growth, and results of fetal ultrasounds. Maternal medications such as epilepsy medications, warfarin, and lithium increase the risk of fetal structural cardiac disease (*Table 247.2*).

Table 247.2
Maternal medications associated with cardiac defects

Alcohol	ASD, VSD
Lithium	Ebsteins
Retinoic acid	Conotruncal malformations
Valproic acid	ASD, VSD, AS, PA/IVS, CoA
Warfarin	ASD, PDA

ASD atrial septal defect, *VSD* ventricular septal defect, *AS* aortic stenosis, *PA/IVS* pulmonary atresia with intact ventricular septum, *CoA* coarctation of the aorta, *PDA* patent ductus arteriosus

Maternal diabetes, especially if poorly controlled, increases the risk of a ventricular septal defect. Abnormal findings on fetal ultrasound or fetal echocardiogram may require follow-up after delivery. Rubella infection early in pregnancy increases the risk of structural cardiac defects. Poor fetal growth may indicate a syndrome or other problem increasing the risk of a heart defect.

Details about the delivery and surrounding events are also important. A delivery that was difficult with signs of fetal or neonatal distress may result in a murmur heard shortly after birth from tricuspid valve regurgitation. Gestational age is relevant as premature infants are more likely to have a patent ductus arteriosus and a murmur from physiologic peripheral pulmonary stenosis. Birth weight allows assessment of both prenatal and postnatal growth. Low birth weight is suggestive of in utero growth problems, syndromes, or in utero infection. Large for gestational age infants are often seen in pregnancies where the mother has diabetes (see *Table 247.3*).

Past medical history should assess for any chronic medical problems. History of structural defects in another organ system may increase the risk of congenital heart disease. Patients with left to right shunt lesions (atrial septal defects, ventricular septal defects) may have a history of recurrent respiratory infections or pneumonia. In older patients, a history of recurrent throat infections may suggest rheumatic heart disease as the etiology for the murmur.

Family history of congenital heart disease, particularly in first degree relatives (mom, dad, or siblings) significantly increases the risk of having congenital heart disease. Overall, the incidence of congenital heart disease is 0.8%. If there is a first degree relative with congenital heart disease, then the risk increases to around 2–3%. However certain types of defects pose a substantially higher risk.

Table 247.3
Syndromes and cardiac defects

Syndrome	Cardiac defect
Down	AVSD, VSD, PDA, TOF
Turner	Coarctation of the aorta, AS
Williams	Supravalve AS, pulmonary artery stenosis
Noonan	PS, HCM
Marfan	MVP, MR, AI, dilated aortic root
DiGeorge	Aortic arch anomalies, TOF, truncus arteriosus
Infant of diabetic mother	HCM, VSD
VACTERL	VSD, ASD, PDA, TOF
Trisomy 18	VSD, PDA, DORV
Trisomy 13	VSD, ASD, PDA

ASD atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *TOF* tetralogy of Fallot, *AS* aortic stenosis, *PS* pulmonary stenosis, *HCM* hypertrophic cardiomyopathy, *MVP* mitral valve prolapse, *MR* mitral regurgitation, *AI* aortic insufficiency, *DORV* double outlet right ventricle

For example, the recurrence risk may be as high as 15–20% if the mother has a history of aortic stenosis. Some genetic syndromes have associated cardiac disease. For example, Marfan syndrome is autosomal dominant in transmission, so if there is an affected parent, half of the children may be affected. A family history of rheumatic fever places the child at increase risk of having rheumatic fever themselves.

Family history should also include questions regarding early or sudden death and history of cardiomyopathy. The latter may be asked best as "anyone in the family with thick hearts or enlarged hearts?" A family history of cardiomyopathy, particularly in a first degree relative warrants referral to a pediatric cardiologist for evaluation.

Symptoms

Assessment of patients found to have a cardiac murmur includes looking for any symptoms that may be related to structural heart disease. Although, the presence of cardiac symptoms with a murmur does not always indicate there is structural heart disease and many patients with structural heart disease are asymptomatic. If a right to left shunt is present, then cyanosis may be noted. Changes in exercise tolerance, chest pain, or syncope in older patients with murmurs may warrant referral to pediatric cardiology for evaluation.

Young children with large left to right shunts may have tachypnea, dyspnea, and puffy eyelids as signs of pulmonary overcirculation or congestive heart failure. The tachypnea is typically worse with feeds and may be associated with diaphoresis. Edema in young children may be noted on the back or as facial puffiness while older children will have lower extremity or dependent edema.

One of the more concerning symptoms that should raise the suspicion of cardiac disease is central cyanosis. Central cyanosis or cyanosis of the mucous membranes or trunk may indicate the presence of a right to left cardiac shunt. This is not the acrocyanosis commonly seen in the normal newborn or the older infant who is cold stressed with the discoloration limited to the extremities. Some fair-complexioned children may have perioral cyanosis when cold which is a benign condition similar to newborn acrocyanosis and is not clinically significant. If there is a history of cyanosis, then asking about details surrounding the event and duration of cyanosis may be helpful in determining an etiology. Any patient with a history of cyanosis should have an oxygen saturation checked during the evaluation.

A decrease or change in exercise tolerance may result from structural heart disease of almost any type. One way to assess exercise tolerance in children is to ask if the child keeps up with their peers when playing. Onset of symptoms, severity, and progression of limitations should be determined. Just because a patient has a change in exercise tolerance does not necessarily mean there is a cardiac reason for the change.

When evaluating older children and adolescents, inquire about chest pain, particularly with exercise, as well as episodes of dizziness, lightheadedness, and syncope. Syncope is especially concerning if it occurs with exercise and without warning. Any of these symptoms coupled with a cardiac murmur is more likely to warrant evaluation by a cardiologist.

Physical Examination

Vital Signs

The physical examination should start with a complete set of vital signs including height, weight, blood pressure, respiratory rate, heart rate, and for neonates, oxygen saturation. Vital signs are preferably obtained in a resting state, since resting vital signs are more reproducible and comparable. If vital signs are obtained in the crying child, then a notation should be made in the chart.

Height and weight should be performed and plotted on an appropriate growth curve to compare to normal values for age and sex. Plot the measurements with any known historical measurements such as birth weight to determine if a patient has been growing well or has fallen on the growth curve.

Blood pressure should be obtained in the right upper extremity and a lower extremity, at a minimum, when evaluating patients for a suspected pathologic cardiac murmur. The right arm is preferred, as the left arm may be involved in a coarctation of the aorta and give a falsely low reading. The blood pressure cuff should be of an appropriate size for the extremity with the width of bladder 40–50% of the circumference (or 125–155% of the diameter) of the limb and bladder length of 80–100% of circumference. The correct size cuff is important. If the blood pressure cuff is too small, the blood pressure obtained will be artificially high so it is better to err with a cuff that is too large than too small.

Auscultation is the preferred method for blood pressure measurement, however, most clinics utilize oscillometric devices to measure blood pressure as these devices are convenient to use and decrease interobserver variability. The blood pressures obtained by an oscillometric device tend to be higher than those obtained manually.

Blood pressure in the upper extremity is best obtained in a patient who has been sitting for 3–5 min, the back supported, feet on the floor, and the arm supported at heart level (level of the right atrium). The average of two to three blood pressure measurements should be used. Following these guidelines will increase the likelihood of having a true resting blood pressure.

For the lower extremity blood pressure, the patient should be supine and an appropriate-sized cuff applied to either the calf or thigh (same rules for cuff size as for the arm). In children, the lower extremity systolic blood pressure should be equal to or slightly higher than the upper extremity blood pressure, often exceeding the upper extremity blood pressure by 5–10 mmHg. If the systolic blood pressure in the lower extremity is lower than the upper extremity by more than 10 mmHg, then a coarctation of the aorta may be present.

The pulse pressure, or the difference between the systolic and diastolic blood pressure may be altered in some types of congenital heart disease. A widened pulse pressure is seen in aortic insufficiency, patent ductus arteriosus, and arteriovenous malformations and results in bounding pulses. Decreased pulse pressure occurs in poor cardiac function.

The heart rate and respiratory rate should be taken for a full minute rather than 15 s and multiplying by 4, as there can be significant variation, particularly in younger children. Tachycardia may be seen in patients with large shunt lesions or decreased cardiac function. Tachypnea can occur secondary to increased pulmonary blood flow in left to right shunt lesions such as a ventricular septal defect or a patent ductus arteriosus. Increasing pulmonary congestion can cause the development of grunting, nasal flaring, and intercostal and subcostal retractions, although most tachypnea associated with pulmonary overcirculation is "quiet tachypnea."

Oxygen saturation should be obtained as part of the evaluation of a murmur in infants in the first couple months of life and in all patients presenting with tachypnea or complaints of cyanosis. Low oxygen saturations in infants with a heart murmur suggests the possibility of cyanotic heart disease.

Cardiac Examination

The cardiac physical examination should be performed in a systematic manner to assure complete evaluation of the patient. The physical examination typically begins with inspection.

Inspection

Much information can be obtained by simple inspection of a patient, a "quick look" when seeing the patient initially. General appearance should be assessed including whether the patient looks well or sick. Is the patient fussy or playful? Look for any obvious findings consistent with chromosomal abnormality or possibility of a syndrome. Assess the respirations looking for tachypnea or increased work of breathing. An idea of the child's general nutritional status can also be obtained during this initial look.

Cyanosis can be evaluated by looking at the mucous membranes and, in older patients, the nail beds. Cyanosis is associated with desaturation of 5 g of hemoglobin and is difficult to detect unless the oxygen saturation is less than 85%. If there is long-standing cyanosis, then digital clubbing may be present. Clubbing is uncommon in early infancy.

Inspect the chest, assessing for any asymmetry. Patients with long-standing cardiomegaly may develop a precordial bulge on the left side of the chest. In Marfan syndrome, patients may have pectus excavatum or

carinatum. Scoliosis may alter the position of landmarks such as the cardiac apex. Chest wall abnormalities may alter findings on electrocardiogram and chest x-ray.

A visible cardiac impulse may also be seen during chest inspection and implies hyperdynamic ventricular function.

Palpation

Palpation of the chest should be performed with the most sensitive part of the hand. For some, this is the metacarpals and for others the fingertips. The point of maximal impulse should be noted, usually it is found in the midclavicular line in the fourth intercostal space in children up to 4 years of age and the fifth intercostal space in older children. The impulse may be displaced medially when there is right ventricular dominance or laterally displaced in patients with left ventricular volume overload (left to right shunts, aortic insufficiency, and mitral valve regurgitation).

Palpation also allows assessment for increased precordial activity such as a ventricular tap or heave. A tap is a more focal increased impulse typically related to hypertrophy of a ventricle whereas a heave is a diffuse impulse that occurs when there is volume overload of a ventricle.

A thrill may be felt in association with a murmur and is a palpable vibratory sensation. Thrills can be found anywhere in the precordium, suprasternal notch, supraclavicular area, and over the carotid arteries. The location of the thrill usually correlates with the structural cardiac lesion causing a cardiac murmur. A thrill from a ventricular septal defect will be at the left lower sternal border, pulmonary stenosis at the left upper sternal border, and aortic stenosis at the right upper sternal border.

A palpable second heart sound may be noted in pulmonary hypertension or from anterior positioning of the aorta, such as in transposition of the great arteries. The first heart sound may be palpable in hyperdynamic states from any cause, including exercise and fever. Heart sounds may be felt during palpation in infants or patients with thin chest walls and does not necessarily indicate cardiac pathology.

Pulses should be assessed in both the upper and lower extremities. Take care to note if pulses are easily palpable, and if regular in rate; also note the quality of the pulse. A coarctation of the aorta should be suspected when the lower extremity pulses are not equal in quality to that of the right upper extremity. Bounding pulses (easily palpable) reflect runoff lesions such as aortic insufficiency or a patent ductus arteriosus, but can also be seen in patients with sepsis. Diminished pulses in all extremities is suggestive of ventricular dysfunction.

Abdominal palpation should assess the size of the liver. In young children the liver may be at the costal margin or just below. If the liver is enlarged, this may be a finding suggesting congestive heart failure (*Table 247.4*).

Table 247.4
Selected aspects of the cardiac physical exam

Inspection		General appearance and nutritional state
		Color
		Clubbing
		Respiratory rate, dyspnea, retraction
		Chest wall abnormalities
		Chromosomal syndromes
		Hereditary and nonhereditary syndromes
		Other systemic malformations
		Diaphoresis on forehead
Palpation	Pulses	Increased, decreased, bounding
		Rate, rhythm, amplitude, symmetry
	Chest	Apical impulse
		Point of maximal impulse
		Precordial activity
		Thrills
	Abdomen	Hepatomegaly
Auscultation	Lungs	Rales
		Rhonchi
		Wheezes
		Stridor
	Cardiac	Murmurs
		Gallops
		Clicks
		Rubs

Auscultation

Auscultation of the heart is a skill learned over weeks to months with the help of an experienced instructor and seeing a sizable number of patients. There is no substitute for practice. Once the skill of assessing cardiac murmurs

and sounds is mastered, ongoing practice is required to maintain those skills at a high level. Auscultation of the heart should be performed sitting, supine, and standing if possible. Sometimes, specific maneuvers may be required to bring out a cardiac murmur.

Proper equipment and the correct setting to perform auscultation are essential. A good stethoscope has both a bell for low frequencies and a diaphragm for high frequencies. The tubing should be long enough (12–18 in.) to be able to perform auscultation comfortably but not too long to diminish sounds. The most important part of the stethoscope, and often neglected, is good fitting and comfortable ear pieces. The ear pieces need to be comfortable and completely occlude the external auditory canal. Which stethoscope works best is an individual perspective, but it is always best to use your own stethoscope.

To maximize the chances for successful auscultation the exam room should be quiet and free from distractions. Both the patient and the examiner should be comfortable. It is hard to concentrate on the exam if performing bodily contortions. The patient should be unclothed, or at least the stethoscope should be placed on the skin. Modesty may require the patient to be in an exam gown. Younger children may be a challenge to examine as they may become fussy or cry during the exam. With small children try simple maneuvers to calm or ease the patient. Consider having an assistant aid in distracting the patient to allow the examiner to focus on the exam. Sometimes, starting with auscultation may be best if the patient appears apprehensive or uncooperative.

Auscultation should occur at least in the four main areas familiar to most providers, pulmonary, aortic, mitral, and tricuspid areas, but should not be limited to just these areas. Additional areas to examine are both infraclavicular areas, both carotids, the axillae in the fourth or fifth intercostal space, and the posterior chest inferior and medial to the scapula. Each area should be examined with the patient sitting, standing, and lying down.

It is important to develop a systematic approach to auscultation to be thorough and note all findings in a patient. One approach to make the exam more manageable is to break down the cardiac cycle listening to only one part at a time. Focus on S1 first, then on S2. Listen to systole and then to diastole for additional sounds or murmurs. Listening to each part of the cardiac cycle should be performed in each area and with the patient supine, sitting, and standing. In infants, it is easy to become distracted by breath sounds. Listen to the breath sounds first, and then see if there are any other sounds present. A complete auscultatory examination may take up to 5–10 min to complete properly.

Cardiac Sounds

The first heart sound (S1) is caused by the closure of the mitral and tricuspid valves (atrioventricular valves). The first heart sound is low-pitched and relatively long compared to the second heart sound. Under most circumstances, the tricuspid component is inaudible because of the low pressure of the right ventricle and closure of the tricuspid valve occurring almost simultaneously with the mitral component. Thus, normally S1 is a single crisp sound. S1 is best heard at the apex and precedes systole and the carotid pulsation. To assist with determining which heart sound is S1, the carotid pulsation can be palpated and S1 is always the heart sound that precedes the carotid pulsation.

Normal splitting of S1 may be noted in some pediatric patients in the tricuspid area. A normal split of S1 needs to be differentiated from an ejection click or an S4 gallop. In normal splitting of S1, the splitting is less noticeable as one moves laterally and should not persist at the anterior axillary line. If still present at the anterior axillary line, then one should suspect presence of an ejection click. Ejection clicks are often at a fixed interval to S1, while a split S1 should vary with the respiratory cycle, increasing with inspiration. Usually, heart sounds are lower pitched than ejection clicks. Fixed splitting of S1 may occur in patients with interventricular conduction delays, bundle branch block, and ventricular rhythms where one ventricle contracts earlier.

A loud S1 can be associated with high cardiac output states such as anemia, thyrotoxicosis, arteriovenous fistula, fever, exercise, anxiety, and epinephrine administration. S1 may be decreased in intensity in low cardiac output states such as hypothyroidism, cardiomyopathy, myocarditis, and shock or when there is increased chest wall thickness or pericardial fluid present.

The second heart sound (S2) is produced by closure of the semilunar valves (aortic and pulmonary). The aortic valve closure (A2) occurs earlier and is louder than the closure of the pulmonary valve (P2). Normally, there is variation in the splitting of S2 related to the respiratory cycle. During inspiration the right ventricle fills more. As a result, the second component of S2 (P2) comes later, splitting S2. In exhalation, the right ventricle fills less resulting in P2 coming earlier with A2 and P2 occurring nearly simultaneously resulting in S2 usually becoming a single sound. This normal or physiologic splitting of S2 (splitting during inspiration and single during expiration) is best appreciated at the high left sternal border in the second to fourth intercostal spaces.

There are some variations in S2 worth noting. A wide and fixed split S2 is noted in patients with an atrial septal defect. This occurs from increased volume flowing through the right heart and a decreased variation in right ventricular volume with respiration. Additionally, the right ventricle is dilated resulting in further distance for electrical activity to travel and excite the right ventricle, resulting in delay of right ventricular emptying. As a result of these physiologic changes, the pulmonary component of S2 continues to occur later than the aortic component resulting in a "fixed split S2."

Similarly, any physiologic change that delays right ventricular emptying may result in a widely split S2. This includes right ventricular outflow tract obstruction (pulmonary valve stenosis or subvalve stenosis), severe mitral valve regurgitation (shortened left ventricular ejection time), dilation of the main pulmonary artery (diminished recoil forces on the pulmonary valve, delaying closure), right bundle branch block, and premature ventricular contractions originating from the left ventricle.

A loud S2 occurs with increased diastolic blood pressure and decreased viscosity of the blood (anemia). It may result from a loud A2 or P2. A loud P2 may be heard in patients with pulmonary hypertension. A loud A2 can be heard in systemic hypertension, coarctation of the aorta, transposition of the great arteries, and aortic insufficiency.

Patients with a single semilunar valve (aortic atresia, pulmonary atresia, truncus arteriosus) will have a single S2. Patients with transposition of the great arteries, tetralogy of Fallot, or other cardiac defects that move the aorta anteriorly can result in a loud single S2. Due to the fast heart rate in newborns, it is often difficult to appreciate if there is a single S2.

Paradoxical splitting of S2 can also occur with A2 heard after P2. This is sometimes noted in left bundle branch block, paced beats, Wolff–Parkinson–White syndrome, aortic stenosis, left ventricular outflow tract obstruction, and a patent ductus arteriosus. The reason for paradoxic splitting in these conditions is the delay in emptying of the left ventricle by either electrical or anatomic changes.

Systolic ejection clicks are medium- to high-pitched sounds which closely follow S1. They are associated with abnormalities of the semilunar valves or sometimes with dilation of the aorta or pulmonary artery. Clicks are high-pitched sounds, best appreciated with the diaphragm of the stethoscope.

Aortic clicks are generally unchanged by the respiratory cycle and are called constant early systolic ejection clicks. Aortic clicks can be heard at the second right intercostal space but are often heard best at the apex. The differential diagnosis for a patient with an aortic click includes a dilated aorta, aortic stenosis, and bicuspid aortic valve.

Pulmonary ejection clicks may fade out or disappear with inspiration and are called variable early systolic ejection clicks. Pulmonary clicks tend to be heard best at the left upper sternal border (second intercostal space) during expiration. The differential diagnosis for a patient with a pulmonary ejection click includes pulmonary valve stenosis or a dilated pulmonary artery.

A mid-systolic click is a high-pitched sound occurring in mid-systole usually associated with mitral valve abnormalities such as mitral valve prolapse. If there is associated mitral valve regurgitation with the mitral valve prolapse, then a regurgitant murmur can be heard after the mid-systolic click. The click should come later in systole with squatting and heard better with the patient standing or with held expiration (*Table 247.5*).

Gallops may also be heard during the cardiac cycle. An S3 gallop occurs at the end of rapid early diastolic filling, secondary to limitation of longitudinal expansion of the ventricular wall. This is a low-frequency sound with a dull or thudding quality that increases with inspiration, and is heard best at the apex or just medial to the apex of the heart with the patient lying supine or on their left side. An S3 gallop can be a normal finding in children, but a loud S3 suggests pathology. Increased intensity of S3 occurs in excitement, anemia, or a large left to right shunt.

S4 gallops occur late in diastole and are associated with atrial contraction. An S4 gallop can be a normal finding in a well-trained athlete or elderly patients. It is usually heard best with the patient recumbent, at the apex, and during expiration utilizing the bell of the stethoscope. Differential diagnosis for a patient with an S4 gallop includes pulmonary hypertension, pulmonary stenosis, Ebsteins anomaly

Table 247.5
Clicks

Click	Etiology	Location	Maneuvers
Aortic	Dilated Ao, AS, bicuspid AoV	Apex	No respiratory variation
Pulmonic	Dilated PA, PS	LUSB	Louder in expiration (variable)
Mid-systolic	Mitral valve prolapse	Apex	Increased with standing

Ao aorta, *AS* aortic valve stenosis, *AoV* aortic valve, *PA* pulmonary artery, *PS* pulmonary valve stenosis, *LUSB* left upper sternal border

of the tricuspid valve, tricuspid valve atresia, total anomalous pulmonary venous return, and complete heart block.

A summation gallop (combination of S3 and S4) is often more intense than either component. It is the most common gallop noted in pediatric patients and is commonly associated with heart failure from large left to right shunts. A summation gallop is pathognomonic for Ebsteins anomaly of the tricuspid valve.

Other Sounds

Patients with pericarditis may have a pericardial friction rub that originates when inflamed visceral and parietal pericardium come into contact. A rub has been described as having a sandpaper-like grating quality. Friction rubs can be intermittent, heard in diastole, systole, or continuously. They are usually best heard along the left sternal border and at the apex with the patient leaning forward. Pericardial friction rubs are best noted with the diaphragm and may be accentuated with inspiration.

Pericardial knocks are associated with restrictive physiology such as restrictive pericarditis. Knocks are a high-pitched sound that occurs prior to an S3 gallop and is best appreciated with the diaphragm. They can be increased in intensity by increasing venous return.

An opening snap is the term associated with the opening of the mitral valve in mitral stenosis from rheumatic heart disease. This sound occurs after the second heart sound and is best appreciated in the mid-precordium in the fourth left intercostal space. An opening snap may also occur with tricuspid valve stenosis. Opening snaps are uncommon in childhood (*Table 247.6*).

Murmur

A complete description of a murmur includes a number of features: location, timing, loudness, type, pitch, quality, and transmission. Given a complete description, most cardiac murmurs can lead to a specific diagnosis, even without an echocardiogram.

Location

Most practitioners are familiar with the usual areas of auscultation to include the pulmonary, aortic, mitral, and tricuspid areas. The pulmonary area is at the left upper sternal border or left second intercostal space at the sternal edge. The aortic area is at the right upper

Table 247.6
Heart sounds

Loud S1	Short PR interval
	Mitral stenosis
	Hyperkinetic states (anemia, thyrotoxicosis, arteriovenous malformations, fever, exercise, anxiety, epinephrine administration)
Changing intensity S1	Atrioventricular dissociation (complete AV block)
	Atrial fibrillation
Soft S1	Long PR interval
	Decreased contractility of left ventricle
	Severe aortic regurgitation
	Mitral regurgitation
	Thick chest wall
	Pericardial effusion
Fixed split S2	Atrial septal defect
Paradoxically split S2	Severe aortic stenosis
	Hypertrophic cardiomyopathy
	Left bundle branch block
	Severe left ventricular systolic dysfunction
	Wollf–Parkinson–White syndrome
	Patent ductus arteriosus
Wide physiologic split S2	Mitral regurgitation
	Large ventricular septal defect
	Pulmonary stenosis
	Right bundle branch block
	Ebsteins anomaly
Single S2	Pulmonary hypertension
	Single semilunar valve (pulmonary atresia, aortic atresia, truncus arteriosus)
	P2 not audible (transposition of the great arteries, tetralogy of Fallot)
	Severe aortic stenosis
Loud A2	Severe hypertension
	Aortic dilation
	Coarctation of the aorta
	Transposition of great arteries
	Aortic regurgitation
Soft A2	Valvar aortic stenosis
Loud P2	Pulmonary hypertension
Soft P2	Pulmonary stenosis
	Tetralogy of Fallot
	Tricuspid stenosis

Table 247.6 (Continued)

S3	Left ventricular or right ventricular systolic dysfunction
	Mitral regurgitation
	Aortic regurgitation
S4	Left ventricular or right ventricular diastolic dysfunction
Opening snap	Mitral stenosis
Clicks	Aortic – bicuspid aortic valve, dilated aortic root
	Pulmonic – pulmonary valve stenosis, dilated main pulmonary artery
Pericardial knock	Constrictive pericarditis
Pericardial friction rub	Pericarditis

sternal border or second right intercostal space at the sternal edge. The mitral area is at the apex or fifth intercostal space in the midclavicular line. The tricuspid area is at the left lower sternal border or fourth and fifth intercostal spaces at the sternal edge. Location of a murmur should be described by where it is the loudest (point of maximal intensity) not by where it is heard by transmission.

Although these are the four primary areas for auscultation, the cardiac examination should not be limited to these four areas. Additional areas to auscultate include the infraclavicular areas, over the carotid arteries, each axilla (at about the fourth and fifth intercostal space), and the posterior aspect of the chest just medial and inferior to each scapula. Examining all these areas allows for full evaluation of a cardiac murmur (*Table 247.7*).

Table 247.7
Murmurs by location

Location	Murmur
LUSB	Pulmonary valve stenosis
	Atrial septal defect
	Peripheral pulmonary stenosis of newborn
	Pulmonary flow murmur
	Pulmonary artery stenosis
	Aortic stenosis
	Tetralogy of Fallot
	Coarctation of the aorta
	Patent ductus arteriosus
	Total anomalous pulmonary venous return
	Partial anomalous pulmonary venous return
RUSB	Aortic valve stenosis
	Subaortic stenosis
	Supravalve aortic stenosis
LLSB	Ventricular septal defect
	Endocardial cushion defect
	Still's murmur
	Hypertrophic cardiomyopathy
	Tricuspid valve regurgitation
	Tetralogy of Fallot
Apex	Mitral valve regurgitation
	Mitral valve prolapse
	Aortic valve stenosis
	Hypertrophic cardiomyopathy
	Still's murmur

LUSB left upper sternal border, *RUSB* right upper sternal border, *LLSB* left lower sternal border

Timing

Murmurs can occur in systole, diastole, or be continuous. At times this is difficult to assess, particularly in younger patients or patients with high heart rates. Palpating a pulse while performing auscultation may allow one to determine the timing of a murmur. Also, a continuous murmur does not mean it is always present; instead the murmur just needs to spill past S2 into diastole to qualify as continuous. Murmurs can occur early, mid, or late in either diastole or systole:

- Early systolic murmurs start abruptly but taper and disappear before S2 and are associated with a small muscular ventricular septal defect that becomes occluded during systole.
- Mid-systolic murmurs are the most common type of murmur heard and include the benign flow murmurs and murmurs associated with aortic or pulmonary stenosis.
- Mid- to late systolic murmurs begin midway through systole and are often heard in association with mid-systolic clicks and insufficiency of mitral valve prolapse.
- Early diastolic murmurs are from aortic insufficiency or pulmonary insufficiency and have a decrescendo pattern.
- Mid-diastolic murmurs are typically flow rumbles from increased flow across the atrioventricular valves associated in large shunt lesions such as ventricular septal defects.

Table 247.8
Cardiac murmur timing

Timing in cardiac cycle	Murmur
Mid-systolic	PPS, PS, AS, HCM, COA, ASD
Early systolic	Muscular VSD that closes in systole
Late systolic	MR associated with MVP
Holosystolic	VSD, MR, TR
Early diastolic	AI, PI
Mid-diastolic	Flow rumble
Late diastolic	MS, TS
Continuous	PDA, AVM
To and fro	AS/AI, PS/PI

PPS peripheral pulmonary stenosis, *PS* pulmonary stenosis, *AS* aortic stenosis, *HCM* hypertrophic cardiomyopathy, *COA* coarctation of the aorta, *ASD* atrial septal defect, *VSD* ventricular septal defect, *MR* mitral valve regurgitation, *MVP* mitral valve prolapse, *TR* tricuspid valve regurgitation, *AI* aortic insufficiency, *PI* pulmonary insufficiency, *MS* mitral valve stenosis, *TS* tricuspid valve stenosis, *PDA* patent ductus arteriosus, *AVM* arteriovenous malformation, *AS/AI* aortic stenosis/aortic insufficiency, *PS/PI* pulmonary stenosis/pulmonary insufficiency

- Late diastolic murmurs are typical of mitral or tricuspid valve stenosis and occur with atrial contraction.

Diastolic murmurs are always felt to be pathologic in origin.

See *Table 247.8* for timing of common murmurs.

Shape/Configuration

Shape, configuration, or type refers to the characteristic pattern of the murmur seen on phonocardiology. This is where the terms "crescendo," "crescendo-decrescendo," "decrescendo," "holosystolic," etc., come from. Systolic murmurs are either ejection (crescendo-decrescendo) or regurgitant (holosystolic). Diastolic murmurs are generally regurgitant or flow rumbles. Continuous murmurs result from communication between any two structures where one has a higher pressure than the other throughout the cardiac cycle. The term "continuous" refers to a murmur that spills past S2 into diastole, rather than a murmur that is always present. The terminology used to describe murmurs can be confusing. *Table 247.9* explains some of the descriptive terms that you may encounter.

Systolic ejection murmurs are crescendo-decrescendo or diamond-shaped murmurs which can be turbulent, grating, or musical. Usually, they represent blood being accelerated then decelerated through a semilunar valve or blood vessel, since the pressure driving the blood along has to accelerate as it builds up to the pressure already present in the downstream vessel. Systolic ejection murmurs are characteristic of turbulence at the semilunar valves (aortic or pulmonary valve stenosis, flow murmurs) or great arteries (supravalve stenosis).

Table 247.9
Murmur descriptions and terminology

Murmur type	Other terminology
Systolic ejection	Crescendo-decrescendo
	Mid-systolic
	Diamond shaped
Holosystolic	Pansystolic
	Regurgitant systolic
	S1 coincident
	Plateau
	Rectangular shaped
	Long systolic
Innocent	Functional
	Benign
	Innocuous
	Physiologic
	Normal
	Flow

S1 first heart sound

Systolic regurgitant murmurs are usually holosystolic but can end before the second heart sound as in the case of muscular ventricular septal defects. Holosystolic or regurgitant murmurs are shown diagrammatically as a rectangular symbol. There is no crescendo-decrescendo quality since there is very little pressure in the downstream chamber, so the murmur starts with the first heart sound, and it may be difficult to appreciate the first heart sound at all. Examples of holosystolic murmurs are mitral valve regurgitation, tricuspid regurgitation, and ventricular septal defects.

Continuous murmurs result from a communication between two structures where there is always a pressure gradient in the same direction. In patent ductus arteriosus, arteriovenous malformations, aortopulmonary windows, collaterals, and shunts, there is continuous flow since there is a gradient from the systemic to the pulmonary side during both systole and diastole. In these lesions the murmur will have an accentuated systolic component. A continuous murmur may also occur in the venous

system due to stenosis in the systemic veins resulting in a continuous, low-pitched murmur. Venous continuous murmurs will have much less systolic accentuation.

Diastolic regurgitant murmurs result from the backward flow of blood through an incompetent aortic or pulmonary valve. They are early in diastole and as the arterial pressure drops, the intensity of the murmur falls, giving a decrescendo quality. Diastolic regurgitant murmurs are always considered pathologic.

Diastolic flow rumbles are very low-pitched sounds during diastole that correspond to flow across the mitral or tricuspid valves. Rumbles usually occur in lesions with an increased amount of flow across an atrioventricular valve, such as large atrial septal defect or large ventricular septal defect, but may also occur in patients with tricuspid or mitral valve stenosis. The intensity of the murmur may increase toward mid to late diastole as the atria contract.

To-and-fro murmurs are the combination of a systolic ejection murmur and a diastolic regurgitant murmur, as is common following repair of pulmonary stenosis, or in patients with aortic stenosis and aortic insufficiency. A to-and-fro murmur is different from a continuous murmur, even though there is a murmur in systole and diastole.

Loudness

The loudness (intensity) of cardiac murmurs is typically described using a 6-point scale. An intensity of 1 means the murmur is noted only after concentrating, a grade 2 murmur is noted easily, and grade 3 is very easily noted. In grade 4, there is a palpable thrill associated with the murmur, a grade 5 murmur can be heard with the stethoscope on edge on the chest, and a grade 6 murmur can be heard with the stethoscope off the chest (*Table 247.10*). A 4-point scale for describing diastolic murmurs is used by some people.

Table 247.10
Murmur intensity

Grade	
1	Only noted when concentrating
2	Easily heard
3	Very easily heard
4	Easily heard and associated thrill
5	Heard with stethoscope on edge on chest
6	Heard with stethoscope off the chest

Loudness of a murmur is a function of the distance from the stethoscope, the energy in a turbulent stream of blood, amplitude of the sound, and the medium the noise travels through. The amount of turbulence and therefore the intensity of a murmur are dependent on the size of the orifice or size of vessel through which blood flows, the pressure difference or gradient across the narrowing, and the blood flow or volume across the site. As sound radiates from the source, intensity decreases with the square of the distance. The tissue that the sound travels through has an impact on the loudness. Fat dampens higher frequency sounds more than dense material such as bone. If lung tissue is positioned between the heart and chest wall, only the loudest sounds will be heard.

The loudness of the murmur does not necessarily indicate underlying structural heart disease. Most innocent murmurs are grade 2 or less in intensity, but sometimes can be grade 3. Grade 4 or higher murmurs are unlikely to be innocent.

Pitch or Frequency

Pitch refers to the highest frequency audible in the murmur and is a function of the gradient across a narrowing. In general, the higher the pressure gradient across a narrowing, the higher the pitch of the murmur. Usually pitch is described as low, medium, or high, although using terms like medium to high is common.

Quality

Quality refers to the timbre (harmonics or overtones) of a murmur. Murmurs can be described as turbulent, blowing, grating or harsh, or musical.

A turbulent murmur refers to the "white noise" or hissing sound that the majority of murmurs have and is caused by disturbed blood flow. The sound is similar to the sound the water in a garden hose makes when it is kinked.

Blowing murmur refers to a high-pitched turbulent murmur that sounds like air escaping from a punctured tire. Mitral regurgitation is a typical blowing murmur.

A turbulent murmur with multiple clicks throughout systole may be described as grating or harsh and sounds like a credit card being dragged across cement. Typical harsh murmurs are pulmonary valve stenosis, patent ductus arteriosus, and truncus arteriosus.

The term "musical" is applied to murmurs with a predominant harmonic frequency that some describe

as a squeak, seagull's cry, or as a twanging of a string. Another term that is commonly used is vibratory. The most common murmur with vibratory quality is a Still's murmur. Occasionally small ventricular septal defects have a slight vibratory component. The vibratory or musical part of the murmur is felt to be caused by resonance of structures within the heart or the blood itself.

Transmission or Radiation

Transmission or radiation refers to other areas on the chest where the murmur can also be heard. This is different than the point of maximal intensity or location described earlier. Usually, the radiation of a murmur is in the direction of the blood flow. For example, in pulmonary stenosis the murmur radiates from the left upper sternal border to the lungs, a mitral regurgitation murmur radiates from the apex to the left axilla, aortic stenosis murmur radiates from the right upper sternal border to the carotids, etc.

Maneuvers

There are a variety of maneuvers that can be performed at the bedside that allow the murmur to be heard better and help to further define the etiology of the murmur. Maneuvers tend to change the volume of blood flow through the heart. The simplest of the maneuvers is patient position, hence the recommendation to examine a patient sitting, supine, and standing. Other maneuvers include Valsalva, exercise, respiration, transient arterial occlusion, response after a premature ventricular contraction, and use of amyl nitrite.

Postural changes are the easiest maneuvers to perform as this only requires the patient to sit, stand, or lie down, making it very likely the patient will comply. Standing is similar to the strain phase of a Valsalva causing a decrease in venous return, decrease in stroke volume, decreased systemic vascular resistance, and an increase in heart rate. These physiologic changes make the murmur of hypertrophic cardiomyopathy and the mid-systolic click of mitral valve prolapse increase in intensity. Murmurs that are flow related such as pulmonary flow murmur, aortic stenosis, aortic regurgitation, and mitral regurgitation murmurs are decreased in intensity with standing.

Squatting increases systemic vascular resistance, increases venous return, and increases stroke volume while decreasing heart rate. These physiologic changes decrease the murmur associated with hypertrophic cardiomyopathy and increases the flow-related murmurs of aortic stenosis, mitral regurgitation, aortic regurgitation, and pulmonary flow murmur.

A supine position favors immediate increased systemic venous return to the right heart and shortly after to the left heart. There is an increase in stroke volume which increases the intensity of many murmurs, including a Still's murmur and the benign pulmonary flow murmur of adolescence. The supine position may also bring out the tricuspid valve diastolic murmur (flow rumble) associated with an atrial septal defect and increases the intensity of the murmurs of a patent ductus arteriosus and pulmonary valve stenosis.

The left lateral supine position with the patient rolled up onto their left side while lying on the exam table brings the heart closer to the lateral chest wall and raises the intensity of mitral valve murmurs, both regurgitation and stenosis. This position also increases an S3 gallop.

Other maneuvers to assist in cardiac auscultation require cooperation by the patient or equipment but may assist in determining the etiology of a murmur. A Valsalva maneuver has four physiologic phases but is clinically a two-part process with a strain phase and a release phase. Phase I occurs as strain commences lasting only 1–3 s and is usually undetectable at the bedside. In phase II of the Valsalva, there is a decrease in systemic venous return, blood pressure, and pulse pressure. Right heart filling is decreased and cardiac output decreases. After 3 or 4 s, there is arterial and venous constriction and increased heart rate. This part of a Valsalva is clinically appreciable. Phase III begins with release of the strain which is very brief and difficult to perceive at the bedside. Phase IV is composed of an overshoot of systemic blood pressure which causes a decrease in heart rate, which can be easily detected at the bedside. Venous return is increased above the baseline prior to the Valsalva and there is a time delay between the filling of the right ventricle and the left ventricle. Right-sided cardiac murmurs usually return to baseline in one to four cardiac cycles, left-sided murmurs in five to ten cycles.

Valsalva maneuver (phase II) decreases both systemic and pulmonary venous return to the heart and is particularly effective in reducing an innocent Stills murmur and decreases the intensity of all left-sided murmurs except mitral valve prolapse and hypertrophic cardiomyopathy. In the release phase of Valsalva (phase IV), the murmurs of mitral valve prolapse and hypertrophic cardiomyopathy are decreased.

Exercise is another simple bedside maneuver that can be used to evaluate the cardiac system. The easiest exercise to perform is a sustained isometric handgrip without Valsalva which causes an increase in heart rate, systemic

vascular resistance (blood pressure), and an increase in cardiac output. These physiologic changes increase the murmurs of mitral stenosis, mitral valve prolapse, mitral regurgitation, ventricular septal defect, and aortic regurgitation with no change in an aortic stenosis murmur. The first and second heart sounds, and gallops will also become louder during this maneuver.

Respiration changes the amount of venous return to the heart and how close the heart is to the chest wall, making some murmurs easier to appreciate. In general, right-sided events are louder on inspiration and left-sided events are louder on expiration. Inspiration causes a decrease in intrathoracic pressure resulting in increased systemic venous return and increased right ventricular stroke volume. This increase in flow in the right heart increases the murmurs of tricuspid regurgitation, tricuspid stenosis, pulmonary stenosis, and pulmonary regurgitation. Notably, a pulmonary ejection click will decrease with inspiration. During expiration, lung volume is decreased and the heart moves closer to the chest wall making the murmurs of aortic regurgitation, mitral regurgitation, and aortic stenosis easier to appreciate.

The next few maneuvers are not likely to be practical in the primary care setting, but are discussed to be complete.

Transient arterial occlusion can be performed with two manual blood pressure cuffs on the upper extremities inflated to 20 mmHg above the patient's blood pressure. This results in increased afterload but no change in systemic vascular resistance, heart rate, cardiac output, or right atrial pressure. The murmurs of aortic regurgitation, mitral regurgitation, and ventricular septal defect are increased. This maneuver requires manual blood pressure cuffs which may not be available in the clinic and may be difficult to perform in young children.

If a patient is having premature ventricular contractions, they may be used to help evaluate cardiac murmurs. For auscultation, the important part of a premature ventricular contraction is the beat following the ectopic beat. The pause after the ectopic beat increases left ventricular filling time, ventricular contractility is enhanced, and aortic diastolic pressure is lower. So, following a premature ventricular contraction there is an increase in the murmur of hypertrophic cardiomyopathy and aortic stenosis but no change in the murmur of mitral regurgitation. This maneuver is only helpful if the patient is having premature ventricular contractions.

Utilization of amyl nitrite is rare in the clinical setting but is included here for completeness. Amyl nitrite inhalation initially causes a decrease in systemic vascular resistance and blood pressure with increase in stroke volume and cardiac output. These physiologic changes decrease the murmurs of mitral regurgitation, aortic regurgitation, ventricular septal defect, and patent ductus arteriosus but increases aortic stenosis murmur. Late effects of amyl nitrite are an increase in heart rate with even further increase in cardiac output and increase in venous return causing the murmurs of mitral stenosis, tricuspid regurgitation, and pulmonary stenosis to increase.

Innocent Murmurs

Innocent heart murmurs are a common finding on examination of children and there are four benign systolic murmurs and two benign continuous murmurs. In general, benign cardiac murmurs are grade 3 or less in intensity, never have an associated thrill, and never occur solely in diastole. Most of the innocent murmurs are accentuated by increased cardiac output related to fever, anemia, or activity (*Table 247.11*).

The benign murmur common to early infancy is referred to as peripheral pulmonary artery stenosis or pulmonary flow murmur of newborns. Prior to birth, there is minimal flow into the branch pulmonary arteries so the branches are relatively small. Also, the branches arise from the main pulmonary artery at a sharper angle than seen later in life. After birth, there is a marked increase in pulmonary blood flow often creating a murmur as the blood makes the turn from the main pulmonary artery into the branch pulmonary arteries. The murmur of peripheral pulmonary stenosis is often initially heard at a couple of weeks of age when the physiologic nadir of the blood count occurs.

Table 247.11
Characteristics of innocent cardiac murmurs

Grade 1–2/6
Left sternal border
Systolic ejection murmur
Normal intensity and physiologic splitting of S2
No other cardiac sounds or murmurs
No evidence of ventricular hypertrophy or dilation
Murmur does not increase with Valsalva or squat to stand
Asymptomatic
Family history negative for HCM or sudden death

HCM hypertrophic cardiomyopathy

A peripheral pulmonary stenosis murmur is usually louder in the axillae and back, but may be heard anteriorly at the left upper sternal border. The murmur is ejection in character and grade 1 or 2 in loudness. The pitch of the murmur is similar to breath sounds and may be difficult to separate from the rapid respiratory noises in infancy, so can easily be missed. This murmur can be differentiated from valvar pulmonary stenosis as there is no associated ejection click. It is more common in premature infants and often resolves by 6–9 months of age. If the murmur persists past this age, then consider a diagnosis of true branch pulmonary artery stenosis, Williams syndrome, or congenital rubella.

A Still's murmur is a common vibratory murmur heard in children, most often between the age of 2 and 6 years. It can however be heard in infancy and may persist into adolescence. Still's murmurs are low to medium in pitch, maximal at the left lower sternal border and out to the apex, and typically grade 1–3 in loudness. The murmur is usually louder and the vibratory component easier to appreciate when the patient is supine. In some children the murmur may only be noted in the supine position.

The defining feature of a Still's murmur is the vibratory component. The murmur is named after George F. Still who described the murmur in 1909 as "a twanging sound, very like that made by twanging a piece of tense string." The murmur is often described as musical in nature and usually resolves by adolescence. A Still's murmur will be louder in conditions with increased cardiac output, so when a patient is seen for evaluation of a fever, the murmur may be heard for the first time.

A pulmonary flow murmur is a common murmur heard in late childhood and adolescence, ages 8–14 years. It is a crescendo-decrescendo murmur heard best at the left upper sternal border without further radiation and usually grade 2–3 in loudness. The murmur is more pronounced in patients with pectus excavatum or kyphoscoliosis, likely due to the right ventricular outflow tract being closer to the chest wall. It also seems to be more common in athletic individuals who may have an increased stroke volume.

In addition to a pulmonary flow murmur, the differential diagnosis of a murmur at the left upper sternal border would include one related to an atrial septal defect or to pulmonary valve stenosis. In an atrial septal defect, there is a fixed split S2 and there may be an increased right ventricular impulse on palpation. With pulmonary valve stenosis, there often is an ejection click present and the murmur tends to be of a longer and higher grade than in the benign flow murmur.

A murmur related to the carotids, or a carotid bruit, can be heard in children and young adults. It is a crescendo-decrescendo murmur heard best above the clavicles and radiates to the neck. Carotid bruits are low to medium in pitch, of abrupt onset, brief, and maximal in the first part of systole. The murmur is felt to be due to flow from the common carotid into the internal and external carotid arteries. Unlike carotid bruits heard in adults, this is a benign finding in children.

A venous hum is a common continuous murmur heard in children 2–6 years of age. It is usually loudest in the infraclavicular area and more common on the right side. The murmur is low in pitch and louder in diastole. A venous hum murmur is often only heard with the patient sitting upright and will dissipate with gentle occlusion of the internal jugular vein on the same side of the neck as the murmur is heard or turning the head toward the side of the murmur. The murmur may be accentuated by having the patient look away from the side of the murmur. A venous hum is thought to occur from flow from the internal jugular vein into the superior vena cava.

A mammary arterial soufflé is a continuous murmur that can occur in late pregnancy and in lactating women, and can rarely occur in adolescence. The murmur is a continuous noise audible maximally on the anterior chest wall, starting in systole and extending well into diastole. There is usually a distinct gap from S1 before the murmur begins. The murmur is high pitched, may vary considerably from day to day, and may decrease with firm pressure from the stethoscope (*Table 247.12*).

Pathologic Murmurs

The following is a brief overview of cardiac murmurs associated with some of the more common structural cardiac defects. For further details on other exam findings and natural history, please see the respective chapter for the cardiac lesion.

The murmur associated with an atrial septal defect is not related to the flow across the atrial septum, but due to an increase in flow across the pulmonary valve. The murmur is grade 1–3, best at the left upper sternal border, medium pitched, and ejection (crescendo-decrescendo) in nature. The murmur may radiate to the lung fields (axillae and back). The finding setting the murmur of an atrial septal defect apart from a benign pulmonary flow murmur is fixed splitting of S2. This is due to decreased variability of right ventricular volume with respiration

Table 247.12
Innocent heart murmurs

Murmur	Age	Timing	Loudness	Location	Pitch	Other
Still's	2–6 years	Systolic	1–3	LLSB, Apex	Low to medium	Vibratory
PPS	Newborn	Systolic	1–2	Axillae and back	Low to medium	
Pulmonary flow murmur	Older children and adolescents	Systolic	1–3	LUSB	Medium	Normal S2, no ejection click
Carotid bruit	Children and young adults	Systolic	1–3	Supraclavicular radiating to neck	Low to medium	No ejection click, occ. thrill
Venous hum	2–6 years	Continuous	1–2	Subclavicular	Low	Dissipates with supination or gentle occlusion of jugular vein
Mammary soufflé	Late pregnancy and lactating women	Continuous	1–3	Anterior chest over breast	High	Varies significantly day to day

LLSB left lower sternal border, *LUSB* left upper sternal border

and an enlarged right ventricle resulting in prolonged ventricular contraction. Additional findings seen in some large atrial septal defects are a diastolic flow rumble associated with flow across the tricuspid valve and an increased right ventricular impulse. Patients with atrial septal defects are often asymptomatic and the murmur is often picked up during routine examination in childhood.

A ventricular septal defect (VSD) murmur is a holosystolic murmur usually heard best at the left lower sternal border, grade 1–6, high pitched, and harsh in nature. The murmur can radiate to the right lower sternal border and to the apex. A palpable thrill may be present. With large ventricular septal defects, a gallop may be present on auscultation and increased precordial activity noted on palpation. There may be a diastolic flow rumble associated with increased flow across the mitral valve. VSD murmurs are rarely heard in the first couple of days of life with the exception of small muscular VSDs where the flow is directed anteriorly. Most VSD murmurs are noted by 2–4 weeks of age.

A patent ductus arteriosus (PDA) murmur is described as a continuous machinery-like murmur heard best at the left upper sternal border or left infraclavicular area, medium to high in pitch, grade 1–6, that can radiate to the back. The murmur may also sound like other murmurs heard at the left upper sternal border such as pulmonary valve stenosis. The key to differentiate the murmur from pulmonary stenosis is that it is continuous, that is, it spills into diastole. Additionally, there may be widened pulse pressures (bounding pulses) and increased left ventricular activity. Patients may have a flow rumble across the mitral valve and a systolic ejection murmur across the aortic valve because of increased flow in the left heart. A PDA murmur may initially be only heard in systole due to the minimal pressure gradient seen in diastole. As the pulmonary vascular resistance decreases to normal levels in the first few weeks of life, the more classic continuous nature of the murmur will be noted.

A pulmonary stenosis murmur is a systolic ejection murmur at the left upper sternal border ranging from grade 1 to 6, with a medium to high pitch. The pitch of the murmur correlates to the degree of valvar gradient: the higher the pitch, the higher the gradient. Usually there is an ejection click associated with valvar pulmonary stenosis. An increased right ventricular impulse may be noted on palpation. A thrill may be present in the suprasternal notch or upper left sternal border.

The murmur of aortic stenosis is a systolic ejection murmur heard best at the right upper sternal border. It is high pitched ranging from grade 1 to 6, harsh in nature, and radiates to the carotids. There is usually an aortic ejection click at the apex. A thrill may be present at the right upper sternal border or in the suprasternal notch. An increased left ventricular impulse may be noted by palpation.

A murmur from mitral valve regurgitation is holosystolic and heard best at the apex with a grade ranging from 1 to 3. The murmur is high pitched and blowing in nature, radiating to the left lower sternal border, left axilla, and left posterior chest. When associated with

Table 247.13
Selected cardiac lesion murmurs

Lesion	Location	Timing	Loudness	Pitch	Shape/type	Radiation
ASD	LUSB	Systolic	1–3	Medium	Ejection	Occ. lungs
VSD	LLSB	Systolic	1–6	Medium to high	Holosystolic	RLSB, apex
PDA	LUSB	Continuous	1–6	Medium to high	Machinery	Lungs
PS	LUSB	Systolic	1–6	Medium to high	Ejection	Lungs
AS	RUSB	Systolic	1–6	Medium to high	Ejection	Carotids
MR	Apex	Systolic	1–3	High	Holosystolic	Left axilla
CoA	Left back	Systolic or continuous	1–3	Medium to high	Ejection or continuous	
HCM	LLSB	Systolic	1–3	Medium	Ejection	RUSB

ASD atrial septal defect, *LUSB* left upper sternal border, *VSD* ventricular septal defect, *LLSB* left lower sternal border, *PDA* patent ductus arteriosus, *PS* pulmonary stenosis, *AS* aortic stenosis, *RUSB* right upper sternal border, *RLSB* right lower sternal border, *MR* mitral regurgitation, *CoA* coarctation of the aorta, *HCM* hypertrophic cardiomyopathy

mitral valve prolapse, there is a mid-systolic click prior to the murmur being noted.

Coarctation of the aorta gives a variable murmur that is rarely greater than grade 3. It is a systolic ejection type murmur, maximal at the left scapula or just below, but may be heard anteriorly at the left upper sternal border. There is an increase in left ventricular activity on palpation, and decreased lower extremity pulses. If the coarctation is severe, there may be a continuous murmur present. A murmur associated with a coarctation may not be noted until the ductus closes (24–48 h for functional closure) and may not be readily heard until complete remodeling of the aorta has occurred in several weeks.

Mitral valve prolapse is not truly a murmur, but a mid-systolic click associated with prolapse of the valve leaflets. Additionally, mitral valve prolapse may be associated with a murmur of mitral regurgitation occurring after the click.

The murmur associated with hypertrophic cardiomyopathy is a grade 1–3 systolic ejection murmur that is medium in pitch and heard best at the mid or lower left sternal border. The murmur increases when going from a squat to a stand or during the strain phase of a Valsalva (*Table 247.13*).

Murmur Evaluation

Once a cardiac murmur has been noted on physical examination a systematic approach is required to evaluate the murmur. The initial part of the evaluation should be to perform a careful cardiac examination to allow for a full description of the cardiac murmur and any associated findings. Benign cardiac murmurs tend to occur in isolation, without other cardiac exam findings, symptoms, or concerning history. Pathologic murmurs, however, are frequently not found in isolation and often have other physical exam findings, symptoms, or positives in the history to indicate possible structural heart disease. These findings include cardiac symptoms (tachypnea, poor growth, etc.), ejection clicks, gallops, the murmur being only in diastole, or positive family history.

Although many providers will feel that their auscultation skills are limited in evaluation of cardiac murmurs, pediatricians do a good job in screening cardiac murmurs. Of patients referred by pediatricians for pediatric cardiology evaluation of a cardiac murmur, 20–30% are found to have structural heart disease, a rate much higher than the incidence of congenital heart disease (0.8%). Pediatricians also correctly classify murmurs as either benign or pathologic 80% of the time, though they are less accurate with the specific diagnosis.

There are different approaches that providers may take to further evaluate cardiac murmurs. Options include referral of all murmurs to a cardiologist, refer only murmurs felt to be pathologic, evaluating with a chest x-ray and electrocardiogram and only referring patients with abnormal studies, or performing an echocardiogram on all patients with a murmur. Of these strategies, referral of murmurs to a cardiologist may be the best and most cost-effective approach. The cardiologist can listen to the patient and determine if an echocardiogram is warranted. Cardiologists can determine pathologic murmurs by physical examination alone with a sensitivity of 92%, but the sensitivity increases to around 97% with selective

utilization of echocardiogram. This approach identifies all significant structural cardiac disease, but may miss hemodynamically insignificant structural defects such as small atrial septal defects or mild valvar abnormalities.

While an echocardiogram is the most sensitive test to determine if a patient has a structural defect as the etiology of a cardiac murmur, it is also the most expensive way to evaluate a murmur. Echocardiography costs about ten times that of a cardiology consultation, so performing echocardiograms on all patients with heart murmurs is not cost effective. Additionally, often a relatively benign disease may be discovered such as a small atrial septal defect. If it is determined that an echocardiogram is needed for a pediatric patient, the study is best performed in a pediatric echocardiography laboratory and interpreted by a pediatric cardiologist. Echocardiograms performed in an adult echocardiography laboratory may not be as detailed in evaluating the anatomy and may miss structural heart disease.

Classic teaching is that a chest x-ray and an electrocardiogram should be performed to assist in defining the etiology of a murmur. However, both of these studies have low sensitivity in detecting structural cardiac disease. Chest x-ray has a 60% false positive rate and 20% false negative rate in pediatric patients. The low sensitivity makes electrocardiograms and chest x-ray poor screening tests for evaluation of congenital heart disease in the asymptomatic patient so are probably not warranted. If these studies are used as part of the evaluation, they are best interpreted by a pediatric cardiologist.

Age of the patient when the murmur was initially noted may assist in deciding about further workup or referral. Murmurs are frequent in newborns with up to 60% having a murmur noted during a careful examination. Some of these murmurs are transient in nature, coming from tricuspid valve regurgitation or a closing patent ductus arteriosus. Murmurs heard in the immediate newborn period that persist to 1 week of age may be related to structural cardiac disease. Utilizing persistence of a newborn murmur to 1 week of age in an otherwise asymptomatic infant as a screening strategy will pick up 60% of all structural heart disease and any life-threatening cardiac disease. Any infant with a murmur should also have an oxygen saturation check and if less than 95% should be considered for further evaluation. Pathologic murmurs noted in the immediate newborn period include stenosis of the pulmonary valve or aortic valve. A pathologic murmur not noted until a few weeks of age may be related to a ventricular septal defect.

For a murmur initially noted at 2–4 years of age, the most likely diagnosis is an innocent murmur, such as a Still's murmur. If the murmur has the classic vibratory quality at this age, then there is little need for referral since that finding is diagnostic. However, parental anxiety about the murmur may be an indication for referral.

If a cardiac murmur is discovered on physical examination, then a complete description of the murmur is essential and should include location, timing, loudness, type, pitch, quality, and transmission. A complete description will allow the development of a limited differential diagnosis. Assess the patient for additional cardiac sounds or exam findings suggesting structural cardiac disease as the etiology of the murmur. The patients past and family history should be reviewed for any positives that may indicate a structural heart defect. If the murmur is consistent with one of the benign cardiac murmurs, the patient is asymptomatic, the murmur is grade 2 or less, the history is unremarkable, and the rest of the physical exam is normal, then the murmur is likely benign in nature and may not require further evaluation. However, if there are positive findings in the history, on the examination, or the patient has cardiac symptoms, then further evaluation is probably warranted. If any doubt about whether a murmur is benign or pathologic, then further evaluation or referral is warranted.

Once a murmur is fully defined, one can use a basic algorithm to determine if further evaluation or referral is needed. Timing in the cardiac cycle is the first component to consider: determine if the murmur is systolic, diastolic, or continuous. If the murmur is systolic then determine if it is mid-systolic (crescendo-decrescendo, ejection type), early or late systolic, or holosystolic. Murmurs greater than or equal to grade 3, or early, late, or holosystolic should be referred to a pediatric cardiologist for evaluation (although, sometimes benign murmurs can be grade 3 if cardiac output is increased). If the murmur is mid-systolic and grade 2 or less in intensity, but the patient is symptomatic or there are other history or physical exam findings suggestive of cardiac disease, then the patient should be referred for evaluation. However, if the patient is asymptomatic and there are no other history or exam findings and the murmur is consistent with a benign murmur, no further workup is needed. A murmur heard only in diastole should be referred for evaluation. A continuous murmur consistent with either a venous hum or a mammary soufflé does not require further workup. But, if the continuous murmur is not consistent with one of the benign continuous murmurs, then further evaluation is warranted (❯ *Fig. 247.1*).

Patients with a cardiac murmur that is not clearly innocent should be referred to a pediatric cardiologist for evaluation. If the distance to a cardiologist is

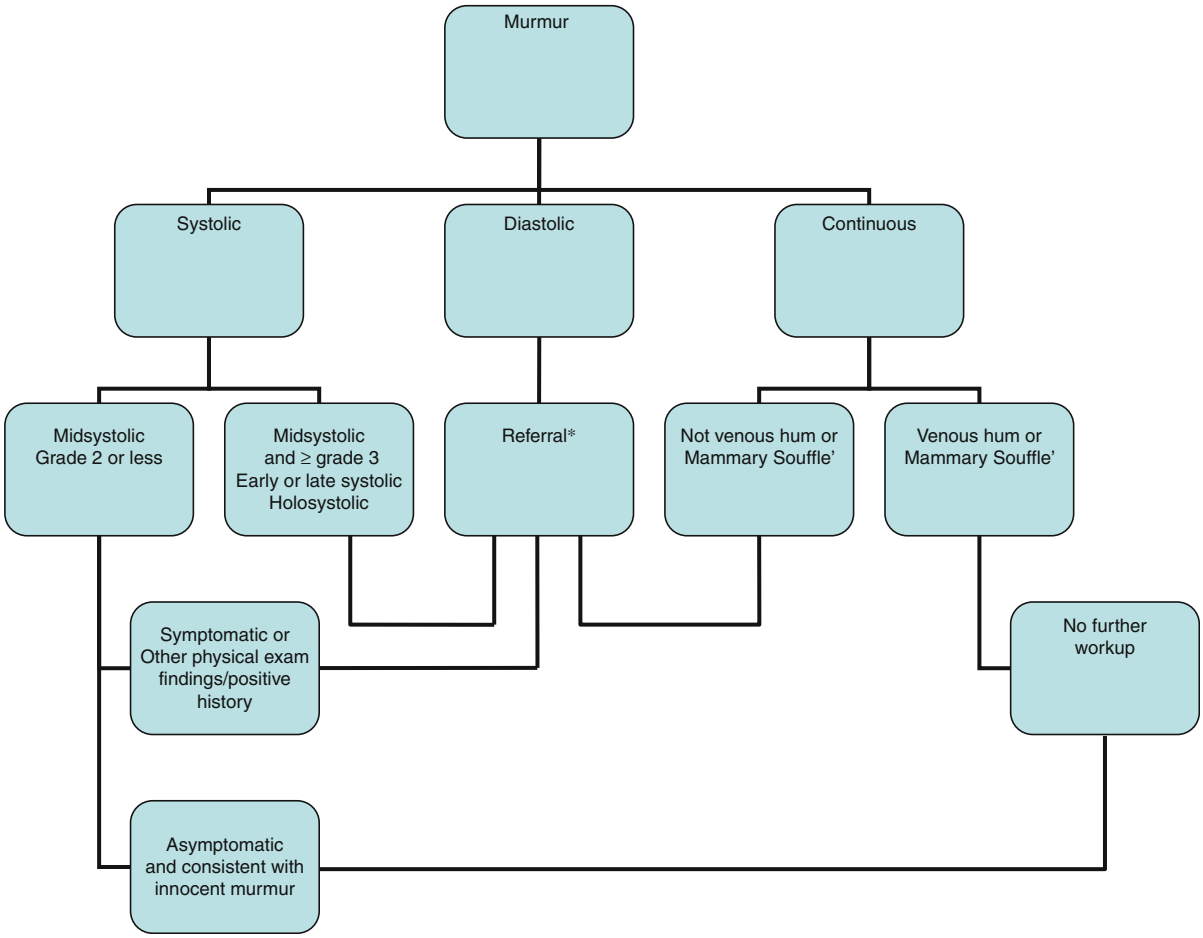

Figure 247.1
Murmur Algorithm. *Echocardiogram performed by telemedicine to a referral center may be appropriate if distance to a pediatric cardiologist is significant

significant, and tele-echocardiography is available, then performing an echocardiogram may be a reasonable alternative to a cardiology consult. Any echocardiogram on a pediatric patient is preferably done in a pediatric echocardiography laboratory and interpreted by a pediatric cardiologist. Patients with positive findings in their history or other findings on examination should be referred to a pediatric cardiologist.

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248 Left to Right Shunt Lesions

Cory Noel · Mark B. Lewin

Atrial Septal Defects

Definition

An atrial septal defect (ASD) is any deficiency in the atrial septum allowing communication between the right and left atria. An atrial septal defect is distinguished from a patent foramen ovale, which is not considered a pathologic finding and occurs due to inadequate fusion of the septum secundum to the septum primum. An atrial septal defect is one of the most common congenital heart anomalies, and can be found in 10–15% of patients with congenital heart disease**.** The foramen ovale is a normal interatrial shunt that is necessary in utero. As a result of increasing left atrial pressure after birth, the valve of the fossa ovalis is pushed against the limbus and is functionally closed. However, in 17–35% of people, the flap does not adequately close the fossa ovalis and a potential communication remains between the atria**.** A patent foramen ovale results from this inadequate closure. There are several types of atrial septal defects, and they are classified by their location relative to the fossa ovalis. A defect in the septum primum near the fossa ovalis is termed a secundum atrial septal defect because as a result of the deficiency, the ostium secundum appears enlarged.

Approximately 5–10% of ASDs are located superior and posterior to the fossa ovalis and are termed sinus venosus or superior vena cava type defects. With this type of interatrial communication, the defect is usually only bordered by atrial septal tissue at the anteroinferior border. The posterior border being the right atrial free wall and the superior border often being absent because of an overriding superior vena cava. Quite frequently this type of defect is associated with anomalous connection of the right pulmonary veins to either the superior vena cava or the right atrium.

A rarer defect is the coronary sinus ASD. Its location is inferior and anterior to the fossa ovalis and results from a defect in the wall of the coronary sinus as it passes the left atrium. It is usually associated with a persistent left superior vena cava that drains to the left atrium.

A final type of the interatrial communication is the primum ASD. The location of this type of defect is cephalad to the atrioventricular valves and is part of the spectrum of atrioventricular septal defects and thus will be discussed in a separate section.

Etiology

In general, ASDs occur sporadically; however, they are associated with some syndromes, namely, Holt-Oram which is characterized by ASDs and upper extremity anomalies. Although the genetic understanding of ASDs is far from complete, two gene mutations have been found to be associated with ASDs. *NKX2.5* and *GATA4* are two genes that have been shown to be linked to nonsyndromic congenital heart defects.

Epidemiology

The most common type of ASD is the secundum type and accounts for 6–10% of all cardiac anomalies. ASDs occur at a 2:1 ratio in females to males. ASDs have an incidence of one child per 1,500 live births.

Pathology/Pathophysiology

When an interatrial communication exists, a left-to-right shunting of blood will occur. The volume and direction of the blood flow is dependent on the size of the defect and the relative compliance of the ventricles. In early infancy the right ventricle is thickened and not very compliant, thus there is very little shunting across the ASD. However, within the first few weeks, left-to-right shunting occurs because the right ventricle becomes the more compliant ventricle, resulting in a lower right atrial pressure in comparison to the left atrial pressure. The left-to-right shunt can place a significant volume load on the right-sided cardiac structures, resulting in dilation of the right atrium and ventricle. If the right ventricular dilation is severe, the annuli of the tricuspid and pulmonary valves may also dilate and become insufficient. Pulmonary blood

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flow may be up to four times that of the systemic blood flow, producing elevated pulmonary artery oxygen saturations.

The pulmonary vascular bed is highly compliant and initially can handle the increased blood flow, as shown by the pulmonary resistance often being normal in the face of significant pulmonary blood flow. However, with chronic overload, the pulmonary vasculature undergoes microscopic change. Within the muscular pulmonary arteries, medial hypertrophy will begin to occur along with intimal proliferation. However, the permanent changes leading to pulmonary hypertension may not occur until the third or fourth decade of life. With unrestrictive ASDs, there is an increasing incidence of pulmonary hypertension with advancing age. There is also a strong female predilection to the development of pulmonary hypertension. Usually despite the increased pulmonary blood flow, the pulmonary artery pressure is within the normal range or only slightly above. Although it is extremely rare for pulmonary vascular obstructive disease to occur in patients with ASDs before their early 20's, there have been studies that have shown it may occur as early as 3 months old. These infants with pulmonary vascular obstructive disease and ASDs may have significant cyanosis and Eisenmenger syndrome.

Clinical Manifestations

The typical course of a secundum ASD during infancy is that it does not cause symptoms and often goes undiagnosed. With the typical left-to-right shunt across the atrial septum, there is a fixed and widely split S2 heart sound and a soft, systolic ejection murmur. The average age of diagnosis is 6 months. Rarely infants will present with congestive heart failure. It is poorly understood why these infants will be in heart failure as their hemodynamic findings on cardiac catheterization are not significantly different from infants not in heart failure. The usual clinical course is dependent on the amount of left-to-right shunting. If the shunting is only moderate, children will often remain asymptomatic. As the shunting increases, children may begin to complain of fatigue and dyspnea. Unlike ventricular septal defects, it is rare for children with ASDs to have growth failure. Because the signs and symptoms of ASDs may be subtle, adults may be diagnosed with the defect. Adults may present with atrial flutter or fibrillation.

Diagnosis

For a small-sized ASD, the electrocardiogram (ECG) is usually normal. The rhythm seen on the ECG is usually normal sinus. However, the rhythm may demonstrate a junctional or supraventricular tachycardic rhythm in a minority of patients, usually older in age. The QRS axis is often time normal, but may demonstrate right axis deviation if right ventricular hypertrophy is present. If right atrial enlargement occurs due to the left-to-right shunting, the P waves may exceed 3 mm. In older patients it is common to see a prolonged P–R interval due to the intra-atrial conduction delay causing first-degree atrioventricular block. An incomplete right bundle branch block with RSR' pattern is also characteristic and found in lead V1.

The chest radiograph usually shows varying degrees of cardiomegaly, depending on the amount of right atrial and right ventricular dilatation. The increased shunt flow causes the pulmonary vascular markings to be increased and the pulmonary arteries to appear engorged. As the pulmonary vascular resistance rises due to pulmonary vascular changes, the lung fields may become clear or oligemic and the main pulmonary artery will appear enlarged.

Transthoracic echocardiography with Doppler color flow can demonstrate the size and the location of the ASD. The atrial septum should be visualized from multiple planes to fully understand its location, size, and relation to other structures. Particular structures that should be noted in relation to the ASD include the superior and inferior vena cava, the pulmonary veins, and the coronary sinus. Color Doppler can demonstrate the direction of shunting across the ASD. The typical flow pattern across the defect is left to right, usually beginning in mid-systole and decreases in velocity and volume until early diastole. It is with early diastole that atrial contraction occurs and this accentuates the left-to-right shunting. Pulse Doppler echocardiography can demonstrate the flow pattern. Right atrial and right ventricular dilatation can be seen by echocardiography as evidence of the left-to-right shunting. While transthoracic echocardiography is usually sufficient in the pediatric population, transesophageal echocardiography is the usual diagnostic method in older patients.

Cardiac catheterization is usually not a needed diagnostic modality. However, in patients where there is concern regarding associated anomalies, particularly those involving the pulmonary veins, or questions regarding the pulmonary pressure or resistance, a cardiac catheterization may be required. The degree of shunting, the Qp:Qs ratio, can be calculated. If the defect is large in size, the pressures will be equal between the left and right atria. Due to the increased flow through the right side of the heart, the right ventricular pressure will be increased. The

pulmonary artery pressure is usually normal or only slightly elevated; however, there is a subset of patients that show a moderate increase in the pulmonary artery pressure. The measuring of the pulmonary vascular resistance becomes critical in patients with concern for pulmonary vascular obstructive disease to assure operability. If the pulmonary vascular resistance is elevated, 100% oxygen or nitric oxide can be given to assess reversibility. Cardiac catheterization will be discussed further in the treatment section, as percutaneous closure is often the first choice of treatment.

Differential Diagnosis

A large ASD may create a significant left-to-right shunt, but can usually be differentiated from other lesions by echocardiography. The defect is normally well visualized by echocardiography and can be differentiated from VSDs and atrioventricular septal defects (AVSD) by the location of the defect. In addition, there is usually more right atrial and ventricular dilation seen in ASDs than in VSDs and AVSDs due to the timing in the cardiac cycle and location of the shunt. The murmur of an ASD can be differentiated from these defects because a VSD and an AVSD usually have a holosystolic murmur while the murmur of an ASD is most commonly a soft, systolic ejection murmur. Another common finding seen with an ASD is the fixed splitting of the S2. A fixed, split S2 may also be found in other lesions such as pulmonary stenosis or partial anomalous pulmonary venous return. The pulmonary stenosis murmur will often be more harsh than that of the ASD. Both of these lesions should be easily differentiated by echocardiography.

Treatment

Prior to the use of interventional catheter procedures to close the ASD, surgical repair was the treatment of choice for any ASD of appreciable size, usually corresponding to a Qp:Qs ratio greater than 1.5:1. Because it is rare that clinical symptoms will occur in childhood from an ASD, the repair is often deferred until the age of 3–5 years old. After this age, there is no advantage in delaying repair. If symptoms of congestive heart failure are developing, or there is concern for pulmonary vascular disease, then the timing for treatment may necessitate intervening at an earlier age. Surgical closure is considered to be a safe and technically easy operation for secundum ASDs as well as sinus venosus defects. The surgical approach for closure of the ASD is typically through a median sternotomy.

Over the last 30 years, a transcatheter approach for ASD closure has become common and results are quite good with the continued advance of ASD occluder devices. In 2001, the Amplatzer septal occluder became the first FDA-approved device for transcatheter closure of ASDs. While the results are typically good for transcatheter closure, there is a slight risk of device erosion and thrombus from this type of procedure. The advantages of a transcatheter approach compared to surgical intervention include faster recovery time, less invasive than open heart with avoidance of cardiopulmonary bypass, and more cosmetically appealing due to the absence of a median sternotomy scar. Limitations of a catheter-based approach include the location and size of the ASD: the septal occluder requires a circumferential rim of septal tissue in order to achieve stable deployment. If the defect is too large or in a peripheral position on the septum, device closure is less suitable.

Prognosis

The natural history of ASDs is usually benign except for those that allow a large left-to-right shunt or are associated with other cardiac defects. Spontaneous closure of small- to medium-sized defects is also quite common. In a study performed by Radzik et al**,** all ASDs less than 3 mm in diameter had closed spontaneously prior to 9 months of age, 87% of those between 3 and 5 mm, 80% of those 5–8 mm, and none of those with defects larger than 8 mm. Other studies have shown that the rate of closure decreases significantly after the age of 3, thus it is often best to wait until this age before embarking on treatment to see if the defect closes spontaneously. As outlined above, it is rare for children to experience symptoms related to an ASD. The severity of symptoms and the likelihood of permanent pulmonary vascular damage increases with age. While congestive heart failure is extremely rare in infants with ASDs, this is a much more common finding in a patient over the age of 40 years. The most debilitating sequelae of an untreated ASD remains pulmonary vascular obstructive disease (PVOD). PVOD occurs in 5–10% of patients with untreated ASDs and has a female predilection. It is rare for PVOD to occur before the age of 20 years. In addition, atrial arrhythmias occur with increasing frequency in those with untreated ASDs. The incidence has been found to be as high as 52% in those over 60 years of age with an untreated ASD.

Ventricular Septal Defects

Definition/Classification

A ventricular septal defect (VSD) is any opening in the septum separating the right and left ventricles that allows communication between them. Excluding bicuspid aortic valve, the ventricular septal defect is the most common form of congenital heart disease. VSDs may be single or multiple. The defects are normally classified by their location in the interventricular septum.

The most common type of VSD is the perimembranous defect. The membranous septum is a relatively small area and is between the anterior and posterior divisions of the septal band and between the outlet and trabecular septum. Perimembranous defects may also be termed infracristal VSDs. The membranous septum is normally divided by the septal leaflet of the tricuspid valve and minor anomalies of the tricuspid valve may occur with perimembranous defects. There can be varying amounts of anterior malalignment between the anterior ventricular septum and the infundibular septum causing the aorta to override the septal defect. A less common occurrence is posterior malalignment which can cause obstruction along the left ventricular outflow tract. Although it is rare, a perimembranous septal defect can cause a left ventricular-to-right atrial shunt if the septal commissure of the tricuspid valve is disrupted.

Outlet defects, which have multiple other synonyms including supracristal, infundibular, conal, or subpulmonary, occur below the pulmonary valve. The right coronary cusp of the aortic valve may prolapse through an outlet defect which can cause aortic insufficiency.

The inlet septum is located posterior and inferior to the membranous septum and beneath the septal leaflet of the tricuspid valve. Occasionally associated with this type of defect is straddling of either the mitral or tricuspid valve.

The final type of VSD is termed the muscular type, found in the muscular septum. Muscular VSDs are often multiple and may be found anywhere in the muscular septum, but most commonly are seen at the apex. The defects may be difficult to visualize from the right ventricle due to the overlying trabeculations, making surgical closure more difficult. The muscular defects are often small and hemodynamically insignificant, many of which close on their own. When the defects are multiple, they often coalesce to form a single defect on the left ventricular side of the interventricular septum.

Etiology

Although no single gene has been identified to be the cause for VSDs, *NKX2.5* and *GATA4* are two genes that have been shown to be linked to nonsyndromic congenital heart defects. However, the concordance rate for identical twins is only 10% and suggests that VSDs are more likely due to random errors in development. The risk of a mother with a VSD to have an offspring with a congenital heart defect is 2–4%.

Epidemiology

An isolated VSD accounts for 20% of patients with congenital heart disease. It is thought that VSDs may be underdiagnosed due to spontaneous closure. Most recently, it was found that VSDs occur at an incidence as high as 5–50 per 1,000 newborns. There is a slight female preponderance.

Pathology/Pathophysiology

After birth, a left-to-right shunt across the VSD will begin to develop. The primary determinant of the blood flow across the defect is the size of the defect and the pulmonary vascular resistance (PVR). If the defect is small or medium in size, the dimension of the defect limits the amount of blood that shunts between the ventricles. The pressure gradient between the left and right ventricles determines the directionality of blood flow in these smaller VSDs. If the defect is larger then there is no restriction to flow across the defect. In these larger defects, the shunt is determined by the relative resistances of the systemic and pulmonary vascular bed. Thus, any condition that increases the systemic vascular resistance, such as a coarctation, will increase the left-to-right shunt. Likewise, any condition that obstructs right ventricular outflow, such as pulmonary stenosis, will decrease the shunt.

In the immediate postnatal period, PVR is high and there is little to no intracardiac shunting. The PVR begins to decrease and reaches near adult levels within 2 weeks, continuing to decline over the first few months of life. With the coincident drop in the PVR, the left-to-right shunting across a large VSD is accentuated and delays the rate of PVR decline. The increasing blood flow through the pulmonary vascular bed will lead to pulmonary overcirculation. In the setting of a large VSD, the pressure is equalized between the left and right ventricles, as well as the great arteries. Because of the elevated right

ventricular pressure, the right ventricle does not undergo its normal involution to a thin-walled, crescent-shaped ventricle. Instead, it remains thick walled to compensate for the increased pulmonary pressure. The left ventricle faces a volume overload because not only is blood being ejected out the left ventricular outflow tract, but the left ventricle also must eject blood through the VSD into the pulmonary circulation. The left ventricle will begin to dilate in the face of the excessive pulmonary venous return. Due to the marked increase in pulmonary circulation, the child will begin to develop congestive heart failure, normally between 2 and 8 weeks of age.

As in other lesions allowing increased pulmonary blood flow, the excessive flow can cause vessel injury to the pulmonary circulation. An unrepaired VSD may lead to chronic injury of the vessels, signaling pulmonary vascular obstructive disease.

Small- and moderate-sized VSDs will offer some resistance to flow. In these smaller types, there is normally a small shunt, and the workload is not increased in the ventricles. In addition there is the absence of an increase in the PVR. In moderate-sized defects, the shunt may be large enough to cause pulmonary overload with resultant dilation of the left atrium and left ventricle, but it is very rare to have an increase in PVR. Smaller VSDs may close spontaneously, usually by 6 months of age. Muscular-type defects are the most common to close spontaneously (by muscular septal growth) followed by perimembranous defects.

Clinical Manifestations

In infants with *small VSDs*, a murmur is often able to be auscultated by the 2 week newborn check-up, but may be heard as early as the first few days of life. The murmur becomes more evident as the PVR falls over the first weeks of life. Smaller defects usually do not cause hemodynamic effect. Infants with small VSDs should be able to take oral feeds without distress and should grow appropriately.

Upon examination, a high-pitched, holosystolic murmur is normally able to be auscultated, usually at the left lower sternal border. The murmur may be associated with a thrill. The murmur may encompass the second heart sound and slightly extend past it. If the defect is an outlet VSD, the murmur is often best heard at the upper left sternal border, due to the ejection of blood into the right ventricular outflow tract. Occasionally small, muscular VSDs will end in mid-systole during ventricular contraction due to VSD impingement of flow by the muscular septal tissue. Although there is blood flow across the defect during diastole, it is a small amount and is not turbulent, thus the lack of a diastolic component of the murmur.

The clinical presentation may vary widely for infants with *moderate- to large-sized VSDs*. If the PVR drops quickly and the defect is large, symptoms may be seen as early as 2 weeks of age. Symptoms include signs of congestive heart failure (tachypnea, diaphoresis with feeds, and poor weight gain). Cardiomegaly and hepatomegaly will often become evident by 2 months of age in those infants with signs of heart failure. Symptoms are often worsened during times of a respiratory illness, and this is a frequent cause for presentation. The tachypnea and signs of respiratory distress usually herald the development of pulmonary edema.

The murmur associated with moderate or large VSDs is holosystolic and best heard along the left sternal border. A thrill is often associated with the murmur. Frequently, a third heart sound can be auscultated as well as diastolic rumble when the pulmonary blood flow is twice that of the systemic blood flow. In moderate-sized VSDs, the second heart sound is usually widely split and varies only slightly with respiration. In large VSDs, the pulmonary component of S2 is loud and splitting is usually narrow but perceptible. A faint diastolic murmur, typically termed a diastolic rumble, heard at the apex often signifies relative mitral stenosis due to increased flow through the left heart.

Children with elevated PVR will be protected from the increased pulmonary blood flow, but lack of symptoms may disguise the worsening pulmonary vascular disease. In infants, transient episodes of cyanosis can be seen; however, if cyanosis persists, this may signify either an anatomic (e.g., right ventricular outflow tract obstruction) or a physiologic (e.g., elevated PVR) mechanism for reduced pulmonary blood flow. A large, unrepaired VSD may lead to episodes of cyanosis as the child enters adolescence and young adulthood, owing to the worsening pulmonary vascular disease. A holosystolic murmur is often auscultated in these patients, but is instead due to tricuspid valve insufficiency, a consequence of elevated right ventricular pressures. The second heart sound is loud, and normally single. This condition is termed Eisenmenger's complex. The pulmonary vascular damage that has occurred by this stage is irreversible and the patient is inoperable due to the elevated PVR.

Diagnosis

An electrocardiogram (ECG) is usually normal in patients with a small VSD. Occasionally there will be an rsR'

pattern in V1 or V4R. In moderate-sized defects that are associated with larger left-to-right shunts, evidence of left or biventricular hypertrophy will be seen on the ECG. Increases in right ventricular pressure may be judged by an increasing amplitude of R' in lead V4R. In patients with large VSDs, the axis may be deviated to the left due to the left ventricular hypertrophy. As pulmonary blood flow increases and the left atrium becomes dilated, the P waves may become wide and biphasic, best seen in leads I and V6.

The chest radiograph usually shows a normal heart size and pulmonary vascularity in children with a small VSD. A chest radiograph will show cardiomegaly, increased pulmonary vascular markings, and increased size of main pulmonary artery by 2–3 months in those children with moderate to large-sized VSDs. In those that develop Eisenmenger syndrome, there will be prominence of the main pulmonary artery and the proximal pulmonary tree, but the pulmonary vasculature distally will have decreased markings.

Echocardiography will allow the cardiologist to define the location, size, and number of defects in the ventricular septum. Color flow Doppler across the defect will demonstrate the direction of the shunting. By echocardiography, the left atrium and left ventricle can be assessed for changes in dimension that may occur with the increased pulmonary blood flow. With VSDs that are identified during infancy, serial echocardiograms may be used to document the change in size of the VSD. Smaller, muscular and perimembranous VSDs may grow smaller or close spontaneously. Aside from gaining information about the VSD, other associated abnormalities may also be identified by echocardiography. These include overriding aorta in the case of the perimembranous defect, straddling atrioventricular valves, pulmonary outflow tract obstruction, and aortic or pulmonary insufficiency.

Normally, echocardiography is sufficient to diagnose VSDs. When echocardiography data is not satisfactory, a cardiac catheterization may be indicated. Cardiac catheterization is especially useful in infants with evidence of elevated PVR and only a small or moderate-sized defect. A right heart cardiac catheterization can be performed and will give an accurate measurement of the right ventricular and pulmonary artery pressures, and PVR. Patients with pulmonary hypertension may not be amenable to surgical repair, thus it is very important in those patients with elevated PVR that they demonstrate reversibility with 100% oxygen or nitric oxide before proceeding.

Differential Diagnosis

In the case of an isolated VSD, the diagnosis may be confused for those other cardiac lesions that cause a significant left-to-right shunt. Atrioventricular septal defects often have a large left-to-right shunt, but are normally able to be differentiated by echocardiography. Another cardiac lesion that may be associated with a large left to right shunt with little or no cyanosis is that of double-outlet right ventricle (DORV). Truncus arteriosus is associated with increased pulmonary blood flow and may not have signs of cyanosis. By auscultation, the S2 is single and often has a click associated with the truncal valve. Echocardiography will easily distinguish this from an isolated VSD.

Treatment

Small VSDs usually do not cause hemodynamic significance and thus do not require medical or surgical treatment. As per the most recent subacute bacterial endocarditis (SBE) prophylaxis guidelines, no prophylaxis is required prior to procedures.

As stated in the Clinical Manifestations section, the symptoms normally associated with moderate or large VSDs are those consistent with congestive heart failure. Even the child where the VSD is likely to necessitate surgical management, a trial of medical management is first initiated. Symptoms are related to pulmonary overcirculation, thus diuretics are the first line of medical therapy. This will help to decrease pulmonary flow, but does have ill effects on electrolytes, most commonly hypokalemia and hypochloremia. If hypokalemia persists, spironolactone may be added for potassium sparing effect. If additional therapy is required for medical management, systemic afterload reduction with an ACE inhibitor is the next choice. Afterload reduction aids in decreasing the systemic vascular resistance as well as decreasing the systemic stimulation associated with the state of congestive heart failure. If symptoms of heart failure persist despite diuresis and afterload reduction, Digoxin may be added. Infants with moderate and large VSDs often have poor growth and will have weight and height plateau. Caloric supplementation is necessary when poor growth occurs. If the infant is unable to take the needed calories orally, a nasogastric tube may be required. With the application of medical therapy, most infants will show clinical improvement. In addition, the VSD may close or become smaller during infancy. However, with a decrease in symptoms, the clinician must be mindful to assure that the

improvement is not due to the PVR increasing or hypertrophy of the right ventricular outflow tract resulting in a reduced left-to-right shunt.

For many infants, the trial of medical therapy is only a bridge to surgical management, allowing symptomatic improvement and weight gain until VSD repair. During infancy, those with symptoms of congestive heart failure not able to be medically managed will require surgical therapy to close the VSD. Children with large defects and shunts of greater than 2:1 are normally repaired prior to 2 years of age, but can be repaired sooner if there is evidence of rising pulmonary pressures. If infants have an outlet-type VSD, the aortic valve is monitored to detect aortic insufficiency.

Children with small VSDs and shunts that are below a Qp:Qs of 1.5:1 typically do not require surgical intervention. A slightly increased risk for endocarditis does remain in those with unrepaired VSDs.

Closure of VSDs by a percutaneous transcatheter approach using a device is less established than device closure of ASDs. This technique appears to be most useful for muscular or residual VSDs. However, further studies are still needed to assess safety and long-term results.

Prognosis

Long-term survival is quite good for isolated VSDs. Patients with large defects normally require medical management and surgical repair. If the defect is only moderate in size, medical management may bridge them to spontaneous closure. Mortality due to VSD is rare, but may be due to associated pulmonary infections or the development of elevated PVR. If surgical repair is undertaken before the age of 2, it is rare to develop pulmonary vascular disease. However, if surgery is not performed before this age, as many as 25% of patients will develop pulmonary vascular disease. This is further evidence that surgical repair between 6 and 12 months should be undertaken in those infants with elevated pulmonary artery pressure. Typically after surgical repair, results are very favorable in terms of activity, growth, and development. Early repair has been shown to be associated with regression of left ventricular dilation and hypertrophy and improved cardiac contractility. Following surgery, care must be taken to monitor for signs of pulmonary hypertension, sinus node or atrioventricular node dysfunction resulting in conduction abnormalities, or aortic insufficiency. These are all rare but documented consequences observed in patients with surgical repair of VSDs.

Patients with small VSDs have an excellent prognosis. Many of these defects will close spontaneously in the first 2 years of life. These patients may be followed infrequently for detection of defect closure and observation for rare complications.

Atrioventricular Septal Defects

Definition

Atrioventricular septal defects (AVSD) are a group of defects that are comprised of a deficiency of the atrial and ventricular septum as well as abnormalities of the atrioventricular (AV) valves. Other common names for this collection of pathology includes endocardial cushion defect or atrioventricular canal defect. AVSDs can be further categorized depending on the defect of the ventricular septum. A partial AVSD is comprised of a primum ASD and typically has two distinct atrioventricular valves: the tricuspid and the mitral. In a partial AVSD the mitral valve will be cleft in the anterior leaflet. The mitral valve also has abnormal attachments to the ventricular septum and may cause left ventricular outflow tract obstruction because of anterior displacement. A complete AVSD will likewise have a primum ASD, but it will be contiguous with an inlet-type VSD. Unlike the partial AVSD with two distinct AV valves, the complete AVSD has a common AV valve with a single annulus. Although the AV valve has a single valve annulus, there may be two distinct valve orifices within the common AV valve. When this occurs, the defect is commonly referred to as an intermediate AVSD. The tissue comprising the AV valve itself has a wide range of variability, ranging from normal-appearing tissue to severely dysplastic leading to significant incompetence. Embryologically, the endocardial cushions give rise to the inferior portion of the atrial septum, the inlet portion of the ventricular septum, and the septal leaflets of both AV valves. Thus, the abnormal or deficient growth in this area produces the defect, and essentially amounts to a hole in the middle of the heart.

Etiology

AVSD is commonly associated with Down syndrome. Children that have Down syndrome are found to have congenital heart disease 40–45% of the time. Of these children that are found to have congenital heart disease, approximately 40% of them will have an AVSD. Most commonly, the type of AVSD is the complete form.

Other syndromes that are associated with AVSD include heterotaxy syndromes as well as Ellis-van Crevald syndrome. Nearly 14% of women with repaired AVSD who have children risk passing along a congenital heart defect trait, usually AVSD or tetralogy of Fallot.

Epidemiology

AVSD has an estimated occurrence of 0.19 in 1,000 live births and does not show any gender predilection. In relation to congenital heart disease, AVSD accounts for 4–5% of all disease.

Pathophysiology/Pathology

There are two separate annuli in partial AVSD and the mitral and tricuspid valves have the same septal insertion level due apical displacement of the mitral annulus. Because of this displacement, an interatrial communication is established through the primum ASD. The primum ASD is usually large and located anteroinferiorly to the fossa ovalis. As described in the section detailing ASDs, this type of lesion is not amenable to transcatheter closure. Because of the apical displacement of the mitral annulus the distance between the apex and the aortic annulus is greater than the distance between the apex and the mitral annulus and is a possible etiology of left ventricular outflow tract obstruction. The anterior leaflet is usually cleft in a partial AVSD. The cleft of the mitral valve in AVSD is directed toward the mid-portion of the ventricular septum. There is commonly a regurgitant jet through the cleft in the mitral valve and over time the mitral leaflets may become dysplastic and thickened.

As described in the section on ASDs, the shunt flow through the primum ASD of a partial AVSD is determined by the relative compliance of the ventricles unless the defect is such a small size that it restricts flow itself. A left-to-right shunt through the atrial communication may cause right ventricular dilation and displace the interventricular septum into the left ventricle. Over time, if there is persistent right ventricular volume overload, the right ventricle (RV) may have decreased systolic function. With increasing RV dysfunction, the RV compliance decreases and the shunt ratio may decrease. The recovery of the RV is often dependent on the timing of repair of the primum ASD. In cases of pulmonary hypertension, the shunt ratio may decrease, but there is still a high volume of shunting. Shunting from right-to-left may cause mild cyanosis and is a herald that the defect may no longer be correctable.

In a partial AVSD, there may be significant right atrial dilation due to increased volume from the shunt across the primum ASD. However, an additional factor is the cleft in the mitral valve. As described earlier, the cleft in a partial AVSD is unique in that it is located in the anterior leaflet and the regurgitant jet is directed at the interatrial septum.

In the complete form of AVSD, the septal defect extends to the interventricular septum, differentiating it from the partial form. In addition, there is a common AV valve rather than two separate AV valves. The left-sided papillary muscles are often rotated in an abnormal orientation, and combined with the anterolateral muscle bundle can create progressive left ventricular outflow tract obstruction. The common AV valve may not relate equally to both ventricles and one ventricle, usually the morphologic left ventricle, may become hypoplastic. This type of AVSD will be discussed further in the chapter on "❯ Single Ventricle Physiology." A frequent problem with the common AV valve is regurgitation. As with the cleft mitral valve in partial AVSD, these valve leaflets often become thickened. In complete AVSD, there is left-to-right shunting at both the atrial level as well as the ventricular. The ventricular level shunting occurs during ventricular systole and can lead to RV dysfunction and elevated pulmonary artery pressure. To combat the torrential pulmonary blood flow, PVR will rise and may remain elevated. Eventually the histologic changes that occur in the pulmonary vascular bed with the raising of PVR are permanent and prevent its return to normal levels even after surgical correction. Cases are typically considered to be inoperable when the PVR reaches markedly elevated (and fixed) levels; fortunately this is extremely rare in the current era.

Clinical Manifestations

Patients with partial AVSD are often asymptomatic through childhood. However, in cases where there is moderate to severe mitral regurgitation associated with the primum ASD, symptoms of excessive pulmonary blood flow such as tachypnea and poor weight gain may be evident during childhood. As many as one in five patients with partial AVSD and severe mitral regurgitation have symptoms of pulmonary overcirculation, dyspnea, or atrial arrhythmias during infancy. Compared to patients with secundum-type ASDs, patients with primum defects are more likely to have symptoms at an earlier age and at a more severe level. As with the secundum ASD, a primum ASD may be suspected during physical examination due to a systolic ejection murmur at the pulmonary position

and a second heart sound that is fixed and widely split. If the mitral regurgitation is severe, a holosystolic murmur may be heard at the apex position.

Symptoms due to excessive pulmonary blood flow will almost always occur during early infancy in complete AVSD. Most common are tachypnea and failure to thrive. If a patient is known to have complete AVSD and symptoms are not developing, that should be concerning for the premature development of pulmonary vascular obstructive disease. Further demonstration of the need for early repair of complete AVSD comes from a study showing that a 1-year-old child with an unrepaired AVSD has only a 15% chance of living until 5 years. The rapid progression to pulmonary vascular disease often occurs earlier in patients with Down syndrome, sometimes as early as 2 months of age. In the absence of elevated PVR, it is unusual to have oxygen desaturation. The excessive pulmonary blood flow will cause an accentuation of S2 and a systolic murmur at the pulmonary position on physical examination. A holosystolic murmur will be present if there is significant ventricular level shunting or AV valve regurgitation.

Diagnosis

A common finding on electrocardiogram is a superior or northwest QRS axis, most commonly between –90° and −120°. This altering of the axis is due to the displacement posteriorly of the atrioventricular node. Another common feature is prolongation of the P−R interval (first degree atrioventricular block). Greater than 50% of patients will display signs of right atrial enlargement. Right ventricular hypertrophy is frequently seen, and there is often some variation of the rsR' in the right precordial leads.

A chest radiograph will often show right atrial enlargement, with a mild to moderate degree of cardiomegaly. The pulmonary vascular markings will often be prominent. If the PVR remains elevated, the lung markings become clearer.

Echocardiography is the standard method for diagnosis of both the partial and complete form. Specific features of interest during the echocardiogram include the size of the atrial defect, the amount of regurgitation through either the cleft mitral valve or the common AV valve, and associated defects. In complete AVSD, it is important to examine the relationship of the common AV valve to the ventricles and if the inflow is asymmetric. In complete AVSD, the location and amount of ventricular level shunting should be identified. An evaluation of the left ventricular outflow tract should be undertaken.

Cardiac catheterization does not have a prominent role in the diagnosis or treatment of AVSD. A catheterization may be undertaken if there are questions regarding the PVR and thus the feasibility of repair.

Differential Diagnosis

In a partial AVSD, the primum ASD can usually be differentiated by echocardiography from other types of ASDs. The primum defects compared to the secundum-type defects will usually cause symptoms at an earlier age. In cases of common AVSD with unbalanced ventricles, associated lesions are often seen, including double inlet left ventricle, double outlet right ventricle, or heterotaxy syndrome. Unbalanced AVSD will be discussed further in the chapter on "Single Ventricle."

Treatment

Patients with partial AVSD are often asymptomatic in childhood. When diagnosed, the indications for repair are similar to those for other types of ASDs. When children do become symptomatic from AVSD, it is usually due to the excessive pulmonary blood flow. In these cases, diuretics and afterload reduction are initiated. Digoxin is also occasionally used in cases of symptomatic partial AVSD. A primum ASD will not close spontaneously, and surgical repair is recommended when patients fail medical management or approach school age, just as in other types of ASDs. The goals of surgical therapy are to close the atrial level shunt and to repair the left AV valve to assure competence. The repair of partial AVSD carries a low risk, with hospital death of 3% or less. Poor prognostic factors related to the repair include cyanosis at time of surgery, failure to thrive, and moderate to severe left AV valve regurgitation. Reoperation is required 11% of the time, most commonly for residual mitral valve stenosis or regurgitation.

Unlike partial AVSD, the diagnosis of complete AVSD is usually made in infancy because most patients are symptomatic. As the PVR falls, substantial left-to-right shunting will ensue and symptoms will begin to develop. Diuretics are initiated for the excessive pulmonary blood flow, and if the common AV valve regurgitation is significant, afterload reduction has been shown to be effective. Growth failure is common among these infants and increasing caloric density is quite common along with gavage feeds. When a contraindication to repair is present (prematurity, noncardiac disease complicating cardiac

surgery, respiratory infection), a pulmonary artery banding may be necessary to decrease the pulmonary blood flow.

Patients with Down syndrome and AVSD often present a unique problem. They are more likely to have complete AVSD than the partial type. Additionally, they are also more likely to have associate defects such as tetralogy of Fallot. It has been shown that patients with Down syndrome have a higher PVR than those without Down syndrome. With this knowledge, a lack of symptoms cannot be looked at as reassuring, but instead should be concerning that the PVR remains elevated. Unlike partial AVSD repair that is typically undertaken at early school age, the repair for complete AVSD must be performed prior to the development of irreversible pulmonary changes. Typically the repair is done before the infant reaches 6 months of age. The goal of repair is to close both the atrial and ventricular level shunts, as well as construct two separate AV valves. Risk factors for the surgical repair include early age of repair, preoperative heart failure class, and severity of AV valve regurgitation.

Prognosis

The long-term survival for partial AVSD is quite good. A Mayo Clinic study demonstrated 20- and 40-year survival of repaired partial AVSD to be 87% and 76%, respectively. Unrepaired partial AVSD has a course quite similar to unrepaired secundum-type ASD. Pulmonary vascular disease increases with each decade of life. If combined with moderate to severe mitral regurgitation, the likelihood of symptoms increases. Atrial dilation from the shunt can cause atrial arrhythmias later in life and is occasionally the presenting symptom. Risk of reoperation is 11% and more likely in those with severe mitral regurgitation. Rarely, a pacemaker is required postoperatively for bradyarrhythmias.

Complete AVSD that goes unrepaired has a grim prognosis due to torrential pulmonary blood flow. One study has shown that the mortality is as high as 80% by 2 years of age in patients who are unrepaired. The pulmonary blood flow along with chamber dilation sets the stage for severe congestive heart failure, arrhythmias, endocarditis, or pulmonary infections. Nearly 90% of patients who reach the age of 1 year will have developed irreversible pulmonary vascular disease if unrepaired. Complete AVSDs are associated with a 17% risk of late reoperation during the first 20 years following surgical repair. As in partial AVSD, AV valve stenosis or regurgitation is the most common reason for reoperation, typically on the left side. Other causes for reoperation include residual ASDs or VSDs, as well as progressive left ventricular outflow tract obstruction. Unlike partial AVSD, repair for complete AVSD carries a higher risk for complete heart block and the subsequent need of a pacemaker.

Patent Ductus Arteriosus

Definition

A patent ductus arteriosus (PDA) is a persistent communication between the descending aorta distal to the left subclavian artery and the main pulmonary artery. The PDA is formed from the left sixth aortic arch and has a vital role in fetal physiology. The PDA will vary in length and is typically 10 mm in diameter in a full-term infant. Typically, there is functional closure of the ductus 10–15 h after birth in a full-term infant. Closure is usually complete by 3 weeks of life resulting in the fibrous ligamentum arteriosum. PDA closure is mediated by vasoactive substances and variations in the pH level, oxygen tension, and prostanoids.

In fetal circulation, the PDA exists to allow blood to bypass the pulmonary circulation. By 6 weeks of gestation, the PDA is large enough to handle the majority of right ventricular output. The PDA is necessary in fetal life to prevent wasted circulation through the high resistance pulmonary vascular bed and an increased workload on the developing right ventricle.

Etiology

Because the closure of the PDA is not completely understood, work continues in order to understand why the vessel may remain patent through infant life. It is known that any condition in which the arterial oxygen content is lowered or the circulating level of prostaglandin is raised will create an environment which may lead to delayed closure. Common etiologies for these scenarios include pulmonary disease at birth such as meconium aspiration, or high-altitude. One of the most recognized conditions associated with persistence of the PDA arises in the premature infant. It is well documented that in low-birth-weight premature infants, a PDA is found in 45% of those with a birth weight $<$1,750 g. A PDA is oftentimes associated with other congenital heart defects and will be discussed as such separately in other chapters.

Epidemiology

The incidence of a PDA is approximately 1 in 2,000–2,500 live births, and increases the greater the degree of prematurity. This incidence represents about 10% of all congenital heart defects. There is a 2:1 female-to-male predilection.

Pathology/Pathophysiology

In the fetal circulation, the purpose of the PDA is to allow blood from the right ventricle to bypass the high resistance pulmonary vascular bed. However, postnatally, the PDA begins to reverse direction as the PVR decreases allowing for increased blood flow into the pulmonary circulation. In addition to the respective resistances between the pulmonary and systemic vascular beds, the diameter and length of the PDA as well as the pressure difference between the aorta and pulmonary artery will determine the direction and amount of shunting. A small PDA will have a small amount of shunting and be restrictive due to its size. However, a large PDA will result in equal pulmonary artery and aortic pressures and the major determinant of shunt flow will be the respective resistances. As the PVR falls in infancy, the left-to-right shunt through the pulmonary vascular bed will increase, as will the pulmonary venous return to the left atrium. The increased volume returning to the left atrium will put a strain on the left ventricle due to the increased volume that it receives. In addition, if the PDA is large, the increased pressure that the right ventricle is pumping against requires an increase in systolic work and eventually may cause right-sided failure. Premature infants are unable to compensate for this increased volume load on the left ventricle as well as full-term infants or older children, and thus often have symptoms of failure at an earlier time period.

As with other left-to-right shunt lesions, an increase in the pulmonary blood flow can delay the typical postnatal pulmonary vascular changes. A small PDA has very little to no effect on the pulmonary arterial circulation. However with a large PDA, the pressure will equalize and the PVR may decrease at a slower rate and not reach its typical nadir. A moderate-sized PDA is more regulated by its size and the shunt flow may only mildly increase the pulmonary artery pressure. The increased volume return to the left atrium is usually well tolerated in these patients. Long-standing left-to-right shunts such as those found with a PDA will eventually cause a fixed elevation in the PVR due to the increased pulmonary blood flow. At that time the PDA will allow right-to-left shunting and right-sided heart failure often ensues. The positive effect of PDA closure would then be lost.

Clinical Manifestations

A small PDA has only a small left-to-right shunt and minimally affects pulmonary artery pressure. Left ventricular failure does not occur in these patients and attention is usually only raised due to the presence of a murmur in childhood.

In an infant with a moderate-sized defect, the shunt volume may be great enough to cause symptoms of congestive heart failure (CHF) such as tachypnea and failure to thrive. The symptoms often increase as the PVR is falling and usually reach their peak at 2–3 months of age. The shunt volume however may not be great enough such that as they grow older, mechanisms such as improved contractility allow for compensation to this increased volume. In this case, the infants actually begin to improve clinically after 3–4 months of age and may go undetected.

A large PDA present in an infant will cause symptoms, most notably growth failure and tachypnea, particularly with oral feeds. The increased pulmonary blood flow also makes these infants more prone to respiratory infections, often coinciding with presentation. Due to the excessive pulmonary blood flow in a large PDA, left ventricular failure may develop at an earlier age and resultant pulmonary edema may be evident early in infancy. If the PDA remains unrepaired, typically by 8–16 months of age the PVR will reach systemic levels and the left-to-right shunting will greatly decrease. If this occurs, symptoms related to the excessive blood flow such as the tachypnea and poor feeding will decrease. Changes become irreversible as early as 15 months of age. Because of pulmonary hypertension, shunting will be right to left and cyanosis will occur, at first with activity but later on a permanent basis.

Rare clinical complications of a PDA include vessel aneurysm and endarteritis. With more efficacious treatment, the occurrence of bacterial endarteritis has become increasingly rare in developed countries. The typical organisms include *Streptococcus viridans* and *Staphylococcus aureus*.

During examination of infants with a moderate- to large-sized PDA, the pulse will often be in a tachycardic range and the pulse pressure is widened. When palpating the peripheral pulses they are typically bounding. The classic murmur associated with a PDA is a continuous,

machinery murmur that is in a crescendo–decrescendo pattern and best heard at the upper left sternal border. The murmur is frequently associated with a thrill. If the PDA is small in size, only a systolic murmur may be present. Because of the increased volume load on the left ventricle, a hyperdynamic precordium is palpated. Due to the increased volume across the mitral valve, a diastolic rumble auscultated at the apex is common. In a patient with an unrepaired PDA, as the PVR begins to rise from the excessive pulmonary blood flow, the murmur will become present only in systole and eventually will disappear.

Diagnosis

The ECG in patients with small- to moderate-sized PDAs may be normal. The increased volume load on the left ventricle can cause evidence of left ventricular hypertrophy manifested by deep Q waves and tall R waves in leads II, III, aVF, and the left precordial leads. As the left atrium enlarges, the P wave will widen in leads II and V1. If pulmonary hypertension begins to develop, signs of right ventricular hypertrophy may become present such as tall R waves in the right precordial leads.

In a patient with a moderate- to large-sized PDA, a chest radiograph will show cardiomegaly with evidence of left atrial enlargement. The pulmonary vascular markings will be increased and pulmonary edema may be present.

Definitive diagnosis of the PDA can be made by two-dimensional echocardiography. Color Doppler through the PDA can demonstrate the direction and the timing of flow during the cardiac cycle. Evidence of left atrial and left ventricular enlargement and hypertrophy can be followed with echocardiography. It is important to look for associated cardiac defects.

Cardiac catheterization is not typically used in the diagnosis of PDA. However, as for other left-to-right shunt lesions, if the PDA is diagnosed later in infancy or there is concern for increased PVR, a cardiac catheterization may be necessary to directly measure pulmonary pressures and resistance to determine feasibility of closure. Oxygen saturations in the pulmonary artery compared to the right ventricle can also be used to estimate the size of the shunt. Angiography during the cardiac catheterization can also further define the anatomy of the PDA and its associated connections. This information is not required for the diagnosis but does aid in possible treatment measures that may be undertaken by catheterization.

Differential Diagnosis

Because of auscultation early in infancy of a continuous murmur, other possible diagnoses must be considered. A venous hum has a continuous murmur, but can be varied with head position and pressure on the neck. Arteriovenous communications and an anomalous origin of the left coronary artery from the pulmonary artery both have continuous murmurs. In the case of the arteriovenous communication, the murmur is usually more superficial. Absent pulmonary valve syndrome may give a "sawing wood" murmur that sounds continuous, but can usually be differentiated by the clinical condition and the enlarged bronchi on the chest radiograph. Perhaps most difficult to distinguish from PDA is the aortopulmonary window. The murmur is very difficult to differentiate from that of the PDA; cardiac imaging is necessary to aid in diagnosis.

Treatment

The treatment of a moderate- to large-sized PDA is similar to other cardiac lesions allowing excessive pulmonary blood flow. The risk of permanent pulmonary vascular disease, left-sided heart failure, growth failure, and persistent pulmonary infections are all reason for early treatment. Because the risk of surgical or transcatheter closure is low, there is not usually a need for sustained medical management prior to definitive treatment. This differs from the typical management of other left-to-right shunt lesions such as VSD or AVSD that are typically managed medically until the patient reaches an acceptable age for surgical treatment. Unlike premature infants, Indomethacin is ineffective for PDA closure in term infants and older children and should not be attempted.

Treatment by transcatheter device closure with occluding coils or duct occluders is now the treatment of choice for PDAs that are larger than 3 mm in diameter and patients that are older than a few months of age. The procedure has essentially no mortality and a low morbidity while being 97% successful. Associated risks of the transcatheter closure include device embolization or device-related hemolysis. In the rare case that this does occur, surgical closure of the PDA can be made more complicated. For infants less than 3 months of age or patients with large PDAs greater than 12 mm in diameter, surgery remains the treatment of choice. The approach is usually a lateral thoracotomy that allows ligation of the PDA. Like transcatheter treatment, surgical ligation carries minimal risk of morbidity and mortality. The

most common complications of surgical closure are recurrent laryngeal nerve palsy and chylothorax. Hospital course may be as short as 2 days with surgical treatment. A technique that remains limited but has shown encouraging results is that of thoracoscopic, minimally invasive surgical closure. Obvious benefits include avoidance of a thoracotomy scar and faster rate of recovery. However, critics argue that unexpected surgical bleeding could cause a very difficult situation to manage and gain control over.

Prognosis

The prognosis for the isolated PDA is quite good if recognized during infancy prior to permanent changes of the pulmonary vasculature. Like other left-to-right shunt lesions, if the PDA is moderate to large in size and left unrepaired, pulmonary vascular disease occurs and these changes can become permanent over time. The natural history of these patients is quite poor as closure of the PDA is contraindicated and right ventricular failure eventually occurs. Typically the risk of treatment either by surgery or transcatheter device is low and the success rate is quite high. Life expectancy is near normal in patients with an isolated PDA that is closed prior to the development of severe pulmonary vascular changes.

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249 Cyanotic Heart Disease

Stephen P. Seslar

Overview

Definition

On the surface, defining cyanotic congenital heart disease seems simple. The word cyanosis originated from the Greek *kyanōsis* from *kyanos*, meaning dark blue color. Sir William Osler concisely conveys its medical definition as "diminished oxygenation of the blood corpuscles." The word "congenital" is defined as "existing at or dating from birth." So at its essence, cyanotic congenital heart disease is a birth defect affecting cardiovascular structure, resulting in decreased oxygenation of red blood cells. Thus, all forms of cyanotic congenital heart disease result in the delivery of deoxygenated red blood cells into the systemic circulation. A mnemonic known as the "five T's" can be helpful in remembering the common forms of cyanotic congenital heart disease: tetralogy of Fallot, transposition of the great vessels, truncus arteriosus, total anomalous pulmonary venous connection, and tricuspid atresia. This is an imperfect pneumonic, and conditions such as pulmonary atresia with intact ventricular septum are included in the broader heading of congenital hypoplastic right-heart lesions represented by tricuspid atresia. This chapter will review each of these conditions in detail, except tricuspid atresia which will be covered in the chapter entitled Chap. 251, "The Single Ventricle".

Classification

In general, cyanotic congenital heart disease can be classified based on morphologic and embryologic grounds or based on physiology. Practically speaking, a physiologic approach is more useful to the clinician because it more readily translates into the clinical picture. One of the more common physiologic classification schemes of cyanotic congenital heart disease is to divide lesions by the presence of "too much" or "too little" pulmonary blood flow. In reality, classifying cyanotic congenital heart disease is challenging due to the marked heterogeneity of the underlying disorders. For example, on the milder end of the spectrum of tetralogy of Fallot, affected individuals will not manifest cyanosis (i.e., "pink tetralogy"). The limitations notwithstanding these classification schemes provide an important framework for understanding cyanotic congenital heart disease.

Etiology

Our understanding of the etiology of cyanotic congenital heart disease is evolving but remains incomplete. The development of a heart defect likely represents a complex interplay between genetic, environmental, and flow dynamic factors. From a genetic perspective, about 20% of congenital heart defects can be attributed to chromosomal abnormalities (e.g., trisomy 21) and Mendelian syndromes (e.g., the 22q11 deletion/DiGeorge syndrome). The remaining cases, once considered "sporadic," are now thought to be, at least in part, due to non-Mendelian/nonchromosomal genetic variants (e.g., NKX2–5). These new discoveries suggest that the genetic contribution to congenital heart disease may have been significantly underestimated in the past. Epidemiology studies have also identified several environmental factors that play a role in the genesis of congenital heart disease, for example, the association between maternal gestational diabetes and conotruncal heart defects. Finally, while genetic and environmental factors reside metaphorically "upstream" in the development of congenital heart disease, the final morphologic outcome in congenital heart disease is often felt to be the result of altered flow dynamics in the developing embryo.

Epidemiology

The incidence of cyanotic congenital heart disease as a group is notably consistent across time and geography. In a recent publication that reviewed and analyzed 44 published studies in which there were at least 100 subjects with cardiac lesions, the incidence of cyanotic congenital heart disease was about 1 per 1,000 live births. The incidence of specific lesions will be discussed under the appropriate subsections presented below.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_249,

Pathology/Pathophysiology

The specific structural defects that comprise the various forms of cyanotic congenital heart disease are distinct and diverse. Each will be reviewed in detail under the appropriate subsections below. Cyanosis can be the result of the heart's inability to deliver blood flow to the pulmonary circuit due to obstruction to flow. Examples of this "too little" pulmonary blood flow physiology include tetralogy of Fallot and various forms of right-sided heart disease (e.g., pulmonary atresia). Alternatively, some forms of cyanotic congenital heart disease have normal or "too much" blood flow, for example, transposition of the great vessels. In these instances, though the total volume of blood flow through the pulmonary circuit may be normal or increased, the amount of *effective* pulmonary blood flow is severely diminished. In all cases, by definition, the structural defects associated with cyanotic congenital heart disease result in the delivery of deoxygenated blood from the heart to the systemic circulation.

Symptoms and Signs

Signs and symptoms specific to each defect will be discussed under the appropriate subheading below. Signs and symptoms of cyanotic congenital heart disease are variable as the underlying heart defects. Even the defining sign of cyanosis is only variably present and often may be difficult to recognize. Depending on the specific heart defect and the severity within a particular lesion and the status of the ductus arteriosus, infants may demonstrate signs of cyanosis, respiratory distress, murmur, and cardiogenic shock. In other instances, infants may have no signs or symptoms apart from mild cyanosis. As a group, patients with cyanotic congenital heart disease are more often diagnosed in the neonatal period prior to hospital discharge than are other forms of congenital heart disease. In addition to signs and symptoms specific to the cardiovascular system, congenital heart disease may also be identified as part of a recognizable pattern of malformation, for example, DiGeorge syndrome which has a characteristic facial phenotype.

Diagnosis

As with any condition, the diagnosis of cyanotic congenital heart disease begins with a careful history and physical exam. While historical elements, signs, and symptoms raise the index of suspicion for cyanotic congenital heart disease, additional testing is performed to confirm and specify the exact nature of the heart defect. The tests used in the diagnosis of cyanotic congenital heart disease are common to those used for all forms of congenital heart disease, though the test performance characteristics of specific modalities may vary based on the type of cardiac defect. Some of the common diagnostic testing modalities are reviewed here.

History and Physical Exam

Simple historical elements such as the age of the patient and chronicity of the presentation can give important clues as to the nature of the heart defect. For example, patients with D-transposition of the great vessels or obstructed total anomalous pulmonary venous connections are likely to present early in the newborn period with signs of cyanosis and clinical compromise. Conversely, tetralogy of Fallot may have a more indolent presentation depending on the severity of the lesion and the timing and completeness of ductus arteriosus closure. The maternal/gestational history should be mined for risk factors such as advanced maternal age, diabetes mellitus, fetal alcohol exposure, or other teratogenic drugs, prescribed or illicit. Family history of congenital heart disease or relevant inherited disorders (DiGeorge syndrome) in a first degree relative should be noted.

Essential physical exam findings are basic but critical in narrowing the differential diagnosis of the cyanotic infant. Cyanosis is detectable at oxygen saturations below 85% (unless anemia is present). Cyanosis may be central or peripheral, and it is important to distinguish between the two because peripheral cyanosis is clinically benign and not associated with congenital heart disease. Peripheral cyanosis is typically noted in the extremities and perioral regions. Importantly, peripheral cyanosis, unlike central cyanosis does not involve the oral mucosa. A rapid clinical assessment should be performed in which the patient's state of arousal, color, respiratory pattern, and perfusion are evaluated. This rapid assessment can set the stage for the urgency of the subsequent evaluation and treatment. The general appearance of the patient may provide clues to a clinical syndrome. For example, the craniofacial features of DiGeorge syndrome may suggest a conotruncal defect such as tetralogy of Fallot. The presence or absence of a murmur should be noted, though it may be present in normal anatomy (e.g., innocent murmurs, ductus arteriosus closure) and absent in complex congenital heart disease (e.g., D-transposition of the great vessels, pulmonary atresia with intact ventricular septum).

Pulse Oximetry

In a study of 38,429 newborn infants, a preductal and post-ductal oxygen saturation <95% or a pre- and post-ductal difference >3% had a 62% sensitivity and a 99.8% specificity for the detection of ductal dependent circulation in this population. While room-air pulse oximetry can be very useful ruling out the presence of cyanotic congenital heart disease, it is not specific to cardiac cyanosis when abnormal.

Hyperoxia Test

Central cyanosis can be the result of lung or heart disease or a combination of both. The response of pulmonary cyanosis to the administration of exogenous oxygen can be used to distinguish it from cyanosis due to a cardiac lesion. This "hyperoxia test" should be performed as follows. The cyanotic patient is provided 100% FiO_2 for 10 min. An arterial blood-gas analysis should then be performed. If the PaO_2 is >200 torr, a cardiac cause for the cyanosis is highly unlikely. Conversely, if the PaO_2 fails to rise above 70 torr (in the setting of a normal pCO_2), congenital heart disease is likely. Intermediate PaO_2 response to hyperoxia challenge is less likely cardiac in nature, but a cardiac etiology cannot be excluded. It is important to base the result on an arterial PaO_2 rather than oxygen saturation due to the possibility of a falsely negative test result when the latter measure is used.

Chest Radiography

In symptomatic infants, chest radiography can facilitate the diagnosis of congenital heart disease and help distinguish primary heart disease from lung disease. Some radiographic signs such as the "boot-shaped heart" for tetralogy of Fallot or the "snow-man" sign for total anomalous pulmonary venous connection can even aid in the diagnosis of a specific cardiac lesion. The chest radiogram can also aid in the physiologic assessment of pulmonary blood flow and thus aid in the clinical management. The utility of chest radiography in asymptomatic infants with murmurs is less clear.

Electrocardiography (ECG)

The electrocardiogram is an inexpensive, noninvasive test. Unfortunately, it is also insensitive and nonspecific in the diagnosis of cyanotic congenital heart disease. This is particularly true in newborns, where there is a natural predominance of right-sided forces. There are some specific instances where ECG findings might facilitate the diagnosis of cyanotic congenital heart disease. Left-heart predominance in a cyanotic infant should raise concern of pulmonary atresia or some other form of hypoplastic right-heart variant. The presence of right ventricular hypertrophy in the older infant or child might facilitate the diagnosis of a right-sided obstructive lesion such as tetralogy of Fallot or pulmonary stenosis. Importantly, a normal ECG does not rule out the presence of cyanotic congenital heart disease and should not provide false reassurance.

Plasma B-Type Natriuretic Peptide (BNP)

A recent prospective study found that in pediatric patients with nonspecific signs and symptoms of a heart disease, elevated plasma BNP had a positive predictive value of 91% for the detection of a significant cardiovascular abnormality in newborn infants (77% in older children). The authors concluded that BNP levels can be helpful in the timely recognition of significant cardiovascular disease in this population.

Echocardiography

Since the early part of the 1980s, echocardiography has been the diagnostic method of choice for essentially all forms of congenital heart disease. More recent technological improvements have strengthened the utility of this testing modality further. It is noninvasive, painless, and requires no radiation exposure. In most instances, the availability of echocardiography has completely supplanted the need for cardiac catheterization in the diagnosis of congenital heart disease. It should be remembered, however, like any testing modality, echocardiography is subject to the rules of Bayesian logic. That is, the pretest probability of disease, in part, determines the predictive value of the test. If time and resources permit, evaluation by pediatric cardiologist and review of the ancillary tests outlined above can improve the test's performance. Simply put, if you have an idea what you are looking for before you start, you are more apt to find it (or more effectively exclude its presence).

Cardiac Catheterization

As stated in the section above, echocardiography has largely supplanted cardiac catheterization in the diagnosis

of congenital heart disease. Occasionally, echocardiography may not be sufficient, and cardiac catheterization is used to better define the anatomy. Practically speaking, this usually involves defining a detailed feature of a more general diagnosis made by echocardiography. For example, angiography can be used to determine the number and distribution of aorto-pulmonary collaterals in patients with tetralogy of Fallot/pulmonary atresia or assess the coronary circulation in patients with pulmonary atresia with intact ventricular septum.

Differential Diagnosis

The differential diagnosis of cyanotic congenital heart disease includes peripheral cyanosis, cyanosis secondary to pulmonary disease, or problems with oxygen transport (e.g., methemoglobinemia). The distinction between peripheral and central cyanosis is usually apparent by physical exam. Rarely, pulse oximetry or arterial blood-gas analysis is required. Pulmonary cyanosis can be distinguished from cardiac by the hyperoxia test (see above), a normal cardiac exam and normal appearing heart on chest radiography. Echocardiography, as noted above, remains the gold standard for defining or excluding suspected cyanotic congenital heart disease.

Treatment

Once identified, the treatment of cyanotic congenital heart disease involves initial resuscitation, stabilization, consultation with a pediatric cardiologist, and (if necessary) transport to a center specializing in the care of these patients. In newborns, after discussion with a pediatric cardiologist, prostaglandin E1 infusion at dose of 0.05–1 μg/kg/min may be initiated. Following this, infants will need to be monitored for apnea, a common side effect of this medication. Laboratory analysis of the acid-base status and blood-gas analysis should be performed. Continuous pulse oximetry can be used for detecting acute changes in oxygenation and to monitor the effects of prostaglandin therapy on ductal patency. Once a specific diagnosis has been established, a consultation by a congenital heart disease surgeon is performed (in conjunction with a pediatric cardiologist) for discussion of surgical options and timing. Ultimately, most forms of cyanotic congenital heart disease will require surgical intervention in infancy for an optimal outcome. The timing, nature, and risks of the surgical procedures will, of course, vary by the specific lesion. These will be reviewed in detail under the specific subheadings below.

Prognosis

The natural (untreated) history of all forms of cyanotic congenital heart disease is grim. The modified natural history of cyanotic congenital heart disease is one the greatest success stories of modern medicine. Indeed for the first time earlier this century, estimates of the number of adults living with congenital heart disease exceeded those of infants and children. Unfortunately, although the mortality rates associated with various forms of congenital heart disease have dramatically improved, adults with congenital heart disease remain at risk for a variety of lesion specific and generic health issues related to their congenital heart disease. As one recent review aptly expressed this sentiment in its title: Congenital heart disease never goes away, even when it has been "treated."

Prevention

The laudable goal of preventing of congenital heart disease remains largely unrealized. The multifactorial etiology and broad clinical spectrum of these conditions makes the discovery of a "magic bullet" for prevention unlikely. There is increasing evidence that folate supplementation may play a role in preventing certain forms of congenital heart disease, though definitive data is still lacking. Good prenatal care and proper management of gestational diabetes are clearly important. Efforts to prevent the development or progression of congenital heart disease through fetal intervention have been reported, but these procedures remain experimental and have only been applied to selected lesions. Presently, perhaps the best we can hope for is that earlier detection and diagnosis through fetal echocardiography will reduce or prevent the negative consequences caused by a missed postnatal diagnosis.

Tetralogy of Fallot

Definition/Classification

The sentinel four features of this form of cyanotic congenital heart disease as originally written by Etienne-Louis Arthur Fallot in 1888 (and subsequently translated from French) are: (1) pulmonary artery stenosis, (2) ventricular septal communication, (3) rightward deviation of the

aorta's origin, and (4) right ventricular hypertrophy. It is important to recognize that although these features are present in the majority of patients with tetralogy of Fallot, there is marked variability in the range of severity, and that these differences have important implications regarding treatment and prognosis. Tetralogy of Fallot is one of the conotruncal cardiac malformations. This implies that the primary malformation occurs in the area of the ventricular outflow tracts and great vessels. Tetralogy of Fallot is the prototypical example of a cyanotic congenital heart disease with "too little" pulmonary blood flow.

Etiology

The precise etiology of Tetralogy of Fallot is unknown. Like other conotruncal defects, it is associated with DiGeorge syndrome, but the majority of cases appear to be non-syndromic. Abnormalities in neural crest migration have been implicated, but the responsible gene(s) involved and the mechanism by which these gene defects result in the development of tetralogy of Fallot have not been elucidated. Though the spectrum of cardiovascular malformations involves the four elements outlined above, the pathogenesis of these anomalies is thought to be the result of a single error in development: hypoplasia or underdevelopment of the sub-pulmonary infundibulum.

Epidemiology

The incidence of tetralogy of Fallot is approximately 0.421 per 1,000 live births and appears to be consistent over time and geography, though an excess incidence has been reported in Malta (0.64 per 1,000 live births). It is the most common of the cyanotic congenital heart defects and most often occurs as an isolated entity. The presence of extra-cardiac abnormalities in patients with tetralogy of Fallot increases the incidence of an associated syndrome and worsens the prognosis. In one population-based study, karyotype abnormalities were present in 13% and extra-cardiac malformations in 17% of the infants. The most common anomalies seen were Down syndrome, cleft palate, cleft lip and palate, and combined skeletal, gastrointestinal, and renal lesions (VACTERL association). In another study, 2% had associated DiGeorge syndrome.

Pathology/Pathophysiology

In the cyanotic forms of tetralogy of Fallot, there is too little pulmonary blood flow secondary to right ventricular outflow tract obstruction. As noted above, the fundamental cause of this obstruction is underdevelopment of the right ventricular outflow tract. There is a large ventricular septal defect that allows equalization of pressure between the left and right ventricles and, over time, right ventricular hypertrophy worsens. As the degree of right ventricular outflow obstruction increases, the ventricular septal defect allows shunting of deoxygenated blood from the right ventricle to the left ventricle where it mixes with oxygenated blood in varying proportions before being pumped into the systemic circulation (*Fig. 249.1*). This ratio is determined by relative resistance between the pulmonary and systemic vascular beds. The greater the right ventricular outflow obstruction, the higher the resistance to pulmonary blood flow and the more deoxygenated blood crosses into the systemic circulation. Without intervention, the degree of right ventricular outflow obstruction increases with time, resulting in increasing cyanosis.

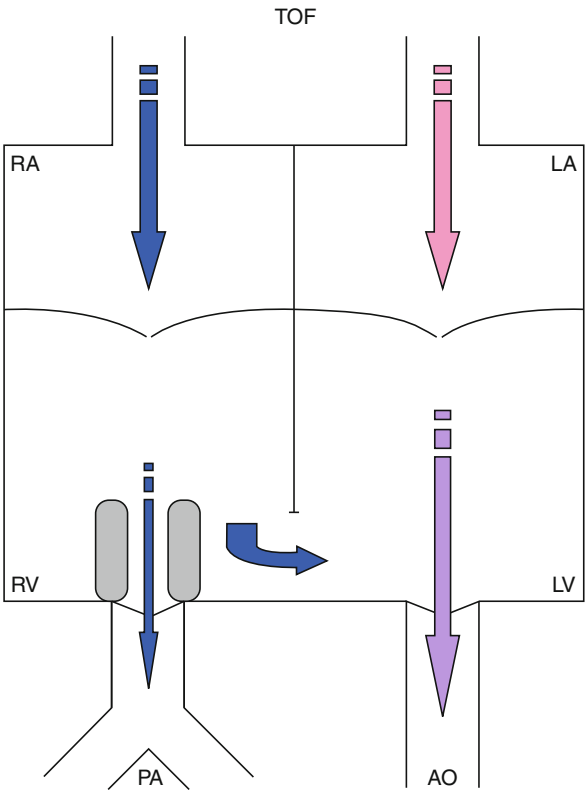

Figure 249.1
In tetralogy of Fallot, pulmonary blood flow is restricted, resulting in variable right to left shunting across the ventricular septal defect (*blue curved arrow*). *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle

Clinical Manifestations

The clinical manifestations of tetralogy of Fallot are determined by the degree of right ventricular outflow obstruction. Severe obstruction results in cyanosis typically recognized in the neonatal period. Tetralogy with more modest obstruction may be diagnosed secondary to the associated murmur with cyanosis being less evident. Patients with "pink" tetralogy of Fallot may develop symptoms of pulmonary overcirculation (e.g., tachypnea, failure to thrive).

One unique clinical manifestation of tetralogy of Fallot (or lesions of similar physiology) is the so-called hypercyanotic or "tet-spell." While there remains debate about the precise etiology of this clinical phenomenon, the net effect is a sudden and self-propagating imbalance between pulmonary and systemic vascular resistance that favors flow of deoxygenated blood across the ventricular septal defect into the systemic circulation, resulting in profound cyanosis and less commonly loss of consciousness, and even brain injury or death. Effective treatment measures are aimed at restoring balance between the systemic and pulmonary circulations by increasing systemic vascular resistance (knee to chest positioning, alpha receptor agonists) and lowering pulmonary vascular resistance (beta-blockers, morphine).

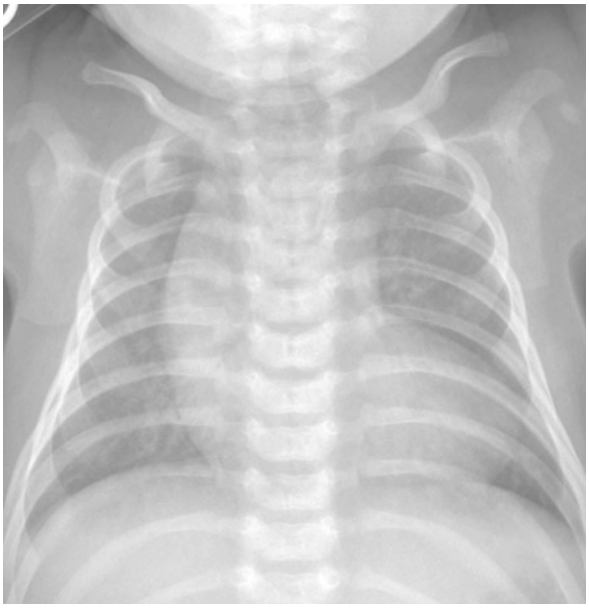

Figure 249.2
The diminutive size of the main pulmonary artery and the right ventricular hypertrophy contribute to create the "boot-shaped" heart appearance on chest X-ray in tetralogy of Fallot

Diagnosis

Physical exam demonstrates a murmur characteristic of pulmonary outflow obstruction (ejection type crescendo-decrescendo, best heard at the left upper sternal border). In most cases, the VSD is large and unrestrictive and does not contribute significantly to the murmur as there is equalization of pressure between the ventricles. The second heart sound is often single as the pulmonic valve component of the second heart sound is usually soft or inaudible. The presence of cyanosis is quite variable and, as discussed above, dependent on the degree of right ventricular outflow tract obstruction. Electrocardiographic findings may include right axis deviation and right ventricular hypertrophy. Given the natural right dominance of the newborn electrocardiograms, these findings may be less apparent in this setting. Chest X-ray may be normal but may also reveal the classic "boot-shaped" heart (*Fig. 249.2*). This appearance is created by a diminutive main pulmonary artery shadow and an upturning of the left ventricular apex, which is seen in the setting of right ventricular hypertrophy. Definitive diagnosis can be made by echocardiography which will identify the cardinal features of this disorder. Diagnosis can also be made by prenatal ultrasound (*Fig. 249.3*). Cardiac catheterization is reserved for select cases to better define specific details such as the integrity and adequacy of the pulmonary arteries and define the presence of aorta to pulmonary collaterals, particularly in the setting of complete or near atresia of the pulmonary valve. Catheterization can also be used to define the coronary anatomy, which can have important implications for surgical intervention.

Differential Diagnosis

The differential diagnosis of tetralogy of Fallot includes other forms of cyanotic congenital heart disease associated with a murmur, including isolated pulmonary stenosis and double outlet right ventricle with tetralogy-like physiology. For more detailed discussion of noncardiac differential diagnosis, see "Overview".

Treatment

The initial management of tetralogy of Fallot depends on the severity of the lesion and in particular the adequacy of pulmonary blood flow. In some cases, adequate pulmonary blood flow in the newborn period will require prostaglandin

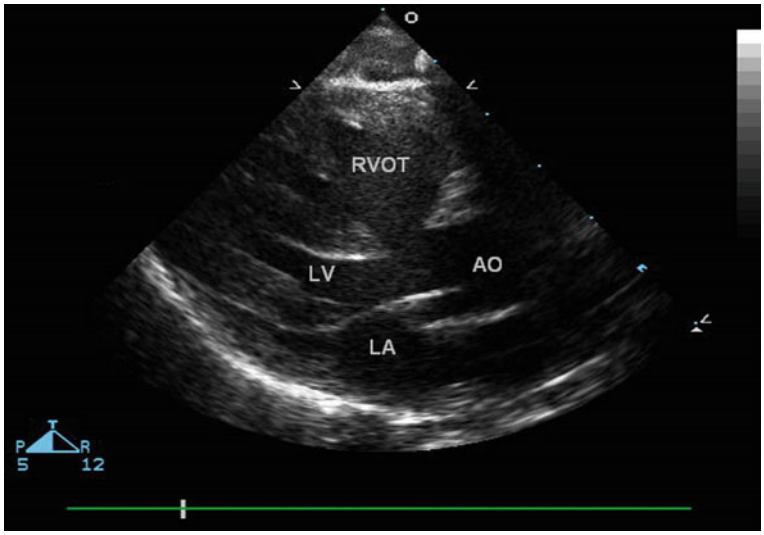

Figure 249.3
This still frame two-dimensional echocardiogram image demonstrates several of the salient features of tetralogy of Fallot, including the ventricular septal defect with the aorta overriding it, and the hypertrophied right ventricle. *LA* left atrium, *LV* left ventricle, *AO* aorta, *RVOT* right ventricular outflow tract

infusion to maintain patency of the ductus arteriosus. Surgical correction is necessary for optimal outcome. The timing of surgical repair and the use of a staged approach vary by institution, the severity of the lesion, and the size and age of the patient. In some centers, a complete repair is performed in the neonatal period. More commonly, complete repair is performed between 3 and 6 months of age. In a staged repair, the initial operation is performed to establish a reliable source of pulmonary blood flow, usually in the form of a shunt from the aorta to the pulmonary artery. Complete repair involves relief of right ventricular outflow obstruction and closure of the ventricular septal defect. When the pulmonary valve itself contributes significantly to the right ventricular outflow tract obstruction, a "transannular" patch-type repair is required which alleviates the obstruction but renders the valve incompetent. In some cases, an artificial connection between the right ventricle and pulmonary arteries is created using a conduit. If at all possible, the right ventricular outflow tract and pulmonary valves are preserved and a "valve-sparing" repair is performed.

Prognosis

The prognosis of unrepaired tetralogy of Fallot is poor. The modified prognosis of repaired tetralogy of Fallot varies with the severity of the underlying condition, the type of repair, patient age at the time of repair, and the presence of extra-cardiac anomalies. The overall 30 year actuarial survival rates of patients after repair of tetralogy of Fallot are impressive at 90%. Late death, when it occurs, is most often sudden. Less commonly, it may be due to congestive heart failure. Recent efforts have been directed at improving our understanding of who is at risk for late sudden death and how that risk can be modified. Perhaps the most important result of these efforts is understanding that the pulmonary valve insufficiency, which results from the transannular patch type of repair, is associated with late adverse clinical outcomes. In patients that demonstrate the adverse effects of long-standing pulmonary insufficiency, it is hoped that timely pulmonary valve replacement will reduce the associated risks, though this remains unproven.

Prevention

It is presently not possible to specifically prevent tetralogy of Fallot. Please see "Overview" of cyanotic congenital heart disease for a more general discussion of preventing congenital heart disease.

Transposition of the Great Vessels

Definition/Classification

Transposition of the great vessels is defined as ventriculoarterial discordance. This, simply stated, means that

the pulmonary trunk arises off of the morphologic left ventricle and the aorta arises off of the morphologic right ventricle. This malposition of the great vessels occurs in the setting of normal arrangements of the atria and ventricles. Often this form of transposition will be referred to as D-transposition (or D-TGA) in which the "D" is used to describe the abnormal relative positions between the aorta and main pulmonary artery. Transposition of the great arteries can be further classified as simple or complex based on the absence or presence of a coexisting congenital heart defects such as a ventricular septal defect, left ventricular outflow tract obstruction, aortic arch anomalies, and anomalous venous systemic connection. Discussion here will be focused on simple uncorrected transposition of the great vessels. Transposition, like tetralogy of Fallot, is classified as a conotruncal malformation. In contrast to tetralogy of Fallot, transposition represents a cyanotic congenital heart lesion with normal or "too much" pulmonary blood flow (see "Overview").

Etiology

The etiology of transposition of the great arteries is unknown. As stated above, transposition is a conotruncal malformation, but unlike truncus arteriosus and tetralogy of Fallot, its association with DiGeorge syndrome and 22q11 deletion is believed to be uncommon. More recently, case reports of micro-deletions in chromosome 22q11.2 in patients with transposition of the great vessels have been published. Though syndromic involvement is rare, a familial risk in transposition has been identified, again suggesting the involvement of non-Mendelian/nonchromosomal genetic variants in the etiology of this disorder. Fetal environmental factors such as maternal hormone imbalance have been suggested but are not widely accepted. The embryologic aberrancy that results in the transposition malformation is also uncertain. Like tetralogy of Fallot, defective conotruncal development is implicated. In transposition of the great vessels, some investigators believe there is failure of the normal balanced regression and enlargement of the tissue below the aortic and pulmonary valves, respectively. This results in abnormal anterior and rightward displacement of the aortic valve, placing it over the right ventricle and posterior leftward displacement of the pulmonary valve positioning it over the left ventricle. Research in the embryology of transposition is ongoing and is the topic of a number of reviews.

Epidemiology

The incidence of transposition of the great vessels is approximately 0.3 per 1,000 live births. It is present in approximately 4% (2–9%) of infants born with congenital heart disease. It is the most common cyanotic lesion diagnosed in the newborn period. There is a male predominance of unclear etiology.

Pathology/Pathophysiology

In transposition of the great vessels, the morphologic right atrium receives the oxygen depleted systemic venous return. This blue blood is passed through the tricuspid valve into the morphologic right ventricle from which it is pumped into the systemic circulation through the aorta. Oxygenated pulmonary venous return is conveyed from the morphologic left atrium through the mitral valve into the morphologic left ventricle where is it pumped into the pulmonary circulation via the pulmonary artery. In this way, the pulmonary and systemic circulations function in parallel rather than in series. In simple transposition of the great vessels, effective blood flow (oxygenated blood entering the systemic circulation, deoxygenated blood entering the pulmonary circulation) is that small portion of the total circulation that crosses the atrial septum, bronchopulmonary collaterals and, if present, the patent ductus arteriosus (*Fig. 249.4*). It is this mixing that allows survival in the postnatal state. So while total pulmonary blood flow in this lesion is not limited and over time is in excess, *effective* pulmonary blood flow (where deoxygenated blood in presented to the pulmonary circulation) is severely limited with obligatory cyanosis resulting.

Clinical Manifestations

Patients with simple transposition of the great vessels usually present in the first hours to days of life with cyanosis. Unless the cyanosis is profound, the infants may exhibit tachypnea but are typically not in distress. Infants are usually normal in size, and most infants appear otherwise normal. If the atrial septum is restrictive and/or the ductus arteriosus is small or closed, infants will be profoundly cyanotic and manifest the effects of severe oxygen deprivation to the tissues (hypoxemia, acidosis, lethargy, hypotonia). In these situations, urgent restoration of ductal patency and/or enlargement or creation of a patent foramen ovale may be lifesaving (see "Treatment").

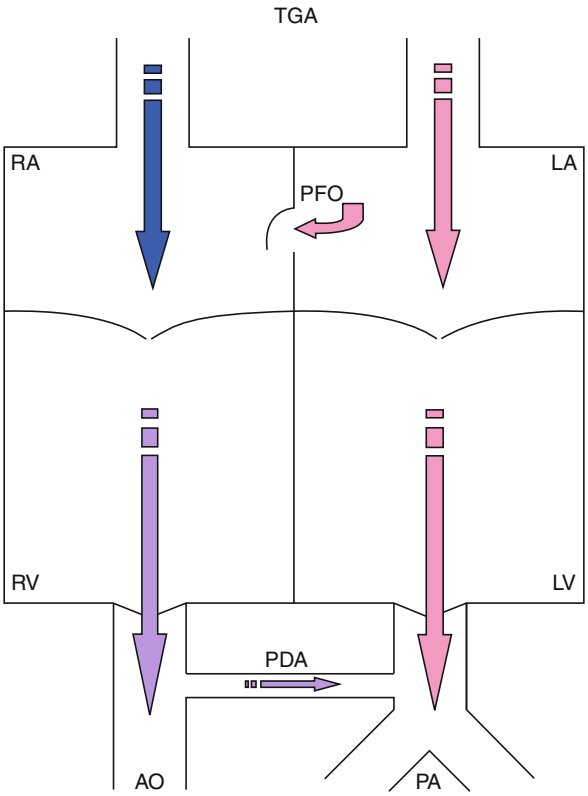

Figure 249.4
In transposition of the great vessels, effective pulmonary blood flow is severely limited (represented by PDA flow arrow). Oxygenated blood is delivered to the pulmonary circulation and deoxygenated blood is delivered to the systemic circulation. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *PFO* patent foramen ovale, *PDA* patent ductus arteriosus

Diagnosis

Physical exam generally reveals evidence of central cyanosis. A murmur is not typical in simple transposition. Tachypnea without distress is common. Infants with an adequate atrial communication and/or patent ductus arteriosus may develop signs of congestive heart failure as pulmonary vascular resistance falls over the first few weeks of life. As stated above, the infant is usually non-dysmorphic. Electrocardiographic findings are nonspecific, especially in the newborn. Chest radiography is often normal in the first few days of life but may reveal the so-called egg on a string appearance due to the altered relationship of the great vessels and the resulting change in the mediastinal shadow (*Fig. 249.5*). Over time, as pulmonary vascular resistance and total pulmonary

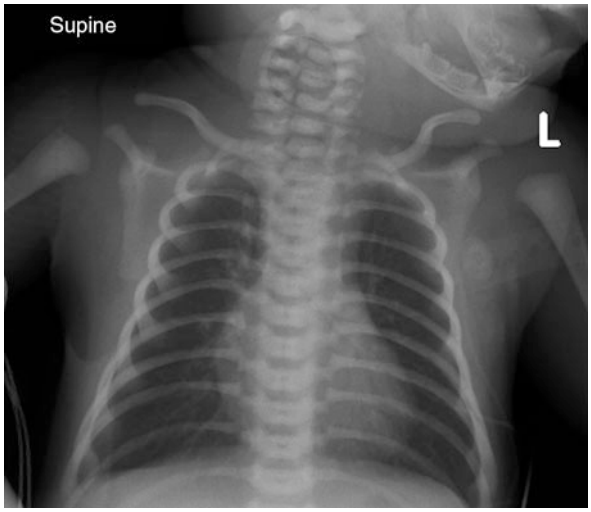

Figure 249.5
The superimposition of the aorta and pulmonary arteries creates a relatively narrow mediastinal shadow and results in an "egg on a string" appearance on chest X-ray in transposition of the great vessels

blood flow, the chest X-ray will show prominent pulmonary vascular markings and cardiomegaly. Echocardiography is the diagnostic modality of choice and can quickly and accurately make the diagnosis demonstrating the pulmonary artery arising from the left ventricle and the aorta from the right ventricle (*Fig. 249.6*). It also determines the status of the ductus arteriosus and foramen ovale. Echocardiography can also be used to guide percutaneous balloon atrial septostomy (BAS) (see "Treatment"). Echocardiography is also useful in delineating the coronary anatomy which can have important implications in the repair. Due to improved obstetric screening practices, transposition of the great vessels is increasingly diagnosed by prenatal echocardiography. Diagnostic cardiac catheterization is not typically performed in simple transposition unless the coronary anatomy is inadequately defined by echocardiography. In some centers, the BAS procedure is preferentially performed in the catheterization laboratory (see "Treatment").

Differential Diagnosis

The differential diagnosis of simple transposition includes other forms of cyanotic congenital heart disease that lack a murmur such as pulmonary atresia with intact ventricular septum or total anomalous pulmonary venous

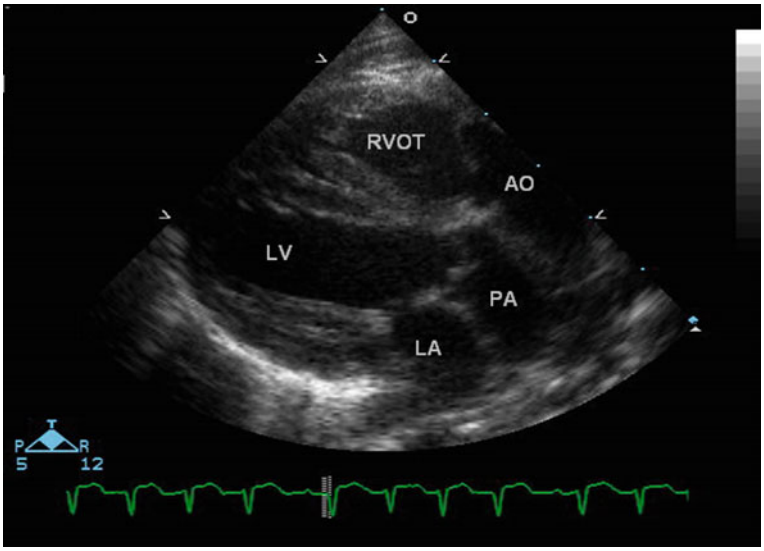

Figure 249.6
This still frame two-dimensional echocardiogram image demonstrates side-by-side great vessels – one of the echocardiographic hallmarks of transposition of the great vessels. *LA* left atrium, *LV* left ventricle, *AO* aorta, *RVOT* right ventricular outflow tract, *PA* pulmonary artery

connections. See "Overview" for discussion of noncardiac differential diagnoses.

Treatment

Initial treatment involves stabilization, correction of acidosis if present, and measures to improve effective pulmonary blood flow. The latter often involves enlarging the atrial level communication by performing a procedure known as the balloon atrial septostomy (BAS). This procedure, pioneered in the 1960s, involves placing a balloon tipped catheter through an existing but inadequate patent foramen ovale. Access to the systemic venous circulation is generally obtained through the umbilical or femoral vein. Once placed into the left atrium, the balloon is inflated with saline and pulled briskly through the patent foramen ovale with the intent to tear the relatively delicate portion of the atrial septum. Though still widely practiced, the safety of this technique has be called into question after a study demonstrated an increased incidence of silent cerebral emboli in infants having undergone BAS. Prostaglandin infusion is commonly used to restore or enhance ductal patency, though it can unfavorably alter tissue properties, rendering the tissue soft and friable and making its use unpopular with some congenital heart surgeons.

Definitive treatment of transposition of the great vessels requires a surgical intervention. Historically, surgical efforts for this condition involved an "*atrial* switch" procedure in which the atrial septum was removed and systemic venous return was baffled to the left ventricle. Pulmonary venous return was, in turn, routed to the right ventricle. Though this approach (often referred to using the eponyms "Senning" or "Mustard" procedure) restores pulmonary and systemic circulation in series, it leaves the right ventricle pumping to the systemic circulation and required extensive atrial reconstruction. Concerns over the adverse late sequela of the atrial switch approach led to a renewed interest in a more physiologic correction strategy: the arterial switch operation. This correction involves transecting the great vessels and reconnecting them to the appropriate ventricular chamber. It avoids the extensive atrial suture lines and baffle construction inherent in the atrial switch procedure and leaves the left ventricle pumping to the systemic circulation. Improved bypass and surgical technique made this strategy a reality in 1975 as first reported by Jatene and colleagues. Since this initial report, there have been a number of important modifications to the arterial switch procedure, and it has became the standard of care in the surgical treatment of transposition of the great vessels.

Prognosis

The prognosis of unrepaired transposition of the great arteries is dismal with >80% of individuals succumbing before their first birthday. The surgically modified natural history of transposition depends largely on the operative approach. Following an atrial switch type repair, the early and midterm prognosis is quite favorable, but there are a number of important late sequela, including arrhythmias, heart failure, and sudden death. Due to its relatively recent implementation as the treatment of choice for simple transposition of the great vessels, data on the long-term outcome of patients undergoing the arterial switch operation is limited. Short- and midterm results appear to be quite promising with relatively infrequent need for reoperation, minimal arrhythmia burden, and good quality of life. Despite these encouraging findings, long-term issues with risk of coronary artery disease and dysfunction of the neoaortic valve after the arterial switch operation will require ongoing assessment.

Prevention

Prevention of transposition of the great vessels is not currently possible. Perhaps the best that can be hoped for is that prenatal detection of transposition of the great arteries might prevent some of the early adverse outcomes associated with missed or late diagnosis, but detection rates remain low and impact on postnatal care remains unclear.

Truncus Arteriosus

Definition/Classification

The congenital heart lesion truncus arteriosus is another form of conotruncal abnormality defined by the presence of a single outlet vessel leaving the heart that supplies the systemic, coronary, and pulmonary circulations. A ventricular septal defect is invariably present and the common trunk overrides the ventricular septum. There should be no remnant of a pulmonary valve or main pulmonary artery connected to the heart. Two similar classification schemes have been described based on the arrangement of the pulmonary arteries arising off the aorta, but neither has significant impact on the basic pathophysiology.

Etiology

The etiology of truncus arteriosus is unknown. Approximately one-third of patients with truncus arteriosus will have a 22q11 deletion. Unlike transposition of the great vessels, syndromic involvement is fairly common with 32% of infants, with truncus arteriosus having multiple associated abnormalities (distinct from 22q11) according to one population-based study. Environmental factors contributing to the malformation of truncus arteriosus are not common, though some risk factors have been reported. There is a 6–12-fold increase in risk of truncus arteriosus in infants of a diabetic mother. Prenatal exposure to retinoic acid may also be a risk factor for the development of conotruncal malformations such as truncus arteriosus. The precise embryologic disturbance that results in truncus arteriosus is not known. At its most basic level, this perturbation of normal development involves the failure of the normal embryonic truncus arteriosus to partition into the pulmonary and aortic roots and associated semilunar valves. Also, since this process of septation contributes to the formation of the superior portion of the ventricular septum, the characteristic ventricular septal defect results. This topic is the subject of a detailed discussion and review.

Epidemiology

Truncus arteriosus is one of the rarer forms of cyanotic congenital heart disease with an estimated incidence of 0.1 per 1,000 live births. There is no gender predilection.

Pathology/Pathophysiology

In truncus arteriosus, the entire cardiac output is directed out of the heart through a common trunk which branches proximally to give off the coronary circulation followed by the pulmonary circulation, and finally the remainder of the systemic circulation in succession (Fig. 249.7). Because the pulmonary and systemic circulations occur in parallel, they are subject to competitive flow with the distribution of flow typically being determined by the relative resistances within each circuit. In the immediate newborn period, the pulmonary vascular resistance is high and the relative amount of pulmonary blood flow may be normal to only slightly increased. With the expected fall in pulmonary vascular resistance and increase in the systemic vascular resistance during parturition, the relative proportion of

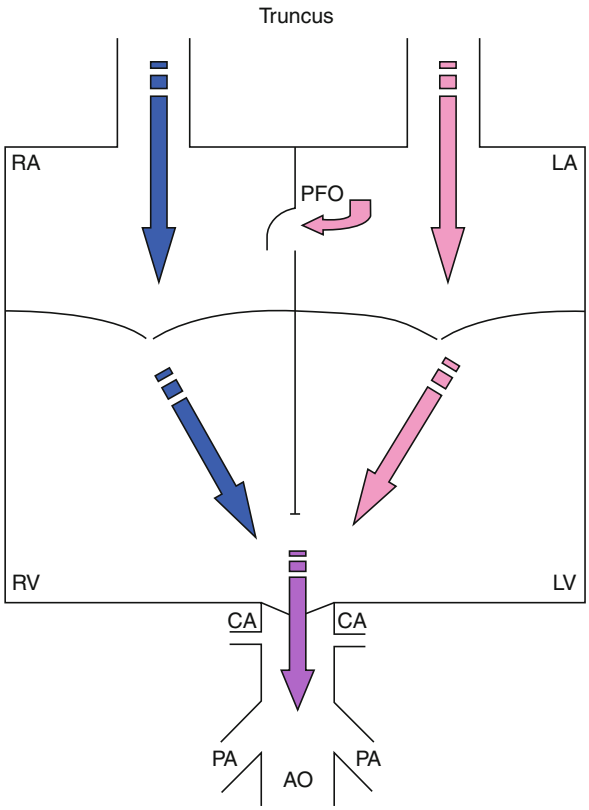

Figure 249.7
In truncus arteriosus, there is mixing of oxygenated and deoxygenated blood that exits the ventricular chambers via a common arterial trunk. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *PFO* patent foramen ovale, *CA* coronary artery, *PA* pulmonary artery, *AO* aorta

pulmonary to systemic blood flow can increase rapidly. This can produce an inordinate work load on the newborn heart and lead to relatively early congestive heart failure, especially in conjunction with a regurgitant or stenotic truncal valve. Because the systemic and pulmonary circulations are in parallel, the oxygen saturations will rise as the proportion of pulmonary blood flow increases. Assuming unobstructed pulmonary arteries, the systemic blood pressure is transmitted to the pulmonary arterial bed. The increased flow and pressure is a recipe for pulmonary vascular disease, which can develop in as little as 6 months, if the lesion goes unrepaired.

Clinical Manifestations

Infants with truncus arteriosus are typically discovered in the first few weeks of life. In the first week of life, they may display mild cyanosis but otherwise appear well. Over the first couple of weeks, as pulmonary vascular resistance falls and the proportion of pulmonary to systemic blood flow increases, cyanosis improves, but signs and symptoms of congestive heart failure due to volume overload ensue, including tachypnea, increased work of breathing, excessive diaphoresis, and failure to thrive. The presence of significant truncal valve regurgitation will result in more rapid development of congestive heart failure and the associated symptoms.

Diagnosis

In the first weeks of life, physical examination of the infant with truncus arteriosus will reveal bounding pulses, a systolic flow murmur, and often a systolic ejection click created by the abnormal truncal valve, in addition to the signs and symptoms of congestive heart failure (outlined above). The precordial activity is increased. If the truncal valve is stenotic or regurgitant, a murmur will be present at birth, and this may lead to earlier diagnosis. Electrocardiography may show evidence of biventricular hypertrophy, though it may be normal in the first couple of days of life. Chest radiography at the time of presentation typically reveals cardiomegaly and increased pulmonary vascular markings. A right aortic arch (present in up to one-third of individuals with truncus arteriosus) in this setting should lead one to suspect truncus arteriosus. As with the other forms of cyanotic congenital heart disease, the diagnosis of truncus arteriosus is typically confirmed with echocardiography (*Fig. 249.8*). In most cases, accurate assessment of the pulmonary artery origins, the function of the truncal valve, coronary anatomy, and the continuity and sidedness of the aortic arch can be well established by echocardiography. Like other forms of congenital heart disease involving the conotruncus, prenatal diagnosis is also possible. Diagnostic cardiac catheterization is not typically performed for patients with truncus arteriosus unless the aortic arch, pulmonary artery, or coronary anatomy is inadequately defined by echocardiography. In the rare patient diagnosed beyond early infancy, cardiac catheterization can be performed to determine the pulmonary vascular resistance.

Differential Diagnosis

The differential diagnosis of truncus arteriosus includes other forms of congenital heart disease that produce mild cyanosis and congestive heart failure, including aorticopulmonary window, certain forms of double-outlet right ventricle, tetralogy of Fallot with pulmonary atresia, and certain forms of univentricular hearts.

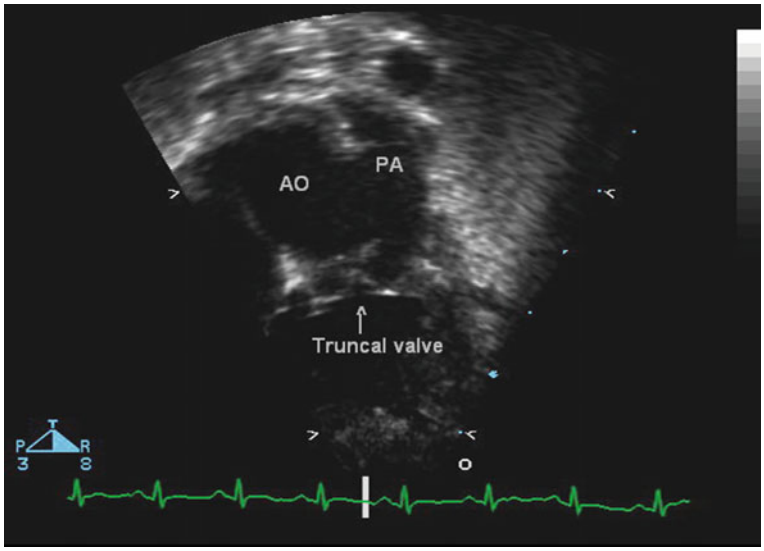

Figure 249.8
This still frame two-dimensional echocardiogram image demonstrates the proximal truncal root dividing into the aorta and pulmonary artery segments. *AO* aorta, *PA* pulmonary artery

Treatment

Though medical therapy, in the form of digoxin and diuretics, can be used to mitigate heart-failure symptoms in the short term, surgical therapy is required to avoid dismal outcome in these patients. In many centers, the surgical correction of truncus arteriosus is performed at the time of diagnosis, in the first few weeks of life. Some centers delay repair until 2–3 months of age if symptoms of heart failure can be managed with medical therapy. Surgical correction involves closure of the ventricular septal defect in such a way that the truncal valve is positioned over the left ventricle and removing the pulmonary arteries from the aorta and connecting them by way of a conduit to the right ventricle. The material used to fashion the conduit has evolved over the years. Typically, a cryopreserved allograft is used, but due to limited availability, effective alternatives have been found. Occasionally, due to stenosis, insufficiency, or both, the truncal valve will need to be repaired or replaced.

Prognosis

For patients with truncus arteriosus, prognosis in the modern era is dependent on the function of the truncal valve, continuity of the aortic arch, and the presence of extra-cardiac malformations. Prior to surgical repair, the prognosis for truncus arteriosus was dismal, with the majority of individuals diagnosed in infancy dying before their first birthday. With introduction and refinement, repair in the newborn period and young infancy is associated with very good short- and long-term survival. Due to the need for conduit replacement and progressive deterioration of the truncal valve, most individuals will require reoperation in childhood or adolescence.

Prevention

Prevention of truncus arteriosus is not currently possible. Please see "Overview" of cyanotic congenital heart disease for a more general discussion of preventing congenital heart disease.

Total Anomalous Pulmonary Venous Connection

Definition/Classification

Total anomalous pulmonary venous connection is defined as drainage of the entirety of pulmonary venous blood flow into the systemic venous circulation. The condition may be further classified as to the location of the anomalous connection: supracardiac (above the heart) or

infracardiac, or perhaps more importantly, by the presence or absence of pulmonary venous obstruction.

Etiology

The etiology of total anomalous pulmonary venous connection is not known. Familial cases have been reported, and more recently, a candidate gene was identified in a large family with non-syndromic total anomalous pulmonary venous connection, suggesting a genetic basis in some individuals. In some cases, total anomalous pulmonary venous connection occurs as part of a pattern of malformations, such as asplenia syndrome. Environmental factors such as maternal exposure to pesticides, paint, and lead in susceptible individuals may be a risk factor in the developing fetus for this condition. In most cases, total anomalous pulmonary venous connection appears to be a sporadic, non-syndromic isolated condition. The embryologic disturbance that results in total anomalous pulmonary venous connection is abnormal obliteration or atresia of the common pulmonary vein which results in failure of the pulmonary veins to connect properly to the left atrium.

Epidemiology

Total anomalous pulmonary venous connection is among the rarest of the conditions presented in this chapter with an estimated incidence of 0.09 per 1,000 live births. For reasons that are not known, Aboriginals from Manitoba and Ontario, Canada, have a significantly higher incidence (0.282 per 1,000 live births) of isolated total anomalous pulmonary venous connection.

Pathology/Pathophysiology

In total anomalous pulmonary venous connection, oxygenated blood returning from the lungs is routed into and mixes with deoxygenated systemic venous return. This admixture of systemic and pulmonary venous flow ultimately returns through normal anatomic channels to the right atrium. It is here that the circulation splits and runs in a parallel fashion with a portion crossing an ever-present atrial septal communication into the left atrium, where it will be passed to the left ventricle and subsequently provide the systemic cardiac output. The other portion of right atrial return will proceed to the right ventricle and be pumped into the pulmonary circulation

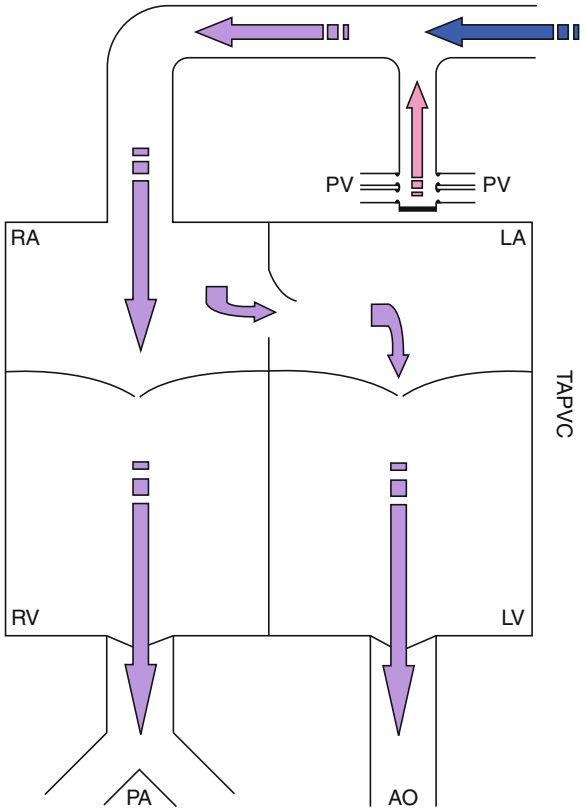

Figure 249.9
In total anomalous pulmonary venous connection, pulmonary blood flow fails to enter the left atrium but instead combines with systemic venous return in some manner, resulting in variably deoxygenated blood being ejected into the systemic circulation. The degree of cyanosis typically depends on the severity of pulmonary venous obstruction. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *AO* aorta, *PA* pulmonary artery, *PV* pulmonary vein

(*Fig. 249.9*). The relative proportion of blood flow entering these two loops is dependent upon the relative resistance to flow in the two vascular beds. As noted below, the clinical presentation is largely determined by this factor. If there is obstruction to flow at any level in the pulmonary circulation (most commonly at the connection between the anomalous pulmonary veins and the systemic venous circulation), blood is shunted preferentially from the right atrium to the left atrium and into the systemic circulation, resulting in little pulmonary blood flow and therefore hypoxemia that is proportional to the degree of obstruction. In contrast, if the pulmonary venous connections are unobstructed, as the normal

newborn transition occurs, the pulmonary vascular resistance falls, and the proportion of pulmonary blood flow increases. In this scenario, there may be progressive pulmonary over-circulation and minimal hypoxemia. When the pulmonary venous connections to the systemic veins occur below the diaphragm, there is typically significant obstruction. In contrast, total anomalous pulmonary venous connections above the diaphragm are often unobstructed.

Clinical Manifestations

In obstructed total anomalous pulmonary venous connections, the affected infant is typically ill within the first couple of hours to days of life. The more severe the obstruction, the earlier symptoms develop. The symptoms are those of severe cyanosis, tachypnea, and respiratory distress. When the anomalous pulmonary veins are unobstructed, the presentation is usually delayed. Indeed, some cases have gone undetected until adulthood. In most cases, patients without obstruction present in the second to fourth month of life with signs of over-circulation and congestive heart failure, including failure to thrive and tachypnea.

Diagnosis

In obstructed anomalous pulmonary venous connections, the exam is notable for moderate to severe cyanosis at birth. Respiratory distress and hepatomegaly may appear within a few hours of life, although may be delayed if the ductus arteriosus remains patent. There may be a soft systolic murmur at the left lower sternal border, but often no murmur is present. The electrocardiogram typically will show right ventricular hypertrophy that may only be distinguishable from the typical RV dominance at a couple of days of age. On chest radiography, there may be evidence of pulmonary venous obstruction pattern characterized by a diffuse reticular appearance. The cardiac silhouette is typically normal is size. The echocardiogram is generally diagnostic (*Fig. 249.10*), though defining the precise pulmonary venous connections may

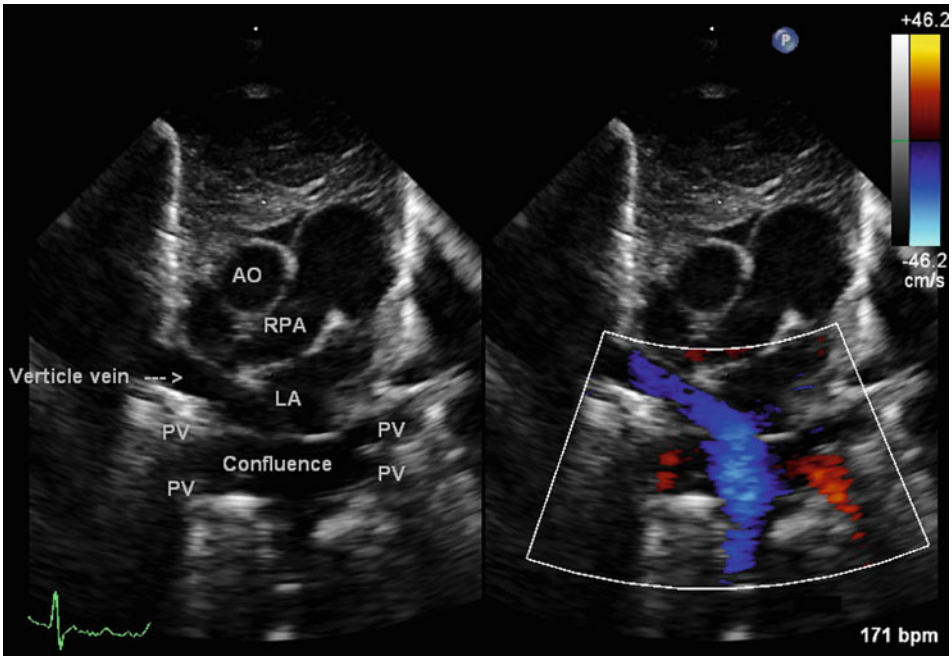

Figure 249.10

This is a still frame two-dimensional echocardiogram image with a simultaneously acquired Doppler color comparison image demonstrating four pulmonary veins entering a confluence behind and separate from the left atrium. A so-called vertical vein is seen exiting the confluence. This vertical vein will connect the pulmonary venous return to systemic venous return. *LA* left atrium, *PV* pulmonary vein, *AO* aorta, *RPA* right pulmonary artery

be difficult particularly in the setting of obstructed pulmonary veins and limited pulmonary blood flow. Historically, cardiac catheterization was performed to delineate the anatomy of the pulmonary veins. Unfortunately, cardiac catheterization carries significant risk in the ill neonate with total anomalous pulmonary venous return. More recently, other imaging techniques such as computed tomography (CT) have provided a noninvasive method for effectively defining the pulmonary venous connections when echocardiography is not sufficient.

Differential Diagnosis

The differential diagnosis of total anomalous pulmonary venous connection includes lung disease and persistent pulmonary hypertension of the newborn. Due to the associated significant cyanosis in the immediate newborn period, transposition of the great vessels can mimic the features of total anomalous pulmonary venous connection. Other congenital heart defects that can present in a similar fashion include hypoplastic left heart syndrome, though cyanosis is less prominent in this condition.

Treatment

Obstructed total anomalous pulmonary venous connection represents one of the few urgent surgical situations in the spectrum of congenital heart disease. There is a very limited role for medical management in the stabilization of the sickest infants in route to the operating room. Extracorporeal membrane oxygenation (ECMO) support has also been used in extreme cases to stabilize infants with severely obstructed anomalous venous connections prior to definitive surgical repair. Operative repair involves the reconnection of pulmonary venous return to the left atrium. The operative technique for repair of total anomalous pulmonary venous connection has evolved over the years due to the high risk of residual pulmonary vein obstruction at the repair site using traditional techniques. Toward this end, more recent surgical efforts have focused on minimizing manipulation of the pulmonary veins as much as possible using the so-called "sutureless" repair, a technique that continues to evolve.

Prognosis

The prognosis in total anomalous pulmonary venous connection is dependent upon the degree of pulmonary venous obstruction, the size of the intra-atrial communication, and the presence of associated cardiac malformations. In infants presenting shortly after birth due to obstruction, the outcome is dismal without surgical intervention. With time and improved operative techniques, the outcome of repaired total anomalous pulmonary venous connection is improving. In a recent retrospective study, the overall postoperative survival in a large single center cohort (with data collected from 1946 to 2005) was 68% at 1 year and 65% at 14 years. There was a marked improvement in operative outcomes in the modern era with a postoperative 5-year survival of 97% in patients undergoing repair since the year 2000. However, even with newer operative techniques and improved perioperative care, patients with obstructed total anomalous pulmonary venous connection requiring neonatal repair remain at high risk for mortality and need for reoperation. In addition, associated cardiac malformations, in particular, single ventricle physiology and heterotaxy are markers for poor outcome.

Prevention

Prevention of total anomalous pulmonary venous connection is not currently possible. Please see "Overview" of cyanotic congenital heart disease for a more general discussion of preventing congenital heart disease.

Pulmonary Atresia with Intact Ventricular Septum

Definition/Classification

This entity is defined by complete obstruction of the pulmonary valve. An "intact ventricular septum" is specified to distinguish this malformation from tetralogy of Fallot and related congenital heart lesions that have distinct developmental origins and physiologic properties. Attempts have been made to classify this disorder based on right ventricular size and morphology, but in practical terms, pulmonary atresia with intact ventricular septum represents a markedly heterogeneous spectrum of disease in terms of the development of the tricuspid valve and right ventricular cavity. The disorder ranges from a severe form of Ebstein's anomaly of the tricuspid valve with severe tricuspid insufficiency and cardiomegaly, to essentially isolated atresia of the pulmonary valve with otherwise normal right-heart development, to severe hypoplasia of the right ventricle and tricuspid valve. Perhaps the most important morphologic feature is the presence or absence

of right ventricular–dependent coronary circulation (see "Pathology/Pathophysiology" below).

Etiology

The etiology of pulmonary atresia with intact ventricular septum is not known. Syndromic involvement is rare, though there have been cases of pulmonary atresia with intact ventricular septum in patients with Down Syndrome. From an embryologic standpoint, pulmonary atresia intact ventricular septum is thought to occur *after* the development of the semilunar (pulmonary and aortic) valves. The process that results in obliteration of the previously formed pulmonary valve is not known. Infection and inflammation have been suggested but evidence is lacking. The degree of right ventricular hypoplasia appears to be determined by when in the developing embryo the valve becomes atretic. Not surprisingly, the earlier the disruption of normal fetal circulation, the more profound the effect on right-heart morphogenesis.

Epidemiology

Pulmonary atresia with intact ventricular septum may be the rarest of the congenital heart lesions discussed in this chapter with reported incidences ranging from 0.042 to 0.132 cases per 1,000 live births.

Pathology/Pathophysiology

In pulmonary atresia with intact ventricular septum, there is, by definition, no direct egress of blood from the pulmonary ventricle to the pulmonary arteries. Blood that enters the right ventricle must either return to the right atrium via tricuspid regurgitation or enter coronary-cameral fistulae that, if present, connect the right ventricle to the coronary circulation (*Fig. 249.11*). In most cases, the right ventricular chamber is hypoplastic to a variable extent, but in cases of an incompetent tricuspid valve (e.g., Ebstein's anomaly of the tricuspid valve), the right ventricular chamber may be normal in size or even enlarged. The development of coronary-cameral fistulae also appears to be dependent on the competency of the tricuspid valve and the pressure developed in the right ventricle. In certain situations, typically where the tricuspid valve is small and competent, the pressure in the right ventricle can exceed twice the systemic systolic blood pressure. This morphologic scenario is associated with the persistence of right ventricular sinusoids and fistulous connections to the coronary circulation. In some cases, these connections can result in abnormal coronary development, and the coronary blood flow becomes dependent on the fistulous connections from the right ventricle rather than from the aorta (i.e., right ventricular–dependent coronary circulation).

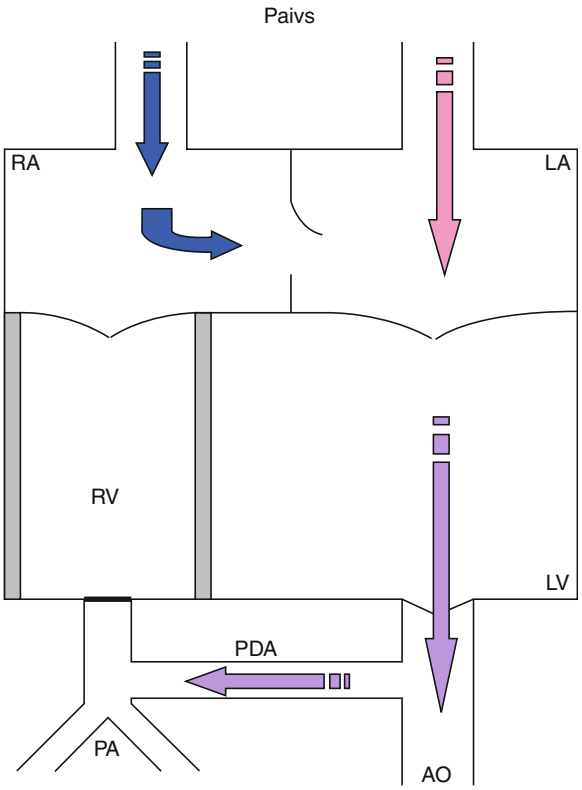

Figure 249.11
In pulmonary atresia with intact ventricular septum, pulmonary blood flow is not ejected from the right ventricle but instead is provided from systemic to pulmonary artery connections such as a patent ductus arteriosus. *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle, *PDA* patent ductus arteriosus

Deoxygenated systemic venous return (excluding the small amount that enters the coronary circulation from the right ventricle) must ultimately cross an ever-present atrial septal communication (usually a patent foramen ovale) and mix with oxygenated pulmonary venous return in the left atrium. From there, this admixture travels to the left ventricle where it is pumped to the systemic circulation. Pulmonary blood flow is supplied by a patent ductus arteriosus connecting the aorta to the pulmonary artery.

Clinical Manifestations

Infants with pulmonary atresia and intact ventricular septum usually appear well at birth with only minimal cyanosis. Cyanosis will generally worsen over the first 24–48 h and will become severe if the ductus arteriosus closes. Affected individuals are typically asymptomatic until severe hypoxemia develops.

Diagnosis

The typical examination of an infant with pulmonary atresia and intact ventricular septum is normal apart from mild cyanosis. There may be a systolic murmur of tricuspid insufficiency in the setting of a hypertensive right ventricle or a continuous murmur caused by a patent ductus arteriosus, but in most cases, a murmur is absent. As discussed above, syndromic involvement is uncommon, and most infants appear morphologically normal. Depending on the degree of right ventricular hypoplasia, the electrocardiogram shows evidence of left ventricular dominance uncharacteristic of a normal newborn EKG. In Ebstein's anomaly of the tricuspid valve, right atrial enlargement and/or preexcitation may be evident. There may be ST-T wave abnormalities if coronary circulation is altered. Chest radiography usually reveals a normal cardiac silhouette (except in the Ebstein's variant, in which case it may be markedly enlarged). Pulmonary vascular markings may appear normal or mildly diminished. As with the other forms of cyanotic congenital heart disease, echocardiography is diagnostic (*Fig. 249.12*) (and prenatal diagnosis through fetal echocardiography is possible). Unlike other forms of cyanotic congenital heart disease, however, cardiac catheterization plays an important diagnostic role for the detection and definition of coronary-cameral fistulae and diagnosis of important coronary structural abnormalities.

Differential Diagnosis

The differential diagnosis of pulmonary atresia with intact ventricular septum includes other forms of cyanotic congenital heart disease that lack a murmur such as transposition of the great arteries, obstructed total anomalous pulmonary venous connection, and single ventricle lesions such as tricuspid atresia.

Treatment

The initial management of the patient identified as having pulmonary atresia with intact ventricular septum centers on establishing and maintaining ductus arteriosus patency using prostaglandin E_1, as this ductal connection is the

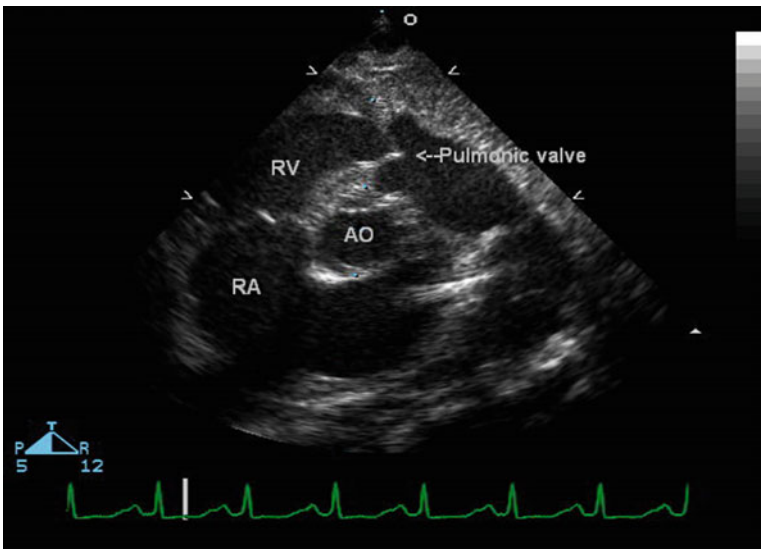

Figure 249.12
This still frame two-dimensional echocardiogram image demonstrates an atretic pulmonary valve that domes but does not open. *RA* right atrium, *RV* right ventricle, *AO* aorta

only source of pulmonary blood flow in these infants. The wide morphologic spectrum of pulmonary atresia with intact ventricular septum underscores the variability in the treatment approaches that follow. The choice of definitive treatment for pulmonary atresia with intact ventricular septum is fundamentally dependent upon the morphology and function of the tricuspid valve, the degree of right-heart hypoplasia and the presence of right ventricular–dependent coronary circulation. In patients without right ventricular–dependent coronary circulation, so-called decompression of the right ventricle through pulmonary valvotomy via surgical- or catheter-based techniques is part of the initial management. Depending on the size of the right ventricle, pulmonary blood flow may need to be augmented with a surgically created systemic to pulmonary artery shunt. In some cases, with adequately sized tricuspid valve and right ventricular growth, a two-ventricle circulation can result. In cases where the right ventricle remains inadequate for pumping the pulmonary cardiac output, patients may undergo surgical palliation in which the right ventricle is not utilized at all (i.e., complete cavopulmonary anastomosis or Fontan palliation) or is only partially utilized (i.e., "one-and-one-half ventricle" palliation) to support the pulmonary circulation. Cardiac transplantation has been suggested for infants with the most severe coronary abnormalities. The interested reader is referred to a recent comprehensive review of this complicated topic.

Prognosis

As with other forms of cyanotic congenital heart disease, prognosis is dismal without intervention. Because in the vast majority of cases pulmonary blood flow in this condition is dependent on ductal patency, most infants will die with spontaneous closure of the ductus arteriosus. With intervention, the prognosis is quite variable and not surprisingly correlates intimately with the underlying substrate and is improving over time. Despite improved perioperative care and surgical techniques, the prognosis of those at the severe ends of the spectrum (Ebstein's malformation of the tricuspid valve with severe tricuspid insufficiency and massive cardiomegaly on one side, or severe right ventricular hypoplasia with right ventricular–dependent coronary circulation on the other) remains relatively poor. In a recent retrospective analysis of a cohort of 210 patients managed in a single center, survival of patients born in the most recent birth cohort (between 1992 and 1998) had the best survival with 1-month, 1-year, and 5-year survival of 85%, 75%, and 67%, respectively (compared to 72%, 57%, and 48% of the group as a whole).

Prevention

In the true sense of the term, prevention of pulmonary atresia with intact ventricular septum is not currently possible. Small series have been reported in which fetal intervention has been attempted. Perforation and dilation of an atretic pulmonary valve in the fetus (after an initial learning curve) has shown some promising early results in altering the morphologic consequences of pulmonary atresia during fetal development and may be associated with improved right-heart growth and postnatal outcomes.

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250 Obstructive Cardiac Lesions

Amy H. Schultz

Introduction

General Definition and Classification

Ordinarily, blood flows through the heart and blood vessels with great efficiency and without any significant pressure gradients across the valves or major blood vessels. Drops in pressure occur only across the resistance capillary beds. The obstructive cardiac lesions encompass any narrowing of the pathways to blood flow in the heart or major blood vessels such that a pressure gradient is generated as the blood traverses the circulation.

Obstructive lesions can be classified as congenital or acquired. The major cause of acquired valvular heart disease in childhood or young adulthood is rheumatic heart disease (Chap. 258, "Rheumatic Heart Disease/Acute Rheumatic Fever"). This chapter focuses primarily on congenital cardiac lesions.

Obstructive lesions can be classified by severity: mild, moderate, severe, or critical. The term "critical" generally refers to a lesion that is so severe that the circulation requires the ductus arteriosus to remain patent to assure stability. These lesions require intervention in the neonatal period.

Finally, in the case of obstruction in the region of the valves, the narrowing can be classified according to the level at which it occurs: the level of the valve itself ("valvular"), above the valve, below the valve, or at multiple levels. One confusing aspect of the nomenclature is in the terms "subvalvular" and "supravalvular." "Sub-" and "supra-" refer roughly to inferior and superior, respectively, such that, for example, a supravalvular mitral ring causes obstruction *proximal* to the valve (the left atrial side) as the blood flows, whereas supravalvular aortic stenosis causes obstruction *distal* to the aortic valve (in the proximal aorta), as the blood flows.

Right Heart Obstructive Lesions

Tricuspid Valve Stenosis and Atresia

The reader is referred to the chapter on *cyanotic heart disease* (Chap. 249, "Cyanotic Heart Disease"), sections on Tricuspid Atresia and Pulmonary Atresia with Intact Ventricular Septum.

Double-Chamber Right Ventricle

Definition and Classification

Double-chamber right ventricle is an entity in which abnormal muscle bundles create stenosis within the body of the right ventricle, subdividing the right ventricle into a high pressure inflow portion and low pressure outflow portion.

Etiology and Epidemiology

Anomalous muscle bundles form during development of the right ventricle. They are typically minimally obstructive in infancy, but become progressively obstructive over time. Frequently, a perimembranous ventricular septal defect and a subaortic membrane are also present. This is a relatively uncommon anomaly, occurring in a small percentage of cases of perimembranous ventricular septal defect and even less commonly as an isolated lesion.

Pathology

The anomalous muscle bundles usually run from the base of the ventricular septum, underneath the septal leaflet of the tricuspid valve, to the anterior wall of the right ventricle. There is associated right ventricular hypertrophy. If there is an associated ventricular septal defect, it can connect to either the low or high pressure chamber, but more commonly to the low pressure outflow portion of the right ventricle.

Pathophysiology

The inflow portion of the right ventricle is at high pressure, triggering the development of right ventricular hypertrophy. A mid-cavitary obstruction is present,

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leading to a significant pressure gradient between the high pressure inflow portion and the low pressure outflow portion of the right ventricle. The degree of obstruction is usually minimal in infancy and increases over time. If a ventricular septal defect is present, the magnitude and direction of shunting is determined by the size of the defect, which portion of the right ventricle it connects to, and the degree of obstruction.

Clinical Manifestations

In mild or moderate degrees of obstruction, patients are typically asymptomatic. Severe obstruction may lead to exercise intolerance or symptoms of right heart failure. Physical examination reveals a harsh systolic ejection murmur at the left lower and upper sternal borders, which may be associated with a thrill and palpable right ventricular impulse if obstruction is moderate to severe. Hepatomegaly and elevated jugular venous pulse may be present if the obstruction is severe enough to cause right heart failure. An associated ventricular septal defect may also generate a holosystolic murmur.

Diagnosis

ECG will demonstrate right ventricular hypertrophy if the obstruction is moderate to severe. Chest radiograph is likely to be normal unless a concomitant ventricular septal defect results in sufficient shunting to enlarge the heart size. Echocardiography can be used to make the diagnosis of double-chamber right ventricle by demonstrating the anomalous muscle bundles and the intracavitary gradient. Right ventricular hypertrophy may be apparent and any associated ventricular septal defect or subaortic membrane should also be documented.

Treatment

Double-chamber right ventricle is treated by surgical excision of the anomalous muscle bundles, usually via a ventriculotomy. An outflow tract patch may be required to alleviate all obstruction. Any associated ventricular septal defect or subaortic membrane is repaired at the same operation.

Prognosis

Surgical resection usually resolves the obstruction which should not recur. Long-term prognosis is excellent. Patients who have had such an operation via a ventriculotomy should be monitored for the development of ventricular arrhythmias.

Pulmonic Stenosis

Definition and Classification

Pulmonary valve stenosis is a narrowing at the level of the leaflets of the pulmonary valve. Supravalvar pulmonic stenosis is a narrowing at the level of the sinotubular junction of the pulmonary artery, just distal to the pulmonary valve. Pulmonic stenosis can be classified as mild, moderate, severe, or critical. Critical pulmonary valve stenosis presents in the neonatal period and requires patency of the ductus arteriosus to maintain adequate oxygenation. Criteria for assigning degrees of stenosis vary and are listed in *Table 250.1*. In the extreme, the pulmonary valve may be atretic; see the Chap. 249, "Cyanotic Heart Disease" for a review of Pulmonary Atresia with Intact Ventricular Septum.

Table 250.1
Various classification criteria for the severity of pulmonary stenosis

Source/indicator	Mild	Moderate	Severe
Natural history study:[a]			
• Peak systolic right ventricular to pulmonary artery pressure gradient (mmHg), at catheterization	<50	50–79	≥80
Bonow RO et al., Adult Valve Guidelines:[b]			
• Echocardiographic jet velocity (m/s)	<3 m/s	3–4 m/s	>4 m/s
• Echocardiographic peak instantaneous gradient (mmHg)	<36	36–60	>60 mmHg

[a]O'Fallon WM et al (1993) Second natural history study of congenital heart defects: materials and methods. Circulation 87(Suppl I):I4–I15
[b]Bonow RO et al (2006) ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice. Circulation 114:e84–e231

Etiology and Epidemiology

Isolated pulmonary valve stenosis occurs in approximately 4 per 10,000 live births and is among the more common forms of congenital heart disease. The etiology of isolated pulmonary valve stenosis is not known. Dysplastic, thickened pulmonary valves are typically associated with Noonan syndrome. Supravalvar pulmonic stenosis is rare and often associated with a syndrome such as Noonan syndrome, Alagille syndrome, Williams syndrome, or congenital rubella syndrome; other cardiac malformations may coexist.

Pathology

Most commonly, pulmonary valve stenosis is a result of partial fusion of all three commissures of the pulmonary valve, with varying degrees of thickening of the leaflets. Bicuspid or unicuspid pulmonary valves can occur, more typically, as part of a more complex defect, such as tetralogy of Fallot. Significant thickening of all leaflets, without commissural fusion, occurs in a small percentage of patients, typically those with Noonan Syndrome. Secondary right ventricular hypertrophy, in proportion to the degree of stenosis, is present.

Supravalvar pulmonic stenosis is characterized by a narrowing at the sinotubular junction of the main pulmonary artery. There may also be associated thickening of the pulmonary valve leaflets.

Pathophysiology

Pulmonary stenosis creates a pressure gradient between the right ventricle and the pulmonary artery. The right ventricular systolic pressure is elevated in proportion to the degree of stenosis, inducing compensatory right ventricular hypertrophy. Cardiac output is maintained in all but critical degrees of stenosis, but the ability to augment cardiac output with exercise may be limited in moderate to severe stenosis. Right to left shunting across a patent foramen ovale or atrial septal defect may occur in moderate to severe pulmonary stenosis with associated prominent right ventricular hypertrophy.

In critical pulmonary valve stenosis, there is insufficient antegrade flow across the pulmonary valve. Some of the systemic venous return to the right atrium passes across the patent foramen ovale to the left atrium, maintaining systemic cardiac output, but resulting in cyanosis. Pathologic degrees of tricuspid regurgitation may be present due to the elevated right ventricular systolic pressure, which is often suprasystemic. The patent ductus arteriosus allows blood to pass from the aorta to the pulmonary artery to maintain a reasonable amount of pulmonary blood flow. If the ductus arteriosus constricts, the patient will become severely cyanotic.

Clinical Manifestations

Most patients with isolated pulmonary valve stenosis are asymptomatic and present with a murmur. Moderate to severe degrees of stenosis may lead to exertional dyspnea. Severe pulmonary stenosis may lead to cyanosis (if there is a concomitant atrial communication), exertional syncope, chest pain, and signs of right heart failure. The murmur is of a systolic ejection type, loudest at the left upper sternal border (pulmonic area) with radiation to the lung fields. The murmur becomes louder and harsher and peaks later as the degree of stenosis increases. An ejection click, which introduces the murmur, is noted in cases of valvar stenosis. The intensity of the click varies with respiration, softer in inspiration and louder in expiration. P_2 may be delayed, in proportion to the severity of the stenosis. In addition, P_2 becomes softer as the degree of obstruction increases. A palpable right ventricular impulse is present. A thrill may be palpable in the second or third left intercostal space in moderate or severe degrees of stenosis.

Neonates with critical pulmonary valve stenosis present with cyanosis and a harsh systolic ejection murmur. A separate systolic regurgitant murmur of tricuspid regurgitation may also be present. Signs of right heart failure (hepatomegaly) are also usually present.

Diagnosis

ECG demonstrates progressive degrees of right axis deviation and right ventricular hypertrophy in the setting of pulmonary valve stenosis. Chest radiographs frequently show a prominent main pulmonary artery segment due to post-stenotic dilation. Heart size is usually normal, except in severe pulmonary stenosis in which it is mildly enlarged. Decompensated severe pulmonary stenosis (with right heart failure) or critical pulmonary stenosis can demonstrate moderate to marked cardiomegaly.

Transthoracic echocardiography is the diagnostic gold standard. Careful attention must be paid to the views of the pulmonary valve and sinotubular junction to distinguish valvular from supravalvar stenosis. An estimate of the gradient can be obtained by Doppler techniques. Right

ventricular hypertrophy, in proportion to the severity of stenosis, will be apparent. The tricuspid valve function should be assessed. If mild or greater tricuspid regurgitation is present, the right ventricular systolic pressure can be estimated accurately.

Cardiac catheterization is usually reserved for situations in which echocardiography predicts that balloon valvuloplasty is indicated. Invasive hemodynamic assessment of pulmonary valve gradient is performed as part of this procedure.

Treatment

Intervention is indicated for symptomatic patients with pulmonary stenosis. Asymptomatic patients with moderate to severe pulmonary stenosis can undergo intervention electively. No intervention is necessary for mild pulmonary stenosis. Pulmonary valve stenosis may either progress or improve spontaneously in infancy, so some period of observation of patients with moderate pulmonary stenosis is indicated prior to intervention. A peak to peak gradient measured invasively in the cardiac catheterization laboratory atleast of 40–50 mmHg is typically considered an indication for intervention. Some practitioners may also employ an intervention threshold of right ventricular systolic pressure >75% of systemic blood pressure.

Balloon pulmonary valvuloplasty via cardiac catheterization has become the standard treatment for pulmonary valve stenosis, although it is generally not effective for supravalvular pulmonic stenosis (see Chap. 253, "Interventional Cardiology"). Inflation of the balloon either splits the fused commissures or results in a tear of the leaflet. Some degree of pulmonary valve insufficiency frequently results. Balloon valvuloplasty is highly efficacious, except in cases of dysplastic pulmonary valve with thickened leaflets but without significant commissural fusion. Supravalvar pulmonic stenosis and pulmonary valve stenosis due to dysplastic leaflets not responsive to balloon dilation are treated surgically. Thickened leaflets may be excised, and narrowing at the sinotubular junction is augmented with a patch.

Prognosis

Mild pulmonary stenosis has an excellent long-term prognosis without intervention. Outcomes after balloon pulmonary valvuloplasty are also very good. Early recurrence of significant obstruction occurs in 8–10% of patients and is often amenable to repeat balloon valvuloplasty. Late recurrence of pulmonary stenosis is rare (1–2%). Actuarial freedom from reintervention is 84% at 10 years. Some degree of pulmonary insufficiency occurs in 40–90% of patients and, to date, rarely requires intervention. However, as balloon pulmonary valvuloplasty was only introduced in 1982, further data needs to be collected as to the frequency of very late (decades) need for reintervention for pulmonary insufficiency. Endocarditis is rare in pulmonary stenosis.

Branch Pulmonary Artery Stenosis

Definition and Classification

Narrowing of the branch pulmonary arteries, also known as peripheral pulmonic stenosis (PPS), can be physiologic, which is common in newborns, or pathologic. Pathologic PPS typically occurs in association with specific syndromes which frequently include additional cardiac abnormalities.

Etiology and Epidemiology

Physiologic peripheral pulmonic stenosis occurs in about 5% of term newborns and a higher percentage of premature newborns. In the fetal circulation, a reduced amount of flow passes through the branch pulmonary arteries, as most of the flow from the main pulmonary artery is directed across the ductus arteriosus to the descending aorta. Postnatally, a relatively acute angle between the main and branch pulmonary arteries is present, and there is a size discrepancy between the relatively large main pulmonary artery and the smaller branch pulmonary arteries.

Pathologic branch pulmonary artery stenosis occurs in the setting of several different syndromes, listed in *Table 250.2*.

Pathology

In physiologic peripheral pulmonic stenosis, structures are fundamentally normal. The size discrepancy between the main and branch pulmonary arteries and the associated small pressure gradient typically resolve by 6 months of age. In pathologic forms, the branch pulmonary arteries may be diffusely hypoplastic or have multiple discrete stenoses. Discussion of the histopathologic findings in the various syndromes is beyond the scope of this chapter.

Table 250.2
Syndromes associated with pathologic branch pulmonary artery stenosis

Syndrome	Etiology	Incidence	Associated cardiovascular abnormalities
Congenital rubella syndrome	Maternal infection with rubella virus during pregnancy	US: 0–2 total cases reported per year Without vaccination program: 0.2–2:1,000 live births Effective vaccination programs exist in the Americas and Europe; Southeast Asia and Africa have little rubella vaccine coverage.	Patent ductus arteriosus Pulmonary valve stenosis Atrial septal defect Coarctation Systemic arterial stenoses More complex congenital heart disease
Alagille syndrome	JAG1 mutations (90%) Chromosome 20 microdeletion (7%) NOTCH2 mutation (rare)	1:20,000–1:70,000	Tetralogy of Fallot Ventricular septal defect Atrial septal defect Aortic stenosis Coarctation of the Aorta
Williams syndrome	Chromosome 7q11.2 microdeletion	1:7,500–1:20,000	Supravalvar aortic stenosis Supravalvar pulmonic stenosis Coarctation/arch hypoplasia
Elastin gene mutation (familial supravalvar aortic stenosis)	ELN mutation, loss of one functional copy	Unknown	Same as above for Williams syndrome
Noonan syndrome	Mutations in: PTPN11 (50%) SOS1 (20%) RAF1 (10–15%) KRAS (5%) Unknown (10–15%)	1:1,000–1:2,500	Pulmonary valve stenosis Hypertrophic cardiomyopathy Atrial septal defect Aortic valve stenosis Coarctation of the aorta
Cutis laxa	Mutation in one of several genes that are involved in assembly of elastic fibers including ELN and FBLN5.	Rare	Supravalvar aortic stenosis
Ehlers–Danlos syndrome	Mutations in multiple genes for different types of collagen or collagen-associated proteins	1:5,000	Mitral valve prolapse Coarctation of the aorta

Pathophysiology

Physiologic PPS imposes a nonsignificant pressure load on the right ventricle as the gradients are typically minimal. This mild degree of stenosis typically resolves spontaneously by 6 months of age.

In pathologic forms of branch pulmonary artery stenosis, the degree of stenosis is variable, ranging from mild to severe. In moderate to severe cases, significant pressure load is imposed on the right ventricle, resulting in compensatory hypertrophy. Right heart failure can result from severe cases.

Clinical Manifestations

Physiologic PPS is usually identified by a blowing systolic ejection murmur heard at the left upper sternal border, radiating to both axillae and the back. The remainder of the cardiac physical examination should be normal and there should be no history of cardiovascular symptoms.

Pathologic branch pulmonary artery stenosis will be asymptomatic if of mild degree. Moderate obstruction may affect exercise performance. Severe obstruction may lead to symptoms of right heart failure, dyspnea, or exercise intolerance. The physical examination reveals

a systolic ejection murmur in the pulmonic area, radiating to the back and axillae. If the obstruction is more severe, the murmur will be harsher and louder and may take on a continuous quality over the lung fields. The pulmonic component of the second heart sound (P_2) may be delayed, leading to wide splitting with normal to increased intensity of P_2. In the setting of right heart failure, hepatomegaly and elevation of the jugular venous pulse will be observed.

Diagnosis

Physiologic PPS can be diagnosed from birth up to about 6 months of age, but most typically in the first 3–4 months of life. Evidence of branch pulmonary artery stenosis persisting beyond 6 months of life should be considered pathologic.

The ECG is normal in physiologic PPS and mild degrees of pathologic stenosis, but typically demonstrates right ventricular hypertrophy in moderate to severe obstruction. A significant incidence of left axis deviation has been reported in congenital rubella syndrome and Noonan syndrome. Chest radiography is normal in physiologic PPS and mild to moderate degrees of pathologic stenosis. With severe branch pulmonary artery stenosis, some enlargement of the right atrium and right ventricle may be apparent.

Echocardiography in physiologic PPS typically identifies mild flow acceleration to 1.5–2.2 m/s in the proximal branch pulmonary arteries in the absence of any other cardiac abnormality. In pathologic branch pulmonary artery stenosis, the proximal portions of the branch pulmonary arteries can be measured and may be small for body surface area. Flow acceleration can be identified and may be greater in velocity than in physiologic PPS. In moderate to severe obstruction, right ventricular hypertrophy is observed. Right ventricular systolic pressure can be estimated from the velocity of the tricuspid regurgitation jet.

Treatment

Physiologic PPS requires no treatment and resolves spontaneously. Mild pathologic branch pulmonary artery stenosis does not require intervention. Moderate to severe degrees of branch pulmonary artery stenosis can be treated in the cardiac catheterization laboratory with balloon dilation and/or vascular stent implantation (see Chap. 253, "Interventional Cardiology"). Surgical augmentation of the main and proximal branch pulmonary arteries is possible up to the hilum of the lung.

Prognosis

Physiologic PPS resolves spontaneously, typically by 6 months of age. Pathologic branch pulmonary artery stenosis may either improve spontaneously with time (in the case of mild to moderate disease) or may be progressive (typically in the setting of severe disease). Severe progressive disease may lead to right heart failure and death.

Left Heart Obstructive Lesions

Cor Triatriatum

Definition and Classification

Cor triatriatum is a rare congenital anomaly in which the left atrium is partitioned into two chambers by a membrane. There is an orifice in the membrane of varying size. The more superior chamber receives the pulmonary veins. The left atrial appendage and the foramen ovale are inferior to the membrane.

Etiology and Epidemiology

During formation of the heart, the pulmonary veins connect to the heart by absorption of a common pulmonary vein into the left atrium. The anomaly of cor triatriatum is thought to result from incomplete absorption of the common pulmonary vein and is a rare entity.

Pathophysiology

Pulmonary venous blood returns from the lungs to the superior chamber and then passes through the orifice in the membrane to reach the inferior chamber. Depending on the size of the orifice relative to the size of the patient, varying degrees of obstruction result at the level of the membrane. The pressure in the pulmonary veins is elevated, and if the obstruction is severe, there may be secondary pulmonary arterial hypertension.

Clinical Manifestations

The more severe the obstruction, the earlier in life the lesion will present. If the obstruction is relatively mild, the patient may present in childhood or beyond with a diastolic inflow murmur at the apex or exercise intolerance. More severe obstruction will present with dyspnea and failure to thrive early in life. Physical examination may

reveal tachypnea, a diastolic inflow murmur over the apex, a loud single second heart sound indicative of pulmonary hypertension, and signs of heart failure including hepatomegaly. In the less severe forms with presentation at an older age, cor triatriatum needs to be distinguished primarily from mitral stenosis. In early infancy, the differential diagnosis of dyspnea and failure to thrive with signs of heart failure is wider and includes congenital mitral stenosis, coarctation of the aorta, hypoplastic left heart syndrome, cardiomyopathy, and total anomalous pulmonary venous return.

Diagnosis

The ECG may demonstrate right ventricular hypertrophy. Chest radiography may show evidence of pulmonary venous congestion and enlargement of the left atrium, pulmonary artery, and right heart chambers. Echocardiography provides visualization of the membrane and identification of the flow acceleration across the orifice of the membrane. The orifice can be measured. Parameters indicative of pulmonary hypertension can be assessed such as tricupsid and pulmonary regurgitation velocities for estimation of pulmonary artery pressure, ventricular septal position, and right ventricular wall thickness.

Treatment and Prognosis

Cor triatriatum is treated by surgical excision of the membrane. Surgery is usually very effective with complete or near-complete resolution of obstruction.

Mitral Stenosis

Definition and Classification

Mitral stenosis is a narrowing of the effective orifice of the mitral valve that results in obstruction to blood flow from the left atrium to the left ventricle. It can be classified as congenital or acquired. The major cause of acquired mitral stenosis is rheumatic heart disease (Chap. 258, "Rheumatic Heart Disease/Acute Rheumatic Fever").

Mitral stenosis can also be classified as mild, moderate, or severe on the basis of the mean gradient across the valve and the pulmonary artery systolic pressure (*Table 250.3*). In adults, mitral valve area is also utilized, but absolute cutoffs for mitral valve area are not useful in the pediatric population due to variation in patient size.

Table 250.3
Classification of severity of mitral stenosis, per adult valve guidelines (Bonow RO et al. (2006) ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice. Circulation 114:e84–e231)

Indicator	Mild	Moderate	Severe
Mean gradient (mmHg)	<5	5–10	>10
Pulmonary artery systolic pressure (mmHg)	<30	30–50	>50
Valve area (cm^2)[a]	*>1.5*	*1.0–1.5*	*<1.0*

[a]Relevant to adult-sized patients

Etiology and Epidemiology

Isolated mitral valve stenosis is a rare anomaly. More frequently, congenital mitral stenosis is associated with other left heart obstructive lesions, including aortic stenosis and coarctation or aortic arch hypoplasia. There is increasing evidence that a variety of left heart obstructive lesions have a heritable basis. Shone's syndrome, as described in 1963, is a constellation of left-sided obstructive lesions, namely supravalvar mitral ring, parachute mitral valve, subaortic stenosis, and coarctation of the aorta.

Pathology

There are multiple different anatomic substrates for mitral stenosis in childhood, summarized in *Table 250.4*. Supravalvar mitral ring is a lesion in which fibrous tissue forms a ring on the left atrial side of the mitral valve, either just above or adherent to the mitral valve leaflets. Although this can occur as an isolated abnormality, most cases of supravalvar mitral ring are associated with an abnormal mitral valve or other left heart obstructive lesions. The mitral stenosis is usually progressive.

Congenital mitral stenosis usually comprises malformations of the leaflets, chordae, and papillary muscles. The leaflets are often thickened, and chordae may be thickened or shortened or insert into abnormal papillary muscles. The obstruction results not just from restriction at the level of the valve leaflets but also from decreased interchordal spaces. Two specific patterns of papillary muscle and chordae malformation have been noted: parachute mitral valve and arcade mitral valve. In parachute mitral valve, there is either only one papillary muscle or significant asymmetry of the papillary muscles, with one

Table 250.4
Etiologies of mitral stenosis in childhood

Congenital	**Supravalvar mitral ring**
	Valvular mitral stenosis
	– Annular hypoplasia
	– Leaflet abnormalities
	– Double orifice mitral valve
	Subvalvar mitral stenosis
	– Parachute mitral valve
	– Arcade mitral valve
	Multilevel obstruction
	Atrioventricular canal
	– Unbalance of the common atrioventricular valve toward the right ventricle
	– After repair of common atrioventricular canal
Degenerative	**Mucopolysaccaridoses**
Acquired	**Rheumatic mitral stenosis**

being much larger and receiving more chordae than the other. In arcade mitral valve, the chordae are shortened or absent and the leaflets may insert directly into abnormal papillary muscles or the ventricular wall.

In the case of atrioventricular canal, the common atrioventricular valve can be committed in a relatively equal fashion to both ventricles ("balanced") or may be more committed to one ventricle ("unbalanced"). If the valve is unbalanced toward the right ventricle, physiologic mitral stenosis may occur following septation of the valve at repair. Judgment is required on the part of the surgeon in deciding how to partition the common atrioventricular valve and to what degree to close the "cleft" in the left portion of the valve. The reader is also referred to the Chap. 248, "Left to Right Shunt Lesions".

One form of non-rheumatic-acquired mitral stenosis occurs in patients with mucopolysaccharidoses. Due to deposition of mucopolysaccharide in the mitral and aortic valve leaflets, the leaflets are thickened and have abnormal mobility; valvular stenosis and regurgitation can result.

Pathophysiology

Obstruction of flow across the mitral valve results in elevation of left atrial, pulmonary venous, and pulmonary arterial pressures. Elevated pulmonary venous pressures may result in pulmonary edema and reactive pulmonary arteriolar constriction. Elevated pulmonary arterial pressures increase the work on the right ventricle, leading to right ventricular hypertrophy and elevated right heart filling pressures. In the decompensated state, there is evidence of right heart failure.

Clinical Manifestations

Mitral stenosis presents with dyspnea, particularly in settings where the heart rate is increased and/or the cardiac output is augmented, both of which will magnify the gradient across the mitral valve. Such circumstances include exercise, emotional stress, fever, and atrial fibrillation. Infants are most likely to be symptomatic while feeding and may also present with failure to thrive.

Physical examination may reveal tachypnea, a loud pulmonic component of the second heart sound (P2) in the setting of pulmonary hypertension, and a diastolic rumble over the mitral area. An opening snap may be generated by limitation of leaflet opening in rheumatic mitral stenosis (Chap. 258, "Rheumatic Heart Disease/Acute Rheumatic Fever"). In mitral stenosis resulting in decompensated heart failure, rales and hepatomegaly or elevated jugular venous pressure may be apparent.

Diagnosis

ECG may demonstrate left atrial enlargement and right ventricular hypertrophy, depending on the severity of the obstruction. Chest radiographs will reveal left atrial enlargement and pulmonary venous congestion. Echocardiography can demonstrate abnormal movement of the mitral valve leaflets, abnormal chordal and papillary muscle structures, and abnormal flow characteristics. Severity of stenosis can be graded using mean transvalvular gradients derived from Doppler velocities, estimation of pulmonary artery pressure from tricuspid and pulmonary regurgitation velocities, and mitral valve area from planimetry (*Table 250.3*). Cardiac catheterization can be performed if more accurate assessment of hemodynamics is required.

Treatment and Prognosis

Diuretics may be helpful in ameliorating symptoms of mitral stenosis, but intervention to relieve obstruction is the more definitive approach in symptomatic patients with moderate or severe stenosis. Surgical excision is the treatment of choice for supravalvar mitral ring. In some instances, the valve may need to be replaced if the ring is adherent to the leaflets and removal is not possible without leaflet damage.

In the case of severe congenital mitral stenosis, transcatheter balloon dilation (balloon valvuloplasty) or surgical valvuloplasty or replacement can be performed. All approaches have a frequent need for reintervention when performed in small infants or children. Balloon valvuloplasty may not have long lasting results or may result in significant mitral regurgitation. Surgical valvuloplasty may not be durable, and replacement often results in obligate re-replacement as the child grows. There are long-term risks for endocarditis and atrial arrhythmias. Significant mortality is also noted in children with severe congenital mitral stenosis. Consequently, if significant congenital mitral stenosis is noted in association with other left heart obstructive lesions of moderate to severe degree, the option of single ventricle pallation is considered (see Chap. 251, "The Single Ventricle").

Subaortic Stenosis

Definition and Classification

Subaortic stenosis is an obstructive lesion localized to the left ventricular outflow tract, proximal to the aortic valve.

Etiology and Epidemiology

Subaortic stenosis is an uncommon lesion with several different anatomic substrates:

- Discrete fibrous subaortic membrane: this is the most common form. Frequently (~70% of cases) other cardiac anomalies are present, but this can also be seen in isolation.
- Tunnel-like subaortic stenosis.
- Posterior deviation of the infundibular portion of the ventricular septum, resulting in a ventricular septal defect and subaortic stenosis. This is often associated with coarctation of the aorta or interrupted aortic arch type B.
- Hypertrophic cardiomyopathy with obstruction resulting from a combination of a hypertrophied septum and abnormal movement of the anterior leaflet of the mitral valve (systolic anterior motion). Please see Cardiomyopathy for further discussion of hypertrophic cardiomyopathy.

Pathology

Discrete subaortic membranes are crescentic structures, typically extending from the membranous ventricular septum, posteriorly across the subaortic region to the mitral valve. Histology shows smooth muscle, fibrous, and fibroelastic layers covered by endothelium. Tunnel-like subaortic stenosis consists of a long segment fibromuscular obstruction.

Pathophysiology

Subaortic stenosis results in a pressure load on the left ventricle with secondary left ventricular hypertrophy. In addition, in the case of a subaortic membrane, the turbulent flow pattern of the blood after it traverses the membrane is thought to damage the aortic valve leaflets and can be associated with progressive aortic valve insufficiency.

Clinical Manifestations

Patients with a mild degree of obstruction are usually asymptomatic and present with a harsh systolic ejection murmur resulting from obstruction within the left ventricular outflow tract. A diastolic decrescendo murmur of aortic insufficiency may also be present. Moderate to severe subaortic stenosis may be manifest by exercise intolerance or exertional angina. Severe subaortic stenosis may lead to signs and symptoms of left-sided heart failure, exertional syncope, or sudden death.

Diagnosis

The ECG may demonstrate left ventricular hypertrophy if the obstruction is moderate or severe. Chest radiographs are generally not helpful. Echocardiography can visualize the nature of the obstruction, degree of left ventricular hypertrophy, and estimate the pressure gradient across the obstruction. Aortic insufficiency can be identified by color Doppler echocardiography. Cardiac catheterization can be performed if further quantification and localization of the gradient (subvalvar versus valvar) is needed.

Treatment and Prognosis

No specific therapy is recommended for mild degrees of obstruction unless significant aortic insufficiency develops in the case of a discrete subaortic membrane. A significant proportion of patients (~50%) may be stable for many years without progression of either obstruction or aortic insufficiency. For significant obstruction (peak to peak

gradient ≥40–50 mmHg) or progressive aortic insufficiency in the case of discrete subaortic membrane, surgical relief of obstruction is indicated, The surgery for a subaortic membrane consists of resection of the membrane and septal muscle; the latter is thought to reduce the relatively high risk of recurrence (~20%). For diffusely small outflow tracts, a Konno procedure can be performed in which the septum is incised inferior to the aortic valve, creating a ventricular septal defect which is patched, enlarging the outflow tract. Patients with subaortic stenosis are at risk for endocarditis.

Aortic Valve Stenosis

Definition and Classification

Aortic valve stenosis results from narrowing of the aortic valve, resulting in a pressure gradient between the left ventricle and the aorta. In childhood, congenital forms of aortic valve stenosis predominate; degenerative aortic stenosis is not seen. Rheumatic aortic stenosis is addressed in Chap. 258, "Rheumatic Heart Disease/ Acute Rheumatic Fever".

Aortic stenosis can be classified as mild, moderate, or severe (*Table 250.5*). In addition, the term "critical" is used to describe neonates who present with ductal dependency or hemodynamic instability due to aortic stenosis.

Etiology and Epidemiology

Bicuspid aortic valve disease is a common disorder, estimated to occur in approximately 1–2% of the population. The etiology is thought to be primarily genetic; studies indicate an autosomal dominant inheritance pattern with reduced penetrance. Bicuspid aortic valve occurs more commonly in males (male to female ratio>3:1) and is also seen commonly in Turner syndrome.

Pathology

The aortic valve normally consists of three leaflets. In the vast majority of cases of congenital aortic stenosis, there is fusion or partial fusion of one or two commissures such that the valve is functionally bicuspid or unicuspid. Unicuspid aortic valves are usually severely stenotic. Bicuspid aortic valve is now recognized to be associated with dilation of the ascending aorta, and this aspect of pathology requires monitoring as patients age, although it is rare to require intervention for a dilated ascending aorta in childhood.

Congenital aortic valve stenosis can much less commonly occur in trileaflet aortic valves whose leaflets are thickened. This pathology is associated with Noonan Syndrome.

Acquired aortic stenosis occurs in patients with mucopolysaccharidoses. Deposition of mucopolysaccharide in the mitral and aortic valve leaflets results in thickening and abnormal mobility; valvular stenosis and insufficiency can result.

Pathophysiology

It should be noted that many bicuspid aortic valves function normally in childhood, without significant stenosis or regurgitation. They are more prone to degeneration in adulthood than trileaflet aortic valves, at earlier ages.

Table 250.5
Various classification criteria for the severity of aortic stenosis

Source/indicator	Mild	Moderate	Severe
Natural history study:[a]			
• Peak systolic left ventricular to aortic pressure gradient (mmHg) at catheterization	<50	50–79	≥80
Bonow RO et al., Adult Valve Guidelines:[b]			
• Echocardiographic jet velocity (m/s)	<3.0	3.0–4.0	>4.0
• Echocardiographic mean gradient (mmHg)	<25	25–40	>40
• *Valve area (cm^2)*[c]	*>1.5*	*1.0–1.5*	*<1.0*
• Valve area index (cm^2/m^2)			<0.6

[a]O'Fallon WM et al. (1993) Second natural history study of congenital heart defects: materials and methods. Circulation 87(suppl I):I4–I15
[b]Bonow RO et al. (2006) ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice. *Circulation* 114:e84–e231
[c]Relevant to adult-sized patients

Aortic valve stenosis results in a pressure load to the left ventricle. With moderate or severe stenosis, left ventricular hypertrophy develops. Elevated left ventricular filling pressures may result. In critical aortic stenosis in the neonate, the severity of the stenosis results in left-sided congestive heart failure and may require perfusion of the body from the right heart via the ductus arteriosus to maintain adequate cardiac output.

Clinical Manifestations

A bicuspid aortic valve with no stenosis or insufficiency will cause no symptoms. A systolic ejection click is ausculated. Greater degrees of stenosis usually present with a harsh systolic ejection murmur, loudest at the right upper sternal border and radiating to the carotid arteries. A thrill may be palpable in the suprasternal notch. Patients with moderate or severe aortic stenosis will demonstrate limitations in exercise capacity. In severe stenosis with elevated left heart filling pressures, signs of left-sided heart failure may be present. Patients with severe stenosis may experience syncope or sudden cardiac death.

Critical aortic stenosis in the neonate may be first recognized by a murmur present from delivery or may present with cardiovascular collapse and respiratory distress within the first few days of life. Adequate cardiac output cannot be maintained without augmentation of the systemic output by the right heart via a patent ductus arteriosus.

Diagnosis

ECG demonstrates left ventricular hypertrophy if stenosis is moderate to severe. Chest radiography is generally unrevealing. Echocardiography is used to define aortic valve morphology and function, with Doppler derived estimates of transvalvular gradients. Left ventricular hypertrophy, if present, is evident. In critical aortic stenosis, the left ventricle is often dilated and dysfunctional.

Treatment and Prognosis

Neonates with critical aortic stenosis, as defined by symptoms rather than gradient, can be stabilized initially with infusion of prostaglandin E_1 and, if necessary, mechanical ventilation. Transcatheter balloon aortic valvuloplasty is then the treatment of choice. Surgical valvotomy is now rarely used. Repeat balloon valvuloplasty or eventual aortic valve replacement may be necessary in these patients.

Beyond the neonatal period, a peak gradient $\geq$ 50 mmHg in the catheterization laboratory is generally considered to justify intervention, particularly if accompanied by symptoms, abnormalities on an exercise test, or evidence of rapid progression. Several options are available: transcatheter balloon valvuloplasty, surgical valvotomy, and surgical valve replacement. Transcatheter balloon valvuloplasty is generally the initial approach, due to its less-invasive nature, unless contraindicated by the presence of significant aortic insufficiency. Surgical valvotomy is now rarely used.

Valve replacement can utilize either a bioprosthetic valve, a mechanical valve, a homograft (cadaver) valve, or the patient's own pulmonary valve (i.e., an autograft: the Ross procedure). Each approach has advantages and disadvantages. Bioprosthetic valves have a limited durability, which may be less in younger patients, and thus require re-replacement. Mechanical valves have a risk of thromboembolism and require long-term anticoagulation. Bioprosthetic and mechanical valves come only in sizes designed for adults, and thus it is generally not possible to place one in a small child. Homograft valves tend to calcify and degenerate relatively quickly. The Ross procedure creates two valve disease for the patient (the patient's pulmonary valve is replaced with a homograft) and the so-called neo-aortic valve may degenerate with time. Thus, it is the goal to delay valve replacement as long as possible, and choice of replacement valve has to be individualized to the situation. Surgical mortality is generally low with excellent long-term survival. Patients are at risk for endocarditis.

Aortic Valve Insufficiency (Regurgitation)

Definition and Classification

Any leakage of blood from the aorta into the left ventricle during diastole is termed "aortic valve insufficiency". The term "aortic valve regurgitation" refers to the same phenomenon. Aortic valve insufficiency may be caused by congenital abnormalities of the valve, secondary effects of other intracardiac abnormalities, rheumatic heart disease, or destruction of the valve by endocarditis. The degree of insufficiency can be classified as trivial, mild, moderate, or severe.

Etiology and Epidemiology

The primary cause of aortic valve insufficiency in childhood is bicuspid aortic valve disease. The reader is referred to the section on Aortic Valve Stenosis above for further

epidemiologic information on bicuspid aortic valves. Only 5% of bicuspid aortic valves were found to have significant (moderate or severe) aortic insufficiency at presentation in one large pediatric series. Aortic valve insufficiency also results from balloon aortic valvuloplasty performed for aortic stenosis.

Aortic valve insufficiency can also be caused by prolapse of one leaflet of the aortic valve into either a perimembranous or subpulmonic ventricular septal defect. A subaortic membrane can lead to secondary damage of the aortic valve with insufficiency.

Acquired aortic insufficiency occurs in patients with mucopolysaccharidoses. Deposition of mucopolysaccharide in the mitral and aortic valve leaflets results in thickening and abnormal mobility; valvular stenosis and insufficiency can result.

Pathology

For a discussion of the pathology of bicuspid aortic valve disease, see the Pathology section under Aortic Valve Stenosis, above. With moderate to severe aortic valve insufficiency, secondary dilation of the left ventricle with compensatory hypertrophy is observed.

Pathophysiology

During diastole, the aortic valve closes, but this does not prevent some quantity of blood from returning to the left ventricular cavity from the ascending aorta. If the degree of aortic insufficiency is moderate to severe, the left ventricle will dilate. Compensatory hypertrophy develops to normalize wall stress.

Clinical Manifestations

Patients with mild to moderate degrees of chronic aortic insufficiency are asymptomatic. Individuals with severe chronic aortic insufficiency can also be asymptomatic for extended periods of time. Eventually, however, exercise intolerance, dyspnea, or angina develops. It should be noted that acute onset of aortic insufficiency is less well tolerated due to abrupt rises in left ventricular filling pressures.

On physical examination, the apical impulse may be prominent and may be shifted laterally if there is significant left ventricular dilation. An ejection click is present in the case of bicuspid aortic valve disease. A_2 may be accentuated. The murmur of aortic insufficiency is a diastolic decrescendo murmur, loudest along the mid-left sternal border. It becomes louder and longer as the degree of aortic insufficiency progresses. An aortic ejection murmur may also be present due to the increased ejection volume or concomitant aortic valve stenosis. A presystolic Austin Flint murmur may be present at the apex due to the jet of aortic insufficiency striking the anterior leaflet of the mitral valve and thus affecting mitral inflow. In severe aortic insufficiency, the carotid and femoral pulses are noted to have a rapid rise and brisk collapse, known as "water hammer" or "pistol shot" pulses. The carotid pulses may be visibly prominent (Corrigan's sign) and flushing and blanching may be visible in the nailbeds (Quincke's pulses).

Diagnosis

ECG may demonstrate left ventricular hypertrophy in moderate or severe aortic insufficiency. Chest radiographs may show cardiomegaly and prominence of the ascending aorta if present. Echocardiography is indicated to confirm the presence of aortic insufficiency, as well as to assess its mechanism and severity. Measurement of the aortic root and ascending aorta should be performed due to the association between bicuspid aortic valve disease and dilation of the ascending aorta. Exercise testing can be used to assess exercise capacity and elicit symptoms if the history is unclear. Cardiac magnetic resonance imaging can quantify aortic regurgitant fraction, but is only routinely recommended if echocardiographic windows are poor. Similarly, cardiac catheterization is only recommended when noninvasive evaluation yields inconclusive or conflicting results.

Treatment and Prognosis

Most patients with isolated aortic insufficiency can be followed conservatively for long periods of time, often for decades. Progression of aortic insufficiency, in the absence of endocarditis, is typically slow. In a large pediatric series of patients with bicuspid aortic valves, after a mean follow-up without intervention or endocarditis of 14.4 years, relatively few patients progressed to moderate to severe aortic insufficiency. Sudden death is a rare complication of chronic severe aortic insufficiency ($<$0.2%/year).

Vasodilators including hydralazine, nifedipine, and ACE inhibitors have been used to reduce afterload, but there is no clear evidence that such therapy prolongs the compensated phase of aortic insufficiency. Thus, adult guidelines recommend use of vasodilators only for (1) short-term symptomatic relief and improvement in left ventricular function prior to surgical aortic valve

replacement in patients with left ventricular dysfunction and (2) symptomatic relief in patients not felt to be a candidate for aortic valve replacement.

Aortic valve surgery is indicated for (1) symptomatic individuals with severe aortic insufficiency and (2) for individuals with severe aortic insufficiency and evidence of decreased left ventricular systolic function, marked ventricular dilation, or rapidly progressive ventricular dilation out of proportion to somatic growth. Aortic valve repair techniques have been developed, although the durability of such repairs may be limited. For a discussion of aortic valve replacement and prosthesis choice in children, see the section on Treatment and Prognosis under Aortic Valve Stenosis above.

Patients with aortic cusp prolapse into a ventricular septal defect and associated aortic insufficiency are approached differently. Generally repair of the ventricular septal defect is recommended when the cusp prolapse is recognized, to prevent further deterioration of aortic valve function.

Supravalvar Aortic Stenosis

Definition and Classification

Supravalvar aortic stenosis is a narrowing at the sinotubular junction of the aorta, just distal to the aortic valve. It results in a pressure gradient between the left ventricle and the aorta. The severity of the narrowing can be classified as mild, moderate, or severe.

Etiology and Epidemiology

Supravalvar aortic stenosis can be caused by loss of one functional copy of the elastin gene. This can occur as part of Williams syndrome, which is caused by a chromosome 7q11.2 microdeletion, deleting multiple continguous genes, including the elastin gene, or as a single gene defect (familial supravalvar aortic stenosis). The incidence of Williams syndrome is approximately 1:7,500–1:20,000. It is not clear yet whether this mechanism explains all cases of supravalvar aortic stenosis or not.

Pathology

The supravalvar narrowing most commonly consists of an hourglass-shaped narrowing at the sinotubular junction of the aorta. Less commonly, there is diffuse hypoplasia of the arch starting at the level of the sinotubular junction. Histology shows a thickened and disorganized media of the aortic wall. There can be associated thickening of the aortic valve leaflets. The ostia of the coronary arteries may be stenotic or inflow into the coronary arteries can be limited by aortic valve tissue adherent to the supravalvar narrowing. Associated cardiac conditions may include diffuse arch hypoplasia, pulmonary valve stenosis, supravalvar pulmonic stenosis, or branch pulmonary artery stenosis.

Pathophysiology

Supravalvar aortic stenosis results in a pressure load to the left ventricle, similar to valvar aortic stenosis. Secondary left ventricular hypertrophy will develop in moderate to severe stenosis, in proportion to the degree of obstruction. Coronary artery ostial stenosis, if present, can lead to ischemic complications, including sudden death.

Clinical Manifestations

Mild degrees of obstruction are generally asymptomatic. Moderate to severe supravalvar aortic stenosis can lead to angina, exercise intolerance, or dyspnea on exertion. Sudden death can occur, particularly during or after procedures or exercise. On physical examination, facial features consistent with Williams syndrome may be present. A thrill may be palpable in the suprasternal notch or carotid arteries. Cardiac auscultation reveals a harsh systolic ejection murmur at the right upper sternal border, similar to valvar aortic stenosis. Ejection clicks are usually absent, but A_2 may be accentuated. Supravalvar aortic stenosis can result in elevated blood pressure readings in the right arm in the absence of arch obstruction or elevations of blood pressure in other extremities. This phenomenon is a manifestation of the Coanda effect, a more general principle of fluid dynamics that causes accelerated jets to adhere to surfaces, even as they curve. The jet in this case is eventually directed into the right subclavian artery.

Diagnosis

ECG may demonstrate left ventricular hypertrophy. Transthoracic echocardiography readily visualizes the area of narrowing, although careful attention may be necessary in some cases to distinguish valvar from supravalvar stenosis.

Estimates of the obstructive gradient can be obtained by Doppler echocardiography. Other associated cardiac lesions can also be assessed. Cardiac catheterization can more precisely define the gradient across the narrowing, and angiography can help identify coronary involvement.

Treatment

Mild degrees of stenosis do not require intervention. Surgical augmentation of the sinotubular junction is indicated for moderate to severe degrees of obstruction. Relief of coronary ostial stenosis, if present, is performed. In more complicated cases, other associated cardiac lesions may also be addressed.

Prognosis

The discrete form of supravalvar aortic stenosis has a better prognosis than the diffuse form, in which it may be difficult to relieve the obstruction without merely moving the level of obstruction farther distal along the aortic arch. Surgical relief of discrete supravalvar aortic stenosis has relatively low rates of mortality or need for reoperation. Residual valvar stenosis (due to thickened leaflets) and regurgitation may persist.

Aortic Arch Obstruction

Definition and Classification

Aortic arch obstruction can be separated into three main categories. Most common is coarctation of the aorta in which there is a relatively discrete narrowing of the aortic arch, typically just distal to the insertion of the left subclavian artery, opposite the former insertion of the ductus arteriosus ("juxtaductal"). The arch can also be more diffusely hypoplastic, involving not only the juxtaductal region but also the transverse arch. Finally, the aortic arch can be interrupted at one of several locations. In interrupted aortic arch type A, the interruption is distal to the left subclavian artery, in the same location as a juxtaductal coarctation; in type B, the interruption is between the origins of the left carotid artery and the left subclavian artery; in type C, the interruption is between the origins of the right and left carotid arteries.

Etiology and Epidemiology

Coarctation of the aorta has an incidence of approximately 4:10,000 live births. Coarctation of the aorta, aortic arch hypoplasia, and interrupted aortic arch type A are frequently associated with bicuspid aortic valve or other left-sided obstructive lesions. These left-sided lesions are increasingly being shown to have a genetic basis. Coarctation is also seen in Turner syndrome. Interrupted aortic arch type B, which is almost always associated with posterior malalignment ventricular septal defect, has a specific genetic etiology in approximately 35% of cases, namely microdeletion of chromosome 22q11 (DiGeorge Syndrome). Interrupted aortic arch type C is extremely rare.

Pathology

Inspection of a juxtaductal coarctation demonstrates a posterior shelf of tissue opposite the former insertion site of the ductus arteriosus, narrowing the lumen. This shelf may extend circumferentially around the vessel. In older children, significant arterial collaterals may develop connecting the proximal and distal segments of the aorta, derived typically from the intercostal arteries. Aortic histopathology may also show evidence of cystic medial necrosis.

Pathophysiology

Due to the obstruction within the aorta, there is hypertension proximal to the obstruction and a pressure load on the left ventricle. Distal to the obstruction, perfusion may be compromised. In critical coarctation and interrupted aortic arch, ductal closure results in inadequate perfusion to the lower body, including the abdominal viscera. Systemic acidosis ensues with risk for necrotizing enterocolitis, renal failure, hepatic infarction, and secondary myocardial dysfunction.

Clinical Manifestations

Critical coarctation or interrupted aortic arch presents in the neonatal period as the ductus closes with circulatory collapse or sudden death. These infants usually have a brief history of feeding poorly, irritability, or poor responsiveness, progressing to respiratory distress and/or seizures as they become acidotic. They typically present with tachypnea, an ashen appearance, poor perfusion, and poor pulses.

Some infants with severe coarctation present a bit later, at a few weeks of age, with symptoms and signs of left-sided congestive heart failure, such as poor feeding, poor weight gain, and tachypnea. These symptoms are a result of left ventricular dysfunction due to the pressure load imposed by the coarctation. Physical examination demonstrates poor femoral pulses as well as findings consistent with congestive heart failure.

In other individuals with coarctation, the physiology is compensated and may present in childhood with a murmur (usually continuous in the back), upper extremity hypertension, or diminished or absent femoral pulses. Leg claudication may be described.

Diagnosis

In long-standing coarctation, the ECG may reveal left ventricular hypertrophy, and the chest x-ray may demonstrate rib notching due to the compressive effect of engorged collateral vessels on the adjacent bony structures. Transthoracic echocardiography can accurately diagnose the range of aortic arch lesions. Occasionally CT or MR angiography or angiography at cardiac catheterization is used to supplement echocardiographic imaging. Karyotype should be considered in female patients with coarctation to evaluate for Turner Syndrome and 22q11 FISH testing is recommended for all patient with interrupted aortic arch type B.

Treatment

Neonates with identified moderate to severe coarctation or interrupted aortic arch are treated with prostaglandin E_1 infusion to maintain ductal patency and avoid circulatory collapse. The arch is then repaired surgically. Those who present with shock are stabilized with infusion of prostaglandin E_1 and supportive care which may include endotracheal intubation, correction of acidosis, inotropic infusions, and control of seizures. These neonates should not be fed enterally and should be evaluated for evidence of necrotizing enterocolitis. Evidence of hypoxic ischemic injury to the brain, kidneys, and liver should be sought. When the patient has recovered from this acute insult, the arch obstruction is addressed surgically.

For older children who present with coarctation, the obstruction can be addressed either surgically or via interventional catheterization (balloon dilation with or without stenting).

Prognosis

Without intervention, survival for patients with coarctation is significantly curtailed. Neonates presenting in shock will die without intervention. In a natural history study by Campbell of patients with coarctation who survived the first year of life, median survival was 31 years without intervention. Mortality was attributable to congestive heart failure, aortic rupture, bacterial endocarditis, and intracranial hemorrhage.

In contrast, survival for repaired coarctation is excellent, approximately 90% at 20 years. Five to ten percent of patients may have a residual gradient following repair or may develop recurrent coarctation following the repair. Hypertension also commonly develops late, in the absence of residual narrowing, and is more likely with later repair of coarctation, particularly after 9 or 10 years of age. Late complications can also include endocarditis, development of aneurysm at the repair site, or intracranial aneurysm.

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251 The Single Ventricle

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Definition

Single ventricle lesions are complex heart defects that result in one of the ventricles being hypoplastic or absent. The most common of these lesions are those that comprise the hypoplastic left heart syndrome (HLHS). Single ventricle lesions are divided into three categories based on the adequacy of pulmonary blood flow (PBF) and systemic blood flow (SBF).

- Lesions with unobstructed PBF and SBF
  - Double inlet left ventricle (DILV) with L-transposition of the great arteries
  - Double outlet right ventricle (DORV)
  - Unbalanced atrioventricular canal (AVC) with a dominant right ventricle
- Lesions with obstructed PBF
  - Tricuspid atresia
  - Pulmonary atresia with intact ventricular septum
  - Unbalanced AVC with a dominant left ventricle
  - D-transposition of the great arteries and pulmonary or subpulmonary stenosis
- Lesions with obstructed SBF
  - HLHS syndrome
  - Interrupted aortic arch with hypoplastic left ventricle
  - DORV with pulmonary or subpulmonary stenosis
  - D-transposition of the great arteries (D-TGA) with aortic or subaortic stenosis

Epidemiology

Depending on the study quoted and the lesions included in the definition of single ventricle, the incidence of single ventricle lesions is 1 in 5–10,000 live births in the United States. No sex predilection is noted.

Etiology

Etiology is still unknown. Single genes targeting alterations in mice have resulted in single ventricle lesions prenatally including Nkx2.5, dHAND, TGF b 2, Bop2, and Has2.

Pathophysiology

In single ventricle physiology the pulmonary and systemic circulations are in parallel rather than in series. When there is associated severe obstruction to pulmonary or systemic blood flow, the circulation is dependent on the patent ductus arteriosus and is thus termed "ductal-dependent circulation." The amount of PBF and SBF depends on the degree of obstruction and the vascular resistance in both circulations. There is complete mixing of systemic and pulmonary venous blood at the ventricular or atrial level. The degree of cyanosis is dependent on the amount of PBF.

In lesions with unobstructed PBF, the high pulmonary vascular resistance present at birth usually prevents symptomatic pulmonary overcirculation in the neonatal period. However as the pulmonary vascular resistance decreases over the first few weeks of life, pulmonary blood flow gradually increases and results in congestive heart failure.

The pulmonary vascular bed is protected from overcirculation in lesions with pulmonary or subpulmonary stenosis. The degree of pulmonary stenosis tends to increase with time and the patient becomes progressively more cyanotic.

In the presence of obstruction to SBF such as mitral atresia, aortic atresia, coarctation of the aorta, and hypoplastic or interrupted aortic arch, systemic perfusion is compromised leading to cardiogenic shock as the ductus arteriosus closes.

Clinical Manifestations

Most single ventricle lesions are diagnosed within the first few days to weeks of life. Neonates with pulmonary or subpulmonary stenosis are cyanotic and hypoxemic. A systolic ejection murmur will be noted on auscultation, a palpable thrill may be felt and the second heart sound is single. In cases of pulmonary atresia the systolic ejection murmur is not present. Instead a soft continuous murmur might be present secondary to the patent ductus arteriosus or aortopulmonary collateral vessels.

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In the absence of significant pulmonary outflow obstruction, patients will exhibit signs of pulmonary overcirculation as the pulmonary vascular resistance drops. They will develop tachypnea, diaphoresis, poor feeding, and failure to thrive associated with congestive heart failure within the first 2–6 weeks of life. Symptoms of congestive heart failure might appear earlier in the presence of AV valve regurgitation, or left-sided obstruction. Irrespective of the presence of a mixing lesion, due to the presence of excessive pulmonary blood flow these patients may not appear grossly cyanotic. They may have a palpable thrill, soft systolic pulmonary murmur due to relative pulmonary stenosis, and a diastolic murmur due to relative AV valve stenosis. Hepatomegaly is detected in the presence of congestive heart failure. Right or left AV valve regurgitation results in a pansystolic murmur at the left mid-sternal border or the apex, respectively.

Patients with left-sided obstruction present with signs of poor peripheral perfusion and metabolic acidosis especially after closure of the ductus arteriosus. The second heart sound is single. A soft continuous murmur secondary to the patent ductus arteriosus might be present. Coarctation is detected by a diminished or delayed lower extremity pulse and/or discrepant blood pressures (in general the right arm blood pressure will be higher than the leg by at least 10 mmHg).

Diagnosis

In the era of fetal echocardiography 60% of patients with single ventricle lesions are diagnosed prenatally. The remaining patients are diagnosed postnatally based on the clinical findings discussed above. The following ancillary tests provide important information that helps diagnose patients with single ventricle lesions, distinguish between lesions with decreased or increased pulmonary blood flow, and determine the appropriate management options.

Chest Radiography

The chest x-ray (CXR) is particularly helpful in distinguishing between lesions that are associated with increased versus decreased pulmonary blood flow. In cases of unobstructed pulmonary blood flow, the cardiac silhouette is enlarged on CXR and the pulmonary vascularity is increased. Lesions associated with decreased pulmonary blood flow have a normal cardiac silhouette and decreased pulmonary vascular markings on CXR.

Echocardiography

The anatomy of single ventricle lesions is delineated in detail by two-dimensional echocardiography (*Fig. 251.1*). Echocardiography identifies:

Morphology of the dominant ventricular chamber
Location of the hypoplastic chamber
Presence of narrowing between the dominant ventricular chamber and the rudimentary chamber
Presence or absence of pulmonary stenosis
Presence or absence of aortic valve disease, arch hypoplasia, or coarctation
Location, commitment, and relationship of the great vessels (normally related or transposed)
Location and competency of the AV valves (single, straddling, or atretic valve)
Other associated defects (atrial septal defects)
Abnormalities of the systemic or pulmonary veins
Ventricular function

Doppler color flow mapping allows detection and quantification of AV valve regurgitation or semilunar valve insufficiency. Pulse wave Doppler identifies and quantifies the degree of stenosis.

The use of echocardiography in the management of infants with single ventricle lesions beyond the initial diagnosis will be discussed below.

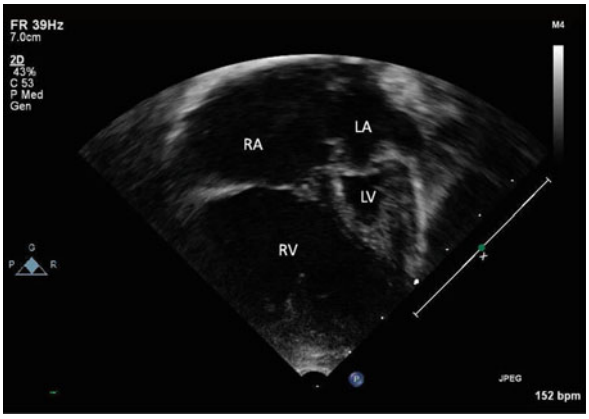

Figure 251.1
Two-dimensional echo apical four chamber view of a hypoplastic left heart syndrome. Large right ventricular and right atrial chamber. The left atrium and left ventricle are severely hypoplastic. *RA* right atrium, *LA* left atrium, *RV* right ventricle, *LV* left ventricle

Cardiac Catheterization

Given the detailed anatomy provided by echocardiography cardiac catheterization is reserved for patients with single ventricle lesions when:

- An anatomic or physiologic question is not answered with certainty by echocardiography.
- Intervention is required (such an atrial septostomy, stent implantation within the ductus arteriosus or pulmonary artery branch, coil occlusion of aortopulmonary collateral vessels, or systemic venovenous collaterals).
- There is the need for assessment of hemodynamics prior to second and third stage palliation surgery.

Electrocardiography (ECG)

The balance of forces between the left and right ventricle is shifted toward the dominant chamber. Right ventricular hypertrophy and right axis deviation are seen in on the ECG of patients with hypoplastic left ventricle. Similarly left ventricular hypertrophy is seen on the ECG of patients with a hypoplastic right ventricle. Left superior axis deviation, also known as northwest axis, is seen in patients with AVC lesions. ECG or other diagnostic tests are utilized when a rhythm disturbance is suspected. Atrial and ventricular arrhythmias as well as disturbances to atrioventricular conduction are common in this patient population.

Management

Neonatal/First Stage Palliation

Early neonatal survival is dependent on achieving a balanced circulation without excessive pulmonary blood flow, but with adequate flow to prevent severe cyanosis. Oxygen saturations are maintained between 75% and 85%. At these saturations pulmonary and systemic blood flow are balanced. Initial resuscitation includes maintaining or reestablishing the patency of the ductus arteriosus with prostaglandin E1 (PGE). It is important to provide a source of blood flow to the ductal-dependent circulation (pulmonary or systemic). A more permanent source of pulmonary or systemic blood flow is then achieved surgically (*Table 251.1*).

Table 251.1
Management of single ventricle lesions

Management of single ventricle lesions in the neonatal period depends on the adequacy of systemic and pulmonary blood flow. Beyond the neonatal period the goal is to separate the SBF and PBF by performing the Glenn/HF procedure at 2–5 months of age followed by the Fontan completion at 2–5 years of age

Single Ventricle Lesions with Unobstructed PBF and SBF

If well balanced at presentation, neonatal surgical intervention may not be necessary for patients in this category. The decrease in pulmonary vascular resistance with the concomitant increase in pulmonary blood flow within the first 6 weeks results in pulmonary overcirculation. In this case adequate regulation of pulmonary blood flow is achieved via banding of the pulmonary artery. This involves placing a ligature at the mid-portion of the main pulmonary artery such that artificial obstruction is created. The degree of restriction to pulmonary blood flow is guided by the oxygen saturation drop during the procedure. If the band is too loose the patient will have too much pulmonary blood flow; excessive constriction will result in cyanosis immediately or progressively as the child grows. Patients should be followed closely since they can outgrow the band, resulting in worsening cyanosis. Bands can also migrate after placement and either damage the pulmonary valve or obstruct the origins of the branch pulmonary arteries. The band is left in place until the patient is ready for the second stage palliation. At that time the band is removed. Banding remains a procedure with a surprisingly high mortality (typically as high as 10%). This is caused less by the procedure itself, and more commonly due to the difficulty in achieving the perfect balance of adequate pulmonary blood flow.

Single Ventricle Lesions with Obstructed PBF

Patients with single ventricle lesions associated with pulmonary outflow obstruction initially benefit from placement of either a prosthetic graft (3.5 mm) between a systemic artery and the pulmonary artery (modified Blalock–Taussig shunt: "m-BT shunt"), or a graft between the right ventricle (RV) and the pulmonary artery (RV to

pulmonary artery shunt). The ductus arteriosus is generally ligated during the same operation to avoid excessive pulmonary blood flow. Pulmonary blood flow is thus controlled by the size of the graft. m-BT shunt placement does not require cardiopulmonary bypass. The shunt is placed well proximal to the first branch of the pulmonary artery to decrease the potential for differential pulmonary artery growth and pulmonary artery distortion. In case of the RV-PA conduit, the long-term effects of a ventriculotomy to the right ventricle remains unknown. Placement of the RV-PA conduit requires cardiopulmonary bypass. Clotting of the m-BT shunt or the RV-PA conduit is a medical emergency addressed surgically or via balloon dilation/stenting in the cardiac catheterization lab due to the resultant development of severe and unrelenting cyanosis.

Single Ventricle Lesions with Obstructed SBF

Several modifications of the Norwood palliation for hypoplastic left heart syndrome (HLHS) have been used for patients with single ventricle lesions and aortic atresia, aortic arch hypoplasia, or subaortic obstruction. The main pulmonary artery is transected just below the bifurcation. The main pulmonary artery is then opened longitudinally and sewn to the ascending aorta. The aortoplasty is extended to distal to the area of obstruction or coarctation. An RV-PA conduit or a BT shunt is then placed to provide pulmonary blood flow. An atrial septostomy is performed to ensure adequate mixing of systemic and pulmonary venous blood at the atrial level. In patients with subaortic stenosis and distal arch obstruction, modifications of the Damus-Kaye-Stansel (DKS) procedure have been used to allow both great vessels to provide unobstructed flow to the systemic circulation. The semilunar roots, main pulmonary artery, and aorta are sewn together to provide unobstructed systemic blood flow. An atrial septectomy is performed if there is restriction to the left AV valve. Pulmonary blood flow is provided through a m-BT shunt or an RV-PA conduit. Both operations (the Norwood procedure or the DKS) require cardiopulmonary bypass (CPB) and in some centers deep hypothermic arrest (DHA). Patients are followed closely for aortic coarctation, shunt stenosis, decreased ventricular function, AV valve regurgitation, and arrhythmias.

Recently the "hybrid palliation" has been introduced as a less invasive alternative to the Norwood procedure. It consists of surgical bilateral pulmonary artery banding, combined with transcatheter balloon atrial septostomy and ductal stenting. It avoids the use of CPB which may be associated with adverse neurologic adverse events in the neonatal period. Experience with the hybrid procedure is limited but encouraging.

Palliative Surgeries Beyond the Neonatal Period

Second Stage Palliation/Cavopulmonary Anastomosis

Regardless of the type of neonatal surgical palliation, young infants with single ventricle lesions are still dependent on pulmonary blood flow from the ventricle. The single ventricle pumps to both the pulmonary and systemic circulation. This chronic work overload eventually leads to hypertrophy, dilatation, and failure of the single ventricle. The cavopulmonary anastomosis unloads the single ventricle and separates the pulmonary and systemic circulation. This is achieved by directing blood from the superior vena cava (SVC) to the pulmonary arteries through a surgically constructed anastomosis. It is performed in patients as young as 4–6 months of age when the pulmonary vascular resistance is low enough to allow passive pulmonary blood flow. The operation takes one of two forms:

- Bidirectional Glenn shunt (BDG): an end-to-side anastomosis of cephalic end the transected superior vena cava to the superior aspect of the right pulmonary artery
- Hemi Fontan (HF): an augmented side-to-side anastomosis between the back of the opened superior vena cava–right atrial junction and the anterior surface of the right pulmonary artery, with an intra-atrial patch placed to close the communication between the atrium and the pulmonary artery

The previously placed systemic to pulmonary artery shunt is taken down. The operation is performed off cardiopulmonary bypass. Major complications include obstruction of the cavopulmonary anastomosis leading to venous congestion, facial and upper extremity swelling, increased head circumference, and worsening cyanosis. Venovenous collaterals or pulmonary arterial venous malformations can form leading to worsening cyanosis.

Third Stage Palliation/Modified Fontan Operation

The relative size of the lower trunk and legs increases as infants grow into children. The ratio of IVC to SVC return

to the heart increases, resulting in increasing cyanosis following the cavopulmonary anastomosis. During the third stage blood from the inferior vena cava (IVC) is directed to the right pulmonary artery. This results in near normal arterial oxygen saturation since all of the systemic venous return (with the exception of flow from the coronary sinus) is directed to the pulmonary vascular bed before its return to the heart. The modified Fontan operation is generally performed in patients 2–5 years of age. It currently involves either a tunnel created within the lateral aspect of the right atrium (the "lateral tunnel") or an extracardiac conduit that directs IVC flow to the pulmonary artery. The extracardiac conduit is a (Gortex, homograft, or pericardial) tube graft interposed between the transected inferior vena cava and the underside of the right pulmonary artery (*Fig. 251.2*). There is still debate whether the extracardiac conduit approach is superior to the lateral tunnel. Approximately two thirds of Fontan operations in recent years have been performed using the extracardiac conduit approach (STS surgical database). In the early 1990s, fenestration of the Fontan was proposed as a new modification. This involves a small connection between the Fontan pathway and the right atrium. It is the physiologic equivalent of an atrial septal defect. If the pressure within the Fontan connection (systemic venous pressure) becomes too high, blood can "pop-off" and flow to the systemic circulation. While this right to left shunt will cause cyanosis, it does serve to maintain cardiac output in the event of adverse physiologic circumstances.

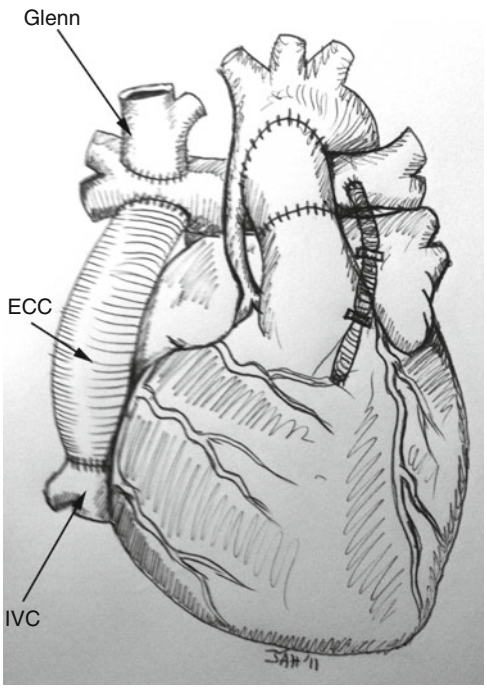

Figure 251.2
Fontan circulation. Courtesy of netterimages.com. Elsevier, INC

Major postoperative complications include pleural effusions, arrhythmias, thromboembolic events, and protein-losing enteropathy.

Pleural effusions are the most common problem after a modified Fontan operation. This has been reduced but not totally eliminated by the use of the Fontan fenestration. Many factors have been examined but the exact reason remains unknown. There is no good definitive treatment. Supportive treatment such as drainage of the effusion is recommended. It is important to maintain adequate fluid replacement and nutrition. If the effusion is chylous then the patient is switched to a fat-free diet or a formula rich in medium chain triglycerides (MCT).

Arrhythmias are common in both the immediate and in the late postoperative periods. These can occur in up to 50% of patients after a Fontan procedure depending on the type of Fontan and include sinus node dysfunction and atrial flutter/fibrillation. Arrhythmias in this population are thought to be secondary to surgical scarring and/or chronic atrial hypertension. Atrial arrhythmias can be managed medically or via ablation in the cardiac catheterization lab. Patients with bradyarrhythmias or sinus node dysfunction may need pacemaker implantation.

Multiple factors may contribute to the formation of thrombus including areas of sluggish flow in the Fontan circuit, atrial arrhythmias, as well as intrinsic or acquired abnormalities in hemostatic pathways. The emboli can occur in the pulmonary and systemic circulation. If a fenestration exists between the pulmonary and systemic sides of the heart, then a cerebral vascular accident or other signs of a paradoxical embolus can be seen. There is no consensus on whether or how to attempt thromboprophylaxis in Fontan patients. Some cardiologists use antiplatelet drugs and others prefer warfarin.

Protein-losing enteropathy (PLE) is an uncommon (3.7%) but dreaded complication of the Fontan operation occurring a median of 2.7 years after surgery and associated with a poor prognosis, with a 5-year mortality nearing 50%. The pathogenesis of PLE is poorly understood. Patients with PLE develop peripheral edema, ascites, and pleural effusions. Low serum albumin and fecal α1-antitrypsin concentration are reliable in identifying enteric protein loss. Management is geared toward therapeutic relief. Options include drainage of pleural and ascitic fluid, afterload reduction, diuresis, albumin

infusion, and a high protein/low fat diet. Various case reports have reported efficacy of oral steroids, heparin, spironolactone, and calcium infusion in the treatment of PLE. Heart transplantation is reserved for patients who have failed medical or surgical therapy.

Outcomes

Although the modified Fontan operation has improved the survival of patients with single ventricle physiology, it is a less than ideal hemodynamic outcome. Multiple studies looking at the results of the Fontan demonstrate a decrease in survival beyond 15 years after surgery. The survival rate and freedom from transplantation 15 years post-Fontan is 70–80%. Death usually is a result of comorbid conditions and complications mentioned above. The quality of life of patients after a Fontan is affected by a lower exercise performance as compared to subjects of the same age and gender. In addition Fontan patients are found to have a higher incidence of attention deficit disorder, learning disabilities, anxiety, and depression. The explanation for these cognitive, psychological, and psychiatric disturbances is likely multifactorial and is an area of active investigation.

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252 Noninvasive Cardiovascular Imaging

Brian D. Soriano

Introduction

With recent advances in technology, initial diagnostic and physiologic assessments of cardiovascular structures can now be accomplished with noninvasive imaging techniques. The armamentarium available to the healthcare provider has expanded to the point that for a particular clinical question, multiple factors must be considered when choosing which modality will be most appropriate. This chapter aims to provide an overview of the various options available in clinical pediatrics, to guide the provider to determine which modality is best suited for their patient, and to recognize each modality's set of advantages and limitations. Metabolic and nuclear scintigraphy imaging will not be covered in this section, since both are more prevalent in adult cardiology and are infrequently employed in clinical pediatrics. Several citations are listed in the reference section for the interested reader.

In order to establish a framework and to better understand the nuances between noninvasive modalities, an overview of imaging terms follows.

Resolution

The ability to distinguish between two items, either visually by space, color, or even time. Resolution can be determined with quantitative means, such as the number of megapixels in a digital camera, or on a relative scale.

Contrast Resolution

Contrast resolution is the ability to distinguish between two points in space based on the differences in amount of light generated or reflected by the points. Low contrast is exemplified when one attempts to travel through dense fog or clouds (◉ *Fig. 252.1*). High contrast would be similar to seeing a black rabbit on a white background, or the moon in a pitch-black sky (◉ *Fig. 252.2*).

Spatial Resolution

Spatial resolution is the ability to distinguish two points in space (◉ *Figs. 252.3* and ◉ *252.4*). A microscope, for example, allows one to view items with high spatial resolution. An example of low spatial resolution is best illustrated during a football game where one is sitting in the highest of seats. At such distance, one cannot read individual letters on a player's jersey.

Temporal Resolution

Temporal resolution is the ability to detect differences in an object's position or appearance between two points in time. The football game analogy can be extended to help explain temporal resolution; the action of handling the ball may be so quick that one did not see how the ball was passed from one player to another – which reflects poor temporal resolution. If you are watching the game on a television and you see the replay in slow-motion, this is an example of high temporal resolution.

Gating

Technique used to reduce blurring of images (also called motion artifact) from patient movements. Acquiring images are timed, or "gated," to the item of motion such as an electrocardiogram tracing, or the breathing movements of the diaphragm.

Signal-to-Noise Ratio

Regardless of the type of imaging modality or its properties, if the image is thought to convey the clinical information that is required or expected, its quality or "signal" is thought to be adequate. A noisy image means that random perturbations in the image are

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_252,

Figure 252.1
Example of an image with poor contrast resolution. The fog makes it difficult to distinguish black from white

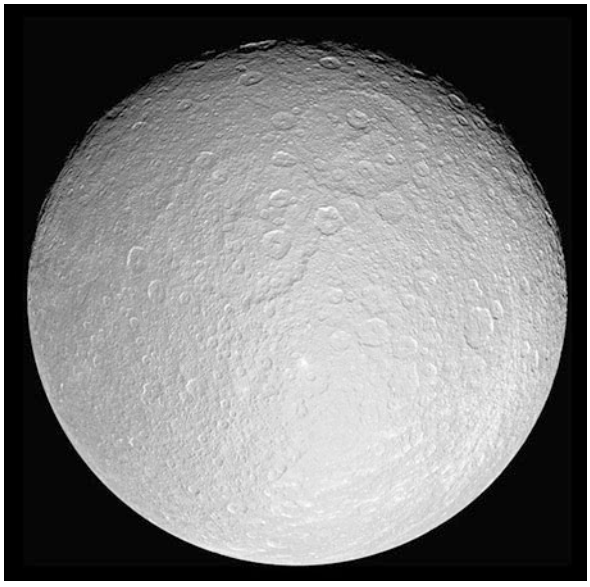


Figure 252.2
Example of an image with high-contrast resolution. The entire photograph is mostly black and white, with few grays

introduced, which can adversely affect the ability to use the images for clinical purposes. Such noise is the same as the static that can be seen on an analog television set (*Fig. 252.5*).

Overview of Modalities

Chest Radiography

The most venerable of noninvasive modalities: a chest radiograph is a 2-dimensional projection of all the structures of the thorax. Contrast is determined by the relative density of tissues, which allows one to identify various structures on a radiograph. Tissues such as bone absorb more of the x-ray energy than less dense tissues such as skin and lungs. Gross anatomic landmarks are readily identified and include the location of the cardiac apex, the sidedness of the aortic arch relative to the trachea, and the relative sizes of the cardiac chambers.

Compared to other noninvasive imaging modalities, when assessing cardiac structures and great vessels, the radiograph provides relatively few anatomic details. Nevertheless, it can provide important clues that would suggest the presence of significant structural heart disease. Vascular congestion and an enlarged heart can suggest left to right shunting such as an atrial septal defect. A cyanotic neonate with respiratory distress and a small heart silhouette can indicate total anomalous pulmonary venous connections. Prominent contours of the cardiac silhouette can also suggest pathologic conditions. If the silhouette bulges to the patient's right, for example, this finding can suggest right atrial enlargement.

Figure 252.3
Example of good (Fig. 252.3) versus poor (Fig. 252.4) spatial resolution. Notice how the coarse pixels of Fig. 252.4 prevent the ability to identify individual bricks of the tower

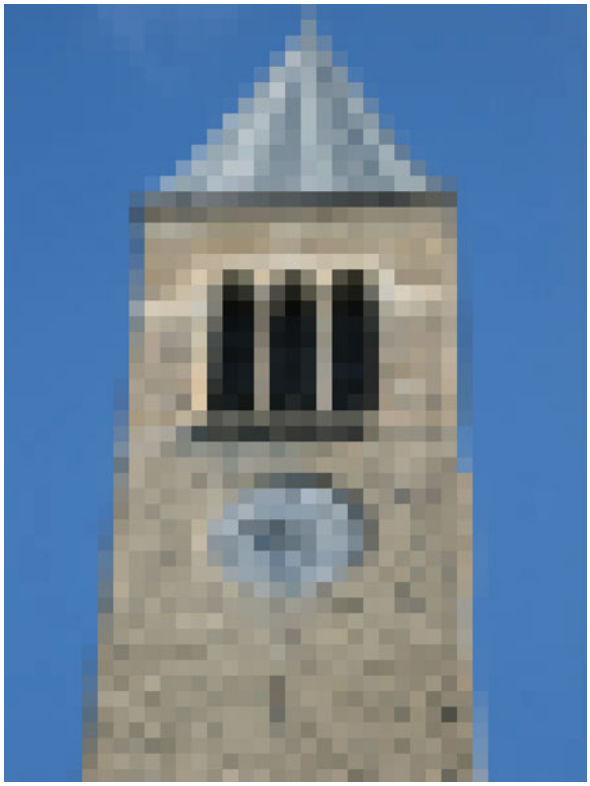


Figure 252.4

The chest radiograph's usefulness in accurately diagnosing or reliably excluding significant cardiac disease has been questioned. For example, the presence or absence of cardiomegaly by radiography has been used as a means to screen for congenital heart disease. In a series of pediatric ambulatory patients, Satou et al. determined the chest radiograph's ability to detect heart disease via cardiomegaly that yielded a high negative predictive value, but with a low positive predictive value. Because of the poor predictive value of chest radiography, in our practice, we do not routinely use radiography in ambulatory patients who are referred to rule out congenital heart disease.

Despite these limitations, radiography's nearly ubiquitous presence and quick acquisition make it an appropriate initial step to evaluate patients. This is especially pertinent when other modalities are not immediately available, or if the patient is critically ill.

Advantages of chest radiography:

- Easily accessible and widely available
- Provides a means to evaluate the cardiac silhouette and lung fields; helpful tool to evaluate for the presence of large vascular or intracardiac shunts
- Images are obtained rapidly

Disadvantages:

- Cannot rule out all congenital heart diseases
- Intracardiac anatomy such as valves and chambers cannot be delineated
- Ionizing radiation is used, though the dose is very small

Echocardiography

Echocardiography, also known as cardiac ultrasound, is the cornerstone of noninvasive cardiac imaging. In clinical pediatrics, a handheld transducer creates sound waves at a frequency that can range between 3 and 12 MHz,

Figure 252.5
Example of a noisy image. If there is more noise in the form of static, the tower would be more difficult to identify

which is well above the ability of human perception. After these inaudible sound waves propagate through the chest to the imaging area of interest, the sound waves reflect off the structure, creating an echo. The reflected sound waves are received by the handheld probe and the signals are digitally processed, yielding a corresponding picture.

While transthoracic echocardiography (TTE) is the most common means to evaluate the pediatric heart, other means of ultrasound imaging – some invasive – are available but are beyond the scope of this chapter. Such examples include intracardiac echocardiography which uses a special catheter-like transducer system, and intravascular ultrasound imaging. Fetal echocardiography is detailed in Chapter xx.

Given its ability to evaluate both anatomy and physiology, echocardiography is the most commonly used modality to diagnose congenital and acquired heart disease. In addition, serial evaluation is useful to follow patients with noncardiac diseases that may have an impact on the heart, such as systemic or pulmonary hypertension. Echocardiography may also be indicated in children with thromboembolic events, indwelling catheters and sepsis, or superior vena cava syndrome. Indications are outlined in ❯ *Table 252.1*. Pallor, acrocyanosis, and chest pain unrelated to exercise are not indications for echocardiography since cardiac pathology is rarely associated with these conditions.

Within echocardiography, several fundamental techniques exist that delineate both anatomy and physiology.

2-Dimensional Echocardiography

Using a variety of commercially available transducers and hardware, echocardiography can create a moving picture that helps evaluate cardiac structures and their function. Rapidly moving structures such as valve leaflet motion can be readily distinguished and carefully defined. Among the different means to image the heart, echocardiography usually has the best temporal resolution. For example, heart motion can be visualized at frame rates up to 200 Hz. To place this value in perspective, this is a temporal resolution that is up to ten times as rapid as a standard movie that plays at 24 Hz. This temporal resolution advantage diminishes in older, larger patients.

Doppler Echocardiography

When imaging moving objects, such as blood flowing through valves, reflected ultrasound can change frequencies, which is known as a Doppler shift. These changes remain inaudible, but are detectable by ultrasound machines, and can be used to evaluate for normal or pathologic flow through the heart.

Spectral Doppler displays the Doppler shift and intensity of ultrasound reflections as a function of time (❯ *Fig. 252.6*); in the clinical setting, this Doppler shift is used to measure velocities.

Color Doppler (❯ *Fig. 252.7*) evaluates these flows and can display a color-coded map to show what objects are moving toward the transducer (red) or away from the transducer (blue). Despite the colors that are displayed, Doppler cannot determine if the blood is oxygenated or deoxygenated.

Tissue Doppler focuses on the motion of the heart tissue rather than the blood, and is used to assess both systolic and diastolic functions.

While echocardiography cannot directly measure pressures within the heart and vessels, pressures can be

Tables 252.1
Indications for echocardiography, adapted from Lai et al

Signs or symptoms
• Central cyanosis*
• Hypoxemia
• Failure to thrive
• Exercise induced chest pain or syncope*
• Respiratory distress
• Murmurs
• Congestive heart failure
• Abnormal arterial pulses
• Cardiomegaly
• Arrhythmias
Indications even in the absence of cardiovascular signs or symptoms
• Certain syndromes known to be associated with congenital heart disease (For example: Turner syndrome, Down syndrome)
• Family history of inherited heart disease (e.g., hypertrophic cardiomyopathy)
• Extracardiac abnormalities that are known to be associated with congenital heart disease (e.g., congenital diaphragmatic hernia)
Abnormalities on other tests
• Fetal echocardiography or obstetric ultrasound
• Chest radiograph
• Electrocardiogram
• Chromosomal
Acquired heart diseases and noncardiac diseases
• Kawasaki disease
• Infective endocarditis
• Cardiomyopathies
• Rheumatic fever
• Systemic lupus erythematosus
• Myocarditis and pericarditis
• Human immunodeficiency virus (HIV) infection
• Exposure to cardiotoxic drugs
• Systemic hypertension
• Pulmonary hypertension

*Echocardiography is not recommended as the initial diagnostic test for pallor, acrocyanosis, or syncope not related with exercise

estimated based on Doppler-derived measurements of blood flow velocities. Using a simplified equation derived from Bernoulli, pressure (mmHg) = $4v^2$, where v is the velocity in m/s. While there are limitations to this derivation, it can be used to estimate pressure differences within the heart, especially in valve stenosis or in patients with tricuspid regurgitation.

In a commonly used indication, the previous equation is useful to determine if pulmonary hypertension is present. For example, if the tricuspid regurgitation jet velocity is measured to be 5 m/s, the predicted right ventricular systolic pressure will be at least 100 mmHg (*Fig. 252.8*). As long as there is no pulmonary stenosis which can confound the measurement, the pulmonary artery pressure will be as high as the right ventricular pressure.

3-Dimensional Echocardiography

Modern computing and processor speeds have advanced enough to the point that structures of the heart can be rendered in 3-dimensions, mitigating the need to mentally reconstruct 2-dimensional images. Valve anatomy can be shown to surgeons from their perspective, which is more challenging to perform with 2D alone. Several authors have advocated its use in imaging complex congenital heart disease. Ventricular volumes, especially of the geometrically complex right ventricle, can be more accurately measured than with 2D echocardiography.

Several limitations exist for echocardiography. The field of view for 2D ultrasound is relatively narrow, which prevents the ability to view all structures from a single location. When viewed on a display screen, echocardiogram images have a fan-shaped configuration, which reflects this narrow field. Because of this limitation, ultrasound requires multiple acoustic "windows" to examine the heart and to perform a complete evaluation (*Fig. 252.9*). Areas that have markedly different densities from their surrounding tissues, such as the interface between the lungs and the heart, prevent ultrasound from penetrating, which leads to inadequate ultrasound pictures. The same inadequacy exists in very large or obese patients, where transthoracic images can be poor. Compared to cardiac MRI, tissue contrast is relatively low in all types of echocardiography, making it difficult to distinguish areas of muscle from fat or from fibrous tissue. For example, when viewing intracardiac masses, it may be difficult to determine if the lesion is a thrombus or a tumor.

To circumvent some of the imaging limitations of transthoracic echocardiography, transesophageal echocardiography (TEE) can be employed. This technique utilizes a specialized ultrasound probe that can be

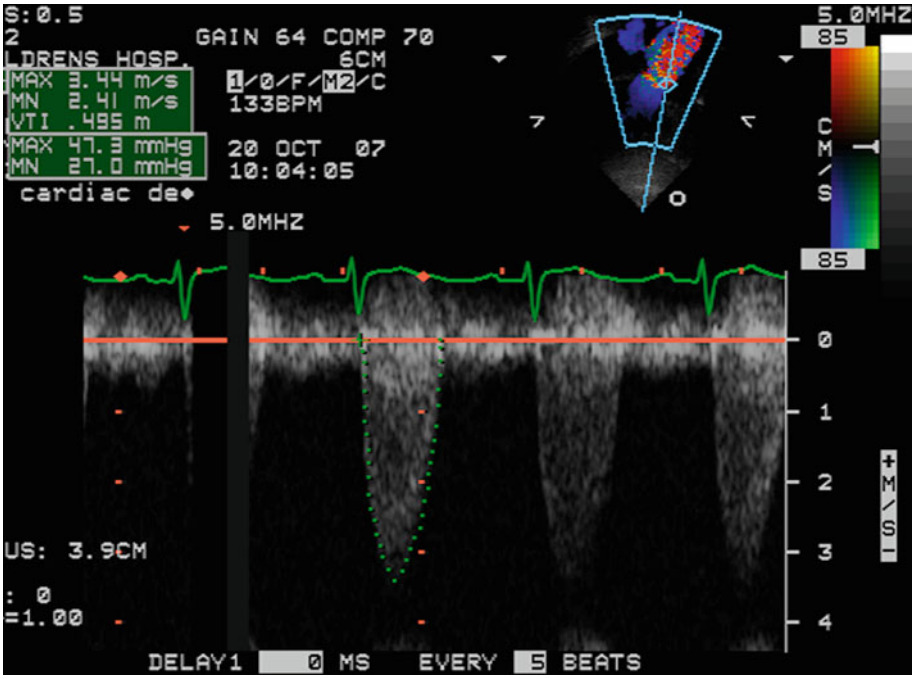


Figure 252.6
Spectral Doppler recording blood flow across the pulmonary valve. The x-axis represents time. The y-axis is velocity of blood flow in meters per second. In this patient, velocities across the valve are over 3 m/s consistent with pulmonary stenosis

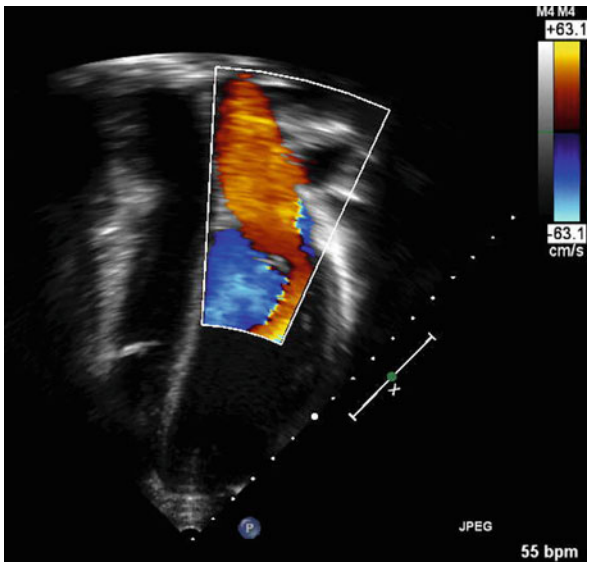


Figure 252.7
Color Doppler image of blood across the mitral valve. Typically, red and blue colors are used to represent flow (shown as gray patterns within the inner box)

passed through the mouth along the esophagus. Since the mid-esophagus is directly behind the heart, images of the heart are unobstructed. TEE still has its own drawbacks; it is the most noxious of the "noninvasive" imaging techniques and requires sedation. Superior mediastinal structures are not well seen, and TEE is contraindicated in esophageal diseases such as tracheoesophageal fistulas.

Advantages of echocardiography:

- Excellent temporal and spatial resolution
- No ionizing radiation
- Does not require confining patient positions
- Well studied and well evaluated. After radiography, it is the oldest and most established of all cardiac imaging techniques
- Can aid in the assessment of physiology and blood flow

Disadvantages:

- Small field of view, requiring multiple angles of imaging.
- Relatively less contrast resolution and signal-to-noise ratio.
- Detailed evaluation of cardiac structures can be hampered in active or morbidly obese patients.

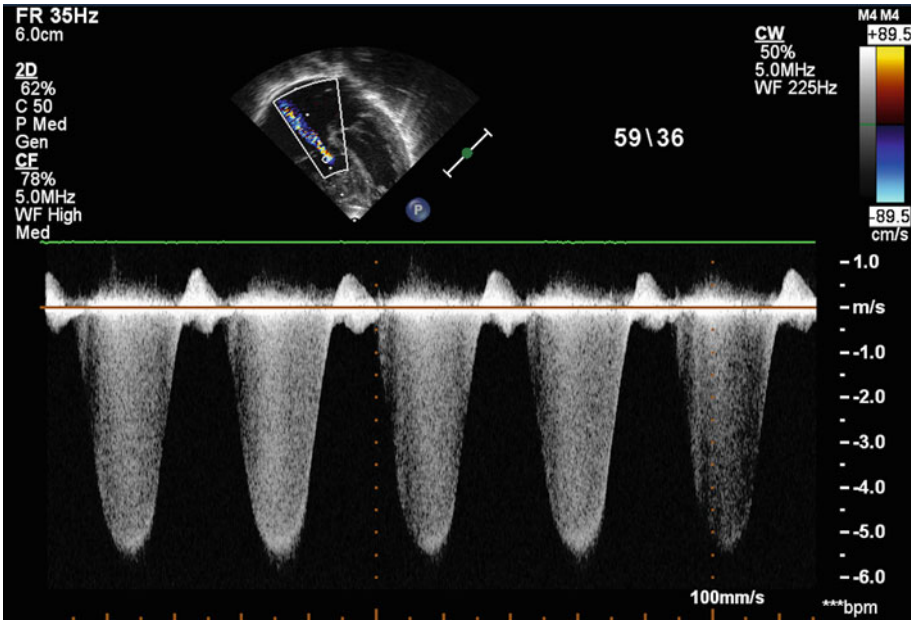


Figure 252.8
Determination of right ventricular pressure based on the tricuspid regurgitation jet. In this example, the velocity exceeds 5 m/s, which means the right ventricular systolic pressure is 100 mmHg

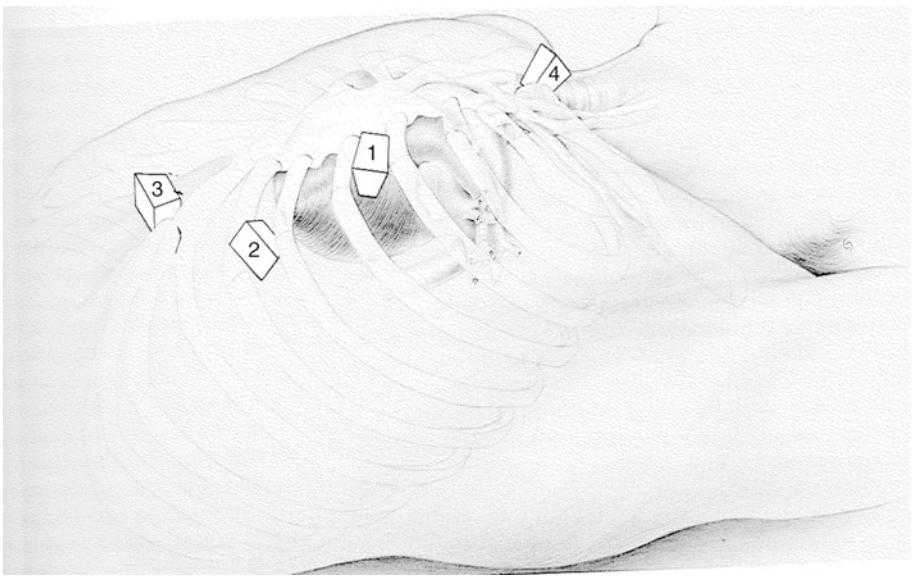


Figure 252.9
Acoustic windows for echocardiography, which shows where the ultrasound probe must be placed. 1 = parasternal, 2 = apical, 3 = subcostal, 4 = suprasternal. Due to ultrasound's small field of view, a full echocardiogram must utilize all windows so that the heart may be imaged from different angles (Figure reprinted with permission. From Sinder, *Echocardiography in Pediatric Heart Disease*, page 25, ©1997 Elsevier)

- Imaging of distal coronary artery anatomy is limited.
- Thoracic great arteries and veins are more difficult to view in larger patients.

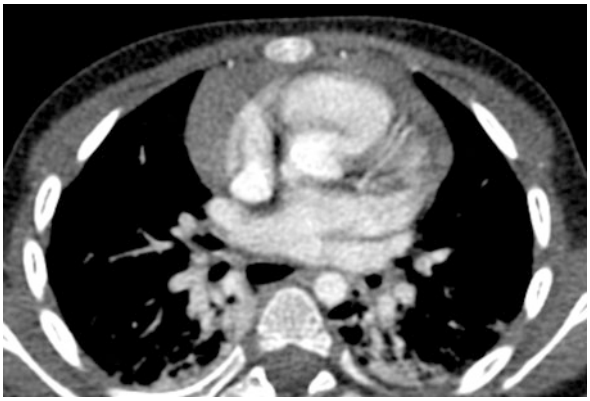
Cardiac CT and CT Angiography

The adaptation of CT imaging in pediatrics has been fostered by rapid advances in hardware and software. Multidetector rows allow multiple simultaneous image acquisitions of the body. Some of the most recently developed scanners offer dual energy/x-ray sources which increases the speed and efficiency of image generation. Accompanied by strategies such as helical scanning, which allows the patient to literally glide through the scanner without staccato-like stops and starts, CT can produce high-quality and detailed images within seconds, which is a distinct advantage over the longer scan times of MRI and echocardiography. Electron beam CT uses a different means to create and direct x-ray energy; technical issues limit its clinical use and are not well documented in pediatrics. For interested readers, a more comprehensive review of cardiac CT advances is detailed by Flohr et al.

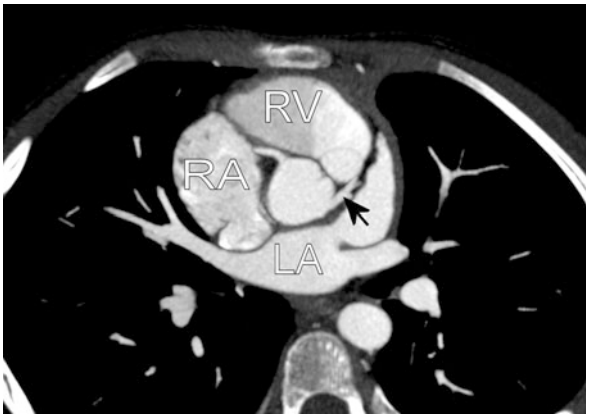
The spatial resolution of CT can be in the submilimeter range, which is finer than MRI or adult echocardiography. In larger pediatric patients, spatial resolution will be superior to echocardiography. This advantage over echocardiography is negated in infants and small children due to their smaller sizes and higher heart rates. CT has the additional advantage of evaluating lung parenchyma and airways. In patients with a suspicion for vascular rings, such as those who present with stridor or dysphagia, CT angiography of the chest can help confirm the diagnosis.

Although scan times are short and usually require only seconds for a complete evaluation, CT images of the heart may be blurred due to a combination of cardiac and respiratory motions. A restless patient would also create artifact if he or she cannot lie still in the scanner. Formally termed "motion artifacts," these problems manifest especially in pediatric patients, whose heart rates are faster than adults. Sometimes sedation is required, although it is used less frequently than with MRI.

To help reduce motion artifacts, a method called ECG gating can be employed. The end of diastole is a period of time within the cardiac cycle when the heart lies very still. On an electrocardiogram, this coincides with the time just before the QRS complex. When ECG gating is employed, the CT scanner obtains images only when cardiac motion has been minimized, producing sharp images of the heart itself (◉ *Figs. 252.10* and ◉ *252.11*). This technique would



◉ **Figure 252.10**
CT of the heart without gating. Notice how the intracardiac anatomy is blurred and difficult to discern. Though not shown here, imaging of the lung and great vessels would not be compromised by the lack of gating (Courtesy of Dr. Randy Otto)



◉ **Figure 252.11**
ECG-gated CT coronary angiography of the same patient. Compared to non-gated and blurry image, this image is crisper and without motion artifacts. The *dark arrow* shows the left coronary artery. RV = Right ventricle, RA = Right atrium, LA = left atrium (Courtesy of Dr. Randy Otto)

be required only if detailed CT evaluation of the coronary arteries or intracardiac structures is required. One disadvantage is that use of gating can increase the total dose of ionizing radiation. In addition, intravenous contrast is necessary to visualize vascular and intracardiac structures, but can be contraindicated in patients with renal insufficiency.

Despite attempts to minimize motion through ECG gating, an ongoing issue with pediatric imaging remains

within the CT hardware itself. The ring that houses and contains the x-ray energy source, and the detectors is called the gantry. In order to collect image information, this gantry must rotate in a 360° circle around the patient; one complete revolution can occur in as little as 0.3 s, but is not rapid enough to effectively obtain images when heart rates are over 65 beats per minute. While increasing gantry speed is theoretically possible, the sheer mass of the hardware within the gantry – which weighs over 1,000 kg – limits this possibility. While heart rate limitations are being overcome with newer, dual-source CT scanners, this technology is still being evaluated for pediatric cardiac applications.

CT imaging is also challenged by the delicate balance of two conflicting needs: minimizing radiation dose while maintaining adequate image quality. Lower doses of radiation can be achieved, but at the cost of increased image noise and a reduction in signal-to-noise ratio. Concerns of the long-term risks associated with ionizing radiation exposure have been raised, but there are constant efforts to reduce the total dose required to obtain a clinically meaningful cardiac CT.

Advantages of CT:

- Very rapid image acquisition, with a scan duration second only to chest radiography
- Wide field of view
- Excellent spatial resolution
- Allows visualization of airways and lung parenchyma
- Allows visualization of vascular structures within the entire thorax when intravenous contrast is used
- Distal coronary arteries can be visualized

Disadvantages:

- Ionizing radiation must be considered
- Poor temporal resolution
- Evaluation of intracardiac anatomy requires incremental doses of radiation
- Cannot reliably evaluate physiology, blood flow, or shunts
- Heart rates in a pediatric patient may limit image quality
- Renal insufficiency is a relative contraindication for intravenous contrast
- More costly study

Cardiac MRI and MR Angiography

Using gated fast imaging techniques, cardiac magnetic resonance imaging is one of the newest noninvasive imaging modalities, and provides the clinician with an additional tool for cardiac assessment. Images are created by taking advantage of electromagnetic properties of human tissue at an atomic level. A high-strength magnetic field, tens of thousands times the strength of the earth's magnetic field, aligns hydrogen atoms so that they are all parallel to each other. Using a precisely directed and carefully timed combination of radiofrequency pulses which create tiny alterations in the MRI's magnetic field, radiofrequency signals or "echoes" return from the heart, are collected by the scanner, and an image is constructed.

Cardiac MRI complements the information provided by more accessible noninvasive modalities such as radiography and echocardiography. It has a wide field of view, allowing one to view structures within the entire thorax and sometimes even the whole body. The temporal resolution is fine enough that – similar to echocardiography – the heart can be visualized in motion. Clinicians have the ability to evaluate ventricular function and flow in a quantitative as well as qualitative fashion. With this combination of abilities, both anatomy and physiology can be determined in a CMR examination.

One particular advantage of MRI over other modalities is its excellent tissue contrast. Even without the use of intravascular contrast agents such as gadolinium, tissues such as fat, muscle, and tendons can be readily distinguished. Intracardiac anatomy is well defined. Heart rates do not limit MRI imaging the same way they would for cardiac CT.

There are multiple applications of cardiac MRI in clinical pediatrics. For cardiac tumors, various sequences can be used to noninvasively predict the type of tumor to the point that MRI can be considered the first-line noninvasive study to determine tumor tissue characteristics. With gadolinium contrast agents, 3-dimensional reconstructions of the heart chambers and thoracic vasculature can be created (Fig. 252.12). The same contrast can help detect cardiac inflammation due to myocarditis, and scarring from infarctions, through a process called delayed enhancement.

The intracellular space of viable tissue "clears" gadolinium from the region while inflamed muscle tissue or scars tend to retain contrast for a longer period of time. Such retention leads to delayed enhancement of the tissue and may become a reliable prognostic indicator in congenital heart disease. In repaired tetralogy of Fallot, for example, presence of increased scarring – as manifested by delayed enhancement – has been associated with adverse outcomes in the adult population. Cardiac MRI has also been proposed as a screen for right ventricular abnormalities such as arrhythmogenic

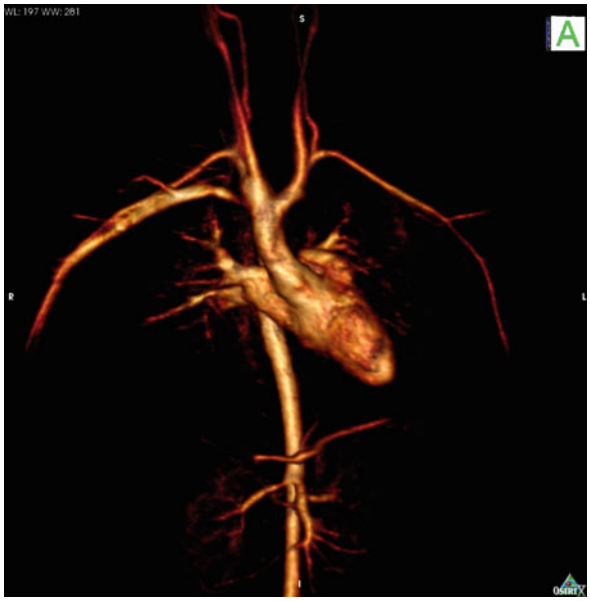


Figure 252.12
MR angiogram of a double aortic arch, using 3D reconstruction techniques (Courtesy of Dr. Randy Otto)

right ventricular dysplasia. Though gadolinium contrast had been considered to be safe in patients with renal insufficiency, such thoughts have changed. Nephrogenic systemic fibrosis is a disorder that has recently been associated in renal failure patients who received higher doses of gadolinium and has led to more cautious use in this population.

While many diagnostic benefits exist with MRI, tradeoffs exist. Not all MRI centers will have the capability to image pediatric patients. As opposed to echocardiography where smaller patients will have better image quality (for both resolution and signal quality), the signal-to-noise ratio in infants and small children is typically worse with MRI. One additional drawback is the length of the study. The duration of time required for a full cardiac MRI can range from 30 min to over 1 h. Because a patient must lie still for the entire study, sedation is usually required for infants and young children. Finally, cardiac MRI may be a suboptimal test for the critically ill patient. The small space where the patient lies, coupled with a longer scan time can challenge assessment, monitoring, and medical intervention.

Advantages of cardiac MRI:

- No ionizing radiation
- Excellent contrast resolution, even without the use of intravenous agents
- Very good spatial resolution
- Allows detailed qualitative and quantitative evaluation of intracardiac anatomy, including proximal coronary arteries
- Wide field of view, allowing imaging of adult and obese patients
- Can evaluate and quantitate the physiology of blood flow and shunts
- Can noninvasively evaluate tissue characteristics

Disadvantages of cardiac MRI:

- Requires a regular cardiac rhythm. Arrhythmias can create artifacts.
- Loud environment. Potentially claustrophobic for some individuals.
- Long scan durations, ranging from 30 min to over 1 h.
- Distal coronary artery anatomy is difficult to see.
- May require sedation or anesthesia in smaller patients.
- Ferromagnetic materials such as pacemakers or some metal implants are contraindications for MRI.
- Small intracardiac shunts may not always be detectable.
- Not as readily available.
- More costly study.

Guidelines for Incorporating Noninvasive Cardiac Imaging

The relative strengths and weaknesses of each modality are outlined in *Table 252.2*. In a patient with known or suspected cardiac pathology, consultation with a specialist in pediatric cardiology should always be considered. If such expertise is not readily accessible, the following are suggestions to help guide the clinician. When there is an initial suspicion of cardiac pathology in the history or physical examination, electrocardiography, chest radiography, and echocardiography are first-line choices for evaluation.

In addition to the advantages and disadvantages outlined above, local practices and availability of expertise will modify the next appropriate choices. Transesophageal echocardiography is an option if transthoracic echocardiography is unable to visualize structures of interest. If coronary artery anatomy is a concern, cardiac catheterization can be considered. If only anatomic and not hemodynamic information is needed, alternatives to catheterization include cardiac CT or CT angiography. This is especially helpful if evaluation of the airways or lung parenchyma is required. Cardiac MRI is most useful in patients where CT intravenous contrast is contraindicated, if the clinician wants to

Table 252.2

The relative strengths and weaknesses of each modality are compared; "++++" indicates a relative strength, while "+" suggests a feature that is less useful

	Echocardiography	MRI	CT	Chest radiography
Spatial resolution	+++ ++++(infants and small children)	++	+++	++++
Temporal resolution	++++	+++	+	None
Contrast resolution	++	++++	+++	++
Duration of test	Medium: 20–45 min	Long: 30 min to over 1 h	Short: seconds to minutes	Seconds
Airway and lung parenchyma visualization	No	Large airways only	++++	+++
Physiology/ Blood flow	++++	+++	+	+
Pericardium visualization	++	++++	+++	+
Field of view	++	++++	++++	+++
Cost	Moderate	Highest	High	Low
Sedation	Infrequent/ideally needed in toddlers	Usually in infants/young children	Infrequent	Never
Ionizing radiation	No	No	Yes	Yes

avoid ionizing radiation, or if echocardiography could not determine the relevant anatomy or physiology. If required, quantitative assessment of intracardiac shunts, vasculature, or chamber volumes can be determined by MRI.

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253 Interventional Cardiology

Troy A. Johnston

Introduction

The field of pediatric interventional cardiology has evolved rapidly over the last several decades. Cardiac catheterization, originally a diagnostic modality, is now primarily therapeutic. The first intervention, balloon atrial septostomy, was described by Rashkind and Miller in 1966. Since then, innovative thinking paired with technological advances has exponentially increased the number of catheterization therapies with each decade.

Interventional therapy is now an acceptable alternate treatment for many forms of congenital heart disease. Elegant devices are available to close atrial septal defects, muscular ventricular septal defects, and patent ductus arteriosus. Balloon angioplasty with and without stenting is used to treat pulmonary arterial stenosis and coarctation of the aorta. More recent developments include the percutaneous placement of semilunar valves, fetal interventions, and hybrid procedures wherein the interventional cardiologist works with the pediatric cardiac surgeon simultaneously.

The increased complexity and number of interventional techniques require highly specialized equipment and skills. Operators with advanced training coupled with sufficient case volume are key components in achieving acceptable results. Several initiatives are now underway to provide better quantification of outcomes. The use of multicenter studies for investigational therapies and outcome research will continue to improve the therapeutic options for a complex patient population.

Balloon Atrial Septostomy

Balloon atrial septostomy is performed by passing a balloon-tipped catheter through either the superior or inferior vena cava into the left atrium. Fluoroscopic or echocardiographic guidance is used. The catheter is passed from the right into the left atrium usually through a patent foramen ovale. The balloon is then inflated and forcefully pulled into the right atrium. This action tears the atrial septum, increasing the size of the intra-atrial communication.

Balloon atrial septostomy was first described as a palliative measure for infants with transposition of the great arteries. The increased size of the atrial communication allows for improved intracardiac mixing of the systemic and pulmonary venous blood. This increases the systemic arterial saturation. Alternatively, it may be used to relieve atrial septal restriction in other forms of complex congenital heart disease. Infants with hypoplastic left heart syndrome may have an inadequate outlet from the left atrium if the patent foramen ovale is too small. Balloon atrial septostomy can be used to palliate these infants until more definitive enlargement of the atrial communication is carried out at the time of surgery.

Balloon atrial septostomy is a safe and effective procedure when performed by experienced operators. Complications, although rare, include avulsion of the pulmonary veins or inferior vena cava and injury to atrioventricular valves.

Patients outside the neonatal period have a thicker atrial septum that is more resistant to balloon atrial septostomy. Standard balloon atrial septostomy is usually inadequate. Often there is no communication between the atria. Access to the left atrium may require transseptal needle puncture. This technique uses a long needle positioned from the femoral vein. After successful puncture, the communication can be enlarged using alternative techniques such as blade septostomy, static balloon dilation, or implantation of balloon-expandable stents. Indications for atrial septal defect creation or enlargement in an older patient include left atrial outlet obstruction or patients with severe pulmonary hypertension. The right-to-left shunt can improve cardiac output at the expense of decreased systemic arterial saturation. Risks to the more complex techniques include cardiac perforation, stent embolization, and increased risk of air embolism.

Balloon Valvuloplasty

The utilization of static balloon dilation to manage valve stenosis began in the early 1980s. Initially it was utilized to treat pulmonary valve stenosis and subsequently aortic valve stenosis. Mitral valvuloplasty for rheumatic mitral

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stenosis has proven effective. It also may have utility in the management of select patients with congenital mitral and tricuspid valve stenosis.

After hemodynamic measurements are obtained, the stenotic valve is crossed with a guide wire. The pulmonary valve is crossed in a prograde fashion. The aortic valve may be crossed retrograde from the aortic root, or prograde utilizing an existing atrial communication or performing a transseptal puncture. After gaining a stable wire position, a balloon-tipped catheter is advanced over the wire and positioned across the stenotic valve. The diameter of the balloon is selected as a ratio of the valve annulus. The ratio is usually less than 100% for aortic valvuloplasty, while a larger balloon to annulus ratio can be used for the pulmonary valve. The balloon is inflated with dilute contrast. When successful, the balloon tears the valve leaflets improving the valve orifice. A successful dilation usually increases the degree of valve insufficiency to some degree. This is assessed, along with hemodynamics after dilation.

Multiple studies have shown the safety and efficacy of balloon valvuloplasty with results similar to surgical intervention. The major long-term complication is clinically significant valve regurgitation. Primarily this has been a concern for the aortic valve. The use of smaller balloons for aortic valvuloplasty has been associated with less insufficiency. Other complications include annulus disruption, vascular injury, and arrhythmias. Embolization of either air or thrombus is a serious complication of dilation of the left-sided valves. Valvuloplasty of either semilunar valve may be associated with damage to the associated atrioventricular valve. Careful attention to wire placement and balloon position minimizes the risk of inadvertent tricuspid or mitral valve regurgitation.

Balloon Angioplasty and Stent Placement

Balloon dilation is most often utilized to treat congenital or postoperative pulmonary artery stenosis. It is also a treatment option for coarctation of the aorta and less frequently venous obstruction. Initially a hemodynamic and angiographic evaluation is performed. The site to be treated is crossed with a catheter and a stiff guide wire is positioned with the tip distal to the obstruction. The stiff wire is then used to position a balloon-tipped catheter in the vessel so that the tubular balloon straddles the obstruction. Static balloon dilation is then carried out. The balloon inflation pressure required is often much higher than that for valvuloplasty. Effective dilation is associated with disruption of the intima or even the media of the vessel wall. After dilation, the balloon catheter is removed and repeat hemodynamic and angiographic assessments are performed.

Vascular stenosis can be very resistant to balloon dilation. If a stenotic vessel is not dilated sufficiently during balloon inflation, favorable results may be achieved with the use of cutting balloons. These balloons have primarily been used for distal pulmonary artery stenosis. The balloon has multiple small metal blades attached to the outside of the balloon parallel to the balloon shaft which serve to circumferentially pierce the intimal layer of the vessel and thus relieve the obstructive process.

Endovascular stents are effective to treat lesions that are very compliant (*Fig. 253.1*). The vessel can be stretched to an acceptable diameter during balloon angioplasty, but recoils as soon as the balloon is deflated. The rigid metal wire mesh stent provides structural support allowing the vessel to stay open. The stents are delivered on balloon catheters and used to treat pulmonary, aortic, and venous stenosis. They are best utilized in children whose vessels are large enough to accommodate stents with the capacity for enlargement to sizes appropriate for adults. The large model stents can be serially dilated to account for somatic growth (*Fig. 253.1*).

Balloon angioplasty with or without stent implantation can be a safe and effective therapy for vascular stenosis. Complications include intimal disruption, aneurysm formation, and vessel rupture. Even temporary occlusion of blood flow can lead to hemodynamic deterioration in fragile patients. Stents are often more technically challenging to deploy. They carry the additional risks of embolization and fracture.

Patent Ductus Arteriosus Closure

Outside the neonatal period, transcatheter closure of the patent ductus arteriosus has replaced surgical intervention. Closure using stainless steel coils was first described in the early 1990s. The technique involves positioning a coil, now usually platinum, with a portion in the pulmonary artery and the majority within the ductus arteriosus. The larger the ductus the more coils are required for complete closure. Alternative devices have been developed that have made closure of larger ducts feasible. The Amplatzer Duct Occluder is a wire mesh device that is well suited for the larger ductus. It is usually deployed using femoral venous access. It is attached to a delivery cable that allows for device positioning and assessment prior to release. It is relatively easy to reposition or even remove the device and replace with a more

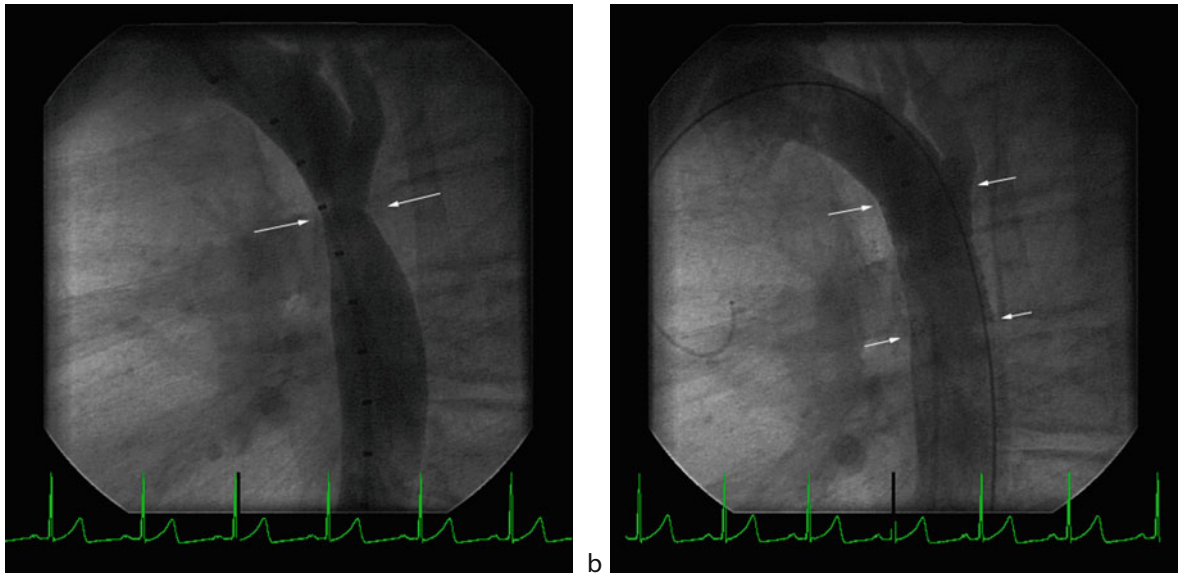

Figure 253.1
(a) Lateral projection of an aortic coarctation in a patient who underwent surgical repair as a neonate. The arrows mark the narrowest diameter, just distal to the origin of the left subclavian artery. (b) Lateral projection from the same patient after deployment of an intravascular stent. The superior and inferior margins of the stent are marked by *arrows*. The narrowest diameter is significantly improved

appropriate sized device. This greatly improves the safety and efficacy of the procedure.

The availability of multiple closure devices has limited surgical intervention to very small children, particularly premature infants. Complications from device closure include device migration, air or thrombus embolization, and infection.

Atrial Septal Defect Closure

Transcatheter device closure has become a safe and effective alternative to surgery for the majority of patients with secundum atrial septal defects. Multiple devices have been developed since the first transcatheter occlusion in the mid-1970s. Currently, the Amplatzer septal occluder and the Helex septal occluder are the only devices with FDA approval for atrial septal defect closure. Both devices consist of wire frames with two disks joined in the center. The devices are positioned with one disk in the left atrium and one in the right atrium. The disks are larger than the defect, which anchors the device in position across the defect. After appropriate echocardiographic imaging of the atrial septum, the defect is usually further sized by placing a compliant balloon in the defect and inflating until there is no flow seen through the defect. After sizing, the device is delivered through a long sheath positioned in the left atrium. The left side of the device is deployed in the left atrium and then the device is pulled into contact with the atrial septum. The right disk is then deployed by retracting the long sheath. If performed properly, the device is seated across the atrial septum with one disk on either side of the septum. If the device is in appropriate position, it is then released by unscrewing the delivery cable (*Fig. 253.2*).

Successful device placement can be achieved in centrally located defects that are not overly large. Devices are placed with echocardiographic and fluoroscopic guidance. Echocardiography allows for visualization of the device and its relation to other intracardiac structures. If the defect location is not central or the defect is very large, the device may interfere with mitral valve function, or pulmonary or systemic venous return. Both devices are designed so that they can be positioned within the heart prior to release from the delivery system. If echocardiography reveals any potential problems, the device can be removed by drawing the device back into the delivery catheter.

Appropriate device size selection is important to reduce the risk of device embolization. An inadequately sized device may embolize to the systemic or pulmonary

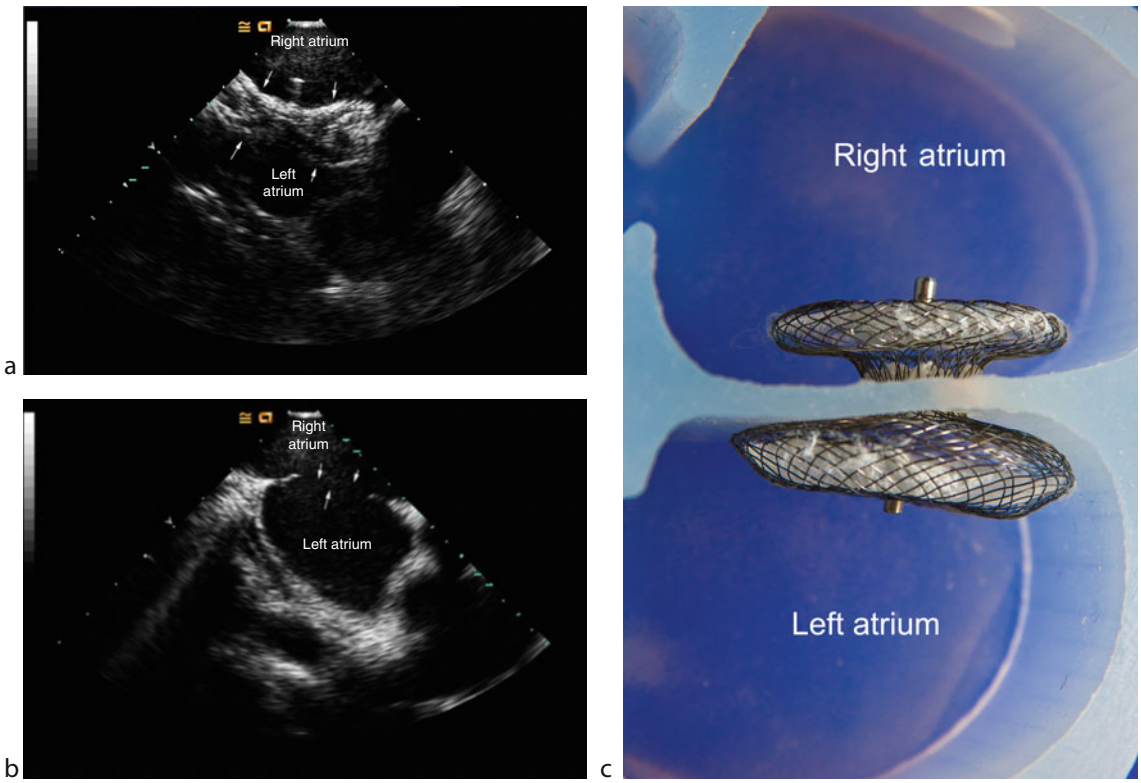

Figure 253.2
(a) Intracardiac echocardiographic image of a large atrial septal defect. *Arrows* mark the secundum atrial septal defect. (b) Intracardiac echocardiographic image of an Ampltzer septal occluder (*arrows*) after deployment. The right atrial disk is slightly smaller than the left atrial disk. (c) Amplatzer septal occluder deployed in a heart model. This image corresponds to the echocardiographic image in *Fig. 253.1b*

circulation. Embolization, if not immediate, occurs within the first hours after placement. Often embolized devices are retrieved percutaneously; however, surgical removal maybe required. Additional complications of percutaneous atrial septal defect closure include air or thrombus embolism, infection, stroke, and arrhythmias. A 6-month course of aspirin at an antiplatelet dose is used to reduce the risk of thrombus formation.

Ventricular Septal Device Closure

Defects in the muscular portion of the ventricular septum can be closed using transcatheter techniques. Currently, the Amplatzer muscular occluder and the Cardioseal are approved for this use in the United States. The Amplatzer device is a woven mesh device that has two disks separated by a wider waist than the Amplatzer atrial septal device. The Cardioseal was originally designed for atrial septal defect closure and consists of two wire frame–supported disks joined in the center. Both devices are deployed so that one disk is on the left side of the ventricular septum and the other on the right. Appropriate device placement requires that the device not interfere with atrioventricular or semilunar valve function. Device placement is usually accomplished using venous access. The long sheath is placed from the right ventricle into the left and therefore the left disk of the device is deployed first followed by the right. A combination of echocardiographic and fluoroscopic guidance is usually used during closure.

Although similar to atrial septal defect closure, the need to cross the tricuspid valve with stiff wires and sheaths combined with a more complex catheter course leads to the potential for more hemodynamic instability during this procedure. The occurrence of intraprocedural ventricular tachyarrhythmias and heart block may occur. Complications also include device migration, air or thrombus embolization, and infection.

Percutaneous Pulmonary Valve Replacement

A large number of patients with repaired congenital heart disease, such as tetralogy of Fallot, will have surgical placement of a tissue valve in the pulmonary position as a treatment for pulmonary regurgitation. These valves have a limited duration of function with the need for eventual replacement for failure due to progressive regurgitation, stenosis, or a combination of both. Previously, these patients would require multiple surgical valve replacements during their lifetimes (*Fig 253.3*).

Transcutaneous pulmonary valve replacement is now an alternative to surgical intervention in select patients. Currently in the United States, the Melody valve has received FDA approval and the Sapien valve is in clinical trial. The Melody valve consists of a small segment of bovine jugular vein containing a venous valve. The Sapien valve utilizes bovine pericardial tissue to construct a valve. Both valves are attached to the inner surface of a balloon-expandable stent. The apparatus can be compressed onto a balloon catheter that allows introduction through the systemic veins in older children and adults. Both femoral and internal jugular approaches have been used. Although technically challenging, this procedure can be performed safely by an experienced operator. Prior to valve placement the anatomy must be carefully assessed, particularly the landing zone for valve placement. It must not be too large to accommodate the valves, both of which have a limited maximum diameter. Additionally, the relationship of the coronary artery position to the conduit must be assessed. The inflated valve could potentially compress a coronary artery if it is in close proximity.

The short-term results of percutaneous pulmonary valve placement appear favorable. Longer-term data, including freedom from reintervention, is not yet available. Complications of the procedure include vascular rupture and device migration.

Hybrid Procedures

Cooperation between interventional cardiologist and cardiac surgeon to facilitate interventions has led to an increasing number of hybrid procedures. Loosely defined, a hybrid procedure is any one that requires the skill set of the surgeon and the interventional cardiologist. Commonly, the surgeon provides access via a sternotomy

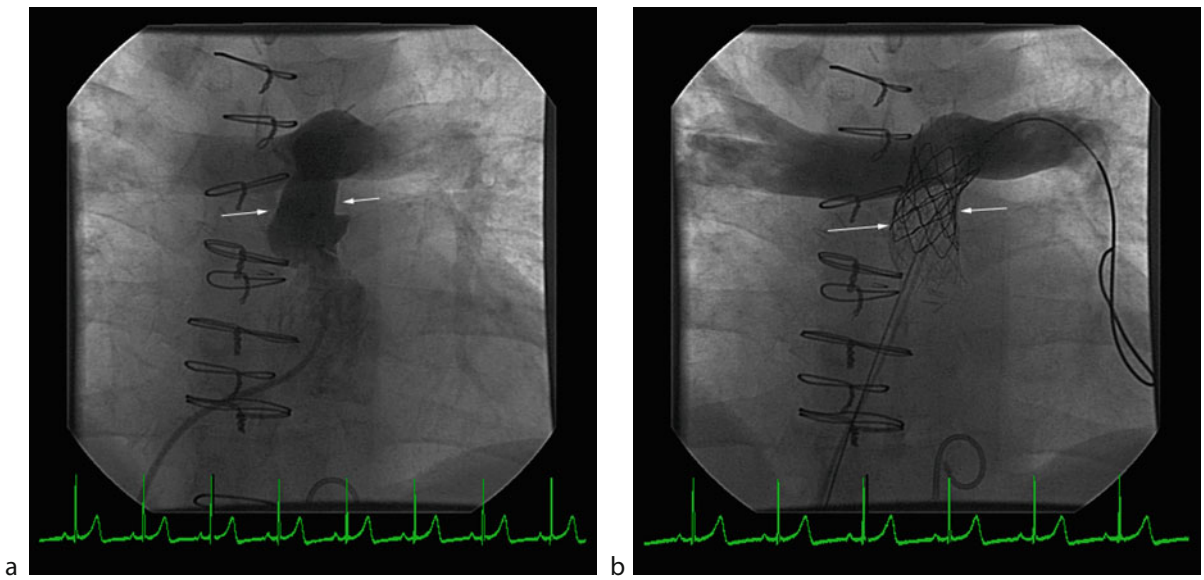

Figure 253.3

(a) Frontal projection of a pulmonary artery angiogram in a patient with tetralogy of Fallot who previously underwent placement of a valved conduit in the pulmonary position. There is stenosis and regurgitaiton of the conduit valve. The mid portion of the conduit is marked by *arrows*. (b) Frontal projection of a pulmonary artery angiogram in the same patient after Melody valve placement. The dark metal struts of the stent (*arrows*) are easily seen. The conduit stenosis is improved and there is no evidence of pulmonary regurgitation

thereby allowing vascular access directly into a vessel or even the heart. Occasionally, percutaneous procedures in small children are difficult or even impossible. By providing direct access through an open chest, the technical challenges inherent to small vessels and complex catheter courses are minimized. One example is perventricular placement of a muscular ventricular closure device. A sternotomy provides direct access to the heart through the free wall of the right ventricle. Needle puncture of the external wall of the right ventricle is used to introduce a wire into the right ventricle through the ventricular septal defect into the left ventricle. The wire is used to introduce a short sheath into the left ventricle through which an appropriate device can be deployed. Transesophageal echocardiographic guidance is used. This technique avoids the need for cardiopulmonary bypass and is an alternative to an often very difficult surgical procedure.

A hybrid approach has also been used as a first stage palliation for patients with hypoplastic left heart syndrome. In this procedure, the interventional cardiologist performs a balloon atrial septostomy providing unobstructed pulmonary venous return. Additionally, the cardiologist stents the patent ductus arteriosus. This provides unobstructed systemic blood flow without the need for prostaglandin infusion. The surgeon places bilateral pulmonary artery bands to prevent pulmonary over circulation. Multiple reports have shown that this technique can be performed safely. In most centers, it has not replaced the traditional surgical approach to patients with hypoplastic left heart syndrome. It may be a valuable alternative for the management of select high-risk neonates.

Fetal Procedures

The role of fetal intervention as a treatment for congenital heart disease remains unclear. It has been proposed as an option for progressive cardiac disease with poor prognosis. Several centers have shown that fetal cardiac intervention is technically possible. The majority of reported interventions have occurred in infants with severe aortic valve stenosis. Fetal critical aortic valve stenosis may progress to hypoplastic left heart syndrome. The rationale for performing fetal balloon aortic valvuloplasty is ultimately to achieve a two-ventricle circulation. The same rationale applies to the use of balloon pulmonary valvuloplasty in patients with pulmonary valve atresia with intact septum. Current work hopefully will clarify the utility of fetal cardiac intervention.

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254 Cardiovascular Surgery

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Introduction

Congenital heart surgery is a relatively young and constantly evolving discipline. The last 20 years have brought about rapid developments in the technologic realm as well as a more thorough understanding of both the anatomy and pathophysiology of congenital heart disease, leading to the improved care of children and adults with congenital heart defects.

One of the most important advancements was the introduction of cardiopulmonary bypass (CPB), which was used for the first time successfully to close an atrial septal defect by Dr. John Gibbon, Jr. on May 6, 1953. CPB allowed surgeons to empty the blood within the heart, stop it from beating if necessary, open any intracardiac chamber, and carry out reparative procedures in a controlled, unhurried manner. A simple CPB circuit includes: a pump, an arterial inflow into the patient, a venous outflow from the patient, a venous reservoir to collect and "store" the venous blood, an oxygenator to oxygenate the venous blood, filters to remove debris or air from the circuit, a heater/cooler to alter the temperature of the blood (or perfusate), and appropriate sized tubing. Although CPB makes heart surgery possible, infants and children provide important challenges in the use of CPB. First, repair of complex congenital heart defects often requires the use of hypothermia, complete arrest of the circulation, or very low flow rates. Second, the large disparity between the CPB circuit size and the patient requires excessive priming volumes that hemodilute important blood components. Postoperative care following congenital heart surgery, therefore, is often directed both at mitigating the deleterious effects of the intraoperative perfusion strategy as well as addressing the anatomic and physiologic aspects of the repair.

Concomitant advancements in the preoperative and postoperative care of patients with congenital heart disease have paralleled the intraoperative innovations.

These new advancements created a paradigm shift in the field of pediatric heart surgery. The traditional strategy of initial palliation followed by definitive correction at a later age, which had pervaded the thinking of most surgeons, began to evolve to one emphasizing early repair, even in the tiniest patients. Furthermore, some of the defects that were virtually uniformly fatal (such as hypoplastic left-heart syndrome) now can be successfully treated with aggressive forms of staged palliation, resulting in outstanding survival for many of these children.

Because the goal in most cases of congenital heart disease (CHD) is now early repair, as opposed to subdividing lesions into cyanotic or noncyanotic lesions, a more useful classification scheme divides particular defects into three categories based on the feasibility of achieving this goal: (1) defects that have no reasonable palliation and for which repair is the only option; (2) defects for which repair is not possible and for which palliation is the only option; and (3) defects that can either be repaired or palliated in infancy. It bears mentioning that all defects in the second category are those in which the appropriate anatomic components either are not present, as in hypoplastic left-heart syndrome, or cannot be created from existing structures. One obvious caveat is that the aforementioned classification scheme is certainly not absolute nor static. The vast morphologic heterogeneity that can manifest even within the same diagnostic subgroup mandates an *individualized* and creative approach to every patient.

Defects Where Repair Is the Only or Best Option

Atrial Septal Defect

An atrial septal defect (ASD), as discussed in previous chapters, is defined as an opening in the interatrial septum that enables the mixing of blood from the systemic venous and pulmonary venous circulations.

ASDs that are not amenable to percutaneous closure can be repaired in a facile manner using standard CPB techniques through a midline sternotomy approach. Because the surgery is usually relatively straightforward, systemic cooling is usually limited to 34°C. The heart is arrested with the infusion of a high potassium solution called cardioplegia into the coronary arteries, through a needle inserted into the ascending aorta. Arrest of the

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heart greatly facilitates the conduct of surgery and prevents the ejection of air into the systemic circulation, but does require the application of an aortic cross-clamp, which renders the coronaries ischemic. Myocardial protection can be improved during periods of coronary ischemia by intermittent (usually every 20 min) infusion of blood cardioplegia into the coronaries, topical and systemic cooling to decrease the metabolic demands of the heart, and by adequate venting of the heart to prevent distension. Closure of ostium secundum defects is accomplished either by primary repair or by insertion of a patch which is sutured to the rim of the defect. Our preference is patch closure using autologous pericardium, which can be "fixed" in glutaraldehyde. The fixation gives the pericardium, which is usually thin, some tensile strength. Although the decision of whether patch closure is necessary can theoretically be determined by the size and shape of the defect as well as by the quality of the edges, most surgeons will utilize a patch to decrease tension on the suture line.

Traditional surgical closure is well established, with a low complication rate and a mortality rate approaching zero.

Left Ventricular Outflow Tract Obstruction

Left ventricular outflow tract obstruction (LVOTO) can be generally subdivided into obstruction beneath the aortic valve (subvalvar aortic stenosis), obstruction at the valve level (valvar aortic stenosis), and obstruction above the valvar level, (supravalvar aortic stenosis). In many instances, these conditions coexist, and therefore, surgical relief of LVOTO may encompass more than one of the techniques described below in concert. The first decision that must be made in the neonate with critical left ventricular outflow tract obstruction is whether the patient is a candidate for biventricular or univentricular repair. Very rarely, if catheter-based therapy is not an option, relief of valvular aortic stenosis in infants and children can be accomplished with surgical valvotomy using standard techniques of CPB and direct exposure to the aortic valve. Cardioplegic arrest, if required, is administered using special catheters that are placed directly into the coronary ostia.

Should aortic valve replacement be required, the surgical therapy is dependent on the size of the aortic annulus, and whether concomitant obstruction exists at the subvalvar or supravalvar level. If the annulus is adequate, then a simple valve replacement using standard CPB and cardioplegic arrest is undertaken. If the annulus is too small to allow a prosthesis appropriate for the patient's body size (i.e., avoiding patient-prosthesis mismatch), an annulus enlarging procedure such as a Konno aortoventriculoplasty may be required. A Konno procedure essentially involves incising the aortic annulus within the left and right coronary commissure. The incision is carried onto the right ventricle. The conal septum is then resected, creating a ventricular septal defect, which can be closed with a patch. Many surgeons previously avoided aortic valve replacement for aortic stenosis in early childhood because the more commonly used mechanical valves would be outgrown and require replacement later, and the obligatory anticoagulation for mechanical valves resulted in a substantial risk for complications. In addition, mechanical valves have an important incidence of bacterial endocarditis or perivalvular leak requiring reintervention.

Given that repair of isolated discrete subaortic stenosis can be done with low rates of morbidity and mortality, some surgeons advocate repair in all cases of discrete subaortic stenosis to avoid progression of stenosis and the development of aortic insufficiency, though more recent data demonstrates that subaortic resection should be delayed until the LV gradient exceeds 30 mmHg, since most children with an initial LV gradient < 30 mmHg have quiescent disease. For discrete subaortic stenosis, the operation involves standard CPB and cardioplegic arrest without the need for systemic cooling below 34°C. The aorta is opened and the valve is inspected in that subaortic obstruction may coexist with valvar aortic stenosis. If the valve function and morphology appear reasonable, the membrane below the valve is excised. Often a portion of left ventricular muscle is resected along with the membrane, termed a myectomy, to completely relieve the obstruction. Diffuse AS is a more complex lesion and often requires aortoventriculoplasty as previously described. Results are generally excellent, with operative mortality less than 5%.

Supravalvar aortic stenosis also can be subdivided into discrete and diffuse types. The localized form of supravalvular aortic stenosis is treated by creating an inverted Y-shaped aortotomy across the area of stenosis, straddling the right coronary artery. The obstructing shelf is then excised and a pantaloon-shaped patch is used to close the incision. The diffuse form of supravalvular stenosis is more variable, and the particular operative approach must be tailored to each specific patient's anatomy. In general, either an aortic endarterectomy with patch augmentation can be performed, or if the narrowing extends past the aorta arch, a prosthetic graft can be placed between the ascending and descending aorta. Operative results for discrete supravalvular aortic stenosis are

generally good, with a hospital mortality of less than 1% and an actuarial survival rate exceeding 90% at 20 years. In contrast, however, the diffuse form is more hazardous to repair, and carried a mortality of 15% in a recent series.

Patent Ductus Arteriosus

The presence of a persistent patent ductus arteriosus is sufficient indication for closure because of the increased mortality and risk of endocarditis. In older patients with pulmonary hypertension, closure may not improve symptoms and is associated with much higher mortality.

Surgical approach employs a posterior lateral thoracotomy in the fourth or fifth intercostal space on the side of the aorta (generally the left). The lung is then retracted anteriorly. The ductus is ligated with a surgical clip or permanent suture.

In premature infants, the surgical mortality is very low, although the overall hospital death rate is significant as a consequence of other complications of prematurity. In older infants and children, mortality is less than 1%. Bleeding, chylothorax, vocal cord paralysis, and the need for reoperation occur infrequently.

Aortic Coarctation

The routine management of hemodynamically significant COA in all age groups has traditionally been surgical. Transcatheter repairs are used with increasing frequency in older patients and those with re-coarctation following surgical repair. Balloon dilatation of native coarctation in neonates has been recently utilized with only transient relief of obstruction. The initial question that must be answered prior to repair is whether the surgery should be performed using a left thoracotomy, which is typical, or a median sternotomy. Generally, if there is a question about transverse arch hypoplasia or other concomitant intracardiac lesions, a median sternotomy should be elected. The most common surgical techniques in current use are resection with end-to-end anastomosis or extended end-to-end anastomosis, taking care to remove all residual ductal tissue. Extended end-to-end anastomosis may also allow the surgeon to treat transverse arch hypoplasia which is commonly encountered in infants with aortic coarctation. An extended end-to-end or simple end-to-end repair usually does not require CPB. For the extended end-to-end repair, occasionally cerebral perfusion using a catheter placed into the innominate artery may be required in cases where both the left common carotid and left subclavian arteries are occluded and there is an incomplete Circle of Willis. The aorta above and below the narrowed segment is widely mobilized, and partial-occluding clamps are utilized to isolate enough aortic wall to fashion an anastomosis along the entire undersurface of the arch. In the simple end-to-end technique, the ascending and descending aorta are simply sutured together. The subclavian flap aortoplasty is another repair, though is used less frequently in the modern era because of the risk of late aneurysm formation and possible underdevelopment of the left upper extremity. In this method, the left subclavian artery is transected and brought down over the coarcted segment as a vascularized patch. The main benefit of these techniques is that they do not involve the use of prosthetic materials, and evidence suggests that extended end-to-end anastomosis may promote arch growth, especially in infants with the smallest initial aortic arch diameters.

Despite the benefits, however, extended end-to-end anastomosis may not be feasible when there is a long segment of coarctation or in the presence of previous surgery, because sufficient mobilization of the aorta above and below the lesion may not be possible. In this instance, prosthetic materials, such as a patch aortoplasty, in which a prosthetic patch is used to enlarge the coarcted segment, or an interposition tube graft must be employed.

The most common complications after COA repair are late restenosis and aneurysm formation at the repair site. Aneurysm formation is particularly common after patch aortoplasty when using Dacron material. In a large series of 891 patients, aneurysms occurred in 5.4% of the total, with 89% occurring in the group who received Dacron-patch aortoplasty, and only 8% in those who received resection with primary end-to-end anastomosis. A further complication, although uncommon, is lower-body paralysis resulting from ischemic spinal cord injury during the repair.

Truncus Arteriosus

Truncus arteriosus was first managed with pulmonary artery banding as described by Armer and colleagues in 1961. However, this technique led to only marginal improvements in 1-year survival rates because ventricular failure inevitably occurred. In 1967, complete repair was accomplished by McGoon and his associates based on the experimental work of Rastelli, who introduced the idea that an extracardiac valved conduit could be used to restore ventricular-to-pulmonary artery continuity. Over

the next 20 years, improved survival rates led to uniform adoption of complete repair even in the youngest and smallest infants.

Surgical correction entails the use of CPB and cardioplegic arrest. Repair is completed by separation of the pulmonary arteries from the aorta, closure of the aortic defect (occasionally with a patch) to minimize coronary flow complications, placement of a valved cryopreserved allograft or jugular venous valved conduit (Contegra) to reconstruct the right ventricular outflow tract, and ventricular septal defect closure. Important branch pulmonary arterial stenosis should be repaired at the time of complete repair, and can usually be accomplished with longitudinal allograft patch arterioplasty. Severe truncal valve insufficiency occasionally requires truncal valve repair, if feasible, or valve replacement. The results of complete repair of truncus have steadily improved. Severe truncal regurgitation, interrupted aortic arch, coexistent coronary anomalies, chromosomal or genetic anomalies, and age younger than 100 days are risk factors associated with perioperative death and poor outcome.

Total Anomalous Pulmonary Venous Connection (TAPVC)

Operative correction of TAPVC requires anastomosis of the common pulmonary venous channel to the left atrium, obliteration of the anomalous venous connection, and closure of the atrial septal defect.

All types of TAPVC are approached through a median sternotomy, and many surgeons use deep hypothermic circulatory arrest (DHCA) in order to achieve an accurate and widely patent anastomosis. DHCA requires systemic perfusion cooling, using the CPB circuit, of the patient over at least 20 min, to a core body temperature of 18°C. Once that core temperature is reached, the head is packed in ice, systemic steroids are often administered, and the perfusion through the CPB pump is stopped. Many surgeons use a catheter placed into the innominate artery with isolation of the other arch vessels, to allow perfusion to the brain during DHCA, termed selective antegrade cerebral perfusion. Once the circulation is arrested, the blood from the patient is drained into the venous reservoir, and the cannulae are removed from the body. Though there have been no definitive studies performed, most surgeons agree that a period of 40 min of DHCA is safe. Once the repair is completed, CPB is resumed, and the patient is slowly rewarmed to normothermia.

The technique for supracardiac TAPVC includes early division of the vertical vein; retraction of the aorta and the superior vena cava laterally to expose the posterior aspect of the left atrium and the pulmonary venous confluence; and a side-to-side anastomosis between a long, horizontal biatrial incision and a longitudinal incision within the pulmonary venous confluence. The ASD can then be closed with an autologous pericardial or synthetic patch.

Repair of infracardiac TAPVC entails ligation of the vertical vein at the diaphragm, followed by construction of a proximal, patulous longitudinal venotomy. This repair is usually performed by "rolling" the heart toward the left, thus exposing the left atrium where it usually overlies the descending vertical vein.

Cautious perioperative management of these infants is crucial because episodes of pulmonary hypertension can occur within the first 48 h, which contribute significantly to mortality following repair.

Results of TAPVC in infancy have markedly improved in recent years, with an operative mortality of 5% or less in some series. This improvement is probably multifactorial, mainly as a consequence of early noninvasive diagnosis and aggressive perioperative management. The routine use of echocardiography; improvements in myocardial protection with specific attention to the right ventricle; creation of a large, tension-free anastomosis with maximal use of the venous confluence and atrial tissue; careful geometric alignment of the pulmonary venous sinus with the body of the left atrium avoiding tension and rotation of the pulmonary veins; and prevention of pulmonary hypertensive events have likely played a major role in reducing operative mortality. The importance of risk factors for early mortality, such as venous obstruction at presentation, urgency of operative repair, and infradiaphragmatic anatomic type, has been debated.

The most significant postoperative complication of TAPVC repair is pulmonary venous obstruction, which occurs 9–11% of the time, regardless of the surgical technique employed. Mortality varies between 30% and 45%, and alternative catheter interventions do not offer definitive solutions.

Defects Requiring Palliation

Tricuspid Atresia

The treatment for tricuspid atresia in the earlier era of palliation was aimed at correcting the defect in the pulmonary circulation. That is, patients with too much pulmonary flow received a pulmonary band, and those with insufficient flow received a systemic-to-pulmonary artery shunt. Systemic-to-pulmonary artery shunts, or

Blalock-Taussig (B-T) shunts, were first applied to patients with tricuspid atresia in the 1940s and 1950s. Likewise pulmonary artery banding was applied to patients with tricuspid atresia and congestive failure in 1957. However, despite the initial relief of either cyanosis or congestive heart failure, long-term mortality was high, as the single ventricle was left unprotected from either volume or pressure overload.

The issues surrounding the approach to palliative surgery are discussed in Chap. 251, "The Single Ventricle". Recognizing the inadequacies of the initial repairs, Glenn described the first successful cavopulmonary anastomosis, an end-to-side right pulmonary artery (RPA)-to-superior vena cava (SVC) shunt in 1958, and later modified this to allow flow to both pulmonary arteries. This end-to-side RPA-to-SVC anastomosis was known as the bidirectional Glenn, and is the second stage to final Fontan repair in widespread use today. The Fontan repair was a major advancement in the treatment of congenital heart disease, as it essentially bypassed the right heart, and allowed separation of the pulmonary and systemic circulations. Multiple modifications of the initial repair, as described by Fontan in 1971, were performed over the next 20 years. One of the most important was the description by deLeval and colleagues of the creation of an interatrial lateral tunnel that allowed the inferior vena caval blood to be channeled exclusively to the superior vena cava. A total cavopulmonary connection could then be accomplished by dividing the SVC and suturing the superior portion to the upper side of the right pulmonary artery and the inferior end to the augmented undersurface of the right pulmonary artery. Pulmonary flow then occurs passively, in a laminar fashion, driven by the central venous pressure. This repair became known as the modified Fontan operation.

Another important modification, the fenestrated Fontan repair, a residual 20–30% right-to-left shunt is either created or left unrepaired at the time of cavopulmonary connection to help sustain systemic output in the face of transient elevations in the PVR postoperatively.

The last notable variation on the original Fontan repair uses an extracardiac prosthetic tube graft, usually 20 mm in diameter, as the conduit directing inferior vena cava (IVC) blood to the pulmonary arteries. This technique has the advantages of decreasing atrial geometric alterations by avoiding intra-atrial suture lines, and improving flow dynamics in the systemic venous pathway by maximizing laminar flow. The extracardiac Fontan operation can be completed without the use of cardiopulmonary bypass in selected cases, which may further improve outcomes. One potential disadvantage of the extracardiac Fontan is that it delays performance of the Fontan in order to allow placement of a conduit of sufficient size. Despite these innovative approaches, the current strategy for operative management still relies on the idea of palliation. Patients are approached in a staged manner, to maximize their physiologic state so that they will survive to undergo a Fontan operation. The therapeutic strategy must begin in the neonatal period and should be directed toward reducing the patient's subsequent risk factors for a Fontan procedure. Accordingly, small systemic-pulmonary artery shunts, which are usually performed through a median sternotomy, should be constructed for palliation of ductal-dependent univentricular physiology. This can easily be replaced with a bidirectional Glenn shunt or hemi-Fontan operation at 6 months of life. In non-ductal-dependent univentricular physiology, the infant can be managed medically until primary construction of a bidirectional cavopulmonary anastomosis becomes feasible.

The Fontan is usually performed when the child is between 2 and 4 years of age, and it is generally successful if the infant was staged properly, with a protected single ventricle, and there is adequate PA growth. The PVR should be below 4 Woods Units, and the ejection fraction should be more than 45% to ensure success. Fenestration of the atrial baffle may be helpful in patients with high PA pressures because their PVR may preclude adequate postoperative cardiac output.

Recent reports of the Fontan procedure for tricuspid atresia have been encouraging, with an overall survival of 86% and an operative mortality of 2%. The main complications following repair are atrial arrhythmias, particularly atrial flutter; conduit obstruction requiring reoperation; protein-losing enteropathy; and decreased exercise tolerance.

A recent prospective multi-institutional study from the Congenital Heart Surgeons Society reported the outcomes of 150 neonates with tricuspid atresia and normally related great vessels. Five-year survival was 86%, and by the age of 2 years, 89% had undergone cavopulmonary anastomosis, and 75% of those surviving cavopulmonary anastomosis underwent Fontan operation within 3 years.

Hypoplastic Left-Heart Syndrome

In 1983, Norwood and colleagues described a two-stage palliative surgical procedure for relief of HLHS that was later modified to the currently used three-stage method of palliation. Stage 1 palliation, also known as the modified Norwood procedure, bypasses the left ventricle by creating a single outflow vessel, the neoaorta, which arises from the right ventricle.

The current technique of arch reconstruction involves completion of a connection between the pulmonary root, the native ascending aorta, and a piece of pulmonary homograft used to augment the diminutive native aorta. There are several modifications of this anastomosis, most notably the Damus-Kaye-Stansel (DKS) anastomosis, which involves dividing both the aorta and the pulmonary artery at the sinotubular junction. The proximal aorta is anastomosed to the proximal pulmonary artery creating a "double-barreled" outlet from the heart. This outlet is anastomosed to the distal aorta, which can be augmented with homograft material if there is an associated coarctation. At the completion of arch reconstruction, a 3.5- or 4-mm shunt is placed from the innominate artery to the right pulmonary artery. The interatrial septum is then widely excised, thereby creating a large interatrial communication and preventing pulmonary venous hypertension.

The postoperative management of infants following stage 1 palliation is complex because favorable outcomes depend on establishing a delicate balance between pulmonary and systemic perfusion. Recent literature suggests that these infants require adequate postoperative cardiac output in order to supply both the pulmonary and the systemic circulations and that the use of oximetric catheters to monitor SVO_2 aids clinicians in both the selection of inotropic agents and in ventilatory management. Recent introduction of a modification that includes arch reconstruction and placement of the shunt between the right ventricle and the pulmonary artery (Sano shunt) diminishes the diastolic flow created by the classical aortopulmonary shunt and may augment coronary perfusion, resulting in improved postoperative cardiac function. A recent prospective, randomized, multi-institutional trial sponsored by the NIH, the systemic ventricle reconstruction (SVR) trial, evaluated neonates having either a modified Blalock-Taussig shunt versus a Sano shunt. The SVR trial showed higher 12-month transplant-free survival in the Sano shunt group, but a higher incidence of unintended reinterventions and complications. Longer follow-up data is currently being collected in this cohort.

Although surgical palliation with the Norwood procedure is still the mainstay of therapy for infants with HLHS, a combined surgical and percutaneous option (Hybrid procedure), which consists of bilateral pulmonary artery banding and placement of a ductus arteriosus stent, has emerged as a promising alternative that obviates the need for cardiopulmonary bypass in the fragile neonatal period. The hybrid procedure can also be used as a bridge to heart transplantation in those infants with severe atrioventricular valve regurgitation or otherwise unsuitable single-ventricle anatomy.

Following stage 1 palliation, the second surgical procedure is the creation of a bidirectional cavopulmonary shunt or Hemi-Fontan as discussed previously, generally at 3–6 months of life when the PVR has decreased to normal levels. Not all patients with HLHS require this three-stage palliative repair. Some infants afflicted with a milder form of HLHS, recently described as hypoplastic left-heart complex (HLHC), have aortic or mitral hypoplasia without intrinsic valve stenosis and antegrade flow in the ascending aorta. In this group, a two-ventricle repair can be achieved with reasonable outcome. Tchervenkov recently published the results with 12 patients with HLHC who underwent biventricular repair at a mean age of 7 days. The operative technique consisted of a pulmonary homograft patch aortoplasty of the aortic arch and ascending aorta and closure of the interatrial and interventricular communications. The left heart was capable of sustaining systemic perfusion in 92% of patients, and early mortality was 15.4%.

Although the Norwood procedure is the most widely performed initial operation for HLHS, transplantation can be used as a first-line therapy and may be preferred when anatomic or physiologic considerations exist that preclude a favorable outcome with palliative repair. Significant tricuspid regurgitation, intractable pulmonary artery hypertension, severe arrhythmias, or progressive right ventricular failure are cases where cardiac replacement may be advantageous. Widespread adaptation of transplantation as first-line treatment for HLHS has been limited by improved Norwood survival rates and by limited organ availability. Organ availability should be considered prior to electing transplantation, as 24% of infants died awaiting transplantation in the largest series to date.

Outcomes for HLHS are still significantly worse than those for other complex cardiac defects. However, with improvements in perioperative care and modifications in surgical technique, the survival following the Norwood procedure now exceeds 80% in experienced centers. The outcome for low-birth-weight infants has improved, but low weight still remains a major predictor of adverse survival, especially when accompanied by additional cardiac defects, such as systemic outflow obstruction or extracardiac anomalies.

Defects That May Be Palliated or Repaired

Transposition of the Great Arteries

The surgical treatment of transposition has evolved from the initial atrial switch operations (Senning and Mustard

operations), which afforded a physiologic correction, to an anatomic repair, the arterial switch operation, described by Jatene in 1975. Following median sternotomy and standard CPB, the arterial switch procedure involves division of the aorta and the pulmonary artery, mobilization of the coronary arteries and creation of coronary "buttons," posterior translocation of the aorta (LeCompte maneuver), proper alignment and anastomosis of the coronary arteries on the neoaorta, and placement of a pantaloon-shaped autologous pericardial patch to reconstruct the neopulmonary artery defect.

The most important consideration is the timing of surgical repair, because arterial switch should be performed within 2 weeks after birth, before the left ventricle loses its ability to pump against systemic pressure. Neonates with a concomitant ventricular septal defect have a pressurized LV, and therefore the timeframe prior to surgery may be more plastic, though, generally, early repair is indicated. In patients presenting later than 2 weeks, the left ventricle can be re-trained with preliminary pulmonary artery banding and aortopulmonary shunt followed by definitive repair. Alternatively, the unprepared left ventricle can be supported following arterial switch with a mechanical assist device for a few days while it recovers ability to manage systemic pressures. Echocardiography can be used to assess left ventricular performance and guide operative planning in these circumstances.

The subset of patients who present with D-TGA complicated by left ventricular outflow tract obstruction (LVOTO) and VSD may not be suitable for an arterial switch operation. The Rastelli operation, first performed in 1968, uses placement of an intracardiac baffle to direct left ventricular blood to the aorta and an extracardiac valved conduit to establish continuity between the right ventricle and the pulmonary artery, which has led to successful outcomes in these complex patients. Another option for this challenging subset of patients is the Nikaidoh procedure, in which the aortic root is mobilized and translocated posteriorly. The hypoplastic pulmonary annulus is incised onto the conal septum, which is also resected. The aortic root is sewn to the posterior portion of the opened pulmonary annulus, and the VSD is closed with a patch that is then sewn to the anterior portion of the aortic root. Reconstruction of the right ventricular outflow tract has been variable, with some surgeons favoring the use of an outflow patch, a valved patch, or a conduit.

For patients with D-TGA, IVS, and VSD, the arterial switch operation provides excellent long-term results with a mortality rate of less than 5%. Operative risk is increased when unfavorable coronary anatomic configurations are present, or when augmentation of the aortic arch is required. The most common complication is supravalvular pulmonary stenosis, occurring 10% of the time, which may require reoperation.

Tetralogy of Fallot (TOF)

John Deanfield said "... long follow-up inevitably means surgery in an earlier era: More recent surgery, at a younger age, with better preoperative, operative, and postoperative care, will improve long-term results. Data from the former (earlier) era will be overly pessimistic." This statement is particularly pertinent as surgical correction of TOF has evolved from a staged approach of antecedent palliation in infancy followed by intracardiac repair to primary repair during the first few months of life without prior palliative surgery.

However, systemic-to-pulmonary shunts, generally a B-T shunt, may still be preferred with an unstable neonate younger than 4 months of age, when an extracardiac conduit is required because of an anomalous left anterior descending coronary artery, or when pulmonary atresia, significant branch pulmonary artery hypoplasia, or severe noncardiac anomalies coexist with TOF.

Traditionally, TOF was repaired through a right ventriculotomy, providing excellent exposure for closure of the VSD and relief of the RVOT obstruction, but concerns that the resultant scar would significantly impair right ventricular function or lead to lethal arrhythmias led to the development of a transatrial approach. Transatrial repair, except in cases when the presence of diffuse RVOT hypoplasia requires insertion of a transannular patch, is now being increasingly advocated by many, although its superiority has not been conclusively demonstrated.

The operative technique involves the use of CPB with cardioplegic arrest and moderate hypothermia. All existing systemic-to-pulmonary arterial shunts, as well as the ductus arteriosus, are ligated. A right atriotomy is then made, and the anatomies of the VSD and the RVOT are assessed by retracting the tricuspid valve. The outflow tract obstruction is relieved by resecting the offending portion of the infundibular septum as well as any muscle trabeculations. If necessary, a pulmonary valvotomy or, alternatively, a longitudinal incision in the main pulmonary artery can be performed to improve exposure. Patch closure of the VSD is then accomplished, taking care when placing sutures along the posteroinferior portion to avoid the conduction system.

Operative mortality for primary repair of TOF in infancy is less than 5% in most series. Previously reported risk factors such as transannular patch insertion or younger age at time of repair have been eliminated secondary to improved intraoperative and postoperative care.

A major complication of repaired TOF is the development of pulmonary insufficiency, which subjects the RV to the adverse effects of acute and chronic volume overload (see Chap. 115, "Cyanotic Congenital Heart Disease"). This is especially problematic if residual lesions such as a VSD or peripheral pulmonary stenosis exist. Pulmonary valve regurgitation after repair of TOF is relatively well tolerated in the short term, partly because the hypertrophied right ventricle usually adapts to the altered hemodynamic load. The detrimental effects of chronic pulmonary valve regurgitation are, however, numerous, and include progressive right ventricular dilatation and failure, tricuspid valve regurgitation, exercise intolerance, arrhythmia, and sudden death.

When significant deterioration of ventricular function occurs, insertion of a pulmonary valve may be required, although this is rarely necessary in infants. Unfortunately, there are no universal criteria establishing the timing of pulmonary valve replacement, though dilation of the right ventricle, prolongation of the QRS duration beyond 180 ms, important atrial arrhythmias, or impaired ventricular function are widely used.

Ventricular Septal Defect

Repair of isolated VSDs requires the use of CPB with moderate hypothermia and cardioplegic arrest. The right atrial approach is preferable for most defects, except apical muscular defects, which often require a left ventriculotomy for adequate exposure. Supracristal defects may alternatively be exposed via a longitudinal incision in the pulmonary artery or a longitudinal incision in the right ventricle below the pulmonary valve. Regardless of the type of defect present, a right atrial approach can be used initially to inspect the anatomy, as this may be abandoned should it offer inadequate exposure for repair. After careful inspection of the heart for any associated malformations, a patch repair is employed, taking care to avoid the conduction system. Routine use of intraoperative transesophageal echocardiography should be used to assess for any residual defects.

Multiple or "Swiss-cheese" VSDs represent a special case, and many cannot be repaired during infancy. In those patients in whom definitive VSD closure cannot be accomplished, temporary placement of a pulmonary artery band can be employed to control pulmonary flow. This allows time for spontaneous closure of many of the smaller defects, thus simplifying surgical repair. Some centers, however, have advocated early definitive repair of the Swiss-cheese septum, by using oversize patches, fibrin glue, and combined intraoperative device closure, as well as techniques to complete the repair transatrially. At the University of California at San Francisco, 69% of patients with multiple VSDs underwent single-stage correction, and the repaired group had improved outcome as compared to the palliated group.

Even in very small infants, closure of VSDs can be safely performed with hospital mortality near 0%. The main risk factor remains the presence of other associated lesions, especially when present in symptomatic neonates with large VSDs.

Atrioventricular Canal Defects

The management of patients with AV canal defects can be especially challenging. Timing of operation is individualized, not only to the intracardiac anatomy, but also to chromosomal defects, such as Down's syndrome. Babies with Down's syndrome have a predilection for the persistence of high PVR. Those patients with partial defects can be electively repaired between 2 and 5 years of age, whereas complete AV canal defects should be repaired within the first year of life to prevent irreversible changes in the pulmonary circulation. Complete repair in infancy should be accomplished, with palliative procedures such as pulmonary artery banding reserved for only those infants with other complex lesions, or who are too ill to tolerate CPB.

The operative technique involves use of either continuous hypothermic CPB or, for small infants, DHCA. Through a median sternotomy, the heart is initially approached through an oblique right atriotomy, and the anatomy is carefully observed. In the case of a partial AV canal, the cleft in the mitral valve is repaired with interrupted sutures and the atrial septal defect is closed with an autologous pericardial patch. Complete AV canal defects are repaired by either a one-patch or two-patch repair. Details of the repair vary according to center, involving patch closure of the VSD, separating the common AV valve into tricuspid and mitral components, suspending the neovalves from the top of the VSD patch, and closing the ASD.

Partial AV canal defects have an excellent outcome, with a mortality rate of 0–2% in most series. Complete AV canal defects are associated with a poorer prognosis, with an operative mortality of 3–13%.

The most frequently encountered postoperative problems are complete heart block (1–2%), right bundle-branch block (22%), arrhythmias (11%), right ventricular outflow tract obstruction (11%), and progressive mitral regurgitation (13–24%). The increasing use of intraoperative transesophageal echocardiography may positively influence outcomes, as the adequacy of repair can be assessed and treated without need for subsequent reoperation.

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255 Abnormalities of Cardiac Rhythm

Terrence U. H. Chun

Introduction

Disorders of cardiac rhythm can occur at any age, from the fetus to adult. The spectrum of arrhythmias ranges from transient phenomena to recurrent arrhythmias. Simple and isolated rhythm abnormalities such as isolated premature atrial complexes may be more bothersome to the care provider than to the patient, but persistent and life-threatening rhythms may require emergent treatment and intervention. While most children with cardiac arrhythmias may have structurally normal hearts, there is certainly an increased incidence of rhythm disorders in children with congenital heart disease. In addition, these patients may be more susceptible to morbidity or mortality than their counterparts with normal hearts. Management of arrhythmias in childhood depends on the expectations of the arrhythmia itself. This may range from expectant management to medical therapy to urgent intervention.

Components of the Normal Cardiac Conduction System

Sinus Node

The sinus node resides at the junction between the superior vena cava and the right atrium. The tissue is histologically distinct from atrial tissue and has no contractile components. Studies have demonstrated that the nodal tissue extends from the junction along the lateral wall of the right atrium. Impulses generated by automatic action potential behavior activate the adjacent atrial myocardium which then propagates by cell-to-cell activation to the additional atrial myocytes.

Atrioventricular (AV) Node

The atrioventricular node is located near the atrioventricular junction between the right atrium and the right ventricle. More well-defined than the sinus node, the compact atrioventricular node is located along the interatrial septum just anterior to the tricuspid valve. Action potential impulses propagating across the atrial myocardium reach the compact AV node. Conduction velocity is slowed in the AV node before it enters the specialized conduction fibers of the His-Purkinje tract.

His-Purkinje System

In the normal heart, the atria and the ventricles are electrically isolated from one another by the atrioventricular rings (mitral and tricuspid annuli). The penetrating bundle of His is usually the only conducting tissue to traverse the atrioventricular rings to the ventricles. The bundle is electrically well insulated from the interventricular septum until it gives off branches. The first branch from the His bundle leads to activation of the septum. The bundle then bifurcates into distinct right and left bundle branches. The left bundle branch itself is separated into anterior and posterior fascicles. At the terminus of each of the bundle branches, the specialized conduction tract divides into an array of short Purkinje fibers which respectively insert onto the ventricular myocardium. When conduction follows the normal conduction system, the ventricles are activated in an electrically synchronized manner that results in mechanically efficient ventricular contraction.

The Electrocardiogram and Normal Cardiac Conduction

Cardiac rhythm that begins in the sinus node and conducts normally to the ventricles is considered sinus rhythm. The rate of normal sinus rhythm and the normal conduction intervals vary significantly from infancy through childhood. The impulse generated sweeps from the sinus node across the right and left atria. On a normal electrocardiogram, this is evident by P waves that are upright in lead I, lead II, and lead aVF. There is typically an isoelectric pause following the P wave, as conduction enters the AV node and specialized conduction system, as there is no depolarizing signal from either the AV node or the His-Purkinje system. This interval, from the onset of the P wave to the onset of ventricular activation, is

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measured as the PR interval. When the ventricles are depolarized, this is manifest as the QRS complex. When ventricular activation occurs in a normal and organized fashion, the QRS complex duration (measured from the onset of the Q wave to the completion of the S wave) is fairly narrow. The ST segment is the period of generally isoelectric time before the onset of the T wave. The T wave represents the repolarization phase of the ventricular mass. The QT interval is the measurement between the onset of the Q wave to the end of the T wave. This can be difficult to measure, as the end of the T wave is often indistinct. The T wave in lead II is traditionally used for this measurement, although the T wave may be more distinct in other leads as well. There will occasionally be a distinct U wave following a T wave. Sometimes this is even fused with the downslope of the T wave (in which case it is often referred to as the TU wave). The U wave has little clinical significance (although it can become prominent during extremes of metabolic derangements, such as in severe hypokalemia or hypothermia). It is not measured as part of the T wave for the QT measurement unless it is at least 50% the height of the T wave. Abnormalities of the depolarization sequence will affect the repolarization sequence as well. Thus, if a patient has an abnormal QRS complex, the QT measurement will often be abnormal. The T wave in leads V1 and V2 are upright at birth, but typically become inverted by the first week of life. The T wave inversion persists until preadolescence or adolescence, when it returns to the upright adult configuration.

Abnormal Atrioventricular Conduction

When the normal sequence of atrioventricular conduction is disturbed, the cardiac rhythm may become irregular. However, many of these electrocardiographic manifestations will only be evident on the electrocardiogram itself and might not be appreciated by physical examination alone. Forms of atrioventricular block can occur with anything that interrupts or impedes conduction through the atrioventricular conduction axis from the AV node through the His-Purkinje system, whether this is intrinsic (due to parasympathetic stimulation) or an acquired problem.

First-Degree Atrioventricular Block

First-degree atrioventricular block describes any conduction delay that prolongs atrioventricular conduction beyond the normal range. However, conduction remains intact and the usual 1:1 atrioventricular association persists. The normal PR interval is up to 140 ms in the first 3 months, to 160 ms until 6 years of age, and up to 180 ms until age 15. First-degree atrioventricular block may be a normal variant or may be caused by factors that increase conduction time through the AV node. Elevated resting vagal tone can be seen in highly trained athletes, and often results in first-degree atrioventricular block on the resting ECG. More pathologic conditions, such as rheumatic fever or neonatal lupus syndrome or lyme disease, may also prolong the PR interval. However, except in cases where the PR interval is extremely prolonged, there is usually no outward manifestation of first-degree atrioventricular block and the physical examination is otherwise unchanged.

Second-Degree Atrioventricular Block

Second-degree atrioventricular block is ascribed when there is incomplete conduction from atrium to ventricle. This can manifest as an occasionally skipped beat on physical examination. Mobitz type I, also known as Wenckebach conduction, describes a pattern wherein the atrioventricular conduction becomes gradually delayed with each successive beat. The PR interval becomes progressively prolonged, and after a number of beats (usually two or three, although this could certainly be longer) there is loss of atrioventricular conduction for a single beat. On the subsequent beat, the PR is normalized and the sequence of prolongation begins again. A Wenckebach pattern can be seen on the electrocardiogram of otherwise normal and healthy young athletes, and is a reflection of increased resting vagal tone.

In Mobitz II conduction block, the PR does not prolong and there is loss of conduction after a stereotyped number of beats. Whereas Wenckebach phenomenon is a common finding that has no pathologic implications, Mobitz II conduction block is always abnormal. The etiology of Mobitz II conduction block does not appear to be due to impairment within AV node, but rather it is loss of conduction in the His bundle or below. Mobitz II conduction block is very rare in pediatrics, as it is usually a sign of a diseased conduction system. Patients with Mobitz II conduction block should be evaluated by electrophysiology study and may require permanent pacemaker implantation; patients with Mobitz I Wenckebach pattern would not require a pacemaker.

Third-Degree (Complete) Atrioventricular Block

Third-degree atrioventricular block occurs when there is complete lack of conduction between the atria and

ventricles. Often, the ventricles and thus cardiac output are supported by an escape mechanism of some form, either a junctional or ventricular escape rhythm (see below). Complete atrioventricular block can be congenital or acquired. Congenital complete atrioventricular block is most commonly associated with maternal lupus. While in severe situations the fetus or neonate may show signs of severe distress and congestive heart failure (manifested by the fetus as hydrops), many patients with congenital complete atrioventricular block may be entirely asymptomatic for many years, provided their escape rate is acceptable. Acquired heart block may occur in the setting of infection, as in the case of Chagas disease or Lyme disease. Severe rheumatic heart disease or myocarditis can also result in complete heart block. Though less common in the current surgical era, heart block can occur following cardiac surgery that involves the interventricular septum in approximately 1–3% of cases.

Bundle Branch Block

A bundle branch block occurs when conduction down the His-Purkinje axis has been interrupted along either the right or the left bundle branch. A right bundle branch block is characterized by an RSR′ pattern in V1 (sometimes described as "rabbit ears") and a broad S wave in leads I and V6 (*Fig. 255.1a*). A left bundle branch has a deep S wave in V1 and a monophasic and notched R wave in leads I and V6 (*Fig. 255.1b*). Often, a bundle branch block (particularly a left bundle branch block) indicates some type of pathology. Right bundle branch block is found in up to 23–29% of patients following surgery for congenital heart disease. Bundle branch block can be seen in the setting of a normal heart, in particular in the setting of the condition called the "athlete's heart." Due to high resting vagal tone, highly conditioned athletes can have a number of conduction abnormities, often first- and second-degree atrioventricular block or bundle branch blocks. These mild electrocardiographic abnormalities are typically normalized during even mild activity.

Functional bundle branch block "aberrancy" can be seen under certain circumstances. Aberrant conduction is seen after the onset of a rapid supraventricular rhythm. It can also be seen in very irregular rhythms such as atrial fibrillation. Functional bundle branch block is a transient phenomenon and resolves when the conditions return to normal. In contrast, permanent bundle branch block (as is seen following cardiac surgery) does not resolve.

Ventricular Preexcitation (Wolff–Parkinson–White Pattern)

Ventricular preexcitation occurs when ventricular myocardium is activated abnormally, usually through an abnormal conduction tract. The finding of preexcitation

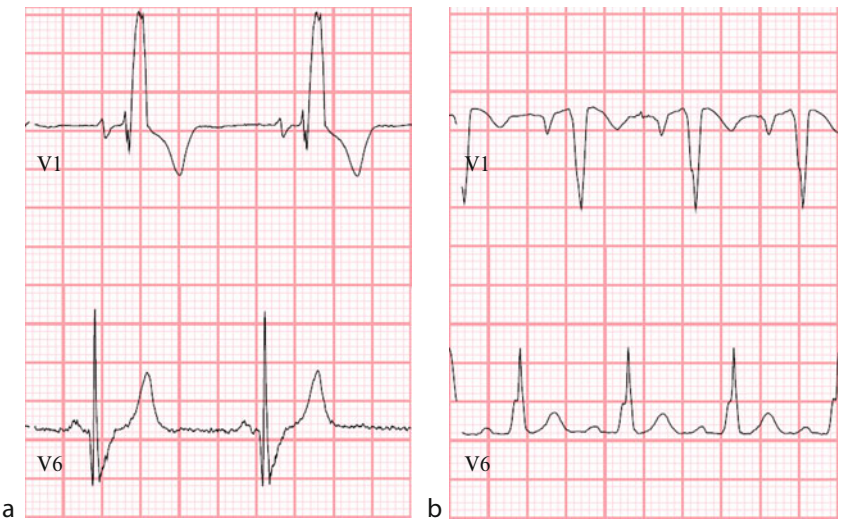

Figure 255.1
(a) Right bundle branch pattern with RSR′ pattern in V1 and wide slurred S wave in V6. (b) Left bundle branch pattern with deep S wave in V1 and tall notched R wave in V6

is indicative of the presence of an "accessory pathway." Typically, these bypass tracts bridge the electrical insulation of the atrioventricular groove, resulting in an anomalous atrioventricular electrical connection. Other variants exist, such as the accessory pathway arising from the AV node (nodo-ventricular pathway) or the His-Purkinje conduction axis (fasciculo-ventricular pathway), although these variants are very rare.

There are three classic electrocardiographic findings that define ventricular preexcitation: (1) widened QRS complex, (2) shortened PR interval, and (3) slurring delta wave (*Fig. 255.1*). The finding of Wolff–Parkinson–White pattern implies the presence of an accessory pathway capable of causing arrhythmias (see below). In most of these examples, the bypass tract does not imply the absence of normal conduction. Rather, it represents the combination of conduction through the abnormal pathway in addition to (or fused with) conduction through the normal His-Purkinje conduction pathways.

Premature Beats

Premature Atrial Complexes

Isolated atrial ectopy is common in childhood. There is no ethnic difference in the amount of presence of ectopy. It can be seen during fetal monitoring, and can be seen in up to one in four normal newborns; however, in the vast majority of the time, this resolves within the first few months of life.

Premature atrial complex occur when there is early depolarization of the atria from an ectopic focus that is different from the sinus node. This is diagnosed by identifying P waves that have a difference axis and appearance than the normal sinus P waves. Most of the time, the P waves will be very different in appearance and easily distinguished from normal sinus beats. However, on occasion premature beats may originate from the right atrium around, but separate from, the sinus node; these may be more difficult to distinguish from normal.

Atrial ectopy is typically conducted normally, meaning that there is a normal-appearing QRS complex that follows the premature atrial complex. The PR interval measured is usually different than normal, which is more a reflection of the atrial depolarization originating from an abnormal location rather than indicating a defect in atrioventricular conduction. Following the premature atrial complex is a normal-appearing QRS complex. Aberrant conduction can occur when the atrial premature beat occurs fairly early after the preceding beat. An aberrantly conducted QRS complex has the appearance of a bundle branch block or may just be slightly wider than the normal QRS complex. Aberrantly conducted premature atrial complexes are often mistaken for premature ventricular complexes due to their wider appearance, but are easily recognized by the presence of a preceding P wave. Premature atrial complexes can also have blocked atrioventricular conduction if they occur early enough after a preceding beat. While this is more pronounced in conditions where there is impaired atrioventricular conduction, it is still commonly seen in the presence of normal atrioventricular conduction and is simply a reflection of the impulse reaching the distal conduction system at a time when it or the ventricular myocardium is still refractory to depolarization. Blocked premature atrial complexes have an ectopic P wave that has no QRS complex following. Often, there will be a pause following the ectopic P wave before the next normally conducted sinus return beat (*Fig. 255.2*).

Premature Ventricular Complexes

Isolated ventricular ectopy is common in neonates and children as well. Ventricular ectopic beats can be distinguished from atrial ectopic beats as the QRS complex is often very wide and the T wave is often in an opposite axis to that of the normal QRS-T complex. There will be no P wave preceding the premature QRS complex. In isolation, ventricular ectopy has no pathologic implication in a child who has no clinical signs or symptoms to suggest any cardiac pathology.

Benign ventricular ectopy occurs in many school-aged children and adolescents. In the setting of a structurally and functionally normal heart, this generally has no clinical implications. Recent data have suggested that significantly elevated ectopy burdens can lead to ventricular dysfunction, but in most cases this does not require any treatment unless symptomatic. Most adolescents with benign ventricular ectopy are largely asymptomatic, even with relatively high ectopy burdens. Frequently, the ectopy will be suppressed by increased sinus rates. However, the absence of this feature does not have any predictive significance. In certain situations, patients may be exquisitely aware of their ventricular ectopy, which when frequent can be highly distracting. Any medication that diminishes spontaneous automaticity will usually decrease ventricular ectopy. Beta blockers and calcium channel blockers are commonly used to this end.

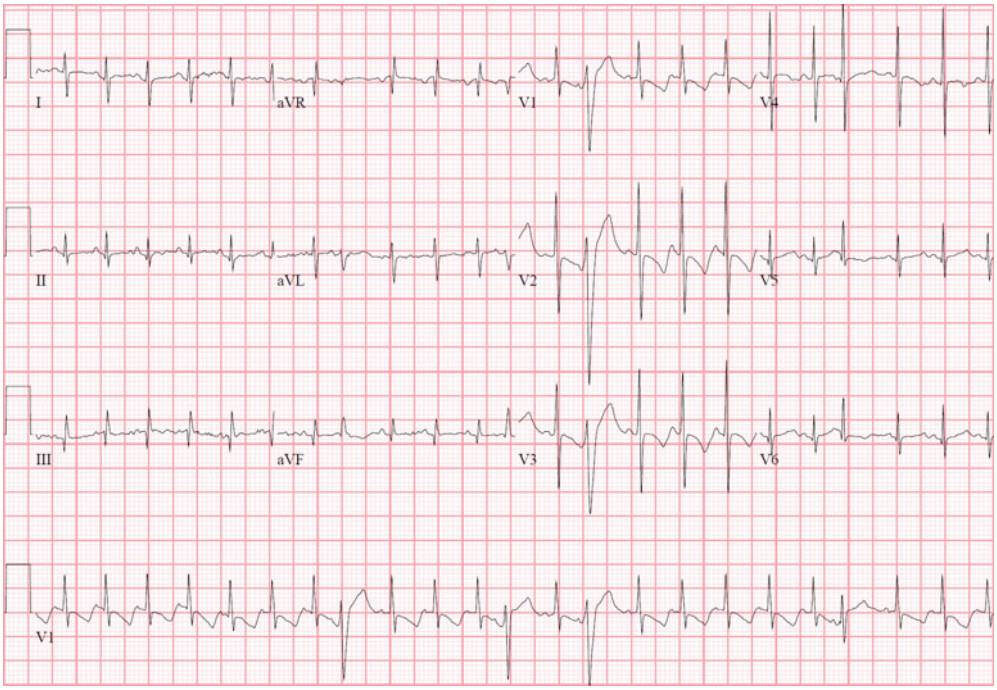

Figure 255.2
Premature atrial complexes. Each of the wide QRS complexes are preceded by P waves, indicating "aberrant" conduction. The last PAC is conducted normally

Bradycardic Rhythms

Sinus Bradycardia

The rate of the sinus node depends upon several factors. There are sympathetic and parasympathetic inputs to this area that influence the rate of automatic discharge from these cells. Sinus bradycardia describes the condition when the rate of impulses from the sinus node is slower than the typical range. This depends on the age of the patient, as the heart rate ranges vary considerably through infancy and childhood. Sinus bradycardia is generally distinguished from other slow atrial rhythms by the presence of a sinus P wave (see above).

Sinus bradycardia can be seen as a consequence of several conditions. It can be a late sequela after certain surgeries for congenital heart disease (such as for tetralogy of Fallot, transposition of the great arteries, or single-ventricle Fontan palliation). Sinus bradycardia may also occur as pharmacologic effect of certain drugs, in particular medications that affect automaticity, such as beta blockers or calcium channel blockers. Metabolic conditions such as hypothyroidism can result in sinus bradycardia.

Sinus bradycardia does not require treatment unless the patient is symptomatic. This is ambiguously defined; however, some symptoms that might fit would include fatigue, exercise intolerance, dizziness, near-syncope, or syncope. Management of sinus bradycardia is directed toward treating any underlying cause. Any offending medication or metabolic abnormality should be removed or corrected. Even in premature infants with frequent episodes of sinus bradycardia, including asystole, the problem is usually self-limited and rarely requires treatment. When symptomatic sinus bradycardia is expected to be more permanent, however, permanent pacemaker implantation may be required (see below).

Junctional Bradycardia

The region of the atrioventricular (AV) junction comprises the AV node and the His bundle. This exhibits automatic behavior in a fashion similar to the sinoatrial

node. Though poorly characterized, cells from the AV junction can originate action potentials that are then conducted from that point normally to the myocardium. The result is a normal-appearing (typically narrow) QRS complex. There will generally be no preceding P wave before the QRS complex. Sometimes P waves will be visible, but not in association with the junctional QRS complexes; although the P waves can also be seen superimposed upon the QRS complex when the atrium is activated simultaneously with the ventricles. When there is no atrial rhythm (e.g., sinus rhythm) to conduct, the AV junction automaticity becomes evident. This is known as a junctional escape rhythm and is usually at a much slower rate than is associated with sinus rhythm. Typical rates are between 45 and 55 beats per minute. However, when sinus nodal activity is faster and exceeds the junctional escape rate, normally conducted sinus rhythm is present (*Fig. 255.3*).

Junctional escape rhythm also occurs in association with complete (third-degree) atrioventricular block. In this setting, the rate of sinus P waves is usually normal for age, but none are conducted through the AV node. The junctional escape rate continues independently of the sinus rhythm. The rhythm of the atria and the ventricles are thus dissociated.

Supraventricular Arrhythmias

Sinus Tachycardia

Sinus tachycardia occurs when the rate of sinus node firing is greater than the upper limits of normal resting heart rate for age. The P wave morphology is typically normal, which differentiates this supraventricular rhythm from other forms of supraventricular tachycardia (see below). Common causes include increased catecholamine states, pain, anxiety, fever, intravascular dehydration, hyperthyroidism, and anemia. Treatment of sinus tachycardia is directed toward identifying and removing the cause of the drive for tachycardia.

The syndrome of inappropriate sinus tachycardia is an uncommon condition in which the average resting rates are faster than the normal range for age. In addition, normal activities that would typically result in mild sinus node acceleration, cause rapid acceleration that is fairly

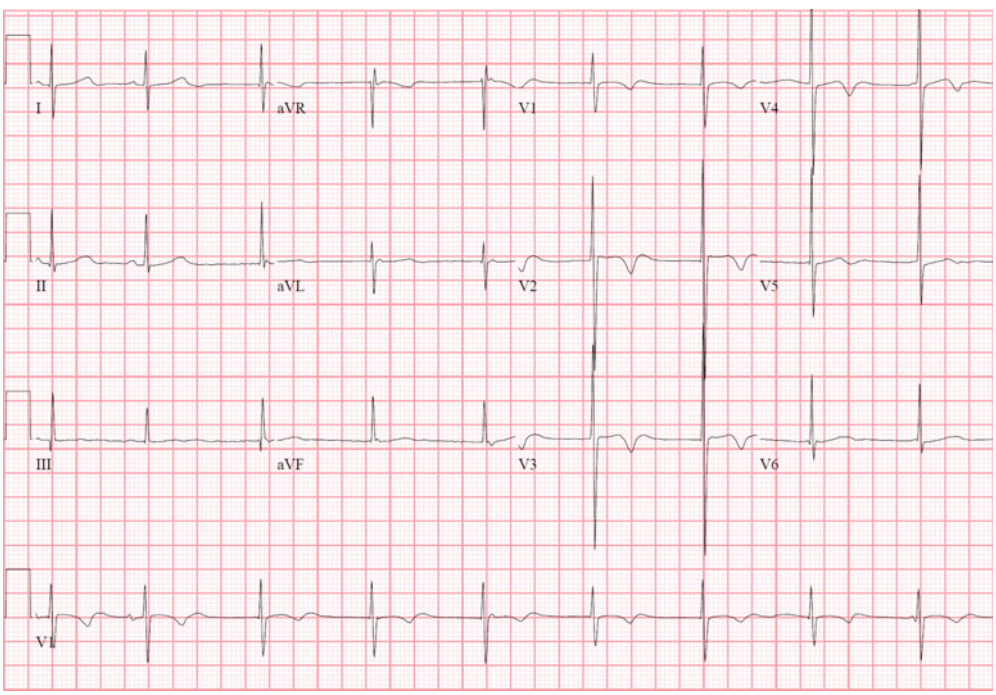

Figure 255.3
Junctional escape rhythm. After the first two sinus beats, there is severe sinus bradycardia with junctional escape rhythm at a rate of 62

symptomatic for the patient. Inappropriate sinus tachycardia is distinguished from other causes of sinus tachycardia by the nearly permanent nature of the arrhythmia, but care must be made to avoid making this diagnosis when there is a treatable cause of sinus tachycardia. This arrhythmia is rare in childhood, and is seen more commonly beginning in the second and third decades of life. Females are affected more often than males. When appropriately diagnosed, this condition is treated with drugs that diminish automaticity, namely, beta blockers or calcium channel blockers. In rare cases of highly symptomatic inappropriate sinus tachycardia that is recalcitrant to medical therapy, catheter-based modification of the sinus node may be used, although this is rarely required in children.

Supraventricular Tachycardia

The term "supraventricular tachycardia" encompasses a spectrum of arrhythmias that result in a rapid rhythm that involves the atria, hence the rhythm is supraventricular, or above the ventricles. These are most commonly divided into reciprocating arrhythmias such as accessory pathway-mediated tachycardia and atrioventricular nodal reentry tachycardia, and the automatic tachyarrhythmias such as atrial ectopic tachycardia and junctional tachycardia. As a group, these arrhythmias are relatively common in childhood. It is estimated that as many as 1 in 250 children will experience supraventricular tachycardia. When supraventricular tachycardia often occurs in an otherwise normal child, it may be highly symptomatic, but in most cases it is entirely benign. These arrhythmias may exact a significant impact on quality of life for the child, their family, and their community, which can influence the decisions regarding management. The exact mechanism of the supraventricular tachycardia may not be entirely obvious upon first presentation, but an accurate diagnosis is important for appropriate treatment.

Accessory Pathway-Mediated Tachycardia

Supraventricular tachycardia that utilizes an accessory pathway as the source of arrhythmia is the most common form of supraventricular tachycardia in childhood, but represents a smaller percentage of arrhythmia mechanism as the child ages. An accessory pathway provides the ability for electrical conduction to occur in an abnormal fashion. Normally, the penetrating fibers of the His bundle are the only mode of conduction across the insulating atrioventricular rings. However, when an accessory pathway bridges this barrier, a potential circuit exists. When conditions are appropriate, electrical impulses not only conduct normally to the ventricles through the His-Purkinje system, but may then conduct retrograde over the accessory pathway back to the atria. If not in their refractory periods, the atria, AV node, and His-Purkinje system conduct the electrical impulse back through to the ventricles, resulting in a rapid repetitive rhythm called atrioventricular reciprocating tachycardia. Heart rates can range between 180 and 250 beats per minute, and typically at a very fixed rate. So called "retrograde" P waves may be visible following the QRS complex, as evidence of the conduction time between activation of the ventricles, passage through the accessory pathway, and subsequent reactivation of the atria.

Most patients are aware of the sensation of rapid heart rate, or palpitations, but may show no other outward signs of the arrhythmia. Dizziness and lightheadedness are common, but not necessary; frank syncope is very rare. Pallor, diaphoresis, and respiratory pattern changes may be present. In the smaller infant there may be no symptoms at all, which can often delay the diagnosis. While this is usually diagnosed at the onset of symptoms, delayed recognition of supraventricular tachycardia is a cause of decreased ventricular function called tachycardia-induced cardiomyopathy, and can possibly lead to cardiovascular collapse.

When an accessory pathway only conducts retrograde, it is called a concealed accessory pathway. That is to say that it is not evident during normal sinus rhythm conditions, and is only active during reciprocating tachycardia. A manifest accessory pathway is one whose presence is obvious during normal sinus rhythm. These are pathways that cause the preexcitation of the Wolff–Parkinson–White pattern (see above). Manifest pathways usually conduct bidirectionally; anterograde conduction results in preexcitation on resting electrocardiogram, and retrograde conduction results in reciprocating tachycardia (*Fig. 255.4*).

Accessory pathways are felt to be embryologic remnants. Histological studies have demonstrated that numerous potential electrical connections exist in the developing heart of chick and human embryos. As fetal development proceeds, most of these excess connections regress as the atrioventricular rings form from the endocardial cushion tissue, with the most notable exception being the penetrating bundle of His. The prevalence of accessory pathways is impossible to know, although it is estimated that 1:1,000 persons have an accessory connection. Most connections are concealed, and therefore

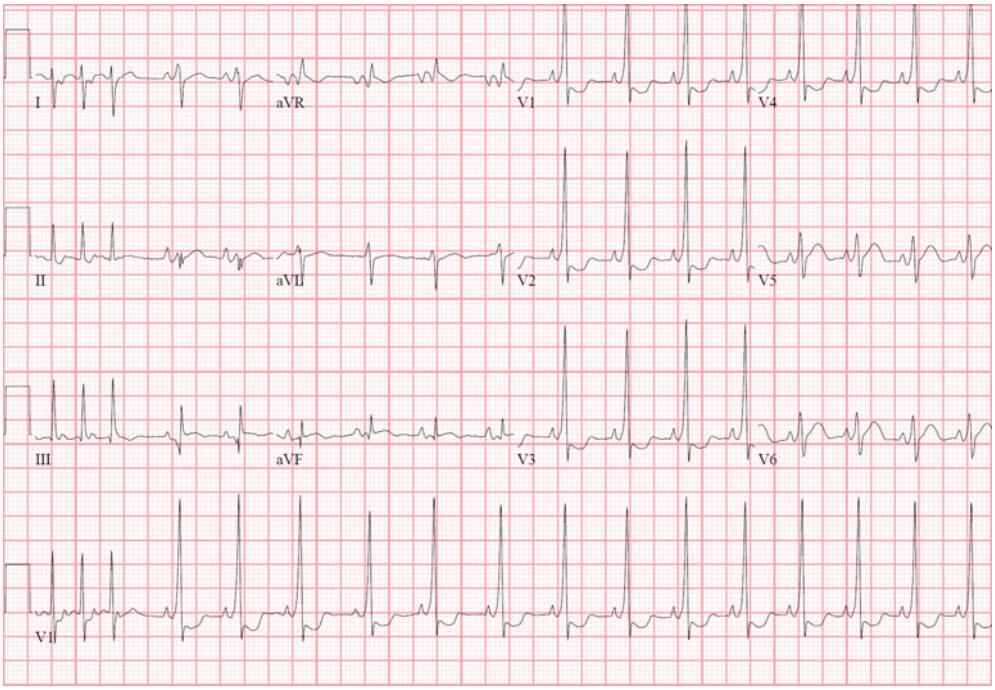

Figure 255.4
Supraventricular tachycardia. Spontaneous termination of SVT followed by sinus rhythm with Wolff–Parkinson–White pattern. Note the widened QRS, short PR, and slurred upstroke delta wave during preexcited rhythm

cannot be diagnosed by regular means unless a person has reciprocating tachycardia and undergoes invasive electrophysiologic testing (see below).

Atrioventricular Nodal Reentry Tachycardia

Another common reciprocating supraventricular tachycardia is atrioventricular nodal reentry tachycardia (AVNRT). With this arrhythmia, the circuit of tachycardia is contained entirely within the AV node itself and its inputs. The requisite for AVNRT is the presence of separate tracts within the AV node, called "fast" and "slow" pathways. This "dual AV nodal physiology" is usually only evident during invasive electrophysiologic testing. AVNRT is very rare in young children, becoming more common in school age and adolescents as well as adults. It is suspected that "dual AV nodal physiology" develops with age and while commonly found in adults is less prevalent in children.

Heart rates during AVNRT are similar to that found in accessory pathway-mediated tachycardia, generally between 180 and 240, although it is occasionally much slower. Palpitations are reported by patients experiencing AVNRT, and the signs and symptoms are similar to other reciprocating tachycardia. As with accessory pathway-mediated tachycardia, the QRS complex is narrow unless rate-related aberrant conduction is present. Generally, as the atria and ventricles are activated simultaneously and P waves are not readily visible, as they are superimposed upon the much higher amplitude QRS complexes. A small R′ can sometimes be seen during tachycardia only. As this is not present during normal sinus rhythm, this "pseudo-RSR′ pattern" is suggestive of this tachycardia, although not entirely pathognomonic.

As with other reciprocating tachycardias, the recurrence of AVNRT can be reduced using nodal blocking drugs. Beta blockers, digoxin, or calcium channel blockers are commonly used alone or in combination. Intravenous adenosine administration can be very successful in acutely terminating the tachycardia. Direct current cardioversion will often terminate the tachycardia, but is usually not necessary. Invasive electrophysiology study with catheter ablation may also be offered in centers where such procedures are provided.

Atrial Ectopic Tachycardia

Less common, but still well represented among pediatric supraventricular arrhythmias is atrial ectopic tachycardia

(AET). This is also known by other monikers such as ectopic atrial tachycardia or focal atrial tachycardia. In contrast to the reciprocating arrhythmias, AET is not caused by a bypass tract. Rather, this arrhythmia is caused by a focus of cells in the atria that have automatic properties (such as the sinus node) that exceeds the rate of the sinus node. The result is paroxysmal bursts of tachycardia; although prolonged and even incessant tachycardia can also be seen. These are frequently catecholamine sensitive, with increased symptoms experienced during times of activity or excitement. Heart rates during tachycardia can be variable, from 120 to over 300 beats per minute. Indeed, this heart rate variability is one of the distinguishing features from reciprocating tachycardias. In addition, the tachycardia accelerates ("warm-up") and decelerates ("cooldown") at the onset and termination. On electrocardiogram, atrial ectopic tachycardia is distinguished from sinus tachycardia by the morphology of the P wave. As the origin of atrial activity is not from the sinus node, the P waves are usually abnormal in appearance, often strongly inverted in the inferior leads (II, III, and aVF) and the anterior precordial (V1 and V2) leads. The P wave morphology on surface ECG can sometimes be used to predict the origin of tachycardia. Most of the time, the ectopic P waves can be demonstrated to be conducted with a normal QRS complex. Second-degree AV block may be observed, with the atrial rhythm continuing unabated despite inconsistent AV conduction (*Fig. 255.5*).

Correct identification of this arrhythmia is important to its appropriate treatment. Purely nodal blocking drugs will have little to no effect on this arrhythmia. Intravenous adenosine administration might demonstrate atrioventricular block with continuation of the atrial arrhythmia, although numerous studies have demonstrated that adenosine can terminate this arrhythmia, if only transiently. Direct current cardioversion is generally unsuccessful in terminating this arrhythmia. Given its automatic nature, cardioversion may temporarily cause the arrhythmia to cease, only to have it reinitiate promptly afterward. For medical management, drugs that diminish automaticity such as beta blockers, calcium blockers, sodium channel blockers are most likely to have an effect. In the long term, medical therapy is generally not successful in controlling this arrhythmia, especially in the setting of concurrent palliated or repaired congenital heart disease. The outlook for patients with AET is variable. Those who have the onset of tachycardia during infancy have a higher likelihood of spontaneous regression of the

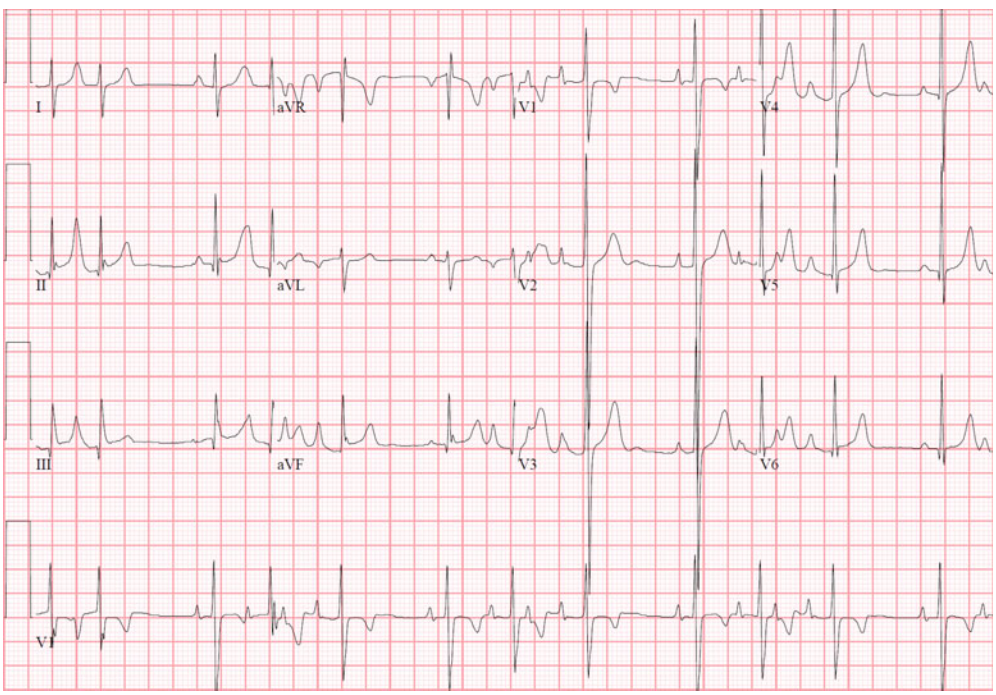

Figure 255.5
Atrial tachycardia. Bursts of atrial tachycardia in a patient presenting with myocarditis

arrhythmia than in those who develop their arrhythmia when older. For patients with recurrent atrial tachycardia, catheter ablation is also a therapeutic option with a high success rate.

Junctional Ectopic Tachycardia

Another automatic supraventricular arrhythmia seen in the pediatric population is junctional ectopic tachycardia (JET). This can be either acquired or congenital. The acquired form typically occurs in 3–10% of patients following cardiopulmonary bypass for congenital cardiac surgeries. While generally self-limited, this can become a significant management problem in a severely compromised postoperative patient. The congenital form is quite rare. In both of these types, the QRS complex is narrow, but usually not preceded by a P wave of any sort; ventriculo-atrial dissociation is present. P waves may be visible but do not precede the QRS complexes in any regular pattern. As an automatic arrhythmia, junctional tachycardia demonstrates the same "warm-up" and "cool-down" behavior as seen in automatic atrial tachycardia. Rates in tachycardia may vary between 170 and 210 beats per minute. Junctional rhythms that are not as fast as JET rates are often described as "accelerated junctional rhythm" and do not necessarily require treatment. At faster rates, the ventriculo-atrial dissociation can result in decreased cardiac output.

Junctional tachycardia is typically seen in an intensive care setting. Treatment includes cooling measures, temporary pacing, medical therapy, or extracorporeal support. JET does not usually respond to the types of antiarrhythmic medications used in other forms of supraventricular tachycardia. Procainamide, sotalol, and amiodarone are commonly utilized. Paroxysmal forms can be seen and may be treated medically, but also may be approached by catheter ablation in selected cases.

Atrial Flutter/Neonatal Flutter

Under certain conditions, a reentrant rhythm circuit can occur entirely within the atria themselves, that is, entirely independent of conduction to the ventricles. This is known as atrial flutter. While atrial flutter is commonly seen in adult, it is relatively rare in the child with a structurally normal heart. When present in the setting of either palliated or repaired congenital heart disease, it is referred to as "intra-atrial reentry tachycardia." During atrial flutter, the atria contract at a rapid rate, anywhere from 250 to well above 300 beats per minute. The atrioventricular node cannot generally conduct at this rate, but will conduct every second (2:1) or third (3:1) impulse; younger patients may conduct every atrial beat (1:1), resulting in a very rapid ventricular rate. On electrocardiogram, characteristic sawtooth "flutter waves" may be seen, particularly in leads II and III. These flutter waves persist at a consistent rate, regardless of the ventricular QRS rate. Administration of nodal blocking medications, in particular intravenous adenosine, can be diagnostic by blocking AV nodal conduction, while the flutter waves continue without interruption.

Atrial flutter can be seen not uncommonly in the late-term fetus and perinatal infant. This is known as fetal or neonatal flutter. In the fetus, brisk AV nodal conduction often results in rapid (1:1) ventricular rate. When undetected and untreated, this can result in congestive heart failure, which manifests as hydrops fetalis. Diagnosis may be difficult as it is unusual to be able to actually obtain a rhythm recording or electrocardiogram. A fetal echocardiogram may be able to demonstrate the rapidly contracting atria. Treatment of fetal flutter may be difficult due to the buffered nature of the fetus within the amniotic sac. Antiarrhythmic medications may be given through the mother, although high maternal doses are often required to achieve adequate transplacental levels within the fetus. For neonates who experience atrial flutter, direct current cardioversion is highly successful in terminating the arrhythmia, with a low rate of recurrence.

Ventricular Arrhythmias

Arrhythmias that predominantly involve the ventricles are known as ventricular tachycardias. Ventricular tachycardia takes many forms, ranging from a benign paroxysmal palpitations to a life-threatening arrhythmia. Early and accurate diagnosis is essential to differentiate between these ends of the spectrum. In general, ventricular tachycardias have a wide QRS complex with rates greater than 120–150 beats per minute. There are several diagnostic features of ventricular tachycardia. (1) Ventriculo-atrial dissociation. The ventricular rate usually exceeds the sino-atrial rate, and more QRS complexes than P waves may be seen on electrocardiogram. (2) Sinus capture beats. When appropriately timed P waves occur, they will conduct normally and be followed by a normal QRS-T complex. (3) Fusion beats. Sometimes, normally conducted QRS complexes will be superimposed by the wide QRS complex of the tachycardia. The result is an "in-between" QRS

complex that is neither wide nor narrow. (4) Wide QRS complex. This is not a necessity for ventricular tachycardia, as some forms of ventricular tachycardia have a relatively narrow QRS complex and can be mistaken for supraventricular tachycardia.

Accelerated Ventricular Rhythm (Accelerated Idioventricular Rhythm)

When the intrinsic ventricular automaticity is enhanced, an accelerated (idio)ventricular rhythm (AIVR) may be observed. This is often due to intrinsic catecholamine states, metabolic or electrolyte disturbances, or other conditions which may lead to increased myocardial automaticity. The QRS morphology is typically wide, differentiating this from other forms of increased automaticity such as accelerated junctional rhythm. The rate in AIVR may only slightly exceed the normal sinus rate or occasionally may be as fast as 120–150 beats per minute. This is generally very well tolerated hemodynamically, except in the extremely compromised child. AIVR can occur in normal individuals and does not portend any more significant arrhythmias. Diagnosis is made by identifying a wide QRS complex rhythm with rates slightly elevated above the patient's resting normal; with the ventricular rate exceeding the atrial rate, generally with ventriculoatrial dissociation. Treatment is directed by symptoms, although most patients are entirely asymptomatic. Drugs which decrease automaticity, such as beta blockers or calcium channel blockers, may decrease the presence of AIVR, but the rhythm itself is usually more bothersome to caregivers than to the patients themselves.

Monomorphic Ventricular Tachycardia

This form of ventricular tachycardia is most commonly due to increased automaticity from a locus within either the right or left ventricles, usually originating in either the right ventricular outflow tract or left ventricular outflow tracts. In the setting of a child with a structurally and functionally normal heart, it is considered benign. The tachycardia rate can range between 150 and 200, and often occurs in short bursts and volleys, although persistent forms can be seen. This is a wide QRS tachycardia typically with an inferior axis (positive QRS complex in lead aVF). Unless associated with other structural or functional heart disease, this does not progress to any more dangerous form of ventricular tachycardia and is treated on a symptomatic basis. As with the automatic supraventricular arrhythmias, medications that diminish myocardial automaticity are the primary medical therapies. Beta blockers and calcium channel blockers are commonly used, although numerous other antiarrhythmic medications have been used with good success. For patients with frequent recurrent episodes, invasive electrophysiology testing with catheter ablation is commonly utilized as well.

Another form of monomorphic ventricular tachycardia encountered in the pediatric population is known as "verapamil-sensitive ventricular tachycardia." As the moniker suggests, this form of arrhythmia is exquisitely sensitive to calcium channel blocker medications, which are the primary form of therapy. This is generally a paroxysmal arrhythmia, often having a very abrupt onset during activity. The tachycardia is a wide QRS complex with rates ranging between 150 and 200. The hallmark electrocardiogram of this arrhythmia is a right bundle branch pattern with a superior frontal plane axis (the QRS complex is negative in lead aVF). Given the relatively slow rates, this is typically very well tolerated, although some patients may have frequent and incessant tachycardia. Acute treatment with intravenous calcium channel blockers followed by oral therapy is indicated. Cardioversion may be used, but is rarely necessary. For those with frequent recurrent episodes, catheter ablation is also an option with good success rates.

Polymorphic Ventricular Tachycardia

In contrast to the stability monomorphic ventricular tachycardia, polymorphic ventricular tachycardia is a much more disorganized and a potentially life-threatening ventricular arrhythmia. It is an associated symptom of many forms of primary arrhythmia diseases, particularly those associated with sudden arrhythmic death. Like other forms of ventricular arrhythmias, this is diagnosed by identifying a rapid wide QRS complex tachycardia on rhythm recording. However, the QRS morphology varies widely from beat to beat, indicative of the generally disordered ventricular depolarizations underlying this arrhythmia. Cardiac output is severely reduced. If self-limited, this rapidly results in loss of consciousness and syncope. If sustained, sudden cardiac death can ensue. A particular variant of polymorphic ventricular tachycardia is known as *torsades de pointes*. Literally, "twisting about a point," the amplitude and axis of the QRS morphology rotates and undulates until eventually degenerating into a more chaotic ventricular fibrillation. It is the characteristic arrhythmia associated with Long QT Syndrome and other sudden arrhythmia death syndromes.

Ventricular Fibrillation

Ventricular fibrillation is an extremely rapid and chaotic ventricular rhythm. It is the final and the ultimate cause of death for many cardiac diseases. The electrocardiogram demonstrates a very fine and rapid disorganized rhythm with no recognizable P waves or QRS complexes. This can be caused by respiratory arrest, severe metabolic derangement, acidosis, or a primary cardiac cause. In rare instances, some people experience spontaneous and self-limited ventricular fibrillation. The cause of this idiopathic ventricular fibrillation is not well understood. Treatment is via immediate direct current defibrillation, either by external or internal defibrillator. Delay to defibrillation therapy rapidly results in brain and other end organ insult, and ultimately death.

Primary Arrhythmia Syndromes

There are several conditions that deserve separate mention. These are the primary arrhythmia syndromes in which arrhythmias are usually the sole symptom, usually without any other associated cardiac or systemic disease.

Wolff–Parkinson–White Syndrome

As has been described above, the Wolff–Parkinson–White syndrome involves the presence of preexcitation pattern on electrocardiogram in association with either palpitations or syncope. This is the result of an accessory pathway bypass tract that causes activation of the ventricles in addition to the normal His-Purkinje activation system. The degree of preexcitation depends largely on the location of the accessory pathway (or pathways) itself, and very little to do with the morbidity associated with this condition. As described previously, these accessory conduction pathways are embryologic remnants and have a prevalence that is estimated to be approximately 1 in 1,000 persons.

The characteristic arrhythmia associated with Wolff–Parkinson–White syndrome is a narrow QRS complex tachycardia mediated by the accessory pathway, called atrioventricular reciprocating tachycardia. During this supraventricular arrhythmia, conduction occurs in a normal antegrade fashion over the His-Purkinje system, resulting in a normal narrow QRS complex. Conduction then passes in a retrograde fashion over the accessory pathway to the atria, after which conduction enters the atrioventricular node and the His-Purkinje system in a repetitive fashion. Patients will experience paroxysmal episodes of rapid heart rate, causing palpitations. Some will have dizziness and chest discomfort; frank syncope during supraventricular tachycardia is rare.

Patients with Wolff–Parkinson–White have an increased risk of other atrial arrhythmias, particularly atrial fibrillation. During rapid atrial arrhythmias, electrical activation over the atria can bypass the atrioventricular node and His-Purkinje system entirely, resulting in extremely rapid conduction to the ventricles, and can lead to ventricular tachycardia or ventricular fibrillation. As a result, there is also an increased incidence of sudden cardiac arrest in those with preexcitation; sometimes this can be the first and sole symptom of this condition. The incidence of sudden death in Wolff–Parkinson–White syndrome is approximately 0.1–0.5% per patient year. The risk factors that have been proposed are numerous, but there is no single feature that adequately characterizes the high-risk patient. Noninvasive strategies to identify patients at greatest risk have been utilized through the years, but particularly in children, these have failed to provide a reliable means of risk stratification. In many centers, the gold standard has become invasive electrophysiology testing for risk stratification with catheter ablation when appropriate, once patients are felt to be appropriate candidates for the procedure.

Long QT Syndrome

The Long QT Syndrome is a family of disorders in which one of the myocardial ion channels (typically one of the potassium or sodium channels) is altered, resulting in prolongation of the cardiomyocyte action potential. The net result is lengthening of the QT interval on electrocardiogram. Patients with LQTS may be entirely asymptomatic, but have a predisposition toward syncope, seizures, ventricular arrhythmias (particularly polymorphic ventricular tachycardia), and sudden cardiac arrest. Formerly considered to be divided into autosomal dominant (Romano-Ward syndrome) and autosomal recessive (Jervell-Lange-Neilsen syndrome, or JLNS) forms, this distinction is now felt to be less clear. Patients with JLNS are homozygous for mutations in one of the myocardial potassium channels that is also expressed in the middle ear, resulting in congenital sensorineural deafness. The overall prevalence of LQTS in the general population is approximately 1:2,500, with JLNS being much less common. In most situations, the absolute QT measurement does not have much clinical significance. Formulae for normalizing this value for heart rate are used, with Bazett's

equation being the most widely used. This equation gives a correct QT interval (QTc) that is equal to the QT measurement divided by the square root of the preceding R–R interval (in seconds). While newborn infants may have resting QTc of up to 480, the upper limits of normal are 460 for a normal female and 450 for a normal male (*Fig. 255.6*).

The risk factors that characterize high-risk LQTS patients remains an active area of research. Certain combinations of specific mutation, resting QTc length, sex of the patient appear to be most useful in predicting risk of cardiac events, although this is far from a perfect method. Some countries (for example, Italy and Japan) have instituted nationwide electrocardiographic screening of newborns, school-aged children, and atheletes in an effort to diminish the incidence of sudden cardiac arrest in otherwise unrecognized and otherwise healthy children and young adults.

The primary therapy for most patients with LQTS is medical therapy with beta blockers and activity restrictions from highly competitive athletics. Selected patients who have either survived cardiac arrest or are felt to be at excessive risk for sudden cardiac death may have an internal defibrillator implanted. Genetic information is becoming helpful in guiding management as there appear to be distinct genotype–phenotype relationships in LQTS not present in other similar types of conditions, however specific genotypic-specific therapies are not yet available.

Brugada Syndrome

The Brugada syndrome is another primary electrical disease characterized by distinctive electrocardiographic changes. Specifically, there is significant ST segment elevation in the anterior (V1 and V2) precordial leads with associated T wave inversions. As with LQTS, the heart is structurally normal in Brugada syndrome. The actual prevalence is difficult to assess, but it is estimated to affect 1–5 per 10,000, but is much more common in Southeast Asian populations. Patients can experience palpitations, ventricular arrhythmias, and syncope. Sudden cardiac death, particularly during sleep, is an unpredictable outcome although this is a rare event in childhood. Genetic testing can identify a sodium channel mutation in approximately 20% of patients with Brugada syndrome. There are no known drugs that have been identified to diminish the symptoms or the risk of life-threatening arrhythmias

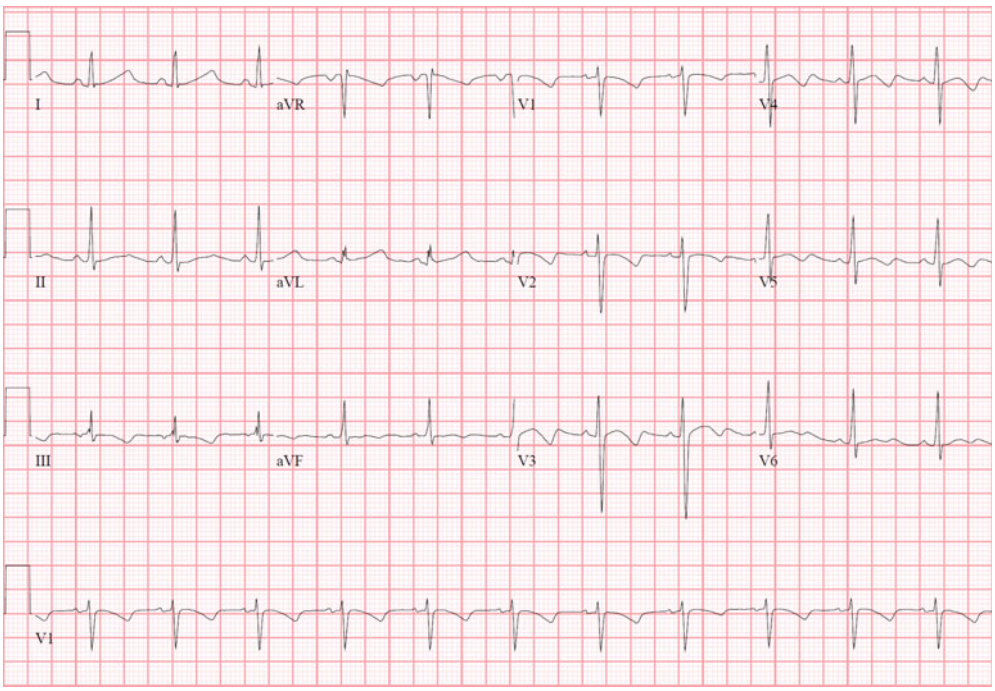

Figure 255.6
Long QT syndrome. Long broad T waves in patient diagnosed after surviving cardiac arrest. Characteristic T wave notching across precordial leads V2–V6 are seen

in Brugada syndrome. Implantable defibrillators have been demonstrated to improve survival in this group, although appropriate patient selection is controversial.

Implantable Arrhythmia Devices

Pacemakers

For patients in whom bradycardia is an irreversible and symptomatic problem, implantable pacemaker therapy may be indicated. By means of leads attached to the heart, a pacemaker can sense either atrial or ventricular activity, and provide electrical activation to either the atria or ventricles when necessary to improve heart rate. This may involve pacing the atrium (atrial pacemaker), pacing the ventricle (ventricular pacemaker), or both (dual chamber pacemaker). Pacemakers can be implanted in a pectoral position, with the leads connecting it to the heart running in a transvenous route to the endocardial surface. In some patients, the device may be placed in an epicardial location, with the leads sewn to the epicardial surface, and the pacemaker generator placed in an adjacent location, often within the abdomen.

Defibrillators

Some patients have a significantly elevated risk of experiencing a lethal ventricular arrhythmia, either because they have already survived a cardiac arrest at least once before or they are felt to have a substantial risk from underlying structural or primary electrical disease, an implantable defibrillator may be used. Implantable cardioverter-defibrillators (ICDs) are implanted in much the same way that implantable pacemakers are. They also have nearly all of the same functionality; that is to say that they can provide pacing to the attached atrium or ventricle when necessary. However, a primary distinction is that an ICD can also detect tachycardic events, primarily ventricular tachycardia and ventricular fibrillation, and have the capacity to deliver a defibrillation shock to terminate the arrhythmia.

Electrophysiology Study and Catheter Ablation

Certain arrhythmias may be amenable to invasive investigation in the electrophysiology laboratory, and potentially to utilize catheter ablation to provide a cure for the arrhythmia. This requires the placement of several multielectrode catheters within the heart via a transvenous approach. By delivering pacing sequences and analyzing the electrical response, specific arrhythmias and rhythm responses can be elicited. The specific timing of activation of the atria, AV node, His-Purkinje system, and ventricles is measured. The presence or absence of accessory pathway conduction can be demonstrated. And the exact mechanism of a child's arrhythmia can be determined. When deemed appropriate, catheter ablation is performed. This utilizes maneuverable catheters that are positioned directly upon the arrhythmia substrate, whether it is an accessory pathway, anomalous conduction tracts of the AV node, or an ectopic arrhythmia focus. Energy is delivered in the form of radiofrequency (heat) or cryoablation (cold) to destroy the arrhythmia targets, while leaving the rest of the myocardium intact. Initially developed in the 1980s, transcatheter ablation has become a highly successful modality for treatment of a number of arrhythmias. In children, the success rate is quite high, and is commonly conducted in centers that perform this procedure.

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256 Sudden Cardiac Death and Preparticipation Sports Screening

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Definition

Sudden cardiac death is usually defined as unexpected death occurring instantaneously or within 1 h of the onset of symptoms or collapse as a result of natural causes in someone without a previously recognized cardiovascular abnormality.

Etiology

Risk of Sudden Death

Sudden cardiac death in an athlete usually occurs either during (80%) or immediately after (20%) physical exercise, suggesting that participation in competitive sports activity increases the likelihood of cardiac arrest. The risk benefit ratio of physical exercise differs between adults and young competitive athletes. This may be explained by the different nature of cardiovascular substrates underlying sport-related sudden death in the two age-groups (*Table 256.1*).

Atherosclerotic coronary artery disease is the most common cause of sudden death in adults and elderly exercising subjects. Epidemiologic studies support the concept that habitual sport activity may offer protection over the long-term against cardiovascular events. Regular exercise prevents development and progression of atherosclerotic coronary artery disease by favorable effects on lipid metabolism and weight reduction, and enhances both coronary artery plaque and myocardial electrical stability.

Unlike older athletes, a broad spectrum of cardiovascular substrates (including congenital and inherited heart disorders) may underlie sudden death in young competitive athletes (age $\leq$35 years). An Italian prospective study demonstrated that adolescent and young adults involved in sports activity have 2.8 greater risk of sudden cardiovascular death (SCD) than their nonathletic counterparts (*Fig. 256.1*). However, sports is not itself the cause of the enhanced mortality, since it triggers cardiac arrest in those athletes who are affected by cardiovascular conditions which predispose to life-threatening ventricular arrhythmias during physical exercise. This reinforces the need for systematic evaluation of adolescent and young individuals embarking in sports activity in order to identify those with potentially lethal cardiovascular diseases and protect them against the increased risk of sudden death.

Causes of Sudden Death

The vast majority of young competitive athletes who die suddenly have underlying structural heart diseases, which provide a substrate for ventricular tachycardia/fibrillation leading to cardiac arrest. As reported in *Table 256.1*, cardiomyopathies have been consistently implicated as the leading cause of sports-related cardiac arrest in younger athletes. Hypertrophic cardiomyopathy (HCM) has been reported to account for more than one third of fatal cases in the USA and arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) for approximately one fourth in the Veneto Region of Italy. Other cardiovascular substrates for sports-related sudden death in the young include premature atherosclerotic coronary artery disease, congenital coronary anomalies, myocarditis, dilated cardiomyopathy, mitral valve prolapse, conduction system diseases, and Wolff–Parkinson–White (WPW) syndrome.

HCM: This is a genetically determined heart muscle disease, which is characterized by a hypertrophied, nondilated left ventricle in the absence of cardiac or systemic diseases capable of producing hypertrophy. Characteristic morphologic and functional cardiac abnormalities include either symmetric or asymmetric (i.e., with disproportionate septal thickening) LV hypertrophy (*Fig. 256.2a*), and reduction in LV chamber size with increased myocardial stiffness, which may critically impair diastolic LV and intramural coronary blood filling. Dynamic LV outflow tract obstruction is also demonstrable at rest or with exercise in a large proportion of patients. The histopathologic hallmark of HCM is myocardial disarray with widespread, bizarre, and disordered

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arrangement of myocytes usually associated with interstitial and/or replacement-type fibrosis (Fig. 256.2b). Myocardial fibrosis is an acquired phenomenon, in part related to abnormalities of the intramural coronary arteries which show dysplasia of the tunica media with luminal narrowing ("small vessel disease").

HCM has been implicated as the principal cause of sudden death during sports in the USA. Cardiac arrest has been attributed to ventricular fibrillation, which is triggered by the interaction between adrenergic stimulation, such that occurring during physical exercise, and the underlying, electrically unstable cardiomyopathic substrate. The observation of acquired myocardial damage, either acute or in the form of large septal scars, supports the hypothesis that myocardial ischemia intervenes in the natural history of the disease and contributes to the arrhythmogenicity.

ECG abnormalities such as an increased QRS voltage, pathologic "q" waves, and repolarization changes have been reported in up to 95% of patients with hypertrophic cardiomiopathy. This explains why preparticipation ECG screening of young competitive athletes in Italy has allowed successful identification and mortality reduction of athletes with HCM.

ARVC/D: This is an inherited heart muscle disorder that is characterized pathologically by fibro-fatty replacement of RV myocardium. The most frequent clinical manifestations consist of ECG depolarization/repolarization changes mostly localized to right precordial leads, global and/or regional morphologic and functional alterations of the right ventricle, and arrhythmias of RV origin which can lead to sudden death, especially during physical exercise. The propensity for sudden arrhythmic death during physical activity is linked to both hemodynamic and neurohumoral factors. Physical exercise may acutely increase RV afterload and cavity enlargement, which in turn, may elicit ventricular arrhythmias by stretching the diseased RV musculature. Alternatively, the hypothesis of "denervation supersensitivity" of the right ventricle to catecholamines has been advanced. Finally, in a subgroup of patients with familial ARVC/D (ARVD2), a cardiac ryanodine receptor (RYR2) missense mutation has been

Table 256.1
Cardiovascular causes of sudden death associated with sports

Age ≥ 35 years
Atherosclerotic coronary artery disease
Age < 35 years
Hypertrophic cardiomyopathy
Arrhythmogenic right ventricular cardiomyopathy/dysplasia
Premature coronary atherosclerosis
Congenital anomalies of coronary arteries
Myocarditis
Aortic rupture
Valvular disease
Preexcitation syndromes and conduction diseases
Ion channel diseases
Congenital heart disease, operated or unoperated

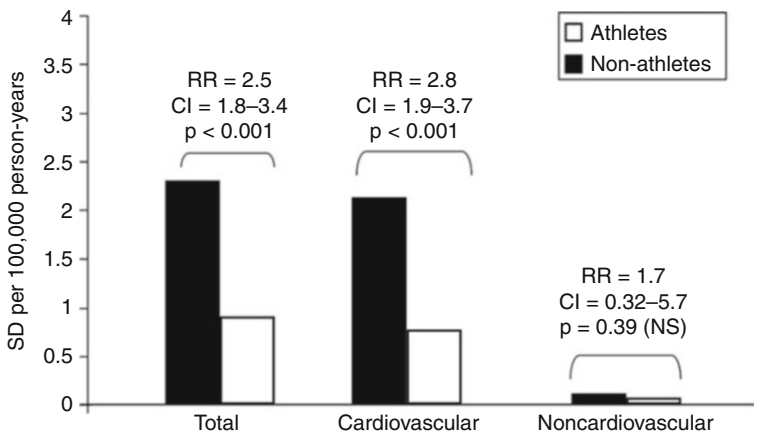

Figure 256.1
Incidence and relative risk (RR) of sudden death among young athletes and nonathletes from total, cardiovascular, and non-cardiovascular causes (Modified from Corrado D, Migliore F, Basso C, Thiene G (2006) Exercise and the risk of sudden cardiac death. Herz 31:553–558)

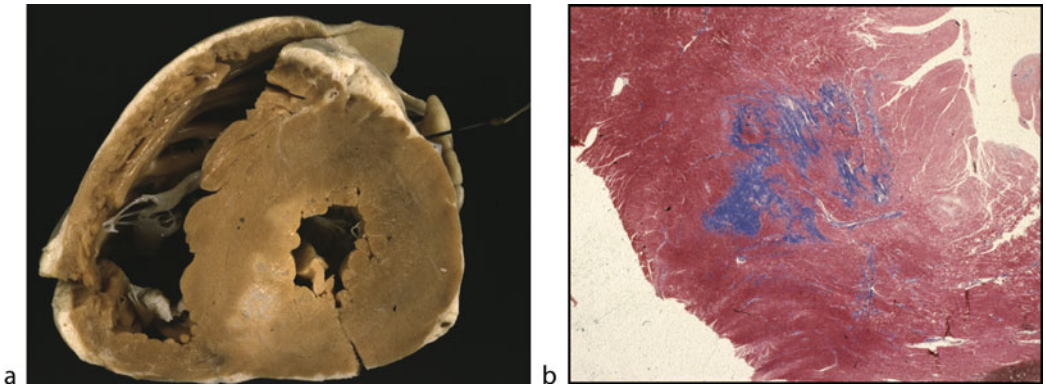

Figure 256.2

A 15-year-old basket player who died suddenly from HCM. (a) Short axis view of the heart showing massive left ventricular hypertrophy and a large scar in the posteroseptal region; (b) corresponding panoramic histologic section showing intraseptal replacement-type fibrosis. Trichrome Heidenhain, original magnification ×3 (Modified from Basso C, Thiene G, Corrado D, Buja GF, Melacini P, Nava A (2000) Hypertrophic cardiomyopathy: pathologic evidence of ischemic damage in young sudden death victims. Hum Pathol 31:988–998)

identified. Such a genetic defect leads to abnormal calcium release from the sarcoplasmic reticulum during effort, which, in turn, induces ventricular arrhythmias due to afterdepolarizations and triggered activity.

The heart of young competitive athletes dying suddenly from ARVC/D demonstrates global RV dilatation and aneurysms of posterobasal, apical, and outflow tract regions, which are potential sources of life-threatening ventricular arrhythmias (*Fig. 256.3*). These pathologic features of the right ventricle allow differential diagnosis with training-induced right ventricular changes ("athlete's heart"), usually consisting of RV enlargement without regional abnormalities.

ARVC/D has been reported to be the leading cause of sports-related sudden death in the Veneto Region of northeastern Italy. The most likely explanation of this finding is that systematic preparticipation screening of young competitive athletes has changed the natural prevalence of cardiovascular causes of sports-related sudden death. In Italy, most sudden deaths due to HCM have been prevented by identification and disqualification of the affected athletes at preparticipation screening. Therefore, other cardiovascular conditions such as ARVC/D have come to account for a greater proportion of all sudden death in Italian athletes.

Early identification of athletes with ARVC/D plays a crucial role in the prevention of sudden death during sport. The disease should be suspected in the presence of inverted T waves in right precordial leads. In this regard, more than 80% of athletes who died from ARVC/D had repolarization ECG changes. In the past, affected athletes had not been identified at preparticipation screening because the disease was unrecognized clinically. More recently, with the increased awareness of the disease, more and more affected athletes are being detected by screening and protected from the risks of athletic competition.

Coronary artery disease: Premature coronary atherosclerosis is an important substrate for sudden death even in young competitive athletes ($\leq$35 years). In these young subjects, coronary artery disease exhibits distinctive characteristics in terms of a warning clinical prodrome and pathological features, such as extent, site, and morphology of obstructive atherosclerotic plaques. Young athletes dying from premature coronary artery disease usually do not have history of angina pectoris or previous myocardial infarction, and sudden death is often the first manifestation of the disease. Exercise testing may fail to show myocardial ischemia or arrhythmias. Fatal coronary atherosclerosis is more often a "single vessel disease" that characteristically affects the proximal left anterior descending coronary artery and is often due to fibrocellular plaques (i.e., fibrous plaques with intimal smooth muscle cell hyperplasia, so-called "accelerated atherosclerosis") and a preserved tunica media in absence of acute thrombosis. These morphological features have been suggested to underlie abnormal hypervasoreactivity, possibly culminating in cardiac arrest by vasospastic myocardial ischemia. Because of the scarcity of warning symptoms and the limitation of exercise testing, early

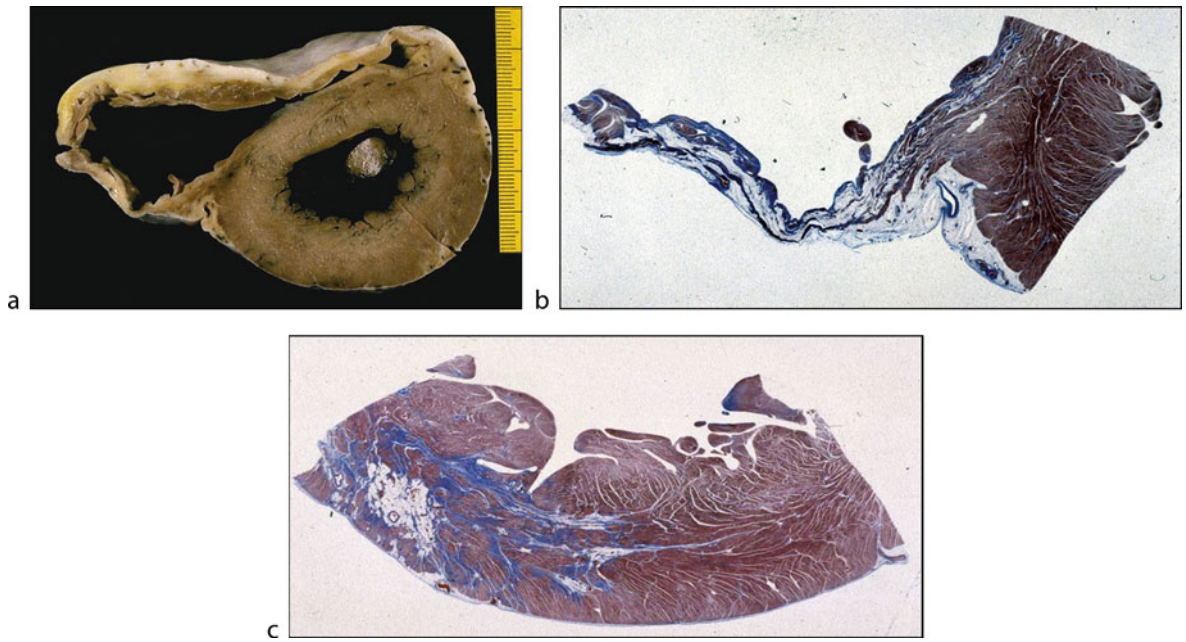

Figure 256.3

A 17-year-old soccer player who died suddenly from ARVC/D. (a) Cross section of the heart specimen with infundibular and inferior sub-tricuspid aneurysms; (b) panoramic histologic view of the aneurysm of the inferior region, showing wall thinning with fibro-fatty replacement. Azan stain, original magnification, × 2.5; (c) panoramic histologic view of the left ventricle showing a spot of fibro-fatty myocardial replacement. Azan stain, original magnification, ×2.5 (Modified from Basso C, Thiene G, Corrado D (1996) Arrhythmogenic right ventricular cardiomyopathy. Dysplasia, dystrophy, or myocarditis? Circulation 94:983–991)

identification of young athletes with premature coronary atherosclerosis at risk of ischemic cardiac arrest remains a challenge.

Congenital coronary artery anomaly: Anomalous origin of a coronary artery from the "wrong" coronary sinus is a congenital malformation with a silent clinical course, which may precipitate sudden and unexpected ischemic cardiac arrest in young competitive athletes. The most frequent anatomic findings consist of both (left and right) coronary arteries arising either from the right or the left coronary sinus. In both conditions, as the anomalous coronary vessel leaves the aorta, it adopts an acute angle with the aortic wall, and, thus, traverses between the aorta and the pulmonary trunk, often following an aortic intramural course, with a "slit-like" lumen (*Fig. 256.4*). Exercise-induced myocardial ischemia has been hypothesized to be caused by aortic root expansion which compresses the anomalous vessel against the pulmonary trunk, increases the acute angulation of the coronary take-off, and aggravates the "slit-like" shape of the lumen of the proximal intramural portion of the aberrant coronary vessel.

Myocarditis: Either in its acute or healed forms, myocarditis may provide a myocardial electrical substrate for ventricular arrhythmias and exercise-related sudden death. Life-threatening ventricular arrhythmias in athletes may also be the result of focal myocarditis, which is clinically silent and difficult to be detected by endomyocardial biopsy.

Other structural causes: Despite its high prevalence in the general population, mitral valve prolapse is a rare cause of sudden death in athletes. The pathogenesis of the sudden cardiac arrest remains unresolved. Fatal coronary embolism from atrial platelet deposits, and cardiac arrest due to malignant ventricular tachyarrhythmias attributed to "valve friction" have been advanced as possible mechanisms.

Ventricular preexcitation syndrome (WPW syndrome) or progressive cardiac conduction disease (Lenègre disease) may represent an uncommon substrate for exercise-related sudden death.

Spontaneous laceration or dissection of the ascending aorta with rupture into pericardial cavity and cardiac tamponade is a rare cause of fatal electromechanical

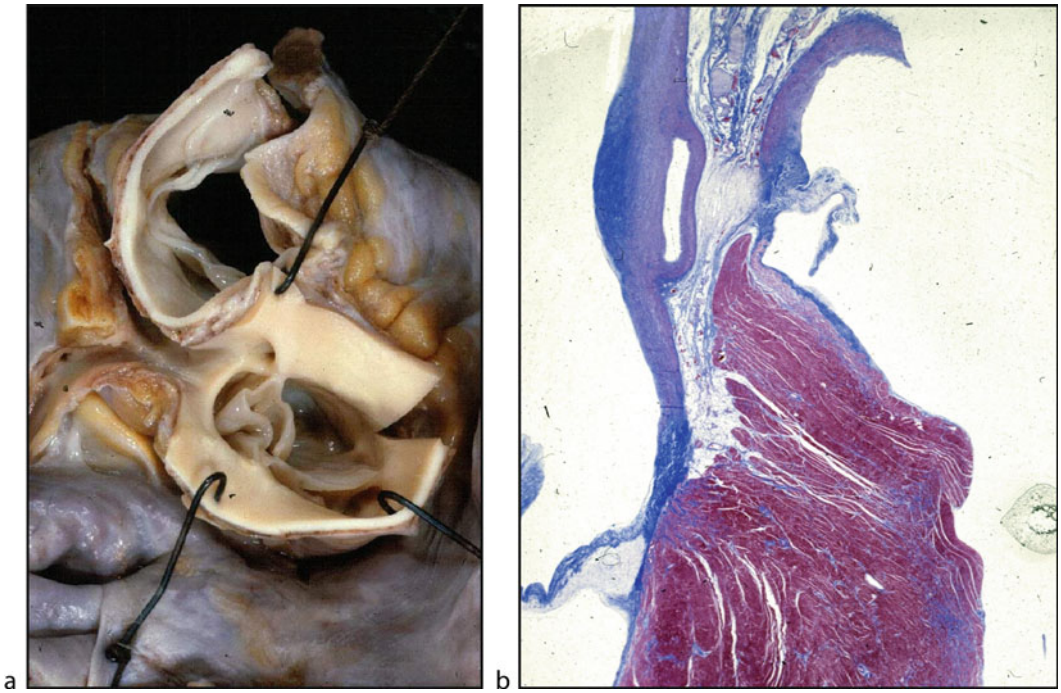

Figure 256.4

A 22-year-old soccer player who died suddenly from congenital coronary anomaly. (a) View of the aortic root showing the right coronary artery ostium arising from the left (wrong) coronary sinus; (b) histology of proximal right coronary artery, which appears to run within the aortic wall (intramural course), with a slit-like lumen (Azan Stain, original stain × 10) (Modified from Corrado D, Thiene G, Nava A, Pennelli N, Rossi L (1990) Sudden death in young competitive athletes: clinico-pathologic correlations in 22 cases. Am J Med 89:588–596)

dissociation during sports. The basic heart defect is an elastic fragmentation of the aortic tunica media with cystic medial necrosis that may rarely present as isolated histologic feature, but more frequently in association with isthmic coartation and/or bicuspid aortic valve, or in the setting of Marfan syndrome.

Nonstructural causes: Two to five percent of young people and athletes who die suddenly have no evidence of structural heart diseases, and the cause of their cardiac arrest is in all likelihood related to a primary electrical heart disease such as inherited cardiac ion channel defects (channelopathies) including long and short QT syndromes, Brugada syndrome, and cathecholaminergic polymorphic ventricular tachycardia.

Long QT syndrome is a genetic disorder characterized by prolonged ventricular repolarization (prolonged QTc interval) that predisposes to life-threatening ventricular arrhythmias such as torsade de pointes. The genetic background resides on defective genes encoding ion channels that regulate myocyte repolarization. According to molecular genetics, seven different variants (LQT1 to LQT7) of long QT syndrome are recognized. Different molecular mechanisms may explain differences seen in clinical manifestations. LQT1 patients are prone to syncope or cardiac arrest during physical exercise, mostly while swimming. On the contrary, LQT3 patients show a bradycardia-dependent QT prolongation, and they experience sudden death events at rest (while sleeping). LQT2 subjects are more susceptible during emotions and under acoustic stimuli.

Brugada syndrome is an inherited ion channel disease characterized by the peculiar ECG pattern consisting of right precordial "coved-type" ST-segment elevation (both spontaneous or induced by pharmacologic sodium channel blockade) in association with arrhythmia-related syncope/cardiac arrest, inducibility at programmed ventricular stimulation, or a familial history of sudden death. A cardiac sodium channel gene (SCN5A) mutation has been detected in up to 30% of Brugada syndrome cases. Ventricular fibrillation leading to sudden death usually occurs at rest and, in many cases, at night (during sleep) as a consequence of an increased vagal stimulation and/or

withdrawal of sympathetic activity. Enhanced adrenergic drive, such as occurs during sports activity, could have an inhibitory effect and theoretically reduce the risk of sudden death. On the other hand, the adaptation of the cardiac autonomic nervous system to systematic training, which results in increased resting vagal tone or during the post-exercise recovery period may enhance the propensity of athletes with Brugada syndrome to die at rest, during sleep, or immediately after effort.

Catecholaminergic ventricular tachycardia is an inherited ion channel disease characterized by exercise-induced polymorphic ventricular tachycardia (most often with the so-called bidirectional pattern) which can degenerate in ventricular fibrillation. Unlike long QT syndrome and Brugada syndrome, this condition is not associated with abnormalities of basal 12-lead ECG and remains unrecognized unless the athlete undergoes ECG stress testing. A genetically defective ryanodine receptor has been reported to account for an abnormal calcium release from the sarcoplasmic reticulum. Accordingly, the potential arrhythmogenic mechanism is triggered activity due to late afterdepolarizations, which are provoked by intracellular calcium overload and enhanced by adrenergic stimulation such as that during sports exercise.

Trauma-related sudden death: Blunt, non-penetrating, and often innocent appearing blows to the precordium may trigger ventricular fibrillation without structural injury to ribs, sternum, or heart itself (commotio cordis). Commotio cordis is most frequently caused by projectiles which are implements of the game and strike the chest at a broad range of velocities, such as hockey pucks, or by virtue of bodily collision, for example, a karate blow. Based on experimental and clinical observations, the mechanism by which ventricular fibrillation and sudden death occurs requires a blow directly over the heart, exquisitely timed to within a narrow 10–30 ms window just prior to the T-wave peak during the vulnerable phase of repolarization. Basic electrophysiologic mechanisms of commotio cordis are largely unresolved, although selective K^+_{ATP} channel activation appears to play a role.

Noncardiac causes: Rarely, sudden death may be caused by noncardiac conditions including bronchial asthma and rupture of a cerebral aneurysm.

Epidemiology of Sudden Death in the Athlete

The sudden and unexpected death of an athlete is always a powerful and tragic event, which devastates families, other competitors, institutions (high school, college, or professional organization), sports-medicine team, and the community. Sudden demise of an athlete has a tremendous impact on the media because it affects apparently healthy individuals who are regarded as the healthiest group in society and, often, as heroes. Instinctively, everyone wonders what intervention might have prevented the death.

The most common mechanism of cardiac arrest in young competitive athletes is abrupt ventricular fibrillation as a consequence of an underlying cardiovascular disease. The culprit disease often is clinically silent and unlikely to be suspected or diagnosed on the basis of spontaneous symptoms. Preparticipation screening of athletic population offers the potential to identify asymptomatic athletes at risk of sudden death during competitive sports.

This section will address efficacy, feasibility, and cost-effectiveness of preparticipation screening for detection of potentially lethal cardiovascular diseases and prevention of SCD.

Incidence of Sudden Death

The assessment of the precise frequency with which sudden death occurs in athletes is hampered by the retrospective nature of most analyses. The sudden death incidence is fortunately low and varies in the different athlete series reported in the literature. In apparently healthy adults (>35 years of age), joggers, or marathon racers, the estimated rate of sports-related fatalities ranges from 1:15,000 to 1:50,000. In comparison, a significantly lower incidence of fatal events has been reported in young competitive athletes (≤35 years of age). Van Camp et al. in a nationally based survey estimated the prevalence of sudden death in high-school and college athletes in the USA to be 0.4 per 100,000 athletes per year. Maron et al. showed the prevalence of cardiovascular sudden deaths in competitive high-school athletes (age 13–19 years, mean 16) from Minnesota to be 0.35 per 100,000 sports participations, and 0.46 per 100,000 individual participants per year (0.77 per 100,000 male athletes). A prospective population-based study in the Veneto Region of Italy reported an incidence of sudden death of 2.3 (2.62 in males and 1.07 in females) per 100,000 athletes per year from all causes, and of 2.1 per 100,000 athletes per year from cardiovascular diseases.

The risk of sudden death in athletes increases with age and is greater in men. This explains why mortality rates found in Italy are significantly higher than those reported in the USA. Compared with US high-school and college participants, the Italian athletic population includes

older athletes (age range 12–35 vs 12–24 years) and a significantly higher proportion of men (82% vs 65%).

The striking male predominance (male to female ratio up to 10:1) of sudden death in athletes has been related to the higher participation rate of male compared with female in competitive sports, as well as the more intensive training load and level of athletic achievement of males. Furthermore, male gender was reported to be an independent predictor of sports-related sudden death, most likely as a consequence of the greater prevalence and/or phenotypic expression in young males of cardiac diseases at risk of arrhythmic cardiac arrest, such as cardiomyopathies and premature coronary artery disease.

Prevention of Sudden Death by Preparticipation Screening

Preparticipation medical evaluation of athletic populations has the ability to identify asymptomatic athletes who have potentially lethal cardiovascular abnormalities and to protect them from the risk of sudden death during sports activity.

Screening Protocol in the USA and Italy

Preparticipation cardiovascular screening has traditionally been performed in the USA by means of history (personal and family) and physical examination without 12-lead ECG or other testing, which are requested largely at the discretion of the examining physician. This screening method has been recommended by the Sudden Death and Congenital Defects Committee of the American Heart Association on the assumption that 12-lead ECG is not cost-effective for screening large population of young athletes due to its low specificity. Such a screening strategy, however, has a limited power to detect potentially lethal cardiovascular abnormalities in young athletes. One retrospective analysis on 134 high-school and collegiate athletes who died suddenly showed that cardiovascular abnormalities were suspected by standard history and physical examination screening only in 3% of the examined athletes and, eventually, less than 1% received an accurate diagnosis.

The addition of 12-lead ECG offers the potential to enhance the sensitivity of the screening process for detection of cardiovascular diseases at risk for sudden death. Italy is the only country in the world where law mandates that every subject engaged in competitive sports activity must undergo a clinical evaluation to obtain eligibility before entering in competitive sports. A nationwide mass preparticipation screening program, essentially based on 12-lead ECG, has been the practice since 1982. The preparticipation evaluation involves nearly six million athletes of all ages annually, representing about 10% of the overall Italian population. A flow chart illustrating the Italian screening protocol is reported in *Fig. 256.5*. The initial cardiovascular evaluation consists of complete personal and family history, physical examination including blood pressure measurement, and 12-lead ECG. The athletic evaluation is performed by a physician with the specific training, medical skill, and cultural background to reliably identify clinical symptoms and signs associated with those cardiovascular diseases responsible for exercise-related sudden death. In Italy, physicians primarily responsible for preparticipation screening and eligibility for competitive sports attend postgraduate residency training programs in sports medicine (and sports cardiology) full time for 4 years. Such specialists work in sports medical centers specifically devoted to periodic evaluation of athletes. The screening starts at the beginning of competitive athletic activity that for the majority of sports disciplines corresponds to an athlete age of 12–14 years, and is repeated on a regular basis (every 1 or 2 years).

Medical history: The majority of conditions at risk of sudden death during sports are genetically determined diseases with an autosomal dominant pattern of inheritance, hence the importance of family history in identifying affected athletes. The family history is considered positive when close relative(s) had experienced a premature heart attack or sudden death (<55 years of age in males and <65 years in females), or in the presence of a family history of cardiomyopathy, Marfan syndrome, long QT syndrome, Brugada syndrome, severe arrhythmias, coronary artery disease, or other disabling cardiovascular diseases. The personal history is considered positive in cases of exertional chest pain or discomfort, syncope or near-syncope, irregular heartbeat or palpitations, and in the presence of shortness of breath or fatigue out of proportion to the degree of exertion.

Physical examination: Positive physical findings include musculoskeletal and ocular features suggestive of Marfan syndrome, diminished and delayed femoral artery pulses, mid-or end-systolic clicks, a second heart sound single or widely split and fixed with respiration, marked heart murmurs (any diastolic and systolic grade $\geq$ 2/6), irregular heart rhythm, and brachial blood pressure >140/90 mmHg (on >1 readings).

ECG: Twelve-lead ECG is considered positive in the presence of one or more of the findings reported in *Table 256.2*.

Subjects who have positive findings at basal evaluation are referred for additional testing, initially "noninvasive," such as echocardiography, 24 h ambulatory Holter

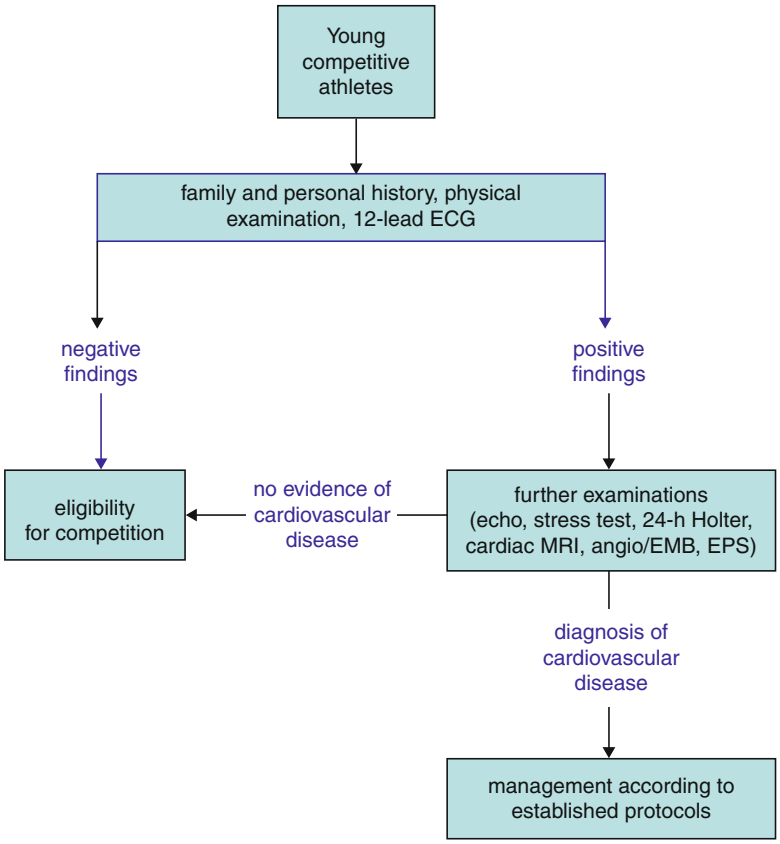

Figure 256.5

Flow chart of the Italian protocol of cardiovascular screening of young competitive athletes (see text for explanation). *Angio/EMB* contrast angiography/endomyocardial biopsy, *EPS* electrophysiologic study with programmed ventricular stimulation, *MRI* magnetic resonance (Corrado D, Basso C, Schiavon M, Pelliccia A, Thiene G (2008) Pre-participation screening of young competitive athletes for prevention of sudden cardiac death. J Am Coll Cardiol 52:1981–1989)

monitoring, and exercise testing. Alternatively or in uncertain cases, "invasive" tests such as contrast ventriculography (both right and left), coronary angiography, endomyocardial biopsy, and electrophysiologic study may be necessary in order to confirm or rule out the suspicion of heart disease. Finally, subjects recognized to be affected by cardiovascular conditions potentially responsible for sudden death in association with exercise and sport participation are managed according to the available recommendations for sports eligibility.

Time of Screening

ECG abnormalities and arrhythmic substrates of most inherited heart diseases at risk of sudden death in the young are age dependent and occur during adolescence or young adulthood. Preparticipation screening of children $\leq$12 years is expected to have a low sensitivity for detection of cardiomyopathies, cardiac ion channel diseases (except for long QT syndrome), and progressive cardiac conduction diseases that usually develop during the later period of life. It is noteworthy that a prospective study in the Veneto region of Italy demonstrated that sport-related sudden death is an exceptional event in individuals less than 12 years. Screening should be repeated on a regular basis at least every 2 years with the aim to timely identify delayed phenotypic manifestations, disease progression, or substrate worsening over the time.

Efficacy of Preparticipation Screening

HCM has been reported to be the leading cause of sudden death in young competitive athletes, accounting for up to 40% of athletic field deaths in the USA. Although

Table 256.2

ECG features of cardiac diseases detectable at preparticipation screening in a young competitive athlete

Disease	QTc interval	P wave	PR interval	QRS complex	ST interval	T wave	Arrhythmias
Hypertrophic cardiomyopathy	Normal	(left atrial enlargement)	Normal	Increased voltages in mid-/ left precordial leads; abnormal "q" waves[b] in inferior and/or lateral leads; (LAD, LBBB); (delta wave)	Down sloping (up sloping)	Inverted in mid-/ left precordial leads; (giant and negative in the "apical" variant)	(atrial fibrillation); (PVB); (VT)
Arrhythmogenic right ventricular cardiomyopathy/ dysplasia	Normal	Normal	Normal	Prolonged >110 ms in right precordial leads; epsilon wave in right precordial leads; reduced voltages ≤0.5 mV in frontal leads; (RBBB)	(up sloping in right precordial leads)	Inverted in right precordial leads	PVB with a LBBB pattern; (VT with a LBBB pattern)
Dilated cardiomyopathy	Normal	(left atrial enlargement)	(prolonged ≥0.21 s)	LBBB	Down sloping (up sloping)	Inverted in inferior and/or lateral leads	PVB; (VT)
Myocarditis	(prolonged)	Normal	Prolonged ≥0.21 s	(abnormal "q" waves)[b]	Down- or up sloping	Inverted in ≥2 leads	(atrial arrhythmias); (PVB); (2nd or 3rd degree AV block); (VT)
Long QT syndrome	prolonged >440 ms in males >460 ms in females	Normal	Normal	Normal	Normal	Bifid or biphasic in all leads	(PVB); (torsade de pointes)
Brugada syndrome	Normal	Normal	Prolonged ≥0.21 s	S1S2S3 pattern; (RBBB/LAD)	Up sloping "coved-type" in right precordial leads	Inverted in right precordial leads	(polymorphic VT); (atrial fibrillation) (sinus bradycardia)
Lenègre disease	Normal	Normal	Prolonged ≥0.21 s	RBBB; RBBB/LAD; LBBB	Normal	Secondary changes	(2nd or 3rd degree AV block)
Short QT syndrome	Shortened <300 ms	Normal	Normal	Normal	Normal	Normal	Atrial fibrillation (polymorphic VT);

Table 256.2 (Continued)

Disease	QTc interval	P wave	PR interval	QRS complex	ST interval	T wave	Arrhythmias
Preexcitation syndrome (WPW)	Normal	Normal	Shortened <0.12 s	Delta wave	Secondary changes	Secondary changes	Supraventricular tachycardia; (atrial fibrillation)
Coronary artery diseases[a]	(prolonged)	Normal	Normal	(abnormal "q" waves)[b]	(down- or up sloping)	Inverted in ≥2 leads	PVB; (VT)

Source: Modified form Corrado et al. (2005) Cardiovascular pre-participation screening of young competitive athletes for prevention of sudden death: proposal for a common European protocol. Consensus statement of the study group of sport cardiology of the working group of cardiac rehabilitation and exercise physiology and the working group of myocardial and pericardial diseases of the European society of cardiology. Eur Heart J 26:516–524

Less common or uncommon ECG findings are reported in brackets

QTc QT interval corrected for heart rate by Bazett's formula, *LBBB* left bundle branch block, *RBBB* right bundle branch block, *LAD* left axis deviation of −30° or more, *PVB* either single or coupled premature ventricular beats, *VT* either nonsustained or sustained ventricular tachycardia

[a]Coronary artery diseases = either premature coronary atherosclerosis or congenital coronary anomalies

[b]Abnormal "q" waves = ≥0.04 s in duration or ≥25% of the height of the ensuing R wave or QS pattern in two or more leads

echocardiography is the main diagnostic tool for recognition of HCM, it is expensive and impractical for screening a large athletic population. The Italian experience demonstrated that a protocol utilizing ECG in addition to history and physical examination successfully identifies HCM in the general population of young competitive athletes. Among 33,735 athletes undergoing preparticipation screening at the Center for Sport Medicine of Padova from 1979 to 1999, 22 (0.07%) showed definitive evidence, both clinical and echocardiographic, of HCM. An absolute value of screening sensitivity for HCM in young competitive athletes cannot be derived from this study because systematic echocardiographic data were not available. However, this 0.07% prevalence of HCM in the white athletic population of the Veneto Region of Italy that was evaluated by history, physical examination, and ECG is similar to that of 0.1% reported in young white individuals in the USA, assessed by echocardiography. This indicates that Italian screening essentially based on 12-lead ECG may be as sensitive as screening by echocardiography in detecting HCM in the young athletic population.

Twelve-lead ECG offers the potential to detect (or to raise clinical suspicion) lethal conditions (other than HCM) manifesting with ECG abnormalities, such as ARVC/D, dilated cardiomyopathy, long QT syndromes, Lenègre disease, Brugada syndrome, short QT syndrome, and WPW syndrome. Overall, these conditions (including HCM) account for up to two thirds of sudden deaths in young competitive athletes.

The possibility of detecting young competitive athletes with either premature coronary atherosclerosis or anomalous coronary artery is limited by the scarcity of baseline ECG signs of myocardial ischemia. However, we reported that approximately one fourth of young athletes who died from coronary artery diseases had warning symptoms and/or ECG abnormalities at preparticipation screening that could raise the suspicion of a cardiac disease.

Echocardiographic study in addition to the basal protocol does not seem to significantly improve efficacy of the preparticipation screening in identifying HCM. Pelliccia et al. did not identify any HCM by routine echocardiographic examination in 4,450 elite athletes previously cleared by ECG at preparticipation evaluation.

The Italian screening modality has proven to be more sensitive than the limited US protocol. Among the 22 Italian athletes (12 males and 2 females, aged 20 ± 4 years) who were identified and disqualified due to HCM, 18 (82%) had shown ECG changes at preparticipation evaluation that included repolarization abnormalities in 14 (87.5%), elevated QRS precordial voltages in 11 (69%), and abnormal Q waves in 5 (31%). Moreover, premature ventricular beats were recorded in 5 (23%). It is noteworthy that only 5 of these 22 athletes (23%) had had a positive family history, a cardiac murmur, or both at preparticipation evaluation. These findings indicate that the Italian screening modality including 12-lead ECG has a 77% greater power for detecting HCM than the protocol limited to history and physical examination recommended by the American Heart Association.

Mortality Reduction

It is noteworthy that none of the 22 young athletes with HCM who were identified in the Padua country

area by preparticipation athletic screening and disqualified from training and competition died during an average 8-year follow-up period. This favorable long-term outcome of former athletes with HCM was the result not only of restriction from competitive sports activity but also of the subsequent close follow-up and clinical management aimed to prevent sudden death. These findings suggest that preparticipation screening does not change merely the mode of death from exercise-related to exercise-unrelated, but reduces mortality from HCM.

A more recent time-trend analysis of the changes in incidence rates and causes of sudden death in young athletes aged 12–35 years in the Veneto region of Italy between 1979 and 2004 definitively demonstrated that preparticipation ECG screening is a life-saving strategy. According to this time-trend analysis, sudden-death mortality from any cardiovascular cause declined in Italian athletes sharply after the introduction of a nationwide screening program in 1982. During the study periods, there were 55 sudden cardiac deaths in screened athletes (1.9 deaths/100,000 person-years) and 265 deaths in unscreened nonathletes (0.79 deaths/100,000 person-years). The annual incidence of sudden cardiac death in athletes decreased by approximately 90%, from 3.6/100,000 person-years in 1979–1980 to 0.4/100,000 person-years in 2001–2004, whereas the incidence of SCD among the unscreened nonathletic population did not change significantly over that time (Fig. 256.6). The decline in the death rate started after mandatory screening was launched and persisted to the late screening period. Compared with the prescreening period (1979–1981), the relative risk of SCD was 44% lower in the early screening period (1982–1992) and 79% lower in the late screening period (1993–2004). Most of the reduced death rate was due to fewer cases of sudden cardiac death from cardiomyopathies. Over the same time interval, a parallel study examined trends in cardiovascular causes of disqualification from competitive sports in 42,386 athletes undergoing preparticipation screening at the Center for Sports Medicine in Padua. The decline of mortality from cardiomyopathies paralleled the concomitant increase in the number of athletes with cardiomyopathies (both HCM and ARVC/D) who were identified by preparticipation screening and disqualified from competitive sports.

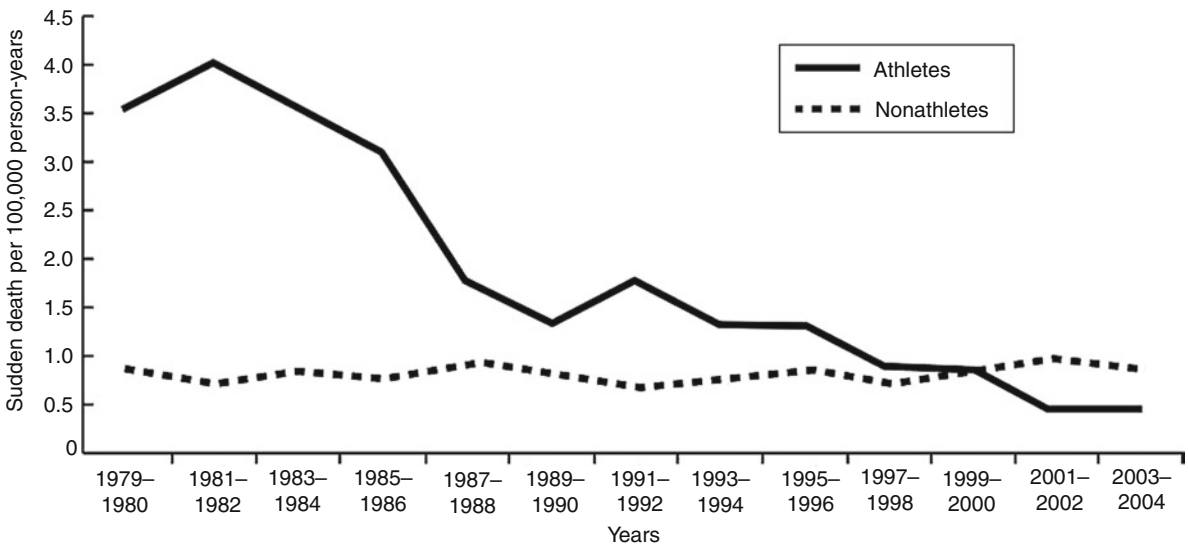

Figure 256.6

Annual incidence rates of SCD per 100,000 screened competitive athletes and unscreened nonathletes 12–35 years of age in the Veneto Region of Italy, from 1979 to 2004. During the study period (the nationwide preparticipation screening program was launched in 1982), the annual incidence of SCD declined by 89% in screened athletes (P for trend <0.001). In contrast, the incidence rate of SCD did not demonstrate consistent changes over time in unscreened nonathletes (Modified from Corrado D, Basso C, Pavei A, Michieli P, Schiavon M, Thiene G (2006) Trends in sudden cardiovascular death in young competitive athletes after implementation of a preparticipation screening program. JAMA 296:1593–1601)

Cost-Benefit Considerations

Screening of large athletic populations has a significant socioeconomic impact. Strategies for implementing the screening program depend on the particular socioeconomic and cultural background as well as on the specific medical systems in place in different countries. In Italy, screening is made feasible thanks to the National Health System, which is developed in terms of health care and prevention services, and to the limited costs of cardiovascular evaluation in the setting of a mass-program. The cost of performing a preparticipation cardiac history, physical examination, and ECG by qualified physicians has been estimated to be ≈30 Euro (approximately US $45) per athlete. The screening cost is covered by the athlete or by the athletic team, except for athletes younger than 18 years, for whom the expense is supported by the National Health System. Moreover, the cost of further evaluation of athletes with positive findings at first-line examination is smaller than expected on the basis of the *presumed* low specificity of athlete's ECG. The percentage of athletes requiring additional testing, mainly echocardiography, did not exceed 9%, with a modest proportional impact on cost.

Costs of infrastructure and training courses for preparticipation screening must also be taken into account in the calculation of the overall screening cost. Strategies for screening implementation should be in the hands of health-care policy makers and services providers, with their program development based on the specific national health and socioeconomic systems.

The young age of the screened athletic population and the genetic nature of the causes of SCD in this age-group profoundly impacts cost-benefit considerations. Unlike older patients with coronary artery diseases or heart failure, adolescents and young adults diagnosed with a genetic disease at risk of arrhythmic SCD will survive for many decades with normal or nearly normal life expectancy thanks to restriction from competition and prophylactic therapy against life-threatening arrhythmias. This large number of life-years saved influences cost-effectiveness analyses and explains why all reports on ECG screening of *young individuals* have provided cost estimates per year of life saved well below $ 50,000, which is the traditional threshold to consider a health intervention cost-effective. The benefit of preparticipation evaluation goes beyond the detection of index athletes with an inherited heart disease because it enables cascade screening of relatives and results in a multiplier effect for identifying other affected family members and thus saves additional lives.

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257 Pulmonary Hypertension/ Eisenmenger Syndrome

Delphine Yung

Introduction

Pulmonary hypertension is an abnormal hemodynamic state not commonly seen in pediatrics. However, outcomes of children with this condition are generally poor if left untreated. Therefore, this chapter is focused on the approach to identifying the clinical forms of pulmonary hypertension that are most likely to be seen in children. The important concepts of treatment are discussed, but specific treatment regimens are not. Further reading for greater comprehension and consideration of consultation with a specialized center for pediatric pulmonary hypertension are encouraged.

Definition

Pulmonary Hypertension Hemodynamics

Pulmonary hypertension is defined as mean pulmonary artery pressure equal to or greater than 25 mmHg at rest by right heart catheterization. Abnormal elevation of pulmonary pressure is due to either increased flow through the pulmonary vessels or increased resistance in the pulmonary vessels.

$$\text{Pressure} = \text{Flow} \times \text{Resistance}$$

Increased flow through the pulmonary bed results from left-to-right shunts of congenital heart disease or other congenital malformations. Increased flow usually occurs in the setting of normal pulmonary vascular resistance. However, pulmonary vascular resistance can become abnormally elevated over time if the shunt is not repaired, causing the initial left-to-right shunt to eventually become a right-to-left shunt. The most severe and irreversible type of this condition is known as Eisenmenger syndrome. Pulmonary vascular resistance can also be elevated in other conditions such as congenital or acquired diseases of the pulmonary vessels, airways, and lungs. Elevation of pressure "downstream" from the lungs may result from pulmonary vein stenosis and heart valve or heart muscle disease, which can in turn cause elevated pulmonary pressure. The prognosis and treatment of pulmonary hypertension depends on identification of the etiology.

Normal Pulmonary Pressure by Age, Including Fetal

Normal changes in pulmonary arterial pressure, pulmonary blood flow, and pulmonary vascular resistance from fetal life to postnatal life are described in the Chap. 245, "Fetal Cardiology and Neonatal Transition". These changes are particularly important for the pediatrician to understand because disease states in the neonate may be due to alterations in these mechanisms. Expansion of the lung, and increase in oxygen concentration lead to a dramatic dilation of the pulmonary vessels immediately after birth. Further reduction in pulmonary vascular resistance takes place over the next 10–14 days as the relatively thick vascular smooth muscle layer of the fetal pulmonary arterioles regress to resemble the adult medial layer. Pulmonary vascular resistance fall to near adult levels about 6–8 weeks after birth, and continues to gradually fall with growth of both alveoli and pulmonary arterioles for the next 4–5 years (*Fig 257.1*).

Classification/Etiology

The clinical classification system has gone through a series of changes that reflects the understanding of pathological, pathophysiological, and therapeutic characteristics (*Table 257.1*). Since 2003, the term PPH "primary pulmonary hypertension" has been abandoned in favor of "pulmonary arterial hypertension" (PAH), and indicates that the disease is found in the precapillary vessels, differentiating it from other forms of pulmonary hypertension (PH). As information and evidence about pulmonary hypertension continues to grow, there will likely be more modifications in the future.

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Epidemiology

The incidence and prevalence of most forms of pediatric pulmonary hypertension is unknown. All forms of pulmonary hypertension in the clinical classification (Table 257.1) have been described in children, but the most common are idiopathic/heritable, associated with congenital heart disease, and chronic lung disease of prematurity.

1. *Persistent Pulmonary Hypertension of the Newborn (PPHN)*: The incidence of PPHN is ~1–2 per 1,000 live births in the USA. Although PPHN has been classified as PAH, its unique natural history, treatment, and outcome should be discussed separately (Neonatology).
2. *Idiopathic PAH*: The best available data is from the French registry, which estimates the prevalence of PAH at 15 cases per million adults and idiopathic PAH at 5.9 cases per million adults.
3. *PAH associated with Congenital Heart Disease (CHD)*: The overall incidence of CHD is approximately 8 in 1,000 live births. Pulmonary hypertension is common in infants and children with congenital heart disease, and based on natural history studies, approximately 30% of all children born with CHD who do not undergo surgical repair will develop pulmonary vascular disease. However, data on pulmonary arterial hypertension and Eisenmenger syndrome in

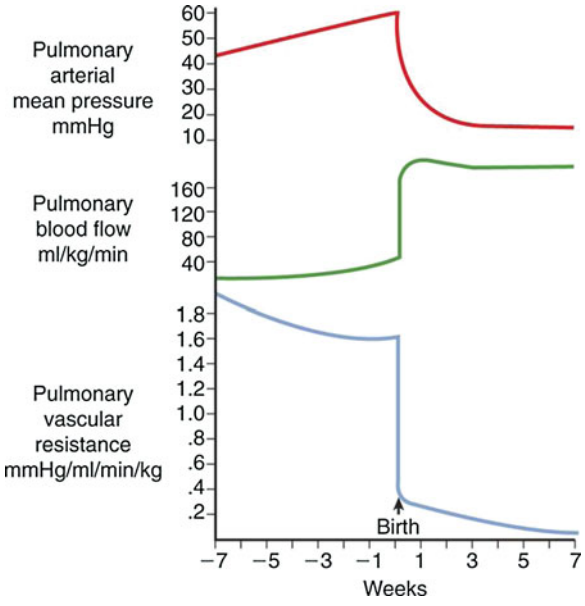

Figure 257.1
Representative changes in pulmonary hemodynamics during transition from the late-term fetal circulation to the neonatal circulation (Adapted from Rudolph AM (2001) Congenital diseases of the heart: clinical-physiological considerations. Futura, New York)

Table 257.1
Updated clinical classification of pulmonary hypertension (Dana Point 2009)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drugs and toxins induced
1.4. Associated with (APAH)
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5. Persistent pulmonary hypertension of the newborn
1′ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
2. Pulmonary hypertension due to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension due to lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension
5. PH with unclear and/or multifactorial mechanisms
5.1. Hematological disorders: myeloproliferative disorders, splenectomy

Table 257.1 (Continued)

5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell, histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

ALK-1 activin receptor-like kinase 1 gene, *APAH* associated pulmonary arterial hypertension, *BMPR2* bone morphogenetic protein receptor, type 2, *HIV* human immunodeficiency virus, *PAH* pulmonary arterial hypertension

the current era have only been reported in adults. One European study estimates that 6–28% of adults with CHD have PAH, and 3–7% have Eisenmenger syndrome; another estimate is that 1.6–12.5 cases per million adults with CHD in Europe have PAH, and 25–50% of these individuals are affected by Eisenmenger syndrome.

4. *PH associated with chronic lung disease of prematurity*: Chronic lung disease of prematurity develops in 10–15,000 newborns in the USA annually, and is also high worldwide. The exact incidence of pulmonary hypertension with chronic lung disease of prematurity is not known, but is associated with a significant increase in mortality.

Pathogenesis

1. *Right Heart Failure*: Elevated pressure in the pulmonary vessels creates increased work for the right ventricle. The right ventricle initially compensates for increased afterload by hypertrophy and dilation, but stroke volume and cardiac output eventually decrease over time, leading to right heart failure. The timing and degree of right ventricular decompensation varies widely among individuals, but the reasons for this are unknown. The function of the right ventricle is a major determinant of the functional status and prognosis in pulmonary hypertension. Therapy aimed at improving right ventricular function may improve functional status.
2. *Elevated Pulmonary Vascular Resistance (PVR)*: In PAH, elevated pulmonary pressure results from restricted flow through the pulmonary arterial vessels leading to a pathological increase in PVR. Increased PVR is predominantly due to a loss of vascular luminal cross section from vascular remodeling and vasoconstriction.
   (a) Remodeling of the small pulmonary arteries (called "resistance arteries" because they regulate regional blood flow in the lung) causes a fixed obstruction, which does not respond to acute vasodilator challenge. The mechanisms of vessel remodeling are endothelial dysfunction, excessive proliferation and decreased apoptosis in pulmonary artery smooth muscle cells (PASMC), abnormal activation of adventitia, thrombosis and inflammation. Endothelial damage can also be caused by shear stress due to increased pulmonary blood flow and increased pulmonary artery pressure of CHD or mechanical stress of lung disease.
   (b) Excessive vasoconstriction has been related to increased expression of potassium channels in the smooth muscle cells and endothelium leading to an overload of intracellular calcium. The increase in the vasomotor tone is reversible with acute vasodilator testing. Vasoconstriction can be a reflex response to stretch receptors in the left atrium and pulmonary veins in left heart disease and to hypoxia from lung disease.
3. *Cellular and Molecular Abnormalities and Targets for Therapy*: Knowledge of multifactorial disease pathways has led to the development of targets for therapy. These pathways are thought to be similar in children and adults.
   (a) There is an imbalance in the major arachidonic acid metabolites with a decrease in prostacyclin and increase in thromboxane A_2. Prostacyclin is a potent vasodilator, inhibits platelet activation, and has antiproliferative properties. Thromboxane A_2 is a potent vasoconstrictor and promotes platelet activation and proliferation. There are increased levels of endothelin-1, a potent vasoconstrictor and stimulator of pulmonary artery smooth muscle cell proliferation. Nitric oxide is a vasodilator and inhibitor of platelet activation and vascular smooth muscle cell proliferation. Decreased nitric oxide synthase has been observed in PAH patients. The nitric oxide second messenger cyclic guanosine monophosphate (cGMP) is inactivated by phosphodiesterase, especially the PDE-5 isoform found in large quantities in the lung.
   (b) Serotonin is a vasoconstrictor and promotes PASMC hypertrophy and hyperplasia, and there

are alterations in the serotonin transporter in patients with PAH. There is decreased vasoactive intestinal peptide, a vasodilator similar to prostacyclin. Mediators of inflammation such as platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), antiapoptotic protein survivin, and transcription factors HIF-1 alpha (hypoxia inducible factor-1 alpha) and NFAT (nuclear factor activating T lymphocytes) play a role in PAH. Drugs in trial for therapy include PDGF receptors antagonists, imatinib and sunitinib, and sorafenib, a VEGF antagonist.

4. Pulmonary vascular disease is being increasingly seen as a problem of angiogenesis. Evidence suggests that lung blood vessels, instead of passively forming alongside airways, actively promote normal alveolar growth during development and contribute to the maintenance of alveolar structures throughout life. These pathways clearly play an important role in pediatric diseases such as PPHN, chronic lung disease of prematurity, and CHD. Stem cells may also play important roles in angiogenesis and vascular remodeling, but their therapeutic value is unknown.
5. Pulmonary hypertension can also result from the passive backward transmission of pressure elevation in left heart disease, where the pulmonary pressure is additive to the elevated downstream pressure, but transpulmonary pressure gradient (TPG = mean PA pressure minus PCWp) and pulmonary vascular resistance is normal, (e.g., mean PA pressure and pulmonary capillary wedge pressure are elevated, but TPG is normal).
6. *Genetics*: The bone morphogenetic protein receptor type 2 (BMPR2) has been recognized in about 20% of cases of idiopathic PAH and more than 70% of familial or heritable PAH. BMPR2 belongs to the superfamily of transforming growth factor beta receptors that control vascular cell growth. Mutations in two other members of this superfamily, activin-like kinase-type 1 (ALK1) and endoglin (ENG) cause hereditary hemorrhagic telangiectasia and rarely also cause heritable PAH. Mutations are autosomal dominant with incomplete penetrance.

Pathology

1. The pathological findings of medial hypertrophy in the muscular and elastic pulmonary arteries, and dilation and intimal thickening of elastic pulmonary arteries are seen in all forms of pulmonary hypertension, regardless of etiology.
2. Pulmonary arterial hypertension is further characterized by lesions of the pre- and intra-acinar pulmonary arteries. Heath and Edwards, in their study of CHD, were the first to systematically describe and classify these lesions by severity, increasing in grade from 1 to 6. Less severe lesions, corresponding to Heath–Edwards grade 1–3, are usually diffuse, and may be considered more reversible. These lesions include isolated medial hypertrophy, medial hypertrophy and intimal thickening of concentric lamellar, eccentric, and concentric nonlaminar types. More severe complex lesions, corresponding to Heath–Edwards grade 4–6, may be focal and include plexiform lesions, dilation lesions, arteritis or inflammation, and thrombosis in situ (*Fig. 257.2*).
3. Adventitial thickening and proliferation is seen in persistent pulmonary hypertension of the newborn, but rarely in other causes of pulmonary arterial hypertension.
4. Pulmonary venous occlusive lesions and capillary proliferation and dilation may be patchy and should be assessed. These findings suggest pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis, two rare diseases that are being increasingly recognized as possibly overlapping with pulmonary arterial hypertension.
5. In pulmonary hypertension due to left heart disease in children, there is medial hypertrophy of the pulmonary arteries and also thickening or "arterialization" of the pulmonary veins, along with proliferation and dilation of lymphatics or lymphangiectasia, and interstitial edema.

Clinical Manifestations

Because pulmonary hypertension is rare, pediatricians unfortunately often do not recognize symptoms and signs of pulmonary hypertension until right heart failure becomes advanced.

Symptoms

Patients with pulmonary hypertension manifest signs and symptoms related to the degree of pulmonary artery pressure elevation and degree of right heart failure. Shortness of breath with exertion, or dyspnea, is a common symptom that can be mistaken for asthma. Other symptoms may include chest pain, dizziness, atrial arrhythmias, hemoptysis, and syncope. Syncope is due to the sudden

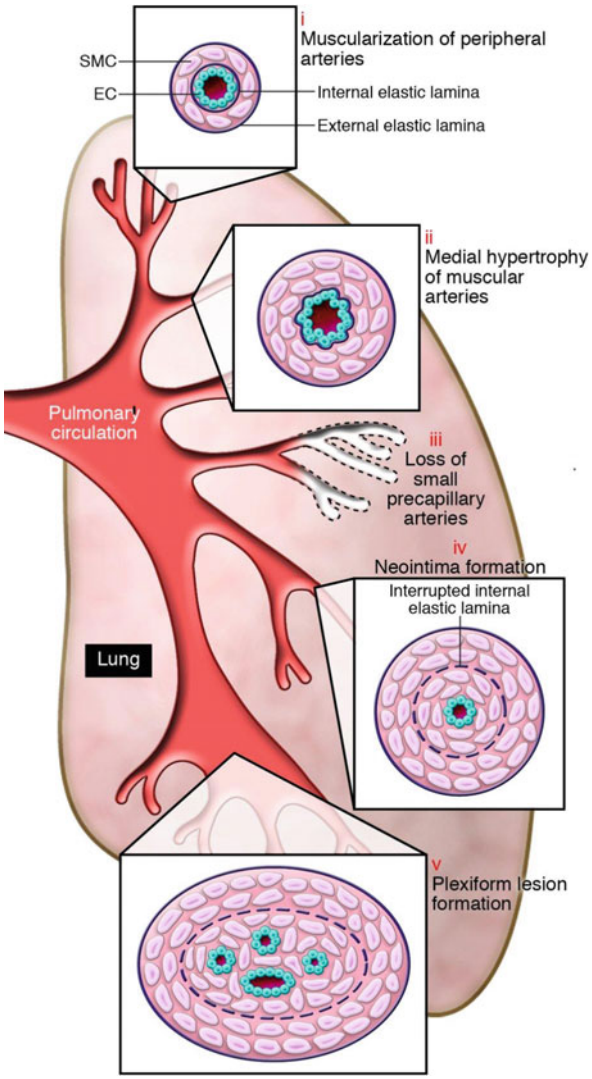

Figure 257.2
Pathobiology of PH. Schema illustrating the different vascular abnormalities compared with normal pulmonary circulation, associated with PH. This schema depicts the abnormalities throughout the pulmonary circulation, including (i) abnormal muscularization of distal precapillary arteries, (ii) medial hypertrophy (thickening) of large pulmonary muscular arteries, (iii) loss of precapillary arteries, (iv) neointimal formation, and (v) formation of plexiform lesions in these vessels

failure of right-sided cardiac output, and occurs in patients without a cardiac shunt (e.g., a patent foramen ovale) that can function as a "pop-off" to support systemic circulation. Syncope and subsequent hypoxic seizures may be misdiagnosed as a seizure disorder.

Signs

The signs of pulmonary hypertension on physical examination can be subtle and frequently missed. However, an increased RV impulse and a loud single second heart sound are usually present, and murmurs of tricuspid regurgitation, pulmonary ejection or pulmonary regurgitation can also be present. In more advanced disease, signs of right heart failure may be observed such as tachycardia, tachypnea, edema, hepatomegaly, and ascites. Cyanosis is not seen in pulmonary hypertension unless there is associated lung disease or a right-to-left cardiac shunt, as in classical Eisenmenger syndrome.

Diagnosis

When pulmonary hypertension is suspected, the goals are to confirm the diagnosis of pulmonary hypertension, and to identify associated diseases. Further classification into pulmonary arterial hypertension (Group 1) or other groups is imperative to develop an appropriate treatment plan. Because of the poor prognosis of the disease if left untreated, evaluation should be comprehensive and timely, and consideration should be given for referral to a specialized center for pediatric pulmonary hypertension.

Diagnostic Tests

(a) *EKG*: The electrocardiogram usually shows right axis deviation, right atrial enlargement, and right ventricular hypertrophy. Atrial arrhythmias can be seen.
(b) *CXR*: The chest x-ray may show right atrial and ventricular enlargement and large central pulmonary arteries (*Fig. 257.3*). The peripheral pulmonary vessels may appear hypovascular due to decreased pulmonary flow in the arterioles. The chest x-ray may also suggest the presence of lung disease.
(c) *Echocardiogram*: The echocardiogram is one of the most important screening tools in the assessment of pulmonary hypertension. The pulmonary pressure can be estimated by measuring tricuspid regurgitation jet velocity, although the tricuspid jet estimation can both overestimate and underestimate pressure. Patients in whom estimated RV systolic pressure is greater than half of systemic pressure, or greater than 40 mmHg, warrant further evaluation. Secondary signs of elevated right ventricular pressure should also be assessed, including right atrial enlargement,

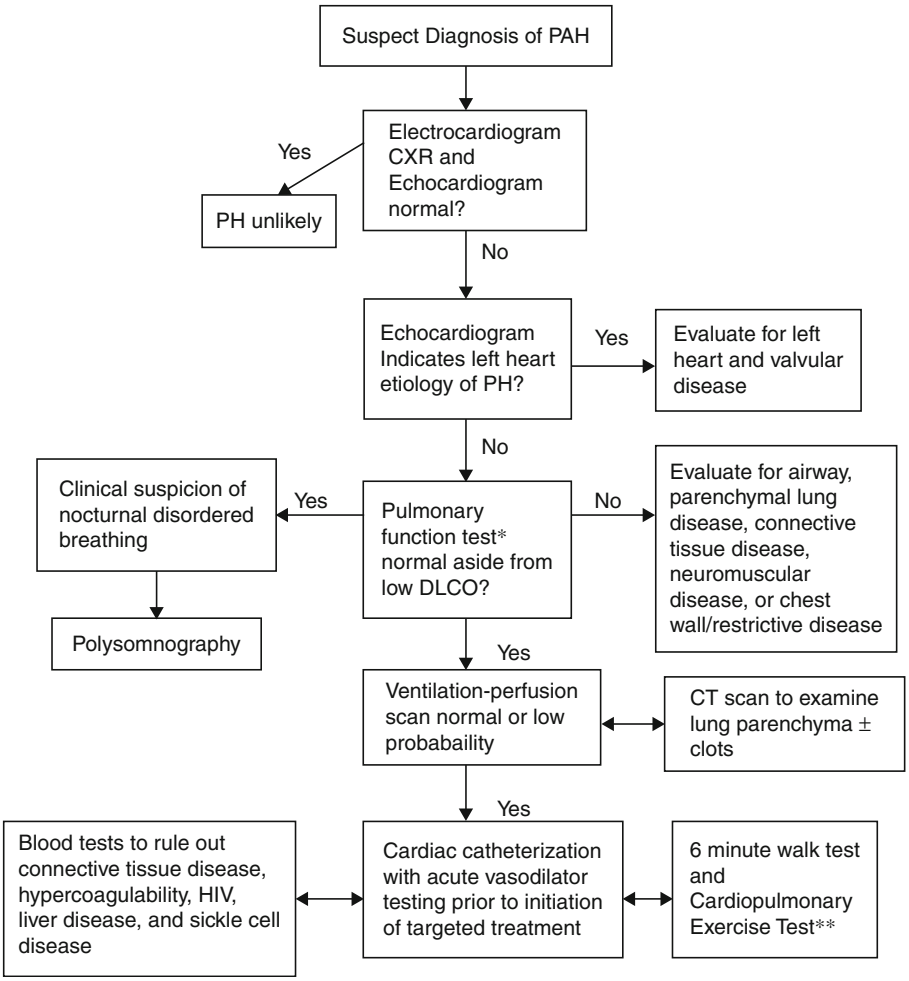

Figure 257.3
Pediatric pulmonary arterial hypertension diagnostic evaluation

right ventricular enlargement and hypertrophy, and interventricular septal wall flattening. Poor right ventricular function and pericardial effusion may accompany signs of right heart failure. The other main purpose of the echocardiogram is to rule out specific causes of pulmonary hypertension, including CHD, cardiomyopathies, and congenital or acquired valve defects. The presence of an interatrial shunt (e.g., patent foramen ovale) may need to be defined contrast echocardiography.

(d) *Pulmonary Function Testing*: PFTs may not be able to be performed by young children. However, it is important to evaluate ventilatory function, including total lung volume and diffusion capacity. Patients with moderate to severe abnormalities should be evaluated for possible underlying lung disease.

(e) *Nocturnal oximetry*: If obstructive sleep apnea is clinically suspected, then nocturnal oximetry is a useful screening test.

(f) *Radionuclide perfusion (V/Q) scan*: This study is important to exclude chronic thromboembolic pulmonary hypertension (Diagnosis group 4), and is more sensitive than the chest CT.

(g) *Chest CT*: The chest CT is valuable in determining the presence and extent of parenchymal lung disease (diagnosis group 3).

(h) *Right heart catheterization*: The right heart catheterization is the gold-standard procedure for measuring

and confirming elevation of pulmonary artery pressure. Performance of the right heart catheterization in children with suspected pulmonary hypertension requires expertise in pediatric anesthesia and in pediatric cardiology due to the significant risk associated with the procedure. Baseline measurements during catheterization should include saturations in all veins and arteries (with blood gases as appropriate) and cardiac chambers if a shunt is suspected. Pressures should be measured in the right atrium, right ventricle, pulmonary artery, pulmonary capillary wedge, systemic artery, and if appropriate, the left atrium and ventricle. Calculations should include cardiac index, pulmonary blood flow, pulmonary vascular resistance (PVR), and systemic vascular resistance (SVR), PVR:SVR ratio, and the presence of any cardiac shunts. Acute vasodilator testing, which is most commonly done with inhaled nitric oxide, is necessary to test for vascular reactivity and to guide treatment. Cardiac catheterization should differentiate pulmonary hypertension into the following hemodynamic definitions:

- *PH*: Pulmonary hypertension is defined as mean pulmonary artery pressure 25 mmHg or greater.
- *PAH*: Pulmonary arterial hypertension is further differentiated by the elevation of pulmonary vascular resistance above 2.5 or 3 Woods units * m^2.
- *Pulmonary venous hypertension*: Conversely, careful pressure measurements will be able to identify left-sided heart disease (diagnosis group 2) and elevation of pulmonary pressure that is passive (normal transpulmonary gradient, <10 mmHg), reflex (elevated transpulmonary gradient, >10 mmHg, that is reversible with acute vasodilator testing), or fixed.
- Pulmonary hypertension caused by increased pulmonary blood flow via intracardiac or extracardiac shunt.

Functional Assessment

Functional ability has been demonstrated in adults to be associated with worse outcome. In children, an assessment of functional ability or clinical assessment of right heart function/failure is important in determining optimal treatment course. The WHO functional classification in pulmonary hypertension was developed for adults, but can also be used as a guideline to assess children (Table 257.2).

Table 257.2
World Health Organization Functional classification in pulmonary hypertension (PH)

Class I	Patients with PH but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnea or fatigue, chest pain, or near syncope.
Class II	Patients with PH resulting in slight limitation of physical activity. Comfortable at rest; ordinary physical activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class III	Patients with PH resulting in marked limitation of physical activity. Comfortable at rest; less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope.
Class IV	Patients with PH with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

(a) Objective and serial measurement of exercise and functional ability may be obtained in older children with the 6-min walk test and cardiopulmonary exercise test. Serial B-type natriuretic peptide BNP levels have also been described as a biomarker for disease severity.

Differential Diagnosis/Concomitant Diagnoses

1. At the outset of the evaluation, all etiologies (see Table 257.1) need to be considered.
2. In children, one of the more common causes of pulmonary hypertension is lung disease, due to a growing population of former premature infants who develop chronic lung disease or "new" bronchopulmonary dysplasia in the post-surfactant era. They are at risk of developing pulmonary hypertension despite treatment for the lung disease. Patients with developmental abnormalities of the lung, such as lung hypoplasia from congenital diaphragmatic hernia, are also at risk for developing PH.
3. Cardiac disease is also a common cause of pediatric pulmonary hypertension. Simple systemic to pulmonary shunt lesions probably account for most of the clinical classification group 1 associated congenital

heart disease. However, complex types of congenital heart disease may be considered a combination of diagnosis group 1 and group 2 (left heart disease). These include left-sided obstructive lesions (and forms of Shone's syndrome), hypoplastic left heart syndrome with restrictive atrial septum, and pulmonary vein stenosis. Cardiomyopathy with elevated left ventricular end diastolic pressure can also lead to pulmonary hypertension. A less common form of pulmonary hypertension occurs with high cardiac output states, such as large arterio-venous malformations or liver failure, due to initially high flow through the pulmonary vessels, and later by elevated left end diastolic pressure as heart failure develops.

4. Patients with pulmonary hypertension should be screened for a history compatible with sleep-disordered breathing or with nocturnal oximetry, followed by formal sleep polysomnography if indicated. Mild sleep apnea, can exacerbate pulmonary hypertension through pulmonary hypoxic vasoconstriction. Sleep apnea is rarely a sole cause of pulmonary hypertension. Treatments include tonsillectomy and adenoidectomy, supplement oxygen and/or positive airway pressure during sleep.
5. Infants with Down syndrome deserve special mention due to the frequency of multiple co-existing conditions that place them at higher risk for developing pulmonary hypertension. These conditions include poor airway tone leading to airway obstruction, gastroesophageal reflux and aspiration, and CHD.
6. Less common diagnoses that require workup include the possibility of a coagulopathic state, hypothyroidism, and connective tissue disease, as the treatment for these is specific. ANA is elevated in 40% of patients with idiopathic disease, and may not represent connective tissue disease. Hemoglobinopathies and HIV should be screened for in all appropriate populations. Pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis are two rare entities that are not well understood, but can be suspected by CT and confirmed by lung biopsy (*Table 257.3*).

Table 257.3
Blood tests for pulmonary arterial hypertension workup

Complete blood count	
Chem-20 with liver function profile	
Urinalysis	
BNP	
Thyroid function tests	
HIV test	
Serum viscosity	
Serum protein electrophoresis	
Hemoglobin electrophoresis	
Quantitative immunoglobulins	
Fractionated plasma catecholamines	
Consider genetic testing of BMPR2	
Coagulation studies	Factor II, V, VII, VIII
	Factor V Leiden
	Von Willebrand Antigen
	Von Willebrand ristocetin cofactor
	Protein C
	Protein S
	Antithrombin III
Connective tissue disease workup	ESR
	Antinuclear antibodies
	Anticardiolipin antibodies
	Lupus anticoagulant
	Anti-DNA
	Total serum complement and components
	Special ANAs
	Anticentromere
	Rheumatoid factor

Treatment

General Care

General care for the patient with pulmonary hypertension begins with identifying the etiology of pulmonary hypertension and all the potential exacerbating factors. Diagnoses of lung disease, coagulopathy, and connective tissue disorders need to be treated with input from a specialist in that area. The repair of CHD should be considered on an individual basis. Right heart failure will develop in untreated pulmonary hypertension, and recognition of the degree of right heart failure will guide treatment decisions.

(a) *Digoxin*: There is little data on the use of digoxin, but it is sometimes used in those patients with right heart failure and a low cardiac output and in patients with atrial arrhythmias.
(b) *Diuretics*: Diuretics are used to manage right ventricular volume overload, which is occasionally seen as hepatomegaly or peripheral edema.
(c) *Anticoagulation*: There is expert consensus to support the use of warfarin for anticoagulation titrated to an INR of 1.5–2.5.
(d) *Bronchodilator*: If there is evidence of mild obstructive airway disease that responds to bronchodilator therapy, bronchodilators may be trialed.
(e) *High altitude (including airplane flights)*: A general measure is to recommend relocation to lower altitude for patients chronically residing at altitudes greater than 2,500 m. Patients with oxygen saturations lower than 92% at rest should be considered for a recommendation of supplemental oxygen therapy with airplane flights.
(f) *Oxygen*: Hypoxia is not common in idiopathic pulmonary arterial hypertension. However, patients with associated lung and heart disease occasionally have oxygen saturations less than 92%. Hypoxic pulmonary vasoconstriction will exacerbate pulmonary hypertension and consideration should be given for treatment by oxygen to a saturation greater than 92%, and higher if appropriate for the specific diagnosis. However, patients with Eisenmenger syndrome do not usually benefit significantly from oxygen therapy.
(g) *Exercise*: Children usually self-limit. In the rare functional class I patient, more strenuous exercise may be considered after a formal cardiopulmonary exercise test.
(h) Immunizations should be given, especially for influenza, pneumococcus, and RSV Ig if indicated by age.

Specific Therapies

1. Children with idiopathic pulmonary arterial hypertension who respond to acute vasodilator testing in the catheterization laboratory with a significant decrease in pulmonary artery pressure to near normal levels have been successfully treated with calcium channel blocker therapy. A significantly greater proportion of children are acute responder compared to adults.
2. Specific pulmonary arterial vasodilators have been developed based on known mechanisms of action to treat pulmonary arterial hypertension. These have been studied in adults with pulmonary arterial hypertension. These classes of medications are prostacyclins (epoprostenol, treprostinil, iloprost, beraprost), endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), and phosphodiesterase inhibitors (sildenafil, tadalafil). There is data on efficacy for epoprostenol and bosentan in children with IPAH and CHD. Guidelines for treatment are based on those for adults.
3. Polycythemia occurs in Eisenmenger patients because of chronic hypoxia, and phlebotomy may be considered in patients with symptoms of hyperviscosity. However, phlebotomy should only be undertaken in centers experienced with the procedure to prevent hemodynamic instability. Iron deficiency and microcytic anemia may also cause symptoms of hyperviscosity.
4. Patients who fail medical therapy and progress to severe heart failure may opt to undergo lung transplant or heart–lung transplant.
5. Atrial septostomy to create a pulmonary to systemic shunt has been shown to improve severe right heart failure and survival. More recently, creation of a Pott's shunt (right pulmonary artery to descending aorta shunt) has been described to improve severe right heart failure in patients with PAH associated with CHD and IPAH.

Prognosis

1. Estimated median survival of adults in the NIH registry was 2.8 years, with 1-, 3-, and 5-year survival rates of 68%, 48%, and 34%, respectively, whereas the mean untreated survival time for children was only 10 months after diagnosis. However, improved survival for children has been shown with epoprostenol, calcium channel blockers, and bosentan. Unfortunately, there is still no cure, so therapy is aimed at improving quality of life, functional status, and survival.
2. The survival for patients with Eisenmenger syndrome is better than that with IPAH. Despite early surgical repair of the congenital heart defect, some patients may go on to develop progressive pulmonary vascular disease for reasons that remain unclear.

Prevention

1. *CHD repair*: Natural history studies guide the timing of repair for VSD, PDA, and ASD to prevent risk of pulmonary vascular disease. The exact timing for these lesions and for more complex lesions is

case-specific and may require further evaluation by cardiac catheterization.

2. Pediatric patients who have a known risk for pulmonary hypertension can be screened at intervals and referred to for further evaluation and treatment if pulmonary hypertension is identified. These diagnoses include premature infants with chronic lung disease, sickle cell disease, scleroderma and other connective tissue disease, lung/liver transplant listing, severe sleep apnea, HIV and those at genetic risk.

Online Resources for Parents and/or Professionals

www.phassociation.org: The *Pulmonary Hypertension Association* is the leading organization connecting PH patients, families, and medical professionals.

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258 Rheumatic Heart Disease/Acute Rheumatic Fever

Bruce G. Hardy

Rheumatic fever (RF) continues to be a major heath concern worldwide, especially in developing countries. It is a complex disease that is a result of an interaction between Group A streptococcus (GAS) and a susceptible host. Although rheumatic heart disease (RHD) is generally the most serious acute and chronic concern, RF also affects the joints, brain, and the skin. It remains the most common cause of acquired cardiac disease in children and adolescents worldwide.

Pathogenesis

Acute rheumatic fever follows an infection of Group A streptococcus (GAS), virtually always a pharyngeal infection. There have been a few reports of RF following GAS skin infection in areas of Australia, but this is unusual.

The risk of developing rheumatic fever following untreated GAS tonsillopharyngitis is approximately 1%. Virulence is dependent on the M protein, a surface protein of the bacterial wall, which carries specific epitopes. There are more than 80 specific serotypes, which lead to rheumatic fever. However, the reason why specific strains within a given serotype have increased RF virulence has not been determined. The causal strain of GAS adheres to the oral and pharyngeal cells and then releases a variety of degradation products that present antigenic determinants which cross-react with certain human tissues, particularly cardiac valve tissue and the myocardium.

The pathologic changes in the heart can be grouped in two phases. The first phase occurs in the first 2–3 weeks after a GAS infection, and consists of infiltration of T cells, B cells, and macrophages and is accompanied by interstitial edema and deposition of eosinophilic granular material. The second phase, that of proliferation, is prolonged, and may occur over months to years. The cardinal finding during this phase is the Aschoff nodule, with a central area of fibrinoid changes surrounded by and infiltrated by large multinucleated "owl eye" cells. It is the mitral valve that is most often affected by RF, often accompanied by aortic valve changes.

During acute RF, the mitral subvalvular structures are usually affected, with chordal elongation and annular dilation, causing mitral insufficiency. There are also changes in the mitral valve leaflets. In the early stages, echocardiography may demonstrate the initial changes of mitral valve leaflet restriction and thickening which exacerbates the mitral insufficiency. The later stages of chronic RF mitral valve disease are characterized by mitral leaflet shortening and rigidity, leaflet retraction, and chordal fusion and shortening. The later stages include both mitral insufficiency and mitral stenosis.

The aortic valve is affected less often than the mitral valve and virtually always occurs with mitral valve disease rather than as an isolated finding. In the acute phase of RF there may be aortic insufficiency, often with leaflet prolapse. In chronic RF, there may be leaflet thickening, fibrosis, and retraction of the leaflets leading to further aortic valve insufficiency.

Epidemiology

Worldwide, it is estimated that there are at least 282,000 new cases of RF and 233,000 deaths each year, most of these occurring in developing countries. This estimate may be quite low because of the difficulties in obtaining accurate surveillance data. The incidence in some areas may be as high as 500 per 100,000 people. The major determinants of rheumatic fever incidence and rheumatic heart disease are poverty, malnutrition, overcrowding, poor housing, and a shortage of health-care resources.

Although there has been a dramatic decline in the number of RF cases in developed countries, there has been a resurgence in various areas. In 1987, Veasy reported a significant number of new cases of RF in the Salt Lake City area of the USA. Although RF has usually been associated with poor socioeconomic status, in this study the affected children were predominantly from white (96%) middle-class families with above-average incomes and with ready access to medical care. In 1989, a survey of pediatric cardiologists in the USA suggested a five- to tenfold increase in the number of new RF cases compared to earlier years.

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Prevention of Rheumatic Fever

Rheumatic fever could essentially be prevented if Group A streptococcal pharyngitis was diagnosed and treated. However, even in developed countries this is not possible. Patients with streptococcal pharyngitis do not all have diagnostic testing done, as it is difficult for families to differentiate streptococcal disease from viral infections. A study by Veasy in the Salt Lake, Utah area found that of 274 confirmed cases of RF, only 17% had sought medical attention for a sore throat. Also, streptococcal infections may be without concerning symptoms, yet may lead to RF. In developed countries, since RF is uncommon, families may not be aware of the need to diagnose and treat streptococcal infections.

The problem is much more severe in developing countries, where there is less availability of diagnostic tests, there are financial difficulties in obtaining care, and there may be inadequate patient awareness of the need to diagnose and treat strep pharyngitis to prevent RF. This is of particular importance in areas with a high prevalence of RF. Kathikeyan et al. recently published a special report in *Circulation* suggesting the use of clinical protocols to inexpensively indicate a high likelihood of strep pharyngitis, allowing for rapid treatment. The authors emphasize the advantage of rapid and efficient primary prevention of RF to avoid the long-term sequelae of chronic rheumatic fever. Primary prevention of RF is clearly favorable to secondary prophylaxis and this paradigm has been shown to be successful in Costa Rica and Cuba, almost eradicating RF with programs of primary prevention.

Diagnosis of Rheumatic Fever

The diagnosis of rheumatic fever remains a challenge, in part because there is no single set of definitive signs or tests, and in part because few clinicians care for many patients with rheumatic fever. In 1944, T. Duckett Jones, Research director of the House of Good Samaritan, in Boston, proposed a set of criteria that would guide physicians in the diagnosis of acute rheumatic fever. These criteria have undergone four major revisions, most recently in 1992, and were reviewed without new changes by an American Heart Association working group in 2002.

The Jones Criteria are meant to be guidelines, and are not meant to be a substitution for the careful judgment of clinicians. The criteria are divided into three groups: major features, minor features, and supportive evidence of a preceding Group A streptococcal infection, as detailed in *Tables 258.1* and *258.2*.

Table 258.1

Major criteria	Minor criteria
Carditis Polyarthritis Chorea Erythema marginatum Subcutaneous nodules	Clinical findings Fever Arthralgia Laboratory findings Elevated sedimentation rate Elevated C-reactive protein ECG finding Prolonged PR interval

Table 258.2

Supporting evidence for a preceding group A streptococcal (GAS) infection
Positive throat culture or rapid streptococcal antigen test
Elevated or rising streptococcal antibody titer

Criteria for the Diagnosis of Rheumatic Fever

Primary episode of rheumatic fever:

1. Two major criteria OR one major criteria and two minor criteria
2. Plus supportive evidence of a preceding Group A streptococcal infection

Rheumatic Fever recurrence in a patient without a history of rheumatic heart disease:

1. Two major criteria OR one major and two minor criteria
2. Plus supportive evidence of an antecedent Group A streptococcal infection

Rheumatic Fever recurrence in a patient with a history of rheumatic heart disease:

1. Two minor criteria
2. Plus supportive evidence of an antecedent Group A streptococcal infection

Chorea or indolent carditis:

1. There is no need for other criteria or evidence of an antecedent Group A streptococcal infection

Major Criteria

Carditis

Carditis is the most serious manifestation of acute rheumatic fever and is the only major manifestation that has long-term sequelae. In developing countries, rheumatic carditis continues to be the leading cause of acquired heart disease.

The criterion for carditis is met when a new murmur of mitral insufficiency and/or aortic insufficiency is evident. Frequent examinations may be necessary since the murmurs may change from day to day. Tachycardia is often an early sign of carditis, but is also present in most febrile and inflammatory diseases. Careful history and examination of patients is necessary to evaluate evidence of cardiac compromise.

Although the primary pathological concern in RF is valvular disease of the mitral and aortic valves, initially there may be a pancarditis with accompanying myocardial dysfunction, exacerbating the heart failure that is secondary to the valve dysfunction. However, troponin levels are not used to diagnose RF since the levels are variable and are not adequately specific or sensitive. Several studies have demonstrated a lack of elevated troponin levels in acute rheumatic fever, indicating the absence of myocardial necrosis in most cases.

The clinical presentation of carditis is quite variable, ranging from the asymptomatic patient with a murmur suggesting mitral insufficiency to the critically ill patient with cardiac failure. Carditis is an early finding, with 90% of those with carditis presenting in the first 2 weeks of the RF illness. If the cardiac involvement is mild, the valvular insufficiency may decrease or even resolve as the inflammatory process subsides. However, patients with moderate to severe carditis often develop chronic and progressive valvular disease.

The Jones criteria are based on auscultatory findings of mitral insufficiency and/or aortic insufficiency. Mitral insufficiency is the most common finding in RF carditis, and is present in approximately 90% of patients. The characteristic murmur of mitral insufficiency is a high-pitched regurgitant holosystolic murmur heard at the apex. The murmur is best heard at end-exhalation with the patient in the left lateral decubitus position. The murmur may be quite soft, even with acute severe mitral insufficiency. Aortic insufficiency is present in approximately 25% of patients with RF carditis, and usually occurs in combination with mitral insufficiency. Only about 5% of patients with RF have isolated aortic insufficiency. The murmur of acute aortic insufficiency is generally a soft early diastolic murmur that is heard at the mid-left sternal border with the patient at end-inhalation and leaning forward in a sitting position.

When mitral insufficiency is moderate to severe, left ventricular filling pressures rise with resultant pulmonary vascular engorgement and pulmonary edema. This is evident clinically as dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Secondary pulmonary hypertension may develop and right ventricular failure may ensue. If mitral insufficiency is mild, patients may be asymptomatic or symptoms may be limited to tachycardia, decreased exercise tolerance, and dyspnea with exertion.

Echocardiography

Although echocardiographic findings by themselves are not yet accepted as fulfilling the criteria for carditis, echocardiography is utilized routinely when available.

The Jones Criteria for the diagnosis of acute rheumatic fever were written long before the availability of echocardiography and there continues to be controversy concerning the specificity and sensitivity of echocardiography for the diagnosis of RF. Since many normal patients have a small amount of mitral and aortic insufficiency, there has been concern that echocardiography may result in the overdiagnosis of RF. On the other hand, echocardiography has the ability to evaluate abnormal mitral and aortic valves even when a murmur may be absent and is therefore more sensitive than auscultation. All patients with suspected RF should have an echocardiogram, and a physician knowledgeable about the specific changes that occur in RF should interpret the study. To differentiate pathologic from normal physiologic mitral and aortic insufficiency, the World Health Organization has recommended the following criteria: (a) color Doppler jet > 1 cm in length, (b) color Doppler jet evident in at least two imaging planes, (c) color Doppler jet mosaic with a velocity > 2.5 m/s, and (d) Doppler spectral tracing holosystolic for mitral insufficiency and holodiastolic for aortic insufficiency. These criteria have been validated by Minich et al. in 1997.

The current WHO recommendations are accepted in developed countries, but there has been concern that these criteria are not adequately sensitive for use in developing countries. A recently published study by Marijon et al. suggested the incorporation of echocardiographic morphologic criteria in addition to the Doppler criteria for the diagnosis of carditis secondary to RF. They studied 2,370 children in Mozambique, an area with a high prevalence of RF. The maximum sensitivity of the WHO

Table 258.3

Combined criteria
Doppler criteria
Any degree of valvular regurgitation seen in at least two planes
Associated with at least two morphological signs
Leaflet restriction
Subvalvular thickening
Valvular thickening

criteria was 25% and the maximal sensitivity of the combined criteria was 97%. They felt that the combined criteria are adequately specific since there are almost no other causes of valve thickening in children. The use of these more sensitive criteria may be useful, especially in developing countries, since diagnosis of the first episode of RF allows secondary prophylaxis, with the possibility of decreasing the risk of recurrent episodes of RF and decreasing the incidence of progressive valve disease.

The echocardiographic criteria suggested are summarized in *Table 258.3*.

Arthritis

Migratory polyarthritis is the most common of the major Jones criteria, occurring in 40–70% of cases. Unfortunately, it is also the least specific of the major criteria. The signs of arthritis may also occur in diseases such as Juvenile Rheumatoid Arthritis. The arthritis generally presents from 10 days to 5 weeks after the initial streptococcal infection. The large joints of the knees, ankles, elbows, and wrists are most commonly involved, and typically there is migration from one joint to another. Because of the migration, only one joint may appear to be involved at one time and serial examinations may be necessary. Although the arthritis is typically polyarticular, in some parts of the world, such as Australia's North Territory, monoarthritis may occur. It is important to differentiate true arthritis, a major criterion, from arthralgia, a minor criterion. The joints affected by arthritis are red, swollen, and are exquisitely tender. The joints affected by arthralgia are painful, but not red or swollen. Even with no treatment, the arthritis often resolves 3–4 weeks and is not associated with chronic abnormalities. There is usually such a dramatic response to aspirin therapy that lack of response within 2–3 days should prompt consideration of other etiologies.

There is an entity termed poststreptococcal reactive arthritis that differs from the typical polyarthritis of RF. It appears after a relatively short latent period of 7–10 days, is usually not migratory, is often persistent, and does not respond rapidly to aspirin therapy. This type of arthritis is not generally associated with RF, but there have been reports of patients that were thought to have this type of arthritis and subsequently developed the valvular changes of RF. Any patient with this form of arthritis should be evaluated carefully for other signs of RF.

Chorea

The word chorea is from a Greco-Latin word implying the act of dancing. In the sixteenth century, the term chorea was used by Paracelsus to describe the frenzied movements of religious fanatics who journeyed to the healing shrine of St. Vitus during the middle ages. Thus the term St Vitus dance, an older term for Sydenham's chorea. In the seventeenth century, the English physician Thomas Sydenham described the physical signs of chorea as a true medical entity, though the association of chorea with rheumatic fever was not noted until the nineteenth century.

Chorea occurs in approximately 10–30% of cases of RF. It presents much later than arthritis and carditis, with a latency period of 1–6 months. Because of the latency, patients may not remember an episode of pharyngitis, may not remember the signs or symptoms of arthritis or carditis, and the evidence of the streptococcal infection may not be present. For this reason, the diagnosis of RF may be made when chorea is evident even without other criteria or without evidence of a preceding streptococcal infection.

Patients with chorea have involuntary and purposeless movements, incoordination of muscular movements, and emotional lability. Mild cases may come to attention because of deteriorating school performance, irritability, poor attention span, and changes in coordination. The clinical manifestations of chorea are secondary to inflammatory changes in the basal ganglia, cerebral cortex, and the cerebellum.

Chorea and carditis coexist in approximately 50% of patients with RF. The cardiac involvement in patients with chorea tends to be mild initially, but even those with no cardiac abnormalities at the time of diagnosis of RF are at risk for progressive valvular disease.

Erythema Marginatum

The rash of erythema marginatum is uncommon in RF, only occurring in 5%. However, it is a helpful major criterion since it is quite specific. The rash rarely occurs as the sole

major criterion, but almost always is associated with carditis. The rash is evanescent and may be missed on a single examination. A hot bath often accentuates the rash. It presents as a bright pink/red papule that spreads with serpiginous borders and has central clearing. The borders are usually macular but may be papular and it does blanch with palpation. The rash is not pruritic and is not painful.

Subcutaneous Nodules

Subcutaneous nodules are quite uncommon in RF, occurring in less than 10% of cases. They are not a strong criterion for RF since they may also occur in rheumatoid arthritis and systemic lupus erythematosus. The nodules are usually on the extensor surfaces of the elbows, wrists, knees, ankles, and spinous processes of the back. They may also occur on the scalp. The nodules are generally 0.5–2 cm in diameter, firm, movable, and are not tender to palpation. Subcutaneous nodules rarely are the sole major criterion, and are almost always associated with carditis.

Minor Criteria

The minor criteria are supportive data, with low specificity.

Fever: Most patients are febrile in the early phase of RF, with temperatures ranging from 38°C to 39.5°C (100–103°F). The fevers resolve in 1–2 weeks even without treatment.

Arthralgias: Arthralgias defined as joint pain with no redness or swelling, usually involve the large joints. The pain may vary from mild to severe and the joint involvement may be migratory. Arthralgia cannot be used as a minor criterion if arthritis is used as a major criterion.

Acute-phase reactants: Most clinicians obtain both an erythrocyte sedimentation rate (ESR) and a C-reactive protein (CRP) level. Both are quite nonspecific and are elevated in most inflammatory processes.

Prolonged PR interval: This is a nonspecific criterion, but an ECG should be done on all patients with possible RF. It is not a specific finding since the PR interval is prolonged in one third of patients with a recent Group A streptococcal infection, regardless of whether RF develops.

Supportive Evidence of an Antecedant Group A Streptococcal Infection

Although a positive throat culture or a positive rapid antigen test is acceptable evidence of an antecedent infection, these tests do not rule out a carrier state instead of an acute infection. Elevated or rising antibody titers yield more reliable evidence of a recent infection. The most commonly measured antibody titers are antistreptolysin O (ASO) and antideoxyribonuclease B (anti-DNase B). When one is measured, 80–85% of patients with RF will have an elevated titer. When both are measured, over 90% will have elevation of at least one titer. Determination of a rising antibody titer may be more useful than a single antibody titer, especially if the initial titer is normal or only mildly elevated. The titers peak about 2–4 weeks after the infection.

Treatment of Acute Rheumatic Fever

The diagnosis of acute rheumatic fever should be substantiated before beginning anti-inflammatory therapy in order to avoid diagnostic confusion by the possible suppression of a variety of other inflammatory diseases. However, comfort measures should be initiated, and any signs of carditis should be treated early.

There are four goals in the initial therapy for RF:

1. Symptomatic relief
2. Eradication of group A beta-hemolytic streptococcus
3. Treatment of the manifestations of carditis, if present
4. Prophylaxis against subsequent infection with GAS, to prevent recurrent RF

Symptomatic Relief

Bed rest has been a mainstay of treatment for RF. In the 1940s, and 1950s patients were treated with bed rest for up to a year based on data that indicated this decreased the severity of carditis and fewer episodes of reactivation. Now, it is usually recommended that patients remain at bed rest or chair for 4–6 weeks, depending on the clinical course.

It is standard to treat patients with aspirin, usually starting at 80–100 mg/kg/day divided in four doses. Serum concentrations should be maintained in the range of 20–30 mg/dl. Aspirin is generally continued until the patient is asymptomatic and the acute-phase reactants have returned to normal.

The arthritis of RF is exquisitely responsive to salicylate therapy, and if there is no improvement after several days other diagnoses should be considered.

Carditis

The severity of carditis should be ascertained frequently, and should be treated aggressively with conventional

therapy for heart failure. Although patients with significant carditis are often treated with corticosteroids, studies have not shown any significant differences in outcome. Steroids have not been shown to improve the long-term outcome of carditis, but treatment with steroids is associated with a more rapid decrease in inflammation, fewer new murmurs, and an earlier disappearance of existing murmurs.

Eradication of Group A Streptococcus

Patients with acute RF should be treated with either 10 days of antibiotic or a single IM dose of antibiotic, even if there is no evidence of pharyngitis at the time of the diagnosis. These recommendations are summarized in Table 258.4.

Prevention of Recurrent Attacks of Rheumatic Fever (Secondary Prevention)

All individuals who have had acute RF are at high risk for a recurrence if they incur another GAS infection. A recurrent episode of RF may worsen any cardiac disease already present and it may cause new cardiac disease in those without carditis during their initial episode of RF. Because many infections with GAS are without symptoms, the most effective course is to institute a regimen of continuous antibacterial prophylaxis as well as treatment of new known acute GAS infections. The recommendations for secondary prevention of recurrent RF are summarized in Table 258.5.

Duration of Prophylaxis

The duration of prophylaxis is not well defined, and should be individualized. Patients at high risk for GSA, such as teachers, physicians, and nurses should be treated as long as they have this exposure. Most physicians suggest that prophylaxis should continue at least until the patient is a young adult, which usually is at least 10 years after acute RF. Guidelines published by the American Heart Association and endorsed by the American Academy of

Table 258.4
Primary prevention of rheumatic fever (RF) (treatment of streptococcal pharyngitis)

Agent	Dose	Mode	Duration
Penicillins		Oral	10 days
Penicillin V	Children ≤27 kg (60 lb): 250 mg 2–3 times daily		
	Children >27 kg (60 lb), adolescents and adults: 500 mg 2–3 times daily		
	OR		
Amoxicillin	50 mg/kg once daily (maximum 1 g)	Oral	10 days
	OR		
Benzathine penicillin G	600,000 units for children ≤27 kg (60 lb)	Intramuscular	Once
	1,200,00 units for patients >kg (60 lb)		
For patients allergic to penicillins:			
Narrow-spectrum cephalosporin[a]	Depends on the specific antibiotic	Oral	10 days
	OR		
Clindamycin	20 mg/kg/day, divided TID (max 1.8 g/day)	Oral	10 days
	OR		
Azithromycin	12 mg/kg once daily (maximum 500 mg)	Oral	5 days
	OR		
Clarithromycin	15 mg/kg divided BID (maximum 250 mg BID)	Oral	10 days

From Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, Taubert KA (2009) Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis. A scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research. Circulation 119(11):1541–1551
[a]Avoid in patients with immediate (type I) hypersensitivity to penicillin

Table 258.5
Secondary prevention of recurrent rheumatic fever (secondary prevention)

Agent	Dose	Mode
Benzathine penicillin G	600,000 units for children ≤27 kg (60 lb)	Intramuscular
	1,200,00 units for patients >kg (60 lb)	
	Every 4 weeks[a]	
Penicillin V	250 mg twice daily	Oral
Sulfadiazine	0.5 g once daily for children ≤27 kg (60 lb)	Oral
	1.0 g once daily for patients >kg (60 lb)	
For patients allergic to penicillin and sulfadiazine		
Macrolide or azalide	Depends on the antibiotic used	Oral

[a]In high-risk situations, administration every 3 weeks is justified and recommended

Pediatrics are in *Table 258.6*. Many clinicians feel that all patients with valvular heart disease secondary to RF should remain on continuous prophylaxis throughout life.

Table 258.6
Duration of secondary rheumatic fever prophylaxis

Category	Duration after last episode of RF
RF with carditis and residual heart disease (persistent valvular disease)	10 years or until 40 years of age (whichever is longer), sometimes lifelong prophylaxis
RF with carditis but no residual heart disease (no valvular disease)	10 years or until 21 years of age (whichever is longer)
RF without carditis	5 years of until 21 years of age (whichever is longer)

Level of confidence: Only consensus of experts, case studies, or standard of care

Bacterial Endocarditis Prophylaxis

The AHA has recently published updated recommendations regarding the use of prophylactic antibiotics to prevent infective endocarditis. These guidelines no longer suggest prophylaxis for patients with a history of RF unless they have a prosthetic valve or prosthetic material used in valve repair. In this situation, it is advised to use an antibiotic other than a penicillin since oral α-hemolytic streptococci would likely have developed resistance to penicillin.

Chronic Rheumatic Heart Disease

Chronic rheumatic heart disease (RHD) remains the most serious complication following acute rheumatic fever worldwide, especially in developing countries. In children, the most common form of RHD is mitral insufficiency rather than mitral stenosis. Aortic insufficiency is less common, and almost always accompanies mitral insufficiency. The cause of the mitral insufficiency is usually shortening, retraction, and deformity of the leaflets and often accompanied by chordal shortening and fusion. These changes result in inadequate leaflet coaptation, allowing insufficiency. There may be secondary left ventricular dilation, which causes annular dilation and an alteration of the papillary muscle orientation allowing for further insufficiency of the mitral valve. Chronic mitral insufficiency causes left ventricular dilation and eventual left ventricular systolic and diastolic dysfunction. The elevated left ventricular end-diastolic pressure and the elevated left atrial pressure lead to dyspnea, especially with exertion, and decreased exercise tolerance.

Aortic insufficiency may accompany mitral insufficiency in the early years of RHD, and may increase the left ventricular dimensions and accelerate left ventricular dysfunction. Aortic insufficiency seldom occurs without associated mitral insufficiency.

Mitral stenosis may develop as early as the second decade of life secondary to leaflet thickening and retraction, fusion of the commissures, and chordal shortening. Eventually, the leaflets may calcify, further increasing the stenosis. In developed countries, mitral stenosis generally does not occur until 15–40 years after the initial occurrence of RF. Mitral stenosis occurs earlier in developing countries, probably because of multiple episodes of acute RF. The result of mitral stenosis is an elevation in left atrial

pressure with the development of dyspnea, decreased exercise tolerance, and pulmonary hypertension. The left atrial enlargement may lead to atrial flutter/fibrillation.

Aortic stenosis may accompany mitral stenosis and is generally a slowly evolving process. Over time, there may be the development of aortic valve thickening, fibrosis, calcification, and fusion of the commissures. Aortic valve insufficiency usually persists, and may even worsen as the leaflets become more thickened and rigid. Over time, left ventricular failure may ensue, as the aortic valve disease is additive to the mitral valve disease.

The treatment of the valvular changes in chronic RHD is related to the hemodynamic effects. Although patients may be treated medically for decades, many eventually need to have replacement of the mitral and/or aortic valves. Mitral stenosis is occasionally treated with dilation during a cardiac catheterization, though this may increase the insufficiency. Aortic stenosis is not generally amenable to dilation and valve replacement is the only effective treatment.

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259 Secondary Cardiac Morbidities

Melanie D. Everitt · Lloyd Y. Tani

Case Presentation

A 12-year-old girl with type 1 diabetes mellitus (DM) for 5 years presents for a routine well-child visit. What is her risk of future cardiovascular events and what additional historical information, physical examination, and laboratory studies should be obtained?

Definition

Secondary cardiac morbidity is heart disease that develops as a result of other systemic disorders. This form of acquired heart disease can affect the coronary arteries, central vasculature, pericardium, myocardium, or the neural regulatory system of the heart depending upon the pathology of the primary disorder and the side effects of its treatment.

Etiology

While acquired heart disease in the overall pediatric population is relatively uncommon, secondary cardiac morbidity can develop from a variety of more common medical conditions in childhood. Examples of these childhood illnesses are listed in *Table 259.1*. Early diagnosis and treatment can affect the progression and severity of secondary heart disease. The key to timely diagnosis is in recognizing that these comorbidities exist, having awareness of the contributing factors, and being mindful that the signs and symptoms of cardiac involvement can mimic those of other more common childhood illnesses.

Epidemiology

Specific cardiac morbidity that can develop in the setting of other diseases includes early coronary artery disease (CAD), neuropathy, heart failure, cor pulmonale, pericardial effusions, arrhythmias, and systemic hypertension (HTN). Early arteriosclerosis is seen in the majority of the diseases discussed herein, with diabetes mellitus, chronic kidney disease, and chronic inflammatory illnesses of particular note. Based on the Third National Health and Nutrition Examination Survey (NHANES III), the prevalence of type 1 diabetes mellitus is 1.7/1000 and that of type 2 is 4.1/1000. By adulthood, over 40% of diabetics older than the age of 35 years have been diagnosed with cardiovascular disease. Children with chronic kidney disease are now surviving longer such that death due to secondary morbidity rather than renal failure is a growing concern. In autopsy series of children with end stage renal disease (ESRD), 50% or more had evidence of early arteriosclerosis. Regarding hospitalizations in children with ESRD, one-third of admissions are related to cardiovascular events.

Most prevalent of all the cardiac morbidities is systemic hypertension. The reported prevalence of systemic hypertension (HTN) in children ranges from 1% to 4% with an increasing prevalence of HTN paralleling the rise in childhood obesity. With respect to HTN secondary to other childhood illnesses, a secondary cause is more likely present in younger children compared to adolescence. Overall secondary HTN accounts for about 50% of childhood HTN. Disease-specific epidemiology is discussed in more detail below.

Pathology

Diabetes Mellitus

Diabetes mellitus (DM) is a well-known risk factor for the development of early and usually subclinical atherosclerosis in childhood and ischemic heart disease and heart failure later in life. HTN and dyslipidemia confer additional risk and frequently coexist in patients with type 2 DM. As the incidence of DM in children rises, pediatricians are poised to impact the future development of CAD and heart failure through the early recognition and treatment of CAD risk factors in conjunction with glycemic control.

A serious complication of DM that is under recognized but highly associated with mortality is cardiovascular autonomic dysfunction. Cardiac autonomic neuropathy (CAN) results from damage to the autonomic nerve fibers that innervate the heart and blood vessels. The clinical

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Table 259.1
Disorders associated with secondary cardiac morbidity

Endocrine disorders
Diabetes mellitus
Hypothyroidism
Hyperthyroidism
Pheochromocytoma
Cushing's disease
Kidney diseases
Chronic renal insufficiency
Renovascular disease
Renal parenchymal disease
Pulmonary disorders
Cystic fibrosis
Bronchopulmonary dysplasia
Hematologic diseases
Sickle cell anemia
Thalassemia
Cancer
Radiation therapy
Chemotherapy (anthracycline)
Immune disorders
Systemic lupus erythematosus
Systemic juvenile rheumatoid arthritis
Systemic scleroderma

manifestations of CAN include resting tachycardia, exercise intolerance, orthostatic hypotension, and silent myocardial ischemia. Screening for CAN is recommended in patients with type 2 DM at the time of diagnosis and in patients with type 1 DM within 5 years of diagnosis. Assessment of heart rate variability to deep breathing, standing, and Valsalva maneuver as well as assessment of blood pressure (BP) response to standing and sustained handgrip are screening recommendations endorsed by the American Diabetes Association. Treatment of CAN involves intensification or reinforcement of glycemic control to slow progression of neural dysfunction as well as symptomatic relief of orthostatic hypotension by increasing fluid and salt intake and avoiding situations that provoke hypotension. The diagnosis of CAN warrants further testing for other forms of diabetic neuropathy.

Thyroid Disorders

Both hypothyroidism and hyperthyroidism yield alterations in cardiac function, heart rate, and vascular resistance. Cardiac manifestations of hyperthyroidism are tachycardia, including sinus tachycardia and supraventricular arrhythmias; systolic HTN related to increased contractility and cardiac output; and low diastolic pressure related to decreased vascular resistance, which is manifest as a widened pulse pressure. Left ventricular dysfunction and overt heart failure can occur but are uncommon. If present, a tachycardia-mediated cardiomyopathy related to the primary thyroid disorder is most likely. The cardiac function usually returns to normal once the hyperthyroidism is treated and/or the heart rate is controlled with beta-blockade. The cardiac manifestations of hypothyroidism include bradycardia and diastolic HTN related to increased vascular resistance, which is manifest as a narrowed pulse pressure. Cardiac dysfunction is rare in hypothyroidism. Pericardial effusions can develop but tend not to be hemodynamically compromising. The development of an effusion tends to correlate with disease severity and, when present, is usually associated with the non-pitting myxedema characteristic of hypothyroidism.

Cardiovascular signs and symptoms related to the effects of thyroid dysfunction may be the primary reason patients with thyroid disease seek medical attention. Patients may present with palpitations, diaphoresis, dyspnea, fatigue, and/or edema. In addition to clues provided by the clinical history and remainder of the examination, ancillary cardiac testing may point to the primary diagnosis of thyroid disease. An electrocardiogram will allow determination of the heart rhythm but may also show low voltages characteristic of hypothyroidism. A 24-h Holter monitor with excessive sinus tachycardia and limited heart rate variability is seen in hyperthyroidism. An enlarged cardiac silhouette on chest radiograph should prompt echocardiographic assessment of ventricular function or the presence of a pericardial effusion. Treatment of the thyroid disorder usually yields resolution of the cardiac morbidity.

Chronic Kidney Disease

The risk of death due to heart disease and the rate of hospitalizations for heart failure, CAD, and stroke are disproportionately higher in individuals with renal insufficiency as opposed to those without kidney disease. Proposed mechanisms for an association between kidney disease and heart disease include the presence of increased levels of inflammatory factors, abnormal Apo lipoprotein levels, elevated plasma homocysteine, disruption of calcium and phosphorus homeostasis, enhanced

coagulability, anemia, left ventricular hypertrophy (LVH), increased arterial calcification, endothelial dysfunction, and arterial stiffness. In pediatric patients with ESRD, approximately one-quarter of deaths is attributable to cardiovascular disease including pericardial disease, arrhythmias, left ventricular dysfunction, and CAD. A Dutch national study of ESRD diagnosed in childhood observed an age-specific all-cause mortality rate 30 times the expected mortality of the general population. Death from cardiovascular disease occurred at a mean age of 17.3 years with a median time between first renal replacement therapy and death of 3.7 years (0.1–25.9).

Even in children with mild degrees of renal insufficiency, cardiac structure and function may be affected early in the course of disease. The largest pediatric study to date to assess cardiac abnormalities in children with chronic renal insufficiency is a sub-study of the Effect of Strict Blood Pressure Control and ACE Inhibition on the Progression of Chronic Renal Insufficiency in PEdiatric Patients (ESCAPE) trial. One-third of the 156 patients examined had LVH and the presence of LVH was independent of BP elevation as assessed by ambulatory BP monitoring. Thus, while BP control is important in these patients, it does not appear to be the sole determinant of LVH in the setting of kidney disease. Subclinical systolic and/or diastolic dysfunction may also develop in children with renal insufficiency. Both can contribute to the reduced exercise capacity that is seen even early in the course of chronic kidney disease.

Renal Parenchymal and Renovascular Diseases

While essential HTN is common in the adolescent and adult, renal parenchymal and renovascular diseases constitute the majority of causes of HTN in the younger child. Renal parenchymal disease is identified as the cause in two-thirds of cases of secondary HTN in childhood. Renal parenchymal disease is most commonly due to reflux, obstruction, or chronic glomerulonephritis. Approximately 10% of cases of secondary HTN in childhood are attributed to renovascular disease. Renovascular disease produces HTN through reduced blood flow to one or both kidneys as occurs in renal artery stenosis, thrombosis, vasculitis, dissection related to trauma or aneurysm, abdominal radiation, or external compression.

Severe HTN related to renal disease can lead to ventricular dysfunction and congestive heart failure. When concurrent, the findings of left ventricular hypertrophy, diastolic dysfunction, and left atrial enlargement support HTN as the etiology of the ventricular dysfunction. In a retrospective review of 11 neonates diagnosed with neonatal cardiomyopathy and systemic HTN, 9 of the infants had HTN due to renovascular disease.

Cystic Fibrosis

A secondary manifestation of cystic fibrosis (CF) is cor pulmonale. Cor pulmonale is abnormal hypertrophy or dilation of the right ventricle that results from pulmonary HTN caused by disorders of lung function or structure. Given the severe pulmonary disease characteristic of cystic fibrosis (CF), it is not surprising that cor pulmonale is an associated cardiac morbidity. Intraluminal obstruction of the bronchi by mucus leads to hypoxemia. As the pulmonary disease and degree of hypoventilation progress, hypercarbia and respiratory acidosis ensue. Low alveolar oxygen tension, hypercarbia, and acidemia promote pulmonary vasoconstriction resulting in pulmonary HTN. Moreover, lung hyperexpansion due to air trapping may also raise the pulmonary vascular resistance. Nasal polyps that develop in the setting of CF can promote obstructive sleep apnea and worsen nighttime hypoxemia. During acute infections, the pulmonary HTN is exacerbated, but it is the chronic pressure overload that drives the development of right ventricular hypertrophy. Intrapulmonary shunts related to dilated bronchial arteries and the exaggerated changes in intrathoracic and intrabdominal pressures play a role in the volume overload and dilation of the right ventricle. Collectively, these derangements lead to right ventricular failure sooner in patients with chronic lung disease than in those with other degrees of right ventricular pressure overload.

Bronchopulmonary Dysplasia

Cor pulmonale as a result of pulmonary arterial hypertension (PAH) is an important cardiovascular comorbidity in the infant with bronchopulmonary dysplasia (BPD). The lung injury in BPD affects not only airspace development but also pulmonary vasculature development such that there are fewer capillaries and abnormal regulation of vascular reactivity. In a study of 42 premature infants with BPD and PAH, 43% had systemic or suprasystemic right ventricular pressures and these infants had a survival rate of only 37% at 1 year.

Systemic HTN is reported in approximately 10% of infants with BPD. Etiologies include altered neurohormonal regulation; increased catecholamine, angiotensin,

and antidiuretic hormone levels; the side effect of steroid or beta-agonist administration; and other morbidities of prematurity such as renovascular disease. Routine BP monitoring is recommended at least weekly for hospitalized infants and at each outpatient visit thereafter. Systemic HTN in infants with BPD is usually transient but responds well to pharmacologic therapy.

Sickle Cell Disease

Cardiac complications of sickle cell anemia (SCA) include diastolic dysfunction, myocardial infarction, exercise-induced ischemia, fatal arrhythmias, and cor pulmonale.

Cardiomegaly is a common finding on chest radiograph in individuals with SCA but is not usually indicative of reduced cardiac function. Increases in heart chamber size and ventricular wall thickness are seen in children with SCA beginning in the first year of life. The degree of cardiomegaly is inversely related to the hemoglobin level and directly related to age or duration of illness. The degree of cardiomegaly seen in patients with SCA tends to be greater than that seen in other patients with chronic anemia despite similar levels of hemoglobin.

Diastolic dysfunction in the absence of systolic dysfunction can occur due to the ventricular hypertrophy and myocardial ischemia that coexist in SCA. A study of 107 children with SCA found impaired diastolic function to be present in over half. The clinical significance of these findings in asymptomatic children is not known but in adults with SCA, diastolic dysfunction is an independent risk factor for death.

The true prevalence of myocardial ischemia is likely underreported in patients with SCA. A number of case reviews cite the occurrence of myocardial infarction in patients with SCA who have no other coronary risk factors, and studies involving asymptomatic children with SCA have frequently detected abnormalities consistent with ischemia by exercise testing and perfusion scanning. Mechanisms of ischemic injury are likely multifactorial including anemia, platelet thrombi, coronary vasospasm, hypoxemia, abnormal sickling in the microcirculation, and increased oxygen demand of the hypertrophied heart muscle. The signs and symptoms of myocardial ischemia in these patients are nonspecific and similar to those of sickle cell crisis or acute chest syndrome, likely resulting in underdiagnosis.

Cor pulmonale due to pulmonary HTN is a cardiac complication of SCA as well. Pulmonary HTN is present in approximately one-third of children with SCA even in the absence of acute illness. Moreover, by the time these patients reach adulthood, the presence of pulmonary HTN is a strong predictor of death. In the setting of severe acute chest syndrome, pulmonary HTN resulting in cor pulmonale and death can occur. The pathophysiology of pulmonary HTN in SCA includes microvascular insults related to sickling along with the vasoconstrictive effects of hypoxemia.

Thalassemia

Heart complications are the leading cause of mortality in thalassemia major. In these patients, severe anemia necessitating regular transfusion therapy develops as early as infancy. The increased iron load resulting from frequent red cell transfusions coupled with greater intestinal absorption of iron lead to iron deposition in the heart. Cardiomegaly related to isolated chamber enlargement may result solely from anemia as occurs in sickle cell disease, but patients with thalassemia major can develop an iron-induced cardiomyopathy. Decreased systolic function, impaired relaxation, pericarditis, or fatal arrhythmias can occur. The development and progression of cardiac involvement is related to the frequency of transfusions. Chelation therapy is essential to minimize iron overload and end-organ damage and has been reported to slowly reverse the damage in some cases.

Cancer

The development of cardiac dysfunction is a serious consequence of cancer treatment in childhood. Among chemotherapeutic agents, the anthracyclines are particularly cardiotoxic, but are also effective in the treatment of over half of all cancer cases in children. Thus, it is not surprising that 15% of all pediatric cardiomyopathies occur in patients treated for malignancy. While higher cumulative doses and longer time since therapy are associated with increased likelihood of myocardial dysfunction, the cardiotoxic effects can occur at lower doses and early in treatment. More commonly, myocardial dysfunction appears at a median of 10 years after cessation of anthracycline therapy. Presentations of cardiac involvement vary and include asymptomatic decline in ventricular function detected upon routine echocardiography, symptomatic congestive heart failure due to systolic and/or diastolic dysfunction, arrhythmia, myocarditis, pericarditis, acute coronary syndrome, and sudden death. The mechanisms implicated in injury involve the

accumulation of anthracyclines and metabolites in cardiac myocytes, the formation of toxic free radicals, and the release of cytokines and vasoactive amine. The end result is irreversible myocyte loss.

Radiation therapy also poses a risk of acute and chronic cardiac toxicity. Younger age at irradiation, higher cumulative dose to the chest, and exposure to other cardiotoxic agents increase the risk of cardiac morbidity. Pericarditis is the most common manifestation of radiation therapy and is seen in up to 20% of patients. Chronic pericarditis tends to develop within 10 years of treatment. Recurrent effusions or constrictive pericardial disease can occur with the need for surgical pericardiectomy in some cases. Acute pericarditis occurring within a few weeks after treatment is rare and usually resolves without the need to discontinue radiation treatment. Radiation can also induce microvascular insufficiency and myocardial ischemia leading to myocyte necrosis and interstitial fibrosis. This insult to the myocardium manifests as a restrictive cardiomyopathy with primarily diastolic dysfunction and pulmonary hypertension or as a dilated cardiomyopathy with systolic dysfunction.

Immune Disorders

A number of immunologic disorders are associated with cardiac involvement. Pericarditis with effusions, valvulitis, myocarditis, vasculitis, and conduction abnormalities or arrhythmias can be the presenting feature or develop in the course of disease. Secondary cardiac morbidity may develop from vasculitis or nephritis-related systemic HTN or from pulmonary HTN related to pulmonary veno-occlusive disease, pneumonitis, or pulmonary fibrosis. Systemic lupus erythematosus, systemic-onset juvenile rheumatoid arthritis, and systemic scleroderma are among the primary immunologic disorders of childhood with both direct and indirect effects on the cardiovascular system.

Therapies directed at the immune system and the primary disease are paramount. In some cases, the injury to the heart may be irreversible. Acute or chronic inflammation can lead to permanent valve injury or myocyte death with resultant scar formation, impairment of systolic or diastolic dysfunction, and a predisposition for ventricular arrhythmias.

Clinical Manifestations

The signs and symptoms of acquired heart disease secondary to systemic illnesses vary depending upon the primary disorder and its impact on the cardiovascular system. Diastolic dysfunction and/or systolic dysfunction may be quite advanced before signs or symptoms of heart failure are detected. Moreover, early findings may be dismissed as related to an exacerbation of the primary disease. Signs and symptoms that should alert one to possible cardiac disease are shown in *Table 259.2*.

Diagnosis

The diagnosis of cardiac comorbidities is dependent upon the awareness of potential cardiac disease and recognition of suspicious signs and symptoms. Electrocardiography and chest radiography may aid in detection or monitoring of heart disease, but in general, the value of these tests to screen for asymptomatic or early heart disease is limited. Electrocardiography allows determination of heart rhythm, but a normal ECG does not exclude the presence of right or left ventricular hypertrophy, chamber enlargement, pulmonary HTN, or CAD. Chest radiography may show cardiomegaly or pulmonary edema, but a normal chest radiograph does not equate to a structurally and functionally normal heart. In CF or BPD when the lungs are hyperinflated, cardiomegaly may not be apparent by chest radiograph until heart failure is advanced. However, serial studies may allow for the detection of incremental changes in the size of the cardiac silhouette.

Table 259.2
Symptoms and signs suggestive of secondary cardiac mordibity

Symptoms	Signs
Activity intolerance • Dyspnea on exertion • Fatigue • Poor feeding in an infant Chest pain Palpitations or irregular heart beat Syncope Orthopnea Abdominal complaints • Pain • Early satiety	Tachypnea Tachycardia/ bradycardia Hypertension/ Hypotension Abnormal breath sounds • Crackles • Rales Abnormal heart sounds • Murmur • Prominent S2 • Muffled heart sounds or rub • Gallop Jugular venous distension Hepatomegaly or ascites Edema

With respect to systemic HTN secondary to chronic disease or as an additional risk factor for heart disease, blood pressure should be assessed at each visit. Once a diagnosis of hypertension has been established, echocardiography should be performed to assess for end-organ effects. Measurement of left ventricular mass, systolic function, and diastolic function should be part of this echocardiographic examination. Echocardiography is useful not only in screening for end-organ remodeling but also in monitoring the efficacy of antihypertensive therapy. Ambulatory BP monitoring can aid in diagnosing "white coat HTN," investigating symptoms of hypotension while on antihypertensive medication, and monitoring response to treatment in patients with refractory HTN or persistent evidence of target organ damage despite apparent BP control.

Echocardiography is a useful noninvasive modality to assess for pulmonary HTN and secondary right heart changes. When tricuspid valve regurgitation and pulmonary valve regurgitation are present, Doppler interrogation can provide an estimation of right ventricular and pulmonary arterial pressures. The presence of right ventricular hypertrophy, right ventricular dysfunction, or abnormal configuration of the interventricular septum suggestive of elevated pulmonary artery pressures can also be identified by echocardiography. Cardiac catheterization, with direct measurement of pulmonary pressures, is the gold standard to evaluate the severity of pulmonary HTN and degree of vascular reactivity to potential therapeutic agents including oxygen, nitric oxide, and prostacyclin. Consultation with a cardiologist can guide the echocardiographic assessment and determine if more invasive testing such as cardiac catheterization is warranted.

With respect to children undergoing treatment for malignancies, specific screening guidelines to detect the cardiotoxic effects of chemotherapy and radiation have been developed by the Children's Oncology Group (COG). Patients undergoing treatment with anthracycline agents or radiation therapy should have baseline and serial electrocardiographic and echocardiographic screening. The frequency of long-term echocardiographic screening as recommended by COG varies based on age at first cardiotoxic therapy, cumulative dose of anthracycline, and the use and dose of radiation therapy. Children who were younger than 5 years old at the time of initial therapy and received any dose of radiation therapy combined with any dose of anthracycline should have an echocardiogram performed every year as part of long-term follow-up. Children who were at least 5 years of age at the time of first anthracycline dosing who received <200 mg/m2 and were not treated with radiation should have echocardiographic screening at 5-year intervals as long as left ventricular systolic function does not decrease on serial testing.

In general, a careful history and physical examination are valuable diagnostic tools, but routine screening ECG and chest radiograph have limited or no value. If cardiac complications are suspected on the basis of history, disease severity or chronicity, risk factors, symptoms, or signs, then referral to a cardiologist for individualized testing using echocardiography, exercise testing with measurement of functional capacity, cardiac MRI, 24-h Holter monitoring, event monitoring, and/or cardiac catheterization is prudent.

Differential Diagnosis

Not infrequently, the signs and symptoms of cardiac disease are nonspecific and can mimic an exacerbation of the primary medical illness. Additionally, the primary illness can obscure important signs indicative of cardiac disease. Such is the case in patients with CF or BPD who have lung hyperexpansion that obscures the auscultatory findings of a narrowly split or prominent second heart sound indicative of pulmonary HTN. Alternatively, the primary illness can yield signs or symptoms of heart disease that lead to undue concern and cardiac testing. For example, hepatic enlargement is a worrisome indicator of heart failure. However, a downwardly displaced liver related to lung hyperexpansion rather than an increased liver span can be mistaken for hepatomegaly. Thus, the differential diagnosis should be broad to include possible secondary morbidities. However, attention to a detailed history and physical examination with expert consultation when deemed necessary is important to avoid unnecessary testing.

Treatment

In some cases, treatment of the primary disorder results in complete resolution of the cardiac disease. Alternatively, medical therapy directed against the cardiovascular morbidity is necessary. *Table 259.3* outlines the general management approach to the patient with secondary cardiac disease including the assessment of additional risk factors.

With respect to HTN in children, blood pressure (BP) should be assessed routinely at clinical visits. HTN should be diagnosed according to published normals based on age, sex, and height. Dietary modification and exercise are

Table 259.3
Treatment approach to the patient with secondary cardiac disease

Risk assessment	Therapy
• Severity and chronicity of primary disorder • Ideal weight or body mass index • Impaired glucose tolerance • Dyslipidemia ▪ Low HDL ▪ Elevated Triglycerides ▪ Elevated LDL • Hypertension • Sedentary lifestyle • Tobacco use • Illicit drug use • Alcohol use • Family history of early CAD or death	• Optimize treatment and compliance with therapy of primary disorder • Dietary modification • Routine exercise • Supplemental oxygen • Lipid-lowering medications • Antihypertensive medications • Anti-congestive medications ▪ ACE inhibitor ▪ Beta-blocker ▪ Diuretic ▪ Digoxin • Cessation of smoking, alcohol use, and illicit drug use

recommended as initial treatment if the systolic or diastolic BP is consistently between the 90–95th percentiles for age, sex, and height. If the BP target is not reached within 6–12 months of lifestyle intervention, pharmacologic treatment is recommended. For systolic or diastolic BP consistently above the 95th percentile or BP >130/80 mmHg in an adolescent, medication should be initiated along with lifestyle intervention as soon as HTN is diagnosed. An angiotensin converting enzyme (ACE) inhibitor is the drug of choice in patients with DM with the goal BP <130/80 mmHg or less than 90th percentile for age, sex, and height, whichever is lower. The choice of antihypertensive for children with other medical conditions should be individualized based upon the etiology, renal function, and presence of interacting medications.

When pulmonary HTN is present, factors that contribute to elevated pulmonary artery pressures should be sought and treated if possible. Oxygen therapy has been shown to confer survival benefit in patients with COPD and hypoxemia (PaO_2 <55 mmHg), and this is extrapolated to CF. However, outcomes research specific to patients with CF is lacking. Supplemental oxygen is recommended for patients with daytime hypoxemia or with hypoxemia during sleep or exercise. Polysomnography is used to determine the presence and degree of nighttime hypoxemia and hypercarbia and to monitor the efficacy of supplemental oxygen. For infants with BPD and hypoxemia or pulmonary hypertension, long-term supplemental oxygen should be prescribed at levels to maintain normal saturations but to minimize the adverse effects of hyperoxia including retinopathy and further lung injury. The safety and efficacy of newer oral agents to treat pulmonary HTN have not been established in infants and may be contraindicated in the setting of liver dysfunction. There are no proven therapies for pulmonary HTN related to SCA, but supplemental oxygen for patients with hypoxemia or oxygen-responsive pulmonary HTN based on direct hemodynamic assessment in the catheterization laboratory is a reasonable first approach. Transfusion therapy also reduces pulmonary HTN in some patients, presumably by decreasing the incidence of vaso-occlusive crises, acute chest syndrome, and lung damage. Similarly, these therapies benefit patients who have myocardial ischemia as they promote oxygen delivery, increase oxygen-carrying capacity, reduce sickling in the microvasculature, and reduce the myocardial demands imposed by anemia.

Assessment and treatment of modifiable risk factors are valuable. If there is a family history of hypercholesterolemia or an early cardiovascular event, children over the age of 2 years old should have a fasting lipid profile. In children with diabetes, the profile is best performed once glycemic control has been achieved. In children without risk factors for CAD and with adequate control of their primary illness, initial lipid screening may be delayed until closer to adolescence, around the age of 10 years. If the lipid profile is abnormal, annual monitoring is recommended with therapy as appropriate. Glycemic control and lifestyle modifications are primary therapy. The addition of statin therapy should be considered in older children when LDL levels remain elevated despite glycemic control and lifestyle modification. If the lipid profile is normal, then screening should be repeated every 5 years.

For the treatment of systolic ventricular dysfunction, medicines with proven survival benefit in adults, such as ACE inhibitors, beta-blockers, and spironolactone, may be beneficial to children with systolic dysfunction. Additional anti-congestive therapies such as diuretics and digoxin are indicated for symptomatic heart failure. However, there is limited data regarding the efficacy of these therapies in children. A randomized trial of ACE inhibition in children with anthracycline-induced cardiomyopathy found no difference in any dimensions of health-related quality of life measures and no significant improvement in exercise function. With respect to the use of beta-blockers, anecdotal benefit has been reported in children, but a large randomized controlled trial in children with heart failure due to a variety of causes did not show a difference in clinical outcomes compared to placebo. Consultation with

a pediatric cardiologist is advised when medical therapy is deemed necessary, and monitoring for adverse effects of medications should be performed. Heart transplantation is an option for a select group of patients with intractable, symptomatic heart failure whose primary disease is well controlled and not expected to influence transplant outcome.

Prognosis

In some cases, the cardiac morbidity is reversible with early diagnosis and treatment of the primary disorder and/or the heart disease. However, cardiovascular events are an important cause of mortality in childhood and in adult survivors of childhood illness. One-quarter of deaths in children with ESRD are attributed to cardiovascular causes, and cardiovascular events are the leading cause of death in adults with ESRD. In patients with CF and overt heart failure, mortality approaches 75% at 1 year. Two-thirds of deaths in patients with thalassemia major are due to cardiac involvement. Among survivors of childhood cancers treated with cardiotoxic therapies, cardiovascular events are the leading nonmalignant cause of death. Specifically, mortality from anthracycline heart failure is reported as high as 20%. With respect to immune disorders, women with SLE have an incidence of myocardial infarction that is 50 times greater than of women without SLE. Thus, prevention, early diagnosis, and treatment of secondary cardiac morbidity may significantly impact the outcome of individual patients.

Prevention

The mainstay of prevention of cardiac disease due to chronic disease in childhood is treatment of the underlying disorder. Assessment for additional cardiovascular risk factors is imperative and should occur on a regular basis. These risk factors include obesity, HTN, dyslipidemia, glucose intolerance, smoking, illicit drug use, alcohol abuse, sedentary lifestyle, and family history of early CAD ($\leq$55 years of age in first-degree male relatives; $\leq$65 years of age in female relatives). Modification of risk factors through lifestyle changes including diet and exercise should be emphasized. If risk reduction goals cannot be met through lifestyle changes and/or intensification of therapy for the primary disorder, antihypertensive and/or lipid-lowering medications are indicated. Regarding the cardiotoxic effects of anthracycline exposure, dexrazone has been shown to be cardioprotective in women with metastatic breast cancer. Studies in children are ongoing.

Summary

A variety of secondary cardiac morbidities are associated with childhood illness. Overt disease may develop in childhood or progress over years to impact cardiovascular well-being in adulthood. The care of the child with chronic medical illness should be comprehensive with awareness of potential comorbidities, intensification of therapies directed toward the primary illness, identification and treatment of the cardiovascular disorder as indicated, and modification of contributing factors. Specific therapies to reduce cardiovascular risk or to treat manifest cardiac changes depend upon the underlying disease, comorbidities, age of the child, and physician as well as patient and family preference. Most therapeutic strategies are derived from trials performed in adults with limited data in children. Consultation with a pediatric cardiologist can guide diagnostic endeavors and medical therapy.

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260 Adult Congenital Heart Disease

Michelle Gurvitz · Karen Stout

Introduction and Scope of the Problem

With advances in pediatric cardiology and cardiac surgery, over 85% of children with congenital heart disease (CHD) now survive to adulthood. Studies estimate that there are approximately one million adults with CHD in the US and that this rapidly growing adult population probably outnumbers the children with CHD (*Fig. 260.1*). Early mortality and multiple morbidities, however, continue to affect these adults as they age.

The adult with CHD brings special challenges to medical care, and managing the needs of these adults is not simply a continuation of that provided to children. The patients have the long-term sequelae of the congenital cardiac condition (native, palliated, or repaired) in addition to superimposed conditions of adulthood. Many adult cardiologists are unfamiliar with CHD and many pediatric cardiologists are unfamiliar with acquired conditions of adulthood. In addition, diagnostic testing may be more difficult as transthoracic echocardiographic (TTE) imaging can be limited with the larger body habitus of adults. Other imaging is often required such as magnetic resonance imaging (MRI), computed tomography (CT), or cardiac catheterization. There are recent guidelines for care published in Canada, Europe, and the United States to give guidance for general adult CHD management issues.

This chapter will outline the most common congenital heart conditions as they present and are managed in adulthood. As anatomy and physiology of the lesions were discussed in other chapters, this chapter will focus on complications and long-term outcomes for each CHD lesion. This chapter will also review common lifestyle issues as they relate to adults with CHD.

Atrial Septal Defects

Presentation

Atrial septal defects (ASDs) of all types may present for the first time in adulthood, either asymptomatic or symptomatic. Diagnosis of an ASD in an asymptomatic adult will most often result from findings that prompt an echocardiogram, such as a newly auscultated murmur or abnormalities seen on screening studies done for other reasons, such as a chest x-ray or ECG.

The typical presentation in adults will be related either to the effects of chronic right-sided volume load or to paradoxical embolus. The initial presentation of the right heart volume load by an ASD may range from subtle progressive exercise intolerance to atrial arrhythmias to right heart failure, though typically the presentation is one of dyspnea and palpitations. Atrial arrhythmias are typically related to right atrial and right ventricular dilation resulting from the volume load posed by the ASD. Systemic embolic events such as stroke or myocardial infarction may be the consequence of paradoxical emboli crossing from the right heart to the left through the ASD. Adults who underwent repair of a simple ASD in childhood are typically asymptomatic.

Complications

The complications of ASD are related to volume load on the right heart, and associated right heart dilation. If the right ventricular dilation is sufficient, concomitant tricuspid regurgitation may lead to additional volume load on the right heart. In some patients, there may be concomitant pulmonary hypertension. Pulmonary hypertension as a consequence of ASD is rarely severe but can complicate management if it is significant. Right heart failure is relatively uncommon as a new presentation, though in elderly adults with concomitant heart disease, the hemodynamic impact of the ASD may change sufficiently to precipitate overt heart failure symptoms.

Atrial flutter, atrial fibrillation, and sick sinus syndrome represent sequelae of right heart volume overload. The behavior of these rhythms will be typical for atrial flutter or fibrillation in adults, with rapid ventricular rates and thromboembolic complications, but the underlying substrate for the arrhythmia may be alleviated with repair of the ASD and improvement in right heart dilation.

In some patients with a sinus venosus defect or other rare ASDs such as a coronary sinus defect, hypoxia may be

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_260,

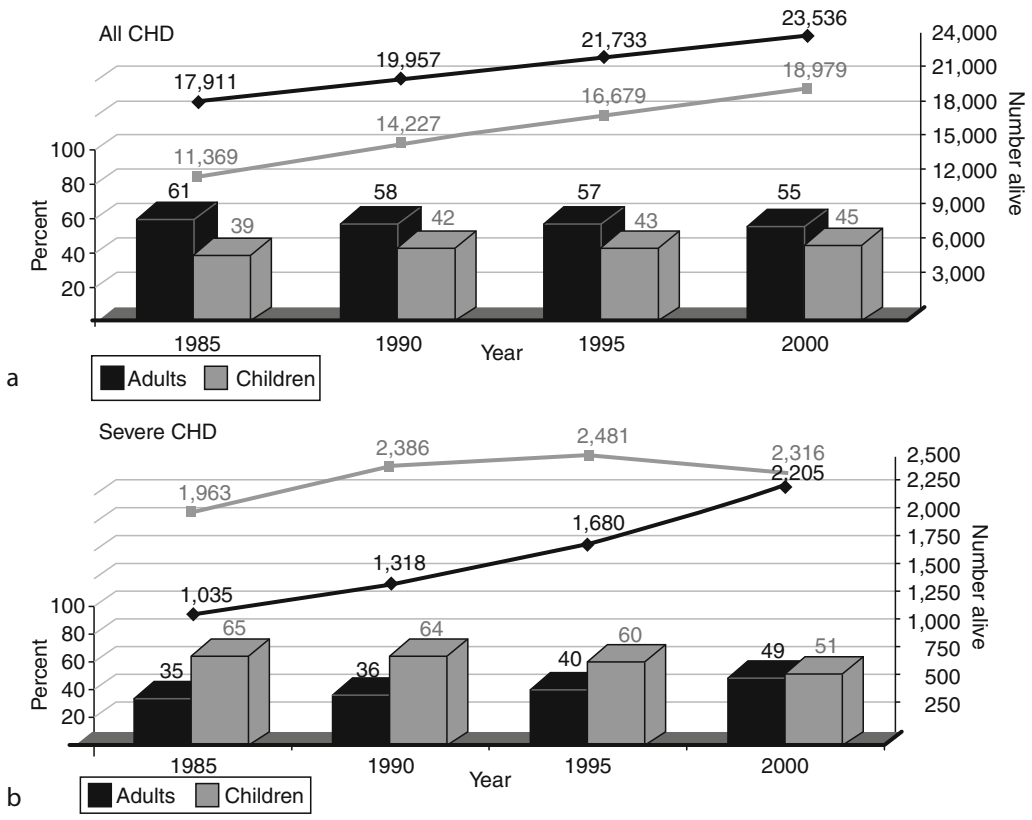


Figure 260.1
Numbers and proportion of adults and children with all CHD (a) and severe CHD (b) in 1985, 1990, and 2000 (From Marelli et al. (2007) J Am Coll Card)

a dominant part of the presentation. In patients who underwent repair of an ASD in childhood or adolescence, they are typically asymptomatic unless the right heart dilation or pulmonary hypertension did not resolve fully after repair. If repaired late, some patients may yet develop atrial arrhythmias or exercise intolerance, even though the volume load itself is alleviated.

Management

For those adults with ASD diagnosed in adulthood, if there is evidence of hemodynamic consequence of the ASD then closure should be considered. In adult patients with an enlarged right heart, a secundum ASD clearly large enough to account for right heart enlargement and no other complicating factors, percutaneous device closure in the cardiac catheterization laboratory is appropriate. However, in many cases the decision to close an ASD in an adult is often multifactorial and requires input from an ACHD center, especially if pulmonary hypertension is present.

After ASD closure, when residual conditions such as right heart enlargement, atrial arrhythmias or pulmonary hypertension persist, these patients should continue to have annual clinical follow-up.

Outcomes

In general, the outcomes for patients who underwent repair of a simple ASD in childhood are excellent. Catheter-based closure also provides excellent outcomes for those patients with secundum ASD with suitable anatomy.

The outcomes for patients with persistent pulmonary hypertension or other cardiac defects are generally determined by those abnormalities, and may not be as good as the outcomes for those patients with simple ASD. Atrial arrhythmias remain a potential concern, even after ASD closure.

Ventricular Septal Defect (VSD)

Presentation

The clinical presentation and treatment of a VSD at any age is dependent on the location and size of the defect and the pulmonary vascular resistance. In adulthood, patients with unrepaired, uncomplicated small VSDs present with a loud, harsh, blowing systolic murmur. Adults with unrepaired, large VSDs present with cyanosis, pulmonary hypertension, and complications of Eisenmenger syndrome (ES, see below). Adults with repaired VSDs should have no significant murmur and no symptoms; the only sign of prior disease is a sternotomy scar and a conduction delay on electrocardiogram (EKG). VSDs with complications present differently depending on the issue involved.

Complications

Large VSDs cause symptoms and cardiac enlargement in childhood. If there is no intervention, patients develop irreversible pulmonary vascular disease and ES. Small defects are well tolerated and patients do not show symptoms or cardiac enlargement. Moderate-sized defects may progress to develop some pulmonary vascular disease or chamber enlargement later in life and require close follow-up.

All unrepaired VSDs, and repaired defects with patch leaks, carry a risk of endocarditis; attention should be given to teeth, nail, and skin hygiene but antibiotic prophylaxis is no longer recommended by the American Heart Association except in cases of patch leaks or prior episodes of endocarditis. Adults with unrepaired small VSDs are also at risk for development of aortic valve prolapse or a double-chambered right ventricle. Either of these complications will often prompt surgical evaluation and intervention.

VSD repairs can be complicated by anatomic and arrhythmic findings. These include VSD patch leaks, sinus node dysfunction, heart block, or tachyarrhythmias.

Management

Adults with repaired or unrepaired VSDs require periodic adult CHD clinic follow-up including exam, electrocardiogram (EKG), and a TTE. Occasionally, further imaging such as MRI or transesophageal echocardiogram is needed. Surgical patients, who had repairs as children, may not have clinical impairment but do carry a risk of conduction abnormalities. A post-operative right bundle branch block is common (up to two thirds of patients), while first degree or higher grade heart block is much less common (<10%). Those with left-sided-chamber enlargement prior to repair may continue to have enlargement and possibly dysfunction depending on the age of repair and the ability of the ventricle to remodel.

Outcomes

Patients with VSDs typically have excellent long-term outcomes. According to the natural history studies, patients with small VSDs that are asymptomatic and acyanotic have very favorable outcomes and 25-year survival is ~96%. Even after surgical repair, the 25-year survival remains high at 89%. It is anticipated these patients will live long into adulthood but formal longer studies have not been performed.

Atrioventricular Septal Defect (Endocardial Cushion Defect)

This section discusses adults with complete or partial atrioventricular septal defects (AVSD) also known as atrioventricular canal or endocardial cushion defects.

Presentation

Patients born with a complete AVSD undergo repair in childhood or will present in adulthood with ES. Patients with partial AVSDs (typically primum ASD and cleft mitral valve) may present as children and have surgical repair at that time or may present unrepaired in adulthood. Patients with repairs present with normal exam findings or murmurs of post-operative defects including VSD patch leaks or residual atrioventricular (AV) valve abnormalities. Unrepaired adults may be asymptomatic and come to cardiology attention due to an abnormal EKG or chest x-ray, and/or a murmur and a wide split second heart sound, and/or symptoms including dyspnea on exertion or rapid heartbeats.

Complications

Those with a repaired AVSD or partial AVSD may have sequelae of the surgical repair. These include patch leaks in the atrial or ventricular septal patch, AV valve abnormalities, or left ventricular outflow tract (LVOT) obstruction. Residual AV valve regurgitation is the most common long-term complication and occurs in up to 18% of repairs. Surgical patients are also at risk for atrial arrhythmias and complete heart block.

Management

As adults, unrepaired partial AVSD patients are usually sent for surgical repair. Generally, repaired partial or complete AVSD patients are seen every 1–2 years for follow-up. TTE imaging and EKG surveillance are recommended at routine visits. Some patients require operations to repair or replace the AV valve (usually the left-sided one) or relieve LVOT obstruction. The valve repair surgery can be difficult and it is recommended that repeat surgery be performed by a surgeon experienced with adult CHD.

Outcomes

After repair of an AVSD, patients can expect to do well and lead active lifestyles. The complications of heart block or AV valve regurgitation requiring repeat surgery create worse outcomes for some patients. However, the outlook is improving as mortality following AV valve replacement has decreased from 30% prior to 1990 to <5% in more recent times.

Tetralogy of Fallot

Presentation

It is rare for adults to present with unrepaired or palliated tetralogy of Fallot (TOF). Reflecting the relatively early ability to perform a complete repair (VSD closure, alleviation of RVOT obstruction), TOF is the most common repaired cyanotic heart disease in adults. Adults with repaired TOF are often asymptomatic, but may present with arrhythmias, syncope, exercise intolerance, sudden death, or heart failure. As with most ACHD, arrhythmias are often markers of hemodynamic abnormalities.

Complications

The most common hemodynamically significant sequelae of TOF repair is pulmonary regurgitation. The repair of TOF often involves a transannular patch across the RVOT, resulting in significant pulmonary regurgitation. Right ventricular dilation will result, and though better tolerated than the initial RVOT obstruction and VSD, may result in significant problems in adulthood. Pulmonary regurgitation and right ventricular dilation are associated with atrial and ventricular arrhythmias, diminished exercise capacity, and heart failure. Some patients may also develop left ventricular dysfunction or aortic regurgitation. Aortic dilation may be progressive in a small subgroup of patients. Sudden death occurs in approximately 6% of patients followed for >20 years.

Management

Adults with TOF should be followed annually by an ACHD cardiologist. Echocardiography is the standard for evaluation, but MRI has evolved to be the standard for assessing RV size and function. Other modalities, such as ECG, exercise testing, ambulatory ECG, and catheterization, may have a role. Many adults with repaired TOF will require pulmonary valve replacement to alleviate the hemodynamic impact of pulmonary regurgitation. Bioprosthetic valves are used in this circumstance; these have a limited life span, hence patients may require multiple valve replacements during their life span. Therefore, decision making regarding the timing of pulmonary valve replacement is not simple. There are multiple indications for pulmonary valve replacement in adults with TOF, which are predicated on the availability of reliable imaging data (*Table 260.1*). A catheter-based option for valve replacement is available, but there is no long-term data on their durability.

Outcomes

Patients with repaired TOF may generally do well and survival is clearly superior to unrepaired tetralogy of Fallot. However, arrhythmias and heart failure may impair quality of life and may also result in significant morbidity and mortality. Current diagnosis and treatment recommendations are intending to minimize the risks associated with the residual hemodynamic lesions such as pulmonary regurgitation. The complexity of evaluation and decision making in adults with TOF is sufficiently

challenging that all adult patients with repaired TOF are recommended to be followed by ACHD cardiologists.

D-Transposition of the Great Arteries

D-Transposition of the great arteries (D-TGA) occurs when the aorta arises anteriorly and rightward from the right ventricle while the pulmonary artery arises posterior and leftward from the left ventricle. It can occur in isolation or with associated lesions such as a VSD or coarctation of the aorta. If unrepaired, it carries a mortality of up to 90% in infancy. The surgical repair of this lesion has evolved over the past 5 to 6 decades. The optimal current repair is the arterial switch procedure and is done in the first few weeks of life. The arterial switch operation began to gain acceptance in the 1980s. Prior to the arterial switch, patients underwent a surgery where atrial flow was redirected, either the Mustard or Senning procedure, so blood flow was physiologically corrected but remained anatomically abnormal. Surviving adults with D-TGA have usually undergone one of the above operations; presentation, complications, management, and follow-up are directly related to the type of surgical intervention.

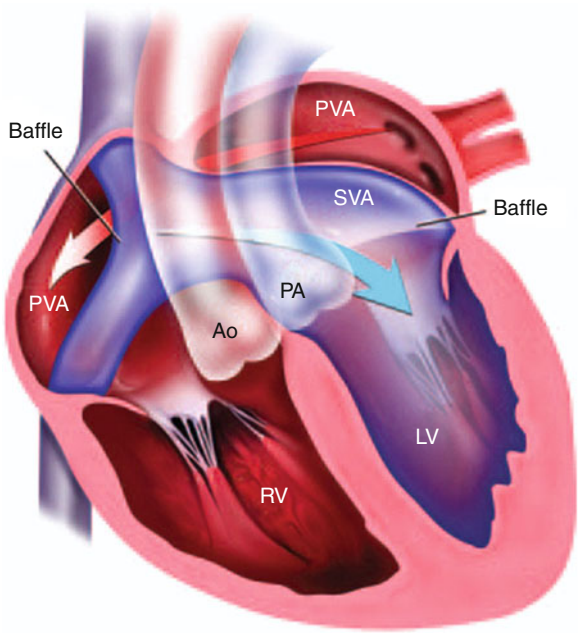
Table 260.1
Indications for pulmonary valve replacement in tetralogy of Fallot ACC/AHA Guidelines (From Warnes CA, Williams RG et al. (2008) ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation 118(23):e714–e833)

Class I
Severe pulmonary regurgitation with symptoms or decreased exercise tolerance
Class IIa
Moderate to severe RV dysfunction
Moderate to severe RV enlargement
Development of sustained and/or symptomatic atrial and/or ventricular arrhythmias
Moderate to severe tricuspid regurgitation
Residual RVOT obstruction with peak echocardiography gradient >50 mmHg
Residual RVOT obstruction with RV/LV pressure ratio gradient >0.7
Residual RVOT obstruction with progressive and/or severe dilatation of the RV
Residual VSD with left to right shunting >1.5:1
A combination of multiple lesions leading to RV enlargement or RV dysfunction

Presentation and Complications

Most arterial switch patients are asymptomatic and come to medical care as routine follow-up. Occasionally, there may be a pathologic murmur of supravalvar stenosis due to stretching of the great vessels during surgery. Rarely, patients will have anginal chest pain. There is concern of coronary artery obstruction related to the operation and there is some data to suggest patients develop early CAD due to abnormal coronary flow hemodynamics.

There is a large body of data on the adult experience of D-TGA patients that have undergone an atrial switch procedure (Mustard or Senning). In these operations, the venous flow in the atria is redirected such that systemic venous blood flows to the left ventricle and out the pulmonary artery, and pulmonary venous blood flows into the right ventricle and out the aorta (*Fig. 260.2*). Patients with this surgery are no longer cyanotic but have



Gaca, Radiology 2008

Figure 260.2
Diagram of the Mustard repair of transposition of the arteries (Gaca, Radiology 2008)

a systemic right ventricle that can eventually develop dysfunction leading to heart failure. Systemic or pulmonary venous obstruction as well as leaks in the atrial patches can develop requiring surgical or catheter-based intervention. Finally, atrial switch patients have a very high risk of both tachy- and bradyarrhythmias as well as a risk of sudden death. If a pacemaker is required, there is the additional potential complication of systemic venous baffle or superior vena cava obstruction due to the pacemaker wires.

Management

The follow-up of D-TGA patients is dictated by the type of surgical intervention. It is recommended that patients with D-TGA and atrial switch have at least annual follow-up with an adult CHD expert; those who have undergone the arterial switch operation may be seen every 2 years. Patients should have routine imaging with TTE at an adult CHD center. Saline contrast studies may be beneficial to look for baffle leaks or venous obstruction. Given the poor echocardiographic windows of adults, intermittent MRI or CT is often required to better define the anatomy. Those with an atrial switch should have exercise testing to track functional status as well as routine EKG and ambulatory ECG to screen for occult arrhythmia. Those with the arterial switch are recommended to have intermittent exercise testing to screen for ischemic changes as they enter adulthood due to the manipulation of the coronary arteries during surgery.

For some complications, medical or surgical therapy may be initiated. For the atrial switch patients, ventricular dysfunction is treated with typical heart failure therapies. If severe tricuspid regurgitation, vena cava, or baffle obstruction or a baffle leak develop, intervention may be required. Similarly, arterial switch patients may require intervention for coronary or great vessel obstructions. In either case, it is recommended that interventions occur at adult CHD centers.

Survival and Long-Term Outcomes

Given the multitude of complications and intricate management, the long-term survival of the atrial switch patients is limited. Some long-term outcome studies suggest 70% survival at 20 years but with extensive morbidity and sudden death occurring in ~5–10%. Those patients who have undergone an arterial switch operation seem to have a better outcome in early reports. The medium-term survival of those with an arterial switch reaches >85% at 15 years. There is limited long-term outcome experience in arterial switch patients as the oldest cohort is in their third decade.

Congenitally Corrected Transposition of the Great Arteries

Presentation

Congenitally corrected transposition of the great arteries (CCTGA) or L-transposition of the great arteries (L-TGA) is a very rare anomaly. It can present in multiple ways depending on anatomy and associated lesions. In this condition, flow is physiologically correct and anatomically inverted. On the right side of the heart, blood flows from the right atrium into a morphologic left ventricle and then into a posterior and rightward pulmonary artery. Similarly, on the left side, blood flows from the left atrium into a morphologic right ventricle and then to the anterior and leftward aorta. The most obvious problem is the presence of a right ventricle subject to systemic blood pressure, similar to the atrial switch patients. Associated abnormalities occur in up to 90% of patients and can include dextrocardia (~20%), VSD (up to 70%), pulmonary stenosis, malformed tricuspid valves (up to 90%), and rhythm abnormalities.

A patient's presentation in adulthood depends on any associated lesions and complications occurring with age. Patients with associated lesions will often present in childhood and require surgery. Presentation can also occur de novo in adulthood with a murmur, heart failure, or a rhythm complication. Occasionally, the adult will be asymptomatic and present to care due to an abnormal finding on EKG or chest x-ray.

Complications

The complications in adults also depend on underlying anatomy and prior interventions. Those with a failing systemic right ventricle or severe systemic AV valve regurgitation will have complications of heart failure. Patients are also at risk for arrhythmia and sudden death, and have a 2% per year risk of developing complete heart block. Those with operations in childhood may have sequelae of the surgeries in addition to the other problems.

Management

It is recommended that all patients have regular follow-up with a specialist in adult CHD and have periodic imaging

with either echocardiography or MRI. Exercise testing to assess functional status is often performed. If there is any suggestion of progressive heart block on EKG or symptoms, Holter monitoring is suggested. Any sign of complete heart block or rapidly progressive lower grade conduction disturbance is an indication for pacemaker consideration. Medical management is recommended for heart failure symptoms and occasionally patients may also require valve surgery on the systemic AV or aortic valves. Some adults may be considered for a surgical intervention called a "double switch" procedure where atrial and arterial switch procedures are performed. This is a highly complex operation, and the indications and results are still being studied; it is not recommended routinely. Any interventions in CCTGA patients should be performed by a surgeon with experience in adult CHD.

Outcomes

As with the presentation and complications, long-term outcome depends on whether or not the patient has associated lesions. The survival and morbidities are highly variable. In one cohort, initial diagnosis was not made until adulthood in two thirds of the patients, with 20% over age 60 years. In small studies of patients with childhood repairs, 20-year survival of 60–70% has been reported. By age 45 years, two thirds of patients with associated lesions and one quarter of patients without associated lesions had developed heart failure.

Single Ventricle

Presentation

Single ventricle physiology in adults may result from a wide variety of underlying anatomic abnormalities, including double inlet left ventricle and tricuspid atresia. Survival into adulthood of completely unoperated single ventricle physiology is extraordinarily rare; some form of surgical palliation is required to allow survival into adulthood. Due to the relatively recent surgical success in treating hypoplastic left heart syndrome, very few of these children have yet reached adulthood. This population will grow in coming years, but currently, their outcomes as adults remain to be seen.

The majority of single ventricle patients have been palliated with some type of Fontan repair, which directs systemic venous return directly to the pulmonary circulation, alleviating cyanosis but resulting in a very unique physiology (see Chap. 251, "The Single Ventricle"). The era of surgical intervention generally dictated the type of Fontan repair, so many adults have variations of the original repair; the intent of all of these variations is to direct right atrial blood directly to the pulmonary artery. Younger patients will more commonly have either lateral tunnel or extracardiac Fontan repairs. The presentation of the adult with single ventricle physiology varies widely. Some may be asymptomatic, though many will present with arrhythmias, thromboembolic events, protein-losing enteropathy, or heart failure symptoms. Arrhythmias are often markers of hemodynamic deterioration and are associated with increased risk of thrombus.

Liver dysfunction is an important complication of the Fontan physiology, the significance of which has only relatively recently been identified. A significant number of Fontan patients will have hepatic fibrosis or cirrhosis, with synthetic dysfunction and the other complications associated with cirrhosis such as varices.

The uniqueness of the Fontan physiology in adults warrants particular attention when non-cardiac issues arise, particularly those which may require surgical intervention. These patients should be treated in centers with experience with adult Fontan patients.

Complications

All Fontan patients may have complications including atrial arrhythmias, sinus node dysfunction, and low cardiac output symptoms. Those patients with more "modern" Fontan repairs, such as lateral tunnel and extracardiac total cavopulmonary connections seem to have fewer complications than the early era of patients who underwent "atriopulmonary" Fontan repairs. The atriopulmonary Fontan results in a massively dilated right atrium that is prone to develop thrombosis due to sluggish blood flow, atrial tachycardias due to elevated atrial pressures and atrial stretch, and sinus node dysfunction due to fibrosis. Though less frequent than the older style Fontan, lateral tunnel and extracardiac Fontans (*Fig. 260.3*) may also develop atrial tachyarrhythmias and sinus node dysfunction. Atrial arrhythmias are generally poorly tolerated and require aggressive treatment.

Thromboembolic events are distinctly detrimental and may be fatal as the Fontan physiology requires a low pulmonary vascular resistance for systemic ventricular filling and maintenance of cardiac output. Ventricular dysfunction can develop over time and may result in heart failure. The long-term impact of liver dysfunction remains

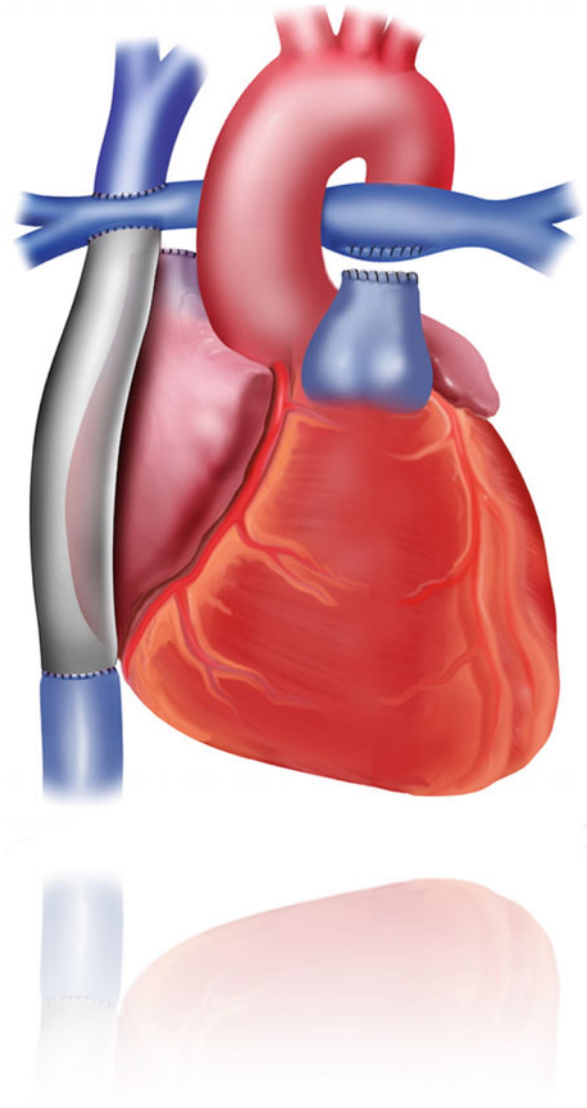


Figure 260.3
Diagram of a lateral tunnel Fontan repair with bidirectional Glenn (Gaca, Radiology 2008)

uncertain, but will likely be a significant cause of morbidity and mortality as adults with Fontan physiology age.

Management

Arrhythmias in this patient population should be managed aggressively, with efforts to ensure patients maintain sinus rhythm. Pacemaker placement may be needed for sinus node dysfunction, but the nature of the surgical repair makes this challenging from a transvenous approach in many cases, and therefore, surgically placed leads placed on the epicardial surface of the heart are often needed. Patients with atriopulmonary Fontan repairs may benefit from conversion to a lateral tunnel or extracardiac Fontan. These conversions are typically done as surgical treatment of atrial arrhythmias, with atrial reduction and intraoperative ablation a standard part of the surgery.

The role of anticoagulation in Fontan patients remains controversial, though patients with atriopulmonary Fontan repair, a history of atrial arrhythmias, known thrombus or a history of thromboembolic events should be anticoagulated.

All adult patients with single ventricle physiology should be followed regularly by ACHD cardiologists.

Outcomes

The survival of Fontan patients is over 80% at 20 years, but there is steady attrition due to heart failure, sudden death, and thromboembolic complications.

Pulmonary Stenosis

Presentation

The initial presentation of pulmonary stenosis in an adult may be identification of a murmur in an otherwise asymptomatic patient. Moderate or greater pulmonary stenosis may present with exercise intolerance. Many adult patients with pulmonary stenosis have undergone either surgical or percutaneous catheter-based balloon valvuloplasty. Those who have undergone intervention may develop pulmonary regurgitation or progressive restenosis.

Complications

If significant, pulmonary stenosis may result in right ventricular hypertrophy and increased right ventricular systolic pressures. In those patients who undergo procedures to alleviate stenosis, residual regurgitation may result in right ventricular dilation. In both cases, atrial or ventricular arrhythmias may result, or patients may have diminished exercise capacity. In patients with only mild stenosis or regurgitation however, the hemodynamic burden rarely causes any significant complications. Unlike the repair of

TOF, a transannular patch is rarely needed in these patients, but if one was used in a surgical repair, the risk of arrhythmias and right ventricular dysfunction will be higher.

Management

Patients with minimal stenosis or regurgitation can be followed expectantly, and guidelines suggest an evaluation every 2–5 years. Those with more significant lesions may require reintervention. Residual pulmonary stenosis can often be treated with balloon valvuloplasty, though those patients with significant regurgitation may require valve replacement. Arrhythmias are managed in the usual fashion, but the evaluation should ensure there is no hemodynamic abnormality that should be addressed concomitantly.

Outcomes

Adults with isolated pulmonary stenosis generally do well, with the degree of stenosis or regurgitation dictating the likelihood of complications. Those patients with minimal valve disease rarely have progressive disease and have life expectancies similar to age-adjusted norms. Those with more severe stenosis require intervention, but also should do well if the stenosis is successfully alleviated.

Aortic Valve Disease/Bicuspid Aortic Valve

Presentation

Bicuspid aortic valves, aortic stenosis, and aortic regurgitation are common in adulthood; consequently there are robust guidelines on the diagnosis and management of aortic valve disease in adults. The majority of adults with aortic valve disease are asymptomatic, but once symptomatic, valve replacement is recommended. This is true regardless of age, as the outcomes of symptomatic aortic valve disease are significantly worse than when asymptomatic. Therefore, a careful history is needed to ensure a patient is asymptomatic, focusing on exercise tolerance, angina, or syncope. Bicuspid aortic valves are often associated with aortic dilation, and in some patients, the aortic dilation may be the more concerning abnormality.

Some adults with aortic valve disease required intervention in childhood. Those interventions may range from balloon valvuloplasty to valve replacement. The Ross repair, in which the pulmonary valve is used to replace the aortic valve, and a bioprosthesis is put into the pulmonary position, is often used in children in the hope that the pulmonary valve used as the "aortic valve replacement" will grow with the child. Adults with prior aortic valve intervention may present with symptoms if there is progressive dysfunction of either the native valve or the prosthesis.

Complications

Severe aortic stenosis may cause syncope, angina, or heart failure in adult patients. In those patients with dilated aortic roots associated with a bicuspid aortic valve, dissection may occur, though the frequency is not clear. Severe aortic regurgitation may result in heart failure or arrhythmias. Mild to moderate valve dysfunction would not be expected to cause symptoms; however, these patients require regular follow-up to assess for progression of valve disease. The vast majority of patients with bicuspid aortic valves will require replacement sometime in adulthood, either due to stenosis, regurgitation or both. Those patients with dilated aortas may require surgical replacement of the dilated segment, either at the time of valve surgery or if the aorta is greater than 5.0 cm.

Management

Adults with aortic valve disease require regular follow-up, including history, exam, and imaging. The frequency of evaluation is dictated by the severity of valve disease, with those patients with severe disease requiring the most frequent follow-up. Symptomatic patients should undergo valve surgery, usually replacement. There is no role for medical therapy in aortic stenosis. The role of vasodilators in aortic regurgitation is controversial, though is reasonable if patients have LV enlargement or hypertension. There is not a clear role for medical therapy solely for aortic aneurysm in BAV, though control of hypertension is important. Patients with significant aortic valve disease should be seen regularly by cardiologists, though the disease is common enough in adults that an ACHD center is not necessarily required.

Outcomes

Outcomes after surgical repair or replacement are generally good, but dependent on left ventricular function at the time

of surgery. The outcomes of valve replacement may vary depending on the type of valve used, mechanical vs. bioprosthesis, but there is not yet clear data that one valve replacement type is clearly better than the other. Thus, while mechanical valves are typically used in young patients due to their superior longevity, the necessary anticoagulation poses its own risks, particularly if patients are poorly compliant with therapy. The outcomes of the Ross repair include a need for pulmonary valve replacement and/or aortic valve replacement in up to 25% of patients at <10 years after initial repair. The survival for young adults with mild bicuspid aortic valve disease is not different than age-adjusted norms, but the severity of aortic stenosis and regurgitation are associated with cardiac events.

Coarctation of Aorta

Coarctation of the aorta (COA) is a narrowing in the aorta that causes restriction of blood flow to more distal organs and vessels. COA can be in one location on the arch (discrete) or associated with a diffusely small arch. This section reviews discrete COA.

Presentation

The adult patient with COA typically presents as: (1) diagnosed in infancy or childhood and had a repair intervention at that time or (2) new diagnosis in adulthood. Those patients with a young age intervention may present in adulthood for follow-up or with hypertension, coronary artery disease (CAD), aneurysm at the COA site, or with a recurrent COA.

Patients with unrepaired COA presenting in adulthood usually have difficult to control hypertension and may have claudication. They also may be identified due to an abnormal chest x-ray with notching under the ribs or EKG with left ventricular hypertrophy. On exam, patients have diminished and delayed femoral pulses compared to right radial pulse and will have a blood pressure gradient between the higher pressure right upper extremity and the lower pressure leg measurement. Rarely, adults present with CAD or a stroke from a ruptured cerebral aneurysm.

Complications

Adults with unrepaired CAO may have the end-stage effects of prolonged hypertension, including left ventricular hypertrophy, heart failure, and coronary artery disease. Those with repair interventions in childhood may have complications of recurrent stenosis or aneurysm formation at the repair site. COA is also associated with other conditions including resting hypertension, exercise-induced hypertension, ascending aortic dilatation, and cerebral aneurysms.

Management

It is recommended that adults with repaired COA have routine follow-up at an adult CHD center and interventions performed by a CHD specialist. Regular imaging is important to screen for recurrent stenosis or for aneurysm formation, including TTE and CT or MRI at regular intervals (*Fig. 260.4*). Upper and lower extremity blood pressure should be checked routinely and some specialists recommend testing for exercise-induced hypertension. Some specialists also recommend screening brain imaging for cerebral aneurysms. Patients with recurrent COA or aortic aneurysm typically require intervention. For the recurrent stenosis a catheter-based approach with balloon angioplasty and stent placement is the usual procedure; otherwise surgical repair is indicated.

Treatment of native coarctation remains controversial. Surgical intervention has been the historical treatment but carries higher risks in the older patient. Catheter intervention is an appealing option as it avoids some of the surgical complications, but it is a new strategy. The largest risk of catheterization is dissection or rupture during or after the procedure. Older patients at the time of repair are more likely to have persistent hypertension and early CAD.

Outcomes

Historical studies suggest that patients with COA have an average life span into the third or fourth decade and die of cardiovascular complications. In the current era of earlier detection and repair, it is expected that outcomes improved significantly. It is hoped that earlier diagnosis and repair and screening for associated abnormalities will prolong the life span and the quality of life.

Ebstein's Anomaly

Presentation

Ebstein's anomaly in adult patients may present as either repaired or unrepaired. Unrepaired patients have varying

Figure 260.4
CT Aortagram of an adult with interposition graft repair of coarctation of the aorta performed in childhood

degrees of tricuspid regurgitation, right atrial and ventricular enlargement, and may have atrial septal defects. If the disease is mild, patients may be asymptomatic. If the disease is severe, patients may have atrial tachyarrhythimas, right-sided heart failure, or cyanosis due to right to left shunting across an atrial septal defect. Patients who have undergone valve repair or replacement are often asymptomatic.

Complications

The complications of Ebstein's anomaly in adults typically result from tricuspid regurgitation and right heart failure. Atrial arrhythmias may occur, including atrial fibrillation or atrial tachycardia related to bypass tracts, such as Wolff–Parkinson–White. Cyanosis is uncommon, and may be provoked with exercise. The cyanosis is due to right to left shunting across an ASD or PFO, and may be related to the jet of tricuspid regurgitant directed at the ASD, rather than due to markedly elevated right atrial pressures.

Management

Adults with unrepaired Ebstein's anomaly may require repair if symptoms develop or if cyanosis is present. Thus, those patients with unrepaired Ebstein's should be followed regularly. Arrhythmias should be treated aggressively, as those patients with significant disease may not tolerate atrial tachycardia well. Those who have undergone repair or replacement will need continued monitoring to ensure valve dysfunction does not develop.

Outcomes

The outcome for unrepaired patients is not well known, but is dependent on the severity of disease. Patients with mild disease will likely do well, while those with more severe disease, right to left shunting or atrial arrhythmias are at higher risk of adverse outcomes. Series evaluating patients who have undergone repair or replacement suggest good outcomes at over 20 years, though arrhythmias remain a concern before and after surgery.

Eisenmenger Syndrome (ES)

Presentation

Adults with ES have a history of a large left to right shunt that went unrepaired in infancy and childhood and led to the development of irreversible pulmonary vascular disease (PVD). The PVD leads to equalization of pulmonary and systemic vascular resistances and to a reversal of the shunt creating systemic cyanosis. Fortunately, patients with this condition are becoming more uncommon with improved diagnostic and therapeutic interventions in childhood; however, many patients still require care. Patients with Eisenmenger physiology commonly present with dyspnea on exertion, palpitations, edema, hemoptysis, syncope, and progressive cyanosis. Many patients begin to develop symptoms toward the third decade of

life and worsen with age. As patients age, they may present with complications of other organ systems related to persistent cyanosis as described below.

Complications

ES can be complicated by right ventricular failure, arrhythmias, hemoptysis, and sudden death. The physiologic changes and cyanosis lead to multiorgan system complications. A secondary erythrocytosis can cause intravascular sludging and organ damage particularly in the cerebrovascular circulation. Renal dysfunction, bone pain, and hyperuricemia can occur.

Management

All patients with ES should be followed by adult CHD physicians. The primary goal of management is to prolong survival, while at the same time improving quality of life as there is no primary surgical correction. For some patients, surgical intervention may include either heart–lung transplant or lung transplant with cardiac repair. However, these are complicated and difficult decisions and must be made independently with the patient and the adult CHD specialist.

Much of the management surrounds lifestyle adjustments to avoid complications. Due to the erythrocytosis, it is highly important to avoid iron deficiency and to maintain adequate hydration. Patients are also asked to avoid strenuous exercise, high-altitude exposure, and pregnancy. At least annual follow-up is recommended and should include digital oximetry and blood tests for hemoglobin, platelets, iron stores, renal function, and uric acid. Any new medications must be evaluated quite closely as any changes in pulmonary and systemic vascular resistance can affect functional status. In general, therapeutic phlebotomy has a very limited role and should only be performed in patients with hemoglobin greater than 20 g/dl and associated symptoms of hyperviscosity and no evidence of dehydration.

Medical therapies for ES patients are limited. Some may benefit from oxygen therapy. Those with ventricular dysfunction may be treated with digoxin or diuretics. Anticoagulation for ES is controversial as there is the risk of hemoptysis and there are in vitro reports of underlying coagulation and platelet abnormalities. Recent studies have shown a beneficial effect of pulmonary vasodilator therapy in patients with ES. These medications were shown to improve exercise intolerance, oxygen saturation, functional capacity and, in some cases, survival.

Outcomes

While survival of ES patients is better than those with primary pulmonary hypertension, outcomes remain poor and morbidity is high. While poor functional class is a predictor of mortality, many patients will survive into their 30s and older. Heart–lung transplantation and lung transplant with cardiac repair are options for some patients. However, as natural survival prospects are improving and better therapeutic options are being developed for pulmonary hypertension, patients considered for these treatments must be carefully selected.

Lifestyle Issues

Adults with congenital heart disease face the same issues as their peers without congenital heart disease. They may be obese, may have poor diets, and may develop typical adult diseases, including acquired heart disease. As with any other patient, it is important to provide counseling regarding maintaining or achieving a normal body weight, eating a heart healthy diet, controlling risk factors for diabetes and acquired heart disease, and regular physical activity. However, many adults with CHD were advised against exercise as children or have exercise limitations due to their heart disease, and thus counseling regarding exercise habits for these patients can be a challenge. In general, moderate aerobic activity is appropriate. Weight lifting may not be appropriate for some patients, or may need to be modified to a "low weight, high repetition" type of exercise; however, all exercise recommendations must be tailored to the individual patient based upon their disease and the severity of disease. There are guidelines available that are lesion specific and that address competitive sports (see Bibliography).

Reproductive health is a common concern among adults with CHD; however, there is data demonstrating that communication between patients and providers regarding family planning is relatively poor. Many women have misinformation regarding their ability to have children, and many may be misinformed regarding contraceptive options. Both contraception and pregnancy can pose unique challenges, and recommendations must again be tailored to the individual patient. There are some patients for whom estrogen-containing birth control is risky and there are some patients for whom pregnancy would be ill advised (*Table 260.2*). Despite those concerns, many women with CHD can successfully carry a pregnancy to term, provided they are evaluated and managed by appropriately trained providers.

Table 260.2
Predictors of adverse maternal events during pregnancy

Cardiac events prior to pregnancy
CHF
Arrhythmia
Poor functional status
NYHA Class II or IV
Cyanosis
Left heart obstruction
Symptomatic or severe mitral stenosis
Severe aortic stenosis
Systemic ventricular dysfunction
EF $<$ 40%
Pulmonary hypertension
Eisenmenger syndrome
Systolic pulmonary pressures $>$50% of systemic pressures
Marfan syndrome with aortic root $>$4.0 cm
Severe symptomatic aortic or mitral regurgitation
NYHA Class III or IV

Contraception recommendations must balance the woman's risk of complications of pregnancy and the risk of the contraceptive method. Estrogen-containing contraception, such as the commonly prescribed oral contraceptive pills, is associated with an increased risk of arterial and venous thrombosis. For women with heart disease that may predispose them to thrombus (mechanical valves or Fontan circulation), the addition of estrogen increases that risk further. Progesterone-only alternatives, such as the mini-pill or DepoProvera, are not thrombogenic, but may be less an effective contraceptive and in the case of DepoProvera, may be associated with bone density loss after long-term use. Intrauterine devices, including the Mirena IUD, which contain levoprogestrone, may be options, but the risk of insertion and endocarditis must be considered. Sterilization is rarely recommended, as the women who are at highest risk of pregnancy are also at highest risk of a surgical procedure, in particular those women with ES. Ultimately, the recommendation of the type of contraception must be individualized to the patient and her heart disease, risk of pregnancy, lifestyle and her desires regarding type of contraception.

There is no data to guide recommendations regarding alcohol use in adults with CHD. While there may be benefit in other acquired heart disease to moderate alcohol use, this has not been studied in CHD. Adults with CHD should not smoke, use tobacco products or recreational drugs.

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261 Cardiomyopathies and Heart Transplantation

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Cardiomyopathies

Definition

Cardiomyopathy refers to a heterogeneous group of diseases which primarily involve the myocardium, leading to symptoms of heart failure. They are most commonly divided into three major phenotypes, based on anatomy, physiology, and symptoms. *Dilated* cardiomyopathy primarily affects the systolic function, while *hypertrophic* cardiomyopathy and *restrictive* cardiomyopathy mostly affect the diastolic function of the heart. Although all three have different characteristics, overlap between these phenotypes does occur. Left ventricular non-compaction was recently recognized as a separate cardiomyopathy with mixed features of dilated and restrictive cardiomyopathy, affecting both systolic and diastolic function.

Dilated Cardiomyopathy

Etiology

Dilated cardiomyopathy accounts for approximately 55% of all cases of cardiomyopathy in children. It is characterized by a dilated left ventricle with decreased systolic function. Most cases of primary cardiomyopathy are idiopathic, although 30–50% of patients have a family history of dilated cardiomyopathy, suggesting a genetic component. Gene mutations that have been identified in primary cardiomyopathy encode regulatory or contractile proteins within the myocyte. Primary cardiomyopathies are sometimes (9%) found in association with neuromuscular disorders, such as Duchenne or Becker's muscular dystrophy, because cardiac and skeletal muscles share many of the same contractile and cytoskeletal proteins.

Damage to the heart muscle can also occur secondary to other disease processes, of which viral myocarditis is the most common. Many viruses can cause *myocarditis*, but the majority of cases are caused by enterovirus, adenovirus, or parvovirus. Viral proteases can cleave the cytoskeletal protein dystrophin, leading to irreversible cardiac injury and dilated cardiomyopathy. An excessive inflammatory response contributes to the myocardial injury. Although the majority (60%) of patients make a full recovery, depressed ventricular function and/or dilated cardiomyopathy is seen in the rest. Freedom from death or transplantation 5 years after experiencing myocarditis is approximately 74%.

In the developing world, *HIV* is the leading infectious cause for dilated cardiomyopathy. Of HIV-infected children, 8–15% develop dilated cardiomyopathy related to direct viral damage, drug toxicity, or nutritional deficiencies.

Nutritional deficiencies can cause dilated cardiomyopathy as well (carnitine, thiamine, selenium, phosphate) and *inborn errors of metabolism* account for approximately 4% of all dilated cardiomyopathies in the USA.

Chemotherapy, especially anthracyclines, is an important cause of childhood dilated cardiomyopathy in the developed world, which can develop long after chemotherapy is completed. Anthracyclines are successfully used to treat many types of childhood cancers, but have a high degree of cardiotoxicity, especially in dosages above 550 mg/m^2. Six years after anthracycline treatment, abnormal left ventricular structure or function is found in almost 65% of childhood acute lymphoblastic leukemia survivors.

A relatively rare but correctable cause for dilated cardiomyopathy in early infancy is *anomalous origin of the left coronary artery from the pulmonary artery* ("ALCAPA"). The left coronary artery originates from the pulmonary artery rather than the aorta. Once the pulmonary vascular resistance falls, around 1–3 months of age, the decrease in pulmonary artery pressure results in a fall in coronary perfusion pressure and reversal of direction of coronary flow leading to myocardial ischemia.

Lastly, incessant or sustained primary *tachyarrhythmias* of the heart can present as heart failure with ventricular dysfunction caused by decreasing diastolic filling time, lack of atrioventricular synchrony, and excessive demand of the myocardium.

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Epidemiology

The annual incidence of dilated cardiomyopathy in all children in the USA is 0.57 per 100,000, tenfold lower than in the adult population. These pediatric incidence rates are similar to rates found in Finland and Australia.

In children, most cases occur in infants less than a year of age (4.4 cases per 100,000/year). There is a predilection for boys versus girls, due to X-linked inheritance patterns (0.66 vs 0.47 cases per 100,000/year) and blacks versus whites (0.98 vs 0.46 cases per 100,000/year).

Pathogenesis

Myocytes do not divide, or at best very slowly. Myocardial injury may lead to compensatory hypertrophy of surrounding myocytes. A myocyte is composed of myofibrils, which in turn are built out of sarcomeres. A sarcomere is the contractile unit of the cell and consists of overlapping contractile proteins (actin, myosin, troponin, tropomyosin) which interact with the cytoskeletal proteins (dystrophin, tafazzin, desmin). Sarcomere contraction requires interaction between contractile and cytoskeletal proteins. Myocyte damage results in less contractile force generation and thus decreased stroke volume and cardiac output.

In the failing heart, compensatory responses try to maintain cardiac output. The two most important are:

1. Frank–Starling mechanism, in which elevated diastolic volume increases the stretch on the myofibers, which in turn increases the stroke volume.
2. Neurohormonal activation through the sympathetic nervous system, renin-angiotensin-aldosterone system, and antidiuretic hormone (ADH), all of which help to maintain blood pressure and cardiac output by increasing heart rate, vasoconstriction, and water and sodium retention. Unfortunately, over time, the continual activation of the neurohormonal axis has detrimental effects on the myocardium, so-called "remodeling."

As the compensatory mechanisms start to fail, the stroke volume decreases, the left ventricle enlarges, and the patient with heart failure decompensates. Left ventricular dilation with decreased contractile function is the hallmark of dilated cardiomyopathy, and it often involves both ventricles. The increase in ventricular end-diastolic pressure and volume ultimately leads to dilation of the atria as well. Further enlargement of the ventricle may cause the mitral and tricuspid valve leaflets to not coapt well, with ensuing valvular regurgitation. The valvular regurgitation further compromises cardiac output and leads to progressive dilation of atria and ventricles.

Pathology

Dilated cardiomyopathy is generally characterized by dilation of all four heart chambers. Microscopically, one can find areas of myocyte degeneration, hypertrophy, and fibrosis.

Clinical Symptoms and Signs

Clinical presentation can vary widely, depending on the age of the child and the degree of heart failure. Patients can be asymptomatic or display one or more symptoms of heart failure. The onset of symptoms can be quite insidious as the heart is initially able to compensate for the decreased cardiac output. Tachycardia is one of the earliest symptoms and occurs when the heart is trying to compensate for the decrease in stroke volume. When heart failure progresses, the heart is unable to meet the metabolic demands of the body and additional symptoms develop. The nature of these symptoms varies strongly with age. Infants frequently present with feeding intolerance and failure to thrive since feeding and growing encompass the majority of their metabolic demand. They may appear too tired to complete a full feed and take frequent small feeds instead, rendering them hungry and irritable. Additional symptoms include tachypnea and increased work of breathing, pallor due to vasoconstriction, and increased sweating due to sympathetic stimulation.

Older kids often present with exercise intolerance consisting of easy fatigue and dyspnea with exertion. More severe heart failure can produce dyspnea in the supine position (orthopnea) or even at rest, as a result of pulmonary venous congestion. Additional symptoms of increased venous pressure include peripheral edema and hepatomegaly. Insufficient cardiac output with forward failure causes abdominal pain, nausea and vomiting due to inadequate mesenteric perfusion. Other symptoms can include palpitations and syncope.

Heart failure symptoms can be graded by the Ross classification (*Table 261.1*), which is similar to the New York Heart Association (NYHA) classification used in adults. A newer classification (*Table 261.2*) classifies patients according to their stage in heart failure.

Table 261.1
Ross classification of heart failure in children

Class	Interpretation
I	Asymptomatic
II	Mild tachypnea or diaphoresis with feeding in infants
	Dyspnea on exertion in older children
III	Marked tachypnea or diaphoresis with feeding in infants; prolonged feeding times with growth failure due to heart failure
	Marked dyspnea on exertion in older children
IV	Symptoms such as tachypnea, retractions, grunting, or diaphoresis at rest

Table 261.2
Heart failure staging in pediatric heart disease

Stage	Interpretation
A	Patients at risk for developing heart failure, who have normal cardiac function
B	Asymptomatic patients with abnormal cardiac structure or function
C	Past or present symptoms of heart failure in patients with abnormal cardiac structure or function
D	End-stage heart failure requiring continuous infusion of inotropic agents or mechanical circulatory or ventilatory support

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Physical examination may reveal tachycardia, increased work of breathing, and weak pulses. Pulmonary crackles can be heard upon auscultation and indicate pulmonary edema. Cardiac auscultation may reveal a gallop rhythm (S3 and/or S4) and occasionally a holosystolic murmur, caused by mitral or tricuspid regurgitation. Venous congestion causes hepatomegaly in all age groups and jugular venous distention in older children. Dependent lower extremity edema is mostly seen in older children, while infants may display facial edema. Special attention should be paid to the existence of symptoms that could provide a clue to the underlying cause of the cardiomyopathy, such as hypotonia, metabolic abnormalities, or dysmorphic features.

Diagnosis

Chest X-Ray

Chest X-ray typically shows cardiomegaly (cardiothoracic ratio >0.5) and features of pulmonary venous congestion. Pleural effusions may be present as well.

ECG

ECG usually reveals sinus tachycardia with nonspecific ST segment and T wave changes, as well as hypertrophy in the left precordial and inferior leads. Occasionally, the ECG provides specific clues toward the etiology of the disease such as Q waves in I, AVL, and V4-6 in ALCAPA. Since long-standing tachyarrhythmias can be associated with ventricular dysfunction, rhythm and P-wave morphology should be carefully assessed.

Echocardiography

The diagnosis of dilated cardiomyopathy is usually established by echocardiography. Characteristic findings include dilated ventricles with globally decreased function. Sometimes mitral valve regurgitation is noted, secondary to left ventricular dilation and/or papillary muscle dysfunction. Echocardiography is used to assess the degree of dysfunction as well as exclude correctable causes of ventricular dysfunction. The coronary arteries should be interrogated with color flow to assess for ALCAPA. Left ventricular outflow tract and aortic arch should be carefully interrogated since left ventricular outflow obstruction in the newborn, such as coarctation, can masquerade as cardiomyopathy. The severity of ventricular dysfunction can be quantified and followed longitudinally by measuring the ejection fraction, fractional shortening, and left ventricular end-diastolic diameter. Atrioventricular inflow patterns and estimates of right ventricular pressure by Doppler exam of tricuspid regurgitation provide information about diastolic dysfunction. Finally, the intraventricular cavity should be carefully evaluated for the presence of thrombi.

Cardiac Catheterization

Cardiac catheterization can provide useful information regarding the hemodynamics and guide therapy, but is not typically used as a diagnostic modality. However, endomyocardial biopsy may be helpful when myocarditis

is being considered. However, findings can be nonspecific, and sensitivity is limited to approximately 50%. In addition, the risk of perforating the ventricular wall is real, especially in infants. If endomyocardial biopsies are obtained, polymerase chain reaction (PCR) can be performed to look for viral nucleic acid from the common viruses that cause myocarditis such as enterovirus, adenovirus, parvovirus B19, human herpes virus 6, and, if clinically indicated, cytomegalovirus, EBV, HSV, HIV, influenza, and RSV.

Holter Monitor

Patients with severely depressed left ventricular function are at increased risk for developing tachyarrhythmias. They can be easily compromised due to lack of cardiac reserve. Annual Holter recordings help identify subclinical tachyarrhythmias.

Metabolic Evaluation

A large number of metabolic conditions can result in cardiomyopathy. It is therefore prudent to consider metabolic screening tests, especially in infants, when the diagnosis of dilated cardiomyopathy is entertained, including plasma acylcarnitine profile, lactate/pyruvate ratio, serum amino acids, urinary organic acids. Creatinine kinase is useful in identifying skeletal myopathy. If a mitochondrial disease is suspected from the screening labs, a skeletal muscle biopsy may be indicated to confirm the diagnosis.

Viral Studies

Viral studies should be obtained if myocarditis is suspected, including serologies, nasal wash, and blood PCRs for the viruses mentioned above.

BNP

Brain-natriuretric protein (BNP) levels are often elevated and can be useful for diagnosis and evaluation of treatment response.

Genetic Testing

Thus far, approximately 25 mutations have been identified in relation to dilated cardiomyopathy, mostly involving regulatory, cytoskeletal, or contractile proteins. Genetic screening in patients with clinical symptoms of dilated cardiomyopathy is costly, and mutations are found in only a quarter of patients. Screening of first-degree relatives for mutations is most effective once a specific mutation is identified in the index patient.

Differential Diagnosis

Other underlying causes for heart failure should be excluded, including congenital heart disease (especially coarctation or other left-sided obstructive lesions), ALCAPA, myocarditis, Kawasaki disease, and arrhythmias.

Treatment

Treatment of dilated cardiomyopathy in children consists of supportive therapies for congestive heart failure, prevention of complications, as well as etiology specific treatment.

Supportive Treatment

Acute Stage

Supportive treatment in the acute decompensated stage of the disease might consist of intravenous inotropic support as well as mechanical ventilation to reduce the workload on the heart. Agents most commonly used for inotropic support are the ß adrenergic agonists dobutamine or dopamine, often in combination with the phosphodiesterase inhibitor milrinone, which possesses inotropic as well as afterload reducing and ventricular relaxation effects. Intravenous loop diuretics are often added in the acute phase, especially if there is evidence of pulmonary or systemic venous congestion.

Chronic Phase

The ultimate goal of chronic treatment is alleviation of symptoms, prevention of cardiac remodeling, and improvement of cardiac function.

Fluid/Feeding Regimen

The benefits of fluid restriction in heart failure are widely accepted. On the other hand, adequate calorie intake should be a high priority in patients with congestive heart failure since the metabolic demands are higher and patients often struggle to feed. To avoid malnutrition, many patients receive high-calorie additives or supplemental enteral feeds.

Diuretics

Diuretic therapy reduces symptoms of systemic and pulmonary congestion by reducing the venous return to the heart. Loop diuretics in combination with aldosterone antagonists to compensate for potassium loss are widely used. In addition, studies show a mortality reduction in patients with severe heart failure treated with aldosterone antagonists, possibly explained by blockage of fibroblast proliferation in the myocardium.

Angiotensin-Converting Enzyme Inhibitors (ACEi) and Angiotensin Receptor Blockers (ARB)

As indicated earlier, neurohormonal compensatory responses in heart failure often lead to excessive vasoconstriction, volume retention, and cardiac remodeling. These effects can be partly reversed by angiotensin-converting enzyme inhibitors (ACEi), whose beneficial effects include vasodilation (afterload reduction) as well as volume excretion. Multiple studies have shown that ACEi extend survival in pediatric and adult patients with heart failure. Angiotensin receptor blockers (ARB) can be used in patients who do not tolerate ACEi, but its efficacy in children with heart failure has yet to be proven.

Beta Blockers

Beta blockers have become one of the mainstays of therapy in adults with heart failure, after large clinical trials in the 1990s showed improved survival with the use of carvedilol and metoprolol in adults with mild or moderate heart failure. Beta blockers ameliorate the damaging effects that chronic sympathetic stimulation has on the heart and thus improve cardiac remodeling. They are best tolerated in stable patients as they can cause a temporary worsening due to their negative inotropic effects. They should be started at low doses and gradually increased. Carvedilol is widely used in children with mild or moderate heart failure. Unfortunately, a recent randomized controlled clinical trial in children studying the effects of carvedilol was inconclusive, hampered by insufficient study power and the relatively high rate of spontaneous improvement in young children with dilated cardiomyopathy.

Digoxin

Digoxin improves cardiac contractility and reduces sympathetic tone. It can improve symptoms in heart failure, but there is no evidence that it improves survival.

Cardiac Resynchronization Therapy

Biventricular pacing or cardiac resynchronization therapy (CRT) may improve the synchrony between right and left ventricular contraction, which is often disturbed in patients with cardiomyopathy due to ventricular dilation and accompanying bundle branch block. A biventricular pacemaker can be programmed to stimulate both ventricles and can resynchronize the ventricular-ventricular interaction, resulting in a more coordinated contraction. Benefits are proven in adult patients with at least moderate heart failure and evidence of ventricular dyssynchrony. Early studies in children with heart failure and evidence of dyssynchrony suggest improvement of measured ejection fraction and functional status, with the best effect seen in children with heart failure due to congenital heart disease, rather than DCM.

Treatment of Complications

Any tachyarrhythmias should be aggressively treated with antiarrhythmic medications.

Anticoagulation with warfarin, heparin, or low molecular-weight heparin is indicated when there is evidence of intracardiac thrombus formation. Some centers use anticoagulation as primary prevention if the left ventricular function is severely impaired.

Ventricular Assist Devices

Multiple ventricular assist devices (VADs) are currently in development, and few models are used in the pediatric population. The Berlin heart and Thoratec VAD have been used as a bridge to heart transplant in children. Newer VADs are being developed that are smaller in size and therefore more tailored for permanent implantation.

Heart Transplantation

If all other therapies fail, heart transplantation can be performed. This is discussed separately in this chapter.

Etiology Specific Treatment

All patients with ventricular dysfunction should be carefully evaluated for treatable causes. Patients with *ALCAPA* usually recover ventricular function after reimplantation of the coronary artery. Immunomodulation with intravenous immune globulin (IVIG) and/or prednisone is commonly used to treat *myocarditis*. Results from an early study suggested an improvement in left ventricular function, but not survival, in children with myocarditis who received IVIG. However, a more recent randomized, prospective trial in adults with recent onset cardiomyopathy or myocarditis did not elicit any benefit from IVIG. Immunosuppression with prednisone is controversial as

well, with studies showing conflicting results. Despite the conflicting evidence, most pediatric cardiologists administer IVIG and/or prednisone when the diagnosis of myocarditis is suspected. Studies in mice have suggested increased viral replication and mortality if immunosuppressive therapy with prednisone is given early in the disease process. It is therefore prudent to administer prednisone only once the acute viral phase has subsided. *Nutritional deficits* should be supplemented, and specific therapy might be indicated for metabolic disorders. Some centers add a vitamin cocktail (riboflavin, carnitine, coenzym Q10, and thiamine) to the therapy if a mitochondrial disorder is suspected.

Future Directions

Gene Therapy

Success has been achieved with gene therapy in animal models, but finding an efficient delivery system (vector) remains a challenge and clinical gene therapy is likely still far away.

Tissue Engineering

Although promising, transplantation of isolated cells (e.g., embryonic stem cells, fetal cardiac cells) is still hampered by lack of sufficient engraftment in the heart.

Prognosis

The Pediatric Cardiomyopathy Registry showed a 5 year freedom from death or transplantation of 55% for all children with dilated cardiomyopathy. However, the outcomes for children with dilated cardiomyopathy depend on age at presentation and the underlying cause for dilated cardiomyopathy. Patients with idiopathic dilated cardiomyopathy or an underlying neuromuscular disorder have the worst long-term prognosis, while patients with a malformation syndrome or metabolic disease have the most favorable long-term outlook (◉ *Fig. 261.1*). Younger patients have a higher likelihood of recovery, while children >6 year are more likely to die or receive a heart transplant.

Prevention

Echocardiographic screening of first-degree relatives is indicated. Screening via mutation analysis in first-degree relatives is possible if a specific mutation is identified in a family member with dilated cardiomyopathy.

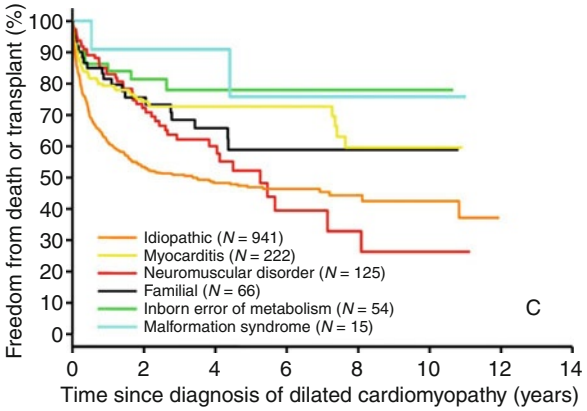

Figure 261.1
Freedom from death or transplantation for children with dilated cardiomyopathy (Reprinted from Wilkinson JD, Sleeper LA, Alvarez JA et al (2008) The Pediatric Cardiomyopathy Registry 1995–2007. Prog Pediatr Cardiol 25(1):31–36. With permission from Elsevier)

Restrictive Cardiomyopathy

Etiology

Restrictive cardiomyopathy (RCM) is a rare disease in which the diastolic function of the heart is affected, while the systolic function is often preserved. It accounts for only about 2.5–5% of all cardiomyopathies in children. A wide array of myocardial diseases can lead to restrictive cardiomyopathy, including many metabolic storage diseases and amyloidosis in adults. However, in the pediatric population, it is most commonly idiopathic, outside of the tropics. Family history is positive in approximately 30% of patients with idiopathic RCM, which alludes to a genetic predisposition. In the tropics, endomyocardial fibrosis is the most common form of RCM. Its geographical distribution suggests a relation to parasitic infections.

Pathogenesis

Increased stiffness and impaired relaxation of the ventricular wall lead to significant diastolic dysfunction. This ventricular noncompliance causes disproportionate increases in ventricular pressure as a result of relatively small changes in ventricular volume. Eventually, both atria become grossly enlarged, and pulmonary hypertension develops due to chronic left atrial hypertension and pulmonary venous congestion. With time, pulmonary vascular remodeling can create irreversible pulmonary hypertension.

Clinical Symptoms and Signs

Children with RCM often present with respiratory symptoms due to the development of pulmonary edema. The median age of presentation is 3–4 years. Not infrequently, a child has been treated for asthma or recurrent respiratory tract infections before the diagnosis of RCM is established. A child may also present with exercise intolerance or syncope. On physical exam, a gallop rhythm can be heard. If the pulmonary artery pressure is elevated, the second heart tone may be loud. Signs of congestive heart failure that can occur with RCM are jugular venous distention, pulmonary rales, hepatomegaly and, occasionally, peripheral edema.

Diagnosis

Cardiomegaly with pulmonary venous congestion on chest X-ray can be the first indicator of RCM in a child with respiratory symptoms. A 12-lead ECG often shows biatrial enlargement, as well as nonspecific ST- and T-wave abnormalities. The diagnosis is established by echocardiogram which classically shows an "ice cream cone appearance" created by grossly enlarged atria resting on top of relatively small ventricles. Echo Doppler indicators demonstrate diastolic dysfunction The systolic function is normal in most patients with RCM. Once the diagnosis is established by echo, cardiac catheterization can be performed to assess atrial and left ventricular end-diastolic pressures ("filling pressures"), as well as pulmonary artery pressures and pulmonary vascular resistance. If a differential diagnosis of constrictive pericarditis is entertained, catheterization may be useful in differentiating between constrictive or restrictive physiology. Filling pressures in constrictive pericarditis are equal in all four heart chambers, whereas the left-sided filling pressures in RCM are consistently 5–10 mmHg higher than the right-sided filling pressures.

Genetic testing may reveal some of the same sarcomeric protein mutations found in patients with hypertrophic or dilated cardiomyopathy. A recent study found a 30% prevalence of sarcomeric mutations in children with RCM.

Differential Diagnosis

Other causes of restrictive cardiomyopathy should be considered, including metabolic storage diseases, infections, or drug therapy. In the adult population, amyloidosis is the leading cause of RCM. It is often quite difficult to distinguish RCM from constrictive pericarditis, although the prognosis and treatment of the two diseases are very different. Constrictive pericarditis is often secondary to connective tissue disease or an infection (most commonly tuberculosis in the developing world), and the majority of these patients recover completely, often after a surgical pericardiectomy.

Treatment

Gentle diuretic therapy is indicated if there is evidence of pulmonary venous congestion. The stiff ventricle requires high filling pressures to preserve cardiac output and, therefore, overdiuresis should be avoided. There is no proven benefit of beta blockers or ACE inhibitors in RCM. Because of the dismal prognosis and lack of effective treatment strategies, heart transplantation is considered early in the disease process before irreversible pulmonary vascular disease develops.

Prognosis

The prognosis in children with idiopathic or familial RCM is thought to be poor. Multiple small series have shown a mortality rate of approximately 30–50% at 2 years with early death caused by progressive heart failure or tachyarrhythmias. However, it remains challenging to predict the prognosis in an individual patient since the occasional patient will survive up to 10 years without transplantation, and prognostic studies are hampered by small patient cohorts due to the rarity of the disease. Left atrial size and elevated pulmonary vascular resistance appear to be predictive of mortality, and an increase in pulmonary vascular resistance should prompt early evaluation for heart transplant since progression to irreversible pulmonary hypertension may preclude successful heart transplantation.

Hypertrophic Cardiomyopathy

Etiology

Hypertrophic cardiomyopathy (HCM) accounts for approximately one third of all cardiomyopathies. It is characterized by excessive hypertrophy of the left or both ventricles in the absence of an external stimulus for cardiac hypertrophy such as hypertension or an infiltrative process from metabolic

disease. Systolic function is often normal, but can be decreased especially in the later stages of the disease. In contrast, diastolic function is often abnormal, due to increased stiffness or abnormal relaxation of the ventricle. Primary HCM is largely a genetic disease. Many gene mutations have been identified, all involving the sarcomeric proteins, including β-myosin, myosin binding protein, troponin T, and α-tropomyosin. We do not yet have the ability to accurately predict the mutation from the hypertrophic phenotype. Furthermore, penetrance is widely variable. Thus, the presentation and phenotype can show remarkable variation, even within the same family. The inheritance pattern is autosomal dominant, but about half of all cases are the result of de novo mutations.

Epidemiology

HCM has an annual incidence of 4 per 1,000,000 in children, increasing to 1:500 in young adults. Similar rates of detection have been found among the adult population of the USA, Japan, and China. The disease has received much press as the number one cause of sudden cardiac death in young athletes.

Pathogenesis

Excessive hypertrophy of part of, or the whole ventricle is the hallmark of the disease, resulting in decreased compliance and relaxation of the affected ventricle. Although more common in the left ventricle, the right ventricle can also be affected in young children. Impaired diastolic function leads to increased filling pressures of the left ventricle, which in turn leads to increased pulmonary venous pressures with pulmonary venous congestion, resulting in dyspnea. In addition, disproportionate hypertrophy of the proximal (subaortic) interventricular septum can lead to left ventricular outflow tract obstruction (LVOTO) during systole. Turbulent flow across the outflow tract creates a suction effect, called the Venturi effect, on the mitral valve leaflet, causing abnormal systolic anterior motion of this leaflet in the direction of the protruding thickened septum, leading to further increase in obstruction and possibly promoting more ventricular hypertrophy.

Pathology

The hypertrophy can involve any part of the ventricle. The distribution can be quite diverse, especially in children, ranging from asymmetric hypertrophy of the septum (most common), to concentric hypertrophy, to localized apical involvement. Microscopically, the myocytes are hypertrophied and myocardial fibers are in a pattern of disarray with increased fibrosis.

Clinical Symptoms and Signs

Many patients with HCM are asymptomatic and are diagnosed during family screening. Symptoms are variable and not necessarily related to the severity of hypertrophy and outflow tract obstruction. Patients most commonly present with dyspnea and exercise intolerance due to diastolic dysfunction with pulmonary venous congestion. Infants most commonly present with increased work of breathing and feeding problems. Patients may experience chest pain, especially in the setting of left ventricular outflow tract obstruction, when the elevated ventricular systolic pressure increases ventricular wall stress and myocardial oxygen consumption. In addition, the coronary arteries may be narrowed, and there is often a significant mismatch between coronary flow and increased left ventricular mass, further contributing to myocardial ischemia. The chest pain can appear atypical in nature, occurring at rest as well as during exercise. Ventricular arrhythmias can cause palpitations and syncope, especially in older children. In addition, there is an association with sudden death, presumably related to ventricular arrhythmia, but perhaps compounded by outflow obstruction and myocardial ischemia.

Physical exam is often normal, especially in mild forms of the disease. It may reveal a S4 gallop due to atrial contraction into a stiff left ventricle. A systolic ejection murmur can be detected in patients with left ventricular outflow tract obstruction. The murmur is loudest at the left lower sternal border and is dynamic in nature, i.e., its loudness is affected by specific maneuvers. During the Valsalva maneuver, which increases the intrathoracic pressure and decreases venous return to the heart, the mitral valve leaflet is brought closer to the septum, which will increase the gradient across the outflow tract and the loudness of the murmur. In contrast, the murmur will be decreased in a squatting position, secondary to increased venous return and volume of the left ventricle in conjunction with increased resistance to outflow, thus lessening the pressure drop across the left ventricular outflow tract. Occasionally, there is mitral valve regurgitation, which produces a holosystolic murmur at the apex. When the right ventricle is involved in the disease process, subpulmonic stenosis can cause a loud systolic ejection murmur at the right upper sternal border.

Diagnosis

Echocardiography is the hallmark of diagnosis and shows inappropriate hypertrophy of the left or both ventricles. The hypertrophy is frequently asymmetrical in nature, affecting the septum more severely than the rest of the heart. However, HCM can manifest as many different patterns of hypertrophy, including apical or concentric hypertrophy. The septal thickness is abnormal if it measures more than two standard deviations above the mean indexed to body surface area (or 15 mm in adults). The left ventricular outflow tract should be carefully interrogated. Diastolic dysfunction can be assessed by Doppler hemodynamics as well as tissue Doppler. A 12-lead ECG may show left ventricular hypertrophy or biventricular hypertrophy, ST- and T-wave changes and abnormal Q waves. Unfortunately, a 12-lead ECG is not sensitive enough for screening since approximately 25% of patients with HCM have a normal ECG. However, the ECG can be helpful in the differential diagnosis since Pompe's disease shows giant QRS complexes.

Exercise testing is usually performed in children once they are at least 8 years of age to objectively assess functional status and risk-stratify the patient. A hypotensive response to exercise or failure to increase blood pressure appropriately (>20 mmHg) represents a risk factor for sudden death. Exercise occasionally elicits high-grade arrhythmias or ischemic changes. Holter recording can show atrial or, more frequently, ventricular arrhythmia with the latter having negative prognostic implications.

Genetic Testing

Over 400 mutations in 10 sarcomeric genes have been identified in HCM, most of them in the myosin heavy chain and myosin binding protein. Additional mutations continue to be identified. The likelihood of finding a sarcomeric mutation in a patient with HCM is between 50% and 80%, depending on the age, familial occurrence, and pattern of hypertrophy. However, there is sufficient heterogeneity in the clinical manifestations of a given gene mutation, that even when a patient's mutation is known, his or her clinical course cannot be predicted with any degree of certainty.

Differential Diagnosis

Other causes for hypertrophy should be excluded, including hypertension, aortic stenosis, and coarctation. In younger children (<2 years), at least half of the cases of HCM can be attributed to another disease, including metabolic or genetic disorders. Infants born to diabetic mothers can have transient biventricular hypertrophy, and 20% of patients with Noonan syndrome have HCM, as do 50% of all patients with Friedreich's ataxia. An Australian population study in 0–10 year old patients with HCM found a 57% incidence of an underlying syndromic, metabolic, or genetic disorder. However, a recent study from the US Pediatric Cardiomyopathy Registry showed that 75% of the pediatric subjects had idiopathic HCM. In older children, the most important differential diagnosis is an "athlete's heart" which is defined as a physiologic hypertrophy of the heart muscle due to intense sports participation, most frequently rowing, biking, or weightlifting. This distinction is important, but can be difficult to make, and often relies on Doppler assessment of diastolic function.

Treatment

Drug therapy is indicated if patients are symptomatic. Some clinicians advocate treatment with beta blockers in asymptomatic high-risk patients (e.g., severe left ventricular outflow tract obstruction or severe left ventricular hypertrophy), but a survival benefit has not been proven in this patient group. Once a patient becomes symptomatic, treatment with beta blockers or calcium channel blockers (verapamil or diltiazem) is initiated. Beta blockers reduce the heart rate, thereby prolonging diastole and giving the hypertrophied ventricle more time to fill. They have a negative inotropic effect which decreases the left ventricular outflow tract gradient and reduces myocardial oxygen demand. Calcium channel blockers work largely through the same mechanism, but may also improve ventricular relaxation and coronary flow. If there is significant left ventricular outflow tract obstruction, beta blockers are preferred over calcium channel blockers because of the vasodilatatory side effects of the latter. If treatment is ineffective, disopyramide may be added. This is an antiarrhythmic drug with negative inotropic properties that also vasoconstricts. As a general rule, diuretics and vasodilatory drugs should be avoided, especially in patients with left ventricular outflow tract obstruction, since decreased filling of the hypertrophied heart will worsen the left ventricular outflow tract gradient and cardiac output. In addition, digoxin is contraindicated because of its positive inotropic effect. However, a small subgroup of patients with advanced HCM have symptoms of congestive heart failure due to decreased systolic function. They might benefit from

diuretics, ACE inhibitors, or beta blockers, conform established treatment recommendations for congestive heart failure with systolic dysfunction.

Nonpharmacologic therapies for HCM include surgical myectomy, in which the subaortic septal ridge is peeled away, and alcohol septal ablation. Both procedures intend to reduce left ventricular outflow tract obstruction. The latter is a catheter-based procedure, during which alcohol is injected directly into a coronary perforator to induce a controlled myocardial infarction. These therapies are only appropriate for patients with refractory symptoms and severe outflow tract obstruction. Since the experience with alcohol septal ablation in children is limited, surgical myectomy is preferred.

Indications for Implantable Cardioverter Defibrillator (ICD) Placement

There are multiple prognostic factors for sudden death, the most important being:

1. History of cardiac arrest or sustained ventricular tachycardia
2. A positive family history for sudden cardiac death
3. Documented non-sustained ventricular tachycardia
4. A hypotensive response to exercise (i.e., decrease of blood pressure with exercise or a lack of increase of at least 20 mmHg)
5. Unexplained syncope
6. Extreme left ventricular hypertrophy (septal thickness >30 mm in adults)

When two or more risk factors are present, or syncope alone in children, the annual mortality rate is estimated to be >5%, and ICD placement is recommended.

Exercise Limitations

Patients with HCM should be excluded from competitive or high-intensity noncompetitive sports and isometric exercises because of the increased risk of sudden death. The Bethesda conference on sports participation from the American College of Cardiology recommends only low-intensity competitive sports for all patients with HCM (bowling, golf, cricket). However, some cardiologists advocate for recreational (noncompetitive) aerobic exercise of moderate intensity (biking, swimming, jogging) in their patients with HCM, based on studies showing an increased risk of sudden death and decreased emotional and physical well-being in patients who do not participate in regular exercise. It would seem prudent to discourage young patients from activities that result in sudden strenuous exertion, particularly when under peer pressure. They should always be allowed to rest as needed during exercise.

Prognosis

The risk of sudden death in adult patients with HCM is approximately 0.5–1% per year in community-based population studies and 3–5% per year in patients referred to tertiary centers. Rates for older children with HCM are similar, but the clinical course is highly dependent on age, and hypertrophic heart disease presenting in infancy carries a worse prognosis, especially if it is secondary to metabolic or genetic disorders. Proposed mechanisms for sudden death include arrhythmic events, myocardial ischemia, and end-stage heart failure. A recent Australian study which evaluated all children with HCM between 0 and 10 years of age found that 83% were free of death or transplantation after 5 years and 76% after 10 years. Approximately 5% of HCM ultimately progresses into a burn-out disease with systolic dysfunction and symptoms of congestive heart failure.

Prevention

Most sarcomeric mutations are inherited in an autosomal dominant pattern and first-degree relatives (parents, siblings, offspring) should be screened by echocardiogram for HCM every 5 years, and yearly through adolescence since the degree of hypertrophy can increase significantly during puberty. If a gene mutation is identified in the diseased family member, first-degree relatives can be screened for the same mutation. A negative mutation analysis would obviate the need for lifelong echocardiograms, whereas a positive test would warrant lifelong screening echocardiograms. The natural history of each mutation varies, and even in families with the same gene mutation, the phenotype might express itself differently among affected family members.

Left Ventricular Non-Compaction

Etiology

Left ventricular non-compaction (LVNC) is a rare form of cardiomyopathy that has been described since the early 1990s. It is characterized by multiple prominent ventricular trabeculations and deep intertrabecular

recesses within the myocardium. Its annual incidence in children is <0.1 per 100,000. There is familial occurrence in 25% of children with LVNC.

Pathogenesis

LVNC can present as isolated noncompaction or in conjunction with other heart disease (20%). Isolated noncompaction is thought to represent an arrest in the normal compaction of the myocardium during organogenesis. Multiple genetic mutations have been identified related to LVNC, including tafazzin (TAZ, leading to Barth syndrome), dystrobrevin (DTNA), and lamin gene mutations (LMNA), as well as sarcomeric protein mutations similar to those found in HCM. In addition, LVNC can occur with chromosomal disorders, neuromuscular diseases, mitochondrial disorders, DiGeorge syndrome, and Fabry's disease.

Pathology

There is hypertrabeculation of the left ventricular myocardium with histopathology showing interstitial fibrosis and endocardial fibroelastosis. Both ventricles are involved in approximately 25% of cases. The clinical phenotype can undulate between ventricular dilation and hypertrophy.

Clinical Symptoms and Signs

Symptoms may be secondary to heart failure, arrhythmias (both atrial and ventricular), or thromboembolic events. Up to two thirds of patients have depressed systolic function, but diastolic dysfunction is common as well. The most common presentation in children is heart failure. Pignatelli reviewed the clinical course in 36 children with LVNC. At a median age of 90 days, 40% of patients presented with symptoms of heart failure, while another 40% were asymptomatic. Thromboembolic events are seen in about 10% of adult patients and are due to thrombus formation in the deep intertrabecular recesses. They are more likely to occur when the systolic function is depressed. Pignatelli did not report any systemic embolism in his pediatric patient group.

Diagnosis

A consensus on features required for a diagnosis of LVNC has not been established. The following echocardiographic criteria have been advocated.

The diagnosis is established by echocardiography when three criteria are met:

1. The presence of multiple echocardiographic trabeculations (>3)
2. Evidence of Doppler flow into the intertrabecular recesses
3. A ratio of non-compacted to compacted myocardium of >2:1 at end-systole; sometimes a ratio of 1.4:1 is used in children

An MRI may be helpful to evaluate the ventricular morphology when echo findings are inconclusive. Abnormal ECG findings are seen in 75% of patients and may include biventricular hypertrophy, T-wave inversion, preexcitation, and premature atrial and ventricular contractions. Annual Holter studies are indicated because of the increased risk of atrial and ventricular tachycardia. Skeletal muscle biopsy may be indicated if urine and blood tests reveal a concern for underlying mitochondrial or metabolic disease.

Genetic testing: Genetic screening should be considered when there is a positive family history or when clinical features suggest the aforementioned mutations. Multiple gene mutations have been linked to LVNC, with both X-linked (TAZ gene mutations) and autosomal dominant inheritance patterns. There are likely still many unidentified genetic mutations related to LVNC. As in HCM, the clinical presentation between patients with the same mutation can vary widely.

Differential Diagnosis

Occasionally, it is hard to differentiate the echocardiographic findings of LVNC from normal occurring ventricular trabeculations. In addition, LVNC may present with a phenotype similar to dilated or hypertrophic cardiomyopathy and disease processes may overlap. Some of the same genetic mutations seen in LVNC, can be found in dilated and hypertrophic cardiomyopathy.

Treatment

The specific treatment depends on the clinical and echocardiographic findings. In patients with systolic dysfunction, therapy with ACE inhibitors and/or beta blockers is warranted. Diuretics should be added if symptoms of venous congestion exist. If there is solely diastolic dysfunction, diuretics may be the only medication needed for symptomatic relief. Patients with a hypertrophied

phenotype could benefit from beta blockers. Many centers routinely start antiplatelet medication (aspirin) or full anticoagulation if there is a history of thromboembolic events or severely depressed systolic function. Some centers add vitamin cocktails (thiamine, carnitine, riboflavin, coenzyme Q10) to the cardiac therapy if there is clinical evidence of mitochondrial dysfunction.

Prognosis

The natural history of LVNC is largely unknown. It is a diverse disorder, and many asymptomatic cases are undiagnosed. On the other hand, some degree of left ventricular trabeculations can be seen in the normal heart, leading to overdiagnosis in other patients. Pignatelli described a 3 year survival of 78% in a pediatric cohort with LVNC. Nine out of 36 patients experienced transient periods of recovery. Prognosis is worse in patients with concomitant congenital heart disease.

Prevention

Prevention of disease is not possible. For the purpose of genetic counseling and early diagnosis, screening echocardiograms can be obtained in first-degree relatives. If a gene mutation is identified in the diseased family member, first-degree relatives can be tested for the same mutation.

Pediatric Heart Transplantation

History

Human heart transplantation was first performed by Dr. Christian Barnard in Cape Town, South Africa, in 1967. The 54 year old recipient lived for 18 days, ultimately succumbing to pneumonia. The first pediatric heart transplant was performed only 3 days later by Dr. Kantrowitz at Maimonides Medical Center in Brooklyn, New York. A donor heart from an anencephalic infant was transplanted into a recipient with severe Ebstein's anomaly of the tricuspid valve with functional pulmonary atresia. The infant lived for 6 hours. In the following years, many centers performed heart transplantations, but results were disappointing due to the lack of effective immunosuppressive drugs to control allograft rejection. The introduction of anti-thymocyte preparations in the 1970s and cyclosporine in the 1980s allowed for a revival and expansion of heart transplantations in adults and children.

Indications

Evidence-based guidelines for heart transplantation in children have been more difficult to establish than in the adult population because of the relatively small patient population and diverse cardiac diagnoses. In addition, criteria for adult heart transplantation hinge heavily on exercise testing, which cannot be reliably performed in younger children. A working group from the American Heart Association recently reexamined and reaffirmed previously used indications for pediatric heart transplantation, which include:

Progressive heart failure with deterioration of functional status despite optimal medical care
Need for ongoing inotropic or mechanical circulatory support
Complex congenital heart disease without good surgical options
Malignant arrhythmias
Progressive pulmonary hypertension secondary to left ventricular failure or restrictive cardiomyopathy
Growth failure secondary to heart disease

Epidemiology

Pediatric heart transplants account for approximately 10% of all heart transplants worldwide with a total of about 400 cases per year. Throughout the years, infants have constituted one quarter of all pediatric transplant recipients. Heart transplantation is now less used as primary therapy in infants with congenital heart disease than it was 10 years ago, due to improved outcomes in congenital heart surgery, especially the Norwood procedure for hypoplastic left heart syndrome. Still, the current majority of infant heart transplant recipients (2/3) carry a diagnosis of congenital heart disease, while the remainder has cardiomyopathy. This distribution is reversed in teenagers and about equally divided in school age children. Dilated cardiomyopathy accounts for 75% of cardiomyopathies, with the remaining 25% almost equally divided between restrictive cardiomyopathy, hypertrophic cardiomyopathy, and myocarditis.

Workup of the Heart Transplant Recipient

A full workup of a heart transplant candidate should include the following:

Lab work: blood type, anti-HLA antibody screen ("Panel Reactive Antibodies or PRA") to evaluate for

preexisting sensitization to HLA antigens, complete blood count, anticoagulation panel, liver and kidney function tests, infectious serologies (see below).

Cardiac catheterization to assess pulmonary vascular resistance and occasionally to delineate the exact anatomy in congenital heart disease. Newborns without risk factors for pulmonary vascular disease do not always need a cardiac catheterization prior to transplant.

Exercise study to help assess functional capacity in older recipients (>8 years old).

Consultations from:

- Nutrition
- Social work, with special attention to whether there are concerns for medical noncompliance
- Psychiatric evaluation, if indicated
- Infectious disease specialist, who will at least request HIV, hepatitis, EBV, CMV, varicella, and toxoplasmosis serologies, as well as up-to-date vaccination status
- Anesthesia
- Cardiovascular surgeon

There are few contraindications to heart transplantation, and most are not absolute. Their purpose is to increase the likelihood that the recipient will survive the transplant, and be able to enjoy a near normal quality of life after transplantation. As mentioned, pulmonary vascular resistance should be evaluated prior to transplant. Patients with significant left ventricular dysfunction often have long-standing pulmonary venous congestion, which can cause vascular remodeling and consequently elevated pulmonary vascular resistance. This can lead to right ventricular failure post transplant since the donor heart is not used to these elevated pulmonary artery pressures. With the introduction of pulmonary vasodilators such as prostacyclin and nitric oxide, the acceptable upper range for pulmonary vascular resistance is expanding. Most centers will accept patients for heart transplantation if their pulmonary vascular resistance drops after administration of pulmonary vasodilators (nitric oxide, prostacyclin, oxygen). The presence of an active, untreated infection precludes transplantation, considering the requirement for immunosuppressive therapy. Renal insufficiency with a creatinine >2 mg/dL decreases the chance of a good outcome after heart transplantation, unless a heart–kidney transplant is planned. A coexisting life-threatening illness forms an absolute contraindication. Potential for noncompliance with medications is a relative contraindication and needs to be carefully addressed prior to transplantation.

Donor Factors

A donor heart is matched to recipient size. A donor to recipient weight ratio of 0.9–2.5 is often used. Donor and recipient blood types need to be matched for non-infant recipients. In 2001, West et al. showed successful transplantation of ABO-incompatible donor hearts in infants. The immaturity of the infant immune system, which has not yet formed antibodies to the major blood-group antigens, is thought to enable the development of tolerance post transplant. This practice is now widely used, thereby broadening the available donor pool for infant recipients. Unlike other solid-organ transplants, heart transplant donor and recipients are generally not matched for HLA type, partly due to the restrictions in donor ischemic time. However, in recipients with preformed HLA antibodies ("sensitized" recipients), donor organs with corresponding HLA antigens will need to be avoided.

Posttransplant Complications

Primary graft failure is the most common cause of death in the first 30 days following heart transplant and is associated with many factors, including poor donor organ quality, prolonged ischemic time, preexisting pulmonary hypertension in the recipient, as well as preexisting congenital heart disease in the recipient.

There is an increased risk of *infection*, especially in the early posttransplant period, when the immunosuppressive burden is the highest. Blood infections and bacterial pneumonias are the most common infections in the immediate posttransplant period due to necessary invasive lines and endotracheal tubes. Viral infections (especially CMV and EBV) may be transmitted from a positive donor into a naïve recipient, or previously infected recipients can experience a reactivation of latent virus. For these reasons, recipients receive prophylaxis with ganciclovir for 3 months after transplant when there is evidence of CMV positivity in donor or recipient.

Rejection remains an ongoing concern, with the highest risk in the first year after transplant, when one third of transplant recipients experience some degree of acute cellular rejection. Multiple immunosuppressive drugs are available and used for prevention of rejection. A distinction should be made between induction therapy and maintenance therapy. *Induction therapy* is the prophylactic administration of immunosuppressive drugs in the immediate postoperative period when donor antigen expression is highest. It is used in approximately 50% of

pediatric heart transplant recipients. While the ultimate goal is to induce graft tolerance, the immediate goal is the prevention of T-cell activation, which can prevent early rejection and allow for later introduction of maintenance immunosuppression with nephrotoxic calcineurin inhibitors. Many centers use corticosteroids as well as polyclonal T-cell antibody preparations (ATG) as induction therapy, whereas other centers use IL-2 receptor antibodies (daclizumab and basiliximab). *Maintenance immunosuppression* is introduced once the renal function has stabilized, usually somewhere within the first 5 days after transplant. Calcineurin inhibitors (cyclosporine, tacrolimus) are the cornerstone of most immunosuppressive protocols. Calcineurin is a phosphatase that regulates cytokine production within the T-cell. Most centers prefer to use multiple classes of immunosuppressive drugs, therefore allowing for lower doses and less side effects of each individual immunosuppressive drug. Besides calcineurin inhibitors, antiproliferative agents are often used. Examples are mycophenolate mofetil or azathioprine, which are purine analogues that inhibit T- and B-cell proliferation. Sirolimus is a different class of antiproliferative drug that has the added advantage of inhibiting smooth muscle and endothelial cell proliferation as well T- and B-cell proliferation. Because of these effects, it can be beneficial in preventing transplant coronary artery disease. It is also used as a partial replacement for calcineurin inhibitors when there is concern for nephrotoxicity. Corticosteroids are part of maintenance immunosuppression in many centers. Because of the many side effects associated with long-term use, there is a trend toward early steroid withdrawal. Currently, about half of centers continue to give corticosteroids at 1 year post transplant.

Frequent monitoring for rejection is mandatory since rejection can occur without symptoms. Monitoring can be performed noninvasively, based on echo parameters of diastolic and systolic function, or invasively by catheter-based cardiac biopsy. Clinical symptoms and signs of rejection include dyspnea, tachycardia, gallop rhythm, general malaise, and other signs of congestive heart failure.

Long-Term Sequela

The risk for rejection and infection continues to be present throughout life, albeit significantly lower than in the early posttransplant period. Allograft vasculopathy is the leading cause of death among pediatric heart transplant recipients who survive >5 years. It differs from classic coronary artery disease: it presents at an earlier age and is more progressive and diffuse in nature. Almost 20% of pediatric heart transplant recipients have evidence of allograft vasculopathy 5 years after transplant, although the infant recipient appears relatively spared (*Fig. 261.2*). The process is likely immune and nonimmune mediated. It is

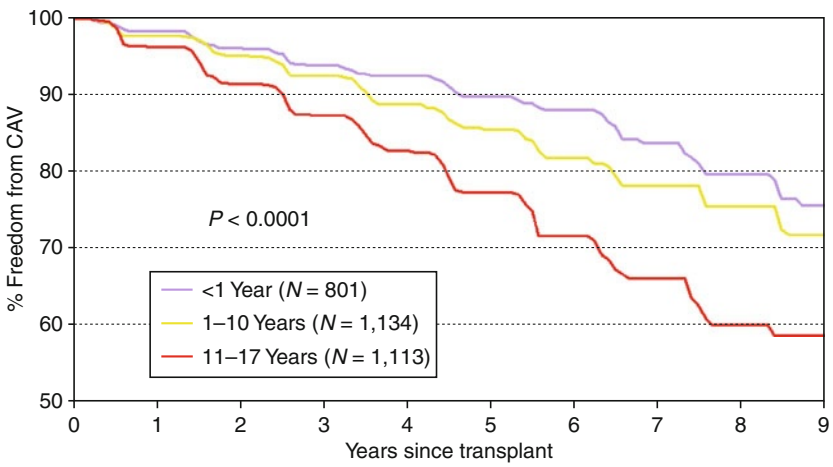

Figure 261.2

Freedom from coronary artery vasculopathy for pediatric heart transplants recipients (data collected by the International Society for Heart and Lung Transplantation 1994–2008), stratified by age group (Reprinted from Kirk R, Edwards LB, Aurora P et al (2009) Registry of the International Society for Heart and Lung Transplantation: twelfth official pediatric heart transplantation report – 2009. J Heart Lung Transplant 28:993–1006. With permission from Elsevier)

associated with rejection, particularly antibody mediated rejection, while traditional cardiovascular risk factors, promoted by immunosuppressive therapy (hyperlipidemia, diabetes, hypertension, CMV infection) are likely to contribute as well. Once it develops, the prognosis is grim, with less than 50% survival at 2 years. Sirolimus appears to help stall the development and progression of allograft vasculopathy. Unfortunately, lesions are usually not amenable to catheter based intervention due to their diffuse nature, and retransplantation is often the only treatment option.

Renal dysfunction is an important consideration, with 10% of heart transplant recipients developing severe renal disease 10 years after transplant, secondary to chronic

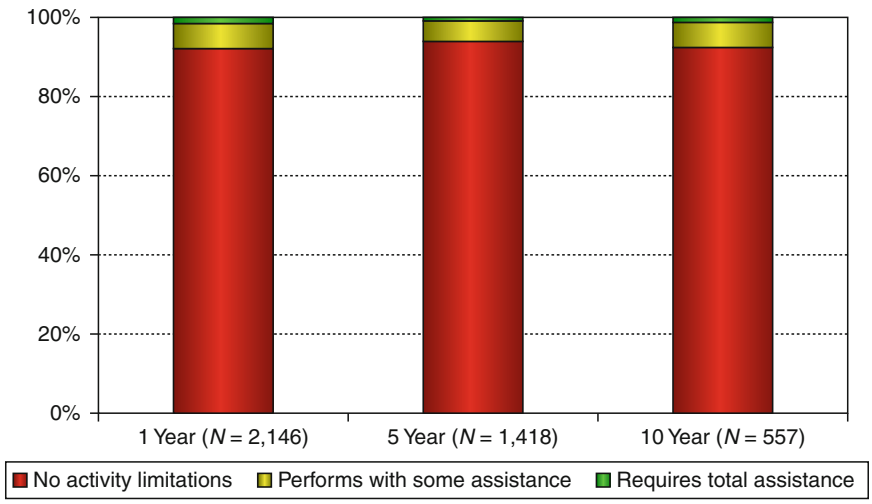

Figure 261.3
Functional status of surviving recipients of pediatric heart transplants (data collected by the International Society for Heart and Lung Transplantation 1994–2008)

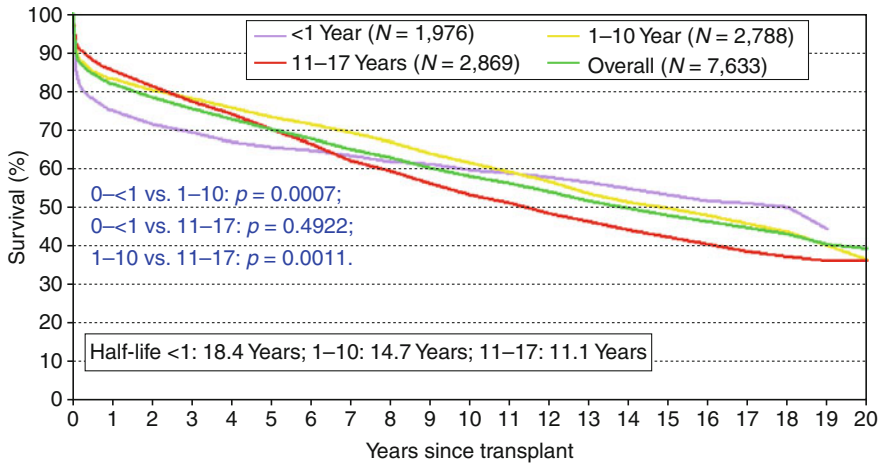

Figure 261.4
Kaplan–Meier survival curve for pediatric heart transplants recipients (data collected by International Society for Heart and Lung Transplantation 1982–2007), stratified by age group (Reprinted from Kirk R, Edwards LB, Aurora P et al (2009) Registry of the International Society for Heart and Lung Transplantation: twelfth official pediatric heart transplantation report – 2009. J Heart Lung Transplant 28:993–1006. With permission from Elsevier)

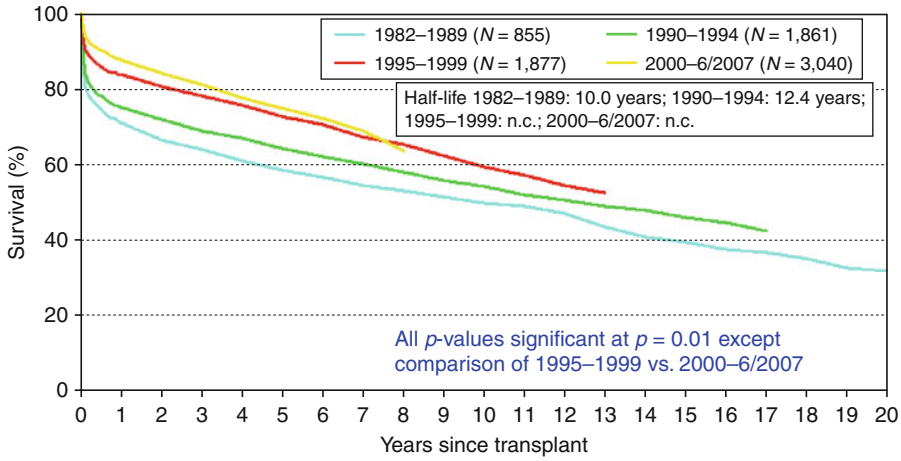

Figure 261.5

Kaplan–Meier survival curve by era for pediatric heart transplants recipients (data collected by International Society for Heart and Lung Transplantation 1982–2007) (Reprinted from Kirk R, Edwards LB, Aurora P et al (2009) Registry of the International Society for Heart and Lung Transplantation: twelfth official pediatric heart transplantation report – 2009. J Heart Lung Transplant 28:993–1006. With permission from Elsevier)

administration of nephrotoxic drugs on top of frequently preexisting renal disease, due to a history of heart failure with low cardiac output. In addition, many heart transplant recipients develop chronic hypertension as an adverse effect of the medications. Another long-term consequence of the immunosuppressive medications is an increased incidence of malignancies (8.3% for 10 year survivors), which are mostly lymphoid tumors. Posttransplant lymphoproliferative disease (PTLD) is associated with primary Epstein Barr virus (EBV) infection post transplant and encompasses a wide spectrum of diseases from benign lymphoid hyperplasia to aggressive monoclonal lymphoma. Reduction of the immunosuppressive burden often provides sufficient treatment, but occasionally additional treatment with chemotherapeutic agents is warranted.

Despite the many long-term medical issues, most heart transplant recipients enjoy a good quality of life with few limitations (*Fig. 261.3*).

Survival

The current 1-year survival after heart transplant is 88% in children >1 year old and 82% in younger children. The 5 year survival for all age groups is 75%. While the infant group has a higher initial mortality (*Fig. 261.4*), they appear to have a survival benefit once they survive the first year ("conditional survival"), likely due to the relative immaturity of the infantile immune system at time of transplant, making graft tolerance more likely. With advancements in immune suppressive management, survival statistics do improve (*Fig. 261.5*). Unfortunately, not all patients listed for transplant survive until transplantation, and waitlist mortality can be as high as 20%.

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Critical Care

Abdul-Rahman M. Abu-Taleb and Peter N. Cox

262 Pediatric Intensive Care Physical Environment

Abdul-Rahman M. Abu-Taleb

Introduction

Pediatric intensive care has progressed over the years and has become a well established and reputable subspecialty. Patient acuity, over the last 10 years, has increased, resulting in a growing need for more Pediatric Intensive Care Unit (PICU) beds and sophisticated monitoring equipment. Cutting edge technological advancements in the treatment of childhood diseases have also contributed to the increased use of pediatric intensive care beds. Along with these positive developments, requirements were identified to set higher standards in all directions, including optimal physical environment for critically ill children and their families. The role of the actual physical environment has a major impact on the successful management and optimal healing outcome of critically ill children. PICU designers must include hospital administrators and the end-users in the planning to overcome many logistic constrains. Meeting the objectives requires good long-term planning taking into consideration growing patient population, establishment of new services, treatment modalities, team composition, and function. This long-term planning will enable the physical requirements of the unit to last longer with only minor modifications in the future, if the need arises. Aside from location, space, and staffing, the potential of future PICUs to fulfill patients and families needs is by fulfilling additional requirements such as ambient and atmospheric features, functional and technological settings, psychological, spiritual, cultural needs, and finally social support for patients and families to meet their psycho-social needs. Unit policies should reflect a patient- and family-centered approach.

Ambient and atmospheric features address acoustic, light, and temperature effects as PICU tends to be a noisy and brightly illuminated place due to continuous procedures and the large number of care providers. The continuous sounds from ventilators and beeping of monitors create a disturbed atmosphere to patients and their families and causes additional stress; consequently, atmospheric intervention (ambience) should be strongly considered in the unit's design to support and promote the healing process. Dim lighting tends to reduce the level of activity and noise of staff in contrast to bright illumination. Temperature (air-conditioning) and lighting controls should be within the reach of staff and families. Private and semi-private rooms as well as soffits will decrease noise level and add more comfort to the patient and family. Additional friendlier physical environment approach in PICU is the selection of appropriate color schemes, decor, and selection of interior finishes that resemble home to create a soothing, reassuring atmosphere. The results are a comfortable, family-focused, state-of-the-art facility that presents a less threatening environment for both the children and their families and offers the best care.

These suggestions should not compromise unit functionality regarding infection control, easy maintenance, durability, stain resistance, flame resistance, non-toxicity, light fastness, aesthetics, and cost. A relaxing atmosphere with positive psychological impact on patients and their parents also include provision of windows for daylight to maintain circadian rhythms, and to have views to outside gardens that can be used as special areas for patients, families, and staff for relaxation.

The design of PICU patient's rooms can incorporate functionality, as well as up-to-date technological requirements to suit the needs of patients, care givers, and families. This can be achieved by applying a zoning system within a patient room. Each room will have three zones for patient, family, and care givers (*Fig. 262.1*). Attention should be devoted also to visibility between patient and care givers in a way that an acceptable level of privacy is still maintained.

A major part of excellence in patient care is addressing family support through frequent and proper counseling and providing social support as needed. A family counseling area and a large family lounge to accommodate different groups of individual families are essential to provide comfort and the image of welcoming and integrating the patient and his parents. It is especially important to involve families in the care of their children and promote

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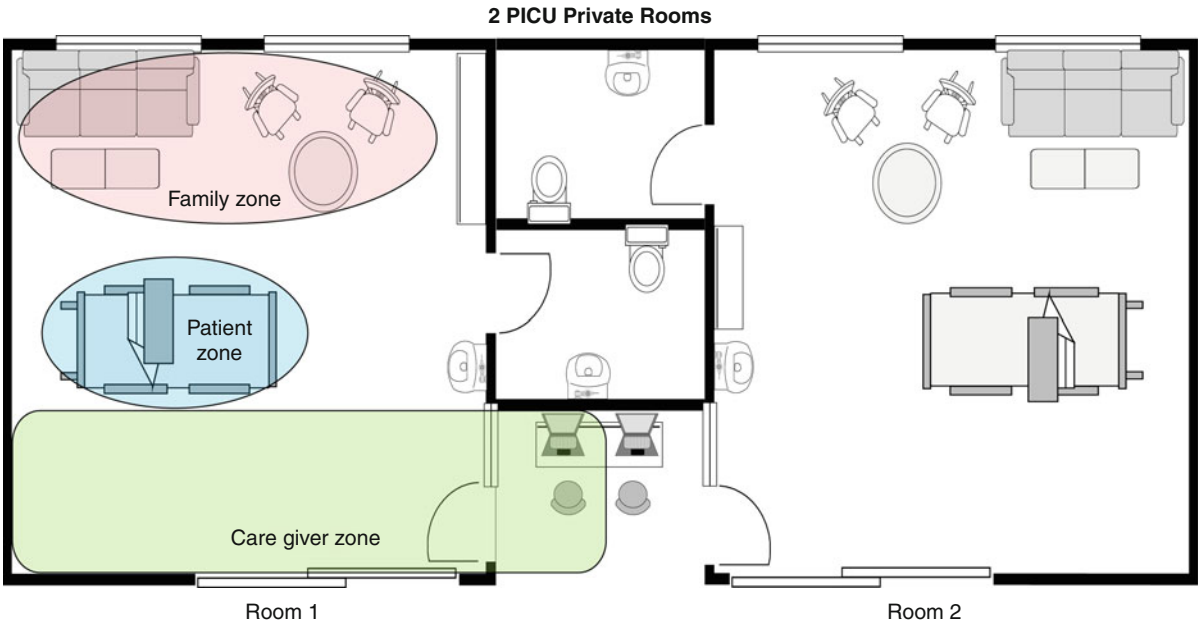

Figure 262.1
Two PICU private rooms with patient zone, care giver zone, and family zone promoting child- and family-centered care

them as partners in the care; not only does it help ease parents' anxiety to be nearby, but also recent studies indicate that their presence can actually reduce recovery time.

Managing critically ill children used to focus mainly on a biomedical approach. Care should move more and take a holistic approach aiming to offer health care providers, in particular the nursing staff, dependent relationship resulting in genuineness, warmth, active listening, nonjudgmental, and empathy. Focusing on a family-centered care and the physical environment in PICU will promote privacy, interaction, social support, comfort, and functionality as mentioned above.

Allocation of Space

The location and size of the unit is important and will vary as a result of differences in hospital architecture, size, space, and design. PICU location should be within or close to pediatric services and simultaneously be as close as possible to important support services such as the operating room, recovery room, emergency department, radiology department, laboratory, cardiac catheterization laboratory, and elevators. Proximity to the physician's on-call rooms, medical and nursing director's offices, and family waiting and sleeping areas is essential. Access to the PICU should be monitored to maintain patient and staff safety and confidentiality.

The amount of space devoted to the unit may constitute a real challenge and is the most difficult decision to make, as the allocated size is essential to the effectiveness and efficient functioning of the unit. Additionally, size of the unit is strongly dependent on the number of beds, isolation rooms, private rooms, semi-private rooms, and support services area needed.

It is highly recommended to have site visits to well-established PICUs around the country and study different PICU designs and consequently selecting the best features and tailoring them to the specific needs of the center.

Patient Care Areas

Caring for critically ill children is a complex task. Thoughts should be given to private and semi-private rooms (enclosed cubicles) versus multiple-bed area (open bay system), or a combination of both, keeping in mind that the need for private rooms and semi-private rooms for pediatric patients has increased over the last decade and is superior to a multiple-bed area system. However, the decision depends on availability of resources (finance and staffing), availability of space, and level of

acuity care. The design of the PICU area (open beds and private rooms) should have a friendly layout, thus maintaining functionality and providing optimal care in a less threatening environment for both the children and their families by making the PICU a patient- and family-centered place of care.

The number of beds has to be identified before the decision about allocating space for the unit can be made. Factors that influence optimal PICU bed number in a given center addresses the population to be served, existing services and planned projects, size of the active pediatric department, number of acutely ill pediatric patients previously treated in the center, maximal occupancy, average length of stay, high turnover, and short stays; all these aspects must be taken into consideration in the final decision of the total PICU bed number. Knowing that the demand for pediatric high acuity and step-down beds has continued to grow is also important. Also the number of isolation and private or semi-private rooms will have a significant impact on the bed number and may limit the overall bed capacity of the unit. Personnel shortages and cost-containment are few of the many reasons faced by the planners in making the decision between a multiple-bed area arrangement or private rooms and semi-private rooms. The recommendation in general is to provide at least one isolation room for each ten beds or one for each unit, if the overall bed capacity is less than ten beds. Test results, however, have shown that usually more than one isolation room is necessary. In fact modern units are moving away from multiple-bed area system (open bay system) toward more private rooms and semi-private rooms, as the need for private rooms for pediatric patients has increased over the last decade. Parents need adequate space in order to stay with their sick child at all times and have the necessary privacy, which is consistent with family-centered care. In addition, infection control requirements have also changed over the last decade. The need for isolation rooms has increased dramatically due to infectious diseases as well as an increase in the number of immunocompromised patients who need to be protected from infectious organisms. Other variables need to be considered that may affect future bed use, such as new programs or expanded services that involve a PICU stay. In addition, thoughts need to be made in case a step-down area is to be included within the unit location which usually has a multiple-bed area arrangement.

Different room types are required within the PICU, including rooms for patient isolation. The minimal space requirement for an open PICU bed is 200–225 sq. ft (18.58–20.9 m^2) with at least 5–8 ft (1.52–2.44 m) distance (clearance) between beds. The required space per bed must be large enough to accommodate routine (monitors, ventilator, IV poles, and pumps) and special equipment such as High Frequency Oscillatory Ventilator (HFOV), hemodialysis, Extracorporeal Membrane Oxygenation (ECMO), echocardiography, ultrasound, and x-ray. The designated space per bed and the clearance between beds must accommodate emergency procedures such as resuscitation and minor or major emergency surgical procedures, as these actions will involve additional care providers and equipment. Sufficient space around the head of each bed or crib must be available for rapid airway access in emergency situations. Equipment columns suspended from the ceiling are very helpful in organizing workspace. Isolation rooms as well as private rooms require at least 250 sq. ft (around 23.23 m^2) to have adequate workspace for the equipment and other life-support systems that is often necessary in critical care situations such as in-room dialysis and other equipment. The isolation rooms, if used for immunocompromised children, are best prepared with an anteroom (including a sink, place to change gowns, and drawers to keep gloves, masks, protective eyewear, and other items) and have controlled airflow (negative and positive pressure airflow capabilities) to minimize the spread of airborne infections. The space in isolation and private rooms can be divided into zones as mentioned earlier (Fig. 262.1). This will optimize the space to accommodate the needs of patient, parents, and care providers. Equipment columns suspended from the ceiling to make the rooms flexible allows PICU staff to arrange bedside equipment for the patient's best care and comfort. With a daybed, recliner or comfort chair, bathroom, TV/VCR, and storage space in each room, parents are able to stay at their child's bedside. Use of regular curtains should be discouraged as they are susceptible to dust build-up and have infection control disadvantage; instead, use of adjustable integral blinds between layers of glass are effective in full blocking of light and/or interior views and have infection control advantage.

Highly technologically sophisticated PICU in tertiary care facilities, regardless of the chosen bed system (multiple bed area system or private and semi-private rooms), will require special considerations regarding individual bed space design. Headwalls or columns that are capable of providing virtually every physical resource needed at the bedside offers great flexibility in space management. All necessary electrical outlets, grounding inlets, vacuum and oxygen and air outlets, alarm buttons, communications systems, temperature and lighting controls, equipment brackets, and storage capabilities can be tailored according to the needs. A multidisciplinary team

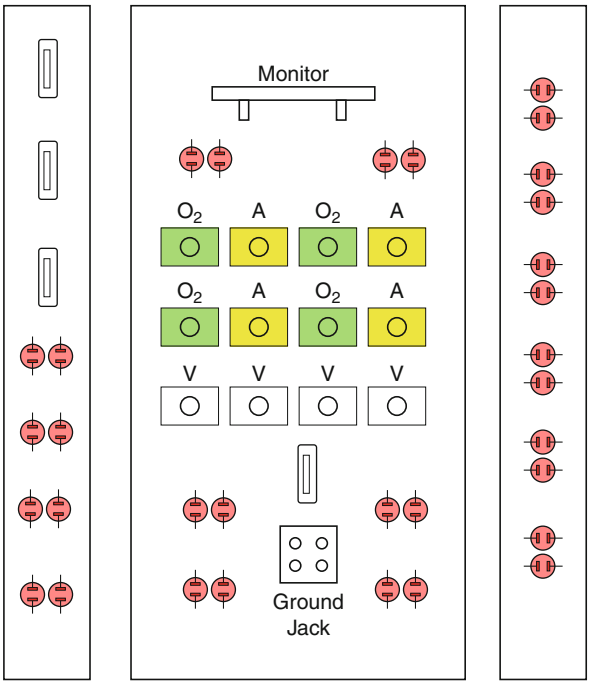

Figure 262.2
Schematic layout drawing of a PICU power-column with example of different outlets

consisting of health care provider groups (physicians, nurses, and respiratory therapists), biomedical engineers, and architects need to collaborate to achieve the best possible layout for headwalls or columns (*Fig. 262.2*). The number of electrical and gas outlets needed per bed to cope with tertiary PICU requirements is usually higher than generally recommended. At least, 24 electrical outlets for each bed are required, 12 out of them should be linked and connected to the emergency power source that will quickly resupply power in the event of power interruption. Gas outlets requirements are four outlets for each, oxygen, vacuum and air, and need to be arranged on the headwalls or columns of each bed. Full range of accessibility to the patient (360°) should be maintained at all times, as well as easy access to equipment and outlets.

Support Services

Requirements for support areas within the PICU include separate rooms for clean and soiled linens, laboratory area for rapid determination of blood gases and other essential studies (electrolytes), respiratory therapist area, medication room (including a refrigerator and a narcotics locker), a satellite pharmacy to provide routine and emergency medications at the point of ordering, a large storage room for equipment to accommodate the needs of a large, technologically sophisticated unit (with numerous electrical outlets at both floor height and counter height so that the chargeable equipment can remain plugged in), staff lounge, restrooms and lockers for staff and families, as well as physician's on-call rooms (for attending physicians, fellows and residents). Nursing stations with enough working space for nurses and fully networked to provide computer access to clinical information system and a central monitor station are placed in the unit to maintain observation and monitoring of patients. Access to patient's information from any electronic nursing station including rapid and reliable system for reporting laboratory results must be made available. The unit must include a multi-level communication system allowing immediate dissemination of information utilizing beepers, overhead paging and nurse call system. The presence of Picture Archiving and Communication System (PACS) terminals or stations to review radiographs in the unit is essential. Pneumatic tube system connecting the PICU with the laboratory, pharmacy and other support services is highly desirable. Offices for unit director, nurse manager and a conference room for staff personnel is essential and should be located in the PICU or near

the unit. These above mentioned support services facilities should be located in the PICU area and additional space needs to be included in the floor plan of the unit. Other services that should be proximate to the unit include dietary, social services, family waiting area, grieving room, quiet room and a separate room for family counseling- necessary for private discussions between the staff and the family. A conference area and staff toilets, as well as secretarial area are essential. A separate facility for patient's families, including space for sleeping and bathing, and an area for storing patients' personal effects is essential.

Requirements of the end users concerning additional space for support services beyond the recommended standards must be taken into consideration and discussed in multidisciplinary meetings with all players including the PICU team, planners, and administration. In these meetings, additional issues can be addressed such as equipment needs, PICU personnel, communication, and the impact of the PICU on other hospital services.

Part of the PICU requirement is to provide sleeping space for parents. Frequent communication and discussion with PICU staff is very important, as patient status usually is a dynamic process and requires the family presence. Space should also be allocated for additional family support facilities (see below).

Family Support Areas

The focus on creating an environment to provide medical care to critically ill patients, while incorporating the needs and support to their families is a basic approach toward patient- and family-centered care. Providing supportive environments for families aims to meet their unique psycho-social needs. Family support areas, therefore, are important and part of the overall care for critically ill children. It helps health care provider teams, with no doubt, in being sensitive and responsive to diversity across ethnic, geographic, age, and economic lines as well as in meeting the unique needs of each child and family. Licensing standards in many countries obligate hospitals to provide family support areas connected to the PICU. These family support facilities consist of providing sleeping areas for parents (plush couches, sleeper chairs or recliner, preferably separate from the visitors waiting area), family consultation rooms, family lounges with several small sections to offer privacy for different family groups, grieving rooms, quiet rooms, lavatories and showers, laundry and locker facilities, kitchenette, vending areas, and telephone booths.

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263 Pediatric Resuscitation

Abdul-Rahman M. Abu-Taleb

Introduction

Cardiopulmonary arrest in children is rare. Cardiac arrest as a sudden, primary event is uncommon in the pediatric age group (Table 263.1). More often, cardiac arrest occurs as a secondary, terminal event precipitated by diverse causes. It occurs following a progressive deterioration of the respiratory or circulatory function leading to respiratory failure with profound hypoxia, acidosis, and tissue hypoperfusion or hemodynamic collapse (Fig. 263.1). Common etiologies and underlying conditions that predispose children to develop cardiopulmonary arrest are summarized in Table 263.2. Respiratory failure resulting in hypoxemia, hypercapnia, and acidosis is the most common pathway especially in the very young child.

The outcome of cardiopulmonary resuscitation (CPR) following cardiac arrest in children is very poor. Survival rate is between 5% and 12%. The reason for this poor outcome following cardiopulmonary arrest in children is multifactorial. In contrast to adults, children have a higher incidence of asystole as the predominant rhythm. In addition, cardiopulmonary arrests in the young child are often unwitnessed, and the initiation of resuscitation efforts may be delayed. Even under the best circumstances, resuscitation of a child who is pulseless and not breathing may not be possible, and the incidence of neurologically damaged survivors post-resuscitation is high. However, patient with witnessed respiratory arrest or sudden cardiac dysfunction can be easily resuscitated. Furthermore, children with respiratory arrest alone do far better when prompt resuscitation is provided, and most patients remain neurologically intact. Long-term survival in these children is between 42% and 82%.

Management

For optimal resuscitation outcome, early initiation of treatment, knowledge, technical skills, and practice in the resuscitation field is essential. Knowledge of age and/or weight-related cardiopulmonary data, and information on equipment size and emergency drugs as outlined in Pediatric Advance Life Support guidelines is required. Training courses in CPR, i.e., basic life support courses (BLS), are offered periodically to health professionals to overcome difficulties in retaining acquired knowledge and technical skills. Attendance at courses, such as Pediatric Advance Life Support (PALS) developed by the American Heart Association (AHA) and the American Academy of Pediatrics (AAP), should be required particularly for emergency department and pediatric intensive care staff, and as well for all health care givers involved in the care of children. PALS guidelines provide a structured and well-described approach to the assessment and treatment of children, and hence, facilitate providers to conduct rapid evaluation and timely intervention for life-threatening conditions.

With the initiation of CPR, a team leader must be identified to assume the responsibility during the resuscitation phase. This team leader is responsible for assigning specific tasks to team members, ensuring timely administration of drugs, and ordering appropriate procedures. The team leader is also responsible for setting limits for the duration of the resuscitation attempt.

The timely recognition of unstable infant or child is important. The health care provider should be able to diagnose and help prevent an impending arrest by a systematic rapid clinical assessment of the cardiopulmonary and neurologic function (Table 263.3), followed by a secondary and tertiary assessment to focus on medical history, laboratory, radiographic, and other advanced tests that help to clarify the child's status. Based on the assessment, the child is categorized as:

1. Stable
2. In compensated respiratory failure or shock
3. In respiratory failure or shock
4. In cardiopulmonary failure

Verifying unresponsiveness is by calling loudly the child's name and tapping the child. The first responder should call for help once unresponsiveness is established and activate immediately the emergency medical services (EMS) system and get an automated external defibrillator (AED) if the child is 1 year of age or older, while the second responder continues

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Table 263.1
Causes of primary cardiac arrest in children

Children with complex congenital heart disease
Cardiomyopathies
Dysrhythmias
Submersion victims
In-hospital cardiac arrest in children

with CPR. If only one health care provider is present, he should activate the EMS and get an AED before starting CPR; however, for lone lay responder it is acceptable to start first and continue with CPR for five cycles (about 2 min) before activating the EMS system and getting an AED. One cycle of CPR for the lone rescuer is 30 compressions and 2 breaths. One CPR cycle for two rescuers is 15 compressions and 2 breaths. In case of only one rescuer and if there is no trauma, rescuer may carry a small child to the telephone. The EMS

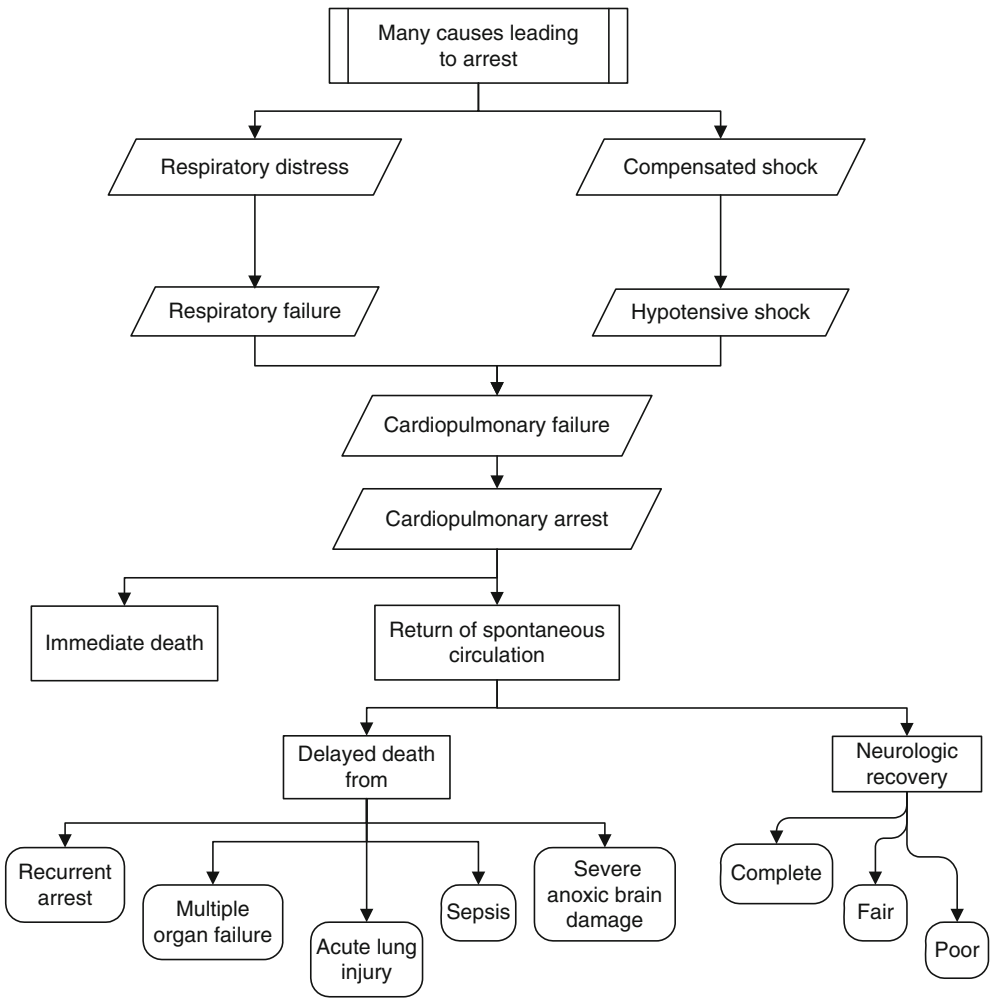


Figure 263.1
Algorithm showing the final common pathways in pediatric arrests

Table 263.2
Common etiologies of pediatric cardiopulmonary arrest

Respiratory failure
Upper airway
Airway obstruction
Croup
Epiglotitis
Foreign body
Suffocation
Strangulation
Trauma
Lower airway
Pneumonia
Asthma
Bronchiolitis
Foreign body-aspiration
Drowning
Smoke inhalation
Pulmonary edema
Trauma
Motor vehicle accident (MVA)
Burns
Electrical injuries
Cancer
Shock
Cardiogenic shock:
Congenital heart disease
Cardiomyopathy
Dysrhythmias
Hypovolemic shock:
Dehydration
Distributive shock:
Sepsis
Anaphylaxis
Central nervous system (CNS)
Meningitis
Encephalitis
Hydrocephalus
Tumors
Head trauma
Metabolic disorders
Hypoglycemia
Hyperkalemia
Hypocalcemia
Intoxication
Sudden infant death syndrome (SIDS)

Table 263.3
Rapid cardiopulmonary and neurologic assessment (ABCDE)

A. *Airway potency*
Able to maintain independently
Requires adjuncts/assistance to maintain
B. *Breathing*
Rate
Mechanics
Retractions
Grunting
Accessory muscles
Nasal flaring
Air entry
Chest expansion
Breath sounds
Stridor
Wheezing
Paradoxical chest movement
Color
C. *Circulation*
Heart rate
Blood pressure
Volume/strength of central pulses
Peripheral pulses
Present/absent
Volume/strength
Skin perfusion
Capillary refill time (consider ambient temperature)
Temperature
Color
Mottling

Table 263.3 (Continued)

D. *Disability (AVPU)* (Central nervous system perfusion)
Responsiveness
Awake: Recognizes parents
Voice: Responds to voice
Pain: Responds to pain
Unresponsive
Glasgow coma scale: GCS
Eye opening
Verbal response
Motor response
Pupillary response to light
Presence of hypoglycemia
(rapid bedside glucose or response to empiric administration of dextrose)
E. *Exposure*
(fever or hypothermia, skin findings, evidence of trauma)

dispatcher can guide the rescuer through the steps of CPR. If trauma is suspect or present, the second rescuer may assist by stabilizing the child's cervical spine (see below) and supporting the head and body to minimize turning, bending, or twisting of the head and neck, if the child must be moved for safety reasons.

Managing the Airway

The primary goal of cardiopulmonary resuscitation is to restore spontaneous circulation. The first priority, however, is managing the airway effectively, which must be open and stable, regardless of the underlying cause. Accessing and securing the airway with sufficient ventilation may need only simple maneuvers including the head tilt and chin lift or jaw positioning in trauma patients (for health care providers only), suctioning, pharyngeal airways, and bag-mask ventilation or mouth-to-mouth ventilation in older children and mouth-to-mouth and nose in infants. Endotracheal intubation is performed when these simple maneuvers fail to maintain adequate ventilation. It should be appreciated that the airway of children is easily obstructed because of obstruction of the hypopharynx by the relative large tongue and the neck soft tissue.

If no trauma is suspected, place the head in a neutral position by using a slight head tilt and chin lift "sniffing position" (*Fig. 263.2*). Through a proper positioning, the airway will be in alignment and accessible. If trauma is present or suspected, the cervical spine must be protected. The head should be in a neutral position avoiding hyperextension of the neck. Opening the airway is done by using the jaw thrust maneuver (*Fig. 263.3*). Suction may be

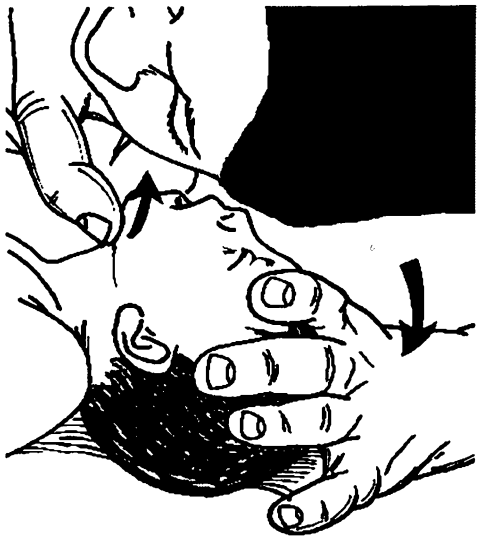


Figure 263.2
Opening the airway with the head tilt-chin lift maneuver. One hand is used to tilt the head and extending the neck. The index finger of the rescuer's other hand lifts the mandible outward by lifting on the chin. Head tilt should not be performed if cervical spine injury is suspected

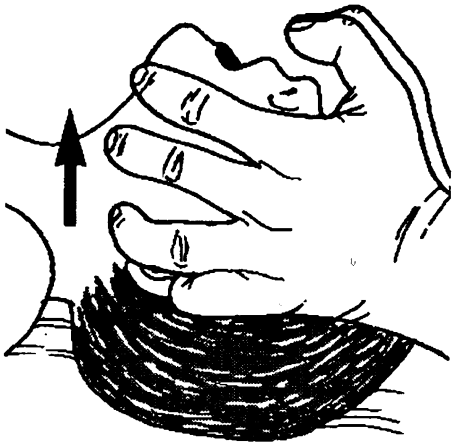


Figure 263.3
Opening the airway with the jaw thrust maneuver. The airway is opened by lifting the angle of the mandible. The rescuer uses two or three fingers of each hand to lift the jaw, while the remaining fingers guide the jaw upward and outward

needed to clean the airway of secretion, vomits, blood, and foreign bodies. If advanced airway management is provided and patient is intubated, checking for proper tube position especially when patient is moved and during transport is essential. Laryngeal mask airways are acceptable when used by experienced providers.

Resuscitation Maneuvers

After establishing unresponsiveness, calling for help, and getting an AED, two slow breaths are given while observing chest rise. If airway remains obstructed after proper repositioning and failure to obtain chest rise, a foreign body airway obstruction (FBAO) is suspected. To relieve a complete upper airway obstruction in a child, Heimlich maneuver (subdiaphragmatic abdominal thrusts) is recommended. This maneuver consists of quick upward abdominal thrusts delivered by placing the heel of the hand just above the umbilicus in the midline and covered by the other hand. The thrusts can be repeated until the FBAO is expelled. The recommendation for infants is to give four back blows, followed by four chest thrusts as indicated. In a hospital setting, removal of foreign objects with direct laryngoscopy using Magill's forceps may be more appropriate. If these procedures do not relieve obstruction and victim becomes unresponsive, endotracheal intubation is indicated. However, very rarely, endotracheal intubation fails to establish an effective airway. In such cases, a Transtracheal Catheter Ventilation to bypass the obstruction can be done by insertion of a 14–16 gauge intravenous cannula into the crycothyroid membrane. The adapter of a 3.0 mm endotracheal tube can be easily connected to the luer adapter of the catheter. This temporizing measure may support the application of oxygen and positive ventilation for a limited period of time and should only be performed by a properly trained health care provider.

Once patient is intubated and chest rise is observed, carotid pulses in older children or brachial pulses in infants are checked for no more than 10 s. If none is palpable, chest compressions deep enough (one-third to one-half the depth of the chest) to generate a pulse are begun with proper hand position and at a rate of 100/min (*Table 263.4*). The back of the patient is supported with the opposite hand or with a pediatric backboard. Chest compressions at a rate of 100/min and ventilation are to be performed simultaneously without pauses for ventilation. "Cycles" of CPR are no longer recommended. The rescuer should allow for complete chest recoil after a compression and minimize interruptions between compressions. The rescuer providing ventilation will deliver eight to ten breaths per minute at the same time. Chest compression effectiveness can be checked by palpating the brachial or femoral pulse. The cardiac output (CO), during chest compression, varies and depends on the effectiveness of the compression. CO during compression can reach between 20% and 80% of normal.

When these basic resuscitation maneuvers fail to restore circulation, advanced life support techniques are indicated. The patient should be attached to a cardiac monitor or paddles to observe the heart rhythm acting on abnormal rhythm in a timely and appropriate manner (see "Defibrillation"). A crucial step in resuscitation is the establishment of vascular access for administration of medications and fluids. The procedure should be done without interrupting CPR. If the approach to venous access (peripheral or central) is difficult and cannot be rapidly instituted, the intraosseous route should be used. The intraosseous or intramedullary infusion is recognized as effective for all resuscitative drugs and fluids in all ages. It is safe and simple. Meanwhile, for immediate drug

Table 263.4
Parameters for cardiopulmonary resuscitation in children

Age	Breathing rate	Compressions		Hand placement for compression
		Rate	Depth	
Neonates and infants	Initial two breaths at 1–1.5 s/breath than 20/min	100–120	0.5–1 in.	Two of three fingers at midsternum, one finger below nipple line, or two thumbs at midsternum with hands encircling chest. Ratio 15:2 (pause for ventilation)
1–7 years	Initial two breaths at 1–1.5 s/breath than 15–20/min	80–100	1–1.5 in.	Three fingers or heel of one hand, two fingers above xyphoid. Ratio 15:2 (pause for ventilation)
Over 7 years	Initial two breaths at 1–1.5 s/breath than 12/min	80–100	1.5–2 in.	Heel of both hands with body pressure, two fingers above xyphoid. Ratio 15:2 (pause for ventilation)

administration the endotracheal route can be used. The four resuscitative drugs acceptable for endotracheal administration are epinephrine, atropine, lidocaine, and naloxone. This in conjunction with the intraosseous route will allow early drug delivery while conventional intravenous access is sought. *Table 263.5* outlines the most important drugs used during resuscitation.

Resuscitation Drugs and Fluid

Resuscitative drugs and fluid are used to increase myocardial perfusion, contractility, pulse rate, and preload; decrease afterload; and correct hypoxemia and acidosis.

Oxygen

Effective airway management is essential for successful cardiopulmonary resuscitation. As respiratory failure is the most common cause leading to cardiac arrest in children, 100% oxygen should be given through a secured airway to prevent irreversible damage to vital organs (brain and heart).

Fluid

Fluid resuscitation in shock and circulatory collapse is essential, as shock can be the primary cause of

Table 263.5
Drug doses in pediatric cardiopulmonary resuscitation

Interventions	Dose	Route	Comment
Epinephrine for asystole or pulseless arrest (1:10,000 solution)	0.01 mg/kg (0.1 ml/kg)	IV, IO	Repeat every 3–5 min
Use (1:1,000 solution) for ET route	0.1 mg/kg (0.1 ml/kg)	ET	Repeat every 3–5 min
Epinephrine for bradycardia (1:10,000 solution)	0.01 mg/kg (0.1 ml/kg)	IV, IO	Same as above
Use (1:1,000 solution) for ET route	0.1 mg/kg (0.1 ml/kg)	ET	
Atropine sulfate 0.1 mg/ml	0.02 mg/kg	ET, IV, IO	Repeat every 5 min
			Minimum dose = 0.1 mg
			Maximum dose = 0.05 mg for infants and 1 mg for children
$NaHCO_3$ 8.4% solution 1 mEq/ml	0.5–1 mEq/kg	IV, IO	Use with caution and only after adequate ventilation
Glucose: D_{50} *W*. Mix D_{50} 1:1 with water or NS to get D_{25} W or D_{25} NS. Use D_{25} for children and $D_{12.5}$ for neonates	0.5–1.0 g/kg (1–2 ml/kg of $D_{12.5}$ for children $<$2 years)	IV, IO	Check Chemstix, give for value $\leq$ 45 mg/dl. Avoid IO administration if possible
Amiodarone 50 mg/ml, 15 mg/ml	5 mg/kg over 20–60 min (maximum 300 mg)	IV, IO	Repeat to maximum daily dose 15 mg/kg (2.2 g in adolescent)
Lidocaine HCL 10 mg/ml	1 mg/kg	ET, IV, IO	Repeat 1 mg/kg $\times$3, every 8 min then follow bolus with infusion at 20–50 mcg/kg/min
	2–3 mg/kg if given via ET route		
Calcium chloride or gluconate	5–7 mg elemental calcium	IV	Only with hypocalcemia
Naloxone 0.4 mg/ml and 1 mg/ml	0.4–2 mg (children)	ET, IV, IO	Pure opiate antagonist
	0.4 mg (neonates)		
Epinephrine infusion	Initial at 0.1 mcg/km/min	IV	Titrate to desired effect (0.1–1.0 mcg/kg/min)
Dopamine infusion	2–20 mcg/kg/min	IV	Titrate to desired effect
			Alpha adrenergic effect at dose $>$15 mcg/kg/min
Doputamine infusion	2–20 mcg/kg/min	IV	Titrate to desired effect

cardiopulmonary arrest. Initially, a bolus of 20 ml/kg of isotonic crystalloid or lactated Ringer's should be used and given over 10–15 min. In trauma patient blood transfusion may be indicated. Subsequent boluses up to 60 ml/kg and more may be needed in circulatory collapse.

Epinephrine

Epinephrine is the drug of choice and is indicated in all pediatric cardiac arrest setting when basic life support does not restore circulation. Restoration of circulation is attributed to the epinephrine action as it stimulates spontaneous cardiac contraction in asystole, in addition to the vigorous CPR and sufficient fluid resuscitation. During the administration of epinephrine, the alpha-adrenergic action of epinephrine will result in peripheral vasoconstriction and, subsequently, increase in both the systemic vascular resistance (SVR) and blood pressure leading to improvement in the coronary perfusion. An increase in the myocardial contractility and heart rate results from the beta-adrenergic action of epinephrine. The increase in SVR and arterial blood pressure during CPR will also improve the cerebral perfusion pressure.

Epinephrine can be given IV, IO and through the endotracheal tube; however, the dose varies depending on the route of administration. The preferred route for epinephrine administration is IV or IO. The recommended initial dose for symptomatic bradycardia and cardiac arrest (pulseless) is 0.01 mg/kg (0.1 ml/kg of the 1:10,000 solution), which is to be given through the intravenous or intraosseous route. Additional doses of epinephrine should be given every 3–5 min, if restoration of circulation did not occur. High dose of epinephrine in pediatric cardiopulmonary arrest is no longer recommended. The recommended endotracheal epinephrine dose is 0.1 mg/kg (0.1 ml/kg of the 1:1,000 solution). To reach an optimal endotracheal drug delivery, epinephrine should be diluted in 3–5 ml normal saline (NS) and instilled into the endotracheal tube through a suction catheter beyond the distal tip of the endotracheal tube and flushed afterward with 3–5 ml NS. It should be kept in mind that the use of two different dilutions of epinephrine can lead to possible errors in concentration selection and dosage.

Atropine

Atropine, a parasympatholytic drug, increases the heart rate. The resulted tachycardia post-atropine administration is usually well tolerated in pediatric patients. It can be administrated through the endotracheal route, IV, and IO. Atropine is effective in an unstable child with bradycardia and in bradyarrhythmia associated with second and/or third degree heart block, and also to block the vagal-induced bradycardia that may occur during suctioning and intubation maneuvers. Its usefulness in asystole is questionable.

Bradycardia (heart rate < 60/min) with hypoperfusion in children must be treated as cardiac output in neonates, infants, and small children is mainly heart rate dependent. Reasons for bradycardia should be sorted out and treated vigorously (hypoxia, hypothermia, hypoglycemia, acidosis, hypotension, and heart block). Epinephrine is more effective in the treatment of bradycardia with hypoperfusion and/or hypotension; however, for blocking vagal-induced bradycardia atropine is the drug of choice.

Atropine dose is 0.02 mg/kg administrated through intravenous and/or intraosseous route. For the endotracheal administration the dose is 0.03 mg/kg, which should be diluted in 3–5 ml NS, instilled into the endotracheal tube through a suction catheter beyond the distal tip of the endotracheal tube, and flushed afterward with 3–5 ml NS. Subsequent doses can be given every 5 min to a maximum of 0.5 mg in infants and 1.0 mg in children. It should be realized that most often bradycardia results from hypoxia, and treatment should initially be directed at ventilation and oxygenation.

Sodium Bicarbonate

Sodium bicarbonate has been used in cardiac arrest to treat acidosis. Severe acidosis (pH < 7.2) has many adverse effects on the cardiovascular function, and treatment of both metabolic and respiratory acidosis is essential. However, it is important to understand that the frequent observed combined respiratory and metabolic acidosis during cardiorespiratory arrest arise from the hypoxia-induced anaerobic metabolism and the respiratory failure. The most effective way to correct the acidosis (metabolic and respiratory) can be often achieved by providing adequate oxygenation, ventilation (decrease $PaCO_2$), fluid resuscitation, and epinephrine treatment to improve tissue perfusion. Increasing the epinephrine dose may counteract some of the effects of acidosis on the cardiovascular function.

There are numerous important side effects of sodium bicarbonate. Hypercapnia (increased PCO_2), which may worsen intracellular acidosis, and myocardial depression are some of the side effects of inappropriate bicarbonate use. For this reason, current recommendation from the

AHA suggests to consider the use of bicarbonate during CPR, only if severe metabolic acidosis is present in association with prolonged cardiac arrest. However, bicarbonate may be life-saving in unstable hemodynamic state (pre-arrest state), hyperkalemia, hypermagnesemia, and intoxication from tricyclic antidepressant or from other sodium channel blocking agents. If cardiac arrest continues after the airway is secured and adequate ventilation is provided, chest compression and epinephrine administration is accomplished. 1 mEq/kg of sodium bicarbonate can be given only through the intravenous or intraosseous route. Additional doses can be given if indicated after obtaining an arterial blood gas and after restoring circulation. If blood gases are not available or unreliable subsequent doses of 0.5 mEq/kg can be given over 1–2 min for every 10 min.

In cases of respiratory arrest, the encountered acidosis is mainly caused by respiratory failure leading to combined metabolic and respiratory acidosis and resolves with adequate ventilation and fluid resuscitation. Sodium bicarbonate in such cases is unnecessary and should be avoided. If sodium bicarbonate is excessively used, metabolic alkalosis may occur with adverse effects (e.g., Hypokalemia, decreased ionized calcium and shift of the oxy-hemoglobin dissociation curve to the left causing reduced oxygen delivery to the tissue). Other adverse effects of sodium bicarbonate are hypernatremia and hyperosmolarity. In general, the routine use of sodium bicarbonate remains controversial due to lack of convincing evidence of benefits and the presence of potential adverse effects.

Calcium

Calcium should not be used during resuscitation. There are very specific indications for the use of calcium during CPR, which are:

- Documented hypocalcemia
- Hyperkalemia
- Hypermagnesemia
- Calcium channel blocker overdose

The current recommended dose for calcium is 5–7 mg/kg elemental calcium. Subsequent doses should be given only if hypocalcemia (low serum ionized calcium level) persists.

Glucose

Hypoglycemia may occur during cardiopulmonary arrest of any etiology, particularly in neonates, infants, and small children. Any disease exposing this age group to extraordinary stress can lead to significant hypoglycemia; hence, checking for glucose level in any stressed young patient is essential to rule in or exclude the presence of hypoglycemia. This is more important in cardiopulmonary arrest, as energy resources are quickly depleted in young children due to increased loses (diarrhea and vomiting) or decreased intake prior to arrest. Once hypoglycemia is manifest, prompt treatment with glucose is essential. Hypoglycemia can imitate the signs and symptoms of patients in shock (tachycardia, poor perfusion, altered mental status, and hypotension); therefore, rapid bedside glucose test should be done in all neonates, infants, and small children who are critically unstable. The consequences of late recognition and/or late treatment of hypoglycemia can lead to brain damage and worsen the overall neurological outcome of patients surviving cardiopulmonary arrest. However, glucose should not be administrated routinely during pediatric cardiopulmonary resuscitation unless hypoglycemia is present, which is more common in neonates and small infants as mentioned before. The controversy in the routine use of glucose is based on the detrimental effects on the brain caused by hyperglycemia. If hypoglycemia is documented (i.e. rapid bedside glucose test), glucose administration of 0.5–1.0 g/kg should be given, diluted to a concentration of 25% for children and 12.5% for neonates (*Table 263.5*).

Complications of Resuscitation

Failure to restore spontaneous circulation after initiating appropriate advance life support (endotracheal intubation, adequate ventilation, oxygenation with 100% oxygen, cardiac compression, and standard administration of epinephrine), the patient's condition should be reassessed for complications. The first priority is to check the patency of the airway and the adequacy of the ventilation. Major problems include endotracheal tube obstruction with mucous plug, tube displacement (intubation of the esophagus or right mainstem bronchus), and tension pneumothorax. Confirmation of tube placement in the presence of a perfusing rhythm can be assessed by checking exhaled carbon dioxide (CO_2), and the placement of an esophageal detector device for children weighing >20 kg may be considered. In addition, adequate chest rise and good breath sounds will most likely eliminate esophageal intubation and endotracheal tube obstruction. Correct placement must be verified during transportation and whenever patient is moved. On the other hand, infants and small children assessment may be difficult, and direct laryngoscopy may be necessary to confirm proper intubation. However, if there is no improvement, a needle

thoracocentesis of both chest sides is indicated to rule out tension pneumothorax. *Table 263.6* shows the most important standard interventions during CPR in sequence. Circulatory complications including cardiac tamponade, fine ventricular fibrillation, and pulseless electrical activity (PEA) can occur and constitute a challenge during CPR. If there is still no improvement after a rapid and thorough reassessment of the airway patency and rhythm, a needle pericardiocentesis can exclude cardiac tamponade as a cause for lack of spontaneous circulation. Possible contributing factors during arrest that needs to be considered and treated are:

- Hypovolemia
- Hypoxia
- Hydrogen ion (acidosis)
- Hypokalemia/hyperkalemia
- Hypoglycemia
- Hypothermia
- Toxins
- Tension pneumothorax
- Trauma
- Tamponade, cardiac
- Thrombosis (coronary or pulmonary)

These can be remembered as the H's and T's of Pulseless Arrest.

Defibrillation

Defibrillation (asynchronous delivery of energy, i.e., the shock is delivered randomly during the cardiac cycle) and cardioversion (delivery of energy that is synchronized to the QRS complex) are methods of delivering electrical energy to the heart through the chest wall, in an attempt to restore the heart's normal rhythm. Defibrillation and cardioversion may be accomplished manually, which requires users to recognize the dysrhythmia and preselect the energy to be delivered. Automated external defibrillators (AEDs) are computerized machines that automatically diagnose ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT) and use voice prompts to instruct rescuers to defibrillate. The ease of use and reliability increased their popularity among health care givers. It can be used in children over 1 year of age according to the AHA and international guidelines.

The majorities of children with cardiopulmonary arrest are out-of-hospital arrests and are apneic and pulseless on arrival to the emergency department (ED). Respiratory failure and subsequently arrest is the leading cause for asystole cardiac arrest, which is not to be treated with defibrillation. However, recent studies have shown an increased incident of VF as the primary pathological rhythm in children 8 years of age and above with an incident

Table 263.6
Standard interventions in advanced life support

Airway	Breathing	Circulation
Head tilt	Mouth-to-mouth	Chest compressions
Chin lift	Mouth-to-face mask	Oxygen
Jaw thrust	Bag-valve-mask device Mechanical ventilation	Trendelenburg positioning
Abdominal compressions	Thoracocentesis	Electrocardiographic monitoring
Back blows		Vascular access:
Finger sweeps		Peripheral
Pharyngeal-suctioning		Central
Nasopharyngeal airway		Intraosseous
Oropharyngeal airway		Volume expansion
Endotracheal intubation		Inotropic agents
Needle cricothyroidotomy		Chronotropic agents
		Dromotropic agents
		Afterload modulator
		Acid-base buffers
		Calcium-potassium balance
		Cardioversion-defibrillation
		Pericardiocentesis

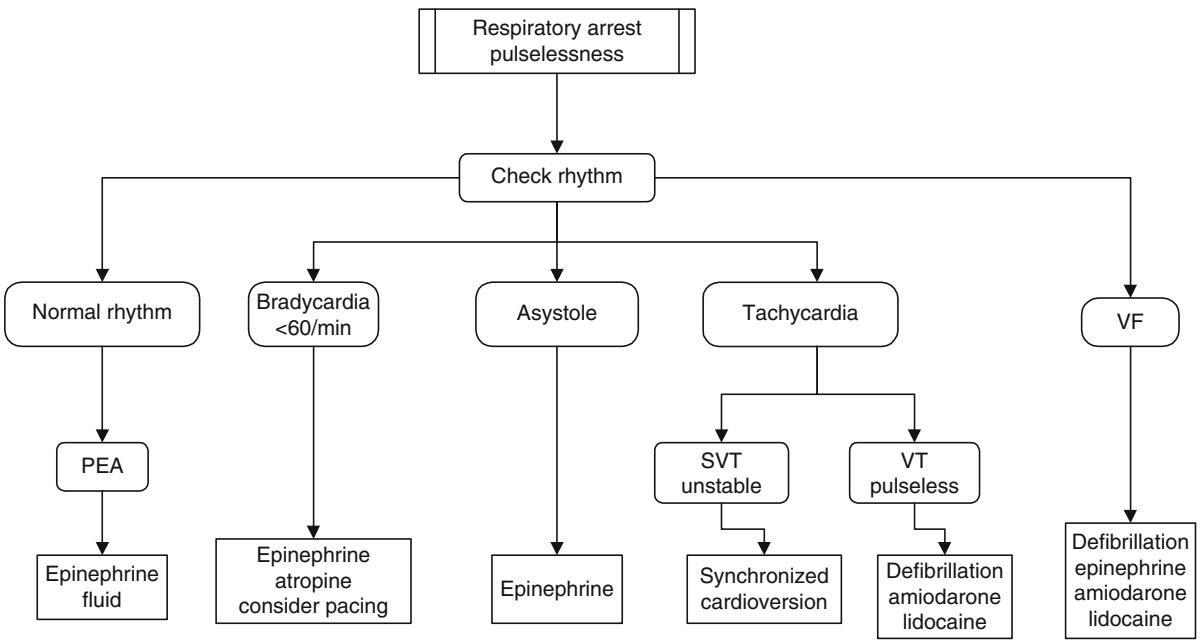
around 27%. VF and/or ventricular tachycardia (VT) are less common in infants and younger children below the age of 8 years. The fact that these new observations indicate that children who had out-of-hospital arrests can experience VF and their survival is better than those with asystole (35% vs 11%) once approached with early defibrillation mandates clinicians caring for children to be well skilled in the methods of counter-shock delivery.

VF and pulseless VT are mostly observed in children with complex congenital heart disease, submersion victims, and in children arresting in the hospital. Conditions that predispose to VF include ischemia, hypoxia, hypothermia, acidosis, and electrolyte imbalances. Defibrillation is the definitive treatment for VF and pulseless VT to reinstate normal cardiac depolarization and contraction, but is inappropriate for asystole (*Fig. 263.4*). If the problem is a fine ventricular fibrillation that is resistant to defibrillation, the use of epinephrine may convert the pattern from fine to coarse that is more responsive for defibrillation. It is, however, important to obtain a second lead to ensure that rhythm is a fine VF, rather than asystole.

Since the routine uses of the biphasic defibrillators have replaced the old monophasic defibrillators, three stacked shocks in rapid sequence are no longer recommended. Instead, one shock will be delivered as newer generation biphasic defibrillators have a first-shock efficacy around 90%. In the event of failure after the first-shock, subsequent shocks in rapid sequence are also likely to fail and in this setting CPR should follow for at least 2 min prior to a second defibrillation attempt. Coordination of shock delivery and chest compressions according to the AHA guidelines recommend that patients who experience unwitnessed arrest should undergo five cycles or 2 min of CPR prior to attempted defibrillation.

For defibrillation, the current recommendation suggests an initial energy dose of 2 J/kg and the subsequent doses of 4 J/kg using the proper paddles or electrode pads (size 4.5 cm for infants and 8–13 cm for older children) with a good electrode interface (i.e., electrode cream). The paddles or electrodes are placed on the chest so that an adequate portion of the delivered shock passes through the myocardium. The anterior/apex position is preferred and for infants the anterior/posterior position to avoid pads contacting each other.

Defibrillation dose is 2 J/kg for the first attempt. If VF or VT without pulse continues after defibrillation, a second attempt with 4 J/kg is made after 2 min of continuous CPR. Subsequent attempts with 4 J/kg remain the standard defibrillation dose for children with VF and pulseless VT.



PEA = Pulseless electrical activity, SVT = supraventricular tachycardia, VF = ventricular febrilation, VT = ventricular tachcardia

Figure 263.4
Algorithm for drugs and defibrillation during CPR

Hence, in the case that VF or pulseless VT persists, a third attempt should be performed with the same energy. CPR should be continued between and after these attempts. If ventricular fibrillationVF or pulseless ventricular tachycardia persists or occurs frequently in the absence or nonavailability of amiodarone, the use of lidocaine may help. Cardiac rhythms that should not be treated with electrical current include sinus rhythm, stable supraventricular tachycardia (SVT), asystole, pulseless electrical activity, and bradycardia.

Cardioversion is the treatment of choice in unstable patients with organized cardiac rhythms such as SVT, which constitutes the most common pediatric arrhythmia requiring cardioversion. Other less frequent rhythms requiring cardioversion are atrial fibrillation, atrial flutter, or ventricular tachycardia with palpable pulse. The dose of synchronized cardioversion for the first attempt is 0.5–1 J/kg and the subsequent doses are 2 J/kg.

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264 Shock Syndrome

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Introduction

The clinical syndrome of shock is one of the most dramatic, progressive, and life-threatening conditions faced by the medical staff in the pediatric critical care setting.

Shock is a condition of sustained and progressive circulatory dysfunction that results in tissue hypoperfusion and inadequate delivery of oxygen and substrates to meet tissue metabolic demands. The status of anaerobic metabolism generates less intracellular adenosine triphosphate (ATP) to meet cell requirements, resulting in accumulation of lactic acid. This acute energy failure will lead to generalized cellular hypoxia and derangement of critical biochemical processes including the delay in removal of the end products of metabolic processes. Once these abnormalities become irreversible it will subsequently result in cell death. Shock may be the end result of many different diseases or injuries. If shock is not early recognized and treated adequately, multiorgan failure (MOF) and death can be the outcome (shock is the final common pathway to death). It accounts for more morbidity and mortality in children worldwide than any other diagnosis; dehydration and hypovolemic shock alone result in more than two million deaths in infants and children worldwide. Mortality rate in children with sepsis is still around 10%. Morbidity may be widespread and can include renal failure, brain damage, gut ischemia, hepatic failure, metabolic derangements, diffuse intravascular coagulation (DIC), acute respiratory distress syndrome (ARDS), and cardiac failure.

Inadequate tissue perfusion and decreased oxygen delivery can result from either limitation or maldistribution of blood flow, which can be the result of failure of one or more of three components of the intact circulation:

1. An adequate circulating blood volume to maintain proper preload status. In the event of hemorrhagic hypovolemia, oxygen carrying capacity is inadequate as well as the preload, resulting in the manifestation of shock.
2. The heart as a pump to generate enough flow to meet the body's variable demands at rest and during stress. Once cardiovascular compromise occurs various compensatory mechanisms drive preload, cardiac contractility, and afterload to interact to improve stroke volume (SV) and cardiac output (CO). However, SV in neonates and infants is relatively fixed. The response to improve cardiac output in this group during hypoperfusion is in an increase in heart rate (tachycardia) rather than an increase in SV. Hence, newborns and infants are particularly dependent upon heart rate to increase their cardiac output.
3. The vascular system as a network of arteries and veins that is able to expand and constrict in order to regulate the flow of blood to various organs and body compartments. By an increase of the systemic vascular resistance (SVR) the perfusion pressure for vital organs (brain, heart) will be maintained in the event of a decrease in cardiac output.

The limitation or maldistribution of blood flow will lead to inadequate tissue perfusion and oxygen delivery leading to the clinical manifestation of shock. The effects of inadequate tissue perfusion and poor oxygen delivery are initially reversible if early goal-directed therapeutic interventions are initiated to reverse the poor tissue perfusion and improve oxygen delivery. However, because of the dynamic and progressive nature of shock, three clinical phases of shock can be identified, which are:

1. *Compensated phase*: A cascade of intrinsic compensatory mechanisms is activated in this phase and patient is presented with early signs of shock (compensated shock). The difficulty to recognize the early stage of shock is explained by the great ability of children to compensate thus, making the diagnosis in this phase very challenging. In the compensated phase, perfusion of vital organs (brain, heart) is maintained by the same intrinsic compensatory mechanisms. Blood pressure at this stage is still within normal range.
2. *Uncompensated phase*: With failure to provide adequate treatment, the patient's intrinsic compensatory mechanism fails and becomes hypotensive (hypotensive shock). In this phase, signs of end organ hypoperfusion are obvious such as altered mental status, oliguria or

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anuria, prolonged capillary refill >2 sec., hypoxia, and hypotension. From this point onwards progression to cardiovascular collapse and subsequently cardiac arrest is only a matter of minutes if aggressive therapeutic intervention is not rapidly applied.

3. *Irreversible phase*: Irreversible shock occurs when significant damage to vital organs is present. At this stage cellular metabolism is no longer able to generate enough energy to sustain cell viability. In many cases with irreversible shock states multiorgan failure will occur and mortality is high.

Children have the ability to compensate very well at the early stage of shock regardless of the cause. Therefore, it is difficult to recognize that the patient is in shock at this stage. However, early diagnosis and treatment of compensated stage of shock is crucial to prevent a catastrophic outcome. In the early stage, most shock forms are similar in their presentation (tachycardia, prolonged capillary refill and irritability) and compensatory mechanisms (increase in heart rate, cardiac contractility, SVR and venous tone). The initial management for all shock forms is in providing adequate oxygenation (100% oxygen) through secured airway and stabilizing the hemodynamic condition (fluid resuscitation, use of inotropes and vasopressors). This initial management is time sensitive and should happen within the first hour of arriving in the hospital. The process is described as early goal-directed therapy for shock and refers to the rapid initiation of aggressive systematic approach to resuscitation regardless of the etiology. During the initial stabilization process, clues to the exact cause or causes of shock must be diagnosed so that subsequent appropriate therapy can take place. The presence of more than one cause for shock in a critically ill patient can constitute a challenge to the care givers during the initial presentation. As an example a child with suspected septic shock can also have significant hypovolemia and cardiac depression. This frequent scenario of overlapping shock forms should be considered and needs early and careful diagnosis of causes for proper therapeutic measures.

Shock Forms

Several etiologic classifications of shock are recognized (◉ *Table 264.1*). The major categories are as follows:

1. Hypovolemic – fall in intravascular volume
2. Cardiogenic – fall in cardiac output
3. Distributive/Vasogenic (most often due to sepsis) – fall in systemic vascular resistance

Hypovolemic Shock

Hypovolemic shock is the most common type of shock encountered in the pediatric population. It is caused by acute decrease in intravascular volume relative to the vascular capacity. The reduction in the intravascular volume is such that ventricular filling (preload) is insufficient and effective tissue perfusion cannot be maintained. In general, previously healthy children can compensate for acute hypovolemia if volume loss does not exceed 15–20% by activating a chain of endogenous (adrenergic) compensatory mechanisms. These compensatory mechanisms will increase the cardiac output by increasing the heart rate, SVR and cardiac contractility to maintain normal blood pressure. Consequently it will result in a redistribution of blood flow from peripheral structures (skin, muscle, kidneys, and splanchnic organs) to the vital organs, heart and brain. At this stage, preserving adequate tissue perfusion to the rest of the body may not be achieved and as a result signs of hypoperfusion will manifest such as prolonged capillary refill >2 sec., cool extremities and low urine output. However, if volume loss exceeds 30%, hypovolemic shock will result in the development of hypotension, cardiovascular collapse, and cardiac arrest. Time to progress from compensated to uncompensated status may take hours; however, it takes only minutes to cardiovascular collapse and subsequent cardiac arrest if shock progresses to uncompensated status. Therefore, delayed or under diagnosed severe dehydration can lead to significant morbidity and mortality. Dehydration and hypovolemic shock result in more than two million deaths annually in infants and children worldwide. In the United States, fluid and electrolyte imbalances from acute gastroenteritis result in 1.5 million outpatient visits, 200,000 hospitalizations, and 300 deaths/year. Severely dehydrated children may have increased morbidity such as protracted vomiting, electrolytes disturbances (e.g., hypernatremia, hyponatremia, and hypoglycemia), metabolic acidosis, and acute renal failure leading to hypovolemic shock within few hours. The common infectious etiologies for gastroenteritis include bacterial causes such as *Salmonella, Shigella, Campylobacter* species, and *Escherichia coli,* and viral causes, such as rotaviruses, adenoviruses, norovirus, and enteroviruses.

Trauma is a leading cause of mortality in older children (>1 year) and acute hemorrhage is a major component leading to death in traumatic children. Rapid loss of intravascular volume will reduce ventricular preload, resulting in decreased stroke volume, cardiac output, and oxygen delivery (DO_2). To prevent cardiovascular collapse, hemorrhagic shock must be quickly identified

Table 264.1
Shock forms and etiologies

Hypovolemic shock	Cardiogenic shock	Distributive/vasogenic shock
1- Blood loss:	1- Cardiomyopathy:	1- Septic shock
- Trauma (external and internal)	- Myo-, peri-, and endocarditis	2- Anaphylactic shock
- Fractures	- Hypoxia	3- Neurogenic shock
- GI-bleeding, intraabdominal	- Ischemia	4- Intoxication (i.e., barbiturate)
- ICH (neonates: IVH/ICH)	- Acidosis	
- Surgery	- Hypoglycemia	
2- Water loss:	- Hypothermia	
- Vomiting	2- Dysrhythmia:	
- Diarrhea	- Bradycardia	
- Diabetic ketoacidosis (DKA)	- AV block	
- Diabetes insipidus (DI)	- SVT	
- Heat stroke	- VT	
- Adrenal insufficiency	3- Congenital heart disease	
3- Plasma loss:	- Aortic stenosis	
- Trauma	- Coarctation	
- Burns	- Severe pulmonary stenosis	
- Hypoproteinemia (i.e., Nephrotic syndrome)	- Left heart hypoplasia	
- Capillary leak (i.e., Sepsis, anaphylaxis)	4- Pneumothorax	
- Third spacing (i.e., Peritonitis, intestinal obstruction)	5- Tamponade	
	6- Pulmonary embolus	
	7- Drug intoxication	

GI gastrointestinal, *ICH* intracranial hemorrhage, *IVH* intraventricular hemorrhage, *DI* diabetes insipidus, *SVT* supraventricular tachycardia, *VT* ventricular tachycardia

and treated (see *Table 264.2* Classification of hemorrhagic shock). Less frequent are the nontraumatic bleeding such as gastrointestinal hemorrhage, acute intraventricular hemorrhage of the newborn, and postoperative hemorrhage. Sequestration crises in sickle cell anemia can occasionally lead to acute hypovolemic shock. Other causes of hypovolemic shock include capillary leak (i.e., sepsis) and tissue third spacing (i.e., peritonitis) where patients are intravascular volume depleted in spite of their edematous appearance (see *Table 264.1*).

On physical examination, the most helpful signs for detecting dehydration (intravascular and interstitial depletion) in children regardless of etiologies are prolonged capillary refill >2 sec., absence of tears, abnormal skin turgor, degree of sunken eyes, mucous membrane dryness, degree of depressed (sunken) anterior fontanel abnormal respiratory pattern, altered mental status, and general appearance. *Table 264.3* shows the clinical signs and symptoms of volume loss in infants and children according to the severity of hypovolemia.

Cardiogenic Shock

Cardiogenic shock results from cardiac dysfunction (pump failure) manifested as impaired myocardial contractility and dysrhythmias leading to poor cardiac output and high SVR. When heart failure is present, neurohumoral vasoactive mechanisms are activated resulting in increasing systemic vascular resistance. Increasing SVR (afterload) increases the work load on the left ventricle and decreases cardiac output, worsening the cardiogenic shock. Proper use of inotropes and reduction of the afterload are necessary to treat progressive heart failure and stop the vicious cycle. Reasons leading to cardiogenic shock are:

1. Decrease in the preload mainly as a result of obstruction to venous return such as tension peumothorax and cardiac tamponade
2. Congenital heart defects with left ventricle outflow obstruction leading to an increase in afterload

Table 264.2
Classification of hemorrhagic shock

	Class I (very mild)	Class II (mild)	Class III (moderate)	Class IV (severe)
Percent blood volume loss	<15%	15–30%	30–40%	>40%
Heart rate	Normal	Slightly	Moderately increased	Markedly increased
Respiratory rate	Normal	Slightly increased	Moderately increased	Markedly increased, markedly decreased, or absent
Blood pressure	Normal or slightly increased	Normal or slightly decreased	Decreased	Decreased
Pulses	Normal	Normal or decreased peripheral	Weak or absent peripheral	Absent peripheral, weak or absent central
Skin	Warm and pink	Cool extremities, mottled	Cool mottling extremities, or pallor	Cold extremities with pallor or cyanosis
Capillary refill	Normal	Prolonged	Markedly prolonged	Markedly prolonged
Mental status	Slightly anxious	Mildly anxious, confused, combative	Very anxious, confused, or lethargic	Very confused, lethargic, or comatose
Urine output	Normal	Slightly decreased	Moderately decreased	Markedly decreased or anuria

Data from: Hazinski, MF, Barkin, RM. Shock. In: Pediatric emergency medicine: Concepts and clinical practice, Barkin, RM (Ed), Mosby-Yearbook Inc, St. Louis, MO 1997. p. 118; and Waltzman, ML, Mooney, DP. Major trauma. In: Textbook of Pediatric Emergency Medicine, Fleisher, GR, Ludwig, S, Henretig, FM (Eds), Lippincott Williams & Wilkins, Philadelphia 2006. p1354

Table 264.3
Clinical signs and symptoms of hypovolemia in children

Clinical signs	Mild 5–7%	Moderate 8–10%	Severe >10%
Skin color	Pale	Gray	Mottled
Perfusion of extremities	Warm to hands/feet	Warm to elbow/knee	Cool throughout
Capillary refill time	1–3 sec	3–5 sec	Over 5 sec
Heart rate	Normal	↑	↑↑
Respiratory rate	Normal	Normal	↑
Pulses	Normal	Distal weak or absent	Proximal weak or absent
Skin turgor	↓	↓↓	Tenting
Eyes	Normal	Sunken	Markedly sunken
Mucous membranes	Dry	Very dry	Cracked
Fontanel	Flat	Depressed	Sunken
Blood pressure	Normal	Normal	↓
Mental status	Normal	Lethargic	Lethargic to coma
Urine output	↓	↓↓	Anuric

3. Poor myocardial contractility resulting mainly from cardiomyopathies of different etiologies

On the other hand, cardiogenic shock during infancy and childhood may represent clinically a diagnostic and therapeutic challenge for several reasons, including:

1. Some of the signs and symptoms of cardiogenic shock are similar to those of hypovolemic shock, for example, poor perfusion (prolonged capillary refill), cool extremities, increased heart rate, altered mental status, and decreased urine output.

2. Cardiac failure can occur in patients with shock that is not primarily due to a myocardial insult.
3. Myocardial dysfunction is frequently a late manifestation of shock of any etiology.

Table 264.4
Reasons leading to cardiogenic shock

Decrease in preload
Obstruction to venous return
Tension pneumothorax
Hemopericardium
Pneumopericardium
Pericardial effusion
Increase in afterload
Obstructive congenital HD
Increase in PVR (i.e., massive pulmonary embolism)
Increase in SVR (i.e., late stage of sepsis)
Decrease in myocardial contractility
Cardiomyopathy due to
Myocarditis
Pericarditis
Endocarditis
Hypoxia
Ischemia
Acidosis (pH $<$ 7.2)
Hypoglycemia
Hypocalcemia
Hypothermia

History of congenital heart disease (CHD), signs of heart failure, and worsening of clinical condition during aggressive fluid management should be immediately linked to a cardiogenic etiology, particularly in those patients without readily apparent cause for shock. Since treatment of this condition depends on restoring and improving pump function, continuing with aggressive fluid administration may cause rapid deterioration. In volume depleted patients with cardiogenic shock, fluid should be administered slowly and given in boluses of 5–10 ml/kg. Reasons for cardiogenic shock apart from CHD are, for example, cardiomyopathies, acute myocarditis, subacute bacterial endocarditis, and drug intoxication (*Table 264.4*).

Cardinal signs of cardiogenic shock include the presence of gallop rhythm, respiratory distress, hepatomegaly, cardiomegaly, and pulmonary venous congestion seen on the chest radiography (*Table 264.5*).

Distributive Shock

Distributive shock is a condition that occurs when inappropriate distribution of blood flow and increased capillary permeability are present. Septic shock is the best example of this form of shock. Timely recognition and treatment of pediatric septic shock improves outcome and saves lives. The early recognition of tachycardia, bounding pulses, prolonged capillary refill $>$2 s, hypoxia, and hypotension on arrival to the hospital sets out a time-sensitive goal-directed treatment approach starting by providing adequate oxygenation (100%), followed by establishing emergency vascular access to enable a goal-directed stepwise administration of fluid and to start infusion of dopamine (can be given through peripheral lines or

Table 264.5
Historical information and clinical signs in different shock forms

	Hypovolemic shock	Cardiogenic shock	Distributive shock
History:	Trauma, vomiting and/or diarrhea	CHD, cardiac surgery, poor feeding, and respiratory distress	Fever, lethargic, poor skin color, and irritability
Clinical signs:			
Heart rate	Increased	Increased	Increased
Chest x-ray			
1- Heart size	Small	Large	Small
2- Lungs	Clear	Wet	Clear (in the early stage)
Gallop rhythm	Not present	Present	Not present
Capillary refill time	Prolonged	Prolonged	Normal (in the early stage)

intraosseous access until central line is established) and epinephrine for reversal of shock within the first hour of arriving in the emergency department. Lastly broad-spectrum antibiotics should be also given within the first hour of arrival to the hospital.

Clinical Recognition of Shock State, Assessment and Monitoring

Survival from shock requires early diagnosis and treatment. Once decompensation and significant hypotension develop, the risk of death is high. Usually (past and present medical) history taken from the parents, and the clinical evaluations taken by the medical team caring for the child prior to admission to the pediatric intensive care unit will facilitate early etiologic classification of shock, and help in directing appropriate treatment (i.e., history of vomiting and diarrhea suggest hypovolemia; history of fever, lethargy, and poor skin color suggest sepsis; history of CHD with poor feeding and respiratory distress suggest heart failure). The clinical presentation of shock, in general, has the following common findings:

- Tachycardia: This is one of the important early indicators of shock. Benign causes of tachycardia are very common (fever, pain, and anxiety) and needs to be ruled-out, particularly at the early stage of shock where most signs and symptoms of shock are not yet very clear.
- Tachypnea: This is most likely to compensate for metabolic acidosis. However, in progressive and advanced stage of shock tachypnea fail to compensate metabolic acidosis.
- Poor skin perfusion: This is present in the form of prolonged capillary refill time >2 s, cool extremities, pale, clammy and mottled skin. Skin hypoperfusion is caused by vasoconstriction to spare the flow and redirect it to vital organs (brain, heart).
- Hypoxia: If shock continues to progress, patient will become hypoxic (O_2 saturation < 95%) requiring oxygen supplement.
- Oliguria: Shunting the renal circulation to the vital organs will lead to renal hypoperfusion resulting in oliguria and anuria in severe shock.
- Hypoglycemia: Hypoglycemia can present in shock particularly in newborns and infants, and requires prompt recognition and treatment.
- Impaired mental status: In compensated shock, normal mental status indicates preserved brain perfusion; however, in deep shock hypoperfusion of the brain is present and altered mental status is apparent.
- Metabolic acidosis: As an outcome of energy failure during shock lactic acid accumulates as cells switch to anaerobic metabolism resulting in metabolic acidosis.
- Hypotension: Hypotension occurs once shock progresses to uncompensated phase. It is a very late and ominous finding. Blood pressure below the 5th percentile for age is defined as hypotension as follows:

Age	Minimum systolic blood pressure (5thpercentile)
– 0–1 month	60 mmHg
– >1 month to 1 year	70 mmHg
– 1–10 years of age	70 mmHg + (2 x age in years)
>10 years of age	90 mmHg

It cannot be overemphasized that the most effective and sensitive physiological monitoring available is the repeated and careful examination of the child's physical status by a competent observer. *Tables 264.5* gives a summary of historical and clinical signs that will help in differentiating shock forms. *Table 264.8* shows the lower values (5th percentile) for heart rate, leukocyte count, and systolic pressure and the upper values (95th percentile) for heart rate, respiration rate, and leukocyte count.

Treatment of Shock States

When confronted with a child in shock, etiology can often be determined from the history and physical examination as discussed earlier. Specific treatment of shock conditions follows as any disease process resuscitation and stabilization. Immediate priorities include establishment of patent airway, administration of 100% oxygen, and establishing IV access (*Fig. 264.1*). This initial management has to be goal directed as mentioned earlier; it is time sensitive and should happen within the first hour of arriving in the emergency department. The American Heart Association recommends quick establishment of intraosseous access in children of any age if peripheral intravenous access is not rapidly obtained.

Hypovolemic Shock

Identification of life-threatening conditions and rapid management is crucial in hypovolemic children. Securing the airway, oxygen supplement and stabilizing the

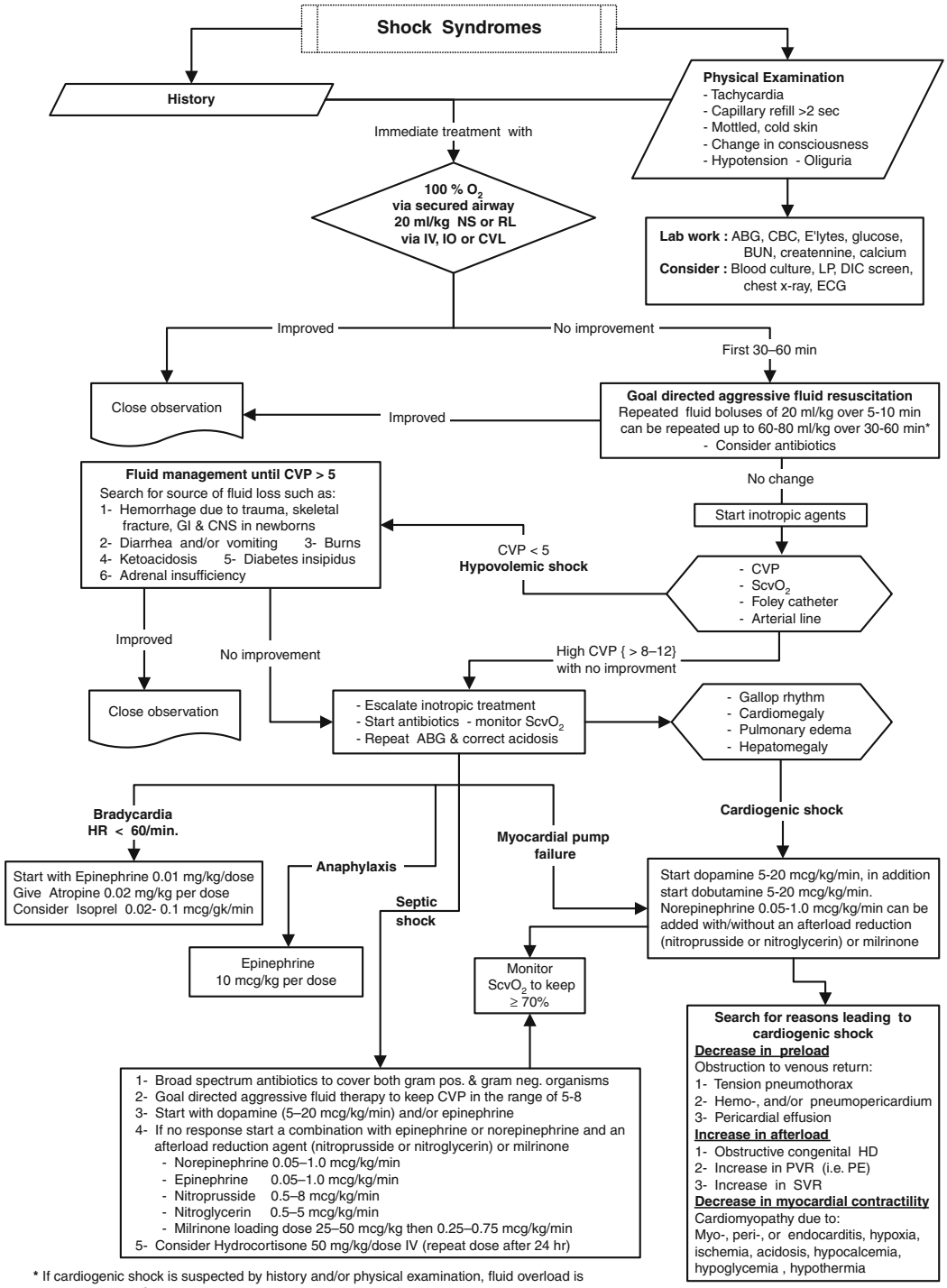

Figure 264.1
Algorithm for treatment of shock syndromes

circulation are the initial steps. If peripheral intravenous access is not rapidly obtained, intraosseous access should be established quickly in patients of any age. Once vascular access is established, aggressive fluid resuscitation with boluses of 20 ml/kg isotonic saline or Ringer's lactate is given. If there is no improvement and hypotension or hypoperfusion remains, patient should receive additional boluses over 5–10 min. Fluid resuscitation can be repeated in some cases up to 60–80 ml/kg until response is evident. Generally the observation is that fluid resuscitation is not given sufficiently to severely dehydrated children. Caution is warranted with aggressive fluid resuscitation in cases of apparent cardiac depression and/or heart failure (i.e., cardiogenic shock) as it may worsen the cardiovascular status. In most situations initiating fluid resuscitation with crystalloid is sufficient, unless obvious hemorrhage is present or hypotension persists. The blood volume should be augmented with a blood transfusion (type O negative, type specific, or cross-matched blood). Any source of fluid loss should be identified. Following the trend of central venous pressure (CVP) readings is very useful in guiding the fluid management. If the child is still hypovolemic, additional fluids are given as mentioned until CVP reading is 5 mmHg or more indicating normovolemia (*Fig. 264.1*). High CVP readings >12 mmHg with persistent hypoperfusion is against hypovolemia as the sole etiology and fluid administration risks fluid overload, and other causes such as right heart failure should be considered. Response to treatment is indicated by an improvement in blood pressure, tissue perfusion (capillary refill time), decreasing heart rate, and an increased urine output. Should the signs of shock persist with an appropriate filling pressure (CVP), vasoactive and inotropic therapy is to be considered. In the absence of central venous access, vasoactive medications and inotropes should not be delayed when clinically indicated. Investigations including arterial blood gases, electrolytes, glucose, chest x-ray, septic workup, and coagulation studies are important to guide therapy and help in the recognition of complicated shock course and possible comorbid causes.

Cardiogenic Shock

The aim of treatment in cardiogenic shock is to increase the cardiac output. This can be achieved by increasing the heart rate and stroke volume. Since neonates have noncompliant ventricles with limited ability to increase stroke volume, cardiac output is heart rate dependent. For this reason, treatment of cardiogenic shock conditions involving neonates with low heart rate (below 120/min) should include atropine or a sympathomemetic agent. Drugs that can improve both the heart rate and contractility are inotropes (i.e., dopamine and epinephrine). Isoproterenol infusion may be used in treating relative or absolute bradycardia (associated with poor perfusion) resistance to atropine (*Fig. 264.1*). Limitation for increasing the heart rate in an infant is obstructive heart lesions. However, heart rate above 170/min should be avoided because stroke volume at that point starts to decrease.

Stroke volume is affected by preload, afterload, and contractility. Maximizing myocardial performance is ensured by optimizing the preload (carful fluid challenges with 10 ml/kg to avoid fluid overload as it can increase pulmonary venous pressure and result in pulmonary edema, diuretics to reduce pulmonary edema, and the use of venodilators), decreasing the afterload (sedation, correction of hypothermia and vasodilators), and improving contractility (oxygen treatment, use of inotropic drugs, and correction of acidosis and other metabolic abnormalities). Arrhythmias should be treated if present. After reaching an optimum CVP level (after which increasing CVP does not improve stroke volume), further volume substitution should be avoided. By this stage an increase in the afterload or decrease in the contractility is most likely present, indicating a high systemic vascular resistance. Treatment can be initiated with a continuous infusion of dopamine, starting at 5–10 mcg/kg/min, and titrating the infusion until improved tissue perfusion is restored (*Fig. 264.1*). The use of dobutamine (starting at 5–10 mcg/kg/min) and/or epinephrine (0.05–1.0 mcg/kg/min) may be necessary. Utilizing the benefits of a strong inotropic agent, and at the same time blocking the undesired vasoconstriction effect can be achieved by using a combination of a strong inotropic drug (epinephrine 0.05–1.0 mcg/kg/min or norepinephrine 0.05–1.0 mcg/kg/min) and an afterload reduction agent (nitroprusside 0.05–8.0 mcg/kg/min or nitroglycerin 1–5 mcg/kg/min). On the other hand, the use of milrinone (25–50 mcg/kg as loading dose then 0.25–0.75 mcg/kg/min), a phosphodiesterase III Inhibitor agent, produces a positive inotropic effect with concurrent vasodilation hence, reducing afterload (decreasing SVR), while at the same time increasing cardiac contractility. Often milrinone is used in combination with epinephrine to offset epinephrine's alpha receptor effects, and also as a first-line drug together with small doses of other inotropes to improve tissue perfusion provided that blood pressure is maintained. *Table 264.6* shows commonly used cardiovascular drugs in shock with their actions, advantages, and side effects.

Table 264.6
Pharmacologic support of the shock patient

Drug	Dose	α-effect	β-effect	Vasodilator effect	Actions and advantages	Disadvantages and side effect
Dopamine	1–20 mcg/kg/min	+ to +++ (dose-related)	+ to +++ (dose-related)	At low doses, renal vasodilation occurs (dopaminergic receptors)	Moderate inotrope, wide and safe dosage range, short half-life.	May cause worsening of pulmonary vasoconstriction
Dobutamine	1–10 mcg/kg/min	0	+++		Moderate inotrope, less chronotropic, fewer dysrhythmias than with isoproterenol or epinephrine.	Marked variation among patients
Epinephrine	0.05–1 mcg/kg/min	++ to +++ (dose-related)	+++		Significant increases in inotropy, chronotropy, and SVR.	Tachycardia, dysrhythmias, renal ischemia, systemic and PVR
Norepinephrine	0.05–1 mcg/kg/min	+++	+++		Powerful vasoconstrictor (systemic and pulmonary); rarely used except possibly in patients with very low SVR or in conjunction with vasodilator.	Reduced cardiac output if afterload is too high, renal ischemia
Isoproterenol	0.05–1 mcg/kg/min	0	+++	Peripheral vasodilation	Significant increase in inotropy and chronotropy. SVR can drop, and PVR should not increase and may decrease.	Significant myocardial oxygen consumption increases, tachycardia, dysrhythmias
Nitroprusside	0.05–8 mcg/kg/min	0	0	Arterial and venous dilation (smooth muscle relaxation)	Decreases SVR and PVR, very short-acting. Blood pressure returns to previous levels within 1–10 min after infusion is stopped.	Toxicities (thiocyanates and cyanide), increased intracranial pressure and ventilation–perfusion mismatch, methemoglobinemia, increased intracranial pressure
Milrinone	0.25–0.75 mcg/kg/min	0	0		Phosphodiesterase III inhibition. Decreases SVR and PVR, increases myocardial contractility with only mild increase in myocardial O_2 consumption. Usually used with low-dose dopamine or dobutamine.	

0, no effect; +, small effect; ++, moderate effect; +++, potent effect
PVR pulmonary vascular resistance, *SVR* systemic vascular resistance

The simultaneous use of these drugs can result in hemodynamic improvement and an increase in the cardiac output by improving the contractility and decreasing the SVR. However, this strategy of treatment has to be well balanced depending on the circulation status, and requires monitoring of arterial blood pressure, CVP, $ScvO_2$ and, if possible, a pulmonary artery catheter (PA). The importance of treating hypoxemia, acidosis, hypoglycemia and other electrolytes disturbance, and hypothermia to improve both the contractility and the efficiency of the inotropic drugs should be emphasized. *Table 264.4* shows reasons leading to cardiogenic shock.

Septic Shock

Sepsis is the most likely cause of distributive shock in children. Once sepsis is suspected, prompt treatment with broad-spectrum antibiotics to cover both gram-negative and gram-positive organisms is essential. It should be given within the first hour of arriving in the Emergency Department. Specific antibiotic treatment follows the sensitivity of the organisms. The source of infection must be treated including drainage and debridement of abscesses. Because of a decrease in the systemic vascular resistance (SVR) during the early stage of septic shock (hyperdynamic stage), the vascular capacity is increased and the circulating blood volume is pooled to the periphery leading to relative volume depletion. Furthermore, capillary leak leads to third spacing of fluid. The consequence is relative and absolute intravascular volume depletion. The proper management in this stage is the early goal-directed aggressive volume replacement therapy of 60–80 ml/kg within 30–60 min, in addition to antibiotics. Despite early and adequate fluid resuscitation hypoxia, acidosis, and hypotension may persist particularly in the later stage of septic shock (cardiogenic stage); increase in SVR, myocardial dysfunction, maldistribution and decrease in cardiac output (CO) dominate the clinical picture (*Table 264.7*). This condition known as fluid-resistant shock status is frequently observed and dictates the early use of inotropic agents during the first hour, and to be titrated to effect (improved tissue perfusion). The choice of inotropic agents is dependent on the myocardial contractility and SVR status. The status of CO and SVR, known as hemodynamic profile can often change during septic shock stages and mandate frequent clinical reassessment to warrant therapeutic end points. Changes to the hemodynamic profile can present as follows:

1.	↑ CO & ↓ SVR	(warm shock)
2.	↓ CO & ↓ SVR	(cold shock)
3.	↓ CO & ↑ SVR	(cold shock)

Table 264.7
Early and late stage of septic shock

Early stage (hyperdynamic)	Late stage (cardiogenic)
– Hyperthermia	– Hypothermia
– Tachycardic	– Tachycardic
– Tachypnea	– Bradypnea
– Warm extremities	– Cold mottled extremities
– Bounding pulse	– Weak, thready pulse
– Normal capillary refill time	– Prolonged capillary refill time
– Normotensive/ hypertensive	– Hypotensive
– Hypoxia	– Hypoxia
– Polyuria	– Oliguria/anuria
– Increased cardiac output	– Decreased cardiac output
– Decreased SVR	– Increased SVR
– Normal CNS	– Obtunded, comatose
– Respiratory alkalosis	– Metabolic acidosis
– Hyperglycemia	– Hypoglycemia
– Normal coagulation	– Disseminated intravascular coagulopathy

In cases of high CO and low SVR (warm shock), the choice of inotropic agents after aggressive fluid resuscitation is dopamine starting at 5–10 mcg/kg/min to a maximum of 20 mcg/kg/min. In cases of dopamine refractory septic shock begin epinephrine or norepinephrine infusion starting at 0.05 mcg/kg/min to a maximum of 1.0 mcg/kg/min. Infusions should be titrated until improved tissue perfusion is restored and shock is reversed. In case where epinephrine-resistant low CO and high SVR (cold shock) is present, management should include as first-line therapy nitrosovasodilators agents (nitropusside 0.05–8.0 mcg/kg/min and nitroglycerin 1–5 mcg/kg/min) or a type III phosphodiesterase inhibitor (milrinone) loading dose 25–50 mcg/kg over 10 min and infusion starting at 0.25 mcg/kg/min to a maximum of 0.75 mcg/kg/min. The nitrosovasodilators act as vasodilators and afterload reduction, both works in reducing the

Table 264.8

5th percentile for HR, leukocyte count, BP and 95th percentile for HR, RR, leukocyte count

Age group	Tachycardia	Bradycardia	RR	Leukocyte count	Systolic BP
	Beats/min		Breaths/min	Leukocytes x 10^3	mmHg
0 days to 1 week	>180	<100	>50	>34	<65
1 week to 1 month	>180	<100	>40	>19.5 or <5	<75
1 month to 1 year	>180	<90	>34	>17.5 or <5	<100
2–5 years	>140	NA	>22	>15.5 or <6	<94
6–12 years	>130	NA	>18	>13.5 or <4.5	<105
13–18 years	>110	NA	>14	>11 or <4.5	<117

Modified from Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004;350:2247–2256

high SVR. Milrinone on the other hand has an excellent inotropic effect and at the same time decreases the SVR. If loading dose of milrinone is used, careful monitoring of the blood pressure is crucial as hypotension can occur or get worse.

Monitoring the central venous O_2 saturation ($ScvO_2 \geq 70\%$) gives an indirect measure of the balance between systemic oxygen delivery and demands, and adds an important monitoring toll of the cardiovascular status. It enables crucial adjustments to fluid and inotropic agents. $ScvO_2 < 70\%$ will indicate most likely more need for fluid boluses and/or increase in the inotropic agents. $ScvO_2 \geq 70\%$ indicates that the hemodynamic status is improving.

Frequently, patients can present with a mixed picture of warm and cold shock. For example, a child with septic shock can also present with significant hypovolemia and cardiac depression. These frequent overlapping shock forms should be considered and needs early and careful diagnosis of causes for proper therapeutic measures. Invasive monitoring can assist the treating team to identify such conditions.

As the hemodynamic profile of children with septic shock often changes as mentioned above, frequent reassessment is required. Once treatment is in progress, clinical and therapeutic end points should be used as indirect markers of cardiac output in order to monitor progress and response to treatment. These end points include capillary refill <2 s, warm extremities, normal mental status, urine output >1 ml/kg/h, central venous O_2 saturation $\geq 70\%$, and normalization of lactate. Presence of these therapeutic end points indicates successful resuscitation and reversal of shock.

Steroids may be considered in the treatment of septic shock with low CO and high SVR hemodynamic profile. The presence of adrenal insufficiency should be considered in any child with epinephrine-resistant shock. Treatment with hydrocortisone should begin with 50 mg/kg followed by the same dose over 24 h. Stress dose is 2 mg/kg followed by the same dose over 24 h. Adrenal insufficiency can be diagnosed if the level of cortisol is less than 18 mg/dl. Hydrocortisone has been preferred due to its glucocorticoid and mineralocorticoid property, and due to its potency. An algorithm summarizing an approach to therapy of shock syndromes is shown in *Fig. 264.1*.

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265 Fluid Management in Children

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Introduction

The knowledge of fluid and electrolyte physiology in health and disease is essential for the proper management of fluid and electrolytes disturbances in the acutely ill child. The aim is to maintain normal volume and composition of body fluids and to ensure the correction of any existing abnormalities if needed. Dehydration leading to hypovolemia due to vomiting and diarrhea remains the most common clinical abnormality requiring fluid and electrolyte replacement therapy in childhood.

Total Body Water and Compartments

In the newborn age, total body water accounts for 75% of the weight. It decreases to account for 60% at 1 year of age and above. The total body water is divided into intracellular and extracellular compartments. The intracellular fluid (ICF) represents the fluid within the living cells. The percentage of the ICF increases from 30% of body weight at birth to 40% at 1 year of age, remaining relatively constant thereafter. The extracellular fluid (ECF) represents all body fluid outside of cells and decreases over the same period from about 45% at birth to 20% at around 1 year of age and above (*Table 265.1*).

The ECF is made up of:

The blood volume
The interstitial fluid
The transcellular fluid (gastrointestinal secretion and spinal, peritoneal, intraocular, and synovial fluid)

The intravascular volume varies from 7% to 8% of body weight or 70–80 mL/kg body weight in newborns, and decreases rapidly in the first year of life and then more gradually toward adult value around 65 mL/kg body weight. The volume of the interstitial fluid within organs, and the accumulation of fluid in potential spaces (intraperitonial, pleural, and pericardial) varies widely in critically ill children. The balance and appropriate distribution of fluid within these interstitial spaces is maintained by:

The colloid oncotic pressure
The membrane permeability
The hydrostatic pressure

Water Balance

Water balance in critically ill children is achieved by administration of maintenance fluid requirements and by replacement of ongoing losses of water and electrolytes occurring via normal physiologic processes (*Table 265.2*). Most losses arise from insensible water losses (respiratory tract system and skin) and sensible losses (mainly urine and to a less extent stool, unless diarrhea is present). The needs of maintenance fluid can vary with physical exertion and complicating clinical conditions that alter either insensible or sensible water losses like cases with colostomy or ileostomy. In addition, special cases such as premature infants will have increased insensible water losses from skin due to large surface area for mass and thinner epidermis. Furthermore, losses are greater if the premature infant is handled in an open radiant heater or exposed to phototherapy. For this reason, premature infants and term newborns need frequent assessment to enable proper calculation of fluid and electrolyte requirements and must account for maintenance requirements and ongoing losses. The fluid requirements for newborns are listed in *Table 265.3*.

There are two commonly used systems for estimating maintenance fluid requirement for children beyond the neonatal period (*Table 265.4*):

1. Estimating maintenance fluid for a 24-h period by the caloric expenditure method: 100 mL of water is required for each 100 metabolized calories (most used method).
2. Estimating maintenance fluid for a 24-h period by the body surface area (BSA) method (using nomograms for BSA): 1,500–1,700 mL/m^2.

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Table 265.1
Body fluid compartments in different age groups

	Premature	Newborn	6 m	1 year	3 year	9 year	Adult
Weight (kg)	1.5	3	6	10	15	30	70
Body surface area (m^2)	0.15	0.2	0.3	0.45	0.6	1	1.73
TBW (% of body weight)	80	75	65	65	65	60	60
ICF (% of body weight)	30	33	40	40	40	40	40
ECF (% of body weight)	50	45	25	25	25	20	20

TBW total body water, *ICF* intracellular fluid, *ECF* extracellular fluid

Table 265.2
Maintenance water loss components (mL/kg/day)

	Newborn	6 m	1–5 year	5–10 year	Adolescent
Urinary (mL/kg/day)	40–60	60–80	40–60	30–50	40
Insensible (mL/kg/day)	40–60	40–60	30–40	20–25	10
Fecal (mL/kg/day)	10–20	10–20	10	–	–
Total	90–140	110–160	80–110	50–75	50

Table 265.3
Fluid requirements in newborns (mL/kg/day)

Birth weight (g)			
	<1,000 g	1,000–1,500 g	>1,500 g
Day 1	(80)[a] 90–100	(70)[a] 80–100	65–80
Day 2	(80)[a] 90–100	(70)[a] 80–100	65–80
Day 3	110	100–120	110
Day 4	140	140	140
> Day 5	150	150	150

[a]Recent trends are to mildly restrict fluid in the first few days to prevent fluid induced morbidities

Maintenance fluid can also be calculated on an hourly basis as follows:

– Weight less than 10 kg	= 4 mL/kg/h
– Weight greater than 10–20 kg	= 40 mL/h for first 10 kg of body weight plus 2 mL/kg/h for any increment of weight over 10 kg
– Weight greater than 20–80 kg	= 60 mL/h for first 20 kg of body weight plus 1 mL/kg/h for any increment of weight over 20 kg, to a maximum of 100 mL/h, up to a maximum of 2,400 mL daily

Appropriate fluid management will provide in addition a vehicle for the administration of adequate calories and medications. However, the total estimated need of fluid must be frequently readjusted considering other losses as mentioned before (*Table 265.5*). Additional information from hemodynamic monitoring, daily body weight, and frequent clinical examination including electrolyte monitoring is essential for a proper fluid management.

Maintenance electrolyte requirements follow the same principle applied for fluid and is estimated based upon caloric energy expenditure method. Sodium and chloride basic requirement is 2–3 mEq/100 mL of water per day and potassium 1–2 mEq/100 mL of water per day. The sodium requirement may need frequent adjustment during parenteral fluid management as ongoing physiological and pathophysiological precesses can lead to hyponatremia especially when hypotonic solutions are in use.

Fluid Management in Dehydration

A wide variety of causes leading to dehydration in small infants and children are to be considered (i.e., diarrhea, vomiting, prolonged fever, poor intake, and any condition where there is a rapid loss of body fluids). Children have the

Table 265.4
Maintenance fluid estimation by the caloric expenditure and surface area method

Maintenance fluid by caloric expenditure method	Maintenance fluid by surface area method
For children ≤10 kg = 100 mL/kg/24 h	1,500–1,700 mL/m^2
For children 10–20 kg = 1,000 mL + 50 mL/kg/24 h for each kg over 10 kg	1,500 –1,700 mL/m^2
For children 20–80 kg = 1,500 mL + 20 mL/kg/24 h for each kg over 20 kg	1,500–1,700 mL/m^2

Table 265.5
Estimated water losses in children and their replacement

Water losses in children	Caloric expenditure method
Urine output	45–55 mL/100 cal (surface area method: 1,000–1,200 mL/m^2)
Insensible	35–45 mL/100 cal (surface area method: 400–600 mL/m^2)
Fever	Increase insensible water loss by 7–10 mL/kg/day for each degree rise in temperature > 37.2°C
Tachypnea, nonhumidified	Add to maintenance l0%–30%
Marked agitation	Add to maintenance l0%–(30%)
Colostomy and iliostomy	Additional fluid to be added equal to losses
Humidified inspired gases and ventilation	May lead to fluid overload due to a decrease in insensible water loss by 20%
Oliguria	Insensible water loss + urine output ± persisting deficit/excess
Anuria	Insensible water loss is decreased to 25 mL/100 calories
Specific losses	
Upper GI	1/3–1/2 NS with KCl 20 mEq/L
Chest tube drains and dressings	Isotonic NS ± protein and RBCs as estimated losses

ability to compensate for acute fluid losses if volume loss does not exceed 15–20%. Signs and symptoms of varying degrees of dehydration are outlined in *Table 265.6*.

The most common type of dehydration in children is isotonic dehydration (i.e., serum sodium 130–150 mmol/L). Other types such as hypotonic and hypertonic dehydration occur less frequently.

The clinical findings in a patient with dehydration may vary, reflecting the type of dehydration present (*Table 265.7*). Fluid losses from different compartments (ECF and ICF) depend on serum osmolarity (Osm/L) and the acuity of dehydration. Dehydration for less than 2–3 days results in fluid loss primarily from the ECF (75–80%). However, dehydration for more than 3 days will result in 60% loss from ECF and 40% from ICF. Equal fluid losses from both compartments are encountered when the duration of the dehydration exceeds 7 days (for management, see below).

Dehydration Management

With severe dehydration (shock), restoration of the intravascular volume is a priority to ensure return of adequate intravascular volume and avoiding tissue damage. The rehydration and stabilization process is best divided into phases (*Table 265.8*). The first phase is devoted to restore the intravascular volume. As needed, the patient should receive isotonic fluid boluses of 20 mL/kg of normal saline (NS) or Ringer's lactate which may exceed 60–80 mL/kg in severe hypovolemic shock status. Should the patient be in shock secondary to bleeding, blood should be given when available to restore the circulation and oxygen delivery. The result of this initial therapy will be reflected in improved vital signs, increased urine flow, and improved state of consciousness.

In mild-to-moderate dehydration with stable hemodynamic and good perfusion, fluid resuscitation as

Table 265.6
Clinical signs and symptoms of dehydration in children

Degree of dehydration			
Clinical signs and symptoms	**5–10%**	**10–15%**	**Over 15%**
Skin color	Pale	Gray	Mottled
Perfusion of extremities	Warm to hands/feet	Warm to elbow/knee	Cool throughout
Capillary refill time	1–3 s	3–5 s	Over 5 s
Heart rate	Normal	↑	↑↑
Respiratory rate	Normal	Normal	↑
Pulses	Normal	Distal weak or absent	Proximal weak or absent
Skin turgor	↓	↓↓	Tenting
Mucous membranes	Dry	Very dry	Cracked
Sunken eyeballs	–	↑	↑
Fontanel	Flat	Depressed	Sunken
Blood pressure	Normal	Normal	↓
Mental status	Normal	Lethargic	Lethargic to coma
Urine output	↓	↓↓	Anuric
pH (arterial)	7.40–7.30	7.30–7.00	< 7.10
Serum BUN	Normal	↑	↑↑
Urine specific gravity	≥1.020	>1.030	>1.035

Table 265.7
Clinical findings by types of dehydration

Clinical signs	Isotonic serum sodium (130–150 mEq/L)	Hypotonic serum sodium (<130 mEq/L)	Hypertonic serum sodium (>150 mEq/L)
Skin color	Gray	Gray	Gray
Skin turgor	↓	↓↓	↓
Skin feel	Dry	Clammy	Thick, doughy
Mucous membranes	Dry	Dry	Cracked
Sunken eyeballs	↑	↑	↑
Fontanel	Sunken	Sunken	Sunken
Pulses	↑↑	↑↑	↑
Blood pressure	↓↓	↓↓↓	↓
Mental status	Lethargic	Coma/seizure	Irritable/seizure

outlined in the first phase may not be necessary. In the following 8-h post-resuscitation, the second phase is aimed to partially restore the ECF deficit as well as to partially correct the acid–base status. Treatment in the remainder of the first 24 h (the third phase) is aimed at restoration of ECF, ICF, and acid–base status to normal. Following this initial period, further correction is achieved by ongoing parenteral and oral (if tolerated) hydration and replacement of additional losses (the fourth phase).

Calculating the amount of fluid deficit depends on an accurate assessment of the degree of dehydration and

Table 265.8
Phases of response to dehydration management

Phase	Therapeutic plan	Clinical response
First phase: (resuscitation phase) Restoration of vascular volume	20 mL/kg D5W 0.9% NS or D5 water Ringer's lactate over 30 min; may repeat 10–20 mL/kg	Improved vital signs
		Increased urine flow
		Improved state of consciousness
Second phase: first 8 h Partial restoration of ECF deficit and acid-base status	50% of deficit fluids + 50% maintenance daily fluids	Stabilization of vital signs
		Improved urine flow
		Partial restoration of normal acid–base status
Third phase: The following 16 h (8–24 h) Restoration of ECF, ICF, and acid–base status	50% of deficit fluids + 50% maintenance daily fluids	Gain in body weight
		Fall in BUN (50% in 24 h)
		Sustained urine flow
		Improved electrolytes
Fourth phase: (24–48 h) Total correction of acid–base, electrolytes, and volume	Ongoing parenteral ± oral hydration maintenance fluids and replacement of ongoing losses	Sustained gain in body weight
		Normal electrolytes

BUN blood urea nitrogen, *D5W* 5% dextrose in water; *ECF* extracellular fluid

previous recent weight if available. The fluid deficit can be easily calculated by multiplying the estimated dehydration by the weight of the child. For example, if the estimated dehydration is 7% and the weight of the child is 10 kg.

$$\text{Fluid deficit} = 7 \times 10 = 70\,\text{mL/kg or}$$
$$\text{Total deficit} = 70 \times 10 = 700\,\text{mL}$$

The calculated fluid deficit is added to the maintenance fluid, aiming for a correction over 24–48 h.

Isotonic Dehydration

In isotonic dehydration, the type of fluid solution recommended to be given is isotonic crystalloid. Normal saline or Ringer's lactate is the isotonic solution of choice for resuscitation in pediatrics. In case of significant dehydration with hypovolemic shock, resuscitation with fluid boluses of 20 mL/kg of NS should be initiated. Further boluses up to 60–80 mL/kg may be necessary. On the other hand, the management of mild-to-moderate isotonic dehydration with the administration of NS and electrolytes is a straightforward procedure. Modifying the fluid management during the course of treatment in the presence of ongoing losses or electrolyte imbalances may be necessary depending on the patient clinical condition. The use of hypotonic or hypertonic crystalloid solutions for emergent volume replacement therapy is never recommended in pediatric patients as it can result in serious complications, including dysnatremias, cerebral edema, and, in children with significant hyponatremia, cerebral demyelination (see "Hypotonic Dehydration"). After initial fluid resuscitation, standard solutions such as 5% dextrose water and one-quarter or one-half normal saline to cover for the fluid deficit and maintenance is started. After assuring good kidney function and urine output, 20 mEq KCL per liter is added to the infusate.

Hypotonic Dehydration

The causes of hypotonic dehydration are mainly from excessive salt loss or excessive water intake (primary polydipsia). It is most frequently observed in children with hypovolemia as a consequence of abnormal gastrointestinal losses and represents a relative excess of water in relation to sodium. However, other pathologies causing hyponatremia such as impaired water excretion resulting from advanced renal failure or from persistent release of inappropriate antidiuretic hormone (ADH), excessive use of diuretics, adrenal insufficiency, hypothyroidism, and water intoxication should be ruled out. Most patients with hyponatremia appear asymptomatic as the development of hyponatremia happens gradually and may only show subtle neurological abnormalities. However, when

significant hyponatremia is present (serum sodium less than 120 mEq/L), it is frequently associated with seizure and can lead to cerebral edema. The initial treatment in such conditions typically consists of rapid correction to a sodium level which can prevent or stop hyponatremic-induced seizure. Treatment with hypertonic saline (3% NaCl) may be necessary (every 2 mL of 3% saline contain 1 mEq of sodium). The desired serum sodium level to protect from hyponatremic-induced seizure and evolving cerebral edema is 125 mEq/L and should be achieved within 3–4 h at a rate not to exceed a rise in serum sodium of 2 mEq/L per hour. Risk of morbidity from delayed therapy in this case is greater than the risk of complication from rapid correction. The following correction after reaching a safe sodium level of 125 mEq/L is a slow correction of the hyponatremia via administration of isotonic saline if volume depletion is present, otherwise fluid restriction if the syndrome of inappropriate antdiuretic hormone secretion (SIADH) is present. Fast and/or aggressive correction of severe hyponatremia has major side effects and can lead to severe and irreversible neurological disorder called osmotic demyelination. Therefore, correction should not exceed 10–12 mEq/L in the first 24 h. In patients with SIADH, isotonic saline may worsen the hyponatremia and fluid restriction or the use of vasopressin receptor antagonists (e.g., tolvaptan) is in this case the appropriate management.

Hypertonic Dehydration

In hypertonic (hypernatremic) dehydration, the circulating volume is relatively preserved at the expense of the ICF. As a result, the degree of dehydration is difficult to assess. Serum sodium level in hypertonic dehydration is usually 150 mEq/L or higher. Conditions with hypernatremic dehydration result usually from a deficit of free water and are often associated with high intake of salt, inadequate intake (especially in breast-fed infants), and/or with the ingestion of boiled milk. However, the most common loss of free water is observed during gastroenteritis illnesses with diluted and watery osmotic diarrhea (most common form of diarrhea illness in children). In contrast to secretory diarrheas, the isosmotic diarrheal fluid has a sodium concentration only between 40 and 100 mEq/L, which is less than the serum sodium concentration leading to loss of free water and consequently to hypernatremic dehydration. Other causes leading to hypernatremic dehydration are increased insensible water losses and diabetes insipidus. If the patient is hemodynamically unstable, fluid resuscitation as described previously is given. Slow rehydration over 48 h, allowing a gradual decrease in sodium serum level between 10 and 12 mEq/L/day (0.5 mEq/L per hour) is the appropriate management. Rapid correction of the hypernatremia should be avoided since this may result in seizures and cerebral edema. The estimated free water needed to lower a serum sodium level of 150 mEq/L or higher by 1 mEq/L is about 4 mL/kg distributed over 48 h.

Fluid Management in Trauma Patient

Traumatized children may suffer from significant hemorrhage due to their injuries. Once ventilation and oxygenation are established, evaluation and management of circulation are the next priorities. Significant blood loss can lead to hypovolemic shock with the consequence of hypoperfusion and multiple organ failure. Controlling active bleeding, establishment of a secure access (peripheral venous access, central line, or intraosseous access), and

Table 265.9
Blood volume deficit and estimated blood/fluid requirement

Percentage of blood volume deficit	Blood volume deficit per kg body weight	Symptoms	Fluid replacement (3:1 rule)[a]
15%	10 mL/kg	Minimal tachycardia, no changes in respiratory rate, pulse pressure blood pressure, CRT	Crystalloid
15–30%	10–20 mL/kg	Tachycardia, tachypnea, decreased pulse pressure, increased CRT, decreased urine output	Crystalloid
30–40%	20–30 mL/kg	Shock, tachycardia, tachypnea, hypotension, oliguria, depressed level of consciousness	Crystalloid and blood
>40%	30 mL/kg	Profound hypotension, tachycardia, tachypnea, anuria, profound depression of consciousness, cold pale skin	Crystalloid and blood

[a]The 3:1 rule (three-for-one) rule is an empirical strategy of fluid management in acute hypovolemic shock due to hemorrhage where most patient require 3 mL of a crystalloid solution for each 1 mL of blood loss

Table 265.10
Estimated fluid requirement in burns for the first 48 h

Formula	Fluid	First 24 h	Second 24 h
Parkland/Baxter	Colloid	0	As indicated to maintain urine output 20–80 mL/kg/24 h
	E-lyt solution (Ringer's lactate)	4 mL/kg/% BSAB, 50% in the first 8 h, the rest 50% in the next 16 h	1/2 to 2/3 of the first 24 h requirement
	Glucose water	0	Add D5W solution as needed for hypoglycemia
Carvajal/Griffith and Galveston	Colloid	12.5 g/L in the main resuscitation fluid	As indicated(optimal albumin level $\geq$ 2 g/dl with colloid osmotic pressure $\geq$ 15 mm Hg)
	E-lyts solution (Ringer's lactate)	5,000 mL/m^2 BSAB Calculating BSAB is by multiplying the percent burn and the BSA + 2,000 mL/m^2 BSA	1,500 mL/m^2 BSA + 3750 mL/m^2 BSAB
	Glucose water	0	Add D5W solution as needed for hypoglycemia

BSA body surface area, *BSAB* body surface area burned

fluid resuscitation are essential to maintain tissue perfusion and avoid complications of shock (Table 265.9). Patients sustaining hemorrhage of 10% to as high as 30% of estimated blood volume may be resuscitated with crystalloid at the rate of 3 mL for every 1 mL blood lost. Blood transfusion may not be necessary at this stage. The response to this initial bolus of fluid determines further management. If blood pressure returns to normal with improved tissue perfusion, maintenance fluid is continued and hemodynamic parameters are monitored at frequent intervals. However, should the child remain hemodynamically unstable after the second fluid bolus, blood transfusion is indicated. Whole blood is preferable to packed red blood cells for preserving coagulation function. The first bolus of blood is usually 20 mL/kg. Subsequent volumes of blood administrated are based on magnitude of blood loss. Arterial blood pressure and central venous pressure (CVP) monitoring for management of severely volume compromised children are recommended.

Fluid Management in Burn Patient

The aim of fluid resuscitation in burned victims is replacement of existing deficit of fluid, electrolytes, and proteins. Compromised children several hours post burn are most likely suffering burn shock with or without associated injuries. Management of circulation is the priority after securing the airway and providing sufficient oxygenation. Conditions with hypovolemic shock should be aggressively treated as highlighted earlier. Calculation of fluid requirements thereafter is based on the BSA and the estimated body surface area burned (BSAB). Heart rate, urine output (1–2 mL/kg/h for children below 30 kg and 0.5–1 mL/kg/h for those greater than 30 kg), capillary refill time, and blood pressure are the parameters to monitor for adequate tissue perfusion. The most commonly used formulas to calculate the fluid requirements in burn children are the Parkland, Galveston, and Carvajal formulas (Table 265.10). Parkland formula is the most used formula (4 mL/kg per percent BSAB, adding maintenance fluid for children below 5 years of age). Galveston and Carvajal formulas (5,000 mL/m^2 per percent BSAB plus 2,000 mL/m^2 per day for maintenance requirements) use the BSA for calculating the fluid need and adding colloids in the first 24 h post burn. However, these formulas used to determine fluid rates provide an estimate of the initial requirements. Observational evidence indicates that they often underestimate the volume of fluid required for adequate resuscitation. For this reason, proper estimation of fluid requirements and monitoring the result of the fluid management is essential. Appropriate body proportion charts corrected to age with wound mapping, proper estimation of body surface area BSA, and BSAB are very important information used in fluids calculation to prevent errors during fluid resuscitation in the first 24 h. Excessive administration of fluid can be as detrimental as administration of insufficient volume during the resuscitation stage.

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266 Acute Respiratory Failure

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Introduction

The human respiratory system is a complex entity that requires both neurologic and mechanical forces to work in a complementary fashion. The signal for initiating a breath starts in the respiratory center located in the medulla oblongata and travels through a network of nerves to stimulate the muscles of respiration. Any abnormality, whether mechanical or neurologic in this relatively complex system, may lead to respiratory failure (*Table. 266.1*).

The primary function of the respiratory system is gas exchange: oxygenation and carbon dioxide clearance. Failure of the respiratory system is failure in one or both of these gas exchange functions. Clinically acute respiratory failure is defined as arterial partial pressure of oxygen (PaO_2) < 60 mmHg or arterial partial pressure of carbon dioxide (PCO_2) > 50 mmHg. Respiratory failure may thus be classified as hypoxemic respiratory failure or hypercarbic respiratory failure.

Hypoxemic respiratory failure is also referred to as type I respiratory failure. Patients with this pathology present with PaO_2 less than 60 mmHg but a normal or even low $PaCO_2$. Clinically, the patient is tachypneic as the hypoxemia stimulates the respiratory centre to initiate breaths. The underlying pathology is usually acute failure of oxygenation at the level of the alveoli secondary to pneumonia or pulmonary edema. The alveolar spaces are obliterated by fluid, inflammatory cells and debris, or atelectasis.

Hypercarbic respiratory failure is type II respiratory failure. In addition to a raised $PaCO_2$, patients are usually hypoxemic. This type of failure is seen in patients with severe airway obstruction. A relatively common example is severe acute asthma exacerbation.

In the management of respiratory failure, it is also useful to differentiate between acute and chronic pathologies. Acute failure usually develops and progresses rapidly. There is very little, if any, compensation by the body buffering systems. This results in respiratory acidosis. The arterial blood gas pH is below 7.35, and the bicarbonate is normal.

On the other hand, if the respiratory failure is chronic, the body buffering systems are able to compensate. The renal compensation becomes evident as the serum bicarbonate level increases in proportion to the level and duration of the $PaCO_2$. The arterial blood gas pH is usually normal or only slightly decreased. To establish chronicity, however, other evidence of long-standing hypoxia and hypercarbia should be present. A full blood count may reveal polycythemia, while an echogardiograph may show elevated right ventricular and pulmonary arterial pressures. It is not uncommon for patients with chronic respiratory failure to present with acute decompensation. In the pediatric age group, the most common scenario is a child with a neuromuscular disorder who presents acutely secondary to aspiration or infectious pneumonia.

Pathophysiology of Acute Respiratory Failure

As described above, respiratory failure develops if any part of the respiratory system is disturbed either directly or secondary to hypoperfusion as in shock states.

In hypoxemic respiratory failure, the alveolar spaces are obliterated by fluid, inflammatory cells and debris, or atelectasis. This results in areas that are not ventilated while their pulmonary blood flow may be relatively normal. Therefore, a ventilation-perfusion (V/Q) mismatch produces hypoxemia. The management in such cases targets the underlying pathology and should include treating the infection and recruiting the collapsed lung segments.

The other mechanism that leads to hypoxemic respiratory failure is the presence of intrapulmonary or intracardiac shunts. Deoxygenated blood bypasses the ventilated alveoli. Severe hypoxemia result and will be refractory to simple oxygen therapy. This mechanism contributes to the development of respiratory failure in pulmonary hypertension and in cases of excessive alveolar distending pressures on mechanical ventilation.

On the other hand, hypercarbic respiratory failure may be better understood as a result of disequilibrium between supply and demand. The body's demand on the work of breathing exceeds its capacity. There is an increased demand on the work of breathing when the

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Table 266.1
Causes of respiratory failure

Decreased respiratory drive	Coma
	Convulsions
	Raised intracranial pressure
	Poisoning
Upper airway obstruction	Croup
	Epiglottitis
	Foreign body
Lower airway obstruction	Tracheitis
	Asthma
	Bronchiolitis
Disorders affecting the lung	Pneumonia
	Pulmonary edema
Disorders surrounding the lung	Pneumothorax
	Empyema
	Rib fracture
Disorders of the peripheral nervous system and respiratory muscles	Muscular dystrophy
	Myasthenia gravis
	Guillian–Barre syndrome

body's basal metabolic rate increases with any infection, exercise, and especially in haemodynamic shock states. In such conditions, there is an increase in oxygen consumption. There may be an increased demand on the work of breathing to clear carbon dioxide in cases of poor respiratory effort, bronchospasm or atelectasis. Respiratory muscle fatigue leads to respiratory failure. Patients with neuromuscular disorders or depression of the central nervous system decompensate rapidly and usually benefit from early ventilator support.

Acute Respiratory Distress Syndrome (ARDS)

Although initially admitted as cases of bronchiolitis or pneumonia, some patients deteriorate rapidly. Respiratory failure in the form of acute respiratory distress syndrome (ARDS) remains a challenge to modern intensive care medicine.

ARDS was first described in a case series published in 1967. This included 12 adult patients with hypoxemia refractory to oxygen therapy, decreased lung compliance, and diffused lung infiltrate on chest radiograph. In 1988, a four-point lung injury scoring system was developed to quantify respiratory distress. This was based on PaO_2/FiO_2 ratio, PEEP, the static lung compliance, and degree of lung infiltration on chest x-ray. However, one of the main problems with this system was its inability to predict outcome in the early stage of the disease. In 1994, the North American-European Consensus Conference published an internationally accepted clinical definition of ARDS. The consensus definition recognized that the severity of clinical lung injury varied. So patients with less severe hypoxemia ($PaO_2/FiO_2 \leq 300$) would be at one end of the spectrum and were considered to have acute lung injury (*ALI*), whereas patients with more severe disease ($PaO_2/FiO_2 \leq 200$) have acute respiratory distress syndrome (*ARDS*). The definition also required that the onset be acute, with bilateral pulmonary infiltrates on CXR and without evidence of left atrial hypertension (PAWP $\leq$ 18 mmHg).

Unfortunately, the simplicity of such a definition ignored factors that influence the outcome, such as the underlying cause and whether other organ systems are affected. In 1988, a prospective observational study published and concluded that the underlying diagnosis has significant bearing on outcome. Mortality from respiratory failure was related to associated disease rather than the severity of initial gas exchange. So patients who develop ARDS secondary to sepsis have a worse outcome than patients whose respiratory insult is the primary pathology.

Studies that have used the consensus definition for ARDS have reported higher annual incidences. The National Institute of Health Acute Respiratory Distress Syndrome Network estimates the incidence as 75 per 100,000. Approximately 10–15% of ICU patients and 20% of mechanically ventilated patients meet the definition criteria. Large trials suggest that the overall mortality of ARDS ranges from 34% to 58%. Mortality increases with age from 24% for patients 15 through 19 years of age to 60% for patients 85 years or older. Some reports suggest that the trend is a decline in overall mortality, possibly attributed to more effective treatments for sepsis, changes in ventilation strategies, and improvement in the supportive care of critically ill patients. However, mortality rate varies with the underlying cause, and most patients die of multiorgan system failure rather than isolated respiratory failure. Factors that predict the risk of death at the time of diagnosis include chronic liver disease, nonpulmonary organ dysfunction, sepsis, and advanced age.

The mechanism of acute lung injury can be either direct (pneumonia, aspiration, inhalation, emboli, near drowning) or indirect (sepsis, trauma, multiple blood transfusion, cardiopulmonary bypass, burns). Sepsis is associated with the highest risk of progression to acute lung injury or ARDS. The presence of multiple predisposing conditions increases the risk, as in patients with chronic lung disease.

Normal lung function requires dry, patent alveoli, and appropriately perfused capillaries. Acute lung injury occurs as the result of inflammatory injury to the alveoli. The exudative phase is characterized by the release of pro-inflammatory cytokines such as TNF, IL-1, IL-6, and IL-8. Neutrophils are recruited to the lungs, where they release toxic mediators such as proteases. In turn, these damage the capillary and alveolar epithelium. Impaired neutrophil apoptosis in the early stages of ARDS augments this process. The result is that air spaces are filled with bloody, proteinaceous edema fluid and debris from degenerating cells; functional surfactant is also lost as type II cells are damaged, resulting in alveolar collapse. This exudative phase could resolve completely with no sequelae or progress to the fibrosing alveolitis (proliferative phase).

In the fibrosing alveolitis phase, there is persisting hypoxemia, increased alveolar dead space, and further decreased lung compliance. Right heart failure may develop secondary to pulmonary hypertension precipitated by obliteration of the pulmonary capillary bed. Chest x-rays show linear streaky opacities, demonstrating the evolving fibrosis (*Fig. 266.1*). Recovery is characterized by gradual improvement of the hypoxia and lung compliance. Radiographic abnormalities resolve completely, and in most patients, pulmonary function returns to normal. However, the degree of histologic resolution of fibrosis is not known. Severe disease and prolonged ventilation are associated with the greater risk of persistent pulmonary function abnormalities.

The pathology of acute lung injury results in significant physiological derangements, including impaired gas exchange, pulmonary hypertension, and decreased lung compliance. Hypoxemia is due to ventilation-perfusion mismatching and physiologic shunting, whereas increase in physiologic dead space interferes with CO_2 clearance. Pulmonary hypertension occurs in up to 25% of ARDS patients. Contributing factors include hypoxic vasoconstriction and vascular compression by positive pressure ventilation. Decreased lung compliance is characteristic of ARDS. The low compliance is due to non-aerated lung rather than changes in the pressure-volume characteristics of residual functioning lung units.

Understanding the pathophysiology of ARDS was enhanced as CT scans changed the "view" of ARDS. There was a shift from the notion of a homogeneously heavy and stiff lung to the concept of the "baby lung," with non-homogenous densities and a much reduced normally aerated tissue at end-expiration. It is well documented that respiratory compliance correlated well with the amount of normally aerated tissue, not the amount of non-aerated tissue. ARDS lung is thus small, not simply stiff. The amount of non-aerated tissue correlated with the degree of hypoxemia, shunt fraction, and pulmonary hypertension. It was also noted that when CT scans were done in prone position, the densities were redistributed in the dependent lung. The "baby lung" is therefore not a discrete anatomical structure.

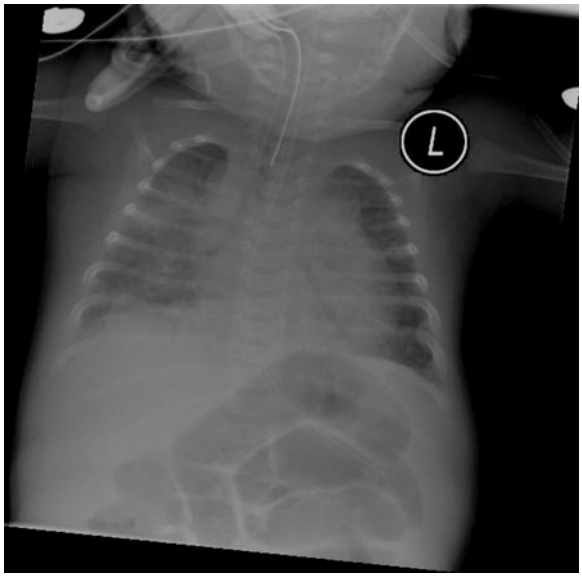

Figure 266.1
X-Rays

The understanding of ARDS evolved further with the concept of "sponge lung." In 1993, the ARDS disease process was described as involving the whole lung parenchyma, so that edema is evenly distributed from the sternum to the vertebra, not a simple gravitational distribution. The increased lung weight due to accumulation of edema raises the hydrostatic pressure which is transmitted through the lung, thus producing a "superimposed pressure." This pressure squeezes gas out of the dependent lung regions. In order to keep the most dependent lung regions open, PEEP must be higher than the superimposed pressure. Inevitably, this leads to overdistension of regions with lower superimposed pressure.

The result of overdistension is ventilator-induced lung injury (*VILI*). The lung skeleton is composed of two fiber systems linked at the level of the alveoli. An axial system is anchored to the hilum and runs along branching airways down to alveolar ducts. The peripheral system, anchored to the visceral pleura, goes centripetally down to the lung acini. The anatomical units of this system are the extensible elastin ("spring") and the inextensible collagen

("string"). The limits of lung distension are dictated by the inextensible collagen. The fibers of the lung skeleton develop an internal tension equal to but opposite to the pressure applied; this is "*stress*." Barotrauma results as stress increases, exceeding the properties of collagen fibers. The internal tension is also associated with elongation of fibers from resting position; this is "*strain*." Volutrauma is the result of increased strain without reaching the levels of physical rupture. Alveolar overdistension added to the repeated collapse and reopening of alveoli leads to activation of mechanosensors; consequently, cytokines are produced and the inflammation cascade is initiated. The pulmonary cytokine response is coupled with a systemic cytokine response, thus contributing to multiorgan failure.

Other factors that contribute to VILI include preexisting lung disease and high inspired oxygen concentrations. Oxygen causes lung injury in ARDS by forming oxygen-free radicals. In addition, high concentrations of inspired oxygen cause rapid deinflation of well-ventilated alveoli, which reduces their volume and increases the risk of collapse. Therefore, more consideration is given to arterial oxygen saturations rather than arterial oxygen tension in ARDS, as tissue oxygenation is primarily dependent on oxygen delivery.

To minimize VILI and prevent disease progression, lung-protective ventilation strategies have been proposed: limiting tidal volumes, maintaining plateau pressures to less than 35 cm H_2O, reducing inspired O_2 concentrations, and maintaining high PEEP.

The NIH Acute Respiratory Distress Syndrome Network compared traditional tidal volume (12 ml/kg) and lower tidal volume (6 ml/kg) in 861 patients. In the lower tidal volume group, plateau pressure did not exceed 30 cm H_2O. Mortality was reduced by 22% in the group treated with lower tidal volumes (31% versus 39.8%).

In addition to low tidal volumes, specialists advocate the "open-lung" approach. Most protocols included raising the level of PEEP above the lower inflection point on the pressure-volume curve for each patient to optimize lung recruitment. However, reliable measurement of the lower inflection point on the pressure-volume curve is technically difficult. Using recruitment maneuvers followed by a PEEP $< P_{inf}$ but above the closing pressure on deflation limb, the lung can be ventilated at optimal compliance.

Recruitment occurring over the entire respiratory cycle can improve oxygenation, but can cause significant barotraumas and cardiovascular instability. Based on literature available, prone positioning and sufficient PEEP appear to be the safest and most effective recruitment maneuvers. Prone positioning, though safe and efficient, has no beneficial effect on morbidity and mortality. Moreover, the effect on oxygenation is usually short lasting and depends on the type and phase of underlying lung disease.

A more recent NIH Acute Respiratory Distress Syndrome Network ventilation trial suggested that in patients with ALI/ARDS who receive mechanical ventilation with a tidal volume of 6 ml per kg and an end-inspiratory plateau-pressure limit of 30 cm H_2O, clinical outcomes are similar whether lower or higher PEEP levels are used.

On the other hand, the benefit of PEEP in pulmonary and extrapulmonary ARDS was examined. At PEEP levels of 0 cm H_2O, both groups had similar respiratory elastance ($\Delta P/\Delta V$) and end-expiratory lung volumes. Increasing PEEP in those with extrapulmonary ARDS correlated with significant lung recruitment while increasing PEEP in those with pulmonary ARDS resulted in minimal lung recruitment. Investigators concluded that the two groups presented different pathologies: Patients with pulmonary ARDS had consolidated lungs while extrapulmonary ARDS resulted in alveolar edema. This would explain the different responses to PEEP.

High-Frequency Oscillation Ventilation (HFOV) appears to incorporate all the lung-protective strategies discussed. Greater lung recruitment is achieved with very small tidal volumes avoiding high peak pressures, while higher end-expiratory lung volumes prevent both overdistension and collapse. Pediatric ARDS patients demonstrated improved oxygenation on HFOV. Unfortunately, defined criteria for transition to HFOV are lacking.

The clinical application of HFOV has been studied in a large multicentre sample of pediatric patients with respiratory failure. Lack of improvement on HFOV was associated with further deterioration, necessitating the use of extracorporeal membrane oxygenation (ECMO), while improvement of oxygenation with HFOV was associated with an increased likelihood of survival. Patients with preexisting lung disease had significantly more days of conventional ventilation before HFOV was initiated, required ECMO more frequently, and had a nonspecific increase in mortality compared to those without prior respiratory pathology.

ECMO could support gas exchange in patients who fail on conventional ventilation techniques. A prospective randomized trial involving 90 patients with severe ARDS found no difference in survival between ECMO-treated and conventionally managed patients. Only four patients in each group survived. Several explanations have been offered. Primarily, ECMO was used as rescue therapy in patients with very poor prognosis. The earlier provision of this form of support may have changed the results.

It was also stressed that similar mechanical ventilation techniques were used in both groups. Therefore, neither group was completely protected from VILI.

As discussed earlier, respiratory failure is not a primary cause of mortality in most nonsurviving ARDS patients. Persistent respiratory failure prolongs ICU stay, which leads to inevitable complications such as nosocomial infections and multiple organ dysfunction syndrome. Uncontrolled inflammation is fundamental in the pathophysiology of ARDS. Persistent inflammation and fibrosis are strongly correlated with poor outcome as are low levels of anti-inflammatory cytokines. Agents that suppress inflammation and promote repair have been studied.

The overall consensus is that there is a possible role for corticosteroids in the later, fibroproliferative phase of ARDS. This phase is clinically characterized by fever, purulent secretions, and new pulmonary infiltrates without evidence of infection. However, data from an NIH ARDS Network trial (2004) suggests no mortality advantage.

Similar lack of sufficient supportive data appears to bring into question the benefit of surfactant and nitric oxide as therapeutic agents used in ARDS. Both therapies tend to produce a temporary improvement in oxygenation but without significant effects on outcome. Treatment with synthetic surfactant has no effect on oxygenation, the duration of mechanical ventilation, or survival. Nitric oxide decreases pulmonary vascular resistance without affecting systemic blood pressure and improves oxygenation by redistributing pulmonary blood flow toward ventilated lung units. Nitric oxide tends to be added on when there is sufficient evidence for pulmonary hypertension in patients with ARDS. However, its relatively high cost and the lack of evidence for significant benefit have made it less popular on pediatric intensive care units.

In outlining the management for a patient with ARDS, one must remember to *first do no harm*. The aim is to provide adequate oxygenation without inducing morbidity from oxygen toxicity, haemodynamic compromise, barotraumas, or alveolar overdistension. Consideration for the underlying etiology must be made, as it brings more insight to the ARDS disease process. For patients with refractory hypoxemia, it is reasonable to consider modes of treatment which have not demonstrated an improvement in mortality according to available literature to date. This may be especially true in pediatric ARDS patients, as much of the literature is based on adult studies. So are there special factors unique to pediatric ARDS. The answer imposes itself: yes. It is known that pediatric physiology is sufficiently different. Unfortunately, though acknowledging this, much of the literature does not include pediatric patients.

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267 Mechanical Ventilation

Omar M. Hijazi

Also called positive pressure ventilation, after initiating the trigger by the machine or the patient, inspiration starts, and a predetermined mixture of gas is pushed into the patient's trachea. The ventilator stops pushing the gas mixture into the patient's airway once predetermined volume, time, or pressure is reached. During exhalation, gas leaves the patient's airway into the machine. The flow of gas from the patient stops when the positive end-expiratory pressure (PEEP) is reached. Mechanical ventilation can be life saving. Sound knowledge in mechanical ventilation, is vital for health-care providers taking care of critically ill children. Although when used properly mechanical ventilation can help us save lives, it is not risk free.

Indications for Mechanical Ventilation

Indications for endotracheal (ET) intubation and mechanical ventilation include: respiratory failure; whether hypoxic respiratory failure (type I), or hypercapnic respiratory failure (type II) or both, loss of upper airway protective reflexes, apnea, need for paralysis as in operative procedures, need for high doses of anticonvulsants and anxiolytics that may compromise oxygenation and ventilation as in the treatment of status epilepticus, need to control of pH and $PaCO_2$ as in patients with head injury and increased intracranial pressure (ICP), breathing muscle fatigue secondary to increased work of breathing, patients who are in shock and poor oxygen delivery, and to help decrease the after load for left ventricle heart failure.

Mechanical ventilation can be used to give full support as in paralyzed patient, or partial support to decrease work of breathing. Mechanical ventilation should not be delayed till the patient decompensates. Unplanned, emergent endotracheal intubation can be risky. The decision to intubate and mechanically ventilate a patient depends mainly on clinical judgment. Many factors will be taken into account including the patient's general condition, level of consciousness, work of breathing, patient's progress, blood gases, and the need for high oxygen supplement.

Advantages of Mechanical Ventilation

The main advantages of endotracheal intubation and mechanical ventilation are improvement in oxygenation and ventilation secondary to improved ventilation perfusion matching, and decrease work of breathing. Work of breathing can increase secondary to increase demand as in sepsis, acidosis, or secondary to abnormal lung or chest wall compliance, or increase airway resistance. In patients with left ventricle dysfunction, positive pressure ventilation will decrease the left ventricle transmural pressure and decrease left ventricle after load. However, right ventricle dysfunction may get worse with positive pressure ventilation. Positive pressure ventilation can decrease the systemic venous return and increase pulmonary vascular resistance (PVR) if not used properly.

While one should not wait for a patient with severe respiratory distress to collapse and intubate him or her on emergency basis, one should not rush to intubate patients that can be managed without invasive positive pressure ventilation. Intubation and mechanical ventilation are not risk free. Unprepared patient with borderline hemodynamics can go in cardiopulmonary arrest during intubation. Furthermore, during intubation the patient can develop aspiration, abdominal distension, pneumothorax, and hemodynamic instability. Noninvasive ventilatory support should be tried first if applicable.

Modes of Mechanical Ventilation

Mode refers for the mechanism of inspiratory support. There is no clear evidence to support the use of certain mode. The mode selection is based on the clinician and the institution preference. Neonatal units have tendency to use the pressure limited, time-cycled ventilation. In general, pediatric critical care units tend to use volume-cycled ventilation. However, some pediatric critical units prefer pressure limited time-cycled ventilation. Studies comparing volume- versus pressure-cycled ventilation did not

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show a significant difference between the two in regard to work of breathing, oxygenation, and mortality. Patients ventilated with pressure-cycled ventilation had lower peak inspiratory pressure (PIP), better patient ventilator synchrony, and more homogeneous gas distribution, while patients ventilated with volume-cycled ventilation had guaranteed minimal minute volume.

There are three types of breaths for a patient who is on mechanical ventilator. These are mandatory, assisted, and spontaneous breaths. Mandatory breaths are initiated and fully supported by the ventilator, assist breaths are initiated by the patient and are fully supported by the ventilator, and spontaneous breaths are initiated by the patient and can be supported by the ventilator. In assist mode of mechanical ventilation, the patient-triggered breaths are completely supported by the ventilator. However, in pressure support mode whether as solo mode or in combination with other modes like synchronized intermittent mandatory ventilation (SIMV) with pressure support, the clinician will decide how much support will be given to the patient-initiated breaths. In pressure support, the support is usually not complete and patient-triggered breaths that are supported by the pressure support will generate a smaller tidal volume (TV) compared to the mandatory breaths.

Volume-Cycled Ventilation

In volume-cycled ventilation, the clinician will define the tidal volume (TV), respiratory rate (RR), inspiratory (I) time, peak flow rate, flow pattern, positive end-expiratory pressure (PEEP), and fraction of inspired oxygen (FiO_2). In volume-cycled ventilation, the inspiratory flow ends after delivering the preset tidal volume. In this mode of mechanical ventilation, airway pressures, peak inspiratory pressure (PIP), plateau pressure, and mean airway pressure (MAP) depend on ventilator and patient factors. Ventilator factors include inspiratory time, peak flow rate, and tidal volume. Peak inspiratory pressure (PIP) increases with increasing flow rate and tidal volume, and decreasing inspiratory time. Patient's related factors include lung compliance, chest wall compliance, and airway resistance. Volume-cycled ventilation can be delivered using the control mode ventilation (CMV), assist control ventilation (ACM), intermittent mandatory ventilation (IMV), and synchronized intermittent mandatory ventilation (SIMV).

Control Mode Ventilation (CMV)

In this mode, the clinician determines the minute volume that the patient is going to receive. This is done by determining respiratory rate (RR) and tidal volume (TV). The clinician will also determine positive end-expiratory pressure (PEEP), fraction of inspired oxygen (FiO_2), flow pattern, and inspiratory to expiratory (E) time ratio. This mode of ventilation is given to a patient who does not trigger the ventilator. Usually the patient is heavily sedated, paralyzed, and very sick. Furthermore, this mode is also given to patients who need high respiratory rate. If the clinician elected to give the patient short inspiratory time, the peak inspiratory flow will be high and will increase the peak inspiratory pressure (PIP). While giving longer inspiratory time will allow the ventilator to deliver the same tidal volume with lower flow rate decreasing the PIP. Should the patient try to initiate breath in control mode, the ventilator will not assist the patient.

Assist Mode

In assist mode, the clinician determines the lower minute volume, FiO_2, flow rate and pattern, PEEP, and I:E ratio. The lower minute volume is set by setting ventilator rate and tidal volume. Minute volume is the product of tidal volume and respiratory rate. In this mode should the patient trigger the ventilator, the ventilator will give support to the patient-initiated breath. This support will be in the form of a full breath with the same tidal volume as the ventilator mandatory breaths.

Intermittent Mandatory Ventilation (IMV) Mode

Intermittent mandatory ventilation like assist mode allows the patient to initiate breaths to increase the minimal minute volume (TV $\times$ RR) that is set by the clinician. However, in this mode the patient-initiated breaths (spontaneous breaths) will not be supported by the ventilator. So, the tidal volume of each patient-initiated breath will depend on the patient's age and health.

Synchronized Intermittent Mandatory Ventilation (SIMV) Mode

In synchronized intermittent mandatory ventilation, the ventilator breaths are in synchrony with the patient's breathing. In IMV and SIMV, the amount of support given to the mechanically ventilated patient is variable. It can give full support. Full support is achieved by setting the ventilator at high respiratory rate above which the

patient will not have spontaneous breaths. On the other hand, the support can be partial or minimal by setting the ventilator on very low rate. Unless the patient is having a major problem with oxygen delivery and the clinician objective is to paralyze the patient, and direct the precious limited oxygen supply to the vital organ, one should not allow the ventilator to take over the full work of breathing since this may lead to deconditioning of the patients' breathing muscles. If one did not train the patients' breathing muscle, deconditioning can take place in few days. This will prolong weaning the patient from mechanical ventilator. SIMV mode is different from control mode in that the ventilator will work in synchrony with the patient. For example if the patient initiated a breath at the same time allocated for a ventilator breath, the ventilator will not give its breath and will allow the patient to take his or her own breath, the ventilator will not start inspiration while the patient in the beginning of exhalation. Pressure support is usually added to SIMV mode to give support to the patient-initiated breaths. However, the support in SIMV and pressure support will be partial support. Since SIMV will allow the ventilator to work in harmony with the patient, it is used much more common than control mode in awake, non-paralyzed patient.

Pressure Regulated Volume Control (PRVC)

PRVC is the most commonly used ventilator mode in some pediatric critical care units. In this mode of mechanical ventilation, the ventilator is capable of control of the inspiratory time and flow rate. So, based on the tidal volume pressure profile from previous breaths, the ventilator will adjust inspiratory time and flow rate to deliver the tidal volume with smaller rise in the plateau pressure.

Pressure-Cycled Ventilation

Can be in two forms; pressure control and pressure support ventilation (PSV). In pressure control mode, the ventilator will deliver a preset pressure above the PEEP at a preset rate and for a preset I:E ratio. The ventilator will stop pushing gas into the patient's trachea, once the PIP is reached. Inspiration ends once the preset inspiratory time is over. By then, exhalation starts, gas leaves the patient to the ventilator until PEEP pressure is reached. In this mode, the peak inspiratory pressure (PIP) and pressure above the PEEP (PAP) are fixed. However, the tidal volume delivered will vary based on the patient's lung and chest wall compliance, and airway and tubing resistance. If the patient was having good lung compliance at the time of setting the ventilator that got worse over time, then the tidal volume given by the ventilator will decrease. The same will happen if the airway resistance increased. This will lead to decrease minute volume and increased $PaCO_2$. While, if the airway resistance and/or the lung and/or chest wall compliance improved, the ventilator will deliver a higher tidal volume that may lead to volutrauma. Pressure-cycled ventilation can be delivered using the same modes used to deliver volume-cycled ventilation. The difference is that tidal volume is fixed in volume-cycled ventilation and pressure above the PEEP is fixed in pressure-cycled ventilation.

Pressure Support Ventilation (PSV)

Pressure support ventilation (PSV), flow-limited ventilation, is a new mode of mechanical ventilation. Pressure support ventilation can be pressure or flow triggered. Pressure support can be the only support given to the patient by the ventilator or it can be in combination with other modes of support like SIMV with pressure support, and/or CPAP (continuous positive airway pressure) with pressure support. In pressure support ventilation, the clinician sets the plateau pressure, while the patient controls the rate, inspiratory time, and expiratory time. The inspiration ends and expiration starts when the inspiratory flow falls to predetermined value, usually less than 25% peak flow rate. The tidal volume will be variable. Since the rate and trigger for PSV are initiated by the patient, PSV does not guarantee a minimal minute volume. Thus, if the patient develops apnea or received paralysis or heavy sedation, PSV will not give the patient the needed support. PSV when added to SIMV gives support to the patient-triggered breath and is thought to improve weaning from the ventilator. Adding PSV to the patient-triggered breaths helps the patient overcome the resistance of the endotracheal tube and the ventilator tubing.

Starting Setup

Adjusting TV, PEEP, PAP, RR, Inspiratory (I) and Expiratory (E) Times

If the health-care provider of the critically ill child decided that the patient needs support for his or her breathing, then based on the patient's condition and health-care provider's experience and the institution's resources, the following points should be tackled: Starting invasive

endotracheal intubation and mechanical ventilation or by noninvasive like nasal-CPAP, if invasive mechanical ventilation to be used, is one going for volume- or pressure-cycled ventilation? What pressures or tidal volume should one use to maintain good ventilation? How much PEEP should one start with? What I and E time and I:E ratio will this patient need? Which is better for this patient, full support (high rate) or partial support (low rate)? What rate should one start with? Should one paralyze this patient or let him or her share the work of breathing. Why did this patient need the ventilatory support and how can one help free him or her from the ventilator? How and when should one start weaning from the ventilator?

Setting the Mode

According to the patient's condition and the operator experience, the mode of ventilation will be chosen. In many pediatric intensive care units, volume mode is the default mode. Pressure regulated volume control (PRVC), a hybrid mode, is the most commonly used mode for mechanical ventilation in pediatric age groups in some centers. Pressure mode is usually chosen when the lung compliance is poor, patient needs high pressures on volume mode for oxygenation, and/or there are problems in ventilation secondary to large leak around the endotracheal tube.

Noninvasive Versus Invasive Mechanical Ventilation

Noninvasive mechanical ventilation can help one avoid the invasive mechanical ventilation complications. CPAP (continuous positive airway pressure) can be applied using nasal cannula, nasopharyngeal tube, and face mask. It can help in patients who are in distress due to heart failure and lung collapse.

Noninvasive positive pressure ventilation delivered through face mask is contraindicated in patients who are vomiting, having lot of secretions, and with depressed mental status.

Setting the Tidal Volume (TV) in Volume Mode, or Pressure Above PEEP (PAP) in Pressure Mode

Tidal volume is usually based on the patient's age, weight, and lung pathology. At bedside, one will titrate up the TV or PAP on the ventilator till there is good but not excessive chest excursion. On blood gases, the minute volume is good, if the pH and $PaCO_2$ are at our target range. The usual tidal volume in the pediatric age group is 8 $\pm$2 ml/kg. Newborn babies usually need much smaller tidal volume starting by 4 ml/kg and titrate as needed. In patients with sick lungs and poor compliance, smaller tidal volume is used. The use of small tidal volume is proven to improve the outcome of patients with acute respiratory distress syndrome (ARDS). While titrating up the tidal volume, auto-PEEP and plateau pressure should be monitored. If the patient developed auto-PEEP more than 5 and/or plateau pressure more than 30 cmH_2O, the tidal volume should be decreased. Large tidal volume can lead to barotraumas and volutrauma. In volume-cycled ventilation, the clinician sets the tidal volume and it is fixed. In pressure-cycled ventilation, the clinician sets the pressure above the PEEP (PAP), delivering fixed pressure and variable tidal volume depending on patient and ventilator variables.

Setting the Trigger

The patient can trigger the ventilator through either pressure or flow triggering. In pressure triggering, the ventilator will give the support if the patient inspiratory effort generated a pressure in the system in excess of the triggering pressure. For example, a patient on the ventilator with trigger pressure of -3 cm H_2O and a PEEP of 4 cm H_2O, should drop the pressure from +4 down to –3 cm H_2O (a change of 7 cm H_2O) for the ventilator to recognize that the patient is trying to breath, so the ventilator will give the preset support. The trigger is usually set at -2 to -4 cm H_2O. Making the trigger too much negative as -9 cm H_2O may exhaust the patient. Setting the trigger at positive or 0 cm H_2O, makes the trigger very sensitive may lead to over triggering. In flow triggering, the ventilator will be triggered if the flow returning to the ventilator is lower than the flow sent by the ventilator to the circuit.

Setting the PEEP

The PEEP, positive end-expiratory pressure, is needed to recruit the lung, to open the lung and keep it open, improve oxygenation, wean FiO_2, and decrease the lung edema. The usual PEEP that one starts with in a normal lung is between 2 and 5 cm H_2O. Lungs with poor compliance, lungs that have tendency to collapse need higher PEEP. While higher PEEP may help recruit collapsed alveoli improving oxygenation, improper use of high PEEP may decrease right ventricle output (decrease preload and increase pulmonary vascular resistance), decreasing

cardiac output and oxygen delivery. On the pressure volume curve, the PEEP should be above the lower inflection point (pressure). Lower inflection pressure is the pressure below which the lung will collapse. Collapsed lung will develop hypoxic pulmonary vasoconstriction increasing the pulmonary vascular resistance. This will increase right ventricle after load and will also decrease oxygen delivery. Clinically, one would increase the PEEP until the patient's oxygen saturation is in the 90% with fraction inspired oxygen (FiO_2) $\leq$ 40%. High PEEP may over distend the alveoli increasing the pulmonary vascular resistance by capillary tamponade. In general, patients with increased intracranial pressure, bronchial asthma, hypovolemia (decreased right ventricular preload), and high pulmonary vascular resistance (PVR) do better with low PEEP. While patients with white stiff lungs need high PEEP to open the lung and keep it open. The lowest pulmonary vascular resistance correlates with lung volume at functional residual capacity (FRC). If the lung volume decreases below FRC, the PVR is going to increase secondary to collapse-induced hypoxic pulmonary vasoconstriction. However, if the lung was inflated over the total lung capacity, PVR is going to increase secondary to pulmonary capillary tamponade. So, to help the right ventricle, to improve flow across the pulmonary vascular bed, to improve cardiac output the PEEP should be high enough to maintain FRC and low enough to avoid lung over inflation.

Setting the Respiratory Rate (RR)

Setting the respiratory rate is influenced by many factors. The younger the patient, the higher the rate he or she needs. The average starting range is around 30–40 breaths/min for newborn, 20–30 breaths/min for child, and 12–20 breaths/min for adolescent. The sicker the patient is, the higher rate he or she will need. Patients who need full support on the ventilator will be given higher rate compared with those who need partial support. A patient with poor lung compliance, who is given small tidal volume, will need higher ventilator rate compared with a patient who has normal lung compliance. Patients who have asthma with increased airway resistance, normal lung compliance (increased time constant), and auto-PEEP will need low rate on the ventilator. Once one has the blood gases results, the rate will be optimized according to the patient's needs. The higher the rate, the more support is given to the patient. Giving full support (high rate) will help the patient's fatigued muscle recover and help optimize oxygen delivery in patients with oxygen debt. However, full support even for as short as 3 days, can lead to deconditioning of the breathing muscles, alkalosis, and shift to the left in oxygen dissociation curve. Low rate that is not meeting the patient needs will not allow the patient's breathing muscle to recover, and will not help the patient optimize oxygen delivery.

Setting the Inspiratory and Expiratory Times (I, E, Respectively)

The inspiratory and expiratory times are set based on the time constant of the patient's lung. Time constant is the product of lung compliance (C) and airway resistance (R). The higher the compliance and the resistance, the longer is the time constant. The longer time constant is, the longer time the lung will take to recruit and derecruit. Sixty-three percent of the recruitable lung volume is recruited after one time constant, 99% after five time constants. Usually, the inspiratory time is set at three to five time constants. Different areas of the lungs have different compliance and resistance. In lung disease, as in pneumonia, collapse, and obstructive airway disease, the variability in time constant is more apparent. The time that is needed to recruit an area of the lung may over distend another area in the same lung. Patients with obstructive airway, like patients with status asthmaticus, need long I and E times. These patients have good lung compliance and increased airway resistance. This increases their lung time constant. Since the main problem in patients with airway obstruction that is more apparent during exhalation, these patients need longer E time. The usual I and E times ratio to start mechanical ventilator with, is based on the patient's pathology and the targeted I:E ratio. The usual starting I:E ratio is 1:2, so a newborn patient who is intubated for apnea, with healthy lungs, with initial respiratory rate of 40/min, then the cycle time is 1.5 s (60 s per minutes/40 breaths per minute), the I time will be 0.5 s, E time will be 1 s, and I:E ratio will be 1:2. On the other hand a 16-year-old ventilated for severe status asthmaticus with severe air trapping will be given low respiratory rate like 12/min, giving a cycle time of 5 s, if I time is set at 0.8 s, this will give the patient long expiratory time of 4.2 s and I:E ratio of 1:5. If such a patient with bronchospasm is not given a long enough expiratory time, he or she will develop air trapping and auto-PEEP. To detect auto-PEEP check what is the setup PEEP (e.g., it is 4 cm H_2O), then press on expiratory pause and look at the pressure (let say it was 7 cm H_2O), this tells one that there is auto-PEEP, that the patient cannot exhale all the air that he or she is given during inspiratory phase, and that the E time is not long enough. Normally the PEEP and

the expiratory pause pressures should be equal. In such a patient with auto-PEEP, the patient can be helped by giving longer E time, smaller tidal volume, and/or improve the airflow by optimizing the bronchodilator therapy.

Setting the Fraction Inspired Oxygen

In general, when starting mechanical ventilation for a patient with respiratory failure one starts with FiO_2 of 100%. As soon as the patient achieves target saturation, the FiO_2 should be weaned. If the patient saturation failed to reach our target, and the lung looks white (under recruited) on the chest X-ray, PEEP should be increased as needed to wean the FiO_2. High FiO_2 can worsen atelectasis, and damage the lung airway and parenchyma. In sick lungs, the usual target oxygen saturation is 85–90% and target $FiO_2 \leq 40\%$.

Monitoring Lung Compliance

Monitoring the lung compliance for a patient on mechanical ventilation gives the health-care provider a good idea about the patient's lung condition, patient's progress, and the need to escalate or wean the mechanical ventilation support. Compliance (C) is change in volume (ΔV) over change in pressure (ΔP). In calculating the compliance, one takes into account the exhaled tidal volume. There are two lung compliances. These are the dynamic and static lung compliances. Dynamic compliance is calculated by dividing exhaled tidal volume (TV) over the difference between the peak inspiratory pressure (PIP) and the PEEP. So, dynamic compliance equals TV/ (PIP-PEEP). Static compliance is calculated by diving exhaled TV over the difference between inspiratory pause (plateau) pressure and PEEP. Inspiratory pause pressure is measured by pressing on the inspiratory pause knob on the ventilator and checking the pressure. For example, a 1-year-old is connected to mechanical ventilator. He is on PRVC mode. Ventilator rate is 20/min. Inspiratory tidal volume is 110 ml. Exhaled tidal volume is 100. The ventilator reads 18 cm H_2O for PIP, 16 cm H_2O for inspiratory pause pressure, and 4 cm H_2O for PEEP. Then for this patient the dynamic compliance is 100 ml/(18–4) cm H_2O and the static compliance is 100 ml/(16–4) cm H_2O.

Monitoring a Patient on MV

The management of a sick patient who needs ventilatory support does not end by intubating the patient's trachea and connecting him or her to the mechanical ventilator. The patient's condition and the patient's lung dynamics do change with time and the setup that may suite the patient now may not suite him or her few hours later. It is a teamwork in which nurses, respiratory therapists, and physician are involved in.

Securing the Endotracheal Tube

Orotracheal route is the most commonly used way for intubating the trachea in children. Nasotracheal intubation, though can give more stability to the endotracheal tube, is associated with complications like nasal ulceration and sinusitis. After intubation, verifying that the ET tube in the trachea, and that the ET tube tip is in the right position which is 1 cm above the carina, the endotracheal tube should be secured so it does not move in or out. There are many ways to secure the ET tube. If adhesive tape is going to be used secure the tube, it should be waterproof tape so it does not peel off in contact with the patient's secretions. To avoid accidental extubation, the bedside nurse and the respiratory therapist should check and document the ET tube position periodically. Most accidental extubation incidents take place when the patient is given bath or being weighed. Health-care providers are advised to avoid head dorsiflexion while serving the intubated patient. With dorsiflexion, the ET tube will move up and this may leads to accidental extubation. A rough way for estimating the level of the ET at the level of the gums is three times the size of the tube. So, for a 4 kg newborn intubated with size 3.5 ET, the tube level at the gum would be at 10.5 cm. Another way for older children is age in years plus 10. So, for a 5-year-old child the tube can be secured initially at 15 cm. Later the position can be checked in the chest X-ray and tube positioned to be around 1 cm above the carina.

Assure That the ET Tube Is Patent

The endotracheal tube should be patent. There are certain indicators that may indicate that the tube is completely or partially occluded. For example, an increase in the peak inspiratory pressure in volume mode or a decrease in the tidal volume in pressure mode may indicate partial tube obstruction. Kinked tube can give the same picture of ET tube occlusion. Suction of the ET tube should be done periodically as needed under sterile technique by the nurse and the respiratory therapist. Certain patients need special preparation before and during ET tube suction. Patients with pulmonary hypertension for example can have severe

desaturation during suction. Before suction of these patients, the patient may need sedation, analgesia, and paralysis. Preoxygenation and installing lidocaine in the ET can also help. Patients with increased intracranial pressure also need special care before and during suction of ET tube. If not done properly, ET tube suction can lead to cough, patient irritation, and further increase in the intracranial pressure leading to serious complications like brain herniation.

Leak Around the Endotracheal Tube

The size of the endotracheal tube is estimated by the formula (age in years + 16)/4. In preparation for intubation, it is good to prepare tubes that are 0.5 mm above and below the calculated size. A good size tube should go into the vocal cord into the cricoid ring easily. After intubation, one should look for air leak around the endotracheal tube. There should be some air leak around the ET tube. Having no air leak at airway pressure of $\geq$25 cm H_2O will increase the risk of mucosal injury and subglottic stenosis. In such scenario, the endotracheal tube cuff should be deflated or the tube should be changed to smaller size as the patient's condition allows. However, too much leak can compromise ventilation and oxygenation. In such case with big leak, one will inflate the balloon if the ET tube was cuffed, or change the ET to a bigger size. Air leak around the endotracheal tube changes with the patient's condition. Edema around the tube will decrease the leak. Worsening lung compliance or airway resistance will increase the leak. Checking for air leak should be part of the daily monitoring of intubated and mechanically ventilated patient. Checking for air leak around ET tube is also a part of preparation for extubation. If there is no leak, one should plan to prevent and treat complications like post-extubation stridor or need for reintubation.

Synchrony Between the Patient and the Ventilator

In a patient who is not paralyzed, who is breathing while on the ventilator, it is important that the patient and ventilator breaths are synchronized. If not, the patient gets agitated and this may increase the patient's oxygen consumption, risk of having ventilator-associated volume or barotraumas, and prolong duration of mechanical ventilation. At the bedside, patient ventilator asynchrony is evident as ventilator fails to initiate a breath after being triggered by the patient. Ineffective triggering may account for 88% of asynchronous breaths. In some patients, the asynchrony is due to highly sensitive trigger. This can be ameliorated by decreasing the sensitivity, others due long inspiratory time that can be overcome by increasing the flow to get the tidal volume with shorter inspiratory time.

Ventilator Humidifier

In spontaneous inspiration, the inhaled air is filtered, humidified, and warmed mainly in the nose. By intubating the patient's trachea, the inhaled air is not getting the advantages of going through the nose. To overcome this problem, a humidifier is attached to the mechanical ventilator. Inhaled air goes through the humidifier to get humidified and warmed. The usual humidifier temperature is set around 35°C. Should the patient be hypothermic, the humidifier temperature can be increased to 39–40°C to warm the patient up. On the other hand in a patient who is febrile, the humidifier temperature can be decreased to 33–34°C to help control the patient's fever. Humidifier temperature less than 33°C will give less humidity to the inhaled air, thickening the patient's secretions leading to mucous plugs, airway occlusion, and lung collapse. Furthermore, dry cold air is irritant to the airway and can lead to bronchospasm especially in a patient with reactive airway disease.

Weaning from Mechanical Ventilator

As soon as the patient is connected to mechanical ventilator, one should start planning for weaning the patient from this machine. As mentioned in the beginning, while mechanical ventilator can help us save lives, this is not risk free. Mechanically ventilated patients are at risk of ventilator-associated lung injury, ventilator-associated pneumonia, and breathing muscles deconditioning. Mechanical ventilator lung injuries can be related to high volume, volume trauma (volutrauma); high pressure, pressure trauma (barotrauma); atelectasis (atelectetrauma); high inspired oxygen concentration; oxygen toxicity; and cytokine release. These mechanical ventilator–associated traumas should be prevented. The target is not optimal blood gas. Our target is to take from the lung as much as it can give us with the least possible ventilator-associated lung damage. To decrease the risk of breathing muscle deconditioning, the patient should not be on full support for long time. The risk of breathing muscle deconditioning increases if the ventilator takes over the work of breathing for $\geq$72 h from the patient. Patients treated with muscle relaxants in combination with steroids like patients with bronchial asthma are at risk of developing critical illness neuromyopathy. The risk increases with the

use of aminoglycosides, diuretics, and electrolytes imbalance. It is preferable to give the muscle relaxant as needed rather continuous infusion in such patients. Should the patient's condition mandate continuous muscle relaxant infusion, the infusion should be held periodically and the health-care provider should assure and document that the patient is moving while off paralysis. One of the measures that helps us titrate the dose of muscle relaxant is to check for train of four. A nerve stimulator gives four electrical stimuli (train of four) applied in series stimulating a peripheral nerve like the ulnar nerve. If the patient is having no response to this series (0/4), the muscle relaxant should be held and the patient should be reassessed clinically and by the nerve stimulator. The target is to prevent the patient from fighting the ventilator. One do not have to have (0/4) response to achieve that. When following the paralyzed patient for mechanical ventilation a response of (2–3/4) is usually adequate. This level of response indicates that the patients' muscles are relaxed enough to facilitate mechanical ventilation.

High Frequency Oscillatory Ventilation (HFOV)

HFOV is the most commonly used type of high frequency ventilation in the pediatric critical care units. In this form of ventilation, the ventilator plays an active role during inspiration and expiration. The ventilator piston pushes air in during inspiration, and it sucks it out from the patient during expiratory phase. The tidal volume in this mode of ventilation is much smaller than the dead space. HFOV used to be offered for patients who are on high pressures on conventional ventilation or patients who fail conventional ventilation. Nowadays, the patient does not have to fail conventional ventilation to justify using HFOV. In many pediatric and neonatal critical care units, HFOV is used along with conventional ventilators as a standard of care for patients who need mechanical ventilation. Compared to conventional mechanical ventilation, HFOV uses higher mean airway pressure. Since the damping effect is higher in HFOV compared to conventional MV, the alveoli are more protected with HFOV. Some patients have better oxygenation and ventilation while on HFOV compared to conventional ventilation. However, there are no clearcut guidelines for which patients do better on HFOV. To start the patient on HFOV, the clinician has to define the following: the mean airway pressure, the power or delta-P, the frequency, and the FiO_2. The mean airway pressure on HFOV is started at 2–4 cm above the mean airway pressure on the conventional mechanical ventilator. FiO_2 started usually at 100% and weaned keeping oxygen saturation around our target usually in the 90–95% range. If the patient desaturate when the FiO_2 is weaned down, and the lung is showing signs of de-recruitment, the mean airway pressure should be increased by 1–2 cm H_2O, to help recruit the lung and wean the FiO_2. Our target is to reach the MAP that will achieve O_2 saturation in the target area with FiO_2 in the safe area ($\leq$40%). Delta-P or the power, which reflects the change in the pressure between inspiration and expiration, is age dependent. The usual staring delta-P is 40 for newborn, 45 for infants, and 50 for older children and teenagers. By looking at the patient, a good delta-P will make the patient shake down to mid-thighs. Delta-P reflects ventilation, and if the patient is having problem washing out CO_2, but with good saturation, the delta-P should be increased. However, if the patient is having inadequate oxygenation and ventilation the MAP would be increased to improve lung recruitment. The frequency in HFOV ranges between 6 and 12 Hz. The starting frequency also is age and size dependent. The usual starting frequency is 12 Hz for newborns, 9 for infants, and 7 for older children. Increasing the frequency on HFOV shortens the inspiratory time giving a smaller tidal volume. This leads to CO_2 retention. Thus, in contrary to conventional mechanical ventilation if the patient is having a problem with CO_2 retention after optimizing the delta-P and MAP, the frequency should be decreased rather than increased. As the patient's condition improves, our target is to wean the FiO_2 to $\leq$40%, then wean the MAP to teens, and then to switch him or her to conventional mechanical ventilation. Patients, who are having lot of secretions that need frequent suction of their endotracheal tube, are not good candidates for HFOV. With suction, the patient will have lung de-recruitment leading to transient desaturation and CO_2 retention. Recruitment takes time on HFOV. To overcome this problem, it may be helpful to increase the MAP by 2 cm after suction to enhance recruitment and to go back to the base line MAP once the O_2 saturation goes back to base line. Patients with borderline hemodynamics may not tolerate HFOV. Before staring HFOV for such patients, the intravascular volume should be optimized.

Permissive Hypercapnia

First described by Wung in neonates treated for persistent fetal circulation, permissive hypercapnia is a strategy in which the clinician will accept higher $PaCO_2$ and lower pH in order to minimize the ventilator-associated lung injury.

This strategy was also described in patients mechanically ventilated for bronchial asthma and acute respiratory distress syndrome (ARDS).

Inverse Ratio Ventilation (IRV)

Inverse ratio ventilation is a strategy that is used to improve oxygenation in patients who failed to respond to other measures like optimizing the PEEP and FiO_2. In this strategy, inspiratory time will be increased to exceed the expiratory time. This leads to increase in mean airway pressure, and potentially improving recruitment and oxygenation. This strategy can be applied for patients who are on volume- or pressure-cycled ventilation. Inverse ratio ventilation may improve oxygenation. However, there is no clear evidence that it improves duration of mechanical ventilation, ICU length of stay or mortality. Because IRV is uncomfortable, patients who are on inverse ratio strategy need deep sedation or paralysis.

Mechanical Ventilation in Different Case Scenarios

Mechanical Ventilation for Patients with Bronchial Asthma

Patients with bronchial asthma can develop severe asthma exacerbations. In some patients, the attacks will be so severe that the patients do not respond to the conventional treatment for such attacks. These patients may get exhausted, lethargic, and develop respiratory failure. Since endotracheal intubation and mechanical ventilation in a patient with bronchial asthma is surrounded with complications, such measures are to be avoided as much as possible. Most of the morbidity and mortality for patients with severe status asthmaticus who were sick enough to need mechanical ventilation are related to intubation and mechanical ventilation. As they need intubation, patients with asthma can be dehydrated secondary to increase insensible loss through hyperventilation, and vomiting and decrease intake. The high doses of beta 2 agonist that these patients are receiving increase vascular capacitance and decrease systemic vascular resistance. To compensate for the relative intravascular volume depletion and beta 2 agonist–induced vasodilatation, the stressed body of these patients releases lot of epinephrine and norepinephrine, which helps increase their cardiac output and their vascular resistance to maintain their perfusion pressure. While preparing such patients for endotracheal intubation, these patients are medicated with anxiolytics, narcotics, and muscular relaxants. Narcotics and anxiolytics suppress the stress-induced release of catecholamines. The muscular relaxants lead to decrease venous return by abolishing the muscle pump effect and changing the intrathoracic pressure during inspiration from negative to positive; these factors lead to sudden drop in the venous return, systemic vascular resistance, and cardiac output and may lead to cardiac arrest if the patient is not well prepared. So, intubating a patient with severe status asthmaticus is to be avoided if possible, to be done by the most experienced health-care provider, patient is to be prepared with good IV access, and reviving circulation by giving fluids (fill the tank) before giving the drugs needed to facilitate endotracheal intubation.

The main problem in bronchial asthma is air trapping. The patient's main problem is in the expiratory phase. Airway diameter is smaller during exhalation and exhalation is usually passive. Patients with bronchial asthma have normal lung compliance and increased airway resistance. So, the time constant in bronchial asthma is increased. To facilitate air exchange in these patients, inspiratory (I) time and expiratory (E) time should be adequate. The usual I:E time ratio that a patient with bronchial asthma needs is 1:3–1:5. To allow good I time that is 3–5 time constant and longer E time these patients need low rate on the ventilator. Patients with bronchial asthma can be ventilated using volume or pressure modes. This is based on the operator experience and comfort. In many critical care units, volume mode is the default mode. PRVC is the most common mode that is used for our patients in general and patients with status asthmaticus are no exception.

Patients with bronchial asthma can be difficult to ventilate and may need muscle relaxants. Usually, these patients are on systemic steroids and if given muscle relaxants, they should be given the smallest dose to help the patient not to fight the ventilator. The bedside nurse should check for the train of four responses. To help decrease the risks of mechanical ventilation and muscle relaxant in such patients, both should be weaned as soon as possible.

Positive end-expiratory pressure (PEEP) is usually applied to the mechanical ventilation strategy for patients with asthma. No PEEP for such patients can lead to increased micro atelectasis increasing ventilation perfusion mismatch which is the most common cause of low saturation in these patients. High PEEP and auto-PEEP can increase air trapping and CO_2 retention. Usually one starts with low PEEP in range of 2–3 for these patients and follows their progress. These patients if not given enough

time during exhalation will develop auto-PEEP. Auto-PEEP is the difference between the expiratory pause pressure and the setup PEEP. Patients with auto-PEEP can be helped with increasing expiratory time, decreasing tidal volume, and/or bronchodilators.

Beta 2 Agonists for Mechanically Ventilated Asthmatic

Beta 2 agonists are essential medication for the treatment of status asthmaticus. To decrease their side effects, these medications are best given by inhalation route. This can be done by metered inhaler puffs or by nebulizer. Both methods are effective in treating patients with severe bronchial asthma exacerbation. However, if the respiratory therapist did not account for the flow coming through the nebulizer, the patient can have excessive flow and develop pneumothorax. In general, in our ICU it is preferred to give these medications to our mechanically ventilated patients by metered dose inhaler (as puffs). In very sick asthmatic with poor air exchange, the beta 2 agonist can be given through the IV route.

Setting the Humidifier for a Patient with Asthma

Some of these patients have thick dry secretions that may obstruct the air worsening the lung collapse. Dry cold air is well known to be irritant to these patients' irritable airway. Thus, the humidifier by warming and humidifying the inhaled gas mixture can be of great help in the treatment of these patients.

Helium Oxygen Mixture and Asthma

Helium oxygen gas mixture can be given to patients with bronchial asthma attach. This can be given for ventilated and non-ventilated patients. The advantage of this mixture is that decreasing the density of the inhaled gas will change the flow of gas mixture from turbulent to linear flow. This will facilitate the gas flow to the lower airway. However, for this gas to be effective and to have low density the helium to oxygen ration has to be high. The best combination is 20% oxygen and 80% helium. If the patient's condition mandate giving high concentration of oxygen $\geq$30%, this mixture will be less effective. Some clinicians will argue that in patients with severe bronchospasm with poor air entry, giving helium will help deliver the medications to the lower airway and improve the patient's condition.

Mechanical Ventilation for Patients with Head Injury and/or Increased Intracranial Pressure (ICP)

There are few points that are worth mentioning in regard to endotracheal (ET) placement and mechanical ventilation in such patients. In preparation for endotracheal intubation, special care should be applied for the stability of the cervical spines while opening the airway. Head tilt chin left to be avoided. Jaw thrust can be applied. While preparing drugs for tracheal intubation, one should not use drugs that increase intracranial pressure (ICP) as succinylcholine and ketamine. Once their circulation is revived, these patients need drugs to help decrease risk of escalating the increased ICP. These drugs include short acting painkillers like fentanyl, anxiolytics like midazolam, anesthetic like lidocaine, non-depolarizing muscle relaxant like vecuronium, and short acting barbiturate as pentothal.

Ventilator setup for patients with increased ICP: Both volume and pressure modes can be used. In our institution volume mode is used. PRVC is our first choice. Ideally, these patients need a ventilator setup that gives the patient good oxygenation with $FiO_2 \leq 40\%$, a PCO_2 between 35 and 38 mmHg with the lowest possible mean airway pressure. So, for these patients PEEP should be the lowest that gives target O_2 saturation with $FiO_2 \leq 40\%$. I time around 0.5–1 s, I:E ratio 1:2, and tidal volume the lowest that gives good chest excursion by inspection and target CO_2 in blood gases. The rationale behind this strategy is to decrease the intrathoracic pressure to enhance the venous return from the head while maintaining good oxygenation and ventilation. This will help decrease ICP and improve the cerebral perfusion pressure (CPP). CPP equals the difference between the mean arterial pressure (MAP) the force pushing the blood into the cranium and intracranial pressure (ICP) or central venous pressure (CVP) whichever is higher. High mean airway pressure which is a reflection of tidal volume or pressure above the PEEP, the PEEP, I time and I:E ratio, increases the resistance for the venous drainage from the head into the thoracic cavity increasing the intracranial pressure and decreasing the cerebral perfusion pressure.

Patients with increased intracranial pressure need also to be covered with sedation, analgesia as needed to tolerate the endotracheal tube and the mechanical ventilator. Muscle relaxants are to be added, if sedation and analgesia

failed. Muscle relaxant will make it difficult to follow the clinical neurostatus progression of the patient. As mentioned above, using the muscle relaxants and taking over the work of breathing from the patient for long time can lead to deconditioning of the breathing muscles. So this should be used as needed and the patient should be monitored with train of four.

To help avoid increase ICP crisis, these patients need to be well prepared for endotracheal suction and/or any irritating or painful procedure. Before extubating such patients, the clinician should assess their capability to protect the airway.

Mechanical Ventilation and Cardiac Function

During spontaneous inspiration, the diaphragm goes down and the ribs rise up to be horizontal increasing the intrathoracic volume. This decreases the intrathoracic and increases the abdominal pressure, increasing the venous return, increasing right ventricle preload, shifting the interventricular septum to the left, increasing the pulmonary vascular capacitance, decreasing left ventricle preload, and increasing left ventricle transmural pressure. The left ventricle transmural pressure is the difference between systemic pressure and intrathoracic pressure. For example, if the systolic pressure was 100 and the intrathoracic pressure was −15, then the transmural pressure is 115. So, the arterial systemic systolic pressure is lower during inspiratory phase. If the patient is in respiratory distress and has to create more negative pressure during inspiration, then the gradient in the systolic pressure is going to be wider between inspiration and expiration. If the difference is more than 10 mmHg, this is called pulsus paradoxus. In general, the right ventricle output is better and the left ventricle output is worse with increasing the negative intrathoracic pressure.

Once the patient is connected to positive pressure ventilation, the pressure gradient that drives the venous return to the right atrium is decreased decreasing the right ventricle preload. Positive pressure ventilation that pushes the lung volume above the functional residual capacity (FRC) will increase the right ventricle after load. On the other hand the left ventricle transmural pressure will decrease. If the patient's main problem was left ventricle failure, his or her intravascular volume, the preload for both ventricles was adequate, then, positive pressure ventilation will improve his or her left ventricle function, and improve his or her cardiac output. However, if the patient was hypovolemic, his or her intravascular volume is depleted, positive pressure ventilation will decrease the preload for the right ventricle, decreasing the cardiac output. In general, left ventricle likes positive pressure ventilation. Right ventricle does not like positive pressure ventilation.

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268 Infections in the PICU

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Introduction

Effective control of infections starts at the community level, outside the hospital. There are a number of important initiatives that, although simple and not necessarily intensive care related, have the greatest impact on the outcomes of infections. These include provision of adequate and age appropriate foods, breast feeding, drinkable water, provision of mosquito nets and shelter, avoidance of overcrowding, sanitization, and prevention of disease by vaccination. These are basic needs and requirements of mankind as a basis of good health. They are attainable in the largest cities or the most remote areas.

Infections are one of the commonest causes of mortality in the pediatric intensive care unit (PICU), with a mortality of up to 50%, depending on the origin of the infection.

Infections in the intensive care unit can be divided into those that occur outside the hospital (community acquired) and those that occur within the walls of the hospital and beyond 48 h of admission (nosocomial). Preventive measures give the most benefit, both outside and inside the hospital. Good hand washing, good respiratory care practice, and judicious use of antibiotics are examples of effective interventions that reduce the rate of nosocomial infections.

Sepsis comprises up to 25% of admissions to a typical pediatric intensive care unit. Shock and management of septic shock are discussed elsewhere in this text. However basic principles of management are the same and are not, and should not be, limited to the intensive care unit. Treatment should commence as soon as the recognition of any septic process is underway be it in the field, the clinics, emergency departments, or on the wards.

In the community, on the hospital wards, and in the PICU, timely identification of illness and access to skilled healthcare personnel are crucial steps limiting the development of organ dysfunction and failure. Early identification means early resuscitation and early treatment. This may be hours or in some cases days prior to the admission to the PICU. This early recognition and intervention gives the patient the greatest chance of surviving a significant infection.

Organization of this Chapter

1. "Catalog" of important microorganisms and diseases they cause in the PICU
   (a) Bacteria
   (b) Fungi
   (c) Viruses
2. Significance of viral infections in the PICU
   (a) Viral epidemics and pandemics
   (b) Viral infections of regional importance
      (i) Dengue fever
      (ii) Viral hemorrhagic fevers
3. Parasitic infections in the PICU
   (a) Malaria
4. Shock syndromes in the PICU
   (a) Staphylococcal toxic shock syndrome
   (b) Streptococcal toxic shock syndrome
   (c) Necrotizing soft tissue infections
5. Anatomical distribution of infections in the PICU
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      - Croup
      - Tracheitis
   (b) Lower respiratory tract infections
      - Community-acquired pneumonia
      - Bronchiolitis
   (c) Cardiac infections
      - Myocarditis
      - Infective endocarditis
      - Infectious pericarditis
      - Wound infection after cardiac surgery
   (d) CNS infections
      - Purulent meningitis
      - Encephalitis
      - ADEM
      - Guillain-Barre syndrome
      - Botulism
6. Infection in the immunocompromised host
   (a) Neutropenia
   (b) Cellular immune deficiency
   (c) Humoral immune deficiency
   (d) Complement deficiency
   (e) Human stem cell transplant (HSTC) patients

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(f) Solid organ transplant patients
(g) HIV/AIDS in the PICU
(h) Brief review of antifungal agents in the PICU
(i) Brief review of antiviral agents in the PICU

7. Nosocomial infections in the PICU
   (a) Blood stream infections
   (b) Central venous access line infections
   (c) Ventilator associated pneumonia (VAP)
   (d) Urinary tract infections (UTI)
   (e) Wound infections
8. Infection control principles in the PICU
9. Summary

Catalog of Important Microorganisms in the PICU

Medically Important Bacteria in the Pediatric Intensive Care Unit

Crucial to the management of any serious infection in the Intensive care unit and elsewhere is the *early* use of *appropriate* antibiotics. Early identification of most bacteria is almost universally by the way of a Gram stain. This can be performed in any microbiology lab, in the field, or a clinic that is suitably equipped.

Though references such as the "Red Book" (American Academy of Pediatrics) give invaluable information on the appropriate antimicrobial therapy for a given microbe or infectious syndrome, there is no substitute for a well informed, up-to-date infectious diseases physician or microbiologist. They are able to provide information on local isolates, patterns of sensitivity, and best management practices for a large variety of infections.

The majority of the bacteria listed below will be referenced elsewhere; they are highlighted to reflect their frequency of identification in the PICU. Additionally, the immunocompromised host will be at risk from a number of opportunistic infections that will be discussed later in this chapter.

Gram-Positive Cocci

Staphylococcus aureus. Pneumonia, disseminated infection/multi site (bone, heart, lungs, CSF), toxic shock syndrome, central venous line (CVL) infection

Staphylococcus epidermidis. CVL infections

Streptococcus pyogenes (Group A Streptococcus). Bacteremia, septicemia, necrotizing fasciitis, toxic shock syndrome

Streptococcus agalactiae (Group B Streptococcus). Early/late onset group B sepsis in neonates

Enterococcus faecalis. Urinary tract infections/VAP (Ventilator Associated Pneumonia)

Streptococcus pneumoniae (Pneumococcus). Bacteremia, septicemia, pneumonia, meningitis

Gram-Positive Rods

Clostridium tetani. Wound-related tetanus, neonatal tetanus in the developing world

Clostridium botulinum. Flaccid paralysis (Botulism)

Clostridium perfringens. Gangrene/sepsis/toxin mediated disease

Clostridium difficile. Antibiotic associated diarrhea, pseudomembranous colitis

Corynebacterium diphtheriae. Diphtheria in unvaccinated

Listeria monocytogenes. Sepsis and meningitis in neonates and immunocompromised

Gram-Negative Cocci

Neisseria meningitidis (Meningococcus). Septicemia, meningitis

Neisseria gonorrhoeae (Gonococcus). Neonatal conjunctivitis, pelvic inflammatory disease, occasionally disseminated infections and involvement of the joints

Gram-Negative Rods

E. coli, Klebsiella pneumoniae, Enterobacter cloacae, Serratia marcescens, Proteus Sp. (e.g., *P. vulgaris, P. mirabilis*), *Bacteroides fragilis.* Urinary tract infection, sepsis (esp. neonates and debilitated), CVL infections, Ventilator Associated Pneumonia (VAP), meningitis in neonates.

Haemophilus influenzae (*type A, B and non-typable*). Otitis media, pneumonia, epiglottitis, and meningitis in the unvaccinated

B. pertussis. "Whooping Cough" in older children, necrotizing/calcifying pneumonia, and cardiovascular collapse in neonates

Pseudomonas aeroginosa, Burkholderia cepacia, Stenotrophomonas maltophilia. Pneumonia/chronic infection/colonization of cystic fibrosis patients and patients with a tracheotomy, VAP

These bacteria have a tendency for multiple antibiotic resistances.

There are a number of other medically significant bacteria that only periodically present in the pediatric intensive care unit. These bacteria are prevalent in some regions and not elsewhere. They will not be discussed further in this chapter.

Fungi (of Importance in the PICU)

Classification

- Yeasts (e.g., *Candida* or *Cryptococcus* sp.)
- Molds – filamentous fungi (e.g., *Aspergillus* sp. and *Trichophyton* sp.)
- Dimorphic fungi – yeasts in tissue but grow in vitro as molds (e.g., Histoplasmosis)

Candida. C. albicans has the highest incidence in the critical care environment followed by *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. Krusei*. Localized and systemic infections in neonates and immunocompromised children. Any organ can be involved: mucous membranes, larynx, esophagus, brain, eyes, lungs, heart, kidneys, liver, and spleen.

Aspergillus. A. fumigatus is the most common species in invasive aspergillosis, followed by *A. Flavus*, and *A. Nigra*. Localized and systemic infection in immunocompromised children (particularly post stem cell transplant and in children with AML); in the skin, subcutaneous tissues, nasopharynx, lungs, brain, and virtually any other organ.

Endemic Mycosis (Histoplasmosis, Blastomycosis). Pneumonitis, hepatosplenomegaly, fever in children with T-cell dysfunction and in those with HIV infection.

Coccidioides immitis. Pneumonia, meningitis in children with T-cell dysfunction and in those with HIV infection.

Cryptococcus neoformans. Pneumonia, meningitis in children with T-cell dysfunction and in those with HIV infection.

Viruses (of Importance in the PICU)

Human Herpes Viruses

1. Herpes Simplex Virus (HSV, types 1 and 2)
   (a) Systemic infection in the neonate with shock and coagulopathy and severe liver failure
   (b) Encephalitis, hepatitis
   (c) Local (mouth, esophagus, larynx, lungs, heart, liver, kidneys, CNS) or systemic disease in organ and stem cell transplant and immunocompromised patients
2. Cytomegalovirus (CMV)
   (a) Congenital infection in the neonate with systemic involvement
   (b) Localized (liver, lungs, heart, kidneys, GI, CNS, eyes) or systemic infection in solid organ and stem cell transplant as well as immunocompromised patients
3. Epstein-Barr Virus (EBV)
   (a) Infectious mononucleosis
   (b) Burkitt's lymphoma, X-linked Lymphoproliferative disorder (XL-LPD), post transplant lymphoproliferative disorder (PTLD)
   (c) Localized (liver, heart, lungs, kidneys, GI, CNS) or systemic infection in solid organ and stem cell transplant and immunocompromised children
4. Varicella-Zoster Virus (VZV)
   (a) Chickenpox and its complications [pneumonia, encephalitis, meningoencephalitis, soft tissue necrotizing infections (caused by streptococcus and staphylococcus and associated with chickenpox)]
   (b) Disseminated Herpes Zoster in immunocompromised children

Parvovirus

1. Hydrops fetalis in the neonate
2. Aplastic crisis in patients with sickle cell anemia
3. Bone marrow failure
4. Myocarditis

Enteroviruses

1. Coxsakie (A and B), and echovirus
   (a) Myocarditis, pericarditis
   (b) Meningitis
2. Poliovirus (types 1 to 3) bulbar poliomyelitis

Adenovirus

1. Upper respiratory infection, pertussis-like syndrome, pneumonia, pharyngoconjunctival fever
2. Acute hemorrhagic cystitis
3. Hepatitis, meningoencephalitis, myocarditis
4. Localized (liver, heart, lungs, kidneys, GI, CNS) or systemic infection in organ and stem cell transplant and immunocompromised children

Hepatitis Viruses (A, B, C, D, E)

Fulminant hepatitis

Retroviruses

HIV/AIDS

Bunyaviridae and Arenaviridae

1. Hemorrhagic fever
2. Encephalitis

Togaviruses and Flaviviruses

1. Dengue
2. Yellow fever
3. Encephalitis

Rhabdoviruses

Rabies

Filoviruses

Marborg and Ebola hemorrhagic fevers

Orthomyxoviruses

Influenza A (H1N1, H2N2, H3N2, $H_{SW}N1$, H5N1), and Influenza B and C

1. Upper respiratory infection; croup, pneumonia, ARDS
2. Encephalitis

Paramyxoviruses

- Measles (pneumonia, croup, encephalitis, subacute sclerosing panencephalitis(SSPE))
- Parainfluenza (bronchiolitis, pneumonia, croup)
- Mumps (parotitis, encephalitis, meningoencephalitis, orchitis, pancreatitis)
- RSV and Human Metapneumovirus (bronchiolitis, pneumonia, ARDS)

Coronaviruses

SARS (severe acute respiratory distress syndrome)

Significance of Viral Infections in the PICU

It is likely that viral infections have been underestimated both in their frequency and the degree of morbidity they cause. Indisputably, in the modern day, HIV (Human Immunodeficiency Virus) is one of the most significant viral pathogens worldwide, particularly in Africa and developing nations that do not have the available resources to prevent spread among the community and more importantly maternal infection of the newborn. This leads to a range of morbidities as discussed in the immunocompromised section of this chapter.

Viral infections are mostly diagnosed clinically on the basis of history and physical examination as well as the regional prevalence of viral diseases. There are a number of ways to test for the presence of a particular virus from either patient blood or other body fluids. These are: tissue culture, serology and seroconversion, immunoflouresence, and PCR (Polymerase Chain Reaction). Only two of these are of any use to the intensivist: PCR and Immunoflouresence. The turnaround time for viral culture and serum serology is inefficient in the critical care context.

Respiratory Viruses (Respiratory Syncytial Virus, Influenzae, Adenovirus, ParaInfluenzae, and Human Metapneumovirus) are the main contributors to viral disease in the PICU, as they are in the general pediatric population. In the PICU the majority of patients that develop significant degrees of illness are those who have significant comorbidities. Conditions such as ex-prematurity, chronic lung disease, neuromuscular diseases, and congenital heart disease are probably the most common of these.

Herpes Virus family, particularly herpes simplex virus (HSV), is the next important contributor to the burden of viral disease. All members of this family (HSV, EBV, CMV, and VZV) can cause serious infections in the neonate and in immunocompromised children.

Viral Epidemics and Pandemics

All services that treat the acutely unwell child (and adult) are at risk of being overwhelmed in an epidemic. National and regional planning needs to be undertaken prior to the advent of any serious infection where ever possible. (Examples are SARS -Severe Acute Respiratory Syndrome,

or H1N1 "Swine Flu.") This is encapsulated in the worldwide pandemic planning taking lessons from the SARS epidemic and the last major (in terms of mortality) influenza epidemic, the "Spanish Flu" that was prevalent from 1918 to 1920.

At a hospital or an organizational level the concept of "surge strategy" is used. This is an organization based contingency plan to deal with large numbers of patients admitted simultaneously (i.e., mass trauma casualties or epidemics). In the case of influenza (or SARS) this is relevant to the intensive care in that there is a finite capacity of any unit to provide mechanical ventilation. In addition to this, the institution is responsible for the protection of health care workers who are at high risk to contract an infectious illness and become a patient themselves. This would further increase the burden of illness and has the potential to limit available human resources.

Regional Viral Infections

The prevalence of HIV in the general population and, in particular, in children in many developing countries poses significant stress on limited resources. Hopefully, with more effective preventive programs to control vertical transmission of the infection and with availability of affordable anti-HIV medications, the quality of care for HIV-infected children will improve and the need for intensive care will diminish.

Regional or local experience is crucial in the management of many infections. Dengue fever and viral hemorrhagic fevers, which are of more global importance, will be reviewed in more detail.

Dengue Fever

Dengue infections, caused by the four antigenically distinct dengue virus serotypes (DEN1, DEN2, DEN3, DEN4) of the family Flaviviridae, are the most important arbovirus diseases. Dengue is the most widely distributed mosquito-borne viral infection of humans, affecting an estimated 100 million people worldwide annually. Dengue hemorrhagic fever usually occurs in children, with peaks in incidence at 7 months of age (with dengue-immune mothers), and at 3–5 years of age (during a second infection with a new serotype). It is spread throughout the tropical and subtropical zones between 30°N and 40°S where environmental conditions are optimal for viral transmission by *Aedes* mosquitoes, principally *Aedes aegypti*. The disease is endemic in SE Asia, the Pacific, West Africa, the Caribbean, and the Americas.

Global warming, by increasing the range of Aedes mosquito, has the potential to lead to more widespread disease.

WHO has classified the severity of dengue infection on the basis of a combination of clinical and laboratory findings (presence of hypotension and shock, tourniquet test, lowest platelet count, plasma leakage represented by high hematocrit level) in to:

- Dengue fever
- Dengue hemorrhagic fever
- Dengue shock syndrome (DSS)

Severe Dengue (Dengue Hemorrhagic Fever and Dengue Shock Syndrome)

1. Increased vascular permeability and "plasma leakage" leading to shock is the hallmark of severe dengue infection in children. High or progressively rising hematocrit is often a sign of plasma leakage. A drop in platelet count to 100,000/mm^3 or less usually precedes a rise in hematocrit. Tachycardia, a narrow pulse pressure (<20 mmHg), prolonged capillary refill time, and cold extremities herald impending shock if appropriate treatment is not rapidly initiated. Hypotension is usually a late sign. Shock often occurs on day 4–5 of illness. Early onset shock (day 2 or 3) suggests very severe disease.
2. Bleeding; skin or mucosal, GI bleeding.
3. Hepatitis; RUQ tenderness and jaundice.
4. Encephalopathy; lethargy or restlessness, coma, seizures.

Management of Dengue Shock Syndrome (DSS)

Treatment is supportive; there is no specific treatment for dengue infections. The only effective treatment in DSS is timely, aggressive fluid resuscitation. There is no evidence that colloids are superior to crystalloids. With appropriate use of fluid resuscitation in DSS, the mortality has dropped from 10% to <0.2%. Steroids have not been shown to be effective. There may be a role for intravenous immunoglobulin (IVIG) or plasma exchange in severe dengue infections. Hypoglycemia and hyponatremia should be avoided and rapidly corrected if present. A platelet count of less than 20,000, or less than 40,000, with associated bleeding warrants platelet transfusion. Ventilation should be supported as needed by noninvasive or invasive mechanical ventilation. If ascites or pleural effusions (which are not uncommon due to vascular leak) cause hemodynamic

or ventilatory compromise, the collection should be drained. Renal dysfunction may need hemofiltration/dialysis.

Viral Hemorrhagic Fevers

Viral Hemorrhagic Fever is a loosely defined category that includes infections from a host of viruses leading to similar clinical syndromes and sharing a similar severity of illness. Otherwise, these viruses are different from each other with regard to their reservoir hosts, geographic distribution, and taxonomy. Risk factors for exposure also vary among these infections and hence the control methods are geared to specific infections and their causative agents and intermediate hosts. In endemic areas diagnosis is by and large clinical and is confirmed by serological tests and viral PCR or culture. There are vaccines developed for some of these viruses.

As a group, the treatment for these infections in the PICU is mainly supportive and includes measures to:

- Optimize hemodynamic state and treat shock
- Monitor and control brain edema and intracranial hypertension
- Support ventilation and gas exchange with noninvasive or invasive ventilation
- Treat coagulopathic state if symptomatic
- Provide renal replacement therapy if needed; monitor and optimize glucose and electrolyte levels

Exhaustive discussion of this topic is beyond the current chapter, so the most important ones are briefly mentioned here.

Yellow Fever

Yellow fever is endemic in tropical Africa between 15°N to 10°S and in parts of Central and South America between 10°N and 40°S. In the life-cycle of this virus, in different parts of the world, mosquitoes (*A. aegypti*, *Haemagogus*, *and Sabethes*), monkeys, and people are involved; however, epidemic mosquito-borne human-to-human transmission can occur.

After an incubation period of 3–10 days, fever, headache, malaise, nausea and vomiting, and musculoskeletal pain occur suddenly. Initially, the clinical signs may include conjunctivitis, flushing of the skin, and relative bradycardia. In about 10% of cases the illness deteriorates with development of shock, systemic toxicity, GI bleeding, renal dysfunction, liver failure and jaundice, encephalopathy, and systemic bleeding. This latter picture is associated with a high mortality rate (30–50%).

Differential diagnosis includes other viral hemorrhagic fevers, viral hepatitis, leptospirosis, malaria, typhus, typhoid fever, brucellosis, rickettsial disease, and some intoxications.

Therapy is supportive and these patients may need intensive care admission for hepatic, renal and circulatory failure.

WHO has recommended routine childhood vaccination in endemic areas (for children >4 months of age). Vector control is important in highly populated areas to reduce the risk of epidemic transmission.

Lassa Fever

Lassa fever causes as many as 300,000 cases and 5,000 deaths each year in West Africa and is a leading cause of maternal and fetal deaths. The virus is carried by *Mastomys huberti* and *Mastomys erythroleucus*, the rodent reservoirs whose infectious excretions are the source of human infections in West Africa.

In adults and children, early illness includes fever, malaise, headache, and musculoskeletal pain. These nonspecific symptoms progress over 4–5 days to include pharyngitis, cough, chest pain, diarrhea, and vomiting. In endemic areas, a purulent pharyngitis, with conjunctivitis, head and neck edema, and mucosal bleeding are highly specific signs of Lassa fever.

In severe cases, the illness may be complicated by hypovolemic shock, encephalopathy, respiratory distress caused by laryngeal edema, pleural effusions, or pneumonitis. Liver failure, systemic and GI/GU bleeding, and myocarditis can occur. Mortality is between 15% and 30%. There are anecdotal reports of the use of intravenous ribavirin in critically ill children with Lassa fever but treatment is mainly supportive.

Lassa fever has been transmitted from person to person during hospitalization. Universal exposure precautions should be observed as well as contact and droplet precautions.

Congo-Crimean Hemorrhagic Fever (CCHF)

CCHF is caused by a nairovirus (family Bunyaviridae), and is transmitted by *Hyalomma* ticks and by contact with infectious body fluids. The geographical distribution of the Hyalomma ticks covers Africa, the Middle East and Mediterranean areas, Eastern Russia, and West Asia.

The incubation period is from 2 to 9 days. Illness onset is abrupt and nonspecific, with fever, chills, rigors, intense headache, and generalized muscle pain. Onset of bleeding

in the skin, mucous membranes, and the GI tract usually occurs after 3–6 days of illness. Hepatitis, liver failure, circulatory failure, shock, and ARDS can ensue with mortality in up to 30% of cases.

Treatment is mainly supportive. The virus is sensitive in vitro to Ribavirin, and this agent has been used in management of CCHF with variable success (WHO). The value of immune plasma from recovered patients for therapeutic purposes has not been demonstrated, although it has been employed on several occasions (WHO).

Patients with suspected or confirmed CCHF should be cared for by staff using added droplet and contact precautions.

Hemorrhagic Fever with Renal Syndrome (HFRS)

HFRS is caused by Old World Hantaviruses (family Bunyaviridae). The reservoirs are small rodents, and humans are infected percutaneously or by direct exposure. Clinical illness has an abrupt onset with fever, severe musculoskeletal pain, renal failure, systemic and GI bleeding, circulatory failure, and shock. This form of the disease is more common in Asia and Eastern Europe.

In Hantavirus pulmonary syndrome (HPS) (mainly seen in the Americas), within 12–24 h of onset of symptoms, most patients develop some degree of hemodynamic instability and pulmonary edema accompanied by hypoxemia to full blown ARDS. Petechiae of the head and neck are common but overt hemorrhagic symptoms are not. Treatment is supportive and in those who survive, recovery is usually rapid.

When given early in the course of illness, intravenous ribavirin has improved survival rate in HFRS but not in HPS. Steroids reduce the severity of the symptoms but do not increase the survival rate.

Parasitic Infections in the PICU

Malaria is singled out here because it is the most significant parasitic disease in humans with an estimated 500 million infections annually that result in 1–3 million deaths. The majority of these deaths are in children younger than 5 years of age and most are in Africa. In developed countries malaria is the most common cause of febrile illness with no localizing signs in travelers returning from developing countries. The most important aspects of severe malaria are reviewed, which, for the most part, is caused by *Plasmodium falciparum.*

Severe Malaria

Indicators of severe and complicated falciparum malaria and prognostic signs (World Health Organization 2000)

Cerebral malaria	Unrousable coma (GCS < 11/15), with peripheral *P. falciparum* parasitemia after exclusion of other causes of encephalopathy
Severe anemia	Hgb < 5 g/dl in the presence of parasitemia >10,000 per ml
Respiratory distress	Pulmonary edema, ARDS, labored "acidotic" breathing
Renal failure	UOP < 0.5 ml/kg/h (<400 ml/24 h in adults), and a serum creatinine >265 micromole/l (>3 mg/dl)
Hypoglycemia	Whole blood glucose <2.2 micromole/l (40 mg/dl)
Shock	
Coagulopathy	Bleeding and/or lab evidence of DIC

Complicated Malaria

Impaired consciousness of any degree, prostration, jaundice, intractable vomiting, parasitemia >2% in nonimmune individuals. Levels of parasitemia should be interpreted in the light of immunity.

Patients with complicated malaria should be managed as severe malaria, i.e., with parenteral antimalarials even though they do not necessarily meet the criteria of severe disease. For details of management, review Chap. 101, "Malaria".

Cerebral Malaria

The World Health Organization defines Cerebral Malaria as unrousable coma in the presence of *P. falciparum* parasitemia when other causes of encephalopathy have been excluded. The precise etiology of cerebral malaria is not certain. Most likely it is caused by sequestration of infected erythrocytes. This condition has a high mortality that likely results from brain micro vascular ischemia, infarction, and secondary cerebral edema.

Cerebral malaria is a medical emergency that requires:

1. Supportive care:
   (a) Continuous monitoring of vital signs.

(b) Monitoring of serum electrolytes and glucose and correction of the abnormal results with appropriate therapy.
(c) Seizures are frequent and will require suppression with anticonvulsants.

2. Specific Parenteral Malarial therapy: Detailed discussion of anti malaria treatment is reviewed in Chap. 101, "Malaria".

   Parenteral quinine remains the first line treatment for severe falciparum malaria. Intravenous administration of this drug requires monitoring of the ECG and cardiac function. For travelers returning from Southeast Asia where quinine resistance is common, advice regarding the use of intravenous artesunate should be sought from specialist centers.
3. Extracorporeal therapy: For severe parasitemia exchange transfusion may be required. Renal replacement therapy may be necessary in those presenting in advanced shock and multiorgan system failure (MOSF).
4. Management of intracranial hypertension: Please read the section on raised intracranial pressure in bacterial meningitis later in this chapter, as the management is similar.

Sepsis Syndromes

For a detailed discussion on Sepsis, and the diagnosis and management of shock, please review the appropriate chapters (Chap. 61, "Bacterial Sepsis and Shock"). Toxic shock and necrotizing fasciitis are two particular sepsis syndromes that require a special reference.

Toxic shock syndrome (TSS) is caused by two bacteria: *Staphylococcus* and S*treptococcus.*

Staphylococcal Toxic Shock

S. aureus is a Gram-positive coccus that is grouped in clusters. It is responsible for a number of infections ranging from skin sepsis, pneumonia, and joint infections to endocarditis. Phage transformed *Staphylococcus* produces a toxin that initiates a syndrome known as toxic shock syndrome (TSS). This came to light in the 1980s with the "Menstrual Shock" syndrome. A non menstrual form was also identified. This was associated with *Staphylococcus* sepsis at surgical sites, skin or joint infections, and with staphylococcal pneumonia.

This syndrome is said to be "superantigen" mediated. The toxin proteins produced by the *Staphylococcus* are able to "cross-link" the T-cell receptor without being processed by an antigen presenting cell (APC). This leads to an uncontrolled cascade of cytokines and immune system up regulation. At the level of the capillary this leads to inflammation and increasing permeability with secondary organ dysfunction (renal impairment, cardiac, pulmonary, and liver dysfunction). Clinically this is manifested by skin erythema, tachycardia, hypotension, hypoxia and other critical organ dysfunction. Initially this is subtle but rapidly develops into multi organ dysfunction. See the table below for the criterion upon which a diagnosis of Staphylococcal toxic shock is made.

Treatment consists of recognition of the process, draining any collections of pus, and debridement, if that is appropriate. At the same time initiation of large volume fluid resuscitation, inotropic support and support of failing lungs with oxygen and ventilation if needed. Anti-staphylococcal antibiotics should be administered (this includes an antibiotic to cover for methicillin resistant *Staphylococcus*). Clindamycin being an anti-ribosomal antibiotic (50S bacterial Ribosome) has a theoretical advantage in reducing the amount of toxin produced prior to antibiotic induced death of the bacterium. Intravenous immunoglobulin (IVIG) is a treatment for severe toxic shock that is progressing to multi-systems dysfunction. It has a proven efficacy in toxic shock in reducing the mortality of severe disease. This is thought to be via two general mechanisms. The first is by binding directly to the toxin. The second is by its immuno-mediatory properties.

Staphylococcal Toxic Shock Syndrome (Case Definition from CDC)

Major criteria (all required)

1. Fever $\geq$38.8°C
2. Hypotension (orthostatic or shock)
3. Rash (erythematous early and desquamative later)

Minor criteria (any three required)

1. Gastrointestinal: vomiting or diarrhea
2. Muscular: severe myalgia or CPK $\geq$2x upper limit of normal
3. Mucous membranes: vaginal, oropharyngeal, or conjunctival hyperemia
4. Renal: urea or creatinine $\geq$2x upper limit of normal, or urinalysis with $>$5 WBC per high-power field
5. Hepatic: total bilirubin, AST or ALT $\geq$2x upper limit of normal
6. Blood: platelet count $<$100,000/µl
7. CNS: disorientation or change in level of consciousness without focality, noted when fever and hypotension are absent

And

1. Absence of other explanations
2. Blood cultures negative (except for *S. aureus*)

Streptococcal Toxic Shock

Streptococcal toxic shock is a syndrome that is analogous to staphyloccal toxic shock syndrome in that it is a superantigen mediated toxin related dysfunction of the immune system. Group A beta-hemolytic *Streptococcus* is most commonly associated with streptococcal toxic shock syndrome. Clinical presentation is very similar to staphylococcal toxic shock. See table below.

Treatment consists of appropriate antibiotics. Clindamycin is used for antimicrobial and antitoxin producing properties as previously mentioned. IVIG here too has a role in reducing the mortality of severe disease. Intensive care therapy consists of fluid resuscitation (large volume) and support of organ dysfunction (inotropes, ventilation, renal replacement therapy).

Streptococcal Toxic Shock Syndrome (Case Definition from CDC)

Hypotension or shock, plus any two of the following:

1. Scarlet fever rash
2. Abnormal liver function tests
3. Renal insufficiency
4. Disseminated intravascular coagulopathy (DIC)
5. Acute Respiratory Distress Syndrome (ARDS)
6. Soft tissue necrosis

Definite: preceding requirements + isolation of group A streptococcus from a normally sterile body site

Probable: preceding requirements + isolation of group A streptococcus from a non sterile body site

Necrotizing Soft Tissue Infections

Necrotizing soft tissue infections are aggressive soft tissue infections that cause extensive necrosis, and include necrotizing cellulitis, fasciitis, and myonecrosis.

The following clinical findings may be present:

- Erythema or discolored skin
- Tense edema
- Discolored/gray wound discharge
- Blister
- Ulcer
- Skin necrosis
- Crepitus

Also the following systemic signs may be present:

- Local pain and tenderness out of proportion to physical findings
- Pain or tenderness that extends past the margin of apparent affected skin area
- Fever
- Persistent tachycardia
- Diaphoresis
- Change in sensorium
- Hypotension

Necrotizing Fasciitis is a *surgical emergency*. It is caused by a number of organisms:

Group A beta-hemolytic *Streptococci* and other streptococci, *Staphylococcus, Clostridium, Pseudomonas, Klebsiella, Serratia, Neisseria, Escherichia, Morganella, Proteus, Shigella, Vibrio, Salmonella, Pasturella, Enterobacter, Corynebacterium, Cryptococcus, Fusobacterium, Peptococcus, Eikenella, Bacteroides.*

The most common causative agent is group A Streptococcus. Pathologically it is characterized by micro angiopathic thrombosis and necrosis along superficial and deep fascial planes. The illness is associated with a breach of the integument. This can be by superficial infection, surgery or trauma. Non steroidal anti-inflammatory drugs are implicated in the pathogenesis. In children there is an association with Varicella (Chickenpox) infection. Clinically the lesions appear either pale or have violaceous discoloration, often edematous, and there may be crepitus from gas forming bacteria. *Pain and tenderness in excess of that expected is a feature.* The concern for the intensivist is the physiological decompensation that can lead to rapid cardiovascular collapse. Broad-spectrum (and appropriate) antibiotics are indicated, and mechanical ventilation and cardiovascular support may be needed. Urgent and wide surgical debridment of the affected areas is indicated. In cases of streptococcal necrotizing fasciitis there may be additional benefit from human immunoglobulin (IVIG) therapy. Though this has not been subjected to clinical trials, given the high mortality rate of necrotizing fasciitis and the biologically plausible consideration that IVIG could neutralize the effects of streptococcal superantigens, its use can be justified.

Other treatments that have been used are:

- Vacuum-assisted wound closure (particularly in patients who have had large wound debridement)
- Hyperbaric oxygen (anecdotal evidence)

Anatomical Location of Infections in the PICU

Upper Airway Infection

The child, especially the infant, presenting with upper airway obstruction (UAO) demands immediate attention. Acute inflammation of the upper airway is of greater importance in small children because of the smaller diameter of the airway, hence the greater degree of obstruction from a similar amount of inflammation (resistance changes inversely to the fourth power of the radius of the airway).

The following signs and symptoms are particularly worrisome:

- Inspiratory AND expiratory stridor
- Active expiration (use of the rectus abdominis muscle when exhaling)
- Apnea or irregular breathing
- Increasing tachycardia (if no intervention is done tachycardia may be followed by decreasing heart rate which is usually a pre-arrest sign)
- Hypoxemia (late sign)
- Change in neurological status (becoming increasingly inconsolable and restless, or a child who "stops fighting" and becomes fatigued and hypotonic)

There are many scoring systems for severity of the UAO in children. The following is one suggested by Downes et al. in 1980. Of note there is no mention of the neurological status in this scoring system. Level of alertness and consolability of a small child are very important indicators of the severity of the UAO.

Score			
	0	1	2
Stridor	None	Inspiratory	Inspiratory and expiratory
Cough	None	Hoarse cry	Bark
Retractions and nasal flaring	None	Flaring and suprasternal retractions	Flaring, and suprasternal, subcostal, intercostals retractions
Cyanosis	None	In air	In 0.4 FiO_2
Inspiratory breath sounds	Normal	Harsh, with wheezing or rhonchi	Delayed

Immediate management of acute severe stridor outside the PICU, independent of underlying cause:

- Keep the child and the parent as calm as possible. Do not separate the child from parent.
- Give the parent an oxygen mask to hold near the child's face.
- Call for help urgently from someone with expertise in airway management (usually an anesthesiologist).
- Give nebulized epinephrine (IM epinephrine if airway obstruction is due to anaphylactic reaction). (Skip nebulized epinephrine if you suspect epiglottitis.)
- Do not send the child to the radiology department for a lateral x-ray of the neck.
- Do not administer any sedative medications to the patient.
- Do not do attempt to draw blood for investigations.
- Place ECG monitoring leads and pulse oximetry probe without disturbing the child.
- Do not attempt to place an IV line (obviously you would place an IV/IO access if the child has already had a respiratory or cardiac arrest).
- The airway expert will decide to take the child to the OR for intubation, or transfer to the PICU.

In children, there are many causes of acute UAO, including infections (viral, bacterial) such as infectious mononucleosis, croup, epiglottitis, tracheitis, peritonsillar abscess, retropharyngeal abscess, diphtheria. Noninfectious causes include foreign body, severe allergic reactions, acute angioneurotic edema, airway burn, trauma, and post-extubation in the PICU.

There are many causes of chronic/recurrent UAO. In the history there may be chronic/recurrent symptoms. These patients may become symptomatic acutely (often with a viral respiratory infection) mimicking acquired acute upper airway obstruction. Examples are: choanal atresia, laryngotracheomalacia, vascular ring, laryngeal web, subglottic stenosis, subglottic haemangioma, vocal cord palsy, recurrent angioneurotic edema.

In this section the infectious causes of UAO are addressed to.

The more common infectious etiologies that may present with severe UAO in children are:

- Croup or viral laryngotracheobronchitis
- Bacterial tracheitis
- Epiglottitis

Croup or Laryngotracheobronchitis

Viral croup is the most common form of UAO in children 6 months to 6 years of age (mostly 6 months to 2 years)

and is more common in the autumn and early winter. The site of obstruction is the subglottic area. Obstruction is caused by inflammation and edema.

The most common viral etiology is parainfluenza, but influenza, enterovirus (coxsakie and echovirus), RSV, adenovirus, paramixovirus, rhinovirus, and HSV can cause a similar clinical picture. Human Metapneumovirus has been implicated in a few reports. In immunocompromised children, *Candida sp.* can cause a similar presentation.

Diagnosis

There is a prodrome of mild fever and URI symptoms for 1–2 days before the onset of stridor. The stridor is characteristically harsh, dry, high pitched, and inspiratory. A "barking" or "seal-like" cough is prominent and usually worse at night. These children do have a voice, though hoarse, and they do not have trismus, dyphagia, or significant drooling.

Management

Children with stridor at rest should be admitted for observation, while those with severe UAO should be admitted to a PICU. Up to 15% of children with croup require hospitalization. Usually no investigations are needed.

Administration of steroids (oral route is as good as intramuscular) in the emergency room has decreased the rate of hospitalization. Hospitalized children with croup should receive a short course of oral or intravenous steroids (an example of a regimen is: Dexamethasone 0.6 mg/kg IV/PO as an initial dose followed by 0.15 mg/kg q 6 h IV/PO). Inhaled nebulized epinephrine 1:1,000 solution (0.5 ml/kg, up to 5 mg) reduces the severity of obstruction and stridor. This can be repeated as required. The child must be observed for at least 2 h after a dose of nebulized epinephrine as the effects are transient.

The decision on when to intubate a child with croup is a clinical one. If, despite maximum medical treatment there is not a clinical improvement or perhaps deterioration, a decision to intubate should be made or at least considered. A gentle and smooth intubation, using a tube one size smaller than usual for the age of the child, should be performed by a skilled and experienced practitioner. These children are at risk of accidental extubation and need proper securing of the ETT, skilled nursing care, and adequate sedation only once the airway has been secured.

Most clinicians extubate the child 2–6 days later, when an audible air leak has developed around the ETT and fever has settled.

Epiglottitis

Epiglottitis, or acute bacterial supraglottitis, is a bacterial infection of the laryngeal inlet, and is usually caused by *H. influenzae* type b (Hib). With "classical" Hib epiglottitis, the peak age of involvement is 2–3 years of age. Since the introduction of the Hib vaccine, the incidence of this disease has fallen dramatically, but the vaccine does not offer 100% protection. Also, other organisms like *S. aureus*, *S. pneumoniae*, group A + B *Streptococcus,* and *N. meningitidis* have been implicated as causative agents. The incidence of these latter organisms is higher in adolescents and older children.

Noninfectious causes of epiglottitis have been described in the following conditions:

Kawasaki's disease, Stevens-Johnson Syndrome, airway burn, caustic ingestion, post-radiotherapy, angioneurotic edema, trauma (including trauma from intubation), leukemia, and lymphohistiocytosis. Granulomatous states can cause a more chronic picture (sarcoidosis, TB, or Wegener's granulomatosis).

Diagnosis

As fewer and fewer physicians have seen even one case of epiglottitis, it is important to have a high index of suspicion in any febrile child with UAO.

The following signs are highly suspicious of epiglottitis:

- Usually there are no prodromal signs and symptoms.
- A few hours of high fever and tachypnea.
- Pain with swallowing, hence drooling is common.
- Reluctance to speak.
- The child looks ill, with circumoral pallor, and a "toxic" appearance.
- There is minimal or no coughing.
- Stridor is low-pitched and muffled, more like a snore.
- Child prefers to sit forward in the tripod position with mouth open and is reluctant to move his head or neck.

Management

If you have suspicion (on clinical grounds) that a child may have epiglottitis:

- Do not make the child lie down.
- Do not separate the child from parent.
- Do not examine the throat.
- Do not place an IV cannula.
- Do not order a lateral x-ray of the neck.
- Do not order any blood work.
- Do not transport a child with epiglottitis between hospitals unintubated.

- The child should be accompanied by an expert in difficult airway management to the operating room for examination under anesthesia and securing airway if needed.

The technique for induction of anesthesia is beyond the scope of this chapter. Generally the inhalational method is performed in the sitting position (position of comfort for the child), and once the child loses consciousness intravenous access is secured and the rest of the monitoring is applied. Laryngoscopy and intubation is only attempted after adequate depth of anesthesia has been obtained.

Blood cultures and a swab from the inflamed epiglottis should be sent and a 3rd generation cephalosporin should be given once an IV is in place. When back in PICU, accidental extubation can have disastrous consequences. Skilled taping of the ETT, nursing care, and adequate anaelgesia/sedation cannot be over emphasized.

Usually after 12–48 h of intravenous antibiotics the patient can be safely extubated, once the fever has subsided and presence of a leak is documented and the child is able to swallow (The child is not drooling). Some practitioners prefer to reevaluate by direct laryngoscopy with the patient deeply sedated or anesthetized.

If the causative organism is proved to be Hib, in families with siblings under 4 years of age or families with an immunocompromised child, prophylaxis with Rifampicin should be provided.

Bacterial Tracheitis

Bacterial tracheitis is characterized by profuse purulent secretions or sometimes by pseudomembrane formation in the tracheal lumen. The median age of the patient is 5 years. *S. aureus* is the most common etiology, though other Gram-positive and less commonly Gram-negative microorganisms might be causative. In immunocompromised children *Candida* and *Aspergillus* can cause tracheitis.

Diagnosis

These children usually have a high fever, they look toxic, and the stridor characteristically is high pitched and composed of both inspiratory and expiratory components. Cough is usually prominent and they may have dysphonia or aphonia. Drooling can be seen with bacterial tracheitis. These patients are at risk of airway obstruction. They require appropriate antimicrobial therapy, observation, and intubation by experts if warranted.

Lower Respiratory Tract Infection

Community-Acquired Pneumonia

Community-acquired pneumonia (as opposed to nosocomial or hospital acquired pneumonia) is a common pediatric diagnosis that leads to admission to hospital for intravenous antibiotics and supportive respiratory therapy. Pneumonia means inflammation of the lung parenchyma caused by infection and the diagnosis is made clinically in a febrile child with respiratory signs and symptoms who has evidence of consolidation on CXR.

Blood cultures frequently fail to reveal the infecting organism in pneumonia. Tracheal aspirate, or more reliably, bronchoalveolar lavage (BAL) and on occasions lung biopsy are required. Children with immunodeficiency or malignancy undergoing therapy are a common example of where BAL and/or lung biopsy may be necessary.

Etiology

Viral

- RSV
- Influenza A, B, C
- Parainfluenza types 1–4
- Human metapneumovirus
- Adenovirus
- Others: Rhinovirus, CMV, VZV, Enterovirus, HSV, Measles

Bacteria-typical

- *S. pneumoniae*
- *S. aureus*
- *H. influenzae*
- *S. pyogenes* (group A streptococcus)
- Enteric Gram negatives (*Klebsiella, E. coli, P. aeroginosa*)

Bacteria-atypical

- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*
- *Legionella pneumoniae*

Bacteria-mycobacteria

- *Mycobacterium tuberculosis*

S. pneumoniae and *S. aureus* are the most important bacterial pathogens in children with pneumonia

who need intensive care admission. As a general rule, truly focal disease, confined to a single lobe, is more likely to be due to bacteria. An ill child with unilateral pleural effusion most likely has *S. pneumoniae* or *S. aureus* pneumonia.

Pathophysiology

Routes to acquire infection:

- Inhalation of infected particles (most common)
- Aspiration
- Hematogenous

Invasion of the lower respiratory tract with viruses and bacteria leads to inflammatory changes characterized by migration of neutrophils into the alveoli. Together with alveolar macrophages they provoke the production of inflammatory exudates and cellular debris that lead to consolidation of the lung parenchyma. The surrounding areas can be affected by atelectasis.

Indications for PICU Admission

- SpO_2 <90% in high concentrations of inspired Oxygen (>60% FiO_2)
- Excessive work of breathing which may lead to exhaustion
- Shock and hemodynamic instability
- Change in neurological status (agitation or alteration of the level of consciousness)

Reasons of failure to respond to treatment on the pediatric ward or as outpatient:

- Development of an empyema or less commonly a lung abscess
- Underlying lung disease such as: bronchopulmonary dysplasia (BPD, in ex-premies), cystic fibrosis, inhaled foreign body, tracheobronchomalacia or post tracheal surgery, or infected congenital lung cyst
- Diagnosed or undiagnosed immunodeficiency states (primary, HIV, leukemia)
- Children with neuromuscular diseases, weakness, or spasticity such as muscular dystrophies, myasthenia, spinal muscular atrophy, or cerebral palsy
- Inappropriate antibiotics, inappropriately low dose or resistant bacteria
- Non bacterial pneumonia (viral pneumonia or alternative pathogen such as Tuberculosis)

Once the culture results (BAL, blood culture, sputum culture) and sensitivities are known the therapy should be tailored to the antibiotic sensitivities of the causative organism(s).

Complications

- Empyema. More commonly seen with *S. pneumoniae* and *S. aureus* pneumonia. Generally a chest drain is needed. The use of fibrinolytics and surgery are areas for debate and local advice from thoracic or general surgeons and physicians from the respiratory and infectious diseases services should be sought.
- Lung abscess. With *S. aureus*, *S. pneumoniae*, Group A streptococcus, *K. pneumonia*, *P. aeroginosa*, anaerobic organisms, and Aspergillus. If there is no rapid response to intravenous antibiotics, early percutaneous drainage under CT guidance and a prolonged course of intravenous antibiotics is indicated.
- Pneumatocele, pneumothorax and "air leak," with *S. aureus* or necrotizing lung infections. May need chest drain(s). If possible, wean positive pressure to spontaneous ventilation.
- HUS associated with *S. pneumoniae* pneumonia. These children are usually very sick, younger, and may have associated meningitis. Majority of them need temporary renal replacement therapy while in the PICU.

Bronchiolitis

Bronchiolitis is a seasonal viral infection of the lower respiratory tract that mainly affects infants. The usual cause is respiratory syncytial virus (RSV), although influenza, parainfluenza, adenovirus, and human metapneumovirus can cause a similar syndrome. In young infants, *Chlamydia* and *B. pertussis* can cause respiratory illness with a more prolonged course that initially may resemble bronchiolitis. 20–25% of infants with bronchiolitis may have a secondary bacterial infection.

Infants with bronchiolitis have fever, cough, difficulty in feeding, and, on occasion, audible wheezing. On examination bronchiolitis is a syndrome characterized by respiratory distress, hyperinflation of the chest, and wheezes with fine inspiratory crackles heard on auscultation.

Apnea may occur even before onset of clinically significant respiratory distress, especially in ex-premature

and very young infants. Though not common, neonates may present with hypothermia and a sepsis like syndrome. The following groups are at increased risk of severe infection:

- Ex-premature infants and neonates
- Infants with congenital heart disease
- Infants with immune deficiency
- Infants with neuromuscular disease

Pathophysiology

The virus causes direct damage to the respiratory epithelium with resultant inflammation, increased secretions, small airway obstruction. Areas of hyperinflation and atelectasis exist simultaneously throughout the lung. This leads to ventilation and perfusion (V/Q) mismatch and hypoxia. Hyperinflation flattens the diaphragm and makes breathing less efficient.

Management Outside the PICU

- Hydration and nutrition: nasogastric feeding (if the infant does not seem to need immediate ventilatory support), intravenous fluids.
- Oxygenation: suction the nasal and nasopharyngeal airways frequently and provide supplemental oxygen via nasal cannulae or head box to keep SpO_2 >90%.
- Drugs: "Routine" use of bronchodilators (salbutamol, ipratropium, and epinephrine) is not recommended. In practice, the response to a single dose of nebulized Salbutamol should be evaluated and continued only if improvement is observed.
- Ribavarin has NOT been shown conclusively to improve the outcome.
- Antibiotics are not routinely recommended, except with bacterial super infection.
- Steroids are not indicated.

Do not over hydrate the child; there are reports that up to one third of these infants have hyponatremia due to excessive levels of ADH.

Indications for Transfer to PICU and Respiratory Support

- SpO_2 < 90% despite high concentrations of supplemental O_2 (> 60%)
- Apnea or irregular respiratory effort
- Excessive work of breathing leading to exhaustion (inability to settle or paucity of spontaneous movement)

Guidelines for Respiratory Care in Infants with Bronchiolitis

Should they require respiratory support, many of these infants can be managed with noninvasive continuous positive airway pressure (CPAP) at 4–8 cm H_2O. This reduces the work of breathing and improves oxygenation. Suction to maintain patency of airways is of crucial importance. If the saturations remain low and/or the infant continues to have frequent apneas despite providing noninvasive ventilatory support intubation of the trachea is indicated.

- Intubation is usually required for several days.
- Inadequate humidification and inadequate tracheal suctioning cause endotracheal tube blockage or lung atelectasis followed by increasing pressure and FiO_2 requirements.
- As a general rule, the best ventilatory mode is one that assists spontaneous respiratory efforts; keep the child's own respiratory and coughing efforts by providing enough comfort (sedation) and pressure support.
- PEEP or CPAP (initially at 4–6 cm H_2O) may reduce the work of breathing.
- Apply enough peak inspiratory pressure (PIP) to achieve visible chest excursions and if higher pressures (>30 cm H_2O) are needed, let the $PaCO_2$ gradually rise to 75–80 mmHg with arterial pH > 7.2 (permissive hypercapnia).

Particular issues in infants with congenital heart disease and bronchiolitis:

- Infants with left to right shunts have more frequent viral and bacterial respiratory infections, and have higher morbidity and more prolonged course with bronchiolitis.
- Infants with palliated single ventricle physiology and those with limited cardiac output (for example severe valvar aortic stenosis) have high morbidity and mortality with bronchiolitis.
- Bronchiolitis and other viral respiratory infections in infants with congenital heart disease lead to operative delays and increasing complications post cardiac bypass surgery (e.g., pulmonary hypertension). In any infant with RSV bronchiolitis and congenital heart disease awaiting surgery, it is suggested to wait for 2–3 weeks before proceeding with bypass and surgery.

The American Academy of Pediatrics has specific recommendations on prophylactic monthly injection of RSV monoclonal antibody in "at risk" infants during the cold season. However, the use of this approach has only been shown to aid a small number of patients.

Cardiac Infections in the Pediatric Intensive Care Unit

This section reviews:

- Myocarditis
- Infective endocarditis
- Infectious pericarditis
- Wound infection after cardiac surgery

Myocarditis

Myocarditis is an inflammatory disease of the heart muscle characterized in its active phase by cellular infiltrates and myocardial necrosis. However myocarditis can have cellular infiltrates with little or no myonecrosis. Most cases of myocarditis are thought to have a viral etiology; however, viruses are infrequently isolated. The most common viral causes include the enterovirus family particularly coxsackievirus B and adenovirus. Other viral causes are influenza, CMV, HSV, parvovirus, rubella, varicella, mumps, HIV, and EBV. Myocarditis has a number of other non viral etiologies, some infective and some not. They include bacteria, rickettsia, fungi, protozoa, pharmaceuticals, toxins, and connective tissue/autoimmune disorders.

Typically viral myocarditis begins as a systemic viral illness with flu-like symptoms. As the virus infects the myocytes the immune system is up regulated and CD4 T-helper cells and CD8 cytotoxic T cells are stimulated along with proinflammatory cytokines. Persistence of the viral RNA and production of NO by the myocytes have been linked to myocardial tissue damage.

Myocarditis can present in a number of ways:

- Out of hospital cardiac arrest/sudden death
- Cardiogenic shock (May mimic sepsis)
- Congestive heart failure (increasing dyspnea, lethargy)
- Dysrhythymias – bradycardia, tachycardia

Whilst sepsis and hypovolemic shock are more common than cardiogenic shock from myocarditis, it should always be in the differential. Sometimes acute "decompensation" of these children is heralded by abdominal distension and vomiting. Teenagers may complain of a feeling of "impending doom" or severe chest discomfort.

Clinically, signs of tachycardia/tachypnea, gallop rhythm, hyperdynamic precordium, and displaced apex are often present. Hepatomegaly and in older children elevated Jugular Venous Pressure (JVP) are usually present. Crackles on auscultation are often present in the chests of older children.

Chest x-ray (CXR) may show an enlarged heart, pulmonary venous congestion, alveolar edema, Kerley B lines, and in some cases pleural effusions. In acute myocarditis the heart may often look normal in size on the CXR. A 12-lead ECG is useful to assess underlying rhythm, assess for ischemia and for the subtle ECG changes that are sometimes evident with myocarditis; ST-T changes, reduced QRS voltage, widened QRS.

Echocardiography is absolutely necessary to assess structure and function of the heart and to assess for a pericardial effusion. Involvement of appropriate specialists is important – cardiologists, intensivists, and cardiothoracic surgeons work cooperatively to manage and stabilize these patients.

Treatment of myocarditis is largely supportive. Immunomodulation using steroids, intravenous immunoglobulin, and immunosuppressive agents is controversial. Identifying any modifiable contributors, i.e., toxins and drugs, is of crucial importance. Supportive therapy for heart failure associated with myocarditis ranges from diuretics and afterload reduction, addition of inotropic support to placing the patient on mechanical circulatory support. Dopamine and Dobutamine increase contractility but also heart rate and myocardial oxygen consumption. Milrinone is an intravenous phosphodiesterase inhibitor that improves contractility and at the same time, reduces the afterload. Enoximone is an oral phosphodiesterase inhibitor that is available in Europe, but not in North America. Levosimendan is a calcium sensitizer and improves contractility. It has limited availability world wide.

Positive intrathoracic pressure, given noninvasively via a face mask (CPAP), reduces LV afterload and may improve cardiac output in the setting of LV dysfunction.

Failed medical therapy or deteriorating function will usually indicate the need for extracorporeal support and ultimately heart transplantation. Mechanical support (ECLS, "Berlin" heart) is frequently used as a "bridge" to recovery or transplant.

Endocarditis

For a complete review of endocarditis review the Cardiology chapter in this book. The major reasons a child with endocarditis may need admission to PICU are:

1. Congestive heart failure due to worsening valvar regurgitation
2. Congestive heart failure with abrupt onset due to valve apparatus rupture/perforation, or dehiscence of a prosthetic valve
3. Systemic to pulmonary artery shunt obstruction
4. Arrhythmia
5. Renal failure
6. Embolic events to
   (a) Brain
   (b) Heart
   (c) Lungs
   (d) Bowel
   (e) Extremities

Infectious Pericarditis

For a complete review of pericarditis and tamponade, please review the Cardiology chapter in this book.

Acute inflammation of the pericardium in a previously healthy child has usually been assumed to be viral. In most cases a causative agent is not detected (hence the term "idiopathic" pericarditis). An upper respiratory infection usually precedes the onset of symptoms by 10–14 days. The reported viral pathogens include coxsackievirus, adenovirus, RSV, varicella, hepatitis B, HIV, and post influenza vaccine.

Primary infectious pericarditis that may need PICU care is usually purulent bacterial pericarditis. These patients are generally toxic looking. The infection in the pericardium rarely occurs in the absence of infection elsewhere (hematogenous spread). In comparison with the viral (idiopathic) pericarditis, the incidence of tamponade and hemodynamic instability is much higher with purulent pericarditis.

S. aureus is the most common cause of purulent pericarditis. Other bacteria include *H. influenzae*, *N. meningitides*, and *S. pneumoniae*.

In developing countries, tubeculous pericarditis is a common cause of chronic constrictive pericarditis.

Treatment of Purulent Pericarditis

Therapy depends on the hemodynamic status of the patient. A toxic-looking child with physiological signs and symptoms of tamponade should be transferred urgently to the catheterization laboratory or to the intensive care unit for percutaneous drainage of the pericardial collection. Sometimes the pus in pericardium is so thick or organized (esp. with *H. influenzae*) that percutaneous drainage may not be sufficient and the child will need open surgical drainage. With tamponade physiology, administration of fluid boluses can temporarily increase the intracardiac "filling" and stabilize the patient until the definitive treatment (percutaneous or surgical drainage) is performed.

Broad-spectrum intravenous antibiotics with good antistaphylocccal coverage should be commenced promptly if purulent pericarditis is suspected.

Wound Infection After Cardiac Surgery

Surgical wound infections after cardiac surgery can be categorized as superficial (cellulitis) or deep (mediastinitis). The patient usually presents a few days after the procedure, but may occur up to 2 months after the initial operation. The important signs are erythema and induration at the surgical incision. The child may be irritable and have a mild fever. There may be a leukocytosis with "left shift" and elevated inflammatory markers such as C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR). In addition to the wound erythema with or without purulent discharge there may be signs of sternal instability with "crepitus" on direct pressure over the sternum. Diagnosis nevertheless is a clinical one and relies on a high index of suspicion. The risk factors are: neonates, long cardiopulmonary bypass time, delayed sternal closure, and reexploration of the chest for postoperative bleeding. The most common organisms associated with sternal wound infections are *S. aureus*, *S. epidermidis*, *Enterococcus* species, and *Candida* species.

Antibiotic treatment should begin as soon as a sternal wound infection is suspected and a wound swab has been sent. Blood cultures should be sent from both peripheral and central venous sites whenever possible. The initial antibiotic regimen should consist of broad-spectrum Gram-positive (anti-staphylococcal) coverage, with the addition of Gram-negative coverage if the patient is septic or mediastinitis is suspected. If there is not a rapid improvement or the patient deteriorates the sternal wound may need to be surgically explored and debrided. Antibiotics should be given for 10 days to 2 weeks for cellulitis and for 4–6 weeks for deep wound infections.

Central Nervous System Infections

Purulent Meningitis

Meningitis is an inflammation of the leptomeninges of the brain. For a review of "aseptic" meningitis which also

includes viral causes of meningitis, please look at the Neurology and Infectious Disease chapters in this textbook. Suffice to mention that patients with "aseptic" meningitis are usually not as sick as those with purulent meningitis, and the CSF abnormalities are not as prominent. Patients with bacterial meningitis have a number of reasons for requiring intensive care. The most common clinical scenarios are coma and seizures.

The local inflammatory response to bacteria multiplying in the CSF involves polymorphonuclear leukocytes, the endothelium, complement, and cytokines. This results in an alteration in the cerebral blood flow and venous drainage, vascular inflammation, and obstruction to CSF flow and reabsorption. The infection within the meninges may extend to the surrounding brain parenchyma.

The commonest bacteria are *S. pneumonia*e, *N. meningitidis*, and *H. infuenzae*. In the neonatal period, the likely causative organisms are different: Group B streptococcus, *L. monocytogenes*, and Gram-negative bacilli are the commonest.

This profile will be modified depending on the local vaccination policy, socioeconomic status of the children in the area, and local/regional epidemics of disease.

None the less the intensive care management is similar:

1. Broad-Spectrum CNS penetrating antibiotics with narrowing of spectrum of antibiotic cover once results of cultures of the blood and CSF are known. Antibiotics with high CSF/brain tissue penetrance must always be used. In areas with high incidence of *S pneumonia* penicillin resistance (including the United States), empiric therapy for community-onset bacterial meningitis is both vancomycin and a 3rd generation cephalosporin.
2. Appropriate level of observation and intensive care support depending on level of consciousness and physiological derangement.
3. Management of raised intracranial pressure (ICP):
   (a) Head in the midline and at 30°, no obstruction to the jugular venous return.
   (b) Sedation and analgesia in intubated and monitored patients.
   (c) Aggressive control of fever and seizures.
   (d) Hyperosmolar agents such as mannitol and 3% sodium chloride.
   (e) In intubated patients, keep $PaCO_2$ in the low normal range (35–40 mmHg) and use hyperventilation temporarily and *only* for acute rises in ICP.
   (f) CSF drainage (via an extraventricular drain), and (rarely) decompressive craniectomy. This is usually in discussion with an infectious diseases expert and a neurosurgeon.

Acute complications of bacterial meningitis are:

- Hyponatremia (serum sodium <135 micromole/l): This is usually due to the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). There is hyponatremia and low serum osmolarity without signs of hypovolemia. Hyponatremia can cause convulsions. Cerebral salt wasting is a much rarer condition that gives hyponatremia *with* signs of volume contraction. SIADH is treated by free water restriction and cerebral salt wasting is treated with sodium (either IV or PO) supplementation. In a hyponatremic child with convulsions give 3% NaCl 3–5 ml/kg intravenously. It is important to note that the change of serum sodium (and hence serum osmolarity) is of more importance in some cases than the absolute serum sodium. A sudden drop in serum sodium (greater than 0.5–1.0 micromole/h) should be treated with hypertonic saline.
- Seizures: Convulsions that occur early in the course of purulent meningitis are usually generalized and have less prognostic significance than those occurring later. Etiology of convulsions in meningitis can be any of the following: brain edema, diffuse ischemia, hyponatremia, subdural collection, sinus venous thrombosis, or focal infarction.
- Subdural effusion: This complication is seen more commonly in neonates and infants. A good practice is to measure the head circumference daily in any infant with meningitis. The diagnosis is made or confirmed by neuroimaging. If the effusion is large, or if it is associated with focal signs, convulsions, or signs of increased intracranial pressure, a neurosurgical consultation is necessary.
- Obstructive hydrocephalus: Obstructive hydrocephalus occurs when the pus (often with high protein content) in the ventricles blocks the outflow of CSF. This situation occurs more frequently in small infants and neonates.

Encephalitis

Similar to meningitis, seizures, focal or generalized signs, and coma, are common presentations. The list of differential diagnosis is long and includes: aseptic meningitis, post infectious encephalitis and noninfectious encephalopathies (metabolic, vascular, demyelinating disease, tumor).

The most frequent causes of acute encephalitis include: enteroviruses, HSV, VZV, EBV, adenovirus, influenza virus, and *M. pneumoniae*. Mumps, measles, and rubella infections are rarely seen in developed countries.

In many parts of the world arboviruses are major causes of endemic encephalitides. Tuberculosis is always high on the list of differential diagnosis in developing countries.

Diagnosis: CSF can be completely normal, but usually contains >10 leukocytes/mm^3 (mainly lymphocytes), mildly increased protein level and mildly reduced to normal glucose level. In children with HSV encephalitis, the CSF may contain red blood cells. CSF in addition to cell count, chemistry and culture should be sent for PCR for viral agents. CSF PCR can be helpful in a number of the infectious encephalopathies. For example: *M. pneumoniae*, Mycobacterium, CMV, EBV, VZV; where the organism may not be cultured from the CSF.

Brain imaging (CT or MRI) can be helpful in the diagnosis. In HSV encephalitis there may be focal edema and enhancement seen in the temporal area. This is relatively specific for HSV infection of the brain.

The electroencephalogram may show focal periodic epileptiform activity in frontal and temporal parts of the brain. This is common in HSV disease. Diffuse slow waves generalized over the cerebral cortex may also be seen. This may either represent encephalitis or be secondary to sedatives and anticonvulsants used in the PICU. The primary use of EEG is in the management of seizures.

Finally, when the etiologic diagnosis is not clear, or the patient is deteriorating despite treatment, brain biopsy may be performed.

Treatment is largely supportive. As for meningitis this consists of appropriate antimicrobial (antiviral) therapy. There should be no delay in starting Acyclovir if HSV is suspected or considered. The dose is 30 mg/kg/day for 10 days. When *M. pneumoniae* is suspected antibiotics with good penetration into the brain (ciprofloxacin, or azithromycin) should be used.

Additional management includes airway protection for coma and seizures. Medical and surgical therapies for management of intracranial hypertension, as discussed above should be adhered to.

Acute Demylinating Encephalomyelitis (ADEM)

ADEM is an acute or sub acute inflammatory demyelinating disease of the CNS (brain and spinal cord). In contrast to multiple sclerosis it is a monophasic illness. ADEM is considered a parainfectious disease and the precipitants include infection with upper respiratory tract viruses, influenza, group A streptococcus, EBV, VZV, measles, mumps, rubella, and *Mycoplasma*.

Clinical presentation may involve fevers, seizures and a constellation of neurological phenomena. Commonly these are coma, focal neurological deficits or alterations in personality and behavior. Often a recent "viral infection" is present in the history.

The lumbar puncture is done to exclude infections. CSF may have normal white cell count or mild pleocytosis (mainly lymphocytes), and mild to significant protein elevation. The cultures and PCR should be negative.

Neuroimaging is the main diagnostic tool for ADEM MRI is the modality of choice, as the CT is normal in 40% of cases. The typical MRI findings are multiple disseminated asymmetrical hyperintense lesions on T2WI and FLAIR in the white matter and basal ganglia.

The cerebrum is more involved than the cerebellum.

Treatment: (1) Continue antibiotics and antivirals until final CSF cultures and PCR results are confirmed to be negative. (2) Once infection is ruled out Methylprednisolone "pulse" dose at 30 mg/kg/day (maximum 1 g) for 3 days followed by oral prednisolone 2 mg/kg/day for 2 weeks. This is followed by a 4 weeks weaning regimen. (3) Plasma exchange or IVIG for relapsed or refractory ADEM.

Guillain-Barre Syndrome (GBS)

GBS is an immune-mediated polyneuropathy that is usually preceded by a viral or bacterial infection of the respiratory or GI tract 1–3 weeks prior to presentation.

GBS is the most common cause of acute paralysis in developed countries and is characterized by progressive, ascending, symmetric motor weakness and loss of reflexes. The sensory symptoms (extremity pain, paresthesia) and autonomic irregularities (tachycardia, bradycardia, hypertension, hypotension, arrhythmia) can be prominent. There are usually no sensory deficits in physical examination.

Infections known to precede the onset of paralysis are: CMV, EBV, VZV, *Campylobacter jejuni*, *Mycobacterium tuberculosis*, HIV, and *M. pneumoniae*. The pathogenesis involves an immune response against the infectious agent and has components that cross-react with those of the peripheral nervous system.

Diagnosis is clinical but is aided by CSF and electrophysiology testing. The CSF shows a high protein content and low/normal white cell count. This may be missed if the lumbar puncture is done early in the first week of the illness.

Electrophysiology will show decreased conduction velocity in the peripheral nerves.

Treatment: IVIG at 2 g/kg/day for 2–5 days or plasma exchange. (Two courses for mild GBS and four to five courses for severe illness.)

Corticosteroids have not demonstrated effectiveness in GBS and are not recommended.

Indications for PICU admission:

- For respiratory support
- For plasma exchange
- Autonomic instability (hypo- or hypertension, arrhythmia)

Botulism

Botulism is a toxin mediated disease caused by *C. botulinum*. Symptoms start a few hours and up to 6 days after exposure to the toxin. The cranial nerves are involved initially with difficulty swallowing, abnormal speech (abnormal cry in infants) and eye movements (ptosis). Other symptoms may include nausea, vomiting, constipation, and abdominal distension. As the illness progresses it causes paralysis of the extremities and respiratory muscles to various degrees. In infants the disease can be mild with hypotonia and constipation as the main findings. Also in infants there is sometimes a history of ingestion of honey before the onset of symptoms (Honey may contain the spores of *C. Botulinum*).

Diagnosis is made from a combination of clinical findings and electromyography. Stool for botulinum toxin or serum serology is confirmatory but takes time.

Treatment is with antitoxin to remove circulating toxin but this will not affect the toxin already present at the neuromuscular junction. Specific botulinum immunoglobulin is not readily available world wide. The cost is prohibitive for a lot of countries and the cost-benefit analysis is only favorable for those patients requiring mechanical ventilation. Penicillin and Metronidazole are given to eradicate the source of toxin production. Aminoglycosides and steroids should not be given as they may worsen the neurosmuscular transmission defect and increase muscular weakness. If the source of the *C. Botulinum* is a wound (i.e., wound botulism) then it will need surgical debridement.

Indications for admission to PICU:

- Respiratory support
- Autonomic instability

Infections in the Immunocompromised Child

Children are increasingly surviving diseases that until recently were considered untreatable. There are more potent, intense chemotherapy regimens being used and increasingly there are more patients who undergo solid organ and stem cell transplants. These treatments and interventions particularly with immunosuppressants, though frequently successful, leave patients at considerable risk for severe infections.

Neutropenia

Neutropenia is defined as the absolute neutrophil count (ANC) [ANC = PMN + band count] $<1{,}000/mm^3$, and is generally associated with cancer and its treatment. The risk of infection is particularly high with:

- Rapid drop in ANC
- ANC $< 100/mm^3$ (profound neutropenia)
- Prolonged neutropenia

Fever in neutropenic patients is defined as an oral/tympanic membrane temperature $>38°C$ in two repeated measurements over a 4 h period or one measurement above 38.5°C. The portals of entry of infectious agents are usually: the oral mucosa, the gut, the upper/lower respiratory tract, and central vascular lines. The most common organisms are Gram-positive cocci (*S. aureus*, *S. epidermidis*, *and Strep. viridans*), Gram-negative bacilli (*E. coli*, *K. pneumoniae*, *P. aeroginosa*), and fungi (*Candida*, *Aspergillus*).

Recently the spectrum of pathogens has begun to change, with the emergence of more Gram-negative and fungal infections. This is likely due to an increase in resistant pathogens in the face of the use of very broad-spectrum antibiotics, intensity of therapy (high-dose chemotherapy and stem cell transplant) and prolonged neutropenia. The single most important risk factor for fungal infection is the duration of neutropenia.

It is standard of practice to start antibiotics for a child with ANC < 500 who is febrile. Initial empiric therapy for febrile neutropenia consists of a β-lactam antibiotic and an aminoglycoside, plus a glycopeptide if a coagulase negative staph or enterococcus is suspected or isolated, if the child is in shock, has an endoprosthesis or a vascular tunnel infection. If patient has a history of Arabinoside-C administration and has severe mucositis *Strep viridans* infection is highly suspected and vancomycin should be added. If perianal

tenderness is present add anaerobic coverage (Metronidazole or clindamycin).

After 4–5 days of fever and neutropenia adding an antifungal is the usual practice of most oncologists.

Cellular Immune Dysfunction

Infants with a severe combined or T-cell immune deficiency usually present early in the first few months. Defects in cell-mediated immunity can result from congenital disorders such as DiGeorge syndrome, severe combined immunodeficiency disease (SCID) and Wiskott–Aldrich syndrome. They can be secondary to lymphomas, immunosuppressive medications or chronic illness. Acute viral infections such as measles and pertussis are also known to decrease a patient's cell-mediated immunity.

Typical infections are *Pneumocystis jiroveci* pneumonia (formerly *carinii*), CMV pneumonitis, RSV pneumonitis, disseminated enteroviral infection, and invasive fungal infection. Patients are highly susceptible to infections with intracellular organisms such as *Salmonella*, *Listeria*, mycobacteria, herpes family viruses (CMV, EBV, and HSV), as well as fungi and protozoa. In older children and those with secondary immunodeficiencies, these infections tend to be reactivated disease.

Children with chronic mucocutaneous candidiasis and chronic granulomatous disease typically present early in life with recurrent candida and staphylococcal infections.

Neonates with adhesion molecule deficiency usually present with delayed separation of the umbilical cord stump, increased polymorphonuclear count, and increased incidence of bacterial infections.

Humoral Immune Dysfunction

Children with primary humoral immune deficiency usually present between 6 months and 5 years of age. The onset is consistent with the time when the level of placentally transferred maternal antibodies (IgG) has declined. These defects as well as complement deficiency and asplenia are more commonly associated with infections by encapsulated microorganism such as *H. influenza*, *N. meningitides*, and *S. pneumoniae*.

Although patients with these conditions are mainly susceptible to bacterial infections involving the upper and lower respiratory tract, they can have protracted diarrhea with *Giardia* or echovirus.

Complement Deficiency

Defects in the late complement component (the "attack" component, C5-9) are prone to recurrent *Neisseria* infections. Children with early complement defects usually have autoimmune and rheumatologic manifestations. Fulminant meningococcemia is also associated with properdin deficiency (alternative complement pathway).

Hematopoietic Stem Cell Transplant Patient (HSCT)

HSCT is now an established treatment for a host of immunologic, metabolic, hematological, and neoplastic disorders. The "stem cells" may be obtained from the patient (autologous). Alternatively from an HLA-compatible related or unrelated donor (allogeneic). There is little risk of acute or chronic Graft Versus Host Disease (GVHD) with autologous HSCT. Currently there are three sources for stem cells: bone marrow, peripheral blood, and umbilical cord blood. Generally with the umbilical cord stem cell transplant the speed of engraftment is lower, but so is the risk of GVHD. With peripheral blood stem cell transplant engraftment occurs faster but the risk of GVHD is also higher. With bone marrow stem cell transplant the speed of engraftment and the risk of GVHD is somewhere between the other two sources.

With unrelated umbilical cord blood and T-cell depleted bone marrow or blood stem cell transplant, the risk of graft failure is higher.

There is a higher risk of infection with occurrence of GVHD, and with graft failure.

The conditioning regimens used to prepare the patients generally consists of high-dose chemotherapy with or without regional or total body irradiation. Post transplant, there is a period of pancytopenia and though the neutrophil count usually normalizes after 3–4 weeks it is not unusual for these patients to need red cell or platelet transfusions for much longer.

The risk of infection is influenced by rapidity of myeloid recovery and the rate of lymphoid reconstitution. The speed of restoration of adequate immune function is highly variable. The stem cell source, HLA compatibility, purging or T-cell depletion of the graft prior to transplant, and severity of GVHD are important factors.

In the early post-transplant period (first 100 days), transplant centers employ prophylactic measures to reduce the risk of infection. These measures vary between different centers, and include:

- Prophylactic antibiotics (for PCP, candida, HSV, CMV)
- Administration of IVIG
- Environmental precautions (isolation and barrier nursing)

In the early post-transplant period, patients are most susceptible to infections caused by both Gram-negative and Gram-positive organisms and by fungi. There is a higher risk of CMV pneumonitis in patients with GVHD (largely due to the need for immunosuppressive treatments). CMV negative recipients who receive transplant from a CMV positive donor are at highest risk for CMV pneumonitis.

Children who have undergone HSCT and are admitted to PICU have a particularly poor prognosis. Pneumonia, mechanical ventilation, and the need for renal replacement therapy are especially poor prognostic factors. Those with septic shock and line sepsis have the best prognosis. In addition to bacteria, the most commonly isolated organisms are CMV, RSV, adenovirus, candida, aspergillus, and PCP. In a recent report from Great Ormond Street Hospital in London, UK, only 56% of these patients survived to discharge.

Solid Organ Transplant Patient (SOT)

Similar to children who have received HSCT, children receiving solid organ transplants are prone to infections before and after the transplant. The main differences are:

1. Patients after solid organ transplants are usually less immunosuppressed than HSCT patients and are not at risk of immune reconstitution syndrome and its associated inflammatory and infectious complications. However they are at risk of surgery-related complications and postsurgical infection issues (wound infection, bacteremia, atelectasis/pneumonia, urinary tract infection).
2. Infection of the transplanted organ due to latent or colonizing organisms present in either the donor or recipient can lead to invasive widespread disease in the immune suppressed post-transplant recipient. An example of this is the child with cystic fibrosis colonized with *Pseudomonas* species; those colonized with *B. cepacia* are particularly at risk of developing resistant infection post lung or combined heart/lung transplants.
3. Children receiving solid organ transplants are at risk of reactivation of latent infections, such as CMV. But, unlike HSCT patients who most commonly present with CMV pneumonitis in recipients of solid organ transplants the CMV disease depends on the sites where the virus is latent and on the organ that has been transplanted. Lung, heart/lung, and liver transplant patients are most vulnerable to systemic disease. CMV infection can precipitate rejection and increase vulnerability to other infections such as fungal infections.
4. EBV-associated post transplant lymphoproliferative disorder (PTLD) is a potentially fatal complication of solid organ transplant. The risk of PTLD is higher in children who were EBV seronegative prior to the SOT. EBV-related infection in SOT patients may present in several different ways: asymptomatic or nonspecific viral syndrome, mononucleosis syndrome, and PTLD. The latter can have a spectrum from fever, lymphadenopathy and diarrhea to full blown lymphoma. Tissue biopsy is necessary to establish the diagnosis of PTLD. The mainstay of therapy consists of decreasing immunosuppression. Chemotherapy and biological treatments (such as anti-CD20 monoclonal antibodies) have been used.

HIV Infection in the PICU

The most common reason children with HIV/AIDS are admitted to the PICU is respiratory distress. Septic shock and CNS involvement (encephalopathy, encephalitis, and meningitis) are other common conditions leading to admission. In addition to the bacteria, viruses and mycoplasma that cause infections of the lower respiratory system in the non-HIV patient, there are a number of other opportunistic infections and inflammatory conditions to consider in the HIV-infected patient. These are commonly:

- *Pneumocystis jiroveci*
- CMV pneumonitis
- Tuberculosis
- Fungal infections
- Lymphoid interstitial pneumonitis (LIP)
- Immune reconstitution inflammatory syndrome (IRIS)

Most infants with respiratory failure will not have a previous diagnosis of HIV infection when they present. In non-endemic areas, especially during the colder season, such infants would be diagnosed and treated initially as cases of bronchiolitis. The possibility of an underlying immune deficiency and or AIDS should be considered in any infant who responds poorly to treatment or who has risk factors. These include failure to thrive, history of recurrent chest infections, hepatosplenomegaly, adenopathty, severe persistent oral thrush, or abnormal neurological signs.

In sub Saharan Africa, TB and other bacterial pneumonias were common in both HIV-infected and uninfected children who presented with respiratory failure. However *Pneumocystis* and CMV pneumonitis occurred almost exclusively in infants who were HIV-infected.

Pneumocystis jiroveci

The majority of cases of *P. jiroveci* pneumonia present in the first 6 months of life. Usually these children are quite hypoxemic. High fever is uncommon compared with bacterial pneumonia. There is a diffuse, bilateral air space or interstitial involvement on the chest x-ray. Occasionally there is a "ground glass" appearance. In an HIV positive patient with bilateral diffuse parenchymal or interstitial infiltrates on CXR, the development of pneumothorax is suggestive of *P. jiroveci* infection.

Diagnosis is by bronchoalveolar lavage (BAL). Even if a child develops *Pneumocystis* while on prophylactic therapy, high-dose intravenous trimethoprim/sulfamethoxazole should be started. Prophylaxis may have failed because of poor compliance. If one suspects drug resistance then other agents should be used (Pentamidine, Dapsone). Methylprednisolone at 2–4 mg/kg/day divided in four doses should be administered in moderate to severe cases (practically all children with *pneumocystis* who are admitted to PICU) for 5 days and then tapered.

Untreated, it is universally fatal. With proper therapy the mortality is less than 10%. The risk factors for mortality are the severity of respiratory failure and the severity of immunosuppression.

Lymphoid Interstitial Pneumonia (LIP)

LIP in children with AIDS is associated with increased risk of lower respiratory tract infections including bronchiectatsis. This condition can produce severe ventilation/perfusion mismatch and hypoxemia but may also be asymptomatic. The CXR shows diffuse infiltrates and hilar lymphadenopathy persisting for >2 months despite antibiotic therapy. Usually CXR changes are worse than clinical symptoms. LIP can be related to EBV infection or to an exaggerated immunological response to inhaled or circulating antigens or both. Steroids have been used in the treatment of symptomatic LIP.

Tuberculosis

Coexistence of HIV and TB accelerates the course of both of these infections. The risk of miliary and extra pulmonary TB is higher in children with AIDS and the course is more likely to be severe and rapid. A child with HIV infection is five to ten times more at risk of active TB. In countries with high prevalence of tuberculosis, the WHO suggests BCG vaccination of ALL neonates at birth but NOT in any child/infant with clinical AIDS.

For treatment of TB, please refer to the chapter in this book.

Mycobacterium Avium Complex (MAC)

MAC can produce a systemic illness in children infected with HIV that is characterized by fever, chronic diarrhea, abdominal pain, malabsorption, lymphadenopathy, and obstructive jaundice. MAC usually would not present with significant lung disease in these children.

Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS occurring weeks after the initiation of specific anti-HIV treatment may on occasion be severe enough to cause respiratory failure warranting admission to the ICU, though it can also indicate latent or incipient mycobacterial disease. This (IRIS) is a diagnosis of exclusion and requires a BAL and possibly a transbronchial biopsy. Management is usually with corticosteroids.

Other than sepsis and respiratory failure, the other conditions that may bring the child with AIDS to the intensive care unit are (to name the more common ones):

- CNS infections (bacterial, Mycobacterium, fungi, Cryptococcus, viruses, and rarely CNS Toxoplasmosis), acute HIV encephalopathy
- HIV-related cardiomyopathy
- Severe diarrhea and shock due to cryptosporidium or other microorganisms
- Liver failure due to infections or drugs
- Complications of antiviral medications such as acute pancreatitis, acute liver failure, Stevens–Johnson Syndrome

An important aspect of care for these children in the PICU for the staff is risk of exposure to body fluids and of needle stick injury. Universal exposure precautions should be strictly adhered to. It is imperative that all staff be aware of the guidelines and procedures after exposure to biological fluids in their institutions and seek advice from the Occupational Health Department immediately if exposed.

Brief Review of Antifungal Agents in the PICU

As increasing numbers of immunocompromised children with fungal and viral infections are admitted to the pediatric intensive care units, common antifungal and antiviral medications that are used against these infections are briefly reviewed. For a complete review of these topics, the reader is referred to chapters on individual fungal and viral infections in this book.

Increasingly systemic fungal infections have become more significant in morbidity and mortality of immunocompromised patients in intensive care units. Factors that have been associated with this increase are:

- Use of more potent and broad-spectrum antibacterial agents
- Prolonged and severe neutropenia
- Prolonged and severe immune dysfunction (primary or secondary)
- Having central venous lines and invasive devices
- Total parenteral nutrition (TPN)

The most common fungal pathogens causing systemic illness in critically ill children are *Candida* and *Aspergillus* species. In recent years there has been an increasing importance of uncommon fungal pathogens such as non-*albicans Candida* species, *Fusarium* species, *Trichosporon* species, and dematiaceous fungi.

In an immunocompromised patient with a positive fungal culture from a central venous line, current guidelines strongly advocate removal of the line.

Traditionally with invasive Candidiasis, amphotericin B (AMB) has been the first-line drug to use. However, intravenous flucanozole and itraconazole could be considered. In non-neutropenic patients positive for *C. albicans* (but not other Candida species) fluconazole is as effective as AMB. In empirical treatment of prolonged febrile neutropenic patients (>4–5 days) AMB should be started. Clinical trials have shown that liposomal preparations of amphotericin B (L-AMB) have similar, but not better, efficacy compared with conventional AMB preparations. Some authors recommend a liposomal preparation of amphotericin as a preferred first-line treatment. Unfortunately, high cost can be prohibitive in many parts of the world. In general, the L-AMB agents cause less fever, rigors, nausea, and vomiting. They are also less nephrotoxic.

Voriconazole, a second generation triazole, can be used for empirical treatment of febrile neutropenic patients in place of L-AMB. In patients with invasive aspergillosis it has been shown that initial therapy with voriconazole leads to a better response and improved survival with fewer side effects.

Echinocandins such as caspofungin have been used in combination with AMB or voriconazole in more resistant cases of invasive aspergillosis with persisting fevers. Micafungin and Anidulafungin are two other agents in this family.

Antifiungals (old and new) have a large potential for side effects and drug–drug interactions. Clinicians need to be aware of the specific profiles of the drugs they use from this antimicrobial family.

Brief Review of Antiviral Agents in the PICU

Below are the common agents likely to be used in the intensive care unit. HIV drugs have not been discussed. Please refer to the chapter on HIV for more detailed discussion of these agents.

There are two main groups of antiviral agents:

1. Inhibitors of viral replication

Agent	Virus	Side effects
Acyclovir, Valcyclovir	HSV, VZV	Kidneys, CNS
Ganciclovir	CMV, HHV-6	Bone marrow, kidneys
Foscarnet	HSV, VZV, CMV, HHV- 6	Kidneys, CNS, liver
Cidofovir	Adenovirus, CMV, HSV, VZV, HHV-6	Kidneys
Ribavarin	RSV, Adenovirus, HCV, Lassa fever virus	Teratogenicity (risk for pregnant staff), hemolytic anemia, deposition in the ventilator circuit in ICU

2. Inhibitors of viral assembly and release

Oseltamivir, Zanamivir	Influenza A, Influenza B

Nosocomial Infections in the PICU

The Pediatric Intensive Care Unit, by its nature, cares for critically ill children. To facilitate this, a number of devices are used that breach the body's normal defense mechanisms. For example, endotracheal tubes to facilitate mechanical ventilation obstruct secretion management hence secretions need to be suctioned; central venous lines (CVL) breach the skin and provide a conduit for bacteria into the blood; Urinary catheters provide conduits for bacteria from the perineum to the internal urinary structures (bladder and kidneys). On top of this, patients may be debilitated medically, nutritionally compromised, victims of traumatic injuries or post operative patients with wounds that can potentially become infected. It is not surprising then that a large number of patients requiring Intensive care acquire some form of nosocomial infection. The frequency of various nosocomial infections in PICU in a review of the US hospitals was 13.9 per 1,000 patient days. The corresponding figure in the neonatal intensive care units was 14.1 per 1,000 patient days. Between the

various types of nosocomial infections in pediatric intensive care units, blood stream infections had the highest incidence, followed by lower respiratory infections and urinary tract infections.

A basic mandate of medicine is "Primum non nocere" – first do no harm. While it is inevitable that some patients may acquire nosocomial infections, these infections cause significant morbitiy and mortality. The overall mortality attributable to the various nosocomial infections within the PICU has been estimated to be between 10% and 15% and infections acquired in the PICU are associated with an increased risk of death, with a relative risk of 3.4.

It is widely appreciated that these infections can be minimized by a number of simple interventions, most important of which is hand washing; "Clean Hands Save Lives." In a review of the related literature between 1990 and 2002, it was shown that between 11% and 48% of nosocomial infections could have been prevented.

Blood Stream Infections

Blood stream infections are common. Not surprisingly they are most common in those patients who are the most debilitated, receiving mechanical ventilation and have central venous lines in situ for longest time, urinary catheters and other artificial surfaces. The spectrum of infections also has a predictable frequency. Gram +ve infections are the most common bacteremias (whether or not associated with a central line) followed by Gram −ve and then fungi. Typically fungi are found in those patients on TPN or long term, broad-spectrum antibiotics and immuosuppressed.

Gram +ve Bacteria	Gram −ve Bacteria	Fungi
Coag Neg Staph (CONS-S. Epidermidis)	*Pseudomonas aeruginosa*	*Candida albicans*
S. aureus	*Escherichia coli*	
Streptococcus sp.	*E. cloacae*	
Enterococcus sp.	*Enterobacter sp.*	
	Klebsiella sp.	

Central Venous Catheter Associated Infection

Central venous lines (CVL) are used to provide secure intravenous access for administration of medications such as vasopressors and inotropes, to monitor pressures, blood oxygen saturations, and for intravenous nutrition. In a survey of PICU's in the United States the rate of CVL infection was 7.6 per 1,000 catheter-days. In neonates the corresponding figure was 11.3 per 1,000 catheter-days. In Europe the CVL infections occurred at a rate of 10.9 infections per 1,000 catheter-days.

Measures taken at time of insertion of the CVL significantly reduce the incidence of infection. Strict aseptic technique (gowns/gloves/mask and wide sterile field), use of Chlorhexidine (as opposed to povodine/iodine), and minimal trauma (use of ultrasound and experienced operators) are all very important factors at the time of insertion. Chlorhexidine disks topically placed upon the skin at the insertion site and antibiotic impregnated lines are used by some units but not proven to be of value.

Cuffed and tunneled lines such as Hickman lines, Port-A-Cath lines and PICC (peripherally inserted central catheter) have a significantly lower rate of infections than standard central lines that are inserted in the intensive care. Where long term therapy >1 week is required consideration should be undertaken to the insertion of one of these types of lines.

Site of insertion is important. The femoral vein is easy to cannulate with fewest insertion complications. However, it is more likely to become infected and thrombosed. It is good as a temporary line but early consideration should be given to removing and/or repositioning access.

To prevent central line infection minimization of the "opening" of the line on a daily basis is important. Asepsis on line ports prior to use (with alcohol or Chlorhexidene) is critically important.

Ultimately to reduce infection rates lines should be kept for the *briefest* time possible. Difficulty of insertion and type of ongoing therapy come into this cost-benefit analysis.

When there is a suspicion that a central venous line has become infected then blood cultures should be drawn from the line and from a peripheral puncture. Broad-spectrum antibiotics that cover the bacteria above (Vancomycin and Gentamicin for example) should be commenced. The line should be removed if at all possible. An attempt to sterilize the line may be made in the circumstances where the line is "precious" and not easily replaced. This can involve alternate infusion of antibiotics through all lumens and the use of antibiotic "locks."

Ventilator Associated Pneumonia (VAP)

This is defined as a respiratory infection that occurs 48 h post admission for mechanical ventilation. The

respiratory infection is defined by: fever/hypothermia, crackles on physical exam, new respiratory infiltrates on CXR, deteriorating ventilatory status (tachypnea), cough, deteriorating gas exchange, elevated or depressed white cell counts. This may or may not be in the presence of bacterial isolates from a sterile respiratory sample (i.e., BAL). There are age specific criteria for the diagnosis of VAP.

The CDC has produced a document that lists the specific criteria. This can be found at:

http://www.cdc.gov/ncidod/hip/NNIS/members/pneumonia/Final/PneumoCriteriaV1.pdf.

The incidence of VAP in the PICU is 6–11.6 per 1,000 ventilator-days. The diagnosis of VAP is challenging and controversial. There are a number of simple interventions to reduce the incidence of VAP.

They are:

1. Elevate head of the bed to 30°
2. Ventilator tubing:
   (a) Dependant positioning of ventilator tubing to avoid aspiration
   (b) Removal of excess condensate
   (c) Limit frequency of Tubing change unless required
3. Suctioning:
   (a) Limiting amount of saline lavage when suctioning
   (b) Sterile technique (Gloves and sterile catheter) + (gowns/masks and eye wear for protection of staff)
4. Mouth care: frequent mouth cares with Chlorhexidene-based wash
5. Feeding:
   (a) Early institution of feeding
   (b) Avoidance of gastric over distension
   (c) Limiting use of antacid therapy to high risk patients (i.e., burns, head injury)
6. Avoid/limit antibiotic therapy to minimize chance of colonization with antibiotic resistant flora

Urinary Tract Infection (UTI)

Urinary tract infection is directly proportional to the length of time that a Foley catheter is in place. Frequently, patients are on antibiotics that will suppress urinary infections. However, virtually all intensive care patients with urinary catheters will acquire urinary sepsis if their stay is prolonged. More than 90% of hospital acquired UTI's occur in catheterized children. The best intervention (as with central lines) is early removal of the catheter. When strict measurement of urinary output is not needed and the likelihood of urinary retention (due to illness or drugs) is not an issue then catheters should be removed. Intermittent catheterization can be considered as an intervention to avoid a permanent Foley catheter where retention is an issue in a longer term patient.

If an ICU patient develops fever or unexplained sepsis then it is mandatory that a urine specimen be sent for microscopy and culture. This is especially important in the patient with a catheter. If urinary sepsis is proven then consideration for catheter removal should be given. Broad-spectrum antibiotics that cover the spectrum of bacteria listed above should be commenced. Antibiotics should be specifically weighted to cover the Gram-negative bacteria as these are most common.

Wound Related Infection

Surgical Site infections are a less frequent infection but none the less important source of infectious morbidity.

If a wound is "dirty" or contaminated such as a traumatic soiled wound or contaminated peritoneum from perforated appendicitis then broad-spectrum antibiotics should be commenced in high dose. At the same time, appropriate surgical management should be undertaken to deal with the contaminated wound. The surgical team will usually offer guidance on this issue.

If a wound is "clean," for example a surgical incision, the surgical team will generally have a preference for antibiotic prophylaxis. Commonly a second generation cephalosporin will be used. This should be given at time of the operation and for a defined and limited time thereafter. Prolonged prophylaxis has been shown not to prevent inevitable wound infections and promotes emergence of multiple antibiotic resistances.

For wounds that become infected in the intensive care unit, swabs should be taken of any discharge. Surgical review should be initiated and the wound dressed (with frequent changes). Appropriate antibiotics should commence. Opening of the wound and drainage/debridement of infected tissue is the responsibility of the managing surgical team.

Infection Control Principles

All Intensive Care Units should have the ability to isolate for airborne and body fluid infectious organisms. Simple hand washing is very important (before and after examining patients or attending the bed side). Where this is not

practical an alcohol-based hand gel can be used. From simple hand washing a graduated appropriate degree of isolation and infection control processes should be undertaken, i.e., gowns, gloves, respiratory protection – masks with increasing filtering ability to full respirators.

Negative pressure rooms (with antechambers) are usually reserved for respiratory isolation for the protection of staff and other patients. Positive pressure rooms are for protective isolation of the patient who is immunocompromised. Negative pressure isolation and strict barrier isolation is reserved for highly infectious pathogens. SARS and Ebola Virus are examples where this may be necessary.

All intensive care staff should strictly adhere to hand washing practices (with a Chlorhexidine based product). Unfortunately this is not the case and medical staff are often the worst offenders in this regard. Active and repeated awareness campaigns should be carried out to reinforce this basic but very important healthcare related activity.

Summary

Severe infectious processes are common reasons for admission to the pediatric intensive care unit. Children in the PICU are at risk for developing severe infections.

Increasingly children with a dysfunctional immune system survive their primary illnesses and are admitted to the PICU with severe infections. Secondary immune deficiency is common in the course of prolonged critical illness.

Rapid sampling of body fluids and commencement of broad-spectrum antibiotic cover is of the utmost importance. It is shown that even 5 min of delay in starting appropriate antibiotics has been associated with increased mortality. If there are reasons to believe there is an anatomical source of infection (collection of pus, infected central venous line, infected prosthesis etc.) often the antibiotics would not achieve their effects until the source of infection is dealt with effectively (surgical evacuation/removal, drainage).

Optimizing the hemodynamic status of the patient (oxygen delivery, addressing preload, after load, and contractility) should start from the moment one considers the diagnosis of sepsis or severe life threatening infection. Diagnostic and therapeutic interventions all go hand in hand and start in parallel from the initial encounter with the patient.

It is vital that every unit has an updated knowledge of the prevalence and sensitivity of the micro organisms prevalent in their community and in the hospital. Colleagues in clinical microbiology or infectious disease departments are invaluable members of any PICU team in dealing with these issues.

Prophylactic measures such as effective hand washing, observing strict sterility while placing central venous lines, measures to reduce incidence of the VAP, discontinuing the invasive lines and catheters when not indicated anymore, and adherence to universal exposure precautions should be implemented and monitored and audited regularly. They save more lives and money than much more expensive interventions.

Effective antibiotic stewardship, tailoring the antibiotic coverage when sensitivities of the causative organisms are known, and discontinuing broad-spectrum antibiotics as soon as clinically prudent will decrease the burden of antimicrobial resistance in the intensive care unit.

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269 Diabetic Ketoacidosis

Omar M. Hijazi

Diabetic ketoacidosis (DKA), a life-threatening complication of diabetes mellitus (DM), is the most common pediatric endocrine emergency. Furthermore, DKA is the leading cause of hospitalization, morbidity, and mortality in children with type 1 diabetes mellitus. The basic pathology in DKA is absolute or relative insulin deficiency. In Pediatrics, insulin deficiency is usually absolute as in type I diabetes mellitus (DM) and can be relative as in Type II DM. Guidelines and experience in DKA management in children, is based on patients with type I DM. Experience with type II DM–related DKA is limited. In up to 67% of the cases of new onset diabetes mellitus (DM), DKA is the initial presenting clinical picture.

Definition and Classification

There is a consensus on the definition of diabetic ketoacidosis (DKA). This consensus is adopted by American and European diabetic societies. As per this consensus, DKA is diagnosed when the patient is having hyperglycemia, serum glucose more than 200 mg/dL, and metabolic acidosis (venous pH less 7.3 and/or bicarbonate less than 15 mmol/L). DKA can be mild (pH 7.2–7.3, HCO3 10–15), moderate (pH 7.1–7.2, HCO3 5–10), and/or severe (pH $<$ 7.1, HCO3 $<$ 5). Furthermore, DKA is also associated with ketonmia, ketonuria, hyperosmolality, dehydration, and electrolyte disturbances.

Etiology

DKA is caused by insulin deficiency and excess of glucagon and counter-regulatory hormones. Insulin deficiency in DKA can be absolute or relative. In pediatric age group, DKA was thought to be associated only with absolute (type I DM), insulin-dependent DM. Now it is known that DKA can occur in and can be the first presenting clinical picture for children with type II DM especially in stressed obese Afro-American children.

Epidemiology

DKA can be the first clinical presentation of type I and II DM. The likelihood of having DKA as the first presentation for type I DM is related to the patient's age (increases with young age less than 5 years), sex (females more than males), and socioeconomic status (more with poor and medically uninsured). In 15–67% of newly diagnosed type I DM, DKA can be the first presenting clinical picture. In type II DM, DKA can be the first presentation especially in obese Afro-American patients who are having significant stress like severe infection. In pediatric patients known to have type I DM, the incidence of DKA is around 8 per 100 person-years. The incidence increases with increasing age in girls (4 per 100 person-years for girls $<$7 years vs. 12 per 100 person-years for girls $>$13 years), increasing HbA1C, increasing insulin dose, lack of medical insurance, and in the presence of psychiatric disorders.

Pathogenesis

DKA usually follows poor hyperglycemic control. Patients with hyperglycemia $>$240 mg/dL need frequent glucose and ketones checks. Poor glycemic control increases the risk of DKA. DKA is also triggered with poor compliance with treatment, stress, and medications. Stress can be due to infection, trauma, and psychological stress. Stress increases glucagon, catecholamines, cortisol, and growth hormone leading to hyperglycemia, acidosis, and ketosis. Medications like corticosteroids, thiazides, and diazoxide can also trigger DKA.

Presentation

As mentioned above, DKA can be the first clinical presentation for new onset type 1 DM. Fifteen to sixty-seven percent of new onset Type I DM in children present with DKA as the first presentation. Children who are young (less than 5 years) and those of low socioeconomic status

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are at increased risk for this presentation. Patients with DKA usually present with signs that are related to insulin deficiency and glucagon excess. Hyperglycemia in excess of the renal threshold leads to osmodiuresis, dehydration, and electrolyte disturbances. Hyperglycemia increases intravascular osmolality. Hyperosmolality stimulates thirst center leading to polydypsia. Insulin deficiency and glucagons excess leads to ketoacidosis. To compensate for the metabolic acidosis, the patient breathes faster and deeper to wash out carbon dioxide. Patients with DKA may have fever and other signs of infection that precipitated the DKA. Infections that precipitate DKA are usually viral. Antibiotics are usually not indicated. Patient's appetite can increase in the beginning but decreases when the patient gets sicker. In severe DKA, the patient may have signs of altered mental status secondary to brain edema.

DIAGNOSTIC EVALUATION — Diagnosis of DKA is based on clinical and laboratory findings. Deep labored breathing in a patient known to have DM will raise suspension of DKA. However, in a patient who is not known to have DM, diagnosis of DKA can be delayed. Some patients with undiagnosed DKA were treated as bronchial asthma with no improvement to be discovered to have DKA only after laboratory results are out. Clinical signs and symptoms of DKA are a reflection of hyperosmolality, dehydration, and acidosis.

Signs and symptoms — Patients present with polyuria secondary to osmotic diuresis, polydypsia secondary to hyperosmolality-stimulating thirst. Polyuria may be associated with nocturia, diurnal enuresis, dehydration, and weight loss.

In very young children, polyuria can be missed; polydypsia cannot be expressed delaying DKA diagnosis. Young children can present with decreased activity, weight loss, dehydration, and irritability. Severe candidal diaper rash, unexplained metabolic acidosis and hypovolemia should raise the suspicion for DKA. DKA Patients may present with nausea, vomiting, and abdominal pain: a picture that can mimic appendicitis. To compensate for the DKA-induced metabolic acidosis, patients breath faster and deeper (Kussmaul), mimicking attack of bronchial asthma. Exhaled acetone can give fruity smell to the patient's breath. Patients with DKA usually have significant volume loss. However, hyperosmolality and water shift from the intra- to the extracellular compartment ameliorate signs of intravascular volume depletion. The level of consciousness in a patient with DKA can range from fully conscious patient to a patient who is in deep coma. Change in blood pH, osmolality, and glucose can be responsible for the depressed level of consciousness. Clinical brain edema occurs in 0.5–1% of children with DKA. Brain edema is the most common cause of morbidity and mortality in DKA This life-threatening complication needs early recognition and intervention.

Fluid and electrolyte deficits — Patients with DKA present with dehydration and electrolyte disturbances. Hyperosmolality helps maintain the intravascular volume. So, clinical examination may underestimate the degree of volume loss. Hyperosmolar renal water loss will lead to sodium, potassium, calcium, and phosphorus loss. Initial serum level of these electrolytes may not reflect this loss. The average losses per kilogram body weight in patients with DKA are as follows: Na 5–13 meq, K 6–7 meq, and water 30–100 ml. DKA patients usually present with 5–10% dehydration. Patients with moderate DKA are managed as 5–7% dehydration. Patients with severe DKA are managed as 10% dehydration. To help decrease the risk of brain edema, initial fluid bolus is limited to 10 ml/kg of glucose free isotonic fluid as 0.9 normal saline. A second bolus will be given only if the patient's intravascular volume is severely compromised.

Laboratory findings: After initial assessment, blood should be collected for serum glucose, bedside glucose testing, blood gases, serum sodium, potassium, phosphorous, creatinine, blood urea nitrogen, hemoglobin, glycoslated hemoglobin, and, if available, blood level of β-hydroxybutyrate. The diagnosis of DKA is confirmed by the findings of hyperglycemia serum glucose >200 mg/dL, a wide anion gap acidosis pH < 7.3 and HCO3 < 15 meq/L, and ketonemia.

Hyperglycemia: Hyperglycemia, serum glucose more than 200 mg/dL and acidosis are the two main biochemical criteria for the diagnosis of DKA. However, hyperglycemia is not a must for the diagnosis of DKA. Patients with DKA may present with normal or low serum glucose as with decreased oral intake or after starting treatment with insulin. Hyperglycemia exceeding the renal threshold will lead to osmodiuresis, dehydration, and increased risk of candidal infection in the genital area.

Metabolic acidosis: Metabolic acidosis with venous pH less than 7.3 and/or serum bicarbonate less than 15 mea/L is the second biochemical criteria for the diagnosis of DKA. The hyperglycemia and the metabolic acidosis are the result of insulin deficiency, and excess of glucagon and other counter-regulatory hormones. The cells need the glucose to produce energy. The glucose needs the insulin to enter the cells. In DKA, with shortage of insulin, the glucose stays in the blood, the cells fast, and the body releases stress hormones leading to hyperglycemia, gluconeogenesis, and lipolysis. Lipolysis will lead to increase free fatty acids and triglyceride in the blood. Glucagon helps the entry and metabolism of free fatty

acids to the mitochondria forming ketone bodies. Acetoacetate, the first ketone body formed can be reduced to β-hydroxybutyrate acid or decarboxylated into acetone. Acetone is an inert compound that does not contribute to the acidosis, but can help in the diagnosis of DKA by giving a fruity smell to the patient's breath and reacting to the nitropruside test. β-hydroxybutyrate is the major ketone body in DKA forming up 75% of the total DKA ketone bodies. β-hydroxybutyrate the major contributor to the acidosis, with DKA treatment it converts back to acetoacetate. B-hydroxybutyrate does not react with nitropruside test. Nitropruside test, by detecting acetone and acetoacetate and missing the major ketone body β-hydroxybutyrate underestimate the ketone level in DKA. On the other hand, during recovery β-hydroxybutyrate is converted to acetoacetate and acetone, which persist for a longer period. As a result, urine testing may give a false impression of worsening ketoacidosis while total ketone bodies and the patient's clinical condition are actually improving. Therefore, direct measurement of serum β-hydroxybutyrate at the laboratory or at bedside should be used whenever possible.

The degree of ketoacidosis in DKA is related to the balance between rate of ketone formation averaged 51 meq/hr, urinary excretion of ketones averaged 15 meq/hr, and conversion of acetoactate to the inert acetone ranging 15–25%. Treatment of DKA with insulin decreases ketone production and enhances its metabolism clearing the ketoacidosis.

Metabolic acidosis in DKA can be multifacorial; insulin deficiency leading ketoacidosis, severe dehydration and poor perfusion leading to lactic acidosis, and late in the course the iatrogenic hyperchloremic acidosis secondary to excess treatment with sodium chloride–containing solutions.

The anion gap in DKA is mainly a reflection of the ketone bodies. The narrowing of the anion gap during the process of DKA treatment is an indication of improvement in ketosis and acidosis. Anion gap can be used to help follow-up for ketosis if blood testing for β-hydroxybutyrate is unavailable. However, the anion gap may also underestimate the degree of acidosis. The loss of ketoacid anions in the urine (as the sodium and potassium salts of β-hydroxybutyrate and to a lesser degree acetoacetate) lowers the anion gap without affecting the plasma bicarbonate concentration or therefore the degree of acidosis.

Ketone bodies are potential HCO3. With insulin treatment, metabolis of ketone bodies will result in the generation of NaHCO3. So, ketone bodies are potential HCO3 donor. Urinary loss of ketone bodies represent loss of potential HCO3.

The serum anion gap is calculated by checking the difference between serum sodium and the sum of chloride and bicarbonate. The normal value in children is 12 ± 2 mmol/L.

Serum sodium — In DKA, patients usually present with hyponatremia. This hyponatreia is due to true and/or factious hyponatremia. True hayponatremia results from intravascular hyperosmolality shifting water from intra- to extracellular compartment leading to dilutional hyponatremia. As per standard correction, serum sodium is estimated to be lowered by 1.6 meq/l per 100 mg/dl increase in serum glucose above 100 mg/dl. However, the physiological decrease is more than that. It was found to be 2.4 meq/L per 100 mg/dL increase in serum glucose above 100 mg/dL. This dilutional hyponatremia is opposed by water depletion resulting from hyperglycemic osmodiuresis, increase insensible loss due hyperventilation and decrease oral intake later in the course of DKA. However, increased water intake stimulated by hyperosmolarity can exaggerate hyponateremia. Hyperlipedemia in patients with DKA, by decreasing the plasma volume in which sodium is present, leads to factious hyponatremia.

Serum potassium: Patients with DKA may be present with normal, low, or high serum potassium. However, total body potassium is depleted. Potassium is lost through kidney hyperglycemic osmodiuresis. Furthermore, vomiting and diarrhea if present will exacerbate potassium loss. In average, a child with DKA potassium losses is 6 meq/kg. This loss of potassium is ameliorated by decrease in intracellular potassium entry due insulin deficiency and intravascular hyperosmolarity induced water and potassium shift to the extracellular compartment. With treatment of DKA, the hydration increasing renal potassium loss, and insulin increasing potassium shift to the intracellular compartment, serum potassium level will be lowered.

Serum phosphate: Patients with DKA usually have depleted body phosphate. Serum phosphate can be normal or high. Insulin deficiency, hyperglycemia, and metabolic acidosis shift phosphate from intra- to extracellular compartment. This helps maintain normal serum phosphate level balancing phosphate loss. Total body phosphate is depleted due to increased renal loss and decreased intake. With treatment, hydration and insulin, shift phosphate to the intracellular compartment uncovering phosphate deficit.

Blood urea nitrogen: High blood urea nitrogen in a patient with severe DKA is an indicator of significant volume loss, and a predictor of increased risk of brain edema.

Differential diagnosis: Polydypsia and polyuria can be seen in uncontrolled diabetes mellitus, diabetes

insipidus, hypokalemic nephropathy, and psychogenic polydupsia. Dehydration and labored breathing can be seen with ketoacidosis and bronchial asthma in a patient who is having increased insensible loss and decreased intake.

Treatment

General Care: Early recognition and proper intervention help improve the outcome of patients presenting with DKA. DKA diagnosis can be straightforward as in a patient who is known to have DM who is presenting with tachypnea and dehydration. However, in a patient who is not known to have DM the same presentation can be initially misdiagnosed as bronchial asthma. Most of the experience in DKA treatment comes from treatment of children with type I DM. The data on the management and outcome of DKA in children with type II DM is limited. Regardless of the severity of DKA, the basics of management are the same. In addition to close clinical bedside monitoring, patients with DKA need appropriate fluid, insulin, electrolyte, and blood gasses monitoring and treatment. However, the setting in which the child with DKA should be placed in is based on the DKA severity that is determined based on clinical and laboratory findings.

Where to treat the patient: Neurological status, degree of dehydration, anion gap, severity of acidosis, and duration of symptoms are used to assess the acuity of DKA presentation. The more depressed the mental status, the more severe the dehydration, the wider the anion gap, the lower the venous pH and HCO3 and the longer the duration of symptoms the more severe is the DKA. Severity determination helps the doctors place the patient in the right setup of care. A patient with depressed mental status and severe dehydration needs critical care setup. While a child with mild DKA, normal neurological examination, and good oral intake, may be managed on outpatient basis with the help of cooperative family.

Once diagnosis is made on clinical and lab findings (hyperglycemia, metabolic acidosis, and ketonemia), treatment should be started. The following points are important in the approach for a patient with DKA.

Laboratory: Before staring the treatment, blood and urine should be collected for appropriate laboratory test mentioned above.

Monitoring: Sick patients with DKA need close monitoring in a critical care area. They should be connected to a monitor for continuous monitoring of heart rate and rhythm, respiratory rate, and oxygen saturation. Blood pressure and temperature should be monitored as the patient's condition mandates. In a patient with DKA, heart rate can be high due dehydration, anxiety, pain, and fever. Bradycardia may indicate increased intracranial pressure. Electrocardiogram may show changes of electrolytes disturbances. Breathing can be fast and labored as a compensation for the metabolic acidosis, it can be normal or it can be slow due to increased intracranial pressure. The patient can be hypotensive due to dehydration and can be hypertensive due to increased intracranial pressure. The patient can be febrile due to precipitating infection. Fever increases insensible loss. In general, fever in DKA is not related to bacterial infections and does not justify starting antibiotics. In any sick patient, oxygen saturation should be monitored. Patients with DKA present with dehydration. Assessing the degree of dehydration in DKA can be difficult. Hyperosmolality of the intravascular compartment helps maintain the intravascular volume on the expense of intracellular compartment. In general, monitoring of the urine output is important to assess the status of hydration and tissue perfusion. However, urine output in a patient with DKA can be misleading; the patient can have increased urine output while dehydrated secondary to hyperglycemic osmodiuresis and can have decreased urine output while well hydrated secondary to syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elevated urine specific gravity is usually an indication of dehydration. In patients with DKA, glucosuria and ketonuria will increase the urine specific gravity. This makes urine specific gravity undependable in assessing the degree of hydration in a patient with DKA. Hematocrit and blood urea nitrogen are good predictors of intravascular volume and degree of dehydration in DKA. Hourly intake output charting should be done. The fluid balance should be monitored. If the patient is having depressed mental status, a urinary catheter should be inserted. Optimizing oxygen delivery is the target of the intensivist. Oxygen supply should be given to the patient as needed to maintain saturation in the mid-90s. In addition neuro-vital should be monitored closely in a sick patient with DKA. The patient can have gradual or sudden deterioration in the level of consciousness. This can be due to many causes as hypoglycemia, brain edema, and hyperosmolar coma. Early recognition and proper intervention for the cause of drop in the level consciousness will help improve the outcome. In addition to vital signs monitoring, DKA patients need close monitoring of serum glucose, electrolytes (Na, K), venous blood gases, blood β-hydroxybutyrate if available, and anion gap. This monitoring is done initially hourly for the first 3–4 h then every 2 h as the patient's condition

stabilizes. If bedside capillary glucocheck is used, readings should be compared to the laboratory results. Patients with DKA usually present with low Na. This hyponatremia can be true (dilutional) or factious (due hyperlipedemia). Serum sodium is monitored closely during DKA treatment. During the course of DKA treatment, glucose should go down while sodium should go up. Should the sodium fail to increase while the glucose is decreasing, the patient needs close monitoring. Such a patient is at higher risk for brain edema. This could be due to excess free water administration or syndrome of inappropriate antidiuretic hormone release (SIADH). In such a case, sodium concentration in the infusate should be increased and/or the volume of infusate should be decreased.

Fluids: DKA patients are dehydrated and have increased intravascular osmolality. This usually happens over time allowing the formation of intracellular osmolar molecules to maintain a balance between intracellular and extracellular osmolality. Fluid boluses will be given only if there are signs of severe intravascular volume depletion. In general, isotonic fluid as 0.9 normal saline 10 ml/kg is given slowly over 60 min. Repeat fluid boluses will be avoided unless the patient is still showing signs of severe intravascular volume depletion. Patients with DKA have fluid deficit that is between 5% and 10%. This deficit is replaced over next 48–72 h. After fluid bolus, plain isotonic fluid (isotonic saline or lactated Ringers) will be started to cover for the maintenance and the deficit. Potassium will be added after assuring urine output and normal or low serum potassium. As an example a 5-year-old, 20 kg, male known diabetic patient presenting with severe DKA tachycardia, hypotension, venous pH 7.0, serum glucose of 700 mg/dL, and ketonemia will be given 200 ml of 0.9 normal saline over 60 min. Based on the diagnosis of severe DKA with10% dehydration will be given 2,000 ml for fluid deficit to be given evenly over the next 48–72 h. For maintenance he will need 1,500 ml. So he will be given 1,000 (half deficit) and 1,500 ml as maintenance evenly over first 24 h. Infusate will be started as 0.9 normal saline. To prevent hypoglycemia, glucose 5% will be added to the infusate once the blood glucose reaches 300 mg/dL. Should the glucose continue to drop before the resolution of DKA, higher concentration of glucose will be added to the infusate.

Insulin: For patients with mild DKA and no vomiting, insulin can be given as subcutaneous (sc). For sick patients with DKA, insulin will be given as continuous IV infusion. The infusion will start after the initial fluid bolus and checking the serum glucose. In general, insulin bolus before starting the insulin infusion is not needed if adequate dose is given. The usual staring dose is 0.1 unit/kg/h. The infusion will start after completion of the fluid bolus. Delaying the initiation of insulin infusion for hour or more, may help decrease the risk of brain edema. At the above infusion dose, an insulin blood level of 100–200 microunit/ml will be reached in an hour. This level is enough to facilitate glucose and ketone metabolism, and suppress gluconeogenesis and ketogenesis. In general in sick patients with DKA, insulin is given as intravenous infusion. Subcutaneous (SC) and intramuscular (IM) routes are to be avoided in such cases. Absorption of SC and IM can be unpredictable especially in a patient with poor perfusion. However, there are reports about treating DKA with SC insulin infusion. Blood glucose will be monitored hourly and whenever there is a change in the level of consciousness. With hydration and insulin blood glucose will decrease. The target is to achieve a gradual drop in glucose at a rate of 50–100 mg/dL/h. If the drop is faster than that, glucose will be added to the infusate. If the glucose continues to drop fast, insulin dose will be decreased and more glucose will be added to the infusate. The aim of using insulin infusion is resolution of the acidosis and ketosis. The target is not to treat hyperglycemia only. The target is to treat ketosis, acidosis, and hyperglycemia. Hyperglycemia usually resolves before the resolution of ketosis and acidosis. Insulin infusion should continue until the resolution of ketoacidosis. Ketoacidosis is resolved when the patient's ph $>$ 7.3 and/or serum bicarbonate $>$15 meq/L, serum ketones negative or trace and plasma glucose $<$200 mg/dL.

Potassium: Patients with DKA, usually present with normal or high serum potassium. Hypokalemia at presentation is uncommon. However, total body K is depleted. In DKA, there is increase in potassium loss by the renal and gastrointestinal systems, while, insulin deficiency and hyperosmolality increase intravascular potassium. With treatment, hydration improving the kidney perfusion and insulin improving the entry of glucose and K to the cells, and resolution of metabolic acidosis serum K will decrease. So, K should be added to the infusate with the start of insulin therapy if the patient is having good urine output and the serum K level is normal or low. If the patient is hypokalemic, potassium should be added immediately to the infusate. Insulin should be delayed or started at low dose until achieving normokalemia. Potassium can be added to the infusate as potassium chloride or a mixture of potassium chloride and potassium phosphate.

Sodium Bicarbonate: With DKA treatment, ketone bodies are metabolized producing bicarbonate. Hydration improves tissue perfusion and control lactic acidosis. Although patients with severe DKA can be very acidotic, NaHCO3 should be avoided. In general, HCO3 should not

be given in the venous pH $\geq$ 7.0. There is no proven benefit from treating DKA acidosis with bicarbonate. Furthermore, treating DKA acidosis with bicarbonate can lead to cerebrospinal fluid (CSF) paradoxical acidosis, delay resolution of ketosis, and hypokalemia. However, in certain conditions as severe DKA with pH $<$ 6.9 and poor myocardial function, and hyperkalemia, bicarbonate may be given.

Phosphate: As with potassium, total body phosphate is depleted in patients with DKA. With DKA treatment, hypophsphatemia becomes more apparent. Studies showed that hypophphatemia did not affect tissue oxygenation and treatment of hypophosphatemia is not essential part in the treatment of DKA. Furthermore, treatment of hypophsphatemia can lead to hypocalcemia and hypomagnesemia. However, if phosphate level is less than 1 mg/dL, it should be treated.

In a febrile patient with DKA it was found that fever, white blood cell (WBC) count, and WBC differential are not significant predictors of bacterial infection. However, it was found that there is correlation between WBC count and pH and serum HCO3. WBC count reflected the severity of DKA, patients with high count had lower venous pH and HCO3. Majority of febrile patients with leukocytosis and DKA are not having bacterial infection and antibiotics are not needed.

When to switch from iv insulin infusion to sc insulin: Once the DKA resolves (pH $>$ 7.3 and HCO3 $>$ 15, glucose $<$ 200 mg/dL and absent or trace ketone bodies or normal anion gap), subcutaneous insulin will be given and 30 min later insulin infusion will be discontinued and the patient will be allowed to eat.

What can go wrong: While taking care of patient with DKA, the patient can have deterioration in the level of consciousness, electrolyte imbalance like hypokalemia, hyperkalemia, hypoglycemia, failure of the Na to increase while the serum glucose is decreasing, hemodynamic instability due to inadequate fluid intake arrhythmia, and brain edema. Reported mortality risk in DKA ranges 0.15–0.5%. The most common cause of death in DKA is brain edema. DKA patients are at increased risk of deep venous thrombosis. DKA patients who had central venous femoral catheters are at higher risk. In two recent studies, 50% of DKA patients who had central venous femoral line inserted had clinical evidence of deep venous thrombosis. DKA patients with altered mental status are at increased risk of aspiration if they vomit. They should be kept NPO (nothing per orem or orally) and have nasogastric tube connected to low grade intermittent suction. Electrolytes imbalance as hyperkalemia and hypokalemia increases the risk of arrhythmia in patients with DKA; these patients need close monitoring of their potassium and heart rhythm. Elevated pancreatic enzymes occur in around 40% of children with DKA. This elevation does not reflect pancreatitis. Pancreatitis diagnosis is based on clinical, radiological, and laboratory basis. Clinical pancreatitis occurs in 2% of DKA cases.

Brain edema complicating DKA: Clinical brain edema complicates 0.3–1% of DKA. The risk is higher in children, and in newly diagnosed DKA. Laboratory risk factors include elevated blood urea nitrogen, low serum bicarbonate, high serum glucose, and failure of the sodium to increase as the glucose decreases during the treatment of DKA. There was no clear association between treatment factors and DKA-related brain edema. Clinical brain edema carries high morbidity and mortality. One third of the patients die or survive in vegetative state. The majority of brain edema in DKA takes place hours after the initiation of treatment. However, in average 20% of DKA-related brain edema declare itself before initiation of DKA treatment. In a recent Canadian study, brain edema was present at presentation in 19% of the DKA-related brain edema cases. It continues to occur even in the optimally managed patients. Once the patient develops signs of increased intracranial pressure and pending herniation, there is limited time to treat. Continuous monitoring of the patient's clinical and laboratory data is essential for early recognition and intervention. High index of suspicion should be applied. Headache, vomiting, irritability, and lethargy may be signs of brain edema. Brain imaging may be normal initially while the patient is having clinical signs. Normal brain imaging, should not delay brain edema treatment.

Prevention: DKA is a serious life-threatening complication of DM. The best way to decrease DKA morbidity and mortality is prevention. Early diagnosis and proper intervention of DM by screening and follow-up of high-risk group can decrease the incidence of DKA. In known diabetic patients, DKA usually follows poor glucose control. If a diabetic demonstrates serum glucose $>$240 mg/dL, frequent testing for glucose level and close follow-up should be done. Patient and family education to help increase awareness about the short- and long-term DM complications is vital. Studies done in the United States and Europe showed up to 60% of the cases of recurrent DKA occur in only 5% of patients with DM. Having multidisciplinary team that include pediatrician, endocrinologist, social worker, diabetic educator that will study the causes of recurrence in these cases, educate, support these high-risk patients will help direct the resources to the needy patients.

The targets of this team are to improve the quality of life, decrease morbidity, mortality, hospitalization, and increase productivity for this high-risk group.

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Pediatric Burns

Fuad Hashem

270 Burns

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Pediatric burns are recognized as a challenging problem. There is a significant contrast between the adult and the child in terms of the anatomy, metabolism, hormonal changes, immune responses, pathophysiology, and therapy of burns. Continuous physical, reconstructive, and psychosocial problems will occur as the child is developing. The goals of treatment are survival of the patient, preservation of function, and restoration of normal appearance.

Epidemiology and Prevention

Burns in children can be caused by heat or cold, chemicals, electricity, or radiation. The average age of occurrence of a pediatric burn is 32 months. The incidence of burns in children varies with age, sex, and socioeconomic status. In the United Sates, 100,000 children per year require hospitalization due to burn injuries. Scald burns are common in children less than 5 years of age, while flame burns occur more between the ages 5 and 10 years. Boys have a higher incidence of burns than girls. Before the age of 2 years, the male-to-female ratio is 1.5:1. This ratio increases to 3.5:1 in the 13–18 year age range. The risk of burns in children increases in low socioeconomic conditions where there is inferior education and reduced supervision of children.

Recently, Sharma et al. studied the epidemiology pediatric burn in a gulf country (Kuwait) and reported an overall incidence of 17/100,000 children aged 0–14 years. In that study, scald was the main cause of burns (67%) followed by flame (23%).

In an interesting review of epidemiology of burns, Al-Qattan and Al Zahrani stressed on several specific etiologies of pediatric burns in various countries in relation to nation-specific traditions, social habits, or religious activities, and these are summarized in *Table 270.1*. Note should be given that most of these burns are preventable.

Education about environment and socioeconomic risks play an important role in reducing the incidence of burns in children. The prevention of accidents requires the continuous supervision of the child and removal of hazards from their environment. Better design of home equipment and more widespread use of flame-proof textiles are the most effective strategies in the prevention of pediatric burns.

An important cause of pediatric burns is child abuse. Recognition of non-accidental injury requires the admission of any child who is suspected of being abused for management and investigation. Child abuse is diagnosed when there is a history inconsistent with physical findings, such as history of delay in seeking medical attention, fearfulness, unexplained injuries, dehydration, malnutrition, and systemic injuries. The pattern of the burn is usually linear and deep. Immersions burns often show sparing of the intertriginous zone by the protective fetal positioning (*Fig. 270.1*), while contact burns are uniform. Evaluation consists of a blood count to rule out anemia, a complete radiologic skeletal survey to rule out fractures, and photographic documentation of injuries.

Emergency Management

An adequate airway and ventilation must be established first. All burned and smoldering clothing should be removed. Intravenous access with large-bore venous cannula for fluid resuscitation should be established and tetanus prophylactics given. A nasogastric tube and bladder catheter should then be inserted. The criteria for the admission of burned child are as follows:

Second- and third-degree burns more than 10% of total body surface area (TBSA)
Second- and third-degree burns involving the face, hands feet, genitalia, perineum, or a major joint
Third-degree burns more than 5% TBSA
Electrical burns
Chemical burns
Inhalation injury
A preexisting medical condition
Associated trauma
Suspected child abuse

Young reviewed the emergency management of burns in children and noted several important and unresolved issues: (1) the care of burned children in hospitals are frequently provided without burns teams, (2) inadequate

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Table 270.1
Pediatric burns related to traditions, social habits, religious activities, and festivals

Country	Mechanism of pediatric burns
Korea	Steel chopsticks are common in Korea. Young children insert the chopsticks into the wall socket
United Kingdom	"Low-lying" disposable barbeques are common. The barbeques are easily reached by young children
Middle Asia	"Sandal" burns in toddlers: "Sandal" is a hole made in the floor of the room for specially prepared line coals (used for heating). Toddlers crawl and fall into the coal
Spain	"Ember" burns: The family burns olive trees to produce incandescent residues. Infants may crawl into it
Developed countries with cold weather	Contact burns to gas fireplaces
Saudi Arabia	"Street soccer" friction burn to the foot: Children play barefoot on the street. As the car tire impacts on the child's foot, the driver stops the car resulting in a friction burn
Israel	"Shabbes" burns: Scald burn in Jewish orthodox children during "sabbath" bath with hot water
Turkey	"Flying toy balloon" burn: Instead of helium, acetylene gas is used to fill flying toy balloons. Acetylene gas is highly flammable
All Countries	Fireworks related burns are common in children all over the world and they can occur during national feast/festivals such as new year's eve, Halloween, the American Fourth of July holiday, and the Muslim Eid

numbers of critical care beds for children with burn, and (3) morbidity after small burns (e.g., toxic shock syndrome is still leading to death in burnt children). Potokar stressed that the situation may be a disaster in certain conditions and gave example of burnt children from the conflict in Iraq.

Inhalation injury occurs in enclosed spaces. Hypoxia caused by inhalation injury should be diagnosed early and treated. Mortality is more than 50% with acute asphyxia and carbon monoxide poisoning being the main causes of early death. Bronchoscopy is important in diagnosis, and changes in the upper airway range from mild erythema to complete desquamation of the epithelium. Humidified 100% oxygen is given by mask to clear the carbon monoxide. Intubation is indicated if there is deterioration of blood gases.

In acute burns, the child's cardiac and pulmonary condition should be evaluated, followed by an assessment of the associated blunt and penetrating trauma, prevention of burn wound contamination by covering burns with clean dressings, and relief of pain by intravenous narcotics (morphine 0.05–0.1 mg/kg every 2–3 h as needed). Cold soaks in the first 15 min reduce pain and tissue damage in partial-thickness burns, but hypothermia should be avoided to decrease the risk of arrhythmia. Circulation in circumferential burns of the extremities is monitored by distal pulses, Doppler, capillary refill, and assessment of the need for early escharotomies or fasciotomies (*Fig. 270.2*). The indications for escharotomy are impaired capillary filling, progressive neurologic changes, loss of palpable pulses, and compartment pressure of more than 30 mmHg.

Pudre et al. stressed upon several specific issues regarding pediatric emergency chemical and electrical burns. Except for hydrofluoric acid burns which require calcium glucorate management, almost all other chemical burns should begin with immediate irrigation with large quantities of tap water. Neutralization of acids or alkalis is not appropriate. Irrigation of eye burns is carried out at the same time. Chemical burns are generally uncommon in children, although domestic chemical burns are seen frequently in developing countries by Pikanen and Al-Qattan.

High voltage electrical burns are caused by current greater than 1,000 V. The hallmarks of electrical burns are the presence of contact points (the so-called entrance and exit wounds). Tissue damage is regions immediately adjacent to contact points is the most severe and is frequently associated with compartment syndrome or muscle necrosis. Therefore, fluid resuscitation in high voltage electrical burns cannot be calculated accurately from the amount of cutaneous burn. Instead adequate resuscitation is given to establish a urine flow of 1, 1.5, and 2 mL/kg/h in older children, younger children, and infants, respectively. Furthermore, initial cardiac monitoring and aggressive management of myoglobinuria (if present) are unique emergency issues in high voltage electrical burn.

In children, the most common low voltage electric burns involve the oral commissure and these will be discussed later in more details.

Definitive Management and Treatment

The treatment of burns includes fluid resuscitation, nutritional support, infection control, burn wound excision, skin grafting, and rehabilitation. The extent and depth of the burn injury determine the severity. In calculating the percentage of the burn, the estimate includes wounds of second- and third-degree depth only. ❯ *Fig. 270.3* shows the burn estimate diagram employed to calculate the extent of pediatric burn injury by body surface area in children of different age groups. First-degree burns are the most superficial and are similar to sunburn. The skin is light red in color, without blisters, and painful, usually healing in 3–6 days. Second-degree burns (❯ *Fig. 270.4*) are divided into superficial and deep dermal injuries. Superficial second-degree burns are bright red in color with a moist surface, are severely sensitive to stimuli, and usually heal within 10–21 days. Deep dermal burns are dark red to yellow-white in color, with a slightly moist surface. They heal in 3 weeks or more and often cause hypertrophic scar formation. Third-degree (❯ *Fig. 270.5*) or full-thickness burns are white and charred, with thrombosed superficial burns that require grafting for the wounds to heal.

The presence of inhalation injury significantly increases mortality in patients with burns. Singed nostril hair is not a reliable indicator of inhalation burn. The presence of inflammation of the mucosa in the oropharynx confirms edema in the upper airway. Other signs are turbulent air flow in the upper airway, wheezing, brochorrhea, a brassy cough, and hoarseness. A partial pressure of O_2 of less than 70 mmHg is an indication for intubation and ventilation. Fiberoptic bronchoscopy assists in the diagnosis and management of inhalation injury. An endotracheal tube can be passed over the fiberoptic scope. Mucosal edema, erythema blebs, and slough can be diagnosed. Carbonaceous debris and brochorrhea are extramucosal findings. Mild edema is seen in mild injuries; the severity depends on the involvement of the supraglottic (false cords) area. In severe cases the true vocal cords are not visualized. Because of the prolapsed of the arytenoids into the airway lumen, there is marked erythema, and the mucosa may slough entirely. False cords bulge together in the midline, causing complete obstruction of the airway. No antibiotics or steroids should be given in the treatment of inhalation burns.

Fluid Resuscitation

The goals of fluid resuscitation are to restore the fluid volume and electrolyte homeostasis, maintain perfusion pressure, and minimize edema. Fluid resuscitation in children differs from that in adults because children have a larger TBSA relative to body weight. Children with second- and third-degree burns of more than 10% TBSA require fluid resuscitation. A central line is inserted if the burn is more than 40% TBSA. The fluid requirement may increase if the burn is associated with trauma or inhalation injury. An indwelling urethral catheter is used to monitor urine output for adequate resuscitation (urine output at 1 mL/kg/h). Severe hypoglycemia may develop in 24 h because of decrease glycogen stores in children. Therefore, glucose-containing fluid should be added to the resuscitation fluid initially.

Many formulas have been used to calculate fluid requirements based on the weight of the child, the size of the burn, and the surface area. Use of the Parkland formula (4 mL/kg/% burn) as the total 24-h fluid replacement underestimates in infants and small children. In young children, estimation of burn-related fluid losses and the maintenance fluid requirement, known as the "two-figure formula," indicate the safe amount of resuscitation fluid required.

In the first 24 h, children weighing less than 30 kg should receive lactated Ringer's solution (4 mL/kg/% burn) plus maintenance fluid; half of the calculated fluid is given in the first 8 h, and half in the next 16 h. In the second 24 h, dextrose in 5% saline and colloid (5% albumin) 0.5 mL/kg/%burn) are required to maintain a urinary output of 1 mL/kg/h. In infants, 5% dextrose in lactated Ringer's solution is given to decrease the risk of hypoglycemia. Children weighing over 30 kg should receive lactated Ringer's solution (4 mL/kg/h) in the first 24 h and colloid fluid (0.5 mL/kg% burn) and 5% dextrose in the second 24 h to maintain urine output at 1 mL/kg/h. In the second 24 h, the volume delivered is an estimate of free water loss plus allowance for urinary output. Colloid is given in the second 24 h (0.5 mL/kg/% burn) because capillary leaks that develop in the first 24 h seal.

The surfaces area formula results in 5,000 mL/m^2 as burn-related fluid losses plus 2,000 mL/m^2 as fluid maintenance in the first 24 h. Half of the calculated fluid is given in the first 8 h and half in the subsequent 16 h.

In the first 24 h after the burn, vascular permeability is increased. Controversy still exists regarding colloid administration in the first 24 h. Brouhard demonstrated extravasation of albumin into the interstitium in burn models. Resuscitation with a formula containing colloids maintains the colloid osmotic pressure and corrects the hemodynamics with smaller amounts of fluids. Adequate resuscitation is monitored by hourly urine output (1 mL/kg/h), vital signs, hematocrit, and electrolyte levels.

Invasive methods, including central pressure measurements, cardiac output, and mean arterial pressure, are used for monitoring large burns.

Metabolic Changes and Nutritional Support

Burn injuries induce hypermetabolic responses and increase energy expenditure, as characterized by protein and fat catabolism. In large burn injuries, the basal metabolic rate may increase up to twice the resting level. The signs of catabolism are persistent tachycardia, tachypnea, hyperpyrexia, and marked body wasting.

In the shock phase, fluid loss causes hypovolemia, and hypoperfusion stimulates the secretion of aldosterone and antidiuretic hormone, causing sodium and water retention. After resuscitation, there is an increase in cardiac output, urinary nitrogen losses, tissue catabolism, and basal metabolic rate. Thermal injury causes the production of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. ACTH stimulates the adrenal cortex to produce cortisol. Cortisol levels remain high for many weeks and cause mobilization of amino acids from skeletal muscle. The adrenal medulla secrets epinephrine, which stimulates hepatic glycogenolysis and gluconeogenesis, together with the release of glucagon and glucocorticoids. There is a decrease in insulin and further glucose production.

Gluconeogenesis depletes body protein. To improve the nitrogen balance, glucose and nitrogen should be added to the diet of a burned child, via the enteral route whenever possible. A nasogastric tube should be inserted for burns more than 20% TBSA. If the patient is stable and there are bowel sounds, enteral feeding should be started within 6–8 h after injury. The hypermetabolic response decreases with early implementation of enteral feeding. The goal of nutritional support is to maintain the body weight at preadmission levels. Many formulas have been proposed to estimate nutritional requirements. As children have a greater body surface area than adults, caloric demands can be accurately calculated using a formula based on surface area. Infants should receive 1,000 kcal/m^2 body surface area burned plus 2,100 kcal/m^2 body surface areas for maintenance per day, and children should receive 1,300 kcal/m^2 body surface burned plus 1,800 kcal/m^2 body surface areas for maintenance. Children should receive supplements of vits C and A, zinc, potassium, and calcium.

Indirect calometry is considered relatively accurate to estimate energy expenditure in pediatric burns and Liusuwan et al. concluded that the WHO formula is more accurate than Harris Benedict and Mayes formula in a pediatric burn population.

Burn Wound Management

The burn wounds are first cleaned and dressed with a topical agent (e.g. 0.5% silver sulfadiazine, 0.5% silver nitrate, and mafenide acetate). Silver sulfadiazine is the most commonly used topical agent. Side effects include thrombocytopenia, leucopenia, and skin rash. Silver nitrate can cause hyponatremia, hypokalemia, hypochloremia, and hypocalcemia, because of the leeching effects of the silver salt. These agents penetrate the burn eschar poorly. Mafenide acetate penetrates the burn eschar well and controls bacteria, but it is painful and can cause allergic reactions. It contains a carbonic anhydrase inhibitor that causes bicarbonate wasting.

If the patient's condition is stable, once- or twice-daily hydrotherapy is started on the second day to remove nonviable tissue and accumulated bacteria. Burn wound infections occur when bacteria multiply in viable tissue beneath the burn eschar. Daily assessment of burn wounds in children is important for detecting early signs of invasive infection. Signs of invasion infection are focal areas of red-brown discoloration of the eschar, accelerated separation of the eschar, and a moth-eaten appearance. Burn biopsy and histologic examination confirm the presence of invasive burn wound infection, which is most commonly caused by gram-negative organisms and Candida. Surgical excision and systemic antibiotics are also considered in the treatment of burn wound infection. After excision of the burn eschar, the wound can be covered with an autograft or temporarily covered with a biologic dressing.

Perhaps the most outstanding and remarkable change in pediatric burn wound management is the use of silver dressing for partial-thickness burns. Cuttle et al. studied burn wound management is an Australian pediatric burn center. Up to 2002, the authors used silver sulfadiazine and then switched to silver dressing. The latter was cost effective and resulted in less admissions, reduced frequency of dressing changes, and quicker healing.

Surgical (Wound Excision) Management of Burn Wounds

Early burn excision has reduced morbidity and mortality in children with large burns. Early excisions improve immunologic, hematologic, metabolic, and functional

status, and decreases both blood loss and the need for later reconstruction. Burns should be excised 3–5 days after the child has been resuscitated and edema has subsided.

Superficial burns heal in 2–3 weeks without hypertrophic scarring. Full-thickness burns require excision and skin grafting, while intermediate-thickness burns may require more than 3 weeks to heal. The healing process may produce hypertrophic scars and contractures. If a burn wound fails to have adequate epithelialization after 3–4 weeks, then it should be excised and grafted. Early excision and grafting of intermediate- and full-thickness burns will reduce the risk of developing hypertrophic scars and burn contractures. Children with large full-thickness burns should have early excision of eschar after completion of resuscitation to reduce complications. Tangenital excision is performed under general anesthesia. Adequate excision is determined by the punctate bleeding pattern. The amount of blood loss during excision should not exceed 50–60% of the total blood volume. Up to 15% of the TBSA can be excised and grafted during the same anesthesia session. To decrease the amount of blood loss, excision is divided into separate areas to control bleeding. Skin grafts are harvested and meshed, homeostasis is established by application of topical thrombin and electrocautery, and adequate blood and crystalloid are given to maintain the normal hematocrit. Intraoperative monitoring should include urinary output, vascular filling pressure, and body temperature. Occasionally, the wound may need to be excised more deeply, to the subcutaneous fat or even to the deep fascia which will lead to significant cosmetic and functional deformity. Skin grafts are then applied to the debrided areas and secured with staples. Meshed grafts should not be used on exposed areas such as the face, neck, and hands. Donor sites are covered with bulky, absorbent dressings for 7–9 days. Allografts provide a temporary covering when there is a shortage of skin grafts and act as a biologic dressing in unhealthy recipient sites. They also prevent wound infection, desiccation, and loss of heat, water, proteins, and red blood cells from the wound.

Postoperatively, splitting is required for grated extremities and joints in neutral positions to increase grafts takes. The dressing is removed on the fifth postoperative day and the grafts are examined. Physiotherapy should be started as early as possible to improve function and decrease the risk of contracture.

Rehabilitation

The burn team includes the physician, burn nurse, physical and occupational therapist, social worker, and nutritionist. Teamwork must be maintained to gain the trust, confidence, and compliance of the child. A long-term relationship develops between the burn team, the child, and the family. The burn outlines comprehensive short-term and long-term plans for the burned child. The goals of rehabilitation are to maintain function and reduce the risk of contracture. The rehabilitation program begins as early as 2–3 days after admission and continues on a daily basis. It includes hydrotherapy, occupational and physical therapy, the upper and lower extremities range of movement, and play therapy.

The range of movement and ambulation are assessed, and any limitations in function are identified. The patient is positioned so as to avoid contracture, with the neck maintained in slight extension, the shoulders abducted, and the upper extremities elevated. Joints are maintained in a functional position (e.g., extension of the wrist, elbow, and knee joints and flexion of the ankle joint) by proper positioning and splitting. Family supports, with involvement of the burn team, increase the compliance of the child.

Rehabilitation after burn wound healing is a continuation of the acute stage. Hypertrophic scars, caused by damage to the reticular dermis, are common after partial-thickness or full-thickness burns. These scars are hard, raised, and red within the boundary of the wound. Initially they are red and itchy, but they fade and soften as they mature (12–18 months). Inadequate treatment of hypertrophic scars causes severe contracture and functional impairment.

Pressure therapy reduces the risk of contracture and accelerates the maturation of hypertrophic scars. Use of pressure garments designed to cause linear organization of collagen is usually started at 6–8 weeks. They are worn continuously except during exercise, bathing, and meals. Splinting continues after burn wound healing and is gradually discontinued.

Growth hormone supplementation as part of the post-burn rehabilitation program in children was recently proposed by Mlcak et al. Children who recovered from major burns received growth hormone (0.05 mg/kg/day) for 12 months. The authors noted that these children had less muscle wasting, more weight gain, and better catch up with their growth curved. Furthermore, these children had better cardiac ejection fraction than controls.

Burn Reconstruction

Scalp

There is very little soft tissue covering the skull, the scalp is often damaged, and excision may expose the underlying

skull. If there is concern over deep involvement of the meninges and brain, especially electrical burns, a computerized tomography scan or magnetic resonance imaging should be obtained to rule out brain involvement and abscess formation. Scalp alopecia, which is found in 25% of children with deep burns, results from burns to hair follicles. Conservative tangential excision and skin grafting are used for wound care. If the bone is exposed, a local scalp flap is used for coverage; if the defect is too large, a free tissue transfer should be used. Small areas of alopecia can be treated with staged excision. Tissue expansion is very effective technique in the treatment of large areas of alopecia of the scalp; there is no donor site defect and lost tissue is replaced with adjacent tissue of the same color and texture. The vascular anatomy of the scalp allows the use of long and narrow flaps. Orticochea used a local flap to cover a large scalp defect. In extensive and deep burns to the scalp, free flaps are indicated for coverage.

Eyelids

Early correction and reconstruction of the burned eyelid is indicated to prevent corneal exposure, which can lead to ulceration and loss of vision. In acute facial burns, careful examination of the eye, including the use of fluorescein dye, should be performed to rule out corneal injuries. If there is a corneal injury, the eye should be irrigated thoroughly and an ophthalmologist consulted. Atrophine (1%) should be applied to prevent ciliary spasm. Topical antibiotics and 1% methylcellulose should be applied. Tarsorrhaphy can cause destruction of the eyelid margin and is not effective in closing the eyelids. There is no risk of corneal exposure in the early days after a burn, owing to eyelid edema. After the edema subsides, early excision and skin grafting can be performed. If the depth of the burn cannot be assessed, the eye can be protected with a sclera lens.

Cicatricial ectropion deformity of the eyelid is released using an incision at the ciliary margin. The release should overcorrect the deformity and extend beyond the medial and lateral canthi; then the defect in the upper eyelid is lined with a medium-thickness skin graft while the lower eyelid defect is lined with a full-thickness skin graft. The upper and the lower eyelids should not be grafted in one sitting as this makes it difficult to produce an adequate correction.

Face

Facial burns and scarring can cause significant disfigurement (❯ *Fig. 270.6*), associated with psychological and social problems to both the child and the family. Treatment in the acute phase involves early excision and skin grafting with a nonmeshed skin graft. Attention should be paid to the donor sites for the skin graft and to the regional esthetic units of the face. Skin grafts harvested from donor sites above the clavicle produce a good color match to the face. Scalp skin is also an excellent donor site. Once all facial burns have been covered, facial elastic pressure garments and molded masks should be used to improve the quality of the scar, speed maturation, and reduce the risk of developing hypertropic scars.

Nose

The nose is commonly affected in facial burns because of its projection in the center of the face. The nasal lining and skeleton are usually spared, except in very severe facial burns, whereas the skin covering the nose is frequently involved. In the early phase, conservative debridement and skin grafting are conducted. After wound healing, an elastic pressure garment and an orthoplastic mask are applied to improve wound maturation. In planning nasal reconstruction, the esthetic units of the nose should be considered. Skin grafts from the supraclavicular area provide an adequate size and good color match for nasal coverage. Local forehead flap and distant flaps are used for nasal reconstruction in patients with extensive burns.

Ears

Burns to the ears are common because of its exposed position. In the early phase it is important to prevent and treat chondritis. Chondritis can be prevented by avoiding pressure and applying topical mafenide acetate. Suppurative chondritis is a serious complication that may lead to contracture and loss of the external ear. It is treated by the early drainage of abscesses and the removal of necrotic cartilage. Reconstruction of the ear may require many stages, and skin coverage is a significant problem. In total ear reconstruction, a partial temporofascial flap is used to cover a cartilage frame or Medpor implant. This flap is then covered with a skin graft.

Neck

Early excision, grafting, and splinting have helped significantly in reducing the development of neck contracture. After complete release of the neck contracture, skin grafts

are used to cover the defect. Linear bands are best treated with Z-plasties. Local transposition flaps are used in mild contracture, while in moderate defects tissue expanders can provide enough skin coverage. Tissue expanders in the neck should be used carefully as they may exert pressure on important structures such as the trachea, internal jugular vein, and carotid arteries.

Mouth

One of the most difficult and common burn injuries in children is electrical burns to the mouth (◉ *Fig. 270.7*), which usually affect children under the age of 5 years. The burn is often caused by the child chewing on an electrical cord, which then becomes defective. The saliva in the mouth helps to produce an electrical short circuit and an arc. Extensive heat is produced (3,000°C), causing destruction of the commissure with its vermilion and the underlying orbicularis oris muscle. Secondary hemorrhage from the labial artery 1–2 weeks after the injury occurs in 25% of cases and it is treated by applying pressure. The wound is conservatively treated with the application of topical antibiotics and splinting. Al-Qattan et al. showed that early splinting of these burns may obviate the need for commissuro platy in the future. Oral commissure reconstruction should be delayed for approximately 1 year, until scar maturation has occurred. Many procedures are available for commissure reconstruction, including mucosal, vermilion, and tongue flaps and Z-plasty.

Breast

Breast thermal burns to the anterior chest in girls may damage the breast buds beneath the nipple and areola. Careful conservative debridement should be performed in the acute phase to preserve the breast buds. Al-Qattan and Zuker recommended debridement of acute deep burns of the female pediatric chest area leaning the breast bud area for spontaneous eschar separation. This is thought to preserve the maximum amount of viable tissue in this important area. As the breasts start developing underneath the burned skin, the skin should be released early and resurfaced with a thick, split-thickness skin graft. Additional release and skin grafting may be required as the breast develops. If the breast buds are damaged, the breast can be reconstructed, either with tissue expanders or by using a latissimus dorsi or rectus abdominis musculocutaneous flap.

Axilla

Axillary contractures are a common problem in children. The shoulder has a great range of motion. Flexion contracture and hypertrophic scars are effectively reduced by the early application of elastic compression and splinting. Multiple Z-plasties are used if the scar contracture involves either the anterior or the posterior axillary fold. Severe contracture is treated by a releasing incision and split-thickness skin grafting. Contractures may develop as the child grows, and can be treated with release and skin grafting. Flap reconstruction is delayed to the final definitive stage of reconstruction.

Hands

Hand burns are common in children. Deep thermal burns to the hand may require escharotomy. Early tangential excision and skin grafting reduce the healing time and improve function. Early physical therapy, elevation, elastic pressure, and splinting reduce edema and increase the range of movement. In children, a claw deformity can develop secondary to hyperextension contracture of the metacarpophalangeal joint. Splinting the hand in the "anticlaw" position is important to reduce the risk of permanent contracture. Other deformities include palmar contracture, burn syndactyly, and, in severe cases, amputation deformity (◉ *Fig. 270.8*). Severe palmar contractures occur in crawling infants around camp fires. Al-Qattan compared the results of release of contractures and coverage using either thick split-thickness skin grafts or full-thickness skin grafts. On long-term following group had less recurrence of contracture indicating that full-thickness grafts may be able to "grow" better than split grafts.

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Pediatric Poisoning

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271 General Management of Poisoned Patients

Khaled M. Al-Haidari

Introduction and Epidemiology

Children are commonly seen sick in emergency departments (ED) after unintentional ingestion of drugs. Due to their nature to explore the surrounding environments using their sense of examining things by their taste, they are led some times to serious toxic exposure to dangerous substances including drugs.

The 2008 Annual Report of the American Association of Poison Control Centers reported that 83.8% of poison exposures were unintentional and 92.9% cases of exposures occurred at the patient's residence.

Children younger than 3 years were involved in 38.7% of exposures and 51.9% occurred in children younger than 6 years. Ingestion was the route of exposure in 79.3% of cases.

Cosmetics/personal cares products, cleaning substances (household), foreign bodies, pesticides, and plants were the most commonly ingested non-pharmaceutical products in the pediatric population in this 2008 report.

Topical preparations, cold and cough preparations, vitamins, antihistamines, gastrointestinal preparations, antimicrobials, hormones and hormone antagonists, cardiovascular drugs, electrolytes, and minerals were the most commonly ingested pharmaceutical products in the pediatric population.

In general, items that are easily accessible and posse attractive colors are most likely to be ingested.

The World Health Organization (WHO) also reported that the common poisoning agents in low-income and middle-income countries are fuels such as paraffin oil (also known is some countries as kerosene), organophosphates, pharmaceuticals, and cleaning agents. Fatal poisoning rates in low-income and middle-income countries are four times that of high-income countries.

Many household cleaners contain caustic substances such as sodium or potassium hydroxide or sulfuric acid. Severity of the injury from ingesting such substances depends on their strength, acidity, dose/quantity, and contact time. Some manifestations of caustic ingestion include local irritation and swelling of the lip or tongue, burning pain, drooling, dysphasia, and red or white plaques on the tongue. Treatment requires that the poisoned child received nothing by mouth and esophageal endoscopic evaluation is performed to determine the severity of injury once the vital functions have been stabilized.

Death after unintentional ingestion of poisons in children is uncommon; this may be due to the improvement in the packaging "child-proof containers," increase in public awareness and education, and improvement in the medical management.

Poison prevention education of parents and caregivers should be provided before children become mobile as it is highly recommended and believed to reduce the risk of mortality and morbidity. Appropriate storage and proper disposal of medications and toxic substances should be part of the routine education.

This chapter focuses on the general management of poisoning in children, and discusses in detail some selected but commonly ingested substances.

General Approach and Management of Poisoned Patients

Initial Management of Poisoned Patients

The primary goal in treating a suspected or poisoned child is to carefully assess and support the vital functions, as the patient's life may be in an immediate danger. The general approach to treat a patient with acute poisoning is listed below:

- **Assessment and treatment**:
  Checking and stabilizing:
  - ABC:
    - **A**irway
    - **B**reathing
    - **C**irculation
  - Central nervous system (CNS): mental status and seizure control
  - BG: correct hypoglycemia
  - Temperature: correct hypothermia
  - Resuscitation antidotes

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- **Physical examination:**
  - Thorough physical examination
  - Reassess the patient's vital signs frequently and monitor the need for supportive care
- **Laboratory (individualize):**
  - Arterial blood gas (ABG) and electrolytes
  - Electrocardiogram (ECG)/cardiac monitor
  - Toxicological screening of suspected medication
- **Patient history once stabilized:**
  - Age, sex, time and type of possible exposure (including any mediation present at home; recent illness medications, visiting family members medications)

The child needs to be reassessed often as the status can change frequently until stabilized.

Only after these functions are stabilized can the poisoning be evaluated. Symptomatic and supportive care to ensure vital organ function shall include:

1. Establishing airway
2. Providing ventilation (O_2 therapy if necessary)
3. Establishing intravenous (IV) access for cardiovascular support and the administration of medications (fluid, electrolytes, pressors)
4. Maintaining adequate body temperature

Pertinent laboratory data such as serum electrolytes, glucose, and arterial blood gases should be obtained on admission and monitored frequently. Once the vital functions have stabilized, the patient should be evaluated carefully by obtaining detailed history and complete physical examination. Asymptomatic or mildly symptomatic patients should be closely observed for at least 4–6 h or longer for patients who ingested slow release preparations. The patient may be discharged if he continues to be asymptomatic after the observation time.

Empirical drug treatment may be indicated in comatose or altered mental status pediatric patients as in adults. Blood glucose level should be checked immediately. If the level is below normal range or not obtainable and any patients who swallowed oral hypoglycemic agents, an initial dose (IV push) of 0.25–1 g dextrose per kilogram of glucose as a 10–20% solution should be administered except in patients with documented hyperglycemia. Empirical Naloxone therapy is important in pediatrics. In the past, dosing recommendations were 0.01–0.1 mg/kg based on body weight. Recently, many clinicians favor a standard dose of 1–2 mg for the acute overdosed patient of all ages (beyond the neonatal period). Administered intravenously, intramuscularly, or endotracheally, Naloxone may be repeated every 2–5 min until a therapeutic response is achieved or a total dose of 10 mg is given (narcotic – induced toxicity should be questioned if there is no response after 10 mg is given). Thiamine 100 mg IV dose should be considered in adolescent patients who may be thiamine deficient (e.g., patients with eating disorders, chronic inflammatory bowel diseases), although routine administration to pediatric patients should be avoided.

History

Once vital functions are stabilized, a brief history should be obtained in an attempt to identify the substance and type of exposure. In a child with known or suspected exposure, questions should include what agent(s) was ingested, quantity, and when. General medical condition and history of allergies should be obtained. Family, medical, and social history may be important and any family member currently ill or taking any medications should be noted (e.g., visiting relative, pregnant or postpartum mother on iron supplement) and retrieval of the container must be attempted. However, in a poisoned child a distinct history of toxic exposure is usually unclear and the following symptoms highly suggest the possibility of poisoning: acute onset of illness, past medical history of accidental ingestion (for children aged 5 years and below), environmental stresses, multiple organ system dysfunctions, altered consciousness, and a puzzling clinical presentation.

Physical Examination (PE)

Complete and careful PE should be performed, since this is often helpful in the diagnosis and guidance for a specific intervention. A complete reassessment of the vital functions and body temperature should also be done. The clinician should focus on the central, autonomic nervous systems, pupil size and reactivity, skin or mucous membrane changes, and presence of any odor on the breath or patient's clothing (See *Table 271.1*). These findings form a collection of signs and symptoms, referred to as toxic dorms (See *Table 271.2*) that will determine possible toxicological agents and guidance for early therapeutic intervention.

Laboratory Findings

This may be helpful in confirming a diagnostic impression or in determining metabolic abnormalities caused by

Table 271.1
Clinical manifestations of selected drugs overdose

Signs	Symptom or sign	Agents
Temperature	Hypothermia	Opiates, sedatives hypnotics, hypoglycemic agents, alcohol, lithium
	Hyperthermia	Amphetamines, anticholinergics, antihistamines, B-blocker, cocaine, cyclic antidepressants, isoniazid, monamine oxidase inhibitors, phencyclidine salicylates, phenothiazines
Respiratory system	Bradypnea	Acetone, barbiturates (late), clonidine, ethanol, ibuprofen, narcotics, nicotine, sedative hypnotics
	Tachypenia	Organophosphates, opiates, barbiturates (early), B-blockers, benzodiazepines, alcohol, clonidine
Respiratory rate	Tachycardia	Anticholinergics, antihistamines, amphetamines, caffeine, cyanide, cyclic antidepressants, propoxyphene, sympathomimetics, theophylline
	Bradycardia	Sedative hypnotics, calcium channel blockers, clonidine, B-blockers, opiates, digitalis, nicotine, alcohols
Blood pressure	Hypotension	Ace inhibitors, calcium channel blockers, digoxin, nitrites, B-blockers, imidazolines, cyclic antidepressants, theophylline, propoxyphene, qunidine sedative hypnotics, heroin, methadone
	Hypertension	Amphetamines, phencyclidine, anticholinergics, nicotine, cocaine, sympathomimetics, thyroid supplements
Neuromuscular	Seizures	Ammonium fluoride, amphetamines, anticholinergics, antihistamine, B-blocker, caffeine, camphor, carbamates, carbon monoxide, cocaine, cyclic antidepressants, diethyltoluamide, dilantin, ergotrate, ethanol, hydrocarbons, hypoglycemics, ibuprofen, imidazolines, isoniazid, lead, lidocaine, lithium, nicotine, opioids, phencyclidine, phenothiazines, phenylpropanolamine, physostigmine, propoxyphene, salicylates, theophylline
Pupil size	Miosis	Barbiturates, carbamates, clonidine, clonidine, ethanol, isopropyl alcohol, organophosphates, opioids, (mepiridine may cause mydriasis) phencyclidine, phenothiazines, physostigmine, pilocarpine
	Mydriasis	Amphetamines, anticholinergics, antihistamine, cocaine, cyclic antidepressants, dopamine, drug withdrawal, glutethimide, lysergic acid diethylamide, monamine oxidase inhibitors, phencyclidine

known ingested toxic substance. Commonly ordered laboratory investigations include: routine chemistries, arterial blood gases (ABGs), osmolar gap, and anion gap (*Table 271.3*). Interpretation of these measurements may be helpful in a patient's management. Detection of toxins in the blood and/or urine may be helpful for seriously ill patients with occult ingestion or for adolescent patients with intentional overdose, when clinical appearance does not fit with the stated history. Drugs such as acetaminophen, anticonvulsant, carboxyhemoglobin, digoxin, ethanol, ethylene glycol, iron, lithium, methanol, salicylate, and theophylline require an immediate quantitative determination of their levels in the management of the poisoned patient.

Initial Treatment

The general treatments of a poisoned child include gastric *evacuation*, as well as blocking the absorption and enhancing elimination.

The traditional treatment practice for poisoned patients which includes gastric decontamination "use of emetics, activated charcoal usage and or gastric lavage" is no longer routinely recommended. Activated charcoal and gastric lavage should be considered for severe cases such as symptomatic patients presented within 1 h of ingestion of a toxic substance, symptomatic patients who ingested substances that decrease the gastrointestinal motility, ingestion of a sustained resale medication, and for patients

Table 271.2
Common toxidromes

Type of poisoning	Agents	Toxic symptoms
Anticholinergic	Antihistamines, atropine, belladonna alkaloids, mushrooms (some), psychoactive drugs	Blurred vision, fever, tachycardia, mydriasis, warm and dry skin, urinary retention, ileus, delirium, seizures
Acetaminophen	Acetaminophen	Abdominal pain, nausea/vomiting, elevated aspartate transaminase level (greater than 1,000 IU/l after 24 h), jaundice, confusion, somnolence, coma, disorientation
Anticoagulant	Warfarin (coumadin), rodenticides	Bleeding ecchymosis, prolonged prothrombin, and bleeding times
Cholinergic	Carbamates, physostigmine, pilocarpine pyridostigmine	(SLUDGE) salivation, lacrimation, urination, diarrhea, GI cramps, emesis, wheezing, diaphoresis, bronchorrhea, bradycardia, miosis
Cyanide	Cyanide	Cyanosis, hypotension, syncope, psychosis
Hallucinogenic	Amphotamines, cannabioniods, cocaine, lysergic acid diethylamide, phencyclidine	Hallucinations, psychosis, panic, fever, mydriasis, hyperthermia
Iron-containing products	Iron-containing products	Dyspepsia, nausea, vomiting, diarrhea, dark stools
Opioid	Opioids (e.g., morphine, hydrocodone methadone)	Hypoventilation, hypotension, miosis, sedation, hyperthermia, ileus
Salicylates	Aspirin-containing products	Disorinatation, fever, lethargy, nausea, vomiting, tachpnea, tinnitus

Table 271.3
Anion gap and osmolar gap use in toxicology

Calculated osmolarity = $2Na^{+}(mEq/L) + \frac{BUN(mg/dl)}{2.8} + \frac{glucose(mg/dl)}{18}$
Osmolar gap = Measured osmolarity − calculated osmolarity (*Normal measured osmolarity is 280–295 mmol/kg*)
If osmolar gap is >10, common drugs and poisons that should be considered: Acetone, ethanol, methanol, ethylene glycol, isopropanol, mannitol-diuretics, glycerol-diuretics, sorbitol-diuretics
Anion gap (AG): AG = $Na^{+} - (Cl^{-} + HCO3^{-})$ (*Normal 8–16 mmol*)
Drugs that may *increase* AG: Magnesium, lithium, bromide Drugs and medical conditions that may *decrease* AG: methanol, uremia, DKA (diabetic ketoacidois), paraldehyde phenformin, iron, isoniazid, lactic acidosis, salicylates, carbon monoxide

that ingested a large quantity of life-threatening substances.

The American Academy of Clinical Toxicology and the European Association of Poisons Centers and Clinical Toxicologists is no longer recommending ipecac for home use. There is not enough evidence that syrup of ipecac improves the outcome of the poisoned patients.

Initial Decontamination

The choice of the GI decontamination method depends on the toxin and the circumstances of the ingestion.

Activated Charcoal

It is an extremely effective adsorbent for most toxins and drugs especially when given during the first several hours after ingestion. It prevents the absorption in the gastrointestinal tract leading to decreasing systemic absorption of the toxin. Initial dose is usually 1 g per kilogram body weight with a minimum dose of 20 g in a child and 50–100 g in an adolescent. A dose of 0.25–1 g per kilogram body weight may be repeated every 1–6 h until the patient is clinically stable (including ingested drug serum concentrations, if indicated). Airway reflexes must be preserved or airway protected.

Procedure: Dilute activated charcoal with water in a 4:1 or 8:1 ratio to increase palatability and then 70% sorbitol (premixed preparations as charcoal with sorbitol are also available) may be added to enhance toxin elimination from the gastrointestinal tract. Shake the mixture until it becomes like a thickened soup or heavy cream. Repeat the dose if patient vomits. Smaller and more frequent doses may be better tolerated and antiemetics may be indicated. Multiple doses of charcoal in water are indicated for select patients (e.g., ingestion of phenobarbital, carbamazepine, digoxin, and theophylline).

Contraindication: Do not administer when bowel sounds are absent or hypoactive or following ingestion of caustic agents or drugs known to be poorly adsorbed (e.g., iron, mineral acids or base, alcohol, lithium, cyanide, and heavy metals).

Toxicity: Constipation, obstruction, poor palatability, and aspiration are the main adverse effects.

Cathartics

These eliminate toxins from the gastrointestinal tract by causing diarrhea and they are also useful in preventing charcoal-induced constipation. Magnesium (sulfate and citrate) and sorbitol are the most commonly used agents and have the advantage of not being adsorbed by the activated charcoal. However, lately it was observed that there is no evidence shown their value. There is no need to administer cathartics with each dose of activated charcoal but should be administered as needed only. Sorbitol is considered the drug of choice due to fewer interactions with serum electrolytes. The usual dosages are 20% magnesium sulfate solution 250 mg/kg (maximum dose), magnesium citrate 4 mL/kg up to 300 mL (10 oz), or 70% sorbitol 0.5 g/kg (10–20 mL in children, and 50–100 mL in adolescents).

Cautious use of cathartics in children is recommended to avoid risk of dehydration and electrolytes imbalance especially in young children.

Contraindications are absent bowel sounds or gastric obstruction, diarrhea, abdominal trauma, and renal failure because magnesium intoxication risk limits the use of cathartics. Oil-based cathartics should be avoided because of the risk of aspiration and the possibility of enhanced toxic absorption.

Whole Bowel Irrigation (WBI)

The entire gastrointestinal tract is flushed of toxins and their absorption is prevented. Preferred solutions are polyethylene glycol such as Colyte or Golytely. The solutions are not absorbed from the gastrointestinal tract and do not lead to fluid and electrolyte abnormalities. WBI has been used in children successfully, and found to be particularly useful in pediatric iron overdose, sustained slow release preparations, and other substances that do not bind to charcoal (e.g., lithium, slow release potassium chloride and theophylline, mercury). The initial dose is 0.5 L per hour for small children and 2 L per hour for adolescents given orally or via a nasogastric tube until the rectal effluent is clear. WBI is not indicated in the presence of bowel obstruction, perforation, ileus, or hemorrhage of the gastrointestinal tract.

WBI should be used with caution in children to avoid risk of dehydration and electrolytes imbalance especially in young children.

Gastric Evacuation ''Emesis''

Ipecac syrup was the drug of choice for emesis induction and can be expected to induce emesis in almost all children at home within 20–60 min after administration for many years. The dose for a child of 6–12 months of age is 10 mL, 15 mL for 1–5 years of age, while 30 mL is recommended for children >5 years old. Ipecac syrup should be taken with one or two glasses of water or any other liquid.

Contraindications to emesis: Children less than 6 months of age; comatose patients or patients with impaired or absent gag reflex due to the risk of aspiration. To avoid the risk of injuries, emesis is not indicated when sharp or solid objects, caustic or corrosive substances, and hydrocarbons have been ingested.

Toxicity to ipecac is uncommon but observes for central nervous system effects such as lethargy, tremors, and convulsions. Gastrointestinal effects include protracted vomiting, diarrhea, and significant bleeding (Mallory–Weiss), and electrocardiographic irregularities and tachycardia are the main cardiovascular adverse effects associated with the administration of ipecac.

However, the routine use of Ipeaca at home is no longer recommended because of its limited outcome or no improvement as well as the toxicity seen above. And the fact that it may prolong vomiting and the patients may not be able to receive additional medications such as activated charcoal or acetylcysteine.

Gastric Lavage

This is used to be an alternative mechanical technique to ipecac-induced emesis for gastric decontamination *and it*

is also not recommended as a routine management of poisoned pediatric patients.

Lavage should only be considered when life-threatening toxins were ingested, mainly when life-threatening singes and symptoms are seen or there is a high risk of toxicity that is suspected. Lavage may be necessary in poisoned pediatric patients after ingestion of certain toxins such as calcium channel blockers, iron, tricyclic antidepressants, lithium, and substances that cannot be absorbed by activated charcoal such as alcohols, heavy metals, and glycols.

Contraindication to gastric lavage is ingestion of caustic or nontoxic substances, and sharp objects.

Procedure: Intubation (endotracheal or nasotracheal) should precede gastric lavage for the unconscious or convulsing patient with or without gag reflex. Patient should be placed on the left side with the head slightly lower than the feet and a tube of appropriate length should be inserted in the stomach through the mouth or the nose (e.g., 16–28-Fr. orogastric tube). Confirmation of the presence of tube in the stomach is essential before lavaging. Aspirate gastric contents initially before lavage fluid is introduced; follow it by a saline lavage solution (0.45% or NS – to prevent hyponatremia) with 50–100 mL aliquot and continue lavage until the return is clear. This usually requires a total volume of 500–1,000 mL in a child. After getting a clear return, the tube may be left in place for the administration of activated charcoal and cathartics.

Complications to gastric lavage may include aspiration, mechanical injury, ventilation, fluid and electrolyte abnormalities, bradycardia, and cardiac arrest (vasovagal effect).

These complications are commonly seen and for this the gastric lavage is not routinely recommended.

Antidotes

A list of commonly used antidotes is included in *Table 271.4*. However, indiscriminate use of antidotes is discouraged. *Other methods of enhanced elimination* are given below.

Table 271.4
Common antidotes

Type of drug/poisoning	Agents	Antidotes
Acetaminophen	Acetaminophen	*N*-acetylcysteine
Anticholinergics	Antihistamines, atropine, belladonna alkaloids, mushrooms (some), psychoactive drugs	Physostigmine
Anticholinesterases		Atropine
Anticoagulant	Warfarin (coumadin), rodenticides	Vitamin K
Benzodiazepines		Flumazenil
Calcium channel blockers		Calcium chloride10% solution
Carbon monoxide		Oxygen
Cholinergic, muscarinic	Carbamates, some mushrooms, organophosphates, physostigmine, pilocarpine pyridostigmine	Atropine/pralidoxime
Cholinergic, nicotinic	Black widow spider bites, carbamates, insecticides, nicotine	Atropine/pralidoxime
Digoxin		Digoxin -specific antibodies
Cyanide	Cyanide	Sodium nitrite 3%, sodium thiosulfate 25%
Ethylene glycol, methanol	Antifreeze, rubbing alcohol	Ethanol 10% or fomepizole, thiamine, and pyridoxine
Iron-containing products	Deferoxamine (desferal)	Iron-containing products
Opioid	Opioids (e.g., morphine, hydrocodone, methadone)	Naloxone
Salicylate	Aspirin products	–
Sulfonylureas	Sulfonylurea	Octreotide

Urinary pH modification may enhance systemic elimination and prevent renal tubular reabsorption of some agents. Hemodialysis and hemoperfusion are also effective for the elimination of dialyzable agents. Binding resins (sodium polystyrene sulfonate) and toxin specific antidotes (e.g., Digibind) are also used.

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272 Acetaminophen

Rania Slika

Acetaminophen is the most commonly used analgesic and antipyretic in pediatrics with few side effects if used in the proper therapeutic doses. The 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (AAPCC-NPDS) documented 140 deaths from acetaminophen only. Acute acetaminophen overdose can lead to hepatotoxicity and is the leading cause of acute liver failure in the United States and United Kingdom. Acetaminophen is available alone or in combination with opioids, antihistamines, and cough and cold preparations.

Acetaminophen is primarily metabolized in the liver by glucuronidation or sulfation to nontoxic metabolites. Approximately 5% of the therapeutic dose is metabolized by cytochrome P450, mainly CYP2E1, to the reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI). This metabolite is toxic to the liver due to covalent binding to proteins and nucleic acids. However, it is detoxified through conjugation with glutathione and excreted in the urine as a mercapturate conjugate. In acute acetaminophen overdose, hepatic glutathione stores are depleted resulting in the accumulation of NAPQI. This accumulation can lead to hepatic necrosis and cell death.

The acute ingestion of more than 150 mg/kg acetaminophen can lead to hepatotoxicity. Several factors can increase the risk for acetaminophen hepatotoxicity including coingestions and nutritional status. Chronic use of certain medications or herbs that induce CYP2E1, which is responsible for the formation of NAPQI, can increase the risk of acetaminophen hepatotoxicity. Fasting as the result of a febrile illness or gastroenteritis can lead to the depletion of the glutathione stores and the accumulation of the toxic metabolite, thus representing another risk factor for acetaminophen hepatotoxicity.

Clinical and Laboratory Manifestations

The signs and symptoms of acetaminophen overdose depend on several factors including the time since ingestion, presence of risk factors, and the use of other medications. The clinical findings are stratified into different stages as shown in *Table 272.1*. In the first stage, the first 24 h post ingestion, patients will develop gastrointestinal disturbances such as anorexia, abdominal pain, nausea, vomiting, lethargy, and diaphoresis. If measured, the laboratory finding will appear normal. In the second stage, the latent phase, 24–72 h following ingestion, patients usually appear well, but biochemical markers of hepatotoxicity begin to rise. Some patients may experience right upper quadrant pain and appear jaundice. Elevations in the serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, and prothrombin time occur. Some patients will develop nephrotoxicity and oliguria in this stage.

Stage three, 72–96 h after ingestion, is the stage where the maximal hepatic injury occurs. Gastrointestinal symptoms will reappear including anorexia, nausea, vomiting, abdominal pain accompanied with malaise, jaundice and central nervous system symptoms like confusion, somnolence, and coma. The liver function tests peak where AST levels exceed 10,000 IU/L. Renal insufficiency occurs in 50% of the patients due to acetaminophen-induced acute tubular necrosis. Metabolic disorders including hypophosphatemia, hypoglycemia, and metabolic acidosis can accompany this stage. Hypoglycemia reflects impaired gluconeogenesis and elevated levels of insulin. Lactic acidosis is due to tissue hypoxia and decreased hepatic clearance of lactate. Coagulation disturbances with elevations in prothrombin time (PT) and International normalized ratio (INR) can be associated with high mortality rate. There are several indicators for poor outcome including: prothrombin time greater than 100 s, grade 3 or 4 encephalopathy, renal failure, development of acute liver failure, cerebral edema, and metabolic acidosis ($pH < 7.3$). In stage four, the recovery phase, 70% of patients will survive acute liver failure by 4 days to 2 weeks after ingestion. If patients are left untreated with toxic acetaminophen levels, death will result within 4–18 days.

Management

Management of acetaminophen overdose depends on the amount ingested, time after ingestion, and serum concentration of acetaminophen. When there is an excessive

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Table 272.1
Stages of acetaminophen toxicity

Stages	Time post ingestion	Clinical manifestations
Stage 1	1–24 h	Anorexia, abdominal pain, nausea, vomiting, lethargy, diaphoresis
Stage 2	24–72 h	Right upper quadrant pain, jaundice; elevated AST, ALT, prothrombin time, total bilirubin; oliguria, flank pain, hematuria, proteinuria
Stage 3	72–96 h	Gastrointestinal symptoms will reappear as anorexia, nausea, vomiting; confusion, somnolence; peak elevation in liver enzymes; hypophosphatemia, hypoglycemia, metabolic acidosis
Stage 4	4 day–2 weeks	Resolution of hepatic injury or deterioration, coma, and death

amount of drug ingested, more than 150 mg/kg or the history is unclear, the patient should be referred to the emergency department and acetaminophen serum levels obtained. The use of ipecac to induce emesis is typically not recommended. If the patient presents within 4 h of ingestion, gastric decontamination with activated charcoal can be useful. Activated charcoal is best effective when given within 1 h of ingestion. Optimum dose is not established; usual dose is 25–50 g in children aged 1–12 years and 10–25 g in infants up to 1 year old. Baseline liver function tests, bilirubin, prothrombin time, serum creatinine, and urinalysis should be obtained upon admission in addition to the acetaminophen serum level.

N-Acetylcysteine (NAC) is the treatment of choice for acetaminophen overdose. It works by binding directly to acetaminophen toxic metabolite and thus replenishing the glutathione stores and enhances nontoxic sulfate conjugation in liver cells. The overall mortality rate decreased

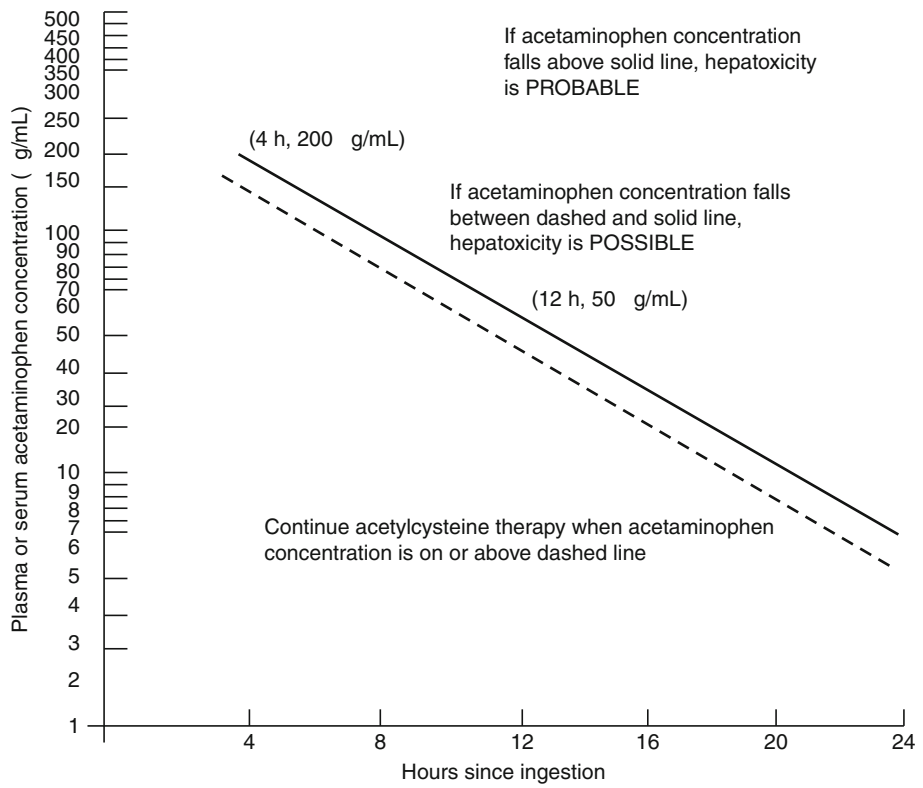

Figure 272.1
Nomogram relating plasma or serum acetaminophen concentration and probability of hepatotoxicity at varying intervals following ingestion of a single toxic dose of acetaminophen. (Modified from Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics* 1975; 55:871–876; and Rumack BH, Peterson RG, Koch GG, et al. Acetaminophen overdose: 662 cases with evaluation of oral N-acetylcysteine treatment. *Arch Intern Med* 1981; 141:380–385)

Table 272.2
Comparison of intravenous and oral regimens for acetylcysteine in the treatment of acute acetaminophen overdose

	Oral route	Intravenous route
Regimen	140 mg/kg loading dose followed 4 h later by 70 mg/kg every 4 h for 17 doses diluted to 5% with juice or soft drinks	Loading dose: 150 mg/kg IV over 60 min
		50 mg/kg IV over 4 h
		100 mg/kg IV over 16 h
Total Dose (mg/kg)	1330	300
Duration (h)	72	21
Adverse events	Anaphylactoid reactions (rash, angioedema, hypotension, bronchospasm), flushing	Nausea and vomiting

from 5% to 0.7% with the use of N-acetylcysteine. Plasma acetaminophen level should be obtained 4 h after ingestion or as soon as possible thereafter.

The Rumack–Matthew nomogram was established to predict patients who would develop hepatotoxicity from acetaminophen overdose (*Fig. 272.1*). According to the nomogram, when the serum acetaminophen concentration is above the treatment line or the possible hepatotoxicity line (150 μg/ml at 4 h), a full course of treatment with acetylcysteine is indicated. For patients having risk factors for increased hepatotoxicity, treatment with acetylcysteine is started if the serum acetaminophen level is above 100 μg/ml at 4 h. The best effective time of administration is within 8–10 h post ingestion, but it can be still indicated for as late as 24 h or more especially in patients with apparent liver toxicity. Patients should receive a full course of acetylcysteine in the absence of any serum acetaminophen level when it is suspected that more than 150 mg/kg have been taken over 24 h.

N-Acetylcysteine is available in both oral and intravenous formulation. No studies have shown better efficacy of the oral or the intravenous mode of administration when N-acetylcysteine is used within 10 h of acetaminophen overdose. *Table 272.2* outlines a comparison between the two regimens. There are certain differences in terms of the total dose administered, the duration of therapy, and adverse reactions. Patients, who vomit after oral acetylcysteine, should take another dose. Patients with coagulopathy or elevated creatinine clearance should be admitted for further monitoring and should receive acetylcysteine at a dose of 150 mg/kg every 24 h until INR falls below 2.

Patients experiencing angioedema, hypotension, and bronchospasm should be treated with diphenhydramine, corticosteroids, and bronchodilators. Acetylcysteine infusion should be stopped and then restarted later at a lower rate. Antiemetics can be used for patients having vomiting like ondansetron, Metoclopramide, or droperidol. Therapy is monitored by obtaining regular acetaminophen blood levels. Liver function tests, prothrombin time, and bilirubin monitoring are important to detect improvement in liver function. Other monitoring parameters during the detoxification process include: creatinine, blood urea nitrogen, glucose, and electrolytes.

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273 Alcohol

Sakra S. Balhareth

Epidemiology

Alcohol is one of the most commonly abused substances globally. Alcohol-related injuries accounted for 10–18% of the total emergency visits in some studies. In 2009 alcohol represented 3.20% of the total poisoning cases in the USA.

Ethanol (Ethyl Alcohol, Absolute Alcohol, and Dehydrated Alcohol)

Ethanol is found mainly in alcoholic beverages, some over-the-counter medications such as mouthwashes, cold and cough preparations, and cleaning products. Ethanol is rapidly absorbed orally (80–90%) with peak onset of 30 min. Inhalation and skin absorption is widely reported. It is readily distributed (volume of distribution of 0.6 mL/kg) and extensively metabolized by the liver. The elimination rate ranges from 10 to 34 mg/dL/h.

Ethanol exerts its action by enhancing the inhibitory effect of gamma-aminobutyric acid (GABA) through binding to GABA receptors in the central nervous system (CNS). Moreover, it antagonizes the excitatory effect of *N*-methyl-D-aspartate (NMDA) glutamate resulting in its sedative effect.

The signs and symptoms of ethanol intoxication range from vomiting, euphoria, and ataxia in mild to moderate toxicity. In severe toxicity, respiratory depression, hypothermia, severe hypoglycemia, coma, and death can occur. Usually, signs and symptoms of intoxication in children >10 years resemble those of adults. In younger children, hypoglycemia is the hallmark. The mechanism of ethanol-induced hypoglycemia involves the inhibition of gluconeogenesis.

Ethanol toxicity is very difficult to diagnose in children; hence, clear and accurate history is extremely important. The general approach to diagnose known or suspected intoxication should be followed. Blood glucose level, electrolytes, and ethanol blood level (EBL) should be obtained. Change in level of consciousness is directly proportional to the ethanol blood level (EBL). However, specific correlation between EBL and symptoms is not well established in children as it is in adults. In young children, dose of 0.5 mL/kg of absolute ethanol (95–99%) resulting in an estimated EBL of 50–75 mg/dL may cause significant intoxication. Ingestion of 3 g/kg of absolute ethanol has been reported to cause death in children.

Isopropyl Alcohol (Isopropanol)

Isopropyl alcohol is widely used in cosmetics, disinfectants, solvents, and mouthwashes. It is metabolized by alcohol dehydrogenase to acetone giving the characteristic fruity odor of the intoxicated patient's breath. Isopropyl alcohol can be toxic upon both topical and oral ingestion. Ingestion of 2–2.5 mL/kg may lead to the same features seen with the ethanol poisoning with the additional complication of severe gastritis. Isopropyl alcohol blood level is of a limited clinical value especially in presence of ketonemia or ketonuria which confirm the diagnosis.

Ethylene Glycol

Ethylene glycol is a sweet-tasting liquid known as antifreeze. It can be found in humectants, pesticides, and solvents. It is rapidly absorbed after oral ingestion and extensively distributed (volume of distribution of 0.5–0.8 L/kg). Toxicity appears rapidly due to the short elimination half-life of 3 h. Ethylene glycol is oxidized via alcohol dehydrogenase (ADH) to two toxic metabolites, glycolic acid and glyoxylic acid. The later is further metabolized to several products such as oxalic acid and glycine. In order for such conversions to take place, thiamine and pyridoxine as cofactors are required. The accumulation of these toxic metabolites can lead to metabolic acidosis, calcium oxalate crystal deposition in all vital organs, and encephalopathy. In children, ingestion of as much as 0.2 mL/kg of 100% solution can be fatal. The signs and symptoms of intoxication are directly proportional to the amount ingested and the period elapsed after ingestion. Intoxicated patient might present with nausea and vomiting in mild cases or renal failure and encephalopathy in severe toxicity.

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Serum electrolytes, renal function tests, and ethylene glycol concentration should be monitored. Ethylene glycol is rapidly metabolized and so the blood level might not be reflective in patient with late presentation after ingestion. Ethylene glycol concentration of >20 mg/dL confirms the diagnosis.

Methanol

Methanol is widely used as an industrial solvent. It is found in windshield washer solution, paint remover, and cleaning solvents. It is rapidly absorbed orally achieving maximal concentration within almost 60 min. Inhalation and skin absorption have been reported. Methanol is hepatically metabolized via alcohol dehydrogenase (ADH) to formaldehyde, which is then converted to formic acid. These toxic metabolites are responsible for methanol toxicity. Onset of methanol toxicity is delayed due to slow metabolism, which allows time for treatment. Signs and symptoms of toxicity can be manifested after the ingestion of 0.1 mL/kg of 100% solution.

High anion gap metabolic acidosis and vision disturbances that might progress to blindness are the main features of methanol toxicity. Methanol level of >20 mg/dL confirms the diagnosis.

Table 273.1
Dosing and administration information of commonly used medications in treatment of alcohol poisoning

	Dose and administration	Comments
Dextrose	IV:	Administer thiamine prior to the administration of dextrose in chronic ethanol abusers. Maximum concentration of dextrose solution that can be administered through peripheral vein is 12.5%
	Infants ≤ 6 months:	
	10% solution: 2.5–5 mL/kg	
	25% solution: 1–2 mL/kg/dose	
	50% solution: 0.5–1 mL/kg	
	Maximum: 25 g/dose	
	Infants >6 months and children:	
	10% solution: 5–10 mL/kg	
	25% solution: 4 mL/kg/dose	
	50% solution: 1–2 mL/kg	
	Maximum: 25 g/dose	
	Adolescents and adults:	
	25% solution: 40–100 mL	
	50% solution: 20–50 mL	
Thiamine	Adults: initial: 100 mg IV, then 50–100 mg/day IM or IV	Administer thiamine prior to the administration of dextrose in chronic ethanol abusers
Folinic acid	1 mg/kg IV over 30–60 min every 4–6 h; maximum 50 mg	
Pyridoxine	50 mg IV every 6 h until the intoxication has resolved	
Fomepizole (Antizol®):	IV: initial: 15 mg/kg, followed by 10 mg/kg every 12 h for four doses, then 15 mg/kg every 12 h thereafter. Adjust in hemodialysis	Fomepizole is the treatment of choice for ethylene glycol and methanol toxicity
Ethanol (Absolute ethyl alcohol 10%)	IV: Initial: 600 mg/kg	Ethanol should only be used when fomepizole is not available or in patients with known hypersensitivity to fomepizole or other pyrazoles
	Maintenance:	*Goal of therapy:* maintain serum ethanol levels >100 mg/dL
	Nondrinker: 66 mg/kg/h	
	Chronic drinker: 154 mg/kg/h	
	Adjust in hemodialysis	

IV intravenous, IM intramuscular

Management of Alcohol Toxicity

Supportive measures should be employed whenever needed. In general, induction of emesis and activated charcoal are not effective and should not be tried. Gastric lavage (decontamination) is only effective if the patient presented within 1 h of ingestion.

Ethanol and isopropyl alcohol have no specific antidote. The mainstay treatment of ethanol poisoning in children is to quickly detect and correct hypoglycemia. In mild to moderate cases, the treatment is mainly supportive. Ethanol and isopropyl alcohol can be removed by hemodialysis. However, this modality should be reserved for patients with severe intoxication not responding to supportive care and patients with impaired hepatic function. Thiamine (vitamin B1), pyridoxine (vitamin B6), and folate are used in patients with suspected chronic ethanol abuse to prevent serious withdrawal symptoms (Wernicke syndrome).

Ethanol and fomepizole (Antizol®) are approved antidotes for ethylene glycol and methanol poisoning. Both are alcohol dehydrogenase blockers. Fomepizole has an affinity to ADH 8,000 times greater than ethanol and is considered the treatment of choice. Compared to ethanol, fomepizole has fewer side effects, can be administered peripherally, does not require intensive care for administration, requires less monitoring, and does not cause CNS depression or hypoglycemia. Available literature suggests that fomepizole might preclude the need for hemodialysis in severe ethylene glycol and methanol toxicity in patients with normal function. Though fomepizole is more expensive than ethanol, the indirect cost of ethanol (continuous administration, frequent monitoring, and possible side effects) may make the cost more comparable. Although fomepizole is not approved for children, it has been used in the literature.

In menthol poisoning, folate should be administered to increase clearance of formate. If ethylene glycol toxicity is suspected, thiamine and pyridoxine should be administered to enhance the formation of less toxic metabolites. Calcium should not be administered routinely due to the risk of increasing the formation of calcium oxalate. It should be reserved for patients with hypocalcemia. Dosing and administration information of commonly used medications in treatment of alcohol poisoning is outlined in *Table 273.1*.

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274 Antidepressants

Rania Slika

According to the 2009 Annual Report of the American Association of Poison Control Centers National Poison Data System (NPDS), there were 1,02,792 human ingestions of antidepressants reported to poison centers in the USA. Children less than 5 years of age accounted for 14,310 of all reported antidepressant exposures.

There are three major classes of medications used for the management of depression including: cyclic antidepressants, selective serotonin reuptake inhibitors, and monoamine oxidase inhibitors (*Table 274.1*). Cyclic antidepressants are considered the second to analgesics as the most common drugs implicated in fatal drug overdose.

Since the use of monoamine oxidase inhibitors in children is uncommon as much safer medications are available, only cyclic antidepressants and selective serotonin reuptake inhibitors overdose management will be discussed.

Cyclic Antidepressants

Ingestion of 10–20 mg/kg of most antidepressants may lead to coma and cardiovascular symptoms and the ingestion of as little as 15 mg/kg may be fatal in a child. The toxic effects from cyclic antidepressants overdose result from exaggeration of their pharmacologic effects. They have four major pharmacologic effects: inhibition of the fast sodium channels leading to decreased myocardial contractility, inhibition of norepinephrine reuptake, direct α adrenergic block, and anticholinergic effects.

Clinical and Laboratory Manifestations

Patients presenting initially after cyclic antidepressant overdose may have no symptoms but deteriorate rapidly within 1 h. The clinical features of cyclic antidepressants overdose can be grouped according to their effects on the central nervous system, the peripheral autonomic system (anticholinergic effects), and the cardiovascular system (*Table 274.2*).

Prolongation of the QRS complex on ECG is the most important toxic effect of cyclic antidepressant overdose. It is due to the inhibition of the sodium channels that delays the propagation of depolarization through the myocardium and conducting tissue with a predisposition to cardiac arrhythmia. Sinus tachycardia, which is due to the inhibition of norepinephrine reuptake and the anticholinergic effects, is the most common cardiovascular effect. Another cardiovascular effect is hypotension that is due to vasodilation and impaired cardiac contractility. Cyclic antidepressant overdose–related mortality is mainly due to refractory hypotension. Delirium manifesting as disorientation and agitation occurs in the initial hours after ingestion and may develop in later stages into coma. Seizures often occur within 2 h and may result in acidosis and hyperthermia.

Electrocardiogram ECG is obtained upon presentation in patients with suspected or known cyclic antidepressant overdose. Serial ECGs should be obtained later. Prolongation of the QRS $>$ 100 ms, abnormal morphology of the QRS, and abnormal size and ratio of the R and S waves in lead AVR (R wave $>$ 23 mm) predict cardiotoxicity and are important tools in diagnosis and management. ECG changes are better predictors of seizures or ventricular arrhythmia than plasma drug levels. Plasma level of cyclic antidepressants has limited therapeutic or prognostic utility.

Management

Patients having cyclic antidepressants overdose should have a baseline electrocardiogram and be monitored for a minimum of 6 h. Patients with significant symptoms or with any ECG changes, or with mild persistent symptoms (sinus tachycardia or lethargy) should be admitted and monitored in the intensive care unit. If the patient remains symptom-free, then the patient may be referred for psychiatric clearance. Aggressive supportive care and alkalinization using sodium bicarbonate represent the mainstay of treatment (*Table 274.3*). Whenever a patient is suspected to have cyclic antidepressant overdose, the initial management would include: securing the patient's airway, breathing and circulation, obtaining baseline ECG with continuous monitoring, pulse oximetry, and have an IV line inserted. Many patients may require

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Table 274.1
The different classes of antidepressants

Cyclic antidepressants	Amoxapine
	Desipramine
	Nortriptyline
	Protriptyline
	Maprotiline
	Imipramine
	Amiriptyline
	Doxepin
	Trimipramine
Selective serotonin reuptake inhibitors	Citalopram
	Escitalopram
	Fluoxetine
	Paroxetine
	Sertraline
	Fluvoxamine
Serotonin/norepinephrine reuptake inhibitor	Duloxetine
	Venlafaxine
Serotonin reuptake inhibitor/antagonist	Trazodone
	Nefazodone
Monoamine oxidase inhibitor	Phenelzine
	Selegiline
Dopamine reuptake inhibitor	Bupropion

Table 274.2
Clinical features of cyclic antidepressant overdose

Cardiovascular effects	Central nervous system effects	Anticholinergic effects
Sinus tachycardia	Drowsiness	Dry mouth
Prolonged PR/QRS/QT	Coma	Blurred vision
Heart block	Seizures	Constipation
Hypotension	Rigidity	Urinary retention
Ventricular fibrillation/ tachycardia	Respiratory depression	Dilated pupils
Asystole		Pyrexia

intubation. Supplemental oxygen should be available if needed. Laboratory tests required include serum electrolytes, blood urea nitrogen, serum creatinine, glucose, and arterial blood gases.

Gastric decontamination with gastric lavage and activated charcoal can be used even on late presentation because of delayed gastric emptying secondary to anticholinergic effects. Ipecac-induced emesis is not recommended because rapid neurologic and hemodynamic deterioration may occur. Gastric lavage can be used if it can be performed within 1 h of ingestion. Activated charcoal is used to enhance elimination by adsorption of the cyclic antidepressant and decreased enterohepatic recirculation. The recommended dose of activated charcoal is 1 g/kg. The use of multiple dose activated charcoals is generally not recommended in cyclic antidepressant overdose because of the potential of adverse effects such as impaction and intestinal infarction.

Intravenous sodium bicarbonate is a first-line treatment for QRS complex prolongation, ventricular tachycardia, and hypotension caused by cyclic antidepressant overdose. Sodium bicarbonate at a dose of 1–2 mEq/kg is administered as a bolus infusion and repeated as necessary to achieve an arterial blood pH of 7.5–7.55. Excessive use of sodium bicarbonate may lead to dangerous alkalemia and ventricular arrhythmia. Sodium bicarbonate is also used to treat ventricular dysrhythmias. For those unresponsive, consider magnesium, beta-sympathomimetics, overdrive pacing, or lidocaine. Class IA (Quinidine, disopyramide, and procainamide) and class IC antiarrhythmics are contraindicated as their effects on myocardial conduction are similar to that of the cyclic antidepressants. Treatment with beta-blockers for supraventricular tachydysrhythmias may be needed if the rate exceeds 160 beats per minute and the patient demonstrates signs and symptoms of hemodynamic instability. Benzodiazepines (diazepam or lorazepam) are used for the treatment of cyclic antidepressant-induced seizures. Phenobarbital is used for seizures refractory to benzodiazepines. Flumazenil is used to antagonize the effects of benzodiazepines, but its use in cyclic antidepressant overdose has been associated with seizures and is contraindicated. Vasopressors such as norepinephrine, phenylephrine, or dopamine are used in patients with hypotension refractory to fluid and sodium bicarbonate. Use of physostigmine, an anticholinesterase, is not recommended since it has been associated with the development of seizures and fatal dysrhythmias.

Selective Serotonin Reuptake Inhibitors

Pediatric ingestions of selective serotonin reuptake inhibitors (SSRIs) are generally well tolerated and much safer than cyclic antidepressants. SSRIs have a wide therapeutic range and thus fatalities are uncommon with pure SSRI overdoses but may occur in the presence of coingestants such as

Table 274.3
Drug therapy for antidepressants overdose

Indication	Drug	Dosage regimen
Gastric decontamination	Activated charcoal	1 g/kg
Wide QRS complex, ventricular arrhythmias, hypotension	Sodium bicarbonate	1–2 mEq/kg bolus infusion
		Repeated to reach arterial blood pH 7.5–7.55
Refractory ventricular arrhythmias	Lidocaine	1 mg/kg IV push initially; followed by 20–50 mcg/kg/min continuous IV infusion
Seizures	Lorazepam	0.05–0.1 mg/kg slow IV over 2–5 min (max 4 mg/dose) repeated every 10–15 min if seizures persist
	Diazepam	0.2–0.5 mg slow I.V every 2–5 min to a maximum of 5 mg ; repeat in 2–4 h if needed
		Children $\geq$ 5 years: 1 mg slow I.V. every 2–5 min to a maximum of 10 mg ; repeat in 2–4 h if needed
Torsade de pointes	Magnesium sulfate	25–50 mg/kg/dose IV ; not to exceed 2 g/dose

benzodiazepines or ethanol. They are unlikely to cause seizures, severe CNS depression, or significant cardiotoxicity. Citalopram is likely the most cardiotoxic SSRI; its use may be associated with prolongation of the QTc interval and can predispose a patient to torsade de pointes. Since SSRIs have little or no antagonist effect on muscarinic, histaminic, or adrenergic receptors, they do not cause anticholinergic symptoms, hypotension, or significant sedation.

Since most selective serotonin reuptake inhibitors overdoses develop no or minimal toxicity, supportive care would be the mainstay of therapy. Management includes: securing airway, breathing and circulation, gastric decontamination with one dose of activated charcoal (1 g/kg), treating seizures with benzodiazepines (diazepam or lorazepam), managing prolonged QRS interval with sodium bicarbonate, and treating torsade de pointes if present with magnesium sulfate. Most cases resolve without complications within 24–36 h with adequate supportive measures. The patient who remains asymptomatic for several hours following an SSRI overdose needs no further medical evaluation and treatment.

Serotonin Syndrome

Serotonin syndrome is a potentially life-threatening condition secondary to excessive serotonin activity in the central nervous system. It results from therapeutic medication use, drug overdose, or interactions between medications. The incidence of serotonin syndrome with selective serotonin reuptake inhibitors overdose is 10–14% and many of these cases have mild presentations. It is characterized by mental status changes, autonomic hyperactivity, and neuromuscular abnormalities. Mental status changes are manifested by confusion, agitation, and coma. Hyperthermia, mydriasis, tachycardia, and hypertension are characteristics of autonomic hyperactivity. Neuromuscular abnormalities are manifested by myoclonus, rigidity, tremors, hypereflexia, clonus, and ataxia. Management of the serotonin syndrome involves the removal of the precipitating drugs, supportive care, the control of agitation with benzodiazepines, the control of autonomic instability, and the administration of serotonin antagonist (cyproheptadine 0.25 mg/kg/day divided twice or three times per day, max: 12 mg) depending on the severity of the illness. Severe cases that develop muscular rigidity and hyperthermia must be treated with neuromuscular paralysis, followed by orotracheal intubation and ventilation.

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275 Digoxin

Nicole Gebran

Digoxin was first introduced as a drug in the treatment of atrial fibrillation in the early twentieth century. Only subsequently was the value of digitalis for the treatment of congestive heart failure established. The syndrome of digoxin toxicity was originally described in 1785 by Withering.

The therapeutic properties of cardiac glycosides such as digoxin, a product of the foxglove plant, have been known since the days of the ancient Romans who used red squill, derived from the sea onion, as a diuretic in heart medicine. Cardiac glycosides are found in certain flowering plants such as oleander and lily-of-the-valley and are components of some herbal dietary supplements. Digitalis toxicity was also well known in previous centuries, and some have suggested that the toxic visual symptoms of digitalis may have played a role in Van Gogh's use of swirling greens and yellows.

The public health burden of digoxin toxicity declined dramatically from 1991 to 2004 in the United Kingdom and the United States. The decline may be attributed to reductions in the overall utilization and dose. However in hospitalized patients, international statistics indicates that approximately 2.1% of inpatients on digoxin and 0.3% of all admissions develop toxicity. In the United States, approximately 0.4% of all hospital admissions and 1.1% of outpatients on digoxin develop toxicity. Data from the 2007 Annual Report of the American Association of Poison Control Centers reported 2,565 adult and pediatric digitalis exposure toxicities with 10 deaths reported.

Toxicity from plants, such as oleander, foxglove, and lily-of-the-valley, is uncommon but potentially lethal. Case reports of toxicity from these sources implicate the preparation of extracts and teas as the usual culprit. The relationship between digoxin toxicity and the serum digoxin level is complex; clinical toxicity results from the interactions between digoxin, various electrolyte abnormalities, and their combined effect on the Na+/K+ ATPase pump.

The mechanism of action of digoxin is by inhibition of Na+K+ATPase. This inhibits the transport of Na+ and K+ across the myocyte membrane, causing a rise in intracellular Na+, thus decreasing efflux of Ca2+ from the myocyte and augmenting myocardial contractility. The elimination half-life of digoxin is 36–48 h in patients with normal renal function. Steady-state levels are reached approximately a week after the initiation of maintenance therapy. Digoxin is excreted by the kidneys but is not cleared by hemodialysis. Skeletal muscles, and not adipose tissue, are the main reservoir and thus dosing should ideally be based on lean body mass. It has a narrow therapeutic index, and daily maintenance doses range from 2.5 to 5 μg/kg in older children to 5–10 μg/kg in younger children and infants. Loading doses may be given orally or intravenously when indicated. Digoxin toxicity occurs more commonly in neonates and infants or in old age and in patients with renal dysfunction and those taking other drugs such as carvedilol or other β-blockers or diuretics.

Clinical and Laboratory Manifestations

Digoxin toxicity may be acute in presentation, as in a toddler who accidentally over-ingests a family member's stock of medicament or chronic, as in a child who is being treated with digoxin and whose serum level exceeds the therapeutic range. Mechanistically, grossly acute poisoning with digoxin differs significantly from chronic toxicity. In acute overdose, the sodium–potassium pump is disrupted, enabling a decrease in intracellular potassium and an increase in extracellular potassium. The normal membrane resting potential is reduced, and electrical conduction is slowed. Eventually, there is a loss of myocardial electrical function that presents clinically as high-grade block and asystole that may be refractory to electrical pacing.

The usual signs and symptoms in acute toxicity include anorexia, nausea, vomiting, lethargy, confusion, weakness, and hyperkalemia. Atrioventricular block and ventricular dysrhythmias are also seen. In the setting of chronic toxicity, signs and symptoms include abdominal pain, anorexia, confusion, delirium, disorientation, headache, hypokalemia and hypomagnesemia, nausea, vomiting, and ocular disturbances.

Management

Diagnosis of toxicity should be made clinically. An ECG should be done to evaluate for rhythm disturbances.

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Table 275.1
Noncardiac signs and symptoms of digitalis toxicity

Manifestation	Prevalence %
Fatigue	95
Visual symptoms	95
Weakness	82
Nausea	81
Anorexia	80
Psychic complaints	65
Abdominal pain	65
Dizziness	59
Abnormal dreams	54
Headache	45
Diarrhea	41
Vomiting	40

From Smith TW, Antman EM, Friedman PL, et al. Digitalis glycosides: mechanisms and manifestations of toxicity. Part III. Prog Cardiovasc Dis 1984; 27: 26, with permission.

Digoxin levels are used to corroborate the diagnosis but may not always correlate with the extent of toxicity, especially after acute ingestion. Children without cardiovascular disease may tolerate higher levels without clinical symptoms. In general, the smaller the infant, the higher the levels may be before toxic effects are observed. Levels drawn within 6–8 h after ingestion of a dose reflect the initial tissue distribution and are not necessarily indicative of toxicity. Normal levels, even in the setting of profound clinical toxicity, can occur with acute ingestion of nondigoxin glycosides such as foxglove and oleander, owing to nonreactivity with the digoxin radioimmunoassay. The clinical presentation of digoxin toxicity is unpredictable. The usual signs and symptoms may be noncardiac (*Table 275.1*), particularly gastrointestinal complaints, or cardiac such as rhythm disturbances. In nearly half the cases of digoxin toxicity, cardiac manifestations precede the noncardiac events. Atrioventricular block is the most common cardiac manifestation of severe digoxin toxicity in pediatrics. This population appears to be more resistant to the cardiotoxic effects of digoxin at a given serum level compared to adults with the same serum level. In more severe intoxication, lethargy, disorientation, and electrolyte disturbances may also occur.

Management of a patient with digoxin toxicity includes stopping administration of the drug and correction of rhythm disturbances. If the patient is asymptomatic, simple observation and monitoring may suffice. Symptomatic sinus bradycardia can be treated with atropine. Cardiac pacing may be required for higher degrees of block. Ventricular ectopics or ventricular tachyarrhythmias can be treated with lidocaine. Cardioversion is relatively contraindicated because it may cause asystole or ventricular fibrillation. In case of dysrhythmias, which are potentially life threatening or are associated with hemodynamic instability, the treatment of choice is intravenous administration of Digibind® or DigiFab™, which contain digoxin specific Fab antibody fragments, cleaved from immunoglobulin G extract from sheep immunized with digoxin. These fragments are not very immunogenic in humans and after binding with digoxin, are rapidly distributed and renally excreted. The Fab-digoxin complexes are inactive, causing rapid resolution of symptoms upon administration. Other indications for use of Digibind® in patients with digoxin toxicity include but are not limited to those with acute ingestion exceeding 0.3 mg/kg of digoxin, serum digoxin exceeding 5 ng/mL, hyperkalemia, or rapidly progressive toxicity. When the ingested amount of digoxin is known, the dosage of Digibind® is calculated: each 38-mg or 40-mg vial binds approximately 0.5 mg or 0.6 mg of digoxin, and 80% of the calculated dose is administered intravenously during a 30-min period to account for incomplete absorption.

Acute Ingestion of an Unknown Amount of Digoxin

If the amount of ingestion is unknown, general dosing guidelines should be used. In children weighing more than 20 kg, 20 vials are adequate to treat most life-threatening ingestions. May be given as a single dose or as 10 vials, then response is observed and a second 10-vial dose is given if indicated. The larger dose (20 vials) has a faster onset of action but may cause a febrile reaction. Digibind is given as an infusion over 30 min using an in-line 0.22 micron membrane filter. If cardiac arrest is imminent, it may be given as a bolus injection. It is important to monitor for volume overload in children.

Acute Ingestion of a Known Amount of Digoxin

To determine the dose of digoxin immune Fab, first determine the total body load of digoxin (TBL) or digitoxin using the following formulas (depending upon which factor is known the amount ingested or the postdistribution serum digoxin/digitoxin concentration (C)): (*Table 275.2* summarizes few examples)

Table 275.2

Infants and children dose estimates of digoxin immune Fab (in mg)[a] from serum digoxin concentration

Patient weight (kg)	Serum digoxin concentration (ng/mL)						
	1	2	4	8	12	16	20
1	0.4 mg[b]	1 mg[b]	1.5 mg[b]	3 mg	5 mg	6–6.5 mg	8 mg
3	1 mg[b]	2–2.5 mg[b]	5 mg	9–10 mg	14 mg	18–19 mg	23–24 mg
5	2 mg[b]	4 mg	8 mg	15–16 mg	23–24 mg	30–32 mg	38–40 mg
10	4 mg	8 mg	15–16 mg	30–32 mg	46–48 mg	61–64 mg	76–80 mg
20	8 mg	15–16 mg	30–32 mg	61–64 mg	91–96 mg	122–128 mg	152–160 mg

From Pediatric Lexi Drugs Online Digoxin Immune Fab Monograph. Lexi-Comp, Inc. 2009, with permission.

[a]When a range in dose is listed, the lower number represents the Digibind® dose and the higher number represents the Digifab™ dose. A single dose is the same for both products.

[b]Dilution of reconstituted vial to 1 mg/mL may be desirable.

$$\text{TBL of digoxin (mg)} = \text{C (in ng/mL)} \times 5.6 \times \text{body weight (in kg)}/1000 \text{ or}$$

$$\text{TBL of digoxin (mg)} = \text{mg of digoxin ingested (as tablets or elixir)} \times 0.8$$

$$\text{TBL of digitoxin (mg)} = \text{C (in ng/mL)} \times 0.56 \times \text{body weight (in kg)}/1000 \text{ or}$$

$$\text{TBL of digitoxin(mg)} = \text{mg digitoxin ingested}$$

$$\text{Dose of Digibind® (in mg) I.V.} = \text{TBL} \times 76$$

$$\text{Dose of DigiFab™ (in mg) I.V.} = \text{TBL} \times 80$$

$$\text{Dose of digioxin immune Fab (Digibind® or DigiFab™) (\# vials) I.V.} = \text{TBL}/0.5$$

Chronic Digoxin Ingestion Toxicity

In infants and small children weighing <20 kg with chronic digoxin toxicity, a single 40-mg vial may be adequate. The ECG disturbances usually disappear 30–40 min after use of Digibind. Electrolyte abnormalities, especially hypokalemia, should be corrected. Hyperkalemia should be corrected if the serum potassium level is greater than 5.5 mEq/L and should be treated with sodium bicarbonate or glucose insulin drip, or both. Intravenous calcium should be avoided in those cases because it may precipitate ventricular fibrillation or cardiac arrest. Kayexalate (Sanofi-Aventis, Bridgewater, NJ) may precipitate hypokalemia if administered to these patients because digoxin-induced hyperkalemia reflects an extracellular shift of potassium rather than an overall increase in body potassium. Hyperkalemia as a manifestation of digoxin toxicity is more common in the acute setting.

Physicians should have a high index of suspicion for digoxin toxicity in a patient who is taking the medication and presents with symptoms of vomiting, visual disturbances, or changes in the cardiac symptoms. Diagnosis of digoxin toxicity should be clinically made and levels should be used only for confirmation. Routine monitoring of levels is neither useful nor indicated. Early diagnosis and appropriate management can help reduce the associated morbidity and mortality.

Morbidity is usually 4.6–10%; however, morbidity is 50% if the digoxin level is greater than 6 ng/mL. Complications related to arrhythmias include hypoxic seizures, encephalopathies, loss of vasoregulation, and acute tubular necrosis. On the other hand, in pediatric patients, hyperkalemia is the major electrolyte complication in acute digoxin poisoning.

Individualizing the dosing of digoxin is the key to its optimal use. The desired plasma concentration endpoint is 2 ng/mL in patients younger than 2 years and 1.5 ng/mL in patients older than 2 years. Parents of patient should be educated about the good home childproofing and preventive measures. Medical, nursing, and pharmacy staff should carefully monitor the prescription, dispensing, and administration of digitalis.

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276 Household Products

Vivian Brown

Introduction

The key to management of suspected or confirmed household product ingestion by children is obtaining as much information as possible. Many household products list emergency measures on the product label in case of accidental ingestion and that the original product container be provided to health care professionals treating the ingestion.

Substances most frequently ingested by children in the developed world include household chemicals, medication, and plants (1) and in more than 90% of cases, the exposure is to a single substance and the vast majority of exposures occur at home. The majority of caustic ingestions occur in children between 12 and 48 months of age. Unintentional poisoning in developing countries can be much more serious, following ingestion of kerosene, caustic agents, herbal remedies, insecticides, or herbicides.

Prevention measures have included community-based strategies (moving toxic cleaning products to higher shelves) and educating consumers (safe storage of household products, use of warning labels, availability of poison control or hospital phone numbers). Warning labels (such as Mr. Yuk and skull and cross bones) are no longer recommended since they tend to attract children rather than deter them.

Age of Patient

Intoxications in children younger than 1 year may reflect accidental administration of an incorrect drug or dose by the caretaker, administration of a pharmaceutical by an older sibling, or parental abuse. Very young children are also subject to toxicity from passive exposure to agents such as smoke from marijuana and "crack" cocaine.

For children younger than 5, especially those aged 2 years and younger, unintentional behavior on the part of the child and parent are typically blamed for intoxication. Exploratory behavior, rather than purposeful harm, generally brings teens and preteens to medical attention, although suicidal gesture or frank suicide attempt might be considered for anyone over 9 years of age.

Nontoxic Household Product Ingestion

Many household products are nontoxic unless taken in huge amounts (*Table 276.1*). Mofenson and Greensher have developed criteria that qualify an ingestion as "nontoxic." These include:

- Assurance exists that only one identifiable product has been ingested and in a well-approximated amount.
- The product label includes no cautionary signal word.
- The child is symptom free and under 5 years old.
- Appropriate telephone follow-up is possible.

Other household products and management worth special note are:

1. Toothpaste containing fluoride typically contains a maximum of 1 mg of fluoride/g of toothpaste. Packaging often has warnings stating that if more than the amount used for brushing is ingested, medical attention is warranted. However, exploratory ingestion of sodium fluoride typically does not produce symptoms if the amount of fluoride ingested is less than 5 mg/kg.
2. Furniture polishes that contain petroleum distillates are not system poisons. They are dangerous if aspirated. There is no treatment indicated for the asymptomatic child who ingests furniture polish.
3. Hand dishwashing detergents can act as emetics; however, automatic dishwasher detergents can be alkali.
4. Diaper rash products are the most common topical preparations involved in pediatric poisonings. These may contain zinc oxide, emollients, and/or small quantities of vitamins A and D. The risk for vitamin A or D toxicity in this setting is negligible. With large ingestions, gastrointestinal upset may result.
5. Hydrogen peroxide 3% for household use/general disinfectant may cause gastrointestinal irritation but is unlikely to result in serious toxicity. However, it also is available as chlorine-free bleach (6%), fabric stain removers (5–15%), contact lens disinfectants (3%), hair dyes (6%), and teeth-whitening agents (15%), as well as concentrated solutions of 35% sold in health food shops for the purpose of "hyper-oxygenation therapy." It can cause toxicity via three main

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Table 276.1

Products that are nontoxic when ingested in small amounts and when the qualifying criteria are applied

Abrasives	Cosmetics	Hydrogen peroxide (medicinal 3%)	Putty (<2 oz)
Adhesives	Crayons (marked AP, CP)	Incense	Rubber cement
Antacids	Dehumidifying packets (silica or charcoal)	Indelible markers	Shampoos (liquid)
Antibiotics	Detergents (phosphate)	Ink (black, blue)	Shaving creams and lotions
Baby-product cosmetics	Deodorants	Laxatives	Soap/soap products
Ballpoint pen inks	Deodorizers (spray and refrigerator)	Lipstick	Suntan preparations
Bath oil	Elmer's glue	Lubricating oils	Sweetening agents (saccharin and cyclamates)
Bathtub floating toys	Etch A Sketch	Magic markers	Teething rings (water sterility)
Bleach (<5% Na hypochlorite)	Eye makeup	Matches	Thermometers (mercury)
Body conditioners	Fabric softener	Mineral oil	Thyroid tablets
Bubble-bath soaps	Fertilizer (if no insecticides or herbicides added)	Newspaper (black and white pages)	Toothpaste
Calamine lotion	Fish-bowl additives	Paint (indoor, latex)	Vitamins (without iron)
Candles (beeswax or paraffin)	Glues and pastes	Pencil (graphite)	Warfarin (rat poison, excluding "superwarfarins")
Caps	Grease	Perfumes	Watercolors
Chalk	Hair products (dyes, sprays, tonics)	Petroleum jelly	Zinc oxide (Desitin)
Cigarettes (<3 butts)	Hand lotions/creams	Phenolphthalein laxatives (Ex-lax)	Zirconium oxide
Clay (modeling)		Porous-tip marking pens	
Colognes			
Contraceptive pills			
Corticosteroids			

Adapted from Mofenson HC, Greensher J (1974) The unknown poison. Pediatrics 54:336–342. With permission.

mechanisms: corrosive damage, oxygen gas formation, and lipid peroxidation. Exposure can be ingestion, inhalation, injection, wound irrigation, rectal administration, dermal exposure, or ocular exposure.

6. Hydrofluoric acid (cleaning solutions) and methacrylic acid (in nail care products) are two products that have been responsible for serious injury and death. Although most cosmetics are of a low-order toxicity, nail care products (artificial nail primer, artificial nail glue, and artificial nail glue removers) can be very toxic causing methemoglobinemia and/or cyanide poisoning.

Toxic Household Product Ingestion

Table 276.2 lists products that are considered toxic if consumed in adequate amounts and provides a quick reference for product categorization. *Table 276.3* lists common non-pharmaceutical products and their symptoms and treatment following ingestion. *Figure 276.1* provides a household cleaning product algorithm. Specific treatment information for ingestion of caustics/corrosives is presented in *Fig. 276.2*; antidotes are listed in *Table 276.4*.

Management of Ingestion

Caustics/Corrosives

The approach to management of ingestion of caustics and/or corrosives begins with rapid clinical assessment of cardio respiratory function, neurologic status, and evidence of gastrointestinal hemorrhage. Gastrointestinal decontamination is not indicated after the ingestion of corrosive agents. Treatment by dilution is indicated only when the toxin produces local irritation or corrosion, in which case water or milk is acceptable. If the eyes are involved, they should be irrigated copiously with water for at least 15 min and then pH testing of fluids should be performed in the ocular cul-de-sac after irrigation to confirm neutralization; the normal pH of tears is 7 (also see *Tables 276.2* and *276.3*).

Hydrocarbons

Although hydrocarbons are still a major cause of pediatric morbidity via aspiration, systemic toxicity is limited and, if they are swallowed, is usually only a few swallows that

Table 276.2
Classification of household poisons by product category

Caustics/corrosives (alkaline)[a]
Cleano granules (caustic soda)
Oven cleaners (easy off)
Destop gel express drain and pipe cleaner (sodium hydroxide 20%)
Drain cleaners (Drano, liquid plumber)
Other products containing sodium hydroxide include: Clinitest tablets, powdered laundry, and dishwasher detergents
Sodium hypochlorite[a]
Clorox (5.25%) (treat as possible corrosive)
Ammonia[a]
Windex
Parson's Ammonia (cleaner)
Alcohols
Isopropyl alcohol 70%
Ethylene glycol (antifreeze)
Methanol (stove fuel, Sterno, paint remover)
Hydrocarbons
Gasoline
Kerosene
Furniture polish
Charcoal lighter
Mineral spirits
Caustics/corrosives (acid)[a]
Lysol toilet bowl cleaner
Organophosphates
Pesticides

[a] See corresponding algorithms in *Figs. 276.1* and *276.2*.

are vomited spontaneously. Hydrocarbons and other water-insoluble compounds are poorly adsorbed by charcoal. Therefore, gastrointestinal decontamination is not indicated and may predispose to hydrocarbon aspiration. The exception to this is significant ingestion of hydrocarbons containing toxic chemicals, which are the halogenated and aromatic compounds.

Organophosphates (Anticholinesterases)

Found in pesticides, symptoms of acute poisoning usually develop during the first 12 h of contact. These include CNS symptoms (dizziness, headache, ataxia, convulsions and coma), nicotinic signs (sweating, muscle twitching, tremors, weakness and paralysis), and muscarinic signs, characterized by the SLUDGE mnemonic (salivation, lacrimation, urination, defecation, gastrointestinal cramping, and emesis). Additionally, miosis, bradycardia, bronchorrhea, and wheezing may occur. In severe cases, pulmonary edema may occur. The best clues to diagnosis are a history of exposure and the above clinical manifestations. Plasma cholinesterase level depression of 25% or more is strong evidence of poisoning, but this laboratory test is rarely readily available.

Aggressive gastrointestinal and dermal decontamination are crucial, and hospital staff must protect themselves from contaminated clothes and body fluids. Decontamination of the skin for topical exposure includes thorough scrubbing with soap to prevent further absorption (and bagging of contaminated clothing to protect medical personnel). Activated charcoal should be administered for oral poisoning. After decontamination, antidotal therapy should begin. (See *Table 276.5* for toxidromes and *Table 276.4* for general guidelines on antidote administration.) Atropine (0.05 mg/kg/dose) is given until an atropine effect is observed (tachycardia, dry flushed skin, mydriasis, fever, and drying of secretions). Atropine doses may be repeated every 1–4 h to maintain the atropine effect. A constant infusion of pralidoxime (10–15 mg/kg/h in a 1–2% solution) may be considered for very severe poisonings.

Alcohols

Treatments for ethylene glycol, methanol, and isopropanolol ingestion are listed in *Table 276.3*. The cornerstone of management includes the correction of acidosis, competitive inhibition of ADH, and hemodialysis-assisted elimination. The introduction of fomepizole as an antidote for ethylene glycol and methanol poisoning in 1998 constitutes a recent success in medical toxicology.

It acts through the binding of ADH 500–1,000 times more effectively than methanol, essentially eliminating the formation of toxic metabolites. Historically, a 10% ethanol solution IV or PO has been used to elicit competitive inhibition of toxic metabolites, keeping the serum ethanol concentration between 100 and 150 mg/dl. Most authorities ascribe an overall cost savings with the use of fomepizole; however, ethanol still exists as a viable option.

Table 276.3

Common non-pharmaceutical products involved in unintentional household poisoning in children (adapted and used with permission)

Product	Characteristics	Symptoms	Treatment
Aftershave, alcohols, cologne, mouthwash, perfumes	Ethanol-containing agents; perfumes contain up to 75–95%	CNS and respiratory depression, hypoglycemia, acidosis	Clinical observation and hospital admission depending on the ingested amount; blood glucose measurement; administer oral or intravenous glucose in hypoglycemic children depending on severity; respiratory support as needed
Bleach	Household solutions contain approximately 3–10% sodium hypochlorite or less commonly 3% hydrogen peroxide; extremely unpalatable; unlikely to cause serious damage. Industrial bleach: up to 50% of sodium hypochlorite	Nausea, emesis, diarrhea; esophageal injury rarely occurs; hypernatremia, hyperchloremic acidsis. External contamination may result in eye or skin irritation	Administer fluids; hospital admission of children at risk of developing esophageal injury (see esophageal burns)
Button batteries	Toxicity occurs when button batteries remain in the esophagus, the nose, the ear, or if they are leaky before ingestion. If they rapidly reach the stomach, toxicity is unlikely	Difficulty swallowing, vomiting, hematemesis. In case of ingestion of leaky battery, hypersalivation, drooling	X-ray to confirm ingestion. Battery lodged in the esophagus should be quickly removed by endoscopy. Same applies to battery impacted in the nose or ear. Batteries in the stomach or the intestine should not be removed unless there are signs of perforation, obstruction, or if they were leaky
Detergents	Three chemical categories: nonionic, anionic, cationic	Nonionic, anionic (low toxicity): Respiratory symptoms secondary to foam aspiration rarely occur. Cationic: corrosive lesions if concentrated solution is involved	Administer oral fluids; further treatment depending on the presence of respiratory symptoms and corrosive lesions (see esophageal burns)
Dishwasher powders, liquids, tablets	Older or professional use products: strongly alkaline; possible severe corrosive injury	Hypersalivation, drooling, vomiting, hematemesis, pain. Esophageal injury may occur in the absence of oral burns	Remaining products must be washed off; administer oral fluids; supportive treatment (see esophageal burns)
Disinfectants and antiseptics	May contain a number of toxic constituents (chlorhexidine, hexylresorcinol, hydrogen peroxide, ichthammol, iodine, phenol, potassium permanganate); usually they are found in very low quantities in diluted solutions	Irritation of the oral mucosa, transient gastrointestinal upset, possibly corrosive effects, aspiration pneumonia. Systemic toxicity: acidosis, CNS depression, hepatic/renal damage depending on substances involved	Administer fluids; precise identification of involved substance is essential. In case of esophageal injury (see esophageal burns)

Table 276.3 (Continued)

Product	Characteristics	Symptoms	Treatment
Essential oils	Volatile mixture of esters, alcohols, and ketones; some substances, e.g., camphor, are very toxic	Initial effects: mucosal irritation, vomiting, epigastric pain; secondary hepatic and renal failure possible; sedation, seizures; respiratory compromise if aspirated	Clinical observation; supportive treatment if indicated
Ethylene glycol	Found in various types of antifreeze and windscreen wash. Rapid absorption from the stomach. Metabolic degradation by alcohol dehydrogenase (ADH) to a variety of toxic metabolites. Increased anion gap	After ingestion of $\geq$0.1 ml/kg: nausea, emesis, abdominal pain, CNS depression, convulsions; $\geq$0.2 ml/kg: metabolic/lactic acidosis, hypocalcaemia, rental failure, CNS depression, convulsions	Hospital admission: Assessment of plasma ethylene glycol as well as measurement of blood gases, serum electrolytes, and renal function. Antidotes in symptomatic children or those with a plasma ethylene glycol level $>$3.2 mmol/l (20 mg/dl): ethanol (initial dosage 0.6–0.8 g/kg, followed by 0.1 g/kg/h). Fomepizole: initial dosage: 15 mg/kg, followed by four-times 10 mg/kg every 12 h. In case of renal failure, hemodialysis is required. Consider hemodialysis if level $>$8 mmol/l (50 mg/dl). Or if resistant metabolic acidosis. Fomepizole and ethanol are dialyzed and the dosage needs to be adjusted when dialysis is performed. Supportive care: correction of acidosis with sodium bicarbonate, and glucose for hypoglycemia
Isopropanol	Alcohol found in various household products (e.g., nail polishes, hairsprays, antifreezes, car screen washes). Rapid absorption from the stomach and mucus membranes. Conversion to acetone by ADH. Excretion through the lungs and kidneys	Gastric irritation, CNS depression, and hypotension. Ketonemia and ketonuria	Asymptomatic children: short period of clinical observations and administration of fluids. Symptomatic patients require intensive support. Hypotension: treatment with intravenous fluids and inotropes. Hemodialysis is rarely useful, but could be considered in patients with failure of supportive measures
Methanol	Constituent of antifreezes, windscreen washes, and various household products. Rapidly absorbed from the gastrointestinal tract; metabolization by ADH. Increased anion gap	Irritation of mucus membranes; abdominal pain, nausea, emesis, retinal toxicity, neuritis of the optic nerve, metabolic acidosis, convulsions, and coma	Hospital admission: measurement of blood gases, electrolytes, renal function, and methanol level. Treatment is similar to ethylene glycol poisoning, both ethanol and fomepizole inhibiting its metabolism. Antidotes in symptomatic children or those with a plasma methanol level $<$8 mmol/l (20 mg/dl). In addition, consider folic acid 1–2 mg/kg every 4–6 h. Consider hemodialysis if level $>$15.6 mmol (50 mg/dl). Or if resistant metabolic acidosis. Fomepizole and ethanol are dialyzed and the dosage needs to be adjusted when dialysis is performed. Supportive care: correction of acidosis with sodium bicarbonate, and hypoglycemia with glucose

Table 276.3 (Continued)

Product	Characteristics	Symptoms	Treatment
Nail care/nail varnish removers	Typically contain acetone or ethyl acetate, but other solvents may be used including methanol; artificial nail products containing methacrylic acid may cause severe caustic injury; artificial nail removers containing nitroethane may cause methemoglobinemia, and acetonitrile may cause cyanide poisoning	Irritation of mucus membranes, vomiting, CNS depression; ketosis, acidosis, hyperglycemia possible	Clinical observation may be indicated; hospital admission needed in symptomatic children; Nitroethane and acetonitrile ingestions require referral to the ED; measurement of blood glucose; monitor respiratory and renal function; supportive care. In case of esophageal injury (see esophageal burns)
Nicotine	Toxic alkaloid found in a range of plants, most notably tobacco and smoking cessation products that contain nicotine (gums, transdermal patches, nasal sprays). Most frequently ingested in the form of cigarette or cigarette butt	Vomiting is the most common symptom. Confusion, convulsions, and dysrhythmias may occur only if large amounts are ingested	Usually no specific treatment is required; consider activated charcoal depending on ingested amount and age; supportive care in case of seizures and cardiovascular compromise
Petroleum distillate (paraffin, kerosene, petrol, diesel, lubricating, engine oils)	Low systemic toxicity	Aliphatic hydrocarbons: Main hazard: chemical pneumonitis. Many aromatic and halogenated hydrocarbons may cause CNS depression, seizures, and cardiac arrhythmias	Clinical observation; hospital admission in symptomatic children; administer fluids; chest X-ray and supportive treatment if indicated. Extracorporeal membrane oxygenation (ECMO) could be used in severe cases of chemical pneumonitis
Rat and mouse poisons (domestic rodenticides)	Accurate identification of the constituents may be difficult; most substances are based on warfarin or long-acting anticoagulant substances; alphachloralose is used rarely; carbamate pesticides are used in some regions	Bleeding, CNS depression with alphachloralose; cholingeric features with carbamates (organophosphate pesticides)	Determination of prothrombin time or INR at 12 and 36–48 h post ingestion if ingested substance exceeds 0.5 mg/kg of warfarin, or if 0.01 mg/kg or any other anticoagulant has been ingested. Consider administering oral charcoal. Administer vitamin K per os if prolongation of prothrombin time
Toilet cleaner blocks	Two types: cistern or rim blocks; acid or detergent based; low systemic toxicity, local corrosive damage may occur	Gastrointestinal irritation/upset	Administer fluids. In case of esophageal injury, see esophageal burns

Table 276.3 (Continued)

Product	Characteristics	Symptoms	Treatment
Turpentine	Essential oil	Irritation of gastrointestinal mucosa, metabolic acidosis, hepatic/renal failure, altered level of consciousness. Respiratory compromise if aspirated into the lungs	Admit to hospital if symptomatic; supportive treatment
Laundry powder	Contains mixture of enzymes, perfumes, softeners, and anionic and nonionic detergents; low toxicity	Vomiting	No specific treatment required; administer oral fluids
White spirit/ turpentine substitutes	Relative low toxicity when ingested	Gastrointestinal irritation, CNS depression if ingested in large quantities. Main toxicity due to aspiration; Symptoms may develop after an interval of 24 h	Assessment of respiratory system in all patients, children with signs of chemical pneumonitis: chest X-ray; supportive treatment. ECMO could be used in severe cases of chemical pneumonitis

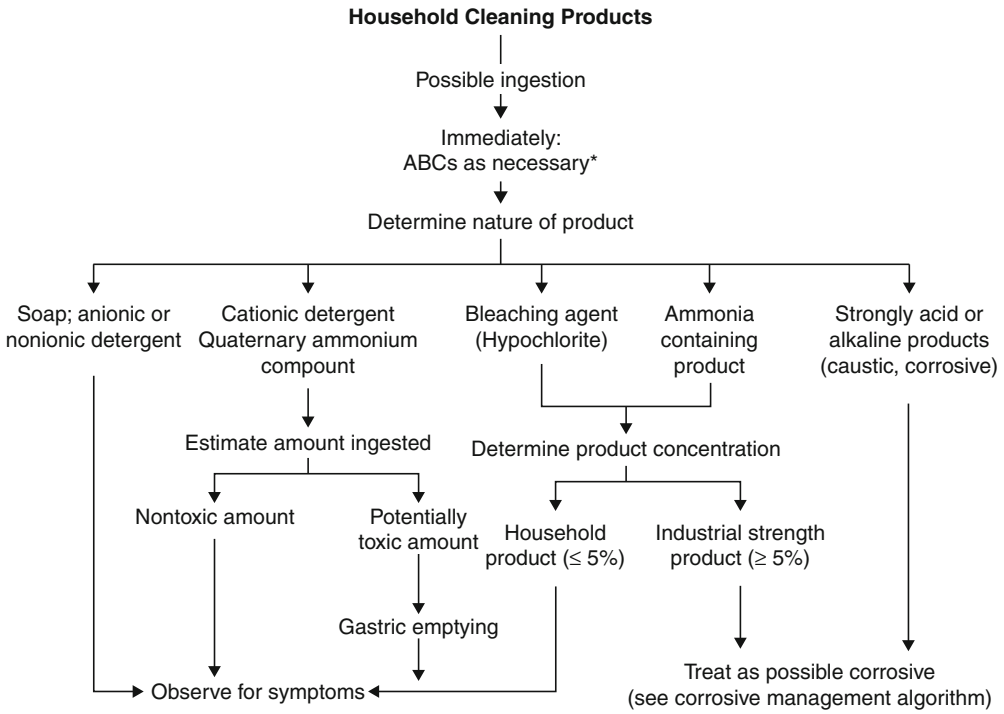

Figure 276.1

Algorithm for management of household cleaning product ingestion. *A, B, and C are airway, breathing, and circulation, the three basics of cardiopulmonary resuscitation (Adapted from Temple AR, Lovejoy FH Jr. (1980) Cleaning products and their accidental ingestion. Soap and Detergent Association, New York. With permission)

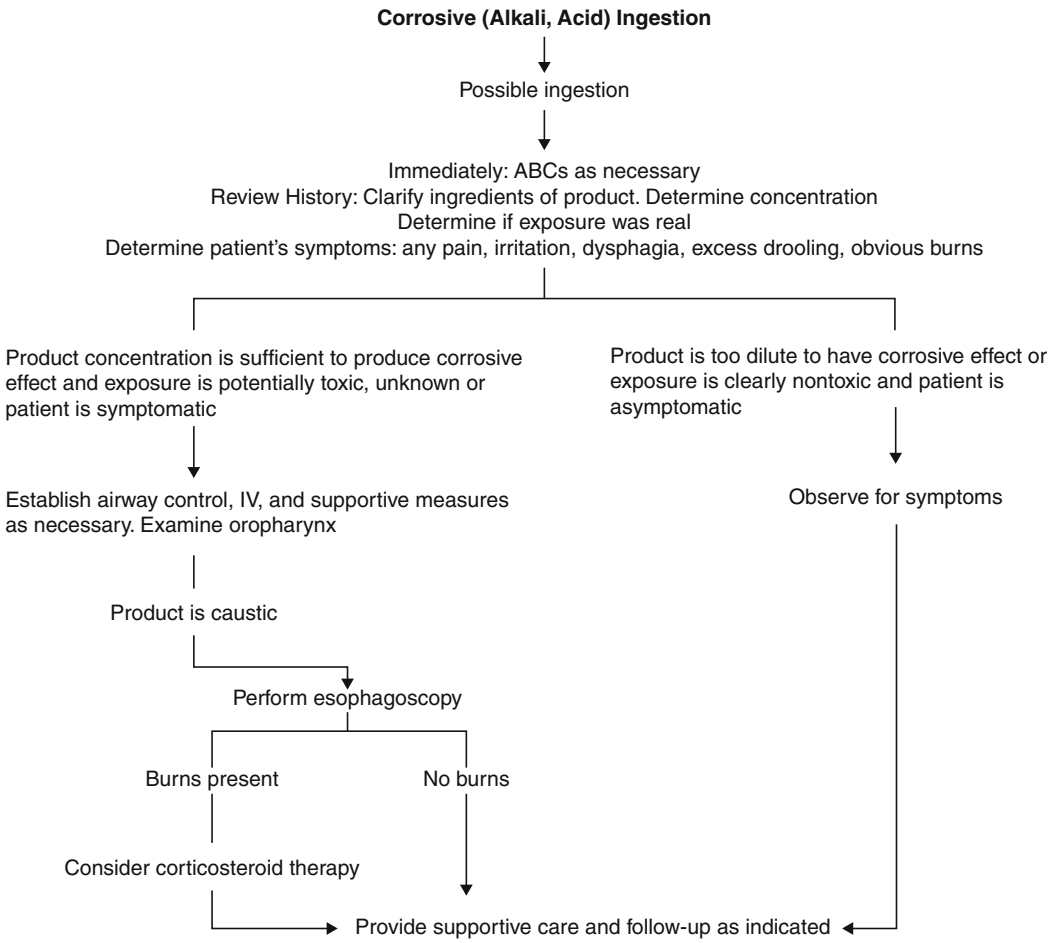

Figure 276.2
Management of ingestion of corrosives (Adapted from Temple AR, Lovejoy FH Jr. (1980) Cleaning products and their accidental ingestion. Soap and Detergent Association, New York. With permission)

For all ingestion assessments, the quantity of substance ingested is best known if the ingestion is witnessed, as well as accounting for original quantity and any amount that might have been spilled. The volume of a swallow is a function of body mass and is 0.27 ml/kg, or roughly 5 ml for a 2-year-old and 20 ml for an adolescent.

Foreign Bodies

1. Disc (button) batteries

   These contain several toxic elements, such as mercury, lithium, and potassium hydroxide, but their reported toxicity lies primarily in corrosive effects when they become dislodged in aural or nasal passages or in the esophagus. After ingestion, a radiograph should be obtained. Batteries lodged in the esophagus require immediate endoscopic removal. If the location is more distal, parental examination of stool until battery passage is required; the battery is usually expelled after 72 h. For any disintegrated battery (as evidenced by X-ray), collection of a 24-h urine for heavy metals (especially mercury) is recommended, with intestinal catharsis and chelation therapy as necessary. Surgical removal is almost never required.
2. Dessicants (such as silica gel) found in medicine bottles have warnings such as "do not eat" or a "skull and crossbones" symbol because they are a choking hazard. Most dessicants are benign, but some exist which contain a strong alkali.
3. Coins are a concern for esophageal lodging rather than systemic toxicity.

Table 276.4
Common pediatric antagonists and antidotes

Poison	Antidote		
Acetaminophen	*N-acetylcysteine (Mycomyst)*: initial dose of 140 mg/kg PO in water, fruit juice, or soda; then 70 mg/kg every 4 h for 68 h (17 doses)		
Anticholinergics	*Physostigmine*: 2 mg (adult), 0.5 mg (child) IV; may repeat in 15 min until desired effect is achieved; subsequent doses every 2–3 h prn		
	Caution: may cause seizures, asystole, cholinergic crisis		
Anticholinesterases	*Atropine*: 2–5 mg (adults), 0.05–0.1 mg/kg (children) IM or IV, repeated every 10–15 min until atropinization is evident		
Organophosphates	*Pralidoxime chloride*: 1–2 g (adults), 25–50 mg/kg (children) IV; repeat dose in 1 h prn, then every 6–8 h for 24–48 h (consider also constant infusion)		
Carbamates	Atropine as above; pralidoxime for severe cases		
Benzodiazepines	*Ftumazenil*: 0.01 mg/kg (not FDA approved for pediatric use as of March 1994)		
β-Adrenergic blockers	*Glucagon*: 50 μg/kg IV, followed by 50 μg/kg/h infusion as needed		
Calcium channel blockers	*Calcium chloride 10%*: 10 ml (adult), 0.2 ml/kg (pediatric) IV or		
	Calcium gluconate 10%: 30 ml (adult), 0.6 ml/kg (pediatric) IV		
	Glucagon: 50 μg/kg IV		
Carbon monoxide	Oxygen 100% by inhalation; consider hyperbaric for severe cases		
Cyanide	*Sodium (A/a) nitrite or thiosulfate*: dose based on body weight and hemoglobin:		
	Hemoglobin	Initial dose 3% IV Na nitrite	Initial dose 25% Na thiosulfate IV
	8 g	0.22 ml (6.6 mg)/kg	1.10 ml/kg
	10 g	0.27 ml (8.7 mg)/kg	1.35 ml/kg
	12 g	0.33 ml (10 mg)/kg	1.65 ml/kg
	14 g	0.39 ml (11.6 mg)/kg	1.95 ml/kg
	Na nitrite should not exceed recommended dose because fatal methemoglobinemia may result		
Digitalis	*Fab antibodies (Digibind)*: dose based on amount ingested and/or digoxin level (see package insert)		
Ethylene glycol	See methanol		
Fluoride	*Calcium gluconate 10%*: 0.6 ml/kg IV slowly until symptoms abate, serum calcium normalizes; repeat prn		
Heavy metals/usual chelators Arsenic/BAL Lead/BAL, EDTA, penicillamine, DMSA Mercury/BAL, DMSA	*BAL (dimercaprol)*: 3–5 mg/kg/dose deep IM every 4 h for 2 days, every 4–6 h for an additional 2 days, then every 4–12 h for up to 7 additional days		

Table 276.4 (Continued)

Poison	Antidote
	EDTA: 50–75 mg/kg/day deep IM or slow IV infusion given in three to six divided doses for up to 5 days; may be repeated for a second course after a minimum of 2 days; each course should not exceed a total of 500 mg/kg body weight
	Penicillamine: 100 mg/kg/day (maximum 1 g) PO in divided doses for up to 5 days; for long-term therapy, do not exceed 40 mg/kg/day
	DMSA (succimer): 350 mg/m^2 (10 mg/kg) PO every 8 h for 5 days, followed by 350 mg/m^2 (10 mg/kg) PO every 12 h for 14 days
Iron	*Deferoxamine*: 15 mg/kg/h IV for severe symptoms
Isoniazid	*Pyridoxine 5–10%*: 1 g per gram of INH ingested (70 mg/kg if dose unknown) IV slowly over 30–60 min
Methanol (and ethylene glycol)	*Ethanol*: loading dose to achieve blood level of 100 mg/dl
	Adult: 0.6 g/kg body weight + 7–10 g to be infused IV over 1 h
	Child: 0.6 g/kg body weight to be infused IV over 1 h
	Maintenance doses should approximate 10 g/kg/h in adults and 100 mg/kg/h in children, to be adjusted according to measured blood ethanol levels
	Folate: 50–100 mg IV every 6 h (methanol)
	Thiamine, 0.5 mg/kg, and *pyridoxine*, 2 mg/kg (ethylene glycol)
Methemoglobinemic agents	*Methylene blue 1%*: 1–2 mg/kg (0.1–0.2 ml/kg) IV slowly over 5–10 min if cyanosis is severe or methemoglobin level >40%
Opioids	*Naloxone*: 1–2 mg IV, IM, sublingual, or by ETT; may repeat up to total of 8–10 mg in adolescent/adult
Phenothiazines (dystonic reaction)	*Diphenhydramine*: 1–2 mg/kg IM or IV *or*
	Benztropine: 0.02 mg/kg, 1 mg max
Tricyclic antidepressants	*Sodium bicarbonate*: 1–2 mEq/kg IV
Warfarin (and "superwarfarin" rat poisons)	*Vitamin K*: 10 mg (adult), 1–5 mg (child) IV, IM, subcutaneous, PO
Animals	*Antivenin*
Snake: Crotalidae (all North American rattlers and moccasins)	Antivenin to Crotalidae, polyvalent (Wyeth)
Snake: coral	
Spider: black widow	Antivenin to *Micrurus fulvius*, monovalent (Wyeth)
	Antivenin to *Latrodectus mactans* (Merck, Sharp, and Dohme)

Adapted from Henretig FM, Shannon M (1996) Toxicologic emergencies. In: Fleisher G, Ludwig S (eds) Textbook of pediatric emergency medicine, 3rd edn. Williams & Wilkins, Baltimore, p 406. With permission.

PO orally, *IV* intravenously, *prn* as needed, *IM* intramuscularly, *FDA* Food and Drug Administration, *BAL* British anti-Lewisite, *EDTA* ethylenediaminetetra-acetic acid, *DMSA* dimercaptosuccinic acid, *INH* isoniazid, *ETT* endotracheal tube

Table 276.5
Common toxidromes in pediatrics

Toxin	Symptom or sign[a]	
Anticholinergics (atropine, antidepressants [tricyclics], antihistamines)	VS	Fever, tachycardia, hypertension/cardiac arrhythmias (TCA)
	CNS	Delirium/psychosis/convulsions/coma
	Eye	Mydriasis
	Skin	Flushed, hot dry skin
Amphetamines/cocaine	VS	Fever, tachycardia, hypertension
	CNS	Hyperactive to delirious and tremor, myoclonus, psychosis, convulsions
	Eye	Mydriasis
	Skin	Sweaty
Narcotics/clonidine	VS	Bradycardia, bradypnea, hypotension, hypothermia
	CNS	Euphoria to coma, hyporeflexia
	Eye	Pinpoint pupils
Organophosphates (and muscarinic mushroom poisoning)	VS	Bradycardia or tachycardia, tachypnea (secondary to pulmonary manifestations)
	CNS	Confusion to drowsiness to coma, convulsions; muscle fasciculations, weakness to paralysis
	Eye	Miosis, blurry vision, lacrimation
	Skin	Sweating
	Odor	Garlic
	Misc.	Salivation; bronchorrhea, bronchospasm, and pulmonary edema; urinary frequency and diarrhea
Barbiturates, sedative-hypnotics	VS	Hypothermia, hypotension, bradypnea
	CNS	Confusion to coma, ataxia
	Eye	Nystagmus, miosis or mydriasis
	Skin	Vesicles, bullae
Salicylates	VS	Fever, hyperpnea
	CNS	Lethargy to coma
	Odor	Oil of wintergreen (with methylsalicylate)
	Misc.	Vomiting
Phenothiazines	VS	Postural hypotension, hypothermia, tachycardia, tachypnea
	CNS	Lethargy to coma, tremor, convulsions
	EPS	Ataxia, torticollis, back arching, oculogyric crisis, trismus, tongue protrusion or heaviness
	Eye	Miosis (majority of cases)
Theophylline	VS	Tachycardia, hypotension, cardiac arrhythmias, tachypnea
	CNS	Agitation, convulsions
	Misc.	Vomiting

Adapted from Mofenson HC, Greensher J (1974) The unknown poison. Pediatrics 54:336–342. With permission.
[a] VS vital signs, CNS central nervous system, EPS extrapyramidal symptoms

Plants

The poinsettia (*Euphorbia pulcherrima*) has an undeserved reputation as being a toxic plant and infrequently causes symptoms after ingestion. Plants that contain calcium oxalates (such as dumbcane and philodendrons) can cause local irritation, edema, and pain. However, systemic symptoms are unusual. Treatment for oxalate-plant ingestions involves symptomatic are, usually cool liquids or an ice pop.

Plants that are considered toxic include: aconite, cantharidin, castor bean, clove oil, comfrey, fox glove, Na Hwang, certain mushrooms, nutmeg, oleander, and pennyroyal oil.

As a follow-up, health care providers should seek reasons for the ingestion to reduce the risk of recurrence. Attention should be given to family stressors, e.g., ill health, including psychiatric disturbances, marital discontent and separation, spousal abuse, unemployment, or other financial burdens since social determinants influence those at risk for exposure or poisoning.

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277 Iron

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A common toxicological emergency in young children is iron poisoning. Signs of iron toxicity can be apparent in children with ingestions of 10–20 mg/kg of elemental iron. Serious toxicity is likely with ingestions of more than 60 mg/kg.

Accordingly, it is important to calculate the elemental content of iron supplements in order to estimate total exposure. Common forms of iron that can be ingested by children include the following percentages of elemental iron: ferrous sulfate (20%), ferrous fumarate (33%), and ferrous gluconate (12%). Children's multivitamins with iron preparations contain 8–18 mg of elemental iron per chewable tablet. A common iron-containing medication is a prenatal vitamin, which has 325-mg ferrous sulfate (65 mg elemental iron) per tablet.

Iron exerts both local and systemic effects and is corrosive to the GI mucosa and can affect the heart, lungs, and liver. The potential severity of iron poisoning is based on the amount of elemental iron ingested. Excess free iron is a mitochondrial toxin that leads to derangements in energy metabolism.

Contributing factors to iron poisoning include the availability of iron tablets and the candy-like appearance of multivitamin tablets. Because perinatal iron therapy is common, the presence of these tablets at home may pose a hazard to a mother's other young children.

Most iron toxicity exposures involve children younger than 6 years who have ingested pediatric multivitamin preparations. Many of the serious acute ingestions occur in children younger than 3 years. A report from the American Association of Poison Control Centers indicates that iron supplements were the single most frequent cause of pediatric unintentional ingestion fatalities, accounting for 30.2% of reported pediatric pharmaceutical unintentional ingestion fatalities over an 8-year period (1984–1992). Antidepressants, cardiovascular medications, and methyl salicylate follow in frequency of pediatric pharmaceutical deaths.

Much of the pathophysiology of iron poisoning is a result of metabolic acidosis and its effect on multiple organ systems. Toxicity manifests as local and systemic effects. Typically, iron poisoning is described in five sequential phases as discussed under clinical manifestations below. Patients may not always demonstrate all of the phases making it difficult for researchers to reach a consensus regarding the number of phases and the time of onset and duration assigned to those phases.

The absorption of iron is normally very tightly controlled by the GI system. However, in overdose, local damage to the GI mucosa allows unregulated absorption, which leads to potentially toxic serum levels.

Clinical and Laboratory Manifestations

Minor findings of iron toxicity include vomiting, diarrhea, and mild lethargy. Major clinical findings include stupor, shock, acidosis, hematemesis, bloody diarrhea, or coma. Leukocytosis and hyperglycemia may be observed but are not typical of acute iron poisoning. The clinical course includes the following phases relative to time post iron ingestion:

Phase I (0.5–6 h): Vomiting, hematemesis, abdominal pain, diarrhea, hematochezia, lethargy, shock, acidosis, and coagulopathy. Necrosis to the gastrointestinal (GI) tract occurs from the direct effect of iron on GI mucosa. Large losses of fluid and blood contribute to shock. Free iron and ferritin produce vasodilation that may also contribute to shock.

Phase II (6–12 h): Apparent recovery that may contribute to a false sense of security. At this stage, the child should be observed very closely.

Phase III (12–24 h): Profound shock, severe acidosis, cyanosis, and fever.

Phase IV (2–3 days): Possible hepatotoxicity and lung injury due to direct action of iron on the mitochondria. Liver function tests and bilirubin should be monitored.

Phase V (2–6 weeks): GI scarring and strictures leading to gastrointestinal obstruction. This should be evaluated with barium studies.

Sustained-release preparations have resulted in small intestinal necrosis with resultant scarring and obstruction. The phases of iron poisoning may not occur in all patients. After massive overdose, patients may present in shock. With less serious overdoses, the initial gastrointestinal symptoms may be the only findings to develop even without treatment.

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Management

Iron toxicity is a clinical diagnosis and any studies are simply adjuncts. Toxic effects of iron may occur at doses of 10–20 mg/kg of elemental iron. Little is known about the absorption rate of iron in an overdose, the timing of peak serum iron levels, or the rate at which serum levels fall from their peak levels. Serum iron levels generally correlate with clinical severity: mild toxicity (level <300 μg/dL), moderate toxicity (level=300–500 μg/dL), and severe toxicity (level> 500 μg/dL).

There are several difficulties involved with the interpretation of serum iron levels. Serum iron levels may not be available in a timely fashion. The ideal serum iron level is a peak level at 2–6 h postingestion, and the time from ingestion is often unknown. Moreover, deferoxamine interferes with standard assays and leads to falsely decreased iron levels. Serum levels obtained more than 8–12 h postingestion may not be useful because iron redistributes into the tissues and the serum level does not reflect the total body burden of iron.

Total iron-binding capacity (TIBC) has traditionally been used to determine toxicity. Previously, a patient with a serum iron level greater than the TIBC was thought to be at risk for developing systemic toxicity. However, determining the TIBC in the presence of large amounts of iron or deferoxamine may yield a falsely elevated number. Hence, a TIBC above the iron level does not indicate sufficient binding capacity, and this test is not useful in determining the likelihood of toxicity.

Because iron levels are not always readily available, the predictive value of other laboratory test results has been explored. Previously, a WBC count greater than 15,000/μL and a serum glucose level greater than 150 mg/dL were said to correlate with iron levels greater than 300 μg/dL. However, more recent studies do not support the predictive value of these ancillary tests, and they are not useful in the setting of iron poisoning.

Abdominal radiography may offer information on the iron ingestion, both initially and subsequent to GI decontamination. However, treatment should not be delayed for radiography. A positive radiographic finding is one that shows radiopaque tablets or particles. This indicates that the ingested iron has not been completely absorbed.

An initial negative radiographic finding may mean that no iron was ingested or that the ingested iron tablets or solution have dissolved. In addition, liquid preparation and chewable vitamins are not visible on radiographs.

Obtaining a radiograph before GI decontamination and after GI decontamination may yield information as to the success of therapy. If the radiographic findings remain positive after decontamination, additional decontamination is required or endoscopy/surgery is needed for iron tablet removal to avoid gastric perforation and severe hemorrhage. If the radiographic findings were initially positive and are negative after GI decontamination, this indicates that GI decontamination was successful, although iron levels should still be monitored because of iron absorption prior to initiation of therapy.

The deferoxamine challenge test consists of administering a single dose of deferoxamine that binds available free iron and is excreted in the urine as the ferrioxamine complex (deferoxamine and iron) which changes the urine color to reddish (vin rosé), indicating the need for chelation. However, this test is not reliable because the urine does not change color reliably even when elevated serum iron levels are present. It does not alleviate the need for monitoring serum iron levels. Therefore, one should not rely on the deferoxamine challenge test.

In treatment of iron poisoning, consider both bowel decontamination with whole bowel irrigation and chelation using intravenous administration of deferoxamine. Although iron poisoning is a clinical diagnosis, serum iron levels are useful in predicting the clinical course of the patient.

The first step in treating a case of acute iron toxicity is to provide appropriate supportive care, with particular attention paid to fluid balance and cardiovascular stabilization. Initial treatment should also address the issue of preventing further absorption of iron by the GI tract.

Ipecac-induced emesis is not recommended especially with iron ingestion. As GI distress is an early finding in iron poisoning and is present in all potentially serious ingestions, Ipecac-induced vomiting may cloud the clinical picture.

Gastric lavage is of unlikely benefit and is not recommended because iron tablets are relatively large and become sticky in gastric fluid.

Whole bowel irrigation has been used to speed the passage of undissolved iron tablets through the GI tract. It is most effective if the ingestion occurred more than 1–2 h previously and in patients with radiographic evidence of multiple pills beyond the pylorus. A polyethylene glycol electrolyte solution (e.g., GoLYTELY) may be administered orally or nasogastrically at a rate of 250–500 mL/h for children 9 months to 6 years of age, 1 L/h for children 6–12 years of age, and 2 L/h for adolescents. Continue irrigation until the repeat radiographic findings are negative or rectal effluent is clear.

Deferoxamine is the chelating agent of choice which binds absorbed iron, forming an iron–deferoxamine

complex that is excreted in the urine. It does not bind iron in hemoglobin, myoglobin, or other iron-carrying proteins. Indications for using deferoxamine should be based on both clinical and laboratory parameters. These include shock, altered mental status, persistent GI symptoms, metabolic acidosis, pills visible on radiographs, serum iron level greater than 500 μg/dL, or estimated dose greater than 60 mg/kg of elemental iron. Chelation should be initiated if a serum iron level is not available and symptoms are present. The administration of deferoxamine may be intramuscular or intravenous. The intramuscular route is not recommended because it is painful and less iron is excreted compared with the intravenous route. The intravenous route is administered as a continuous infusion. The standard dose is 15 mg/kg/h, with an initial dose administered for 6 h. No clear end point of therapy is noted; however, indications for cessation include significant resolution of shock and acidosis. Deferoxamine, administered 6–12 h, has been suggested for moderate toxicity. For severe toxicity, 24 h of administration have been suggested. Because these end points are arbitrary, the patient should be observed for the recurrence of toxicity 2–3 h after the deferoxamine has been stopped. Adverse effects from deferoxamine include pulmonary symptoms (i.e., acute respiratory distress syndrome, tachypnea), especially in patients treated for more than 24 h. Rate-related hypotension may also occur. Therefore, patient monitoring is needed while titrating the infusion rate upward to a final rate of 15 mg/kg/h. *Experimentally*, deferoxamine and activated charcoal given as an oral slurry have reduced the GI absorption of ferrous sulfate in a small number of healthy volunteers. Animal data did not support this finding, but oral deferoxamine was found to increase the rate of iron excretion from the body, which could be enhanced by the coadministration of sodium bicarbonate. Oral deferoxamine has not been studied for the treatment of acute iron poisoning, and its routine clinical use is not recommended at this time.

Supportive treatment may include intravenous crystalloid fluids to treat shock, as well as dopamine and norepinephrine if the hypotension persists. Blood component therapy may be needed for those patients with blood loss. Exchange transfusion is sometimes considered in young patients who worsen despite deferoxamine therapy although its effectiveness is questionable.

Patients may be discharged home from the emergency department after 4–6 h of observation if they are asymptomatic, have serum iron levels less than 300–500 mcg/dl, and have a negative abdominal X-ray. Mortality is low in iron poisoning patients if they do not have shock or coma. With supportive treatment of patients with shock or coma, the mortality rate is about 50%. If deferoxamine treatment is added, the mortality rate drops to 10%. For cases of intentional ingestion, a psychiatric evaluation may be warranted.

Pregnancy is a major risk factor for iron poisoning in young children, and the period immediately after delivery is associated with the greatest risk. Almost half of all hospital admissions for iron poisoning in young children could be prevented by keeping iron supplements safely out of reach in the year before and after the birth of a sibling.

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278 Salicylates

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Salicylates are common ingredients in a variety of prescription and nonprescription preparations. The most common is aspirin (acetylsalicylic acid) which is available as an over-the-counter medication in almost all households. Despite major reductions in recent years in acute childhood salicylate poisonings due to the reliance on alternative analgesics and the use of child-resistant containers, salicylates are still an important cause of accidental childhood and intentional adolescent poisoning.

Salicylate toxicity has multiple cellular and systemic effects that define its clinical presentations during intoxication. Initially, it stimulates the respiratory center and causes hyperventilation leading to respiratory alkalosis. As a compensatory mechanism, renal excretion of bicarbonate, sodium, and potassium is increased resulting in metabolic acidosis. In addition, salicylates directly interfere with aerobic metabolism via uncoupling of oxidative phosphorylation; consequently, anaerobic metabolism is increased and lactic acid accumulates. Salicylates also inhibit key dehydrogenase enzymes within the Krebs cycle, resulting in increased levels of pyruvate and lactate. Glycolysis, gluconeogensis, and protein and lipid catabolism occur eventually leading to the accumulation of ketone bodies and amino acids and an increased anion gap.

Other clinical features that may occur include hyperpyrexia and CNS toxicity (e.g., agitation, confusion, restlessness, and coma).

Clinical and Laboratory Manifestations

Children may be at greater risk of toxicity due to decreased hepatic metabolism and/or renal elimination with enhanced distribution to organs including brain, kidney, and liver. Children are also more likely to lose their natural respiratory drive (hyperventilation and respiratory alkalosis may be minimal); therefore, they are more likely to present with metabolic acidosis and are more susceptible to CNS toxicity. The type of salicylate intoxication may be acute, chronic, or acute-on-chronic. Chronic and acute-on-chronic toxicity are uncommon in children, since aspirin is rarely used on a daily basis in children.

The clinical manifestations of salicylate ingestion are dependent, to some extent, upon the ingested dose. Acute ingestion of less than 300 mg/kg (serum concentration $<$50 mg/dL) is associated with mild symptoms manifested by gastrointestinal upset, tinnitus, and mild tachypnea; ingestions of 300–500 mg/kg (serum concentration 50–100 mg/dL) are associated with moderate toxicity with fever, diaphoresis, and agitation; and ingestions of $>$500 mg (serum concentration $>$100 mg/dL) are associated with consistent coma and death. Death typically results from severe CNS toxicity with complete loss of function of the cardiorespiratory centers.

Management

Optimal management of salicylate poisoning depends on whether the exposure is acute or chronic. Gastric lavage and activated charcoal (1 g/kg) are useful for acute ingestion but not in cases of chronic salicylism. The use of multidose activated charcoal to enhance elimination is controversial. Specific therapeutic goals should include fluid and electrolyte correction plus enhancement of salicylate excretion. Generally a large volume of fluid must be given, such as 10–15 mL/kg/h for the first 1–2 h. Subsequent hydration with 4–8 mL/kg/h should be maintained until the salicylate level is therapeutic. For patients with serum salicylate concentrations greater than 50 mg/dL and severe metabolic acidosis, IV bicarbonate may be needed. The rationale for alkalinization is to increase urinary pH, ionize filtered aspirin, and inhibit its tubular reabsorption. Raising urinary pH from 6.1 to 8.1 results in 18-folds increase in renal excretion by preventing nonionic tubular back-diffusion. This decreases the half-life from 20 to 8 h. The initial fluid should contain 5% dextrose with 50–100 mEq/L of sodium bicarbonate.

Care must be taken to avoid hypokalemia, which prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ion. Urinary alkalinization must be used with caution in the presence of alkalemia due to salicylate-induced hyperventilation. Forced diuresis does not appear to increase the efficacy of urinary alkalinization. Repetitive determination of

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plasma salicylate levels should be obtained to confirm a declining level. Hemodialysis should be reserved for serious salicylate intoxication where the plasma level is >120 mg/dL acutely, or >100 mg/dL 6 h postingestion, refractory acidosis, coma or seizures, noncardiogenic pulmonary edema, volume overload, and renal failure.

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279 Self-Poisoning

James Krebs

Suicide is the second most common cause of death, worldwide, in the 15–24 year-old age group. In the USA, the overall suicide rate for the 5–14 year-old age group is approximately 0.7 per 100,000 population, while the 5–14 year-old age group is approximately 10 per 100,000 population accounting for over 4,450 deaths per year. In European countries, the rate is similar or slightly higher. Suicide rates and suicide attempts have increased by 60% worldwide in the last 45 years. Rates among young people have been increasing to such an extent that they are now the group at the highest risk in a third of the countries, in both the developed and developing countries. Attempts are up to 20 times more frequent than completed suicide. While young women have higher rates of suicide attempts, young men complete suicide approximately four times greater than young women. The most common means of suicide are firearms, poisoning, and hanging.

Management of the patient who had attempted suicide by poisoning involves treating the acute manifestations of the ingestion, as well as an assessment of risk factors for suicide and a psychiatric evaluation. Follow-up to prevent future attempts is also very important.

Assessment of Risk Factors

Suicide is complex with psychological, social, biological, cultural, and environmental factors involved. Mental disorders (particularly depression and alcohol use disorders) are a major risk factor for suicide in Europe and North America; however in Asian countries impulsiveness plays an important role.

The following lists a variety of risk factors associated with suicide attempts. The presence of more than one risk factor in a child increases the overall risk for suicide. The strongest predictor is a psychiatric disorder. Approximately 80% of adolescent suicide attempters have a diagnosable psychiatric illness, with depression being the most common. Substance abuse plays a significant role in suicide and suicide attempts in adolescence. The increase in substance abuse among adolescents may be associated with the increase in adolescent suicide rates. Risk factors unique to the adolescent population include a history of child abuse and exposure to the suicidal behavior of others.

Risk factors for attempted suicide

- Presence of psychiatric illness (e.g., depression, personality disorder)
- History of suicide attempt
- Substance and alcohol abuse
- Interpersonal loss (e.g., breakup of a romantic relationship, death of someone close)
- History of parent-child conflict
- History of physical or sexual abuse
- Exposure to suicidal behavior of others
- Social isolation (e.g., period of absence from school, frequent moves)
- Presence of chronic illness (e.g., acquired immunodeficiency disorder, anorexia nervosa, seizure disorder)
- Family history of suicide
- Impulsive behavior

When a patient presents to the ED after an intentional self-poisoning ingestion, the actual risk of suicide must be assessed. Several direct questions must be asked, with the most important information to determine being intent and method. Questions include:

Have you thought about death or killing yourself?
Have you thought about how you would kill yourself?
Do you have the means available (e.g., gun, pills)?
How close have you come to carrying out this plan?
Do you tend to be impulsive?
What stops you from killing yourself?

From the patient who presents to the ED after an intentional ingestion, some of these questions will already have been answered.

Press and Khan proposed a model to obtain this information from a psychiatric examination based on the four basic components of a physical examination: observation (of the patients body language and level of distress), auscultation (listening), palpation (basic questions), and percussion (deeper understanding/questioning). To facilitate information gathering, they recommend the use of the mnemonic MALPRACTICE (*Table 279.1*). The risk

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Table 279.1
MALPRACTICE mnemonic for psychiatric examination of suicidal patients

*M*ental health	Does the patient have a psychiatric disorder? A family history of mental illness?
*A*ttempts	Has the patient attempted suicide before? When?
*L*ethality	Does the patient have access to lethal means of self-harm? Did the patient want to die?
*P*lans	Is the patient able to make plans for the future (e.g., school, marriage, job)?
*R*isk-taking behavior	Is the patient engaged in risk-taking behavior?
*A*lcohol and drugs	What substances are being used?
Conflict	Was there an interpersonal conflict in the family?
*T*rauma	Is there a history of physical or sexual abuse?
*I*mpulsivity	How much planning went into the suicide attempt? Did the patient tell anybody about the attempt?
Community resources	Is there a social support system for the patient (family, friends)?
*E*xposure	Is there a history of attempted or completed suicide by family of friends? Has the patient recently been exposed to suicide on television or in the news?

level of the patient – high risk, with a genuine intent to die, a definite plan, and access to lethal means, versus low risk, with no definite plan and limited access to lethal means – will play an important part in further management and disposition of the patient. Since children as young as 5–14 years of age may attempt suicide, the ED physician should not hesitate to raise the topic of suicide and discuss it with a child of any age who may be at risk.

Management

The emergency department treatment of the suicidal patient consists of five main objectives: (1) protect the patient from further self-harm until the suicidal feelings have passed, (2) treat any medical complications of the ingestion, (3) identify the acute problem that precipitated the suicide attempt, (4) diagnose and treat any underlying psychiatric disorder predisposing the patient to suicidal behavior, and (5) deal with the acute reactions of family members to the suicide attempt.

Patient Protection and Medical Treatment

While in the ED, suicidal patients should be under some form of constant observation. All potentially lethal objects (e.g., scissors, needles, medications, and weapons) should be removed from the patient's immediate area. Physical and/or chemical restraints should be used only for patients who cannot be relied on not to hurt themselves further.

The treatment of any medical complications of an intentional ingestion is best done in the ED before deciding on the disposition of the patient.

Diagnosis and Treatment of Underlying Psychiatric Disorder

All suicidal patients should be considered to have an underlying psychiatric illness until proven otherwise. After a thorough assessment, the ED physician should be able to make a preliminary psychiatric diagnosis. The issue of whether, and when, to have a psychiatrist involved in the ED management of suicidal patients is controversial. Some studies have found that assessments made by ED physicians are not as complete or as well documented as assessments made by a psychiatrist. However, other studies have shown that the outcomes of patients evaluated by ED physicians or a general medical team are the same as those of patients referred to a psychiatrist. The rates of repeated self-poisoning or suicide were the same whether patients were referred to a psychiatrist or not.

In most patients, drug therapy for any psychiatric disorder should not be started in the ED. The acutely psychotic patient is an exception. Most psychotropic drugs used for chronic treatment require close follow-up by a physician when initiating therapy and also have a delayed onset of action (weeks, not hours or days). If the ED physician must prescribe medication for a patient being discharged, a drug that is nonlethal in an overdose should be selected and the smallest possible quantity prescribed (no more than 1 week's worth of medication).

For patients with depression, traditional therapy consisted of a tricyclic antidepressant (e.g., amitriptyline, imipramine) or a monoamine oxidase inhibitor (e.g., phenelzine). However, these drugs have many side effects and can be lethal in overdose. The new antidepressants, such as SSRIs (e.g., fluoxetine, paroxetine, sertraline),

nefazodone, and venalfaxine, are much safer when taken in overdose. These agents have been recommended as the treatment of choice in depressed, suicidal adolescent patients. Caution must still be used with these newer drugs due to the risk of converting the depression into a manic episode. Also, conflicting data exists about the effects of SSRIs on suicidal ideation. Case reports have described patients on fluoxetine who developed intense suicidal thoughts. On the other hand, some studies suggested that SSRIs might produce a more rapid improvement in suicidal ideation compared to other antidepressants.

A final factor to consider when initiating antidepressant therapy is the risk of suicide once the patient begins to come out of the depression. When a patient is severely depressed, he or she may not have the energy to carry out suicidal thoughts. However, when the patient starts to improve, he or she may gain the energy and drive to act on these ideations. This will often include taking an overdose of the medication that was prescribed to treat the depression.

Patient Disposition

Once the patient has been stabilized in the ED and an initial psychiatric evaluation has been completed, the disposition of the patient must be determined. Does the patient need to be admitted to the hospital, or can he or she be discharged with follow-up as an outpatient? If the patient needs further management of complications of the acute ingestion, then admission to the appropriate hospital service (e.g., general medicine or intensive care unit) is required.

Criteria that must be met before a patient can be discharged home from the ED include:

1. The patient must be medically stable and no longer suicidal.
2. The patient and caregivers must agree to the discharge plan, and to return to the ED if the suicidal feelings return.
3. The patient must not be intoxicated, delirious, or psychotic.
4. Potentially lethal means of self-harm must be removed from the patient's home.
5. The problem that precipitated the suicide attempt must have been identified and addressed.
6. Treatment for any psychiatric illness must be arranged.

If these criteria are not met, the patient must remain in the ED until all issues are resolved, or he or she must be admitted to a hospital (specialized psychiatric facility, if available). Patients discharged from the ED should have a relatively early follow-up (within days) with either their primary care physician or a psychiatrist.

Injury Prevention Education

Recent research concluded that the majority of the caregivers of adolescent suicide attempters (86%) did not receive injury prevention education in the ED. The caregivers who did receive injury prevention education were more likely to take action to limit access to means of suicide (e.g., locking up or disposing of medications). Another study reviewing all cases of pediatric injuries presenting to the ED found that the most common type of injury where injury prevention education was indicated was poisoning.

Suicide can be prevented by ensuring that young people have access to life skills training, promoting positive parental involvement in the lives of the young people, reducing the use of alcohol by young people, and reducing their access to lethal means (including firearms, knives, pesticides, medications). ED staff are in a good position to provide injury prevention education. At the time of a self-poisoning ingestion, the child and caregivers may be most receptive to this information and most likely to comply with the recommendations. This type of information may help to reduce the risk of future suicide attempts.

Conclusion

Self-poisoning is one of the most common means of attempted and completed suicide among children and adolescents. The management of those patients would include a thorough assessment of suicide risk factors and psychiatric evaluation to define any underlying mental illness. Whether the patient needs to be admitted to a hospital or referred for outpatient follow-up must also be determined. Providing injury prevention education in the ED may decrease the risk of future suicide attempts.

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280 Snakebites and Spider Bites

Roaa Al Gain

Snakebites

Venomous animal bites cause considerable rate of morbidity and mortality among pediatrics. Those caused by reptiles as snakes could be the commonest. It was estimated that at least 421,000 envenomations and 20,000 deaths occur worldwide from snakebite annually. These figures may be as high as 1,841,000 enovenomations and 94,000 deaths annually with incidence of 6.28–27.5/100,000 person per year. India reported highest snakebites envenomation and death rate. Epidemiologic study conducted in 2007 estimated an average of two million snakebites per year in India, resulting in 35,000–50,000 deaths. In 2009, the American National Drug and Poison Center (NDPC) reported 3,361 snakebites in USA; 40% caused by copperhead snake and about 37% due to rattlesnake envenomation. Children 12 years or younger represents 12% of the total snakebites. According to the NDPC report, snakebites were associated with the highest death rate among other animal bites and envenomation; three out of five cases were due to rattlesnake. The report includes 789 envenomations in children who were younger than 19 years. Generally, children have been estimated to represent more than 20% of rattlesnake envenomation, but poison centers data suggests over 50% of all reported cases may involve pediatric patients in USA. In contrast, European countries has lower incidence of venomous bites compared to tropical parts of the world. In 2001, the annual incidence of snakebites estimated to be around 15,000–20,000 cases, resulting in about 50 deaths per year. In the Middle East, snakes are responsible for most bites and tend to be more venomous than European species, but deaths are rare with some estimating 100 fatal bites annually. In Australia, the majority of snake species are venomous. Death from snakebite is rare in Australia. This is because of wide availability and access to antivenoms.

Overall, snakebites peak in summer season. Agricultural and tropical regions report more snakebites than other regions. Male children are more likely than female children to be bitten by snake. Snakebite envenomation can be "dry" nonvenomous or "wet" venomous. Severity of snakebite envenomation varies among taxonomic species, which differ by the geographical region (see *Table 280.1*). The harm of venomous snake depends on the venom amount, venom type, bitten site, species and size of the snake, victim bodyweight, and individual sensitivity to the venom. Several studies showed that systemic envenomation in children are more apparent due to their smaller body mass. Consequently, children are at higher risk of death or permanent disability from snakebite envenoming.

Snake venom is a mixture of enzymes (e.g., hyaluronidase), metallic ions, lipids, carbohydrates, amino acids, active proteins, and peptides. The mechanism venom exerts its effect varies based on its components. Venom can result in direct injury of vascular endothelial cells, which increases permeability to plasma and erythrocytes into the extravascular space. Increased intracellular calcium in skeletal muscle may occur and result in prolonged contraction and necrosis. Hemolysis may occur as a result of increased permeability of erythrocyte membranes. Histamine is released if mast cell membrane is damaged. Fibrinolysis and thrombin-like peptide actions result in coagulopathy. Thrombocytopenia can result from platelet aggregation at sites of tissue injury or by direct venom effect on platelets.

Accordingly, each venom produces its clinical effect which can help in snake identification. Snake venoms are classified as either hemotoxin, that is, venom causes coagulopathy; neurotoxin, that is, venom causes weakness and muscle paralysis; or/and cardiotoxin, that is, venom causes circulatory failure and shock.

Clinical manifestations range from local reactions as pain, edema, erythema, to systemic manifestation of various degree of severity. Systemic symptoms may occur immediately after bite or delayed for a few hours. Petechia or ecchymosis may occur as early sign of coagulopathy. The venom may distribute through the lymphatic system and cause lymphangitis. Gastrointestinal signs and symptoms as vomiting, abdominal pain, and diarrhea are commonly encountered. Hypotension and tachycardia are other manifestations that occur especially after direct intravenous envenomations. Neurologic signs as ptosis, oculomotor paralyses, and dysphagia may occur especially with Mogave rattlesnake. Although fatality is very rare,

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Table 280.1
Examples of common snakes

Snake family (common names)	Region	Comments
Acrochordidae (File snakes, wart snakes) *3 species*	South Pacific islands, Northern Australia, and Southern Asia	
Aniliidae (The Pipe Snake) *1 specie*	South America	
Atractaspididae (burrowing asps, stiletto snakes) *55 species*	Middle East, Africa	Venomous
Boidae (Boids) *70 species (include boa species and the python)*	*Subtropical and tropical regions*	*Non-venomous*
Colubridae (Colubrids) *1,800 species*	*Worldwide*	*Venomous and harmless species make up about two-thirds of the species of snakes in the world*
Elapidae (Elapids) *Over 250 species (*e.g., *Australian black snake, death adder, taipan, tiger snake cobras, mambas, and sea snakes)*	*Australia, Middle East*	*Venomous*
Loxocemidae (The Mexican Burrowing Snake) *1 specie*	*Central America and Mexico*	
Pythonidae (Pythons)	*Asia, Africa, and Australia*	
Typhlopidae (Blind Snakes)		
Uropeltidae (Shield-tailed snakes) *45 species*	*Southern India and Sri Lanka*	
Viperidae (Vipers) Pit vipers: 100 species and true vipers: ~50 species Pit vipers: North American rattlesnakes, copperheads, water moccasins True vipers: Gaboon viper, European viper	Pit vipers: North American True vipers: Asia, Middle East, Europe, and Africa	
Xenopeltidae (Sunbeam Snakes) *1 specie*	*Southeastern Asia*	
Hydrophiidae (Sea snakes) multiple species	Australia	

children have higher risk of death due to cardiovascular collapse, respiratory failure, sepsis or bleeding. Pit viper venoms produce acute local tissue damage and edema. However, subcutaneous and dermal tissue injury might occur and can reach the muscle in rare cases. Local tissue damage can lead to fluid loss and ischemia. In a multicenter study carried out in pediatric patients bitten by *Bothrops* spp, majority of them developed acute-phase reaction, characterized by increase of several serum cytokine concentrations (e.g., interleukin-6 and 8, TNF). Fasciotomy was required more often in patients with high cytokine levels. In contrast, local tissue injury is uncommon following coral snakebites. Their venom tends to inhibit acetylcholine receptors at the neuronal synapse and causes paresthesias and paralysis.

If the venom is sprayed into the eye, painful conjunctivitis and corneal ulceration may occur and in rare cases vision loss happen.

Renal failure and rhabdomyolysis may occur. Acute renal failure complicated about 30% of 100 cases followed in Brazil bitten by rattlesnake. Age less than 12 years was an independent risk factor for acute renal failure. Overall, delaying antivenom administration increased the risk of acute renal failure 10 times. Renal failure is commonly reported in victims of Russell's viper, hump-nosed viper, and sea snakebites. Severity of snakebite symptoms can be

graded into mild, moderate, and severe. The Snakebite Severity Score (SSS) is a validated and objective scale to assess severity of envenomation including six body categories: local wound, pulmonary, cardiovascular, gastrointestinal, hematologic, and nervous system effects. Severity can be categorized according to clinical manifestations. See *Table 280.2*.

Diagnosis can be made by physical assessment of bite site if fang marks are visible or local pain and edema. In very rare cases, fangless snakes may produce envenoming through skin or eye contact with venomous saliva.

Table 280.2
Snakebites severity grades

Grade	Severity	Signs and symptoms
0	*Absent*	Nonenvenomation, i.e., dry bite puncture wounds only; no systemic effect; no laboratory evidence of coagulation abnormalities; and no clinical evidence of abnormal bleeding
1–2	*Mild*	Swelling, pain, and ecchymosis limited to the immediate bite site; no systemic effect; coagulation parameters normal with no clinical evidence of bleeding
2	*Moderate*	Swelling, pain, and ecchymosis involving less than a full extremity or, if bite was sustained on the trunk, head, or neck, extending <50 cm; systemic signs and symptoms may be present but not life threatening, including but not limited to nausea, vomiting, oral paresthesia, or unusual tastes, mild hypotension (systolic blood pressure <90 mmHg), mild tachycardia (heart rate <150), and tachypnea; coagulation parameters may be abnormal, but no clinical evidence of bleeding present. Minor hematuria, gum bleeding, and nosebleeds are allowed if they are not considered severe in the clinical judgment
3	*Severe*	Swelling, pain, and ecchymosis involving more than an entire extremity or threatening the airway; systemic signs and symptoms are markedly abnormal, including severe alteration of mental status, severe hypotension, severe tachycardia, tachypnea, or respiratory insufficiency; coagulation parameters are abnormal, with serious bleeding or severe threat of bleeding

Source: Protherics Inc. 2008 (Modified)

Diagnosis can be confirmed if the snake is known or caught. In children, this might be challenging as most bites occur when children are left unattended. The venom identification (detection) kit can be used if available as in Australia.

First Aid Management

The ultimate goal is transporting the victim to nearest medical facility to initiate appropriate management. The national/private poison control centers, hospital drug information centers, herpetologists, and zoo personnel are vital source of information for identification, first aid management following snakebite envenomation.

Using traditional treatment, electrical shock, oral suction of venom, mechanical extractors, wound excision or incisions are strongly discouraged due to lack of evidence. Generally, victim shall remain still, immobilize the bitten area, keep affected limb at or below the heart level until transferred.

Pressure Immobilization

Pressure immobilization is recommended for neurotoxic snakebites (e.g., Australian elapids) or if delay in transportation is expected; however, it should not be employed in case of local necrotic snakebite (e.g., cobra, viper). Tight tourniquets might be harmful and can potentiate the local effect of necrotic venom and should be avoided. Applying appropriate pressure is crucial; if suitable, affected limb should be immobilized using splint with an average pressure of 50–70 mmHg or pressure pad applied on the bitten site. The efficacy of pressure immobilization has not been well established.

Wound Care

The need for cleansing snakebite wounds is not recommended outside medical facility with the exception of eye injuries. If the venom is sprayed on the eyes (e.g., spitting cobra), the eyes should be irrigated thoroughly with water. Unskilled cleansing at the bite site may worsen the tissue damage and introduce risk of secondary infection. Cleansing bite site should be carried with strict aseptic techniques. No evidence supports immersion of the bitten limb to slow envenomation or the use of cold water versus hot water. The venom presents on the bitten site can be used to identify the snake type if venom detection kit is available.

Snake Identification

Although identification of the offending snake is crucial, most of the reported children snakebite envenomations failed to identify the snake type. Snakebite in children occurs usually in unattended children, or during sleeping. Another way to identify the snake is through the characteristic envenomation features of the different snake type. In 2009, the WHO developed a database (http://apps.who.int/bloodproducts/snakeantivenoms/database/) to assess in identifying snakes among the different geographical regions, appropriate antivenom, access to antivenom, and poison control centers. The database is a great tool for all emergency personnel; it can be searched using the snake common name, family, or specie; region or location; or antivenom products.

Medical Management

At initial presentations all victims should be stabilized; maintaining airway, breathing, and circulation. Initial hospitalization should be considered for all children. For cases which require no medical management, observation shall be continued for minimum of 8 h and up to 24 h before discharge. This is important if Mojave rattlesnake bite is expected as it might be associated with delayed onset of significant neurotoxicity. Symptomatic management is indicated for the correction of hypovolemia and shock, allergic or anaphylactoid reactions, pulmonary edema, renal insufficiency, and hematologic/coagulation disorders. In cases of severe neurotoxic envenoming (e.g., respiratory paralysis), mechanical ventilation is warranted. Dialysis may be required if complications such as acute renal failure and rhabdomyolysis occur. Analgesics such as narcotics are indicated to control pain. Masking the venom neurotoxic effect should be considered when opioids are used for pain control. All pediatrics should be considered for tetanus prophylaxis if immunization history is unclear or incomplete. Doses and regimen shall follow the local or international guidelines (e.g., CDC).

Snake Antivenom

Antivenom binds and neutralizes the toxic venom and systemic effect will be ameliorated. The antivenom–venom complex will be eliminated thereafter in the urine. In children, there is limited clinical data describing the use of different snake antivenoms including FabAV approved by United States Food and Drug Administration (US-FDA). The majority of data stem from case reports and retrospective reviews of hospital data. The data showing efficacy of antivenom in pediatrics reported is available for all age groups including neonates. The first case of neonate treated successfully with polyvalent snake antivenom was reported in India, 2009. General limitations to antivenoms are the following: Hypersensitivity to papain or papayas is a contraindication; high cost; ineffective for fasciculations; potential for immediate or delayed hypersensitivity reactions; recurrence of local tissue swelling or hematologic abnormalities after treatment; coagulopathy may be refractory to antivenom treatment. Historically, the utility of antivenoms was limited by the frequency of significant reactions. In the literature, hypersensitivity reactions were reported in about 25–50% of patients given the unpurified products (mainly equine) and more than 50% developed serum sickness. This incidence reduced to 5% with the highly purified antivenom preparations development. Despite this, care should be taken especially with pediatric patients.

Antivenom is recommended to be used in the presence of signs of systemic and/or severe local envenoming and only in patients in whom the benefits of treatment are considered to exceed the risks of antivenom reactions (see *Table 280.2*). Generally, plasma venom concentration reaches a peak between 30 min and 4 h after the bite (half-life is $\sim$ 8 h). Antivenom administration within 4–6 h is preferable to control local symptoms and coagulation abnormalities.

Antivenom Regimen

Snakes inject the same dose of venom into children and adults; therefore, children must receive the same dose of antivenom as adults. It is recommended to use the molar dose of venom protein not based on the weight or age of the victim. Some might argue with this because the delivered venom amount to the body size is higher in infants and children than in adults. Although randomized clinical trials are not available to support this recommendation, majority of the retrospective studies and case reports used adult doses for pediatric patients regardless of their bodyweight. Another important factor is the similarity between the pharmacokinetics of venom–antivenom complex in both children and adults. The amount of antivenom administered corresponds on the severity of the envenomation. For specific dosing, the product information of each antivenom or local guideline shall be consulted.

Generally, antivenom shall be prepared and diluted in appropriate fluid (usually sodium chloride) and administered intravenously at slow rate to minimize risk of

infusion reactions. Infusion rate should be gradually increased. Close monitoring for acute reaction shall continue even after the end of infusion up to 1 h. Fluid adjustment must be considered for children weighing less than 10 kg or in case of fluid restrictions. If initial antivenom dose was ineffective in controlling the symptoms, second dose must be given. Maintenance doses every 6 h for up to 18 h post envenomation are advocated especially with the new formulation which has shorter half-life than the unpurified products.

Due to recirculation of the venom or its components recurrence may happen and repeated doses may be required. Recurrence of envenomation is defined as the reoccurrence of venom effect after that abnormality had previously resolved. Recurrence may happen early after discharge. Patient should be assessed after 2–3 days. Late recurrence after 1 week of envenomation has been reported. This would be return of progression of swelling or coagulopathy or increase in pain intensity. Coagulopathy recurrence may present as return of thrombocytopenia, hypofibrinogenemia, prolongation of prothrombin time (PT), or elevation of fibrinogen. Recurrence of coagulation abnormalities has been reported in more than 50% of patients treated with CroFab™ (US-FDA approved antivenom). This is probably related to its smaller Fab molecule that has shorter half-life than IgG molecules and may allow recurrence of venom effects. In one case report, coagulopathy recurrence was accompanied with significant bleeding (IV puncture site and ginigival) in a 3-year-old patient. Bleeding was significant and resulted in profound anemia. In such cases, blood product transfusion must be considered along with repeated administration of antivenom.

Allergy Testing and Premedication

Skin/conjunctival hypersensitivity testing is not recommended as negative result does not exclude hypersensitivity antivenom reactions. Currently, no intervention has proved effective for preventing antivenom reactions, including administration of prophylactic epinephrine. In order to minimize reactions, the antivenom should be administered by intravenous infusion at slow rate. Acute allergy treatment shall be always available at bedside. Premedication with corticosteroids, epinephrine, and antihistamines has been described in several pediatric reports. Efficacy results were inconsistent and final recommendation cannot be withdrawn.

Safety concerns exist with the prophylactic use of epinephrine because of the increased rate of fatality, due to intracranial bleeding, hypertension, and arrhythmias, especially if used routinely in children, pregnant, or cardiac patients.

Antivenom Side Effects

Patient may develop serum sickness which is more common with traditional antivenoms than the purified preparations (e.g., CroFab™). Flu-like symptoms with fever, malaise, arthralgias, lymphadenopathy, rash, pruritus, and urticarial can occur 10–20 days after antivenom administration. The higher dose administered of antivenom the higher risk of side effects. Side effects are self-limited. Administration of antihistamine and corticosteroids can control the symptoms effectively.

Antivenom Availability

In March 2007, snake antivenom immunoglobulins were included in the WHO Model List of Essential Medicines, acknowledging their role in the primary health care system. Antivenoms were discovered more than 100 years ago; however, they are produced by limited number of manufacturers worldwide and their availability is scarce in some regions. Snake antivenom immunoglobulins are either monospecific (monovalent) or polyspecific (polyvalent) antivenom. Antivenom neutralizes specific snake venom; however, certain polyvalent antivenoms have cross-activity against other snake species venom. The earlier antivenom preparations developed using equine origin. More purified preparations, such as the F(ab)2 equine antivenom and ovine Fab fragments were developed thereafter. The use of the traditional antivenoms (e.g., Polyvalent Crotalidae Antivenin, made by Wyeth) was limited by the possibility of hypersensitivity reactions to the equine component. The newer F(ab)2 preparations are less immunogenic and resulted in lower incidences of hypersensitivity reactions. In 2000, the US-FDA approved Crotalidae Polyvalent Immune Fab Ovine (CroFab™) and replaced the older Antivenom Crotalidae Polyvalent (ACP) available since 1954. See *Table 280.3*.

Antibiotics Use

Prophylactic antibiotic therapy is not well supported for all snake bitten victims. Initiation of antibiotic may be considered only if clinical signs and symptoms of infection

Table 280.3
Examples of available snake antivenom

Region	Snake type	Antivenom
Costa Rica	Coral snakes	Anticoral monovalent, Anti-mipartitus antivenom
Argentina	Coral snakes	Antimicrurus
Mexico	Coral snakes	Coralmyn
Colombia	Coral snakes	Anti micruricoscorales
Brazil	Coral snakes	Soro anti-elapidico, Antielapidico
South Africa	Boomslang	SAIMR Boomslang antivenom
South Africa	Saw-scaled vipers	SAIMR echis antivenom
South Africa	Mambas, Cobras, Rinkhalses, Puff adders (small adders: *B. worthingtoni*, *B. atropos*, *B. caudalis*, *B. cornuta*, *B. heraldica*, *B. inornata*, *B. peringueyi*, *B. schneideri*, *B. xeropaga*)	SAIMR polyvalent antivenom
Brazil	Pit vipers and rattlesnakes	Soro antibotropicocrotalico
USA	North American pit vipers (all rattlesnakes, copperheads, and cottonmouths)	Polyvalent crotalid antivenin (CroFab TM)
USA	Vipera spp.	Vipera tab
India	Saw-scaled viper (*Echis carinatus)*, Russell's viper (*Daboia russelli)*, spectacled cobra (*Naja naja)*, common krait (*Bungarus caeruleus)*	Polyvalent snake antivenom
Australia	Sea snakes	Sea snake antivenom
Australia	Many Australian snakes	Polyvalent snake antivenom
Australia	Brown snakes	Brown snake antivenom
Australia	Australian copperheads, Tiger snakes, Pseudechis spp., rough-scaled snake	Tiger snake antivenom
Australia	Pseudechis spp	Black snake antivenom
Australia	Taipan	Taipan antivenom
Australia	Death adder	Death adder antivenom
Saudi Arabia (Gulf Region)	Saudi snakes: *bitis arietans, cerastes cerastes, echis carinatus, echis coloratus, naja haje, walterinnesia aegyptia* venoms	Polyvalent snake antivenom
Saudi Arabia (Gulf Region)	Arabian cobra (*naja haje arabicus*) and the black desert cobra (*walterinnesia aegyptia*).	Bivalent snake antivenom

are apparent. The most frequently isolated organisms from venomous snake oral cavity were *Staphylococcus aureus and Enterobacteriaceae.* Anaerobes also were isolated including *Clostridium* spp. Secondary infection was quite common in children after snakebite envenomation; however, early initiation of antibiotics was not effective for prevention of local infection, reduce hospitalization or morbidity.

Surgical Intervention

Another controversy is soft-tissue debridement and fasciotomy after snakebite. Data showed that early and appropriate antivenom therapy would limit the need for surgical intervention in children. Only sparse data found that infectious complications were less frequent in patients who underwent early fasciotomy in comparison with those who did not have or delayed surgical intervention. Therefore, surgical consultation is recommended. The development of clinical signs and symptoms of compartment syndrome despite limb elevation (if applicable) and administration of adequate antivenom doses should be the only rational for fasciotomy. Before fasciotomy is performed, high intra-compartmental pressure shall be confirmed by direct measurement and haemostatics are secured. Limb amputation is rarely needed in children.

Laboratory Monitoring

Laboratory tests as complete blood cell count (CBC), prothrombin time (PT), activated partial thromboplastin

time (aPTT), international normalized ration (INR), and fibrinogen shall be obtained at baseline and then repeated to assess for improvement/worsening in thrombocytopenia and coagulopathy. If initial results are normal and minimal pain and edema present, repeat the test in 2–6 h. Creatinine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, and urinalysis should be monitored if signs of rhabdomyolysis, myoglobinuria, or renal insufficiency are present. Coagulation test should be repeated 2–3 days after initiation of antivenom therapy.

Blood cultures are not indicated for all patients and may reveal negative in most cases. Tissue swapping may be needed if clinical manifestations of infection occur.

Spider Bites

Spiders belong to the phylum Arthropoda in the animal kingdom, which consists of animals with segmented bodies and jointed appendages. They are different from insects. Spiders are found commonly worldwide. There are more than 100,000 different types of spiders in the world. Most spiders are harmless. Because spiders are very small, their venom is usually too little to cause significant clinical envenomation. Only few are venomous (e.g., Tegenaria, Dysdera, Cheiracanthium, Lampona, Missulena (mouse), Loxosceles, redback (black widow), Atrax robustus (Sydney funnel web) and Hadrychone). Spider bites are frequent but morbidity and mortality is of low incidence. Human contact with spiders is usually accidental. In children, spider bites occur at night while sleeping, indoor or outdoor.

In USA, around 2,700 spider bites reported in children less than 19 years old. Majority of bites were due to black widow spider. Fatality was not reported neither in adults nor in children in 2009 NDPC report. In Europe only black widow spider reported to cause envenomations. Australian funnel back spiders are common in Australia and cause at least two envenomations annually.

Spider venom is complex mixture of protein toxins. Toxins vary between species. For example, robustoxin is the main protein toxin responsible for envenoming caused by funnel web spider. In Redback spider venom, latrotoxins is the prominent protein.

Clinical Manifestations

Most spider bites are unnoticed by victims until late manifestations occur. Some could present 2–3 days after the injury which complicate the diagnosis. Spider bites are often diagnosed by the sign and symptoms of venom toxicity or if spider bite was witnessed or caught. Spider bites are usually single lesion on limited part of the body. Spider bites are either necrotic or neurotoxic based on the involved species. Common local reactions are wheals, pustules, redness, swelling, itching, and pain. However, spider bites are not always painful. Spider bite may cause systemic effects as well. Infection may result from spider bites and it implicates the development of tissue necrosis in many cases. Certain spider bites require antivenom administration for managing systemic symptoms (e.g., bites by widow spiders (worldwide), funnel web spiders (Australia), and banana spiders (Brazil)). Rarely allergic reaction to a spider (contact rather than bite) may be developed by both venomous and nonvenomous spiders (*Table 280.5*).

First Aids

Victims should stay still with limited movement to minimize venom spread. Elevate the affected limb to minimize swelling. Bite site should be washed with soap and water. Apply cold compresses or ice to alleviate pain and minimize swelling. Transfer to medical facility is mandatory if severe envenomation present or if symptoms persist for more than 24 h or worsen.

Regular doses around the clock of antihistamine and analgesics can be given orally. Avoid aspirin, nonsteroidal anti-inflammatory analgesics. Opioids may be given in severe pain at hospital setting. Topical antihistamine can be used to minimize local reactions (i.e., itching). Corticosteroid topical preparations should be avoided; may impair wound healing. In most cases, local reactions resolve spontaneously or with the aid of home management within 10 days. Generally, spider bites heal quickly unless tissue ulcer or necrosis happens.

Traditional home remedies as applying meat tenderizer (papain) is not supported by evidence and can be harmful. Avoid tourniquets, suctions, incision of wound. Do not apply any heat to the bite site.

Medical Management

All pediatrics victims bitten with black widow spider or hobo spider (with rapidly expanding lesion or necrotic area and evidence of hemolysis) shall be admitted for observation and pain control. Transfer to intensive care unit if cardiac or respiratory complications or convulsions

occur. Supportive therapy shall be carried out based on the clinical presentation of the victim. Black widow envenomation may cause hypocalcemia which precipitate muscle spasms. It can be treated by oral or parenteral benzodiazepines. Administration of calcium gluconate did not show to be effective and is not recommended.

Use of prophylactic antibiotics has not proven to be effective for spider bites unless clear evidence of infection present. Tetanus prophylaxis should be considered for all pediatrics if immunization history is unclear or incomplete.

Spider Antivenom

Antivenom shall be considered for severe symptoms (e.g., excessive salivation, lacrimation, twitching of the tongue, respiratory distress, or persistent hypertension) that are not controlled by supportive therapy and pain control including opioids and benzodiazepines. However, antivenom may be considered earlier in young children with severe toxicity.

Wound Care

Antivenoms are usually available in areas with frequent bites (see *Table 280.4*). It is administered intravenously or intramuscularly. Treatment for acute allergic reactions shall be readily available. For dosing regimen, the product information or local guidelines shall be consulted. Generally, if only mild symptoms present start with the usual doses. Double the dose if severe symptoms are apparent.

Recirculation of venom may cause the systemic toxicity to occur again after initial response to antivenom (e.g., salivation, respiratory depression). Repeated doses of antivenom are needed. In children symptoms of fluid overload may be confused with venom-related pulmonary edema and respiratory depression. The exact cause should be ruled out before administration of additional antivenom. Diuretics may be needed in such situation.

Serum sickness (e.g., rash, fever, joint pain, malaise) may happen 4–14 days later although it is uncommon. Treatment with antihistamines and/or corticosteroid is effective. Patients discharged after severe envenomation shall be followed for possible reaction. Most spider antivenoms are associated with low rate of side effects because of the small administered volume. Routine prophylactic epinephrine use is not well established. In Canadian systematic review for funnel spider bite, all infants and children tolerated the antivenom without side effects.

Dapsone is polymorphonuclear leukocyte inhibitor, historically used to minimize wound scarring. However, dapson is not recommended due to lack of beneficial evidence and safety concerns (i.e., methemoglobinemia and hemolytic anemia in patients with G6PD). Hyperbaric oxygen showed some benefit in treating necrotic wounds following brown recluse spider bites. Its routine use is not advised. Debridement may be needed for necrotic tissues. Discharged victims are followed up with wound care for 24–48 h.

Table 280.4
Available spider antivenom

Spider antivenom	Species	Country
Funnel web spider antivenom	Sydney funnel-web spider	Australia
Soro antiaracnidico	Brazilian wandering spider	Brazil
Soro antiloxoscelico	Recluse spider	Brazil
Suero antiloxoscelico	Chilean recluse	Peru
Aracmyn	All species of Loxosceles and Latrodectus	Mexico
Redback spider antivenom	Redback spider	Australia
Black widow antivenin	Black widow spider	USA
SAIMR Spider antivenom	Button spider	South Africa
Anti Latrodectus antivenom	Black widow spider	Argentina

Laboratory Monitoring

No commercial identification test or detection kit for identifying spider venom is available. Baseline coagulation profile, renal profile, and CBC shall be obtained upon admission. Common laboratory findings include leukocytosis, albuminuria, and elevated creatine-phosphokinases (CPK). Usually progress for about 24 h and then resolve gradually during the following days, even in the absence of treatment.

Table 280.5
Medically important spider bites

Spider	Region	Features	Envenomation manifestations	Treatment
Funnel web spider (Atrax robustus)	Australia	Large fangs and acidic venom	• Intense local pain • Systemic envenomations occur early after bite: tingling around the lips, twitching of the tongue, profuse salivation, lacrimation, sweating, piloerection, and muscle twitching/spasms • Hypertension and tachycardia occur, and respiratory distress due to rapid development of pulmonary edema; may be fatal • Early symptoms resemble those of organophosphate poisoning. Convulsions may occur. Few cases of death are reported due to funnel web spider bite	Antivenom and supportive
Widow Spiders (Latrodectus spp)	North America *(Black widow spider)*, South Africa (shoe-button spiders), New Zealand (Katipo), Australia (Redback spiders), Europe (Malmignatte or Karakurt), Middle East	• Female black widow is poisonous but males are not • Most dangerous spiders in the world • 15% of bites to humans are non-envenomating • Venom releases neurotransmitters (i.e., norepinephrine, gamma-aminobutyric acid, acetylcholine) • Venom toxin causes nerve cell dysfunction, hypocalcemia, and muscle cell twitching • Venom is neurotoxic	• Victim will feel pinprick sensation and sharp pain but goes unnoticed • Forms faint red halo mark and swelling of the skin symptoms may last 3–5 days if left untreated • Within 1–3 h, up to 24 h, victim may experience stiffness and intense pain • Generalized pain in lymph nodes, chest, and abdomen • Others: numbness, tingling, rashes, sweating, nausea, vomiting, dizziness, cramps, abdominal pain, chest tightness, weakness, and difficulty breathing, hypertension • Infants and young children present with irritability, refusal of feeds, crying, nonspecific erythematous rash, eyelid swelling, salivation, lacrimation, tremors especially in the legs • Compartment syndrome of the upper extremity and priapism may occur but uncommon • Rarely fatal, if happened due to respiratory or cardiac failure, with an overall mortality of $<5\%$	Antivenom and supportive

Table 280.5 (Continued)

Spider	Region	Features	Envenomation manifestations	Treatment
Recluse Spider (known as Violin or Fiddleback spider) (*Loxosceles spp)*	Warm dry climate Worldwide: North and South America, Australia, and tropical regions, Middle East	• Venom is necrotic • Venom cause direct cell wall destruction and immediate cell death. • It contains calcium-dependent enzyme and cause RBC hemolysis • Clotting abnormalities, local polymorphonuclear leukocyte infiltration	• Mild sting and pain at bite site (90%). • May progress to blister and profound swelling in 4–8 h • Tissue necrosis and ulceration may occur over 3–4 days (10%) • Skin grafting may be needed in 10% of the cases • Mild fever, nausea, vomiting (24–72 h) • *Rare:* renal impairment, bleeding, coagulopathies, respiratory depression, hypotension, jaundice, disseminated intravascular coagulation (DIC), convulsions, hemolytic anemia • Death is rare but children are at higher risk	Most resolve spontaneously No antivenom available in the USA Controversial: dapsone
Hobo Spider (known as Northwester Brown Spider) *(Tegenaria spp)*	Europe and central Asia, USA and Canada	• Venom is necrotic	• Once bitten the skin becomes red within a few minutes • Numbness and tingling around the bite • Blister will form within 36 h, tissue necrosis may occur later • Wound is less severe than that caused by recluse spider bite • Headaches, weakness, drowsiness, and hallucinations can last up to 1 week	Due to similarity of symptoms, brown recluse spider may be confused with Hobo spider bites
Wolf Spider (Lycosa spp)	Australia, USA	• Venom is mildly cytotoxic • Has large fangs	• Pain at bite site, redness, and swelling last for up to 10 days • Tearing of the skin may occurs	Most resolve spontaneously
Sac Spider (Chiracanthium spp) (100 species)	Worldwide Yellow Sac Spider in USA	• Nontoxic to humans • Venom is necrotic • Bites can cause damage to tissue and leave large open wound	• Pain at bite site, redness, swelling, and itchiness • Slight necrotic wound or ulcer may develop • Necrosis often heals without scarring or minimal scarring • Less necrotic than recluse spider	Local wound care and tetanus prophylaxis
Tarantula Spider (*Rheostica* or *Aphonopelma* spp)	USA (deserts)	Largest of all spiders Rarely bite, handling a tarantula can irritate the skin	• Minimal pain, surrounding edema, urticaria and pruritis that may persist for several weeks • Little or no tissue necrosis • No serious systemic effect • Hairs may cause keratoconjunctivitis or ophthalmia nodosa, a nodular, eye granulomatous lesion	Local wound care and tetanus prophylaxis Ophthalmology consultation

Table 280.5 (Continued)

Spider	Region	Features	Envenomation manifestations	Treatment
Jumping Spider (Phidippus spp)	*USA*		• *Painful, itchy, redness, significant swelling* • Serious: muscles, joints pain, headache, fever, chills, nausea and vomiting; last from 1 to 4 days	Supportive
King Baboon Spider (Harpactirinae spp)	Middle East, Africa		• Local pain, swelling, bruising • Lymph nodes swelling	Supportive
Banana Spider (known as Brazilian Wandering Spider) (Phoneutria spp)	Brazil (mainly), South and Central America	• Aggressive and highly venomous • Venom is potent neurotoxic • Has high concentration of serotonin • Inhibit calcium channel blocker	• Pinprick sensation, high and intense severe pain • Cause priapism • Muscle twitching, tachycardia, hypotension, parasthesia • Respiratory depression may result in death	Antivenom, supportive

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281 Theophylline

Nada S. Al-Qadheeb

Theophylline is a dimethylxanthine bronchodilator used in the management of patients with obstructive lung disease. Despite declining use, it remains an important cause of intoxication with significant morbidity and mortality. It is available in a variety of dosage forms, including regular release tablets, sustained-release tablets and capsules, oral solutions, IV solution, and suppositories. The reasons for toxicity include the following: narrow therapeutic index, patient and physician dosing errors, and conditions or drugs that may decrease drug clearance (*Table 281.1*). Mild toxicity can occur within the therapeutic range (5–20 mg/L), but significant toxicity occurs with plasma levels >25 mg/L.

The metabolism of theophylline changes with a child's age. Neonates metabolize a portion of theophylline (less than 10%) to caffeine. As a child ages, the metabolic enzyme system matures and theophylline metabolism more closely resembles that of adults. However, children maintain a more rapid rate of metabolism. In the overdose setting, metabolic pathway saturation may occur, resulting in prolonged high serum theophylline concentrations.

The exact mechanism of action of theophylline is unknown. However, several potential mechanisms have been identified that may contribute to both its therapeutic and toxic effects. These include stimulating the release of catecholamines, increasing cyclic AMP concentrations through inhibition of phosphodiesterase, adenosine receptor blockade, stimulating the respiratory center, and enhancing diaphragmatic contractility.

Clinical and Laboratory Manifestations

Clinical features of theophylline overdose are classified into neurologic, cardiovascular, and metabolic manifestations. The occurrence of these manifestations depends on the type of overdose. Three forms of overdose exist: (1) acute – the result of a single, large, intentional ingestion; (2) chronic – the result of unintentional overmedication in a patient maintained on theophylline; and (3) acute-on-chronic – the result of a patient chronically on theophylline taking a large additional ingestion. *Table 281.2* lists the manifestations of theophylline overdose according to the type of overdose.

The onset of toxicity after acute ingestion of theophylline usually occurs within 1–2 h. However, onset maybe delayed more than 6–8 h after ingestion of sustained-release preparations. In acute ingestions, cardiovascular and CNS effects occur at a much higher serum concentrations than in chronic toxicity. In general, serum concentrations greater than 500 μmol/L (90 mg/L) in acute overdose are predictive of life-threatening events. In the chronic overdose setting, serum concentrations have little or no correlation with the clinical manifestations.

Management

Initially, evaluate and correct immediate life-threatening complications (e.g., airway, breathing, and circulation). The most serious complications of acute theophylline toxicity include seizures and tachyarrhythmia. Mortality is caused by intractable cardiac arrhythmias.

Gastric decontamination and extracorporeal removal of theophylline form the cornerstones of management of theophylline toxicity. The preferred mode of gastric decontamination is gastric lavage followed by activated charcoal for ingestions of >50 mg/kg. Gastric lavage may be useful for several hours after ingestion of sustained-release preparations. Because of high risk of seizure, emesis is contraindicated.

Since theophylline undergoes significant enterohepatic circulation, multidose activated charcoal (1 g/kg without sorbitol every 2–4 h) can enhance elimination. Serum theophylline levels may be repeated as often as hourly to help guide the management of patients.

Emesis associated with activated charcoal can be managed with antiemetic therapy; administration of smaller, more frequent doses; or continuous nasogastric administration of charcoal (0.25–0.5 g/kg/h). Activated charcoal should be administered even after extracorporeal removal is instituted.

Indications for extracorporeal removal of theophylline include intractable seizures, persistent hypotension

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Table 281.1
Factors affecting theophylline clearance

Increase clearance	Decrease clearance
Drugs	
Carbamazepine Tobacco Ethanol (acute) Phenobarbital Phenytoin Rifampin	Allopurinol Cimetidine Ciprofloxacin Clarithromycin Erythromycin Oral contraceptives Propranolol Verapamil
Diseases	
Hyperthyroidism Cystic fibrosis	Congestive heart failure Liver cirrhosis Viral illnesses (acute) Chronic obstructive pulmonary disease Hypothyroidism
Food	
High-protein diet	High-carbohydrate diet

Table 281.2
Manifestations of theophylline overdose

Manifestations	Acute overdose	Chronic overdose
Nausea, vomiting, tremors, agitation	Common	Less common
Seizures	Observed when serum levels approach 80 mcg/mL	May occur without warning and at lower serum concentrations than acute ingestions
Sinus tachycardia, arrhythmias (atrial fibrillation, multifocal atrial tachycardia, ventricular tachyarrhythmias), and hypotension	Observed when serum levels approach 80 mcg/mL	May occur without warning and at lower serum concentrations than acute ingestions
Metabolic effects (hypokalemia, hypophosphatemia, hyperglycemia, metabolic acidosis)	More pronounced	Less pronounced

unresponsive to fluids and vasopressors, life-threatening arrhythmias, and serum theophylline concentrations greater than 500 μmol/L (90 mg/L) following acute ingestion or 333 μmol/L (60 mg/L) with chronic overmedication. Charcoal hemoperfusion is considered the removal method of choice due to the high affinity of activated charcoal. Hemodialysis also increases theophylline clearance and may be used when hemoperfusion is not available. Due to the technical difficulties with hemoperfusion in neonates and very small children, whole-blood exchange transfusions are another option to increase theophylline clearance.

Hypotension and tachycardia should initially be managed with IV fluids. Sinus tachycardia rarely requires further intervention. Vasopressors with alpha-adrenergic activity (e.g., norepinephrine) may be used for refractory hypotension. Since the hypotension is due to stimulation of β receptors, theoretically, a β-blocker (e.g., propranolol) would be useful. However, β-blockers must be used with caution since they may worsen the bronchoconstriction in patients with underlying pulmonary disease. Lidocaine and calcium channel blocking agents (e.g., diltiazem, verapamil) may be used to treat life-threatening cardiac arrhythmias.

Patients who develop seizures are at high risk for further morbidity and mortality. Benzodiazepines (e.g., diazepam) are the first-line therapy for seizures. For intractable seizures, phenobarbital and general anesthesia may be necessary. In animal models, phenytoin has been shown to be less effective or even harmful. Thus, its use is not recommended.

Theophylline has a narrow therapeutic index and a resultant high risk for serious morbidity and mortality. The clinical manifestations of overdose differ between large, acute ingestion and chronic overmedication. Aggressive supportive care, gastric decontamination, and extracorporeal removal are necessary in the management of theophylline overdose. Finally, the molecular adsorbent recirculating system (MARS) has been cited in case reports as being efficacious in the removal of protein-bound drugs such as theophylline. However, the literature is quite limited in the use of MARS in the pediatric population, especially for the treatment of drug toxicity.

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Disturbances in Acid-base and Electrolytes Disorders

F. Bruder Stapleton

282 Maintenance Fluid Therapy

Jordan M. Symons

Introduction

Multiple physiologic processes work in concert to maintain appropriate fluid and electrolyte balance. In health, interactions between the kidney, hormonal secretion, and neuronal signals preserve effective circulating volume and osmolar homeostasis. An important participant in this carefully calibrated scenario is the individual's perception of thirst and ability to consume water. In certain clinical situations, a child may not be able to take in the appropriate amount of water necessary to keep up with ongoing losses. Nausea, emesis, sedation, mechanical ventilation, and numerous other conditions encountered with a hospitalized child may limit enteral intake of fluids and jeopardize the ability to preserve physiologic balance. In these settings, one may provide intravenous fluids to deliver the daily requirement of water and electrolyte. Such fluids, designed to maintain homeostatic balance and compensate for normal daily losses, are often referred to as maintenance intravenous fluids.

Maintenance fluids replace the usual insensible losses and anticipated urinary output when a child cannot do so on their own by autoregulation, kidney function, thirst, and oral intake. Maintenance fluids are designed to prevent dehydration or volume depletion from occurring. They are not designed to correct fluid depleted states or to compensate for abnormal shifts of fluids between body compartments, nor are they intended to expand vascular volume prophylactically. In addition to providing the daily requirement of water, maintenance prescriptions usually also provide a daily amount of sodium, chloride, and potassium, the basic electrolytes lost in normal urinary excretion.

Systems to determine maintenance prescriptions rely on a series of assumptions, including normal volume status, normal renal function and urinary output, normal insensible losses, and a lack of additional ongoing losses. Situations where these assumptions do not hold will require review and adjustment to the maintenance fluid prescription.

Recently there has been controversy about the appropriate method for prescribing maintenance fluids, noting the potential for complications and calling into question the traditional system. The counterargument to this thesis has been that the original concepts underlying the maintenance theory have been forgotten and the traditional methods of maintenance therapy have been misused. Review of the history of maintenance intravenous therapy and the theory behind the maintenance prescription, coupled with a clear understanding of the potential for complications, can assist the practitioner in providing safe and appropriate therapy for the hospitalized child.

History

In a seminal paper published in 1957, Holliday and Segar described the maintenance need for daily water in children receiving parenteral therapy. Their method was based on older data that related energy expenditure to water requirements. They estimated the energy expenditure of a typical hospitalized patient and determined the average physiologic losses through urinary and insensible (respiratory and evaporative) routes. They proposed a system to calculate these losses and thus the appropriate amount of water to be given in daily parenteral therapy. They further extended their approach to include recommendations for daily needs for sodium, chloride, and potassium. The Holliday–Segar method for maintenance intravenous fluids has been adopted throughout the world.

Review of Holliday and Segar's original paper reveals that they included several caveats regarding the use of the maintenance fluid system. They made it clear that the prescription would need to be reevaluated and adjusted in situations where either insensible losses or urinary losses differed from the norm. In addition, they made it clear that there was no intention for their system to be used for replacement of a volume deficit or any other need beyond daily fluid requirements: "Finally, it should be emphasized that these figures provide only maintenance needs for water. It is beyond the scope of this paper to consider repair of deficits or replacement of continuing abnormal losses of water. These must be considered separately and must be added to the needs for maintenance."

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Theory and Concepts

As noted above, maintenance fluid therapy is based on assumptions about water need as related to metabolism and energy expenditure. Basal metabolism generates heat which is dissipated through insensible water loss via the skin and the respiratory tract. Metabolism also generates waste solutes which are excreted by the kidney, leading to an obligate daily water loss in the urine. Thus the ability to predict energy expenditure would guide the need for the amount of water required to balance these daily losses.

Of several methods to predict energy expenditure, the Holliday–Segar method is among the simplest and has become the most widely used. Their equation computed the expected energy expenditure for the average hospitalized patient, making the assumption that this level of expenditure would fall in between basal metabolic rate and previously described estimates of total expenditure with normal activity. They derived a simple construct based on the patient's weight:

- For patients who weigh up to 10 kg, anticipate expenditure of 100 kcal/kg/day
- For patients who weigh 10–20 kg, anticipate expenditure of 1,000 kcal/day (i.e., 100 kcal/kg/day for the first 10 kg) plus an additional 50 kcal/kg/day for each kg over 10 kg
- For patients who weigh 20 kg and over, anticipate expenditure of 1,500 kcal/day (i.e., 100 kcal/kg/day for the first 10 kg plus 50 kcal/kg/day for the second 10 kg) plus an additional 20 kcal/kg/day for each kg over 20 kg

See *Table 282.1* for a summary of this system.

Holliday and Segar further described the relationship between energy expenditure and physiologic water loss through insensible and urinary routes. Based on data from other investigators, they estimated that the average insensible water loss was 50 mL for every 100 kcal of energy expended per day. For urinary loss of water, Holliday and Segar recognized that variable solute loads to the patient and differing ability of the kidney to concentrate or dilute the urine would lead to variation in daily urinary output. Based on a presumed average solute load, they chose to target a mid-range urinary concentration of 375 mOsm/kg (i.e., a urinary specific gravity near 1.010) to avoid providing too little or too much water to a patient who may not have fully competent urinary concentrating or diluting capacity. This calculated to 66.7 mL of water for every 100 kcal of energy per day, making the total need to balance physiologic losses (insensible and urinary) 116.7 mL/100 kcal/day. Holliday and Segar then assumed that oxidative metabolism would likely generate 16.7 mL of water/100 kcal of energy expended, rounding their water–energy equation to 100 mL water/100 kcal of energy expended per day, noting, "Fortuitously then, average needs for water expressed in milliliters equals estimated energy expenditure in calories."

For maintenance electrolyte needs, Holliday and Segar noted that "less precise data are available." Recognizing the kidney's ability to regulate and adjust for errors in estimation, they chose to target daily needs for sodium, chloride, and potassium based on values between those provided by human milk and those provided by cow milk; these levels proved to be in agreement with values that had already been recommended for adults. Relating their recommendations for daily electrolyte needs to energy expenditure much as they had for daily water, they suggested providing sodium at 3 mEq/100 kcal/day, chloride at 2 mEq/100 kcal/day, and potassium at 2 mEq/100 kcal/day. These requirements are summarized in *Table 282.2*.

Prescribing Maintenance Water

Using the method as outlined by Holliday and Segar, one may easily develop a prescription for maintenance intravenous fluids. For example, consider a 25 kg child for whom maintenance intravenous fluids are indicated. The Holliday–Segar method allows one to calculate average

Table 282.1
Holliday–Segar method to calculate energy expenditure or maintenance water need, based on body weight

Weight (kg)	Energy expenditure (kcal) or maintenance water need (mL)
0–10	100/kg/day
10–20	1,000/day + 50/kg/day (for each kg > 10 kg)
>20	1,500/day + 20/kg/day (for each kg > 20 kg)

Table 282.2
Holliday–Segar estimates for daily maintenance electrolyte requirements, based on energy expenditure

Electrolyte	Maintenance need
Sodium	3 mEq/100 kcal/day
Chloride	2 mEq/100 kcal/day
Potassium	2 mEq/100 kcal/day

energy expenditure and, working on the assumption that 100 mL of water is required for every 100 kcal expended, we may substitute milliliters of water for kcal in the equations as follows:

1,000 mL/day for the first 10 kg (10 kg × 100 mL/kg/day)
PLUS
500 mL/day for the second 10 kg (10 kg × 50 mL/kg/day)
PLUS
100 mL/day for the 5 kg over 20 kg (5 kg × 20 mL/kg/day)
EQUALS
1,600 mL/day TOTAL WATER for 25 kg child

If given as a continuous intravenous infusion, this would call for a rate of about 67 mL/h (i.e., 1,600 mL/day divided by 24 h/day).

An adaptation of these equations has been developed to approximate this result in terms of milliliters of fluid to deliver per hour. Sometimes referred to colloquially as the "4-2-1 rule," it is constructed as follows:

- For the first 10 kg of body weight, deliver 4 mL/kg/h of intravenous fluid.
- For every kg of body weight between 10 and 20 kg, deliver an additional 2 mL/kg/h.
- For every kg of body weight over 20 kg, deliver an additional 1 mL/kg/h.

See *Table 282.3* for a summary of this method for calculating maintenance fluids.

Taking the example previously derived for the 25 kg child, the calculations would be:

40 mL/h for the first 10 kg (10 kg × 4 mL/kg/h)
PLUS
20 mL/h for the second 10 kg (10 kg × 2 mL/kg/h)
PLUS
5 mL/h for the 5 kg over 20 kg (5 kg × 1 mL/kg/h)
EQUALS
65 mL/h TOTAL WATER for 25 kg child

Table 282.3
Simplified "4-2-1 rule" for calculating hourly maintenance fluid rate

Weight (kg)	Hourly fluid rate for maintenance water
0–10	4 mL/kg/h
10–20	40 mL/h + 2 mL/kg/h (for each kg > 10 kg)
>20	60 mL/h + 1 mL/kg/h (for each kg > 20 kg)

Note: that this method is based on the standard Holliday–Segar method for calculating energy expenditure and daily maintenance needs

Prescribing Maintenance Electrolytes

Insensible losses are considered to be water; therefore, daily losses of electrolytes, which need to be replaced in a maintenance prescription, come entirely from urinary output. The Holliday–Segar method addresses electrolyte losses but, as noted above, the recommendations are based on less robust data than that available for determining water requirements. If following the Holliday–Segar plan for the 25 kg child previously described, and again assuming that 100 mL of water is required for every 100 kcal of energy expended, electrolyte requirements would be calculated as follows:

- Total daily water intake 1,600 mL/day
- Sodium requirement: 48 mEq/day (3 mEq/100 mL water/day)
- Chloride requirement: 32 mEq/day (2 mEq/100 mL water/day)
- Potassium requirement: 32 mEq/day (2 mEq/100 mL water/day)

This sodium content (48 mEq in 1,600 mL, or 30 mEq/L) is roughly equivalent to that found in standard hypotonic saline available for infusion (0.18–0.3% sodium chloride solution). Potassium content calculates to 20 mEq/L, a concentration also found frequently in standardized solutions. Chloride content in standardized solutions may deliver quantities in excess of those recommended by the Holliday–Segar calculation due to the necessity of maintaining electroneutrality in the intravenous fluid. However, as noted by Holliday and Segar with respect to electrolyte maintenance, "figures considerably in excess of the minimum requirements are readily handled."

Controversy

Recently, controversy has developed regarding the use of the Holliday–Segar method. Several authors have suggested that the use of hypotonic intravenous solutions, as suggested by Holliday and Segar, increases the risk for complications related to hyponatremia. While not challenging the fundamental basis of determining maintenance needs for water based on energy expenditure, it is proposed that isotonic intravenous solutions such as normal saline (0.9% sodium chloride solution) should be the intravenous maintenance fluid of choice. In support of this argument, authors note reported cases of hyponatremia, some with neurological sequelae, associated with the use of hypotonic intravenous solution. They

accurately note that hospitalized patients may have non-osmotic stimuli for the release of antidiuretic hormone (ADH), such as nausea, vomiting, pain, or volume depletion. Postoperative patients are also known to have secretion of ADH on a non-osmotic basis. ADH in these settings would promote the retention of free water and could lead to hyponatremia.

Inappropriate use of the maintenance fluid concept can easily lead to the complications cited above. Holliday and Segar clearly delineated that maintenance intravenous fluids were to be used for replacement of physiologic losses and should not be employed for correction of volume deficits, and that adjustments to the standard prescription would be required depending on the clinical situation.

Considerations

While the maintenance fluid method of Holliday and Segar remains a useful tool, it is clear that the system is based on a series of assumptions and generalizations that are not always true for every patient. This is especially true of the acutely ill child admitted to the hospital, or the child in the perioperative period. Urinary output may not achieve the levels predicted by Holliday and Segar, either due to volume depletion and activation of sodium-retaining mechanisms (renin/angiotensin II/aldosterone) or due to non-osmotic stimulation of ADH. Such patients could receive too much free water using the standard maintenance equations, putting them at risk for hyponatremia as described above. Holliday and Segar's estimates of energy expenditure may be overly generous for a given patient, such as a child who is immobilized following surgery or a child who is critically ill and sedated. Adhering to the maintenance theory, lower energy expenditure would obligate a smaller amount of water; thus, the standard equations for maintenance would again provide too much water for those with reduced caloric requirements. These examples demonstrate the importance of adjusting the intravenous fluid plan for a given patient, taking into consideration the clinical circumstances; rote application of the maintenance equations to all scenarios would be inappropriate.

Further, Holliday and Segar were very clear that the maintenance concept should not be applied to the child who requires deficit replacement; such clinical situations would be addressed better with the use of sufficient isotonic intravenous solution to correct the volume deficit while prescribing maintenance fluids (or an adaptation thereof) to balance anticipated routine daily losses from urinary and insensible routes. Consequently, provision of intravenous fluids using simple multiples of volumes calculated through maintenance equations (e.g., "one-and-a-half times maintenance," "twice maintenance") clearly goes outside of the construct developed by Holliday and Segar and may put the patient at risk for excessive free water delivery.

Recommendations

Review of the traditional method for calculating maintenance intravenous fluids demonstrates a relatively straightforward system that can be employed successfully in many hospitalized patients. Analysis of the potential risks, especially for hyponatremia and its complications, reveals the complexity of illness in childhood and serves as a reminder that careful thought and clinical judgment must be employed when caring for sick children. The majority of the time the standard approach for maintenance fluids will work, due in large part to the very effective autoregulatory ability of the functional kidney and associated neurohumoral systems. Recognizing the limitations of the method and those patients at risk for complications will help to avoid untoward outcomes. Whenever possible, discontinuation of intravenous fluids with return to normal oral intake of food and water is most appropriate.

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283 Hyponatremia and Hypernatremia

Aaron Friedman

Abnormalities in water homeostasis, as manifested by low or high serum sodium, are a commonly encountered electrolyte disorder especially in hospitalized patients. *Hypo*natremia is far more common than *hyper*natremia. With either condition in the overwhelming majority of cases, the underlying etiology is water imbalance – not sodium imbalance. An understanding of how sodium and water homeostasis are maintained and why imbalances occur allow the clinician to appropriately diagnose, approach, and treat disorders of water imbalance.

Principles of Sodium and Water Balance

The plasma sodium concentration is normally 140 mmol/L with a normal range of 135–145 mmol/L. Sodium is the major extracellular cation and along with the anions, chloride and bicarbonate, accounts for nearly all of the milliosmoles (mOsm) in extracellular fluid. Intracellular cations that maintain electroneutrality and counterbalance the osmotic effects of extracellular ions are potassium (cation) and the anions, phosphate and proteins (*Table 283.1*). The normal extracellular (and intracellular) osmolality is 290 mOsm/kg H_2O. Since 1 mmol of sodium (potassium chloride or bicarbonate) contributes 1 mOsm to the osmolality, sodium is vital to maintaining extracellular volume, osmolality, and plasma volume. A handy quick equation for determining plasma osmolality is: plasma osmolality (mOsm/kg H_2O) = [2 × Na (mmol/L)] + glucose (mg/dL)/18 + BUN (mg/dL)/2.8. The division by 18 for glucose and 2.8 for BUN accounts for molecular weight and takes the concentration in mg/dL and converts it to mmol/L.

Water homeostasis is critical to all mammals. Thus careful regulation of water intake and excretion is necessary. The important physiologic components to water regulation include the hypothalamus and surrounding brain tissue, the circulating antidiuretic hormone or arginine vasopressin (AVP), and the kidney.

Since AVP plays such a central role in water homeostasis, the physiology of AVP production, release, and action on the kidney is important. In the late 1940s, Verney demonstrated that osmolality plays a role in the release of AVP from the hypothalamus. Under otherwise normal conditions, a small (1–2%) increase in serum osmolality sensed by paraventricular nuclei adjacent to the hypothalamus will result in the release of AVP from the hypothalamus. Conversely, a small (1–2%) decrease in serum osmolality will shutdown AVP release and decrease production.

Osmolality is not the only trigger to AVP release. Gauer and Henry demonstrated that "effective" circulating plasma volume is sensed by pressure or stretch receptors in the left atrium or large arteries in the chest. With a decrease in effective circulating volume, the pressure or stretch receptors sense a decrease and signal through the vagus and glossopharyngeal nerve resulting in the release and increased production of AVP. This type of AVP release is termed non-osmotic AVP release. Other stimuli for non-osmotic AVP release are listed in *Table 283.2*.

Once released into the circulation, AVP stimulates brain centers to increase thirst. The other important action in water homeostasis for AVP is water conservation by the kidney. AVP stimulates the active transport of urea by the thick ascending limb of the loop of Henle epithelial cells. This results in the creation and/or maintenance of a large osmotic gradient between the tubule lumen and the renal interstitium favorable to the movement of water from the tubule lumen into the interstitium and eventually into the extracellular space. AVP also results in the transtubular (transepithelial) transport of water in the collecting duct of the kidney. AVP acts primarily on the principle cells of the collecting duct by binding onto receptors on the basolateral (non-luminal) surface of principle cells leading to the opening of water channels – termed "aquaporins" – which serve as channels allowing solute-free water to traverse cells.

Following the release of AVP, action by the kidney is rapid. AVP circulates unbound and is metabolized by the liver or excreted by the kidney. Circulating half-life is approximately 20 min. The arrangement of water channels in the renal collecting duct under the influence of AVP does not require new protein synthesis. All of this means that the release of AVP under normal conditions results in water reabsorption by the kidney within minutes to hours.

Total body water is distributed within cells and in interstitial (between cells) fluid compartments. Except in

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Table 283.1
Ion composition of ECF and ICF

	ICF	ECF
Na^+	135–145	10–20
K^+	3.5–5.0	120–145
Cl^-	95–105	0–3
HCO_3^-	22–29	8–10
Phosphate	2	110–120

ECF extracellular fluid, *ICF* intracellular fluid
Cations: Na-sodium; potassium
Anions: Cl-chloride; HCO_3-bicarbonate; phosphate
All ions mmol/L

Table 283.2
Causes of non-osmotic release of vasopressin

1. Malignancy	Adenocarcinoma (lung, pancreas, gastrointestinal); lymphoma (Hodgkins, histiocytic); thymoma; acute leukemia
2. Intrathoracic disorders	Infection (tuberculosis, bacterial, viral, fungal, mycoplasma); positive pressure ventilation; asthma; cystic fibrosis; atelectasis; pneumothorax; mitral valve
3. CNS disorders	Infection (encephalitis, meningitis, abscess, tuberculosis); trauma; intracranial hemorrhage; tumor; surgery; Guillain–Barre syndrome; idiopathic
4. Drugs	Antipsychotic (phenothiazines, haloperidol); antidepressants (SSRIs, tricyclics, MAO inhibitors, Bupropion); anticonvulsants, (carbamazepine, oxcarbazepine, valproate); analgesics (barbiturates, NSAIDs) cardiovascular meds (diuretics, isoproterenal, antihypertensives, aldosterone antagonists) antidiabetics (chlorpropamide, tolbutamide, glipizide); clofibrate; bromocriptine; antineoplastics (cyclo-phosphomide,vincristine/ vinblastine, cisplatin, adenosine arabinoside); antibiotics (macrolides, TMP/SZ; sulbactam)

newborns total body water comprises 60% (or so) of total body weight. The distribution is essentially 2/3 within cells (intracellular fluid, ICF) and 1/3 outside of cells (extracellular fluid, ECF); 25% of ECF is in plasma. In the first 24–28 h after birth, total body water is 75–80% of total body weight with up to 70% in the ECF.

Sodium homeostasis is maintained by balancing intake, extracellular volume, and output. Intake of sodium in the industrialized world is ample, averaging 4–5 g/day in adults. The primary site of sodium excretion is the kidney. At the glomerulus, the filtered load of sodium is 140 mmol/L of filtrates. Approximately 60–70% of the sodium filtered per day is reabsorbed by the proximal tubule, 20–30% of the filtered sodium load is reabsorbed in the ascending limb of the loop of Henle and the remaining reabsorption occurs at the distal tubule and collecting duct under the influence of aldosterone.

Aldosterone secretion by the adrenal gland is mainly influenced through the renin-angiotensin aldosterone axis. In situations of extracellular volume contraction, stretch and volume sensors in the large vessels of the chest, and messages from renal efferent arterioles result in the release of renin from juxtaglomerular cells in the kidney. Renin then catalyzes the cleavage of circulating angiotensinogen to angiotensin I. Angiotensin-converting enzyme, also in the circulation, converts angiotensin I to angiotensin II. It is angiotensin II which stimulates the release of aldosterone from the adrenal cortex, increases the reabsorption of sodium by the proximal tubule, and feedbacks on the kidney to reduce renin release. Thus, in situations of extracellular volume contraction through the action of aldosterone, renal sodium reabsorption increases, and through the action of AVP, water reabsorption increases, which serves to help restore extracellular volume.

Hyponatremia

Hyponatremia is defined as plasma sodium under 135 mmol/L when the normal range is 135–145 mmol/L. Hyponatremia often occurs in situations of extracellular volume contraction, but can occur in situations of no perturbation of extracellular volume or extracellular volume expansion such as syndrome of inappropriate antidiuretic hormone (AVP) release termed "SIADH release." An elevated AVP *alone* does not result in hyponatremia. AVP elevated levels plus the intake of water or the provision of a hypotonic solution (intravenous fluids) leads to hyponatremia and hypoosmolality. *Tables 283.3–283.5* provide an algorithm for the approach to hyponatremia in children.

The clinical manifestations of a low serum sodium and hypoosmolality depend on the level of serum sodium or hypoosmolality and the rate of decline. Mild reductions in the osmolality usually do not result in significant symptoms. Symptoms typically become more apparent when

the sodium falls below 130 mmol/L and especially below 125 mmol/L. However, rapid changes, decreases that occur over a few hours, could result in symptoms. The symptoms are mainly neurologic and include agitation, anorexia, anxiety, malaise/lethargy, muscle weakness, hypothermia, which can then progress to disorientation, significant cognition defects, depressed deep tendon reflexes, seizures, coma, and death (usually due to brain herniation).

The approach to hyponatremia is to remember that hyponatremia usually, but not always, is representative of hypoosmolality. In order to appropriately manage a patient with a low serum sodium, knowing if the low sodium also means a low osmolality is crucial. *Tables 283.3–283.5* describe the approach to hyponatremia depending on whether it is associated with isoosmolality (*Table 283.3*), hyperosmolality (*Table 283.4*), or hypoosmolality (*Table 283.5*).

A common clinical situation in pediatrics is hyponatremic (hypoosmolality) dehydration often associated with gastroenteritis. The pathophysiology of this condition is loss of fluid and electrolyte from the gastrointestinal track leading to extracellular fluid volume contraction. As a result, both aldosterone and AVP are secreted. Aldosterone will increase renal sodium reabsorption and secretion, which can result in hypokalemia. AVP will increase renal water reabsorption. Hyponatremia (and hypoosmolality) can result when the patient consumes or receives hypotonic solution.

The signs and symptoms of dehydration are well described in *Table 283.6*.

The treatment of hyponatremic (hypoosmodal) dehydration is the restoration of extracellular volume. For mild to moderate dehydration, oral restoration fluid is often sufficient unless vomiting is persistent and even small amounts of fluid delivered frequently is not retained. For moderate dehydration, The World Health Organization recommends oral rehydration solutions. Such solutions contain at least 45 mmol/L of sodium with some solutions containing up to 90 mmol/L. The potassium content is usually 20–25 mmol/L. Many clinicians prefer to use intravenous fluids for moderate to severe dehydration. To restore extracellular volume, the intravenous solutions of choice are isotonic saline or lactated Ringers solution. An intravenous bolus of 20–40 mL/kg delivered over 1–2 h (especially in patients with tachycardia, hypotension and/or increased capillary refill time) will improve signs of dehydration and patient well-being. The improvement in extracellular volume will also improve gut perfusion, which will make oral rehydration better tolerated. This approach will also bring the serum sodium closer to normal.

An all too frequently used, but erroneous approach to treating children with dehydration, is to provide maintenance fluid to restore extracellular volume depletion. Maintenance fluid therapy is an estimate of the anticipated fluid and electrolyte needs of the euvolemic patient. It is based on caloric expenditure (*Table 283.7*). This solution is *not* a fluid that should be used to restore extracellular volume. The inappropriate use of

Table 283.3
Approach to hyponatremia: normal serum osmolality

Hyponatremia
[Na] < 135 mmol/L
↓
Measure plasma osmolality
↓
Normal or isotonic
285–295 mOsm/kg H_2O
↓
Hyperlipidemia or Hyperproteineuria
(hypertriglycerides)

Table 283.4
Approach to Hyponatremia: elevated serum osmolality

Hyponatremia
↓
Measure serum osmolality
↓
>295 mOsm/kg H_2O
↓
Hyperglycemia or mannitol infusion
- For every 100mg/dL of glucose above normal, serum Na will decrease 1.6 mmol/L
- For every 0.5 gm/kg of mannitol infused, serum Na will decrease 4–5 mmol/L

Table 283.5

Approach to hyponatremia: low serum osmolality

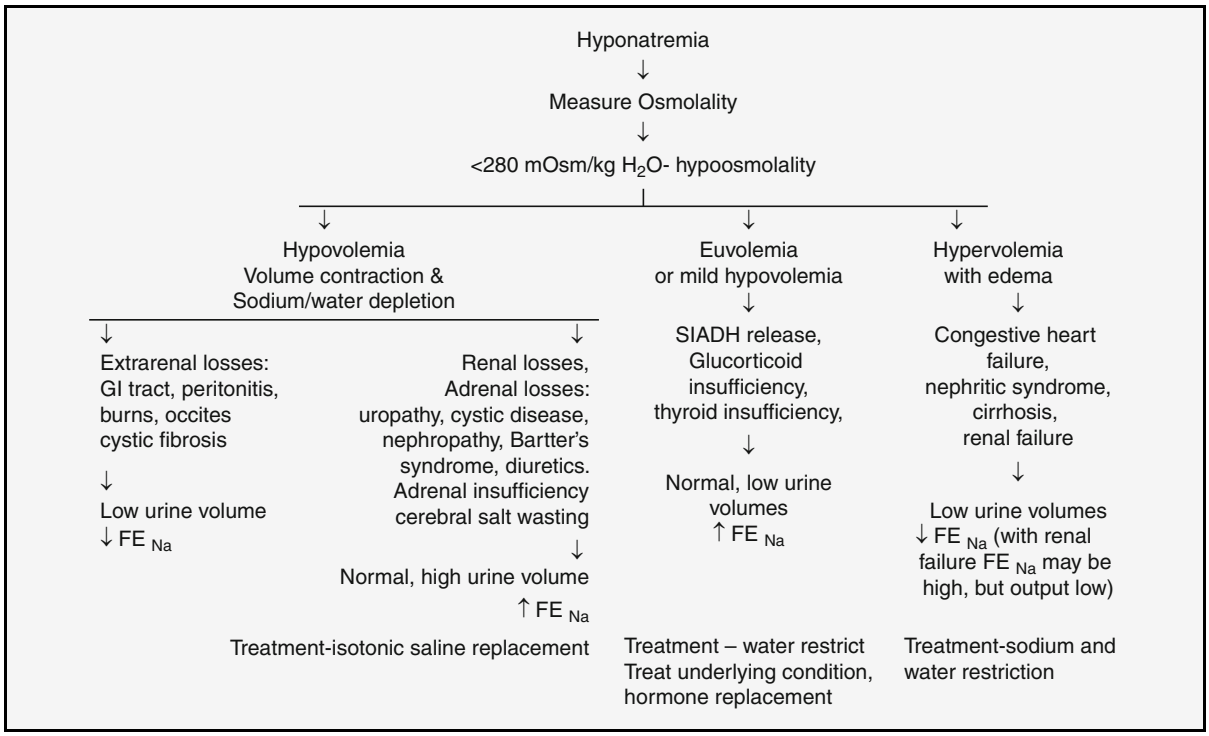


Table 283.6

Signs and symptoms of dehydration

	Mild	Moderate	Severe
	1–4%	5–7%	>7%
Skin	Normal	Cool	Cool, mottled
Capillary refill	Normal	Decreased	Markedly decreased
Skin turgor	Normal	Loose	Tenting
Buccal mucosa	Slightly dry	Dry	Parched
Eyes	Normal	Sunken	Markedly sunken
Fontanelle[a]	Normal	Sunken	Markedly sunken
Pulse	Normal (full)	Rapid	Rapid, thready
Urine output	Normal	Decreased	Oliguria (<1 mL/kg/h)
Systolic BP	Normal	Normal, low	Low → shock

[a]Infants <9 month of age

maintenance fluid solutions in situations of extracellular fluid volume contraction or other causes of nonosmotic release of antidiuretic hormone have resulted in serious injury or death due to cerebral edema. As a result, a modification of maintenance therapy was proposed that substitutes isotonic saline for the hypotonic solution published over 5 decades ago by Holliday and Segar. Studies, to date, across the full range of hospitalized children comparing isotonic and hypotonic maintenance solutions are still lacking.

Table 283.7
Caloric, water, and basic electrolyte requirements based on weight

Body weight (kg)	Calories	Water	Sodium mEq/ 100 mL H_2O	Chloride mEq/ 100 mL H_2O	Potassium mEq/ 100 mL H_2O
3–10 kg	100 mL/kg	100 mL/kg Or 4 mL/kg/h	3	2	2
11–20 kg	50 mL/kg	1000 mL+50 mL/kg Or 40 mL/h+2 mL/kg/h	3	2	2
>20 kg	20 mL/kg	1500 mL+20 mL/kg Or 60 mL/h+1 mL/kg/h	3	2	2

Example: Hyponatremic Dehydration

A 15 kg child has a 3-day history of fever, vomiting, and diarrhea. Your assessment is the patient is 7% dehydrated. The patient's serum electrolytes are sodium 127 mmol/L, potassium 3.7 mmol/L, chloride 95 mmol/L, bicarbonate 22 mmol/L, and glucose 100 mg/dL. You decide to use intravenous fluids to manage this patient.

Step 1. Treat extracellular volume depletion with 40 mL/kg or 600 mL of isotonic fluid over 1–2 h. 40 mL/kg is 4% of body weight.
Step 2. Reexamine patient for changes in signs and symptoms of dehydration.
Step 3. Attempt oral fluids or continue isotonic fluids 30 mL/kg over next 6–8 h. This should restore extracellular fluid unless vomiting and diarrheal losses remain high.
Step 4. Recheck serum sodium and other electrolytes.
Step 5. Consider oral fluids initiation or maintenance fluids only after extracellular volume is restored as demonstrated by increased urine output and decreasing urine osmolality.

In situations where the serum sodium is low, especially below 125 mmol/L, or the patient is exhibiting central nervous system symptoms noted above, then a more rapid increase in serum sodium and osmolality may be desired. Fortunately, central nervous system symptoms are rare. Hypertonic saline (3% NaCl) is the usual solution. 3% NaCl is 500 mmol/L or 0.5 mmol/mL. Changes in the serum sodium *should not* exceed 10 mmol/L/24 h or 20 mOsm/kg H_2O/24 h. To calculate the amount of sodium needed to raise the serum sodium concentration, the equation is:

$$(\text{Desired[Na]} - \text{Measure[Na]}) \times 0.6 \times \text{BW}$$

where [Na] is the serum sodium concentration in mmol/L; BW is the body weight in kg. Body weight multiplied by 0.6 is total body water (except in prematures and early newborns whose total body weight is closer to 0.7).

The entire body water space must be used in this calculation because the addition of sodium into the extracellular space will raise extracellular osmolality and draw water from the intracellular to extracellular space equalizing osmolality throughout the total body water space. In the 15 kg patient example above, if the serum sodium were 120 mmol/L and the patient was symptomatic using the equation above, the desire [Na] should be no higher than 130 mmol/L, the measure [Na] is 120 mmol/L, thus: (130–120) × 0.6 × 15 = 90 mmol. 3% NaCl has 0.5 mmol/mL, which will require 180 mL of 3% NaCl. A safe approach is to provide approximately 5 ml/kg/h of 3% NaCl (2.5 mmol/kg/h). In this patient, 75 mL of 3% NaCl per hour will deliver 37.5 mmol of sodium. Measuring the serum sodium after 1 h of infusion is prudent and recalculation may be necessary.

The Syndrome of Inappropriate Antidiuretic Hormone (SIADH) Release

Bartter and Schwartz described a syndrome of hyponatremia and hypoosmolality of serum, urine osmolality that is inappropriately high and higher than the serum osmolality, high urine sodium excretion, and normal renal, adrenal, and thyroid function. SIADH release is a condition of nonphysiologic AVP release. AVP release due to a high serum osmolality or extracellular volume depletion does not represent inappropriate AVP release. Thus, SIADH release is really due to (1) ectopic production, (2) abnormal release from the pituitary, or (3) exogenous administration. *Table 283.8* lists some of the causes of SIADH release.

With SIADH release, plasma sodium declines only if the patient continues to consume (or receive) water in excess of that which is lost in urine, sweat, and respiration.

Table 283.8
Comparison of syndrome of inappropriate ADH (SIADH) release and cerebral salt wasting (CSW)

	SIADH	CSW
Serum sodium	Low	Low
Extracellular fluid volume	Normal, high	Low
Blood pressure	Normal	Normal, low
Orthostatic hypotension	Absent	May be present
Serum AVP	High	Normal, high
Urine volume	Low	High
Urine osmolality	High	High
Urine osmolality with volume expansion	High	Decreased
Urine sodium excretion	>40 mmol/L	Very high
Serum uric acid	Low	Normal, low
Serum Albumin	Low	Normal, high
BUN, serum creatinine	Normal, low	Normal, high
Hematocrit	Normal, low	Normal, high
Brain natriuretic peptide	Normal	High

Because patients with SIADH release are *not* extracellular volume depleted (in fact, extracellular volume is usually expanded), urinary sodium excretion is not low.

The treatment of choice for SIADH release is to address the underlying condition, thus eliminating any exogenous source or shutting off endogenous production and release. This is often difficult, if not impossible. Fluid restriction is often effective. The goal is for total fluid intake/24 h to be less than the water lost in urine and through the insensible losses of breathing and sweating. This approach will slowly increase the serum sodium and serum osmolality. Other medical approaches include doxycycline, which interferes with the action of AVP but cannot be used in young children and is limited in its effectiveness and fludrocortisone, which increases sodium retention but also raises blood pressure and results in hypokalemia and AVP antagonists. AVP antagonists appear promising in short-term studies, but are untested in children.

Cerebral Salt Wasting (CSW)

Cerebral salt wasting is a less well-understood and probably infrequent cause of hypoosmolality/hyponatremia. Cerebral salt wasting is usually associated with central nervous system injury such as brain injury or brain surgery. The clinical manifestation includes hyponatremia and serum hypoosmolality, but urine volumes are high, urine sodiums are extremely high (concentrations can be greater than the plasma sodium concentration), and extracellular volume contraction. *Table 283.8* highlights the difference between SIADH release and CSW in both diagnosis and treatment. Making the distinction is important since fluid restriction is the primary approach to SIADH release, whereas, isotonic saline, sometimes in large volumes, is the recommended approach to CSW. Other therapies proposed in CSW include: AVP administration with concomitant sodium administration and the use of fludrocortisone to enhance sodium reabsorption. The use of fludrocortisone may necessitate the use of supplemental potassium.

Hypernatremia (Hyperosmolality)

Hypernatremia occurs less frequently than hyponatremia. The most important causes of hypernatremia are excessive water losses and/or inadequate water intake. Hypernatremia is always associated with hyperosmolality. In very rare instances, hypernatremia is due to the provision of too much salt. Normally the protection against hypernatremia includes activation of the thirst mechanism and increased water consumption as well as the excretion of concentrated urine initiated by the release of AVP. The major consequences of hypernatremia pertain to the loss of cell volume due to water shifting from the intracellular to extracellular, and the loss of interstitial and plasma volume as water is lost, and eventually from the body as a whole. The brain, especially in infants and young children, is particularly at risk.

The signs and symptoms of hypernatremia are: thirst, lethargy, and/or irritability, in infants a high-pitched cry, doughy feeling skin, nausea, vomiting, and eventually obtundation, coma, and death. The approach to the evaluation of hypernatremia is described in *Tables 283.9–283.11*. As noted above, with rare exception, hypernatremia is due to the loss of water or hypotonic fluid from the body and inadequate replacement. In children, gastrointestinal dehydration with stool and volume losses associated with inadequate fluid intake is the most common cause of hypernatremia. Patients with hypernatremic dehydration will demonstrate signs and symptoms of dehydration (*Table 283.2*). However, the percentage of dehydration will be greater than the signs and symptoms suggest. Thus, a hypotensive child with hypernatremia dehydration is critically ill. In newborns and young infants, inadequate fluid volume (inadequate

Table 283.9

Approach to hypernatremia

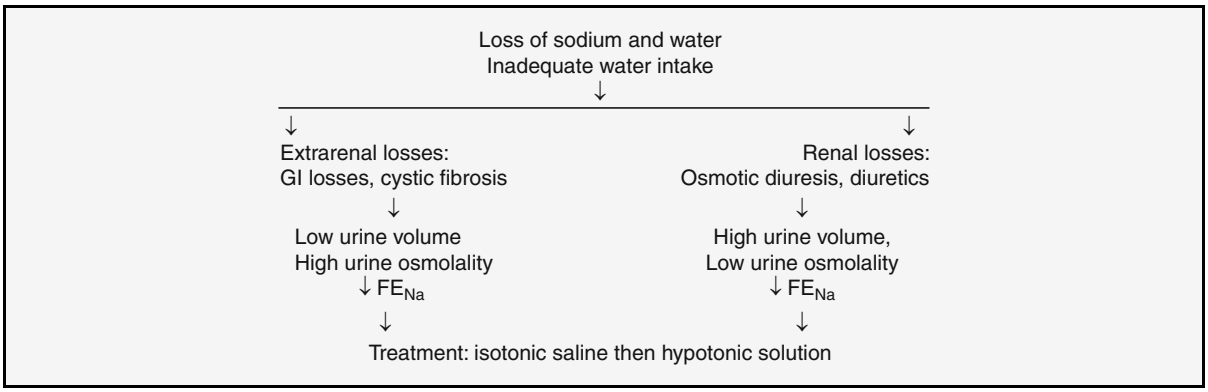


Table 283.10

Approach to hypernatremia

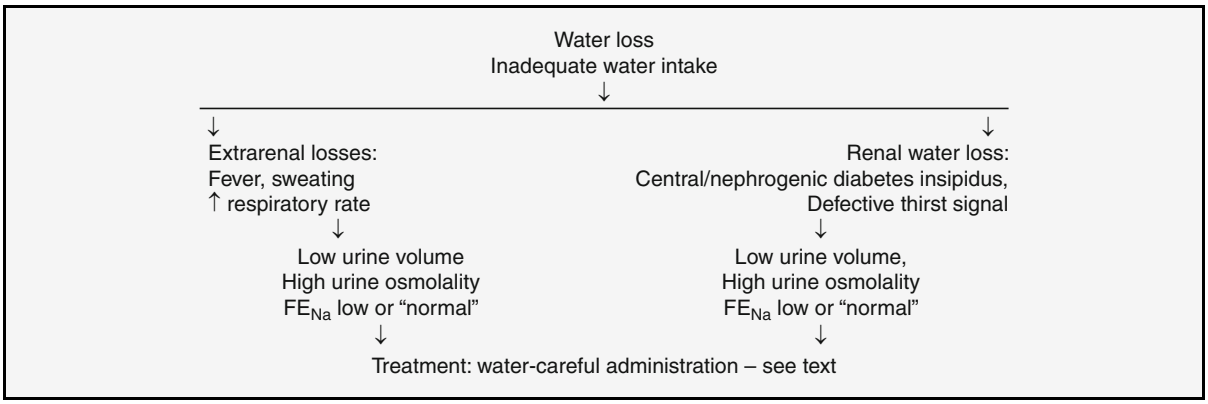
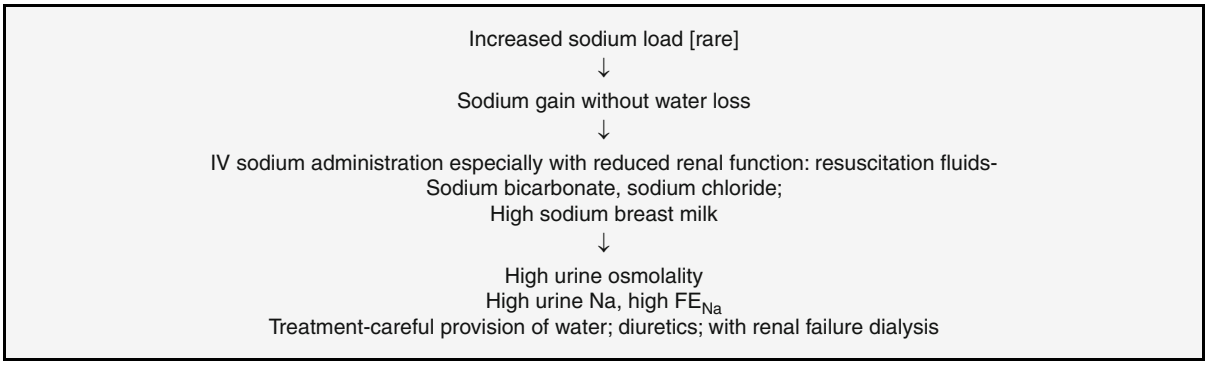


Table 283.11

Approach to hypernatremia



breast milk volume, for example) is an important cause of hypernatremia. Another important etiology for hypernatremia is renal water loss associated with reduced (chronic kidney disease, obstructive uropathy) or nonexistent (central or nephrogenic diabetes insipidus) ability to reabsorb water. With extrarenal losses, but normal renal function, the extracellular volume depletion and hyperosmolality of the serum will lead to low urine volume, high urine osmolality, and low urine sodium, as well as low fractional excretion of sodium (FE_{Na}). With polyuria associated with loss of the ability of the kidney to reabsorb water, urine volumes are high and urine osmolality is low. The evaluation of polyuria is described in *Table 283.12*.

Diabetes insipidus (DI) leads to polyuria because of inability to excrete concentrated urine either due to absent or deficient AVP secretion (central DI) or renal resistance to the action of AVP (nephrogenic DI). *Table 283.13* lists causes of central or nephrogenic DI. Central DI may be idiopathic, but is more often the result of central nervous system trauma, infection, malignancy, or surgery. Patients will have polyuria, polydipsia, and dilute urine

Table 283.12
Approach to polyuria

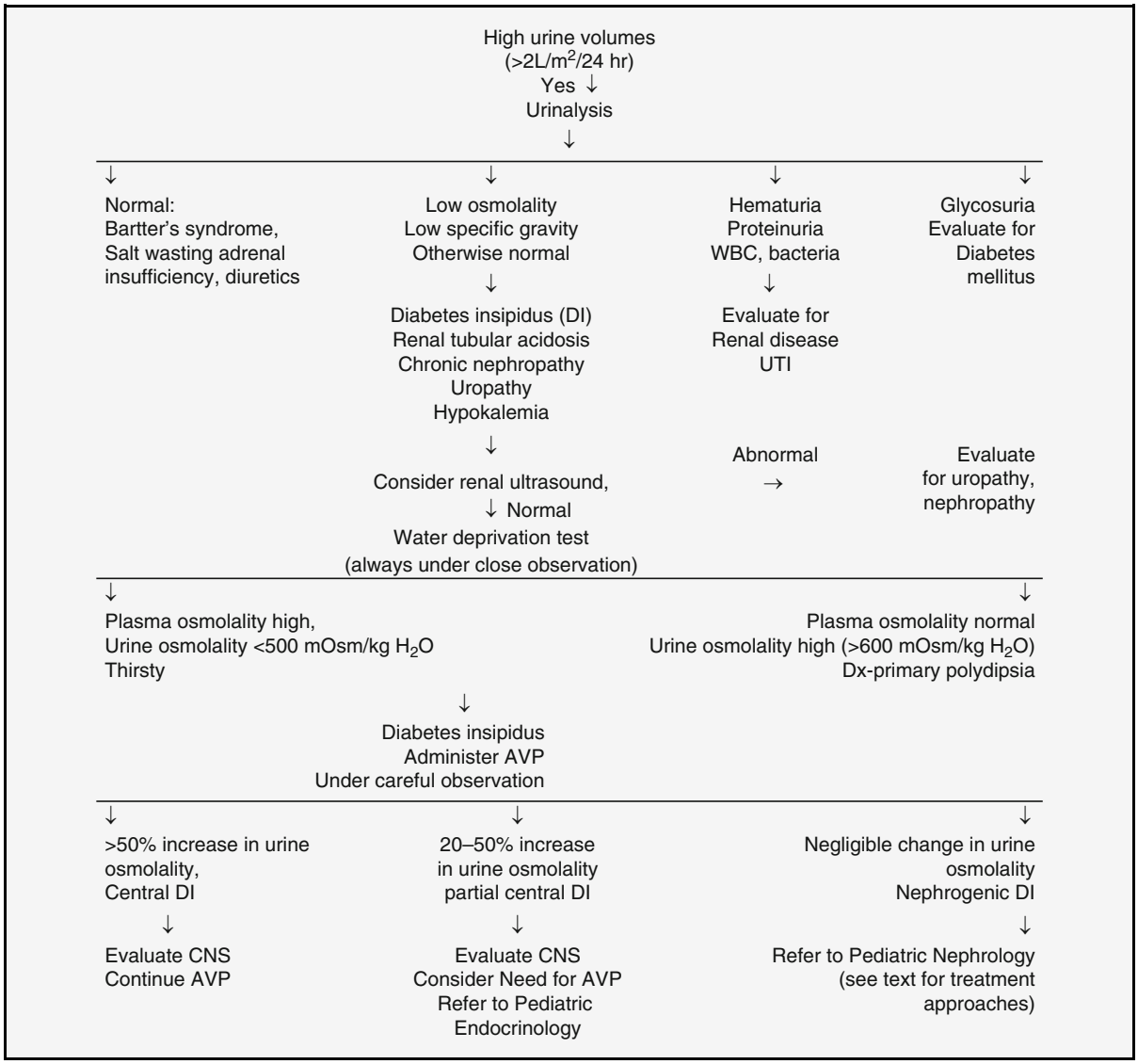


Table 283.13
Etiology: central vs. nephrogenic diabetes insipidus

Central diabetes Insipidus	Idiopathic
	Hereditary – autosomal recessive and autosomal dominant
	CNS condition – surgery, trauma, malignancy, especially near hypothalamus and pituitary
	Infection – tuberculosis, meningitis, encephalitis; granulomatous disease
	Histocytosis
Nephrogenic diabetes Insipidus	Congenital – ADH receptor defect (x linked), aquaporin defect (autosomal)
	Renal disease – obstructive uropathy, dysplasia, medullary cystic disease, polycystic disease, reflux nephropathy
	Systemic disease – sick cell, amyloid, sarcoid, multiple myeloma
	Hypokalemia
	Hypercalcemia
	Drugs – lithium, diuretics, aminoglycosides, phenytoin, vinblastine, amphotericin

with a decrease in urine volume and an increased urine osmolality associated with the provision of exogenous AVP. Nephrogenic DI results from the inability of the renal distal tubule and collecting duct to respond to AVP. Two receptors respond to AVP, V1 (AVPR1), and V2 (AVPR2). V2 is the receptor on the distal tubule and collecting duct. The gene is located on X chromosome (Xq-28). Familial nephrogenic diabetes insipidus accounts for 90% or more of the *heritable* forms of nephrogenic DI and demonstrates X-linked inheritance with mutations in the AVP-2 receptor. The condition usually presents in the neonatal period with polyuria, polydipsia, poor weight gain, unexplained fever, and hypernatremic dehydration. A far less common cause of nephrogenic DI is a defect in the AVP water channel, aquaporin-2, (AQP2) in distal tubule and collecting duct. The mutations in the AQP2 gene present with autosomal dominant or recessive mode of inheritance. In families with a known history of X-linked nephrogenic DI, prenatal diagnosis is possible and can help prevent early injury to baby from hypernatremic dehydration. Acquired nephrogenic DI is more common than heritable forms. Chronic kidney disease, the result of obstructive uropathy, cystic kidney disease, renal dysplasia, metabolic conditions such as hypokalemia, hypercalcemia, and diseases such as sickle cell disease result in nephrogenic DI.

With central DI, the treatment is the provision of AVP usually as desmopressin. *Table 283.12* describes the approach to both central and nephrogenic DI. The therapeutic approach to the child with nephrogenic DI is: first, assure access to water and second, decrease urinary volume by carefully restricting protein intake (1.6 g/kg/24 h) and restricting salt intake (0.7 mmol/kg/24 h). Additionally, the use of hydrochlorothiazide (1–2 mg/kg/24 h) will result in mild volume depletion and enhanced proximal tubule sodium and water reabsorption. The use of hydrochlorothiazide long term will result in hypokalemia prevented by the concomitant use of amiloside, indomethacin (a prostaglandin inhibitor), will further reduce urinary volume.

Excessive sodium intake is an unusual cause of hypernatremia. The intravenous administration of hypertonic sodium solutions such as sodium bicarbonate or sodium chloride or blood products high in sodium such as platelets can result in hypernatremia. Improper preparation of infant formula or boiling of skim milk may result in hypernatremia. In these situations (excluding acute renal failure), urine osmolality will be high and urine sodium will be elevated (FE_{Na} high as well).

Treatment of Hypernatremic Dehydration

The approach to treatment involves:

1. Identify the underlying cause.
2. If possible, treat underlying cause and minimize ongoing losses.
3. Treat extracellular volume contraction.
4. Replace water deficit.
5. Address ongoing losses.
6. Consider maintenance fluid therapy after extracellular volume contraction is treated. The treatment of extracellular volume contraction involves the use of isotonic saline or lactated Ringer's solution. Patients with hypernatremic dehydration are at least 10% dehydrated. Therefore, expect to provide at least 100 mL/kg of replacement fluid. The important caveat to the treatment of children with hypernatremic dehydration is that the serum sodium should *not* drop more than 10 mmol/24 h (approximately 0.5 mmol/h). With hypernatremic (hyperosmotic) dehydration, water leaves the intracellular space including the brain.

The response within the brain to this form of dehydration is the elaboration of intracellular osmoles, which reduces the volume loss by cells in the brain. Thus, too rapid a decline in extracellular osmolality will result in intracellular swelling and cerebral edema. Therefore, it is prudent when providing fluid therapy to a patient with hypernatremic dehydration to regularly follow the serum sodium.

Replacing the water deficit should begin after at least 50% of the extracellular volume deficit is treated (50 mL/kg of an isotonic solution) and rechecking the serum sodium. To calculate the water deficit and how much would be needed to restore normal osmolality, the equation is: water deficit = TBW × (Na measured – Na desired)/Na desired. TBW = total body water = 0.6 × weight in kg.

For example: a 10 kg infant with a serum sodium of 160 mmol/L. TBW is 0.6 × 10 or 6 L. 6 × (160–145/145) or 6 × 0.1 = 600 mL.

The desired final serum sodium should be 145 mmol/L – the upper limit of normal. In this example, the change from 160 to 145 in the serum sodium should be planned over 36 to 48 h to avoid a fall in serum sodium of greater than 10 mmol/L/24 h. Another approach would be to consider the water deficit to be provided in the next 24 h and set the Na measured – Na desired to 10 mmol. Thus, the same patient above a 10 kg infant with a serum sodium of 160 mmol/L:

1. The patient is at least 10% dehydrated. 10% is 1 L. Provide 50 mL/kg isotonic saline (sodium content 154 mmol/L) over 2–4 h. Reassess signs and symptoms, carefully monitor urine volume, and remeasure serum sodium.
2. Continue isotonic fluid therapy over the next 16–20 h to provide an additional 50 mL/kg to replace extracellular volume. Start water deficit replacement. Total body water is 6 L.

   Na measured = 160, Na desired in the next 24 h – 150 assuring the change in sodium is no greater than 10 mmol/24 h. 160−150 = 10.

   Water deficit = 6 L × (10/150) = 400 mL of free water. Slowly provide the free water over 24 h.
3. Continue monitoring serum sodium every 2 h to assure slow decline of serum sodium. Also continue careful measurement of urine volumes and monitoring of signs and symptoms of dehydration.
4. Provide additional free water the next 24 h (200 mL) and initiate maintenance fluids or oral intake.

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284 Clinical Disorders Associated with Altered Potassium Metabolism

Farahnak Assadi

Pathophysiology

Ninety-eight percent of total body potassium (K^+) is confined to the intracellular compartment, primarily as a result of the activity of the cell membrane Na^+–K^+–ATPase. The intracellular fluid (ICF) K^+ concentration is approximately 120–150 mEq/L, while extracellular fluid (ECF) K^+ concentration is maintained at about 4 mEq/L. Clinically, a subject with an extracellular K^+ concentration of less than 3.5 mEq/L is referred to as *hypokalemia,* while a subject with an extracellular K^+ concentration of more than 5.5 mEq/L is referred to as *hyperkalemia.*

As a primary intracellular cation, K^+ plays an important role in cell growth and division, in the regulation of enzyme activity, and in volume regulation. The considerable concentration difference between intracellular and extracellular K^+ is also essential to the maintenance of the membrane potential. Changes in the intracellular K^+ concentration can therefore have particularly adverse effects on electrically excitable tissues such as the heart and nervous system. In general, both increases and decreases in plasma K^+ concentration can have adverse effects on neuromuscular activity, can suppress intestinal motility, and can cause ventricular arrhythmias. An increase in extracellular K^+ concentration reduces the resting membrane potential, while a decrease in extracellular K^+ concentration increases the resting membrane potential.

The ability to maintain a stable K^+ concentration is dependent on matching K^+ excretion to K^+ intake. For practical purposes, in a 60-kg person, the ECF volume is 12 L. Therefore, the total amount of K^+ contained within the ECF is 12×4 or 48 mEq. A typical daily diet may contain 100 mEq of K^+, 90% of which is reabsorbed into the body. Since this absorbed K^+ initially enters the ECF space, total K^+ content and therefore concentration could also triple ($48 + 90 = 138$ mEq $\div$ 12 L = 11.5 mEq/L. The marked increase in the plasma K^+ is faster than the kidneys to excrete it. However, this does not occur, since plasma K^+ of 11.5 mEq/L would be lethal. How is this avoided? The fact of the matter is that most of the K^+ absorbed from the gastrointestinal tract is initially rapidly taken up into the intracellular pool to prevent abrupt increases in plasma K^+ concentration. This excess K^+ is then excreted in the urine. To maintain overall body homeostasis, the balance concept dictates that if 90 mEq is taken in daily, then 90 mEq must be eliminated daily by the kidney.

This rapid cellular uptake of K^+ is stimulated by insulin and probably by aldosterone. These hormones increase the activity of the Na^+–K^+–ATPase, particularly in muscle, liver, and adipose tissue. The principal stimulus for increased aldosterone release is a rise in plasma K^+. There is also evidence to suggest that insulin release is K^+ sensitive and has an effect on cellular K^+ uptake through absorption of glucose and amino acids from the gastrointestinal tract.

Renal Handling of Potassium

Under normal condition, the filtered load of K^+ is extremely low (4 mEq/L $\times$ 180 L = 720 mEq/day). Approximately 65% of the filtered K^+ is reabsorbed in the proximal tubule. An additional 25% of the filtered K^+ is reabsorbed by the thick ascending limb of the Henle's loop. Thus, approximately 10% of the filtered load of K^+ (72 mEq/day) is delivered to the distal nephron. However, the kidney typically excretes an amount of K^+ that is equivalent to approximately 20% of the filtered load (144 mEq/day). Since only 10% of the filtered load (72 mEq/day) is delivered to the distal nephron, secretion into the tubular lumen must occur at the level of collecting tubule. This is possible because of the principal cells of the collecting tubule are capable of secreting K^+ into the tubular lumen. The rate of K^+ excretion is determined by rate of K^+ secretion into the collecting tubule.

Under conditions of K^+ deficit, tubular secretion effectively stops, and there is further net reabsorption of K^+ along the late segment of the collecting tubule, thereby reducing K^+ excretion to 1–2% of the filtered load (7–14 mEq/day). In contrast, under conditions of K^+ excess, K^+ excretion may reach levels that are equal to or greater than the filtered load. Suppose that plasma K^+

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concentration has increased to 6 mEq/L. Under this condition, the daily filtered load of K^+ would be 180 L/day × 6 mEq/L = 1,080 mEq/day. Approximately 10% of the filtered load, or 108 mEq, is delivered to the distal nephron. However, the amount of K^+ excreted would be greater than the filtered load. Since 108 mEq K^+ is delivered to the distal nephron, this suggests that 972 mEq/day of K^+ (1,080 − 108 mEq) must be secreted by the distal and collecting tubules. Obviously, this quantity of excreted K^+ is not delivered exclusively from the ECF compartment but rather from K^+ fluxes into the ECF from intracellular stores. Several factors can affect the rate of K^+ section including plasma K^+ concentration, tubular flow rate, and a change in ECF pH. Hypertonicity, cell lysis, exercise, and a fall in ECF pH (metabolic acidosis) can cause hyperkalemia as a result of enhanced flux of K^+ from ICF to ECF. In comparison, increased ECF pH (metabolic alkalosis) promotes an efflux of H^+ from the ICF. To maintain electrical balance across the membrane, there is a reciprocal flux of K^+ from the ECF to the ICF, thereby reducing ECF K^+ concentration.

The rate of K^+ secretion increases as ECF K^+ concentration increases. Increase in plasma K^+ directly stimulates aldosterone release which, in turn, increases NA^+–K^+–ATPase activity in the collecting tubule. Any reduction in reabsorptive capacity of proximal tubule and thick ascending tubule reduces K^+ reabsorption, and more K^+ is delivered to the collecting tubule under this condition. In addition, if more sodium is delivered to the distal nephron as a result of the upstream diuretic, sodium reabsorption at this site will be increased. The increased sodium entry into cell stimulates basolateral membrane Na^+–K^+–ATPase activity, and therefore increases intracellular K^+ concentration and also increases lumen-negative potential, thereby increasing the electrical gradient for K^+ efflux across this membrane.

Hypokalemia

Mild hypokalemia (>3.0 mEq/L) rarely causes symptoms and may be treated with oral K^+ supplements. Moderate-to-severe hypokalemia (<3.0 mEq/L) generally produces muscle weakness and may lead to cardiac and respiratory failure and require intravenous K^+ supplementation. Other symptoms may include nausea, vomiting, illus, tetany, and cardiac arrhythmias and ECG abnormalities (ST segment depression, short T wave with the appearance of U wave at the end of T wave.

Hypokalemia can result from poor intake, excessive loss from the body, or sudden shift of K^+ from extracellular fluid into cells. The most common causes are excess losses from the kidneys or gastrointestinal tract. The most common mechanisms leading to hypokalemia is increased urinary losses due to increased sodium delivery to distal nephron. Typically, this is often associated with mineralocorticoid excess, use of diuretics, or losses associated with increased urine flow, such as osmotic diuresis. Hypomagnesemia can also cause hypokalemia. Magnesium is required for adequate renal handling of K^+. This may become apparent when hypokalemia persists despite K^+ supplementation. A special case of K^+ loss occurs with diabetic ketoacidosis. In addition to urinary losses from polyuria and volume depletion, there is also obligate loss of K^+ from renal tubules as a cation partner to the negatively charged β-hydroxybutyrate. Familial hypokalemic periodic paralysis is a rare autosomal-dominant disease characterized by transient episodes of profound hypokalemia due to a sudden transcellular shift of K^+ into cells. Episodes are typically precipitated by a large carbohydrate meal or strenuous exercise, but variants have been described without these features.

Diagnostic Approach

It is helpful to proceed to the diagnosis of hypokalemia from the history, physical examination, and laboratory studies in a stepwise fashion. Potential processes that can be identified in the history include diet, vomiting, diarrhea, and the use of laxatives, insulin, diuretics, or bicarbonate supplements and muscle weakness and polyuria. First, check the urinary K^+ excretion in a random urine sample to differentiate between gastrointestinal and urinary losses as the major contributor. Next, evaluate acid–base and blood pressure status to help in the differential (Fig. 284.1).

A random urine K^+ value <15 mEq/L is evidence of appropriate urinary K^+ excretion and suggests poor intake, gastrointestinal losses, or a shift of potassium into cells. If hypokalemia is associated with episodic muscle weakness, then consider hyperthyroidism, familial or sporadic periodic paralysis. In the presence of metabolic alkalosis and a urine K^+ <15 consider surreptitious vomiting or congenital pyloric stenosis. A random urine K^+ value ≥ 15 mEq/L indicates renal K^+ wasting.

In a patient with a urine K^+ >15 who denies diarrhea, consider diabetic ketoacidosis or renal tubular acidosis (RTA-1 and RTA-2) in the presence of metabolic acidosis. The presence of hypertension, coexistent metabolic alkalosis, and urine K^+ >15 indicates that all causes of primary

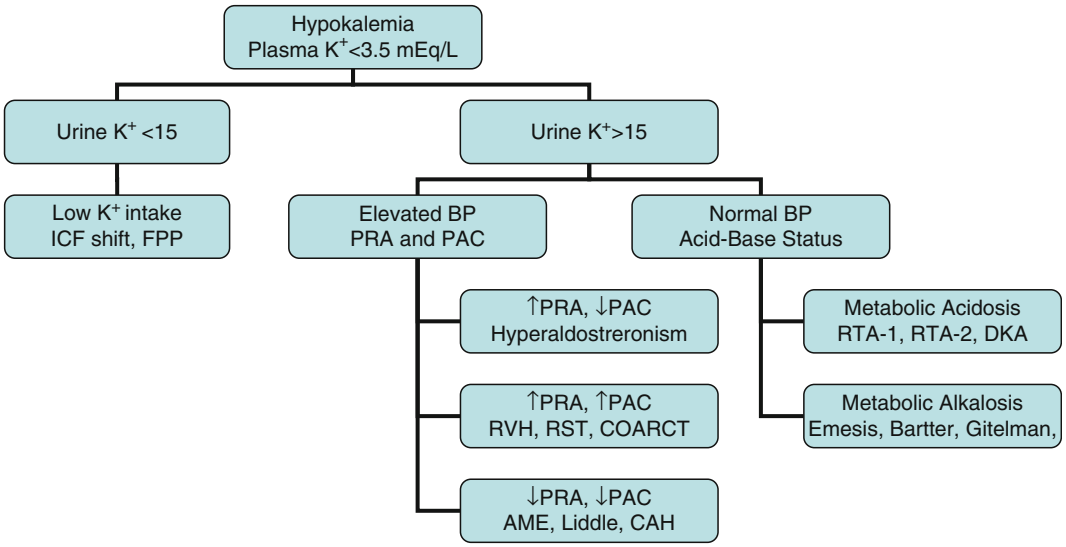

Figure 284.1

Diagnostic algorithm in hypokalemia. *Cr* creatinine, *ICF* intracellular fluid, *FPP* familial periodic paralysis, *BP* blood pressure, *PRA* plasma renin activity, *PAC* plasma aldosterone concentration, *RVH* renal vascular hypertension, *RST* renin-secreting tumor, *COARCT* coarctation of the aorta, *MAE* apparent mineralocorticoid excess, *CAH* congenital adrenal hyperplasia, *RTA* renal tubular acidosis, *DKA* diabetic ketoacidosis

and secondary hyperaldosteronism, Liddle syndrome, diuretic abuse in a patient with hypertension, as well as the various forms of apparent mineralocorticoid excess (AME). Measurements of plasma renin and aldosterone levels are necessary to differentiate these conditions.

Primary aldosteronism should be suspected when plasma renin activity (PRA) is suppressed and plasma aldosterone concentration (PAC) is increased. Secondary hyperaldosteronism (e.g., renal vascular hypertension, rennin-secreting tumor, and coarctation of the aorta) should be suspected when both plasma PRA and PAC are increased.

Liddle syndrome is a rare autosomal-dominant disorder characterized by severe hypertension, metabolic alkalosis, and hypokalemia. Liddle syndrome is caused by a genetic abnormality that increases the activity of the collecting tubule sodium channel in the absence of mineralocorticoid excess.

The presence of AME should be considered when both PRA and PAC are suppressed. The syndrome of AME is an autosomal-recessive form of hypertension in which 11-β hydroxysteroid dehydrogenase is defective. This enzyme converts cortisol to its inactive metabolite, cortisone. Because mineralocorticoid receptors themselves have similar affinitive for cortisol and aldosterone, decreased enzyme activity allows these receptors to be occupied by cortisol, which circulates at much higher plasma level than aldosterone. This can also occur in patients with congenital adrenal hyperplasia (17-α-hydroxylase deficiency) or familial cortisol resistance and in patients with severe Cushing syndrome. Licorice contains glycyrrhetinic acid and mimics the hereditary AME syndrome because it inhibits 11-βhydroxysteroid dehydrogenase. Diagnosis of AME syndrome is usually done by demonstration of an excess of free urinary cortisol over free urinary cortisone in a 24-h urine collection, although genetic testing can identify the congenital defect.

In the absence of hypertension, coexistent metabolic alkalosis associated with urine $K^+ > 15$, high levels of PRA and PAC are consistent with surreptitious vomiting, diuretic abuse, Bartter syndrome, or Gitelman syndrome. Bartter syndrome is caused by mutations in a furosemide-sensitive ion transport mechanism in the loop of Henle and is associated with hypercalciuria. Gitelman syndrome is caused by loss of function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron and is associated with hypocalciuria. The differential rests upon measurement of urine calcium excretion, diuretic screen in urine, and genetic testing. A patient with Gitleman syndrome, unlike patients with Bartter syndrome, their calcium excretion is normal.

Treatment

Intravenous K^+ must be given to patients with severe hypokalemia (serum K^+ <2.5–3.0 mEq/L) or symptomatic (arrhythmias, marked muscle weakness) patients. Typically, 0.9% of saline is infused with 40 mEq KCl per liter at a rate of 10 mEq/h over 3–4 h. Giving intravenous K^+ at faster rate is not recommended as it may predispose to ventricular arrhythmia. Glucose solutions are avoided because elevation in the plasma insulin levels could result in transient worsening of hypokalemia. When giving K^+ intravenously, infusion via central line is encouraged to avoid the rare occurrence of phlebitis. Hypokalemia due to the renal losses of K^+ may be amenable to a K-sparing diuretic such as amiloride or spironolactone, as these diuretics reduce the renal excretion of K^+.

Hyperkalemia

In many patients, the cause of hyperkalemia is multifactorial and never clearly defined. The most common are renal disease, the ingestion of medications known to cause hyperkalemia or aldosterone deficiency. Other less common causes of hyperkalemia include massive crushing injury with resultant muscle damage, burns, high-volume blood transfusions, human immunodeficiency virus infection, tumor lysis syndrome, congenital adrenal hyperplasia, autosomal-dominant pseudohypoaldosteronism type 1, autosomal-dominant pseudohypoaldosteronism type 2 (Gordon syndrome), and hyperkalemic familial periodic paralysis.

The signs and symptoms induced by hyperkalemia are related to impaired neuromuscular transmission. Symptoms generally do not become manifest until the plasma K^+ concentration is >7.0 mEq/L or the rise in plasma K^+ concentration has been rapid. Muscle weakness, respiratory muscle weakness, cardiac conductive abnormalities (tall peaked T wave with shortened QT, prolonged PR interval, and wide QRS) are the most common manifestations. Other symptoms related to the underlying cause may be present, such as hypertension, renal failure, or diabetes mellitus.

Asymptomatic patients with a plasma K^+ concentration of <6.5 mEq/L whose electrocardiogram does not manifest signs of hyperkalemia can be treated with a cation exchange resin, a low potassium diet, and diuretics. In comparison, patients with plasma K^+ concentration of $\geq$ 7.0 mEq/L with severe muscle weakness or cardiac conduction abnormality require immediate treatment. The quickest, most efficient way to remove K^+ is through the use of hemodialysis. Hemodialysis should be instituted in patients with renal failure or if emergency treatment is ineffective.

Diagnostic Approach

The diagnosis of hyperkalemia must be considered in any patient with clinical risk factors that would predispose them to its development. Measurement of urinary K^+ excretion is of limited value in patients with persistent hyperkalemia, as most patients have underlying renal dysfunction, aldosterone deficiency, or are taking a medication known to impair urinary K^+ excretion. Patients should be questioned about the use of any drug that can impair K^+ excretion, such as angiotensin converting enzyme inhibitors, K^+-sparing diuretics, nonsteroidal anti-inflammatory drugs, heparin, cyclosporine, or the presence of a disease that can impair K^+ excretion such as diabetes mellitus, renal failure, Addison disease, and acquired immune deficiency syndrome. These conditions can be differentiated by measurement of serum electrolytes, BUN, creatinine, plasma renin activity, plasma aldosterone, and cortisol levels. Hyperkalemic patients with normal renal function, normal sodium handling, and aldosterone release who deny taking any medication probably have a selective impairment of K^+ secretion (*Fig. 284.2*).

Treatment

The initial treatment of severe hyperkalemia should be the infusion of calcium. Calcium antagonizes the effects of hyperkalemia at the cellular level to prevent the development of fatal cardiac arrhythmias. Calcium gluconate is the preferred preparation of intravenous calcium. The dose should be 10 mL of a 10% calcium gluconate solution infused over 2–3 min.

The effects of intravenous calcium occur within 1–3 min but last for only 30–60 min. Therefore, further, more definitive treatment is needed to lower serum potassium levels. Insulin, with glucose, and β_2-adrenergic agonists should then be quickly administered to decrease extracellular K levels. Intravenous insulin (10 units) is typically given, followed by close monitoring of serum blood sugar. Fifty milliliter of 50% dextrose is frequently coadministered with insulin in normoglycemic patients to prevent hypoglycemia. The effect of the insulin is seen within 10–20 min of administration and can be expected to decrease K^+ level by 0.6–1.0 mEq/L.

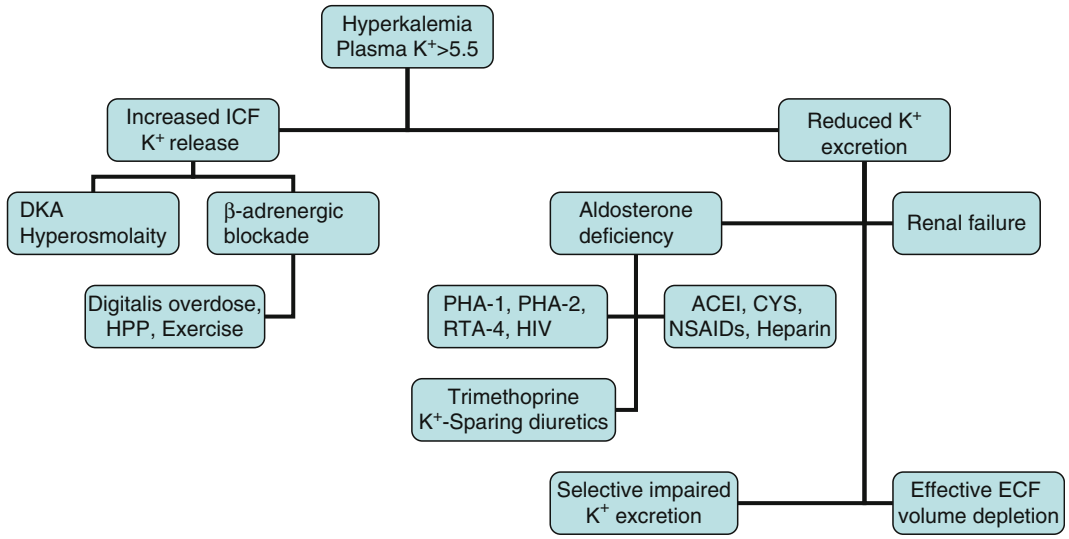

Figure 284.2

Diagnostic algorithm in hyperkalemia. *DKA* diabetic ketoacidosis, *HHP* hyperkalemic periodic hyperkalemia, *PHA*-1 pseudohypoaldosteronism type 1, *PHA*-2 pseudohypoaldosteronism type 2, *RTA*-4 renal tubular acidosis type 4, *HIV* acquired immune deficiency syndrome, *ACEI* angiotensin converting enzyme inhibitor, *NSAIDs* nonsteroidal anti-inflammatory drugs

Nebulized albuterol, when given in very high doses (10–20 mg), can safely lower plasma K^+ level by 0.5–1.5 mEq/L. The onset of action for inhaled albuterol is immediate and lasts for 1–2 h. Sodium bicarbonate infusion can shift K^+ from the extracellular to intracellular space by increasing blood pH. However, sodium bicarbonate therapy has little use in the routine treatment of hyperkalemia unless severe metabolic acidosis is present or there is another indication for its administration. Ion exchange resins can be administered orally or rectally and work by exchanging gut cations, most importantly K^+, for sodium ions that are released from the resin. Most studies have found exchange resins to decrease serum K^+ levels by about 1 mEq/L over a 24-h period.

Exchange resins can cause significant constipation and are typically given in combination with a laxative such as sorbitol. Although generally safe, the combination of a resin and sorbitol has been reported to cause intestinal necrosis, and as such should be used cautiously and only when necessary.

Case Study

A 15-year-old girl was referred for evaluation of hypokalemia. She has no significant past medical history and denies the use of any medications. Recently, she began to experience occasional fatigue and muscle weakness during exercise. She also noted occasional abdominal pain for which she saw her regular physician. Laboratory studies in the office indicated hypokalemia and she was referred to you for evaluation. Repeat laboratory data show hemoglobin 13 g/dL, BUN 16 mg/dL, serum creatinine 1.0 mg/dL, sodium 140 mEq/L, K^+ 2.4 mEq/L, chloride 101 mEq/L, $HCO3^-$ 32 mEq/L, calcium 9.0 mg/dL, phosphate 3.9 mg/dL, magnesium 1.2 mg/dL, and albumin 4.6 g/dL.

If we proceed in a stepwise fashion to make the diagnosis, which study would be the best initial laboratory study for the diagnosis of the altered electrolytes disorders?

(a) Urine diuretic screen
(b) 24-h urine for calcium, magnesium, and creatinine
(c) Plasma renin and aldosterone levels
(d) Arterial blood gas
(e) 24-h urine for sodium, K^+, and creatinine

The answer is b. Measurement of the urinary magnesium excretion will help to distinguish between gastrointestinal loss of magnesium and renal magnesium wasting.

The urinary magnesium excretion was 120 mg/day, the urinary calcium 485 mg/day, and urinary creatinine 820 mg/dL.

Which diagnoses should receive further consideration (select all that apply)?

(a) Primary aldosteronism
(b) Bartter syndrome
(c) Laxative abuse
(d) Primary renal magnesium wasting
(e) Loop diuretic abuse
(f) Gitelman syndrome

The answers are b and e. Metabolic alkalosis, hypercalciuria (calcium to creatinine ratio 0.59), renal magnesium wasting, and hypomagnesemia all can occur in Bartter syndrome. Diuretic abuse is also a good choice because it causes the same type of transport defect.

Which study would you like now to differentiate between Bartter syndrome and diuretic abuse?

(a) Urine diuretic screen
(b) 24-h urine for calcium, magnesium, and creatinine
(c) 24-h urine for sodium, K^+, and creatinine
(d) Plasma renin and aldosterone levels

The answer is a. A diuretic screen is the only way to rule out diuretic abuse.

The urine diuretic screen was negative. However, the laboratory calls to tell you that the urinary calcium excretion in the 24-h collection was misreported – the correct value is 120 mg/24-h, not 485.

What is the likely diagnosis now? (select all that apply)

(a) Bartter syndrome
(b) Gitelman syndrome
(c) Primary aldosteronism
(d) Primary renal magnesium wasting

The answer is b. Gitelman syndrome is the only one of these conditions which is associated with hypercalciuria. Gitelman syndrome is a variant of Bartter syndrome, characterized by hypokalemia, hypomagnesemia, hypocalcemia, and hypovolemia.

Which ONE of the following statements is true?

(a) Hypokalemia can alter the renal handling of magnesium and cause hypomagnesemia
(b) Hypomagnesemia can alter the renal handling of K^+ and cause hypokalemia
(c) Both statements are true
(d) Neither statement is true?

The answer is b. Hypomagnesemia causes renal K^+ wasting likely by opening K^+ channels in the cortical thick ascending limb of the Henle's loop. For this reason, the diagnosis of combined hypokalemia and hypomagnesemia is best approached by considering causes of hypomagnesemia.

Case Study

A 19-year-old female who has had diabetes mellitus for more than 7 years was admitted to the emergency department because of a recent history of pneumonia. The diabetes has been in good control as a result of dietary measures and the use of oral hypoglycemic drug. She lost her appetite and noted more frequent voiding especially during the night. On examination, she was acutely ill, her mucous membranes were dry, temperature 38.5 C, blood pressure 127/75 mmHg, heart rate 130 beats/min, and respiratory rate 24 breaths/min. Urine was collected for 1 h, and the volume was 250 mL. Urinalysis revealed pH 6.0, specific gravity 1.012, glucose, 4+, ketones, trace, blood and protein negative. Urine osmolality was 305 mosm/kg, sodium 25 mEq/L, and K^+ 30 mEq/L. A venous blood sample revealed sodium 132 mEq/L, K 5.8 mEq/L, chloride 90 mEq/L, bicarbonate 24 mEq/L, glucose 750 mg/dL, creatinine 1.5 mg/dL, and BUN 40 mg/dL.

Which ONE of the following statements about this patient's potassium stores is MOST correct?

(a) The total body K^+ is increased due to volume contraction
(b) The total body K^+ is reduced due to osmotic diuresis
(c) Total body K^+ is increased due to metabolic acidosis
(d) The total body K^+ is normal

The correct answer is b. This patient was experiencing many of the symptoms of uncontrolled diabetes mellitus such as high blood glucose concentration and high glucose content of the urine. Plasma K^+ concentration is in the hyperkalemic range. High blood glucose concentration creates an osmotic driving force for efflux of water out of the intracellular space. As a result, intracellular K^+ concentration rises, which in turn increases the efflux of K into the ECF. The lack of insulin or reduced responsiveness to endogenous insulin also reduces the uptake of K^+ into intracellular stores. The urine volume was also very high. The 1-h collection of 250 mL translated to a daily urine output of 6 L. This increased urine output was caused by the high filtered load of glucose, which acts as an osmotic diuretic, and the increased urine flow rate contributed to the high rate of K^+ excretion of 180 mEq/day. Since this patient was not eating as a result of the pneumonia, this rate of K^+ excretion almost certainly exceeded intake. Therefore, despite an elevated

extracellular K^+ concentration, her total body K was probably reduced.

Which ONE of the following evaluation strategies would be MOST appropriate when ACE inhibitor is initiated in a patient with serum creatinine of 2.6 mg/dL and urinary protein excretion of 2.0 g/day?

(a) Evaluate serum K^+ and creatinine levels 2 weeks after initiating therapy, and stop therapy if hyperkalemia cannot be controlled by loop diuretics and dietary counseling, or if the serum creatinine increases >30% over baseline level.
(b) Evaluate serum K^+ and serum creatinine 2 months after initiating therapy
(c) Use of ACE inhibitor is contraindicated in such patient
(d) Such therapy should only be used in patients with type 1 diabetes mellitus

The correct answer is a. The risk of hyperkalemia in patients who would benefit from ACE inhibitor therapy can be minimized by the appropriate use of diuretics, a low potassium diet, and the use of low dose of potassium-binding resin. If metabolic acidosis is present, sodium bicarbonate should be given.

Case Study

A 17-year-old boy with type 1 diabetes mellitus and chronic renal disease develops muscle weakness. Laboratory data include serum sodium 128 mEq/L, K^+ 7.4 mEq/L, bicarbonate 15 mEq/L, Bun 63 mg/dL, creatinine 3.1 mg/dL, and glucose 276 mg/dL. When an electrocardiogram shows peaked T wave, he is given calcium gluconate.

In addition to this treatment, which ONE of the following would be the most consistently effective therapy for his hyperkalemia?

(a) Subcutaneous insulin and a slow intravenous infusion of glucose
(b) β2-adrenergic agonist
(c) Intravenous insulin
(d) Intravenous bicarbonate
(e) Oral cation exchange resin (Kayexalate)

The answer is c. Insulin directly activates Na^+–K^+–ATPase, augmenting cellular uptake of K^+. Concurrent administration of glucose is only necessary to prevent hypoglycemia Administration of 20 units of intravenous insulin causes a 1-mEq/L decrease in serum K^+ in less than 1 h. Intravenous insulin is preferable to subcutaneous insulin because the bolus infusion produces much higher plasma insulin level. β2-adrenergic agonist, like albuterol, also activates Na^+–K^+–ATPase, but approximately 20% of patients are resistant to this therapy and it is not possible to predict who will not respond. Serum bicarbonate and the cation exchange resin (Kayexalate) take several hours to lower the serum K^+ level.

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285 A Practical Approach to Metabolic Acidosis

Farahnak Assadi

Pathophsiology

Hydrogen (H^+) concentration in the body is governed by a balance between intake and output. Most H^+ in the body is generated indirectly in the cells from formation of the ingested nutrients. It is the free H^+ concentration in the body (measured as pH) that is physiologically important. At a normal plasma pH of 7.40, the free H^+ concentration is 40 nmol/L. Metabolism of carbohydrates, proteins, and fats in the cells can generate a large amount of free H^+. However, the buffer system, the lungs, and the kidneys act in an integrated fashion to minimize any change in free H^+ concentration. Buffers are molecules that accept or donate free H^+. Phosphate, HCO_3^-, protein and hemoglobin are some of the most important buffers in the body.

The kidney regulates plasma HCO_3^- by secreting H^+ into the tubular lumen and returning HCO_3^- to the blood. The kidney forms titratable acids by combining H^+ with buffers in the tubular fluid. The H^+ generated from CO_2 and H_2O by carbonic anhydrase in the cell is secreted into the tubule lumen and combines with a titratable acid (HPO_4^{2-} to H_2PO_4). The titratable acids are then excreted in the urine. In the process of secreting H^+, the kidney simultaneously replenishes the plasma HCO_3^- used in the buffering. The net result is excretion of a bound H^+ and the formation of new HCO_3^-, which is added to the body. Although HPO_4^{2-} is the major titratable acid in the urine, any compound that can combine with the secreted H^+, including creatinine, sulfate, and the anion of fatty acids, may serve the function of a titratable acid and be excreted in the urine.

The kidney also forms NH_4^+ in the tubule fluid by combing secreted H^+ with lipid soluble NH_3 generated by the renal tubule cells ($NH_3 + H^+ \leftrightarrow NH_4^+$). The resulting NH_4^+ in the tubular fluid is lipid insoluble and is trapped. The NH_4^+ is then excreted in the urine, and the HCO_3^- is returned to the body as new HCO_3^-. Chronic increases in plasma H^+ concentration stimulates the production of NH_3 by the renal tubule cells.

The primary function of the kidney in the regulation of acid–base balance is to conserve the body store of HCO_3^- and maintain the plasma HCO_3^- concentration constant. Increased filtered HCO_3^-, increased plasma H^+ concentration, and increased arterial P_{CO2} increase renal tubular H^+ secretion and HCO_3^- generation. Aldosterone increases tubular H^+ secretion and HCO_3^- generation by stimulating H^+-ATPase in the distal nephron. Aldosterone also stimulates Na^+ reabsorption in distal nephron, resulting in increased H^+ secretion.

The simplest way to increase the body HCO_3^- stores is to increase its generation in the kidney. However, the major stimulus for HCO_3^- generation in the renal tubular cells is the arterial P_{CO2}, but because of the respiratory compensation, the P_{CO2} is decreased. Where then is the stimulus for increased HCO_3^- generation? The answer to this question lies in the quantitative relationship between the filtered load of HCO_3^- and H^+ secreted by the kidney. It has been shown that in both metabolic acidosis and metabolic alkalosis there is an advantageous physiologic mismatch between filtered HCO_3^- and the amount of H^+ secreted, so that the plasma HCO_3^- concentration eventually returns to normal levels. Therefore in the case of metabolic acidosis, the H^+ secretion is decreased, but it is still sufficient to reabsorb all the filtered HCO_3^- and increase the amount of new HCO_3^- (50–60 mEq) returned to the plasma as a result of the formation of titratable acids and NH_4^+. For every titrarable acid and NH_4^+ excreted in the urine, a new HCO_3^- is added to the plasma. The relationship between plasma HCO_3^- and P_{CO2} can be accurately estimated as determined by the Henderson–Hasselback equation:

$$[H^+] = 24(P_{CO2}) \div (HCO_3^-)$$

Diagnostic Approach

A metabolic acidosis can be characterized by decreased plasma HCO_3^- and a compensatory decrease in arterial P_{CO2}. The respiratory compensation for a metabolic

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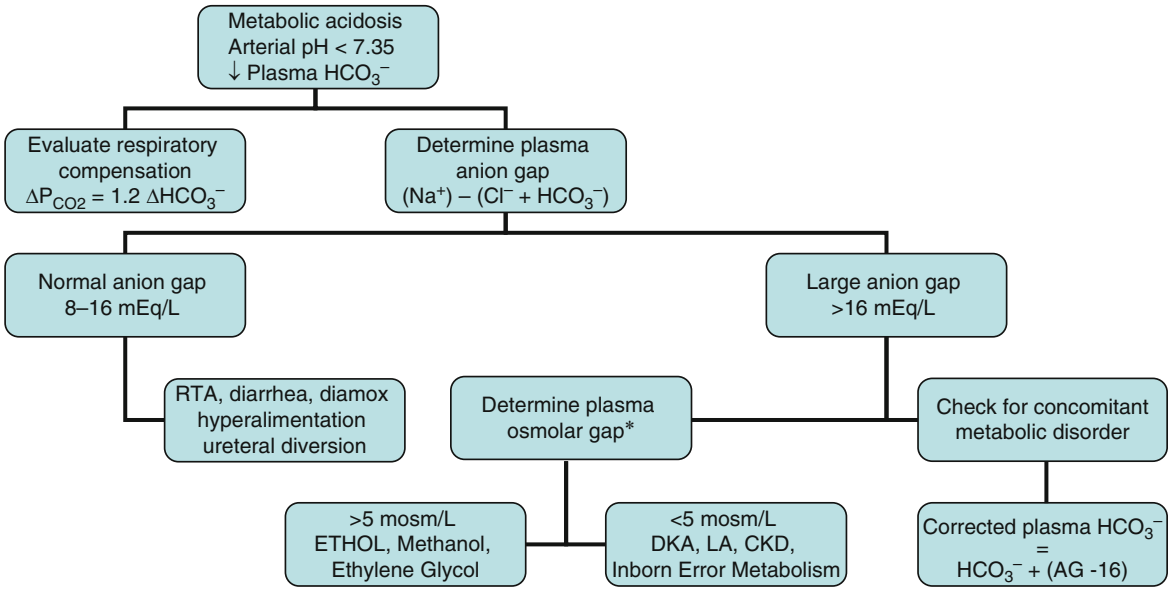

Figure 285.1

Diagnostic algorithm in patients with metabolic acidosis. DKA; diabetic ketoacidosis LA; lactic acidosis, CKD, chronic kidney disease. *osmolar gap is calculated as the differences between measured plasma osmolality and estimated plasma osmolality [2 (Na^+) + (BUN/mg/dL ÷ 2.8) + (glucose/mg/dL ÷ 18)]

acidosis is hyperventilation and an appropriate decrease in arterial P_{CO2} to minimize the acid–base disturbance. The diagnostic approach to metabolic acidosis utilizes information from the history and physical examination, and laboratory studies in a stepwise fashion (*Fig. 285.1*).

Step 1: Review history and physical examination – Identify potential processes in the history, and recognize the situations that often are associated with metabolic acidosis and review the physical examination for clue to diagnosis. Potential processes which can be identified in the history include diarrhea, diabetic ketoacidosis, renal failure, hypotension, hypoxia, sepsis, cardiopulmonary arrest, and inborn error of metabolism.

Step 2: Evaluate serum electrolytes and calculate serum anion gap – Diagnosis of the underlying causes of metabolic acidosis can be simplified by determining whether the disorder is associated with an increased or a normal anion gap. The anion gap is the concentration differences between the major cation, sodium, and the two major anions, chloride and HCO_3^-. In a normal individual, it typically ranges between 10 and 16 mEq/L with the sodium concentration greater than the sum of the chloride and HCO_3^- concentrations. This does not mean that the plasma is not electrically neutral. The anions are there, but they are simply not measured during a routine chemical analysis of the plasma.

$$\text{Anion gap} = (Na^+) - (Cl^- + HCO_3^-)$$

Metabolic acidosis occurring with a normal anion gap is usually caused by either gastrointestinal bicarbonate loss or renal tubular acidosis and the use of carbonic anhydrase inhibitors. Normal anion gap acidosis has also been reported in ureteral diversions, NH_4Cl infusions, and during hyperalimentation. The anion gap acidosis can be divided into five major categories: (1) renal failure; (2) ketoacidosis (diabetes, hypoglycemic ketoacidosis); (3) lactic acidosis (hepatic failure, circulatory failure, sepsis); (4) drugs and poisons (salicylate, paraldehyde, ethanol, ethylene glycol); and (5) inborn errors of metabolism. One important exception must be considered at this point. First, a patient may have an anion gap acidosis even with a normal anion gap. Because one of the most important unmeasured anions is albumin, a patient who is severely hypoalbuminemic may have a normal anion gap of only 4 or 5. In such a patient, an anion gap of 12 would represent a significant elevation and indicate the presence of an anion gap acidosis. Disorders associated with low serum albumin levels include cirrhosis, nephrotic syndrome, and severe malnutrition.

Step 3: Assess the degree of respiratory compensation – Is the respiratory system compensating adequately? The response of the respiratory system (i.e., the degree of

hyperventilation) is predictable because there is a linear relationship between P_{CO2} and serum HCO_3^- concentration in metabolic acidosis. In simple metabolic acidosis for each mEq decrease in HCO_3^- there is a 1.2 mEq decrease in the arterial P_{CO2}.

$$\text{Expected fall in } P_{CO2} = 1.2(25 - \text{patient's } HCO_3^-) \text{ or}$$
$$\Delta P_{CO2} = 1.2\ \Delta HCO_3^-$$

To illustrate, a patient with a measured serum HCO_3^- level of 10 mEq/L should have a P_{CO2} of 22 mmHg [(ΔP_{CO2} = 1.2 ΔHCO_3^- or 18; P_{CO2} (40–18)]. If this patient's P_{CO2} is outside the range of 22 mmHg, a primary respiratory disorder exists in addition to the metabolic acidosis. In this case, a $P_{CO2} < 22$ mmHg indicates a concomitant primary respiratory alkalosis. If the same patient had a $P_{CO2} > 22$ mmHg, a primary respiratory acidosis would be indicated even though the P_{CO2} is subnormal.

Step 4: **Identify concomitant metabolic disorder** – Is the anion gap increased above normal value (>16 mEq/L)? If yes, there should be concordance between the fall in the HCO_3^- concentration and the increase in anion gap. This relationship works because, for each mEq increase in the anion gap, there is a mEq decrease in the serum HCO_3^- concentration.

As an example, a patient who presents with diabetic ketoacidosis has serum HCO_3^- of 15 mEq/L and anion gap of 26 mEq/L. The anion gap has increased by 10 mEq/L from a normal value of 16 mEq/L. The HCO_3^- has fallen by 10 from a normal value of 25. Therefore, the concordance in the change in the HCO_3^- and the anion gap is consistent with a simple disturbance of metabolic acidosis.

$$\text{Corrected } HCO_3^- = \text{patient's } HCO_3^- + (\text{aniongap} - 16)$$

However, if the values were HCO_3^- 10 mEq/L and anion gap 22 mEq/L, concordance. would be lacking because the anion gap had increased by 6 from the normal value while the HCO_3^- had fallen by 15 from the normal value. Thus, some process in addition to increased metabolic acid production is contributing to the fall in HCO_3^- without affecting anion gap. This could be due to a concomitant respiratory acidosis or a mixed anion gap acidosis with a normal anion gap acidosis.

Case History

A 10-year old girl is brought to the emergency department because of increasing weakness. She has been having low grade fever and severe diarrhea for 4 days. Laboratory studies reveal sodium 140 mEq/L, potassium 2.4 mEq/L, chloride 115 mEq/L, HCO_3^- 15 mEq/L, BUN 18 mg/dL, creatinine 0.6 mg/dL, glucose 90 mg/dL, calcium 9.5 mg/dL, and plasma osmolality 284 mosm/L.

What Do You Estimate Her Arterial pH and p_{CO2} to be?

A. 7.20
B. 7.25
C. 7.30
D. 7.35
E. 7.40

The answer is C. The acid–base disturbance diagnosis is a simple metabolic acidosis due to severe diarrhea. This would allow estimating her P_{CO2} using the following equation:

$$\Delta P_{CO2} = 1.2(\Delta HCO_3^-) \text{ or } 12 \text{ mmHg}$$

$$\text{Predicted } P_{CO2} = 40 - 12 \text{ or } 28 \text{ mmHg}$$

The pH can then be calculated with the modified Henderson–Hasselback equation:

$$H^+ = 24(P_{CO2}) \div HCO_3^-$$

The value obtained is 45 nmol/L, which is equivalent to a pH of 7.35 (every 0.1 fall in pH is equivalent to a 10 nmol rise in blood H concentration).

Case History

A 19-year old male was found unconscious on the street and was brought into the emergency room. The patient was stuporous without focal neurological signs. Temperature was 37°C, blood pressure 120/80 mmHg, pulse 80 beats/min, and respiratory rate 20/min. Examination of the head, eyes, ears, nose, and throat was unremarkable. Chest was clear to auscultation and percussion. The remainder of the physical examination was unremarkable. Laboratory data showed a serum sodium concentration of 144 mEq/L, potassium 4.6 mEq/L, chloride 103 mEq/L, HCO_3^- 15 mEq/L, BUN 20 mg/dL, creatinine 0.7 mg/dL, and glucose 95 mg/dL. Serum ketones were trace positive and serum osmolality was 330 mosm/L. An arterial pH was 7.34 and P_{CO2} 28 mmHg.

What Is the Acid–Base Diagnosis?

A. Metabolic acidosis with respiratory acidosis
B. Metabolic acidosis with respiratory compensation
C. Metabolic compensation for respiratory alkalosis
D. Metabolic alkalosis with respiratory compensation

The answer is B. The blood gas data are compatible with anion gap metabolic acidosis and an appropriate respiratory compensation. The plasma HCO_3^- concentration decreased by 10 mEq/L and the P_{CO2} is depressed by 12 mmHg ($\Delta P_{CO2} = 1.2\ \Delta HCO_3^-$). Thus, the predicted P_{CO2} is 28 (40–12) mmHg. This level of respiratory compensation is appropriate for the steady state level of HCO_3^-.

What Is the Likely Cause of the Anion Gap Metabolic Acidosis in This Patient?

A. Alcohol intoxication
B. Primary lactic acidosis
C. Toxic ingestion (methanol, ethylene glycol)
D. Renal failure
E. Starvation ketoacidosis

The answer is A. The anion gap is 26 and it has increased by 10 from a normal value of 16 mEq/L. The HCO_3^- has also fallen by 10 from a normal value of 25 mEq/L. Thus, the concordance in the HCO_3^- and the anion gap is consistent with a simple metabolic disturbance. The potential causes of anion gap metabolic acidosis include starvation ketoacidosis, diabetic ketoacidosis, alcohol intoxication, methanol intoxication, ethylene glycol intoxication, lactic acidosis, inborn error of metabolism, and renal failure. In this patient, blood ketones are only trace positive, and the serum creatinine and blood glucose levels are normal. However, the measured serum osmolality is considerably higher than the estimated osmolality.

The difference between the measured and the estimated serum osmolality is often termed the osmolal gap. Methanol intoxication, ethylene glycol intoxication, and alcohol intoxication are disorders associated with anion gap metabolic acidosis and increased serum osmolality (osmolar gap). The measured serum osmolality in this patient was 330 mosm/L and the estimated serum osmolality 300 mosm/L ($2\ Na^+$ + BUN (mg/dL) ÷ 2.8 + glucose (mg/dL ÷18), giving an osmolal gap of 30 mosm/L. The patient had no oxalate crystals in the urine as found in the ethylene glycol intoxication and there was no evidence of optic papillitis on fundoscopic examination as might be anticipated in a patient with methanol intoxication. Thus, this patient's clinical and laboratory studies are consistent with acute alcohol intoxication. A very high blood alcohol level supported this diagnosis.

Case History

You are asked to see a 4-year old boy found to be stuporous at home. On examination, he appears well developed; stuporous; his temperature is 37°C; blood pressure, 114/65 mmHg; pulse, 88 beats/min; respiratory rate, 34/min; weight, 25 kg; and height, 88 cm. The heart rate is regular; there are no extra sounds or murmurs. The lungs are clear without rales or rhonchi. The abdomen is soft without palpable masses or organomegaly. Bowel sounds are present. There is no edema. Several ecchymoses are present over his trunk and limbs. Laboratory data reveals serum sodium 140 mEq/L, potassium 3.8 mEq/L, chloride 108 mEq/L, HCO_3^- 13 mEq/L, BUN 14 mg/dL, creatinine 0.6 mg/dL, glucose 89 mg/dL, calcium 9.3 mg/dL, albumin 4.0 g/dL, ketones 2+, plasma osmolality 284 mosm/L, arterial pH 7.36, and P_{CO2} 20 mmHg.

What Is the Acid–Base Diagnosis? (Select All that Apply)

A. Metabolic acidosis and respiratory acidosis
B. Metabolic alkalosis and respiratory acidosis
C. Metabolic acidosis and respiratory alkalosis
D. Metabolic alkalosis and respiratory alkalosis

The answer is C. This is a mixed disturbance of metabolic acidosis and chronic respiratory alkalosis. The P_{CO2} is decrease by 20 and the plasma HCO_3^- is decreased by 12. If this were a single metabolic acidosis, the fall in P_{CO2} should be 14 ($\Delta P_{CO2} = 1.2\ \Delta HCO_3^-$) and as a result the predicted P_{CO2} should be 26 (40 − 14) not 20. Therefore, there is a mixed disturbance with metabolic acidosis and respiratory alkalosis. Laboratory data also reveal that the anion gap is 19, and it has increased by 3 from a normal value of 16 mEq/L. The increased anion gap is consistent with the presence of large anion gap metabolic acidosis. However, the fall in bicarbonate concentration (−12 mEq/L) is greater than the increase in the anion gap (+9 mEq/L) suggesting the presence of another process which lowers the HCO_3^-; either chronic respiratory alkalosis or non-anion gap metabolic acidosis. The physical exam suggests that hyperventilation is present, which could indicate severe acidosis or primary alkalosis. The combination of anion gap metabolic acidosis and primary respiratory alkalosis occurs in several situations including

sepsis, salicylate intoxication, and the lactic acidosis in a patient with liver failure. Salicylate intoxication is the likely diagnosis in this patient in view of the presence of ecchymoses.

Case History

A 17-year old male was admitted to the emergency department in a semicomatose condition. Blood pressure was 110/70 mmHg; pulse, 87/min; and respiratory rate, 22/min. Laboratory data on admission revealed serum sodium of 135 mEq/L, potassium 2.1 mEq/L, chloride 111 mEq/L, and HCO_3^- 10 mEq/L. Arterial blood pH was 7.1 and P_{CO2} 33mmHg. Urinalysis showed a pH of 7.0. The urine sediment was normal. The patient was intubated, and potassium was given intravenously.

What Is the Most Likely Diagnosis? (Select All that Apply)

A. Proximal renal tubular acidosis (RTA-2)
B. Distal renal tubular acidosis (RTA-1)
C. Hyperkalemic distal renal tubular acidosis (TRA-4)
D. All of the above

The answer is B. The clinical diagnosis is distal renal tubular acidosis (RTA-1). This patient has normal anion gap metabolic acidosis and hypokalemia with an inappropriately high urine pH. The normal anion gap metabolic acidosis is complicated with respiratory acidosis. If this were a single metabolic acidosis, the fall in P_{CO2} should be 18 ($\Delta P_{CO2} = 1.2\ \Delta HCO_3^-$) and as a result the predicted P_{CO2} should be 22 (40–18) not 30. Therefore, there is a mixed disturbance with metabolic acidosis with respiratory acidosis. The respiratory acidosis is likely the result of weakness of the muscles of respiration secondary to profound hypokalemia.

The classic feature of distal RTA (RTA-1) is the presence of a normal anion gap metabolic acidosis with a urine pH that is persistently above 5.5 (*Fig. 285.2*). In addition to this defect in acid–base balance, K^+ is also frequently abnormal in this disorder. In most cases, hypokalemia is observed because, since H^+ excretion is impaired, more Na^+ must be reabsorbed in the cortical collecting tubule in exchange for K^+ to maintain electroneutrality. Type 1 RTA is frequently associated with renal calculi and nephrocalcinosis. Reduced excretion of citrate, a urinary inhibitor of calcium stone formation, is the principal cause for nephrolithiasis in distal RTA. In children, growth failure and bone disease are also observed. Autoimmune diseases like Sjogren syndrome, thyroiditis, and chronic active hepatitis are the major causes of this condition in adults, whereas hereditary RTA is most common in children. Amphotericin B is known to cause RTA-1.

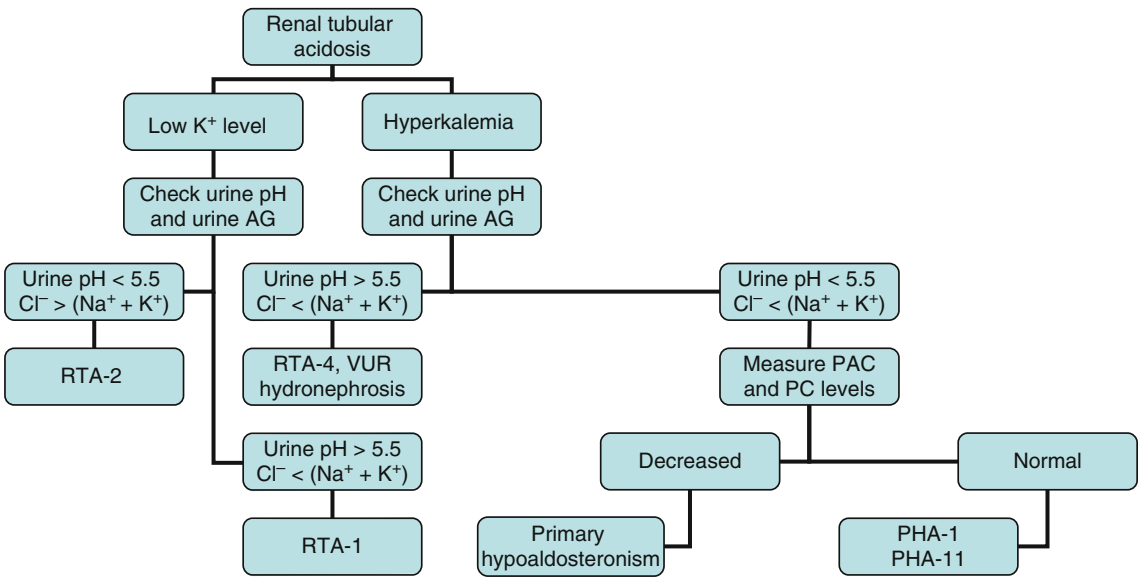

Figure 285.2
Diagnostic algorithm in renal tubular acidosis (RTA). AG; urine anion gap (Na^+, K^+, Cl^-), PAC; plasma aldosterone concentration, PC; plasma cortisol, PHA; psudohypoladosteronism

What Investigations Were Needed in the Emergency Department to Confirm the Diagnosis? (Select All that Apply)

A. Flat plate film of abdomen
B. Kidney ultrasound
C. Measurement of urine anion gap (Na^+, K^+, and Cl^-)
D. MRI of the brain

The answers are A, B, and C. A flat plate of the abdomen taken in the emergency department demonstrated bilateral nephrocalcinosis, a typical feature of this type of distal renal tubular acidosis, a finding never seen in proximal renal tubular acidosis. Measurement of the urinary anion gap is useful in the differentiation between proximal and distal renal tubular acidosis. A positive urine anion gap ($Na^+ + K^+ > Cl^-$) suggests distal renal tubular acidosis (RTA) type 1 or type 4. Measurement of serum potassium can be helpful in the differentiation between these disorders. In classic distal renal tubular acidosis (RTA-1), serum potassium level is markedly low. In comparison, an elevated serum potassium level suggests the presence of hyperkalemic distal RTA (RTA-4).

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286 A Practical Approach to Metabolic Alkalosis

Farahnak Assadi

Pathophysiology

Metabolic alkalosis is the result of an increased plasma HCO_3^- concentration. The increased HCO_3^- results in a decreased H^+ concentration. The respiratory compensation for metabolic alkalosis is hypoventilation and the arterial P_{CO_2} increases. The appropriate renal response should be decreased HCO_3^- reabsorption and loss of HCO_3^- in the urine to lower the plasma HCO_3^- concentration. However, the respiratory compensation for metabolic alkalosis is not nearly as powerful as the respiratory compensation for metabolic acidosis. In severe cases of metabolic acidosis, the P_{CO_2} may fall to less than 20 mmHg, while in metabolic alkalosis the P_{CO_2} may increase by a few mmHg. This happens because increased arterial P_{CO_2} is a very potent stimulus to increase ventilation and thus P_{CO_2} slightly increases. Nevertheless, the relationship between plasma HCO_3^- and P_{CO_2} is predictable; that is, if the plasma HCO_3^- is known, the P_{CO_2} can be accurately estimated as determined by the Henderson–Hasselbalch equation

$$[H^+] = 24(P_{CO_2}) \div (HCO_3^-)$$

How then does the kidney decrease HCO_3^- reabsorption in the presence of increased arterial P_{CO_2}? The answer to this question lies in the quantitative relationship between the filtered load of HCO_3^- and H^+ secreted by the kidney. It has been shown that in both metabolic acidosis and metabolic alkalosis there is an advantageous physiologic mismatch between filtered HCO_3^- and the amount of H^+ secreted, so that the plasma HCO_3^- concentration eventually returns to normal levels. In the case of metabolic alkalosis, the plasma HCO_3^- concentration is increased. The appropriate respiratory compensation increases the arterial P_{CO_2} and the H^+ secretion will increase, but the increase in P_{CO_2} is inadequate to reabsorb all filtered HCO_3^-. As a result, the HCO_3^- will be lost in the urine, and plasma HCO_3^- concentration will decrease.

Diagnostic Approach

The first step in the diagnosis of metabolic alkalosis is to determine the acid–base condition of the blood. This can be determined by looking at the arterial pH. Any value greater than 7.40 is considered alkalosis. The second step is to identify the primary cause of alkalosis. There are only two possibilities for alkalosis. Either the arterial P_{CO_2} is decreased (respiratory alkalosis) or the plasma HCO_3^- is increased (metabolic alkalosis). Metabolic alkalosis is characterized by increased plasma HCO_3^- concentration and a compensatory increase in arterial P_{CO_2}. The next step is to determine the quantitative relationship between the change in the metabolic alkalosis and the change in the respiratory response. In an otherwise healthy individual with metabolic alkalosis, a 1 mEq/L increase in plasma HCO_3^- concentration should result in a 0.6 mmHg increase in arterial P_{CO_2} ($\Delta P_{CO_2} = 0.6\ \Delta\ HCO_3^-$). If the patient's blood gas agree with the predicated changes, a single disorder is most likely. If they do not, more than one disorder should be considered (mixed disorder). The next most important step is the determination of the cause of sustained metabolic alkalosis.

At least two mechanisms allow metabolic alkalosis to persist, and they are both related to the volume contraction and chloride depletion (Fig. 286.1). One mechanism by which the kidney reacts to volume depletion is to increase the proximal tubular reabsorption of filtered HCO_3^-. A second and probably the most important mechanism is related to the renin–angiotensin–aldosterone system. A decrease in the effective circulating volume leads to activation of the renin–angiotensin system and a subsequent increase in plasma aldosterone concentration. In addition to its Na^+ retaining effect, aldosterone also increases H^+ secretion in the distal nephron. For every H^+ secreted in the kidney, a HCO_3^- is added to the body.

The measurement of urinary chloride is useful in the differentiation between these disorders. The urinary

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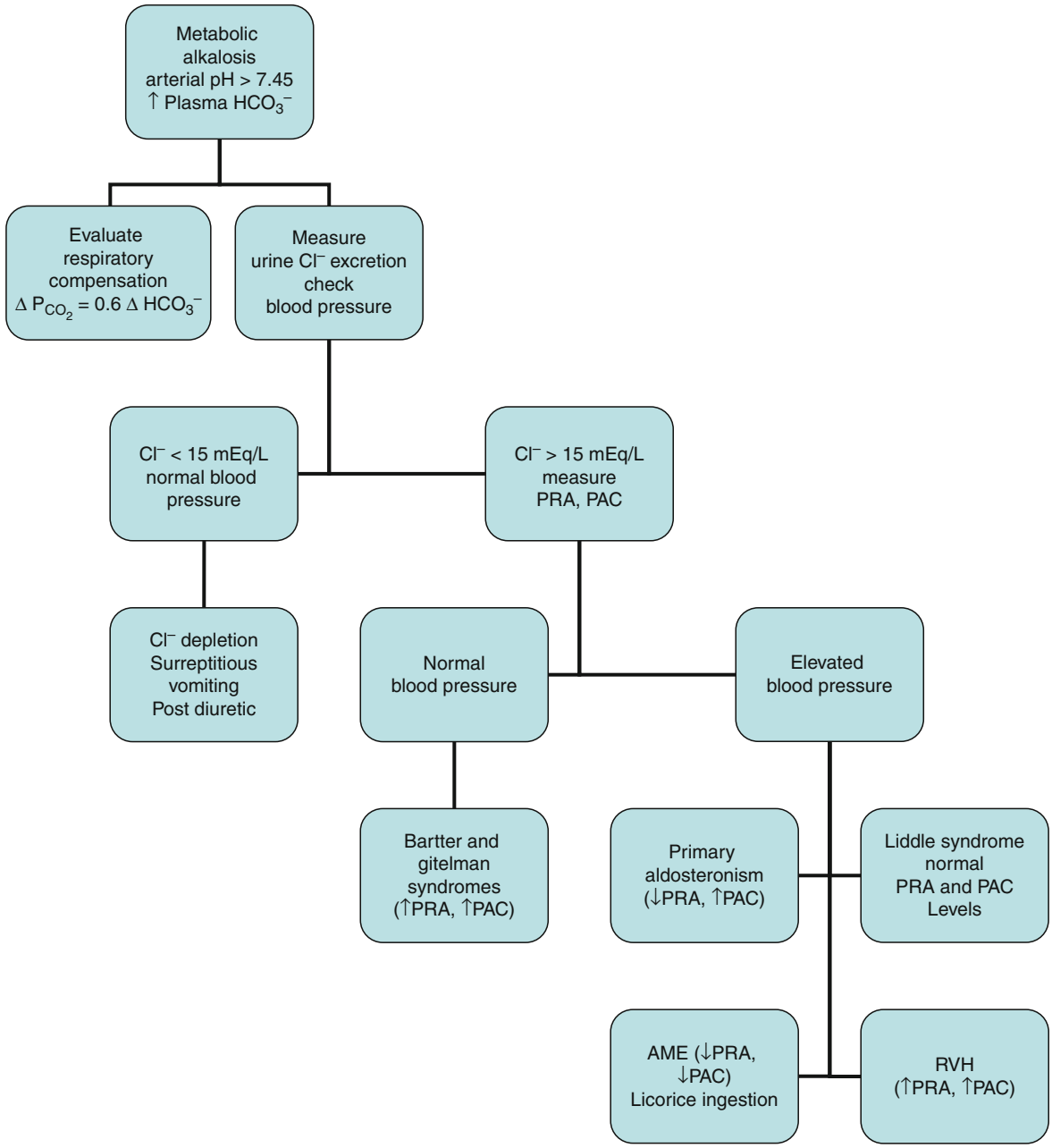

Figure 286.1

Diagnostic algorithm in metabolic alkalosis. *PRA* plasma rennin activity, *PAC* plasma aldosterone concentration, *AME* apparent mineralocorticoid excess, *RVH* renal vascular hypertension, ↑ increased, and ↓ decreased

chloride concentration is typically <15 mEq/L with hypovolemia and chloride depletion due to surreptitious vomiting or post diuretic therapy. In contrast, higher values are seen if the diuretic is still active, as in Bartter syndrome, severe hypokalemia, or primary aldosteronism. Screening the urine for diuretics is indicated if surreptitious ingestion is suspected.

The urine chloride is used in metabolic alkalosis because there may be a tendency to sodium wasting, particularly in the first few days. As the plasma HCO_3^-

concentration, and therefore, the filter HCO_3^- load increases during the generation of metabolic alkalosis, the capacity for tubular sodium HCO_3^- reabsorption decreases. The resulting loss of HCO_3^- in the urine is accompanied by a cation, predominantly, sodium, to maintain electroneutrality. In this setting, the urinary sodium concentration may be >20 mEq/L despite the presence of volume depletion; in contrast, the urinary chloride concentration is low due both to chloride and volume loss. HCO_3^- wasting can be detected by measurement of the urine pH, which will be above 7.5.

Metabolic alkalosis due to volume contraction and chloride depletion is usually correctable with administration of chloride (chloride-responsive metabolic alkalosis). Restoration of the extracellular volume will return the proximal tubule reabsorption to normal and also return plasma aldosterone concentration to normal, both of which will allow the filtered HCO_3^- to escape reabsorption. In comparison, giving chloride is ineffective when hyperaldosteronism, marked hypokalemia, or renal failure is responsible for the defect in bicarbonate excretion (chloride-resistant metabolic alkalosis).

Chloride-Sensitive Metabolic Alkalosis

The two most common causes of metabolic alkalosis are the loss of gastric secretions due to vomiting or nasogastric suction and diuretic therapy. The process of gastric acid secretion results in the retention of 1 mEq of HCO_3^- for each mEq of hydrogen ion that is secreted. This process does not lead to metabolic alkalosis in normal subjects, since 100–200 mEq of HCl secreted by the stomach each day enters the duodenum where it stimulates an equivalent of HCO_3^- secretion from the pancreas. When vomiting or nasogastric suctioning is present, the hydrogen ion secreted by the stomach cannot stimulate pancreatic HCO_3^- secretion, thereby leading to net retention of plasma HCO_3^-. Hypokalemia, which is often present due to concurrent renal or gastrointestinal losses, also can enhance HCO_3^- reabsorption and contribute to maintenance of the alkalosis. When potassium is lost from the extracellular fluid due to diuretics, or vomiting, potassium moves out of the cells to partially replete the extracellular stores. This process is accompanied by sodium and H^+ movement into the cells to maintain electroneutrality. The ensuing intracellular acidosis can, in renal tubular cells, stimulate H^+ secretion and, therefore, HCO_3^- reabsorption. Furthermore, the transcellular shift of H^+ out of the extracellular fluid can directly raise the plasma HCO_3^- concentration and exacerbate the alkalosis.

The treatment of metabolic alkalosis is more complex in edematous patients with congestive heart failure, hepatic cirrhosis, or the nephrotic syndrome. Renal perfusion is often reduced in these disorders, and the urine chloride concentration is typically below 15 mEq/L. However, saline administration will exacerbate the edema and will not sufficiently expand the effective circulating volume to permit excretion of the excess HCO_3^-. In this setting, the carbonic anhydrase inhibitor, acetazolamide, may be extremely effective. Potassium-sparing diuretics should be added if necessary.

If these combined modalities are ineffective, HCl should be given intravenously to lower the plasma HCO_3^- concentration. The desired bicarbonate concentration to lower the blood pH to 7.50 (equivalent to H^+ of 30 nmol/L) can be calculated as determined by the Henderson–Hasselbalch equation.

$$H^+ = 24(P_{CO_2}) \div \text{desired } HCO_3^-$$

As an example, a 30-kg patient presents with metabolic alkalosis and the following set of laboratory studies is obtained: arterial blood pH 7.60, P_{CO_2} 49, and serum HCO_3^- 40 mEq/L. Assume that the P_{CO_2} will remain at 40 mmHg, correct the pH from 7.60 to 7.50 (equivalent to H^+ of 30 nmol/L). The amount of the H^+ that will be needed can be calculated as follows:

$$30 = (24 \times 40) \div \text{desired } HCO_3^-$$
$$\text{Desired } HCO_3^- = 32 \text{ mEq/L}$$
$$\text{HCl(mEq)} = 0.4 \text{ weight}(\text{desired } HCO_3^-) - (\text{patient's } HCO_3^-)$$
$$\text{HCl(mEq)} = 12(32 - 40)$$

Patient's HCO_3^- is 40 and desired HCO_3 is 32, thus, patient's plasma HCO_3^- must be lowered by 8 mEq/L. The HCO_3^- space is 12 L (patient's weight × 0.4). Therefore, this patient needs 8 mEq of H^+ for each liter of the 12 L of HCO_3^- space or 96 mEq of H^+. The standard 0.1 M HCl solution contains 100 mEq of H^+/L. The amount of HCl needed to reduce the serum HCO_3^- concentration should be given slowly over 12–24 h using a large bore central vein needle to avoid corrosive damage to veins.

Chloride-Resistant Metabolic Alkalosis

Metabolic alkalosis with the urine chloride excretion greater than 15 mEq/L can be observed in patients with primary hyperaldosteronism, Liddle syndrome, apparent mineralocorticois excess (AME), Bartter syndrome, Gitelman syndrome, or severe hypokalemia. In these

disorders, hyperaldosteronism and hypokalemia are usually responsible for maintenance of the alkalosis by their ability to enhance renal H^+ excretion and, therefore HCO_3^- reabsorption. Volume depletion is generally absent, explaining the lack of dependence on chloride.

The presence of mineralocorticoid excess should be suspected in any patient with the triad of hypertension, hypokalemia, and metabolic alkalosis. Although there is initial sodium retention and volume expansion, a spontaneous natriuresis occurs within a few days, returning the extracellular volume to normal. It is possible that atrial natriuretic peptide, released in the response to volume expansion, contributes to this phenomenon. In addition to the direct effect of aldosterone on H^+ secretion, concurrent hypokalemia also is essential if a substantial rise in the plasma HCO_3^- concentration is to occur. As described above, this is largely due to intracellular acidosis induced by transcellular $K^+ - H^+$ exchange, a change that enhances H^+ secretion and HCO_3^- reabsorption. Primary aldosteronism should be suspected when plasma renin activity (PRA) is suppressed and plasma aldosterone concentration (PAC) is increased. Secondary hyperaldosteronism (e.g., renal artery stenosis, renin-secreting tumors, and coarctation of the aorta) should be considered when both PRA and PAC are increased.

Liddle syndrome is a rare autosomal dominant disorder characterized by severe hypertension, metabolic alkalosis, and hypokalemia associated with normal PRA and PAC. Liddle syndrome is caused by a genetic abnormality that increases the activity of the collecting tubule sodium channel in the absence of mineralocorticoid excess. Bartter syndrome or Gitelman syndrome cause hypokalemia, metabolic alkalosis, and associated with high levels of plasma PRA and PAC without hypertension, in a manner similar to that of diuretics. Gitelman syndrome is caused by loss of function mutations in a thiazide-sensitive ion transport mechanism in the distal nephron and is associated with hypocalciuria. Bartter syndrome is caused by mutations in a furosemide–sensitive ion transport mechanism in the loop of Henle and is associated with hypercalciuria. The diagnosis of Bartter syndrome is confirmed by demonstrating that, during 5% dextrose infusion, the fractional chloride excretion is greater than 15 mEq/100 mL glomerular filtration rate (GFR) or fractional distal chloride reabsorption ($C_{H_2O} \div C_{H_2O} + C_{Cl^-}$) is less than 85 mEq/100 mL GFR.

AME (deficiency of 11-β-hydroxysteroid dehydrogenase) should be suspected when both PRA and PAC are suppressed. Decreased enzyme activity allows glucocorticoids to act as mineralocorticoids and produce hypertension, hypokalemia, and metabolic alkalosis with low levels of renin and aldosterone. Diagnosis of AME is currently based on detection of an excess of free urinary cortisol over free urinary cortisone in 24-h urine samples.

Severe hypokalemia in addition to lowering the renal tubular cell pH can also impair distal chloride reabsorption. Thus, some of the sodium that is reabsorbed occurs in exchange for hydrogen rather than with chloride. In this setting, the urine chloride concentration is typically above 15 mEq/L even in the presence of volume depletion, a change that is reversible only after partial repletion of the potassium deficit.

Patients who have a urine chloride concentration greater than 15 mEq/L are unlikely to respond to sodium chloride and correction of metabolic alkalosis. The administered chloride in this setting is excreted in the urine since chloride deficiency is not a limiting factor in bicarbonate excretion. Furthermore, the high sodium intake will enhance urinary potassium losses and exacerbate the hypokalemia in patients with primary mineralocorticoid excess. Thus, treatment is aimed at decreasing the activity of the renin–angiotensin–aldosterone system as a means of decreasing urinary potassium and hydrogen losses. Nonsteroidal anti-inflammatory drugs, converting enzyme inhibitors, and mineralocorticoid antagonist (potassium-sparing diuretics) such as spironolactone and amyloride are usually effective in returning the plasma potassium and bicarbonate concentration to or near normal. Continued potassium administration is also required to return potassium deficit to normal.

Case Study

A 19-year-old girl on diuretic therapy for many months to control hypertension complains of weakness. She otherwise appears healthy. Laboratory data reveal sodium 132 mEq/L, potassium 2.5 mEq/L, chloride 93 mEq/L, and HCO_3^- 35 mEq/L.

What is the acid–base diagnosis?

A. A metabolic compensation for respiratory acidosis
B. Mixed metabolic alkalosis and respiratory acidosis
C. Mixed metabolic alkalosis and respiratory alkalosis
D. Metabolic alkaosis

The answer is D. The venous plasma HCO_3^- is elevated, which indicates a metabolic alkalosis or a compensated respiratory acidosis. If the condition were an acidosis, it may be anticipated that the plasma potassium concentration would be increased as the result of H^+ and potassium exchange in the cells. Since the plasma potassium is very low, the metabolic alkalosis is the most likely

diagnosis. The only way to make the diagnosis is to determine the acid–base status and all of the information necessary to calculate the H^+ is available. The appropriate respiratory compensation can be estimated by the following equation: ($\Delta P_{CO_2} = 0.6\ \Delta HCO_3^-$ or 6). Thus, the predicted P_{CO_2} is 46 mmHg. Using the Henderson–Hasselbalch equation ($H^+ = 24\ [P_{CO_2}] \div [HCO_3^-]$), the H^+ concentration is 30 nmol/L, which is equivalent to pH 7.50. Metabolic alkalosis results from long-term diuretic use. The decrease in total body sodium reduces the effective circulating volume and leads to activation of the renin–-angiotensin–aldosterone system. The increased aldosterone results in increased potassium secretion.

Case Study

A 15-year-old girl with a recent history of duodenal ulcer was admitted to the emergency department because of severe headache. She denies taking any medications. Physical examination revealed a thin female in no acute distress. Temperature is 37°C, blood pressure 122/70 mmHg, pulse 77 beats/min, respiratory rate 17/min, weight 51 kg, and height 165 cm. The heart is normal, lungs are clear, and abdomen is soft, non-tender without palpable masses or organomegaly. Neurological examination is intact. Laboratory data revealed sodium 136 mEq/L, chloride 95 mEq/L, potassium 3.0 mEq/L, HCO_3^- 32 mEq/L, BUN 15 mg/dL, phosphate 3.6 mg/dL, magnesium 1.7 mg/dL, and albumin 4.6 mg/dL. The arterial blood pH is 7.48 mmHg and P_{CO_2} 44 mmHg.

What further diagnostic tests should be done? (select all that apply)

A. Measurement of urinary aldosterone concentration
B. Measurement of urinary chloride excretion
C. Urinary diuretic screen
D. All of the above
E. None of the above

The answers are B and C. The findings of hypokalemia, metabolic alkalosis, and a normal blood pressure suggest the diagnosis of secondary hyperaldosteronism caused by surreptitious vomiting, diuretic abuse, Bartter syndrome, or Gitelman syndrome. Other forms of mineralocorticoid excess (primary hyperaldosteronism, Liddle syndrome, Cushing syndrome, renal artery stenosis, or apparent mineralocorticoid excess including licorice ingestion) are excluded by the normal blood pressure. Diet pills are often diuretics that may cause metabolic alkalosis. Urinary chloride excretion helps to distinguish between diuretics and vomiting or Bartter and Gitelman syndromes as causes of metabolic alkalosis. Vomiting is associated with extracellular fluid volume depletion, chloride depletion, and a urinary chloride excretion less than 15 mEq/L. In contrast, urinary chloride excretion is usually greater than 40 mEq/L in conditions associated with Bartter syndrome, Gitelman syndrome, or use of diuretics. Surreptitious diuretic abuse can be confirmed by obtaining a urinary diuretic screen. Therefore, the urine should be screened for the presence of diuretics and the plasma renin and aldosterone levels determined.

Case Study

A 17-year-old boy with a chronic history of obstructive pulmonary disease returns for follow-up examination. He has been complaining of shortness of breath on exertion as well as chronic cough with sputum production in the morning. He was placed on furosemide several weeks ago. On examination, his temperature is 37°C, blood pressure 136/88 mmHg, pulse 86 beats/min, respiratory rate 23/min, weight 61 kg, and height 165 cm. The heart rate is regular; there are no extra sounds or murmurs. Respiratory excursions are shallow and there is occasional wheezing. The abdomen is soft without palpable masses. Bowel sounds are present. There is 2+edema on lower extremities. Laboratory studies revealed a hemoglobin 12.0 mg/dL, WBC 6,600/mL, sodium 140 mEq/L, potassium 3.4 mEq/L, chloride 88 mEq/L, bicarbonate 42 mEq/L, calcium 9.3 mg/dL, magnesium 1.6 mg/dL, phosphate 3.5 mg/dL, glucose 95 mg/dL, and plasma osmolality 284 mOsm/L. The only available acid–base data is the P_{CO_2} 60.

What is the acid–base diagnosis? (Select all that apply)

A. Metabolic alkalosis
B. Respiratory acidosis
C. Respiratory alkalosis
D. Mixed metabolic alkalosis and metabolic acidosis

The answers are A and B. Since the P_{CO_2} and the HCO_3^- are both elevated, there could be either a respiratory acidosis with metabolic compensation or a metabolic alkalosis with respiratory compensation. The only way to make the diagnosis is to determine the acid–base status and all of the information necessary to calculate the H^+ and pH that is available. Using the Henderson–Hasselbalch equation [$H^+ = 24\ (P_{CO_2}) \div (HCO_3^-)$], the H^+ concentration is 33.5 nmol/L, which is equivalent to a pH of 7.56. Thus, this patient is alkalotic. The rise in P_{CO_2} represents an inappropriate respiratory compensation. If it were a single metabolic alkalosis, the P_{CO_2} should be increased by 10 ($\Delta P_{CO_2} = 0.6\ \Delta HCO_3^-$) and the predicted P_{CO_2} should be

50 mmHg not 60 mmHg. Therefore, the correct diagnosis is a mixed metabolic alkalosis and respiratory acidosis. The history and the physical examination indicate that the patient has chronic bronchitis and obstructive lung disease that can produce chronic respiratory acidosis.

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287 Idiopathic Hypercalciuria

Fernando Santos

Definition and Epidemiology

Urinary elimination of calcium (1 mmol/L = 4 mg/dL = 2 mEq/L) is highly dependent on diet and child's age. Under identical dietary conditions, urine calcium has been shown to be lower in black than white children. Keeping this variability in mind, hypercalciuria is usually diagnosed in the clinical setting when urinary calcium excretion exceeds 4–5 mg/kg/day and suspected when urine calcium/creatinine ratio (UCa/Cr) is above 0.20–0.25 mg/mg. On the assumption that daily calcium elimination in urine follows a Gaussian distribution, approximately 5% of healthy children will be hypercalciuric. These limits cannot be used in infants in whom calciuria per unit of weight is physiologically much higher. UCa/Cr values as high as 0.80 or 0.40–0.50 mg/mg in spot urine samples are probably in the upper limit of normality during the first year of life and in early childhood, respectively. In fact, the diagnosis of hypercalciuria "per se" in an infant is rather questionable and variations in calcium elimination must be used to estimate the hypercalciuric effect of a disease or exogenous agent at this early age.

The diagnosis of idiopathic hypercalciuria requires the presence of normocalcemia and the absence of identifiable causes leading to intestinal hyperabsorption of calcium (vitamin D, high calcium intake), decreased tubular calcium reabsorption (furosemide, tubulopathies), or exacerbated bone resorption (immobilization, metabolic acidosis, corticosteroids).

Pathogenesis

Regarding the origin of the excess of urinary calcium in individuals with idiopathic hypercalciuria, attempts have been made to set different pathophysiological categories, that is, renal, absorptive, fasting, diet dependent, resorptive, etc. These classifications are of poor clinical benefit because the role played by bone, gastrointestinal tract, and kidney in the elevation of urinary calcium is difficult to differentiate in clinical practice. Nowadays, idiopathic hypercalciuria tends to be considered a single complex disorder determined to a great extent by a polygenic inheritance and the interaction with environmental factors. Approximately 50% of children with idiopathic hypercalciuria have at least one hypercalciuric first-degree relative.

Clinical Manifestations

Due to its frequent occurrence, idiopathic hypercalciuria can be diagnosed in association with a wide array of manifestations. However, the majority of hypercalciuric children are asymptomatic and few symptoms have a demonstrated cause–effect relationship with idiopathic hypercalciuria. Twenty-six to 36% of children have no identifiable basis for hematuria other than hypercalciuria; inversely, 31% of children with hypercalciuria have hematuria. The mechanism of hematuria caused by hypercalciuria is not known but it may be assumed that urinary calcium microcrystals produce a transient injury in the urothelial epithelium. This agrees with the typical presentation of idiopathic hypercalciuria in a child who, though otherwise asymptomatic, transiently voids 2–3 three urinations with macroscopic hematuria. The relationship between hypercalciuria and persistent microscopic hematuria is less convincing because of the likelihood of casual association between two prevalent disorders and the difficulty to find a common pathogenic mechanism. The passing of calcium crystals may explain the appearance of voiding symptoms such as dysuria, frequency, and urinary urgency found as presenting manifestations in some hypercalciuric children. Hypercalciuria is the most common metabolic abnormality detected in children with urolithiasis, found as a single risk factor in 19% of children with stones and in combination with other risk factors, such as hyperuricosuria, hypocitraturia, hyperoxaluria, cystinuria, etc., in up to 40–70% of cases. Urolithiasis is diagnosed in 5% of symptomatic children with idiopathic hypercalciuria. There is no way of predicting which children with idiopathic hypercalciuria will develop a urinary calculus during their childhood. The risk, although not well defined, is low but increases in the presence of very high levels of calciuria, positive family history of urolithiasis, and recurrent episodes of gross hematuria. To this respect, the prognostic significance of small hyperechogenic spots sometimes detected, as isolated and often transient findings, in the

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renal ultrasounds of children with idiopathic hypercalciuria is unknown but probably do not indicate an increased risk of developing urolithiasis. The causal relation of idiopathic hypercalciuria with vesicoureteral reflux, recurrent urinary tract infections, enuresis, recurrent abdominal pain, proteinuria, etc. claimed in some studies remains to be demonstrated. Low bone mineral density, *z* score less than −1, has been reported to be up to 30–40% in some series of children with idiopathic hypercalciuria, the risk of reduced bone density being related with the presence of urolithiasis, hypocitraturia and family history of osteopenia. The pathogenesis of reduced bone density in these patients is probably not uniform and it is not clear if it results from decreased bone formation and/or increased bone resorption. It should be pointed out that the high percentage of low bone mineral density mentioned above does not likely correspond to the whole population of hypercalciuric children.

Diagnosis

Table 287.1 summarizes the studies recommended in the initial diagnostic approach of idiopathic hypercalciuria

Table 287.1
Diagnostic approach to idiopathic hypercalciuria

Medical history	Personal and family antecedents of urolithiasis, hematuria, and/or hypercalciuria
	Administration of vitamin D, furosemide, calcium salts, corticosteroids
	Characteristics of diet
Physical examination	Detailed physical examination including growth parameters: weight, height
Lab work-up – blood	Total calcium, phosphate, alkaline phosphatase, acid–base equilibrium, ionized calcium, magnesium, albumin, total proteins, creatinine, uric acid, sodium, potassium, osmolality, parathyroid hormone, 25 (OH) vitamin D
Lab work-up – random urine	Elemental uroanalysis, culture, calcium/creatinine ratio
Lab work-up – 24-h urine	Calcium, phosphate, magnesium, creatinine, urea, uric acid, sodium, potassium, osmolality, citrate
Image studies	Nephro-urological ultrasonography

in children. It is of note that hypercalciuria and hyperuricosuria are frequently associated and both disorders have been related with hematuria, calculi, and lower urinary tract symptoms. Measurement of bone density by DEXA should be restricted to patients with associated urolithiasis, family history of osteoporosis or very high levels of urinary calcium. Special functional tests to ascertain the pathophysiological type of idiopathic hypercalciuria are not routinely indicated. In special cases, an oral strontium load can be used to assess calcium absorption.

Treatment

Most children with idiopathic hypercalciuria do not need treatment. Families must be encouraged to dilute the child's urine by providing a high intake of fluids and to reducing calcium excretion, by limiting the excessive oral ingestion of animal proteins and sodium chloride, as happens very often in the case of children in Western societies. Families must be instructed against providing a low calcium diet because of the risk of adverse effects on body growth and bone health. In addition, some forms of hypercalciuria do not depend on diet and do not benefit from a dietary restriction of calcium which may, in turn, increase the urinary excretion of oxalate. Even if hypercalciuria persists, pharmacological treatment or more strict dietary limitations are not indicated in the vast majority of patients and should be reserved for those patients who have severe symptoms or develop progressive urolithiasis. A recent systematic review of the medical literature on the pharmacological interventions for preventing complications in idiopathic hypercalciuria concluded that thiazides and neutral potassium phosphate decreased calciuria in symptomatic patients and that administration of thiazides from 5 months to 3 years reduced the number of stone recurrence and the stone formation rate. Potassium supplementation and thiazides have also been shown to exert a beneficial effect on calculus formation in adults. In a small number of children and adolescents with idiopathic hypercalciuria and low bone mineral density, mean Z score in the lumbar spine of -2.0 ± 0.3, administration of bisphosphonates for 6–18 months normalized urine calcium excretion and improved bone density, up to a Z score value of -0.8 ± 0.8. Thus, selected patients with idiopathic hypercalciuria might benefit from pharmacological therapy although the duration of the treatment in these patients is an unsolved issue and the undesirable side effects of these drugs need to be closely monitored and counterbalanced with the potential benefits.

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Kidney and Urinary Tract Disorders

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288 Overview of Renal Function

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The main role of the kidney is to maintain the constancy of the extracellular volume (ECV) and composition. This is accomplished by fine tuning the rates at which water and solutes are excreted in the final urine. Thus, in spite of major daily variations in our food and water intake, extra renal losses of fluid and electrolytes, and the ongoing generation of metabolic waste products, the kidneys are able to maintain a remarkable constancy of the "internal milieu." The kidneys also play a major role in keeping the concentration of individual solutes such as sodium, potassium, calcium, hydrogen ion (pH), chloride, bicarbonate, and many others within a narrow range of normal variation.

The major aspects of kidney function may be summarized under five categories.

Glomerular Filtration

Compared to other organs, the kidneys are highly perfused with blood, receiving 20–25% of the cardiac output and a renal blood flow of about 700 mL/min/m^2. Glomerular filtration derives its force from the hydraulic pressure transmitted from left ventricular contraction. Other important factors that enhance filtration include the hydraulic pressure across the glomerular capillaries, the oncotic pressure (Starling's forces) of glomerular capillaries, the ultrafiltration coefficient, and the glomerular plasma flow. Plasma is filtered across the glomerular barrier with all its solutes, but with only a minimal amount of protein. Compared to the volume of the final urine excreted, the glomerular filtration rate (GFR) is very large. Thus, in a 10-year-old child (surface area 1 m^2), 100 L of plasma are filtered daily, compared to 1 L of urine excreted indicating that 99% of the glomerular filtrate is reabsorbed before final urine formation (*Fig. 288.1*, *Table 288.1*).

The GFR is usually calculated by standard clearance techniques. Inulin clearance is the gold standard used for GFR. Inulin is ideal because it is metabolically inert, is freely filtered by the glomerulus, and is neither reabsorbed nor secreted by the renal tubules. For practical purposes, however, the endogenous clearance of creatinine is a more convenient measurement of GFR in the usual clinical setting. Creatinine clearance, however, tends to overestimate GFR, particularly when GFR is low. The renal clearance of creatinine is calculated by the formula:

$$C_{Cr} = \frac{U_{\mathrm{Cr}} \times V}{P_{\mathrm{Cr}}}$$

where U_{Cr} and P_{Cr} represent the urinary and plasma concentration of creatinine in mg/dL or μmol/L, respectively, and V is the urine flow rate (usually in mL/min). Because creatinine clearance requires accurately timed urine collection, it may yield falsely high or low values, especially in an outpatient setting. The use of radioisotopes such as Cr-EDTA and I^{125} iothalamate have gained considerable popularity in estimating GFR which may be calculated from the rate of disappearance of the isotope from the plasma without the need for urine collection.

Several formulas have been derived for rapid estimation of the creatinine clearance. Of these, the Schwartz formula is the most widely used:

$$C_{Cr} = \frac{K \times L}{P_{\mathrm{Cr}}}$$

where L is length or height in centimeters, and K is a "constant" that varies with the child's size. $K = 0.33$ in pre-term infants; 0.45 in full-term infants; 0.55 in children and adolescent females; and 0.7 in adolescent males. P_{Cr} is plasma creatinine in mg/dL.

Alternative Markers of GFR

New markers of GFR have been introduced recently. Among these, Cystatin C, a cysteine protease produced by all nucleated cells, appears to be the most promising. Serum levels of Cystatin C may be superior to serum creatinine as a measurement of GFR. This is particularly true in the blind range of creatinine and in children with low muscle mass.

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Tubular Reabsorption and Secretion: The Regulation of Extracellular Fluid Volume (ECV) and Composition

While a detailed account of the different reabsorptive and secretory processes taking place along the renal tubule is beyond the scope of this chapter, a brief description will contribute to a better understanding of the different pathological states that lead to renal tubular dysfunction. *Figure 288.1* illustrates the reabsorption of sodium along the various segments of the renal tubule. Note that two thirds of the filtered sodium is reabsorbed in the proximal tubule and that only 1% is excreted in the final urine.

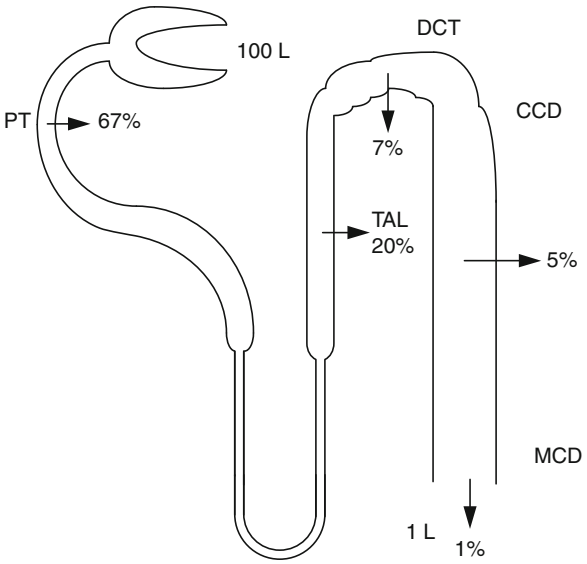

Figure 288.1
Sodium reabsorption along the different segments of the renal tubule. *PT* proximal tubule, *TAL* thick ascending limb of Henle, *DCT* distal convoluted tubule, *CCD* cortical collecting duct, *MCD* medullary collecting duct

The tonicity (osmolality) of the extracellular fluid is maintained fairly constant in spite of wide variations in water intake. This is accomplished by the kidneys' ability to concentrate or dilute the urine as needed. The ECV, on the other hand, is determined by the balance between sodium intake and sodium excretion by the kidneys. Thus, any event that threatens ECV integrity sets in motion several afferent and efferent pathways which result in sodium conservation by the proximal and distal tubules leading to reduced salt excretion. The reverse takes place when ECV is increased (except in edematous states). Under normal, physiologic states, urinary sodium excretion reflects dietary intake. By the age of 1 year, the renal tubules have matured and are capable, if the demand arises, of lowering the excretion of sodium to less than 5 mEq/24 h.

Proximal Tubular Function

Tubular reabsorption of the glomerular filtrate and its accompanying solutes constitutes one of the most important functions of the kidney. Because of the large number of invaginations, or microvilli, along their luminal (apical) membrane, the proximal tubular cells are particularly fit for that purpose due to the relatively large surface area for

Table 288.1
The magnitude of tubular function in a 10-year-old child (1.0 m^2 surface area)

	Plasma concentration	Glomerular filtrate	Urine excretion/24 h	% Reabsorption
Vol	1 L	100 L	0.3–1.0 L	98–99
Na	140 mEq	14,000 mEq	50–150 mEq	>99
Cl	100 mEq	10,000 mEq	30–90 mEq	>99
K	4 mEq	400 mEq	25–75 mEq	80–90
HCO_3	24 mEq	2,400 mEq	Trace	100
Phosphate	4 mg/dL	4,000 mg	600 mg	85
Glucose	100 mg/dL	100 g	0	100
TA	–	–	10–15 mEq	–
NH_4^+	–	–	15–30 mEq	–
pH	7.4	7.4	4.4–8.0	–
Osm	285	285 mosm/kg/H_2O	50–1,200 mosm/kg/H_2O	–

TA titratable acid, *Osm* osmolality

reabsorption. The microvilli are equipped with a brush border which contains specific carrier proteins that translocate solutes across the cell. Many of these carrier proteins have been determined by DNA sequencing and seem to exhibit a high degree of homology, but in many instances the molecular mechanism for a carrier protein to transport a specific substance has not been determined. Megalin, as the name implies, is a very large transmembrane protein that plays a crucial role in the endocytic reabsorption of a large number of low molecular weight proteins at the brush border of the proximal tubular cells. These include vitamin D binding protein, retinol binding protein, and alpha 1-microglobulin among others. The microvilli also contain the enzyme carbonic anhydrase IV which is crucial for bicarbonate reabsorption.

Reabsorption of the glomerular filtrate in the proximal tubule occurs isoosmotically, with no net change in filtrate tonicity. Both active and passive transport mechanisms are operative in solute reabsorption. Active transport implies the consumption of energy and takes place against an electrochemical gradient. The energy is provided by a Na–K-ATPase pump located in the basolateral cell membrane which maintains a low intracellular sodium concentration. It is worth emphasizing that sodium reabsorption along the whole length of the renal tubule takes place by a two-step process: (a) down an electrochemical gradient from tubular fluid across the luminal (apical) membrane to the tubular cell and (b) uphill, against an electrochemical gradient from the cell across the basolateral membrane to the peritubular capillary (Na–K-ATPase pump mediated). About two thirds of the sodium reabsorbed in the proximal tubule is by an active, transcellular mechanism; the remaining one third is by passive, paracellular reabsorption (*Fig. 288.1*).

Sodium Reabsorption and Hydrogen Secretion

Sodium is cotransported across the luminal membrane with several other solutes. These include D-glucose, D-galactose, L-amino acids, phosphate, lactate, sulfate, urate, and many other organic metabolites (*Fig. 288.2*).

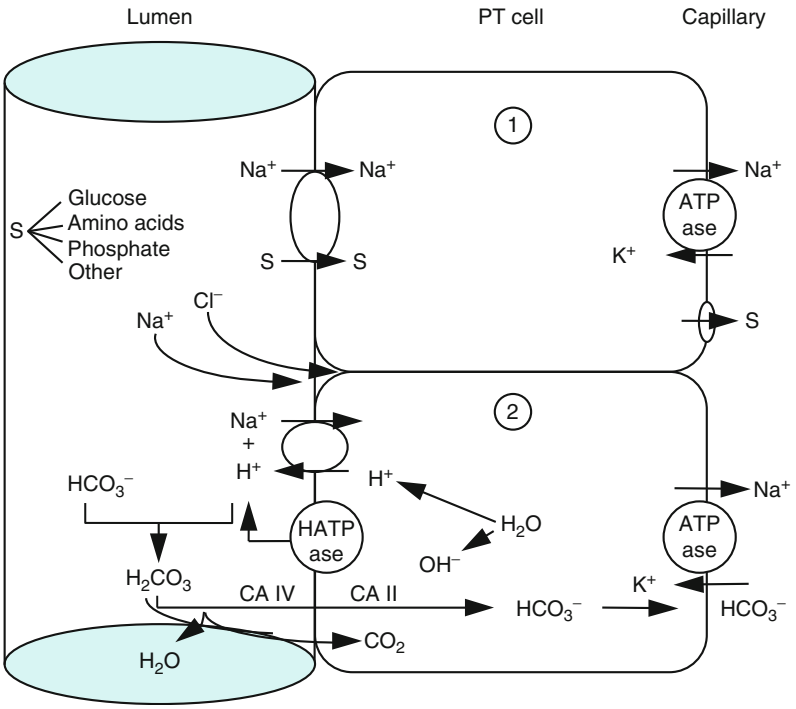

Fig. 288.2

Solute reabsorption by proximal tubular cells. The upper cell ① depicts a Na-solute cotransport mechanism facilitated by specific solute carrier proteins. The energy for this process is due to the low intracellular Na^+ concentration generated by the Na–K-ATPase pump on the basolateral cell membrane. The lower cell ② demonstrates the processes of proton secretion and bicarbonate reabsorption. About two thirds of H^+ secreted is by a countertransport with Na^+ (Na–H antiporter) and one third by a H-ATPase pump in the luminal membrane

Along with sodium, these solutes are reabsorbed with specific carrier proteins located in the brush border of the luminal membrane. Sodium is also counter transported or exchanged for hydrogen ion secreted from the cell to the tubular fluid. It is this phase of sodium reabsorption that is responsible for a significant regeneration of bicarbonate. Secreted hydrogen combines with filtered bicarbonate to form H_2CO_3, which, due to the presence of carbonic anhydrase IV in the luminal membrane, is rapidly dehydrated to form CO_2. The latter diffuses into the cell to combine with hydroxyl ion to generate bicarbonate, a reaction catalyzed by cellular carbonic anhydrase II. This "new" bicarbonate may now be returned, along with sodium via a Na^+-HCO_3 cotransporter (NBC1) at the basolateral membrane, to the peritubular capillaries (not shown). In addition to these electroneutral processes, the proximal tubular cell is equipped with an electrogenic H^+-ATPase pump located in the apical cell membrane, which contributes about one third of the proton secretion and bicarbonate reabsorption.

Normally, 85% of the filtered bicarbonate is reabsorbed in the proximal tubules by these mechanisms. Bicarbonate reabsorption in the proximal tubule represents a high capacity, low gradient process that bears an inverse proportion to changes in ECV. The remaining 15% of the filtered bicarbonate is reabsorbed in the more distal segments of the tubule. Proximal renal tubular acidosis (type 2 RTA) could occur if any of the forces involved in bicarbonate reabsorption, singly, or in combination became defective. These might be secondary to defects in the Na–H antiporter (NHE3), the Na–HCO_3 cotransporter (NBC1), carbonic anhydrase II or IV, or the H-ATPase pump. An abnormality in the Na–K-ATPase pump would result in impaired reabsorption of all solutes ordinarily cotransported with sodium and result in the Fanconi syndrome.

Potassium

Sixty-five percent of the filtered potassium is reabsorbed by the proximal tubules primarily by a process of diffusion and solvent drag through the intercellular (paracellular) pathways into the peritubular capillaries. Potassium transport in the proximal tubule has no specific role in the regulation of potassium balance.

Glucose

Glucose is freely filtered by the glomerulus and is actively reabsorbed in the proximal convoluted tubule by a sodium cotransport mechanism. Reabsorption has a tubular maximum (Tm) above which no further glucose is reabsorbed. The value for glucose Tm is 300 mg/min/1.73 m^2 and occurs at a plasma glucose concentration of 180 mg/dL. In the absence of hyperglycemia, urinary excretion of glucose is negligible. Euglycemic glucosuria is indicative of an isolated defect in proximal glucose transport, known as renal glucosuria, or due to multiple tubular defects in association with the Fanconi syndrome.

Phosphate

Eighty to ninety percent of the filtered phosphate is reabsorbed in the proximal tubule by an active sodium-coupled cotransport. Phosphate is an important urinary buffer that enhances excretion of hydrogen ion as titratable acid. Parathyroid hormone inhibits phosphate reabsorption leading to phosphaturia and hypophosphatemia. Tubular reabsorption of phosphate (TRP) is also impaired in vitamin D resistant rickets and in the Fanconi syndrome as part of a generalized proximal tubular dysfunction. The recently discovered phosphatonin, FGF23, seems to have an important phosphaturic property and may have an important role in phosphate homeostasis.

In addition to the reabsorptive processes described above, the proximal tubule has several secretory processes for organic anions and cations.

Distal Tubular Function

The major functions of the distal tubular cells are: (a) further reabsorption of sodium and chloride, (b) absorption and secretion of potassium, (c) hydrogen secretion into the lumen (urine acidification), and (d) concentration of the urine by the action of vasopressin on the collecting ducts.

Sodium Reabsorption

In the thick ascending limb of Henle, sodium is cotransported by an electroneutral process with one K and 2 Cl. The driving force for this transport is the downhill movement of sodium across the apical membrane. The intracellular sodium concentration is kept low by the Na–K-ATPase pump at the basolateral cell membrane. Loop diuretics such as furosemide, bumetanide, and ethacrynic acid are known inhibitors of this Na–K-2Cl cotransport. It is thought that they exert their effect by combining with the symporter (cotransporter) protein in the apical membrane and prevent its translocation

into the tubular cell. It has been shown recently that Bartter's syndrome is caused by mutations in this Na–K-2Cl cotransporter gene NKCC2. This is very much in keeping with the biochemical similarities seen between patients receiving loop diuretics and patients with Bartter's syndrome.

In the distal convoluted tubules (DCT), sodium and chloride are reabsorbed by a cotransport mechanism. The Na–K-ATPase pump is more active in this segment than any other part of the renal tubule. The Na–Cl cotransport in this part of the tubule is inhibited by the thiazide group of diuretics. Gitelman's variant of Bartter's syndrome is caused by mutations in this thiazide-sensitive Na–Cl cotransporter. Further down in the cortical collecting duct (CCD) sodium transport takes place across epithelial channels (ENaC) in the apical membrane by simple diffusion. As in other segments of the nephron, the driving force for this transport is the electrochemical generated by the basolateral Na–K-ATPase pump which keeps cell sodium concentration low. These sodium channels are inhibited by the diuretics amiloride and triamterene. Mutations in the sodium epithelial channel beta and gamma subunits causes Liddle's syndrome, an autosomal form of salt-sensitive hypertension associated with hypokalemic alkalosis. Inactivating mutations in the ENaC subunits causes pseudohypoaldosteronism type 1.

Potassium Reabsorption and Secretion

About two thirds of the filtered potassium is reabsorbed in the proximal convoluted tubule regardless of the final urinary excretion. Another 25% of the filtered potassium is reabsorbed along with sodium and chloride in the thick ascending limb of Henle (Na–K-2Cl cotransporter). In potassium depletion states, further reabsorption takes place by the intercalated cells of the DCT (3%) and CCD (9%). Potassium secretion occurs during normal rates of intake. As potassium intake increases, secretion by the principal cells of the DCT and CCD may be as much as 80% of the filtered potassium load. In addition to potassium intake, there are several factors that enhance potassium secretion. These include tubule fluid flow rate, sodium delivery to the distal tubule, mineralocorticoid activity, alkalosis, the presence of unreabsorbable anions, and vasopressin activity. Factors inhibiting potassium secretion include a high luminal potassium concentration, high chloride concentration, amiloride and triamterene, acidosis, and high urinary calcium.

A recently introduced value that has received considerable attention in clinical practice is the transtubular potassium gradient (TTKG). It is calculated from simultaneous measurements of plasma and urine potassium, and plasma and urine osmolality:

$$\mathrm{TTKG} = \frac{U_K \times P_{OSM}}{P_K \times U_{OSM}}$$

The TTKG is an approximation of the potassium concentration at the end of the CCD and is an indirect assessment of endogenous aldosterone activity in vivo. Under normal situations of dietary potassium intake, TTKG ranges between 4 and 10. A value below 4 in children and below 5 in infants is reflective of little or no mineralocorticoid activity. A high potassium intake or acute mineralocorticoid administration raises TTKG above 10–12.

Hydrogen Secretion: Urine Acidification

In the CCD and MCD, hydrogen secretion takes place by an electrogenic active transport with energy derived from an H^+-ATPase and an H–K-ATPase pump. Hydrogen secretion is accomplished by the alpha-intercalated cells which can establish much steeper hydrogen gradients than the Na–H antiporter mechanism that prevails in the proximal tubule. Thus, a 1,000-fold gradient (3 pH units) may be attained between plasma and urine at maximum urine acidity with a pH of 4.4.

Ammonium Secretion

Ammonium (NH_4^+) synthesis from the deamination of glutamine takes place primarily in the proximal tubular cells. The NH_4^+ is secreted into the luminal fluid by a Na–NH_4^+ exchange, but some NH_3 diffusion occurs as well. A significant portion of the secreted NH_4^+ is reabsorbed in the thick ascending limb of Henle and accumulates in the medullary interstitium as NH_4^+ and NH_3. The latter diffuses into the lumen of the distal tubule and collecting duct, where it combines with secreted hydrogen to form NH_4^+ which becomes trapped in the tubular lumen and excreted in the urine. Ammonium secretion by the renal tubules is stimulated by acidosis, potassium depletion, and glucocorticoids and inhibited by alkalosis, hyperkalemia, and adrenal insufficiency.

Titratable Acid

Hydrogen ion secreted in exchange for sodium can also combine with non-bicarbonate buffers. This fraction of secreted hydrogen can be measured in the urine by back

titration and is referred to as titratable acid. The most abundant of these non-bicarbonate buffers is phosphate. The rate of titratable acid excretion is influenced by the amount of buffer in the tubular fluid, the pH of the buffer and the pH of the tubular fluid. The hydrogen excreted with NH_3, as NH_4^+, and with phosphate, as titratable acid, accounts for the bulk of fixed acid excretion. This is also known as net acid excretion (NAE) which is equivalent to the amount of endogenous acid production (40–60 mEq/m^2/day) (*Fig. 288.3*).

Of note is that the distal tubular cells lack intraluminal carbonic anhydrase IV. Thus, the dissociation of H_2CO_3 in the luminal fluid into CO_2 and H_2O occurs very slowly. The CO_2 generated may be measured in the urine during bicarbonate infusion and is an indirect reflection of hydrogen secretion in the distal nephron.

Vasopressin and Other Hormonal Receptor Sites in the Distal Nephron

In the distal tubules and collecting ducts, further reabsorption of filtrate takes place. The DCT, CCD, as well as the medullary CD contain receptors for several hormone systems that participate in the modulation of electrolyte and water reabsorption: (a) vasopressin (ADH) increases water permeability in the CCD and MCD and results in the formation of concentrated urine. This occurs through passive reabsorption of water by means of an elaborate countercurrent mechanism generated by the hairpin configuration of the limbs of Henle. Because the ascending limb of Henle is impermeable to water, progressive hyperosmolality of the medullary interstitium takes place allowing for ADH-mediated water extraction from the distal tubules and collecting ducts, resulting in a hyperosmotic urine. Vasopressin binds to the V2R receptor on the basolateral membrane of the principal cell initiating adenyl cyclate activation and cAMP generation and protein kinase A stimulation. The latter enhances the redistribution of aquaporin2 (AQP2) water channels from intracellular vesicles to the apical basal membrane rendering the latter water permeable. (b) aldosterone enhances sodium reabsorption with concomitant hydrogen and potassium secretion, (c) parathyroid hormone increases calcium reabsorption, (d) other hormones having an effect on sodium reabsorption include glucagon, estrogens, thyroid, calcitonin, and the powerful atrial natriuretic peptides.

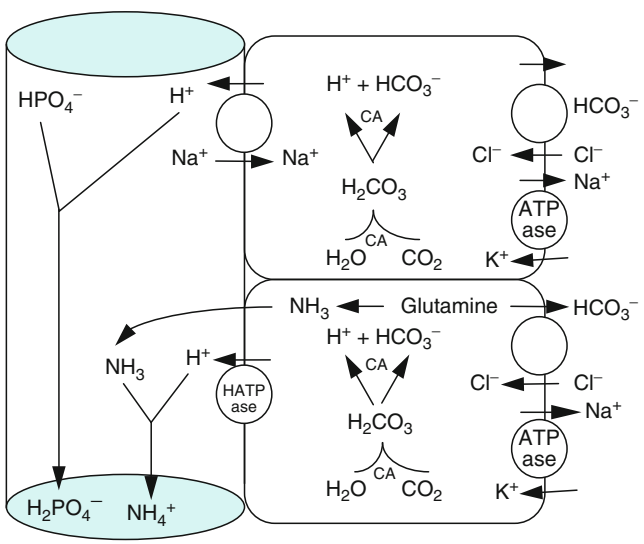

Fig. 288.3

Excretion of fixed acids of the distal nephron. Hydrogen secretion by the alpha-intercalated cells takes place via the H^+-ATPase pump in the luminal basement membrane. About 40% of the secreted hydrogen ions combine with filtered phosphate to form titratable acid. Most of remaining hydrogen secreted combines with NH_3 to form NH_4^+, but a small amount remains as full hydrogen ions and regulates urinary pH. Another small amount of secreted hydrogen combines with residual filtered bicarbonate that escaped absorption in the proximal tubule

Endocrine Function of the Kidney

The kidney is the site of production and release of many hormones affecting other target organs and tissues as well as autacoids which act locally. Renin acts on angiotensinogen leading to angiotensin I and angiotensin II production; kallikrein controls bradykinin formation resulting in local and systemic vasodilatation; erythropoietin stimulates the bone marrow for hemoglobin synthesis; 1-alpha hydroxylation of vitamin D in the proximal tubules yields the active metabolite 1,25 $(OH)_2D3$.

Prostaglandins and leukotrienes probably exert a local effect on sodium reabsorption and vasodilatation.

The Kidney as a Metabolic Organ

The kidney is an important organ in energy metabolism. It is second only to the liver as a source of gluconeogenesis during prolonged fasting. In addition, the kidney plays a significant role in lipid and amino acid metabolism. Respiratory fuels in the renal cortex include short and long chain fatty acids, ketone bodies, lactate, and amino acids. In the outer medulla, succinate and lactate and, in the inner medulla, glucose are the preferred substrates.

The Kidney as an Excretory Organ

In addition to secretory processes enhancing excretion of substances produced from normal metabolism, the kidney plays an important role in the excretion of many endogenous and exogenous toxins and drugs. Organic anions secreted by the proximal tubules include the thiazide diuretics, furosemide, salycilates, and penicillin. Organic cations include atropine, amiloride, cimetidine, and morphine.

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289 Approach to Renal Disease in the Neonate

Robert L. Chevalier

The transition from fetal to postnatal life requires dramatic physiologic adaptation by many organ systems: the kidneys must suddenly completely assume the role provided by the placenta in maintaining neonatal homeostasis. The pediatrician must recognize that in the full term infant, the kidney is programmed for this transition with an initial diuresis and natriuresis followed in several days by avid sodium retention, which is necessary for normal growth. While these responses were formerly regarded as "limitations" of the immature kidney, they are physiologically appropriate. However, because the neonate has an attenuated renal response to acute volume expansion compared to the older child, the composition and rate of administration of fluids and electrolytes must be carefully monitored. In the preterm infant, renal function reflects a developmental stage adapted to fetal rather than extrauterine life and glomerular and tubular function are even more restricted. Identification of renal abnormalities or dysfunction in the neonate therefore requires familiarity with the normal range of parameters for preterm and term infants (*Table 289.1*). This chapter addresses the most frequently encountered renal disorders of the neonate.

Fetal kidney development. The development of the fetal kidney is a delicate process that involves differentiation of the metanephros in the first trimester. Abnormalities of embryogenesis in this period can result in ectopic kidney, duplex or horseshoe kidney, or in renal agenesis, dysplasia, or hypoplasia (*Table 289.2*).

Congenital anomalies of the kidneys or urinary tract (CAKUT) comprise over 50% of the causes of renal failure in infants and children. In addition to the structural anomalies comprising CAKUT, it is now recognized that the number of nephrons in each kidney varies by a factor of tenfold across the normal population: low nephron number represents a significant risk factor for long-term progression of renal insufficiency of any cause. Very low birth weight infants or those with intrauterine or extrauterine growth restriction are also subject to a permanent reduction in nephron number associated with an early deficit in protein-calorie intake.

Obstruction of the urinary tract at any point from the ureteropelvic junction to the urethra can impair renal growth and development in the fetus, and may even result in dysplastic changes. The ureteropelvic junction is the most common site for congenital obstructive nephropathy, and fortunately is generally unilateral (although the contralateral kidney or urinary tract is often also abnormal). An extreme example of the effects of ureteral atresia is the development of multicystic dysplasia, which is the most common cause of an abdominal mass in the neonate. In most cases, a multicystic dysplastic kidney undergoes involution and does not require surgical removal unless it is causing hypertension. Although posterior urethral valves are less common, this lesion involves both kidneys that generally exhibit dysplastic changes that are not completely reversible even after surgical relief of the obstruction. Such infants require the early involvement of the pediatric urologist. The indications for prenatal intervention are unclear at present, and in general should be considered in the realm of experimental therapy. Prenatal diagnosis, however, can alert the pediatrician to evaluation of the infant's renal status shortly after birth, in order to optimize growth and function of the kidney.

Renal anomalies. For reasons that remain poorly understood, the prevalence of CAKUT is significantly higher in males than females, approaching 2:1 in many reports. Renal anomalies are often associated with abnormalities of other organs. The phenotype of Potter syndrome includes large flat ears, infraorbital skin folds, and flat nasal bridge. These changes, in addition to pulmonary hypoplasia, result from oligohydramnios due to fetal oliguria or anuria. Thus, Potter syndrome can result from bilateral renal agenesis, or any other severe bilateral renal malformation, including hypoplasia, dysplasia, cystic kidney disease, or bilateral obstructive uropathy (*Table 289.2*). The placental corollary of Potter syndrome, amnion nodosum, consists of nodules of amorphous granular material on the surface of the amnion, fibrosis of chorionic villi, and placental edema.

A palpable abdominal mass in the neonate is generally due to an enlarged kidney. This may result from

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Table 289.1
Renal parameters in healthy neonates during the first 2 months

Parameter	Preterm infant	Term infant
Kidney length (ultrasound)	2–4 cm in fetus 22–32 weeks; EGA 3–5 cm in fetus >32 weeks EGA	4–5 cm in neonate
Renal pelvic diameter (ultrasound)	<5 mm in fetus >24 weeks EGA (not reliable for EGA < 24 weeks)	<7 mm 5 days of age; <10 mm 3 months old
Systolic blood pressure	<70 mmHg	<90 mmHg
Plasma creatinine concentration	<2.0 mg/dl (1–2 weeks); <0.8 mg/dl (>2 weeks)	<1.0 mg/dl (1–2 weeks); <0.6 mg/dl (>2 weeks)
Plasma potassium concentration	4–6 mEq/l	4–6 mEq/l
Plasma bicarbonate concentration	15–25 mEq/l	>20–25 mEq/l
Fractional excretion of sodium (FE_{Na})	<1% (EGA >32 weeks; not helpful for EGA < 32 weeks)	<1%
Urine calcium/creatinine ratio (mg/mg)	<0.8	<0.4

EGA estimated gestational age

Table 289.2
Congenital anomalies of the kidneys or urinary tract (CAKUT)

Ectopic kidney
Duplex/horseshoe kidney, duplicated collecting system
Renal agenesis
Renal dysplasia/hypoplasia (including multicystic dysplastic kidney)
Obstructive nephropathy (ureteropelvic junction obstruction, vesicoureteral junction obstruction, posterior urethral valves)
Vesicoureteral reflux
Exstrophy of the bladder
Myelodysplasia and neurospinal dysraphisms with neurogenic bladder
Polycystic kidney disease (autosomal recessive, autosomal dominant)

obstructive nephropathy, cystic kidney disease, renal vein thrombosis, or tumor. Infants with the prune belly syndrome have redundant and wrinkled abdominal skin, undescended testes, and bilateral hydronephrosis. These patients often have an element of renal dysplasia and renal insufficiency. It should be noted that cryptorchism may be associated with renal anomalies even in the absence of the prune belly syndrome. An additional constellation of abnormalities often associated with renal insufficiency in the neonate is the VATER association. This is an acronym for vertebral defects, imperforate anus, tracheoesophageal fistula, and radial dysplasia. Over half of these patients have abnormal renal development. The VACTERL association adds cardiac defects, most commonly ventricular septal defect. Myelomeningocele is associated with variable degrees of bladder dysfunction, which may lead to reflux nephropathy or hydroureteronephrosis and renal insufficiency. For all of these infants with lower urinary tract abnormalities, close monitoring of bladder function (including residual bladder capacity) is important, since intermittent bladder catheterization may prevent the progression of renal insufficiency. A number of chromosomal defects may include renal abnormalities. The most common are Down Syndrome (associated with hydroureteronephrosis), and Turner Syndrome (associated with horseshoe kidney or duplicated collecting system) (*Table 289.2*).

Signs of Renal Disease in the Neonate

Oliguria. The signs suggestive of renal disease in the neonate are nonspecific, and include pallor, poor feeding, vomiting, and convulsions. Fever and jaundice are compatible with urosepsis, which may accompany renal malformations. Of all the signs associated with neonatal

urinary disorders, oliguria is the most helpful. It should be noted that all normal newborns void within the first 24 h of life. Thus, an infant remaining anuric beyond the first day of age should be investigated. Abdominal examination may reveal a distended bladder consistent with bladder outlet obstruction (most commonly due to posterior urethral valves). Based on the ordinary dietary solute load and the maximal renal concentrating capacity of the newborn, the infant must produce 0.5–1.0 ml/kg/h of urine to remain in solute balance. Thus, by definition, neonatal oliguria is a urine output of less than 0.5–1.0 ml/kg/h.

Hypertension. Hypertension in the neonate is usually renovascular in origin (Table 289.3). This may be associated with microemboli from an indwelling umbilical artery catheter. Additional causes of hypertension include acute kidney injury, polycystic kidney disease, and obstructive nephropathy. However, non-renal causes of hypertension should also be considered, including bronchopulmonary dysplasia, congenital virilizing adrenal hyperplasia, intracranial hemorrhage, and neoplasms (Table 289.3).

Maternal drug and neonatal medication exposure should also be considered. Systolic blood pressure in term infants should be less than 90 mmHg during the first week of age, and less than 70 mmHg in the preterm infant (Table 289.1).

Edema. Neonatal edema may be associated with hydrops fetalis, which can result from Rh isoimmunization or fetal supraventricular tachycardia. The primary renal causes of neonatal edema are congenital nephrotic syndrome and lower urinary tract obstruction. Congenital nephrotic syndrome should be suspected in utero if the maternal serum alpha fetoprotein is elevated. In view of the loss of thyroid binding globulin in the urine of these infants, it is critical that thyroid function tests be monitored closely in infancy to allow appropriate thyroid replacement.

Table 289.3
Causes of hypertension in the neonate

Renovascular (aortic coarctation, renal artery stenosis or embolism, renal vein thrombosis)
Acute kidney injury, renal cortical necrosis, birth asphyxia
Polycystic kidney disease (autosomal recessive)
Renal hypoplasia/dysplasia, ureteropelvic junction obstruction
Bronchopulmonary dysplasia
Congenital adrenal hyperplasia, hyperthyroidism
Intracranial hemorrhage, increased intracranial pressure
Neoplasms (Wilms tumor, neuroblastoma)
Medications (dexamethasone, theophylline, caffeine, phenylephrine)
Maternal drugs (cocaine, heroin)

Hematuria. Gross hematuria in a newborn with a palpable abdominal mass, anemia, and thrombocytopenia strongly suggests renal vein thrombosis. Renal vein thrombosis should be suspected in the infant of a diabetic mother or in neonates with severe asphyxia. Cystic kidney disease and hydronephrosis can be associated with hematuria, and tumors such as mesoblastic nephroma or nephroblastomatosis may present with hematuria in the neonatal period. A number of drugs have been associated with hematuria in the neonate, including aminoglycosides, penicillins, anticonvulsants, aminophylline, and furosemide. Glomerulonephritis is a relatively rare cause of hematuria in the infant, although neonatal infections that can cause renal inflammation include syphilis, toxoplasmosis, and cytomegalovirus.

Proteinuria. Protein excretion is approximately 0.5 g/l on the first day of age, and falls rapidly to normal adult concentrations by the second week of age. Proteinuria may be seen with vascular disorders or inflammatory disorders described above. Heavy proteinuria in the neonate is most often associated with congenital nephrotic syndrome, which, unlike most nephrotic syndrome in young children, is not responsive to corticosteroids.

Bacteriuria. Less than 1% of neonates have asymptomatic bacteriuria, such that routine screening of neonates for bacteriuria is generally not indicated. Bacterial contamination of urine collected by plastic bag in neonates is over 6%. Febrile infants, however, are more likely to have bacteriuria as a manifestation of urosepsis, septicemia, vesicoureteral reflux, or obstructive nephropathy, and should have urine culture obtained by suprapubic aspiration or bladder catheterization.

Diagnostic Imaging of the Neonate with Prenatal Discovery of CAKUT

Ultrasound. Any neonate with a palpable abdominal mass or oliguria should have an abdominal sonogram. Normal values for length of neonatal kidneys measured by ultrasonography have been reported for term and preterm infants (Table 289.1), and it is important to relate measurements to gestational age. The position and echotexture of the kidneys can be determined, and Doppler ultrasound also permits the measurement of renal blood flow. Although polycystic kidney disease (including the autosomal

dominant form) can present in the neonatal period, the smallest cyst that can be resolved by sonography is approximately 5 mm so that not all cysts will be detected.

Postnatal evaluation of the neonate with prenatal hydronephrosis (renal pelvic diameter >5 mm) discovered by maternal ultrasonography should follow a sequence of steps to rule out correctible lesions, while minimizing invasive procedures or parental anxiety. An ultrasound examination of the kidneys and bladder should be performed at 5 days of age, and if normal, the ultrasound should be repeated at 1 month of age to rule out hydronephrosis that may only become apparent after this period of postnatal renal maturation. If the initial ultrasound is abnormal at either 5 days or 1 month, a voiding cystourethrogram (VCUG) should be obtained to rule out vesicoureteral reflux or bladder outlet obstruction (see below). If the VCUG is normal, a repeat ultrasound should be obtained at 3 months of age: infants with pelvic dilatation greater than 10 mm should undergo further evaluation (*Table 289.1*), including diuretic renography (see below). Preterm infants have a greater risk of adverse outcome, and should have prolonged follow-up.

Diuretic renography. The function of each kidney can be evaluated by renal scintigraphy using [^{99}Tc] tagged mercaptoacetyl triglycine (MAG3). This is preferable to intravenous pyelography in the neonate because radiation exposure is less, there is no significant osmotic load to the isotope, and renal visualization is superior. To evaluate functional ureteral obstruction, furosemide is administered, and the time required to clear half of the renal MAG3 ($T_{1/2}$) is determined for each kidney: $T_{1/2} < 10$ min is generally normal, while $T_{1/2} > 20$ min is indicative of obstruction ($T_{1/2}$ is indeterminate). While diuretic renography remains the best generally available technique to identify urinary tract obstruction in the neonate, there are many pitfalls in the procedure and its interpretation. For this reason, attempts have been made to standardize the protocol: one of the most widely used is the "well-tempered" renogram developed by the Society for Fetal Urology.

Voiding cystourethrogram. A VCUG should be performed in any infant found to have hydronephrosis or a significant renal anomaly by sonography. In addition to ruling out vesicoureteral reflux, VCUG also reveals details of bladder structural or functional abnormalities.

Measurement of Renal Function in the Neonate

Plasma creatinine concentration. Renal insufficiency in the hospitalized neonate is often detected first by an elevation in serum creatinine concentration. Unfortunately, serum creatinine concentration is notoriously unreliable in the neonatal period because of the lack of a steady state condition, and measurement at the lower limit of detection for the assay. Moreover, recent studies have shown that filtered creatinine undergoes tubular reabsorption in the neonate, which contributes to spuriously elevated values. The normal plasma creatinine concentration in 1–2-week-old term infants is 0.6–1.0 mg/dl (up to 2.0 mg/dl in the preterm infant) (*Table 289.1*). By 2 weeks of age, the concentration should fall to 0.2–0.6 mg/dl in the term infant, and 0.4–0.8 mg/dl in the preterm baby. Most useful is the determination of serial creatinine measurements in individual patients. An increase in plasma creatinine concentration over time is abnormal except for a transient increase in the first 2 weeks in very low birth weight infants. It should be recognized that renal maturation continues for at least the first 9 months of age, and that plasma creatinine concentration can plateau or decrease even in the face of a reduced number of nephrons (due to hyperfiltration by the remaining nephrons). In such patients, renal insufficiency may not be detected until later childhood or even adulthood.

Creatinine clearance. To track the glomerular filtration rate during growth of the infant (in whom body surface area is rapidly changing), it is useful to estimate the creatinine clearance using Schwartz's formula:

$$\text{Creatinine clearance}\left(\text{ml/min/1.73m}^2\right) = k \times L/P_{Cr},$$

where k equals an empiric constant (0.4), L equals body length in centimeters, and P_{Cr} equals plasma creatinine concentration in mg/dl. This measurement of renal function is adjusted for adult surface area: in very low birth weight neonates, creatinine clearance at birth is normally below 10 ml/min/1.73 m^2, a level that would be considered inadequate to support life in the older patient. However, glomerular filtration rate normally increases several fold during the first 2 months of age.

Renal concentrating and acidifying capacity in the neonate. While the neonate is able to produce dilute urine due to immaturity of the renal medulla, concentrating capacity is limited for the first 2 months of age to a maximum of 500–700 mOsm/kg (versus 1,200 mOsm/kg in the adult). For this reason, volume-contracted neonates are obligated to maintain a higher urine output than older children in order to stay in osmotic balance (to prevent a rise in BUN and creatinine). Neonates also have a reduced threshold for bicarbonate reabsorption, ranging from 15 to 25 mEq/l (*Table 289.1*): bicarbonate supplementation for neonates with plasma bicarbonate in this range do not exhibit

accelerated weight gain. The limited ability of neonates to excrete an acid load also improves by 6 weeks of age, and is more prolonged in the preterm infant.

Acute Kidney Injury

Most cases of acute kidney injury in the neonatal period are related to circulatory disorders (Table 289.4). Reduced renal perfusion due to hypovolemia may be a consequence of perinatal blood loss, asphyxia, septicemia, or vascular thrombosis with disseminated intravascular coagulation. Since a smaller proportion of the cardiac output supplies the kidneys of the neonate compared to the adult, heart failure may also profoundly reduce renal perfusion and glomerular filtration rate. Polycythemia (venous hematocrit greater than 65%) may cause hyperviscosity, and reduced renal plasma flow and glomerular filtration rate. In such cases, lowering the hematocrit by reduction exchange transfusion may restore glomerular filtration and urine output. Intravascular volume contraction may arise from severe hypoproteinemia due to congenital nephrotic syndrome. In each of these conditions of decreased effective circulating volume, fractional sodium excretion would be expected to be less than 1% for infants greater than 32 weeks gestational age (for lower gestational age infants, values are higher due to renal tubular immaturity).

Table 289.4
Causes of acute kidney injury in the neonate

Circulatory disorders
Hypovolemia (hemorrhage, dehydration)
Asphyxia
Septicemia
Vascular thrombosis, disseminated intravascular coagulation
Congenital heart disease (patent ductus arteriosus, aortic coarctation)
Polycythemia
Hypoproteinemia
Iatrogenic/toxic nephropathy (maternal or neonatal administration)
Angiotensin inhibitors
Prostaglandin synthase inhibitors (NSAIDs)
Aminoglycosides
Congenital anomalies of the kidneys and urinary tract (see Table 289.2)

The fractional sodium excretion can be calculated from urine obtained by in-and-out bladder catheterization, using the following formula:

$$FE_{Na} = 100\%(U_{Na} \times P_{Cr})/(P_{Na} \times U_{Cr}),$$

where P_{Cr} and P_{Na} represent plasma creatinine sodium concentration and U_{Cr} and U_{Na} are the urine creatinine and urine sodium concentrations, respectively. If an infant has a fractional sodium excretion less than 1% and evidence of hypovolemia without edema or congestive heart failure, intravascular volume expansion may restore urine output (Table 289.1). This must be done cautiously in the very low birth weight infant because rapid expansion may induce intraventricular hemorrhage or opening of the ductus arteriosus. With the development of established acute kidney injury, FE_{NA} exceeds 1% despite oliguria. Severe renal ischemia may lead to renal cortical necrosis. This is generally seen in the context of septicemia and disseminated intravascular coagulation.

Fetal exposure to maternal administration of angiotensin inhibitors (either angiotensin converting enzyme inhibitors or angiotensin receptor blockers) or nonsteroidal anti-inflammatory drugs can impair renal development and may result in severe perinatal renal insufficiency. As discussed below, neonates are exquisitely sensitive to angiotensin inhibitors administered postnatally, and may develop acute oliguria even with doses 10% of those used in older children. Prostaglandin synthase inhibitors, generally administered to infants with patent ductus arteriosus, can cause profound renal vasoconstriction and oliguria. It should be noted that acute kidney injury in a neonate resulting from administration of nephrotoxic antibiotics is often not oliguric, and may be detected only by following serial plasma creatinine concentration.

Management of acute kidney injury in the neonate. The initial priorities in a neonate with acute kidney injury include treatment of infection with broad spectrum antibiotics, maintenance of adequate tissue perfusion, and acid–base and electrolyte balance. One of the most useful parameters to follow is body weight. This should be determined accurately every 12 h. In the anuric infant, replacement of insensible losses may be estimated at 0.5–1.0 ml/kg/h for a term infant, but should be reassessed often with measurements of weight and serum electrolyte concentrations. Insensible losses are proportionately greater in the preterm infant (at least 1.5 ml/kg/h for a 1,000 g infant). Insensible losses should be replaced with 10–15% dextrose in water without added electrolytes. Additional losses in urine, gastrointestinal drainage, or other body fluid drainage, should be replaced with fluids of similar

composition or adjusted to compensate for electrolyte imbalances.

Arterial pH should be maintained above 7.2. Frequent administration of sodium bicarbonate solution to oliguric infants can result in significant hypernatremia, hypertension, congestive heart failure, patency of the ductus arteriosus, and intracranial hemorrhage. Peritoneal dialysis or hemofiltration should be considered in infants with uncontrolled fluid retention.

Although hyponatremia may be associated with overhydration, infants with hyponatremia and hyperkalemia may have congenital virilizing adrenal hyperplasia. Fractional sodium excretion is elevated (greater than 2.5%) in neonates with adrenal insufficiency regardless of glomerular filtration rate or state of hydration. Serum potassium concentration in the neonate is generally well tolerated up to 6 mEq/l (◉ *Table 289.1*). For higher potassium concentrations (or electrocardiographic evidence of hyperkalemia), infusion of calcium, glucose, and bicarbonate will reduce extracellular potassium concentration, but will not result in net removal of potassium from the body. Exchange transfusion with low potassium washed red blood cells reconstituted with fresh frozen plasma can reverse hyperkalemia in the neonate and may postpone the need for dialysis. Administration of ion exchange resin (Kayexalate) suspended in sorbitol can be given per rectum. This will also result in net removal of potassium from the infant but can lead to hypernatremia or bowel obstruction.

Careful attention must be paid to calcium and phosphorus balance. Infants should be given a formula with high calcium to phosphorus ratio and low potassium content. Calcium carbonate, administered orally in divided doses, should be used to control serum phosphorus in the normal range. Plasma calcium concentration should be monitored along with phosphorus, as infants with renal insufficiency may develop hypercalcemia. Aluminum containing compounds should be avoided due to the increased risks of aluminum encephalopathy and bone toxicity in infants.

Severe hypertension can be treated with intravenous hydralazine (0.15–0.6 mg/kg/dose), although a continuous intravenous infusion is preferable (0.75–5.0 μg/kg/min). To ensure adequate cerebral perfusion, hypotension should be avoided by continuous blood pressure monitoring via an indwelling arterial catheter or frequent cuff measurements (10–15 min intervals). Although angiotensin converting enzyme inhibitors can be administered at very low doses (0.1 mg/kg/day for captopril), these drugs are best avoided in very low birth weight infants because of an exaggerated hypotensive response.

Drugs in the infant with renal insufficiency. The optimal 1 h post-dose peak serum concentration for gentamicin is 4–8 mcg/ml, whereas the trough concentration should be 0.5–2 mcg/ml. The interval between doses of gentamicin in the sick, very low birth weight infant may be as long as 36 h if renal insufficiency is present. Careful monitoring of blood levels is therefore imperative.

Infants with cardiopulmonary or renal disease frequently receive furosemide. It should be remembered that the half-life of furosemide in the neonate is prolonged compared to adults, and doses should optimally be limited to no more than 2 mg/kg/day to avoid the development of ototoxicity. Prolonged use of furosemide (particularly when combined with glucocorticoids) predisposes infants to hypercalciuria, nephrocalcinosis, and urolithiasis. If chronic administration of furosemide is necessary, urine calcium/creatinine ratios should be checked weekly. In the term infant receiving breast milk, the ratio (mg/mg) should be less than 0.4 (up to 0.8 in the preterm infant) (◉ *Table 289.1*).

In addition to their effects on renal development, angiotensin converting enzyme inhibitors can severely lower glomerular filtration rate in neonates, and may even precipitate acute kidney injury. This is true also of cyclooxygenase inhibitors such as indomethacin, which is used to treat patent ductus arteriosus. It is best to avoid use of either angiotensin converting enzyme inhibitors or prostaglandin synthase inhibitors in infants with renal insufficiency or reduced functioning renal mass.

Long-Term Implications of Neonatal Renal Disorders

With increasing survival of very low birth weight and critically ill neonates, the long-term prognosis of these fragile patients is of growing importance. Acute kidney injury is independently associated with mortality in preterm infants weighing less than 1,500 g (a 1 mg/dl increase in serum creatinine concentration doubles the odds of death). As noted earlier, a perinatal reduction in nephron number increases the risk for cardiovascular and renal disease in older childhood or adulthood. Unfortunately, it appears that in very low birth weight infants, nephrogenesis does not progress normally (even if birth weight is appropriate for gestational age and regardless of additional perinatal renal insults). Given the growing epidemic of childhood obesity, even more disturbing is the discovery that obesity and preterm birth comprise additive risks for progression of kidney disease. Thus, every effort must be made by the pediatrician to avoid delay in

the detection of renal anomalies, renal injury, and renal dysfunction in the neonate. There is much justification for the continued follow-up (through adulthood) of renal function and blood pressure of every infant discharged from a neonatal intensive care unit.

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290 Approach to the Child with Hematuria

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Hematuria is a common finding in children and adolescents, often causing significant anxiety and prompting an extensive evaluation. Hematuria may be the initial manifestation of significant genitourinary disease although in many cases a diagnosis is not established even after consultation with a specialist. When microscopic hematuria (without proteinuria) is found as an incidental finding, significant pathology is rarely identified. If significant pathology is suspected, a logical approach to this common pediatric issue should be pursued. A careful assessment is required to determine the need for further testing or referral to a specialist.

Definition and Classification of Hematuria

Microscopic hematuria is defined by the presence of more than five red blood cells per high power field (hpf). In reality, hematuria is often detected initially by a urine dipstick. While this testing method is convenient, it is critical that the urine be examined under the microscope to establish the diagnosis of hematuria. A positive finding for blood on the strip indicates the presence of red cells, free hemoglobin, or myoglobin. A peroxidase substrate impregnated in the strip is oxidized in the presence of hemoglobin or myoglobin, which leads to a color change. These strips are very sensitive and can detect as few as two to five red cells per hpf. False-positive results may occur due to contamination with detergents used to clean the perineum, urine ph >9, heavy bacteriuria, or menstrual blood. False negatives may occur with a high intake of ascorbic acid. Practitioners should note that red cells may lyse in old or very dilute urine, giving the impression of a false-positive result. Once confirmed, hematuria should be classified as gross (visibly discolored) or microscopic, asymptomatic or symptomatic, and isolated or accompanied by proteinuria. Gross or visible hematuria and symptomatic microscopic hematuria will require prompt evaluation. In asymptomatic patients, persistence of hematuria should be confirmed on three samples over 2–3 weeks prior to conducting further investigation.

Gross Hematuria

Visible discoloration of the urine is frightening to children and parents and usually results in an urgent visit to the emergency room or doctor's office. The incidence of gross hematuria is not well established, but it is certainly much less common than microscopic hematuria. Gross hematuria is reported to account for 1.3/1,000 pediatric emergency clinic visits. Although the etiology is often easily determined, the diagnosis remains elusive in many. Greenfield et al. recently reviewed their 10-year experience and found that no etiology could be established in 118 of 342 children (34%) seen in a pediatric urology clinic. Similarly, two studies from pediatric nephrology practices have reported a failure to rmake a diagnosis in 38–44% of children.

Initial evaluation must include a microscopic exam of the urine sediment to confirm the presence of red cells (see *Fig. 290.1*). Other substances that may cause red or brown urine include medications, food and dyes, and some disease states. Microscopic exam of the urine also allows for identification of casts, white blood cells, epithelial cells, crystals, and/or bacteria. The finding of few red cells on microscopic exam in the face of red or brown urine supports a diagnosis of hemoglobinuria or myoglobinuria. Examination of the serum will further aid in differentiating between these two entities as the urinary supernatant will be pink in both conditions but the serum will only be pink in hemoglobinuria.

Once hematuria has been confirmed, it is helpful to categorize the hematuria as glomerular or non-glomerular in origin so that the evaluation can be focused on a limited set of diagnoses. Determination of the location of the bleeding will be guided by the associated complaints, past medical history, family history, physical exam, and the characteristics of the urine.

Gross Hematuria: Non-glomerular Source

Red or pink urine is suggestive of non-glomerular bleeding. Under the microscope, the red cells will appear

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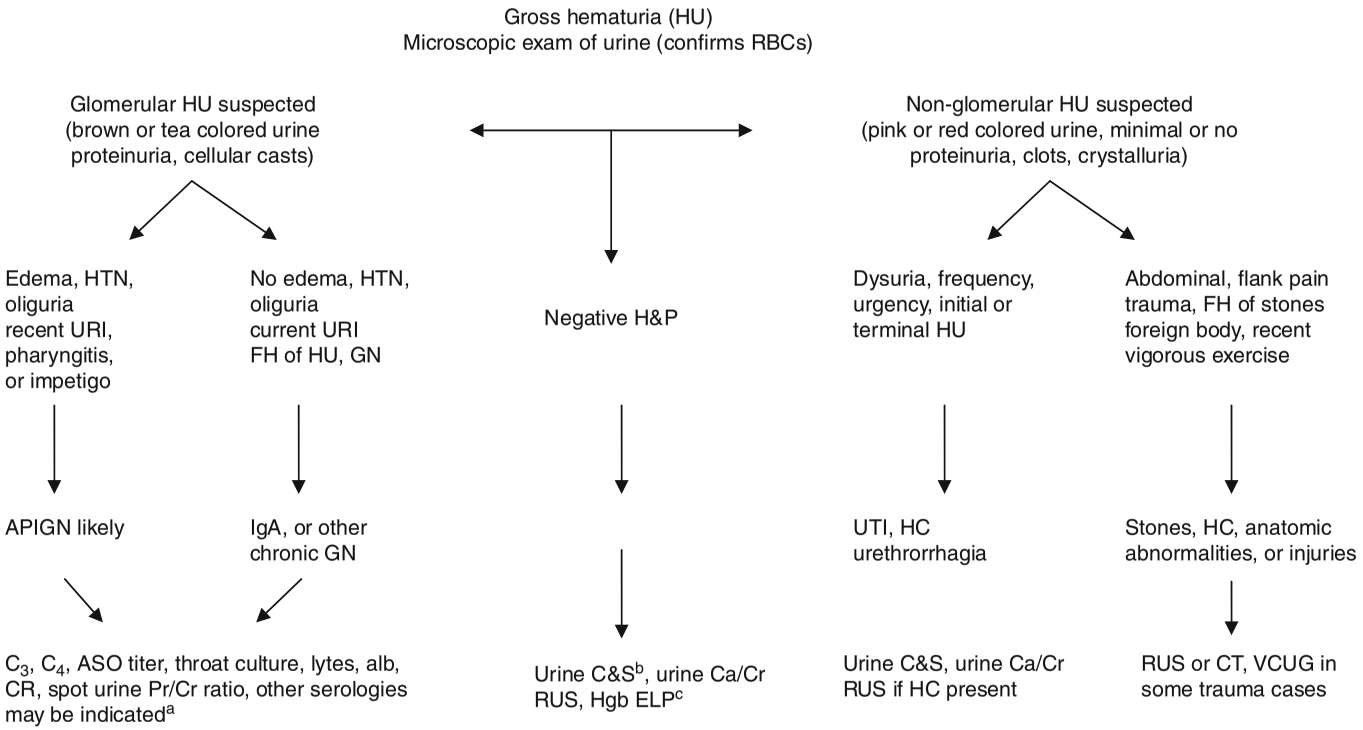

Figure 290.1

Algorithm for evaluation of gross hematuria.

[a]A more extensive evaluation may be indicated in selected patients with additional symptoms or findings. [b]Urine culture should be performed if other findings on urinalysis are suggestive of urinary tract infection. [c]Hemoglobin electrophoresis may be indicated in selected patients. Abbreviations: Alb, albumin, APIGN, acute post-infectious glomerulonephritis, ASO, antistreptolysin antibody titer, C&S, culture and sensitivity, C_3, complement C_3, C_4, Complement C_4, CT, computed tomography, CR, serum creatinine, ELP, electrophoresis, FH, family history, GN, glomerulonephritis, Hgb, hemoglobin, HTN, hypertension, HU, hematuria, HC, hypercalciuria, IgA, IgA nephropathy, RBCs, red blood cells, RUS, renal and bladder ultrasound, Urine Ca/Cr, urine calcium/creatinine ratio, Urine Pr/Cr, urine protein/creatinine ratio, URI, upper respiratory infection, UTI, urinary tract infection, VCUG, voiding cystourethrogram

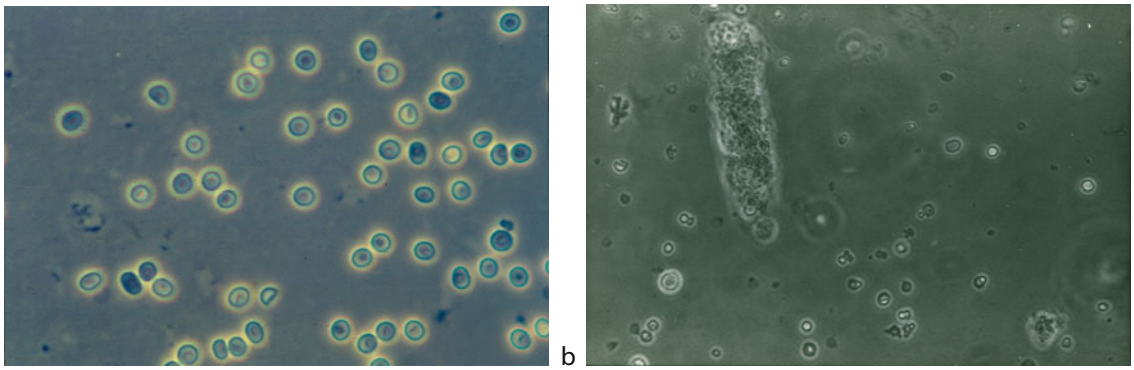

Figure 290.2
Red blood cells on microscopic examination of urinary sediment. Panel (a) shows eumorphic red cells with uniform size characteristic of non-glomerular hematuria. Panel (b) demonstrates dysmorphic red cells with variable sizes, shapes, and cytoplasmic blebs. A red cell cast is also demonstrated

uniform (see *Fig. 290.2a*). Proteinuria is typically minimal, but if urine is very bloody, proteinuria of +2 (or 100 mg/dL) may be seen in non-glomerular hematuria. The presence of clots or crystals would offer further support for a non-glomerular cause. It is helpful to determine if the urinary stream is discolored throughout the stream. Initial or terminal hematuria would indicate bleeding in the urethra or bladder trigone.

Common causes of non-glomerular gross hematuria include urinary tract infections, urethrorrhagia, trauma, hypercalciuria, nephrolithiasis, and exercise. Other causes include foreign bodies, autosomal-dominant polycystic kidney disease, coagulopathies, sickle-cell trait and anemia, and Wilms' tumor. Occurrence of hematuria after minor trauma raises concern about a preexisting anatomic abnormality such as hydronephrosis or a cystic kidney. Occasionally, non-glomerular hematuria may be factitious in nature. Associated symptoms such as abdominal or back pain, dysuria, frequency, urgency suggest a non-glomerular cause. A past history of urinary infections, hydronephrosis, renal cysts, sickle-cell trait or disease, and bleeding disorders would be pertinent. Relevant findings from the family history would include nephrolithiasis, vesicoureteral reflux, urinary infections, and sickle-cell trait or disease. On physical examination, the child should be assessed for an abdominal mass, costovertebral angle tenderness, abdominal or suprapubic tenderness, and evidence of trauma or abuse. Examination of the genitalia is always indicated to assess for evidence of abuse, trauma, or anatomic abnormalities.

Initial testing for non-glomerular hematuria may include urine culture, spot urine calcium/creatinine ratio, and imaging of the kidneys and bladder. A computed tomography (CT) scan with contrast is the best diagnostic study to investigate trauma, particularly in an unstable patient. A CT without contrast is the gold standard for identification of nephrolithiasis. However, if radiation exposure is a concern, an ultrasound is an acceptable alternative. Ultrasound will visualize most stones but may not reliably demonstrate small calculi and/or ureteral stones. Hypercalciuria has been reported to account for 16–43% of gross hematuria even if nephrolithiasis is not present. Abdominal pain, dysuria, and other urinary symptoms may also be associated with hypercalciuria. In a recent series, urethrorrhagia was identified as the etiology in 14–19% of the cases of gross hematuria. Urethrorrhagia occurs primarily in prepubertal boys and may be accompanied by dysuria and/or frequency. Spots of blood are often noted in the underwear. If the stream is observed the gross hematuria is usually terminal. The etiology of this process remains unclear, but the problem is usually self limited with resolution reported in 71% and 92% of the children within 1 and 2 years, respectively. Infrequently, painless gross hematuria occurs in patients with sickle-cell trait or sickle-cell anemia and typically originates from the left kidney. Although coagulation defects may result in hematuria, urinary bleeding is rarely the initial presentation for the defect.

Gross Hematuria: Glomerular Source

Brown- or tea-colored urine is characteristic of glomerular hematuria. In some cases, however, the urine will appear dark red, leading to some doubt as to the location of

bleeding. The concomitant finding of significant proteinuria (+2 or greater) and cellular casts would suggest a glomerular disease. Under the microscope, the red cells may show variability in size, and may have cytoplasmic blebs (see *Fig. 290.2b*).

Common causes of glomerular hematuria include post-infectious glomerulonephritis, Henoch–Schönlein purpura, IgA nephropathy, and, less often, Alport syndrome, systemic lupus erythematosus (SLE), and other types of acute or chronic glomerulonephritis. Symptoms of oliguria, unexplained weight gain, arthritis, arthralgias, recent pharyngitis or impetigo, rash, dyspnea, or fatigue would raise concern about glomerular disease. The family history should be reviewed for hematuria, hearing loss in adolescence or early adulthood, renal failure, and specific disorders such as SLE or Alport syndrome. On physical examination, findings of edema, hypertension, rash, purpura, arthritis, cough, or rales would be consistent with glomerulonephritis. Poor growth might suggest an underlying chronic kidney disease.

If glomerular hematuria is suspected, initial laboratory studies should include a serum creatinine, electrolytes, albumin, complete blood count, complement C_3 level (C_3), an antistreptolysin antibody titer (ASO titer), and a throat culture. The amount of proteinuria should be quantitated with a spot urine for protein and creatinine. A protein/creatinine ratio <0.2 mg/mg is normal. It should be noted that a negative ASO titer does not exclude post-infectious glomerulonephritis, which can follow a variety of bacterial, viral, and parasitic infections. However, the C_3 will be low with most post-infectious glomerulonephritis if the level is checked at the time of presentation. Hypertension and edema are frequently noted as well. Recurrent episodes of hematuria during upper respiratory illnesses would be suggestive of IgA nephropathy. In contrast to post-infectious glomerulonephritis, the C_3 is normal in IgA nephropathy, as is the blood pressure. Another differentiating point is the latent period, which is typically less than 5 days in IgA nephropathy versus 10–21 days following respiratory infections in post-infectious glomerulonephritis. Families should be educated on the need for follow-up after an initial diagnosis is made. Hematuria may persist on microscopic exam even after gross hematuria resolves. Exercise and illness can exacerbate an underlying chronic glomerulonephritis leading to episodes of gross hematuria superimposed on chronic microscopic hematuria. Significant proteinuria, hypertension, reduced renal function, oliguria, edema, or other systemic symptoms should prompt referral to a pediatric nephrologist for further evaluation and treatment.

Microscopic Hematuria

Microscopic hematuria is much more common than gross hematuria; screening of unselected populations in the past demonstrated a prevalence of 0.4–2% in children aged 6–15 years. While routine urine screening is no longer recommended by the American Academy of Pediatrics, microscopic hematuria may be detected when a urinalysis is performed in response to a symptom or a finding on physical exam. Not infrequently, the symptom or finding prompting the urinalysis resolves, leaving persistent, and often unexplained, hematuria.

When microscopic hematuria is detected, a complete history and physical exam should be performed addressing key points as mentioned in the discussion of gross hematuria. A genitourinary exam should be performed to exclude perineal irritation or anatomic abnormalities. The urine should be examined under the microscope at least once to confirm the presence of red cells and to assess for associated findings. In the absence of symptoms or signs, characteristics of the urine may offer the only clues as to the site of bleeding (as noted under gross hematuria). A very active urinary sediment with many red cells accompanied by white cells or cellular casts would raise concern for the possibility of significant glomerular disease. If there is no obvious cause for the hematuria, the child should be asked to avoid exercise for 24–48 h prior to subsequent checks to eliminate exercise as an etiology. If the child is symptomatic or if there are concerning findings from the history, the physical examination, or the urinalysis then a similar evaluation to that described for gross hematuria should be carried out.

Evaluation of Microscopic Hematuria

Common causes of microscopic hematuria include urinary tract infection, hypercalciuria, benign familial hematuria, IgA nephropathy, post-infectious glomerulonephritis, exercise, nephrolithiasis, and sickle-cell trait or anemia. In asymptomatic children, hypercalciuria, benign familial hematuria, and IgA nephropathy are the more frequently identified causes. In view of the favorable prognosis of microscopic hematuria, a limited evaluation is recommended. If the history and physical are not suggestive of an etiology, initial evaluation can be restricted to a spot urine calcium and creatinine, a check of urine samples from the parents for hematuria, and a hemoglobin electrophoresis in selected patients. Other studies are not necessary, but may be obtained in some cases to

alleviate parental anxiety. Parents may be reassured by checking a serum creatinine and renal ultrasound to demonstrate that renal function is normal and to exclude a renal or bladder mass. In fact, Wilms' tumor and other renal malignancies rarely present with isolated asymptomatic microscopic hematuria.

Common Causes of Microscopic Hematuria

Hypercalciuria has been implicated as a cause of microscopic hematuria in 11–16% of children. A higher prevalence of hypercalciuria is reported in children from the southern United States. While a 24-h urine is the ideal test, it is appropriate to screen for hypercalciuria with a random spot urine for calcium and creatinine. The urine calcium/creatinine ratio should be under 0.86 mg/mg for infants under 6 months, under 0.60 mg/mg for infants ages 6–18 months, under 0.42 mg/mg for children ages 19 months to 6 years, and under 0.2 mg/mg for children over 6 years. Hematuria may occur even in the absence of nephrolithiasis and has been attributed to mucosal irritation.

Benign familial hematuria is a frequent cause of microscopic hematuria. A large study of children with microscopic hematuria reported that a family history of hematuria may be present in up to 25% of children with microscopic hematuria. A urine sample should be obtained from the parents, if possible, to check for hematuria rather than relying on historical information. Recent studies have suggested that benign familial hematuria is inherited in an autosomal-dominant pattern. This entity is also referred to as thin membrane disease as the renal biopsy is characterized by exceeding thin glomerular basement membranes. While progressive disease has rarely been reported, most patients with this condition remain asymptomatic, maintain normal renal function, and have no extrarenal manifestations. Gross hematuria is not typical but may occur. Alport syndrome occurs less frequently and is usually inherited in a X-linked dominant pattern. Males without a positive family history could represent a new mutation or have autosomal-recessive disease. Males typically develop hearing loss, proteinuria, and progressive renal insufficiency in the second or third decade of life. Manifestations are generally less severe in females who generally maintain normal renal function and are less likely to develop hearing loss. Microscopic hematuria in a boy's father and a negative family history for males with hearing loss and renal failure in adolescence or young adulthood would support a diagnosis of benign familial hematuria. A hearing test to check for high frequency hearing loss may be helpful in older boys. While the diagnosis is usually made based on the clinical picture and family history, further diagnostic testing including genetic testing, or tissue biopsy may be indicated in some cases.

IgA nephropathy, the most common type of primary glomerulonephritis worldwide, may also present with isolated microscopic hematuria. Other presentations include intermittent gross hematuria with interim microscopic hematuria, a combination of hematuria and proteinuria, isolated proteinuria, or nephrotic syndrome. Although this entity may be suspected on clinical grounds, a kidney biopsy is required to definitively establish the diagnosis. Biopsy is usually deferred if manifestations are limited to microscopic hematuria as there is no recommended intervention in the absence of proteinuria. Follow-up of hematuria is crucial as up to 40% of patients with IgA nephropathy develop proteinuria and progressive disease over time. IgA nephropathy can be difficult to differentiate from post-infectious glomerulonephritis, which may present with microscopic hematuria as the sole manifestation. With post-infectious glomerulonephritis, the hematuria typically resolves within 4–6 months but will likely persist with IgA nephropathy.

Natural History of Microscopic Hematuria

If the child is asymptomatic and initial studies do not reveal a cause, observation is suggested. Follow-up should be performed every 4–6 months for the first year, and then yearly, to screen for the development of proteinuria, hypertension, or new related complaints. Many families need reassurance that observation is acceptable. Several studies support a limited evaluation for asymptomatic microscopic hematuria. In a retrospective review of 325 patients referred to two pediatric nephrology practices, the authors found that studies such as renal ultrasound, voiding cystourethrogram, C_3, and creatinine did not yield meaningful data in children with isolated asymptomatic microscopic hematuria. A large review of cases referred to a nephrology clinic reported that no cause was identified in 80% of children with microscopic hematuria. These investigators emphasized the need for follow-up. Over time, the prognosis of microscopic hematuria is excellent, with few children showing evolution to more significant disease. In many cases, the hematuria resolves over several months to years. Remission occurs at the rate of 25–30% per year. Children with more significant hematuria (more than 10–20 red cells per hpf) are more likely to show persistence of hematuria over time.

Criteria for Referral to Specialist

Gross and microscopic hematuria occur commonly in children and the pediatrician should follow a logical approach to the evaluation based on findings from the urinalysis, history, and physical examination. Consultation with a pediatric nephrologist should be considered in children with associated systemic complaints or disorders, edema, oliguria, significant proteinuria, an elevated creatinine, recurrent gross hematuria, and/or family history of renal failure, nephritis, or early onset hearing loss. In some cases, a referral may be indicated to offer reassurance to the family. Referral to a pediatric urologist is indicated in children with nephrolithiasis, anatomic defects, a history of trauma, or unexplained non-glomerular gross hematuria. The vast majority of children with hematuria can be managed by their primary care provider.

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291 Approach to the Child with Proteinuria

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Introduction

Protein in the urine, termed proteinuria, is a common urinary finding among pediatric and adolescent patients and can be indicative of a normal, benign process or of numerous types of pathologic renal diseases. This distinction can be determined through a stepwise evaluation process of the type and degree of proteinuria and associated systemic findings. In the 1800s, Dr. Richard Bright first described an association between proteinuria and renal disease. Since that time, many clinical diagnoses have been identified with the associated finding of proteinuria, which can be accompanied by edema, hypoalbuminemia, macroscopic or microscopic hematuria, hypertension, abnormal kidney function, or systemic findings. The general practitioner should begin initial urinary testing and then proceed to a pediatric nephrology referral depending upon the results of the initial evaluation.

Definition

Proteinuria is defined as urinary protein excretion at levels higher than 100–150 mg/m^2/24-h period. The main components of urinary protein include albumin, beta$_2$-microglobulin, immunoglobulins, and Tamm–Horsfall mucoproteins although many other plasma proteins may be present, depending upon the underlying disease process. High levels of protein excretion characterize nephrotic-range proteinuria and nephrotic syndrome. Abnormalities occurring at various locations of the nephron will lead to various types and degrees of proteinuria.

Proteinuria Measurement

Proteinuria can be evaluated in the following ways: urinary dipstick reagent testing, sulfosalicyclic acid (SSA) turbidity testing, random or first morning urine specimen evaluation for a urine protein-to-creatinine ratio (U_{Pr}/U_{Cr}), 24-h quantitative urine collection for urinary protein and creatinine content, urine protein electrophoresis, or urinary microalbumin level (*Table 291.1*). The most commonly used screening tool for urinary abnormalities and renal disease is the urinary dipstick test. This is a qualitative and semiquantitative method. Freshly voided specimens are preferred, but if this is not feasible, the urine should be refrigerated and then brought to room temperature before analysis. The reagent strip should be quickly removed from the bottle, immersed in the fresh urine specimen, blotted to remove any excess urine, and then analyzed within 30 s to 2 min. The reagent strip is impregnated with a chromatophore called tetrabromophenol blue, which is a pH indicator that changes color based upon the amount of amino acids in the urine. The color change begins with yellow at normal levels and changes to green and then bluish-green with higher levels of proteinuria.

The urinary dipstick method is most sensitive to the albumin content in the urine and is less sensitive to other types of proteins, such as low molecular weight proteins, globulins, and plasma proteins. A graded scale is then reported as follows: negative (less than 10 mg [mg] per deciliter [dL]), trace (10–20 mg/dL), 1+ (30 mg/dL), 2+ (100 mg/dL), 3+ (300 mg/dL), or 4+ ($\geq$2,000 mg/dL). False-positive results can occur when the reagent strip is immersed too long in the fresh urine specimen or with alkaline or highly concentrated specimens, pyuria, macroscopic hematuria, and certain detergents. False-negative results can occur in very dilute urine specimens or when the urinary protein content is not primarily albumin. A dipstick urine test is considered positive for proteinuria if at least three specimens collected one or more weeks apart are 1+ (30 mg/dL) or greater, depending upon the concentration and pH of the urine.

The qualitative SSA test is less commonly used but has the advantage of detecting a broader range of proteins in the urine, including albumin, immunoglobulins, and Bence-Jones proteins. This is a turbidometric method of urine testing. The SSA reagent is added to a freshly voided specimen, and the degree of turbidity is correlated to the amount of proteinuria based upon a predetermined scale. Acidification of the urine causes precipitation of urinary

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Table 291.1
Different types of urinary proteinuria measurements

Method	Technique	Normal range	Advantages	Disadvantages
Dipstick testing	Random or first morning specimen	Negative or trace (<20 mg/dL)	Ease of collection, screening tool, most sensitive to albumin	Qualitative, results sensitive to urine pH and specific gravity
SSA test[a]	Random or first morning specimen	Negative or trace (<10 mg/dL)	Broader range of urinary protein detection, including low molecular weight proteins	Subjectivity of results scale, sensitive to urine pH and specific gravity
(U_{Pr}/U_{Cr})[b]	Random or first morning specimen	<0.8; <6 months of age <0.5; 6–24 months of age <0.2; >2 years old	Semiquantitative, approximates 24-h collection	Unreliable if malnourished, low muscle mass, low GFR[c]
24-h urine collection	Total or recumbent versus upright collection	<150 mg/m^2/24 h	Most accurate quantitative method	Inadequate collection leads to inaccuracy, difficult to perform if incontinent and in children
Protein electrophoresis	Random specimen	N/A[d]	Detects percentage of albumin and low molecular weight proteins	Cost, test specificity may lead to result delays
Microalbumin level	First morning specimen	<20 mg albumin/g creatinine	Useful in diabetic patients	Ongoing research for appropriate interpretation

[a]Sulfosalicyclic acid (SSA) turbidity test
[b]Urine protein-to-creatinine ratio
[c]Glomerular filtration rate (GFR)
[d]Not applicable

proteins, which is graded in a fashion similar to urinary dipstick testing. A disadvantage to this type of testing is the subjectivity in the grading scale, and thus this technique is rarely used. False-positive results can occur with recent exposure to radiographic contrast material, high concentrations of penicillin or cephalosporin antibiotics, or with high uric acid concentration in the urine. False-negative results can occur in the setting of highly buffered alkaline or diluted urine specimens.

The urine protein-to-creatinine ratio is a highly useful tool for quantitative measurements of proteinuria in the pediatric population because 24-h urine collections are prone to inaccuracies in collection or are not possible in an infant or younger child who is not yet toilet trained. The correlation between (U_{Pr}/U_{Cr}) and 24-h urine collection results has been established in several studies and among many disease processes. The (U_{Pr}/U_{Cr}) can be calculated on a random, or untimed, specimen or on a first morning urine (FMU) specimen. Accuracy in the FMU collection is imperative in the diagnosis of certain types of proteinuria (*Fig. 291.1*). FMU analysis is preferred due to the large degree of variability in urinary protein levels throughout the day. A freshly voided urine specimen is sent for urine protein and urine creatinine levels in mg/dL units, and then the ratio is determined. The ratio result is then estimated to a 24-h urine collection. For example, a (U_{Pr}/U_{Cr}) of 0.2 is approximately equivalent to 150–200 mg of protein in a 24-h collection. The normal (U_{Pr}/U_{Cr}) range for infants less than 6 months of age is not clearly defined, but it has been shown that protein excretion rates in infants are higher than in older infants and children; ratio values higher than 0.8–1 in young infants are generally considered abnormal. The normal ratio for children 6–24 months of age is less than 0.5 and for children older than 2 years of age and adults is less than 0.2. Pathologic proteinuria occurs at ratio values greater than 1–2 in a pediatric population, but this value can also be considered normal in certain situations, as discussed below.

Although the (U_{Pr}/U_{Cr}) is utilized frequently for pediatric patients, there are some limitations to its use. The ratio is dependent upon the production and excretion of creatinine, which can be variable depending upon the child's body habitus. In children with severe malnutrition or low

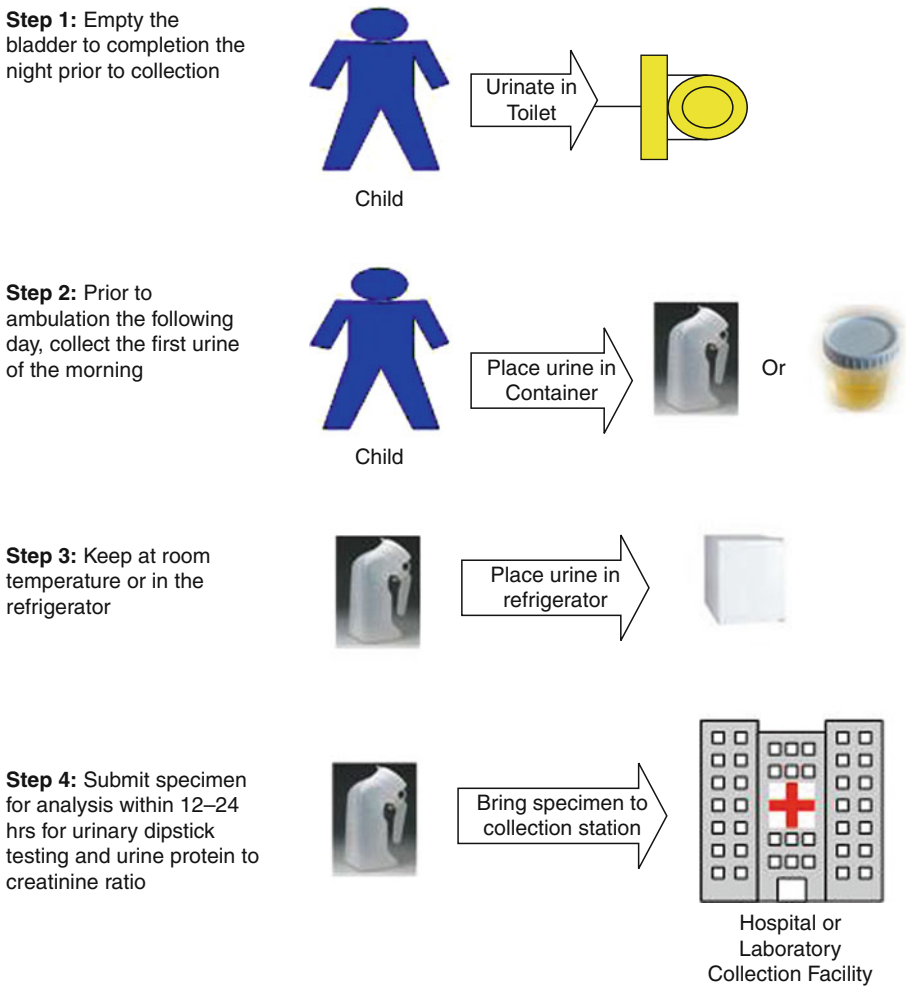

Figure 291.1
First morning urine (FMU) collection technique to assess for orthostatic proteinuria

muscle mass, creatinine excretion is expected to be low, which will result in an elevated (U_{Pr}/U_{Cr}). In patients with orthostatic, or postural, proteinuria, higher values are acceptable and expected for untimed urine specimens, and therefore first morning urine specimens should be utilized to more accurately assess protein excretion rates. Febrile patients or those who have exercised recently may demonstrate transient elevations in protein excretion, thus a (U_{Pr}/U_{Cr}) should be performed for afebrile patients at rest. Finally, the interpretation of (U_{Pr}/U_{Cr}) in patients with low glomerular filtration rates may be difficult and should be reserved for a pediatric nephrologist. If the results are potentially misleading, a 24-h urine collection should be attempted to confirm urinary protein quantification. Despite these potential limitations, the (U_{Pr}/U_{Cr}) is a highly useful assessment tool for proteinuria quantification in the pediatric population and can be utilized to track protein excretion over time in many clinical situations.

The gold standard for urinary protein quantitation among all populations is the 24-h urine collection. This can be performed as a total 24-h collection or as a split collection, with upright (ambulatory) versus supine specimens evaluated separately. The latter is primarily performed if orthostatic proteinuria is suspected. Most authors regard protein levels of 100–150 mg/m^2/24 h (mg/m^2/day) to be normal for infants, children, and adolescents; preterm infants and neonates have high levels of basal protein excretion and, therefore, higher amounts of proteinuria are acceptable. Proteinuria in pediatric patients greater than 1,000–2,000 mg in 24 h is generally

observed to be pathologic, except if orthostatic proteinuria is suspected. Variations in quantifying proteinuria can be diminished using body surface area with 24-h urine collection results as follows: normal $\leq$4 mg/m^2/h, abnormal 4–40 mg/m^2/h, and nephrotic-range proteinuria >40 mg/m^2/h. As noted previously, these collections can be cumbersome to perform, may have a high degree of under-collection leading to inadequate specimens (such as with incontinent patients), may delay the diagnostic work-up due to the length of time needed for collection and analysis, and cannot be performed in non-toilet-trained patients, limiting its utility in pediatric populations. Despite these limitations, this is the most accurate method to specifically quantitate the degree of proteinuria and can be quite useful in determining if further evaluation is warranted.

Two special situations may warrant additional evaluations for proteinuria. The first is in the setting of low molecular weight proteinuria, in contrast to albuminuria, which can be seen in tubular or interstitial renal diseases. Tubular proteinuria may be underestimated on urinary dipstick testing, due to the lower levels of albuminuria. In this circumstance, a urine protein electrophoresis should be evaluated on a urine bag specimen in infants or from a clean catch urine collection in older children and adolescents. This testing will elucidate the percent of proteinuria content, that is, albumin, beta$_2$-microglobulin, alpha globulins, monoclonal proteins, etc. If a malignancy involving the over-production of immunoglobulins is suspected, a urine immunofixation electrophoresis can also be assessed.

Second, in the setting of children with diabetes mellitus, more specific quantitation of lower levels of proteinuria than can be detected on urinary dipstick testing is required. The urine microalbumin level can be determined, and a urine microalbumin to creatinine ratio (MA:Cr) can be calculated, similar to a urine protein-to-creatinine ratio. The normal range is less than 20–30 mg of urine albumin per gram of creatinine on a first morning specimen. A consensus group defined microalbuminuria as a urine albumin excretion level of 20–200 μg/min/1.73 m^2 or 30–300 mg albumin per gram creatinine per 24 h and frank proteinuria as greater than 200 μg/min/1.73 m^2. This ratio should be assessed on a first morning urine specimen. In patients with type I and type II diabetes mellitus, microalbuminuria has been shown in numerous studies to be a predictor of progressive renal disease and potentially cardiovascular morbidity and mortality. One recent study, however, did not demonstrate a correlation between elevated urine microalbumin levels and progressive renal disease. Currently, the recommendation is to follow this ratio periodically in patients with diabetes mellitus and initiate therapy when the MA:Cr is above the normal range. Some have also proposed utilizing this ratio in hypertensive patients and in other clinical situations as an early indicator for end organ damage and deleterious long-term cardiovascular effects.

Epidemiology

The prevalence of protein in the urine will vary based upon the definition of proteinuria used and the number of urine specimens evaluated. Proteinuria is a common finding in urine specimens with an overall prevalence ranging between 5% and 15% in a single void specimen. One study of over 1,000 patients with abnormal urinary findings detected in a mass school urine screening process in Korea reported proteinuria in over 50% of the abnormal urine specimens; the majority of these patients had either transient or orthostatic proteinuria. Pathologic or persistent proteinuria occurs in a minority of patients, with rates ranging from 0.1% to 2%. About 1 in 1,000 school-aged children will have persistent proteinuria after testing of three or more specimens. The prevalence increases with increasing age and peaks in adolescence. One study reported that the peak prevalence in females is 13 years of age and in boys is 16 years of age. The incidence of idiopathic nephrotic syndrome (NS) has been reported to occur in a range of 2–7/100,000 children and a prevalence of about 16 cases per 100,000 children per year. Despite overall low rates of proteinuria among pediatric patients, early detection, evaluation, and treatment of pathologic proteinuria is critical due to the potential for significant long-term renal parenchymal disease and progression to end-stage renal disease.

Etiology of Proteinuria

Many renal diseases are associated with proteinuria, which may be asymptomatic or associated with other findings such as edema, hematuria, or diverse systemic symptoms. Various classification systems have been developed to distinguish different forms of proteinuria. There are important differences among the following classes of proteinuria: transient, orthostatic, isolated, and persistent (*Table 291.2*). Each of these categories will be discussed separately below and have different levels of concern for the primary care provider and pediatric nephrologists.

Transient proteinuria is not typically associated with significant renal parenchymal disease and will resolve when the inciting factor ceases. This type of proteinuria

Table 291.2
Categorization of proteinuria

Category	Testing method	Examples	Monitoring
Transient	Urinary dipstick	Fever, stress, dehydration, cold exposure, seizure activity, strenuous exercise	Repeat urine testing when inciting factor resolves to confirm negative result
Orthostatic	First morning urine dipstick test or (U_{Pr}/U_{Cr})[a] (rarely 24-h urine recumbent versus upright collection)	Common in older children and adolescents	Intermittent first morning urine and blood pressure assessments
Isolated	Urinary dipstick, (U_{Pr}/U_{Cr}), or 24-h urine collection	Asymptomatic patient with normal laboratory tests, physical exam and blood pressure	Periodic monitoring, consider pediatric nephrology referral
Persistent	Urinary dipstick, (U_{Pr}/U_{Cr}), or 24-h urine collection	Nephrotic syndrome, glomerular or systemic diseases	Detailed evaluation, long-term monitoring, pediatric nephrology referral warranted

[a]Urine protein-to-creatinine ratio

can be observed in the setting of fever, stress, dehydration, cold exposure, seizure activity, or strenuous exercise. Exercise-induced proteinuria usually remits within a few hours but may last as long as 48 h after completion of strenuous exercise. This proteinuria may be due to hemodynamic changes in glomerular blood flow resulting in increased protein diffusion into the urine. Urine dipstick test results are usually 2+ or lower and resolve on subsequent testing. Further evaluation is not necessary.

Orthostatic, or postural, proteinuria is a common finding in older children and adolescents, accounting for over 60% of all proteinuria and occurring in approximately 3–5% of adolescents. The hallmark of orthostatic proteinuria is elevated protein excretion in ambulatory, or untimed, urine specimens and normal or minimal protein excretion during recumbency. Precise first morning urine specimen collection by the patient is critical to accurately diagnose this type or proteinuria. Urinary dipstick testing via first morning urine collection, (U_{Pr}/U_{Cr}), and 24-h urine collections can all be used for diagnosis, but 24-h collections are rarely required if the FMU is collected appropriately. The total urinary protein excretion in orthostatic proteinuria rarely exceeds 1 g in a 24-h urine collection although some collections may exceed this value; a split 24-h urine collection with supine, or recumbent, versus upright specimens evaluated separately can easily yield the diagnosis, and affords more accurate distinction in proteinuria levels based on patient behavior. The precise etiology of this type of proteinuria is unclear, and some have proposed that renal hemodynamic changes, partial renal vein occlusion, increased permeability of the glomerular capillary wall, or circulating immune complexes may be factors. Follow-up studies of 20–50 years have observed that orthostatic proteinuria is a benign process with few to no long-term renal effects; however, rare cases of later onset glomerulosclerosis or other abnormalities have been reported. Therefore, periodic monitoring of first morning urine specimens and blood pressures is currently recommended and can be performed either by the primary care provider or by a pediatric nephrologist. Parents and patients can be counseled that the long-term prognosis is generally excellent.

Isolated proteinuria is characterized by asymptomatic proteinuria in an otherwise healthy patient with normal physical exam findings, blood pressure readings, urinary sediment, and laboratory findings at the time of diagnosis. Usually the degree of proteinuria is less than 2 g in 24 h; higher values indicate the need for a further investigation into the etiology of the proteinuria. The majority of these individuals do not have progressive renal disease, although in some studies, a minority of renal biopsy specimens revealed abnormal histology such as focal segmental glomerulosclerosis. Some studies predict a 20% risk for progressive renal damage over a 10-year period. Therefore, an initial thorough evaluation as well as close long-term monitoring is indicated, and a referral to a pediatric nephrologist is recommended.

Persistent proteinuria is defined as urinary dipstick results of 1+ (>30 mg/dL) or higher levels of proteinuria on three or more specimens separated by several weeks. A (U_{Pr}/U_{Cr}) and possibly a 24-h urine collection should be performed, assuming that orthostatic proteinuria has been excluded. A detailed patient history, physical exam, and family history should be followed by a more extensive

evaluation including laboratory and radiology studies. The list of potential etiologies is extensive and includes nephrotic syndrome, glomerulonephritis, and systemic renal diseases. A referral to pediatric nephrology should be initiated early in the evaluation process to help direct the evaluation and for counseling of patients and families. Depending upon the results of the aforementioned evaluations, a renal biopsy may also be warranted. Close long-term monitoring by a specialist in renal diseases will be required for this type of proteinuria.

Pathophysiology

In normal individuals, only low amounts of protein are excreted into the urine as a result of two processes that restrict passage of higher levels of protein. First, filtration of large serum proteins such as albumin is restricted at the level of the glomerulus. Second, low molecular weight proteins are filtered at the glomerulus but then are reabsorbed by the proximal tubule. These low levels of proteinuria are generally not detected on urinary dipstick testing. The approximate composition of normally excreted protein is 40% of high molecular weight albumin (approximately 65,000 Da), 40% of Tamm–Horsfall mucoproteins secreted by the ascending limb of the loop of Henle, and 20% of low molecular weight proteins such as $beta_2$-microglobulin (11,000 Da). Normal hemodynamic mechanisms in glomerular blood flow also prevent urinary protein loss.

In patients with renal disease, excessive urinary protein losses can occur as a result of increased permeability of the glomeruli, termed glomerular proteinuria, decreased reabsorption of low molecular weight proteins by the renal tubules, termed tubular proteinuria, or variations in glomerular blood flow. The size, charge, and concentration of a molecule determine the effectiveness of filtration and the subsequent amount in the urine. The normal glomerulus permits passage of fluid and small solutes with molecular weights less than 20,000 Da but restricts passage of larger molecules. Additionally, the glomerular basement membrane contains negatively charged heparin sulfate proteoglycans, which repel negatively charged molecules, such as albumin. In many renal diseases, one or both of these normal mechanisms is disrupted, thus allowing inappropriate passage of molecules into the urine at the glomerular level. Glomerular proteinuria is therefore mostly composed of albumin and generally leads to high levels of proteinuria. Some examples of diseases characterized by glomerular proteinuria include minimal change nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, IgA nephropathy, and diabetic nephropathy.

Normally, small amounts of protein are filtered at the glomerulus, and then the majority of these filtered proteins are reabsorbed by the proximal tubule. In tubulointerstitial diseases, this reabsorption does not occur normally, leading to increased amounts of low molecular weight molecules in the urine such as $beta_2$-microglobulin. The degree of tubular proteinuria is generally less than that seen in glomerular proteinuria, with typical amounts less than 2 g/day. Some examples of diseases associated with tubular proteinuria include interstitial nephritis, Fanconi syndrome, and sickle cell disease nephropathy. Alternatively, overflow proteinuria can occur if low molecular weight proteins, such as immunoglobulins, cannot be efficiently reabsorbed by the proximal tubule. This is rarely seen in pediatric patients but is common in adult patients with multiple myeloma. An example of overflow proteinuria seen in pediatric patients is myoglobulinuria in the setting of rhabdomyolysis. Urine protein electrophoresis can effectively be used to diagnose both of these types of proteinuria.

There are also identifiable genetic abnormalities that lead to proteinuria, as seen in some forms of congenital nephrotic syndrome and focal segmental glomerulosclerosis. Expressed in the podocyte foot processes and slit diaphragm, abnormalities in the proteins termed nephrin and podocin lead to steroid-resistant forms of nephrotic syndrome. The *NPHS1* gene encodes the transmembrane protein called nephrin, which is located within the slit diaphragm and interacts with the epithelial cell, or podocyte foot processes, and the glomerular basement membrane. Several mutations in this gene have been shown to result in congenital nephrotic syndrome (CNS) of the Finnish type. Alternatively, the *NPHS2* gene encodes the podocyte protein called podocin, which can lead to steroid-resistant nephrotic syndrome such as focal segmental glomerulosclerosis. Other proteins that interact with the proteins nephrin and podocin include CD2AP, NEPH1, filtrin, alpha-actinin 4, and densin. A great deal of research is ongoing to further elucidate the role of genetic mutations that lead to abnormal protein products in the glomerulus for certain renal diseases and types of nephrotic syndromes.

Clinical Manifestations

The clinical manifestations of proteinuria occur along a broad spectrum, from entirely asymptomatic to systemic manifestations requiring hospitalization and an

expeditious evaluation. Asymptomatic proteinuria is the most common presentation and is detected with a screening urinalysis, typically performed by the primary care provider. Additionally, a child may present with nonspecific symptoms, and a screening urinalysis will reveal proteinuria with or without other abnormal findings. Alternatively, pediatric patients may present with classic nephrotic syndrome features including periorbital and lower extremity edema, ascites, and abdominal pain. Finally, some patients present with a myriad of systemic symptoms in addition to abnormal urinary results and require a prompt evaluation.

Nephrotic syndrome (NS) is defined by nephrotic-range proteinuria, hypoalbuminemia (<2.5 g/dL), edema, and hypercholesterolemia. Nephrotic-range proteinuria can be defined using different methods such as a (U_{Pr}/U_{Cr}) greater than 1–2, or a 24-h urine collection with greater than 50 mg/kg/day of proteinuria or greater than 40 mg/m^2/h of proteinuria.

Systemic renal diseases with proteinuria in addition to other renal findings such as hematuria or hypertension may manifest with classic physical exam findings, significantly aiding the diagnosis (Table 291.3). With post-infectious glomerulonephritis, patients will have a prodromal illness 2–4 weeks prior to the onset of the renal manifestations of macroscopic hematuria, proteinuria, and possible elevated creatinine levels. The preceding illness may include pharyngitis or skin lesions such as impetigo, especially in the setting of Streptococcal infections. Patients with IgA nephropathy will often present with abdominal or flank pain, fever, and macroscopic hematuria within 72 h of an upper or lower respiratory illness. The potential clinical manifestations of systemic lupus erythematosus are numerous and can include facial rash and other dermatologic findings, fatigue, fever, weight loss, mouth sores, shortness of breath, chest pain, joint pain or edema, and alopecia. Henoch–Schönlein purpura may present with lower extremity and buttock petechial and purpuric lesions, significant abdominal discomfort, migrating edema, and joint pain and edema. Patients with diarrhea-positive hemolytic uremic syndrome may have a history of bloody diarrhea, abdominal

Table 291.3
Clinical manifestations of systemic renal diseases associated with persistent proteinuria

Systemic disease	Renal findings	Physical findings	Laboratory tests
Post-infectious GN[a]	Macroscopic or microscopic hematuria, pyuria, urine cellular casts, elevated creatinine level	Streptococcal pharyngitis or skin lesions or other infectious symptoms 2 to 4 weeks prior to renal findings	Positive anti-streptolysin O or anti-DNase B titer, decreased complement C3 level
IgA nephropathy	Macroscopic or microscopic hematuria, rarely elevated creatinine level	Abdominal or flank pain, fever, URI symptoms[b] 2 to 3 days prior to renal findings	Normal complement – C3 and C4 levels
Henoch–Schönlein purpura	Macroscopic or microscopic hematuria	Abdominal pain, lower extremity and buttock purpura, arthralgia, arthritis, peripheral edema	Normal complement – C3 and C4 levels
Hemolytic uremic syndrome	Macroscopic hematuria, oliguria, elevated BUN and creatinine levels	Bloody diarrhea, abdominal pain, emesis, pallor, anorexia	Anemia, thrombocytopenia, elevated LDH level,[c] normal complement – C3 and C4 levels
Systemic lupus erythematosus	Microscopic hematuria, urine cellular casts, elevated creatinine	Fever, weight loss, alopecia, facial rash, chest pain, shortness of breath, arthralgia, arthritis	Positive ANA and anti-ds DNA titer, decreased complement C3 and C4 levels, elevated ESR[d]
Interstitial nephritis	Elevated urine eosinophil level, sterile pyuria, dysuria, microscopic hematuria, elevated creatinine level	Fever, rash, nausea, emesis, infectious symptoms, recent exposure to antibiotics or other medications, back pain	Elevated ESR level, eosinophilia, anemia

[a]Glomerulonephritis (GN)
[b]Upper respiratory infection (URI) symptoms
[c]Lactate dehydrogenase (LDH)
[d]Antinuclear antibody (ANA), anti-double-stranded DNA (anti-ds DNA), erythrocyte sedimentation rate (ESR)

pain, emesis, anorexia, pallor due to anemia, decreased urine output, and rarely petechiae. Interstitial nephritis may present with allergic symptoms such as rash or a history of recent exposure to antibiotics or other medications. Utilizing the history and physical exam features can assist in detecting systemic renal diseases associated with proteinuria.

Diagnosis

When proteinuria is discovered, a microscopic urinary evaluation should be performed to determine the presence or absence of hematuria with eumorphic or dysmorphic red blood cells, pyuria, bacteriuria, cellular or noncellular casts, urine eosinophils, oval fat bodies, or crystals (*Table 291.4*). Abnormal urinary microscopic sediment findings should prompt a pediatric nephrology evaluation, since many of these findings suggest an underlying renal disease. In the absence of an abnormal urinary microscopic analysis, an initial systematic evaluation process should be implemented when proteinuria is detected in a pediatric patient. Utilization of a stepwise approach affords an efficient and cost-effective approach to the work-up of proteinuria (*Fig. 291.2*). The initial steps can be performed by the primary care provider, while the more specific and extensive evaluation should be reserved for a pediatric nephrologist.

Table 291.4
Urine microscopy interpretation

Urine microscopy result	Suggested interpretation
Eumorphic RBC[a]	Upper or lower urinary tract process
Dysmorphic RBC	Upper urinary tract process such as glomerulonephritis
WBC[b]	Infection, exudative glomerulonephritis, interstitial nephritis
Hyaline casts	Volume depletion
Granular casts	Chronic renal disease
Fatty casts or oval fat bodies	Nephrotic syndrome, systemic lupus erythematosus nephritis
WBC casts	Pyelonephritis, exudative glomerulonephritis, interstitial nephritis
RBC casts	Glomerulonephritis, vasculitis
Urine eosinophils[c]	Interstitial nephritis

[a]Red blood cells (RBC)
[b]White blood cells (WBC)
[c]To detect the presence of urine eosinophils, request the laboratory to perform Wright, Giemsa, or Hansel staining of the urine

The first step in the evaluation process is to complete a detailed patient and family history and physical exam. Specific attention toward signs or symptoms suggesting an underlying renal disease should be the focus, including accurate blood pressure and growth assessments. Pertinent findings in the patient history include recent infections, changes in weight, appearance of edema, symptoms of hypertension, macroscopic hematuria, oliguria, polyuria, skin lesions, joint symptoms, pain, previous abnormal urinalyses, and a list of recent medications. A family history of renal disease, hypertension, autoimmune disease, deafness, or visual impairment is pertinent. Random and first morning urine specimens may be collected and analyzed; if orthostatic proteinuria is diagnosed, no further evaluation is needed except for periodic monitoring of FMU specimens on an every 6–12 month basis in addition to blood pressure monitoring. If three separate urine specimens that are separated by weeks continue to demonstrate proteinuria $\geq$1+ (30 mg/dL) on a dipstick test, the next step in the assessment process should be performed.

As part of the second step, laboratory studies including a complete blood count, electrolytes, renal function, serum albumin level, and a complement C3 level with or without a complement C4 level should be included. Consideration for additional tests including streptococcal markers such as the anti-streptolysin O titer or anti-DNase B titer, an antinuclear antibody (ANA) level, and a cholesterol level can be ordered in certain circumstances. More specific quantification of the degree of proteinuria is necessary at this stage and can be accomplished with either a (U_{Pr}/U_{Cr}) or a 24-h urine collection, if feasible. From a radiology perspective, a chest X-ray or a renal ultrasound may be beneficial to review, looking for evidence of volume overload or structural renal abnormalities, respectively. Other laboratory or radiology studies should be reserved for the next level of testing to be performed by a pediatric nephrologist.

A referral to a pediatric nephrologist can occur at any stage of the work-up depending upon the primary care provider's level of comfort with the evaluation, but certain findings should initiate an immediate evaluation by a specialist. These include persistent non-orthostatic proteinuria, the additional finding of hematuria or abnormal urine microscopy, associated systemic manifestations, hypertension, peripheral edema, elevated blood urea nitrogen or creatinine levels, electrolyte abnormalities, an

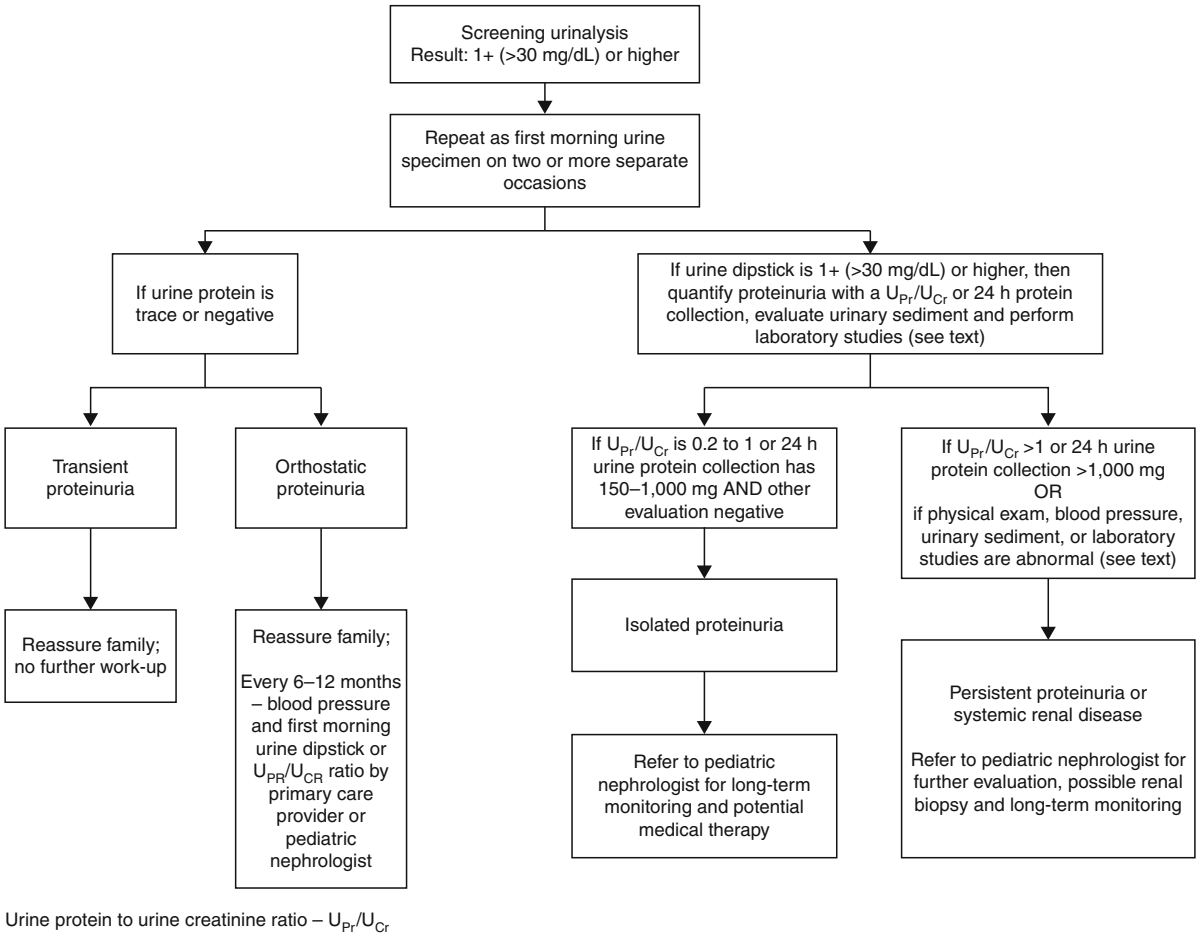

Figure 291.2
Algorithm of the stepwise diagnostic approach for the evaluation of proteinuria

abnormal renal ultrasound or other renal imaging study, or a family history of significant renal disease. Further testing may comprise of an HIV test, hepatitis B and C serologic testing, more specific autoimmune or vasculitis laboratory studies, further quantification of the degree and perhaps the type of proteinuria, and potentially a renal biopsy.

A percutaneous renal biopsy is reserved for special situations and concerning clinical findings in order to confirm a diagnosis (*Table 291.5*). Oftentimes, patients with presumed MCNS are initiated on corticosteroid therapy at presentation without histologic confirmation. If the patients do not respond predictably, a renal biopsy is frequently recommended. This is especially proposed if the patients demonstrate a frequently relapsing,

Table 291.5
Possible indications for percutaneous renal biopsy in patients with persistent proteinuria

Elevated creatinine concentration
Persistent macroscopic or microscopic hematuria
Hypertension
Persistent hypocomplementemia
Suspicion of ANCA vasculitis
Consider with frequently relapsing, steroid-dependent and steroid-resistant nephrotic syndrome
Family history of chronic renal disease or end-stage renal disease
Parental anxiety

steroid-dependent, or steroid-resistant pattern to their nephrotic syndrome, which suggests an alternative diagnosis to MCNS. Other indications for pursuing a renal biopsy in patients with significant proteinuria include concomitant persistent hematuria, either microscopic or macroscopic, hypertension, an elevated creatinine level, or persistent hypocomplementemia. Any suspicion of a systemic disease with persistent proteinuria warrants close monitoring and likely a renal biopsy to determine the diagnosis, treatment regimen, and long-term prognosis. Patients with a concerning family history of renal disease may also merit histologic evaluation via a renal biopsy. Finally, parental or patient anxiety about an underlying renal disorder may prompt a thorough discussion of the risks and benefits of pursuing a renal biopsy. A percutaneous renal biopsy is performed by either a nephrologist or a radiologist trained in renal biopsy procedures. Rarely, a renal biopsy may need to be performed by a general or transplant surgeon.

Differential Diagnosis

The differential diagnosis of proteinuria is broad, given the differing degree and types of proteinuria that may be observed in pediatric patients. Differentiation among transient, orthostatic, isolated and persistent proteinuria is the initial step in developing a list of potential etiologies for the proteinuria. If persistent proteinuria is identified, the potential etiologies for the underlying process are extensive.

In patients with nephrotic-range proteinuria or nephrotic syndrome, consideration should be given to the following diagnoses: minimal change nephrotic syndrome, focal segmental glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephritis, and, rarely, IgA nephropathy. If the patient is less than 12 months of age, congenital and infantile NS need to be considered. Nephrotic syndrome can be confused with an allergic reaction, angioedema, protein-losing enteropathies, congestive heart failure, significant liver disease, or hepatic failure, and therefore these diagnoses should be excluded during the evaluation process. When both proteinuria and hematuria are present, the following diagnoses should be considered: post-infectious glomerulonephritis, IgA nephropathy, familial nephritis, membranoproliferative glomerulonephritis, and systemic lupus erythematosus. If both proteinuria and systemic findings are found, the list of potential etiologies include Henoch–Schönlein purpura, systemic lupus erythematosus, hemolytic uremic syndrome, Wegener's granulomatosis or other forms of Anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis, and Goodpasture's disease.

Treatment

Depending upon the type and degree of proteinuria, numerous treatment recommendations have been established. For confirmed transient and orthostatic proteinuria, no therapy is needed. Intermittent long-term monitoring of first morning urine specimens and blood pressure readings should be performed by the primary care provider in the setting of orthostatic proteinuria. For isolated proteinuria, therapeutic recommendations vary from no treatment to consideration of proteinuria lowering agents such as angiotensin-converting-enzyme inhibitor (ACE I) or angiotensin receptor blocker (ARB) medications. Mostly, these medications are reserved for use in patients with persistent proteinuria and thus will be discussed below.

Patients with persistent proteinuria represent a heterogeneous group; therefore, both general and specific therapeutic recommendations are prudent. Among patients with higher grade or nephrotic-range proteinuria, ACE I medications can be useful as primary or adjunctive therapy. Among patients with type 1 and type 2 diabetes mellitus, ACE inhibitors are usually started at the onset of abnormal levels of microalbuminuria, although one recent study did not demonstrate a long-term advantage in this particular patient population. Other important treatments to address in patients with diabetes mellitus and microalbuminuria are strict blood glucose and blood pressure control. At low doses, ACE I medications have been shown to reduce proteinuria and have the additional benefit of lowering blood pressure in hypertensive patients. Advantages specific for pediatric patients include ease of dosing with suspension or tablet formulations and a one-time-per-day dosing schedule.

Most patients tolerate ACE I medications well, although there are side effects and monitoring parameters that need to be considered prior to initiation. First, laboratory studies to evaluate for bone marrow suppression, electrolyte abnormalities, and renal function changes need to be periodically monitored. In a minority of patients, development of a dry cough due to bradykinin effects may prohibit long-term usage and should prompt discontinuation of this group of medications. Due to the intrarenal glomerular mechanism of action of ACE I medications, patients with acute or chronic volume depletion should not continue ACE I treatment as this could lead to acute renal failure. Finally, women of child-bearing age should be thoroughly counseled about the potential teratogenic effects of ACE I use during pregnancy. If patients are considering pregnancy, discontinuation of ACE I medications should occur immediately, as the potential

teratogenic effects begin early in the first trimester. Many physicians will not prescribe ACE I therapy in this population unless consistent oral contraceptive use is employed. Rarely, angioedema can occur with this group of medications.

ARB medications have similar advantages and disadvantages as ACE I, except that they are primarily utilized in older adolescent and adult patients and currently do not have an available suspension formulation. Studies among pediatric patients with proteinuria, hypertension, or both in addition to ARB safety and efficacy informative studies are currently ongoing. Adult studies have observed significant advantages using combined ACE I and ARB therapy for proteinuria reduction and improved long-term cardiovascular health. These advantages may also be observed in the pediatric population and may be recommended in the future for younger age groups.

The treatment for nephrotic syndrome and other systemic diseases associated primarily with proteinuria are discussed elsewhere.

Prognosis

Transient and orthostatic proteinuria renders an excellent long-term prognosis, while isolated and persistent proteinuria often portends poorer long-term outcomes.

Prevention

Although there are no specific recommendations for proteinuria prevention, the initial evaluation and continued long-term monitoring of these patients can significantly alter potential progression of the underlying process. This monitoring should be done by the primary care provider in conjunction with a pediatric nephrologist in most situations. Prompt diagnosis and treatment is beneficial for long-term outcomes. In a pediatric population, protein restriction is rarely advised given the potential deleterious effects on growth and development. Therefore, children should receive the recommended daily intake of protein, based upon age. Other dietary or fluid restrictions are also generally not recommended, except in specific circumstances. Family and age-appropriate patient education and counseling should be performed at or soon after the diagnosis of significant proteinuria is confirmed and then continued over time by a multidisciplinary team. Specific parameters to call the primary care provider or pediatric nephrologist should also be provided to the parent or guardian and patient in order to avoid potential complications associated with persistent proteinuria.

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292 Systemic Hypertension

Joseph T. Flynn

In this chapter, key features of childhood hypertension will be reviewed, with a focus on diagnosis and management.

Classification

Classification of Childhood Blood Pressure

The National Heart, Lung and Blood Institute (NHLBI) has issued consensus guidelines with recommendations for the identification and management of elevated blood pressure (BP) in childhood on four occasions since 1977. The most recent of these, "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" (National High Blood Pressure Education Program [NHBPEP] Working Group, 2004) adapted terminology and staging criteria utilized in consensus guidelines for adult hypertension to pediatric hypertension, and also emphasized the possibility of preventing adult cardiovascular disease by early intervention in children and adolescents with elevated BP.

The diagnostic criteria for elevated BP in childhood are based on the concept that BP in children increases with age and with body size, which makes it impossible to utilize a single BP level to define hypertension as is done in adults. Furthermore, the lack of cardiovascular end points in childhood necessitates that the definitions of normal and elevated BP be statistical criteria derived from large-scale, cross-sectional studies of BP in normal children. The NHLBI database of childhood blood pressure, upon which the current normative BP values are based, now contains BP information on over 83,000 healthy children aged 1–17 years.

Normal BP in children aged 1–17 years is defined in the Fourth Report as systolic AND diastolic BP $<$ the 90th percentile for age, gender, and height, and hypertension is defined as systolic AND/OR diastolic BP persistently $\geq$ the 95th percentile (*Tables 292.1* and *292.2*). Children with systolic or diastolic BP between the 90th and 95th percentiles, or adolescents with BP $\geq$120/80, are now classified as pre-hypertensive, as opposed to the "high-normal" classification that was used previously.

The Fourth Report additionally provides guidelines for staging the severity of hypertension in children and adolescents, which can then be used clinically to guide evaluation and management (*Fig. 292.1* and *Table 292.3*). As indicated in the table, children or adolescents with stage 2 hypertension should be evaluated and treated more quickly and/or aggressively than those with lower degrees of BP elevation.

Etiology

Causes of Hypertension in Children and Adolescents

Given the many influences on blood pressure (see below), it is not surprising that the differential diagnosis of pediatric hypertension can be extensive. This is reflected in the traditional teaching that most hypertension in children should be considered secondary to an underlying disorder. As can be seen in *Table 292.4*, this is certainly the case for infants and young children. In hypertensive children in these age groups, renal disease, renovascular disease, or cardiac disease will often be found after an appropriate diagnostic evaluation. Primary hypertension in young children is, therefore, usually considered a diagnosis of exclusion, making it necessary to undertake at least some advanced testing to arrive at the correct diagnosis.

In adolescents, however, hypertension is most likely to be primary in origin (*Table 292.4*). In many case series published since the mid-1990s, the vast majority of adolescents with persistent BP elevation have no identifiable underlying cause. Features that support the diagnosis of primary hypertension in teenagers include normal growth (and/or obesity), lack of symptoms of hypertension, unremarkable past medical history, and a family history of hypertension. Hypertensive adolescents who fit this profile may not need as extensive an evaluation as those who do not.

Neonates compromise a unique population with respect to the causes of hypertension. In this age group, coarctation of the aorta and renovascular disease constitute the most frequent causes of hypertension (*Table 292.4*), with other diagnoses such as congenital structural renal

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Table 292.1

Blood pressure levels for boys by age and height percentile. To use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile (Reproduced from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, 2005.)

Age (Year)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89

Table 292.1 (Continued)

Age (Year)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

BP: blood pressure

disease and bronchopulmonary dysplasia also being relatively frequent. Most infants with renovascular hypertension have a history of umbilical catheter placement, which may lead to hypertension from intraparenchymal thromboembolism. Clearly, it is important to keep this unique differential in mind when approaching neonates with hypertension.

Epidemiology

Epidemiology of Hypertension and Impact of the Childhood Obesity Epidemic

Through the 1990s, the prevalence of hypertension in children and adolescents was felt to be low, approximately

Table 292.2

Blood pressure levels for girls by age and height percentile. To use the table, first plot the child's height on a standard growth curve (www.cdc.gov/growthcharts). The child's measured SBP and DBP are compared with the numbers provided in the table according to the child's age and height percentile. (Reproduced from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents, 2005.)

Age (Year)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87

Table 292.2 (Continued)

Age (Year)	BP Percentile	Systolic BP (mmHg)							Diastolic BP (mmHg)						
		Percentile of height							Percentile of height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

BP: blood pressure

2% or less. However, over the past decade, it has become apparent that the prevalence of hypertension has increased, with recent population surveys demonstrating that nearly 4% of children are hypertensive, and up to 10% pre-hypertensive. Most of this increase can be attributed to the childhood obesity epidemic, which has emerged as a significant issue affecting child health worldwide.

In the USA, the prevalence of childhood obesity has more than trebled over the past 30 years, and now approaches 20% in children aged 6–11 years. A similar picture is emerging among younger children as well: in New York City, among 16,000 children (mean age 3.5 years) enrolled in the Head Start Program in 2004, 27% were obese and 15% were overweight. Recent school

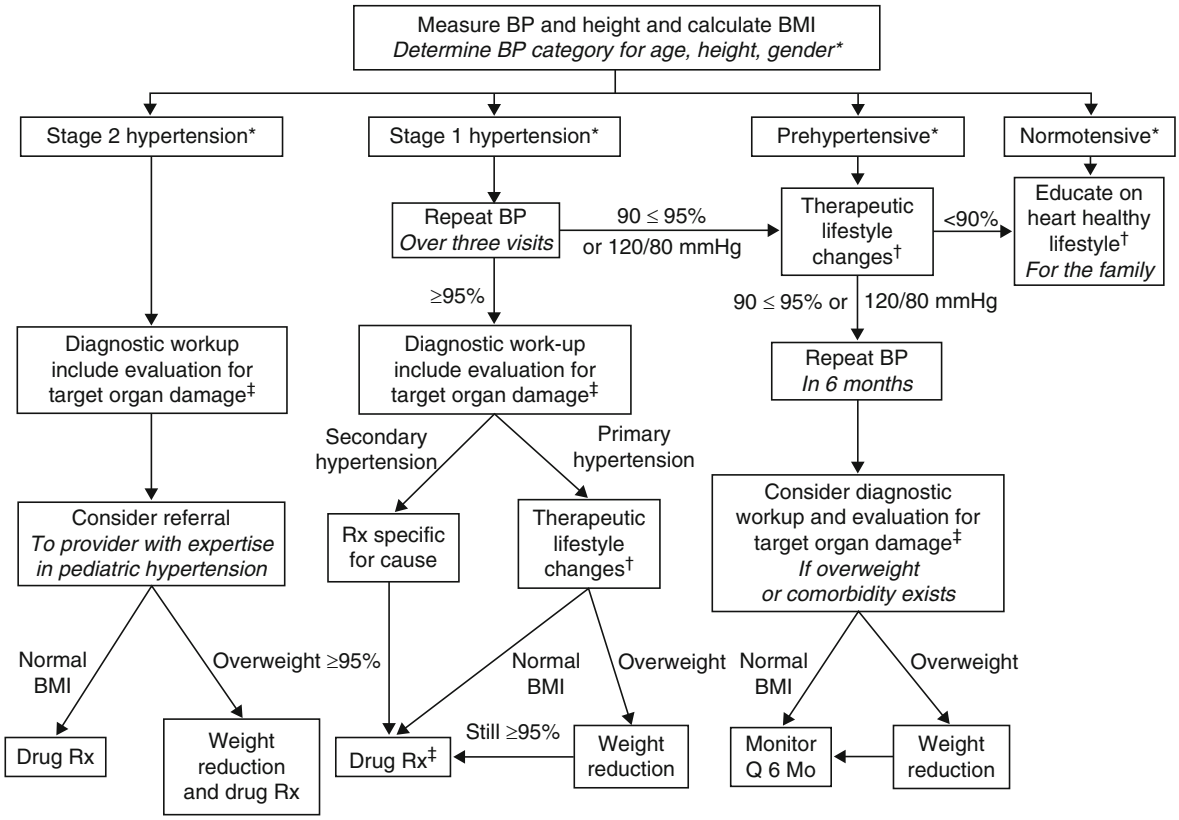

Figure 292.1

Summary of classification of BP and recommended management of children and adolescents with elevated blood pressure. BMI, body mass index; BP, blood pressure; Q, every; RX, treatment. *, See *Table 292.3*; †, diet modification and physical activity; ‡, especially if younger, very high BP, little or no family history, diabetic, or other risk factors. (Reproduced from "The Fourth Report on the Diagnosis, Evaluation and Treatment of High Blood Pressure in Children and Adolescents," 2005)

screening studies conducted in the USA over the past several years have provided ample evidence of the effect that obesity has had on the prevalence of hypertension. In Houston, Texas, for example, the prevalence of hypertension in adolescents has been shown to be as high as 10% among those with body mass index (BMI) ≥97th percentile. Strong associations between overweight and elevated BP have also recently been reported in sixth graders in Seminole County, Florida and in even younger children in Anadarko, Oklahoma.

Significant increases in childhood obesity have been documented in several European countries, including Poland and Italy. Among a randomly selected sample of children and adolescents in Catanzaro Italy, 18% of children were classified as being at risk for overweight (BMI percentile 85–94%) and another 11% were classified as obese (BMI percentile ≥95%). Lesser-developed countries are experiencing significant increases in childhood obesity as well. Anthropometric data obtained in 23,459 children in the Seychelles demonstrate an increase in the prevalence of obesity from 2.1% to 5.2% in boys and from 3.1% to 6.2% in girls between 1998 and 2004, with analogous increases in the percentage of children at risk of overweight.

Obese children in the Italian study mentioned above were more likely to have elevated systolic or diastolic BP than non-obese children, and BMI was a significant predictor of elevated BP. In another Italian study, the prevalence of pre-hypertension was nearly 12 times that in a control group of normal-weight children and pre-hypertension was associated with insulin resistance. Thus, the epidemic of childhood obesity appears to be having enormous effects on the prevalence and epidemiology of hypertension across the globe, and unless appropriate, population-based preventative measures are instituted, an epidemic of early adult cardiovascular disease is likely on the horizon.

Table 292.3
Classification of hypertension in children and adolescents, with measurement frequency and therapy recommendations (Reproduced from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents," 2005.)

	SBP or DBP percentile[a]	Frequency of BP measurement	Therapeutic lifestyle changes	Pharmacologic therapy
Normal	<90th	Recheck at next scheduled physical examination	Encourage healthy diet, sleep, and physical activity	—
Prehypertension	90th–<95th or if BP exceeds 120/80 even if below 90th percentile up to <95th percentile[b]	Recheck in 6 months	Weight management counseling if overweight, introduce physical activity and diet management	None unless compelling indications such as CKD, diabetes mellitus, heart failure, LVH
Stage 1 hypertension	95th percentile to the 99th percentile plus 5 mmHg	Recheck in 1–2 weeks or sooner if the patient is symptomatic; if persistently elevated on two additional occasions, evaluate or refer to source of care within 1 month	Weight management counseling if overweight, introduce physical activity and diet management	Initiate therapy based on indications in text or if compelling indications as above
Stage 2 hypertension	>99th percentile plus 5 mmHg	Evaluate or refer to source of care within 1 week (or immediately) if the patient is symptomatic	Weight management counseling if overweight, introduce exercise and diet management	Initiate therapy

BP, blood pressure; CKD, chronic kidney disease; DBP, diastolic blood pressure; LVH, left ventricular hypertrophy; SBP, systolic blood pressure
[a] For sex, age, and height measured on at least three separate occasions; if systolic and diastolic categories are different, categorize by the higher value
[b] This occurs typically at 12 years old for SBP and at 16 years old for DBP

Pathogenesis

Pathophysiology of Hypertension

Blood pressure can fundamentally be viewed as a function of cardiac output and systemic vascular resistance. Cardiac output depends on cardiac stroke volume and heart rate. Stroke volume in turn depends on myocontractility and preload. Systemic vascular resistance is dependent on vessel elasticity, myocontractility, and afterload. Numerous hormonal and neuronal factors, as well as relationships at the cellular and molecular levels, exert important effects on blood pressure, all in the context of the patient's genetic background. Derangements in any of these myriad processes can influence either cardiac output or systemic vascular resistance, thereby leading to the development of hypertension. Given the many potential mechanisms, a detailed discussion of pathophysiology is beyond the scope of this chapter; however, a few important mechanisms will be highlighted.

Abnormalities of renal sodium handling are central to the development of hypertension in many patients. Important insight into the role of renal sodium handling has been gained from the study of several Mendelian forms of hypertension, including Liddle's syndrome, apparent mineralocorticoid excess, Gordon's syndrome, and glucocorticoid-remediable aldosteronism. All of these disorders lead to increased sodium reabsorption in the distal nephron, producing volume overload hypertension. An important diagnostic clue in these patients is suppressed plasma renin activity.

The other major mechanism that leads to the development of hypertension in many patients is insulin resistance, which can be present in both obese and non-obese hypertensives. Insulin resistance has been associated with altered renal sodium handling, activation of the

Table 292.4
Differential diagnosis of childhood hypertension by age

Age Group	Causes[a]
Newborn infants	Umbilical catheter-related thromboembolism
	Bronchopulmonary dysplasia
	Congenital renal disease/ malformations
	Renal venous thrombosis
	Aortic coarctation
	Medications
Infants and toddlers	Renal parenchymal disease
	Congenital renal disease/ malformations
	Renal artery stenosis
	Aortic coarctation
	Endocrine causes
Pre-adolescent children	Renal parenchymal disease
	Renal artery stenosis
	Primary hypertension
	Aortic coarctation
	Endocrine causes
Adolescents	Primary hypertension
	Renal parenchymal disease
	Renal artery stenosis
	Substance use[b]
	Aortic coarctation
	Endocrine causes

[a] Listed roughly in descending order of frequency
[b] See Table 292.8

sympathetic nervous system, and alterations of vascular structure and function – all processes that have significant effects on blood pressure. Finally, new research on uric acid has suggested that hyperuricemia may also contribute to the development of hypertension in some patients, probably through altered endothelial function.

Pathology

Consequences of Childhood Hypertension

Hypertensive Target-Organ Damage

Left ventricular hypertrophy (LVH), increased carotid intima-media thickness (cIMT), and even impaired cognitive function stand as concrete evidence of the consequences of elevated BP in childhood and the potential for life-long morbidity. LVH was first demonstrated to occur in hypertensive youth by Laird and Fixler in the early 1980s, and has subsequently been shown to occur in a significant proportion of hypertensive children and adolescents, with reported prevalences ranging between 20% and 41% depending upon the diagnostic criteria utilized. It is especially interesting that the development of LVH in the young may not be related to the level of blood pressure elevation. While studies from a center in Houston have repeatedly demonstrated a correlation between the severity of blood pressure elevation and the likelihood of developing LVH, a larger multicenter study failed to demonstrate any relationship between LVH and specific parameters of blood pressure elevation. As will be discussed later, this underscores the need to perform echocardiography at the diagnosis of hypertension and periodically thereafter in children and adolescents, as recommended in the Fourth Report.

Vascular effects of elevated BP that can be seen in childhood include retinal changes and increased carotid intimal-medial thickness (cIMT). Hypertensive retinopathy has long been known to occur in childhood. The relationship between elevated childhood BP and retinal arteriolar narrowing was recently confirmed in a study of over 1,900 children in Australia and Singapore. Increased cIMT, well-documented as a cardiovascular consequence of elevated BP in large population studies has also been found in children and adolescents with primary hypertension in single-center reports. While early studies of cIMT in hypertensive youth were confounded by the effects of obesity, one carefully conducted study that controlled for BMI demonstrated a definitive relationship between elevated BP itself and increased cIMT in young patients.

An additional target-organ effect of elevated BP recently described in the young is impaired cognitive function. While long-standing hypertension has long been recognized as a risk factor for development of cognitive impairment and even dementia in the elderly, this study demonstrated that children and adolescents with BP >90th percentile had poorer performance on selected tests of cognition compared to normotensive children. This provocative finding, while requiring confirmation, adds impetus to consensus recommendations for instituting antihypertensive drug therapy in children and adolescents with persistently elevated BP.

Fewer pediatric data are available on the other major target-organ effect of hypertension, namely, renal damage. Although hypertension commonly accompanies chronic kidney disease in children, it is rarely its cause. Even

microalbuminuria, which is commonly seen in hypertensive adults, is infrequently seen in children with isolated hypertension, even when LVH is present. However, a more recent study demonstrated that approximately 58% of hypertensive adolescents had microalbuminuria, with an increased prevalence in Stage 2 hypertension compared to Stage 1. Reduction of BP in the latter study was accompanied by a reduction in both microalbuminuria and LVH. Given these conflicting data, additional studies are clearly needed to determine the renal effects of elevated BP in the young.

Diagnosis

Approach to the Child or Adolescent with Elevated Blood Pressure

Clinical Vignette

A 14 year-old soccer player presents to your office after an elevated BP was detected at a pre-sports participation screening at her school. Blood pressures obtained at the screening ranged from 139–149/71–77. She is at the 50th percentile for height and weight and has no other chronic health problems or abnormal physical exam findings. Her mother is obese, hypertensive and has type 2 diabetes; her paternal grandfather died at age 50 from a myocardial infarction.

Confirmation of Hypertension

As emphasized in the Fourth Report, one of the most important steps in the evaluation of children with suspected hypertension is to ensure that the blood pressure is being measured correctly. Whatever device is being used to measure blood pressure, the first step is to choose an appropriately sized cuff. The bladder of the cuff should encircle 80–100% of the circumference of the upper arm, and its width should be at 40% of the upper arm circumference. Since too narrow of a cuff will create a falsely elevated blood pressure reading, children with longer upper arms than others of the same age will require a wider cuff. A variety of cuff sizes should be kept on hand so that the proper size will be available. Not to be overlooked is a large adult or thigh cuff for use in obese children.

The patient should be seated quietly for at least 5 min prior to BP determination. The arm should be supported at heart level. Infants' blood pressures should be obtained in the supine position. When BP is measured by auscultation, the disappearance of the fifth Korotkoff sound should be used for the diastolic reading. If the initial elevated BP was obtained using an automated device, it should be repeated manually at the same visit. Given the current unavailability of mercury column sphygmomanometers, an aneroid device should be used for the repeat reading. The exception to this would be infants and young toddlers who cannot cooperate with manual blood pressure determination.

A single isolated elevated BP reading does not diagnose hypertension, but does indicate the need for repeated measurements over time. The Fourth Report recommends that in most cases, at least three abnormal readings, obtained at different times, should be obtained before the "diagnosis" of hypertension should be entertained and a work-up initiated (*Table 292.3*).

Role of Ambulatory BP Monitoring

Ambulatory BP monitoring (ABPM) has been endorsed as an appropriate technique for the evaluation of elevated BP in children and adolescents in recommendations from several consensus panels. Potential applications of ABPM in children include identification of white coat and masked hypertension (*Table 292.5*), assessment of BP control in those treated with antihypertensive medications, and investigation of hypotensive episodes. ABPM has also been demonstrated to reduce the cost of evaluation of elevated BP by identifying those with white-coat hypertension, who then could receive a less extensive work-up, and to identify those children more likely to have secondary causes of hypertension.

Table 292.5
Classification of BP and cardiovascular risk using office and ambulatory BP

	Ambulatory BP	Office BP	Cardiovascular risk
Normal BP	Normal	Normal	No additional effect
Sustained HTN	Elevated	Elevated	Increased
White Coat HTN	Normal	Elevated	Possibly increased
Masked HTN	Elevated	Normal	Increased

BP, blood pressure; HTN, hypertension

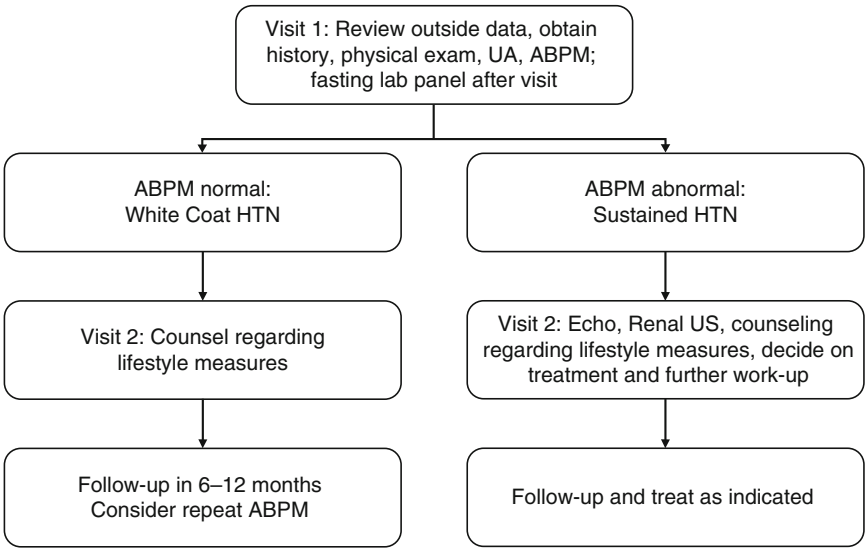

Figure 292.2
Proposed algorithm for incorporation of ambulatory blood pressure monitoring into evaluation of children and adolescents with elevated blood pressure. ABPM, ambulatory blood pressure monitoring; echo, echocardiogram; HTN, hypertension; UA, urinalysis; US, ultrasound

White coat hypertension, defined as elevated office BP but normal out-of-office BP, appears to be at least as common in children as it is in adults. In adults, white coat hypertension is not felt to be associated with significant cardiovascular morbidity or mortality, so pharmacologic treatment of such patients is not recommended. Although proving that a child has white coat hypertension could help avoid unnecessary exposure to medications and reduce unnecessary diagnostic testing, a few recent studies have indicated that children found to have white coat hypertension actually have early signs of target-organ damage such as increased left ventricular mass. These data, in combination with data from tracking studies that suggest that these children are likely at increased risk of development of hypertension in the future, imply that children found to have white coat hypertension should receive lifestyle modification and should be followed prospectively for the development of definite or sustained hypertension.

Masked hypertension, defined as elevated out-of-office BP in a patient with normal office BP, has also been recently described in pediatric populations, and is associated with hypertensive target-organ damage, specifically left ventricular hypertrophy. Such children probably merit further evaluation for underlying secondary causes of hypertension, and institution of pharmacologic treatment. In adults, masked hypertension is clearly associated with increased risk of cardiovascular disease (*Table 292.5*).

Given the above, and given the need to confirm the presence of hypertension before beginning an extensive diagnostic evaluation, wider use of ABPM has been advocated. A proposed algorithm for incorporation of ABPM into the evaluation of children with elevated BP is presented in *Fig. 292.2*. However, despite its potential utility, ABPM is still considered a specialized technique, necessitating referral to a dedicated pediatric hypertension clinic (*Fig. 292.3*).

Diagnostic Evaluation

The evaluation of a child with elevated BP can be divided into distinct phases, beginning with confirmation that the blood pressure is indeed elevated, then proceeding through a series of more specific and specialized studies until the correct diagnosis is made and treatment initiated (*Table 292.6*).

As in any patient, a thorough history and physical examination will often provide sufficient information to at least substantially narrow the differential diagnosis. Symptoms of hypertension may be caused by the hypertension itself, may be produced by the underlying cause of the hypertension, or may be completely absent. Given this,

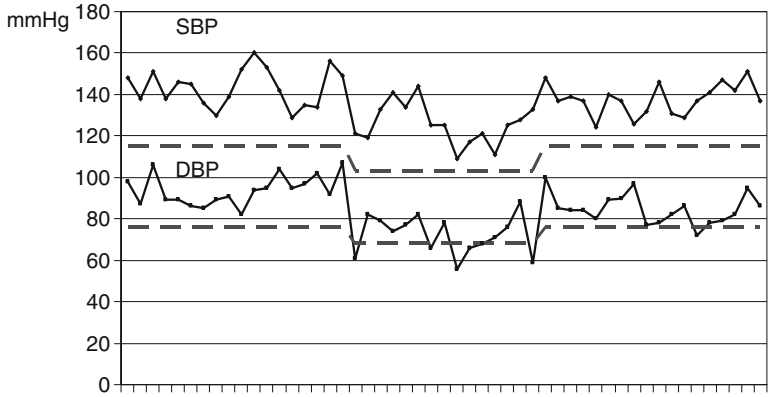

Figure 292.3

Ambulatory BP study in a child with sustained hypertension. The solid lines are the patient's systolic and diastolic BP's over the monitoring period, and the heavy dashed lines represent the 95th percentile ambulatory BP value. The patient was later found to have reflux nephropathy

and given the potentially wide differential diagnosis of hypertension, especially in an infant or younger child, a high index of suspicion should be maintained. It is especially important to try to elicit clues to underlying secondary causes (*Table 292.7*).

Other important aspects of the history include past medical history and family history. A history of recurrent urinary infections in early childhood may be a clue to underlying reflux nephropathy. Recent infections such as pharyngitis suggest acute glomerulonephritis. A family history of early-onset hypertension can be seen in patients with single-gene hypertensive disorders such as Liddle's syndrome. The family history should also include questions about other cardiovascular diseases such as hyperlipidemia and stroke. Since many substances can elevate BP (*Table 292.8*), a careful medication review should be included, and questions asked about illicit substance used, when appropriate.

The physical examination should begin with determining the child's height and weight percentiles, and calculation of BMI. Whether or not a child is normally grown is an enormously important clue to the presence of an underlying chronic illness. Following this, obtain seated blood pressures in each arm, and no matter what the child's age, supine blood pressures in one arm and one leg in order to rule out coarctation of the aorta. The remainder of the physical examination should focus on discovering specific findings that may provide clues to the etiology and/or degree of hypertension. Common examples of physical exam findings that are associated with specific secondary causes of hypertension are listed in *Table 292.7*.

Patients with confirmed hypertension should then undergo laboratory testing and diagnostic imaging to follow up on findings from the history and physical examination, and to assess for other coexisting cardiovascular risk factors. As outlined in *Table 292.6*, it is customary to begin with a basic set of screening studies in all patients, which should also serve to screen for other coexisting conditions such as impaired glucose tolerance or dyslipidemia. Plasma renin activity is sometimes also included in this initial set of studies, especially when the patient's hypertension is severe, or if both systolic and diastolic hypertension are present.

Of the more specific tests, only those indicated by the history, physical examination, and screening test results should be obtained. For example, chest radiographs need only be obtained in hypertensive children with heart murmurs, or those with a gradient of more than 30 mmHg between the upper and lower extremity blood pressures. Renin and aldosterone should be obtained if there is hypokalemia on the screening electrolytes, as a suppressed renin in conjunction with hypokalemia strongly suggests a single-gene disorder such as Liddle's syndrome. Renal ultrasounds (*Fig. 292.4*), which should be routinely obtained in all hypertensive pre-adolescent patients, may be omitted in adolescents and some older pre-adolescent children with stage 1 hypertension if the screening studies are normal, and if other features of primary hypertension are present, including obesity, a positive family history, and isolated systolic hypertension. Those with stage 2 hypertension, with abnormal screening studies, or with diastolic hypertension should get an ultrasound.

Table 292.6
Diagnostic testing for children with elevated blood pressure

Phase	Studies
Confirmation of BP elevation	Repeated office measurements
	Home/self-measured blood pressure
	Ambulatory BP monitoring
Screening tests	Urinalysis (+ culture if indicated)
	Electrolytes, BUN, creatinine, calcium, phosphorus
	Fasting glucose and lipid panel (cholesterol, triglycerides, etc.)
	Consider: CBC with differential, platelet count
	Plasma renin activity
Specific tests	24 h urine collection (protein excretion, creatinine clearance)
	Plasma normetanephrine to norepinephrine ratio
	Other hormone levels (thyroid, adrenal, etc.)
	Echocardiogram, retinal exam
	Renal ultrasound (± Doppler)
	Polysomnography
Specialized studies	Renin profile (plasma renin and 24 h urine sodium excretion)
	Captopril renal scan
	MR or CT angiography
	Renal angiography (± renal vein renin sampling)
	Renal biopsy

Table 292.7
History and physical exam findings suggestive of secondary hypertension

Present in history	Suggests
Known UTI/UTI symptoms	Reflux nephropathy
Joint pains, rash, fever	Vasculitis, SLE
Acute onset of gross hematuria	Glomerulonephritis, Renal venous thrombosis
Renal trauma	Renal infarct, RAS
Abdominal radiation	Radiation nephritis, RAS
Renal transplant	Transplant RAS
Precocious puberty	Adrenal disorder
Muscle cramping, constipation	Hyperaldosteronism
Excessive sweating, headache, pallor and/or flushing	Pheochromocytoma
Illicit drug use	Drug-induced hypertension
Present on examination	**Suggests**
BP > 140/100 at any age	Secondary hypertension
Nocturnal HTN on ABPM	Secondary hypertension
Leg BP < arm BP	Aortic coarctation
Poor growth, pallor	Chronic renal disease
Turner syndrome	Aortic coarctation
Cafe-au-lait spots	Renal artery stenosis
Delayed leg pulses	Aortic coarctation
Precocious puberty	Adrenal disorder
Bruits over upper abdomen	Renal artery stenosis
Edema	Renal disease
Excessive sweating	Pheochromocytoma
Excessive pigmentation	Adrenal disorder
Striae in a male	Drug-induced HTN

ABPM, ambulatory blood pressure monitoring; BP, blood pressure; HTN, hypertension; RAS, renal artery stenosis; SLE, systemic lupus erythematosus; UTI, urinary tract infection

As recommended in the Fourth Report, additional imaging studies, including renal angiography, nuclear renal scans, and voiding cystourethrograms should only be obtained as indicated based upon the results of the history, physical examination, and initial diagnostic studies. With respect to angiography, it is now common in many centers to begin with a noninvasive modality such as magnetic resonance (MR) or computed tomographic (CT) angiography (*Fig. 292.5*), before proceeding to traditional arteriography. A negative MR or CT angiogram in an adolescent can effectively rule out renal artery stenosis, but may still need to be followed by arteriography in a younger child given their smaller blood vessels and the propensity for intrarenal involvement in young children with fibromuscular dysplasia.

As discussed previously, left ventricular hypertrophy occurs commonly in hypertensive children, so echocardiograms should be obtained routinely in patients with confirmed hypertension. Ophthalmologic exams should be obtained, but should be performed by an experienced pediatric ophthalmologist as hypertensive retinal changes are likely to be subtle in the young. The presence of hypertensive target-organ damage indicates that the blood pressure elevation has been long-standing, and that pharmacologic therapy is warranted.

Table 292.8
Substances that can elevate blood pressure in children and adolescents

Prescription medications	Non-prescription medications	Others
Calcineurin inhibitors (cyclosporine, tacrolimus)	Caffeine	Cocaine
COX-2 inhibitors (celecoxib, others)	Ephedrine	DHEA (dehydroepiandosterone)
Erythropoietin, darbepoetin	Non-steroidal anti-inflammatory drugs[a]	Ethanol
Glucocorticoids	Pseudoephedrine	Heavy metals (lead, mercury)
Migraine mediacations (ergotamine, sumatriptan)		Herbal preparations (*Ephedra, Glycyrrhiza, Yohimbine*)
Oral contraceptives		MDMA ("Ecstasy")
Phenylpropanolamine		Tobacco
Pseudoephedrine		
Stimulant medications[a] (dexedrine, methylphenidate, amphetamine derivatives)		
Tricyclic antidepressants[a]		

[a]These cause elevated blood pressure relatively infrequently compared with the other agents in the table

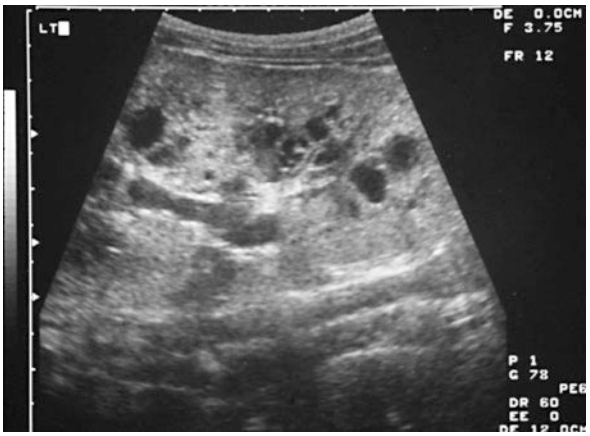

Figure 292.4
Renal ultrasound demonstrating multiple large cortical cysts consistent with autosomal dominant polycystic kidney disease

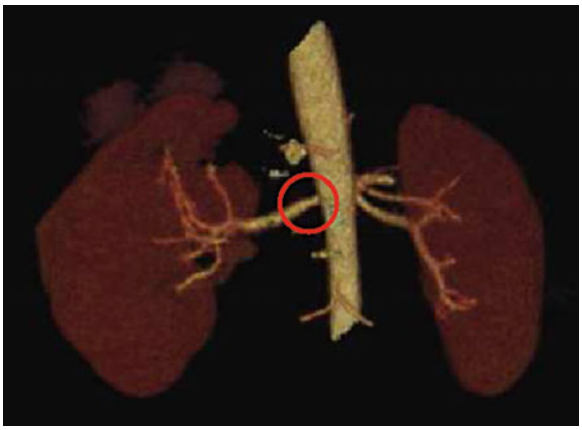

Figure 292.5
Three-dimensional reconstruction of CT angiogram images demonstrating stenosis at origin of left renal artery

Treatment

Management of Hypertension

Non-pharmacologic Measures

Non-pharmacologic measures are currently recommended as the initial approach for children and adolescents with less severe hypertension, or those with primary hypertension and no hypertensive target-organ disease (*Fig. 292.1*). Although the magnitude of change in BP may be modest, dietary modification, weight loss, and exercise have all been shown to successfully reduce blood pressure in children and adolescents.

Once hypertension has been established, "salt sensitivity" becomes more common, and reduction in sodium intake is likely to be of benefit in lowering blood pressure. Other nutrients that have been examined in patients with

hypertension include potassium and calcium, both of which have been shown to have antihypertensive effects. Therefore, a diet that is low in sodium and enriched in potassium and calcium may be more effective in reducing blood pressure than a diet that restricts sodium only. An example of such a diet is the so-called DASH diet (Dietary Approaches to Stop Hypertension; http://www.dashdiet.org), which has been shown to have an antihypertensive effect even in patients receiving antihypertensive medication. Successful blood pressure reduction has recently been demonstrated in a study of the DASH eating plan in adolescents.

Numerous studies have demonstrated that weight loss in obese adolescents can lower blood pressure. In studies where a reduction in BMI of about 10% was achieved, short-term reductions in blood pressure were in the range of 8–12 mmHg. Unfortunately, weight loss is notoriously difficult and usually unsuccessful, especially in the primary care setting. However, identifying a medical complication of obesity such as hypertension can perhaps provide the necessary motivation for patients and families to institute appropriate lifestyle changes.

Increasing physical activity may also have beneficial effects on BP, particularly for children who are overweight and need to improve their BMI. Increased physical activity may have a number of other beneficial effects such as improvement in vascular function and should be recommended for children with hypertension. In addition to increasing physical activity, children should have limitations placed on their sedentary time, with no more than 2 h/day spent on television, computers, video games, and other sedentary pursuits. Recent studies have demonstrated that short-term dietary and exercise interventions can result in weight loss, reduced BP, and improvements in laboratory abnormalities associated with the metabolic syndrome in overweight children and adolescents. These studies support the recommendation made by the NHBPEP Working Group that therapeutic lifestyle changes should be considered primary therapy for obesity-related hypertension in children and adolescents. These measures should be incorporated into the treatment plan of all hypertensive children and adolescents, even those who require antihypertensive medications.

Pharmacologic Therapy

Given the intensive nature of non-pharmacologic approaches, and since some hypertensive children may have hypertensive target-organ damage that could be reversed with effective treatment, antihypertensive medications may be needed. As has already been noted, the long-term consequences of untreated hypertension in an asymptomatic, otherwise healthy child or adolescent remain unknown. Additionally, there are few data available on the long-term effects of antihypertensive medications on the growth and development of children. Therefore, use of pharmacologic therapy is usually limited to children and adolescents with one of the following indications:

- Symptomatic hypertension
- Secondary hypertension
- Hypertensive target-organ damage
- Diabetes (Types 1 & 2)
- Persistent hypertension despite non-pharmacologic measures

The historical lack of pediatric drug trials has been largely rectified by passage of the Food and Drug Administration Modernization Act (FDAMA) in the USA in 1997. This legislation contained a provision that granted six additional months of patent protection to drug manufacturers if they conducted pediatric trials. Subsequent legislation (Best Pharmaceuticals for Children Act, Pediatric Research Equity Act, FDA Amendments Act of 2007) has extended this provision and also has led to other initiatives, including posting of internal FDA pharmacology and efficacy reviews on the Internet, and mechanisms to promote studies of medications with lapsed patent protection. These initiatives have led to a significant number of pediatric clinical trials of antihypertensive medications and have also increased the number of such medications with specific pediatric labeling, thereby significantly increasing the amount of clinically useful information for practitioners. Similar legislation has recently been adopted in the European Union.

Unlike in adults, large-scale comparative trials of different classes of antihypertensive agents have not been conducted in children. Therefore, the choice of initial antihypertensive agent for use in children still remains up to the preference of the individual practitioner. Diuretics and beta-adrenergic blockers, which were recommended as initial therapy in the First and Second Task Force Reports, have a long track record of safety and efficacy in hypertensive children and are still appropriate for pediatric use, although they are now mostly used as second-line agents. Newer classes of agents, including angiotensin converting enzyme inhibitors (ACEIs), calcium channel blockers, and angiotensin receptor blockers (ARBs), have now been shown to be safe and well tolerated in hypertensive children in recent industry-sponsored trials, and may be prescribed if indicated. As a matter of fact, these newer agents, particularly calcium channel blockers and ACE inhibitors, have become the most widely utilized initial agents in the pediatric age group.

It is reasonable to try to base the choice of agent upon the assumed pathophysiology of the child's hypertension. Additionally, consideration should be given to using specific classes of antihypertensive medications in certain hypertensive children and adolescents with specific underlying or concurrent medical conditions. The best example of this would be the use of ACEIs or ARBs in children with diabetes or proteinuric renal diseases, in whom such agents may have a beneficial effect in slowing progression. An additional example would be children with hypertension who are receiving stimulant medications for attention deficit hyperactivity disorder – such children are commonly tachycardic and could benefit from treatment with a beta-blocker.

Antihypertensive drugs in children and adolescents are generally prescribed in a stepped-care manner (*Fig. 292.6*). The patient is started on the lowest recommended dose of the initial agent and the dose is increased until the highest recommended dose is reached, or until the child experiences adverse effects from the medication. At this point a second drug from a different class should be added, until the desired goal BP is reached. Since many antihypertensive drugs now have specific FDA-approved pediatric labeling, the generalist should restrict their choices to those agents. Recommended doses for selected antihypertensive agents for use in hypertensive children and adolescents are given in *Table 292.9*.

Many children and adolescents with "uncomplicated" primary hypertension may require two or more drugs to achieve target BP. Children with secondary hypertension, particularly those with renal disease, almost always require multidrug regimens to achieve adequate BP control. Combination antihypertensive preparations are widely available and offer advantages that may improve adherence to treatment. Although only one such preparation has been studied in children to date, they may be very useful in certain children, particularly those who require an ACE inhibitor or angiotensin receptor antagonist plus a diuretic; many preparations offering this combination are available.

BP treatment goals for children and adolescents were clarified in the Fourth Report. For children with uncomplicated primary hypertension and no hypertensive target-organ damage, the recommended target BP is <95th percentile for age, gender, and height, whereas for children with secondary hypertension, diabetes, or hypertensive target-organ damage, target BP should be <90th percentile

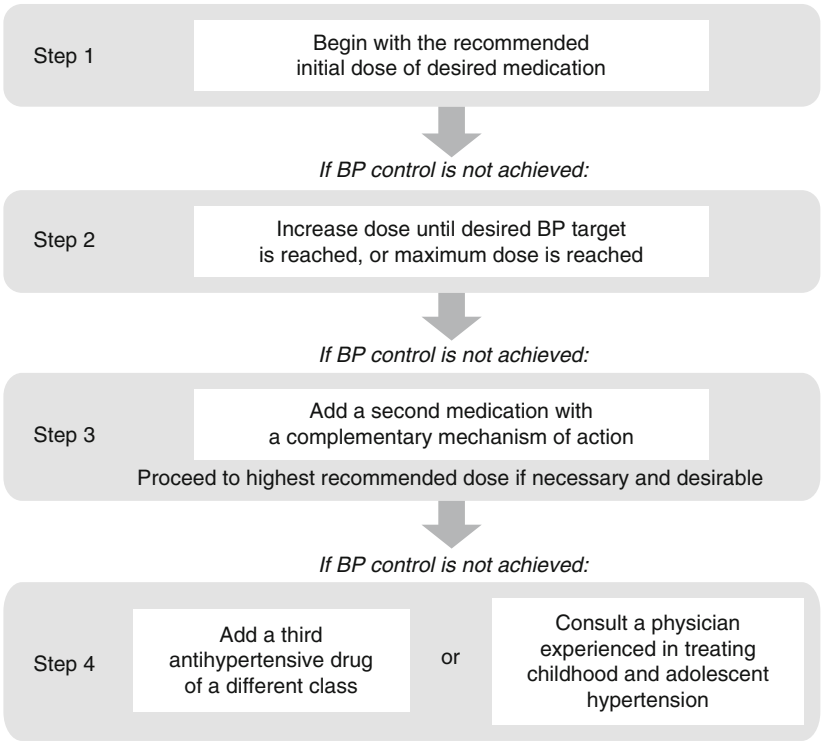

Figure 292.6
Stepped-care approach to pharmacologic management of hypertension in children and adolescents (BP, blood pressure)

Table 292.9

Recommended doses for selected antihypertensive agents for use in hypertensive children and adolescents

Class	Drug	Starting dose	Interval	Maximum dose[a]
Aldosterone receptor antagonists	Eplerenone	25 mg/day	QD-BID	100 mg/day
	Spironolactone[b]	1 mg/kg/day	QD-BID	3.3 mg/kg/day up to 100 mg/day
Angiotensin-converting enzyme (ACE) inhibitors	Benazepril[b]	0.2 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Captopril[b]	0.3–0.5 mg/kg/dose	BID–TID	6 mg/kg/day up to 450 mg/day
	Enalapril[b]	0.08 mg/kg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Fosinopril	0.1 mg/kg/day up to 10 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Lisinopril[b]	0.07 mg/kg/day up to 5 mg/day	QD	0.6 mg/kg/day up to 40 mg/day
	Quinapril	5–10 mg/day	QD	80 mg/day
Angiotensin-receptor blockers	Candesartan	4 mg/day	QD	32 mg/day
	Losartan[b]	0.70 mg/kg/day up to 50 mg/day	QD	1.4 mg/kg/day up to 100 mg/day
	Olmesartan	2.5 mg/day	QD	40 mg/day
	Valsartan[b]	1.3 mg/kg/day up to 40 mg/day <6 years: 5–10 mg/day	QD	2.7 mg/kg/day up to 160 mg/day <6 years: 80 mg/day
α- and β-adrenergic antagonists	Labetalol[b]	2–3 mg/kg/day	BID	10–12 mg/kg/day up to 1.2 mg/day
	Carvedilol	0.1 mg/kg/dose up to 12.5 mg BID	BID	0.5 mg/kg/dose up to 25 mg BID
β-adrenergic antagonists	Atenolol[b]	0.5–1 mg/kg/day	QD–BID	2 mg/kg/day up to 100 mg/day
	Bisoprolol/ HCTZ	0.04 mg/kg/day up to 2.5/6.25 mg/day	QD	10/6.25 mg/day
	Metoprolol	1–2 mg/kg/day	BID	6 mg/kg/day up to 200 mg/day
	Propranolol	1 mg/kg/day	BID–TID	16 mg/kg/day up to 640 mg/day
Calcium channel blockers	Amlodipine[b]	0.06 mg/kg/day	QD	0.3 mg/kg/day up to 10 mg/day
	Felodipine	2.5 mg/day	QD	10 mg/day
	Isradipine[b]	0.05–0.15 mg/kg/dose	TID–QID	0.8 mg/kg/day up to 20 mg/day
	Extended-release nifedipine	0.25–0.5 mg/kg/day	QD–BID	3 mg/kg/day up to 120 mg/day
Centralα-agonist	Clonidine[b]	5–10 mcg/kg/day	BID-TID	25 mcg/kg/day up to 0.9 mg/day
Diuretics	Amiloride	5–10 mg/day	QD	20 mg/day
	Chlorthalidone	0.3 mg/kg/day	QD	2 mg/kg/day up to 50 mg/day
	Furosemide	0.5–2.0 mg/kg/dose	QD-BID	6 mg/kg/day
	HCTZ	0.5–1 mg/kg/day	QD	3 mg/kg/day up to 50 mg/day
Vasodilators	Hydralazine	0.25 mg/kg/dose	TID–QID	7.5 mg/kg/day up to 200 mg/day
	Minoxidil	0.1–0.2 mg/kg/day	BID–TID	1 mg/kg/day up to 50 mg/day

[a]The maximum recommended adult dose should never be exceeded

[b]Information on preparation of a stable extemporaneous suspension is available for these agents

BID, twice-daily; HCTZ, hydrochlorothiazide; QD, once-daily; QID, four times daily; TID, three times daily

for age, gender, and height. Recent studies have suggested that an even lower BP goal is needed in those with chronic kidney disease. Home blood pressure measurement can be helpful in ensuring that blood pressure control has been achieved. In some patients, repeat ambulatory BP monitoring may be necessary if office BP measurements appear to indicate "resistant hypertension."

In addition to ongoing monitoring of blood pressure, treatment of hypertension should include surveillance for medication side effects, periodic monitoring of electrolytes (in children treated with ACEIs, ARBs or diuretics), counseling regarding other cardiovascular risk factors, and continued emphasis on therapeutic lifestyle changes. Hypertensive target-organ damage such as left ventricular hypertrophy, if present, should be reassessed periodically. Children with uncomplicated primary hypertension, especially obese adolescents who successfully lose weight and maintain their weight loss, may be candidates for gradual withdrawal of drug therapy. These children should receive continued BP monitoring after drug therapy is withdrawn, and should continue non-pharmacologic treatment.

Prognosis

Childhood BP and Subsequent CV Disease

There are no data at present that clearly document a relationship between childhood BP and cardiovascular morbidity and mortality in adulthood. However, a number of studies have shown that BP and other traditional cardiovascular risk factors in childhood predict the subsequent presence of cIMT and arterial stiffness, two well-accepted surrogate markers for atherosclerosis and cardiovascular events.

Additionally, longitudinal studies have demonstrated that children with elevated BP are at increased risk of development of the metabolic syndrome as adults, and that, components of the metabolic syndrome, an important risk factor for cardiovascular morbidity, track over time from childhood to adulthood. Taken together, these data indicate that over time, adult morbidity and mortality will be more tightly connected with childhood precursors, and emphasize the need for early intervention.

Acute Severe Hypertension

Clinical Vignette

An 8 year-old boy is brought to the Emergency Department by ambulance after having a generalized tonic-clonic seizure at school. Lorazepam was administered in the field and there has been no further seizure activity. Blood pressures in the ambulance ranged from 150–162/97–110 and a repeat reading in the Emergency Department is 154/102. His mother arrives from work and mentions that his urine has been dark brown in color for the past 2 days.

Presentation and Differential Diagnosis

Acute severe hypertension has traditionally been divided into hypertensive emergencies and hypertensive urgencies. The clinician should understand that there is a spectrum of severity of acute hypertension, and that any classification scheme dividing the clinical presentation of acute severe hypertension into separate categories is by its nature arbitrary. That said, severe symptomatic elevation in BP *with* evidence of acute target-organ damage has classically been classified as a hypertensive emergency; while severe symptomatic elevation in BP *without* evidence of acute target-organ damage has classically been classified as a hypertensive urgency.

Hypertensive encephalopathy is the most frequent life-threatening symptom in children and adolescents with severe hypertension, emphasizing the need for slow, controlled reduction in BP to prevent complications arising through loss of normal autoregulatory processes. Other severe symptoms sometimes seen in pediatric patients with severe hypertension include cortical blindness and congestive heart failure. Less severe symptoms may include nausea, vomiting, or unusual irritability; since these may be somewhat nonspecific, especially in younger children, a high degree of clinical suspicion must be maintained.

Nearly every child or adolescent who presents with severe acute hypertension has secondary hypertension. Common underlying conditions that may produce acute severe hypertension in a child or adolescent include acute or chronic renal disease, solid organ transplantation, renal artery stenosis, or congenital renal disease such as autosomal recessive polycystic kidney disease. Medication non-adherence in patients with established primary hypertension, the most common cause of acute severe hypertension in adults, occurs rarely in pediatric patients (except perhaps in those with chronic kidney disease).

Evaluation and Management

The child with acute severe hypertension requires prompt evaluation and therapy in order to avoid further development of target-organ effects. In most such children, the

underlying diagnosis will be obvious from the medical history, and little additional information will be needed other than determining the severity of symptoms the patient is experiencing, as this will guide treatment. For patients newly presenting with severe hypertension who have no prior history, in addition to assessing symptom severity, questions will need to be asked regarding the onset of symptoms, as well as recent and past medical history, focusing on eliciting clues to whatever underlying condition is producing the severe hypertension.

Usually, only a brief physical examination is necessary in evaluating children with acute severe hypertension. Just as in the outpatient with elevated BP, it is important to confirm that the BP has been accurately measured. The examination should then focus on assessment of volume status, cardiac status, and neurologic status. Other parts of the examination will help narrow the differential diagnosis in those children without prior histories of hypertension. Extensive diagnostic studies will not be necessary in most patients, but laboratory assessment of renal function, urinalysis (if possible), electrolytes, and assessment of cardiopulmonary status by chest x-ray and/or echocardiography should be obtained. Renal or abdominal ultrasonography may be helpful in confirming findings on physical examination, but usually can be deferred until BP has been lowered to a safe level. Other

Table 292.10
Antihypertensive drugs for management of severe hypertension in children and adolescents

Useful for severely hypertensive patients with life-threatening symptoms				
Drug	**Class**	**Dose**	**Route**	**Comments**
Esmolol	β-adrenergic blocker	100–500 mcg/kg/min	IV Infusion	Very short-acting–constant infusion preferred. May cause profound bradycardia
Hydralazine	Direct vasodilator	0.2–0.6 mg/kg/dose	IV, IM	Should be given q 4 h when given IV bolus
Labetalol	α- and β-adrenergic blocker	Bolus: 0.20–1.0 mg/kg/dose, up to 40 mg/dose Infusion: 0.25–3.0 mg/kg/h	IV Bolus or infusion	Asthma and overt heart failure are relative contraindications
Nicardipine	Calcium channel blocker	Bolus: 30 mcg/kg up to 2 mg/dose Infusion: 0.5–4 mcg/kg/min	IV Bolus or infusion	May cause reflex tachycardia
Sodium Nitroprusside	Direct vasodilator	0.5–10 mcg/kg/min	IV Infusion	Monitor cyanide levels with prolonged (>72 h) use or in renal failure; or co-administer with sodium thiosulfate
Useful for severely hypertensive patients with less significant symptoms				
Drug	**Class**	**Dose**	**Route**	**Comments**
Clonidine	Central α-agonist	0.05–0.1 mg/dose, may be repeated up to 0.8 mg total dose	PO	Side effects include dry mouth and drowsiness
Enalaprilat	ACE inhibitor	0.05–0.10 mg/kg/dose up to 1.25 mg/dose	IV bolus	May cause prolonged hypotension and acute renal failure, especially in neonates
Fenoldopam	Dopamine receptor agonist	0.2–0.8 mcg/kg/min	IV infusion	Clinical trial demonstrated modest BP reductions in patients ≤12 years
Hydralazine	Direct vasodilator	0.25 mg/kg/dose up to 25 mg/dose	PO	Extemporaneous suspension stable for only 1 week
Isradipine	Calcium channel blocker	0.05–0.1 mg/kg/dose up to 5 mg/dose	PO	Stable suspension can be compounded
Minoxidil	Direct vasodilator	0.1–0.2 mg/kg/dose up to 10 mg/dose	PO	Most potent oral vasodilator; long-acting

ACE, angiotensin-converting enzyme; BP, blood pressure; IM, intramuscular; IV, intravenous; PO, oral

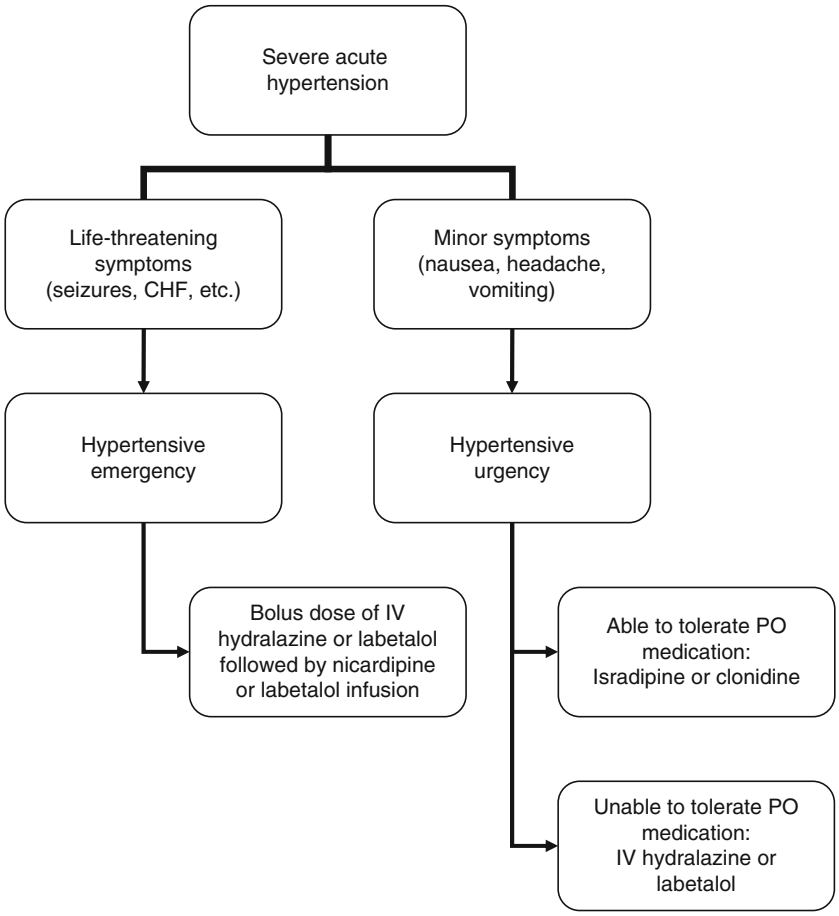

Figure 292.7
Proposed algorithm for management of severe acute hypertension in children and adolescents (CHF, congestive heart failure; IV, intravenous; PO, oral)

diagnostic studies suggested by the physical examination or initial lab tests can also be obtained at a later stage of management.

Although evidence-based recommendations are lacking, the usual goal in treatment of a hypertensive emergency is to reduce the BP by no more than 25% over the first 8 h, with a gradual return to normal/goal BP over 24–48 h. Treatment of hypertensive emergencies in children should be initiated with a continuous infusion of an intravenous antihypertensive, with nicardipine and labetalol being the agents most commonly used. Oral antihypertensive agents can be used in patients with acute severe hypertension who do not have life-threatening symptoms. The choice of oral antihypertensives for use in management of severe hypertension in pediatric patients is fairly limited. Short-acting nifedipine, which had remained in use in children until recently, is no longer recommended. For suggested doses of oral and intravenous drugs useful in treatment of acute severe hypertension in children and adolescents, see *Table 292.10*. An algorithm to the classification and suggested management of the child or adolescent with acute severe hypertension is presented in *Fig. 292.7*.

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293 Poststreptococcal Acute Glomerulonephritis

Abdelaziz Y. Elzouki

Definition

Acute glomerulonephritis (AGN) is a clinical complex characterized by the presence of hematuria or red blood cell (RBC) casts accompanied by at least two of the following clinical findings: edema (periorbital in most of the cases), azotemia, oliguria, and hypertension.

AGN can be classified etiologically into four main clinical categories (*Table 293.1*): (1) postinfectious AGN, (2) AGN associated with systemic diseases, (3) idiopathic glomerulonephritis, and (4) familial nephritis.

In children, the majority of cases of AGN are postinfectious, which include bacterial, viral, and parasitic causes (*Table 293.2*). The most common postinfectious AGN cases are those following infection of the throat or skin with group A β hemolytic streptococci. Poststreptococcal acute glomerulonephritis (PSAGN) occurs in two forms, the epidemic form and the sporadic form.

Incidence and Prevalence

Streptococcal infection continues to be the most common cause of AGN in children living in Thailand, China, India, South Africa, South America, Southeast Asia, Turkey, and Arab countries. Environmental conditions that can explain the difference in incidence in different countries include:

(a) the density in terms of number of people per unit area of living space (i.e., the number of residents per household is much higher in countries with high incidence compared to Europe and North America) and (b) the prevalence of nephritogenic strains of streptococcus in the population.

Data on the incidence of AGN following documented infection with group A β hemolytic streptococci reveal attack rates as low as 1% to as high as 20%.

Age and Sex Distribution and Familial Cases

The disease occurs most commonly in children between the ages of 3 and 7 years. It is rare in infants and children younger than 2 years of age, and is more common in boys by a ratio of 2:1. In a study of 302 children with sporadic PSAGN (*Table 293.3*), the mean age was 7.1 years, 85% were 4 years or above, and the ratio of boys to girls was 1.6:1. Cases of PSAGN frequently cluster in an individual family. One study reported that 20% of the sibling contacts of patients with PSAGN developed clinical or subclinical glomerulonephritis. In a study of 302 patients (*Table 293.3*), seven of 302 patients (2%) had siblings who were admitted to the hospital with symptomatic PSAGN within 3 weeks of their own diagnosis.

Association with Pharyngitis and Pyoderma

PSAGN may follow group A streptococcal infection of either the skin or pharynx. Unlike rheumatic fever, only certain M types are associated with this sequelae. Distinct M types are associated with each site of infection: types 1, 3, 4, 12, and 25 are associated with pharyngitis-related PSAGN and types 2, 6, 49, 55, and 57, are associated with pyoderma-related PSAGN. Pharyngitis-related PSAGN tends to peak in the winter and spring month, whereas pyoderma-related PSAGN is more prevalent in the summer and fall. The interval between the preceding streptococcal infection and the development of PSAGN is 1–2 weeks (average 10 days) in pharyngitis-related PSAGN; the interval is longer (4–8 weeks) in pyoderma-related PSAGN.

Pathogenesis

The exact mechanism by which renal injury is produced in this disease is not completely understood. It was suggested that circulating immune complexes that traverse the glomerular basement membrane activate the complement system, which leads to release of substances that attract neutrophils; lysosomal enzymes released by neutrophils are at least in part responsible for the damage to the

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Table 293.1
Causes of acute glomerulonephritis

Postinfectious acute glomerulonephritis
Systemic Diseases
Systemic lupus erythematosus
Henoch schonlein purpura
Goodpasture Syndrome (anti glomerular basement membrane disease) (Glomerulonephritis + pulmonary hemorrhage)
Wegener granulomatosis
Periarteritis and hypersensitivity angitis
Cryoimmunoglobulinemia
Hemolytic-uremic syndrome
Idiopathic glomerulonephritis
Immunoglobulin A nephritis (Berger disease)
Mesangiocapillary proliferative glomerulonephritis (membranoproliferative glomerulonephritis)
Rapidly progressive glomerulonephritis
Familial Nephritis (Alport Disease)

glomeruli. However, similar circulating immune complexes have also been found in patients with rheumatic fever without glomerulonephritis and may occur in normal individuals.

Previous studies have shown elevated levels of plasma interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF alpha), and urinary IL-6 and IL-8, in patients with PSAGN. Increased renal expression of IL-8 and transforming growth factor-beta (TGF-B) has also been reported in this disease. The streptococcal erythrogenic exotoxin type B (ETB) and its precursor (ETBP) have been shown to be involved in the pathogenesis of PSAGN. ETB has been found in renal biopsies from patients with PSAGN.

In a recent study, it has been reported that there was a significant increase in IL-6, IL-8, TNF alpha, and TGF-B1 in ETB- or ETBP-treated human mononuclear leukocytes culture.

Clinical Features

Subclinical cases occur about four times more frequently than easily recognized cases; however nearly all the patients have abnormal urine analysis.

The initial clinical manifestations of 302 children with sporadic PSAGN are shown in (*Table 293.3*).

Table 293.2
Infectious agents associated with postinfectious acute glomerulonephritis

Bacterial
• Group A β hemolytic streptococci
• Streptococcus viridans (subacute bacterial endocarditis nephritis)
• Staphylococcus aureus
• Staphylococcus albus (shunt nephritis)
• Streptococcus pneumoniae (pneumococcus)
• Salmonella typhi
• Klebsiella pneumoniae
• Brucella
• Treponema pallidum (syphilis)
• Mycoplasma pneumoniae
Viral
• Hepatitis A
• Hepatitis B
• Hepatitis C
• Epstein-Barr virus
• Mumps virus
• Varicella-zoster virus
• Coxsackievirus
• Rubeola virus
• Human immunodeficiency virus
Parasitic
• Plasmodium malariae and falciparum
• Schistosoma mansoni
• Toxoplasma gondii
• Echinococcus (hydatid disease)
• Loa loa
• Onchocerca volvulus
• Leishmania

Edema

Edema is the most common clinical finding in patients with PSAGN, present in 90% and constituting the chief complaint in 62% of children with PSAGN. Characteristically, early morning periorbital edema is an initial clinical manifestation. The lower extremities are the second site for fluid retention. Usually there is no ascites or pleural effusion except in patients who presented with nephrotic syndrome. The degree of edema depends on

Table 293.3
Epidemiologic and clinical presentations of 302 children with sporadic poststreptococcal acute nephritis

Mean age (range) (year)	7.1 (2–14)
Male:female ratio	1.6:1
Average residents per household	8.2
Familial occurrence	2%
Edema	98%
Gross hematuria	60%
Hypertension	64%
Encephalopathy	6%
Pulmonary edema	18%
Low C3	90%
Serum creatinine $\succ$ 2 mg/dl	10%
Nephrotic-range proteinuria	10%

Adapted from [7]. With permission

the sodium content of the diet. Patients without obvious edema at presentation often lose 1–2 kg of body weight during recovery.

Hematuria

Gross hematuria is a common presentation in children with PSAGN. Usually the parents describe the urine as tea colored or cola colored. The brown color is caused by hemolysis with liberation of hemoglobin, which is then transformed to hematin in an acid urine.

Hypertension

Hypertension occurs in 70–82% of patients, and can be severe in over half of these patients. Hypertension is usually present at the onset of PSAGN. Hypertension in patients with PSAGN has been related to expansion of intravascular or extravascular volume and to vasospasm resulting from neurogenic or hormonal factor. Results of previous studies suggest that renin secretion is not the primary cause of hypertension in patients with PSAGN.

These data indicate that hypertension in PSAGN is "volume-dependent hypertension"; therefore, prompt fluid and sodium restriction, diuretics, and addition of a vasodilator (e.g., hydralazine) can control the hypertension optimally.

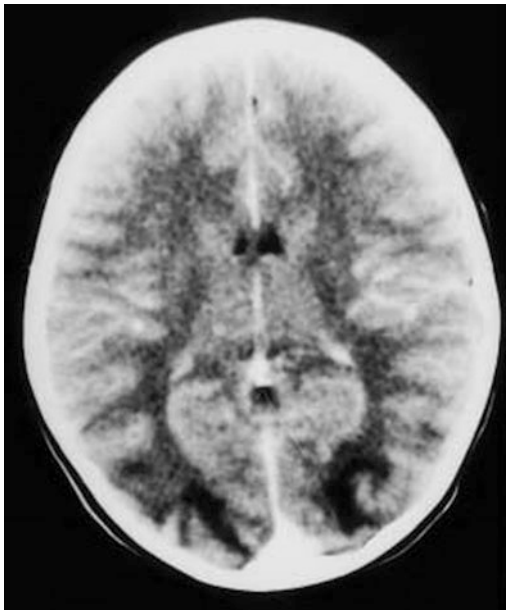

Figure 293.1
Axial computed tomography section demonstrating hypodensity in the occipital lobes (Reproduced from [20])

Hypertensive Encephalopathy/Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cerebral symptoms are usually related to an acute increase in the blood pressure ("hypertensive encephalopathy"). These symptoms have been reported to occur in 5–10% of patients. The most frequent acute cerebral manifestations are headache, nausea, vomiting, disturbances of consciousness, and convulsions.

Posterior reversible encephalopathy syndrome (PRES), other name reversible posterior leukoencephalopathy syndrome (RPLS), is a recently described clinico-imaging related entity; this syndrome has been reported in patients with PSAGN.

The clinical manifestations include sudden visual loss, seizures, and specific magnetic resonance imaging. MRI reveal areas of hyperintensities in the bilateral, parietal, and occipital lobs; these hyperintensities resolve in 2 weeks (*Figs. 293.1–293.3*).

Congestive Heart Failure/Pulmonary Edema

Clinical evidence of congestive heart failure (i.e., tachycardia, tachypnea, respiratory distress, gallop rhythm, hepatic enlargement) and radiologic evidence of pulmonary

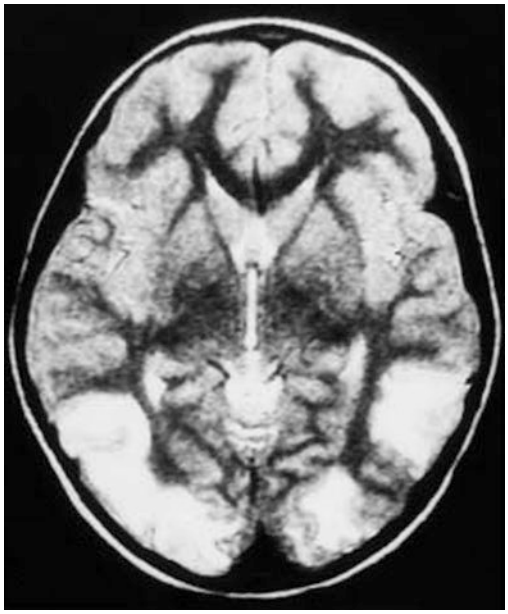

Figure 293.2
T2-weighted axial magnetic resonance imaging (MRI) sections showing hyperdensity in the accipitoparietal and to lesser extent, frontal lobes (Reproduced from [20])

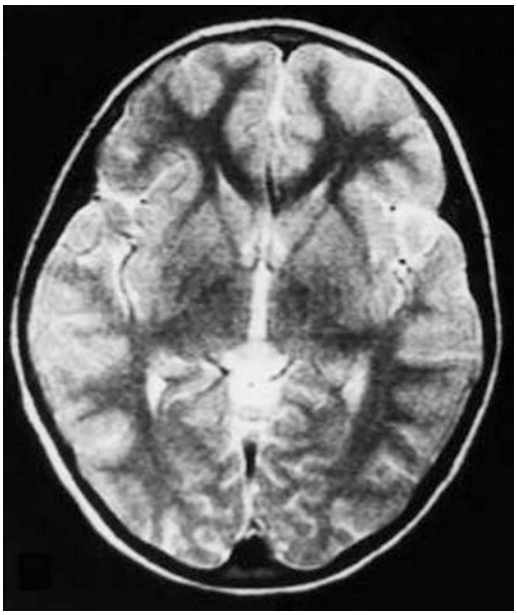

Figure 293.3
T2-weighted axial MRI section obtained 2 months later, demonstrating normalization white matter changes (Reproduced from [20])

edema (pulmonary alveolar infiltrates, cardiomegaly, and prominent septal thickening) are manifestations that occur in 20% of patients.

Hypertension and hypervolemia are the primary factors producing symptoms of congestive heart failure. In previous studies, it has been shown that the plasma volume of patients with PSAGN is increased and that a correlation exists between the blood volume and signs or symptoms of pulmonary edema.

In children who present with respiratory distress and chest X-ray showing cardiomegaly and pulmonary edema, blood pressure recording and urine analyses should be performed immediately to rule out acute glomerulonephritis.

Hemoptysis (pulmonary hemorrhage) has been reported to occur with PSAGN.

Laboratory Findings

1. Microscopic hematuria usually present in all patients. Urine examination reveals numerous RBCs with evidence of glomerular hematuria, and RBC casts can be seen in fresh urine specimens.
2. Proteinuria is present in 80% of patients with PSAGN; however, massive proteinuria (i.e., nephrotic-range proteinuria) is present in only 4–10% of patients.
3. Serum complement C3 level was found to be decreased in 80–95% of patients if measurements were made during the first 2 weeks of illness. The complement levels usually returned to normal within 6–8 weeks. Persistently low complement levels beyond 8 weeks indicate the need to investigate other possible causes of glomerular nephritis, which include membranoproliferative glomerulonephritis and lupus nephritis.
4. Renal function: Azotemia is present in PSAGN; usually there is a mild to moderate reduction in glomerular filtration rate. The serum creatinine usually does not exceed 150 micromole/L in the majority of patients; however, a few patients (up to 8%) can present with acute renal failure, with very high serum creatinine as clinical evidence of rapidly progressive glomerulonephritis (RPGN). In a follow-up study 1–16 years of the acute episode of PSAGN, it was found that these patients has basal creatinine clearance similar to normal control; however, the renal function reserve (RFR) was significantly reduced compared to control group.
5. Anemia is usually mild and related to the degree of plasma volume expansion (i.e., dilutional anemia). Recently, in three cases of PSAGN reported associated with autoimmune hemolytic anemia, (AIHA) the

patients had a positive direct antiglobulin test (DAT). Patients with PSAGN and significant anemia should have a DAT performed.
6. Sedimentation rate is usually increased during the cute phase of the disease.

Evidence of Streptococcal Infection

Isolation of streptococci from the throat or skin and/or evidence of host response are confirmatory of streptococcal infection. Cultures of the throat and any skin lesions may yield a β hemolytic streptococcus. Humoral antibodies to specific streptococcal extracellular products can be demonstrated by neutralizing assays. The antistreptolysin o (ASO) assay is the most commonly used. Eighty percent of untreated children will have a fourfold rise in ASO titer.

After pyoderma, response to ASO is frequently slight or absent. In contrast, the antideoxyribonuclease B (antiDNAse B) and the antihyaluronidase (AH) assays are useful after skin as well as throat infection. The streptozyme agglutination slide test can detect five antibodies (ASO, antiDNAse B, AH, and antistreptokinase) within 7–10 days. It was demonstrated that increased streptococcal zymogen antibody titers are the best available marker for streptococcal infection associated with AGN.

In a recent study, it was reported that the combination of ASO and AntiDNAse B was a very sensitive and specific combination for identifying non-suppurative post streptococcal disease (sensitivity 95.5%, specificity 88.6%).

Pathology

The characteristic pathologic findings of PSAGN include light microscopic demonstration of diffuse exudative proliferative glomerulonephritis. The glomeruli are enlarged, with a pronounced lobular configuration. There is endothelial and mesangial cell proliferation. Capillary lumens are extensively obliterated. Inflammatory cells are commonly present in the glomeruli; they are mainly polymorphonuclear leukocytes (*Fig. 293.4*), but occasionally eosinophils, lymphocytes, F macrophages, and plasma cells are identified as part of the exudative component. Focal and segmental crescents are common, but diffuse crescentic glomerulonephritis involving more than 50% of the glomeruli (i.e., RPGN) is rare. On immunofluorescence microscopy, there is fine granular staining for immunoglobulin G, C3, and C1q along the capillary loops and within the mesangium. On electron microscopic examination, the most characteristic change seen ultrastructurally is the presence of subepithelial discrete electron-dense, dome-shaped "humps" that project outward from the epithelial side of the basement membrane.

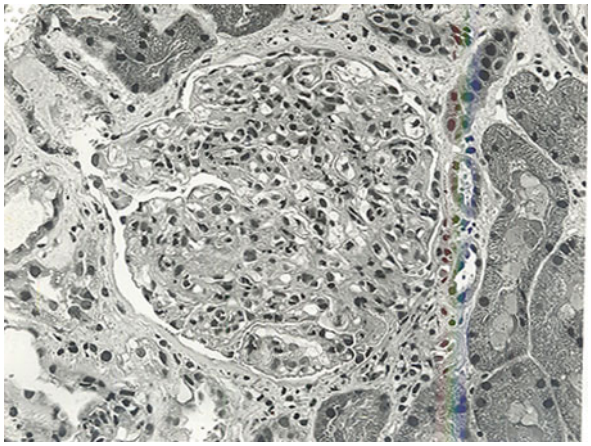

Figure 293.4
Glomerulus in postinfetious glomerulonephritis. The glomerulus is hypercellular due to increased mesangial and endothelial cells along with infiltration by polymorphonuclear cells (courtesy of Dr. M. Akhtar)

Clinical Course

The natural course of PSAGN in children is as follows:

Oliguria and azotemia resolve within 7–14 days, hypertension resolves within 7–21 days, gross hematuria resolves within 3 weeks, C3 becomes normal within 6 weeks, proteinuria may persist for 6 months, and microscopic hematuria may persist for 1–2 years.

Diagnosis and Differential Diagnosis

The diagnosis of PSAGN can be established by the following clinical and laboratory criteria:

1. Clinical diagnosis of acute nephritis (i.e., acute onset and presence of hematuria, edema, hypertension, azotemia)
2. Decreased serum level of C3
3. Bacteriologic or serologic evidence of streptococcal infection
4. Spontaneous improvement in the clinical and laboratory indicators as stated above in "Clinical Course"

Other causes of acute nephritis, including systemic diseases affecting the kidney and primary renal disease, should be considered in the differential diagnosis:

1. Henoch–Schonlein nephritis: presence of purpuric rash, abdominal pain, gastrointestinal bleeding, arthritis, normal C3, elevated immunoglobulin A
2. Systemic lupus erythematosus: systemic manifestations that include rash, fever, arthralgia/arthritis, positive antinuclear antibodies, persistently depressed C3 and C4
3. Hereditary nephritis: family history of renal disease, sensorineural hearing deficit of patient or family member, normal C3
4. Membranoproliferative glomerulonephritis: persistent depressed C3, intractable hypertension

Treatment

The management of the child with PSAGN centers on adequate treatment of hypertension and reducing the volume expansion. In a study of 302 children with sporadic PSAGN, the management included fluid and sodium restriction, diuretics (furosemide), and other antihypertensives, including hydralazine and propranolol; there was no mortality and there was a clinical complete recovery. A few patients may develop RPGN. The latter group may require dialysis and pulse methylprednisolone therapy and eventually may recover completely.

Prognosis

Most of the follow-up studies of children with PSAGN have shown that short- and long-term outcome is excellent, with complete recovery and no progression to chronic renal failure.

PSAGN rarely recurs.

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294 IgA Nephropathy

Rosanna Coppo

Case

A previously healthy 10-year old boy developed a cough, clear nasal discharge, and a temperature of 101°F. Approximately 12 h after the onset of symptoms, the mother became alarmed when the boy's urine turned brown. The boy was playing normally and did not appear ill. The amount of urine was normal. The boy had grown normally and had had excellent primary medical care; he had had no previous urinary problems or urinalyses. Because his urine remained brown, the mother and child visited a pediatrician. At the pediatrician's office, he appeared healthy except for the upper airway congestion. His blood pressure and other physical examination were normal. A urinalysis demonstrated large amounts of hemoglobin, 1+ protein, a high red blood cell count, and many red blood cell casts. Serum creatinine and complete blood count were normal.

What is your differential diagnosis? Could this be IgA nephropathy?

Definition

IgA nephropathy (IgAN) is a glomerular disease characterized by renal IgA deposits, prevalent over other classes of immunoglobulins, mostly in the mesangial area (*Fig. 294.1*). It can be observed in association with features of systemic vasculitis in Henoch-Schoenlein purpura or can be limited to the kidney, as described by Berger (primary IgA nephropathy). IgAN is common in children and adolescents presenting with persistent isolated microscopic hematuria or hematuria associated with moderate proteinuria.

Epidemiology

Primary IgAN is more frequent in males than in females. Its prevalence in children is variable around the world. In Japan, Korea, and Taiwan, all children are screened annually, and those thought to have glomerular hematuria have a renal biopsy. In these countries, the prevalence of IgAN is about 30% of all the glomerular diseases. The prevelance of IgAN in the USA is unknown, although it is less common in Afro-Americans. In Europe, IgAN represents almost 20% of all the renal biopsies in children. In South America, IgAN represents 25% of biopsies for suspected glomerular disease.

Etiology

A role for mucosal infections in IgAN has been hypothesized due to the typical manifestation of gross hematuria coincident with upper respiratory tract infections. Several experimental models have reproduced IgA mesangial deposits with pathogen administration, including intranasal delivery of Sendai virus, a common respiratory pathogen, immunization with Hemophilus parainfluenzae antigens, Coxsackie B4, Staphylococcus Aureus cell envelope, and others. IgAN was reproduced in experimental animals also by oral immunization with gliadin or other alimentary antigens. In humans, relationships between IgAN and infection have been claimed for Staphylococcus antigens, Cytomegalovirus, Epstein virus, Enterovirus, Helicobacter pylori, and others. All these data suggest that exogenous antigens derived from pathogens or environmental antigens could play a role in pathogenesis of IgAN, however the mechanism is still unclear.

Pathogenesis

The accumulation within glomeruli of IgA-containing immune material together with complement fractions, usually C3, was initially ascribed to deposition of IgA immune complexes (IgAIC) formed in response to mucosal pathogens. This hypothesis offered a simple explanation of the relationship between mucosal infections and gross hematuria. High levels of IgAIC are detectable in 30–70% of patients, mostly containing polymeric IgA1. However, no specific viral or alimentary antigens have been found in renal mesangial deposits, which suggests a role for a dysregulated IgA immune response.

Attention has been focused on the properties of the IgA produced by patients with IgAN, particularly IgA1

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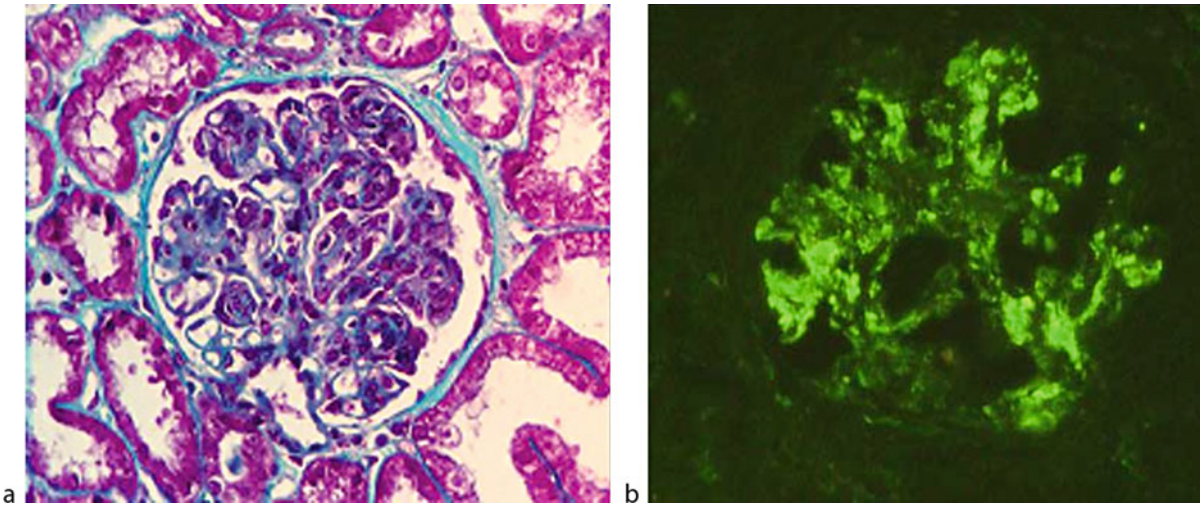

Figure 294.1
Renal tissue obtained by renal biopsy from a child with IgA nephropathy. Panel (a): Light microscopy examination of one glomerulus showing increase in mesangial matrix and variable increase in cellularity involving mesangial regions (periodic acid-Schiff stain). Panel (b): Immunofluorescent deposits of IgA in IgA nephropathy (immunofluorescence with anti IgA antibody X 250)

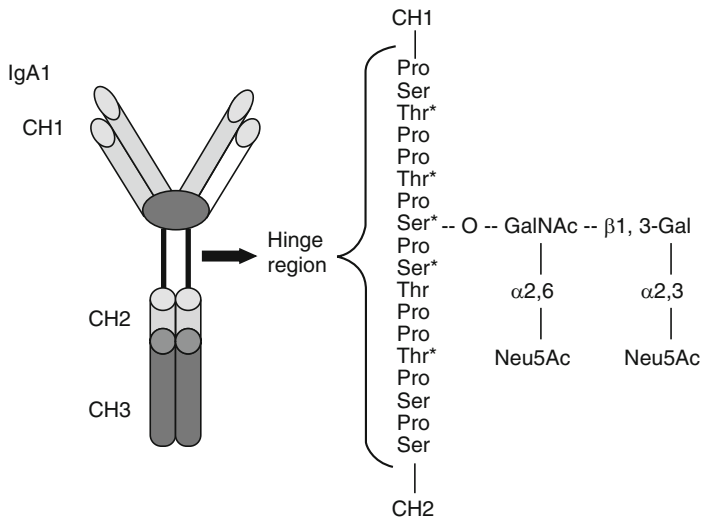

Figure 294.2
Structure of immunoglobulin A1

subclass (*Fig. 294.2*), the most representative of deposits in glomeruli of patients with this disease. An insertion of 18 aminoacids in the hinge region between CH1 and CH2 domains represents the major structural difference between IgA1 and IgA2. In this insertion three threonine and three serine residues are bound to five short O-linked oligosaccharide chains. The O-glycosylation consists of a core N-acetyl galactosamine (GalNAc) which occurs alone or extended with β1, 3 linked Gal or further with sialic acid in α2, 3 and / or α2, 6 linkage. In healthy subjects, serum IgA1 consists of a mixture of molecules with different O-glycoforms, whereas an abnormal IgA1

O-glycoform pattern has been detected in IgAN by using different techniques which demonstrated a high frequency of O-glycans consisting of GalNAc defective in β1,3 Gal. Such aberrantly glycosylated IgA1 can circulate as a monomer or participate in macromolecular self-aggregates; they can elicit an IgG autoimmune response forming IgG/IgA1IC or react with antigens and form true IgAIC. IgAIC constituted by aberrantly glycosylated IgA1 likely escape clearance by hepatic receptors and have a preferential renal deposition by virtue of enhanced lectinic reactivity with fibronectin, laminin, and collagen within the mesangial matrix. Currently, genetic and immunological studies support a hypothesis that IgA nephropathy is a multifactorial disease in which one or more genes, probably in combination with the effects of environmental factors, may be responsible for the onset of the disease.

Among other pathogenetic influences, increased production of IL-4 and IL-5 by Th2 subset lymphocytes in IgAN may explain the production of abnormally glycosylated IgA1 molecules which deposit in the glomeruli and could reduce terminal galactosylation and sialylation. The interaction with Fcα receptors on mesangial cells results in cellular activation and flogistic mediator synthesis including a variety of cytokines (IL6, PDGF, IL1, TNF-α, TGFβ), vasoactive factors (prostaglandins, thromboxane, leukotrienes, endothelin, PAF, NO), or chemokines (MCP-1, IL-8, MIP-1, RANTES). The influx of monocytes and lymphocytes into the mesangium is enhanced by the C3 codeposition. The activation of mesangial cells leads to cell contraction, hemodynamic modifications, and activation of the Renin-Angiotensin System (RAS). Angiotensin II enhances the activation of cytokines and chemokines and potentiates the actions of PDGF and TGFβ as growth factors for mesangial cells, favoring proliferation and accumulation of extracellular matrix, ultimately promoting sclerosis. Particular attention has been recently devoted to genes possibly involved in IgAN progression, as the polymorphism of RAS genes, due to a correlation between angiotensin II levels in tissue and the activity of the gene encoding ACE. In IgAN, there is no clear evidence of a significant alteration in the ACE genotype frequency, but several reports associate one genotype (DD) with a greater rate of progression in IgAN.

Pathology

The changes observed by light microscopy are not specific for this nephropathy, and IgAN is identified by the detection of predominance of IgA deposits in mesangial areas with codeposition of IgG and C3 in one third of the cases (Fig. 294.1). At light microscopy, primary IgAN presents with focal or diffuse proliferation of mesangial cells and expansion of the extracellular matrix. Other glomerular lesions are frequently associated, including focal or diffuse endocapillary proliferation, extracapillary proliferation with crescent formation, glomerular hyalinosis, and segmental or global sclerosis. Limited areas of tuft necrosis, indistinguishable from those seen in association with small vessel vasculitis, are detectable in IgAN with particularly acute disease. Rapidly progressive forms with crescents involving more than 50% of glomeruli are very rare. Interstitial and arteriolar changes are infrequently found.

Several authors have proposed classifications of IgAN grouping and stratifying the lesions. A new classification has recently been produced by a consensus of pathologists and nephrologists. This Oxford clinicopathological classification consists of a combined report of scores related to four lesions (mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, and tubular atrophy/interstitial fibrosis) that were found to be predictive of outcome independently of clinical assessment. Cross-sectional correlations between pathology and clinical features, including proteinuria at the time of biopsy, were similar in adults and children. Although children with IgAN displayed more proliferative lesions and fewer chronic changes than adults, the predictive value of each lesion in the Oxford IgAN clinicopathological classification on renal survival was not modified by age at biopsy.

Clinical Features

The most typical clinical feature of IgAN is macroscopic hematuria concomitant with upper respiratory tract infections or other mucosal inflammatory processes; it rarely occurs after vaccination or heavy physical exercise. Symptoms and/or urinary signs before the age of 3 years; are rare but increase with age. Gross hematuria affects 30–40% of children with IgAN. The interval between the precipitating event and the appearance of macrohaematuria is very short (12–72 h). The macrohaematuria persists for few days (usually less than 3 days), infrequently accompanied by flank and loin pain and fever. The color of the urine is red or brown (coke-colored); red blood cell casts are common. These episodes can recur and microscopic hematuria of various degree isolated or associated with low amounts of proteinuria can be residual between episodes of macroscopic hematuria. Thirty to fifty percent of the children biopsied for persistent microscopic hematuria with or without proteinuria have a diagnosis of IgAN. Proteinuria may

be found in 3–13% of chilren with asymptomatic hematuria and IgAN. A transient increase in proteinuria occurs coinciding with episodes of gross hematuria. In some children (6%), the clinical onset of IgAN can appear as nephrotic syndrome.

In a few cases, at the onset of disease, there is an acute nephritic syndrome, similar to poststreptococcal glomerulonephritis. In these children, macrohaematuria is associated with increased serum creatinine and urea, and also hypertension. In rare cases, the onset may be severe nephritic syndrome progressing to chronic renal failure due to crescentic lesions. Furthermore, in a few patients acute oliguric failure, usually spontaneously reversible, accompanies the episodes of macrohaematuria, attributed to tubular obstruction by red blood cells. Hypertension usually develops during a follow-up of several years or in severe cases.

Diagnosis

The hallmark of this nephritis is glomerular deposition of IgA; hence the diagnosis is possible only after renal biopsy, using immunofluorescence or immunohistochemistry investigations.

High serum levels of IgA are found in 35–50% of patients. This marker, particularly in cases with typical and recurrent macroscopic hamaturia, may suggest the possible presence of the disease, as well as the more sophisticated detection of high levels of aberrantly glycosylated serum IgA1, but the diagnosis is made on a histological basis only. It is common to find high levels of macromolecular IgA (IgAIC, mixed IgA/IgGIC, IgA/fibronectin aggregates), particularly during the phases of clinical activity.

Complement values are generally within the limits when C3 or C4 are measured, while signs of subclinical complement activation can be detected by measuring the C3d breakdown product.

Serial measurement of 24 h protein excretion or urinary protein/creatinine ratio is highly recommended as one of the most useful parameters to follow over the years. Urinary excretion of cytokines, mostly MCP-1 and IL6, is increased in patients with progressive course, but not generally available for clinical use.

Differential Diagnosis

As mentioned above, the diagnosis is histological only, performed on renal biopsy.

Other conditions presenting with gross hematuria should be considered to assess the need for renal biopsy, mostly postinfectious acute glomerulonephritis. The interval between upper respiratory tract infection and macrohematuria in IgAN is very short (hours or 1–3 days), compared with 1–3 weeks in postinfectious acute glomerulonephritis.

Besides renal biopsy features, the diagnosis is made in the absence of any recognizable systemic disease (lupus erythematosis, Henoch–Schönlein purpura, cryoglobulinemia), or chronic liver disease, which may present IgA mesangial deposits as well.

Treatment

Attempts to intervene in the pathogenic sequences leading to IgAN would consider a reduction in antigen challenge and since tonsils are frequent source of infections, interest has been focused on tonsillectomy. Abandoned as a routine approach in Europe and North America, tonsillectomy is still favored in some regions of the world, notably in Japan. This procedure may be of some value in preventing episodic gross hematuria in the short term, but the long-term effects are uncertain. Tonsillectomy is supported by two large retrospective studies from Japan and China, which reported that the benefit on renal function decline is evident in a follow-up longer then 10 years. Tonsillectomy has a clear indication when tonsils are a true infectious focus, otherwise the benefit is unclear. Other attempts to reduce the antigen exposure include long term antibiotics and gluten-free diet, which resulted not effective on functional decline, even though the latter significantly reduces the IgA immunological abnormalities.

Current therapeutic strategies for IgAN have been directed toward modulating the glomerular response to immune deposits, in order to decrease the resultant tissue damage and progression toward sclerosis.

Patients at risk for progressive renal injury should be detected. Therapeutic intervention must be attempted in rapidly progressive IgAN (i.e., with florid crescent formation involving more than 50% of glomeruli, hypertension, and/or severe proteinuria). The protocols include a cycle of 10 plasmaphereses, cyclophosphamide 3 mg/kg/day, and prednisone 1 mg/kg/day for 8 weeks or a course of high dose methylprednisolone pulses alone or in association with 2 mg/kg/day cyclophosphamide for 8 weeks. In a cohort of children with severe IgAN and slowly progressive course, the treatment with prednisone and azathioprine for 1 year reported favorable outcome. A similar protocol in association with heparin-warfarin and

dipyridamole may be used for children with histologic signs of diffuse mesangial proliferation.

Children with IgAN and high levels of proteinuria are at risk for progressive disease. Patients with severe proteinuria >3 g/day/1.73 m^2 even if they still have normal renal function should be treated. Prednisone 1 mg/kg/day for 4 weeks, with a progressive reduction over the following 8 weeks, and then small doses for a total time period of 1–3 years has a good indication for patients with nephrotic-range proteinuria and eicosapentanoic acid (fish-oil) for 2 years in those with high or moderate proteinuria (>1<2 g/m^2 day) with initial contraction in glomerular filtration rate. In adults, three pulses of methylprednisolone at months 1,3,5, followed by low doses of prednisone, provided a significant protective effect on the functional decline. It is of interest that the benefit of this therapy last for several years after the pulses, protecting the treated patients from proteinuria and even more from loss of renal function. No controlled study is available in children. Results of a randomized, placebo-controlled, double-blind trial in North America using prednisone (60 mg/m^2 every other day for 3 months, followed by 40 mg/m^2 every other day for 9 months, and then 30 mg/m^2 every other day for 12 months) or fish oil (4 g/day for 2 years) found no benefit in treatments groups versus the placebo group.

ACE inhibitors (ACE-I) have a strong basis for use in the treatment of IgAN, not only because they improve two principal progression factors (hypertension and proteinuria) but because their use may inhibit the long series of potentially negative Angiotensin II effects.

In a European multicenter controlled trial including children and young subjects (3–35 years old) with a constant level of moderate proteinuria (>1<3.5 g/day/1.73m^2 over the 3 months before enrollment) and normal or moderately reduced renal function, patients were randomized to receive benazepril 0.2 mg/kg/day or placebo. The primary outcome of renal disease progression, defined as >30% decrease in baseline creatinine clearance and/or worsening of proteinuria to nephritic range, found significant differences between the two groups. A stable remission of proteinuria (<0.5g/day/1.73 m^2) was observed in 56% of ACE-I patients versus 8% of placebo patients. The multivariate Cox analysis showed that treatment with ACE-I was the independent predictor of prognosis, while no influence on the progression of renal damage was found for gender, age, baseline glomerular filtration rate, systolic or diastolic blood pressure, and proteinuria.

Vitamin E, used as anti-oxidant drug, showed significant reduction in proteinuria, with a statistically non-significant trend toward a better preservation of renal function in one trial. Cyclosporine A does not provide protective effects on the recurrence of IgAN in transplanted kidneys, indirectly indicating no benefit on the original disease. The effectiveness of mycophenolate mofetil is still debated.

Prognosis

The prognosis of IgAN was initially considered to be more benign in children than in adults, but long-term studies have failed to confirm this assessment. The natural history of IgAN in children represents, with few exceptions, the early phase of a chronic disease. Severe clinical signs usually develop after 5–15 years requiring the need for long follow-up including adult life in order to define the history and the progression of IgAN in an individual patient. In the first report by Levy et al., a follow-up of 13 years in 90 French children demonstrated that only 9% progressed to renal failure. However, persistent signs of active renal disease develop at long-term follow-up as reported in 47% of Swedish children after 10 years, including proteinuria in 35%, hypertension in 9%, and decreased glomerular filtration rate in 3%. In a report from Japan in 200 children who were followed for a mean period of 5 years, urinary abnormalities were detected in 38%, persistent heavy proteinuria in 10%, and progression to chronic renal failure in 5%. A Finnish study reported that subjects with IgAN originated in childhood after 2 decades may have no signs of urinary disease in one third of the cases, and minor urinary abnormalities in another third, but the last third had chronic kidney disease and 10% needed renal replacement treatment.

In short-term follow-up studies in both adults and children, a better prognosis is observed in children, while a 20 year survival analysis showed that IgAN in children was as progressive as in adults. In a cohort of 103 American children mostly of Caucasian or Afro-American race, a report in 1995 predicted a kidney survival rate from the time of biopsy of 85% at 10 years and 73% at 20 years. The Caucasian American cohort data have been recently updated and the survival at 10 years now results to be 91% and at 20 years 80%, similar to a Finnish report, predicting renal survival rates of 93% and 87% at 10 and 20 years respectively. An investigation from Japan that followed 181 IgAN patients for a mean of 7 years from onset, reported 50% in clinical remission and a predicted survival rate of 92% at 10 years and 89% at 20 years. A multicenter study in the USA reviewed clinical and pathological features in 80 children with primary IgAN,

who were followed for at least 4 years. Seven markers were found to be predictive of end-stage kidney disease in children: the presence of glomerular sclerotic changes, especially when these were associated with proliferation or when sclerosis affected 20% or more of the glomeruli; Afro-American race; hypertension at biopsy; proteinuria at biopsy; age at presentation; crescents; male gender.

Some children, usually those presenting with moderate microscopic hematuria without proteinuria and displaying the mildest lesions, do not progress to end-stage renal failure over decades of observation. In children with progressive IgAN, the clinical course is often slow and indolent. Proteinuria is a relevant risk factor for progression both in children and adults. As for adults, follow-up proteinuria (percent duration of massive proteinuria) or proteinuria at 1 year have the strongest predictive value for disease progression. The composition of proteinuria also has been correlated with clinical outcome. An elevated excretion of tubular proteinuria (low molecular weight proteins and particularly α1 microglobulin) has been found to be a negative prognostic index. Similarly, an increased excretion of cytokines and chemokines, such as IL-6 or chemokines (MCP-1), with reduced excretion of EGF were found to be significant risk factors. Gross hematuria does not carry an increased risk of progression.

In conclusion, IgAN in children should be considered to be potentially progressive over decades, and life-long follow-up is needed in order to detect progressive disease and determine the need for therapy.

Prevention

As the disease is thought to originate from an abnormal response of the immune system to common antigens, no prevention is presently envisaged.

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295 Alport Syndrome

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Definition

Alport syndrome (AS) is an inherited disorder of basement membranes that affects a type IV collagen network composed of α3, α4, and α5(IV) chains. Functional and structural abnormalities of basement membranes result in hematuria and progressive renal disease, sensorineural deafness, and ocular abnormalities. Risk of progression to end-stage renal disease is virtually 100% in affected males.

Etiology

The defects in type IV collagen characteristic of AS arise from mutations in the COL4A3, COL4A4, and COL4A5 genes, which encode the α3, α4, and α5 chains of type IV collagen, respectively.

Epidemiology

It has been estimated that 1 in 50,000 European infants have AS. The gene frequency in the United States is approximately 1 in 5,000 to 1 in 10,000. AS accounts for about 2% of children with chronic renal failure and about 2% of children who receive renal transplants, according to the 2008 report of the North American Pediatric Renal Trials and Collaborative Studies.

Pathogenesis

There are three genetic forms of AS. X-linked AS (XLAS) is caused by mutations in the COL4A5 gene and is the predominant form of the disease, accounting for approximately 80% of patients. Affected males are hemizygotes carrying a single mutant COL4A5 allele. Affected females carry a normal COL4A5 allele as well as a mutant allele and are therefore heterozygotes. About 15% of patients with AS have the recessive form of the disease (ARAS) due to mutations in both alleles of the COL4A3 or COL4A4 gene, located on chromosome 2. These patients are either homozygotes who have the identical mutation in both alleles of the affected gene (and who may have consanguineous parents) or compound heterozygotes who have inherited different mutations in the affected gene. About 5% of patients have autosomal dominant AS (ADAS) caused by heterozygous mutations in COL4A3 or COL4A4. Most individuals with heterozygous COL4A3 or COL4A4 mutations are asymptomatic or exhibit isolated, nonprogressive microscopic hematuria associated with thin glomerular basement membranes (thin basement membrane nephropathy or TBMN). Why some people with heterozygous mutations in COL4A3 or COL4A4 have a progressive course leading to chronic renal failure or end-stage renal disease is uncertain.

Several hundred different mutations in the COL4A5 gene have been identified in patients and families with XLAS. Reported mutations include large rearrangements (∼20%), small deletions and insertions (∼20%), missense mutations that alter a glycine residue in the collagenous domain of the α5(IV) chains (∼30%), other missense mutations (∼8%), nonsense mutations (∼5%), and splice-site mutations (∼15%).

The α3, α4, and α5 chains of type IV collagen form a distinct network in several basement membranes of the kidney, cochlea, and eye. Mutations causing AS prevent deposition of normal α3α4α5(IV) networks in basement membranes, triggering incompletely understood pathologic processes that result in the clinical manifestations of AS.

Pathology

Renal. Light microscopic changes are unusual before 5 years of age. Mesangial hypercellularity and matrix expansion, and eventually focal segmental glomerulosclerosis, are common in older children and adolescents, especially boys. Increasing tubular atrophy and interstitial fibrosis develop after age 10.

Electron microscopy may reveal pathognomonic changes depending on the patient's age and gender. The earliest abnormality is diffuse attenuation of the glomerular basement membrane (GBM). During childhood and

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adolescence, the great majority of boys with XLAS and both boys and girls with ARAS develop the classic Alport GBM lesion, consisting of diffuse thickening accompanied by "basket-weave" transformation of the lamina densa, intramembranous vesicles and densities, scalloping of the epithelial surface of the GBM and foot process effacement. The percentage of GBM displaying this lesion increases progressively with age in boys with XLAS. Females with XLAS display a range of GBM alteration, from focal GBM attenuation to diffuse thickening and basket weaving, with no consistent correlation of GBM findings and age.

Routine immunofluorescence is normal or shows nonspecific immunoprotein deposition. Because disease-causing mutations result in abnormal expression of type IV collagen in basement membranes of most AS patients, specific immunostaining for type IV collagen α chains is useful for both diagnosis and differentiation of XLAS and ARAS. Expression of α3(IV), α4(IV), and α5(IV) chains is completely absent in approximately 80% of XLAS males, and 60–70% of XLAS females exhibit mosaic expression of these chains. In most ARAS patients, GBM is nonreactive with antibodies to α3(IV), α4(IV), and α5(IV) chains, and Bowman's capsules and tubular basement membranes are also negative for the α3(IV) and α4(IV) chains. However, immunostaining for α5(IV) chains in Bowman's capsules and tubular basement membranes is positive. It is important to note that the altered immunostaining for the α3(IV)–α6(IV) chains in patients with XLAS and ARAS is not age dependent. Therefore, this method can provide diagnostic information even in patients who are too young to display characteristic abnormalities in GBM ultrastructure.

Normal epidermal basement membranes (EBM) express α5(IV) chains. EBM staining for α5(IV) chains is negative in about 80% of XLAS males, and mosaic expression of α5(IV) is observed in 60–70% of XLAS females, allowing diagnosis of XLAS by skin biopsy. Skin biopsy is not useful for the diagnosis of ARAS, since expression of α5(IV) in EBM is normal.

Cochlear. The hearing loss of AS arises from cochlear dysfunction. Normal cochleae express type IV collagen α3α4α5 networks in the spiral limbus, spiral ligament, and in the basement membrane interposed between the organ of Corti and the basilar membrane. However, expression of these networks is absent in AS cochleae. Careful examination of well-preserved cochleae from men with XLAS and deafness revealed a zone of separation between the organ of Corti and the underlying basilar membrane, and cellular infiltration of the tunnel of Corti and the spaces of Nuel. These changes are not observed in similarly well-preserved cochleae obtained from normal individuals or patients with other causes of deafness. The structural changes observed in AS cochleae may be associated with defective attuning of basilar membrane motion and hair cell stimulation, resulting in reduced acuity of hearing.

Ocular. Type IV collagen α3α4α5 networks are normal components of several basement membranes in the eye, including corneal basement membrane, Descemet's membrane, lens capsule, internal limiting membrane of the retina, and retinal pigment epithelium basement membrane. The ocular manifestations of AS likely arise from the absence or the abnormality of α3α4α5(IV) networks in eye basement membranes. Lens capsules of AS patients with anterior lenticonus exhibit marked attenuation and focal areas of dehiscence, suggesting that the lens capsule lacks the mechanical strength to maintain the normal lens shape.

Clinical Manifestations

Renal. Persistent microscopic hematuria starting in early childhood is the cardinal clinical feature of AS, occurring in all XLAS males, 95% of XLAS females, and in all ARAS patients. Episodic gross hematuria is not unusual, especially during childhood. Some children with AS have virtually constant gross hematuria.

Overt proteinuria typically appears during later childhood or adolescence in XLAS males and in ARAS patients and increases progressively, often into the nephrotic range. About 75% of XLAS females ultimately develop proteinuria of some degree. Most children with AS have normal blood pressures, but hypertension is common in adolescent males with XLAS and teenaged ARAS patients.

Glomerular filtration rate is typically well preserved during childhood and begins to decline during adolescence. The impacts of gender and genotype on the rate of loss of renal function are discussed below under Prognosis.

Cochlear. Hearing is normal at birth and during early childhood. Symmetrical deficits in sensitivity for high frequency sounds often become detectable by audiometry in late childhood. In XLAS males, the probability of hearing loss is 50% by age 15, 75% by age 25, and 90% by age 40. In XLAS females, the probability of hearing loss is 10% by age 40 and 20% by age 60. Most ARAS patients develop deafness, although precise data on timing is not available.

Over time, the hearing deficit progresses into the frequency range of conversational speech. Because the deficit typically does not exceed 60–70 dB and speech discrimination is preserved, hearing aids are effective in most affected individuals.

Ocular. Anomalies of the lens, retina, and cornea are common in AS, especially among XLAS males and ARAS

patients, often becoming apparent during adolescence and young adulthood. About 15% of XLAS males exhibit anterior lenticonus, in which the central portion of the lens protrudes into the anterior chamber. While this lesion may be asymptomatic, it may be associated with reduced visual acuity and cataracts, and even rupture of the lens may occur. Abnormal retinal pigmentation, consisting of whitish-yellow perimacular flecks, occurs in about 15% of XLAS males, often in association with lenticonus. Corneal abnormalities include recurrent corneal erosions and posterior polymorphous dystrophy.

Other. The association of XLAS with smooth muscle tumors (leiomyomas) of the esophagus, tracheobronchial tree, and in women, with the external genitalia, has been described in several dozen families. Symptoms such as dysphagia, postprandial vomiting, epigastric or retrosternal pain, recurrent bronchitis, dyspnea, cough, and stridor often appear in late childhood. The Alport syndrome-diffuse leiomyomatosis complex arises from X-chromosomal deletions involving COL4A5 and the proximal portion of the adjacent COL4A6 gene.

Mental retardation, midface hypoplasia, and elliptocytosis have been described in a small number of XLAS males who carry deletions that extend downstream of the 3' end of the COL4A5 gene.

Diagnosis

Diagnosis of AS depends on the presence of hematuria associated with one of the following:

1. Mutation(s) in COL4A3, COL4A4, or COL4A5
2. Diagnostic abnormalities of immunostaining for type IV collagen in skin or kidney biopsy
3. Confirmed AS in a first-degree relative
4. Anterior lenticonus or perimacular flecks

AS should be strongly suspected when hematuria is associated with bilateral high frequency sensorineural deafness and/or pathognomonic ultrastructural changes in GBM, and the diagnosis should be confirmed by genetic testing or type IV collagen immunostaining.

Differential Diagnosis

Differentiation of AS from other causes of familial and sporadic glomerular hematuria is based upon careful clinical evaluation, reliable pedigree data, and thoughtful consideration of the relative merits of skin biopsy, kidney biopsy, and molecular analysis. In a child with isolated hematuria, a positive family history of hematuria in the absence of a history of ESRD suggests a diagnosis of thin basement membrane nephropathy (TBMN). Two rare causes of familial hematuria associated with macrothrombocytopenia, Epstein and Fechtner syndromes, can be excluded if the platelet count is normal. Familial IgA nephropathy and membranoproliferative glomerulonephritis are uncommon causes of familial hematuria.

In the absence of a family history of hematuria, the differential diagnosis of glomerular hematuria includes AS, TBMN, IgA nephropathy, membranoproliferative glomerulonephritis, membranous nephropathy, lupus nephritis, postinfectious glomerulonephritis, and Henoch–Schonlein nephritis. Associated clinical findings (e.g., rash, arthritis) or laboratory findings (e.g., hypocomplementemia) will suggest diagnoses other than AS in many patients.

While the results of hearing evaluation are likely to be normal in young children with AS, audiometry may be very useful in children over 6–8 years of age. Ophthalmologic assessment may also provide valuable information, although ocular lesions are more prevalent in those with advanced disease and less common in young patients in whom differentiation of AS from TBMN is more difficult.

Tissue studies can complement clinical and pedigree information. Skin biopsy with immunostaining for the α5(IV) chain may be diagnostic, especially when clinical and pedigree data strongly suggest XLAS. Normal expression of the α5(IV) chain in EBM may indicate that (1) the patient has XLAS, but his or her COL4A5 mutation does not change the α5(IV) expression; (2) the patient has ARAS or ADAS, in which expression of α5(IV) in EBM is not affected; or (3) the patient does not have AS. Whereas skin biopsy is useful only if it provides definitive confirmation of a diagnosis of XLAS, renal biopsy carries the advantage of enabling the diagnosis of XLAS, ARAS, and non-Alport kidney disease.

Mutation detection rates of 80–90% are attainable in XLAS males by COL4A5 sequencing. Comparable data for detection of COL4A3 and COL4A4 mutations in patients with ARAS are lacking. Information about laboratories providing type IV collagen gene sequencing can be found on the web sites of GeneReviews (www.genereviews.org) and the Alport Syndrome Foundation (www.alportsyndrome.org).

Treatment

As there have been no controlled therapeutic trials in human AS, treatment recommendations must be derived

from animal studies and anecdotal reports. In murine ARAS, several interventions have improved renal outcomes, including angiotensin antagonism, TGFβ-1 inhibition, chemokine receptor 1 suppression, administration of bone morphogenic protein-7, blockade of matrix metalloproteinases, bone marrow transplantation, and irradiation. Inhibition of angiotensin converting enzyme (ACE) resulted in an improved survival in dogs with XLAS. In uncontrolled studies of human AS, ACE inhibition reduced proteinuria, at least transiently. Cyclosporine treatment also resulted in prolongation of survival in male XLAS dogs. Cyclosporine treatment diminished proteinuria and appeared to stabilize renal function in a small, uncontrolled study of AS males. However, apparent acceleration of renal fibrosis was suggested by the results of another study of cyclosporine treatment in AS patients.

At present, angiotensin antagonism aimed at suppression of proteinuria appears to be the least risky of available treatment options. With advancing disease, management of hypertension, nephrotic syndrome, and chronic renal failure is required.

AS patients typically have excellent renal transplant outcomes. Two issues require special attention: First, evaluation of potential related donors must identify affected individuals. Second, monitoring after transplant must allow early diagnosis of post-transplant anti-glomerular basement membrane antibody-mediated glomerulonephritis (anti-GBM nephritis), a complication of transplantation that is unique to AS.

Familiarity with the genetics and clinical features of AS is required for informed donor evaluation. Since 100% of males with XLAS have hematuria, absence of hematuria excludes AS in male relatives of XLAS patients. About 95% of females with XLAS have hematuria, so there is only a 5% chance that a female without hematuria is affected. Given that by age 60 there is an estimated risk of ESRD of 30% in women with XLAS, female members of XLAS families who have hematuria should generally be discouraged from kidney donation.

Anti-GBM nephritis occurs in approximately 3% of transplanted AS males, typically occurs during the first year after transplantation, and usually results in irreversible graft failure. There is a high rate of recurrence in subsequent allografts. In XLAS males, the primary target of anti-GBM antibodies is the α5(IV) chain. Females with XLAS who require transplantation are at little or no risk of developing anti-GBM nephritis. However, both males and females with ARAS can develop anti-GBM nephritis after transplantation. The α3(IV) chain is the primary target of anti-GBM antibodies in ARAS patients.

Prognosis

Gender and genotype are the main determinants of prognosis in AS. Although virtually 100% of males with Alport syndrome will ultimately develop ESRD, the pace of progression is heavily influenced by genetic factors. Men with ADAS exhibit relatively slow loss of renal function, with a half-life of renal survival that is about twice that of men with XLAS.

In XLAS males, the probability of ESRD is 50% by age 25, 80% by age 40, and 100% by age 60. Those with major rearrangements or premature stop codons in COL4A5 progress about twice as rapidly to ESRD as those with missense mutations. Large deletions, nonsense mutations, and small mutations that alter the translational reading frame are associated with a 90% probability of progression to ESRD by age 30. The risk of ESRD by age 30 is 70% in patients with a splice-site mutation and 50% in those with a missense mutation.

The timing of deafness and the occurrence of ocular lesions are also influenced by COL4A5 genotype. The risk of developing deafness before age 30 is 90% in those with deletions, nonsense mutations, or splice-site mutations, compared to 60% in those with missense mutations.

These genotype–phenotype correlations are not apparent in XLAS females perhaps because of the overwhelming influence of random X-chromosome inactivation on disease course in XLAS females. The risk of ESRD in women with XLAS is 12% by age 45, 30% by age 60, and 40% by age 80, and is substantially higher in XLAS females who have proteinuria.

Prevention

Prevention of AS depends on the reproductive decisions of affected individuals. Information regarding prenatal diagnosis is available at genereviews.org.

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296 Henoch Schönlein Purpura Nephritis

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Definition

Henoch Schönlein Purpura (HSP) is primarily a disease of childhood and is one of the most common forms of systemic vasculitis diagnosed in children. The clinical manifestations are legion, but most characteristic is the triad of a purpuric rash affecting the lower extremities, gastrointestinal symptoms principally abdominal pain, and arthritis. The majority of patients recover completely within a month of the onset of the initial symptoms.

Historical Note

Schönlein is usually credited with the original description of a characteristic rash and arthralgia, and Henoch with the association of a similar rash with abdominal symptoms and subsequently with renal disease. However, as early as 1801, Heberden had described repeated attacks of purpuric rashes with painful swelling, abdominal discomfort, and hematuria.

> ▶ Another boy, five years old, was seized with pains and swellings in various parts and the penis in particular was so distended, though not discoloured, that he could hardly make water. He had sometimes pains in his belly, with vomiting, and at the time some streaks of blood were perceived in his stools, and the urine was tinged with blood. When the pain attacked his leg, he was unable to walk; and presently the skin of his leg was all over full of bloody points. After a truce of three to four days the swelling returned, and the bloody dots, as before.

Epidemiology

The majority of patients are Caucasian or oriental, and contributions to the literature over the past decades give the impression that the condition is more common in Europe and Japan than in North America. The estimated annual incidence of Henoch Schönlein Purpura Nephritis (HSPN) is 20 per 100,000 children. Ethnicity may be an important etiopathological factor with a preponderance of Caucasian children affected, 17 per 100,000, compared to African American 6 per 100,000, or Asian children 5 per 100,000.

HSP mainly affects children between the ages of 3 and 10 years and boys are affected more often than girls (1.5:1). In about two thirds of children, an upper respiratory tract infection precedes the onset of HSP by 1–3 weeks. The incidence shows a seasonal variation with a peak around November to January in the Northern Hemisphere. In general, children are ill and pyrexial with a temperature usually not higher than 38°C.

Pathogenesis

The etiology remains unknown. At the beginning of the last century, Osler likened the condition to serum sickness and other anaphylactoid reactions. The term "anaphylactoid purpura" was introduced by Frank. Since then the idea that HSP is caused by hypersensitivity reaction has developed into the concept that HSP is due to an allergy to antigens derived from microorganisms, food, or drugs.

HSP is now generally considered to be an immune complex-mediated disease characterized by the presence of polymeric IgA contained in dermal, gastrointestinal, and glomerular capillaries. Capillary IgA immune complexes are probably the result of either circulating immune complex deposition or in situ formation. It is known that patients with HSP and IgA nephropathy demonstrate abnormalities of IgA glycosylation leading to mesangial cell deposition and injury.

The pathognomonic IgA and C3 deposits in the mesangial cells of the kidney are indistinguishable from those seen in IgA nephropathy. Although there is evidence that the glomerular injury may be attributable to the deposition of C3 complement and activation of the alternate pathway of complement the role of a biological mediator for inflammation has as yet not been identified.

In healthy subjects, IgA is found abundantly in mucosal fluids but the serum concentration is low. Both increased IgA synthesis and reduced clearance have been implicated in the pathogenesis of IgA immune complex deposition. Antigens presenting to the mucosa may be the

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stimulus to the increased production of IgA and thus be the trigger for the development of HSP. Many viruses, bacteria, medications, and food hypersensitivity have been implicated in precipitating HSP but no exogenous antigen has been consistently identified in either the circulating immune complexes or in mesangial deposits in the kidney.

Clinical Manifestations

Skin

The characteristic skin rash is purpuric and is symmetrically distributed over the extensor surfaces of the lower legs and arms and over the side of the buttocks. It is invariably present in the area of the lateral malleolus and sometimes is present only at that site. Pressure areas, e.g., beneath the waistband are commonly affected and spots may appear on the penis. The onset is usually as a red maculopapular rash that becomes purpuric and eventually takes on a fawn color as it fades. The rash is not itchy and may not always have a purpuric stage. Patches of purpura may vary in size. In young children under 5 years of age, the illness may start with a generalized urticarial rash that becomes purpuric. Edema of the dorsa of the hands and feet, scalp, and face are not uncommon and correlate with the vasculitic activity and not with any degree of proteinuria. Subcutaneous bleeding can occur at any site and is frequently seen in the eyelids and conjunctiva and in the scrotum mimicking torsion of the testis.

Joints

The joints are affected in up to 75% of cases. The arthralgia most commonly affects the knees and ankles and less frequently the wrists and hands. The joints may become painful and swollen because of periarticular edema. Joint effusions are rare and the arthralgia recovers without residual damage.

Gastrointestinal Tract

Abdominal pain is common affecting at least two thirds of patients with HSP. The pain may be sufficiently severe to mimic an acute abdominal emergency. Abdominal symptoms may precede the rash and joint manifestations in up to 30% of cases. Vomiting, diarrhea, periumblical pain mimicking acute appendicitis, hematemesis, and malena are the main symptoms. Major gastrointestinal disease occurs in approximately 5% of patients, intussusception being the most common. Petechiae and ecchymoses have been observed endoscopically in the stomach, duodenum, sigmoid colon, and rectum. In recent years, ultrasonography has been extremely valuable for diagnosing intra-abdominal pathology particularly intussusception, bowel wall edema and dilatation, and ileus.

Kidney

Renal manifestations are found in 20–100% of patients with HSP and tend to be more common and severe in older children. The reported variable incidence of renal involvement can be accounted for by the differing criteria used to define renal involvement as well as by different methods used to detect microscopic hematuria. In the majority of patients with a nephropathy, urinary abnormalities follow the onset of the typical rash within 4 weeks. However, urinary abnormalities may also precede the onset of the rash or follow it by many months. In older patients severe gastrointestinal system involvement, frequent relapses of and late skin lesions beyond 3 months have been associated with an increased risk of renal involvement.

At presentation, microscopic hematuria with or without proteinuria, occurs in 70–80% of cases of HSP nephropathy, only 20% will have macroscopic hematuria. Variable proteinuria may be present even in urine that does not contain blood, and the patient may develop nephrotic syndrome. The child who presents with a severe acute nephritic syndrome is more likely to develop nephrotic syndrome and or renal insufficiency. Varying degrees of renal failure, often transient is found in approximately 20% of cases. Long-term renal morbidity, i.e., progression to end-stage disease is rare and observed in 2–5% of patients with HSPN.

Laboratory Investigations

Blood

No laboratory test has been found to be diagnostic for HSP. The peripheral blood may show a neutrophil leukocytosis. The erythrocyte sedimentation rate can be elevated. Platelet count and clotting times are normal. Positive throat cultures, elevated ASO, anti-DNase B and anti-NADase titers are of no diagnostic significance. Tests for antinuclear antibodies and rheumatoid factor are negative.

Serum IgA levels may be elevated in approximately 50% of children with HSP. About half of the children with HSP have cryoglobulins in their sera. Analysis of the cryoglobulins reveals IgA and properidin suggesting activation of complement via the alternative pathway. IgA containing immune complexes have been detected in patients with HSP whether or not they developed acute nephritis.

Although recently identified genetic polymorphisms may not contribute to the susceptibility to HSP, there is the potential that their presence could be a risk factor for the development of nephrotic syndrome.

Histopathology

Light Microscopy

The lesion most typical of HSPN consists of a leucoblastic vasculitis characterized by a transmural and perivascular infiltration with polymorphonuclear leucocytes, histiocytes, and sometimes eosinophils in association with fibrinoid necrosis, nuclear debris, and extravasation of erythrocytes. This lesion is frequently found in the superficial postcapillary venules in the skin.

The predominant renal lesion is found in the glomerulus and is characterized by focal and or segmental mesangial injury or a mesangial proliferative glomerulonephritis with varying degrees of hypercellularity. The lesions are similar to those found in IgA nephropathy. The development of epithelial cell crescents represents an extension of the severity of the disease and may result in glomerular tuft necrosis and segmental capillary thrombosis. The International Study of Kidney Disease in Children classification of HSPN describes a broad correlation between the clinical presentation and the renal histopathology (*Table 296.1*). Those with hematuria and insignificant proteinuria generally have less severe histological changes that are likely to resolve spontaneously whereas those with heavy proteinuria and a refractory nephritic or nephrotic syndrome will have more severe changes unlikely to resolve.

Immunofluorescence

In contrast to the more focal and segmental changes observed on light microscopy, the striking feature on immunofluorescent staining of the renal biopsy is the global glomerular involvement with mesangial deposition of IgA.

Table 296.1
Histological classification of Henoch Schönlein Purpura Nephritis (HSPN)

1. Minimal change
2. Mesangial cell proliferation
3. Focal/diffuse proliferation or sclerosis with >50% crescents
4. Focal/diffuse mesangial proliferation or sclerosis with 50–75% crescents
5. Focal/diffuse mesangial proliferation or sclerosis with >75% crescents
6. Membranoproliferative type lesion

Electron Microscopy

Electron-dense IgA containing deposits are predominantly mesangial but are also seen in subendothelial areas. The latter are frequently associated with glomerular basement membrane disruption and these changes correlate well with the severe glomerular injury seen on light microscopy and associated with heavy proteinuria.

Treatment

For decades, prediction of outcome of HSPN has been the focus of attention and the challenge has been to find good prognostic criteria in order to make educated decisions concerning treatment. Can HSPN in patients with HSP be prevented is a tantalizing question and has been the subject of much study. Similarly in patients with HSPN, prevention of progression to end-stage renal disease remains the principal objective when considering a therapeutic intervention.

Prevention of HSPN

Retrospective and prospective reviews of patients with HSP with no signs of nephropathy at the time of presentation and treated with corticosteroid therapy, usually oral prednisone or intravenous methylprednisolone have been reviewed. Although some patients with unpleasant symptoms may have benefited from early treatment, there is little evidence to support the hypothesis that prophylaxis with prednisone treatment for 2–4 weeks can prevent renal involvement.

Immunosuppression

The large majority of children with HSP are mild and are associated with a good prognosis. Immunosuppressive therapy is therefore not indicated and patients should be managed symptomatically. There are few prospective data describing the treatment of renal disease associated with HSP. Dudley et al. reported data from a prospective double-blind placebo-controlled trial of 353 children who presented with HSP and were randomized to treatment with prednisolone (2 mg/kg for 7 days followed by 1 mg/kg for 7 days) compared to placebo. At 1 year of follow-up, there was no difference in the incidence of proteinuria between the two groups. This study provides compelling evidence of absence of a beneficial effect of early treatment with prednisolone in the development of HSPN.

It is very difficult to assess any beneficial effect of multiple drug therapy prescribed to treat severe HSPN usually associated with a rapidly progressive glomerulonephritis. Most studies describing the combination of corticosteroids plus cyclophosphamide or cyclosporine A or azathioprine or mycophenolate mofetil are all hampered by limitations. The majority of studies contain very small numbers of patients and contain patients with varying severity of disease. Similarly, there are insufficient data to support treatment with intravenous immunoglobulin, angiotensin-converting enzyme inhibitors, and tonsillectomy.

Plasma Exchange

The use of early plasma exchange either alone or in combination with immunosuppressive therapy cannot be recommended in view of the paucity of available data.

General Management

As in the treatment of any patient with an acute nephritic syndrome, careful attention must be paid to the treatment of hypertension with salt and water restriction in combination with a loop diuretic and if the blood pressure does not reduce specific antihypertensive therapy may be required. A nephrotic syndrome may require similar fluid restriction and diuretic therapy with careful attention to avoid hypovolemia.

Long-Term Outcome

The overwhelming majority of the long-term morbidity in HSP is associated with a nephropathy. The risk of developing acute or chronic renal impairment is greatest in those children who have a nephritic/nephrotic clinical presentation and in those who have evidence of a crescentic glomerulonephritis on renal biopsy. The incidence of long-term chronic renal disease is subject to center bias in that tertiary renal centers report up to 20% versus 2–5% from unselected general pediatric centers.

All patients with significant renal impairment at presentation require follow-up for life. It is recognized that in women who as children had HSPN there is a risk of developing hypertension in pregnancy. Children with no evidence of a nephropathy at presentation should be reviewed for at least 6 months following resolution of the rash in order to ensure no late presentation of a nephropathy, i.e., proteinuria or hypertension. Those children who remain with persistent microscopic hematuria or nonnephrotic range proteinuria must be followed up until the urinalysis becomes clear.

Transplantation

In the very small number of children who progress to end-stage renal disease, renal transplantation may become necessary. There is no contraindication to either deceased donor or living related transplantation. There is a risk of recurrence of HSPN in the engrafted kidney. However, the observed mesangial cell IgA deposits can occur in the transplanted kidney where the original cause of renal failure was neither HSPN nor IgA nephropathy.

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297 Hemolytic Uremic Syndrome

Sandra L. Watkins

Definition

Hemolytic uremic syndrome (HUS) was first described by Conrad von Gasser in 1955. Today HUS is a frequent cause of acute renal failure in children, most commonly preceded by a diarrheal illness, and termed Typical or D+ HUS. The classic triad is thrombocytopenia, nonimmune hemolytic anemia, and renal failure. Although other organs such as the brain, heart, gut, and pancreas can be involved, the kidney is the principal site of major damage. D+ HUS is the most common form of HUS, while atypical HUS (D-HUS) is much rarer and is beyond the scope of this review.

Etiology

D+ HUS generally occurs following gastrointestinal infection with Shiga toxin (Stx)-producing *Escherichia coli* (STEC), organisms first incriminated by Karmali et al. as an etiological factor in the development of HUS. The diarrheal prodrome is caused by ingestion of foods contaminated with an STEC, most commonly *E. coli* 0157:H7. Other less common serotypes have also been described. Undercooked ground beef is often the contaminated food, although other sources, such as unpasteurized apple cider or milk, salad greens, and water, have also been identified as the source of infection.

Epidemiology

The incidence of D+ HUS in North America is one to three new cases per 100,000 population per year. However, the incidence appears to be greater in northern climes and in rural areas. In 1992, a massive outbreak of *E. coli* O157:H7 infections caused by consuming poorly cooked ground beef at a fast-food restaurant chain in the western United States brought public awareness to this entity. However most cases are endemic, sporadic infections. Most D+ HUS occur in the summer and fall, with rural populations more often involved than urban.

Pathogenesis

The gastroenteric infections preceding D+ HUS are almost never bacteremic but systemic complications arise from circulating Stx, with bloody diarrhea caused by mesenteric vascular ischemia initiated by circulating Stx. Interactions between Stx and circulating leukocytes and platelets may also play a role in pathogenesis. Stxs bind to the glycosphingolipid globotriaosylceramide (GB_3), which can be demonstrated on renal glomerular endothelial, mesangial, and tubular epithelial cells. Profound hematological abnormalities during HUS and histopathologic analyses demonstrate the thrombotic basis of HUS. The plasma of patients with HUS demonstrates elevated levels of plasminogen activator inhibitor (PAI)-1 activity, elevated levels of circulating D-dimers, and generation of thrombin.

Pathology

The classic renal lesion of D+ HUS is a glomerular thrombotic microangiopathy with capillary and arteriolar wall thickening.

Clinical Manifestations

The interval between ingesting contaminated food and the first day of diarrhea ranges between 2 and 12 days. Typically, *E. coli* O157:H7 infections cause 1–3 days of nonbloody diarrhea after which the diarrhea becomes bloody. It is the bloody diarrhea, which occurs in about 90% of cases, that usually prompts patients or their families to seek medical advice. Fever is usually absent and fecal leukocytes are rarely detected. The colon can be quite severely affected with edema and thickening causing severe cramping, abdominal pain, and rectal prolapse. Diarrhea resolves with no sequelae in 85% of infected patients, but in 15%, as the diarrhea resolves the hematologic abnormalities, heralded by thrombocytopenia, becomes manifest closely followed by renal involvement. HUS findings occur between days 5 and 13 of illness with

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the median time of onset approximately 1 week after the onset of diarrhea.

Some infected children develop "partial" or "incomplete" HUS with thrombocytopenia, with or without anemia, while maintaining a normal serum creatinine, leading to complete resolution in a few days. However, once renal failure has developed resolution can be delayed by several days to months.

Diagnosis

The diagnosis of D+ HUS is made by demonstrating hemolytic anemia with hematocrit less than 30% and evidence of erythrocyte destruction on peripheral blood smear; platelet count less than 150,000 platelets per mm^3; and serum creatinine greater than the upper limit for age. Fibrinogen is normal or elevated, and the prothrombin time is only modestly prolonged, unlike classic disseminated intravascular coagulation. Hematuria or proteinuria may also be present.

Differential Diagnosis

A clinical microangiopathic picture similar to D+ HUS without the preceding diarrhea can be seen in systemic vasculitis, malignant hypertension, pregnancy, idiopathic thrombotic thrombocytopenia, various forms of D-HUS, including pneumococcal pneumonia and familial HUS, and drug-induced HUS associated with cyclosporine A, mitomycin-C, and oral contraceptives.

Management of D+ HUS

Fluid management is often difficult in early HUS. In the face of prolific diarrhea, vomiting, and poor intake, it is important to maintain intravascular volume to support renal perfusion. However, as azotemia develops one must avoid fluid overload. Accurate assessment of intravascular volume is difficult as patients are often hypoalbuminemic due to the diarrhea and develop vascular leakage due to endothelial damage, leading to edema despite being intravascularly depleted. Thus one must carefully determine daily weights and fluid balance. As oligoanuria develops fluids must be restricted at the first indication of cardiopulmonary overload. Diuretics should be avoided. Their use should be restricted to severe central volume overload in a non-oliguric patient, but dialysis is likely to be more effective. Vasodilators are useful for the treatment of hypertension. Angiotensin-converting enzyme inhibitors should be avoided because of concern that they might exacerbate kidney injury by diminishing renal perfusion.

Nephrotoxic medications should be avoided and the dosages of all medications that are renally excreted should be adjusted accordingly. Antibiotics should not be given to patients with STEC infections as antibiotic use has been associated with an increased risk of developing HUS. Similarly, antimotility agents should be avoided and narcotics should be used with caution, because there may be an increased risk of HUS or neurological complications. Nonrenal complications of HUS should be anticipated and treated appropriately. Neurological complications are the most worrisome and can include irritability, lethargy, confusion, stroke (thrombotic or hemorrhagic), seizures, and coma, with severe complications occurring in about 10% of patients. Cardiac dysfunction and congestive heart failure can develop. The most common pulmonary consequence is fluid overload and pleural effusions, but adult respiratory distress syndrome can also occur. Intestinal complications during acute HUS include rectal prolapse, colon perforation, and necrosis. Acidosis that does not correct easily with dialysis suggests ischemic or necrotic bowel. Clinically significant pancreatitis and glucose intolerance can occur during HUS, but mildly elevated amylase and lipase are generally asymptomatic. Oligoanuric patients should have potassium and phosphate restriction. Sodium restriction may be necessary to reduce edema and hypertension. With initiation of dialysis diets can be liberalized.

Eighty percent of HUS patients develop severe anemia, some without renal failure. The usual indications for erythrocyte transfusion should be followed with vigilance for rapid volume expansion causing hypertension or volume overload. Blood products should be volume- and leuko-reduced and administered on dialysis in the oliguric patient. Platelet transfusions should be avoided unless there is clinically significant hemorrhage or invasive procedures are planned because platelets could conceivably exacerbate thrombosis. Hemolysis and anemia can be the last abnormality to correct as HUS resolves, often requiring late transfusions. Iron is generally not needed as iron from hemolyzed cells is available for erythropoiesis. Erythropoietin may be useful in some cases.

Indications for dialysis in HUS are similar to those in other forms of acute renal failure and include hyperkalemia, uremia, persistent acidosis, hypertension, volume overload leading to respiratory compromise, and oligoanuria when limiting nutritional support and blood product administration. While hemodialysis (HD), peritoneal dialysis (PD), and continuous venovenous

hemodialfiltration (CVVHD) are all effective, cardiac instability may preclude HD and severe intestinal involvement may restrict the use of PD. CVVHD generally offers the most effective clearances and volume control while allowing parenteral nutrition and transfusions.

Multiple therapies, including corticosteroids, heparin, aspirin, dypyridamole, streptokinase, Synsorb Pk, plasmapheresis, and plasma infusions, have been unsuccessful in HUS and are not generally recommended, although anecdotal evidence supports the use of plasma infusions and/or pheresis in severe neurological complications.

Prognosis

Oligoanuria, volume depletion, severe leukocytosis, and Hct <23% at presentation predict morbidity and mortality in the acute phase. Five to ten percent of patients with HUS die in the acute phase, but most survivors appear to demonstrate full recovery from the acute episode. However, recent long-term follow-up studies suggest a high incidence of sequelae, perhaps up to 50%. The most concerning sequelae are related to renal dysfunction and include hematuria, proteinuria, chronic renal failure, including ESRD, and hypertension. Rarely, insulin-dependent diabetes mellitus can persist or develop as a late sequela. In cases with severe neurologic complications, permanent deficits can occur. Clinicians should be alert for late gastrointestinal complications including stricture and cholelithiasis. The severity of the initial illness and the need for and length of dialysis are risk factors for long-term renal sequelae.

Prevention

D+ HUS can largely be prevented by preventing infection with STEC bacteria, through thorough cooking of ground beef, washing fruits and vegetables, and avoiding unpasteurized liquids. Upon occurrence of STEC colitis, avoidance of antimotility agents and antibiotics, and early intravascular volume support may prevent or reduce the severity of HUS.

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298 Lupus Nephritis

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Definition/Classification

Systemic lupus erythematosus (SLE) is a chronic life-threatening disease with autoantibody-induced organ damage. The long-term prognosis depends mainly upon kidney involvement, which is observed in 50–90% of children. The gravity of lupus nephritis (LN) depends as much on the clinical progress (i.e., bad prognosis in acute kidney failure with rapidly escalating loss of function) as on the histological changes (i.e., poor prognosis in class IV LN). In the long term, the avoidance of renal replacement therapy is paramount in cases with the development of chronic kidney insufficiency. LN is the heterogeneous renal manifestation of SLE and is characterized by a high variability of clinical and histological presentations with an unpredictable course of renal disorders and extrarenal comorbidity.

Etiology

The etiology of SLE is unclear. UV light, viral infections, and drugs may trigger the initial attack and relapses of SLE. The causes for different organ manifestations of SLE are unclear. Almost 90% of all pediatric patients with SLE develop renal involvement.

Epidemiology

There are considerable regional differences in the epidemiology of SLE, with the lowest incidence rates observed in Caucasian populations. More severe courses of SLE and LN were reported in the African and Afro-American population. One third of patients with SLE develop the first symptoms during childhood. The incidence of SLE in children under 19 years of age was in the range of 0.6/100,000 children and year. There has been a trend toward an increased incidence and prevalence of SLE for Caucasians in the USA, while the incidence has been stable in Sweden. The female to male ratio was 4.5:1.

Pathogenesis

Many pathogenetic pathways have been implicated in SLE. The racial and a familial component to SLE susceptibility were suggested by data demonstrating familial clusters of SLE, concordance among twins, and a fourfold increased risk for SLE in first-degree relatives of women with SLE. More than 25 genes are now known to contribute to the mechanisms that predispose individuals to lupus reasoned that functional inherited genetic variation in pathways deranged in SLE may alter susceptibility or be associated with severity of disease.

The following mechanisms, cells, and proteins were linked to SLE: B cells, altered antibodies, immune complexes (IC), T cells, dendritic cells, apoptosis, cytokines, hormones, and complement components. However, their SLE-specific interaction is unclear, and there is currently no spectrum of immunological markers that may predict the clinical or histopathological course of SLE. For many years circulating IC or in situ IC were regarded as the main pathogenetic factors of LN. In fact, especially LN has been regarded as the prototype for IC-mediated glomerular disease. It was argued that the morphologic spectrum of glomerular pathology represented an entity that depended mainly on the severity of IC-induced damage. Hence, the broad clinical spectrum of LN disease ranging from isolated hematuria and proteinuria to nephrotic syndrome (NoS), nephritic syndrome (NiS), and finally chronic renal insufficiency has been interpreted as being the result of the same IC-mediated process. Furthermore, focal segmental LN has been interpreted as being the localized result of the same IC-mediated process than the more extensive lesions in diffuse proliferative LN. The pathogenetic explanation of the IC-induced variability of renal involvement in SLE must be questioned. It is unclear if all deposited IC are nephritogenic in LN and whether they are "Goodies or Baddies." There may be cases where the mesangial area is full of IC, and the inflammatory reactions may be scarce.

Controversial results were reported on the role of anti-nucleosome, high-avidity anti-dsDNA antibodies, and anti-alpha-actinin antibodies in the pathogenesis of LN. The role of B cells in SLE has historically focused on their

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autoantibody production; however, Stohl et al. suggested that B cells have multiple autoantibody-independent roles in SLE as well. B cells can efficiently present antigens and activate T cells. They can augment T cell activation through co-stimulatory interactions, and they can produce numerous cytokines that affect inflammation, lymphogenesis, and immune regulation. Not surprisingly, B cells have become attractive therapeutic targets in SLE. In summary, LN is not a disease entity in terms of pathogenesis and clinical picture, but instead is a group of lesions of unknown pathophysiological mechanisms that are treated with immunosuppressive drugs of which the mechanisms of renal and systemic interactions are poorly understood.

Pathology

All children with SLE and renal involvement such as proteinuria and/or hematuria should undergo a renal biopsy after associated coagulation disorders were excluded or treated. Triple diagnosis using light, immune, and electron microscopy should be performed to identify the histopathological type of LN-associated glomerulopathies as well as associated vascular and tubulointerstitial involvement. The role of renal biopsy in the evaluation of LN in childhood-onset SLE remains controversial. Historically, the principal criteria for the staging of lupus nephritis are glomerular abnormalities. Tubular dysfunction and pathology was mostly not routinely assessed in LN patients, despite the fact that SLE may be associated with a variety of tubular defects. There are children with SLE in whom LN is not suspected due to the absence of hematuria, glomerular proteinuria, hypertension, and decrease in GFR but who may have tubulointerstitial nephritis (TIN).

Based on the 1982 WHO classification, the revised classification of 2004 proposed that class I and II LN be used for purely mesangial involvement (class I = mesangial immune deposits without mesangial hypercellularity; class II = mesangial immune deposits with mesangial hypercellularity); class III for focal glomerulonephritis (involving $<$50% of total number of glomeruli) with subdivisions for active and sclerotic lesions; class IV for diffuse glomerulonephritis (involving $\geq$50% of total number of glomeruli) either with segmental (class IV-S) or global (class IV-G) involvement, and also with subdivisions for active and sclerotic lesions; class V for membranous LN; and class VI for advanced sclerosing lesions (*Table 298.2*). Tubulointerstitial inflammation and fibrosis was usually found in patients with class III, IV, and VI LN.

Renal biopsies should be examined by electron microscopy to identify glomerular podocytopathy with diffuse epithelial cell process effacement in the absence of peripheral glomerular immune deposits. A "full house" immunofluorescence pattern with the presence of IgA, IgG, IgM, C1q, C3, and tubular reticular structures by electron microscopy and mesangial deposits in an otherwise typical membranous nephropathy may indicate LN in seronegative SLE patients.

SLE patients may rarely have isolated tubulointerstitial nephritis. The most common intrarenal vascular lesions were nonspecific sclerotic changes. The other common vascular lesions were immunoglobulin microvascular casts (IMCs). IMCs ("lupus vasculopathy") were characterized by the presence of immunoglobulin deposition within the glomerular capillaries and small arterioles. Vasculitis and thrombotic microangiopathy were rare lesions.

The clinicopathological correlation demonstrated a significant relationship between histopathology and clinical course in LN; however, the biopsy findings did not uniformly correlate with the clinical features. The predominant histological type was class IV LN in patients with NiS. Active and chronic lesions were more likely to occur in patients of class III/IV LN; these patients were also more likely to have evidence of clinical renal disease than patients in class II. There was a significant association between NoS and class V LN. The status prediction of LN patients based on clinical information alone was significantly enhanced by information obtained from renal biopsy.

The classes of glomerular pathology may change during follow-up. It is unclear to what extent these changes are due to immune-modulating effects of treatment or reactivation of the disease. Repeat biopsies are indicated especially in patients with class II LN if renal function is deteriorating. The role of protocol biopsies in the management of patients with LN is unclear because neither the time point of renal biopsy nor their superiority have been identified in controlled studies.

Clinical Manifestations

The initial clinical manifestation of LN is characterized mostly by glomerular dysfunction ranging from isolated glomerular proteinuria and hematuria (in ca 20% of patients) to nephritic syndrome (in ca 40%) or nephrotic syndrome (in ca 40–50%) and chronic renal failure (CRF $<$ 10%) (*Table 298.1*). SLE patients rarely develop nonoliguric renal failure and tubular proteinuria as a consequence of isolated tubulointerstitial nephritis (TIN). Approximately one third of children with LN suffer from arterial hypertension at onset of the disease.

One third of lupus patients may develop the antiphospholipid syndrome (APS) nephropathy that is

Table 298.1
Clinical classification of lupus nephritides

1. Isolated glomerular hematuria
2. Isolated proteinuria
3. Combined hematuria/proteinuria
4. Nephritic syndrome (NiS) with hematuria, proteinuria >500 mg/day, arterial hypertension and with or without a decrease in glomerular filtration rate (GFR)
5. Nephrotic syndrome (NoS) with a proteinuria >1.66 g/m^2/day, low serum albumin <25 g/L, edema and hypercholesterolemia, with or without a decrease in glomerular filtration rate
6. Acute kidney failure with a reversible decrease of GFR <60 mL/min/1.73 m^2
7. Chronic kidney failure with an irreversible decrease of GFR <60 mL/min/1.73 m^2
8. Antiphospholipid antibody syndrome nephropathy
9. Hemolytic-uremic syndrome (HUS)

characterized by arterial hypertension, proteinuria, hematuria, and renal insufficiency. Renal artery occlusion is reported in patients with SLE and antiphospholipid antibodies. Thrombosis of the inferior vena cava and the renal veins are also described in SLE with APS.

Thrombotic thrombocytopenic purpura (TTP) is observed in patients with SLE. TTP may be difficult to identify because of the overlapping manifestations with SLE. Hemolytic anemia, thrombocytopenia, renal impairment, fever, and neurological abnormalities are characteristic of each disease process. The role of ADAMTS 13 activity in SLE-induced TTP remains to be clarified. The association of a hemolytic-uremic syndrome (HUS) with SLE is occasionally reported.

Laboratory Diagnosis

The erythrocyte sedimentation rate is usually increased in children with SLE indicating disease activity. By contrast, CRP is mostly normal. The complement system is consisting of three pathways and more than 30 proteins play a major role in the pathogenesis of SLE. On the one hand, the complement system appears to have protective features in that hereditary homozygous deficiencies of classic pathway components are associated with an increased risk for SLE. On the other hand, immune complex–mediated activation of complement may be responsible for pathological features of LN.

Immunological tests should look for hypocomplementemia (low C3 and low C4). C3 complement usually normalizes after remission; however, C4 mostly remains decreased. Double-strand DNA autoantibodies are usually elevated and normalized when LN comes into remission. All patients should be examined for a rise of antiphospholipid antibodies. Severity of LN should be clarified by estimating glomerular filtration rate (GFR), e.g., by cystatin C-based equations. Screening for renal involvement in patients with SLE is mandatory; however, the use of urinary dipsticks to detect proteinuria is inadequate and all lupus patients should be tested quantitatively for albumin excretion. Glomerular and tubular proteinuria can be differentiated by measuring urinary albumin and α-1-microglobulin. Glomerular hematuria can be distinguished from post-renal hematuria by microscopy. The renal function should be measured at regular intervals (e.g., every 3 months during the first 3 years) testing for proteinuria, hematuria, and GFR. B-cell-attracting chemokine CXCL13 was found to be a marker of disease activity and renal involvement in SLE. Urinary TNF-like weak inducer of apoptosis (TWEAK) has been implicated as a candidate clinical biomarker for LN. It is unclear which clinical biomarkers will turn out to be the most suitable ones for measuring disease activity before the appearance of renal dysfunction.

Differential Diagnosis

Other types of hypocomplementemic glomerulonephritides, other vasculitides and bacterial sepsis associated renal failure should be differentiated from LN. Inborn complement deficiencies (e.g., C1q deficiency, factor H disorders) may be associated with NiS, NoS, or atypical HUS.

Controversy and Consensus

The treatment of LN in children and adolescents is up to now, evidence-based, barely feasible. Contrary to adult medicine, there is no data from prospective controlled treatment studies in pediatric patients with LN. It is, e.g., unclear if the presently propagated oral treatment of mycophenolate mofetil (MMF) to induce remission of a severe LN in adults is also equally effective as intravenous Cyclophosphamide (IV-CYC) treatment in adolescents in view of the often inadequate medication compliance rate within this age group. Many of the drugs used in the treatment of LN and mentioned in this article are not licensed for children and adolescents in indications of SLE (off-label use). Due to the low case numbers of children and adolescents, controlled conclusive studies were just not possible in most countries. On the other

hand, the attending pediatrician is responsible for medical regularity and possible side effects. Off-label medication should therefore only be prescribed in light of currently applicable guidelines, recommendations, or from renowned scientific literature. The following treatment recommendations in LN in children and adolescents are mostly opinion-based.

The stratification of treatment modalities of LN was based on severity of LN pathology (mild, moderate, or severe glomerular involvement). However, pathological classification may not detect pathogenetic or clinical differences among patients with severe LN. Therefore, it is proposed that the choice of immunosuppressive agents for the treatment of the heterogeneous group of types of LN should include the main three clinical pictures such as NoS, NiS, or none of these two. Treatment of LN was controversially discussed in the literature and there was no universally accepted treatment protocol in 2009 for all classes of LN. The target cells for treatment and the precise mechanisms of anti-glomerulonephritic action of drug-induced immunosuppression in LN were unclear. Theoretically, all treatment modalities should aim at reducing the amount of deposited glomerular immune complexes. Podocytes have been identified as the target cell for immunosuppressive therapy of NoS of idiopathic focal segmental glomerulosclerosis suggesting that treatment of NoS may benefit especially from cyclosporine A (CSA) and predniso(lo)ne (PRED). In analogy, mesangial cells, endothelial cells as well as invading mononuclear cells and granulocytes may play a more important role in the development of NiS leading to a decrease of GFR. Thus, SLE patients having steroid-resistant NoS may benefit from other immunosuppressive agents than patients with NiS, irrespectively of the underlying histological type of glomerulonephritis. Unfortunately, there are no controlled studies available that attributed the patients to specific modes of therapy after combining both the clinical and histopathological appearance of LN. It may be argued that there is some correlation between the type of clinical involvement and histological alteration; however, this correlation is not a close one. NoS, for instance, is the major clinical manifestation of class V LN; however, almost all other histological types of LN may also be associated with a NoS, e.g., class IV diffuse LN may be characterized by a severe NoS and a reduced GFR. In summary, the purpose of future studies should be to further investigate the evidence of disparate mechanisms of glomerular injury in the inflammatory glomerular lesions and pathophysiologies of renal dysfunction.

There is a consensus that – for classification of LN – baseline data of SLE should be recorded including patients' demographics, renal function, and extrarenal comorbidity such as antiphospholipid syndrome and validated activity indices, as well as current medication. Renal biopsies using light, immunofluorescence, and electron microscopy should show 20 glomeruli on histology to allow a safe histopathological classification according to *Table 298.2*.

The categorization of different classes of LN has helped considerably to decide upon treatment options. Most guidelines recommend the use of combination therapy with intravenous PRED and other immunosuppressants to induce remission in proliferative LN class III and IV. Class I and II LN may not require the use of immunosuppressants in addition to oral PRED.

Most experts agreed that *induction therapy* should be given for at least 3–6 months. Expanded induction treatment may be necessary in those patients who have not yet entered a complete remission of LN. Serological measurements were not regarded as key markers of LN activity. No single renal marker has been identified for measuring response to treatment. Instead, the combination of a GFR >90 mL/min/1.73 m^2, with proteinuria <0.2 mg/mg creatinine and absence of hematuria defines a complete remission. Repeat renal biopsies are not required to define a complete remission. In fact, there may be a discrepancy between biopsy results and clinical markers, the meaning of which is unclear. Some nephrologists preferred the term "response" over "remission" in assessing the effects of LN treatment as some patients showed major benefit from treatment without reaching a complete remission. A more useful term is probably "partial response," however, this term was only well defined for NoS (partial response = proteinuria between 166 mg/1.73 m^2/day and 2 g/1.73 m^2/day, and serum albumin >25 g/L) and not for NiS. A sustained remission was defined as a complete remission for more than 6 months. A relapse of LN was defined as a reappearance of clinical symptoms of SLE and a new episode of renal involvement in those children reaching a complete remission during induction therapy or after relapse therapy. Some nephrologists preferred the term "flare" over relapse because patients with a partial remission may develop a new episode of disease activity requiring a new course of therapy or an intensified maintenance therapy. Flares of SLE may not be accompanied by flares of LN; however, recurrent episodes of LN may also be accompanied by a change of the histological class of LN. Likewise, a patient with an initial NoS of LN may reach a complete remission and may later on develop a NiS while on maintenance therapy or after stopping all treatment. This "nephritic flare" should not be regarded as a relapse of the NoS but as a new manifestation of LN with

Table 298.2
Histopathological classification of lupus nephritides (International Society of Nephrology/Renal Pathology Society 2003, according to Weening et al.)

Classification of lupus nephritis	
Class I	Minimal mesangial lupus nephritis
	Normal glomeruli by light microscopy, but mesangial immune deposits by immunofluorescence
Class II	Mesangial proliferative lupus nephritis
	Purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy, with mesangial immune deposits
	May be a few isolated subepithelial or subendothelial deposits visible by immunofluorescence or electron microscopy, but not by light microscopy
Class III	Focal lupus nephritis[a]
	Active or inactive focal, segmental, or global endo- or extracapillary glomerulonephritis involving $<$50% of all glomeruli, typically with focal subendothelial immune deposits, with or without mesangial alterations
Class III (A)	Active lesions: focal proliferative lupus nephritis
Class III (A/C)	Active and chronic lesions: focal proliferative and sclerosing lupus nephritis
Class III (C)	Chronic inactive lesions with glomerular scars: focal sclerosing lupus nephritis
Class IV	Diffuse lupus nephritis[b]
	Active or inactive diffuse, segmental, or global endo- or extracapillary glomerulonephritis involving $\geq$50% of all glomeruli, typically with diffuse subendothelial immune deposits, with or without mesangial alterations. This class is divided into diffuse segmental (IV-S) lupus nephritis when $\geq$50% of the involved glomeruli have segmental lesions, and diffuse global (IV-G) lupus nephritis when $\geq$50% of the involved glomeruli have global lesions. Segmental is defined as a glomerular lesion that involves less than half of the glomerular tuft. This class includes cases with diffuse wire loop deposits but with little or no glomerular proliferation
Class IV-S (A)	Active lesions: diffuse segmental proliferative lupus nephritis
Class IV-G (A)	Active lesions: diffuse global proliferative lupus nephritis
Class IV-S (A/C)	Active and chronic lesions: diffuse segmental proliferative and sclerosing lupus nephritis
	Active and chronic lesions: diffuse global proliferative and sclerosing lupus nephritis
Class IV-S (C)	Chronic inactive lesions with scars: diffuse segmental sclerosing lupus nephritis
Class IV-G (C)	Chronic inactive lesions with scars: diffuse global sclerosing lupus nephritis
Class V	Membranous lupus nephritis
	Global or segmental subepithelial immune deposits or their morphologic sequelae by light microscopy and by immunofluorescence or electron microscopy, with or without mesangial alterations
	Class V lupus nephritis may occur in combination with class III or IV in which case both will be diagnosed
	Class V lupus nephritis show advanced sclerosis
Class VI	Advanced sclerosis lupus nephritis
	$\geq$90% of glomeruli globally sclerosed without residual activity

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis, or other vascular lesions
[a]Indicate the proportion of glomeruli with active and with sclerotic lesions
[b]Indicate the proportion of glomeruli with fibrinoid necrosis and/or cellular crescents

a possible change of renal histology. Thus, the *relapse therapy* may have to differ from the initial induction therapy. Several types of "flares" can be differentiated: (1) isolated proteinuria, (2) combined hematuria and proteinuria, (3) NoS, and (4) NiS. Flares of LN may rarely manifest as a HUS.

Maintenance is the period of less intensive immunosuppressive therapy following induction therapy. *Maintenance therapy* of LN is poorly defined and randomized controlled studies are lacking. It can be given to patients in remission to prevent relapses and it can be applied to patients in partial remission or with stable baseline

measurements to prevent progression of the disease. Maintenance therapy with long-term oral PRED should be avoided to prevent steroidal toxicity. Low doses of MMF, Azathioprine (AZA), or CSA should be given to sustain remission. The duration of maintenance therapy is unclear and it may last for many years in patients with multiple relapses of LN. Symptomatic maintenance therapy includes treatment of arterial hypertension and hyperlipidemia.

Rescue therapies were poorly defined in children with LN unresponsive to known types of immunosuppressive therapies. Some rescue therapies included "new" drugs that had not yet been tested before or they consisted in new combinations of known drugs thus increasing the "immunological attack" during treatment. As rescue therapies such as Rituximab (RIT) have a considerable risk of side effects, they should be restricted to specialized pediatric nephrology centers.

Treatment recommendations have taken into account that therapeutic decisions are substantially influenced by the costs of drug treatment. There may be no "right and wrong" when deciding upon a treatment regimen because "availability and nonavailability" will decide upon "how and when" to treat. Several countries may lack the financial resources for offering expensive drugs such MMF, CSA, and RIT to all patients. As intravenous prednisolone (IV-PRED), IV-CYC, and AZA are available in most countries, these drugs may be the most frequently used in LN worldwide.

There is a risk of doctors' noncompliance to standardized treatment protocols, and in addition patients' nonadherence to long-term drug treatment severely influences outcome of LN. Therefore, a team of caregivers should be responsible for psychosocial care and for a guided transfer from pediatric into adult care.

The treatment of LN is typified by popular misconceptions: that there is a standard of care, that treatment has well-defined aims, and that the optimum length of treatment is established. In conclusion, level 1a evidence was not achieved for any therapy of LN. In reality, uncertainties still exist and the evidence base remains weak. Most studies on the outcome of LN are difficult to interpret because the choice of combination treatment, the dosage of different immunosuppressive agents, and the duration of induction and maintenance therapy were poorly standardized. Moreover, the response to treatment was analyzed according to different criteria such as normalization of GFR, and/or reduction of proteinuria, etc.; however, response to treatment thus is not the same as disease remission. Proteinuria can take a long time to reach baseline levels, and normalization of urine is not the same as loss of histological disease activity.

Several standardized treatment protocols were tested in controlled and uncontrolled trials on LN; however, very few have gained an international acceptance. It is also unclear if children with LN should be treated by individualized treatment modalities because the individual needs of lupus patients are ill defined. In fact, many pediatric nephrologists will have to treat less than 50 children with LN during their professional life span, which will not lead to a "proper learning curve." Ideally, all pediatric nephrologists should include their patients in multicenter therapeutic trials to test the best possible treatment and control of disease activity. However, there were no such international trials available in 2009.

Drug Alternatives

Several multicenter, randomized, open-label trials were conducted in adult patients to analyze the therapeutic response to different immunosuppressive regimen. However, most studies were inadequately powered with small number of patients, short-term follow-up, inclusion of heterogeneous mixtures of patients in terms of race and severity. Eligibility criteria included (1) the SLE meeting for classification criteria of the American College of Rheumatology (*Table 298.3*), (2) renal biopsy documenting LN according to the classification of the World Health Organization (*Table 298.2*), and (3) clinical activity as defined by one or more of the following: incident decrease in renal function as defined by GFR, PU, and HU (*Table 298.1*) or serologic abnormality such as anti-DNA antibodies or hypo-complementemia (*Table 298.4*).

Because therapeutic responses may differ depending on the pattern of renal histological features, the patients were stratified according to renal biopsy as having proliferative glomerulonephritis as compared with membranous glomerulonephritis and other types. Permuted blocks of patients of variable size were used within each subgroup. The primary end point was (1) complete remission at different intervals (12–24 weeks), (2) partial remission, (3) maintenance of baseline measurements, or (4) progression of renal dysfunction. The clinical studies were conducted in adults to analyze the efficacy of induction therapy to achieve a complete remission or of maintenance therapy to prevent relapses. Studies on relapse therapy or rescue therapy were rarely systematically performed. The stratification of most studies was based

Table 298.3

Lupus erythematosus disease activity index (SLEDAI)

Wtd score	Descriptor	Definition
8	Seizure	Recent onset. Exclude metabolic, infectious, or drug-related causes
8	Psychosis	Altered ability to function in normal activity due to severe disturbance in the perception of reality. Includes hallucinations; incoherence; marked loose associations; impoverished thought content; marked illogical thinking; bizarre, disorganized, or catatonic behavior. Exclude the presence of uremia and offending drugs
8	Organic brain syndrome	Altered mental function with impaired orientation or impaired memory or syndrome other intellectual function, with rapid onset and fluctuating clinical features. Includes a clouding of consciousness with a reduced capacity to focus and an inability to sustain attention on environment, and at least two of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, increased or decreased psychomotor activity. Exclude metabolic, infectious, and drug-related causes
8	Visual	Retinal changes from systemic lupus erythematosus: cytoid bodies, retinal hemorrhages, serous exudates or hemorrhages in the choroid, optic neuritis (not due to hypertension, drugs, or infection)
8	Cranial nerve	New onset of a sensory or motor neuropathy involving a cranial nerve
8	Lupus headache	Severe, persistent headache; may be migrainous; unresponsive to narcotics
8	Cerebrovascular accident	New syndrome. Exclude arteriosclerosis
8	Vasculitis	Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages. Vasculitis confirmed by biopsy or angiogram
4	Arthritis	More than two joints with pain and signs of inflammation
4	Myositis	Proximal muscle aching or weakness associated with elevated creatine phosphokinase/aldolase levels, electromyographic changes, or a biopsy showing myositis
4	Casts	Heme, granular, or erythrocyte
4	Hematuria	More than five erythrocytes per high-power field. Exclude other causes (stone, infection)
4	Proteinuria	More than 0.5 g of urinary protein excreted per 24 h. New onset or recent increase of $>$0.5 g/24 h
4	Pyuria	More than five leukocytes per high-power field. Exclude infection.
2	New malar rash	New onset or recurrence of an inflammatory type of rash
2	Alopecia	New or recurrent. A patch of abnormal, diffuse hair loss
2	Mucous membranes	New onset or recurrence of oral or nasal ulcerations
2	Pleurisy	Pleuritic chest pain with pleural rub or effusion, or pleural thickening
2	Pericarditis	Pericardial pain with at least one of rub or effusion. Confirmation by electro- or echocardiography
2	Low complement	A decrease in CH50, C3, or C4 level (to less than the lower limit of the laboratory-determined normal range)
2	Increased DNA binding	More than 25% binding by Farr assay (to $>$ the upper limit of the laboratory-determined normal range, e.g., 25%)
2	Fever	More than 38°C after the exclusion of infection
2	Thrombocytopenia	Fewer than 100,000 platelets
2	Leukopenia	Leukocyte count of $<$3,000/mm^3 (not due to drugs)

Adapted from Bombardier (1992)

Table 298.4
Lupus criteria

Clinical Criteria
1. Acute or subacute cutaneous lupus
2. Chronic cutaneous lupus
3. Oral/Nasal ulcers
4. Nonscarring alopecia
5. Inflammatory synovitis with physician-observed swelling of two or more joints or tender joints with morning stiffness
6. Serositis
7. Renal: urine protein/creatinine (or 24-h urine protein) representing at least 500 mg of protein/24 h or red blood cell casts
8. Neurologic: seizures, psychosis, mononeuritis multiplex, myelitis, peripheral or cranial neuropathy, cerebritis (acute confusional state)
9. Hemolytic anemia
10. Leukopenia ($<$4,000/mm^3 at least once) or Lymphopenia ($<$1,000/mm^3 at least once)
11. Thrombocytopenia ($<$100,000/mm^3) at least once
Immunologic Criteria
1. ANA above laboratory reference range
2. Anti-dsDNA above laboratory reference range (except ELISA: twice above laboratory reference range)
3. Anti-Sm
4. Antiphospholipid antibody Lupus anticoagulant False-positive test for syphilis Anticardiolipin – at least twice normal or medium-high titer Anti-b2 glycoprotein 1
5. Low complement Low C3 Low C4 Low CH50
6. Direct Coombs test in absence of hemolytic anemia

on renal histology and interestingly not so much on the clinical presentation of LN, e.g., NiS or NoS. Most studies concentrated on moderate or severe lupus nephritis including gross proteinuria, decrease of GFR, hematuria, and arterial hypertension. Treatment protocols for induction and maintenance therapy included PRED, CYC, MMF, AZA, CSA, RIT, and others. Monotherapeutic trials were seldom, most studies included a combination therapy using more than one immunosuppressive agent.

Predniso(lo)ne

Once the diagnosis of a LN has been established, the child should be admitted to hospital and an immunosuppressive treatment including daily oral PRED should be started with the aim to induce remission. One of the most widely used initial regimen consists of 60 mg/day/m^2 body surface area (BSA) PRED, not exceeding the total daily dose of 80 mg. The dosage of PRED may be referred to BSA or to body weight: 60 mg/day/m^2 BSA will correspond approximately to 2 mg/day/kg body weight. There is no data available to compare the efficacy of PRED with other corticosteroids in LN. PRED is generally given in three divided doses with the highest dose in the morning and the lowest dose in the evening, e.g., 30–20–10 mg in a child with one square meter BSA. There is no data available addressing the efficacy of the time intervals of PRED dosage during daytime, e.g., once or twice instead of three times daily.

Intravenous prednisolone of methylprednisolone therapy (IV-PRED) has been shown to be effective in children with either NoS or NiS in increasing the steroid-induced immune attack if given in addition to oral steroids. However, neither the number of pulses, nor the intervals or dosages have been standardized in pediatric nephrology nor it is clear if IV-PRED has to be adjusted to different causes of glomerulonephritides. Six pulses on alternate days with 300 mg/m^2 PRED is recommended. Oral PRED should be given on the IV-PRED free days. Pulses of IV-PRED should be given to patients with class III–V LN. Continuous steroidal treatment is an essential part of combination therapies using CYC or MMF; however, the duration of high-dose PRED should be limited to 6 weeks because of threatening steroidal side effects. The risk–benefit effect of low-dose continuous PRED – though being part of many protocols – is unclear.

In order to sustain remission and to prevent an early relapse, continuous oral PRED treatment is usually followed by alternate-day PRED (40 mg/48 h/m^2) given in a single morning dose.

It is the aim of corticosteroid therapy to induce a complete and long-lasting remission. There are, however, many patients with LN who will only enter a partial or short-term remission after receiving PRED monotherapy and therefore a combination therapy of PRED with other immunosuppressive drugs is recommended in all types of LN.

Cyclosporine A

Apart from class V LN the positive role of CSA in the induction treatment of the other types of LN has never

been clarified. Several authors reported an effective induction of remission in patients with different histological types of LN using CSA in addition to PRED. It is impossible to calculate the exact remission rate from the pooled data of 63 articles found in Pub Med because some of these were lacking an analysis on the rate of patients with a complete remission. Last but not least, the positive effect of additional immunosuppressive agents given concomitantly to CSA could not always be differentiated from the CSA effect itself. In summary, the pooled data on the articles for "CSA and LN" reveal that CSA had a steroid sparing effect during induction therapy and that it had a proven effect on decreasing proteinuria in patients with LN.

In our center, 11 children with an initial attack of nephrotic LN (class II LN = 4, IV = 4, V = 3 patients) with normal GFR received CSA (150 mg/m^2/day) and continuous PRED (60 mg/m^2/day) as induction therapy. Three patients had been previously unresponsive to oral PRED + CYC pulses given at monthly intervals. Maintenance therapy included a tapering of PRED over 5–8 months to 5 mg/m^2/48 h followed by a switch to alternate-day PRED (10 mg/m^2/48 h), and CSA dosage was given to achieve target trough levels between 80 and 120 ng/mL. All 11 patients entered complete remission of NoS after induction therapy with CSA + PRED. Maintenance therapy with CSA plus alternate-day PRED effectively prevented a relapse in 7/11 children. Four of 11 patients developed 1 or 2 relapses while having CSA trough levels below 60 ng/mL. From our own data and from the literature it is concluded that the combination of CSA + PRED is a safe treatment in patients with NoS and a normal GFR at onset of LN.

The role of CSA in the induction treatment of nephritic LN is unclear. In those patients with LN achieving a partial remission with persistent proteinuria after PRED and CYC or MMF the additional use of CSA may effectively contribute to inducing a complete remission. CSA has also been shown to prevent relapses and flares during maintenance therapy if combined with AZA or PRED.

The role of Tacrolimus in the treatment of LN in children is unclear because of lacking data.

Cyclophosphamide

A decisive advancement in the treatment of LN was brought about by the long-term studies carried out in the early 1990s by the National Institute of Health with an observation period of up to 20 years. These studies showed that CYC led to a better renal survival over a long period (10–20 years) than that achieved with the exclusive use of PRED. Furthermore it could be shown that IV-CYC pulse therapy (7 pulses of 500–1,000 mg/m^2 in monthly intervals) was equivalent to a daily oral CYC dose with regard to preservation of remission and with lower toxicity. Boumpas et al. showed that the continuation of IV-CYC pulse treatment (three-monthly dose) over a period of 3 years led to a better remission rate and found that CYC plus additional monthly IV-PRED pulses produced an improved long-term outcome in patients with proliferative LN if compared to CYC monotherapy.

Altogether in these studies, a remission in approximately 80% of patients was achieved. Regardless of the type of maintenance therapy, approximately one third of the responsive patients showed relapses under continued immunosuppression. End-stage kidney failure insufficiency developed in 10–20% of the patients within 5–10 years.

A major problem of the treatment with IV-CYC and IV-PRED pulses was the high rate of serious side effects (30–50%) such as gonadal and gastrointestinal toxicity, alopecia, bone marrow depression, hemorrhagic cystitis, lymphoproliferative diseases as well as life-threatening infections. CYC-induced gonadal toxicity was observed in cumulative dosages exceeding 250 mg/kg body weight. Because of the high proportion of postpubertal male patients developing a disturbed spermatogenesis, it is advisable to perform a cryo-conservation of sperm before cytotoxic drug treatment of LN patients. A secondary amenorrhea was found in female patients with increasing age, ranging in the order of 13% at the age of 20 years, 50% from the age of 20–30 years, and almost 100% in patients over 30 years of age. There are positive reports on the use of GnRH agonists such as Leuproreline acetate to protect the ovaries.

The Euro-Lupus trial evaluated a reduced dosage of CYC pulses giving a maximum of 500 mg (6 mini-pulses every 2 weeks) compared to the classical NIH protocol using 500 mg/m^2 per month (7 pulses followed by and then one pulse after 3 and 6 months). Thus, the cumulative dosage in a patient of 70 kg and 175 cm was 3 g CYC in the Euro-LN trial and approximately 8 g CYC in the NIH protocol. Both groups of patients received AZA after stopping CYC. A total of 90 patients were included having class III or IV LN and a proteinuria above 500 mg per day. After a mean follow-up of 5 years, the results of both groups were comparable and approximately 80% of patients were in remission after 5 years. However, the rate of side effects was twice as high in the high-dose CYC group if compared with the low-dose CYC group.

Mycophenolate Mofetil

Several controlled studies were performed in adult patients with LN to test the hypothesis that MMF may be more efficient than the previous gold standard using IV-CYC and IV-PRED to induce and sustain remission of LN. Most studies had a short follow-up of less than 12 months, a small number of patients, or no patient with a severe decrease of GFR below 30% of the norm.

The authors Zhu B et al. and Chan TM et al. analyzed 24 patients with class IV LN and MMF/PRED versus oral CYC/PRED followed by AZA/PRED after 6 months. Eighty-one percent of patients in the MMF group achieved complete remission within 12 months compared to 76% of patients in the CYC group. After a mean follow-up of 5 years, there were no statistical differences concerning the remission and relapse rates. However, the number of patients was less than 20 after follow-up of 3 years and the long-term results of the study may have to be interpreted with great care. The rate of side effects was one third of patients in the CYC group compared to 10% in the MMF group. End-stage renal disease developed in 5% of patients of both groups after 5 years.

Hu et al. reported on 46 patients with class IV LN; group 1 received MMF and group 2 IV-CYC pulses in addition to PRED. After a short follow-up of 6 months, proteinuria decreased by 70% in the MMF group and by 48% in the CYC group, and hematuria by 90% versus 65%, respectively. MMF induced a more rapid decrease in dsDNA antibodies in the blood and a more pronounced regression of glomerular immune complex deposits in the control biopsy than CYC.

Ginzler et al. studied 140 adult patients with LN (15% class III, 55% class IV, 20% class V, 10% mixed membrano-proliferative GN) giving MMF to group 1 and monthly IV-CYC to group 2 B in addition to PRED. Complete remission was achieved in 22% of the MMF group and 5.8% in the CYC group within 6 months. A partial remission was found in 30% of patients receiving MMF and in 25% of patients receiving CYC. Side effects such as severe infections and hospitalizations were less frequent in the MMF group; however, the MMF patients had a higher rate of diarrhea. Patients had been submitted to a high dosage of MMF (3 g per day) exceeding dosages of MMF in other studies. The efficacy of CYC was dose dependent.

The ALMS trial studied 370 patients with an initial attack of class III or IV LN for 24 weeks comparing MMF/PRED with IV-CYC/PRED. MMF was not superior to IV-CYC as induction therapy. The incidence of serious adverse events was similar in both groups. Race, ethnicity, and geographical region were shown to affect treatment response; more Black and Hispanic patients responded to MMF than to IV-CYC.

Contreras et al. performed a study on MMF maintenance therapy in LN. After a 6-month induction therapy using IV-CYC in patients with severe LN, MMF maintenance therapy had a lower rate of side effects than three-monthly IV-CYC pulses. Fujinaga et al. reported that four children with severe LN experienced no flares during maintenance therapy with MMF and tapered PRED. Maintenance therapy with MMF is efficacious and safe for the treatment of high-risk patients with proliferative LN. The dose of MMF during maintenance should be reduced if patients receive a co-medication with CSA to avoid MMF toxicity.

Azathioprine

The induction therapy with AZA was inferior to IV-CYC pulses and PRED. During a follow-up of 5.7 years, patients receiving AZA had a fourfold increased risk of developing chronic renal insufficiency with a doubling of serum creatinine and a ninefold increased relapse rate of LN. In conclusion, AZA induction therapy should not be given to patients with severe class IV LN. Maintenance therapy with AZA is efficacious and safe for the treatment of high-risk patients with proliferative LN. AZA should be started after end of induction therapy at a dosage of 1–3 mg/kg/day. Azathioprine is a prodrug of mercaptopurine, a substance that is subsequently metabolized by thiopurine methyltransferase (TPMT). Approximately 6 in 1,000 people have deficiency of TPMT because of genetic mutations. These people are at great risk of developing life-threatening bone marrow toxicity. It is recommended to test LN patients for TPMT activity before starting AZA.

Rituximab

The monoclonal antibody RIT is directed against CD 20 positive cells, and in more than 30 retrospective studies, in small numbers of patients, it was shown to induce a complete remission in more than 50% of patients if used as a combination therapy with PRED and CYC or MMF. The French multicenter retrospective study of childhood-onset SLE reported eight girls with class IV or V LN. Patients received 2–12 intravenous infusions of RIT (350–450 mg/m^2/infusion) with PRED. Six patients also received different standard immunosuppressive agents.

Remission was achieved in six of eight patients. It was concluded that RIT may be an effective rescue or co-therapy. Caution is necessary with respect to minimizing the number of doses and treatments with RIT. The treatment with RIT is an off-label use and parents should be informed about possible side effects and complications, such as life-threatening infections and leukencephalopathy syndrome.

Plasmapheresis and Immunoglobulins

The large differences that exist in the use of plasmapheresis/immunoadsorption in the treatment of LN practiced in different centers/countries seem to be based on the local habits or national character and not so much on scientific findings. Although not proven, plasmapheresis might be beneficial as rescue therapy in patients with acute life-threatening disease, for which high-dose immunosuppressive therapy may not be possible, or as an adjunct procedure for patients not responding to conventional therapy. Clear-cut recommendations regarding type of adsorption column, intensity and duration of treatment, and accompanying immunosuppressive treatment cannot be given.

The role of intravenous immunoglobulin infusions in the rescue therapy of LN is unclear. High sucrose immunoglobulin preparations should be avoided because they may be associated with acute renal failure due to tubular damage.

Recommendations for Induction Therapy of Different Clinical and Pathological Types of Lupus Nephritis

The following four therapeutic protocols are taking into account both the clinical and histopathological heterogeneities of LN:

Protocol 1. Severe nephritic LN including a decrease of GFR ($<$90 mL/min/1.73 m^2), proteinuria above 500 mg/m^2/day, arterial hypertension, and hematuria showing class III or IV LN on renal biopsy.

Protocol 2. Nephrotic LN and normal or mildly reduced GFR (60–90 mL/min/1.73 m^2) with classes II, III, IV, or V on renal biopsy.

Protocol 3. Mild or moderate nephritic class II–IV LN with proteinuria above 500 mg/m^2/day, hematuria, with or without hypertension and normal GFR.

Protocol 4. Other groups of LN.

The rationale of these treatment recommendations is based on the following findings and conclusions:

1. Children with LN should receive a combination therapy of several drugs instead of monotherapy.
2. The initial immunosuppressive attack should be massive. A start with a mild immunosuppression followed by a slowly escalating intensity with successively added drugs should be avoided.
3. PRED has been shown to be an effective component of all combination therapies in LN; IV-PRED is more effective than oral PRED.
4. CYC has been shown to be an effective part of combination therapy; IV-CYC pulses being more efficient than oral CYC, however, high cumulative dosages may lead to persistent side effects.
5. MMF has been shown to be an effective part of combination therapy in adult patients with LN and should be tested in children because of a lower rate of side effects than CYC. Furthermore, MMF is an integrated part of maintenance therapy.
6. CSA is a useful component of combination therapy for children with LN and NoS both during induction and maintenance therapy.
7. AZA is a steroid-sparing agent and its use is limited to maintenance therapy.
8. RIT has been shown to be effective as part of a combination rescue therapy in those patients who have previously been unresponsive to the above-mentioned drugs.
9. The choice of four different protocols for all types of LN may be criticized because less or more than four regimen may be offered to patients to allow either a standard procedure for all or a more individually tailored treatment for some patients. Unfortunately, the published guidelines did not allow to develop a uniform approach.

It is unclear to what extent the lessons from the treatment of adult patients with LN can be transferred from adults to children. Several authors have emphasized that a LN in children and adolescents had a more severe course than in adults. Anecdotal reports indicate that there seems to be a similarly good efficacy of IV-CYC pulses and IV-PRED in children with severe LN; however, the side effects on growth and on pubertal development were poorly studied. The gold standard for the induction treatment of patients with severe class IV LN includes initial IV-PRED pulses, oral PRED, and monthly IV-CYC pulses for at least 3–6 months. Patients with milder LN were treated by several combination therapies using either PRED + AZA, or PRED + MMF, or PRED + CYC, or PRED + CSA as induction therapy.

Many authors give MMF or AZA and low-dose PRED as maintenance therapy. Maintenance therapy is mostly individually tailored according to presence or absence of side effects.

Protocol 1. Severe Lupus Nephritis

Induction therapy of severe nephritic LN should include a combination therapy of IV-PRED pulses, oral PRED, and IV-CYC pulses or alternatively MMF (Fig. 298.1). Maintenance therapy in responders includes MMF and oral PRED. Partial responders should be put on maintenance therapy if renal dysfunction is mild such as proteinuria less than 1 g/day to wait for a late complete response. Nonresponders should undergo rescue therapy. Relapse therapy should be given to relapse patients and to patients with flares using MMF and IV-PRED plus oral PRED. The intensity and duration of relapse therapy with PRED depends on the severity of corticosteroid toxicity.

Induction Therapy

Corticosteroids: 3–6 IV-PRED pulses (300 mg/m^2 on alternate days) plus oral PRED (60 mg/m^2/day, a maximum dose of 80 mg/day) are given for 4 weeks. Patients entering complete remission should be switched from continuous PRED to alternate-day PRED (starting with 40 mg/m^2/day with a tapering of PRED to reach a baseline alternate-day PRED dosage of 5–10 mg/m^2/48 h). Side effects of PRED should be studied at regular intervals and alternate-day PRED may be stopped completely in responsive patients during the first year after initial treatment.

Cyclophosphamide: IV-CYC (500–750 mg/m^2) should be given 1 day after the initial IV-PRED pulse. Anuric children should receive a lower dosage of 250–500 mg/m^2/day. Further IV-CYC pulses are given in monthly intervals. As the response to IV-CYC pulses was shown to be dose dependent, patients with very severe LN may be treated with high doses of CYC reaching 1,000 mg/m^2. The IV-CYC dosage has to be reduced in those patients developing leukopenia below 4,000/μL. Patients receiving IV-CYC pulses should also be treated with a prophylaxis to prevent hemorrhagic cystitis and vomiting. Mesna (400 mg/m^2 iv) can be given prior to and following CYC pulses. Anti-emetics like Ondansetrone (5 mg/m^2 iv) should be given prior to IV-CYC pulses and may be repeated at lower dosages.

Intravenous volume loading with half-isotonic sodium chloride solutions will depend on the GFR and on the hydration of the child. Severe edema should be avoided.

Mycophenolate mofetil may be given as an alternative to IV-CYC: MMF is given orally at a dosage of 1,000–1,200 mg/m^2/day (maximum 2 g/day). MMF dosage should be adjusted according to the results of a Mini-AUC requiring three blood samples: C_0, $C_{0.5}$, and C_2 according to the equation: MPA-AUC (area under the curve) = $10.01 + 3.94 \times C_0 + 3.24 \times C_{0.5} + 1.01 \times C_2$. The MPA-mini-AUC should aim at levels ranging between 60 and 80 mg × h/L. Patients developing leucopenia should receive a lower MMF dosage. Patients developing diarrhea while on MMF may be switched to enteric-coated mycophenolate sodium.

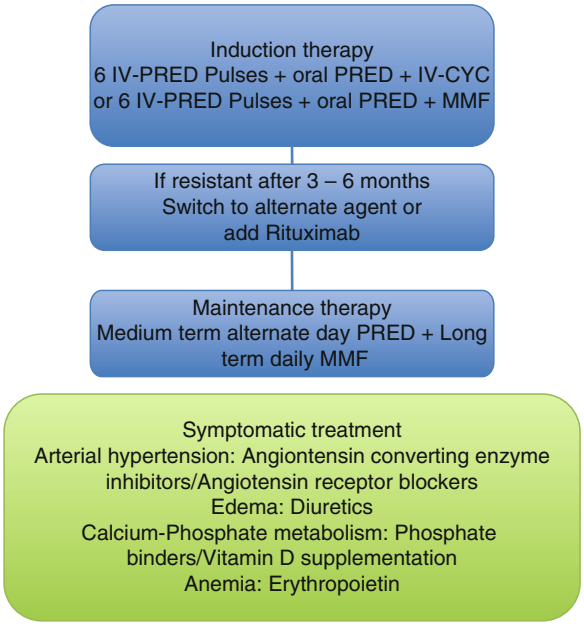

Figure 298.1
Treatment protocol for severe lupus nephritis (LN) with nephritic syndrome (Nis)

Maintenance Therapy

PRED should be switched from continuous application to alternate-day therapy as soon as the patient has entered a remission to prevent steroidal side effects. Tapering of PRED dosage is mostly individually tailored; however, the criteria for this maneuver are poorly standardized. AZA should be started after end of induction therapy at a dosage of 1–3 mg/kg/day. MMF should be started with 1,000/m^2/day and MMF dosage should be adjusted to MPA-mini-AUC levels ranging between 60 and 80 mg × h/L.

Rescue Therapy

There is no universal definition of treatment resistance in LN. If patients with severe LN do not respond to induction therapy after 6 months, or if LN progresses during the initial 6-month treatment period, patients should be treated by a rescue therapy. This triple therapy includes IV-PRED pulses + oral PRED, MMF, and RIT. The treatment protocol for PRED and MMF is similar to the general induction therapy. RIT (375 mg/m^2 BSA) should be given on day 0 and 15. Further injections may be given to relapsing patients. Paracetamol and antihistamines should be given prior to RIT.

Protocol 2. Nephrotic Syndrome with Class II–V LN

Glomerular podocytopathy with 80% foot process effacement is specific for patients with SLE-induced NoS regardless of the underlying class of LN. The development of nephrotic range proteinuria in patients with LN without peripheral immune deposits was described to be a manifestation of SLE in the podocytes. It is concluded from therapeutic studies on FSGS and NoS that CSA may also effectively reduce proteinuria in patients with LN and NoS. Children with class V LN and those children with other class II–IV LN who did not achieve complete remission of proteinuria after other types of immunosuppression should receive a combination therapy of IV-PRED, oral PRED, and CSA.

Induction therapy should be started with 3–6 IV-PRED pulses on alternate days (300 mg/m^2 PRED) (*Fig. 298.2*). Oral PRED (60 mg/m^2) should be given on the IV-PRED free days for 4–6 weeks and should be switched to alternate-day PRED in those patients entering remission. Continuous PRED may be prolonged and tapered in nonresponders for a maximum of 6 months.

CSA (150 mg/m^2/day) is started together with IV-PRED and the CSA dosage should be adjusted to achieve target trough levels between 100 and 140 ng/mL until remission. Patients with a NoS and an initial GFR below 60 mL/min/1.73 m^2 may develop a transient decrease in GFR during CSA therapy. Therefore, these patients may be switched from CSA to MMF.

As soon as the patients have achieved a complete remission, the oral prednisone therapy should be switched to alternate-day PRED and maintenance therapy should consist of alternate-day PRED + CSA (or MMF if given successfully for induction therapy). Therapeutic trough levels of CSA should aim at C_O concentrations of

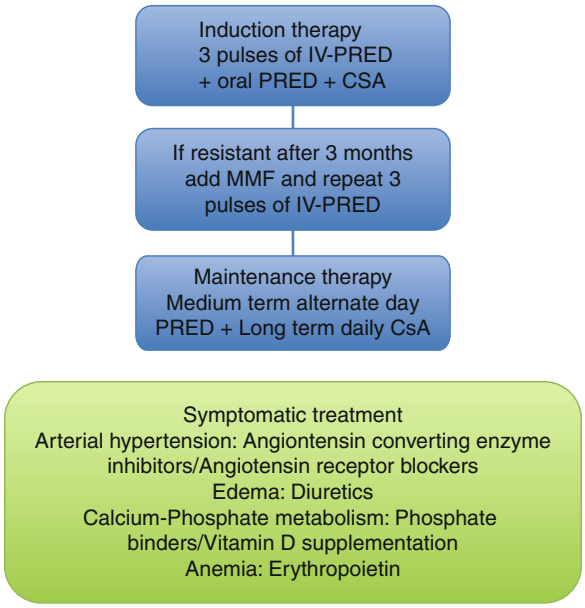

Figure 298.2
Treatment protocol for lupus nephritis with nephrotic syndrome (Nos)

80–120 ng/mL during maintenance therapy. Patients experiencing a relapse during CSA maintenance therapy should receive a second course of IV-PRED pulses + oral PRED. Patients developing CSA nephrotoxicity during maintenance therapy may be switched from CSA to MMF maintenance therapy. Frequent relapses may receive a maintenance therapy with a combination of CSA + MMF. Those patients who did not respond to induction therapy with PRED + CSA may be switched to IV-CYC, or MMF.

Class V LN may be further differentiated into subclasses Va to Vd LN. There is presently no finding supporting the finding that patients with membranous LN should be treated differently according to these subclasses.

Protocol 3. Mild or Moderate Nephritic Syndrome and Class II–IV LN with Proteinuria Above 500 mg/m^2/day, Hematuria, With or Without Hypertension and Normal GFR

Induction therapy should be started with 3 pulses IV-PRED and low-dose IV-CYC or MMF (*Fig. 298.3*). Oral PRED (60 mg/m^2/day, a maximum dose of 80 mg/day) is given for 4 weeks and then tapered to lower dosages. Patients entering complete remission should be switched

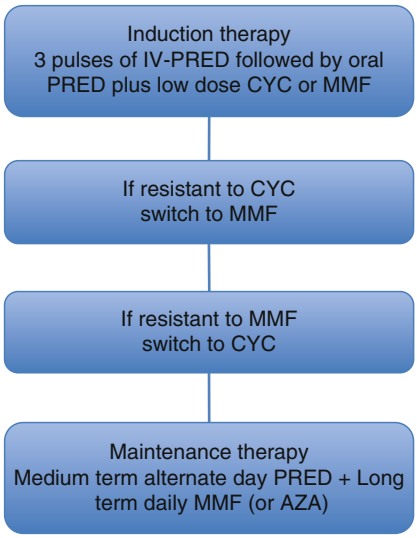

Figure 298.3
Treatment protocol for mild and moderate lupus nephritis with nephritic syndrome

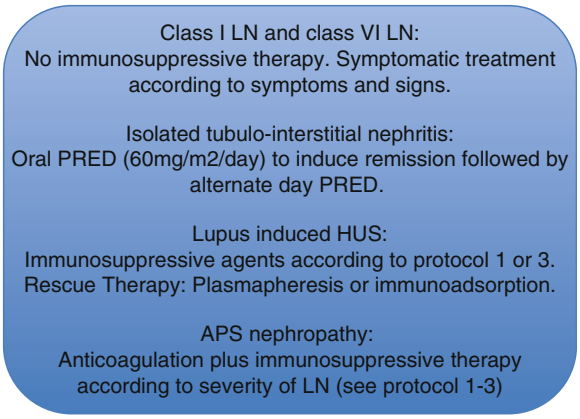

Figure 298.4
Treatment options for other types of lupus nephritis

from continuous PRED to alternate-day PRED (starting with 40 mg/m^2/day with a tapering of PRED to reach a baseline alternate-day PRED dosage of 5–10 mg/m^2/48 h. Side effects of PRED should be studied at regular intervals and alternate-day PRED may be stopped completely in responsive patients during the first year after initial treatment. Six "low-dose" IV-CYC pulses (500 mg/m^2) should be given at monthly interval starting 1 day after onset of PRED. MMF may be given orally at a dosage of 1,000 mg/m^2/day as an alternative to IV-CYC.

Maintenance therapy may include MMF, AZA, or CSA in addition to low-dose alternate-day PRED.

Protocol 4. Other Groups of Lupus Nephritis

Patients with class I LN need no immunosuppressive therapy as long as there is no progressive renal dysfunction. On the other side of the severity spectrum is class VI LN, which should be regarded as the final stage of renal involvement with little inflammatory lesions and mostly scarring. These patients should neither undergo induction therapy nor rescue therapies to avoid unnecessary side effects. Nephroprotection including antihypertensive and antiproteinuric treatment is indicated in these patients.

Children with lupus-induced isolated tubulointerstitial nephritis should be treated with oral PRED (60 mg/m^2/day) to induce remission (*Fig. 298.4*).

Patients with lupus-induced HUS or TTP should be treated by immunosuppressive agents and anticoagulation and may receive plasmapheresis or immunoadsorption.

Patients with APS nephropathy will require anticoagulation in addition to immunosuppressive therapy.

Prognosis

SLE can be a lifelong disease. The prognosis of different LN depends on the underlying classes and also on the different therapeutic regimen. Under-immunosuppression may lead to progression of CKD and overtreatment to an increase of side effects such as severe infections.

All published data on the follow-up of different classes of LN in children suffer from the missing standardization of immunosuppressive therapies and the lack of long-term evaluation of children into adult life. Factors indicating a poor prognosis are persistent proteinuria, hypertension, and an increase in serum creatinine.

Approximately one fifth of all Caucasian children with LN have class I and II LN and a good prognosis, however, class II LN may deteriorate to the higher classes, thus worsening the initial prognosis.

The prognosis of LN class III representing one fifth of all LN patients in childhood depends on the percentage of affected glomeruli, and those patients having fewer than 20% damaged glomeruli may have a 95% 5-year renal survival.

Class IV is the most severe type of LN and is usually found in approximately 40–50% of all children with LN. The prognosis depends substantially on the intensity of

immunosuppressive treatment and 5-year renal survival rates of 80% were achieved by intensified treatment protocols.

Class V lesions can be found in approximately one tenth of children with LN. It has a good prognosis if treated properly and less than 20% of patients will develop a renal failure after 5 years.

Class VI LN is defined by more than 90% of sclerosed glomeruli. The renal prognosis is poor and the kidneys do no longer benefit from immunosuppressive treatment.

In Europe, 0.7% of all children on renal replacement therapy suffered from LN, this percentage was 5% in the US American population. Those patients entering terminal renal failure will require transplantation with or without prior dialysis. Recurrence of LN in the graft was rarely reported. Patients with LN and an APS nephropathy have a high risk to develop a graft thrombosis.

SLE is a systemic disease with wide-ranging effects on physical, psychological, and social well-being. Comprehensive assessment of quality of life and economic costs in addition to disease activity and disabilities is important. New outcome measures are needed to allow for improvement of patient care.

Prevention

Maintenance therapy should aim at preventing relapses and progression of renal dysfunction. It is unclear how soon immunosuppressive treatment can be stopped after a successful induction therapy. Avoidance of intense UV-light exposure should be kept lifelong. In patients lacking a complete response after induction therapy, immunosuppressive agents may have to be given for many years. Maintenance therapy should especially aim at preventing long-term side effects of PRED, CYC, and CSA.

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299 Goodpasture Syndrome

Karyn Yonekawa

Definition

In 1919, EW Goodpasture described an 18-year-old male who initially presented with the clinical manifestations of influenza. His course was atypical however and his post-mortem evaluation discovered evidence of systemic disease with massive alveolar hemorrhage and glomerular cell proliferation. Stanton and Tange, in 1958, summarized the literature to date reporting 12 cases plus 9 of their own with the same clinical presentation. They suggested that the syndrome of pulmonary hemorrhage and glomerulonephritis be given the eponym of Goodpasture's syndrome. The etiology was unknown until the link between glomerulonephritis and anti-glomerular basement membrane (anti-GBM) antibodies was suggested in the years to follow. Although pulmonary-renal syndrome is now recognized to have many causes, the presence of anti-GBM antibodies, pulmonary hemorrhage, and a proliferative glomerulonephritis is the triad that defines Goodpasture's syndrome.

Incidence and Risk Factors

Most references to incidence are describing the occurrence of anti-GBM disease with or without pulmonary involvement, not specifically to the incidence of Goodpasture's syndrome as defined above. Anti-GBM disease is estimated by most to be responsible for less than 2% of all glomerular diseases. There is a bimodal distribution of incidence with respect to age, with the peak during the third decade of life in males and during the sixth in females. Goodpasture's syndrome seems to occur more commonly in males under the age of 50. However, patients of all ages and either sex can be affected. Although there are reports of Goodpasture's syndrome in children as young as 4.5 years, the diagnosis is rare in pediatrics. It is also less frequently reported in Asians and Africans; Caucasians are predominantly affected. The Maori, the indigenous Polynesian people of New Zealand, may be particularly susceptible as well. Familial cases have been reported including identical twins.

Potential risk factors for developing Goodpasture's syndrome include smoking, inhaling cocaine, and being exposed to hydrocarbons such as toluene. Of note, an upper respiratory infection has been reported as preceding the onset of symptoms in 20–60% of cases.

Pathogenesis

Goodpasture's syndrome is an autoimmune disease characterized by the presence of anti-GBM antibodies directed at type IV collagen. The specific targets of most anti-GBM antibodies are epitopes in the non-collagenase domain (NC1) of type IV collagen's α3 chain. However, a significant proportion of patients express antineutrophil cytoplasmic antibodies (ANCA) in addition to anti-GBM. In these patients, the range of autoantibodies is broader, including antibodies to the α1(IV), α4(IV), and α5(IV) NC1. Rarely, antibodies are found against α2(IV) NC1. As the NC1 epitopes are normally sequestered, it is proposed that an oxidant, environmental or endogenous, exposes the hidden antigen.

Kidney injury occurs directly from the antigen–antibody interaction, with secondary mediators inflicting further damage. Complement and leukocytes invade causing cellular proliferation within the glomeruli. Bowman's capsule is often compromised and cells enter into the urinary space resulting in crescent formation.

A similarly destructive capillitis affects the alveolar basement membranes. Neutrophils enter the pulmonary interstitium and disrupt the alveolocapillary barrier allowing blood to extravasate into the alveoli.

Genetics

There is a strong link between human leukocyte antigen (HLA) types and Goodpasture's. HLA DR15 (DRB1-1501 and DRB1-1502 alleles) and DR4 are positively associated with the development of Goodpasture's disease. HLA-DR7 and DR1 may be protective.

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Pathology

Renal biopsy demonstrates a proliferative glomerulonephritis usually with crescent formation. Segmental and global glomerular sclerosis and interstitial fibrosis can be seen if the biopsy is done late in the disease course. Immunofluorescence shows a linear pattern of immunoglobulin G (IgG) staining in the glomerular capillary basement membrane with frequent incorporation of C3 in a more granular or discontinuous distribution (*Fig. 299.1*). Less frequently found are codeposits of IgM, IgA, or C1q. Electron microscopy reveals widening of the basement membrane with some distortion of glomerular capillaries and endothelial cell hypertrophy plus hyperplasia.

Lung biopsy sections on light microscopy reveal red blood cells and hemosiderin laden macrophages. Electron microscopy shows a thickened basement membrane with hyperplasia of type I and type II pneumocytes. Immunofluorescence demonstrates characteristic linear deposits of IgG along alveolar septa.

Clinical Features

Most patients with Goodpasture's syndrome present with pulmonary involvement either preceding or concurrent with glomerulonephritis. The pulmonary manifestations may include cough and dyspnea with hemoptysis ranging from mild to massive hemorrhage. Blood or hemosiderin laden macrophages may be seen in the bronchiole alveolar lavage fluid. Although non-specific, chest radiograph is usually abnormal demonstrating interstitial or alveolar infiltrates. A microcytic anemia may be present even without clinically apparent pulmonary hemorrhage.

Renal manifestations include microscopic hematuria or gross hematuria, proteinuria and decreased renal function. A rapidly progressive glomerulonephritis resulting in renal failure within days or weeks may occur. Alternately, cases of normal creatinine at presentation have been reported.

Systemic complaints of fever, fatigue, weakness, rashes, and arthralgias are more commonly seen in patients with coexistent positive ANCA titers. Hypertension is possible, but a minority have high blood pressure at onset. Anti-GBM antibodies are demonstrated in the serum in most patients. Serum complements and an anti-nuclear antibody titer are usually normal.

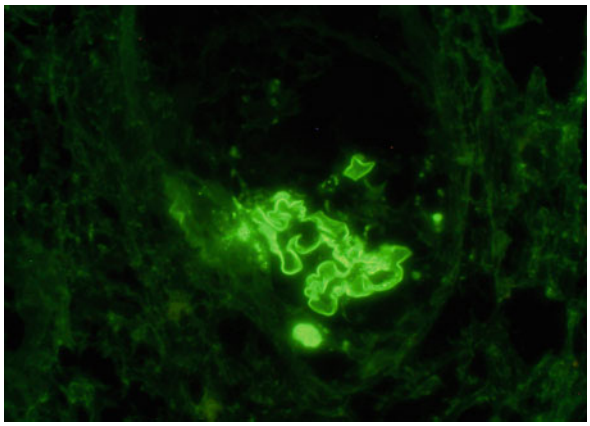

Figure 299.1
Immunofluorescence of a partial glomerulus demonstrates intense linear staining for IgG, characteristic of the renal biopsy findings in Goodpasture's syndrome (Photo courtesy of Laura Finn, MD)

Treatment

High dose corticosteroids appear to be effective in controlling symptoms of alveolar hemorrhage, but as monotherapy, they are not effective in restoring renal function. Plasmapheresis in combination with an immunosuppression regimen, such as prednisone and cyclophosphamide, has been shown to control pulmonary hemorrhage and decrease the progression of renal disease. Immunosuppressive therapy suppresses de novo rebound antibody production while plasmapheresis removes the circulating antibodies. Intensive plasmapheresis may be used for weeks depending on the clinical response. Immunosuppression can continue for up to a year.

Prognosis

Most patients with a significantly elevated creatinine, oliguria, and interstitial fibrosis on renal biopsy progress to end-stage renal disease. Those with a serum creatinine above 8 mg/dL (704 µmol/L) are unlikely to respond to therapy although some have been able to come off dialysis with an aggressive approach commenced early. Transplantation can be safely considered once the patient's anti-GBM antibody titer normalizes for a sustained period. Rarely, Goodpasture's can recur in the transplanted kidney.

In contrast to the renal outcomes, patients are generally left with little pulmonary deficit, regardless of the amount of lung hemorrhage they have experienced.

Additionally, overall morbidity and mortality have improved tremendously compared to the preplasmapheresis era, which was associated with a mortality of 75–90%. Now with early and aggressive therapy, it is 1 year survival that is 75–90%.

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300 Congenital Nephrotic Syndrome

Patrick Niaudet

Congenital nephrotic syndrome is present at birth or appears during the first 3 months of life. Onset of nephrotic syndrome between 3 months and 1 year defines infantile nephrotic syndrome. Most cases have a genetic basis (*Table 300.1*) and a poor outcome. The diagnosis of the disease responsible for the nephrotic syndrome is based on clinical, biological, histological, and genetic studies.

Congenital Nephrotic Syndrome of the Finnish Type (CNF)

This type of congenital nephrotic syndrome initially described by Hallman et al. is more frequent in Finland with an incidence of 1.2 per 10,000 births. It has also been reported in various ethnic groups around the world.

Genetics

The disease is inherited as an autosomal recessive trait. The gene was mapped to chromosome 19q13.1 in 17 Finnish families and other families around the world, and no genetic heterogeneity has been reported. The gene, called *NPHS1*, has a 26 kb size and contains 29 exons. It encodes for a 1,241-residue transmembrane protein of the immunoglobulin superfamily of cell adhesion molecules named "nephrin." Many different mutations of *NPHS1* have been reported. In Finnish patients, the two most common mutations, Fin-major and Fin-minor account for 90% of all patients, as homozygous mutations or compound heterozygous mutations. Fin-major mutation is a two base pair deletion in exon 2 that causes a frameshift and a translation stop in the same exon. Fin-minor is a nonsense mutation in exon 26.

The same gene is responsible for the disease in non-Finnish patients with CNF. The mutation-carrying chromosomes descend from different ancestors without evidence of a founder effect. Beside the two "Finnish mutations," more than 50 other mutations have been detected mainly outside Finland. The mutations including deletions, insertions, nonsense, missense, and splicing mutations are scattered along the entire gene. Interestingly, eight out of nine patients with an atypically mild disease (of which five were in remission) were homozygous for R1160X, a mutation also associated with the classical form suggesting the presence of genetic or other modifying events.

By immunoelectron microscopy, it has been shown that nephrin is specifically located at the slit diaphragm between the podocyte foot processes. Two decades ago, electron microscopic observations revealed a zipper-like structure at the slit diaphragm, with a width between 20 and 50 nm. It has been hypothesized that nephrin molecules extending between two opposite foot processes may interact with each other in the slit diaphragm through homophilic interactions. Since nephrin mutations are associated with massive proteinuria, it can be concluded that this protein is crucial for the maintenance of the glomerular filtration size-selective barrier.

Pathology

The kidneys are enlarged in the initial stages of the disease. Light microscopic examination early in the course of the disease show mild mesangial hypercellularity and increased mesangial matrix in the glomeruli. Irregular microcystic dilatation of proximal tubules is the most striking feature, although this change is not specific. No immune deposits are detected by immunofluorescence studies. Later in the course, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy, and periglomerular fibrosis develop in parallel with glomerular sclerosis.

Clinical Features

Massive proteinuria occurs in utero and the symptoms at birth are related to the protein deficiency. Most infants are born prematurely (35–38 weeks), with a low birth weight for gestational age. The placenta is enlarged, being more

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Table 300.1
Genetic forms of congenital and infantile nephrotic syndrome

Disease	Locus	Transmission	Gene	Protein
Finnish type NS	19q13.1	AR	*NPHS1*	Nephrin
SRNS	1q25-31	AR	*NPHS2*	Podocine
SRNS or DMS	10q23	AR	*NPHS3*	Phospholipase C ε 1
Denys–Drash syndrome or isolated DMS	11p13	AD	*WT1*	WT1 protein
Galloway syndrome	?	AR	?	
Pierson syndrome	3p21	AR	*LAMB2*	Laminine beta 2
Nail–patella syndrome	9q34.1	AD	*LMX1B*	Transcription factor
Mitochondrial cytopathies	mtADN	Maternal	mtADN	Respiratory chain protein

than 25% of the total birth weight. Fetal distress is frequent. The cranial sutures are widely separated due to delayed ossification. Infants often have a small nose and low ears. Flexion deformities of the hips, knees, and elbows are frequent.

Edema is present at birth or appears during the first week of life. The nephrotic syndrome is severe with marked ascites. The proteinuria is highly selective early in the course of the disease and hematuria is uncommon. The urinary protein losses are accompanied by profound hypoalbuminemia and severe hypogammaglobulinemia. As a result, nutritional status and statural growth are poor, and affected infants are highly susceptible to bacterial infections (peritonitis, respiratory infections) and to thromboembolic complications due to the severity of the nephrotic syndrome. Hypothyroidism due to urinary losses of thyroxine-binding protein is also common. Cholesterol and triglycerides are markedly elevated. The blood urea and creatinine concentrations are initially normal.

Renal ultrasonography shows enlarged hyperechogenic kidneys without the normal corticomedullary differentiation.

End-stage renal failure usually occurs between 3 and 8 years of age. However, some *NPHS1* mutations are associated with end-stage renal failure occurring much later in life.

Prenatal Diagnosis

CNF can be diagnosed prenatally as it becomes manifest during early fetal life, beginning at the gestation age of 15–16 weeks. Fetal proteinuria leads to a more than tenfold increase in the amniotic fluid alpha-fetoprotein (AFP) concentration. A parallel, but less important increase in the maternal plasma AFP level is observed. However, positive results may occur in heterozygous carriers leading to false diagnosis.

Genetic linkage and haplotype analyses may diminish the risk of false positive results in informative families. The four major haplotypes, which cover 90% of the CNF alleles in Finland, have been identified, resulting in a test with up to 95% accuracy. When the mutation responsible for the disease has been identified in a child, antenatal diagnosis may be proposed for a sibling following trophoblast biopsy.

Treatment

The nephrotic syndrome in CNF is always resistant to corticosteroids and immunosuppressive drugs. Furthermore, these drugs may be harmful due to the already high susceptibility to infection.

Standard conservative treatment includes daily or every other day albumin infusion, gamma globulin replacement, nutrition with a high-protein, low-salt diet, vitamin and thyroxine substitution, and prevention of infections and thrombotic complications. The diet is often provided by tube feeding. The rate of intercurrent complications remains high and growth and development are usually retarded. Some patients may require bilateral nephrectomy to prevent continued massive protein losses before the development of renal failure.

A possible medical alternative to nephrectomy is the combination of an angiotensin converting enzyme inhibitor and indomethacin therapy, which in some children lead to a decrease in protein excretion and improvement in nutritional status and growth.

If nephrectomy is performed, dialysis is provided until the patient reaches a weight of 8–9 kg. At this stage, renal transplantation can be considered. Nephrotic syndrome

can develop after transplantation. This occurred in 13 of 51 allografts (25%), but only in children with the Fin-major/Fin-major genotype, which is associated with the absence of nephrin in the native kidneys. Anti-nephrin antibodies were observed in most affected patients. Plasma exchanges and oral cyclophosphamide may induce a remission.

Idiopathic Nephrotic Syndrome and *NPHS2* Mutations

Idiopathic nephrosis rarely occurs at birth, more commonly presenting during the first year of life. All the morphological variants of idiopathic nephrotic syndrome seen in older children can occur at this time including minimal change disease, diffuse mesangial proliferation, and focal and segmental glomerular sclerosis.

Steroid-responsiveness with a favorable course can be seen. However, most affected infants are resistant to therapy and many progress to end-stage renal disease. *NPHS2* mutations have been detected in some of these cases. *NPHS2* encodes an integral membrane protein, podocin, which is found exclusively in glomerular podocytes. Some patients with congenital nephrotic syndrome were found to lack *NPHS1* mutations. In two of five such patients, Koziell et al. found homozygous *NPHS2* mutations. Schulteiss et al. found homozygous or compound heterozygous *NPHS2* gene mutations in 11 out of 27 (41%) patients with CNS. Two additional cases had similar findings in terms of mutations in *NPHS2*, but not NPHS1, were also reported in a study of 13 unrelated patients from Japan.

In addition, some patients have both *NPHS1* and *NPHS2* mutations, resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other). These findings demonstrate the genetic heterogeneity of congenital nephrotic syndrome and the absence of genotype/phenotype correlations.

Diffuse Mesangial Sclerosis

Diffuse mesangial sclerosis is the second cause of early nephrotic syndrome progressing to end-stage renal failure. It is seen exclusively in young children. Homozygous truncating mutations of the *PLCE1* gene, which encodes phospholipase C epsilon, was reported in eight children out of 12 children from six families with isolated diffuse mesangial sclerosis. Other patients have a Pierson syndrome, a Denys–Drash syndrome or an isolated form of diffuse mesangial sclerosis.

Clinical Features

Nephrotic syndrome may be present at birth or even detected in utero on the finding of elevated maternal alpha-fetoprotein serum level. The antenatal discovery of large hyperechogenic kidneys mimicking polycystic kidneys may be the first symptom of the disease. Most often, the patients are normal at birth and have a normal birth weight. Nephrotic syndrome develops progressively during the first or the first 2 years of life after a period of increasing proteinuria. Renal insufficiency may be present from the onset of renal symptoms. Various types of extrarenal signs have been reported in a few patients: nystagmus, nystagmus with mental retardation, cataract, mental retardation with microcephaly and myocarditis, severe myopia with cardiac arrhythmia, muscular dystrophy and dysmorphic features of the face.

Pathology

The glomerular lesions are characterized in the early stages by a fibrillar increase in mesangial matrix without mesangial cell proliferation. The capillary walls are lined by hypertrophied podocytes. The fully developed lesion consists of the combination of thickening of the glomerular basement membranes and massive enlargement of mesangial areas, leading to reduction of the capillary lumens. The mesangial sclerosis contracts the glomerular tuft into a sclerotic mass within a dilated urinary space (Fig. 300.1). There is usually a corticomedullary

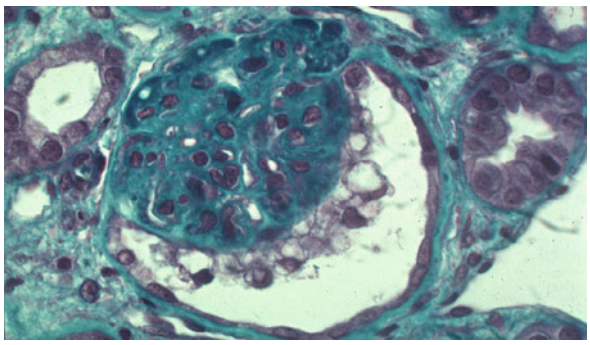

Figure 300.1

gradient of involvement, with the deepest glomeruli being less affected. Tubules are severely damaged, especially in the deeper cortex where they are markedly dilated and often contain hyaline casts.

Electron microscopy reveals hypertrophic mesangial cells surrounded by an abundant mesangial matrix, which often contains collagen fibrils. The podocytes are hypertrophied and contain many vacuoles. There is also irregular effacement of foot processes with focal detachment of the epithelial cell from the glomerular basement membrane.

Immunofluorescence shows mesangial deposits of IgM, C3, and C1q in the least affected glomeruli, while deposits of IgM and C3 outline the periphery of the sclerosed glomeruli. These deposits are probably nonspecific, occurring in areas of previous injury.

Therapy

Nephrotic syndrome secondary to diffuse mesangial sclerosis is always resistant to corticosteroids and immunosuppressive drugs. The nephrotic syndrome is usually less severe than in the CNF. Treatment is supportive and consists of maintenance of electrolyte and water balance and adequate nutrition, prevention and treatment of infectious complications, and management of renal failure. Bilateral nephrectomy is considered at the time of transplantation because of the theoretical risk of developing a Wilms' tumor. It is mandatory if a *WT1* mutation has been identified. Recurrent disease does not develop in the transplant.

Denys–Drash Syndrome

Denys–Drash syndrome (DDS) is characterized by the triad of severe glomerulopathy with diffuse mesangial sclerosis progressing rapidly to end-stage renal disease, male pseudohermaphroditism, and Wilms' tumor.

Genetics

The Denys–Drash syndrome is usually sporadic, and heterozygous germline mutations in the Wilms' tumor predisposing gene are observed in nearly all affected patients.

The *WT1* gene, located on chromosome 11p13, encodes a transcription factor presumed to regulate the expression of a series of target genes through DNA binding. It plays a critical role in kidney and gonad development and, when mutated, in the occurrence of kidney tumor and glomerular nephropathies. The target genes potentially regulated, most often negatively, by *WT1* include genes which code for transcription factors as well as for growth factors or their receptors.

WT1 is strongly expressed during embryofoetal life. In the mature kidney, *WT1* expression persists only in podocytes and epithelial cells of the Bowman's capsule. Disruption of *WT1* gene in mice results in the absence of both kidneys and gonads suggesting a crucial role of *WT1* in the development of the genitourinary tract. *WT1* play a major role in the induction of the ureteric bud, the mesenchymal to epithelial differentiation, the progression of nephrogenesis, and the maintenance of podocyte function.

More than 60 germline mutations have been reported in patients presenting with complete or incomplete DDS. They are de novo mutations, most of them missense mutations located within exons 8 or 9 encoding zinc fingers 2 and 3, respectively. The most common *WT1* lesion is a missense 1180 C to T transition converting the arginine located at the top of the third zinc finger (ZF3) to tryptophan (R394W). These *WT1* mutations change the structural organization of the respective zinc fingers and, consequently, result in loss or alteration of their DNA binding ability as confirmed by in vitro experiments. DDS mutations appear to act in a dominant negative fashion. *WT1* gene mutations, identical to those observed in DDS, have been reported in a few patients with isolated diffuse mesangial sclerosis.

Clinical Features

The nephropathy is usually discovered after several months of life, sometimes at birth. Proteinuria is accompanied by nephrotic syndrome. There is no hematuria. Blood pressure is often elevated. Progression to ESRD before the age of 4 years is the rule. Some patients progress rapidly within a few weeks to end-stage renal failure. There is no recurrence of the original disease after renal transplantation. Diffuse mesangial sclerosis is a constant feature of the Denys–Drash syndrome. It is associated with the two other components of the triad in the complete form, but with only one of the two in the incomplete forms. Wilms' tumor may be the first clinical manifestation of the syndrome. Thus, careful renal ultrasonography should be performed, looking for nephroblastoma, in any patient found to have diffuse mesangial sclerosis. The tumor may be unilateral or bilateral. Male

pseudohermaphroditism, characterized by ambiguous genitalia or female phenotype with dysgenetic testis or streak gonads, is observed in all 46 XY patients. In contrast, 46 XX children appear to have a normal female phenotype.

Pierson Syndrome

Pierson syndrome is an autosomal recessive syndrome with congenital nephrotic syndrome with diffuse mesangial sclerosis and ocular malformations (microcoria, abnormal lens with cataracts, and retinal abnormalities). This disorder is due to mutations in the *LAMB2* gene, which encodes laminin beta 2. Laminin beta 2 is abundantly expressed in the glomerular basement membrane where it plays a role in anchoring and in the development of podocyte foot processes. *LAMB2* knockout mice exhibit congenital nephrotic syndrome in association with anomalies of the retina and neuromuscular junction. *LAMB2* mutations have also been found in patients with congenital nephrotic syndrome and either no or less severe ocular abnormalities.

Galloway Syndrome

The Galloway syndrome is characterized by microcephaly, mental retardation, hiatus hernia, and the nephrotic syndrome of early onset with a mean age at discovery of 3 months. It appears to be transmitted as an autosomal recessive trait. The nephrotic syndrome is usually severe, resistant to steroid therapy, and progresses to end-stage renal failure. Renal biopsy reveals minimal changes or focal and segmental glomerulosclerosis. The underlying defect is not known.

Congenital Nephrotic Syndrome Secondary to Infections

Congenital syphilis can cause membranous nephropathy. Histological examination often shows a mixed pattern with membranous nephropathy and mesangial proliferation. Penicillin treatment leads to the resolution of the syphilis and the renal abnormalities.

The nephrotic syndrome may be induced by congenital toxoplasmosis. Proteinuria may be present at birth or may develop during the first 3 months, in association with ocular or neurologic symptoms. Histological examination often shows mesangial proliferation with or without focal glomerulosclerosis. Treatment of toxoplasmosis or steroid therapy usually leads to remission of the proteinuria.

Congenital or infantile nephrotic syndrome has been reported in association with cytomegalovirus, rubeola virus, human immunodeficiency virus, and mercury intoxication.

Other Causes of Congenital Nephrotic Syndrome

Congenital nephrotic syndrome has been reported in association with type I carbohydrate-deficient glycoprotein syndrome in a neonate with neurologic abnormalities and diffuse mesangial sclerosis. It has also been reported in association with infantile sialic acid storage disease and more recently in association with mitochondrial respiratory chain deficiency.

Antenatal nephrotic syndrome due to membranous nephropathy has been reported in infants whose mothers have mutations in the metallomembrane endopeptidase gene, which encodes the podocyte protein neutral endopeptidase (NEP). During pregnancy, the absence of NEP protein induces an alloimmunisation against NEP presented by fetal cells, resulting in a fetal podocyte injury which may lead to chronic renal failure.

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301 Nephrotic Syndrome in Children

Patrick Niaudet

Nephrotic syndrome is defined by a proteinuria higher than 50 mg/kgBW/day and hypoalbuminemia <30 g/l. A nephrotic syndrome is always secondary to a glomerular disease.

Different mechanisms have been described in the nephrotic syndrome: circulating nonimmune factors in idiopathic nephrotic syndrome, circulating immune factors in several types of glomerulonephritis, mutations in podocyte, or slit diaphragm proteins in inherited forms of nephrotic syndrome.

Proteinuria in glomerular disease is due to increased filtration of macromolecules (such as albumin) across the glomerular capillary wall. The latter consists of three components: the fenestrated endothelial cell, the glomerular basement membrane (GBM), and the epithelial cell foot processes. The pores between the foot processes are closed by a thin membrane called the slit diaphragm. The filtration of macromolecules across the glomerular capillary wall is normally restricted by charge-selectivity and size-selectivity. The GBM have a net negative charge which creates a barrier to the filtration of anions such as albumin. In comparison, circulating IgG is predominantly neutral or cationic and its filtration is not limited by charge.

In minimal change disease, the most common cause of nephrotic syndrome in children, there is a loss of anionic charge without structural damage by light microscopy. However, electron microscopy demonstrates epithelial foot processes effacement. In glomerular diseases other than idiopathic nephrotic syndrome, structural injury seen by light microscopy results in an increase in the number of large pores in the GBM. This structural damage allows movement of normally restricted proteins of varying sizes (including large neutral proteins, such as IgG) across the filtration barrier.

Clinical Features

The nephrotic syndrome is responsible for edema which increases gradually and becomes detectable when fluid retention exceeds 3–5% of body weight. It is often initially apparent around the eyes and misdiagnosed as an allergy. Edema is gravity dependent. During the day, periorbital edema decreases while it localizes to the lower extremities. In the reclining position, it localizes to the back. It is white, soft, and pitting. Edema of the scotum and penis or labiae may also be observed. Anasarca may develop. The abdomen may bulge with umbilical or inguinal hernias. When ascitis build up rapidly, the child complains of abdominal pain and malaise. Abdominal pain may also result from severe hypovolemia, peritonitis, pancreatitis, thrombosis, or steroid-induced gastritis. Blood pressure is often normal, but may be elevated depending on the underlying disease. Shock is not unusual after sudden fall of plasma albumin as observed in idiopathic nephrotic syndrome.

The nephrotic syndrome may be discovered during routine urine analysis or during the evaluation of a patient with hematuria. It may also be revealed by a complication such as peritonitis, deep vein or arterial thrombosis, or pulmonary embolism.

Laboratory Findings

Urine Analysis

Nephrotic range proteinuria is defined as urinary protein excretion greater than 50 mg/kg/day or 40 mg/m^2/h. It is higher at onset and decreases as plasma albumin concentration falls. In young children, it may be difficult to obtain a 24-h urine collection, and urinary protein to creatinine ratio or albumin to creatinine ratio in untimed urine specimens is useful. For these two indices, the nephrotic range is 200–400 mg/mmol. The selectivity of proteinuria may be appreciated by polyacrylamide gel electrophoresis or by the evaluation of the Cameron index that is the ratio of IgG to transferrin clearances. A favorable index would be below 0.05 and 0.10; a poor index is above 0.15 or 0.20. Proteinuria is most often highly selective, consisting of albumin and lower-molecular-weight proteins in case of minimal change disease whereas a poor Cameron index is often associated with more severe histologic lesions. However, there is a considerable overlap in results, and the test has limited value.

The urine sediment often contains fat bodies. Hyaline casts are also usually found in patients with massive

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proteinuria, but granular casts are not present unless there is associated acute renal failure and acute tubular necrosis. Urinary sodium is low, 1–2 mmol/day, resulting in sodium retention and edema

Blood

Plasma protein levels are markedly reduced, less than 50 g/l, due to hypoalbuminemia. Plasma albumin level is lower than 30 g/l and may be less than 10 g/l. Electrophoresis shows a typical pattern with low albumin, increased α2-globulins, and, to a lesser extent, β-globulins, whereas the level of γ-globulins depends on the cause of the nephrotic syndrome. For example, IgG levels are markedly reduced in minimal change disease and elevated in systemic lupus erythematosus. Lipid abnormalities include high levels of cholesterol, triglyceride, and lipoproteins. The result is that prolonged nephrotic syndrome contributes to the development of atherosclerosis and possibly to theprogression of renal damage. Total cholesterol and low-density lipoprotein cholesterol are elevated, whereas high-density lipoprotein cholesterol remains unchanged or low, particularly high-density lipoprotein 2, leading to an increased low-density lipoprotein to high-density lipoprotein cholesterol ratio. Patients with severe hypoalbuminemia have increased triglycerides and very-low-density lipoprotein. Apoproteins and apolipoproteins B, CII, and CIII are also elevated. The levels of lipoprotein (a) are elevated in nephrotic patients.

Serum sodium is often reduced due in part to hyperlipemia and in part to the dilution from renal retention of water due to hypovolemia and inappropriate antidiuretic hormone secretion. Hyperkalemia may be observed in cases of renal insufficiency. Hypocalcemia is related to hypoalbuminemia, and the level of ionized calcium is usually normal.

Hemoglobin levels and hematocrit are increased in patients with plasma volume contraction. Thrombocytosis is common and may reach 5×10^8/l or 10^9/l. Fibrinogen and factors V, VII, VIII, and X are increased, whereas antithrombin III, the heparin cofactor, and factors XI and XII are decreased. These abnormalities contribute to a hypercoagulable state.

Complications

Acute renal failure: Some patients with idiopathic nephrotic syndrome have a reduction of the glomerular filtration rate (GFR) attributed to hypovolemia, with complete return to normal after remission. A reduced GFR may be found despite normal effective plasma flow. This reduction is transitory, with a rapid return to normal after remission.

Renal failure may be secondary to bilateral renal vein thrombosis that can be diagnosed by sonography. Acute renal failure has also been reported with interstitial nephritis. Skin rash and eosinophilia are suggestive of this diagnosis, which is often associated with furosemide or other medication

Acute renal failure is usually reversible, often with intravenous albumin and high-dose furosemide-induced diuresis.

Renal failure may be related to severe histologic lesions in patients with primary or secondary glomerulonephritis.

Infections: Bacterial infections are frequent in nephrotic children. Sepsis may occur at the onset of the disease. The most common infection is peritonitis, often with *S. pneumoniae*. Other organisms may be responsible: *Escherichia coli*, *Streptococcus bovis*, *Haemophilus influenzae*, and other Gram-negative organisms. Apart from peritonitis, children may develop meningitis, pneumonitis, or cellulitis. Viral infections may be observed in patients receiving corticosteroids or immunosuppressive agents. Varicella is often observed in young children and may be life threatening if acyclovir therapy is not promptly initiated.

Thrombosis: Nephrotic patients are at risk of developing thromboembolic complications. Several factors contribute to this increased risk of thrombosis: a hypercoagulable state, hypovolemia, immobilization, and infection. The incidence of thromboembolic complications in nephrotic children is reported to be approximately 3%. However, this percentage may underestimate the true incidence. In one series, systematic evaluation by ventilation-perfusion scans showed defects consistent with pulmonary embolism in 28% of all patients with steroid-dependent minimal change disease. Pulmonary embolism should be suspected in cases with pulmonary or cardiovascular symptoms and may be confirmed by angiography or angioscintigraphy. Renal vein thrombosis should be suspected in patients with nephrotic syndrome who develop sudden macroscopic hematuria or acute renal failure. In such cases, Doppler ultrasonography shows an increase in kidney size and the absence of blood flow in the renal vein. Thrombosis may also affect the arteries (e.g., pulmonary arteries) or other deep veins (cerebral veins).

Hypovolemia: Hypovolemia is common and typically observed at onset of idiopathic nephrotic syndrome or early during a relapse. Sepsis, diarrhea, or diuretics may precipitate hypovolemia. Hypovolemic children often

have abdominal pain, low blood pressure, and cold extremities. Hemoconcentration with a raised hematocrit accompanies hypovolemia.

Symptomatic Treatment

Diet: Diet includes a protein intake of 130–140% of the normal daily allowance according to statural age. Salt restriction is necessary for the prevention and treatment of edema. A very-low-salt diet is necessary in case of edema. Fluid restriction is recommended for moderate to severe hyponatremia (plasma sodium concentration <125 mmol/l). A reduction of saturated fat is advisable. Carbohydrates are given preferentially as starch or dextrin-maltose, avoiding sucrose, which increases lipid disturbances.

Hypovolemia: Hypovolemia, a consequence of rapid loss of serum albumin may be aggravated by diuretics. When symptomatic, this complication requires emergency treatment by rapid infusion of plasma (20 ml/kg) or albumin 20% (1 g/kg) administrated with monitoring of heart rate, respiratory rate, and blood pressure.

Diuretics: Diuretics should only be used in cases of severe edema, after hypovolemia has been corrected. Patients with anasarca may be treated with furosemide (1–2 mg/kg) or, if necessary, furosemide and salt-poor albumin (1 g/kg infused over 4 h) to increase the rate of diuretic delivery to the kidney. This approach is immediately effective, but not long lasting. Moreover, respiratory distress with congestive heart failure has been observed in some patients. Spironolactone (5–10 mg/kg) may be prescribed, provided serum creatinine is normal. Amiloride may also be used in combination with furosemide. Diuretics may induce intravascular volume depletion with a risk of thromboemboli and of acute renal failure. Refractory edema with serous effusions may require drainage of ascites and/or pleural effusions. Head-out immersion has been reported to be helpful in these cases.

Thromboemboli: Patients with severe hypoalbuminemia are at risk for thromboembolic complications. Prevention includes mobilization, avoiding hemoconcentration and treating early sepsis or volume depletion. Prophylactic warfarin may be given to patients with a plasma albumin concentration below 20 g/l, a fibrinogen level >6 g/l, or an antithrombin III level <70% of normal. Patients at risk may be treated with low-dose aspirin and dipyridamole, although no controlled trials have been performed to demonstrate their efficacy for preventing thrombosis.

Heparin is given initially if thrombosis occurs, alone or with thrombolytic agents. The heparin dose necessary to obtain a therapeutic effect is often greater than normally, due to decreased antithrombin III levels.

Antihypertensive drugs: Hypertension is treated, using a β-blocker or a calcium channel blocker during acute episodes. In cases of permanent hypertension, an angiotensin converting enzyme inhibitor or an inhibitor of angiotensin II receptor is preferred.

Infections and immunizations: Prophylaxis of *S pneumoniæ* with oral penicillin is often prescribed to children during initial corticosteroid treatment. Vaccination with the conjugated pneumococcal vaccine (7vPCV) is recommended. In cases of peritonitis, antibiotics against both *S pneumoniæ* and Gram-negative organisms are started after peritoneal fluid sampling. Varicella is a serious disease in patients receiving immunosuppressive treatment or daily corticosteroids. Varicella immunity status should therefore be assessed. In case of exposure, early prevention by acyclovir must be instituted. Immunization with the varicella vaccine is effective and safe in children on low-dose alternate day steroid therapy.

Reduction of proteinuria: There is evidence that proteinuria per se is toxic for the tubules and can favor the progression of renal fibrosis. Therefore, reduction of proteinuria should be a goal in patients with persistent proteinuria. The best results are obtained with ACE inhibitors and AT1 receptor antagonists, alone or in combination. Several studies have demonstrated the renoprotective effects of ACE inhibitors in proteinuric patients, suggesting that this strategy is appropriate in patients with prolonged nephrotic syndrome.

Causes of Nephrotic Syndrome in Children

Idiopathic Nephrotic Syndrome

It is the main cause of nephrotic syndrome in children (INS) representing more than 90% of cases before age 10 years and 50% after 10 years. INS is defined by the association of a nephrotic syndrome with minimal glomerular changes (Fig 301.1) or nonspecific histological lesions such as focal and segmental glomerular sclerosis or diffuse mesangial proliferation. Most often, no immunoglobulin or complement deposit is seen on immunofluorescent examination. However, IgM deposits may be observed and the clinical significance of such deposits is controversial. Electron microscopy shows an effacement of the podocyte foot processes.

Most patients with minimal change lesions respond to corticosteroids with complete remission. Conversely,

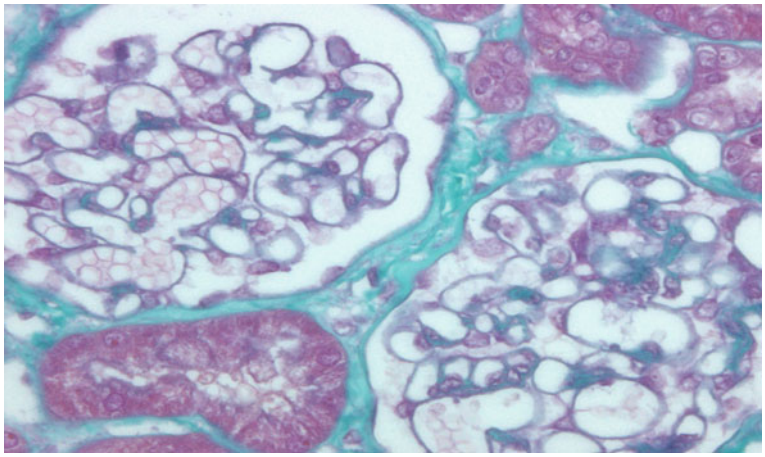

Figure 301.1

patients in whom the renal biopsy shows FSGS or diffuse mesangial proliferation often do not respond to corticosteroids. This is the reason why several authors believe that minimal change disease is a distinct entity, and FSGS, diffuse mesangial proliferation, and IgM nephropathy are also distinct entities. However, serial renal biopsies show that some patients with minimal changes on initial biopsy may later develop FSGS. Furthermore, some patients with FSGS respond to corticosteroids and have a favorable long-term outcome. Experience has shown that response to steroid therapy carries a greater prognostic weight than the histological features on initial biopsy. Therefore, two types of INS are described according to the response to corticosteroids; steroid sensitive INS in which proteinuria rapidly resolves and steroid-resistant INS in which proteinuria persists despite corticosteroids.

Initial Treatment

Steroid therapy is started when the diagnosis of INS is most likely in a child older than 1 year and younger than 11 years of age, without hypertension, gross hematuria or extra-renal symptoms, and normal complement levels. In some cases, the treatment is started after a renal biopsy has been performed. Prednisone remains the reference drug. Prednisolone has the advantage of being soluble in water, making treatment easier in young children. The ISKDC regimen consists of prednisone, 60 mg/m^2/day with a maximum of 80 mg/day, in divided doses for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks. A response occurs in most cases within 10–15 days. Approximately 90% of responders enter in remission within 4 weeks after starting steroids, whereas less than 10% go into remission after 2–4 more weeks of a daily regimen or three to four pulses of methylprednisolone (1 g/1.73 m^2). This latter regimen seems to be associated with fewer side effects than prolongation of daily high-dose steroids.

The number of children with frequent relapses is decreased with a longer course of prednisone. A longer duration is more important than the cumulative dose of prednisone in reducing the risk of relapse. This relative risk decreases by 0.133 (13%) for every additional month of treatment up to 7 months.

Steroid-responsive INS

In the majority of children, INS is steroid responsive. Approximately 30% of them have only one attack and are definitively cured after a single course of steroids. Ten to 20% of patients experience relapses several months after stopping treatment and most of them are cured after three to four relapses which respond to a standard course of steroids. The remaining 50–60% relapse as soon as steroid therapy is stopped or when the dosage is decreased. These steroid-dependent patients often raise difficult therapeutic problems. As long as the nephrotic syndrome responds to therapy, there is very little risk of progression to chronic renal failure.

Treatment of Relapses

Fifty to sixty percent of children experience relapses as soon as steroid therapy is stopped or when dosage is

decreased. Steroid-dependent patients may be treated with repeated courses of prednisone. Another option consists of treating relapses with daily prednisone, 40–60 mg/m^2, until proteinuria has disappeared for 4–5 days. Thereafter, prednisone is switched to alternate days and the dosage is tapered to 15–20 mg/m^2 every other day, according to the steroid threshold. Treatment is then continued for 12–18 months. This regimen is associated with less steroid side effects as the cumulative dosage is lower. The risk of relapse during upper respiratory tract infections is decreased when steroid therapy is given daily for 5–7 days rather than on alternate days.

Alternative Treatments

An alternative treatment is indicated in children who develop severe side effects of steroid therapy such as statural growth impairment, in children at risk of toxicity (diabetes or during puberty), in children with severe relapses accompanied by thrombotic complications or severe hypovolemia, and in those with poor compliance.

Levamisole at a dose of 2.5 mg/kg every other day reduces the risk of relapse in steroid-dependent patients. However, the beneficial effect of levamisole is not sustained after stopping treatment. Side effects occasionally include neutropenia, agranulocytosis, vomiting, cutaneous rash, vasculitis, and neurological symptoms including insomnia, hyperactivity, and seizure.

Alkylating agents such as cyclophosphamide and chlorambucil can induce long-lasting remissions in patients who are frequent relapsers or steroid dependent. Data from the literature show a remission rate of 67–93% at 1 year and 36–66% at 5 years following a course of cyclophosphamide. The therapeutic effect is related to the duration of treatment. The response to cyclophosphamide is also related to the pattern of response to steroids. The duration of remission is higher in frequent relapsers as compared to steroid-dependent patients. Cyclophosphamide is given at a dose of 2 mg/kg/day (cumulative dose 168 mg) to patients with steroid dependency who have evidence of steroid toxicity.

Remissions may also be obtained with chlorambucil. The recommended dosage is 0.2 mg/kgBW for 2 months.

Side effects of alkylating agents limit their use. Bone marrow toxicity requires regular blood cell counts. The treatment should also be discontinued in case of infection. The risks of varicella should be explained to the parents in order to rapidly start acyclovir treatment. Alopecia and hemorrhagic cystitis rarely occurs with the dosage used in these patients. Gonadal toxicity is well established and the risk is greater in boys than in girls. The gonadal toxicity threshold is between 200 and 300 mg/kgBW for cyclophosphamide and 8–10 mg/kgBW for chlorambucil.

Mycophenolate mofetil (MMF) treatment has a beneficial effect in children with steroid-dependent INS and allows to decrease or stop steroid therapy in 40–75% of children. However, relapses are nearly constant after cessation of treatment. Doses of 450–600 mg/m^2 day in two divided doses are usually given. Side effects including gastrointestinal disturbances (abdominal pain, diarrhea) and hematologic abnormalities are rare. Many authors now recommend the use of MMF rather than alkylating agents in children with steroid-dependent INS who suffer from side effects of steroid therapy.

Cyclosporine is effective in inducing or maintaining remission in 85% of patients with frequently relapsing or steroid-dependent NS, thereby allowing withdrawal of prednisone. The dose should preferably not exceed 5 mg/kg/day in two oral doses. Most patients relapse within the few months following cessation of treatment. Thus, cyclosporine may have to be administered for long periods of time, exposing patients to its potential nephrotoxicity. As a result, the plasma creatinine concentration should be monitored regularly. Serial renal biopsies after 18 months of therapy can demonstrate histologic lesions of nephrotoxicity without clinical evidence of renal function impairment. Other side effects include hypertension, hyperkalemia, hypertrichosis, gum hypertrophy, and hypomagnesemia.

Rituximab has been reported to be effective in patients with severe steroid-dependent nephrotic syndrome. In a multicenter series, 22 children with severe steroid-dependent nephrotic syndrome or steroid-resistant but cyclosporin-sensitive INS were treated with two to four infusions of rituximab. Rituximab was effective in all patients when administered during a proteinuria-free period in association with other immunosuppressive agents. Remission was induced in three of the seven proteinuric patients. One or more immunosuppressive treatments could be withdrawn in 19 patients (85%), with no relapse. When relapses occurred, they were always associated with an increase in CD19 cell count. Adverse effects were observed in 45% of cases, but most of them were mild and transient.

Steroid-resistant INS

It represents 10% of cases of INS and is a heterogeneous entity as different diseases are included under the same denomination.

During the recent years, there have been several reports on the molecular basis of familial cases of FSGS.

Mutations in several genes such as NPHS2, NPHS1, or WT1 may be responsible for steroid-resistant nephrotic syndrome with FSGS (Table 301.1). Podocin mutations are found in more than 40% of autosomal recessive steroid-resistant INS and 10–20% cases of sporadic steroid-resistant INS. Because immunosuppressive therapy has not been shown to be effective in treating children with SRNS due to NPHS2, NPHS1, or WTI mutations, identifying these patients can avoid unnecessary exposure to these medications and their side effects. Thus, screening for such mutations should be performed in those with a familial history of SRNS and children with steroid-resistant disease

The optimal approach to the treatment of steroid-resistant INS not due to a genetic defect is uncertain. A treatment with cyclosporine and prednisone may be given provided the glomerular filtration rate is normal. There is evidence that tacrolimus is effective in a significant proportion of patients with steroid-resistant INS. A course of methylprednisolone pulses with alkylating agents may be another option. There is no evidence that mycophenolate mofetil is beneficial to these patients.

The long-term prognosis of steroid-resistant INS is dominated by the risk of progression to end-stage renal failure. Renal survival rate in Caucasian children is approximately 50% at 10 years. Progression to ESRF has been reported to be more frequent and more rapid in patients with African or Hispanic descent when compared to Whites.

About 30% of patients with steroid-resistant INS who progress to renal insufficiency present a recurrence of proteinuria after renal transplantation. Several risk factors for recurrence have been identified: onset of disease after 6 years of age, a rapid progression to renal failure, diffuse mesangial proliferation on initial renal biopsy, and a recurrence on a first graft.

Primary Glomerulonephritis

Membranous glomerulonephritis (MGN) is characterized by a diffuse thickening of the capillary walls due to immune deposits on the epithelial side of the GBM. By immunofluorescence, these deposits are granular and peripheral. They are stained mainly with anti-IgG serum. Patients with MGN develop proteinuria which may be asymptomatic and responsible for a nephrotic syndrome. Microscopic hematuria is frequent. Hypertension and renal insufficiency are exceptional early in the course of the disease. The prognosis is often good with a disappearance of proteinuria within a few months or years. Less than 10% of cases progress to renal failure. MGN may be secondary to systemic lupus erythematosus, an infection (hepatitis B, congenital syphilis), or to the administration of drugs such as penicillamin or gold salts. The treatment depends on the underlying disease and the severity of the clinical manifestations.

Membranoproliferative glomerulonephritis (MPGN) is characterized by mesangial hypercellularity, an increase of mesangial matrix, and a thickening of the capillary walls secondary to subendothelial extension of the mesangium. MPGN have been subdivided in three types according to morphological features. Type I MPGN, with subendothelial deposits, the most frequent, is associated with classical complement pathway activation. Type II MPGN or dense deposit disease is associated with an alternate complement pathway activation and intramembranous dense deposits and represent 10–20%

Table 301.1
Genetic forms of nephrotic syndrome with FSGS

Disease	Locus	Transmission	Gene	Protein
SRNS + FSGS	1q25–31	AR	*NPHS2*	Podocine
SRNS + FSGS or DMS	10q23	AR	*NPHS3*	Phospholipase C ε 1
CNS ou SRNS	19q13.1	AR	*NPHS1*	Nephrin
Susceptibility to FSGS	2q34–36	AR	*CD2AP*	CD2 associated protein
SRNS + FSGS	9q13	AD	*ACTN4*	α-Actinine
SRNS + FSGS	11q	AD	*TRPC6*	Calcium channel
Schimke syndrome	6p12	AR	*SMARCAL1*	Regulator of chromatin
Frasier syndrome	11p13	AD	*WT1*	WT1 protein
Mitochondrial cytopathies	mtADN	Maternal	mtADN	Respiratory chain protein

of cases. Type III MPGN, observed in less than 5% of cases, is characterized by subenthothelial and subepithelial deposits and by complex alterations of the GBM. More than 50% of patients have a low concentration of C3 due to the activation of the C3 convertase by autoantibodies, called nephritic factors (NeF). The C3NeF of the amplification loop is an IgG autoantibody which reacts with activated factor B of the C3 convertase and is observed in dense deposit disease with or without partial lipodystrophy. The C3NeF of the terminal pathway is observed in type III MPGN and also in some patients with Type I MPGN. Patients may present with acute nephritic syndrome, asymptomatic proteinuria, or nephrotic syndrome. Hematuria, macroscopic or microscopic, is most often present. MPGN may occur in patients with HBV or HCV infection. In the long term, more than 50% of patients progress to renal failure. Some children with MPGN respond to steroid therapy.

IgA nephropathy (Berger disease) is a frequent glomerular disease which affects boys more often than girls. The age at discovery is variable, but more often between 7 and 13 years. Macroscopic hematuria is the presenting symptom in 75% of cases. Recurrent episodes of macroscopic hematuria occur often within 2 days following an episode of upper respiratory tract infection. In other children, the disease is discovered at routine urine analysis because of microscopic hematuria and proteinuria. Blood pressure is usually normal. Serum IgA levels are increased in 50% of cases. Renal biopsy shows moderate histological lesions with mesangial deposits and mesangial hypercellularity, and less frequently segmental and focal glomerulonephritis (*Fig 301.2*) or endo-extracapillary glomerulonephritis. Mesangial deposits stains mainly for IgA, and less for IgG and C3. The presence of permanent proteinuria with or without nephrotic syndrome is a factor of poor prognosis with a possible progression to renal failure which occurs in 10% of cases after 10–15 years.

Anti-GBM nephritis is rare in children. It may be isolated or present with pulmonary hemorrhage (Goodpasture syndrome). Renal symptoms consist of hematuria, proteinuria with nephrotic syndrome, and renal failure. The diagnosis is confirmed by the presence of circulating IgG antibodies to the GBM by ELISA assay or by indirect immunofluorescence on normal kidney. Renal biopsy shows crescentis glomerulonephritis with linear deposits of IgG along the GBM by immunofluorescence. A prompt diagnosis is mandatory as only an early treatment with steroids, cyclophosphamide, and plasma exchanges may prevent the progression to end-stage renal failure.

Renal vasculitis the most frequent type of glomerulonepritis is microscopic polyangiitis involving glomerular capillaries. ANCA are present in most cases and are directed against myeloperoxydase (P-ANCA). In children, Wegener's granulomatosis is rare. Upper-respiratory symptoms are frequent and ANCA are directed against proteinase 3 (C-ANCA). Renal biopsy shows

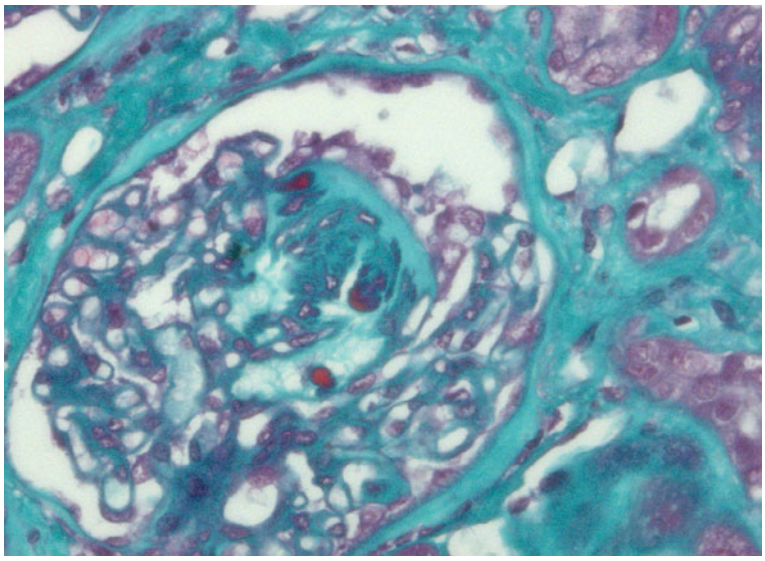

Figure 301.2

necrotizing glomerulonephritis with extracapillary proliferation without immune deposits. Corticosteroids and cyclophosphamide have greatly improved the prognosis.

Secondary Glomerulonephritis

Acute post-infectious glomerulonephritis occurs most often 10–20 days after a streptococcal infection. The child presents with an acute nephritic syndrome including hematuria, proteinuria, hypertension, and renal failure. Some patients develop nephrotic syndrome. Complement abnormalities include low CH50 and low C3. Renal biopsy, when performed, shows proliferative glomerulonephritis with infiltrating neutrophils and subepithelial humps. In severe cases, cellular crescents develop. C3 deposits are present in the mesangium and along the capillary walls. Most patients recover normal renal function within 3 weeks with supportive therapy. Steroid-pulse therapy is proposed to patients with rapidly progressive glomerulonephritis and extensive crescent formation.

Schönlein-Henoch purpura (SHP) nephritis is observed in 30–50% of children with SHP and manifests most often during the first 3 months. Hematuria, almost constant, may be accompanied by proteinuria and nephrotic syndrome. Renal biopsy shows IgA deposits and variable mesangial and extracapillary cell proliferation. Patients with nephrotic syndrome often have severe histological lesions with crescentic glomerulonephritis and a risk of progression to end-stage renal failure. In such cases, steroid therapy may be proposed.

Systemic lupus erythematosus renal disease is frequent in children with SLE. Nephrotic syndrome is observed in patients with more severe renal involvement, often in association with acute renal failure. Renal biopsy may show diffuse proliferative glomerulonephritis or membranous nephropathy with immunoglobulin and complement deposits. The presence of anti-DNA antibodies is highly suggestive of SLE and low C3 concentration is suggestive of an active disease.

Bacterial infections infective endocarditis may be associated with glomerulonephritis. The clinical manifestations are similar to those observed in acute glomerulonephritis. Nephrotic syndrome is unusual. Nephrotic syndrome is more frequent in shunt nephritis secondary to infected ventriculoatrial shunt. C3 and C4 levels are reduced in both conditions, and renal biopsy may show a pattern of membranoproliferative glomerulonephritis or acute post-streptococcal glomerulonephritis.

Other Causes

Amyloidosis

In children, amyloidosis is most often secondary to chronic inflammatory diseases (chronic juvenile arthritis, Crohn disease), to prolonged infections (tuberculosis, osteomyelitis, bronchestasis), to cystic fibrosis or familial Mediterranean fever. Amyloid deposits are present in the mesangium, the capillary walls, and the tubular basement membranes. In case of glomerular deposits, patients often present with proteinuria and nephrotic syndrome. The treatment of the cause, if possible, may prevent the progression to renal failure.

Alport Syndrome

Alport syndrome is an inherited renal disorder characterized by a progressive hematuric nephritis with ultrastructural changes of the glomerular basal membrane and sensorineural hearing loss. Mutations in the *COL4A5* gene are responsible for the more frequent X-linked form of the disease. All affected males progress to renal failure, whereas in most female patients, the course is considered to be benign. Mutations in the *COL4A3* or *COL4A4* genes are responsible for an autosomal recessive form of the disease observed in approximately 15% of patients. The disease is as severe in male as in female. The presence of massive proteinuria with nephrotic syndrome is suggestive of a poor prognosis and is associated with a progression to ESRD.

Nail–Patella Syndrome

The nail–patella syndrome or osteo-onychodysplasia is an autosomal dominant disorder characterized by hypoplastic or absent patella, dystrophic fingernails and toenails, and dysplasia of elbows and iliac horns. Renal symptoms are present in approximately 50% of patients. The most frequent symptoms are proteinuria, sometimes with a nephrotic syndrome, and hematuria. End-stage renal disease develops in approximately 30% of cases. The abnormal gene, located at the distal end of the long arm of chromosome 9, encodes a transcription factor of the LIM-homeodomain type named *LMX1B*, which plays an important role for limb development in vertebrates.

Hemolytic Uremic Syndrome

Hemolytic and uremic syndrome is characterized by the association of hemolytic anemia, thrombopenia, and renal disease secondary to thrombotic microangiopathy. The typical form is the most frequent in children occurring after an episode of diarrhea caused by *Escherichia coli*. Other germs may be responsible for HUS such as *Shigella dysenteriae* or *Streptococcus pneumoniae*. Children present with acute renal failure which is reversible in most cases. Atypical HUS is less frequent but of poorer prognosis. The patients may develop nephrotic syndrome and renal failure. Atypical HUS may be associated with mutations in the genes for complement proteins including C3, factors H, B, and I, and CD46. It is estimated that approximately 50 percent of cases of atypical HUS result from mutations in these genes. Atypical HUS may also be associated with von Willebrand factor-cleaving protease deficiency, congenital intracellular defects of vitamine B12 metabolism, or may be of unknown origin. Familial forms are frequent.

Sickle Cell Disease

Proteinuria with nephrotic syndrome and sometimes renal failure may develop in patients with sickle cell disease. Renal biopsy shows glomerular enlargement and focal and segmental glomerular sclerosis and less often a picture of membranoproliferative glomerulonephritis with IgG and C3 deposits.

Renal Hypoplasia and or Dysplasia

Children with renal hypoplasia or renal dysplasia usually do not have signs of glomerular involvement. The occurrence of proteinuria is often related to lesions of focal and segmental glomerular sclerosis secondary to severe nephron reduction and is observed in association to chronic renal failure.

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302 Juvenile Nephronophthisis

Abdelaziz Y. Elzouki · Laurel Steinmetz

Renal cysts are derived from tubular epithelium that proliferates abnormally to generate the wall delineating the cyst; fully developed renal cysts are, in fact, tumor masses that are filled with liquid rather than with cells. Cysts may occur in cortex, medulla, or both regions. Hereditary renal cystic disorders are a diverse group of clinical categories having in common only the presence of cystic structures in renal parenchyma. The following two chapters focus on the major hereditary renal cystic diseases that have clinical importance in the pediatric population, including juvenile nephronophthisis (NPH), medullary cystic kidney disease (MCD), autosomal recessive polycystic kidney disease (ARPKD), and autosomal dominant polycystic kidney disease (ADPKD).

Juvenile Nephronophthisis

Juvenile NPH is responsible for 10–20% of chronic renal failure in children and is the most common genetic cause of end-stage renal disease in children. The onset of NPH is insidious, and the condition is usually not clinically diagnosed until the patient is in advanced renal failure. MCD is clinically and histologically indistinguishable from NPH; nevertheless, the two forms can be distinguished on the basis of inheritance and evolution – NPH is an autosomal recessive disorder while MCD is autosomal dominant disorder, in NPH end-stage renal failure is encountered during early adolescence while it occurs after fourth decade of life in MCD.

Epidemiology

NPH affects girls and boys equally.The incidence is approximately 0.13 for 10,000 live births in Finland, whereas in Canada, it is 1 per 50,000 live births and in United States 9 per 8.3 million. The disorder has been reported worldwide.

Genetics

These disorders include juvenile nephronophthisis, Senior-Loken syndrome, Joubert syndrome, Meckel-Gruber syndrome, and medullary cystic kidney disease. While renal imaging and histology are similar, there is a diverse phenotypic range in both renal disease progression and extrarenal manifestations. Several different gene mutations have been implicated in this heterogeneous group of disorders. Amongst those are NPHP1-9 and AHI1 in nephronophthisis (*Table 302.1*) and MCDK1-2 in MCDK. NPHP1 was the first gene mutation identified and the most prevalent. NPHP1 homozygous deletion is present in 20–40% of nephronophthisis cases. The other mutations are much less common accounting for less than 2% of the cases individually. While most of these mutations have been associated with retinitis pigmentosa, NPHP5 and 6 are often associated with more severe retinal disease such as Leber's congenital amaurosis.

Etiology

Through recognition of these genes and others implicated in cystic kidney diseases, a new unifying theory of renal cystogenesis has emerged. This theory states that proteins implicated in renal cyst development are expressed in the centrosome, basal body, or primary cilia. Cilia are hair-like structures found on almost every type of vertebrate cell explaining the extrarenal involvement associated with these disorders. The proteins involved in ciliary function are highly conserved amongst organisms and many of the gene products implicated in renal cystic disease interact with each other in the ciliary complex. These findings support reclassification of many cystic kidney diseases as ciliopathies. Several potential mechanisms for renal cyst development in nephronophthisis exist. They include: (1) the mechanosensory mechanism whereby ciliary bending defects lead to changes in calcium influx altering cell

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Table 302.1
Genetic heterogeneity and overlap of nephronophthisis (NPH), Senior–Loken, Joubert, and Meckel-Gruber syndromes

Locus	Chromosome	Gene[a]	Clinical manifestations
NPHP1/SLSN1	2q13	*NPHP1* (nephrocystin-1)	Juvenile nph (mild JBTS, mild RP, Cogan)
NPHP2	9q31	*NPHP2/INVS* (Inversin)	Infantile nph (RP, liver fibrosis, HT)
NPHP3/SLSN3	3q22	*NPHP3* (nephrocystin-3)	Juvenile nph (liver fibrosis, RP)
NPHP4/SLSN4	1p36	*NPHP4* (nephrocystin-4 or nephroretinin)	Juvenile nph (Cogan, RP)
NPHP5/SLSN5	3q21	*NPHP5/IQCB1*	Juvenile nph + severe RP
NPHP6/SLSN6/JBTS5/MKS4	12q21	*NPHP6/CEP290*	Juvenile nph + JBTS + severe RP, isolated RP, (MKS)
NPHP7	16p	*NPHP7/GLIS2*	Juvenile nph
NPHP8/JBTS7/MKS5	16q	*NPHP8/RPGRIP1L*	Juvenile nph + JBTS (MKS)
NPHP9	17q11	*NPHP9/NEK8*	Juvenile and infantile nph

Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, Table 1
JBTS Joubert syndrome type B, *RP* retinitis pigmentosa, *MKS* Meckel-Gruber syndrome, *HT* arterial hypertension
[a]The name of the protein is indicated when it is not the same as the gene

signaling pathways, (2) defective membrane and centrosome proteins lead to disruption of normal cell–cell and cell–matrix signaling, (3) improper planar polarity of tubules due to dysregulation of the WNT pathway, (4) abnormal apoptosis of normal renal cells leading to proliferation of cystic lesions at the expense of normal kidney tissue which is unique to nephronophthisis compared to the polycystic kidney diseases with enlarged kidneys.

Pathology

The disease is characterized by the presence of cysts in the medulla and corticomedullary junction. The size of the cysts ranges from less than 0.5 mm to 2 cm in diameter. The characteristic pathologic feature in renal biopsy is the presence of chronic tubulointerstitial inflammation and fibrosis (*Fig. 302.1*).

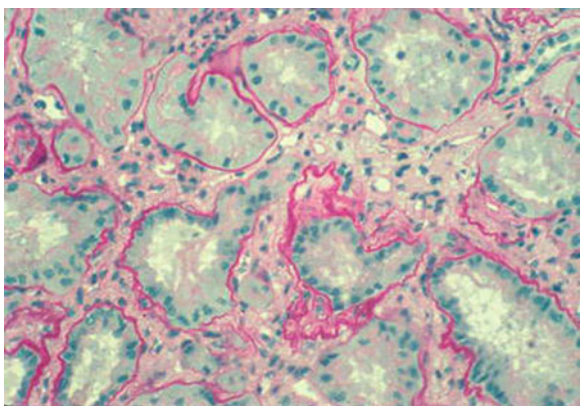

Figure 302.1
Renal histology of nephronophthisis showing diffuse interstitial fibrosis and various tubular changes (Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, fig. 1)

Clinical Features

Usually the child presents with clinical and laboratory findings of chronic renal failure at the age of 10–12 years. Other characteristic clinical features include history of polyuria and polydipsia, history of salt craving, failure to thrive, normal blood pressure, parental consanguinity, and the presence of retinal abnormalities. Urinalysis is unremarkable, but urinary concentrating ability is impaired.

Extrarenal manifestations (*Table 302.2*):

1. A retinopathy known as a tapetoretinal degeneration also known as retinitis pigmentosa (*Fig. 302.2*) (Senior-Loken syndrome), seen in 18% of cases.

Table 302.2
Extrarenal manifestations in nephronophthisis

Ocular
Isolated oculomotor apraxia (Cogan syndrome)
Retinitis pigmentosa (Senior-Løken syndrome)
Coloboma
Nystagmus (Joubert syndrome)
Ptosis (Joubert syndrome)
Neurological
Mental retardation (Joubert syndrome or isolated)
Cerebellar ataxia with vermis hypoplasia (Joubert syndrome)
Hypopituitarism (RHYNS syndrome)
Liver
Elevation of hepatic enzymes
Fibrosis, biliary duct proliferation (Boichis syndrome)
Skeletal
Phalangeal cone-shaped epiphyses (Saldino-Mainzer or cono-renal syndrome)
Short ribs (Jeune or asphyxiating thoracic dystrophy syndrome)
Postaxial polydactyly
Skeletal dysplasia (Sensenbrenner syndrome or cranioectodermal dysplasia)
Other:
Situs inversus
Cardiac malformations
Bronchitis[a]
Sterility[a]
Hyperlipemia[a]
Ectodermal dysplasia (Sensenbrenner syndrome)

Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, Table 2
[a]Personal data

Retinitis pigmentosa(RP) has been observed in association with mutations in most NPHP genes (except NPHP7), but whereas RP is always present and severe in patients with NPHP 5 and NPHP 6 mutations, the symptoms are in general mild in patients with mutations in the other NPHP genes.

2. Leber congenital amaurosis. In the early-onset form, affected children are blind from birth, have specific electroretinogram findings, and develop retinitis pigmentosa. In the late-onset type, blindness occurs later in childhood. Other eye abnormalities include coloboma, cataracts, amblyopia, and nystagmus.
3. Neurologic associations such as cerebellar ataxia, developmental delay (Joubert syndrome) JS is autosomal recessive neurological disorders can be associated with NPH and is characterized by complex cerebellar and brain stem malformation the so called "molar tooth sign" observed by MRI (*Fig. 302.3*).

   Other neurological associations with NPH include recurrent seizures and mental retardation.
4. Congenital hepatic fibrosis.
5. Skeletal abnormalities, including cone-shaped epiphyses in the hand phalanges, metaphyscal chondrodysplasia of the femoral necks (Saldino-Mainzen syndrome), and Jeune asphyxiating thoracic dysplasia.
6. Other syndromes that feature NPH are described in *Table 302.3*.

Diagnosis

Medullary cysts, although regarded as the hallmark of this condition, are seldom seen in percutaneous renal biopsy specimens, even though medullary tissue may be present, presumably because of their uneven distribution. Ultrasonography has been used, but there are many other medical causes of chronic renal failure that show parenchymal heperechogenicity and loss of corticomedullary differentiation echogenic, and cysts may be too small to be detected by ultrasonography. Computerized tomography (CT) scan has been underutilized as a diagnostic tool in this disease entity. The recommended technique for CT scan examinations is contrast-enhanced 1- to 2-mm sections throughout the kidneys. Lesions are usually shown as multiple cysts, typically located at the medulla and corticomedullary region (*Fig. 302.4*). The thin 1- to 2-mm sections recommendation is based on the fact that the size of the cysts ranges from less than 0.5 mm to 2 cm in diameter.

The detection of homozygous mutations by polymerase chain reaction (PCR) amplification permit fast and accurate diagnostic evidence. When a deletion has been demonstrated in one child, it should be sought in siblings to determine those who are affected.

Management

Usually the patient presented with clinical features of chronic renal failure. The immediate and long-term

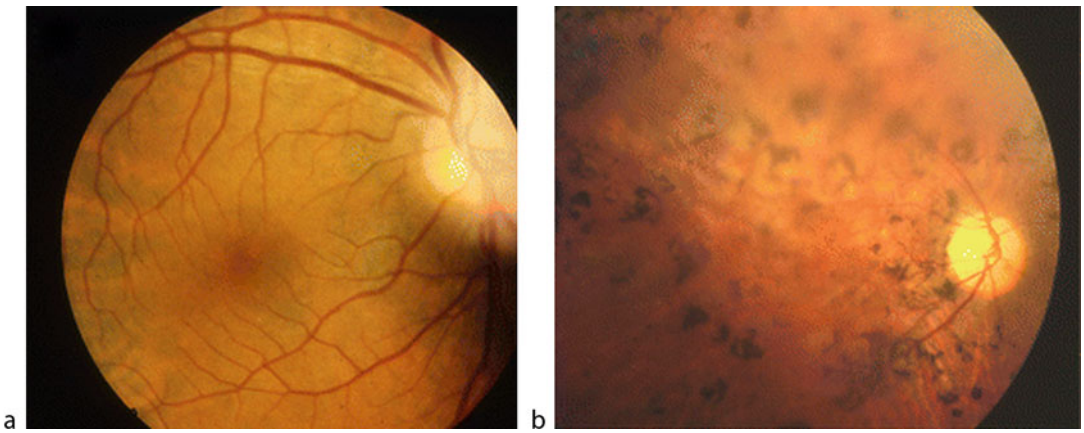

Figure 302.2
Retinitis pigmentosa ophthalmoscopic examinations of a control subject (a) and an affected individual (b) showing typical retinitis pigmentosa fundus characterized by very thin retinal vessels, retinal pigment epithelium atrophy, abnormal pigmentary migrations, and pallor of the optic disk (Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, fig. 2)

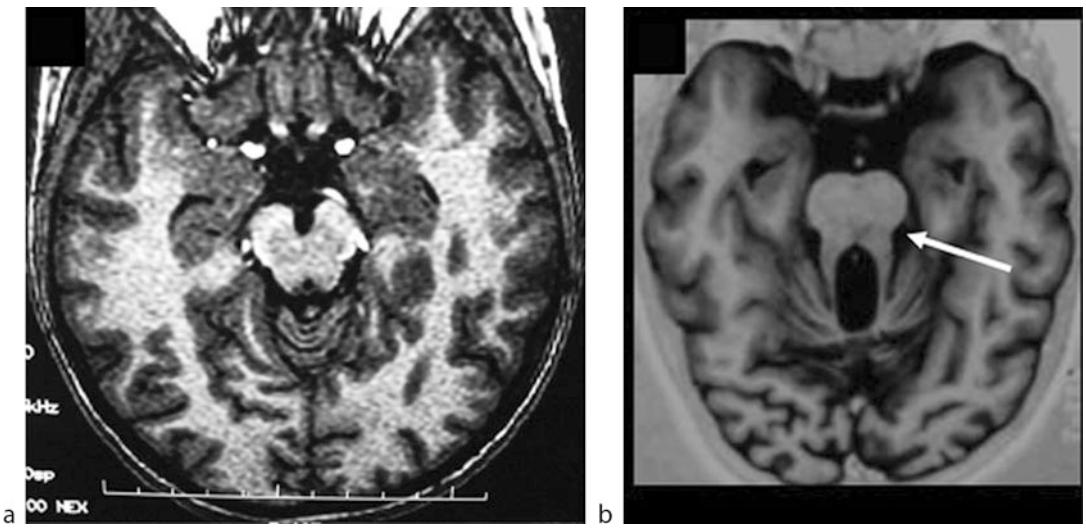

Figure 302.3
Molar tooth sign on brain magnetic resonance imaging (MRI) axial image at the level of superior cerebellar peduncles of a control subject (a) and an affected individual (b) showing abnormally increased depth of the interpeduncular fossa, narrowing of the midbrain tegmentum, and thickening of the superior cerebellar peduncles, all of which contribute to the radiologic feature known as the molar tooth sign (*white arrow*) (Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, fig. 3)

Table 302.3
Syndromes featuring nephronophthisis or associated with mutations of NPHP genes

Senior-Løken
Cogan
Joubert (type B)
Meckel-Gruber
Saldino-Mainzer (cono-renal syndrome)
Sensenbrenner (cranioectodermal dysplasia)
Ellis van Creveld (ectodermal dysplasia)
Jeune (asphyxiating thoracic dystrophy syndrome)
RHYNS (retinitis pigmentosa, hypopituitarism, and skeletal dysplasia)
Alstrom (retinal dystrophy, hearing impairment, obesity, type two diabetes mellitus)
Arima-Dekaban
Boichis

Reproduced from Salomon R, Saunier S, Niaudet P (2009) Nephronophthisis. Pediatr Nephrol 24(12):2333–2344, Table 3

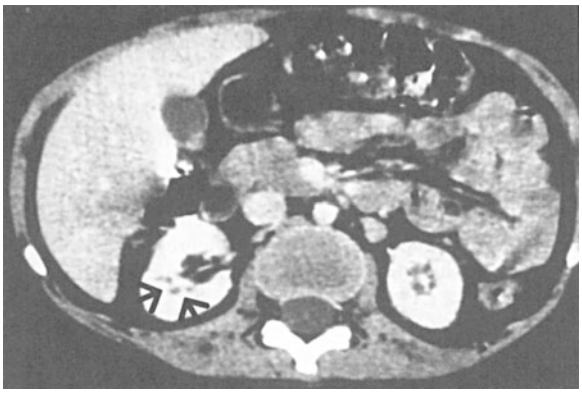

Figure 302.4
Contrast-enhanced computerized tomography cut through kidneys in a child with a diagnosis of juvenile nephronophthisis. Note the multiple small medullary and corticmedullary cysts in both kidneys (*arrows*) (Reproduced from chap. 108, first edition, fig.1)

management is as for children with chronic renal failure (see Chap. 313, "Chronic Renal Failure"), which includes correction of metabolic acidosis and electrolyte imbalance, treatment of osteodystrophy, nutritional support, and dialysis or kidney transplant.

Infantile Nephronophthisis

A chronic autosomal recessive tubulointerstitial nephritis with cortical microcysts progressing to end-stage renal disease before 2 years of age, severe hypertension is common. Ultrasonography usually shows moderately enlarged kidneys.

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303 Autosomal Dominant Polycystic Kidney Disease/Autosomal Recessive Polycystic Kidney Disease

Abdelaziz Y. Elzouki · Laurel Steinmetz

Autosomal Dominant Polycystic Kidney Disease

ADPKD, the most prevalent hereditary renal cystic disorder, affects approximately 1:400 to 1:1,000 persons in the United States and is the fourth leading cause of chronic renal failure throughout the world. ADPKD is rarely diagnosed in infancy and childhood. Most reported cases present at birth with an abdominal mass or are found through screening members of families with ADPKD.

Genetics

ADPKD is inherited in an autosomal dominant fashion with full penetrance. A family history of ADPKD is elicited in approximately 60% of affected persons. A lack of family history is probably related to the variability of expression of the disease. ADPKD is a genetically heterogeneous disease with multiple different mutations in two genes, PKD1 and PKD2. PKD1 mutations tend to lead to end-stage renal disease at a younger age than mutations in PKD2. However, no specific mutations have been correlated with disease phenotype. PKD1 is a large gene on chromosome 16p13.3 and its mutations account for 85% of cases. PKD2 is a smaller gene on 4q21–23 and accounts for 14% of cases.

Only 5–10% of mutations are sporadic.

Preliminary evidence indicates that a third genotype, PKD3, has been identified in 1% of patients, but no genomic locus has been assigned.

Etiology

Cystogenesis in ADPKD is related to defects in polycystins, proteins, which localize to the cell membrane and cilia. Specifically defects in polycystin 1, coded for by PKD1, and polycystin 2, coded for by PKD2 contribute to cyst development. Polycystin 1 is expressed in heart, brain, bone, and muscle while polycystin 2 is expressed in reproductive organs, vascular smooth muscle, kidney, heart, and small intestine. Evidence suggests that these two proteins form a complex in the primary cilia contributing to its mechanosensory ability and that disruption of this ability contributes to cystogenesis. Polycystin 1 is also involved in cell–cell signaling, mechanosensory machinery, intracellular signaling including cell cycle regulation and proliferation, fluid production, and cell polarity. Polycystin 2 is responsible for intracellular calcium influx thought to alter gene expression. Evidence suggests that cystogenesis in ADPKD requires a two hit hypothesis where a patient inherits one mutation and then later develops a second somatic mutation leading to cyst development. The two hit hypothesis would explain why the cyst pattern in ADPKD is focal. This theory may also explain why cysts form at different times even amongst individuals who inherit the same genetic mutations.

Pathology

Renal architecture is distorted by multiple cysts whose number and size increase with increasing age. Cysts may be seen in liver and pancreas. Approximately 10% of patients develop berry aneurysms of the cerebral circulation, and hepatic fibrosis occurs occasionally.

Clinical Features

There are four ways in which ADPKD presents in childhood: (1) prenatal or neonatal presentation, which resembles the clinical presentation of ARPKD (i.e., bilateral renal mass, hypertension, respiratory distress, and renal insufficiency; (2) evaluation of asymptomatic siblings of families with ADPKD; (3) symptomatic children with a family history of ADPKD; and (4) symptomatic patients

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with no family history of polycystic kidney disease (PKD) for whom a parent is found to have PKD as a result of the evaluation of the parents. Usually these symptomatic children present with gross hematuria or hypertension and renal cysts on ultrasonography.

Extrarenal complications include cardiac valve abnormalities, cerebral berry aneurysms, hepatic, pancreatic, and spleen cysts.

Many studies in adults have been shown that patients with mutations in the PKD2 gene have a better prognosis than do PKD1 patients: In a study on genotype–phenotype correlation in children with ADPKD, PKD1 children had more and larger renal cysts, larger kidneys, and higher ambulatory blood pressure than PKD2 children. Prenatal finding of renal cysts or postnatal enlarged kidneys were observed only in patients with mutations in PKD1 gene.

Diagnosis

The renal ultrasonography of a neonate with ADPKD demonstrates large kidneys with hyperechoic parenchyma and no differentiation between cortex and medulla. It is possible to diagnose ADPKD prenatally with the use of DNA obtained from amniocentesis or chorionic villus sampling by the gene linkage techniques, but clinicians do not think this late-onset disease warrants interruption of pregnancy. In older children the renal ultrasonography demonstrates the cyst (*Fig. 303.1*). The sensitivity of CT scan is greater than that of ultrasonography (*Fig. 303.2*).

In adult patients younger than 30 years of age, the presence of two cysts, either unilateral or bilateral, is sufficient to make the diagnosis. In patients 30–59 years old, at least two cysts in each kidney are essential for the diagnosis. DNA linkage analysis testing is useful in determining the disease status of relatives with normal kidneys who wish to be considered as potential donors for living kidney transplantation.

Treatment

Early disease detection has traditionally led to problem with insurability and later employment but has offered these individuals little benefit if any in term of treatment option. New potential targets for therapies stemming from animal and bench research have been surfaced these include:

1. Clinical trials to explore the role of inhibition of renin-angiotensin-aldosterone system(RAAS), utilizing combination therapy ACEI and ARB in treatment of hypertensive individuals with ADPKD.
2. Agents that inhibit cell growth and proliferation utilizing an inhibitor of the mammalian target of rapamycin mTOR, treatment studies are now underway in adults with ADPKD to determine if Sirolimus that is widely used in transplant recipients is effective in slowing the progression of the disease.
3. Vasopressin V2 receptor antagonists are also demonstrating potential therapeutic benefits in APKD.

Although the translation of these new potential targets for therapies into meaningful safe remedies in human will

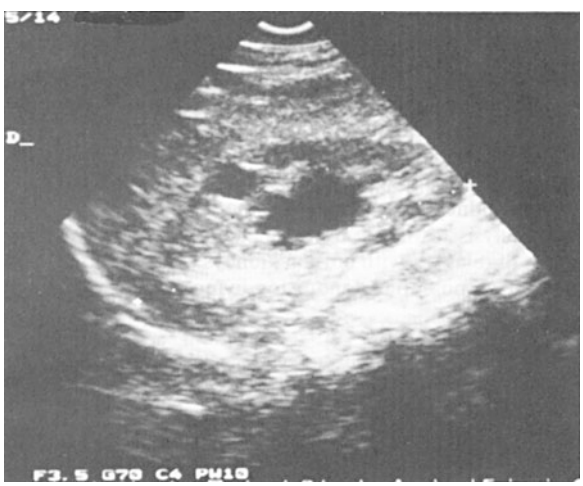


Figure 303.1
Renal ultrasonography in a child with a diagnosis of ADPKD. Note the large cyst (Reproduced from chap. 108, first edition, fig. 2)

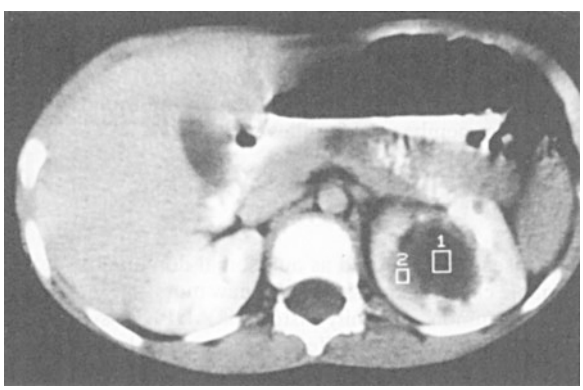


Figure 303.2
Contrast-enhanced computerized tomography scan demonstrates large cyst in left kidney in a child with a diagnosis of ADPKD (Reproduced from chap. 108, first edition, fig. 3)

take time and scrutiny, it is likely that children with ADPKD will benefit from those outstanding scientific contributions in near future.

Autosomal Recessive Polycystic Kidney Disease

ARPKD has previously been referred to as "infantile polycystic kidney disease"; however, the disease can present at any age, from the prenatal period through adolescence, and in a few patients ARPKD is not recognized until adulthood.

The pathologic findings of the disease include varying degrees of cystic dilation of the distal tubules and collecting ducts throughout the cortex and medulla, varying degrees of biliary dysgenesis, and hepatic fibrosis.

Epidemiology

The reported prevalence varies from 1:600 to 1:55,000 live births. Gene frequency is in a range from 1:40 to 1:100.

Genetics

This disease is inherited in an autosomal recessive pattern. Mutations have been found in the PKHD1 gene on chromosome 6p21. This gene is large and multiple different types of mutations have been found. Variability in age of onset is related to different expression of mutation and modifier genes. Patients with two truncating mutations will die in the perinatal period. Missense mutations tend to cause less severe phenotypes. PKHD1 encodes the protein fibrocystin, also known as polyductin.

Etiology

Fibrocystin is thought to contribute to normal ciliary development. However, its precise function has not been elucidated. Studies suggest that it complexes with polycystin 1 and 2 and plays a role in intracellular calcium signaling. It also may contribute to normal tubule morphogenesis. In addition, cyclic AMP and epidermal growth factor receptor also play a role in cystogenesis in ARPKD models.

Clinical Presentation

Prenatally the findings of oligohydramnios, bilateral enlarged kidneys that are diffusely echogenic, and the absence of fluid in the fetal bladder are consistent with a diagnosis of ARPKD. Elevation of α-fetoprotein levels in maternal serum and amniotic fluid may complement the prenatal ultrasonographic diagnosis.

The newborn usually presents with bilateral massively enlarged kidneys and respiratory distress, which is a complication of pulmonary hypoplasia or pneumothorax. Severely affected neonates may demonstrate the Potter phenotype (i.e., deep-set eyes, flat beaked nose, micrognathia, low-set ears, and joint deformities). Later in infancy and childhood, those who survive the neonatal period will develop the sequelae of renal insufficiency (i.e., failure to thrive, anemia, and renal osteodystrophy). The majority of patients have a concentrating defect with polyuria and polydipsia. Hyponatremia and metabolic acidosis have been described.

Hypertension occurs in nearly all patients with ARPKD. It was reported that all affected infants who had blood pressure measurements at 3 months of age were hypertensive. The degree of hypertension has been noted to be most severe in the first year of life and may be responsible for early death in many of these patients.

Extrarenal manifestations include:

Liver Disease. The liver disease in ARPKD is primarly manifest by two major types of pathophysiology biliary disease and portal hypertension.There is considerable variability in the severity of liver disease in ARPKD.

The complications of hepatic fibrosis and portal hypertension are seen more frequently in older children. These complications include hepatosplenomegaly, bleeding esophageal varices, and hypersplenism sequelae (i.e., anemia, thrombocytopenia, and leukopenia).

The most common manifestations of biliary disease are sepsis/cholangitis and or complication of cholelithiasis.

Standard liver biochemical testing is typically normal in children with ARPKD with liver disease and thus may not necessary be useful as screening tools.

A combination of physical examination (finding of splenomegly) and CBC (finding of cytopenia) and abdominal ultrasonography is a reliable method for screening for evidence of portal hypertension.

Intracranial Aneurysm. The incidence of intracranial aneurysm is well-known extrarenal manifestation of ADPKD, the incidence is about 10%; there are reported cases of intracranial aneurysm in patients with ARPKD (*Fig. 303.3*).

Diagnostic Imaging

The abdominal ultrasound usually shows enlarged kidneys with hyperechoic parenchyma and no differentiation

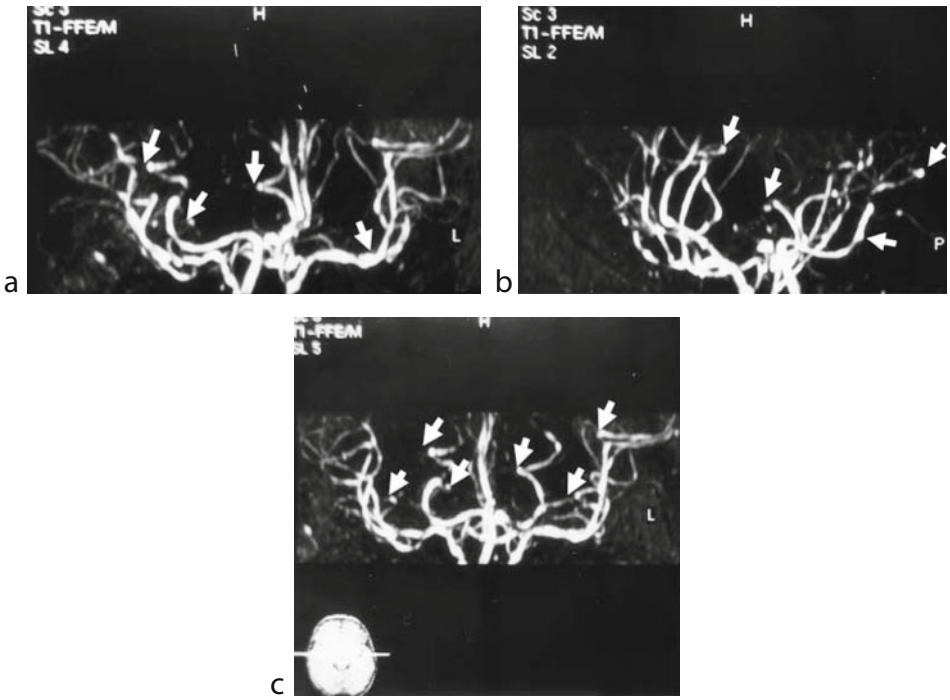


Figure 303.3
Magnetic resonance of brain angiography of multiple intracranial aneurysms in the branches of middle and posterior cerebral arteries (Reproduced from Lilova MI, Petkov DL (2001) Intracranial aneurysm in a child with Autosomal Recessive Polycystic Kidney Disease. Pediatr Nephrol 16:1030–1032)

between cortex and medulla (*Fig. 303.4*). The liver is usually normal in size and less echogenic than the kidney; dilated intrahepatic biliary ducts may be demonstrated. The presence of portal hypertension on Doppler ultrasonography indirectly indicates the presence of hepatic fibrosis. The intravenous pyelogram usually shows the classic findings of enlarged kidneys, and delayed nephrogram with medullary streaking (accumulation of contrast in dilated medullary collecting ducts). The intravenous pyelogram is not essential for diagnosis and certainly not recommended.

Magnetic Resonance (MR) cholangiography is more sensitive test for identifying biliary ectasia, recommended the MR cholangiography be performed at least once in children with ARPKD.

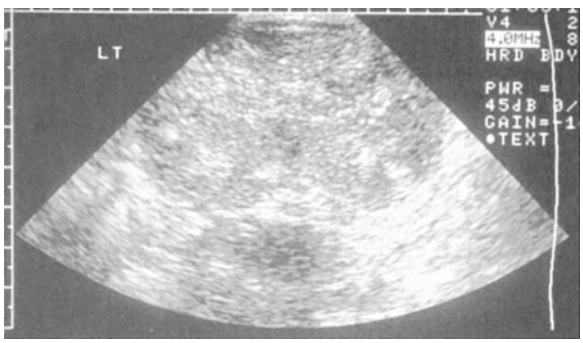


Figure 303.4
Renal ultrasonography in a child with a diagnosis of ARPKD. Note enlarged kidney with hyperechoic parenchyma and no differentiation between cortex and medulla (Reproduced from chap. 108, first edition, Fig. 4)

Management

Hypertension can be treated with calcium-channel blockers, β blockers, angiotensin-converting enzyme inhibitors, and vasodilators. Hypertension may require multiple antihypertensive agents for effective control. Supplemental bicarbonate therapy is needed for those with metabolic acidosis. The same treatment as that used for chronic renal failure (see Chap. 313, "Chronic Kidney Disease"), as well as dialysis and/or transplant, are indicated when children with ARPKD reach end-stage renal disease. For hepatic involvement, close

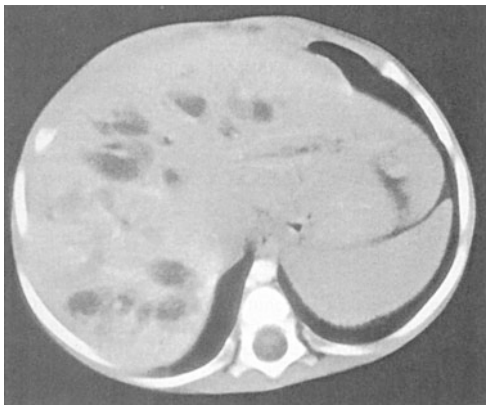
monitoring for the complications of portal hypertension and hypersplenism is necessary. Surgical intervention with portocaval and splenorenal shunts may be needed. Appropriate antimicrobial therapy should be given to those patients with a suspected diagnosis of cholangitis.

Caroli Syndrome

Caroli syndrome is characterized by the presence of autosomal recessive polycystic kidney disease, congenital hepatic fibrosis, and nonobstructive dilation of the intrahepatic bile ducts. On hepatic ultrasonography, there are saccular dilated bile ducts containing intraluminal protrusions and crossbridges, and contrast-enhanced CT scan reveals liver cysts with a "central dot sign" (◉ *Fig. 303.5*).

How to Differentiate Between ADPKD and ARPKD

Distinguishing between ADPKD and ARPKD based on clinical findings may be unreliable. Both ADPKD and ARPKD produce renal masses and hypertension in childhood. Ultrasonography may show enlarged hyperechoic kidneys in both entities; conversely, macroscopic cysts may be detected in older patients with ARPKD. The use of liver biopsy has been proposed as a means of distinguishing between ADPKD and ARPKD. The diagnosis of ARPKD cannot be supported in the presence of a normal liver. The presence of hepatic fibrosis, however, does not exclude a diagnosis of ADPKD. Congenital hepatic fibrosis has occurred in association with ADPKD. The single most useful investigation in the evaluation of a child with early onset of cystic renal disease is ultrasound of the parents and/or genetic analysis, the detection of homozygous mutations by polymerase chain reaction (PCR) amplification permit fast and accurate diagnosis evidence.



◘ Figure 303.5
Computerized tomography scan demonstrates liver cysts with a "central dot sign" in a child with a diagnosis of Caroli syndrome (Reproduced from chap. 108, first edition, Fig. 5)

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304 Proximal Renal Tubular Disorders

Sami A. Sanjad

Definition and Classification

Diseases affecting the renal tubules occur due to structural or functional abnormalities in the different segments of the nephron. From a quantitative point of view the proximal tubular cells perform a remarkable job in reabsorbing the filtered plasma and its accompanying solutes. The distal tubules continue that process but are more involved in fine tuning operations, acidification of the urine, and diluting or concentrating it as necessary. In diseases of the proximal tubules, variable qualitative and quantitative degrees of aminoaciduria may be present with or without bicarbonaturia, glucosuria, uricosuria, or phosphaturia. Any combination of abnormal solute excretion is theoretically conceivable and may be found in different syndromes of proximal tubular dysfunction.

Etiology: General

Disorders of proximal tubular function may be secondary to congenital or hereditary diseases or due to acquired defects. The hereditary or congenital defects are much more prevalent and may be due to: (a) absent or defective Na-solute cotransport system in the proximal tubular cells, as seen in cystinuria, Hartnup disease, renal glucosuria, vitamin D resistant rickets, and proximal renal tubular acidosis; (b) altered gene affecting more than one transport system – adult Fanconi syndrome; (c) mutant genes resulting in endogenous tubulotoxic substances accumulated from extra renal metabolic pathways (cystinosis, galactosemia, tyrosinemia, hereditary fructose intolerance, Wilson's disease); (d) abnormal solute transport due to structural changes associated with congenital renal and urinary tract malformations (cystic diseases, nephronophthisis, and hydronephrosis).

Acquired defects of proximal tubular function are usually drug induced or related to intrinsic renal diseases (see below). This chapter covers three major disease entities associated with proximal tubular dysfunction: (1) Fanconi syndrome, (2) proximal renal tubular acidosis, and (3) disorders of phosphate transport.

Fanconi Syndrome

Also known by many other eponyms (Lignac-Fanconi, de Toni-Debré-Fanconi syndrome), the Fanconi syndrome represents a heterogeneous group of disorders which may be hereditary or acquired with a common denominator being abnormalities in the transport of multiple solutes by the proximal tubular cells. Solutes normally reabsorbed by the proximal tubules are lost in the urine in variable proportions. These include glucose, amino acids, phosphate, bicarbonate, uric acid, and low-molecular-weight proteins and cations. Most cases of Fanconi syndrome in children are secondary to inherited metabolic diseases associated with specific enzyme defects, or due to transport abnormalities across the tubular cells. Acquired Fanconi syndrome is usually due to tubulotoxic effect of several drugs and toxins or due to intrinsic renal diseases with a significant tubulointerstitial component (*Table 304.1*). When no identifiable cause is found, the Fanconi is known as primary or idiopathic and may be familial or occur sporadically.

Clinical Findings

The clinical manifestations of the Fanconi syndrome and the onset of symptoms vary with the underlying etiology. Most patients with inherited disorders present in the first year of life with failure to thrive, frequently with anorexia and vomiting. Polyuria and polydipsia with bouts of fever and dehydration may also be present. Rickets is invariably seen at some stage of the disease and may be the presenting manifestation in some children.

Pathogenesis

The pathogenesis of the Fanconi syndrome is incompletely understood and probably varies with the underlying

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Table 304.1
Etiology of the Fanconi syndrome

Hereditary causes	Acquired causes
Cystinosis Glycogen storage disease Tyrosinemia type I Galactosemia Hereditary fructose intolerance Lowe's syndrome	Drugs and Toxins Ifosfamide Heavy metals Glue sniffing Gentamicin Outdated tetracycline
Mitochondrial cytopathies	
Metachromatic leukodystrophy Glutathione synthetase deficiency	Disorders of Protein Metabolism Light chain proteinuria Amyloidosis Nephrotic syndrome Multiple myeloma Other Renal transplantation

etiology. It is quite possible that a dysfunction of the basolateral membrane Na-K-ATPase pump, brought about by an endogenous or exogenous toxin, would result in impaired energy production for solute reabsorption by the proximal tubule. This has been observed in several clinical and experimental disorders associated with the Fanconi syndrome.

Diagnosis

The diagnosis of the Fanconi syndrome is easily made when the above constellation of findings are seen in association with euglycemic glucosuria and mild proteinuria on routine urinalysis. Proteinuria is primarily tubular in origin and is characterized by low-molecular-weight proteins, usually less than 30,000 Da. They include lysozyme and beta$_2$-microglobulin but also a small amount of filtered albumin that escapes reabsorption by the proximal tubule. Serum analysis reveals hyperchloremic metabolic acidosis, normal urea and creatinine levels (unless severe dehydration is present), hypophosphatemia, hypokalemia, hypouricemia, and hyponatremia. This low plasma solute concentration is a reflection of their losses in the urine as a result of decreased reabsorption by the proximal tubular cells. Urine amino acid analysis reveals generalized, nonspecific aminoaciduria. Once the diagnosis of Fanconi syndrome has been reached on clinical grounds, every effort should be made to obtain an etiologic diagnosis.

Etiology of Specific Forms of the Fanconi Syndrome

Hereditary Causes of the Fanconi Syndrome

Cystinosis

Cystinosis is cited in the western literature as the most common cause of the Fanconi syndrome with an incidence of 1:200,000 live births. It is not to be confused with cystinuria which (a) does not cause the Fanconi syndrome; (b) is predominantly associated with increased urinary excretion of cystine, ornithine, lysine, and arginine; and (c) is frequently associated with cystine urolithiasis.

Cystinosis is an autosomal recessive lysosomal storage disease characterized by the accumulation of cystine in several organs including the kidney, liver, gut, spleen, bone marrow, lymphatic system, leukocytes, cornea, thyroid, and other organs. The biochemical defect is unknown but a defective transport of cystine across the lysosomal membrane appears to be the most likely cause. Three forms of cystinosis are recognized: (1) infantile or nephropathic form being the most common, (2) adolescent or late form, and (3) adult or benign ocular cystinosis.

Clinical Findings in Cystinosis

The clinical and laboratory manifestations of nephropathic cystinosis are those of the Fanconi syndrome described above and they usually become apparent in early infancy. Polyuria and polydipsia are particularly common early manifestations. Some patients may present with severe hypokalemia and alkalosis mimicking Bartter's syndrome. Growth failure is severe and associated with hypophosphatemic rickets and hyperchloremic acidosis. Although glomerular filtration rate is normal in the early phases of the disease, progressive deterioration is the rule. By the end of the first decade most children with nephropathic cystinosis will develop end stage renal disease necessitating dialysis and renal transplantation.

The extra renal manifestations of cystinosis are secondary to the accumulation of cystine crystals in different organs. Thus, corneal deposition is responsible for photophobia, excessive tearing, and blepharospasm. Hypothyroidism, characterized by high TSH levels, is a frequent occurrence, particularly in older children, but clinical hypothyroidism is uncommon. Muscular weakness and hypotonia secondary to hypokalemia and carnitine deficiency are commonly observed. Testicular deposition of

cystine crystals may explain the incomplete pubertal development frequently seen in males with cystinosis. This is associated with reduced plasma levels of testosterone but normal pituitary function. The central nervous system, initially thought to be spared in cystinosis, is now a well-known site of involvement in older patients with the disease. Symptoms vary from difficulty in walking to dysphagia, speech difficulty, and dementia. Cranial nerve involvement and pyramidal tract signs may also be seen. Retinopathy develops in a few patients and may be progressive and lead to blindness.

Adolescent and adult type cystinosis are less frequent. The clinical manifestations are insidious and the Fanconi syndrome is usually milder, occurring after the age of 8 years in the adolescent form. In the adult form of cystinosis, also known as ocular cystinosis, there is no renal involvement, but patients may complain of photophobia due to cystine deposition in the cornea.

Diagnosis

Cystinosis may be diagnosed by slit lamp examination of the cornea where cystine crystals may be seen. Bone marrow, liver or kidney biopsy may also reveal cystine crystals. Unequivocal diagnosis is made by demonstrating increased cystine content in leukocytes or rectal mucosa from affected individuals. The leukocyte cystine content is 5–15 nmol of ½ cystine/mg protein in the infantile form and less than 0.2 in normal individuals. Prenatal diagnosis is now possible by measuring amniotic fluid or cultured fibroblasts for cystine content. Molecular genetic studies have shown mapping of the cystinosis gene to chromosome 17p13. The *CTNS* gene encodes a 367-amino acid protein called cystinosin which is widely expressed in many organs, particularly pancreas, kidney and muscle. All patients with cystinosis tested have had mutations in the CTNS gene with no evidence thus far of genetic heterogeneity.

Glycogen Storage Disease (GSD)

The proximal tubular dysfunction associated with GSD is referred to as Fanconi-Bickel syndrome (GSD type 11) and was first described in 1949. Patients present typically in early infancy with failure to thrive, hypotonia, hepatomegaly, and rickets. Hyperchloremic acidosis with bicarbonate wasting is usually severe. The kidneys are usually enlarged and are loaded with glycogen. Many patients develop hypoglycemia with prolonged fasting and show impaired galactose utilization. One of the most striking abnormalities that characterizes this syndrome is the massive glucosuria, which may reach 100 g/m^2/day in some patients.

GSD appears to be relatively common in certain parts of the world. In Saudi Arabia it was diagnosed in more than one half of the cases of Fanconi syndrome (15 of 29) referred to a tertiary care center. In our experience many of these patients have a decreased or absent activity of the enzyme phosphorylase b kinase (pbk) involving liver and kidney. This was documented on liver homogenates from several patients with GSD and Fanconi syndrome who also had renal glycogen storage documented by histochemical assay. It has been subsequently shown, however, that mutations in the facilitative glucose transporter GLUT2 are causative of this syndrome and the low pbk activity detected in our patients is probably a secondary phenomenon that contributes to the deposition of glycogen in response to the intracellular glucose retention caused by GLUT2 deficiency.

Proximal tubular dysfunction has been described in a few patients with GSD type 1 (von Gierke's disease) but these are usually mild and not associated with a complete Fanconi syndrome. A more prevalent and serious finding in these patients who now are living longer than before is focal glomerulosclerosis with proteinuria and at times progressive renal failure.

Tyrosinemia Type I

Also known as hepatorenal tyrosinemia, this autosomal recessive disorder is characterized clinically by early onset of nodular hepatic cirrhosis, failure to thrive, and Fanconi syndrome. Rickets may be severe and crippling in untreated patients (*Figs. 304.1* and *304.2*). Abdominal ultrasonography reveals hepatosplenomegaly and enlarged kidneys which, combined with the biochemical findings of the Fanconi syndrome, should arouse suspicion of tyrosinemia. A presumptive diagnosis of tyrosinemia is made when the urinary excretion of succinyl acetone (SA) is elevated. Delta aminolevulenic acid (DALA) is also excreted in large amounts in the urine of patients with tyrosinemia. The metabolic defect is related to deficiency of the enzyme fumaryl acetoacetate hydrolase (FAH) which leads to accumulation of toxic precursors including SA and DALA. The FAH gene has been cloned recently and mapped to chromosome 15 (15q23–q25). Several missense mutations have been described with no evidence of phenotype genotype correlation with different clinical manifestations sometimes observed

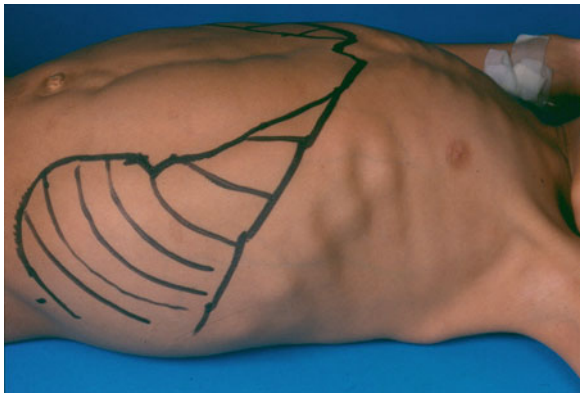

Figure 304.1
Massive splenomegaly and rachitic rosary in a 7-year-old male with tyrosinemia type 1

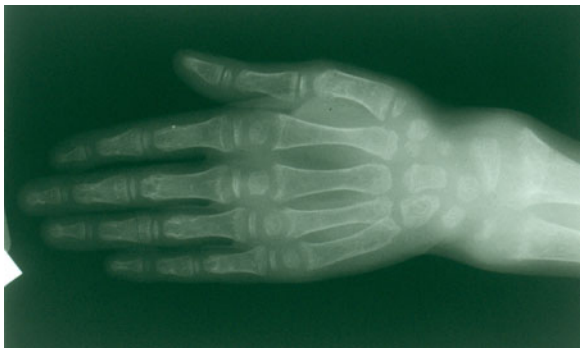

Figure 304.2
Severe rachitic changes in a patient with hepatorenal tyrosinemia

within the same family. This phenomenon may due to mutation reversion which has been described in patients with tyrosinemia.

Galactosemia

Galactosemia may result from many inherited enzyme deficiencies. Only that associated with Gal-1-PO_4 uridyl transferase deficiency results in the Fanconi's syndrome, which is incomplete, in that glucosuria is absent and phosphaturia is seldom severe to result in hypophosphatemia. Renal tubular acidosis is probably of the proximal type and associated with bicarbonaturia. Galactosemia and galactosuria are invariably seen. The diagnosis should be suspected in any infant with a history of failure to thrive, jaundice, hepatomegaly with or without cataracts, and non-glucose reducing substance in the urine. Definitive diagnosis is made by determining red blood cell Gal-1-PO_4 uridyl transferase activity. The molecular diagnosis of galactosemia has been identified recently by mutations in the GALT gene located on chromosome 9p13. The most common of these is a missense mutation of *Q188R* (replacement of glutamine-188 by arginine) but several other mutations have been identified as well.

Hereditary Fructose Intolerance

Hereditary fructose intolerance is an autosomal recessive inborn error of fructose metabolism caused by deficiency of fructose-1-phosphate (F1-PO_4) aldolase B activity in the liver, renal cortex, and small intestine. Several mutations in the human aldolase *B* gene have been identified, the most common being the A149P mutation in exon 5 located on chromosome 9_q 21.3_q 22.2. The clinical manifestations that develop following fructose ingestion are acute in nature and consist of nausea, vomiting, and diarrhea. Liver failure may develop within days. An acute Fanconi syndrome with *hyperuricemia*, hyperlactic acidemia, and hypermagnesemia develops within 30–60 min of ingestion of a large amount of fructose. In extreme cases, seizures, lethargy, and coma may develop. Ingestion of small amounts of fructose is not associated with symptoms.

The renal tubular abnormalities as well as the other manifestations of the disease are probably secondary to accumulation of F-1-PO_4 with depletion of inorganic phosphate, thus limiting ATP regeneration. This may lead to reduced transport of multiple solutes across the proximal tubular epithelial cell characteristic of the Fanconi's syndrome. Fructose withdrawal promptly reverses the acute changes and the renal tubular dysfunction. In patients with chronic fructose ingestion, however, liver damage may be irreversible.

Lowe's Syndrome (Oculocerebrorenal Syndrome)

Lowe's syndrome is an X-linked recessive disease characterized by congenital cataracts, glaucoma, developmental and growth retardation, hypotonia, and a renal Fanconi syndrome. The gene locus (OCRL) has been mapped to X 25–26 by linkage analysis. More specifically the gene product is a 105 kD protein localized to the Golgi complex.

The Fanconi syndrome is usually mild or incomplete but it may be quite severe in some cases. In many patients glomerular insufficiency develops later in childhood in spite of adequate symptomatic treatment for the tubular abnormalities. Dialysis and transplantation are usually not prescribed because of the moderate to severe mental retardation seen in most patients with Lowe's syndrome.

Dent's Disease

This is a rare X-linked disorder characterized by hypercalciuria, hyperphosphaturia, low-molecular-weight proteinuria, and aminoaciduria, and an incomplete Fanconi syndrome. If untreated, many patients develop nephrolithiasis and renal failure. In addition, one third of the patients develop rickets or osteomalacia. The gene has been localized to chromosome Xp11.22 and has been identified as a chloride channel gene *CLCN5*. There are actually four diseases associated with mutations in this gene: Dent disease, X-linked recessive nephrolithiasis (XRN), X-linked recessive hypophosphatemic rickets (XLRH), and idiopathic low-molecular-weight proteinuria of Japanese children (ILMWP). All share many similarities as described above but patients with Dent disease and XLRH develop rickets while the others do not. Renal failure is only seen in patients with Dent disease and XRN. Female carriers are asymptomatic but frequently have low-molecular-weight proteinuria.

Wilson's Disease

Wilson's disease is an autosomal recessive disease primarily affecting the liver and brain where marked amounts of copper are deposited. It is caused by mutations in the *ATP7B* gene located on chromosome 13 (13q14.3) and is expressed primarily in the liver, kidney, and placenta. The gene codes for a P-type (cation transport enzyme) ATPase that transports copper into bile and incorporates it into ceruloplasmin. Mutations can be detected in 90% of patients and most of these are homozygous.

The classical triad of hepatic cirrhosis, Kayser-Fleischer rings in the cornea, and neurological symptoms are pathognomonic findings. Renal involvement appears later with more advanced liver disease but it may precede hepatic failure. It is characterized by tubular dysfunction as seen in other cases of the Fanconi syndrome, but glucosuria is infrequent.

Other Hereditary Causes of the Fanconi Syndrome

The Fanconi syndrome has been described in association with several other rare inborn errors of metabolism including mitochondrial cytopathies, metachromatic leukodystrophy, pyruvate carboxylase deficiency (Leigh's syndrome), and glutathione synthetase deficiency. *Table 304.2* outlines some of the inherited disorders of proximal tubular function with and without the Fanconi syndrome. It includes some of the salient clinical findings, enzymatic defects, and inheritance pattern.

Acquired Disorders Causing the Fanconi Syndrome

These are primarily disorders associated with heavy metal exposure (lead, mercury, platinum), drug induced lesions as with ifosfamide, outdated tetracycline, aminoglycosides, toluene inhalation, and with abnormalities in protein metabolism as in amyloidosis, Sjögren's syndrome, and the nephrotic syndrome. The development of Fanconi syndrome in a child with nephrosis is an ominous sign indicating tubulointerstitial nephropathy, usually in association with focal segmental glomerulosclerosis. The Fanconi syndrome may also be acquired following renal transplantation where the mechanism is probably immune mediated.

Of all the drugs causally related to the Fanconi syndrome, ifosfamide is probably the most predictable since tubular dysfunction occurs in a relatively high percentage of treated patients. Ifosfamide is a cyclophosphamide analog used to treat several solid tumors. The Fanconi syndrome develops acutely during treatment and is usually heralded by glucosuria and hypophosphatemia. Both proximal and distal RTA may be observed in addition to aminoaciduria and uricosuria. Hypokalemia may be severe and beta$_2$-microglobulinuria is quite pronounced. The tubular toxicity is thought to be due to chloracetaldehyde, one of the metabolites of ifosfamide. Glomerular toxicity and reduced GFR may also occur with ifosfamide toxicity. Hemorrhagic cystitis occurs with much less frequency than with cyclophosphamide.

General Treatment of the Fanconi Syndrome

Metabolic Acidosis and Electrolyte Abnormalities

Patients with Fanconi syndrome frequently require large doses of bicarbonate or citrate to replace the ongoing losses

Table 304.2
Inherited disorders of proximal tubular function

Disorder	Clinical findings	Biochemical defect	Urine abnormalities	Inheritance, gene locus, mutations
Fanconi syndrome Cystinosis	Progressive renal failure; cystine storage in multiple organs	Defective cystine transport across lysosomal membrane	Usual for FS	AR 17p13, D17S1584, CTNS
GSD 11 Fanconi-Bickel syndrome	Hepatomegaly Nephromegaly Hypoglycemia	Phosphorylase b kinase deficiency in some patients due to massive glycogen accumulation secondary to impaired glucose transport	Massive glucosuria	AR 3q26.1–26.3 Mutations in *GLUT2*
Tyrosinemia	Nodular cirrhosis Portal hypertension Liver failure, hepatosplenomegaly nephromegaly	Fumaryl acetoacetate hydrolase deficiency	SA, DALA	AR 15q23–q25
Galactosemia	Jaundice Hepatosplenomegaly Cataracts Mental retardation	Gal-I-PO_4 uridyl transferase deficiency	Galactose No glucosuria	AR *GALT* gene on 9p13 Mutation of *Q188R*
Hereditary fructose intolerance	Hypoglycemia, seizures, jaundice, hyperuricemia, ↑Mg	F-I-PO_4 aldolase B deficiency	Fructose	AR chromosome 9q213–q22.2 *A149P* mutations
Lowe's syndrome	Mental retardation, cataracts, glaucoma	Abnormal inositol PO_4 metabolism	Usual for FS	XLR Xq25–26 OCRL-1 is 105 kD protein located in Golgi complex
Other P.T. disorders Proximal RTA with osteopetrosis	Growth failure Mental retardation Cranial nerve abnormalities Fractures	↓T_{HCO3} CAII deficiency	Bicarbonaturia Bicarbonaturia	AD, AR 8q22 – several mutations – intron 2
HVDRR	Rickets, hypophosphatemia	↓TRP Impaired calcitriol synthesis	Phosphaturia	XLD, AD *Hyp* gene Xp22.1 *PHEX, FGF23*
Cystinuria	None, urolithiasis, renal failure from obstructive uropathy	Defective transport of cystine and dibasic amino acids in proximal tubules and intestine	Cystine, ornithine, lysine, arginine	Chromosome 2p Mutations in *SLC3A1* gene

AD autosomal dominant, *AR* autosomal recessive, *XLD* X-linked dominant, *XLR* X-linked recessive, *SA* succinyl acetone, *DALA* delta aminolevulenic acid, *FS* Fanconi syndrome, *TRP* tubular reabsorption of phosphate, *CA* carbonic anhydrase, T_{HCO3} tubular reabsorption, bicarbonate

through the urine. If the fractional excretion of bicarbonate is very high the alkali requirement is proportionately larger. Some patients require 10–20 mEq/kg/day in four or more divided doses. If higher doses are needed, the large amount of sodium may lead to ECV expansion and further bicarbonate wasting. In such cases, salt and water should be restricted and a thiazide diuretic (2 mg/kg/day hydrochlorothiazide) administered to produce a mild ECV contraction and enhance bicarbonate reabsorption. Potassium supplements are frequently needed to replace renal potassium wasting and treat hypokalemia. Potassium citrate or lactate is ideally suited for treatment because they will also help in correcting metabolic acidosis. Calcium and magnesium supplements may be needed in patients with hypocalcemia and renal magnesium wasting. A prostaglandin synthetase inhibitor such as Indomethacin

(1–3 mg/kg/day) may be useful in reducing the urinary sodium, potassium, and water losses that are frequently seen in many patients with the Fanconi syndrome. Their use is contraindicated in the face of deterioration of renal function as seen in later stages of nephropathic cystinosis.

Hypophosphatemia and Bone Disease

While hypophosphatemia plays a major role in the bone disease in Fanconi syndrome, other factors including reduced calcitriol synthesis, chronic acidosis, and hypercalciuria are also important. Vitamin D therapy in the form calcitriol or one-alpha hydroxy-D3 is frequently needed to correct rickets. Doses vary from 0.25 to 3.0 μg/day. Phosphate supplements are always needed in high and frequent doses, depending on the severity of the phosphaturia. Most patients require 1–2 g/day in four divided doses. With adequate phosphate supplementation it is possible to promote bone healing with smaller doses of vitamin D.

Specific Treatment of the Fanconi Syndrome

Cystinosis

The use of the aminothiols cysteamine or phosphocysteamine has shown promising results in depleting cystine from the lysosome of affected cells. This is accomplished by an intralysosomal reaction between cystine and cysteamine to form a cysteine-cysteamine disulfide that exits the cell via a lysine carrier system. Treatment should be started as soon as the diagnosis of cystinosis is confirmed. The starting dose is 10 mg/kg/day in four divided doses. This is raised progressively to 60 mg/kg/day and titrated against leukocyte cystine content. Cysteamine treatment has been associated with improvement in the Fanconi syndrome and possible delay in the onset of renal failure. If and when renal failure develops, dialysis and transplantation offer the only hope for prolonged survival. The results of renal transplantation in patients with cystinosis are more successful than renal transplantation performed for other chronic renal diseases. This may be due to reduced immune responsiveness induced by intracellular cystine accumulation. The Fanconi syndrome does not recur but interstitial and mesangial accumulation of cystine has been reported.

Tyrosinemia Type 1

Until recently the only effective therapy for tyrosinemia type 1 was liver transplantation, preferably prior to the development of severe liver failure and hepatocellular carcinoma, known complications of nodular cirrhosis. An experimental drug that underwent clinical trials over the past 10 years or so appears to have stood the test of time and has shown promising results for patients with tyrosinemia type 1. The drug, 2-nitro-trifluoromethylbenzoyl-1, 3-cyclohexanedione (NTBC), inhibits 4-OH-phenylpyruvate dioxygenase, the second enzyme in the degradation pathway of tyrosine which is two steps proximal to the enzyme defect in tyrosinemia. The drug was recently approved for commercial use as an orphan drug and marketed as Nitisinone. Studies with NTBC therapy show an impressive reduction in the plasma level and the urinary excretion of SA and DALA and alpha-fetoprotein levels with a marked reduction in hepatosplenomegaly. Tubular dysfunction also improves significantly with NTBC treatment.

Other

In some cases of the Fanconi syndrome where the underlying cause is known, withdrawing the offending agent will reverse the tubular dysfunction. This is true for galactose in galactosemia and fructose in hereditary fructose intolerance. A diet low in tyrosine and methionine in patients with tyrosinemia results in moderate improvement in the Fanconi syndrome associated with the disease. Cornstarch therapy for GSD may cause regression of hepatomegaly but has no effect on the tubular dysfunction. Chelating agents such as Penicillamine-D and Zinc therapy for Wilson's disease are associated with significant reduction in serum copper levels as well as clinical improvement.

Prognosis in Fanconi Syndrome

Prognosis depends on the underlying etiology of the Fanconi syndrome. For patients with cystinosis, the most common cause of the syndrome, long term treatment with cysteamine improves long term patient outcome, but even in patients who have undergone successful renal transplantation a significant number of extra renal abnormalities persisted or worsened over time. These included hypothyroidism, pulmonary insufficiency, myopathy, diabetes mellitus, and others. One third of the transplanted patients died at a mean age of 28 years or 16 years post

transplant. In tyrosinemia, long term outcome has improved appreciably with early institution of Nitisinone therapy (see above) which should be started prior to development of nodular cirrhosis.

Proximal Renal Tubular Acidosis (Type II, PRTA)

Definition

Defective bicarbonate reclamation by the proximal tubule is referred to as proximal RTA. It is usually seen in association with other proximal tubular transport defects as part of the Fanconi syndrome, but it may also be observed less commonly as an isolated condition where it is referred to as primary proximal RTA.

Etiology/Pathophysiology

The basic defect in PRTA is impaired renal bicarbonate reabsorption by the proximal tubules. Hypothetically, any of the mechanisms responsible for the reclamation of bicarbonate from the proximal tubular cells could be implicated in the etiology of PRTA. For a better understanding of PRTA a brief review of the mechanisms involved in bicarbonate reabsorption is in order (Fig. 304.3).

In the proximal tubular cells, a specific electroneutral Na^+–H_+ exchanger (NHE-3) at the luminal basement membrane, together with basolateral transport of bicarbonate by an electrogenic Na^+-HCO_3^- cotransporter (NBC-1), accounts for the reabsorption of 85% of the filtered bicarbonate back to the plasma. The remaining 15% of the filtered bicarbonate is reabsorbed in the more distal segments of the tubule, primarily by the thick ascending limb of Henle's loop (TALH). *NHE-3* is the main isoform of the NHE family responsible for the Na^+ exchange with H^+. It is localized exclusively in the apical cells of the proximal tubules and the cells of the TALH. The human *NHE-3* gene (*SLC9A3*) maps to chromosome 5p15.3.

Filtered bicarbonate combines with hydrogen (exchanged for sodium) to form carbonic acid (H_2CO_3) which is rapidly dehydrated to CO_2 and water, a process catalyzed by luminal carbonic anhydrase (CA IV) in the brush border of the proximal tubular cell. Luminal CO_2 diffuses freely into the cell and is rehydrated by cellular carbonic anhydrase (CA II) to form carbonic acid, which dissociates into H^+ and HCO_3^-. Both CA IV and CA II are maximally stimulated in chronic metabolic acidosis. The regenerated bicarbonate is returned to the blood via the NBC-1 to maintain normal bicarbonate levels. About one third of the hydrogen secreted and exchanged for sodium is derived from an electrogenic H-ATPase pump in the luminal basement membrane. PRTA (type 2 RTA) could occur if any of the forces involved in bicarbonate reabsorption, singly, or in combination became defective.

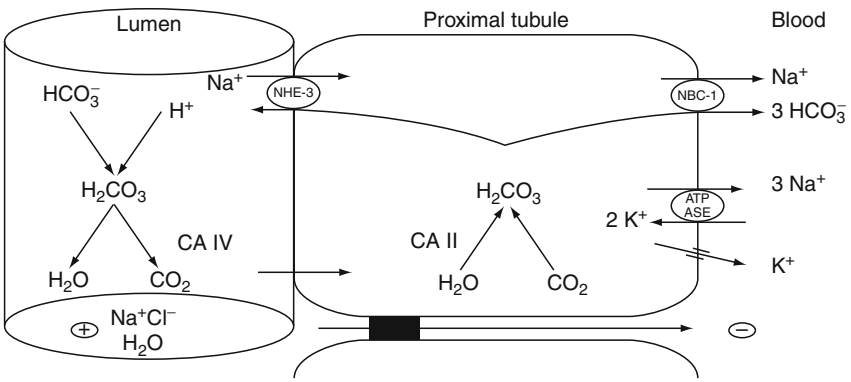

Figure 304.3

Bicarbonate reabsorption in proximal tubular cell. About two third of H^+ secreted is counter-transported with Na (NHE-3) and one third by a H^+-ATPase pump in the luminal membrane. HCO_3^- transport at the basolateral membrane is via a 1 Na^++3HCO_3 cotransporter (NBC-1). Cellular carbonic anhydrase II (CA II) and membrane-bound carbonic anhydrase IV (CA IV) are necessary for HCO_3^- reabsorption

These might be secondary to mutations in NHE3, NBC-1, carbonic anhydrase II or IV, or the H-ATPase pump. An abnormality in the Na-K-ATPase pump causes impaired reabsorption of all solutes ordinarily cotransported with sodium and results in the Fanconi syndrome. Bicarbonate reabsorption in the proximal tubule is a high capacity, low gradient process that bears an inverse proportion to changes in extracellular fluid volume. Other factors influencing HCO_3^- reabsorption include intraluminal flow rate, tubular and peritubular HCO_3-concentration, parathyroid hormone, pCO_2, chloride and potassium concentrations.

Incomplete bicarbonate reabsorption results in a large excretion of the filtered load of bicarbonate causing a fall in the plasma bicarbonate level. This excess bicarbonate will flood the distal tubules and impair urinary acidification. The urine pH will be alkaline and remain so until plasma bicarbonate falls below the renal threshold, after which it becomes bicarbonate free and properly acidified by the intact distal secretion of hydrogen ion. During acidemia in untreated patients, the urine pH is always less than 5.5.

PRTA in Association with the Fanconi Syndrome

The hereditary forms of the renal Fanconi syndrome are usually secondary to autosomal recessive metabolic diseases, the most common being cystinosis, tyrosinemia type 1, and glycogen storage disease (below). Renal bicarbonate wasting in the Fanconi syndrome occurs as part of a generalized proximal tubular transport defect. This is the result of a dysfunctional basolateral Na-K ATPase pump which is the driving source of energy for solute reabsorption. Glycogen storage disease appears to be a relatively common cause of the Fanconi syndrome in the Middle East, particularly in Saudi Arabia. This form of GSD, known as the Fanconi-Bickel syndrome, is due to mutations in the glucose transporter gene GLUT2. Other disease entities associated with the Fanconi syndrome and PRTA are listed in *Table 304.1*.

Isolated PRTA

This is a rare disease entity. The clinical features of isolated PRTA are those of failure to thrive and vomiting usually detected in early infancy, but the disease may not be diagnosed until early childhood. Unlike patients with the Fanconi syndrome, rickets, hypercalciuria are not features of this disease but hypokalemia has been observed in some patients. Most reported cases have been (a) sporadic, (b) autosomal dominant, and (c) autosomal recessive with ocular abnormalities.

Sporadic PRTA

Most cases of sporadic PRTA occur in early infancy and may be explained on an immature NHE3 or NBC1 transporter systems. Patients with this condition require therapy with alkalinizing agents but the majority outgrows the disease with time.

Autosomal Dominant PRTA

This variant of PRTA must be extremely rare and was reported once in a Costa Rican family about 30 years ago. All affected members had moderately severe hyperchloremic acidosis associated with growth retardation. Family pedigree in these patients was compatible with an autosomal dominant pattern of inheritance. Molecular studies have not been performed but the gene encoding the NHE3 appears to be a good candidate. Studies in knockout mice lacking the gene encoding NHE3 (*SLC9A3*) reveal significant reduction in proximal tubular reabsorption of bicarbonate but with only a mild degree of metabolic acidosis.

Autosomal Recessive PRTA

This entity was first described about 30 years ago by Donckerwolcke et al. This is another rare disorder which is invariably associated with ocular abnormalities including glaucoma, cataracts, and band keratopathy and, at times, physical and mental retardation, basal ganglia calcification, and enamel defects. The metabolic abnormalities reveal a fairly severe hyperchloremic, hypokalemic metabolic acidosis. The few patients described with this disease have been mostly from Europe and Japan. At the molecular level, several inactivating mutations in the gene encoding NBC-1 (*SLC4A4*) have been identified. These include nonsense mutations R298S, R510H, and a stop codon Q29X. The ocular abnormalities can be explained by the fact that the *NBC1* gene is expressed in several ocular tissues.

PRTA with Osteopetrosis

A unique syndrome of PRTA associated with osteopetrosis, cerebral calcification, and carbonic anhydrase II deficiency has been reported in several families from the Arab world. The syndrome is inherited as an autosomal recessive trait and is characterized clinically by failure to thrive, recurrent fractures, mental retardation in the majority of patients, and cranial nerve abnormalities. Over two third of the cases have been from Middle Eastern and North African countries where genetic heterogeneity is suggested by a more severe variant of the disease. In addition to the PRTA, a distal acidification defect has been suggested in many of these patients. The gene locus has been mapped to chromosome 8q22. Several mutations have been identified in patients with carbonic anhydrase II deficiency, but the most common is the Arabic one, which is a splice junction mutation in intron 2. More recently, mutations in the gene OC16, encoding the a3 subunit of the osteoclast V H^+-ATPase, have been shown to cause infantile malignant osteopetrosis.

Acquired PRTA

Drugs inhibiting carbonic anhydrase such as acetazolamide will cause a reduction in bicarbonate reabsorption in the proximal tubular cell (*Fig. 304.3*) resulting in a mild form of PRTA. More recently, Topiramate, a drug initially approved as an antiepileptic agent, is being increasingly used in the treatment of several neurologic and metabolic disorders. The drug also inhibits renal carbonic anhydrase activity, resulting in a proximal acidification defect similar to that observed with acetazolamide. The drug also causes hypocitraturia, hypercalciuria, and increased urine pH, all conducive to increased risk for kidney stone disease.

Diagnosis of PRTA

The diagnosis of PRTA should be considered in any infant (male > female) with failure to thrive and unexplained hyperchloremic acidosis. A urinary pH below 5.5 is strong evidence against distal RTA. If urinary pH falls in the equivocal zone (5.5–6.0) an acute acid load test with ammonium chloride should clarify the issue. This test is not necessary, and could be hazardous, if moderate to severe acidosis is present to begin with. The urine pH in PRTA is variable and depends on the plasma bicarbonate concentration. The diagnosis is confirmed by demonstrating a fractional excretion of bicarbonate (FE_{HCO3}) in excess of 15%. FE_{HCO3} is calculated during intravenous bicarbonate infusion or oral bicarbonate therapy by simultaneous measurement of urine and plasma bicarbonate and levels after ensuring an adequate rise in plasma bicarbonate:

$$FE_{HCO3} = \frac{U_{HCO3} \times P_{Cr}}{U_{Cr} \times P_{HCO3}}$$

where U and P represent urine and plasma concentration of bicarbonate (HCO_3) and creatinine (Cr) respectively.

Treatment of Proximal RTA

Treatment of PRTA usually requires large and frequent doses of sodium bicarbonate or citrate (5–20 mEq/kg/day). Potassium supplements may be necessary especially with large doses of bicarbonate, as this will aggravate potassium wasting by the kidney. In patients requiring large doses of alkali therapy, a thiazide diuretic may be used to reduce ECV expansion and enhance bicarbonate reabsorption by the proximal tubules.

Prognosis of PRTA

The prognosis of PRTA depends on the underlying etiology. If associated with the Fanconi syndrome, as the majority of cases are, the outcome will vary with the specific etiology of the Fanconi syndrome and its response to therapy (see above).

Disorder of Renal Phosphate Transport

Several disease entities have been described in association with hypophosphatemia, some are heredofamilial and some are acquired.

Heredofamilial Hypophosphatemia

Several terms have been used to describe this entity: vitamin D resistant rickets, X-linked hypophosphatemic rickets, primary hypophosphatemic rickets, familial hypophosphatemia, and phosphate diabetes. The disease represents the most common form of rachitic bone disease in North America, Western Europe, and in industrialized countries where nutritional rickets is no longer a significant problem.

Heredofamilial hypophosphatemia is transmitted as an X-linked dominant (XLH) or autosomal dominant trait (ADHR) with the former being much more prevalent (1 in 20,000). A rare autosomal recessive variant (ARHR) was also described recently.

XLH

In XLH, affected males (hemizygotes) will always manifest the disease, whereas females (heterozygotes) have a milder form of hypophosphatemia with mild bowing of the legs.

Etiology, Genetics, and Pathogenesis

The mutant gene of XLH has been mapped recently to the short arm of the X chromosome (Xp 22). One third of cases occur sporadically and may represent new mutations. Two murine homologues, *Hyp* and *Gy*, have helped significantly in detecting the mechanisms for renal phosphate wasting in XLH. The gene responsible for XLH was identified recently by positional cloning and designated *PHEX* (*PH*osphate regulating gene with homology to *E*ndopeptidases on the *X* chromosome). Several inactivating mutations in this gene have been identified in patients with XLH and in the murine models as well. It is thought that under normal circumstances, *PHEX* is involved in the inactivation of a phosphaturic hormone or the activation of a phosphate conserving hormone. Therefore loss *of PHEX* function is associated with either an excess of this phosphaturic hormone or a deficiency in the phosphate conserving hormone. In either case, renal other Na/P cotransporter would be down regulated and phosphaturia would ensue. However, endogenous *PHEX* substrates have not yet been identified. Recently it has been shown that *FGF23* gene expression is increased in Hyp mouse bone and Hyp osteoblast cultures, suggesting that *PHEX* normally inhibits FGF23 expression. Thus, an inactivating PHEX mutation results in abnormal regulation of FGF23 and possibly other molecules, resulting in the phenotype of XLH.

Clinical Findings

Children with XLH present at the onset of walking or later when weight bearing will lead to the classical bone deformities and growth failure. Genu varum occurs more frequently than genu valgum. Coxa vara is common, leading to the typical waddling and unsteady gait. Craniotabes and rachitic rosary, commonly seen with vitamin D deficiency rickets, are seldom observed with XLH. Tooth eruption may be delayed, but unlike in hypocalcemic forms of rickets, the enamel is normal. Sensorineural deafness appears to be relatively common. Radiologically, the findings are those of rickets with loss of provisional zone of calcification, widening of the epiphyseal plate, and coarse trabecular pattern. These changes are more pronounced in the lower extremities. Long bones are short and thickened, resulting in short and stubby appearance.

Pathophysiology

The pathophysiology of bone disease in XLH remains a controversial issue. It is possible that the primary genetic defect (*PHEX* mutations) causes (a) decreased renal tubular transport of phosphate leading to phosphaturia and hypophosphatemia (b) defective renal 1-alpha hydroxylase activity leading to inappropriately low levels of 1,25 $(OH)_2D_3$ relative to the low serum phosphate. This latter defect could be acquired since calcitonin stimulation of 1-alpha hydroxylase is normal in patients with HVDRR. This combination (a and b) is synergistic in causing the bone disease characteristic of XLH. The inadequate levels of 1, 25 $(OH)_2$ D_3 will also lead to reduced calcium and phosphate absorption from the gut, further contributing to the pathogenesis of the disease. Although PTH levels in XLH are usually normal, increased proximal tubular sensitivity to PTH may contribute to the renal phosphate wasting.

Diagnosis

The clinical manifestations described above are usually suggestive of the diagnosis. This is confirmed Biochemically where XLH is characterized by variable degrees of hypophosphatemia with normal serum calcium, elevated alkaline phosphatase and normal or slightly elevated PTH levels. The urinary findings reveal evidence of hyperphosphaturia with urinary phosphate excretion exceeding 20 mg/kg/day. Tubular reabsorption of phosphate (TRP) is derived by simultaneous measurement of urine and plasma phosphate and creatinine and calculated by the formula:

$$\mathrm{TRP} = 1 - \frac{U_p \times P_{Cr}}{U_{Cr} \times P_p}$$

where U_p and U_{Cr} indicate urine phosphate and creatinine concentrations, respectively, and P_{Cr} and P_p represent

plasma creatinine and phosphate concentrations. Normally, TRP ranges between 0.80 and 0.90. In patients with XLH, TRP is frequently below 0.50 (0.40–0.70). The test should be done while the patient is receiving adequate phosphate supplements for a few days.

ADHR

Patients with ADHR have similar clinical findings as those with XLH but differ in their mode of inheritance. The *ADHR* gene locus was mapped to chromosome 12p13.3. The gene responsible for ADHR has been found by positional cloning to be a fibroblast growth factor, *FGF23*. It has been subsequently shown that infusion of FGF23 in experimental animals results in phosphaturia and hypophosphatemia. At the renal proximal tubule brush border, FGF23 infusion rapidly decreases expression of Na/P cotransporter. Parathyroid hormone (PTH) also directly decreases Na/P cotransporter at the renal proximal tubule brush border *via* a cAMP/protein kinase A–mediated pathway, but infusion of FGF23 in thyroparathyroidectomized rats causes hypophosphatemia suggesting that the action of FGF23 on renal phosphate reabsorption is independent of PTH and may be complementary.

Treatment and Prognosis of XLH and ADHR

Since rickets in XLH and ADHR is primarily due to hypophosphatemia the goal of therapy is directed at raising plasma phosphate to normal levels. Phosphate supplements, in large and frequent doses, were recommended in the past to compensate for the ongoing urinary losses. Large doses of phosphate are usually associated with gastrointestinal complaints (vomiting and diarrhea) which may be a limiting factor in the treatment. Another drawback of raising plasma phosphate is the simultaneous lowering of the plasma ionized calcium which will lead to secondary hyperparathyroidism that can further aggravate the bone disease and increase the phosphaturia. For these reasons the addition of calcitriol to the therapeutic regimen offers the following advantages: (1) less phosphate will be needed and less gastrointestinal complications; (2) calcium and, to a lesser degree, phosphate absorption from the gut are enhanced leading to bone healing and improved linear growth; and (3) low incidence of hyperparathyroidism. The recommended dose for oral phosphate supplement is 1–2 g/day in four to five divided doses. Calcitriol in a dose of 0.25–1.0 μg/day is usually sufficient but some patients may require higher doses. Lower limb deformities appear to correct better if treatment is started before the age of 6 years, but final adult height remains significantly lower than the expected mean for age. Many patients require unilateral or bilateral corrective osteotomies for severe and persistent rachitic changes in the lower extremities. Some patients may benefit from growth hormone therapy.

Recent data suggest that adjunctive therapy with thiazide diuretics in combination with salt restriction will enhance proximal tubular reabsorption of phosphate. We have tried this combination in 6 patients with XLH but were not encouraged with the results, but thiazides may be effective in reducing the hypercalciuria and nephrocalcinosis associated with vitamin D therapy.

Other Hypophosphatemic Syndromes

Hypophosphatemic rickets or osteomalacia may be seen with chronic intake of phosphate binding gels.

Oncogenic hypophosphatemia with osteomalacia also known as tumor induced osteomalacia (TIO) has been reported with certain tumors of mesenchymal origin, usually sclerosing hemangiomas. Patients with TIO may present with fatigue, bone pain, fractures, and proximal muscle weakness. Children develop rickets and lower extremity deformities similar to those in ADHR and XLH. Many of these tumors are small and may be difficult to locate. Multiple imaging techniques including, magnetic resonance imaging, and positron emission tomography may be required to localize the tumor, which when found and removed reverses the phosphate, vitamin D, and bone abnormalities. The vast majority of these tumors are benign. Tumors that cause TIO usually overexpress FGF23, a known phosphaturic substance. Pathologic samples of patients with TIO have detected FGF23 in more than 80% of specimens tested.

The syndromes of hereditary hypophosphatemia with hypercalciuria must be differentiated from HLH and ADHR. Two forms are recognized. One is a rare autosomal recessive with phosphaturia and hypophosphatemia but appropriately elevated calcitriol levels. Hypercalciuria is probably due to increased intestinal absorption of calcium. Phosphate supplement without vitamin D reverses the rickets and osteomalacia. The other form is known as Dent's disease and is associated with X-linked nephrolithiasis and hypophosphatemic rickets. Hypercalciuria, uricosuria, and renal potassium wasting with progression to chronic renal failure is frequently observed.

Hyperphosphatemic Syndromes

Disorders associated with hypoparathyroidism, whether congenital or acquired are associated with hyperphosphatemia and hypocalcemia. The various conditions associated with these abnormalities are discussed in the section of endocrinology. A new syndrome of congenital hypoparathyroidism, dysmorphic features, severe growth failure, and mental retardation was reported recently in Arabian infants with normal cardiovascular systems and normal cellular immunity. Their dysmorphic features are quite distinctive from those of DiGeorge's syndrome and consist of deep-set eyes, microcephaly, thin lips, beaked nose tip, external ear anomalies, depressed nasal bridge, micrognathia, and other minor anomalies. The mode of inheritance of this syndrome is autosomal recessive as suggested by the very high rate of consanguinity (11 of 12 patients), equal occurrence in both sexes, and familial incidence. Molecular studies have recently identified the genetic basis of this disease. Mutations in the tubulin-specific chaperone, *TBCE*, have been found consistently in these patients. Treatment with pharmacologic doses of vitamin D and calcium supplements improves their biochemical abnormalities but growth retardation shows no response.

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305 Disorders of Distal Tubular Transport of Sodium and Potassium

Sami A. Sanjad · John W. Foreman

Under normal circumstances, the urinary excretion of sodium matches the dietary intake such that a zero external balance is maintained. The factors that control sodium balance have been briefly alluded to in the section on renal function. A detailed account of the different factors modulating sodium balance are beyond the scope of this chapter, but suffice it to say that after the first year of life, the kidney is able to reduce urinary excretion of sodium to negligible values if the need arises (low-salt diet, ECV contraction).

Disorders Associated with Isolated Renal Salt Wasting

Etiology

Solute Diuresis Associated with Nephron Hyperfiltration

This is typically seen in patients with chronic renal failure, particularly those with a significant tubulointerstitial component. Renal salt wasting is usually mild but occasionally can be severe enough to cause ECV contraction, hypotension, and further deterioration of renal function. The diagnosis is made from the history and physical examination and tests of renal function which reveal increasing azotemia, hyponatremia, hyperkalemia, and metabolic acidosis. Urinary sodium is usually in excess of 60–120 meq/L in spite of ECV contraction.

Impaired Tubular Sodium Transport

Both congenital and acquired defects in sodium transport along different segments of the nephron may be associated with variable degrees of renal salt wasting.

Acute and chronic interstitial nephritis – Various segments of the nephron may be involved in abnormalities of sodium transport. Many renal diseases with a prominent tubulointerstitial involvement may be associated with renal salt wasting. These include obstructive uropathies, nephrocalcinosis, analgesic nephropathy, allergic interstitial nephritis, amyloidosis, and others.

Medullary cystic disease/Juvenile nephronophthisis – Renal salt wasting may be a prominent feature in children and adolescents with this disease.

Drugs – Several drugs known to cause interstitial nephritis may cause some degree of salt wasting. Prominent among these are *cis*-platinum and Amphotericin B.

Renal tubular acidosis – Patients with both proximal and distal RTA exhibit variable degree of salt wasting. In proximal RTA, this occurs only with sodium bicarbonate treatment when plasma bicarbonate exceeds the renal tubular threshold. In distal RTA, a mild degree of renal salt wasting occurs at all levels of plasma bicarbonate, and fractional excretion of sodium is usually between 2% and 5% (normal $<1\%$).

Transient Pathophysiologic States Associated with Renal Salt Wasting

Transient renal salt wasting may be seen during the recovery phase of acute tubular necrosis. In children recovering from acute post streptococcal glomerulonephritis, a mild degree of salt wasting may occur for a few months following recovery, but this is of no clinical significance. Massive renal salt wasting may occur in the early post renal transplant period, and to a lesser degree following relief of urinary tract obstruction. Diuretics, by definition, interfere with sodium reabsorption at different sites of the nephron and thus will cause reversible renal salt wasting.

Conditions Associated with Deficient Mineralocorticoid Activity

These are typically observed in patients with Addison's disease, isolated hypoaldosteronism, and pseudohypoaldosteronism type 1. Congenital adrenal hyperplasia,

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due to 21-α-hydroxylase deficiency is one of the most common extra renal causes of renal salt wasting. This entity is discussed separately in the section on endocrinology.

Treatment

Treatment of isolated renal salt wasting states will depend on the underlying mechanism and the severity of the renal sodium losses, its effect on renal function, blood pressure, serum sodium, potassium, and acid–base balance (see below). Liberalizing salt intake, parenterally, or orally if tolerated, will usually reverse these abnormalities. If concomitant metabolic acidosis is present, sodium bicarbonate or citrate should be used in addition to sodium chloride.

Disorders Associated with Renal Salt Wasting and Hypokalemia

Bartter's Syndrome

Since Bartter and colleagues' original description of two patients with severe hypokalemic metabolic alkalosis and hyperaldosteronism in 1962, there have been several series and case reports describing a similar clinical presentation.

Clinical Manifestations

Older patients with Bartter's syndrome present typically with hypokalemia, fatigue, muscle weakness and cramps, neuromuscular irritability, polyuria, and polydipsia. The hypokalemia is usually moderate to severe and is secondary to renal potassium wasting, with urinary potassium concentrations frequently exceeding 40 meq/L. Serum bicarbonate values usually exceed 30 meq/L and are accompanied by arterial pH values that are often above 7.50. This metabolic alkalosis is chloride resistant as urine chloride levels exceed 20 meq/L with resultant hypochloremia.

Many other abnormalities have been described in patients with Bartter's syndrome. Urine concentrating ability is impaired, presumably from the long-standing hypokalemia. Hyperplasia of the juxtagomerular cells is common but this is not pathognomonic of Bartter's syndrome as originally thought because it may be seen in other conditions associated with extracellular volume contraction and hyperreninemia, such as Addison's disease, laxative or diuretic abuse. Hyperplasia of renal medullary interstitial cells, the probable source of the increased prostaglandin secretion typically observed in this syndrome, has also been described. In children, growth retardation is common and may be the presenting complaint. Mild mental retardation and facial dysmorphism has also been noted in some patients. A more severe and common variant of Bartter's syndrome is seen in the neonate or early infancy and is referred to as antenatal Bartter's syndrome. These babies have a history of maternal polyhydramnios and are usually born prematurely and small for gestational age. Hypercalciuria is invariably present in association with nephrocalcinosis. Prostaglandin E2 is markedly elevated and has led to the name hyperprostaglandin E2 syndrome. These infants have been reported to respond especially well to cyclooxygenase inhibitors.

Etiology and Pathogenesis

The past 12 years have witnessed major developments in the fields of molecular and cell biology that have led to our understanding of the pathogenesis of Bartter's syndrome. Until the mid-1990s, the pathogenesis of this syndrome remained elusive and pathophysiologic constructs of the syndrome were circular making the initiating event difficult to define.

Because the biochemical and physiologic changes in Bartter syndrome are similar to those seen in patients receiving loop diuretics, the Bumetanide-sensitive Na–K-2Cl cotransporter, *NKCC2*, was sought as a candidate gene due to its role in Cl and Na reabsorption in the TALH segment. This transporter is the site of action for loop diuretics where they inhibit sodium, potassium, and chloride reabsorption. Thus, chronic administration of loop diuretics will result in hypokalemia, metabolic alkalosis, hyperreninemia, hyperaldosteronism, chloride wasting, hypercalciuria, and hyperprostaglandinism which are findings typically observed in patients with Bartter's syndrome (*Fig. 305.1*). Also, physiologic studies with hypotonic saline or water diuresis had clearly demonstrated impaired sodium chloride reabsorption in the thick ascending limb of Henle's loop in the majority of patients studied.

The etiology of Bartter's syndrome has been characterized recently at the molecular level. Simon and associates demonstrated linkage of Bartter's syndrome to the renal Na–K-2Cl cotransporter gene *NKCC2* and identified several inactivating mutations for this gene that cosegregate with the disease – Bartter's type 1. Genetic heterogeneity was demonstrated subsequently by the

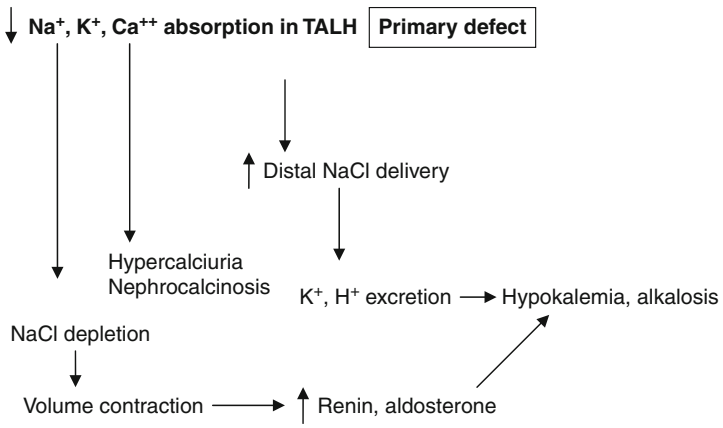

Figure 305.1
Pathophysiology of Bartter's syndrome

Table 305.1
Hereditary renal hypokalemic alkalosis

Disorder	Bartter's 1	Bartter's 2	Bartter's 3	Bartter's 4	Bartter's 5	Gitelman's
Inheritance	AR	AR	AR	AR	AD	AR
Gene/Locus	*SLC12A1*/15q15-21	*KCNJ1*/11q24	*CLCNKB*/1p36	*BSND*/1p31	*CASR*/3q21	*SLC12A3*/16q13
Protein	NKCC2	ROMK	ClCN-Kb	Barttin	CaR	NCCT
Polyuria, dehydration, polyhydramnios	Yes	Yes	Variable	Yes Deafness	Hypocalcemia, convulsions	Rare
Nephrocalcinosis hypercalciuria	Yes	Yes	Rare	Yes	Yes	Hypocalciuria
Antenatal Variant	Yes	Yes	Very rare	Yes	No	No

same group of investigators who identified mutations in two additional genes that act as regulators of the Na–K-2Cl cotransporter. The first is ROMK, an ATP-sensitive K channel, which recycles reabsorbed K back to the tubular lumen to allow sustained cotransport activity – Bartter's type 2. The second is a chloride channel gene *CLCNKB* which is important in Cl absorption across the basolateral membrane to the peritubular blood – Bartter's type 3. A fourth genotype of Bartter's syndrome was identified by positional cloning in ten families with the usual abnormalities but in association with sensorineural deafness. The gene encodes a protein called Barttin, a beta subunit of the *CLCNKB,* which is also expressed in the potassium-secreting epithelial cells of the inner ear. Thus, inactivating mutations of the gene impair function of the chloride channel, causing Bartter's syndrome and sensorineural deafness – Bartter's type 4. All these variants of Bartter's syndrome are inherited by autosomal recessive genes and disease prevalence is more common in communities with high rate of consanguineous marriages. Lastly, a fifth variant of Bartter's syndrome was discovered in association with another rare syndrome of autosomal dominant hypocalcemia. The mutated gene is the Calcium Sensor Receptor, *CASR,* which is also expressed in the TALH. When maximally activated due to gain of function mutations, this results in decreased sodium and chloride reabsorption primarily due to inhibition of the ROMK channel. With the advent of the molecular identification of the various types of Bartter's syndrome, it is now possible to develop phenotype–genotype correlations, although considerable overlap remains. *Table 305.1* and *Fig. 305.2* summarize the various phenotypes and genotypes of Bartter's syndrome.

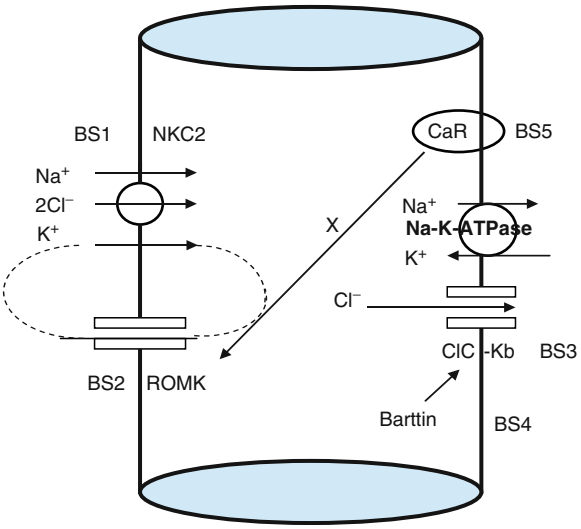

Figure 305.2
The main transport proteins and ion channels in the TALH. Mutations in the NKCC2, ROMK, CLC-KB, Barttin, and CaR cause Bartter's syndrome (BS) types 1, 2, 3, 4, 5, respectively

Table 305.2
Hypokalemic, metabolic alkalosis in children

Non-hypertensive	Hypertensive
Pyloric stenosis	Renal artery stenosis
Gastric suction	Primary aldosteronism
Cystic Fibrosis	Cortisol synthesis enzyme defects
Diuretics – laxatives	11-Beta-hydroxylase
Chloride deficient formula	17-Alpha-hydroxylase
Bartter's syndrome	Cortisol degradation enzyme defect
Gitelman's syndrome	11-Beta-cortisol dehydrogenase
Neonatal Bartter's – hyperprostaglandin E syndrome	Glucocorticoid remediable hypertension
	Liddle's syndrome
Congenital chloride diarrhea	Licorice abuse

Differential Diagnosis

The differential diagnosis of Bartter's syndrome and other forms of hypokalemic, metabolic alkalosis in children is shown in *Table 305.2*.

Gitelman's Syndrome

In 1966, Gitelman and Welt described a familial disorder characterized by hypokalemia, metabolic alkalosis, and hypomagnesemia. Most patients presented in late childhood, or as young adults, frequently with tetany. Compared to Bartter's syndrome, they have less pronounced hypokalemia, hyperreninemia, and hyperaldosteronism. Hypocalciuria and hypomagnesemia are other distinguishing features and they usually have normal stature. Genetic studies of patients with Gitelman's syndrome have identified several inactivating mutations in the thiazide-sensitive Na–Cl cotransporter (NCCT) in the early distal tubule. Impaired function of this transporter would increase sodium delivery to the more distal portions of the nephron leading to increased potassium and hydrogen ion secretion. The cause of the increased magnesium excretion seen in this syndrome is unclear, but it may also be seen in patients receiving thiazides chronically. *Table 305.3* shows some of the salient features that differentiate Bartter's from Gitelman's syndromes.

Treatment and Prognosis

The major goal in treating Bartter's syndrome is to normalize the serum potassium. However, this is usually difficult to achieve and patients require large doses of supplemental KCl. "Potassium sparing" agents, such as amiloride, spironolactone, and triamterene, are helpful but many of these patients remain hypokalemic in spite of large doses of KCl and potassium sparing drugs. Nonsteroidal anti-inflammatory drugs (NSAIDS) are somewhat useful in correcting the hypokalemia and volume contraction, presumably by inhibiting prostaglandin synthesis and their effect on blocking the tubuloglomerular feedback caused by decreased chloride reabsorption. Prostaglandin inhibitors also reduce the hypercalciuria and are reported to be especially useful in "neonatal Bartter's" or hyperprostaglandin E2 syndrome. In many patients, these agents are useful initially, but not on a long-term basis. Angiotensin converting enzyme inhibitors have been shown to improve the hypokalemia, but many patients cannot tolerate their hypotensive effects. In spite of the severe and long-standing potassium depletion, cardiac arrhythmias are infrequent and these patients tolerate general anesthesia relatively well. In Gitelman's syndrome, magnesium supplementation is especially important, in addition to potassium. In contrast to Bartter's syndrome patients,

Table 305.3
Differentiation between Bartter's and Gitelman's syndromes

	Bartter's syndrome	Gitelman's syndrome
Age of presentation	Early (may be neonatal)	Anytime – often as adults
Presenting complaint	Polyuria, polydipsia, FTT	Tetany
Inheritance	Autosomal recessive or sporadic	Autosomal recessive
Maximal urine concentration	Decreased	Usually normal
Serum magnesium	Normal	Low
Urinary calcium	>4 mg/kg/day	Low or normal
Defect	Mutations in cotransporter NKCC2, ROMK, CLCNKB/A Channels, Barttin, CaSR	Mutations in thiazide-sensitive NaCl transporter in renal distal tubule

Gitelman's syndrome patients require relatively modest doses of KCl to correct the potassium defect and NSAIDS are not required.

Disorders Associated with Renal Salt Wasting and Hyperkalemia

Autosomal Recessive Pseudohypoaldosteronism Type 1 (AR PHA1)

This is a rare autosomal recessive disorder characterized by life-threatening dehydration in neonatal life and early infancy secondary to severe renal salt wasting, hypotension, hyponatremia, and hyperkalemic metabolic acidosis. There is also marked elevation of plasma renin activity and aldosterone levels. Genetic analysis of affected offspring showed linkage to chromosomes 12p13 and 16p13 which contain genes encoding different subunits of the sodium epithelial channel, ENaC. Several inactivating homozygous mutations in the three subunits (α-, β-, and γ-ENaC) of this gene have been identified. These mutations are associated with persistent and longer open probability of the channels leading to renal salt wasting from the distal collecting tubules and a secondary defect in hydrogen and potassium ion secretion with resultant hyperkalemia and metabolic acidosis (*Figs. 305.3* and *305.5*). Since the ENaC is also expressed in the respiratory epithelial cells, from the nose to the terminal bronchioles and alveoli, patients with the PHA1 frequently present with increased airway secretions and lower respiratory infections.

The differential diagnosis of PHA1 includes (1) salt wasting congenital adrenal hyperplasia with mineralocorticoid deficiency, (2) isolated hypoaldosteronism (very rare), and (3) autosomal dominant PHA1.

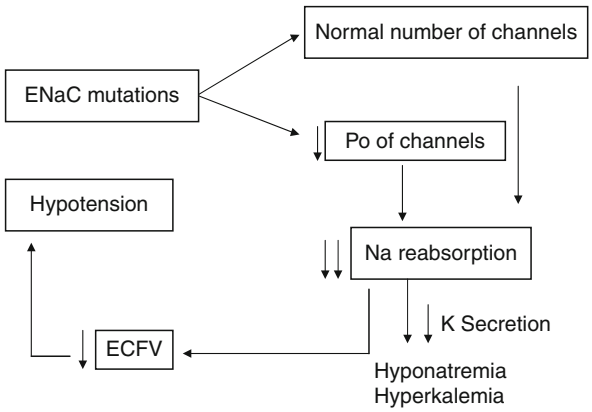

Figure 305.3
Pathophysiology of AR pseudohypoaldosteronism type 1. *ENaC* sodium epithelial channel, *Po* open probability

Autosomal Dominant Pseudohypoaldosteronism Type 1 (AD PHA1)

This entity has a similar but, usually, a less severe clinical presentation than the recessive type. Heterozygous mutations in the gene (*NR3C2*) encoding the mineralocorticoid receptor are found in 75% of reported families as well as in some sporadic cases. In many patients, the symptoms related to renal salt wasting remit with time.

Treatment of PHA1

In order to keep up with high urinary losses of sodium, a high salt intake is an essential aspect of the management of patients with PHA1 with some requiring as much as 20–30 mmol of sodium/kg/day. In addition, most infants

and children will require K-binding resins to prevent hyperkalemia which may be lethal at times.

Disorders with Renal Salt Retention and Hypokalemia

Liddle's Syndrome

Liddle and colleagues described a family with hypokalemia and hypertension in which the clinical manifestations resembled primary aldosteronism, but the serum and urine aldosterone levels were suppressed. It was also noted that an inhibitor of the aldosterone receptor was not effective in treating hypertension, but triamterene, which inhibits potassium secretion through a mechanism other than aldosterone receptor blockade, was effective. Several kindreds have been described to date and this syndrome is inherited as an autosomal dominant disorder. The signal feature, besides hypertension, is hypokalemia, occurring in 50% of patients. Hypertension typically begins in adolescence, but has been noted in infants. The severity of the hypertension varies between patients, but there is an excess of cerebral hemorrhage and premature death in most kindreds.

Pathogenesis

Linkage analysis of the original kindred showed complete linkage of the disease to the beta subunit of the amiloride-sensitive epithelial sodium channel (β-ENaC). This sodium channel resides on the luminal membrane of the renal cortical collecting duct and plays an important role in sodium reabsorption in this nephron segment. It has been subsequently shown that activating, gain of function, mutations in both β and γ subunits of the ENaC are causative of Liddle's syndrome presumably, the defective subunit increases the number of open channels and maintains the distal nephron in a sodium avid state, even when the patients are salt repleted and aldosterone is inhibited. The avid sodium reabsorption maintains a lumen negative electrical gradient, which enhances potassium and hydrogen ion excretion. This leads to hypokalemia, volume expansion, hypertension, and metabolic alkalosis (*Figs. 305.4* and *305.5*).

Diagnosis

The diagnosis of Liddle's syndrome should be suspected in patients with hypertension and hypokalemia. The finding of suppressed aldosterone levels confirms this suspicion, especially if there is a strong family history of hypertension. A urine aldosterone to potassium ratio of <60 (ng/mmol) appears to be the most sensitive measure of aldosterone suppression. Patients with Liddle's syndrome usually have high TTKG values (greater than 9–10) which fall to low levels following treatment with sodium channel blockers (see below).

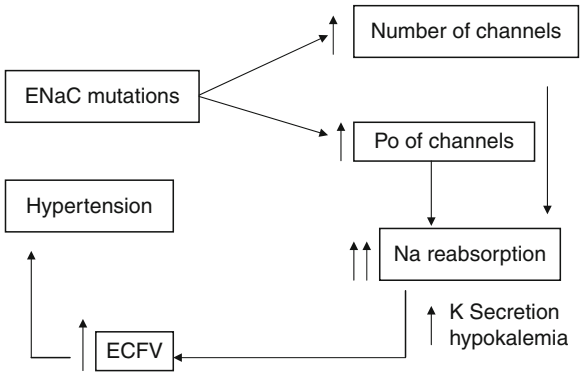

Figure 305.4
Pathophysiology of Liddle' Syndrome. *ENaC* sodium epithelial channel, *Po* open probability

Differential Diagnosis

Other causes of hypokalemic hypertension include renal artery stenosis, renin secreting tumor, primary hyperaldosteronism, and glucocorticoid remediable aldosteronism (GRA). All of these can be distinguished from Liddle's syndrome by the presence of hyperaldosteronism. Enzymatic deficiencies that lead to hypokalemic hypertension include 11-beta-hydroxylase and 17-alpha-hydroxylase in the cortisol and aldosterone biosynthetic pathway. Deficiency of 11-beta-hydroxylase is characterized by virilization and deficiency of 17-alpha-hydroxylase with hypergonadotropic hypogonadism. Both are also associated with decreased cortisol levels that stimulate corticotropin release. This stimulates steroid formation proximal to the block, including deoxycorticosterone that has mineralocortoid effects through the aldosterone receptor. These patients have low cortisol levels and abnormal levels of steroid metabolites in their urine. They respond to spironolactone, unlike patients with Liddle's syndrome. The enzyme, 11-beta-hydroxysteroid dehydrogenase, protects the aldosterone receptor from interacting with cortisol by converting it to cortisone. Patients with 11-beta-hydroxysterone dehydrogenase deficiency have low levels of aldosterone and abnormal levels

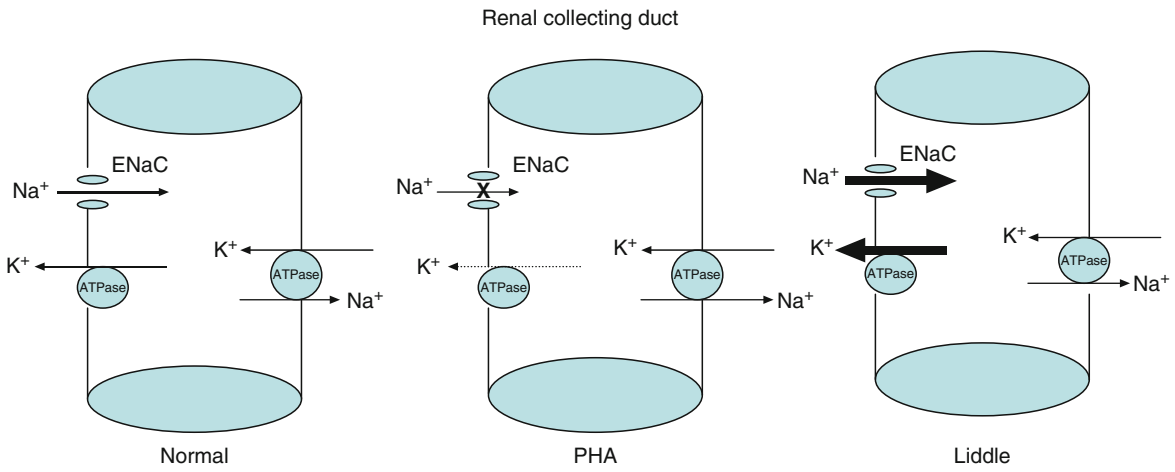

Figure 305.5
Pathophysiology of Pseudohypoaldosteronism type 1 and Liddle's syndrome

of cortisol to cortisone metabolites in their urine. Glycyrrhetinic acid found in licorice inhibits this enzyme mimicking 11-beta-hydroxysterone dehydrogenase deficiency. GRA results from an abnormal gene that consists of the ACTH responsive portion of the gene coding 11-beta-hydroxylase to aldosterone synthetase gene. This gene fusion mutation confers ACTH regulation to aldosterone synthesis, leading to excess aldosterone. All these enzyme defects demonstrate a reduction in blood pressure with physiologic doses of dexamethasone.

Treatment

The first aspect of Liddle's syndrome treatment is to block the open sodium channel with the potassium sparing diuretics, amiloride or triamterene. Spironolactone, acting through the aldosterone receptor is not useful. However, sodium restriction may still be necessary in some patients to reduce the volume expansion and maintain blood pressure control. In spite of maximal doses of amiloride and sodium restriction, some patients will require additional antihypertensive agents.

Disorders with Salt Retention and Hyperkalemia

Pseudohypoaldosteronism Type 2 (Gordon Syndrome)

In 1970, Gordon and associates described a 10-year-old girl with hypertension, severe hyperkalemia, acidosis, suppressed renin and aldosterone activity, and normal GFR. At least 40 patients with similar findings have been reported since then. Many of these have been members of the same family and an autosomal dominant inheritance has been suggested, but a clear-cut mode of transmission has not been determined in most cases. The syndrome is very rare and has been reported in both children and adults, and represents the prototype of pseudohypoaldosteronism type II. Hyperkalemia may be quite severe and is associated with hyperchloremic acidosis, moderate to severe hypertension, and ECV expansion, with secondary suppression of renin, aldosterone, and prostaglandins. These findings are diametrically opposite to those of Bartter's and Gitelman's syndromes. The proximate cause of this rather unique salt-sensitive syndrome of hypertension and hyperkalemic acidosis has been found recently to be due to activating, gain of function, mutations in the novel genes *WNK1* and *WNK4* both of which enhance the activity of the thiazide-sensitive NaCl cotransporter, NCC, in the distal collecting tubule. In addition, these mutated genes have an inhibitory effect on the potassium channel ROMK thus leading to avid sodium chloride reabsorption and potassium retention.

Treatment

Treatment consists of moderate salt restriction alone, or in combination with furosemide or thiazides. This completely reverses the hyperkalemic acidosis, restores renin, aldosterone, and prostaglandins, and normalizes blood pressure. In some patients with refractory hyperkalemia, cation exchange resins may be necessary.

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306 Distal Renal Tubular Acidosis (TYPE I, DRTA)

Sami A. Sanjad

Introduction

The kidney plays a major role in acid–base homeostasis. This is accomplished by two essential mechanisms, both involving the exchange of filtered sodium from the tubular lumen with secreted hydrogen from the tubular cells. The first mechanism is quantitatively more important and occurs primarily in the proximal tubule. It accounts for the reabsorption or reclamation of 85–90% of the filtered bicarbonate back to peritubular capillaries, thus maintaining the concentration of bicarbonate in the plasma fairly constant. This process is catalyzed both by: (a) luminal carbonic anhydrase IV, which causes the dehydration of carbonic acid; and (b) cellular carbonic anhydrase II, which rehydrates the absorbed CO_2 to form carbonic acid. The latter dissociates into H^+ and HCO_3. This regenerated bicarbonate is returned to the blood and maintains normal bicarbonate levels (Fig. 288.2, Chap. 288, "Overview of Renal Function").

The second mechanism also involves the exchange of luminal sodium for cellular hydrogen ions secreted in the distal tubule. The hydrogen ions combine with filtered buffers (mainly phosphate) and are excreted in the final urine as titratable acid. As this is not enough to excrete all the daily acid load, a new buffer, NH_3, derived from the deamination of glutamine in the tubular cells, diffuses passively into the lumen and combines with hydrogen ion, also secreted from the tubular cells. The resulting NH_4^+ ion is "trapped" (does not diffuse back into the cell) and is excreted in the final urine (Fig. 288.3, Chap. 288, "Overview of Renal Function"). Net acid excretion (NAE) is the term used to express the sum of TA and NH_4^+ minus any HCO_3 (negligible) that may be excreted. The steady state net acid excretion is equal to hydrogen ion generated from endogenous and exogenous (diet) sources. This is also equal to the net addition of bicarbonate by the kidneys to the body fluids (40–60 meq/m^2/day).

Definition

DRTA is a rare renal tubulopathy characterized by persistent hyperchloremic (normal anion gap) metabolic acidosis due to impaired secretion of hydrogen ion from the distal collecting duct cells to the tubular lumen resulting in relatively high urine pH in the face of systemic acidosis. Although frequently considered in the differential diagnosis of infants and children with failure to thrive, it is seldom detected as the cause.

Pathophysiology of DRTA

Until recently, all patients with DRTA were thought to have a single underlying pathogenetic mechanism: an inability of the distal nephron to generate and maintain steep pH gradients between peritubular blood and urine. The implication was that the distal tubular cells were capable of proton secretion but, because of a leaky membrane, hydrogen ions back diffused to the circulation leaving behind a relatively alkaline urine. This was referred to as gradient defect RTA. The prototype of such a defect in acidification is seen in patients treated with Amphotericin B.

Three types of cells in the distal nephron contribute to acid–base homeostasis: (1) the alpha-intercalated cells, which contain a luminal H^+-ATPase pump and an H^+–K^+-ATPase pump; (2) the principal cells, which have an indirect but important effect in urine acidification (see below, Voltage-dependent DRTA); and (3) the beta intercalated cells, which have a limited role in acidification but may be involved in bicarbonate secretion in vegetarians ingesting an alkaline ash diet. With this background, it is now possible to characterize DRTA from a mechanistic point of view (*Fig. 306.1*).

The alpha-intercalated cell of the distal collecting ducts plays a pivotal role in the fine regulation of acid–base balance by the human kidney. This is accomplished by the H^+-ATPase pump at the luminal membrane, which

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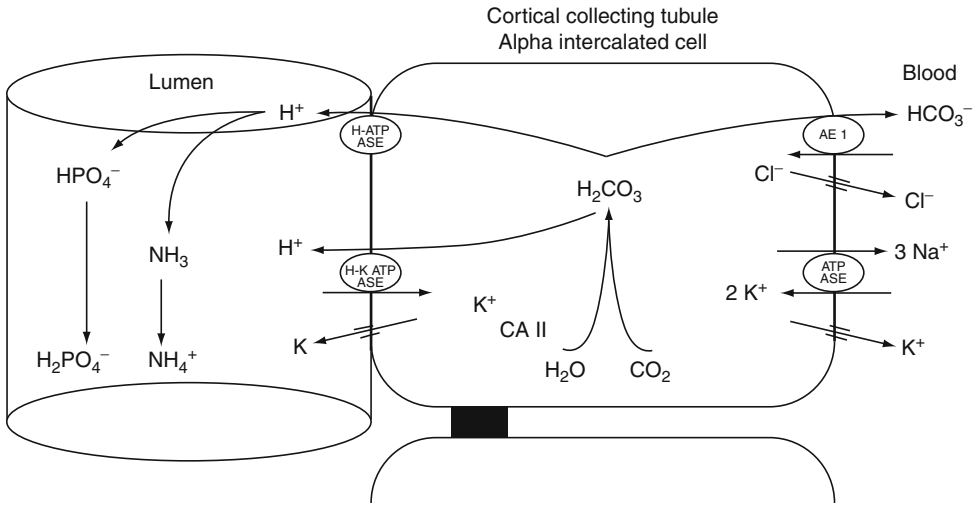

Fig. 306.1

Excretion of fixed acids in the distal nephron. Hydrogen secretion by the alpha-intercalated cells takes place via the H^+-ATPase pump in the luminal basement membrane. About 40% of the secreted hydrogen ions combine with filtered phosphate to form titratable acid. Most of the remaining hydrogen secreted combines with NH_3 to form NH_4^+, but a small amount remains as free hydrogen ions and regulates urinary pH. Bicarbonate reclamation occurs by Cl^-/HCO_3^- exchanger AE1 at the basolateral membrane

secretes H^+, and by the HCO_3^-/Cl^- (AE1) exchanger at the basolateral membrane, which is responsible for bicarbonate regeneration. Failure of either mechanism underlies the cellular and molecular etiology of distal RTA. Several mutations in the genes responsible for these transport systems have been identified recently, revolutionizing our understanding of the molecular basis of DRTA. Both hereditary and acquired forms are recognized in patients with DRTA, but this chapter will deal primarily with the hereditary forms of DRTA that prevail in infants and children.

Etiology of DRTA

Hereditary DRTA

The past 10 years have witnessed major advances in molecular biology that have allowed for a better understanding and classification of the hereditary forms of DRTA at the cellular and subcellular level. In infants and children, the autosomal recessive forms of RTA are more prevalent, whereas in adults the less severe, dominant forms are more common.

Autosomal Dominant Distal RTA

Randall and Targgart were the first to report RTA with nephrocalcinosis and osteomalacia in successive generations suggesting an autosomal dominant transmission. Subsequent reports confirmed this mode of transmission in several families. Clinical manifestations and the degree of acidosis in reported patients have been milder and therefore detected much later in life than in those with autosomal recessive distal RTA.

Chaabani and colleagues reported on large kindred with RTA with evidence of autosomal dominant transmission. As in previously reported cases, metabolic acidosis was well tolerated and often asymptomatic. Only 3 of 28 patients, with both parents affected, developed hypercalciuria, nephrocalcinosis, and growth retardation.

More recently, molecular studies in several kindreds with autosomal dominant RTA have consistently revealed mutations in the *SLC4A1* gene encoding the Cl^-/HCO_3^- exchanger AE1. These have been mostly missense mutations in codon Arg 589 suggesting an important role for this residue in the normal acidification process. It has been shown that these mutations in the *AE1* gene are not associated with loss of function of the Cl^-/HCO_3^- exchanger and that they probably affect the acidification process by targeting of *AE1* from the basolateral to the luminal membrane of the alpha-intercalated cell. Mutations in the erythrocyte isoform of the *AE1* are associated with hemolytic anemias due to ovalocytosis or spherocytosis, but seldom with RTA.

Autosomal Recessive DRTA

This entity appears to be relatively common in Middle Eastern countries. Karet et al. have elucidated the mechanisms responsible for the acidification defect in patients with recessive distal RTA. Molecular studies involving genome-wide linkage analysis in a cohort of several, mostly consanguineous, kindreds with distal RTA localized two genes: one on chromosome 2p13 associated with sensory-neural deafness (SND) and another on chromosome 7q33–34 associated with normal hearing. Both genes encode kidney-specific subunits of the proton pump of the alpha-intercalated cell. The majority of patients in both groups were of Arab or Turkish descent. Patients with distal RTA and SND were found to have several mutations in the gene encoding the B-1 subunit of the H^+-ATPase, *ATP6V1B1*, which is localized on chromosome 2p. Most of these mutations were found to disrupt the structure or alter the production of the normal B-1 subunit protein. It was also demonstrated that *ATP6V1B1* messenger RNA was expressed in the fetal and adult cochlea as well as the endolymphatic sac, findings that may explain the SND in these patients.

In patients with distal RTA and normal hearing, linkage analysis led to a defective gene on chromosome 7. This gene (*ATP6V0A4*) encodes a newly identified kidney-specific a4 isoform of the H^+-ATPase pump subunit. The clinical and biochemical manifestations are indistinguishable from patients with RTA with SND. Long-term follow-up, however, has revealed that many patients in this group develop mild hearing loss in later life. Stover and colleagues have recently demonstrated that the *ATP6V0A4* gene is also expressed within the human cochlea, again providing an explanation for the hearing defect. Recent reports from the Far East have identified different mutations in the AE1 in association with autosomal recessive distal RTA with or without ovalocytosis. This appears to be confined to Thailand and has not been documented in Caucasians.

Mixed RTA (Type 3)

Renal tubular acidosis combining features of both proximal and distal acidification defects may be observed in infants and children as a transient defect (previously known as type 3 RTA) and could be related to immaturity of one or more of the several transport systems described above. A syndrome of mixed RTA associated with osteopetrosis, cerebral calcification, and carbonic anhydrase II (CA II) deficiency has been reported in several families from the Arab world (Chap. 304, "Proximal Renal Tubular Disorders"). The syndrome is inherited as an autosomal recessive trait and is characterized clinically by failure to thrive, recurrent fractures, mental retardation, and cranial nerve abnormalities. Over 70% of the cases have been from Middle Eastern and North African countries where genetic heterogeneity is suggested by a more severe variant of the disease. More than 70 cases have been documented in the literature, with more than half from Saudi Arabia. A recent study by Fathallah and colleagues documents evidence for a founder effect in 24 patients with osteopetrosis and CAII deficiency from 14 Tunisian families. A filiation study led to the tracing of a gene to a common Arabic tribe that settled in the Maghreb in the tenth century. The gene locus for CAII has been mapped to chromosome 8q2 with several mutations identified, the most common being the Arabic one, which is a splice junction mutation in intron 2. More recently, mutations in the gene *OC16*, encoding the a3 subunit of the osteoclast V-H^+-ATPase, have been shown to cause infantile malignant osteopetrosis.

Clinical Findings in DRTA

In infants and children the clinical manifestations of proximal and DRTA are similar, namely, growth failure, vomiting, and recurrent bouts of dehydration. Hypokalemia occurs in about 30% of patients with DRTA. Muscle weakness, sometimes progressing to skeletal or respiratory muscle paralysis may occur if hypokalemia is severe. Potassium depletion will also cause impaired urinary concentration resulting in polyuria and polydipsia with a tendency for extracellular fluid volume contraction and secondary hyperaldosteronism, which will further aggravate renal potassium wasting. Rickets or osteomalacia are frequently observed in untreated DRTA. Hypocitraturia, together with the alkaline urine, and hypercalciuria in patients with DRTA play an important role in the pathogenesis of nephrocalcinosis, which is found in more than two thirds of the cases (*Fig. 306.2*). Nephrocalcinosis is seldom observed in patients with PRTA. The sequelae of impaired hydrogen ion secretion by the distal tubule are illustrated in *Fig. 306.3*

Differential Diagnosis of DRTA

Table 306.1 lists the different clinical entities considered in the differential diagnosis of DRTA. In infants the hereditary forms should be suspected in the face of a positive family history and consanguineous parents. The acquired

forms of DRTA may be seen at any age and should be considered in patients with tubulointerstitial renal diseases such as chronic pyelonephritis, obstructive uropathies, and post-renal transplantation.

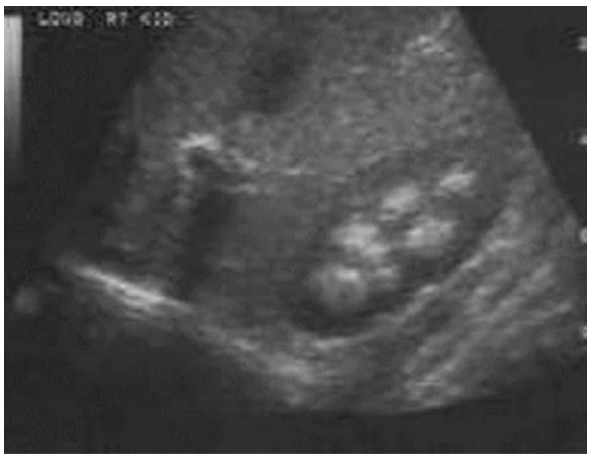

Fig. 306.2
Medullary nephrocalcinosis in an infant with dRTA

Hyperkalemic DRTA (Type 4)

The hereditary forms of hyperkalemic RTA are extremely rare and are usually seen in association with pseudohypoaldosteronism of which two types are recognized (see Chap. 305, "Disorders of Distal Tubular Transport of Sodium and Potassium").

Type I Pseudohypoaldosteronism

Clinically, these patients present in early infancy with renal salt wasting, hypovolemia, hyperchloremic acidosis, and hyperkalemia. Plasma and urinary aldosterone are elevated. Two modes of inheritance are recognized. The autosomal dominant is relatively mild and the defect is restricted to the kidneys. It is caused by heterozygous mutations in the mineralocorticoid receptor gene. The autosomal recessive form is much more serious and associated with severe renal salt wasting and potentially lethal hyperkalemia. The disease has been characterized recently at the molecular level and found to be due to loss of

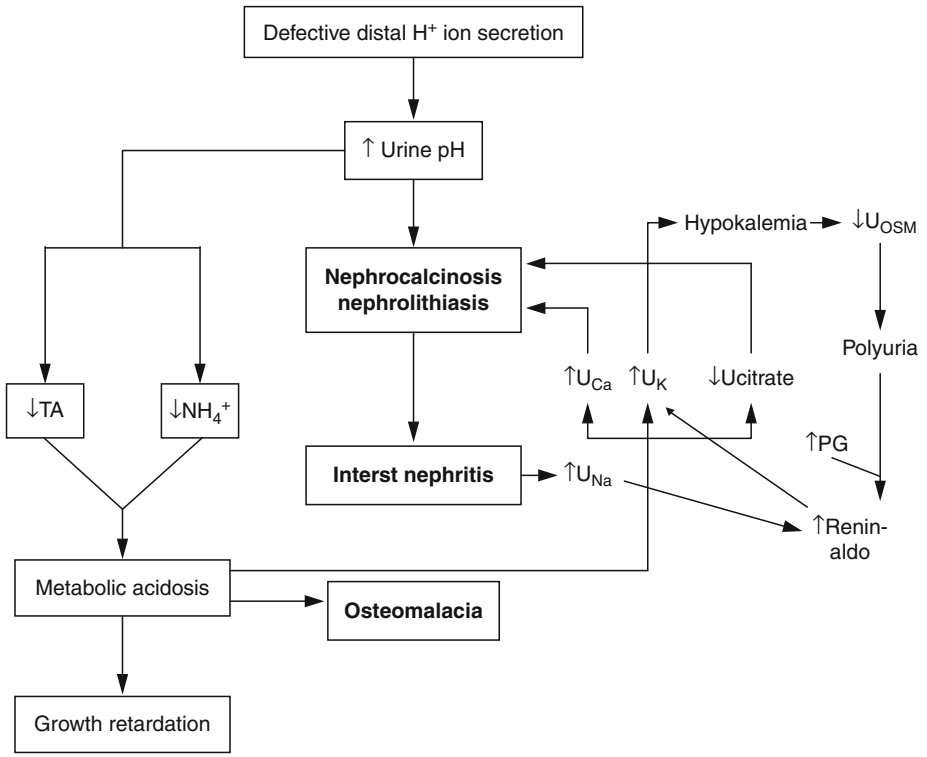

Fig. 306.3
The sequelae of impaired distal H^+ ion secretion by the distal collecting ducts

Table 306.1
Some diseases associated with DRTA

(A) Primary
Hereditary-permanent
1. Autosomal dominant: mutations in *SLC4A1* gene encoding the Cl-/HCO3- exchanger AE1.
2. Autosomal Recessive: Mutations in V-H-ATPase
(a) B1 subunit on chromosome 2p13 with SND (b) a-4 subunit on chromosome 7q33-34 no or late onset SND
Sporadic-transient
(B) Secondary to associated diseases
1. Renal diseases
(a) Chronic pyelonephritis (b) Obstructive uropathy (c) Interstitial nephritis (d) Renal transplantation
2. Genetic diseases
(a) Sickle-cell anemia – nephropathy (b) Hereditary elliptocytosis (c) Ehlers–Danlos syndrome (d) Associated with sensory-neural deafness
3. Auto-immune diseases
(a) Systemic lupus erythematosus (b) Thyroiditis (c) Sjögren's syndrome
4. Associated with nephrocalcinosis
(a) Hyperparathyroidism (b) Hypercalciuria (c) Medullary sponge kidney
5. Drug induced
(a) Amphotericin B (b) Lithium

function mutations in the alpha, beta, and gamma subunits of the sodium epithelial channel, ENaC. In addition to the kidney, the salivary glands, the gastrointestinal and pulmonary systems may be also affected.

Type II Pseudohypoaldosteronism

This is a rare autosomal dominant disease with few case reports having appeared in the literature since the original description by Gordon and associates (see Chap. 305, "Disorders of Distal Tubular Transport of Sodium and Potassium"). It is characterized by hyperkalemic acidosis, hypertension secondary to plasma volume expansion, and suppression of renin and aldosterone. The proximate cause has been discovered recently to be secondary to gain of function mutations in the WNK1 and WNK4 kinases, which may enhance transcellular and paracellular chloride conductance as well as decreasing potassium efflux by inhibition of the potassium channel ROMK.

Voltage-Dependent RTA

Electronegativity of the distal luminal fluid is maintained by the principal cell that is involved in sodium absorption and potassium secretion. A lumen negative voltage due to reduced sodium reabsorption will indirectly impair hydrogen secretion by the alpha-intercalated cells and potassium secretion by the principal cells. Loss of sodium uptake into the cells of the distal nephron reduces the transepithelial potential for potassium and proton secretion, explaining the hyperkalemia and metabolic acidosis. The urinary pH is greater than 5.5, but will be appropriately acidic if the defect in sodium reabsorption is reversible. Voltage-dependent RTA may be observed in children with severe ECV contraction in which distal sodium delivery is significantly reduced. It may also be seen with urinary obstruction, sickle-cell disease, and lupus nephritis and as a side effect of several drugs, such as amiloride, triamterene, lithium, and trimethoprim.

Combined Voltage and Secretory Defects

Such a combined defect might explain the distal RTA observed in clinical states associated with reduced nephron mass and aldosterone deficiency or resistance. Patients with type IV RTA fall into this category and may be classified under various syndromes of hypoaldosteronism. In this subtype there is substantial reduction in renin production usually associated with chronic interstitial nephropathy. As a result, renin-dependent aldosterone secretion falls leading to low circulating levels with subsequent hyperkalemia and hyperchloremic acidosis. The condition is usually seen in adult patients with mild azotemia due to diabetic nephropathy, gout, chronic pyelonephritis, and interstitial nephropathy. It may also be seen in children with hydronephrosis and as a side effect of several drugs including nonsteroidal anti-inflammatory drugs, heparin and spironolactone.

Aldosterone Deficiency

This may occur with glucocorticoid deficiency as in adrenogenital syndrome and Addison's disease or as an isolated defect due to reduced aldosterone biosynthesis. Salt wasting is usually severe and hyperkalemia may be life threatening.

Infantile Type IV RTA (Partial Aldosterone Resistance)

This represents a relatively common type of hyperkalemic RTA in infants and young children. In this condition there seems to be partial resistance to the action of aldosterone with hydrogen and potassium retention, but normal sodium reabsorption and therefore no renal salt wasting. The clinical presentation is like that of other types of RTA, with failure to thrive and vomiting. There is no sex predilection and familial occurrence has been reported. This condition tends to be self-limited and most patients will no longer require alkali therapy by the age of 5 years. It is quite possible, therefore, that the condition represents a maturational defect in distal tubular physiology that may be related to the mineralocorticoid receptor gene or the sodium epithelial channel. A transient post-receptor defect remains a possibility. Some of the clinical findings and differential diagnosis of hyperkalemic RTA are outlined in *Table 306.2*.

Other Types of DRTA

Rate-Dependent DRTA

This is a rather mild defect in acidification also involving the alpha-intercalated cells of the collecting ducts and is due to a decreased number of H^+-ATPase pumps or their rate of operation. Patients with rate-dependent RTA are able to lower urine pH when properly challenged but have a reduced maximal rate of hydrogen ion excretion. Rate-dependent RTA is typically seen in patients with mild renal transplant rejection and in some cases of interstitial nephritis.

Incomplete DRTA

This entity is rare in children and is defined as an inability of the distal nephron to acidify the urine maximally with an exogenous acid load in the absence of systemic acidemia. It is often discovered in patients being investigated for nephrolithiasis and nephrocalcinosis. Incomplete RTA may also be seen in some patients with familial renal magnesium wasting and hypercalciuria.

With any of the above defects, excretion of titratable acid and ammonium (net acid excretion) will be reduced resulting in positive hydrogen ion balance. In patients with type IV hyperkalemic RTA, urinary pH is appropriately acidic and titratable acid is usually normal, but ammoniagenesis and ammonium transport are suppressed

Table 306.2
Hyperkalemic distal RTA (Type IV RTA)

	PRA	ALDO	BP	URINE Na
Hypoaldosteronism				
1.0 Mineralocorticoid deficiency	↑	↓	↓	↑
Hyporeninemic hypoaldosteronism	↓	↓	N↑	–
Renal disease – diabetes, gout, interstitial nephritis				
Drugs				
NSAIDS, cyclosporin, trimethoprim	↓	↓	↑	↓
ACE inhibitors	↑	↓	↓	↑
Pseudohypoaldosteronism				
PHA1 AR	↑	↑	↓	↑
PHA 1 AD	↑N	↑N	N	N
PHA 2 (Gordon's syndrome)	↓	↓	↑	↓

PRA plasma renin activity, *ALDO* aldosterone, *NSAIDS* nonsteroidal anti-inflammatory drugs, *PHA* 1,2 pseudohypoaldosteronism types 1 and 2, *AD* autosomal dominant, *AR* autosomal recessive

by the high serum potassium resulting in decreased ammonium and net acid excretion. A mild degree of renal bicarbonate wasting may be seen in patients with distal RTA. Moderate bicarbonaturia (up to 15% of the filtered load) is commonly seen in infants with a secretory defect but tends to improve with time.

The clinical and laboratory findings that help distinguish the different types of RTA, including PRTA, appear in ❯ *Table 306.3*.

Diagnostic Evaluation of Patients with DRTA

1. Determine serum anion gap: $Na-[Cl+HCO_3]=12-16$ mmol/L. In the absence of diarrhea or carbonic anhydrase inhibitors, a normal anion gap acidosis establishes the presence of RTA.
2. Measure capillary pH and pCO_2 and serum potassium to establish the severity of acidemia and the degree of respiratory compensation and diagnose hypo- or hyperkalemia.
3. Urine pH on a freshly voided specimen. If less than 5.5 and serum potassium is normal or low in the presence of acidemia, proximal RTA is the most likely diagnosis. This is confirmed if urine anion gap is negative (see below).
4. Assess glomerular function by blood urea and creatinine levels, creatinine clearance, and radionuclide scan if indicated. These are usually normal.
5. Assess global tubular function by measuring urine osmolality, glucose, amino acids, phosphate, uric acid, sodium, potassium, calcium, and magnesium to rule out Fanconi syndrome.
6. Radiologic evaluation to rule out nephrocalcinosis and rickets.
7. Determine urine anion gap (U_{AG}) by subtracting urine chloride from the sum of urine sodium and potassium concentrations: $U_{AG}=[U_{Na}+U_K]-U_{Cl}$. A negative value indicates that there is another unmeasured cation, ammonium (NH_4^+), signifying a normal distal acidification and ruling out distal RTA. A positive U_{AG} with a normal or low serum potassium and urine pH of >5.5 is highly suggestive of a secretory or gradient defect RTA. This can be substantiated by simultaneous determination of urine and blood pCO_2 (U-B pCO_2) during bicarbonate loading or following carbonic

Table 306.3
Clinical and laboratory findings in RTA

	Proximal RTA (Type II)	Distal RTA		
		Type I		Type IV
		Secretory or gradient defect	Voltage defect	Hypoaldosteronism Pseudohypoaldosteronism
Age	Infancy, childhood	Infancy	Any age	Any age
Sex	M>F	F>M	M>F	M>F
Nephrocalcinosis	Rare	Common	Rare	Unknown
Rickets osteomalacia	Common (with Fanconi syndrome)	Occurs	Rare	No
Urine pH (during acidosis)	<5.5	>5.5	>5.5	<5.5
NAE	N	↓	↓	↓
Serum K^+	N,↓	Usually ↓	↑	↑
Urine Ca	N,↑	↑	N↑	N↑
Urine citrate	N	↓	↓	N
Urine AG	Neg	Pos	Pos	Pos
IV_{HCO3^-}				
U-$BpCO_2$	>20 mmHg	<20 mmHg	<20 mmHg	>20 mmHg
FE_{HCO3}	>15%	3–15%	<5%	5%–15%
Alkali requirement (mg/kg/day)	5–20	2–14	2–3	2–3

NAE net acid excretion=(NH_4^+ titratable acid), *Urine AG* urine anion gap, *U-BpCO₂* simultaneous measurements of pCO_2 in urine and blood during intravenous bicarbonate infusion and urine alkalization (U pH>7.5), *FE_{HCO3}* fractional excretion of HCO_3 – or percentage of filtered load of bicarbonate excreted in the urine

anhydrase inhibition and urine alkalinization. If distal hydrogen ion secretion is intact, hydrogen will combine with bicarbonate to form H_2CO_3. Due to the absence of luminal carbonic anhydrase IV in the distal tubule, H_2CO_3 will be dehydrated slowly to CO_2, and will raise tubular urine pCO_2 levels (*Fig. 306.4* and *Table 306.3*).

Because of the impermeant nature of the uroepithelial membranes, this rise in pCO_2 will be reflected in the final urine. With normal distal hydrogen ion secretion, urine pCO_2 values rise above 70 or 80 mmHg and the U-B pCO_2 is greater than 20 mmHg. If the U_{AG} is positive (low NH_4^+) in the presence of hyperkalemic RTA, a urine pH above 5.5 is indicative of a voltage-dependent RTA. If urine pH is below 5.5, the diagnosis of hypoaldosteronism or any of the syndromes of pseudohypoaldosteronism should be considered.

8. Ammonium Chloride Load: (100 meq/m^2 po)/ Furosemide-Fludrocortsone. This test of urine acidification should be used only in equivocal or borderline cases of suspected RTA when plasma bicarbonate is above 16–17 mmol/L and the urine pH is greater than 5.5. A normal test will result in lowering of the urine pH to less than 5.5 (usually less than 5.0) and yield a net acid excretion in excess of 40 μeq/min/m^2. Many patients tolerate NH_4Cl ingestion poorly because of gastric irritation and develop nausea and vomiting.

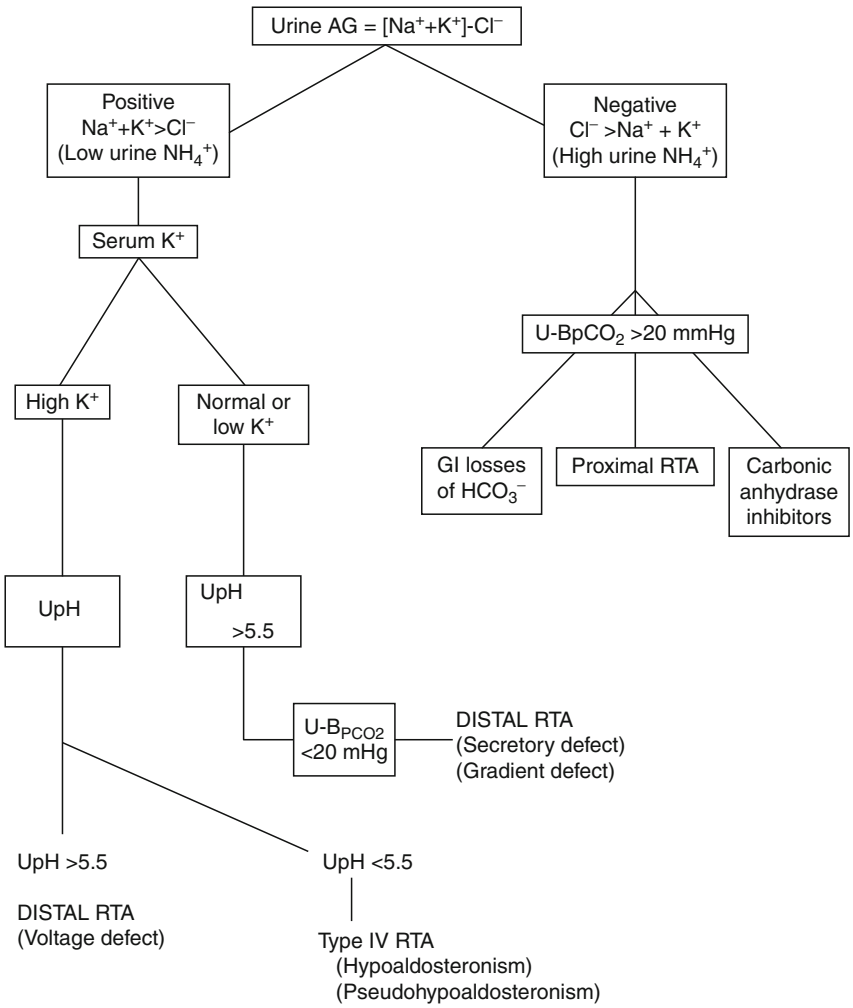

Fig. 306.4
Urine anion gap in the differential diagnosis of RTA (Modified from Lash and Arruda (1993)

An alternative way to test the capacity for distal acidification is to administer furosemide and mineralocorticoid fludrocortisone simultaneously. The combination of both, increased distal Na^+ delivery and mineralocorticoid effect, will stimulate distal H^+ secretion by both increasing the luminal electronegativity and having a direct stimulatory on H^+ secretion.

Treatment and Prognosis of DRTA

The treatment of distal RTA consists of adequate alkali replacement to normalize plasma bicarbonate. Infants with the classical variety require 2–3 meq/kg/daily in three divided doses. This corresponds to the endogenous acid production. Those with renal bicarbonate wasting may require higher doses of alkali (3–14 meq/kg/day) in four or more divided doses depending on the extent of their urinary losses. For patients with moderate or severe hypokalemic RTA, potassium citrate alone or in combination with sodium citrate (Polycitra) is the treatment of choice. One milliliter of Polycitra yields 2 meq of bicarbonate, 1 meq of sodium, and 1 meq of potassium. With correction of acidosis a "catch-up" growth is seen within a few months and normal stature is eventually attained. Correction of acidosis also corrects the hypocitraturia and prevents nephrocalcinosis and deterioration in renal function, if treatment is instituted before the age of 3 years. Partial correction of metabolic acidosis with inadequate alkali replacement will not prevent the development of nephrocalcinosis and possible chronic renal failure. The sensorineural deafness associated with autosomal recessive DRTA does not improve with treatment, even if initiated early in the course of the disease.

In the secondary forms of distal RTA, the therapy will depend on the underlying disease. Most patients will require 2–3 meq/kg/day of sodium bicarbonate in divided doses. In patients with severe rachitic bone disease a short course of vitamin D will accelerate the healing process.

In patients with hyperkalemic RTA, treatment is tailored to the underlying disease process. In voltage-dependent hyperkalemic RTA, a high sodium and low potassium intake with or without a thiazide or loop diuretic will lower serum potassium and raise bicarbonate to normal levels, but alkali therapy may be required in some patients. For patients with the various syndromes of hypoaldosteronism, and pseudoaldosteronism, treatment will consist of adequate salt intake to replace urinary losses and a mineralocorticoid supplement if necessary (Florinef .05–0.1 mg/day). In patients with hyporeninemic hypoaldosteronism, the use of Furosemide 1–2 meq/kg/day may be sufficient to correct the hyperkalemia and acidosis, but alkali therapy may also be necessary in some patients.

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307 Nephrogenic Diabetes Insipidus

Deborah P. Jones

Definition/Classification

Diabetes insipidus (DI, *insipidis*, from Greek, "to pass through" and Latin, "without taste") is a disorder characterized by inability of the kidney to concentrate urine. It is complicated by polyuria, polydipsia, and increased risk for hypertonic dehydration. DI may result from defects in the central nervous system, which impair production/release of antidiuretic hormone (ADH, also known as vasopressin), a condition known as central DI, or from inability of the kidney to respond to ADH, known as nephrogenic DI (NDI). In central DI, because the kidney's response to ADH is preserved, ADH is used as therapy.

Etiology

Proper concentration of urine requires a hypertonic renal medulla (the result of normal function of the ascending limb of the loop of Henle) and normal function of the collecting duct, which controls water excretion. In the collecting duct, ADH increases luminal permeability to water by its action on the membrane abundance of apical water channels (aquaporin 2 channels, AQP2). Activation of the vasopressin 2 receptor (V2R) stimulates an intracellular signaling cascade, which stimulates the recruitment of previously synthesized water channels contained in endocytic vesicles to be inserted into the luminal membrane thus allowing the passive movement of water into the cell; water exits via other aquaporin channels (type 3 and 4) found on the basolateral membrane of the collecting duct cell.

Pathogenesis

In childhood, NDI is most often the result of congenital disease resulting from mutations of the transport systems required for active water reabsorption in response to vasopressin. (❯ *Fig. 307.1*) Genetic mutations of the vasopressin receptor are responsible for 90% of affected individuals with NDI, and mutations of the aquaporin 2 channel account for 10%. The X-linked form of NDI resulting from mutations in the AVPR2 gene, located on the X chromosome, explains the male predominance of this disorder. The incidence of X-linked NDI in the province of Quebec, Canada is estimated at 8.8/million live male births. In Nova Scotia, another Canadian province, the incidence is much higher (58/million male births) due to a founder effect from those who arrived to the region on the Ship Hopewell. Although most affected individuals are able to translate the V2R protein, it is not properly folded and thus not translocated to its proper location on the basolateral membrane; thus, absence of receptor or abnormal receptor interrupts the G-protein coupled cellular response following V2R activation.

Autosomal dominant and recessive modes of inheritance result from mutations of the AQP2 gene located on chromosome 12. Affected individuals with this form of NDI also appear to have intracellular trafficking abnormalities, which lead to retention of the protein within the endoplasmic reticulum instead of endosomes ready for recruitment to the apical membrane. The lack of apical AQP2 on the apical membrane prevents normal water movement in response to a normal vasopressin-induced intracellular signaling cascade. To date, there are no clinical characteristics that allow distinction between the two major underlying genetic forms of NDI. In addition, some individuals with clinical NDI have not been found to have either of these known defects in collecting duct water transport.

Case

A 2-year-old WM was referred by his pediatrician for polyuria and polydipsia. His mother reports that he drinks 200–300 oz of water each day. He wakes up every night to drink water and requires numerous diaper changes during the night due to a large urinary volume. When deprived of fluids, his lips become red and dry; he has been seen drinking water from the garden hose, gutter downspout drain, toilet, and pet bowl. He was the 8 lb product of an uneventful pregnancy. He was nursed until the age of

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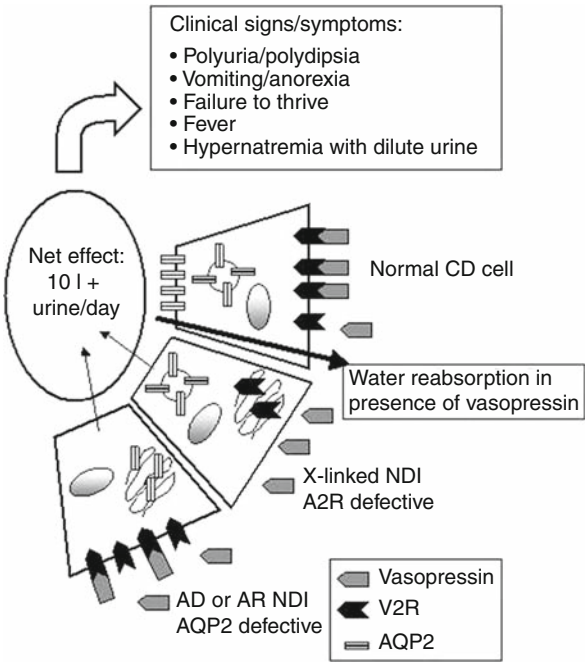

Figure 307.1
Cellular events involved in the vasopressin-induced water reabsorption in the normal collecting duct cell and in those resulting from mutations of either the V2R or AQ2 gene are represented. Common clinical symptoms/signs that accompany the underlying defect in water transport (reabsorption) are listed

6 months. Mother was often told that she was feeding him too much as he nursed constantly and also had vomiting during early infancy. Past medical history is without serious illness or hospitalization. Developmental milestones have been met. Family history is negative for kidney disease, specifically conditions with polyuria. Physical exam reveals an active and well-appearing boy who is drinking water directly from the exam room faucet. Weight was at the 50th and height at the 10th percentile.

Clinical Manifestations

The clinical presentation of NDI can be nonspecific particularly in infancy. The most common symptoms and signs at presentation are vomiting/anorexia (72%), failure to thrive (52%), fever (41%), constipation (34%), polydipsia (14%), and psychomotor retardation (3%). In a recent case series of genetically confirmed cases (30 males) the median age at diagnosis was 9 months, and mean age was 25 months. More than half were diagnosed by 12 months of age, and 87% were diagnosed by 18 months. Serum sodium is often increased, along with signs of dehydration and inappropriately dilute urine is found. Interestingly, family history was present in 25% of cases and six previous infant deaths were discovered to have likely been the result of undiagnosed NDI among families of identified cases. Given the nonspecific symptoms and often the lack of family history, diagnosis of NDI may be delayed. Previous case series indicated that up to 80% of affected individuals had signs of mental retardation. This is suspected to have been the result of repeated episodes of dehydration, fever, etc. With the trend toward earlier diagnosis in the past 2 decades, the prevalence of psychomotor retardation in children with NDI appears to be decreasing. Infants who receive mother's milk, which has a lower solute load, may also be somewhat protected. In the experience of this author, parents often give impressive histories describing extraordinary water craving: i.e., drinking from the outdoor waterspout, from the dog's bowl, and from the toilet. In, addition, infants with NDI often prefer water to milk or food in contrast to otherwise healthy children.

Case, continued: Laboratory evaluation sent at referral included a sodium level of 140 mmol/L, creatinine 0.5 mg/dL, urine specific gravity 1.005, and urine osmolality was 72 mOsm/kg. He underwent an abbreviated water deprivation test. At 4 h, the plasma osmolality was 309 mOsm/kg, sodium 149 mmol/L, and urine osmolality was 118 mOsm/kg. An ADH level was drawn and he was given DDAVP 1.5 mg/m^2 by subcutaneous injection; the highest urine osmolality obtained was 141 mOsm/kg, and at 1 h post ADH, the test concluded. His plasma ADH level was high – 38.1 pg/mL.

Differential Diagnosis

Polyuria, which is the clinical manifestation of inability to concentrate urine, may result from disorders other than DI. These disorders include other congenital renal tubular disorders such as Bartter/Gitelman syndrome and Fanconi syndrome. In contrast to NDI, these conditions are characterized by abnormalities in electrolyte handling, which are accompanied by hypokalemic metabolic alkalosis with or without hypomagnesemia (Bartter/Gitelman syndrome) and by hypokalemic, hypophosphatemic acidosis often with rickets (Fanconi syndrome). In addition, primary polydipsic syndromes may also cause polyuria. Acquired forms of NDI include lithium intoxication, hypercalcemia, protein malnutrition, sickle cell

nephropathy, hypokalemia, juvenile nephronopthisis, and obstructive uropathy.

Diagnosis is dependent upon demonstration of inappropriately dilute urine in the setting of hyperosmolar plasma. In the case of individuals who present with hypernatremia and hyperosmolality, water deprivation is not required. In such a clinical setting, documentation of a urine osmolality of less than 300 mOsm (should be >800 in a normal child) is sufficient to indicate a significant concentrating defect. Administration of vasopressin is followed by measurement of urinary osmolality; individuals with central DI are able to increase the urine osmolality by at least 200 mOsm. Those with NDI show no significant increase in urine osmolality after vasopressin. In some cases in which the primary complaint is polydipsia and polyuria in the presence of normal serum sodium and plasma osmolality a short water deprivation test may be performed under close supervision. It is advised that this test be performed by those experienced in its procedure and interpretation. Measurement of plasma vasopressin may also be helpful in differentiating central from nephrogenic DI, as levels are lower than normal in central DI and elevated in NDI. Although NDI is much more common among males, females may be affected. The mutation may be expressed in females depending upon which X chromosome becomes inactivated in early embryogenesis. Therefore, the presence of clinical symptoms and signs suggestive of a concentrating defect in a female does not eliminate the possibility of NDI.

Given that 10 L of urine may be required to be excreted by the urinary tract, urologic complications of NDI are not uncommon. These complications include severe hydronephrosis, renal pelvic dilation, transient ureteral dilation, acute urinary retention, urinary infection, and nocturnal enuresis. Therefore, interval renal ultrasounds are recommended in the management of these patients. Growth may also be abnormal particularly in the first year of life. This aspect may be related to the feeding intolerance and the need to consume large volumes of water rather than food.

Case, continued: Imaging of the kidneys and bladder by ultrasound was normal. He was started on hydrochlorothiazide and amiloride. His mother reported a marked decrease in urine volume and increased appetite after initiation of treatment. A de novo mutation in the patient's vasopressin receptor gene was confirmed; his mother was not a carrier. Renal imaging studies at 5 years of age were still normal. At last follow-up, at 5 years of age, his height was at the 50th and weight at the 75th percentile. He continues to have polyuria and polydipsia, which is manageable during the day. Nighttime urine volume continues to be challenging.

Treatment

Treatment starts with access to water at all times. For infants, this may require creative methods. The mother of one of the author's patients fashioned a nipple attached to a large water bottle, which traveled wherever the child went – in stroller or bed. Dietary therapy is aimed at reduction of renal solute load. Previously prescribed low-protein diets are no longer recommended as they result in protein malnutrition. Low dietary salt is still recommended. Drug therapy most often initiates with thiazide diuretics (HCTZ 3 mg/kg/day, divided BID) in combination with the potassium sparing diuretic amiloride (0.3 mg/kg/day) and/or potassium supplementation. Although administration of diuretics to patients with polyuria seems counter intuitive, the thiazide diuretic hydrochlorothiazide reduces urine volume. This effect was initially attributed to increased proximal tubular water and solute reabsorption; however, recent studies indicate that thiazide diuretics increase water permeablility in the inner medullary collecting duct. In addition, hypokalemia should be avoided due to its potential contribution to abnormal urinary concentration. Nonsteroidal anti-inflammatory drugs such as indomethacin (2–3 mg/kg/day, divided BID) have also proven useful for NDI. These agents increase proximal tubular fluid and solute reabsorption; they seem to be tolerated fairly well. Unfortunately, they may be accompanied by gastrointestinal and renal toxicity. Although reduced by as much as 70% below baseline values with pharmacologic therapy, urine volumes and water intake are still excessive: one case series reported that despite therapy with HCTZ/amiloride, oral intake ranged from 125 mL/kg/day to 250 mL/kg/day and urine output from 3 mL/kg/h to 10 mL/kg/h. Most children continue to awaken at night to drink water and continue to demonstrate nocturnal enuresis despite optimal drug therapy. An algorithm for evaluating a child with polyuria is found in *Fig. 307.2*.

Although rare, the diagnosis of NDI should be considered in any child with polyuria and polydipsia, and in the setting of hypertonic dehydration in which dilute urine is found. Molecular characterization of the results of genetic mutations in the V2R and AQP2 have allowed a much better understanding of the underlying defects commonly found in children with NDI. Drug therapy is available which appears to be well tolerated and to support near normal growth. Unfortunately, most affected children

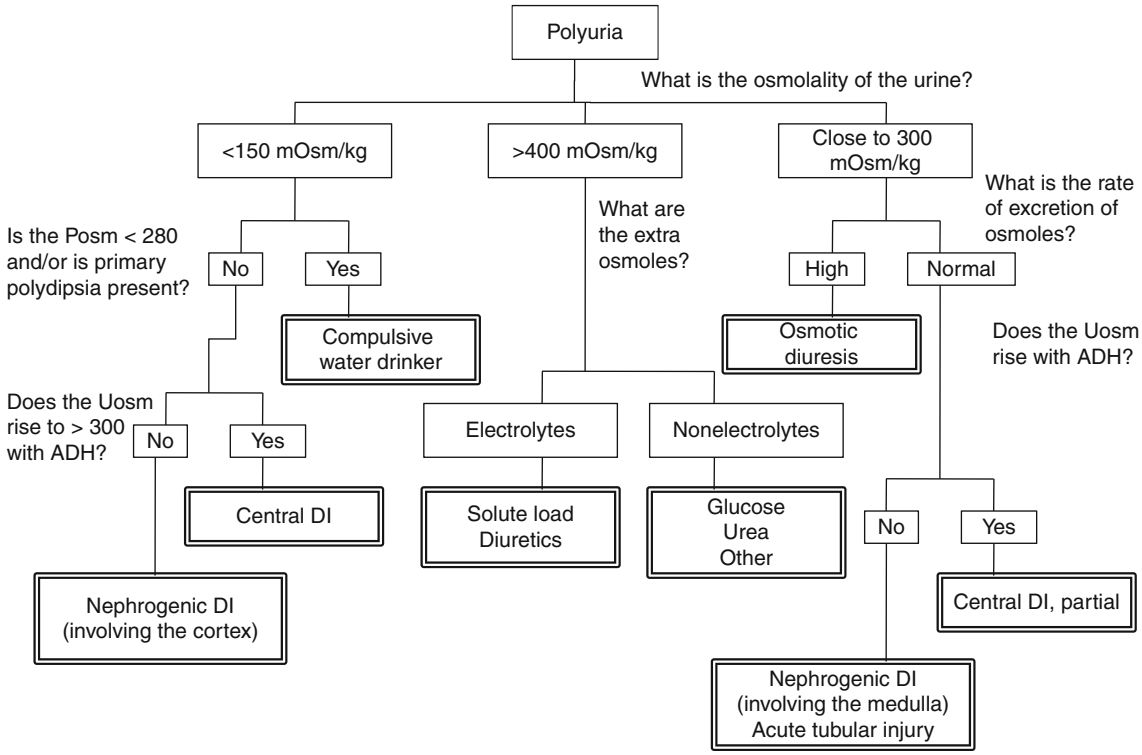

Figure 307.2
An algorithm for evaluating a child with polyuria

continue to display some symptoms and signs of excessive urinary volume.

Treatment: Future Development

Given that both V2R and AQP2 mutations have been associated with protein trafficking abnormalities, the potential for specific drug therapies aimed at escorting the miss-targeted proteins to their appropriate location on the basolateral or apical membrane of the collecting duct may eventually be available.

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308 Urinary Stone Disease

Burhan Edrees · Soud Al Rasheed

Overview

Definition

Nephrolithiasis is the formation of stones in the kidney, while urolithiasis is stone in the urinary system. The existence of nephrolithiasis was known to Hippocrates, who described the symptoms of renal colic: "An acute pain is felt in the kidney, the loins, the flank and the testis of the affected side; the patient passes urine frequently; gradually the urine is suppressed. With the urine, sand is passed."

Nephrocalcinosis, when there is generalized increase in Calcium content of the kidney, which can be microscopic or macroscopic when you can see abnormal renal tissue using radiologic evaluation.

Epidemiology

Geographical Distribution

The incidence of urolithiasis in a given population is dependent on the geographic area, racial distribution, and socioeconomic status of the community.

Changes in socioeconomic conditions over time, and the subsequent changes in dietary habits, have affected not only the incidence but also the site and chemical composition of calculi.

In different series of patients of all ages with renal stone, prevalence in children ranges from 2 to 2.7%, can go up to 17% in some countries like Turkey, where urolithiasis is considered to be endemic. In the pediatric population, recent studies have shown that the annual incidence in children may be increasing in the West. In a series from Iceland, the annual incidence of kidney stones was 5.6 and 6.3 per 100,000 children under 18 and 16 years of age. The overall probability that an individual will form stones varies in different parts of the world. In view of adult literatures, the risk of developing urolithiasis in adults appears to be higher in the western hemisphere (5–9% in Europe, 12% in Canada, 13–15% in the USA) than in the eastern hemisphere (1–5%), although the highest risks have been reported in some Asian countries such as Saudi Arabia (20.1%). In Europe, it is reported that the occurrence of urolithias in the nineteenth century population was quite similar to that of the twentieth century in Asia. The rate of hospital admissions due to renal stone disease varies widely in different geographic regions, from 0.001 to 0.1% in the USA to 7% in Asia. This rate is one tenth of that seen in the adult population. Boys show a mild preponderance for stone disease, with a male to female ratio of 1.4:1 to 2.1:1, with more preponderance in white children in USA, and with African American and Asian children only rarely affected.

Renoureteral calculosis featuring mainly calcium oxalate and phosphate is currently more frequent in economically developed countries, whereas vesical calculosis (urinary bladder stone) is fairly widespread in Asia, with calculi composed of ammonium urate and calcium oxalate.

Stone composition has changed substantially over the past decades, with a progressive increase in frequency of calcium oxalate and calcium phosphate stones. Recent epidemiology studies from different continents and countries report that calcium oxalate accounts for 60–90% of stones in children, followed by calcium phosphate (10–20%), struvite (1–14%), uric acid (5–10%), cystine (1–5%), and mixed or miscellaneous (4%). Hypercalciuria is recognized worldwide as the most frequent underlying factor in calcium oxalate stones, although, in some countries of the eastern hemisphere, hypocitraturia has been reported as the leading cause. Other less frequent metabolic risk factors are hyperuricosuria and hyperoxaluria. However, increased urinary oxalate excretion might be underestimated and might even be a more prevalent risk factor than hypercalciuria for stone disease in some populations. Struvite or infection-related stones, which were very common in children until the last century, are rarely seen today in industrialized countries, possibly due to improved management of both pediatric obstructive uropathy and urinary tract infections. Bladder stones based on malnutrition during the first years of life are currently a frequent finding in various areas of Turkey,

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_308,

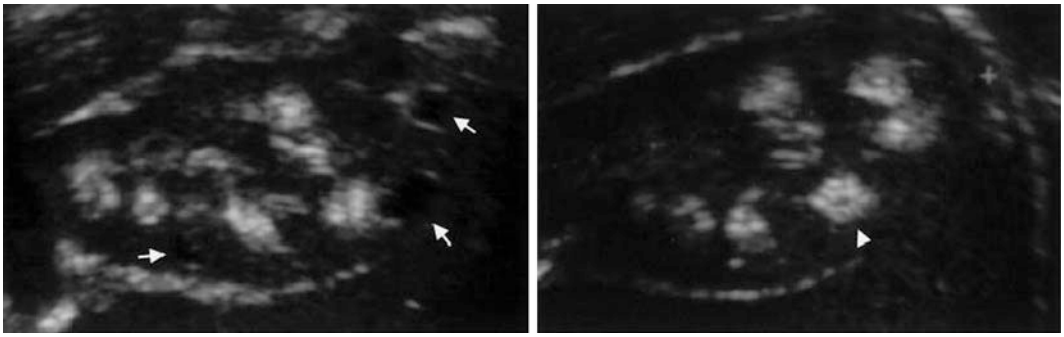

Figure 308.1
Renal ultrasound showing hypoechoic areas consistent with cysts *(arrows) in the left panel* and increased echogenicity consistent with nephrocalcinosis *(arrowhead) in the right panel*

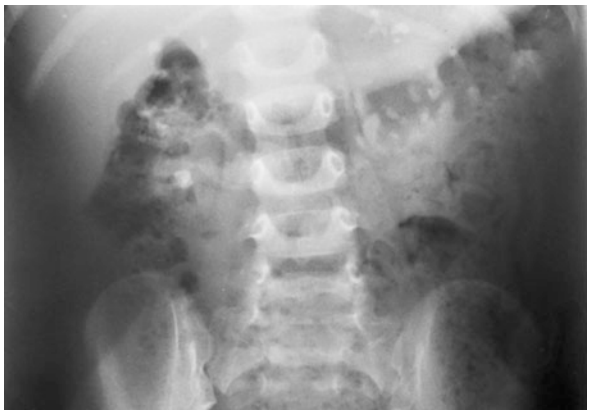

Figure 308.2
Plain abdominal radiographs demonstrating bilateral nephrocalcinosis

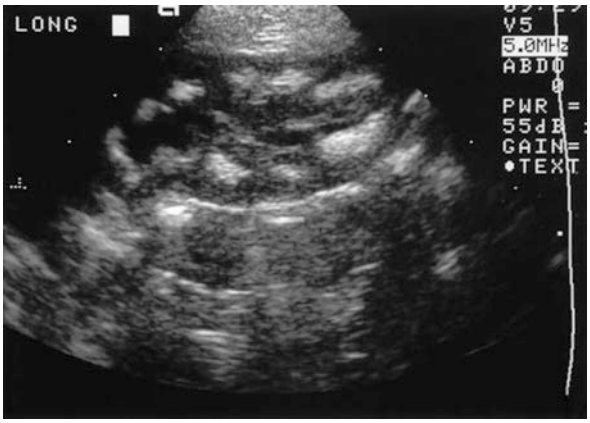

Figure 308.3
Renal ultrasound scan showing bilateral dense nephrocalcinosis with mild left pelvicalyceal dilatation (anterior-posterior diameter 7 mm)

Iran, India, China, Indochina, and Indonesia. Although the incidence is proportionally decreasing as social conditions improve. This trend defined as "stone wave" has been explained in terms of changing social conditions and the consequent changes in eating habits. In Europe, Northern America, Australia, Japan, and, more recently, Saudi Arabia, affluence has spread to all social classes and with it the tendency for individuals to increase protein intake in large quantities.

The Afro-Asian stone-sucess forming belt stretches from Sudan, the Arab Republic of Egypt, Saudi Arabia, the United Arab Emirates, the Islamic Republic of Iran, Pakistan, India, Myanmar, Thailand, and Indonesia to the Philippines (*Fig. 308.5*). In this area of the world, the disease affects all age groups, from less than 1 year old to more than 70 years old, with a male-to-female ratio of 2 to 1. The prevalence of calculi ranges from 4% to 20%. The higher prevalence of urolithiasis in many of those countries is possibly determined by the high consanguinity that prevails among ethnic groups that live in those geographical areas.

Other risk factors involved in this geographical pattern are cultural practices such as the chewing of betel quid, which is common in many countries of the world, particularly in Southeast Asia. The quid consists of a preparation of areca nut, betel leaf, and calcium hydroxide "lime" paste, which produces a high incidence of hypercalciuria and hypocitraturia.

In the north Indian population, the absence of Oxalobacter formigenes, an intestinal oxalate degrading bacteria, can lead to a significant increase in the risk of absorptive hyperoxaluria.

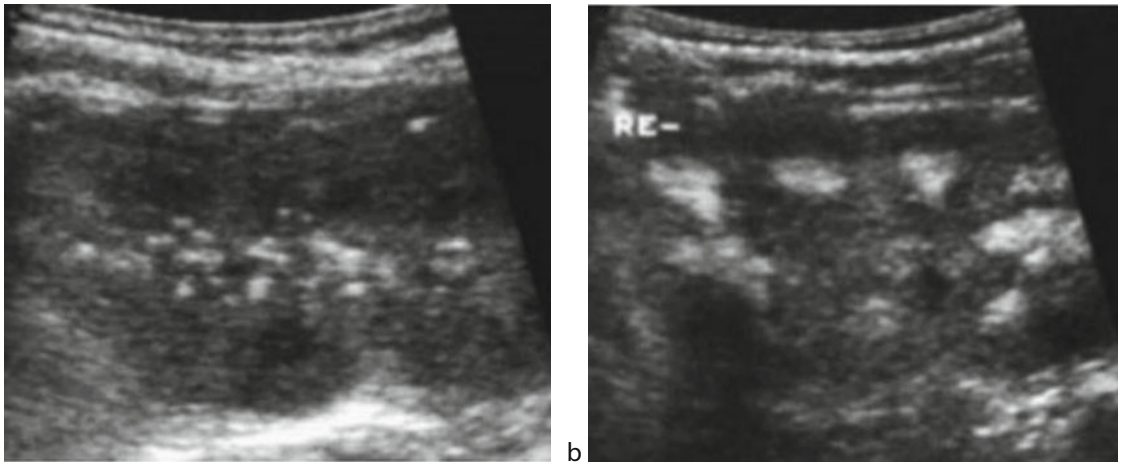

Figure 308.4
(a) Renal ultrasound of a preterm neonate with moderate nephrocalcinosis, with small white flecks in the tip of the pyramids. (b) Ultrasound of kidney of a preterm neonate with severe nephrocalcinosis. White dots almost entirely fill the pyramids

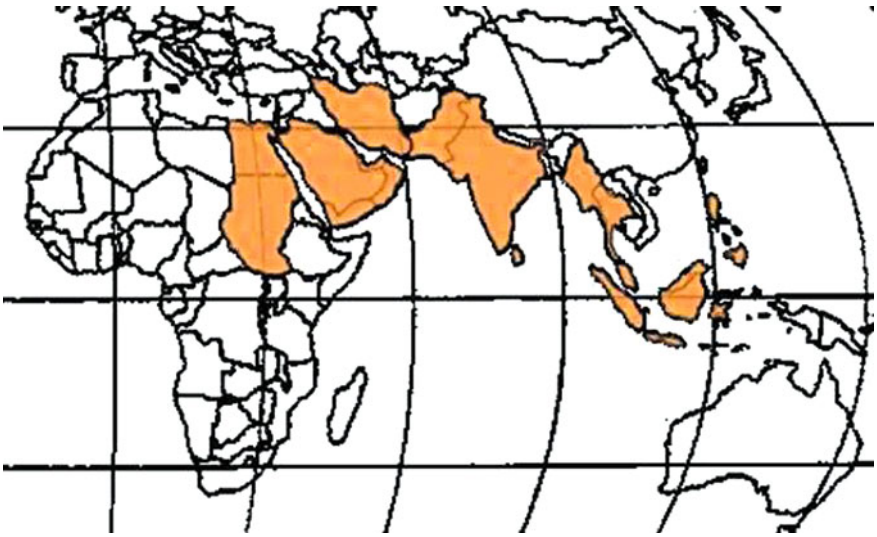

Figure 308.5
North African–Asian stone belt

Urolithiasis is most common in the southeastern region of USA, where the states of Virginia, North Carolina, Georgia, Tennessee, and Kentucky are described collectively as the North American "stone belt" (*Fig. 308.6*).

In summary, the epidemiology of renal stones with regard to stone composition is continuing to change all over the world toward a predominance of calcium oxalate stones. Major differences in the frequency of the other constituents, particularly uric acid and struvite, reflect particular eating habits and infection risk factors specific to certain population.

Pathogenesis

Stone formation is due to imbalance between *promoter* (which increases the tendency to form stone) and *inhibitor* (which increases solubility of stone constituents).

Figure 308.6
North American stone belt

The first step in the pathogenesis of nephrolithiasis is the formation of crystal nuclei. This occurs when the concentration of a salt exceeds the solubility limit "supersaturation." This is sometimes accompanied by a deficit of the protective substances known as crystallization inhibitors (e.g., citrate, magnesium, potassium etc.) The term "urinary stone risk factor" refers to conditions that promote the crystallization of a salt.

Widely recognized urinary stone risk factors are low urinary volume and increase in salt urinary excretion, and an excessively alkaline urinary pH (>7.0), or excessively acid urinary pH (<5.5), according to the type of stone. Alternatively if the urine is very concentrated due to decreased fluid intake a stone is most likely to be produced, and this is why a stone is most likely to occur in hot weather or in people who do not drink much fluid.

Etiology

There are different causes of renal stone, majority in children being metabolic causes. We can elaborate some of those causes as follows:

1. Hypercalciuria:

   Hypercalciuria is the most important pathophysiologic risk factor in calcium stone formation.

   Types of hypercalciuria:

   Absorptive hypercalciuria:

   Occurs in approximately 20–40% of stone formers, and is characterized by increased intestinal absorption of calcium. The positive calcium balance suppresses parathyroid hormone (PTH) secretion and increases the renal filtered load of calcium, leading to increased urinary calcium excretion. It was deduced that the 4q33-qter segment contains the putative gene for absorptive hypercalciuria.

   A severe form of absorptive hypercalciuria has been mapped to chromosome 1q23.3-q24.

   It is classified as Type I or II, according to the response to dietary calcium restriction. Type I is diet-unresponsive and Type II, urinary calcium normalizes in response to a low calcium diet.

   Renal Hypercalciuria:

   Secondary to Impaired renal tubular reabsorption of calcium. Renal loss of calcium reduces serum calcium and secondarily stimulates PTH secretion. Consequently, increased intestinal calcium absorption caused by enhanced 1,25-[OH]2D synthesis and mobilization of calcium from bone caused by increased PTH lead to hypercalciuria. The pathogenesis of renal calcium leak is unknown. Renal hypercalciuria is relatively uncommon, occurring in approximately 5–8% of stone formers.

   Resorptive hypercalciuria:

   Rare cause of stone disease, 3–5%, that is most commonly associated with primary hyperparathyroidism. Excessive PTH secretion from a parathyroid adenoma leads to bone resorption, increased renal synthesis of 1,25-[OH]2D (calcitriol), and enhanced intestinal absorption of calcium.

   Other causes of hypercalciuria

   A number of conditions like hypercalciuria associated with special inherited diseases, see *Table 308.3*,

Table 308.1
Frequency of urolithiasis according to age, stone location, gender, and stone composition in populations of different socioeconomic levels

Variable	Socioeconomic level	
	Low	High
Overall frequency in children	High	Low
Bladder stones (%)	>40	<10
Female patients (%)	<20	>25
Calcium oxalate (%)	<40	>60
Uric acid (%)	>30	<20

History, epidemiology and regional diversities of urolithiasis
Source: López M, Hoppe B (2010) Pediatr Nephrol doi: 10.1007/s00467-008-0960-5

granulomatous diseases, including sarcoidosis, tuberculosis, and histoplasmosis, have been reported to cause hypercalcemia; bedridden patients like cerebral palsy if not discovered early will have bone resorption and hypercalciuria, in which conditions weight bearing exercises and increased fluid intake can be of help.

2. Hypocitraturia
Citrate is the most abundant organic anion in human urine, and is a well-recognized inhibitor of stone formation. Hypocitraturia is a well-known risk factor for calcium nephrolithiasis, and has been identified in 20–60% of calcium stone formers.

Citrate complexes with calcium in solution forms a soluble complex and decreases urinary saturation of stone-forming calcium salts (CaOx and calcium phosphate).

By that it inhibits crystallization, aggregation, and agglomeration of CaOx and calcium phosphate, thereby further reducing stone formation. Acid load promotes proximal tubular reabsorption of citrate and reduced citrate synthesis, leading to hypocitraturia, whereas alkali load reduces tubular reabsorption and enhances citrate synthesis, thereby increasing urinary citrate excretion. A variety of pathology associated with acidosis leads to hypocitraturia. Distal renal tubular acidosis (RTA) is associated with systemic acidosis, and is characterized by high urine pH, and low serum bicarbonate and potassium.

Chronic diarrhea is associated with systemic acidosis because of alkali loss in the stool. Excessive animal protein provides an acid load that promotes bone loss and causes hypocitraturia. Other causes of acidosis associated with hypocitraturia are thiazide-induced hypokalemia, which produces intracellular acidosis, and vigorous exercise, which produces lactic acidosis. Overweight status in children might be associated with an elevated risk of stone formation in both sexes owing to the alterations in urine composition, with status of hypocitraturia. Finally, idiopathic hypocitraturia may represent an isolated abnormality, unrelated to an acidotic state.

3. Hyperoxaluria
Is thought to increase the risk of stone formation by increasing urinary saturation of CaOx. The effect of oxalate on stone formation depends on the interaction between calcium and oxalate that takes place in the intestine and urine.

In the intestine, oxalate absorption is modulated by dietary oxalate and the formation of a poorly absorbed calcium-oxalate complex. In the setting of dietary calcium restriction, calcium-oxalate complex formation is reduced, thereby increasing luminal free oxalate that is absorbed from the intestine and excreted in the urine.

Hyperoxaluria can be associated with primary disorders in biosynthetic pathways (primary hyperoxaluria), or high substrate levels (excessive vitamin C).

Primary hyperoxaluria is caused by a rare inherited autosomal recessive disorder in glyoxalate metabolism by which the normal conversion of glyoxalate to glycine is prevented, leading to oxidative conversion of excess glyoxalate to oxalate, an end product of metabolism. Systemic oxalosis ensues, and leads to excretion of markedly high levels of urinary oxalate. The risk of stone formation is increased when urine oxalate exceeds 0.4 mmol/L, especially if urine calcium concentration is elevated (i.e., more than 4 mmol/L), leading to the formation of monohydrated calcium oxalate (whewellite) crystals, causing stone formation and nephrocalcinosis (*Fig. 308.7*). At diagnosis, 54% of hyperoxaluric patients have had stones and 30% had nephrocalcinosis. Without treatment, end stage renal failure occurs in 50% of patients by age 15 years, with an overall mortality ~30%.

Two forms of primary hyperoxaluria have been identified: primary hyperoxaluria type 1 (PH1) [online Mendelian Inheritance in Man (MIM) 259900] is an autosomal recessive disorder (~1:120,000 live births per year in Europe), and alanine-glyoxalate aminotransferase (AGT) activity is either absent or mistargeted to the mitochondria. Primary hyperoxaluria type 2 (PH2) (MIM 260000) has been documented in fewer than 50 patients, which differ in the enzyme defect responsible for the disease,

Table 308.2

Genetics of disorders presenting with urolithiasis and/or nephrocalcinosis

Group of defects	MIM	Locus, gene	Inheritance	Gene product	Phenotype
Hypercalciuria-induced urolithiasis/nephrocalcinosis					
Autosomal dominant hypocalcemic hypercalciuria	146200; 601199	3q13.3-q21, CASR	AD	CASR	Hypercalciuria Hypocalcemia CRF
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)	248250; 603959	3q27, 1p34.2, CLDN16, CLDN 19	AR	Paracellin 1, (Claudin 16, 19)	Hypercalciuria, hypercalcemia, hypomagnesemia, dRTA, CRF, hypermagnesuria, polyuria, tetany seizures
Dent's disease, (Dent 1)	300009; 310468; 300008	Xp11.22, CLCN5	XLR	CLC-5	Hypercalciuria, renal phosphate leak (variable), LMW proteinuria, hypophosphatemia (variable)
Lowe syndrome, (Dent 2)	309000	Xq.25–26, OCRL1	XLR	OCRL1 protein	Hypercalciuria, megalin deficiency, phosphate leak, Fanconi syndrome
Bartter's syndrome type 1	600839	15q15-q21.1, NKCC2	AR	SLC12A1	Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis
Bartter's syndrome type 2	600359	11q24, ROMK	AR	KCNJ1	Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis
Infantile Bartter's syndrome with sensorineural deafness	602522; 606412; 602024; 602023	1p31, 1p36, BSND CLCNKB	AR		Salt wasting, hypokalemic metabolic alkalosis, and hypercalciuria, nephrocalcinosis
Williams–Beuren syndrome	194050; 130160; 601329; 600404	contiguous gene deletion syndrome 7q11.23, ELN, LIMK1, RFC2	AD	Elastin, LIMkinase1	Hypercalcemia, hypercalciuria, mental retardation "happy party manner," aortic stenosis, "Elfin-faces", Nephrocalcinosis
Nephrolithiasis and osteoporosis associated with hypophosphatemia due to mutation in the type 2 sodium phosphate co-transporter	182309	5q.35	Unknown	NPTZa	Renal phosphate leak, hypercalciuria, osteoporosis, 1,25 dihydroxy-vitamin D
Hyperoxaluria-induced urolithiasis/nephrocalcinosis					
Primary hyperoxaluria, type I	259900; 604285	2q.37.3, AGXT	AR	AGT	Hyperoxaluria, hyperglycolic aciduria, CRF, systemic oxalosis
Primary hyperoxaluria, type II	260000; 604296	9q.11, GR/HPR	AR	GR/HPR	Hyperoxaluria, L-gylceric aciduria, CRF
Cystinuria and urolithiasis					
Cystinuria type A	104614	2p q.16.3, SLC3A1	AR	r BAT	Elevated urinary excretion of cystine (and other dibasic amino acids) Urine microscopy: hexagonal cystine crystals, recurrent

Table 308.2 (Continued)

Group of defects	MIM	Locus, gene	Inheritance	Gene product	Phenotype
Cystinuria type B	604144	19 q.13.1/ SLC7A9	Inc AR	B α + AT	Elevated urinary excretion of cystine (and other dibasic amino acids) Urine microscopy: hexagonal cystine crystals, recurrent urolithiasis, (CRF)
Cystinuria type A/B	220100	SLC3A1/SLC7A1			
Purine/pyrimidine-induced urolithiasis/nephrocalcinosis					
Lesch–Nyhan syndrome	300322	Xq26, HPRT	XLR	HPRT	Hyperuricosuria, gout, automutilation, recurrent urolithiasis
Partial HPRT deficiency	308000	Xq.26–27.2, HPRT	XLR	HPRT	Hyperuricosuria
Glycogenosis type 1a	232200	17q.21, G6PC	AR	Glucose-6-phosphatase	Hyperuricosuria
Glycogenosis type 1b	232220	11q.23, SLC37A4	AR	Transporter	Hyperuricosuria
Phosphoribosylphosphate synthetase 1 superactivity	311850	Xq21, PRPS1	XL		Hyperuricosuria
APRT deficiency	102600	16q.24.3, APRT	AR	APRT	8 dihydroxy-adeninuria, recurrent crystalluria (round + brown), urolithiasis (radiolucent), rarely renal failure from crystal nephropathy
Xanthinuria (classical)	278300	2p.22, XDH	AR	Xanthine oxydoreductase or dehydrogenase	Xanthinuria, hypouricemia
Distal renal tubular acidosis					
Renal tubular acidosis autosomal dominant	179800; 109270	17q.21–q.22, SLC4A1,AE1	AD	AE1	Hypocitric aciduria, hypercalciuria, hypokalemia, osteomalacia
Autosomal recessive dRTA with hearing loss	267300; 192132	2cen-q13, ATP6B1	AR	B1	Hypercalciuria, hypocitric aciduria, hypokalemia,rickets, hearing loss
Autosomal recessive dRTA	602722; 605239	7q.33-34, SLC4A1	AR	A4	Hypercalciuria, hypocitric aciduria, hypokalemia

Source: Hoppe B, Kempe MJ (2010) Diagnostic examination of the child with urolithiasis or nephrocalcinosis. Pediatr Nephrol 25:403–413

glyoxylate reductase/hydroxypyruvate reductase (GR/HPR), and absence of GR/HPR activity both in the liver and lymphocytes. The median age at onset is 1–2 years, and the classical presentation is urolithiasis (whewellite), including hematuria and obstruction, but stone-forming activity is lower than in PH1. GFR is usually maintained during childhood, and systemic involvement is exceptional. The biochemical hallmark is the increased urinary excretion of L-glycerate, but the definitive diagnosis requires DNA analysis and screening of the most frequent mutation (c.103delG). PH1 is the most common and the most challenging form. The median age of patients when symptoms first appear is 5–6 years, and end-stage renal disease (ESRD) is reached between 25 years and 40 years of age in half of the patients. It is responsible for less than 0.5% of ESRD in children in Europe and 10–13% in countries with a high rate of consanguineous marriages. Along with progressive decline of glomerular filtration rate (GFR $<$ 30–50 mL/min per 1.73 m^2) due

to renal parenchymal involvement, continued overproduction of oxalate by the liver and reduced oxalate excretion by the kidneys lead to systemic involvement (oxalosis), bone becomes the major compartment of the poorly soluble oxalate pool. The combination of both clinical and sonographic signs is a strong argument for PH1, i.e., the association of renal calculi, nephrocalcinosis, and renal impairment; in addition, family history may bring additional information. PH1 grossly fits five presentations: (1) infantile form with early nephrocalcinosis and kidney failure; (2) recurrent urolithiasis and progressive renal failure, leading to a diagnosis of PH1 in childhood or adolescence; (3) late-onset form with occasional stone passage in adulthood; (4) diagnosis given by post-transplantation recurrence; and (5) presymptomatic subjects with a family history of PH1. Crystalluria and infrared spectroscopy are of major interest for identification and quantitative analysis of crystals and stones showing whewellite (*Fig. 308.7*).

Currently, a polymerase chain reaction using a serum sample can identify the three most common mutations in the involved genes. The AGXT gene is located on chromosome 2q37.3; numerous mutations and polymorphisms have been identified. Prenatal diagnosis can be performed from DNA obtained from chorionic villi or amniocytes. Indeed, one study reported that 66% of patients who had hyperoxaluria were diagnosed without the need for liver biopsy. The diagnosis of primary hyperoxaluria should be suspected in any calcium stone-forming child, because nephrolithiasis is the most common presenting symptom of the disease. Transplantation of the kidney and/or liver is generally required.

Malabsorptive state is the most common cause of hyperoxaluria with intestinal disease–associated stone formers. In the setting of fat malabsorption, saponification of fatty acids with luminal calcium reduces

Table 308.3
Steps in diagnosis

Steps	Diagnostic findings
History including family history	Diet, fluid intake, medications, vitamin supplementation, chronic disease? Malabsorption syndrome? immobilization?
Clinical findings	Pain, hematuria, vomiting, UTI, passage of stones, gravel
Imaging	Ultrasonography, plain film, non-contrast-enhanced CT, (MRI) intravenous urography
Urine	Density, specific gravity, osmolality, pH, glucose, protein, sediment, culture, spot urine (molar creatinine ratio of calcium, oxalate, uric acid, citrate, magnesium, cystine screening {nitroprusside test, amino acid screen}), 24 h urine (volume, pH, lithogenic and stone-inhibitory parameters, calculation of urinary saturation).
Blood/serum	Electrolyte, calcium, phosphorus, magnesium, creatinine, urea, uric acid, alkaline phosphatase, (PTH, Vitamin D/A, plasma oxalate, serum Vitamin B6 level)
Stone analysis	Infrared spectroscopy or X-ray diffraction
Indication for metabolic stone valuation	Recurrent stone formers
	Intestinal disease (particularly chronic diarrhea)
	Pathologic skeletal fractures
	Osteoporosis
	History of urinary tract infection with calculi
	Personal history of gout
	Infirm health (unable to tolerate repeated stone episodes
	Solitary kidney
	Anatomic abnormalities
	Renal insufficiency
	Stones composed of cystine, uric acid, or struvite

Source: Hoppe B, Kemper MJ (2010) Pediatr Nephrol 25:403–413

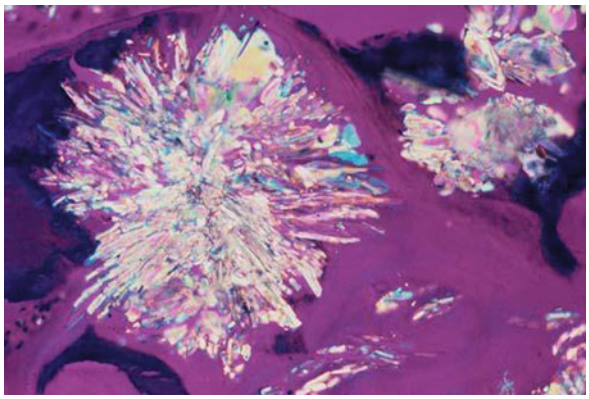

Figure 308.7
Bone biopsy in an adolescent with primary hyperoxaluria type 1. Examination under polarized light shows calcium oxalate crystals

calcium-oxalate complex formation in the gut, increasing the pool of unbound oxalate available for absorption.

Hyperoxaluria can occur from excessive dietary intake of oxalate-rich foods such as nuts, chocolate, brewed tea, spinach, and rhubarb. Severe calcium restriction may reduce intestinal oxalate binding, thereby increasing intestinal oxalate absorption. Excessive vitamin C intake has also been shown to increase oxalate excretion by in vivo conversion of ascorbate to oxalate. Oxalate-degrading bacteria such as Oxalobacter formigenes have been shown to colonize the intestine of normal individuals, and may reduce intestinal oxalate; absence of these bacteria has been linked to increased urinary oxalate levels.

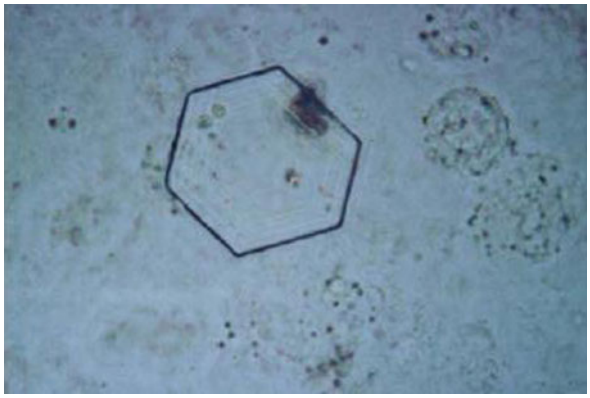

Figure 308.8
Examination of urinary sediment discloses a hexagonal crystal of cystine

4. Hyperuricosuria
Hyperuricosuria can lead to CaOx stone formation by heterologous nucleation on the surface of monosodium urate crystals. The most common cause of hyperuricosuria is increased dietary purine intake, as uric acid is the end product of purine metabolism.

Numerous hereditary (see *Table 308.3*) and acquired diseases can lead to hyperuricosuria, including gout, myelo- and lymphoproliferative disorders, multiple myeloma, hemolytic disorders, and hemoglobinopathies. The pathophysiology of hyperuricosuric CaOx nephrolithiasis is intimately related to urinary pH. At pH less than 5.5, poorly soluble undissociated uric acid precipitates, leading to uric acid or CaOx stone formation. At pH greater than 5.5, uric acid is found predominantly in its dissociated form. In special cases of excessive uric acid formation, increased urinary saturation of monosodium urate ensues, promoting CaOx stone formation through heterogeneous nucleation.

5. Cystinuria:
Cystinuria (MIM 220100) is an autosomal recessive inherited aminoaciduria that leads to recurrent nephrolithiasis, accounting for approximately 6% of metabolic stones in the pediatric population with prevalence varying throughout different global locations but is approximately 1 in 7,000 in the general population of Europe and the United States. Newborn screening programs have estimated the disease frequency at 1:100,000 in Sweden. On the other hand, high frequency of the disease has been reported for Libyan Jews living in Israel with a prevalence rate of 1/2,500. In Turkey in Sivas province, the prevalence of cystinuria is 1/772; this prevalence ratio is the highest ever among those

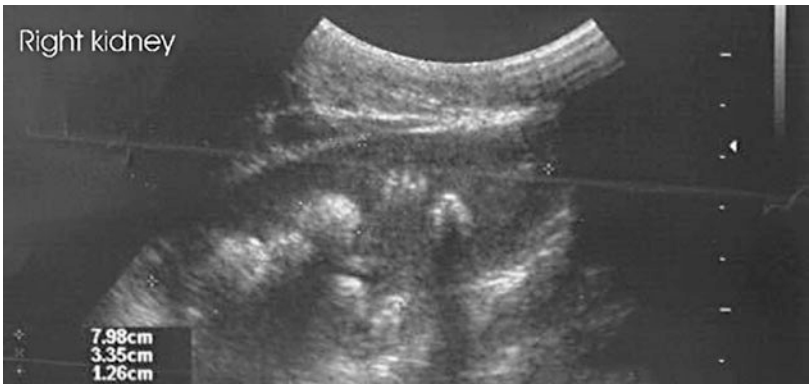

Figure 308.9
Ultrasound: staghorn urolithiasis of the right kidney

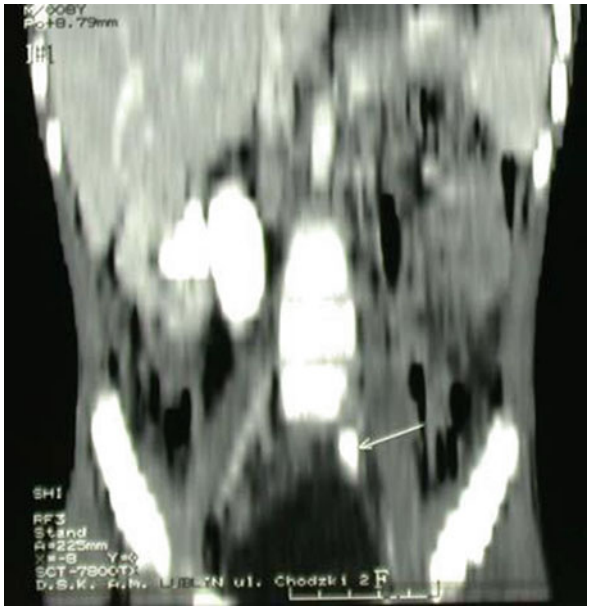

Figure 308.10
CT scan: staghorn urolithiasis of the right kidney and stones in the left ureter (*arrow*). Stones within the left kidney are not visible on this scan

reported for other countries. Three different types of cystinuria (types I, II and III) have been described. This classification has been modified as type I and non-type I (divided clinically as types II and III). In1994, a cystinuria gene (*SLC3A1*) was cloned and mapped on chromosome 2p16.3. The gene encodes the protein rBAT, a b0, +AT transporter-related protein expressed in the renal and intestinal epithelium. The glycoprotein rBAT causes cystinuria type I. It is thought that b0, +AT represents the catalytic subunit of the transporter complex and that rBAT is mainly involved in the trafficking and possible stabilization of the transporter in the brush border membrane. rBAT may also modify the functional transport properties of the complete transporter complex. The transporter functions as a tertiary active exchanger taking up cystine, arginine, lysine, and ornithine from urine in exchange for neutral amino acids. To date, more than 80 mutations in *SLC3A1* have been documented as cited by Škopková et al. The International Cystinuria Consortium has described a new classification system based on the chromosomal localization of the mutation, with type A cystinuria (45% of patients with cystinuria), mutations of the SLC3A1 gene on chromosome arm 2p encoding the rBAT protein called (type I) before.

Type B cystinuria (53% of patients with cystinuria), mutations of the SLC7A9 gene on chromosome 19, was called (non-type I) previously.

Type AB with mutations on both chromosomes is found in 2% of patients with cystinuria. Homozygous, compound heterozygous, and obligate heterozygous subtypes have been described, with homozygotes excreting the greatest amount of cystine; affected individuals demonstrate excretion of cystine and the dibasic amino acids ornithine, arginine and lysine in the proximal tubule. Due to a pH drop in the collecting duct, cystine (soluble at normal urinary pH) exceeds the solubility limit in urine and forms typical crystals and eventually kidney stones; diminished reabsorption of these amino acids in the intestine is not pathologic because these are not essential amino acids and their di-peptide forms are still transported.

By 1 year of age, a homozygous patient's urinary excretion of cystine is usually more than 1,000 mmol/g creatinine with a mean excretion rate of 4,500 mmol/g creatinine. At usual urine volumes, this excretion rate exceeds its solubility. Life-long recurrent stone formation is a characteristic of patients with the homozygous forms of cystinuria.

Heterozygote carriers may also form stones because they have been shown to excrete up to 2,400 mmol/g creatinine; parents of cystinuria Type A have normal levels of cystine and lysine excretion. Therefore, this type was also referred to as the fully recessive form. In type B, elevated levels of cystine and lysine are observed in obligate heterozygotes. It is currently well established that the clinical manifestations of cystinuria are exclusively renal. Their early recognition is important for timely treatment and genetic counseling.

Cystinuria may be diagnosed by the finding of hexagonal crystals (*Fig. 308.8*).

A prenatal approach to cystinuria has been suggested by the presence of hyperechoic colon during the third trimester of pregnancy, which may be due to the presence of large amounts of cystine in the colon wall.

The follow-up of these patients is based on urine volume (urine specific gravity target <1,010), urine pH (target ~7.5 – < 8), free urine cystine concentration (target < 1 mmol/L or < 100 μmol/mol creatinine), renal ultrasonography and, sometimes, urinary sodium (in order to estimate sodium intake), and crystal volume assessment (target < 3,000 $\mu m^3/mm^3$).

6. Infection:
   Children with a history of multiple urinary tract infections may be at risk of nephrolithiasis (struvite stones), especially if the organisms contain the enzyme urease, which results in a high urine pH that promotes the supersaturation of urine with struvite and calcium phosphate apatites. Patients with surgically augmented bladders are at risk of developing bladder stones, most commonly struvite stones.

Clinical Manifestations

The most common findings of urolithiasis in pediatric age groups are abdominal pain and hematuria; they might have vomiting and dysuria. The observation of a 33% hematuria rate in the metabolic group and a 26% dysuria rate in the infection group is clinically significant. Many studies reported that urine oxalate, uric acid, and calcium cause hematuria by damaging the uroepithelium, and in these cases urinary N-acetyl-glucoseaminoglycan (NAG) levels, as a marker of tubular injury, were elevated . These previous findings support the association of metabolic etiology and hematuria. Recent studies from various countries reported a mean age for urolithiasis of 4.2–8.2 years. The mean ages of the groups with metabolic etiology and infectious etiology were found to be lower compared with the other groups; a family history of urolithiasis was reported in 11.8–21.9% of patients. Diagnosis is often only made when nephrocalcinosis is incidentally noted on an imaging study performed for other reasons or when symptoms of reduced concentrating capacity of the renal tubules are obvious. The underlying pathological condition is not always evident and requires a detailed history and workup. Renal colic has been reported in some infants with nephrocalcinosis, but it is more likely due to passage of tiny calculi than to nephrocalcinosis per se. It is not unusual for nephrocalcinosis to be diagnosed during systematic renal ultrasound examination of high-risk infants or as part of the diagnostic evaluation of urinary tract infection. The first clinical symptoms, if any, are gross or microscopic hematuria and/or sterile leukocyturia that may be misdiagnosed as urinary tract infection. Single family member involvement was found more than multiple involvements. Stone occurrence was more in the immediate family members than distant relatives, especially brothers of affected patients. Study of stone risk in the family members should be centered on brothers and sons of stone patients.

Diagnosis

We should start with good history including immediate close relatives (brothers and sons), medications, possible risk factors like malabsorption, and immobilizations.

Clinical findings may not be very informative, but finding of hematuria, leukocyturia, passage of stone, abdominal pain, and dysuria may be of some help.

Laboratory evaluation can help especially in metabolic caused stones:

Serum levels of uric acid, electrolytes, creatinine, calcium, phosphorus, and bicarbonate should be measured. Serum parathyroid hormone level should be obtained in children who have hypercalciuria, hypercalcemia, or hypophosphatemia, vitamin A (for patients with hypercalciuria), serum vitamin B6 levels, and plasma oxalate (for patients with primary hyperoxaluria) and, of course, molecular genetic testing will later be necessary (*Table 308.3*).

Elevated serum alkaline phosphatase may indicate possible bone resorption. Twenty-four hour urine collection for sodium, calcium, urate, oxalate, cystine, citrate, and creatinine [determine tubular reabsorption of phosphate (TRP) or tubular maximum for phosphate corrected for glomerular filtration rate (TmP/GFR)] should be evaluated. Since many urinary components are influenced by dietary intake, 24 h urine collections (to exclude diurnal fluctuations related to intake of food and beverages) provide the best information and also provide an objective assessment of the child's daily intake of fluid. Advise the patient or the parent to maintain the normal fluid intake and the normal dietary habits, before 24 h urine collected (avoid urine sampling under parenteral infusions). Also keep in mind that stones in situ may diminish the excretion of urinary lithogenic material, as these substances may concurrently be absorbed by the stone. For urine collection, a preservative should ideally be placed directly into the sampling bottle; however, urine may be collected without initial preservation, so long as it is kept cool (at 4°C) and adequately preserved within 24 h. Ideally, the urine collection is to be obtained at least 6 weeks after the passage of a stone. Collecting two 24-h samples may be recommended. Determination of urinary supersaturation for calcium oxalate, calcium phosphate, and urate may be helpful (*Table 308.4*). Most children with elevated supersaturation values had urine volumes ≤ 1 mL/kg/h. The urinary creatinine excretion rate may be used to verify an adequate urine collection, with most children excreting ~15 to 20 mg/kg/24 h. If the creatinine

excretion is significantly more or less, it may indicate either an over- or undercollection.

If a 24-hour collection is difficult, especially in younger children, urinary standards based on single specimens, corrected to urine creatinine concentration, have been developed (*Tables 308.4* and *308.5*).

The calcium-to-creatinine ratio changes with age. If hypercalciuria is suspected on a single random sample, confirmation with 24-hour urine collection is needed.

A urine culture should be considered to exclude the possibility of acute or chronic urinary tract infection. Urinalysis may be helpful, particularly if crystals are noted. Cystine crystals are colorless, flat, and hexagonal, and if they are found in the urine, they are diagnostic for cystinuria. Cystine is screened for by nitroprusside test or by chromatography for amino acids.

Since the pH of the urine is a major factor in the formation of many stones, its measurement, preferably by glass electrode, or, if a pH electrode is not available, by pH paper with the specific and adequately distinguishable range of pH 2 to 9, is of utmost importance. Sometimes, it is advisable to determine a daily profile of both the pH and the density (specific gravity or osmolality) of the urine. This may also be used for follow-up, e.g., to assess the effect of the administration of alkali or to check the patient's compliance regarding sufficient fluid intake. To discriminate the primary from the secondary forms of hyperoxaluria, a [13 C2] oxalate absorption test can be performed, which is safe and reliable in children, as in adults. Intestinal oxalate absorption is normal in patients with primary hyperoxaluria and would be significantly increased in those with dietary or enteric hyperoxaluria. Also, a stool analysis for the absence of oxalate-degrading

Table 308.4
Normal values for 24 h urine

Chemical component	Value
Calcium	<4 mg (0.1 mmol)/kg per 24 h
Sodium	<3 mEq (3 mmol)/kg per 24 h
Potassium	>3 mEq (3 mmol)/kg per 24 h
Magnesium	>88 mg (44 mmol)/1.73 m^2 per 24 h
Citrate	>180 mg (94 μmol/g (8.84 mmol) creatinine
Oxalate	<52 mg (593 mmol)/1.73 m^2 per 24 h
	<2 mg (23 mmol)/kg per 24 h
Cystine	<60 mg (0.5 mmol)/1.73 m^2 per 24 h
Uric Acid	<815 mg (4.9 mmol)/1.73 m^2 per 24 h
	<35 mg (0.21 mmol)/kg per 24 h
Xanthine	30–90 μg (20–60 μmol)/24 h

Source: Alon US (2009) Pediatr Nephrol. doi 10.1007/s00467-007-0740-7

Table 308.5
Normal values for spot urine samples

Parameter age	Ratio of solute to creatinine		Remarks
	mol/mol	mg/mg	
Calcium			
<12 months	<2	0.81	Highest Ca excretion with breast milk feeding, ratio increasing after meals (up to 40%),by loop diuretics, immobilization and steroids
1–3 years	<1.5	0.53	
1–5 years	<1.1	0.39	
5–7 years	<0.8	0.28	
>7 years	<0.6	0.21	
Oxalate			
0–6 months	<325–360	288–260	Primary hyperoxaluria types I/II for constant excessive elevation, check also urinary glycolate, L-glycerate, and plasma oxalate. Secondary hyperoxaluria: determine intestinal oxalate absorption and stool. Oxalobacter formigenes colonization
7–24 months	<132−174	110−139	
2−5 years	<98−101	80	
5−14 years	<70−82	60−65	
>16 years	<40	32	
Citrate			
0–5 years	>0.25	0.42	Low with tubular dysfunction: RTA, prematurity, hypokalemia, renal transplantation
>5 years	>0.15	0.25	
Magnesium			
	>0.63	> 0.13	For <2 years, no reliable data
Uric acid			
>2 years	<0.56 mg/dL (33 μmol/L) per GFR (ratio × plasma creatinine)		Higher than in adults throughout childhood; no reliable data for age <2 years

Source: Hoppe B, Kemper MJ (2010) Pediatr Nephrol 25:403–441

bacteria, especially Oxalobacter formigenes, will give further evidence of the existence of a secondary reason for hyperoxaluria.

Qualitative analysis of the stone obtained after intervention or spontaneous stone passage is one of the most important diagnostic measures. The methods of choice are infrared spectroscopy or X-ray diffraction. Even amounts of $\leq$ 1 mg can be analyzed. Chemical stone analysis is inappropriate, as it is prone to errors and is obsolete. The analytic principle of X-ray diffraction is based on the crystal structure of the stone substances. With infrared spectroscopy the loss of energy in the infrared spectrum due to the circulation of the activated chemical molecules is determined.

Recurrent stones should be analyzed again, since the stone composition may change. After lithotripsy only stone fragments are available, and these can be recovered by straining the urine. All fragments should be sent for analysis to allow additional tests, if needed.

Radiologic Evaluations

Ultrasound of the kidney and bladder can show nephrocalcinosis and renal or pelvic stone; KUB does not add significant diagnostic utility above clinical evaluation with symptoms of renal colic; helical CT is the best method of testing for urinary tract stones, more sensitive and safer method than IV pyelography (IVP). The appearance on imaging studies depends upon the stone's composition. Those composed of calcium oxalate or calcium phosphate have a very dense image on conventional radiographs and on CT scans. Struvite (magnesium ammonium phosphate) and cystine stones are of intermediate density, and small stones of all compositions can be difficult to appreciate by conventional radiography. Uric acid stones are radiolucent on radiographs, requiring the administration of contrast agents for adequate visualization, and have a low density image on CT scans. Stones of all composition, with the exception of drugs (e.g., indinavir) and matrix (protein), have distinguishing characteristics of echogenicity and shadowing on ultrasonography.

Ultrasonography has the additional advantages of wide availability, avoidance of ionizing radiation, ready detection of hydronephrosis, and ability to define some aspects of the anatomy of the urinary tract; it is not as sensitive as CT is for the detection of small (smallest size between 1.5–2 mm in diameter) stones in the ureter.

Most stones can be imaged without the use of contrast agents. However, when obstruction is a concern, when radiolucent or low density stones require careful delineation, or when details of urinary tract anatomy are needed (such as confirmation of a duplicated collecting system), contrast agents (CT urography, intravenous pyelography, or retrograde ureteroscopy/pyelography, or orthograde pyelography) are usually required.

For the detecting and monitoring of nephrocalcinosis, high-resolution ultrasonography is the optimal imaging method (◉ *Fig. 308.11*).

Some pitfalls in the renal ultrasonography of neonates, and especially preterm infants, have to be noted: Tamm–Horsfall protein (THP) deposits within the renal calyces may look like nephrocalcinosis (◉ *Fig. 308.11*). THP deposition, however, disappears within 1–2 weeks, and follow-up will show completely normal kidneys. Furthermore, the echogenicity of the renal cortex in neonates is physiologically increased, hence detection of cortical nephrocalcinosis can be difficult and may become evident only some weeks later when a rim of cortical calcification becomes visible. However, diffuse cortical nephrocalcinosis may already be detectable shortly after birth in patients with suspected primary hyperoxaluria, and it is directly visible both by US and X-ray.

Treatment

Non-specific Treatment

Acute episode: During the acute phase when the stone is being passed, management is directed toward pain control, and facilitating passage or removal of the stone(s).

The acute management of nephrolithiasis depends upon the severity of the pain, and the presence of obstruction or infection. In some patients, outpatient medical management with oral analgesics and hydration is possible. However, in others, especially those with nausea, vomiting, and severe pain, hospitalization is required for parenteral fluid and pain medication. Other indications for hospitalization include urinary obstruction and infection.

Pain control: Both nonsteroidal antiinflammatory drugs (NSAIDs) and opioid therapy are used to control pain associated with nephrolithiasis. In studies of adult patients, both classes of analgesics are effective in pain relief. Combination therapy of the two has also been reported to be effective and in some cases superior to either agent alone.

Urologic removal of stones may be required in patients with unremitting severe pain that is refractory to analgesic therapy, or in those with obstruction or infection.

Prevention of recurrent disease: Aim for medical treatment is to decrease or prevent stone formation or growth,

Table 308.6
Diet variables with different sodium concentrations

Category	High sodium food	Low sodium alternative
Meats, poultry, fish, eggs	Burritos, pizzas, canned meat, ham, salted nuts	Fresh beef, fish or pork; Low sodium peanut butter; dry beans
Dairy products	Butter milk, cottage cheese, regular cheese	Milk, mozarella cheese, ice cream
Bread, grains, cereals	Salted bread, biscuits, pancakes, pasta	Non-salted breads, muffins; unsalted popcorn, pretzels
Soups	Canned and dehydrated soup	Low sodium canned soup; home-made soup without salt
Desserts and sweets	Bottled salad dressings, salted butter, instant cake	Unsalted butter, low sodium salad dressings, homemade cake

and decrease need for surgical intervention. This includes an evaluation to identify any underlying cause or risk factors for stone formation. Based upon this assessment, interventions are tailored to reduce the risk of recurrent stone formation.

Dietary and Fluids Management

Dietary management can reduce urinary excretion of stone constituents or increase urinary inhibitors. In low-risk stone formers, dietary measures alone may be sufficient to prevent stone recurrence without the need for drug therapy. A number of factors have been shown to influence stone formation, including fluids, sodium, potassium, animal protein, calcium, and oxalate.

Fluids

A high fluid intake will cause increased urine output, which will reduce urinary saturation of stone-forming calcium salts. Keeping urine flow of >1 mL/kg per hour is needed to decrease risk of supersaturation for calcium oxalate, calcium phosphate, and uric acid, thus protecting from the formation of the corresponding kidney stones. Long-term compliance with an increased fluid regimen is often poor. Coffee and tea were shown in observational studies to reduce the risk of stone formation. Potassium-rich fruit juices such as orange or lemonade juice but not potassium-poor juices, like cranberry juice, provide organic anions that are metabolized to

Table 308.7
Diet variables with different potassium concentrations

Foods high in potassium		
Group of food	**Serving size**	**Potassium (mg)**
Cereals		
Kellogg's All Bran	1/2 cup	532
Nabisco 100% Bran	1/2 cup	354
Bran Flakes	1 cup	251
Shredded Wheat	1 cup	155
Fruit		
Orange juice	1 cup	479
Dried apricots	1/4 cup	454
Cantaloupe	1/4 medium	412
Primes	1/4 cup	353
Banana	1 small	338
Grapefruit juice (canned)	1 cup	360
Tomato juice	1 cup	552
Avocado	1/2	510
Peaches, dried	4 medium halves	330
Raisins	3 tablespoons	225
Cooked beans		
Pinto beans	1/2 cup	531
Kidney beans	1/2 cup	452
Lentils	1/2 cup	374
Black beans	1/2 cup	309
Canned beans	1/2 cup	332
Vegetables		
Baked potato	1 medium	593
Baked winter squash	1 cup	590
Baked sweet potato	3/4 cup	528
Beet greens	1/2 cup	417
Chard (large leaves)	1/2 cup	563
Peas (cooked)	1/2 cup	296
Spinach (fresh)	1/2 cup	440
Lima beans (canned or frozen)	1/2 cup	473
Other		
Canned tomato sauce	1/2 cup	459
Blackstrap molasses	2 tablespoons	1,218
Sardines (canned in oil)	3 oz	459
Chocolate (unsweetened/bitter)	1 oz	249

Source: Adapted in part from the Canyon Ranch Dietary Department (1994)

Table 308.8
Diet variables with different oxalate concentrations

Food	Oxalate content
Artichokes (French)	Moderate = 5.0–9.9 mg
Baker's yeast	
Bananas	
Basil	
Broccoli, raw	
Brussell sprouts, raw	
Cabbage, green, steamed	
Carrots, boiled	
Celeriac, canned	
Chick peas	
Collard greens, boiled	
Cornstarch	
Eggplant	
Garbanzo beans	
Grape juice, red	
Lentils, boiled	
Lima beans	
Limes	
Mandarin oranges	
Mung beans	
Oats	
Papayas	
Pears, unpeeled	
Peppers, green	
Potatoes, red, peeled	
Tomato juice	
Green tea	
Broccoli, steamed	High = 10.0–14.9 mg
Brussels sprouts, steamed	
Chili peppers	
Chocolate milk	
Cinnamon	
Date sugar	
Dates	
Gooseberries	
Kidney beans	
Lemon Peel	
Lime peel	
Orange pee	
Oranges	
Oregano	
Pepper, black (spice)	
Peppercorn	
Persimmons	
Pistachio nuts	
Raspberries, red	
Tomato paste, canned; tomato purée, canned; tomato sauce, canned	
Almonds	Very high = 15.0 mg & up
Beets	
Black beans	
Blackberries	
Carrots, raw	
Carrots, steamed	
Cashews	
Celery, raw	
Chocolate	
Cocoa powder	
Durum flour	
Figs, dried; figs, fresh	
Filberts (Hazelnuts)	
Flour (Wheat)	
Hazelnuts (Filberts)	
Kiwi fruit	
Macadamia nuts	
Olives, black; olives, green	
Peanut butter	
Peanuts	
Pecans	
Pine nuts	
Pinto beans	
Potatoes, peeled; potatoes, unpeeled	
Rhubarb	
Rye	
Sesame oil	
Sesame seeds	
Soy	
Soybean milk, soybeans	
Spinach, fresh; spinach, frozen	
Sweet potatoes	
Turmeric	
Walnuts	
Wheat	

alkali, thereby increasing urinary pH and citrate. Grape fruit juice may cause concomitant increase in urinary oxalate.

Approximate fluid per day at different ages are as follows:

Infants – $\geq$ 750 mL
Small children below 5 years of age – $\geq$ 1,000 mL
Children between 5 and 10 years of age – $\geq$ 1,500 mL
Children greater than 10 years of age – $\geq$ 2,000 mL

Sodium

A high salt intake increases stone risk by reducing renal tubular calcium reabsorption and increasing urinary calcium.

High urinary sodium increases urinary saturation of monosodium urate, and reduces urinary citrate via sodium-induced bicarbonate loss. Consequently, inhibitory activity against CaOx and calcium phosphate is reduced, monosodium urate-induced CaOx crystallization is enhanced, and urinary saturation of CaOx and calcium phosphate is increased.

Furthermore, high urinary sodium reduces the efficacy of thiazide treatment for hypercalciuria by blunting the hypocalciuric effect.

A low sodium diet is allowing less than 1 teaspoon per day. The majority of sodium consumed comes from sodium chloride (NaCl), better known as salt. The average American gets 6% of their total salt added at the table, 5% added during cooking, and natural sources in food another 11%, and the remaining comes from prepared foods. Many packaged meats, canned and frozen foods, contain a surprising amount of salt, as a preservative, adds flavor to foods, and helps to keep foods from drying out. Most canned vegetables have a much higher salt content than the same fresh vegetable, in general, salt intake should be limited.

Optimal daily intake of sodium according to ages is as follows: 1.2–1.9 g for ages 4–8 years and, 1.5–2.3 g for ages 9–18 years.

Most Americans consume between 3,000 and 5,000 mg of sodium per day. The National Academy of Sciences' Institute of Medicine advises that children under the age of 11 should not be given more than 2.4 g of sodium in a day. There are few rules to be followed when following a low sodium diet for children.

Start the diet by removing salty foods (packaged foods) from the child's diet.

Lower the amount of seasoning salt used in cooking.

Use different herbs and spices like black pepper or basil to enhance the taste of certain eatables.

For few dishes, natural fruit juices can also enhance the flavor of certain meals.

Use moderate amount of soy sauce and ketchup. They contain high amounts of sodium

Measuring the urine sodium/potassium ratio, which optimally should be below 2.5, assesses compliance with the dietary recommendations related to sodium and potassium.

Potassium

High potassium intake decreases urine calcium. The optimal daily potassium intake, provided mostly in the form of fruit, vegetable, and dairy products is 3.8 g at ages 4–8 years and 4.5 g at ages 9–18 years.

Animal Protein

Animal protein provides an acid load because of the sulfur-containing amino acids. A high protein intake reduces urine pH and citrate, and enhances urinary calcium excretion via bone resorption and reduced renal calcium reabsorption; the purine load potentially increases urinary uric acid. Restriction of animal protein (red meat, fish, poultry) to two servings daily is recommended.

Calcium

Hypercalciuric patients may be optimally treated with a program of modest calcium and oxalate restriction, along with pharmacologic therapy. Severe calcium restriction should always be avoided so as to prevent a negative calcium balance; however, mild calcium restriction (less than one serving of dairy daily) should be part of a program of broad dietary modification in patients who have hypercalciuria. Normocalciuric patients do not benefit from dietary calcium restriction, and therefore, a liberal calcium intake is recommended in this group of patients.

Oxalate

The relative contribution of dietary oxalate and endogenous oxalate production to urinary oxalate is controversial. Dietary oxalate has been estimated to account

Table 308.9
Suggested therapy for urolithiasis caused by metabolic abnormalities

Metabolic abnormality	Initial treatment	Second-line treatment
Hypercalciuria	Reduction of dietary Na+	Potassium citrate
	Dietary calcium at RDA	Neutral phosphate
		Thiazides
		Alendronate (bisphosphonate) esp. in resorptive hypercalciuria
Hyperoxaluria	Adjustment of dietary oxalate	Neutral phosphate
		Potassium citrate Magnesium
		Pyridoxine
		Oral ingestion of Oxalobacter formigenes
Hypocitric aciduria	Potassium citrate	Bicarbonate
Hyperuricosuria	Alkalinization	Allopurinol
Cystinuria	Alkalinization	Tiopronin (Thiola)
	Reduction of dietary Na+	D-penicillamine (+pyridoxine)
		Captopril
		The goal of treatment is to keep urinary cystine concentration $\leq$ 250 mg (1 mmol/L.)

Source: From Milliner DS (2004). Urolithiasis. In: Pediatric nephrology. Lippincott Williams & Wilkins, Philadelphia, p 1104

for 10–50% of urinary oxalate, depending on dietary calcium and oxalate intake, and the bioavailability of oxalate in foods. In general, restriction of oxalate-rich foods, such as nuts, chocolate, tea, and dark roughage is recommended. Vitamin C has been implicated in calcium stone formation because of in vivo conversion of ascorbic acid to oxalate. Limitation of vitamin C supplements is recommended.

Other Diet Components

Other nutrients, such as sucrose, fructose, may be associated with higher risk for kidney stone disease, whereas phytate and magnesium may decrease it.

Drug Therapy

For those patients in whom conservative dietary measures fail or those who have more aggressive stone disease or identifiable metabolic abnormalities, pharmacologic therapy, along with dietary management, should be initiated.

Thiazide Diuretics

Thiazide diuretics are reserved for patients who have severe hypercalciuria not responding to conservative measures.

Doses can be divided according to ages: <6 months: 1–3 mg/kg/day in 2 divided doses;

>6 months to 2 years: 1–3 mg/kg/day in 2 divided doses; maximum: 37.5 mg/day

>2–17 years: Initial: 1 mg/kg/day; maximum: 3 mg/kg/day (50 mg/day).

Its mechanism resorts in enhancing sodium and calcium reabsorption in the distal renal tubule leading to a reduction in urinary calcium excretion. The diuresis induced may be accompanied by a fall in urinary calcium excretion of as much as 50–150 mg (1.3–3.8 mmol) per day This hypocalciuric effect is reduced if sodium intake is not limited. Stone recurrences can decrease from 50% (untreated) to 20% (treated) over 5 years. Thiazides have many other effects on the body. They increase serum calcium and uric acid levels while decreasing urinary citrate levels. Hyperuricemia or acute gout rarely develops in individuals receiving thiazides. A risk of dehydration, hypokalemia, and hyponatremia exists. They can cause magnesium loss and increase cholesterol. Adverse effects occur in about one third of patients but are usually mild. The most bothersome clinical adverse effect is lethargy, but muscle aches, depression, decreased libido, generalized weakness, and malaise also can occur. About 20% of patients stop thiazide therapy because of these adverse effects. These medications originally were intended solely for use as diuretics for hypertension. They have become the primary medical treatment for hypercalciuria because of their unique ability to remove calcium from the urine and return it to the general circulation. They can be used in virtually any type of hypercalciuria, with the possible exception of resorptive hypercalciuria, in which they can exacerbate hypercalcemia.

Potassium Citrate

Potassium citrate is effective in the treatment of patients who have calcium stones providing an alkali load,

(potassium or sodium citrate, 100–150 mg/kg per day in 3–4 divided doses) increased urinary pH and citrate, thereby increasing urinary inhibitory activity especially for urate stone, cystine, and also Hypercalciuric patients. Potassium citrate can reduce stone recurrence rates by 75% among hypocitraturic stone former. It is recommended that the urine pH should not exceed 8.5, a high alkaline urine promotes formation of calcium phosphate stones.

Allopurinol

In calcium stone formers, who have moderate to severe hyperuricosuria and in whom other conservative measures fail, including high fluid intake, alkalinaization of urine and in older children diet modification, allopurinol has been shown to reduce urinary uric acid levels and prevent recurrent stone formation. Allopurinol is a xanthine oxidase inhibitor that prevents the conversion of hypoxanthine to xanthine, the precursor of uric acid, which decreases in about 2 to 3 days, in both serum and urine. Allopurinol should be discontinued at first appearance of skin rash or any sign of adverse reactions.

The skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial, or purpuric lesions, as well as Stevens-Johnson syndrome (erythema multiforme) and, very rarely, a generalized vasculitis that may lead to irreversible hepatotoxicity and death. There have been occasional reports of reduction in the number of circulating-formed elements of the blood, including bone marrow suppression, granulocytopenia, and thrombocytopenia, usually in association with renal and/or hepatic disorders or in whom concomitant drugs have been administered that have a potential for causing these reactions.

Periodic liver function tests, renal function tests and complete blood cell counts should be performed in all patients on allopurinol.

Observe patients with impaired renal or hepatic functions carefully during the early stages of allopurinol administration and withdraw the drug if increased abnormalities in hepatic or renal function appear.

In cases of patients using diuretics, such as Thiazides and ethacrynic acid, when given with allopurinol, it may increase serum oxypurinol concentrations and may thereby increase the risk of serious allopurinol toxicity, including hypersensitivity reactions, particularly in patients with decreased renal function.

Allopurinol should not be given to children except those with hyperuricemia secondary to malignancy or with Lesch–Nyhan syndrome, because safety and effectiveness have not been established in other conditions.

Since allopurinol and its metabolites are excreted by the kidney, drug accumulation can occur in renal failure and the initial dose of allopurinol should consequently be reduced. In children with recurrent renal stone >10 years and adults – Oral dose: 200–300 mg daily is divided or single daily dosage.

Pyridoxine

Promotes the conversion of glyoxalate to glycine, thereby reducing the substrate for oxalate production. Pyridoxine is used for treatment of PH1, not all patients of PH1 respond to Pyridoxine, a test dose of 5–10 mg/kg per day is given. It is likely to be of limited value in patients of enteric hyperoxaluria.

Specific Treatment

Stone Removal

Indications for stone removal – severe pain, infection, severe obstruction, growth of calculus, nonprogression, interference with lifestyle, any stone can be removed by open procedure (rarely done), percutaneous nephrostomy (for kidney and upper ureter), large calculi fragmented first by ultrasound, electrohydraulic (EHL, spark in water tub) or laser lithotripters, (more effective for simple renal stones than branched or ureteral calculi), transurethral removal (calculi below pelvic rim) use basket for removal.

Extracorporeal Shock Wave Lithotripsy (ESWL)

According to the guidelines of the European Association of Urology, ESWL should be the first surgical choice for most renal pediatric stones. The underlying function of all types of ESWL machines is to generate and focus shock-wave energy at a focal point that is clustered at the calculus. Ideally, the impact of the shock wave disintegrates the stone so the fragments can pass the ureter.

ESWL may not be as effective as ureteroscopic management of ureteric stones, but associated with fewer complications, comparing ESWL versus ureteroscopic management, 73% vs. 90% stone-free rate. ESWL is

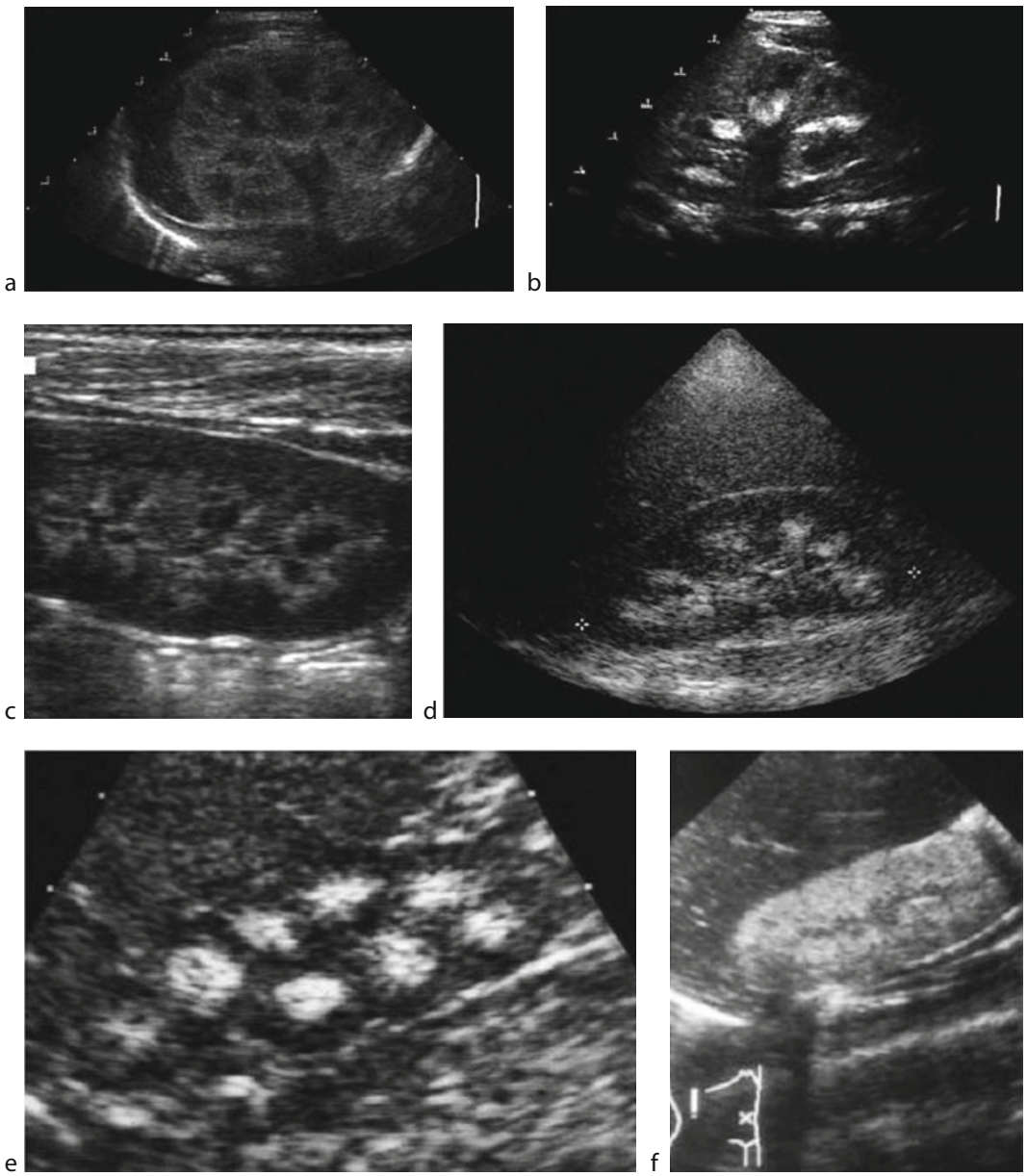

Figure 308.11
(a) Normal, still hyperechoic kidney of a preterm infant. (b) Tamm–Horsfall kidney. (c)Medullary nephrocalcinosis (NC) grade I (mild increase of echogenicity around the pyramidal border). (d) Medullary NC grade II (mild increase of echogenicity at whole pyramid). (e) Medullary NC grade III (more severe hyperechogenicity of entire pyramid). (f) Diffuse corticomedullary NC

associated with shorter length of hospital stay. Studies demonstrated that there are short-term effects such as perirenal hematomas, hematuria, and reduced GFR directly after ESWL therapy. However, there has been no evidence for long-term damage in children.

It is of utmost importance that no stone material is left behind, no matter what therapy is employed, as recurrence rates are higher than in adults. Thirty-three percent of patients with small remaining stone fragments after extracorporeal shock-wave lithotripsy (ESWL) (<3 mm),

which were formerly called clinically insignificant residual fragments (CIRFs) in the early era of ESWL, had an increasing stone mass on median follow-up of 24 months.

Compared with stone-free individuals, patients with residual fragments had an increased risk for adverse clinical outcome, with an odds ratio (OR) of 3.9.

If an underlying metabolic disorder was existent, the OR for growth of residual fragments was 11.4.

Before choosing the appropriate treatment, it is indispensable to know the number, size, location, and composition of a stone, and in addition, any information about the urinary tract below the stone.

ESWL is the preferred treatment in pediatric urolithiasis patients with calculi <20 mm. Stone-free rates after ESWL in children range between 57% and 92%.

In suspected cystine stones, the maximum diameter should not exceed 15 mm because of the hardness of the stone. Hardness of cystine stones, a ureteroscopic or minipercutaneous nephrolithotomy approach is coequal, if not the new first-line therapy. Thus, large and hard stones, such as cystine and whewellite, decrease ESWL success rates.

Another important aspect in treatment planning is urinary tract anatomy and stone location. ESWL treatment of stones in lower calices has a lower success rate due to the special anatomy and gravity situation.

Minipercutaneous Nephrolithotomy

A percutaneous approach (PCNL) could be used for bigger and more complex calculi.

Although there are no international guidelines as to when PCNL should be the primary treatment in children, there are relative indications, such as large stones (>1.5 cm) or >1 cm for lower-pole concrements. Especially if there are anatomical abnormalities that prevent good fragment clearance (i.e., ureteropelvic junction obstruction, calyceal diverticulum, ureter stricture), and depending on stone composition, PCNL can be the treatment of choice. Although PCNL is an invasive treatment, it achieves excellent stone free rates and comes with a relatively low risk in experienced hands.

Ureterorenoscopy

URS is ideally suited for calculi in the mid and distal ureter; this procedure has become a first-line treatment for ureteral stones and can even be considered a good treatment option for renal calculi.

Laparoscopic Surgery/Open Surgery

In developed countries, open surgery remains the treatment of choice for 0.3–5.4% of children. In general patients with anatomical abnormalities i.e., ureteropelvic junction obstruction, obstructive megaureter, urolithiasis will receive open surgery if stone removal and anatomical correction can be combined in one operation. In developing countries, open surgery is used in 14% of cases, which is likely due to the fact that open surgery is more cost-effective in those countries.

Prevention

The best treatment both for calcium containing stones and for other stones remains prevention. A stone requires supersaturation, a nidus, and time to form. Thus, ample hydration, avoidance of infection, and good voiding habits minimize the chance of stone formation, whether initial or recurrent.

Once a stone has formed, however, there is more than a 50% chance that a second stone will form at some point.

Based upon these observations, prevention of recurrent stone disease should be a major clinical goal. Preventive measures are directed toward reducing risk factors associated with stone formation. In all children with nephrolithiasis, adequate fluid intake is a key component to reducing the risk of recurrent stones. High fluid intake increases the urine flow rate and lowers the urine solute concentration, thereby reducing the likelihood of new stone formation. The therapeutic preventive interventions are based upon the underlying metabolic condition.

Surgical success based on less complication and complete removal of the stone to reduce risk of recurrence.

Prognosis

Ninety percent of patients will pass the stone if < 4 mm in distal ureter, 50% 4–6 mm, only 20% > 6 mm pass stones. Small non-uric acid stones in upper pole appear least likely to progress; most lower pole calyceal stones < 20 mm can be adequately cleared with extracorporeal shock wave lithotripsy (ESWL); asymptomatic lower pole caliceal stones may be safe to observe.

In recent articles a recurrence rate of 67% during a mean follow-up of 59 months is quoted. Despite the excellent response to treatment noted in most children with urolithiasis, long-term nephrologic care is indicated, particularly for children who have more complex forms of

renal stone disease, because renal insufficiency or end-stage renal disease may develop.

In general, increased water intake can be used for primary prevention of urinary calculi; reducing soft drink consumption reduced risk of stone recurrence among men; greater increase in urine volume associated with reduced risk of recurrence among patients who had stones, low-animal-protein, low-salt diet may prevent recurrent stones in selected patients, thiazides and allopurinol reduced 3-year recurrence rate from 55% to 15–25% in randomized trials. Restricted animal protein and salt with normal calcium intake is more effective than low-calcium diet in preventing recurrent stones in men with recurrent calcium oxalate stones and hypercalciuria.

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309 Interstitial Nephritis and Primary Hyperoxaluria

Pierre Cochat

Tubulointerstitial Nephritis

The definition of tubulointerstitial nephritis (TIN) is based on histopathological findings, so kidney biopsy remains the only definitive diagnostic investigation. TIN may be due to various causes and is probably underdiagnosed both in adults and children.

Acute Tubulointerstitial Nephritis (ATIN)

Presentation

Children with ATIN usually present with non-oliguric acute renal failure without edema, sometimes with loin pain, which develops over a period of days to several weeks; in case of drug-induced ATIN, symptoms typically begin 3–5 days after drug (re)exposure. Renal presentation may also include leukocyturia, and various degree of tubular impairment (polyuria, glucosuria, tubular proteinuria). Blood pressure is normal and there is neither hematuria nor heavy proteinuria. Renal ultrasonography may show normal or enlarged kidneys with increased echogenicity.

According to the primary disease, extrarenal signs such as low-grade fever, maculopapular rash, mild arthralgias, anemia, weight loss, and malaise may be associated (in 50% of cases). In the case of drug-induced ATIN, hypereosinophilia and eosinophiluria may be found. More specific organ involvement may be of major interest, and ophthalmologic examination should be recommended in most cases looking for uveitis. However it is likely that many patients with mild ATIN are often clinically silent.

Etiology

ATIN accounts for 5–10% of acute renal failure in the pediatric setting, and may have various causes, which are summarized in ❯ *Table 309.1*. However, the role of drug-related ATIN seems to be increasing during the recent years both in children and adults.

A few biological investigations are of interest: erythrocyte sedimentation rate, urinary β-2 microglobulin, antitubular cell antibodies, serum immunoglobulins, etc. In difficult cases, serum sample should be stored at −20°C for further immunological assessment.

Pathology

Renal biopsy may be useful in some patients but is not required for all. ATIN prevalence was 11.3% of biopsy-confirmed acute renal failure in a recent large series that included both children and adults.

Light microscopy shows interstitial edema with inflammatory cellular infiltrate (majority of T cells, together with macrophages and plasma cells), sometimes with granulomatous lesions or eosinophils according to etiology (mainly drug-induced ATIN). Patients with diffuse infiltrate had a worse prognosis than those with focal interstitial infiltrate. Tubes and capillaries may be sometimes involved.

Immunofluorescence staining for antibodies and complement uses to be negative, but linear or granular deposits of immunoglobulin G or M may be occasionally present along the tubular basement membranes.

Treatment

The overall outcome of ATIN is usually good without any specific treatment; the mean recovery time to the nadir creatinine level is 1–2 months. When drug-induced ATIN is suspected, the presumed causative drug should be withdrawn first, and rechallenge must be excluded.

In adults, 58% of cases require acute renal replacement therapy. According to pathological features and etiology, early short course oral corticosteroid therapy may be indicated but results are controversial. The best results have been obtained with TINU syndrome and some drug-induced (antibiotics, non-steroidal anti-inflammatory drugs) ATIN.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_309,

Table 309.1
Etiologies of acute tubulointerstitial nephritis

Drugs and toxins +++	Hypersensitivity to drugs (acyclovir, indinavir, tenofovir; beta-lactams, cephalosporins, ciprofloxacin, rifampicin, isoniazid, sulfonamides, vancomycin, macrolides; non-steroidal anti-inflammatory drugs; frusemide, thiazides, triamterene; allopurinol; phenytoin, carbamazepine; ranitidine, cimetidine; omeprazole; bisphosphonates; alpha interferon; azathioprine)
	Mushrooms (*Cortinarius*)
	Creatine
Crystal-induced ATIN	Drugs (acyclovir, indinavir, triamterene)
	Uric acid
	Calcium salt (phosphate, oxalate)
Infections ++	Acute pyelonephritis (*Escherichia coli*)
	Systemic bacterial infection (streptococcus, staphylococcus, leptospirosis)
	Mycoplasma infection
	Viral infection (Epstein-Barr, HIV, Hantaan, BK polyoma, adenovirus)
Systemic disorders	Sarcoidosis, Sjögren syndrome, systemic lupus, inflammatory bowel disease
	Vasculitides
	"TINU" syndrome (idiopathic TubuloInterstitial Nephritis with Uveitis)
	Lymphoma, leukemia
Primary ATIN	Isolated idiopathic tubulointerstitial nephritis

Chronic Interstitial Nephritis (CTIN)

CTIN develops over months or years and is a common unspecific feature, which may also have specific causes.

Presentation

CTIN is often diagnosed late because clinical signs are usually limited. Patients present with progressive chronic kidney disease, variable degrees of arterial hypertension, tubular dysfunction (tubular proteinuria, polyuria, enzymuria, increased natriuresis, acidosis), leukocyturia, hematuria, and hyporeninemic hypoaldosteronism. Small kidneys with increased echogenicity and anemia are suggestive of a long-standing process.

Etiology

CTIN may have various causes, which are summarized in *Table 309.2*. Some specific biological investigations may be of interest: erythrocyte sedimentation rate, urinary β-2 microglobulin, antitubular basement membrane antibodies, anti-tubulointerstitial nephritis antibodies, serum immunoglobulins, etc. In difficult cases, serum should be stored at −20°C for further immunological assessment.

Pathology

CTIN associates various degrees of interstitial inflammatory infiltrate (lymphocytes, monocytes, macrophages), tubular involvement (tubular atrophy, flattened epithelial cells, tubular dilation, tubular basement membrane thickening), glomerulosclerosis, and interstitial fibrosis; vessels may also be involved.

Immunofluorescence microscopy is usually negative, except in systemic diseases. The extent of disease on renal biopsy inversely correlates with renal function and may accurately predict renal prognosis.

Treatment

In case of drug- or toxin-induced nephropathy, the causative agent should be ruled out. In most other cases, nephroprotection is recommended, such as conservative management of electrolyte disturbances, blood pressure control, angiotensin-converting enzyme inhibitor, and angiotensin-2 receptor antagonist.

Primary Hyperoxaluria

Hyperoxaluria may be either a secondary or a primary disease. Two autosomal recessive inherited enzyme defects of glyoxylate metabolism are related to type 1 and type 2 primary hyperoxalurias (PH), that is, alanine: glyoxylate aminotransferase (AGT; *AGXT* gene located on chromosome 2q37.3) and glyoxylate reductase/hydroxypyruvate reductase (GRHPR; *GRHPR* gene on chromosome 9q11), respectively. A gene for PH3 has been recently identified. Among all PH patients, type 1 accounts for ∼80%, type 2 for ∼10%, and non-type 1 non-type 2 for ∼10%.

Patient information: www.ohf.org – www.oxaleurope.com

Table 309.2
Etiologies of chronic tubulointerstitial nephritis (CTIN)

Infections	Renal scarring post-acute pyelonephritis
	Bacterial infections
	Viral infections (Epstein Barr, BK polyoma)
Drugs and toxins	Antibiotics
	Non-steroidal anti-inflammatory drugs
	Diuretics
	Calcineurin inhibitors (cyclosporin, tacrolimus)
	Alkylating agents (iphosphamide, cis-platinum)
	Bisphosphonates
	Analgesic nephropathy
	Anorexia nervosa (hypokalemia due to diuretic and/or laxative)
	Heavy metals (cadmium, lead, lithium)
	Aristolochic acid (Chinese herbs, Balkan nephropathy) [adult]
	Radiation nephritis
Immunological disorders	CTIN due to anti-tubular basement membrane antibodies
	Systemic lupus and other immune-mediated glomerulonephritis
	T cell-induced CTIN (renal allograft rejection, TINU syndrome)
Genetic diseases	Nephronophthisis
	Cystinosis
Nephrocalcinosis	Inherited (hypercalciuria, distal tubular acidosis, hyperoxaluria)
	Acquired (drug-induced, cortical necrosis, HIV)

Primary Hyperoxaluria Type 1

Pathophysiology

The functional defect of AGT leads to oxalate overproduction by the liver. Since calcium oxalate is insoluble in urine, PH1 usually presents with symptoms referable to the urinary tract. The median age at initial symptoms is 5–6 years and end-stage renal disease (ESRD) is reached between 25 and 40 years of age in half of the patients. Along with progressive decline of glomerular filtration rate (GFR), oxalate deposition occurs in many organs, leading to systemic involvement (named "oxalosis") and bone is the main compartment of the insoluble oxalate pool.

Presentation

The combination of both clinical and renal sonographic findings is a strong argument for PH1, that is, the association of renal calculi, nephrocalcinosis, and renal impairment; in addition, family history may bring additional information.

PH1 grossly fits five presentations: (i) infantile form with early nephrocalcinosis and kidney failure, (ii) recurrent urolithiasis and progressive renal failure, leading to a diagnosis of PH1 in childhood or adolescence, (iii) late-onset form, with occasional stone passage, in adulthood, (iv) diagnosis given by post-transplantation recurrence, and (v) presymptomatic subjects with a family history of PH1.

Diagnosis

The diagnosis is based on urine crystals analysis (calcium oxalate monohydrate, i.e., whewellite), infrared spectroscopy and concomitant hyperoxaluria (urine oxalate >1 mmol/1.73 m^2/day, normal <0.5). In patients with well-defined phenotype, genotyping (DNA sequencing) can be further proposed in order to screen the most common mutations according to local background. Prenatal diagnosis can be performed from DNA obtained from crude chorionic villi or amniocytes.

The assessment of oxalate burden is a major issue when GFR falls to below 30–50 mL/min/1.73 m^2. It is mainly based on repeated plasma oxalate assessment, fundus examination, bone imaging and sometimes bone biopsy examination.

Management

Conservative measures should be started as soon as the diagnosis has been suspected. The aims are to increase urinary solubility of calcium oxalate and to decrease oxalate production (*Table 309.3*).

The treatment of stones should avoid open and percutaneous surgery because further renal lesions will alter renal function, so that the use of extracorporeal shock wave lithotripsy is an available option in selected patients. In patients with repeated renal colic, stone removal can be

Table 309.3

Supportive treatment for patients with primary hyperoxaluria type 1 with preserved renal function

Mode of action	Compound	Dose (per 24 h)
Urine dilution +++	Water	2–3 L/m^2
Crystallization inhibitor	Potassium/sodium citrate	100–150 mg/kg
Normalize urine calcium	Hydrochlorothiazide	0.5–2.0 mg/kg
Decrease oxalate production	Pyridoxine (AGT cofactor)	5–10 mg/kg

attained by ureteroscopy and a ureteral JJ stent may be helpful for pain control and protection of renal damage.

Dialysis is unsuitable for patients who have reached ESRD because it cannot overcome the continuous excess production of oxalate by the liver in spite of its small molecular mass. Peritoneal dialysis alone is unable to clear enough oxalate and is rather contraindicated in such patients. Conventional maintenance long-term hemodialysis is also associated with unacceptable quality of life and may be a life-threatening option in the long term. Therefore, daily hemodialysis is currently the preferred option despite technical challenges in infants, and it may be combined with PD in most children in order to enhance overall oxalate clearance and therefore minimize systemic involvement prior to transplantation.

There are different approaches to organ transplantation strategy, which may be influenced by the local allocation system. The largest experience has been obtained with a one-step combined liver-kidney transplantation leading to acceptable results. The option of a two-step procedure (liver transplantation followed by renal transplantation) should be kept in mind according to local experience and when the prospective waiting time is long enough to jeopardize both patient quality of life and survival. Patient survival after combined liver and kidney transplantation approximates 80% at 5 years and 70% at 10 years. Isolated kidney transplantation is not recommended due to ~100% disease recurrence, and preemptive isolated liver transplantation has limited indications due to ethical reasons.

Non-type-1 Primary Hyperoxaluria

In patients with overt hyperoxaluria, the pattern of urinary metabolites is indicative but no longer a diagnosis of PH. In patients with a clinical picture of PH1, 10–30% have normal AGT activity that may lead to a diagnosis of PH2 or of another inherited disorder causing hyperoxaluria. The overall long-term prognosis is better than for PH1.

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310 Urinary Tract Infection

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Background

Urinary tract infection (UTI) is one of the commonest bacterial infections in children. A single UTI may lead to significant acute morbidity and often recurs. Rare but serious long-term sequelae of UTI include hypertension and chronic kidney disease. The knowledge that a significant number of young children with UTI will have an underlying anomaly of the urinary tract, most commonly vesicoureteral reflux (VUR), and that those with more severe anomalies are more likely to suffer recurrent infections and chronic injury, has led to considerable research and ongoing debate. Whilst much progress has been made in understanding the links between UTI, VUR, and chronic kidney injury, many unanswered questions remain.

Definitions

The term urinary tract infection (UTI) is used to describe both symptomatic infections as well as situations when bacterial growth is detected in children who lack any other signs or symptoms of UTI. This latter situation, known as asymptomatic bacteriuria, is a benign condition that does not require treatment unless the patient has a kidney transplant or is pregnant. In the rest of this chapter UTI refers to growth of microorganisms in the urinary tract coexistent with signs and/or symptoms of infection.

UTI can be further classified based on site of infection. Pyelonephritis is the term used for infections involving one or both kidneys. Cystitis is a lower urinary tract infection confined to the bladder.

The distinction between pyelonephritis and cystitis is usually based on clinical signs and symptoms. The classical features of pyelonephritis are fever, loin pain, and tenderness. However pain and tenderness can only rarely be elicited in young children and infants. Therefore the clinical diagnosis of pyelonephritis rests upon the presence of fever $\geq$38°C in a child with a UTI. The presence of infection in the kidney is suggested by elevated circulating inflammatory markers such as procalcitonin and may be confirmed by dimercaptosuccinic acid (DMSA) scanning at the time of infection (see below).

A recurrent UTI is any UTI occurring after an initial infection has been fully treated.

Etiology

Gram-negative organisms cause the majority of UTI, with *Escherichia coli* accounting for at least 75% of first infections. Other common organisms include *Klebsiella* and *Proteus* species. Less common pathogens include *Enterobacter*, *Citrobacter*, and *Enterococci*.

Staphylococcus saprophyticus has been reported to cause between 7% and 15% episodes of cystitis in young women but is only rarely isolated in young children.

Staphylococcus aureus and *Pseudomonas* species are uncommon causes of UTI that are more likely to be found in children with anatomical or functional abnormalities of the urinary tract.

Chronic or recurrent infections with urease producing organisms, particularly *proteus*, may lead to precipitation of struvite (magnesium ammonium phosphate) which can form stag horn calculi. *Proteus mirabilis* can be grown from the periurethral areas of >22% of uncircumcised male infants.

Other uncommon causes of UTI in children include viruses (e.g., adenovirus) and fungi (e.g., *Candida* spp.). Adenovirus typically causes a haemorrhagic cystitis that may present as macroscopic haematuria. Fungal UTI usually occurs in association with risk factors such as long-term urinary catheterization and immunosuppression.

Tuberculous infection should be considered in a child from an area where TB is endemic who has otherwise unexplained pyuria. Tuberculous infections of the kidney and urinary tract usually occur as a result of haematogenous spread of mycobacteria. The renal infection begins in the glomeruli and, although usually asymptomatic, can cause progressive renal injury and scarring. Lower tract infection may arise secondary to shedding of mycobacteria in urine.

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Chronic infection with *schistosoma haematobia* is associated with bladder granulomata and may present as dysuria, frequency, and terminal haematuria.

Epidemiology

The incidence of UTI differs according to age and gender. Up to 10% of girls will have had a UTI by adulthood with the majority of cases occurring after the age of 2 years. On the other hand, only 2–3% of boys will be diagnosed with a UTI during childhood and more than 60% of these occur before the age of 2. UTIs are an uncommon occurrence in boys older than 4 years of age.

UTI is the cause of up to 10% of all episodes of fever without focus in children younger than 2 years of age. Uncircumcised male infants have a higher incidence of UTI than circumcised boys and UTIs cause up to 20% of febrile episodes in uncircumcised boys less than 3 months of age.

Children with UTI are more likely to have a family history of UTI in first-degree relatives than children without UTI.

Other risk factors for UTI include previous UTI, constipation, voiding dysfunction, neurogenic bladder, and structural anomalies of the urinary tract including vesicoureteral reflux (VUR). VUR is present in at least 20–30% of children having their first UTI compared to only 1–3% of the general pediatric population.

Voiding dysfunction is a broad term used to describe a urination pattern abnormal for the child's age. It may present with symptoms, including urgency, frequency, and incontinence, with onset after daytime continence has been achieved at about 4–5 years of age. Voiding dysfunction is associated with VUR but often occurs independently.

Voiding dysfunction is caused by abnormal (or immature) regulation of bladder filling and emptying, and can be classified as:

- Overactive bladder (also known as unstable bladder, or urge incontinence)
- Underactive bladder
- Dysfunctional voiding, marked by uncoordinated relaxation of the muscles of the external sphincter

Voiding dysfunction may be suggested by a history of incontinence or urgency. Overactive bladder typically is seen in young girls who have urgency and often adopt postures to prevent micturition, such as crossing of legs or squatting. It is frequently associated with constipation, and the presence of the two conditions is labelled dysfunctional elimination syndrome.

Underactive bladder is also more often seen in girls than boys and is characterized by infrequent voiding often associated with constipation. Incomplete bladder emptying may result from hypoactive detrussor function and UTI may ensue.

Neurogenic dysfunction of the bladder is most commonly due to spinal dysraphism, often as an open myelomeningocoele (*spina bifida*). Closed or occult spinal lesions may also affect bladder function. Other spinal causes of neurogenic bladder include sacral agenesis, tethered spinal cord associated with imperforate anus, cloacal malformations, and spinal cord injuries from sporting injuries. Neurogenic bladder is infrequently due to a central nervous system abnormality such as cerebral palsy.

Nonneurogenic neurogenic bladder (or Hinman's syndrome) is a term used to describe the most severe form of dysfunctional voiding. It is often associated with recurrent UTI and constipation and may lead to chronic kidney injury. The mechanisms underlying the detrusor–sphincter incoordination are not fully understood. Management may include bladder training; however, intermittent catheterization is often required.

Pathogenesis

The urinary tract above the distal urethra is usually sterile. Most infections are caused by bowel organisms that have ascended via the urethra to colonize the bladder. Uropathogenic *E. coli* characteristically have surface fimbriae (Type II or P fimbriae) that promote attachment to urinary epithelium allowing colonization. The process of attachment involves adherence of bacterial fimbriae to specific receptors expressed on the surface of urinary epithelium. The receptor for certain uropathogenic *E. coli* is a glycosphingolipid that is also expressed on red blood cells.

The urinary tract relies on several defense mechanisms to prevent infections. The primary defense is regular and complete emptying of the bladder. Other protective mechanisms include the systemic innate immune response and inherent antibacterial properties of normal bladder cells. Toll like receptor-4 (TLR4) is intricately involved in the innate immune response to UTI.

Infants may be more susceptible to UTI because of immaturity of their immune defenses, both systemic and local to the urinary tract. Other reasons for high rates of UTI during infancy include altered gut flora and colonization of periurethral areas by pathogenic organisms.

Breast fed infants have a reduced incidence of UTI relative to formula fed infants. The reasons for the

protective effect of breast milk have not been elucidated but may include the transfer of secretory IgA and other immunoactive molecules.

The presence of UTI caused by organisms that usually have a low virulence for the urinary tract, such as *S. aureus*, *Enterococci* and *Pseudomonas* species, suggests that normal host defenses have been altered. The commonest reasons for this are incomplete emptying of the urinary tract due to obstruction, high-grade VUR, or dysfunctional voiding.

UTIs are rarely the result of haematogenous spread of organisms. However this should be suspected in children with UTI secondary to an atypical organism, particularly *S. aureus*, and an otherwise normal urinary tract.

Clinical Manifestations: Symptoms, Signs

Fever is the most common presenting feature of UTI in infants and young children. Children younger than 3 months of age with UTI are more prone to develop septicaemia and severe illness including meningitis. Neonates with UTI may not develop a high fever and at times may be hypothermic.

Other clinical features of UTI differ according to age and site of infection. Nonspecific signs of UTI in the first weeks of life include drowsiness, vomiting, poor feeding, lack of weight gain, and prolonged jaundice.

Infants and young children typically do not present with localizing signs of infection, consequently fever may be the only sign. Parents will occasionally notice malodorous urine and children who are out of nappies may show urinary frequency or enuresis and, rarely, dysuria.

Older children, particularly those who are verbal and fully toilet trained are more likely to present with specific symptoms such as urinary frequency and dysuria or abdominal pain.

The physical examination of a child with a suspected or proven UTI should be thorough and aim to assess for predisposing factors and complications. Hypertension may be a sign of underlying renal disease or may be a consequence of renal scarring secondary to previous UTI. Abdominal or flank masses may indicate hydronephrosis, urinary retention, or other renal pathology. *Constipation* may be identified by finding palpable feces in the left iliac fossa. Periurethral inflammation, balanitis, or phimosis may either be a source of ascending infection or alternatively may give rise to dysuria and pyuria and masquerade as a UTI. Spinal anomalies may be suggested by midline pits, dimples, birthmarks, and hairy patches, as well as reduced anal tone, an abnormal gait, and abnormal lower limb reflexes.

Diagnosis

The diagnosis of a UTI depends on collection of an uncontaminated urine sample. An older child or adolescent may be able to provide a mid stream urine (MSU) with or without the assistance of a parent; however, the majority of children with suspected UTIs will be too young to collect an uncontaminated sample for themselves. *Table 310.1* lists the methods by which urine can be collected in young children and babies.

Prompt collection of an uncontaminated urine specimen is necessary in acutely unwell babies and children to allow empiric treatment while awaiting culture results. In these situations either suprapubic aspiration (SPA) or perurethral catheterization should be used to collect a specimen. SPA is a simple and safe procedure. It can be performed in children under 2 years of age as a full bladder in this age group normally sits above the bony pelvis. The likelihood of urine being in the bladder is increased by timing the procedure to be at least 60 min from the last void and after a feed. Many centers use an ultrasound bladder scan beforehand to confirm that urine is present in the bladder.

Urine collected by an adhesive plastic bag will be contaminated by skin or bowel flora in up to 50% of cases, therefore bag collections (even if the skin has been carefully washed beforehand) should not be used to diagnose a UTI. Another simple, noninvasive method of urine collection from babies is use of a urine collection pad, but again this method is prone to contamination and should generally not be relied upon. The usefulness of these two methods is in their ability to exclude a UTI, that is, if urine collected by bag or pad does not grow a significant growth of bacteria, then a UTI is not present.

Table 310.1
Methods of urine collection for microbiological culture

Method	Diagnostic criteria
Clean catch	$>10^5$ cfu/mL of a single organism
Suprapubic aspiration	Any growth of bacteria
Transurethral catheterization	>10,000 cfu/mL of a single organism
Adhesive bag	A negative culture excludes a UTI
Absorbant pad	A negative culture excludes a UTI

UTI is defined by a significant growth of a single organism in a clean catch urine, MSU, SPA, or catheter urine. Because each of these techniques has its own risk of contamination, the diagnostic criteria for UTI depends on collection method (Table 310.1). Urine collected by SPA should be sterile unless a UTI is present, therefore any growth of bacteria should be considered to be significant. A significant growth of bacteria from an MSU or clean catch urine is 10^5 cfu/mL of a single organism. A mixed growth or a lower colony count (10^4–10^5 cfu/mL) may also be indicative of infection if the clinical features support a diagnosis and collection of a further specimen for culture may be warranted. The laboratory should always be informed of the method used for collection.

Urine microscopy and biochemical dipstick analysis can be used to guide decisions on initial management and the need for urine culture (Table 310.2). The presence of organisms on microscopic examination of unspun urine and/or on Gram stain of urine is strongly suggestive of a UTI. Therefore urgent microscopy of urine should be utilized if available to diagnose UTI in young children with fever without focus.

The presence of urinary nitrites detected by dipstick in a child with a fever suggests the presence of a UTI. Urinary nitrites are produced by urease splitting organisms; however, not all UTI causing organisms convert nitrate to nitrite and urease splitting bacteria may take up to 4 h to produce detectable nitrites in urine. A positive test for nitrites is therefore highly specific but lacks sensitivity to allow the diagnosis of all UTIs (Table 310.2).

Urinary leukocytes are usually present during a UTI, but they may also be present in a large proportion of febrile children without UTI as well as in otherwise healthy children. The diagnostic utility of urinary dipsticks is maximal when the results of leukocyte esterase and nitrite tests are considered together. If both tests are negative then it is unlikely that a UTI is present. If nitrites are present then the likelihood of a UTI being present is high (>95% positive predictive value) and this likelihood is increased further if the leukocyte esterase test is also positive (Table 310.2). The least useful result is positive leukocyte esterase with negative nitrites, as this finding is nonspecific (Table 310.2).

Confirmation of UTI by culture is important not only for management of the current illness but also as young children with a confirmed UTI should undergo further investigation. Culture and sensitivity results will guide antibiotic management.

Blood tests are not required to make the diagnosis of UTI but may be useful to guide management, detect complications, and possibly localize the infection. Electrolyte abnormalities (e.g., *hyponatremia*, *hyperkalemia* and *acidosis*) may complicate infections in infants or children with urological anomalies and require judicious management. Leucocytosis is commonly seen in febrile children. C-reactive protein and plasma procalcitonin levels may both be elevated and higher levels (procalcitonin >0.5 ng/mL) are more likely in instances of pyelonephritis.

Differential Diagnosis of UTI in Children

The differential diagnosis of febrile UTI in young children is broad and includes both minor and life threatening infections. The differential diagnosis of acute cystitis in older children and adolescents includes dysfunctional voiding, urethritis, vulvovaginitis, prostatitis, epididymoorchitis, and *nephrolithiasis*.

Treatment

Any symptomatic UTI should be treated with antibiotics. Parenteral antibiotics are indicated in children less than 3 months of age or any child who appears toxic. Parenteral antibiotics should also be considered in any child who is vomiting or who is unable to tolerate oral antibiotics for any reason, and in older children with high fever and

Table 310.2
Utility of urine microscopy and dipstick analysis for guiding decisions about management and investigations of a child with a suspected UTI

Test result	Sensitivity (%)	Specificity (%)	Interpretation
Gram stain +	93	95	UTI likely
Leukocyte −, nitrite +	50	98	UTI likely
Leukocyte +, nitrite −	83	84	UTI possible
Leukocyte +, nitrite +	72	96	UTI likely
Leukocyte −, nitrite −			UTI unlikely

marked loin tenderness. Parenteral antibiotics should be continued until the defervescence occurs and the patient is able to tolerate oral medications.

In children older than 6 months there is good evidence to suggest that oral antibiotics are as efficacious as parenteral. There is less evidence to guide the duration of antibiotic therapy. Pyelonephritis is usually treated with 7–10 days of antibiotics. Antibiotic therapy should be reviewed in any child with a UTI whose fever does not settle after 48 h of appropriate therapy or if fever recurs later in the course of therapy.

Empiric antibiotics should be commenced promptly in infants that appear toxic, generally after a collection of specimens for culture, which may include cerebrospinal fluid.

Older children and those with less severe presentation should have empiric antibiotics commenced if there is a strong clinical suspicion of UTI based on presenting features, risk factor assessment, and/or urinary dipstick analysis or microscopy (*Table 310.2*).

Empiric antibiotics should be active against *E. coli* and other common uropathogens (*Table 310.3*). The choice of specific antibiotics should be guided by local patterns of bacterial resistance. Uropathogenic *E. coli* in most areas have a high degree of resistance to amoxicillin; therefore this antibiotic should generally be avoided for empiric use. The susceptibility of *E. coli* to first generation cephalosporins and trimethoprim/sulphamethazole varies widely.

Empiric parenteral therapy should include agents with good tissue penetration. In seriously ill young children a second agent should be added to broaden antibacterial coverage. Antibiotics that are likely to be active against *enterococci* (e.g., ampicillin) should be used empirically in children less than 3 months or those with known urological anomalies. Oral antibiotics that are excreted in the urine but do not achieve therapeutic serum levels (e.g., nitrofurantoin) should not be used to treat UTI in febrile infants and young children in whom pyelonephritis is likely.

Antibiotic therapy should be rationalized once culture results and antibiotic sensitivities are known.

The clinical condition of most patients, including normalization of temperature, improves within 24–48 h of initiation of appropriate antibiotic therapy. Repeat urine culture to confirm the success of therapy is not required if a child responds well to antibiotics and completes the full course. Non-adherence with a full course of therapy is common and may lead to inadequate treatment and relapsing infection.

Table 310.3
Empiric antibiotics for suspected UTI

Clinical features	Suitable empiric antibiotics[a]	Management guide
Age <6 months or toxic at any age	Cefuroxime 50 mg/kg 8 hourly	Parenteral antibiotics until afebrile for 48 h. Then continue appropriate oral antibiotic for a total of 7–10 days
	Cefotaxime 50 mg/kg 6 hourly	
	Ceftriaxone 100 mg/kg 24 hourly	
	Gentamicin 2.5 mg/kg 8 hourly[a] with the addition of Ampicillin 25 mg/kg 6 hourly	
Age >6 months and fever ≥38°C or other signs/symptoms of pyelonephritis	Parenteral agents as above or the following oral agents	Continue appropriate antibiotic for a total of 7 to 10 days
	Cefixime 8 mg/kg 24 hourly	
	Amoxycillin/clavulanate 12.5 mg/kg 12 hourly[b]	
	Cefuroxime 15 mg/kg 12 hourly	
	Cephalexin 12.5 mg/kg 6 hourly	
	Sulphamethoxazole/trimethoprim 4 mg/kg[c] 12 hourly	
Temp <38°C and symptoms of cystitis	Oral agents as above	Oral antibiotics for 3–5 days in total

[a]Choice of empiric antibiotics should be based on local patterns of antibiotic resistance
[b]Once daily gentamicin 7 mg kg^{-1} day^{-1} may be an alternative
[c]Dosage based on amoxicillin component
[d]Dosage based on trimethoprim component

Suppurative Complications

One uncommon complication of pyelonephritis is acute focal bacterial nephritis (also referred to as lobar nephronia or focal pyelonephritis) – a well-localized renal infection without frank abscess formation. If inadequately treated it may progress to abscess formation. At least a 3-week course of appropriate antibiotic therapy is recommended for treatment.

The presence of acute focal bacterial nephritis or abscess should be suspected if fever persists after 4 days of appropriate antibiotic treatment. The diagnosis is usually made by ultrasonography. Findings on ultrasound include appearance of an ill-defined mass with disruption of the corticomedullary junction and lack of vascularity (*Fig. 310.1*).

CT scanning (with and without contrast) may be used to confirm the diagnosis and potentially to discriminate between a complex abscess and a malignancy. Findings suggestive of renal abscess include a poorly defined, wedge-shaped, hypodense area that may involve liquefaction and does not enhance after contrast administration.

Renal Scarring

Renal scarring is the primary sequelae of pyelonephritis. A scar is a discrete area of tubular atrophy, tubulointerstitial fibrosis, and chronic inflammation. Between 5% and 30% of young children will develop a renal scar after an initial febrile UTI. Risk factors for scarring include: age less than 4 years, recurrent febrile UTI, delay in treatment of UTI, dysfunctional elimination, and VUR.

New scars rarely develop in children older than 4 years of age, except in those with neurogenic bladder, severe anatomical anomalies, or transplanted kidneys. Studies of kidney transplants suggest that scarring is possible if VUR is present, regardless of age.

The most sensitive imaging technique for diagnosis of scarring is the 99m-dimercaptosuccinic acid (DMSA) scan (*Fig. 310.2*). A scar is shown by diminished radioisotope uptake in a discrete area. Acute pyelonephritis is also associated with photopenia on DMSA scanning, which will resolve over time. Therefore a scar should only be diagnosed if an abnormality is detected on DMSA scan performed after a wait of at least 3 months from the time of UTI (6 months is generally preferred).

More severe degrees of renal scarring may be evident on renal ultrasonography. A clue to scarring is an unusually small kidney or a discrepancy in size between left and right kidney on ultrasound. A left kidney longer than the right by more than 10 mm or a right kidney longer than the left by 7 mm or more suggests the presence of a DMSA abnormality.

The reported long-term consequences of renal scarring are variable. Small discrete scars do not cause an appreciable impairment of renal function but may increase the risk of hypertension. Early studies suggested that up to 10% of children with renal scars will develop hypertension by early adulthood. However these studies were small and probably included more severely damaged kidneys detected by intravenous pyelograms. Larger long-term studies, including children with lesser degrees of

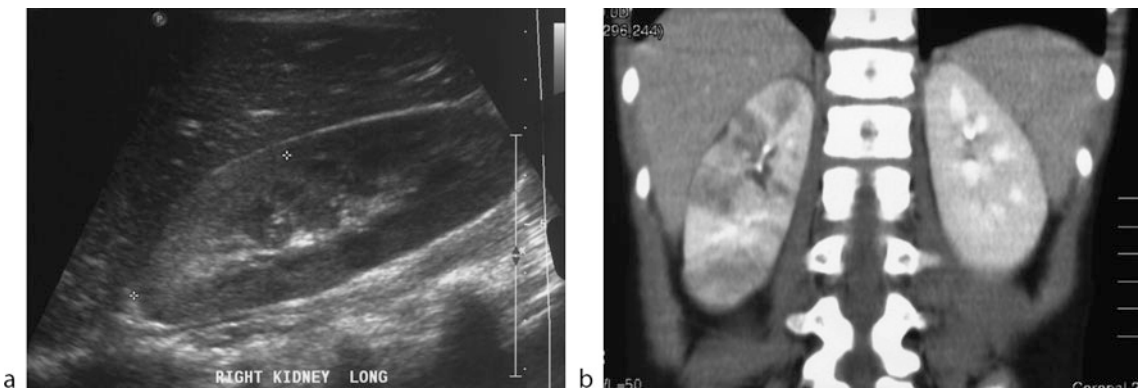

Figure 310.1

Acute focal bacterial nephritis due to E. coli in a 7 year old girl who presented with fever, right iliac fossa pain and psoas muscle spasm. (a) Ultrasound of right kidney showing a focal area of increased echogenicity and poor corticomedullary differentiation in the upper pole between markers. (b) Post-contrast CT scan of same patient showing patchy enhancement of right kidney particularly involving the lateral aspect of the upper pole, the lower pole is also affected

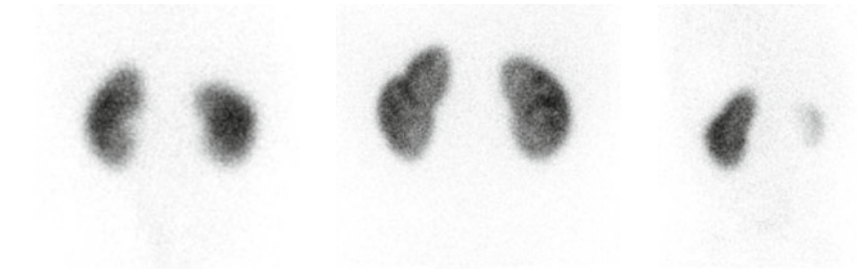

Figure 310.2

Renal DMSA Scans performed 6 months after UTI. (a) Normal scan showing symmetrical renal function and smooth renal outlines. (b) Abnormal scan of a 5-year-old girl with a history of recurrent UTIs showing a discrete cortical scar in the upper pole of the left kidney. (c) Abnormal scan from a 15-month-old boy who had a febrile UTI at age 9 months. Scan shows a small right kidney with an irregular outline and poor function. This appearance is consistent with congenital reflux nephropathy. Further investigations revealed grade IV right sided vesicoureteral reflux

scarring detected by DMSA, have failed to show similar rates of hypertension. Renal scarring increases the risk of complications during pregnancy including hypertension and pre-eclampsia.

Children with severe scarring may develop chronic kidney disease; this outcome is known as reflux nephropathy and is described below.

Vesicoureteral Reflux

VUR is the retrograde flow of urine from the bladder into one or both ureters. It is diagnosed by micturating cystourethrogram (MCUG) and is stratified into five grades of severity, depending on the radiological appearance (*Fig. 310.3*). Radionucleotide cystourethrogram is an alternative imaging modality with less radiation exposure but it provides less anatomical detail. VUR cannot be reliably diagnosed by ultrasonography.

VUR is usually an isolated finding which occurs because the submucosal tunnel through which the ureter attaches to the bladder is short and does not close on voiding.

VUR has a genetic basis and can be detected in 30% of first-degree relatives of an index case; the concordance rate in monozygotic twins is 80–100%. Inheritance patterns are usually consistent with autosomal dominant transmission with incomplete penetrance, but a causative gene/s has not been identified.

Children with neurogenic bladder, dysfunctional voiding, or bladder outlet obstruction (e.g., *posterior urethral valves*) are at risk for developing secondary VUR.

VUR is detected in 25–40% of preschool children who have had a UTI. The true prevalence of VUR in the normal population is uncertain; the most often quoted figure is 1% of all infants, but the true frequency may be higher. The prevalence of VUR is increased in children with the dysfunctional elimination syndrome.

Most children diagnosed with VUR after a UTI have low-grade reflux (grades 1 and 2) and the natural history is for resolution over time. Most low-grade cases and up to 50% of higher-grade cases will resolve by 4 years of age. VUR is less likely to resolve if it is associated with other anomalies of the urinary tract.

VUR potentially increases the risk for UTI by allowing incomplete voiding and may increase the risk of pyelonephritis by promoting passage of infected urine to the upper tract. The presence of VUR is probably the strongest single determinant of whether a child will develop a scar after pyelonephritis. However, VUR is not a prerequisite for scarring.

Surgical correction of VUR has traditionally been by ureteral re-implantation, with the aim of producing a longer intramural segment of ureter. The success rate of this surgery is 95–99%. Re-implantation surgery may reduce the risk of recurrent pyelonephritis. Whether or not this confers protection from scarring has not been established.

An alternative approach to antireflux surgery is the endoscopic injection of a bulking agent into the subureteral region of the bladder wall (subureteric transurethral injection [STING]). The rate of reflux correction overall may be less than with re-implantation surgery and the procedure appears best suited to less severe cases. A recent multicenter randomized controlled trial showed that endoscopic antireflux treatment reduced the recurrence rate of febrile UTI in young girls with high grade VUR.

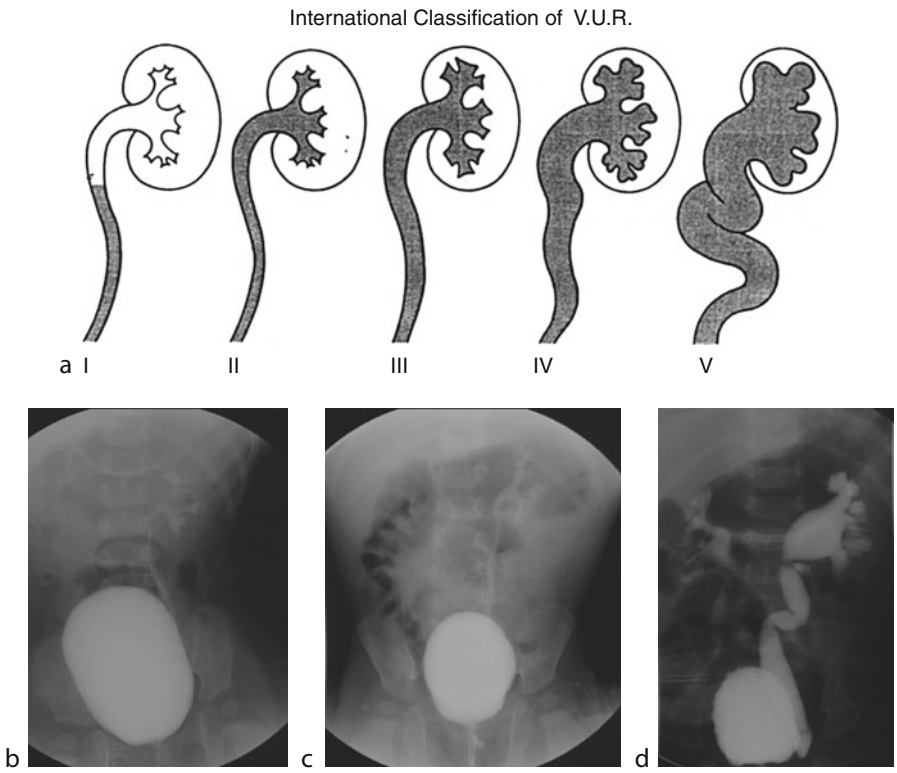

Figure 310.3

Vesicoureteral reflux. (a) Grading system proposed by the International Reflux Study Committee 1981 (Report of the International Reflux Study Committee: Medical versus surgical treatment of vesicoureteral reflux: a prospective international reflux study in children. (1981) Pediatrics 67: 392). (b) Micturating cystourethrogram (MCUG) performed after a febrile UTI in a 9 month old girl. Left sided grade II VUR. The renal ultrasound was normal. (c) MCUG performed after a febrile UTI in another 9-month-old girl. Left sided grade III VUR is demonstrated by reflux of radiocontrast into a dilated ureter. The renal ultrasound was normal. (d) MCUG performed after a febrile *Escherichia coli* UTI in a 2-week-old male infant. Bilateral high-grade VUR, grade IV on *right* and grade V on *left*. Ultrasound demonstrated bilateral ureteric dilation and mild left pelvicalyceal dilatation. DMSA showed scarring of right kidney

Reflux Nephropathy

Reflux nephropathy is the term originally proposed to describe renal scarring associated with VUR and UTI and replaced the misleading label of chronic pyelonephritis. Reflux nephropathy itself is something of a misnomer, as it is now recognized that scarring can develop after UTI without VUR being present. On the other hand, children with high-grade reflux may have abnormal kidneys without ever having a UTI.

Reflux nephropathy causes 2–5% of cases of end-stage kidney disease (ESKD). However the vast majority of children with UTI do not proceed to ESKD, reflecting the fact that reflux nephropathy includes a wide range of pathology, from small functionally insignificant scars through to badly damaged kidneys and ESKD.

The more severe end of the spectrum of reflux nephropathy includes children who have dysplastic and/or hypoplastic kidneys at birth, coexistent with VUR that is usually high grade.

Proteinuria and hypertension may be signs of reflux nephropathy. Strict blood pressure control and treatment with Angiotensin converting enzyme inhibitors may delay progression of kidney impairment.

Investigations After UTI

Most occurrences of UTI will occur in children with anatomically normal urinary tracts and will not lead to any significant complications. However, up to 30% of children will develop irreversible renal damage (scar) after a UTI

and in a significant minority UTI will be the first sign of a serious urological anomaly, early detection of which may allow appropriate management and limit further renal damage. Furthermore, approximately one third of children will have recurrent UTI and detection of risk factors such as VUR can be used to direct preventative therapy. Therefore, investigation of children after an initial or recurrent UTI has two main goals:

1. Detection of underlying urological anomalies
2. Detection of complications

Several guidelines and consensus statements have been published advising on investigations after an initial UTI, these have been developed in light of considerable uncertainties about the significance of renal scarring and a lack of evidence with regard to the effectiveness of preventative strategies. Therefore the advice has ranged from the interventional approach proposed by the American Academy of Pediatrics (perform ultrasound and micturating cystogram in all young children after an initial UTI) to the relatively minimalist approach of the United Kingdom's National Institute of Clinical Excellence (www.nice.org.uk/cg54).

Routine imaging with ultrasound should be performed in any child after an initial UTI with the possible exception of adolescent girls who have cystitis on clinical grounds. Ultrasound may be avoided if a good quality antenatal ultrasound, performed after 30-week gestation, did not detect any renal anomaly. Renal ultrasound should be performed during the initial course of antibiotics to assess for obstruction or acute focal bacterial nephritis if there is a lack of response to appropriate antibiotics.

The approach to further investigation of any child should be guided by the ultrasound appearance as well as the child's age, clinical features and local resources. Urological anomalies are more likely to be present in children with UTI caused by pathogens other than *E. coli* and in children who would otherwise be considered to have a low risk of UTI (e.g., boys older than 2 years).

An MCU is often performed after resolution of the acute infection to assess for VUR. VUR is more likely to be present and significant in children who are younger, have infection with an organism other than *E. coli*, have had recurrent infections, have pyelonephritis, and/or have an abnormal ultrasound (e.g., ureteric or pelvicalyceal dilatation, or abnormal size kidneys). Evidence of pyelonephritis is provided by high plasma procalcitonin levels and by an abnormal DMSA scan at the time of infection; if either of these are present there is a greater chance of grade 3–5 VUR.

Two suggested approaches to imaging after UTI in young children are outlined in ❯ *Fig. 310.4*. Imaging of older children should be individualized based on risk factors for recurrent infections, renal scarring, and VUR.

Prevention

Recurrent UTI occurs in between 15% and 40% of children after a first infection. The majority of recurrences occur during the following 2 years after the initial UTI. Factors that are associated with recurrence include young age at first UTI, female gender, anomalies of the urinary tract including VUR, and voiding dysfunction.

Voiding dysfunction can be managed by encouraging regular and complete bladder emptying (e.g., scheduled voiding every 2–3 h) with or without the addition of anticholinergic agents. Older children may be amenable to bladder training. *Constipation* should be treated by dietary and behavioral modifications as well as laxatives as required.

Prophylactic Antibiotics

The results of two large randomized controlled trials in children recently published confirm that prophylactic antibiotics confer a small but significant degree of protection from recurrent UTI. Antibiotic prophylaxis may be of particular benefit in young girls with high grade VUR as a recent study found prophylactic antibiotics reduced the rate of recurrent febrile UTI and new scar development in this population. Once-daily therapy with antibiotics such as cotrimoxazole, trimethoprim, or nitrofurantoin has been found to be safe; however, there is some concern about prophylactic antibiotics promoting growth of resistant organisms.

Prophylactic therapy is usually discontinued when the risk of severe infection and scarring is judged to be low.

Cranberry Juice

Cranberry juice may prevent recurrent UTI in women and older girls but as yet there is no evidence to show it is effective in younger children. The mechanism of action of cranberry juice is uncertain; it appears that substances in the berries may interfere with the adherence of *E. coli* to uroepithelium. The most effective dose and formulation of cranberry juice have not been established. Cranberry juice should not be used for treating a UTI.

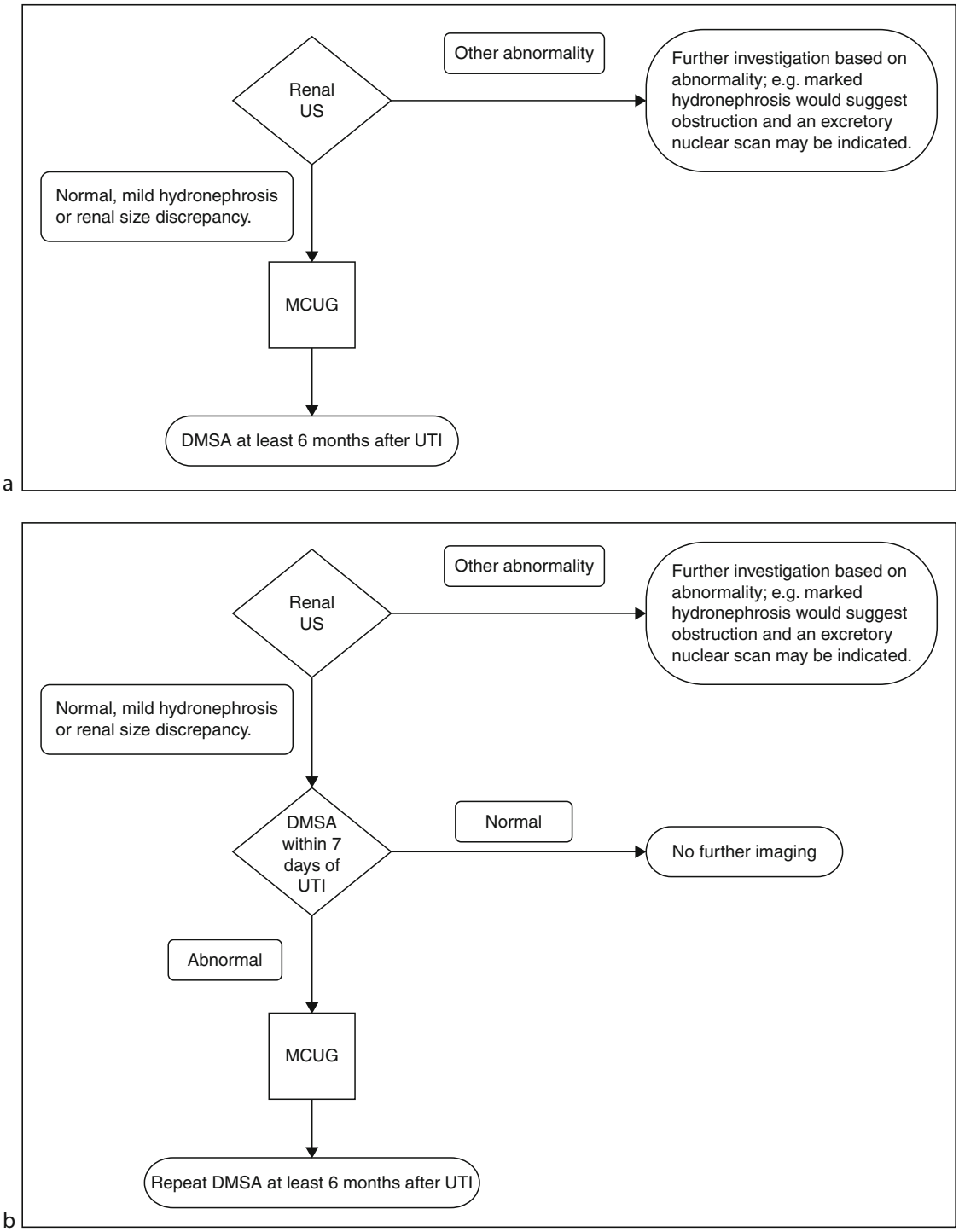

Figure 310.4

Investigation after UTI of children less than 2 years of age. (a) Suggested approach to screen all young children with UTI for vesicoureteral reflux (VUR). (b) Alternative approach using an acute DMSA as a screening modality. Such an approach could lead to about a 50% reduction in MCUG rates. An abnormal acute DMSA will be present in >90% of cases of dilating VUR

Probiotics

There is no good evidence to support the use of probiotics as a preventive strategy for UTI.

Circumcision

Circumcised males have a lower rate of UTI during childhood than uncircumcised males. Given the low incidence of UTIs in boys, the vast majority of uncircumcised boys will not develop a UTI and more than 100 circumcisions would be needed to prevent one UTI. The risk: benefit ratio does not justify circumcision of all boys, but circumcision could be considered as a means to prevent UTI in boys with recurrent UTI or those at high risk of recurrence and scarring because of underlying urological abnormalities.

Antireflux Surgery

Surgical intervention to correct VUR should be considered in children with VUR, recurrent infections (despite prophylactic antibiotics), and renal damage.

Prognosis and Follow-up

Parents of children who have had a UTI should be educated about the signs of UTI to allow prompt treatment of any recurrences.

The overall prognosis for children after UTI is favorable; however, a small number, particularly those with high-grade VUR and bilateral renal damage, are at risk of *hypertension* and *chronic kidney disease*. Any child with renal scarring should have annual review for blood pressure measurement. Children who have bilateral renal scarring should be monitored for signs of progression of renal disease including proteinuria and appropriate management should be initiated for hypertension or impaired glomerular filtration rate.

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311 Obstructive Nephropathy

Stephanya Shear · Martin A. Koyle

Introduction

Congenital obstructive nephropathy represents a spectrum of disease from the partially obstructive ureteropelvic junction to severe bilateral disease associated with posterior urethral valves (PUVs). In this latter situation, the renal manifestations can lead to the extreme situation of bilateral renal dysplasia, oligohydraminos, and resultant pulmonary dysplasia resulting in Potters syndrome and fetal demise. In between these extremes lie the majority of patients who may or may not have long-term renal function deterioration. We are challenged in determining those patients who will have long-term renal damage, especially those where this deterioration can be minimized by appropriate investigation and therapy.

To date, we have no markers or studies that indicate which children will benefit from early intervention, especially in utero. In fact, many studies would argue that intervention does not change the natural history of the disease; indeed damage is more likely to have occurred during renal development and has early in gestation, determined that the kidney will carry on a path of dysplasia.

As the clinical use of prenatal ultrasound has increased to at least 80% of pregnancies in the United States, the incidence of early detection of urinary anomalies has increased. Only 1% of prenatal ultrasounds will have any anomaly, with all genitourinary anomalies composing only 20% of that 1%. The overall percentage of obstructive urinary abnormalities is thus more likely to be present in 0.04–0.3% of all antenatal evaluations by ultrasound.

As noted earlier, there is very little evidence that fetal intervention improves outcomes in renal units or infant pulmonary morbidity. However, if intervention for antenatal hydronephrosis is to be considered, the following parameters would need to be present: (1) normal chromosomes in a male fetus, with (2) no other existing urologic or non-urological abnormalities, and (3) evidence of increasing hydronephrosis with corresponding decreases in amniotic fluid level late in pregnancy. This scenario is most often associated in a male with PUV and the goal of intervention is to restore amniotic fluid with the hope of allowing improved lung maturation.

Obstructive nephropathy describes renal damage and pathology secondary to obstruction and is distinct from hydronephrosis. Hydronephrosis is a "generic" radiographic finding, meaning "water on the kidney," that can be a sign of obstructive renal damage; however hydronephrosis is not synonymous with obstructive nephropathy. Most cases of hydronephrosis are associated with a benign clinical course. The majority of fetuses will fall into the category of mild hydronephrosis; with renal pelvis diameters less than 1 mm or Society for Fetal urology (SFU) grade I-2see (*Table 311.1*). Very few of these kidneys will require intervention after birth. Thirty percent of infants with AP diameters greater than 7 mm at 33 weeks gestation will have normal renal ultrasounds at 5 days of age.

Renal Damage and Hydronephrosis

The pathogenesis of renal damage after obstruction has been the subject of many well-crafted animal studies; however the natural history is poorly understood in humans, although there has been increasingly more knowledge regarding the cellular changes in renal units after obstruction.

Renal Damage, Renal Insufficiency, and Hypertension

In obstructed units, it is not the delay in emptying or hydronephrosis per se that is the primary concern. Instead, it is the resulting compromise of renal function that might lead to renal insufficiency and possibly renal failure.

The consequences of obstruction on renal function have been elucidated using animal models. When counseling patients and families, it may be useful to answer questions regarding the types of damaged obstructed

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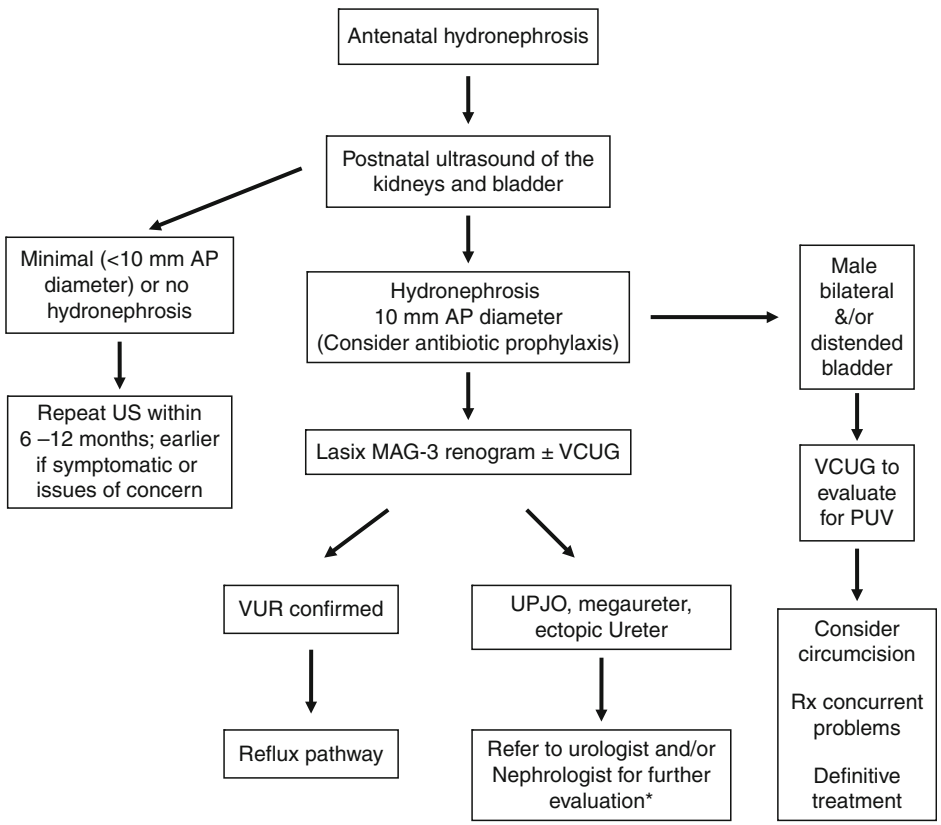
Table 311.1
Society for Fetal Urology (SFU) grading system for Antenatal Detected Hydronephrosis (ANH) J Pediatr Urol (2010) 6, 212–231

Grade	Description
0	No hydronephrosis
1	Slight dilation of renal pelvis; normal calyces
2	Moderate renal pelvis dilation; mild caliectasis
3	Large renal pelvis with calyceal dilation but preserved renal parenchyma
4	Very large renal pelvis with severe caliectasis and thinning of renal parenchyma

kidney can incur, but care must be made when translating animal models to the human patient. Animal models differ from human natural history of the disease in time of the obstruction and species specific variations in gene expression. Chronic partial urinary obstruction has been shown to cause tubular atrophy, interstitial fibrosis, and retarded renal growth. Marked inflammation is also seen. Early relief of obstruction can restore nephrogenesis and reduce progression of renal damage with the potentially greatest ability before nephrogenesis is complete in the antenatal period. However some damage, such as fibrosis, may continue even after obstruction is alleviated. Results from these studies have both supported early intervention in the infant period as well as theories that damage in



utero has already destined those poorly functioning kidneys to fail and intervention postnatally does not alter their course.

Since congenital obstruction is thought to be particularly damaging to the maturing kidney, researchers have looked for evidence of renal dysplasia in children affected with obstruction. It is still unknown to what extent obstruction in utero results in the parenchymal maldevelopment and what histological finding predicts renal function. Huang et al. performed 70 biopsies on 61 patients undergoing open pyeloplasty for ureteropelvic junction obstruction. They found epithelial proliferation, glomeruli sclerosis, and cystic dilatation; however, the degree of these changes did not correlate with hydronephrosis, age, or renogram split function levels. When comparing obstructed kidneys to autopsy controls that found in obstructed kidneys decreased proximal tubules size and a decrease concentration of distal tubules independent of glomeruli injury. Tubules were seen to have atrophy with and without overt fibrosis. The decrease in size of the proximal tubule may represent immaturity of these structures and they found a correlation between smaller proximal tubule size and longer washout times. Other studies while showing histological changes at the time of pyeloplasty, these changes correlate poorly to the differential function of the affected kidney.

Renal insufficiency is a worrisome complication in patients with congenital urinary obstruction. The true incidence of renal insufficiency is difficult to obtain since many studies of obstruction use surrogate marker such as wash out times or split function of renograms as a measurement of renal function before or after intervention. In one study, of the most severe cases of PUV, a quarter of boys have chronic renal insufficiency. In recent long-term studies, again 25% of patients may have renal insufficiency and some of those boys progress to ESRD by young adulthood. It is also true that in children with PUV with initial normal renal function from ages 5 to 11 may progress to renal insufficiency and ESRD. The degree to which this deterioration may be ameliorated by surgery is debated. One study showed no significant difference in renal outcomes based on initial surgical technique. Looking at 100 patients, chronic renal disease was seen in 51% of the boys by the age of 20 years and 40% had ESRD. Similar proportions in each surgical group had evidence of chronic disease and renal failure. Childhood cases of ESRD were rare, and insufficiency before the age of 10 was seen only in one third of patients. These results speak to theories that in utero obstruction of the kidneys sets up a path toward significant renal impairment. It also underscores the need for long-term follow-up in these children to assess renal function.

Some patients, especially those with PUV, can have hypertension. Those patients with bilateral obstruction more commonly have hypertension. Although several studies of PUV found evidence of chronic renal insufficiency (CRI), no study reports significant numbers of children with hypertension. In spite of the relatively large numbers of studies in the ureteropelvic junction obstruction (UPJO) and PUV populations, no study has directly studied the incidence of hypertension as predictive of clinical outcome.

Radiological Evaluation

Patients with suspected obstructed renal systems will be evaluated radiographically. The timing of these studies, as well as which studies are performed, may differ depending on the clinical and radiological evaluations. Although some general comments can be made, there is great variability in the frequency of studies and the merits of the various imaging modalities differ see (*Fig. 311.1*) (*Table 311.2*).

Unless PUV or severe obstruction is suspected, a renal and bladder ultrasound is usually performed after 72 h following birth, and in healthy infants, initial studies can be deferred until the second month of life. The delay in the neonate allows for the improved hydration and lessens the chance of missing hydronephrosis due to depleted volume status. Serial ultrasounds can be performed thereafter, depending on the diagnosis and patient's clinical picture. Ultrasounds are components of the routine management and are advantageous in that they are easy to perform, noninvasive, tolerated well by children, do not expose the child to radiation, reproducible, and relatively inexpensive.

A voiding cystourethrogram might be considered if dilatation is seen on the initial ultrasounds is suggestive of obstruction due to PUV; voiding cystourethrogram (VCUG) can also diagnose ureteroceles and ectopic ureters. Unfortunately, a VCUG exposes the patient to radiation and catheterization. Sedation is usually not required in infants but may be considered in older children.

Nuclear renal scans are used to measure obstruction, evaluate renal scars, and determine relative split renal function, and are currently the most commonly used studies used to evaluate obstruction. Current nuclear scans employ technetium-99. A comparison of the various nuclear renal scans is shown below (*Table 311.3*). As

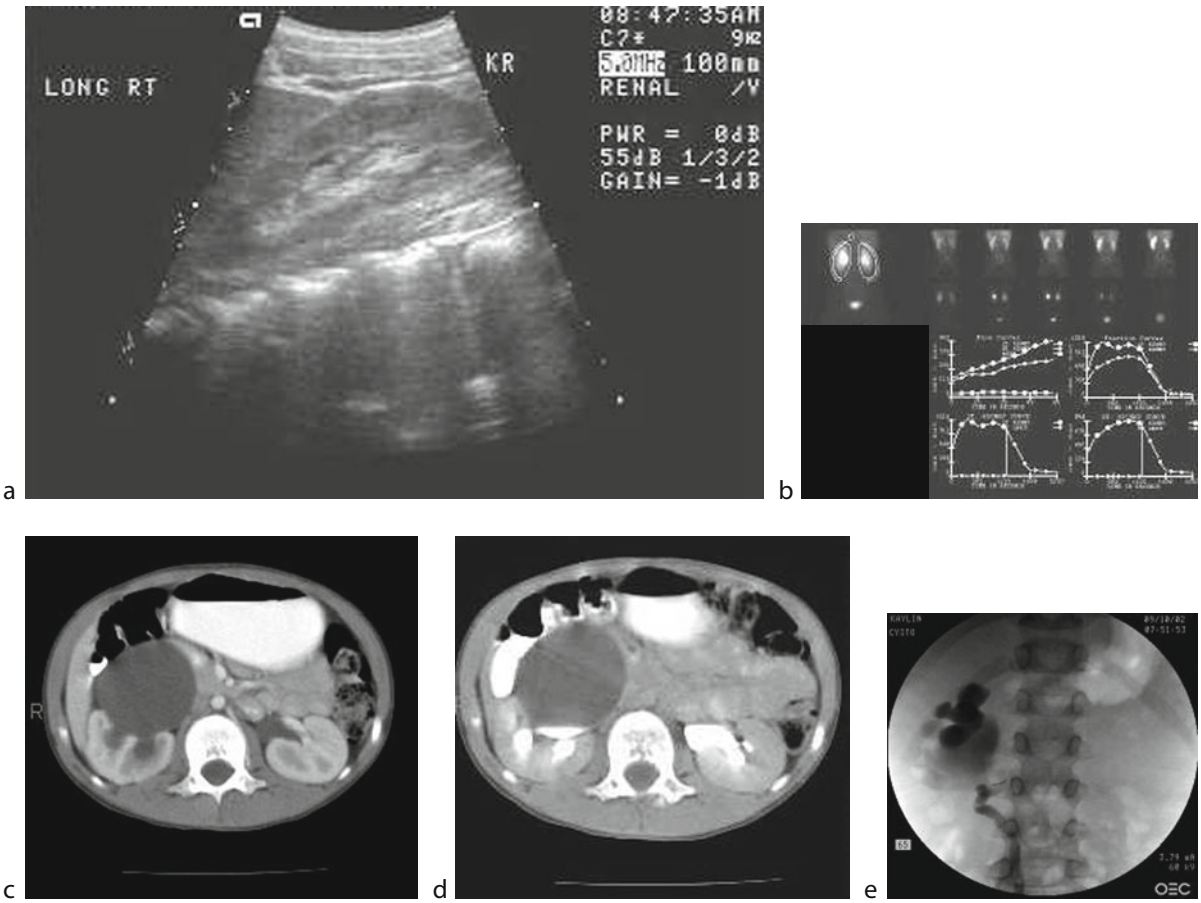


Figure 311.1

This case illustrates the imperfection of imaging in detecting intermittent obstruction. This 3-year-old child had been seen for repeated bouts of abdominal pain. The ultrasound (a) and nuclear imaging study (b) demonstrate a normal right kidney, without hydronpehrosis, and with excellent function and drainage. The CT scan performed without (c) and with contrast (d) 2 weeks later when the child presented with abdominal pain, reveals marked pelviectasis and moderate caliectasis. A retrograde pyelogram (e) performed at the time of pyeloplasty further substantiates a ureteropelvic junction

with ultrasounds, there is significant variability in the use of these scans and there is significant variability in interpretation. All nuclear renal scan expose the child to significant radiation exposure and some require bladder catheterization. The child does not require sedation. Different radiopharmaceuticals are utilized depending on the information desired. When evaluating for obstruction, MAG-3 (mercaptoacetyltriglycine), which is predominately excreted by the tubules, is the preferred agent (*Table 311.3*). If MAG-3 is unavailable, DTPA or GC can be used (*Table 311.3*).

CT scans are ideal for imaging the parenchyma. Excretory CT scans can be used as a method to detect obstruction. However, CT scans have considerable higher radiation exposure that plain radiography and require children unable to lie still for 20 min be sedated. They also do not provide quantitative measurements regarding relative renal function.

MRI renograms are not used routinely for baseline or follow-up studies. Although they do not expose the child to radiation, they require sedation, are expensive, and like CT scans do not provide quantitative information. They do offer information about detailed anatomy but can be extremely helpful in complex circumstances, such as diagnosing ectopic ureters and duplex collecting systems. Ongoing work with this modality has been promising in

Table 311.2
Imaging techniques utilized in the evaluation of suspected obstructed hydronephrosis

Study	Utility
VCUG	Selectively utilized to diagnose posterior urethral valves, reflux and intravesical abnormalites such as diverticulcum and ureterocele.
IVP	Rarely utilized today.
Ultrasound	Almost always the initial anatomical *screening test* due to lack of radiation, rapidity of study, reproducibility, and cost. Very little functional information provided.
Renography	May be *dynamic* (MAG-3 with furosemide), to study for obstruction, or *static* (DMSA), where more precise determination of function can be elucidated. DMSA may require sedation.
CT scanning	May be useful because of anatomical detail but suffers because of significant radiation dose.
MR urography	Provides superb anatomic detail and can also provide functional information. In younger patients it may require sedation or general anesthesia and hence cost is an issue that prohibits routine use.
Invasive techniques	Cystoscopy and retrograde pyelography can be used to more clearly define an anatomical problem such as ectopic ureter, ureterocele, ureterovesical or ureteropelvic junction obstructions, and are generally performed at the time of definitive repair. Interventional radiology can be helpful in the diagnosis and treatment of come complicated obstructive pathologies. The Whithaker or pressure- flow study is rarely used in selective cases of obstructive uropathy.

Table 311.3
Basic technetium scans and their characteristics

	Technetium-99 (^{99m}TC) nuclear renal scans	
Scan	Agent	Characteristics
MAG-3	Mercaptoacetyltriglycine	Tubular clearance
		Lower radiation exposure
		High quality
		Not influenced by GFR
DPTA	Diethylenetriamine pentaacetic acid	Requires the highest concentration of ^{99m}TC
		Rapidly cleared from system
		Measures GFR
		Poor quality to measure obstruction
DMSA	Dimercaptosuccinic acid	Binds tightly to tubular cells
		Best study to assess renal cortex
		Reflect renal mass
		Partially influenced by GFR
GC	Glucoheptonate	Influenced by GFR but cannot measure
		Tubular secretion
		Visualizes cortex
		Cannot measure obstruction

not only demonstrating complex anatomy with extraordinary clarity, but also as a functional, dynamic instrument that might ultimately surpass the current nuclear medicine studies.

With modern imaging, it is rare that cystoscopy and retrograde pyelography are utilized as a routine, separate diagnostic procedure. If performed, it is often done by some pediatric urologists at the time of a definitive

procedure. Likewise, the intravenous pyelogram or urogram is rarely useful.

Use of Antibiotics and Circumcision

Prescribing of antibiotic prophylaxis for all uropathies has undergone scrutiny and many question the utility of antibiotic use, even in cases of reflux. In patients with obstruction and concomitant vesicoureteral reflux, antibiotics may be of some benefit in reducing febrile urinary tract infections in some cases. Until better controlled trials yield results that define their true role, antibiotic prophylaxis should be utilized after assessing the pros and cons with the family, for those children with obstruction and reflux, ureteroceles, and/or megaureters. In essence, until studies clarify the currently conflicting data, practitioners should question their utility of prophylactic antibiotics and should manage each child individually.

Another area of practice variation is routine circumcision. Historically, in the United States, all boys with signs of neonatal uropathies, obstruction included, underwent routine neonatal circumcision as a prophylactic measure. Just as the use of antibiotics has been scrutinized, so has circumcision. The PUV population has generated the most information on the value of circumcision. It is more difficult to make statements of benefit in cases of ureteropelvic junction obstruction, megaureter, or ureterocele. Urinary tract infections can be reduced by circumcision, and the clinical benefit of the procedure is the greatest in patients with a high risk for febrile infection such as boys with PUV. The incidence of urinary tract infection may be reduced by as much as 83%. Families should be counseled in order to make an informed decision regarding circumcision, as with antibiotic prophylaxis, as part of the management options.

Major Causes of Obstruction

Ureteropelvic Junction Obstruction

Ureteropelvic junction obstruction (UPJO) is the most common cause of congenital urinary obstruction. Current theories to the cause of obstruction include deposition of collagen causing internal constriction, presence of crossing vessels that compress the pelvis, or obstructing polyps. Inherited differences in peristaltic function may contribute to the range of disease phenotypes seen in UPJO. Regardless of the cause of UPJO, the significant outcomes are hydronephrosis and presumed impact on renal function due to back pressure from the obstruction.

Prior to the widespread use of prenatal ultrasounds, children with UPJO presented in infancy with palpable abdominal masses, failure to thrive, urinary tract infections, and/or renal failure. Older children presented with flank pain usually accompanied with emesis. Although infants and children continue to present for evaluation in this manner, an increasingly greater number of children are diagnosed as a result of prenatal ultrasounds.

The use of prenatal ultrasound in the early detection and diagnosis of obstruction has increased over the last 3 decades as the use of ultrasound has become a routine part of prenatal care in the United States. Sensitivity for detection increases as ultrasounds are performed in later trimesters resulting in 1% of pregnancies indicating urinary abnormalities. Hydronephrosis is the most common finding. Most cases of prenatally detected hydronephrosis do not persist post partum. Large series indicate up to 50% of cases of prenatal hydronephrosis will resolve within 16 months of the postnatal period.

Ureteropelvic junction obstruction accounts for over 65% of the cases of prenatal hydronephrosis. Prenatal ultrasound has become the primary mode of diagnosing UPJO. Concerns arose that widespread use of prenatal ultrasound would lead to an increase in unnecessary surgery. Indeed, early detection and diagnosis has lead to earlier intervention. It is debatable to whether early detection has manifested in significant long-term outcomes. Patients with prenatal diagnosis have similar outcomes in regards to renal function when compared to patients presenting with symptoms. Both groups have similar gain of renal function, and pyeloplasty did not significantly improve renal function.

Indications for surgical intervention are a subject of debate with practitioners using consistent but different criteria for surgical correction. The use of diuretic (Lasix) renal scans has provided additional information for the clinician but interpretation and execution of tests may be confusing. Mercapto-acetyl tri glycine (MAG-3), a technetium-99 labeled compound that is secreted by the renal tubules, has significant fidelity regardless of underlying renal function, and is considered the best current agent for estimating renal obstruction and function. Since these studies are open to interpretation, these studies are best conducted as part of a comprehensive management strategy by surgeons or nephrologists.

Many children can be followed conservatively with 10–25% ultimately requiring surgical correction usually within the first 2 years of life. And some studies show that

even when requiring surgical correction, delay in surgery does not impair recovery of renal function.

Important to the practicing general pediatrician is that these children need to be followed closely in order to detect clinical and radiographic changes that may indicate renal deterioration. Blood pressure measurements, urine analysis, and repeated ultrasounds or renograms maybe recommended while under the care of an urologist and/or a nephrologist. Early consultation with these specialties will insure close follow-up. It is controversial whether children without a history of UTIs or vesicoureteral reflux need to be maintained on prophylactic antibiotics and many current physicians will not routinely use them.

Posterior Urethral Valves

Posterior urethral valves (PUV) are a congenital urethral anomaly seen in boys due to an obstructing membrane. PUV accounts for 3–9% of all cases of hydronephrosis. The degree of obstruction varies and the resulting phenotype can be from mild dilation to severe obstruction affecting both the bladder and kidneys. Obstructing urine can produce a distended, poorly contractile bladder and significant bilateral vesicoureteral reflux that dilates ureters and the renal collecting system. Oligohydraminos can be associated with sever obstruction that ultimately impacts lung maturity of the developing fetus. Although less common than UPJO, it represents a significant cause of morbidity and mortality from obstruction from both a respiratory and renal perspective. Mortality was as high as 35% in the 1960s. Now, 90% of boys with PUV survive infancy. Improved outcomes are due both to aggressive antenatal care in intensive care units as well as the developments of renal dialysis and transplantation. Sever obstruction is a neonatal medical emergency requiring urinary tract drainage respiratory support, and when indicated, correction of electrolyte imbalances. Severely affected newborns may require some form of renal replacement therapy. Presence of PUV is often suspected antenatally, but is confirmed by a postnatal voiding cystourethrogram (VCUG). Bladder drainage via the urethral catheter remains in place until the child is both stable and large enough to undergo endoscopic resection of the valves or urinary diversion.

Endoscopic ablation of the valves has a high rate of success; however ablation must be confirmed by post-procedure VCUG. Boys, especially those of low birth weight, with presumed small urethras drainage can also be managed by performing a cutaneous vesicostomy that allows the bladder to drain through the abdominal wall bypassing the obstructed urethra or cutaneous ureterostomies where the ureters are brought out to the skin. Some groups suggest a stepwise approach to treat as many patients with valve ablation and then proceed to diversion if decompression of the urinary system is not achieved by ablation alone; however limited evidence exists that this alters the progression of renal damage.

Patients with significant sequela from PUV require close follow-up usually with both nephrologists and urologists. However, with aggressive management of the newborn and experience in renal dialysis and transplantation, mortality for all children with PUV is less than 5% (Parkhouse). Early aggressive measures have not changed the rate of renal insufficiently or renal failure. Ureteral dilatation and reflux are often present even after valve ablation and patients are maintained on prophylactic antibiotics. The degree of obstructive nephropathy can be significant ranging from chronic renal insufficiency, requirements for dialysis, and potential end-stage renal disease culminating in renal transplantation. As many as 35% of boys with PUV may go onto renal failure. Risk factors for renal failure include late diagnosis of PUV and bilateral reflux. Many patients have small, poorly compliant bladders that lack adequate contractile capability. Patients have varying degrees of bladder dysfunction and may need to perform clean intermittent catheterization to empty their bladders, require bladder augmentation for an adequate capacity, or need the creation of catheterizable channels. Progression of bladder dysfunction will require urodynamic evaluation as part of ongoing urological follow-up.

Bladder function remains an ongoing challenge in the management of these patients and contributes to both significant morbidity and reduced quality of life. Without aggressive management of the valve bladder, renal transplantation is associated with lower graft survival. The increasing success of renal transplantation has been one of the major factors in the recent lower mortality rates for patients with PUV.

Obstructing Megaureter

Megaureter is a descriptive term applied to all ureters that have significant dilatation (greater than 0.7–1 cm). Only a small portion of megaureters are truly obstructing. Distinguishing dilated ureters that are obstructed from those that are merely dilated is an important step. Some

clinicians rely on drainage pattern from diuretic renograms. However, dilated ureter empty less efficiently and thus a delayed time to empty could potentially represent only a capacious ureter. Ultrasound findings of a progressively increasing hydronephrosis or dilatation to a level near the bladder that then sharply tapers off, is also used by some for evidence for obstruction. Those megaureters that are both obstructing and refluxing can be diagnosed by voiding cystourethrograms where the ureter is seen to taper significantly as it approaches the bladder. And as with UPJO, the insult potentially resulting in the obstruction has been linked to increased collagen deposition. In the cases of megaureter, the location of collagen deposition is near or at the ureterovesical junction. As with other causes of obstruction, many megaureters are diagnosed by prenatal ultrasounds. Prior to the widespread use of ultrasound, children presented with failure to thrive, urinary track infections, and hematuria. Although the true natural history of megaureters is unknown, many prenatally detected megaureters can be managed conservatively, at least initially. Management is similar to ureteropelvic junction obstruction in that patients are followed expectantly with serial ultrasounds and renograms. Greater controversy exists on what modality to use to determine obstruction in the cases of megaureter. Given the tortuousity and dilation of the megaureter, there is often delayed emptying of the ureter such that time to emptying becomes a less reliable marker of obstruction. Instead many physicians will use serial split renal function or sonographic evidence of thinning parenchyma as indication for intervention. Many patients are maintained on prophylactic antibiotics. Patients are more likely to undergo surgical correction when high grades of hydronephrosis are seen in combination with diminished renal function. Break through urinary tract infections while on prophylaxis is also a reason for intervention; however it is unclear if surgery decreased the incidence of further infections. Prior studies do not show significant regain of renal function after surgical correction.

Surgical repair of obstructing megaureters has consisted of separation of the ureter from the bladder, removal of the affected segment, tapering of the ureter and reimplantation into the bladder. Although the ureter may empty more efficiently after surgical correction, dilatation of the ureter may persist. Goals of the surgery are focused on alleviating obstruction so as to disrupt the continued pressure on the renal segment. As with other patients with obstructing nephropathy, these patients with megaureters are followed long term to assess their renal function and urinary tract function.

Ureteroceles

Ureteroceles are seen when the distal portion of a ureter is dilated sometimes distorting the bladder. Obstruction is thought to be caused by an anomaly at the ureteral orifice. It is not clear if this anomaly represents a partially obstructing membrane or an error in the normal development of the ureteric bud in utero. The anomaly is found four times more often in females and is associated with ureteral duplication in 80% of the time. In cases of renal duplication, the upper pole moiety is most often associated with the ureterocele. Ureteroceles are often associated with ectopic insertion of the ureteral orifice. In girls insertion can occur at the bladder neck, vagina, or urethra. In boys, ectopic insertion occurs in the urethra, seminal vesicles, prostate, or vas deferens. Up to 50% of children with ectopic ureters will have reflux into the ipsilateral lower pole kidney. Even those ureteroceles that are not ectopic can be quite large and may obstruct the bladder neck. A patient with an ureterocele most commonly presents with urinary tract infections and/or sepsis. Patents can present with urinary obstruction due to the extension of ureterocele beyond the bladder neck, or incontinence in the case of ectopic insertion. In recent years, more ureterocele are diagnosed with prenatal ultrasounds, but still a significant number are detected symptomatically. Although early detection has not altered renal function, it has been shown to decrease the morbidity associated with ureteroceles by instituting early use of antibiotic prophylaxis and resulting lower rates of UTI.

Treatment of the ureterocele is tailored to the individual patient in regards to symptoms, age, presence or absence of duplication, relative function of the upper pole moiety if present, presence or absence of reflux, location of insertion of the ureter, renal function, and history of infection. Asymptomatic patients, most often those diagnosed prenatally, can be managed conservatively with serial renal ultrasounds; however limited information is available to whether this represents a course for most patients. Various surgical options are available with the goal of treatment being assuring adequate drainage, minimizing the risk for infection, preservation of renal function, and management of reflux if present. Surgical techniques include endoscopic incision of the ureterocele, upper pole heminephrectomy with or without lower tract reconstruction, ureteroureterostomy, and complete nephroureterectomy. Increasingly, treatment plans have maintained renal tissue by performing ureteroureterostomies with only limited indications for heminephrectomy.

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312 Acute Kidney Injury

Hui-Kim Yap

Definition

Acute renal failure occurs when there is a rapid decline in glomerular filtration rate, resulting in impairment of excretion of nitrogenous waste product, and loss of water and electrolyte regulation as well as acid-base regulation. This is reflected clinically by an abrupt increase in serum creatinine, and/or an abrupt decrease in urine output. Although oliguria, defined as urine volume less than 400 mL/m^2 per day, is common in acute renal failure, non-oliguric renal failure in which urine volume is normal is a well-recognized entity occurring in conditions such as aminoglycoside toxicity.

More recently, the Acute Kidney Injury Network (AKIN) proposed to use the term "acute kidney injury" (AKI) to redefine the entire spectrum of acute renal dysfunction, encompassing early and mild forms all the way to severe forms requiring renal replacement therapy. In adults, a classification system known as the RIFLE criteria, to define the severity of AKI, has been proposed by the Acute Dialysis Quality Intitiative. This defines risk, injury, and failure based on changes in serum creatinine and/or urine output, combined with the clinical outcome classes based on persistence of renal failure, namely, loss and end-stage kidney disease. Studies in the adult intensive care setting suggest that use of the RIFLE criteria conveys significant prognostic information, and may therefore aid in clinical decision making, especially the timing to institute renal replacement therapy. Similarly, modified criteria for pediatric patients have been proposed based on estimated creatinine clearances and urine output (*Fig. 312.1*), although there are concerns regarding the validity of estimated glomerular filtration rates when plasma creatinine is not in equilibrium as is the case in AKI.

Etiology

Causes of acute kidney insufficiency in children can be broadly classified into pre-renal, renal, and post-renal causes (*Table 312.1*).

Pre-renal vasomotor causes are potentially reversible if hypoperfusion can be corrected before tubular damage is established. Hypoperfusion may result from intravascular volume depletion as seen in blood loss, severe dehydration, or "third-spacing" in intestinal obstruction, as well as hypotension following sepsis or shock, and ineffective circulatory volume as in cardiac failure or states of severe hypoproteinemia. Failure to adequately reverse these predisposing conditions will result in hypoxic-ischemic AKI. Recognizing that various "toxins" can cause AKI is important, as there is evidence that preventive measures may be effective. These nephrotoxic compounds include intravascular radiocontrast agents, aminoglycoside antibiotics, amphotericin B, chemotherapeutic agents such as ifosfamide and cisplatin, acyclovir, acetaminophen, and calcineurin inhibitors.

Renal causes include the rapidly progressive forms of glomerulonephritis, including post-infectious glomerulonephritis, lupus nephritis, Henoch-Schönlein nephritis, membranoproliferative glomerulonephritis, anti-neutrophil cytoplasmic antibody-associated glomerulonephritis, and anti-glomerular basement membrane disease. Thrombosis of the renal vessels, especially in the critically ill neonate, may lead to AKI. Hemolytic-uremic syndrome which may follow diarrheal illnesses or pneumococcal infection is not uncommon in young children. Other renal causes include acute pyelonephritis; acute tubulointerstitial nephritis, which may be secondary to infections or drugs such as ampicillin; and tumor infiltration such as that seen in lymphoid malignancies.

In tropical countries, infections such as falciparum malaria which cause pigment injury secondary to intravascular hemolysis, and leptospirosis associated with hepatorenal failure, are important causes of AKI. Additionally, in populations where glucose-6-phosphate dehydrogenase deficiency is prevalent, drug-induced acute intravascular hemolysis may result in renal failure. Heat stroke and exercise-induced rhabdomyolysis must be considered in adolescents presenting with AKI.

Post-renal causes especially obstructive uropathies should be excluded as these are potentially reversible causes of AKI. Bladder outlet obstruction, such as that seen in posterior urethral valves in boys and neurogenic bladder, is an important cause. Ureteral obstruction of a single functioning kidney must be considered, unless

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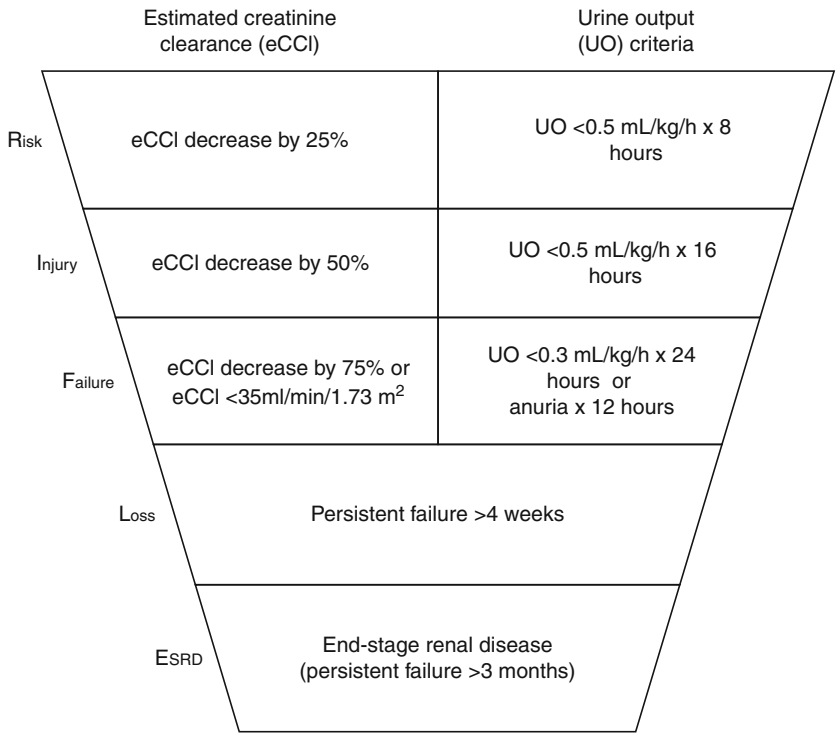

Figure 312.1
The pediatric-modified RIFLE (pRIFLE) criteria for the diagnosis of AKI. RIFLE: Risk, Injury, and Failure with the outcome classes Loss and End-stage kidney disease (Modified from Ackan-Arikan A et al., Kidney Int 10:963–964)

Table 312.1
Causes of acute kidney injury in children

Pre-renal (vasomotor nephropathy)	Renal	Post-renal
Ischemic • Hypovolemia including hemorrhage, gastrointestinal losses, burns, renal salt-wasting conditions • Hypotension • Hypoxia • Cardiac failure • Sepsis • Intestinal obstruction • Hepatorenal syndrome Toxic • Aminoglycosides • Wasp sting • Plant toxins • Snake-bite • Pigments eg hemoglobin or myoglobin • Radiocontrast agents	Glomerulonephritis (GN) • Post-infectious GN • Systemic lupus erythematosus • Henoch-Schönlein nephritis • Membranoproliferative GN • Anti-neutrophil cytoplasmic antibody-associated GN • Anti-glomerular basement membrane disease • Idiopathic rapidly progressive GN Vascular • Hemolytic-uremic syndrome • Renal artery thrombosis • Renal vein thrombosis Acute tubulointerstitial nephritis • Infections, e.g., Ebstein Barr virus and leptospirosis • Drugs including herbal preparations Acute pyelonephritis Tumor infiltration	Structural • Posterior urethral valve • Ureteric obstruction • Neurogenic bladder Crystalluria • Tumor lysis syndrome • Melamine Calculi Blood clot

obstruction occurs bilaterally. Another cause of significant obstruction in children is crystal precipitation in the renal tubules. Children with acute lymphoblastic leukemia and B-cell lymphoma are at the highest risk of AKI due to tumor lysis syndrome following chemotherapy. This results in tubular precipitation of uric acid crystals and its precursors, xanthine and hypoxanthine, as well as calcium phosphate crystals.

Epidemiology

Epidemiological data on the incidence and prevalence of AKI in children is difficult to ascertain. A retrospective review from England estimated a yearly incidence for AKI in children as 0.8 per 100,000 population. Geographic differences in the causes of AKI do exist (*Fig. 312.2*). In developing countries, primary renal diseases such as post-infectious glomerulonephritis and hemolytic-uremic syndrome are important causes of AKI. Although survival is generally better in children with primary renal disease, lack of access to medical care coupled with the poor socio-economic conditions in these countries contribute to the poor outcomes in these patients. Unfortunately the real tragedy in these areas is that AKI secondary to pre-renal causes such as gastroenteritis would have been preventable if they were able to have timely volume replacement.

Recent pediatric AKI epidemiological data for critically ill children demonstrate a shift from primary renal disease to injury secondary to other systemic illnesses and/or their treatment. With the development of pediatric intensive care in tertiary hospitals catering for specialties such as cardiac surgery, oncology, and solid organ and bone marrow transplant, a larger proportion of pediatric AKI is due to ischemic or toxic injury (*Fig. 312.2*). The mortality in this group of infants and children is higher, ranging from 33% to 78%, due to the concomitant presence of multiorgan failure. The most important predictors

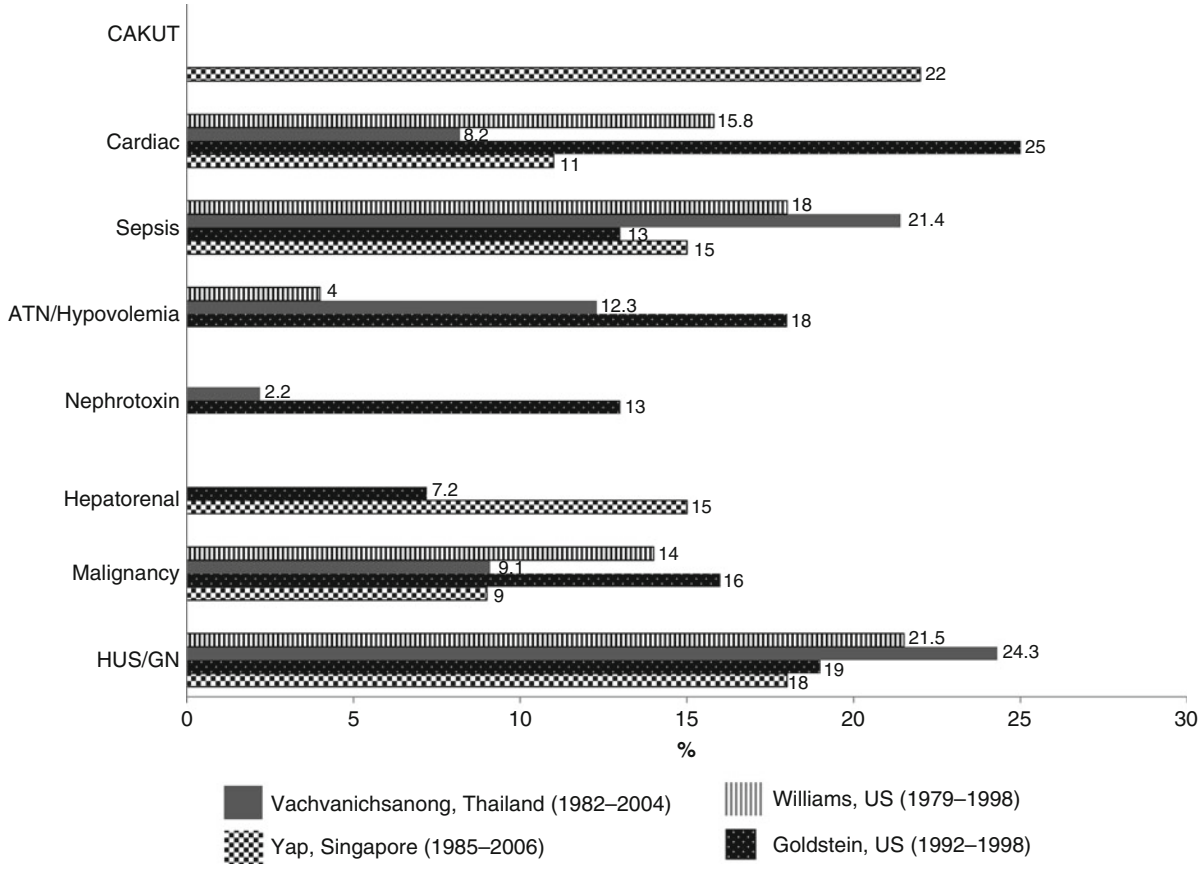

Figure 312.2
Causes of AKI worldwide. CAKUT: congenital abnormalities of the kidney and urinary tract. ATN: acute tubular necrosis

of mortality among these critically ill children include the severity of the underlying systemic illness, hemodynamic stability, and the degree of fluid overload at initiation of renal replacement therapy.

Similarly AKI affects approximately 8–24% of severely ill newborns treated in the neonatal ICU, with a mortality rate of between 10% and 61%. Data from the literature suggest that the incidence of AKI in asphyxiated newborns is high, and portends a poor outcome. Other factors associated with development of AKI in neonates include very low birth weight (less than 1,500 g), a low Apgar score, persistent arterial duct, and maternal use of antibiotics and nonsteroidal anti-inflammatory drugs.

Pathogenesis

Molitoris proposed a mechanistic classification that delineates four distinct phases in AKI: initiation, extension, maintenance, and recovery (*Fig. 312.3*). In the "initiation phase," numerous ischemic insults, alone or in synergistic combination with nephrotoxins, initiate epithelial and vascular cell injury, resulting in patchy tubular necrosis and a rapid decline in glomerular filtration rate. Hypoxic or ischemic AKI is characterized by early vasoconstriction followed by patchy tubular necrosis. Following reperfusion, loss of endothelial cell function with distorted peritubular pericapillary morphology occurs. Possible mechanisms of cellular injury include perturbation in endothelin or nitric oxide regulation of vascular tone, ATP depletion with resultant cytoskeletal alterations, changes in heat shock proteins, induction of the systemic inflammatory response, and the generation of reactive oxygen and nitrogen molecules.

The "extension phase" immediately follows the "initiation phase," where multiple interrelated events lead to a worsening of epithelial and endothelial cell injury and cell death, primarily in the cortico-medullary region. A phase of stabilization of injury known as the "maintenance phase" precedes the "recovery phase" where cellular repair, division, and redifferentiation occurs, resulting in improved epithelial and endothelial cell function and recovery of the glomerular filtration rate. Previously, it was thought that recovery from hypoxic-ischemic and nephrotoxic AKI was complete with normalization of renal function; however, recent studies have shown that recovery may be partial and patients may be at higher risk for chronic kidney disease.

This pathogenetic concept provides an important framework upon which therapy can be based. (*Fig. 312.3*). Utilizing this approach, it is easy to understand why studies that initiate therapy during the maintenance phase have proven uniformly unsuccessful. On the other hand, significant progress has been made in the prevention of ischemic AKI, especially with regards to the high-risk population, defined as children with conditions associated with hypovolemia or underlying renal disease. Finally, renal replacement therapy should be appropriately instituted in established AKI.

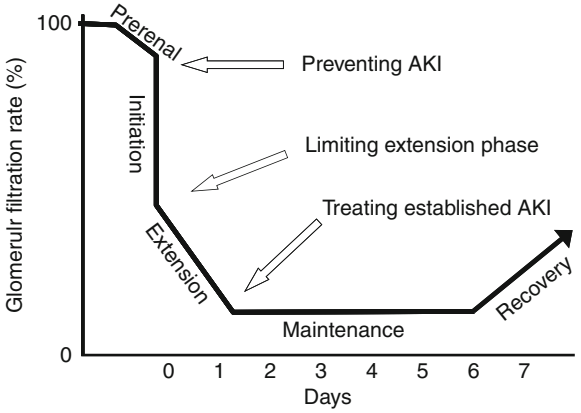

Figure 312.3
Mechanistic basis for the treatment of AKI (Modified from Molitoris J (2003) J Am Soc Nephrol 14:265–267)

Clinical Manifestations

A high index of suspicion is required to diagnose AKI. There are typically four scenarios where AKI should be considered in infants or children with oliguria.

Children Presenting with Conditions Associated with Severe Hypovolemia

Children who present with vomiting, diarrhea, and decreased oral intake are at risk of developing severe hypovolemia and AKI. On the other hand, in some conditions associated with polyuria, such as diabetic ketoacidosis, renal tubular acidosis and chronic tubulopathies, these children can develop severe hypovolemia and pre-renal AKI if their fluid intake is insufficient for any reason to keep up with the urine loss. Physical signs of hypovolemia are prominent, such as tachycardia, poor capillary refill, decreased skin turgor, dry mucous membranes, sunken eyes, and orthostatic blood pressure changes.

Children Presenting Acutely with Symptoms Suggestive of Renal Disease

Acute onset of oliguria, edema, and gross hematuria, with a preceding history of pharyngitis or impetigo, is consistent with post-infectious glomerulonephritis, where AKI requiring dialysis occurs in less than 1%. Bloody diarrhea with oliguria or anuria suggests diarrhea-associated hemolytic-uremic syndrome, whereas in children with pneumonia, development of oliguria accompanied by anemia and thrombocytopenia is indicative of pneumonia-associated hemolytic-uremic syndrome. In children with nephrotic syndrome, AKI though uncommon, should be suspected if there is severe hypovolemia with hypotension and tachycardia, accompanied by marked decrease in urine output. Systemic signs and symptoms of vasculitis, such as purpuric or malar rash, joint pain or swelling, and hemoptysis, suggest the possibility of rapidly progressive glomerulonephritis associated with systemic vasculitis.

Critically Ill Children with Predisposing Factors for Multiorgan Failure

Critically ill children with sepsis and hypotension frequently have multiorgan failure resulting in AKI with oligoanuria, especially with the use of inotropes such as noradrenaline or adrenaline. Often these children are immunosuppressed or neutropenic such as in oncology patients undergoing chemotherapy or bone marrow transplantation. A history of nephrotoxic medications is often present, including antibiotics such as aminoglycosides or amphotericin-B, chemotherapeutic agents such as cisplastin, and calcineurin inhibitors.

Newborn Infants with Oliguria or Anuria

Oliguria in the newborn beyond 72 h is worrying and should be investigated. In the absence of ischemic injury, anuria or oliguria suggests a major congenital malformation such as posterior urethral valves, or genetic disease such as autosomal recessive polycystic kidney disease. In the sick neonate with hematuria, bilateral renal vein thrombosis should be suspected.

Diagnostic Approach

The modified RIFLE criteria for pediatric patients (*Fig. 312.1*) will help in standardizing the definition of AKI so that the appropriate therapeutic decisions can be made. These criteria are based importantly on either the degree of oliguria over a timed period or a change in the estimated creatinine clearance.

Having defined the presence of AKI, the next step is to differentiate the various causes using several noninvasive methods. Early diagnosis of pre-renal and obstructive causes is important as prompt corrective measures may prevent the onset of established renal injury.

Urinary Sediment

The urinary sediment should be examined for the presence of cells, crystals, cellular debris, and casts. The presence of hematuria associated with dysmorphic red cells and red cell casts suggests a diagnosis of glomerulonephritis, while renal tubular epithelial cells, tubular cell casts, or coarsely granular pigmented casts suggest acute tubular necrosis. Pyuria may suggest pyelonephritis, although tubulointerstitial disorders may present with sterile pyuria. Moreover, the presence of eosinophils is highly suggestive of acute allergic interstitial nephritis. Crystals in the urine such as uric acid or calcium oxalate crystals may be useful indicators of the underlying etiology in the appropriate clinical setting with AKI, namely, tumor lysis syndrome and ethylene glycol poisoning, respectively. If there are scant findings on microscopy examination of the urine, this may be consistent with pre-renal or obstructive causes of AKI.

Blood and Urinary Indices to Differentiate Between Pre-renal and Established Renal Failure

Blood and urinary indices used to differentiate between pre-renal and established acute renal failure are based on the premise that the proximal renal tubular transport mechanisms are still able to respond to the hypovolemic stimulus in pre-renal failure, as compared to the failure of these transport mechanisms in acute tubular necrosis. The serum urea/creatinine ratio has been used to distinguish between pre-renal and established renal failure, in older children and adolescents with hypovolemia. This ratio is usually high in pre-renal disease due to increased urea reabsorption following enhanced proximal transport of sodium and water. A ratio greater than 20:1 for urea and creatinine measured in mg/dL or 0.10 for urea measured in mmol/L and creatinine in μmol/L is seen in pre-renal disease. Unfortunately, in conditions of increased catabolism,

gastrointestinal hemorrhage and corticosteroid administration, the ratio can be elevated. Conversely, a normal ratio can be seen in liver disease or protein malnutrition.

Urinary indices derived from measurements on simultaneous random urine and plasma specimens, in the absence of diuretic use, can help differentiate pre-renal versus established renal failure (*Table 312.2*). In hypovolemia, there is marked urinary sodium reabsorption and concentration of the urine, whereas in irreversible tubular injury, the tubules are unable to appropriately conserve sodium. As urinary sodium concentration can also be low as a result of dilution, the fractional excretion of sodium (FeNa) is a better index to take into account renal water handling. In conditions where there is relative renal hypoperfusion such as hypovolemic dehydration, nephrotic syndrome, congestive cardiac failure, or cirrhosis, the FeNa is less than 1%. In contrast, tubular damage results in FeNa ranging from 2% to 3%. As the renal tubules in newborns are relatively immature compared to older infants and children, the corresponding FeNa in newborns with hypovolemia is less than 2.5%. However, in patients given diuretics, and in salt-losing conditions, such as Bartter's syndrome, interstitial nephritis, and chronic renal disease, urinary sodium may be high, thus obviating the value of indices based on urinary sodium excretion. In these situations, the fractional excretion of urea (FeUN) has been proposed as a better index to distinguish between pre-renal failure and established tubular necrosis. The FeUN should be less than 35% in conditions of hypovolemia, whereas in acute tubular necrosis, the value is greater than 50%.

Table 312.2
Use of urinary indices to differentiate pre-renal and intrinsic renal causes of AKI

	Pre-renal cause*	Intrinsic renal cause*
Urine sodium (mmol/L)	<20 (<20)	>40 (>50)
Urine osmolality (mOsm/kg)	>500 (>400)	<350 (<400)
Urine/plasma urea	>8	<3
Urine/plasma osmolality	>1.15 (>1.2)	<1.1 (<1.2)
Urine/plasma creatinine	>40	<20
Fractional sodium excretion (FeNa)	<1 (<2.5)	>1 (>2.5)
Fractional urea excretion (FeUN)	<35%	>50%

FeNa = (urine sodium/plasma sodium) × (plasma creatinine/urine creatinine) × 100%
FeUN = (urine urea/plasma urea) × (plasma creatinine/urine creatinine) × 100%
These indices must be used with caution in premature neonates less than 32 weeks gestation, since a high urinary sodium excretion is commonly observed
*Values in parenthesis are the criteria for neonates

Other Laboratory Tests

Other laboratory tests may provide some clues as to the underlying etiology of the AKI. The complete blood count is important to look for anemia and thrombocytopenia, suggestive of hemolytic-uremic syndrome or a vasculitis-associated glomerulonephritis. The peripheral blood smear should also be done to look for schistocytes in hemolytic-uremic syndrome, or spherocytes in lupus nephritis. The urine should be tested for hemoglobin or myoglobin to exclude pigment nephropathy, if the history is suggestive of intravascular hemolysis or rhabdomyolysis. Decreased serum complement levels (C3 with or without C4), elevated anti-nuclear antibodies, anti-neutrophil cytoplasmic antibodies, and anti-glomerular basement membrane antibodies are useful to distinguish the various glomerular diseases resulting in AKI. The serum complement C3 is low at presentation in post-infectious glomerulonephritis, lupus nephritis, and membranoproliferative glomerulonephritis. Specific patterns of biochemical abnormalities may be seen in certain causes of AKI. Hypocalcemia, hyperphosphatemia, and hyperuricemia occur in tumor lysis syndrome, while in rhabdomyolysis, there is additional elevation of the serum creatine kinase levels. An increase in anion and osmolar gaps in the presence of AKI is suggestive of ethylene glycol poisoning.

Novel Biomarkers of AKI

Serum creatinine is a poor marker of early renal dysfunction, especially in AKI where the patients are not in steady state. Substantial elevation in serum creatinine is often not witnessed until 48–72 h after the initial insult to the kidney. The tools of modern science have provided promising novel plasma and urinary biomarkers for AKI, with potentially high sensitivity and specificity. These include a plasma panel comprising neutrophil gelatinase-associated lipocalin (NGAL) and cystatin C, and a urine panel comprising NGAL, interleukin-18 (IL-18), and kidney injury molecule-1 (KIM-1).

Cystatin C is a cysteine protease inhibitor that is produced at a constant rate, freely filtered by the kidneys, and

is almost completely reabsorbed by the proximal renal tubular cells. Prospective studies have shown that an increase in cystatin C levels occurred 1½ days before AKI developed.

Circulating NGAL is normally reabsorbed in the proximal tubule. Following kidney injury, NGAL is secreted in the thick ascending limb of the loop of Henle, and is found in the urine, and the NGAL protein is detected in the blood and urine very early in the course of AKI. In a prospective study of children undergoing cardiopulmonary bypass, plasma and urinary NGAL levels were elevated within 2–6 h of surgery, and was able to predict the development of AKI, compared to serum creatinine levels which rose by at least 50% only 1–3 days after surgery. However, NGAL is also increased in infections, inflammatory conditions, and malignancies, and thus may have limited value in predicting AKI in these clinical situations.

Urinary IL-18 is a pro-inflammatory cytokine that is induced and cleaved in the proximal tubule. It is detected in the urine following ischemic AKI, but not in chronic kidney disease, urinary tract infections, nephrotic syndrome, or pre-renal failure. In the intensive care setting, urine IL-18 measurements were able to predict AKI about 2 days prior to the rise in serum creatinine, and was an independent predictor of mortality in these critically ill children with AKI.

KIM-1 is a type 1 transmembrane protein that is not detectable in normal kidney tissue or urine, but is expressed at very high levels in dedifferentiated proximal tubule epithelial cells in human kidneys after ischemic or toxic injury. Earlier studies have shown that KIM-1 measurement was able to distinguish between ischemic AKI from pre-renal azotemia and chronic kidney disease. More recently, urinary KIM-1 levels were shown to be predictive of AKI in children undergoing cardiopulmonary bypass. In fact, urinary KIM-1 performed best as an early marker of AKI compared to other urinary biomarkers such as N-acetyl-beta-D-glucosaminidase (NAG), NGAL, IL-18, cystatin C, and alpha-1 microglobulin. However, urinary KIM-1 measurements may be also induced in a variety of chronic proteinuric, inflammatory, and fibrotic disease states, as well as upregulated by nephrotoxins, including cyclosporine, cisplatin, and gentamicin, thus limiting its value in predicting AKI in the presence of these confounding factors.

Imaging

Imaging of the urinary tract is important in the diagnostic workup of children with AKI, as it is crucial for the exclusion of obstructive uropathies. In addition, assessment of kidney size is a useful indicator of the chronicity of the renal failure. Enlarged kidneys standardized to patient's age and size is suggestive of AKI, whereas small contracted kidneys suggest chronic renal failure. These imaging modalities include ultrasonography, CT urogram, radionuclide imaging, magnetic resonance imaging, and, occasionally, plain film of the abdomen.

Ultrasonography should be the initial imaging modality in the diagnostic workup of children with AKI to detect bilateral upper tract obstruction, bladder outlet obstruction, or obstruction of a solitary functioning kidney. Dilatation of the pelvicalyceal system can be detected within 24–36 h of the onset of acute urinary obstruction. It is important to realize that dilatation of the upper tract may not be seen in the acute stage of ureteral obstruction if this is accompanied by a decrease in urine output. In lower tract obstruction, ureteral dilatation, bladder size, and wall hypertrophy, as well as the presence of associated lesions such as ureterocele can be identified by ultrasonography. An increase in echogenicity is seen in both acute and chronic kidney disease. In neonates with renal vein thrombosis, Doppler flow scanning will be able to demonstrate decreased blood flow.

Radionuclide imaging using ^{99m}Tc mercaptoacetyltriglycine (MAG3) or ^{131}I-iodohippurate is used to assess blood flow and the severity of functional obstruction. Noncontrast CT scans are able to demonstrate the renal pelvis and proximal ureter, and may be helpful in identifying sites of ureteral obstruction, stones, tumors, or congenital abnormalities. Contrast-enhanced scans will add functional information of the individual kidney; however, this should be avoided in AKI due to the risk of contrast nephropathy. Magnetic resonance urogram, both static and gadolinium enhanced, is a useful study to identify collecting system morphology in obstructive uropathies, regardless of excretory fuction. Unfortunately, infants and young children require sedation for this study. Moreover, the risk of nephrogenic systemic fibrosis following gadolinium-based contrast agents in patients with renal failure limits the use of the dynamic scan in AKI.

Renal Biopsy

Renal biopsy should be considered if there is clinical suspicion of a rapidly progressive form of glomerulonephritis or acute allergic interstitial nephritis. A definitive histological diagnosis in these instances will be important as immunosuppressive therapy can alter the outcome of the disease.

Clinical Management

Medical Management

The main aim in managing AKI is to maintain homeostasis, while awaiting improvement in renal function, either spontaneously or while the underlying cause is being treated. Because of the availability and efficacy of dialysis, patients with AKI often succumb not due to AKI, but to other comorbidities. The main goals in medical management are therefore to maintain adequate renal perfusion, prevent fluid overload and hypertension, maintain normal electrolytes and acid-base status, and ensure adequate nutrition.

Maintaining Adequate Renal Perfusion

In severely ill patients who are at risk of ischemic AKI, correction of pre-renal factors such as dehydration, poor cardiac output, hypovolemia, and acid-base and electrolyte abnormalities is important to prevent development of AKI (*Fig. 312.4*). Unless contraindicated due to fluid overload or cardiac failure, a child with clinical evidence of hypovolemia and oliguria should be administered an intravenous fluid challenge over 20–30 min, with either crystalloid solutions such as normal saline (10–20 mL/kg) or colloid solutions such as 5% albumin if hypotensive. This can be repeated if the child is still hypovolemic. Restoration of adequate urine flow and improvement in renal function with fluid resuscitation is consistent with pre-renal disease. However, if urine output does not increase and renal function fails to improve with restoration of intravascular volume, invasive monitoring may be required to adequately assess the child's fluid status and help guide further therapy.

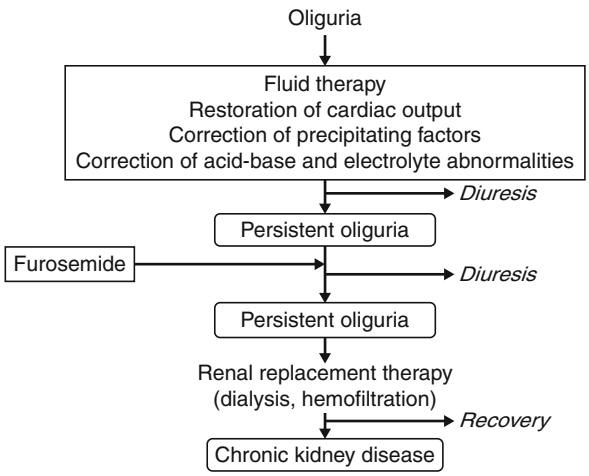

Figure 312.4
Algorithm for intervention in vasomotor nephropathy

If oliguria persists despite adequate correction of pre-renal factors, a trial of loop diuretics such as furosemide (2–5 mg/kg) may be attempted to promote diuresis, converting the child from oliguric to non-oliguric renal failure, thus facilitating fluid balance without the need for dialysis. Low dose dopamine infusion (1–5 mcg/kg per hour) is thought to promote renal vasodilatation, however, the evidence that this has a beneficial effect in limiting or preventing established AKI is lacking. Fenoldopam, a potent, short-acting, selective, dopamine-1 receptor agonist that decreases vascular resistance while increasing renal blood flow, has been shown in a meta-analysis to decrease the incidence of AKI and the need for renal replacement therapy in critically ill adults. Although there are some good results with its use in children, additional studies need to be performed to determine its value. On the other hand, use of vasoactive agents in hypotensive patients to maintain adequate blood pressure may improve renal perfusion.

Preventing Fluid Overload and Hypertension

In general, infants and children with AKI are not severely uremic, but their major problem is fluid overload following oliguria or anuria. Fluid overload is potentially fatal in AKI due to pulmonary edema, and the first line of treatment in these oliguric or anuric patients is fluid restriction and intravenous diuretics. Fluid volume should be restricted to insensible water loss calculated at 400 mL/m^2 per day, in addition to replacing urine, gastrointestinal, and other losses. Therapy should be aimed at decreasing the body weight by 0.5–1% daily.

Fluid overload may aggravate hypertension in patients with glomerulonephritis, resulting in hypertensive urgencies or emergencies. These children are symptomatic with complaints of nausea, headache, and blurred vision. Uncontrolled hypertension often leads to acute end-organ injury such as posterior reversible encephalopathy syndrome with altered mental state and seizures, cerebral infarction, cerebral hemorrhage, left heart failure, and grade III–IV retinopathy with exudates, hemorrhage, and papilledema. It is important to treat these hypertensive emergencies with intravenous antihypertensive agents that can produce a controlled reduction of blood pressure in order to avoid worsening of the cerebral edema due to disruption of cerebral autoregulation.

Maintaining Normal Electrolytes and Acid-Base Status

The common electrolyte disorders in AKI are hyperkalemia, hyponatraemia, hypocalcemia, and hyperphosphatemia. Hyperkalemic emergencies, where serum potassium levels are greater than 7 mmol/L accompanied by electrocardiographic changes such as peaked T waves, flattened P waves, increased PR interval, and widening of the QRS complex, can be managed with intravenous calcium (0.5 mL/kg up to a maximum of 20 mg given slowly over 15 min) to stabilize the cardiac membrane, followed by nebulized (2.5 mg for body weight less than 25 kg or 5 mg for body weight 25 kg or more) or intravenous salbutamol (4 mg/kg) or intravenous insulin (1 IU/5 g dextrose) and dextrose (0.5 g/kg) to temporarily lower the serum potassium levels, prior to dialysis. Less urgent elevations of serum potassium (6–7 mmol/L) can be managed with oral or rectal kayexylate (1 g/kg to a maximum of 30 g) or other ion exchangers, and correction of concomitant acidosis. Hyponatraemia due to fluid overload can be corrected with fluid restriction and loop diuretics. If there is renal salt wasting, then sodium supplementation may be necessary. Hypocalcemia and hyperphosphatemia can be managed with calcium-based phosphate binders. Severe metabolic acidosis where serum bicarbonate is less than 15 mmol/L or pH less than 7.2 may be corrected with oral sodium citrate or intravenous sodium bicarbonate. The latter has the adverse effect of hypernatremia, and exacerbating fluid overload, necessitating dialysis.

Ensuring Adequate Nutrition

Ensuring adequate nutrition is often a real challenge in the critically ill patient. Energy balance studies on patients with AKI have demonstrated that cumulative energy deficits are associated with increased mortality. In infants and children with AKI, given their limited reserves, these nutritional issues will be further amplified. Because of the necessity for fluid restriction, increasing the concentration of the enteral feeds or parenteral hyperalimentation will improve caloric delivery. However, this is often limited by the consequent increase in osmolarity of the feeds. Early institution of dialysis will allow better optimization of nutrition in these patients.

Acute Renal Replacement Therapy

The traditional indications for renal replacement therapy in AKI include severe hyperkalemia unresponsive to conservative therapy, uncontrolled acidosis that cannot be safely corrected because of risk of sodium or volume overload, severe volume overload with uncontrolled hypertension, pulmonary edema or cardiac failure, progressive uremia with deterioration in the general condition, and hypercatabolic states with increase in blood urea by greater than 10 mmol/L per day.

The critically ill child is often on a downward spiral, with sepsis, shock, acute respiratory distress syndrome, often leading to multiorgan failure which forms the final common pathway of lethal infective and non-infective complications. In this setting, where there is hypotension, effective hypovolemia, hypoxemia, hypercapnia, and hypothermia, coupled with the use of a multitude of vasoactive and nephrotoxic drugs, AKI is inevitable. This is often associated with a poor outcome. In general, these children may not be severely uremic, but their major problem is fluid overload and electrolyte perturbations especially acidosis, hyponatremia, and hyperkalemia. Conservative management with severe fluid restriction is not the answer, as this has its attendant problems of inadequate nutrition, propensity to hypoglycemia, insufficient volume space for blood products, and difficulty in drug delivery, such as inotropic support and antibiotic infusions. Therefore, early institution of dialysis is important in these critically ill children with AKI to maintain homeostasis and create enough volume space so that the nutritional and therapeutic needs may be met.

There are various strategies for the dialytic treatment of children with AKI, including peritoneal dialysis (PD), intermittent hemodialysis (HD), and continuous renal replacement therapy (CRRT). Choice of dialysis modality is largely influenced by the age and size of the child or infant, clinical presentation, presence or absence of multiorgan system failure, indication for renal replacement therapy, experience of the center, and the available resources (*Table 312.3*).

Acute Peritoneal Dialysis

Acute PD is still the modality of choice in many countries, especially in the developing world. It is a relatively cheap form of dialysis, and does not require sophisticated equipment or complicated technical expertise. Acute PD is associated with less hemodynamic instability, and has the advantage of avoiding the need for vascular access and blood priming. It can be done in very young infants, and does not require anticoagulation in the child with disseminated intravascular coagulopathy.

Table 312.3
Comparison of different dialytic modalities in AKI

Variable	PD	HD	CRRT
Continuous therapy	Yes	No	Yes
Hemodynamic stability	Yes	No	Yes
Fluid balance achieved	Variable	Yes (intermittent)	Yes
Optimal nutrition	No	No	Yes
Metabolic control	Yes	Yes (intermittent)	Yes
Easy to perform	Yes	No	No
Anticoagulation	Not required	Heparin anticoagulation or heparin free	Heparin or citrate anticoagulation
Vascular access required	No	Yes	Yes

Although PD has certain advantages over filter dependent procedures, there are several problems that make PD difficult especially in the small infant. Catheter problems are common such as leakage into the subcutaneous tissue and hernia sites, especially inguinal. Drainage is frequently a problem because of catheter malposition, kinking, omental wrapping, and fibrin clot. In young infants, it is often not possible to increase the dwell to the desired volume due to splinting of the diaphragm in the critically ill infants with acute respiratory distress syndrome. The slow and relatively inefficient removal of all types of molecules, as well as unreliable ultrafiltration, represents a considerable drawback compared to other modalities of acute dialysis, especially in patients with hypotension and poor peritoneal perfusion. Hence, acute PD may not provide adequate clearances in the hypercatabolic patient with severe hyperkalemia and hyperphosphatemia. Moreover, acute PD is contraindicated in patients with recent abdominal surgery, necrotizing enterocolitis, and presence of ventriculo-peritoneal shunts. Therefore acute PD is currently best for "uncomplicated" or medical causes of AKI.

Intermittent Hemodialysis

Intermittent HD is still the mainstay of dialysis for AKI in older children and is performed in adult centers in many countries. Its main advantage is the rapid removal of uremic toxins and fluid volume. Therefore it is indicated in the emergency treatment of hyperkalemia, lactic acidosis and myoglobinuria. However, HD in young children is notoriously difficult in view of the smaller blood volumes. This is especially accentuated in the critically ill child, where inotropes are usually required to support the systemic blood pressure. Moreover, these children often have acute respiratory distress syndrome, and are hypoxemic, resulting in hemodynamic instability during intermittent HD. Rapid HD may also result in dialysis dysequilibrium. In view of the difficulties of HD in the critically ill pediatric patient, this dialytic modality is generally limited to children with "uncomplicated" AKI.

Continuous Renal Replacement Therapy (CRRT)

This decade has seen much enthusiasm for the use of CRRT for the critically ill child. CRRT encompasses a wide range of strategies, which include slow continuous ultrafiltration, continuous venovenous hemofiltration, continuous venovenous hemodialysis, to a combination of continuous venovenous hemodiafiltration. There are many advantages of continuous modalities of dialysis in the critically ill patient. Despite removal of large volumes of fluid by ultrafiltration, the critically ill patient on CRRT remains hemodynamically stable. In a large randomized controlled trial comparing CRRT with intermittent HD in critically ill patients, CRRT resulted in more efficacious solute clearances. Studies have also shown that inflammatory mediators, cytokines, and toxins may be removed by continuous hemofiltration in patients with sepsis, not only by adsorption to certain hemofilter membranes, but also through the ultrafiltrate, providing a rationale for the use of high volume ultrafiltration.

Some of the disadvantages of CRRT include bleeding complications following the use of heparin. Citrate anticoagulation is now widely used to circumvent this problem. Other problems include temperature instability, requiring warming of either the dialysate or blood

returning to the patient. Small molecular sized nutrients such as oligosaccharides, peptides, and amino acids, and electrolytes such as phosphate and magnesium can be lost through the hemofilter, and therefore need to be replaced. The bradykinin release syndrome is an important complication seen specifically with the commonly used polyacrylonitrile (AN69) membranes. Blood contact with the AN69 membrane results in generation of bradykinin, especially in the presence of acidosis. Hence priming of the dialysis lines with banked blood should be avoided.

Prognosis

The prognosis of AKI is highly dependent on the underlying etiology. Mortality is high in critically ill children with multiorgan failure. Recovery from intrinsic renal disease is also highly dependent on the underlying etiology. Children with nephrotoxic AKI and hypoxic/ischemic AKI usually recover normal renal function; however, those who have suffered substantial nephron loss, such as in hemolytic-uremic syndrome or rapidly progressive glomerulonephritis, may progress to chronic kidney disease. Therefore these children need to be followed up in the long-term for blood pressure monitoring and development of proteinuria.

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313 Chronic Kidney Disease (CKD)

Lesley Rees

Definition

Chronic kidney disease (CKD) means any abnormality of the renal parenchyma that will not recover. A progressive decline in kidney function may occur, but only if both kidneys are abnormal.

Classification

Staging of CKD

CKD is divided into stages according to its severity (*Table 313.1*). As renal function declines, uremia, electrolyte disturbances and anemia become more common, and lead to uremic complications such as lethargy and poor appetite, sodium retention and hypertension, acidosis, bone disease and vascular calcification. By CKD stage 5, renal replacement therapy (RRT) may become necessary, but some children who maintain good urine output may manage without for many years with a glomerular filtration rate (GFR) as low as this. Renal function may remain stable or even show some improvement in infancy and early childhood. Decline in renal function occurs thereafter, particularly, in the peripubertal years.

Etiology

The commonest cause of CKD in childhood is renal dysplasia, representing up to 70% of cases. Renal dysplasia is due to abnormal renal development, either because of intra uterine obstruction or in association with vesicoureteric reflux, syndromes, genetic defects such as branchio-oto-renal syndrome or renal coloboma syndrome, or causes as yet undefined. In boys, most cases are due to a posterior urethral valve. Abnormal urinary tract drainage will predispose to urinary tract infection (UTI), which can cause further renal damage.

Renal cystic diseases are the second commonest cause. Autosomal recessive polycystic kidney disease (ARPKD) is often diagnosed antenatally or is recognized in infancy when palpable kidneys, hepatosplenomegaly and hypertension are found. Autosomal dominant PKD (ADPKD) rarely causes problems in childhood, unless there is disruption of TSC2 and the adjacent PKD1 gene (contiguous gene syndrome), as in 2% of patients with tuberose sclerosis. Patients with Bardet–Biedel Syndrome may have cystic kidney disease and there may be (but not always) cysts with nephronophthisis. Nephronophthisis may occur in isolation or in association with retinitis pigmentosa (Senior-Loken Syndrome). Glomerulocystic disease is becoming a more frequent diagnosis with the identification of the renal cysts and diabetes syndrome due to HNF1β gene mutations.

The next commonest causes are the nephrotic syndromes (NS), including congenital NS, which presents in infancy, and focal segmental glomerulosclerosis (FSGS). FSGS is a unifying term used to describe steroid resistant NS with a particular histological appearance that is due to different genetic abnormalities. Another NS, membranoproliferative glomerulonephritis, is a less common cause of CKD.

Other causes include renal vascular events (particularly neonatal arterial and venous thromboses), atypical Hemolytic Uremic Syndrome (HUS), renal stone diseases, subsequent to acute kidney injury (AKI) due to any cause (including rapidly progressive glomerulonephritis, HUS, dehydration with cortical necrosis), hereditary nephropathies, systemic diseases such as SLE and the vasculitides, renal diseases that occur in association with syndromes, and in some patients the cause is not known. As time goes by, more and more genes that cause CKD are being identified.

Epidemiology

Although the identification of CKD in children has improved due to antenatal screening programs, the true incidence is unknown and may be higher than suspected. Studies suggest an annual acceptance rate for new pediatric patients with a GFR < 75 ml/min.1.73 m^2 of around 12 cases per million child population. It is easier to be more precise about the incidence of children needing to enter RRT programs because such data are collected by national registries, being 9 per million child population per year in the UK, 10 in Australia and New Zealand, and 15 in the USA.

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Table 313.1
Staging of CKD

Stage	GFR ml/min/1.73 m^2	Features
1	>90	Renal parenchymal disease present
2	60–90	Usually no symptoms but may develop biochemical abnormalities at the lower end of the GFR range
3	30–60	Biochemical abnormalities and anemia and in addition may develop poor growth and appetite
4	15–30	Symptoms more severe
5	<15	Renal replacement therapy may be required

Pathogenesis

Although the etiologies of CKD are multiple, progressive destruction of renal tissue occurs through a common pathway regardless of the cause. Intrarenal pathology leads to abnormal hemodynamics, chronic hypoxia, inflammation, cellular dysfunction and the activation of fibrogenic biochemical pathways. The end result is the replacement of normal structures with extracellular matrix, culminating in fibrosis.

Clinical Manifestations

Presentation of CKD: Symptoms and Signs

The commonest way for CKD to present is during antenatal scanning. Around 50% of children are diagnosed antenatally; some can be missed if there has not been a third trimester ultrasound scan. The next commonest way is with a complicating episode of AKI, which can be precipitated by infection or dehydration. Children may also present with nonspecific symptoms, such as anorexia and lethargy, which may be severe enough to cause failure to grow normally. Diseases that predominantly affect the renal tubular concentrating mechanisms, such as juvenile nephronophthisis or renal dysplasia, may present with polydipsia and polyuria. Less commonly, children may present with hypertension or with an incidental finding of proteinuria, or to orthopedic surgeons with bony abnormalities such as knock knees or bow legs. They may be detected by screening because of another affected family member.

Case No 1

A male infant was diagnosed antenatally with one bright kidney and one hydronephrotic kidney with oligohydramnios. He was delivered prematurely due to the spontaneous onset of labor and developed respiratory distress and a pneumothorax. Subsequent imaging showed a posterior urethral valve, which was ablated urethrally. He had bilateral renal dysplasia. His renal function progressively declined throughout childhood and declined rapidly during puberty, so that he needed a renal transplant at the age of 16.

Diagnosis

Investigations

Assessment of Renal Function

The easiest way to assess renal function on a day-to-day basis is to use the plasma creatinine. Creatinine is produced at a constant rate from the breakdown of creatine phosphate from muscle and is excreted by filtration without reabsorption; therefore, it is a good representation of renal function. There are pitfalls in the interpretation of the plasma creatinine: first, plasma levels do not rise until renal function has halved; second, as creatinine levels increase progressively with muscle bulk and, therefore growth, the level has to be interpreted according to age; third, levels will be lower than expected in a child who is malnourished. This means that formulae used to calculate the GFR may give results that are higher than the true result. One such formula is shown below:

$$\text{GFR} = \frac{40 \times \text{height (cm)}}{\text{creatinine } (\mu\text{mol/l})}$$

GFR can be more accurately assessed by measuring the rate of disappearance from the plasma of a substance that is freely filtered by the glomerulus but not reabsorbed by the tubules, but in practice this is rarely needed. It can also be calculated by measuring the clearance of creatinine, but as a timed urine collection is needed for this, it is not often undertaken in childhood.

Investigation of the Cause of CKD; Differential Diagnosis

The History and Examination

It is always important to find out the results of antenatal scans, amniotic fluid status (as this represents fetal urine

production), and the neonatal and family history. The physical examination should include a general examination, but should focus on growth, the BP, and look for evidence of bone disease.

Investigations

There are two investigations that are crucial for the diagnosis of the cause of CKD: ultrasound (US) and urine stick testing for protein. The appearances of the kidneys (i.e., renal sizes, the presence of cysts, and evidence of obstruction or calculi) on US (*Table 313.2*) will then guide further more selective investigations. Additional imaging may be necessary if a structural or cystic lesion or calculi are the cause and will depend on the US appearances.

Urine stick testing can also be very helpful: heavy proteinuria suggests a nephrotic syndrome; proteinuria and hematuria suggest a glomerulonephritis or familial nephropathy; and no proteinuria may be present with cystic diseases and dysplasias. However, proteinuria may result from any cause due to hyperfiltration, when reduced nephron number leads to increased glomerular pressure within the remaining glomeruli. Proteinuria may be tubular in cases of tubulopathy, when urinary retinol binding protein and N-acetyl glucosaminidase levels will be raised.

Complement levels, anti-DNA antibodies, anti-neutrophil cytoplasmic antibodies and IgA levels should be measured if glomerulonephritis is suspected; plasma and urine calcium, oxalate and purines if calculi; and urine pH and white cell cystine if a tubulopathy is suspected. Genetic analysis may be available for some conditions. Renal biopsy may be necessary if the cause of CKD remains unclear.

Case No 2

A 12 year old boy presented with a 3 month history of bone pain, loss of appetite, lethargy, and vomiting. He had a long history of polydipsia and polyuria. His younger brother was taller than him. On examination he was on the second centile for height, he was pale, his BP was normal, and there were no other abnormalities. Investigations showed his hemoglobin to be 8 gm/dl, creatinine 1,200 mcmol/l, potassium normal, calcium low, and phosphate high. He had no proteinuria. His kidneys were normal sized and bright with poor cortico-medullary differentiation and some small cysts at the corticomedullary junction. Nephronophthisis was suspected and this was confirmed by DNA analysis for the presence of the commonest gene for this condition, which has been designated NPHP1, rendering renal biopsy unnecessary.

Measurements to be Made at Each Clinic Visit

Height and weight, and head circumference in young children and pubertal stage in older ones, should be plotted on a growth chart and BP checked at each clinic visit. Early morning urine should be tested for albumin to creatinine ratio. Routine blood tests include a full blood count, urea, electrolytes, bicarbonate, creatinine, calcium,

Table 313.2
Appearance of kidneys on renal ultrasound

Cystic	Small	Normal sized	Obstruction	Calculi
Dysplasia	Dysplasia ± vesico-ureteric reflux	Glomerulo-nephritides	Dysplasia with posterior urethral valves	Recurrent UTIs ± obstruction/reflux
Autosomal recessive polycystic kidney disease	Vascular insults (venous or arterial)	Familial nephropathies	Dysplasia with VUJ obstruction	Calcium disorders
Autosomal dominant polycystic kidney disease	All causes may result in small kidneys by Stage 5 CKD	Nephrotic syndromes	Dysplasia with PUJ obstruction	Hyperoxaluria
Tuberose Sclerosis		Nephronophthisis (may be cystic)	Neuropathic bladder	Purine disorders
Glomerulocystic diseases		Tubulopathies		Cystine

phosphate, alkaline phosphatase, intact PTH, and albumin. Fasting HDL and LDL cholesterol and triglycerides and iron status may be checked less often.

One very important aspect of the management of the child with CKD is care of the blood vessels. The use of antecubital veins should be avoided when possible as they will be needed in the future for fistula formation. Similarly damage resulting in stenosis of the subclavian veins would preclude creation of a fistula in that arm.

Treatment

Prevention of Progression of CKD

The first aim of management of CKD is to reduce its progression as far as is possible. Progression can be attenuated by the maintenance of the BP within the normal range for age and height, and by the use of an ACE inhibitor (e.g., ramipril) ± an AT1 receptor blocker (e.g., losartan) to dilate the glomerular afferent arteriole, reduce intraglomerular pressure and, therefore, reduce proteinuria, which is thought to contribute to the development of fibrosis. Dyslipidemia may play a role in the progression of CKD. Increased LDL cholesterol is a particular problem for children with nephrotic syndrome. Hypertriglyceridemia and abnormal apolipoprotein metabolism is a feature of CKD. Dietary intervention may be necessary, and some children (particularly those with nephrotic syndrome) may need lipid lowering agents.

Growth, Nutrition, and Electrolytes

Growth retardation occurs in up to 50% of children with CKD stages 3–5. Children with congenital nephropathies are particularly severely affected. This is because growth in the first 2 years of life is as high as 25 cm/year at birth, falling to 18 cm/year at 1 year and 10 cm/year at the age of 2, by which time half of the final adult height has been achieved. It is, therefore, possible to lose considerable height potential at that age, which can be as much as 2SD in the first 6 months of life in infants with severe CKD. The calorie and protein requirement is extremely high during this period of rapid growth, and an adequate nutritional intake can be very difficult to maintain. After this age, when the role of growth hormone (GH) becomes more important, the rate of growth can be normal. Growth may also be adversely affected at the time of puberty, which may be delayed, with an attenuated pubertal growth spurt. Growth retardation increases with the severity of CKD. However, it has to be remembered that there are children with CKD who have associated syndromes that in themselves affect growth. Successful renal transplantation can normalize growth in some children, but may be counteracted by corticosteroid therapy used as immunosuppression and poor transplant function.

There are many different causes for poor nutritional intake: CKD is characterized by a predisposition to anorexia and vomiting. Poor appetite may be due to abnormal taste sensation, the requirement for multiple medications, the preference for water in the polyuric child, and elevated circulating cytokines such as leptin, TNF-α and IL-1 and -6, which act through the hypothalamus to affect appetite and satiety. Vomiting may result from gastroesophageal reflux and delayed gastric emptying in association with increased polypeptide hormones, and may be so profound that as much as one third of feed can be lost. Other factors that contribute to insufficient nutrition include episodes of fasting surrounding surgical procedures and episodes of sepsis, which may have a significant effect on growth, principally in the infant. Importantly, many children with severe CKD have associated co-morbidities that influence feeding and growth in their own right.

The child on dialysis has even more issues that affect their nutritional intake. They are likely to be on a fluid restriction, appetite may be affected by the presence of a full abdomen and constipation in patients on peritoneal dialysis (PD), and there may be considerable losses of protein in the dialysate in PD and amino-acids in hemodialysis (HD).

Ensuring adequate nutrition is one of the most important aspects of care of the child with CKD. As well as its obvious importance in promoting adequate growth, nutritional manipulation can control symptoms and prevent complications, particularly uremia and bone disease, such that it is possible to delay the need for dialysis.

Case No 3

A boy was referred at age 2 with prune belly and CKD stage 5 (creatinine 400 mcmol/l). He was lethargic and refusing food and was on the second centile for height. A gastrostomy was placed and provision of adequate calories and protein allowed catch-up growth to the 25th centile. He continued to grow along that centile and symptomatically improved. Dialysis was not needed until nearly 6 years of age despite a creatinine in the high 500s mcmol/l.

The type of diet recommended depends on the cause and severity of CKD and mode of RRT. If dietary intake

is inadequate, the first thing is to try an oral dietary supplement in addition to a normal diet. There are various types of supplements, with different ratios of calories and protein. In the young child with vomiting it is possible to increase the feed concentration and, therefore, decrease the feed volume. However, the rate-limiting step for this is that vomiting may worsen and diarrhea can occur with increasing feed density. Medications such as prokinetic agents (domperidone), H2-receptor antagonists (ranitidine), proton pump inhibitors (lansoprazole), and 5HT3 receptor antagonists (ondansetron) may be of benefit. The stress on the family of trying to feed an anorexic child cannot be overestimated, and this, along with a declining rate of growth, can only be resolved by the use of enteral feeding.

A nasogastric tube is acceptable for a short time, and is the method of choice in the infant weighing <4 kg, but most families prefer the placement of a gastrostomy as it is hidden under clothing. Enteral feeding via any route, but particularly gastrostomy, is associated with decreased vomiting and improved appetite, nutrition, and growth. The tube has the additional benefit of its potential use in the administration of medications, and the large fluid volumes that may be prescribed post transplant.

Overall, calorie and protein allowances should be the same as for the normal child. However, as CKD progresses it may become necessary to ensure that the protein intake is not above requirements, aiming to keep the serum albumin in the normal range with a plasma urea below 20 mmol/l. Above this level of urea, nausea, lethargy, itching, and worsening anemia may occur. The child on PD absorbs up to 12 kcal/kg/day from the dialysate, but may lose protein in the dialysate effluent. The child on HD may lose amino acids in the same way. Supplements of protein of up to 50% of the dietary requirements may, therefore, be needed in very young children on PD, who have the highest protein losses.

Structural renal diseases have a predominant effect on the renal tubule, so that reabsorption of sodium bicarbonate and water from the glomerular filtrate is inadequate. Therefore, these children are often polyuric and polydipsic, and need salt and bicarbonate supplementation and free access to water. However, children with CKD due to predominantly glomerular disease may retain salt and develop hypertension. Such children should be managed with a salt restricted diet and medications as necessary. A low potassium diet is usually only necessary at CKD stage 5.

Recombinant human growth hormone is effective in some children with CKD, and can be considered when growth has failed to respond to correction of inadequate diet and biochemical abnormalities and optimization of dialysis, and, for children on steroid therapy, when the dose of steroids has been reduced to the lowest possible.

Anemia

The anemia of CKD is normochromic and normocytic, with a low reticulocyte count. It is important to exclude iron, vitamin B12, or folate deficiency, which may play a role due to the anorexia of CKD. However, when the GFR falls below 35 ml/min/1.73 m^2, decreased production of erythropoietin is common and responds well to subcutaneous injection of this hormone, which can usually be administered weekly or even less often with some newer erythropoietin preparations. Uremia itself may cause decreased red cell survival and bone marrow inhibition. Bone marrow fibrosis occurs with severe hyperparathyroidism (osteitis fibrosa). Blood loss occurs during HD and the anticoagulation required during the HD process can result in chronic blood loss from the gastro-intestinal tract.

Chronic Kidney Disease – Mineral and Bone Disorder (CKD-MBD)

Effects of CKD on Mineral Metabolism

CKD leads to abnormal calcium, phosphate, parathyroid hormone (PTH), and vitamin D metabolism resulting not only in disordered bone turnover, mineralization and growth, but also cardiovascular and soft tissue calcification. For this reason, the term CKD-MBD is now used to encompass all these abnormalities, and the term renal osteodystrophy should be reserved for the bony abnormalities that are seen on histology.

Calcium absorption and, therefore, plasma calcium levels are usually low in untreated CKD. Calcium absorption is under the control of vitamin D, levels of which are also usually low in CKD. This is for two reasons. First, there is deficiency of the substrate 25(OH)D due to poor appetite and protein and dairy food restriction, reduced production in the skin due to reduced outdoor activity and, therefore, sunlight exposure, and loss of vitamin D binding protein in the urine. Second, there is decreased 1α hydroxylation in the kidney of 25(OH)D to the active form of vitamin D, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Another contributory factor is that dietary calcium is reduced for similar reasons to vitamin D.

Conversely, it would be expected that phosphate levels would be high, due to decreased renal phosphate excretion. Although this is the case as CKD progresses, in early

CKD normophosphatemia is maintained. This is because the high phosphate load stimulates the production of fibroblast growth factor 23 (FGF23), a phosphaturic hormone produced by the osteocyte. FGF23 induces a negative phosphate balance in two ways: it decreases renal tubular phosphate reabsorption, and decreases the production of 1,25 $(OH)_2D$; 1,25$(OH)_2D$ increases gut phosphate absorption as well as calcium.

As CKD progresses, FGF23 is no longer able to prevent hyperphosphatemia, so phosphate levels rise. This, along with low plasma calcium and 1,25$(OH)_2D$ levels, stimulate PTH secretion through the calcium sensing receptors and vitamin D receptors in the parathyroid gland. All the actions of PTH are to restore the plasma calcium to normal. It effects this by mobilizing calcium from bone, increasing tubular reabsorption of calcium, increasing hydroxylation of 25(OH)D, thereby promoting gut absorption of calcium and decreasing tubular reabsorption of phosphate.

The Role of PTH in CKD-MBD

PTH is thought to be the main player in the evolution of CKD-MBD: persistent stimulation of the parathyroid glands leads to hypertrophy, progressing to nodular hyperplasia, and culminating in the need for parathyroidectomy. The logic, therefore, has to be that prevention of the process starting must be beneficial.

PTH and Renal Osteodystrophy

The effect of PTH on the skeleton is to increase the activity of osteoclasts and osteoblasts such that high PTH levels cause high turnover (osteitis fibrosa), and low levels low turnover (adynamic) bone disease. Both types lead to bone pain, fractures, and growth problems. They can also lead to cardiovascular and soft tissue calcification because of hypercalcemia and hyperphosphatemia: in high turnover bone disease, calcium and phosphate are removed from bone into the circulation, and in low turnover, bone is unable to buffer changes in plasma calcium and phosphate.

Aims of Management of CKD-MBD

The aim of management of CKD-MBD is to maintain normal bone turnover and, therefore, prevent symptoms of bone pain and fractures, allow normal growth and prevent vascular disease and soft tissue calcification. It is important to intervene early in the course of CKD to prevent escape of the parathyroid glands from normal control mechanisms.

Phosphate Control

Plasma phosphate levels fall progressively from birth to the age of 3 and then remain stable. Maintenance of a normal age-related plasma phosphate is crucial to the prevention of hyperparathyroidism. Dietary phosphate is principally in protein containing foods, and dairy products in particular, and these foods should be restricted if the phosphate is above normal.

Reduction in phosphate load results in a reduction in FGF23 and an increase in 1,25$(OH)_2D$, which increases calcium absorption and plasma calcium and, therefore, suppresses PTH. However, 1,25$(OH)_2D$ increases phosphate absorption to as much as 80–90% of dietary intake, so it is usually the case that phosphate binders, which latch on to phosphate in the gut and prevent its absorption, are needed. The principal phosphate binders contain calcium Calcium carbonate is the cheapest and most used, followed by calcium acetate. If required in large quantities such binders present a large calcium load; calcium free phosphate binders are available if there are problems with hypercalcemia. Phosphate, being predominantly intracellular, is poorly removed by dialysis. It is one of the most toxic molecules that circulates in excess in CKD, and plays an important role in vascular calcification. Maintenance of the plasma phosphate well below the upper limit of the age-related normal range is, therefore, crucial.

Calcium

The requirement for calcium varies with age, from 0.4 to 1 g daily, and is relatively higher when growth is fastest, that is, in the first 2 years of life. Plasma calcium is, like phosphate, age dependent, falling over the first 3–4 years of life. Interpretation of the plasma calcium requires adjustment for the albumin and pH, or ionized calcium can be used.

Vitamin D

The benefits of vitamin D extend beyond its effect on bone disease, as it has anti-inflammatory properties and beneficial effects on the cardiovascular system. Conversely, this has to be balanced against the risks of hypercalcemia and its depressive effect on the chondrocyte. If it is possible to measure 25(OH)D, and this proves to be low, ergo, or cholecalciferol should be prescribed. If the PTH remains high, the smallest possible dose of 1,25$(OH)_2D$ to suppress the PTH can then be added. If hypercalcemia develops, the 1,25$(OH)_2D$ should be stopped.

PTH

Guidelines for the management of CKD-MBD hinge on the need to keep the PTH level within a fixed range, which is one that maintains normal bone turnover. European guidelines recommend maintaining the PTH in the normal range until dialysis, when up to 3 × the upper limit of normal (ULN) is acceptable. KDOQI recommends the normal range until CKD 4, when 1–2 × ULN is recommended and then 3–5 × ULN for patients on dialysis, in order to allow for skeletal resistance to PTH as CKD evolves. These guidelines were written as the understanding of the interplay with cardiovascular disease was emerging. They are predominantly opinion-based as they are extrapolated from adult studies and a small number of pediatric studies, and are largely out-of-date. When hyperparathyroidism becomes tertiary, with persistent hypercalcemia and radiological changes, new therapies that block the calcium sensing receptor are beneficial in adults and have been successfully used in children. Severe, uncontrolled hyperparathyroidism may necessitate parathyroidectomies.

Radiological Changes

Radiological changes of CKD-MBD include rickets, hyperparathyroidism, and osteosclerosis. Features include periosteal erosions and elevation and widening of the zone of provisional calcification with a coarse trabecular pattern. Vertebral collapse, alternating with areas of osteosclerosis, gives the appearance called rugger jersey spine. Radiological changes occur late and may be normal even with moderate hyperparathyroidism.

Vascular Calcification

Vascular calcification has been demonstrated in children on dialysis. Disorders of phosphate, calcium, PTH, and vitamin D have all been shown to contribute. Large epidemiological studies in adults have shown that mortality rises exponentially as the plasma phosphate rises; the risk of death increases by 6% for every 0.3 mmol/l rise in plasma phosphate. Mortality also increases exponentially as the calcium × phosphate product rises above 5 $mmol^2/l^2$. PTH itself is a risk actor for vascular disease in several studies of children on dialysis. The most risk is when the level is >2 × ULN. Vitamin D has a bimodal effect, such that vitamin D levels above and below the normal range are associated with vascular calcification.

Prognosis

The diagnosis of CKD implies progressive decline in renal function, but whether mild impairment progresses, is unknown. Studies have shown that the probability of kidney survival at 20 years of age with a diagnosis of a GFR in early childhood of 51–75 ml/min.1.73 m^2 is 63%, 30% in those with a GFR of 25–50, and 3% in those with a GFR <25 mL/min/1.73 m^2. The diagnosis of CKD has implications for survival: the overall mortality rate has been estimated to be 1.4% for children before RRT is needed, but much higher for children on dialysis, when lifespan is reduced by 40–60 years.

Prevention

Prevention of CKD is the Holy Grail for the nephrologist. At present, however, there are only a few situations where prevention is possible, such as relief of urinary tract obstruction or prevention of infection. It is important to identify children with CKD as early as possible because the mainstay of treatment is to attenuate the rate of progression of CKD by normalization of BP and reduction of proteinuria. Careful attention to nutrition, electrolytes, and anemia is essential to maintain well-being and growth.

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314 Dialysis in Children

Bradley A. Warady

Incidence, Prevalence and Causes of End-Stage Renal Disease in Children

End-stage renal disease (ESRD) is an uncommon disorder in children, with an incidence rate in the USA of approximately 14 patients per million children of similar age. The incidence varies within the pediatric population with a rate of 29 per million for children 15–19 years, in contrast to a rate of 9 per million for children 0–4 years. The incidence in children is also significantly different from that which is experienced by adults in whom rates of 127 per million and 625 per million characterize the 20–44 and 45–64 year age groups, respectively. Similarly, pediatric patients only account for a small percentage of the total dialysis population. In 2007, of a total of 354,753 patients on dialysis in the USA, only 2,177 (0.6%) were younger than 20 years (*Table 314.1*). Approximately one-half of children who initiate chronic dialysis have a congenital or hereditary disorder, such as aplastic/hypoplastic/dysplastic kidneys or obstructive uropathy (e.g., posterior urethral valves), whereas the remainder have an acquired cause of ESRD such as focal segmental glomerulosclerosis (FSGS). In all cases, the development of ESRD, as defined by an estimated glomerular filtration rate (eGFR) of 8 mL/min/1.73 m^2 or the development of treatment-resistant signs and symptoms of uremia (e.g., lethargy, recurrent emesis, poor growth, anemia, elevated blood pressure, acidosis, fluid overload, poor school performance), mandate the provision of renal replacement therapy in the form of dialysis or transplantation. Although kidney transplantation is the nearly universal goal for children who develop ESRD, approximately 75% of patients initially receive chronic peritoneal dialysis (CPD), hemodialysis (HD), or both, prior to receipt of a kidney transplant.

Choice of Dialysis Modality in Children

The percentage of children that receive one form of chronic dialysis versus the other varies globally. For instance, nearly 80% of prevalent pediatric (0–19 years) dialysis patients in Russia receive HD, in contrast to Spain where almost 60% receive CPD. The choice is most often made based on patient age and size, dialysis center experience and philosophy, family preference, assessment of whether the individual patient and family can be adherent with a home dialysis regimen, and the availability of the specific modality. Careful evaluation of the family's social, psychological, and economic background, ideally by a multiprofessional team including the family physician and nephrologist, dialysis nurse, psychologist, and social worker, is mandatory if a fully informed decision regarding modality selection is to be made. The quality of life (QOL) of the patient and family and the potential impact of the dialysis modality on this parameter also assumes great importance in the decision process. In all cases, HD is the modality of choice when the family is unwilling or unable to conduct dialysis at home. Although few in number, absolute contraindications to CPD include the presence of the following:

- Omphalocele
- Gastroschisis
- Bladder extrophy
- Diaphragmatic hernia
- Obliterated peritoneal cavity and peritoneal membrane failure

At present, there is no clear evidence that one form of dialysis is preferable over another for most children with ESRD. In all cases, patients and families should understand that, at some point during the clinical management with dialysis, a change in modality may be necessary as a result of compromised efficacy and/or the development of complications associated with their current therapy.

Chronic Peritoneal Dialysis

Peritoneal dialysis is frequently the preferred initial dialysis modality in pediatric programs, primarily for psychosocial reasons. CPD, which is characteristically performed at home following the training of patients/parents/caregivers by dialysis staff, permits flexibility of the treatment schedule and normal attendance at school, does not

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Table 314.1
Prevalent dialysis patients (Data from US patients in 2007)

Age	HD	PD
0–19	1,253	860
20–44	46,105	5,842
45–64	133,637	11,510
65–74	74,674	4,748
75+	72,084	3,122

require venipuncture during the dialysis procedure, and allows for a reasonable fluid intake because dialysis is conducted on a daily basis.

Peritoneal dialysis makes use of the peritoneal membrane as a natural dialyzing membrane. The dialysis solution is instilled and dwells within the peritoneal cavity, during which time bloodstream derived solutes (e.g., urea, creatinine) move down a concentration (electrochemical) gradient based on the principle of diffusion. At the same time, the osmotic component of the dialysis solution, typically glucose, causes fluids to move from blood to dialysate (e.g., ultrafiltration) as a result of the osmotic gradient. Peritoneal dialysis solutions are commercially available in standard dextrose concentrations of 1.5%, 2.5%, and 4.25%. The inflow, dwell, and drainage of dialysate characterize a single dialysis cycle or exchange.

A reliable peritoneal catheter is the cornerstone of successful CPD. Most long-term catheters are constructed of either silastic or polyurethane. The Tenckhoff catheter is the one most commonly used and, like all CPD catheters, is comprised of an intraperitoneal and an extraperitoneal portion. The former contains holes through which the dialysis solution flows into the peritoneal cavity and then subsequently drains. A portion of the extraperitoneal segment of the catheter is tunneled subcutaneously within the abdominal wall and has one or two Dacron cuffs that primarily fix the catheter's position at its exit site.

The CPD prescription takes into account the amount and dextrose concentration of the dialysis solution to be used for each cycle and the length of the cycle. In part, the prescribed cycle length is determined by the time it takes for solute and osmotic equilibration to take place between plasma and dialysate such that the infusion of fresh dialysis solution would be advantageous. The speed with which solutes and water move across the peritoneal membrane (e.g., transport capacity) can be determined clinically by performance of the peritoneal equilibration test (PET). Continuous ambulatory peritoneal dialysis (CAPD) is a manual form of CPD in which the patient or caregiver attaches and instills a bag of sterile dialysis solution into the peritoneal cavity four times per 24 h, with each of the three daytime exchanges lasting approximately 5 h and the nighttime exchange, 9 h. In contrast, the most frequently used CPD modality for children in many countries, automated peritoneal dialysis (APD), uses an automated device which can measure, heat, deliver, drain, remeasure, and discard dialysate in patterns determined by the prescribing team. The greatest percentage of children receiving APD utilize a regimen consisting of 6–12 exchanges over 8 to 10 h per night with a daytime dwell consisting of approximately 50% of the nocturnal exchange volume. Guidelines for the performance of CPD in children recommend an individual exchange volume of 1,000–1,200 mL/m^2 for patients >2 years of age; younger patients should be prescribed a lower initial volume (600–800 mL/m^2) to promote tolerance. The efficacy or "adequacy" of CPD has historically been characterized by the measurement of small solute clearance, most commonly in terms of the Kt/V_{urea}. However, recently published guidelines by the National Kidney Foundation emphasize the clinical status of the patient as an important qualitative target and state that "adequate dialysis is likely provided if the patient's clinical status is characterized by adequate growth, blood pressure control, and nutritional status; avoidance of hypovolemia (or hypervolemia) and sodium depletion; and adequate psychomotor development." Factors that might contribute to inadequate CPD include:

- Loss of residual native kidney function
- Reduced peritoneal surface area caused by intra-abdominal adhesions
- Loss of membrane solute transport capacity/ultrafiltration capacity because of peritonitis
- Noncompliance with CPD prescription
- Poorly functioning PD catheter

Complications of CPD

The single most common complication that occurs in children maintained on CPD is peritonitis. Peritonitis contributes to significant morbidity and can lead to irreversible technique failure. The frequency of peritonitis in children regularly exceeds that in adults. The most recent annual report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) includes information on 3,999 episodes of peritonitis in 6,008 years of follow-up for an annualized rate of 0.67 (one episode every 18.0 months). Young patient age and catheter

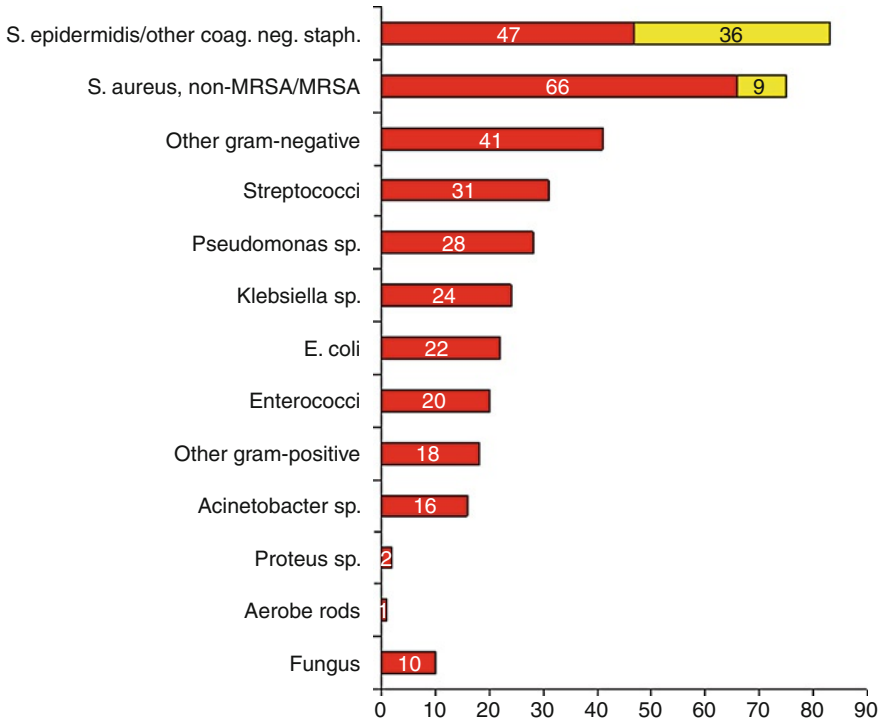

Figure 314.1
Distribution of peritonitis (n = 350) causative organisms in children receiving peritoneal dialysis

exit-site and tunnel infections, often secondary to *Staphylococcus* or *Pseudomonas*, are important risk factors for peritonitis. Approximately 50% of peritonitis episodes are caused by Gram-positive bacteria, particularly *Staphylococcus epidermidis* and *Staphylococcus aureus*, 20–30% by Gram-negative organisms, with the cultures remaining negative in a substantial percentage (<20%) of episodes (*Fig. 314.1*). Peritoneal dialysis patients presenting with abdominal pain and/or cloudy drained dialysis fluid (effluent) should be presumed to have peritonitis and should be evaluated for this infection. The diagnosis is confirmed when the effluent white blood cell (WBC) count is $>100/mm^3$ and at least 50% of the WBCs are polymorphonuclear leukocytes. When peritonitis is suspected and following collection of dialysate effluent for culture and cell count, empiric antibiotic therapy should be administered through the intraperitoneal route and consist of a combination of a first generation cephalosporin or a glycopeptide, with a third-generation cephalosporin or an aminoglycoside. To minimize the risk for antibiotic-related toxicity associated with the use of either vancomycin or an aminoglycoside, maintenance antibiotic therapy with alternative choices should be instituted as soon as the antibiotic susceptibilities are known.

Chronic Hemodialysis

Hemodialysis is currently the dialysis modality used by nearly 60% of prevalent pediatric patients in the USA and in almost all cases, is performed in a dialysis center. A HD system consists of a blood circuit, a dialysate circuit, and a dialyzer. Blood is pumped from the patient's vascular access to the dialyzer (the "arterial segment") and uremic toxins and water are removed. A separate pump delivers anticoagulants to prevent clotting within the extracorporeal circuit. The clearance of solutes is a function of the blood and dialysate flow rates and the permeability of the dialyzer's membrane to the solutes as clearance occurs by diffusion down a concentration gradient between plasma and dialysate. Ultrafiltration occurs because a transmembrane hydrostatic gradient is created from the blood to the dialysate compartment. The dialyzed blood is subsequently recirculated to the patient through the "venous segment" of the circuit. Throughout this process, ultrafiltration control systems and monitors that evaluate pressures within the blood lines and airleaks are engaged and alert the dialysis staff if adjustments are needed.

The vascular access is a crucial aspect of the blood circuit as the efficiency of HD is in large part dependent

on access function and blood delivery. HD access is divided into two categories: permanent access in the form of an arteriovenous fistula (AVF) or arteriovenous graft (AVG) and semipermanent access in the form of catheters with a subcutaneous cuff. Catheters currently serve as the most common form of access for children receiving HD, being present in more than 60% of patients at dialysis initiation. While these devices allow for the blood flow necessary for HD in patients who have relatively small vessels that do not permit the surgical connection between the native artery and vein necessary for an AVF or AVG, catheters have a much greater complication rate than either of the permanent accesses. For this reason, it is recommended that children more than 20 kg who are expected to receive HD for more than 1 year should be evaluated for permanent vascular access placement.

The HD prescription incorporates the size of the dialyzer to be used, the blood and dialysate flow rates and the length of the treatment. To prevent hemodynamic instability, the extracorporeal circuit should not exceed 10% of the patient's blood volume, a requirement that often dictates dialyzer size. Blood flow rates are generally less than 400 mL/min/1.73 m^2 to minimize the risk for cardiovascular compromise and the dialysate rate is >1.5 times the blood flow rate to prevent dialysate saturation and the associated limitation of clearance. In most cases, HD is provided three times weekly, with each session lasting 3.5–4 h. Recent positive experiences with frequent HD (e.g., >5 days weekly) suggest that this approach may become more common. The urea reduction ratio is an approximation of the fraction of blood urea nitrogen (BUN) removed in a single dialysis session and is a method of quantitating HD adequacy. It is determined in the following manner:

$$\text{URR} = (\text{preBUN} - \text{postBUN})/\text{preBUN} \times 100\%$$

Although simplistic, the URR has a number of shortcomings: most importantly, the inability to provide any information about a patient's nutritional status. As a result, Kt/V has become the preferred method for measuring delivered dialysis as it more accurately reflects urea removal than does URR, and it provides information on patient nutrition by allowing for the calculation of the protein catabolic rate. Like in adults, the Kt/V in children should be >1.2 per dialysis session. Factors that might contribute to inadequate HD include:

- Underprescription
- Inadequate vascular access
- Shortened treatment time
- Dialyzer clotting

Complications of HD

Hypotension is the most common acute complication of HD and often arises as a result of the removal of large volumes of fluid by ultrafiltration and depletion of the intravascular volume during the dialysis session. At times, this may be accompanied by muscle cramps, nausea, dizziness, or headache. Noninvasive monitoring of the hematocrit within the dialysis circuit may help "predict" this complication since changes in hematocrit are inversely proportional to changes in intravascular volume. Treatment consists of stopping (or slowing) ultrafiltration, providing saline as deemed necessary to maintain blood pressure and minimize symptoms, and placing the patient in the Trendelenburg position. Adjusting the timing of antihypertensive medications on dialysis days and decreasing fluid gain between dialysis sessions are often effective preventative measures.

The most common complication associated with dialysis catheter usage is infection and sepsis. Infection rates of catheters are 60% higher than the rates for AVF and AVGs and often require removal/replacement of the access along with systemic antibiotic therapy. Catheter usage can also be complicated by the development of vascular stenosis and the inability to create a permanent vascular access.

Additional Clinical Issues for the Pediatric Dialysis Patient

Optimal management of the dialysis patient requires attention to a variety of clinical manifestations for which treatment guidelines do exist. Issues to be addressed include anemia management with iron and erythropoiesis stimulating agents (ESA), nutrition, growth and the possible use of recombinant growth hormone therapy (rhGH), bone-mineral management with phosphate binders and vitamin D therapy, blood pressure management, education, and health-related quality of life (HRQOL). In all cases, centers providing chronic dialysis to children should have access to the expertise needed to address these important concerns.

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315 Pediatric Kidney Transplantation

Peter F. Hoyer

Introduction

Dr. Murray performed the first successful kidney transplantation more than 50 years ago among identical twins. At that time immunological and immunosuppressive concepts did not exist. About 15 years later, transplantation became an accepted treatment modality for adults with renal failure but was regarded as unethical for children. Today kidney transplantation is the preferred treatment for renal replacement therapy in children.

Major side effects of chronic renal failure like growth retardation, developmental delay, anemia, renal osteodystrophic bone disease as well as poor school attendance improve dramatically after successful kidney transplantation. Contraindications against kidney transplantations are few, i.e., malignancies or chronic infections. A major problem is still shortage of suitable and compatible organs. Unsolved challenges remain the preservation of renal function, prevention of infections, long-term cardiovascular problems, side effects of chronic drug administration, and long-term rehabilitation.

Underlying Diseases Leading to Kidney Transplantation

Underlying diseases leading to kidney transplantation are in one-third urinary tract malformations, one-third nephronophthisis and cystic kidney disease, and one-third acquired diseases like non genetic hemolytic uremic syndrome (HUS) and other glomerulopathies (*Table 315.1*). Multiorgan diseases, which may deteriorate after transplantation, are important for the prognosis after transplantation. Syndromatic diseases with mental retardation require very intensive and long-term care.

Pretransplant Assessment and Preparing for the Waiting List

Outcome after transplantation clearly depends on careful pretransplant evaluation and preparation. Infections after transplantation are a major problem due to chronic immunosuppression. Therefore, care must be given to get all information about previous vaccinations and to complete missings recommended vaccinations. Especially life-attenuated vaccines should be completed before immunosuppression starts.

Complete assessment of the recipient includes a general physical status, evaluation of organ functions, mental and cognitive status. The immunological status includes blood groups and human leukocyte antigens, i.e., HLA antigens, and in case of autoimmune disease activity parameters including complement, anti-DNA antibodies or ANCAs. Chronic infections like tuberculosis must be excluded. In case of urinary tract malformation, a careful planning together with the pediatric urologist is mandatory; this may include nephrectomy of chronic infected kidneys as well as evaluation of the bladder by urodynamic studies. A miction cysturethrogram is recommended for almost all patients in order to diagnose a relevant vesicoureteral reflux.

Attention must be given to medications, which inhibit or enhance the drug metabolizing system cytochrome p450 of the liver, because this might have a tremendous effect on doses and drug levels of calcineurin inhibitors (*Table 315.2*).

Living Transplantation Versus Deceased Donor Organ Transplantation

Nowadays most families wish to contribute to the treatment of renal failure by offering living transplantation to their children. It is important to inform the families as early as possible about such options, but very balanced information about the pros and cons is necessary. The pros for living-related transplantation are a short waiting time or even a preemptive transplantation, optimal timing of the transplantation, early and excellent graft function, almost no delayed graft function and fewer rejection episodes (*Fig. 315.1*). In general, in the long-term run the prognosis of a living-related kidney is superior to a deceased donor organ (*Fig. 315.2*). On the other hand, ethical issues have to be addressed. It is absolutely mandatory, that the transplantation is self-motivated and

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Table 315.1
Underlying diseases in pediatric kidney transplant recipients (NAPRTCS 2008)

Recipient and transplant characteristics	*N*	%
Total	9,854	100.0
Sex		
Male	5,853	59.4
Female	4,001	40.6
Primary diagnosis		
Aplasia/hypoplasia/dysplasia kidney	1,564	15.9
Obstructive uropathy	1,538	15.6
Focal segmental glomerulosclerosis	1,154	11.7
Reflux nephropathy	515	5.2
Chronic glomerulonephritis	328	3.3
Polycystic disease	287	2.9
Medullary cystic disease	271	2.8
Hemolytic uremic syndrome	260	2.6
Prune belly syndrome	254	2.6
Congenital nephrotic syndrome	254	2.6
Familial nephritis	225	2.3
Cystinosis	201	2.0
Pyelonephritis/interstitial nephritis	173	1.8
Membranoproliferative glomerulonephritis – Type I	171	1.7
Idiopathic crescentic glomerulonephritis	171	1.7
SLE nephritis	150	1.5
Renal infarct	136	1.4
Berger's (IgA) nephritis	127	1.3
Henoch–Schonlein nephritis	110	1.1
Membranoproliferative glomerulonephritis – Type II	81	0.8
Wegener's granulomatosis	55	0.6
Wilms' tumor	52	0.5
Drash syndrome	52	0.5
Oxalosis	52	0.5
Membranous nephropathy	44	0.4
Other systemic immunologic disease	32	0.3
Sickle cell nephropathy	16	0.2
Diabetic glomerulonephritis	11	0.1
Other	962	9.8
Unknown	608	6.2

Table 315.2
Drugs inducing or inhibiting the metabolizing system *Cytochrome P450 3A4* in the liver with the consequence of lowering or increasing blood levels of calcineurin inhibitors

Induction (CNI level down)	Inhibition (CNI level up)
Phenobarbital	Erythromycin
Phenytoin	Clarithromycin
Carbamacepin	Ketoconazole
Rifampicin	Fluconazole
Gluco-corticosteroids	Itraconazole
St. John´s wort etc.	Verpamil
	Diltiazem
	Grapefruit etc.

a free decision without any coercion. A careful clinical, laboratory and radiological evaluation of the donor is a prerequisite for transplantation. The safety of the donor has a high priority and donors with diseases that are occasionally unknown before evaluation must be excluded from living donation. In general, 30–50% of parents are acceptable as donors. Unrelated living donor transplantation has become an option if a clear relationship among donor and recipient is granted but any commercial organ transplantation has to be rejected.

Access to Transplantation and the Waiting List

In almost all countries, possible transplant recipients have to be registered on a waiting list in a local organ sharing network like in the *Eurotransplant foundation, UK Transplant, Scandinavian Transplant* network, or in the *UNOS* network in the United States. Waiting time for a transplant is by no means uniform and several factors are taken into consideration for an algorithm for organ allocation. ABO blood types continue to have a major effect and also HLA typing and histocompatibility are still considered as a major predictor for transplant success. Specific cytotoxic antibodies have to be measured on a regular basis. In case of competing for a same organ because of equal histocompatibility, time on a waiting list and medical urgency play a major role. Patients with special medical risk factors get some priority. In some countries, children get a preference on the waiting list, while in other countries this is not the case. Recently, data from UNOS suggest that children should preferentially receive organs from donors younger than 35 years and that HLA matching has less impact on outcome for a first transplant.

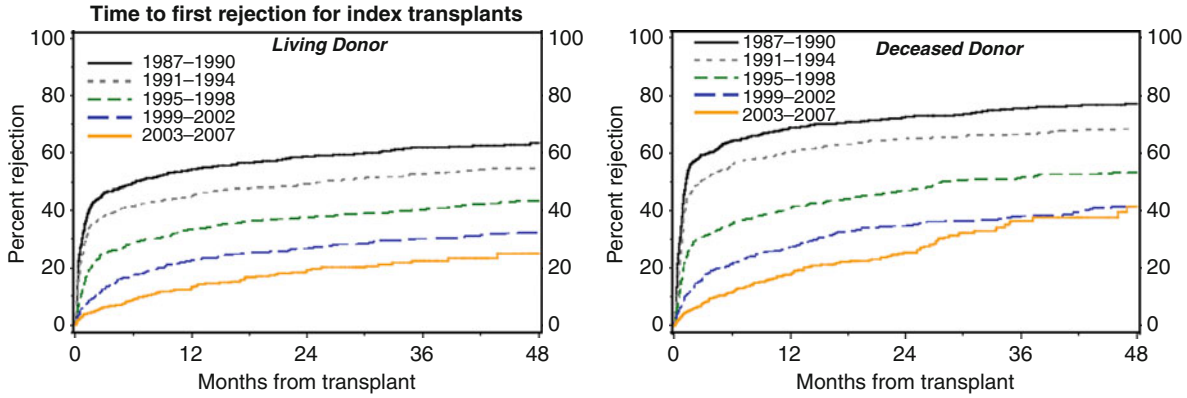

Figure 315.1

Time to first rejection episode in living donor transplantation and in deceased donor transplantation. There is a remarkable improvement over time (NAPRTCS 2008)

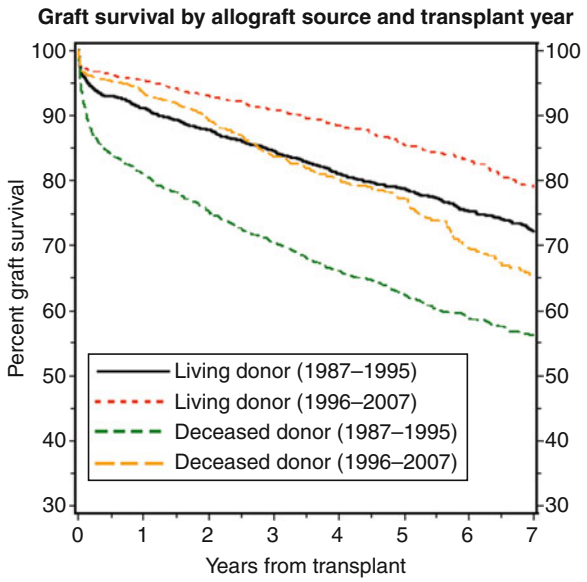

Figure 315.2

Improvement of graft survival over time in living and deceased donor transplantation. Five year graft survival after living donor transplantation is now in the order of 90% (NAPRTCS 2008)

Technical Aspects of Kidney Transplantation

In most children, the transplant kidney is placed like in adults in the right or left fossa iliaca with an anastomosis to the iliac artery and iliac vein. However, in the very young, large kidneys have not enough space and blood supply from the iliac artery may be insufficient. Therefore, the vascular anastomosis should be placed between the aorta and caval vein in the middle of abdomen (*Fig. 315.3*). Careful consideration has to be given to the kidney size and the recipient's size because a large transplanted kidney may require a high blood supply, which will not be achievable in very small recipients. Therefore, most centers recommend to transplant a kidney to a recipient with a minimum weight of 8–10 kg and to take into consideration the diameter of the aorta.

Perioperative Management

The perioperative management of kidney transplantation is standardized. Successes are clearly related to a center experience, which includes pretransplant preparation, experienced anesthesiology, specially trained transplant surgeons, as well as postoperative care. Adequate hydration should be measured by a central venous line, and fluid and electrolytes have to be balanced according to circulatory parameters and urine output. Most centers have a standard operation procedure with the administration of diuretics such as furosemide and infusion of mannitol before the anastomoses are opened. Dopamine infusion is widely accepted to enhance kidney perfusion and to maintain blood pressure adequately high; however, this recommendation has never been tested in a prospective trial in children.

Postoperative application of Doppler sonography in the operation room is important in order to exclude organ compression or early thrombosis. Urine output via transurethral catheter or suprapubic catheter should be checked hourly and any obstruction must be detected early in order to prevent a leakage of the vesicoureteral anastomosis.

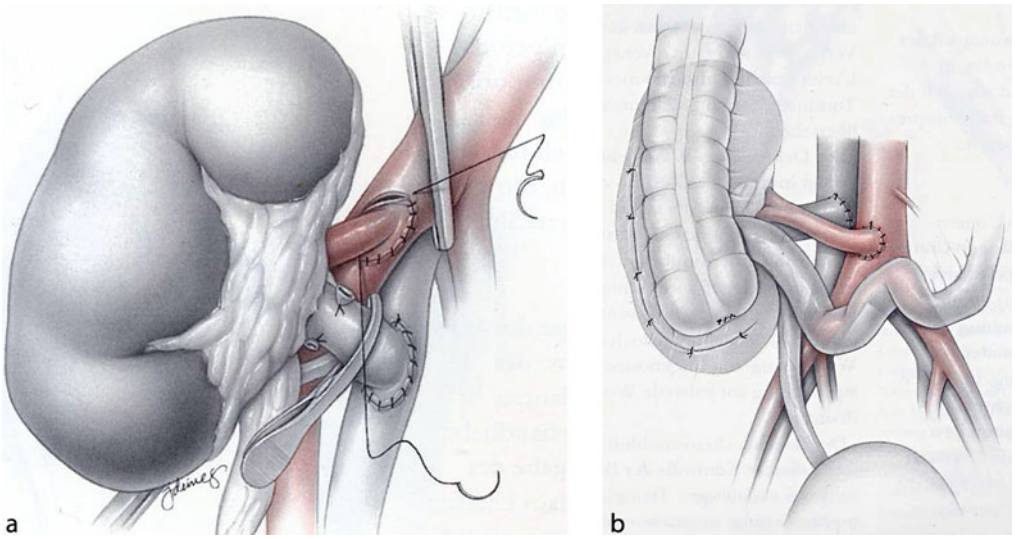

Figure 315.3
Surgical technique in the standard situation panel a and in small children panel b. In panel b, the renal artery is anastomosed to the aorta and the renal vein to the caval vein (Courtesy of Professor Paul, Clinic for Transplantation Surgery University Clinic Essen)

Immunosuppression

Immunosuppressive drugs can be classified in different categories:

- Steroids
- Lymphocyte-directed antibodies such as ATG, OKT3, thymoglobulin or IL2 receptor antibodies
- Calcineurin inhibitors like cyclosporine or tacrolimus
- mTOR-inhibitors (mammalian target of rapamycin): sirolimus and everolimus
- Antiproliferative agents like azathioprine or mycophenolic acid

Newer agents like co-stimulatory pathway blocking agents are used in adults but have not been tested in children so far. Major side effects of immunosuppressive drugs are listed in *Table 315.3*.

Steroids have been used as a basic drug in transplantation long time before newer drugs were developed. Most protocols still include steroids. Because of the major side effects, especially on growth in pediatric transplantation a search for steroid avoidance protocols or steroid withdrawal is going on. First trials without steroid treatment seem promising; however, a translation into daily routine outside from studies needs further confirmation.

The monoclonal antibodies OKT3 and ATG have been recommended as induction therapy by the NAPRTCS registry some years ago, but the superiority to treatment without the induction antibodies have not been demonstrated. The monoclonal antibody basiliximab, which is directed against the alpha chain of the interleukin 2 receptor on activated lymphocytes, should be in theory synergistic to treatment with calcineurin inhibitors. In large trials and meta-analysis, a reduction in early acute rejection episodes has been demonstrated but no benefit with

Table 315.3
Major specific side effects of immunosuppressive drugs

Steroids	Obesity, arterial hypertension, growth retardation
Cyclosporine A	Nephrotoxicity, hypertrichosis, gingival hyperplasia, elevated lipids
Tacrolimus	Nephrotoxicity, beta cell toxicity, EBV infectious problems
mTOR inhibitors	Elevated lipids, wound healing problems, enhancing cyclosporine toxicity, hypergonadotropic hypogonadism
MMF; MPA	Gastrointestinal tract, diarrhea, leucopenia, anemia, viral infections
IL2 R-AB	Antibody development, impact on CD4+CD25+ T_{regs}?

MMF mycophenolate mofetil, *MPA* mycophenolate acid, *IL2R-AB* interleukin 2 receptor antibody, T_{regs} regulatory T-cells

regard to long-term outcome. In a prospective randomized double blind trial basiliximab was tested versus placebo with a standard immunosuppression consisting of cyclosporine steroids and mycophenolate mofetil. In this trial, no benefit with regard to rejection episodes was visible for basiliximab, however, the overall data were extremely good compared to results which are analyzed by registries (◉ *Fig. 315.1*) and which are much inferior. Therefore, a benefit of a monoclonal antibody against the IL2-receptor cannot be excluded under standard situation.

Cyclosporine A has become a corner stone in kidney transplantation in the late 1980s. Major side effects are nephrotoxicity, hypertrichosis, gingival hyperplasia, and elevated lipids. The calcineurin inhibitor tacrolimus is more powerful in terms of dosis and blood levels, but has the same nephrotoxic side effects. In addition to that, some beta cell toxicity has been reported in trials with adult patients and higher doses are associated with PTLD, especially in patients who are EBV naïve before transplantation. With regard to cosmetic side effects and compliance in young adolescents, tacrolimus is gaining preference by many centers.

mTOR inhibitors were introduced with the promise to lead to less nephrotoxicity and improved kidney function. However, high lipids early after transplantation, wound healing problems, and enhanced cyclosporine toxicity has reduced the enthusiasm. A recent trial by NAPRTCS combining sirolimus with tacrolimus has lead to unacceptable high PTLD rates. Nevertheless, mTor inhibitors with their specific profile have a place in a subgroup of patients with special problems. Mycophenolate mofetil (MMF) and the compound mycophenolic acid are the most widely used immunosuppressive drugs in about 80% of patients. Generally, they are used in combination with calcineurin inhibitors allowing a substantial reduction of these nephrotoxic compounds. MMF has become a substitute for azathioprine over the last 15 years. However, in terms of cost-effectiveness and long-term benefit azathioprine needs new consideration.

Due to the importance of the immunosuppressive therapy most drugs require a pharmacokinetic monitoring. The therapeutic window is rather small; undertreatment may lead to rejection and graft loss while overtreatment to toxicity or severe infections. In addition to that, many drugs may interfere with metabolism of calcineurin inhibitors (◉ *Table 315.2*) and also mycophenolate acid. The average dose of drugs used in various combinations after transplantation has been evaluated by NAPRTCS (◉ *Fig. 315.4*). It is of note that a combination of tacrolimus and MMF requires about half the dose of MMF, which is required with the combination of cyclosporine and MMF. Drug levels are measured as predose trough level or at certain time points to calculate drug exposure as area under the curve (AUC). This is essential to adjust drug dosing.

Reasons for Graft Failure

Under the current immunosuppressive therapies, graft loss due to rejection has become less important. The NAPRTCS registry reported in 2006 that the leading cause of graft failure are thrombosis with 21%, chronic rejection 20%, acute rejection 10%, death 8%, recurrence of original disease 9%, and all other different reasons 32%. Therefore, prevention of graft thrombosis has the major impact on outcome. Although there are no prospective trials, several factors may reduce the risk for thrombosis: meticulous surgical techniques with anastomosis guarantee in high kidney perfusion are of major importance. Identification of a hypercoagulable state with APC resistance, or a previous history of multiple thrombotic events may point to an increased risk after transplantation. While some centers report almost no graft thrombosis by prophylactic use of heparin, others have not seen a benefit. However, these results are difficult to interpret, because immediate postoperative monitoring of anticoagulation is not always reported and some publications are biased by large historical data.

Acute Rejection Episodes

Most acute rejection episodes are observed during the first 3 months after transplantation. The percentage of patients who are treated for acute rejections during the first year after transplantation has continued to decline from 30% to 20–15%. An acute rejection is defined as an acute deterioration of the graft function associated with specific pathologic changes. These pathologic changes have been classified by the Banff consortium (◉ *Table 315.4*).

The gold standard for diagnosing a rejection episode is a kidney biopsy. An ultrasound-guided kidney biopsy is a safe procedure and has the advantage to provide a clear diagnosis and to prevent unnecessary treatment. Other causes for functional deterioration of the graft can also be described by a kidney biopsy, i.e., drug toxicity (◉ *Fig. 315.5a*), unspecific tubular injury, recurrence of original diseases, and chronic allograft nephropathy (◉ *Fig. 315.5b*).

In case of acute rejection, steroid therapy usually can reverse rejection episodes. Steroid-resistant rejection is a rare event, which may require intensified immunosuppression

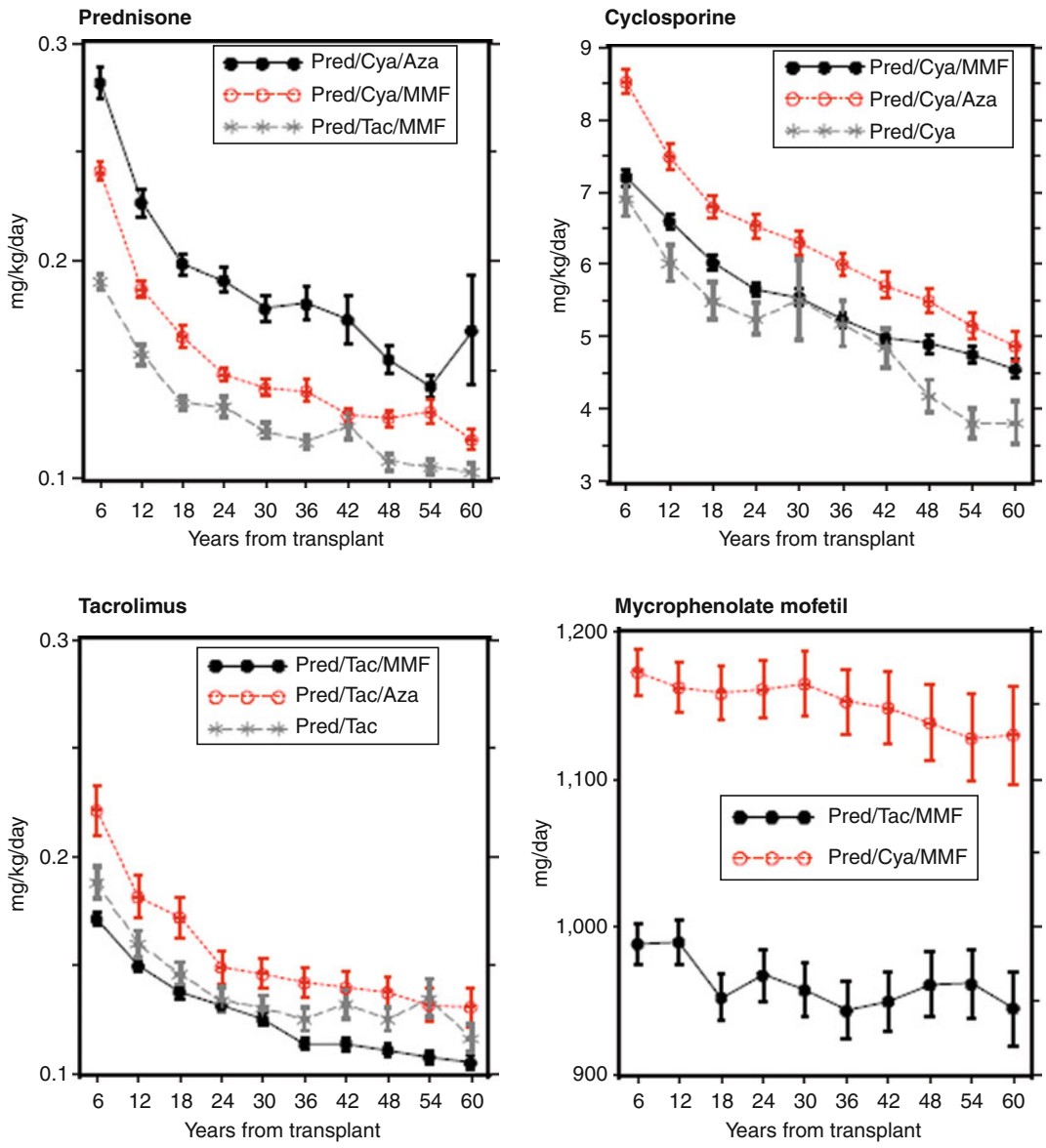

Figure 315.4

Mean drug concentrations used after transplantation in relation to combined drug therapies (NAPRTCS 2008)

with antibody therapy. In case of acute rejection, inadequate immunosuppression induced by poor drug absorption or noncompliance must be excluded. Switching to other drug combinations may be advisable.

Chronic Allograft Dysfunction

Chronic allograft dysfunction is an unsolved problem in kidney transplantation. While rejection episodes are rare events in younger children, poor compliance in adolescence may lead to chronic inadequate immunosuppression. Other reasons for chronic allograft nephropathy are not well-defined chronic immunologically mediated injury, arterial hypertension, chronic calcineurin inhibitor toxicity, the senescence of renal cells, and de novo diseases in the kidney such as transplant glomerulopathy or tubular interstitial nephritis by recurrent urinary tract infection.

Table 315.4
Banff 2005 diagnostic categories for renal allograft biopsies (2005 revision)[a]

1. Normal
2. AMR
Acute AMR ($C4d^+$) type
(a) ATN-like
(b) Capillary margination and/or thrombosis
(c) Arterial
Chronic active AMR[b]
glomerular double contours, peritubular capillary basement membrane multilayering. interstitial fibrosis, tubular atrophy, fibrous intimal thickening
3. Borderline changes
4. T cell–mediated rejection
Acute
• (a) Significant interstitial infiltration (<25% of parenchyma) and moderate tubulitis
(b) Significant interstitial infiltration (>25% of parenchyma) and severe tubulitis
• (a) Mild to moderate intimal arteritis
(b) Cases with severe intimal arteritis comprising >25% of the luminal area
• Transmural arteritis
Chronic active T cell–mediated rejection[b]
5. Interstitial fibrosis and tubular atrophy, no evidence of any specific cause
Grade
(a) Mild (<25% of cortex)
(b) Moderate (26–50% of cortex)
(c) Severe (>50% of cortex)
6. Other: Categories not considered to be due to rejection; may coincide with categories 2 through 5

[a]Adapted from reference
[b]Changes in the updated Banff 2005 schema
AMR = antibody mediated rejection

Infections After Transplantation

Infections after transplantation may be related to the disease of organs, to the recipient's immune status or to the immunosuppression itself. In a recent prospective trial with cyclosporine, MMF and basiliximab almost any infection was encountered in 95.4%, a cytomegalovirus infection in 12.8%, EBV virus infection in 9.2%, gastroenteritis in 23.9%, herpes simplex 10.1%, pyelonephritis 9.2%, rhinitis 21.1%, upper respiratory tract infection in 34.9%, and urinary tract infection 34.9%. Since CMV infection has an impact on graft function, the CMV recipient donor constellation is of great importance. In general, studies suggest a prophylactic gancyclovir therapy for at least 3 months in case of CMV mismatch, i.e., a positive donor in a negative recipient. In addition to that, monitoring of cytomegalovirus replication by measuring PP65 is established in many pediatric transplant programs.

EBV infection has also an impact on outcome. EBV infection rates increases with the amount of immunosuppression. EBV naïve children are at risk to develop an infection with a high viral DNA load and a prolonged course. Some studies reported coincidence with a cyclomegalovirus infection. A primary EBV infection in an EBV naïve recipient is a risk factor for the development of posttransplant lymphoproliferative disease (PTLD). The EBV viral load is measured in many centers, since it may point to a risk for PTLD, but there seems to be no definite correlation.

Urinary tract infections are common problems in patients with obstructive uropathy or bladder dysfunction. There is a high risk that this problem continues after transplantation. Operative removal of the recipient's diseased kidney and ureters, evaluation of the bladder

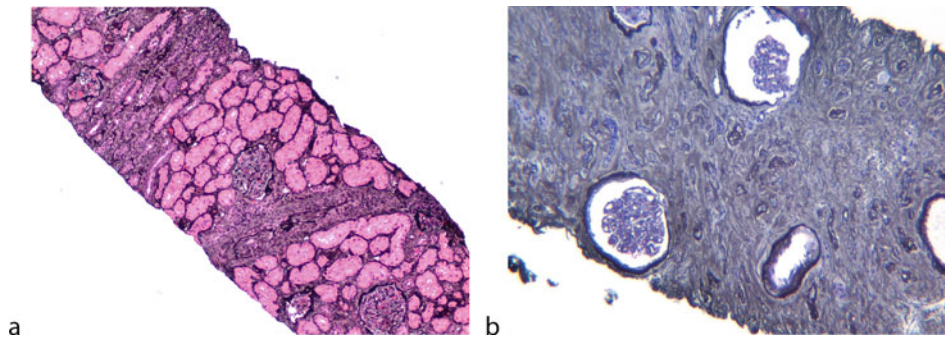

Figure 315.5
(a) Kidney biopsy with a striped form of interstitial fibrosis as can be seen as sign of calcineurin inhibitor toxicity or perfusion injury. (b) Chronic allograft dysfunction. Biopsy with severe interstitial fibrosis

function as well as treatment of bladder dysfunction should ameliorate the situation. Some cases can only be managed by continuous prophylactic antibiotic therapy.

Besides these classical infections, chronic immunosuppression may pose the patients to the risk of fungal infections or pneumocystis carini pneumonia (PCP). Due to a high fatality rate of PCP, intensive immunosuppressive protocols should get PCP prophylaxis with trimethoprim sulfamethoxazole.

Long-Term Problems After Organ Transplantation

After successful organ transplantation many problems may interfere with a good rehabilitation. These problems may be categorized as follows:

- Recurrence of original disease
- Progress of extra renal complications of the disease
- Consequences of chronic immunosuppression, i.e., direct toxicity of immunosuppressive drugs or consequences of over immunosuppression
- Cardiovascular diseases
- Progressive deterioration of the graft function

Recurrence of Original Diseases

With a transplantation of a new organ as a substitute to a failing organ, there is a hope, that the problem is cured. A look to the underlying diseases leading to renal transplantation makes clear, that different original diseases may not be cured in the same way by renal transplantation. A recurrence of original diseases after kidney transplantation is a relevant problem (Table 315.5).

FSGS has been described for a long time to have a considerable risk to reoccur in a transplanted organ. Up to 30% have been reported to lose their organ due to recurrent FSGS. Treatment options that have been tried are intensified immunosuppression and plasmapheresis. The increasing knowledge about the etiology of FSGS allows a new perspective on this problem. In pediatric patients, about one-third of cases with FSGS may have an underlying gene mutation in genes that have been described to lead to FSGS, i.e., *NPHS1*, *NPHS2* (podocine), *NPHS3*, *Wt1*, *CD2AP*, *TRPC6*, *Laminin beta 2*, etc. By discriminating genetic and non-genetic FSGS it has been demonstrated, that genetic FSGS has a very low risk to reoccur in a transplanted organ while the rate of recurrence in non-genetic FSGS is high. These findings are very important for counseling parents who wish to donate a kidney.

Table 315.5
Recurrences of original diseases after kidney transplantation in children

	Recurrence (%)	Grade	Loss of kidney transplant (%)
HUS, atypic	>40	++	>50
FSGS	25–30	++	>50
MPGN I	70	+	12–30
MPGN II	100	(+)	10–20
Lupus erythematodes	5–40	(+)	5
IgA nephritis	55–85	+	5–20

HUS hemolytic uremic syndrome, *FSGS* focal segmental glomerulosclerosis, *MSGN* membrano proliferative glomerulonephritis

In Alport syndrome, mutations in the collagen gene (*X-linked Col4A5 and autosomal Col4A3/Col4A4*) have been described. After successful transplantation, deafness may progress. Some rare cases may develop a picture like a Goodpasture syndrome. An explanation for this is that a patient with a mutated collagen will receive a new antigen by a transplanted kidney which then causes anti-GBM antibodies.

Hemolytic uremic syndrome is one of the most common causes for acute renal failure. While the shigatoxine-associated HUS has a good chance for full recovery, the so-called atypical HUS, which is not caused by shigatoxine, may have a high risk for recurrence after transplantation. Various mutations in the complement/factor H system have been described to cause atypical HUS. In these cases, the kidney is a target for uncontrolled complement activation. While the transplantation procedure itself may activate the complement system, an insufficient inhibitory potential may then lead to the recurrence of the HUS in the transplanted kidney. Therefore, patients with atypical HUS should have an intensive workup to look for mutations in factor H, factor I, and factor B or to detect antibodies against factor H. The prognosis of recurrent HUS after transplantation is poor. Intensive plasmapheresis and plasma infusion may be an option in some patient. Besides recurrence of atypical HUS, a de novo HUS in a transplanted kidney has been described and explanations point toward a possible rule of calcineurin inhibitors.

In lupus nephritis, recurrence of the original disease is a rare event. Other immunological diseases like Wegner's

granulomatosis or pauci-immune glomerulonephritis may have some risk for relapses after transplantation.

Data on the recurrence of Henoch Schönlein Purpura after transplantation are not conclusive.

In IgA nephropathy, IgA deposits in the mesangium can be demonstrated in almost all transplanted kidneys. However, this cannot be correlated with a further deterioration of the graft function.

In primary hyperoxaluria, the transplanted kidney may still be a target for continuous calcium oxalate deposition and early graft failure. In patients with primary hyperoxaluria, combined kidney liver transplantation should be considered, before a high oxalate load may worsen the general prognosis.

Progress of extra renal manifestation of systemic diseases is important in patients with autosomal recessive polycystic kidney disease (ARPKD). A liver involvement with liver fibrosis is obligatory. In addition to that, some patients have cholangiodysplastic features. The consequence of liver fibrosis is the development of portal hypertension, splenomegaly, and hypersplenism. Cholangiodysplasia may lead to cholangitis. Some patients with ARPKD may need a liver transplantation later in their course after kidney transplantation, in other patients; the liver involvement requires early combined liver kidney transplantation.

Patients with autosomal dominant polycystic kidney disease (ADPKD) rarely need a renal replacement therapy during childhood or adolescence phase. Some patients may develop liver cysts or mitral ballooning. Cerebral aneurisms have not been reported in pediatric patients.

Juvenile nephronophthisis is a common cause for chronic renal failure and transplantation in children. The disease may be very complex and many subtypes have been described. Major problems due to the progress of underlying disease are liver involvement with cholangiodysplasia and liver fibrosis, or tapetoretinal degeneration like in Senior–Loken syndrome.

Rare diseases with multiorgan involvement, which continue to be a problem after transplantation, are Joubert syndrome, Jeune syndrome, spondyloepiphyseal dysplasia, Bardet–Biedl syndrome, or juvenile cystinosis. Long-term problems are cerebellar ataxia, mental retardation, failure to growth, cerebral ischemia, or vision loss in case with tapetoretinal degeneration. Patients with cystinosis suffer from crystal deposition in the cornea, diabetes, and hypergonadotropic hypogonadism.

Malignancies After Organ Transplantation

The rate of malignancy is correlated to the intensity of immunosuppression. Lymphoproliferative diseases have been described in 2–5% of patients. First infection with EBV early after transplantation may be a risk for further development of PTLD (*Fig. 315.6a*). PTLD may appear as polymorphic or monomorphic lymphoma (*Fig. 315.6b*). While in milder cases, stopping of calcineurin inhibitor therapy may lead to tumor regression, others with monoclonal elements and CD20 expression (*Fig. 315.6c*) improve after therapy with rituximab. Patients with undifferentiated lymphoproliferative diseases have a much less favorable prognosis despite intensive chemotherapy. Lymphomas, which appear beyond the early transplant phase after 1 or 2 years, are more likely to be Non-Hodgkin lymphomas. Then a standard chemotherapy is required. All children with chronic

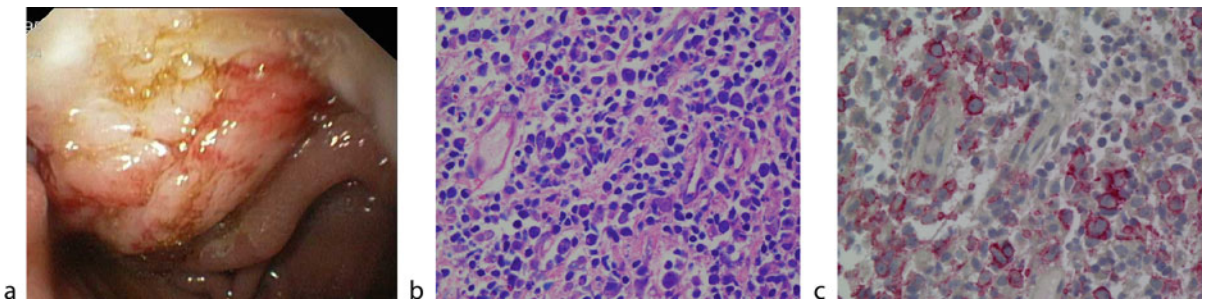

Figure 315.6

(a) Six years old boy 8 months after transplantation. Endoscopy of the distal esophagus: polypous swelling in the cardia region. (b) HE staining of the biopsy reveals a monomorphic lymphoma. (c) Biopsy of the lymphoproliferation with positive staining for the marker CD20

immunosuppressive therapy have an increased risk to develop skin cancer. Therefore, special attention must be given to suspicious skin lesions.

Cardiovascular Problems

An unsolved problem after solid organ transplantation is a high cardiovascular mortality. Major risk factors for that are long time on dialysis, chronic hyperphosphatemia, hyperlipidemia, arterial hypertension, and long-term administration of steroids and calcineurin inhibitors. Recent studies have shown calcifications in the coronary arteries in young adults and an increased arterial stiffness in patients with renal insufficiency on dialysis and also after transplantation. Future research for long-term rehabilitation for patients with chronic renal failure and transplantation should address the high impact of cardiovascular disease on patient's survival.

Noncompliance

Worldwide there are reports of high rejection rates and up to 20% of organ losses in young adolescents. Patients who are transferred to adult units are at highest risk. This age group has been described not to follow the multidrug regimes. Adolescents have an increased readiness for risks and decreased capability to estimate the future consequences of their acts and omissions. They are teenagers and they want to behave like teenagers. Pediatrics transplant centers pay increasing attention to this problem and many programs are under development to improve the noncompliance in young adolescents.

Summary

Pediatric kidney transplantation is a well-established therapy for chronic renal failure. Sophisticated surgical techniques and modern drug combinations lead to excellent short-term results; however, long-term problems like deterioration of graft function, infections, and cardiovascular morbidity beyond the child and adolescent phase remain challenges for future research activities.

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Blood Diseases

Michael Recht

316 Practical Approach to Anemia in Children

Ahmad A. Mallouh

Introduction

Like any other health problem, the etiologic diagnosis of anemia depends on interpreting information obtained from history, physical examination, and appropriately ordered laboratory tests. Before embarking on an extensive and expensive "laundry list" of laboratory testing, the physician needs to determine if the patient is truly anemic, taking into consideration the normal values for age, sex, and ethnicity (*Table 316.1*).

Classification of Anemia in Children

Anemia is classified into two ways: erythrokinetic (physiologic) and morphologic classification.

Erythrokinetic (Physiologic) Classification

This classification utilizes the pathophysiology of anemia, whether it resulted from (a) underproduction (bone marrow suppression or infiltration), (b) shortened red blood cell (RBC) survival (hemolysis), (c) blood loss, or (d) the combination of more than one factor. A normal or low reticulocyte count indicates bone marrow suppression (aplasia or hypoplasia), infiltration (malignancy or storage disease), replacement (myelofibrosis or osteopetroses), deficient or poor utilization of iron (iron deficiency, anemia of chronic disease) or acute blood loss or early acute hemolysis (before the bone marrow has the time to respond), while a high reticulocyte count and/or the presence of nucleated RBCs in the peripheral circulation indicate an active bone marrow, such as hemolysis, recovery from transient aplasia, response to anemia caused by acute blood loss, or response to iron therapy in iron deficient patients (*Table 316.2*).

Morphologic Classification

Based on the RBC morphology, anemia is classified according to the RBC size (mean corpuscular volume or MCV), mean hemoglobin concentration (MCHC), or mean hemoglobin content (MCH). Morphologically, anemia can be classified as normocytic (normal MCV), microcytic (low MCV), or macrocytic (high MCV). Depending on the hemoglobin concentration and content, anemias can be classified as normochromic (normal MCHC and MCH) or hypochromic (low MCHC and MCH). Development changes of these parameters should be taken in to consideration (*Tables 316.1* and *316.3*).

Clinical Findings

History, physical examination, results from a complete blood count (CBC), and inspection of a well-prepared blood smear are the essential first steps in the workup for anemia. A systematic analysis of the information obtained in such a way enables the physician to establish a correct diagnosis in some cases and narrow the differential diagnosis for others, thus limiting the number of the needed specific tests.

History

Age, gender, ethnicity, dietary history, history of acute or repeated blood loss, dark colored stools, history suggestive of associated or causative diseases (fever, arthritis, skin rash, weight loss), history suggestive of inflammatory bowel disease, prolonged menstruation in teenaged girls, history of pica, history of drug or toxin exposure, past history of blood transfusion, present or past history of jaundice and red colored urine, family history of anemia, blood transfusion, splenectomy, or cholecystectomy represent only a short list of important information which direct the workup of children with anemia. These factors, alone or in various combinations, can direct the investigation toward or away from a possible diagnosis. Inherited anemias usually present early in childhood. RBC membrane disorders (hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, etc.),

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_316,

Table 316.1
Normal hematologic values at various ages

Age	Hemoglobin (g/dl)	RBC ($\times 10^{12}$/l)	Hematocrit (%)	MCV (ft)	MCH (pg)	MCHC (%)	Reticulocytes
Cord blood	16.6	5.25	63	120	34	31.7	3.2
1 day	19.0	5.14	61	119	36.9	31.6	3.2
3 days	18.7	5.11	62	116	36.5	31.1	3.8
7 days	17.9	4.86	56	115	36.2	32.0	0.5
2 weeks	17.3	4.80	54	112	36.8	32.1	0.5
3 weeks	15.6	4.20	46	111	37.1	33.9	0.8
4 weeks	14.2	4.00	43	1–5	35.5	33.5	0.6
2 months	10.7	3.40	31	93	31.5	34.1	1.8
3 months	11.3	3.70	33	88	30.5	34.8	0.7
6 months	12.3	4.60	36	78	27	34	1.4
8 months	12.1	4.60	36	77	26	34	1.1
10 months	11.9	4.60	36	77	26	34	1.0
1 year	11.6	4.60	36	78	25	33	0.9
2 years	11.7	4.70	38	79	25	33	1.0
4 years	12.6	4.70	38	80	27	34	1.0
6 years	12.7	4.70	39	81	27	33	1.0
8 years	12.9	4.70	40	83	27	33	1.0
10–12 years	13.0	4.80	40	83	27	33	1.0
Men	16.0	5.40	47	87	29	34	1.0
Women	14.0	4.80	42	87	29	34	1.0

RBC red blood cells, *MCV* mean corpuscular volume, *MCH* mean corpuscular hemoglobin, *MCHC* mean corpuscular hemoglobin concentration

disorders of alpha globin chain (α-thalassemia), and RBC enzymopathies (G6PD, pyruvate kinase deficiency) may present in the neonatal period, while beta globin chain disorders (sickle cell disease, β-thalassemia) do not manifest clinically until at least 2–3 months of age. X-linked anemias, such as G6PD deficiency, affect mainly boys. However, it should be kept in mind that homozygous females are not uncommon in communities with high rates of consanguineous marriage. Race and ethnicity help in directing the investigations toward certain disease entities. Sickle cell disease is common in people of African origin, parts of the Arabian Peninsula, and parts of India. β-thalassemia is common in people of Mediterranean origin. α-thalassemia is common in people of African origin, Arabs in the Gulf area and in Southeast Asia. Hemoglobin E is common in Southeast Asian origin and parts of the Indian subcontinent. G6PD deficiency is common in people of Mediterranean origin (Greek, Arabs, Sardinians), in people of African origin, and in Southeast Asia. Nutritional anemia (iron deficiency, folate deficiency) and chronic lead poisoning are more common in children of low socioeconomic class. Iron deficiency is common in exclusively breast-fed infants and those taking non-iron-fortified formulas. Folate deficiency may occur in infants exclusively fed on goat's milk. Vitamin B12 deficiency may occur in vegetarians. Acute blood loss is usually evident and can be a cause of significant anemia depending on the amount of the lost blood. Chronic and repeated blood loss, on the other hand, can be missed without a specific and detailed history. Heavy menstrual periods, upper or lower gastrointestinal tract bleeding, manifesting as hemopytisis, melena, or fresh blood in the stools (esophageal varices, peptic ulcer, Meckle's diverticulum, intestinal hemangioma) might be the cause of iron deficiency anemia. A history of jaundice and/or dark colored urine suggests an acute hemolytic anemia. Hemolytic anemia after ingestion of fava beans, sulfa drugs, or antimalarial medications suggests the diagnosis G6PD deficiency. Aplastic anemia may result from ingestion of benzene, chemotherapeutic drugs, or myelosuppresive medication, i.e., chloramphenicol. Exposure to certain "folk medications" may lead to chronic lead poisoning.

Table 316.2
Erythrokinetic classification of anemia

Decreased or absent production of red blood cells
Aplastic/hypoplastic anemia
Congenital aplastic/hypoplastic anemia
Fanconi anemia
Diamond–Blackfan anemia
Dyskeratosis congenital
Schwachman–Diamond syndrome (pancreatic insufficiency and bone marrow failure syndrome)
Paroxysmal nocturnal hemoglobinuria, acquired aplastic/hypoplastic anemia
Acquired constitutional aplastic anemia (idiopathic or secondary to known causes, i.e., post hepatitis)
Transient erythroblastopenia of childhood (TEC).
Aplastic anemia secondary to Parvovirus B 19 in patients with chronic hemolytic anemia
Bone marrow failure due to drugs, toxins, irradiation, or infection
Bone marrow replacement malignancies (leukemia, lymphoma, disseminated solid tumor)
Myelofibrosis
Osteopetrosis
Myelodysplasia
Deficiency syndromes due to deficiency of substance needed for red blood cell production
Iron deficiency
Vitamin B12 deficiency
Folate deficiency
Copper deficiency
Zinc deficiency
Pyridoxine deficiency
Thiamine deficiency
Protein deficiency
Anemia secondary to erythropoietin deficiency
Chronic renal failure
Anemia of prematurity
Chronic malnutrition
Hypothyroidism, hypopituitarism
Ineffective erythropoiesis
Dyserythropoietic anemias
Vitamin B12 and folate deficiencies
Sideroblastic anemia
Chronic lead poisoning
Thalassemia syndrome
Thiamine-responsive megaloblastic anemias
Orotic aciduria with megaloblastic anemia
Ineffective utilization of iron by bone marrow
Chronic inflammatory diseases
Acute or chronic infection
Viral diseases
Excessive red blood cell destruction (shortened red blood cell survival)
Hemolytic anemias
Congenital hemolytic anemias
Hemoglobinopathies (sickle cell disease, hemoglobin C, hemoglobin E, etc.)
Thalassemia syndrome (α and β thalassemia)
Unstable hemoglobin mutation
Red blood cell membrane disorders (hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, hereditary pyknocytosis, hereditary stomatocytosis, and paroxysmal nocturnal hemoglobinuria)
Red blood cells, enzyme deficiency (glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency)
Acquired hemolytic anemias
Immune hemolytic anemia
Autoimmune hemolytic anemia
Allo-immune hemolytic anemia
Drug-induced immune hemolytic anemia
Immune hemolytic anemia associated with collagen-vascular diseases, lymphoma, or infections
Nonimmune acquired hemolytic anemia
Disseminated intravascular coagulopathy (DIC)
Hemolytic–uremic syndrome (HUS)
Thrombotic thrombocytopenic purpura (TTP)
Kasabach–Merritt syndrome (KMS)
Hemolytic anemia associated with bacterial or parasitic infection
Microangiopathic hemolytic anemia associated with congenital heart disease or prosthetic heart valves
Hypersplenism
Acute splenic sequestration (in sickle cell disease)
Anemia due to blood loss

Associated symptoms can direct investigation to certain diagnostic entities. History of recurrent painful attacks suggests sickle cell disease. History of petecheal rash, echymosis, epistaxis, or easy bruisability may indicate thrombocytopenia. History of severe or recurrent infection may indicate the presence of severe neutropenia

Table 316.3
Morphologic classification of anemia

Microcytic anemias
Iron deficiency anemia
Thalassemia syndromes
Chronic lead poisoning
Sideroblastic anemia
Pyridoxine deficiency/dependency
Anemia of chronic inflammatory disease
Some anemias associated with unstable hemoglobins
Macrocytic anemia
A. With megaloblastic features
Vitamin B1 deficiency
Folate deficiency
Orotic aciduria
Thiamine-responsive megaloblastic anemia
Drug-induced megaloblastic anemia (methotrexate, 6MP, anticonvulsants, Bactrim)
B. Without megaloblastic features
Reticulocytosis
Aplastic/hypoplastic anemia (may be normocytic or macrocytic)
Dyserythropoietic anemia
Liver disease
Hypothyroidism
Normocytic anemia
Aplastic anemia
Hemoglobinopathies
Red blood cell membrane disorders
Red blood cell enzymopathies
Immune hemolytic anemia
Microangiopathic hemolytic anemia
Acute blood loss
Hypersplenism
Anemia associated with acute infection
Anemia of chronic renal failure

either as a separate entity or in association with pancytopenia, i.e., aplastic anemia or hypersplenism. A history of systemic disease may give a clue to the etiologic diagnosis of the anemia. A history of chronic disease may cause anemia either by improper utilization of iron by the bone marrow, malabsorption, poor diet intake, or occult blood loss. A past history of blood transfusion suggests a chronic or recurrent process. A history of neonatal jaundice and/or anemia may suggest an inherited disease. A past history of cholelithiasis suggests a chronic hemolytic process. A family history of a specific type of anemia suggests a similar diagnosis in the child. Family history of splenectomy or cholelithiasis at a young age suggests an inherited chronic hemolytic anemia. Family history of a hypochromic microcytic anemia not responding to iron therapy in a parent or sibling suggests the diagnosis of thalassemia.

Physical Examination

The clinical manifestations of anemia are nonspecific. They are related to the severity and acuteness of the anemia. Pallor, tachycardia, and lethargy may be present in severe anemia; however, these are not sensitive, especially in chronic anemia. Anemia is often diagnosed on routine CBC done prior to a surgical procedure, routine clinic visit, or on hospitalization for other medical problems. Associated findings may suggest the etiologic diagnosis:

- Hepatosplenomegaly and chronic hypochromic microcytic hemolytic anemia together with family history or certain ethnic background suggests the diagnosis of β-thalassemia major
- Splenomegaly with chronic hemolytic anemia and family history of splenectomy or cholecystectomy suggest hereditary spherocytosis
- Lymphadenopathy with or without hepatosplenomegaly associated with a petecheal rash may suggest hematologic malignancy
- Jaundice and/or dark colored urine suggest a hemolytic process
- A petecheal rash and/or ecchymoses suggest pancytopenia
- Various dysmorphic features may suggest a specific type of anemia, i.e., Fanconi anemia, Blackfan–Diamond syndrome, or thalassemia major

Complete Blood Count and Inspection of the Blood Smear

The physician needs to look at and try to interpret every item in the CBC. RBC indices form the bases of the morphologic classification of anemia (*Table 316.3*). The degree of bone marrow activity forms the basis of the erythrokinetic classification of anemia (*Table 316.2*). Some types of anemia can be diagnosed

simply by inspecting a peripheral blood smear (RBC membrane disorders and microangiopathic anemias). Target cells are suggestive of hemoglobinopathies. The presence of hypersegmented neutrophils is suggestive of folic acid or vitamin B12 deficiency. Abnormal malignant cells (blasts) are suggestive of leukemia. Basophilic stippling of the RBCs suggests chronic lead poisoning (although, it must be remembered that basophilic stippling may be present in other disease entities such as congenital nonspherocytic hemolytic anemias and unstable hemoglobins). Thrombocytopenia and/or neutropenia indicate involvement of other cellular blood elements rather than isolated anemia.

Diagnosis of Anemia

Once it is decided that a patient has anemia, several questions must be answered prior to a plan for specific laboratory testing is pursued:

- Does the patient have isolated anemia or pancytopenia?
- Is the anemia due to underproduction (bone marrow failure), hyperdestruction (hemolysis) or underproduction on top of hyperdestruction (aplastic crisis in patients with chronic hemolytic anemia)?
- Is the anemia acute or chronic?
- Is there a family history of a similar condition?
- Are there any dysmorphic features present on physical exam?
- Are the RBCs microcytic, normocytic, or microcytic?

Further investigations should be planned using the answers to these questions and using the morphologic and erythrokinetic classification.

Hypochromic Microcytic Anemia

For practical purposes, the differential diagnosis of hypochromic microcytic anemia in children includes: iron deficiency anemia, β-thalassemia trait, hemoglobin E disease, α-thalassemia trait, chronic lead poisoning, anemia of chronic disease, and the sideroblastic anemias (*Tables 316.4* and *316.5*). Hemoglobin electrophoresis is the preferred diagnostic test for β-thalassemia trait. A high hemoglobin A2 level is diagnostic. Hemoglobin A2, however, can be normal if β-thalassemia trait is associated with severe iron deficiency, δ/β-thalassemia, or α-thalassemia. Hemoglobin F is also often elevated in β-thalassemia trait. Hemoglobin electrophoresis also is diagnostic for other hemoglobinopathies with microcytic anemia, i.e., Hb E, Hb C, Hb D, and Hb H. Low serum iron, high total iron binding capacity (TIBC), and low serum ferritin are characteristic of iron deficiency. The serum ferritin level is the most sensitive and specific none invasive test, as it is a reflection of iron stores. Serum

Table 316.4
Differential diagnosis and expected laboratory values for microcytic hypochromic anemia

Laboratory value[a]	Iron deficiency	β-thalassemia trait	α-thalassemia trait	Hemoglobin H disease	Chronic lead poison	Sideroblastic anemia	Chronic disease
MCV	↓	↓	↓	↓	↓	↓ or N	↓ or N
RDW	↑	N	N	↑	N	↑	N
Parents' MCV	N	↓ One parent	↓ One parent	↓ One parent	N	N	N
Serum iron	↓	N	N	↑	N	↓ or N	↓
TIBC	↑	N	N	↑	N	↓ or N	↓ or N
Serum ferritin	↓	N	N	↑	N	↑ or N	↓
FEP	↑	N	N	N	N	↑ or N	↑
Hemoglobin electrophoresis	N	↑A_2 ↑F	N	Hb H present	N	N	N
Brilliant crystal blue stain	Neg	Neg	Neg	Neg	Neg	Neg	Neg

[a]*MCV* mean corpuscular volume, *RDW* red blood cell distribution width index, *TIBC* total iron-binding capacity, *FEP* free erythrocyte protoporphyrin

Table 316.5
Laboratory values in iron deficiency anemia versus anemia of chronic disease

	Normal range	Iron deficiency (mean)	Chronic disease (mean)
Iron (μg/dl)	70–190	≤30	>30
TIBC (μg/dl)	250–400	≥450	>200
Transferrin saturation	30	≤7	≤14
Ferritin	20–220	≤10	≤150
Macrophage iron in marrow	2+	0	3+

TIBC total iron-binding capacity

ferritin, however, is an acute phase reactant and can be normal if iron deficiency is associated with inflammatory disease, infection, hepatitis, or pregnancy. A therapeutic trial of iron therapy can be used as a diagnostic and therapeutic test. A significant rise in the reticulocyte count after 5–7 days or a significant rise of hemoglobin (1–1.5 gms/dl) after one month of oral iron therapy are diagnostic of iron deficiency. Failure to respond almost always exclude iron deficiency. It should be remembered; however that noncompliance is one of the most causes of failure to respond. Isolated iron malabsorbtion is extremly rare. The RDW and Mentzer index (MCV/RBC) are useful in differentiating iron deficiency from thalassemia trait. A higher RDW (>20) and high Mentzer index (>13) are suggestive of iron deficiency. α-thalassemia is diagnosed by exclusion, except for hemoglobin H disease which can be diagnosed by supravital stain (brilliant cresyle blue) and hemoglobin electrophoresis. The presence of high levels of hemoglobin Barts in newborn blood is diagnostic of α-thalassemia trait.

Chronic lead poisoning is characterized by hypochromic microcytic anemia and basophilic stippling of the RBCs. High whole blood lead level is diagnostic. The sideroblastic anemias are rare in children. Bone marrow examination is required for diagnosis. The presence of ringed sideroblasts in the bone marrow is diagnostic. Anemia of chronic disease can be differentiated from iron deficiency by (in addition to the clinical picture) normal to high serum iron and serum ferritin and normal TIBC.

Macrocytic Anemias

Macrocytosis denotes large red blood cells (high MCV). While megaloblastic anemia is the most common cause of macrocytosis and while megaloblasts are by definition macrocytes, not every macrocyte is a megaloblast. Megaloblastic anemia results from impaired DNA synthesis resulting in large RBCs. Bone marrow RBC precursors are dysblastic with the maturation of the nucleus, and cytoplasm is asynchronous. Macrocytic anemias can be divided into two subtypes: the megaloblastic anemias and the non-megaloblastic macrocytic anemias.

Megaloblastic Anemia

Megaloblastic anemias are characterized by macrocytic RBCs, macro-ovalocytes, hypersegmented neutrophils, and megaloblastic erythroid precursors in the bone marrow. The most common causes of megaloblastic anemia are folate deficiency (diagnosis is confirmed by low RBC folate level) and vitamin B12 deficiency (diagnosis is made by low serum vitamin B12 level).

Further studies are needed to confirm the diagnosis of megaloblastic anemia and to identify an etiology (e.g., the Schilling test, anti-parietal cell antibodies, anti-intrinsic factor antibody). Several drugs interfere with DNA synthesis and cause megaloblastic changes in the RBC precursors with or without anemia. These drugs include anticonvulsants (phenytoin, phenobarbital), chemotherapeutic agents (methotrexate, 6-mercaptopurine, hydroxyurea), and trimethoprim-sulfamethoxazole. Diagnosis in these cases is clearly based on the history of drug intake. Several inborn errors of metabolism can cause megaloblastic anemia (orotic aciduria, homocystinuria, methylemalonic aciduria). Patients affected by these conditions have complex clinical manifestations. The diagnosis depends on the clinical picture and specific tests for the suspected disease. Thiamine-responsive anemia is usually associated with sideroblastc anemia. The diagnosis is suggested by the exclusion of other causes of megaloblastosis and response to thiamine therapy.

Non-megaloblastic Macrocytic Anemia

Macrocytic anemia without megaloblastic bone marrow changes can be due to reticulocytosis, aplastic anemia, Blackfan–Diamond anemia, myelodysplastic syndromes, and dyserythropoietic anemias. Reticulocytes are large cells. A high reticulocyte count can be the cause of an elevated MCV. The diagnosis of aplastic anemia is suggested by reticulocytopenia and is confirmed by the examination of bone marrow biopsy. Myelodysplastic syndromes and dyserythropoietic anemias require bone marrow examination for diagnosis.

Normocytic Anemias

Normocytic anemias are due to either RBC underproduction or hyperdestruction (hemolysis):

1. Anemias due to underproduction (bone marrow failure): This group includes the aplastic anemias (congenital or acquired), bone marrow infiltration (leukemia, lymphoma, disseminated malignant solid tumors etc.), myelofibrosis, and osteopetrosis. In addition to the clinical picture, which may suggest the diagnosis in some cases, these anemias are characterized by a low reticulocyte count. The diagnosis is confirmed by bone marrow examination.
2. Anemias due to hyperdestruction (hemolytic anemias): These anemias are characterized by laboratory evidence of hyperactive bone marrow (high reticulocytes count and/or the presence of nucleated RBCS in the peripheral circulation). They include:
   (a) Red blood cells membrane disorders such as hereditary spherocytosis, hereditary elliptocytosis, and hereditary pyropoikilocytosis. A family history of one of these diseases, a family history of splenectomy and/or cholelithiasis at a young age may suggest the diagnosis. These diagnoses are confirmed by inspection of a well-prepared blood smear. Specific tests such as the osmotic fragility may be required to confirm the diagnosis.
   (b) Hemoglobinopathies (sickle cell disease, Hb C, Hb D) are diagnosed by hemoglobin electrophoresis.
   (c) Red blood cells enzymopathies (G6PD deficiency, pyruvate kinase deficiency) are diagnosed by specific enzyme assays.
   (d) Autoimmune hemolytic anemia is diagnosed by a positive direct anti-globulin test.
   (e) The microangiopathic hemolytic anemias (DIC, hemolytic uremic syndrome) are diagnosed by inspection of the peripheral blood smear. Thrombocytopenia and schistocytes (fragmented RBCs) are often present.

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317 Immune Hemolytic Disease of the Newborn

Jason Glover · Bill H. Chang

Definition/Classification

Hemolytic disease of the newborn (HDN) is a form of IgG-mediated red blood cell (RBC) destruction whereby maternal antibodies cross the placenta and cause hemolytic anemia in the newborn. It is classified as a congenital anemia due to peripheral destruction of the red blood cells.

Etiology

The first description of HDN is thought to have been in 1609 by a French midwife named Louyse Bourgeois about a twin birth. The first infant died of hydrops fetalis and the second died of jaundice and opisthotonis a few days later. It was not until 1932 when Diamond et al. coined the term "erythroblastosis fetalis" as a syndrome linking congenital anemia, jaundice, and hydrops fetalis with evidence of extramedullary hematopoiesis and erythroblastemia. During the 1930s and 1940s, Landsteiner and Weiner described the Rhesus (Rh) blood groups, while Levine and associates described the link between the Rh groups and HDN. This description involved a case of a woman who had a recent delivery of a hydropic stillborn then had a severe transfusion reaction to her husband's blood. Levine postulated that she had become sensitized to her husband's blood from the fetus. They later showed that the mother was Rh-negative and her husband was Rh-positive. Later, Chown's description of how Rh-negative mothers could be sensitized by a transplacental hemorrhage led to clinical trials in both the UK and the US suppressing allo-immunization. Women given anti-D IgG intramuscularly at the time of delivery had a dramatic decrease in the risk of HDN. Therefore, the history and management of HDN have led to many breakthroughs including immunoprophylaxis using human antibodies and development of screening programs for maternal blood group antibodies.

Epidemiology

Prior to immunoprophylaxis, HDN due to the Rh was a major source of long-term morbidity and early mortality in the developing fetus and newborn. Since the majority of HDN is due to Rh allo-immunization, the incidence is closely linked with the proportion of a population who are Rh-negative. For example, about 10% of live births in the UK were of Rh-positive children to Rh-negative mothers. It is thought that about 1 pregnancy in 200 is susceptible to hemolytic disease of the newborn with a historical mortality rate of 1 in 400. Prior to the use of immunoprophylaxis, approximately 16% of Rh-negative women became sensitized in their first ABO compatible Rh-positive pregnancy and one half would have detectable anti-D immunoglobulin 6 months after delivery. This usually occurs as a result of exposure to fetal antigens during pregnancy. Although fetal cells can be detected in maternal blood during all trimesters of most pregnancies, the largest exposure to fetal blood occurs in the third trimester and delivery. Interestingly, about 25% of D-negative women will either not become sensitized or will become tolerant. Partial protection can also come from ABO incompatibility by unknown mechanisms. By their fifth pregnancy the probability of sensitization is about 50%. With the advent of Rh immunoprophylaxis, the incidence of HDN due to Rh has decreased to approximately 1.8% of susceptible pregnancies.

Pathogenesis

The Rh blood group system is a complex system comprised of a tetramer of several proteins. Rh-positive blood type is mainly comprised of one D subunit, one CE subunit, and two RhAg subunits, whereas Rh-negative blood type consists only of two CE subunits and two RhAg subunits. Therefore, sensitization occurs due to exposure of the RhD subunit. At first exposure a primary

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weak IgM response will not affect the fetus because IgM does not cross the placenta. The subsequent IgG response will then affect the fetus causing hemolysis. After a primary response, a subsequent exposure produces a rapid IgG response that then crosses the placenta. Therefore, repeated exposures increase the severity of HDN in subsequent pregnancies. The fundamental cause of erythroblastosis is an immune-mediated red cell destruction causing increased erythropoiesis. Due to peripheral red cell destruction, extramedullary erythropoiesis can be found in the liver, spleen, kidneys, skin, intestines, and adrenal glands with subsequent immature nucleated RBCs found in the peripheral blood.

Other rare causes of varying degrees of HDN are due to at least 26 other blood group systems. These molecules include transporter and channels such as Diego or Kidd, pathogen receptors such as Duffy, adhesion molecules, enzymes such as ABO and Kell, structural proteins, and complement receptors. With the advent of immunoprophylaxis and decreasing family sizes, the incidence of HDN due to Rh has been decreasing whereas other causes appear to be slightly increasing. Of the multitude of antibodies that have been reported to cause HDN, most have been single case reports or cause a mild form of the disease. In contrast, disease caused by antibodies to Kell has been described as severe. It is second to RhD in its immunizing potential. Since this antigen is expressed in early erythroid progenitors, it may suppress erythrogenesis causing early hydrops. HDN due to ABO incompatibility accounts for approximately 5% of infants with jaundice. It usually causes a milder form of HDN except in southeast Asia, Africa, and Latin America for unknown reasons.

Pathology

Once sensitization occurs, the factors affecting the severity of HDN include the placental transfer of antibody, the characteristics of the antibody and antigen, the maturation of the spleen, and fetal erythropoiesis. All four IgG subclasses can be transported across the placenta with fetal levels reaching the mother's levels by 17–20 weeks' gestation. Typically, in Rh HDN, antibodies do not fix complement. Instead, Fc-mediated pathways lead to opsonization of the RBCs. Anti-D coated RBCs adhere to macrophages in rosettes, especially in the spleen. The RBCs are then consumed by the macrophages, or their membranes become damaged and fragile leading to lysis. Antibody-dependent cellular toxicity also accounts for some RBC destruction through myeloid and NK cell activity.

On occasion antibodies that bind to the RBCs can fix complement (as in ABO incompatible transfusion reactions). If a high enough concentration fixes complement, red cell extravascular destruction occurs which can lead to hemoglobinemia, shock, and disseminated intravascular coagulopathy. End products of red cell destruction are then predominantly cleared by the liver. Antigens such as Rh and Kell are restricted to the erythroid cells expressed in the fetus and neonate. Therefore, infants with this disease can present in hydrops due to early severe anemia.

Clinical Manifestation

Since the 1950s, degrees of severity of HDN have been used to assist in classification, research, and treatment of the disease. Mild HDN is described as having antibody-coated red cells that are identifiable by Coomb's test, without an associated anemia. This group accounts for close to 50% of the affected fetuses and requires almost no treatment. Infants with moderate HDN have elevated bilirubin and are at risk for neural toxicity and kernicterus without treatment. They will have signs of anemia without acidosis or signs of hydrops. Peripheral blood will show polychromasia, anisocytosis, and reticulocytosis. This group accounts for approximately 30% of affected fetuses and requires intensive phototherapy and exchange transfusion to manage the jaundice. Severe HDN present with severe anemia, hydrops, or impending hydrops and can die before, during, or after birth without intensive management (including intrauterine transfusion). If untreated, one half will develop hydrops between 18 and 34 weeks' gestation with polyhydramnios. Ascites, pleural, and pericardial effusions may develop with subsequent compression hypoplasia of the lungs making respiration difficult at birth.

Diagnosis

Initial prenatal diagnosis for infants at risk of Rh-mediated HDN can be performed by blood type and antibody screen on the mother. A thorough prenatal history should include whether the mother had previous pregnancies and/or blood transfusions. Maternal antibody screening and typing for both ABO and D-antigen is the standard of care at the first prenatal visit. This should include elective abortions, due to the sensitization of the mother and risk of HDN to complicate future

pregnancies. In a mother who is Rh-negative and an initial antibody screen is weak or negative, testing should be repeated at 24–28 weeks into the pregnancy, prior to the administration of anti-D immunoglobulin. Mothers with maternal serum red cell antibody titers $\geq$1:16 should then undergo Doppler ultrasound for peak systolic blood flow of the middle cerebral artery to predict moderate to severe anemia. Fetuses diagnosed with early anemia should undergo prenatal treatment.

In 1997, Lo et al. were able to identify the presence of free fetal DNA from a maternal blood sample. This discovery had obvious implications in reducing the need for invasive procedures such as chorionic villus sampling and amniocentesis to determine a fetus' blood type. The fetal DNA obtained from the mother's serum can be used to determine the fetal blood group phenotype for the D-antigen as well as the minor antigens c, E, C, K. Prenatal determination of fetal D-antigen status may reduce the rate of unnecessary anti-D immunoglobulin injections (40% of D-negative mothers will have a D-negative fetus). Typing of all D-negative mothers has been determined to be feasible and will likely become standard of care.

HDN in the newborn is typically diagnosed through clinical symptoms and laboratory tests that are common to any hemolytic process. Clinical symptoms include jaundice, pallor, hepatosplenomegaly, and may progress to tachycardia. The jaundice associated with HDN often presents within the first 24 h of life. A thorough laboratory evaluation would include complete blood counts with differential, manual examination of the smear for schistocytes, and increased reticulocytes. An elevated unconjugated serum bilirubin can aid in establishing the diagnosis of HDN from other types of jaundice, assessing the degree of hemolysis, and estimating the risk of developing kernicterus. Microspherocytes may be seen in HDN due to ABO incompatibility but is usually not seen in HDN due to Rh incompatibility.

Either the direct antiglobulin test (Coomb's) or the indirect antigen test may be used to detect an antibody-mediated HDN. The direct antiglobulin test is utilized to show the presence of maternal antibody on the child's red blood cells. The maternal antibody will cause agglutination of the child's red blood cells in a standard serum that is known to contain antibodies to IgG. An indirect antiglobulin test is used to screen for very low concentrations of IgG antibodies present in the mother's serum that can cross the placenta. The Kleihauer-Betke test can be used to estimate the degree of fetal hemoglobin transferred from either placental hemorrhage, or the normal transfer of the fetal components of the placenta.

Differential Diagnosis

The differential diagnosis of HDN is dependent on the severity of the disease. Causes of hydrops fetalis in the fetus or newborn include other blood disorders such as severe iron deficiency anemia; alpha thalassemia; cardiac dysrhythmias such as supraventricular tachycardia; metabolic disorders such as lysosomal storage diseases; genetic disorders such as Turner's (XO) Syndrome; maternal infections such as syphilis and parvovirus B19; and tumors such as teratomas.

Neonatal jaundice can be subdivided into indirect (unconjugated) and direct (conjugated) hyperbilirubinemia. Causes of unconjugated hyperbilirubinemia, if left untreated may develop into kernicterus, including HDN, bacterial and viral sepsis, normal physiologic jaundice, dehydration, cephalohematomas, hypothyroidism, or metabolic disorders such as Crigler–Najjar syndrome and Gilbert's Syndrome. The etiology of hemolysis in a newborn (*Table 317.1*) should also include the broad categories of sepsis/infection, red blood cell membrane defects, red blood cell enzyme deficiencies, hemoglobinopathies, and medication associated red cell destruction.

Treatment

Maternal Treatment

Attempts to suppress the maternal immune response in cases with a prior history of HDN have been attempted. Although Rh-immune globulin is effective in preventing the mother's immune response, it is known to be ineffective in stopping a response once it has begun. Plasma exchange of the mother has also been attempted to lower the maternal antibody levels. However, this decrease is only transient, and higher rebound can occur. The procedure is costly, can be painful, and vascular access is necessary. Administration of pooled IVIG to the mother has also been attempted in cases of expected severe disease, although the exact mechanism of action is not well defined. Clinical research trials are continuing to investigate IVIG's safety and efficacy.

Fetal Treatment

Prior to immunoprophylaxis, 8% of fetuses would develop hydrops before 32 weeks making early intervention important for the outcome of the fetus. Early attempts at intraperitoneal fetal transfusion proved to be efficacious.

Table 317.1
Causes of hemolytic anemias in the newborn

General etiologies	Specific etiologies	Special features
Immune-mediated	– Rh incompatibility – ABO incompatibility – Minor antigen mismatch: Kell, Duffy	– The most common cause of severe early jaundice
Sepsis	– Bacterial – Viral sepsis (such as herpes simplex viremia)	Jaundice may be conjugated and unconjugated, due to hemolysis- and endotoxin-mediated reduction of bile secretion
RBC membrane defect	– Hereditary spherocytosis – Hereditary elliptocytosis – Hereditary stomatocytosis – Hereditary ovalocytosis	– Family history may be positive for anemia and gallstones at an age <40 years
RBC enzyme deficiency	– Glucose-6-phosphate – Pyruvate kinase – Hexokinase – Glucose-6-phosphate isomerase – Phosphofructokinase – Aldolase – Triose phophate – Glyceraldehyde-3-phophate isomerase – Phosphoglycerate	– Rare other than G6PD – Associated with metabolic and severe neurologic disorders
Hemoglobinopathies	– Thalassemias – Sickle cell diseases	β-thalassemia may present with significant severe hemolysis
Drug-induced	– Oxytocin – Drugs that cause oxidative stress in G6PD	– May be worsened by drug passage in the breast milk – May increase the hemolysis in G6PD

Later, fetal intravascular transfusion became the preferable procedure as it dramatically reversed hydrops and increased survival. This procedure is usually performed under ultrasound guidance into the umbilical vein at its insertion into the placenta. Intraperitoneal fetal transfusion remains a technique used for the severely affected fetus with small cord vessels, or more commonly, the older fetus where fetal size and placement of the placenta preclude access to the umbilical vessels.

Neonatal Treatment

General Care

Fortunately, in the post-Rh-immunoprophylaxis era, cases of severe hydrops fetalis are rare. This has made the study of interventions in the management of severe HDN in clinical trials difficult. Many of the procedures such as drainage of pleural and peritoneal effusions, and what level to perform exchange transfusion remain studied in small numbers. Standard treatment of issues from prematurity such as surfactant administration need to be more aggressive in the child with HDN as they may compound systemic problems. Top-up transfusions should be considered in anemic neonates who are acidotic, hypoxic, and hypotensive. However, if multiple top-up transfusions are needed then iron studies should be followed for signs of overload, especially in cases of liver dysfunction.

Infants with mild to moderate disease should undergo early and aggressive phototherapy with both spotlights and a fiber-optic blanket. A bilirubin level at which to institute phototherapy is largely arbitrary; however, it is accepted that premature infants should start phototherapy at a much lower level. The rate of rise of the bilirubin may be more concerning than a stably high level. Although dehydration is a potential risk of phototherapy, it is less compared to the risks associated with exchange transfusion.

Feeding should be encouraged early as long as exchange transfusion is not anticipated, given exchange transfusion's increased risk of necrotizing enterocolitis.

Although breast milk and colostrum contain Rh antibodies, very little antibody is absorbed across the intestine of the infant. Folate supplementation may be necessary in children who have had exchange transfusion from adult sources which have a lower folate level. Folic acid supplementation (100–200 μg/day) is recommended for several weeks after exchange transfusion. Iron supplementation is not needed in cases of HDN as the iron will be reabsorbed, and additional transfusion may cause overload. Vitamin B12 is usually adequate in the mother's breast milk.

Exchange Transfusion

Originally performed in the 1920s through the anterior fontanelle, exchange transfusion is now performed using umbilical catheterizations. This technique not only replaces the antigen-coated RBCs of the newborn with fresh RBCs, but also corrects the anemia, prevents hyperbilirubinemia, and modestly removes unbound anti-D antibody. Exchange transfusion can produce a significant drop in neutrophil levels and a reduction in platelets that are both generally well tolerated. Other complications include apnea and bradycardia, hypocalcemia, bleeding, and catheter-associated thrombosis. These complications are mostly mild and asymptomatic but rarely can be catastrophic leading to the death of the patient. Because of these risks, there are no specific thresholds for the indication of exchange transfusion. Instead, most providers will perform the procedure on their experience for significant anemia or when conservative measures do not control the bilirubin. Since the risk of serious complications are higher in the ill patient versus the mildly symptomatic patient, early exchange may be warranted.

IVIG

Several small studies have examined the use of IVIG on the infant to potentially treat HDN. However, there is a lack of evidence to indicate the safety and efficacy of IVIG. Therefore, IVIG should only be recommended in a well-defined clinical trial.

Prognosis

Both the morbidity and mortality of the disease is dependent on the successful treatment of the hemolysis and anemia. With successful prevention and treatment there should be minimal long-term effects from this disease. Patients with mild HDN (about 50% of cases) will most likely suffer no long-term effects. Newborns with moderate disease (about 30% of cases), however, are at risk for kernicterus if they do not receive treatment. Again, with successful treatment of the anemia and hyperbilirubinemia, minimal sequelae should occur. The maternal anti-D-titers of these infants are usually $>$1:64. They will have some degree of a symptomatic anemia but are not usually hydropic. In the past they would have received exchange transfusion, however, with current aggressive management with intense phototherapy this may be avoided. Cases of severe HDN have hydrops or are progressing toward hydrops in utero. They will die in utero or shortly after birth if aggressive interventions such as fetal intravascular transfusion are not undertaken. Polyhydramnios may be the first sign in utero of a hydropic infant. Anasarca, ascites, pleural, and peritoneal effusions may develop and cause hypoplasia of crucial organ formation such as the lungs.

Prevention

Prevention of Rh sensitization hinges on immunoprophylaxis by injecting anti-RhD immunoglobulin to the recipient. Originally tested to prevent sensitization in males, successful trials were undertaken in which Rh-negative, unsensitized females were given anti-D intramuscularly after delivery of an Rh-positive infant. Post-natal Anti-D prophylaxis of 200–300 μg given within 72 h of pregnancy lowered the incidence of RhD alloimmunization 6 months after delivery and in subsequent deliveries. Further, prenatal administration of 100 μg (500 international units) of anti-D at 28 weeks and 34 weeks' gestation to women in their first pregnancy can reduce the risk to about 0.2%. Therefore, most guidelines recommend routine administration of Rh immunoglobulin to all D-negative pregnant women in the early and mid-third trimester. Both pre- and post-natal prophylaxis will prevent 96% of RhD isoimmunization. Earlier antenatal prophylaxis for women who are likely to abort or undergo amniocentesis or chorionic villus sampling is safe and may reduce further sensitization. Although small amounts of anti-D may cross the placenta, there appears to be no adverse effects to the fetus. In rare occasions, a large fetal-to-maternal transplacental hemorrhage may occur at the time of delivery needing prompt assessment and a titrated dose of anti-D.

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318 Iron Metabolism and Iron Deficiency Anemia

Heather Bradeen · Samir Shehab · Michael Recht

Background

Anemia is defined as a reduction in red blood cell mass or blood hemoglobin concentration. In practice, these are most often signaled by reductions of either the hemoglobin, a measure of the concentration of hemoglobin in the whole blood expressed as grams per 100 mL (dL), or hematocrit, the fractional volume of a whole blood sample occupied by red blood cells. The age variation for the hemoglobin and hematocrit varies widely in the pediatric population. It is particularly important to use age- and sex-adjusted norms when evaluating a pediatric patient for anemia. Iron deficiency is the most common nutritional deficiency in children. The World Health Organization estimates that anemia, largely caused by iron deficiency, affects between 500 million and two billion people worldwide. In some developing countries, up to 50% of preschool children and pregnant mothers have iron deficiency anemia (IDA). In the United States, the prevalence of IDA among children has been declining as a result of improved dietary iron supplementation.

Iron Metabolism

Iron is an abundant element in the natural world. Iron plays a critical role in mammalian cells. It is essential for oxygen delivery as well as numerous enzymatic systems. However, excess iron is toxic to cells and a deficiency of iron impairs cellular functions. Iron homeostasis is tightly regulated. Its excretion from the body is limited either through blood loss or sloughing of mucosal cells of the gastrointestinal lining. There are no known pathways for regulated iron excretion. Complex systems control iron absorption from dietary sources. Efficient recycling of iron is necessary to maintain its balance in the body. Disturbances to iron homeostasis have a significant impact on children's health. Insufficient iron intake leads to iron deficiency anemia, the most common pediatric hematology disorder worldwide. An excess of iron also causes problems particularly in children receiving chronic blood transfusions. Iron overload causes serious chronic organ dysfunction particularly in the liver, the heart, and the endocrine glands.

Normal Iron Endowment

Full term infants are born with approximately 350 mg of total body iron. By adulthood, an individual's iron endowment increases to 3–5 g. Normal adult men usually absorb 0.5–1 mg of iron each day from the diet. Menstruating women absorb more, approximately 1–2 mg of iron each day, to account for iron losses through blood loss. In pregnancy, iron absorption increases to approximately 2–4 mg daily to support the iron needs of the developing fetus. Approximately 75% of the total iron is within the erythrocyte and erythrocyte precursor population, and 10–20% is in storage form in the body. The remaining iron is utilized iron-dependent enzymatic pathways and biochemical reactions.

Iron Absorption

Total iron absorption depends on the bioavailability of dietary iron as well as regulation of iron absorption from the intestinal cells (*Fig. 318.1*).

Dietary Iron

Animal sources provide iron in the form of heme iron. Heme iron is a component of hemoglobin and myoglobin. It is the most bioavailable form of iron and is efficiently absorbed from the diet. Heme iron passes into the cytoplasm unchanged, where the iron molecule is then released. Nonheme iron, in the form of an insoluble ferric salt, is less bioavailable than heme iron. Nonheme iron is absorbed using a different cellular pathway. The ferric iron must first be converted to ferrous form, and then it is transported through the intestinal cell membranes with

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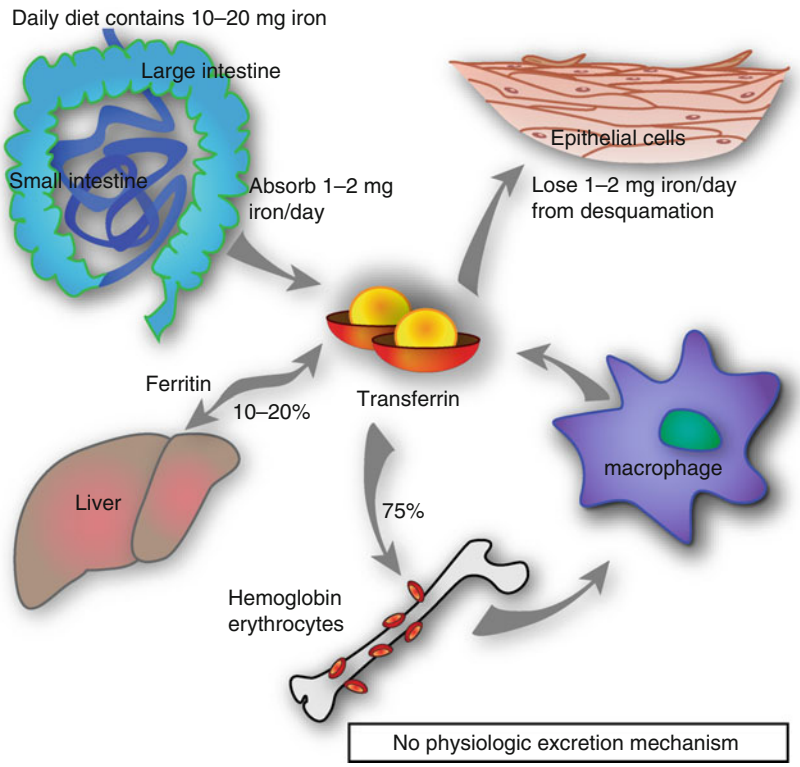

Fig. 318.1
Iron absorption

iron transport proteins. A variety of factors influence the absorption of nonheme iron. Acidic foods such as food rich in vitamin C enhance conversion of iron in the ferric form to the soluble ferrous form. The presence of dietary meat proteins in the intestinal lumen also enhances the absorption of nonheme iron. On the other hand, certain foods can impede absorption, such as tannates (tea and coffee), phosphates, antacids, and egg yolks. The decreased bioavailability of nonheme iron puts the vegan at risk for developing iron deficiency. Human breast milk, although low in total iron content, contains iron in a highly bioavailable form.

Intestinal Iron Absorption

Iron is absorbed in the proximal duodenum. Intestinal iron absorption is controlled at the level of mucosal transport and absorption. When total body iron stores are low, iron absorption is increased. Hypoxia and increased erythropoietic demand increase intestinal iron absorption. Both inflammation and increases in body iron have an opposing effect and decrease iron absorption.

Iron Storage and Recycling

Most of the body's iron is within a closed loop involving circulating transferrin, the erythroid bone marrow, senescent erythrocytes, and the reticuloendothelial macrophages. There is additional gain and loss through the intestinal mucosa. Excess iron is stored as ferritin in the liver. Smaller amounts of iron are utilized in muscle by myoglobin (not shown). The potential reactivity of iron molecules necessitates mechanisms for its safe transport and storage. Several important proteins are required for the safe handling of iron.

- Transferrin is the plasma transport protein for iron. Transferrin binds iron with extremely high affinity and prevents iron from reacting with other molecules so that iron may be delivered to tissues in a nontoxic form.
- Ferritin is a protein that stores iron and prevents it from reacting with other molecules. Iron stored as ferritin is relatively available for iron metabolism when iron needs arise. The liver is the primary location for ferritin. Plasma ferritin measurement is related to cellular iron stores.

- Hemosiderin is another form of stored iron, but its iron is much less available and is difficult to mobilize in the regulation of iron hemostasis. Its primary role is probably to keep iron from causing damage to surrounding molecules.

Iron Deficiency Anemia

Prevalence

In the United States, about 9% of toddlers have iron deficiency, with 3% affected by iron deficiency anemia. Rates decrease with advancing age until adolescence, when up to 16% of girls develop iron deficiency and 3% have iron deficiency anemia. The overall rate of iron deficiency in young children has declined only slightly during the past 4 decades. In the United States, iron deficiency is higher among children living at or below the poverty level, and in Black and Hispanic children. Other risk factors for IDA include childhood obesity and a history of prematurity or low birth weight. These findings demonstrate the need for ongoing surveillance and early intervention to prevent iron deficiency during infancy and early childhood, particularly among high-risk groups.

Clinical Features

Although iron deficiency anemia is often asymptomatic, the ability to recognize its clinical signs and symptoms is essential to preventing long-term neurodevelopmental delay. Additionally, appropriate therapy for those who are otherwise symptomatic has been shown to effectively treat symptoms as well as correct the underlying deficiency. Although its correlation with the severity of anemia is poor, pallor is the most easily recognizable sign of iron deficiency anemia. It is most prominent in the conjunctivae, gingiva, palmar creases, and nailbeds. Physical exam often also reveals tachycardia and systolic flow murmurs, and, less commonly, glossitis, stomatitis, koilonychias, and blue sclerae.

Children with mild to moderate iron deficiency anemia, defined as having hemoglobin concentrations of 6–10 g/dL, may be asymptomatic as a result of effective compensatory mechanisms. However, when iron deficiency becomes severe, with hemoglobin concentrations <5 g/dL, irritability, fatigue, and anorexia are common. Pica (which may also be a sign of lead toxicity) and pagophagia (craving and eating ice) are relatively common behavioral indicators of iron deficiency anemia. Older children and adolescents may present with exercise intolerance and shortness of breath. Of note, iron replacement therapy has been shown to improve symptoms even before laboratory values reflect changes.

In early infancy, iron deficiency anemia has been correlated with lower scores on mental and motor developmental assessments, although the exact mechanism by which this occurs has yet to be fully elucidated. Evaluations of toddlers have demonstrated similar results. Adolescent females are at a particularly high risk for iron deficiency. Poor dietary intake in this population as well as increased iron demand due to menstruation, rapid growth, and vigorous exercise contribute to this phenomenon. Anemia in teenage girls has been linked to impairments in verbal memory and learning, which can improve with iron replacement therapy, and girls with iron deficiency with and without anemia have been shown to score below average in math assessments. Of note, the cognitive sequelae of iron deficiency may precede the anemia itself as CNS iron is decreased before red blood cell production is impaired.

Populations at Risk for Iron Deficiency Anemia

Neonatal and Infant Iron Deficiency Anemia

Neonates of mothers with iron deficiency are at increased risk for IDA in early infancy. During the first 5–6 months of life, the normal term infant is iron replete. However, several conditions in the newborn period can lead to the development of IDA:

- Prematurity
- The administration of erythropoietin for anemia of prematurity
- Fetal-maternal hemorrhage
- Twin–twin transfusion syndrome
- Other perinatal hemorrhagic events
- Insufficient dietary intake

Premature infants are at increased risk for IDA in early infancy because of a smaller total blood volume at birth, increased loss through phlebotomy, and poor gastrointestinal absorption. Dietary issues contribute significantly to the evolution of IDA in infancy and early childhood. Common factors leading to IDA include the following:

- Insufficient iron intake
- Decreased absorption because of poor dietary sources of iron

- Early introduction of whole cow's milk
- Occult blood loss secondary to cow's milk intolerance
- Medications
- Malabsorption states

Recommendations for the prevention of iron deficiency in infants include the following:

- Encourage breast-feeding for the first 4–6 months; after this time, consider adding iron-fortified cereals. Two or more servings a day meet an infant's requirement for iron.
- For breast-fed preterm or low-birth weight infants, begin iron supplementation (1–2 mg/kg/day) at 1 month and continue until 12 months.
- For infants younger than 12 months of age who are not breast-fed or are partially breast-fed, use only iron-fortified formulas.
- At 6 months of age, encourage one feeding per day of foods rich in vitamin C.
- After 6 months of age, or when developmentally ready, consider introducing pureed meats, which increase the absorption of nonheme iron.
- Avoid low iron formulas or cow's milk until 12 months of age.
- Children aged 1–5 years should consume no more than 600 mL (20 oz) of milk daily. They should consume an adequate amount of iron-containing foods to meet daily requirements.

Toddler Iron Deficiency Anemia

Although the rapid growth rates of infancy are complete, iron deficiency anemia is most prevalent at this stage of development, particularly between 1 and 2 years of age. Many children have low iron stores early in the toddler years, particularly those who have received whole cows' milk throughout many months of infancy. Further, the dietary forms of iron consumed during these ages are often the nonheme forms of iron salts, iron that is much less bioavailable. Although insufficient stores and poor dietary intake are common in this age group, microcytic anemia presenting after the age of 3 years must be further investigated. Further investigation should aim to exclude malabsorption, bleeding, or chronic illnesses with true or apparent iron deficiency. Inflammatory bowel disease may occasionally present in toddlers. Ulcerative colitis presents as bloody diarrhea with incidental anemia. Crohn's disease is often more insidious, sometimes only vague ill heath and anemia are found.

Adolescent Iron Deficiency Anemia

The Third National Health and Nutrition Examination Survey (NHANES III) found a 9% incidence of iron deficiency and a 2% incidence of iron deficiency anemia among American females between the ages 12 and 15 years; the respective values were 11% and 3% in girls between the ages of 16 and 19 years. Less than 1% of adolescent males had iron deficiency. Studies in other countries have found higher rates of iron deficiency in male and female adolescents. Adolescents with chronic illness, heavy menstrual blood loss (>80 mL/month), or who are underweight or malnourished are at increased risk for iron deficiency and should be screened during health supervision or specialty clinic visits. Overweight and obese adolescents also appear to be at increased risk for iron deficiency and should undergo screening. Obesity was a risk factor for iron deficiency anemia in both boys and girls, but rates were approximately three times higher in girls. In addition, adolescent athletes, particularly those participating in endurance training, following alternative diets (vegetarian), or females at menarche, appear to be at risk for iron deficiency and should be screened as part of the pre-sport physical examination.

Differential Diagnosis

The differential diagnosis of microcytic anemia must be considered when iron deficiency anemia is suspected. Most commonly, microcytosis results from either iron deficiency, alpha or beta thalassemia trait, or heterozygous hemoglobin E disease. Hemoglobin electrophoresis is useful in differentiating and diagnosing thalassemias and hemoglobinopathies. Less common causes include inflammation, lead toxicity, thalassemia major, and sideroblastic anemia. Infection and anemia of chronic disease, while usually associated with normocytic anemia, may cause a mild microcytic anemia as well.

Blood loss must also be ruled out in children presenting with features of anemia. Most frequently, a dietary history of foods not fortified with iron and/or excessive cow's milk intake (>24 oz/day) may be elicited in these patients, especially those between the ages of 6 months and 2 years. Cow's milk iron is poorly absorbed in comparison to human breast milk, and excessive consumption results in early satiety and delayed gastric emptying. This, in turn, leads to decreased intake of iron-rich foods. Additionally, cow's milk often causes microscopic blood loss and may cause gross blood loss

if a significant milk-protein inflammatory colitis develops. It is therefore recommended that children ideally consume <16 oz of cow's milk daily and eat iron-fortified foods. Other sources of blood loss, such as gastrointestinal abnormalities or infections, should also be considered. Peptic ulcers, polyps, Meckel diverticula, hemangiomas, and inflammatory bowel disease may present with anemia. Hookworm infestation and *Helicobacter pylori* infection are important infectious causes of iron deficiency anemia and should be considered in geographic areas in which these infections are prevalent. Consideration of the patient's ethnicity may be useful in differentiating the causes of anemia. Alpha thalassemia is found in children of African, Chinese, and Southeast Asian descent. Beta thalassemia occurs in those of Mediterranean, African, and Asian origins. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is more commonly found in children of Mediterranean descent. Hemoglobinopathies, such as sickle cell disease and sickle cell thalassemia, are found more frequently in those of African descent.

Laboratory Features

Red Blood Cell Indices

Even before anemia occurs, the red cell indices fall and they fall progressively as the anemia becomes more severe. The blood film shows hypochromic, microcytic cells with occasional target cells. The reticulocyte count is low in relation to the degree of anemia. The platelet count is often moderately raised in iron deficiency, particularly when hemorrhage is ongoing.

Serum Iron and Total Iron-Binding Capacity

The serum iron falls and the total iron-binding capacity (TIBC) rises so that the TIBC is less than 10% saturated. This contrasts both with the anemia of chronic disorders when the serum iron and TIBC are both reduced and with other hypochromic anemias, where the serum iron is normal or even raised.

Serum Transferrin Receptor

Transferrin receptor is shed from cells into plasma. The level of serum transferrin receptor is increased in iron deficiency anemia but not in the anemia of chronic conditions or thalassemia trait. The level is also raised if the overall level of erythropoiesis is increased.

Serum Ferritin

A small fraction of body ferritin circulates in the serum, the concentration being related to tissue, particularly reticuloendothelial, iron stores. The normal range in men is higher in men than in women. In iron deficiency anemia, the serum ferritin is low. A raised serum ferritin indicates iron overload. Other causes of increased ferritin include excess release of ferritin from damaged tissues or an acute phase response (e.g., inflammation). The serum ferritin is normal or increased in the anemia of chronic disorders.

Therapy

For infants and children presenting with a mild microcytic anemia and a presumptive diagnosis of IDA, the most cost-effective strategy is a therapeutic trial of oral iron supplementation. Ferrous sulfate (3–6 mg/kg of elemental iron, once or twice daily between meals) should produce a rise of more than 1 g/dL in patients with IDA. For infants with confirmed IDA, ferrous sulfate (3–6 mg/kg/day of elemental iron) remains the standard therapy. Iron-fortified formulas and iron supplementation at these doses are infrequent causes of gastrointestinal symptoms. In children with severe IDA, a reticulocyte response may be seen within 72 h. If a child does not respond to adequate oral iron supplementation, potential causes for refractory IDA include the following:

- Failure to adhere to recommendations
- Intolerance to medication
- Ongoing gastrointestinal blood loss
- Chronic inflammatory disease
- Pulmonary hemosiderosis
- Incorrect diagnosis

Parenteral iron therapy should be reserved for patients with severe, persistent anemia who have proven intolerance to oral supplements, malabsorption, or poor compliance to oral therapy. Parenteral iron should be used with caution because there is a 2–3% risk for anaphylaxis, some cases of which result in death. Iron dextran is the parenteral form most commonly used preparation for pediatric patients. Sodium ferric gluconate and iron sucrose are also available, but these were developed for use in dialysis patients and are not

approved by the US Food and Drug Administration for use in children.

Transfusion therapy is rarely necessary for severe IDA, even with hemoglobin concentrations of 4–5 g/dL. Transfusions should be reserved for patients in distress (heart rate greater than 160/min, respiratory rate greater than 30/min, lethargy, not feeding well). Transfusions should be administered with caution to such patients, giving transfusion volumes of 5 mL/kg over 3–4 h to avoid inducing heart failure.

Follow-up

Follow-up is essential because of the effects of iron deficiency on neurodevelopment. Unfortunately, failure to follow up is a common occurrence, even among children who present with severe anemia. It is essential that the health care provider develop a proactive plan to ensure adequate compliance and follow-up of these patients during a critical time of neurodevelopment.

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319 Autoimmune Hemolytic Anemia

Veronica H. Flood · Michael Recht

Definition/Classification

Autoimmune hemolytic anemia (AIHA) is a condition in which red blood cell (RBC) destruction occurs due to antibody formation directed against self RBC antigens. In children, AIHA typically occurs following viral infection. AIHA can be due to either warm or cold antibodies, with the temperature referring to the optimal binding temperature of the antibody. AIHA is less likely to be chronic in children than in adults, but the anemia may be severe on initial presentation. In adults, the incidence of AIHA is approximately 1–3/100,000. Warm AIHA is more common than cold AIHA, accounting for about 90% of adult cases. The prevalence of cold AIHA in adults is 16/million. In children, the incidence is unknown, but mild AIHA may be more frequent, with some cases never coming to medical attention.

Pathology

Warm AIHA is due to IgG antibodies directed against RBC membrane proteins (*Table 319.1*). These antibodies bind maximally at body temperature (37°C), causing extravascular hemolysis. Most RBC destruction occurs via splenic macrophages, although liver sequestration may occur. Pediatric AIHA is thought to result from antecedent viral infection inducing anti-RBC antibodies, possibly through molecular mimicry as has been described for infection-associated ITP. Additional mechanisms include self-ignorance, loss of tolerance, polyclonal T or B cell activation, and immunoregulatory disorders.

Antibodies may be directed against any RBC antigen, but anti-Rh antibodies are the most common, usually anti-e or anti-c. Epitope mapping studies performed for the Rh D autoantigen have identified specific peptides important in IL10-mediated T cell response, although the clinical significance is not yet defined. Glycophorin is another common antigenic site. In addition, antibodies have been reported against Wr^b, En^a, LW, U, Ge, Sc1, Kell, and band 3. Warm AIHA antibodies are usually polyclonal.

Evans syndrome refers to those patients with both AIHA and ITP. The disorders may occur sequentially or simultaneously, and relapse is frequent. Underlying immune dysregulation may be present, with new evidence suggesting Evans syndrome is part of a spectrum with autoimmune lymphoproliferative disease (ALPS). Seif and colleagues studied 45 children with Evans syndrome and diagnosed 47% with ALPS. Treatment of refractory Evans syndrome and ALPS differs from that of isolated pediatric AIHA in that these patients may require additional immune modulatory agents. Many, however, do respond to corticosteroids.

Cold AIHA is due to IgM antibodies, also referred to as cold agglutinins. These antibodies bind at lower temperatures, with maximal reactivity typically at 4°C. Mycoplasma infection is the most frequent triggering agent for cold AIHA in children. Antibody specificity is usually anti-I or anti-i. Cold AIHA antibodies are usually monoclonal and hemolysis is primarily intravascular.

Paroxysmal cold hemoglobinuria (PCH) is caused by IgG antibodies that bind at cold temperatures but cause RBC lysis at warmer temperatures. These are often referred to as Donath-Landsteiner antibodies. The Donath-Landsteiner antibody is directed against the P antigen. The classic presentation of PCH in adults is associated with syphilis, but in children viral infections are the most common cause. Many different viral and bacterial pathogens have been reported in childhood PCH, including *Staphylococcus aureus*, *Haemophilis influenzae*, and adenovirus.

Clinical Manifestations

Hemolytic anemia is the hallmark of AIHA. Patients may present with fatigue or pallor due to the anemia. Dizziness, headache, and shortness of breath are signs of more severe anemia. Jaundice or scleral icterus may be noted due to elevated bilirubin from extravascular hemolysis. Dark, cola colored urine occurs in the presence of intravascular hemolysis. Fever may also be seen, particularly with viral illnesses as the precipitating factor. On exam, patients may demonstrate splenomegaly, but spleen size may also be

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Table 319.1
Classification of AIHA

Type	Antibody	Temperature	Specificity
Warm AIHA	IgG	37°C	Anti-Rh most common
Cold AIHA	IgM	0–4°C	Anti-I or anti-i
PCH	IgG	0–4°C	Anti-P

AIHA autoimmune hemolytic anemia, *PCH* paroxysmal cold hemoglobinuria

Table 319.2
Laboratory workup for AIHA

Initial testing	Confirmatory testing
Complete blood count	Direct antigen test (Coombs)
Review of peripheral blood smear	Donath-Landsteiner testing
Reticulocyte count	
Lactate dehydrogenase	
Bilirubin (total and indirect)	
Haptoglobin	
Urinalysis	

normal. Tachycardia may be present, particularly if the anemia is of recent onset. Lymphadenopathy is common in patients with viral infections. Cold AIHA may present with acrocyanosis similar to that seen in Raynaud's syndrome.

Diagnosis

Diagnosis of AIHA involves a variety of laboratory tests, with the typical workup summarized in *Table 319.2*. A complete blood count will show anemia, typically with a normal MCV. The RDW is usually high due to concurrent elevation in the reticulocyte count. Except in the setting of marrow suppression due to parvovirus, there is usually a brisk reticulocytosis. Review of the peripheral blood smear should show spherocytes, formed when part of the antibody-coated RBC membrane is removed by the spleen, resulting in spherocytes rather than the classic biconcave disk shape. Increased hemolysis will result in increased spherocytosis. Cold AIHA may result in RBC agglutination on the peripheral smear. Erythrophagocytosis may also be observed (*Fig. 319.1*).

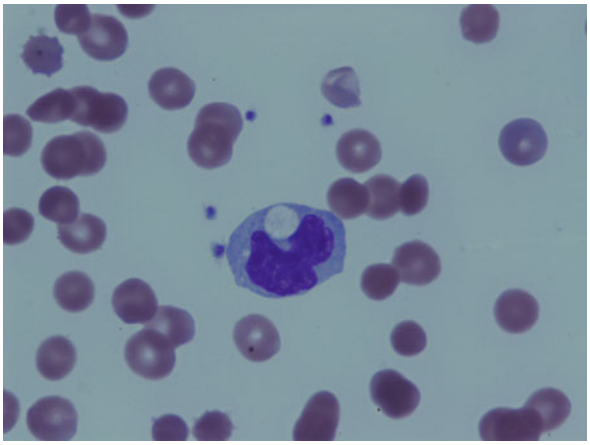

Figure 319.1
Peripheral smear demonstrating spherocytes and erythrophagocytosis (courtesy of Dr. Gabriela Gheorghe, Medical College of Wisconsin)

Blood chemistries will show elevated unconjugated bilirubin levels. Conjugated bilirubin should be normal in AIHA. Lactate dehydrogenase is also elevated due to increased RBC turnover. Haptoglobin will be decreased due to scavenging of free hemoglobin. Hemoglobinuria is uncommon in warm AIHA but frequently seen in cold AIHA and paroxysmal cold hemoglobinuria.

The pathognomonic test for AIHA is the direct Coombs test, or direct antiglobulin test (DAT). The DAT detects IgG antibodies or complement (C3) bound to the patient's RBCs. In warm AIHA, the IgG DAT will be positive, while in cold AIHA, the complement DAT will be positive, demonstrating the presence of complement on the RBC surface. The DAT is performed by incubating patient RBCs with reagents containing either anti-IgG or anti-complement to detect bound antibodies. Occasionally, symptoms of AIHA will be present with a negative DAT. Rare patients will have a positive DAT without symptoms. Thermal amplitude testing may be helpful, particularly for cold AIHA. Testing is performed at 4°, 22°, 30°, and 37°C to determine at what temperature maximal agglutination occurs.

Donath-Landsteiner testing should be performed when paroxysmal cold hemoglobinuria is suspected. If patient serum is incubated with normal RBCs at 0°C or 37°C, no lysis is observed, but when the incubation first occurs at 0°C and is then moved to 37°C, lysis will occur. Thermal amplitude may vary, with some antibodies binding at intermediate temperatures.

Table 319.3
Treatment options for AIHA

First line treatment	Second line treatment	Third line treatment
Corticosteroids	Rituximab	Plasmapheresis
Transfusion	Splenectomy	Cytotoxic agents Cyclophosphamide 6-Mercaptopurine Azathioprine 6-Thioguanine Danazol
IVIG		Immune suppressive agents Cyclosporine Mycophenolate mofetil

Differential Diagnosis

AIHA is due to antibody-mediated RBC destruction. Other causes of hemolysis should be considered and excluded on the basis of patient and family history as well as laboratory testing. Hereditary spherocytosis (HS) can present with anemia and spherocytosis, although the DAT should be negative in HS. Enzymopathies and other RBC membrane defects may also present with anemia and hemolysis. Family history may be useful in evaluation for the presence of inherited RBC defects, as many patients will have affected parents or other family members. Dark urine due to intravascular hemolysis is common in cold AIHA, but may also be a presenting feature of paroxysmal nocturnal hemoglobinuria (PNH). Anemia and hemolysis are also seen in microangiopathic disorders such as hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP) although thrombocytopenia and schistocytes on the peripheral blood smear should help to differentiate these from the anemia of AIHA.

In addition, AIHA may be secondary to other underlying disorders. Systemic lupus erythematosis has been associated with AIHA as has lymphoma. Infections such as HIV may also be responsible for AIHA. Hemolytic anemias may occur following solid organ or bone marrow transplant when there is an ABO mismatch between donor and recipient, with antibodies produced either by the grafted marrow or organ against recipient RBCs, or by the recipient against the donor RBCs. Adults are more likely to have AIHA secondary to an underlying condition than young children.

Drug-induced hemolytic anemia has been reported following administration of numerous medications, including penicillins, cephalosporins, and methyldopa. While original reports of drug-induced immune hemolysis were common with penicillin and methyldopa, cephalosphorins are now responsible for the majority of cases. Reactions have been reported with other frequently used medications, including NSAIDs and trimethoprim.

Treatment

Transfusion may be required in severe AIHA. Symptomatic patients should receive the least incompatible unit available, but extensive testing should not delay transfusion when clinically indicated. Most children with AIHA are previously healthy, and are unlikely to have previous exposures such as pregnancy or transfusions that could have led to the development of an underlying alloantibody. Since most AIHA antibodies are directed against common RBC antigens such as the Rh epitope, finding a perfectly compatible unit may be impossible. In such instances, slow RBC transfusion is acceptable, with close monitoring for a possible transfusion reaction. Survival of the transfused cells will likely be affected by the autoantibody as well, but may suffice to reduce symptoms while other therapeutic measures are employed. Some clinicians recommend using the "least incompatible" unit but transfusion guidelines at present support transfusion regardless of the crossmatch results once a significant alloantibody has been ruled out. Hemoglobin levels less than four merit transfusion, as do children with significant symptoms, particularly with concurrent reticulocytopenia. For cold AIHA, a blood warmer should be used to maintain a temperature of 37°C. Additional treatment options are summarized in *Table 319.3*.

Steroids are the mainstay of AIHA treatment. In warm AIHA, steroids decrease RBC sequestration and antibody formation. Glucocorticoids are thought to inhibit clearance of RBCs via the Fc receptors. Their effect, however, is not instantaneous, as improvement in symptoms usually takes several days. Dosing varies widely in pediatrics, with typical dosing of prednisone at 1–4 mg/kg/day given for at least 5 days or until the hemolysis slows. Most clinicians will then wean steroids over several weeks but no standard protocol exists. IV methylprednisolone may be used in severe cases. Response rates to oral steroids are excellent, with typical response rates of 80% in both adults and children. Relapses are infrequent in children, but may occur, so close monitoring following recovery is

warranted. Parents should be counseled regarding signs and symptoms of anemia.

Cold avoidance is important in paroxysmal cold hemoglobinuria. Since these antibodies bind only at cold temperatures, preventing binding will reduce hemolysis. Room temperature should be raised as high as comfortable. In addition, patients should avoid cold foods, such as ice cream and popsicles, as these may precipitate a bout of hemolysis. Warm clothes, including hats and gloves, should be worn when outside, and extreme cold temperatures avoided if possible. IV fluids and medications, including RBC transfusions, should be administered via a blood warmer.

IVIG may be useful, either alone or in combination with steroids. Trials of IVIG in adult patients demonstrated a response rate of 40%. Early pediatric trials showed a response in 3 of 4 children. A larger study demonstrated a response rate of 40%, but children tended to fare better than adults. IVIG may work by several mechanisms, including Fc receptor blockade or decrease in antibody production. Cold AIHA is thought to be generally less responsive to IVIG than warm AIHA.

Splenectomy is generally reserved for those children refractory to medical therapy for two reasons. First, the risk of infection following splenectomy in children is not insubstantial, and therefore should be avoided in younger children if at all possible. Second, the response rate to splenectomy is only about 60%, with at present no clear indication of which patients will respond best to splenectomy. In theory, removing the spleen will remove the site of RBC destruction, but some patients have continued hemolysis, suggesting that alternate sites of RBC removal are present.

Recently, the monoclonal anti-CD20 antibody rituximab has been used for a variety of autoimmune conditions, including AIHA. Rituximab is a chimeric antibody composed of human IgG heavy and light chains fused to a murine variable region. It binds to CD20, removing B cells from circulation and thus decreasing antibody production. Reactivation of hepatitis B has been reported following rituximab treatment. The risk of serious infection, however, appears to be low despite B cell depletion. Some clinicians administer IVIG following rituximab, but there are no strong data to support its use. Adult trials suggest approximately 50% will respond to rituximab, and those who relapse following rituximab may respond to retreatment. One pediatric trial showed response in 13 of 15 patients, although 3 of the responders later relapsed. Response rates in children appear to be greater than those in adults, with over 90% remission in a collection of case reports. Publication bias, however, must be taken into account, as it is likely there are many non-responders that have not shown up in case reports. At present, rituximab and splenectomy are both considered second line treatment following steroids and/or IVIG.

Plasmapheresis may be of some utility in cold AIHA to remove the inciting IgM antibody. A blood warmer should be utilized to keep blood products at 37°C. Plasmapheresis has also been utilized in warm AIHA. No clinical studies exist, but case reports in adults with severe AIHA suggest a response rate of around 65%. The necessity of catheter placement limits this procedure to pediatric intensive care units in most hospitals, and plasma exchange may not be rapidly available for small children, limiting the use of this therapeutic modality. However, it may be beneficial in refractory cases.

Numerous other cytotoxic agents have been utilized in refractory AIHA, including cyclophosphamide, 6-mercaptopurine, azathioprine, 6-thioguanine, and danazol. Immune suppressants such as cyclosporine or mycophenolate mofetil have been tried with some success. In pediatric AIHA patients, a recent study by Sobota and colleagues in 29 refractory AIHA patients demonstrated an 83% response rate to 6-mercaptopurine. Consideration of immune suppressive agents for refractory patients should take into account cost and convenience of administration as there is at present no clear order of precedence given the limited data available on these medications in pediatric AIHA.

Summary

AIHA is not uncommon in children. Although warm AIHA is observed most frequently, cold AIHA and PCH may also occur in this age group. Viral infections are thought to be the initiating agent in pediatric AIHA. Children typically present with anemia, reticulocytosis, and signs of hemolysis. The diagnosis of AIHA relies on the ability to demonstrate the presence of anti-RBC antibodies, typically through a positive DAT. Treatment may be required, with steroids the mainstay of AIHA therapy. Alternate treatment options are available for refractory patients.

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320 Glucose-6-Phosphate Dehydrogenase Deficiency

Hassan M. Yaish

> The indiscriminate selection of a battery of hematologically oriented tests, such as obtaining a Coomb's test and levels of serum iron, Vitamin B12, and folic acid in every anemic patient is wasteful, unwise, and unnecessary.
>
> Maxwell Wintrobe, 1930

Among the various red cell enzymes disorders, glucose-6-phosphate dehydrogenase (G6PD) deficiency is by far the most common and most significant clinical entity. The several disorders resulting from this enzymopathy affect more than 400 million people worldwide and probably twice as many heterozygous girls. The highest incidence is encountered in the tropics or the subtropics where malaria was endemic in the past. A highest incidence of G6PD deficiency is found around the Mediterranean region, affecting Southern Europeans, Middle Easterners, and North Africans. Both the rate of incidence and the type of G6PD may vary from one region to another in the same country. More than 50% of the populations of certain oases in the Eastern Province of Saudi Arabia, for instance, were found to have G6PD deficiency, in contrast to less than 2% in the central region. G6PD deficiency is also encountered in certain parts of India and Southeast Asia.

G6PD Function

This enzyme catalyzes the first reaction in the oxidative pentose phosphate pathway, through which less than 5% of the red cells' glucose is metabolized. It is clear, therefore, that the main function of this pathway is not glucose metabolism but to provide a continuous supply of the reduced nicotinamide dinucleotide phosphate (NADPH) necessary for conversion of the oxidized form of glutathione (GSSG) to the reduced form (GSH), in a second reaction mediated by glutathione reductase (*Fig. 320.1*). Reduced glutathione, in turn, plays a critical role in the detoxification and reduction of the various oxidants accumulating in the red cells, such as hydrogen peroxide and other oxygen radicals. For this reason, G6PD was classified as a "housekeeping" enzyme. The last reaction in this pathway is usually mediated by glutathione peroxidase and is crucial for the protection of the integrity of the red cell, which is already handicapped by the lack of a nucleus and mitochondria that render it unable to produce G6PD. In addition, the red cell's oxygen load represents an occupational hazard for the cell itself. It acts as a continuous source for oxidants with damaging potential for the cell integrity. These red cell characteristics explain why, among all cells that lack G6PD activity, red blood cells are the most vulnerable. Many children with G6PD deficiency develop episodic hemolysis upon exposure to oxidants.

G6PD Polymorphism

The G6PD gene (Gd) is located on the long arm of chromosome X in close proximity to the color blindness and the classic hemophilia A genes. Inherited as an X-linked disorder, it affects primarily hemizygous boys (Gd−), homozygous girls (Gd−/Gd−), and occasionally heterozygous girls (Gd−/Gd+). More than 400 different variants of G6PD have been identified so far. Almost all such variants are the results of point mutations rather than actual deletions. Amino acid substitutions at different points of the G6PD gene's polypeptide chain characterize the various mutants, similar to the substitutions encountered in the different hemoglobinopathies. The G6PD enzyme mutants include:

G6PD B+: Refers to the normal enzyme found in most populations.

G6PD A+: Designation for another normal enzyme mutant present in people of African origin.

G6PD A−: The designation for the African mutant once activity drops to 5–15% of normal.

G6PD B− (Mediterranean): Designation for the variant exhibited by people of Mediterranean, North African, and Far East descent with activity less than 5% of normal.

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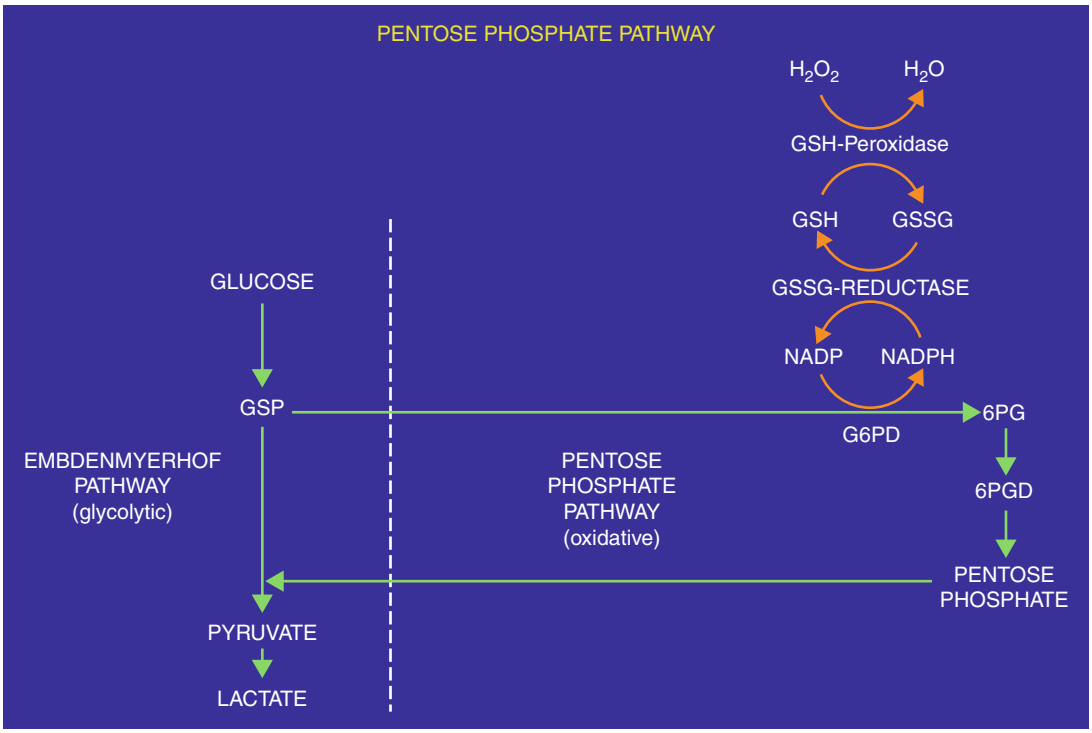

Figure 320.1

Chronic Nonspherocytic Hemolytic Anemia

Small minorities of individuals with G6PD deficiency tend to manifest a variable degree of hemolysis that can be easily detected at all times. Such patients are constantly symptomatic with anemia that ranges from slight to transfusion dependent. Reticulocytosis, jaundice, and splenomegaly are frequent findings. The hemolysis is extravascular, and the picture is that of a chronic hemolytic anemia. Various G6PD mutants are now known to cause congenital nonspherocytic hemolytic anemia (CNSHA), many of which have had their molecular defect and amino acid substitutions elucidated. The reason for the peculiar clinical behavior of this entity remains largely unexplained.

Patients are invariably males and the condition is encountered anywhere in the world especially in Europe and Japan. Symptoms may present at birth with neonatal jaundice (NNJ), which does not clear later on. The condition is caused by special G6PD mutations, commonly clustered in exon 10. Such mutations do not require a triggering exogenous factor to induce hemolytic crisis, hence anemia and hemolysis are always present. Acute exacerbation of hemolysis, however, may occur after exposure to the same oxidative agents that cause acute hemolytic anemia (AHA) in patients with the more common forms of G6PD deficiency. Several mutants of G6PD deficiency are known to manifest CNSHA, which may explain the variation in the severity of the condition.

Red cell morphology is usually normal; anemia, hyperbilirubinemia, low haptoglobin, and elevated LDH are frequently encountered. Lack of hemoglobinuria suggests that the hemolysis is extravascular and splenomegaly is frequently present.

G6PD Deficiency and Malaria

The "malaria hypothesis" was formulated nearly half a century ago based on the observation of the striking correlation between the world distribution of G6PD deficiency and *Plasmodium falciparum* malaria. Several epidemiologic and clinical studies since then have confirmed that G6PD deficiency confers some degree of protection from the potentially lethal malaria parasite. Even though all the clinical studies have agreed that such protection exists, nevertheless there was no agreement on who is

protected. Some studies have shown that the protection involves only the G6PD deficient male, while others concluded that the heterozygous female shows resistance to the parasite. Several factors have been suggested as a potential explanation for such differences. The mechanism of this phenomenon is not fully understood. One of the theories indicates that macrophages are able to recognize the parasite-infected G6PD deficient red blood cells more efficiently, accelerating the removal of the cells (suicidal infection).

Clinical Manifestations of G6PD Deficiency

Symptoms in G6PD-deficient individuals vary significantly in their severity depending on the particular G6PD variant involved. Red cell life span is always somewhat shortened in all types of G6PD deficiency, even though, in most cases, this finding is subclinical and not easily detected. For this reason, it is probably appropriate to describe the clinical manifestations separately for each clinical entity in G6PD-deficient children. Three clinical entities are encountered in patients with G6PD deficiency: acute hemolytic anemia, neonatal jaundice, and chronic nonspherocytic hemolytic anemia. The first two are the most common with AHA usually presenting as an episodic crisis upon exposure to oxidants, or in the neonatal period as jaundice mostly without anemia. The third form however is characterized by chronic life-long hemolytic process.

Acute Hemolytic Anemia

This condition is usually triggered by exposure to certain drugs such as the antimalarials, some sulphonamides, analgesics, and antimicrobials. Of interest, there have been reports of hemolytic reactions due to the use of the cosmetic dye henna applied to different parts of the body in certain populations around the world. Infections such as hepatitis, pneumonia, typhoid fever, and brucellosis were all incriminated in inducing hemolysis in G6PD deficient individuals. Ingestion of fava beans or inhalation of its pollen have caused significant hemolytic crisis in some deficient individuals resulting in the condition known as favism.

Except for the CNSHA mutant, described earlier, children with G6PD deficiency in the steady state are usually asymptomatic and hematologically normal. A hemolytic crisis can begin within a few hours to 3 days after the exposure to the responsible agent. The length of the interval as well as the severity of the reaction is both functions of the offending factor as well as the type of the deficient enzyme. G6PD B− (Mediterranean), for instance, is characterized by a disease that is more severe than G6PD A− (African), with intervals of hours rather than days and the potential of being fatal in rare occasions, rather than self-limited because of the extreme short half-life of the enzyme, even in the newly produced reticulocytes.

Diagnosis

The diagnosis is straight forward if the patient with a history of fava bean ingestion or exposure to its pollen develops hemoglobinuria. Rarely, a hemolytic crisis can occur in breast-feeding infants whose mothers have ingested fava beans. In the absence of such history, however, and in patients with hemoglobinuria, one should consider other forms of hemolytic anemia. A coomb's test is positive in autoimmune hemolytic anemia. Malaria and babesiosis need also to be considered in epidemic regions.

Favism

Ingestion of fava beans by the child with G6PD B− may result in the condition known as favism. This is a term used to describe the harmful effects of fava beans (*Vicia faba*) in certain individuals with G6PD deficiency. The condition has been known for centuries, probably dating from the early Greek and Roman times, as reflected by the observations attributed to Hippocrates and Pythagoras who warned his disciples against dangers of eating fava beans. The etiology of favism remained a mystery, however, until the mid-1950s, when the cause of acute hemolysis in African-American soldiers who were given antimalarial drugs was identified and attributed to the deficient G6PD enzyme. This condition occurs most often in people of Mediterranean, Middle Eastern, or Far Eastern origin. It is described as an episodic intravascular hemolysis associated with hemoglobinuria, described by the parents or the patients as dark urine resembling the color of dark tea or cola. Jaundice, abdominal pain, and vomiting are sometimes described. Laboratory findings reveal anemia with hemoglobins measured as low as 2–3 g/dL, hemoglobinemia, and hemoglobinuria early in the process. The presence of Heinz bodies (Fig. 320.2) on supravital stain or reticulocyte stain preparations supports

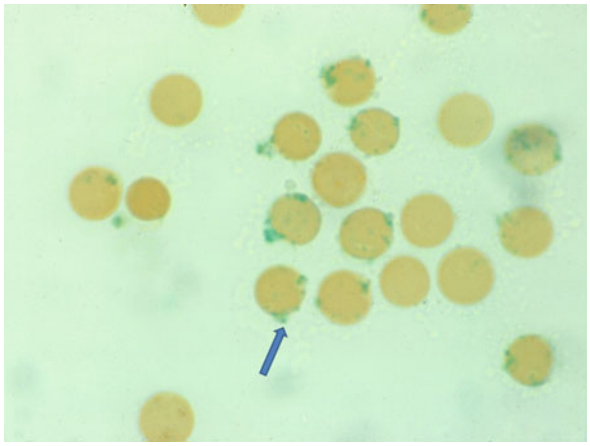

Figure 320.2

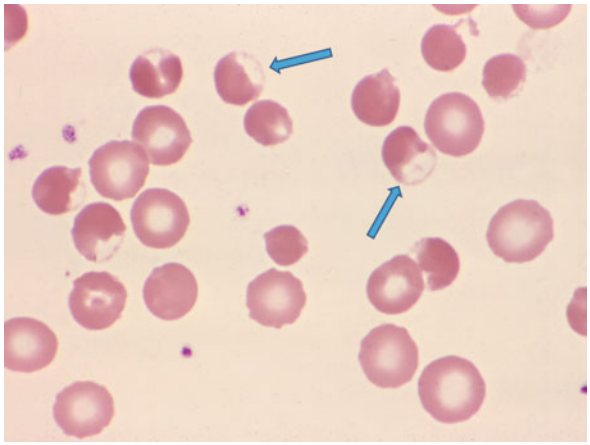

Figure 320.3

the diagnosis. Heinz bodies represent precipitated hemoglobin that is quickly pinched off by the spleen, leaving the characteristic blister or basket-shaped cell (*Fig. 320.3*). The morphology of the red blood cell is striking in that marked anisocytosis, contracted, and spherocytic-like cells are usually seen. Reticulocytes peak may be as high as 30% or more. Even though many patients require red blood cell transfusion, in many others the hemolytic crisis is self-limited and resolves spontaneously.

Not all deficient individuals develop favism upon ingestion of fava beans or inhaling the bean pollen. Furthermore, many individuals have eaten fava beans frequently before and after their first hemolytic crises without any similar episodes. This indicates that other etiologic factors are involved even though they have never been documented.

Neonatal Jaundice

The issue of hyperbilirubinemia in G6PD-deficient neonates of different ethnic groups has been a subject of debate for many years. At the present time, there is enough evidence to suggest that more neonates with G6PD deficiency of any type develop hyperbilirubinemia than do non-deficient ones. Earlier studies have confirmed such findings in newborns with G6PD B− (Mediterranean) and only the premature baby with G6PD A−. A recent report, however, demonstrated that despite the low incidence of hyperbilirubinemia in African-American newborns, 25% of children who develop kernicterus occur in this population of newborns. Sixty percent of the cases were due to G6PD deficiency while 40% were caused by preterm births and ABO hemolytic disease. In almost all such instances, no offending agent was identified and the etiology of the hyperbilirubinemia, which had presented as an exaggerated physiologic jaundice. Once a responsible agent becomes active, however, the potential response is expected to occur in any infant regardless of term or ethnicity. In such circumstances, the clinical picture may present more like hemolytic anemia and hyperbilirubinemia rather than exaggerated jaundice without anemia.

Evidence of cholestasis with significant elevation of conjugated bilirubin without any evidence of hepatobiliary disease was reported in a neonate with novel mutation resulting in CNSHA. A new, previously unrecognized agent has been incriminated as a cause of hemolysis and jaundice in newborns in certain regions of the world, mainly the Middle East, India, and North Africa. Neonatal hyperbilirubinemia of G6PD deficiency is rarely manifested at birth, and it usually peaks between days 3 and 4 of age, which coincides with time of discharge or after being discharged home.

Testing for G6PD Deficiency

All tests for G6PD activity are based on the detection of the presence of NADPH in the red cell by spectrophotometric methods. Leukocytes, which have much higher level of G6PD than erythrocytes, should be removed from the hemolysate for accurate measurements. Two kinds of tests are usually utilized: a screening test designed to identify deficient individuals and a quantitative method that measures the rate of formation of NADPH by spectrophotometric means. Dye decolorization, methemoglobin reduction, and the fluorescence spot test as well are all used for screening purposes. Once a positive test is identified, confirmation by a quantitative method is required.

Samples with less than 30% activity are considered deficient since any level that exceeds 30% is usually asymptomatic. G6PD activity in normal mature red cells is in the range of 7–10 IU/g of hemoglobin. In order to appropriately evaluate the results of G6PD testing, one should be aware of two major causes of false-negative results in deficient individuals at the time of testing. First, because leukocytes and platelets have higher G6PD activity than mature erythrocytes, when these cells contaminate the specimen, artificially elevated G6PD activity will be seen. Secondly, when G6PD is measured in a reticulocyte-rich specimen, levels can be artificially elevated.

Preventive Medicine in G6PD Deficiency

Universal screening for the deficiency is neither feasible nor recommended except in a very few circumstances where the condition is common and the symptomatology is relatively severe. Cord blood screening is currently utilized in several countries of the world where the condition is very common. Once an infant is identified as deficient, oxidant drugs, chemicals, and cosmetics (henna) are to be avoided. In addition, close monitoring for at least the first 4–5 days of life will ensure appropriate and timely management of any otherwise unexplained hyperbilirubinemia. The parents are instructed to avoid certain medications and chemicals in the older child, and to ask the child to give up eating fava beans or any foods that have fava bean as an ingredient (e.g., falafel). The physician should also know that most of the newly introduced drugs, regardless of the indications for its use, are not tested and may carry a potential risk for the deficient child.

It is known that hemolytic anemia and neonatal jaundice are the most common and well-recognized clinical manifestations in G6PD deficient individuals. Many other indirect effects of the deficiency are now being described. High blood sugar in patients with type 2 diabetes have been incriminated in inhibiting G6PD expression causing increased oxidative stress leading to gradual loss of beta cells in patients with diabetes.

The more pronounced effect of the enzyme deficiency on the RBCs is attributed to the fact that the cell is anucleated and unable to produce the enzyme. The eye lens is another example of an organ composed of non-nucleated cells, which might be the site of developing juvenile cataracts in young people with G6PD deficiency. Nucleated cells in the deficient individuals however retain the ability to produce some limited amounts of the enzyme as found in the granulocytes which may maintain a level of 30% of normal compared to only 5% in the RBCs. Despite this fact, some types of G6PD deficiency have been associated with increased incidence of infections, and poor healing after trauma as a result of leukocytes dysfunction.

Treatment

In acute hemolysis that develops after exposure to drugs or chemicals, particularly in patients with the G6PD A− mutant, the course is frequently mild and self-limited. On the other hand, in the G6PD B− (Mediterranean) type of G6PD deficiency, the hemolysis is frequently more severe and intervention is usually required. In many of the Middle Eastern countries, as is true elsewhere, blood transfusion has been used indiscriminately. To avoid such practice and minimize the various risks of blood transfusion, the physician is urged to evaluate the patient's clinical status carefully before blood transfusion is administered. On many occasions, the child presents to the physician toward the end of the course of illness with reticulocytes already rising, urine clearing, and none of the classic morphologic findings (blister cells, Heinz bodies) present. Such patients, even with their hemoglobin at 6–7 g/dL, can be closely observed for 24–48 h. On the other hand, a child with severe anemia and a hemoglobin causing symptoms, or in the face of ongoing hemolysis, should be considered for transfusion. All other acute episodes in between these two extremes should be evaluated carefully and treated accordingly.

Even though renal failure rarely occurs in children, one should always be aware of such a complication. In neonatal jaundice, on should always exclude other causes of hyperbilirubinemia and manage the baby according to the severity of the condition. Phototherapy has decreased the need for exchange transfusion in many neonates with hyperbilirubinemia. In such infants, one is rarely faced with severe anemia similar to the condition observed in hemolytic disease of the newborn. In most cases such infants are usually hyperbilirubinemic rather than anemic, and, unless they were exposed to an oxidant, they do not show any of the classic morphologic findings.

In CNSHA, the treatment depends on the severity of the anemia, which may be very mild, requiring only monitoring of the hemoglobin level and avoiding any oxidant that may exaggerate the existing anemia. Severe transfusion-dependent anemias are also encountered in such patients, and, based on the frequency of the transfusions, iron chelation might be required. Splenectomy was shown to

be effective in some children in either decreasing the frequency of transfusions or to treat a hypersplenic state. Genetic counseling and prenatal diagnosis should be considered in severe cases.

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321 Other Red Cell Enzymopathies

Ahmad A. Mallouh

Introduction

Congenital nonspherocytic hemolytic anemia was described for the first time by Dacie in 1952. In addition to a variable degree of hemolytic anemia, these disorders are characterized by the absence of spherocytes in the peripheral blood and normal osmotic fragility of the Red Blood Cells (RBCs). The term "Congenital NonSpherocytic Hemolytic Anemia" (CNSHA) is used to describe a heterogeneous group of congenital hemolytic anemias that results from the inherited deficiency of RBC glycolytic enzymes of the Embden-Meyerhof or pentose phosphate metabolic pathway. As these are anaerobic pathways, in which glucose is catabolized to pyruvate and lactate and thus produce Adenosine TriPhosphate (ATP), deficiency of any enzyme in this pathway results in decreased level or complete absence of ATP in the RBCs. ATP plays a major role in maintaining the red blood cells' membrane integrity. Glucose-6-Phosphate Dehydrogenase (G6PD) deficiency, the most common red blood cells enzyme deficiency, affects around 100 million people around the world. Pyruvate Kinase (PK) deficiency, the second most common red cell enzyme deficiency, affects a few thousand individuals globally. All the other red cell enzyme deficiencies affect a few hundred persons.

Pyruvate Kinase Deficiency

The production of the pyruvate kinase enzyme in human is controlled by two genes. The M gene (located on chromosome 15q22) is responsible for PK production in muscle, brain, white blood cells and platelets, while the L gene (located on chromosome 1q21) is responsible for the enzyme production in the red blood cell and liver. Hemolytic anemia with PK deficiency is limited to the L gene mutation that results in quantitative or qualitative deficiency in the red blood cell and liver with normal enzyme level in other tissues. Several (around 180) mutations of the L gene in association with PK-deficient hemolytic anemia have been identified. Clinically significant hemolytic anemia occurs in patients who are homozygous for the same gene mutation or doubly heterozygous for two different mutations. Heterozygous persons have intermediate level of the enzyme in the red blood cells and they are clinically and hematologically normal without evidence of hemolysis.

Pathophysiology

Pyruvate kinase is involved in the anaerobic glycolytic pathway which results in the production of ATP and lactate. Blockage of this pathway in the pyruvate kinase deficient patients leads to markedly decreased level or absent ATP in the red blood cells. ATP is thought to be essential to maintaining the red blood cell milieu. Reduced or absent levels or activity of PK lead to potassium and water leak from the RBCs resulting in dehydrated, shrunken and spiculated cells (echynocytes) and shortened red cell survival (hemolysis). In vitro, addition of ATP to incubated PK deficient red blood cells corrects this defect, while addition of glucose fails to do so. ATP deficiency, however, is not sufficient to explain the mechanism of hemolysis. It is difficult to demonstrate ATP deficiency in some patients with severe hemolysis, while hemolysis is not found in some disorders with more severe ATP deficiency. PK deficiency results in an increased level of 2,3 diphosphoglycerate (2,3-DPG), which leads to a rightward shift of the oxygen dissociation curve. This shift results in better oxygen delivery to the tissues, which explain the adequate exercise tolerance despite significant anemia in those affected by PK deficiency.

The pyruvate kinase deficiency phenotype is thought to be more common among people of the northern European extraction, with prevalence ranging between 0.14 to more than 1%. Other reports, however, have demonstrated a higher prevalence in other ethnic groups (Indians, Chinese, Saudi Arabs, Turks and Iranians). The prevalence of clinically significant anemia (homozygous or doubly heterozygous) is expected to be higher with high rate of consanguinity.

Clinical Picture

Pyruvate kinase (PK) deficiency is the most common cause of congenital nonspherocytic anemia (CNSHA).

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It affects males and females equally because it is inherited as a recessive trait. The severity of anemia is highly variable, ranging from a severe transfusion dependent hemolytic anemia beginning at birth to a well-compensated asymptomatic hemolytic process recognized in later life because of the worsening of anemia (aplastic or hemolytic crisis) or because of the development of complications (cholelithiasis). In some extreme conditions, the anemia is severe enough to cause non-immune hydrops fetalis. The degree of severity is typically similar within a family with PK deficiency. The severity is probably related to influence of the L gene and the compensatory effect of the M2 gene, which is widely distributed in various tissues including the red blood cells. Absence of this compensatory mechanism results in severe life threatening anemia. In severe cases, patients present, at birth, with evidence of hemolysis (pallor, jaundice and splenomegaly). Reticulocytes are usually extremely high (40–70%), especially after splenectomy. This interesting phenomenon of increased reticulocytes after splenectomy is thought to be due to the interaction between the PK deficient reticulocytes and some unknown factor in the splenic environment (possibly hypoxia due to hemostasis). The anemia and hyperbilirubinemia might be severe enough to require phototherapy with or without simple or exchange blood transfusion. Patients may present with one or more complications of disease, which include hepatosplenomegaly, gallbladder stones, transient aplastic crisis caused by parvovirus B19, megaloblastic anemia due to folic acid deficiency or a hyper-hemolytic event.

Diagnosis

Diagnosis of PK deficiency is based on clinical and laboratory findings described above and confirmed by the assay of the red blood cells' PK enzyme level. Specific gene mutation can be identified in specialized laboratories.

Treatment

Treatment of PK deficiency consists of supportive care, splenectomy, treatment or prevention of complications, stem cell transplantation and gene therapy. Intra-uterine transfusion is indicated for severe anemia with hydrops. Newborn infants with severe anemia and/or hyperbilirubinemia should be treated with phototherapy, simple transfusion, or exchange transfusion as appropriate. Infants and children who have severe anemia may require repeated transfusions. Transfusion may be sporadically required in patients with mild disease during transient aplastic or hemolytic events. As with all chronic hemolytic anemias, folic acid supplementation is recommended. Splenectomy is recommended for children with severe, transfusion-dependent anemia. Splenectomy results in the amelioration of the hemolytic process leading to either the abolishment or greatly decreasing the need for transfusion. Splenectomy should be delayed until 5–6 years of age to avoid post-splenectomy sepsis, unless otherwise absolutely necessary. Complications which require treatment and/or prevention include cholelithiasis, which often requires surgery. Post splenectomy sepsis by the encapsulated organisms (streptococcus pneumoniae, haemophilus influenzae and neisseria meningitidis) can be prevented by pre splenectomy immunization and post splenectomy antibiotic prophylaxis. Iron overload caused by blood transfusion may require chelation therapy. Hematopoietic stem cell transplantation has been successfully performed in some severe cases. Gene therapy is still experimental.

Deficiencies of Other Glycolytic Enzymes

Congenital nonspherocytic hemolytic anemia had been reported with several other glycolytic erythrocyte enzyme deficiencies, including hexokinase, glucose-6 phosphate isomerase, glyceraldehyde-3-phosphate isomerase, phosphofructokinase, triosephosphate isomerase, aldolase and phosphoglycerate kinase deficiencies. These rare inherited enzymopathies have in common, an autosomal recessive mode of inheritance and a nonspherocytic hemolytic anemia with variable severity, which usually starts in infancy. The anemia in the newborn might be severe enough and may be associated with hyperbilirubinemia that require phototherapy and simple or exchange transfusion. The anemia during infancy and childhood may be compensated and asymptomatic, or severe transfusion dependant. The anemia may be exacerbated with transient bone marrow aplasia or acute hemolytic event in association with infection. Red blood cell morphology is normal and osmotic fragility is normal. However, spiculated red cells and target red blood cells might be seen in some patients. The reticulocyte count is elevated, especially after splenectomy. Clinical manifestations are those of hemolytic anemia and its complications. Pallor, jaundice and splenomegaly are present in patients with severe disease. Gallbladder stones may develop early in childhood. Of interest is the reported association of these disorders with other hematologic, neurologic, metabolic, or glycogen storage diseases. Hexokinase deficiency was reported with Fanconi aplastic anemia, triosephosphate isomerase

deficiency with progressive neurologic disorder, phosphofructokinase deficiency with myopathy, phosphoglycerate kinase deficiency with mental retardation and aldolase deficiency with disorders of glycogen metabolism. Diagnosis of these disorders is confirmed by the enzymatic assay. Treatment is mainly supportive with blood transfusion as needed, phototherapy and/or exchange transfusion for severe neonatal anemia and hyperbilirubinemia, folic acid supplementation and cholecystectomy for symptomatic gallbladder stones. Splenectomy resulted in amelioration, but not complete resolution of hemolysis. After splenectomy, transfusion requirements is decreased or completely abolished.

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322 Red Blood Cell Membrane Disorders

Ahmad A. Mallouh

Introduction

The red blood cell (RBC) membrane is a complex structure consisting of approximately 50% proteins, 40% lipids, and 10% carbohydrates, containing 10–12 major proteins and possibly hundreds of minor ones. RBC membrane proteins are divided into those that are integral to the membrane (glycophorins A, B, C, and D that contain membrane receptors and antigens and protein 3 which is responsible for anion exchange) and those that play a role in the cytoskeleton. Spectrin is the major skeletal protein of the RBC membrane; it constitutes 50–70% of the skeletal part of the membrane. The RBC membrane has two major functions: maintenance of the structural integrity of the cell and control of cations, anions, and water permeability. As the membrane is semipermeable, water and some cations and anions can migrate passively through the RBC membrane. However, some cations (Na, K, and Ca) are transported through the membrane both passively and by an active mechanism (Na/K pump and calcium efflux pump) using energy produced by ATP. Changes in the membrane surface area in relation to the red cell volume result in changes in the shape and deformability of the cells. These changes render the abnormal RBCs susceptible to destruction by the reticuloendothelial system. Loss of surface area without loss in volume from either inherited or acquired causes results in formation of spherocytes. Following is discussion of inherited RBCs membrane disorders.

Hereditary Spherocytosis

Around 75% of hereditary spherocytosis (HS) is inherited in an autosomal dominant pattern. The remaining 25% are mostly inherited as an autosomal recessive trait. Some cases (up to 10% in some studies) are thought to be new mutation or mild cases of the dominant type. Homozygous of the dominantly inhireted HS has not been reported and is thought to be incompatible with life. The incidence of HS is about 200–300 per million in the Caucasians, but this figure is likely to an underestimation as mild cases are often not diagnosed. Some studies suggest that the true incidence is probably four to five times greater. The incidence in other ethnic groups is not known but thought to be much lower than that of the Caucasians.

Pathophysiology

The primary problem in HS is loss of the RBC membrane surface area leading to a change of the cell shape from a biconcave disk-like to a spherocyte. This change in the shape makes the cells less deformable and more susceptible to hemolysis in hypotonic solution (increased osmotic fragility). The reticulocytes and the younger red cells are not spherical. As these cell age they become more spherical and their membrane more rigid. The most common defect is spectrin deficiency. However three other abnormalities had been identified as the main causes of HS: combined spectrin and ankyrin, protein 3 deficiency, and protein 4.2 abnormality. The spherical RBCs with a rigid membrane are trapped and hemolyzed in the spleen (extravascular). The severity of anemia depends on this chronic process of intrasplenic hemolysis.

Clinical Picture

The disease is variable in severity ranging from the asymptomatic patient who is diagnosed only because of family history or because they develop cholelithiasis; to the severe patient who may be packed red cell (PRBC) transfusion dependent. Some patients present in the neonatal period with anemia, which may require PRBC transfusion, and/or jaundice, which requires phototherapy, or even exchange transfusion. In such patients, a family history of HS may be the first clue of the diagnosis. Other aspects of the family history that would raise the possibility of HS include "chronic anemia," jaundice in the neonatal period or later, splenomegaly, cholelithiasis, and/or history of HS. A child may present with severe abdominal pain and jaundice with or without fever and chills as a result of the cholelithiasis and/or cholecystitis. The degree of anemia is variable and so its manifestations. Around 5% of patients with HS have severe anemia, reticulocytosis, and significant splenomegaly. Anemia in these patients can be

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severe enough to cause hydrops fetalis and intrauterine death. Postnatally these patients often require repeated PRBCs transfusion. Up to 75% of patients with HS have moderate anemia with mild to moderate splenomegaly and moderate reticulocytosis, ranging from 5% to 10%. These patients usually, but not always, have the dominantly inherited condition. Patients with mild HS (20–30% of all patients) usually have a dominant type inheritance. As mentioned above these patients are asymptomatic and are diagnosed only on family study or when they develop complications as cholelithiasis or aplastic crisis. The spleen is palpable in 75–95% of people with HS. Splenomegaly in mild cases might be absent. In some patients (usually in the most severe ones who have a recessive type of inheritance), splenomegaly can be massive and may be the main presenting complaint. About 30–50% of adults with HS have history of jaundice. The jaundice in the newborn can be severe and may require exchange transfusion. In older children and adults it is usually mild and intermittent. In addition to the above-mentioned manifestations, patients may present with more acute complication. These include hemolytic events, aplastic events, megaloblastic events, cholelithiasis, cholecystitis, and severe neonatal hyperbilirubinemia. Hemolytic events are usually triggered by a viral infection that stimulates the reticuloendothelial system mainly in the spleen. The patient presents with anemia, jaundice, and reticulocytosis and often increased splenic size. Aplastic events are oftentimes caused by human parvovirus 19 (B19). These patients present with anemia, reticulocytopenia, and no jaundice. Megaloblastic events are due to folic acid deficiency. Therefore, folic acid supplementation is recommended for all patients with HS. Unlike the other types of events, a megaloblastic event usually develops slowly. Cholelithiasis can occur at any early age, having been reported in children as young as 3 years old. The incidence, however, increases with age; upto 75% of all patients with HS after the fifth decade of life. Most patients are diagnosed with gallstones in the second and third decade of life. Many patients with cholelithiasis are asymptomatic. However, several studies suggest that around 50% of patients with pigmented gall bladder stones have or are expected to develop symptoms of cholecystitis and/or biliary colic with jaundice.

Diagnosis

Diagnosis of HS depends on history, physical examination, and appropriately ordered laboratory tests. A family history of chronic anemia, confirmed HS, cholelithiasis at young age, or history of splenectomy is of paramount importance in suggesting the diagnosis. A history of anemia and or jaundice in the neonatal period which is not explained by other causes (blood group incompatibility) may suggest an inherited cause of hemolysis including HS. A history of previous blood transfusions in the patient or other family members might be present. Depending on the severity of anemia, patients may have exercise intolerance. Physical findings may include pallor (depending on level of anemia), jaundice, and splenomegaly. Biliary colic with jaundice may be the first presenting sign. Manifestations of cholecystitis (abdominal pain, fever, chills, and jaundice) may also be the first presenting problem. Growth retardation and delayed sexual maturation may be present in severe cases. Severe cases also may have bone marrow expansion mostly in the facial and other skull bones causing frontal bossing and dental malocclusion.

The degree of anemia is variable, ranging from compensated state with normal hemoglobin to severe, transfusion-dependent anemia. Most cases however have compensated mild to moderate anemia (hemoglobin >10 g/dl). Patients who present early during infancy usually have more severe anemia (hemoglobin 8–9 g/dl). Reticulocytosis is usually present. Its value depends on the severity of the anemia and the appropriateness of the bone marrow response. During aplastic events, reticulocytopenia is present. Unconjugated bilirubin may be high especially in jaundiced patients. Serum haptoglobin is usually low but it is not required for diagnosis. The hallmark of the disease is the presence of microspherocytes on a peripheral blood smear. The blood smear (*Fig. 322.1*) should be inspected by a qualified or experienced observer.

The most commonly used test to confirm the diagnosis of HS is the osmotic fragility. This test detects hemolysis of RBCs from patients affected with HS at higher concentration of saline than those of normal RBC. The unincubated osmotic fragility test, performed on fresh RBCs, may miss up to a third of the cases. Incubation of the blood for 24 h makes the test more sensitive. A newly described flow cytometry assessment can provide a rapid and reliable diagnosis, but is not generally available. Analysis of the cell membrane for determination of the specific protein defect is available only in specialized laboratories and is of no clinical value.

Treatment

As with other chronic hemolytic anemia, daily folic acid supplementation should be given to avoid megaloblastic events. PRBC transfusion might be needed in severe cases of hemolytic events or aplastic events. Phototherapy and/or

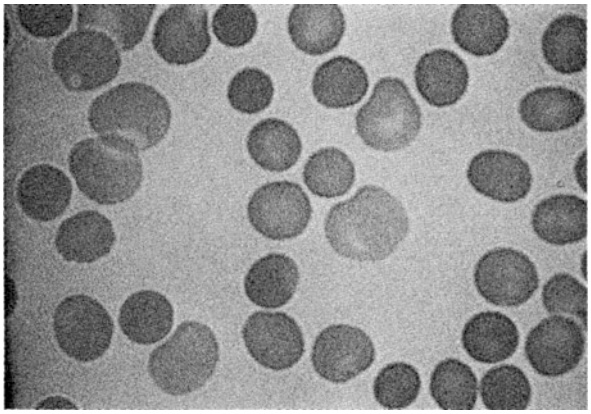

Figure 322.1
Blood smear in hereditary spherocytosis. Note the spherical RBCs without central pallor

exchange transfusion is indicated for newborn infants with severe anemia or hyperbilirubinemia.

Splenectomy usually results in complete or partial correction of the anemia associated with HS. RBCs maintain their spherical shape but their life span increases even though it is usually shorter than normal RBCs. Before proceeding with splenectomy, the following should be considered:

- Indications
- Potential benefits
- Potential risks and their prevention and/or treatment
- Type of the procedure
- Timing
- Potential failure and its causes

In patients with clinically mild HS, the only benefit of splenectomy is prevention of gall stone formation. The risk and cost of the procedure in this setting is higher than the expected benefit. If splenectomy is to be done, some studies suggest doing prophylactic cholecystectomy in the same setting. In patients with clinically severe HS, those who require repeated blood transfusion and those with moderate but symptomatic anemia, splenectomy is recommended. This procedure is expected to correct the anemia to normal values except in some patients with autosomal recessive HS, in which the anemia may be only partially corrected. In those patients with moderate but asymptomatic anemia (hemoglobin concentration from 8 to 10 g/dl), splenectomy may be indicated, even though there is a paucity of studies demonstrating benefit. The expected benefits of splenectomy include correction of anemia, prevention of development of cholelithiasis, prevention of bone marrow expansion and growth failure, decreased serum bilirubin level, and decreased reticulocyte count.

In addition to the risks of anesthesia and the surgical procedure, the most serious risk is post-splenectomy infection caused by encapsulated organisms (*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*). These infections are life threatening. Even though these infections can occur at any age they are more common when splenectomy is performed before 6 years of age. This serious problem can be minimized by:

- Delaying splenectomy until 6 years of age (unless absolutely necessary)
- Giving immunizations against the above-mentioned organism a few weeks before the procedure
- Giving antibiotic prophylaxis (usually penicillin)

The duration of the prophylaxis is not well established. Some authorities recommend a minimum of at least 3 years post splenectomy and probably for life.

Other post-splenectomy complications include an increased incidence of venous and arterial thrombosis and thromboembolism. An increased risk of arteriosclerosis later in life has been reported. Laparoscopic splenectomies are preferred by many centers because they may shorten hospital stay, decrease postoperative pain, and decrease scarring. Partial splenectomy (removing 80–90% of the spleen) results in significant improvement, but not complete resolution of the anemia. It however retains splenic function and decreases or prevents post-splenectomy sepsis. Total splenectomy is often needed later because the spleen regrows in most patients to its original size and hemolysis accordingly increases in severity. In one study near total (98%), splenectomy was found to correct anemia without significant regrowth of the spleen. In some patients, the hemolytic anemia in HS is only partially corrected or recurs after splenectomy, because of:

- The presence of a severe recessive phenotype
- Partial splenectomy
- The presence of accessory spleen which is not removed during surgery
- The presence of splenosis that results from spillage and peritoneal implantation of splenic tissue

Accessory spleens and splenosis should be suspected if Howell–Jolly bodies are not identified postoperatively. Confirmation of this diagnosis can be obtained by radiological means mainly nuclear scan.

Management of asymptomatic cholelithiasis is controversial. Some authorities recommend cholecystectomy with or without splenectomy, while the others suggest expectant observation. Performing the procedure when the patient's condition is stable and the timing is

appropriate for the patient and family is warranted. Management of symptomatic cholelithiasis is urgent.

Hereditary Elliptocytosis

Hereditary elliptocytosis (HE) is a genetically phenotypically and biochemically inherited type of hemolytic anemia characterized by the presence of elliptical, oval, or elongated (rod-like) and sometimes spherical RBCS in the peripheral blood smear (*Fig. 322.2*). The incidence is estimated to be from 250 to 500 per million. The mode of inheritance is autosomal dominant in most cases. However, a recessive inheritance is typical of the subtype called hereditary pyropoikilocytosis (HPP). HE results from a defect in the skeleton of the RBC membrane. Defects in several RBC membrane proteins have been identified, including spectrin, protein 3, protein 4.1, and protein 4.2 alone or in combination.

Clinical Picture

The clinical picture of HE is variable and ranges between a hematologically normal to a severe and occasionally fatal anemia. Most cases, however, are mild. The following subtypes have been described:

- Common HE: This most common type of HE is divided clinically into the following subtypes.
  - Silent carrier: These patients are clinically and hematologically normal. They have normal hemoglobin, normal RBC morphology, a normal reticulocyte count, normal LDH, and normal haptoglobin. Patients who are silent carriers of HE are usually diagnosed on family studies of an affected member.

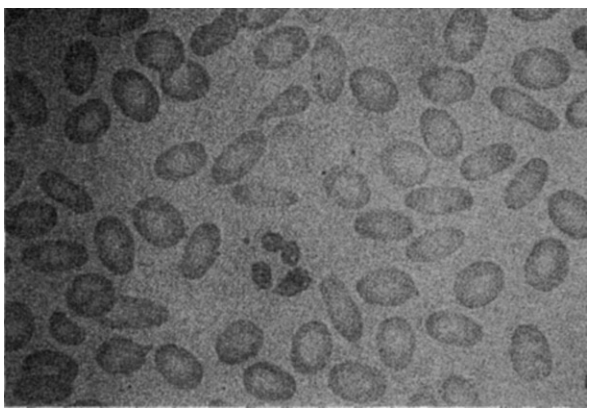

Figure 322.2
Blood smear in hereditary elliptocytosis

- Mild HE: These patients usually have a mild compensated hemolytic anemia with a mild reticulocytosis. They are clinically asymptomatic. They are diagnosed when elliptocytes are seen on a routine CBC. They may develop mild hemolytic events on exposure to certain infections.
- HE with chronic hemolysis: Several families had been reported with moderate hemolytic anemia with reticulocytosis without known trigger. Mild splenomegaly and mild RBC fragmentation can be present in these patients.
- HE with infantile poikilocytosis: In this interesting type of HE, infants have severe hemolytic anemia requiring repeated PRBC transfusions in the first 12–24 months. Their RBC morphologic and laboratory findings are similar to HPP (see below). One of the parents usually has common-type HE. The hemolytic process decreases over time. By 12–24 months of age, the clinical course is similar to those with mild HE. This type seems to be common in certain ethnic groups. The author has seen more than 100 cases in Saudi Arabian infants.
- Severe HE: In this type of HE, patients are often transfusion dependent. The disease can be fatal. Severe HE is thought to be a homozygous or doubly heterozygous form of mild HE.
- Hereditary pyropoikilocytosis (HPP): This type of recessively inherited hemolytic anemia was thought to be a specific entity, however further studies suggest that it a relatively severe subtype of HE. Both parents are often clinically and hematologically normal (silent carriers) but in other families at least one parent may have mild HE. HPP affects mostly people of African descent; however, it has been reported in other ethnic groups including a Saudi Arabian family reported by this author. HPP is characterized by moderately severe hemolytic anemia that usually starts in infancy and is lifelong. Many patients need repeated PRBC transfusions. Patients often have splenomegaly. The hallmark of this condition is the bizarre RBC morphology including spherocytes, microspherocytes, fragmented cells, cell membrane budding, schistocytes, and poikilocytosis. These morphologic changes are exaggerated with in vitro exposure to a relatively low temperature, resulting in increased fragmentation and more budding. Osmotic fragility is increased in patients with HPP. In most patients, the MCV is low, sometimes in the 50 or 60 femtoliter range.

- Spherocytic elliptocytosis: This type of HE is inherited in an autosomal dominant pattern. Spherocytic elliptocytosis has been reported only in Caucasians. The anemia is mild to moderate. Most patients have splenomegaly. Examination of the peripheral blood smear can be confusing as the number of elliptocytes can be lower than the number of spherocytes. Spherocytic elliptocytosis is considered a hybrid of ES an HS.
- Southeast Asian ovalocytosis: As the name implies, this type of HE is preset in the area of the world where malaria is or was endemic. Southeast Asian ovalocytosis is inherited in an autosomal dominant pattern. Heterozygous Southeast Asian ovalocytosis is asymptomatic, does not cause anemia, and is thought to be protective against malaria. The homozygous form is not compatible with life. Review of the peripheral blood smear is characteristic with the presence of "stomatocytic elliptocytes."

Diagnosis

Diagnosis of HE is straightforward, requiring a complete blood count, reticulocyte count, and a peripheral blood smear. Other tests (osmotic fragility, heat stability, and structural study of the RBCS membrane) are often of academic interest and rarely add any significant clinical diagnostic value. When considering the diagnosis of HE, several points should be kept in mind:

- Unaffected people may have up to 5% elliptocytes in their peripheral blood.
- Elliptocytes are increased in some acquired conditions, for example, megaloblastic anemias and iron efficiency anemia.
- Silent carrier HE can be diagnosed only with a RBC member structural study. This is rarely clinically indicated.
- HE with infantile poikilocytosis cannot be differentiated from true HPP except by time.
- Spherocytic HE can be confused with HS.

Treatment

Most patients with HE do not need any treatment except folic acid supplementation (especially when there is evidence of hemolysis) and observation for development of cholelithiasis. Blood transfusion is usually needed for severe episodes of anemia especially in homozygous common HE, HPP, infantile poikilocytosis in the first 12–24 months of life, and occasionally in the common type after a hemolytic event. Splenectomy might be needed in HPP and homozygous common HE if and when anemia is severe and repeated transfusion is required.

Hereditary Stomatocytosis

This rare RBC membrane defect is characterized by the presence of elongated RBCs with a slit-like pallor resembling a mouth (stoma). It is inherited in an autosomal dominant manner. The change in the shape of the RBCs results from a decrease in the ratio between surface area and cell volume, usually due to increased volume. The exact pathogenesis is not well understood. Alteration of the membrane permeability leads to sodium and water movement into the RBC causing increased cell volume. With increased water and sodium, the RBCs become swollen. The clinical and hematologic findings are variable. Approximately one third of the patients are asymptomatic with normal hematological values and no evidence of hemolysis. The remainder of the patients have mild to moderate and occasionally severe transfusion-dependent chronic hemolytic anemia, jaundice, and splenomegaly. Some patients with hereditary stomatocytosis have recurrent vaso-occlusive events (similar to those of sickle cell disease) and an increased incidence of thromboembolic complications especially after splenectomy. These two complications are thought to be due to increased adherence of the elongated RBC to the endothelium. Stomatocytes may be present on the blood smear of several congenital and acquired conditions. Stomatocytosis with thrombocytopenia and large platelets had been reported in people of Mediterranean origin. Stomatocytosis is associated with two hereditary diseases: cryohydrocytosis and familial pseudohyperkalemia. A syndrome of stomatocytosis with mental retardation and cataracts has been reported. Acquired stomatocytosis can occur with acute alcohol intoxication, chronic liver disease, and with administration of vinca alkaloids (vincristine or vinblastine). Stomatocytosis is often an artifact. Diagnosis of hereditary stomatocytosis is supported by the presence of a macrocytic, hypochromic hemolytic anemia with a high number of stomatocytes on the peripheral blood smear (up to 60%). Treatment is usually supportive (folic acid supplementation and blood transfusion in severe cases). Splenectomy for severe cases may be necessary and may improve the anemia. However, splenectomy may increase the risk of serious thrombotic complications.

Acanthocytosis and Echynocytosis

Acanthocytes have a small number (5–10) of irregularly spaced, long spicules that arise from the RBC membrane. Echinocytes, or crenated cells, on the other hand, have 10–30 regularly spaced, short projections that arise from the surface of red cells. Spur cells are remodeled acanthocytes in which spicules become blunt and short. Acanthocytes and echynocytes, separately or in combination, can be associated with several congenital or acquired conditions. They both are often found in end stage renal disease, advanced hepatocellular disease, and vitamin E deficiency. Echynocytes may be seen in association with pyruvate kinase deficiency. Echynocytes are commonly seen as artifact of the preparation of the peripheral blood smear. Acanthocytosis is a typical feature of abetalipoproteinemia, in which progressive ataxia, retinitis pigmentosa, and fat malabsorption are present. Acanthocytosis may be associated with hypothyroidism, myelodysplasia, having no expression of the Lutheran or McLeod blood groups, and infantile pyknocytosis. Acanthocytes are also associated with several neurological diseases including McLeod syndrome, various mitochondrial diseases, choreo-acanthocytosis, familial acanthocytosis with paroxysmal exertion-induced dyskinesias, and epilepsy and Huntington's disease. The significance and pathogenesis of this association is not understood. In most cases, the presence of acanthocytes and/or echynocytes is of no clinical significance except as a diagnostic tool for certain diseases.

Hereditary Xerocytosis

Xerocytosis is a chronic hemolytic anemia inherited as autosomal dominant trait. It is characterized by the presence of densely stained contracted and sometimes spiculated red cells. The hemoglobin may "puddle" in one part of the cell. The pathophysiology is due a defect in RBC membrane permeability, with an increased potassium efflux resulting in low potassium content. These changes lead to decreased deformability, increased rigidity, and increased susceptibility to shear cell damage. The diagnosis is based on the presence of chronic hemolytic anemia and the presence of xerocytes on peripheral smear. The MCV and MCHC are both elevated. Target cells are usually present. The osmotic fragility is decreased. The severity of anemia is variable, particularly during the newborn period, in which anemia may be severe enough to require exchange transfusion. The anemia may be exacerbated by viral infections. Transient aplastic events have been reported. A subtype of xerocytosis (called stomatocytic xerocytosis) is often difficult to differentiate from classic stomatocytosis. Both stomatocytes and dehydrated target cells are present on the peripheral blood smear. Unlike stomatocytosis, the osmotic fragility is reduced in stomatocytic xerocytosis. Like the classic form of hereditary xerocytosis, the MCV and MCHC are elevated. Treatment for xerocytosis is symptomatic. Folic acid supplementation is recommended. Splenectomy has been performed with amelioration of the anemia. However, there have been reports of an increased risk of deep venous thrombosis after this procedure in patients with this diagnosis.

Infantile Pyknocytosis

Infantile pyknocytosis is a transient hemolytic anemia that occurs in the newborn infants, particularly those born preterm. It is characterized by a hemolytic anemia and jaundice without splenomegaly. The severity of anemia is variable and may pass unnoticed. In some infants, however, the anemia is severe enough to require PRBC transfusion. The anemia peaks at 3–4 weeks of age and resolves spontaneously by 4–6 months of age. Pyknocytes are densely stained, spiculated, and irregularly contracted cells. Up to 5% of pyknocytes can be found on the peripheral blood smear in unaffected premature infants. Pyknocytes may be associated with many inherited or acquired disease including severe G6PD deficiency, neonatal hepatitis, hereditary elliptocytosis, vitamin E deficiency, and microangiopathic hemolytic anemia.

Vitamin E Deficiency

Vitamin E deficiency may occur in premature infants and in children with malabsorption disorders such as liver cirrhosis, cholestatic liver disease, cystic fibrosis, celiac disease, Crohn's disease, and pancreatic insufficiency. Hemolytic anemia, thrombocytosis, and the presence of a variable number of spiculated and contracted RBCs are the hallmark of the hematological manifestation of vitamin E deficiency. Generalized or pedal edema may be seen in severely affected infants. When suspected, measuring serum vitamin E levels makes the diagnosis. Oral vitamin E supplementation may be needed especially in premature infants. In patients with chronic malabsorption, the treatment of the original disease together with vitamin E supplementation is required.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired disorder characterized by episodes of hemolysis

during sleep as well as early morning hemoglobinuria. Approximately 15% of the reported cases occur in children 6–20 years old. The basic defect is in the glycosylphosphatidylinositol (GPI) anchor. This defect leads to partial or complete absence of all GPI-linked membrane proteins, including CD59 and CD55. Occasionally CD8 expression may be decreased. These changes in the RBC-binding membrane proteins results in increased sensitivity of affected red cells to hemolysis by the activated complement system.

Clinical Presentation

Patients with PNH usually present with episodes of intravascular hemolysis that occur during sleep and lead to early morning hemoglobinuria. The anemia is variable in severity. Some patients have chronic hemolysis. Hemolysis can be induced or exacerbated by infection, whole blood transfusion, vaccine administration, iron therapy, or exercise. The severity of hemolysis is related to the size of the PNH clone, the degree of the abnormality (partial or complete absence of CD59 and CD55), and the degree of complement activation. Patients often present with other hematological or with nonhematological complications. Hematologic complications include venous or arterial thromboembolism, aplastic anemia, leukemia, myelodysplastic syndrome, and iron deficiency anemia. Venous thrombosis is much more common than arterial. Thrombosis may involve any vein, large or small. However, they most often involve the large intra-abdominal veins, particularly the hepatic, portal, and splenic veins, as well as the inferior vena cava. Thrombosis of the cerebral veins, specially the major venous sinuses, occurs less frequently than the intra-abdominal veins. Hepatic venous thrombosis may cause splenomegaly, hepatomegaly, and ascites (Budd–Chiari syndrome). Thrombosis of the small splanchnic veins may cause severe abdominal pain. The prevalence of thrombosis in Japanese patients is lower (6%) than among the American patients (38%). Aplastic anemia may develop after the diagnosis of PNH or it may be the presenting problem. The incidence is not known and it may appear years after the diagnosis of PNH. Leukemia, usually acute myeloid leukemia, develops years after the diagnosis of PNH. The reported incidence ranges from $<1\%$ up to 5%. Myelodysplastic and myeloproliferative disorders have been associated with PNH. Iron deficiency anemia is common in patients with PNH because of the urinary loss of iron caused by hemosiderinuria and/or hemoglobinuria. Nonhematological presentations include acute renal failure (from hemoglobinuria), proximal tubular dysfunction, and chronic renal failure. Esophageal spasm and erectile dysfunction has been reported in patients with PNH, though only in adults.

Diagnosis

Traditionally PNH was diagnosed by inducing in vitro hemolysis using the sucrose lysis test and the Ham acid hemolysis test. Both of these tests depend on activation of the complement system. Recently, flow cytometry using monoclonal antibodies against CD59 and CD55 has largely replaced the sucrose lysis and Ham tests for accurate diagnosis of PNH.

Treatment

The treatment of the anemia associated with PNH is supportive. Iron supplementation for iron deficiency anemia and folic acid supplementation to prevent megaloblastic anemia are indicated. PRBC transfusion should be given if clinically indicated. Caution should be given when iron or blood is given as they may induce acute hemolytic episodes. Whole blood should be avoided and only washed and preferably leukoreduced RBCs are recommended to decrease the possibility of transfusion-induced hemolysis. A humanized monoclonal antibody (eculizumab) that inhibits terminal complement activation by binding to the C5 was found to reduce hemolysis, transfusion requirements, and thromboembolic event rates. Prednisone and androgenic hormones (danazol) have been effective in diminishing anemia in some reports. Their role in PNH, however, is controversial. The thromboembolic complications should be treated in the same therapeutic modality as other patients. Hematopoietic cell transplantation (HCT) from an HLA identical sibling is indicated in the patient with severe aplastic anemia. Immunotherapy with cyclosporine and antithymocyte globulin (ATG) has been successful in some patients with aplastic anemia. Their role remains to be determent by further studies.

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323 Microangiopathic Hemolytic Anemias

Ahmad A. Mallouh

Introduction

The hallmark of the microangiopathic hemolytic anemia is the presence of fragmented, distorted red blood cells (schistocytes) on the peripheral blood smear of a patient with hemolytic anemia (*Fig. 323.1*). It does not represent a specific diagnostic entity, but rather a morphologic manifestation of mechanical destruction and fragmentation of the red blood cells by shear stress as they pass through fibrin strands deposited on the vascular endothelium or within small blood vessels. Its clinical value lies in narrowing the differential diagnosis in a patient with hemolytic anemia. It should be remembered that a small number of schistocytes may be present in normal individuals. Mild increase in the number of schistocytes may be seen in some diseases with no evidence of hemolysis, i.e., renal disease, prosthetic heart valve, and preeclampsia. The presence of more than 1% of schistocytes or two schistocytes per high power field on a well prepared blood smear is suggestive of microangiopathic hemolytic anemia. Several disease processes may be associated with microangiopathic hemolytic anemia (*Table 323.1*). The clinical manifestations are those of the hemolytic anemia and the manifestations of the underlying precipitating condition. Following is a discussion of disease entities associated with microangiopathic hemolytic anemia.

Disseminated Intravascular Coagulation (DIC)

Introduction

Human blood remains in a fluid state without bleeding or intravascular thrombosis by a delicate balance between the vascular system and the coagulation, anticoagulation, fibrinolytic and antifibrinolytic pathways. When a blood vessel is injured, it constricts immediately to limit blood loss. This is followed by the formation of a reversible platelet plug. Local activation of the coagulation cascade results in formation of thrombin, which stabilizes the platelet plug and generates fibrin from fibrinogen forming a stable haemostatic plug. The fibrinolytic system is locally activated to remove the unneeded thrombus to keep the injured blood vessel open. As these processes are transient, localized and compensated by production of the consumed factors (platelets and coagulation factors) by the liver and bone marrow, no excessive or prolonged bleeding or harmful thrombosis occur.

Pathogenesis

Uncontrolled and excessive activation of the extrinsic pathway of the coagulation cascade produces large amounts of thrombin. Activation of the coagulation cascade results from exposure of the blood to large amounts of the tissue factor and activated factor VII (FVIIa), which results from tissue injury (by trauma), injury of the vascular endothelium (usually by endotoxin) or increased release or expression in the monocytes. Prothrombin leads to widespread intravascular coagulation and deposition of fibrin in the deferent organs causing tissue ischemia and organ damage. The fibrinolytic system is activated to dissolve the fibrin deposits producing fibrinogen degradation products (FDP) and D-Dimers. Platelets and coagulation factors (fibrinogen, prothrombin, and factors V and VIII) are depleted leading to spontaneous bleeding. Excess FDP enhances bleeding by interfering with platelets aggregation and fibrin polymerization. In addition, excessive amounts of plasmin (which is produced from plasminogen) causes degradation of the clotting factors causing further drop in their level and leading to more bleeding. Destruction of the red blood cells (RBCs) by passing through the fibrin mesh results in the classic finding of Schistocytic hemolytic anemia. Activation of the intrinsic pathway of coagulation is thought to cause hypotension but not DIC.

Etiology

Disseminated intravascular coagulation (DIC) may be triggered by a number of serious disease processes. The

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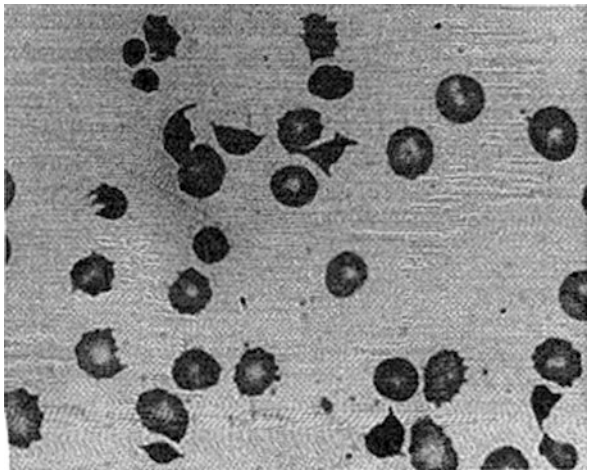

Figure 323.1
Blood smear from a patient with hemolytic-uremic syndrome showing schistocytes and other forms of deformed and fragmented red blood cells

Table 323.1
Conditions associated with microangiopathic hemolytic anemia

Disseminated intravascular coagulation (DIC)
Hemolytic-uremic syndrome (HUS)
Thrombotic thrombocytopenic purpura (TTP)
Giant hemangioma (Kasabach–Merritt syndrome)
Extracorporeal circulation (after open heart surgery)
Intracardiac prosthesis
Malignant hypertension
Strenuous exercise

most common causes are infection, trauma (accidental or surgical), and malignancy. However, it may be associated with other disease processes, including, giant hemangioma, acute hemolytic transfusion reaction, paroxysmal nocturnal hemoglobinuria (PNH), snake bites, fulminant hepatic failure, burns, severe hypoxia, shock, heat stroke, and severe metabolic disturbances. In newborn infants, septicemia, severe respiratory distress syndrome, hypoxia, shock, necrotizing enterocolitis and homozygous proteins C or S deficiency are known to cause DIC.

Severe infections, including bacterial, systemic viral (i.e., varicella), parasitic (malaria), fungus (systemic canididemia, aspergillosis) and rickettsial infections are the most common cause of DIC in children. Gram negative sepsis may be present in up to 50% of all children with DIC. Severe trauma (accidental, burn, or major surgery) is the second most common cause of DIC. The possibility of the development of DIC depends on the severity of the trauma and the extent of tissue damage. Head injury is more likely to be associated with DIC, when compared with injuries of similar extent in other organs. The severity of coagulopathy and the development of systemic inflammatory response syndrome (SIRS) are strong determinants of the outcome of trauma associated DIC. DIC develops in most patients with acute promyelocytic leukemia (APL) due to the release of the tissue factor from the blasts. Even though it may be present at presentation, it often develops after starting chemotherapy. DIC also often develops with other types of Hematologic malignancy or disseminated solid tumors.

Clinical Picture

DIC is a secondary syndrome associated with or caused by any of several serious and often clinically obvious causes. Even though the exact incidence is not known, it is estimated that around 1% of the hospitalized patients develop coagulopathy. Clinical picture is that of the triggering disease process together with bleeding tendency, disseminated thrombosis causing organ damage and microangiopathic hemolytic anemia. External (skin, mucous membranes, venipuncture site, or wounds) and/or internal (central nervous system, lungs, gastrointestinal tract, urogenital tract, or adrenal glands) bleeding are usually present. Pallor, jaundice, tachycardia, hypotension, and/or hemoglobinuria are manifestations of hemolysis and may be present depending on the severity of the anemia. Purpura fulminats with skin necrosis and/or gangrene of the fingers and toes may be present. Acute renal, hepatic, pulmonary or CNS injury may occur due to hemorrhage, and microthrombosis of feeding vessels and/or hypoperfusion due to hypotension. It should be remembered that even though activation of the intrinsic coagulation pathway dose not play a role in the pathogenesis of DIC, it may cause or exasperate hypotension and shock, which in turn exasperate tissue hypoxia and organ damage.

Chronic DIC is often associated with solid tumors. It results from release of small amounts of tissue factor and a compensatory response from the liver, which replete the consumed coagulation factors, and the bone marrow, which compensate for the consumed platelets. Patients with chronic DIC have no or minor bleeding tendency. However, they are liable to develop venous or arterial thrombosis.

Diagnosis

DIC should be suspected in any patient with increased bleeding tendency, thrombotic episodes or microangiopathic hemolytic anemia in association with severe disease, especially, the causative entities described above. Diagnosis is confirmed by a combination of laboratory findings which include thrombocytopenia or steadily falling platelets count, prolonged prothrombin (PT) and partial activated thromboplastin times (PTT), low levels of fibrinogen, and elevated levels of fibrinogen degradation product (FDP) and D-dimers. Hemolytic anemia with the characteristic schistocytes is always present. Coagulation factors (especially factors V and VIII) are usually low. Thrombin time and reptilase time are usually prolonged; however they are not usually required for diagnosis or management of DIC. Diagnosis of chronic DIC can be problematic because PT, aPTT, and platelet count may be normal, as the consumed coagulation factors and platelets are compensated for by the liver and bone marrow, respectively. In addition to the clinical picture (usually thrombosis) and the presence of the initiating disease (usually disseminated solid tumor), diagnosis depends on the presence of microangiopathic hemolytic anemia and elevated FDP and D-dimers.

Differential Diagnosis

Even though all causes of bleeding diathesis, hypercoagulable states and hemolytic anemia should be considered in the differential diagnosis, in most case scenarios, the diagnosis is clear based on the clinical findings and simple laboratory tests. Liver disease, hemolytic-uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) and heparin induced thrombocytopenia (HIT) are sometimes difficult to differentiate from DIC. The clinical picture, however, is often suggestive of the diagnosis. Liver disease in particular can be a difficult diagnostic problem. It should be remembered that severe liver disease may cause DIC and liver damage can be caused by the same triggering disease which causes DIC (i.e. sepsis, trauma, shock). Thrombocytopenia, microangiopathic hemolytic anemia and elevated FDP are usually absent in primary liver disease. Thrombocytopenia, however, may result from congestive splenomegaly and hypersplenism. Hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura (see below) both cause thrombocytopenia and microangiopathic hemolytic anemia. They, however, usually have normal PT, aPTT, fibrinogen, and FDP. Heparin induced thrombocytopenia (HIT) can be differentiated based on the history of heparin administration in the prior few days, the absence of DIC causing diseases (sepsis, trauma, or malignancy), and normal fibrinogen and FDP. PT and aPTT might be prolonged, if the patient is still receiving heparin.

Prognosis

DIC is a serious medical problem with high morbidity and mortality. Multiple organ damage may result from the initiating disease (sepsis, trauma, malignancy, etc.) or from bleeding, thrombosis or hypoxia due to the anemia or shock. Mortality, which can be as high as 80%, depends on the original causative disease (sepsis, trauma, malignance, etc.) and its severity, the severity of the coagulopathy, organs involved and the degree of their damage, the development of systemic inflammatory response syndrome (SIRS) and the appropriateness and promptness of therapy.

Treatment

Other than treating the original initiating disease, which is essential to hope for a good outcome, treatment of DIC is mainly symptomatic. Aggressive treatment of shock is essential part of therapy. Hypo-perfusion and tissue hypoxia furthers tissue damage and mortality. Anemia is treated with packed red blood cells transfusion as required. Platelets and fresh frozen (FFP) transfusion is recommended to stop or prevent anticipated bleeding. They should not be given to correct abnormal laboratory results. Cryoprecipitate should be given if bleeding could not be stopped with platelets and FFP. The transfused elements (red cells, coagulation factors, and platelets) are consumed rapidly; however, their administration helps to stop or decrease bleeding and correct the anemia until the triggering factor is corrected. Anticoagulant therapy, mainly with unfractionated or low-molecular heparin, is often recommended in chronic DIC with major thrombosis. The use of anticoagulant in acute DIC is of questionable value and should be avoided specially in patients with CNS bleeding. Some studies showed that protein C concentrates decreases mortality in adult patients with sepsis and DIC. However further studies are needed before recommending its routine use.

Hemolytic-Uremic Syndrome

Introduction

Hemolytic-uremic syndrome (HUS) is an acquired disease characterized by an acute onset of the triad of

microangiopathic hemolytic anemia, thrombocytopenia, and nephropathy. The disease is classified into two types, the typical type (shiga-like toxin associated, postdiarrheal, D+) and the atypical type (non-shiga associated, non-postdiarrheal, D-). The two types have deferent etiology, epidemiology, clinical picture, clinical course, and prognosis. The typical type constitutes around 90%, while the atypical type constitutes around 10% of the reported cases.

Pathophysiology

Endothelial damage in the capillaries and/or arterioles leading to thrombotic microangiopathy and red blood cells fragmentation is the main lesion in both types of HUS (see section "Nephrology").

Etiology

The typical type (also called classic, epidemic, postdiarrheal, D+ and shiga-like toxin associated) is caused by shiga-like toxin producing organisms. In North America, around 70% of the typical type is caused by enterohemorrhagic *E. coli*, around 80% of which is *E. coli* O157:H7. In contrast, in other countries (Australia, Germany and Austria), the majority of postdiarrheal HUS is caused by non-O157:H7 *E. coli*, while in Asia and Africa, the most common cause is *Shigella dysenteriae* type 1. The atypical type is divided into two types, the genetic and the non-genetic types. The genetic type results from deficiency of complements components (mainly C3, factors H, B, I and the so called membrane factor), Von Willebrand factor cleaving protease (ADAMTS13) or defects of vitamin B12 metabolism. Some cases are inherited, but without known complement deficiency or abnormal metabolic etiology. The atypical non-genetic type is caused by non-enteric infections. *Streptococcus pneumoniae* causes up to 40% of the non-diarrheal type and up to 14% of all HUS in children. HUS has been reported with viral infection (especially HIV), systemic lupus erythematosus, antiphospholipid syndrome, and malignancy.

Epidemiology and Incidence

HUS occurs worldwide. Its incidence, causative agents, and age distribution differ from one area to another. In North America and Western Europe, around 90% of the cases are of the typical and around 10% are of the atypical type. The annual incidence is around 2–3 per 100,000 in children less than 5 years old. The peak incidence is in the summer and fall. However, the atypical type caused by *Streptococcus pneumoniae* occurs more commonly in winter months. The inherited types have no seasonal predilection. Most cases occur sporadically; however, epidemics often occur in day care center either because of exposure to a common source of infection or due to cross infection. Cases may occur in several family members either because they are exposed to the same source of infection or due to inherited type of the disease.

Clinical Picture

Most cases of the typical (shiga-like toxin associated) type occur in children less than 5 years old. Patients usually present with prodromal symptoms of diarrhea (often bloody), abdominal pain, fever, and vomiting. The full blown picture of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure follows in 5–10 days. Diarrhea precedes the development of HUS in over 90% of the cases. However, it is bloody only in 50–60% of the cases. Extra-gastrointestinal infection (urinary tract) with enterohemorrhagic *E. coli* may cause HUS without preceding bloody diarrhea. CNS involvement including irritability, seizures, coma, stroke, or hemiparesis occurs in one fifth to one fourth of the cases of HUS. Renal involvement, which occurs in over 95% of the cases, ranges between simple proteinuria, hematuria and severe acute renal failure. Anuria occurs in around half of the cases. The severity of renal involvement does not correlate with the severity of the prodromal symptoms, anemia, or thrombocytopenia. Hypertension occurs in around 50% of the cases. In addition to the bloody diarrhea, gastrointestinal complications may include intestinal gangrene, perforation, intussusception, or rectal prolapse. Other organs that may be involved include liver and pancreas. The atypical type is heterogeneous in its clinical presentation, severity, complications, and prognosis. It is not preceded by diarrhea. It usually presents in more insidious onset. Patients are at higher risk of severe acute renal failure, chronic renal failure, hypertension, recurrence, and death. It usually occurs at older age. However, recent studies showed that, depending on the etiology, some patients with the atypical type may present at early age and have milder course than the typical type.

Diagnosis and Deferential Diagnosis

With high index of suspicion, diagnosis is usually easily made based on the clinical picture and the presence of

microangiopathic hemolytic anemia, thrombocytopenia, and evidence of renal injury. Isolating *E. coli* or *Shigella* from the stools is helpful but not essential for diagnosis. Serologic detection of the shiga toxin in the stools can be done, but it is neither essential nor available in most settings.

Deferential diagnosis in the prodromal phase includes all causes of infectious (*Shigella*, *Salmonella*, *Campylobacter*, *Yersinia*, ameba) and noninfectious (ulcerative colitis, Henoch–Schonlien purpura) bloody diarrhea. All causes of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure should be included in the deferential diagnosis of HUS. Most of these cases, however, can be easily differentiated based on the clinical and laboratory finding. Patients with disseminated intravascular coagulopathy (DIC) have the triad of HUS, but they also have prolonged PT and PTT, low fibrinogen, and high FDP and low coagulation factors (mainly factors V and VIII). The typical type of childhood HUS can be differentiated from thrombotic thrombocytopenic purpura (TTP) by the presence of bloody diarrhea and the isolation of the pathogenic *E. coli*.

Treatment

The need for and modality of treatments depend on the organ/system involved and the severity of involvement. Acute renal failure and its related problems (hypertension, electrolytes disturbance, and fluid imbalance) is managed like other types of acute renal failure (see section "Nephrology"). Indications for dialysis are the same as for other forms of acute failure. It is required in around 50% of the typical type. Early dialysis, as previously suggested, does not improve the final outcome. Anemia might be severe enough to require packed red blood cells transfusion. Blood transfusion is usually recommended, if the hemoglobin drops to <6 g/dl. This indication, however, is not based on solid scientific grounds. The indication for transfusion should be individualized and be based on the clinical picture, the bone marrow activity as evidenced by the reticulocytes count, and the direction in which hemoglobin level is going (upward, downward, or stable). Platelets transfusion should be reserved for patients with uncontrolled active bleeding or those who are at risk of developing bleeding (planned surgical procedures). Careful fluid and electrolytes management is essential, especially in patients with oliguria or Anuria. Treatment of other involved organs (CNS, heart, pancreas, liver, or lungs) is similar to their treatment in other diseases. The role of plasma simple or exchange transfusion is controversial and its efficacy is doubtful in shiga-like toxin associated type. It is, however, recommended by some authorities in cases with severe CNS involvement. Plasma exchange is recommended in the atypical type. The response to this therapy, however, depends on the affected complement. Antibiotic to treat *E. coli* should be avoided, as it was shown to increase the risk of HUS without shortening the course of the gastrointestinal symptoms. Antibiotics may be used in *Shigella* associated HUS, as they do not appear to increase the risk of HUS. Renal transplantation is recommended for the typical type with end stage renal disease. Success rate is similar to other causes of end stage renal disease (ESRD). Recurrence rate is between 0% and 10%. The indication for renal transplant in the atypical type is controversial because of the high rate of recurrence.

Prognosis

Hematologic problems resolve in almost all cases of the typical type. Complete renal function recovery occurs in around 80% of the cases. However, recent long-term follow-up showed that renal dysfunction (clinical or subclinical) persists in much higher percentage (up to 30% of the cases). Around 5% of the patients die from the disease or its complications. Several bad prognostic factors were identified including prolonged oliguria or anuria, leukocytosis, the need for dialysis in the acute stage and the presence of arteriolar microangiopathy, cortical necrosis or microangiopathy involving over 50% of the glomeruli. Prognosis for the atypical type depends on the etiology or the mutated gene. *Streptococcus pneumonia* associated disease has bad early prognosis, caused mainly by death due to the infection itself (sepsis or meningitis), but it has better long-term renal function (inpatients who survive the acute phase) than the typical type. Most patients with HIV associated HUS end with ESRD. The prognosis for the inherited types depends on the mutated gene. Dominantly inherited cases have a better prognosis than the recessive cases. Mutation of factors H, I, C3, and ADAMTS 13 is usually associated with severe and progressive renal disease, while HUS associated with the mutation of membrane cofactor protein (MCP) deficiency rarely leads to ESRD.

Thrombotic Thrombocytopenic Purpura

Thrombotic thrombocytopenic purpura (TTP) is characterized by the sudden onset of microangiopathic hemolytic anemia and consumptive thrombocytopenia, often associated with neurologic dysfunction, impairment of renal function, and fever. It is primarily a disease of the adults. However, both acquired and congenital types are

known to occur in children. In adults, the clinical picture and pathology TTP overlap with hemolytic-uremic syndrome (HUS). The two syndromes are usually considered as one disease (TTP/HUS) and they are managed in the same way. In children, however, the typical type (shiga toxin associated, diarrhea associated) HUS is distinct from TTP in its etiology, clinical picture, therapy, and prognosis. The atypical type (non-shiga toxin associated) can be confused with TTP.

Pathogenesis and Pathology

The hallmark of TTP is the formation of platelets-rich microthrombi in the microcirculation of deferent organs. Obstruction of the blood supply results in ischemic damage of the involved organs. The development of these microthrombi is triggered by the presence of unusually large VWF (ULVWF) multimers in the circulation. In normal individuals, these multimers are cleaved to smaller inactive form by a protease identified as ADAMTS13. Acquired or congenital ADAMTS13 deficiency results in intravascular accumulation of the ULVWF multimers. These multimers promote platelets adhesion and aggregation, causing platelets-rich microthrombi. ADAMTS13 deficiency results from an autoimmune mechanism in the acquired (idiopathic) TTP and from an autosomally inherited gene in the congenital type.

Clinical Picture

The clinical picture and prognosis of TTP depend largely on the organs involved, degree of organ damage, and the type and timing of therapy. The classic required diagnostic criteria are the pentad of microangiopathic hemolytic anemia, thrombocytopenia, neurologic abnormalities, renal dysfunction, and fever. However, because of the efficacy of early plasma exchange in inducing remission and cure in a disease with high mortality, less stringent criteria are presently accepted as a presumptive diagnosis in adult patients and those who (based on family history) are suspected to have congenital ADAMTS13 deficiency. The sudden onset of Coomb's negative microangiopathic hemolytic anemia and thrombocytopenia without an apparent cause is an indication to start therapy. CNS involvement, which is present in most cases, ranges between headache, confusion, transient ischemic attacks and seizures, hemiparesis, coma, or death. Unlike HUS, TTP involves CNS more often than the kidneys. However, both diseases can cause deferent degrees of CNS and/or renal damage.

Diagnosis

For practical purposes, diagnosis depends on the clinical picture. Treatment should be started as soon as the diagnosis is made or highly suspected. Low plasma level of DAMTS13 is important to confirm the diagnosis, but it is not essential to start therapy. ADAMTS13 may be found in normal people and diseases other than TTP, i.e., sepsis and in some cases of HUS. The diagnostic sensitivity and specificity is 89% and 91%, respectively.

Treatment

Plasma exchange is the primary treatment for TTP. It should be started as soon as the diagnosis is highly suspected. Plasma exchange is given once daily (in severe cases twice daily) until complete clinical remission and platelets recovery. In the acquired TTP, plasma exchange removes ULVWF and the auto antibodies against ADAMTS 13 and it increases the level of the deficient ADAMTS 13. In the congenital type, simple rather than exchange plasma transfusion (10–15 ml/k daily) is usually adequate.

Rituximab (an anti-CD20 antibody) is effective in achieving remission and possibly preventing relapse in some refractory or relapsing cases. Steroids, cyclosporine, and cyclophosphamide were used in refractory and relapsing cases with variable results. Splenectomy was effective in some refractory cases. However, nowadays, it is rarely needed and it should be avoided specially in children.

Prognosis

The prognosis used to be dismal with a mortality rate approaching 100. Early plasma exchange decreased mortality rate to around 20%. (It should be remembered that these therapeutic and prognostic data are extrapolated mainly from adult studies because the disease is rare in children.).

Giant Hemangioma and Thrombocytopenia (Kasabach–Merritt Syndrome)

The association of microangiopathic hemolytic anemia, thrombocytopenia with or without evidence of coagulopathy (prolonged PT and PTT, low fibrinogen level and high level of fibrinogen degradation products

and D-dimers) with cutaneous or visceral kaposiform hemangioendothelioma or tufted angioma is referred to as Kasabach–Merritt Syndrome (KMS).

Pathology and Pathogenesis

Recent literature suggests that all cases of KMS are associated with kaposiform hemangioendothelioma or tufted angioma rather than the classic infantile hemangioma. This confusion is thought to be caused by imprecise definition and imprecise histological diagnosis of "hemangioma." However, some other recent literature suggests that it can be associated with other types of vascular tumors (hepatic hemangioma, splenic hemangioma, lymphangioma, and diffuse neonatal hemangioma). Thrombocytopenia results from trapping in vascular spaces of the hemangioma and activation of these platelets by the proliferating endothelium of the tumor. Platelets activation results in thrombin production, which causes local and/or disseminated fragmentation of the red blood cells leading to microangiopathic hemolytic anemia that results from the shear stress (while passing through the small blood vessels) and/or due to the consumptive coagulopathy. Thrombocytopenia and consumption of the plasma coagulation factors may cause localized or generalized bleeding.

Clinical Picture

KMS is a disease of infancy and childhood. Most cases are diagnosed in the first 5 years of age. Cutaneous "hemangioma" may be present at birth or develop or enlarge over few months or occasionally few years. Diagnosis of KMS is usually clear. An infant or a child with cutaneous hemangioma develops thrombocytopenia and microangiopathic hemolytic anemia. In patients with visceral hemangioma, unexplained thrombocytopenia and microangiopathic hemolytic anemia might be the first and the only manifestation of KMS. The clinical picture of KMS depends on the size, location and local complications of the tumor, and the severity of the thrombocytopenia and consumptive coagulopathy. "Hemangiomas" can be of any size, be located in anywhere, and can be single or multiple. The most common site is the skin. Visceral lesion may be located in the liver, spleen, retroperitoneal, mediastinum, or CNS. Clinical manifestations caused by the hemangioma may include (depending on the location, size, and infiltration of adjacent structures) obvious cutaneous lesion, abdominal distention, abnormal live function tests, respiratory compromise, seizures, bony deformity, or obstructive uropathy. High output heart failure may occur. Bleeding due to thrombocytopenia (with or without consumptive coagulopathy) may occur anywhere including skin (petechiae, bruising), mucus membranes (including epistaxis, gastrointestinal, or urogenital), CNS, or within the hemangioma itself. Bleeding in the hemangioma results in sudden increase in size of the visible mass, increased abdominal distention, increased respiratory compromise or CNS complications, i.e., seizure, coma, stroke, etc. Patients may present with complications of the hemangioma, which may include ulceration, infection or infiltration or compression of vital structures, e.g., the eye.

Diagnosis

Diagnosis is usually obvious. Most patients present with a visible subcutaneous mass, with or without evidence of bleeding. Investigations show microangiopathic hemolytic anemia and severe thrombocytopenia. PT and PTT are often high; fibrinogen may be low and FDP may be high depending on the presence and severity of DIC. MRI and/or CT scans of the visible lesion should be done to delineate the extent of the tumor and to decide if surgical removal is feasible. MRA and/or CT scans and Doppler ultrasound may identify large feeding vessels. MRI and/or CT scans of the head, chest, abdomen, and pelvis are indicated in cases of cutaneous lesions to look for multifocal lesions. The same radiological investigations are required when primary visceral hemangioma is suspected. Unexplained thrombocytopenia and microangiopathic hemolytic anemia may be the only manifestation of KMS in which a search for visceral hemangioma is indicated. Biopsy is not routinely indicated.

Deferential Diagnosis

When hemangioma is located in the skin, it is easily identified clinically. MRI or Doppler ultrasonography can differentiate visceral and ambiguous superficial hemangioma from solid tumors. Differentiating hemangioma from vascular malformation is important but often difficult. All causes of consumptive coagulopathy and thrombocytopenia are usually easily differentiated from KMS, except in the case of unrecognized visceral hemangioma in which other causes of DIC should be considered.

Treatment

Supportive treatment is required in symptomatic patients and those who are planned for surgical procedures.

It includes packed red blood cells transfusion as indicated by the severity of the anemia and the clinical picture. Platelets transfusion should be reserved for patients with active and uncontrolled bleeding or those who are planned to have a surgical procedure. Fresh frozen plasma (FFP) is indicated for patients with evidence of consumptive coagulopathy and active bleeding or prior to surgical procedures. Cryoprecipitate is indicated in an actively bleeding patient with severe hypofibrinogenemia. Treatment of the hemangioma depends on its size, site, number, and complications (KMS, bleeding, ulceration, heart failure, or infection). Most hemangiomas run their natural course of proliferative phase followed by involution. Involution usually starts after 1 year of age. Around 75% of them are completely involuted by 5–7 years of age. However, many are left with residual lesions. Asymptomatic patients or those with minimal problems need no active therapy. Surgical removal of a small single lesion or few lesions is recommended if surgically feasible without mutilation. Embolization or ligation of large feeding arteries, if present, can be done in a single or a few lesions. Most lesions are large, infiltrating or visceral and not accessible for surgical removal or embolization. Medical therapy is indicated in such cases. Systemic steroid therapy is the first line of medical therapy. Different dosing regimens were found to be effective (2–3 mg/kg/day for 4 weeks, 5 mg/kg/day for 2 weeks, and megadose of 30 mg/kg/day for 3 days). Response usually starts after few days. Around 90% of cutaneous hemangioma has a good response; however, only 30–50% of KMS patients have a good response because most, if not all, lesions are not true hemangiomas. Alternative therapies which were found to be effective in some cases include alpha interferon, vincristine, cyclophosphamide, and actinomycin-D. Antifibrinolytic, antiplatelet, and anticoagulants should be avoided as their efficacy is controversial and they might increase the chances of bleeding. Even though radiotherapy was effective in many studies, it should be used only in resistant cases with life-threatening situation.

Prognosis

Prognosis depends on the location, extent, infiltration of vital organs, severity of consumptive coagulopathy, and therapeutic intervention. Mortality is more common in visceral lesions and large infiltrating lesions and in those with severe thrombocytopenia with or without DIC. Mortality rate ranges between 10% and 37%. Morbidly includes residual tumor, scar, and residual damage in the involved organs, i.e., CNS, liver.

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324 Sickle Cell Disease

Ahmad A. Mallouh

Introduction

Human hemoglobin is composed of two parts: (a) the iron-containing part (heme), which is a porphyrin ring responsible for the reversible combination with and transport of oxygen, and (b) a protein part (globin), which is a tetramer made up of two α and two non-α (β, γ, or δ) polypeptide chains, each formed from a large numbers of amino acids (α = 141, β, γ, and δ = 145 amino acids) attached to each other in a linear sequence. There are three types of normal human hemoglobins:

- Hemoglobin A (α2β2) is the main hemoglobin beyond the neonatal period.
- Hemoglobin F (α2γ2) is the main hemoglobin in the fetus and the newborn. Hemoglobin F is gradually replaced by hemoglobin A after birth reaching an adult level by 9–12 months of age.
- Hemoglobin A2 (α2δ2) constitutes 2.5–3.5% of the total hemoglobin in children and adults.

Hemoglobinopathies result from the substitution of one or more amino acids in the globin chain or by the shortening or elongation of the globin chain by deleting or adding amino acids. To date, more than 800 structurally abnormal hemoglobins have been described. Most structurally abnormal hemoglobins are only of academic interest as they are physiologically normal. Others have abnormal solubility, molecular stability, and/or oxygen affinity, resulting in significant clinical problems. Hemoglobins S, C, E, D, O Arab, unstable hemoglobins, and hemoglobins M are among the clinically important types.

Sickle Cell Disease (SS)

Sickle cell disease usually refers to either homozygous (SS) disease or doubly heterozygous hemoglobin S and other abnormal hemoglobins or β-thalassemia (SC, SD, SE, S O Arab or S β-thal).

Pathophysiology

Sickle hemoglobin (Hb S) results from the substitution of the amino acid valine for glutamic acid (Glutamic acid →Valine) in position number six of the β globin chain of hemoglobin. When deoxygenated, hemoglobin S molecules polymerize, forming an elongated rope-like fiber that aligns with other fibers inside the red blood cells, eventually forming parallel bundles oriented along the axis of sickle-shaped red blood cells (RBCs). This process results in increased RBC membrane rigidity, abnormal membrane function, and deceased RBC deformability. Even though hemoglobin S polymerization is an essential event of the pathogenesis of vaso-occlusion, polymerization does not by itself explain the whole clinical picture. Previously, it was thought that the sickle-shaped cells became entangled in the small capillaries, thus occluding them. In fact, vessel occlusion often occurs in medium sized blood vessels. It is accepted now that vaso-occlusion is a complex process which includes, in addition to Hb S polymerization, increased adhesion of the RBCs to the vascular endothelium, structural and functional RBC membrane abnormalities, increased leukocyte adhesion, platelets and coagulation activation, endothelial damage, and an increased tendency to vasoconstriction. Sickle-promoting factors include hemoglobin S concentration, hypoxia, acidosis, hemoconcentration (increased blood viscosity), hemostasis, hypothermia, and hypotension. Sickling is influenced by the coexistence of hemoglobin S with other hemoglobins. Coexistence of hemoglobins F, A, C, or O Arab increases hemoglobin S solubility which explains the asymptomatic course of sickle cell trait and sickle cell-hereditary persistence of fetal hemoglobin (S-HPF) and the relatively mild course of homozygous Indian–Arabian SS disease (known to have high hemoglobin F levels) and S-C disease, S-D, and A-O Arab. In vivo, hemoglobin S-containing red blood cells undergo sickling and unsickling continuously. They sickle when they pass through the slow capillary circulation and the venous system due to local hypoxia, relative stasis, and acidosis.

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They unsickle as they return to the larger blood vessels with higher blood velocity and better oxygenation. When the process of sickling and unsickling is repeated several times, the RBC membrane becomes stiff, and the RBCs stay in an irreversible sickle form (*Fig. 324.1*). The number of irreversibly sickled cells in a freshly prepared blood smear may be an indication of the severity of the disease.

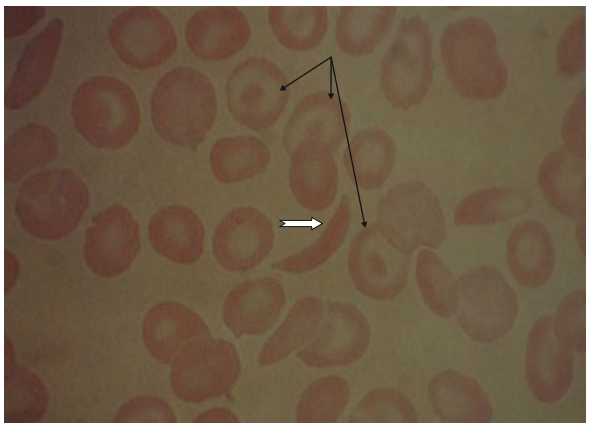

Figure 324.1
Peripheral blood smear in sickle cell disease showing the sickled-shaped irreversibly sickled red blood cell (open arrow). Target cells (solid arrows) are not uncommon in sickle cell disease

Epidemiology

The sickle cell gene is prevalent in parts of the world were falciparum malaria was or is still endemic. The distribution of gene coincides with that of malaria (*Fig. 324.2*). The highest incidence is in sub-Saharan Africa, where the incidence reaches around 30%. It is also common in the Middle East (southern and eastern parts of the Arabian Peninsula) and in other countries around the Persian Gulf (Eastern province of Saudi Arabia, Bahrain, Qatar, southern Iraq, and southern Iran), East and West Africa, Mediterranean countries (southern Italy, Sicily, and certain parts of Greece), and parts of the Indian subcontinent. The incidence in African American is around 8–10%. Sickle cell trait provides protection against severe falciparum infection (up to 90% protection against cerebral malaria and severe malaria-induced hemolytic anemia). Hospitalization and mortality from severe falciparum malaria infection is decreased by around 60% in patients with sickle cell trait as compared with those normal hemoglobin (HbAA). Its protection against mild malaria is controversial.

Diagnosis

The diagnosis of sickle cell disease starts with the clinical suspicion (see below). The diagnosis is then confirmed by:

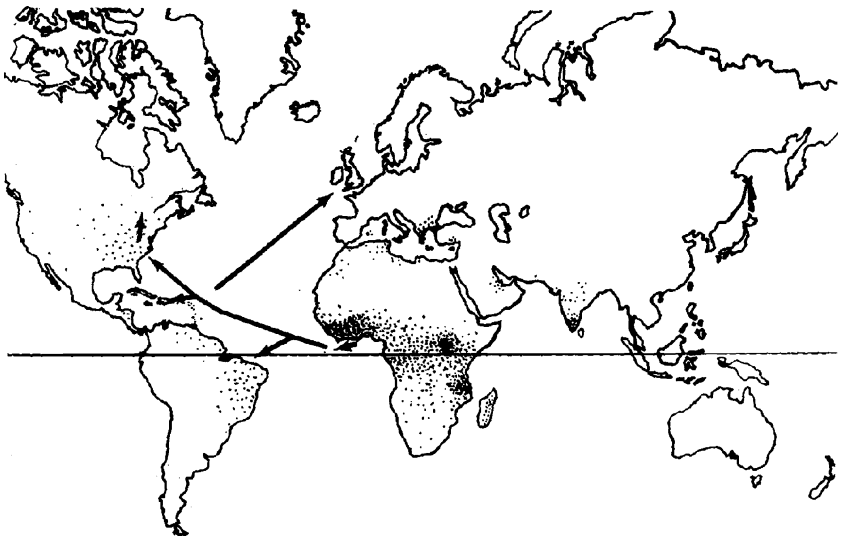

Figure 324.2
Global distribution of sickle hemoglobin gene

- The presence of sickle-shaped cells in a freshly prepared blood smear (irreversibly sickled red blood cells).
- Precipitation tests in which the red blood cells or hemoglobin is exposed to hypoxic environment. The red blood cells take sickle shape in the first, and the hemoglobin precipitates in the second. The above mentioned two methods are not sensitive and do not differentiate homozygous sickle cell disease form sickle cell trait or doubly heterozygous diseases (S-HPFH, S-C, S-D, S-O Arab, or S-E).
- Hemoglobin electrophoresis in cellulose acetate at pH 8.4. It should be kept in mind that hemoglobins S, D, and G have the same mobility in alkaline media. Electrophoresis at acid pH (citrate agar at pH 6.2) separates these hemoglobins.
- High-performance liquid chromatography (HPLC) and isoelectric focusing are sensitive and can be used to diagnose sickle cell disease. Sickle cell disease can be diagnosed in the neonatal periods with some limitation. The presence of hemoglobins S and F with no hemoglobin A is consistent with homozygous sickle cell disease (SS), sickle cell-β° thalassemia, or sickle cell-hereditary persistence of fetal hemoglobin (S-HPFH). Differentiating these diseases is made by family studies. Both parents are expected to have sickle cell trait in SS disease, while one parent has sickle cell trait in the other two entities and the other has β° thalassemia trait or HPFH, respectively. Prenatal diagnosis is technically possible using fetal blood or fetal fibroblasts, or using DNA techniques.

Clinical Manifestations

Infants born with homozygous sickle cell disease are asymptomatic at birth and in the first few months of life because of the protective effect of hemoglobin F. As the production of hemoglobin S increases and replaces hemoglobin F, clinical manifestations start appearing. Vaso-occlusive events may manifest as early as 3 months of age, while chronic hemolytic anemia is usually present by the fourth month of life. Approximately 6% of infants with homozygous sickle cell disease are symptomatic at 6 months, 32% at 1 year, 61% at 2 years, 92% at 6 years, and 96% at 8 years of age. The severity of sickle cell disease is variable. The reason/reasons for this variable clinical expression are not fully understood. However, early onset of dactylitis (hand-foot syndrome), high steady state leukocytes, and low steady state hemoglobin were found to be predictors of a more severe clinical picture. The co-inheritance of α thalassemia with sickle cell disease has been suggested to result in milder anemia; however, its effect on the whole clinical picture is variable. The clinical severity varies among sickle cell genotypes with a milder course in the Arabian-Indian and to a lesser extent in the Singhalese genotypes. This difference is due to persistently high levels of hemoglobin F in these two genotypes.

Sickle cell disease complications can involve any organ. Its clinical manifestations or complications can mimic any disease process involving almost any part of the body. Clinical manifestations can be acute, chronic, acute on top of chronic, or recurrent. They may be divided according to their etiology:

- Manifestations due anemia, whether acute, chronic, or acute on top of chronic.
- Manifestations due the vaso-occlusion phenomenon.
- Manifestations due to infection.

Manifestations due to Anemia

Patients with sickle cell disease usually have moderately severe chronic anemia with appropriate bone marrow response. Hemoglobin concentration levels range between 6 and 10 g/dl (mean 7.9 g/dl). Reticulocyte counts range between 10% and 15%. The major contributing cause of anemia is hemolysis. The mean life span of a hemoglobin S-containing (SS) RBC is approximately 17 days. Folate deficiency due to increased utilization by the hyperactive bone marrow, iron deficiency caused by urinary blood loss due to renal infarction, and erythropoietin deficiency due to renal damage may contribute to the chronic anemia. Iron deficiency was found in up to 20% of patients in some studies. Patients are usually clinically stable. The possible signs and symptoms depend on the severity and acuteness of the anemia.

Acute anemia may develop due to aplastic events, splenic sequestration, hyperhemolytic events, or delayed hemolytic transfusion reaction.

Aplastic Events (Aplastic Crises)

Aplastic events are characterized by a transient drop in the hemoglobin level with bone marrow suppression, as evidenced by reticulocytopenia and decreased erythroid cell precursors in the bone marrow. Most aplastic events are secondary to the human parvovirus B19 which has special affinity to attack the erythroid precursors. Other viruses (EpsteinBarr) or bacterial infections (*Streptococcus pneumoniae*, *Salmonella*) may cause transient aplasia in

patients with sickle cell disease. Human parvovirus B19 is common among all people, especially in children less than 15 years. Because of the short duration of the bone marrow suppression and long red blood cells life span, anemia is not noticed in the population unaffected by hemolytic anemias. Patients with any chronic hemolytic anemia, whose RBC life span is shortened, may develop significant anemia. Erythroid aplasia is usually short lived, lasting a few days. Recovery is often spontaneous without a need for blood transfusion. If the anemia is severe and the patient is symptomatic, packed red blood cells transfusion is indicated. Patients often present at the end of the aplastic episode with high reticulocyte counts and jaundice from the chronic hemolysis. A hemolytic rather than aplastic event might be suggested. Combined aplastic event and splenic sequestration had been reported in association with parvovirus infection. Infection with human parvovirus B19 usually confers a long-lasting immunity. Recurrent aplastic events; however, may be caused by other infectious agents.

Splenic sequestration: Splenic sequestration is defined as a precipitous drop in the steady-state hemoglobin concentration by at least 2 g/dl, sudden enlargement of the spleen (secondary to pooling of the blood in the spleen), and a compensatory bone marrow response as evidenced by reticulocytosis and/or the presence of nucleated red blood cells in the peripheral blood. Splenic sequestration occurs mostly in infants and young children before autosplenectomy due to repeated splenic infarctions occurs. Even though it has been reported in infants as young as a few weeks of age, most cases occur in children between 8 months and 5 years old. Splenic sequestration is not unusual in older children with mild forms of sickle cell syndromes (S-C, S-β thalassemia and in genetically mild homozygous sickle cell diseases, i.e., the Arabian–Indian genotype). The exact etiology of splenic sequestration is not known. It is often associated with viral infection (human parvovirus B19) and/or bacterial infections. Splenic sequestration events often present with sudden onset of severe anemia (pallor, decreased activity, generalized weakness, tachycardia, and tachypnea), hypotension, and abdominal distention due to massive splenomegaly. Splenic sequestration is the initial presenting clinical event in approximately 20% of all infants with homozygous sickle cell disease and 30% in those below 2 years of age. It carries high mortality rates (almost 12% in a Jamaican study). Patients can die prior to presenting for medical care before the diagnosis is made. Association with acute chest syndrome occurs in up to 20% of the splenic sequestration episodes. The recurrence rate can be as high as 50% and carries the same risk of mortality as the first episode. Recurrence is not uncommon even while the patient is on chronic blood transfusion. Subacute splenic sequestration events are characterized by increased splenic size, a modest (up to 25%) drop in the hemoglobin level, and no hypotension.

Splenic sequestration is a medical emergency. Restoration of intravascular volume and improvement of oxygen delivery to various organs are the main goals of treatment. Slow and fractionated PRBC transfusion should be started as soon as possible. Rapid transfusion may lead to congestive heart failure because the sequestered blood returns from the spleen to the vascular system as normal red blood cells are given. Splenectomy is recommended by most authorities after the first episode because of the high recurrence rate and high mortality. Chronic blood transfusion to avoid recurrence and to delay splenectomy has been recommended by some. However recurrence may occur while the patient is on or after chronic transfusion is discontinued and often splenectomy is needed. Some studies showed that the incidence of bacterial infection did not increase after splenectomy in infants with homozygous sickle cell disease because these infants often have functional asplenia. This argument might not apply to the mild forms (SC, SE, SD, and the Arabian–Indian homozygous disease) of sickle cell disease in which the splenic function is maintained for long time. In these cases, splenectomy can be delayed or avoided especially if the sequestration even is of the subacute type.

Hyperhemolytic Events

Hyperhemolytic events are characterized by a sudden drop in the hemoglobin level, unconjugated hyperbilirubinemia, and reticulocytosis. Several authorities doubt its existence and believe that this presentation is due to either aplastic events presenting in the recovery state or a mild splenic sequestration. Sickle cell disease is often associated with G6PD deficiency, which might be the cause of the acute hemolytic episode. Most episodes are self-limiting and require no treatment. If anemia is severe and the patient is symptomatic, blood transfusion may be indicated.

Delayed Hemolytic Transfusion Reactions (DHTR)

Delayed hemolytic transfusion reaction is a posttransfusion hemolytic reaction characterized by hemolytic anemia, reticulocytopenia and posttransfusion hemoglobin levels lower than the pre-transfusion level. Hemolysis

usually occurs 4–10 days (mean 5 days) after transfusion. Even though it has been reported in patients who have received a single transfusions, most cases occur in repeatedly transfused patient with sickle cell disease with a reported incidence of 4–11%. Severe cases can be life threatening and are often associated with other severe complications, including painful events, fever, hemoglobinuria, acute chest syndrome, DIC, pancreatitis, congestive heart failure, acute renal failure, and splenic sequestration. Mild cases can pass unnoticed. The mechanism of the anemia is thought to be due to an immune process. Most patients have a positive direct antiglobulin test (DAT) at presentation. However, 20–30% of the patients never develop detectable antibodies. It is believed that these patients have antibodies below detectable level. Hemolysis of the donor as well as recipient RBCs possibly explains the drop of hemoglobin to a level below that of the pre-transfusion level. Recipient RBC hemolysis is also suggested by the decrease in hemoglobin S percentage. Reticulocytopenia is thought to be secondary transfusion-induced bone marrow suppression. Treatment is mainly by avoiding transfusion as much as possible. Intravenous IgG (IVIg) and steroids were successful in preventing of hemolysis in some cases.

Vaso-Occlusive Events

Vaso-occlusive events are the most common manifestation of sickle cell disease (for pathophysiology see above). It can involve any organ. Repeated attacks of the same organ result in chronic organ damage.

Acute Painful Events

Commonly known as acute vaso-occlusive or thrombotic events, acute painful events are the most common manifestation of sickle cell disease, resulting in the majority of emergency room visits and hospitalizations. The frequency, severity, and anatomic location of the pain differ from one patient to another and from one episode to another in the same patient. Up to 40% of patients with homozygous sickle cell disease (SS) have no painful episodes. In one large study, one third of the patients had three to six episodes per year and one third had more than six episodes per year. Painful events may involve any part of the body. Low back, extremities, or abdomen are common sites. Multiple site involvement is not unusual. The pain may migrate from one site to another during the same episode. The events are usually self-limiting and last for only a few hours in most episodes. However, the pain can last for days and, occasionally, for weeks. Fever, localized tenderness, swelling, warmth, and limitation of joint movement may be present. When local signs are severe, differentiating painful vaso-occlusive event; involving bones; from osteomyelitis may be difficult. Abdominal vaso-occlusive events are of particular concern. Differentiating an abdominal vaso-occlusive event from a surgical abdomen is often difficult, but essential. Appendicitis, cholelithiasis, cholecystitis, and intestinal obstruction can all occur in patients with sickle cell disease and may mimic an acute painful event. Every effort should be made to differentiate vaso-occlusive events from these entities in order to plan proper management and avoid unnecessary high-risk surgical intervention.

Treatment: A first and an important step in the management of painful events is a search for a cause other than vaso-occlusion. Once the diagnosis of vaso-occlusive event is made, every effort should be made to relieve the pain using pharmacologic and/or nonpharmacologic methods. It should always be remembered that the patient is the one who is suffering, not the physician or nurse. Inadequate pain relief results in mistrust between the patient and his or her health care provider. Pain management depends on the severity of the pain and the patient's perception of it. Previous painful events may be used as a general guide to what the patient needs.

The use of pharmacologic agents for adequate pain relief is the mainstay of management of painful events. Acetaminophen, paracetamol, and other nonsteroidal anti-inflammatory drugs together with oral hydration may be tried as a home therapy in mild episodes. Opioids should be used to treat moderate to severe painful episodes. The initial suggested dose of morphine is 0.1–0.15 mg/kg IV, followed by maintenance therapy either by continuous IV infusion or patient-controlled analgesia (PCA). Repeated smaller doses (0.05–0.1 mg/kg) can be given every 15–30 min with close monitoring for respiratory depression until complete pain relieve is obtained. The morphine dosage should be individualized. History of previous painful episodes and their management can be used as a guide. Hydromorphone and fentanyl can be used as an alternative to morphine. Meperidine should be avoided because of its potential CNS toxicity. Adjuvant drugs, which may help in pain relief, include antihistamines, muscle relaxants, and antidepressants. Nonpharmacological therapies which may be helpful include local warm compresses, hypnosis, acupuncture, and behavioral techniques. A short course of steroids was found to shorten the course of the painful episodes. However, severe

rebound pain occurred after discontinuation of steroids. Patients should be continued on oral medication after discharge to avoid pain recurrence. Spinal anesthesia may be required in severe cases. Patients with severe debilitating pain may be treated with chronic RBC transfusions or stem cell transplantation.

Health-care providers often avoid using opioids because of the fear of addiction. It should be stressed that this belief is unfounded. Withholding needed analgesia results in patient suffering, mistrust of health-care providers, and patient's drug-seeking behavior.

Central Nervous System Events

Cerebrovascular accidents (CVAs) are the leading cause of morbidity and mortality in both children and adult patients with sickle cell disease. Cerebrovascular accidents include ischemic stroke, hemorrhagic stroke, transient ischemic accidents (TIAs), and silent infarcts. CVAs occur in 8–15% of children with homozygous sickle cell disease. In the cooperative study of sickle cell disease of 3,647 patients, CVAs occurred in 11% of children (below 20 years of age) with homozygous sickle cell disease. Ischemic stroke (which results from occlusion or stenosis of large intracranial arteries) is most common in children between 2 and 9 years of age, while hemorrhagic stroke occurs most commonly between 20 and 29 years. Hemorrhagic stroke occurs in 3% of children below 20 years of age. Clinical manifestations are similar to those of strokes in people not affected by sickle cell anemia and depend on the location of the lesion, degree of the damage, and etiology (ischemic vs hemorrhagic stroke). Manifestations include seizures, hemiparesis, dysphasia, visual disturbances, abnormal gait, headaches, vomiting, and/or coma. The mortality rate in hemorrhagic stroke is between 25% and 50% and may reach 20% in untreated ischemic stroke. With early and aggressive therapy, mortality is low in the ischemic stroke; however, up to 70% of the survivors are expected to have significant residual neurologic defects or cognitive problems. Computerized tomography (CT) or magnetic resonance imaging (MRI or MRA) are the recommended diagnostic modalities. CT easily detects hemorrhagic lesions, although changes of an ischemic stroke may be delayed for a few hours. MRI is more sensitive in the first few hours (up to 6 h) after an ischemic infarct. MRA has replaced conventional angiography in identifying vascular lesions, e.g., moyamoya, aneurysm, and venous malformations. Conventional angiography may be required in hemorrhagic stroke if MRA is not conclusive. Care should be taken if hypertonic contrast solution is used as this may cause vascular occlusion. Lowering hemoglobin S level before the procedure is recommended.

Treatment: Patients should be managed in the intensive care unit. Treatment of seizures, fever, hypotension, hypoxia, or respiratory compromised (if present) should be managed urgently. A search for and treatment of other causes of the stroke, i.e., trauma, infection, etc. is essential. As the recurrence rate is high (44–67%), chronic blood transfusion to keep hemoglobin S levels below 30% is recommended. This practice results in reduction of recurrence rate to less than 10%. The duration for chronic transfusion is unknown. Stroke recurrence is high after discontinuing transfusion regardless of the duration of the chronic transfusion. Lifelong transfusion with iron-chelation therapy is currently the most reliable method to prevent recurrence. Some authorities recommend stopping chronic transfusion after 5 years or at the age of 18 years. Recurrence can occur while on transfusion in several of these cases hemoglobin S level was found to be higher than the recommended 30%. A recent report showed that progressive cerebral infarcts occurred in 45% (27.5% overt and 17.5% silent) in children with previous overt stroke while receiving transfusion therapy. Hematopoietic stem cell (HSC) transplantation is recommended by several authorities if a donor and resources are available (see bone marrow transplant below). Small studies have demonstrated that hydroxyurea may be effective in preventing stroke recurrence in those patients who are unable to receive blood transfusion (those who have developed alloantibodies, those who are nonadherent with chelation, etc.). However, further studies are needed before recommending its routine use. Treatment of the hemorrhagic stroke depends on the location of the bleeding and if an associated vascular abnormality is present. The benefit of exchange transfusion in the therapy of hemorrhagic stroke is not clear. However, many authorities recommend transfusion, especially if large-vessel disease or abnormal velocity is present.

Transient ischemic attacks are defined as ischemic events in which symptoms resolve in less than 24 h. They are a strong predictor of development of overt stroke. These patients should be evaluated by Transcranial Doppler (TCD) and MRI. Patients who have abnormal velocity on TCD or significant large-vessel disease on MRI/MRA should begin a chronic transfusion regimen.

Silent infarcts were found in up to 30% of children with homozygous sickle cell anemia on screening of asymptomatic patients using MRI. These patients should be evaluated and followed closely if the TCD is normal. Primary prevention using TCD ultrasonography screening

is recommended to identify patients at risk of developing stroke. Screening should start at 2 years of age. Chronic transfusion is recommended for those who had abnormal results (>200 cm/s). The optimal frequency of TCD scanning is not established; however, repeating the study every 3–12 months has been recommended by most authorities.

Acute Chest Syndrome

Acute chest syndrome (ACS) is characterized by the radiographic appearance of new pulmonary infiltrates, fever, respiratory compromise (manifested by cough, tachypnea, wheezing, labored breathing and/or hypoxia), chest pain, and leukocytosis. Radiographic findings may lag behind the clinical picture. Repeat X-ray should be done 24–48 h later if the clinical picture is suggestive of ACS. Many patients (up to 60% in one study) who have fever and chest pain without clinical evidence of pulmonary problems were found to have radiographic evidence of ACS on repeat chest X-ray (*Fig. 324.3*). Over 50% of ACS develops after hospitalization. Triggering factors, which cause local hypoxia and induce local sickling, include splinting in patients with acute pain involving the ribs, abdomen and/or back, respiratory depression as a result of the use of pain medications, postoperative splinting in abdominal or thoracic surgery, or due to under ventilation due to atelectasis and bronchospasm in asthmatic children. ACS is the most common cause of death in children with sickle cell disease (around 2%) and the second cause of hospitalization after acute pain events. Even though ACS occurs at any age and any time of the year, it peaks between 2 and 4 years of age and in the winter.

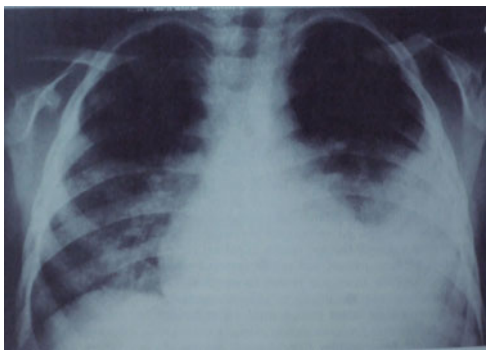

Figure 324.3
Chest X-ray of a child with sickle cell disease and acute chest syndrome (ACS)

The pathogenesis of ACS is complex and includes vasculopathy of SCD and hypoxia induced by pulmonary infection and/or the presence of one or more the sickling-promoting factors mentioned above. Early studies suggested that infection is the main causes of this syndrome in children as opposed to the adults in whom pulmonary infarction is the major mechanism of ACS. Recently, however, it has been shown that pulmonary infarction, caused by fat emboli or local hypoxia due to vaso-occlusion, is a common cause of ACS in children. Whatever the initiating process, the end result is a combination of infection and infarction. Devitalized infarcted lung tissue promotes infection, while infection causes local edema and occlusion of the small blood vessels causing local hypoxia and sickling. An infectious cause is found in 30–40% of ACS in children. Infectious agents include mycoplasma, chlamydia, viral, and bacteria. In over 50% of the cases, no specific etiology was found. Recurrence rate is high, occurring in up to 80% of the cases, especially in those who have been affected before 3 years of age. Hypoxia induced by ACS may lead to worsening of pulmonary involvement, CNS infarction, generalized vaso-occlusion or multisystem failure, and death. Repeated episodes of ACS may lead to lung fibrosis.

Treatment: Acute treatment consists of respiratory support, fluid management, antibiotics, pain management, PRBC transfusion, as well as the possible use of steroids. Long-term, preventative management can include the use of hydroxyurea and hematopoietic stem cell transplantation. Respiratory support includes oxygen supplementation to maintain arterial oxygen saturation ≥92%, incentive spirometry, and nitrous oxide. Mechanical ventilation may be required in severe cases. Dehydration and acidosis should be corrected. Overhydration should be avoided as it may cause pulmonary edema. Third generation cephalosporins and macrolides are a reasonable initial empiric antibiotic combination for coverage of expected pathogens (*Streptococcus pneumoniae*, H influenzae, mycoplasma, and chlamydia). Vancomycin should be added in severe cases or when resistant organisms are suspected or proven by culture. Simple or exchange transfusion should be started early except in the clinically and radiologically mild cases. Simple transfusion is adequate in most cases, particularly in patients with low hemoglobin. Exchange transfusion is indicated in severe cases, progressive cases, hypoxic cases, cases with multiple-lobe involvement, and in those who do not respond to simple transfusion. Hemoglobin levels should not exceed 11–12 g/dl to avoid hyperviscosity, which promotes sickling and thrombosis. With exchange transfusion, the aim is to decrease hemoglobin S level to <30%.

Pain management is important not only because it decreases the suffering and apprehension of the patient but also it controls splinting which may be a factor in increasing hypoxia and worsening the condition. Systemic steroids have been found to be beneficial in mild and moderate cases of ACS. However relapse and readmission was found to be high in patients who received steroid therapy. Further studies are needed before their routine use is recommended. Hydroxyurea is effective in reducing the frequency of recurrence. It is recommended in recurrent cases, especially severe ones (see below). Allogenic hematopoietic cell transplant is curative in 80–90% of cases of SCD. It is recommended for recurrent severe cases of ACS if a matched sibling is available.

Bones and Joints

Cortical bone infarction: Painful vaso-occlusive events are the most common manifestation of sickle cell disease. These events are thought to result from marrow infarction. A less common form of painful event is thought to result from cortical bone infarction. It manifests with local swelling, tenderness redness, hotness, imitation of movement, and fever. Bone destruction and periosteal new bone formation are common. Differentiating this type of event from osteomyelitis is often difficult. A toxic appearance and high-grade fever are suggestive but not diagnostic of osteomyelitis. Even histology can be confusing unless an organism is isolated as both may demonstrate an inflammatory process. Treatment of cortical bone infarction is similar to that of acute painful events.

Osteomyelitis and septic arthritis: Osteomyelitis may involve any bone; however, it most commonly involves the diaphysis of long bones and often involves multiple sites. Technetium bone scan, CT, and MRI are of limited value in differentiating osteomyelitis from cortical bone infarction. Isolating an organism from the local lesion or from blood culture is the only definitive diagnosis of osteomyelitis/septic arthritis. The most common cause of osteomyelitis in children with sickle cell anemia is *Staphylococcus aureus*. However, it is well known that in children with sickle cell disease who develop osteomyelitis, infection is often attributable to *Salmonella*, especially in areas where gastrointestinal infection by salmonella is common. It has been postulated that salmonella egress through microinfarcts of the intestinal wall and settle in the previously infarcted bone. Gram-negative bacilli (*E. coli, Klebsiella*) are relatively common causes of osteomyelitis in the sickle cell population, especially in older children and adults.

Treatment: Surgical drainage and parental antibiotic therapy are the primary therapeutic modality. The initial choice of antibiotic should include coverage for Salmonella species and coagulase-positive staphylococci. The duration of antibiotic coverage is not well established; however, 6–8 weeks are usually recommended. It has been suggested that early surgical drainage is important to assure good and early recovery and avoid chronicity and extensive bone destruction (Fig. 324.4).

Arthritis (non-septic): Arthritis may due synovial infarction or reactive arthritis secondary to adjacent osteonecrosis. Treatment is symptomatic.

Dactylitis (hand–foot syndrome): The vast majority of dactylitis occurs in the first 2 years of life. It is uncommon after 4 years of age. It occurs in over 40% of children with homozygous sickle cell disease. It presents with bilateral swelling of the hands and/or feet. It may involve all four extremities at the same time. It may cause excessive destruction of the affected bones (Fig. 324.5). Dactylitis in the first 2 years of life predicts a more severe clinical course of sickle cell disease. Treatment is similar to that of acute painful events. Most patients recover completely. Some may end with shortening of the involved bones.

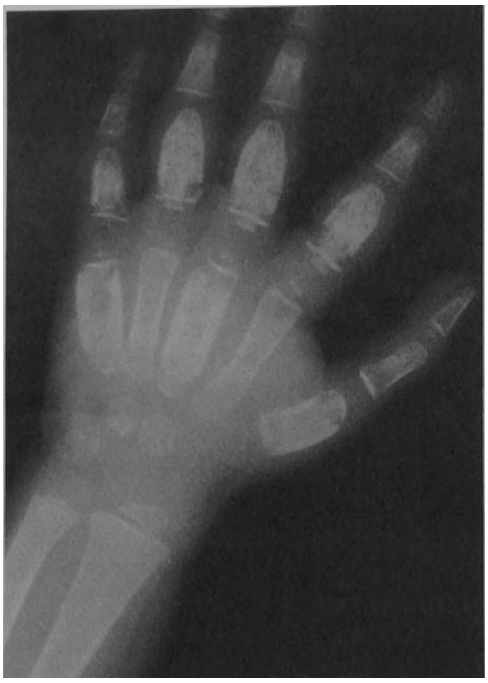

Figure 324.4
X-ray of the hand of a child with sickle cell disease with hand-foot syndrome

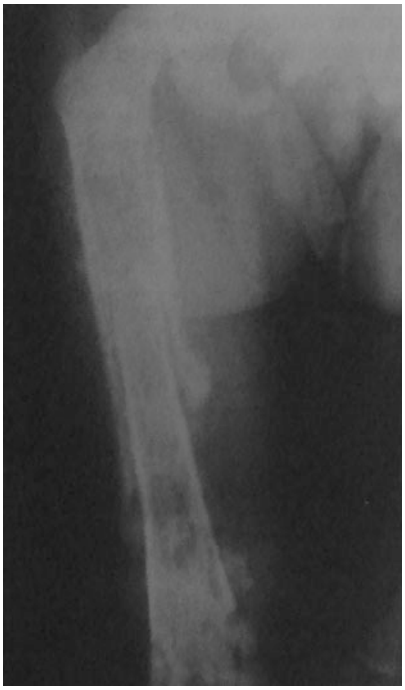

Figure 324.5
X-ray of the femur of a child with sickle cell disease and salmonella osteomyelitis

Avascular necrosis (AVN): Avascular necrosis of the femoral and humeral head is a common and serious complication of sickle cell disease. The true incidence is not known. In a large study, 10% of the patients were found to have AVN of the femoral head, and 5.6% of patients had AVN of the humeral head. The incidence of AVN is higher in patients with concomitant α-thalassemia. AVN may occur as early as 5 years of age. The prevalence increases with age. AVN of the femoral head is bilateral in over 50% of patients. Clinical manifestations include pain, limp, and limitation of movement. Conservative treatment of AVN in children below 12 years of age usually results in healing and remodeling of the femoral or humeral heads with good function. The natural history in older children and adults is progressive. Permanent damage is the expected result in most patients. Diagnosis can be made by plain x-ray in advanced cases. Expected early or mild lesions should be diagnosed by MRI. Treatment is conservative and includes avoidance of weight bearing (crutches and bed rest), analgesics, and nonsteroidal anti-inflammatory drugs. Surgical intervention in the form of core decompression, osteotomy, or arthroplasty has a low success rate and high rate of complication and failure. These procedures should be reserved for the most severe cases.

Bone marrow hyperplasia: Bone marrow hyperplasia is a consequence of bone marrow hyperactivity in response to the hemolytic anemia, resulting in widening of the marrow space and bone deformities such as frontal bossing, hair on end appearance of the skull x-ray, and protrusion of the incisors with associated overbite. Pathologic bone fracture may result from osteopenia and thinning of the cortex of the long bones. Vertebral collapse due to marrow necrosis and marrow hyperplasia leads to biconcave deformity. Compression fractures may cause a biconcave deformity with or without kyphosis.

Orbital compression syndrome: A rare but serious skeletal complication is the orbital compression syndrome that is caused by bone infarction around the globe. It is associated with pain, periorbital swelling with or without proptosis, ophthalmoplegia, visual impairment, and subperiosteal hematoma. The few reported cases were treated conservatively as other cases of vaso-occlusion.

Hepatobiliary System

Hepatobiliary complications of sickle cell disease include hepatomegaly, hepatic vaso-occlusive events, intrahepatic cholestasis, benign hyperbilirubinemia, hepatic sequestration events, and cholelithiasis with or without cholecystitis. Therapy of other sickle cell complications may also induce hepatobiliary complications. The frequency of hepatomegaly is not known because of different types of reporting (clinical vs radiologic vs autopsy). Hepatomegaly was found in 90% in an autopsy report. Hepatic vaso-occlusive events present with pain and tenderness in the right upper quadrant and jaundice with or without low-grade fever. Liver enzymes and bilirubin are usually modestly elevated (ALT and AST $<$500 IU/l, bilirubin $<$15 mg/dl). Treatment with analgesics and hydration is usually adequate and recovery is the rule. Intrahepatic cholestasis, as evidenced by markedly elevated liver enzymes, may end in hepatic failure. This syndrome is often associated with renal failure. The fatality rate is extremely high. Exchange transfusion and fresh frozen plasma can reverse this process. Liver transplantation is the only option for severe nonresponsive cases.

Benign hyperbilirubinemia is characterized by marked conjugated hyperbilirubinemia, modest elevation of liver enzymes with mild or no symptoms. The patient may look extremely yellow, but feels well. This process usually resolves without any treatment.

Hepatic sequestration events are less common and less severe than splenic sequestration. They present with right upper quadrant pain, a rapid drop in hemoglobin level,

and significant increase in liver size. The frequency of hepatic sequestration events is possibly underestimated as mild episodes might be missed because most patients have steady state hepatomegaly. The treatment depends on the severity of the anemia and the clinical picture. Mild cases resolve spontaneously. In most cases, the liver size decreases and the hemoglobin rises as the sequestered blood returns to the circulation. Treatment of severe, symptomatic cases is similar to that of splenic sequestration and includes restoration of the intravascular volume and simple or exchange transfusion.

Cholelithiasis has been reported in children as young as 2 years old. The incidence increases with age, eventually reaching 70% in adults. Diagnosis is made by ultrasonography that shows stones, sludge, or both. Most patients are asymptomatic. However, cholelithiasis may be complicated with cholecystitis and/or common bile duct obstruction. Cholecystectomy is indicated for the symptomatic patient and for those in whom differentiating hepatic vaso-occlusion from cholelithiasis-related symptoms is not possible. Elective cholecystectomy in patients with asymptomatic cholelithiasis is suggested by some authorities to avoid potential complications at inappropriate times and to alleviate patient and family anxiety. Sludge should be followed by repeated ultrasonography as it may resolve spontaneously. Cholecystectomy is to be done in symptomatic cases. Treatment of cholecystitis is similar to the same problem in other settings and includes antibiotics and cholecystectomy after stabilizing the patient. Common bile duct stones may be removed prior to surgery by ERCP.

Renal System

Renal complications of sickle cell disease include hyposthenuria, hematuria, proteinuria, tubular acidosis, nephrotic syndrome, renal infarction, acute renal failure, urinary tract infection, and end-stage renal disease. Hyposthenuria is almost universal in patients with sickle cell disease. Sickling in the hypertonic environment and slow circulation in the renal medulla leads to poor urinary concentration. Polyuria and enuresis are common manifestation of SCD. No treatment is available or needed. However, patients should be encouraged to drink fluids sufficient to avoid dehydration. Microscopic or gross hematuria is common in both sickle cell trait and sickle cell disease. It is due to papillary necrosis caused by vaso-occlusion in the hypertonic, hypoxic, and acidic environment of the renal tubular system. Bleeding is usually painless and unilateral (most commonly from the left kidney). Hematuria is usually mild and self-limiting. Supportive care in the form of bed rest, hydration, urine alkalization, and diuretics is usually adequate. Occasionally, hematuria may be severe enough to necessitate blood transfusion. Nephrotic syndrome, acute or chronic renal failure, and renal infarction are rare but serious complications in children with sickle cell disease. Treatment is the same as the treatment of similar conditions in patients not affected by sickle cell anemia. Dialysis and renal transplantation is indicated in end-stage renal disease.

Spleen: The presence of a palpable spleen is common in infants with homozygous sickle cell disease (SS) and in young children with compound SC, S β thalassemia, and homozygous sickle cell disease with high hemoglobin F. Splenic infarction (which is more common at high altitude) presents with acute abdominal and pleuritic chest pain. Functional, reversible hyposplenia, or asplenia is found in over 90% of children with homozygous SCD (SS) between 6 months and 3 years of age. Functional hyposplenia/asplenia is due to the slow circulation and local hypoxia in the splenic sinusoids. Functional impairment of the splenic reticuloendothelial system can be demonstrated by an increased number of pocked or pitted red blood cells or by technetium liver/spleen scan. This functional asplenia can be reversed by simple or partial exchange transfusion. Anatomic irreversible asplenia is caused by repeated splenic infarctions which lead to splenic atrophy and shrinkage. The spleen becomes fibrosed or calcified. This anatomic, irreversible asplenia is evident by 5–8 years of age. Hypersplenism, as evidenced by splenomegaly and pancytopenia with evidence of bone marrow hyperplasia, may be present in some infants with homozygous sickle cell disease (SS). Hypersplenism is more common in patients with milder forms of sickle cell disease, i.e., SC, SD, Sβ thalassemia, and homozygous sickle cell disease with high hemoglobin F level. Splenectomy is recommended in patients with significant hypersplenism and massive splenomegaly.

Priapism is defined as sustained painful erection lasting for more than 2 h. Priapism is common in patients with sickle cell disease after puberty. The reported prevalence varies widely from 5% to more than 40%. Priapism in patients with sickle cell disease is a low flow type of priapism. It is due to vaso-occlusion of the venous drainage of the corpus cavernosum. Sickling in the corpus cavernosum is due to stasis, hypoxia, and acidosis. Priapism can be classified as stuttering, an episode which lasts more than few minutes but less than 3 h, and prolonged, which lasts more than 3 h. The peak incidence is 12–15 years of age (some studies showed two peaks; 13–15 and 20–29 years). Up to 90% of the first events occur before 20 years of age. Diagnosis is usually based on

physical exam. The patient presents with unwanted painful erection with a rigid penis and soft glands. Doppler ultrasonography can differentiate low-flow, the usual type in SCD, from high-flow priapism. Prolonged (over 12 h) or repeated attacks may result in necrosis and fibrosis of the corpus cavernosum and erectile dysfunction and impotence in 25–35% of the patients. Conservative management, including hydration, analgesia, and frequent urination, is recommended for cases lasting more than 2 h but less than 6 h. The role of simple or exchange transfusion is controversial because of the lack of evidence of its benefit and the reported high complication rate (headache, seizures, and obtundation). Aspiration of the corpus cavernosa followed by saline irrigation has been demonstrated to be effective for those nonresponsive to conservative management and for episodes lasting more than 2 h. Instillation of α and β adrenergic agonists in the corpus cavernosa together with aspiration was effective in inducing detumescence in 95% of the cases. Surgical shunting is indicated in prolonged nonresponsive cases (over 6–12 h). Creating a shunt from the corpus cavernosa to the corpus spongiosum is the most commonly used procedure.

Skin: Leg ulcers occur mainly over the medial or the lateral malleolus and occasionally on the dorsum of the foot. The ulcers are often painful, indolent, and disfiguring. They occur in 10–20% of patients with homozygous sickle cell disease. The ulcers usually occur between 20 and 50 years of age. Ulcers are caused by skin ischemia due to hypoxic vascular occlusion and may be exaggerated by infection, trauma, or high temperature. The natural course is rapid healing in some cases, recurrent ulcerations in others, and chronic and protracted ulceration in most cases. Secondary local infection is common but systemic infection is unusual. A reasonable approach to the treatment of sickle cell–associated leg ulcers is adequate analgesia, bed rest, elastic compression, leg elevation, good local hygiene, debridement and local antiseptic, and the use of systemic antibiotics if cellulitis, lymphadenitis, or systemic infection is present. Other modalities, which had been used in resistant cases, include local and systemic zinc oxide, hyperbaric oxygen, and skin grafting.

Ophthalmologic manifestations/complications: Vaso-occlusion may involve any blood vessel in the eye or the globe. The clinical significance depends on the involved tissue and the degree of damage. Tortuosity of the conjunctival blood vessels is of diagnostic but not clinically significance. Retinopathy is classified into proliferative and nonproliferative types. Proliferative retinopathy is a serious complication which may lead to vitreous hemorrhage or retinal detachment ending in visual loss. The proliferative process starts with vaso-occlusion of the peripheral retinal arteries which stimulates neovascularization. Proliferative retinopathy is classified in five stages, including:

- Stage 1, peripheral retinal arteries occlusion
- Stage 2, arteriovenous anastomoses
- Stage 3, neovascularization
- Stage 4, vitreous hemorrhage
- Stage 5, retinal detachment

Nonproliferative retinopathy results from retinal infarction and adjacent hemorrhage. It may result in several retinal findings but rarely cause visual problems. Acute loss of vision due to central retinal artery occlusion has been reported. Hyphema may result from trauma. If untreated, it may lead to glaucoma and blindness.

Unlike hyphema in the patient not affected by sickle cell anemia, in which hypemas usually resolve spontaneously, hyphema in sickle cell disease requires immediate evacuation to avoid loss of vision. Treatment is indicated in bilateral disease, rapidly progressive disease, and in case of spontaneous hemorrhage. Laser photocoagulation is the preferred procedure with the least rate of complications. Surgical intervention is required for retinal detachment or unresolving vitreous hemorrhage.

Cardiovascular system: Cardiovascular manifestations are common in patients with sickle cell disease. Systolic heart murmurs are found in most patients and are caused by the anemia. Exercise tolerance is markedly impaired because of the anemia. Cardiomegaly is present in both children and adults and secondary to the anemia and microvascular disease. Detailed studies showed that most patients have dilatation of the ventricles and interventricular septum. However, ventricular contractility is normal in most patients. Heart failure, when it occurs, is usually due to sudden drop in hemoglobin (splenic sequestration) or fluid overload (rapid blood transfusion, especially for splenic sequestration).

Multiorgan failure: Multisystem failure syndrome, defined as failure of two or more systems (hepatic, renal, pulmonary, and cardiac), is a rare and potentially fatal complication in patients with sickle cell disease. It is often associated with severe painful vaso-occlusive event or sepsis. Aggressive exchange transfusion may be life saving.

Hearing: Sensorineural hearing loss occurs in around 10% of patients with sickle cell anemia disease. The frequency increases with age. It is caused by sickling in the cochlear vasculature, which results in destruction of hair cells.

Infection: Bacterial and viral infection is a major cause of morbidity and mortality in patients with sickle cell disease. Hyposplenia/asplenia caused by repeated splenic

infarction is the main reason of increased susceptibility to the encapsulated organisms (*Streptococcus pneumoniae and Haemophilus influenzae*). Impaired opsonization and abnormal alternative complement pathway activation increases the susceptibility to *Salmonella*, *E. coli*, *Staphylococcus aureus*, and *Mycoplasma pneumoniae*. Abnormalities in neutrophil function have been demonstrated in several studies. Devascularized tissue due to vaso-occlusive episodes in the bone, lungs, or skin provides a suitable environment for bacterial invasion and growth. Microinfarcts of the wall of the gastrointestinal tract provide egress of the *Salmonella* to the circulation, causing sepsis and/or osteomyelitis. The incidence of *Streptococcus pneumoniae* and *H. influenzae* infection (sepsis, pneumonia, or meningitis) was 400–600 and 4 times more frequent, respectively, compared with children not affected by sickle cell anemia. The mortality rate is 30% and 10% for sepsis and meningitis, respectively. The incidence of and the mortality/morbidity caused by infection by these two organisms decreased significantly since the universal use of immunization and penicillin prophylaxis. A further drop in the rate of complications from these organisms is expected with the recent approval of the 13-valent pneumococcal vaccine. Infection with the two organisms, however, remains a major cause of morbidity and mortality, especially in children less than 5 years old. Infection by other organisms is less frequent and probably less fulminant than *Streptococcus pneumoniae* and *H. influenzae*. Aggressive antibiotic treatment should be started as soon as bacterial infection is suspected. The choice of the antibiotic depends on the suspected organism. Empiric antibiotics should be started immediately in a febrile child after obtaining the appropriate cultures (blood, urine, local aspirate etc.). Ceftriaxone is recommended as an empiric antibiotic by most authorities. Vancomycin should be reserved for severely sick patients (e.g., those in shock), patients suspected to have meningitis, or in areas where penicillin resistant streptococcus pneumoniae is prevalent. Macrolide antibiotics should be given for febrile patients with pneumonia/acute chest syndrome to cover for mycoplasma and Chlamydia. There is no evidence that children with the sickle cell disease are more susceptible to virus infection than their normal counterparts. The incidence of parvovirus B19 infection is similar to that of general population; however, it may cause transient but severe aplastic anemia.

Prevention: Penicillin prophylaxis was shown to decrease pneumococcal infection by 85%. However, it should be remembered that these results were obtained when almost all isolates of *Streptococcus pneumoniae* were susceptible to penicillin. Oral penicillin or amoxicillin prophylaxis is still recommended for children with SCD as soon as the diagnosis is made. The goal of newborn screening programs is to get penicillin prophylaxis started by 2 weeks of age. The duration of the prophylaxis is not known. At least one study suggested that it should be stopped at 5 years of age. A first generation cephalosporin is a good alternative. Macrolides or trimethroprim-sulfamethoxazole is recommended for patients who are allergic to penicillin. Conjugate *H. influenzae* and conjugate (PCV7) or the most recently approved 13-valent streptococcus pneumoniae are part of routine childhood immunization. Twenty-three-valent pneumococcal vaccine (PCV23) is recommended after 2 years of age and repeated once after 3–5 years. Meningococcal conjugate vaccine is recommended after 2 years of age. Hepatitis B and A vaccination are also recommended.

Psychosocial: The patient with sickle cell anemia as well as their families are under severe psychological, social, and financial stress. Recurrent painful events, frequent hospitalizations, inability to keep up with peer's exercise activities, delayed sexual and physical maturation, school absenteeism, job-related problems, financial and insurance problems, and fear of premature death puts severe pressure on the families. Comprehensive and sympathetic programs for early diagnosis, education, physical and psychological treatment, and financial support are needed. Participation of hematologists, psychologists/psychiatrists, nurses, social workers, self-help groups, and government and nongovernment organizations are essential to assure proper care for patients and their families. Special sickle cell clinics are also important.

Growth and development: The weight and height of infants with sickle cell disease is normal. This is not surprising as the levels of hemoglobin S levels are low intrauterinely as well as in the first few months of life. With increasing age and rising hemoglobin S levels, however, patients become more anemic and fall behind in weight and height. Weight is more affected than height. Growth deficits may be evident as early as 2 years of age and become more pronounced with increasing age. Sexual maturation is delayed in both sexes. Females have delayed onset of menarche. Both males and females have delays in attaining normal Tanner development stages. Development delay is multifactorial. The severe chronic anemia is probably the most important factor. Other implicated factors include, malnutrition, vitamin and mineral deficiency, infection, and the stress of chronic disease. Most patients with sickle cell disease do not require therapy for physical or sexual delays unless they have slow growth velocity.

Cognitive function: For a long time, patients with sickle cell disease were thought to have learning,

neuropsychological, and cognitive problems. Recent evidence suggests that silent CNS infarction may be the major cause of these problems. MRI scans have identified several brain lesions in children without a history of clinical CNS problems.

Neonatal screening: Neonatal screening is recommended in areas where sickle cell gene is prevalent. The interpretation of screening results is shown in Table 324.1. Screening programs, together with close follow-up and parental education programs, have resulted in decreased mortality and morbidity and a better lifestyle in children with sickle cell disease. This improved outcome is the result of:

- Antibiotic prophylaxis
- Appropriate and timely immunization programs
- Aggressive treatment of febrile episodes
- Aggressive management of splenic sequestration events
- Comprehensive multidisciplinary sickle cell programs
- Parental education about the potential complications (splenic sequestration fever, seizures respiratory distress, etc.) and the necessity of urgent medical consultation
- Prenatal diagnosis and counseling of pregnant women
- Premarital counseling of patients with sickle cell trait
- Parental and children guidance on methods of coping with the stress of the condition and its complications

Surgery and General Anesthesia

Children with sickle cell disease are at high risk of developing severe complications with surgery and general or regional anesthesia. Postoperative complications include acute chest syndrome, painful events, infection, fever, CNS events, and death. Sickling-promoting factors that may be induced or exaggerated by surgery and anesthesia include hypoxia, dehydration, acidosis, stasis, hypotension, hypothermia or hyperthermia, hypoperfusion, and pressure on major blood vessels by tourniquets or improper positioning. These factors may be induced by medications, improper preparation, improper positioning (immobility, pressure on major blood vessels), the operating room environment (hypo or hyperthermia), the disease itself (pulmonary or cardiac disease). Generalized sickling leading to serious complications (respiratory failure) and/or death or localized sickling leading to organ damage (loss of a limb) may be the end result. Complications may occur intraoperativly or postoperatively. It is important to remember that complications occur more commonly in the recovery room when patient monitoring may be less intense.

These complications can be avoided by careful monitoring, adequate oxygenation, hydration, avoidance of hypotension, hypovolemia, hypothermia, local or generalized stasis, and acidosis are essential. The use of tourniquets should be avoided, and care should be taken to avoid pressure on major blood vessels due to improper positioning. These measures need to be started prior to general anesthesia and continued during surgery and through postoperative period, until the patient is fully awake. Close monitoring of temperature, blood pressure, oxygen saturation, and blood loss is essential. These measures are more important in patients with compromised pulmonary or cardiac function and in those who require surgery that compromises these organs (i.e., cardiac, CNS, or chest surgery).

The need for preoperative blood transfusion is controversial. Recent evidence suggests that transfusion may not be necessary in all patients. Preoperative blood transfusion to raise the hemoglobin level to 10 g/dl was found to be as effective as exchange transfusion to lower the level of hemoglobin S to less than 30%. Until further studies are completed, preoperative simple blood transfusion is indicated for all patients. Exchange transfusion should be reserved for patients with significant anemia (to avoid CHF), patients with compromised cardiac or pulmonary function, and those undergoing thoracic, cardiac, or CNS surgery.

Table 324.1
Interpretation of hemoglobin electrophones in the newborn

FA	Normal
FAS	Sickle cell trait
FS	1. Homozygous sickle cell disease (SS)
	2. Sickle-β° thalassemia
	3. Sickle hereditary persistent hemoglobin F (HPHF) disease
FS+C,D,E,O Arab, etc.	Double heterozygous of sickle with Hbs C, D, E, or O Arab, etc.
FA+C,D,E, O-Arab	Trait for hemoglobins C, D, E, or O-Arab the present Hb

Any of the above could be associated with alpha gene hemoglobinopathy, mainly α thalassemia.

Pregnancy in Sickle Cell Disease

Fetal and neonatal related issues: Complications associated with maternal sickle cell anemia include spontaneous abortion, intrauterine growth retardation, low birth weight, prematurity, and increased perinatal mortality.

These complications are mainly due to placental compromise caused by decreased uterine blood flow. Other factors which may contribute to fetal problems include maternal anemia, maternal malnutrition, and increased incidence of placenta previa and abruption placenta in mothers with sickle cell disease. Perinatal mortality was as high as 20–50%. However, improvement in obstetric care leads to a significant decrease in the perinatal mortality. Routine prophylactic blood transfusion is not recommended.

Hematopoietic stem cell transplantation (HPSC): Hematopoietic transplantation is the only curative therapy for patients with sickle cell disease. Overall survival and event-free survival range between 91–100% and 73–93%, respectively, with the higher figures in the more recent studies. Transplant early in the course of sickle cell related complications is associated with a better outcome with overall and disease free survival of 100% and 93%, respectively, as compared with 88% and 80% for transplants later in the course of the condition. The majority of the reported cases were from matched siblings. Few cases were from cord blood of matched siblings with overall and disease-free survival of 100% and 90%, respectively. The main limiting factors for HPSC transplant are the variable clinical severity and the lack of known predictors of severity of SCD. Indications for HPSC vary between transplant centers. Accepted indications include a history of stroke, repeated severe acute chest syndrome, and frequent severe and debilitating vaso-occlusive events. It should be remembered that HLA-matched siblings with sickle cell trait can be used as donors.

Augmentation of Hemoglobin F Production

Several pharmacologic agents (5-Azacytidine, 5-Azadeoxycytidine, butyric acid, arginine butyrate, and erythropoietin) have been used in animal model and/or humans to increase hemoglobin F levels. Hydroxyurea is the agent commonly used in clinical practice in patients with sickle cell anemia. Several studies in both adults and children proved its efficacy in decreasing the frequency and severity of painful events, acute chest syndrome, blood transfusion, hospitalization, and mortality. Limited observational studies with small numbers of patients provided evidence that hydroxyurea prevents primary and secondary stroke, reverses splenic function, prevents or reverses chronic organ damage, improves oxygenation, and reduces proteinuria. Currently, hydroxyurea is indicated for patients with recurrent severe painful episodes, recurrent acute chest syndrome, and recurrent hospitalizations. Further studies are needed before recommendation can be made for its use for other indications. It is generally believed that the benefits of hydroxyurea are due to the increase in hemoglobin F level. However, the improvement in many patients was noticed with minimal or no change in hemoglobin F levels. Other possible mechanisms of action include neutropenia (neutrophil count correlates with event rate), reduction of reticulocytes, and young red blood cell which have high tendency to adhere to the vascular wall and induce vaso-occlusion and generation of nitric oxide. The major limiting factor in the routine use of hydroxyurea is neutropenia. However this complication is reversible with reduction of the dose or temporally discontinuing the drug. An unproved but serious concern is the possible carcinogenic effect of hydroxyurea. This concern originated from the observation that hydroxyurea increased the incidence of malignancy in patients with polycythemia vera and myelodysplastic syndromes. These diseases, however, are monoclonal and premalignant. There is no evidence that the hydroxyurea is carcinogenic in patients with sickle cell disease. The recommended starting dose is 15 mg/kg given once daily. The dose is increased every 8 weeks to the maximum tolerated dose.

Blood transfusion in sickle cell disease: Blood transfusion is an integral tool in the treatment of patients with sickle cell disease. When used appropriately, transfusions may treat or prevent complications, prevent organ damage, alleviate suffering, and prevent death. As any patients with SCD are expected to receive repeated blood transfusion, care should be taken to avoid unnecessary transfusion and to avoid or minimize potential complications. In addition to the precaution necessary for transfusion in other patients (donor screening for infectious agents, proper cross matching, etc.), the following steps are essential:

- Donors should be screened for sickle cell disease and trait.
- Antigenic phenotypes of the patient should be known and records well kept for future reference.
- Limited matching for ABO, Rh, E, C, and Kell is essential to minimize the incidence of alloimmunization.
- The use of leukodepleted blood units reduces febrile reactions, platelet refractoriness, infections, and cytokine-induced complications.

The indications for blood transfusion is not precisely defined and most recommendations are based on experience or uncontrolled studies. Most patients with sickle cell disease tolerate their anemia. Indications for packed red blood cell transfusion include:

- Severe symptomatic anemia (splenic sequestration event, aplastic event, hypersplenism, and hyperhemolytic event). The indication of transfusion in these cases depends on the clinical picture (real or pending heart failure, hypotension, tachypnea, tachycardia or pallor hypoactivity, and generalized weakness), degree of the drop in hemoglobin level (2 g/dl) and bone marrow activity as evidenced by reticulocyte count and/or the presence of NRBCS in the peripheral blood. These patients should receive simple transfusion.
- *Acute chest syndrome*: Most patients with ACS present with low hemoglobin. Simple transfusion is usually adequate in mild and moderate case of ACS. Partial or total exchange transfusion is recommended in severe, progressive cases and those patients with high hemoglobin level.
- Preparation for general anesthesia (see "Surgery and General Anesthesia").
- *Stroke*: Immediate exchange transfusion is indicated for ischemic stroke. Chronic transfusions with iron-chelating therapy are recommended for primary and secondary stroke prevention and for patients with recurrent debilitating painful event.
- *Multisystem failure*: Exchange transfusion might be life saving.

Controversial indications include priapism, skin ulcers, preparation for infusion of contrast media, and silent CNS infarction. Some authorities recommend chronic transfusion in infants with ASSC to delay splenectomy. Recent literature, however, suggests that splenectomy does not increase the chances of serious bacterial infection in children with sickle cell disease because these children have functional asplenia. The hematocrit should not exceed 36% in any kind of transfusion. Higher levels result in exponential increase in blood viscosity, leading to painful events. Potential complications of transfusion should be kept in mind when considering such therapy. In addition to the known complications, patients with sickle cell disease have a higher incidence of alloimmunization and delayed hemolytic transfusion reactions. Alloimmunization occurs in 8–35% (mean, 25%) of transfused sickle cell disease patients.

Mild Sickle Cell Disease

An interesting and relatively mild form of homozygous sickle cell disease is known to occur in the Shiite Muslims population of the Arabian Gulf area. These patients have a less severe course, a higher percentage of splenomegaly and normal splenic function in most patients; at least in young children and adolescents, a lower incidence of pneumococcal infection, and a longer life expectancy. The reasons for the relatively mild course are not fully understood. High levels of hemoglobin F, which is common in this population and the common association with the α-thalassemia gene, may be the major contributing factors. This kind of sickle cell disease is not completely benign (as previously reported) as many patients develop serious complications, such as sepsis, meningitis, osteomyelitis, aseptic necrosis of femoral and humeral heads, ACS, and cerebrovascular accidents.

Sickle Cell Trait (AS)

Patients with sickle cell trait are clinically, hematologically, and developmentally normal. Around 40% of their hemoglobin is sickle hemoglobin (hemoglobin S). Hematuria and hyposthenuria are common. Extreme conditions including severe hypoxia may lead to sickling and even death. Flying in an unpressurized plane, strenuous exercise at high altitude, and severe pulmonary or cardiac disease are examples of situations in which complications and death have been reported. During general anesthesia, tourniquets and pressure on major blood vessels should be avoided to prevent severe hypoxia distal to the tourniquet, which may result in sickling and loss of an extremity.

Compound heterozygous sickle cell disease: The term "sickle cell disease" is usually used to describe patients with homozygous sickle cell disease (SS) and compound (doubly) heterozygous disease which results from coinheritance of hemoglobin S and another abnormal hemoglobin or thalassemia. SC, SD, S/O-Arab, and SE diseases are discussed in the chapter on "hemoglobinopathies other than sickle cell disease."

Sickle cell β thalassemia: Compound heterozygous sickle cell-beta thalassemia results from inheritance of a sickle cell gene from one parent and β thalassemia gene from the other. The clinical manifestations are extremely variable ranging from asymptomatic to a clinical picture similar to that of homozygous sickle cell disease. The clinical severity depends on the amount of hemoglobin A produced. Sickle-β+ thalassemia is usually milder than homozygous sickle cell disease and sickle-β° thalassemia. However, both sickle-β° thalassemia and Sickle-β+ thalassemia have a higher incidence of splenomegaly than homozygous sickle cell disease. Retinopathy is more common in sickle-β+ thalassemia than homozygous sickle cell disease and sickle-β° thalassemia. Patients with sickle-β+ thalassemia tends to have a higher hemoglobin

concentration (10–12 g/dl) and lower reticulocyte count than that of sickle-β° thalassemia (8–10 g/dl) who, in turn, have a higher hemoglobin concentration and lower reticulocyte count than those affected by homozygous sickle cell disease. The anemia in sickle-β° thalassemia and sickle-β+ thalassemia is hypochromic and microcytic. Hemoglobin electrophoresis of sickle-β° thalassemia is similar to that of homozygous sickle cell disease with higher hemoglobin A2 level (4–5%) and with no hemoglobin A. Hemoglobin electrophoresis in sickle-β+ thalassemia reveals hemoglobin S, with variable amounts of hemoglobins A, F, and A2. One parent has sickle cell trait while the other has β thalassemia and hypochromic, microcytic red blood cells.

Homozygous Sickle Cell Disease with α Thalassemia

The association of α-thalassemia with homozygous sickle cell disease (SS) results in a hypochromic microcytic anemia. The red blood cells of the newborn infant are usually microcytic (mean corpuscular volume <94 fl). Results of hemoglobin electrophoresis later in life are similar to those of homozygous sickle cell disease (SS). The anemia is usually less severe, and the reticulocyte count is lower than those of sickle cell disease (SS). The clinical effects are variable. Some studies showed that the increased frequency of painful vaso-occlusion is related to the higher hemoglobin level which is usually found in patients with sickle cell/α thalassemia. The incidence of acute chest syndrome was higher in some studies and lower in others. Some studies suggested an increased incidence of avascular necrosis of the femoral head and decreased incidence of leg ulcers.

Sickle cell with hereditary persistence of fetal hemoglobin (HPFH): Two types of HPFH have been described. One type (deletion type) results in higher levels and a pancellular distribution of hemoglobin F. Patients who coinherit this type of HPFH with sickle cell gene (sickle cell trait) are usually asymptomatic and have normal hematologic parameters. The second type (non-deletion) results in a heterogeneous distribution of hemoglobin F. The clinical picture in these patients is variable and depends on hemoglobin F level and the pattern of its distribution. Parents' studies should show that one parent has sickle cell trait, while the other has high hemoglobin F level.

Sickle cell/Hb Lepore disease: Co-inheritance of sickle cell gene with hemoglobin Lepore is rare. The clinical severity is similar to sickle-β+ thalassemia.

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325 Hemoglobinopathies-Non-Sickle Cell

Ahmad A. Mallouh

Introduction

The globin part of the normal human hemoglobins (Hb A, F, and A2) consists of two alpha and two non-alpha chains (β in hemoglobin A, γ in hemoglobin F and δ in hemoglobin A2). Hemoglobinopathies result from genetic mutations causing structural changes in one of the globin chains by adding, deleting, or exchange of one or more amino acid. Over 800 mutations have been identified. The majority of these mutant hemoglobins are innocuous. A few of them, however, cause lifelong serious and sometimes fatal health problems. The following hemoglobinopathies will be discussed in this chapter, either because of high prevalence in certain ethnic groups or geographical area and/or their clinical severity either alone or in co-inheritance with sickle cell disease or thalassemia:

- Hemoglobin C
- Hemoglobin E
- Hemoglobin D
- Hemoglobin O Arab
- Unstable hemoglobins
- High oxygen affinity hemoglobins

Hemoglobin C

Pathogenesis and Incidence

Hemoglobin C results from a genetic mutation, resulting in the replacement of glutamic acid with lysine in the β chain subunit at position 6. It is less soluble than hemoglobin A. It precipitates into hexagonal crystals inside the RBCs. The red blood cells (RBCs) become less deformable and are easily removed by the spleen. The prevalence of Hemoglobin C is approximately 40–50% in West Africa, 3.5% in Carribbeans of African descent, 3% in African Americans, and 1–10% in North Africa. It has been also reported in other countries, for example, Italy and Turkey. This geographic distribution is probably due its protective effect against falciparum malaria.

Clinical Picture

Patients with hemoglobin C trait (Hgb AC) are asymptomatic with normal hematological values, except for a mild microcytosis and target red blood cells. Homozygous patients (Hb CC) usually have a mild, compensated hemolytic anemia and splenomegaly. Like other chronic hemolytic anemias, patients affected by homozygous hemoglobin C may develop cholelithiasis. Parvovirus infection may induce a transient aplastic crisis.

Co-inheritance with Thalassemia or Other Hemoglobinopathy

Patients with double heterozygous hemoglobin S/hemoglobin C (Hb SC) disease have a clinical picture similar but usually milder than homozygous hemoglobin S (Hb SS). Approximately 2% of these patients have severe disease. Aseptic necrosis of the femoral head and proliferative retinopathy are, in particular, common in patients with SC disease. Patients with C/β-0 thalassemia usually have a thalassemia intermedia-like picture. Those with C/β+ thalassemia usually have a mild, compensated hemolytic anemia. Patients with C/E, C/Lepore, and C/δ β thalassemia have a moderate hemolytic anemia. Patients with C/O Arab usually have a mild, compensated hemolytic anemia.

Diagnosis

Heterozygous hemoglobin C is usually diagnosed on hemoglobin electrophoresis either as a part of neonatal screening or as part of the investigation of a patient with mild chronic hemolytic anemia. The blood indices typically demonstrate a mild microcytosis. Target cells are seen on the peripheral blood smear of patients with hemoglobin C trait. The peripheral blood smear has a high number of target red blood cells with the presence of xerocytes and hexagonal crystals, inside the red blood cells. Hemoglobin C has the

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same mobility as hemoglobins E, O Arab, and A2 in alkaline media. Hemoglobin electrophoresis in acid citrate agar or high performance liquid chromatography (HPLC) is required for definitive diagnosis. The electrophoresis pattern of C/β-0 thalassemia is similar to that of Hb CC disease. Both demonstrate a high Hb C levels (over 95%) and no hemoglobin A. Hb C/β-0 thalassemia, however, has a marked microcytosis. At least one parent would have β thalassemia trait.

Treatment

No specific therapy is needed for patients with AC or CC. Parvovirus induced aplastic crisis anemia is usually mild and compensated. Folic acid supplementation is recommended in homozygous or doubly heterozygous patients (SC, C/β thalassemia, etc.). Treatment of SC disease is similar to that for SS disease. Treatment for C/β thalassemia depends on the severity of the anemia and may require blood transfusion. Splenectomy is rarely required in CC disease, but might be necessary in SC or Hb C/β thalassemia disease.

Hemoglobin E

Pathophysiology and Incidence

Hemoglobin E results from substitution of glutamic acid by lysine in position 26 of the β globin chain. The β chain of Hb E is synthesized at a slower rate compared with that of Hb A. This leads to imbalance of globin chain synthesis which results in a thalassemia-like morphology of the RBCs. Hemoglobin E is the second most common hemoglobinopathy worldwide. The highest prevalence of Hb E is found in South East Asia (Thailand, Cambodia, and Laos), where the prevalence reaches 20–30%. It is also common in the Indian subcontinent (India, Pakistan, Bangladesh, and Sri Lanka), Vietnam, Nepal, China, Turkey, Malaysia, and the Phillipines. This distribution is probably due to its protective function against falciparum malaria. It has been brought to North America and Europe through immigration.

Clinical Picture

Heterozygous patients (Hb AE) have normal hematologic values except for a mild microcytosis and target cells identified on the peripheral blood smear. Homozygous patients (Hb EE) have a mild compensated hypochromic microcytic anemia. Mild splenomegaly may be present. Co-inheritance of Hb E with β-thalassemia is the major concern for patients with Hb E. Patients with E/β-thalassemia disease have a highly variable clinical and hematologic manifestations ranging from mild thalassemia trait-like hypochromic, microcytic anemia to severe transfusion-dependant hemolytic anemia. Around 50% of the patients are phenotypically similar to β-thalassemia major. The severity seems to be influenced by several factors including the type of the inherited β gene (E/β0 vs E/β+ disease), associated inheritance of α-thalassemia, and possibly environmental factors. Co-inheritance with Hb S (ES) results in a phenotypically mild sickle cell disease. Patients have fewer problems with vaso-occlusive crisis, splenic sequestration crisis, and increased susceptibility to infection than patients with Hb SS.

Diagnosis

Hemoglobin E should be considered in a patient with hypochromic, microcytic anemia, especially if the family history or ethnicity is suggestive of the gene inheritance. It has the same mobility as Hb C and Hb A2 in alkaline medium. It can be differentiated from Hb C by electrophoresis at acid pH, in which its mobility is the same as Hb A and Hb A2. High performance liquid chromatography separates Hb E from hemoglobins A and C.

Treatment

No treatment is needed for Hb E. Treatment for E/β-thalassemia depends on the severity of the anemia and its complications. Mild cases require no therapy except folic acid supplementation. Treatment of severe case is the same as β-thalassemia major. ES disease is managed as patients with SS disease.

Counseling

Patients with heterozygous and homozygous Hb E should be counseled when having children with individuals who have β-thalassemia, Hb SS, β-thalassemia trait, or sickle cell trait.

Hemoglobin D

There are a number of hemoglobins termed "hemoglobin D". Hemoglobin D-Punjab (also called Hb Los

Angeles) and hemoglobin Ibadan are the most common ones. Hemoglobin D-Punjab is a mutant hemoglobin that results from the genetic substitution of glutamic acid by glutamine at position 121 in the β globin chain. It occurs most commonly in the Punjab part of the Indian subcontinent and Iran, where the reported prevalence is around 2%. It is also reported in the Turkish, Algerian, West African, Saudi Arabian, African American, Native American, English, and Irish population. The occurrence of the gene in the United Kingdom and Ireland is mostly a result of immigration from and intermarriage with people from the Indian subcontinent.

Clinical Picture

People with hemoglobin D trait (Hb AD) are asymptomatic and they have normal hemoglobin level and normal red blood cells indices. Homozygous disease (Hb DD) is extremely rare. Patients usually have normal hemoglobin level and normal red blood cells indices. Co-inheritance with hemoglobin S (Hb SD) results in a mild form of sickle cell disease. Patients usually have fewer problems with vaso-occlusive crisis, infection, organ damage or splenic sequestration crisis than Hb SS patients. Some patients, however, develop serious complications including stroke. Co-inheritance with β-thalassemia (Hb D/β-thal) results in mild to moderate hypochromic, microcytic anemia.

Diagnosis

Hemoglobin D has the same mobility as hemoglobin S in alkaline media. It can be differentiated from hemoglobin S by their distinct mobility in acid media, in which hemoglobin D migrates with hemoglobin A and by the fact that hemoglobin D does not sickle. An increased number of target cells is seen on review of the peripheral blood smear. Red blood cells' osmotic fragility is decreased. Differentiating Hb DD from D/β-0thal can be a problem, as both have over 95% hemoglobin D with no hemoglobin A. Red blood cells in patients affected by Hb D/β0-thal are hypochromic and microcytic. At least one parent is expected to have β-thalassemia or β-thalassemia trait.

Treatment

No treatment is needed for Hb AD or Hb DD except for folic acid supplementation, as the patients are clinically and hematologically normal. Patients with Hb SD and Hb D/β-thal are treated as those with Hb SS and β-thalassemia intermedia or thalassemia major, respectively. Therapy depends on the severity and/or complications of the disease.

Counseling

Patients with either heterozygous or homozygous hemoglobin D should be counseled when having children with individuals who have β-thalassemia, Hb SS, β-thalassemia trait, or sickle cell trait.

Hemoglobin O Arab

Hemoglobin O Arab results from genetic substitution of lysine for glutamic acid at position121 in the β globin chain. It is mainly found in the Middle East, the Balkans, Greece, North Africa, West Africa, and in African Americans.

Clinical Picture

Persons with hemoglobin O-Arab trait (Hb A/O Arab) are asymptomatic and have normal hemoglobin levels and normal or mildly microcytic red blood cells. Homozygous disease is extremely rare. Patients are asymptomatic with normal hemoglobin or mild compensated hemolytic anemia. Red blood cells are microcytic with high MCHC. Co-inheritance with hemoglobin S (S/O Arab) results in a moderate sickle cell disease–like clinical picture with variable severity. Patients may have vaso-occlusive events, splenomegaly, jaundice, and reticulocytosis. Hemoglobin level ranges betweem7 and 8 g/dl. Co-inheritance with β-thalassemia results in a thalassemia intermedia picture.

Diagnosis

The red blood cells in patients with heterozygous or homozygous hemoglobin O-Arab are either morphologically normal or mildly microcytic. Hemoglobin O Arab migrates with Hb C in alkaline media and it migrates between hemoglobins A and S in acid media. It can be identified by high performance liquid chromatography.

Treatment

No treatment (except folic acid supplementation) is needed for Hg A/O Arab or Hb O Arab/O Arab, as the

patients are clinically and hematologically normal. Patients with Hb S/O Arab and Hb O Arab/β-thal are treated as those with Hb SS and β-thalassemia intermedia or thalassemia major, respectively. Therapy depends on the severity and/or complications of the disease.

Unstable Hemoglobins

Unstable hemoglobins are inherited structurally abnormal hemoglobins characterized by decreased solubility, resulting in intracellular hemoglobin precipitation forming intracorpuscular Heinz bodies and shortened red blood cells survival.

Pathophysiology

Unstable hemoglobins result from substitution or deletion of amino acids in one of the globin chains. (α, β, or γ). Decreased solubility of the unstable hemoglobins results from the weak binding between globin and heme parts of the hemoglobin and from interference with the tertiary and quaternary structure of the subunits. As a result, hemoglobin is denatured and precipitated inside the red blood cell as Heinz bodies. Heinz bodies attach to the cell membrane and make red blood cells susceptible to destruction by the spleen.

Clinical Picture

Unstable hemoglobins are rare. They are mostly inherited as dominant disorders. Approximately, 250 mutations have been identified so far. Chronic hemolytic anemia of variable severity is the main clinical manifestation. The severity of anemia and the age of its onset depend on the type of the mutation and are modified by extrinsic factors. Mutations involving the γ chain (Hb Poole) are associated with transient hemolytic anemia and jaundice in the newborn, which lasts for the first few months of life. It resolves as hemoglobin A replaces hemoglobin F. Mutations involving the α chain (Hb Hasharon) presents with anemia and jaundice in the neonatal period and persists lifelong. People who inherit an unstable hemoglobin involving the β chain (Hb Koln and Hb Zurich) are hematologically normal at birth. Anemia and dark colored urine (pigmenturia) develop at 2–4 months of age, as hemoglobin F is replaced with hemoglobin A. Patients may develop acute hemolytic episodes triggered by infection or exposure to oxidant drugs and may develop transient aplastic crisis with parvovirus B19 infection. As in other chronic hemolytic anemia, patients may develop cholelithiasis. Patients with the rare types of unstable hemoglobin named "hyperunstable hemoglobin" have a thalassemia intermedia-like clinical and hematologic picture. They have moderately severe hypochromic, microcytic anemia with or without splenomegaly.

Diagnosis

Diagnosis should be suspected in a patient with hemolytic anemia and RBC Heinz bodies found using supravital stains. Diagnosis is confirmed by the heat stability test or isopropanol stability test. Hemoglobin electrophoresis is usually not useful for diagnosis of the unstable or hyperunstable hemoglobins. In these cases, globin chain sequencing using DNA based methods is required to confirm the diagnosis.

Treatment

Treatment is mainly supportive with folic acid and avoidance of oxidant drugs. Blood transfusion is rarely needed as most patients are asymptomatic or have compensated anemia. Splenectomy may be required in the very few severe cases. Splenectomy does not always ameliorate anemia.

High Oxygen Affinity Hemoglobins

Over 200 variants of high oxygen affinity hemoglobins have been described. The oxygen dissociation curve in these patients is shifted to the left. Oxygen delivery to the tissues is poor resulting in tissue hypoxia, increased erythropoietin level and secondary erythrocytosis. Individuals with these hemoglobin variants are usually asymptomatic and require no therapy. However, they should be considered in the differential diagnosis of erythrocytosis.

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326 Thalassemia

Nameeta P. Richard · Kristina M. Haley · Michael Recht

General Considerations

A red blood cell (RBC) contains approximately 640 million hemoglobin molecules, which allow the red cell to perform its essential function of oxygen delivery in exchange for carbon dioxide. Alteration of the hemoglobin molecule can result in various forms of anemia and their subsequent long-term complications. Hemoglobin abnormalities can be a result of synthesis of abnormal hemoglobin as in Sickle Cell Disease, or abnormalities can result from reduced synthesis of normal hemoglobin, as in thalassemia.

Hemoglobin synthesis, a process that predominantly occurs in the mitochondria of the cells, changes as a fetus develops, is born, and becomes an adult. At any point of hemoglobin development, though, a hemoglobin molecule is made up of four polypeptide chains. In order to accommodate for differences in oxygen delivery requirements as a fetus develops and enters extrauterine life, different polypeptide chains come together to create hemoglobin molecules with oxygen affinity specific for their current environment. The genes for the polypeptide chains are located on chromosomes 11 and 16, and the genes result in the synthesis of six different globin chains: alpha, beta, gamma, delta, epsilon, and zelta. Pairs of these globin chains come together to form tetramers, resulting in functional hemoglobin molecules. In embryonic development, the predominant hemoglobin molecules are $\zeta_2\varepsilon_2$ (Hemoglobin Gower 1), $\zeta_2\gamma_2$ (Hemoglobin Portland), and $\alpha_2\varepsilon_2$ (Hemoglobin Gower 2). Hemoglobin F ($\alpha_2\gamma_2$) is the most prevalent hemoglobin in later fetal development, while the primary hemoglobin in an older infant and an adult is Hemoglobin A1 ($\alpha_2\beta_2$), with small portions of Hemoglobin F as well as Hemoglobin A2 ($\alpha_2\delta_2$) (*Fig. 326.1*). In the first 3–6 months of life, the amount of β chain production increases, and the γ-chain is mostly replaced by β-chain (*Fig. 326.2*). Eventually, the cell synthesizes α-chains in proportion to β-chains in order to match the two together and create adult hemoglobin.

Problems arise when the cells are unable to synthesize the normal amount of α- or β-chain as the two will become mismatched, resulting in decreased synthesis of normal, adult hemoglobin. The general-term thalassemia refers to a group of genetic anemias that are a result of inadequate or absent synthesis of normal globin chains. Thus, in contrast to Sickle Cell Anemia where an abnormal hemoglobin is created, thalassemia is a *quantitative defect* in hemoglobin synthesis. The clinical picture of a patient with thalassemia depends on which chain is affected and how many genes are deleted or mutated.

Epidemiology

The genes producing the different types of thalassemia can be found throughout the world, but they are concentrated in the Mediterranean area, Southeast Asia, India, and Middle East (*Fig. 326.3*). It appears that the heterozygote state provides increased resistance to *falciparum* malaria, much like the genes for Sickle Cell Anemia and Glucose-6-Phosphate Dehydrogenase Deficiency.

Categories of Thalassemia

The thalassemias are a heterogeneous group of anemias resulting from a reduced or absent rate of production of one or more of the globin chains. This quantitative decrease in globin chain synthesis results in the microcytic, hypochromic anemias, called α-thalassemia and β-thalassemia. The classification of thalassemias can be based on which globin chain is decreased or absent.

α-Thalassemia

General Information

The majority of α-thalassemia is a result of deletion of one or more of the α-globin genes. Normal cells have four α-globin genes, and the clinical variability seen in α-thalassemia is in direct relation to the number of genes deleted (*Fig. 326.4*). Deletion of one gene results in a silent carrier state of α-thalassemia. If two genes are deleted (on either chromosome), then the patient has α-thalassemia trait. Hemoglobin H disease refers to the state of three genes being deleted, and results in

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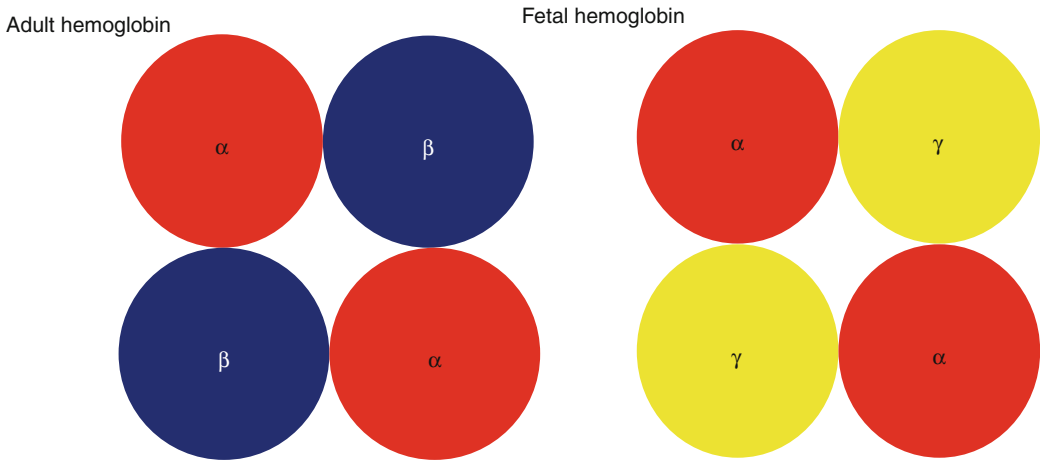

Figure 326.1

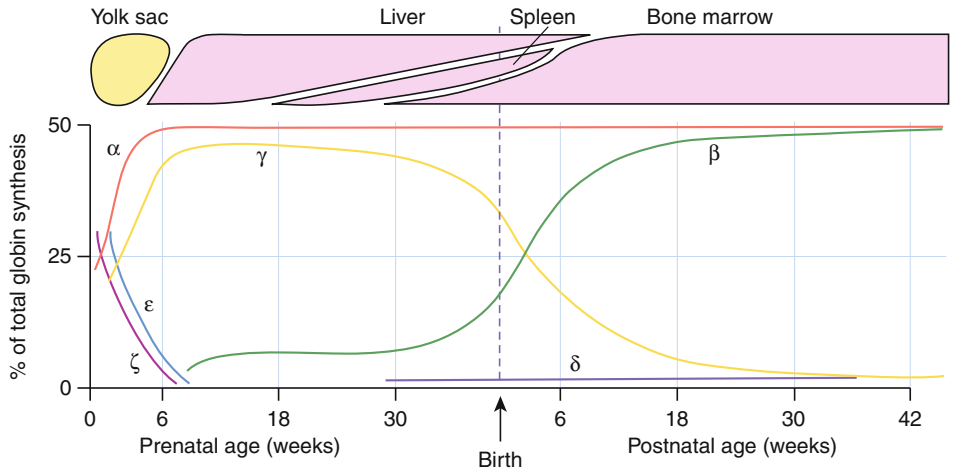

Figure 326.2

a moderately severe anemia. Deletion of all four genes results in hydrops fetalis and is incompatible with extrauterine life.

Clinical Characteristics

As stated previously, the clinical features seen in α-thalassemia are directly related to the number of genes deleted. See *Table 326.1* for a summary of α-thalassemia syndromes, clinical features, and hemoglobin electrophoresis findings.

Individuals who have three α-globin genes present are asymptomatic and have normal hemoglobin levels and mean corpuscular volume (MCV). These silent carriers may come to the pediatrician's attention as a result of a newborn screen report of Hemoglobin Bart's (*Fig. 326.5*). Hemoglobin Bart's is a type of hemoglobin made of four γ-globin chains. Silent carriers show 0–3% hemoglobin Bart's during the newborn period. Eventually, as the γ-chain is replaced by β-chain, the Hemoglobin Bart's disappears. A follow-up hemoglobin electrophoresis at 6 months of age would be normal but is largely unnecessary.

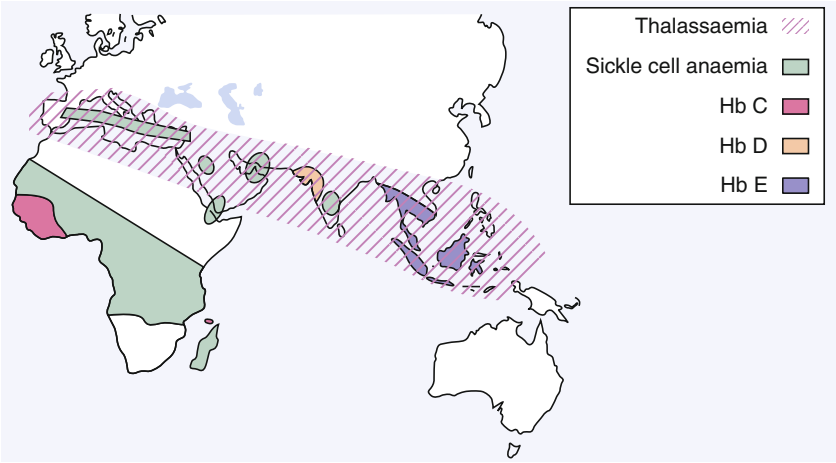

Figure 326.3
Caption missing

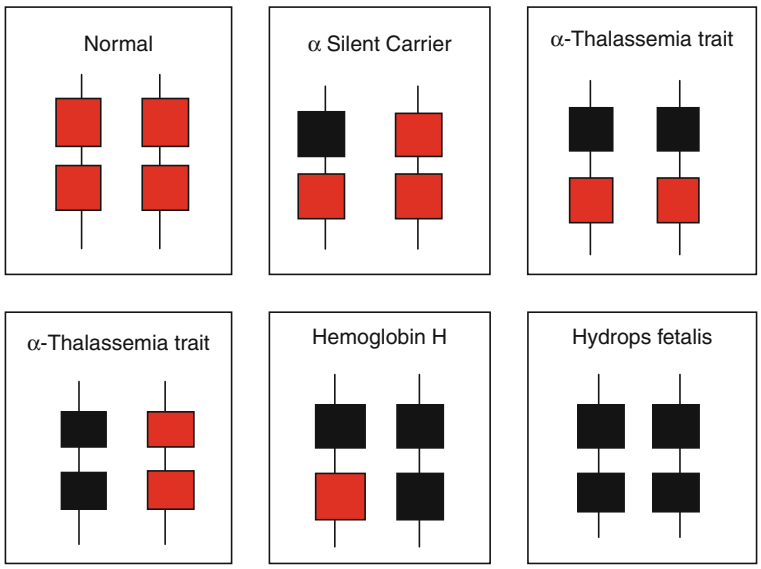

Figure 326.4
The genetics of α-thalassemia. ■ = normal genes ■ = gene deletions

Individuals with only two α-globin genes present are usually asymptomatic as well, and this is termed α-thalassemia trait. As an infant, the MCV will likely be <100, the hemoglobin may be slightly low, and the peripheral smear will appear slightly hypochromic with few target cells. On hemoglobin electrophoresis, α-thalassemia trait patients have 2–10% hemoglobin Bart's at birth, but the electrophoresis is normal after >6 months of age.

When three out of the four α-globin genes are deleted, an individual will have mild to moderately severe microcytic, hypochromic anemia (Hgb 7–11g/dL). This is known as hemoglobin H disease. Hemoglobin H is created when excess β-globins come together to form a tetramer (β_4). Hemoglobin H can aggregate within a red blood cell, forming an inclusion body and resulting in hemolysis. The peripheral blood smear shows

Table 326.1
The α thalassemias

Genotype	# of α genes present	Clinical characteristics	Hgb electrophoresis at birth	Hgb electrophoresis >6 months
αα / αα	4	Normal	Normal	Normal
-α / αα	3	Silent carrier	0–3% Hgb Bart's	Normal
- - / αα or -α/-α	2	α-Thal trait	2–10% Hgb Bart's	Normal
- - / - α	1	Hgb H disease	15–30% Hgb Bart's	β4
- - / - -	0	Fetal hydrops	>75% Hgb Bart's	None

α refers to presence of α globin gene, - indicates deletion of α globin gene, Hgb = hemoglobin, Hgb Bart's = γ4

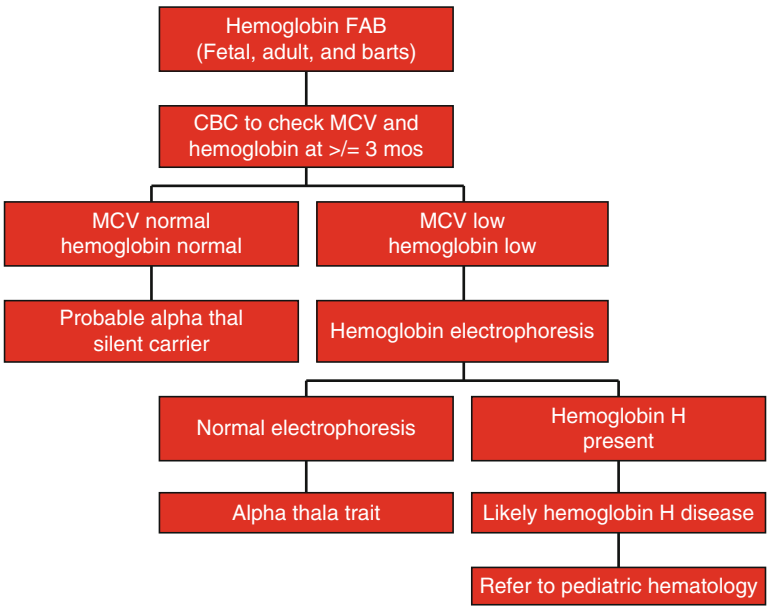

Figure 326.5
α-thalassemia newborn screen results

microcytosis, hypochromia, and poikilocytosis (abnormal cell shape). On hemoglobin electrophoresis, patients with hemoglobin H disease have 15–30% hemoglobin Bart's at birth. As older infants and children, hemoglobin H will continue to be present on electrophoresis. Patients with Hemoglobin H disease generally do well in the first decade of life and do not require many transfusions. However, they will likely show evidence of chronic hemolysis with hepatosplenomegaly, elevated indirect bilirubin, and increased susceptibility to aplastic crisis. In addition, because of ineffective eythropoiesis, patients may have skeletal abnormalities and hepatosplenomegaly, which is less severe than in β-thalassemia (see ❯ "Clinical Characteristics" in β-Thalassemia). As the patient ages, they may require more frequent and eventually chronic transfusions and begin to experience the consequences of iron overload (see ❯ "Complications" in β-Thalassemia). Finally, Hemoglobin H is readily oxidized and makes the patient especially susceptible to oxidative stress as in Glucose-6-Phosphate Dehydrogenase Deficiency, and oxidative stressors should be avoided.

Individuals with deletion of all four α-globin chains have intrauterine anemia and hydrops fetalis, which is incompatible with extrauterine life. This is the most severe form of α-thalassemia. On hemoglobin electrophoresis,

these patients have mostly Hemoglobin Bart's and absent fetal or adult hemoglobin.

Differential Diagnosis

Patient's with α-thalassemia trait will have evidence of microcytosis, and other causes of microcytic anemia should be considered such as iron deficiency, lead exposure, β-thalassemia minor, and other hemoglobinopathies. When compared to children with iron deficiency anemia, patients with α-thalassemia trait have normal or increased ferritin and serum iron. When compared to children with β-thalassemia minor, patients with α-thalassemia trait have normal hemoglobin electrophoresis as older infants and children. Newborns with Hemoglobin Bart's on newborn screen may be a silent carrier of α-thalassemia, may have α-thalassemia trait, or may have α-thalassemia. In an infant with hydrops fetalis, one must also consider other causes of intrauterine anemia such as alloimmunization.

Complications

A common scenario seen in patients with α-thalassemia is unnecessary prescription of oral iron because a child has microcytic anemia thought to be due to iron deficiency. Patients with hemoglobin H disease may require blood transfusions when exposed to oxidant stressors or as they age. Chronic transfusions may result in iron overload and subsequent cardiac, hepatic, endocrine, pulmonary, and renal effects. Mothers of infants with fetal hydrops have complications such as hemorrhage after delivery, and if possible, should be counseled on therapeutic termination of pregnancy.

Treatment and Prognosis

Children with α-thalassemia trait generally do not require treatment and lead a normal life. Similar to patients with G6PD deficiency, individuals with hemoglobin H disease should take folic acid and avoid medications which cause oxidant stress. In addition, hemoglobin H patients may require splenectomy due to the development of hypersplenism. However, the prognosis for most patients with Hemoglobin H disease is excellent, but there are some exceptions that require more extensive treatment and experience more severe complications. Finally, mothers of children with fetal hydrops should have genetic counseling in order to plan for future pregnancies.

β Thalassemia

General Information

In β-thalassemia, the genetic abnormality is most commonly a result of a point mutation. Normal cells, in contrast to the α-globin genes, have only two β-globin genes. Similar to α-thalassemia, though, the phenotypic heterogeneity is a result of the number of normal genes present. If the gene is altered in such a way that no β-globin is produced, then it is termed β^0. If instead the gene is altered in a way that results in a deficit of β-globin, then it is termed β^+. An individual may be heterozygote or homozygote for the altered β gene. Patients that are heterozygotes and produce enough β-globin chain to not develop clinically significant disease typically have β-thalassemia minor. Homozygotes may have β-thalassemia major (also known as Cooley Anemia) or thalassemia intermedia, depending on if they are β^0 or if they are β^+ with a more significant deficiency (*Fig. 326.6*). In addition to the anemia that results from decreased normal adult hemoglobin synthesis, there can be marked hemolysis as the result of precipitation of unpaired α-globin chains.

Clinical Characteristics

Individuals with β-thalassemia minor are asymptomatic, but their complete blood count will be significant for microcytosis with or without a mild anemia. The peripheral blood smear shows hypochromia, target cells, and basophilic stippling (as a result of α-globin chain precipitation). The hemoglobin electrophoresis at birth will be normal, but after 6 months of age, it will show elevated hemoglobin A_2 and hemoglobin F.

Patients with β-thalassemia intermedia fall somewhere between β-thalassemia minor and β-thalassemia major and have varying degrees of anemia. The anemia is typically significant but does not require transfusions as frequently as β-thalassemia major. However, a patient with anemia and a marked microcytosis with splenomegaly and skeletal changes consistent with bone marrow expansion should raise suspicion for β-thalassemia intermedia.

Individuals with β-thalassemia major are normal at birth because β-globin gene production is not necessary for embryonic or fetal hemoglobin. However, it is unlikely for these patients to be missed because the newborn screen will be abnormal as no hemoglobin A will be present. At 3–6 months of life, the infant will become symptomatic as γ-globin production switches to β-globin production.

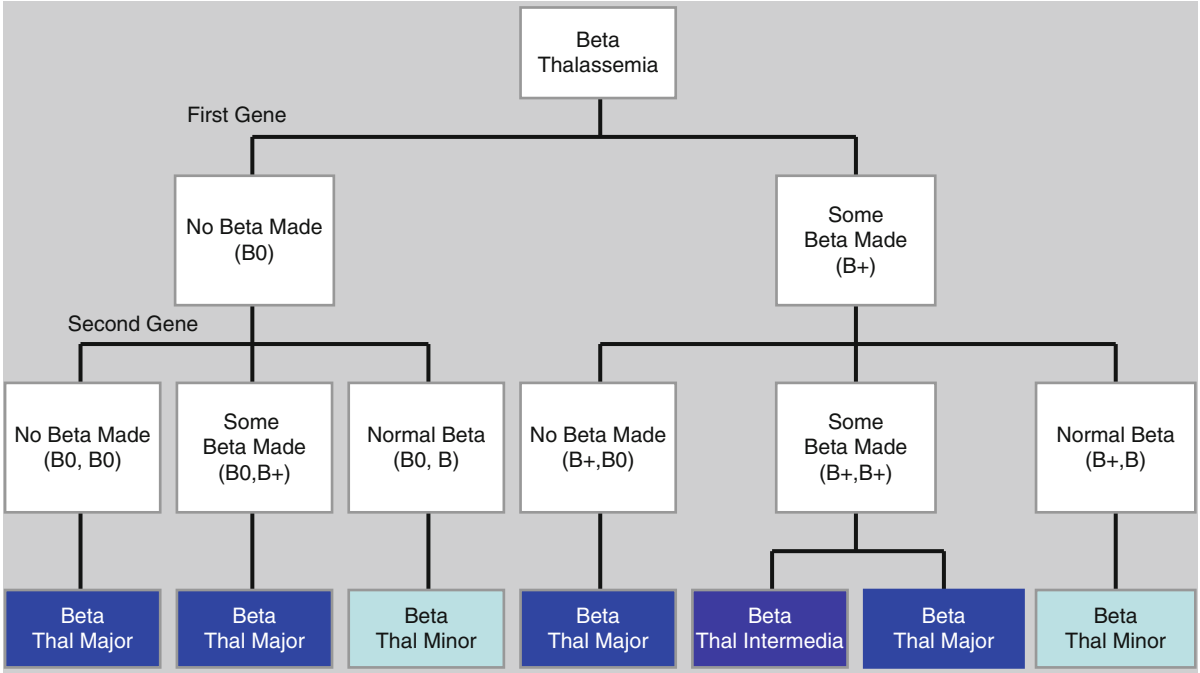

Figure 326.6

Genetics of Beta Thalassemia. The genetic abnormality seen in Beta Thalassemia is a result of a point mutation, which means that the gene is present but altered. The alteration determines, when the gene is expressed, how much Beta globin is made. There can be a variety of Beta globin production when some Beta is expressed as in Beta +. The phenotype of Beta thalassemia can vary for a given genotype

Because little to no β-globin chains will be produced, excess α-globin accumulates. These excess α-globin chains precipitate in red cells at all stages of their development and result in ineffective erythropoiesis and hemolysis. Thus, severe anemia is present because of deceased hemoglobin production as well as destruction of red cells. Similarly, symptoms are present both because of inadequate hemoglobin synthesis as well as hemolysis. The peripheral blood smear of these patients shows severe hypochromic, microcytic anemia with anisocytosis (variety of cell size) and poikilocytosis (abnormal cell shape). A plethora of target cells is a hallmark of the β-thalassemia peripheral blood smear.

The clinical features of β-thalassemia major are many and affect nearly every organ system. As a result of red blood cell destruction, there is extensive extramedullary hematopoiesis within the liver, spleen, kidneys, and entire skeletal system. Hepatomegaly develops and changes in the liver are similar to those seen in viral hepatitis and can result in variable liver dysfunction. Splenomegaly further accentuates the anemia by resulting in increased red cell destruction as well as red cell pooling. Some patients require splenectomy, which places them at increased risk for serious bacterial infection with encapsulated organisms. The expansion of bones for additional hematopoiesis leads to the characteristic thalassemia facies with bossed skull, prominent frontal and parietal bones, and enlarged maxilla. A skull x-ray in β-thalassemia major shows a "hair-on-end" appearance because of extramedullary hematopoiesis. Other bones may be at increased risk of fracture due to thinning of the cortex.

Chronic hemolysis results in elevated indirect bilirubin with subsequent gallstone formation, elevated LDH, increased susceptibility to aplastic crisis (as in Parvovirus B19 infection), and hypersplenism. In addition, patients with β-thalassemia major can experience high-output cardiac failure if frequent transfusions are not administered.

Patients with β-thalassemia major are typically managed with chronic transfusions. The iron overload that results from chronic transfusions is compounded by the fact that patients with β-thalassemia major have increased dietary iron absorption. Iron overload in these patients affects many different organ systems and is further discussed in the "Complications".

Differential Diagnosis

The differential for microcytic, hypochromic anemias includes iron deficiency anemia, α-thalassemia, β-thalassemias, lead poisoning, and other hemoglobinopathies. One way to begin to differentiate iron deficiency and thalassemia is to calculate the Mentzer Index (mean corpuscular volume divided by red blood cell number). Individuals with β-thalassemia minor have a Mentzer Index <13, while iron deficient patients typically have a Mentzer Index >13. An elevated hemoglobin A_2 is diagnostic for β-thalassemia minor, but a normal hemoglobin A_2 level can be misleading since it can be decreased in iron deficiency. In order to differentiate the most common cause of transfusion dependent anemia worldwide, β-thalassemia major, from hemoglobin E/β-thalassemia, one should obtain a hemoglobin electrophoresis.

Treatment

Children with β-thalassemia minor should not receive long-term iron therapy and do not require folic acid supplementation. The two main treatments for β-thalassemia major are chronic transfusions with iron chelation therapy and bone marrow transplantation. Due to the severity of their anemia, children with β-thalassemia intermedia and major need referral to a pediatric hematologist in early childhood to manage issues such as chronic transfusions, prevention of iron overload with chelation therapy, and management of hypersplenism. Children with β-thalassemia major and hemoglobin <6 g/dL should receive chronic transfusions with usual target hemoglobin of 10 g/dL to maintain growth and decrease frequency of infections. Chelation therapy options to avoid iron overload include IV deferoxamine or oral deferasirox (Exjade), which prevents or, at least, limits cardiac, liver, and endocrine complications such as congestive heart failure, hepatic failure, diabetes mellitus, osteoporosis, and delayed puberty. The addition of Vitamin C increases the excretion of iron produced by deferoxamine.

Complications

Like α-thalassemia minor, the most common complication of β-thalassemia minor is the unnecessary prescription of oral iron because a child has microcytic anemia thought to be due to iron deficiency. The most significant complication in β-thalassemia major is iron overload as a result of chronic transfusion and increased iron absorption. Iron overload affects nearly every body system. In the liver, iron accumulates in the Kupffer cells and eventually will result in hepatic fibrosis and potentially end-stage liver disease. Endocrine dysfunctions from chronic iron overload include hyopogonadism, growth failure, diabetes, and hypothyroidism. Iron often infiltrates the cardiac muscle in overload states and can result in a restrictive cardiomyopathy and arrhythmias. Iron deposition can also occur in the skin and result in a gray skin color. However, without blood transfusions, these children will suffer from inadequate growth, increased susceptibility to infections, and high-output cardiac failure. Many patients will develop splenomegaly and hypersplenism, which may necessitate splenectomy. In patients undergoing splenectomy, pneumococcal and *Haemophilus* influenza type B vaccine should be administered prior to surgery. After splenectomy, these children should remain on prophylactic penicillin and seek immediate medical attention for febrile illnesses.

Prognosis

Life expectancy for β-thalassemia depends on the severity of the anemia and requirement for chronic blood transfusions. Specifically, without bone marrow transplantation, children with β-thalassemia major will likely die in their third decade of life as a result of complications from chronic blood transfusions and iron overload symptoms.

Other Thalassemias

In addition to α- and β-thalassemia, there are many other abnormalities of globin chains, which can result in the thalassemia phenotype either alone or in combination with α- or β-thalassemia. Furthermore, a patient can be affected simultaneously by both a qualitative abnormality of hemoglobin synthesis as well as a quantitative defect. Although gene deletions are the most common cause of α-thalassemia, some cases of α-thalassemia are a result of point mutations. Hemoglobin Constant Spring is a result of a mutation that alters termination of translation causing an elongated, unstable α-globin chain. If a patient with two alpha gene deletions also has Hemoglobin Constant Spring, they will have a clinical syndrome similar to Hemoglobin H disease but may require more frequent transfusions. Hemoglobin E is a result of an amino acid substitution on the β-chain, and this mutation results in activation of an mRNA splice site and subsequent

reduced β-chain synthesis. Hemoglobin E/β-thalassemia is common in Southeast Asia and typically results in a β-thalassemia major phenotype, and the patient requires chronic transfusions. In addition, β-thalassemia can combine with Sickle Cell Anemia in a variety of clinical scenarios that largely depend on the extent of β-gene production.

Future Directions

Current treatment for thalassemia involves chronic transfusions and therapy to prevent or treat the complications of iron overload. However, transfusions treat the symptoms of the disease, not the disease itself. If there were more fetal hemoglobin present, then the need for adult hemoglobin would be reduced. In Sickle Cell Disease, Hydroxyurea has become a commonly used agent to increase the proportion of fetal hemoglobin made. Hydroxyurea has been shown in clinical trials to increase hemoglobin and MCV and reduce the need for transfusions in patients with thalassemia intermedia and thalassemia major. However, further work needs to be done prior to Hydroxyurea becoming a mainstay of thalassemia treatment. Bone Marrow Transplant is currently the only known cure for thalassemia, however; bone marrow transplant requires that the patient be healthy enough to undergo the myeloablative pre-transplant conditioning and that there is an available donor source. Extensive work-up must be done prior to transplant in order to assess pre-transplant morbidity, and the family must be well counseled on the possible complications of transplant, including but not limited to graft rejection, graft failure, graft versus host disease, and death. Despite these complications, there have been many successful matched related donor transplants for thalassemia patients. Finally, gene therapy has been proposed as a cure for thalassemia major. The idea of replacing the abnormal β-globin gene with a normal β-globin gene transported via an autologous Hematopoietic stem cell transplant seems plausible, but this therapeutic strategy has met a variety of challenges and has not yet become a part of thalassemia treatment.

In summary, the microcytic, hypochromic anemia that results from the quantitative defects of hemoglobin production seen in thalassemia have a wide range of clinical significance. Disease severity is a function of the number of absent or abnormal genes as well as the aggregation of excess globin chains. Many patients will be brought to the pediatrician's attention as a result of an abnormal newborn screen, but the diagnosis should be included in the differential for any patient who presents with a microcytic anemia. In taking care of patients with more significant disease states, it is important to recognize the signs and symptoms of hemolysis and chronic iron overload.

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327 Polycythemia

Hassan M. Yaish

Polycythemia is a condition characterized by an increase in both the total red blood cells mass and blood volume, resulting in hemoglobin and hematocrit levels significantly higher than normal for the patient's age. It is divided into three types: (1) Primary polycythemia, or polycythemia vera (PV), a condition classified as myeloproliferative disease (MPD) and is rarely encountered in children. (2) Secondary polycythemia, resulting from: physiologically appropriate increase in production of erythropoietin in response to hypoxia of various causes or inappropriate secretion of erythropoietin by a tumor, hemoglobinopathy associated with hemoglobin of low oxygen affinity, and decreased level 2–3 DPG in the red blood cells. (3) Relative polycythemia. In the first two types, the red blood cell mass is increased, while in the third type, the plasma volume is decreased, causing relative rather than real increase in red blood cell counts while red blood cell mass is normal.

Primary Polycythemia

Definition: Primary polycythemia, or polycythemia vera (PV), is a myeloproliferative disease resulting from the clonal expansion of an abnormal multipotent stem cell that produces erythroid progenitors which can proliferate without the presence of erythropoietin (EPO), a feature which is frequently utilized as a diagnostic mean for PV. This multipotent stem cell is unlike the normal fetal progenitor stem cells and those cells with a mutation in the EPO receptor in that they still require erythropoietin for clonal expansion.

Incidence and epidemiology: The prevalence of PV has not been well documented in the USA. In 2003, a study from Connecticut demonstrated an incidence of PV of 22 per 100,000 people. Generalized to the population of the USA, this would reflect approximately 65,243 patients with PV in the USA. The median age at presentation of PV is 60 years. Less than 1% of the patients are less than 25 years of age.

Pathology and laboratory findings: The condition is characterized by polycythemia, leukocytosis, thrombocytosis, and a hypercellular bone marrow.

Signs and Symptoms: Patients with erythrocytosis may develop cardiac and CNS related symptoms such as dyspnea, hypertension, paresthesias, and dizziness. Thrombocytosis may result in thrombosis and bleeding. Pruritus and GI symptoms are frequently seen in adults with PV. They are thought to be the result of increased histamine turnover due to granulocytes proliferation. Patients frequently have splenomegaly.

Prognosis: It is common to see long survivors of PV, even though spontaneous remissions are very rare. Disease-related morbidities are mainly the result of vascular occlusion, bleeding, marrow fibrosis, and leukemia transformation.

Diagnosis: In the past, the diagnosis of PV used to be a diagnosis of exclusion. Both secondary as well as relative polycythemias have to be excluded. At the present time, however, a newly described somatically acquired clonal V617F mutation in the Janus 2 kinase (Jak2) as found to be positive in 90% of adults with PV. The incidence of Jak-2 mutation is significantly less in children. A proportion of children with PV were misdiagnosed as a result of relying on the presence of the Jak-2 mutation. This emphasizes the need for separate diagnostic criteria in children (*Table 327.1*). CD 117, polycythemia rubra vera-1 RNA (PRV-1 RNA) over-expression is another myeloproliferative marker found more frequently in children with PV and sporadic ET. In contrast to the acquired nature of the mutation leading to PV, inborn mutations have been described resulting in what is known as primary familial and congenital polycythemia (PFCP). This condition was shown to be a result of erythropoietin receptor mutation as was described in a report on two new such mutations. The condition, also known as familial erythrocytosis, is characterized by elevated red blood cell mass, low serum erythropoietin, normal oxygen affinity, and autosomal dominant inheritance. Other mutations involving exon 12 of the Jak2 were described in patients with PV and negative Jak2 V617F mutation. A variant of the primary familial and congenital polycythemia (PFCP) is known as Chuvash polycythemia. It was first described in an endemic Russian population and was found to be caused by a mutation in the Von Hippel- Landau (VHL) gene. This gene is associated with mutation in oxygen-sensing

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Table 327.1
Suggested criteria for childhood polycythemia vera (the presence of both major and one minor are required for the diagnosis)

Major criteria: elevated red cell mass
No cause of secondary erythrocytosis, including:
(a) Absence of familial erythrocytosis (e.g., hereditary mutations of erythropoietin (EPO) receptor)
(b) No elevation of EPO caused by
• Hypoxia (arterial po2 < 92%)
• High oxygen affinity hemoglobin
• Truncated EPO receptor
• Inappropriate EPO production by tumor
Minor criteria
(a) Presence of JAK2 V617F mutation
(b) Endogenous erythroid colony formation
(c) Hypercellular bone marrow with trilineage proliferation
(d) Low serum EPO levels

pathway that regulates EPO synthesis. Children with similar conditions outside Russia is referred to as, primary proliferative polycythemia.

Treatment: The goal of PV treatment is to reduce the numbers of the proliferating cells so as to prevent the symptoms associated with high RBCs, platelets, and WBCs. Phlebotomy or isovolemic erythropheresis, are the most commonly used procedures to achieve this goal. Iron replacement is essential to prevent hyperviscosity associated with iron deficiency. Low dose aspirin can also be beneficial. Among agents known to control cell counts, hydroxyurea is thought to be safer and have less side effects than other agents, especially in children. Anagrelide, an agent that targets megakaryocytes differentiation and proliferation, has proven effective in eliminating the thrombocythemia-related symptoms in 80% of patients with PV. Erlotinib, a specific inhibitor of *Jak2* mutation, is currently undergoing clinical trials in PV and other myeloproliferative disorders. Stem cell transplantation has been successfully utilized in some patients.

Secondary Polycythemia

Definition: Secondary polycythemia is defined as a reactive polycythemia as a result of any clinical condition associated with chronic decreased tissue oxygenation, which in turn triggers the physiologic reaction of excess erythropoietin production. Cyanotic congenital heart disease with right-to-left shunts and various chronic pulmonary diseases compromising proper oxygenation are the most common causes of secondary polycythemia. Living at high altitudes, congenital methemoglobinemia, and abnormal hemoglobin with increased oxygen affinity are some of the other common causes of secondary polycythemia. Certain vascular or renal tumors are associated with polycythemia due to erythropoietin secretion by the tumor itself.

Signs and Symptoms: Cyanosis, hyperemia of the sclera and mucous membranes, and clubbing of the fingers are the most frequently encountered clinical manifestations. The oxygen saturation of arterial blood is decreased, and, as the hematocrit rises above 65%, symptoms of hyperviscosity may develop, requiring frequent phlebotomy. To maintain such a high hemoglobin level, and as a result of frequent phlebotomies, iron deficiency develops. In the presence of high viscosity and the rigid iron-deficient red blood cells, the risk of intracranial thrombosis has been reported to be increased. As indicated earlier, iron therapy is recommended despite the high hemoglobin level.

Prognosis: the prognosis of secondary polycythemia is that of the original disease process which have resulted in this condition.

Relative Polycythemia

In contrast to the first two types, relative polycythemia is not associated with true increase in red cell mass, but instead a decrease in plasma volume. Dehydration and burns are classic causes of this type of polycythemia. It is a preventable condition and could be corrected by hydration or treatment of the precipitating cause.

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328 Transfusion of Blood and Blood Products

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Our knowledge of blood compatibility and safety has come a long way since the first documented blood transfusion from a sheep to a human in 1667. In developed countries, transfusions are primarily used to support patients undergoing invasive procedures and complex medical treatments for diseases such as cancer and complex surgical procedures. In developing countries, blood is given mostly to children with anemia and women with pregnancy-related complications. Transfusion of blood products can significantly reduce morbidity and mortality, but still carries risks. Children undergoing complicated therapies often depend on transfusions for survival. As the demand for blood component transfusions increase, so must the inventory of safe blood components and the knowledge of transfusion medicine.

Blood Groups

Blood groups are determined by inherited antigenic molecules on the surface of blood cells. These antigens can be proteins, carbohydrates, glycoproteins, or glycolipids depending on the blood group system. A total of 308 blood group antigens are currently recognized, 270 of which are clustered into 30 blood group systems, *Table 328.1*. Once exposed to foreign red blood cells, the immune system can form alloantibodies against blood group antigens that are not present on the recipient's own red blood cells (RBCs). In general, red cell alloantibodies can only be formed following exposure to another person's red blood cells through blood transfusion or pregnancy. Subsequent transfusion of incompatible blood can cause these pre-formed antibodies to trigger hemolysis of transfused cells. Unlike alloantibodies, ABO antibodies are "naturally occurring" and are formed as a result of exposure to A and B-like substances from bacteria, plants, and other exogenous material in the gastrointestinal tract. The most clinically relevant groups will be discussed here.

ABO is the most important blood group for transfusion because nearly all people have naturally occurring ABO antibodies capable of causing hemolysis of incompatible red cells. Each person's RBCs demonstrate A antigens (type A), B antigens (type B), both (type AB), or neither (type O), *Table 328.2*. A person will only make antibodies to ABO antigens that they are lacking; for example, a group A person makes anti-B antibody, *Table 328.2*. ABO antibodies are both IgG and IgM class and can fix complement, which leads to brisk hemolysis. Transfusion of ABO-incompatible RBCs is likely to cause severe morbidity or death. Thus, it is imperative that safety procedures are followed to ensure patient safety. ABO incompatibility is the most common cause of maternal-fetal incompatibility, but it is rarely a cause of severe hemolytic disease of the fetus and newborn (HDFN). ABO antigens are not fully developed in infants <4 months of age and infants do not form natural ABO antibodies until approximately 6 months of age.

The Rh system contains at least 50 antigens of which the major antigens are D, C, E, c, and e coded on two distinct genes. The D antigen (RhD) has greater immunogenicity than any other non-ABO RBC antigen. Antibodies to Rh antigens are mostly IgG and do not bind complement. Therefore, they tend to lead to extravascular hemolysis and can cause mild to severe delayed transfusion reactions. Anti-D antibodies made by multiparous, RhD-negative mothers are able to cross the placenta and are capable of causing HDFN in RhD-positive fetuses.

Hundreds of other blood cell antigen groups have been described. Antibodies to the clinically significant blood groups such as ABO, Rh, Kell, Duffy, Kidd, and Ss are capable of causing HDFN. Antibodies to other blood groups can also cause HDFN if the antibody is IgG and can cross the placenta. In neonates, certain classes of antigens are not fully expressed, including the Lewis system, I, P, Lutheran, and Xg systems. Expression of all blood groups can usually be detected around 1 year of age.

Blood Donation

Blood transfusions would be impossible without a consistent, reliable pool of blood products. Until blood

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Table 328.1
International Society of Blood Transfusion defined blood group systems (system symbol)

ABO (ABO)	Yt (YT)	Cromer (CROM)
MNS (MNS)	Xg (XG)	Knops (KN)
P (P1)	Scianna (SC)	Indian (IN)
Rh (RH)	Dombrock (DO)	Ok (OK)
Lutheran (LU)	Colton (CO)	RAPH (RAPH)
Kell (KEL)	Landsteiner- Weiner (LW)	John Milton Hagen (JMH)
Lewis (LE)	Chido-Rogers (CH/RG)	I (I)
Duffy (FY)	Hh (H)	Globoside (GLOB)
Kidd (JK)	Kx (XK)	Gil (GIL)
Diego (DI)	Gerbich	RhAg (RHAG)

Table 328.2
ABO antigens, antibodies, and compatible blood products

Patient blood type	ABO antigen(s) on RBCs	Antibodies in plasma	Compatible RBCs	Compatible plasma products
A	A	Anti-B	A, O	A, AB
B	B	Anti-A	B, O	B, AB
AB	A, B	None	AB, A, B, O	AB
O	None	Anti-A, Anti-B	O	O, A, B, AB

can be manufactured using synthetic materials, living human donors are the only source. From the time the donor presents for blood collection until the blood is transfused into the recipient, dozens of carefully regulated steps are completed to ensure the safety and efficacy of the blood product.

Donor Screening

Screening donors to identify those at high risk for transfusion-transmitted disease is the first and most cost-effective step in maintaining a safe blood supply. There is a higher frequency of transfusion-transmitted infections when donors are compensated for their donation with monetary or material incentives. As a result, the World Health Organization advocates making all blood donation voluntary. Unfortunately, there are not enough voluntary donors to meet the needs of the blood supply in many developing countries, which still rely on family members and replacement or paid donors. An ideal donor is a healthy adult free of viral disease who does not participate in high-risk behaviors (intravenous drug use, multiple sex partners, etc.) and is willing to donate blood for free. In the United States, donated blood undergoes testing for transfusion-transmitted infectious diseases, including cytomegalovirus (CMV), human immunodeficiency virus (HIV), hepatitis B, hepatitis C, human T-cell lymphotropic virus 1 and 2 (HTLV-1,2), West Nile Virus, *Trypanosoma cruzi*, syphilis, and bacteria (*Table 328.5*).

Autologous Donation

Prior to an elective procedure, a patient may donate blood for their own use during or after surgery. Autologous donations increase the risk of pre-operative anemia and can carry risk if the unit is contaminated ex vivo or if it is transfused to the wrong patient. In addition, autologous donation for a pediatric patient is difficult for ethical and logistical reasons. The child may be unable to consent or assent to phlebotomy and/or the child's size may limit the amount of blood that can be collected. Intraoperative blood salvage, in which blood is removed from the surgical field, washed, and returned to the patient, is another method of transfusing a patient with their own blood.

Directed Donation

Directed blood donation is uncommon in developed countries, but is a common source of blood in developing countries. The strength of directed donation is the ease of identifying a donor. In many places, directed donation is logistically complex. Generally, directed donation is discouraged in places that have access to a safe, volunteer blood supply, as research has shown that directed donation increases blood wastage and carries a higher rate of donor deferral for increased infectious disease risks. Moreover, all red cell and platelet donations from blood relatives must be irradiated to prevent transfusion-associated graft versus host disease (TA-GVHD), a rare but fatal complication of transfusion (see further discussion about TA-GHVD below). If maternal blood is given to her newborn, it should also be washed to prevent antibodies in her serum from reacting to the infant's RBCs. If paternal blood is given to an infant, it may express cognate antigens to clinically significant antibodies which the infant received passively from the mother prior to birth, which could lead to a severe hemolytic reaction.

Collection

In most developed countries, the collection of blood is highly regulated by the government. In other countries, collection processes follow the recommendations of health organizations such as the AABB (formerly known as American Association of Blood Banks), World Health Organization, or American Red Cross or a local government or hospital.

There is a worldwide initiative to use only volunteer blood donors. In the absence of sufficient volunteers, alternate donors are often used. In places where it is expensive to collect a unit of blood and the prevalence of viral disease is high, pre-donation viral testing is done. Once a donor is cleared for donation, whole blood is collected into a sterile storage container containing anticoagulant, buffer, and preservative. To minimize the risk of contamination, the system of needles, tubes, and containers must remain closed, ensuring no contact with the environment. Generally, the maximum amount of blood that can be collected from each donor is 10.5 ml/kg, or around 500 ml. The most common adverse reaction to donating blood is a bruise or hematoma at the site of the venipuncture. A vasovagal event, ranging from lightheadedness to complete loss of consciousness, is seen in 2–3% of donations. Donors experiencing this complication should be kept either supine or in trendelenburg position and provided with electrolyte-containing fluids until they have recovered.

Storage

Preparation and storage of blood components will vary based on the regulations that apply in different countries. In general, whole blood is separated into components to make efficient use of the donor pool and to allow clinicians the flexibility to transfuse only the component(s) needed by the patient. Each unit must be tested for ABO and RhD type and infectious agents prior to release. Once testing is completed and the unit is deemed eligible, it is stored at the proper temperature until it is needed for transfusion or until it expires, ❯ *Table 328.3*. The expiration date of packed red blood cells (PRBCs) varies with the storage solution of the component. The use of additive

Table 328.3
Storage temperature and expiration date for blood components

Product	Storage temperature	Expiration (additive solution)
Whole blood	1–6°C	21 days (CPD)
		35 days (CPD-A)
Packed RBCs	1–6°C	21 days (CPD)
		35 days (CPD-A)
		42 days (AS-1,3,5)
FFP and cryoprecipitate	≤−18°C	24 h after thawing
Platelets	20–24°C	4–7 days
Granulocytes	20–24°C	24 h
RBCs frozen in 40% glycerol	≤−65°C	24 h after deglycerolizing
RBCs frozen in 20% glycerol	≤ −120°C	

solutions lengthens the time for red cell unit storage and has allowed blood banks to maintain larger inventories and minimize the risk of blood shortages. Detailed records of the entire process are maintained for every blood component in order to ensure that each was processed under appropriately controlled conditions. These records are also required so that look-back studies can be done if a unit needs to be recalled or tracked for any reason.

Compatibility

In the United States, tests done routinely to determine donor and recipient compatibility are forward and reverse typing to determine the patient's ABO and RhD type, antibody screen, and crossmatching. To determine the forward ABO-typing (also known as "front type"), reagent antisera is used to test for the presence of A or B antigens on the RBC surface. Reverse ABO-typing ("back type") is done using reagent red cells to test for the presence of ABO antibodies in the serum. The front and back type should always agree. If not, the underlying reason for the discrepancy must be determined prior to transfusion. Red cell antigens other than ABO and RhD are not determined on a routine basis. Exceptions may include chronically transfused patients, such as those with sickle cell disease or women of childbearing age. In the United States, the standard of care for sickle cell disease patients is to provide ABO, RhD, RhCE and Kell blood group antigen matched red cells to prevent alloimmunization.

The antibody screen tests for the presence of red cell alloantibodies in the plasma. The test methodology is an indirect antiglobulin test (IAT), *Fig. 328.1*. The recipient's plasma is incubated separately with at least two reagent RBCs that express a known phenotype of common red cell antigens. Antihuman globulin (AHG or "Coombs reagent") is added to help magnify the agglutination reaction to detect any RBC alloantibody that is present in the recipient's serum. If a clinically significant red cell alloantibody is detected, it is identified by further IAT testing of the serum using more extensive reagent red cell panels. Once identified, antigen negative, crossmatch-compatible RBCs must be transfused.

The direct antiglobulin test (DAT), also called the direct Coombs test, is typically done if autoimmune hemolysis is suspected. The DAT determines if a recipient's RBCs are coated with antibody, *Fig. 328.1*. This evaluation is done by mixing the recipient's red blood cells with Coombs reagent and scoring the reaction for agglutination. If the DAT is positive, follow-up testing requires identification of the antibody using IAT as

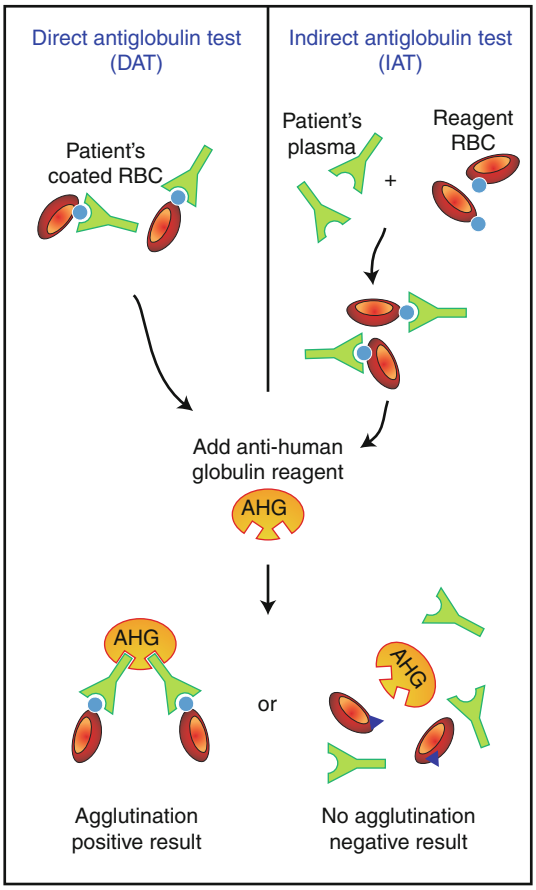

Figure 328.1
Comparison of the direct and indirect antiglobulin tests. The indirect antiglobulin test is also known as an antibody screen. If the antigen and corresponding antibody are present in the reaction, AHG reagent will agglutinate the red cells resulting in visible clumping. If the corresponding antibody or antigen is not present, the antibody cannot bind and agglutination will not occur

described above. In neonates, the DAT is routinely performed using only anti-IgG reagent since any antibody found in the neonate is an IgG antibody that was passively transferred from the mother.

Once a unit of blood is identified for possible transfusion, the patient's plasma is mixed with the donor red cells to ensure that they are compatible; this is called a crossmatch. In emergency situations, the physician may choose to use uncrossmatched group O, RhD-negative blood. Since no compatibility testing is conducted, this should only be done when there is insufficient time to conduct crossmatching. In order of descending preference, the RBC products that should be used during an

emergency are crossmatch compatible RBCs, ABO/RhD-type specific RBCs, and uncrossmatched group O RBCs. Physicians must weigh the risk of a hemolytic transfusion reaction against the need for blood transfusion in a hemorrhaging patient. In these situations, crossmatching can be conducted post-transfusion. Neonates <4 months old typically do not require a crossmatch as long as group O RBCs are given and the antibody screen is negative. If anything other than group O cells are intended, a crossmatch is done to determine if the neonate passively received anti-A or anti-B from the mother.

Causes of incompatibility between donor and patient include red cell alloantibodies, passive maternal immunoglobulin in neonates, recipients of plasma or IVIG, hematopoietic stem cell transplant, laboratory or phlebotomist error, or cold or warm autoantibodies. In most countries, patients require a repeat crossmatch sample every 3 days to detect the development of new red cell alloantibodies. Neonates are unlikely to form alloantibodies, thus only require compatibility testing once per hospitalization when under the age of 4 months. This approach lessens the amount of blood phlebotomized from neonatal patients.

Blood Products

Whole Blood

Whole blood (WB) is rarely used in developed countries because individual component therapy is better tailored to the needs of the patient and more efficiently uses the blood supply. Fresh WB contains RBCs, plasma, clotting factors, platelets, and leukocytes. However, following 24 h of storage at 4°C, the platelets are non-functional. Granulocyte function is also not reliable in WB transfusions. Activity of coagulation proteins will decrease over the duration of the 21 days storage. When large-volume transfusion is necessary, such as in trauma or in exchange transfusion, WB may be used to minimize dilutional coagulopathy. Because WB contains a relatively large amount of plasma containing ABO antibodies, it must be ABO-identical to the recipient to prevent hemolytic reactions.

Packed Red Blood Cells

Packed red blood cell (PRBC) transfusion is indicated to increase the oxygen carrying capacity to vital organs. A unit of PRBCs is made by centrifuging a unit of WB and removing most of the plasma and platelets. PRBCs have a hematocrit of 50–80%, and therefore must be infused slowly due to the high viscosity. In pediatric patients, 10–15 ml/kg is transfused over 2–4 h for routine transfusion. If the patient is not losing blood concurrently, 10 ml/kg should raise the hemoglobin by 1–2 g/dl or the hematocrit by 3–6%. As with every transfusion, the benefit of increased red cell mass must be vigilantly weighed against the risks of exposure.

Platelets

Platelet transfusion is indicated in some patients with thrombocytopenia or platelet function defects, *Table 328.4*. Platelet units can be collected from a single donor during an apheresis procedure or extracted from multiple units of whole blood. The shelf life of platelets is usually limited to 5–7 days because platelets must be kept at room temperature in order to remain viable and efficacious. The risk of bacterial growth is approximately 1 in 5,400 units in the United States and is significantly increased with storage beyond 5 days. This risk has been decreased in some countries by the use of pathogen inactivation protocols.

Typically 10–15 ml/kg of platelets is transfused over 30–60 min. This should increase the platelet count by

Table 328.4
Indications for platelet transfusion in children

Platelet count < 10,000 and decreased platelet production, without other risk factors for bleeding
Platelet count < 20,000 and planned minor procedure, such as lumbar puncture
Platelet count < 50,000 with DIC, active bleeding, or planned major procedure in patient with decreased platelet production
Platelet count < 100,000 with multiple traumas, CNS bleeding, or undergoing surgery in critical sites, such as CNS or eyes

Table 328.5
Estimated prevalence of transfusion-transmitted viruses by country

	Sub-Saharan Africa	United States	Japan
HIV	1:1,000	1 : 2,135,000	1 : 11,000,000
HBV	1:4,300	1 : 205,000	1 : 340,000 – 1 : 450,000
HCV	1:2,500	1 : 1,935,000	1 : 22,000,000

approximately 50,000/μl. However, patients with sepsis, splenomegaly, bleeding, drug-induced thrombocytopenia, disseminated intravascular coagulopathy (DIC), or other illnesses may have lower than expected post-transfusion platelet recovery. Platelets express ABO, but not RhD antigens. Transfusion of ABO-compatible platelets are preferred as they result in improved posttransfusion platelet recovery and reduced rates of alloimmunization. In addition, platelets should be compatible with the patient's RhD type since platelet units contain small amounts of red blood cells. If Rh-positive platelets must be given to a Rh-negative patient, a dose of Rh Immune Globulin (RhIG) may be given to prevent RhD alloimmunization as per the institution's policy. Rather than provide RhIG to all RhD-negative patients who received RhD-positive platelets, some centers choose to give it only to females of child-bearing potential. One 300 ug dose of RhIG neutralizes 15 ml of RBCs, which contains sufficient anti-D to cover several adult-sized transfusions of contemporary platelets derived from whole blood, plateletphersis, or buffy coats.

Platelets express many membrane antigens, including HLA class I antigens. As a result, patients who have been pregnant or exposed to multiple blood donors are at risk of HLA-alloimmunization. Once a patient is HLA alloimmunized, the antibodies may cause the transfused platelets to be destroyed rapidly and the post-transfusion platelet count will not rise as expected. This is called platelet transfusion refractoriness. Three options exist for platelet refractory patients: (a) select HLA-compatible donors from an HLA-typed registry of apheresis donors; (b) identify HLA-antibody specificities and select antigen-compatible apheresis donors; and (c) perform platelet cross-match testing to select compatible platelets.

Plasma Products

Fresh Frozen Plasma

Plasma is the liquid, acellular portion of WB which contains proteins, colloids, nutrients, crystalloids, hormones and vitamins. Plasma can be prepared and stored in several ways resulting in numerous types of plasma products, but fresh frozen plasma (FFP) is most commonly used. FFP is frozen within 8 h of collection to maintain the optimal activity of the coagulation factors. Once thawed, FFP should be given within 24 h. However, plasma used within 5 days of thawing is still considered efficacious for treatment of coagulation factor deficiencies, though there is slightly decreased activity of clotting factors (F) V and VIII. As plasma is rich in clotting factors, the main indication of plasma transfusion is to increase clotting factor levels in a coagulopathic patient. The typical dose of 10–20 ml/kg is expected to increase the coagulation factor concentrations by 30% in a non-bleeding patient. Plasma must be ABO-compatible but does not require Rh-compatibility, crossmatching, or product modifications such as irradiation or leukoreduction because it is acellular.

Cryoprecipitate

When plasma is frozen and subsequently thawed in a refrigerator, an insoluble precipitate forms that is very rich in FVIII, von Willebrand factor (VWF), FXIII, and fibrinogen. Historically, cryoprecipitate was used to treat patients deficient in VWF (von Willebrand disease) or FVIII (hemophilia A). Today, it is primarily used to replete fibrinogen, especially in patients with DIC or dilutional coagulopathy. One pool of cryoprecipitate (six to ten donors) will typically increase the fibrinogen level by 60–100 mg/dl in an adult. The equivalent pediatric dose is one unit of cryoprecipitate for every 10 kg of patient weight.

Albumin

Albumin is the most abundant protein in plasma. Commercially-available human albumin is purified using cold ethanol fractionation, pooled, and sold in either a 5% or 25% solution. The main indication is to increase oncotic pressure in patients with low albumin levels, such as those with liver disease or nephrotic syndrome.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIG) is a commercial product prepared by purifying and pooling immunoglobulins from human plasma. Indications for IVIG include idiopathic thrombocytopenia purpura, severe combined immunodeficiency, acquired immunodeficiencies, and Kawasaki syndrome. Its mechanism of action in these disease processes is poorly understood. Mild flushing, headache, rash, and allergic reactions are common following infusion of IVIG. More serious side effects, including renal failure, aseptic meningitis, and pulmonary edema, can occur. Because IVIG contains small amounts of all immunoglobulin classes, anaphylaxis has been described in patients with absence of IgA.

Clotting Factors

For patients with a congenital deficiency of a clotting factor, plasma was once the only source of clotting factors. Cryoprecipitate offered a more efficient clotting factor source for those deficient in FVIII and VWF. As technology advanced, various purification techniques allowed for individual clotting factor concentrates to be isolated with minimal contamination by other clotting factors. Recombinant or plasma-derived clotting factor concentrates are the preferred treatment for hemophilia and VWD patients worldwide. With new viral deactivation techniques, plasma-derived products are considered extremely safe but still possess a theoretical risk of transmitting an emerging infectious agent.

Granulocytes

The main indication for infusing granulocytes is a refractory bacterial, yeast, or fungal infection in a severely neutropenic patient. In most cases of granulocyte transfusions, volunteer donors are mobilized with corticosteroids and/or granulocyte colony stimulating factor (G-CSF) to increase their peripheral white blood cell count prior to undergoing donor apheresis. The goal is to maintain the recipient's granulocyte count above 500 granulocytes/ul. Adverse effects are common and include fever, shaking chills, dyspnea, wheezing, and pulmonary infiltrates. Prophylactic granulocyte transfusions are not recommended in patients who are neutropenic without overt signs of serious infection. Granulocytes must be stored at room temperature and given within 24 h of collection in order to preserve granulocyte function. Because granulocytes contain significant amounts of red blood cells, they must be crossmatch-compatible and irradiated in order to decrease the risk of transfusion-associated graft versus host disease (TA-GVHD).

Product Preparation

Upon completion of compatibility testing for cellular components, the most appropriate blood product must be identified for each patient. Factors to consider when selecting a unit for transfusion include using autologous or directed donor cells if available, ABO/RhD typing, antibody screen results, diagnosis, age, transfusion history, volume of blood component needed, and time and date the blood is required. As discussed here, the treating physician may also request specific attributes of cellular blood products depending on the patient's age, diagnosis, and transfusion history.

Leukocyte Reduction

Reducing the number of leukocytes in cellular blood components, such as platelets or red cells, is accomplished by filtration. Indications for leukocyte reduction include prevention of recurrent febrile non-hemolytic transfusion reactions, prevention of primary HLA-alloimunization, and to decrease transfusion-transmitted cytomegalovirus (CMV) infections in immunocompromised patients. As per the standards of the AABB, leukoreduced products must contain fewer than 5×10^6 white blood cells for apheresis platelets and PRBC and fewer than 8.3×10^5 for pooled platelets. Some blood banks universally leukoreduce cellular components while others do so at the discretion of the ordering physician.

CMV-Negative Components

Transfusion-associated cytomegalovirus (CMV) infection is usually of no clinical significance in immunocompetent recipients. However, CMV can result in serious morbidity and even mortality in immunocompromised patients, young children, and fetuses. At-risk people may include fetuses, neonates with immature immune systems, patients with a congenital or acquired immunodeficiency, patients on immunosuppressive medications as part of treatment for cancer or a solid organ or hematopoietic stem cell transplant. Leukocytes are the only hematopoietic reservoir for CMV, thus transfusion of leukoreduced blood products is considered an acceptable substitute to blood products from a CMV-seronegative donor. However, transfusing blood from patients who are CMV-negative may be safer for patients most at risk.

Irradiated

Blood products are irradiated to prevent transfusion-associated graft versus host disease (TA-GVHD), an often fatal transfusion reaction. TA-GVHD occurs when lymphocytes in the blood unit escape detection by the recipient's immune system. The donor lymphocytes then proliferate, detect the recipient's antigens as foreign, and

mount an inflammatory reaction that can cause severe morbidity and mortality. In pediatrics, irradiation is indicated for fetuses receiving intrauterine transfusions, patients with lymphoma or a congenital immunodeficiency, or recipients of granulocyte transfusions or a hematopoietic stem cell transplant. Less evidence supports irradiation of blood products given to premature or term infants, or those receiving immunosuppressants for a hematologic malignancy, solid tumor, or solid organ transplant. In addition, irradiation is indicated for blood products from blood-related donors or in populations with restricted HLA diversity, as their histocompatibility may be similar enough as to go undetected by the competent immune system.

Volume Reduced

Plasma in which red cells or platelets are suspended may be removed from the blood product for several reasons. Volume reduction is accomplished by centrifugation and discarding the plasma from the unit. Plasma may be reduced from RBCs to obtain a concentrated product (hematocrit >90%), which can be used for patients who require tight regulation of volume, such as neonates or patients with congenital cardiac defects. Incompatible plasma can be removed when ABO-incompatible platelets must be transfused. Other indications include reducing the risk of recurrent, moderate allergic transfusion reactions or circulatory overload.

Washed

Washing PRBCs or platelets is done by volume reduction and subsequent suspension of the cells in saline or albumin. There are very few indications for washing cellular blood products. Blood components transfused to patients with congenital absence of IgA should be washed prior to transfusion to avoid anaphylactic reactions triggered by donor IgA. Other indications include removal of residual plasma following recurrent, severe allergic or anaphylactic reactions, reducing potassium accumulated in blood units prior to large-volume transfusions (>25 ml/kg), removing plasma in the case of neonatal alloimmune thrombocytopenia, or removing additive solution prior to transfusion. Routine washing is not recommended because it can lead to loss of cells or functional impairment. When washing cannot be accomplished for potassium or additive solution removal, volume reduction may be an alternative choice. Use of PRBC products without additives (PRBC in CPD solution, *Table 328.2*) can also be used to avoid transfusion of large quantities of additives to small pediatric patients.

Satellite Packs

Sick neonates and small children may require repeated, small-volume units of red cell transfusions. To limit the exposure to different donors, transfer systems that remain closed to the environment can be used to divide a single blood donation into four to eight small aliquots. The aliquots from one donor can be designated for one neonate. By minimizing donor exposure, the risks of transfusion-transmitted infections and alloimmunization are minimized. Satellite packs waste less blood and are proven to be cost-effective. Because these units are given in small doses, the risk of hyperkalemia or other adverse effects of storage are minimal.

Complications

Infectious Complications

The three most clinically significant transfusion-transmitted infectious agents are human immunodeficiency virus (HIV), hepatitis B (HBV), and hepatitis C (HCV). Though the risk of HIV, HBV, or HCV viral transmission via transfusion is low in the United States, such is not the case worldwide, *Table 328.5*. Additionally, many other known or potential pathogens are transmissible by blood, *Table 328.6*. Certain opportunistic infections, such as human parvovirus B19, cytomegalovirus (CMV), and other herpesviruses, may cause serious disease in immunocompromised transfusion recipients. Fortunately, advances in virology, donor screening techniques, and viral detection assays have resulted in a worldwide decrease in the incidences of these and other transfusion-transmitted infections in the last decades. However, vigilance must continue in order to ensure that the blood supply remains free of known and emerging infectious agents.

Non-infectious Complications

Non-infectious complications of transfusion are equally as important as infectious complications and far more common. *Table 328.7* briefly describes the majority of clinically-significant transfusion reactions.

Table 328.6
Categories of transfusion-transmitted infectious agents by AABB

Agents for which donors are routinely screened
Hepatitis B virus
Human immunodeficiency virus
Hepatitis C virus
Human T-cell lymphotropic virus
West Nile virus
Bacteria
Trypanosoma cruzi (Chagas disease)
Cytomegalovirus
Agents with scientific evidence of risk and potential for severe clinical outcome, but not currently screened
Human variant Creutzfeldt-Jakob disease
Dengue viruses
Babesia species
Agents with sufficient scientific evidence of risk that might support elevation to a higher priority in future
Chikungunya virus
St. Louis encephalitis virus
Leishmania species
Plasmodium species
Agents with absent or low scientific evidence of risk but public and/or regulatory concern present
Chronic wasting disease prion
Human herpesvirus 8
HIV variants
Human parvovirus B19
Influenza A virus, subtype H5N1
Simian foamy virus
Borrelia burgdorferi (Lyme disease)
Hepatitis A virus
Agents to monitor but do not currently represent risk or concern
Hepatitis E virus
Anaplasma phagocytophilum (Human granuloyctyic anaplasmosis)
Others – AABB monitoring 51 other low risk prion, viral, rickettsial, and protozoan agents
Agents currently with unclear scientific evidence of risk
Xenotropic Murine Leukemia Virus-Related Virus (XMRV)

Human error in drawing, labeling, and administration of blood is the leading cause of ABO-incompatible hemolytic transfusion reactions, underscoring the importance of maintaining strict and clear procedures during all phases of transfusion. When a transfusion reaction is suspected, the transfusion should be stopped and supportive care instated immediately. The unit label and patient identification should be re-checked to detect possible errors in patient identification. The unit of blood should be sent to the blood bank along with a post-transfusion blood sample from the patient. The blood bank will conduct testing to identify potential causative factors, such as clerical errors, hemolysis, or bacterial contamination.

Transfusion-related acute lung injury (TRALI) is a rapid onset of non-cardiogenic pulmonary edema within 6 h of transfusion and is the leading cause of death from transfusion in the United States. There are three proposed mechanisms for TRALI: (a) donor-derived anti-granulocyte or (b) anti-HLA antibodies, and (c) biologic response modifiers such as cellular membrane fragments of donor cells that stimulate an inflammatory response in the recipient's pulmonary vasculature. These etiologies lead to hypoxic respiratory failure that is not responsive to diuretics. Supportive care is only required for the recipient. TRALI investigations are intended to help the blood center manage their donor pool since a donor with granulocyte or HLA antibodies, most of which are multiparous women, should be deferred from further donations of high plasma-volume components. To this end, the United Kingdom implemented a policy in 2003 to minimize the donations of FFP and platelets from females. This strategy has yielded a significant decrease in the rate of reported cases of probable TRALI.

Some adverse effects are more commonly associated with the pediatric population. Rapid infusion may cause fluid shifts in the intravascular compartment and can cause significant metabolic derangements. As RBCs age during storage, potassium levels increase in the supernatant. Large-volume transfusions of older red cell units to small children can result in hyperkalemic cardiac arrest and death. Hyperkalemia can be avoided by using fresher units, washing the cells, reducing the plasma volume before transfusion, or transfusing red cells slowly. Because blood products contain citrate, a calcium-binding anticoagulant, hypocalcemia may result from rapid infusion of blood products. In order to avoid hypothermia during large volume transfusions, blood can be passed through a blood warmer. Red cell additive solutions contain adenine, which carry a low risk of renal or liver insult when infused at high doses; plasma reduction or washing may decrease the risk. Hyperosmolality, hyperglycemia, hypernatremia, and hyperphosphatemia are theoretical concerns in children based on calculations of these constituents in storage media.

Table 328.7

Non-infectious transfusion reactions

Adverse effect	Etiology	Symptoms	Treatment or prophylaxis
Acute (<24 h) transfusion reactions, immunologic			
Acute hemolytic transfusion reaction	Immune destruction of transfused RBCs by a naturally occurring ABO-antibody or an alloantibody produced following immunization from a previous transfusion or pregnancy	Chills, fever, hemoglobinuria, renal failure, DIC, back pain, pain along infusion catheter, anxiety, shock. Gross hemoglobinemia in vitro	Supportive treatment
Febrile, non-hemolytic transfusion reaction	Accumulated cytokines or antibody to donor white cells	Fever, chills/rigors, headache, vomiting, exacerbation of cardiovascular or respiratory distress	Leukocyte reduction, premedication with acetaminophen
Urticarial transfusion reaction	Antibody to donor plasma proteins	Urticaria, pruritis, flushing	Antihistamine. May restart transfusion if symptoms resolve
Anaphylactic transfusion reaction	Antibody to donor plasma proteins, cytokines	Hypotension, urticaria, bronchospasm, angioedema, anxiety	Fluids, epinephrine, antihistamine, corticosteroids, beta-2-agonists, IgA deficient components
Transfusion Related Acute Lung Injury (TRALI)	Donor-derived antibodies to granulocytes or HLA antigens; or other WBC-activating agent	Hypoxemia, respiratory failure, hypotension, fever, bilateral pulmonary edema	Supportive care until recovery, defer implicated donor(s) if implicated antibody detected
Acute (<24 h) transfusion reactions, non-immunologic			
Sepsis	Bacterial contamination	Fever, chills, hypotension, shock	Supportive care, empiric broad spectrum antibiotics until sensitivity testing completed
Circulatory Overload	Volume overload due to transfused blood products	Dyspnea, orthopnea, cough, tachycardia, hypertension, headache	Upright posture, oxygen, IV diuretics, rarely phlebotomy
Non-immune hemolysis	Physical or chemical destruction of blood (heating, freezing, hemolytic drug or solution)	Hemoglobinuria, hemoglobinemia, jaundice	Identify and eliminate underlying cause
Air embolus	Infusion of air bubble	Sudden dyspnea, acute cyanosis, pain, cough, hypotension, arrhythemia	Place patient on left side with legs elevated above chest and head
Hypocalcemia	Rapid citrate infusion (massive transfusion)	Parasthesia, arrhythmia, tetany	Oral calcium for mild symptoms, slow IV calcium with close monitoring for more severe reactions
Hypothermia	Rapid infusion of cold or room temperature blood	Arrhythmia	Warm patient and use a blood warmer
Hyperkalemia	Leak of potassium into supernatant plasma from RBCs as they age. Pediatric and renal failure patients most at risk	Arrhythmia	Transfuse slowly. Transfuse fresh, washed, or volume reduced units to at-risk patients. Treat same as hyperkalemia from other causes (ie: IV calcium, insulin/glucose)

Table 328.7 (Continued)

Adverse effect	Etiology	Symptoms	Treatment or prophylaxis
Delayed (>24 h) transfusion reactions, immunologic			
Alloimmunization, HLA antigens	Exposure to foreign HLA antigens on WBC or platelet through prior transfusions or pregnancies	Platelet transfusion refractoriness	Avoid unnecessary blood, leukoreduction, transfuse HLA-matched or crossmatched platelet products
Delayed hemolytic transfusion reaction	Anamnestic immune response to RBC antigen; alloantibody titer increases after re-stimulation	Positive antibody screen in vitro following exposure to red cell transfusion, fever, hemolysis, jaundice in vivo 7–14 days after transfusion	Identify antibody, transfuse antigen negative, crossmatch compatible RBCs as needed
Transfusion-assocaiated graft-vs-host disease	Donor lymphocytes engraft in recipient and mount attack on tissues (see section on irradiation of blood components)	Fever, erythroderma, maculopapular rash, anorexia, nausea, vomiting, diarrhea, hepatitis, pancytopenia	Prevent with irradiation of blood components for at-risk patients. Stem cell transplant, corticosteroids, cytotoxic agents
Posttransfusion purpura (PTP)	Recipient-derived antibodies to human platelet antigens (HPA system) destroy donor *and* autologous platelets after re-exposure to platelet fragments (usually through a red cell transfusion)	Thrombocytopia and severe bleeding typically 8–10 days following RBC transfusion	IVIG, plasmapheresis, corticosteroids, antigen-negative platelets preferred
Delayed (>24 h) transfusion reactions, non-immunologic			
Iron overload	Storage of iron in organs and tissues in chronically transfused patients	Diabetes, cirrhosis, cardiomyopathy	Avoid unnecessary transfusions, phlebotomy if possible, iron chelation

Special Considerations

Massive Transfusion

The use of blood products has decreased mortality in hemorrhaging patients. A massive transfusion is defined as replacement of a patient's entire blood volume in 24 h, transfusion of more than ten PRBC units in adults, or replacement of more than 50% of the circulating blood volume within 3 h. In children <1 year, one adult-sized red cell unit can constitute massive transfusion. PRBCs are transfused rapidly to maintain adequate blood pressure and oxygen carrying capacity. For females of childbearing potential, group O, RhD-negative products should be used to protect against sensitization to RhD in cases of emergency, which could later cause HDFN. In the case of life threatening bleeding, however, group O PRBCs of any RhD type are acceptable, and may actually be preferentially used for male patients if medical center policy allows. A blood sample must be drawn early during resuscitation so that the sample reflects the patient's blood type prior to replacement with donated blood products. This is essential if the bleeding patient is to be switched to ABO-type specific products to preserve the inventory of universal donor products (group O RBC and group AB plasma products) in the blood bank.

Many institutions have a massive transfusion protocol that mandates a set ratio of the number of plasma and platelet components transfused per number of PRBC units transfused. This ratio is used to treat active hemorrhage and prevent dilutional coagulopathy. Alternatively, ABO/RhD-specific whole blood can be used if available. Due to a lack of controlled trials, no specific recommendation has been set for the ratio of PRBCs to platelets and plasma, so medical centers must create their own. All patients undergoing massive transfusion should have hematocrit, platelet count, prothrombin time, and fibrinogen checked regularly to assess coagulation status and to guide component therapy. Children undergoing massive transfusion should have electrolytes monitored as they are at higher risk of metabolic derangements including hyperkalemia, hypoglycemia, hypothermia, hypocalcemia, and fluid

overload. Because hypothermia and acidosis can inactivate clotting factors, it is imperative that these be tightly regulated to control bleeding effectively.

Exchange Transfusion

The more common indications for red cell or whole blood exchange transfusion include HDFN with kernicterus, sickle cell crisis, malaria, and hyperleukoctyosis seen in acute leukemia. Exchange transfusions can be accomplished by manual or automated techniques. Warmed, fresh, whole blood or PRBCs reconstituted with compatible plasma should be used to avoid the risks that accompany massive transfusion in whole blood exchange. The reported rate of mortality is 0–3.6% and adverse effects occur in 4–15.3% of patients. Complications includes sepsis, bradycardia, thrombocytopenia, apnea, cyanosis, hypocalcemia, hypoglycemia, and central catheter-related thrombi. Two times the blood volume is usually exchanged, *Table 328.8*. For the treatment of HDFN, this will replace about 75–90% of the recipient's RBCs, and remove 50% of the bilirubin and 75–90% of the causative antibody.

Chronic Transfusions

Some patients require RBC transfusions on a regular basis. The goal of chronic transfusions for patients with hemoglobinopathies (thalassemia or sickle cell disease) is to increase oxygen-carrying capacity, replace the defective red cells with normal RBCs, and to suppress erythropoiesis. Patients with a pure quantitative defect, such as Diamond Blackfan anemia, require transfusions to correct a qualitative defect while patients with myelodyplastic syndrome may have both quantitative and qualitative RBC defects. These patients may require lifelong transfusions if unable to obtain more definitive treatment. The most significant consequence of chronic transfusion is the deposition of iron into organs such as the liver and heart, which can lead to end-organ dysfunction. The effects of iron overload can be ameliorated by conducting exchange transfusion instead of simple transfusions or by starting iron chelation therapy. Neither of these options is without adverse effects, thus the risks and benefits must be heavily considered. Those receiving chronic transfusions also have a higher risk of alloimmunization and of contracting transfusion-transmitted infections based on the number of donors they are exposed to throughout life.

Table 328.8
Estimated blood volume

Age group	Approximate blood volume
Preterm neonate	100 ml/kg
Term neonate	85 ml/kg
>1 month	75 ml/kg

Extracoporeal Circuits Requiring Blood Products

Extracoporeal membrane oxygenation (ECMO), cardiopulmonary bypass (CPB), and automated apheresis are medical therapeutics that require significant blood bank participation. All of these treatment modalities use a circuit with an inline pump which draws blood out, processes it, and infuses it back into the patient. The modalities differ in clinical utility and methodology, as discussed below.

ECMO and CPB both provide artificial oxygenation and cardiac output. CPB is used by pediatric anesthesia during cardiac surgery in order to circulate blood while providing a bloodless, asystolic heart. ECMO is reserved for patients with potentially reversible respiratory and/or cardiac failure who have failed more conventional, less invasive techniques. Automated apheresis is a technique used to separate a cellular component or antibody from the blood and remove it. Apheresis can be used to remove blood cells (cytapheresis) in the case of polycythemia, thrombocythemia, sickle cell disease, or leukocytosis. Plasma can be removed via plasmapheresis and replaced with donor plasma and/or albumin. This is typically used to deplete a pathological IgG immunoglobulin in immune-mediated or malignant disease.

Although these techniques can potentially save lives and improve health, they are invasive, complex procedures that require hospital resources and carry risks. A variety of commercial instruments are available for each technique but each require specialized personnel to operate. Donor blood is usually necessary to prime the circuit in each scenario for small children. An anticoagulant, typically heparin or citrate, is added to the circuit to minimize the risk of a clot forming in the circuit tubing during operation. This can increase the risk of bleeding and/or hypocalcemia in patients. Any of these extracorporeal techniques can cause significant shifts of fluid. In addition, these techniques subsume all the infectious, immunological, and thrombotic risks due to the necessity of an indwelling central line and exposure to multiple blood donors.

Summary

Transfusions of blood and blood products have significantly reduced morbidity and mortality in children worldwide. A readily-available, safe supply of blood is now available to more physicians around the world, although significant disparities in testing and capabilities still exist between regions. Despite the advances, the potential complications of blood transfusion can be significant. The benefits and risks of the transfusion to individual patients must also be weighed against the conservation of the precious community resource. Efficacy and safety will continue to improve as the knowledge of pediatric transfusions increases.

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329 Care of the Child Refusing Blood Products

Lynn Boshkov

Background: Jehovah's Witnesses and Prohibitions on Transfusion of Blood

The Watch Tower Bible and Tract Society web site (http://www.watchtower.org/e/statistics/worldwide_report.htm accessed January 29, 2011) indicates that in 2009, there were over 7.3 million Jehovah's Witnesses in 236 countries worldwide. The greatest number of these (over 1.1 million) live in the USA, with numbers in excess of 100,000 being found in other countries in North America (Canada, Mexico), South America (Argentina, Brazil, Columbia, Peru), Eurasia (France, Germany, Great Britain, Poland, Russia, Spain), the Far East (Japan, Philippines), and Africa (Congo, Nigeria, Zambia). Thus, it is likely that the medical practitioner treating children almost anywhere in the world will come into contact with a Jehovah's Witness family.

Jehovah's Witnesses believe that the Bible prohibits ingesting blood and do not accept transfusion of whole blood or any of its four primary components – red cells, platelets, plasma, or white cells. This prohibition applies even in clinical contexts where such refusal may result in serious harm or death. The transfusion prohibition also extends to predonation and storage of a patient's own blood for later transfusion back to the patient. However, it is worth noting that Jehovah's Witnesses are not one of the religious groups who shun medical care generally, and that acceptability of sophisticated medical interventions where their own blood is kept in contact with the body (cardiopulmonary bypass, dialysis), as well as receipt of organ transplants, are considered "matters of conscience" to be decided by each individual Witness. Other "matters of conscience" to Witnesses are intraoperative blood salvage where the blood is kept in contact with the body ("Cell Saver" type devices, perioperative hemodilution) and a range of "minor fractions" of blood (discussed in greater detail below). While most countries legally permit refusal of medical interventions by adults, the desire of Jehovah's Witness parents and guardians to extend refusal of blood therapy to their minor children often results in legal and ethical tensions between the family and health-care providers treating the child, as those providers are most often both legally obligated to provide medical intervention that will save life or prevent serious harm, and also obligated to do so by personal ethical imperatives. This tension may be particularly acute in the case of patients who are "mature minors," and who are themselves also refusing blood.

Faced with such a conflict, what is the best way to proceed? Several general guiding precepts may be helpful:

1. Work in partnership with the patient and family and Jehovah's Witness community; act as the patient's and the family's advocate.
2. Know and explore the acceptability of the full range of "matters of conscience" minor fractions and non-blood therapeutic options with the patient and family and use them prior to resorting to unacceptable interventions.
3. Act preemptively if possible to prevent anemia and coagulopathy and use combined interventions to treat these.
4. Realize physiological tolerance of anemia is generally greater than one might think.
5. Make the family aware of the legal obligation to transfuse a minor to prevent serious harm or death.

If the treating physician truly adheres to these guiding precepts, even though the child ends up receiving a blood product, tensions are minimized to the extent this is possible and the therapeutic relationship is served. Elaborating on these guiding precepts:

Work in partnership with the patient and family and Jehovah's Witness community; act as the patient's and the family's advocate.

In difficult cases, it is especially useful to have access to other physicians who have managed Jehovah's Witness cases (hospitals with Bloodless Medicine and Surgery programs are good places to start), and, if possible, to work in partnership with a local Jehovah's Witness Hospital Liaison Committee Elder. The Hospital Information Services (HIS) branch of the Watch Tower Society, headquartered in Brooklyn, New York, has as its mandate provision of education and facilitation of bloodless medicine and

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surgery. HIS has a web site (http://www.watchtower.org/e/vcnr/article_01.htm, accessed January, 2011) with videos showing transfusion alternatives; it also has a contact phone number for physicians listed on that web site: 1-718-560-4300. When HIS was contacted by this writer regarding a contact number for physicians using this chapter they also suggested their e-mail address: his@jw.org.

HIS services also include Hospital Liaison Committees (HLCs) with specially trained Jehovah's Witness HLC Elders whose function is to support the patient and family and to work in cooperation with treating health-care professionals. There are 131 HLCs in the USA and 1,650 worldwide in over 200 countries. HLC Elders can be contacted through inquiries directed by the Witness family to leaders at their local centers of worship; HLC Elders can also be reached through contact with HIS. HLCs have access to a large database of medical literature on bloodless medicine and surgery and preprinted general information on management of the surgical patient, the critically ill patient, the ob/gyn patient, etc. HLC Elders will often bring such literature to the attention of the treating physician for his or her perusal regarding relevance to the case at hand. More importantly to the treating practitioner, HLC Elders also have access through HIS to a worldwide network of physicians who have extensive experience in treating Jehovah's Witness patients and who are often willing to provide timely telephone and electronic (pertinent papers, etc.) consultation to less-experienced health-care providers. Simply seeing interaction between their treating health-care providers and HLC Elders is often tremendously reassuring to families, and these Elders can also help with support of the family and the child if transfusion is ultimately necessary. Health-care providers are frequently fearful that the transfused child will be ostracized by the Jehovah's Witness community. In this writer's extensive Canadian and US experience, this has not been the case.

Know and explore the acceptability of the full range of "matters of conscience" minor fractions and non-blood therapeutic options with the patient and family and use them prior to resorting to unacceptable blood options, time permitting.

In the Developing World, the only blood product available may be whole blood, and this is unacceptable to Witnesses. Also unacceptable are the four primary components of whole blood (red cells, platelets, plasma, white cells) which are usually prepared by simple centrifugation of whole blood or some modification of this. However, once primary components of whole blood are further subseparated into their constituent parts, receipt of the resulting "fraction" is considered a "matter of conscience." For example, from a 500 ml whole blood donation, a 250–300 ml unit of plasma may be separated. Neither the whole blood nor the plasma is acceptable to Witnesses. However, if that unit of plasma is chilled, and the flocculent white precipitate is centrifuged out to prepare a unit of cryoprecipitate (usually about 10–15 ml), that cryoprecipitate "fraction" is considered to be a matter of conscience – as is the fibrin glue that can be further prepared from a pool of cryoprecipitate activated with bovine thrombin.

The use of cryoprecipitate, if acceptable, can be helpful in avoiding transfusion of unacceptable blood components. As a unit of cryoprecipitate contains, in very concentrated form, about half the Von Willebrand Factor (important in platelet adhesion), half the Factor VIII, and half the fibrinogen in the original unit of plasma, cryoprecipitate given at ~1 unit/5–10 kg can often help improve platelet function and provide at least some crucial coagulation factors necessary for hemostasis.

Large plasma pools (~2,000–20,000 donors) may also be fractionated into a variety of plasma derivatives such as albumin, plasma-derived clotting proteins (FVIII, FIX, fibrinogen, antithrombin, and others), intravenous immune globulins, Rh immune globulin, and many others. Such plasma derivatives may also be used to make local fibrin glue or topical thrombin hemostatic agents. Such plasma "fractions" are all considered to be "matters of conscience" to individual Witnesses and all may be useful in avoiding transfusion of unacceptable primary components in selected situations.

It is worth noting that many adult Witnesses in the USA and elsewhere carry "Advance Directives." These are concise statements of the individual's wishes regarding medical interventions and end-of-life care and include a section dealing with blood and blood fractions. Usually, if one blood fraction is acceptable, all are. However, it is often helpful for the practitioner to be able to explain where the fractions come from in relation to whole blood, as many Advance Directives state the patient might be willing to accept fractions but needs to know more about them.

In explaining fractions to Jehovah's Witness, several things may be helpful. First, the practitioner should make it explicit that the "fraction" discussion is being motivated not by a desire to coerce, but rather to use the full armamentarium of products and interventions available and acceptable to the patient to improve medical outcome and to prevent administration of unacceptable products and interventions. Second, it may be helpful to emphasize plasma's general role as a sort of "carrier river," not only for cellular blood elements made in the bone marrow

(red cells, white cells, and platelets), but also for blood sugar, hormones, waste products, liver and kidney function enzymes, and for clotting proteins made in the liver and linings of the blood vessels (such as Von Willebrand Factor, fibrinogen, and other clotting factors), and for albumin (a protein made in the liver which helps blood stay in vessels and stabilizes many hormones). Third, that use of fractions can truly spare use of unacceptable products at times and even be lifesaving – for example, although neither platelets nor plasma is acceptable to Witnesses, cryoprecipitate can help platelets work better, fibrin glue and topical thrombin hemostatic agents can help make local clots when used during surgery or invasive procedures, and albumin can help blood stay in the vessels. Fourth, it may be helpful to note that while cellular blood elements do not normally traffic across the placenta, the other fractions do. (This was a personal observation made to this writer by a HLC Elder when queried regarding his own "matters of conscience" beliefs, and used with his permission subsequently in explaining fractions to other Jehovah's Witness patients). Lastly, it is also worth noting that HLC Elders can often assist in explaining fractions and transfusion-sparing interventions where the blood is kept in contact with the body (Cell Saver, perioperative hemodilution) to patients and families. They can also help provide the patient and family with information – written, videos – explaining these.

As the whole issue of acceptability of different fractions and interventions can vary greatly according to the individual conscience of a particular Witness family, it can be useful for hospitals and transfusing institutions to have a special "Blood Refusal" Form which concisely summarizes these. As a model, the Oregon Health & Science University "Transfusion Blood Refusal" form is shown in *Fig. 329.1.*

Interestingly, hemoglobin-based oxygen carriers (HBOCs), derived from human or animal red cells, are also considered "fractions" and "matters of conscience" by Witnesses. Only one HBOC (Hemopure by Biopure) was ever licensed worldwide and then only in South Africa, although several have been available on a "Compassionate Release" basis in the past, with the Compassionate Release Programs being made available by the companies and overseen by national regulatory agencies such as the US FDA. Compassionate Release Programs exclude minors, however, and, as of this writing (January 2011), to this writer's knowledge, no Compassionate Release Programs currently exist anywhere worldwide. Also, to this writer's knowledge, manufacture of essentially all HBOCs has currently been terminated or suspended due to unfavorable phase 3 trial outcomes and such products were no longer available anywhere worldwide as of January 2011, apart from residual stores in South Africa.

As mentioned, other "matters of conscience" to Witnesses are intraoperative blood salvage where the blood is kept in contact with the body ("Cell Saver"–type devices, perioperative hemodilution). These interventions are generally not suitable for small children. The "Cell Saver" is most useful in large volume "clean" losses (no infection or malignancy present) such as vascular surgery. Perioperative hemodilution is generally most useful in patients with high starting hematocrits and large volume losses, and may be used in malignancy cases.

Act preemptively if possible to prevent anemia and coagulopathy and use combined interventions to treat these.

Routine supplementation of Witness patients with hematinics, especially in the context of hospitalization and perisurgically is often advisable. This should include consideration of full marrow repletion doses of iron preferably given IV, as oral iron may be poorly tolerated and often cannot be given quickly enough in large enough doses. The iron sucrose preparations and other iron preparations associated with very low reaction rates are recommended. It should be noted that in sick patients, iron studies and ferritin are unreliable and that normal ferritins do not rule out absent bone marrow iron stores. Daily folate either PO or IV should also be given. Vitamin K supplementation PO or IV twice weekly is also often helpful.

The issue of use of erythroid-stimulating agents (ESAs) such as erythropoietin (epo) and darbepoietin (darbe) should be considered. There is more experience with the use of epo in pediatric patients and it alone may be approved for pediatric use. Although neither epo nor darbe is derived from blood, epo is stabilized with traces of albumin and may therefore be unacceptable to certain Witnesses, whereas darbe is albumin free. Iron repletion is essential for ESAs to act most effectively and should be assured prior to ESA administration. ESAs are most effective given preoperatively as there is antagonism to the effect of ESAs mediated by inflammatory cytokines postoperatively and in the context of intercurrent illness. To obtain a reticulocyte rise with ESAs usually takes 3–4 days (rises of five- to tenfold above baseline are usual), and to obtain a meaningful increase in the hemoglobin (>1 g/dl) usually takes 10–14 days. To significantly augment the hemoglobin (Hb) preoperatively with an ESA can therefore take 3–4 weeks. Weekly doses of epo at 300–500 U/kg (or equivalent doses of darbe) are recommended for this purpose, preferably given SQ rather than IV. In the postoperative setting, and in the setting of illness, there is usually inflammatory cytokine-mediated (IL-1, TNF, and

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TRANSFUSION BLOOD REFUSAL

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ACCOUNT NO.
MED. REC. NO.
NAME
BIRTHDATE

Patient Identification

Please check one: ( ) I myself or
( ) My minor child (aged_____) or
( ) The person I am signing this Refusal for because: _____

_____

am one of **Jehovah's Witnesses** and refuse transfusion of whole blood or any of its primary components (red cells, white cells, platelets or plasma). Jehovah's Witnesses consider a number of fractions of primary components to be matters of conscience. Other matters of conscience are erythropoietin and intra-operative blood salvage. I am indicating below whether any of these blood fractions or blood alternatives are acceptable to me (or person I am signing for).

Blood Fraction or Transfusion Alternative	Acceptable	Unacceptable
Erythropoietin (EPO) (stabilized with traces of albumin)	( )	( )
Intra-operative blood salvage where the blood is kept in contact with my body ("Cell-Saver," perioperative hemodilution)	( )	( )
Cryoprecipitate	( )	( )
Fibrin Glue	( )	( )
Plasma derived clotting factor concentrates	( )	( )
Albumin	( )	( )
Rh immune globulin, intravenous gamma globulin and other gamma globulin preparations	( )	( )
Topical Thrombin Hemostatic Agents	( )	( )

( ) I am not a Jehovah's Witness but refuse the following blood products:

_____

The risk attendant to my refusal has been explained to me, and I understand that my refusal may in some cases seriously reduce my chances of regaining normal health or even threaten my life. I further understand that every effort will be made to deliver highest quality medical care using all available means despite my refusal; also that I am free to modify this refusal at any time. I release the Hospital, its personnel and other persons participating in my care from any responsibility for respecting and following my express wishes and directions.

Refusal of Blood transfusion for a minor. As the parent/guardian of a minor child I understand that the doctor(s) treating my child will make every effort to respect my beliefs regarding the transfusion of blood products as indicated above. However I also recognize that my child's physicians have a legal obligation not to withhold therapy the think is necessary to keep my child alive or to keep him/her from serious harm or permanent injury or disability. I understand therefore that, if the treating physician believes transfusion, after evaluating alternative non-blood medical management, is necessary to save my child's life, or to prevent serious irreversible harm, my child may be transfused, although every effort will be made to avoid this.

_____ _____

Patient's Parent's Guardian's Consenter's (circle one) Signature **Date and time**

If Consenter specify relationship to patient: _____

_____ _____

Signature of Witness to this Refusal **Date and time**

The staff physician should notify the Multnomah County Juvenile Court at (503) 988-3460 (M-F, 8am – 5pm) and ask to speak to someone in the Intake Department regarding an emergency medical court order, after 5pm and on weekends call (503) 988-3489 or (503) 988-3475 and ask to speak to someone in the Custody Intake Department regarding an emergency medical court order.

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Figure 329.1

others) resistance to the action of epo. This can often be at least partially overcome by pharmacological doses of epo (300–500 U/kg SQ daily).

ESA use in adults with critical illness and with malignancy is associated with increased thrombogenicity (blood clots, heart failure, myocardial infarction, stroke). It is unclear if this is also the case in pediatrics. In older children requiring sustained high dose epo therapy, consideration should be given to prophylactic doses of antithrombotics. In the case of cancer in adult populations, use of ESAs is also associated with increases in mortality independent of thrombogenicity and possibly mediated by tumor receptors for ESAs and promotion of angiogenesis. The US Food and Drug Administration (FDA) issued a block box warning for ESAs in 2007 prompting a series of revised clinical guidelines and, as of 2010, the FDA is requiring that all ESAs given to patients with malignancy be prescribed under a Risk Evaluation and Mitigation Strategy (REMS) which includes a medication guide to explain risks to patients and caregivers, and the ESA APPRISE (Assisting Providers and cancer Patients with Risk Information for the Safe use of ESAs) Oncology Program (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200297.htm, accessed January 29, 2011). Thus, in pediatric patients with cancer, careful weighing of the risk benefit of ESA administration needs to be done.

Regarding management of thrombocytopenia or thrombocytopathy in Witnesses refusing platelet transfusion, cryoprecipitate, if acceptable, at 1 U/5–10 kg is often effective in the treatment of petechaie and minor platelet-type bleeding in patients, and this dose may be administered prophylactically daily if the platelet count is under 10×10^{-9}/l. Adult anecdotal and published experience, and anecdotal pediatric experience, suggests administration of either aminocaproic acid or tranexamic acid may also be helpful in preventing and treating bleeding if the platelet count is $<10^{-30} \times 10^{-9}$/l. Tranexamic acid if available is a more potent antifibrinolytic agent than aminocaproic acid. Consideration may also be given to the use of thrombopoietin (tpo) mimetics if available (romiplostim, eltrombopag).

It should be noted that Witnesses have no issues with the use of a variety of non-blood-derived and non-albumin-stabilized pharmacological hemostatic agents such as ddAVP, antifibrinolytics, and recombinant factor VIIa. As well, as discussed in the section on fractions above, fibrin glues and topical thrombin-based hemostatic agents may be acceptable and transfusion-sparing in the setting of surgery or invasive procedures.

Realize physiological tolerance of anemia is generally greater than one might think.

Tolerance of anemia is determined by multiple factors including chronicity of development, underlying cardiovascular status, age, and oxygen demands. Animal studies suggest the lower limit of tolerance to sustained anemia in animals with a normal cardiovascular system is a Hb of around 3–5 g/dl and in those animals with coronary stenosis is a Hb around 7–10 g/dl. The largest published series of morbidity and mortality in the perioperative setting in adult patients refusing blood transfusion suggests that survival with a Hb < 2 g/dl is very infrequent and that both morbidity and mortality rise substantially when the Hb falls to less than 5–6 g/dl. That said, the Transfusion in Critical Care (TRICC) trial indicates that in adult ICU patients, there is at least an equivalent outcome in patients randomized to a restrictive (target Hb 7–9 g/dl) rather than liberal (target Hb 10–12 g/dl) transfusion strategy. This has recently also been confirmed in the pediatric critical care setting. Thus, as a general rule, concerns regarding adverse effects of anemia should probably begin to rise only when the Hb falls below 7 g/dl, and the decision to intervene subsequently needs to be tempered by the anticipated chronicity of further fall in the Hb, the underlying cardiovascular status of the patient, and the anticipated oxygen demands the patient will face (sepsis, surgery, etc.). In children, it is probably unwise to wait to transfuse until frank florid physiological decompensation as children appear to manifest signs and symptoms of impending decompensation later than adults.

Make the family aware of the legal obligation to transfuse a minor to prevent serious harm or death.

Witnesses generally abide by the law despite strong objection at times to its dictates (transfusion of minor children). In the USA, in the case of impending serious irreversible harm or death, traditionally "court orders" have been obtained mandating transfusion of minor children whose Jehovah's Witness parents or guardians have refused to sign permission for blood transfusion. Court orders are often traumatic to Witness families not only because of the transfusion itself, but because court orders are usually subsets of child abuse laws, and when a court order is obtained the child is made a ward of the court, and a court-appointed representative thereafter legally signs permission for surgeries, dialysis, etc. If a court order is obtained therefore it is advisable to ask that it be limited only to blood. At the author's institution, Oregon Health & Science University (OHSU), the Transfusion Blood Refusal Form (*Fig. 329.1.*) tries to avoid court orders by incorporating specific language indicating that the parent or guardian, while not giving permission for the transfusion, nonetheless recognizes the legal obligation of

the treating physician to transfuse to save life or prevent irreversible harm. If the parent or guardian signs this form, it is the opinion of both OHSU Legal and Risk Management that a court order is not necessary, and very few have been obtained subsequent to this form's adoption.

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330 Disorders of Heme Biosynthesis

Thomas G. DeLoughery

Porphyria

The porphyrias are a group of rare diseases of heme metabolism (*Table 330.1*). They have a protean array of symptoms and can represent a diagnostic challenge. Although rare, diagnosis is important as a mainstay of therapy for most porphyria is avoidance of precipitating factors.

Symptoms

One fundamental principle is that the pathogenesis of symptoms of porphyria is due to accumulations of the metabolites of heme synthesis (*Fig. 330.1*). These metabolites can be neurotoxic (ALA, PGB), acutely toxic to the skin (protoporphyrins), or chronically toxic to the skin (uropophyrinogen and coproporphyrinogen) (*Table 330.2*). Thus, there are three basic ways porphyria can present:

1. Neurovisceral – The neurovisceral symptoms consist of autonomic neuropathies (constipation, colicky abdominal pain, vomiting, hypertension), peripheral neuropathy (most often motor), seizures, delirium, coma, and depression. The abdominal pain is severe and lasts for several days. Severe abdomen pain of short (less than one day) duration or chronic abdominal pain is unusual. The sequence of events in attacks is usually: first abdominal pain, then psychiatric symptoms such as hysteria, and then the peripheral neuropathies. Most patients are completely free of symptoms between attacks. Hyponatremia due to SIADH can be seen in severe cases. These symptoms can be seen with AIP, HCP, and VP.
2. Acute cutaneous – Symptoms occur quickly (minutes) of being exposed to the sun – redness, edema, and itching and is seen with EP, CEP, and HP.
3. Chronic cutaneous – The cutaneous manifestations are characterized by bullae formation in sun exposed areas, fragile skin, and hypertrichosis and is seen with PCT, HCP, VP, CEP, and HP.

Most porphyrias present at puberty or older. The exceptions are the rare ALA dehydratase porphyria, congenital erythropoietic porphyria, or hepateoerythropoietic porphyria which present soon after birth. Also, symptoms of EP can start in childhood.

Diagnosis

The diagnosis of any porphyria is based on both the clinical presentation and the demonstration of excessive porphyrin excretion in relation to these symptoms. The essential procedure in ascribing any neurovisceral symptoms to porphyria is to establish that there is an increase in porphyrin precursors at the time of these problems. These precursors are PorphoBilinoGen (PBG) and AminoLevulinic Acid (ALA). A common mistake in diagnosing porphyria is to observe just an elevated level of porphyrins (not precursors) in the urine or stool and label the patient as having porphyria. Neurovisceral attacks are only associated with over-excretion of PGB and ALA. This is most common in AIP, but can be seen in VP and HCP. Another difficulty in diagnosing porphyria is many patients have minor (less than 3–5 times) elevation of urine and/or stool porphyrins. This can be a normal variant or seen in fasting, iron deficiency, ingestion of meat, or any illness. The chronic cutaneous porphyrias – PCT, HCP, and VP – have classic dermatological manifestations. The key testing is urine and stool for the formed porphyrins such as uropophyrinogen. There is an entity known as "Pseudoporphyria" where patients have the skin manifestations of porphyria but urine and stools demonstrate normal porphyrin excretion. This can be seen as a complication of certain medications such as naproxen or in dialysis patients. The acute cutaneous porphyrias are diagnosed by finding increased erythrocyte porphyrins.

A very simple bedside assay for acute porphyrias is examination of a fresh urine sample. It is clear at first, but will darken with exposure to the sun. If available, the presence of PBG can be confirmed by adding Ehrlich's aldehyde reagent in a 1:1 ratio to the urine; the presence of a pink color confirms the presence of PBG. Definitive

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Table 330.1
The porphyria

	Presentation	Urine	Stool	RBC	Inheritance
Neurovisceral porphyria		PBG, ALA, porphyrins			
Acute intermittent porphyria (AIP)	Acute attacks				AD
Neurovisceral +/− cutaneous					
Coproporphyria (HCP)	Acute attacks, skin blisters	PBG, ALA, porphyrins	Copro		AD
Variegate porphyria (VP)	Acute attacks, skin blisters	PBG, ALA, porphyrins	Proto IX > Copro		AD
Cutaneous					
Porphyria cutanea tarda (PCT)	Skin blisters	Uro, Hepta	Isocopro, hepta		AD
Photosensitivity					
Erythropoietic protoporphyria (EP)	Acute photosensitivity	Normal	Proto IX	Free proto	AD
X-linked protoporphyria	Acute photosensitivity	Normal	Proto IX	Free and Zn proto	X-Linked
Recessive					
ALA dehydratase porphyria	Neuropathy	ALA, copro	Normal	Proto IX	AR
Congenital erythropoietic porphyria (CEP)	Severe photosensitivity	Uro, Copro	Copro	Uro, copro	AR
Hepateoerythropoietic porphyria (HP)	Severe photosensitivity	Uro, Hepta	Isocopro, hepta	Proto IX	AR

PBG porphobilinogen, *ALA* aminolevulic acid, *copro* coporphyrin, *uro* uroporphyrin, *isocopro* isocoproporphyrin, *proto* protoporphyrin, *AD* autosomal dominant, *AR* autosome recessive

diagnosis of the different porphyrias requires analysis of urine, stool, and blood samples for the specific porphyrins and their precursors. In theory, since most porphyrias are due to mutations in the genes encoding the enzymes for heme synthesis, DNA analysis or assays of enzymes active would be useful. But given the low penetrance of the porphyria, this testing is useful only in selected cases.

Acute (Neurovisceral) Porphyrias

Acute intermittent porphyria has onset in puberty with only neurovisceral symptoms. Many more patients have the genetic defect than express clinical disease. Most patients will only have one attack. Attacks are provoked by anything that leads to increase in the heme synthesis pathway. The classics are starvation (glucose suppresses heme synthesis) and a multitude of drugs. The classic drugs are estrogen, barbiturates, and ethanol. There are lists of "safe" and "unsafe," easily found on the Internet. http://www.drugs-porphyria.org and http://www.porphyriafoundation.com are the two most researched and complete websites.

Diagnosis is by a demonstrated increase – greater than tenfold – in urine porphobilinogen. Levels can remain raised for years after the attack. One can verify by checking the activity level of PBG deaminase, but this will be normal in 10% of patients as only the hepatic form is affected and not the form measured in the circulating red cells.

The therapy of the neurovisceral symptoms of AIP is based on shutting down the heme synthesis pathway to prevent accumulation of the toxic precursors. High doses of glucose (300 g/day) can mildly inhibit the pathway and is used for mild attacks. Hematin, which is intravenous preparation of heme, is used for severe attacks to stop the heme synthesis pathway. Either heme-arginine (250 mg × 5 days) or hematin (4 mg/kg × 4 days) can be used to suppress the heme synthetic pathway and is effective for severe acute attacks or attacks associated with neurological defects. These agents are well tolerated but can lead to

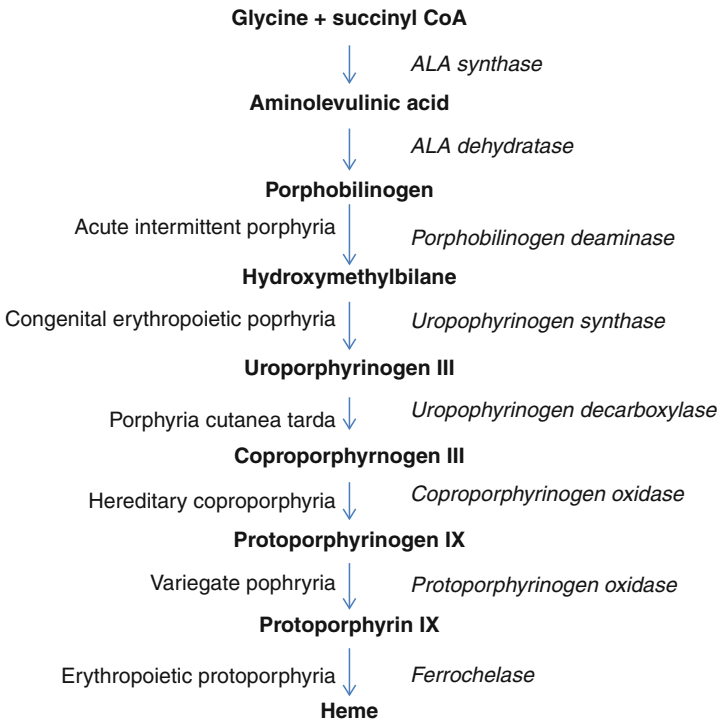

Figure 330.1
Heme synthesis

Table 330.2
The porphyrias: symptoms and therapy

	Therapy
Neurovisceral	Acute: increase glucose, hematin Chronic: avoid fasting and precipitating drugs
Acute intermittent porphyria (AIP)	
Coproporphyria (HCP)	
Variegate porphyria (VP)	
Cutaneous	Phlebotomized to reduce ferritin, avoid sun exposure, avoid precipitating medications
Porphyria cutanea tarda (PCT)	
Photosensitivity	Avoid sun exposure, beta-carotene
Erythropoietic protoporphyria (EP)	
X-linked protoporphyria	
Recessive	
ALA dehydratase porphyria	Hematin
Congenital erythropoietic porphyria (CEP)	Stem cell transplant
Hepateoerythropoietic porphyria (HP)	Avoid sun exposure

thrombophlebitis and often need to be given via central venous access. Rarely, there can be a severe sympathetic crisis manifesting with severe hypertension and seizures. Patients with repeated attacks can be treated with weekly heme infusions. In patients with severe intractable symptoms, liver transplantation can be considered. Prevention of future attacks is by avoiding precipitating factors such as fasting, medications, and alcohol.

Hereditary coproporphyria has both neurovisceral and skin manifestations (described under PCT). Patients are rarely symptomatic. Diagnosis is by demonstrating markedly increased urine and stool coproporphyrinogens. As noted above, mild elevations of coproporphyrinogens is common and not pathogenic. Treatment is the same as AIP.

Variegate porphyria has both neurovisceral and skin manifestations (described under PCT). Patients are sporadically symptomatic. Diagnosis is by demonstrating markedly increased urine and stool coproporphyrinogen and protoporphyrinogen. Treatment is the same as AIP.

Chronic Cutaneous (Blistering) Porphyrias

Porphyria cutanea tarda presents with skin disease in sun exposed areas. The first signs are fragile skin with, then, the formation of blisters and bulla that can take weeks to heal. This over time leads to chronic skin damage with increased pigmentation and hair growth. Given the relationship with sun exposure, the skin involved is on the upper hands, face, and neck. Most patients have an acquired inhibitor of uropophyrinogen decarboxylase, with only a minority (∼25%) having a mutation in the gene encoding for this enzyme; but even, patients with the mutation will only manifest symptoms with acquitted risk factors. The risk factors for PCT are liver damage – from alcohol – iron overload and hepatitis, estrogens, and HIV. Iron overload appears to be crucial given the relationship of the hemochromatosis genotype and iron overload with PCT.

Diagnosis is the combination of the classic skin findings and demonstration of excess urine uropophyrinogen and stool isocoproporphyrinogen. Therapy is by reduction of iron stores. Phlebotomy with a goal ferritin of under 50 mg/L is very effective. Patients must be cautious that their skin disease resolution can lag by months, as the porphyrin laden skin must be shed for symptoms to abate. Chloroquine (100–200 mg two times weekly) can also be effective especially in the rare patient who cannot be phlebotomized. Also helpful is avoidance of risk factors such as excess sun exposure, estrogen, or alcohol.

Acute Cutaneous (Photosensitive) Porphyrias

Erythropoietic protoporphyria has early onset of acute photosensitive. Patients noticed with sun exposure will have a burning, stinging sensation in their skin. This can be accompanied by swelling and redness. Cold water or compression can bring symptom-relief. Over time, there can be chronic skin damage with skin thickening, crusting, and waxy-changes. In ∼10% of patients, there can be liver disease due to accumulation of protoporphyrins that, over time, can lead to liver failure. Diagnosis is established by showing increased levels of stool and red cell protoporphyrins. The vast majority of patients have mutations in the ferrochelase gene, but about 2% have an X-linked mutation in the ALA synthase gene.

Therapy is by protecting the skin from sunlight. Clothing, large hats, and sun screen can be used. Beta-carotene (75–200 mg/day) can help symptoms in some patients. Patients need to be screened yearly for liver disease, for which liver transplantation may sometimes be required.

Neonatal Porphyrias

ALA dehydratase porphyria is extremely rare but can cause neurovisceral attacks in children. Diagnosis is made by demonstrating marked over-excretion of ALA in the urine. Therapy is with hematin, but some patients have had a progressive course despite therapy.

Congenital erythropoietic porphyria is marked by severe photosensitivity starting at an early age that can lead to mutilating changes and disfigurement with loss of appendages. Teeth can be pink to red due to accumulation of porphyrins. Patient can have bone disease leading to fractures. Many patients have a hemolytic anemia that can be severe with associated large spleen.

Diagnosis can be suggested by the clinical findings and red urine in the diapers. Diagnosis is established by finding excess isomer I of uropophyrinogen and coproporphyrin in urine, stool, and red cells.

Curative therapy is with stem cell transplantation. If this cannot be done, then supportive care can be tried with avoidance of sun exposure and splenectomy if hypersplenism is present.

Hepateoerythropoietic porphyria can lead to a severe PCT syndrome in childhood. The main differential diagnosis is CEP, but the skin disease tends to be more scarring than mutilating. The defect is a homozygous mutation in the uropophyrinogen decarboxylase gene and diagnosis is made by demonstrating excess urine uropophyrinogen and stool isocoproporphyrinogen. Therapy is supportive with avoiding sun exposure. Unlike PCT, reduction of iron stores and chloroquine are not effective.

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331 Platelet Structure, Function, and Disorders

Daniel Greenberg

Introduction

Platelets are anucleate cells that circulate in the bloodstream. They are essential for normal hemostasis, and patients with a very low concentration of circulating platelets or disorders that result in severe platelet dysfunction have serious bleeding disorders. They are also essential for normal clot retraction and wound healing. Conversely, platelet adhesions to vascular atherosclerotic lesions are a major cause of myocardial infarction and ischemic stroke. Over the past several years, numerous elegant experimental observations suggest platelets also play a key role in angiogenesis and in pathological processes such as infection and cancer metastasis.

Platelets are derived from bone marrow progenitor stem cells in a process known as thrombopoiesis. During this process, the pluripotent marrow stem cell first undergoes a transformation into a giant cell with a large cytoplasm and a polyploid nucleus, called a megakaryocyte. Platelets are created when the cytoplasm of the megakaryocyte divides into thousands of individual platelets that are released into the circulation through the bone marrow sinusoids (see *Fig. 331.1*). Accordingly, platelets can be thought of little packages of the megakaryocyte cytoplasm wrapped up in a specialized membrane. Thrombopoiesis is regulated, in large part, by the hepatic production of the cytokine thrombopoietin (TPO). TPO is homologous with erythropoietin (EPO); however, the TPO receptor (Mpl) is primarily expressed by stem cells and megakaryocytes in the bone marrow, whereas the EPO receptor is primarily expressed by erythroblasts and developing erythroid cells. Although TPO is not known to have a direct biological effect on mature platelets, TPO is cleared from the plasma by platelets through the process of receptor-induced endocytosis. The concentration of TPO in the plasma and its biological effect of inducing thrombopoiesis are largely regulated by the platelet count through this negative feedback pathway: Because of the clearance of TPO by platelets, a high platelet count has the effect of decreasing the concentration of biologically active TPO. Conversely, a low concentration of platelets results in an increased concentration of free TPO in the plasma. For almost all normal individuals, this feedback mechanism results in circulating a platelet concentration between 150,000 and 350,000/μl of whole blood.

During normal hemostasis, platelets are recruited to a site of vascular injury where they become activated to form a plug over the disrupted vessel(s). This process of platelet activation is mediated by complex array of membrane receptors and other integral membrane and cytoskeleton proteins which are essential for normal platelet activation and hemostasis. The receptors present on the platelet plasma membrane range from specialized adhesive receptors that recognize complex polymeric proteins such as fibrinogen, collagen, and Von Willebrand Factor to specific single molecule receptors (e.g., ADP, thrombin, and collagen) that mediate platelet activation through intracellular signal transduction pathways. *Figure 331.2* shows a schematic representation of platelets adhering to the sub-endothelium by VWF and aggregating in the presence of fibrinogen. The aggregated platelet plug provides a surface for the coagulation proteins to form fibrin (secondary phase of hemostasis).

Most clinical laboratory testing of platelet activation relies on the ability of platelets to aggregate in the presence of fibrinogen after the platelets are stimulated with a platelet agonist such as thrombin, collagen, or ADP. These agonists act on specific platelet receptors (see below) all of which end up causing the activation of the platelet fibrinogen receptor to recognize and bind fibrinogen. Fibrinogen is a large hetero-heximeric protein that forms bridges between activated platelets piled one on top of another to form a stable aggregate. In the commonly practiced platelet aggregation test, a solution containing the patient's platelets (either platelet rich plasma or whole blood) is treated with the appropriate agonists in the presence of fibrinogen. The solution is then analyzed to determine the extent to which the platelets have aggregated into clumps relative to a standard, positive control. Full activation of platelet function requires, but is not limited to, platelet aggregation. As discussed below, platelet activation involves much more than the ability to

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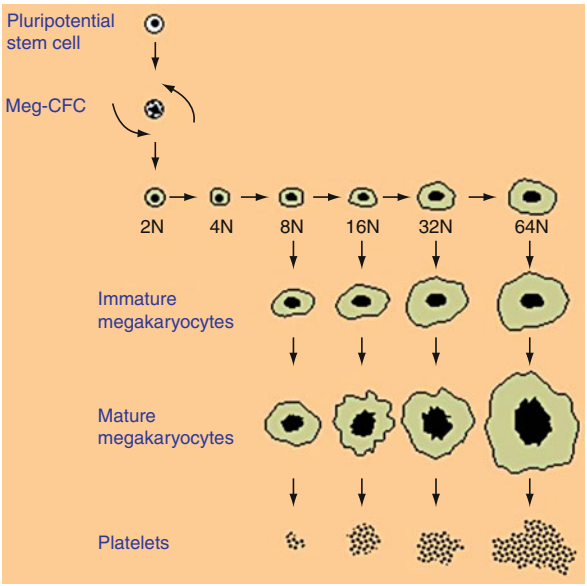

Figure 331.1
Thrombopoiesis. Illustration of the process of megakaryocytic differentiation and thrombopoiesis from the pluripotent bone marrow stem cell. The megakaryocyte first reaches a state of nuclear multiploidy and increases the size of the cytoplasm. Platelets are formed when hundreds of small cytoplasmic fragments are packaged in specialized phopholipid membranes surrounded by a central microtubular ring. Megakarocytic differentiation and thrombopoiesis are controlled by the hepatic production of the cytokine thrombopoietin

aggregate in the presence of fibrinogen. Like other coagulation assays, platelet aggregation and other tests of platelet function require careful interpretation and a firm grasp of their limitations.

Platelet Structure

Cytoskeleton

Normal circulating platelets are about 10 μm in diameter, and appear discoid in shape. The platelet plasma membrane consists of a complex arrangement of constituents including cholesterol, phospholipids, and integral membrane proteins. Many integral membrane proteins, including the adhesive receptors to fibrinogen and Von Willebrand factor, are anchored to an extensive platelet cytoskeleton composed chiefly of actin filaments. These actin filaments are arranged in a fine meshwork just below the plasma membrane and become less dense and more orthogonal in configuration deeper into the platelet cytoplasm. Just under the plasma membrane and surrounding the diameter of the platelet is a thick microtubule filament composed alpha and beta tubulin. *Figure 331.3* shows a circulating discoid platelet with the membrane peeled back and the cytoskeleton exposed. When platelets are activated to cover a vascular defect, the sub-plasma membrane microtubule ring contracts toward the center of the platelet as the actin cytoskeleton undergoes extensive rearrangement. This results in a dramatic shape change from the inactive, discoid platelet to a flattened platelet that looks somewhat like a "fried egg" spread out over an adhesive surface such a Von Willebrand factor, fibrinogen, or collagen.

The Plasma Membrane

Coincidental with the cytoskeletal changes that occur when platelets are activated to spread over a vascular defect, dramatic changes in structure of the activated platelet plasma membrane also occur and are critical to maintaining normal hemostasis. These events are summarized in *Fig. 331.4*. The overall effect of these plasma membrane changes is to form a phospholipid surface for the assembly of coagulation cascade components, particularly the *tenase* (FVIIIa/FIXa) and *prothrombinase* (FVa/FXa) complexes. These complexes require the "clottable" phospholipids (phophatidylserine and phosphatidylethanolamine) to achieve their maximal activity. In the resting or inactive state, circulating discoid platelets have an asymmetrical distribution of the phopholipid bilayer of the plasma membrane: Phophatidylcholine and phophatidylinositol, which do not support clotting ("non-clottable" phospholipids) are present predominantly on the outer plasma membrane. Phosphatidylserine and phosphatidylethanolamine, which efficiently support clotting, are present predominantly on the inner plasma membrane. This phopholipid membrane asymmetry is an energy-dependent process mediated, in part, by the integral membrane protein complex *aminophospholipid translocase*. Once platelets are activated to participate in hemostasis, the distribution of the membrane phospholipids is "scrambled" by another integral membrane protein called *scramblase*. The favorable clotting surface provided by phosphatidylserine and phosphatidylethanolamine translocates from the inner leaflet to the outer leaflet of the plasma membrane. In this activated phopholipid membrane configuration, the phospholipid-dependent

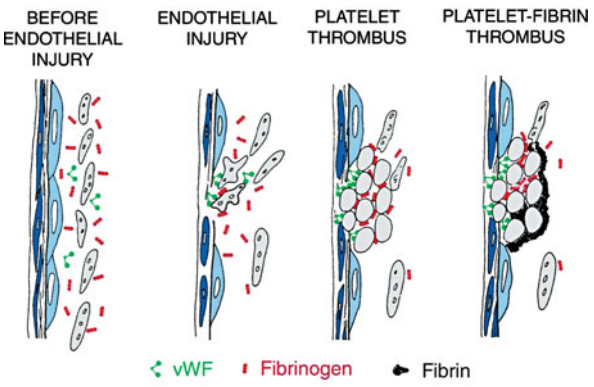

Figure 331.2

Primary and secondary phases of hemostasis. Formation of the platelet plug over a vascular defect is illustrated when Von Willebrand factor (*green*) binds to exposed sub-endothelial collagen and the platelet gpIB receptor. Once a layer of platelets cover the vascular defect, fibrinogen (*red*) further aggregates platelets on top of one another (through activation of platelet gpIIB-IIIA) to form a platelet plug. At the same time, tissue factor generated by injured endothelial cells associates with factor VIIa to start the extrinsic pathway of coagulation. With the platelet plug in place, the coagulation factors assemble on the activated platelet membrane surface to form a strong fibrin (*black*) covering that stabilizes and secures the platelet plug. The formation of the platelet plug by Von Willebrand factor and fibrinogen is referred to as the primary phase of hemostasis, and the production of fibrin by the plasma coagulation factors is referred to as the secondary phase of hemostasis

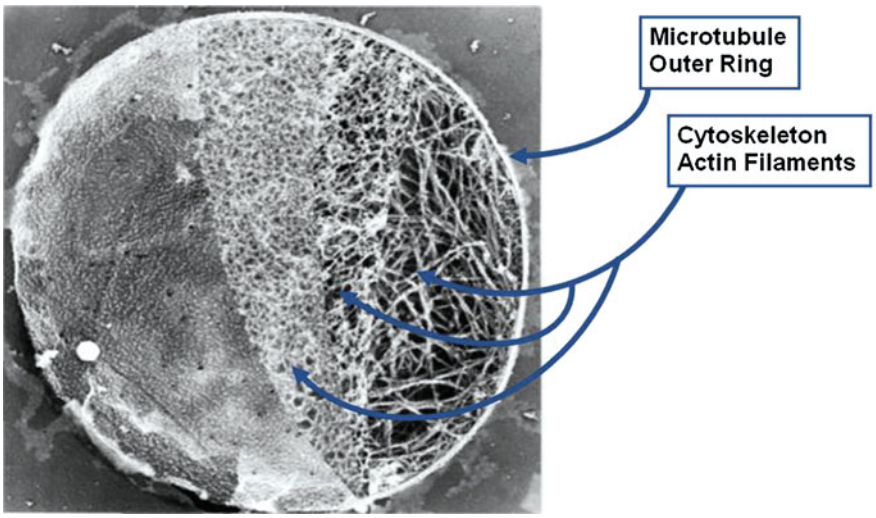

Figure 331.3

Platelet cytoskeleton. The cytoskeleton of the circulating discoid platelet is shown by electron micrograph. Immediately beneath the plasma membrane is a fine meshwork of filamentous actin which becomes more orthogonal and less dense deeper into the cytoplasm. An outer microtubule ring composed of a tubulin filament surrounds the platelet and contracts toward the center upon platelet activation and granular secretion

steps of the coagulation cascade are able to assemble on the platelet surface to generate a fibrin covering that anchors and protects the platelet plug. Accordingly, hemostasis is often divided into two phases: the primary phase in which platelets are localized to the wound by VWF and aggregated on top of the wound by fibrinogen, and a secondary phase in which the coagulation cascade (which is dependent on a "clottable"

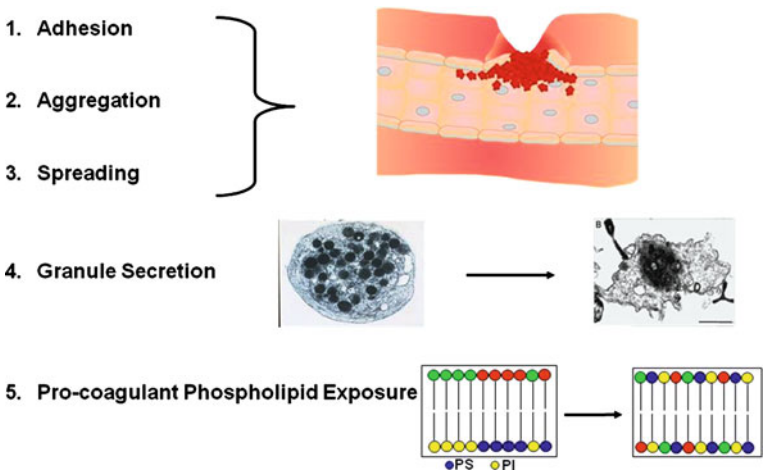

Figure 331.4

Multistep process of platelet activation. The process of platelet activation starts with platelet adhesion, aggregation, and spreading (Steps 1–3). Simultaneous central contraction of the microtubule ring with granule secretion as well as translocation of phophatidylserine [(PS) ''clottable'' phospholipid (Steps 4 and 5)] and ''non-clottable'' phosphatidylinositol (PI) are also illustrated

phospholipid surface provided by the localized, activated platelets) results in the activation of thrombin and the conversion of fibrinogen to fibrin.

Cytoplasmic Granules

Platelets also contain unique granules within their cytoplasm. These granules are of two distinct types: dense (or delta) granules and alpha granules. Dense granules are smaller than alpha granules and are composed mainly of calcium and magnesium ions, non-metabolic ATP and ADP, and the vasoconstrictive agent 5-hydroxytryptamine. Dense granules are composed chiefly of fibrinogen, Von Willebrand factor, P-selectin (an adhesion protein that is thought to play an important role in atherosclerosis), and platelet factor 4 (a homo-tetramer of uncertain function that is associated with heparin-induced thrombocytopenia). Both alpha and dense granules release their contents from the platelet cytosplasm after the platelet undergoes activation. During platelet activation, these granules merge with a specialized membranous system called the open canalicular system (OCS). The OCS is a complex membranous structure that is contiguous with the plasma membrane and serves as the pathway for transport of substances into the platelet and as conduits for the discharge of granule products secreted during the platelet release reaction (activation). Inherited deficiencies in platelet granule structure or function often result in mild to moderate bleeding disorders.

Adhesion Receptors: Von Willebrand Factor Receptor and Fibrinogen Receptor

Platelets express a number of important receptors on the plasma membrane surface that is essential for normal platelet function. These receptors can be grouped as adhesive, such as the fibrinogen and Von Willebrand factor receptors, or activating, such as the thrombin and collagen receptors. First the adhesive receptors will be discussed followed by the activating and other receptors. *Figure 331.5* shows a diagram of the major platelet receptors discussed below.

The Von Willebrand receptor is also known as platelet glycoprotein IB complex (gpIB). The complex is composed of two Ib-alpha, two Ib-beta, two gpV, and one gpIX polypeptides. This receptor complex is essential for localization of the platelet to the vascular defect and exposed sub-endothelium. Deficiencies of gpIB complex, known as Bernard–Soulier syndrome, have a severe lifelong bleeding disorder. A normal human platelet expresses about 25,000 gpIB receptor complexes. While gpIB is essential to localizing the platelet to the site of injury, it does not appear to have a major role in platelet activation. Accordingly, the gpIB-Von Willebrand factor interaction is critical but not sufficient for normal platelet function.

The other major adhesion receptor present on platelets is the glycoprotein IIB-IIIA complex (gpIIB-IIIA), also known as the fibrinogen receptor. This receptor complex, numbering about 50,000 copies per cell, is also

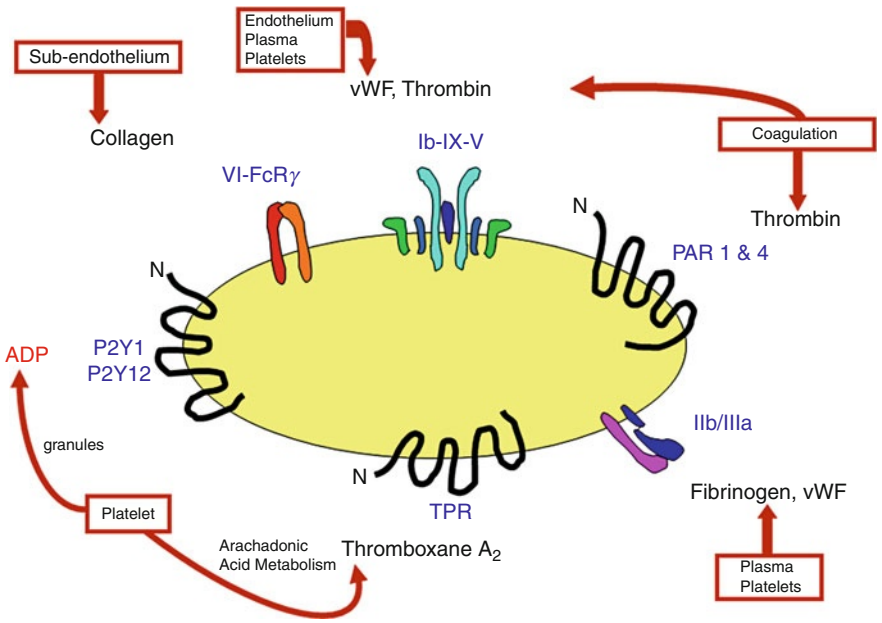

Figure 331.5

Platelet receptors. Representational view of platelet receptors is shown with their corresponding activating ligands. The most abundant receptors on the platelet surface are the adhesive receptors gpIIB-IIIA (50,000 copies/cell) and the gpIB complex (25,000 copies/cell). The other platelet receptors shown activate platelets by "priming" the gpIIB-IIIA receptor to bind fibrinogen

essential for normal platelet function. Accordingly, inherited deficiencies of gpIIB-IIIA, known as Glanzman's thrombasthenia, confers a lifelong bleeding disorder. The gpIIB-IIIA complex is a heterodimer, composed of one gpIIB and one gpIIIA polypeptide. The function of the gpIIB-IIIA complex is to aggregate platelets on top of the initial platelet plug. Once a thin layer of platelets is localized to the wound by the gpIB receptor complex and Von Willebrand factor, circulating fibrinogen binds to the platelet gpIIB-IIIA receptors, acting as a bridge between platelets. This aggregating step localizes more platelets to the site of injury and greatly strengthens the integrity of the platelet plug. Platelets that have not been sufficiently activated will not aggregate in the presence of fibrinogen. Accordingly, platelets must be "primed" by other platelet receptor agonists before they will aggregate. This platelet priming is sometimes referred to as inside-out signaling because it involves the release of intracellular calcium within the platelet cytoplasm in response to the priming step. The increase in intracellular calcium concentration causes a conformational change in the structure of the gpIIB-IIIA complex which allows tight binding with circulating fibrinogen. Thus, fibrinogen has two functions in normal hemostasis: It forms fibrin when digested by thrombin and it mediates platelet aggregation at the site of injury.

Nonadhesive Activating Receptors

There are several important activating receptors present on the platelet plasma membrane. These receptors "prime" the platelet by activating the gpIIB-IIIA receptor complex to bind fibrinogen, as discussed above. There are two major classes of receptor-activating agonists: weak and strong. For example, the thrombin receptor is a strong platelet agonist, while the epinephrine receptor is a relatively weak one. By weak or strong agonist, we mean the extent to which the agonist in question supports platelet aggregation through activation of the gpIIB-IIIA complex. What follows is a brief discussion about the major platelet-activating receptors and their corresponding agonists.

Thrombin is the most powerful physiologic platelet agonist known. Resting platelets exposed to physiologic concentrations of thrombin rapidly form aggregates in the presence of fibrinogen. Three distinct thrombin receptors have been characterized, two of which are present in human platelets. Thrombin receptors have thrombin recognition sequences and specific thrombin cleavage sites. When thrombin is present, the extracellular amino terminus of the receptor is cleaved by limited proteolysis. Cleavage of this amino terminus exposes a series of critical amino acid residues that results in activation of the

receptor and intracellular signaling which activates the receptor. Thrombin receptors are also known as protease-activated receptors (PAR). PAR1 is the most numerous and potent thrombin receptor and is the major pathway by which platelets respond to thrombin. Human platelets also express PAR4, a relatively weak platelet agonist with unclear physiologic significance. Treatment with thrombin inhibitors (e.g., argatroban, hirudin, and heparin) inhibits platelet activation because thrombin is such a potent platelet agonist. Thus, in addition to the decreased generation of fibrin afforded by heparin and the direct thrombin inhibitors, platelet activation by thrombin is also diminished. This may account, in part, for the success of heparin in the treatment of acute arterial thromboembolic settings such as an evolving myocardial or cerebral infarction. Heparin's antiplatelet properties also contribute to its usefulness in an adjuvant therapy with thrombolytics (tPA and *urokinase*) and angioplasty procedures in similar clinical settings.

Platelets also contain two types of adenosine diphosphate (ADP) receptors: the P2Y1 and P2Y12 receptors. ADP is considered a relatively weak platelet agonist relative to thrombin in that treatment of platelets in solution with varying concentrations of ADP results in about 50% the amount of platelet aggregation than with thrombin. ADP is present in the platelet dense granules and is also secreted by endothelium and other cell types. After a layer of platelets is localized by VWF to the site of vascular injury, more platelets must aggregate on top of the base layer for normal hemostasis to proceed. Accordingly, the platelet must be "primed" by an agonist in order for the gpIIB-IIIA complex to recognize and bind fibrinogen (as discussed above). Thrombin plays such a role since it is a very strong platelet agonist and is being generated simultaneously through tissue factor exposure and the coagulation cascade. However, circulating thrombin inhibitors and binding of thrombin to the endothelium and other cell types limit the ability for thrombin to completely sustain platelet aggregation in the absence of ADP. Clinical evidence of the importance of the ADP pathway is demonstrated by the fact that rare inherited abnormalities of the P2Y12 receptor confer a moderate bleeding disorder similar to that of moderate type I or II Von Willebrand disease. The drug clopidogrel, currently used to treat coronary and peripheral artery diseases, is a P2Y12 inhibitor. The P2Y1 receptor is a much weaker agonist than even the P2Y12 receptor, and has not been shown to directly result in the activation of the gpIIIB-IIIA receptor.

The thromboxane receptor is also considered a moderately weak platelet agonist. Thromboxane (TX2) is a prostaglandin that is produced from membrane-derived arachadonic acid after platelet activation. The production of TX2, like many other prostaglandins, is dependent on the activity of the membrane-bound enzyme *cycloxegenase 1* (COX1). Inherited deficiencies in TX2 synthesis or the thromboxane receptor are rare. These patients have mild to moderate lifelong bleeding disorders. Interestingly, analysis of their platelet function shows a deficiency in dense granule secretion, an observation that has been confirmed experimentally by inhibiting TXA2 receptor signaling.

The use of aspirin (salicylic acid) for the prevention and treatment of heart disease and stroke is based on its ability to irreversibly inhibit platelet COX1 by covalent modification of a key serine residue (Ser 529) that blocks entry of the eicosanoid substrate to the active site of the enzyme. Non-aspirin anti-inflammatory drugs (such as ibuprofen and the majority of other NSAID class members) also inhibit platelet COX1, but unlike aspirin these drugs do not covalently modify the enzyme. Accordingly, the antiplatelet effect of the NSAID group is reversible and dependent on the half-life of the particular drug.

The major collagen receptor present on the platelet plasma membrane surface is glycoprotein VI or gpVI. Compared to thrombin, collagen is considered a moderately weak platelet activator. Accordingly, treatment of platelets with collagen in solution results in an aggregation response similar to that of ADP. Inherited defects of gpVI are rare and confer a mild to moderate bleeding disorder. The function of the collagen receptor is to activate the platelets to aggregate after they have been localized to the vascular sub-endothelium by VWF and the gpIB receptor complex. It is important to keep in mind that the platelet gpVI is not an adhesion receptor, although it does bind collagen. Adhesion of the platelets to collagen is primarily mediated by VWF and gpIB. Once localized to the collagen surface, the interaction between collagen and gpVI results in the activation of gpIIB-IIIA and aggregation to form a stable primary platelet plug over the vascular defect.

Platelets undergo a relatively weak aggregation response when exposed to epinephrine through activation of the alpha-2 adrenergic receptor. The activation of gpIIB-IIIA, and hence platelet aggregation in response to alpha-2-andrenergic receptor activation, is heavily dependent on the synthesis of TXA2 (thromboxane) and signaling through the TXA2 receptor. TXA2 is synthesized from arachadonic acid present in the plasma membrane as a result of intracellular signaling by the alpha-2-andrenergic receptor through the COX1 pathway. As a result of this TXA2-dependent aggregation in response to epinephrine, platelets that have been exposed to aspirin (or other NSAIDs that inhibit COX1 activity) do not aggregate

normally in response to epinephrine. For this reason, epinephrine is often used as an agonist in clinical platelet aggregation studies.

Another weak platelet agonist is 5-hydroxytryptamine (serotonin), a constituent of the platelet dense granules. The corresponding receptor present on platelets is the 5HT2A isoform. Platelets do not synthesize serotonin but actively transport it into the dense granules by endocytosis in a process that is inhibited by selective serotonin uptake inhibitor drugs (SSRIs). With the widespread use of SSRI, there was concern that diminished activation of platelets by the decreased concentration of serotonin in the dense granules might cause bleeding due to platelet dysfunction. However, there does not appear to be an increased risk of bleeding or thrombosis associated with the use of SSRI medications.

Platelet Function

As mentioned in the introduction, platelet localization to site of a vascular injury is essential for normal hemostasis. Patients with platelet disorders or defects in the localization of platelets to the site of injury have mild to severe bleeding. On the other hand, activation of platelets near or on the site of a vascular atherosclerotic plaque (such as might occur in the setting of an acute myocardial infarction or stroke) is the leading cause of death in the modern industrialized world. Platelets are also important for normal wound healing and have been associated with the infectivity of malaria and other infections as well as the process of cancer metastasis. As a result of these observations, there is a great deal of interest in the physiology of platelet function. What follows is primarily a description of the role platelets play in normal hemostasis.

When a vessel is disrupted to cause bleeding, there is an almost instantaneous constriction of the lumen of the vessel near the injury site by reflex neurological pathways and the local release of vasoconstrictive substances. This vasoconstriction and the mechanical damage to the vessel wall and surrounding tissues results in a disruption of laminar blood flow and produces high shear forces at the site of injury. At the same time, the injured tissue exposes collagen, which is a main constituent of the basement membranes of almost every imaginable blood vessel. The high shear forces result in a conformational change in the structure of VWF from a globular to a linear configuration. In the linear configuration, the VWF is able to recognize and bind collagen and tether the platelet to the site via binding to gpIB, the VWF receptor complex. The exposed collagen also results in the activation of gpVI, the platelet collagen receptor. Signaling via gpVI results in the activation of the fibrinogen receptor, gpIIB-IIIA and platelets aggregate on top of the VWF bound platelets. Signaling through gpVI also results in the synthesis of TXA2 and release of ADP, epinephrine, and 5-hydroxytryptamine by the platelet dense granules. The effect of this "second wave" of platelet activation after localization by VWF and activation by collagen is to further strengthen the aggregation response. In fact, the activation of platelets to aggregate is a very redundant system such that defects in one component or another are unlikely to cause major bleeding [with the notable exception of disorders involving gpIIB-IIIA (Glanzman's thrombasthenia), gpIB (Bernard–Soulier disease), or the absence of VWF (type III Von Willebrand's disease)]. Tissue factor, which initiates the extrinsic pathway of coagulation when it binds factor VIIa, is also expressed by the injured endothelial cells and circulating monocytes which are localized to the site of the vascular injury. Tissue factor binding to circulating factor VIIa results in an initial burst of thrombin generation. Since thrombin is the most powerful physiologic activator of platelets to undergo aggregation, its production at the site of injury is critical to insure the adequate recruitment of platelets to form a platelet plug. Thrombin also activates fibrinogen to form a tough fibrin layer over the surface of the aggregated platelets. Accordingly, thrombin provides a key link between the primary phase of hemostasis, in which the platelets are localized and aggregated to the site of vascular injury, and the secondary phase of hemostasis, in which the coagulation proteins form fibrin.

Platelet function, as indicated in the preceding sections, involves more than plugging up a defect. The platelet membrane and cytoskeleton also undergo dramatic changes upon adhesion and activation. The platelet membrane changes its phopholipid distribution so that the high levels of "clottable" phophatidylserine and phosphatidylethanolamine appear on the outer leaflet of the plasma membrane. These membrane changes are essential to the localization of the clotting cascade protein complexes (*tenase* and *prothrombinase,* see above) and the efficient formation of thrombin and fibrin. The circulating discoid platelet also spreads and flattens over the vascular defect as a result of intracellular signaling pathways which rearrange the actin cytoskeleton filaments in an orthogonal configuration, with bundles of fibers composed of filamentous actin and myosin (stress fibers) arranged in a pattern connecting adjacent gpIIB-IIIA adhesion points (focal adhesions). The result is a firmly attached platelet plug covered by a thick fibrin meshwork.

Once the platelet forms a plug over the vascular defect that is anchored and covered with fibrin, clot retraction

must then occur for normal wound healing to take place. The platelet-dependent process of clot retraction is poorly understood, but is an energy-dependent process in which the actin–myosin stress fibers contract in a manner similar to striated muscle. This filamentous contraction by the platelet brings the margins of the wound together and facilitates tissue repair with the recruitment of epithelium, fibroblast, and other cells. This process of clot retraction is distinct from thrombolysis, which involves the digestion of fibrin, though both processes overlap with respect to timing and their importance in normal wound healing.

Platelet Disorders

Platelet disorders are broadly grouped according to whether they are acquired or hereditary. Acquired platelet disorders will be covered first, followed by a brief discussion of selected hereditary disorders. *Table 331.1* summarizes the acquired and hereditary platelet disorders discussed below.

Acquired Platelet Disorders

Platelet function deficiencies can be acquired or hereditary. Most are acquired and due to drugs such as aspirin, which inhibits platelet function by interfering with COX1 activity (see above). Other mechanisms of drug-induced platelet dysfunction result from thrombocytopenia. Drug-induced thrombocytopenia is difficult to diagnose as many drugs are rare causes of thrombocytopenia that must be excluded by the largely empirical process of elimination of other causes. Severe thrombocytopenia soon after the start of a medication is the most straightforward presentation of drug-induced thrombocytopenia. For example, drugs such as the antibiotic vancomycin result in rapid immunologic clearance of platelets in some individuals. The mechanism of vancomycin-induced thrombocytopenia is due to antibody formation to the complex of vancomycin associated with the adhesive platelet receptor gpIIB-IIIA. Quinine may also cause an immune-mediated severe thrombocytopenia. In general, drug-induced immune thrombocytopenia resolves within a week or two of stopping the drug but may recur when the drug is reintroduced. Other drugs such as thiazide diuretics and some of the earlier NSAIDs which are not commonly used such as phenylbutazone and antineoplastic agents can cause amegakaryocytic thrombocytopenia. Treatment involves stopping the offending medication and supporting the patient with platelet transfusion as necessary to prevent or treat bleeding. In the setting of acute myocardial infarction or after revascularization procedures, gpIIB-IIIA antagonists have proved very effective at reducing the rate of post-revascularization thrombosis. These antagonists are powerful antiplatelet agents that directly interfere with the binding of fibrinogen to gpIIB-IIIA, and hence stop platelet aggregation. These drugs are never administered outside the intensive care setting with close monitoring because of the high risk of bleeding. The gpIIB-IIIA antagonists are usually stopped within 24 h after the revascularization procedure. These drugs are available as an antibody (abciximab) or as small molecules (tirofiban, eptifibatide). The major side effect is thrombocytopenia and bleeding. The thrombocytopenia is characterized by the appearance of clumps of aggregated platelets on the peripheral smear together with a falling

Table 331.1
Acquired and hereditary platelet disorders. Selected examples of common acquired and hereditary platelet disorders are shown with the primary mechanisms of platelet malfunction. See text for details

	Disorder	Mechanism of platelet dysfunction
Acquired	Drugs	Decrease production
		Immune clearance
	Liver disease	Decreased production
		Increased sequestration
		Membrane defects
	Vitamin B12 and folate	
	Deficiencies	Decreased production
	Marrow stem cell disorders	Decreased production
		Structural defects
	ITP	Immune clearance
	Microangiopathic anemias	Platelet activation and consumption
Inherited	Membrane defects	Bernard–Soulier (gpIB)
		Glanzman's (gpIIB-IIIA)
	Storage pool disease	Alpha granule and dense granule
	Macrothrombocytopenia	May–Hegglin anomaly

platelet count. The treatment is to stop the drug as soon as possible and consider administering platelet transfusions if there is bleeding or the platelet count is less than 50,000/μl.

Most drug-induced platelet disorders involve the occurrence of thrombocytopenia and bleeding with the notable exception being heparin-induced thrombocytopenia (HIT) or type II heparin-induced thrombocytopenia. In this case, the offending drug, unfractionated heparin, causes a platelet activation syndrome with a high risk of intravascular clotting. HIT usually develops within 4 days to 2 weeks of initiating unfractionated heparin with the onset of mild to moderate thrombocytopenia and often life-threatening venous and/or arterial thrombosis. The mechanism appears to be the formation of endogenous IgG antibodies to standard heparin in complex with platelet factor 4 (PF4). This antibody-heparin-PF4 complex activates platelets by associating with the FCR-gamma receptor present on the surface of the platelet plasma membrane. The FCR-gamma receptor is normally paired with the collagen receptor gpVI, where it functions as a moderately weak platelet agonist. However, when the FCR-gamma receptor is activated by the antibody-heparin-PF4 complex, the platelet aggregation response is similar to thrombin – the strongest physiological platelet agonist. Patients who develop thrombocytopenia within 2 weeks of starting unfractionated heparin demonstrate anti-PF4 antibodies in their serum and whose plasma confers brisk platelet aggregation in the presence of heparin are considered to have HIT. The treatment for HIT is to stop all heparin infusions of any kind. Furthermore, due to the risk of thrombosis in the setting of HIT, patients are treated with a non-heparin anticoagulant such as the direct thrombin inhibitors argatroban or hirudin until the platelet count returns to normal. If the patient with HIT has a thrombosis, heparin-free anticoagulation is maintained for at least 3 months.

There are many other causes of acquired thrombocytopenia which are often grouped according to whether the mechanism is due to decreased production, increased destruction, or sequestration. The most common cause of decreased platelet production (after drug toxicity) is liver disease. Hepatic dysfunction results in thrombocytopenia because of diminished thrombopoietin production by hepatocytes and synthetic membrane defects which shorten the circulating life of the platelet. Hypersplenism with increased platelet sequestration is also commonly associated with liver disease. Vitamin B12 and folate deficiencies are also important causes of thrombocytopenia due to poor platelet production. Finally, bone marrow stem cell disorders such as myelodysplasia, aplastic anemia, and acute and chronic leukemia adversely affect the production of megakaryocytes and the process of thrombopoiesis. Thrombocytopenia due to increased peripheral destruction is most commonly seen in immune disorders such as idiopathic thrombocytopenic purpura (ITP) and rheumatologic disorders.

ITP is an immune disorder that results in the clearance of platelets from the circulation by antibodies formed against platelet surface antigens. The most common target of the platelet autoantibodies is the gpIB receptor complexes; however, other platelet surface proteins and receptors have also been reported as targets. The mechanism behind the formation of these platelet autoantibodies is unclear. However, ITP is associated with low-grade lymphoproliferative disorders such as CLL as well as other immunological disorders such as AIDS. Interestingly, in children, ITP is almost always a self-limited disease, while in adults, the disease is almost always chronic or relapsing. While ITP can result in very low platelet counts, life-threatening spontaneous bleeding such as intracranial hemorrhage occurs in less than 1% of patients. Treatment of acute episodes of ITP in the adult or child usually includes immunosuppression agents. The first line of therapy is usually corticosteroids, which increases the platelet count to normal levels in about two thirds of patients. A favorable response to corticosteroids is associated with an increased chance of cure with splenectomy in adult patients. Patients who do not respond to corticosteroids are sometimes treated with the anti-CD20 monoclonal antibody rituximab. High-dose intravenous immune globulin and anti-Rh antibodies (Rho-D) can be used successfully to rapidly increase the platelet count within a day or two, but these medications usually result in short-lived remissions and are expensive. Because of the relatively low incidence of spontaneous bleeding in patients with ITP and the relatively high toxicity of the immunosuppressive drugs used to treat the disorder, patients are often left untreated if they maintain a platelet count of at least 30,000/μl. For patients with lower platelet counts or bleeding who have chronic ITP, thrombopoietin (TPO) is now available. There are two TPO preparations currently manufactured: one is taken orally on a daily basis and the other is given as a weekly subcutaneous injection. These TPO preparations have about a 90% response rate and are generally well tolerated. However, the thrombocytopenia returns when TPO is discontinued and long-term studies regarding the safety of these drugs is ongoing.

Other important platelet destructive or consumptive disorders are the microangiopathic hemolytic anemias, thrombocytopenic thrombotic purpura (TTP), disseminated intravascular coagulation (DIC), and the hemolytic-uremic

syndrome (HUS). These disorders are characterized by microvascular thrombosis and thrombocytopenia due to systemic activation of platelets by ultra-large VWF (TTP and HUS) or by thrombin (DIC). These are life-threatening disorders with high mortality rates. Treatment of DIC and HUS involves addressing the underlying cause, which is often infection or malignancy. Successful treatment of TTP involves daily plasma exchange until the platelet count reaches normal levels. DIC and HUS do not respond to plasma exchange. About one third of patients diagnosed with TTP have a chronic relapsing form of the disease and must be treated with immunosuppression and plasma exchange at regular intervals. TTP treatment is best done at a major medical facility with the resources to perform plasma exchange and physicians with expertise in plasma exchange and blood banking.

Inherited Platelet Disorders

There are many rare familial platelet disorders that occur in isolated families. While these disorders are of scientific interest, they are rarely encountered by most physicians. Inherited disorders are grouped according to whether they involve membrane defects, disorders of granules, or macrothrombocytopenia.

The most important membrane defects are those which involve the adhesion receptors gpIB and gpIIB-IIIA, known as Bernard–Soulier syndrome and Glanzman's thrombasthenia. These disorders, like almost all inherited platelet disorders, are autosomal recessive in their inheritance pattern. Multiple genetic mutations in the genes coding for these disorders have been reported. Homozygous mutations result in severe, lifelong bleeding disorders. In the heterozygous state, these patients usually have mild bleeding disorders characterized by excessive post-traumatic bleeding. The diagnosis is usually suspected when the patient's platelets fail to aggregate in response to weak or strong agonists and confirmed by platelet flow cytometry using antibodies which recognize the corresponding surface receptors. Treatment for these disorders with platelet transfusions usually results in the development of allo-immunization or antibodies against the receptor. Recombinant factor VIIa has been used successfully to prevent perioperative and post-traumatic bleeding. Bone marrow stem cell transplantation would provide definitive treatment, but the mortality rate is unacceptably high with this therapy.

Platelet granule disorders, also known as platelet storage pool disease, encompass a range of disorders with variable reduction in the concentration and structure of dense granules, alpha granules, or both. These disorders are generally inherited in an autosomal-recessive pattern. The most common of these disorders is dense granule deficiency. These patients all have a mild to moderate bleeding disorder, characterized by bleeding when challenged by trauma or surgery. The formation and secretion of granules is a complex process involving many genes. Accordingly, the specific genetic mutations that cause platelet storage pool disease are largely undetermined. The diagnosis is made by analysis of platelet structure with electron microscopy or by flow cytometry using chemical probes that specifically recognize platelet granules. Treatment involves the appropriate use of DDAVP, antifibrinolytics such as epsilon aminocarproic acid or tranexamic acid, and platelet transfusions.

The macrothrobocytopenias are rare disorders that usually involve multiple inherited birth defects together with large platelets and thrombocytopenia. These patients generally have mild bleeding disorders, with most episodes of bleeding occurring after trauma or surgical procedures. The most common macrothrombocytopnenia is the May–Hegglin anomaly, a disorder that affects only leukocytes and platelets. The peripheral blood smear is often suggestive of this disorder because of the prevalent appearance of leukocyte cytoplasmic inclusion bodies and large platelets with mild thrombocytopenia.

Some specific genetic mutations have been found which account for a subset of May–Hegglin patients. These tests are available through specialized genetic laboratories.

Summary

Blood platelets have several important functions. They adhere to sites of vascular injury and spread over the defect, secrete their procoagulant granular contents, and serve as a "clottable" surface upon which coagulation can occur. Accordingly, platelets are essential for normal hemostasis, and patients with acquired or inherited defects in platelet function have mild to severe bleeding. The diagnosis and classification of platelet disorders is complex and often requires the assistance of specialized regional laboratories capable of ultrastructural analysis, DNA sequencing, and platelet function testing. Treatment for bleeding disorders in patients with platelet defects is variable, and may involve platelet transfusion, antifibrinolytic medications, recombinant factor VIIa, DDAVP, and cryoprecipitate.

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332 The Phagocytic System

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Function and Morphology of the Phagocytic System

Phagocytes play a critical role in the initial response to infections with bacteria and fungi. They follow certain immune responses in order to combat and clear the infection. They adhere to the endothelial wall and subsequently migrate to the site of infection (chemotaxis). Once they ingest the pathogen (phagocytosis), they kill via different mechanisms including oxidative burst, proteases, and other toxic peptides. The phagocytes are also involved in the production of cytokines and other cellular mediators that participate in the inflammatory response. In addition, they contribute to the recognition of certain pathogens (opsonization or coating objects with certain proteins). Phagocytes originate within the bone marrow and move into the circulation (mobilization), and then exit to sites of inflammation (chemotaxis).

The phagocytic system consists of monocytes (mononuclear), neutrophils (polymorphonuclear), and eosinophils. Neutrophils and monocytes share many morphologic and functional characteristics. They originate from the same stem cell progenitors in the bone marrow. The proliferation and differentiation into mature leukocytes require stimulation by a variety of cytokines: interleukins and lineage-specific cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (GCSF), and macrophage colony-stimulating factor (M-CSF). The neutrophils have nuclei with three to five segments and constitute the predominant type of phagocytes. Monocytes are characterized by their large size with lobulated nuclei and azurophilic granules. The eosinophils are distinguished by large red granules and are involved in the inflammatory and parasitic reactions.

Disorders of the Phagocytic System

The phagocytic disorders can be classified to abnormality in number, function, or both. Affected patients typically present with recurrent and severe bacterial and fungal infections in early childhood. Respiratory tract and skin dominate the affected organs. However, deep-seated abscesses and oral stomatitis are commonly encountered. In the last few decades, our knowledge of the phagocytic disorders has clearly been revolutionized by the discovery of the underlying molecular defects in many clinical phenotypes, largely through international collaborations. However, many remain to be identified. Nevertheless, addressing the details of all known phagocytic disorders is beyond the scope of this chapter and the most common disorders of the phagocytic system will only be discussed.

Abnormality in the Number of Phagocytes

Neutropenia

Neutropenia is defined as an absolute decrease in the number of circulating neutrophils in the peripheral blood. Neutropenia is considered severe if the absolute neutrophil count (ANC) is less than 0.5×10^9 cells/L, moderate if the ANC is $0.5–1.0\times10^9$ cells/L, and mild if the ANC is $1.0–1.5\times10^9$ cells/L. Neutropenia can be classified based on pathophysiology (disorders of production, maturation, or peripheral utilization) or on intrinsic defects in the myeloid progenitors as compared to extrinsic factors to the bone marrow, causing acquired neutropenia (*Table 332.1*).

Congenital Neutropenia (CN)

Severe congenital Neutropenia (SCN) is a heterogeneous group of primary immune deficiency diseases conferring susceptibility to infections due to lack of neutrophils. It follows different mendelian inheritance, including autosomal dominant (AD), autosomal recessive (AR), and X-linked. There are some sporadic cases. Moreover, many syndromes are associated with severe neutropenia. SCN classically presents with persistent low neutrophil counts with typical myeloid maturation arrest at the level of promyelocytes in bone marrow studies. Recent discoveries have elucidated the underlying molecular defect of many SCN phenotypes.

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Table 332.1
Neutropenia in childhood

Congenital neutropenia (CN)
Non-syndromic CN
AD and sporadic SCN/ cyclic neutropenia due to mutations in ELA2
AR SCN due to mutations in HAX1
X-lined SCN due to mutations in WAS
SCN due to mutations in GFI1
CN associated with syndromic features
Reticular dysgenesis
Shwachman–Diamond–Oski syndrome
Chediak–Higashi Syndrome
Griscelli syndrome type 2
Hermansky–Pudlak syndrome type 2
p14 deficiency
Glycogen-storage disease
WHIM syndrome
Shwachman–Diamond Syndrome
Dykeratosis congenita
Neutropenia associated with T- and B-lymphocyte abnormalities
Acquired neutropenia
Bone marrow replacement
Infection
Ineffective granulopoiesis due to nutritional deficiencies
Neutropenia associated with metabolic diseases
Drug-induced neutropenia
Autoimmune neutropenia
Isoimmune neutropenia

Non-syndromic SCN

AD and Sporadic ELA2 Defect The most common form of SCN is caused by mutation in *ELA2*, the gene encoding neutrophil elastase. This disease presents as autosomal dominant or in a sporadic pattern. A subgroup of patients with the ELA2 mutation presents in an oscillatory cyclic pattern with a nadir every 3 weeks, giving rise to what is known as "Cyclic Neutropenia" with subsequent periodicity of clinical manifestations, including bacterial infections and stomatitis. Patients with cyclic neutropenia usually have a mild phenotype; however, death occurs in 10% due to overwhelming infections during the neutropenic nadir. Patients harboring the ELA2 mutation have a higher risk of myloid dysplasia and leukemia associated with somatic mutation in the granulocyte colony-stimulating factor receptor (GCSFR) gene.

AR: Kostmann Syndrome Although this is the classical autosomal recessive SCN that was described more than 50 years ago by Kostmann, the underlying molecular defect was only recently identified with a deficiency in HAX1, leading to increased apoptosis of myeloid cells. Patients might present with neurological abnormalities.

Other Rare Non-syndromic SCN These include X-linked neutropenia caused by mutation in *WAS*, the gene encoding Wiskott–Aldrich Syndrome protein and *GFI1*, a transcriptional repressor and splice control factor of the zinc-finger family of transcription factors with similar clinical presentation to common SCN.

Congenital Neutropenia Associated with Syndromic Features

Reticular Dysgenesis This is an autosomal recessive disease characterized by severe neutropenia and lymphopenia, resembling severe combined immune deficiency. The underlying molecular defect has been recently identified by mutations in the gene-encoding mitochondrial adenylate kinase 2. Patients usually die soon after birth with overwhelming infection in the early neonatal period unless offered hematopoietic stem cell transplantation. Bone marrow studies typically reveal arrest in myeloid differentiation at the promyelocytic stage, whereas erythrocytic and megakaryocytic maturation is generally normal.

Congenital Neutropenia with Hyperpigmentation Chediak–Higashi Syndrome (CHS) and Griscelli syndrome type 2 are associated with transient neutropenia and abnormal skin pigmentation. Hermansky–Pudlak syndrome type 2 (HPS2) and p14 deficiency are two other syndromes associated with abnormal pigmentation and neutropenia that is persistent. HPS2 consists primarily of hypopigmentation and prolonged bleeding times due to defective platelet granules. Patients with P14 deficiency may present with other features, including short stature, hypogammaglobulinemia and reduced numbers of B-cell subsets, and defective function of cytotoxic T cells. In contrast to the SCN, the bone marrow studies in all these four syndromes show normal maturation of the neutrophils. In CHS, GS2, and P14 deficiency, the abnormality is due to low levels of neutrophils and their impaired killing ability.

Congenital Neutropenia Associated with Glycogen-Storage Disease (GSD) Patents with GSD1b are not only characterized by abnormal glycogen storage, hypoglycemia, and lactic acidosis, but also demonstrate congenital neutropenia. This disease is caused by mutations in the

glucose-6-phosphate translocase (G6PT, encoded by the gene SLC37A4), a transporter mediating translocation of G6P into the endoplasmic reticulum.

Another glucose metabolic disease was recently described, where, in addition to congenital neutropenia, patients may present with various congenital defects of the cardiovascular and/or urogenital system and increased visibility of superficial veins. It is caused by a defect in G6PC3.

WHIM Syndrome (Warts, Hypogammaglobulinemia, Immunodeficiency, Myelokathexis) WHIM is a rare autosomal dominant disease caused by mutation in the chemokine receptor gene *CXCR4*. It is characterized by multiple warts and hypogammaglobulinemia. Myelokathexis indicates dysregulated granulopoiesis which includes hypersegmentation and increased apoptosis. Severe infections are not typical because of the adequacy of neutrophils in the circulation during infection.

Shwachman–Diamond Syndrome This is a rare autosomal recessive disorder, characterized by exocrine pancreatic insufficiency, skeletal abnormalities, bone marrow dysfunction, and recurrent infections. Almost all patients suffer intermittent or cyclic neutropenia. Pancytopenia occurs in 25% of patients. Patients are at higher risk of bone marrow aplasia, myelodysplasia, and leukemia.

Dyskeratosis Congenita This is an X-linked recessive disorder characterized by nail dystrophy and skin hyperpigmentation. Some patients have marrow hypoplasia, and others (one third) have neutropenia.

Neutropenia Associated with T- and B-Lymphocyte Abnormalities Neutropenia has been described in severe combined immunodeficiency diseases, common variable immunodeficiency, agammaglobulinemia, and typically with hyper IgM syndrome, especially CD40 deficiency

Acquired Neutropenia

Bone Marrow Replacement

Neoplasms infiltrating the bone marrow induce neutropenia. Leukemia and lymphoma are the most common neoplasms that can cause neutropenia. Other disorders, such as osteopetrosis, myelofibrosis, and myelodysplastic syndrome, can result in severe neutropenia and pancytopenia.

Infection

Viral infection is the most common cause of transient neutropenia in children. Epstein–Barr virus, influenza A and B, measles, hepatitis A and B, respiratory syncytial virus, rubella, and varicella are noted to induce neutropenia. Other infections, such as typhoid, paratyphoid, tuberculosis, brucellosis, malaria, and rickettsial infections, can induce neutropenia through different mechanisms.

Ineffective Granulopoiesis due to Nutritional Deficiencies

Megalobalstic anemia secondary to nutritional deficiencies of folic acid or vitamin B12 has been associated with neutropenia.

Neutropenia Associated with Metabolic Diseases

Neutropenia can occur in children with metabolic disorders due to impairment of proliferation and differentiation of myeloid cells. These disorders include hyperglycinemia, propionic acidemia, methylmalonic acidemia, glycogen-storage disease type IB, and isovaleric acidemia.

Drug-Induced Neutropenia

The underlying cause of neutropenia associated with certain drugs is unclear. However, damage to the microenvironment of the bone marrow and/or immune-mediated destruction of neutrophils are the most likely mechanisms. The list of drugs reported to cause neutropenia includes antibiotics such as sulfonamides and penicillins; phenothiazines; antipyretics such as aspirin, acetaminophen, phenybutazone; anti-inflammatory agents such as penicillamine, levamisole, gold; and sedatives such as benzodiazepines and barbiturates.

Autoimmune Neutropenia

Patients may develop antineutrophil antibodies, causing rapid removal of neutrophils by the reticuloendothelial system. These patients may have recurrent infections and frequent hospitalizations. Therapy with corticosteroids has been shown to improve the neutrophil count in 50% of patients. High-dose intravenous immunoglobulin or splenectomy has been tried, but their efficacy is still unproven.

Isoimmune Neutropenia

Neutropenia occurring in the neonatal period can be due to neutrophil antibodies crossing the placenta from the mother after sensitization to the fetal neutrophil antigens. Usually, by the age of 7 weeks, the neutrophil count becomes normal.

Approach to Diagnosis and Therapy of Neutropenia

The diagnostic approach to neutropenia should focus through the history and physical examination on the

following: duration, frequency, site, and severity of infection; family history; recent viral infection; medications; dysmorphic features; lymphadenopathy; and hepatosplenomegaly. Patients should have white blood cell counts and differentials twice per week for 6 weeks to evaluate the possibility of cyclic neutropenia. Patients with persistent neutropenia should undergo a bone marrow aspiration and biopsy for detecting malignant disorders and congenital etiologies. Antineutrophil antibody may be helpful to detect immune-mediated neutropenia. The Rebuck skin window test can assess neutrophil mobilization. The steroid mobilization test evaluates the storage pool size. Immunologic evaluation can detect immune deficiency disorders. Plasma and urine amino acid screening can be helpful in the diagnosis of metabolic diseases associated with neutropenia. Chromosomal studies can establish the diagnosis of Fanconi anemia. Exocrine pancreatic function tests can detect Shwachman syndrome.

In spite of improvement in antibiotic therapy and supportive care, infections and septicemia are still a major cause of morbidity and mortality. A patient with severe neutropenia presenting with a febrile illness has at least a 60% chance of having a bacterial infection. Accordingly, broad-spectrum antibiotics to cover gram-positive (especially Staphylococcus) and gram-negative organisms should be started immediately. Blood, urine, and, if indicated, throat and sputum cultures should be done, and the appropriate radiologic imaging should he performed. Patients should receive antibiotics for a few days (duration to be determined by the clinical course, results of cultures, and neutrophil levels). If the patient continues to be febrile for more than 5–7 days in spite of adequate antibiotic coverage, then antifungal therapy should be initiated empirically. Patients with proven bacterial or fungal sepsis may benefit from granulocyte transfusions if they are still neutropenic, especially for critically ill patients, although this still has not been studied in a randomized trial. Caution should be taken regarding transmission of infections such as hepatitis, toxoplasma, and cytomegalovirus. Also, there is a potential risk for pulmonary toxicity and transfusion-associated graft-versus-host disease. Patients with immune-mediated neutropenia may respond to steroid therapy. Cytokines, such as granulocyte colony stimulating factor (GCSF), have been instrumental in improving the outcome of many congenital neutropenia. In fact, before the GCSF era, most patients affected by the SCNs succumbed to severe sepsis. Since its introduction into the clinical practice, the morbidity and mortality of infection have decreased significantly. In spite of all this supportive therapy, the definite cure is only possible by hematopoietic stem cell transplantation in most SCNs.

Neutrophilia

When the ANC exceeds 7.5×10^9 cells/L, patients can be considered to have neutrophilia. Neutrophilia can occur as a result of any one or a combination of the following: increased production, enhanced release from marrow storage pool, decreased exit from the circulation, and reduced margination. *Table 332.2* lists possible etiologies of neutrophilia.

Eosinophilia

Allergic disorders are the most common cause of eosinophilia in the developed countries, and parasitic infections account for a large proportion of patients with esoinophilia in the developing countries. Other causes include tumors such as Hodgkin disease, and hypereosinophilic syndromes (eosinophilic leukemia and Löffler syndrome).

Basophilia

Hypersensitivity reactions are the most common cause of basophilia. Other disorders that are associated

Table 332.2
Causes of neutrophilia

Increased production
Infection
Chronic inflammation
Myeloproliferative disease
Leukemoid reactions
Tumors (nonhematologic)
Drug-induced neutrophilia (lithium)
Hemolytic anemia
Enhanced release from marrow storage pool and/or reduced margination stress
Exercise
Postsurgery
Postictal
Heat stroke
Steroids
Decreased exit from circulation
Splenectomy

with basophilia include ulcerative colitis, rheumatoid arthritis, chronic renal failure, tuberculosis, and myeloproliferative disorders.

Monocytosis

In malignant hematologic disorders such as preleukemia, juvenile chronic myeloid leukemia, and lymphoma are associated with monocytosis. Other causes include infections such as tuberculosis, bacterial endocarditis, and granulomatous diseases.

Disorders of the Phagocyte Morphology

Morphologic Variations in Neutrophils

These disorders affecting the morphology of neutrophils include nuclear as well as cytoplasmic abnormalities.

1. *Pelger–Huet Anomaly.* Neutrophils of patients with this anomaly have a limitation of segmentation of the nucleus to two lobes. The disorder is inherited as an autosomal dominant trait; however, it can he acquired in infections such as mycoplasma and malaria or in malignant diseases such as leukemia or lymphoma.
2. *Hereditary Hypersegmentation of Neurophils.* This is a benign condition characterized by hypersegmentation of the nucleus in the neutrophil into four to five lobes.
3. *Prevalence of Nuclear Appendages.* In women, nuclear appendages (female specific) are present in about 2–10% of neutrophils. An excessive number of appendages may be present in trisomy 13–15.
4. *Vacuolization.* Cytoplasmic vacuolization has been noted in neutrophils in association with infections and burns.
5. *Alder-Reilly Anomaly.* Prominent granules in neutrophils are present in Hurler syndrome. Other cells, such as monocytes and lymphocytes, may have similar granules.
6. *Chédiak–Higashi Syndrome.* The neutrophils and other leukocytes of patients with Chédiak–Higashi syndrome contain giant granules.
7. *Hermansky–Pudlak Syndrome.* This is an autosomal recessive disorder characterized by albinism and increased bleeding tendency due to platelet dysfunction. The macrophages in the bone marrow have ceroid-like pigment.
8. *May–Hegglin Anomaly.* This disorder is characterized by thrombocytopenia with giant platelets. There are pale blue inclusions present in neutrophils, eosinophils, monocytes, and basophils. It has an autosomal dominant inheritance.

Abnormality in the Function of Phagocytes

Abnormal function of phagocytes may occur at any step involved in the process of engulfment and destruction of foreign particles described at the beginning of this chapter (*Fig. 332.1*).

Disorders of Adhesion

Leukocyte Adhesion Deficiency (LAD)

LAD is a heterogeneous group of disorders characterized by impairment of adhesion or chemotaxis of leukocytes to the site of infection. It is inherited as an autosomal recessive disorder. LAD-I is the most common and is caused by lack of glycoprotein molecules, the α subunits of the β2 integrin (CD18) shared by LFA-1 (CD11a), MAC-1 (CD11b), and P 150, 95 (CD11c).

Patients present with severe infections early in infancy without pus formation. They also have impaired wound healing manifesting early as delayed separation of the umbilical cord and omphalitis. Severe periodontitis, cellulitis, ulcerative skin lesions, and pneumonia are typical manifestation. Due to impaired trafficking of leukocytes, patients have an elevated peripheral neutrophil count. Flow cytometry using monoclonal antibodies to detect expression of the subunits of the β2 integrin can provide the diagnosis. The treatment of LAD should focus on the management of infections using appropriate antimicrobial therapy. Trimethoprim-sulfamethoxazole can be used for prophylaxis, and adequate oral hygiene is very important to prevent recurrent infections. Hematopoietic stem cell transplantation is the only modality which may provide definite cure in LAD.

LAD-II is caused by mutations in a GDP-fucose transporter. It was initially reported in two boys of Arab origin causing lack of expression of Sialyl Lewis^X, the ligand for E-selectin with subsequent impaired rolling of the leukocyte along the endothelium. In addition to the clinical manifestations of LAD-I, patients with this defect have short stature, facial dysmorphism, mental retardation, and Bombay blood-type phenotype due to generalized defect of fucose metabolism.

LAD-III is caused by a mutation of kindlin-3, which is involved in integrin signaling. Patients may have bleeding tendency due to impaired platelets adhesion.

A very rare clinical phenotype resembling LAD-I has been described with a mutation in Rac2 GTPase. It is

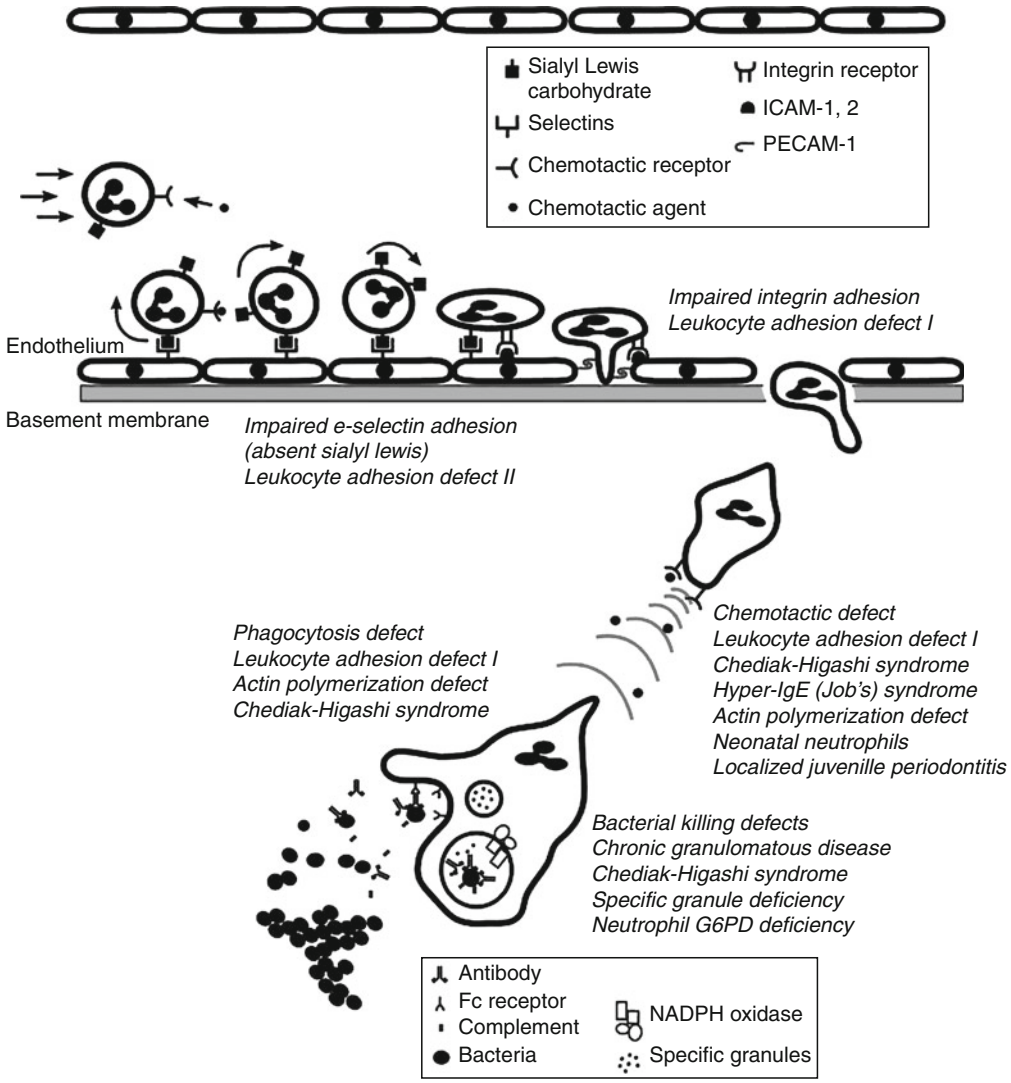


Figure 332.1

Steps in the response of circulating neutrophils to infection or inflammation (Reprinted with permission from Dinauer MC, Coates TD (2005) Disorders of phagocyte function and number. In Hoffman R, Benz J, Shattil S et al. (eds) Hematology: basic principles and practices. Elsevier Churchill Livingstone, Philadelphia, pp 787–830)

characterized by impaired neutrophil adhesion and motility, along with decreased neutrophil glucose-6-phosphate dehydrogenase (NADPH) oxidase activation and degranulation in response to chemoattractants.

Disorders of Chemotaxis

Patients with chemotactic disorders have recurrent bacterial (gram-positive and gram-negative) and fungal infections. The most common microorganism is Staphylococcus aureus. Several conditions are associated with defective chemotaxis, including inactivation of chemotactic factors (Hodgkin disease and cirrhosis of the liver); inhibitors of neutrophil responses (hyperimmunoglobulin E syndrome, localized juvenile periodontitis, rheumatoid arthritis, bone marrow transplantation, and drugs); deactivation of increased levels of chemotactic factors (Wiskott–Aldrich syndrome and bacterial sepsis); and phagocytic defects (neonatal neutrophilia, LAD,

Chédiak–Higashi syndrome, specific granule deficiency, and "lazy leukocyte" syndrome).

Hyperimmunoglobulin E (Job) Syndrome (HIGE)

HIGE a heterogeneous group of inherited disorders characterized by recurrent staphylococcal infections of the skin (cold abscesses) and lungs with subsequent formation of pneumatoceles. Candida infection is commonly encountered among HIGE patients. On the other hand, aspergillous frequently causes secondary pneumatocele infection. Chronic eczema and high levels of immunoglobulin E are consistent features of HIGE. AD and AR forms have been recently identified. The AD HIGE is caused by mutation in STAT-3 and is characterized by additional features, including defective shedding of primary teeth with double rows, scoliosis, easily bone fractures, joint hyperextensibility, coarse facial features, and aneurysms. In AR HIGE, patients might suffer viral infections but unlikely to present with skeletal or dental abnormalities. Vasculitis and autoimmunity are common in this phenotype. Mutations of the tyrosine kinase 2 gene (TYK2) have been identified as one of the causes of AR HIGE. Recently, a mutation in DOCK8 has been identified as a genetic cause of many AR HIGE patients. It is characterized by severe viral infection with HSV, extensive molluscum contagiosum, and several patients develop squamous-cell carcinomas. This phenotype is described as combined immunodeficiency with dysregulated IgE production. Patients with HIGE have variable defects in neutrophil chemotaxis. Treatment includes antibiotics for *S. aureus* infections and surgical drainage if indicated. Trimethoprim-sulfamethoxazole prophylaxis helps in decreasing the incidence of serious infections and improving the outcome. There is no definite treatment available for HIGE syndrome to date.

Neonatal Neutrophils

Neonatal neutrophils have defects in adhesion, chemotaxis, phagocytosis, and bactericidal activity, particularly in premature infants. The chemotactic deficiency is the most important one and has been attributed to abnormal regulation of cell adhesion molecules and decreased polymerization of F-actin in neutrophils after stimulation.

Disorders of Recognition

Complement (C3) deficiency is inherited as an autosomal recessive disorder, leading to recurrent infections due to absence of two major opsonins, C3b and C3bi.

Disorders of Ingestion

Neutrophilia in patients with LAD involves deficiency in ingestion of opsonized particles. Also, patients with deficiency of cytoskeleton-related 89-kDa protein or neutrophil actin polymerization have abnormal phagocytic function. Patients with paroxysmal nocturnal hemoglobinuria have deficiency of receptors (FcR III) that are important in the process of ingestion.

Disorders of Degranulation

Two main disorders belong to this category: Chédiak–Higashi syndrome and specific granule deficiency. Both are rare and inherited as autosomal recessive traits.

Chediak–Higashi Syndrome

CHS is a rare AR inherited disorder caused by mutation in *CHS1*, which encodes a large protein thought to regulate lysosomal and granule trafficking. It is characterized by partial oculocutaneous albinism, frequent and severe bacterial infections (*Staphylocuccs aureus*), and neuropathies (cranial and peripheral). Those who survive the recurrent infections develop diffuse lymphohistiocytic infiltration and pancytopenia "accelerated phase" and succumb to its complications. In addition to ineffective granulopoiesis, neutrophils have deficiency in chemotaxis and degranulation. Neutrophils from patients with Chédiak–Higashi syndrome have giant granules that appear to be a coalescence of azurophilic and specific granules. BM studies are often indicated as they are often more prominent in bone marrow neutrophils than in peripheral blood neutrophils. Management includes treatment of infections, such as prophylaxis with trimethoprim-sulfamethoxazole. If a suitable donor is available, hematopoietic stem cell transplantation can offer cure for this fatal disease.

Specific Granule Deficiency

Specific granule deficiency (SGD) is a rare disorder characterized by the absence of specific or secondary granules in developing neutrophils. It is caused by molecular defect involving the myeloid transcription factor C/EBPå. SGD neutrophils also demonstrate relatively severe chemotactic defect. Therefore, they present with severe infections of the skin, ears, lungs, and lymph nodes (*S. aureus*, *Proteus*, *Pseudomonas aeruginosa*, and *Candida*). The neutrophils lack or have empty specific granule vesicles (by electron microscopy) due to deficiency of certain proteins

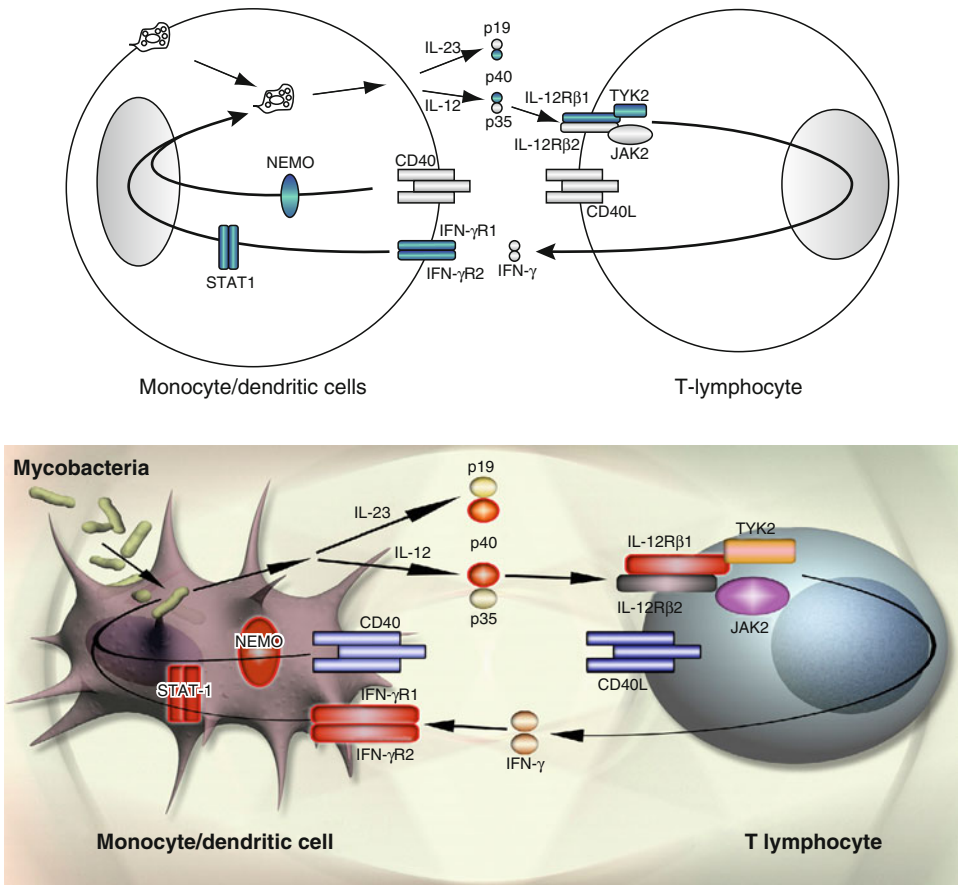
(defensins and lactoferrin). Treatment of SGD is supportive with prophylactic antibiotics, and prompt and prolonged treatment of infections.

Disorder of Signaling (Defect in IL-12/IFN-γ Axis)

The mononuclear phagocyte interaction with lymphocytes and monocytes through IL-12/IFN-γ axis is critical for the immune response against intracellular microorganisms, such as mycobacteria, salmonella, and listeria. The presence of pathogens as Mycobacterium triggers macrophages to produce IL-12. It binds to a specific receptor expressed by T and NK lymphocytes and induces secretion of IFN-γ that triggers macrophage microbicide on binding to the IFN-γ receptor. Defects of this crucial signaling pathway account for mendelian susceptibility to mycobacterial disease (MSMD). There are six MSMD-causing genes, including one X-linked gene (nuclear factor-kB–essential modulator [NEMO]) and five autosomal genes (IFN- γ receptor 1 [IFNGR1], IFN- γ receptor 2 [IFNGR2], signal transducer and activator of transcription 1 [STAT1], IL-12 p40 subunit [IL12P40], and IL-12 receptor b-subunit [IL12RB1]), producing heterogeneous clinical phenotypes of MSMD (◉ *Fig. 332.2*).

All forms of MSMD are characterized by increased susceptibility to environmental mycobacteria and to BCG vaccine strain. Salmonella, Listeria, and Histoplasma species infections can also be observed, especially in patients with IL12RB1 mutations.

Management of MSMD relies on aggressive therapy of infections, long-term prophylaxis. IFN-γ might be useful in patients with AD IFN- γ R1 deficiency, IL-12 p40 deficiency,



◘ Figure 332.2

MSMD-causing genes in the IL-12/23-IFN-g pathway. Schematic representation of host immune response against mycobacterial infection(Reprinted with permission from Al-Muhsen S, Casanova JL (2008). The genetic heterogeneity of mendelian susceptibility to mycobacterial diseases. J Allergy Clin Immunol 122(6):1043–1051)

or IL-12R defects. Bone marrow transplantation may provide cure for severe cases. However, the high mortality associated with graft rejection has limited this curative option.

Disorders of Intracellular Killing (Oxidative Metabolism)

Chronic Granulomatous Disease (CGD)

CGD is a heterogeneous group of inherited disorders caused by genetic defects in the components of the phagocyte's NADPH oxidase complex. Hence, the phagocytes are unable to generate the microbicidal reactive oxidant superoxide anion and its metabolites. As a result of the defect in this key host defense pathway, CGD patients suffer from recurrent life-threatening bacterial and fungal infections. Five genetic mutations involving the phagocytic oxidase system have been identified so far. The most common is an X-linked recessive defect in gP91phox, while three other AR defects were reported in P22phox, P47phox, and P67phox components of the NADPH oxidase system. A novel mutation in *NCF4*, the gene encoding P40phox, has also recently been reported in a boy who presented with granulomatous colitis, delineating the fourth AR form of CGD. International data indicate that X-linked is more common (65%); however, in highly inbred populations, the AR forms of the condition seem to be more frequent. Clinically, patients with CGD present with recurrent bacterial (*Staphylococcus aureus, Serratia marcescens, Salmonella*, and *Burkholdaria cepacia*) and fungal (*Aspergillus*) infections. In addition to susceptibility to infections, CGD patients are prone to develop noninfectious complications characterized by unregulated inflammation such as granulomatous colitis, chorioretinal lesions, and lupus-like disease. The diagnosis of CGD is based on a compatible clinical presentation and demonstration of a defective respiratory burst by nitroblue tetrazolium test which relies on the intracellular reduction of NBT by superoxide anion to a blue formozan precipitate that can be seen microscopically. More recently, a sensitive tool using flow cytometry to detect dihydrorhodamine 123 oxidative burst assay has been widely used in clinical practice. Genetic confirmation is the gold standard diagnostic test. Prenatal diagnosis can be done by percutaneous umbilical sampling or by puncture of placental vessels using fetoscopy. Treatment of patients with CGD includes appropriate management of infections (antibiotics and antifungal). Prophylaxis with trimethoprim-sulfamethoxazole and itraconazole antifungal prophylaxis have reduced the rate of serious infections substantially and hence improved the outcome. Introducing Interferon-γ prophylaxis was shown to be beneficial in reducing the frequency of serious infections. Hematopietic stem cell transplantation may provide definite cure for severe cases. CGD was formerly associated with a high mortality, but the current practice of prophylaxis with antimicrobials and IFN-γ, aggressive surgery, and early hematopoietic stem cell transplantation or gene therapy have improved the outcome substantially.

Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency

G6PD is an X-linked inherited disorder leading to a low concentration of NADPH. Patients have recurrent bacterial infections and hemolytic anemia. Diagnosis is made by testing neutrophil G6PD activity (<5% of normal) and erythrocyte G6PD levels. Treatment focuses mainly on appropriate management of infections.

Myeloperoxidase Deficiency (MPO)

MPO is the most common disorder of phagocyte function. It is inherited as autosomal recessive with variable expression. The defect results in diminished production of hydrochlorous acid (HOCI) required for killing of microorganisms (especially *Candida*). Usually patients are clinically asymptomatic but rarely may present with disseminated candidiasis. The deficiency may be acquired in acute myeloid leukemia. Diagnosis is made by testing neutrophils and monocytes for peroxidase (by histochemical analysis). Patients with MPO deficiency and diabetes are usually treated aggressively to prevent fungal infections. Otherwise, MPO does not require prophylactic antibiotics. Prognosis is usually excellent.

Glutathione Metabolism Disorders

Glutathione reductase deficiency and glutathione synthetase deficiency are uncommon and inherited as autosomal recessive traits. Diminished levels of these enzymes lead to toxic accumulation of hydrogen peroxidase due to decreased catabolism by glutathione. Patients may have hemolysis with oxidant stress and usually have a benign course (patients with glutathione synthetase deficiency may have metabolic acidosis, recurrent otitis media, and intermittent neutropenia).

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333 Bone Marrow Failure Disorders

Hassan El Solh · Abdallah Al-Nasser · Peter Kurre

The term "bone marrow failure syndromes" (BMF) captures a heterogeneous group of disorders that result in an effective mismatch between blood and immune cell production in the bone marrow and peripheral demand. Most often clinical symptoms of cytopenia bring children to medical attention and prompt laboratory evaluation. However, in children, given the compensatory capacity of their cardiovascular system, relatively greater baseline incidence of infections and their general propensity for minor trauma, they often present relatively late in the process. The clinical presentation is further compounded by the frequently insidious nature of onset and can be masked by disease specific symptoms in other organs. For example, children with cytopenia following infection may undergo evaluation for predominant fevers and skin findings. Indeed, with some regularity the diagnosis is unsuspected and even incidental during evaluation for more common childhood problems, especially infections, recurrent bleeding, or failure to thrive. On rare occasions, patients will be referred because siblings or family members have been diagnosed with a specific BMF disorder. Notwithstanding specific symptoms, the hemogram often reveals a variable degree and combination of multi- or single lineage count decrements.

Etiologic considerations are broad, covering specific acquired and multi-system heritable genetic disorders. Medical history and physical evaluation can provide critical clues to guide differential diagnosis and tailor choice of ancillary studies. However, in the absence of acute blood loss or evidence of immune mediated destruction, further evaluation will almost always require a bone marrow evaluation and, where available, more specialized biochemical and genetic testing. Setting appropriate expectations with patient, family, and other providers, the often extensive evaluation may not always establish a definitive diagnosis, but is crucial in making appropriate treatment recommendations and excluding heritable etiologies that require family counseling.

General Considerations

Definitive hematopoiesis during human development follows a carefully orchestrated series of in utero developmental phases. Beginning in the aorta-gonadomesonephros region of the early fetus, production of blood and immune cells passes through a placental phase with subsequent expansion in the fetal liver before ultimately moving to the bone marrow at 22 weeks of gestation. Trabecular bone provides the scaffold structure that supports the stromal, hematopoietic, osteoblastic, as well as endothelial cellular components and extracellular matrix that comprise the hematopoietic microenvironment. It is widely believed that hematopoiesis and immunopoiesis are hierarchically organized in a system of successive steps of differentiation and progressive restriction with functional specializations of cells. All mature cells in the blood stream are derived from rare hematopoietic stem cells residing in the bone marrow microenvironment and capable of asymmetric division. Cell fate decisions determine self-renewal and differentiation activity and match blood and immune cell production to physiologic needs. Driving the process of amplification and specification is a network of endocrine and paracrine signaling molecules and their cognate cellular receptors. Hematopoietically active cytokines, interleukins, adhesion molecules, and growth factors are responsible for maintaining cells in quiescence and providing hierarchically specific cues to initiate proliferation and cell type specific coordinated expansion. For example, during adjustment to lower partial oxygen pressures at high elevations, hypoxia signaling in the kidney will result in erythropoietin secretion and selective activation of red blood cell progenitors in the bone marrow to increase production of oxygen carrier capacity. Similarly, pathophysiologic events such as infection or bleeding can trigger massive increases in production and mobilization of leukocytes or platelets. Expansion of virus specific T-cells on the other hand provides an instructive model for interleukin-2 and its role during induced clonal proliferation of immune cells in response to a very specific viral agent. The often remarkably advanced and tightly controlled signaling effects reflect the combined diversity of ligands and receptors.

Differential Diagnosis

Children presenting with signs of single or multilineage cytopenias offer a broad differential diagnosis. Patient age,

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physical findings, and specific circumstances can help guide the work up and narrow relevant diagnoses. Principally, infections, environmental exposures, nutritional deficiencies, immune dysregulation, malignant, or benign infiltrative bone marrow processes must be considered.

Evaluation

Physical examination and thorough patient and family history are cornerstones in the diagnosis of BMF, often providing critical clues to tailor additional investigations. The relatively greater proportion of children in whom marrow aplasia is merely the presenting manifestation of an underlying heritable condition emphasizes their critical importance. The distinction between acquired and inherited etiologies in children is crucial, not only for proper treatment and to avoid unnecessary toxicities, but also to initiate family counseling. In some conditions, such as Fanconi Anemia, characteristic physical stigmata are obvious in only a minority of patients and their absence should never lead the clinician to dismiss the diagnosis. In other instances, such as thrombocytopenia with absent radii, abnormalities on physical exam are obvious and the diagnosis more straightforward. Several ancillary studies are useful to ascertain the diagnosis and begin to delineate more specific etiologies:

Quantitative cytopenic abnormalities of individual or all hematopoietic lineages in the peripheral blood often lead to symptomatic presentation, prompt further work up and lead to specialty referral. The complete hemogram provides a wealth of information about the patient's hematological status and may help narrow the differential diagnoses to be pursued. Normal range values for blood cell counts and indices should be interpreted with consideration of age, gender, and laboratory reference standards. Separately, a blood smear for microscopic evaluation and reticulocyte stains should be included to assess cell morphology and bone marrow red cell compensatory activity, respectively.

The bone marrow evaluation is a key for the classification of cytopenias and provides an opportunity for several separate tests. Ideally, the decalcified Giemsa stained bone marrow biopsy captures the architecture, cellular composition, and extracellular matrix of hematopoietic tissue. Additional, more specific histochemical stains can help answer questions of iron stores, infection, malignant (e.g., leukemia) or nonmalignant (e.g., glycogen storage disease) displacement of hematopoietic cells. However, the hallmark finding in bone marrow failure is the adipose replacement and proportional decrease of hematopoietic elements inappropriate for age. Reduced cellularity (defined as $<30\%$ averaged for multiple fields of view) and variable peripheral cytopenias are defining diagnostic features of bone marrow failure, regardless of etiology. A bone marrow aspirate is usually obtained to evaluate size and morphology (dysplasia, nuclear bridging), but also cytogenetic analysis for karyotype abnormalities. Depending on circumstance, immunophenotyping, or fluorescence in situ hybridization (FISH) studies may be desired to delineate aplastic anemia (AA) from hypoplastic myelodysplastic syndrome (MDS) or lymphomatous invasion. Incidental diagnosis of fatty marrow replacement has been reported in patients who underwent magnetic resonance imaging for unrelated causes, but radiologic evaluation, other than for specific symptoms, has no routine role in the diagnostic algorithm. Additionally indicated diagnostic tests are discussed in the context of specific diagnoses below.

Acquired Aplastic Anemia (AAA)

Pathophysiologically AA is widely considered to reflect immune destruction of stem cells with the resulting progressive depletion of mature blood and immune cells. The degree of peripheral blood neutropenia, reticulocytopenia, thrombocytopenia, and the proportion of hematopoietic elements in the bone marrow are usually used to grade severity. Values of $<500 \times 10^9$/l for neutrophils, $<1\%$ reticulocytes, $<20{,}000 \times 10^9$ platelets, and $<30\%$ cellularity define severe disease, often associated with a transfusion requirement for red blood cells and platelets. Most practitioners will consider therapeutic intervention only in such cases, whereas moderately severe disease may progress or resolve in up to 30% of cases without intervention. The incidence ranges from two to six cases per million without ethnic or gender predilections, but with notable regional differences between western and eastern hemisphere.

Etiology

Paul Ehrlich's initial description associated with pregnancy in a young woman is now considered exceedingly rare. But, notwithstanding its shared pathophysiology, the most common finding will be idiopathic bone marrow failure without a known cause even though several specific etiologies and common associations that alter treatment decision making must be considered in children.

Infections

A wide range of infections has been associated with prolonged cytopenias. Especially in children, these can be asymptomatic and are often transient. However, congenital or postnatal infection with parvovirus (*B19* strain), human immunodeficiency virus (HIV-1, or rarely -2), Epstein Barr Virus (EBV), or Cytomegalovirus (CMV) may result in sustained low blood counts. Failure to eradicate these infections may also provide clues to underlying immunodeficiencies. Hypocellular cytopenias have long been appreciated as sequelae of, or rarely concurrent with, A, B, or C viral hepatitis. Regionally different incidences for AA range from 2% to 5% of children with hepatitis and a slightly higher percentage in patients who received orthotopic liver grafts. Clinically heterogeneous, even patients with substantial and life-threatening liver failure, organ function recovers and does not necessarily affect treatment, complications, response to therapy, or ultimate prognosis. Serological or pathogen-specific nucleic acid based laboratory evidence will help distinguish past from active infection and can be helpful guiding successful treatment.

Drugs

When it was in more widespread medical use, chloramphenicol was linked to aplastic anemia. Case reports also implicate more commonly used drugs, including sulfonamides, carbamazepines, cimetidine and quinacrine, and others. Mechanistic insight into this etiology is missing and no specific test will be helpful in ascertaining this etiology.

Chemicals and Toxins

Environmental exposure to aerosolized benzene in particular is an established cause of marrow dysfunction and occasionally myelodysplasia. But, while patients and caregivers often focus on this etiology, it is in fact very rare in industrialized western society. A particularly informative recent study suggests that environmental exposure to pesticides and other agents including organophosphates may be a problem in other parts of the world. An extensive exposure and occupational history is important in making the diagnosis.

Etiologies such as ionizing radiation or graft versus host disease (GVHD) are well-established causes of marrow aplasia and pancytopenia, but the context dependence makes their diagnosis more straightforward.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a clonal stem cell disorder resulting from somatic mutations in PIG-A gene and the production of blood cells defective for glycosylphosphatidyl-inositol (GPI) anchorage of several cell surface proteins. Clinically PNH is characterized by periodic lysis of red blood cells with resulting intravascular hemolysis. However, considerable overlap exists in the clinical presentation and diagnostic findings of patients with idiopathic AA and those with PNH. Indeed, commonalities between the two entities have been interpreted to indicate an immune pathophysiology for PNH, as well. Care should be exercised to distinguish the two from each other, and the existence of coagulation abnormalities and symptoms of thrombosis may be considered defining features of classic PNH. Accordingly, the demonstration of clonal deficiencies of select cell surface proteins in red blood cell or leukocyte lineages should not be automatically considered diagnostic of PNH since positive tests have been found in many patients with marrow failure. Historically, testing relied on sucrose lysis, with more recent flow-cytometry based assays greatly increasing sensitivity and quantitation. A prognostic role for PNH clones and the value of sequential analyses in guiding treatment has been suggested.

Complicating matters further, PNH has been well documented as a potential late complication after treatment with immunosuppressive agents.

Myelodysplasia (MDS)

Primary, non-treatment related myelodysplasia is a rare form of bone marrow dysfunction in childhood that may progress to acute myeloid leukemia. Cytopenias bringing the patients to medical attention and the diagnosis of a hypocellular bone marrow overlap with those of AA. Importantly, many patients present evidence not only of morphologic dysplasia on examination of smears, but also hallmark chromosomal aberrations. Accordingly, all patients with bone marrow failure undergoing a marrow aspiration procedure should have a cytogenetic analysis for karyotypic abnormalities. Numeric and gross structural abnormalities will be readily apparent. Depending on availabilities of laboratory facilities for further testing, additional studies for characteristic abnormalities such as loss of chromosome 7 or gains in chromosome 8 using FISH are indicated. Myelodysplasia and leukemia can be the initial presenting sign of cancer prone genetic disorders, including Fanconi Anemia and Shwachman–Diamond Syndrome. This, along with the generally infrequent

occurrence of myelodysplasia in children, implies the need to test these children for genetic disorders, especially in the very young.

Laboratory Findings

The backbone of the diagnostic work up is a complete peripheral blood count with indices, reticulocyte count and leukocyte differential. A blood film may hold additional valuable information on cell shape, morphology, and size. The bone marrow aspirate and biopsy should be evaluated for morphology and cellular composition and cellularity. Cytogenetic testing to exclude cases of myelodysplasia is important. When available, flowcytometric immunophenotyping to exclude leukemic involvement is helpful. Additional studies helpful in confirming the diagnoses and considering differential etiology include peripheral blood chromosome breakage testing to exclude Fanconi Anemia. Immunologic evaluation may include determination of immunoglobulin subclasses, lymphocyte subsets, the presence, and compositions of PI negative clones. Underlying viral infections should be excluded, especially HIV, hepatitis, and parvovirus. Radiological imaging has no routine role in the diagnostic work up of AA.

Therapy

Supportive Care is the backbone of treatment of patients with AA. Because most will present with cytopenias, diagnosis and treatment of infections as well as the need for transfusions are principal concerns in newly presenting patients. Neutropenic patients frequently come to medical attention with recurrent febrile episodes, oral mucosal ulcers, and fevers of unexplained origin. Symptom-guided diagnostics are indicated, although frequently unrevealing, and appropriate broad-spectrum antibiotics should be considered under these circumstances, especially in patients with indwelling central venous catheters. The role of empiric antibiotic coverage in patients is more controversial, although many practitioners consider antifungal coverage and prophylaxis against *pneumocystis carini* important. Children have profound cardiovascular reserve and the signs and symptoms of anemia routinely occur late with hemoglobin values often <6 g/dl. The transfusion of chronically adjusted patients requires judicious and slow correction, often over the course of several days. Normal hemoglobin values are not the goal, rather, improving oxygen delivery to tissues to relieve immediate symptoms of fatigue and exertion with post-transfusion target range between 8 and 10 g/dl. Because, patients are often neutropenic and lymphopenic, they should be considered immunocompromised even before receiving treatment. Therefore, to avoid transfusion associated immune reactions and minimize transmission of pathogens, transfusions of whole blood, red blood cells, or platelets should be prepared to eliminate viable lymphocytes (γ-irradiation) and filtered to remove trace leukocyte carriers of cytomegalovirus whenever possible. Long-term complications of transfusions include blood group and human leukocyte antigen (HLA) sensitization. They may accelerate transfusion requirements and sensitize the patient to transfusion associated immune reactions. HLA matching of platelets or family directed donation is often technically feasible, but should be strenuously avoided so as to not increase the risk of subsequent rejection in any patient who is considered for a stem cell transplant procedure in the future. The hemoglobin contained in red blood cells is complexed with iron, and transfusion of blood in patients unable to mobilize stores during red blood cell production in the bone marrow can lead to iron deposition and end organ dysfunction in liver, heart, and pancreas. Therefore, transfusion of blood products should always be judicious to minimize side effects. White blood cells and especially granulocytes are rarely transfused in cases of severe invasive infections.

Hematopoietic growth factors in the treatment of AA produce no sustained responses by themselves, but may have a role in the context of immunosuppressive therapy. Whether long-term use of G-CSF contributes to clonal evolution of myelodysplasia or acute myeloblastic leukemia is controversial. Androgenic steroids can temporarily improve hematopoietic output and are widely used in some parts of the world, but their side effects make long-term use problematic.

The treatment algorithm for idiopathic severe AA is subject to patient specific considerations and available resources and can therefore be regionally different. However, because the pathophysiology of AA is widely agreed to be an immune elimination of bone marrow stem cells, suppression or replacement of immune function are the principal considerations. Based on risk-benefit ratio and local resources, stem cell transplantation from an HLA matched sibling is the primary modality, followed by a variety of immunosuppressive strategies. Transplantation of stem cells from an unrelated donor is a potentially curative option for patients who fail immune suppression.

Immunosuppression Therapy (IST)

The incidental observation of sustained endogenous recovery following graft failure in AA patients undergoing transplantation provides powerful evidence for the immunological basis of AA. Based on a landmark randomized trial, the modern backbone of AA treatment is a course of rabbit or horse derived anti-lymphocyte or anti-thymocyte globulin (ATG). The combination with calcineurin inhibitor cyclosporine in particular has proved effective in inducing partial or complete remission in a majority of patients. Response to treatment is notoriously slow, but white blood cell count recovery can be hastened by addition of granulocyte colony stimulating factor. Responses may be drug dependent and the disease may recur, but immunosuppression can present a viable functional cure allowing independence from transfusions and high survival rates in children. Re-treatment with a second course of ATG will provide remission in about half the patients, without gains after switching between globulin preparations. Survival after IST is improved for younger patients with less severe disease who respond to treatment early, whereas clonal evolution to myelodysplasia or leukemia is frequently fatal. In aggregate, between 15% and 20% of long-term survivors develop late clonal disease (MDS, AML, and PNH).

Corticosteroids have not been effective in producing sustained remissions whereas cyclopshophamide can be successful, but immunosuppression is profound and complications can be severe.

Bone Marrow Transplantation

Transplantation of bone marrow stem cells is the only curative treatment of AA. Resources and donor availability permitting, transplantation of hematopoietic stem cells from an HLA matched related sibling donor is the treatment of choice. Improvements in supportive care and transfusion practices result in long-term survival rates in children exceeding 90%. Conditioning with ATG and high dose cyclopshophamide combined with adequate stem cell dose leads to stable donor chimerism with acceptable toxicities and effective prophylaxis against graft versus host disease. Unlike patients with malignancy, those with AA do not benefit from GVHD and the use of peripheral blood stem cell grafts worsens outcomes. Endocrine late effects on growth, thyroid, and gonadal functions are less frequent than following high dose radiation conditioning, but secondary malignancies have been seen.

Inherited Bone Marrow Failure Disorders

Fanconi Anemia (FA, OMIM: 227650)

A heritable multi-system disorder with great phenotypic diversity, Fanconi Anemia comprises a combination of physical anomalies, progressive bone marrow failure, and propensity to develop cancer. Mutations in at least 12 genes are the basis for predominantly autosomal inheritance, except for one rare form inherited in autosomal dominant fashion. Remarkably, most of the affected proteins functionally cooperate in a molecular pathway involved in genome damage repair. The phenotypic presentation of these subgroups, referred to as complementation groups, show considerable overlap, although some groups seem to follow a more severe and rapidly progressive course. Historically, radii and thenar abnormalities, microcephaly, as well as short stature have been considered characteristic physical findings, prompting a diagnostic work up. However, more recent studies of presymptomatic siblings and routine screening for excessive chromosomal breakage of children with any form of marrow failure reveal that over one third of patients ultimately diagnosed with FA do not have obvious findings on physical exam. Therefore, specific screening for chromosome breakage must be considered in any child with marrow failure, whether single or multilineage. FA is a multi-system disorder and many patients suffer from endocrine dysfunction with thyroid and growth hormone imbalance, glucose homeostasis, and reproductive function. Patients should be followed at routine intervals.

Bone marrow failure in FA is characteristically progressive and slow. Children commonly present with symptoms of cytopenias and are often followed for years before definitive intervention. Guidelines for transfusion and infection apply as in any form of aplastic anemia. Temporary responses to androgenic steroids and use of granulocyte colony stimulating factor have been described. The only curative treatment remains transplantation of hematopoietic stem cells from and unaffected HLA matched individual, preferably a matched family member who has tested negative for FA. However, caution must be exercised in selecting conditioning regimens, as patients will suffer excessive mucosal toxicities from chemotherapeutic regimen and especially higher doses of radiation used in AA. Low doses of cyclopshophamide combined with ATG produce rapid and reliable engraftment of unmanipulated marrow grafts. An alternative approach intended to reduce rates of GVHD has been to deplete the graft of T-cells. Especially in the unrelated donor setting, where

graft failure, frequently severe GVHD, and invasive infections compromise outcomes, this can be of benefit. The risk of FA patients developing myelodysplasia or leukemia is several hundred folds in excess of those in the general population. While the successful replacement of blood and immune system in FA presents a cure for the bone marrow manifestations of the disease, other organ systems remain at risk. Most notably, the risk for epithelial cancers of the head/neck region and the female genital tract is high. As follows from observations on conditioning regimen toxicity, selecting chemotherapeutic agents, or radiation doses, effective at eradicating cancer cells, while limiting toxicity is a challenge that applies to treatment of any cancer in children with FA. Early detection is of key importance and screening for head-neck and gynecological cancers are recommended where available. The lifespan for children with FA has greatly improved with an improved understanding of disease biology, supportive care, and advances in modifying conventional treatment regimens. However, genetic counseling remains important.

Dyskeratosis Congenita (DC, OMIM: 127550)

Children with congenital dyskeratosis show characteristic reticular skin changes, dysplastic nails, oral leukoplakia, and progressive bone marrow failure. Presentation and severity are heterogeneous and can vary among individuals within affected families. Longitudinal studies reveal an increased risk of solid tumors, MDS, leukemias, and pulmonary fibrosis. Classic dyskeratosis is thought to be a severe form in a spectrum of disorders of telomere biology. Rare forms of DC can present with significant neurologic and cognitive dysfunction. Most patients come to medical attention with macrocytic anemia. Evaluation of bone marrow and peripheral blood smear in conjunction with clinical findings is the key to establishing the diagnosis. More recently the diagnosis of shortened telomeres in multiple leukocyte subsets has been proposed as a sensitive and specific assay, though limited in availability. This test can be useful for screening children fulfilling clinical criteria. Subsequent mutation sequencing can be confirmatory for patients and helpful for family carrier screening. Depending on which genes harbor mutations, inheritance mode can be autosomal dominant, recessive (*TERC, TERT, TINF, NHP2 NOP10*) or even x-linked (*DKC1*). Treatment is symptomatic as in other BMF syndromes, relying on transfusion support and aggressive treatment of infections. Androgens, growth factors, erythropoietin, and G-CSF have been used with variable success, but the risk of complications including virilization and rare reports of splenic rupture, respectively, should be carefully weighed. In patients with symptomatic bone marrow failure who have an available HLA matched and non-affected sibling donor, transplantation of hematopoietic stem cells is the recommended treatment. Pulmonary and hepatic cirrhosis can complicate transplantation suggesting that non-myeloablative conditioning strategies result in improved long-term outcomes.

Shwachman–Diamond Syndrome (SDS, OMIM 260400)

The combination of exocrine pancreatic insufficiency, marrow failure and metaphyseal dysostoses comprise the principal findings in Shwachman–Diamond Syndrome. The overwhelming majority of cases reflect mutations in the Shwachman–Bodian–Diamond gene on chromosome 7. The gene product has prominent functions in mitotic spindle formation and ribosome biogenesis. Patients most commonly present with chronic or intermittent neutropenia, but other cell lines are also frequently affected, reflecting the underlying quantitative and qualitative stem cell abnormalities. Additionally, immune function can be abnormal in SDS patients with variable cellular defects of neutrophil polarization and migration, B, T, and NK cell number. Like patients with other bone marrow failure syndromes, SDS patients are at greatly increased risk for developing MDS and myeloid leukemia. These often go hand in hand with cytogenetic abnormalities, such as loss of chromosome 7. Notwithstanding, cytogenetic abnormalities also occur without over signs of dysplasia and can wax and wane, putting their clinical significance in question. Compromised exocrine pancreatic function results in steatorrhea and reduced absorption of fat-soluble vitamins. Failure to thrive and growth failure are frequent presenting signs. Imaging studies will reveal a small pancreas. Liver abnormalities are also common. Pathologic correlates in liver and pancreas are fatty replacements. Remarkably, symptoms may vary over time with many patients recovering sufficient pancreatic function in later years. Specific testing for fecal elastase or serum pancreatic trypsinogen with a negative sweat chloride test to exclude cystic fibrosis will help establish the diagnosis. Metaphyseal dysostosis of the long bones are found in roughly half the patients, although they are frequently asymptomatic. Rarely, rib cage anomalies can result in respiratory compromise. Structural cardiac anomalies have been described in several patients and cardiovascular complications can manifest after high dose therapy in the context of transplantation.

Treatment is predominantly symptom based and should include supplemental vitamins, antibiotics to treat infections, and transfusions when needed. Routine follow up by hematologist, gastroenterologist, endocrinologist, and genetic counselor are recommended. Stem cell transplantation can be curative for hematological manifestations and has been performed successfully using matched related and non-affected, as well as unrelated donors. Different conditioning strategies have been used depending in part on donor availability and whether patients progressed to MDS and AML. The ideal timing in patients with asymptomatic cytopenias is a matter of discussion and institutional preference.

Reticular Dysgenesis (OMIM 267500)

This is a severe form of inherited immunodeficiency and an exceedingly rare disorder of leukocyte and immune function manifesting in infancy. Patients will present with agranulocytosis, lymphopenia, thymic hypoplasia and absent immune function. Recent evidence suggests that a defect in mitochondrial metabolism may be causative. Overwhelming infections are frequent causes of death, but stem cell transplantation is potentially curative.

Congenital Amegakaryocytic Thrombocytopenia (CAMT, OMIM: 604498)

CAMT is a hypomegakaryocytopenic thrombocytopenia commonly diagnosed during infancy with an inherent propensity to progress to AA. Thrombocytopenia in these patients can be severe, with potentially life-threatening bleeding requiring transfusion of platelets. Additional congenital anomalies can be seen, mostly involving heart, kidney, or neuromotor function. The differential diagnosis should include TAR (below) and the Wiskott–Aldrich Syndrome as well as neonatal alloimmune thrombocytopenia. The diagnosis is often established on clinical grounds with bone marrow confirmation and where available genetic testing. The molecular defect rests on mutations in the thrombopoietin (TPO) receptor, c-MPL, coinciding with high levels of the cytokine in patients. The role of TPO in stem cell pool maintenance and differentiation is consistent with the frequent evolution to AA in patients. Cytokine and steroid treatment can have transient benefit, but transfusion is the main therapeutic recourse to treat symptoms. The definitive treatment and only known cure is the transplantation of stem cells from unaffected HLA matched donors. It is unclear if patients with CAMT suffer an increased risk of malignancy.

Pure Red Cell Aplasia

Diamond Blackfan Anemia (DBA, OMIM;105650)

DBA is the principal cause of inherited erythroid specific bone marrow failure. Care should be taken to distinguish it from acquired causes of red cell aplasia, namely Pearson Syndrome; transient erythroblastopenia of childhood (TEC); and secondary immune or malignancy associated forms. The incidence in the population is 5–7 cases per million without gender or ethnic predilection. DBA is inherited in autosomal dominant mode in 45%, but de novo mutations are frequent. More than 90% of patients are diagnosed within the first year of life based on anemia, either related to symptoms or in the work up of the cephalic, thumb, cardiac or urogenital malformations seen in up to 50% of DBA patients. Short stature is diagnosed in 30%. At the extremes of the spectrum, some carriers are clinically silent while other patients present with nonclassical DBA picture indistinguishable from AA. There is no significant correlation between patient presentation, disease severity, clinical response to treatment and genotype. A macrocytic normochromic anemia with reticulocytopenia is found most often in the context of a normal bone marrow cellularity with dramatically reduced (<5%) erythroid precursors resulting from increased apoptosis in the erythroid precursors. In distinction to TEC, the anemia tends to be macrocytic and red cell adenosine deaminase (ADA) is elevated in 85% of individuals. Haploinsufficiency in one of at least seven responsible genes identified to date results in ribosomal dysfunction. But, while mutation sequencing in patients can therefore be useful, where available, for confirmation, family or prenatal screening, these genes account for only 43% of DBA patients. Erythropoietic failure in DBA is characteristically responsive to steroids, the mainstay of treatment. Up to 80% of patients respond to steroids, with about half each experiencing sustained responses and drug-dependent erythropoiesis versus relapse to transfusion dependence, respectively. Up to 20% will remit over time. However, related to potentially severe and debilitating effects steroids can have on immune function, neuromotor and musculoskeletal development, many practitioners favor transfusion for infants. In general, hemoglobin levels between 8 and 9 g/dl permit

musculoskeletal growth without undue suppression of hematopoiesis and excessive transfusional iron loading. Surveillance bone densitometry measurements may be indicated where available to detect developing osteoporosis early. As in cases of multilineage bone marrow failure, or hemoglobinopathies, the only curative treatment for DBA is transplantation. The indication for transplantation is often predicated on development of side effects of steroids treatment and transfusion associated iron overload. Outcomes for patients less than 10 years of age with available HLA matched sibling donors is up to 90% survival, while results in older patients and following unrelated donor transplantation are significantly worse. Anecdotal reports indicate occasional response to cyclosporine, metoclopramide and leucine in steroid resistant patients. Finally, it must be noted that patients with DBA, as with other BMF syndromes suffer an excessive risk for cancer at a generally earlier onset than the general population. Reports show predominant leukemia, MDS, lymphoma, and sporadic breast cancer or melanoma.

Transient Erythroblastopenia of Childhood (TEC)

Often the principal competing diagnostic consideration, TEC is an acquired, self-limiting disorder of erythropoiesis in children 1–4 years old and rarely in infants younger than 6 months. A normochromic and normocytic anemia with reticulocytopenia can last up to several months. A bone marrow evaluation is usually not indicated, only revealing erythroblastopenia while mostly normal red cell ADA levels are potentially useful in distinguishing DBA in the acute setting. A viral etiology has been suggested and there may be overlap with herpes, or parvovirus B19 infections. Close follow up and supportive care including transfusions for symptomatic patients may be required. The prognosis for complete recovery is excellent and treatment is not usually indicated, although empiric use of IVIG has been proposed for persistence.

Congenital Dyserythropoetic Anemia (CDA, type I–III)

CDA comprises a group of rare inherited disorders defined by ineffective erythropoiesis. CDA I (OMIM: 224120) presents with congenital macrocytic anemia and occasionally intrauterine hydrops. Infants tend to show signs of hepatomegaly and jaundice. However, some patients are not diagnosed until well into child and even adulthood. A moderate anemia is lifelong with jaundice and splenomegaly that may be delayed in onset. Additionally, some patients come to attention with dyskeratotic skin pigment changes and limb anomalies, specifically syndactily and metatarsal bone duplication. Autosomal recessive inheritance based on mutations in *CDAN1* has been reported in Bedouin populations. CDA is diagnosed based on evidence of ineffective erythropoiesis with high reticulocyte counts and low serum haptoglobin. Elevated indirect bilirubin is evidence of intramedullary and extramedullary hemolysis. The bone marrow exam shows characteristic erythroid hyperplasia with double nucleated erythroblasts and prominent ultrastructural abnormalities. Chromatin bridging occurs in over 50% and occasionally increased non-ringed sideroblasts and peripheral elliptocytosis are seen. It is important to exclude megaloblastic anemias, MDS, and myeloid leukemia, subtype M6. The administration of interferon alpha 2a can increase hemoglobin values.

Hemochromatosis is a frequent long-term complication, secondary to transfusion and increased intestinal absorptions. Patients requiring transfusions need to be monitored for iron load and end organ functions. Surveillance evaluation of hemoglobin, bilirubin, and ferritin is recommended. Similarly, where available, gall bladder ultrasound to evaluate for cholelithiasis and T2 MRI to determine cardiac as well as hepatic iron load is helpful. Chelation therapy may be indicated.

CDA type II (OMIM: 224100) is a more frequent and potentially more severe anemia characteristically associated with expression of an antigen that reacts with a naturally occurring cold reacting IgM antibody and abnormal glycoprotein band 3. Bone marrow evaluation shows multinuclearity in $>$50% of erythroblasts. Splenectomy has been found to be helpful in reducing bilirubin and improve anemia. Those benefits are sustained, but do not alter iron absorption. Malformations are less common.

CDA type III (OMIM: 105600) is a very rare form running a mild course with autosomal dominant inheritance. Diagnostically, it is distinguished by giant multinucleated erythroblasts and occasional monoclonal gammopathy.

Thrombocytopenia with Absent Radii (TAR, OMIM: 274000)

The characteristic association of an absent radial bone and isolated thrombocytopenia makes this rare syndrome straightforward to diagnose. The majority of patients are diagnosed with associated bleeding during the neonatal

period and many have additional orthopedic anomalies of other long bones. Bleeding can be severe, frequently gastrointestinal and occasionally intracranial. Thrombocytopenia typically resolves with time, but transfusions may be required. Not all patients recover normal platelet counts and resolution often takes until school age. No specific genetic test is indicated and a bone marrow is not required. The inheritance pattern is unknown.

Neutropenia Syndromes

Bone marrow failure with predominant neutropenia, including *ELANE* related congenital and cyclic neutropenia, is discussed elsewhere in this book.

Unclassified Bone Marrow Dysfunction

Not all bone marrow failure syndromes can be classified. This often causes considerable anguish and uncertainty among patients, parents, and practitioners. While symptomatic treatment is unaffected and should follow the standard of care for transfusions and in treating infections, clinical judgment has to be exercised to determine appropriate surveillance of blood counts and bone marrow status. As research into bone marrow failure has seen a recent resurgence, new genetic abnormalities and testing will become available.

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334 Developmental Hemostasis

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The Hemostatic System in the Neonate

In neonates, the coagulation system is dynamic and its development continues after birth. This phenomenon is more evident in premature neonates. *Figure 334.1* shows the prenatal development of components of the hemostatic system. Establishing reference ranges is complicated, as multiple reference ranges are needed, blood samples are difficult to obtain, and the amount of blood obtained is limited. In addition, more subjects are needed because of greater variability. Therefore, interpretation of coagulation test results in infants should take into account the age-dependent normal values.

Overall, in newborns, there is enhanced primary hemostasis, but decreased thrombin generation; in turn, there is reduced ability for anticoagulation and a hypofibrinolytic state. In the healthy newborn, all of these factors balance out and, therefore, do not lead to increased bleeding or thrombosis. In sick and preterm neonates, there are many acquired disturbances that can predispose to either bleeding or thrombosis.

Primary Hemostasis

Platelets can be found in the peripheral circulation at 11 weeks of gestation and have generally reached adult levels by 18 weeks of gestation (*Fig. 334.1*). Platelet function in neonates is slightly different than that seen in adults, with most studies indicating decreased responsiveness to the agonists ADP, collagen, epinephrine, and thrombin. Ristocetin-induced platelet aggregation is increased, likely secondary to higher von Willebrand factor levels in the neonate. Activation of platelets may occur in the neonate during childbirth. Neonates are not, however, at high risk of bleeding from platelet dysfunction despite these physiologic changes.

Coagulation

Neonates have overall decreased thrombin generation. Levels of the vitamin K–dependent factors (II, VII, IX, and X) and factor XI are significantly decreased compared to values in adults; the levels of fibrinogen and factors V and VIII are similar to adult values (*Table 334.1*). In healthy neonates, the prothrombin time (PT) is prolonged up to 2s above the adult reference ranges, while the activated partial thromboplastin time (aPTT) is $\geq$20 s or more above adult values. Von Willebrand factor is increased and ultra large molecular weight multimers are present at birth, which may explain the shorter bleeding time. Progressive maturation of the coagulation system occurs unless a coincident problem is present, with adult levels achieved by 6 months of age for some clotting factors but not until adolescence for others. Premature neonates are somewhat more likely than term neonates to have achieved adult levels by age 6 months. In otherwise well infants, the decreased coagulant factor levels are not associated with clinical bleeding.

Anticoagulation and Fibrinolysis

Both anticoagulation and fibrinolysis are thought to be downregulated in newborns. Plasma concentrations of naturally occurring anticoagulant proteins (antithrombin, protein C, and protein S) are significantly lower at birth than during later childhood and adulthood. Plasminogen and plasmin generation are reduced and plasmin inhibitors are increased. These observed decreases in anticoagulant and fibrinolytic factors usually do not cause thrombosis in otherwise healthy newborns. Being a sick neonate is a known risk factor for thrombosis, but the contribution of these decreased levels to this risk is unknown. All these differences need to be taken into account when interpreting lab values and managing anticoagulation in neonates.

Hemorrhagic Disorders in the Neonate

Most hemorrhagic disorders in the neonate are acquired. Thrombocytopenia likely contributes to most of these, but often coexists with other coagulation disturbances. Several inherited coagulation problems can also manifest in this age group.

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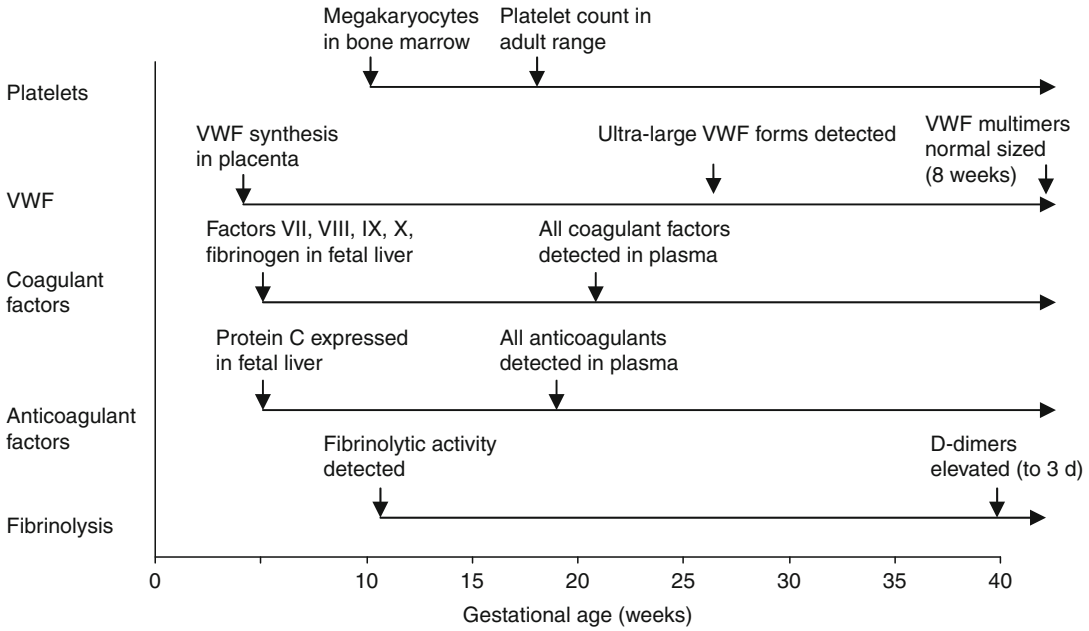

Adapted frpm Manco-Johnson, 2005 and Cantor, 2009
VWF, von Willebrand factor

Figure 334.1
Fetal development of the hemostatic system. *VWF* von Willebrand factor (Cited from Manco-Johnson MJ (2005) Development of hemostasis in the fetus. Thromb Res 115:55–63; Cantor A (2009) Developmental hemostasis: Relevance to newborns and infants. In: Orkin SA, Fisher DE, Look AT, Lux SE, Ginsburg D, Nathan DG (eds) Nathan and Oski's hematology of infancy and childhood. Saunders Elsevier, Philadelphia)

Evaluation of the Bleeding Neonate

The most important consideration in the initial evaluation of the bleeding neonate is the clinical setting in which the bleeding occurs. Bleeding in an otherwise healthy neonate is more suggestive of an inherited coagulation disorder or immune-mediated thrombocytopenia. In a sick or premature neonate, abnormal bleeding is usually from acquired causes and often is multifactorial, including medications. Sepsis or surgery can cause a consumptive coagulopathy or disseminated intravascular coagulation (DIC). Protein loss (from chest or peritoneal drainage) can involve coagulation factors, but this is usually balanced by loss of anticoagulant factors as well. Maternal factors, including drugs (anticoagulants, antiepileptics, and antituberculosis drugs) and illness (preeclampsia) should always be considered. Complications during delivery can cause activation of the coagulation system and DIC. As discussed below, vitamin K deficiency may cause significant bleeding in the neonatal period. Finally, family history should be investigated, although not all affected infants will have a family history of bleeding disorders.

The bleeding manifestation is another very important consideration, especially in the presentation of an inherited bleeding disorder. Congenital coagulation disorders may present with oozing from the umbilical cord stump, scalp bleeding, cephalohematomas, bleeding from IV puncture sites, bleeding with circumcision, mucocutaneous bleeding, and bleeding with invasive procedures (*Table 334.2*). Sometimes, anemia may be the only manifestation of increased bleeding, so for unexplained anemia a source of bleeding should always be sought. Although not uncommon in premature infants, intracranial hemorrhage (ICH) in a term or late preterm infant without significant trauma should prompt an investigation for a bleeding disorder. In 349 newborns with hemophilia, bleeding consisted of ICH, more commonly subdural (27%) and increased bleeding with circumcision (30%) and heel stick (16%).

Laboratory Testing in Neonates

In the laboratory evaluation of a neonate with abnormal bleeding, it is important to consider sampling problems.

Table 334.1

Reference values for coagulation tests in healthy infants [mean (range of 95% of the population)][a]

Test or level	30–36 Weeks gestation infant	Term infant	1 Month–1 year	Children 1–5 years	Adults
Screening tests					
PT (s)	13 (10.6–16.2)	15.6 (14.4–16.4)	13.1 (12.1–14.6)	13.3 (12.1–14.5)	13 (11.5–14.5)
aPTT (s)	53.6 (27.5–79.4)	38.7 (34.3–44.8)	39.3 (35.1–46.3)	37.7 (33.6–43.8)	33.2 (28.6–38.2)
Platelet function screen					
Collagen/epinephrine closure time (s)		81 (61–108)		109 (92–126)	106 (82–142)
Collagen/ADP closure time (s)		56 (48–65)		89 (69–109)	85 (67–111)
Bleeding time (min)	3.4 (1.7–5.2)	1.8 (1.2–2.4)		6 (2.5–10)	4 (1–7)
Coagulant factors					
Fibrinogen (g/L)	243 (150–373)	2.8 (1.92–3.74)	2.42 (0.82–3.83)	2.82 (1.62–4.01)	3.1 (1.9–4.3)
Factor II (%)	45 (20–77)	54 (41–69)	90 (62–103)	89 (70–109)	110 (78–138)
Factor V (%)	88 (41–144)	81 (64–103)	113 (94–141)	97 (67–127)	118 (78–152)
Factor VII (%)	67 (21–113)	70 (52–88)	128 (83–160)	111 (72–150)	129 (61–199)
Factor VIII (%)	111 (50–213)	182 (105–329)	94 (54–145)	110 (36–185)	160 (52–290)
Factor IX (%)	35 (19–65)	48 (35–56)	71 (43–121)	85 (44–127)	130 (59–254)
Factor X (%)	41 (11–71)	55 (46–67)	95 (77–122)	98 (72–125)	124 (96–171)
Factor XI (%)	30 (8–52)	30 (7–41)	89 (62–125)	113 (65–162)	112 (67–196)
Factor XII (%)	38 (10–66)	58 (43–80)	79 (20–132)	85 (36–136)	115 (35–207)
VWF (%)	136 (78–210)	153 (86–220)	107 (62–152)		92 (59–125)
Anticoagulants and fibrinolytics					
Antithrombin (%)	38 (14–62)	76 (58–90)	109 (72–134)	116 (101–131)	96 (66–124)
Protein C (%)	28 (12–44)	32 (24–40)	77 (28–124)	94 (50–134)	103 (54–166)
Protein S (%)	26 (14–38)	36 (28–47)	102 (29–162)	101 (67–136)	75 (54–103)
Plasminogen (U/mL)	1.7 (1.12–2.48)	1.95 (1.25–2.65)	3.01 (2.21–3.01)[b]		3.36 (2.84–4.24)
tPA (ng/mL)	8.48 (3–16.7)	9.6 (5–18.9)	2.8 (1–6.0)[b]		4.9 (1.4–8.4)
α_2AP (U/mL)	0.78 (0.4–1.16)	0.85 (0.55–1.15)	1.11 (0.83–1.39)[b]		1.02 (0.63–1.35)
PAI (U/mL)	5.4 (0–12.2)	6.4 (2–15.1)	8.1 (6–13)[b]		3.6 (0–11)

PT prothrombin time, *aPTT* activated partial thromboplastin time, *VWF* von Willebrand factor, *tPA* tissue plasminogen activator, α_2*AP* α_2 antiplasmin-1, *PAI* plasminogen activator inhibitor

[a]Adapted from Monagle P, Barnes C, Ignjatovic V, Furmedge J, Newall F, Chan A, De Rosa L, Hamilton S, Ragg P, Robinson S, Auldist A, Crock C, Roy N, Rowlands S (2006) Developmental haemostasis. impact for clinical haemostasis laboratories. Thromb Haemost 95:362–372; Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P (1987) Development of the human coagulation system in the full-term infant. Blood 70:165– 172; Carcao MD, Blanchette VS, Dean JA, He L, Kern MA, Stain AM, Sparling CR, Stephens D, Ryan G, Freedman J, Rand ML (1998) The platelet function analyzer (PFA-100): A novel in-vitro system for evaluation of primary haemostasis in children. Br J Haematol 101:70–73; Lippi G, Manzato F, Franchini M, Brocco G, Florenziani G, Guidi G (2001) Establishment of reference values for the PFA-100 platelet function analyzer in pediatrics. Clin Exp Med 1:69–70; Del Vecchio A, Latini G, Henry E, Christensen RD (2008) Template bleeding times of 240 neonates born at 24 to 41 weeks gestation. J Perinatol 28:427–431

[b]Value at 180 days

In newborns, there is often a volume limit to the amount of blood that can be collected, so the appropriate tubes that will yield the correct anticoagulant-to-blood sample ratio should be used. This is particularly important in neonates with polycythemia, which can cause spurious prolongation of the PT and aPTT. Activation of coagulation of the blood sample may occur more often in neonates because of the often difficult blood draws. Sample contamination, for instance, with heparin from central line sites of blood draw, may be more common in neonates

Table 334.2
Clinical presentation and treatment of rare congenital coagulation disorders

Factor deficiency	Clinical presentation	Treatment
Fibrinogen[a]	Umbilical stump bleeding, circumcision bleeding, soft tissue bleeding; infrequent ICH	Cryoprecipitate, FFP, fibrinogen concentrate
Factor II	Mucosal bleeding; surgical or trauma bleeding; rare joint bleed, ICH	FFP, PCC Aminocaproic acid
Factor V	Factor level does not predict severity of bleed, but homozygotes usually have spontaneous bleeding; mucous membrane bleed; ICH, subdural bleed; umbilical stump bleed; GI bleed; surgery/trauma bleed	FFP rFVIIa, FEIBA, platelets for those with inhibitors
Factor VII[a]	ICH, GI bleeding, soft tissue bleeding in very young; epistaxis, bruising, gum bleeding, postoperative bleeding; menorrhagia	rFVIIa PCC, FFP
Factor X[a]	ICH, umbilical stump bleed, GI bleed, bleed from needle punctures; menorrhagia, easy bruising, epistaxis, hematoma, hemarthrosis	PCC, FFP Factor X concentrate (Switzerland)
Factor XI	Circumcision bleeding, subdural hemorrhage; surgical (especially mucosal surgery) bleeding	FFP Factor XI concentrate
Factor XIII[a]	Umbilical stump bleed (80%); ICH (20–25%); delayed wound healing, abnormal scar, mucosal bleed, recurrent soft tissue bleed	Cryoprecipitate, FFP Factor XIII concentrate
Alpha2 antiplasmin-1	Umbilical stump bleed	Tranexamic acid Aminocaproic acid (no data in neonates)

Source: Modified from Saxonhouse MA, Manco-Johnson MJ (2009) The evaluation and management of neonatal coagulation disorders. Semin Perinatol 33:52–65
ICH intracranial hemorrhage, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate
[a]Disorders most likely to present in the neonatal period

because of the smaller blood volumes. As above, age-appropriate reference ranges should always be used when interpreting results (*Table 334.1*). However, even those values should be interpreted with care, as there can be overlap of the abnormal and normal values. A striking example of this is the values for aPTT, which can be physiologically prolonged in neonates, but may be "normal" in the presence of hemophilia.

Evaluation of hemostasis in neonates is similar to that performed in older children. A complete blood count is essential to determine platelet number. Review of the peripheral blood smear is useful to evaluate platelet size and granularity. PT and aPTT provide a general screen of clotting factors. Fibrinogen levels may also be useful to detect consumption or decreased fibrinogen production. The platelet function analyzer (PFA), although intended to provide an assessment of platelet function, has suboptimal sensitivity and specificity for diagnosis of both von Willebrand disease and platelet function defects. Some studies have shown shorter PFA closure times in term infants, but no data exists for premature infants and a normal range is not well established for neonates. Platelet aggregation studies will demonstrate platelet function, but the amount of blood required and need for a specialty laboratory restrict the general application of this test. *Table 334.3* details the laboratory studies useful in workup of neonatal hemostasis.

Congenital Deficiency of Coagulant Factors

The most common congenital disorders of coagulation are deficiencies of factors VIII and IX (hemophilia A and B, respectively). These, along with congenital disorders of primary hemostasis (von Willebrand disease, platelet function defects), are discussed in a previous chapter.

Clinically significant congenital deficiencies of fibrinogen, prothrombin, and factors V, combined V/VIII, VII, X, XI, and XIII, combined vitamin K–dependent factors (prothrombin and factors VII, IX, X), and the contact

Table 334.3
Evaluation of neonatal hemostasis

Screening tests	Diagnostic tests
CBC	Factor VIII
PT	Factor IX
aPTT	Factor XIII
Fibrinogen	Von Willebrand factor (antigen, activity)
d-Dimer	Platelet glycoprotein expression
Platelet function analysis	Platelet aggregation

factors are rare and usually inherited as autosomal-recessive traits. Those most likely to present in the neonatal period include deficiencies of factors VII, X, and XIII, and deficiency or dysfunction of fibrinogen (*Table 334.2*). Of note, recent studies show that deficiencies in factor XII, prekallikrein, and high-molecular-weight kininogen may prolong the aPTT but do not cause abnormal bleeding. Patients with congenital coagulant factor deficiencies are usually treated episodically for acute bleeding or surgery. The mainstay of treatment is coagulation factor replacement. Generally, neonates with single-factor deficiencies are treated with either recombinant or plasma-derived concentrates for the specific factor whenever available, which allows the administration of adequate and precise doses in relatively small volumes. These products have also been treated to minimize the risk of viral disease transmission. Recombinant factor VIIa (rFVIIa) is used both as bypassing agent in the treatment of hemophilia with inhibitors and replacement therapy for bleeding or surgery for patients with factor VII deficiency. Cryoprecipitated antihemophilic factor is used as a source most frequently of fibrinogen and rarely of factor XIII. However, purified factor XIII concentrate and a virus-inactivated fibrinogen concentrate are available. A factor XI concentrate is available in Europe. Prothrombin complex concentrates or plasma may be used for the treatment and prophylaxis of bleeding in patients with deficiency of prothrombin, factor VII and X, and the vitamin K–dependent factors. There is no factor V concentrate available.

Acquired Coagulant Factor Deficiency

Common acquired disorders include liver disease, DIC, and hemorrhagic disease of the newborn.

Liver Disease in the Neonate

Liver disease in neonates may lead to disorders of coagulation. Since the liver is the site of synthesis for the majority of coagulation factors, hepatic dysfunction will lead to a decrease in procoagulant factors as well as some anticoagulant factors. The PT and PTT will be prolonged, and fibrinogen should be low. Bleeding, particularly mucosal bleeding, is common. Treatment consists of coagulation factor replacement via plasma infusions and cryoprecipitate. Fresh frozen plasma at a dose of 10–20 mL/kg should increase clotting factors by approximately 1% per mL given per kilogram of body weight. Evaluation and treatment for the underlying cause of liver disease will be required.

Disseminated Intravascular Coagulation

Prolonged PT and PTT may also represent consumption of coagulation factors due to DIC. Sepsis is the most common cause in neonates, particularly those in intensive care units. Infants with DIC may present with either bleeding or thrombosis. Congenital protein C or protein S deficiency should be suspected in the setting of purpura fulminans, although infection may also cause this presentation. D-dimers are usually elevated in DIC, but these elevations are usually non-specific. Treatment is aimed at eradicating the underlying cause. Administration of plasma, cryoprecipitate, or platelets may be required, but should be reserved for those infants who are actually symptomatic. Heparin anticoagulation in DIC is occasionally used in patients with evidence of thrombosis, but there is a paucity of evidence to support its effectiveness.

Previously, treatment of patients with coagulopathy due to synthetic or consumptive processes was restricted to replacement with fresh frozen plasma to replete all coagulation factors, and/or cryoprecipitate to replete fibrinogen, factor VIII, and von Willebrand factor. Recently, rFVIIa has become available and has been widely used in this setting, although it is not generally recommended due to the potential risk of thrombosis.

Hemorrhagic Disease of the Newborn

Vitamin K is a cofactor in γ-carboxylation of procoagulant factors II, VII, IX, and X, as well as anticoagulant factors such as protein C and S. Vitamin K levels are decreased in the newborn as compared to adults. Therefore, those

clotting factors that depend on vitamin K–mediated posttranslational modification will be decreased in the newborn period. Deficiency of vitamin K leads to a relative decrease in procoagulant factors, which may lead to clinically significant bleeding. Such bleeding, originally termed hemorrhagic disease of the newborn, is now referred to as vitamin K–dependent bleeding, or VKDB.

Early VKDB presents within the first day of life with severe bleeding, often intracranial hemorrhage or GI bleeds. Early VKDB may be due to maternal medications such as anticonvulsants leading to chronically low vitamin K levels throughout pregnancy. Classic VKDB presents in the first week of life in infants with inadequate intake. The incidence is approximately 1 in 10,000 births without prophylaxis. Late VKDB presents within 6 months of birth in breast-fed infants or infants with malabsorption disorders such as cystic fibrosis or celiac disease. Usual sites of bleeding include the skin and GI tract, although intracranial hemorrhage is unfortunately not an uncommon presenting feature.

Supplementation with vitamin K is recommended for newborn infants to increase levels of the vitamin K–dependent proteins and prevent bleeding in the neonatal period. A great deal of debate has occurred regarding the relative merits of IM versus oral vitamin K, particularly due to the concern for an increased risk of leukemia which had been reported in an earlier British study. Subsequent studies, however, have failed to show a link between IM vitamin K and cancer. Some countries, however, recommend the use of oral vitamin K preferentially. If vitamin K is administered orally, it is important to recognize that multiple doses are required to prevent late VKDB. IM vitamin K at a dose of 0.5–1 mg is recommended for all neonates. In the event that an oral regimen is chosen, typical dosing is 1–2 mg on day of life 1, then again around 1 week and around 4 weeks of age. Alternate regimens prescribe 2 mg of oral vitamin K weekly until the infant is 3 months of age.

Diagnosis of VKDB is made on the basis of a prolonged PT and prolonged PTT, with a greater prolongation in the PT as compared to the PTT. Vitamin K–dependent clotting factors will be low, with normal levels of nonvitamin K–dependent clotting factors such as factor V and factor VIII. Treatment should not wait for confirmation of the diagnosis, but rather vitamin K should be administered as soon as the diagnosis is suspected. If severe bleeding, such as intracranial hemorrhage or GI bleeding, is present, emergent treatment may be required. Fresh frozen plasma is usually readily available, but other treatment options include prothrombin complex concentrates or rFVIIa.

Neonatal Thrombocytopenia and Other Platelet Defects

Quantitative platelet disorders in neonates may be due to decreased production or increased destruction (*Table 334.4*). Decreased production is typically secondary to inherited platelet disorders. Congenital amegakaryocytic thrombocytopenia, a disorder where megakaryocytes are absent or significantly reduced, presents with petechiae or bruising. Thrombocytopenia-absent radii (TAR) syndrome is, as the name implies,

Table 334.4
Differential diagnosis of neonatal thrombocytopenia

Immune-mediated	Inherited quantitative defects	Qualitative defects	Acquired thrombocytopenias
Neonatal alloimmune thrombocytopenia	Congenital amegakaryocytic thrombocytopenia	Drugs: aspirin, indomethacin	Sepsis
Maternal ITP	TAR syndrome	Diet	DIC
Neonatal ITP	Wiskott–Aldrich syndrome	Maternal alcohol use	Necrotizing enterocolitis
Drug-dependent antibodies	Jacobsen syndrome	Maternal tobacco use	Kasabach–Merritt syndrome
	X-linked macrothrombocytopenia	Maternal diabetes	Perinatal asphyxiation
	Bernard–Soulier syndrome	Nitric oxide	
	Velocardiofacial syndrome	ECMO	
	MYH-9 disorders		

ITP immune-mediated thrombocytopenic purpura, *ECMO* extracorporeal membrane oxygenation

a syndrome where thrombocytopenia is associated with skeletal abnormalities including radial hypoplasia. The diagnosis is generally not difficult due to the characteristic limb appearance. Wiskott–Aldrich syndrome is an X-linked thrombocytopenia which also manifests with eczema and immune deficiency. Platelets are characteristically small. Neonates may present with bloody diarrhea, but infection due to the immune deficiency is also a serious risk.

There are several disorders that lead to decreased platelet production and large platelets. Jacobsen syndrome, otherwise known as Paris–Trousseau syndrome, involves macrothrombocytopenia as well as mental retardation, facial dysmorphogenesis, and cardiac abnormalities. The defect has been localized to a deletion of part of chromosome 11. X-linked macrothrombocytopenia is due to mutations in GATA-1 and may also present with anemia. Bernard–Soulier syndrome is a defect in glycoprotein (GP) Ib or associated proteins GPIX or GPV. Platelets are large and characterized by defective aggregation in response to ristocetin, which induces VWF binding to platelet GPIb. Platelet aggregation with other agonists, however, is normal in Bernard–Soulier syndrome. Velocardiofacial syndrome, a gene deletion syndrome involving chromosome 22q11.2, may manifest with macrothrombocytopenia similar to that seen in Bernard–Soulier syndrome due to deletion of the GPIbα gene in this region. Macrothrombocytopenia may also be caused by a defect in MYH-9, the myosin heavy chain, which has now been found to be the underlying problem in a number of platelet disorders, including Epstein syndrome, Fechtner syndrome, May–Hegglin anomaly, and Sebastian syndrome.

Qualitative platelet disorders are generally due to medications or other treatments the neonate is receiving. Maternal medications, diet, alcohol, or tobacco use may also induce temporary platelet dysfunction. Maternal diabetes may actually lead to platelet hyperreactivity with increased platelet aggregation, although the clinical significance of this finding is unclear. Aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) lead to platelet dysfunction, either permanently with the use of aspirin or temporarily with the use of other NSAIDs. Indomethacin is frequently used to induce closure of a patent ductus arteriosus in premature infants, and may contribute to qualitative platelet dysfunction in newborns. Nitric oxide also interferes with platelet adhesion by inhibition of platelet aggregation in response to ADP. Extracorporeal membrane oxygenation (ECMO) is associated with bleeding complications, primarily due to the need for anticoagulation and depletion of clotting factors, but is also associated with platelet dysfunction due to chronic activation.

Neonatal Alloimmune Thrombocytopenia

Platelet destruction may occur through immune-mediated or nonimmune mechanisms. The most common cause of immune-mediated thrombocytopenia in neonates is neonatal alloimmune thrombocytopenia (NAIT). NAIT is quite common, with an incidence of around 1:1,000. In NAIT, the father's platelets have an antigen not present on maternal platelets. When the infant inherits this antigen, the mother recognizes it as foreign and makes antibodies, which cross the placenta and lead to thrombocytopenia in the fetus. Thrombocytopenia may be severe. NAIT carries a high risk of intracranial hemorrhage, up to 20% of affected neonates. Diagnosis is made by testing the reactivity of maternal serum against the father's platelets. The most frequent antigen responsible for NAIT is HPA-1a, or PI^{A1}, although other antigens may also cause NAIT. Treatment involves infusion of platelets lacking the causative antigen. Until a suitable donor is found, washed maternal platelets may be used, as these are typically the most readily available. Some blood banks stock HPA-1a negative platelets for use in such cases. While waiting for suitable platelets to become available, random donor platelets may be used, as infants may still respond. In addition, IVIG may be used for NAIT, typically at a dose of 1 g/kg. Head ultrasound is recommended to evaluate any infant at risk of intracranial hemorrhage.

Maternal autoimmune thrombocytopenia may lead to temporary thrombocytopenia in the neonate due to IgG antibodies crossing the placenta in mothers affected with immune-mediated thrombocytopenic purpura (ITP) or systemic lupus erythematosus (SLE). Passive antibodies are more common with true ITP in neonates due to an endogenous antibody, a rare occurrence except in the setting of immune dysfunction. Drug-dependent antibodies may also cause immune-mediated thrombocytopenia less commonly in this age group. Thrombocytopenia due to acquired antibodies will resolve within the first several months of life.

Nonimmune Thrombocytopenia

Destruction may also be nonimmune-mediated. Thrombocytopenia is common in the NICU setting, present in anywhere from 6% to 22% of infants. The most common

cause in sick neonates is sepsis, which commonly presents with thrombocytopenia and may also present with DIC. Both bacterial and viral infections may be the cause. Some infections may also lead to decreased production. Premature infants may also experience thrombocytopenia related to necrotizing enterocolitis, respiratory distress syndrome, and persistent pulmonary hypertension. Perinatal asphyxiation has been associated with thrombocytopenia. Vascular malformations such as Kasabach–Merritt syndrome lead to consumption of platelets (and coagulation factors). Affected infants may present with systemic bleeding due to the severe thrombocytopenia.

Treatment of decreased platelet function or decreased platelet number due to a production defect consists of administration of platelets, generally at a dose of 10–15 mL/kg. Unless there is a treatable underlying cause, platelet support may need to be continued for some time. The precise threshold for transfusion is not entirely clear. Most physicians consider a platelet count less than 50,000 to signify an increased risk of bleeding. A survey of neonatologists showed that most transfused a bleeding neonate with a platelet count of <50,000, but most used a platelet count of <20,000 as the threshold for prophylactic transfusions. Transfusion thresholds of 30,000 as compared to 50,000 in one study did not demonstrate a difference in risk of hemorrhage.

Thrombotic Disorders in the Neonate

Like the neonate, the study of thrombosis in infants and children is rapidly evolving. During childhood, the greatest risk of thromboembolism is in the neonatal period. The greatest incidence reported, from the Canadian childhood thrombosis registry, is 2.4 per 1,000 admissions to the neonatal intensive care unit. As in hemostasis, the delicate balance between coagulation and anticoagulation proteins may be disturbed by a number of acquired conditions, which then can predispose to thromboembolism. Most infants who develop abnormal clots have comorbid conditions that predispose to thrombosis. However, given that not all sick neonates develop clots and that thrombosis sometimes occur in newborns who are otherwise healthy, genetic factors may also play a role. Virchow's triad, the intersection between the vasculature, blood flow, and blood clotting proteins, applies to neonatal thrombosis as well (*Table 334.5*).

Thrombophilia is the term used to describe a range of defects in coagulation, fibrinolysis, endothelial cells, and primary hemostasis that can predispose to thrombosis. Most of these conditions are inherited, but some, like antiphospholipid syndrome, may be acquired (*Table 334.6*). In the neonate, antiphospholipid antibodies are most likely maternal.

Table 334.5
Virchow's triad in the neonate

Abnormal vessel wall	Inflammation
	Intravascular catheters damage endothelium
	Thrombosed chorionic vessels embolize to fetal vessels
	Local thrombi from patent ductus arteriosus
Stasis of blood flow	Large catheters in small veins
	Increased blood viscosity, polycythemia
	Poor deformability of newborn red cells
Altered constituents of blood	Shock/consumption
	Sepsis/inflammation
	Extracorporeal membrane oxygenation (ECMO)
	Congenital disorders

Source: Modified from Thornburg C, Pipe S (2006) Neonatal thromboembolic emergencies. Semin Fetal Neonatal Med 11:198–206

Deficiency of Anticoagulant Proteins

Of the congenital anticoagulant factor deficiencies, homozygous protein C and protein S deficiency are the most clinically significant. Purpura fulminans is characterized by acute onset of microvascular thrombosis followed by perivascular hemorrhage. Although purpura fulminans can be associated with acquired factors (like DIC and meningococcal infections), if it occurs in the newborn period, inherited protein C (and less commonly protein S) deficiency needs to be ruled out. Protein C concentrate (nonactivated) may be used for the management of both acquired and congenital protein C deficiency. A plasma transfusion would be needed to replace protein S.

Also, aside from the physiologically low anticoagulant protein levels in neonates, many acquired conditions can affect these levels. Congenital heart disease, hepatic dysfunction, and nephrotic syndrome have all been associated with decreased anticoagulant protein levels in the plasma. Antithrombin deficiency in the newborn is most commonly acquired, in association with cardiopulmonary bypass or ECMO, which can cause activation of the coagulation system and consumption of coagulant and anticoagulant proteins because of the interaction with the

Table 334.6
Prothrombotic risk factors

Inherited thrombophilia	Acquired conditions
Factor V Leiden mutation	Central venous line
Prothrombin G20210A mutation	Cancer
Hyperhomocysteinemia	Congenital heart disease
Increased lipoprotein (a) levels	Hyperalimentation
Protein C deficiency	Infection
Protein S deficiency	Nephrotic syndrome
Antithrombin deficiency	Liver failure
Dysfibrinogenemia	Antiphospholipid syndrome
Increased fibrinogen, factor VIII (probably inherited)	ECMO
	Polycythemia
	Perinatal complications
	Sepsis

Source: Modified from Thornburg C, Pipe S (2006) Neonatal thromboembolic emergencies. Semin Fetal Neonatal Med 11:198–206; Andrew (1994); deVeber (2001)

biomaterials in the circuit, as well as a systemic inflammatory reaction; this deficiency is usually manifested by difficulty in obtaining therapeutic heparin effect. A purified antithrombin concentrate is available. However, because thrombosis in neonates is likely multifactorial, in the absence of an actual thrombus, it is unclear whether factor replacement would be of benefit in these situations.

Thrombotic Manifestations in the Neonate

Thrombotic manifestations in neonates include ischemic perinatal stroke (IPS), cerebral sinus venous thrombosis (CSVT), venous systemic thrombosis, renal vein thrombosis, portal vein thrombosis, and arterial systemic thrombosis.

The clinical presentation of IPS is often subtle and nonspecific, including seizures, poor feeding, and lethargy. Often diagnosis is delayed until hemiparesis is evident, sometimes months later. The etiology of IPS remains unclear. In a recent meta-analysis, it was found that genetic prothrombotic risk factors significantly contributed to the risk of stroke in children; as other risk factors were also present in many instances, the significance of this is unclear. IPS does not seem to independently increase the risk of recurrent thromboembolic disease. Given that the diagnosis of IPS is frequently delayed, the prognosis generally better than in older children and adults, and the risk of bleeding is high, anticoagulation or aspirin therapy is not generally recommended for neonates with initial IPS unless there is an embolic source.

In the Canadian pediatric stroke registry, the incidence of CSVT was 0.67 per 100,000 children per year, and neonates were the most commonly affected group. Risk factors include head and neck disorders, dehydration, perinatal complications, and bacterial sepsis; of note, prothrombotic disorders were found in 20% of neonates with CSVT. In pediatric CSVT, in contrast to adults, non-anticoagulation resulted in increased thrombus propagation, while anticoagulation (with heparin, low-molecular-weight heparin, or warfarin) did not increase the risk of fatal bleeding or bad outcome, with neonates having the best outcome. Evidence-based practice guidelines for anticoagulation in children recommend, but not strongly, anticoagulation for neonatal CSVT for 6 weeks to 3 months.

The incidence of venous thromboembolism in children varies among registries, but the association with acquired risk factors is consistent with the presence of a central venous line (CVL), the most common association. These thrombi are often asymptomatic or associated only with CVL dysfunction. Other risk factors in neonates include congenital heart disease, sepsis, and hyperalimentation. Despite the risk of thrombosis associated with CVL in children, prophylactic anticoagulation has not been proven effective at prevention.

Renal vein thrombosis (RVT) comprises up to 33–58% of neonatal thrombotic events according to registry data. In a recent meta-analysis, 7% occurred in utero and 67% occurred in the first day of life; most children were born >36 weeks age of gestation (73%). Features at presentation included macroscopic hematuria (55%), thrombocytopenia (47%), and a palpable mass (42%). Associated conditions included perinatal asphyxia (29%), maternal diabetes (8%), and dehydration (1.5%). The thrombus extended into the inferior vena cava in 44%, and there was adrenal hemorrhage in 14%. Fifty-three percent of those tested had at least one thrombophilia. Anticoagulation or thrombolytic therapy does not seem to change the long-term outcome in children with RVT. Evidence-based guidelines recommend observation for unilateral RVT and anticoagulation or fibrinolytic therapy for bilateral RVT, depending on the renal dysfunction.

Portal vein thrombosis (PVT) can be associated with umbilical vein catheterization and omphalitis. Diagnosis is by ultrasound, and it is often found incidentally. Treatment with anticoagulation and catheter removal is usually indicated as portal hypertension can develop over time.

Arterial systemic thrombosis in neonates is usually iatrogenic, associated with catheterization. Spontaneous arterial thrombosis is uncommon in neonates, usually involves the aorta, and can have a mortality rate of up to 33%. For extensive arterial thrombosis, thrombolysis or surgical thrombectomy should be performed; for less extensive thrombosis, anticoagulation may be considered.

Testing for Thrombophilia

Although older guidelines recommend testing for genetic thrombophilia for all neonates with thrombosis, more recent studies have questioned the utility of such testing given that the ability of such testing to improve clinical outcome even in adults is unclear. This lack of evidence is even more apparent in children, such that the effect of thrombophilia on duration of anticoagulation is not addressed in the most recent evidence-based practice guidelines. Clearly, neonates with purpura fulminans and, possibly, those with very extensive unexplained thrombi, should be tested, as replacement therapy may be necessary.

Treatment of Neonatal Thrombosis

Although heparin and low-molecular-weight heparin have been used safely in neonates with thrombosis, efficacy has not been clearly established, except possibly in CSVT. There are no randomized control trials, and current evidence supports anticoagulation for neonates with thrombi only weakly. Consultation with a hematologist is recommended. When needed, low-molecular-weight heparin and heparin are given at higher doses per kilogram body weight than those in adults because of the increased volume of distribution in infants. Initial check of the low-molecular-weight heparin level and periodic monitoring of aPTT and heparin level are recommended.

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335 Bleeding Disorders

Hassan M. Yaish · Eugenia Chang

Familial bleeding disorders affecting males have been described in religious and historical texts for thousands of years. Hemophilia A (classic hemophilia) and B (Christmas Disease) are clinically indistinguishable and discussed together in this chapter. Some of most famous individuals affected with hemophilia have been the descendents of Queen Victoria of England and the Empress of the Indies, including Czar Alexis. The downfall of the Russian aristocracy is partially attributed to the poor health of Czar Alexis and the royal family's dependence upon their physician, Rasputin, for advice. Analysis of Czar Alexis' DNA revealed a substitution in exon 4 of the factor IX gene. Schonlein termed the disease hemophilia in the 1820s. In the early twentieth century, experiments by several investigators determined that the plasma and, more specifically, the "globulin fraction" of blood plasma could correct the clotting defect of the blood of affected patients in vivo and in vitro, leading to identification of coagulation factors VIII and IX in the 1940s and eventually to the characterization and sequencing of factor VIII and IX in the 1980s. Since the 1980s, rapid progress has been made in high purity factor replacement and prophylactic therapy for these populations and has opened the door to the potential for gene therapy.

Classification

The incidence of hemophilia is 1:6,000 live male births with no racial predilection. Eighty to eighty-five percent of patients have factor VIII deficiency (hemophilia A) and 10–15% of patients with factor IX deficiency (hemophilia B), 2–3% with factor XI deficiency (hemophilia C). Severity is determined by the patient's baseline level of factor VIII or IX. factor levels are expressed as % activity, with 1 ml of normal plasma containing 100% activity and expressed as units/dL. In both hemophilia A and B, severe patients have levels of $<1\%$, moderate with levels of 1–5% and mild with levels of $>5\%$. Plasma factor levels correlate with frequency and severity of bleeding episodes.

Diagnosis

Hemophilia is suspected in a bleeding male patient with a prolonged aPTT on screening tests. However, some patients with mild factor VIII and IX deficiencies may have a normal aPTT. A hemophilia patient typically has a normal PT, platelet count, and bleeding time/PFA testing. Mixing studies exclude inhibitors and confirm the presence of a factor deficiency. Definitive diagnosis is based in direct assays of plasma factor VIII and IX activity levels.

The diagnosis of hemophilia is suspected based upon family history in two third of patients. One third of patients have a new mutation. Although severe patients tend to present within the first year of life, mild or moderate patients may not present until after injury or surgery in adulthood. Because inheritance is X-linked, almost all patients are male, with very rare homozygous female patients. Female carriers are variably affected and are more commonly detected by screening and treated as necessary.

Factor IX is a vitamin K-dependent factor, with low, normal neonatal levels, reaching the level of adult normals at 4–6 months of age. Factor VIII levels in newborns are similar to adult normals. Patients with mild factor VIII deficiency should also have von Willebrand factor (VWF) levels measured to differentiate mild von Willebrand disease from mild hemophilia A. The normal range of activity is 50–150%, with a typical ratio of factor VIII:VWF of 1:1. Overall, hemophilia A affected individuals and carriers have decreased levels of factor VIII, but normal plasma levels of the carrier, VWF, thus resulting in a factor VIII:VWF ratio of less than 1:1. On the other hand, patient with von Willebrands disease have decreased levels of both with a relative decrease in VWF. In the case of factor IX deficiency, carriers may have decreased levels of Factor IX activity as well. There are rare families with mutations in hormone-dependent promoters (factor IX Leyden) that have bleeding symptoms that improve with age.

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Prenatal Diagnosis and Carrier Detection

Since description and sequencing of the Factor VIII and IX molecules, more than 2,000 different mutations of factor VIII and factor IX have been described. Utilizing this data has allowed earlier and more accurate detection of affected patients and carriers. The genes for factor VIII and factor IX are both located on the X chromosome at q28 and q27.1, respectively. The factor VIII gene is 186 kb with 26 exons. The factor IX gene is considerably smaller at 34 kb and 8 exons. Both genes have a number of normal allelic variants that can be associated with ethnicity.

In the case of hemophilia A, 45% of severe cases are due to "inversions" of the factor VIII gene at intron 22, which result from intrachromosomal recombination. Nearly all spontaneous mutations are due to an inversion of intron 22. Point or small mutations resulting in truncated proteins and inversions of intron 1 and the inverted repeat 5′ end of the factor VIII gene cause the remaining cases of severe factor VIII deficiency. Missense mutations comprise of nearly all patients with moderate or mild hemophilia A.

In the case of Hemophilia B, there is also a high spontaneous rate of mutation, but there is no single common mutation. While most patients with mild or moderate disease have missense point mutations, patients with severe disease have a variety of large mutations, frame shift splice junction, nonsense or missense mutations. This heterogeneity makes the screening of carriers of factor IX deficiency more complex than that of factor VIII deficiency.

Carriers for Hemophilia A and B can be detected by direct gene mutation analysis, linkage studies, or by measurement of reduced plasma factor VIII or IX activity. Only two third of carriers are detected by reduced plasma factor activity, with the remainder having normal plasma levels.

Prenatal and antenatal screening is available to those families in whom the mutation is known or linkage analysis has been performed. While helpful for the expectant families, the infant's factor levels are not essential to make delivery room recommendations, discussed later in this chapter. Genetic counseling is recommended for all known carriers to discuss testing options and optimal delivery room management of potentially affected males.

Preimplantation diagnosis can be performed using molecular techniques or preimplantation sex screening by biopsying the embryo at the cleavage stage or biopsy of the polar body of the oocyte. Prenatal diagnosis can be performed as early as 10–12 weeks gestation using chorionic villus sampling or at 15 weeks' gestation using amniocentesis. If DNA markers are not known, fetal blood sampling for the purpose of measuring factor VIII activity can be done at 20 weeks gestation. Unfortunately, measuring fetal factor IX levels are not helpful in detecting factor IX deficiency because of the physiologically low factor IX levels in the normal fetus and newborn.

Presentation and Clinical Manifestation

Patients with both hemophilia A and B present in a similar manner. These patients have decreased thrombin formation resulting in friable and delayed clot formation. They commonly present with bleeding following minor or no trauma. Bleeding is frequently prolonged or recurrent. Thirty percent of patients present with bleeding with circumcision, 1–2% present with intracranial hemorrhage. Other bleeding manifestations include deep muscle and joint hemorrhage, bruising, hematomas, posttraumatic bleeding, postsurgical bleeding, oozing after dental procedures or oral injury, epistaxis, gastrointestinal, renal, and retroperitoneal bleeding. The most disabling long-term sequellae are related to repeated joint and muscular hemorrhages. Many patients treated prior to 1985 also have acquired HIV and/or slowly progressive liver disease from hepatitis C. These associated diseases and the cost of hemophilia treatment add social and economic difficulties to the psychological and physical challenges that this population faces.

In the severe patient (70% of A and 50% of B), bleeding in the neonatal period and muscular bleeding associated with immunization is common. Once the child begins to walk, both spontaneous and posttraumatic joint and muscle bleeds are seen. Moderate hemophiliacs (15% of hemophilia A and 30% of B) more commonly present with posttraumatic bleeding. Mild patients (15% of hemophilia A and 20% of B) frequently are not diagnosed until they have prolonged or severe posttraumatic or postsurgical bleeding.

Hemarthrosis is the hallmark of hemophilia, accounting for 90% of serious bleeding episodes. Knees, elbows, and other large joints are involved in 80% of the bleeding episodes. Bleeds can be spontaneous or following minimal trauma. Patients describe an "aura" of warmth or tingling sensation hours before the joint bleed is evident. While mild bleeds can resolve in several hours, severe bleeds can cause significant joint swelling, lasting for weeks. Once several bleeds occur in a joint, the synovium, which normally makes lubricating fluid for the joint, begins to proliferate and becomes hypertrophied, friable, leading

to increased risk of repeated bleeding, cartilaginous damage, and eventual severe arthropathy. There are validated radiologic and joint examination scoring systems to assist in quantification and follow-up of joint outcomes in hemophilia (*Tables 335.1* and *335.2*).

Repeated bleeding episodes eventually cause loss of joint space, bone cysts, crippling arthritis, and eventual fusion of the joint. Chronic synovitis can be treated with surgical or radiosynovectomy, while end-stage arthropathy is frequently treated with joint fusion or replacement.

Deep muscle bleeding is another common manifestation of hemophilia. Of particular interest is bleeding within the retroperitoneal muscles. Large bleeds can occur in the iliopsoas muscles, causing lower quadrant abdominal pain that can mimic appedicitis or referred pain to the groin or hip, easily confused with hip

Table 335.1
Orthopedic joint scoring system (Gilbert score)

	Score[a]			
	0	1	2	3
Chronic Pain	No pain	Mild pain	Moderate pain partial or occasional interference with occupation or ADL	Severe pain
	No functional deficit	Does not interfere with occupation or activities of daily living (ADL)	Use of non-narcotic medications	Interferes with occupation or ADL
	No analgesic use (except with acute hemarthrosis)	May require non-narcotic analgesic	May require occasional narcotic medications	Requires frequent use of non-narcotic and narcotic medications
Axial deformity				
Elbow	None	$\leq$10° varus or valgus	>10° varus or valgus	–
Knee	No deformity (0–7°valgus)	8–15° valgus or 0–5° varus	>15° valgus or >5° varus	–
Ankle	No deformity	$\leq$10° valgus or$\leq$5° varus	>10° valgus or >5° varus	–
Contracture Flexion	<15° fixed flexion contracture (FFC)	–	$\geq$15° FFC	–
Equinus	<15°	–	$\geq$15°	–
Joint physical findings				
Instability range of motion[b]	None	Slight (noted on examination but does not interfere with function or require bracing)	Severe (creates a function deficit or requires bracing)	–
Pronation and supination[b]	0–10%	11–33%	33–100%	–
Chronic swelling	None	–	Present	–
Atrophy	None/minimal (<1 cm)	Present	–	–
Crepitus on motion	None	Present	–	–

[a]Sum of the elbows, knees, and ankles = joint score; maximum possible score = 90
[b]Expressed as percentage loss of full range of motion.
Source: Adapted from Pipe SW, Valentino LA (2007) Hemophilia 13(suppl 4):1–16

Table 335.2
Radiologic joint score (Pettersson score)

Type of change	Finding	Score[a]
Osteoporosis	Absent	0
	Present	1
Enlarged epiphysis	Absent	0
	Present	1
Irregular subchondral surface	Absent	0
	Partially involved	1
	Totally involved	2
Narrowing of joint space	Absent	0
	Present; joint space >1 mm	1
	Present; joint space <1mm	2
Subchondral cyst formation	Absent	0
	1 Cyst	1
	>1 Cyst	2
Erosion of joint margins	Absent	0
	Present	1
Gross incongruence of articulating bone ends	Absent	0
	Slight	1
Joint deformity	Absent	0
	Slight	1
	Pronounced	2

[a]Maximum possible joint score = 13; maximum possible total joint score (Sum of elbows, knees, and ankles) =78.
Source: Adapted from Gilbert MS (1993) Semin Hematol 30:3–6

hemarthrosis. The patient with an iliopsoas bleed will hold his leg flexed and inwardly rotated. Non-contrast CT scan of the abdomen and pelvis or ultrasound can confirm the diagnosis. Large muscle bleeds of the extremities can lead to a compartment syndrome, where the hematoma can compromise the neurovascular integrity of the limb, requiring surgical fasciotomy to save the limb.

Gross hematuria is another characteristic manifestation of hemophilia. These episodes are typically spontaneous and painless. Severe pain should raise the suspicion of urinary tract obstruction due to blood clot. Treatment is controversial, but most practitioners treat with hydration, corticosteroids, and factor replacement. Antifibrinolytics are contraindicated.

Intracranial hemorrhages and bleeds around the airway are among the most life-threatening complications of hemophilia and account for 25% of hemorrhagic deaths in hemophilia.

Treatment for Hemophilia

Treatment is focused on prevention of injury, local control of bleeding, and replacement therapy. The surroundings of the infant should be cleared of objects that may cause injury. Once the child starts walking, close supervision and guidance are essential to prevent trauma. As the child becomes older, sports, such as swimming, should be encouraged and contact sports should be avoided. Participation in physical activity and physiotherapy improves strength and mobility, decreases bleeding, and prevents the development of hemophilic muscle atrophy.

Local control of a bleeding episode is a helpful adjunct to replacement therapy. RICE is a frequently used mnemonic by the National Hemophilia Foundation to teach essentials of local control: Rest, Ice, Compression, and Elevation. Topical therapies to stop an active bleeding can also be useful to reduce usage of factor replacement therapy.

Replacement Therapy

The earliest attempts to treat hemophiliacs by providing them with blood obtained from normal individuals were undertaken by a British physician 100 years before the relationship between effective blood transfusion and the temporary replacement of a missing blood coagulation factor was understood and appreciated. For many years, blood transfusion was the only effective mode of therapy until fresh frozen plasma (FFP) was developed. FFP was more practical to administer and provided more factor per volume than whole blood. Cryoprecipitate was introduced later and became the treatment of choice until lyophilized factor concentrates were available in the 1970s. Development of factor concentrates has enabled patients with hemophilia to undergo orthopedic and dental treatment, followed by home infusion therapy with factor concentrates. Life expectancy for patients with hemophilia without inhibitor increased from 11 years in 1921 to 71.2 years after 2000, now approaching the life expectancy of a normal male.

One of the great tragedies of the hemophilia population was the HIV epidemic. Between 1979 and 1985, 55% of treated hemophiliacs were infected with HIV-1 virus and 60–95% with hepatitis C, due to exposure to factor replacement products. Each lot of these factor concentrates is manufactured from more than 2,000 blood donors. In response to the HIV epidemic, the 1980s brought numerous methods of factor purification including monoclonal antibody purification of factors, viral inactivation with heat and solvent detergent treatment methods, as well as recombinant factor VIII and factor IX products.

Several types of purified factor VIII concentrates are currently available. Lower-purity, plasma-derived, VIII concentrate products containing VWF and VIII can be used to treat hemophilia A, but this has been largely replaced by high purity factor concentrates. Since the late 1980s, monoclonal antibody purified products that are virally inactivated with a combination of pasteurization, dry heat treatment, and solvent detergent methods have been available (Monarc-P(no longer available)®, Hemophil M®). Over the last 20 years, recombinant factor VIII products have been widely used. Purity in these products has progressively improved over the three generations of recombinant factor products. First-generation products include human albumin in the final product (Recombinate®), second-generation products (Helixate FS®, Kogenate FS®) only contain human or animal albumen in the cell culture medium, and third-generation products contain no human or animal albumin in their production (Advate®). Since deleting the B domain of the factor VIII molecule does not alter its activity but increases yields of the recombinant protein, several B domain–deleted second- and third-generation products have also been used (Refacto(no longer available), Xyntha®).

Much of the emphasis of newer factor VIII products has been on purity and safety, but currently commercially available products contain essentially the same factor VIII molecule. Future factor VIII products may have more favorable properties that improve its ease of use.

For patients with factor IX deficiency, previously, only low purity prothrombin complex concentrates (PCC) were available. These products contain factors II, variably activated VII, IX, and X. These products have been largely replaced by plasma-derived, monoclonal antibody–purified factor IX concentrates (Mononine®, AlphaNine SD®) and third-generation recombinant factor IX products (Benefix®).

Despite the number of factor concentrate products available, the fundamentals of factor replacement therapy have remained the same: prompt and adequate therapy to achieve a hemostatic level for the type of bleeding being treated. One milliliter of normal plasma contains 1u of clotting activity of all coagulation factors, including factor VIII and IX (*Table 335.3*). Since plasma volume is 45 mL/kg of body weight and has 100% activity for both factor VIII

Table 335.3
Guidelines for factor replacement therapy for hemophilia A and B

Type of bleed	Goal hemostatic level	Factor VIII dose	Factor IX dose
Soft tissue, muscle, joint	40–80%	20–40 u/kg daily	40–80 u/kg
Oral mucosa	50%	25 u/kg	50 u/kg
Epistaxis, GI, GU	100% initially then 30% until healing	50 u/kg initially then 15 u/kg	100 u/kg initially then 30 u/kg
CNS, trauma, surgery or life threatening	100% initially then 50–100% until wound healing	50 u/kg initially then 25–50 u/kg until wound healing	100 u/kg initially then 50–100 u/kg until wound healing

and IX, in a normal individual, infusion of 45 u/kg would be expected to raise the factor level from 0–100% of normal. In the case of factor VIII, 1 U factor VIII/kg will raise the level 2%, with a half-life of 8–12 h. Because of the increased rate of diffusion of the smaller factor IX molecule to the extravascular space, 1U factor IX/kg will raise the factor level by 1%, with a half-life of 18–24 h.

Home Infusion/Self Therapy Program

Virtually, all patients with reliable family support and adequate vascular access are candidates for home infusion therapy. Most families can be trained when the patient is 3–8 years of age to perform home infusion therapy. Families with even younger patients can be trained, if a permanent indwelling vascular access device (portacath) or arteriovenous fistula is placed. Refer to Sangostino for a review of vascular access issues in patients with hemophilia.

This has opened the door to routine prophylactic treatment that permits these patients to participate in most physical activities.

Infusion Schedules

Many older and mild/moderate hemophilia patients treat themselves "on demand" (episodic factor replacement for bleeding episodes or trauma). Mild or moderate hemophiliacs will frequently infuse prior to higher risk physical activity, such as downhill skiing. However, the mainstay of treatment for a severe hemophiliac is routine scheduled prophylactic infusion therapy. Joint outcomes in severe hemophiliacs that are treated "on demand" are poor, prompting clinical trials that have demonstrated improved long-term joint outcomes in patients that receive routine prophylactic infusions. Many patients that are treated on demand will begin secondary prophylaxis after repeated bleeding episodes in order to decrease symptoms in a target joint (a joint with recurrent bleeding).

In essence, severe hemophiliacs can be converted to a moderate phenotype with routine infusions of factor VIII (25–40 units/kg) one to four times per week or factor IX (50 units/kg) one to two times per week. A study by Collins et al., elegantly demonstrated that decreasing the time with factor VIII levels of $<1\%$ in patients with hemophilia A by infusing with factor VIII replacement therapy at least three times per week correlated with decreased total bleeding episodes and hemarthrosis. Studies performed in patients with factor IX deficiency also demonstrated the efficacy of prophylactic infusions (15–50 units/kg) in preventing bleeding episodes. With the advent of routine prophylaxis, many severe hemophiliacs lead a life full of activities much like their healthy peers without daily fear of life-threatening hemorrhage.

Ancillary Pharmacologic Therapies

Desmopressin: Desmopressin or 1-deamino-8-D-argnine vasopressin (DDAVP) stimulates a transient, fourfold increase in factor VIII levels by releasing factor VIII stored in endothelial cells and platelets. This is an effective alternative therapy for patients with mild hemophilia A. Administration of 0.3 mcg/kg of DDAVP in 30–50 mL of saline IV over 15–30 min results in peak factor VIII level at 30–60 min. A concentrated nasal spray (Stimate®) administers 150 mcg/spray and can be self-administered in the home. 150 mcg is sufficient for a child <50 kg, 300 mcg is indicated for a >50 kg person, with the nasal spray peak levels are attained at 60–90 min. Fluids should be restricted in patients receiving DDAVP because of the risk of hyponatremia. Tachyphylaxis (temporary cessation of response) can occur with repeated doses of DDAVP, even if given no more frequently than daily. Transient facial flushing, hyponatremia, hypertension, and headache can occur after administration.

Antifibrinolytic therapy: Another effective method of controlling bleeding in the hemophilia patient is the use of antifibrinolytics to stabilize and protect the friable clot. Clots in the oropharynx are particularly sensitive to degradation due to the high levels of fibrinolytic enzymes in saliva. Two agents are available, ϵ-aminocaproic acid (EACA, Amicar®) and tranexamic acid (Cyclokapron®). Both can be administered intravenously or orally. Generally these agents are administered in patients with oronasopharyngeal bleeding, for 2–5 days to permit healing of the mucosa. The greatest risk with these agents is thrombosis. Administration with prothrombin complex concentrates or with urinary tract bleeding is relatively contraindicated due to the risk of thrombosis and urinary tract obstruction, respectively.

Topical therapy: There are three categories of topical treatments: sealants, matrix dressings, and other topical therapies. Sealants include Tisseel VH®, topical thrombin, and cyanoacrylate. The matrix dressings promote fibrin formation. Finally, other materials such as zeolite and hydrophilic polymers that form artificial scabs can be used to assist with hemostasis.

Future therapeutic strategies: Due to improved understanding of the factor VIIa, VIII, and IX molecules, one future avenue of treatment would be to improve the stability, potency, and half-life of the molecules and facilitate alternative delivery systems such as oral and intrapulmonary routes. Current clinical trials include agents with extended half-lives, improving the convenience of prophylactic factor infusion. Even more attractive is the potential to cure disease using gene therapy or hepatocyte transfer. While a number of these approaches utilizing adenoviral, adeno-associated viral, and retroviral vectors have been tried in clinical trials, thus far these approaches have not resulted in sufficient long-term factor VIII or IX protein levels and have been limited by immunologic response.

Delivery Room Management of Potential Hemophilia Patients

The risk of intracranial hemorrhage in hemophilia patients delivered vaginally is 4% compared to 0.5% in patients delivered by cesarean section. The risk is tripled in deliveries assisted by forceps or vacuum extraction which is contraindicated when delivering a potential hemophilia patient. Fetal scalp electrodes also increase the risk of bleeding in affected infants and should be avoided. After delivery, umbilical cord blood specimens can be sent to determine if the infant is affected and requires additional care or observation. Ideally, a 4.5 mL specimen should be drawn from a double clamped 10 in. section of cord, drawn from the umbilical vein, and placed into a citrated syringe or tube after discarding the initial 1–2 mL. This method decreases the risk of hemorrhage in the affected infant due to difficult venopuncture. Routine factor infusion after delivery is not indicated, but a high index of suspicion for bleeding and low threshold for prompt intervention with factor replacement therapy for bleeding episodes is essential.

Management of Carriers

There is great variability to symptomatology of carriers for factor VIII and IX deficiency. Ten percent of carriers of factor VIII and IX deficiency are symptomatic with levels of less than 35% and 30%, respectively. Patients with depressed factor VIII and IX levels of <50% (50 IU/dL) may require factor replacement therapy for severe bleeding episodes, delivery, or surgery. Factor VIII levels increase during pregnancy and should be evaluated in the event of unusual bleeding and during the last trimester to determine if intervention is necessary. Factor VIII levels also rise in response to inflammation, estrogen therapy, and aerobic exercise. Carriers with blood type O also have factor VIII levels that are 25% lower than those with blood group A, B, or AB. Factor IX levels do not increase during pregnancy, so a postpubertal baseline level should be adequate to determine the necessity of treatment for delivery.

Management of Hemophiliac Patients with Inhibitors to Factor VIII or IX

Ten to fifteen percent of patients with severe hemophilia A, 3% of patients with severe hemophilia B, and 2.7–13% of mild/moderate hemophilia A eventually become refractory to factor replacement therapy due to the development of immunoglobulin G (IgG) antibodies to factor VIII or IX. The risk factors for inhibitor development include genotype, major histocompatibility class II alleles, polymorphisms in immune response genes (IL10, TNFa, CTLA4), reason for first treatment (surgery vs routine infusion), >5 days of initial exposure, and some suggestion that initial continuous infusion may increase the risk. There are two preferred methods of evaluating inhibitors: the Nijmegen assay and the Bethesda assay. The Nijmegen assay is a modification of the Bethesda assay that has improved specificity and inter-laboratory reliability, but the Bethesda assay continues to be more widely used. Both assays quantify inhibitors to the A2 domain better than for inhibitors to the C2 domain. The unit utilized to measure the titer of inhibitor is the Bethesda unit (BU). This is defined as the amount of inhibitor present in 1 ml of the patient's plasma that neutralizes 50% of the factor VIII or IX in 1 ml of normal plasma. Patients with inhibitors to factor VIII and IX are divided into low titer (<5 BU), high titer (5–30 BU), and very high titer patients (>30 BU) for purposes of treatment recommendations. Patients with low-titer inhibitors that do not increase in response to factor replacement therapy are known as low responders (25% of hemophilia A inhibitor patients), whereas those that have rapidly increasing titers with repeated exposure to factor replacement are high responders (75% of hemophilia A inhibitor patients). Typically, the inhibitor titer begins to rise 2–3 days after reexposure to replacement therapy and reaches a peak at 7–21 days, decreasing slowly if there are no further exposures to factor replacement. The highest risk of development of inhibitors is in the first 50 days of exposure to factor replacement therapy, with only rare patients developing inhibitors after 150 exposure days. Once formed, high-titer inhibitors in high responders tend

to persist and low-titer inhibitors in low responders tend to disappear without recurrence.

Treatment of these patients is challenging and complex. Low-titer, low-responder patients can generally be treated with higher and more frequent doses of factor replacement therapy. Some treating physicians will change from a recombinant factor to a plasma-derived factor in inhibitor patients. For patients with high titer inhibitors or high responders, plasmapheresis can reduce titers temporarily to permit emergent treatment of a life-threatening hemorrhage with factor replacement.

There are other options for the treatment of hemophilia A in the presence of inhibitors. Porcine factor VIII (Hyate:C) at a dose of 100–150 u/kg can be used to treat acute bleeds, but is associated with allergic reactions and hematologic side effects. It may cause an amnestic response to both human and porcine factor VIII. Once anti-porcine inhibitor titers rise to 15–20 BU, the product becomes less effective.

Bypass therapy with prothrombin complex concentrates (PCC, Proplex® at 100 u/kg) and activated prothrombin complex concentrates (aPCC, FEIBA® at 50–75 u/kg) is effective for treatment of acute bleeds in inhibitor patients with both hemophilia A and B, but is not used for prophylaxis because of the risks of thrombosis and amnesis associated with their use. Both of these products contain Vitamin K–dependent factors, including activated factor II, VII, IX, X, explaining their ability to bypass factor VIII and IX with the activated factor X and VII.

There is now 20 years of experience administering recombinant activated factor VII (NovoSeven®). It is highly effective in hemophilia A and B patients with inhibitors. Dosing is variable and can range from (35–300 mcg/kg). Its use is limited by its short half-life (2.7 h in adults and 1.3 h in children) and its cost. In the subset of hemophilia B patients with inhibitors and anaphylaxis associated with factor IX administration, it is currently the only treatment option for acute bleeds, as they can develop proteinuria due to immune complex formation with repeated factor IX exposure. There is in vitro evidence that demonstrates a synergistic effect between the use of aPCC with recombinant VIIa, but clinical trials are needed, given the potential risk of thrombosis with concurrent use.

The best solution for hemophilia patients with inhibitors is to eradicate them with immune tolerance therapy. When successful, this permits the use of factor replacement products, frequently at normal dosing. Induction of immune tolerance is possible in 60–80% of hemophilia A patients. The success rate in hemophilia B patients with inhibitors appears to be significantly lower. The process of immune tolerance is time consuming and expensive. There are several methods currently being utilized including high dose factor replacement therapy (frequently by continuous infusion), cyclophosphamide, corticosteroids, and intravenous immunoglobulins. There are promising preliminary findings with the use of cyclosporin, mycophenylate mofetil, and rituximab therapy.

Comprehensive Hemophilia Clinic

Because of the complexity of the ongoing care of these patients, most patients in the USA are managed in a federally funded network of comprehensive hemophilia clinics. These clinics have a staff experienced in the complex medical and psychosocial needs of this population. Comprehensive clinics usually include hemophilia physicians, nurses, orthopedists, infectious disease specialists, dentists, social workers, genetic counselors, nutritionists, and physical therapists.

Factor XI Deficiency (Hemophilia C)

Hemophilia C comprises only 2–3% of hemophilia. The gene is 23 kb and located on the long arm of chromosome 4. It is autosomal recessive and most symptomatic patients have factor XI levels of 1–10% of normal. Symptoms are most typically post surgical, posttraumatic, epistaxis, menorrhagia, and hematuria. Spontaneous bleeding is rare. Bleeding tendency and factor levels do not always correlate, likely due to coinheritance of additional hemostatic defects, VWF levels, reduced thrombin-activatable fibrinolysis inhibitor levels (TAFI), and abnormalities in platelet associated factor XI. Over half of the reported cases are in the Jewish population with a gene frequency of 1:8 of Ashkenazi Jews. The half-life of factor XI is 45–55 h. Treatment is FFP or solvent detergent pooled plasma. In France, a plasma-derived factor XI concentrate (Hemoleven) is available as well. DDAVP and antifibrinolytic therapy can be an effective adjunct. Rare patients with abnormalities in platelet-associated factor XI may require platelet transfusion as well.

Factor Deficiencies Associated with Laboratory Abnormalities but No Bleeding Tendency

Factor XII deficiency, prekallikrein (Fletcher factor), and HMW kininogen (Fitzgerald factor) deficiency can all

result in impressive prolongation of the aPTT but are not associated with bleeding tendency. In patients with a prolonged aPTT and absence of bleeding, this diagnosis is suggested with a mixing study demonstrating factor deficiency but normal factor VIII, IX, and XI levels. The diagnosis can be confirmed with factor assays.

von Willebrand disease

General

von Willebrand disease (VWD) is the most common congenital bleeding disorder, with an incidence of over 1% in the general population. VWD was initially described by Eric A. von Willebrand in 1926 in a family with a bleeding disorder affecting both males and females and distinctive from hemophilia. Many patients have symptoms and laboratory findings that can be confused with hemophilia A (*Table 335.4*). Mucocutaneous bleeding is more common than joint bleeding. The disease is caused by qualitatively abnormal and quantitatively decreased levels of von Willebrand factor (VWF). VWF is a carrier protein for factor VIII, complexed together in a 1:1 ratio. The gene for VWF is located on chromosome 12. Among the three main clinical subtypes of VWD, a significant overlap between normal individuals and patients with type 1 VWD, makes the diagnosis very challenging.

Physiologic Regulation of von WF Synthesis and Release

VWF is a multimeric glycoprotein consisting of dimeric subunits. The multimers are classified as low, intermediate, and high depending upon their molecular weight. The protein is synthesized by both the megakaryocyte and the endothelial cell. VWF produced by the endothelial cell is high molecular weight (HMW) and stored in Weibel–Palade bodies. VWF produced in the megakaryocytes is LMW and stored in the alpha granules of the platelets. Secretion is facilitated by two pathways, constitutive from the platelets and regulated from endothelial cells in response to vascular endothelial damage and other endothelial cell stimulation. Levels vary according to inflammation, exercise, vasopressin, pregnancy, and blood group type, with blood type O individuals having significantly lower levels of VWF.

Function of von Willebrand Factor

VWF serves two key roles in normal hemostatis: it is a cofactor for platelet adhesion and the carrier protein for factor VIII procoagulant. In platelet adhesion, VWF promotes the attachment of platelets to the areas of vessel injury. To optimize the availability of VWF at the site of injury, a highly active form of the protein (HMW multimers) is stored in the α granules of the platelets

Table 335.4
Differences between von Willebrand disease and hemophilia

	von Willebrand disease	Hemophilia A
Symptoms	Mucous membrane bleeds and bruising (epistaxis, menorrhagia)	Joint and muscle bleeds
Sexual distribution	Males and females	Males
Incidence	1/100 or more	1/6,000 males
Abnormal protein	von Willebrand factor	Factor VIII
Function	Platelet adhesion and carrier to factor VIII	Clotting cofactor
Site of synthesis	Endothelial cells and megakaryocytes	Liver
Gene location	Chromosome 12	X chromosome
BT	Often prolonged	Normal
PTT	Prolonged or normal	Prolonged
Factor VIII	Low normal or decreased	Decreased or absent
VWF:Ag	Decreased or absent	Normal or increased
VWF:Rcof	Decreased or abnormal	Normal or increased

BT bleeding time, *PTT* partial thromboplastin time, *VWF:Ag* von Willebrand factor antigen, *VWF:Rcof* von Willebrand factor/ristocetin cofactor activity

and the endothelial cells. When such cells sense tissue injury (e.g., by contact with thrombin), they instantly mobilize the stored protein. Each HMW multimeric unit has a binding site for (a) the receptor glycoprotein (GP) Ib on nonactivated platelets, (b) the integrin-type receptors (GPIIb/IIIa on activated platelets), and (c) fibrillar collagen and heparin-like molecules. Each multimeric unit can also facilitate factor VIII binding onto platelet surface templates to mediate the coagulation process. The result is bridging of the platelets and vascular endothelium (adhesion) to GPIb as well as the platelets with other platelets (aggregation) via GPIIb/IIIa, resulting in the formation of the platelet plug. Adhesive proteins such as fibrinogen also react with the GPIIb/IIIa on the surface of the activated platelets and contribute to platelet aggregation and platelet plug formation in primary hemostasis.

LMW and intermediate-molecular-weight (IMW) multimers have fewer platelet binding sites and serve as carriers for factor VIII, unlike the HMW multimers, which are rich in platelet bridging sites. In secondary hemostasis, which facilitates fibrin clot formation, VWF, a carrier of factor VIII, will deliver this important component to the site of adherent platelets, resulting in clot formation. VWF also stabilizes factor VIII, protecting it from premature activation by activated factor X or inactivation by protein C, and preventing it from binding to phospholipids and activated circulating platelets. Unbound factor VIII is an unstable molecule that decays rapidly in the circulation. This probably explains, at least in part, the low factor VIII activity (factor VIII:C) in some types of VWD, such as type 2N.

Genetics of von Willebrand Disease

Typically, VWD is a heterozygous autosomally inherited disorder with depressed levels of VWF or function. Patients with severe disease are usually homozygotes or double heterozygotes, with an autosomal recessive pattern of inheritance (◉ *Table 335.5*).

Classification of VWD

There are three types of von Willebrand Disease and a group of individuals that are classified as "low von Willebrand factor" (◉ *Table 335.6*).

Type I: The most common subtype of VWD is type I, accounting for 80% of affected individuals. These patients have a heterozygous or partial deficiency of structurally normal VWF. There is an overrepresentation of individuals with the blood group O due to the lower levels in this population. Ten percent of patients have the Y1584C missense mutation. Most other known mutations are also missense mutations. A distinct variant of type I VWD is type 1 Vicenza, characterized by a markedly decreased half-life. Adding to the mystery of VWD, there are affected patients that do not have detectable mutations in the VWF gene and do not demonstrate linkage, suggesting that there may be other genetic interactions that modify level of VWF:Rcof. These patients range from those with mild bleeding disorder to those who are asymptomatic. The diagnosis can be challenging because of the many factors affecting circulating VWF levels. Because these patients have present but reduced levels of VWF and factor VIII in the platelets and endothelial cells, they respond to DDAVP.

Low VWF: There is considerable controversy in the diagnosis of individuals with VWF 30–50IU/dL. 2.5% of the general population has a VWF level in this range. Many of the individuals with levels in this range do not demonstrate typical inheritance for VWD or abnormalities in the VWF gene. Linkage to VWF gene abnormalities was only present in 51% of these individuals. These individuals have a mild bleeding tendency, occasionally can require treatment for bleeding, and may have some protective effect against thrombosis. This group of individuals is currently classified as having low von Willebrand factor, a risk factor for bleeding.

Type 2: 15–20% of patients belong to this type. These patients have both qualitative and quantitative abnormalities in VWF. These variants can have decreased numbers of HMW and IMW VWF multimers with variable bleeding tendency. Inheritance is can be dominant or recessive. There are a number of subgroups of this type. All of these subtypes have missense mutations that impair functional domains of the VWF molecule responsible for binding to GP1b, factor VIII, or multimerization.

Type 2a: This is the most common type 2 variant. This subtype has a lack or relative decrease of high and intermediate weight multimers of VWF. Mutations are in the A2 domain. Sixty percent of cases are either R1597W or Q or Y, or S1506L. These mutations affect the multimerization of VWF. There are two groups of these patients: group I that have impaired secretion of HMW multimers due to abnormal transport and group II that have mutations with a greater susceptibility to in vivo proteolysis.

Type 2b: This subtype also has a lack of high molecular weight multimers, with the exception of the New York/Malmo variant. Mutations are in the A1 domain. Ninety percent of cases are due to R1306W, R1308C, V1316M,

Table 335.5

Main characteristics of von Willebrand disease types

Type of VWD	Laboratory	Multimers	Mutations associated	Comments
Type 1	Concurrent reduction of FVIII:C and VWF in plasma; VWF:RCo/VWF:Ag $\geq$ 0.6	All multimers present; some minor abnormalities may be evident using sensitive methods	Missense mutations scattered over the entire gene. Possible dominant-negative effect. Y1584C in about 10%. Single null allele not associated with bleeding.	Usually co-dominant or dominant-negative. Ideal candidates for desmopressin. Short VWF half-life in VWD Vicenza (R1205H) and other rare mutations.
Type 2A	Usually VWF:RCo/VWF:Ag $<$ 0.6	Lack or relative decrease of the high molecular weight (HMW) and of intermediate multimers	Mutations in A2 domain; R1597W or Q or Y and S1506L represent about 60% of cases.	Usually co-dominant. Two mechanisms demonstrated by expression experiments. Group I: impaired secretion of HMW multimers, due to defective intracellular transport. Group II: normal synthesis and secretion of a VWF with greater susceptibility to in vivo proteolysis. Patients of the latter group may respond to desmopressin.[27]
Type 2B	Usually VWF:RCo/VWF:Ag $<$ 0.6; RIPA occurs at low ristocetin concentration	Lack of HMW multimers; a normal pattern is present in New York/Malmö variant	Mutations in A1 domain; 90% of cases are due to R1306W, R1308C, V1316M, and R1341Q.[51] P1266L associated with gene conversion and New York/Malmö phenotype.[12]	Usually co-dominant. Enhanced affinity of abnormal VWF for platelet GpIb receptor. Thrombocytopenia after desmopressin and sometimes during pregnancy or stress situations; thrombocytopenia may aggravate bleeding risk conferred by the abnormal VWF.
Type 2M	Usually VWF:RCo/VWF:Ag $<$ 0.6;	Large multimers present; inner abnormalities may be evident (e.g., ''smeary pattern'')	A few heterogeneous mutations recurrent (e.g., R1315C, G1324S/A, R1374C/H).	Usually co-dominant. Some overlap with Type 2A may occur. Desmopressin may be useful in selected cases.
Type 2N	VWF may be normal or only slightly reduced; FVIII:C/VWF:Ag $<$ 0.5; defective FVIII-VWF binding	All multimers present	Mutations in NH2-terminus; R854Q largely the most frequent mutation.	Usually recessive. Bleeding only for homozygosity or compound heterozygosity. Heterozygosity for R854Q in up to 2% of population in Northern Europe. Desmopressin may be useful for the majority of minor bleedings
Type 3	Virtual absence of VWF; markedly reduced FVIII:C ($<$5 IU/dL)	Lack of multimers	Mutations scattered over the entire gene, but some (e.g., 2,430delC exon 18[a] or Arg2535stop) are particularly recurrent in North Europe. High prevalence of null mutations (stop codons, frameshift, gene deletions).	Recessive. Desmopressin does not work since cellular storage is devoid of VWF

[a]Mutation responsible for VWD in the original family described by E von Willebrand.

Source: Adapted from Rodeghiero et al. (2009) Hematology 2009:113–123

Table 335.6
Laboratory findings and inheritance in von Willebrand disease variants

	Type 1	Type 2A	Type 2B	Type 2M	Type 2N	Type 3
Test	P	R	R	P	N	P
BT						
VIII:C	R	R/N	R/N	R/N	R	R
VWF:Ag	R	R/N	R/N	N	N	R
VWF:Rcof	R	R	R	R	N	R
RIPA	N/R	R	I	R	R	R
Multimer	N	Abn	Abn	N	N	Usually absent
Inheritance	AD	AD	AD	AD	AD	AR
Frequency	70–80%	10–12%	3–5%	0–1%	0–1%	1–3%

BT bleeding time, *VIII:C* factor VIII procoagulant, *VWF:Ag* von Willebrand factor antigen, *VWF:Rcof* von Willebrand factor/ristocetin cofactor activity, *RIPA*, ristocetin-induced platelet aggregation, *P* prolonged, *R* reduced, *N* normal, *I* increased, *Abn* abnormal, *AD* autosomal dominant, *AR* autosomal recessive

and R1341Q. The New York/Malmo phenotype has the P1266L mutation. These mutations are associated with an increased affinity for the platelet Gp1b receptor leading to increased thrombocytopenia after desmopressin, pregnancy, or stress.

Type 2M: This subtype is characterized by the presence of large multimers, but have decreased function of the VWF, resulting in a VWF:Rcof/VWF:Ag of <0.6. Mutations are heterogeneous and there is some overlap with type 2a.

Type 2N (Normandy): This subtype is characterized by mutations in the NH2 terminus leading to impaired binding and subsequent rapid decay of factor VIII. The most frequent mutation is R854Q. Up to 2% of the Northern European population is heterozygous for this mutation. Bleeding is only seen in individuals that are homozygous or double heterozygotes. These patients mimic hemophilia A patients.

Type 3: These patients inherit disease in an autosomal recessive manner. They are severely affected with virtual absence of VWF and markedly reduced FVIII:C. The mutations associated with this subtype are scattered over the entire gene, many of which are null mutations. This subtype has an increased risk of inhibitor development with exposure to VWF. DDAVP does not work in this population.

Platelet-type Pseudo VWD: This disorder is actually a mutation in the platelet GP1b gene resulting in increased affinity for the VWF. This disease clinically resembles type 2B. There are reduced levels of HMW multimers in these individuals because of the adsorption of VWF by the platelets.

Acquired VWD: Some autoimmune and lymphoproliferative diseases and less frequently solid tumors, such as Wilms tumor, congenital heart disease, hypothyroidism, or liver diseases are occasionally associated with a hemorrhagic diathesis resembling congenital VWD, but characterized by the presence of antibodies to VWF. Some pharmacologic agents have also been implicated in the development of acquired VWD, such as dextran, valproate, and ciprofloxacin. A prolonged infusion of factor VIII preparations devoid of VWF (recombinant preparations) has resulted in a similar syndrome due to binding of all available VWF by the excessive factor VIII, resulting in complete consumption of VWF, leaving behind a large amount of unbound factor VIII that is then rapidly cleared from the circulation.

Clinical Presentation and Diagnosis

The clinical manifestations of VWD are frequently mild and might go unnoticed until the patient is subjected to physical or surgical trauma. Many patients do not recognize their symptoms as abnormal and go undiagnosed. The most frequent symptoms are easy bruising and mucous membrane bleeding, such as epistaxis, menorrhagia, dental, and gastrointestinal bleeding. Deep muscle bleeds and hemarthrosis are uncommon, with the exception of individuals with type 3 VWD. Differentiating between normal individuals and those with mild VWD requires a combination of family history, characterization of bleeding symptoms, and careful laboratory evaluation.

Given the variation of VWF levels within a single individual, diagnosis may require repeating assays numerous times. In the adult literature bleeding scores distinguish between affected individuals and normal with low levels. Unfortunately, bleeding scores have not proven to be consistent in children, given their limited past bleeding history.

Laboratory Diagnosis of VWD

Laboratory diagnosis of VWD can be difficult because of the overlap between normal and affected individuals. In the most characteristic cases, aPTT is prolonged, bleeding time is prolonged, but PT, platelet counts, and platelet morphology is normal. Unfortunately normal screening tests are relatively insensitive and a number of patients will require specific testing for VWD. In patients with suspected VWD, it is important to exclude bleeding disorders that present with similar symptoms such as primary disorders of platelet function and number.

The bleeding time is abnormal in the presence of qualitative or quantitative platelet abnormalities, or abnormalities of connective tissues. It is variably prolonged in VWD and is occasionally normal in mild forms of disease. Ingestion of medications such as aspirin and nonsteroidal anti-inflammatory drugs can inhibit platelet function, resulting in a prolonged bleeding time, so it is not sufficient for diagnosis of VWD. Because of inherent variability in the Ivy bleeding time, many centers have replaced its use with automated platelet functional analyzers such as PFA-100™. The analyzers use either collagen/epinephrine or collagen/ADP to stimulate platelet adherence to block a small aperture, and this appears to be more reproducible than the Ivy bleeding time.

Initial evaluation includes measurement of VWF antigen (VWF:Ag), VWF activity by evaluating the ability to bind to platelet GP1b in the presence of ristocetin (VWF:Rco), factor VIII activity (VWF:VIIIc) and ABO blood type. The diagnosis of VWD is complex and may require serial evaluations of suspected patients and/or performing platelet aggregations. It is particularly difficult to diagnose individuals on hormone replacement therapy or during acute infections, as both of these factors increase the circulating VWF. Menstruating female patients have variation in their VWF levels during the menstrual cycle, with lowest levels day 1–4 and highest levels on day 9–10 of the menstrual cycle. Diagnosis of VWD is confirmed with a VWF:Rcof of <30%. Depending upon the subtype, the individuals may have a normal or decreased VWF:Ag. When the VWF:Rcof is 30–50%, individuals with a family history, abnormal multimeric analysis, or detectable VWF mutation have VWD. Other individuals are classified as low VWF and have a bleeding tendency, likely due to factors outside of the VWF gene that modulate activity or levels of VWF. Additional tests are performed in patients with confirmed VWD to classify their disease and determine therapeutic options (*Table 335.7*).

Table 335.7
Phenotypic analysis of VWD

Test	Type	Measurement
VWF:Ag[a]	Initial	Antigen; quantity of protein
VWF:Rco[a]	Initial	Ristocetin cofactor activity; ability to bind platelet GpIb in the presence of ristocetin
FVIII:C[a]	Initial	FVIII coagulant activity
VWF:A[c]	Initial	Monoclonal antibody binding to a functional epitope of the A1 loop: immunoassay of GpIb binding
RIPA	Subtyping	Ability to aggregate platelets at varying doses of ristocetin. Aggregation at low doses of ~0.5 mg/ml indicates 2B VWD
VWF:FVIIIB[a]	Subtyping	FVIII binding capacity. Reduced values indicate 2N VWD
VWF:CB[a]	Subtyping	Collagen binding capacity. Reduced values correlate with reduction in HMW multimers
VWFpp[b]	Subtyping	Quantity of propeptide. Elevated VWFpp/VWF:Ag ratio indicates enhanced clearance rate from plasma
Multimer profile	Subtyping	Aberrant profiles can indicate reduction in dimerisation/multimerisation HMW multimer loss enhanced or reduced ADAMTS13 cleavage enhanced clearance and mutations that replace/introduce cysteine residues affecting disulphide bonding

[a]Abbreviations recommended for VWF and its activities
[b]Abbreviations approved at ISTH-SSC on VWF 2009
Source: Goodeve AC (2010) Blood Reviews 24:123–134

Treatment of VWD

The goals of treatment of VWD are to prevent spontaneous bleeding, hasten hemostasis, or prevent postoperative bleeding. This can be achieved by administration of several different treatments. The first is DDAVP, to stimulate the release of VWF and factor VIII from tissue storage sites. The next is plasma-derived factor VIII concentrates rich in VWF. Currently not available in the USA are purified VWF and recombinant VWF.

Desmopressin: This agent is the first line of therapy for individuals with low von Willebrand, VWD types 1, 2a. Some patients with 2B, 2M, and 2N can also be treated with DDAVP. Pretesting is indicated for patients to determine response and to evaluate for degree of resultant thrombocytopenia in type 2b patients. Desmopressin is available for intravenous and intranasal administration. Dosing is identical to that for mild hemophilia. The intravenous dosing is 0.3 mcg/kg over 20–30 min in normal saline. The intranasal dosing is one puff (150 mcg) for patients <50 kg and two puffs (300 mcg) for those over 50 kg, similar to that of hemophilia A.

Plasma-derived products: Intermediate purity factor VIII/VWF virally inactivated factor VIII products are the treatment of choice for individuals with type 3 and most type 2B patients. Dosing is dependent upon the product and can be dosed in VWF:Rcof or factor VIII units. Products currently licensed in the USA for the treatment of VWD include Alphanate®, Humate-P®, and Wilate®. Koate-DVI is not currently licensed for use in VWD, but contains both factor VIII and VWF. Each of these products contains a different ratio of VWF:factor VIII. Dosing and products are not interchangeable. Only in emergent, life-threatening bleeding should cryoprecipitate (1 unit/5kg) be administered.

Purified VWF products: There are purified VWF products that are currently in clinical development. Initial studies of purified, plasma-derived products were limited by the need to either coinfuse factor VIII or allow 24 h for native factor VIII to bind to the VWF. A recombinant VWF product coexpressed with recombinant factor VIII is currently under development as well.

Recombinant factor VIII products: Most types of VWD cannot be treated with recombinant factor VIII products. The exception to this is severe type 3 patients. These patients are at increased risk for development of VWF inhibitors and are occasionally treated with recombinant factor VIII products.

Ancillary therapy: The antifibrinolytic agents described for the treatment of mucous membrane bleed in hemophilia, namely, EACA (Amicar®) or Tranexamic acid (Cyklocapron®), are also recommended in the management of mucous membrane bleeding in VWD.

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336 Introduction to Hemostasis and Bleeding Disorders Other Than Hemophilia

Hassan M. Yaish · Eugenia Chang

► *Gone are the days of simply saying, "Pass the fresh frozen plasma; if something is missing, it is bound to be there."*

Hemostasis is defined as arrest of blood flow within or outside blood vessel. Thrombosis, on the other hand, indicates "the formation and propagation of blood clot in a vessel."

Thrombotic events were described by Virchow in 1856; he believed at the time that elements leading to the formation of thromboembolism in the veins are related to alterations in blood flow, blood vessels, and constitution of the blood. Even though such facts were individually known and have been described by others earlier, they were put together and came to be known as "Virchow's Triad."

What is currently known about the pathophysiology of thrombus formation is very similar to the description provided by Virchow. Slowing of blood flow by any means, damaging the endothelium of the blood vessels, or alteration in procoagulants or inhibitors component of the blood are the main activities leading to thrombotic events.

In the physiologic state, hemostasis is a balance between closely coordinated groups of plasma factors designed to keep the blood in a fluid state and yet capable of forming efficient clotting when blood vessels are damaged. These factors are categorized as *procoagulants* (clot promoting) *anticoagulant* proteins (clotting inhibitors), and *fibrinolytic* proteins (clot lysing). They interact with physiologic surfaces such as the platelets, vascular endothelium, and subendothelial matrix, all of which are known to promote the function of the various clotting factors.

The physiology of the hemostatic system in infancy and childhood is profoundly different from that in adults. It is a dynamic and constantly maturing system with multiple reference ranges that reflect both gestational and postnatal age. After the age of 6 months, however, adult reference ranges are usually used in children, with the exception of Protein C (PC), which remains lower until adolescence.

Physiology of Hemostasis

As a result of injury to the blood vessel endothelium, several events take place simultaneously, as the affected vessel constricts (vascular phase) and the homostatic process proceeds through four well-coordinated functional phases:

1. The *initiation* phase of "platelets plug formation," or the primary hemostatic phase
2. The *propagation* phase by the activated clotting factors leading to fibrin clot formation (the secondary or plasma phase)
3. The *termination* phase by the coagulation inhibitors
4. The *fibrinolytic* phase leading to clot lyses by the fibrinolytic system

Initiation Phase

In the *initiation* phase, the functional response of activated platelets at the site of injury includes four different phases:

1. *Adhesion* which involves the deposition of platelets on the damaged endothelium with the exposed collagen acting as strong platelets activator and the Von Willebrand's factor as adhesive to bridge the platelets to the endothelium
2. *Aggregation* which is the formation of platelets clump by platelet–platelet interaction utilizing fibrinogen as another adhesive protein in the plasma
3. *Release reaction* which is the secretion of various platelets chemicals and proteins (ADP, Thromboxane A2) from storage sites to aid in the process of plug formation (Fig. 336.1)
4. *Procoagulant activity* (PF3) which contributes to thrombin generation

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_336,

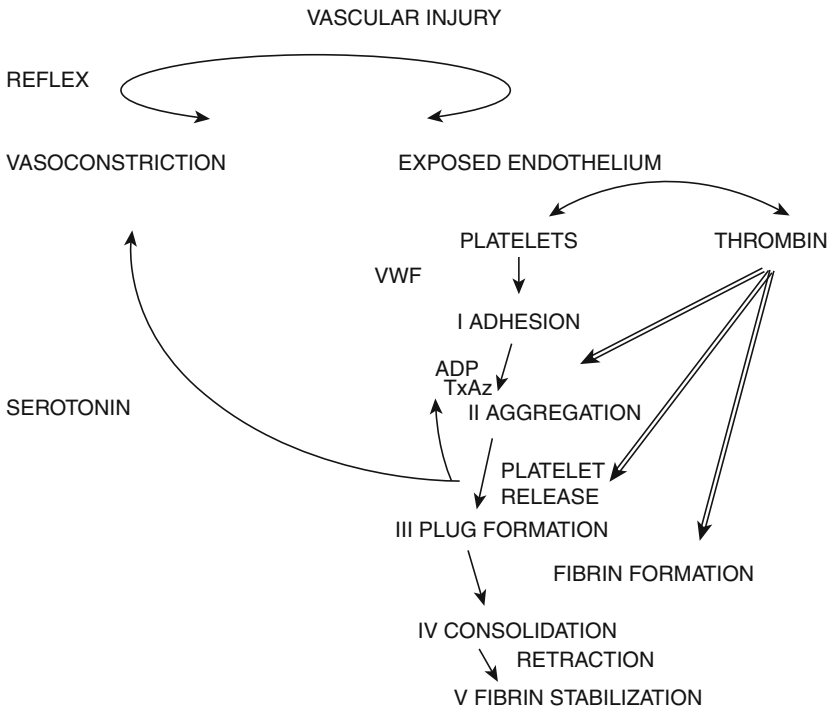

Figure 336.1
The formation of platelet plug (primary hemostatic mechanism)

Propagation Phase

Propagation phase results from a sequential activation of a series of zymogens (proenzymes) to active enzymes resulting in significant stepwise response amplification. This process represents the coagulation cascade which proceeds in three phases through one of two pathways, the *intrinsic* and the *extrinsic* pathways which were initially thought to be distinct and independent pathways. At the present time, however, it is known that they are closely interrelated and the extrinsic pathway is not actually intrinsic, since the tissue factor itself is now known to be present in the circulation and is the main element in the initiation of coagulation and not the intrinsic system as it was believed earlier. The formation of *multiple component macromolecular complexes* such as the intrinsic and extrinsic Tenases (X-ase) and the prothrombinase (*Fig. 336.2*), the first to activate FX and the second to activate FII in the process of thrombin generation), support the function of the various enzymes involved in the process of coagulation. Such complexes amplify the response in the various reactions significantly. For example, thrombin is generated from prothrombin through the prothrombinase complex 300,000 times more efficient than when produced from Prothrombin and Xa alone. The role of the platelets in providing surfaces for the various reactions and the role of its procoagulant function are very essential in the coagulation process. Patients with thrombocytopenia however do not exhibit the major bleeding manifestations that patients with clotting factors deficiencies show, unless the platelets counts are profoundly low. This suggests that small numbers of normal platelets is adequate for the clotting process.

The two traditional coagulation pathways are capable of producing *thromboplastin* in the initial phase, for the purpose of activating FX which activates FII into thrombin, which in turn carries out the last step of the coagulation cascade converting fibrinogen into fibrin to enforce and strengthen the platelet plug.

In the *intrinsic pathway* is activated by the exposure of the blood to the negatively charged surfaces (such as the Kaolin in vitro for measuring the aPTT). The *extrinsic pathway* on the other hand is activated by the Tissue factor (TF) exposure, or tissue factor–like material such as thromboplastin used in the in vitro process of measuring prothrombin time (PT). Activation of FX is the end result of both pathways that activates FII to FIIa or thrombin which in turn activates the soluble plasma fibrinogen to insoluble fibrin clot by splitting it into four small peptides

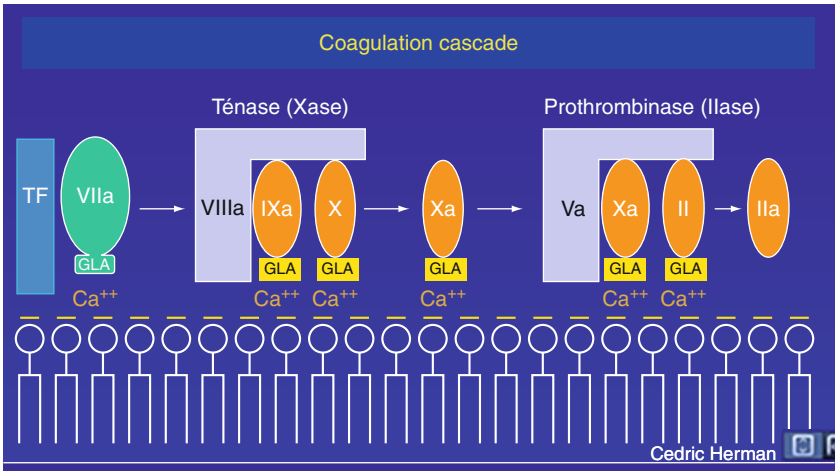

Figure 336.2
Macromolecular complexes for activation of FX (Tenase) and FII (II ase)

(two fibrinopeptide A and two fibrinopeptide B molecules). These fibrin monomers then polymerize spontaneously to form fibrin. Another one of the many functions of thrombin is activation of FXIII (fibrin stabilizing agent) to FXIIIa which in turn causes covalent bonding of the fibrin strands resulting in stable clot (*Fig. 336.3*).

It is now known that the exposure of TF at the wound site and its interaction with FVIIa is the primary physiologic event in initiating the clotting process. Only a small amount of thrombin is generated in this reaction which is capable of priming the clotting cascade, activating platelets and components of the intrinsic pathway (FVIII, FIX, FXI) which will be responsible for the amplification and the bulk generation of thrombin in the propagation phase. This interpretation of the clotting process is supported by the fact that deficiencies in FXII, HK, and PK (members of the contact factors) do not cause any bleeding disorder. Deficiency of FXI (contact factor), however, may be associated with mild bleeding symptoms. It is clear now that the classical classification of the clotting pathways into intrinsic and extrinsic (even though useful for interpretation of the clotting tests) is not physiologically accurate as was indicated earlier. The term "extrinsic" was initially introduced to indicate that TF is present only in tissues extrinsic to circulation. It is known now that TF is present in the circulation. Furthermore, the separation of the two pathways is also theoretical, since they clearly interact together. Finally, the major role of thrombin in sustaining the clotting process through a feedback mechanism is recognized (*Fig. 336.3*).

Termination Phase

The two main circulating enzymatic inhibitors are involved in this process, the antithrombin (AT), (previously antithrombin III), and the tissue factor pathway inhibitor (TFPI). In addition a clotting-initiated inhibitory process, the protein C pathway (PC), and other platelets and vascular modulators such as prostacyclin, thromboxane A2, and nitric oxide (NO) are also involved in the termination phase (*Fig. 336.4*). In the newborn and young infants, AT, PC, and PS are deficient which explain in part the high incidence of thrombotic events in this age group. Thrombin which is known to be a major procoagulant now plays a different role in the termination phase. Once it is bound to thrombomodulin and AT, it creates a conformational change which activates PC, forming another multiple macromolecular complex, of inhibitory nature, and no longer activates platelets or cleaves fibrinogen (*Fig. 336.5*). FVa and FVIIIa are cleaved by this complex, thus Tenase and Prothrombinase are inhibited. TFPI, an enzymatic inhibitor which circulates in the plasma (20%) and on endothelial surfaces (80%), inhibits FXa, directly and could form complex with such factor to inhibit TF/FVIIa. The level of this inhibitor increases significantly in plasma after parenteral administration of heparin, a phenomena that explains the effective anticoagulation effect of LMW heparin despite its weak antithrombin activity. The role of prostacyclin and thromboxane A2 in the termination phase is mainly by blocking platelet activation which is discussed under the topic of Platelets.

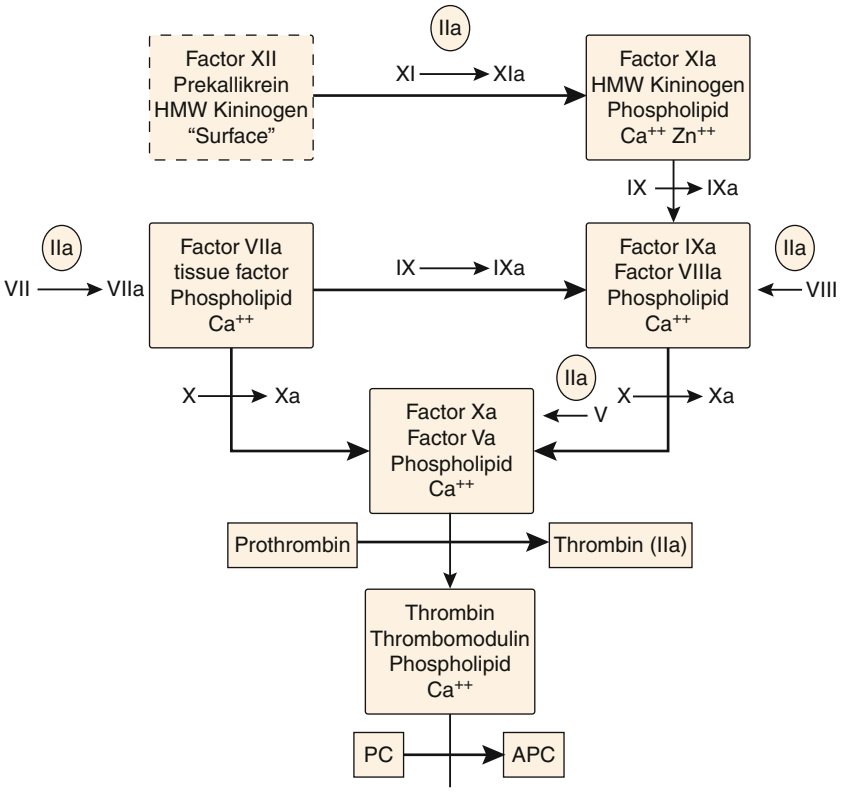

Figure 336.3

The revised coagulation cascade showing the role of TF in initiating the clotting system The interaction between the intrinsic and the extrinsic pathways. And the feed back mechanism of the Thrombin (IIa) in mediating various reactions

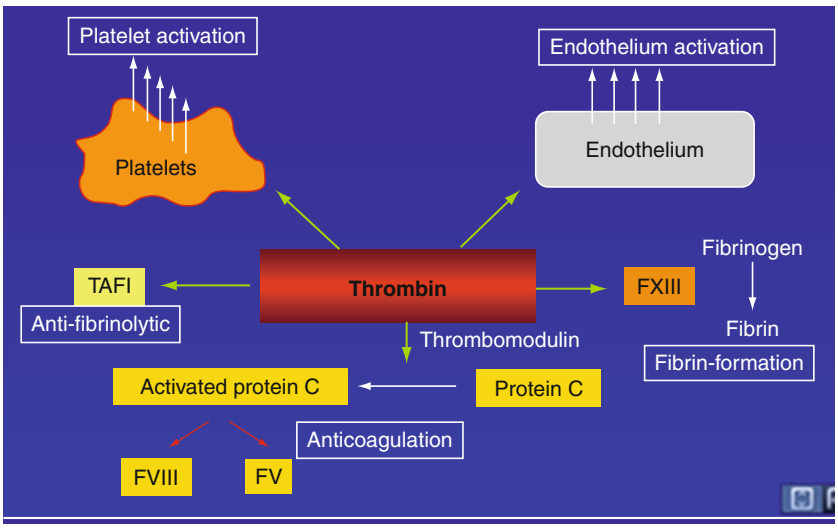

Figure 336.4

Thrombin multiple thrombotic and antithrombotic functions

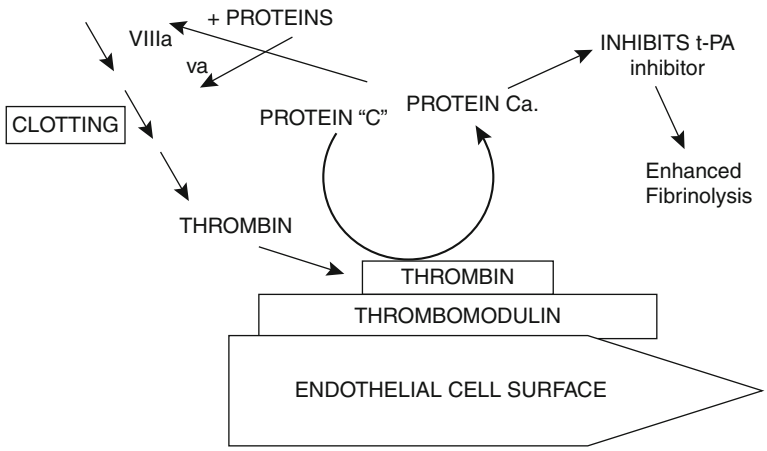

Figure 336.5
Protein C/protein S pathway

Clot Termination and Fibrinolysis

The residual clot in this stage lyses by the activation of plasminogen to plasmin, a process mediated by the intravascular activator tPA. Urokinase on the other hand is the major activator of plasminogen in the extravascular compartment. Plasmin cleaves fibrin, fibrinogen, and other proteins and clotting factors. It cleaves the polymerized fibrin strands at multiple sites resulting in the production of fibrin degradation products (FDP), one of such products is the D-Dimers which represent monomers that have been cross-linked by FXIIIa. Plasmin activator inhibitor (PAI) and alpha-2 anti-plasmin are inhibitors of the fibrinolytic process, the first is an anti-tPA and the second inhibits plasmin. They prevent the process of over fibrinolysis and if deficient, some thrombotic disorders may develop.

Evaluation of the Patient with a Suspected Hemostatic Defect

History and Physical Examination

It is said that the medical history in the patient with suspected bleeding or thrombotic disorder, when done effectively, is the most sensitive "test" for such disorders. The history and the physical examination should focus on (a) whether the suspected defect is hereditary or acquired, and (b) whether it is related to a primary or secondary hemostatic mechanism defect. The first is usually determined by the finding of documented bleeding disorders in family members or manifestations highly suggestive of such disorders. The second requires determination of the site and the nature of the bleeding manifestations. Mucous membrane bleeds (epistaxis, menorrhagia, hematuria, or gastrointestinal bleeds), petechiae of the skin, and multiple small ecchymoses are all characteristic of the defect in the primary hemostatic mechanism in patients with quantitative or qualitative platelet disorders or blood vessel abnormalities. Patients with a defective secondary hemostatic mechanism (coagulation system) usually present with joint and deep muscle bleeds, hematomas, and large spreading ecchymotic lesions. A combination of both manifestations may be encountered in the occasional patient with severe von Willebrand disease (VWD). It is also important to evaluate the severity and duration of the bleed, whether it was spontaneous or induced, and what was required to control it.

Previous surgical procedures should be reviewed. Tooth extraction, tonsillectomy, and circumcision are of particular value, even though the absence of bleed after this last procedure does not exclude a coagulation defect. The age of onset of the bleeding or thrombotic episode may give a clue to the diagnosis. A history of poor wound healing or delayed umbilical cord stump separation may suggest factor XIII deficiency. Epistaxis, a frequent manifestation of coagulation defect in the child, should be evaluated carefully. Several other conditions are known to cause epistaxis and should be considered. Epistaxis in the teenager has more significance than in the younger child. Epistaxis episodes occurring in clusters during a respiratory infection or in certain seasons are less likely to represent a coagulation problem, unlike epistaxis that causes anemia or requires cautery. Drug history is also significant in both determining the cause of the bleed and interpreting an abnormal coagulation test (e.g., bleeding time (BT) or platelet function tests after NSAID drugs

ingestion). Evaluation of the adolescent with menorrhagia also requires certain skills in determining the significance of the symptom. Young women going into menarche may not know what is normal. It is important in such cases to quantitate the amount of bleeding (pads per day), length of bleeding in days, and timing of cycle. Chronic anemia in such patients may indicate a clotting defect. Strokes and thrombosis are most common at the extremes of life, with preterm infants and elderly adults each having a natural predisposition to thrombosis. The occurrence of stroke in a child beyond the neonatal period is often an indication of inherited thrombophilia such as AT, protein C, or protein S deficiency.

In addition to the previously mentioned elements, physical examination should include looking for loose skin (hyperelasticity) and hyperflexibility of the joints. Telangiectasia should also be sought on skin and mucous membranes. Both conditions may give clues to the presence of a systemic disease known to be associated with a hemostatic defect.

Laboratory Evaluation

The laboratory evaluation of children of all ages presenting with bleeding complications should include a prothrombin time (PT), activated partial thromboplastin time (aPTT), BT (or PFA if indicated), thrombin time (TT), and fibrinogen level. One should remember, however, that the laboratory evaluation is not conclusive in many hemorrhagic conditions and may even be in the normal range in the presence of a bleeding disorder that requires a completely different set of tests. For this reason, the importance of a careful history and good physical examination in directing the clinician to an appropriate laboratory evaluation cannot be overemphasized. It is also important to know the normal values for each of the tests performed in relation to the patient's age, since many of the coagulation factors do not reach adult values until the child is 6 months of age or older.

Prothrombin Time

This test measures phase II of coagulation or, more precisely, the function of the extrinsic pathway. The test is performed by adding exogenous thromboplastin (tissue factor) and calcium to the patient's plasma. Thromboplastin complexes with factor VIIa to activate the extrinsic pathway clotting system. The test is most sensitive to deficiencies of factors at the initiation of the extrinsic pathway, such as factor VII and factor X. It is less sensitive to deficiencies of prothrombin itself. The normal values range from 11.5 to 14 S. This test does not measure the activities of factors XII, XI, IX, VIII, or XIII. Since the thrombopalstin reagent differs by the lab and the manufacturer, and so the instruments used in different laboratories to measure the PT, one expects the sensitivity of the test to the effect of Wafarin (for which the test is usually used) to vary as well. For this reason, the INR (International Normalized Ratio), a derivative of the PT was introduced to correct this deficiency and to standardize the test. The INR is calculated by dividing the patient's PT by the control PT (the midpoint of the normal range for that lab) multiplied by the ISI (International Sensitivity Index); this value is provided by the manufacturer based on the sensitivity of their reagent to the effect of Warfarin. If the reagent is less sensitive, the ISI will have a greater value. The INR should not be utilized for evaluation of liver functions, since it is calibrated with plasma from individuals on Warfarin and thus its sensitivity to factor deficiencies related to liver disease cannot be predicted.

Activated Partial Thromboplastin Time

This test measures the time required for the clotting of plasma that has been activated by incubation with an inert activator (kaolin, celite, etc.) when calcium and platelets (or lipid substitute for platelets) are added. In this process, thromboplastin is formed internally (intrinsic system) by activation of the clotting factors. Unlike in the PT testing procedure, thromboplastin is not added in this test, therefore, it is described as "partial." The test therefore measures the function of the intrinsic pathway, and it is most sensitive to deficiencies of factors at the initiation of the intrinsic pathway, such as factor XII, Fletcher factor (prekallikrein), and Fitzgerald factor (HMW kininogen). These three factors, when deficient, give the longest partial thromboplastin times (PTTs), despite the fact that they are not associated with any bleeding disorder. The sensitivity of the PTT reagents is variable, and the normal value should be established for each of the PTT reagents in each laboratory. The variation of sensitivity can be appreciated when a PTT is found to be normal with factor IX as low as 10–13% or prolonged in patients with a factor VIII level of 60% (normal range). The optimal PTT, however, should be prolonged when factor VIII or factor IX is below 30–40% of normal (*Table 336.1*).

The PTT measures factors XII, XI, IX, and VIII. It does not measure factors VII or XIII. In both the PT and the PTT, a prolonged value may indicate a relevant factor

Table 336.1
The clotting factors

Factors	Common name	Biologic half-life(h)	Plasma level
I	Fibrinogen	90	200–400
II	Prothrombin	60	50–150
III	Total thromboplastin	?	0
IV	Calcium		
V	Labile factor	12–36	50–150
VI	Activated labile factor	Part of V	
VII	Stable factor	6–8	50–150
VIII	Antihemophilic factor	8–12	50–150
IX	Christmas factor	12–24	50–150
VWF	Von Willebrand factor	8–12	50–150
X	Stuart factor	32–58	50–150
XI	Plasma thromboplastin antecedent	48–72	50–150
XII	Hageman factor	48–52	50–150
XIII	Fibrin-stabilizing factor	72–120	50–150
High-molecular-weight kininogen	Fitzgerald factor	136	
Prekallikrein	Fletcher factor		

deficiency or the presence of an inhibitor. To determine which condition is present, an inhibitor mix is performed where equal amounts of the patient's and normal plasmas are mixed and a PTT is performed. A normal PTT indicates a factor deficiency, while lack of correction indicates the presence of inhibitor; a low inhibitor titer could be misdiagnosed as deficiency since the mixing study could correct a weak titer, which usually neutralizes the factor activity present in the normal plasma. Should a bleeding tendency exist in addition to the prolonged PTT, then the inhibitor is probably directed against factor VIII, IX, or XI. If no bleeding manifestations are present, the inhibitor is probably of the "lupus anticoagulant" type.

Heparin Anti-Xa

The heparin anti-Xa test is listed here not as a diagnostic test for patients with bleeding disorders, but for the sake of comparison with aPTT test when used for monitoring of anticoagulation therapy with heparin. This test is becoming available in almost all centers, and has gained grounds in replacing aPTT for monitoring UH therapy, in addition to monitoring the treatment with LMW heparin. The many shortcomings of aPTT for monitoring UH treatment make this test a very attractive alternative. It is basically the same test used to derive the therapeutic range for aPTT each time a new reagent is used. It is an ideal test for patients with heparin resistance, and for monitoring UH therapy in the newborn whose base line aPTT is already prolonged. The test is not affected by tube under fill, elevated FVIII or FI due to inflammation, or factors deficiency except for AT.

Bleeding Time

The bleeding time is currently underutilized or unavailable in many laboratories for various reasons, even though a quick, relatively not expensive, and noninvasive test to replace it is not available. The most commonly used method for measuring the BT is the modified Ivy method. An incision is made on the volar surface of the forearm using a standardized template that controls the depth and the length of the incision while a blood pressure cuff is applied to the arm and inflated to 20–40 mmHg. At 30-s intervals, drops of blood are blotted from the margin of the incision. Normally, blood flow stops at 4–8 min. Despite all efforts to standardize this test, a high degree of variability continues to exist. Therefore, it is usually advantageous, whenever possible, to have a technologist in the laboratory to perform this test at all times. This test is not perfect, and it has a high degree of variability and poor sensitivity, yet for lack of alternative tests, it continues to be the best screening test available for assessing the vascular and platelet phases of hemostasis. Bleeding times are prolonged in the presence of thrombocytopenia, thrombocytopathy, connective tissue diseases (Ehlers-Danlos syndrome), and some cases of VWD.

Thrombin Time

This test evaluates phase III of the coagulation cascade. It measures the time required for plasma to clot after the addition of thrombin (factor IIa), which converts fibrinogen to fibrin. The normal TT is 15–20 s. It is prolonged by heparin, fibrin split products, uremia, decreased fibrinogen, or dysfibrinogenemia. In the presence of heparin, the TT can be performed by adding snake venom (reptilase)

instead of thrombin, since this agent is not usually affected by heparin. Other coagulation tests are more specific for certain hemostatic processes. Euglobulin clot lysis time (ELT), for instance, is a crude test designed to measure the fibrinolytic activity. It is performed by using acetic acid to precipitate a euglobulin fraction of the plasma. This fraction is then clotted with thrombin or calcium. The time required for the clot to lyse is then measured (usually 2–4 h). A long ELT may be related to a low plasminogen level, reduced activator, or an extremely increased level of fibrinogen. A short ELT, however, indicates increased activators and/or reduced fibrinogen. Plasminogen, plasminogen activators, and inhibitor assays, as well as assays for fibrin degradation products (FDPs) are other tests for the assessment of the fibrinolytic system.

The marked differences in the various clotting factor levels between newborns and older children and adults make it necessary to discuss the neonatal coagulation system separately. *Table 336.2* shows reference values for coagulation tests in the healthy full-term infant during the first 6 months of life compared to adult values. The striking differences at this stage in life include a prolonged PT, mostly related to the low level of vitamin K–dependent factors; a prolonged PTT, attributed to low levels of the four contact factors (XI, XII, prekallikrein, and HMW kininogen); a BT that is slightly short; and a prolonged TT, which is probably related to the presence of the "fetal" type of fibrinogen at this age. Factors V and VIII, Von Willebrand Factor (VWF), and fibrinogen are not decreased at birth and might actually be elevated. The inhibitors levels are either elevated or low; AT, protein C, and protein S are all low at birth; and other inhibitors are usually higher than adult levels. As for fibrinolysis in the newborn, plasminogen and α_2-antiplasmin are decreased while tissue plasminogen activator (tPA) and PAI are twice the adult values (*Table 336.3*).

Platelet Counts

The platelet component of hemostasis is less difficult to evaluate. Both its quantitative and qualitative aspects can be measured. Thrombocytopenia in infants and children, including premature babies, is defined as it is in adults: a platelet count of less than 150×10^9/L. There is a linear relationship between platelet counts and the BT – the

Table 336.2
Normal coagulation values in the healthy full-term infant during the first 6 months of life[a]

Test	Day 1	Day 5	Day 30	Day 90	Day 180	Adult
PT (s)	13.0(10.1–15.9)[b]	12.4(10.0–15.3)[b]	11.8(10.0–14.3)[b]	11.9(10.0–14.2)[b]	12.3(10.7–13.9)[b]	12.4(10.8–13.9)
INR	1.00(0.53–1.62)	0.89(0.53–1.48)	0.79(0.53–1.26)	0.81(0.53–1.26)	0.88(0.61–1.17)	0.89(0.64–1.17)
APTT (s)	42.9(31.3–54.3)	42.6(25.4–59.8)	40.4(32.0–55.2)	37.1(29.0–50.1)[b]	35.5(28.1–42.9)[b]	33.5(26.6–40.3)
TCT (s)	23.5(19.0–28.3)[b]	23.1(18.0–29.2)	24.3(19.4–29.2)	25.1(20.5–29.7)[b]	25.5(19.8–31.2)[b]	25.0(19.7–30.3)
Fibrinogen (g/L)	2.83(1.67–3.99)[b]	3.12(1.62–4.62)[b]	2.70(1.62–3.78)[b]	2.43(1.50–3.79)[b]	2.51(1.50–3.87)[b]	2.78(1.56–4.00)
II	0.48(0.26–0.70)	0.63(0.33–0.93)	0.68(0.34–1.02)	0.75(0.45–1.05)	0.88(0.60–1.12)	1.08(0.70–1.46)
V	0.72(0.34–1.08)	0.95(0.45–1.45)	0.98(0.62–1.34)	0.90(0.48–1.32)	0.91(0.55–1.27)	1.06(0.62–1.50)
VII	0.66(0.28–1.04)	0.89(0.35–1.43)	0.90(0.42–1.38)	0.91(0.39–1.43)	0.87(0.47–1.27)	1.05(0.67–1.43)
VIII	1.00(0.50–1.78)[b]	0.88(0.50–1.54)[b]	0.91(0.50–1.57)[b]	0.79(0.50–1.25)[b]	0.73(0.50–1.09)	0.99(0.50–1.49)
vWf	1.53(0.50–2.87)	1.40(0.50–2.54)	1.28(0.50–2.46)	1.18(0.50–2.06)	1.07(0.50–1.97)	0.92(0.50–1.58)
IX	0.53(0.15–0.91)	0.53(0.15–0.91)	0.51(0.21–0.81)	0.67(0.21–1.13)	0.86(0.36–1.36)	1.09(0.55–1.63)
X	0.40(0.12–0.68)	0.49(0.19–0.79)	0.59(0.31–0.87)	0.71(0.35–1.07)	0.78(0.38–1.18)	1.06(0.70–1.52)
XI	0.38(0.10–0.66)	0.55(0.23–0.87)	0.53(0.27–0.79)	0.69(0.41–0.97)	0.86(0.49–1.34)	0.97(0.67–1.27)
XII	0.53(0.13–0.93)	0.47(0.11–0.83)	0.49(0.17–0.81)	0.67(0.25–1.09)	0.77(0.39–1.15)	1.08(0.52–1.64)
PK	0.37(0.18–0.69)	0.48(0.20–0.76)	0.57(0.23–0.91)	0.73(0.41–1.05)	0.86(0.56–1.16)	1.12(0.62–1.62)
HK	0.54(0.06–1.02)	0.74(0.16–1.32)	0.77(0.33–1.21)	0.82(0.30–1.46)[b]	0.82(0.36–1.28)[b]	0.92(0.50–1.36)
XIIIa	0.79(0.27–1.31)	0.94(0.44–1.44)[b]	0.93(0.39–1.47)[b]	1.04(0.36–1.72)[b]	1.04(0.46–1.62)[b]	1.05(0.55–1.55)
XIIIb	0.76(0.30–1.22)	1.06(0.32–1.80)	1.11(0.39–1.73)[b]	1.16(0.48–1.84)[b]	1.10(0.50–1.70)[b]	0.97(0.57–1.37)

[a]Values are expressed as means followed by lower and upper normals in 95% of the population
[b]Values similar to those in adults

Table 336.3
Hemostatic mechanisms of the newborn compared to older children and adults

Hemostatic mechanism	Typical values versus adults
Coagulation Factors	
Fibrinogen	Normal limit
Factors II, VII, IX, X	Very low
Factors VIII, VWF	Normal to increased
Factors XI, XII, high-molecular-weight kininogen	Slightly low–low normal
Prekallikrein	
Factors V and XIII	Low normal
Inhibitors	
Antithrombin III	Low
Proteins C and S	Low
Heparin cofactor II	Low
α_2-Macroglobulin	High
α_1-Antitrypsin	Normal
Fibrinolytic components	
Plasminogen	Low
Plasminogen activators	High
Plasminogen activator inhibitors	Normal/high
Plasmin inhibitors	Low

lower the platelet count, the more prolonged the BT. The etiology of thrombocytopenia, however, plays a role in this relation. Patients whose thrombocytopenia is due to lack of marrow production of platelets, as in aplastic anemia or leukemia, may reveal prolonged BTs at a platelet count of 80,000/μL or lower. In consumptive thrombocytopenias (e.g., idiopathic thrombocytopenic purpura), however, the BT will remain normal until the platelet count drops below 30,000–40,000/μL. If the BT is disproportionate to the platelet count, a qualitative platelet defect, VWD, or a vascular defect should be suspected. Ingestion of anti-inflammatory agents, including aspirin, may prolong the BT; therefore, such testing should be delayed for a minimum of 1 week after the drug ingestion.

Platelet Function Tests

These studies delineate the functional abnormalities of the platelet. One test is based on the increase in light transmittance of a platelet suspension when a platelet activator is added to the suspension. This increase in light transmittance is recorded on a chart for interpretation. Various disorders of platelet function have specific aggregation pattern. Release of platelet-specific proteins (platelet factor 4 and platelet factor 3) is one of the other studies that may be performed to delineate platelet participation in the secondary hemostatic mechanism.

Platelet Function Analyzer-100

(PFA-100) is a relatively new, rapid, and simple in vitro test for the evaluation of platelet function. Some clinicians hoped that the test will be able to replace the vanishing bleeding time (BT), and decrease the need for the traditional, more complicated, and demanding platelet aggregation testing with various agonists. The test is based on simulating the in vivo hemostatic plug formation and is initiated by aspiration of a citrated whole blood sample at high shear rate through a 150 μm aperture in a membrane coated with collagen and epinephrine (CEPI) or collagen and ADP (CADP). Mediated by VWF, platelets adhere to the collagen on the membrane causing them to aggregate in and around the aperture which results in closure of the aperture and arrest of blood flow. The time in seconds needed to reach this point is called "the closure time." Several pre-analytic variables were found to interfere with the test results including: a low level of VWF in the plasma, the high concentration of the citrate in the specimen, an O blood group, low platelet counts or low hematocrit, as well as ingestion of drugs which may affect platelet function such as NSAIDs. All could prolong the closure time giving the impression of a platelet function defect. PFA-100 is now commonly used in clinical practice for the purpose of screening for platelet defects. In our experience, the test is frequently abnormal in many patients with VWD especially those with significantly low VWF.

Congenital Coagulation Disorders

Phase I Disorders: The Hemophilias

The hemophilias are the most common severe inherited bleeding disorders of children and adults. Probably originally named hemorrhaphilia, the disorder was referred to as hemophilia by Schönlein in the early 1800s. Its sex-linked inheritance was recognized 50 years before the Mendelian principles of genetics were introduced. Legg further distinguished hemophilia from other known bleeding disorders on the basis of clinical symptoms, i.e., a congenital tendency to bleed into joints and muscles. It

was not until 1920 that the etiology of hemophilia was attributed to a defect in blood clotting rather than gout or tuberculosis. In the 1940s and 1950s, coagulation factors VIII and IX were identified: the first as the deficient factor in hemophilia A (classic hemophilia) and the second as the deficient protein in hemophilia B (Christmas disease). In the 1970s, factor VIII was isolated from its carrier protein in the plasma, VWF, which has helped to distinguish two previously confused bleeding disorders, hemophilia A and VWD. Since both hemophilia A and B are indistinguishable clinically, they are discussed together in the chapter on bleeding disorders in hemophilia. VWD will also be discussed in that chapter. Hemophilia C, a significantly less common type of hemophilia resulting from deficiency of factor XI, is discussed separately.

Disorders of the Second Phase of Coagulation

The factors that might be involved in this phase are factor II (prothrombin), factor V, factor VII, and factor X. All are produced in the liver, and, with the exception of factor V, they all require vitamin K for their synthesis. Together with factor IX (which is also vitamin K dependent), they are called the "prothrombin complex factors." Vitamin K is needed for the Y-carboxylation of glutamic acid residues, which converts the inactive precursors into active forms. These precursors are described as protein induced by vitamin K absence (PIVKA). The precursor protein for factor II, for instance, is called PIVKA-II.

Factor II (Prothrombin) Deficiency

Quick reported the first case of prothrombin deficiency and, fewer than 100 cases were reported so far. The condition is of autosomal recessive inheritance and could be homozygous, heterozygous, or compound heterozygous. In the first and the third conditions, the activity level may range from <1% to 20% based on the variants reported. This level is about 50% in the heterozygous. The antigen however is usually normal in almost all cases, suggesting a dysprothrombinemia. Heterozygous are usually asymptomatic while homozygous patients present with easy bruising, epistaxis, menorrhagia, and, rarely, joint bleeds. The PT is usually prolonged in the presence of normal TT, and the diagnosis is confirmed by measuring the functional level of the factor. FFP was the treatment of choice for significant bleed (half-life of FII is 3 days). Prothrombin complex concentrates (PCCs) could be used in severe cases after the prothrombin content of that particular brand is checked.

Factor V Deficiency: Owren's Disease

This is a very rare condition with an incidence of one in a million. It is inherited as autosomal recessive and in the severe form (<1% level) is associated with umbilical stump bleed, easy bruising, epistaxis, and menorrhagia. Facor V was previously known as the labile factor since it is not stable in the plasma. Unlike FVIII and IX deficiency, spontaneous Joint bleeds are very unusual. The severity is frequently attributed to the deficient FV in the platelets. Both PT and PTT are prolonged, with normal TCT. FFP (less than 2–3 months old) is the treatment of choice for significant bleed (half-life is 36 h), with local and antifibrinolytic agents for the mild bleed. Platelet transfusion could be considered in the very rare situation of severe nonresponding bleed.

Factor VII Deficiency

The incidence of this deficiency is about 1:500,000. It has a similar mode of inheritance (AR) like the other factors described earlier. The level does not correlate well with the bleeding manifestations in many cases due to the fact that it depends on the reagent used in measuring the factor level. Human tissue factor gives more accurate values which correlate more with the clinical symptoms. This could explain why some patients with <1% level have no bleeding manifestations while others manifest severe disease with hemophilia A and B–like symptoms including hemarthrosis and ICH. The PT is prolonged with normal PTT and TCT. A level of 5–10% is adequate for hemostasis in mild bleed and 15–25% for surgery. Since half-life of FVII is very short (3–4 h), FFP is not practical for treatment. PCCs or recombinant VIIa are usually used.

Factor X Deficiency

This is another rare inherited coagulation factor deficiency with an incidence of 1:500,000. Bleeding manifestations seem to correlate well with the level of the factor. They range from mild to very severe with hemophilia-like symptoms including severe hemarthrosis. Both PT and PTT are prolonged, and so the Russell's viper venum time (measures direct activation of FX). Patients with

amyloidosis may have an associated FX deficiency which is difficult to manage due to the shortened half-life in this disease. FFP and PCCs products are used for treatment of bleeds in FX deficiency. A level of 10–15% is usually adequate. Since half-life is about 40 h, the patients could be managed with FFP.

Factor XI Deficiency (Hemophilia C)

In the individual homozygous for factor XII deficiency, a marked prolongation of the PTT is usually encountered without any evidence of bleeding tendency. Similar findings are encountered with deficiencies of two other contact factors. The prekallikrien (Fletcher) factor and the HMW kininogen (Fitzgerald) factor both result in prolonged PTTs without any bleeding tendency.

Factor XII Deficiency (Hageman Factor)

The deficiency of factor XII is not associated with bleeding and does not require any treatment. The PTT is usually very long in the homozygous (>100 s). Adults with FXII deficiency were reported to have tendency for thrombosis, spontaneous abortion, myocardial infarction, and pulmonary embolism.

Factor XIII Deficiency (Fibrin Stabilizing Factor)

Since this deficiency was first described in 1960, 200 proved cases were reported. The condition is extremely rare and estimated at one in several millions. The protein is present in the plasma as well as the platelets (50% of body total FXIII activity). The condition could be suspected in a bleeder when all coagulation tests are normal. The bleeding manifestations start very early in life with umbilical stump hemorrhage in 80% of the cases. Poor wound healing, bleeding after circumcision, and gum bleed during teething. Females develop recurrent spontaneous abortions, and males develop oligospermia and infertility. ICH could occur in as many as 30% of the cases and is the leading cause of death in this deficiency. The diagnosis is made by clot solubility in urea or by factor level measurement. Only low level of this factor is needed for hemostasis (5%), and since half-life is 9–10 days, prophylactic therapy to prevent intracranial bleed is effective. FFP or cryoprecipitate every 4–6 weeks or, FXIII concentrate by IV infusion every 5–6 weeks will be adequate.

Disorders of the Third Phase of Coagulation

The inherited disorders of fibrinogen (α-fibrinogenemia, hypofibrinogenemia, and dysfibrinogenemia) may present in the homozygous newborn with a clinical picture of delayed umbilical cord bleeds (similar to factor XIII deficiency). Heterozygous newborns are usually asymptomatic except after major challenge. Cryoprecipitate provides effective therapy. Each bag contains 200–250 mg of fibrinogen; 100-mg/kg infusions provide adequate hemostatic levels. Frequent infusions are not necessary since the half-life of fibrinogen is 3–5 days. In dysfibrinogenemia, the fibrinogen level is usually normal despite bleeding manifestations and prolonged TT. This disorder is usually inherited as an autosomal dominant trait.

Aquired Coagulation Disorders

Vitamin K Deficiency

Neonatal vitamin K deficiency (hemorrhagic disease of the newborn) is discussed somewhere else in this text; therefore, only postnatal vitamin K deficiency is presented here. Late manifestations of vitamin K deficiency are reported more frequently in breast-fed infants (low vitamin K in breast milk) and infants with chronic diarrhea, fat malabsorption (celiac disease, systic fibrosis), biliary atresia, hepatitis, and α_1-antitrypsin deficiency. Infants and children on chronic broad-spectrum antibiotics are also susceptible to vitamin K–deficiency hemorrhagic complications. Prophylactic oral administration of water-soluble vitamin K to such infants is indicated (2–3 mg/day for children and 5–10 mg/day for adolescents and adults). In advanced liver disease, the production of the precursor proteins is defective, so vitamin K supplementation is not expected to be of any value. Prolonged PTs and PTTs are the only abnormal coagulation findings. Factor assays may delineate the nature of the problem.

Liver Disease and Liver Transplant

As many as 85% of children with significant liver disease manifest coagulation abnormalities that are directly proportional to the severity of the liver condition. About 15% of such patients manifest significant clinical hemorrhagic disorders. Decreased synthesis of clotting proteins is the major contributing factor, even though other factors, such

as poor clearance of the products of hemostasis, activation of the clotting and fibrinolytic systems, and loss of clotting factors into ascitic fluid, may also be involved. Fulminant liver disease in both newborns and older children may result from viral hepatitis, hypoxia, and shock. Treatment involves replacement therapy. FFP contains all the coagulation factors except fibrinogen, which is provided by cryoprecipitate. Lethal hepatic disorders have been treated with liver transplant since the mid-1980s. Survival rates for such children are on the order of 80%. Two major causes of morbidity and mortality in such patients are intraoperative bleeding and postoperative vascular thrombotic events in the transplanted vessels (portal vein and hepatic artery). This second complication is significantly more common in infants less than 1 year of age (20–25%) than in adults (3–5%).

The incidence is also related to the quality of the graft. Damaged blood vessels for instance increase the rate of thrombotic complications. The clinical features and precipitating factors for coagulopathy in liver transplant vary according to the stage of the procedure. In the preimplant stage for instance, the coagulopathy reflects the underlying liver disease, as well as the effect of clotting factors dilution due to frequent blood product replacement. In the a hepatic stage, the lack of clotting factors synthesis as well as lack of clearance of activated products are the main reasons for the profound coagulopathy, fibrinolysis, and possible DIC encountered in this stage. A very high level of tPA is generated within minutes after the donor liver is placed. In the reimplantation stage, factors and inhibitors of coagulation are gradually restored, fibrinolysis begins to resolve, fibrinogen and plasminogen levels increase while FDPs gradually decrease.

Disseminated Intravascular Coagulation (Consumptive Coagulopathy)

DIC is not a disorder in itself but a process that is secondary to a large variety of underlying conditions. The name indicates the presence of diffuse fibrin deposits scattered in the microvasculature. Both hemorrhagic and thrombotic complications are usually encountered. The first are the result of reduced clotting factors, which were consumed in the circulation, in addition to active fibrinolysis, which also contributes to the bleeding process. The thrombotic complications are the result of increased clotting triggered by various precipitating factors. Underlying disease processes may occur at all ages or be unique to a certain age group. Unique to newborns are adverse events affecting the fetoplacental unit that result in asphyxia and shock, which cause release of tissue thromboplastin that triggers the intravascular clotting process. Other pathologic disorders related to prematurity, such as respiratory distress syndrome, congenital viral infection, hypothermia, and meconium aspiration, may all initiate disseminated intravascular coagulation (DIC). The recent improvements in the care of neonates, together with a better understanding of the DIC process, have significantly changed both the classic clinical picture and the outcome of the affected newborns.

The diagnosis of DIC is based on compatible clinical features in conjunction with abnormal screening tests (PT, aPTT), low levels of certain coagulation factors (fibrinogen, factor V, factor VIII) and inhibitors (AT, heparin cofactor II, protein C), elevated fibrinogen/fibrin split products (FDPs), thrombocytopenia, and fragmented red blood cells (*Table 336.4*). Milder forms of DIC are diagnosed by tests that measure the subtle effects of small amounts of thrombin or plasmin. These include fibrin monomers, thrombin–AT complexes, FDPs, and *D*-dimer. Positive tests alone, however, cannot confirm the process of DIC.

The cornerstone of the management of DIC is the treatment of the underlying disease and its complications. The decision to treat the secondary hemostatic complications has been an issue of debate for some time. Currently, however, the old argument that replacement therapy with plasma products may "fuel the fire" is believed to be theoretical and not true. If the patient is symptomatic

Table 336.4
Laboratory findings in children with three acquired coagulation defects

Test	Disseminated intravascular coagulation	Vitamin K deficiency	Liver disease
Partial thromboplastin time	P	P	P
Prothrombin time	P	P	P
Thrombin time	P	N	P
Platelet counts	L	N	N/L
Fibrin split products	+	N	±
Fibrinogen	L	N	L
Factor VIII	L	N	N
Factor V	L	N	L

P prolonged, *L* low, *N* normal, *N/L* normal or low, + increased

due to hemostatic abnormalities, replacement therapy with FFP, exchange transfusion, cryoprecipitate, or platelet transfusion should be initiated. A reasonable therapeutic approach is to maintain a normal PTT, platelets of 50×10^9/L, and fibrinogen of 1.0 g/L. Treatment with anticoagulants such as heparin has also been an issue of controversy. The current recommendation is to restrict heparin therapy to infants with purpura fulminans, usually secondary to meningococcemia. This disorder is characterized by small and large vessel thrombi leading to organ and limb damage. Heparin is probably not indicated in children with skin necrosis only. Heparin is given either as intermittent intravenous administrations in a dose of 75–100 IU/kg every 4 h or as continuous infusion with 50–70 IU/kg as a bolus followed by 1525 IU/kg/h. This therapy should be closely monitored with serial measurements of the anti-Xa or aPTT. In children with evidence of organ or limb necrosis, anticoagulant therapy with heparin may be helpful.

Fibrinolysis

Fibrinolysis is the process responsible for the removal and degradation of the fibrin clot, whether the clot is formed physiologically, as a result of inflammation, tissue repair, or hemostasis, or precipitated by a pathologic process, such as deep vein thrombosis, pulmonary embolism, or DIC. In the first situation, the clot plays a temporary role and must be removed when normal tissue structure and function are restored. In pathologic circumstances, however, the fibrinolytic system, for some reason, fails to dissolve the fibrin clot. Similar to the other coagulation and thrombosis processes, the fibrinolytic system action is coordinated through the interaction of activators, zymogens, enzymes, and inhibitors to provide local activation at sites of fibrin deposition. Activation of the fibrinolytic system can also be achieved by intrinsic or extrinsic pathways. In intrinsic pathway, the activated contact factors (XIIa, XIa, prekallikrein) are known to activate plasminogen to plasmin while the intrinsic coagulation system is being activated. In the extrinsic system (activators are not in the plasma), however, two serine proteases tissue activators have been identified: the first is tPA and the second is urokinase-type plasminogen activator. Both have been produced by recombinant DNA and are available for therapeutic purposes.

Plasminogen is the precursor of the active fibrinolytic enzyme plasmin. It is produced by the liver and present in the plasma as a single-chain molecule. When activated to a two-chain plasmin molecule, a smaller molecule cleaved by plasmin with an amino-terminal lysine is produced (lys-plasminogen). This molecule has higher affinity for binding to fibrin and greater reactivity with plasminogen activators, through sites known as lysine-binding sites. Lysine analogs such as EACA are capable of binding to these sites on plasminogen, thus competing with the lysine-like sites on fibrin, resulting in inhibition of fibrinolysis by rendering the fibrin protected from binding with plasmin or plasminogen. The physiologic fibrinolytic inhibitor α_2-antiplasmin is also mediated in part by binding to the same sites of plasminogen. Plasmin is capable of hydrolyzing proteins other than fibrin and fibrinogen; factor V, factor VIII, complement components, adrenocorticotropic hormone, growth hormone, and glucagon are some examples. Together with other fibrinolytic system inhibitors such as PAI, α_2-antiplasmin plays an important role in the regulation of fibrinolysis.

Once the clot is physiologically formed, fibrinolysis is instantly stimulated. Plasminogen, activated by tPA and single-chain urokinase plasminogen activator (SCU-PA), binds to fibrin while fast-acting inhibitors such as α_2-antiplasmin and PAI-1 go into action. Both are more efficient when their substrates (plasmin for the first and tPA for the second) are free in the plasma rather than bound to other proteins. This allows plasminogen activation on the fibrin while avoiding its effect systemically. When therapeutic quantities of tPA are infused, however, virtually all the plasminogen in the plasma is converted to plasmin, overcoming the neutralizing capacity of antiplasmin and leading eventually to fibrinogenolysis (the lytic state).

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337 Pediatric Venous Thromboembolism

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The incidence of pediatric venous thromboembolism (VTE) is increasing and has become a significant cause of morbidity and mortality in infants and children. It is therefore crucial for the primary care pediatrician and subspecialist alike to appreciate the epidemiology, etiologies, presentations, diagnostic evaluation, management, and outcomes of VTE in neonates and older children.

The objectives of this narrative review are to: (1) briefly consider physiologic mechanisms of hemostasis; (2) discuss epidemiology, etiology, and clinical presentation of VTE in children; and (3) present diagnostic measures and treatment options.

Background: Brief review of physiologic mechanisms of hemostasis.

Coagulation is not, in itself, a pathologic condition. Indeed, coagulation and fibrinolysis dynamically interact in the normal physiological state, and it is only when coagulation is insufficiently inhibited or fibrinolysis is excessively inhibited that pathologic thrombosis results. Understanding these processes in normal physiology will facilitate a comprehension of pathologic thrombosis.

Hemostasis is defined as the process by which blood flow from within a vessel is arrested. It is helpful to conceive of hemostasis in two major phases – primary and secondary – that interact in dynamic fashion. Primary hemostasis is triggered when blood vessel damage (i.e., endothelial injury) exposes subendothelial tissue factor (TF) and collagen to flowing blood. Von Willebrand factor and fibrinogen then mediate platelet adhesion and aggregation, resulting in the formation of a platelet plug. Additionally, platelet activation results in surface exposure of phospholipid, forming the scaffold for the plasma clotting reactions of secondary hemostasis. In secondary hemostasis, coagulation activation is initiated as exposed subendothelial TF combines with small amounts of circulating activated factor VII, forming a complex that directly activates factor X (Xa). This is known as the TF pathway (formerly called the extrinsic pathway) of the coagulation cascade. Subsequently, through the common pathway, Xa combines with activated factor V (Va) as the prothrombinase complex, converting prothrombin to thrombin. This process of thrombin generation via the TF pathway is described as thrombin initiation. Thrombin generation is greatly upregulated (described as thrombin propagation) when thrombin activates factor XI, which in turn activates factors VIII (VIIIa) and IX (IXa) through the "contact pathway" (historically known as the "intrinsic pathway") of the coagulation cascade. VIIIa and XIa form a "tenase" complex, converting factor X to Xa, ultimately generating thrombin through the common pathway. The thrombin propagation phase of secondary hemostasis is also mediated by thrombin-induced activation of factors VIII and V. Thrombin is important in the conversion of soluble fibrinogen to insoluble fibrin, forming polymers (fibrils) that are cross-linked by factor XIII to form a hemostatic clot that, in the venous system, is rich in fibrin and interspersed with platelets. Thrombin also serves to activate platelets, thereby fueling further platelet plug and clot formation.

Principal regulators of coagulation activation include the native anticoagulants (antithrombin, protein C, and protein S), thrombomodulin, and tissue factor pathway inhibitor. Antithrombin (formerly known as antithrombin III) is the primary inhibitor of circulating thrombin. Protein C inhibits activation of factors V and VIII. Protein S and thrombomodulin serves as cofactors for protein C.

The coagulation system is in dynamic balance with the fibrinolytic system. In the fibrinolytic system, clot-bound plasminogen is converted by tissue plasminogen activator to plasmin, which cleaves fibrin into monomers and dimers. This process mediates clot lysis, and the fibrin monomers and dimers produced also inhibit further fibrin polymerization.

Further discussion of genetic and acquired thrombophilia traits is beyond the scope of this review, but details can be found in several other texts.

Epidemiology

Historically, the incidence of VTE in children has been perceived to be low. Review of data from multiple recent patient registries revealed an estimated cumulative incidence of 0.07 per 10,000 individuals (5.3 per 10,000 hospitalizations) for extremity deep venous thrombosis (DVT) and/or pulmonary embolism (PE) among non-neonatal Canadian children, and an incidence rate of 0.14

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per 10,000 Dutch children per year for VTE in general. An evaluation of the National Hospital Discharge Survey and census data for VTE in the United States from 1979 to 2001 disclosed an overall incidence rate of 0.49 per 10,000 individuals per year. During a recent 7-year period of study the annual rate of pediatric VTE increased by 70%, from 34 to 58 cases per 10,000 hospital admissions.

A bimodal age distribution of the incidence rate for childhood VTE is noted, with peak rates in neonates and adolescents. The Dutch registry, for example, indicated a VTE incidence rate of 14.5 per 10,000 per year in the neonatal period, approximately 100 times greater than the overall rate in childhood, while the VTE-specific incidence rate in the United States among adolescents 15–17 years of age was determined to be 1.1 per 10,000 per year, a rate nearly threefold that observed overall in childhood.

Most recently, an analysis of the Pediatric Health Information System (PHIS) database from 2001 to 2007 revealed that approximately 1 in 200 hospitalized children are diagnosed with VTE. This figure likely includes both patients who developed VTE in hospital as well as those children admitted for VTE that developed outside the hospital.

Etiology

Virchow's triad consists of venous stasis, endothelial damage, and the hypercoagulable state. This group of clinical situations encapsulates the primary risk factors responsible for pathogenesis of VTE. In children, greater than 90% of VTE are risk-associated (as compared to approximately 60% in adults), with risk factors in children often disclosed from more than one component of this triad. Of the clinical prothrombotic risk factors, one of the most common is an indwelling central venous catheter. Over 50% of cases of DVT in children and over 80% of cases in newborns occur in association with central venous catheters. The presence of an indwelling central venous catheter, underlying malignancy or disorder for which bone marrow transplantation was undertaken, and congenital cardiac disease and its corrective surgery were all highly prevalent in the Canadian pediatric thrombosis registry, whereas underlying infectious illness and the presence of an indwelling central venous catheter were identified as pervasive clinical risk factors in a recent cohort study analysis from the United States. A recent review of the Pediatric Health Information System revealed that a majority (63%) of children with VTE had >1 coexisting chronic complex medical condition and that pediatric malignancy was the medical comorbid condition associated most strongly with recurrent VTE.

As noted above, thrombophilia may be caused by any alteration in hemostatic balance that increases thrombin production, enhances platelet activation/aggregation, mediates endothelial activation/damage, or inhibits fibrinolysis. Regarding the hypercoagulable state, blood-based risk factors for VTE in children include both inherited and acquired thrombophilic conditions. Potent thrombophilic conditions (e.g., severe anticoagulant deficiencies, antiphospholipid antibodies) in children are frequently acquired, rather than congenital. By contrast, the common congenital thrombophilia traits (e.g., heterozygosity for the factor V Leiden or prothrombin G20210A polymorphisms) tend to be more mild.

Common examples of acquired thrombophilia in children include: increased factor VIII activity with significant infection and inflammatory states; anticoagulant deficiencies due to consumption in bacterial sepsis and disseminated intravascular coagulopathy (DIC) or to the production of inhibitory antibodies in acute viral infection; and para-infectious development of antiphospholipid antibodies (APA). In order to provide an appreciation of the magnitude of VTE risk increase associated with several congenital/genetically influenced thrombophilia traits, population-based VTE risk estimates derived from the adult literature are shown in *Table 337.1*. As seen in the Table, the addition of standard-dose estrogen oral contraceptive pill to an underlying heterozygous factor V Leiden (in large part by virtue of a "double-hit" to the protein C pathway) would be expected to increase the risk for VTE from a baseline risk of 15 per 10,000 US females aged 15–17 years per year to a risk of over 500 per 10,000, or 5%, per year.

Table 337.1
VTE risk estimates for selected thrombophilia traits and conditions

Trait/condition	VTE risk estimate (× baseline)
Hyperhomocysteinemia	2.5
Prothrombin 20210 mutation, heterozygous	2–3
Oral contraceptive pill (OCP; standard-dose estrogen)	4
Factor V Leiden mutation, heterozygous	2–7
OCP+Factor V Leiden mutation, heterozygous	35
Factor V Leiden mutation, homozygous	80

Clinical Presentation

The degree of clinical suspicion for acute VTE in children should be primarily influenced by the following characteristics: (1) clinical signs and symptoms; (2) personal history of VTE; (3) clinical prothrombotic risk factors; (4) family history of early (e.g., before age 50 years) VTE or other vascular events; and (5) known thrombophilia traits/risk factors. In many cases, information from this last category is not available at the time of clinical presentation with possible VTE.

The signs and symptoms of VTE vary based upon anatomic location.

Limb Deep Venous Thrombosis

The classic manifestation of acute limb DVT is painful unilateral extremity swelling. The presence of Homan's sign (pain upon manual calf compression or with forced dorsiflexion of the foot while the knee is flexed) or the presence of a palpable cord in the popliteal fossa may suggest lower extremity DVT; however, these physical findings are both insensitive and nonspecific. In upper extremity DVT with extension into, and occlusion of, the superior vena cava (SVC), signs and symptoms may include swelling and/or erythema of neck and face, visualization of superficial collateral vessels in the chest, bilateral periorbital edema, and headache.

Pulmonary Embolism

Pulmonary embolism usually presents with sudden- or progressive-onset dyspnea and/or pleuritic chest pain, and is occasionally accompanied with hypoxemia (particularly in settings of extensive or proximal PA involvement). Associated right heart failure (cor pulmonale) may manifest with hepatomegaly, visible superficial collateral vessels in the abdomen, and/or peripheral edema. Proximal PE and especially saddle embolus can present with cyanosis or sudden cardiopulmonary collapse. In many cases, however, PE may be asymptomatic or subtle in children, especially when involving limited segmental or subsegmental branches of the pulmonary arteries. At the same time, the most peripheral PE near the pleura frequently causes pleuritic reactions (pleuritis) and/or effusions that are quite symptomatic. In one retrospective series, only 50% of affected children had clinical symptoms attributable to PE.

Cerebral Sinovenous Thrombosis

Signs and symptoms of acute cerebral sinovenous thrombosis (CSVT) may include severe and persistent headache, blurred vision, neurologic signs (e.g., cranial nerve palsy, papilledema), or seizures. Although not signs and symptoms of the CSVT per se, one must also be attentive to the constellation of findings in otitic hydrocephalus and Gradenigo's syndrome (the triad of suppurative otitis media, pain in the distribution of the trigeminal nerve, and abducens nerve palsy), in which otitis media is complicated by mastoiditis and petrositis, with development of thrombus in the adjacent sigmoid or lateral sinus. Mastoid tenderness, fever, and findings (or recent history) of otitis media should therefore prompt suspicion for this disorder.

Renal Vein Thrombosis

Renal vein thrombosis (RVT) is classically associated with hematuria and thrombocytopenia, sometimes accompanied by anemia and hypertension. Bilateral involvement is sometimes associated with uremia and/or oliguria. RVT is most common during the neonatal period and may be noted on physical exam as a flank mass. RVT in older children is often associated with nephrotic syndrome (a risk factor for VTE in general), and may therefore present with peripheral and/or periorbital edema.

Portal Vein Thrombosis and Hepatic Vein Thrombosis

Portal vein thrombosis (PVT) characteristically presents with splenomegaly, and is associated with thrombocytopenia and, often, anemia; gastrointestinal bleeding at presentation typically signals the presence of gastroesophageal varices due to portal hypertension.

Hepatic vein thrombosis without PVT is typically asymptomatic, and usually found incidentally upon abdominal imaging.

Intracardiac Deep Venous Thrombosis

Isolated intracardiac thrombosis in association with cardiac surgery or central venous catheter placement is most often asymptomatic. Thrombocytopenia, described for RVT above, can also be seen with intracardiac (e.g., right atrial) thrombus.

Internal Jugular DVT and Lemierre's Syndrome

Internal jugular vein thrombosis may manifest with neck pain or swelling. Lemierre's syndrome (classically caused by Fusobacterium, but occasionally identified with other potentially causative organisms) is associated with fever, trismus, and a palpable thrombus in the lateral triangle of the neck.

Diagnosis

Radiologic Evaluation

The importance of radiologic imaging lies in its dual ability to confirm the clinical diagnosis of VTE as well as define both the extent and occlusiveness of thrombosis. The gold-standard for diagnosis of venous thrombosis is conventional venography, but the utility of this modality is limited by its invasive nature and the associated risks.

Currently, when DVT of an extremity is suspected, compression ultrasonography with Doppler color flow imaging is typically used for confirmation. When the thrombus may involve or extend into deep pelvic or abdominal veins, computed tomography venography (CTV) or magnetic resonance venography (MRV) is often required.

If involvement of the central thoracic vasculature (e.g., right atrial thrombosis, SVC thrombosis) is suspected, echocardiogram may be used in addition to CT or MRI. In the case of asymptomatic non-occlusive extremity DVT disclosed by ultrasound, CTV, MRV with gadolinium contrast, or conventional venography may be necessary for diagnostic confirmation. To establish a diagnosis of DVT of the jugular venous system (such as in suspected cases of Lemierre's syndrome), compression ultrasound with Doppler imaging is typically used.

PE in children is commonly evaluated with spiral CT angiography or by ventilation-perfusion scan. The latter, however, is generally suboptimal in cases involving other potentially confounding lung pathologies or at centers without sufficient expertice with this modality. CSVT is typically diagnosed by MRV or CTV. This diagnosis occasionally is made in the course of head imaging (e.g., plain CT or MRI) for another cause. RVT is most often diagnosed clinically in neonates and is supported by Doppler ultrasound findings of intrarenal vascular resistive indices; however, in some cases a discrete thrombus may be suggested by Doppler ultrasound (especially when extending into the inferior vena cava) or may be further disclosed via MRV. When RVT occurs in older children, Doppler ultrasound or CTV is often diagnostic. Similarly, portal vein thrombosis is typically visualized by Doppler ultrasound or CTV.

In some cases, new-onset venous thrombosis is being evaluated in patients with anatomic abnormalities of the venous system, including extensive collateral venous circulation due to a prior VTE episode, May-Thurner anomaly (left iliac vein is compressed by right iliac artery, causing increased risk of DVT due to compressive stasis), or atretic IVC with azygous continuation. For these patients, more sensitive methods such as CTV or MRV are often required to define the vascular anatomy as well as the presence, extent, and occlusiveness of thrombosis. Conventional venography may also be required.

Disadvantages of MRV include its expense, and necessity of sedation in young, developmentally delayed, or anxious children. Additionally, its use during acute VTE evaluation requires availability of MR-trained technologists. However, MRV offers a significant advantage over CTV by providing diagnostic sensitivity at least as great as CTV (particularly when gadolinium enhancement is used for scenarios in which non-occlusive thrombus must be distinguished from flow artifact), without significant radiation exposure.

Laboratory Evaluation

A thorough diagnostic laboratory evaluation in the setting of pediatric acute VTE should include a complete blood count, DIC panel, comprehensive thrombophilia evaluation (see Etiology, above), and beta-HCG testing in postmenarchal females. Additional laboratory studies may also be necessary depending upon associated medical conditions and possible VTE involvement of specific organ systems. *Table 337.2* summarizes a panel of thrombophilia traits and markers that each have been identified as risk factors for VTE in pediatric studies, and as such have been recommended by the Scientific and Standardization Committee Subcommittee on Perinatal and Pediatric Haemostasis of the International Society on Thrombosis and Haemostasis for the diagnostic laboratory evaluation of acute VTE in children. This comprehensive panel includes tests of anticoagulant deficiency (e.g., protein C, protein S, antithrombin), procoagulant excess (e.g., factor VIII), mediators of hypercoagulablity and/or endothelial damage (e.g., APA, lipoprotein(a), homocysteine), and markers of coagulation activation (e.g., D-dimer).

Significant debate currently surrounds the issue of comprehensive laboratory testing for thrombophilia traits

Table 337.2
Thrombophilic conditions and markers tested during comprehensive diagnostic laboratory evaluation of acute VTE in children

Condition/marker	Testing method(s)
Genetic	
Factor V Leiden polymorphism	PCR
Prothrombin 20210 polymorphism	PCR
Elevated plasma lipoprotein(a) concentration[a]	ELISA
Acquired or genetic	
Antithrombin deficiency	Chromogenic (functional) assay
Protein C deficiency	Chromogenic (functional) assay
Protein S deficiency	ELISA for free (i.e., functionally active) protein S antigen
Elevated plasma factor VIII activity[b]	One-stage clotting assay (aPTT-based)
Hyperhomocysteinemia	Mass spectroscopy
Antiphospholipid antibodies	ELISA for anticardiolipin and anti-beta-2-glycoprotein-I IgG and IgM; clotting assay (dilute Russell Viper Venom time or aPTT-based phospholipid neutralization method for lupus anticoagulant)
Disseminated intravascular coagulation	Includes platelet count, fibrinogen by clotting method (Clauss), and D-dimer by semiquantitative or quantitative immunoassay (e.g., latex agglutination)
Activated protein C resistance	Clotting assay (aPTT-based)

[a]Although designated here as genetic, lipoprotein(a) may also be elevated as part of the acute phase response
[b]Noted as worthy of consideration in original International Society on Thrombosis and Haemostasis recommendations; this has since been shown to be a prognostic marker in pediatric thrombosis. Additional testing involving the fibrinolytic system and systemic inflammatory response is also noted as worthy of consideration

in children with, or at heightened risk of, VTE. Many of the current guidelines are based upon consensus expert opinion or low-grade clinical evidence. Indeed, given the low incidence of VTE in the general pediatric population, widespread, unselected thrombophilia screening would neither be ethical nor cost-effective.

A comprehensive thrombophilia assessment is likely to have greatest clinical utility among individuals with a personal or close family history of a thrombotic event before the age of 55 years. A recent analysis of comprehensive laboratory evaluation in 56 children with positive family history of early VTE, but negative personal history of the same, advocated a risk-stratified approach to laboratory-based thrombophilia evaluation in these asymptomatic children that would target individuals with familial early VTE. Particularly in children and young adults, populations in which the incidence of VTE is low, efforts to identify individuals with clinical risk factors for VTE who have meaningful underlying thrombophilia may provide a rational approach to VTE prevention by targeting a subpopulation at heightened risk, in which comprehensive laboratory testing would be more beneficial.

Conventional Therapy

Table 337.3 provides a summary of conventional antithrombotic agents and corresponding target anticoagulant levels, based upon recent pediatric recommendations for both initial (i.e., acute phase) and extended (i.e., subacute phase) treatment. Conventional anticoagulants attenuate hypercoagulability, decreasing the risk of thrombus progression and embolism, while relying principally upon intrinsic fibrinolytic mechanisms to dissolve the thrombus. The most commonly employed conventional anticoagulants in children include heparins (either unfractionated [UFH] or low molecular weight heparin [LMWH] varieties) and warfarin. Heparins work by enhancing the activity of antithrombin, as discussed above. Warfarin acts through antagonism of vitamin K, thus interfering with gamma-carboxylation of the vitamin K-dependent procoagulant factors II, VII, IX, and X, as well as intrinsic anticoagulant proteins C and S.

Initial anticoagulant therapy for the acute phase of VTE in children involves UFH or LMWH. Two LMWH agents commonly employed in the United States (based upon labeling for adult VTE) are enoxaparin and

Table 337.3
Recommended intensities and durations of conventional antithrombotic therapies in children, by etiology and treatment agent (adapted from current consensus-based recommendations)

Episode	Agents and target anticoagulant activities				Duration of therapy, by etiology
	Initial treatment		Extended treatment		
First	UFH	03–0.7 anti-Xa U/mL	Warfarin	INR 2.0–3.0	Resolved risk factor: 3–6 months
	LMWH	0.5–1.0 anti-Xa U/mL	LMWH	0.5–1.0 anti-Xa U/mL	No known clinical risk factor: 6–12 months
					Chronic clinical risk factor: for duration of risk factor (often with prophylactic dosing, after initial 3–6 months of therapeutic dosing)
					Potent congenital thrombophilia: indefinite
Recurrent	UFH	0.3–0.7 anti-Xa U/mL	Warfarin	INR 2.0–3.0	Resolved risk factor: 3–6 months
	LMWH	0.5–1.0 anti-Xa U/mL	LMWH	0.5–1.0 anti-Xa U/mL	No known clinical risk factor: indefinite
					Chronic clinical risk factor: for duration of risk factor (often with prophylactic dosing, after initial 3–6 months of therapeutic dosing)
					Potent congenital thrombophilia: indefinite

dalteparin. In recent years, LMWH has become increasingly popular as the first-line agent for initial anticoagulant therapy in children given the relative ease of subcutaneous administration, the decreased need for blood monitoring of anticoagulant efficacy, and a decreased risk of the development of heparin-induced thrombocytopenia (HIT). LMWH is not ideal in all situations, however. UFH has a much shorter half-life than LMWH, and is therefore preferred in circumstances of heightened bleeding risk, upcoming surgery/invasive procedure, or labile acute clinical status, since the anticoagulant effect rapidly dissipates following cessation of the drug. Additionally, because LMWH is partly eliminated through the renal system, UFH (which is largely heptically eliminated) is more appropriate for acute VTE therapy in the setting of significantly impaired renal function.

Common initial dosing for UFH in non-neonatal children begins with an IV loading dose of 50–75 U/kg followed by a continuous IV infusion of 15–20 U/kg/h. Due to lower antithrombin levels in full-term neonates, a maintenance dose of up to 50 U/kg/h may be required for these patients, especially if the clinical condition is complicated by antithrombin consumption. The starting dose for enoxaparin in non-neonatal children commonly ranges between 1.0 and 1.375 mg/kg subcutaneously on an every-12-h schedule and does not require a bolus dose. In full-term neonates, a dose of 1.5 mg/kg is typically necessary. For dalteparin, on the other hand, initial maintenance dosing of 1.0–1.5 mg/kg (100–150 anti-Xa U/kg) appears appropriate based upon available pediatric data.

Anti-factor Xa activity levels can be used to follow either type of heparin therapy, whether UFH or LMWH. Anti-Xa level should be obtained 6–8 h after initiation of UFH infusion or 4 h following any one of the first few doses of LMWH. For UFH, the therapeutic range is 0.3–0.7 anti-Xa activity U/mL, while for LMWH the therapeutic range is 0.5–1.0 U/mL. When the anti-Xa assay is not available, the activated partial thromboplastin time (aPTT) may be used (with a goal aPTT of approximately 1.5–2 times the upper limit of age-appropriate normal values); however, this approach is especially suboptimal in the pediatric age group, in which transient antiphospholipid antibodies are common and may alter the clotting endpoint. Notably, one study of pediatric heparin monitoring demonstrated inaccuracy of aPTT approximately 30% of the time. When dosed by weight in childhood, LMWH does not require frequent monitoring, but anti-Xa activity should be evaluated with changes in renal function, weight shifts $>10\%$ of baseline, or in clinical situations where bleeding side effect is of particular concern. In addition, there are cases of acute VTE in which acquired antithrombin deficiency is related to consumption in acute infection or inflammation. In these instances, the anti-Xa activity may rise as antithrombin levels normalize with resolution of the acute illness, warranting follow-up evaluation of anti-Xa in the subacute period.

Controversy exists regarding length of therapy during both the acute and subacute phases of anticoagulation for VTE in children. Due to lack of pediatric data, the recommended duration of heparinization of 5–10 days during the initial therapy for acute VTE has been extrapolated

from adult data. UFH treatment is rarely maintained beyond the acute period, given the risk of osteoporosis with extended administration and the inconvenience of continuous intravenous administration. Although adult data suggest efficacy of subcutaneous administration of unfractionated heparin for acute VTE, this has only been evaluated for the acute therapy period prior to extended therapy with warfarin, and the appropriateness of such an approach in children has not been established.

Extended anticoagulant therapy (i.e., subacute phase) for VTE in children may employ LMWH or warfarin. For warfarin anticoagulation, warfarin is often started during the acute phase. As above, however, severe congenital PC deficiencies can present as VTE in early childhood and are associated with warfarin skin necrosis. Warfarinization should, therefore, be initiated only after therapeutic anticoagulation is achieved with a heparin agent. Due to the relatively short half-life of PC, warfarin's interference with its activation can result in a transient hypercoagulable state. It is therefore also important to use LMWH or UFH as a "bridge" until warfarin reaches effective levels.

A common starting dose for warfarin in children is 0.1 mg/kg orally once daily. Warfarin is monitored by international normalized ratio (INR), derived from the measured prothrombin time. The therapeutic INR range for warfarin anticoagulation in VTE is 2.0–3.0. Recent adult data do not agree with the historical evidence for maintaining a higher INR (2.5–3.5) in the presence of APA; however, pediatric data are lacking with regard to both optimal dose intensity and duration in children with APA syndrome. The INR is typically checked after the first 5 days of initiation of (or dosing change in) warfarin therapy, and weekly thereafter until stable. As levels become more stable, less frequent monitoring is often feasible. The INR should also be evaluated at the time of any bleeding manifestations or increased bruising. Warfarin must be discontinued at least 5 days prior to invasive procedures, with an INR obtained prior to the procedure to ensure resolution of anticoagulant effect. In some situations, an anticoagulant transition, or "bridge," to LMWH can be performed, to minimize the time off anticoagulation perioperatively.

As mentioned above, clear recommendations for long-term duration of anticoagulant therapy are not available, and depend heavily on clinical situation, as well as provider preference. For initial VTE in children in the absence of potent chronic thrombophilia (e.g., APA syndrome, homozygous anticoagulant deficiency, homozygous factor V Leiden or prothrombin 20210), the recommended duration of anticoagulant therapy is 3–6 months in the presence of an underlying reversible risk factor (e.g., postoperative VTE) and 6–12 months when idiopathic. In the case of chronic risk factors (systemic lupus erythematosus), the initial 3–6 months consist of therapeutic dosing, followed by prophylactic dosing for the duration of the risk factor's presence. Recurrent VTE is treated for 3–6 months in the presence of an underlying reversible risk factor, and indefinitely when idiopathic. As above in the case of chronic risk factors (systemic lupus erythematosus), the initial 3–6 months of therapy for recurrent VTE consist of therapeutic dosing, followed by prophylactic dosing for the duration of the risk factor's presence. In the setting of APA syndrome or potent congenital thrombophilia, the treatment duration for first-episode VTE is often indefinite. Some evidence suggests that children with SLE and persistence of the lupus anticoagulant (LA) have a 16- to 25-fold greater risk of TEs than children with SLE and no LA. However, in children with primary (i.e., idiopathic) or secondary (i.e., associated with SLE or other underlying chronic inflammatory condition) APA syndrome, it is possible that the autoimmune disease will become quiescent in later years, such that the benefit of continued therapeutic anticoagulation as secondary VTE prophylaxis may be reevaluated. Some experts have recommended consideration of low-dose anticoagulation as secondary VTE prophylaxis following a conventional 3- to 6-month course of therapeutic anticoagulation for VTE in children with SLE who have APA syndrome. Such low-dose, or prophylactic, anticoagulation might, for example, consist of enoxaparin 1.0–1.5 mg/kg subcutaneously once daily, enoxaparin 0.5 mg/kg subcutaneously twice daily, or daily warfarin with a goal INR of 1.5. However, further study to optimize the intensity and duration of therapy/secondary prophylaxis for VTE in children with APA syndrome is urgently needed, especially given the recent evidence in adult VTE that secondary prophylaxis with low-dose warfarin not only may offer little risk reduction beyond no anticoagulation, but also is associated with bleeding complications despite a reduced warfarin dose.

A multicenter randomized trial is underway to determine whether a shorter duration of anticoagulant therapy (i.e., 6 weeks) is appropriate for pediatric VTE associated with identifiable reversible risk factors and no potent genetic thrombophilia state.

Novel/Emerging Therapies and New/Alternative Anticoagulants

Direct Thrombin Inhibitors

Direct thrombin inhibitors inhibit thrombin directly via its active site or by binding to its target on fibrin. This class

includes intravenously administered drugs such as bivalirudin and argatroban, as well as oral alternatives such as dabigatran.

The intravenous direct thrombin inhibitors are indicated for the treatment of heparin-induced thrombocytopenia (HIT), particularly when associated with acute thrombosis (HITT), and are also used in patients with a history of HIT.

Dabigatran is an oral direct thrombin inhibitor, which has been approved in Europe and Canada since 2008 for venous thromboembolism (VTE) prophylaxis in the setting of orthopedic surgery, and was recently approved in the US for stroke prevention in adults with atrial fibrillation. A recent meta-analysis of the three phase-3 studies, RE-MODEL, RE-MOBILIZE, and RE-NOVATE, supported the individual trials' conclusions of noninferiority to enoxaparin. Results of the RE-COVER study which compared dabigatran with warfarin for the treatment of acute VTE in 2,539 patients were recently reported and showed equivalent rates of recurrent VTE without significantly different major bleeding episodes in patients treated with dabigatran versus those who received warfarin.

Xa Inhibitors

Factor Xa inhibitors, including fondaparinux, inhibit the activation of factor X, thereby indirectly inhibiting thrombin. Fondaparinux is an entirely synthetic pentasaccharide that is structurally related to the antithrombin-binding site of heparin. In contrast to heparin, which interacts with many plasma components, the pentasaccharide selectively binds to antithrombin, causing it to rapidly inhibit factor Xa, a key enzyme in the coagulation pathway.

Rivaroxaban, an oral factor Xa inhibitor, is already approved for VTE prophylaxis following hip and knee replacement in Europe and Canada, and appears near to approval in the United States. The RECORD series of clinical trials compared rivaroxaban to subcutaneous enoxaparin for the prevention of venous thromboembolism after orthopedic surgery and illustrated both efficacy and safety. Another Factor Xa inhibitor, apixaban, is currently in trials for VTE treatment and post-orthopedic surgery prophylaxis.

Intravenous direct thrombin inhibitors are routinely monitored by aPTT, with the therapeutic goal ranging from a 1.5- to 3.0-fold aPTT prolongation. A variety of factor Xa inhibitors and oral direct thrombin inhibitors are undergoing preclinical development or evaluation in adult clinical trials.

Both the factor Xa inhibitors and the direct thrombin inhibitors are also being evaluated for their efficacy in stroke prevention in the setting of atrial fibrillation. Though these new agents may allow for similar efficacy and safety as warfarin for long-term oral anticoagulation therapy or prevention, significant cost may be prohibitive. Also, despite the inconvenience of frequent lab monitoring of warfarin, it is an effective means of evaluating compliance. An effective antidote or reversal agent for these drugs (such as protamine sulfate might be used for overdose of unfractionated heparin or LMWH) is not currently available. Therefore, optimal safety information regarding dosing regimens is of vital importance. It is hoped that head-to-head trials of these new anticoagulants will provide useful information regarding the challenges that will arise in optimal therapeutic selection.

Thrombolytic Modalities

Systemic TPA

One treatment approach that is becoming more common in children with hemodynamically significant PE or extensive limb-threatening VTE is the use of thrombolysis. The conventional anticoagulants discussed above act by attenuating clot progression while intrinsic fibrinolysis occurs physiologically. Thrombolytics, on the other hand, promote fibrinolysis directly. Tissue-type plasminogen activator (TPA) is an intrinsic activator of the fibrinolytic system, and can be administered in its recombinant form by various routes (e.g., systemic bolus, systemic short-duration infusion, systemic low-dose continuous infusion, local catheter-directed infusion with or without interventional mechanical thrombectomy/thrombolysis). A recent cohort study analysis of children with acute lower extremity DVT, who had an a priori high risk of poor post-thrombotic outcomes by virtue of completely veno-occlusive thrombus and plasma FVIII activity >150 U/dL or D-dimer concentration >500 ng/mL, revealed that a thrombolysis regimen followed by standard anticoagulation may substantially reduce the risk of post-thrombotic syndrome when compared to standard anticoagulation alone. However, bleeding risk must be carefully assessed prior to the use of this approach.

Percutaneous Mechanical/ Pharmacomechanical Thrombolysis (PMT/PPMT)

Percutaneous mechanical/pharmacomechanical thrombolysis (PMT/PPMT), using a combination of

intravenous mechanical clot disruption and local TPA infusion, is a therapeutic option that is gaining popularity. This procedure may be followed by catheter-directed thrombolytic infusion (CDTI), a practice in which TPA is administered locally over a period of 1–2 days following the procedure.

One recent prospective cohort study evaluated 16 children who suffered from completely occlusive proximal limb DVT in association with acute elevation of FVIII and D-dimer who elected to undergo PMT/PPMT within 60 days of symptom onset. PMT/PPMT was successfully conducted in 15 cases and CDTI was employed adjunctively in 11 of these for the purpose of providing local therapy only, thereby reducing the risks of systemic thrombolysis (including systemic bleeding risks involving critical sites such as the central nervous system). There were no peri-procedural major bleeding events, but one symptomatic pulmonary embolism occurred. Clot lysis was achieved in 94% of cases. There were five acute local recurrences within 1 week (all of which were successfully re-lysed). Despite acute local re-thrombosis in 40%, 83% of these were successfully re-lysed, and late recurrent DVT occurred in 31% overall. These data suggest that PMT with/without adjunctive CDTI can be used safely in adolescents with DVT known to be at high a priori risk for PTS. Although signs and/or symptoms of PTS were still observed in some patients even when PMT was performed within 10 days of symptom onset, the rate of functionally significant PTS occurred in only 25% of these high-risk patients.

At the time of this writing, the existing literature contains no randomized control trials of PMT, in children or adults. Indeed, prospective data on this lytic intervention for DVT are limited to two adult studies, which were actually focused more upon CDTI, and PMT was reported in just a few cases in each study. Retrospective studies, on the other hand, are somewhat more numerous. Eight retrospective studies exist, totaling approximately 200 adult DVT patients treated by PMT with/without adjunctive CDTI. However, published experience with a regimen of PMT followed by adjunctive CDTI as described above is limited to three retrospective adult studies.

Regarding the safety of PMT with/without CDTI, only six cases of acute major bleeding and zero cases of acute symptomatic PE were reported among the nine retrospective studies, out of a total of 279 patients. Acute thrombolysis rates were high across the eight retrospective studies, suggesting potential efficacy. However, long-term patency was only reported by Lin and colleagues, who determined a rate of 65%. No cases of acute recurrent DVT were reported among a cumulative total of 62 subjects in the retrospective studies wherein this outcome was assessed. These findings identify PMT with adjunctive CDTI as a therapeutic option worthy of further prospective study as an effective and potentially safer (decreased systemic bleeding risks involving critical sites such as the central nervous system) alternative to systemic thrombolysis in children with occlusive proximal limb DVT who have adverse prognostic biomarkers at acute presentation.

Other Antithrombotic Agents

Various other antithrombotic products await further clinical trials to demonstrate efficacy. For example, as mentioned above, protein C concentrate can be useful as an adjunct to standard heparin therapy for VTE or purpura fulminans due to microvascular thrombosis in severe congenital protein C deficiency or in children with sepsis, particularly in meningococcemia. In addition, various case series have suggested a role for antithrombin replacement in VTE prevention in children and young adults with congenital severe antithrombin deficiency, for the prevention of L-asparaginase-associated VTE in pediatric acute lymphoblastic leukemia (ALL), and as combination therapy with defibrotide in the prevention and treatment of hepatic sinusoidal obstruction syndrome (formerly termed veno-occlusive disease) in children undergoing hematopoietic stem cell transplantation. The potential benefit for VTE risk reduction using a regimen of antithrombin replacement combined with daily prophylactic LMWH during induction and consolidation phases of therapy in ALL has now also been suggested by a historically controlled cohort study of the BFM 2000 protocol experience in Europe. As noted above, antithrombin replacement may also be worthy of consideration in patients receiving heparin therapy for acute VTE in whom significant antithrombin deficiency prevents the achievement of therapeutic anti-Xa levels (i.e., heparin "resistance"). This may be the case in nephrotic syndrome-associated VTE. Additionally, neonates with clinical conditions complicated by antithrombin consumption as described above are particularly predisposed to such heparin "resistance," due to a physiologic relative deficiency of this key intrinsic thrombin inhibitor.

Another complementary therapy to consider in children of appropriate size with persistent prothrombotic risk factor(s) who suffer from recurrent VTE (especially PE) is the placement of temporary vena caval filters. However, recommended use of these devices in pediatric VTE is generally restricted to the setting of inability or contraindication to anticoagulate (typically transient). The impact of

non-retrievable devices upon the vena cava of the developing child has not been well studied, and experience with surgical removal of non-retrievable vena caval filters is quite limited. Consequently, the use of non-retrievable vena caval filters in pediatrics should be undertaken with caution.

Outcomes

Both acute and long-term complications of VTEs, and their associated therapy, must be considered. Short-term adverse outcomes of the thrombotic event itself may include post-thrombotic hemorrhage (in the brain, testis, or adrenal gland), early recurrent VTE (including DVT and PE), SVC syndrome in upper extremity DVT, acute renal insufficiency in RVT, catheter-related sepsis or malfunction (sometimes necessitating surgical replacement) in CRT, severe acute venous insufficiency leading to venous infarction with limb gangrene in rare cases of occlusive DVT involving the extremities, and/or death from hemodynamic instability in extensive intracardiac thrombosis or proximal PE. Additionally, one must consider the major hemorrhagic complications of antithrombotic interventions.

Given the long-term risks of recurrence, disease sequelae, and functional impairment, VTE must also be considered as a chronic disorder in children. Long-term adverse outcomes in pediatric VTE have recently been reviewed, and include: recurrent VTE, chronic hypertension and renal insufficiency in RVT, variceal hemorrhage in portal vein thrombosis, chronic SVC syndrome involving occlusion in upper extremity VTE, and development of the post-thrombotic syndrome (PTS): a condition of chronic venous insufficiency following DVT.

Mortality

While VTE-specific mortality in children is quite low, ranging from 0% to 2%, a considerably higher all-cause mortality reflects the severity of underlying conditions (e.g., sepsis, cancer, congenital cardiac disease) in pediatric VTE. Neonate-specific outcomes data in pediatric non-RVT VTE reflect an all-cause mortality of 12–18%, including one series of premature infants with CRT treated with enoxaparin.

Recurrent Venous Thromboembolism

Registry and cohort study data in all types of pediatric VTE indicate that children appear to have a lower risk of recurrent thromboembolism than adults (cumulative incidences at 1–2 years of 6–11% versus 12–22%, respectively). However, the risk of PTS in children with DVT of the limbs appears to be at least as great as that in adults (cumulative incidences at 1–2 years of 33–70% versus 29%, respectively). Additionally, it should be noted that a German cohort study of children with spontaneous VTE (i.e., VTE in the absence of identified clinical risk factors) revealed that the cumulative incidence of recurrent VTE at a median follow-up time of 7 years was 21%. These findings suggest that, in this subgroup of pediatric VTE, the risk for recurrent events is long-lived.

Major Bleeding

With regard to major bleeding complications occurring during the anticoagulation period, frequencies in children range from 0% to 9% in recent studies.

Post-thrombotic Syndrome

The manifestations of PTS (as described above) may include edema, visibly dilated superficial collateral veins, venous stasis dermatitis, and (in the most severe cases) venous stasis ulcers. A recent systematic review of 19 studies totaling 977 patients with upper and lower extremity DVT, revealed a PTS frequency of 26%. The pathophysiology of PTS is thought to derive from venous valvular reflux and/or persistent thrombotic veno-occlusion following DVT, both of which ultimately result in venous hypertension.

Outcomes by Thrombus Type/Location

A clot's location has been found to be quite important with regard to long-term sequelae. Specifically, outcomes of VTE in children may differ among particular anatomic sites. In a Canadian study of CRT in children from 1990 to 1996, VTE-specific mortality was 4% among all children, and was 20% among those children in whom CRT was complicated by PE. No major bleeding episodes were observed. At a median follow-up of 2 years, the cumulative incidence of symptomatic recurrent VTE was 6.5%, and PTS developed in 9% of children. In other series of RVT (primarily among neonates), VTE-related death has been quite uncommon, and the cumulative incidence of recurrent VTE has ranged from 0% to 4%. The cumulative incidence of chronic hypertension in RVT in these studies

was reported at 22–33%. For CSVT, the pediatric literature reflects a VTE-specific mortality ranging from 4% to 20%, with a cumulative incidence of recurrent VTE of 8% for neonatal CSVT cases and 17% for CSVT occurring in older children. Long-term neurologic sequelae were noted in 17–26% of neonatal CSVT cases and the cumulative incidence of such sequelae in childhood (i.e., non-neonatal) CSVT has ranged widely between 8% and 47%. It should be noted that both the proportion of children anticoagulated, and the duration of therapy, in the aforementioned pediatric series of RVT and CSVT varied considerably across studies. With regard to portal vein thrombosis, few pediatric series reporting outcomes have been published; however, it appears that the risk of developing recurrent gastrovariceal bleeding in this population is substantial, occurring in many cases even after surgical interventions have been undertaken to reduce portal hypertension. For PE in childhood, long-term outcomes such as chronic pulmonary hypertension and pulmonary function have yet to be established, but remain important to evaluate.

Residual thrombus burden is an additional outcome of interest, but of unclear prognostic significance. A correlation has been shown between D-dimer levels and residual thrombosis at time of anticoagulant treatment discontinuation and the risk of recurrence. Additionally, some evidence indicates that persistent thrombosis is associated with the development of venous valvular insufficiency, an important risk factor for (albeit an imperfect correlate of) the development of PTS. The prevalence of residual thrombosis despite adequate anticoagulation in neonatal VTE has ranged from 12% in a small series of premature newborns with CRT to 62% in full-term neonatal VTE survivors. Among primarily older children, the prevalences of persistent thrombosis have ranged broadly from 37% to 68% in the few longitudinal studies that have employed systematic radiological evaluation of thrombus evolution.

Prognostic Factors and Predictors of Outcome

It has been reported that thrombophilia and markers of coagulation activation are common in pediatric VTE, while potent genetic thrombophilia states are less frequently encountered; nevertheless, the latter are more likely to present in the pediatric age than in older adulthood.

Part of the difficulty with treating childhood VTE is lack of knowledge regarding the natural course of the disease in this population. The ability to predict clinically relevant long-term outcomes of VTE at diagnosis and during the acute/subacute phases of treatment is essential to establishing a future risk-stratified approach to antithrombotic management in children.

As VTE becomes increasingly recognized in children, discussion regarding the appropriate laboratory evaluation for thrombophilia continues. Comprehensive thrombophilia evaluation is recommended in children with VTE. In the future, validated global assays of overall coagulative and fibrinolytic capacities may provide an initial diagnostic evaluation tool to direct more specific testing, and could perhaps be prognostically important.

Previous studies have defined the strong associations of homozygous anticoagulant deficiencies and APA syndrome with recurrent VTE. Over the past several years, the presence of multiple thrombophilia traits has been identified as prognostic for recurrent VTE, and the radiologic finding of complete veno-occlusion at diagnosis of DVT has been associated with an increased risk of persistent thrombosis (which in turn has been associated with the development of venous valvular insufficiency, as noted above). A recent meta-analysis of searches of electronic databases from 1970 to 2007 evaluated the impact of certain thrombophilia traits on recurrence of VTE, reported as odds ratios (OR), which ranged from 2.63 for the factor II variant to 9.44 for antithrombin deficiency. Significant association was found for all inherited thrombophilia traits except factor V Leiden (OR 0.64) and elevated lipoprotein(a) (OR 0.81).

In addition, plasma FVIII activity >150 U/dL and D-dimer concentration >500 ng/mL at the time of diagnosis of VTE in children, as well as following 3–6 months of standard anticoagulation have been shown to predict a composite adverse thrombotic outcome, characterized by persistent thrombosis, recurrent VTE, and/or the development of PTS, adding to evidence for the prognostic utility of these markers in adult VTE.

The finding that evaluation of thrombophilic states in children with VTE may be useful in predicting these pediatric thrombotic outcomes provides optimism that a risk-stratified approach to intensity and duration of antithrombotic therapy may soon be established.

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Pediatric Oncology

H. Stacy Nicholson

338 Incidence, Epidemiology and Survival

H. Stacy Nicholson

Introduction

Compared to cancer during adulthood, childhood cancer is rare. In the USA, the incidence of cancer between ages 0–19 is 16.7 per 100,000 (15.2 per 100,000 for ages 0–14). The most common malignancy is acute lymphoblastic leukemia (ALL) with 3.5 per 100,000 followed by central nervous system (CNS) tumors at 2.9 per 100,000. Over the past three decades, survival has improved for most pediatric cancers. In the USA, 81.4% of children and adolescents diagnosed with cancer between the ages of 0 and 19 between 1999 and 2006 survived for more than 5 years. The incidence rates and chances of surviving at least 5 years for the major childhood cancers are shown in *Table 338.1*.

Cancer in Developing Nations

Childhood cancer incidence and mortality differs in high- vs. low-income nations, and these differences should be further studied in order to better understand etiology, in particular. While cancer survival rates for children are similar in all high-income nations to what is seen in the USA, most of the world's children live in middle- and low-income nations. In developing nations, the proportion of children relative to the total population is greater, and access to health care is often lower. As the treatment for infectious diseases and other more common diseases in children has improved, the impact of childhood cancer in developing counties has increased. We shouldn't accept that survival rates will always remain lower in developing nations. "Twinning" countries – creating partnerships between developed and developing countries in order to improve the treatment of childhood cancer – is an approach that holds great promise for bringing the benefits of effective anticancer therapy to more of the world's children.

Etiology

In most cases of childhood cancer, the cause is unknown. Environmental factors do not play a large causal role in childhood cancer in contrast to many adult malignancies. Cancer in childhood or adolescence differs significantly from adult malignancies. Adult cancers are primarily carcinomas, while children get leukemia, brain tumors, embryonic cancers, and sarcomas. Thus, in children, the etiology is more likely to be genetic, rather than environmental. There are exceptions – benzene can lead to leukemia, and radiation can lead to brain tumors and other solid malignancies. Also, in Sub-Saharan Africa, the Epstein–Barr virus (EBV) is known to cause Burkitt lymphoma, and EBV is also associated with lymphoproliferative diseases in transplant survivors. Human Papilloma Virus (HPV) is associated with cervical, penile, and some head and neck cancers – while these tumors do not often affect children and adolescents, the prevention of these cancers is becoming possible with the advent of

Table 338.1
Incidence and survival of major childhood cancers in the United States (diagnosed before age 20)

Cancer	Incidence (per 100,000)	5 year relative survival (%)
Bone	0.8	70.1
Brain	3.0	74.8
Hodgkin's lymphoma	1.4	96.1
Acute lympoblastic leukemia (ALL)	3.2	85.9
Acute myeloid leukemia	0.8	56.5
Neuroblastoma	1.0	71.7
Non-Hodgkin lymphoma	1.2	84.1
Soft tissue sarcoma	1.1	76.3
Wilms' tumor	0.6	92.1
OVERALL	16.7	81.4

Incidence rates are per 100,000 and are age-adjusted to the 2000 US standard population. 2007 data given. Survival data are for children diagnosed at ages 0–19 between 1999 and 2006

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vaccines against HPV. HIV is associated with Kaposi's sarcoma and non-Hodgkin's lymphoma, and Hepatitis B and other viruses may be causal in some liver tumors.

Secondary cancers occur in a small proportion of cancer survivors due to therapies such as chemotherapy and radiotherapy and, in some, a genetic predisposition to cancer. Secondary cancers are discussed in the chapter on late complications of therapy.

The incidence of cancer in children who are genetically predisposed to cancer is higher. This predisposition may be due to genetic factors that have either been inherited or develop spontaneously. Some of the more common-known cancer predisposition syndromes are outlined in *Table 338.2*. Rarely, the same cancer may occur in multiple members of a family. Bilateral cancers in paired organs, such as bilateral retinoblastoma or bilateral Wilms tumor, is evidence for a genetic predisposition as are positive family histories. Familial cancers have been most commonly reported in retinoblastoma, childhood leukemia, and Wilms tumor. Mathematical modeling of the earlier

Table 338.2
Cancer predisposition syndromes in children

Condition	Tumors	Genetic defect	Comments
Hereditary retinoblastoma (RB)	Retinoblastoma; osteosarcoma	RB1	80% with bilateral RB will have a negative family history
Down syndrome	Acute lymphoblastic leukemia; acute megakaryoblastic leukemia; JMML	Trisomy 21	Contribution of trisomy to tumorigenesis is not known
Li Fraumeni syndrome	Sarcomas; breast cancer; brain tumors; leukemia	p53	Family history key
Fanconi anemia	Acute leukemia	Multiple Fanconi	Chromosomal breakage syndrome
	Head and neck carcinomas		
	Cervical carcinoma		
Bloom syndrome	Acute leukemias		
Ataxia telangiectasia	Lymphoma	ATM (11q22–q23)	Truncal ataxia; oculocutaneous telangiectasias
	Leukemia		
	Gastric carcinoma		
Neurofibromatosis type I	Neurofibromas; optic nerve gliomas; astrocytomas; pheochromocytoma; AML; myelodysplasia; myeloproliferative syndromes;	NF1 gene (17q11.2)	Variable severity of NF1; very large gene
Neurofibromatosis type II	Vestibular schwanomas; meningiomas;	NF2 (19)	Most often diagnosed in adulthood
Tuberous sclerosis	Subependymal giant cell astrocytomas (SEGA); renal angiomyolipomas	TSC1 (9q34)	Variable intelligence; seizures
		TSC2 (16p13.3)	
Gorlin syndrome	Medulloblastoma	PTCH	
	Basal cell carcinomas		
Turcot syndrome	Colon cancer and CNS tumors (medulloblastoma, high-grade astrocytomas)	APC gene; hereditary nonpolyposis colon cancer (HNPCC)	Family history of colon cancer, particularly at a young age.
WAGR	Wilms tumor	WT1 (11p13)	Wilms tumor, aniridia, genitourinary abnormalities; mental retardation
Beckwith Wiedeman syndrome (BWS)	Wilms tumor	11p15	Screening for liver, adrenal and kidney tumors key during childhood
	Hepatoblastoma		
	Adrenocortical carcinoma		

age at onset of bilateral retinoblastoma led to Knudsen's two-hit model of cancer etiology. Furthermore, children with an underlying cancer predisposition syndrome have an increased risk of a second cancer. Thus, updating the family history for cancer in all first- and second-degree relatives should occur at diagnosis and periodically throughout treatment and follow-up as new cancers occurring in adult relatives may be informative. Finally, children with immunodeficiencies have an increased risk of lymphoma and lymphoproliferative diseases.

Cancer During Infancy

During the first year of life, the types of cancers that occur differ from what is seen in later childhood. While leukemia remains the most common cancer during infancy, its incidence is less than half of what occurs at age 2, and acute myelogenous leukemia (AML) is more common relative to *all* than in older children. As in other ages, brain and other Central Nervous System (CNS) tumors are the most common solid malignancy, and neuroblastoma is also common. Neuroblastoma is the most common cancer in the first month of life.

Adolescent and Young (Aya) Adult Cancers

In the USA, older adolescents (15 years and older) and young adults (up to 40 years) have not seen the same degree of improvement in survival compared to children and older adults. This is likely due to differing tumor biology, impaired access to care, and insufficient supportive care infrastructure. Efforts to improve outcomes in the AYA population are being studied.

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339 Evaluation of Abdominal Masses and Enlarged Lymph Nodes in Children

Gregory Blaschke · H. Stacy Nicholson

Abdominal Masses

Childhood tumors that commonly present with an abdominal mass include neuroblastoma, Wilms' tumor, hepatoblastoma, rhabdomyosarcoma, lymphoma, and ovarian tumors. Prompt investigation of suspected abdominal masses leads to more effective and more cost effective treatment.

Often, abdominal masses are discovered by parents or by physicians during health maintenance visits. In order to maximize the chances of discovering abdominal masses, a careful history and physical exam should be part of each health maintenance visit during childhood. In addition to allowing the parents to describe any concerns, including the following items in a review of systems will be helpful in uncovering abdominal masses:

- Abdominal pain
- Hematuria
- Irritability
- Weight loss
- Vomiting
- Changes in bowel habits

The physical examination should include careful palpation of the entire abdomen, and this may be done in any position that ensures cooperation and a successful exam. The history and physical can yield clues as to the diagnosis. Hematuria suggests Wilms' tumor or a rhabdomyosarcoma of the genitourinary system. Hypertension may accompany neuroblastoma, and symptoms of intestinal obstruction suggest a Burkitt's lymphoma of the bowel wall.

Any suspected abdominal mass should be promptly evaluated, and an abdominal ultrasound (US) is useful as the initial imaging modality as it is typically readily available and spares the child from radiation exposure that accompanies computerized tomography (CT).

Once an abdominal mass is confirmed, surgical consultation is warranted. The history, exam, and imaging often suggest a likely diagnosis; based on this presumed diagnosis, any indicated staging tests may be done before surgery. This will assist the surgeon in surgical planning, and a preoperative chest CT eliminates confusion regarding whether findings represent postoperative atelectasis or metastatic disease.

Enlarged Lymph Nodes

Enlarged lymph nodes are a common finding in healthy children, and few such nodes represent malignancy. Lymph nodes are most often enlarged in response to an infection, and one generally sees resolution with successful treatment of the underlying cause. Pyomyositis is more common in many tropical parts of the world. Common infectious causes include staph aureus, tuberculosis, or sarcoidosis. Preceding trauma may be in the history and drainage is part of treatment. Nontender, firm nodes in unusual locations or ones that continue to increase after 2 weeks or fail to regress in 4–6 weeks should lead to biopsy. Tender adenitis may require a trial of antibiotics.

Table 339.1
Typical differences between benign and malignant causes of enlarged lymph nodes

Characteristic	Benign adenopathy	Malignancy
Onset	Rapid and associated with other signs and symptoms of infection, such as fever.	Progresses slowly over time. May be the only symptom present.
Size	Usually <3 cm	Can be small or large; will generally increase in size over time and may become confluent
Consistency	Soft, warm	Firm, rubbery, or hard
Tenderness	Usually present	Usually absent

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Fluctuant adenopathy may require cautious surgical involvement or drainage, and usually excision to avoid chronic drainage tracks depending on infectious etiology. However, enlarged nodes may be the initial manifestation of leukemia (particularly T-cell acute lymphoblastic leukemia (ALL)), Hodgkin Disease, non-Hodgkin lymphoma, or histiocytosis. Rarely, an enlarged node may represent regional or metastatic spread from an undiagnosed solid tumor. Adenopathy associated with malignancy does not resolve and typically progresses over time. *Table 339.1* lists clinical features that typically accompany both benign and malignant adenopathy.

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340 Principles of Diagnosis

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Introduction

When a child is suspected of having a malignancy, there is an urgent need to obtain the correct specific histopathological diagnosis and to fully document the stage (degree of spread). A precise diagnosis and correct staging informs both the prognosis and determines the correct treatment plan. Thus, ensuring that all tissues are handled correctly and that all required staging tests are obtained is crucial. In general, a histopathological diagnosis, either from tumor excision, biopsy, or needle aspiration, must be obtained. Exceptions to this rule include sites where biopsies pose excessive risk (such as brainstem tumors) and some oncologic emergencies, such as when a child with a mediastinal mass presents with severe respiratory and/or circulatory compromise. Each cancer has a distinct panel of diagnostic studies needed for proper staging, and these are discussed in each disease entity. Guiding general principles are the topic of this chapter.

When a primary care physician diagnoses or strongly suspects a childhood malignancy, prompt referral to a center with pediatric oncologists, pediatric surgeons, advanced imaging resources, and pathological resources is indicated.

Diagnostic Studies

Blood, Bone Marrow, and Spinal Fluid

A complete blood count (CBC) is generally performed whenever leukemia or a solid tumor is suspected. Children with leukemia will usually have blasts on the blood smear; however, cytopenias in one or more cell lines may be the only evidence for leukemia. Similarly, solid tumors with metastatic spread to the bone marrow may lead to cytopenias on the CBC.

Serum chemistries should be obtained to ensure adequate hepatic, renal, and other organ function prior to initiating therapy. LDH should be measured if lymphoma is suspected, and uric acid must be measured in leukemias and lymphomas in order to minimize the risk of tumor lysis syndrome with the initiation of therapy. When applicable, serum tumor markers should be obtained. Tumor markers are discussed with each disease entity.

Bone marrow aspiration is required to establish the diagnosis of leukemia and in staging solid tumors that can metastasize to marrow. In addition to standard morphology, cytogenetic studies and flow cytometry need to be obtained. In leukemia, chromosomal number (ploidy), some chromosomal translocations and cell surface markers have prognostic and treatment implications. Bone marrow biopsies are also important in the staffing workup for lymphomas and for some solid tumors.

Performing a lumbar puncture for cerebrospinal fluid (CSF) cytology is indicated in some brain tumors (medulloblastoma, ependymoma, primitive neuroectodermal tumors (PNET)), in leukemia and lymphoma, and in parameningeal rhabdomyosarcomas.

Radiological Studies

Chest X-rays (CXR) are frequently obtained in children with newly diagnosed cancer, and an urgent CXR should be obtained in children with leukemia or lymphoma to check for a mediastinal mass (*Fig. 340.1*). A CXR is typically obtained in children with a solid tumor, but computerized tomography (CT) of the chest should also be done, making a CXR less important. Abdominal ultrasound may be useful as a screening tool, but the degree of information obtained from CT scans or magnetic resonance imaging (MRI) has made these modalities the gold standard. MRI is the imaging modality of choice in CNS tumors, while CT scans are typically better in evaluating bone. Nuclear medicine scans are used to evaluate for bony metastases and are used in staging and following patients with lymphoma.

Tissue Diagnosis

Proper treatment is only possible following a correct pathological diagnosis. Biopsies can be obtained via surgery or by a needle biopsy. Consultation with the pathologist prior to the procedure can be helpful, particularly when a needle biopsy is planned, in order to ensure that enough tissue is available to establish the diagnosis and perform all required studies. Frozen-section examination of the tumor

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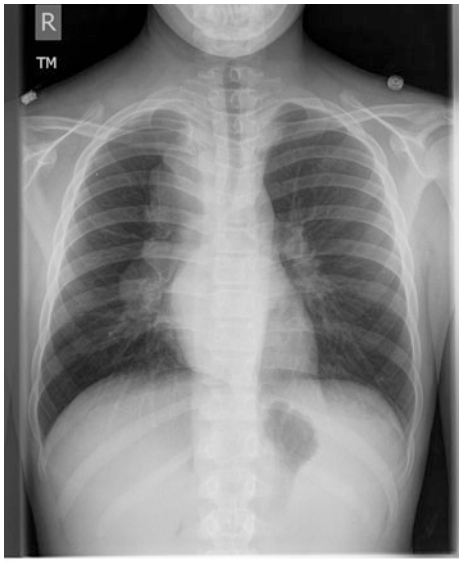

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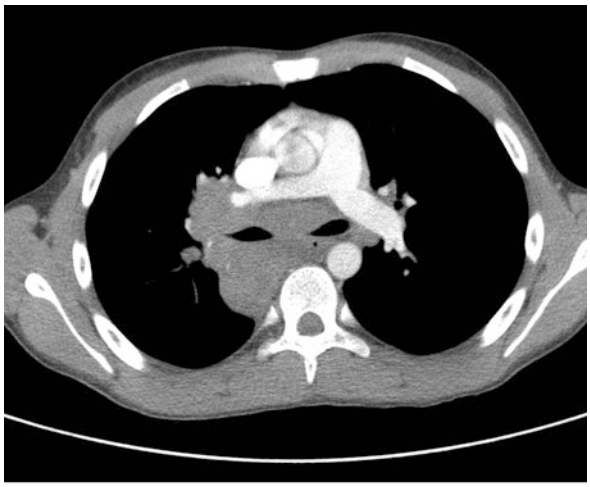

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Figure 340.1
(a) CXR of 18-year-old male with respiratory distress showing anterior mediastinal mass. (b) Chest CT with intravenous contrast showing mediastinal mass with compression of both main-stem bronchi.Images courtesy of Katharine Hopkins, MD

during surgery can ensure that the tumor has indeed been biopsied and guide the surgeon in making clinical decisions. In some tumors, evaluating the margins of the excised mass for active tumor must be done to assist in determining prognosis and assigning treatment. Providing the pathologist with fresh tissue may be required for cytogenetics, molecular studies and flow cytometry. Such studies are becoming more important with molecular staging of tumors and leukemias. Again, preoperative consultation with the pathologist can ensure that the proper studies are performed.

Family- and Community-Centered Care

While the primary care provider may not make the definitive diagnosis, it is always helpful to collaboratively "break the news" regarding the concern for cancer to the family as part of referral process. Indeed, the desires and abilities in the context of the family and community will often determine the initial referral location. Definitive care may require additional referral to alternative sites that specialize in specific treatments or cancers. Many family, community, and multidisciplinary partners can assist in informing the family and assisting with the process of referral.

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341 Principles of Cancer Chemotherapy in Children

H. Stacy Nicholson

Introduction

Children and adolescents with cancer are best treated at a referral center with adequate resources to assemble a team consisting of pediatric oncologists, radiation oncologists, and surgeons, as well as nursing staff and others who support the children and families. The pediatric oncologist typically leads the team, and most pediatric cancers are treated with chemotherapy, either alone or in combination with surgery and radiation.

Chemotherapy simply means using medicines to treat cancer, and there are a few key principles and definitions that broadly apply, regardless of diagnosis. Using chemotherapy in solid tumors following surgery, even without evidence of metastatic disease, is defined as adjuvant chemotherapy. Chemotherapy administered before the definitive surgical procedure is referred to as neoadjuvant chemotherapy. One of the most important advances in the use of chemotherapy was the recognition that combination chemotherapy, using two or more drugs with differing mechanisms of action, would help overcome drug resistance. Dose intensity, the amount of chemotherapy delivered over a specified interval of time, is another key principle of associated with improved efficacy and survival.

Chemotherapy dosing is typically based on the body surface area (BSA), which more closely correlates to the patient's volume than weight. In infants (less than 12 months) or children weighing less than 12 kg, BSA-based dosing often results in an overdose, so weight-based dosing is used. During the first month of life, in particular, drug clearance may be slow due to immature liver and renal function.

Protocol-driven therapy is the standard of care in children with cancer, and randomized phase III clinical trials have resulted in steady improvements in survival. When available, such trials are usually offered to families at diagnosis.

Major Classes of Chemotherapy

Most chemotherapy agents interfere in the process of cell replication. The most commonly used chemotherapy drugs in children are listed in *Table 341.1*.

Alkylating Agents

Alkylating agents are used against most pediatric cancers. These highly reactive compounds form covalent bonds by attaching an alkyl group to DNA, creating DNA-DNA and DNA-protein crosslinks. Alkylating agents include mechlorethamine (nitrogen mustard), cyclophosphamide, ifosfamide, thiotepa, the nitrosoureas, melphalan, and busulfan. Cyclophosphamide and ifosfamide are prodrugs, requiring activation by hepatic metabolism. Their dose-limiting toxicity is hematological toxicity, and all can cause nausea and vomiting and mucositis. Cyclophosphamide and ifosfamide can cause hemorrhagic cystitis, which can be prevented by the concomitant use of mesna.

There are related drugs that also covalently bond to DNA. The platinators cisplatin and carboplatin bind a platinum group to DNA and dacarbazine, procarbazine and temozolomide covalently bind methyl groups to DNA.

Antimetabolites

Antimetabolites are structural analogues of the building blocks or cofactors used in the synthesis of DNA and/or RNA. These agents are active against many childhood cancers and are critical in the treatment for childhood acute lymphoblastic leukemia (ALL). Methotrexate, a folate analogue, can be given by multiple routes: oral (PO), intravenous (IV), intramuscular (IM), or

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Table 341.1

Chemotherapy agents most commonly used in children and adolescents

Drug	Mode of administration	Precautions	Major toxicity	Major use in pediatric oncology
Alkylating agents				
Nitrogen mustard (NM)	IV	Avoid extravasation	Myelosuppression	Hodgkin disease (HD)
			N/V	
Cyclophosphamide (cytoxan, CTX)	IV, PO	Brisk diuresis, use mesna with high doses	Hemorrhagic cystitis, myelosuppression, infertility	Leukemias
			N/V	Lymphomas
				Sarcomas
				Neuroblastoma
Ifosfamide	IV	Brisk diuresis, mesna must be used	Hemorrhagic cystitis, myelosuppression, infertility	Sarcomas
			N/V	Germ cell tumors
Cisplatin (CDDP)	IV	Brisk diuresis	Renal dysfunction	Medulloblastoma
			Hearing loss	Neuroblastoma
			Severe N/V	Germ cell tumors
				Osteosarcoma
Carboplatin	IV		Myelosuppression	Brain tumors
			Hearing loss	Germ cell tumors
			N/V	Neuroblastoma
			Allergic reactions	Sarcomas
Plant products				
Vincristine	IV	Avoid extravasation	Peripheral neuropathy	Leukemia
				Lymphoma
				Rhabdomyosarcoma
				Wilms
Vinblastine	IV	Avoid extravasation	Myelosuppression	HD
				Germ cell tumors
Etoposide (VP-16)	IV, PO	Avoid rapid infusion	Myelosuppression	ALL, AML, NHL, Neuroblastoma
				Sarcomas
				Brain tumors
Antimetabolites				
Methotrexate	PO, IV, IT	Adjust dose if renal function is poor; do not use if patient has effusions	Myelosuppression, mucositis	ALL
				Non-Hodgkin Lymphoma (NHL)
				Osteosarcoma
6-Mercaptopurine	PO	Adjust dose with hepatic dysfunction	Myelosuppression, hepatic dysfunction	ALL
6-Thioguanine	PO	Adjust dose with hepatic dysfunction	Myelosuppression, hepatic dysfunction	ALL
				AML
Cytosine arabinoside (Ara C)	IV, IT		Myelosuppression, mucositis	ALL
				AML

Table 341.1 (Continued)

Drug	Mode of administration	Precautions	Major toxicity	Major use in pediatric oncology
Antitumor antibiotics				
Doxorubicin (adriamycin)	IV	Avoid extravasation	Cardiomyopathy	ALL
		Cumulative dose cannot exceed 550 mg/m^2	Myelosuppression	AML
			Mucositis	Most solid tumors
Daunomycin	IV	Avoid extravasation	Cardiomyopathy	ALL
		Cumulative dose cannot exceed 550 mg/m^2	Myelosuppression	AML
			Mucositis	
Bleomycin	IV	Cumulative dose cannot exceed 250 mg/m^2	Pulmonary fibrosis	HD
				Germ cell tumors
Dactinomycin (actinomycin D)	IV	High dose associated with severe hepatic damage	Myelosuppression	Wilms
			N/V	Sarcomas
			Veno-occlusive disease (VOD)	
			Mucositis	
Miscellaneous				
L-Asparaginase	IM	Allergic reaction (can be delayed)	Myelosuppression	ALL
			Anaphylaxis	
			Coagulation issues	
			Pancreatitis	
			Hyperglycemia	
Prednisone	PO		Hyperglycemia	ALL
			Weight gain	NHL
			Hypertension	HD

ALL Acute lymphoblastic leukemia, *AML* acute myelogenous leukemia, *HD* Hodgkin disease, *NHL* non-Hodgkin disease, *N/V* nausea and vomiting

intrathecal (IT). Dosing varies widely, including high-dose therapy with leucovorin rescue. The thiopurines, mercaptopurine and thioguanine, are oral agents active in ALL, during the maintenance phase. Failure to comply with maintenance therapy is associated with relapse, especially in adolescents. Cytarabine, a pyrimidine analog, is active against lymphoid malignancies and can be given IT.

Anthracyclines

The anthracyclines doxorubicin and daunomycin are effective against most childhood cancers, although their poor penetration of the blood-brain barrier limits their use against central nervous system tumors. Anthracyclines have several mechanisms of action, including becoming intercalated into DNA and inhibition of topoisomerase II, a key DNA repair enzyme. Monitoring cardiac function and limiting the cumulative dose is important, as these drugs are associated with cardiomyopathy as a late complication.

Tyrosine Kinase Inhibitors

The use of imatinib mesylate in chronic myelogenous leukemia (CML) has transformed the treatment of CML and is the first broad application of rationally designed therapy. Imatinib inhibits the action of the abnormal tyrosine kinase that is the *BCR-ABL* fusion protein. Imatinib is similarly effective in pediatric CML, and trials

are ongoing in pediatric ALL with the Philadelphia chromosome. Such drugs will be increasingly important in the coming decades.

Other Agents

The vinca alkaloids vincristine and vinblastine bind to tubulin and interfere with the microtubular spindles involved in mitosis. Vincristine is more widely used, and has neurotoxicity (pain and/or weakness) as its dose-limiting toxicity. Etoposide is a topoisomerase II inhibitor active in both solid tumors and leukemia, and asparaginase is an enzyme that deletes asparagine, an essential amino acid in lymphoblasts.

Steroids, including prednisone and dexamethasone, are active against lymphoid malignancies. These medications induce apoptosis, in both malignant and normal lymphoid cells.

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342 Pediatric Radiation Therapy

Carol Marquez

Treating children with radiation therapy presents unique challenges. Fortunately, in the last 20 years, many improvements have occurred that address and mitigate these challenges. Those improvements have been in the field of radiation oncology, in the development and results of pediatric clinical trials, and in the care and management of children in designated children's hospitals. Taken together, they represent a significant advance on the prognosis of pediatric malignancies and on the quality of life of the pediatric patients.

Improvements in Radiation Therapy

There have been significant advances in the planning and delivery of radiation therapy in the last two decades. In the early 1990s, treatment planning became based on CT images versus plain x-ray images. This switch allowed for a 3D rendering of the tumor and normal structures and for a "beams' eye view (BEV)" perspective of those relationships (see *Fig. 342.1*). The linear accelerator is designed to deliver dose from a wide variety of table positions and gantry positions. Only by having a BEV can the radiation oncologist visualize the tumor and normal tissue in oblique and noncoplanar angles. With this perspective, the radiation oncologist is able to design a treatment field that may spare more normal tissues. Having the CT information about normal structures also allowed for more accurate information about the dose delivered to those structures. With the development of the multileaf collimator (see *Fig. 342.2*), a device that is part of the linear accelerator that allows for precise, rapid, computer-controlled shaping of the beam of radiation, a treatment planning technique called intensity modulated radiation therapy (IMRT) was possible. The multileaf collimator shapes the beam while the dose is being delivered, thereby varying the intensity of the radiation and the subsequent dose within each beam of radiation that is used. This modulation of the dose produces a heterogeneous dose distribution within the treatment field. With IMRT, doses to nearby critical structures can be significantly reduced, especially in those tumors that wrap around critical normal structures, such as the spinal cord or parotid gland, where a concave dose distribution is desirable. IMRT is very useful in pediatric tumors that arise near these critical structures such as rhabdomyosarcoma or Ewing's sarcoma.

Given the rapid fall off of the dose outside of the target volume in IMRT plans, it is necessary to verify the accuracy of the patient's position immediately prior to treatment delivery. This need required the development of image-guided radiation therapy (IGRT). With IGRT, imaging of the patient is performed on the treatment table and the images are compared to the images obtained at the time of treatment simulation to verify that the patient is in the same position so that the dose is delivered accurately. The imaging modalities that may be used for IGRT include ultrasound, orthogonal films, or a CT that is part of the treatment machine (cone beam CT) (see *Fig. 342.3*). This process of verifying treatment position means that the patient and the target volume are within millimeter accuracy on a daily basis. This level of accuracy provides less variability in day-to-day setup. This decrease in variability and increase in accuracy in turn allows for a decrease in the additional margin placed around the tumor that has been historically necessary. The potential downside for the patient especially in the pediatric population is the increased exposure to x-rays when kV x-rays or cone beam CT is used as the modality for IGRT.

Stereotactic radiosurgery (SRS) is a technique of delivering a high single dose of radiation to a small volume (<2 cm) with high precision using stereotactic guidance often with rigid immobilization such as a frame or a relocatable mask. Multiple intersecting beams are used so that a high dose is given at the point of intersection (the "isocenter") and a lower dose is given to the surrounding brain because multiple beams are used. This technique is ideally suited for intracranial well-circumscribed spherical targets such as brain metastasis but is also indicated in the treatment of primary tumors such as acoustic neuromas, meningiomas or pituitary adenomas, and in the benign conditions of arteriovenous malformations or trigeminal neuralgia. In the pediatric population, SRS has been used for the treatment of astrocytomas, recurrent medulloblastomas, and recurrent ependymomas. Radiosurgery is helpful in the setting of recurrent disease because the

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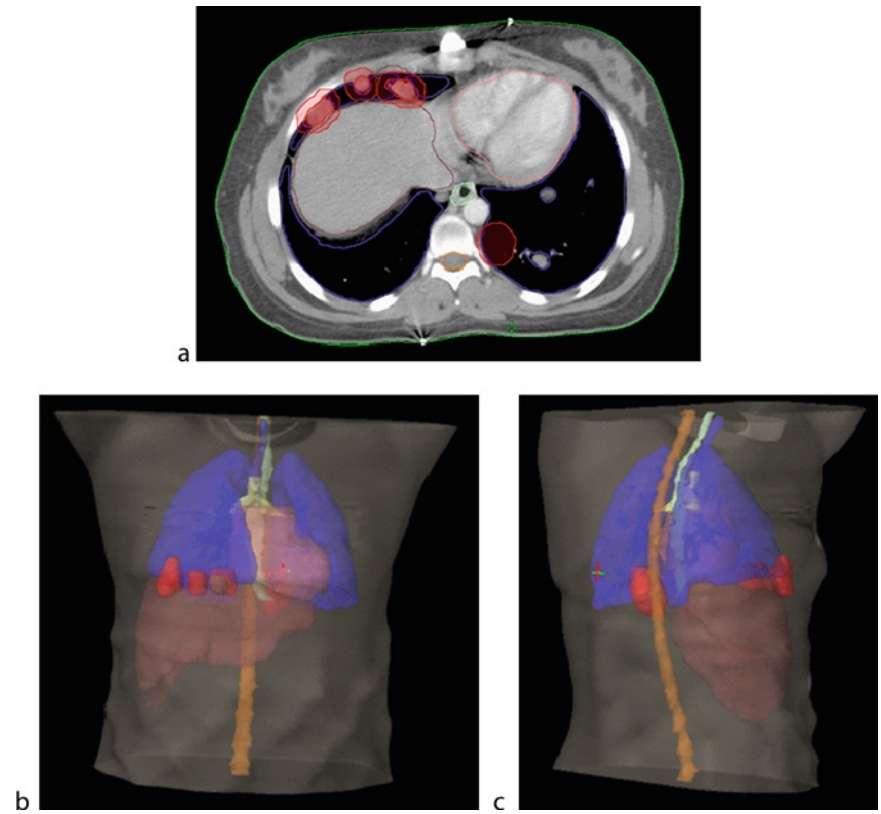

Figure 342.1
(a) CT for treatment planning with metastatic lung lesions contoured in *red*; (b) Beam's eye view (BEV) of tumor volume and relationship to lung, liver in AP view; and (c) BEV of tumor volume and relationship to spinal cord in oblique view

Figure 342.2
Multileaf collimator with computer-controlled leaves that shape the radiation beam to conform to the target volume

amount of dose given beyond the target is very limited which is important in patients who have previously received a larger field of radiation. There are several technologies that are available to perform SRS and they include gamma knife, cyberknife, and a linear accelerator.

In the last 10 years, the principles of SRS have been applied to extracranial targets such as small primary lung tumors or liver tumors, so-called stereotactic body radiotherapy (SBRT). In SBRT, the treatment is delivered over 2–5 fractions usually separated by several days. Each fraction delivers a dose of 4–20 Gy, which is determined by the volume being treated, the disease being treated, and the location of the target volume with respect to nearby critical structures. With SBRT, the use of IGRT is mandatory because of the high dose being given and the few numbers of fractions delivered. In pediatric patients, SBRT has shown promising results in lung metastases from Ewing's sarcoma but the results are otherwise limited in the pediatric setting.

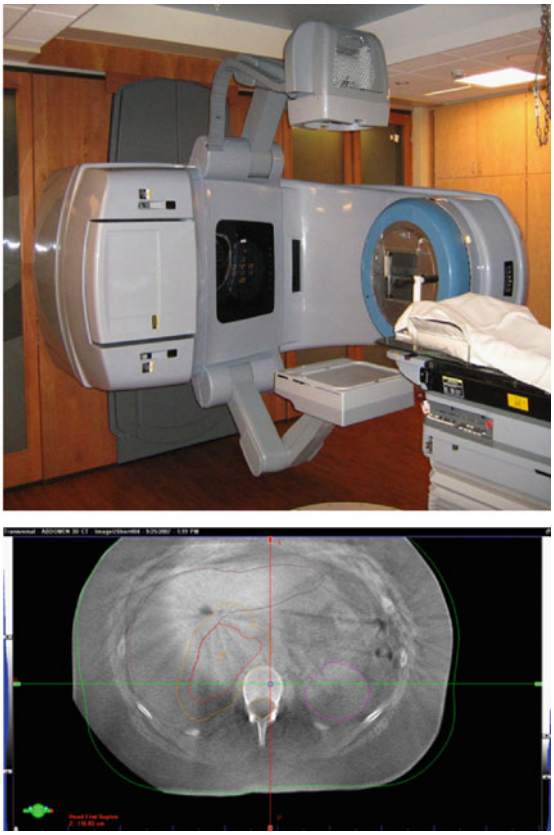

Figure 342.3
(a) Linear accelerator with cone beam CT, arms that are perpendicular to the head of the machine. This device generates kV photons and, when rotated completely around the patient, a CT is generated; (b) CT image generated by the cone beam CT

One of the more promising innovative technologies for the treatment of pediatric malignancies is proton beam therapy. Protons are a particle form of radiation, not photons or x-rays which are produced in therapeutic linear accelerators. The pattern of protons' dose deposition is unique where the dose is deposited at a finite range or depth. When protons reach this depth, they deposit all of their radiation, something called the Bragg peak (see *Fig. 342.4*). This pattern of dose deposition results in a lower entrance and exit dose. Having this Bragg peak means that, if there is a critical structure near a target volume, then proton radiation therapy has the potential to deliver a lower dose to that critical structure. This difference in dose distribution may mean a lower total dose to the entire body as in the craniospinal irradiation for medulloblastoma or to a nearby critical structure in a patient with rhabdomyosarcoma. The limitation on proton radiation therapy is the cost of building and running a facility which has results in a limited number of facilities. Protons have a physical dose distribution advantage over x-rays or photons but no biologic advantage. The next technology that has both a spatial dose distribution and biologic effect advantage is carbon ions. There are very few of these facilities (none in the USA) and little experience in pediatric patients in part due to the concern of lack of long-term follow-up with its use and the potential for increased long-term toxicity given its unique biologic properties.

While technologic improvements have significantly improved the care of pediatric patients, parallel improvements in combined modality therapy have allowed for the reduction of treatment volume, dose reduction, and careful selection of patients for radiation therapy. As stated previously, the use of IMRT and IGRT have provided improved conformity of dose and accuracy of delivery so that normal tissue margins may be reduced. Improvements in imaging of low and intermediate brain tumors and the ability to fuse those images with the treatment planning CT may allow for treatment volume reduction, a critical endpoint in brain tumors. This concept is the study of children's oncology group (COG) protocol ACNS 0221 where patients with low-grade gliodmas who have progressive non-resectable disease are given radiation therapy and the margin of normal brain is reduced from the traditional 2 cm to 0.8–1 cm. This reduction in the volume of normal brain that is within the target volume of radiation may result in a significant improvement in the long-term functional outcome of these patients who have an excellent prognosis. Volume reduction is also achieved through the use of pre-radiation chemotherapy. In Hodgkin's lymphoma when radiation is given with chemotherapy, it is delivered only to the involved field and not to a traditional mantle or subtotal nodal field. This modification allows for (in some patients) a significant reduction in the amount of lung, heart, and, in females, breast tissue that is included in the radiation therapy field.

Dose reduction is another important means of reducing the long-term toxicity of radiation therapy. An excellent example of this concept is medulloblastoma where in patients with standard risk disease who receive chemotherapy, a dose of 23.4 Gy is given to the craniospinal axis as opposed to 36 Gy for those who do not or who have high-risk disease. This dose reduction provides a decrease in overall toxicity while maintaining excellent cure rates, progression-free survival of 79% at 5 years. A further dose reduction is currently being investigated in COG ACNS 0331. In this study, patients with standard risk disease who are less than 7 years old are randomized to

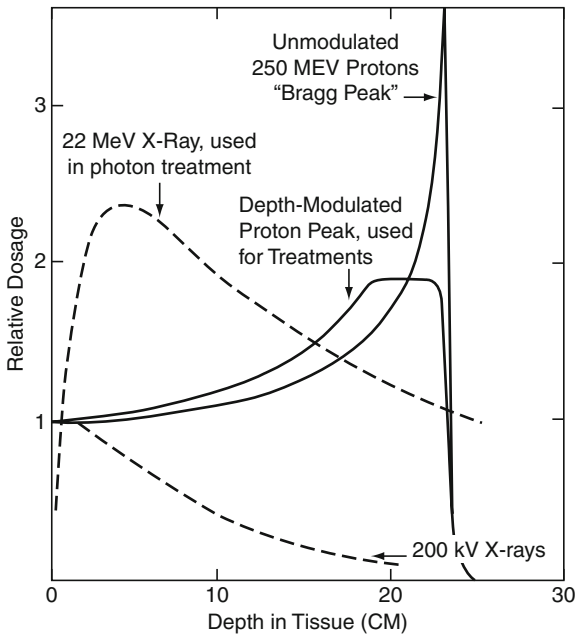

Figure 342.4
Bragg peak for protons demonstrating decrease in both entrance and exit dose when compared to x-rays (photons) of low (200 kV) or high (22 MeV) energy

either 18 Gy or 23.4 Gy for the craniospinal portion of their treatment. In addition, all of the patients regardless of age are randomized to either have the entire posterior fossa boosted to 55.8 Gy or to only the tumor bed plus 2 cm margin. This approach has been piloted at other institutions with success. This age cutoff of 7 years is chosen for the randomization because the deleterious impact of radiation is more evident in younger children.

Patient selection or eliminating radiation therapy altogether in certain groups of patients is probably the most important method of reducing its toxicity. Over the last 20 years, the use of radiation therapy has been stopped in patients with Stage 1, Group I rhabdomyosarcoma, several groups of patients with acute lymphoblastic leukemia (ALL) for prophylactic cranial irradiation, and for Stage I Wilm's tumor with favorable histology. There is a current COG protocol AREN 0533 that investigates the elimination of whole-lung irradiation in patients with Stage IV Wilm's disease, favorable histology with spread to the lungs. For those patients who have a complete response to chemotherapy based on CT performed at 6 weeks and no loss of heterozygosity at 1p16q, no whole-lung irradiation will be given. If successful, this elimination of radiation therapy in this group of patients will decrease both their pulmonary and cardiac toxicity.

Importance of Clinical Trials

One of the most notable contrasts between the management of pediatric and adult oncology patients is the increased enrollment in clinical trials in pediatric patients. It is widely believed that this participation in clinical trials is one of the major factors contributing to the continued success in managing childhood cancers. There are several advantages to a strong clinical trial group such as the COG. These advantages include the ability to ask and answer therapeutic questions reliably, several of which have been outlined above. Another advantage is the relative standardization of care, where a randomized clinical trial clearly outlines what the standard arm is and how it should be followed. A final advantage that is especially important for radiation therapy in the era of emerging technologies is that quality assurance is required prior to the use of any emerging technology. This quality assurance review is performed at a national center, quality assurance review center (QARC) prior to any patient being treated using a technique such as IMRT, SRS, or image fusion, when the patient is being treated on a cooperative group study or a pharmaceutical industry study. In addition, treatment plans are reviewed at a central location and feedback is given to the investigator so that, if necessary, modifications can be made. This same process of central review of treatment fields and plans has also been instituted in the German Hodgkin Study Group (GHSG) with a resultant improvement in the quality of radiation delivered on those studies.

Receiving Care in a Children's Hospital

The care of an ill child requires an array of specialized services. By having a hospital that focuses only on the care of pediatric patients, all of those specialized services can be brought together and together they are improved. In treating a child with cancer, the modalities of surgery, chemotherapy, and radiation therapy all are often part of the treatment regimen. Having these groups of physicians working closely together in multidisciplinary teams allows for improved communication and collaboration. In radiation therapy, young patients often need to be sedated for their daily treatments so it is essential to have pediatric sedation services that are available, reliable, and safe. Also, in most radiation therapy departments, pediatric patients will be the minority of patients treated. Yet it is important that the staff have a comfort level in working with patients and, importantly, their families. For those departments who rarely treat a child, this comfort can be hard

to achieve and both the child and the family find the treatment difficult.

As more children are cured of their cancer, there will be more survivors who will need to transition to care as adolescents and young adults and who may experience the long-term toxicity of radiation therapy. Unfortunately, the effects of radiation therapy may continue to be seen many years after treatment is complete. Issues regarding growth, fertility, and the occurrence of second malignant neoplasms (SMNs) are of particular importance. This area of interest, adolescent and young adult (AYA), is growing and new research and programs are being developed specifically for it. Again, the issues facing these survivors require a multidisciplinary team.

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343 Hematopoietic Stem Cell Transplantation

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Hematopoietic Stem Cell Transplantation (HSCT) can cure many malignant and nonmalignant childhood diseases. As new indications for HSCT arise, and donor and stem cell sources expand, the number of bone marrow transplants performed is increasing. This modality, once only available in limited institutions, is now used worldwide. Many pediatric care providers encounter patients in their practice who will or have undergone HSCT, thus it is important for pediatricians to understand the basics of this therapeutic modality, its potential benefits, and acute and long-term risks.

Stem Cell Sources

The main goal of HSCT is to infuse hematopoietic progenitor cells in a host to totally or partially replace host defective cells affected by cancer or other disorders. Bone marrow is the most direct source for hematopoetic progenitor cells, but they can also be obtained from peripheral blood and placental (cord) blood.

Marrow is obtained from donors through a procedure referred to as *bone marrow harvest*. A harvest is performed in an operating room under general anesthesia, and involves directly extracting bone marrow, usually from the posterior iliac crests using bone marrow aspirate needles. The extracted marrow product is filtered to remove debris and collected in a bag mixed with anticoagulant. The amount of marrow volume removed is limited by the weight of the donor (maximum of 15 ml/kg) recipient and usually does not exceed 20 ml/kg of the intended recipient weight. Bone marrow can be harvested from donors of any age. The procedure is usually performed as outpatient procedure or may involve a short overnight hospital stay. The harvest procedure is well tolerated by the donor. The most common side effect is mild to moderate pain at the aspiration sites usually lasting a few days. Blood transfusion to a donor is rarely needed but may be indicated when the donor is substantially smaller than the recipient. The incidence of significant complications for donors has been reported to be very low.

A second source of hematopoietic progenitors is *peripheral blood stem cells*. The donor receives subcutaneous injections of granulocyte colony-stimulating factor for several days to mobilize the stem cells from the bone marrow to the peripheral blood, after which the cells are collected by apheresis. For this procedure, the donor has two venous catheters placed and is connected to an apheresis machine, which separates and collects the stem cells and returns other blood components back to the patient. Some donors, particularly those of small size, require central venous catheters for this procedure and may need transfusions or red cell priming of the apheresis machine to undergo this procedure, making it a less appealing approach to obtain cells from young children donors. Umbilical *cord blood* is a rich source of hematopoietic progenitors. After delivering the baby and clamping of the cord, placental blood can be collected using sterile technique by direct venipuncture of the cord vessels. Cord blood collection poses no risk to the mother or newborn. The collected cord blood can then be cryopreserved and stored until used.

Donor Selection

Hematopoietic cells can be obtained from the recipient, also referred to as *autologous*, or from another donor (*allogeneic*). When the donor is an identical twin sibling, it is referred to as *syngeneic*.

An Autologous transplant is traditionally used to "rescue" patients after high-dose chemotherapy for lymphoma or other solid tumors. Allogeneic transplant is used for treatment of patients with malignancies considered at high risk for relapse with conventional chemotherapy and for some patients with nonmalignant disorders.

An allogeneic donor may be a sibling, a parent, another relative, or unrelated. The selection of an allogeneic donor is determined primarily by compatibility of the human leukocyte antigen (HLA) system. Improvement in the understanding of the genetics of the HLA system has played a major role in advancing the field of transplantation. The HLA system contains a set of tightly linked genes

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located on chromosome 6. These genes are inherited as one group from each parent, called a haplotype. The overall chance that two siblings inherit the same set of maternal and paternal haplotypes is 25%. Due to heterogeneity in HLA types, in addition to other contributing factors such as the trend towards reduced family size in developed countries, there is only a 30% chance of finding an HLA-identical sibling for a given patient. The chance of a parent or other relatives fully matching a child is very small, but they may serve as partially matched or haploidentical ("half-matched") donors. This latter type of donor is sometimes the only choice available for patients with ethnicities poorly represented in the donor registries. Approximately 45% of all allogeneic transplants performed worldwide are from adult unrelated donors. These individuals join donor registries voluntarily where their HLA typing data become available to search coordinators looking for a match for a potential recipient anywhere in the world. This process is conducted with a great degree of confidentiality to protect the identity and safety of both donor and recipient. Unrelated donors are ideally matched at 8 of 8 HLA loci, or in some cases partially mismatched at one or 2 HLA loci.

Indications for HSCT in Childhood Diseases

The list of diseases for which marrow transplantation is clinically used continues to grow and includes a wide variety of malignant and nonmalignant disorders (Table 343.1). The choice of donor and stem cell source are influenced by the type of disease being treated and time constraints.

Table 343.1
Indications for HSCT in children

Allogeneic	Autologous
Malignant disorders	Ewing sarcoma
Acute lymphoblastic leukemia	Recurrent germ cell tumors
Acute myeloid leukemia	Malignant Brain tumors
Chronic myeloid leukemia	Recurrent Lymphoma
Juvenile myelomonocytic leukemia /Juvenile chronic myeloid leukemia	High-risk Neuroblastoma
Myelodysplastic syndrome	
Lymphoma relapsed after autologous transplantation	
Nonmalignant disorders	
Severe aplastic anemia	
Bone Marrow Failure syndromes	
Hemoglobinopathies (Thalassemia major, Sickle cell disease)	
Primary (congenital) immunodeficiency diseases	
Hemophagocytic lymphohistiocytosis	
Inborn errors of metabolism (Mucopolysaccharidosis, Sphingolipidosis, Malignant osteopetrosis, Adrenoleukodystrophy)	

Allogeneic HSCT

Allogeneic BMT has been proven to be an effective treatment for hematologic malignancies, bone marrow failure syndromes, primary immunodeficiency disorders and inborn errors of metabolism. According to reports from the Center for International Blood and Marrow Transplant Research (CIBMTR), the most common source of allogeneic stem cells for children is bone marrow (52%) followed by peripheral blood stem cells (28%) and cord blood (20%).

In malignancies the primary goal is to eradicate all malignant cells, usually by administering high doses of chemotherapy agents and/or total body irradiation, and infusing the normal blood cells of the donor. The donor cells repopulate the host bone marrow space and may also mediate an immunological response against the cancer cells, referred to as the "graft-versus-leukemia" or "graft-versus-tumor" effect. Many patients with hematologic malignancies not cured with conventional chemotherapy treatment have benefited from allogeneic HSCT. The 3-year probability of survival for patients with acute leukemia younger than 20 years ranges between 70% for those with disease in first remission and 37% for those with more advanced disease at the time of transplant. Acute myeloid leukemia in first or greater remission and acute lymphoblastic leukemia in second or greater remission are the most common indications for allogeneic HSCT In children. Chronic myeloid leukemia (CML), juvenile myelomonocytic leukemia, and myelodysplastic syndrome, are rare malignant hematologic disorders in

children treated with allogeneic stem cell transplantation. The number of transplants for adult CML has significantly decreased since the development of oral tyrosine kinase inhibitors such as imatinib mesylate, and is reserved primarily for patients not responding to treatment with these biological modifiers. For children with CML, the emphasis is still on transplantation.

The indications for allogeneic HSCT for nonmalignant diseases are varied. The goal of HSCT in the nonmalignant setting is to fully or partially replace defective cells of the host with normal cells from a healthy donor. Severe aplastic anemia and bone marrow failure syndromes where one or more of the hematopoietic cell lines are defective such as Diamond-Blackfan anemia, congenital neutropenia and Fanconi anemia have been cured with HSCT. The long-term survival of children undergoing allogeneic HSCT for severe aplastic anemia is 70–80%. Inherited hemoglobinopathies such as sickle cell anemia and thalassemias can also be cured by allogeneic BMT. Around 70% of patients with severe combined immunodeficiency have long-term survival with full immunoreconstitution within 6 months after HLA-matched allogeneic transplant. Similarly, many other primary immundeficiencies can be corrected with HSCT. Inborn errors of metablism such as malignant osteopetrosis and lysosomal storage diseases have been reported to be cured by allogeneic HSCT. However, there is still a paucity of data from prospective clinical trials for these disorders.

Autologous HSCT

Autologous HSCT in children is used in the setting of malignant disorders, usually solid tumors or recurrent lymphomas, to facilitate blood count recovery after administration of high doses of chemotherapy agents. One of the most common indications for autologous HSCT in children is high-risk neuroblastoma. Randomized clinical trials have shown a modest clinical advantage of consolidative therapy with autologous HSCT over conventional chemotherapy, with long-term survival of 50% for patients with disease in complete or good partial remission prior to transplant. Patients with recurrent chemoresponsive Hodgkin or non-Hodgkin lymphoma may also benefit from consolidation with autologous BMT, with long-term survival ranging between 40% and 50% depending on the type of lymphoma and disease burden at the time of transplantation. Other less common indications for autologous BMT include brain tumors and other neoplasms such as germ cell tumors and Ewing sarcoma.

The Transplant Process

Prior to transplant, both patient and allogeneic HSCT donor must undergo extensive multidisciplinary evaluations. This typically includes a comprehensive history and physical exam, laboratory evaluations such as complete blood counts, serum chemistries, and infectious serology testing. The recipient also undergoes testing to confirm disease status, general health status, and organ functions (echocardiogram, electrocardiogram, pulmonary function testing, creatinine clearance, etc.). Assessment of family support and psychosocial needs is also an integral part of the pre-transplant assessment. Once the patient and donor receive medical clearance, the recipient starts the transplant preparative regimen, also referred to as conditioning regimen.

The intensity of the conditioning regimen depends on the disease being treated, type of donor used, and the general health status of the recipient and its predicted ability to tolerate such therapy. Conditioning starts usually about 1 week before the infusion of stem cells. More intense myeloablative regimens are used to treat malignant disorders. Regimens of reduced or minimal intensity may be used to treat patients with nonmalignant disorders and those with malignancies who due to poor health status are deemed unable to tolerate full myeloablative regimens. After conditioning, the patient receives the hematopoietic cells on "day zero."

During the acute phase of transplant, the patient has profound pancytopenia and immunosuppression and may also experience acute side effects from the conditioning therapy. Patients remain isolated in the hospital for about 3–4 weeks until the new donor cells engraft and they are free of major complications from the transplant process. Patients are usually followed by the transplant team until at least 3 months post transplant, after which they return to the care of their primary care or oncology providers.

Early Complications of HSCT

The early complications are related to infections, toxicities related to the preparative regimen, graft-versus-host disease (GVHD), and graft rejection.

The most common cause of morbidity and mortality during the early phase of transplant is infections. Risk factors for infections include immunosuppression, indwelling venous catheters, GVHD, and coexisting toxicities such as mucositis. Various measures have been taken to isolate the transplant patient from possible

infections. Protection measures include hand washing, wearing a mask, minimizing nonessential contacts, and using hospital rooms equipped with high-energy particulate air (HEPA) filters, when available. Infections prophylaxis has significantly improved the outcome of HSCT by reducing the number of infectious complications. Patients should be aggressively monitored and promptly treated for symptoms or signs of systemic infections. The absence of neutropenia does not necessarily mean that the patient is not immunosuppressed. The ability to fight infections is also affected by absence of cellular and humoral responses, and by the multiple medications used to suppress the immune system to prevent GVHD. Infections can be caused by bacterial, fungal, or viral pathogens and can present in any form, from localized to overwhelming sepsis. Empirical broad-spectrum antibiotics should be started during the neutropenic period and continued until neutrophil engraftment is achieved. Patients should receive Pneumocystis prophyalxis, antifungal prophylaxis to cover for Candida species and molds, and antiviral prophylaxis with acyclovir until off immunosuppressive therapy. Cytomegalovirus (CMV) infection or reactivation has decreased significantly with the use of CMV-negative blood products CMV-serosurveillance and preemptive antiviral prophylaxis with ganciclovir or foscarnet. Other viruses such as adenovirus, respiratory syncytial virus, and parainfluenza and influenza virus continue to be causes of major morbidity and infectious mortality in transplant patients. Prevention of infections and, when available, prompt institution of antiviral therapy are the recommended management for these viral pathogens.

Regimen-related toxicities are the second most common cause of death during the first 100 days post transplant. Any organ can be affected during transplant. The most common organ toxicity is mucositis of the oropharyngeal region. Diarrhea and enteritis may also occur in a high percentage of patients, particularly those receiving myeloablative therapy. Some other manifestations of toxicity include noninfectious pneumonitis, veno-occlusive disease of the liver, hemorrhagic cystitis, acute renal insufficiency or failure, and cardiac dysfunction. Veno-occlusive disease of the liver presents as weight gain, fluid retention, hyperbilirubinemia, and right upper quadrant (hepatic) tenderness. Although most toxicities are reversible and respond to supportive medical management, some can be irreversible or fatal. The average incidence of severe/fatal regimen-related toxicities in children is about 15%, ranging from 0 to 50% depending on predisposing factors. Some factors associated with an increased risk for toxicity are age (infants are at higher risk), intense pre-transplant treatment, and use of myeloablative regimens. Aggressive and prompt institution of supportive care and/or intensive care is key to prevent irreversible injury or death from toxicities in transplant patients.

Graft-Versus-Host Disease

As the new allogeneic donor cells establish within their new environment, they can recognize host antigens as foreign and generate an immune response. This response, known as graft-versus-host disease (GVHD), ranges from subclinical to a severe reaction with multiple manifestations.

Acute GVHD typically presents in the first 3 months post transplant. The organs most commonly affected are skin (rash, erythema, bullae formation), gut (anorexia, nausea/vomiting, watery or bloody diarrhea, abdominal cramps), or liver (elevation of hepatic enzymes with hyperbilirubinemia and liver dysfunction). Since acute immune reactions between the donor and host are expected events in the transplant setting, immunosuppressive medications are given prophylactically before and during the first 3 months post transplant. GVHD prophylaxis usually consists of combinations of two or more drugs that act by reducing the number and function of T-cells. The most common combinations are calcineurin inhibitors (cyclopsporine or tacrolimus) with methotrexate, mycophenolate mofetil, anti-thymocyte, or alemtuzumab globulin. Drugs are used at therapeutic doses early during transplant, and then slowly tapered over 3–6 months if there is no evidence of GVHD. Despite prophylaxis, the incidence of acute GVHD ranges from 25% in matched sibling transplants to 70% in unrelated donor transplants. Acute GVHD is graded depending on the extent and areas of disease involvement.

Chronic GVHD usually occurs after the first 3 months post transplant, although in some patients clinical signs and symptoms have been described at an earlier time after transplant. Skin manifestations of chronic GVHD include desquamation, scleroderma-like changes, pigmentation, and lichenoid changes. Chronic GVHD of the liver is characterized by hyperbilirubinemia and elevation of the hepatic enzymes. Patients with chronic GVHD of the intestine may have abdominal pain, diarrhea, malabsorption, wasting syndrome, and, in the late phases, strictures of the gastrointestinal tract. Lungs acan be affected by chronic GVHD, manifesting as obstructive lung disease

or bronchiolitis obliterans. Involvement of the eyes is also common, with keratoconjunctivitis sicca, blurred vision, and photophobia. Oral manifestations include ulcers, leukoplakia, dry mouth, dysphagia, and sensitivity to certain foods. Joints can be affected by serositis or scleroderma. Thrombocytopenia may occur in chronic GVHD, and it is usually one of the poor prognostic factors of the disease.

There are several alternatives for therapy of GVHD. The goal in the treatment of GVHD is to provide therapy that is sufficient to ameliorate the signs and symptoms without excessively compromising the immune system of the host, a challenging task. Drugs and therapies are added/tapered in response to changes in clinical status until the desired effect is observed. Systemic steroids (prednisone, methylprednisolone) are the first line of therapy. About 50% of patients with acute GVHD respond to steroid therapy, but many require extended therapy with steroids or other agents. Prolonged use of steroids is associated with many side effects including weight gain, myalgia, arthralgia, hyperglycemia, hypertension, increased risk for infections, osteopenia, avascular necrosis of the bones typically the hip, and mood changes, among others. Second line therapies for patients not responding to steroids include monoclonal antibodies against T-cells or cytokines (anti-thymocyte globulin, alemtuzumab, daclizumab, etanercept), macrolide antibiotics (sirolimus or rapamycin), and antimetabolites (pentostatin). Localized skin disease can sometimes be treated with topical therapies (tacrolimus or steroid creams) or with ultraviolet light therapy (psoralens and ultraviolet light absorber, PUVA). Extracorporeal photopheresis (ECP) is a new technique that applies the PUVA concept to systemic GVHD, currently reserved for patients resistant to other modalities. This technique consists of removing a fraction of the lymphocytes of the patient by apheresis, exposing the cell fraction ex vivo to PUVA, and returning the treated cells to the patient. Through complex mechanisms, this procedure generates an immunomodulatory effect and increases immune tolerance of the donor T-cells toward the host.

Long-Term Complications of HSCT

With an increasing number of long-term survivors of HSCT and extended observation periods, long-term sequelae are becoming of significant importance and primary concern for all physicians who care for HSCT patients. After engraftment of stem cells and recovery of blood counts, it takes approximately 1 year after HSCT to recover a fully functional immune system; until then, cellular and humoral responses are impaired. Many patients, especially those with GVHD, have hypogammaglobulinemia and require intravenous gammaglobulin replacement. Patients are at risk for reactivation of dormant viruses (Herpes and Varicella) during the first year post transplant. After transplant, most children lose titers to previously administered immunizations. Most cannot mount adequate responses to immunizations for the first year post transplant. After a year post transplant, most children need to be re-immunized for childhood diseases. Live virus vaccines are not given until 2 years post transplant because of the potential risk of acquiring primary viral infections or complications from the vaccine.

As more patients survive the intense transplant process, the incidence of other long-term sequelae increases as well. Risk factors for the development of late effects include younger age at time of transplant, use of radiation in the conditioning regimen, and presence of chronic GVHD. The most frequent late sequelae of transplant are endocrine deficiencies. Manifestations include growth hormone deficiency and growth failure, hypogonadism and infertility, hypothyroidism, adrenal insufficiency, and diabetes. Endocrine problems are much more common in patients receiving TBI and/or cranial radiation. Chronic organ dysfunction may also occur. Lung problems include obstructive or restrictive disease and bronchiolitis obliterans; an inflammatory disease of unknown etiology that is almost always associated with chronic GVHD. Other late effects include cataracts, dental problems, cardiotoxicity, chronic renal insufficiency, learning disabilities, psychosocial adjustment problems, and secondary malignancies.

Monitoring of late effects and guidance significantly improve the quality of life of transplant patients. In addition to routine care by their primary providers, many transplant centers patients offer comprehensive long-term follow-up evaluations. Patients and their primary health care providers are informed of the results of these evaluations, and recommendations are given to address existing problems.

Transplant is a life-changing experience for patients and their families. Although most of the physical effects of transplant resolve within the first years post transplant, patients and families take years to recover from the psychosocial impact of this process. Hence the involvement of support staff such as social workers, child life specialists and counseling, early and through the transplant is extremely important. Despite the many complications

associated with HSCT, most patients and their families report good quality of life post transplant. The pediatrician is an important part of the transplant process by facilitating prompt referral to the transplant center and, once the transplant is completed and the patient has returned back to their care, by providing adequate surveillance for side effects and late effects of bone marrow transplantation.

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344 Supportive Care of the Child with Cancer

H. Stacy Nicholson

Introduction

Curing a child with cancer requires prompt and accurate diagnosis and staging, and safe delivery of risk-adjusted therapy. In addition, supportive treatments that decrease side effects, increase patient safety, and support health and healing are also important and ensure improved health and quality of life during anticancer therapy. Supportive care can also be life saving.

Venous Access

Most chemotherapy drugs are administered by the intravenous (IV) route. Repeated IV infusions and blood tests are the norm. IV chemotherapy can be delivered via a peripheral vein or via an indwelling central venous catheter. Using peripheral IVs risk extravasations of medications into surrounding soft tissues, and some chemotherapy agents (particularly the vinca alkaloids and anthracyclines) can cause tissue destruction. The surgical implantation of indwelling central venous catheters facilitates both chemotherapy delivery and blood tests. There are two main types of devices: those that end with an external catheter and those that end in a reservoir under the skin.

Procedures and Sedation

There are several routine procedures associated with childhood cancer. Bone marrow aspirations (BMA) are performed to diagnose and monitor leukemia and are required for staging some solid tumors. Marrow fluid is aspirated using a specially designed needle, and the site most commonly used is the posterior superior iliac spine. During a BMA, children are under deep sedation, delivered by an anesthesiologist or other highly trained provider, or are more lightly sedated (conscious sedation) with the concomitant use of locally injected analgesia. Conscious sedation, often using the combination of an opiate and a benzodiazepine, can be delivered by the practitioner performing the BMA and his or her team. Bone marrow biopsies should always be done with the patient under deep sedation or general anesthesia.

Lumbar punctures (LP) generally require less sedation than BMAs, but local analgesia is important. Preventing pain during procedures will improve comfort and increase compliance with care. In older children, using distraction or other non-medicinal techniques can be very effective for LPs and IV placement.

Pain Control

Pain in children with cancer may be caused by the cancer itself (at diagnosis, relapse, or during the terminal phase of illness), procedures (see above), surgical procedures, or as a side effect of therapy, such as mucositis (mouth sores). Using a pain scale so that the child can effectively communicate his or her pain can be helpful in monitoring the effectiveness of the analgesia. Depending upon severity, pain medications will range from acetaminophen to opiates. When opiates are used for more than a few days, children may develop tachyphylaxis, requiring an increasing amount of medication to achieve the same results. If prolonged use of opiates is required, long-acting formulations may be used to deliver a baseline level of analgesia combined with short acting opiates for breakthrough pain.

Antiemetics

Many chemotherapy drugs and radiation cause nausea and vomiting. Fortunately, the past two decades have brought new antiemetic medications that are highly effective. Drugs used to control nausea in children undergoing chemotherapy include 5-HT_3 receptor inhibitors (ondansetron, granisetron, and dolasetron), steroids (dexamethasone), phenothiazines, and/or metoclopramide. Although expensive, 5-HT_3 receptor inhibitors have become the agents of choice as they are highly effective in most patients and

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have a low risk of side effects. Children whose nausea cannot be controlled with a single medication may require combination therapy.

Transfusion Therapy

Children with cancer often experience cytopenias, either from disease (in leukemia or solid tumors metastatic to bone marrow) or as a side effect of therapy. Myelosuppression is the most common dose-limiting side effect of chemotherapy. Packed red cells and platelets are most commonly used blood components. Indications for transfusion based on blood count results will vary by institution, but symptoms that warrant red cell transfusions include tachycardia, orthostatic hypotension, and fatigue. The transfusion of prophylactic platelets is supported by some, but many centers only use platelets when children experience bleeding. White cell transfusions are sometime done in neutropenic patients with persistent sepsis; however, white cell transfusions are controversial. All blood products should be irradiated prior to transfusion to prevent graft-versus-host disease, and leukodepletion by filtration can decrease cytomegalovirus (CMV) transmission.

Nutrition

Children are often malnourished at diagnosis, and children need good nutrition to heal following radiation and chemotherapy treatments. Nutritional status should be assessed in all patients and support offered if needed. The oral route is preferred when possible, and success can be enhanced by enriching the calorie content and ensuring effective pain management for mucositis. Appetite stimulants can help in some children. If a patient cannot take sufficient calories by mouth, the use of a nasogastric (NG) tube or gastrostomy tube (G-tube) to facilitate delivery of enteral nutrition may be effective. If enteral nutrition cannot be tolerated, total parenteral nutrition (TPN) can be delivered by a central venous catheter.

Oncologic Emergencies

There are several unique emergencies that occur in children with cancer, including mediastinal masses with respiratory compromise and spinal cord compression. Similarly, anticancer therapy can cause serious side effects that require immediate attention, such as serious life-threatening infections.

Superior Vena Cava Syndrome

The anterior mediastinum in children is rich in lymphoid tissue, and these structures are in close proximity with the trachea and both main-stem bronchi, the heart, and major blood vessels, including the superior vena cava (SVC). Some lymphomas or leukemias are accompanies by rapid lymph node growth. In the anterior mediastinum, such growth can lead to a mass that compresses the SVC, leading to facial plethora, cyanosis, and petechiae. Impairment of venous drainage from the brain may result in somnolence and confusion. Airway compression may lead to severe respiratory compromise and is the greatest concern in these patients. Sedation should be avoided and therapy with steroids and/or radiation needs to be administered as a life-saving measure, even if the ability to make a histopathological diagnosis is compromised.

Spinal Cord Compression

Masses that involve or invade the spinal canal can present with spinal cord compression (SCC), either at diagnosis or at relapse. Symptoms include back pain, weakness, inability to walk, sensory changes, or changes in bowel or bladder function. In children, SCC occurs most commonly in children with sarcomas, neuroblastomas, or brain tumors. The time from symptom onset to treatment is inversely related to the chances of the patient recovering lost function. Thus, treatment decisions must be made promptly and immediately initiated. Treatment can include surgical decompression, steroids, or external beam radiation.

Fever and Neutropenia

Infections are the most common complications of anticancer therapy and can be life threatening. Parents must be educated about the risk of infections so that the child is immediately brought to medical attention immediately upon developing a fever. Upon arrival at the clinic or emergency department, the child should be promptly evaluated with a detailed history and thorough physical examination, blood count, and blood cultures. The physical examination should especially focus on seeking specific sites of infection, and extra attention should be given to the oral cavity, sinuses, lungs, abdomen, perianal region, and any tunneled catheters. If neutropenic (absolute neutrophil count (ANC) $<500/mm^3$ or $<1{,}000/mm^3$ and likely to be decreasing), broad-spectrum antibiotics

should be administered, the child should be admitted to the hospital for further antibiotics and monitoring. Antibiotics will continue until the child is no longer neutropenic. Any signs of septic shock should be promptly addressed with fluid resuscitation and consultation with a pediatric critical care unit.

Infections

Throughout therapy, children with cancer are immunosuppressed and susceptible to infection from bacteria, viruses, and fungi. Serious bacterial infections are more likely when children are neutropenic, and prolonged neutropenia increases the risk of invasive fungal disease. The likelihood of a specific organism varies by institution and may change over time, so knowing which bacteria typically cause sepsis in a given population and hospital will inform the antibiotic choice. Empiric antibiotics for fever and neutropenia should include coverage for gram-negative organisms, including Pseudomonas species and for gram-positive organisms such as Staph aureus and coagulase negative Staphylococcus. If fever persists for 5–7 days, empiric antifungal therapy is indicated. Typical antimicrobial choices are listed in *Table 344.1*.

In addition to bacteremia, immunocompromised hosts are susceptible to other bacterial infections, including sinusitis, pneumonia, perianal cellulitis, typhlitis, and other areas of cellulitis. Invasive fungal disease can include candidal esophagitis, fungal sinusitis, and invasive fungal pneumonia, either with candida or mucor. Mucor has a poor prognosis and must include aggressive surgical management in addition to antifungal medical therapy.

Viral infections that are dangerous in immunocompromised hosts include varicella zoster, herpes simplex, Epstein–Barr virus, and cytomegalovirus (CMV). Disseminated varicella is particularly problematic, with a high degree of lethality from encephalitis, pneumonia, or hepatic failure. Following a Varicella exposure, prophylaxis with varicella immune globulin within 72 h can prevent or ameliorate illness, and if varicella occurs, hospitalization and treatment with acyclovir is indicated. Varicella vaccine, although a live attenuated vaccine, is safe and effective in immunocompromised hosts. Zoster also requires treatment but is less likely than primary Varicella to disseminate.

Immunization with live-attenuated viruses (measles, mumps, rubella, polio (Sabin)) should not be given before the child completes chemotherapy and immune mechanisms are restored. Killed virus vaccines, such as those against diphtheria, tetanus, pertussis, and polio (Salk only), can be used safely in children receiving chemotherapy (*Table 344.2*).

Table 344.1
Common infectious complications in immmunocompromised hosts and treatment

Indication	Treatment of choice	Comments
Fever and neutropenia (F&N)	Third-generation cephalosporin (ceftazadime)	Alternatively, use three-drug combination, including:
		• Anti-pseudomonas penicillin (ticarcillin, piperacillin)
		• Anti-staphylococcal penicillin (oxacillin, nafcillin)
		• Aminoglycoside (gentamycin)
		If a specific site of infection is identified, it should be treated in addition to empiric coverage
Persistent F&N (5–7 days)	Amphotericin B	Alternatively, use may fluconazole
		Lipid encapsulated formulations of amphotericin may be less toxic
Pneumocystis jiroveci	1. TMP/SMX	Must be used as prophylaxis – 2 consecutive days per week
	2. Pentamadine	Used at therapeutic doses for treatment
Varicella	Acyclovir	Use high-dose therapy with sufficient fluids. Monitor renal function closely

Pneumocystis jirovecii (previously known as *P.carinii*) is a yeast-like fungus that causes opportunistic pneumonia in immunocompromised hosts. This pneumonia is universally fatal if not treated but can be easily and effectively prevented with prophylactic trimethoprim-sulfamethoxazole (TMP/SMX) given on 2 successive days each week. In patients with contraindications to TMP/SMX, a monthly infusion of pentamadine is used as prophylaxis. At therapeutic doses, these medications are also used for treatment.

There are additional and unique infectious risks associated with bone marrow transplantation (BMT). These are discussed in the chapter on BMT.

Table 344.2
Antibiotic usage in immunocompromised hosts

Drug	Dose	Organisms	Comments
Antibiotics			
Ceftazadime	100 mg/kg/day divided every 8 h	Pseudomonas	Third-generation cephalosporin
			Most common antibiotic for empiric coverage of fever and neutropenia (F&N)
Cefepime	100 mg/kg/day divided every 8 h	Pseudomonas, gram negative, gram positive	Can be used in setting of resistance to ceftazadime
Imipenem	50 mg/kg/day divided every 6 h	Pseudomonas, gram negative, gram positive	Excellent anaerobic coverage
Aztreonam	100–150 mg/kg/day divided every 6 h	Gram negative	No gram-positive coverage
Vancomycin	25–40 mg/kg/day divided every 6–12 h	Gram positive	Use only when clinically indicated
			Monitor levels and renal function
Antifungals			
Amphotericin B	0.5 mg/kg daily (empiric)	Candida	Monitor renal function closely
	1–1.5 mg/kg daily (therapeutic)	Aspergillus	Sodium loading prior to infusion protective for kidneys
Fluconazole	3–12 mg/kg/day	Candida	Use high doses in life-threatening conditions
Acyclovir	1500 mg/m^2 divided every 8 h	Varicella Zoster (VZV)	May use half this dose for HSV
		Herpes simplex (HSV)	Adequate hydration with high doses will limit nephrotoxicity
Anti-pneumocystis agents			
Trimethoprim – sulfamethoxazole	20 mg/kg/day divided every 12 h	Pneumocistis jiroveci	Monitor for bone marrow suppression
Pentamadine	4 mg/kg/day	Pneumocistis jiroveci	Use in TMP/SMX contraindication or treatment failure

Psychosocial Support

Providing psychosocial support to patients and their families is an important aspect of care in pediatric oncology. Helping them deal with accepting the diagnosis, ensuring compliance with therapy, and adjusting to being a cancer survivor are all important aspects of support. Practical supportive measures may include assisting families with housing for those who must travel to get care and helping ensure access to prescription medications. Supporting the child during procedures with medical play and distractions can help diminish the pain experienced with these procedures.

Support for the medical, nursing, and other staff is also important as there can be an emotional toll in dealing with children who have cancer.

Rehabilitation

Maximizing function and quality of life in children undergoing anticancer therapy may require rehabilitation services. Children with central nervous system (CNS) tumors may require intensive rehabilitation, including physical therapy, occupational therapy, and speech therapy following tumor resection, and this should be done in a way that does not interfere with the timely initiation of adjuvant therapies. Children with CNS tumors and others who receive cranial radiation may have learning difficulties after therapy and may benefit from cognitive remediation and accommodations from their teachers. Children with bone and other extremity sarcomas may also need physical therapy to adjust to amputation or following a limb-sparing surgical procedure.

Unique Aspects in Developing Countries

In developing countries, children often present with higher-stage disease, and they are more likely to be malnourished and impoverished. Medical resources may also be decreased compared to developed nations. Knowing the usual differences for a given country or region will help physicians design local standards of care.

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345 Childhood Leukemia

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Definition/Classification

Leukemias are a group of malignant diseases with a unifying origin from hematopoietic cells. They result from clonal proliferation of a malignantly transformed cell of hematopoietic lineage with differentiation arrest. The type of leukemia is determined by the normal counterpart of the malignant clone and also by the stage of differentiation at the time of arrest. As such, leukemias can be lymphoid or myeloid; and even within these broad categories further sub-classifications can be made based on the particular cell involved. The most common subtype of leukemia seen in children is acute lymphoblastic leukemia (ALL).

Although by far the majority of leukemias originates from and involves the bone marrow, this in itself is not a requisite and in rare cases a diagnosis of leukemia can be made without bone marrow involvement by conventional diagnostic methods.

Etiology

The precise etiology of leukemia in humans is not known. There are, however, several factors which may play a presumed role in the pathogenesis of human leukemia, including genetic predisposition, viral infection, congenital immune deficiency diseases, ionizing radiation, and certain toxic chemicals that can facilitate its development. Leukemia-associated genetic changes have been identified in umbilical cord blood samples, indicating a prenatal initiation of at least common childhood acute lymphoblastic leukemia. However, such prenatal cytogenetic changes are probably only predisposing factors and require post natal events, such as viral infections, to fully realize the leukemic phenotype. Constitutional chromosomal abnormalities are associated with childhood leukemia. Children with trisomy 21 (Down syndrome) are approximately 15-times more likely to develop leukemia, particularly acute myeloid leukemia, than normal children. Congenital syndromes that result in DNA instability, such as Fanconi anemia, Bloom syndrome and ataxia telangiectasia, also result in an increased predisposition to leukemogenesis. Although environmental factors, such as ionizing radiation or toxic chemicals, have the potential to produce leukemias, these are rarely associated with childhood leukemia in practice.

Epidemiology

Leukemias are the most common malignancy in children, constituting about 30% of all pediatric cancers. The average annual incidence of childhood leukemias from developed countries is about three to four cases per 100,000 children. The incidence reported from Saudi Arabia is somewhat lower, between two and three cases per 100,000 children. The data from India report an incidence that varies considerably from 1.5 to 5.6 per 100,000 children, with the lower incidence in the rural areas and the highest in the urban centers. Whether development and urbanization contribute to leukemogenesis or, as is more likely, case acquisition is better in the cities is as yet undetermined. Within the pediatric age group the incidence is highest between 1 and 4 year of age and corresponds to the peak incidence for common childhood ALL.

Acute lymphoblastic leukemia (ALL) accounts for 70–75% of all leukemias seen in this age group. Precursor B-cell ALL constitutes the majority of cases seen, with T-ALL accounting for about 15–20% in most reports. The proportion of T-ALL seems to be higher and significantly variable (20–60%) in less developed rural populations, which may be related to environmental factors. Acute myeloid leukemia (AML) accounts for about 25% of all cases. Chronic myeloid leukemia (CML) and juvenile myelomonocytic leukemia (JMML) are rare and together account for 5% of all childhood leukemias. The peak incidence of ALL occurs at approximately 3–4 years of age. The incidence of AML remains stable from birth to age 10 years and increases slightly during the teen ages.

Pathogenesis

Like all malignant disorders, leukemia is a clonal disease, originating from a single cell. Genetic mutations within this

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cell provide an evolutionary "survival advantage." Such "advantageous" mutations also result in a predisposition for further genetic mutation which, as they accumulate, result in the development of a malignant phenotype, the leukemic cell. There is clear evidence that the initiating steps in a significant proportion of childhood leukemia begins in utero. This is certainly true for infantile leukemia harboring the *MLL* gene, and has also been noted in a significant proportion of post-infancy childhood ALL and AML. What is also evident is that the leukemic predisposition induced by the in utero genetic changes requires a postnatal "second-hit." Current evidence seems to indicate an aberrant immune response to common infectious exposures which may be one of the intervening events leading to phenotypic leukemia. The pre-leukemic latent phase often lasts 2–4 years but may be as long as 14 years. The monoclonal and intrauterine origin of leukemia is most evident in the concordance of acute leukemia in monozygotic twins, which is estimated to be as high as 25%. The risk is higher in infancy and diminishes with age.

Clinical Manifestations

Presenting signs and symptoms of leukemia are usually nonspecific and are usually a manifestation of the underlying anemia, thrombocytopenia, and neutropenia. Pallor, fatigue, petechiae, purpura, bleeding, and fever are often present. Bone pain particularly affecting the long bones is common. In addition, joint effusions and arthralgias may be present due to leukemic infiltration of the peri-articular bone. Evidence for leukemic infiltration of organs, such as hepatomegaly, splenomegaly, and lymphadenopathy, may be evident on physical examination. Chloromas or granulocytic sarcomas are discrete tumors seen in patients with AML. Central nervous system (CNS) involvement can manifest as seizures, cranial nerve palsy, and/or symptoms and signs of increased intracranial pressure.

Laboratory abnormalities most often reflect the underlying failure of production of normal blood elements. Although white blood cell counts are often increased in patients with leukemia, many patients, in fact, have reduced white blood cells (WBC) counts. Thrombocytopenia and anemia are seen almost universally. Electrolyte abnormalities may also be seen, particularly if there is ongoing tumor lysis syndrome (TLS). In such cases elevated serum potassium, phosphate and uric acid, and hypocalcemia may be seen even prior to initiation of chemotherapy. Leukemic infiltration of the kidneys may result in renal dysfunction with elevation of serum creatinine. Disseminated intravascular coagulopathy (DIC) may occur in any type of leukemia, but this is more common in the acute promyelocytic leukemia.

Differential diagnosis includes nonmalignant conditions like juvenile rheumatoid arthritis, infectious mononucleosis, aplastic anemia, and idiopathic (immune) thrombocytopenic purpura. In infants any infection may result in a marked elevation of WBC counts and a leukoerythroblastic picture, mimicking leukemia.

Diagnosis

Childhood leukemias are systemic diseases that may affect any organ of the body, causing manifestations that may mimic other diseases. Children with leukemia are usually referred to a tertiary care center, where comprehensive programs for treatment of such diseases are available.

Although leukemic blast cells may be present in the peripheral blood, the definitive diagnosis is usually established upon examination of bone marrow aspirate specimens. Most patients have anemia and thrombocytopenia at diagnosis. Leukocyte counts may be elevated, normal, or low. Blast cells may be present in the peripheral blood. Bone marrow aspirate should be done in order to more completely characterize the leukemic cells. On occasion, when the peripheral white blood cell count is elevated the diagnosis can be completed without performing a bone marrow aspirate. The characterization of the leukemic blasts is done by morphologic assessment utilizing special stains, immuno phenotyping, cytogenetic and molecular studies. Establishment of the immune phenotype by flow-cytometric analysis is now considered the cornerstone of leukemia diagnosis. This is essential in defining the cell-type of origin, and helps in determining the treatment strategy that would be used.

Cytogenetic and molecular genetic studies have now become extremely important in determining the prognosis and in risk stratification of therapy. In ALL, genetic abnormalities within the leukemic cell have been shown to confer either a good-risk or a poor-risk genotype. This obviously would determine treatment intensity and outcome. This is probably even more evident in AML, where cytogenetic abnormalities now form the basis for AML subtype categorization, according to the current World Health Organization (WHO) Classification.

Other diagnostic studies include evaluation of the cerebrospinal fluid (CSF), and testicular-evaluation in boys. In patients with T-cell ALL, chest X-ray may show a mediastinal mass.

Treatment

General Concepts in the Initial Management of Childhood Leukemias

Chemotherapy remains the mainstay of therapy for children with leukemias. Over the years the use of radiation therapy, particularly cranial radiation therapy, has lost some of its value, and now indications for radiation therapy are limited. Bone marrow transplantation is used for a limited number of higher risk leukemia patients and does contribute toward achieving a higher cure rate. These treatment strategies are different for the different types of leukemias encountered and are outlined in more detail below.

Supportive measures are critical in stabilizing the patients prior to initiation of therapy. Hydration and correction of electrolyte disturbances are essential. As all patients with leukemia are at risk of tumor lysis syndrome (TLS) and the resultant renal compromise due to hyperuricemia, they all should be well hydrated to maintain a brisk urine output. Although urine alkalinization has been a component of TLS prevention for many years, it is now evident that alkalinization does not add to the beneficial effect of a high urine flow, and is no longer recommended.

Even with normal or high WBC counts, newly diagnosed patients with leukemia should be considered as immunocompromised. Any evidence or even suspicion of infection should be treated aggressively with broad spectrum intravenous antibiotics. While blood product transfusion for anemia or thrombocytopenia is indicated, this should be undertaken judiciously, particularly in patients with markedly elevated WBC count. Hyperleukocytosis, particularly in patients with AML, may result in hyperviscosity and resultant obstruction of small vasculature. Red blood cell transfusions may aggravate the signs and symptoms of hyperviscosity. Adequate hydration is usually sufficient in preventing hyperviscosity, although some patients with very high WBC counts may need leukapheresis in order to induce rapid reductions in the WBC counts. Such patients with high WBC counts and those with massive organomegaly have a large tumor load and with initiation of therapy remain at a high risk for TLS. The best treatment for TLS is its prevention with good hydration and the use of agents such as allopurinol and urate oxidase to decrease uric acid levels.

Good nutritional support, including total parenteral nutrition (TPN) when needed for critically ill patients, should be provided. Psychosocial support of the patient and the family including education about the disease and its therapy is of extreme importance to enable the treating team to deliver therapy.

Acute Lymphoblastic Leukemia

Childhood ALL is a heterogeneous group of leukemias, all sharing a common characteristic of lymphoid origin. This is reflected in the cellular differentiation markers and the morphology. Broadly, ALL can be divided into B-cell and T-cell types; however, the true nomenclature for these should be precursor B-cell and precursor T-cell lymphoblastic leukemias. Mature B-cell ALL, which was previously also categorized morphologically as the FAB L3 subtype, is now no longer included within this group of diseases and is reclassified as Burkitt leukemia/lymphoma. Distinct subtypes of precursor B-ALL with recurrent genetic lesions are now identified.

Central Nervous System (CNS) leukemia is diagnosed by the presence of lymphoblasts in the cerebrospinal fluid (CSF) as detected by centrifugation. For diagnosis of leukemic involvement of the testis, fine-needle aspiration or open biopsy is required to determine the presence of lymphoblasts. In the bone marrow, the lymphoblasts can be characterized by morphologic, biochemical markers, immunologic, and cytogenetic.

Morphology

Morphologic features of the leukemic lymphoblasts are best determined on examination of a bone marrow aspirate specimen. Most often the bone marrow is diffusedly infiltrated with the monomorphic leukemic lymphoblasts, with marked reduction in the normal marrow elements. Occasionally the numbers of lymphoblasts in the bone marrow may be less, making a distinction between ALL and bone marrow involvement of a lymphoblastic lymphoma difficult. An arbitrary cut off of 25% has been used to make this distinction. The lymphoblasts vary in size from small to medium sized cells. The cytoplasm is often scanty, but can be of a moderate amount and occasionally (10% of cases) may have coarse azurophilic granules. Generally, the nuclear cytoplasm (N/C) ratio is high and the nuclei often have prominent nucleoli.

The FAB classification of lymphoblastic leukemias, which is based primarily on the morphological characteristics, is no longer considered to be of clinical significance and is not used any more.

Biochemical Characterization

With current available diagnostic tools, cytochemistry seldom contributes to the diagnosis of ALL. Lymphoblasts

are universally negative for myeloperoxidase, Sudan black, and esterase stains. Periodic acid-Schiff (PAS) reaction is positive in most cases and is present in a coarse granular distribution. Terminal deoxynucleotidyl transferase (TdT) is found in the majority of patients with ALL.

Immuno Phenotype

Immuno phenotyping is the mainstay of ALL diagnosis and is used to characterize the leukemic cell. The leukemic transformation and clonal expansion can occur at different stages of maturation in the process of lymphoid differentiation and this is reflected in the expression pattern of cellular proteins in the malignant cells. Although most immunophenotyping is conducted using flowcytometry, immunohistochemical staining can also be used. The basic principle involves the use of monoclonal antibodies (moAbs) directed at surface and cytoplasmic proteins of the malignant cells. These moAbs are then identified by using fluorescent or chromogenic tags. Expression of lineage-specific markers such as CD19, cytoplasmic CD79a and cytoplasmic CD22 for B-cells, and cytoplasmic CD3 surface CD2 and CD7 for T-cells is indicative. However no individual marker is enough on its own to finalize the diagnosis and most often a pattern of expression is utilized. Some markers have been shown to have a prognostic association, such as CD10 which is commonly seen in patients with B-cell precursor ALL and is indicative of a more favorable prognosis.

Precursor B-ALL constitutes approximately 80–85% of all ALL, while 15–20% of ALL cases are T-cell ALL. This distinction is also of clinical importance as there are differences in disease presentation and response to therapy. T-ALL tends to occur in older children as compared to B-lineage ALL and generally presents with a higher WBC count. T-ALL is also associated with thymic infiltration presenting as a mediastinal mass. Patients with T-ALL require more intensive therapy, in spite of which they have a somewhat worse outcome than B-lineage ALL.

Not all ALL cases adhere to a specific lineage. Although occasional aberrant myeloid marker positivity is seen in ALL, this does not necessarily result in a diagnosis of mixed phenotype acute leukemia (MPAL). Clear guidelines are now available for the diagnosis of MPAL and require the expression of lineage specific markers of more than one cellular lineage. These MPAL tend to confer a worse prognosis, but may be amenable to therapy which includes agents effective against both lymphoid and myeloid leukemias.

Cytogenetic Studies

With the advances in cell culture methodology and improved chromosomal banding techniques, cytogenetic analysis has contributed significantly to the understanding of the biology and treatment of ALL. More recently the availability of molecular tools, such as polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH), has made it easier to identify genetic lesions. These techniques have also allowed the identification of cryptic translocations that are not evident on routine chromosomal banding. Certain recurrent cytogenetic abnormalities have been identified in ALL that have clinical and prognostic importance and these are now categorized separately.

Numerical abnormalities, with duplications and deletions of whole chromosomes, are seen quite frequently in leukemic blasts. These are non-random with extra copies of chromosomes 21, X, 14, and 4 encountered most often. Children with more than 52 chromosomes in their leukemia cells (hyperdiploid >52) tend to have a significantly better prognosis. This is determined either by routine karyotyping, or by the DNA index (the ratio of the average number of chromosomes in the lymphoblasts/normal diploid number 46) which can be determined by flowcytometry or FISH. Patients with DNA index >1.16 have a good prognosis. Extremes of chromosome numbers, near haploid or near tetraploid, confer an extremely poor prognosis. Recent studies have identified that trisomies of specific chromosomes (chromosomes 4, 10, and 17) rather than the total chromosome number may in fact be more important in determining the prognosis.

Specific structural chromosomal abnormalities also occur in ALL and several are considered clinically significant enough to warrant separate categorization. Precursor B-ALL with the Philadelphia chromosome (t(9:22); *BCR-ABL1* translocation) and those with rearrangements of the *MLL* gene at the 11q23 locus have a poor prognosis. *MLL* gene rearrangements occur due to translocations between chromosome 11 at the q23 locus and several variable partner chromosomes (t(v;11q23)); however, chromosome 4 is the most common. These translocations characterize the leukemias seen in infancy and are related to the poor prognosis of these patients. Translocation (12;21) (p13;q22) (*TEL-AML1 or ETV6-RUNX1*) is a cryptic translocation that is found in 20–25% of precursor B-ALL and is now considered the most common cytogenetic abnormality in ALL. Patients with this translocation have good prognosis. Other encountered translocations include t(1:19) and t(9;11).

Although several translocations are also encountered in patients with T-ALL, none are clearly identified as having a prognostic or clinical impact.

Prognostic Factors

Age at diagnosis and initial WBC count are the most significant clinical prognostic factors identified. In fact, patients with a WBC count$<50 \times 10^9$/L and age between 1 and 10 years are considered to have an especially good risk. Infancy (age <1 year) is universally recognized as a poor prognostic factor, particularly due to its association with *MLL* gene rearrangements. Older patients ($\geq$10 years of age) have a relatively poor prognosis which may be related to a higher proportion of patients with the T-cell phenotype and the absence of good-risk cytogenetic features. Cytogenetic abnormalities, as outlined above, have prognostic significance. Several studies reported that girls have a better prognosis than boys, although with recent treatment protocols this difference is less evident. Immune phenotype also appears to correlate with prognosis, with T-ALL being associated with a worse outcome than precursor B-ALL. Patients with T-ALL tend also to present with higher WBC counts and have more extramedullary involvement, particularly CNS involvement.

Leukemic infiltration of extramedullary sanctuary sites, such as the CNS and testicles, confers a worse outcome. This is especially significant for patients with CNS involvement who tend to have a higher risk of relapse, including bone marrow recurrences. The best outcome is seen in younger, non-infant, patients with B-ALL who have either the t(12;21) or hyperdiploidy with trisomies of chromosomes 4, 10, and 17.

Treatment

Treatment of ALL is primarily chemotherapy based and is risk-stratified. Risk stratification implies the use of higher intensity of therapy for those patients who are at a greater risk for relapse, and less intense therapy for those who at lower risk for relapse in order to avoid treatment-related toxicity. Risk stratification is based on the prognostic features available at diagnosis as outlined above, and also on response to therapy. Early response to therapy is determined by peripheral blood and bone marrow evaluation following 1 and 2 weeks of induction therapy.

Although different ALL treatment protocols utilize somewhat differing chemotherapeutic agents, certain universally applied features are present. Treatment for ALL is composed of well defined phases of therapy. The initial phase is induction, which usually utilizes three or four drugs (vincristine, prednisone, L-asparaginase, and daunomycin). This phase of therapy is aimed at rapid reduction of leukemic infiltrates and results in a 2–4 log reduction in the lymphoblasts burden.This phase is followed by the consolidation phase which further reduces systemic leukemic infiltrates. Therapy during the consolidation phase is also aimed at prevention of relapse in the CNS. The preventive therapy involves administration of intrathecal chemotherapy. Post consolidation the patients are placed on a prolonged continuation therapy phase which primarily includes antimetabolite (mercaptopurine and methotrexate) chemotherapy. This continuation phase is interspersed with either one or two intensification phases which are reminiscent of induction and consolidation. Total duration of therapy is usually between 2 and 3 years.

Radiation therapy was a standard component of ALL treatment; however, over the past 2 decades the need and indications for radiation therapy have been severely restricted. Currently, craniospinal radiation therapy is still required for patients diagnosed with CNS leukemia and testicular radiation therapy is administered to those boys with testicular leukemia. Clinical trials exploring further reductions in these indications are underway. These restrictions are desirable due to concerns that radiotherapy contributes to the long-term neurotoxicity.

Hematopoietic Stem Cell Transplantation (HSCT) is not required for the majority of patients with ALL. However, certain categories of patients with very high risk features, such as those with *BCR-ABLX* translocation or with *MLL* gene rearrangements, do benefit from BMT in first remission.

Outcome and Prognosis

Bone marrow relapse is the principal form of treatment failure in patients with ALL. Other sites of relapse include the CNS and, in boys, the testicles.

Prognosis of patients with ALL has improved significantly in recent years. Currently, approximately 70–80% of children with ALL achieve prolonged disease-free survival ($>$5 years after finishing therapy) and are considered cured. In patients with low risk features, this figure has reached 90%.

Acute Myelogenous Leukemia

The transformation event in AML could theoretically occur in any cell along the pathway from pluripotent

stem cell to committed hematopoietic cells. Although derived from cells of the myeloid lineage, AML is a heterogeneous group that can originate from and be reminiscent of any hematopoietic cell lineage, including erythroid and megakaryocytic.

Morphology

As with ALL, the morphologic classification, according to the FAB system, has lost its reliability and is no longer used. Lineage assignment and prognosis is now better determined by immunophenotype and genetic characteristics. Due to the various cell lineages involved and the fact that AML may occur at any phase of myeloid differentiation, no unifying morphologic characteristics can be enumerated for AML myeloblasts. These myeloblasts are described according to the presumed cells of origin (myeloid, monocytic, megakaryocytic, and erythroid) and the degree of cellular differentiation/maturation. In general, myeloblasts are larger in size than lymphoblasts and have more copious cytoplasm. Granularity is often encountered and Auer rods are considered diagnostic of myeloid malignancy. Myeloperoxidase detection by cytochemistry or flowcytometry conclusively assigns myeloid lineage to the leukemic cells; this however is not positive in all AML subtypes.

Immuno Phenotype

As with ALL, immuno phenotyping is the mainstay of AML diagnosis and subtype assignment. Often a relatively large panel of moAbs is applied, and the patterns of expression are used to reach a diagnosis. Certain markers are seen more consistently, with at least one of the following markers, CD33, CDI3, CD15, CD11b, CD 14, and CD34, being expressed in more than 90% of AML cases.

Cytogenetic Studies

Genetic alterations form the basis of AML subclassification and prognostic risk assignment. Certain recurrent genetic abnormalities are frequently seen in AML cells. These structural changes are associated with specific subtypes of AML and have prognostic implications. Translocation (8;21)(q22;q22)/*RUNX1-RUNX1T1* is the most commonly occurring translocation in de novo AML. This is found mostly in myeloid leukemia with maturation (prior FAB M2 subtype). Related genetic abnormalities include inv(16)(p13.1q22) (p13.1;q22)/*CBFB-MYH11* or the t(16;16), which is often associated with the myelomonocytic subtype of AML. This translocation and t(8;21) involve the genes for the subunits of the heterodimeric DNA binding transcriptional regulator, the Core Binding Factor (CBF), which has been shown to be essential for the normal development of all hematopoietic lineages. The presence of either of these translocations confers a more chemo-sensitive phenotype and results in better disease free survivals. Interestingly, the *RUNX1* gene is also involved in the t(12;21)/*RUNX1-ETV6* translocation in ALL which also results in improved prognosis.

AML with the t(15:17)(q22;q12)/*PML-RARA* translocation is uniquely associated with a more mature myeloid cell type (Acute promyelocytic leukemia; prior FAB M3 subtype). This AML also has a better outcome, which is primarily associated with the use of *all-trans* retinoic acid (ATRA) as a component of treatment. As in ALL the *MLL* gene rearrangements involving translocations of the chromosome 11q23 are often seen and can involve numerous translocation partner genes. These translocations are more often seen in the younger age group and tend to confer a worse overall outcome, except for t(9;11)(p22;q23)/*MLLT3-MLL* which has an intermediate prognosis. In addition to their presence in *de novo* AML, *MLL* gene rearrangements are frequently seen in cases of treatment-related AML, particularly those associated with prior topoisomerase II inhibitor therapy. Numeric changes in certain chromosomes or loss/gain of major chromosomal segments are often seen in AML associated with myelodysplasia. Most commonly associated changes include −7/del(7q), −5/del(5q), and trisomy 8.

Several other gene mutations, in addition to the structural chromosomal abnormalities, are seen in AML. These include mutations in genes such as *FLT3, NPM, WT1*, *and KIT.* These mutations have varying effects on prognosis.

Prognostic Factors

Prognostic risk stratification in AML is determined more by the primary cell of origin and the cytogenetic aberration than by specific clinical features. As mentioned above, t(8;21) and inv(16)/t(16:16) have a favorable outcome, as does APL with t(15;17). Myelodysplastic syndrome (MDS) associated cytogenetic abnormalities such as −7, del(5q) and +8 are associated with a significantly poor outcome, which is probably related to the association with MDS rather than the effect of any particular genetic abnormality. *MLL* gene rearrangements in *de novo* AML is not necessarily associated with a poor outcome, but

confers a particularly bad prognosis in patients with outcome and treatment-related AML (t-AML).

Certain AML subtypes generally are known to have a worse outcome. These include acute megakaryocytic leukemia and erythroleukemia. Interestingly, megakaryocytic leukemia in children with Down's syndrome (DS), 4 years of age, has a particularly good outcome to chemotherapy.

Treatment

The treatment strategy for AML requires therapy to be intensive, multi-agent, and sequential. Although clear phases of therapy are well not defined, as in all treatment, the first two cycles of chemotherapy are generally considered to constitute the remission induction phase. Cytosine arabinoside and anthracyclines are considered to be the effective agents for remission induction. Often other chemotherapy agents, such as thioguanine or etoposide, are included in the induction regime. With current treatment approximately 85% of AML patients are expected to achieve remission following first line induction therapy.

Post remission induction therapy includes either two or three further cycles of multi-agent chemotherapy, or allogeneic hematopoietic stem cell transplantation (HSCT). Most often HSCT is timed to follow either second or third cycle of chemotherapy, depending on the timing of achievement of remission. Indication for HSCT has evolved over the last decade, and not all patients now need transplantation. Patients within the lower risk group, with good-risk cytogenetic changes, can be treated effectively with chemotherapy alone. Most physicians would now offer HSCT to patients with intermediate risk status only if there is a matched related donor. Patients in the poorest risk group, those with MDS-related AML, t-AML, or non DS megakaryocytic leukemia, continue to be candidates for HSCT even from alternative donor sources. Autologous SCT is no longer considered an option for treatment of pediatric AML.

Special consideration must be given to t(15;17) positive APL. In addition to the anthracycline and cytosine arabinoside these patients are induced with ATRA. Pharmacological doses of ATRA act by overcoming the effect of the retinoic acid receptor α (RARA) mutation and inducing cellular differentiation, maturation, and apoptosis. Due to the good outcome with chemotherapy, HSCT is not indicated in APL. Post remission therapy now includes a maintenance phase using antimetabolites (mercaptopurine and methotrexate) with pulses of ATRA.

Prognosis

With current intensive therapy around 50–60% of children with AML are expected to survive long term. This survival is dependent on risk stratification, with over 70% survival for the low risk AML patients and around 30% for those with high risk AML.

Chronic Myeloid Leukemia

Chronic Myeloid Leukemia (CML) is rare in the pediatric age group, accounting for less than 5% of all leukemias. It is a myeloproliferative neoplastic disease that originates in an abnormal pluripotent hematopoietic stem cell. CML is characterized by the presence of the *BCR-ABL* translocation (t(9;22)(q34;q11.2)). This translocation results in the abnormally small chromosome 22, known as the Philadelphia chromosome. Although the initial presentation primarily includes neutrophilic leukocytosis, all myeloid lineages are involved. In fact, some lymphoid and endothelial cells may also harbor the *BCR-AB*[1] translocation.

Patients most often present in the chronic phase with marked hyperleukocytosis, and massive hepatosplenomegaly. As opposed to the acute leukemias, even with very high WBC counts, the platelet count is not reduced and may be elevated. Generalized lymphadenopathy may present and occasionally there is leukemic blast infiltration of skin or other soft tissues. The natural history of CML is triphasic, with the initial presentation usually in the chronic phase; untreated CML progresses on to accelerated and blastic phases. Rarely, patients with CML will present in the later phases, which most often is myeloid in origin and resembles AML. In some cases blastic transformation can be lymphoid and patients may present with disease indistinguishable clinically from ALL.

The *BCR-ABL* translocation driven abnormal Eyrosine kinase activity that defines CML has been the target also resulted in the development of the treatment approach to this disease. Treatment of CML is now based upon the use of tyrosine kinase inhibitors (TKI) that target the abnormally enhanced tyrosine kinase activity of the chimeric BCR-ABL protein. Imatinib mesylate was the first such TKI to be developed and remains the standard agent for fist line therapy. Imatinib mesylate monotherapy has resulted in not only complete cytogenetic remissions, but also in reductions in the leukemic clone to levels less than 1 in 10^5 cells. However, it is still unclear if TKI therapy can achieve durable cures and current treatment approaches recommend indefinite continuation of the TKI therapy.

Allogeneic HSCT remains the only proven curative therapeutic option for patients with CML. However, with the advent of TKI therapy the status of HSCT has become controversial. While transplant has become significantly uncommon in the treatment of chronic phase CML in adult patients, many pediatric oncologists still opt for transplantation for their patients. The need for possible lifelong TKI therapy has to be balanced against the potential toxic morbidity and mortality associated with HSCT. Many pediatric oncologists will now recommend HSCT if a matched related donor is available, and continue with TKI therapy for all other patients. Patients with advanced phase CML need to be treated more aggressively and HSCT remains the unequivocal treatment of choice.

Juvenile Myelomonocytic Leukemia (JMML)

Juvenile myelomonocytic leukemia (JMML) is a clonal proliferative hematopoietic disorder which occurs in infancy or early childhood. It primarily results in monocytosis andgranulocytosis and is distinguished from CML by the absence of the *BCR-ABL* fusion gene. It is quite rare and comprises only 2–3% of all childhood leukemias. Diagnostic criteria for JMML include not only the absence of *BCR-ABL*[1], but also require peripheral blood monocytosis and less than 20% blasts in the blood marrow. Other features that may be seen are elevated hemoglobin F, immature granulocytes in the peripheral blood, elevated WBC count to more than 10×10^9/L, and clonal chromosomal abnormalities including monosomy 7.

While chemotherapy and differentiation agents, such as cis-retinoic acid, have been used for cytoreduction, curative therapy is only achievable with HSCT. Without transplantation most children die of organ dysfunction due to leukemic infiltration at a median survival of less than 1 year.

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346 Non-Hodgkin Lymphoma

H. Stacy Nicholson

Introduction

Non-Hodgkin lymphoma (NHL) is the term applied to all solid lymphoid neoplasms other than Hodgkin disease (HD). Some are closely related to acute lymphoblastic leukemia (ALL) and are treated similarly. The incidence of NHL in children below 15 years of age in the USA is 7.4 per 100,000. NHL is much more common than HD in the first decade of life, and children with immunodeficiencies have a greater risk of NHL. NHL is the third most common childhood cancer, following leukemia and brain tumors.

Histological Subtypes

NHL is a group of diverse lymphoid malignancies. Improved understanding of tumor immunology, cytogenetics, and molecular biology has improved both the classification and treatment strategies for NHL. Each major subtype NHL needs to be understood separately. Major subtypes of NHL include Burkitt Lymphoma (BL), lymphoblastic lymphoma (LL), diffuse large B-Cell lymphoma, and anaplastic large-cell lymphoma.

Burkitt lymphoma is a fast-growing B-cell malignancy with a high proliferation rate. The pathology generally shows sheets of homogeneous cells with a classical "starry sky" appearance. Cell surface antigens include CD19, CD20, CD79a, and CD10, and surface immunoglobulin. Most BLs have characteristic translocations, including t(8;14), t(2;8) or t(8;22); these translocations fuse an immunoglobulin component gene with an oncogene.

Lymphoblastic lymphoma (LL) is closely related to ALL and can be either of B or T-cell origin. Cell surface antigens, cytogenetic abnormalities, and molecular biology of LL are identical to the corresponding cell origin ALL.

Diffuse large B-cell Lymphoma accounts for about one-third of all childhood NHLs. Cells express a number of B-cell antigens, including CD19, CD20, CD22, and Cd79a.

Clinical Features

NHL often presents with either persistent, progressive adenopathy, or as a medical emergency, including respiratory distress from a mediastinal mass or intestinal obstruction due to a mass arising from a Peyer's patch in the small intestine (most commonly terminal ileum). Most NHLs have a high rate of growth, and prompt referral to a childhood cancer center is important. Clinical features differ by type of NHL.

There are at least two main types of Burkitt lymphoma. In developed countries, BL often primarily involves the intestine and presents as an abdominal mass with or without intestinal obstruction. African BL is often associated with the Epstein–Barr Virus (EBV) and presents as a large facial mass.

Lymphoblastic lymphoma often presents with a mediastinal mass and may have malignant effusions, often leading to respiratory distress or failure. LL can be of either B- or T-cell origin, and clinical features are similar to ALL of the same lineage. For example, both T-cell ALL and T-cell LL are likely to present with a mediastinal mass and are more likely to involve the central nervous system (CNS).

Diffuse large B-cell lymphomas can present in a large variety of ways, but typically with sizable adenopathy, including mediastinal masses. This subtype is often disseminated and is the subtype most associated with immunodeficiencies.

Laboratory Features

Unless the bone marrow is involved, the complete blood count is usually normal. Similarly, unless there is hepatic involvement or renal failure from the acute tumor lysis syndrome (ATLS), blood chemistries are often normal. Lactate dehydrogenase (LDH) is usually markedly elevated. Uric acid, electrolytes, and renal function must be following closely at diagnosis and during the first few days of treatment, to prevent or treat ATLS.

Diagnostic Studies and Staging

Diagnosis depends upon a biopsy, and pathological tests should include cytogenetics and flow cytometry.

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Table 346.1
St. Jude (Murphy) staging system for non-Hodgkin lymphoma (NHL)

Stage	Description
I	• A single extranodal tumor or single nodal group, exclusive of the mediastinum or abdomen
II	• A single extranodal tumor with regional node involvement
	• Two or more nodal groups, on the same side of the diaphragm
	• Two extranodal tumors with or without regional node involvement on the same side of the diaphragm
	• Primary GI tract tumor (usually ileocecal) with or without regional node involvement
III	• Two extranodal tumors involving both sides of the diaphragm
	• Two or more nodal groups, involving both sides of the diaphragm
	• All primary intrathoracic tumors (mediastinal, pleural)
	• All extensive primary intra-abdominal tumors
	• All paraspinal or epidural tumors
IV	• Any of the above stages, with bone marrow or central nervous system involvement

In children with an effusion, malignant cells from an aspirate will usually yield the diagnosis. Performing the staging workup rapidly is important, given the urgent need to start therapy. Computerized tomography (CT) of the neck, chest, abdomen, and pelvis should be done, including the Waldeyer Ring, and bone marrow and cerebrospinal fluid should be tested in all NHL patients. A modification of the Murphy staging system is used in NHL (see *Table 346.1*), supplemented by a risk stratification schema for B-cell lymphomas (*Table 346.2*).

Treatment

Treatment differs by subtype, but all are treated with chemotherapy. Beyond establishing the diagnosis, there is little role for surgery in the treatment of NHL. Patients with intestinal obstruction need an emergency laparotomy with tumor resection. Radiotherapy is not part of standard therapies for NHL but may be used for palliation in patients with recurrent disease.

Chemotherapy is the mainstay of NHL therapy and has many similarities to treatment strategies used in ALL.

Table 346.2
Risk stratification of B-cell lymphomas

Stratum	Description
A	• Resected stage I and abdominal stage II
B	• Multiple extraabdominal sites, nonresected stage I, II, III
	• Stage IV may be in this group if less than 25% of bone marrow or cells in CSF are malignant
C	• Intra-abdominal stage IV
	• Bone marrow involvement with greater than 25% of cells being malignant

This system is used in addition to the Murphy staging system

CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) is the most commonly used combination chemotherapy and is effective in Burkitt lymphoma, diffuse large B-cell lymphoma and anaplastic large-cell lymphoma. In addition, COPAD (cyclophosphamide, doxorubicin, vincristine, and prednisone), COPADM (cyclophosphamide, doxorubicin, vincristine, prednisone, and high-dose methotrexate), and COMP (cyclophosphamide, vincristine, methotrexate, and prednisone) are used in BL. COPAD and COPADM are also used in large B-cell lymphoma. These are all dose-intensive combinations with significant toxicities and need to be administered in a pediatric oncology referral center. Lymphoblastic lymphomas are treated very similarly to ALL, and treatment may include CHOP with an ALL-Type maintenance using oral mercaptopurine and methotrexate. Monoclonal antibodies directed at cell surface markers have activity in NHL and are being studied in combination with chemotherapy.

Prognosis

Most types and stages of NHL have an excellent prognosis. Low stage BL has a 90–95% survival rate, and large B-cell lymphoma and anaplastic large-cell lymphoma have 90% survival rates. Even with advanced stages, most children have at least a 70% chance of survival. However, recurrent NHL can be quite difficult to treat.

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347 Hodgkin Disease

H. Stacy Nicholson

Introduction

Hodgkin disease (HD) is a B-cell lymphoid malignancy that occurs in 2 per 100,000 children before the age of 15 years in the USA. In the USA and other developed nations, HD is primarily a disease of adolescence and young adults with a second peak in older adulthood (>50 years). In the developing world, the age distribution is shifted toward younger children.

Pathology

HD is diagnosed from a lymph node biopsy and requires the demonstration of the classic Reed–Sternberg (RS) cells in a background of lymphocytes, histiocytes, eosinophils, and plasma cells. The RS cell is the malignant cell of HD and is of B-cell lineage. There are four histopathological subtypes of HD: lymphocyte predominance (LP), nodular sclerosis (NS), mixed cellularity (MC), and lymphocyte depletion (LD). NS is the most common subtype in the USA and Western Europe, and MC is the most common in the developing world. Subtype is related to prognosis – LP rarely disseminates and has a good prognosis, while LD is likely to disseminate and has a poor prognosis (*Fig. 347.1*).

Clinical Features

HD usually presents as painless progressive adenopathy which ultimately will coalesce into a large mass. Most commonly, HD starts above the diaphragm and involves cervical, axillary, or intrathoracic nodes. In one-third of patients, the initial site is below the diaphragm and can include the inguinal and/or intraabdominal nodes. HD can spread to other organs, including spleen, liver, and bone marrow.

Some patients with HD have a classic constellation of symptoms, including fever, night sweats, and weight loss – these are called "B" symptoms and are important in staging newly diagnosed patients. Severe pruritis can also be a presenting symptom.

Diagnostic Studies and Staging

Following histopathological diagnosis, the staging workup in HD requires that all major nodal groups on both side of the diaphragm be imaged. The most common imaging modality is computerized tomography (CT), which should include the neck (including the Waldeyer ring), chest, abdomen, and pelvis. Nuclear scintography (gallium or PET) may be useful, but staging laparatomy and lymphangiograms are no longer routinely used. Bone marrow aspirates and biopsies are done in all but those with stages IA or IIA HD, and bone scans are needed only if symptoms suggest bony involvement.

The Ann Arbor staging system is the accepted standard (*Table 347.1*). Based on the number and site of involved lymph node chains, patients are stratified into four main stages, I–IV. Furthermore, patients are classified as having either A or B disease based on the absence or presence, respectively, of the classic triad of constitutional symptoms (fever, weight loss, night sweats.) Untreated, HD will predictably progress to a higher stage, although stage at diagnosis usually reflects the underlying tumor biology.

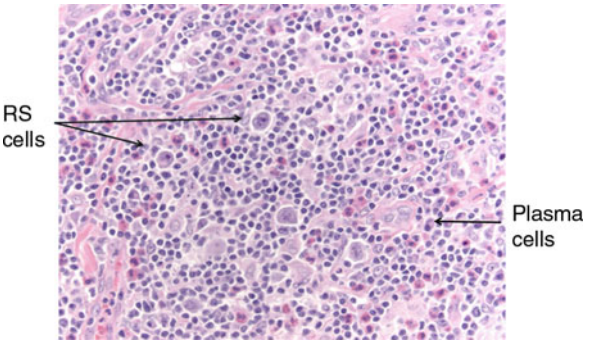

Figure 347.1
Nodular sclerosing Hodgkin disease: Hematoxalin-eosin stain – 20×: Reed–Sternberg cells with binuclear and mononuclear forms in the background of fibrosis, admixed with eosinophils, plasma cells, and small lymphocytes (Courtesy of Guang Fan, MD, PhD)

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Table 347.1
Ann Arbor staging of Hodgkin disease

Stage	
I	Disease is limited to one lymphatic region or one extra nodal site, excluding liver or bone marrow.
II	Disease involves two or more lymphatic regions on one side of the diaphragm
III	Disease involves lymphatic regions on both sides of the diaphragm (may involve spleen).
IV	Disease involves lymph nodes in any pattern. In addition, liver, bone marrow, lungs, CNS, or other organs are involved.

Treatment

Treatment is based on stage and may involve chemotherapy, radiation, or both. Generally, the role of surgery is limited to establishing the diagnosis. Treatment has evolved over the past few decades, resulting in excellent survival. Chemotherapy is now used in all but very low-stage patients, and radiation is being used more sparingly. With the realization that women who received chest radiation for HD during adolescence have a high risk of breast cancer, treatment strategies for males vs. females have diverged, with radiation being used less in females.

Radiotherapy

Radiation is an effective treatment for HD and has been used since the 1940s and is used without chemotherapy for low-risk patients with low-stage disease. Dosage varies by stage and site but generally does not exceed 40 Gy.

Chemotherapy

MOPP (mechlorethamine, vincristine (Oncovine®), procarbazine, and prednisone) chemotherapy was one of the first combinations of chemotherapy demonstrated to be effective in cancer. MOPP and variations of MOPP are still used in the treatment of HD. However, MOPP has significant long-term toxicities, including infertility and secondary malignancies. A second combination, ABVD (Adriamycin, bleomycin, vinblastine, and dacarbazine) is also effective. Combination therapy for HD continues to evolve, with combinations that use both MOPP and ABVD, and modifications of MOPP, most commonly with cyclophosphamide being substituted for mechlorethamine (COPP).

Prognosis

With stage-appropriate therapy, most children and adolescents with HD will become long-term survivors, and patients with low-stage disease have survival rates in excess of 90%. Even with stage IV disease, most become long-term survivors. However, HD is one of the few childhood malignancies where a relapse can occur more than 5 years after diagnosis. Thus, close follow-up is required through the first decade and lifelong follow-up is advised to monitor for late effects of therapy. Following relapse, some children have been cured using high-dose chemotherapy and autologous bone marrow transplantation.

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348 The Histiocytoses

Suman Malempati · H. Stacy Nicholson

Introduction

The histiocytoses of childhood are a diverse and relatively uncommon group of disorders. Despite considerable heterogeneity in clinical manifestations, these diseases have in common the proliferation of cells of the mononuclear phagocyte system. The World Health Organization (WHO) has utilized a general classification scheme that is based on both clinical presentation as well as histologic features (*Table 348.1*). According to this scheme, Class I defines Langerhans cell histiocytosis, Class II includes histiocytoses of mononuclear phagocytes other than Langerhans cells, and Class III denotes malignant histiocytic disorders.

Class I Histiocytosis

Langerhans Cell Histiocytosis (LCH) is characterized by a non-malignant clonal proliferation of a specific-type of dendritic cell, known as the Langerhans cell. Until the 1980s, LCH was known as Histiocytosis X, as the cell of origin was undetermined. Histiocytosis X, which was coined in 1953, was a term used to unify several related clinical syndromes, including Hand-Schuller-Christian syndrome, Letterer-Siwe disease, eosinophilic granuloma, and Hashimoto-Pritzker syndrome into one clinical entity. Despite the wide variation in clinical manifestations, the central role of the Langerhans Cell unites these disorders.

Epidemiology

It is difficult to obtain an exact incidence rate of LCH due to heterogeneity of clinical manifestations of the disease and possible underrecognition of this condition. The annual pediatric incidence of LCH has been estimated to be 2–6 cases per million children. LCH tends to occur in young children with a peak incidence between 1 and 4 years of age. Young children with LCH have a higher frequency of more severe disease, and most cases with multisystem involvement occur before the age of 2 years. Older children and adults are more likely to have disease limited to bony sites. There appears to be a higher incidence of cancer in patients with LCH, although a causal association has never been demonstrated.

Pathogenesis

LCH is characterized by a clonal proliferation of Langerhans cells. Langerhans cells are antigen-presenting cells of monocyte lineage that are normally found in the skin and other organs. The typical LCH lesion contains histiocytes including Langerhans cells, lymphocytes, eosinophils, and sometimes neutrophils and plasma cells. While the disease is thought to be immunologically mediated and result from disordered immune regulation, an exact cause of the disease has not been elucidated. Evidence suggests that the abnormal proliferation of histiocytes, though clonal, is reactive rather than malignant.

Clinical Manifestations

The manifestations of LCH range from an idolent localized lesion to widely disseminated aggressive disease. The most commonly affected system is the skeleton, with bone lesions present in 80% of cases. In the past, eosinophilic granuloma was the term used to describe LCH involving single or multiple bone sites without visceral involvement. A unifocal bone lesion is the most common manifestation of the disease and comprises approximately 30% of cases. Bone lesions are often painless and are usually accompanied by a soft-tissue mass. The skull is the most common site. Skull lesions may be associated with other head and/or neck manifestations such as chronic otitis media, mastoiditis, “floating teeth” with mandible involvement, and cervical lymphadenopathy. Patients with base of skull lesions are also at risk for intracranial complications – most commonly diabetes insipidus (DI). Involvement of the spine can result in vertebral collapse, and there can be risk of spinal cord impingement. Extremity lesions may be painful or painless and can sometimes lead to pathologic fracture.

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Skin is the next most commonly involved organ, and skin rash is often part of disseminated disease. The rash associated with LCH is characterized by a crusting vesiculopustular exanthem with a similar appearance to seborrheic dermatitis. It frequently occurs on the scalp and postauricular region, but can also be seen on the trunk and inguinal region. A syndrome associated with skin-only involvement of LCH in the neonate is known as congenital self-healing histiocytosis or Hashimoto-Pritzker syndrome. As the name suggests, the lesions typically resolve by 3–4 months of age without treatment.

Disseminated LCH usually occurs in children less than 1–2 years of age and can be life-threatening. The organs most commonly involved include the liver, spleen, lymph nodes, and bone marrow. Pulmonary involvement is rare in children, but can occur with disseminated disease. This is in contrast to primary pulmonary LCH that occurs in adults without other systemic involvement. Pulmonary LCH in adults is often associated with smoking tobacco.

Central nervous system involvement of LCH is common and can lead to devastating consequences. DI results from infiltration of LCH cells into the hypothalamus or pituitary stalk and occurs in up to 20% of patients with LCH. DI often occurs after other manifestations of the disease and is typically seen in patients with multisystem disease and those with skull bone involvement. Cranial nerve palsies and lesions in the cerebellum resulting in ataxia can also occur.

Diagnostic Evaluation

The diagnostic evaluation of patients with suspected LCH should begin with a thorough history and physical examination. Evaluation of patients with skull bone lesions and suspected LCH should include appraisal of CNS symptoms as well as symptoms of polyuria and polydypsia. Physical examination must include assessment for skin rash, lymphadenopathy, hepatosplenomegaly, and cranial nerve deficits. Imaging is necessary to characterize any suspected bone lesions. The classic radiologic findings are "punched out" lesions on plain x-rays (*Figs. 348.1* and *348.2*). Lesions are typically well demarcated, and reactive sclerosis is unusual at diagnosis. Other evaluations are helpful to determine extent of disease. A complete bone survey is necessary to evaluate for occult bone lesions in any patient diagnosed with LCH. Cytopenias see on a peripheral complete blood count may indicate bone marrow involvement. Bone marrow aspirates and biopsies should also be performed if cytopenias are present. A brain MRI is important to evaluate for intracranial lesions in patients who have skull bone involvement. Guidelines for diagnostic evaluation for patients with suspected LCH are shown in *Table 348.2*.

While clinical and radiographic features may suggest a diagnosis of LCH, pathologic evaluation of involved tissue is necessary for definitive diagnosis. On light microscopy, LCH lesions will show mixed population of cells that includes large histiocytes with few cytoplasmic vacuoles (Langerhans cells) along with an abundance of eosinophils

Table 348.1
Classification of histiocytic disorders

Class I	Class II	Class III
Langerhans cell histiocytosis	*Non-langerhans histiocytoses*	*Malignant histiocytoses*
• Eosinophilic Granuloma	• HLH – Familial HLH – Secondary HLH	• *Acute Monocytic Leukemia*
• Hand-Schuller Christian		• *Malignant Histiocytosis*
• Letterer-Siwe		• *Histiocytic Sarcoma*
• Hashimoto-Pritzker	• Rosai-Dorfman	
	• Juvenile Xanthogranuloma	

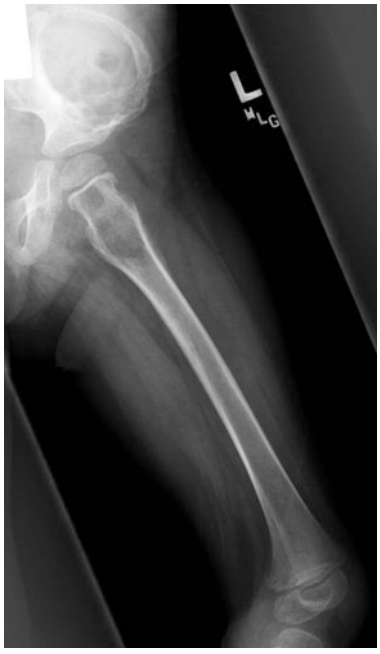

Figure 348.1
Lateral radiograph showing a large lytic lesion in the neck and intertrochanteric region of the femur

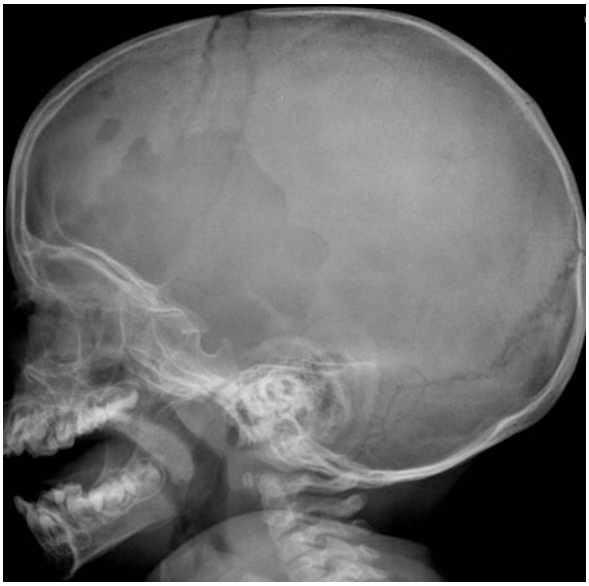

Figure 348.2
Radiograph of the skull showing a large geographic lytic lesion in the right fronto-parietal bone with 2 smaller lesions nearby

Table 348.2
Diagnostic evaluation for suspected LCH

• History
– Neurologic symptoms
– Polyuria/polydypsia
• Physical exam
– Bone lesions/masses
– Skin rash
– Lymphadenopathy
– Liver and Spleen Size
– Neurologic Exam/Cranial Nerves
• Laboratory tests:
– CBC
– Serum chemistries, LFTs
– Urine and serum osmolarity
• Imaging tests:
– Complete skeletal survey
– Brain MRI (if skull bone lesions present)
• Tissue diagnosis:
– Biopsy of involved lesion or organ
– Bone marrow aspirates/biopsies (if multisystem disease or cytopenias present)

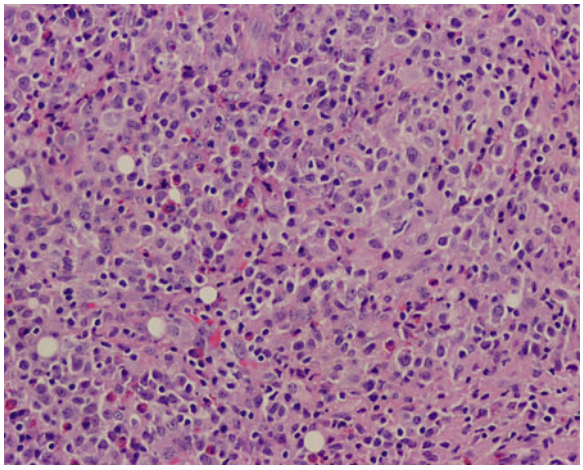

Figure 348.3
Light microscopy of LCH lesion

and lymphocytes (*Fig. 348.3*). Immunohistochemical staining shows positivity for CD1a antigen and S-100 protein. More recently staining for CD207 also known as Langerin has been used. Presence of the typical light microscopic findings along with positivity for CD1a or CD207 is diagnostic of LCH. Demonstration of rod-shaped organelles known as Birbeck granules by electron microscopy is also diagnostic.

Treatment and Prognosis

The appropriate management of patients with LCH depends on the location and extent of disease. The goal of treatment should be control of disease and prevention of long-term consequences rather than complete ablation. Patients with single-system disease may require minimal to no treatment as the natural history can include spontaneous resolution. Solitary bone lesions may be treated with curettage alone. Aggressive surgical resection is not necessary. Low-dose radiation therapy may also be used to treat bone lesions that are in locations that cause risk for permanent damage to underlying structures. Patients with skin-only disease may not need to be treated or can be treated with topical corticosteroids. The prognosis for patients with single-system disease is excellent.

Patients with multisystem disease and organ dysfunction have a significant risk of death and require systemic treatment. Chemotherapy has been used effectively to induce disease regression. Effective agents against LCH include prednisone, vinblastine, mercaptopurine, methotrexate, and more recently, 2-chlorodeoxyadenosine

(2-CDA). Combinations of these agents have been evaluated in multinational randomized clinical trials by the Histiocyte Society. Allogeneic hematopoeitic stem cell transplant has also been used for patients with refractory, progressive LCH.

While the prognosis for most patients with LCH is very good, the risk of late sequelae is high. Long-term complications of LCH occur in up to 30–50% of survivors of LCH. These permanent sequelae include diabetes insipidus and other endocrinopathies, neurologic and developmental abnormalities, orthopedic problems, and hearing impairment. Whether systemic therapy may decrease the frequency of these complications is debatable.

Class II Histiocytosis

The Class II histiocytoses are a heterogeneous group of disorders that are characterized by a proliferation of phagocytic cells. These disorders are thought to be reactive processes which result in infiltration of normal cells of monocyte/macrophage lineage. The major disease in this category is hemophagocytic lymphohistiocytosis (HLH), which has both familial and secondary forms. Other benign disorders in this category include sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman Disease) and juvenile xanthogranuloma.

Epidemiology

The primary familial form of HLH typically manifests in infancy or early childhood. There are multiple genetic abnormalities that can lead to the clinical manifestations of HLH syndrome. The disease is typically inherited in an autosomal recessive pattern, although there is often no family history. Familial HLH is rare with an estimated incidence of 1 in 50,000 live births. Among familial cases, the most common genetic abnormalities found involve mutations of the *perforin* gene, which are found in about one-third of patients with HLH.

Secondary HLH results from an abnormal immune response to an infection or other process. The incidence of secondary HLH is unclear as the disease is likely underdiagnosed. It is possible that the condition is now being recognized and diagnosed more frequently. Infection-associated secondary HLH has been reported after viral, bacterial, fungal, and parasitic infections. HLH is a known complication of EBV infection, particularly in patients with x-linked lymphoproliferative disease. It occurs more frequently in children with underlying immunodeficiency.

Clinical Manifestations

The most common clinical features of HLH are prolonged fever, hepatosplenomegaly, and cytopenias. Patients also often present with rash, lymphadenopathy, and coagulopathy. The Histiocyte Society has developed a set of diagnostic criteria for HLH based on clinical signs and specific laboratory abnormalities (Table 348.3). These diagnostic guidelines are valid for both familial and secondary HLH. While HLH is a non-malignant disorder, patients are often critically ill at presentation and the disease is often fatal without treatment. Most of the signs and symptoms and HLH are non-specific and the condition can be difficult to distinguish from sepsis or hepatitis. Patients can also have CNS involvement which may manifest as seizures or ataxia.

Diagnostic Evaluation

The presenting signs and symptoms of HLH are non-specific and establishing a definitive diagnosis can be difficult. Physical exam should include evaluation for organomegaly and lymphadenopathy. The splenomegaly is often profound and out of proportion to what would be expected from an underlying bacterial of viral infection. Laboratory evaluation should include a complete blood count, coagulation profile, serum ferritin, and serum triglycerides. Biopsy of bone marrow, lymph nodes, spleen, or liver may show a lymphohistiocytic infiltrate with

Table 348.3
Diagnostic criteria for HLH

Detection of a characteristic genetic abnormality (i.e., perforin or MUNC 13-4 mutations) OR Presence of at least 5 of 8 criteria listed below:
• Fever (persistent daily)
• Splenomegaly
• Cytopenia of at least 2 cell lines
– Hemoglobin < 9 g/dL
– Platelets < 100,000/μL
– Neutrophils < 1,000/μL
• Hypertriglyceridemia and/or hypofibrinogenemia
• Hemophagocytosis in bone marrow, spleen, or lymph nodes without evidence of malignancy
• Elevated serum ferritin (> 500 μg/L)
• Elevated soluble IL-receptor alpha (CD25)
• Low or absent NK-cell function

hemophagocytosis. However, hemophagocytosis is not always identified and is not required for the diagnosis of HLH. Specialized tests that include measurement of soluble interleukin-2 receptor and NK-cell activity may need to be sent to a reference laboratory. A definitive diagnosis of familial HLH can be made by detection of one of the characteristic genetic mutations, which are present in approximately 50% of cases.

Treatment and Prognosis

Initial therapy for HLH consists of chemotherapy with immunosuppressive agents. The Histiocyte Society's HLH-2004 protocol treats patients with a combination of etoposide, cyclosporin A, and dexamethasone. Hematopoietic stem cell transplant is commonly used and is the treatment of choice for patients with familial HLH.

Without treatment HLH is usually rapidly fatal. Survival rates with stem cell transplant for familial HLH are better than 50%.

Other Class II Histiocytoses

Sinus histiocytosis with massive lymphadenopathy, also known as Rosai-Dorfman disease, is a benign, reactive process characterized by enlargement of cervical lymph nodes associated with systemic symptoms. Patients with this condition often have fevers, night sweats, and weight loss. The disease usually resolves spontaneously, but may require treatment due to life-threatening airway obstruction. Effective treatments include corticosteroids, chemotherapy, and radiation.

Juvenile xanthogranuloma is benign histiocytic process that occurs in infants and young children. Lesions are usually confined to the skin, but multisystem involvement can occur. Solitary cutaneous lesions almost always regress spontaneously. Treatment with chemotherapy as has been used for LCH is effective for systemic disease.

Class III Histiocytoses

The Class III Histiocytoses consist of malignant disorders of mononuclear phagocyte lineage, including acute monocytic leukemia, malignant histiocytosis, and histiocytic sarcoma. Acute monocytic leukemia is considered a subtype of acute myelogenous leukemia (M5) and is discussed in more detail in Chap. 345, "Childhood Leukemias". True malignant histiocytosis is a very rare systemic disease. The clinical manifestations may be very similar to HLH. Fever, lymphadenopathy, hepatosplenomegaly, and skin lesions are common signs. It is now recognized that many malignancies previously diagnosed as malignant histiocytosis actually represent anaplastic large cell lymphoma (see Chap. 346, "Non-Hodgkin Lymphoma"). Systemic chemotherapy can be effective in the treatment of the malignant histiocytoses.

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349 Central Nervous System Tumors in Children

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Introduction

Brain tumors are the most common solid tumor in children and are the second most common malignancy of childhood. The incidence of brain tumors peaks in the first decade and then again in later adulthood. Supratentorial tumors predominate during the first 2 years of life and then again in adolescence and young adulthood. Throughout the rest of the first decade, infratentorial tumors are more common. Tumors with embryonal histology such as medulloblastoma, supratentorial primitive neuroectodermal tumor (PNET), atypical teratoid rhabdoid tumor (AT/RT), and pineoblastoma occur more frequently in children than adults, and medulloblastoma is the most common type of malignant brain tumor in children. Gliomas can be benign or malignant and can occur anywhere along the neuroaxis.

Cancer arises from mutations that occur in genes that regulate cell growth and death. These mutations can occur in the entire germline or only within the somatic cells of the tumor itself. A small fraction of children with brain tumors have germline mutations, either inherited or de novo, which predisposes them to develop central nervous system (CNS) tumors. Several inherited syndromes, such as neurofibromatosis and tuberous sclerosis, are associated with an increased risk of CNS tumors. There is also an increased incidence of CNS tumors with previous exposure to ionizing radiation. However, in the majority of cases, the cause of a brain or spinal cord tumor in a child is unknown and is likely multifactorial.

CNS tumors and their treatment can cause significant physical, neurocognitive, psychological, and neuroendocrine morbidity. Long-term morbidity often exceeds that of other childhood malignancies, and mortality is the highest of all pediatric cancers.

Signs and Symptoms of Central Nervous System Tumors

The presentation of brain tumors can generally be classified into two categories: increased intracranial pressure (ICP) and localizing signs/symptoms. CNS tumors often cause increased ICP by causing obstruction of CSF pathways. Signs and symptoms of increased ICP can be vague and generalized or can be more severe and life threatening. The classic presentation is early morning headaches relieved with vomiting, and a late finding is mental status decline. The early signs of increased ICP can be similar to other common childhood complaints, so many children with brain tumors have been initially treated for more common childhood illnesses, such as viral gastroenteritis or influenza.

Nearly two-thirds of patients with newly diagnosed pediatric brain tumors have a history of chronic or frequent headaches. In elementary school children, the prevalence of headache is approximately 40–50% and up to 60–80% in adolescents. Typically, headaches associated with a brain tumor worsen over time. Clear indicators that something serious is occurring are headaches that awaken a child from sleep, headaches associated with vomiting, or headaches in addition to an objective neurologic finding. The location of the headache is not typically helpful, but a constant occipital headache and neck pain with hyperextension is an ominous sign of tonsillar herniation. The structures of the posterior fossa and the back of the head are both innervated by branches of the upper cervical roots, so a complaint of worsening occipital headache may be a sign of an infratentorial tumor causing increased ICP. This scenario warrants urgent neuroimaging and referral to a neurosurgeon in the setting of an Emergency Department.

A study conducted by the Childhood Brain Tumor Consortium showed that more than 98% of newly diagnosed brain tumor patients who complained of a headache at presentation also had at least one objective neurologic finding. These included mental status changes, abnormal eye movements, optic disc distortion, asymmetric motor or sensory examination, coordination problems, or abnormal deep tendon reflexes. Therefore, it is very important to do a complete neurologic examination on any child presenting with a headache.

In infants and young children, the signs and symptoms of a brain tumor can be more subtle. Increased ICP can be

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demonstrated by macrocephaly, irritability, poor feeding, and lethargy. In very young children, cranial sutures can separate due to increased ICP even after closure of the fontanelles. Head circumference should be measured and plotted for all children up to at least 3 years of age. This should be done at every routine primary care visit, as well as any visit for headaches or other unexplained symptoms in a younger child. A late and ominous sign of increased ICP in very young children is the "setting sun sign" of the eyes which is caused by pressure on the nerves that control eye movement. The eyes are forced downward and pupillary responses are typically sluggish.

Localizing signs of CNS tumors may include seizures, cranial nerve dysfunction, endocrine dysfunction, cerebellar dysfunction (ataxia or dysmetria), bowel or bladder dysfunction, abnormal or asymmetric strength, abnormal sensation, or asymmetric deep tendon reflexes. Declining school performance or personality/behavioral changes are other common complaints, but are less easily classified as localizing signs. Lesions of the pineal region are associated with Parinaud's Ophthalmoplegia. This is a triad including severely impaired upward gaze, dilated pupils that react to accommodation but not to light, and a specific form of nystagmus called convergence retraction nystagmus. The latter is more easily recognized by an ophthalmologist, but is best recognized when the patient attempts to look up.

Tumors confined to the optic nerve produce monocular vision loss. Chiasmatic tumors present with complex visual field loss as well as loss of acuity. In infants, these tumors may present with unilateral or bilateral nystagmus with head nodding and head tilt, also known as spasmus nutans. Those that are located more posteriorly in the optic tract present with hemianopsia. Optic pathway tumors are very common in patients with Neurofibromatosis Type I. These patients must be screened by annual ophthalmologic examination, but MRI is only recommended if there is abnormality or change in their vision or visual fields because treatment is only indicated when there is evidence of vision change.

Tumors located in the hypothalamus in infants may present with the diencephalic syndrome, which is characterized by failure to thrive, emaciation, paradoxical euphoric mood, and increased appetite.

Diagnosis of Central Nervous System Tumors

Magnetic Resonance Imaging (MRI) of the brain and/or spine is the best diagnostic study to order when a CNS tumor is suspected. It offers the best diagnostic sensitivity and does not expose the patient to radiation. Although CT scanning does cause radiation exposure, it is sometimes needed for initial urgent evaluation of patients with increased ICP. MRI "quick brain" is a newer technique that may offer the information needed in an urgent situation, without the radiation exposure associated with CT scanning. Indications for neuroimaging with MRI in the child that has a headache include, but are not limited to: association with seizures, association with recumbent position or vomiting, occipital location, exacerbation with straining, presence of other ominous signs such as Cushing's Triad (bradycardia, hypertension, irregular respirations), altered mental status, presence of objective neurologic findings, optic disc distortion or papilledema, asymmetry on physical examination, coordination problems, and macrocephaly in infants and toddlers.

Seizures due to non-oncologic causes are more common than seizures due to brain tumors, so they do not always warrant urgent neuroimaging. However, unless the presentation is clearly consistent with a simple febrile seizure or absence seizure, MRI of the brain is recommended because of the severe consequences that could arise if a brain tumor is not recognized. Any patient with an EEG showing focal abnormalities should be further evaluated with MRI. All simple and complex partial seizures and most unexplained generalized seizures should prompt imaging. Seizure features associated with an increased risk of a brain tumor include a change in preexisting seizure features, status epilepticus as first presentation of a seizure, resistance of seizures to medical control, and prolonged postictal focal symptoms or deficits.

Once a CNS tumor is identified, neurosurgical intervention is often indicated, for diagnostic and treatment purposes. Initial care may require urgent treatment of hydrocephalus. Ultimately, histologic examination of the tumor by a neuropathologist will guide further treatment planning in most cases. There are several scenarios in which neurosurgical intervention may not be appropriate, so it is important that newly diagnosed pediatric brain tumor patients are evaluated at a center that has specialists in pediatric neurosurgery and pediatric neuro-oncology.

Common Types of Pediatric CNS Tumors

Embryonal Tumors: Medulloblastoma, sPNET, AT/RT

Medulloblastoma is an embryonal neuroepithelial tumor and is the most common malignant brain tumor in childhood. It accounts for 20% of all primary pediatric brain

tumors and 40% of posterior fossa tumors. There is a peak incidence in the first decade of life around ages 5–7 and there is a male predominance of 2:1. Medulloblastoma has the greatest propensity of the CNS tumors to metastasize outside of the neuroaxis at a rate of about 4–7%. The most common sites of metastasis are bone, bone marrow, liver, lung, and lymph nodes.

Research continues on the genetic and biologic properties of medulloblastoma, and the most common chromosomal abnormality is isochromosome 17q. Trisomy 7 is the second most common abnormality. Several prognostic features have been identified and influence treatment recommendations. In general, age less than 3 years, residual tumor bulk of >1.5 cm^2 after surgical resection, and presence of metastasis either within or outside of the CNS have been associated with high-risk disease and a worse prognosis. There are newer histopathologic markers of high-risk disease as well.

Supratentorial primitive neuroectodermal tumor (sPNET) has been called cerebral medulloblastoma in the past but recent molecular evidence indicates that this tumor is different from medulloblastoma, though the two are often discussed together. sPNET is a rare type of CNS tumor accounting for only 2–3% of all CNS tumors. It is more common during the first decade and 90% occur in the cerebral hemispheres. Males and females are affected equally. This tumor also has a propensity to metastasize with up to 30% with CSF seeding in some series. It can also metastasize outside of the neuroaxis and has been reported in the bone and lung. Treatment for sPNET has historically been based on treatment for medulloblastoma; however, the overall outcome of these patients is significantly worse than those with medulloblastoma, suggesting inherent biologic differences.

Pineoblastoma is a primitive undifferentiated tumor that is distinguished from medulloblastoma and sPNET by its location. It occurs most frequently in the first decade of life and there is an equal incidence among males and females. These tumors can spread within the CNS; however, seeding outside of the CNS is rare.

Therapy for medulloblastoma, sPNET, and pineoblastoma consists of maximal safe surgical resection, crainospinal radiation with focal boost to the local tumor site, and systemic chemotherapy. Ongoing research is aimed at further delineating clinical and biologic prognostic factors as well as optimization of therapy for these patients.

Historically, atypical teratoid rhabdoid tumor (AT/RT) was probably mistaken for medulloblastoma or sPNET. But further research identified distinct histologic and cytogenetic features that distinguish it from other tumor types. Deletion of chromosome 22 and alterations of the hSNF5/INI-1 gene have been described. Lack of INI-1 expression has been shown to be a characteristic feature of AT/RT, and the immunohistochemical stain is now used routinely by neuropathologists.

AT/RT is a rare tumor that occurs more commonly in young children with a median age of 24 months. About 60% of these tumors are supratentorial and there is a male predominance of 2:1. It is known to metastasize and leptomeningeal spread at diagnosis has been reported to occur in 20–25% of patients. These tumors tend to be very aggressive, with formerly reported median event-free survival reported of 10 months and median survival about 17 months from diagnosis. In spite of the historically poor prognosis and aggressive nature of this disease, a more recent treatment regimen has been reported by Chi et al. showing promising results for many patients. In general, these patients are treated with maximal surgical resection, radiation, and systemic chemotherapy.

Ependymoma

Ependymomas account for approximately 9% of all primary CNS tumors in children. These tumors are generally located within or adjacent to the ependymal lining of the ventricular system or the central canal of the spinal cord. Ninety percent are intracranial, and of these, 60% are located in the posterior fossa. The remaining 10% are located in the spinal cord and these tend to occur in adolescents. The highest incidence of these tumors is in the first 7 years of life and there is a slight predominance in males. Typically, ependymomas are locally invasive, although the reported incidence of systemic metastasis is approximately 7%. The single most important prognostic factor in ependymoma treatment is the degree of surgical resection. Survival rates are higher (about 70%) following a gross total resection compared with 0–50% survival following less than a complete resection. It has also been found that ependymomas of the spinal cord are associated with the best outcome. Children less than age three have had historically poorer outcomes, though the reasons for this are unclear. These patients are more likely to have tumors located in the posterior fossa and gross total resection is often more difficult in this location because of its characteristic wrapping around the brainstem and cranial nerves. Due to their age, these children often receive delayed radiation therapy which may also impact their overall survival. Focal radiation therapy increases survival rates in most scenarios. Chemotherapy has not been shown to improve overall survival for patients with completely or incompletely resected ependymomas.

Low-Grade Gliomas

Low-grade gliomas are a diverse tumor group that includes grade I (pilocytic) astrocytoma, grade II (fibrillary or diffuse) astrocytoma low-grade oligodendroglioma, low-grade ganglioglioma, pleiomorphic xanthoastrocytoma (PXA), and a variety of low-grade mixed glial tumors such as oligoastrocytoma. In general, they are slow-growing tumors with insidious onset of symptoms and relatively benign histologic appearance. Long-term outcomes are most dependent on the ability to achieve complete surgical resection. The average age at diagnosis is between 6 and 9 years and boys are affected more than girls. Dissemination outside of the CNS is very rare and reported in only about 5% of cases.

Most supratentorial and cerebellar low-grade gliomas are astrocytomas. Classic cerebellar pilocytic astrocytomas are the most common type of low-grade glioma and account for 80–85% of low-grade tumors in the cerebellum. Diffuse or fibrillary astrocytomas account for approximately 15% of cerebellar astrocytomas and are more likely to undergo anaplastic transformation compared to the pilocytic variant, though this malignant transformation is observed less in the pediatric population than it is in adults. Prognostic factors for low-grade gliomas are inconsistent in the literature. Complete surgical resection is thought to be very important for long-term disease-free survival in most series, and these tumors tend to be amenable to repeat surgical resection.

The standard of care for this group of tumors is complete surgical resection when possible. When complete resection is accomplished for pilocytic astrocytomas, cure rates are as high as 90–100%. If there is residual disease after initial resection or if there is tumor recurrence, repeat resection should be attempted if it can be done safely and it is felt that a complete resection can be achieved. Adjuvant therapy, such as radiation or chemotherapy, is often used for progressive or symptomatic residual tumors that cannot be completely resected. Radiation is known to be effective in delaying time to further progression, but it has not been shown to significantly affect overall survival in patients with unresectable tumors. Chemotherapy is often used in preadolescent children to avoid radiation in this young population. There are multiple outpatient chemotherapy regimens that offer a modest rate of disease stabilization or partial response. Complete regression of these tumors is rare with chemotherapy and ultimately, many patients experience progression of their disease and require multiple treatment regimens over a period of many years.

Brainstem Glioma

Brainstem gliomas are a heterogenous group of tumors with distinct subtypes. They are subdivided into non-diffuse brainstem tumors and diffuse intrinsic pontine gliomas (DIPG). Non-diffuse tumors of the brainstem account for 20% of all brainstem gliomas and include focal midbrain, dorsally exophytic, and cervicomedullary tumors. The non-diffuse brainstem tumors tend to be slow-growing, low-grade tumors with a more favorable prognosis and treatment response than DIPG. The majority of DIPG arise from the pons and can infiltrate into surrounding structures making them extremely difficult to treat and contributing to their overall dismal prognosis. Brainstem tumors make up 10–20% of all CNS tumors in children less than 15 years of age and the majority occur in children less than 10 years old with a median age of 6–7 years at diagnosis. Ninety percent are of glial origin and there is an equal incidence among males and females. Overall, the 5 year survival for all types of brainstem tumors is between 20% and 30%.

Brainstem gliomas are classified by their location rather than histology. The current standard of care does not include biopsy when radiographic features are classic for a DIPG, but historically most have been found to be diffuse astrocytoma (grades II, III, or IV). The majority of non-diffuse brainstem gliomas are low-grade astrocytomas.

Surgical treatment of non-diffuse brainstem gliomas is dependent on the degree of infiltration into normal structures, and often due to their location, surgical resection is not possible. However, if possible, debulking of dorsally exophytic, tegmental and non-tectal midbrain tumors, and cervicomedullary tumors should be considered. Radiation therapy is the conventional treatment for brainstem gliomas. The role of chemotherapy in the treatment of non-diffuse brainstem gliomas remains unknown and trials are ongoing, but the outpatient regimens of low-grade gliomas are sometimes used.

Diffuse intrinsic pontine gliomas have a universally poor prognosis and treatment of these lesions has historically been directed toward symptom relief rather than cure. The conventional treatment has been radiation therapy and several studies have investigated the use of hyperfractionated external beam radiotherapy (HFRT) versus standard radiotherapy. However no statistically significant difference in progression-free or overall survival was found between patients treated with HFRT vs. standard radiation therapy. The role of chemotherapy in DIPG is not currently known, and there is little evidence to suggest that the use of chemotherapy has a significant impact on the overall outcome of these patients. If left

untreated, the median survival of DIPG patients is 20 weeks. Radiation is thought to increase this median survival by approximately 2–3 months. Due to the overall dismal prognosis of DIPG, any treatment that could provide even a modest improvement in survival would have a large impact in the outcomes of these patients. Clinical trials are ongoing.

Germ Cell Tumors

Two-thirds of germ cell tumors are located in the region of the pineal gland and the remaining one-third are in the suprasellar region. They account for 40–65% of tumors in the pineal region, and are more common in the second decade of life with a peak incidence between 10 and 14 years of age. There is a male-to-female predominance of at least 2:1.

These tumors are a spectrum of embryonal neoplasms and teratomas thought to arise from totipotent germ cells. Sixty percent of these tumors are germinoma, 30% teratomas or mixed nonmalignant histology, and 10% malignant histology such as choriocarcinoma, endodermal sinus tumor (yolk sac tumor), and embryonal carcinoma. Collectively, immature teratomas, mixed germ cell tumors, endodermal sinus tumor, choriocarcinoma, and embryonal carcinomas are referred to as non-germinomatous germ cell tumors (NGGCT). Leptomeningeal spread occurs in approximately 10% of cases and in the highly malignant subgroups, systemic metastases can occur to the lungs, bone, and lymph nodes. Evaluation of the spine with MRI is important in the work up of these tumors due to their propensity to seed the CNS.

The histology of these tumors is prognostically significant. Germinomas are highly curable with 5 year survival rates as high as 95%. However, NGGCT generally have much poorer survival rates ranging from 20% to 75%. Disseminated disease and young age have also been associated with a worse prognosis; however, in younger patients this may be due to the fact that they often have disseminated disease at diagnosis and cannot safely receive crainospinal radiation which may be important in some cases.

Patients with NGGCT often have one or two associated tumor markers present in the serum or cerebrospinal fluid, alpha fetoprotein (AFP), and beta human chorionic gonadotropin (beta-hCG). If so, up-front surgical resection and even biopsy are not indicated. The presence of a pineal and/or suprasellar mass and elevated tumor markers is pathognomonic for NGGCT. Neoadjuvant chemotherapy has become the standard of care for NGGCT because of the high-risk nature of surgical manipulation in the pineal region. Germinomas can also have slightly elevated tumor markers, but the levels are modest compared to the more malignant germ cell tumors. Because the treatment for germinoma differs from that of NGGCT, it is generally recommended that tumor biopsies be obtained when there is not a significant elevation in at least one of the tumor markers.

Due to the location of these tumors, complete surgical resection is often not possible without causing significant morbidity. Surgery is no longer the up-front treatment approach for this group of tumors. Germinomas are extremely radiation sensitive and surgery can often be avoided using chemotherapy and radiation alone. NGGCT are also treated initially with chemotherapy, and definitive therapy is radiation. Surgical resection is often used in germ cell tumors when there is residual tumor following initial chemotherapy. The histology of the residual tumor is often a benign or mature form of germ cell tumor. These tumors are also known to have a propensity for CSF seeding, but there is great debate about the extent of radiation needed to optimize therapy in patients who do not have documented dissemination at the time of diagnosis. Focal radiation at the site of the initial tumor is standard, but debate resides in whether ventricular volume radiation or craniospinal radiation is most appropriate in these patients. Chemotherapy regimens are platinum based, and in combination with other chemotherapy agents and radiation therapy are capable of producing response rates of 48–90% depending on the tumor type. It is important to note that mature teratomas have a unique treatment approach among germ cell tumors. They are not thought to be sensitive to radiation or chemotherapy, and are therefore treated with maximal surgical resection alone.

Supratentorial High-Grade Gliomas

Supratentorial high-grade gliomas account for 7–11% of all pediatric CNS tumors. Sixty-six percent occur within the cerebral hemispheres, 20% are in deep midline structures of the cerebrum midline, and 15% are located in the posterior fossa or brainstem. The median age at diagnosis is 9 years and the male-to-female ratio is 1:1. The most common malignant glial neoplasms are high-grade astrocytomas such as anaplastic astrocytoma (grade III) and glioblastoma multiforme (grade IV), but this broad category can also include anaplastic oligodendroglioma, anaplastic ganglioglioma, high-grade pleomorphic xanthoastrocytoma (PXA), and high-grade mixed glial tumors such as anaplastic oligoastrocytoma. These lesions

tend to be clinically aggressive, locally and regionally invasive, and can rarely disseminate to the lung, lymph nodes, bone, and liver.

The most important prognostic factor in these patients is the extent of surgical resection. As a group, those who have had a near-complete or complete resection experience significantly longer progression-free survival than those with incomplete resections. Disease site has also been shown to be prognostic of outcome. Patients with tumor in deep midline structures have poorer survival rates compared to those with hemispheric lesions, presumably due to the inability to safely resect tumors in the deep midline structures.

Radiation therapy is considered a standard component of therapy for these patients. It is rarely curative, but when used in combination with chemotherapy has been shown to provide a small improvement in survival. Many different combination regimens have been studied in both the adult and pediatric populations with little to no improvement in prolonging time to progression. Regimens using myeloablative chemotherapy with peripheral stem cell rescue have a high up-front morbidity/mortality and have not shown improvement in outcomes for these patients. Multiple phase I and II trials are underway in the adult and pediatric populations in an effort to identify effective therapeutic agents.

Choroid Plexus Tumors

Tumors of the choroid plexus account for approximately 1–4% of brain tumors in children. These are tumors of young children and the median age at diagnosis is 10–32 months, with males and females being equally affected. Eighty-five percent arise in the lateral ventricles, 10–15% in the fourth ventricle, and 5–10% in the third ventricle. These tumors are classified as either choroid plexus papilloma (CPP) or choroid plexus carcinoma (CPC). CPP are more common, accounting for 80–90% of choroid plexus tumors, are typically very slow growing, and are treated with surgical resection only. CPC accounts for 10–20% of choroid plexus tumors and behave more aggressively because they are less differentiated and more anaplastic. Leptomeningeal spread can be seen in CPC and in atypical CPP, a form of papilloma with some anaplastic features.

The degree of surgical resection and tumor histology are the important prognostic factors in these tumors. With complete resection of a CPP, long-term survival is almost 100%. In CPC, outcomes tend to be less favorable due to local invasion and propensity of this tumor to disseminate throughout the CNS. However, studies of CPC treatment have shown that complete resection does appear to affect long-term survival and this should therefore be the surgical goal. Ventriculoperitoneal shunting may be required following tumor resection because of persistent hydrocephalus, which can occur in up to 60% of patients postoperatively. Radiation therapy is frequently used postoperatively in patients with CPC if there is evidence of residual disease and/or leptomeningeal dissemination, but its use must be carefully considered in this young patient population and can often be delayed by using chemotherapy. It has been difficult to clearly define the role of chemotherapy in CPC because it is so rare and therefore difficult to establish clinical trials with enough power to answer questions about efficacy. Treatment protocols for malignant brain tumors in children under the age of 3 years are often used.

Optic Pathway Gliomas

Optic pathway tumors arise in the optic nerves, optic chiasm, or optic tracts. They account for 5% of pediatric CNS tumors. Seventy-five percent occur in the first decade of life and males and females are equally affected. The incidence of optic pathway tumors is increased in patients with Neurofibromatosis Type I (NF-1) with up to 28% of patients with NF-1 being affected in some reports. Involvement of the optic chiasm appears to be more common in patients without NF-1 and unilateral or bilateral optic nerve involvement is more commonly seen in patients with NF-1. Histologically these tumors are typically low-grade pilocytic or fibrillary astrocytomas and malignant degeneration is very rare. Tumor growth tends to be slow, though there can be local spread of disease into surrounding brain parenchyma, and vision decline can sometimes occur in the absence of radiographic increase in tumor size. Serial ophthalmologic evaluation is at least as important, if not more important, than the routine imaging that is done after diagnosis of an optic pathway tumor.

Three prognostic variables have been shown to have an impact on outcome in optic pathway tumors. Tumors involving the chiasm and hypothalamus tend to have a worse prognosis, as do those that occur in children younger than 3–5 years of age. Optic gliomas in the setting of NF-1 tend to have a more indolent course and can even regress without any treatment. For this reason, optic gliomas in NF-1 patients are monitored with serial MRIs and ophthalmologic exams including visual fields. When a decline in vision is documented, chemotherapy should

be initiated to prevent any further impact on vision. Regimens including alkylating agents should be avoided in NF-1 patients because of the increased risk of second malignancies.

Biopsy of these tumors can cause vision impairment, so biopsy of these lesions must be considered very carefully. Because these tumors are so common in patients with NF-1, this diagnosis can be made based on radiographic appearance of an optic pathway tumor alone. For patients who do not have NF-1, biopsy is often recommended in order to define the histological type and further direct therapy. In cases in which a unilateral tumor has already caused severe vision changes, then surgical resection could be considered. Radiation therapy has been shown to be effective in stabilizing or improving existing disease, and it has been shown to improve vision in some patients and can also prevent further vision loss. Toxicity from radiation therapy should be taken into consideration as up to 50% of prepubertal patients will experience endocrine toxicity due to radiation of the adjacent hypothalamic-pituitary axis. In preadolescent children, delaying radiation therapy by using chemotherapy may help avoid or decrease the endocrinologic sequelae that can occur after radiation to this region. Chemotherapy is also used for patients with NF-1 who require treatment for an optic pathway tumor, in order to avoid radiation altogether in this patient population, if at all possible. The risk of second malignancy associated with radiation, such as glioblastoma multiforme or sarcomas, is likely higher in patients with NF-1. All patients with optic pathway tumors should undergo serial ophthalmologic exams regardless of the treatment or observation approach.

Craniopharyngioma

Craniopharyngiomas account for 6–9% of all childhood primary CNS tumors. There is a bimodal age distribution with a peak at age 8–10 years and again in older adults (50–74 years). This tumor is rarely seen in children less than age 2. There is an equal predominance among males and females. These tumors are generally suprasellar in location. Histologically, they are benign, but they often become functionally malignant due to the location and impairment of the hypothalamic-pituitary axis.

The extent of tumor resection is an important prognostic factor in craniopharyngioma. Those with complete resection have significantly better survival rates compared to those with incomplete resection. Tumor size has also been shown to be of prognostic significance; however, this may be secondary to degree of resectability. Patients with pure cystic lesions appear to have better survival than those with solid or mixed solid and cystic tumors, and children less than 5 years of age seem to have a worse prognosis compared to older children.

Surgical resection is the mainstay of treatment for craniopharyngioma. Approximately 90% of children with craniopharyngioma will have neuroendocrine deficits at the time of presentation, and 50–90% will have visual field defects. Tumor resection may exacerbate neuroendocrine deficits and their management needs to be optimized prior to surgery. Preoperative stress dosing of steroids followed by a postoperative taper are important in the management of these patients. Due to the location of these tumors, significant morbidity can be encountered if a radical complete resection is attempted. Debate continues in the neurosurgical literature regarding radical resection of these tumors versus less radical surgery and postoperative radiation therapy. Approximately 50–75% of patients will have recurrence of their disease after a partial resection; however, cure rates improve to 60–85% if radiation therapy is given postoperatively. Chemotherapy has no established role in the treatment of craniopharyngioma.

Late Effects of Childhood CNS Tumors

The 5 year overall survival of a child with a brain tumor has improved to 60% over the past several decades. However, despite successful treatment for a brain tumor, many children will experience significant long-term side effects either directly because of their tumor or as sequelae from treatment. These patients may experience physical, cognitive, neurologic, and endocrinologic side effects that may diminish their overall quality of life.

Radiation therapy alone is responsible for several adverse side effects including endocrine dysfunction, neuropsychological deficits, radiation necrosis, vasculopathy such as stroke or Moya Moya disease, and an increased risk of a secondary tumor. Radiation effects are inversely related to age at treatment; those who are treated at a younger age experience a higher degree of sequelae from their treatment. Full brain irradiation to children less than 3 years of age has been associated with severe intellectual deficits and significant impairment diminishing the likelihood that they will be independent, functioning adults. For this reason, full cranial radiation therapy should be avoided in children less than 3 years of age.

Growth failure is also a common side effect seen in patients who undergo radiation therapy. Radiation therapy impairs the secretion of growth hormone, decreases the growth of the spinal cord and vertebral column in

those undergoing spinal radiation, and can induce precocious puberty which prematurely fuses bony epiphyses. The concomitant use of chemotherapy further exacerbates the severity of growth failure experienced in these patients. Due to the concern of stimulating tumor recurrence, the use of growth hormone replacement remains controversial and is generally not recommended until many years after disease control or stabilization.

Secondary to the use of platinum agents in the treatment of many pediatric brain tumors, sensorineural hearing loss is a frequent complication among survivors. Radiation therapy can also exacerbate these deficits.

Management of survivors of childhood brain tumors should include a multidisciplinary team consisting of pediatric oncologists, endocrinologists, neurosurgeons, radiation oncologists, neuroradiologists, nurses, nurse practioners, neuropsychologists, psychologists, physical and occupational therapists, speech therapists, school teachers, and social workers. The child should be seen at least yearly for both physical and neuropsychological exams for at least the first 5 years after therapy is completed. Surveillance for recurrence of disease is also an important part of the long-term management of these patients. Recurrence or progression can occur several months to years after therapy has been completed.

A childhood diagnosis of a brain tumor or spinal cord tumor is a major challenge in the lives of patients and their families. Treatment of these types of cancers requires a highly specialized team to treat not only the acute disease process, but also to manage the long-term physical and emotional effects these tumors and their therapies have. Therapies for CNS tumors of childhood have improved over the past several decades, but there is still much work to be done. Further research is mandatory to better understand these tumors biologically, improve therapeutic approaches, and ultimately, improve survival and quality of life for these patients.

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350 Neuroblastoma and Other Sympathetic Nervous System Tumors

Stephen S. Roberts

Definition

Tumors of the sympathetic nervous system in children consist of neuroblastoma and its variants, ganglioneuroblastoma, and ganglioneuroma, as well as pheochromocytoma/paraganglioma. Pheochromocytomas and paragangliomas are very rare in children, with an incidence of less than 0.3 cases per million per year. They are called pheochromocytomas when arising from the adrenal gland and paragangliomas when extra-adrenal and can occur anywhere from the neck to the pelvis. The majority of these tumors are benign (∼90%) and present because of systemic symptoms such as hypertension due to catecholamine secretion. Because these tumors are quite rare and usually benign, we will confine the remainder of this discussion to neuroblastoma only.

Few tumors exhibit such diversity of behavior and outcome as neuroblastoma. This varies from spontaneous regression and differentiation, often without therapy, to aggressive, treatment-resistant disease that is frequently fatal despite intensive multimodality therapy.

Etiology

The etiology of neuroblastoma is unknown. Although several studies have investigated potential links between environmental factors, maternal drug exposures, and parental occupations and increased risk of neuroblastoma, to date, no consistent and definitive associations have been identified. Neuroblastoma has been positively associated with various congenital anomalies, especially urogenital and cardiac abnormalities, and in patients with congenital central hypoventilation syndrome (CCHS) and Hirschsprung's disease. Presumably this represents disordered development in shared neurodevelopmental pathways but the exact cause and relationship remains unknown.

Epidemiology

Neuroblastoma is the most common extracranial solid tumor of childhood and the most common cancer of infancy, accounting for 8–10% of all childhood cancers. In industrialized countries, the prevalence is roughly 1 case per 7,000 births, with an incidence of approximately 8–10 per million per year. This incidence appears to be similar throughout the developed world. Rates in developing countries are less clear; several reports have suggested that rates are lower, particularly in sub-Saharan Africa. However, it is unknown if this represents true lower incidence or underreporting. There is a very slight increase in incidence among boys versus girls (1.1:1).

Because neuroblastomas generally produce and secrete catecholamines whose metabolites (vanillylmandelic acid, VMA and homovanillic acid, HVA) are detectable in the urine, there have been several attempts at mass screenings of infants. These screenings were conducted in Japan, Germany, and Montreal, Canada in the 1980s and 1990s with the hope of detecting neuroblastoma at an earlier stage. Unfortunately, while these screening efforts did lead to an increased detection of low-stage neuroblastoma in infants, they did not lower the prevalence or the mortality rates of those children over 1 year of age with higher stage disease. Therefore, at this time, routine screening of infants for neuroblastoma is not recommended. It is possible that in the future, screening may be recommended for children with identifiable predisposition syndromes.

Pathogenesis

Neuroblastoma serves as a model disease where detailed genetic analyses have enabled biology-based risk stratification and treatment. There are multiple genetic changes that have been identified in NB, several of which are strongly correlated with disease outcome and are an integral part of our understanding of the development and treatment of this disease. Recently, several different groups

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reported germline mutations in the anaplastic lymphoma kinase (ALK) and PHOX2B genes in a small subset of neuroblastoma patients with familial predisposition. Mutations in these genes strongly predispose to development of neuroblastoma. However, the vast majority of children with NB do not have heritable risk factors predisposing them to the development of the disease. Instead, acquired somatic changes in neural crest stem cells appear to be the underlying cause leading to NB development.

Most neuroblastomas contain genomic level aberrations, including amplifications, translocations, and whole chromosome losses and gains. Many of these changes are nonrandom and have prognostic significance. Detailed analysis of these recurrent changes has led Maris et al. to propose a model for neuroblastoma development and progression. This model proposes that all neuroblastomas arise from a common precursor but that different types of genomic changes lead to two distinct subtypes of NB with very different clinical behaviors. Further, their model suggests that neuroblastomas that are biologically unfavorable do not evolve from favorable tumors but are distinct subtypes from the beginning. The first type of NB is characterized by loss and gain of whole chromosomes and few or no segmental chromosome abnormalities. These NBs are generally hyperdiploid, lack genetic changes associated with biologically unfavorable disease, and are most common in young children under 18 months of age. The prognosis for these tumors is generally excellent, with many undergoing spontaneous differentiation and/or apoptosis. In contrast, the second type of NB is characterized by recurrent segmental chromosome abnormalities. Nonrandom alterations of numerous chromosomes have been identified, including deletions of 1p36 and 11q and unbalanced gain of chromosome 17q. However, the most important genomic alteration is amplification of the MYCN oncogene, which tends to portend a particularly grim prognosis. MYCN amplification is associated with advanced disease, older age (>18 months), and poor outcome. The overall prevalence of MYCN amplification is approximately 20% and is essentially always present at the time of diagnosis, strongly suggesting it is an inherent feature of a subset of aggressive neuroblastomas and not an acquired late event. Thus, determination of MYCN amplification status is a standard part of neuroblastoma characterization at diagnosis due to its clear biological importance.

Pathology

Neuroblastoma is classically defined as a small, round, blue-cell tumor of childhood. Other malignancies in this group include non-Hodgkin lymphomas, Ewing sarcoma family tumors, and soft tissue sarcomas such as rhabdomyosarcoma. There are three histopathological subtypes: neuroblastoma, ganglioneuroblastoma, and ganglioneuroma. These three types represent a spectrum of differentiation from malignant to benign. Typically, the cells are small and uniform in size, with dark nuclei and little cytoplasm. Nearly all neuroblastoma form neuropil, collections of primitive neurites, and the Homer-Wright pseudorosette, a classic finding, is a ring of neuroblasts surrounding a core of eosinophilic neuropil. These pseudorosettes, however, are found in a minority of tumors. Ganglioneuromas represent a fully mature, benign collection of ganglion cells, Schwann cells, and neuropil. Ganglioneuroblastomas represent the spectrum of differentiation between malignant neuroblastoma and mature, benign ganglioneuromas.

Histopathology has been used to prognostically classify neuroblastomas; the most common system was developed by Shimada et al., and utilizes patient age, Schwannian cell stroma, mitosis-karyorrhexis index, and differentiation state to classify tumors as favorable or unfavorable. This system was recently modified with the goal of making it more reproducible around the world and is now known as the International Neuroblastoma Pathology Classification (INPC) system.

Clinical Manifestations

The clinical manifestations depend on the primary site of the tumor as well as any metastases that may be present. Approximately 65% of primary tumors arise in the abdomen; most of the remainder are thoracic or cervical in origin. No primary tumor is found in about 1% of patients. Most children with NB are diagnosed by age 5 and nearly all occur before age 10. Neuroblastoma is often disseminated at diagnosis, with spread most commonly involving locoregional lymph nodes as well as bone, bone marrow, liver, and skin. Lung and central nervous system metastases are rare.

Abdominal neuroblastoma may present with abdominal pain or fullness but is often asymptomatic and discovered incidentally, frequently by a caregiver. Thoracic neuroblastoma is frequently discovered incidentally on chest radiographs obtained for other reasons. Rarely, large thoracic tumors can cause mechanical obstruction and lead to compression of the superior vena cava and/or trachea (superior vena cava and superior mediastinal syndromes, respectively). High-level thoracic lesions and cervical neuroblastomas can cause Horner Syndrome

(unilateral ptosis, myosis, and anhydrosis). Any paraspinal neuroblastoma may extend through the neural foramina of the vertebral bodies and cause nerve root or spinal cord compression. This may lead to symptoms such as weakness, paralysis, bowel and/or bladder dysfunction, and radicular pain. Bone marrow involvement may lead to anemia and bleeding, while widespread cortical bone metastases are frequently seen and cause pain, limp, and significant irritability in younger patients.

Neuroblastoma is classically associated with several distinct presentations. Tumor infiltration of the periorbital bones causing proptosis and periorbital ecchymoses is a frequent manifestation of disseminated disease (*Fig. 350.1*). Likewise, infants less than 1 year of age will frequently present with multiple bluish, painless, subcutaneous nodular lesions. These are generally associated with stage 4S disease, spontaneous regression, and an excellent prognosis.

Two distinct paraneoplastic syndromes have been associated with neuroblastoma. The first, opsoclonus-myoclonus syndrome, is found in 2–4% of patients with neuroblastoma and is characterized by rapid, jerking eye movements, myoclonus, and ataxia. Thought to be an immune-mediated cross reaction between antibodies against the tumor and elements of the normal nervous system, these children tend to have low-stage disease and an excellent prognosis. Unfortunately, as many as 80% will have long-term neurologic sequelae, including significant cognitive deficits. The other paraneoplastic syndrome is intractable secretory diarrhea, hypokalemia, and dehydration caused by tumor secretion of vasoactive intestinal peptide, known as VIP syndrome. These tumors are usually ganglioneuroblastomas or ganglioneuromas and removal of the primary tumor generally leads to resolution of the diarrhea and excellent long-term survival.

Systemic manifestations such as hypertension, tachycardia, and flushing are rarely seen with neuroblastoma, as opposed to pheochromocytomas, because they do not secrete epinephrine.

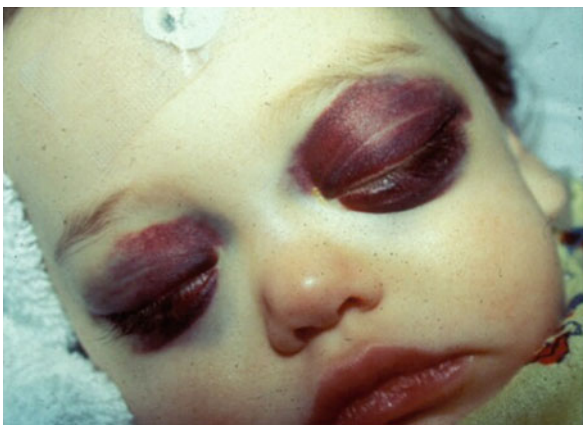

Figure 350.1
Periorbital ecchymoses in a child with high-risk neuroblastoma

Diagnosis

All patients suspected to have neuroblastoma require a comprehensive evaluation to ensure accurate staging and risk stratification. The diagnosis of neuroblastoma is made by either pathologic identification of neuroblasts from tumor biopsy or unequivocal presence of neuroblastoma in a bone marrow aspirate along with the presence of elevated serum or urine catecholamine levels. Whenever feasible, every effort should be made to perform a tumor biopsy, especially in young children under 18 months of age, as the biological information obtained is critical in proper determination of risk category and subsequent therapy planning.

A thorough physical exam should include evaluation of any masses, palpation for presence of hepatomegaly, neurological evaluation for weakness or paralysis, and examination of lymph nodes, skin, and skull for evidence of metastases. The imaging modality of choice for delineation of the primary tumor is CT scan. In general, most patients should receive a CT of the chest, abdomen, and pelvis, with evaluation of the head, neck, and spine if clinically indicated. All patients should have bilateral bone marrow aspirates and biopsies to evaluate for the presence of marrow disease. Likewise, evaluation of the bony skeleton should be performed. This has classically been done with plain radiography and Technetium-99 scintigraphy. More recently, radiolabeled metaiodobenzylguanidine (MIBG) scans, using either ^{123}I- or ^{131}I-MIBG, have become increasingly important in evaluating NB. ^{123}I-MIBG is more sensitive and specific than a Tc-99 bone scan or ^{131}I-MIBG. Whenever possible, both Tc-99 and ^{123}I-MIBG scanning should be performed at diagnosis as approximately 10% of tumors are not MIBG avid. Positron emission tomography is generally less sensitive than MIBG scanning and does not currently play a role in routine diagnostic imaging of neuroblastoma.

Tissue samples obtained should be evaluated for the presence of specific cytogenetic abnormalities, DNA ploidy, and the presence of MYCN amplification. Standard cytogenetic testing or specific fluorescent in situ hybridization techniques are routinely used. This information is

critical for subsequent risk stratification, with all major cooperative groups worldwide incorporating this information in their schema.

Differential Diagnosis

The differential diagnosis includes ganglioneuroma, which occurs in the same sites as its malignant counterpart. Intrathoracic neurofibromatosis tumors can mimic neuroblastomas radiologically, but they tend to be more nodular in outline, and grow along the course of the intercostal nerves, which results in characteristic indentations along the inferior costal margin. Tumors arising in the retroperitoneum may be confused with Wilms' tumor; the latter, however, tend to feel smooth to palpation in contrast to the nodular feel of a neuroblastoma and generally lack the characteristic intratumoral calcifications seen in imaging studies of neuroblastomas. Cervical neuroblastomas may be confused with cervical adenitis or lymphomas. Lack of tenderness upon palpation of the mass is a key finding allowing differentiation between NB and infectious etiologies. Additionally, neuroblastomas may present with weakness or paralysis of the lower extremities due to tumor extension through the neural foramina causing spinal cord compression. A thorough history, physical exam, and imaging studies are needed to differentiate NB from other primary neurologic causes of weakness and paralysis. Since NB frequently metastasizes to bone marrow, its presenting symptoms can mimic leukemia with pallor, fatigue, recurrent fevers, and bruising and petechiae being common; bone marrow aspiration will distinguish between these entities.

Pathologically, neuroblastoma must be distinguished from the other small round blue-cell tumors of childhood mentioned above. This can be done by identification of neuropil and pseudorosettes and more specifically by immunohistochemical staining for neural markers such as neurofilament proteins, synaptophysin, and neuron-specific enolase (NSE).

Treatment

Treatment is determined by risk group stratification. Currently, all of the major cooperative groups use similar risk group classification schemes that include disease stage, patient age (less than 12–18 months versus greater than 12–18 months) at diagnosis, and MYCN amplification status. DNA ploidy, additional cytogenetic analyses, and histopathology are incorporated with some variability. Stage of disease is a key component of risk group assignment.

Table 350.1
International neuroblastoma staging system

Stage 1	Localized tumor confined to the area of origin; complete gross excision, with or without microscopic residual disease; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage 2A	Unilateral tumor with incomplete gross excision; identifiable ipsilateral and contralateral lymph nodes negative microscopically
Stage 2B	Unilateral tumor with complete or incomplete gross excision; positive ipsilateral regional lymph nodes; identifiable contralateral lymph nodes negative microscopically
Stage 3	Tumor infiltrating across the midline with or without regional lymph node involvement, or midline tumor with bilateral regional lymph node involvement
Stage 4	Dissemination of tumor to distant lymph nodes, bone, bone marrow, liver, and/or other organs (except as defined in stage 4S)
Stage 4S	Localized primary tumor as defined for stage 1 or 2 with dissemination limited to liver, skin, and/or less than 10% of bone marrow; limited to infants less than 1 year of age

Currently, the international neuroblastoma staging system (INSS) is used around the world as the primary staging system (*Table 350.1*). Recently, an international consensus group developed a newer staging and risk stratification system called the international neuroblastoma risk group (INRG) staging and classification systems. These will likely be the future international standards.

All of the risk stratification systems used allow assignment into one of generally three risk groups: low, intermediate, and high risk.

Low-risk patients include those with low-stage (INSS stage 1 or 2) disease, and are generally of a younger age (<18 months) and do not have MYCN amplification. Treatment for this group involves surgical resection only. Importantly, complete resection is not necessary in these low-risk patients and therefore aggressive and potentially morbid surgeries should be avoided. Chemotherapy and radiation therapy are rarely needed and should be reserved for the patient that experiences disease recurrence. Some patients with low-risk disease (INSS stage 4S and incidentally found perinatal tumors) are successfully managed through observation only with no active intervention.

Treatment of intermediate risk patients is somewhat more complex and includes local control surgery followed

by moderately intensive chemotherapy, with the precise regimen varying by cooperative group. Radiation therapy is reserved for those intermediate risk patients with residual disease that has not responded to chemotherapy.

High-risk neuroblastoma is treated with aggressive, multimodality therapy including surgery, radiotherapy, chemotherapy, and biological/immunotherapy. The current standard therapy for high-risk patients in North America, Europe, and Japan includes intensive induction chemotherapy followed by surgery, radiation therapy, and autologous stem cell supported myeloablative therapy. This is then followed by a period of biological/immunotherapy targeting remaining minimal residual disease that uses 13-*cis* retinoic acid as a differentiating agent. Additionally, the Children's Oncology Group recently reported that the addition of immunotherapy directed at the neuroblastoma tumor antigen GD2 significantly improved survival in these patients, and future therapies will likely include some form of immune-based treatment.

Prognosis

Prognosis varies greatly by risk group. Currently, with observation and/or surgical resection alone, patients with low-risk disease have survival rates in excess of 95% in the developed world. Intermediate risk patients also do very well with moderate chemotherapy and have survival rates of over 90%. Prognosis for high-risk disease, however, remains poor. Historically, 5-year event-free survival rates have been less than 20%. Using the current intensive, multimodality therapy regimens, survival rates have increased to 40–50%. While this is an improvement over historical rates, there is room for substantial improvement. Additionally, significant long-term side effects of intensive therapy remain a large issue for those high-risk patients that are cured of their disease.

Prevention

Currently, there is no known preventive strategy for neuroblastoma.

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351 Wilms' Tumor and Other Primary Renal Neoplasms

Susan J. Lindemulder

Definition/Classification

Wilms' tumor is the most common primary tumor of the kidney in children. There are several other tumor types including clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, congenital mesoblastic nephroma, and renal cell carcinoma that also arise from the kidney, but they are much less common. The development of modern treatment regimens using a combination of surgery, chemotherapy, and radiation therapy has greatly improved the cure rate for Wilms' tumor.

Epidemiology

Wilms' tumor is typically diagnosed in children younger than 15 years and approximately 500 new cases are diagnosed per year in the United States. The prevalence worldwide is approximately 1 in 10,000 children under the age of 15 years. Globally, the incidence is substantially lower in Asian populations. Although various studies have explored environmental risk factors, it is likely that genetics play a larger role than the environment.

Wilms' tumor most often occurs in previously healthy children; however, there is a higher incidence of Wilms' tumor in children with certain recognized syndromes which are associated with other congenital malformations. These syndromes can typically be grouped into either overgrowth syndromes or non-overgrowth syndromes. The overgrowth syndromes are characterized by malformations such as macroglossia, nephromegaly, and hemihypertrophy, and include: Beckwith–Wiedemann syndrome, isolated hemihypertrophy, Perlman syndrome, Sotos syndrome, and Simpson-Golabi-Behemel syndrome. The non-overgrowth syndromes are characterized by various other malformations and include: isolated aniridia, trisomy 18, WAGR syndrome, Blooms syndrome, Alagille syndrome, Denys–Drash syndrome, and Frasier syndrome. The phenotypic characteristics of these syndromes are summarized in ❯ *Table 351.1*.

Pathogenesis

Multiple genes have been identified as playing a role in the development of Wilms' tumor. The first gene identified and the most studied is WT1 which was discovered through the study of patients with WAGR syndrome. WT1 is located on chromosome 11p13 in a region which also contains the gene responsible for aniridia. The gene is a tumor suppressor gene which codes for a transcription factor responsible for regulating other transcription factors important in cell growth and differentiation. A second gene important to the development of Wilms' tumor was discovered through the study of BWS patients. The WT2 gene is located on chromosome 11p15, and Wilms' tumor develops when there is loss of heterozygosity. The loss of heterozygosity is thought to upregulate an oncogene, resulting in tumor formation.

There is a recognized familial predisposition for Wilms' tumor which is rare and only accounts for a small percentage of new cases. Two genes have been identified as playing a role in familial Wilms' tumor, FWT1 located on chromosome 17q and FWT2 located on chromosome 19q.

Other chromosomal abnormalities are seen with increased incidence in studies of Wilms' tumor samples. Loss of heterozygosity in chromosome 16q and 11p have been suggested to be associated with poor prognosis unrelated to stage of disease. The role of p53 in the development of Wilms' tumor is also under investigation, although Wilms' tumor is not commonly seen in the Li Fraumeni syndrome.

Pathology

Three cell types are commonly seen in the histology of Wilms' tumor: blastemal, stromal, and epithelial. These three cell types reflect stages of normal renal development. A single specimen does not need to include all three cell types to be diagnostic for Wilms' tumor. Histology is further classified as

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Table 351.1
Characteristics of syndromes associated with Wilms' tumor

Syndrome	Phenotypic characteristics
Overgrowth syndromes	
Beckwith–Wiedemann syndrome	Macrosomia, macroglossia, visceromegaly, embryonal tumors, omphalocele, neonatal hypoglycemia, ear creases/pits, adrenocortical cytomegaly, renal abnormalities
Isolated hemihyperplasia	Asymmetric growth without other abnormalities
Perlman syndrome	Polyhydramnios, neonatal macrosomia, visceromegaly, nephromegaly, distinctive facial appearance, renal dysplasia
Sotos syndrome	Typical facial appearance, tall stature, learning disability, behavioral problems, congenital cardiac anomalies, neonatal jaundice, renal anomalies, scoliosis, seizures
Simpson-Golabi-Behemel syndrome	Macrosomia, distinctive craniofacial features, mental retardation, skeletal anomalies, hand anomalies
Non-overgrowth syndromes	
Isolated aniridia	Panocular abnormalities
Trisomy 18	Prominent occiput, short eye fissures with droopy eyelids, micrognathia, external ear variations, rocker-bottom feet, redundant skin on back of neck, congenital heart defects, hand anomalies
WAGR syndrome	Wilms' tumor, aniridia, genitourinary anomalies, mental retardation
Blooms syndrome	Small body size, immunodeficiency, sun-sensitive facial erythema
Alagille syndrome	Bile duct paucity, congenital cardiomyopahty, facial dysmorphy, vertebral defects, ocular abnormalities, renal anomalies
Denys–Drash syndrome	Ambiguous genitalia, congenital nephropathy leading to renal failure
Frasier syndrome	Complete gonadal dysgenesis and nephritic syndrome

"favorable" or "unfavorable" based on the absence or presence of anaplastic nuclear changes. Anaplasia is characterized by multipolar mitotic figures and marked nuclear enlargement. Nephrogenic rests can also be found within areas of the kidney not affected by Wilms' tumor and increase the risk for developing tumor in the remaining kidney.

Clear cell sarcoma of the kidney is the second most common renal cancer in children and has a poorer prognosis than Wilms' tumor. It requires more aggressive treatment and has a wider range of metastatic spread (lungs, bone, brain, soft tissues). Clear cell sarcoma was named for the classic pale-stained tumor cells that are seen in cords and nests separated by vascular septa.

Rhabdoid tumor of the kidney is highly aggressive and occurs more commonly in children less than 2 years. Patients often present with widely metastatic disease, and the majority die within 1 year. Cells in rhabdoid tumors have nuclei with a large single nucleolus, giving the appearance of an "owl's eye."

Congenital mesoblastic nephroma occurs in infants with a median age of 2 months. There are three histological types: the classic type, the cellular type, and the mixed type. The cellular type is the most common and shares histologic features with infantile fibrosarcoma and also has the chromosomal translocation t(12;15) which is seen in infantile fibrosarcoma. Congenital mesoblastic nephromas tend to grow into the hilar areas and perirenal soft tissues, and they require radical surgical excision for cure.

Renal cell carcinoma is the most common primary cancer of the kidney in adults but it is rare in children. The histologic features are papillary, clear cell, and mixed. The papillary subtype is the most common in children. Renal cell carcinoma is difficult to treat, and survival is often limited to weeks or months after diagnosis.

Clinical Manifestations: Symptoms, Signs

The most common clinical presentation of renal masses in children is painless abdominal swelling or mass noted by the parents. At diagnosis, abdominal pain or hematuria are often also present. Hypertension is diagnosed in a significant percentage of patients during the initial work-up of a renal mass.

On physical exam, a large mass can be palpated, and it is noted to arise from the flank. It often will not move with respiration. Signs of venous obstruction can be noted if tumor thrombus has invaded the renal vein or inferior vena cava. Given the link between Wilms' tumor and various syndromes, physical examination should include assessment for the stigmata of these syndromes including: aniridia, facial dysmorphism, hemihypertrophy, macroglosia, genitourinary abnormalities, cryptorchidism, and pseudohermaphroditism.

Diagnosis

The diagnostic work-up for a renal mass includes laboratory evaluation, radiology studies, and pathologic analysis of tissue. A complete blood count, liver, and renal function testing should be done to evaluate organ function. A urinalysis should be done to evaluate for hematuria.

Imaging studies are very important in the diagnosis of a renal mass as, in some cases, treatment is initiated based on the characteristic imaging of these tumors. Commonly, an abdominal ultrasound is the first study completed and shows whether the mass is solid or cystic in character, the size of the mass, involvement of other organs and, if Doppler measurement is done, the presence of tumor thrombus in the inferior vena cava. These are all vital aspects in considering initial surgical management. Computed tomography (CT) scan with contract enhancement is often also done to further evaluate the extent of the mass and further define involvement in the other kidney. The typical appearance of a Wilms' tumor on CT is a well-defined mass pushing other structures out of the way but not invading them. The remaining normal kidney is often seen appearing like a "claw" on one aspect of the mass. This can often distinguish Wilms' tumor from neuroblastoma arising from the adrenal gland as neuroblastoma often has an ill-defined margin and almost always invades the surrounding structures. Abdominal MRI may be useful to characterize nephrogenic rests in the other kidney. Chest x-ray is done to evaluate for presence of pulmonary metastases, and CT of the chest can be done to evaluate for masses which may not be seen on chest x-ray.

Other radiologic studies may be indicated based on the diagnosis. Clear cell sarcoma and renal cell carcinoma can spread to the bones, and therefore a bone scan and skeletal survey should be done for patients with clear cell sarcoma and bone scan for those with renal cell carcinoma. Clear cell sarcoma, rhabdoid tumor, and renal cell carcinoma can also spread to the brain, and a MRI or CT with contrast should be done to assess for metastases.

Once all diagnostic studies have been completed to confirm the diagnosis, the patient is staged to determine the appropriate treatment. The staging characteristics for Wilms' tumor are documented in *Table 351.2*.

Differential Diagnosis

The differential diagnosis includes both benign and malignant etiologies. Primary renal cancers would include Wilms' tumor, congenital mesoblastic nephroma, clear cell sarcoma of the kidney, rhabdoid tumor of the kidney, and renal cell carcinoma. Neuroblastoma is a childhood cancer often arising from the adrenal gland which is also included in the differential diagnosis. Benign etiologies include polycystic kidney disease, renal abscess, and hydronephrosis.

Treatment

Surgery is required for all patients with Wilms' tumor and other renal tumors. The objective of surgery is to remove the entire tumor without rupturing the tumor capsule. This almost always requires a nephrectomy. In addition, the surgeon can visually examine the abdomen for other suspicious lesions in the lymph nodes and other structures and biopsy as needed. There are two approaches to the timing of surgery. North American practice is to attempt pretreatment resection whenever possible to facilitate careful examination of histologic characteristics before treatment related changes occur. The approach outside of North America has been resection after delivery of some chemotherapy to lessen the risk of intraoperative rupture and facilitate an easier surgical procedure. The results with combined modality therapy are very good with both surgical approaches.

Table 351.2
Staging for Wilms' tumor

Stage	Characteristics
I	• Tumor limited to the kidney and completely resected • Renal capsule intact (no previous biopsy) • No involvement of renal sinus vessels or evidence of tumor beyond the margin of resection
II	• Tumor extends beyond the kidney but is completely resected (margins negative) • One of the following: penetration of renal capsule, invasion of renal sinus vessels
III	• Gross or microscopic tumor remaining • Tumor spillage before or during surgery • Lymph nodes within the abdomen or pelvis involved by tumor • Extension of tumor thrombus within the vena cava • Previous biopsy
IV	• Hematogenous spread or lymph node metastases outside of the abdomen
V	• Bilateral tumor at diagnosis

The surgical approach to bilateral disease is different with a goal to salvage as much renal function as possible. Therefore, patients undergo an initial biopsy and staging of both kidneys with exploration for suspicious lymph nodes or other lesions. Then, preoperative chemotherapy is given to allow for response before surgery is undertaken to remove the tumors and maximize the amount of kidney remaining.

Radiation to the flank is indicated for Stage III tumors. The recommended dose is 10.5 Gy of radiation to the affected flank. Whole abdomen radiation is only indicated for patients who have ascites positive for tumor cells or tumor rupture. Whole lung irradiation at a dose of 12 Gy is recommended for patients presenting with lung metastases seen on diagnostic chest x-ray. Irradiation of other involved metastatic sites, including the brain, liver, bone, and lymph nodes, is also indicated for patients who have metastatic involvement. In patients with anaplasia, clear cell sarcoma or rhabdoid tumor, radiation is recommended for the flank and all involved sites of disease.

For favorable histology Wilms' tumor the treatment regimen involves combined chemotherapy treatment with Vincristine and Dactinomycin for Stage I and II disease with the addition of Doxorubicin for Stage III and IV disease. Cyclophosphamide or cyclophosphamide and etoposide have been studied for patients with stage IV disease, anaplasia, or clear cell sarcoma. The prognosis for rhabdoid tumor and renal cell carcinoma remain poor and no optimal chemotherapy regimen has been determined. The benefit of chemotherapy in the treatment of congenital mesoblastic nephroma is under investigation.

Prognosis

Overall, all stages of Wilms' tumor are highly curable. Specific prognostic considerations are based on tumor size, patient age, histology, lymph node mestastases, and local features. The most important prognostic feature is the presence of anaplasia. Although the outcomes of patients with Stage I disease do not vary significantly according to anaplasia, for all other stages, the presence of anaplasia confers a worsened prognosis. Patients younger than 2 years of age appear to have a much better prognosis than older children.

The prognosis for clear cell sarcoma of the kidney has improved with the addition of chemotherapy agents. Congential mesoblastic nephroma has an excellent prognosis often with surgery alone. The prognosis for rhabdoid tumor of the kidney and renal cell carcinoma remains very poor in children.

Prevention

Screening ultrasound is recommended every 3 months until the age of 8 years for children with recognized syndromes which carry a predisposition for Wilms' tumor.

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352 Hepatic Tumors

H. Stacy Nicholson · Suman Malempati

Introduction

Primary liver tumors are rare in children, and in the USA, occur at a rate of 1.8 per million before the age of 15 years. In infants and children less than 5 years of age, hepatoblastoma (HB) accounts for nearly all liver tumors, and hepatocellular carcinoma (HCC) becomes more common in older children; HCC is the primary hepatic tumor in adolescents. In areas where Hepatitis B is prevalent, the incidence of primary liver tumors in children is higher, and the relative proportion of tumors that are HCC is higher. Benign primary liver tumors also occur and include hemangiomas and hamartomas. The liver is also a common site for metastases of other childhood malignancies, including neuroblastoma. This chapter focuses on the malignant hepatic tumors.

Pathology

Diagnosis is made by histopathological examination of the resected tumor or biopsy. HB is further divided into pure fetal, embryonal, or mixed fetal-embryonal histology. Alpha-fetoprotein (AFP), the predominant protein in serum before birth, is produced by embryonic hepatocytes and remains present for the first few months of life; thus, one must take care in interpreting AFP levels in infants. Serum AFP is elevated in 40% of children with HCC and in nearly all patients with HB. AFP should be measured at diagnosis in all patients, and if elevated, should be followed during treatment and follow-up. Normal or low AFP levels at the diagnosis of HB is associated with worse prognosis.

Clinical Features

Hepatoblastoma most commonly occurs in infants and very young children. Patients typically present with an abdominal mass, most often noted by a parent or physician. However, children with advanced disease may also present with abdominal pain, malaise, and weight loss. Jaundice is rare, and when present, suggests a primary hepatobiliary tumor, such as rhabdomyosarcoma.

Diagnostic Studies and Staging

Ultrasound is often used as the initial imaging modality in a child with an abdominal mass; however, computerized tomography (CT) or magnetic resonance imaging (MRI) of the abdomen is needed to define the extent of the mass and its relationship to hepatic landmarks. The importance of this imaging cannot be overemphasized, as surgical planning will be dependent upon this information. Abdominal radiographs are rarely helpful. All patients should be evaluated for metastases with a chest X-ray (CXR) and CT of the lungs.

Treatment

Once the imaging studies indicate a primary hepatic tumor, a team approach to treatment planning, involving the pediatric surgeon and pediatric oncologist, ensures that a coordinated plan for surgery and chemotherapy is in place. Radiotherapy is of limited use and is typically limited to a few children with unresectable disease or following recurrence.

Surgery

For patients with HB and HCC, complete resection is necessary for cure. Patients who undergo primary complete resection of HB have an excellent prognosis with a 90% long-term survival rate. However, only one-third to one-half of liver tumors in children can be safely resected at initial diagnosis. For children with hepatoblastoma, chemotherapy can induce significant tumor shrinkage, which may allow a tumor becoming resectable in up to two-thirds of patients. Chemotherapy is less effective for HCC. In children without metastatic disease but whose primary tumor remains unresectable, liver transplantation can be curative. Finally, in some patients, surgical excision of pulmonary metastases has improved survival.

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Chemotherapy

Cisplatin-based chemotherapy has greatly improved the survival of children with HB, and the use of combination chemotherapy is recommended for most children with HB or HCC, including those who have had a complete resection. In addition, chemotherapy may make a previously unresectable tumor amenable to surgery. Chemotherapy is not necessary for children with resectable pure fetal histology HB, as complete surgical resection alone is curative. Agents with the most activity against HB include doxorubicin, cisplatin, 5-fluorouracil, and vincristine, which are commonly used in combination. While similar approaches are used in both HB and HCC, HCC is much less chemosensitive.

Prognosis

Prognosis is related to the extent of disease at diagnosis, the histologic subtype, and whether the tumor can be surgically excised. Multi-modality therapy has resulted in long-term survival rates in excess of 75%.

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353 Soft Tissue Sarcomas

Suman Malempati · H. Stacy Nicholson

Introduction

As a group, soft tissue sarcomas are the most common solid tumor in children outside the central nervous system (CNS). In general, these tumors arise from the primitive embryonic mesenchyme, and include neoplasms of muscle, connective tissue, supportive tissue, and vascular tissue. Tumors may arise anywhere in the body where these tissues occur, but are most commonly seen in the extremities, head and neck regions, and genitourinary tract. Rhabdomyosarcoma is the most common soft tissue sarcoma in children and is the primary focus of this chapter.

Rhabdomyosarcoma

The cause of rhabdomyosarcoma is unknown; however, improved understanding of its biology may lead to an improved understanding of its etiology and to new treatments. The annual incidence in the USA in children less than 20 years of age is 4.3 cases per million. Rhabdomyosarcoma occurs in all ages, from birth to adulthood, but there are two distinct age peaks. Two-third of cases of rhabdomyosarcoma are diagnosed in children less than 6 years of age, but a second peak occurs in adolescents between the ages of 14 and 18 years. Adolescents with rhabdomyosarcoma are more likely to have tumors of the extremities. Rhabdomyosarcoma is slightly more common in males, and compared to Caucasians, rates are lower in African-Americans and in Asian populations. Rhabdomyosarcoma occurs more frequently in certain familial cancer predisposition syndromes, including Li–Fraumeni, neurofibromatosis type 1, and Gardner syndrome.

Histologic Types and Histopathology

Rhabdomyosarcoma is one of the "small round blue cell" tumors of childhood, and requires a skilled pathologist to confirm the diagnosis. The primary histopathological subtypes are embryonal (including botryoid), alveolar, and pleomorphic histologies. Alveolar rhabdomyosarcoma is associated with a specific chromosomal translocation, t(2;13), resulting in Pax3-FOXO fusion transcription factor that drives pathogenesis. Alveolar rhabdomyosarcoma more commonly occurs in extremity sites in adolescents and young adults and is associated with a worse prognosis. Pleomorphic rhabdomyosarcoma typically occurs in adults and can be very difficult to treat.

Clinical Features

Although rhabdomyosarcoma is a tumor of primitive skeletal muscle cells, it can occur in sites in the body that do not normally contain skeletal muscle. Common sites of involvement are the head and neck region (orbit, nasopharynx, sinuses, and superficial face), the genitourinary tract (bladder, vagina, and testis), extremities, and the trunk including retroperitoneum. Adolescents with rhabdomyosarcoma are more likely to have tumors of the extremities.

Signs and symptoms depend upon the site of the primary tumor. Head and neck tumors may present with pain, proptosis, orbital swelling, nasal obstruction, sinusitis, epistaxis, dysphasia, or hoarseness. Acquired denasalized speech, asymptomatic serous otitis media, persistent earache or aural discharge or unexplained facial palsy should raise the suspicion about such tumors. Approximately 25% of head and neck rhabdomyosarcoma in children occur in the orbit, and 50% occur in parameningeal regions.

Hematuria or urinary retention may be the presenting symptoms of tumors arising in the bladder or prostate, which are common sites in young children. Vaginal rhabdomyosarcoma, often called botryoides, due to the characteristic grapelike cluster of tumor may present with bloody mucoid discharge in young girls before a mass is seen. Paratesticular tumors are usually painless and can be mistaken for hydroceles. Patients with rhabdomyosarcoma of the extremities typically present with a painless mass.

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Diagnostic Studies and Staging

Diagnosis is made by histopathological examination of a tumor or biopsy, and all patients need to be evaluated for metastases. Rhabdomyosarcoma may involve regional lymph nodes, and distant spread most often involves the lungs, bone, and bone marrow. Imaging of the primary site may involve X-rays, computerized tomography (CT), and/or magnetic resonance imaging (MRI). To evaluate for metastases, CT scanning of the chest, abdomen and pelvis, bone scan, and bone marrow biopsies are typically done. Imaging of regional lymph nodes is important and lymph node sampling may be necessary for complete staging. For parameningeal tumors, a lumbar puncture should be performed to evaluate CSF cytology. Correct staging is important in assigning treatment and in counseling the patients and families about prognosis.

Treatment

Treatment needs to be assigned based on site, histology, and extent of metastatic spread. The clinical grouping system developed by the Intergroup Rhabdomyosarcoma Study (*Table 353.1*) is used to assign treatment, which generally includes surgery and chemotherapy, with or without radiotherapy.

Table 353.1
Intergroup rhabdomyosarcoma study clinical grouping system

Group	
I	Localized disease, completely resected. Regional nodes not involved. No metastases. (a) Confined to the muscle or organ of origin. (b) Infiltration outside the muscle or organ of origin – continuous with primary tumor.
II	(a) Grossly resected tumor with microscopic residual disease. No lymph node involvement; no metastases. (b) Regional disease, completely resected. Lymph nodes can be positive or negative; no metastases. (c) Regional disease with completely resected involved lymph nodes, with microscopic residual disease; no metastases.
III	Incomplete resection or biopsy. Gross residual disease is present.
IV	Metastatic disease present at onset.

Surgery

When the primary tumor can be surgically removed with negative margins, that is the preferred initial approach. However, tumors at many sites, including most head and neck tumors, cannot be completely excised and are simply biopsied. The initial surgical approach is key in assigning patients to the appropriate clinical group (*Table 353.1*).

Radiotherapy

External beam radiation is used in combination with surgery and chemotherapy in most patients with rhabdomyosarcoma. However, if the initial surgery results in a complete resection with negative margins, radiation may not be needed. Conversely, if only a biopsy is performed at diagnosis, radiation is often part of the treatment plan, even if a second surgery results in a complete resection. Doses are typically between 3,600 to 5,000 cGy.

Chemotherapy

The use of combination chemotherapy with vincristine, actinomycin-D, and cyclophosphamide (VAC) has improved the survival rates for children with rhabdomyosarcoma and has been the standard since the 1970s. VAC chemotherapy is typically given every 3 weeks and the duration of therapy depends upon clinical group and histology. Patients with embryonal histology occurring in "favorable" sites may be treated with vincristine and actinomycin-D alone. There are other active chemotherapy drugs in rhabdomyosarcoma, but addition of these agents has generally not improved survival compared to VAC. As more is understood about the biology of rhabdomyosarcoma, targeted therapy will increasingly be studied and may be added to combination therapy with surgery, chemotherapy, and radiation.

Prognosis

Prognosis varies by histology, clinical group, and, increasingly, molecular characterization. Patients with Group I disease have a 5-year survival rate that exceeds 90%. At the other end of the spectrum, those with Group IV disease (distant metastases) have a 5-year survival rate of approximately 25%. Favorable sites include orbital and paratesticular tumors, and masses in the trunk and extremities typically have a worse prognosis.

Other Soft Tissue Sarcomas

Other soft tissue sarcomas that occur in children include synovial sarcoma, malignant peripheral nerve sheath tumor, undifferentiated sarcoma, fibrosarcoma, liposarcoma, leiomyosarcoma, and others. These tumors typically arise in the extremities and trunk, and, unlike rhabdomyosarcoma, are unusual in the head and neck. Non-rhabdomyosarcomatous soft tissue sarcoma (NRSTS) usually presents as a painless mass. NRSTS can occur as secondary malignancies within a field of prior radiation in patients previously treated for cancer. While the surgical approach is similar to that used for rhabdomyosarcoma, these tumors are typically less susceptible to chemotherapy in particular. These tumors also vary in degree of aggressiveness and propensity to spread. The rarity of these tumors has impaired the ability to conduct robust clinical trials, and surgeons and oncologists must collaborate closely in determining the best treatment approach for each patient.

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354 Primary Malignant Tumors of Bone

Suman Malempati

Introduction

As a group, malignant bone tumors account for 5% of all cancers in children (age 0–19 years) in the USA. The vast majority of bone cancers that occur in the pediatric population are osteosarcoma and Ewing sarcoma. Both of these are aggressive high-grade malignancies that are diagnosed most frequently in the second decade of life. Chondrosarcoma can occur in children, but is much less common. There are a variety of nonmalignant conditions from which bone malignancies must be distinguished.

Epidemiology

Osteosarcoma is the most common malignant tumor of bone with an annual incidence rate of approximately five cases per million children in the USA. The incidence of osteosarcoma is similar in many Western European countries, but tends to be lower in Asian and many African countries. The annual incidence of Ewing sarcoma is approximately 3/million children in the USA, and is almost exclusively diagnosed in Caucasians. Ewing sarcoma very rarely occurs in persons of African or Asian descent. There is a slight male predominance of both osteosarcoma and Ewing sarcoma. Chondrosarcoma is diagnosed much less frequently with an annual incidence rate of 0.3–0.4/million children.

The peak incidence of malignant bone tumors is during the second decade of life. Both osteosarcoma and Ewing sarcoma are most commonly diagnosed around the time of the adolescent growth spurt. The average age of onset for Ewing sarcoma is younger than for osteosarcoma. In contrast to osteosarcoma, which very rarely occurs before the age of 8, Ewing sarcoma may be diagnosed in younger children and infants. Both Ewing sarcoma and osteosarcoma also occur in young adults in the 3rd and 4th decades of life. Osteosarcoma diagnosed in older adults is typically associated with previous radiation exposure.

Pathogenesis

The cause of bone malignancies is unknown in most cases. However, a variety of genetic and environmental factors predispose patients to the development of osteosarcoma (*Table 354.1*). Hereditary retinoblastoma with germline mutations of loss of the Rb tumor suppressor gene, germline p53 mutations (Li-Fraumeni syndrome), and Rothmund–Thompson syndrome are all associated with a very high risk of osteosarcoma. In addition, children with Paget's disease of bone and osteogenesis imperfecta, and those who have been exposed to ionizing radiation have a higher incidence of osteosarcoma.

In contrast, Ewing sarcoma is not typically associated with radiation exposure or cancer predisposition syndromes. The pathogenesis of Ewing sarcoma is related to chimeric proteins that are the result of recurrent translocations involving the *ews* gene at 22q12 locus and members of the *ets* family of transcription factors. It is now known that the EWS-ETS fusion proteins play an essential role in the tumorigenesis of Ewing sarcoma.

Clinical Manifestations

The most common presenting symptom in patients diagnosed with bone tumors is pain with or without swelling at the involved site. Initially, the pain is often intermittent, but becomes more constant and more severe over time. There is often a history of trauma at the onset of symptoms, but there is no evidence that trauma is causative. The trauma likely draws the patient's and caregiver's attention to the affected site. Patients eventually diagnosed with bone tumors are often initially treated with rest, ice and anti-inflammatory medication for presumed injury. It is common for there to be delay of several months from onset of symptoms to diagnosis of a bone tumor. A malignant bone tumor should be suspected with any "pathologic fracture" that occurs in an unusual site or after seemingly minor trauma. Systemic symptoms such

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Table 354.1
Conditions associated with increased risk of osteosarcoma

• Hereditary retinoblastoma
• Li-Fraumeni syndrome
• Rothmund–Thompson syndrome
• Bloom syndrome
• Werner syndrome
• Paget disease
• Enchondromatosis
• Osteogenesis imperfecta

Table 354.2
Conditions that mimic malignant bone tumors

Infections
• Osteomyelitis
Benign lesions
• Osteoid osteoma
• Chondroblastoma
• Osteochondroma
• Aneurysmal bone cyst
• Langerhans cell histiocytosis (Eosinophilic granuloma)
Other malignancies
• Lymphoma
• Metastatic small round blue cell tumor

as fever and weight loss may be seen, particularly with Ewing sarcoma.

Osteosarcoma typically arises at the metaphyses of long bones, with almost one-half of primary tumors occurring around the knee joint (distal femur or proximal tibia). The proximal humerus is the next most common site. In contrast, Ewing sarcoma more commonly occurs in flat bones. When long bones are affected with Ewing sarcoma, the diaphyses are usually the involved sites rather than the metaphyses. The bones of the pelvis are the most frequently involved sites of Ewing sarcoma, accounting for approximately 25% of cases.

Diagnostic Evaluation

The initial evaluation of patients with suspected bone tumors should include a thorough history and physical examination. Signs and symptoms may be nonspecific. *Table 354.2* lists a variety of conditions that mimic

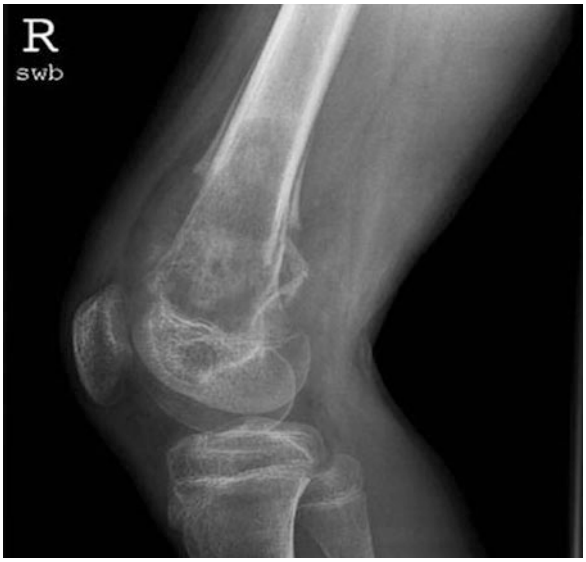

Figure 354.1
Lateral radiograph of the knee showing "Codman's triangle" resulting from elevation of periosteum from underlying bone

malignant bone tumors. A history of fever, weight loss, and/or night sweats should alert the physician to the possibility of cancer, although patients with bone tumors often have no symptoms other than pain. Suspected bone tumors must be distinguished from injuries. Injury-associated pain usually gets better with rest, whereas pain due to a malignant bone tumor does not remit and progressively worsens over time. Pain that is severe enough to wake a child or adolescent from sleep deserves further evaluation. Physical exam reveals tenderness at the involved site. There is also often a soft-tissue mass associated with primary tumors of bone.

The initial radiographic evaluation should be a plain radiograph of the involved bone. Plain x-ray will show a destructive lesion in the involved bone with disruption of the cortex. A classic radiographic finding in osteosarcoma and Ewing sarcoma, known as "Codman triangle," results from elevation and detachment of periosteum from bone along with subperiosteal new bone formation (*Fig. 354.1*). A "sunburst" periosteal reaction is often seen in osteosarcoma due to a rapidly growing mass (*Fig. 354.2*).

In order to better determine the extent of bone involvement of a suspected bone tumor, either magnetic resonance imaging (MRI) or computed tomography (CT) is necessary. In regard to surgical planning, MRI is more accurate and useful for evaluating intraosseus tumor

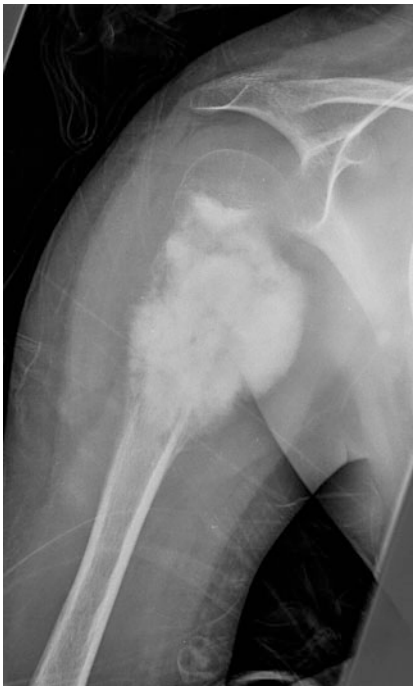

Figure 354.2
Radiograph showing the classic "Sunburst" pattern of periosteal reaction in a patient with osteosarcoma of the proximal humerus

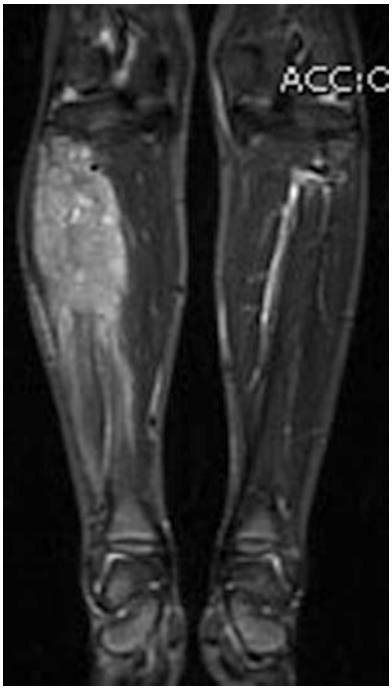

Figure 354.3
T1-weighted MRI image of Ewing sarcoma of the fibula with large soft-tissue component

extent, joint involvement, subcutaneous fat planes, and association with neurovascular structures (*Fig. 354.3*).

Evaluation for distant metastases is critical. Approximately 20–25% of patients with Ewing sarcoma and osteosarcoma have detectable metastases at diagnosis. The most common site of metastases is the lungs. While plain radiographs of the chest can often detect metastatic lesions, chest CT scan is considerably more sensitive (*Fig. 354.4*). Radionuclide bone scan (technetium-99m) is also standard in the USA for detection of bone metastases, which occur in approximately 10% of patients with newly diagnosed malignant bone tumors. In addition, approximately 10% of patients with Ewing sarcoma will have detectable metastases to bone marrow. Therefore, bone marrow biopsies from bilateral posterior iliac crests are critical.

While presenting signs and symptoms, location and pattern of the lesion, and characteristic findings on imaging may suggest the presence of a malignant bone tumor, definitive diagnosis requires biopsy and histologic assessment. The approach to the biopsy is critical as the biopsy tract will also need to be resected at the time of surgical resection. Biopsy without consideration of planning for the definitive local control surgery can hinder the ability to perform a future limb-salvage procedure in the patient.

Histologic evaluation of conventional osteosarcoma reveals a high-grade malignant lesion with large spindle-shaped cells, irregular nuclei, and mitotic figures intermixed with a stroma containing areas of osteoid. Conventional high-grade osteosarcoma is often further characterized as osteoblastic, chondroblastic, or fibroblastic based on the pattern of differentiation. This distinction, however, is clinically meaningless. Other variants that are similar to conventional osteosarcoma include telangiectatic, small cell, and periosteal osteosarcoma. An additional variant, parosteal osteosarcoma, is similar to periosteal in that it arises from the cortex of bone, but does not invade into the medullary cavity. Parosteal osteosarcoma tends to behave more indolently than conventional osteosarcoma and does not metastasize.

Ewing sarcoma is one of the "small round blue cell tumors" of childhood. It can be distinguished from rhabdomyosarcoma, neuroblastoma, and lymphoma based on the pattern of histochemical staining. The pattern of staining shows some evidence of neural differentiation with typical expression of CD99, S-100, and neuron-specific enolase.

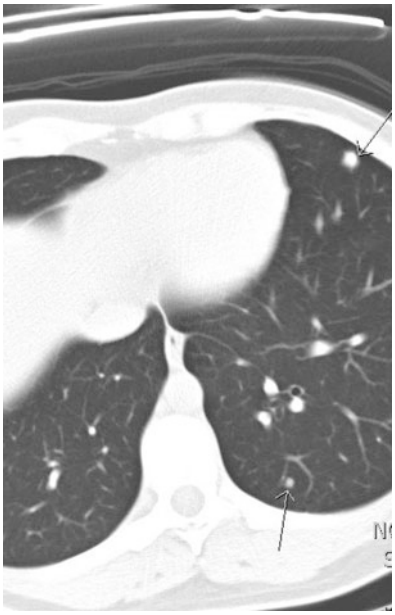

Figure 354.4
Chest CT scan demonstrating metastatic osteosarcoma

Fluorescent in situ hybridization or chromosome analysis of tumor cells is critical to assess for rearrangements of the *ews* gene on chromosome 22, which can be detected in more than 95% of cases of Ewing sarcoma. The most common rearrangement is the characteristic t(11;22)(q24;q12) reciprocal translocation, which results in the chimeric EWS-FLI1 transcription factor. Presence of this translocation is pathognomic for Ewing sarcoma.

Treatment and Prognosis

Treatment of malignant bone tumors involves both systemic and local therapy. Significant improvements have been made in both systemic therapies as well local control techniques over the past few decades. Currently, at least two-thirds of patients with Ewing sarcoma and osteosarcoma without detectable metastatic disease can be cured. A comparison of clinical features, treatment, and prognosis between Ewing sarcoma and osteosarcoma is shown in *Table 354.3*.

Osteosarcoma

Since the 1970s, chemotherapy has been a vital component to the treatment of patients with osteosarcoma. Prior to the use of chemotherapy, survival rate with surgical resection alone was less than 20%. Most patients died from metastatic disease to lungs. Neo-adjuvant chemotherapy is now standard. Chemotherapy given before surgical resection allows for early initiation of systemic control as well as the histologic assessment of tumor necrosis in response to chemotherapy. Degree of tumor necrosis after initial chemotherapy has been shown to be prognostic, as patients with 10% or greater viable tumor at the time of definitive surgery have a significantly higher risk of recurrence.

Chemotherapeutic agents that are most active against osteosarcoma are doxorubicin, cisplatin, methotrexate, and ifosfamide. Standard therapy in North America and Europe involve combinations of these agents before and after definitive surgery. While chemotherapy has improved prognosis, complete surgical resection of all tumor with clear margins remains essential for cure. Amputation has been a traditional approach and remains effective. However, improved surgical techniques and neo-adjuvant chemotherapy allow a higher proportion of patients to undergo limb-sparing procedures (*Fig. 354.5*). Radiation therapy is not considered a viable option for local control as osteosarcoma tumors are relatively radioresistant. However, for tumors that not resectable (such as primary tumors of the pelvis), radiation therapy can be effective as palliation.

Patients who present with metastatic disease have a poor prognosis. Less than 20% of patients with metastatic disease will be long-term survivors. Along with standard chemotherapy, local control to all metastatic sites, including pulmonary metastatecomy, is critical to offer any chance of long-term cure.

Patients diagnosed with parosteal osteosarcoma have a much more favorable prognosis with complete surgical resection alone. These tumors can recur locally without complete resection with wide margins, but metastatic spread is not typically seen. These patients can be treated without chemotherapy.

Ewing Sarcoma

Current treatment for Ewing sarcoma involves multimodal therapy. Neo-adjuvant chemotherapy is now standard. For patients with localized disease, the addition of Ifosfamide and Etoposide to Vincristine, Doxorubicin, and Cyclophosphamide has been shown to improve survival. Dose intensity is critical and a recent study has shown that delivering the agents on a compressed every 2 week schedule is more effective at preventing disease recurrence.

Table 354.3
Comparison of osteosarcoma and Ewing sarcoma

	Osteosarcoma	Ewing sarcoma
Annual incidence rate (age 0–19 in Western countries)	~5/million	~3/million
Race	All races	Caucasian (rare in persons of African or Asian descent)
Primary tumor site	Metaphyses of long bones	Flat bones
		Diaphyses of long bones
		Extraskeletal
Radiographic signs	"Sunburst"	"Onion-skinning"
	Sclerotic destruction	Lytic lesion
Treatment	Chemotherapy	Chemotherapy
	Surgery	Surgery
		Radiation
Prognosis (long-term survival)		
Localized	~65%	~75%
Metastatic	<20%	~20–30%

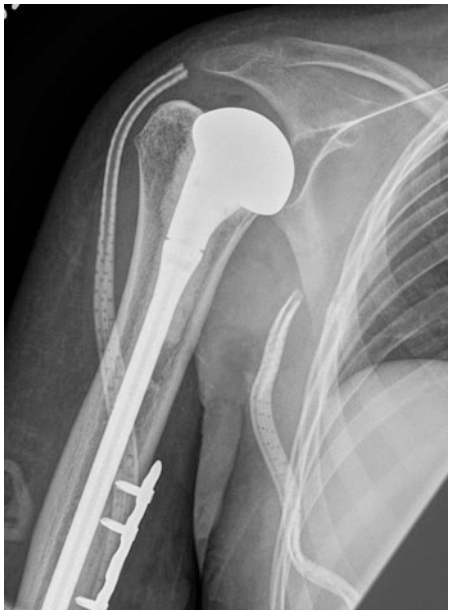

Figure 354.5
Radiograph demonstrating limb salvage surgery with reconstruction using a composite allograft/metal prosthesis

As with osteosarcoma, local control is also critical. In general, complete surgical resection with clear margins is considered the most effective means of local control. However, Ewing sarcoma is much more radiosensitive than osteosarcoma. Therefore, radiation therapy may be an effective means of local control if the alternative would be a mutilating operative surgery. Prognosis depends on site of primary tumor and presence of metastatic disease. Up to 75% of patients with localized extremity tumors can be cured. Patients with centrally located tumors (such as in the pelvis) and those with metastatic disease have poorer outcomes.

Chondrosarcoma

The only known curative therapy for chondrosarcoma is surgical resection. Chemotherapy has no proven benefit in regard to preventing recurrence if complete surgical resection is achieved. Prognosis is poor for patients in whom surgical resection cannot be achieved. Chemotherapy and radiation therapy may be used to slow tumor progression, but neither modality has been shown to affect long-term outcome.

Summary and Future Directions

As malignant tumors of bone are relatively uncommon in children, diagnosis can be difficult. Both Ewing sarcoma and osteosarcoma most commonly occur in adolescents during the second decade of life. While there is a higher incidence of osteosarcoma in some familial cancer predisposition syndromes and after radiation exposure, the

etiology of most cases of bone tumors is unknown. Bone malignancy should be suspected for persistent pain, swelling, and palpable mass as well as if a pathologic fracture occurs. The outlook for patients with malignant bone tumors has improved considerably with multimodal therapy. Future advances in treatment will likely include better risk stratification of patients based on tumor biology, improved local control techniques (both surgical and radiation therapy), and the incorporation of molecular targeted therapies into current treatment plans.

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355 Retinoblastoma

H. Stacy Nicholson

Retinoblastoma (RB) is a highly malignant tumor of the retina, occurring in infants and young children. Many cases are probably congenital, and RB occurs in 1 of 18,000 live births in the USA. RB can be either genetic or sporadic. Familial RB occurs at an earlier age and is often bilateral. It can be inherited from a parent, usually in an autosomal dominant fashion, or can develop from spontaneous mutations. An estimated 15% of unilateral RB is genetic, with the remainder being sporadic. The RB1 gene is located at 13q14.

Histology

Retinoblastoma is one of the embryonal neoplasms of childhood. Often the histological examination shows sheets of malignant cells, similar to other small round blue cell tumors. The degree of retinal differentiation varies.

Clinical Features

The most common presentation is of leukocoria, or of a "white reflex." Sometimes, the child may present with a "squint." Untreated, RB will cause complete loss of vision, globe destruction, and direct extension into the orbit, orbital bones, and central nervous system. Metastases can occur in lymph nodes, bone, and bone marrow (*Figs.355.1* and *355.2*).

Figure 355.1
Leukocoria in a 3-year-old girl with newly diagnosed unilateral retinoblastoma (Courtesy of Tim Stout, MD, PhD)

Diagnostic Studies and Staging

The diagnosis is initially established by an examination of the retina under anesthesia by an ophthalmologist. Biopsy is not done, in order to prevent seeding of the orbit. To assess the degree of tumor, orbital ultrasound or computerized tomography (CT) may be used. In patients with suspected optic nerve invasion or extensive choroidal invasion, a magnetic resonance image (MRI) of the orbits and brain should be obtained, as well as cerebrospinal fluid (CSF) for cytology. The MRI should show whether the pineal gland also is involved – this is known as "trilateral" retinoblastoma. Bone scan and bone marrow aspirates should be performed if distant metastases are suspected clinically.

Treatment

Treatment needs to be individualized and may involve surgery, cryotherapy and photocoagulation, radiation, and/or chemotherapy. Close collaboration between the pediatric ophthalmologist and pediatric oncologist in creating an individualized treatment plan is needed.

Surgery and Other Local Therapies

For advanced RB, enucleation is the treatment of choice. This includes tumors with invasion of the optic nerve, choroid or obits, as well as anterior chamber invasion. In small tumors that are away from the macula, cryotherapy, thermotherapy, and/or photocoagulation can be used as a means of saving the globe.

Radiotherapy

Retinoblastoma is radiosensitive and external beam radiation is used in children with advanced disease. Brachytherapy can also be delivered using "plaque radiotherapy."

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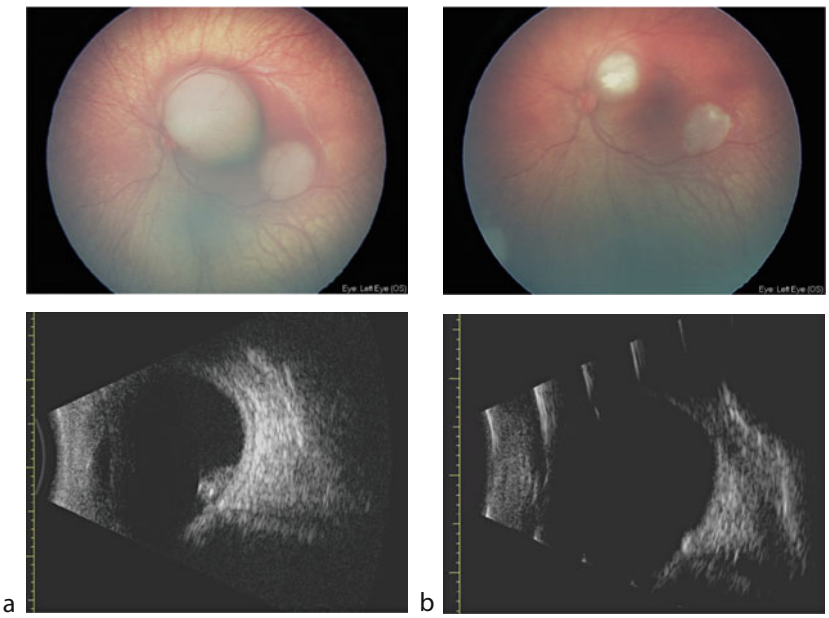

Figure 355.2
Unilateral retinoblastoma in a 6-month-old boy. The upper panels show the retina and the lower panel shows the ultrasound: (a) is at presentation and (b) shows the results following treatment with laser combined with chemotherapy (etoposide, vincristine, and carboplatin) (Courtesy of Tim Stout, MD, PhD)

Radiation carries a substantial risk of secondary cancers, especially in children with bilateral or other forms of genetic RB.

Chemotherapy

Chemotherapy is used in all patients with metastatic disease. Furthermore, chemotherapy is increasingly being used to shrink tumors so that they are amenable to local globe-sparing therapy. Agents that are active in RB include carboplatin, vincristine, etoposide, teniposide, cyclophosphamide, and doxorubicin.

Prognosis

In early stage unilateral disease, the prognosis is excellent, with more than 90% of children surviving. Most of these will have intact vision. Follow-up examinations of the retina under anesthesia to ensure that disease does not develop in the contralateral eye should be done until age 3. Patients with metastatic disease at diagnosis have a poor prognosis.

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356 Germ Cell Tumors

Suman Malempati · H. Stacy Nicholson

Introduction

Germ cell tumors in children develop from the primordial germ cells, and arise in either the gonads or in sites associated with the normal migration of germ cells during embryogenesis. When these tumors occur outside the gonads, presumably they arise from germ cells that did not migrate properly. Germ cell tumors in children are rare, occurring at a rate of 10.7 per million children less than 19 years of age. When combined, these tumors represent 2–4% of all childhood malignancies in the USA. Extragonadal germ cell tumors typically occur in the pelvis, retroperitoneum, mediastinum, and in the central nervous system (CNS). CNS germ cell tumors are covered in the CNS tumor Chap. 349, "Central Nervous System Tumors in Children".

Pathology

The category of germ cell tumors is comprised of a variety of histologic subtypes. However, regardless of site, there are common pathological features that all germ cell tumors share. As the name suggests, germ cell tumors arise from primordial germ cells that undergo embryonal or extraembryonic differentiation. Histologic subtypes include benign and mature teratomas, yolk sac tumor, choriocarcinoma, and germinomas (also known as dysgerminomas or seminomas) among others. All of the different subtypes can be components of a mixed malignant germ cell tumor. Benign teratomas commonly occur soon after birth, yolk sac tumors typically occur between the ages of 1 and 5 years, and dysgerminomas and malignant teratomas occur predominately in adolescents. Teratomas have well-differentiated tissues from all three germ layers – endoderm, ectoderm, and mesoderm – and can be either cystic or solid. Many germ cell tumors may produce tumor markers that can be used in establishing the diagnosis and in monitoring for therapeutic response and disease recurrence. Tumors with a trophoblastic element (such as choriocarcinoma) may produce beta-human chorionic gonadotrophin (β-hCG) and those with a yolk sac element may produce alpha-fetoprotein (AFP).

Treatment Issues Common to All Sites

Complete surgical resection is the goal for all tumors and is often curative in benign teratomas and low-stage malignant germ cell tumors. However, as germ cell tumors are typically chemosensitive, surgeons should avoid an operative approach that would be disfiguring or compromise fertility. For a given patient, treatment is guided by both site and histology.

Testicular Germ Cell Tumors

Although most testicular tumors in children (75%) are germ cell tumors, one must also consider the possibility of a paratesticular rhabdomyosarcoma or leukemic infiltration when evaluating a new patient with a testicular mass. Typically, a testicular germ cell tumor will present as a rapidly growing, nontender, scrotal mass. While most testicular germ cell tumors in children are localized, a metastatic workup should be performed, including computerized tomography (CT) of the chest, abdomen, and pelvis, and a bone scintigraphy. Following surgery, a scrotal ultrasound within a month should be performed, and AFP should be followed in those with elevated levels at diagnosis.

For those without metastatic disease, treatment requires orchiectomy with a high excision of the cord via an inguinal approach. Retroperitoneal node dissection is not indicated and chemotherapy is not necessary. Patients with metastatic disease respond well to chemotherapy consisting of cisplatin, bleomycin, and etoposide (PEB) or cisplatin, bleomycin, and vinblastine (PVB). The prognosis is generally excellent with up to 90% survival even in patients with metastatic disease.

Ovarian Germ Cell Tumors

Ovarian germ cell tumors typically occur in early adolescence, and most ovarian tumors in children are of germ cell origin. Patients present with either abdominal pain or a mass, and other causes, such as ovarian torsion, should be considered. Ultrasound of the abdomen is usually

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the initial study obtained. Additional studies should include measurement of serum levels of AFP and β-hCG and CT scan of the chest, abdomen, and pelvis, and bone scintigraphy. There are four main histological subtypes: mature (benign) teratoma, immature (malignant) teratoma, dysgerminoma, and yolk sac tumors. Treatment may include surgery, with or without chemotherapy, depending upon the tumor type and extent of disease. Standard chemotherapy is the same as for testicular germ cell tumors and the prognosis is excellent.

Sacrococcygeal Tumors

Although rare (one per 40,000 live births), sacrococcygeal teratomas are among the most common tumors in the newborn. Females are more often affected than males (4:1), and the presentation is typically a large mass between the coccyx and rectum. Complete excision, including the coccyx, is usually curative. Most of these are benign teratomas, but a small percentage may have malignant components. Close follow-up after surgery is necessary because of a small risk of recurrent tumor with malignant elements. Serial measurements of the serum AFP level are recommended as persistently elevated AFP for age may be a marker of previously unrecognized malignant elements.

Mediastinal Tumors

Thoracic germ cell tumors typically occur in the anterior mediastinum in adolescent males and occur at a higher frequency in those with Klinefelter syndrome (47, XXY). Histology can be mixed and often includes yolk sac tumor, germinoma, choriocarcinoma, and teratoma. Tumor markers including AFP and β-hCG are often elevated in serum. Treatment usually includes surgery and chemotherapy, and if a complete resection can be accomplished, this improves survival. Rarely, these tumors are sometimes associated with hematological malignancies or can contain foci of sarcomatous elements.

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357 Late Effects of Cancer Chemotherapy in Children

Susan J. Lindemulder

Introduction

Overall 5-year survival rates for childhood cancer in developed countries is approaching 80%, and while the overall survival rates for childhood cancer in developing countries is significantly lower, improvements are being made. These improved survival rates are the result of improvements in treatment, access and delivery of care, adherence to treatment regimens, and improvements in supportive care. As the survival rates continue to grow globally there is a growing population of children, adolescents, and young adults who are at risk for late effects related to their cancer therapy.

While children generally tolerate the acute effects of cancer therapy relatively well compared to adult patients, cancer therapy received at an early age can lead to complications that may not be seen for many years. The Childhood Cancer Survivor study follows a large cohort of long-term childhood cancer survivors treated in the United States and found that 65% of patients had at least one chronic health condition, and 28% had a severe or life threatening health condition. These results are being confirmed by large cohort studies of long-term survivors, being conducted in multiple other countries around the world.

The late effects of childhood cancer therapy involve almost every organ in the body including the heart, lungs, kidneys, gastrointestinal tract, musculoskeletal system, hearing, and vision. There are also effects on growth and development, neurocognitive function, potential for future fertility, and psychosocial impact.

Treatment Summary

Given the wide variety of medications and other modalities utilized in treating childhood cancer and the multiple treatment protocols being used, the potential for late effects can vary greatly between different survivors of childhood cancer. There are many approaches to delivery of survivorship care, but all approaches require an accurate outline of what treatment the patient has received. This is commonly referred to as a Cancer Treatment Summary. *Table 357.1* details the items that should be included. The treatment summary should be created by the primary oncologist after the treatment is complete and is reviewed with the patient. This can then be used by any provider in combination with published screening guidelines such as the Children's Oncology Group Long-Term Follow-Up Guidelines to guide follow-up care and screening.

Common Late Effects

Some of the most common late effects are detailed in the rest of this chapter and are summarized in *Table 357.2*.

Infection

Children and adolescents often require at least one transfusion of a blood product during the course of their cancer treatment. Exposure to blood products increases the risk of transmission of blood born infections including Hepatitis B, Hepatitis C, Human Immunodeficiency Virus (HIV), and others. Screening of the blood supply varies by country with regard to the types of infection screened and the methods by which screening is done.

According to the World Health Organization (WHO) 2007 Blood Safety Survey, 42 countries collected less than 25% of their supply from voluntary unpaid donors (considered the safest source) and 31 countries reported still using paid donations (the least safe source). WHO recommends that at minimum, all blood be screened for HIV, Hepatitis B, Hepatitis C, and syphilis but 41 one out of 162 countries are not able to screen all donated blood for one or more of these infections.

Given these statistics, practitioners should determine whether the patient received any blood product during treatment and where that transfusion was given. Based on transfusion information, information regarding other

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Table 357.1
Components of a cancer treatment summary

Component	Description
Patient information	• Patient name
	• Date of birth
	• Treating institution
Diagnosis information	• Initial diagnosis including stage and site
	• Date of initial diagnosis
	• Date of relapse including site
	• Second cancers including diagnosis, site, and date (if applicable)
Chemotherapy	• List all chemotherapy agents and route (IV, IM, IT)[a]
	• Cumulative doses for anthracyclines, alkylators, bleomycin and others if available
	• When methotrexate or cytarabine were given, include dose or designate high dose or low dose
Radiation	• List all radiation sites
	• For each site, date and dose
Surgeries	• Procedure and date
Stem cell transplant	• Type of transplant and date
	• Graft-versus-Host disease prophylaxis and treatment
Therapy completion	• Date last therapy was received

[a]*IV* Intravenous, *IM* intramuscular, *IT* intrathecal

high risk health behaviors, living in a hyperendemic area, and available blood product screening information, patients may need to be tested for one or more infectious complications. All screening can be done on a sample of peripheral blood. Recommended screening for Hepatitis B is a Hepatitis B Surface antigen and Hepatitis B core antibody, for Hepatitis C is a Hepatitis C Antibody, and for HIV is antibodies for HIV-1 and HIV-2.

Cardiopulmonary

Pulmonary fibrosis and interstitial pneumonitis with resultant restrictive or obstructive lung disease can occur after treatment with various chemotherapy agents or after receiving radiation to the chest. The most recognized chemotherapy agent causing pulmonary effects is bleomycin, but other agents including carmustine (BCNU), lomustine (CCNU), and busulfan are also recognized as having these effects. These agents produce effects in a dose-dependent fashion with higher doses and more intensive treatment regimens resulting in higher risk. Chemotherapy combined with radiation doses greater than 15 Gy are associated with the highest risk.

Some patients will have clinical symptoms of pulmonary disease including cough, shortness of breath, dyspnea on exertion or wheezing, but many are diagnosed through screening pulmonary function testing, which shows lung volumes consistent with either restrictive or obstructive disease or decreased DLCO. Patients at risk should be interviewed yearly for symptoms such as chronic cough and shortness of breath. They should be evaluated by a physical exam and, where available, patients should have baseline pulmonary function testing with follow-up testing for abnormal results or new clinical symptoms.

Cardiac late effects are emerging as a growing concern as the survivor population ages. All cause cardiovascular events and are behind only cancer recurrence and development of second malignancies as a leading cause of mortality in this population. The mechanism and pathology vary with treatment exposure. Anthracycline chemotherapeutic agents cause cardiomyopathy with potential for congestive heart failure and radiation produces effects such as valvular disease, pericardial disease, and coronary artery disease.

Anthracycline chemotherapy agents include doxorubicin, daunorubicin, idarubicin, mitoxantrone, and epirubicin. They are thought to cause damage and death of cardiac myocytes during treatment. This leads to hypertrophic changes in the remaining myocytes, ultimately leading to inadequate left ventricular mass and decreased function. While some patients experience an acute decrease in function during treatment, this effect is often not seen for years, on average at least 15–20 years, and onset can be insidious or clinically dramatic. The risk of cardiomyopathy increases with increasing cumulative anthracycline dose, defined in doxorubicin dose equivalents.

Radiation to the heart can increase the risk of cardiomyopathy when part of a treatment regimen that includes anthracycline chemotherapy, but radiation alone causes pericardial disease, valvular disease and coronary artery disease. It is important to remember that many radiation fields include the heart. In addition to the obvious fields of chest, whole lung, mediastinal, mantle and total body, fields such as flank, spleen, whole abdomen, and paraaortic also include the heart. The risk increases with increasing dose and is highest for those who have received greater than 30 Gy (with anthracycline) or 40 Gy (without anthracycline). Other medical conditions that often result

Table 357.2

Common long-term effects, risk factors, and screening recommendations[a]

Late effect	Therapy exposure	Screening recommendations
Cataracts	Corticosteroids, busulfan, radiation (orbit)	– Yearly fundoscopic and visual acuity exam – Full ophthalmologic exam for those exposed to radiation
	Modifiers: combined treatment, higher radiation dose	
Dental problems	Chemotherapy, radiation	– Dental exam and cleaning every 6 months
	Modifiers: younger age (<5 years)	
Hearing loss	Cisplatin (highest risk with cumulative dose $\geq$360 mg/m^2), radiation (cranial)	– Baseline audiology exam – Routine follow-up audiology exam if hearing loss is detected
	Modifiers: combined treatment, other ototoxic drugs (aminoglycosides, loop diuretics), younger age (<4 years)	
Pulmonary fibrosis	Bleomycin (highest risk with cumulative dose $\geq$400 U/m^2), carmustine, radiation (chest)	– Yearly exam and history – Baseline pulmonary function testing (spirometry and DLCO) – Repeat pulmonary function testing as indicated
	Modifiers: combined treatment, younger age	
Cardiomyopathy/ congestive heart failure	Anthracyclines (highest risk with cumulative dose $\geq$300 mg/m^2), high dose cyclophosphamide, radiation (heart)	– Yearly exam and history – Baseline echocardiogram – Interval echocardiograms determined by risk (every 1–5 years)
	Modifiers: combined treatment, younger age, female gender, obesity, pregnancy	
Blood-borne illness (Hepatitis B, C or HIV)	Transfusion of unscreened blood product	– Hepatitis B surface antigen and hepatitis B core antibody – Hepatitis C antibody – HIV 1 and 2 antibodies – Other as indicated
	Modifiers: living in hyperendemic area, other lifestyle high risk behaviors	
Impaired sexual maturation/function	Alkylating agents, radiation (craniospinal, pelvic, gonadal)	– Yearly exam for secondary sexual characteristics – Baseline evaluation (LH, FSH, estrodiol, testosterone) timing dependent on age and gender – Additional evaluations as indicated (semen analysis)
	Modifiers: combined treatment	
Secondary leukemia or myelodysplastic syndrome	Epipodophyllotoxins (etoposide), alkylating agents, anthracyclines	– Yearly CBC until 10 years from exposure
	Modifiers: older age, less than 5 years from exposure	
Neurocognitive deficits	Intrathecal chemotherapy, cranial radiation	– Baseline neuropsychological testing – Vigilance regarding educational and vocational progress
	Modifiers: combined treatment, female gender, younger age	
Renal/urinary	Cyclophosphamide, ifosfamide, cisplatin, radiation (abdomen/pelvis)	– Yearly blood pressure – Baseline BUN, creatinine, electrolytes and urinalysis – Follow-up as indicated for risk
	Modifiers: combined treatment, higher dose	
Growth	Cranial radiation or radiation to epiphyses of long bones	– Measurement of height and weight every 6 months until sexual maturity – Referral to endocrine for growth hormone evaluation if cross one percentile on growth curve
	Modifiers: younger age, higher radiation dose, surgery to the suprasellar region	

Table 357.2 (Continued)

Late effect	Therapy exposure	Screening recommendations
Musculoskeletal	Corticosteroids, high-dose methotrexate, radiation	– Encourage good calcium and vitamin D intake – Baseline bone density evaluation at maturity – Follow-up bone density evaluation as indicated
	Modifiers: combined treatment, older age, prolonged corticosteroids, growth hormone deficiency, hypogonadism	

[a]Screening recommendations taken from Children's Oncology Group Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, www.survivorshipguidelines.org

from treatment can potentiate the cardiovascular risks including hypertension, obesity, dyslipidemia, and diabetes mellitus.

Screening for cardiovascular disease should include a yearly interview for symptoms of shortness of breath, dyspnea on exertion, orthopnea, chest pain, palpitations, and abdominal symptoms for younger patients. A complete physical exam should include careful evaluation of the heart for murmur, extra heart sounds (S3, S4 and increased P2), and pericardial rub and careful evaluation for signs of cardiac failure including rales, wheezes, jugular venous distention, and peripheral edema. Screening testing should include echocardiograms at intervals from every year to every five years depending on risk, a baseline EKG, and periodic fasting glucose and lipid profiles.

Genitourinary

Genitourinary late effects are generally related to specific chemotherapy agents or single kidney status after surgery. The chemotherapy agents with the most potent renal effects are cisplatin and ifosfamide. Both agents damage the ability of the kidney to filter efficiently. Cisplatin damages the distal renal tubule causing electrolyte wasting of magnesium, calcium, potassium, and sodium. Ifosfamide damages the proximal renal tubules causing wasting of potassium, phosphorus, glucose, protein, and bicarbonate (Fanconi's renal syndrome). Treatment with multiple chemotherapy agents increases risk, as does concomitant treatment with other nephrotoxic antibiotics or medications, radiation, or surgery. Children should be screened yearly with a blood pressure, creatinine, blood urea nitrogen, and chemistries, as well as urinalysis. Electrolyte replacement should be given to patients with ongoing wasting. Patients should be counseled to avoid further injury to the kidneys including avoiding nephrotoxic medications and injury to the remaining kidney (if single kidney status), and early treatment for hypertension and urinary tract infections.

Treatment with the chemotherapy agents, cyclophosphamide and ifosfamide, can cause hemorrhagic cystitis during treatment due to the accumulation of the toxic metabolite acrolein in the bladder. Bladder cancer can develop in patients who have received these agents or radiation to the pelvis. Yearly urinalysis should be done to evaluate for microscopic hematuria.

Musculoskeletal

Chemotherapy agents including corticosteroids and antimetabolite chemotherapy such as methotrexate can lead to musculoskeletal abnormalities, most notably osteoporosis or osteopenia which increase risk for future fracture. This risk is potentiated by the evidence that increasing proportions of the general population are calcium and vitamin-D deficient. In survivors of childhood cancer, these effects can also be increased due to treatment-related gonadal and growth-hormone deficiency, hyperthyroidism, chronic wasting of calcium and phosphorus due to treatment-related renal injury, and by increased body weight.

Another source of chemotherapy-related musculoskeletal damage is avascular necrosis (AVN) related to treatment with corticosteroids. AVN typically occurs during treatment but new cases can be diagnosed for many years after treatment. Clinically, children usually present with pain and limitation of activity. The large joints of the lower extremities, hip and knee, are most commonly affected, but AVN can occur in any bone.

Radiation to any bone or soft tissue can result in poor growth and tissue wasting which can contribute to the chemotherapy-related effects as well as producing effects in isolation. Children should be screened by interview yearly for symptoms of bone pain and a careful physical exam of all bones and tissues looking for asymmetry or decreased range

of motion. All children should be encouraged to maximize calcium and vitamin-D intake and possibly have vitamin-D levels measured in the blood. Medicines to increase bone density are not currently approved for use in children, except in extreme circumstances. Any bony abnormality or concern for AVN should be further evaluated by plain x-ray or MRI with referral for surgical intervention as indicated.

Sensory

Platinum-based chemotherapy agents can cause long term ototoxicity. The hearing loss is sensorineural loss, but may also manifest as tinnitus or vertigo. The risk of hearing loss is increased when treatment occurs before the age of 4 years and when chemotherapy is combined with radiation or other ototoxic agents such as aminoglycoside antibiotics or loop diuretics. Children who have risk for hearing loss should undergo yearly interview for symptoms of hearing difficulty, tinnitus or vertigo as well as a complete audiological evaluation to follow loss. There should also be an emphasis on preventing further injury including avoidance of loud noises, using ear protection where indicated and avoiding further exposure to ototoxic medications.

Some treatment regimens can result in visual impairment. Children treated with chemotherapy agents such as busulfan or long-term corticosteroids are at life-long risk for the development of cataracts. This risk is increased when radiation to the total body, brain, head, or orbit was also given. Corticosteroid treatment can also increase the risk for developing glaucoma. Radiation increases the risk of chronic dry eye (Sjogren's syndrome) due to effects on the lacrimal glands. Children who have risk for these complications should be screened through a collaborative effort between ophthalmology and the primary provider and early intervention should be considered for any visual disturbance with the ultimate goal of preserving vision.

Dental

Treatment regimens including chemotherapy and radiation therapy can cause damage to or loss of teeth. Chemotherapy agents can damage the enamel of the teeth leading to an increase in the number of dental caries a patient experiences. This damage is seen in the erupted teeth, as well as the unerupted teeth. High dose chemotherapy regimens can also lead to the loss or misalignment of the adult teeth if treatment was received at a young age. Radiation therapy contributes to dental damage if the salivary glands are in the field of radiation. Damage to the salivary glands causes a decrease in saliva production leading to chronic dry mouth. The saliva plays an important role in cleaning the mouth and a decrease in saliva potentiates the damage done by other agents. It is recommended that all patients receive regular dental evaluation every six months for preventative maintenance and early intervention for dental caries.

Growth and Development

Children show a significant decreased in linear growth during and after cancer therapy. Most often, this decrease is due to radiation therapy. Chemotherapy alone can lead to decreased growth velocity while on treatment, but this is usually temporary and children experience an increased linear growth velocity after treatment and often catch up to children of a similar age.

Radiation therapy can contribute to decreased linear growth in a number of ways. First, whole brain radiation can damage the hypothalamus or pituitary gland leading to short stature. Risk factors include increasing dose, greater than 18 Gy and younger age children (age less than 5 years) showing more damage. This is thought to occur due to growth hormone deficiency or disturbance in the gonadal axis leading to early closure of the epiphyseal growth plates. Radiation also decreases linear growth through a direct effect on bones including the spine and femoral heads. This direct inhibition can lead to impaired growth locally, sometimes resulting in asymmetric growth patterns (decreased sitting height, decreased leg length, etc.). These effects are seen at doses of 20 Gy to the epiphyses.

Children at risk for decreases in linear growth should be followed carefully. If possible, height should be measured at least twice yearly until sexual maturation is complete. An accurate height should be obtained and recorded on a standardized growth curve and followed for trends. If a patient has a risk factor and crosses percentiles or is less than the third percentile, early referral for an endocrine evaluation is recommended.

Neurocognitive Function

The effects of cranial radiation on neurocognitive functioning are well documented. There is evidence that some chemotherapeutic agents also have an impact on neurocognitive functioning. These agents include intrathecal chemotherapy such as intrathecal methotrexate, high-dose cytarabine, and high-dose methotrexate. A wide array of neurocognitive effects have been described and can vary as the patient ages. Vigilance is recommended with regard to academic performance and vocation. When possible and available, neuropsychological evaluation early in treatment

with repeat testing over time can inform intervention to help with deficits.

Fertility

Exposure to various chemotherapy agents and radiation in males produces gonadal dysfunction by damage to both the germ cells and leydig cells in the testicle, resulting in variable effects on spermatogenesis, testosterone production, and sexual function. As with males, exposure to chemotherapy and radiation produces impairment of gonadal function of the ovary in females. All chemotherapy agents are thought to pose some degree of risk but the largest risk is seen after treatment with the alkylating agents (cyclophosphamide, ifosfamide, procarbazine, etc.). These agents are commonly used for all cancers but notably for treatment of Hodgkin's lymphoma and solid tumors. Cumulative doses of cyclophosphamide greater than 7.5 g/m^2 are thought to greatly increase the risk for future infertility. Both the testicle and ovary are radiosensitive such that even low doses can impact function and radiation to the brain can interfere with the normal hypothalamic-pituitary-gonadal axis function, also resulting in impaired gonadal function.

There has been a focus on developing treatment regimens which limit the dosing of agents thought to have the highest impact on fertility outcomes, but this is not always possible. This has most notably been attempted in the treatment for Hodgkin's lymphoma. Other approaches are pretreatment fertility preservation techniques such as sperm cryopreservation for post-pubertal males and embryo cryopreservation for females with an identified partner and time to complete the in vitro fertilization process. Currently there are not good options for pre-pubertal males and females and females without identified partners.

Second Cancers

Longitudinal cohort studies of childhood cancer survivors from multiple countries have consistently demonstrated an increased risk of second cancers. This risk shows a steady increase with increasing time since completion of treatment. Treatment with chemotherapy agents can increase the risk for development of acute myelogenous leukemia or myelodysplatic syndromes. The chemotherapy agent, etoposide, appears to pose the greatest risk but this is seen with multiple categories of chemotherapy including the anthracyclines, alkylating agents, and the heavy metals. This risk appears to be greatest in the first 5 years from diagnosis and is thought to be virtually gone after 10 years. Screening recommendations include a yearly Complete Blood Count (CBC) for 10 years after treatment and follow-up for clinical symptoms.

The risk for other second cancers is mainly due to radiation exposure. There is increased risk for any skin cancer, soft tissue, or bone tumor in a previously irradiated field and this requires close monitoring for suspicious skin lesions and masses. In particular, radiation to the breast tissue increases the risk for development of breast cancer and this has been most notable in survivors of Hodgkin's lymphoma who underwent chest radiation. Women with a history of radiation to breast tissue should begin annual screening mammogram and/or breast MRI usually at the age of 25 years. Similarly, there is an increased risk of colorectal cancer in those patients who previously received radiation to the abdomen or pelvis and screening colonoscopy should begin usually at the age of 35 years. There should be a low threshold for investigation of any unusual mass or lesion in a previous radiation field.

Conclusion

As therapy improves for childhood cancer, there is a growing population of childhood cancer survivors at risk for late effects related to their treatment. Providers caring for these patients must be aware of these late effects and the screening recommendations to provide optimal care and prevent future morbidity and mortality.

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Neurology

Generoso G. Gascon

358 Clinical Approach to Infants, Children, and Adolescents with Neurologic Problems

Generoso G. Gascon

Neurological symptoms comprise approximately 10% of presenting complaints to primary care practitioners, family medicine physicians, and general pediatricians. Generalists can manage these efficiently by developing a systematic approach. This chapter takes a developmental, age-related, symptom-oriented approach to evaluating and managing a child presenting with neurologic complaints. Detailed treatment and management of specific disease entities mentioned in this introductory chapter is covered in the subsequent chapters.

The clinical approach needs to be flexible, depending on the age of the patient, and the informants giving the history. The setting, whether it is the normal newborn nursery, neonatal or pediatric intensive care unit, the emergency room, the hospital clinic or private office determines the pace and sequence of different parts of history taking and the neurological examination. A complete history and neurological examination need not be done in the first encounter. A focused neurological exam, sufficient enough to make an acute management decision, whether diagnostic or therapeutic, is appropriate for an acute triage situation, such as the emergency room. The presenting problem, whether acute or chronic, and the setting also influence the amount of time spent explaining the working diagnosis and management plan, as well as that spent on educating and counseling patients and families.

In this chapter the developmental ages introduced are arbitrarily divided into:

The neonate
The infant and toddler
The preschool child
Elementary school child
The middle school child
The high school child and adolescent

Clinical Approach to the Newborn with Neurological Problems

The most common acute neonatal neurological symptoms in the neonatal intensive care unit (NICU) are seizures, with or without impaired sensorium, qualifying as encephalopathy. The most common etiologies are hypoxia and/or ischemia, infection, stroke, metabolic abnormalities (hypoglycemia, hypocalcemia). Less common are metabolic diseases like aminoacidurias (maple syrup urine disease), organic acidurias (methylmalonic and propionic aciduras), and urea cycle and fatty acid oxidation disorders. Rarely, genetic epilepsies (benign familial neonatal convulsions) present in the newborn period.

In the normal newborn nursery, the common problems for which neurological consultation is sought are brachial plexus palsy (Erb's), and various involuntary movements that mimic seizures, such as benign familial neonatal myoclonus, benign nocturnal myoclonus, jitteriness, abstinence syndromes, or phasic movements normally seen in active (rapid eye movement [REM]) sleep.

History and examination of the newborn are covered in detail in the Chaps. 360, "Neonatal Neurological Disorders" and 361, "Neonatal Seizures".

History in the NICU is most commonly obtained from the bedside nurses, though the neonatologist poses the question. Parents need to be queried for the prenatal and perinatal history, and family history. One symptom, seizures, is highlighted here.

Seizures. The first important decision is to decide whether the events observed are, in fact, seizures. If so, the next decision is to classify the seizures, whether only of one kind, such as focal motor, or of many different kinds, such as focal clonic, myoclonic, focal onset but migrating, or subtle seizures. This can be done by retrospective history from the observing nurses or parents, or prospective

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observation using seizure charts. In tertiary care centers that have the technology and neurological expertise, the gold standard is continuous video-EEG monitoring.

Classifying seizures has a practical aspect. Focal clonic seizures bode, generally, for a good prognosis, because focal clonic seizures are often secondary to a transient metabolic abnormality, such as hypocalcemia. Myoclonic and subtle seizures bode for a guarded prognosis since they are usually due to hypoxia-ischemia, neurometabolic disease or brain dysgenesis.

For those working in secondary or tertiary care centers, having a once yearly teaching session with nurses on the classification of neonatal seizures, using videotapes of such seizures, if available, would be a good practice for obtaining consistent and accurate observations. Bedside nurses and nurse practitioners should be sensitized to the onset, progression of movements, whether there is more than one kind of seizure, duration, and postictal findings.

Neurological Examination

In the *general physical examination*, most important for neurology are size and shape of the head and dysmorphic features. The tape measure surrounds the head from the occipital protuberance to the forehead. Head circumference is plotted on a standard growth chart. Recognizing dysmorphic facial features may, by itself, make a diagnosis; for example, Down syndrome, Zellweger syndrome (see Genetics section and chapters).

The *mental status* exam in the newborn is essentially a determination of the level of consciousness or sleep state and general responsiveness. In a two to three-day full term infant, parts of the Brazelton neonatal assessment exam can be applied, in a clinical fashion.

Cranial nerve examination. The most important functions to determine immediately are vision (C.N. II) and hearing (C.N. VIII); then, the muscles necessary for sucking and swallowing (motor V, VII, IX, X, XII).

Motor examination. The most reliable motor exam is performed while the neonate is in Brazelton State 4. States 1 and 2 are sleep states (active and quiet sleep). State 3 is drowsiness-arousal. State 4 is awake, relaxed, and alert. State 5 is awake and active. State 6 is awake, active, and crying.

Developmental reflexes. The most important newborn developmental reflex is the Moro. It is best elicited by cradling the newborn in the horizontal supine position, with one hand under head, then suddenly letting the head drop in neck extension. There are two parts to the Moro: initial abduction and extension, then adduction and flexion, of the arms. One looks for its presence or absence. If present, any asymmetry is noted, then that suggests a hemi-syndrome.

The asymmetric tonic neck reflex (ATNR) is not normally present in the newborn, but is usually seen between 2 and 6 months of age. If present, it is abnormal because it is too obligatory. Other developmental reflexes that should be present, and best elicited about the third day of life after the neonate has "recovered" from the trauma of birth, are the grasp and traction responses, elicited by the pull-to-sit maneuver, watching also for excessive head lag. Plantar grasps are elicited by pushing the thumb into the balls of the feet and watching the toes flex. Placing and stepping reactions are elicited by holding the infant in the vertical suspension position and brushing the dorsum of the feet up against the examining bed. Automatic walking is elicited by holding the newborn upright, then pulling forward with the infant leaning forward, letting the toes brush the examining bed.

One sign, hypotonia, is highlighted here.

Hypotonia may occur with or without weakness, may be variable according to state, and may even coexist with increased tone (for example, axial hypotonia with appendicular spasticity). Central hypotonia must be distinguished from peripheral/neuromuscular causes. Weakness may be lateralized (as in a hemiplegia), or localized (as in a brachial plexus palsy, or congenital absence of the depressor anguli oris). Weakness may be bilateral and localized, as in Moebius syndrome (bilateral peripheral facial palsies).

Generalized profound hypotonia is seen in some metabolic diseases (peroxisomal disorders like Zellweger's, aminoacidurias like non-ketotic hyperglycinemia (NKH)). Neuromuscular diseases like congenital myotonic dystrophy, congenital myasthenia, and congenital myopathies, present in the newborn period with hypotonia, and definite weakness. CAVEAT: Some diseases have both brain and muscular involvement, such as mitochondrial disorders, and rare congenital muscular dystrophies (Fukuyama, muscle-eye-brain disease).

Ancillary Investigations

In many hospitals in the USA and around the world, newborn screening for treatable congenital metabolic diseases by sending blood spots for tandem mass spectroscopy, usually in regional laboratories, and other blood tests (thyroid) is now being done. This is an enormous advance in the prevention and early treatment of otherwise crippling and disabling diseases (see ❯ Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism").

Continuous video-EEG monitoring is the gold standard not only for diagnosis, but also to follow results of

treatment, in neonatal seizures, since clinical-EEG dissociation is not uncommon in neonatal seizures.

Doppler ultrasound is noninvasive and portable, and is particularly useful for intracranial hemorrhages and conditions which change ventricular size. CT brain adds gray-white matter differentiation, with higher resolution than ultrasound, and fast acquisition speed. CT angiography has increasing utility in stroke. MRI, with its various sequences–FLAIR, DWI, along with its permutations–MRS, MRV, and MRA, gives the highest resolution, visualizes the brainstem, and has the advantage of being repeatable without exposing the infant to radiation. Neuroimaging in hypoxic ischemic encephalopathy is discussed in detail in the Chap. 360, "Neonatal Neurological Disorders".

Infant and Toddler (Up to 3 Years of Age)

The general approach to history taking in the infant and toddler with a neurological problem is to elicit a prenatal and perinatal history that might point to possible brain damaging events, an interval history since birth for acquired brain damaging events, and a family history that might point to genetic or familial conditions. The examination is both a neurodevelopmental assessment as well as a neurological examination (see Chap. 42, "Normal Child Development").

Milestones: The two most important milestones that physicians can determine just from history and examination are motor and speech/language. Infants should be rolling over by 4 months, sitting alone by 6 months, reaching out at 6 months, and walking alone by 14 months. A shovel grasp is followed by a pincer grasp by the early second year.

Regarding speech, babies should be cooing at 3 months, interactive babbling till 7–8 months, consonant-vowel combinations, like "da-da" by 8–9 months, single words by 16 months, short sentences by 24 months. Conditioning games such as waving bye-bye, "peek-a-boo," clapping hands occur around 12 months. Putting blocks into a 3-hole form board is usually achieved by 18 months. However, these milestones may be achieved at different times in cultures with infant-raising practices different from that of North America (see Chap. 49, "Global Perspectives on Child Development and Behavior").

Examination

In this age group, the exam needs to seem like play in order to establish rapport. The least invasive items, such as testing the teloreceptors (hearing and vision) should be done first. Examination items that require actual handling of the baby—muscle tone (pull-to-sit maneuver), deep tendon reflexes, and the developmental reflexes should be done last.

Measuring head circumference and looking at the shape of the head is mandatory. Nowadays, with the standard of practice being to advise mothers to lay infants supine to lessen the risk of sudden infant death syndrome (SIDS), the incidence of positional plagiocephaly, flattening of the skull posteriorly, is increasing. This needs to be recognized early, since molding helmets are not effective after the sutures have fused, after about 8 months of age. Microcephaly and macrocephaly usually requires that the head circumference be two standard deviations above or below the mean expected for that age. Another clinical guideline would be whether there is a 50 percentile difference between head circumference and length or weight. In babies with enlarged heads, and in geographic areas where CT head scans are not easily available, percussing the skull and listening for a "cracked pot" sign due to split sutures can still be useful. Auscultating for bruits, using the bell portion of a stethoscope, over the orbits and the skull may detect vein of Galen malformations or large arteriovenous malformations.

Of the four items of classical physical diagnosis, observation, palpation, percussion, and auscultation, observation is the most important at this age. Observations include the interrelatedness between the baby and parents and the baby and the examiner, degree of eye contact, presence of spontaneous speech, and nonverbal communication (pointing, gestures) in toddlers who have delayed speech.

General: Specific parts in the general physical examination that may suggest neurological disease are the skin, looking for neurocutaneous stigmata, and the abdominal exam, looking for hepatosplenomegaly.

Occasional café-au-lait spots are fairly common, but six or more should raise suspicion for neurofibromatosis Type I, in which case parents' skin should be examined. Ultraviolet light by a Wood's lamp can bring out the vitiliginous or hypopigmented spots of tuberous sclerosis, particularly in light-skinned patients. Hepatosplenomegaly would raise the possibility of a storage disease (see Chap. 39, "Lysosomal Storage Diseases").

When a toy is held before the child, one can watch to see if only one hand reaches out, suggesting hemiparesis, and whether tremor is present. In observing crawling, a hemiparesis is suggested if the infant pulls forward using only one side of the body. Walking on tiptoes suggests a spastic diparesis, muscular dystrophy involving calf muscles, or autism.

Cranial nerves: Infants are more likely to follow visually interesting objects, such as the distorted human face, finger puppets, or rotating concentric circles, such as pinwheels. Similarly, hearing behavior can be elicited with a bell, a clacker, or toys that reproduce animal sounds. Infants turn their head toward sound at 6 months. Prior to that they may merely become still and have an alert, listening facial expression.

Developmental reflexes: The ATNR, elicited by turning the head of the supine infant to one side, appears about 2 months and should disappear completely by 6 months. The ATNR begins to recede at 4 months, when the body-righting reflex replaces it. At 6 months, the infant is transitioning from the reflexes of a quadripedal animal, to that of a bipedal animal who stands on two legs in the upright position.

The first bipedal reflexes appear at 6 months. If the infant in the sitting position is suddenly pushed backward, the legs should kick out; if the infant is pushed sideways to either side, the arms should thrust out sideward. The parachute response appears at 8 months. It is elicited by holding the infant at the chest, face down, and propelling toward the examining table. Both arms should suddenly thrust forward (as if to break a fall) at the same time. This is a good reflex to observe any asymmetries that suggest hemiparesis. Proximal weakness at the shoulder girdle can be determined by leaving the child momentarily in the resulting wheelbarrow position, and see if the baby can bear its weight, temporarily.

Common Problems

Common problems in the infant and toddler are:

1. Delayed development.
2. Seizures. The most severe epilepsy syndromes are infantile spasms; Lennox-Gastaut; and infantile myoclonic epilepsies. The most common seizure disorder, however, is febrile seizures (see ❯ Chaps. 361, "Neonatal Seizures" and ❯ 362, "Epilepsy in Infancy and Childhood").
3. Breath-holding spells (see ❯ Chaps. 361, "Neonatal Seizures" and ❯ 362, "Epilepsy in Infancy and Childhood").
4. Movement disorders. Most common are transient tics, dystonic-like postures secondary to gastroesophageal reflux, similar to Sandifer syndrome (see ❯ Chap. 363, "Movement Disorders").
5. Sleep-related rhythmic movement disturbances (head-banging, tremors upon awakening, shuddering attacks), parasomnias (night terrors at age 3) (see ❯ Chap. 364, "Sleep and Its Disorders in Childhood").

Delayed development. (For the perspective of developmental pediatricians, see ❯ Chap. 42, "Normal Child Development", and Nancy Lamphear, Disorders of Learning and Attention.) The physician must distinguish between global developmental delay and specific developmental delay. Global usually means in two or more domains, usually specified as motor, language, social, and adaptive. When the etiology is neurological, delayed motor development, most commonly, has a cerebral cause, the most important of which is cerebral palsy–atonic in infancy, which may evolve into diplegic, hemiplegic, or choreoathetotic. Motor developmental arrest and/or deterioration, with relative preservation of mental functions, point to neuromuscular conditions such as spinal muscular atrophy, muscular dystrophy, or congenital myopathies.

Delayed language development, with preservation of motor function, intact hearing, and normal intelligence, may signify a developmental language disorder (developmental dysphasia). Delayed language may also suggest an autistic spectrum disorder, particularly if there is language regression in the second year of life. Language regression may also occur in rare conditions like the Landau-Kleffner syndrome and Continuous Spike Waves in Slow Wave Sleep (CSWSS).

At some point, usually in the preschool years, if an infant who is globally delayed shows no evidence of catching up to a normal developmental curve, mental retardation, mild, moderate, or severe needs to be considered. Although the Bayley Infant Scales are used by psychologists, formal IQ testing does not begin to be reliable until the preschool age, when the Wechsler Pre-Primary Scale for Children (WPPSI) is available. However, the primary care physician can approximate IQ, using the concept of DQ (developmental quotient). The formula is:

$$\text{DQ} = \text{developmental age}/\text{chronological age} \times 100.$$

For example, if an infant is 12 months old, and has the first bipedal reflexes and is just beginning to sit unsupported (6 month developmental milestones), the motor DQ is $6/12 \times 100$, or 50 (on borderline between moderate to mildly delayed, if parallel to IQ). This should lead to a recommendation for infant stimulation programs.

Because of the reported worldwide increase in prevalence of the autistic spectrum disorders, autism needs to be distinguished from mental retardation. The American Academy of Pediatrics, in its July, 2006 policy statement, recognizes the benefits of early detection. It recommends developmental screening at 9, 18, 24, and 30 months.

Table 358.1
Absolute indications for diagnostic referral for autism

No babbling by 12 months
No gesturing (pointing, wave bye-bye) by 12 months
No single words by 16 months
No 2 word spontaneous phrases (not echolalia) by 24 months
Loss of ANY language or social skills

There is some controversy about what constitutes quality screens, although the Denver Developmental Screening Tests are commonly used in practice. In the state of Massachusetts, screening for autism is mandated at 18 months, with a choice of various standardized screens, although the M-CHAT is probably the most widely used (Table 358.1).

The "Parents' Evaluations of Developmental Status (PEDS)" is a screening questionnaire that can be easily completed by parents in a few minutes in the waiting room. Printed in English, Spanish, and Vietnamese, additional translations like Hmong, Somali, Russian, Chinese, Thai, etc, can be licensed by e-mailing the publisher. The online application also offers the Modified Checklist of Autism in Toddlers (M-CHAT), automated scoring and ICD-9 codes.

Developmental screens requiring direct elicitation of children's skills are the Bayley Infant Neurodevelopmental Screener (BINS), the Brigance Screens II, and the Battelle Developmental Inventory Screening Test (BDIST), 2nd edition. Busy pediatricians rarely have the time to administer these, so in practice, they are most often administered by psychologists, although office personnel such as nurses, nurse practitioners, and probably even medical assistants could probably be trained to do these. Internationally, for validity and reliability, screens like these, and, I.Q. tests for later ages, should be standardized for language and culture.

In the USA, pediatricians can refer infants with developmental delays for publicly funded Early Intervention services, where developmental specialists, physical and occupational therapists, speech and language therapists provide services in the home, up to the age of 3 years. After the age of 3, if delays have not resolved, children are eligible for early education services in the public schools, where individual education plans (IEPs) are made and carried out. These services are a resource for pediatricians, as well as sources for obtaining up to date ongoing observations of developmental progress.

Developmental regression should always bring up the possibility of a progressive encephalopathy, discussed in detail in the chapter by G. Gascon.

The Preschool Child (3–6 Year Olds)

The approach to history taking is to listen carefully to the concerns of parents, other caretakers in the home, and elicit histories, when appropriate, from day care workers or preschool teachers. If complaints are unfocused, the physician's task is to help the historians clarify their concerns and priorities. The initial explicit chief complaint may mask underlying implicit concerns that are not verbalized, for fear that the child may have something viewed as devastating, such as mental retardation or autism.

The common problems at this age are global and specific developmental delays, febrile seizures and breath holding spells, and behavioral problems, from high functioning autistic spectrum disorders, to disruptive behavioral disorders, which may present first with hyperactivity and impulsivity (Attention Deficit Hyperactivity Disorder [ADHD] plus). The term "sensory integration problems" is not a diagnosis by itself, but is seen in different disorders such as autism or in children with obsessive-compulsive traits or disorder.

With video capabilities practically universal in cell phones and digital cameras, parents can help, in questions of seizures or abnormal involuntary movements, by recording the events. Having them keep sleep logs can establish a baseline, as well as help in diagnosis (see Chap. 364, "Sleep and Its Disorders in Childhood").

Asking children what television shows they watch, and asking them to name favorite characters, asking parents whether the child pays attention and follows the story lines, laughs at the appropriate situations, and a sense of humor can reveal intelligence.

Asking about how well the child plays with playground equipment, such as swings, slides, and jungle gyms, as well as when the child was able to ride a tricycle and a bicycle can give a good idea about motor coordination. How complicated a puzzle the child can manage tells something about visual perceptual motor skills. Asking about favorite toys and how the child plays with them and with other children can give an idea of rigidity, imagination, symbolic play, and development of parallel versus interactive play.

Accident proneness and sleep difficulties in this age group, particularly difficulty falling asleep after going to bed (increased sleep latency), are not uncommon antecedents of ADHD.

Finally detailed family histories and drawing a three generation family pedigree, looking not only for single gene disorders, but also paroxysmal and neuropsychiatric disorders, should be routine.

Neurological Examination

At this age one still approaches the examination in the office as if it is play. Having toys in the examining room appropriate for this developmental age helps, for example, puzzles, form boards for visual perceptual motor and fine motor coordination; cars, trains, dolls, a doll house if space warrants for imaginative play; large balls for general motor coordination. These reinforce the ambience of a child-friendly environment, put the child at ease, and enhance cooperation in the more formal parts of the neurological examination performed later.

Much can be learned from observing the child with these toys, while obtaining the history from the parents. Special attention to speech and language is important, to distinguish developmental articulation problems from developmental language disorders and the characteristic disorders of pragmatics in the language of high functioning autistic children. Whether they can remember words while singing and keep in tune should be noted. Universal songs, like the "Happy Birthday" song, are part of the repertoire.

The simplest pre-academic readiness skills to predict early literacy skills is the ability to name colors and letters of the alphabet., which nowadays is usually achieved before kindergarten. By then most middle class children have book awareness, having been exposed to books being read to them by parents, and some early phonics.

In pre-academic math skills, one to one correspondence, that is, the ability to match numbers to objects (one sock to one shoe), counting from one to ten, and understanding of measurement, length and weight, big and small, and some elementary understanding of money predict acquisition of elementary mathematics.

Visual perceptual motor skills can be tested by having the child copy shapes–circle (age 3), distinguishing + and x (cross from x) (age 4), triangle (age 5), square (age 6), diamond (age 7), British flag (age 8). Another way is putting together and taking apart constructional toys, like Legos and building blocks. Spatial relations. Up/down, in front of/behind, over/under.

In gross motor testing, children should be able to stand on one foot for a few seconds, and then hop in place for a few hops, at 4 years. They should be able to kick a soccer ball. Throwing a small ball like a baseball may still not be accurate. Preferred handedness and footedness should be noted.

Common Problems

Global Developmental Delay

Global developmental delay is taken to mean delay in at least two of the four usual domains–motor, language, social, and adaptive. In the preschool child, persisting global developmental delays since infancy would warrant etiological investigation for mental retardation or autism, if not previously done.

The American Academy of Neurology has published a practice parameter with an algorithm on how to proceed stepwise. Nonsyndromic mental retardation, characterized by the absence of associated morphologic, radiologic, or metabolic features, comprises the majority of cases. The genetic factors underlying nonsyndromic MR are not presently understood. The present standard of care, therefore, is to order the highest resolution chromosome studies available, chromosomal microarrays. Since Fragile-X Syndrome accounts for a significant fraction of MR and the characteristic morphological features are not obvious at this age, fragile-x gene studies are recommended.

As of early 2009, linkage and cytogenetic analyses have identified 29 X-linked and five autosomal recessive genes associated with nonsyndromic mental retardation, which account, however, for less than 10% of cases. Autosomal dominant genes have yet to be identified. However, *de novo* chromosomal rearrangements, usually involving a change in copy number of genomic regions, are the most commonly recognized cause of mental retardation. This suggests that monoallelic lesions are sufficient to cause MR, and therefore raises the possibility that *de novo* genetic lesions, such as point mutations, may explain a number of cases of MR. Nonsyndromic MR is not amenable to linkage or association approaches, and therefore relies on the sequencing of candidate genes. The hypothesis that *de novo* mutations of autosomal genes, involved in synaptic plasticity, recently found support in the discovery of mutations in SYNGAP1.

Specific Developmental Delay

Specific developmental delays are delays in one domain only. When two, or more, domains are involved, however, the question arises on whether these are independent, comorbid specific delays, rather than global developmental delay, which often implies cognitive subnormality.

For example, specific delays in language, that is, developmental language disorders, may be comorbid with

ADHD, or visual-perceptual motor difficulties, or excessive incoordination (developmental coordination disorder), in a cognitively normal child. Language delay must be distinguished from language regression, the loss of previously acquired speech and language. The differential diagnosis then includes progressive encephalopathy, autistic regression, Landau-Kleffer syndrome or Continuous Spike Waves in Slow Wave Sleep (CSWSS).

In the motor sphere, arrest and regression, as in the dystrophinopathies (Duchenne-Becker muscular dystrophy), need to be distinguished from just delay, as in spastic diparesis due to nonprogressive encephalopathies (cerebral palsy).

Behavioral Problems

Behavioral issues, like persisting temper tantrums, sleep issues like parasomnias, and hyperactivity always bring up the question as to whether these are still within the wide variation of normal behavior at this age, or whether they are at risk behaviors for other disorders. The child with disruptive behavior may just be having prolonged "terrible two's," but then again, may be exhibiting the beginnings of an oppositional-defiant disorder.

Incessant hyperactivity and impulsivity, excessive tantrums, more than the terrible two's, irritability, easy to anger yet repentant and overly loving afterward, cruelty to pets, hitting out to peers in day care, rapid mood swings, sometimes multiple in a day, suggest a severe disorder of mood regulation in the bipolar spectrum. However, one should make this diagnosis with caution, in the absence of a family history of bipolar disorder.

Higher functioning autistic disorders, like pervasive developmental disorder not otherwise specified (PDD. NOS), may have escaped detection before the age of three, but should not be missed in the preschool child. These two disorders – autism and childhood bipolar disorder, parallel the two poles of mental illness in adolescents and adults, schizophrenia and affective disorders (depression, bipolar disorder).

Paroxysmal Disorders (See Gaitanis Chapter)

The most common paroxysmal disorders in the preschool age group are febrile seizures and breath holding spells (BHS). Assuming that seizures with fever are not symptomatic of a CNS infection like meningitis or encephalitis, and they are not focal in onset, they would be classified as simple febrile seizures. However, they may be an expression of a familial genetic syndrome, generalized epilepsy febrile seizures plus, if there are other members of the family with febrile seizures and generalized epilepsies. Fortunately, response to antiepileptic medications for generalized seizures is very good.

The course needs to be watched, however, because, rarely, myoclonic and non-febrile generalized convulsions may follow febrile seizures, simple or complex, with developmental arrest, and evolution into the syndrome of severe myoclonic epilepsy (SME, Dravet syndrome).

This is also the age where the two most common benign epilepsies of childhood may begin, benign Rolandic epilepsy and benign occipital epilepsy (the Gastaut type).

BHS are either cyanotic (blue type), where the child cries so hard, often stimulated by denial of something she/he wants, that they turn blue, hold their breath, and then go limp. Pallid syncope (the pale type) usually occurs after sudden, unexpected painful stimuli, such as hitting the head, or stubbing a toe, where the child turns white, then falls limp. Sometimes tonic stiffening occurs, but this is usually an anoxic seizure, caused by temporary ischemia of the brain stem, mimicking "brain stem fits." Rarely does a convulsive seizure occur after a breath-holding episode, and the coexistence of both must be considered.

Screens

The same screening tests mentioned in the previous section (0–3 years old), except for the Bayley Infant Neurodevelopmental Screen, are still applicable as developmental screening tests for the preschool child (age 3–6 years).

Elementary School Child (KG Through 3rd Grade)

At this age many children are able to describe their symptoms. So, to establish rapport with the child, start with the child. Greet the child first, start with some easy banter (Whose idea was it that you come to see me? How's school?) This emphasizes that they are the center of attention, even though much of the rest of the visit may be eliciting history from the parents, and later giving information and counseling. Determine whether the child's chief concerns are the same as the parents. This gives some idea of their awareness of the presenting complaint.

In the examination, starting off with gross motor activities often loosens up the patient. Ordinary walking,

walking on tiptoes, heels, side of the feet, hopping on one foot, walking tandem, also doubles as an initial screening exam, looking for hemisyndromes and general coordination. Starting right off with mental status questions may intimidate the child and should be left till later when the child is at ease.

Common Problems

Problems often presenting for the first time at this age are absence seizures versus nonepileptic staring, tics, headaches, and learning and behavioral disorders.

Attention Deficit Hyperactivity Disorder (ADHD)

History-taking in ADHD focuses first on eliciting a history of the four major symptoms–short attention span, distractibility, impulsivity and hyperactivity, and determining whether they occur in two different environments, usually home and school and whether such behavior occurs in social settings (family gatherings, playground, play dates, and organized sports activities). Whether these are occurring in the physician's office requires observation of the child while taking a history from the parents, and watching how the child responds to commands during the physical/neurological exam. Do you have to repeat commands (inattention)? Does the child start to respond before you finish giving a command (impulsivity)? Does the child interrupt the doctor-parent conversation inappropriately (verbal impulsivity)? Does the child wander around the room touching things inappropriately (hyperactivity)?

There are questionnaires which can be filled out by parents before a physicians' visit, but some, like the Vanderbilt parent and teacher assessment scales, are proprietary and take time for the primary care physician to score. A common one used by schools in the USA is the Conners rating scales, which may come already scored to the physician, if the school is the instigator for the referral.

Special examinations looking for minor neurological dysfunction ("soft sign exams") again usually take more time than a busy pediatrician has, if he/she has not been trained in such exams, and interpretation depends on experience, and is best left to subspecialists (like developmental pediatricians, pediatric neurologists, or developmental neuropsychiatrists).

Headaches (See Ken Mack chapter)

The PedMIDAS (Pediatric Migraine Disability Scale) questionnaire, filled out by parents or patients prior to a visit, will cut down history-taking time, since it asks about frequency and severity of headaches, and degree of disability, as manifested by days missed going to school or other social or sports events.

In history taking the temporal profile of a headache distinguishes between two major patterns; that of a typical migraine attack (rapid rise, slower resolution, over hours), and that of tension-type headaches (low grade waxing and waning). At this age, however, recurrent headaches are almost always migraine-vascular.

If a verbal description of a visual aura is unclear, the child can be asked to draw it, using colored pencils or crayons, on a plain sheet of white paper. Children find it difficult to describe the quality of the headache pain. Nonverbal clues – milking hands or pounding fists that connote a throbbing or pulsating quality help. Another tactic is to give the child multiple choices – squeezing, bursting, sharp and stabbing, throbbing or pounding.

Learning Disorders

By third grade, learning disabilities should be evident – in reading (dyslexia) or arithmetic (dyscalculia). A specific learning disability is a marked delay in the acquisition of basic academic skills (reading, writing, arithmetic) despite normal intelligence, adequate hearing and vision, and adequate teaching. Operationally, schools usually use the criteria of, for example, reading level 2 years below grade level (see Nancy Lamphear, Disorders of Learning and Attention).

Neurobehavioral Disorders

The primary care physician can be aided in suspecting these conditions by using rating scales, such as:

Vanderbilt Parent and Teacher Assessment Questionnaires (ADHD, Oppositional Defiant Disorder, Conduct Disorder, Anxiety, Depression)
PARS (Pediatric Anxiety Rating Scale)
YMRS (Young Mania Rating Scale), for bipolar spectrum disorders
YBOCS (Yale-Brown Obsessive Compulsive Scale), children's version
Weinberg Affective Scale, for depression
Australian Asperger Scale, for Asperger's Disorder

Epilepsy

Common epilepsy syndromes apt to occur at this age are primary generalized absence seizures (Petit Mal Epilepsy) and benign Rolandic epilepsy. Non-epileptic staring, usually in children with attention deficit disorders are often mistaken by school personnel for absence seizures. Absence seizures can often be elicited in the office by having the child hyperventilate for at least 1 min One can determine that there is loss of consciousness by reciting a nursery rhyme ("one, two buckle my shoe, three, four, shut the door," etc.) and asking the child what she recalls hearing, if anything. Both of these epilepsy syndromes have characteristic epileptiform EEG patterns – synchronous and symmetrical three cycles per second spike waves in absence seizures, and sharp waves or spikes in the central-temporal areas that are sleep-activated.

For any kind of seizure syndrome, the use of seizure calendars which log seizure type and frequency, are a useful management tool.

The Middle School Child (4th Through 7th Grades)

At this age, children can give histories and usually cooperate with a formal neurological exam.

Common Office Problems

1. ADHD, inattentive subtype (attention deficit disorder without hyperactivity)
2. Migraine, and its variants
3. Syncope
4. Neuropsychiatric disorders – anxiety, OCD, Asperger's disorder

ADHD, Inattentive Subtype

This syndrome usually does not come to the attention of teachers until the middle school years. It affects girls more than boys and often presents as "underachieving for their potential" or "reading comprehension" difficulties, when there has been no earlier dyslexic difficulties. Executive function deficits become more evident. Executive skills are mediated through the frontal lobe, the last part of the brain to fully develop, and their deficits appear in middle school because of the requirement for more planning and organizational skills. It shows up in deficient homework management, low grades because of not handing in book reports, theme papers, or science projects on time. Medications alone do not correct executive dysfunction. Some schools recognize this by offering organizational skills training classes, but many children need daily monitoring at school and at home. Behavior management techniques, that is, the use of reward and punishment, are not effective. Executive function skills have to be taught.

Migraine and Variants

Idiopathic stabbing headaches, also called "ice pick headaches" or "indomethacin responsive headaches" can be missed, because they present as head pains more than headaches. Acute confusional migraine tends to occur around puberty and early adolescence. Headache calendars, which log frequency, severity, presence of triggers, and results of medication can clarify history taking.

Neuropsychiatric Disorders

Asperger's disorder may not be diagnosed until this period when the magnitude of social skills deficits becomes recognized. Delay in diagnosis is often due to the high I.Q.'s these children have. Parents commonly say "he has no friends," is considered weird, has "off the wall" conversational talk, and highly focused interests. Guidance counselors and school psychologists may offer social skills training classes.

Anxiety disorders, obsessive-compulsive disorder (OCD) may also become evident, if disruptive behavior is a symptom. Children with suspected neuropsychiatric disorders usually take too much time to be handled well by primary care physicians, and should, therefore, be referred to developmental pediatricians, pediatric neurologists with interest in behavioral neurology, or child and adolescent psychiatrists.

Tics which may have been minor may now become more prominent and evoke secondary emotional reactions. More likely, the highly associated disorders are apt to emerge as obstacles in school performance; particularly ADHD, but also OCD.

High School and Adolescents

As much as possible, histories should be obtained by talking directly with adolescents alone, separate from the parents. This immediately establishes that they are the focus of attention, not their parents, but also conveys

to them their responsibility for managing their condition. One has to judge the capacity to introspect, and therefore, the reliability of their views. Parents can be called in later, prior to performing the neurological exam, to hear "their side of the story."

A characteristic adolescent issue is sleep. A detailed review of systems checklist filled out before the office visit can insure that the primary care physician does not miss an issue like sleep, which may not be the initial chief complaint. A complaint of fatigue or ADHD-like symptoms affecting school performance might be traced to sleep deprivation.

Another characteristic issue with adolescents is compliance – in keeping headache, seizure, or sleep logs, or even doctor's appointments, as well as in taking medication. The motivation to keep a driver's license can be used to insure compliance with taking antiepileptic medication.

Substance abuse, particularly alcohol, can be the reason for a variety of neurological symptoms, and should be inquired about in the history.

In the neurological examination, at this age a good adult type mental status examination can be done, testing orientation; immediate, short-term, and long-term memory, digit span forward and backward, serial-7 subtractions from 100, a three word retention test, interpretation of proverbs, and general information. Adolescents are also able to fully cooperate in detailed muscle testing.

Common Problems

Head Trauma – Concussions (See Chapter by Tsze and Chun)

With children and adolescents participating more and more in recreational and competitive contact sports such as football (both American and soccer), basketball, ice hockey, and lacrosse, the long-term consequences of repeated concussions has emerged as a major concern. Return to play guidelines have been changing over the years, starting with the Cantu concussion grading schemes and two subsequent international modifications, to the relatively recent use of guidelines for trainers to use on the field at the time of the accident, then on the sidelines, and then the use of ImPACT (immediate post-concussion assessment and cognitive testing). ImPACT is a computer administered neuropsychological test battery, originated at the University of Pittsburgh that measures aspects of attention, memory, reaction time, and processing speed. Athletes are not returned to play until testing has returned to their baseline, obtained at the start of the season. Even then, return to play involves a gradual return, from light aerobic, full aerobic, light contact, to full contact participation.

Chronic Daily Headache syndrome (See Chapter by Ken Mack)

A majority, about 60%, are due to transformed migraine. The rest is due to tension-type headaches, or a mixture of migraine and tension-type. Emotional factors may be present – anxiety, depression. Medication overuse may have contributed to the formation of this pattern. It is defined as headaches occurring at least 15 days out of 30, for at least 3 months. The primary care physician needs to recognize this syndrome early because it is very difficult to break and warrants referral to a neurologist or specialty headache clinic.

The most common complicated migraine syndrome at this age is the basilar migraine syndrome, commonly affecting mid-teenage females. The other occurring in puberty or early adolescence is acute confusional migraine.

Special headache examination

1. Tap over frontal, maxillary, ethmoid sinuses, for acute sinusitis.
2. Examine for possible cranio-cervical junction problems. Hold a palm on the head, then pound slightly on the palm with the other fist. Ask for any pain when testing face-turning (sternocleidomastoid) and trapezius against resistance. Check for a Lhermitte Sign.
3. Palpate occipitalis and frontalis muscles for isometric contraction, as in muscle contraction (tension-type) headaches.
4. Have patient keep jaw open, while trying to close, or push from either side for temporal-mandibular joint problems.
5. Check the fundus, looking primarily for papilledema, as in pseudotumor cerebri.

Syncope

Vasovagal syncope is the most common cause. There is often a history of breath holding spells in early childhood, a family history of syncope, and of migraine. What they have in common is they are all disorders of neurovascular instability. Cardiac syncope, due, for example, to the Long Q-T syndrome, will require an EKG and pediatric cardiology consultation. Orthostatic syncope can be documented by tilt table tests.

A special form of vasovagal syncope, reflex syncope, may occur at this age. This is fainting triggered by physically or emotionally painful stimuli, such as drawing blood or hearing bad news. A preceding history of pallid syncope, the pale type of breath holding spells, in early childhood can often be elicited.

Epilepsy

The generalized epilepsy syndromes that can begin at this age are generalized convulsions upon awakening, juvenile absences, and juvenile myoclonic epilepsy (JME) Complex partial seizures due to temporal lobe epilepsy (TLE) often begin at this age. A surgically treatable epilepsy, if refractory to antiepileptic drugs, is TLE due to mesial temporal sclerosis occurring in patients with early childhood history of febrile seizures.

Conversion Reactions

Pseudoseizures are not an uncommon symptom at this age. They may be psychogenic, but the challenge here is that patients who present with pseudoseizures often also have true epilepsy. Other common conversion symptoms are inability to stand and walk, called astasia-abasia, which looks like a pseudo-ataxia; sensory symptoms because the sensory examination, relying on subjective responses, may be a subtle presentation of demyelinating disease; and intermittent weakness, even with a normal neurological examination, may be an early presentation of myasthenia gravis. DOPA-responsive dystonia may be missed if the patient is examined in the morning, and the diurnal pattern is not appreciated.

Demyelinating Disease (See Tanuja Chitnis Chapter)

Although relatively rare, multiple sclerosis can present for the first time in adolescence. More common are post-infectious demyelinating diseases, such as Guillain-Barre syndrome, transverse myelitis, or acute demyelinating encephalomyelopathy (ADEM).

ADHD Complications

By this time the behaviors which comprise conduct disorder, which are essentially pre-delinquent behaviors (fire setting, cruelty to animals), should have been recognized and treated, because conduct disorder complicating earlier ADHD is the most important risk factor for the subsequent development of substance abuse, delinquent and criminal behavior. By the same token neuropsychiatric disorders which may have presented in early childhood with an ADHD symptom complex and disruptive behavior, which may evolve into the bipolar disorder spectrum, are a risk for impulse control problems ("anger issues") and even explode into homicide, witness the Columbine school mass shootings.

Disorders Occurring at any Age

Some neurological disorders can occur at any age, but may have different etiologies at different ages:

Stroke
Demyelinating disorders, post-infectious like ADEM, transverse myelitis, Guillain-Barre syndrome
Head trauma
Progressive encephalopathies
CNS infections
Acute toxic-metabolic encephalopathies

Seizure incidence is greatest in early childhood and late life, but partial or focal seizures, or focal-onset secondarily generalized seizures can occur at any age due to any congenital or acquired focal brain structural lesion, such as brain tumors, vascular malformations, gliosis, secondary to cerebral contusions, CNS infections, progressive cerebral degenerative disease, or stroke.

Modifications of Clinical Approach According to Clinical Setting

In the Emergency Room

The priorities are – *Treatment first (save life and limb) then diagnosis.* Cone down on the chief presenting complaint, perform a focused exam, treat immediately if necessary (for example, status epilepticus), and then go back to get more complete history of the present illness, family history (draw a family pedigree), prenatal/perinatal/developmental history, allergies (Table 358.2).

In the P ICU

The priorities are *stabilization, recovery, and then acute rehabilitation* (See Chap. 379, "Pediatric

Table 358.2
Pediatric neurologic emergencies

Status epilepticus
Status migrainosus
Metabolic-toxic coma
Acute stroke
Acute weakness
Acute ataxia
Head and spinal cord trauma

Neurorehabilitation"). Intensivists put much reliance on monitoring devices for vital signs, cardiac and respiratory functions. Patients cannot have a "complete neurological exam" because they often have impaired consciousness or are in coma, and because of the monitoring equipment, intubation, and IV lines they cannot be moved. The mental status exam is essentially a classification of the level of consciousness, and standardized scales, such as the pediatric version of the Glasgow Coma Scale. Of the cranial nerve examination, reaction to visual threat, which can come centrally or peripherally, is a gross way to ascertain vision and field defects. The ophthalmoscopic exam needs to be repeated frequently to look for papilledema, which supplements intracranial pressure monitoring. The motor examination is limited to observation of spontaneous movement and passive range of movement for muscle tone. Sensory examination is limited to applying noxious stimuli, often to gauge level of consciousness, rather than test for distribution of sensory loss. Criteria for brain death can be found in the Chap. 365, "Coma".

In the Office

The priorities are *screening, diagnosis, and prevention*. For the busy pediatrician, developmental screening is easiest with parent-answered questionnaires, filled out prior to the visit or in the waiting room. Equipping the examining room with developmental toys, or having a playroom, enhances the "child friendliness" of the doctor's office.

Primary care physicians need to become familiar with school and community resources for early intervention, preschool early education, rehabilitation facilities with multidisciplinary services like physical therapy, occupational therapy, and speech and language therapy, parent education and support groups, and consumer organizations in the USA like the Epilepsy Foundation, the Muscular Dystrophy Association, Children and Adults with Attention Deficit Disorder, the Tourette Syndrome Association, or their equivalents in the rest of the world.

Perspectives

Common diseases are common, and physicians should think of these first, before looking for exotic or rare causes.

However, what is common and what is rare depends on which part of the world one practices. Subacute sclerosing panencephalitis is endemic in Turkey, India, and the Philippines, while so rare to the point of near extinction in North America. Glutaric aciduria Type 1 is a relatively common organic aciduria in Saudi Arabia, while relatively rare in North America (except among the Amish) and Europe. Tuberculomas are common in South and Southeast Asia, while a rarity in North America. Genetic neurometabolic diseases are common in the Middle East, while rare in North America. The neurologic complications of AIDS may be seen more frequently in Africa, where HIV is still an epidemic and where the latest combination of drugs is not highly available. Neurocysticercosis is much more common in Central and South America, than in North America. Seizures and epilepsy, headaches, and cerebral palsy are common neurological problems in children all over the world. A relatively rare disease, spinal muscular atrophy, is still the most common neuromuscular disease of infancy and early childhood throughout the world.

In developed countries, where the premium on education as a means of upward mobility in society is high, ADHD, learning and neurobehavioral problems take up a large portion of the office practice of pediatricians. In developing countries where the health care mind-set, in providers as well as patients, is often crisis-oriented, and centers around life and death issues, developmental neuropsychiatric disorders may receive short shrift.

The art of medicine begins with attentive listening to the patient and family. The primary care physician needs to inquire about the psychosocial and environmental circumstances in which they live, their dietary habits, and, in genetic diseases, elicit a detailed family history and draw a three-generation family pedigree. A 10+ systems review completes the history taking. This brings into conscious differential diagnosis the possibility that symptoms attributable to the nervous system are manifestations of a systemic disease. Symptoms in other systems, together with neurologic signs and symptoms can bring to mind a syndrome or disease involving multiple systems.

An important trend that will make it easier for primary care practitioners in office practice to care efficiently

for their patients is the use of hospitalists devoted entirely to inpatient care, freeing more time for the office-based physician to practice preventive measures and counseling. Another growing trend is the use of electronic medical records, which will reduce medication errors, avoid duplication in laboratory studies and investigations, and ease communication between specialists and primary care physicians.

Developmental Screening Tests

Pediatrics, 2006 (July), 118(1):413 Table of developmental screening tests.

Medical Diagnostic Thinking

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http://www-personal.umich.edu/~leber/c-n/ (This site aims to coordinate the available internet resources in Child Neurology, both for professionals and patients.)
www.genetests.org (tells you which clinical and research labs in the world are doing genetic tests)
www.clinicaltrials.gov (for ongoing studies)
www.cochrane.org/reviews (for evidence-based medicine)
www.mdconsult.com (requires subscription)
www.epocrates.com (resource for drug dosages, adverse reactions, drug interactions; for Epocrates Online, requires registration)
www.medicalive.net Pediatric Neurological Examination—Introduction (09:34) and Pediatric Neurological Examination—3 months (09:16), Google Videos

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359 Congenital Brain Malformations and Hydrocephalus

John N. Gaitanis

Classification

This chapter arranges cortical malformations according to the earliest embryological stage in which the abnormality has its origin. Yet, this is an artificial distinction since the stages of cortical development overlap in time and lack discrete boundaries. Moreover, some gene defects exert influence in more than one developmental stage. Thus, the classification system presented here will undoubtedly be modified as understanding of these conditions evolves.

Overview of Embryology

The brain and spinal cord form from the dorsal aspect of the embryo in the third and fourth weeks of gestation through neurulation, the process of neural tube formation. In the fifth and sixth weeks, prosencephalic development, the process by which the brain takes shape, begins. Cortical formation in humans spans weeks 8–24 of gestation and can be divided into stages of cell proliferation (both neural and glial precursor cells are formed), neuronal migration (cells travel to their designated destination), and cortical organization (cell networks are determined). Myelination is the final step of brain development and continues well beyond birth. As noted above, assigning strict temporal divisions is misleading, since different stages take place concurrently.

Disorders of Neurulation

Fusion of the neural tube begins at the level of the hindbrain (medulla and pons) and proceeds rostrally and caudally. Failure of rostral fusion results in dysraphic states of the brain (anencephaly and encephalocele), and incomplete caudal fusion causes spinal dysraphism (myelomeningocele). The anterior end of the neural tube closes by 24 days and posterior closure happens by day 26. Disorders of neurulation differ in severity depending on the timing of the disruption. The most severe disorder, craniorachischisis totalis, in which the brain and spinal cord fail to develop because of a complete absence of neurulation, occurs no later than 20–22 days of gestation. Anencephaly, a complete failure of anterior neural tube closure resulting in an absence of brain formation, occurs no later than 24 days. Encephalocele, a restricted failure of anterior neural tube closure, happens around day 26. Likewise, myelomeningocele, a restricted failure of posterior neural tube closure, also occurs by day 26.

Myelomeningocele is the most clinically important disorder of neurulation since patients with it usually survive. Its incidence in the United States is approximately 0.2–0.4 per 1,000 live births. The neurological features of myelomeningocele relate to the level of involvement, presence of hydrocephalus, and other associated malformations.

Impairment of motor, sensory, and sphincter function relates directly to the level of involvement. Ambulation is one of the most important clinical concerns, and retained strength of the iliopsoas and quadriceps muscles are required for walking. Lesions at or below S1 rarely affect ambulation, whereas higher defects, above L2, almost always do. Among patients with intermediate lesions (L3, L4, L5), approximately half will walk, but braces or other assistive devices may be required.

Hydrocephalus is seen in approximately 90% of patients with lumbar lesions. The usual signs of increased intracranial pressure (lethargy, irritability, limited upward gaze, rapidly expanding head circumference) are not essential for diagnosis and are present in only 15% of newborns with myelomeningocele. If clinical signs are present, they usually develop 2–3 weeks after birth and are almost certain to be present by 6 weeks. Their frequent absence necessitates serial neuroimaging for the prompt diagnosis of hydrocephalus. Infants demonstrating hydrocephalus at birth require shunt placement immediately following myelomeningocele closure. The closure stops CSF leakage, and can therefore worsen hydrocephalus if a shunt is not placed.

When myelomeningocele and hydrocephalus are combined with inferior displacement of the medulla and lower

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cerebellum through the foramen magnum, it is termed the Arnold–Chiari malformation (Chiari type II). Other features of this disorder include elongation and thinning of the upper medulla and pons and bony defects of the foramen magnum, occiput, and upper cervical vertebrae. Brain stem and cortical malformations are common. Resulting brainstem dysfunction is a significant cause of morbidity and mortality. It may result in apnea, stridor, cyanotic spells, and dysphagia. The overall mortality rate in patients with brainstem dysfunction is 21%, but when all four symptoms are present, the mortality rate is as high as 60%. Cortical malformations are an important cause of morbidity such as intellectual disability and epilepsy. They are also very common in patients with Arnold–Chiari malformations, being present in as many as 92%.

Disorders of Prosencephalic Development

Prosencephalic development is the process by which the forebrain takes shape. It begins during the fifth week and continues through the second and third months of gestation. Prosencephalic development influences formation of the face, so severe disruptions at this stage result in facial anomalies. Development of the forebrain can be divided into three stages: formation, cleavage, and midline development. The resulting disorders depend on the stage affected.

Holoprosencephaly

In holoprosencephaly (HPE), disruption of the roof plate and absence of hemispheric separation result in a single, large, forebrain ventricle. In its most severe form, alobar HPE, the brain is a single spherical structure with a common ventricle and a malformed cortical mantle. The optic nerves are dysplastic and the olfactory bulbs and tracts may be absent. The hypothalamus does not separate normally into two halves. Facial anomalies, ranging from cyclopia to a single central incisor, are observed. Less-severe forms, semilobar and lobar HPE, have milder degrees of the same anomalies. For instance, in semilobar HPE, the frontal and parietal lobes remain fused and the interhemispheric fissure is only present posteriorly. In contrast, with lobar HPE most of the left and right hemispheres and lateral ventricles are separated and fusion is seen only at the most ventral aspect of the frontal lobes.

Clinical severity relates to the degree of structural change. Neurological dysfunction inversely correlates with the degree of hemispheric separation, with less separation resulting in greater impairment. Endocrinopathies correlate with the severity of hypothalamic separation. Associated cortical malformations frequently cause epilepsy, which is often refractory. Careful attention to neuroimaging is necessary for providing an accurate prognosis.

HPE is a heterogeneous condition, with both genetic and environmental causes. The most common environmental cause is maternal diabetes, which carries a 1% risk of HPE. Cytogenetic abnormalities account for approximately 25–50% of cases, with trisomy 13 and 18 being the most common. Single-gene mutations are found in roughly 25% of patients. Several genes are known to be causative. The first gene discovered, the sonic hedgehog gene at 7q36, is the most common. The evaluation typically begins with a karyotype followed by molecular genetic testing if the karyotype is unremarkable.

Abnormalities of midline prosencephalic development are less severe than HPE. They include agenesis of the corpus callosum and septo-optic dysplasia (SOD). Agenesis of the corpus callosum can be either partial or complete. With partial agenesis, the posterior portion is more affected. It is commonly associated with other brain anomalies including Arnold–Chiari II malformations and neuronal migration disorders. SOD, on the other hand, is characterized by optic nerve hypoplasia in combination with the absence of the septum pellucidum and pituitary dysfunction. Clinically, it presents with visual impairment, endocrinopathies, or both. The causes are heterogeneous, including both environmental and genetic etiologies (*Fig. 359.1*).

Disorders of Neuronal Proliferation

Neuronal proliferation takes place between the second and fourth months of gestation. Neurons and glia have their origin in the ventricular and subventricular zones. In the earliest phases of neuronal proliferation, neuronal-glial stem cells divide to form further stem cells. Later, stem cell division becomes asymmetric so that one daughter cell is postmitotic, while the other remains a stem cell. Eventually, fewer and fewer stem cells are produced and all of the neurons within the proliferative unit are postmitotic. Abnormal neuronal proliferation results in conditions characterized by too many or too few neurons.

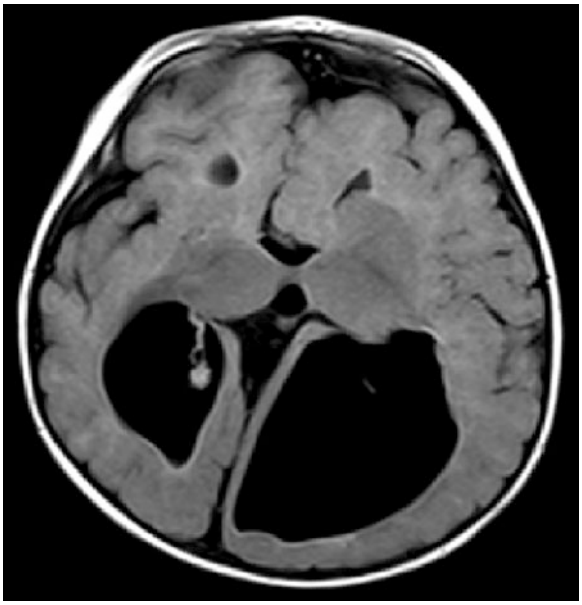

Figure 359.1
Agenesis of the corpus callosum with colpocephaly

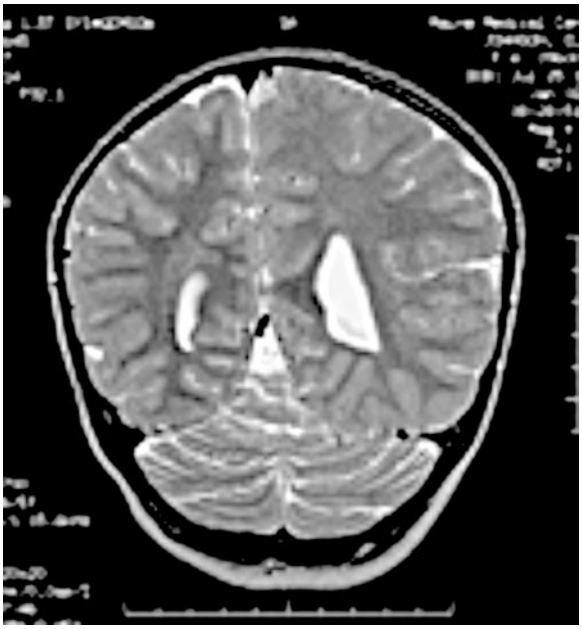

Figure 359.2
Hemimegalencephaly

Decreased Proliferation

Microcephaly/microlissencephaly primary microcephaly (microcephaly vera) is diagnosed when the head circumference at birth is three or more standard deviations below normal. Primary microcephaly is a heterogeneous condition and can be caused by in utero brain injury or from a genetically determined reduction in neuronal proliferation. Most genetic forms are recessively inherited. Microcephaly is sometimes associated with a more simplified gyral pattern or, in severe cases, with a smooth cortex, termed microlissencephaly. Seizures and global developmental delays are uniformly present.

Disordered Proliferation

Hemimegalencephaly

When there is enlargement of just one cerebral hemisphere, it is termed hemimegalencephaly. It probably results when a disturbance of cellular differentiation and proliferation interacts with the genetic expression of body symmetry. In addition to increased size of the affected hemisphere, neuroimaging may reveal abnormal gyration, ventriculomegaly, and increased T2 signal of the white matter. Histology reveals disorganized cortical lamination, subcortical heterotopia, and large, dysmorphic neurons, termed balloon neurons. The opposite hemisphere may be normal or have mild dysplasia and heterotopia. All patients have epilepsy, and hemispherectomy is often required for intractable cases (*Fig. 359.2*).

Abnormal neuronal differentiation/maturation in abnormalities of maturation or differentiation, neurons exhibit immature or glial features. Balloon neurons contain abnormally large amounts of cytoplasm and stain for both neuronal and glial markers, indicating a failure to commit to a specific cell lineage. Balloon and dysplastic neurons are seen in cortical dysplasia and in the cortical hamartomas of tuberous sclerosis complex. Evidence of disrupted neuronal migration, including disorganized or absent lamination, malpositioned neurons, and heterotopic neurons within the white matter, are also present in these disorders. Such conditions must, therefore, involve abnormalities of both maturation and migration, indicating that dysplastic and balloon neurons lack the cellular machinery to migrate properly through the cortical plate.

Tuberous Sclerosis Complex

Tuberous sclerosis complex (TSC) is a multisystem, dominantly inherited condition. It has a high rate of

spontaneous mutations and approximately half of all patients do not have an affected parent. Two genes have been cloned for TSC. Both result in similar clinical features. The TSC1 gene, located on chromosome 9q34, codes for a novel protein called hamartin, which indirectly links the cell membrane to the cytoskeleton. TSC2, located at chromosome 16p13.3 encodes for the protein tuberin, which may function in cellular signaling pathways. Hamartin and tuberin interact together as part of a larger protein complex which functions to negatively regulate mTOR. When tuberin or hamartin is nonfunctional, mTOR is active, resulting in increased cell growth and proliferation. Rapamycin acts as an mTOR inhibitor and has shown efficacy in the treatment of subependymal giant cell astrocytomas in patients with TSC (*Fig. 359.3*).

The clinical diagnosis of TSC is divided into three subheadings: definite, probable, and suspect based on the type and number of abnormalities. The clinical expression of TSC is based on the location and severity of organ involvement. The primary targets are the skin, kidneys, heart, and central nervous system. Hypopigmented macules are the most common skin lesions and are present in as many as 90% of affected patients. Adenoma sebaceum, an angiofibromatous lesion occurring in a butterfly distribution about the nose and cheeks, is seen in 50%. Other skin lesions include the shagreen patch over the lumbosacral region, café au lait spots, and subungual fibromas. Tumors are common and include renal angiomyolipomas, cardiac rhabdomyomas, and retinal hamartomas.

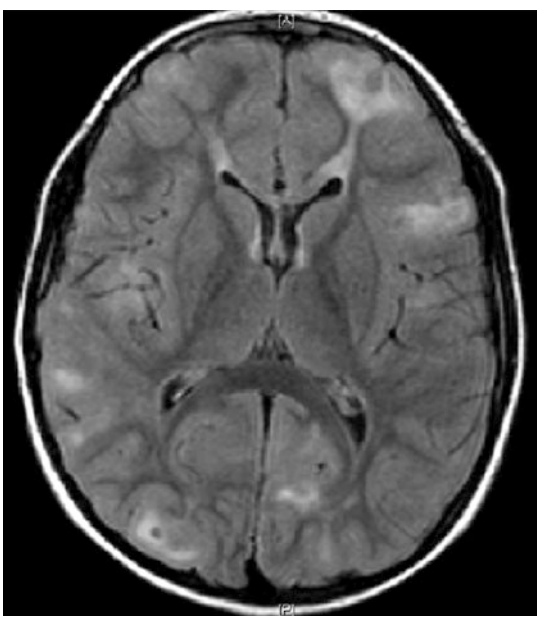

Figure 359.3
Tuberous sclerosis in a 4-year-old girl with multiple, bilateral cortical tubers

In the brain, the characteristic features include cortical hamartomas (cortical tubers), subependymal hamartomas (subependymal nodules), and giant cell astrocytomas. Cortical tubers are firm and nodular, with a consistency resembling the potato tubers for which they are named. On MRI, cortical tubers appear as enlarged, atypically shaped gyri with abnormal signal intensity in the subcortical white matter. Microscopically, they resemble focal cortical dysplasia with disorganized lamination and balloon neurons. Beneath the cortex, subependymal nodules are at risk of transforming into subependymal giant cell astrocytomas.

Cortical tubers often result in epilepsy. Under 1 year of age, infantile spasms predominate. Vigabatrin is a particularly effective treatment for infantile spasms in TSC patients, and is widely considered to be first-line therapy in this setting. Later in life, generalized tonic–clonic seizures predominate, but simple and complex partial seizures are also common. Refractory epilepsy is a common problem in TSC; surgical resection of an epileptogenic cortical tuber is possible, and is most successful when a single epileptogenic area is identified.

The presence of epilepsy is a predictor of cognitive impairment – this is particularly true when seizures develop under 2 years of age or when infantile spasms occur. Cognitive impairment can also be predicted by the burden of cortical tubers, with more tubers correlating with greater impairment.

Autism is common in patients with TSC. It is more likely to develop in those with temporal tubers, seizure onset before age 3, or a history of infantile spasms. Attention, language, and behavioral problems are also observed. In general, TSC patients who are cognitively normal are seizure free and vice versa.

Subependymal nodules are common in TSC and consist of periventricular collections of small cells resembling candle drippings. In some instances, they transform into subependymal giant cell astrocytomas (SEGAs). SEGAs typically develop in the region of the foramen of Monro and can obstruct cerebral spinal fluid flow, resulting in hydrocephalus. Presenting symptoms include headache, vomiting, obtundation, or focal neurological deficits. Early recognition is important. Incompletely calcified periventricular nodules greater than 5 mm and nodules demonstrating gadolinium enhancement are at greater

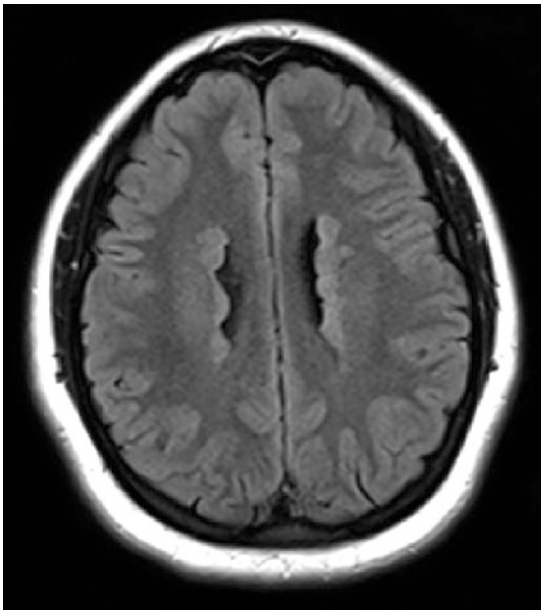

Figure 359.4
Periventricular nodular heterotopia in a 20-year-old woman

risk of transformation. Yet, the most important criterion for recognizing SEGAs is a progressive enlargement of the lesion. Neuroimaging is recommended prior to 2 years to screen for such lesions, and yearly follow-up may be necessary if suspicious periventricular nodules are observed (*Fig. 359.4*).

Focal Cortical Dysplasia

Focal cortical dysplasia (FCD) is essentially indistinguishable from the cortical tubers of TSC. Macroscopically, the lesions display wide gyri and blurring of the gray–white junction. Microscopic findings include disordered cortical lamination with dysplastic neurons and balloon cells. The underlying white matter is hypomyelinated and contains radially oriented balloon cells. The histology of FCD resembles tuberous sclerosis to such an extent that they have been postulated to be the same entity, with FCD representing a forme fruste of TSC. On MRI, FCD are slightly hyperintense on T2-weighted sequences. The hyperintense regions have a funnel-shaped appearance, with the base of the funnel oriented toward the pial surface and the tip extending to the white matter. Seizures resulting from FCD are commonly refractory to pharmacotherapy and surgical resection may be required to control the seizures.

Hypomelanosis of Ito

The brain malformations of hypomelanosis of Ito (HI) include abnormalities of neuronal differentiation (cortical dysplasia and hemimegalencephaly) and migration (heterotopia and polymicrogyria). The skin lesions of HI consist of whorls and streaks of decreased pigmentation, which follow the lines of Blaschko. There are no preceding inflammatory or vesicular eruptions as in incontinentia pigmenti, and the palms, soles, and mucous membranes are spared. The skin lesions are more prominent over the ventral surface of the torso and on the flexor surface of the extremities. They may be unilateral and exibit a midline cutoff. In patients with HI and hemimegalencephaly, the skin lesions are contralateral to the brain abnormality. Systemic manifestations include ophthalmologic, cardiac, musculoskeletal, and genital anomalies.

The neurological manifestations include epilepsy and mental retardation. Generalized tonic–clonic seizures are the most common, but infantile spasms, focal, and myoclonic seizures are also observed. Autistic behaviors are sometimes seen and are usually present in children with epilepsy. Pathology may reveal polymicrogyria, heterotopia, cortical dysplasia, or hemimegalencephaly. The etiology of HI is likely to be heterogeneous since several different choromosomal abnormalities have been associated with it.

Schizencephaly

The term "schizencephaly" refers to a cleft extending between the pial and lateral ventricular surfaces. Lining the cleft on both sides are polymicrogyria (abnormally small gyri). The presence of polymicrogyria helps distinguish this malformative lesion from the destructive disorder porencephaly, which has a similar appearance. Schizencephaly is heterogeneous in appearance. Lesions vary in size from small close-lip to large open-lip malformations. They may occur in one or both hemispheres. Possible etiologies are similarly heterogeneous. Environmental causes include fetal hypotension, exposure to organic solvents, and viral infections. Vascular anomalies have also been reported in association with schizencephaly. Familial cases exist, indicating a genetic mechanism in some patients. Mutations in the homeobox gene EMX2 have been reported in some cases.

The clinical severity relates to the degree of structural involvement. Unilateral clefts commonly present with hemiparesis and mild cognitive delay. Bilateral clefts, on the other hand, are associated with quadriparesis and

significant cognitive impairment. Likewise, the size of the lesion is an important determinant of outcome. For example, patients with large or medium open-lip schizencephaly display significantly worse motor and intellectual function than patients with close-lip or small open-lip lesions. The severity of epilepsy, however, is generally unrelated to the structural findings.

Disorders of Neuronal Migration

Neuronal migration takes place between the third and fifth months of gestation. During migration, postmitotic neurons move from the ventricular and subventricular layers to their final sites within the cerebral cortex. Migration occurs in radial (perpendicular to the pial surface) and tangential (parallel to the pial surface) fashions.

Heterotopia

Heterotopia are collections of ectopic neurons located outside of the cortex. Unlike cortical dysplasia, the neurons within heterotopia are normal. On imaging, heterotopia are isointense with normal gray matter, lacking the abnormal signal intensity seen in dysplasia. The cortex overlying heterotopia is abnormally thin with shallow sulci.

Familial periventricular heterotopia (PH) are characterized by periventricular nodules of neurons resting beneath an otherwise normal-appearing cortex. In PH, some neurons migrate fully to form a normal-appearing six-layer cortex, while others have a complete failure of migration and remain in nodular collections within the subependymal region. Most patients have normal intelligence, but epilepsy is common and generally develops in the midteenage years.

Familial PH commonly displays X-linked dominant inheritance and is lethal in hemizygous male embryos. Approximately half of patients have a de novo mutation. Because epilepsy is mild or absent in approximately one-quarter of all patients, a family history is not always confirmed until neuroimaging of a patient's mother is performed. PH results from a mutation of the filamin A (FLNA) gene, which encodes a large actin-binding protein involved in structuring actin networks at the leading edge of motile cells.

Lissencephaly

Lissencephaly refers to a paucity of normal gyri and sulci resulting in a "smooth brain." It is a heterogeneous condition, which is traditionally divided into two pathologic subtypes: classical (type I) and cobblestone (type II). Radiographically, the cortex appears smooth in both types, but beyond that, few similarities exist. Classical lissencephaly results from an arrest of neuronal migration, whereas cobblestone lissencephaly results from overmigration. In both cases, lissencephaly is associated with epilepsy and severe developmental delay (*Fig. 359.5*).

Classical Lissencephaly (Agyria–Pachygyria Complex)

Most patients with classical (type I) lissencephaly have a combination of agyria (a total absence of gyri) and pachygyria (a reduced number of abnormally large gyri). Radiographically, the surface of the brain appears smooth in agyria, with diminished white matter and shallow sylvian fissures. In pachygyria, gyri are reduced in number and are abnormally broad and flat. Microscopically, agyria has a disorganized outer cortical layer and a thick layer of ectopic neurons in the periventricular region, whereas pachygyria displays better cortical organization. Clinical severity is largely related to the degree of structural abnormality, with greater gyral simplification resulting

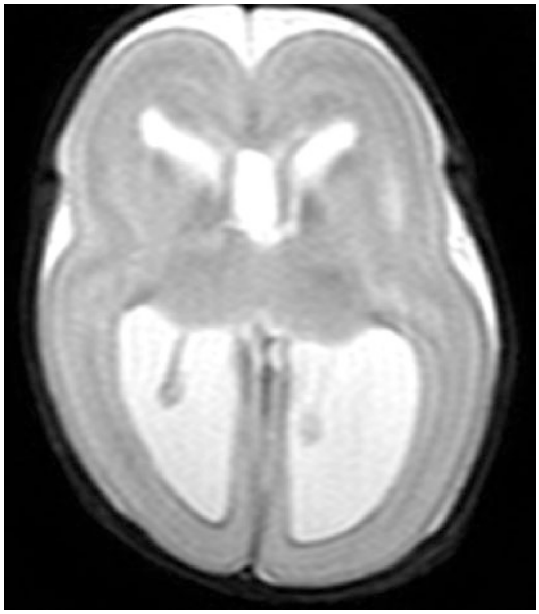

Figure 359.5
Classical lissencephaly in a patient with Miller–Dieker syndrome

in greater neurological impairment. In agyria, neurodevelopmental disabilities are severe. Patients exhibit mental retardation, spastic quadriparesis, and microcephaly. Epilepsy is universal and infantile spasms are a particularly common seizure type. In patients with pachygyria, epilepsy and developmental delays are common but are less severe. Electroencephalography reveals characteristic, high-voltage beta activity.

Classical lissencephaly is most commonly caused by a disruption of the platelet-activating factor, acetylhydrolase gene (PAFAH1B1; also known as LIS1) located on chromosome 17p13.3. Almost all patients have spontaneous, heterozygous deletions of LIS1, which are not present in the parents. The risk of having a second affected child is therefore low. When a large deletion occurs, other congenital anomalies (craniofacial, renal, cardiac, or gastrointestinal malformations) can result and together are termed the Miller–Dieker syndrome.

Abnormalities of the doublecortin (DCX or XLIS) gene, located on the X chromosome, are also known to cause classical lissencephaly. In hemizygous males, the phenotype is nearly indistinguishable from LIS1. Yet, in heterozygous females, a disorder termed double cortex (DC), also known as subcortical band heterotopia, results (*Fig. 359.6*). In DC, the outer cortex displays normal six-layered architecture, but an inappropriate accumulation of neurons exists in the subcortical white matter. Random inactivation of the X chromosome accounts for this pattern. Half of the neurons express a normal copy of the doublecortin gene and undergo normal migration, whereas the other half express the mutant copy and remain arrested in the subcortical white matter. In males, only one X chromosome exists, so the mutation affects all neurons. Hence, the more severe phenotype of classical lissencephaly occurs in males.

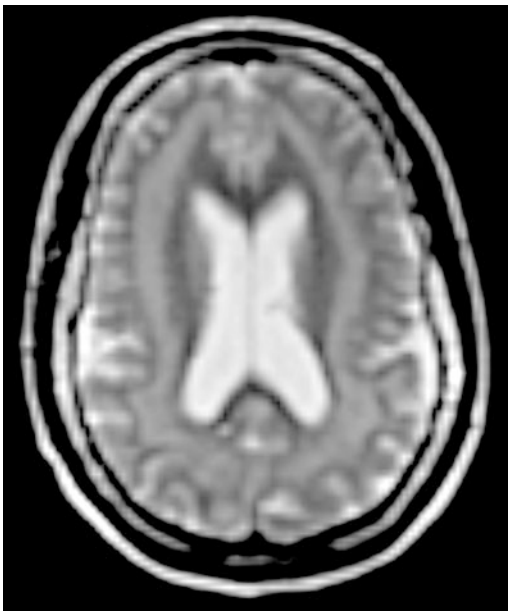

Figure 359.6
Double cortex (subcortical band heterotopia) in a 6-year-old girl with a heterozygous mutation of the doublecortin gene

Cobblestone (Type II) Lissencephaly

Cobblestone lissencephaly develops from an overmigration of neurons beyond the pial surface and onto the overlying subarachnoid tissue. Cobblestone lissencephaly is associated with congenital muscular dystrophy and eye abnormalities in Fukuyama congenital muscular dystrophy (FCMD), Walker–Warburg syndrome (WWS), and muscle–eye–brain disease (MEB). These disorders result from an impairment of glycosylation. They affect O-mannosylation, which is important to brain, nerve, and skeletal muscle, accounting for the distribution of involved tissues in these disorders.

Of all three disorders, WWS has the most severe phenotype and is often fatal in the first year of life. Genetically, WWS is recessively inherited. MEB is also an autosomal recessive condition and is most prevalent in Finland. The clinical severity is intermediate to WWS and FCMD as is the radiographic appearance. FCMD is the mildest of the three disorders. It presents with hypotonia and global developmental delays. Seizures develop in the first year of life in half of patients. FCMD is seen primarily in Japan, where 94% of the affected individuals share a common haplotype, indicating a single founder in the Japanese population. Patients who are homozygous for the founder mutation have a higher residual activity of fukutin and a milder phenotype than patients with a spontaneous point mutation on the second allele (compound heterozygotes).

Symmetric Polymicrogyria

Polymicrogyria is thought to develop at the latest stages of neuronal migration. It often results from external causes such as intrauterine cytomegalovirus infection or impairments in placental perfusion. Genetic causes also exist and tend to result in focal but symmetrical lesions in the frontoparietal, perisylvian, or parieto-occipital regions. Epilepsy and cognitive delays are common among all of

the syndromes; additional symptoms depend upon the specific areas involved.

Disorders of Myelination and Cortical Organization

Cortical organization and myelination are the final steps of brain development and continue well after birth. Abnormalities at these stages may be less obvious on neuroimaging than earlier malformations, but they nonetheless have profound effects. Cognitive and motor impairments are associated with both abnormalities; spasticity is more specific to problems with myelination, whereas hypotonia is more likely in disorders of cortical organization.

Cortical organization begins in the fifth month of gestation and continues through the first several years of life. Abnormalities of cortical organization are commonly associated with mental retardation. The most consistent anatomical correlates of mental retardation are dendritic anomalies, such as deficient branching. Such abnormalities cannot be detected by neuroimaging, explaining why many patients with mental retardation have normal MRIs.

Myelination begins in the second trimester of pregnancy and continues into adulthood. Myelination is impaired when oligodrendrocytes are deficient in number or in myelin deposition around axons. Insufficient oligodendrocytes are observed in periventricular leukomalacia, in which differentiating oligodendroglia are injured and therefore unable to produce myelin. Other disorders, such as hypothyroidism, malnutrition, and organic acidopathies, cause functional impairment of myelination. Primary disturbances of myelination are distinguished from leukodystrophies in that leukodystrophies result from injury to previously myelinated axons.

Neurofibromatosis Type I

The primary disorder in neurofibromatosis relates to oncogene regulation and tumor formation. Given the white matter abnormalities in NF, it is categorized here as a disorder of myelination, but increased gray matter volume is also seen, highlighting a larger disorder of brain overgrowth in neurofibromatosis.

Neurofibromatosis type 1 (NF1), also known as peripheral neurofibromatosis, is an autosomal-dominant, single-gene defect affecting multiple organ systems. The NF1 gene localizes to chromosome 17q11.2 and encodes the protein product neurofibromin. The incidence of NF1 ranges between 1 in 3,000 and 1 in 4,000. Approximately 50% of patients with NF1 lack a family history and likely represent new mutations. The diagnosis is based on NIH consensus criteria and requires two or more of the following: six or more café au lait spots (0.5 mm or larger in prepubertal and 1.5 mm or larger in postpubertal individuals), two or more neurofibromas of any type or one plexiform neurofibroma, axillary or groin freckling, two or more Lisch nodules, optic nerve glioma, dysplasia of the sphenoid bone or long bone cortex, or a first-degree relative with NF1. Of these features, café au lait spots are the most easily recognized and are often the presenting feature of the disease. They are evenly pigmented macules, which increase in size and number with age. They may be the only sign present in infancy, making a definitive diagnosis difficult to establish until later in life.

In childhood, the most common complication of NF1 is cognitive impairment. A broad range of effects are seen including low IQ, behavioral problems, and learning disabilities. IQ scores in NF1 patients have a bimodal distribution; some children have intellectual impairment, whereas others do not. This separation may have its basis in the white matter T2 hyperintensities, also known as unidentified bright objects (UBOs), common to NF1 patients. They represent dysplastic glial proliferation and aberrant myelination in the underdeveloped brain. When compared to children without T2 hyperintensities, those with the lesions have significantly lower mean values for IQ and language scores and significantly impaired visuomotor integration and coordination. T2 hyperintensities in childhood are also a predictor of cognitive dysfunction in adulthood. A correlation is also seen between increased white matter volume and visual-perceptual deficits, suggesting that brain overgrowth is a factor in the associated cognitive deficits.

Tumors and malignancies are common in NF1, and are a major cause of morbidity. Neurofibromas, the tumors for which the disorder takes its name, are peripheral nerve sheath tumors with unpredictable growth patterns. They are benign tumors without risk of malignant transformation, and typically develop in adolescence. Although they are unlikely to cause neurological deficit, spinal neurofibromas arising from the dorsal nerve roots can lead to severe pain. Plexiform neurofibromas, on the other hand, are more likely to be present at birth. They can be found anywhere within the body and cause a variety of presenting symptoms depending on their location. Serious complications include pain, spinal cord compression, and spread to the orbit with resulting sphenoid wing

dysplasia and pulsating exophthalmos. Plexiform neurofibromas can undergo transformation to malignant peripheral nerve sheath tumors.

Optic nerve gliomas are pilocytic astrocytomas involving the optic nerve, chiasm, or tract. They usually develop prior to age 7 and can be insidious in their onset. Yearly ophthalmologic assessments are important for early diagnosis and management of these tumors. Abnormalities on the ophthalmologic exam necessitate an MRI. Other malignancies observed in NF1 include CNS tumors (particularly astrocytomas), pheochromocytomas, and leukemia. Given the prevalence of tumors in NF1, it should come as no surprise that neurofibromin functions as a tumor suppressor protein, the loss of which promotes tumor formation.

The workup for NF1 is aimed at the early identification of potential complications, with tumor formation being the main concern. The American Academy of Pediatrics Committee on Genetics recommends yearly physical examinations and ophthalmologic assessments. The physical examination focuses on the organ systems involved. The skin is screened for new neurofibromas or plexiform neurofibromas. Blood pressure is followed to assess for renal or endocrine abnormalities. A skeletal examination looks for pseudoarthrosis of the tibia, bowing of the long bones, scoliosis, and orbital defects. The neurological examination may reveal macrocephaly, learning disabilities, or cognitive impairment. The ophthalmologic evaluation helps exclude optic nerve gliomas, choroidal hamartomas, and Lisch nodules.

Neurofibromatosis Type II

Like NF1, neurofibromatosis type II (NF2) is an autosomal-dominant, single-gene deficit, which, in NF2, localizes to chromosome 22. The gene product, merlin, also has tumor suppressor function. Tumors and malignancies are, therefore, common in both conditions. Beyond that, few similarities exist. Café au lait spots are rarely seen in NF2 and neurofibromas are uncommon. NF2 is much less common than NF1, with an incidence of only 1:30,000–1:40,000.

Common tumors in NF2 include schwannomas (which are usually multiple), meningiomas, ependymomas, and gliomas. Vestibulocochlear schwannomas are particularly common and sometimes bilateral. Roughly half of NF2 patients present because of hearing loss, tinnitus, and vertigo resulting from a vestibulocochlear schwannoma. The peak age of diagnosis is the third decade. In children, ocular abnormalities are the most common presenting symptoms. These are caused by hamartomas of the retina, optic nerve sheath meningiomas, or juvenile posterior subcapsular lenticular opacities. Meningiomas at a young age should also raise a suspicion of NF2. Schwannomas and ependymomas may develop in the spine, in which case back pain and paraplegia may result.

Vascular Disorders

The following disorders result from vascular abnormalities, and therefore cannot be organized within the embryological classification presented above even though each results in developmental abnormalities of the brain.

Bilateral Parasagittal Parieto-Occipital Polymicrogyria

Unlike the other symmetrical polymicrogyria syndromes, bilateral parasagittal parieto-occipital polymicrogyria is unlikely to have a genetic basis. Of the patients described, none had a familial distribution. Given that the lesion occurs in a vascular watershed region, perfusion failure is postulated to be the cause. All patients develop seizures and cognitive abilities range from normal to mild retardation.

Incontinentia Pigmenti

Incontinentia pigmenti is a rare, X-linked, dominant, neurocutaneous disorder with the onset of skin changes in the first 6 weeks of life. The cutaneous disorder follows a characteristic evolution from vesicular to verrucous to hyperpigmented and finally atrophic changes. The vesicles and bullae from the original eruption in infancy later give rise to the characteristic swirling pattern of hyperpigmentation. Hair, nail, dental, and ophthalmologic abnormalities are also observed. Neurologically, these infants may develop epilepsy, mental retardation, microcephaly, spasticity, or ataxia. The gene for incontinentia pigmenti is NEMO (NF-kappaB essential modulator)/IKKgamma (IkappaB kinase-gamma) and is located on Xq28. NEMO is 200 kilobases proximal to the factor VIII locus and is important for immune, inflammatory, and apoptotic pathways. The disorder is lethal in most males, accounting for its 20:1 female-to-male predominance. Males with IP have been described, but commonly have

only a limited distribution. Somatic mosaicism is a likely mechanism in such cases.

Sturge–Weber Syndrome

Sturge–Weber syndrome is characterized by angiomata of the leptomeninges and skin. The cutaneous lesion, also known as a port-wine stain, typically involves the ophthalmic and maxillary distributions of the trigeminal nerve. The leptomeningeal angiomata may be either unilateral or bilateral, but unilateral lesions are more common. The specific neurological effects are dependent on the location of the lesion, which is most commonly parietal or occipital. Neurological impairment results from stasis and a vascular steal phenomenon. Laminar cortical necrosis with neuronal loss, gliosis, cerebral atrophy, and calcifications are seen histologically. The calcifications take on a classic train-track appearance on plain films and CT. MRI, if done, should be performed with gadolinium to allow for diagnosis of the angiomata. The clinical manifestations include hemiparesis, stroke-like episodes, mental retardation, epilepsy, and headaches. Epilepsy is present in 75–90% of patients, and the seizures are typically focal. Many patients have refractory epilepsy, in which case cortical resection or hemispherectomy are considered. An important non-neurological effect is glaucoma, which can occur at any age.

Conclusion

For children with disorders of nervous system development, there are few specific therapeutic interventions available beyond physical, occupational, and speech therapy and remedial education. Epilepsy resulting from brain malformations is often refractory to pharmacotherapy, but surgical resection of epileptogenic cortical malformations may be an option for some of these children. A crucial role for the treating physician is to provide counseling and guidance. This is particularly important in newly diagnosed children whose parents are burdened by uncertainty. A thoughtful, compassionate approach to the radiographic and genetic assessment can offer the parents insight into their child's condition, and the genetic evaluation is particularly important for purposes of family planning.

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360 Neonatal Neurological Disorders

William D. Brown · Mara G. Coyle

Introduction

At no time in life are the limitations of the neurological assessment more obvious than during the neonatal (0–28 days) period. The reflex hammer, light, and bell do no justice to the transformation taking place within the nervous system. Myelination exposes already present reflexes to the possibility of change and allows for new abilities to evolve, though the function of many unmyelinated systems is well established and acquisition of function is not always related to the occurrence of myelination. Within related functional systems, myelination generally progresses in a predictable pattern from the neuron along the axon in the direction of information flow, with the important exception of the optic system that proceeds in the reverse direction (see ❯ *Table 360.1*). In this context, the neurologist is frequently called upon to interpret the meaning of subtleties within the examination, and to divine prognosis from them. Rapid advancement in imaging techniques is allowing for more informed divination, but the use of technology to inform clinical judgment is necessarily imprecise.

This is not to say that the neurologist or pediatrician is without tools. Assessment of the neonate begins with an accounting of antecedent events that may or may not modify the clinical situation. Family history and the maternal medical history prior to pregnancy may be relevant. The quality of the gestational environment – maternal nutrition, exposure to prescription or over-the-counter medications, drugs of abuse, or physical trauma – should be assessed. Perinatal factors such as the use of forceps or vacuum extractors, the presence of a nuchal or knotted umbilical cord, placental abruption, or need for emergency caesarean section could be important to the neurological outcome. If cardiopulmonary resuscitation of the infant is required, a detailed chronological recitation of events should be reviewed.

Basic Physical Examination

The physical examination begins with simple observation, using the presence or absence of dysmorphic features or skeletal abnormalities, the facial appearance, and head shape and size to determine further actions. This examination is best performed during times of quiet wakefulness as is found between feedings although in the preterm or acutely ill neonate such an opportunity may not exist.

In order to interpret physical findings, accurate gestational age estimates are important. First trimester ultrasound examination is the most accurate way of estimating gestational age, with a range of error of 3 days. Additional methods used to estimate gestational age include the date of the mother's last menstrual period and the Dubowitz or Ballard examination, all of which have a range of error in the postnatal period of ± 2 weeks.

Healthy term infants will present a position of limb flexion while preterm or sick term infants are likely to appear more flaccid. Growth parameters should be documented at the time of delivery in order to determine if the infant is appropriate, small, or large for gestational age. This determination may direct the clinician to look for size-specific patterns of medical and neurological complications. Large for gestational age infants (LGA, birthweight >2 SD above the mean for age), for example, are at risk for hypoglycemia, polycythemia, and shoulder dystocia with or without brachial plexus injuries, while growth-restricted infants are at risk for long-term developmental and academic morbidities, including a fivefold to tenfold risk of death.

For those infants suspected of being small for gestational age (SGA, birthweight <2 SD below the mean for age), the occipital frontal circumference (OFC, measured using the middle of the forehead and the inion as reference points) will determine if they are symmetrically or asymmetrically growth restricted, an important distinction since variations in growth imply a risk for certain morbidities. Growth restriction affects up to 10% of all newborn infants, but it should be remembered that an infant designated as having intrauterine growth retardation can still be size-appropriate for gestational age.

When *symmetric* growth restriction is present (weight, length, and head circumference all <10th percentile for age) the cause is often related to chromosomal anomalies,

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Table 360.1
Correlation of brain and organ development with neurological function and gestational age in neonates

Gestational age (weeks)	Organ development	Brain development			Neurological function		
		Sulci and Fissures	Gyri	Myelination	Arousal	Examination	Reflexes
20–21		Rolandic, collateral superior temporal; Germinal matrix still increasing in size	Parahippocampal, superior temporal	Medullary and pontine MLF			
22				Mesencephalic MLF			
23				Medullary MLF, trapezoid body	Eyes tend to remain closed, opening briefly only in response to sustained noxious stimulation		
24	Surfactant formation begins	Pre- and postrolandic, middle temporal, interparietal, superior frontal, lateral occipital; Germinal matrix begins rapid phase of volume loss at 26 weeks, losing half of volume between 26 and 28 weeks of gestational age	Pre- and postrolandic, middle temporal, superior and inferior parietal lobules, superior and middle frontal, superior and inferior occipital, cuneus and lingual, fusiform	Inferior cerebellar peduncle, spinal trigeminal tract, pontine and mesencephalic lateral lemniscus, pontine medial lemniscus			
25				Pontine medial lemniscus		Extraocular movements present to Dolls' eyes maneuver	Extraocular movements present to Doll's Eye maneuver
26				Pontine and mesencephalic superior cerebellar peduncle		Blinks to light	
27	Pulmonary primitive alveoli appear			Parasagittal cerebellum		Response to noxious stimulus present	Pectoralis major reflex present
28		Inferior temporal, inferior frontal	Inferior temporal, triangular, medial and lateral orbital, callosomarginal, transverse temporal, angular and supramarginal, external occipitotemporal	Ansa lenticularis, amiculum	Eyes tend to remain closed, opening for prolonged periods of time with gentle stimuli; eyes open spontaneously	Sucking and swallowing but not breathing coordinated; resistance to passive limb manipulation minimal	Blinks or startles to sudden noise, rooting reflex present; palmar grasp present

29	Glomerular filtration rate 0.3–0.5 cm^3/min			Optic tract, capsule red nucleus			
30	Active alveolation begins; glomerular filtration rate 0.5–1.0 cm^3/min					Pupils may constrict to light	Cold calorics cause ipsilateral eye deviation
31							
32	Bowel motility allows passage of contrast through small bowel to colon;	Marginal, secondary superior, middle, inferior frontal, temporal, parietal, occipital, insular; germinal matrix involution nearly complete	Paracentral	Posterior limb internal capsule, optic chiasm	Eyes open spontaneously, with roving eye movements present; sleeping and waking periods are observable	Eyes closed as long as light shone in them; visual fixation present, pupils consistently constrict to light, spontaneous movements present; some lower extremity flexor tone present	Incomplete response to Moro
33							Achilles, patellar, biceps, thigh adductor, brachioradialis reflexes present
34				Corona radiata, mesencephalic corticospinal tract		Visual tracking present; sucking, swallowing, and breathing coordinated for limited oral feeding	
35				Transpontine middle cerebellar peduncle, pontine corticospinal tract, pyramid		Some visual pattern preference present	Tonic neck response present

Table 360.1 (Continued)

Gestational age (weeks)	Organ development	Brain development			Neurological function		
		Sulci and Fissures	Gyri	Myelination	Arousal	Examination	Reflexes
36	Bilirubin no longer found in amniotic fluid	Secondary transverse and inferior temporal and cingulate, tertiary superior, middle inferior frontal and superior parietal sulci; germinal matrix absent	Anterior and posterior orbital		Crying may accompany waking periods	Flexor tone present in upper and lower extremities; head remains briefly upright when held in sitting position	Head turning to noxious stimulation of face
37						Visual orientation to light, opticokinetic nystagmus present	Classic Moro reflex present; placing and stepping reflexes present. Palmar grasp strong enough to lift trunk off the bed
38				Cingulum, anterior limb internal capsule, rostral optic radiation and lateral mesencephalic peduncle, cerebellar hemisphere			
39							
40	Glomerular filtration rate (<24°) 2–3.5 cm^3/h; (>72°) 4–8 cm^3/h	Secondary orbital, callosomarginal, and insular, tertiary inferior temporal and superior and inferior occipital			Orients to both visual and auditory stimuli	Visual fixation and following present; acuity 20/150; flexion tone obvious; fists remain closed; little head lag when pulled to sit;	Symmetric unsustained ankle clonus and Babinski reflex present

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environmental toxic exposures especially alcohol, and intrauterine infections. These infants are at risk for neurodevelopmental delay, neurosensory deficits, and academic impairment.

Asymmetric growth restriction results in weight and length measures below the 10th percentile for age, but preserves head growth. This occurs in the last trimester and is usually associated with placental insufficiency. These infants are at a significant disadvantage with respect to growth potential and cognitive performance. More than 80% of these infants will "catch up" in their growth during the first year, but those who do not by age 2 years have an even chance of being short adults. For both symmetric and asymmetric growth-restricted infants, the ratio of head circumference to birth weight $\times$ 100 (cephalization index) has the most significant correlation with both neurodevelopmental status and cognitive performance by 10 years of age.

In addition to the OFC, the shape of the head should be assessed. Excess scalp edema, swelling, or subgaleal hemorrhage can contribute to the circumference so the OFC should be remeasured after their resolution. Head shape may also affect the circumference, as is seen in the various craniosynostoses: premature closure of the sagittal suture will result in dolichocephaly while early closure of the coronal sutures results in brachycephaly. The majority of children with these lesions do not have associated genetic syndromes. The presence of visible cutaneous tracts, dimples, or palpable subcutaneous masses should raise the suspicion of an encephalocele or tumor, especially when they are in the midline near the nasion or inion. The spine should be inspected to look for dimples, pimples, pits, and tufts of hair, with the level of suspicion for associated spinal dysraphism (lipomas, spina bifida, dermal sinuses, and tethered spinal cord) increasing with more rostral lesions.

Palpation of the skull is important when traumatic lesions such as a cephalohematoma, caput succedaneum, or skull fracture are suspected. The diamond-shaped anterior fontanel should be flat and its center gives way to gentle manual compression, while the borders of the triangular posterior fontanel may not always be appreciated particularly if the sutures are overriding. The presence of a large or bulging fontanel can suggest a skeletal dysplasia or increased intracranial pressure. The final assessment of the head should include the hair pattern. The location of the hairline (widow's peak, low hairline), absence or sparsity (alopecia), quality (wiry, curly, twisted), or color of the hair (gray, blonde, white forelock) is important to note, as these may be associated with genetic or metabolic disorders.

Evidence of minor malformations such as abnormally positioned or rotated ears or eyes, syndactyly, or polydactyly should suggest the possibility of a major systemic malformation since there is a 90% chance of a major malformation when three or more "minor" malformations are identified. When examining the mouth, particular attention should be given to the palate and tongue. A large tongue can be seen in multiple disorders with neurological implications including hypothyroidism, *Beckwith–Wiedemann Syndrome*, and lysosomal storage disorders, while fasciculations of the tongue can be seen in lower motor neuron disease such as Werdnig–Hoffmann (*spinal muscular atrophy, type I*). A high arched palate in a newborn implies hypotonia preceding delivery.

Dermatoglyphics are the dermal ridges on the palmar aspect of the digits, palms, and soles; when abnormal, a variety of syndromes are implicated. The two general categories of dermatoglyphic alterations are an aberrant pattern or unusual frequency or disruption of a typical pattern on the fingertips.

Organomegaly can be seen in infectious diseases as well as storage disorders. The skin exam is important when considering infectious illnesses (petechiae, purpura) or neurocutaneous disorders. Loose or redundant skin can be seen in the SGA infant with a paucity of subcutaneous fat, or in connective tissue disorders such as *Ehlers–Danlos Syndrome*. Disorders of skin color (hyperpigmented, hypopigmented, café-au-lait, nevi) may, depending upon their number or distribution, represent a multitude of diagnoses or be of no clinical significance. Vascular malformations such as the strawberry hemangioma may not always be evident right at birth, or be quite obvious. A port wine stain or capillary hemangioma on the face should always suggest diagnosis of leptomeningeal capillary venous angiomatosis, which can be associated with seizures or glaucoma.

The shape of the thorax may suggest the presence of neurological disease. A narrow superior thorax with a flared, wider base suggests the possibility of pulmonary hypoplasia and respiratory weakness associated with spinal muscular atrophy.

Evaluation of the extremities should include the presence or absence of contractures or arthrogryposis. Limitation of movement in utero can be due to a primary neurological abnormality (meningomyelocele, anencephaly, holoprosencephaly), a muscle disorder (fetal myopathies, myotonic dystrophy, muscle agenesis), a joint or tissue disorder (synostosis, lack of joint development, laxity of joint), or external constraint as is seen in twin or triplet pregnancies.

Neurological Examination

Level of Arousal

The neurological assessment is best performed without overhead lighting directly in the neonate's eyes, as this will in many cases preclude the examiner's ability to visualize the retina and optic disk, or to obtain papillary reflexes. If the infant will not open the eyes, then it will not be possible to make any statements about visual tracking or fixation or to record the presence or absence of even basic observations such as nystagmus or papillary responses. The notion of a level of arousal in a newborn infant does not have the same meaning as in an older infant, but Brazleton's descriptions of six states of arousal: (1) deep sleep (eyes closed, no spontaneous movements except for respirations, limbs flaccid), (2) quiet sleep (eyes closed, eye movements present rare spontaneous limb or head movements, limbs demonstrate some tone), (3) active sleep (frequent spontaneous movements, eyes closed), (4) quiet awake (eyes open, rare spontaneous movements), (5) active awake (eyes open, spontaneous limb movements), and (6) crying – are useful in consideration of an infant's arousal state. Most normal term infants tend to fluctuate between the active sleep and quiet awake states, with other states achieved only briefly or with stimulation. The infant with an encephalopathy, drug toxicity, or neonatal abstinence will tend to assume one of the other states, and be more difficult to coax to the quiet awake or active sleep states. Coaxing may require a soothing voice, dimming of the lights, a gentle touch, pacifier, swaddling, or pharmacological intervention; the difficulty or ease with which calming may be induced may also shed light on the infant's "state."

Habituation

Habituation is the extinction of an observed behavioral response to repetitive external stimulation and may be considered in the assessment of the neonate. A blinking response to light or glabellar tapping, withdrawal of the foot to stroking, or the sudden upper extremity extension and abduction response to noise (Moro reflex) are examples of reflex behaviors that are normally present. Repetition of the stimulus in a normal newborn will reliably produce a response over a limited number of trials (usually 4–8), but then the response disappears. Obligatory occurrence of the response beyond this is abnormal and suggests an impairment of neurological functioning, but should be considered in the context of the rest of the examination.

Eye Examination

Any attempts to examine the eyes should be done in a quiet, darkened room, with the intensity of the ophthalmoscope at the minimum to allow for adequate visualization; high intensity halogen light sources will simply produce lid closure, a resistant baby, and a frustrated examiner. The infant should be swaddled, recently fed if possible, and held in front of the examiner at a 45° vertical angle to facilitate spontaneous eye opening and looking. Retinal hemorrhages may occasionally be seen after a vaginal delivery; their presence is important to note along with the presence of a normal optic disk. Optic atrophy may be the first indication that a more significant neurological disorder such as septo-optic dysplasia may be present. Ipsilateral dilation of the pupil in response to noxious stimulation of the skin is the ciliospinal reflex and may be very useful to the examiner when the integrity of the spinal cord is in doubt as the pupillary dilation response will be absent at spinal segments below the level of the lesion.

Convincing demonstration of visual tracking may require a bright red or highly contrasting white and black object such as a ring target since visual acuity of the newborn is poor. A dimmed pinpoint or penlight light source moved across the visual field in a darkened room may also elicit a visual "grasping" reflex. The twisted end of a sterile cotton swab may be used when necessary to elicit a corneal reflex. Using the vertical axis of the examiner as a reference, clockwise or counterclockwise rotation of the baby will produce leftward or rightward deviation of the infant's eyes, respectively, for the duration of the rotation.

The Face

Useful landmarks are the nasolabial folds, angles of the mouth, and eye lids. Observation of facial symmetry should be performed during differing arousal states, with the quiet awake and crying states most useful. A common source of concern is drooping of the lower portion of the mouth, noted best when the infant cries. When this is the only abnormality on examination, the most likely explanation is hypoplasia or aplasia of the depressor anguli oris muscle of the *opposite* side rather than a central parenchymal or peripheral nerve injury. The presence of a triangular or persistently open mouth should suggest the possibility of a myopathy or muscular dystrophy. The palpebral fissure is the vertical distance between the upper and lower eyelids, and may be difficult to assess in the

recently delivered infant due to edema of the eyelids; attempts to pry the eyelids open will generally result in their eversion. When the eyes are open, the presence or absence of unilateral or bilateral ptosis should be combined with the eye examination to determine whether the ptosis is likely to be related to a focal brain stem or nerve injury rather than generalized weakness as is seen in maternally acquired or congenital myasthenia gravis. Pinching the toes may produce crying: this is a good opportunity to compare the symmetry of movement of both sides of the face as well as the nasolabial folds and forehead creases to the spontaneous facial movements of the awake infant at rest.

The Oropharynx

In utero movements of the tongue will tend to mold the hard palate into a gentle arch during gestation; when oropharyngeal or lingual muscle strength is deficient, the palate develops into a shape like a furrow with a high arch and narrowed distance between the maxillary alveolar ridges. Insertion of a finger into the mouth of a term baby will induce a sucking reflex wherein the finger is forced into the hard palate by the tongue and an undulating anterior to posterior movement of the tongue is combined with a suctioning action. The undersurface of the tongue is a good place to look for muscle fasiculations suggestive of anterior horn cell disease in the weak patient. Mechanical or sensory stimulation of the soft palate, posterior tongue, or superior oropharynx will produce coughing or gagging in the awake infant. The presence of a cleft in the soft or hard palate should alert the observer to the possibility of other midline malformations affecting the hypothalamus or pituitary when clinically suspected. The presence of a single midline incisor or the absence of the upper lip frenulum should raise suspicions that a disorder of prosencephalic development such as holoprosencephaly is present.

The Ear

The shape, size, and orientation of the auricles should be noted; the superior attachment of the ear should be tangential to a line extended from one lateral eye canthus to the other. Malformations of the ear should suggest the possibility of branchial arch anomalies and raise suspicions of accompanying malformations of the middle and inner ear. These may be easily confirmed by computed tomography of the temporal bones. The external auditory meatus receives sensory input from four nerves: the second and third cervical, trigeminal, and vagus nerves. The presence of aberrant sensory input from the vagus nerve may rarely account for unexplained coughing or gagging when the external auditory meatus is stimulated. Bedside tests of audition with a bell, shouting, or a striking of the bed with an open palm are unreliable predictors of intact hearing; any suspicions that a hearing deficit is present should be confirmed by auditory evoked potentials.

Motor Examination

No voluntary motor movements are possible in the newborn of any gestational age, so the traditional methods of assessing muscle strength may not be applied. All movements are involuntary, reflex, or spontaneous; it is the spontaneous movements that are most relevant to the condition of the nervous system. Small for gestational age and premature infants will normally have decreased muscle bulk which in turn affects the ability to hold up the head or resist traction maneuvers, and this may falsely suggest muscle weakness. When hypotonia is present, care must be taken not to assume that muscles must therefore have diminished strength, for both hypotonia and normal strength may be simultaneously present.

Traction maneuvers are the traditional method to assess motor tone in the newborn as well as to make a subjective estimate of relative muscle strength. In the lower extremity the malleoli are grasped between the thumb and first fingers with the baby supine, and the heel is gently lifted upward until the buttocks begins to leave the bed. The popliteal angle so generated is noted, and compared with normal values enumerated by Amiel-Tison for each gestational age. An angle less than specified suggests increased tone; greater suggests relative hypotonia. A similar procedure is possible for the upper extremities: the wrist is gently pulled upward until the shoulder comes off the bed, and the angle at the elbow estimated.

There is by necessity some subjectivity involved in these assessments of tone, leading some authors to question their usefulness. However, observation of posture alone does not always inform the examiner of the degree of muscle tone present since an assessment of tone (intrinsic resistance to passive movement offered by the ligaments, tendons, and muscles) requires actually moving the limbs. Spasticity (an increase in the degree resistance to passive movement when the velocity of induced movement is increased) is rarely present in the newborn, as its appearance implies a passage of time in weeks or months since the causative injury occurred; when marked hypertonia, rigidity, or spasticity is present, other causes such as

severe diffuse cerebral injury, meningitis, posterior fossa lesion, increased intracranial pressure, or the pharmacological abstinence syndrome should be suspected. Finally, hypertonia may be present because of excessive intrinsic muscle contractions seen with myotonic and paramyotonic disorders as well as hyperkalemic periodic paralyses.

Reflexes

Three general categories of reflexes are present in the infant: tendon reflexes, postural reflexes, and brain stem reflexes. Tendon reflexes are generally easy to obtain at the pectoralis, biceps, knee, and ankle jerks. In the term newborn, reflex spread (occurrence of a muscle contraction more than one joint away from the tested reflex) in the form of crossed adductors at the knees is normally present as is ankle clonus, though clonus is always abnormal when sustained or asymmetric. Postural reflexes are the intrinsic changes in tone or posture induced by movement, tactile stimuli, or the position of a body part. These include the rooting, glabellar, palmomental, palmar and plantar grasping, Moro, tonic neck, righting, placing and stepping, Landau, Galant, Santmyer swallow, vertical and horizontal suspension reflexes. Postural reflexes generally disappear with time and may reappear late in life either as a part of normal aging or in the context of various progressive or degenerative disorders as "release" phenomena. Brain stem reflexes have been described elsewhere in this chapter. The presence or absence and symmetry of the reflex responses should be noted.

Sensation

The sensory examination is of limited value in the newborn, as there are few ways to determine whether stimulation is perceived. Gradations of sensory stimulation (tickling, touching, firm pressure, or forceful pinching) may be used to generate responses varying from toe flexion, head turning, limb withdrawal, or crying, and are of most use in two situations: determining level of responsiveness and in assessing whether sensation is present in a paretic limb.

Clinical Problems

The seven categories are:

1. Excessive spontaneous motor movements
2. Diminished spontaneous motor movements
3. Alteration of mental status
4. Changes in head size and pressure
5. Hypoxic-ischemic encephalopathy
6. Imaging abnormalities
7. Brain death determination

Excessive Movements (Non-epileptic)

Jitteriness

Neonates often display abnormal movements that may suggest the possibility of seizures such as jitteriness, excessive startling, pedaling or stepping movements of the limbs, oral-lingual-buccal movements, or transient dystonic posturing. The traditional definition of seizures requires that neuronal paroxysmal discharges as documented by the electroencephalogram accompany the behavior in question. When such discharges are present, the diagnosis of seizures is not in doubt. When discharges cannot be documented in the neonate, however, the diagnosis of seizures is called into question but not necessarily excluded. This particular situation is discussed in the chapter on neonatal seizures. This section concerns movements that are *not* epileptic in origin.

Jitteriness is a low frequency, large amplitude tremulousness of the limbs and jaw that may be both spontaneous and provoked by innocuous visual, sensory, or auditory stimulation. Eye movements and gaze are normal, and help to distinguish jitteriness from seizures. While jitteriness may be regarded as a sign of central nervous system irritability, it may also be seen in up to 40% of normal term newborn infants. Tendon reflexes, a spontaneous Moro, and clonus are concomitantly exaggerated and easy to elicit. Gentle suppression of the limb movements with the examiner's hand will generally inhibit jitteriness; when it does not, seizures should be suspected. The more common causes of jitteriness include perinatal asphyxia, hypocalcemia, hypoglycemia, hypoxic-ischemic encephalopathy, and drug withdrawal. Correction of hypocalcemia or hypoglycemia will usually abolish jitteriness.

Neonatal Abstinence

Infants withdrawing from maternal drug exposure may develop seizures if their abstinence is severe, but more often they have tremors, jitteriness, and irritability, and are very difficult to console due to a heightened level of

arousal with persistent crying. The common maternally used drugs known to cause neonatal abstinence include opiates, cocaine, benzodiazepines, nicotine, and the selective serotonin reuptake inhibitors. Many infants may require only environmental comfort measures to reduce the symptoms, while others require pharmacotherapy. Opiates alone or in conjunction with phenobarbital are used to treat opiate withdrawal, while phenobarbital is the drug of choice for non-opiate withdrawal. Withdrawal behaviors typically appear within the first 3 days of life, although withdrawal signs and symptoms sufficient to require medication have been reported to occur as late as 1 week of age and may persist for months. While only small amounts of maternal opiates are known to cross into breast milk, if an opiate-using mother nurses her infant then abruptly stops, the infant can develop withdrawal symptoms.

Myoclonus and Clonus

Myoclonus is a sudden, brief contraction of a muscle or muscle groups. It can be generalized and can occur in the neonate as a non-epileptic paroxysmal phenomenon. Benign neonatal sleep myoclonus occurs only with (non-rapid eye movement) sleep and begins in the first week of life, with episodes lasting several minutes. They may be provoked during sleep by jarring or rocking the bed or by exposure to benzodiazepines, and disappear upon awakening. EEG is normal with no electrographic correlate, and spells generally end before the third month of life. No other neurological or developmental impairment is present.

In otherwise healthy full-term infants, persistent multifocal clonic movements appearing toward the end of the first week of life and lasting a day or so (rarely up to 2 weeks) may suggest benign idiopathic neonatal seizures or "fifth day fits." This poorly understood condition has a generally good prognosis and a normal outcome, though the paroxysms may progress to status epilepticus and require anticonvulsants.

Hyperekplexia is an exaggerated provoked startling followed by rigidity and stiffness. Innocuous sensory stimulation brings the resting infant into an appearance of repeated startling, then increasing truncal and extremity tone, jitteriness, and dystonic posturing. Apnea may result when stiffness is excessive, and in this way hyperekplexia may be life threatening. "Breaking" the tone by forcibly overcoming the stiffness may abort the attack, and benzodiazepines may prove to be useful in reducing all symptoms. EEG during the attacks shows no electrographic correlate. Hyperekplexia has been linked to abnormal functioning of the alpha-1 subunit of glycine receptors, with inhibition of the inhibitory interneurons within the brain stem reticular formation resulting in excessive startling.

When cerebral anoxia is both prolonged and severe and the resulting encephalopathy profound, persistent spontaneous and stimulus-evoked myoclonus (Lance–Adams syndrome) may be present. The myoclonic jerks in this circumstance are generalized, frequent, and give the appearance of status epilepticus, though the electroencephalogram shows no accompanying paroxysmal discharges; anticonvulsants generally have no effect and do not modify the neurological outcome, which is uniformly poor.

Torticollis

There are two components to true torticollis: there is a tilting of the head on the neck as well as a cervical rotational component so that the chin is turned toward the shoulder. Head tilting alone should not be considered as torticollis; other causes for head tilting such as nuchal or posterior fossa masses, anatomical anomalies of the craniovertebral junction, or cervical vertebral malformations should be investigated. Shortening or limitation of movement of the ipsilateral sternocleidomastoid muscle is the final common pathway to torticollis, with the precipitating causes ranging from intrauterine malpositioning or constraint and breech presentation to intramuscular fibrosis with or without hemorrhage. When fibrosis is present, palpation of the affected muscle or ultrasound may identify the lesion. Physical therapy in most cases will result in improvement, as long as both rotational components of the torticollis are addressed independently. Untreated or unrecognized torticollis may lead to ipsilateral usually posterior plagiocephaly and may rarely result in anterior displacement of the ear, ipsilateral forehead, temporomandibular joint, and orbit.

Opisthotonos

The opisthion is the anatomic posterior-most point of the foramen magnum. In opisthotonic posturing, the head is persistently and abnormally retroflexed about this point (retrocollis), and the trunk is arched posteriorly due to abnormal contraction of the midline truncal extensor muscles. Opisthotonos may be seen in meningismus, in the presence of large posterior fossa mass lesions, in aminoacidopathies, urea cycle defects, organic acidurias,

disorders of trace elements, the porphyrias, and when intracranial pressure is elevated. Opisthotonic posturing should not be confused with the similar but more transient posturing of the term infant delivered with a face presentation. Opisthotonos has been associated with acute bilirubin encephalopathy and kernicterus, but in this circumstance is more of a dystonic posturing of extrapyramidal origin than a phenomenon related to obstruction of cerebrospinal flow or meningeal inflammation.

In the newborn period and during infancy, gastroesophageal reflux is commonly associated with more transient episodes of opisthotonic and frankly dystonic truncal posturing. This association is frequently mislabeled as the Sandifer syndrome and has entered common usage this way although Sandifer's original description was in older children with both episodic dystonia and hiatus hernia; when the hernia was surgically corrected, the movement disorder disappeared. Episodic opisthotonus or dystonia in a newborn may be easily confused with seizures and may have no direct relationship with feeding, though prone positioning frequently exacerbates the reflux and subsequent motor behaviors. Treatment with histamine-2 receptor blocking agents does not generally reduce reflux, but may reduce the acidity of the refluxed fluid. Pharmacologic agents that modify gastrointestinal motility are more effective treatments for reflux, especially when combined with reverse Trendelenburg positioning of the infants. Some commonly used agents such as metoclopramide must be used with care, since drug-induced extrapyramidal side effects may be difficult to differentiate from the GER-induced dystonic or opisthotonic posturing.

Myotonia

Myotonia is a transient but sustained (seconds long) contraction of a muscle or muscle group in response to percussion. This is most easily done with a triangular (Taylor) or ball type (Tromner) reflex hammer. The thenar eminence of the hand is the most accessible group of muscles, with percussion producing a visible tonic opposition of the thumb. Percussion of other large muscles such as the biceps or quadriceps may not result in visible movements, though palpation of the just-percussed muscle will easily detect the local contraction. Myotonia is most closely associated with myotonic dystrophy; when myotonic dystrophy is present in the newborn period, the most likely genetic donor is the mother as discussed later in the chapter.

Muscle Fasciculations

Fasciculation is a spontaneous irregular contraction of the muscles subserved by a motor unit, and does not generally result in visible movement of a joint, the contractions limited instead to the muscle itself. Fasciculations are best observed in the newborn on the undersurface of the tongue of the newborn. Irregular contractions of the superior surface of the tongue of the otherwise normal newborn should not be confused with the "bag-of-worms" appearance of the inferior tongue surface in the infant with anterior horn cell or lower motor neuron disease. In type I *spinal muscular atrophy*, the presence of significant weakness, reduced or absent tendon reflexes, and abnormal shape of the thorax are regularly present and should suggest the diagnosis.

Deficiency of Movement

Brachial Plexus Injuries

In the newborn, deficiency of movement implies muscle weakness. Weakness can be of myogenic or neurogenic origin, and be limited to a single limb or portion of the body or be generalized. When weakness is isolated to a single limb, the weakness is unlikely to be myogenic. Paresis of a single arm at delivery is a fairly common cause for neurological consultation, especially in large infants or when excessive traction has been applied to the arm during delivery. There are five spinal segments and nerve roots from which the brachial plexus originates: cervical segments 5–8 and the first thoracic. These nerve roots combine to form upper, middle, and lower nerve trunks which, with the insertion of the roots into the spinal cord, are the most common sites of injury when traction is excessive.

Two general patterns of injury are seen in the term infant. When upper cervical roots (C5, C6) are injured, the pattern of weakness is as originally described by Erb: weakness or paresis of shoulder abduction and external rotation, biceps, brachioradialis, and supination. Wrist and finger extensors may sometimes be weak as well. Ipsilateral diaphragmatic weakness may be present when the C4 and C3 roots are simultaneously affected. The biceps reflex is absent in the affected arm, and the Moro is typically asymmetric. The best way to demonstrate the Moro is as he originally described it: to strike the bed next to the infant with the palm of the hand. Finger and palmar grasp reflexes are unaffected in Erb palsy.

When the lowermost roots and trunks of the brachial plexus are injured, the distal upper extremity is paretic with no finger or wrist movements elicitable, as described by Klumpke. This is an uncommon injury in the newborn, for whom a lack of finger movements usually implies a lesion involving the entire origin of the plexus at the spinal roots. In this circumstance an ipsilateral Horner syndrome is typically present.

While outcome is generally good unless nerve roots are avulsed, treatment options are limited and intended to minimize the possibility of joint contractures developing during the weeks or months required for recovery at a time when the infant is simultaneously growing. Range of motion exercises for all of the upper extremity joints including the shoulder, and splinting, where necessary, are generally sufficient. Most infants have recovery of function to the point where a routine neurological examination shows no deficits by 6 months of age, with the majority of improvement within the first few weeks to months. When weakness is present still at 6 months of age, a permanent degree of weakness becomes increasingly likely. Surgical intervention should be considered earlier rather than later, although the most appropriate time of surgery is still uncertain. The first consideration of neurosurgical referral for lysis of fibrotic tissue, neuromas, and grafting of viable roots should be considered at 2 months of age so that surgical intervention by 4 months of age can be performed in the event that weakness still has not improved.

Lumbosacral Plexus Injuries

Paralysis of a leg is seldom seen in the newborn, and occurs when traction of the leg during frank breech deliveries results in injury to the lumbar (L2-4) or sacral (L4-S3) plexuses. The rarity of this injury should lead to consideration of other causes such as occult dysraphism, though spinal dysraphism is very unlikely to involve a single limb alone. Prognosis for complete recovery is much less optimistic for the paretic leg than for the acutely paretic arm in the newborn.

Unilateral Facial Weakness

Congenital aplasia or hypoplasia of the depressor anguli oris results in an abnormal appearance of the crying or, in an older infant, smiling face. The corner of the mouth does not move inferolaterally, giving the illusion of a contralateral facial weakness. This is usually an isolated phenomenon, but may rarely be associated with other congenital defects or as a sign of the *Cayler cardiofacial syndrome* in which various cardiac defects may be present.

The facial nerve is vulnerable to traumatic injury; its emergence from the stylomastoid foramen just inferior and medial to the inferior attachment of the ear and subsequent branching to supply the muscles of facial expression makes it especially susceptible to compressive injury by external forces. Unilateral facial weakness is most frequently noticed shortly after delivery and involves both the upper and lower halves of the face. A flattening of the nasolabial fold and forehead creases may be noted, especially during crying, and feeding may be complicated by the leakage of milk from the ipsilateral corner of the mouth. In the context of the use of forceps during delivery, mechanical pressure on the nerve at its emergence may result in weakness, but facial weakness can also be seen when no forceps or vacuum-assisted extraction has occurred. Prolonged intrauterine impaction of the angle of the jaw onto the ipsilateral shoulder, a bony projection of a twin, or the maternal sacrum may result in a facial paresis; in such cases the normally excellent prognosis for a complete recovery is not as optimistic. Treatment with artificial tears or forced closure of the ipsilateral eyelids with gauze and tape is directed at preventing corneal ulcerations because of the inability to blink.

Bilateral Facial Weakness

Paresis of both sides of the face is evident when the child has an expressionless face even when provoked to the point of crying by noxious stimulation. Acquired transient weakness in the form of maternal myasthenia gravis should be differentiated from other forms of generalized motor weakness such as myotonic and other muscle dystrophies, and from the *Möbius sequence*, classically described as the presence of bilateral facial and abducens paresis in a newborn. The source of the paresis is aplasia or hypoplasia of two or more pairs of cranial motor nuclei within the dorsum of the brain stem, so the classic signs of the Möbius sequence should provoke a clinical search for weakness mediated by involvement of the other cranial nerves including the hypoglossal nerve which will affect feeding. Causation is unknown, and may be developmental or acquired. Treatment is directed at finding a method of feeding that allows for sufficient intake, since inability to seal the lips around a nipple poses a major hazard to the

infant. Associated incomplete eyelid closure is managed in the same way as in unilateral facial paresis.

Ophthalmoplegia

Ophthalmoplegia and ptosis may occur independently, and can be acquired or "congenital." In contrast to older children with myasthenia gravis, infants with maternally acquired transient myasthenia gravis do not typically have either ophthalmoplegia or ptosis, presenting instead with hypotonia, generalized weakness, and feeding difficulties in the first hours of life. Administration of cholinesterase inhibitors may be necessary for this condition, one that generally abates by 3 weeks of age. Cholinesterase inhibitors may or may not be useful in the treatment of *congenital* myasthenic syndromes, which are *not* transient and *do* present with prominent ptosis and ophthalmoplegia.

The congenital myasthenic syndrome comprises a heterogeneous group of rare disorders that reflect genetically determined defects of the neuromuscular junction, with only a few generating clinical suspicion in the newborn period and are discussed later in the chapter in the section on Weakness.

Waxing and waning paresis of extraocular muscles in the newborn, especially in the presence of other signs such as internuclear ophthalmoplegia, facial weakness, or glossopharyngeal dysfunction should suggest the possibility of a metabolic encephalopathies such as *maple syrup urine disease*.

The clinical signs of Möbius sequence have already been discussed, and should be differentiated from congenital third nerve palsy, familial congenital ptosis, and the Duane syndrome, in which the pareses are generally restricted to the oculomotor system. In the *Duane retraction syndrome*, there is partial abduction of the eye and upon attempted abduction, retraction of the globe of the eye into the orbit causing the palpebral fissure to narrow. This is caused by a usually unilateral absence of the abducens nerve along with its nucleus in the pons. There is often an accompanying fibrosis of the lateral rectus muscle, linking this syndrome with other conditions leading to fibrosis of the extraocular muscles such as Congenital Fibrosis of the Extraocular Muscles (*CFEOM*) in which the eyes are fixed in a position of strabismus, and ptosis is prominent. Coaxing the newborn infant to voluntarily move the eyes in order to make any of these clinical diagnoses is difficult; the examiner may have to resort to the use of oculovestibular maneuvers, caloric stimulation of the tympanic membranes, or retreat to a dark room as described in the section on the neurological examination.

Laryngeal, Vocal Cord, and Pharyngeal Weakness

Abnormalities of sucking, swallowing, crying, and breathing are not uncommon in the newborn. Apart from the normal developmental evolution of the coordination of sucking, swallowing, and breathing in the preterm infants, the presence of such dyscoordination in the term infant may be life threatening. The laryngeal nerve has two branches of interest, the recurrent laryngeal and superior branches. The recurrent branch may be injured when the thyroid cartilage is forced against the cricoid cartilage during prolonged lateral neck flexion in utero or during delivery causing unilateral vocal cord paresis and an abnormal stridorous cry. The superior branch may be similarly compressed by the thyroid cartilage against the hyoid bone, causing trouble with swallowing and a substantial risk of aspiration with feeding. Isolated pharyngeal weakness is probably more common than the literature would suggest, and is not always evident until the first feeding when cyanosis, choking, and aspiration simultaneously appear (Table 360.2). The most useful diagnostic testing is with direct laryngoscopy and videofluoroscopy; magnetic resonance imaging is necessary when other malformations are present, there are focal neurological findings on examination, or when cerebral malformations are suspected.

Hemiparesis and Stroke

Hemiparesis resulting from large middle cerebral arterial infarctions may be clinically unapparent in the neonate, with no obvious limb use asymmetry until the infant begins to crawl or walk. The cause of large cerebral arterial

Table 360.2
Pattern of clinical signs and symptoms of laryngeal and pharyngeal dysfunction

	Laryngeal	Vocal cord	Pharynx
Aspiration	+	+	+
Choking with feeding	+	+	+
Cyanosis with feeding	–	–	+
Diaphragmatic paresis	+/–	–	–
Dysphonia	+	+	–
Respiratory distress with feeding	+	–/+	+
Stridor	+	+	–

infarctions, which occur in more than 5% of infants, remains unknown in the majority of cases. Ischemic stroke is more common in the newborn than in older children, and has been estimated to occur in 1 of every 4,000 live births. Although the timing of stroke discovered in the newborn period has been considered as *fetal* (focal ischemic, thrombotic, and/or hemorrhagic event occurring between 14 weeks gestation and the onset of labor resulting in delivery) or *neonatal* (occurring between labor resulting in delivery and 28 days of life), this distinction may be somewhat arbitrary since clear etiologic or prognostic differences for strokes in these two epochs are not present. Most infarctions are ischemic and unilateral, with the majority of these involving the middle cerebral artery. The remainder is related to hemorrhage and cerebral venous sinus thrombosis. Unexplained is why the left middle cerebral arterial distribution is affected more commonly than the right side. Infarction from arterial occlusion is more common in the term than the preterm infant with the incidence increasing from 5% of infants between 28 and 32 weeks gestational age to 15% in infants between 37 and 40 weeks.

Two patterns of arterial occlusion are present on neuroimaging when hemiparesis is present, and they do offer some guidance in an investigation of cause. Most identifiable causes are related to adverse maternal conditions (i.e., diabetes, hypercoagulable states, anticonvulsant or warfarin use, gastroenteritis with fever, idiopathic thrombocytopenic purpura), pregnancy disorders (i.e., preeclampsia, abruption, in utero growth retardation, twins, oligohydramnios, chorioamnionitis), or fetal disorders (i.e., TORCH-type infections, Rh isoimmunization, alloimmune thrombocytopenia, protein C deficiency).

The presence of multiple arterial infarctions should suggest the possibility of congenital heart disease, polycythemia (venous hematocrit of >65% or hemoglobin >22 g/100 mL in a symptomatic term infant), disseminated intravascular coagulation, or perinatal distress.

Single artery distribution infarctions should raise the possibility of a focal arterial vascular anomaly or thrombotic occlusion, ischemic proliferative vasculopathy when twins are present, or vasospasm related to maternal substance abuse, especially cocaine.

When the infarctions are remote, there is an increasing recognition that genetic factors may be present, such as the *hypoprothombinemia, 5, 20-methylenetetrahydrofolate reductase*, and *COL4A1* genetic deficiencies. The latter has been associated with familial cases of *porencephaly*.

Mechanical occlusion of cerebral arteries may occur during or after delivery, resulting in ischemic parenchymal injury and focal neurological symptoms. When the neck is hyperextended and rotated, the lumen of the internal carotid artery may be narrowed or occluded as it passes over the lateral portion of the upper cervical vertebrae. A similar injury may occur in the *posterior* circulation during hyperextension and rotation of the neck. At birth, the foramen magnum is almost its adult size, but both the lateral mass of the atlas and the atlantooccipital condyle are hypoplastic. These conditions result in a narrowing of the spinal canal within the atlas. In addition, the ligaments between atlas, occiput, and axis are lax, so that the vertebral arteries are vulnerable to compression between the bony lamina of the atlas and the exoccipital bone when even mild hyperextension of the neck occurs. The compressed vertebral arteries will reduce blood flow to the brain stem, cerebellum, and upper cervical cord, and may result in stroke.

Acute strokes of either venous or arterial origin most often present as focal motor seizures involving a single extremity rather than hemiparesis, and have been estimated to account for up to 10% of all seizures in neonates.

Weakness associated with remote (weeks to months old) arterial occlusions may not be immediately apparent. The abrupt appearance of weakness in an arm and leg (face is usually not affected) when normal movement had been documented previously should suggest an acute arterial occlusion and should provoke a more energetic investigation as to cause than remote occlusions, for which an etiology can only rarely be discovered. A suggested diagnostic panel is given in Table 360.3. One purpose of a diagnostic workup, even when the chances of discovery of an etiology is unlikely, is to estimate the risk of stroke recurrence. Recurrent thromboembolism, acute ischemic stroke, and cerebral venous sinus thrombosis do occur, and are more likely when factors promoting thrombosis such as complex congenital heart disease, sepsis, or hypovolemia are present.

Treatment of neonatal stroke is supportive. The safety of medical thrombolysis is unproven in the neonate, and the deployment of agents to promote thrombolysis such as unfractionated or low molecular weight heparin is not common. The exception to this is when cardiac or multiple systemic thrombi or a clear tendency to prothrombosis is present. Low platelet counts and coagulation factor deficiencies should be corrected. Vitamin K should always be administered to the newborn, especially when exogenous pharmacological agents such as warfarin, barbiturates, or phenytoin have been administered to the mother during the pregnancy or when biliary atresia is present.

Outcome and prognosis in neonatal stroke is variable, with estimates of disability differing widely. A "normal" outcome is possible, but so too is mild to dense

Table 360.3
Prothrombotic laboratory evaluation of the newborn

Humoral factors (Blood, Serum)
Complete blood count[a]
Prothrombin and partial Thromboplastin time (PT, PTT)[a]
International normalized ratio (INR)[a]
Electrolytes[a]
Proteins C and S activity[a]
Activated protein C resistance screen[a]
Homocysteine[a]
Factor VIIIc
Lipoprotein a
Antibodies
Antiphospholipid antibody screen
Antithrombin III activity[a]
Genetic Deficiencies
Factor V Leiden mutation[a]
Prothrombin 20210 gene defect
Methylene tetrahydrofolate reductase (MTHFR), C677T[a], A1298C gene defects
Plasminogen activator inhibitor-1 gene 4G/5G polymorphism
Imaging
Computed tomography brain (CT)[a]
CT angiography or venography
Magnetic resonance (MR) imaging brain; include diffusion weighted imaging[a]
MR angiography, venography
Echocardiogram[a]

[a]Minimum recommended testing; remaining tests where available and suggested by history. The removed volume of blood necessary for testing may be excessive in small or very premature neonates and force prioritization of tests or preclude obtaining all studies on a timely basis

hemiplegia. Most children with a history of neonatal stroke will learn to walk independently before the end of the second year of life. Epilepsy after the neonatal period, even when seizures are the presenting sign of stroke, is uncommon. Cognitive impairment may range from severe to none at all. The possibility of clinically and academically significant disabilities should be anticipated including cognitive and learning deficits, non-progressive impairment of motor functioning (cerebral palsy), sensory and visual deficits, and epilepsy. When hypoxic-ischemic injury is complicated by or superimposed upon stroke, outcome is generally worse.

Paraparesis

Simultaneous weakness of both legs is rarely seen in the neonate. Congenital malformations of the caudal spinal cord, conus medullaris, and cauda equina may produce variable degrees of asymmetric weakness, tendon reflexes, and sensory impairment, making it difficult to differentiate central from peripheral causes of paraparesis on clinical grounds alone. Cerebral lesions may produce weakness of the legs. Parasagittal primary motor cortex corresponding with the lower extremities may be injured after prolonged hypotension and hypoperfusion, causing a borderzone infarction between the middle and anterior cerebral arterial supplies. Arm weakness may be similarly produced with more lateral anatomical displacement of the borderzone area. Cystic or hydrocephalic disruption of periventricular white matter tracts in the preterm infant will produce bilateral leg weakness although this is not generally clinically apparent in the newborn period. Disruption of the spinal cord may occur when excessive spinal traction has taken place during delivery, and cause a flaccid weakness and areflexia below the torn spinal segment.

Quadriparesis, Generalized Weakness, and Hypotonia

Quadriparesis is rare in the neonate. Posterior fossa lesions and upper cervical spinal cord injuries should be suspected and excluded by appropriate neuroimaging. Quadriparesis should be differentiated from generalized weakness and hypotonia wherein the presence of muscle tone can generally be documented. When it is present in the newborn period, quadriparesis due to compressive or disruptive spinal cord injuries results in a relative *absence* rather than an *increase* of tone. Spasticity and hypertonia following quadriparesis will frequently appear in the weeks to months after injury but are not seen during the first month of life unless the cerebral injury has preceded delivery by the same time interval.

Inability to move the limbs may occur when their joints are limited in their excursion as is seen in the clinical entities described by the term *arthrogryposis multiplex congenita*. This is not a single disease but a final common clinical observation for a number of disorders that may affect any part of the nervous system. Many additional congenital anomalies are often present along with the joint limitations and reflect underlying muscle hypotrophy or atrophy, weakness, and hypo- or areflexia. More than 150 distinct clinical syndromes are known to result in the

physical finding of arthrogryposis. Talipes equinovarus, micrognathia and retrognathia, clinodactyly, and camptodactyly occur when there is insufficient in utero movement of the joints; polyhydramnios and a high arched palate with narrowed alveolar ridges reflect weakness and lack of movement of the muscles of deglutition. Arthrogryposis has been associated with central nervous system malformations at every level, from migrational disorders in the brain and cerebellum to dysplasia of anterior horn cells and meningomyelocele in the spinal cord, to myasthenic syndromes, merosin-related dystrophies, glycogen storage disorders, and mitochondrial cytopathies affecting muscle, to hypomyelination syndromes affecting the peripheral nerves.

Transient maternally acquired myasthenia gravis occurs in as many as one in five infants born to myasthenic mothers. The weakness is usually apparent within the first hours of birth, but may become evident after an initial brief period during which no weakness can be observed, and may rarely become evident as late as the second postnatal day. The predominant clinical feature is feeding difficulty, with sucking and swallowing problems quickly leading to respiratory distress. Mechanical ventilatory support and gavage or nasogastric tube feedings are required in about one in three infants. The remainder of treatment is generally supportive since duration of symptoms does not generally last for more than 3 weeks. Circulating maternal acetylcholine receptor protein antibodies may be transmitted across the placenta to the infant and exert their pathogenic effect on acetylcholine receptors at the postsynaptic muscle membrane causing receptors to be degraded, displacing acetylcholine from the receptors, and inducing local degradation of the receptor expressing muscle membrane via complement. Diagnosis is made clinically, and may be confirmed by demonstrating an electrodecremental response to repetitive stimulation on electromyography. Expertise in neonatal electromyography is not widely available, and is not therefore practical for the vast majority of hospitalized infants throughout the world. An alternative confirmatory procedure is the test administration of an anticholinesterase agent such as the short acting edrophonium (0.15 mg/kg administered intravenously in fractions over a several minute period after an initial dose of 0.03 mg/kg) or the longer acting neostigmine methylsulfate (0.04 mg/kg administered intramuscularly or subcutaneously). Each medication yields a positive result when clinical improvement in the form of sucking or swallowing, crying, breathing, or facial movement is seen. The duration of improvement is short lived, with edrophonium-induced improvement appearing within 5 min and persisting for up to 15 min. Neostigmine-induced improvements may not appear for up to a half hour after administration. For administration of either anticholinesterase there is risk of excessive muscarinic side effects, and so atropine should be simultaneously available at the moment of injection.

Neonatal maternally acquired myasthenia gravis is a transient phenomenon; while the infant may become quite ill and require complete ventilatory and feeding support, improvement will occur and prognosis for normal outcome is excellent. It is common practice to use exogenous anticholinesterase medications such as neostigmine (intravenous dose of 0.04 mg/kg or nasogastric dose of 0.4 mg/kg) a half hour before feedings for the first weeks of life.

A complete discussion of the congenital, non-acquired myasthenic syndromes is beyond the scope of this chapter. More than a dozen such syndromes are known, variously affecting individual steps within the pathway associated with the assembly of acetylcholine, its vesicles within the presynaptic terminal, or its receptor on the postsynaptic membrane. A clinical response to the administration of acetylcholinesterase may not be seen in the congenital myasthenic syndromes, and should not be used to exclude the diagnosis that requires electrophysiologic investigation.

Other genetic causes of generalized hypotonia include myotonic dystrophy and Prader–Willi syndrome; these are common enough that genetic testing should be considered in all infants presenting in the neonatal period with symmetric muscle weakness and hypotonia. In *Prader–Willi syndrome*, hypotonia is severe, reflexes diminished or absent, feeding and crying weak, and subtle dysmorphic features such as a narrow bifrontal diameter, almond shaped eyes, small mouth, or hypogonadism present. There is frequently a history of diminished movement preceding delivery.

Although *congenital myotonic dystrophy* is an autosomal dominant disorder, when it is present in the newborn the parent contributing the trait is almost always the mother. It is one of a number of disorders known to be associated with an increased number of CTG trinucleotide repeats, in this case in an unstable DNA sequence on the 3′ untranslated end of the myotonic dystrophy gene on chromosome 19. While paternal transmission of the gene does rarely occur in the newborn period, maternal transmission is the rule, and the severity of disease is highly correlated with the total number of repeats. With each female transmission, the number of repeats increases, further worsening severity and causing symptoms earlier in life, a phenomenon referred to as anticipation. Prognosis is dependent at some level on the number of CTG

repeats, and further determined by the severity of weakness, respiratory compromise, gastrointestinal motility, and cognitive impairment universally present. The *mother's* appearance should therefore give the first clinical clues as to the potential presence of myotonic dystrophy in the hypotonic infant; upon shaking her hand at the first meeting, her hand may not immediately release its clasp due to myotonia.

Diaphragmatic Paresis

Persistent unexplained respiratory difficulty in the first hours of life may be caused by unilateral diaphragmatic paralysis. Cyanosis and arterial blood gas determinations may suggest the possibility of hypoventilation and congenital heart or primary pulmonary disease. Routine chest radiographs may not show the familiar hemidiaphragmatic elevation characteristic of paresis in the older child or adult. After an initial period of respiratory distress, there may be a stabilization or improvement with oxygen supplementation, but a more severely paretic infant may instead acutely deteriorate. Diagnosis is made by ultrasonic or fluoroscopic real time imaging of respirations, demonstrating the paradoxical upward movements of the affected hemidiaphragm with breathing. Any such imaging will yield a false negative result if positive pressure ventilation is in use at the time of the test. Diaphragmatic paralysis results from injury to the 3rd, 4th, and 5th cervical nerve roots, and thereby complicates about 5% of brachial plexus injuries, but it may occur without arm weakness as well. Long-term prognosis depends upon the response to ventilatory interventions such as intermittent positive pressure ventilation, but when it becomes clear that there has been no improvement, surgical plication of the hemidiaphragm may be indicated.

Alteration of Consciousness

Encephalopathy

The traditional definition of encephalopathy as the clinical condition resulting when any two of (1) seizures, (2) alteration in the state of consciousness, or (3) alteration in cognition or personality are present cannot be applied easily to infants, for whom changes in cognition are not possible to detect and personality is not present. Instead, neonatal encephalopathy may be better defined as a condition in which there is altered consciousness, difficulty in initiating and maintaining spontaneous respirations, and associated depression of reflexes and muscle tone with or without seizures. Major categories of causes for neonatal encephalopathy can be separated into *intrinsic* deficiencies (genetic, enzymatic, subcellular organelle dysfunction) and *acquired* disorders (infection, cerebral hemorrhage or thrombosis, hypoxic-ischemic).

The clinician should be aware that other conditions such as congenital heart disease, neuromuscular disorders, congenital myopathies, and cerebral malformations may give the infant the *appearance* of an encephalopathy because of accompanying profound hypotonia or weakness when an *actual* encephalopathy, best determined by electroencephalography, is absent.

Important enzymatic deficiencies producing encephalopathy in the newborn, especially the amino and organic acidopathies, are covered in the chapter on metabolic disorders. These generally evolve over the first days of life, and yield as clues altered levels of glucose, ammonia, serum ketones, and sometimes an obvious clinical deterioration after feedings. Deficient levels of glucose, sodium, calcium, and magnesium are commonly present in the newborn and need to be recognized and treated before the encephalopathy is corrected.

Incipient or evolving infection, especially in the context of diminished peripheral perfusion, tachycardia, and hypotension should always be considered as an emergent cause for encephalopathy. A well-appearing infant can be dead in a matter of hours from certain bacterial infections, with Group B *Streptococcus*, *Escherichia coli*, and *Klebsiella* being the most notorious. A complete septic workup including lumbar puncture, blood cultures, and urine culture is necessary to identify and properly isolate the offending bacterium. Congenital cytomegalovirus and herpesvirus infections are usually readily identifiable in retrospect on clinical grounds but may pose diagnostic dilemmas if they are not considered or when typical ocular or cutaneous lesions are absent.

Herpesvirus infections are usually acquired during delivery when asymptomatic maternal vaginal lesions are present, when there are active lesions in a mother not known to have had prior herpes infections (type II), or from infected hospital personnel or family members handling the infant (type I). The resulting symptoms in the newborn appear by the end of the first week of life in the form of poor feeding and lethargy. Irritability or its opposite, somnolence, is followed by focal seizures with rapid progression to stupor and coma. Lumbar puncture should be performed in all such infants with care taken to distinguish traumatic lumbar puncture (many red cells, clear, colorless supernatant) from the xanthochromia, white

blood cell pleocytosis, and elevated protein in cerebrospinal fluid when herpes is present. Treatment with acyclovir should never be postponed or delayed until laboratory testing or PCR results are returned as the acyclovir is viro*static* rather than viro*cidal*, and the hemorrhagic encephalitis-induced destruction of brain parenchyma is already under way. Prognosis in such an event is grave.

Intracranial Hemorrhage and Post Hemorrhagic Hydrocephalus

Intracranial hemorrhage is an important cause of altered mental status and neurological debilitation in the newborn, and has many sources. Subdural, subarachnoid, intraparenchymal, and intraventricular hemorrhages are the most common. During vaginal delivery, especially when vacuum extractors are applied, the relative motion of the bones of the deforming cranial vault may exert traction on the major venous sinuses affixed to them. The confluence of the straight and transverse sinuses, vein of Galen, and the free tentorial edges at the junction of the double layered falcine and tentorial dura is especially vulnerable to tearing, with leakage of venous blood into the juxtatentorial or parafalcine spaces. There may be a rapid and extensive accumulation of venous blood, with a full fontanel, depressed level of consciousness, skew eye deviation, pupillary asymmetry, abnormal response to light, and nuchal rigidity. Coma, fixed dilated pupils, and respiratory rhythm disturbances follow over the next hours. A similar progression of events follows the disruption and displacement of the occipital bone (occipital osteodiastasis) with difficult breech deliveries; in this circumstance, the transverse sinuses or the vein of Galen may be disrupted and death follows.

Subdural blood may appear in the *infratentorial* space without producing any clinical symptoms and be noted incidentally upon routine neuroimaging. Blood also may slowly accumulate in the posterior fossa leading to signs of brain stem dysfunction (apnea, bradycardia, eye deviations) and compression (irritability or lethargy, full fontanel, increasing OFC) suggestive of increased intracranial pressure. No clinical signs may be present when subdural blood appears in the *supratentorial* space or there may be clinical signs (hemiparesis, eye deviation, dilated pupil) of an evolving herniation when the volume of blood is large. The volume of subdural blood present may be easily underestimated on neuroimaging, especially when the width of the observed blood on MR or CT slices is small but the number of images showing blood present is large.

Subarachnoid hemorrhages are relatively common in the newborn. They may be seen incidentally on imaging in an infant with no clinical signs, or be associated with focal seizures in an otherwise healthy looking infant. Diagnosis is made by CT or MRI, and may be suspected when the spinal fluid of an infant with seizures shows an excessive number of RBCs and an elevated protein. Lumbar puncture is usually done in such an infant for other reasons such as to exclude infection and the abnormal CSF is found incidentally; care should be taken to differentiate this clinical presentation from that described in extensive subdural supratentorial or infratentorial hemorrhage, for which lumbar puncture may provoke cerebral herniation. Prognosis in most cases of subarachnoid hemorrhage is generally good and seizures can be expected to remit spontaneously.

Intraparenchymal hemorrhage in the newborn is not uncommon and disproportionately affects premature infants, with the most premature among them bearing the greatest risk. Primary hemorrhage may be conceptually distinguished from hemorrhage that secondarily complicates venous infarction or ischemic parenchyma, but from a clinical and management standpoint there is little to distinguish them. The cerebellar hemisphere is a common location for hemorrhage in very premature infants, and produces signs and symptoms similar to infratentorial subdural hemorrhage already described. CT and MRI are preferred to ultrasound at documenting the extent and location of cerebellar hemorrhage. Surgical intervention other than ventriculoperitoneal shunting when obstructive hydrocephalus complicates cerebellar hemorrhage does not demonstrate clear advantages over medical management in term infants, and probably contributes to morbidity and mortality in preterm infants. Recent evidence suggests that prior assumptions regarding the benign nature of cerebellar hemorrhage are incomplete. Long-term follow-up of such infants suggests that there is a markedly increased risk of significant cognitive impairment including pervasive developmental disorder, and reflects an evolving recognition of the importance of the cerebellum to cognitive processes other than coordination including emotional affect, language development, and mathematical abilities.

Intraventricular hemorrhages are relatively common in the term infant, and should not be confused with the entity of the same name as applied to premature infants. The latter should be more appropriately described as germinal matrix hemorrhages, even when blood within the germinal matrix escapes into the ventricle. In term infants, the source for the intraventricular blood is usually the choroid plexus. Some authors have attributed the source

of intraventricular blood in term infants to the germinal matrix, although the normal involution of the germinal matrix is mostly complete by 32 weeks, and the germinal matrix is absent by 36 weeks (see *Table 360.1*). Another locus of intraventricular hemorrhage in the term infant is the thalamus. Venous sinus thrombosis in the vein of Galen and straight and transverse sinuses may be complicated by thalamic infarction and secondary hemorrhage, suggesting a role for coagulation disorders in the genesis of intraventricular hemorrhage. Outcome is dependent upon the degree to which symptoms are present and medical or surgical intervention is necessary.

Changing Head Size and Increased Intracranial Pressure

Hydrocephalus

Small intraventricular hemorrhages in the term newborn may be asymptomatic; larger hemorrhages may obstruct CSF outflow and be complicated by hydrocephalus. Other neonatal causes of obstructive hydrocephalus such as aqueductal stenosis will generally be apparent upon delivery. Clinical evidence of increased intracranial pressure includes a tense or bulging fontanel, splitting of coronal, sagittal, or metopic sutures, apnea, bradycardia, extraocular dysmotility, hypertonia, lethargy or irritability, and blood oxygen desaturations. A head circumference growth velocity of more than 2 mm/day is highly suggestive, and ultrasound or CT/MRI is confirmatory.

Hydrocephalus may require medical or surgical intervention. Ventriculoperitoneal shunting is the conventional management for obstructive and communicating hydrocephalus. Surgical shunting adversely affects outcome, especially when it is performed in very small infants or complicated by infection and the subsequent need for external ventricular drainage and repeated shunt revisions. Management should therefore be directed towards minimizing the need for surgical intervention.

A common practice has been to perform serial lumbar punctures, despite a lack of evidence that such a practice reduces the need for later surgical intervention or disability. The small volume of the CSF space relative to the size of the patient should be considered, and excessive amounts of CSF should not be removed without increasing the likelihood of producing clinically significant apnea, bradycardia, or blood oxygen desaturations. Extraction of less than 20 mL/kg of CSF at a rate of less than 1 mL/kg/min is recommended to minimize the risk of iatrogenic symptoms. Pharmacological reduction of CSF production with acetazolamide and diuretics does not yield any measurable clinical benefit and may worsen outcome. Another strategy for the management of hydrocephalus is to use an Ommaya reservoir. This is an implanted device with a subcutaneous reservoir and a tubular channel that can be inserted into the ventricular space. When CSF continues to accumulate to the point where head circumference continues to grow excessively and symptoms of increased intracranial pressure recur, an Ommaya reservoir can be placed to allow easier access for repeated CSF removal. In expert neurosurgical hands, complication rates are low, even in very small infants. Daily taps of 10 mL/kg from the reservoir are recommended in the first days after implantation, with up to 20 mL/kg once or twice a day after this to control head enlargement. If this degree of CSF removal still fails to control excessive head enlargement and head circumference growth exceeds 2 mm/day, ventriculostomy may be necessary. Prognosis is heavily dependent upon the need for ventriculoperitoneal placement, duration of the hydrocephalus before recognition and treatment, and the occurrence of surgical complications.

When the degree of head enlargement due to hydrocephalus is large and ventriculoperitoneal shunting is required, the acute relative reduction in the size of the dilated ventricles can result in a collapse of the head with overriding bony sutures and redundancy of the scalp. If the degree of collapse is excessive, bridging cortical veins may be ruptured and subdural bleeding may occur as a complication. This is less likely to occur when more gradual reduction of head size occurs for other reasons such as cerebral parenchymal dissolution and absorption after severe global parenchymal injury due to infection, prolonged asphyxia, ischemia, or bilateral hemispheric infarction.

Hypoxia, Ischemia, and Encephalopathy

Acquired newborn encephalopathy is the final manifestation of a number of pathophysiologic sequences, only one of which is hypoxic-ischemic injury. Pure ischemia (insufficient blood flow) or hypoxia (insufficient quantity of dissolved blood oxygen) virtually never occur in isolation, since both are almost always accompanied by hypercarbia. This in turn influences cerebral arterial caliber via autoregulation, a response that may be lost when hypercarbia is progressive – especially in the ventilated preterm newborn.

Ischemia not only fails to deliver a sufficient supply of oxygen to the tissues but it prevents the removal of the

metabolic byproducts of aerobic metabolism, allowing local accumulation of toxic metabolites including lactic acid and excitatory neurotransmitters, as well as the loss of ionic homeostasis. ATP and phosphocreatine are depleted, impaired osmoregulation follows, and calcium is released activating tissue lipases, proteases, and endonucleases. This first phase of hypoxic-ischemic injury is best viewed as a failure of energy production and supply.

A second phase of injury can occur at a later time and differs from this first failure of energy production and supply in that it occurs in the absence of cerebral acidosis. In this phase, the initiating event alters cerebral metabolic pathways linking neuronal and glial protein synthesis, growth factor production, and inflammatory byproducts to produce parenchymal injury. The most obvious form of this type of injury is when asphyxia is present. Although the complication of asphyxia is as old as childbirth, our understanding of it is incomplete in part because it is defined in so many disparate ways in the literature, making comparisons of treatment strategies and outcomes difficult. The most recent consensus definition of neonatal asphyxia is that of the American Academy of Pediatrics and the College of Obstetricians and Gynecologists: (1) fetal acidemia, (2) umbilical cord pH <7.0, (3) Apgar score of 0–3 after 5 min, (4) neurological dysfunction, and (5) multisystem organ dysfunction.

The occurrence of asphyxia as defined does *not* inevitably lead to permanent injury such as cerebral palsy, since so many other variables also influence outcome. These include the extent of encephalopathy present along with obstetric risk factors, perinatal events, and neonatal signs. Genetic factors may also play an important role in long-term outcome. Heterozygosity for endothelial protein C receptor single nucleotide polymorphism in term infants and possession of the variant A allele of interleukin 8 and heterozygosity for the β-2 adrenergic receptor in preterm newborns have been associated with the spastic diplegic form of cerebral palsy.

The interval between the first and second phases of cerebral energy depletion does provide an opportunity for therapeutic intervention. Numerous treatments have been proposed with generally disappointing results (see *Table 360.4*). Benefits of various treatments demonstrated in animal models of asphyxia do not generally translate well into the human newborn, so that none of the interventions listed can be endorsed as effective or recommended as a standard of care for the asphyxiated newborn.

This leaves supportive care as the treatment standard, with careful attention to ventilatory and blood gas management, fluid and electrolyte status, maintenance of perfusion, and careful manipulation of serum glucose levels so that they neither drop below 40 mg/dL nor rise above 200 mg/dL. Both hyperglycemia and hypoglycemia will worsen the extent of cerebral parenchymal injury due to hypoxia and ischemia.

There has been recent interest in and research into the possibility that cerebral cooling of the asphyxiated newborn may be a treatment modality that can be implemented before the second stage of energy depletion occurs. Using highly selected cohorts, both systemic cooling and systemic + head cooling have been shown to reduce adverse outcome, with a relative risk for death or moderate/severe disability of 0.69 compared with control groups. Target core temperatures in both studies were 33.5–35°C achieved by cooling over a 2 h period for a duration of 72 h. The rate of rewarming was 0.5°C/h in

Table 360.4
Proposed pharmacological therapeutic interventions for hypoxic-ischemic encephalopathy

Intervention	Proposed mechanism of effect			
	FRI/S	NMDA	CCB	Misc
Allopurinol	+			
Catalase	+			
Desferoxamine	+			
Destromethorphan		+		
Dizocilpine (MK-801)		+		
Erythropoietin				+
Flunarizine			+	
Ketamine		+		
Insulin growth factor-1				+
Magnesium		+		
Minocycline				+
Monosialoganglioside GM_1				+
Nerve growth factor				+
Nicardipine			+	
Nimodipine			+	
Oxypurinol		+		
Phencyclidine (PCP)		+		
Phenobarbital				+
Platelet activating factors				+
Superoxide dismutase	+			

HIE hypoxic-ischemic encephalopathy, *NMDA* N-methyl-D-aspartate antagonist, *FRI/S* free radical inhibitor/scavenger, *CCB* calcium channel blocker, *Misc* miscellaneous

both studies. In both studies, cooling was started before 6 h of age. Further investigation and standardization of selection criteria are necessary before brain cooling can be widely deployed as an intervention for hypoxic-ischemic encephalopathy in a non-research setting.

Neuroimaging Abnormalities in the Neonate

A full recitation of possible acquired cerebral imaging abnormalities in the newborn is beyond the scope of this chapter. Congenital infections and malformations are covered in other chapters. The use of neuroimaging in the setting of three common brain injuries in the neonate, however, will be described. These are germinal matrix hemorrhage, hypoxic-ischemic encephalopathy, and periventricular leukomalacia.

Germinal Matrix Hemorrhages

Between 10 and 20 weeks gestation, the subependymal germinal matrix is interposed between the caudate nucleus, the caudothalamic groove, and the ventricle, and is the primary generator of cerebral neuronal and glial cell precursors during this time. By 23 weeks, the germinal matrix (GM) begins an involution that will not be completed until about 36 weeks, with the process mostly completed by 32 weeks gestation (see *Table 360.1*). The dissolution of the GM is an apoptotic process taking place within a gelatinous structure that is devoid of arteries, veins, or capillaries. The GM does have a disorganized sponge-like internal structure that is suffused with blood, and has major vessels such as the superior thalamostriate (terminal) vein embedded within it. The minimum age of viability of the premature neonate unfortunately coincides with the occurrence of the weeks long dissolution of the GM; the unique generative and devolving structure of this metabolically active tissue poses an especially high risk for hemorrhage (*Table 360.5*).

Some GM hemorrhages may occur prenatally, but the majority of all GM hemorrhages occur within the first 72 h of life in a preterm infant who may be critically ill. For this reason the most commonly deployed neuroimaging tool is ultrasound, with an initial scan performed in a preterm newborn at 24° and again at 72°, with follow-up scans at a week and at hospital discharge. Grading the severity of germinal matrix hemorrhages is based upon the schema as first described by Papile, and best visualized by cranial ultrasound. Grade I GM hemorrhages are confined to the anatomical boundaries of the subependymal germinal matrix. The greatest volume of the GM is anatomically correlated with the greatest volume of the caudate nucleus at its head in the frontal portion of the lateral ventricle, but the GM does follow the head, body, and tail of the caudate into the temporal horn of the ventricle so that GM hemorrhages may rarely be seen in the temporal GM.

Grade II GM hemorrhages differ from Grade I in that blood escapes from the GM into the cerebrospinal fluid *without* causing ventricular dilatation. In a Grade III hemorrhage, not only does blood escape into the ventricle, but the resulting impairment of cerebrospinal drainage through the narrow aqueduct of Sylvius and of absorption through the arachnoid granulations causes ventricular enlargement.

Grade IV GM hemorrhage should not properly be considered as an "extension" of a Grade III hemorrhage since its pathological correlate, periventricular hemorrhagic infarction, has a different set of antecedent risk factors and markedly different implications for prognosis. In addition to the destruction of local white matter, the germinal matrix is itself ablated with consequences for cerebral development as production of neuronal and glial precursors is still under way. Grade IV GM hemorrhage significantly increases the risk of permanent neurological injury, with major cognitive and motor deficits likely if the infant survives the initial injury.

Hypoxic-Ischemic Encephalopathy

Imaging abnormalities suggestive of hypoxic-ischemic encephalopathy (HIE) will not occur without a suggestive clinical history, but imaging can be quite helpful. Magnetic resonance imaging (MR) is the most useful diagnostic tool in the setting of HIE. Important advantages of MR over other imaging modalities in this setting include superior anatomical resolution and localization and, based upon the pattern of abnormality seen, an ability to make inferences about the mechanism of injury.

Three general patterns of cerebral injury related to HIE may be seen in the *term* infant. These are (1) parasagittal arterial borderzone lesions, (2) structure-specific ("selective") neuronal necrosis, and (3) focal or multifocal neuronal necrosis. The first of these is associated with pre- or perinatal systemic hypotension of sufficient duration to impair distal flow of cerebral arteries and, because major cerebral arteries (middle [MCA], anterior [ACA], posterior [PCA]) in their termini supply the same parenchymal tissues, those tissues are deprived of blood flow and are susceptible to injury. Parasagittal cortex and adjacent

Table 360.5
Selected disorders with genetic correlation

Disorder	Gene	OMIM™	Gene location
Beckwith–Wiedemann syndrome	BWS	130650[a]	11p15.5, 5q35
Cardiofacial syndrome of Cayler	ACF	125520[b]	22q11
CFEOM	CFEOM1	135700[a]	12q12
COL4A1	COL4A1	120130[c]	13q34
Convulsions, benign familial infantile	BFIC3	607745[a]	2q23-q24.3
Duane retraction syndrome	DURS1	126800[b]	8q13
Ehlers–Danlos syndrome	EDS	130050[a]	2q31
Epilepsy, Benign Neonatal	KCNQ3	121200[a]	20q13.3
Hyperexplexia	GLRA1	149400[a]	14q24, 11p15.2-p15.1, 5q32, 4q31.3
Maple syrup urine disease	MSUD	248600[a]	7q31-q32, 1p31, 6q14, 19q13.1-q13.2
5,10-Methylenetetrahydrofolate reductase	MTHFR	607093[c]	1p36.3
Myasthenia syndrome, congenital	CMS1D	608931[a]	7p12-p11, 17p13-p12, 11p11.2-p11.1, 9q31.3-q32
Myotonic dystrophy	MDPK	160900[a]	19q13.2-q13.3
Möbius syndrome	MBS	157900[b]	13q12.2-q13
Prader–Willi syndrome	PWS	176270[a]	15q12, 15q11-q13
Prothrombin	F2	176930[d]	11p11-q12
Ptosis, congenital	PTOS2	300245[b]	Xq24-q27.1
Spinal muscular atrophy type I	SMA1	253300[a]	5q12.2-q13.3

OMIM Online Mendelian Inheritance in man based upon the text *Mendelian Inheritance in Man*, authored and edited by Dr. Victor A. McKusick and a team of science writers and editors at Johns Hopkins University and elsewhere. *Mendelian Inheritance in Man* is now in its 12th edition. See McKusick VA (1998) Mendelian Inheritance in Man. 12th edn. Johns Hopkins University Press, Baltimore. http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim

[a]Usually a phenotype and not representing a unique locus

[b]A confirmed Mendelian phenotype or phenotypic locus for which the underlying molecular basis is not known

[c]A gene of known sequence

[d]A phenotype with a gene of known sequence

subcortical white matter are affected with a posterior to anterior severity gradient due to the additional susceptibility of the posterior cortex to injury since this is the borderzone between three (MCA, ACA, PCA) rather than two (MCA, ACA) arteries. An unrecognized nuchal umbilical cord with restriction of arterial flow represents one possible cause.

The duration and extent of the hypoxic-ischemic event will influence the type of injury seen on imaging. Very severe, very prolonged events will lead to diffuse injury of the entire neuraxis, with diffuse neuronal necrosis present. When the duration of the event is less prolonged, and the extent moderate to severe, "selective" injury to the cerebral cortex, basal ganglia (putamen in the term, globus pallidus in the preterm infant), and thalamus is prominent. Severe but less lengthy events will lead to a different pattern of "selective" necrosis involving the basal ganglia, thalamus, and brain stem with relative sparing of the cerebral and cerebellar cortex. Event etiologies include uterine rupture, placental abruption, and umbilical cord prolapse.

Focal and multifocal cortical necrosis is readily distinguished from the parasagittal and selective patterns because the associated injury occurs within an arterial vascular distribution rather than a regional injury that does not conform to a particular arterial or venous supply. Systemic circulatory insufficiency at any time prior to, during, or immediately after delivery promotes this type of hypoxic-ischemic parenchymal injury.

Periventricular Leukomalacia

Two general patterns of periventricular white matter injury may be imaged in neonates. The first is a blush of periventricular white matter echogenicity seen on cranial

ultrasound. The location of the echogenicity is adjacent to the frontal horns and atria of the lateral ventricles. This early finding has an MR correlate of increased T1W, T2W, and FLAIR signal. The second pattern is that of small or sometimes large cystic cavitations (leukomalacia) in the same anatomical distribution. It is likely that these two patterns represent opposite ends of a continuum of injury that begins with focal areas of *microscopic* white matter gliosis and necrosis, and ends with *macroscopic* cystic degeneration of periventricular white matter. While white matter gliosis is commonly seen in the brains of *dead* premature infants, the incidence of cystic periventricular leukomalacia (PVL) in *live* preterm infants is by comparison rare. So too is the observation of PVL in the *neonate*, as this imaging finding has few clinical correlates in the newborn period, and is most commonly documented in infants with emerging neurological deficits or signs *after* the neonatal period.

Neonatal Brain Death Determination

Death occurs when the heart stops, the lungs no longer allow for respiration, *and* the brain ceases to function. With modern therapy, the heart and lungs can recover from injury and remain functional for extended periods of time, leaving a need to better define when brain functioning has ceased *and no recovery is possible*. The American Bar Association, the American Medical Association, the National Conference of Commissioners on Uniform State Laws, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research and the Academy of Pediatrics (AAP) have all endorsed the following language in determining brain death: "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions or (2) irreversible cessation of all functions of the entire brain including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards."

In the United States, as in most countries, the clinical neurological exam is the standard used to determine whether brain death has occurred. There are two important prerequisites that must be satisfied before determining that brain death has occurred. The first is that all possible alternative causes for the clinical presentation of brain inactivity be excluded, and the second is that the examination must be unchanged at two different points in time. Therefore, the following conditions must be excluded: toxic and metabolic disorders, use of sedative-hypnotic or paralytic drugs, hypothermia, and hypotension.

In the neonate, the maternal and perinatal history is important in helping to rule out reversible or remediable causes of coma. According to the Special Task Force convened by the AAP, the criteria used in older children to confirm brain death are useful in the *term* infant ($\geq$38 weeks) but not until 7 days *after* the insult, as the brain death examination and understanding the proximate cause of the insult can be difficult to determine prior to this time.

Application of these criteria to the *preterm* infant is much more difficult. Hypotonia and apnea, for example, may be normal findings in the very preterm infant, so that there are no indisputable criteria for these patients. The British Pediatric Association believes that it is difficult to confirm brain death at all in the *full-term* newborn, and does not recognize an acceptable definition of brain stem death in the *preterm* infant.

The clinical examination for brain death determination in the term newborn has the following minimum elements:

1. Normothermia ($\geq$36.5°C) and normal blood pressure (or positive fluid balance in the previous 6 h) must be present.
2. Intoxicant levels are within a range that would not normally be expected to interfere with consciousness. Sedative drugs, aminoglycosides, tricyclic antidepressants, anticholinergics, antiepileptic drugs, or neuromuscular blocking agents should all be considered.
3. Absent pupillary responses to light and ciliospinal stimulation. Pupils should be fixed and either midposition or dilated.
4. Absence of spontaneous eye movements.
5. Absence of evoked eye movements (caloric, oculovestibular stimulation). Caloric stimulation is generally performed with cold water to minimize the possibility of thermal injury. A minute after water infusion should be allowed before determining a negative response, and 5 min allowed between sides.
6. Absence of facial or tongue movements, as well as absent swallowing, cough, gag, sucking, and rooting reflexes. Stimulation of the posterior pharynx should elicit no response.
7. Absent corneal reflexes.
8. Absent spontaneous motor movements. Reflex withdrawal to noxious stimulation and reflex myoclonus are allowable.
9. Absent respiratory activity. This requires the completion of an apnea test upon conclusion of the second clinical examination. Pure oxygen is delivered into the trachea. Arterial PO_2, PCO_2, and pH are determined

after 5 min. If PCO_2 is 60 mm Hg or is $\geq$20 mm Hg greater than baseline, and no respiratory movements are present, the apnea test is positive, supporting the diagnosis of brain death. If respiratory movements occur, the test is negative, and brain death is not supported.

10. Two examinations separated by at least 48 h must show identical findings.
11. Additional testing is not necessary unless anatomical abnormalities of the face, brain, or pharynx are present, cardiac dysrhythmias during the apnea testing, or other factors preclude the completion of the examination. In that case confirmatory testing may be deployed.

Confirmatory testing may include EEG, nuclear brain scanning, somatosensory evoked potentials, transcranial Doppler ultrasonography, and angiography. These may be of limited utility in the newborn, and have the potential to be unhelpful, so their use should be carefully considered. Cerebral angiography is rarely used in newborns, and is not recommended due to the small size of the patient and the potential for severe renal injury. Somatosensory evoked potentials (SEP) may show the absence of N20-P22 responses, but few neurophysiologists have any experience with SEP in newborns and the test interpretations may be unreliable.

EEG and radionuclide scanning may be misleading as well, since in newborns both types of tests can fail to confirm clinically determined brain death in nearly half of cases. Persisting EEG activity may be present even when brain death is certain, so EEG activity does not obviate the diagnosis of brain death. Conversely, electrocerebral silence does not always imply brain death, particularly when phenobarbital levels are supratherapeutic ($\geq$25 mg/dL), hypothermia is evident, or a brain malformation is present. Term infants who meet clinical criteria for brain death for 2 days, and preterm infants who meet clinical criteria for brain death for 3 days do not survive independent of their EEG or cerebral blood flow status, so an unchanged clinical examination remains the most reliable indicator of an irreversible lack of brain function.

Despite the absence of clear and clinically reliable criteria for the determination of brain death in critically ill preterm newborn infants, neurological prognosis is grave when brain activity is persistently absent, and this needs to be clearly imparted to the family who is invested on many levels in the decision making process, the outcome, and subsequent care of the child.

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361 Neonatal Seizures

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Definitions

Seizures are self-limited clinical events resulting from an abnormal and excessive firing of cortical neurons. Neonatal seizures (NS) occur within the first 4 weeks of life in a full-term infant and up to 44 weeks from conception in premature infants. Neonatal seizures can be classified as symptomatic, cryptogenic, or idiopathic. Symptomatic seizures are associated with identifiable brain insults. Cryptogenic seizures are believed to be symptomatic, but the underlying insult has not been confirmed. Idiopathic seizures are not associated with an underlying brain lesion and are generally presumed to be genetic in origin. Most seizures in neonates are focal, arising from one region of the brain, or multifocal, arising independently from multiple different regions. Generalized seizures, which originate in deep midline structures and spread rapidly through both hemispheres, are uncommon in neonates. The clinical appearance of seizures can be described as tonic, clonic, myoclonic, or subtle. Tonic seizures involve sustained contraction of one or more muscle groups, whereas clonic seizures refer to contraction alternating with relaxation with a frequency generally ranging between 1 and 3 Hz. Myoclonic seizures involve a rapid, nonrhythmic jerking movement of one or more extremities. Subtle seizures are the most difficult to clinically diagnose. They involve alterations of behavior, motor, or autonomic function that can be difficult to distinguish from normal neonatal patterns. Examples of subtle seizures include bicycling or sucking movements, extraocular movement abnormalities, and apneic spells.

Etiology

In the neonatal period, the development of seizures most often represents a manifestation of an underlying neurological insult (*Table 361.1*). However, in some cases, NS occur in the absence of any identifiable cause. Identification and treatment of the primary cause of NS is the most important determinant of outcome. Four major etiologic groups have been described in previous classifications: neonatal encephalopathy (including hypoxic-ischemic encephalopathy), metabolic disturbances, CNS or systemic infections, and structural brain lesions (see *Table 361.1*).

Neonatal Encephalopathy

Neonatal encephalopathy is a heterogeneous syndrome characterized by central nervous system dysfunction, affecting term or near-term infants ($\geq$36 weeks gestation). These infants may have an abnormal state of consciousness (i.e., hyper-alertness, irritability, lethargy, obtundation), respiratory difficulties, hypotonia, or seizures. The causative factors of neonatal encephalopathy are varied, and although its true incidence is unclear, birth asphyxia is a well-known contributor to this condition. Administration of chest compressions for >1 min, onset of regular respirations >30 min after birth, and a base deficit >16 mmol/L on any blood gas analysis within the first 4 h from birth are predictors of severe adverse outcome (death or severe disability).

Permanent neurologic sequelae vary from learning difficulties and attention deficit, to cerebral palsy, epilepsy, visual impairment, and severe cognitive and developmental disorders. The severity of neonatal encephalopathy can be categorized as follows: mild (hyper-alertness, hyper-exitability, normal muscle tone, no seizures), moderate (hypotonia, decreased movements, and seizures), and severe (stuporous, flaccid, absent primitive reflexes, and frequent seizures). There is a correlation between the degree of encephalopathy and neurologic outcome. Mild neonatal encephalopathy carries a good prognosis, with a high probability of normal neurological outcome. Moderate encephalopathy carries a 20–35% risk of later sequelae. Neonates with severe encephalopathy have a 75% mortality risk in the neonatal period, and neurologic consequences are almost universal in this group. In addition to clinical predictors,

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Table 361.1
Most common causes of neonatal seizures (From UCSF Intensive Care House Staff Manual)

Cause	Usual age at onset	Preterm	Term
Hypoxic-ischemic encephalopathy	<3 days	+++	+++
Metabolic			
Hypoglycemia	<2 days	+	+
Hypocalcemia			
Early onset	2–3 days	+	+
Late-onset	>7 days	+	
Hypomagnesemia (often with hypocalcemia)			
Hyper/hyponatremia			
Drug withdrawal	<3 days	+	+
Local anesthetic toxicity			
Pyridoxine (vitamin B6) dependency			
Disorders of small molecules (amino acid, organic acid, and urea cycle disorders)			
Disorders of subcellular organelles (mitochondrial and peroxisomal disorders)			
Intracranial infection			
Bacterial meningitis (*E. coli*, Group B Strep., *Listeria*)	<3 days	++	++
Viral encephalitis (Herpes simplex, Enterovirus)			
Intrauterine infection (CMV, Toxoplasm., HIV, Rubella, Syphilis)	>3 days	++	++
Cerebral vascular			
Intraventricular hemorrhage	<3 days	++	
Primary subarachnoid bleed	<1 day		++
Subdural/epidural hematoma			
Focal ischemic necrosis (stroke)	Variable		++
Sinus thrombosis	Variable		+
Developmental defects			
Neurocutaneous disorders (tuberous sclerosis complex, incontinentia pigmenti)	Variable	++	++
Epilepsy syndromes			
Epileptic encephalopathies (early myoclonic encephalopathy, early infantile epileptic encephalopathy)			
Benign familial neonatal convulsions			

Relative Frequency: +++ = most common; ++ = less common; + = least common. If no +, then uncommon

MRI and EEG abnormalities have been linked to poor neurologic outcome.

Metabolic Disturbances

Metabolic abnormalities are among the most common causes of seizures in the neonatal period. Electrolyte imbalances such as hypocalcemia, hypomagnesemia, and hypoglycemia have been linked to the development of seizures. In addition, rare but potentially treatable metabolic causes of seizures are biotinidase and pyridoxine deficiency. Inborn errors of metabolism such as aminoacidurias, urea cycle defects, and organic acidurias are other rare causes of neonatal seizures.

CNS Infections

Bacterial as well as viral infections are common causes of seizures in the newborn period. Infectious agents

Table 361.2
Diagnostic workup for neonatal seizures (From Tharp: Neonatal seizures)

Serum glucose, calcium, magnesium, ammonia, lactate, pH, and a complete chemistry panel
Cerebrospinal fluid
Cranial ultrasound
EEG with perfusion of pyridoxine
Toxicology screen
Urine organic acids, serum and cerebrospinal fluid amino acids
Maternal and fetal titers for congenital infection
CT scan (hemorrhage and calcium) or MRI scan (cerebral dysgenesis, stroke)

transmitted vertically during pregnancy also put neonates at risk for developing seizures (*Table 361.2*).

Structural Brain Lesions

Structural brain lesions such as hemorrhages (intracerebral, subarachnoid, and intraventricular), infarctions, and anomalies of brain development are associated with seizures.

Epidemiology

The incidence of seizures in neonates is higher than in any other age group and is estimated to be 1–3.5 per 1,000 live births in full-term newborns. In the third world, the risk may be much higher. One study in rural Kenya reported an incidence of 39.5 per 1,000 live births. Preterm infants have the greatest risk, with an incidence as high as 227 per 1,000 live births. In the first world, the most common etiology is hypoxic-ischemic encephalopathy, which accounts for approximately two-thirds of cases. In third world countries, infectious causes are more common and account for up to three-fourths of cases. The risk of seizures is higher in male infants. Other risk factors for seizures in full-term newborns include nulliparity, diabetes, maternal infection, or fever, and delivery after 42 weeks gestation.

Pathogenesis

The mechanisms underlying neonatal seizures are distinct from those of other age groups. There are several major differences between neonatal and adult brains that are relevant to the development of seizures. In the balance between inhibition versus excitation, the neonatal brain tends toward excitation. This shift occurs, in part, because neurotransmitter systems are not yet fully developed.

Inhibition

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter of the central nervous system. Unlike glutamate receptors, which may have reduced expression in neonates, GABA receptors are present very early in development and are even expressed at embryonic stages. Once released into the synaptic cleft, GABA binds to its target receptors on the postsynaptic cell. Two classes of GABA receptors exist: ionotropic and metabotropic. Activation of ionotropic GABA(A) receptors results in opening of the ion channel, which, in adults, causes influx of chloride. Yet, in neonates, intracellular Cl^- concentrations are elevated when compared to adults. Hence, activation of GABA(A) receptors results in an efflux rather than an influx of Cl^-. The net result is that GABA(A) activation is excitatory in the neonate rather than inhibitory. This paradoxical effect of GABA receptor activation in newborns results from the developmental expression of the two Cl^- transporters responsible for determining intracellular Cl^- levels. In neonates, the Na+-K+-Cl^- cotransporter (NKCC1), which causes Cl^- influx, is highly expressed. Conversely, expression of the K+-Cl^- cotransporter (KCC2), resulting in Cl^- efflux, is virtually absent. The net result is an elevation of intracellular Cl^- in newborns. Hence, activation of GABA receptors in neonates results in Cl^- efflux and is thus excitatory. GABA becomes inhibitory as neuronal efflux of Cl(–) increases throughout development.

Excitation

Considering the rapid rate of learning and development in newborns, it should come as no surprise that neonatal brains are balanced toward excitation. Glutamate, the most abundant free amino acid in the brain and the predominant excitatory neurotransmitter of the central nervous system, is necessary for synaptogenesis and plasticity. It contributes to learning and memory through use-dependent changes in synaptic function, such as long-term potentiation and depression. Glutamate receptors can be divided into two types: ionotropic and metabotropic. Ionotropic receptors are cation channels with varying permeabilities for Na^+ and Ca^{2+}. By contrast,

metabotropic glutamate receptor (mGluR) activation occurs through second-messenger pathways. For the most part, glutamate receptors are overexpressed in the developing brain, and the timing of that heightened expression overlaps with the ages of greatest seizure susceptibility. Thus, an overexpression of glutamate receptors may predispose the neonate to heightened excitation and seizure susceptibility.

Glutamate transporters, referred to as excitatory amino acid transporters (EAATs), are necessary for ending glutamatergic transmission and keeping glutamate levels below a toxic range. EAATs are present in both neurons and glia. Dysfunction of glutamate transporters can result in cell death and has been implicated in a number of neurological disorders, including epilepsy. Both temporal and regional differences occur throughout development in the expression of EAATs. Hypoxic-ischemic encephalopathy, the most common cause of neonatal seizures, induces a loss of glutamate transporters in specific brain regions, such as the CA1 region of the hippocampus. Such reductions in EAATs further promote excitotoxic injury and seizures. This is observed in animal models in which diminished expression of glutamate transporters results in a reduced seizure threshold.

Clinical Manifestations

In neonates, seizures are difficult to recognize since they often mimic non-epileptic behaviors (See *Table 361.3*). Thus, video EEG is often required to confirm the diagnosis. The most difficult type of seizures to diagnose are termed subtle seizures. These consist of behavioral, motor, or autonomic alterations that appear similar to normal newborn behaviors. They include chewing, bicycling, ocular movements, and apnea. The sudden or sustained onset of these behaviors combined with their frequent recurrence help distinguish them from non-epileptic events. The most reliable seizures to diagnose clinically are clonic seizures. They consist of rhythmic movements (generally ranging between 1 and 3 Hz) of one or more extremities. They are also likely to have an EEG correlate. Tonic seizures, which involve sustained muscular contraction, may involve one extremity or the whole body. Myoclonic seizures, on the other hand, consist of rapid jerking movements and may be either focal, multifocal, or generalized. Myoclonus can also result from non-epileptic causes in newborns.

Neonatal seizures are further characterized by their relationship to findings on EEG (See *Table 361.4*). An electrographic seizure is a discrete event visualized on EEG that has a definable beginning, middle, and end.

Table 361.3
Clinical characteristics, classification, and presumed pathophysiology of neonatal seizures (From Mizrahi EM, Kellaway P (1998) Diagnosis and management of neonatal seizures. Lippincott-Raven, Philadelphia, p 181. Copyright © 1998 Lippincott Williams & Wilkins)

Focal clonic
Repetitive, rhythmic contracts of muscle groups of the limbs, face, or trunk
May be unifocal or multifocal
May occur synchronously or asynchronously in muscle groups on one side of the body
May occur simultaneously, but asynchronously on both sides
Cannot be suppressed by restraint
Pathophysiology: epileptic
Focal tonic
Sustained posturing of single limbs
Sustained asymmetrical posturing of the trunk
Sustained eye deviation
Cannot be provoked by stimulation or suppressed by restraint
Pathophysiology: epileptic
Generalized tonic
Sustained symmetrical posturing of limbs, trunk and neck
May be flexor, extensor or mixed extensor/flexor
May be provoked or intensified by stimulation
May be suppressed by restraint or repositioning
Presumed pathophysiology: nonepileptic
Myoclonic
Random, single, rapid contractions of muscle groups of the limbs, face, or trunk
Typically not repetitive or may recur at a slow rate
May be generalized, focal, or fragmentary
May be provoked by stimulation
Presumed pathophysiology: may be epileptic or nonepileptic
Spasms
May be flexor, extensor, or mixed extensor/flexor
May occur in clusters
Cannot be provoked by stimulation or suppressed by restraint
Pathophysiology: Epileptic
Motor Automatisms
Oral-buccal-lingual movements
Random and roving eye movements or nystagmus (distinct from tonic eye deviation)
Progression movements (rowing, swimming, bicycling)
May be provoked or intensified by stimulation
Presumed pathophysiology: nonepileptic

Table 361.4
Classification of neonatal seizures based upon electroclinical findings (Modified from Mizrahi EM, Clancy RR (2000) Neonatal seizures: early-onset seizure syndromes and their consequences for development. Ment Retard dev Disabil Res Rev 6:229. Copyright © 2000 Wiley-Liss)

Clinical seizures with a consistent electrocortical signature (pathophysiology epileptic)
Focal clonic
Unifocal
Multifocal
Hemiconvulsive
Axial
Focal tonic
Asymmetrical truncal posturing
Limb posturing
Sustained eye deviation
Myoclonic
Generalized
Focal
Spasms
Flexor
Extensor
Mixed extensor/flexor
Clinical seizures without a consistent electrocortical signature (pathophysiology presumed nonepileptic)
Myoclonic
Generalized
Focal
Fragmentary
Generalized tonic
Flexor
Extensor
Mixed extensor/flexor
Motor automatisms
Oral-buccal-lingual movements
Ocular signs
Progression movements
Complex purposeless movements
Electrical seizures without clinical seizure activity

Electroclinical seizures are those clinical seizures that occur in correlation with electrographic seizure activity. If the seizure does not correlate with EEG seizure activity, it is denominated clinical only. A significant number of infants have electrographic seizures only. These seizures occur in infants who have severe encephalopathy, those who have received antiepileptic drugs (AEDs), or in infants with drug-induced paralysis.

Diagnosis

As mentioned above, neonatal seizures are symptomatic and most likely secondary to an underlying abnormality. More rarely, these seizures are part of a more extensive epilepsy syndrome. Four neonatal syndromes have been described: benign neonatal convulsions (BNC), benign neonatal familial convulsions (BNFC), early myoclonic encephalopathy (EME), and early infantile epileptic encephalopathy (EIEE). The first two syndromes are considered benign, and are associated with relatively good prognosis and survival. The latter two exhibit a suppression-burst pattern on EEG and are categorized as catastrophic for their poor prognosis.

Benign Neonatal Convulsions

The cause of this syndrome, which comprises 2–7% of all neonatal seizures, is unknown; however, acute zinc deficiency in the cerebrospinal fluid (CSF) of affected neonates as well as rotavirus infection have been postulated as possible etiologies. The seizures affect mostly term or near-term infants after an uneventful pregnancy and delivery, and with no family history of seizures. The incidence is higher in the first 7 days of life, with 90% occurring between days 4 and 6. The seizures are brief and self-limited, although some evolve to prolonged seizures. They are most commonly focal clonic or focal tonic, and usually recur in a period of 24–48 hours. EEG findings associated with these seizures include nonreactive rhythmic activity, discontinuity, interhemispheric asynchrony, and multifocal sharp waves. This pattern is known as "theta pointu alternant"; it is nonspecific, and is seen only in 60% of the patients. Due to the resemblance of this syndrome with other seizure types, this diagnosis remains a diagnosis of exclusion, after other most common etiologies have been ruled out. Diagnostic criteria have been proposed for this syndrome, which include an Apgar score greater than 7 at 1 min, a typical interval between birth and seizure onset (4–6 days), a normal neurologic examination before and between the seizures, normal laboratory findings (e.g., metabolic studies, neuroimaging, and cerebrospinal fluid analysis), and no family history of neonatal seizures. The treatment of these seizures is similar to other seizures in

the neonatal period. If AEDs are used, they can be stopped once the infant is beyond the 24–48 hours period of recurrence risk. The prognosis of this syndrome is relatively good in terms of neurologic status, development, and postneonatal epilepsy. However, some data suggest a variable outcome, with 15% of infants manifesting transient "psychomotor delay" at 4–6 months of age, implying that the seizures may adversely affect the infant.

Benign Familial Neonatal Convulsions (BFNC)

This is an autosomal dominant disorder that affects approximately 14.4 per 100,000 live births. There are two types of BFNC: EBN1 is the result of a mutation in the voltage-gated potassium channel KCNQ2, whereas EBN2 is the result of a deletion in the chromosome 8q24, which encodes for another potassium channel known as KCNQ3. This syndrome is characterized by focal or multifocal clonic or tonic seizures, a family history of neonatal seizures, and no other neurologic abnormalities. It is characterized by brief seizures, which in some cases may recur until the age of 2–3 months, when spontaneous resolution typically occurs. The interictal EEG is usually normal. The treatment of this syndrome is similar to that of other neonatal seizures. Even if this syndrome is thought to be benign, recent data suggests an increased rate of postnatal epilepsy in these patients.

Early Myoclonic Encephalopathy (EME)

This disorder peaks in the early neonatal period. Its etiology is unknown, but it has been associated with inborn errors of metabolism, such as non-ketotic hyperglycemia, D-glycemic academia, methylmalonic academia, propionic academia, and hyperammonemia due to carbamyl phosphate synthetase deficiency. This syndrome is characterized by myoclonic seizures in the first week of life. This is followed by partial seizures, myoclonus, infantile spasms, and infrequently, tonic seizures. The EEG shows a characteristic suppression burst pattern (S-B; bursts of spikes, sharp waves, and slow activity lasting 5–6 s, alternating with 4- to 12-s periods of attenuation), that progresses to a hypsarrythmic pattern or a markedly abnormal background with multifocal spikes and sharp waves. Neonates with this syndrome present with an altered state of consciousness, with manifestly delayed milestones, hypotonia, and microcephaly from cerebral atrophy. The myoclonus present at birth tends to resolve; however, the focal motor seizures become refractory to antiepileptic therapy. Approximately 50% of the infants die, most within the first year of life. The focal motor seizures are treated with standard AEDs.

Early Infantile Epileptic Encephalopathy

This disease is characterized by intractable tonic seizures in the neonatal or infantile period. On EEG, a suppression-burst pattern is seen. The bursts are relatively prolonged (2–6 s) and shorter periods of suppression is seen when compared to EME. There is associated synchronization with the tonic spasms, with an initial high-voltage slow wave followed by generalized fast activity. The EEG abnormalities in EME and EIEE are similar, and the etiologies may overlap. The majority of anomalies associated with EIEE, however, are structural in origin, that is, porencephaly, Aicardi's syndrome, cerebral atrophy, hemimegalencephaly, dentate-olivary dysplasia, and migrational defects. Inborn errors of metabolism are rarely associated with EIEE. This is in contrast to disorders associated with EME, which are mostly metabolic in origin. This syndrome occurs during the first months of life. Affected infants have an abnormal neurological exam, with spasticity, motor asymmetries, and developmental delay. Tonic spasms are the predominant seizure type. Additional seizures include focal motor seizures and hemiconvulsive seizures. Erratic myoclonus is absent in EIEE, which is in contrast with EME where it is an early characteristic, and tonic spasms occur late in the disease. Several different approaches have been implemented in the treatment of EIEE, including AEDs, steroids, ACTH, and vitamin B6. The outcome, however, is still poor, with approximately a 50% mortality during infancy, and survivors being severely affected and sometimes progressing to develop infantile spasms.

Differential Diagnosis

Normal behaviors of the newborn sometimes raise suspicion of seizures. Nonspecific random movements, including sucking, coughing, and gagging, are among these behaviors. Neonates may also experience normal myoclonus during REM as well as non-REM sleep. Jitteriness, a tremulous movement that is suppressible when holding the limb, is normal in newborns and is generally not a manifestation of seizure activity. Apnea, bradycardia, and tonic posturing can be seen from gastroesophageal reflux (Sandifer syndrome). A barium swallow or pH probe may be required to confirm this diagnosis. Hyperekplexia, an exaggerated startle response to an

unexpected stimulus, may resemble generalized myoclonus. However, hyperekplexia is non-fatigable, and can be elicited repeatedly by finger tap on the infant's glabella.

Treatment

The first step in treatment is to assess the general medical condition of the child, beginning with airway, breathing, and circulation. It is important to determine the underlying etiology of the seizures, since some conditions can result in brain injury if not treated promptly. Meningitis and hypoglycemia are two particularly important conditions to consider. After medically stabilizing the patient, antiseizure medications should be initiated to prevent recurrence. Pharmacotherapy is generally continued until the underlying cause has resolved, the seizures have subsided, and the patient is fully alert. Achieving these conditions often requires 1–3 months.

CNS Infection

Treatment of infection, if present, is of extreme importance in controlling seizures in the neonate. Broad spectrum antibiotics in high doses should be instituted after CSF has been obtained to evaluate for the presence of meningitis. In neonates, the first choice of antibiotics is ampicillin (100 mg/Kg/dose) and gentamycin (dose in accordance with gestational age).

Metabolic Abnormalities

Hypoglycemia, hypocalcemia, and hypomagnesemia are common electrolyte imbalances that should be corrected promptly. Pyridoxine dependency must also be considered in refractory seizures and can be diagnosed by administering intravenous pyridoxine (100 mg; the dose may be repeated four times to a total of 500 mg if needed) under EEG monitoring. If pyridoxine dependency is present, the seizures and epileptic changes on EEG will resolve within seconds of administration. Folinic acid–responsive seizures should also be considered in refractory cases, and may be combined with pyridoxine.

Institution of Antiseizure Medications

The acute treatment of neonatal seizures is not different from the management of any other emergency (see *Table 361.6*). After airway, breathing, and circulation have been addressed, and the above-mentioned causes of seizures have been investigated and treated, the physician is left with the decision of whether to institute antiseizure medications. In so doing, there are a few issues that need to be considered. Not all the clinical events in the neonate are seizures in origin, and may therefore not require treatment. Further, some benign causes of neonatal seizures are transient and resolve without associated morbidity. In these cases, instituting therapy will expose the neonate to medication side effects with limited benefit. More aggressive seizures, on the other hand, can be associated with severe neurological impairment and future morbidity. Such seizures therefore require treatment.

Table 361.5
Long-term outcome of neonatal seizures (From Tharp: neonatal seizures)

High mortality (30%) and morbidity (50% of survivors)
Approximately 30% of survivors develop epilepsy
Worst outcome in infants with hypoxic – ischemic encephalopathy, meningitis, and cerebral dysplasia
Better outcome with transient neonatal hypocalcemia, idiopathic and familial seizures, and stroke
Neonatal EEG, neurologic examination, and imaging results are best predictors of outcome

Phenobarbital

As stated above, this is the first drug of choice in the treatment of neonatal seizures. Phenobarbital is metabolized in the liver, and eliminated by the kidney. In infants with impaired function of these two organs, such as HIE patients, phenobarbital levels can be elevated and cause toxicity. Additionally, as the neonate matures, the metabolism of this drug augments, and the levels drop. This has the potential to cause breakthrough seizures. Phenobarbital levels should be monitored in neonates to avoid this phenomenon.

Phenytoin

This drug has variable pharmacokinetics in the developing neonate, with potential for subtherapeutic levels. Therefore, phenytoin levels should be monitored and its dose should be adjusted to each particular patient. In a randomized trial comparing phenobarbital and phenytoin, both drugs controlled seizures in less than 50% of patients.

Table 361.6

Doses of AEDs (Reproduced with permission from Mizrahi EM, Kellaway P (1998) Diagnosis and management of neonatal seizures. Lippincott-Raven, Philadelphia, p 181. Copyright © 1998 Lippincott Williams & Wilkins)

Drug	Loading	Maintenance	Average therapeutic range	Apparent half-life
Diazepam	0.25 mg/IV (bolus)	May be repeated 1–2 times		31–54 h
	0.5 mg/kg (rectal)			
Lorazepam	0.05 mg/kg (IV) (over 2–5 min)	May be repeated		31–54 h
Phenobarbital	20 mg/kg IV (up to 40 mg)	3–4 mg/kg in two doses	20–40 mcg/L	100 h after day 5–7
Phenytoin	20 mg/kg IV (over 30–45 min)	3–4 mg/kg in 2–4 doses	15–25 mcg/L	100 h (40–200)

Other Antiseizure Medications

Third-line antiseizure medications that have been tested include clonazepam, lidocaine, midazolam, and paraldehyde. Oral AEDs have also been employed including carbamazepine, primidone, valproate, vigabatrin, and lamotrigine. There is little known regarding the efficacy of these therapies, but some have shown promise in limited trials. In one study, 13 out of 13 newborns who failed to achieve seizure control on phenobarbital or phenytoin were seizure-free following the addition of midazolam. No adverse effects of the medication were reported and the patients demonstrated improved neurodevelopmental outcome. In a pilot study of levetiracetam monotherapy, six out of six neonates were seizure-free within 6 days of starting it. In a smaller case series, three infants, aged 2 days to 3 months, exhibited seizure freedom and had no side effects on levetiracetam. In a recent survey of child neurologists, 73% recommended treatment of neonatal seizures with either levetiracetam or topiramate, although adverse reactions were felt to occur more frequently from topiramate.

Prognosis

Neonatal seizures are mostly self-limited and disappear when the provoking insult resolves. Many infants, however, will experience seizure relapses after a seizure-free period. Other patients will continue to have seizures without a seizure-free interval. Epileptogenesis (the development of epilepsy) has been observed in several animal models of neonatal seizures. Rodent models of seizures and status epilepticus in the first 2–3 postnatal weeks generally cause very little cell death, and the synaptic sprouting associated with cell death in adult models of epilepsy are not observed in most neonatal models. Furthermore, neuronal death may not be observed even when epileptogenesis occurs. Initially, it was assumed that the lack of neuronal death indicated a relative absence of sequelae. More recently, however, the changes following neonatal seizures have come to be recognized as functional rather than structural. For example, limbic cognitive deficits are seen following neonatal seizures despite the absence of pathological abnormalities. Thus, a dissociation exists between pathological and functional deficits following neonatal seizures, and cell death may not be required for functional injury or subsequent epilepsy to occur within the hippocampal/limbic network. The long-term outcome of NS is illustrated in *Table 361.5*.

Prevention

Prevention of neonatal seizures centers on reducing known causes of brain injury. These include, but are not limited to, hypoxic-ischemic encephalopathy, intracranial hemorrhage, CNS infection, hypoglycemia, and stroke. Prompt recognition of hypoglycemia and infection are particularly important since these conditions worsen if not treated early. For causes of brain injury that are more difficult to avoid, neuroprotection may play a role in the future. A major development in the treatment of perinatal hypoxic-ischemic encephalopathy, the most common cause of neonatal seizures, is the administration of therapeutic hypothermia to prevent neuronal injury. In a recent meta-analysis that examined the 18-month outcome of newborns with HIE, therapeutic hypothermia significantly reduced the risk of death and neurodevelopmental disabilities, such as cerebral palsy and psychomotor retardation. In the largest study reviewed in that meta-analysis, there was a nonsignificant trend toward reduced rates of continued seizures in survivors (12/116 vs. 16/116, *P* value 0.42). A longer period of follow-up may be required to determine if epilepsy rates are truly improved in patients receiving hypothermia.

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362 Epilepsy in Infancy and Childhood

John N. Gaitanis

Definitions

Seizures are self-limited clinical events resulting from an abnormal and excessive firing of cortical neurons (Table 362.1). They manifest as transient motor, sensory, autonomic, or psychic symptoms with or without an alteration of consciousness (Table 362.2). *Epilepsy*, on the other hand, is a condition characterized by recurrent, unprovoked seizures. Epilepsy does not constitute a single entity and is instead a heterogeneous group of disorders, with multiple etiologies and clinical manifestations. Subdivisions of epilepsy are based upon the etiology or the clinical features. The International League Against Epilepsy published a classification system for seizures in 1981, and for epilepsies in 1989. In it, epilepsy is categorized as either *localization-related* (focal onset beginning over one region of brain) or *generalized* (having a simultaneous onset over both hemispheres). Epilepsy is further subdivided as *idiopathic* (no underlying cause other than a possible hereditary predisposition), *symptomatic* (a consequence of a known or suspected disorder), or *cryptogenic* (presumed to be symptomatic, but the cause is unknown). This classification scheme is based largely on clinical and electroencephalographic data. Significant advances in molecular biology, neuroimaging, and genetics have since taken place and will likely play a role in the development of future classification schemes.

When seizures are so frequently repeated or so prolonged as to create a "fixed and enduring epileptic condition," they are termed status epilepticus (SE). The most commonly chosen duration for seizures to qualify as SE has been 30 min, based on the belief that seizures persisting longer than that result in brain injury. More recently, however, an "operational" definition of SE has been proposed as 5 min or more of continuous seizures or "two or more discrete seizures between which there is incomplete recovery of consciousness." This definition, which applies primarily to GCSE, may be used clinically to direct treatment and help avoid refractory SE.

Etiology

Epilepsy is a heterogeneous condition with a multitude of etiologies (Table 362.3). Idiopathic and cryptogenic etiologies account for 60–70% of cases while symptomatic causes account for 30–40%. These rates are similar in industrialized and developing countries. Idiopathic epilepsies have an underlying genetic basis. Many idiopathic cases result from channelopathies, which impair neurotransmission. Others involve genes that are important for broader aspects of development, which may also result in mental retardation, autism, or brain malformations. Symptomatic etiologies of epilepsy, on the other hand, develop following brain injury. In children, perinatal insults are important causes and include hypoxic-ischemic encephalopathy, stroke, intracranial hemorrhage, periventricular leukomalacia, and hypoglycemia. Later in childhood, head trauma, infections, and brain tumors are more common. In developing nations, neurocystercircosis is a particularly important cause and may account for as many as 60% of first-time seizures and one-third of symptomatic epilepsies.

Epidemiology

Epilepsy is estimated to affect 50 million people worldwide, and it accounts for 1% of the global burden of disease. In industrialized countries, its prevalence ranges between 4 and 10 active cases per 1,000 persons. Prevalence estimates are only slightly higher in the developing world, ranging between 3.8 and 15.4 per 1,000. The incidence of epilepsy, however, is noticeably higher in developing nations. It ranges between 114 and 190 per 100,000 in developing countries, but is only 24–53 per 100,000 in industrialized nations. Developing countries have higher mortality rates for epilepsy, accounting in part for the disparity in incidence and prevalence data.

The age of onset also differs between regions. In industrialized countries, the onset of epilepsy occurs at the extremes of life, whereas in developing nations, the onset

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Table 362.1
Seizure terminology

Seizure: A clinical event, displaying signs or symptoms, resulting from an abnormal and excessive discharge of cortical neurons
Epilepsy: Recurrent, unprovoked seizures
Generalized: The initial seizure discharge involves a large number of neurons throughout both hemispheres and the clinical manifestations indicate bilateral onset
Partial: The initial seizure discharge involves a limited number of neurons in just one hemisphere
Simple: A seizure that does not cause alteration in consciousness
Complex: A seizure involving alteration in consciousness
Idiopathic: Epilepsy with a genetic cause
Cryptogenic: Non-idiopathic epilepsy without a known cause
Symptomatic: Non-idiopathic epilepsy with a known cause (usually a brain insult or other lesion)
Tonic: Sustained posturing of a body part
Clonic: Rhythmic jerking of a body part
Myoclonic: Brief, irregular contractions of a body part
Atonic: An abrupt loss of muscle tone
Tonic-clonic: Tonic activity alternating with clonic movements
Absence: A transient discontinuation of activity with loss of awareness

Table 362.2
Seizure classification

I. Partial (Focal)
A. Simple
1. Motor
2. Sensory
3. Autonomic
4. Psychic
B. Complex
II. Generalized
A. Absence
1. Typical
2. Atypical
B. Myoclonic
C. Clonic
D. Tonic
E. Tonic-clonic
F. Atonic

is highest in young and middle-aged adults. Parasitic diseases, more endemic in the developing world, likely account for this difference.

The incidence of status epilepticus ranges between 18.1 and 41 per 100,000 patients per year. In the United States, this amounts to 102,000–152,000 cases and 22,000–42,000 deaths annually.

Pathogenesis

The pathogenesis of epilepsy is as varied as the etiologies. Idiopathic and symptomatic causes of epilepsy have entirely different mechanisms of disease. Symptomatic epilepsy results from brain injury, whereas idiopathic forms result from genetic alterations involving proteins necessary for normal neurotransmission. Idiopathic epilepsy is therefore less likely to reveal neuroimaging abnormalities and more likely to be associated with a family history of epilepsy. There is considerable genotype-phenotype heterogeneity within genetic causes of epilepsy, even within the same family.

For example, mutations of the sodium channel gene, SCN1A, result in six different phenotypes, ranging from generalized epilepsy with febrile seizures plus syndrome (GEFS+) on the milder end of the spectrum to severe myoclonic epilepsy of infancy at the severe end. SCN1A codes for the alpha subunit of the neuronal voltage-gated sodium channel. The alpha subunit forms the membrane pore of sodium channels. There is some correlation between genotype and phenotype. Mutations resulting in premature protein truncation are more likely to lead to a severe phenotype whereas missense mutations are associated with milder phenotypes.

Multiple ion channels are now known to play a role in epilepsy. They include the sodium channel genes SCN1A and SCN1B, potassium channel mutations of KCNQ2 and KCNQ3, chloride channel mutations in CLCN2, and calcium channel impairments of CACNB4. Genetic alterations of neurotransmitter receptors, such as the GABA receptor genes GABRD and GABRG2, also result in epilepsy. Just as mutations of a single gene result in varied phenotypes, mutations of two completely unrelated genes can lead to identical phenotypes. GEFS+, for example, can result from mutations of SCN1A, SCN1B, SCN2A, SCN9A, GABRG2, or GABRD. Confirmation of the specific genetic cause may be clinically useful when determining the correct treatment plan. Sodium channelopathies,

Table 362.3
Etiologies of epilepsy

Symptomatic
Perinatal brain injury
HIE
PVL
ICH
Hypoglycemia
Stroke
Infection
Neurocystercircosis
Meningitis
Encephalitis
Trauma
Stroke
Hemorrhagic
Ischemic
Metabolic (i.e., MELAS)
Inborn errors of metabolism
Mitochondrial disorders
Lysosomal disorders
Peroxysomal disorders
Amino and organic acidopathies
Urea cycle disorders
Congenital brain malformations
Lissencephaly
Polymicrogyria
Focal cortical dysplasia/tuberous sclerosis
Heterotopia
Idiopathic
Channelopathies
Generalized epilepsy with febrile seizures plus
Childhood absence epilepsy
Juvenile myoclonic epilepsy
Chromosomal disorders
Trisomy 21
Wolf–Hirschhorn syndrome (4p-)
Ring Chromosome 20
Single gene disorders
Rett syndrome (MECP2, CDKL5, FOXG1)
Angelman's syndrome
Unverricht–Lundborg disease
Autosomal-dominant nocturnal frontal lobe epilepsy
Benign familial neonatal seizures
Cryptogenic
Undiagnosed cases associated with other neurological disorders such as autism, mental retardation, apraxia, or other developmental delays

for example, may worsen with sodium channel–blocking agents such as carbamazepine and phenytoin. Genetic confirmation is also helpful when counseling families.

Symptomatic epilepsy, on the other hand, results from environmental rather than genetic causes. Traumatic, ischemic, and infectious insults all result in epilepsy. Epilepsy develops from different types of injury through common mechanisms. Breakdown of the blood-brain barrier (BBB) is observed in brain injury. When the BBB is disrupted, intravascular albumin leaks into the extracellular space, resulting in glial dysfunction. Without proper glial function, glutamate cannot be cleared from the extracellular space. Elevation of glutamate results in hyperexcitability and an influx of intracellular neuronal calcium, which in turn causes neuronal injury and seizures. The initial injury, caused in part by excessive glutamatergic activity, is followed by a latent period, during which time no seizure activity takes place. During that period, pathophysiological and structural alterations are occurring which will later culminate in epilepsy. Further understanding of how injury leads to epileptogenesis may provide targeted treatments, which can prevent the onset of epilepsy.

Excessive glutamatergic activity also plays a role in the development of status epilepticus. As an illustration of this, an outbreak of toxic encephalopathy caused by ingestion of mussels contaminated with domoic acid, a glutamate analogue, caused prolonged seizures in many of the affected patients. Excitatory amino acids, especially glutamate, also contribute to the neuronal injury caused by SE. As seizures persist, there is also downregulation of inhibitory mechanisms, further contributing to SE. GABA-A receptors become less susceptible to the GABA agonist effects of benzodiazepines. This causes refractoriness to treatment with the GABA-acting medications, benzodiazepines and barbiturates.

Pathology

Temporal lobe structures, particularly the hippocampus and amygdala, are the most susceptible regions to epileptogenesis following brain injury. The resulting

neuronal loss and fibrillary gliosis of the mesial temporal structures is termed mesial temporal sclerosis (MTS). MTS is the most common pathological finding in patients with temporal lobe epilepsy and is seen in 65% of temporal lobectomy specimens. In approximately one-third of patients with MTS, dual pathology is observed. Additional findings may include dysplastic neuroepithelial tumors, cavernous angiomas, caudate atrophy, inflammatory changes, and focal cortical dysplasia. The significance of dual pathology is not known, but it calls into question whether MTS is the cause or effect of active epilepsy. Neuronal migration disorders, for instance, may predispose the patient to febrile seizures, which later result in MTS. Alternatively, the pathological changes seen in MTS can mimic dysplastic tissue, erroneously pointing toward a dual diagnosis. A final possibility is that both dysplastic tissue and MTS share a common embryological origin, and that both act together in the development of epilepsy.

Clinical Manifestations

Epilepsy should be suspected whenever a patient reports transient, repetitive, and stereotyped symptoms. Seizure semiology, the signs and symptoms of how a seizure is expressed, differs depending on the seizure type. Partial seizures involve a localized region of the cerebral cortex, and their symptoms reflect the area of involvement. For example, occipital seizures result in visual hallucinations whereas frontal seizures are more likely to cause motor symptoms. There are two main subdivisions of partial-onset seizures: simple and complex. Simple partial seizures do not involve impairment of consciousness. The symptoms can include sensory, motor, autonomic, or psychic (emotional sensation, dream-like state, or déjà vu) changes. Complex partial seizures, on the other hand, involve impairment of consciousness. They typically manifest as behavioral arrest and may involve staring or automatisms (repetitive movements such as chewing, lip smacking, or fumbling with hands). The patient often has no memory for these behaviors. Simple and complex partial seizures can secondarily generalize into generalized tonic-clonic seizures. Distinguishing between a primary versus secondary generalized seizure can be difficult. Secondary generalized seizures are recognized by a preceding aura, which represents a simple partial seizure preceding generalization. Primary generalized seizures, on the other hand, are not associated with a preceding aura.

There are six major categories of generalized seizures: absence, tonic, clonic, myoclonic, tonic-clonic, and atonic (see *Table 362.2*). Absence seizures are often difficult to distinguish from complex partial seizures since both manifest as staring spells. When compared to complex partial seizures, absence seizures are shorter (under 20 s), occur more frequently (often multiple times daily), and are less likely to be associated with automatisms or a prolonged postictal state. Many patients with primary generalized epilepsy experience more than one generalized seizure type. In juvenile myoclonic epilepsy, for example, patients exhibit generalized tonic-clonic, myoclonic, and absence seizures.

Just as seizures can take multiple forms, status epilepticus also presents in varied ways. *Generalized Convulsive Status Epilepticus* is the most dramatic and life-threatening form of SE. Fortunately, it is readily recognizable. It may begin with a partial seizure (simple or complex) that generalizes secondarily, or it can start as a generalized convulsion. There may be tonic and clonic movements, typically bilateral and symmetric, although the onset may occur on just one side. Consciousness is always impaired from the time the seizure generalizes. Afterward, the patient is stuporous. If the patient does not recover from the postictal stupor within a reasonable time, the possibility of continuing epileptic brain activity must be considered. This sort of decoupling of the electrical and motor systems constitutes "subtle" nonconvulsive SE, sometimes with just twitching or blinking or even no movement at all. Electroencephalography (EEG) is often helpful in confirming this.

Diagnosis

The diagnosis of seizures begins with a careful history. A detailed description of the episode, focusing on its onset, progression, time course, and recovery, helps establish if seizures are a likely etiology. If parents have a video camera, recordings of the event are particularly helpful in determining its clinical characteristics. The physical examination looks for neurological dysfunction, as might be present in a symptomatic etiology. Laboratory evaluations search for items missed on the history and examination. Two studies are particularly valuable: electroencephalography (EEG) and magnetic resonance imaging (MRI). EEG measures the brain's electrical activity. Transient electrical disruptions (spike waves or slowing) can indicate a predisposition for seizures and help determine if the seizures are focal or generalized. In addition, the appearance of abnormalities can be specific for particular seizure types or epilepsy syndromes. EEG is far from a perfect test, and can be normal in as many as 50% of patients with known epilepsy. Similarly, patients without a history of

seizures can display EEG abnormalities. Thus, the study has to be interpreted within its clinical context. Prolonged inpatient or ambulatory EEG, both of which can be combined with video, is an effective way to capture an event and confidently diagnose epilepsy. MRI provides a structural assessment of the brain, helping to determine if an epileptic focus is present. It is particularly useful in patients with a focal seizure onset, localized exam, or lateralized EEG abnormalities.

Once a diagnosis of seizures has been established, it is incumbent upon the treating physician to establish whether the patient's seizure type and EEG characteristics fall within a well-described epilepsy syndrome. These are important to recognize since each syndrome exhibits a characteristic treatment response and prognosis.

Febrile Seizures are the most common form of childhood seizures, affecting between 2% and 4% of all children. They occur between 6 months and 5 years of age, but the peak incidence is 18 months. Febrile seizures can be divided into simple and complex types. Simple febrile seizures are generalized, last less than 15 min, and do not recur within a 24-h period. All others are considered complex. Overall, one-third of children with a first febrile seizure will experience a recurrence. Risk factors for recurrence include a family history of febrile seizures and an age of onset less than 18 months. In children with febrile seizures, the overall risk of later epilepsy is approximately 2%. This risk is higher in the presence of neurological or developmental abnormalities, complex febrile seizures, or a family history of epilepsy.

Severe myoclonic epilepsy of infancy (SMEI or Dravet Syndrome) can mimic febrile seizures early in its course. Seizures begin in the first year of life. They are often associated with a fever and can be prolonged. By age 2, multiple seizure types develop, including atypical absence, complex partial, and myoclonic. The child is initially developmentally appropriate, but a decline occurs between 1 and 4 years of age. By age 4, most children exhibit intractable seizures and developmental delays. In approximately 80% of patients, the condition occurs from mutations of SCN1A (see section on Pathogenesis). Mutations of SCN1A are also found in patients with febrile seizures and Generalized Epilepsy with Febrile Seizures Plus (GEFS+) syndrome.

Infantile spasms are one of the most worrisome epilepsy syndromes, since the seizures are subtle and the prognosis is often poor (*Fig. 362.1*). They typically develop during the first year, with a peak age of onset between 4 and 6 months. Brief (1–5 s), symmetric contractions of the trunk with extension and elevation of the arms and tonic extension of the legs characterize the typical spasm. They occur in clusters shortly after waking. During a cluster, the infant may appear irritable. The triad of infantile spasms, hypsarrhythmia (a chaotic EEG pattern), and developmental regression is termed West's syndrome. The *Lennox–Gastaut syndrome* will develop in as many as 50% of children with infantile spasms. This syndrome, which occurs between 1 and 7 years of age, is comprised of mixed seizure types, cognitive decline, and a slow spike and wave pattern on EEG (<3 Hz) (*Figs. 362.2* and *362.3*).

Absence seizures are common to three epilepsy syndromes: childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy. *Childhood absence epilepsy* develops between 4 and 10 years of age and manifests with brief (5–15 s) periods of behavioral cessation or staring spells (*Fig. 362.4*). They can be exacerbated by hyperventilation. This can be a useful feature when diagnosing absence seizures in the office or EEG laboratory. The EEG reveals generalized 3 Hz spike and slow wave discharges in association with the clinical event. *Juvenile absence epilepsy* is similar, but has a later age of onset (6–10 years) and a greater frequency of generalized tonic-clonic seizures than childhood absence epilepsy. *Juvenile myoclonic epilepsy* has an onset between 12 and 18 years, and patients exhibit absence, generalized tonic-clonic, and myoclonic seizures. The myoclonic jerks typically occur in the early morning hours. The EEG displays fast (3.5–6 Hz), generalized spike and wave or polyspike and wave activity.

Benign childhood focal seizures account for 22% of children with epilepsy. These syndromes develop in school age and are outgrown in adolescence. They are characterized by their semiology, EEG features, and absence of neuroimaging abnormalities. The most common of these conditions is *benign epilepsy with centrotemporal spikes* (BECTS), which represents approximately 15% of all childhood epilepsies (*Fig. 362.5*). The most common seizure type is simple partial, involving motor or sensory symptoms of the hands or face. Generalized tonic-clonic seizures may also develop. Both seizure types commonly occur during sleep. The characteristic EEG pattern includes broad centrotemporal spikes that show an anterior-to-posterior dipole. In *Panayiotopoulos syndrome* (PS), children develop autonomic symptoms, with vomiting being the most common. Patients may appear restless or agitated during a seizure, and usually become confused or unresponsive over its course. Two-thirds of the seizures begin in sleep, and they are often prolonged (lasting greater than 30 min). EEG in PS reveals multifocal, high-amplitude, sharp slow wave complexes that shift between regions and hemispheres, but predominate in the occipital leads. *Idiopathic childhood occipital*

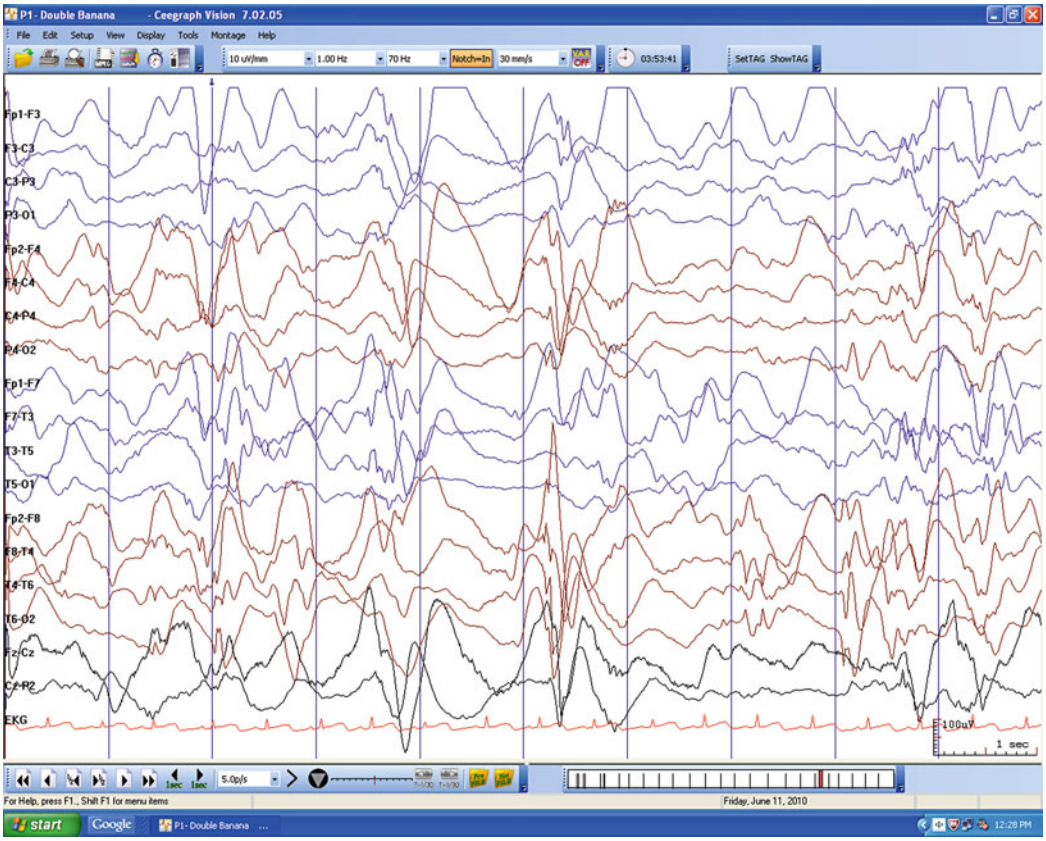

Figure 362.1
Twelve-month boy with infantile spasms. The interictal EEG shows a discontinuous background with high voltage delta slowing and spike waves interrupted by periods of voltage attenuation

epilepsy of Gastaut (ICOE-G) is also characterized by occipital spike waves on EEG. They are sometimes observed only in sleep and may be intermixed with centrotemporal discharges. The semiology differs from PS and is characterized by visual hallucinations, blindness, or both. The seizures are short, lasting 1–3 min, and occur frequently (sometimes daily). They may be followed by a postictal headache which is indistinguishable from migraine. ICOE-G is outgrown later than the other benign focal epilepsies of childhood, and may sometimes evolve into atypical absence epilepsy (*Fig. 362.6*).

Differential Diagnosis

The first challenge in evaluating a patient with suspected seizures is to determine if the clinical events are epileptic or nonepileptic in etiology. There are several nonepileptic events (NEE) that resemble seizures, and the considerations change based on the patient's age.

The diagnosis of seizures is hardest to make in neonates, in whom subtle nonspecific clinical findings, such as eye deviation, apneas, bicycling, or buccolingual movements, may be the only manifestations. Many of these subtle signs are easily misdiagnosed. Suspected seizures are actually NEE in as many as 90% of neonates. The clinical event with the greatest specificity for epileptic seizures is focal clonic activity, which is epileptic in approximately 44% of newborns. Jitteriness, on the other hand, is nearly always a nonepileptic phenomenon. Because of the difficulty in confidently diagnosing seizures in the neonate, video EEG is often required.

In infancy, tonic posturing is a common event, and is often misdiagnosed. Without other associated signs or symptoms, tonic posturing is epileptic only 30% of the time. One common nonepileptic cause in infants is Sandifer syndrome. This refers to abnormal tonic posturing of the neck, trunk, or limbs, resulting from gastroesophageal reflux. There is often a temporal association with feeds, or there is a past history of spitting up or feeding intolerance. A gastrointestinal evaluation is needed to confirm this diagnosis.

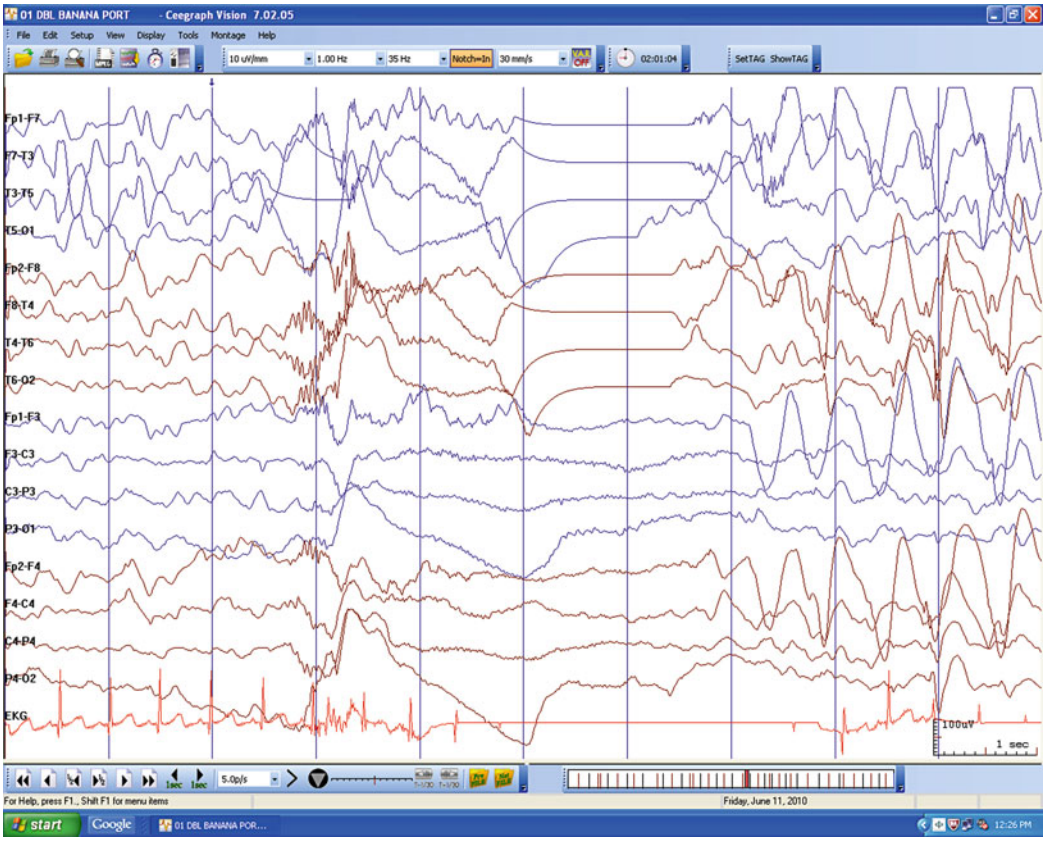

Figure 362.2

Twelve-month boy with infantile spasms. During his clinical spasms, there is a generalized decrement of the background activity with superimposed fast frequencies

Myoclonus is another event that is frequently misdiagnosed. Although myoclonic epilepsies can develop in infancy, there are two nonepileptic myoclonic syndromes that must be considered. These are benign neonatal sleep myoclonus and benign myoclonus of infancy. In benign neonatal sleep myoclonus, focal, multifocal, or generalized myclonic movements occur only during sleep. Each movement is brief, lasting a second or less, but the events may cluster. They end abruptly upon awakening. The movements usually begin in the first month and subside by 6 months of age, rarely persisting into childhood. The infant is otherwise neurologically normal. Benign myoclonus of infancy, on the other hand, begins at a later age (between 3 and 15 months) and involves tonic or myoclonic movements during wakefulness. The course is self-limited, and the events usually regress by age 2.

In early childhood, breath-holding spells are a common event. They may develop as early as infancy and will resolve prior to school age. Although most occur in response to an upsetting incident, the preceding cause is sometimes not observed by the parent. The child will display a color change, either pallor or cyanosis. Some children will have convulsive movements mimicking seizures and many are followed by a period of lethargy.

Later in childhood, most NEE can be distinguished from seizures based on a careful history or direct observation of the spells. Some include movement disorders such as motor tics, paroxysmal choreoathetosis, or focal dystonias. Narcolepsy, staring spells, complicated migraines, and syncope can also be difficult to distinguish from seizures. If all other causes have been excluded, psychogenic seizures must be considered. Many children with psychogenic seizure have epileptic seizures as well, so video EEG is often required for diagnosis.

Treatment

Once a correct diagnosis of epilepsy has been made, there are several reasons to consider treatment: (1) Reduce the risk of

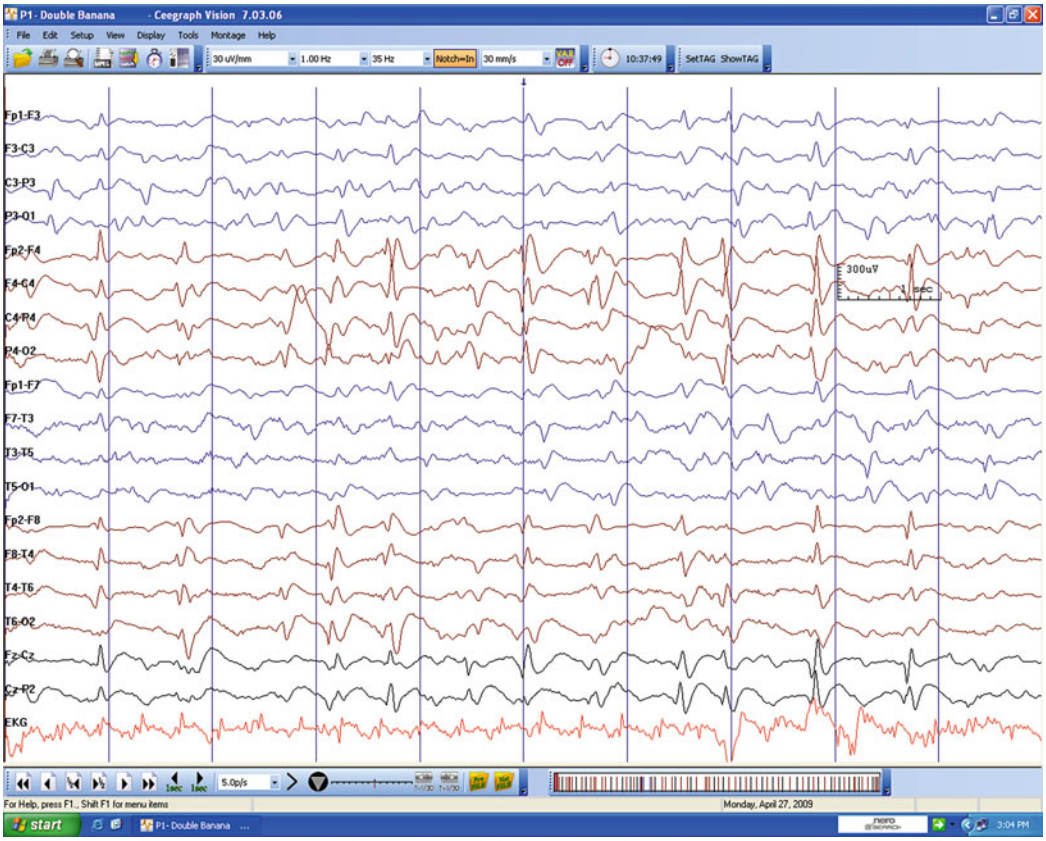

Figure 362.3

Seven-year-old boy with a history of infantile spasms and profound global developmental delays. He has multiple seizure types including generalized tonic-clonic, atypical absence, and drop spells. His EEG shows prolonged runs of slow spike and slow waves (approximately 1–2 Hz) and frequent delta slowing

epilepsy-induced injury. (2) Lessen the risk of prolonged seizures (status epilepticus). (3) Prevent sudden unexplained death in epilepsy (which is fortunately a rare occurrence in children). (4) Lessen cognitive effects from frequent seizures. (5) Improve the patient's overall quality of life. As with any medical intervention, the benefits that the patient derives from treatment will need to outweigh potential risks. The decision to treat is individualized and based on both seizure (type, frequency, duration) and patient (age, compliance, level of activity) specific factors.

Because epilepsy treatment is aimed at prevention, a decision to treat cannot be made without first estimating the recurrence risk (see section on Prognosis). Once a decision has been made to treat, choosing the right antiepileptic drug (AED) becomes the next major consideration (*Table 362.4*). The optimal choice for a given patient depends on many factors, the two most important of which are efficacy and side effects. Efficacy differs based on the seizure type. For each seizure phenotype, there are first-, second-, and third-line treatments (*Table 362.5*). There is often more than one accepted first-line therapy. Deciding which therapy has the most favorable side-effect profile helps narrow this choice down to a single agent. Other important considerations include the frequency of dosing, ease of administration, and cost. In children, taste and the availability of a liquid or chewable preparation can be among the most important considerations since they impact greatly on compliance.

The seizure type is very important when choosing the correct AED. Generalized seizures respond best to broad-spectrum medications, and can be exacerbated by medications geared toward partial seizures, such as carbamazepine. Matching the correct treatment to the individual epilepsy syndrome is also important.

In febrile seizures, epidemiologic data indicate that the seizures are benign, so aggressive treatment measures are

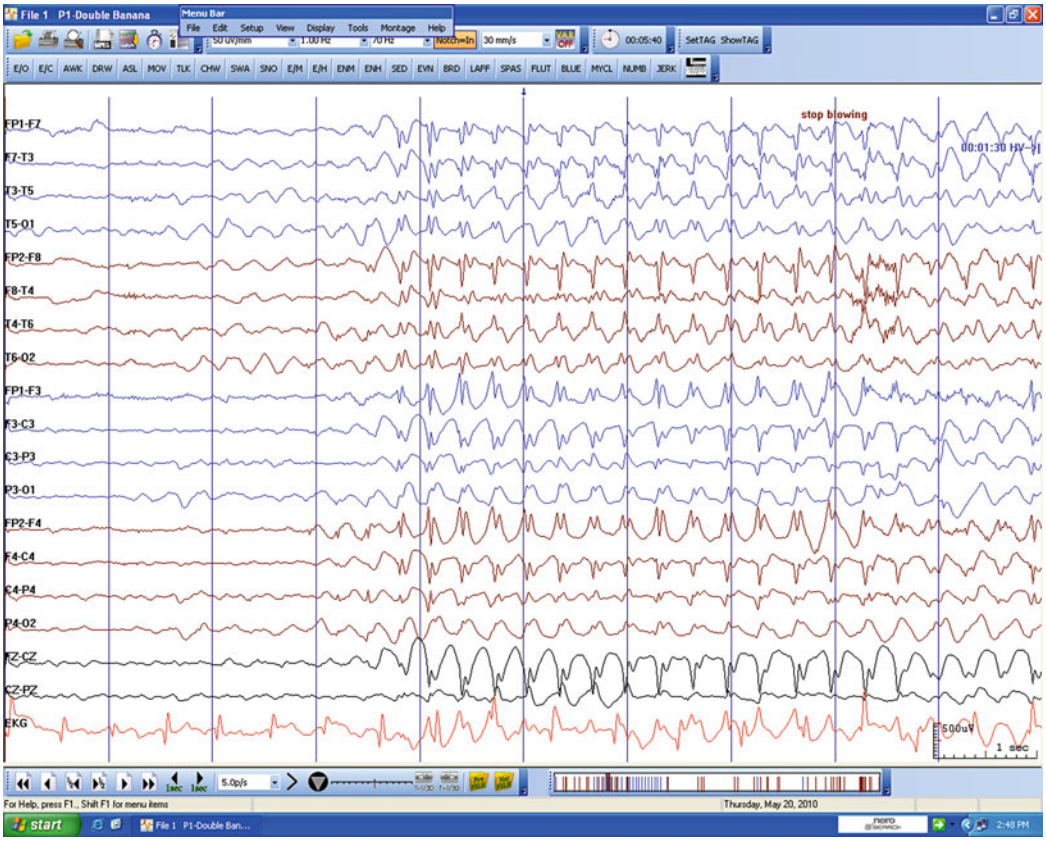

Figure 362.4

Eight-year-old girl with absence epilepsy. During her staring spells, bursts of generalized, 3 Hz spike and slow waves are seen on EEG

not required. The simplest preventative strategy is to use analgesics during febrile illnesses, although this approach has not demonstrated efficacy in clinical trials. Diazepam can also be given during febrile illnesses, but this results in only a modest reduction in recurrence. Additionally, rectal diazepam can be used acutely to abort a prolonged febrile seizure. Daily prophylaxis is rarely used in febrile seizures. Phenobarbital and valproic acid are effective for this purpose, but both have potential side effects. Treatment with a daily antiepileptic agent is therefore reserved for only the most severe cases.

Some patients initially diagnosed with febrile seizures go on to develop SMEI. Since this syndrome results from a mutation of voltage-gated sodium channel, sodium channel–blocking medications, such as carbamazepine and lamotrigine, can exacerbate seizures and should be avoided. Levetiracetam, topiramate, and stiripentol all offer better treatment success. The ketogenic diet can also be an effective option.

In infantile spasms, two treatment options are most effective: ACTH and vigabatrin. A course of pyridoxine may also be considered to exclude pyridoxine-dependent seizures. The Lennox–Gastaut syndrome may evolve from infantile spasms, and can be very refractory to treatment. Valproate and felbamate are two of the more effective options in this condition. The ketogenic diet can be effective in some patients, and vagus nerve stimulation may help prevent drop spells.

In absence seizures, ethosuximide is typically the first-line agent, but valproate and lamotrigine are also effective. In juvenile absence epilepsy and juvenile myoclonic epilepsy, valproate, levetiracetam, and lamotrigine are all effective options to consider.

For benign childhood focal seizures (PS, BECTS, and ICOE-G), treatment is optional since there is no evidence that the long-term prognosis is worse in untreated children. Daily prophylaxis depends largely on the presence of generalized convulsive seizures, since the simple partial seizures are typically not harmful. In ICOE-G, seizures can be

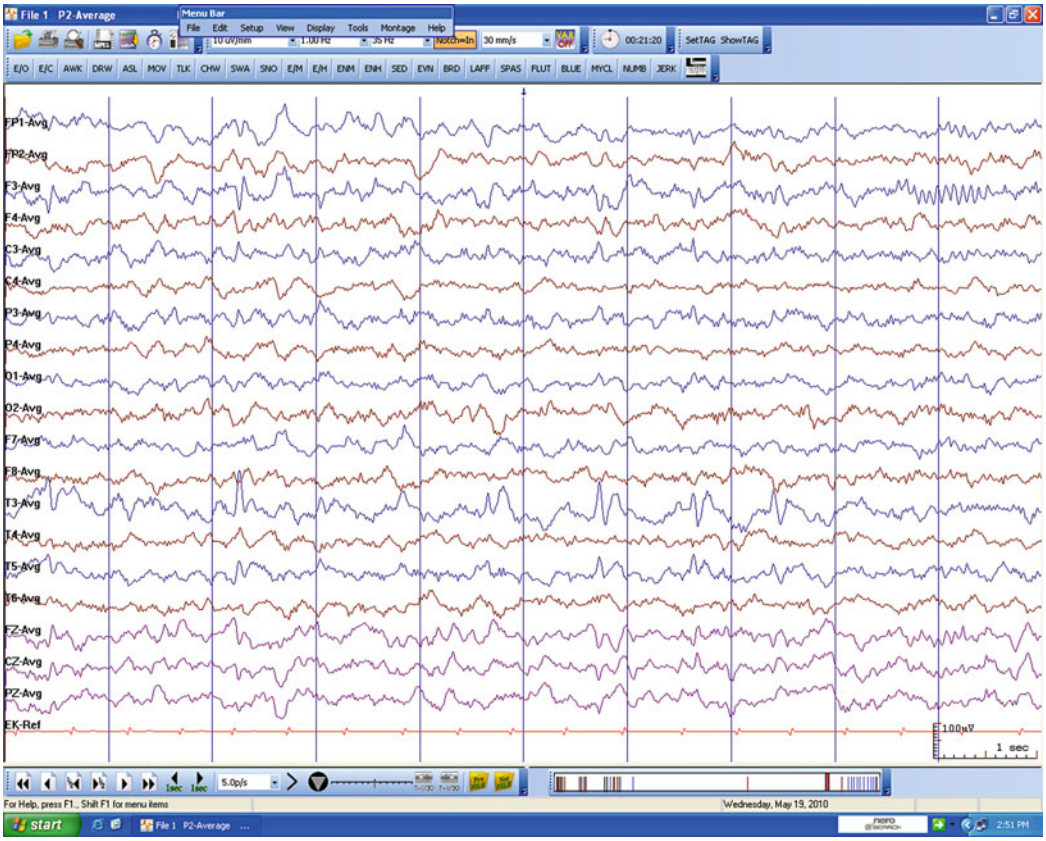

Figure 362.5

Seven-year-old boy with BECTS. His seizures are nocturnal and begin with a clicking sound of the throat followed by clonic activity of the face and hand. The involved side alternates between seizures. His EEG shows sleep-activated spike and slow waves over the left central and temporal regions (T3, T5, C3) which are accompanied by positive deflections over the frontal leads (F3) indicating a tangential dipole

frequent and may generalize, so continuous treatment is most needed more often in this syndrome than it is in PS and BECTS. If instituted, therapy consists of medications proven to be effective in partial seizures, and may include carbamazepine or valproic acid. In general, carbamazepine is preferred in the USA, and valproic acid has greater use in Europe. Newer medications, including gabapentin, lamotrigine, and levetiracetam, may also be effective. For BECTS, sulthiame is particularly effective and can normalize the EEG, but may result in cognitive impairment.

Regardless of which medication is chosen, the goal is the same – for the patient to be free of both seizures and side effects. With careful administration of the right medication, this goal can usually be achieved. In general, most AEDs are started at a low dose and increased gradually. This allows for early detection of side effects. If side effects occur, the dose is lowered. If seizures return, the dose is raised. If neither is present, no dose change is required. Unfortunately, some patients will have continued seizures and side effects, in which case, a medication change is generally needed.

Of patients who have never received an AED, approximately 47% will become seizure free with the first medication given. If a second drug is needed, only 13% will respond. If a third drug is used, the response rate is only 4%. A high initial seizure frequency before treatment, slowing on the EEG, and a symptomatic etiology are risk factors for developing medically intractable epilepsy.

After a patient has failed multiple AEDs, non-medication therapies must be considered. There are three non-medication options that are commonly used: the ketogenic diet, vagal nerve stimulator, and epilepsy surgery. All involve a multidisciplinary approach and require a comprehensive epilepsy center for their implementation and management.

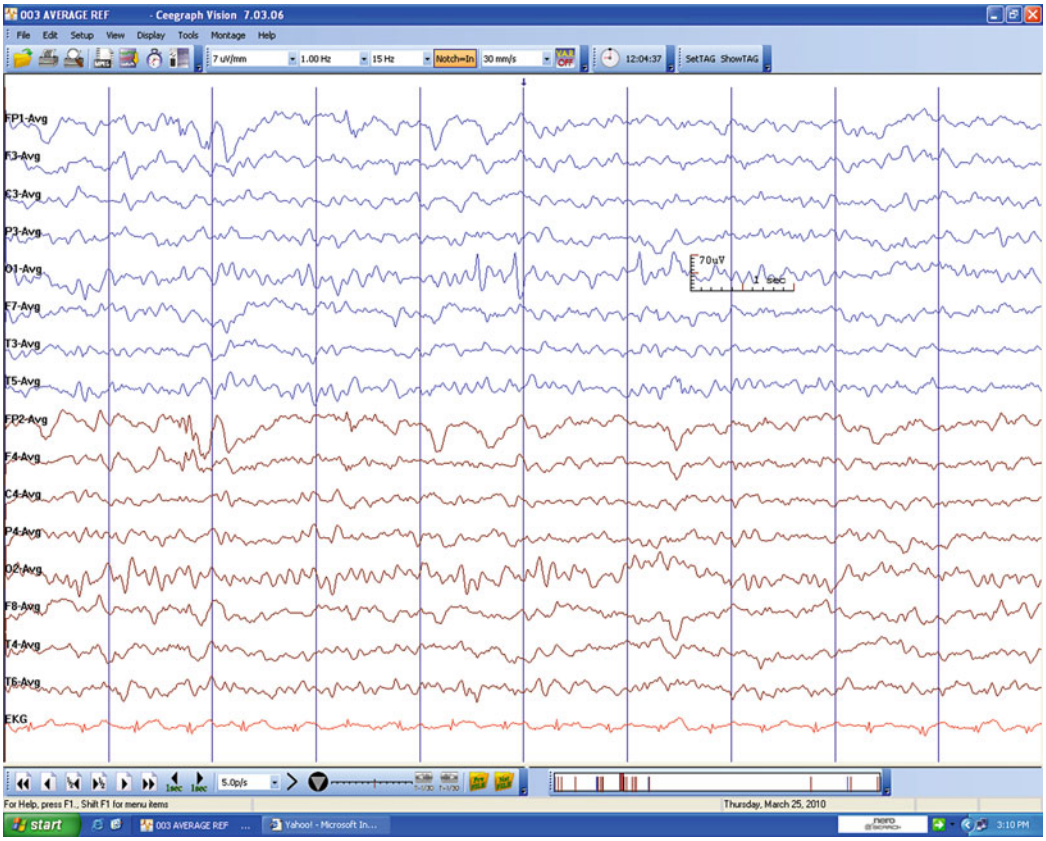

Figure 362.6

Nine-year-old boy with ICOE-G. His seizures cause him to wake from sleep with transient blindness followed by a headache. The EEG shows spike waves over the left occipital region (O1)

For status epilepticus, the ideal treatment acts rapidly, has long-lasting effects, produces little sedation, is easy to administer, safe, inexpensive, and can be pharmacologically reversed if needed. No single medication possesses all of these criteria, but the key requirements can usually be met.

In the largest prospective study on early treatment of SE, the Veterans Affairs Status Epilepticus Cooperative Study Group performed a randomized, double-blinded, multicenter trial using four i.v. treatments for status epilepticus: diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg), lorazepam (0.1 mg/kg), phenobarbital (15 mg/kg), and phenytoin (18 mg/kg). In patients with generalized convulsive status epilepticus, lorazepam had the best success rate, but this was statistically significant only when compared to phenytoin alone. No significant differences were observed among any of the four treatments with subtle SE. All of these trials lend support to intravenous lorazepam as initial therapy for SE.

An appropriate approach is to initiate therapy with lorazepam 0.1 mg/kg. If seizures persist, then phenytoin (20 mg/kg) or fosphenytoin (20 mg/kg phenytoin equivalents) should follow, with an additional 5–10 mg/kg of phenytoin/fosphenytoin if needed. In many cases, phenobarbital (20 mg/kg initially followed by an additional 5–10 mg/kg if needed) follows, with induction of anesthesia if the seizure persists beyond that. With the low success rate for subsequent drugs in the VA study, it is reasonable to consider moving on to definitive treatment with high-dose barbiturates, benzodiazepines, or propofol if SE remains refractory.

Prognosis

There are many ways to assess prognosis in patients with epilepsy. The most direct outcome measure is quantification of the seizures themselves. This includes an examination of seizure frequency, relapse rates following drug withdrawal, and the probability of outgrowing the condition. Assessment of comorbidities is also important, including developmental delays, intellectual impairment, and psychiatric disorders.

Table 362.4
Commonly used antiepileptic medications

Agent	Pediatric dose (mg/kg/day)	Half-life (h)[a]	Dosing schedule	Side effects
Carbamazepine (Tegretol)	10–35	25–65 (initial)	BID-QID	r, hep, bd, s,n
		12–17 (chronic)		dip, hypn, ost
Clonazepam(Klonopin)	0.01–0.2	18–50	BID-TID	s, a, h, b
Ethosuximide (Zarontin)	10–15 (initial)	30–40	QD-TID	gi, n, an, s, d, b
	15–40 (maint)			r, bd
Gabapentin (Neurontin)	30–60	5–7	TID-QID	s, d, a, ny, wg
Lamotrigine (Lamictal)				
Off valproate:	0.6 (initial)	7	BID	r, hep, d, a, s, n
	5–15 (maint)			
On valproate:	0.15 (initial)	45	QD-BID	
	1–5 (maint)			
Levetiracetam (Keppra)	20–60	6–8	BID	s, d, ha, b
Oxcarbazepine (Trileptal)	8–10 (initial)	8–10	BID	r, hep, s, diz, n
	20–50 (maint)			dip, a, ha, hyp
Topiramate (Topamax)	1–3 (initial)	18–30	BID	s, an, ks, ps, wl
	5–9 (maint)			
Valproic acid (Depakote)	15–60	9–20	BID-QID	hep, bd, n, s, d, wg, hl, r, gi
Zonisamide (Zonegran)	2–4 (initial)	50–70	QD-BID	r, bd, hep,s
	4–8 (maint)			diz, an, n, ha
				wl, ks

r rash, *hep* hepatotoxicity, *bd* blood dyscrasia, *n* nausea, *ny* nystagmus *dip* diplopia, *hypn* hyponatremia, *ost* osteomalacia, *s* sedation, *a* ataxia, *h* hyperactivity, *d* dizziness, *b* behavioral difficulties, *gi* gastrointestinal distress, *an* anorexia, *ha* headache, *ks* kidney stones, *ps* psychomotor slowing, *wg* weight gain, *hl* hair loss, *wl* weight loss, *maint* maintenance
[a]Half-life is based on monotherapy and assumes normal renal function.

Other measures of clinical significance are quality of life and mortality risk in epilepsy patients. Some childhood epilepsy syndromes are labeled as "benign." The use of this term refers to the prognosis of the seizures themselves, and not to the severity of associated conditions. For example, BECTS is often associated with motor or language delay. These features can have profound effects on patients, yet the condition is still labeled as "benign" since the seizures are characteristically outgrown.

Overall, the recurrence risk following a first unprovoked seizure in childhood ranges between 44% and 64%. The recurrence risk is highest in patients with an abnormal neurological examination, an abnormal electroencephalogram, or a remote-symptomatic etiology. In patients with only a single non-symptomatic seizure who have a normal examination and EEG, the risk of recurrent seizures is low (approximately 25%), and observation off of antiepileptic medications is generally favored. Should a second seizure occur, the recurrence risk jumps to approximately 79%. Thus, treatment is often started following a second seizure.

When seizures remain in remission on antiepileptic medications, the question of when to end treatment arises. Of patients who have been seizure free for over 2 years, 60–75% will remain seizure free when medication is withdrawn. A remote-symptomatic etiology and an abnormal EEG portend a higher relapse risk. Moreover, some epilepsy syndromes, such as juvenile myoclonic epilepsy, have a high relapse rate requiring a prolonged treatment course whereas others, such as BECTS, have no chance of relapse once outgrown. The ultimate decision of withdrawing antiepileptic medications is therefore dependent on individual patient factors. Overall, following 2 years of seizure remission on medication, roughly two-thirds of children will remain seizure free following discontinuation of their antiseizure treatment. If seizures are to recur, they will do so within 1 year in 60–80% of patients. Late recurrences (greater than 2 years after stopping AEDs) can develop, but are rare.

Table 362.5
Which medications for which seizure types?

Seizure type	First-line therapy	Second-line	Third-line
Partial (all types)	CBZ, OXC	LTG, VPA, GBP	TGB, ZNS, PB, LAC
		TPM, PHT, LEV	
Generalized			
Tonic-clonic	VPA, LEV	LTG, TPM, PHT	PB, ZNS
Myoclonic	VPA, LEV	LTG, CZP	PB, ZNS
Tonic	VPA, LEV	LTG	CZP, TPM, ZNS
Absence (Before age 10)	ESM[a]	VPA, LTG	ZNS, TPM
(After age 10)	VPA	LTG, LEV	ESM, TPM, ZNS
Epilepsy syndromes			
CAE	ESM	VPA, LTG, LEV	ZNS, TPM
JAE	VPA	LTG, LEV	ESM, TPM, ZNS
JME	VPA, LTG, LEV	TPM, ZNS	CZP, PHT
Lennox–Gastaut	VPA	LTG, TPM, LEV	CZP, ZNS, FBM, RUF
Infantile Spasms	ACTH, VGB	VPA, TPM, TGB, CZP	FBM, ZNS, LEV
BECTS	CBZ, GBP	VPA, PHT, CBZ, LEV	LTG, TPM

ACTH Adrenocorticotropic hormone, *CZP* clonazepam(Klonopin), *CBZ* carbamazepine(Tegretol), *GBP* gabapentin(Neurontin), *ESM* ethosuximide (Zarontin), *FBM* felbamate(Felbatol), *LEV* levetiracetam(Keppra), *LTG* lamotrigine(Lamictal), *OXC* oxcarbazepine(Trileptal), PB phenobarbital, *PHT* phenytoin(Dilantin), *TGB* tiagabine (Gabitril), *VGB* vigabatrin(Sabril), *ZNS* zonisamide(Zonegran), *RUF* rufinamide, *LAC* lacosamide, *CAE* childhood absence epilepsy, *JAE* Juvenile absence epilepsy, *JME* Juvenile Myoclonic Epilepsy, *BECTS* Benign Epilepsy of Childhood with Centrotemporal Spikes
[a]Assuming no convulsive seizures.

Overall, the prognosis for most epilepsy patients is favorable. Approximately two-thirds will achieve long-term remission of greater than 5 years, and nearly half of those will do so off of medications. Positive predictors for remission include a rapid response to therapy (greater than a 75% seizure reduction within 3 months), and idiopathic epilepsy. Remission is less likely in patients with an underlying structural cause or abnormal EEG. When followed into adulthood, children with epilepsy are at greater risk of school dropout and unemployment, and are less likely to be married or have children.

Prevention

Strategies for epilepsy prevention differ depending on the etiology. In genetic epilepsies, the only form of prevention currently available is family counseling. The recurrence risk can be as high as 50% for autosomal-dominant inheritance or less than 1% for spontaneous mutations involving only a single child within the family. Diagnostic confirmation through genetic testing now makes it possible to provide an accurate risk assessment prior to family planning. As genetic causes are better understood, treatment strategies directed at the mechanisms of disease may offer potential for averting epilepsy onset.

Symptomatic causes of epilepsy offer the greatest prospects for prevention. Since symptomatic causes generally develop following known brain injury, the possibility exists of either averting the injury or disrupting epileptogenesis following the insult. In children, neonatal causes of brain injury, such as hypoxic-ischemic encephalopathy and complications from prematurity, are major preventable etiologies. In adults, stroke is the most common identifiable etiology, and can be avoided through lifestyle modifications and management of hypertension and hypercholesterolemia.

In the third world, cysticercosis remains a major cause of epilepsy and is potentially eradicable. Since the only animal reservoirs are humans and pigs, breaking the life cycle of *Taenia solium* is possible. Strategies include concomitant treatment of both human and porcine populations. In pigs, treatment with oxfendazole is effective and confers protection for at least 3 months. Other strategies include immunization of pigs and improved meat inspection.

If the injury itself cannot be prevented, perhaps the mechanisms of epileptogenesis, which follow the injury, can be. Presently, no such interventions are known to exist, but many are theorized. One possibility is to initiate antiseizure medications immediately following injury, and prior to the development of seizures. Current data for head trauma suggests that, although prophylactic treatment may reduce early seizures, it does not prevent late seizures or reduce neurological disability. Similar conclusions are observed following brain tumors and strokes. Given those results, antiseizure medications are not routinely started prior to the development of seizures, but more research is needed in this area. A different approach is to use neuroprotective agents immediately following injury in an effort to prevent epilepsy and improve neurological outcome. To date, no such agents have demonstrated proven clinical efficacy in reducing injury or preventing epilepsy. Stem cell therapy also offers potential. In a rat model of pilocarpine-induced epilepsy, intravenous transplantation of bone marrow mononuclear cells prevented the development of chronic seizures and reduced neuronal loss. One challenge to bringing such therapies to clinical use is the increased time and cost of studying epileptogenesis as the primary outcome. Since it can take years for epilepsy to develop, the use of biomarkers for epileptogenesis may be the best solution to making such trials feasible.

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363 Movement Disorders

Yasser Awaad

Movement disorders in childhood have received little attention, especially when compared with such conditions as epilepsy or neuromuscular disorders. The information on movement disorders in childhood is scattered in multiple neurological and pediatric journals. This chapter attempts to put together information from these various sources in a form accessible to clinically oriented pediatricians.

Only disorders of children and adolescents under 18 years of age are dealt with. The differences in movement disorders between children and adults are striking. The clinical manifestations of extrapyramidal disease are profoundly influenced by the age of onset. A good example is the difference between Huntington disease in adults and children. Moreover, a number of disease processes occur almost exclusively in the pediatric age, for example, transient disorders. So the prevalence of the various movement disorders in children, their clinical presentation, course, prognosis, and management differ considerably from those in adults.

Movement disorders are syndromes characterized by impaired voluntarily movement, presence of involuntary movements, or both. There may be targeting and velocity of intended movements, abnormal involuntary movements, abnormal postures, or excessive normal-appearing movements at inappropriate or unintended times. Movement disorders in children include athetosis, chorea, dystonia, myoclonus, Parkinsonism, stereotypies, tics, and tremor. Movement disorders may be accompanied by weakness, spasticity, hypotonia, ataxia, apraxia, and other motor deficits, although many authors do not include these accompanying deficits among the movement disorders.

Movement disorders have been divided into hyperkinetic disorders in which there is excessive movement, and hypokinetic disorders in which there is a paucity of movement. Hyperkinetic disorders consist of abnormal, repetitive involuntary movements and include most of childhood movement disorders such as chorea, dystonia, myoclonus, stereotypies, tics, and tremor. Hypokinetic disorders are primarily akinetic or rigid. The primary syndrome in this category is Parkinsonism, occurring mostly in adulthood as Parkinson disease or one of the many forms of secondary Parkinsonism. In children, hypokinetic disorders are much less common than hyperkinetic disorders.

Abnormalities of movement that are presumed to be due to central nervous system disorders are typically divided into two primary categories: pyramidal and extrapyramidal. Many authors consider only the extrapyramidal symptoms to be movement disorders. "Extrapyramidal diseases" is the oldest but has fallen into disuse because of its lack of precision. The term includes other systems of control of movement that are not usually termed extrapyramidal, for example, the cerebellum. Pyramidal symptoms typically involve weakness, specific patterns of weakness, or spasticity. Pyramidal symptoms are thought to be due to injury to the pyramidal tract, including the corticospinal tract, and therefore to represent, to some extent, the effect of a denervated spinal cord. Extrapyramidal disorders are often described as everything that is not a pyramidal disorder. In particular, the term usually includes disorders of movement that are not due to weakness.

"Disorders of the basal ganglia" is also inadequate as not all abnormal movements are the result of involvement of these structures, and, conversely, lesions of the basal ganglia can manifest with cognitive deficit rather than with movement disorders. For these reasons, the term "movement disorders" seemed least inadequate, as it is merely descriptive and does not imply any hypothesis regarding the anatomical location of defects.

Movement disorder terminology has been well defined for adults but less so for children. Therefore, it is likely that movement disorders are underreported in children and that there is inconsistent terminology. Recently there have been attempts to provide specific definitions of childhood hypertonic disorders, including dystonia and rigidity. The prevalence in children of different types of hypertonic disorders, as well as other movement disorders, is not well known, although there have been studies investigating this in certain populations. Consistent definitions of non-hypertonic disorders in childhood are not yet available.

In adult movement disorders, it is frequently helpful to divide disorders into primary and secondary disorders, although there is no consistent definition of these terms. Many authors refer to disorders as primary if there is only a single dominant symptom and the underlying cause is presumably genetic or is due to an identified gene; however, the existence of a single symptom in childhood movement disorders is probably the exception rather than the rule.

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Since Sydenham in 1686 identified the first disease characterized by a movement disorder, a long time has elapsed and, especially in the past 35 years, knowledge of the pathophysiology of abnormal movements has increased extraordinarily as a result of better understanding of neurotransmitter function, of modern neuroimaging techniques (especially MRI but also functional neuroimaging with MR spectroscopy, PET, and functional MR), and of the advent of molecular genetics. This last not only provides new bases for neurological classification, previously based exclusively on clinical/pathological data, but also raises the hope of prevention and possible cure of genetically determined movement disorders.

Although new disorders are being identified with such methods, progress in patient care has remained rather patchy, and much has to be done to improve the management of many movement disorders. Therapeutic difficulties are even greater where children are concerned. The consequences on learning and on the neurological and psychological development of children with chronic movement disorders are largely unknown. Even drug doses are often poorly established and extrapolated from adult practice, even though there are well-known differences in the handling of pharmacological agents between children and adults.

Movement disorders in children differ from those in adults in several important aspects. Perhaps the most important is that movement disorders in childhood are primarily symptoms of other diseases, rather than diseases by themselves. In adults, dystonia and Parkinsonism are usually due to primary dystonia or idiopathic Parkinson's disease, respectively. However, dystonia or Parkinsonism in children is more likely to be a feature of underlying static or progressive neurologic disorder. Diagnosis in children is complicated by the fact that many symptoms have more than one cause, and any particular underlying pathophysiology may lead to complex combinations of symptoms. The diagnostic evaluation in children is guided by symptoms, but the existence of a large class of diseases that can lead to the same set of symptoms often necessitates a broad etiologic evaluation. There may be specific etiologic treatments and symptomatic treatments, both of which may be beneficial in an individual child. In particular, many of the causes of childhood movement disorders do not yet have any specific treatment, yet symptomatic treatment for the resulting movement disorder can be extremely helpful and lead to improvement in quality of life.

Another distinction between movement disorders in adults and children is that many adult neurologic disorders can be attributed to anatomically localized injury, but childhood disorder frequently results from a global or multifocal injury that may affect particular cell types, receptor types, or metabolic pathways. Therefore in children, the injury is open sparse but global, with manifestations across multiple areas of function, including sensorimotor and cognitive functions.

The clinical manifestations of movement disorders will depend on the child's developmental stage. The same illness may present differently depending on the age at onset of symptoms. Detection of a progressive disorder may be complicated by superimposition of a progressive disorder on the natural improvement of function that is expected throughout childhood. Therefore, a child with a progressive movement disorder may continue to develop new skills despite falling further and further behind in age-appropriate behavior. The presence of a movement disorder may affect the current and continuing development of the child's normal motor and cognitive abilities. Therefore, an acute illness may have developmental consequences that outlast the duration of the injury itself.

Classification of the movement disorder based on temporal pattern is essential for diagnosis. It is also important to define the context in which the movements occur. Although it is often helpful to list the characteristics of the movements, the diagnosis relies on pattern recognition, and the clinician must see the movements. If the movements are not apparent during the neurologic examination, repeating the examination at another time or obtaining video recordings of the movements is essential. The widespread availability of video cameras has substantially improved diagnosis of movement disorders.

When approaching a patient with a movement disorder, it is helpful to determine the answers to some key questions:

1. Is the number of movements excessive (hyperkinetic) or diminished (hypokinetic)?
2. If hyperkinetic, do the individual movements appear normal or abnormal?
3. Is the movement paroxysmal (sudden onset and offset), continual (repeated again and again), or continuous (without stop)?
4. What is the developmental stage of the child, and has the development been normal?
5. How does voluntary movement affect the movement disorder? Are the symptoms and signs present at rest (body part supported against gravity), with maintained posture, with action, with approach to a target (intention), or a combination?
6. Has the movement disorder changed over time?
7. Do environmental stimuli or emotional states precipitate, exacerbate, or alleviate the movement disorder?
8. Is the patient aware of the movements?

9. Can the movements be suppressed voluntarily?
10. Are the movements heralded by a premonitory sensation or urge? (It may be helpful to ask the patient, "Why do you do that?")
11. Does the movement disorder abate with sleep?
12. Are there other findings on the examination suggestive of focal neurologic deficit or systemic disease?
13. Is there a family history of a similar or related condition?

Laboratory tests, imaging, and other diagnostic testing should be based on the specific movement disorder. There is no universal "movement disorder workup" because the causes are varied and some movement disorders (e.g., tics) are rarely symptomatic of an underlying disease (*Table 363.1*).

Movement disorders may be difficult to characterize unless other symptoms and behavioral context are taken into account. Chorea can resemble myoclonus. Dystonia can resemble spasticity. Paroxysmal movement disorders such as dystonia and tics may resemble seizure. Movements in some contexts may be normal and in others may indicate underlying pathology. For example, frequent eye blinking can be perfectly normal and appropriate in one setting, but excessive in another (tics). Movements that raise concern about a degenerative disorder in older children (progressive myoclonus) may be completely normal in an infant (benign neonatal myoclonus). Thus, it is important to view the movement disorder in the context of a complete history and neurologic examination.

The etiology of movement disorders in children is extensive and is discussed further below. The most common cause of secondary disorders is likely to be cerebral palsy, with a prevalence of 2 per 1,000. However, cerebral palsy itself represents a constellation of both injuries and symptoms (Surveillance of Cerebral Palsy in Europe, 2002). Cerebral palsy can be associated with almost all forms of childhood movement disorders, and despite the lack of an ongoing destructive process, the clinical picture may change during the development. The diagnosis and management of cerebral palsy is complex.

Specific types of movement disorders may represent injury to particular localized regions of the central nervous system. Ataxia most likely results from injury to the cerebellum or its inflow and outflow. Bradykinesia most likely occurs with injury to the substantia nigra or striatum of the basal ganglia leading to either presynaptic or postsynaptic failure of dopaminergic transmission. Chorea occurs in severe cortical injury or basal ganglia injury, particularly if the subthalamic nucleus is involved. Dystonia most likely involves injury to basal ganglia, but the possibility of cortical or cerebellar abnormalities cannot be excluded as contributors. Myoclonus most likely involves cortical, brainstem, or spinal injury to gray matter. The localization of tremor depends on the type, but some forms of tremor involve cerebellum or brainstem circuits. Tic disorders probably involve an abnormality of the basal ganglia, but cortical mechanisms may also contribute.

Treatment of childhood movement disorders is based primarily on symptomatology independent of the underlying cause. When a specific treatment for the underlying cause is available, certainly this should be applied, but in many cases such treatment is only partly effective. The goal of symptomatic treatment is to break the connection between the pathophysiology and the expression of clinical impairment.

It is essential to ask both the child and the parents for the most significant cause of disability. In some children, the impairment that is most evident to the clinician is not

Table 363.1
Phenomenologic classification of movement disorders

Movement disorder	Brief description
Athetosis	Slow, continuous writing movements of distal body parts, especially the fingers and hands
Chorea, ballism	Chaotic, random, repetitive, brief, purposeless movements. Rapid but not as rapid as myoclonus. When very large amplitude affecting proximal joints, choreic limb movements are often called *ballism*
Dystonia	Repetitive, sustained, abnormal postures typically have a twisting quality
Myoclonus	Sudden, brief, shock-like movements that may be repetitive or rhythmic
Parkinsonism	Hypokinetic syndrome characterized by a combination of reset tremor, slow movement (bradykinesia), rigidity, and postural instability
Stereotypy	Patterned, episodic, repetitive, purposeless, rhythmic movements
Tics	Stereotyped intermittent, sudden, discrete, repetitive, nonrhythmic movements, most frequently involving head and upper body
Tremor	Rhythmic oscillation around a central point or position involving any one body part or more than one

the primary cause of disability. Sometimes treatment of a disability is more effective, less time-consuming, and less risky than attempts to treat the underlying pathophysiology, and therefore it is essential to be certain that any treatment addresses the needs and goals of the child and family. In particular, it is usually neither necessary nor possible to treat all symptoms. It is most helpful to pick specific goals and to monitor progress toward those goals. In many cases, a team approach has been found to be helpful, particularly when there are multiple impairments leading to disability, and the team approach allows appropriate focusing and selection of interventions. In some individuals, a supportive environment and adaptive equipment are more effective than any medical intervention.

TIC Disorders and Tourette Syndrome

Tic disorders and related conditions are among the most common clinical conditions encountered by pediatric neurologists. The evaluation and management of these conditions is usually fairly straightforward and may follow predictable, relatively simple paradigms. On the other hand, more complex cases require considerable effort, numerous treatment strategies, and intensive management of patients and families. Gilles de la Tourette syndrome (TS) is a chronic neuropsychiatric disorder characterized by the presence of involuntary motor and phonic tics that wax and wane. Once considered a rare disorder, the prevalence of TS is estimated to be up to 1% of children and adolescents. In his late nineteenth-century description, Georges Gilles de la Tourette suggested a familial pattern and a psychogenic origin. Since then, there is further evidence for a genetic inheritance pattern, but accumulating data support a neurobiological disorder than emotional basis. In addition, those children with TS often suffer from a variety of concomitant psychopathologies, including obsessive–compulsive disorder, attention-deficit hyperactivity disorder, mood disorders, episodic outbursts, learning difficulties, sleep abnormalities, and other behavioral problems. Although the presence of neurobehavioral problems is not required for the diagnosis of TS, they are very common, and their clinical impact on the affected patient is often more significant than the impact of the tics themselves. The physician caring for a child with tics and complex psychopathologies must be able to recognize the various problems, understand their individual complexities, and develop an appropriate treatment plan.

Dystonia

Description

Dystonia is defined as a movement disorder in which involuntary sustained or intermittent muscle contractions cause twisting and repetitive movements, abnormal postures, or both.

Dystonia usually occurs only during voluntary movement or with voluntary maintenance of a posture of the limbs or body. For example, flexion of the fingers to hold a pen may lead to flexion of additional fingers, extension of the wrist, or movements of the opposite hand or the neck.

There is often no abnormal muscle tone in children with dystonia. A dystonic limb may or may not have increased resistance to movement, it may be either stiff or floppy, or change with time.

Focal dystonia is described if only one body part is involved, such as a hand, foot, or the neck. On the other hand, if two contiguous parts are involved, such as the face and neck, then it is termed a "segmental dystonia." If two noncontiguous parts of the body are involved, such as the face and one leg, it is termed a "multifocal dystonia." Hemidystonia involves one half of the body. If both legs, as well as one additional body part are involved, then it is termed "generalized dystonia." A focal dystonia that progresses to become generalized or generalized dystonia itself are the most common patterns observed in children.

Dystonia may occur at rest or with action and it may be triggered by the movement of other body parties. Task-specific dystonia occurs only rarely in children.

Primary dystonia includes the genetic dystonias, and some adult onset, focal dystonias, is not due to another disease. When dystonia is due to another identified disease, then it is called "secondary dystonia." Secondary dystonia is due to different causes, for example, cerebral palsy, metabolic disease, or head trauma.

The mechanism of dystonia is understood. Studies in humans and animals have not been able to find a good explanation that can relate particular injuries to the emergence of dystonic symptoms. Dystonia is frequently associated with injury to the basal ganglia, in particular the sensory-motor regions of the putamen. In children, dystonia may also occur with decreased dopamine as occurs in dopa-responsive dystonia (DRD). Low dopamine level can cause many childhood dystonias. Acute dystonic reactions in children and adults are caused by medications that selectively block the dopamine receptors in the indirect pathway. These reactions are treated with anticholinergic

medications that may increase the effectiveness of dopamine in both the direct and indirect pathways (Tables 363.2 and 363.3).

Examination

The child must be observed at rest, during the action of the parts of the body affected by dystonia, as well as actions unrelated to the dystonia. For example, a child with foot dystonia must be observed while sitting, standing, walking, and performing tasks with the hands. Mental distraction is helpful to elicit the dystonia. Distractions may help to determine the specific triggers for the dystonic movements and also assist in evaluating if other body parts are subtly affected. It is important to test the child during certain activities (reaching movements of the arms, speaking, and tongue movement).

When dystonia is present at rest, it is important to examine children when they are as relaxed as possible. Any stress or discomfort may worsen the symptoms.

Muscle tone is not usually increased in children with dystonia; it might be increased and there will be difficulty in differentiating dystonia from spasticity or rigidity. This will be difficult when dystonia and spasticity are simultaneously present (e.g., cerebral palsy). It is equally important to examine for other movement disorders, such as ataxia or myoclonus, which might lead to a specific diagnosis.

Dystonia is usually not present during sleep. Stiffness of the limbs during sleep suggests possible spasticity or fixed joint contractures. Dopa-responsive dystonia may improve

Table 363.2
Etiologic classification of dystonia

Primary: Dystonia is the only neurological sign and evaluation does not reveal an identifiable exogenous cause or other inherited or degenerative disease	*Secondary*: Variety of lesions, mostly involving the basal ganglia and/or dopamine synthesis
Childhood- and adolescent-onset	*Inherited non-degenerative* (*dystonia plus*)
• DYT1: Autosomal-dominant with reduced penetrance (approx. 30%), early limb-onset with predominant family phenotype	• Dopa-responsive dystonia (DRD): due to DYT5 and other genetic defects
• Other genes to be identified	• Myoclonus-dystonia: due to DYT11 and possibly other genetic defects
	• Rapid-onset dystonia-Parkinsonism due to DYT12
Adult onset	*Inherited degenerative*
• DYT7: Autosomal-dominant, cervical onset in adult life	Autosomal-dominant, autosomal-recessive, X-linked (DYT3), mitochondrial
• Other genes to be identified	
Mixed phenotype	*Degenerative disorders of unknown etiology*
• DYT6, DYT13: Autosomal-dominant, early- and late-onset, with possible cranial, cervical, and sometimes limb-onset and variable spread	• Parkinson's disease
• Other genes to be identified	• Progressive supranuclear palsy
	• Corticobasal ganglionic degeneration
	Acquired
	• Drugs (dopamine receptor blockers), other toxins
	• Head trauma
	• Stroke, hypoxia
	• Encephalitis, infectious, and post-infectious
	• Tumors
	• Peripheral injuries
	Other movement disorders with dystonic phenomenology
	• Tics, paroxysmal dyskinesias (DYT8, 9, 10)
	Psychogenic dystonia

Table 363.3
Classification of genetic loci associated with dystonia

Gene	Location	Inheritance	Phenotype	Gene Product
DYT1	9q34	AD	Early limb-onset PTD	Torsin A
DYT2	Not mapped	AR	Early onset	
DYT3	Xq13.1	XR	Lubag dystonia/Parkinsonism	Not identified
DYT4	Not mapped	AD	Whispering dysphonia	
DYT5	14q22.1	AD	DRD/Parkinsonism	GCHI
DYT6	8p21-p22	AD	"Mixed" cranial/cervical/limb-onset	Not identified
DYT7	18p	AD	Adult cervical	Not identified
DYT8	2q33-25	AD	PDC/PNKD	Not identified
DYT9	Ip21	AD	Episodic choreoathetosis/ataxia with spasticity	Not identified
DYT10	16	AD	PKC/PKD (EKDl & 2)	Not identified
DYT11	7q21	AD	Myoclonus-dystonia	Epsilon-sarcoglycan
DYT12	19q	AD	Rapid-onset dystonia-Parkinsonism	Not identified
DYT13	Ip36	AD	Cervical/cranial/brachial	Not identified
DYT14	14q13	AD	DRD	Not identified

Abbreviations: *AD* autosomal-dominant, *AR* autosomal-recessive, *XR* X-linked recessive, *PTD* primary torsion dystonia, *DRD* DOPA-responsive dystonia, *PDC* paroxysmal dystonic non-kinesigenic choreoathetosis, *PNKD* paroxysmal non-kinesigenic dystonia, *PKC* paroxysmal kinesigenic choreoathetosis, *PKD* paroxysmal kinesigenic dyskinesia, *GHC*1 GTP Cyclohydrolase 1

upon awakening in the morning or after a nap; but the symptoms worsen throughout the day. Other forms of dystonia may be worse upon morning awakening.

Dystonia has several genetic causes with autosomal-dominant inheritance. Therefore, a thorough family history of dystonia or other neurological diseases is very important. The onset of dystonia is important, but dystonia may start many years after the causative event. Toxin exposure and medications use (neuroleptics and psychiatric medications) must be investigated. Such medicines may cause dystonia even after they have been stopped. Autosomal-dominant inheritance is caused by too many different genes. The most common genes are DYT1 (9q34, encodes torsinA) and DYT5 (14q22.1-2, encodes GTP cyclohydrolase I, causing Dopa-responsive dystonia or Segawa's disease). DYT2 can cause an autosomal-recessive trait. DYT3 causes an X-linked dystonia-Parkinsonism syndrome of Lubag (Xq13). The familial rapid-onset dystonia-Parkinsonism is linked to chromosome 19.

Structural lesions like cerebral palsy, kernicterus, hypoxic injury, head trauma, encephalitis, tumors, basal ganglia stroke, Moyamoya disease, and congenital malformations can cause dystonia.

Different neurodegenerative diseases can cause dystonias like Fahr's disease (or basal ganglia calcification), pantothenate-kinase associated neurodegenerative disease (PKAN, formerly neurodegeneration with brain iron accumulation type I, formerly Hallervorden–Spatz disease, PANK2 gene at 20p12.3-p13), Huntington's disease (Westphal variant, IT15-4p16.3), spinocerebellar ataxias (SCAs), neuronal ceroid lipofuscinosis, Rett syndrome, Tay–Sachs disease, Sandhoff's disease, Niemann–Pick type C, metachromatic leukodystrophy, striatal necrosis, Leigh's disease, neuroacanthocytosis, vitamin E deficiency, HARP syndrome (hypoprebetalipoproteinemia, acanthocytosis, retinitis pigmentosa, and pallidal degeneration), Pelizaeus–Merzbacher disease, and ataxia telangiectasia (AT).

Other chemical and metabolic disorders like glutaric aciduria, acyl-CoA dehydrogenase deficiency dopa-responsive dystonia or DRD (biopterin metabolic defect DYT5 or tyrosine hydroxylase deficiency), dopamine agonist-responsive dystonia (or ALAD: aromatic L-amino acid decarboxylase deficiency), mitochondrial disorders, Wilson's disease, homocystinuria, GM1 gangliosidosis, metachromatic leukodystrophy, Lesch–Nyhan disease, methylmalonic aciduria, and tyrosinemia could lead to dystonia.

Different drugs and toxins can induce dystonia, for example, neuroleptic and antiemetic medications (haloperidol, Thorazine, olanzapine, risperidone, quetiapine, promethazine, prochlorperazine, etc.), calcium channel blockers, stimulants (amphetamine, cocaine, ergot alkaloids, etc.), anticonvulsants (carbamazepine, phenytoin, etc.), thallium, manganese, carbon monoxide, ethylene glycol, cyanide, methanol, and wasp sting. Drug- or

toxin-induced dystonia may occur while taking the drug or months after stopping the drug. Other paroxysmal disorders could induce dystonia, paroxysmal kinesogenic choreoathetosis (PKC), paroxysmal non-kinesogenic choreoathetosis (PNKC), familial periodic paralysis, exercise-induced dystonia, complex migraine, alternating hemiplegia, and paroxysmal torticollis of infancy.

There are some disorders that misdiagnosed as dystonia, like tonic seizures (including paroxysmal nocturnal dystonia caused by nocturnal frontal lobe seizures); syringomyelia; Arnold–Chiari malformation type II; atlantoaxial subluxation; posterior fossa mass; cervical spine malformation (including Klippel–Feil anomaly); ocular skew deviation with vertical double vision causing neck twisting, juvenile rheumatoid arthritis; Sandifer's syndrome (gastrointestinal disorder associated with hiatus hernia in infants); spasmus nutans; tics; self-stimulation; spasticity; myotonia; rigidity; stiff-person syndrome; Isaac's syndrome; startle disease (hyperexplexia); neuroleptic malignant syndrome; and psychogenic disorders.

The investigation of dystonia depends on the specific type of dystonia. In hemidystonia MRI will show a localized injury to the brain, often at or before birth.

In many cases, dystonia will start before early adulthood without obvious cause, and then become progressively worse. In these cases, there may be a genetic mutation in the *DYT1* gene. The child should be tested for the presence of this gene, particularly if symptoms began in the foot and progressed to other areas of the body.

Metabolic causes for dystonia are treatable and should be excluded. Dopa-responsive dystonia (DRD) is a rare disorder of the enzyme pathway responsible for synthesizing dopamine. DRD is tested by measuring chemicals in the CSF and in the blood, following an oral dose of phenylalanine (known as the phenylalanine loading test).

Metabolic disorders, such as Wilson's disease, amino acid or organic acid disorders, and lysosomal storage diseases may be tested for in certain children. An MRI is helpful during the workup for many metabolic diseases.

Treatment

It is recommended that any child with unexplained dystonia should receive a trial of L-dopa therapy (*Table 363.4*). If the child does have DRD, the response is often dramatic and further testing may be arranged. L-dopa may also be helpful in some children with dystonia due to cerebral palsy, or perhaps in other metabolic disorders or structural abnormalities.

Table 363.4
Treatment Options for Dystonia

Oral Medication
1. L-dopa therapy
2. Trihexyphenidyl (Artane®)
3. Diazepam (Valium®)
4. Clonazepam (Klonopin®)
5. Valproate (Depakote®)
6. Baclofen
7. Carbamazepine (Tegretol®)
8. Reserpine or tetrabenazine (Nitoman®, not available in the USA)
Choice of the best regimen is usually by trial and error. It is difficult to predict which medicine will be most effective for a particular child
Botulinum toxin injections
For focal dystonias
Deep brain stimulation (DBS)
Particularly in children who have a mutation in the *DYT1* gene
Intrathecal baclofen pump (ITB therapy)
A very promising treatment
Other surgical procedures
1. Tendons lengthening or cutting muscles
2. Dorsal rhizotomy

Trihexyphenidyl (Artane®) is the most commonly used medication for children with dystonia. Sometimes requires very high doses of 50 mg or 100 mg per day, or even more in some children. Slow titration will help to tolerate the medicine with relatively few side effects. Other medicines that have used include diazepam (Valium®), clonazepam (Klonopin®), valproate (Depakote®), baclofen, carbamazepine (Tegretol®), reserpine, or tetrabenazine (Nitoman®, not available in the USA). Choice of the best regimen is usually by trial and error. It is difficult to predict which medicine will be most effective for a particular child.

Focal dystonias can be treated with botulinum toxin injections into those specific muscles. The goal of the injections is to reduce the symptoms of dystonia, without causing significant muscle weakness. Toxin injections usually need to be repeated every 3–6 months.

Deep brain stimulation (DBS) has been used to improve dystonia particularly in children who have a mutation in the *DYT1* gene. Implantation of the stimulator electrode in the globus pallidus led to gradual resolution of symptoms over 2–12 months.

Intrathecal baclofen pump (ITB therapy) is a very promising treatment. Although originally developed as a treatment for spasticity, recent results suggest that there may be benefit in dystonia as well.

Other surgical procedures like tendons lengthening or cutting muscles help to reduce the effect of the dystonic muscles. Dorsal rhizotomy, cutting the sensory nerves from muscles where they enter the spine is helpful; however, this procedure is more likely to improve spasticity, rather than dystonia.

Dopa-Responsive Dystonia

Other names for dopa-responsive dystonia *(DYTS)* include *dystonia-Parkinsonism syndrome*, *dystonia with diurnal variation*, and *Segawa disease.* The cause of the syndrome is either of two different genetic abnormalities. The inheritance of one type is as an autosomal-dominant trait and the other is as an autosomal-recessive trait. The dominant type is due to mutations in the gene for guanosine triphosphate cyclohydrolase 1, the cofactor for tyrosine hydroxylase, and the recessive form is due to mutations in the tyrosine hydroxylase gene. Most reported cases of "juvenile Parkinsonism" are probably variants of dopa-responsive dystonia.

Clinical Features

Marked variation in expressivity occurs between affected members of the same kindred and even between monozygotic twins. Age at onset is usually between 4 and 8 years but ranges from infancy to 12 years. Incorrect diagnosis of early onset cases is common; cerebral palsy is the common misdiagnosis. The initial feature is nearly always a gait disturbance caused by leg dystonia. Flexion at the hip and knee and plantar flexion of the foot cause toe walking. Flexor and extensor posturing of the arms develop. Finally, Parkinsonian features, such as cogwheel rigidity, masklike faces, and bradykinesia, appear. The disease reaches a plateau in adolescence. Postural or intention tremor occurs in almost half of patients, but typical Parkinsonian tremor is unusual.

Diurnal fluctuation in symptoms occurs in more than half of patients. Symptoms improve considerably on awakening and worsen later in the day. Movement and exercise exacerbate dystonia in some patients. Other disorders with exercise-induced dystonia as the main or only clinical feature may be expressions of the same genetic error.

Diagnosis

Dopa-responsive dystonia may be difficult to differentiate from other genetic disorders with dystonia because of phenotypic variation among family members. Diagnosis by mutation analysis is available. Important clues to diagnosis are features of Parkinsonism without other neurological signs, diurnal variation in severity of symptoms, exacerbation of symptoms with exercise, and response to levodopa.

Management

A small dose of levodopa usually provides immediate and complete relief in most patients, even when initiating treatment long after symptoms begin. No other dystonia responds so well. Initiate carbidopa-levodopa therapy at the lowest possible dose, and slowly increase the dose until a response is established. Long-term therapy is beneficial and required; symptoms return after discontinuing the drug. Trihexyphenidyl, in doses lower than ordinarily needed to treat also idiopathic torsion dystonia, and bromocriptine are partially effective.

Chorea

Chorea is a hyperkinetic movement disorder characterized by frequent, brief, and purposeless movements that tend to flow from one body part to another body part in an unpredictable manner. The affected child often appears fidgety or restless and unable to sit still. The word "chorea" comes from the Greek word for dance. The jerky movements of the feet or hands are often similar to dancing or piano playing. Chorea and ballismus are a spectrum sharing the same differential diagnosis. When chorea is severe, the movements may cause flailing motions of the arms or legs that results in throwing whatever is in the hand or falling to the ground. This form of severe chorea is referred to as "ballism." Akathisia can appear as chorea, but it is the result of a sense of a need to move, whereas chorea refers to involuntary movements. Choreaic movements can be sudden and jerky or can be more continuous and flow-in. Choreiform is often used to describe the benign piano-playing movements seen in normal young children when arms are extended during the neurologic exam. When chorea is the primary manifestation, a substantial differential diagnosis can be obtained. Athetosis is a slower writhing and twisting movement. Choreoathetosis is a movement of intermediate speed, between the quick, flitting movements

of chorea and the slower, writhing movements of athetosis. Choreoathetosis is the most common form in children. Choreoathetosis tends to worsen with attempts at movement and often occurs only while the child is attempting to move. Chorea may affect the hands, feet, trunk, neck, and face. In the face, they often lead to nose wrinkling, continual flitting eye movements, and mouth or tongue movements. These disorders may be distinguished from tics, as tics tend to repeat the same set of movements. In addition, the child often describes a "buildup" in the need to make the tic, with a sense of release afterward. There is no such sense of release following chorea; the movements are continually changing and flowing from one body part to another.

Etiologies

Chorea can be classified into primary (inherited) and secondary (acquired) disorders. Primary causes include essential chorea and benign familial (hereditary) chorea. Autosomal-dominant, recessive, and X-linked inheritances have been described. Huntington's disease is the most famous inherited cause of chorea; the autosomal-dominant transmission of a triplet repeat (CAG) at the Huntington site on chromosome 4. Huntington's disease rarely presents in childhood with chorea. Juvenile-onset Huntington's disease (also known as the Westphal variant) is characterized by Parkinsonism (bradykinesia and rigidity) and dystonia. The number of CAG triplet repeats predicts the onset of Huntington's disease. The normal repeat number is <35. When the number is >70, onset of symptoms occurs at less than 18 years of age. The majority of chorea in childhood is secondary or acquired. Many causes of secondary chorea have been identified, but for most patients chorea is not the only sign or symptom. The most common cause of chorea in childhood is acute rheumatic fever (ARF). Other causes include metabolic disorder (hypo- or hypernatremia, hypocalcemia, hyperthyroid, pregnancy, or hypo- or hyperglycemia), perinatal brain injury (cerebral palsy), infectious or peri- or post-infectious disease (acute disseminated encephalomyelitis, viral encephalitis, and celiac disease), other autoimmune disease (systemic lupus erythematosus [SLE] or antiphospholipid antibody [APLA] syndrome), vascular disorders (Moyamoya syndrome, or basal ganglia stroke), toxins (methanol, carbon monoxide, manganese), other heredodegenerative disorders (Wilson's disease, ataxia telangiectasia, Niemann–Pick type C disease, Friedreich's ataxia, Machado–Joseph disease, gangliosidoses, other lysosomal storage diseases), and disorders of intermediary metabolism (glutaricaciduria, Lesch–Nyhan syndrome). Chorea can be the manifestation of conversion. It is very important to note that because behavioral changes are often observed as part of rheumatic chorea, one must avoid misconstruing the chorea of Sydenham's chorea as psychogenic. Common iatrogenic causes of chorea or exacerbations of extant chorea include dopamimetics, antiepileptics (e.g., phenytoin), antidepressants (e.g., selective serotonin reuptake inhibitors), methylphenidate (and other stimulants), antihistamines, anticholinergics, calcium channel blockers, digoxin, and oral estrogens.

Diagnostic Evaluation

A diagnostic test for treatable causes includes: throat culture with rapid group A ®-hemolytic streptococcal (GABHS) testing, serum antistreptolysin O and antideooxyribonuclease (AntiDNase) B titers, electrocardiogram, echocardiogram, thyroid function tests, complete blood count (for acanthocytes), antinuclear antibody test, erythrocyte sedimentation rate, electrolytes (i.e., sodium, potassium, chloride, bicarbonate), magnesium, calcium, serum ceruloplasmin, APLAs (including lupus anticoagulant, anticardiolipin, and anti-®2 glycoprotein 1), urine drug screen, and urine pregnancy test, uric acid, quantitative immunoglobulin (ataxia telangiectasia), α-fetoprotein, serum amino acid, urine organic acid, and arterial (or cerebrospinal fluid) lactate and pyruvate testing, Epstein–Barr virus titers, Lyme disease titers, human immunodeficiency virus, serum calcium, and genetic testing for Friedreich's ataxia, spinocerebellar ataxia type 3 (Machado–Joseph disease), and possibly dentatorubropallidoluysian atrophy (DRPLA). Brain magnetic resonance imaging (MRI) with and without contrast is recommended in order to look for structural abnormalities, such as those related to a tumor, stroke, metabolic or degenerative disorders, or a previous injury due to low oxygen.

Sydenham's (Rheumatic) Chorea

Chorea is one of the major Jones criteria for the diagnosis of ARF. The revised Jones criteria indicate the presence of chorea without any other criteria is sufficient to make the diagnosis of ARF. The development of ARF after a GABHS infection is thought to occur in only 1–2% of those infected. Only a fraction of those patients with ARF will develop Sydenham's chorea. Sydenham's chorea is most common in children aged 5–15 years old. There is enough evidence that suggests individuals who develop ARF have a genetic susceptibility. There is a roughly 2:1 female

predominance after age 10. Typically, the clinical manifestations of Sydenham's chorea begin several weeks to several months after a GABHS infection

The onset is insidious, with gradually progressive clumsiness and behavior and personality change, usually with emotional labiality, aggression, impulsivity, and obsessive–compulsive behaviors. The emotional labiality and personality change presents the most salient morbidity. The typical natural history of Sydenham's chorea is weeks to months of a waxing and waning course, with ultimate resolution of the chorea. Some individuals have behavioral changes that persist for months. Relapse of chorea can occur with or without subsequent GABHS infection. Therefore, it can be very difficult to distinguish between recurrences and relapse. There is a recognized increased risk of relapse associated with pregnancy (chorea gravidarum), oral contraceptives, and probably with intercurrent infection other than GABHS. Ten to twenty percent of patients, and perhaps as many as 50%, have a relapsing course. Recurrence and relapse provoke consideration of whether prophylactic penicillin is effective and whether follow-up investigations of cardiac function are needed. An additional confounding factor is that pharyngeal carriage of GABHS is common and is not necessarily eradicated by antibiotic prophylaxis. Therefore, surveillance testing for GABHS may produce false-positives. Certainly, signs, such as new murmur or abnormal rhythm, and symptoms, such as fatigue, palpitations, and shortness of breath, demand cardiac reassessment.

The diagnosis of Sydenham's chorea is made on the basis of clinical history and can be supported by laboratory data. However, laboratory data should be viewed as ancillary, not confirmatory. Most children with Sydenham's chorea have positive serology (antistreptolysin O and AntiDNase B antibodies) for GABHS, but over 25% are serologically negative. Most children with Sydenham's chorea have negative throat cultures for GABHS. MRI scans occasionally show signal abnormalities in the basal ganglia, but a clear clinical-radiographic linkage has not been seen. Therefore, structural imaging is neither diagnostically sensitive nor specific for Sydenham's chorea. Presence of carditis or valvitis or other manifestations of ARF supports the diagnosis of Sydenham's chorea. Every child thought to have Sydenham's chorea should be evaluated for rheumatic heart disease. Cerebrospinal fluid parameters in Sydenham's chorea have not been well studied. ARF remains a quintessential example of post-infectious or peri-infectious autoimmune disease. Although anti-brain antibodies have been recognized in a proportion of Sydenham's chorea patients for 30 years, the nature of the pathogenic mechanism has only recently been elucidated. Specifically, sera from patients with active Sydenham's chorea contain antibodies directed at brain lysoganglioside and GABHS glucosamine. Thus, there appears to be a direct effect of antibody on neuronal cell signaling, perhaps leading to inappropriate release of striatal dopamine.

SLE and APLA Syndrome

Chorea is an uncommon sign of SLE. When it is the only sign of SLE, it remains so for years. Less than 10% of children will have chorea, 50% are younger than 16 years of age. Usually it will have a poor prognosis. Chorea of SLE is clinically identical to that seen in ARF. Treatment of the underlying SLE is indicated. Chorea in SLE may be iatrogenic (drug-induced). Haloperidol may be effective for SLE chorea, but the other treatments for Sydenham's chorea may also be effective. The chorea of APLA syndrome is indistinguishable from that of SLE. Autoimmune mechanisms for chorea should include investigations for (antiphospholipid antibodies lupus anticoagulant, anticardiolipin, and anti-®2 glycoprotein 1), even if recurrent venous or arterial thrombosis have not occurred.

Chorea Associated with Viral Encephalitis

Post- or peri-infectious chorea is common and is very difficult to treat. There might be an MRI signal abnormalities in deep gray matter brain structures, such as basal ganglia and thalamus, as part of an aseptic meningitis or meningoencephalitis as well as in acute disseminated encephalomyelitis.

Wilson's Disease

Wilson's disease (hepatolenticular degeneration) is rare, but it has to be ruled out because it is treatable. It is an autosomal-recessive disease on chromosome 13, resulting in deficient ceruloplasmin; it leads to an intracellular accumulation of copper in the brain (particularly the basal ganglia) and liver. When Wilson's disease presents with chorea, hepatic function is already compromised. Slit-lamp examination often reveals copper deposits in the margin of the iris (Kayser–Fleischer ring). Although abnormal copper accumulation begins at birth, the symptoms of Wilson's disease may not become apparent until late childhood or adolescence. In all patients, copper initially accumulates in the liver. This may cause acute or chronic hepatitis or liver cirrhosis. The degree of liver involvement is variable and may range from mild elevations of certain

liver enzymes to complete liver failure. Associated symptoms may include fatigue, anorexia, weight loss, generalized weakness, ascites and abdominal swelling, or jaundice. Other findings may include hepatomegaly, splenomegaly, or both (hepatosplenomegaly). In general, the younger the age at symptom onset, the greater the degree of liver involvement. In patients with Wilson's disease, neurologic symptoms seem to be predominant after age 20.

Many individuals with Wilson's disease experience symptoms associated with damage to the nervous system. These symptoms usually become apparent during the second decade of life or, in some patients, during the third decade; however, such findings have been known to appear as late as age 50. Neurologic abnormalities rarely occur in patients younger than age 10. These neurologic symptoms may include tremor of the head, arms, or legs; generalized dystonia; and bradykinesia, particularly those of the tongue, lips, and jaw. Patients may also experience clumsiness, ataxia, or slowness of finger movements and loss of fine motor skills. Tremor or trembling may be present in one hand or leg and gradually progress to involve all four limbs. Speech may become increasingly slurred or slowed (dysarthria). The voice may also have a hoarse or "whispering" quality (whispering dysphonia). In some patients, swallowing may become increasingly difficult (dysphagia).

Psychiatric problems also occur in some individuals with Wilson's disease. These may include increasing agitation and irritability, mood swings, hysteria, neurotic anxiety, bizarre behaviors, or depression accompanied by thoughts of suicide. A relatively small percentage of people with Wilson's disease may experience dementia or, in severe cases, psychosis (e.g., manic-depressive disease, schizoaffective disorder, or schizophrenia).

The goal of drug therapy in individuals with Wilson's disease is to remove excess copper from the body and prevent ongoing copper accumulation and deposition. Therefore, drug therapy must be continued throughout life. Inadequate treatment or disruption of drug therapy may result in life-threatening complications or irreversible organ damage. The initial approach is the removal of excessive copper with chelating agents. The most common agent used for this purpose is D-penicillamine (Cuprimine®, Depen®). D-penicillamine depletes pyridoxine or Vitamin B6 from the body. Therefore, dietary supplementation with pyridoxine is required. The side effects of D-penicillamine range from minor disturbances to severe or life-threatening complications, such as aplastic anemia, immune complex nephritis, systemic lupus erythematosus, or myasthenia gravis. In some individuals, neurologic symptoms may worsen during penicillamine therapy. Other chelating agents used are trientine (Syprine) as well as a drug known as tetrathiomolybdate. There are indications that neurologic symptoms may not worsen during tetrathiomolybdate therapy. Ongoing maintenance therapy usually involves use of zinc acetate (Galzin®), which blocks the absorption of copper in the intestines and promotes the elimination of copper in the stool. Patients with Wilson's disease must avoid copper-rich foods such as cocoa, chocolate, liver, mushrooms, nuts, and shellfish and ensure that their copper intake is restricted to less than 1 mg/day. Liver transplantation may be considered in patients with severe, overwhelming (fulminant) liver disease. Other treatment is symptomatic and supportive.

Chorea of Hyperthyroidism

Hyperthyroidism must be ruled out in any patient with chorea or hyperkinesis. Treatment of hyperthyroidism is dictated by the etiology. The chorea secondary to hyperthyroidism is indistinguishable from that of other causes. Manifestations of hyperthyroid disease, such as weight loss, anxiety, and altered thermoregulation, may be helpful in diagnosis.

Treatment

The decision to treat the Chorea should be granted if symptoms bother the child or interfere with activities of daily living. If chorea is secondary to a treatable etiology, such as hyperthyroidism, SLE, or drug reaction, treatment of the underlying disease may alleviate the chorea. If the child is taking any medications that can cause or worsen chorea, these should be tapered and discontinued, if possible. Dopamine blockers (such as neuroleptics) and presynaptic depleters for neurotransmitters (such as reserpine and tetrabenazine) have been used to treat Chorea. These drugs selectively enhance the function of the indirect pathway by blocking the inhibitory effect of dopamine on this pathway. However, the incidence of side effects in children from neuroleptics has been reported to be as high as 20%. Therefore, it is often safer to start with an alternative medication, such as a benzodiazepine, particularly clonazepam, diazepam, or clobazam. Hypotension is a side effect of the presynaptic depleters. Neuroleptics have significant side effects (tardive dyskinesia, weight gain, prolongation of the QT interval). Tetrabenazine is a very effective medication for chorea, but it is not available in the USA. The antiepileptic drug valproate is considered to be an effective treatment for chorea, but reports vary.

Its mechanism of action is not known but may be through nonspecific − aminobutyric acid (GABA) potentiation. Other GABA-mimetic medications, such as baclofen and clonazepam, appear to have efficacy as well.

Treatment of Syndeham's chorea depends on the disability associated with the chorea. In many cases, the chorea causes only mild disability and symptomatic treatment is not required, because Syndeham's chorea is usually self-limited. When treatment is acquired, antiepileptics like valproate can be effective and are usually associated with fewer side effects than phenothiazines or butyrophenones. Benzodiazepines may be used. Symptomatic treatment for 2–4 months is usually sufficient. Corticosteroids, intravenous immunoglobulin, or plasma exchange have been used on the basis of the presumptive autoimmune mechanism. Antibiotic prophylaxis to prevent GABHS recurrence is recommended to prevent carditis or valvitis, not to prevent chorea. The cardiac manifestations of ARF cause a great deal of morbidity (and mortality) and are irreversible. Penicillin still is the first-line treatment for prevention. Penicillin intramuscular injection of 1.2 million units of benzathine G. can be administered as a monthly, oral form (e.g., Pen V®) and can be given at 250 mg twice daily. The antibiotic sulfadiazine is another option. Patients allergic to penicillin and sulfadiazine, erythromycin can be administered at 250 mg orally bid. The duration of treatment has not been determined, but the American Heart Association recommendations are available. Patients with carditis or valvitis, but no persistent cardiac or valve disease, prophylaxis should continue for 10 years from diagnosis, or "well into adulthood" (whichever is longer). For patients with cardiac disease, the duration of prophylaxis should be for at least 10 years subsequent to the prior episode and until the patient is older than 40 years of age. For patients without cardiac disease (the most common scenario), prophylaxis should continue for 5 years or until 21 years of age.

Pediatric Movement Disorders: Myoclonus

Description

Myoclonus is "sudden, brief, jerky, shock-like, involuntary movements." The movements are quite rapid and may be triggered by attempts at voluntary movement, sensory stimulation, or startle. Myoclonus may cause rhythmic jerks, in which case, it is termed a "myoclonic tremor." Myoclonus is categorized based upon the likely source of movement. Such sources include cortical or subcortical areas or the spinal cord.

Cortical myoclonus is thought to be due to a lack of inhibition in the sensory or motor cortex. Subcortical myoclonus is often due to abnormalities in the brainstem; spinal myoclonus is presumed to be due to abnormalities in spinal inhibitory circuits. Myoclonus may be severely disabling, particularly when it is triggered by movement. In some cases, it may also be very mild. The most common example of a mild myoclonus is sleep myoclonus. In this form of myoclonus, children or adults have occasional brief jerks of an arm or a leg; these "jerks" occur while the individual is falling asleep. Negative myoclonus is a sudden involuntary relaxation of a muscle, rather than a contraction; this is thought to be due to mechanisms similar to those of sleep myoclonus. Cortical reflex myoclonus is triggered by attempts to obtain a knee jerk or other tendon reflex. Epilepsia partialis continua is a type of focal epilepsy that causes myoclonic tremor. Myoclonus is often associated with epilepsy; there is a particular class of degenerative disorders called "progressive myoclonus epilepsies (PME)" in which the association of myoclonus and epilepsy is common.

Examination

As with other movement disorders, it is important to determine which parts of the body are affected by myoclonus. It may occur in a single limb, the neck, the back, or the face. In other cases, it may affect the entire body. When severe, myoclonus may cause the child to fall. It is important to determine whether symptoms improve or worsen with voluntary activity. This is often tested by observing the child attempting to drink from a cup. In some cases, a myoclonic jerk may be caused by an unexpected, loud noise or a gentle tap on the tip of the nose or on the forehead.

To test for negative myoclonus, also known as asterixis, children are asked to extend their arms with the wrists back or to perform some other movement that requires holding the limb against gravity. In this way, a sudden loss of muscle contraction causes the hand or the arm to fall in a downward direction. Since myoclonus may occur along with other movement disorders, it is important to look for evidence of dystonia, tremor, ataxia, or spasticity. It is also important to look for opsoclonus, which is a random, dance-like jerking of the eyes in all directions. This eye movement occurs in the opsoclonus-myoclonus-ataxia syndrome.

Mechanism

The mechanism of myoclonus is not well understood. Cortical myoclonus is possibly a disorder of decreased inhibition in the cortex. The frequent association with seizure disorders suggests that there may be a common cause for myoclonus and some types of epilepsy. However, the reason for the reduced inhibition is not known. The mechanism of subcortical and spinal myoclonus is even less well understood. A group of disorders called "startle syndromes" probably involves hyperexcitability of the normal brainstem startle circuits and decreased inhibition in spinal circuits. This may be due to a mutation in the receptor for the neurotransmitter glycine.

Etiology

Etiological Classification of Myoclonus

Physiological
- Anxiety-induced
- Exercise-induced
- Sleep jerks and nocturnal myoclonus

Essential

Epileptic

Symptomatic
- Postcentral nervous system injury
  - Hypoxia
  - Trauma
  - Stroke
- Basal ganglia degenerations
- Idiopathic torsion dystonia
- Hallervorden–Spatz disease
- Hepatolenticular degeneration (Wilson's disease)
- Huntington disease
- Drug-induced
- Carbamazepine
- Levodopa
- Tricyclic antidepressants
- Lysosomal storage diseases
- Metabolic encephalopathies
- Dialysis syndromes
- Disorders of osmolality
- Hepatic failure
- Renal failure
- Myoclonic encephalopathy
- Idiopathic
- Neuroblastoma
- Spinal cord tumor
- Spinocerebellar degenerations
- Toxic encephalopathies
- Viral encephalitis

Physiological

Sleep myoclonus, benign myoclonus of infancy

Essential Myoclonus

Familial essential myoclonus, essential myoclonus-dystonia, stimulus-sensitive myoclonus

Epileptic

Juvenile myoclonic epilepsy, progressive myoclonic epilepsies, epilepsia partialis continua, Rasmussen's encephalitis, early infantile myoclonic encephalopathy, infantile spasms (West syndrome), Lennox–Gastaut syndrome, benign familial myoclonic epilepsy, Angelman syndrome.

Idiopathic epilepsy without any other neurological problem may have myoclonus as a major clinical expression. This includes entities such as benign myoclonus of infancy, myoclonic absences, juvenile myoclonic epilepsy of Janz, and photosensitive epileptic myoclonus. In such instances, the jerks are usually generalized and occur spontaneously, are frequently facilitated by lack of sleep, alcohol, etc., and may be triggered by visual stimuli.

Myoclonus may also be present in patients with generalized tonic-clonic epilepsy in the setting of a progressive encephalopathy (progressive myoclonic epilepsy), which will be discussed in another section.

Symptomatic

- *Fixed injury*: Carbon-monoxide poisoning, hypoxic injury or near-drowning (Lance-Adams syndrome), heatstroke, trauma, stroke, and electrocution
- *Storage/degenerative*: Sialidoses (cherry-red-spot myoclonus), lipidosis, lysosomal storage disease (Niemann–Pick type C, Tay–Sachs, Sandhoff's), other storage disorders (neuronal ceroid lipofuscinosis), pantothenate-kinase associated neurodegenerative disease (PKAN, formerly neuronal brain iron accumulation

type 1, formerly Hallervorden–Spatz disease), Wilson's disease, Lafora body disease, Rett syndrome, Baltic myoclonus, spinocerebellar ataxias (SCAs), dentatorubropallidoluysian atrophy (DRPLA), multiple sclerosis, and mitochondrial disorders (e.g., myoclonic epilepsy with ragged-red fibers [MERRF] and others)
- *Infections/para-infectious*: New-variant Creutzfeldt–Jacob disease (nvCJD), subacute sclerosing panencephalitis (SSPE), viral encephalitis, and *Streptococcus*
- *Endocrine*: Hyperthyroidism, hyponatremia, and hypoglycemia
- *Structural*: Tumors that irritate the brain in a direct manner, tumors that release chemicals into the blood (as in abdominal or thoracic neuroblastoma [which causes the opsoclonus-myoclonus-ataxia syndrome]), and palatal myoclonus (with injury to the Guillain–Mollaret triangle in the brainstem or cerebellum)
- *Drug-induced/toxins*: Antiseizure medications (valproate, carbamazepine, etc.), antidepressants (amitryptaline, nortryptaline, desipramine, fluoxetine, sertraline, lithium, etc.), stimulants (amphetamine, dexedrine, methylphenidate, some asthma inhalers, caffeine, etc.), liver toxic medications, respiratory depressants, corticosteroids, amiodarone, acyclovir, bismuth, thallium, and L-dopa
- *Associated with systemic illness*: Dialysis, renal failure, liver failure, pulmonary disease, and carbon dioxide intoxication

Workup

Myoclonus may be tested by looking at the electrical activities in brain and affected muscle(s). Electromyography (EMG) of the muscles typically shows the duration and frequency of the myoclonic bursts, and whether these bursts spread to other spinal segments (as is seen in propriospinal myoclonus). It may also be helpful in determining whether jerking movements occur simultaneously in more than one limb, or whether they flow gradually down the body. In cortical myoclonus, there may be an excessively large brain electrical response to electrical stimulation of the hands or feet. This response is tested by using somatosensory-evoked potentials (SSEPs). In some cases, it is also possible to demonstrate the myoclonic electrical signal in muscle following a tendon tap. This may be helpful in diagnosing cortical reflex myoclonus.

In any form of myoclonus, it is important to look for a cause. Any medication or toxin that could produce the symptoms should be removed if possible. Family history needs to be investigated and metabolic studies may be appropriate, particularly if there are other symptoms or if symptoms become progressively worse. Metabolic tests may include screening for treatable disorders such as Wilson's disease. Since myoclonus may be a symptom of general systemic illness, including liver failure and some types of tumors, it is important to screen for general health problems. In particular, in the opsoclonus-myoclonus syndrome, the child should have a CT or nuclear medicine scan of the chest and abdomen as well as blood and urine tests. These tests look for evidence of a neuroblastoma tumor. If there is a suspicion of an epilepsy syndrome, an electroencephalogram (EEG) is recommended. Brain MRI is important to look for tumors, stroke, malformations, or other structural lesions near the cortex, brainstem, or cerebellum. This is particularly true if the myoclonus is focal or if the child is suspected of having the syndrome of epilepsia partialis continua. Since certain viral infections can cause myoclonus, a spinal tap is sometimes needed for this diagnosis.

Many cases of essential myoclonus or essential myoclonus-dystonia will improve with small amounts of alcohol. Although this is useful for diagnosis, it is not helpful for long-term treatment.

Treatment

- If a specific cause can be found, then the myoclonus will usually resolve if treatment of the underlying disease is effective. Immune-mediated myoclonus (such as occurs in opsoclonus-myoclonus) usually requires treatment with oral steroids such as prednisone, in addition to removal of the tumor if one is found.
- Intravenous immunoglobulin and plasmapheresis has also been attempted in some cases. Juvenile myoclonus epilepsy usually responds to valproate, and may require lifelong treatment. Symptomatic treatment usually includes benzodiazepines such as clonazepam or diazepam. Cortical myoclonus may respond to valproate, piracetam, or lamotrigine. There are reports of myoclonus due to a hypoxic event responding to 5-hydroxy-tryptophan (5HT), and this may be helpful in other causes as well. Carbamazepine may worsen myoclonus and should be avoided.

Startle Disease or Hyperekplexia

Excessive startle or complex motor reactions in response to sudden unexpected stimuli occur in startle disease or hyperekplexia. When severe, there may be generalized muscle contraction resulting in postural instability and falls. After the fall, there is recovery of normal tone and control. The attacks are worsened by stress and fatigue and ameliorated by central nervous system (CNS) depressants. Hyperekplexia may be sporadic or familial with dominant inheritance (chromosome 5q). Disorders such as the Jumping Frenchmen of Maine, Latah, and Myriachit probably represent variants of startle disease. Abnormal startle and hyperekplexia have also been described in brainstem lesions. In the neonatal variety of startle disease, slight stimuli induce a nonepileptic convulsion that may be tonic or clonic or a mixture of the two. A quivering vocalization precedes the silence when a profound syncope ensues, with subsequent anoxic seizure. The clinical diagnosis is made by the nose-tap test: percussion of the tip of the nose induces an obvious startle. Ictal treatment is by repeatedly flexing the baby (face to knee); further episodes are prevented by clonazepam or clobazam.

Benign Nocturnal Myoclonus

Sudden jerking movements of the limbs during sleep occur in normal people of all ages. They appear primarily during the early stages of sleep as repeated flexion movements of the fingers, wrists, and elbows. The jerks do not localize consistently, stop with gentle restraint, and end abruptly with arousal. When prolonged, the usual misdiagnosis is focal clonic or myoclonic seizures. The distinction between nocturnal myoclonus and seizures or jitteriness is that it occurs solely during sleep, it is not activated by a stimulus, and the EEG is normal. Treatment is not required. Anticonvulsant drugs may increase the frequency of benign nocturnal myoclonus by causing sedation.

Benign Myoclonus of Infancy

Many series of patients with infantile spasms include a few with normal EEG results. These infants cannot be distinguished from others with infantile spasms by clinical features because the age at onset and the appearance of the movements are the same. The spasms occur in clusters, frequently at mealtime. Clusters increase in intensity and severity over weeks or months, and then abate spontaneously. After 3 months, the spasms usually stop altogether, and although they may recur occasionally, no spasms occur after 2 years of age. Affected infants are normal neurologically and developmentally and remain so afterward. The term "benign myoclonus" suggests that the spasms are an involuntary movement rather than a seizure. A normal EEG result distinguishes this condition from other types of myoclonus in infancy. No other tests are required. Treatment is not required.

Tremor

Tremor is a rhythmic, involuntary back-and-forth oscillation of part of the body. Tremor in children may be caused by many disorders including familial essential tremor, focal epilepsy, or a psychogenic movement disorder. Tremor is often seen with ataxia, dystonia, or myoclonus. Physiologic tremor is the normal shaking that occurs when people attempt to exert large forces or lift heavy objects. If a child has weakness, this type of tremor may be accentuated. Ataxia may lead to tremor when the inaccurate movements are corrected and then repeatedly over corrected.

Tremor may occur at rest, while maintaining a fixed arm position or posture (postural tremor) or with movement or kinetic, action, or intention tremor.

Tremor may occur in the hands, feet, back, neck, face, voice, or other parts of the body. The frequency of the tremor may be described by the number of cycles per second, or Hertz (Hz). Tremor may appear suddenly, or worsen gradually over months or years. Most types of tremor disappear during sleep, only to return the next day upon awakening. Tremor is often associated with other neurological disorders; therefore, it is important to look for the cause of tremor.

In familial essential tremor, the onset may occur at any age. Once started, this type of tremor often continues or becomes slowly worse with time. Some family members may notice that the tremor improves briefly after drinking alcohol. This type of tremor is usually postural, and may be particularly evident while the child attempts to eat or drink from an open cup.

Types of Tremor

There are still many controversial issues with regard to tremor. The Movement Disorder Society has suggested

definitions as well as clinical and syndromic classifications of tremors. Because of the numerous etiologies for tremor, a practical etiologic classification or a valid physiologic classification is not available.

Tremor is a rhythmic, involuntary, oscillatory movement of a body part. The amplitude and frequency of tremor is not crucial to this definition. For practical purposes, the following categories are presented.

Resting Tremor

Resting tremor occurs in a body part that is supported in such a way that skeletal muscle activation is neither necessary nor intended. Resting tremor is mostly found in Parkinson's disease and other basal ganglia disorders. This is a rarity in childhood and will not be considered further here.

Action Tremor

Tremors not occurring at rest are categorized as action tremor. This occurs during any voluntary contraction of skeletal muscle. The most relevant forms of action tremor are postural tremor, kinetic tremor, and intention tremor.

Postural Tremor

Postural tremor occurs during an attempt to hold a body part motionless against the force of gravity.

Kinetic Tremor

These are tremors occurring during any voluntary movement.

Tremor During Target-Directed Movements (Intention Tremor)

Classic intention tremor is present when amplitude increases during visually guided movements toward a target at the determination of the movement. It can be inferred that a disturbance of the cerebellum and its afferent or efferent pathway is present. The type and distribution of the tremors in hyperthyroidism and due to sympathomimetic drugs correspond to those of physiologic tremor; most drug-induced tremors are a mixture of postural and kinetic tremors.

Essential Tremor

Essential tremor (ET) is the most frequent movement disorder. Patients exhibit a mixed postural and kinetic tremor without other neurologic abnormalities. The upper limbs are predominantly involved. Other body parts are less commonly involved. Many patients with ET inherit the disease through an autosomal-dominant gene; however, the ratio of hereditary versus sporadic ET is unknown. This diagnosis can be made on clinical grounds if this tremor type is of long duration. The "red flags" are rapid onset, unilateral tremor, rest tremor, and gait disturbance.

Examination

The child is examined to determine which body parts are affected, as well as the frequency and amplitude of the tremor. The tremor is observed while the child is at rest, while holding a posture against gravity (e.g., as with the arms outstretched), and while reaching for targets. Tremor may be accentuated by attempting to drink from a nearly full cup of water. It may be difficult to distinguish myoclonic or dystonic tremor from "true" tremor. Frequently, the distinction depends upon whether or not other symptoms are present, such as dystonic posturing or stimulus sensitivity. In dystonic tremor, there is often a "null point" or a position of the joint at which the tremor disappears, and then reverses direction as the joint is moved farther. The child's strength must be assessed, as enhanced physiologic tremor may become more apparent if there is muscle weakness. Family history of tremor is important, as several types of tremor, myoclonus, or dystonia may be inherited. It is also important to look for medications or toxins that are known to cause tremor (such as valproate, sympathomimetics, or centrally acting substances). The following information should also be obtained in the history taking and examination: past history of neurologic disorders, type of tremor, onset, asymmetry, evidence of systemic disease (e.g., hyperthyroidism), and evidence of additional neurologic symptoms (such as dystonia, gait disturbance).

Mechanisms

There are probably many mechanisms that may cause tremor. In some cases, there is alternating muscle activity in the flexors and extensors about a joint. This suggests the

presence of an oscillatory signal in the nervous system. In other cases, there is rhythmic contraction or relaxation of a single muscle or group of muscles. Tremor may be generated in muscles, when they are strongly contracted, the spinal cord, the brainstem, the basal ganglia, as in Parkinson's disease, and the cortex. Occasionally, anxiety and hyperthyroidism might increase tremors in children.

Workup

The workup of tremor depends upon the specific type of tremor and its possible cause. Any medications that may worsen tremor should be avoided, if possible. If the constellation is typical for ET, no additional investigations (neuroimaging) are mandatory. If the tremor had sudden onset, an MRI of the head may be able to show a stroke, multiple sclerosis, or other lesion. Treatable conditions, in particular hyperthyroidism and Wilson's disease, should be considered. Wilson's disease may present in the first decade as hemolytic anemia or as a hepatic problem; a neurologic presentation is not encountered before the second decade and not as an isolated tremor. Electroencephalogram (EEG), which measures electrical activity in the brain, is important if there is a suspicion that the tremor is due to focal seizures. If there has been gradual onset, it is important to check electrolytes, including glucose, calcium and magnesium, thyroid function, copper in the urine (for Wilson's disease), and possibly the amount of adrenaline metabolites (for pheochromocytoma). If Parkinsonian features are present, a trial of L-DOPA may be helpful. Rarely, an EMG may help to determine if the tremor is more likely to be due to dystonia or myoclonus. Tests for myoclonus, including EEG with back-averaging and SEP (somatosensory-evoked potentials), may help to confirm the presence of dystonia or myoclonus. If there is a family history of tremor, it may be helpful to try the use of alcohol. This is often tried with an adult family member, rather than the child. If the tremor improves with alcohol, this suggests that it will also improve with other medications such as primidone.

Treatment

There is no general treatment for tremor per se. Mild tremor does not require treatment. If there is a specific illness such as Parkinson's or Wilson's disease, tremor will improve with appropriate therapy. For the underlying condition ET may be improved with propranolol (0.5–1.5 mg/kg bodyweight) and primidone. However, most children and adults with ET are not functionally impaired and manage without drug treatment. Medication can be limited to particular (stressful) events. In all cases, the child should start with a very small dose. The dose should be increased gradually in order to avoid side effects. Long-term use of primidone, which is metabolized, in part, to phenobarbital, is probably not desirable. If the tremor is felt to be psychogenic, then psychotherapy may be helpful in determining and avoiding any psychiatric triggers for the movement. Patients especially adolescents have to avoid certain dietary products like caffeine, recreational drugs, and alcohol.

Non-movement Disorders of Infancy and Childhood

Movement disorders can be classified as transient, paroxysmal, and chronic. Transient movement disorders (TMDs) are simply defined as those that stop over time. In a review by Fernandez-Alvarez (1998), 19% of 356 children under the age of 18 with movement disorders had a TMD. Most common in infancy, TMDs are readily recognized with experience. The generally benign and transient nature of these disorders has resulted in a lack of understanding (but no shortage of theories) as to the underlying cause in most cases. The following discussion approaches the TMDs on the basis of their age of presentation. The aim is to provide a practical approach to the recognition of the more common TMDs. There is insufficient space to discuss the possible theoretical basis of most of these conditions.

The differentiation between a transient and a paroxysmal movement disorder is clearly somewhat artificial as many of the latter diminish or stop with time.

Benign Neonatal Sleep Myoclonus

Benign neonatal sleep myoclonus (BNSM) was described by Coulter and Allen in 1982. Myoclonic jerks confined to sleep start in the neonatal period. They abruptly stop with arousal and are never seen in the awake state. The jerks are most frequent during NREM sleep but may appear during all stages. They may be unilateral or bilateral and often appear in short clusters and shift sides. The severity of individual jerks and duration of clusters may vary considerably. The EEG is normal both during the jerks and interictally. Detailed neurophysiological studies with back-averaging have not been performed.

Rocking the basinet or crib, touch and simple restraint do not abolish the jerks and may actually induce them. Neurological examination and metabolic investigations

are normal. BNSM is more common in preterm newborns. Usually the jerks cease by 2–7 months of age. A recent report described completely normal follow-up in five siblings with BNSM seen 3–10 years after remission. The relationship between BNSM and benign myoclonus of early infancy (BMEI) is not clear, although in one series 2/21 patients with BNSM were reported to have developed BMEI on follow-up.

Benign Myoclonus of Early Infancy

Benign myoclonus of early infancy (BMEI) was described by Lombroso and Fejerman in 1977. The usual age of presentation is between 3 and 15 months. The history is suggestive of infantile spasms with episodes of limb stiffening occurring in clusters. However, unlike infantile spasms the episodes usually occur in the awake state rather than in drowsiness and are often provoked by excitement or frustration.

There are rarely more than 10 events in a cluster, whereas with established infantile spasms many more episodes can be seen. There is no developmental delay or regression and the neurological examination is normal. Interictal EEG is normal.

Typically there were tonic spasms of the limbs with associated shuddering-like movements of the trunk. EMG of the tonic limb spasms revealed durations as long as 2 s. The EEG was normal during the spasms. Therefore the term "myoclonus" is probably not appropriate for these events. There was a close similarity between BMEI and "nonepileptic reflex tonic seizures," a condition described by the same group where sustained tonic contractions occur only when the infant is held in someone's arms.

The jerking episodes become more prominent for a few weeks or months after onset but, within an average of 3 months, decrease considerably in most infants. They disappear spontaneously by 2 years of age. Antiepileptic drugs do not stop the episodes.

Most of the cases have been sporadic; however familial occurrence has been reported.

As well as infantile spasms, the differential diagnosis includes benign myoclonic epilepsy of infancy, when there are generalized ictal and interictal EEG abnormalities.

Transient Idiopathic Dystonia of Infancy

This condition was first reported by Willemse in 1986 and other reports followed. Onset is usually in the first 6 months. There is dystonic posturing of an upper limb and sometimes the trunk or a leg. The typical arm posture is forearm pronation with hyperflexion of the wrist. When prone, the affected arm often rests on the dorsum of the hand. Typically, the posture disappears with intentional movement, for example, when reaching out to grab an object. Motor and mental development is usually normal. The posturing usually stops before the age of 2 years. Some cases seem to have more prominent dystonia and a more prolonged clinical course. Genetic factors may have a role.

Symptomatic forms of dystonia are not uncommon in the first year of life and investigations are usually required, but the normal development and the lack of functional abnormality suggest idiopathic dystonia. Investigations have been reported to be normal, including imaging and tests for metabolic disorders. However, one report has documented a decreased perfusion of the basal ganglia and left temporomesial cortex using SPECT and decreased glucose metabolism in the basal ganglia and cerebellum in one patient. Worsening of the dystonic posturing apparently induced by cisapride, a 5-HT receptor antagonist, has been described in two patients.

Beltran and Coker described transient dystonia beginning in the newborn period to 3 months of age in four infants exposed to cocaine in *utero*. Torticollis was a particular feature. Angelini described nine patients with paroxysmal episodes of dystonia involving limbs and trunk. The episodes lasted minutes to hours. It is not clear if this is the same condition.

Benign Paroxysmal Torticollis

Snyder first reported this condition in 1969. Drigo et al. have recently reported a large series of 22 patients. It is characterized by recurrent episodes of torticollis without persistent or obligatory head tilt, followed by subsequent spontaneous resolution. Onset is usually in the first year often between 2 and 8 months of age but sometimes as early as in the first week of life or as late as 30 months. Attacks tend to occur frequently at the onset (1–2 months) and sometimes with a striking regularity.

Truncal posturing (retrocollis and tortipelvis) may also be seen. A few cases have been familial. The episodes last from 10 min to 14 days, may recur two or three times a month, and involve either side. Drigo et al. have suggested the attacks can be subdivided into the more common "periodic torticollis" lasting hours or days and a "paroxysmal" form lasting only minutes and accompanied by ptosis and mydriasis. Many episodes appear in the morning and may be precipitated by

postural changes, for example, changing from the upright to the supine position. There may be a prodrome of irritability, pallor, ataxia, distress, or vomiting prior to the attack. Ataxia may be a dominant feature. Neurological examination between attacks is normal. In most cases the attacks stop by 2–3 years of age without treatment. EEG and neuroimaging are normal. The pathophysiology of benign paroxysmal torticollis is subject to speculation. The observation of eye rolling or deviation in some cases suggests labyrinthine involvement. Abnormal oculo-vestibular function has also been suggested. Some believe that benign paroxysmal torticollis is related to benign paroxysmal vertigo and is a migraine equivalent and may precede these conditions. In a recent report, two of four patients belonged to kindred with familial hemiplegic migraine and linked to the CACNA I A mutation giving further support that BPT may be a "migraine equivalent" or a channelopathy.

Children with apparent benign paroxysmal torticollis need to be carefully investigated. The differential diagnosis includes seizures, vertigo, gastroesophageal reflux, and Sandifer's syndrome, dystonic reaction to drugs, posterior fossa, and craniocervical junction abnormalities (basilar impression, platybasia, atlantoaxial instability, Arnold–Chiari malformation, and Klippel–Feil syndrome). Vestibular testing may be difficult to perform and interpret in young children. EEG during the paroxysms is normal. Neuroimaging studies are necessary to exclude congenital and acquired lesions involving the craniocervical region.

Treatment with dimenhydrinate. Meclizine and chlorpromazine has not been successful. The prognosis, however, is favorable and follow-up studies suggest spontaneous resolution in most cases.

Shuddering Attacks

Shuddering attacks are benign paroxysmal spells of childhood that can mimic epileptic seizures. They may superficially resemble several seizure types, including tonic, absence (typical and atypical), and myoclonic seizures. The pathophysiology is unknown, although a relationship with essential tremor has been postulated. The origin is unclear, but shuddering attacks are not epileptic in nature. Incidence is unknown, but shuddering attacks are relatively uncommon. These episodes are usually benign and non-disabling. They are not associated with increased morbidity or mortality and tend to remit spontaneously. No sex predilection is reported. The condition is seen in older infants and young children.

Parents describe the paroxysmal episodes of shuddering attacks as a sudden flexion of the neck and trunk and adduction of the arms. A shiver-like movement of the trunk ("like a chill") occurs, and the body may stiffen. Consciousness does not seem to be altered, but this can be difficult to confirm. The episode usually lasts 5–15 s. Unlike epileptic seizures, shuddering attacks do not occur during sleep. General and neurological examination findings are normal. The cause is unknown. A relationship with essential tremor has been postulated because there may be an increased frequency of essential tremor in the families of these children.

Absence seizures, benign childhood epilepsy, complex partial seizures, dizziness, vertigo and imbalance, epilepsy, juvenile myoclonic, essential tremor, febrile seizures, frontal lobe epilepsy, psychogenic nonepileptic seizures, seizures, and epilepsy: overview and classification, simple partial seizures, syncope and related paroxysmal spells and tonic-clonic seizures. No laboratory studies are helpful for the diagnosis of shuddering attacks. EEG, brain CT scan, or MRI may be performed because epileptic seizures are in the differential diagnosis. However, the results of these studies are normal.

Reviewing the appearance of a typical episode as captured on video camera by the parents is helpful in suggesting the diagnosis; however, prolonged electroencephalography (EEG) video monitoring to record a typical episode definitively differentiates shuddering attacks from epileptic seizures. Recordings of the spells confirm that typical characteristics of an episode are 5–10 s of shiver-like movements of the trunk and limbs with no impairment of consciousness and no EEG discharge during the episode. A normal EEG result helps to rule out an epileptic origin. Ambulatory EEG without video recording is useful for diagnosis because it records the EEG, but not the clinical event, although eyewitnesses marking the event with a pushbutton can vouch that the event was the kind in question. Routine EEG results are typically normal. In most cases, no treatment is necessary for shuddering attacks. Occasionally, if the episodes are unusually frequent or disabling, treatment may be attempted. However, there is no consistently effective treatment. Antiepileptic drugs are ineffective. Propranolol can be helpful in isolated cases, although pediatric dosages are not established. Infants and children with shuddering attacks are typically referred to a neurologist to check for possible seizures. Shuddering attack episodes tend to remit. A relationship to essential tremor occurring later in life has not been definitively established. The primary care physician should educate the family concerning the benign nature of this condition and the excellent long-term prognosis.

Sandifer Syndrome

Sandifer syndrome involves spasmodic torsional dystonia with arching of the back and rigid opisthotonic, posturing, mainly involving the neck, back, and upper extremities, associated with symptomatic gastro esophageal reflux, esophagitis, or the presence of hiatal hernia. Pediatric neurologists may be the first to see patients with Sandifer syndrome because the primary care provider and the parents may believe that the spasms represent seizures. Pediatric emergency department physicians, pediatric neurologists, and gastroenterologists see patients with this complex with some frequency. The syndrome is most certainly under recognized, and delays in diagnosis are due to atypical presentations or cases in which the diagnosis is not part of the differential. The true pathophysiological mechanisms of this condition remain unclear. The incidence is unknown, although there is some suggestion that in clinical practice, it occurs in less than 1% of children with gastroesophageal reflux. Mortality is not typically associated with Sandifer syndrome. Morbidity consists of the discomfort associated with this syndrome. Infants may lose weight if persistent or severe gastroesophageal reflux disease (GERD) is present. Associated morbidities may also include the presence of a hiatal hernia and esophagitis. Race does not seem to influence incidence. No sex predilection is recognized. Typically, Sandifer syndrome is observed from infancy to early childhood. Peak prevalence is in individuals younger than 24 months. Children with mental impairment or spasticity may experience Sandifer syndrome into adolescence. Sandifer syndrome is most commonly mistaken for seizures. The child typically appears to have an alteration in mental status associated with the tonic posturing. A relationship with feeding may suggest a diagnosis of Sandifer syndrome, which commonly occurs after feeding. The child may have a sudden rotation of the head and neck to one side and the legs to the opposite side with a stretched out appearance. Typically, the back is arched posteriorly with hyperextension of the spine and elbows may be flexed and held posteriorly with hyperextended hips. Torticollis may be present. Although the intermittent stiff tonic posture and periods of crying and apparent discomfort may suggest seizures, in many cases the rhythmic clonic component, which may be present in seizures, is not described. Various stiff, bizarre postures can be observed.

- Typically, the duration of the posture is 1–3 min.
- This brief, paroxysmal pattern of posturing accounts for the fact that the movement observed in Sandifer syndrome may be mistaken for seizures.
- During the posture, the infant may become very quiet or, less commonly, become very fussy. Fussiness and evident discomfort is most commonly observed as the posture abates.
- If a significant volume of gastroesophageal reflux is observed, even without actual vomitus, some infants and children may manifest evidence of respiratory tract irritation as well, including cough, wheezing, and stridor, depending on the degree and volume of reflux.

In children with Sandifer syndrome without mental impairment, the examination findings are normal. Children with Sandifer syndrome with mental impairment often have evidence of spasticity and may be diagnosed with cerebral palsy. Sandifer syndrome in infants is most commonly associated with normal examination findings. Sandifer syndrome in older children may be associated with mental impairment. Dysfunction of the lower esophagus is thought to be the most common precipitating factor. In some children, a cause cannot be found. Gastroesophageal reflux disease (GERD) with varying degrees of esophageal inflammation is common. Esophageal dysmotility, characterized by low-amplitude waves, lack of normal propagation, and low lower esophageal sphincter (LES) pressure, is not the cause but most likely the consequence of esophagitis: gastroesophageal reflux, seizure, infantile spasms, tonic seizures, torticollis, and dystonia. In patients with Sandifer syndrome, pH monitoring is useful in demonstrating gastroesophageal reflux and in clarifying any temporal association of reflux and posturing. Barium swallow studies are used less frequently, although they may be useful in documenting anatomy and the possible association with hiatal hernia. Cranial MRI is helpful in defining the nature of the neurologic deficits in children with mental impairment. Video-EEG monitoring helps differentiate seizures from posturing related to reflux and can be combined with a pH probe study to demonstrate the nature of the spells. Endoscopy may confirm anatomy via visualization and allows biopsy samples to be obtained to confirm mucosal changes due to esophagitis.

Sandifer syndrome does not require treatment unless the spasms are the result of gastroesophageal disease significant enough to interfere with growth and feeding. In the latter case, therapy should be directed toward the specific cause (see Chap. 178, "Gastroesophageal Reflux"). The American Gastroenterological Association has issued recent guidelines for the management of gastroesophageal reflux disease (GERD). The primary aim of medical care is to identify Sandifer syndrome. This can be accomplished most often by soliciting a careful history of

the times of day the spasms occur and the precipitating causes. If recognizing the complex is difficult, then video-EEG monitoring may be of value. Often, parent education and explanation regarding the nature of the spasms are all that is required in treatment of this condition. If the patient does have pathologic gastroesophageal reflux or complications from gastroesophageal reflux such as esophagitis, then therapy for gastroesophageal reflux, or specifically for esophageal peptic disease, is indicated. Muscle relaxants could be used in patients with Sandifer syndrome in whom a GI cause has been excluded and seizure-like postures are causing distress and discomfort for the patient or their family. However, muscle relaxants have not been demonstrated to relieve the seizure-like manifestations of Sandifer syndrome.

In cases with severe, confirmed gastroesophageal disease that is interfering with growth and development, some evidence suggests that fundoplication may alleviate symptoms (Fig. 363. 1).

Primary consultations should be with a gastroenterologist. If any doubt surrounds the nature of the seizure-like activity or if the child has underlying neurological impairment, a consultation with a pediatric neurologist could be beneficial. When gastroesophageal reflux is discovered, treatment must be directed at the reflux.

Therapeutic response for the treatment of gastroesophageal reflux disease may take as long as 2 weeks. If treatment is successful, weight increases and vomiting episodes decrease. Prokinetic agents are used to augment cholinergic activity. Prokinetic pharmacotherapy is often used before acid suppression therapy in children without evidence of esophagitis because of the predominance of motility-related problems over increased acid (and regurgitation over pain) in the pathogenesis and presentation. Different medications have been used to treat this disorder. Dopaminergic antagonist (Metoclopramide (*Reglan*)) that works by increasing LES tone gastric emptying stimulates muscular activity, leading to decrease in reflux. *Antacids* are agents used as diagnostic tools in providing symptomatic relief in infants. Associated benefits include symptomatic alleviation of constipation (aluminum antacids) or loose stools (magnesium antacids). *H2 receptor antagonists* like antacids are agents that do not reduce the frequency of reflux, but they decrease the amount of acid in the refluxate by inhibiting acid production. All are equipotent when used in equivalent doses. They work best in patients with nonerosive esophagitis. Because of proton pump inhibitor (PPI) superiority, H2 blockers are reserved for use in patients unable to tolerate PPIs. *Ranitidine* (*Zantac*) inhibits histamine stimulation of the H2 receptor in gastric parietal cells, which reduces gastric acid secretion, gastric volume, and hydrogen ion concentrations. *Famotidine* (*Pepcid*) competitively inhibits histamine at H2 receptor of gastric parietal cells, resulting in reduced gastric acid secretion, gastric volume, and hydrogen ion concentrations. *Proton pump inhibitors* are agents indicated in patients who need complete acid suppression (e.g., infants with chronic respiratory disease or neurological disabilities). Administer with the first meal of the day (children with nasogastric or gastrostomy tubes may have granules mixed with an acidic juice, then flush tubes to prevent blockage). *Omeprazole* (*Prilosec*) decreases gastric acid secretion by inhibiting the parietal cell H^+/K^+ -ATP pump. It is used for the short-term treatment (4–8 weeks) of GERD. Lansoprazole (*Previcid*) *suppresses* gastric acid secretion by specific inhibition of the (H+, K+)-ATPase enzyme system (i.e., proton pump) at the secretory surface of the gastric parietal cell. It blocks the final step of acid production. The effect is dose-related and inhibits both basal and stimulated gastric acid secretion, thus increasing gastric pH. *Esomeprazole magnesium* (*Nexium*), S-isomer of omeprazole, inhibits gastric acid secretion by inhibiting H^+/K^+-ATPase enzyme system at secretory surface of gastric parietal cells. Used in severe cases of and patients not responding to H2 antagonist therapy. Sandifer syndrome is not life threatening. Many patients with the condition eventually outgrow the spasms in later childhood. The diagnosis of Sandifer syndrome should not be made without

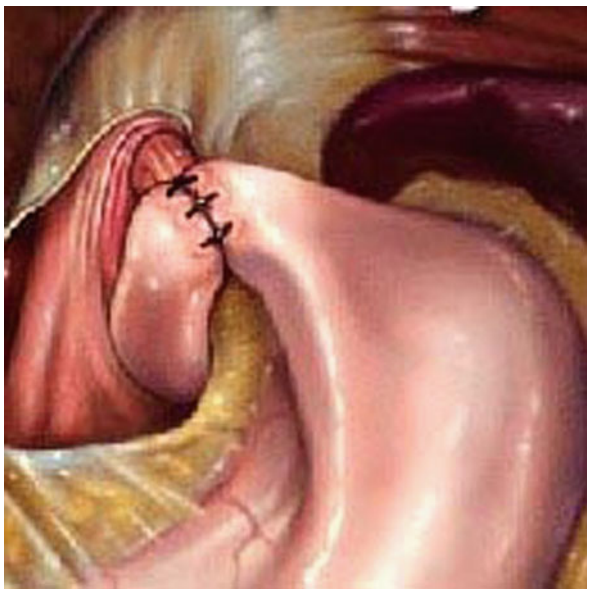

Figure 363. 1

adequate study. It is important to exclude infantile spasms, require relatively rapid treatment and management. In infantile spasms, a hypsarrhythmia pattern is observed on EEG.

Stereotypies in Normal Children

A wide variety of repetitive movements is readily recognized by parents as part of normal development and these are not considered as TMDs. Body rocking occurs in 6–19% of normal young children, thumb-sucking in 21%, nail-biting in around 12% of preschool children, and hair twisting in approximately16% of normal children.

Stereotypic movements are well recognized among neurologically impaired children, for example, in autism and Rett syndrome. However, they are also commonly seen in children without major neurological impairment. They are the most common movement disorder of childhood after tics. Tan et al. defined stereotypies as "involuntary coordinated, patterned, repetitive, rhythmic, non-reflex non-goal directed motor activity that is carried out in exactly the same way during each repetition." They described ten normal children with stereotypies.

Seven were boys. Only two of the ten children seemed to be completely normal, the others had mild learning difficulties, speech problems, and attention-deficit disorder.

The onset of the stereotypies was at 12 months or younger in five of the children. The oldest age of onset was 6 years. A large variety of movements were seen. The commonest were arm flapping and leg shaking. The movements appeared when the child was excited, stressed, bored, or unoccupied. Follow-up was available to a maximum age of 11 years in nine children and the stereotypies had completely stopped in only two.

Stereotypies usually appear earlier than tics. Typically, the same basic movement persists over time although often with elaboration. This is in contrast to tics, where there is usually a constant changing, with one tic dominating for a while and then another taking over. The phenomenology of a stereotypic movement may be identical to that of a complex tic or a compulsion. The child's description of the event may help in the differentiation. There may be a sense of pleasure obtained from performing the stereotypy. This is in contrast to the feeling of physical discomfort and need to perform a tic to relieve the discomfort. Older children may report the association of obsessive thoughts with a compulsion.

Stereotypies may superficially resemble seizures but calling the child or interacting with them, for example, by tickling, can immediately stop the movements. There is generally no need to attempt treatment. Even if the movements persist for a number of years, over time, the child tends to restrict the movements to times when they are not observed by others, for example, when they are alone in their bedroom.

Self-stimulation (Infant Masturbation)

Infant masturbation is usually only a diagnostic problem in young girls as it is readily recognized in boys. Infant masturbation can be mistaken for epileptic seizures, abdominal pain, and paroxysmal dystonia. Typically, the legs are tightly opposed and the feet crossed at the ankles.

There may also be mechanical pressure over the suprapubic or pubic area. Pelvic thrusting may be prominent. Irregular breathing, facial flushing sweating, irritable cries, and grunting give an impression that the child is in pain. The episodes can last minutes to several hours. A fixed and glazed look may give the impression of altered consciousness but the episode can usually be stopped immediately by picking up the child. This may produce annoyance and resumption of the activity as soon as the child is put down again. Multiple observers have suggested that the infant experiences orgasm and this is often followed by exhaustion, or sleep giving the impression of a postictal state.

Still and many others, since, postulated that the behavior begins after an episode of local vulval irritation, which sensitizes the child to pleasurable sensations arising from genital stimulation. Some young girls persist in the activity for many hours a day (so-called malignant masturbators). Sexual abuse, family stress, deprivation of affectionate parental physical contact, parental feelings of guilt, anger, shame, or perception of the child as vulnerable have all been suggested as underlying causes with very limited proof.

There are few follow-up studies. Bakwin described three girls. One continued to perform the movements at 4 years of age. Another stopped at 6–7 months and there had been no recurrence up to age 8 years. The third child, at 12 months carried a large rag doll with her constantly and repeatedly threw it to the floor and would rhythmically press her body against it "as in the sexual act." By 4 years, she rarely exhibited the behavior and when last seen was a medical student.

No treatment is necessary. It is important to explain to the parents that this is a normal behavior, more pronounced in some children. Self-stimulation is a better term than masturbation, which carries with it thousands of years of both moral and medical prejudice. Considerable

explanation may be required to prevent the use of unsuccessful coercive measures to try to stop this benign activity.

Midazolam Withdrawal Syndrome

Midazolam infusions have been increasingly used in intensive care units to provide sedation and analgesia for critically ill children. Sudden cessation of the midazolam can result in a withdrawal syndrome characterized by altered state of consciousness, restlessness, irritability, vomiting, tremors, and choreoathetoid and dystonic movements. This may occur more frequently when the midazolam is combined with fentanyl. In this setting, investigations are required to exclude metabolic disorders and nonconvulsive status epilepticus, but the possibility of a withdrawal syndrome should be kept in mind as it may be more common than is generally recognized.

Conclusion

The transient movement disorders of childhood are a distinctive group of disorders that are not rare. Over a number of years of practice, most general pediatric neurologists become familiar with them. They are usually seen in infants. Most require some investigation but recognition allows a limitation of what otherwise could be a very expensive diagnostic workup. They are a satisfying group of disorders to deal with, as most need no specific treatment and settle with time. The long-term neurological outcome is generally good, although some children subsequently are found to have learning and attention problems.

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364 Sleep and Its Disorders in Childhood

Jonathan Lipton · Sanjeev Kothare

Introduction

Sleep disorders are common in pediatrics and a major cause of both child and parental morbidity. It is estimated that approximately 25% of children experience a sleep problem during childhood. Epidemiologic data increasingly suggest that children in the United States do not get the adequate sleep for optimum academic, physiological, psychological, and social functioning. Insufficient sleep can have profound, potentially detrimental physiological and metabolic effects, and associate with an increase in symptoms of anxiety or depression, impairment of attention mechanisms, and behavioral problems. Even modest sleep loss in school-age children results in an increased risk of obesity consistent with sleep deprivation experiments in healthy young adults that result in the metabolic syndrome. It has been estimated that there is a 226% increase in health care utilization in children with obstructive sleep apnea. This represents a significant financial burden further underscoring the importance of childhood sleep disorders as a public health problem.

Sleep Structure and Physiology

Sleep can operationally be defined as a *reversible* behavioral state of quiescence characterized by a relative lack of motor activity, decreased level of consciousness, and an increased arousal threshold as an adoption of species-specific, state-dependent postures. Sleep is not a single "offline" physiological condition but rather a dynamic series of connected, yet distinct, behavioral and physiological states (*Table 364.1*). Sleep is divided between rapid eye movement (REM) sleep and non-REM (NREM) sleep. NREM is further subdivided into N1, N2, and N3 manifest as progressive slowing and synchronization of the electroencephalogram. REM sleep, in contrast, is characterized by a relative activation of the cortex with reemergence of certain waking EEG frequencies, eponymic, rapid, phasic, eye movements, fluctuations in heart rate and respirations, and a decrease muscle tone on EMG. A night's sleep has a remarkably stable, developmentally specific architecture.

Sleep Architecture from Birth to Adolescence

Sleep is the primary activity of the brain during early development, and also to a large extent during childhood and adolescence, accounting for about 40% of an average day's behavior. Significant changes in sleep architecture occur throughout early childhood. While changes occur across the entire lifespan, the most significant changes occur within the first few years (*Figs. 364.1* and *364.2*).

Newborn (0–3 months). The normal newborn sleeps 16–20 h per day. Sleep generally occurs in 1–4 h periods, followed by 1–2 h wake periods. Classic EEG patterns are not present in the first months of life, and sleep staging is divided equally into active sleep and quiet sleep.

Infants (3–12 months). NREM stages 1 through 3/4 can be identified, and sleep is entered through one of these stages. The proportion of REM sleep begins to decline around 3 months of age (*Figs. 364.1* and *364.2*). Throughout the first 12 months of life, total sleep time (TST) decreases to about 14 h per day. Sleep consolidation into a 6–8 h nighttime period occurs in about 75% by age 9 months and in nearly all children by 12 months. Naps persist about twice a day in 2–4 h blocks.

Toddlers (1–3 years). TST decreases to about 12 h per day with one nap per day, but the duration of the nap decreases to 1–3 h. Up to 25% of toddlers have sleep problems with bedtime resistance and frequent night awakenings. Behavioral insomnia of childhood is the primary sleep disorder in this age group.

Preschool (3–6 years). TST may decrease slightly and generally is 11–12 h per day. Most children stop taking naps by age 5. Bedtime resistance, nightmares, and nighttime fears are common in this age group. Obstructive sleep apnea syndrome (OSAS) and arousal parasomnias peak during this stage.

School-aged children (6–12 years). Children still require 10–11 h of sleep, with rare naps. Sleep problems in this group include insufficient sleep, bedtime resistance, OSAS, and poor sleep hygiene. Sleep restriction in this age group has been related to behavioral problems.

Adolescence (13–18 years). Sleep requirements are 8–9 h (*Fig. 364.3*), however most adolescents are sleep deprived due to social and school activities. Delayed

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_364,

Table 364.1
Sleep stages

Stage	Polysomnographic characteristics	Behavioral characteristics
Wake	Alpha rhythm (8–13 Hz) over occipital region with eye closure attenuating with eye opening, rapid eye blinks, EMG variable	Variable
NREM 1 (N1)	Low amplitude theta (4–7 Hz), vertex waves, slow conjugate eye movements	Light sleep
NREM 2 (N2)	K complexes, sleep spindles	Limb movements commonly seen
NREM 3/4 (N3)	Slow high amplitude delta frequency (0.5–2 Hz) adopts at least 20% of 30 s epoch	Highest arousal threshold
REM	Variable low amplitude mixed frequency, runs of central theta (e.g., sawtooth waves), alpha, rapid phasic eye movements, decreased muscle tone, variability heart rate and respirations	Dreaming, paralysis of extremities

NREM non-rapid eye movement, *REM* rapid eye movement

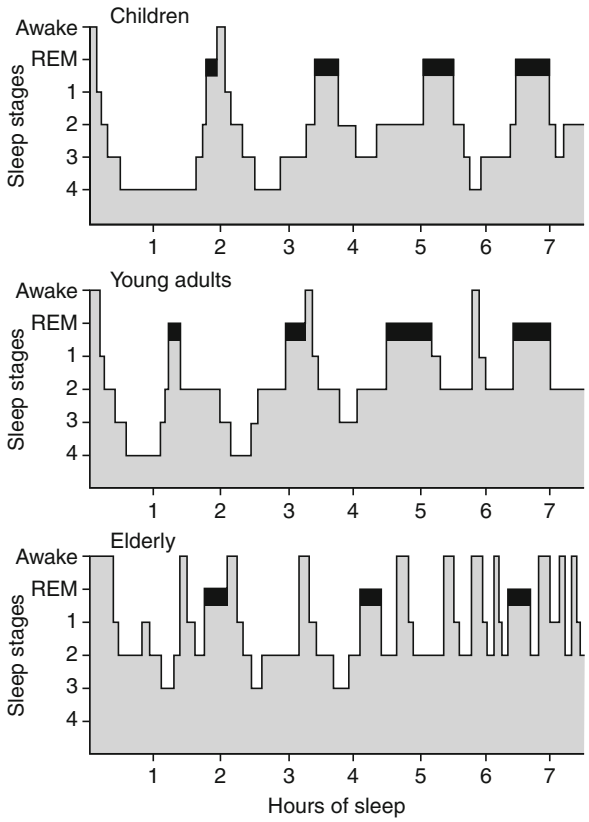

Figure 364.1
Sleep architecture changes with age **(Modified from Mindell JA, Owens JA (2003) A clinical guide to pediatric sleep: diagnosis and management of sleep problems in children and adolescents. Lippincott Williams and Wilkins, Philadelphia)**

sleep phase syndrome, OSAS, insufficient sleep, insomnia, restless legs syndrome (RLS), periodic limb movements of sleep (PLMS), and narcolepsy are seen in this age group (see below).

Mechanisms of Sleep

The biological mechanisms that govern sleep are still largely mysterious. A "two-process" model has been widely adopted that predicts the interaction between homeostatic sleep drive ("Process S") and the circadian timing system ("Process C") (*Fig. 364.3*). Process S is manifest as sleep drive (or sleep "pressure") that accrues proportionally to the duration of wakefulness and dissipates rapidly during sleep. Thus, sleep drive is predicted to be greatest just before sleep and least just after sleep. Process C refers to the 24-h (circadian) periodic oscillations of sleep propensity regulated by the endogenous and autonomous circadian timing mechanism. The core circadian clock comprises an evolutionarily conserved transcriptional, translational, and posttranslational feedback loop that is chiefly orchestrated by the master circadian regulator in the suprachiasmatic nucleus (SCN) of the hypothalamus (*Fig. 364.4*). The SCN is both necessary and sufficient to synchronize the biological clock. The endogenous clock is precisely entrained to the geophysical world by various *zeitgebers* ("time-givers"), including the light-dark cycle, feeding cues, and social interactions. Importantly, the circadian clock appears to be ubiquitous, present in most if not all tissues. The mechanisms by which the central timekeeper in the SCN conveys synchronizing information to peripheral tissues remain obscure.

Neuroanatomy and Neurochemistry of Sleep

The neuroanatomical substrates of arousal comprise monoaminergic nuclei in the brainstem including

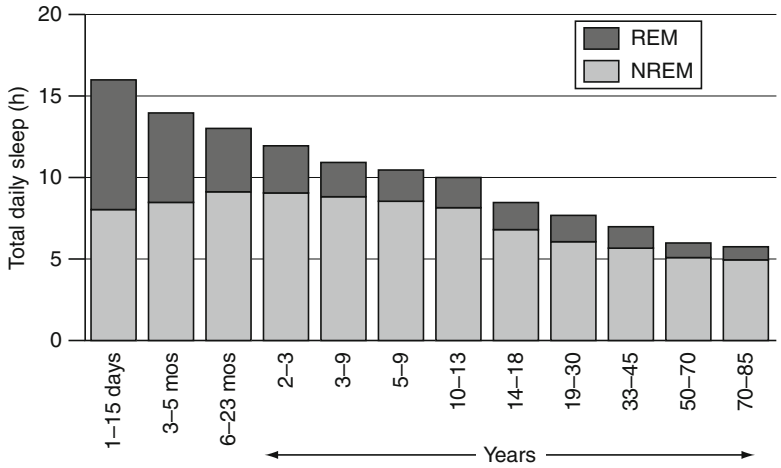

Figure 364.2
Ontogeny of REM/NREM sleep **(Modified from Roffwarg HP, Muzzio JN, Dement WC (1966) Ontogenic development of the human sleep–dream cycle. Science 152:604–619)**

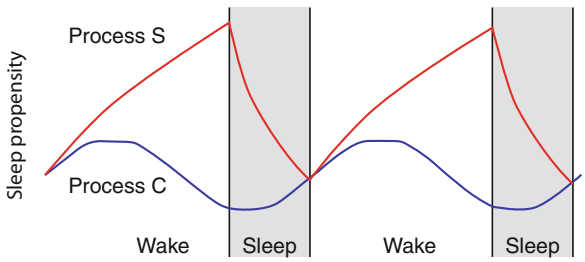

Figure 364.3
The two process model of regulation in sleep propensity. **Shown is the relationship of the circadian timing mechanism (Process C) to homeostatic sleep drive (Process S). Note that homeostatic drive is always greatest just before sleep and least just after sleep. Importantly, in the hours before sleep note opposite effects of Process C and Process S on sleep propensity; this can result in significant insomnia in the hours prior to the appropriate bedtime**

the locus coeruleus (noradrenergic), dorsal raphe (serotonergic), tuberomamillary nucleus (histaminergic), ventral periaqueductal gray (dopaminergic), and pedunculopontine nucleus (cholinergic) that project toward the basal forebrain and thalamus (*Fig. 364.5*). The ventro-lateral preoptic nucleus (VLPO), containing GABA-ergic and galanin-ergic nuclei appears to be a final common pathway in the stimulation of sleep as lesions in this region result in profound insomnia. The stability of state transitions between sleep and wake is modulated by the orexin/hypocretin system that originates in the lateral hypothalamic nucleus. Dysfunction of this system results in narcolepsy. Several sleep-promoting factors have been identified including adenosine, tumor necrosis factor-α, and interleukin-1. The precise mechanism by which the experience of clinical sleepiness arises, however, remains poorly understood.

Physiological Correlates of Sleep States

Sleep influences most major physiologic systems including breathing, cardiovascular function, the endocrine system, and muscle tone. Heart rate, blood pressure, and respiratory rate decrease dramatically during NREM sleep but extraordinary variability in both pulse and respirations are seen in phasic REM sleep. There is an increase in hypoxic ventilatory response during REM sleep as well as a modification of the hypocapnic control of respiration. These phenomena may contribute to the physiological instability associated with REM–NREM transitions as well as sleep–wake transitions.

Core body temperature (Tb) shows a circadian variation independent of sleep. The amplitude of temperature variation is about one degree. Secondly, there is a reduction in the body's thermal set point (the result of increased heat dissipation and decreased heat generation). In REM sleep, there is an absence

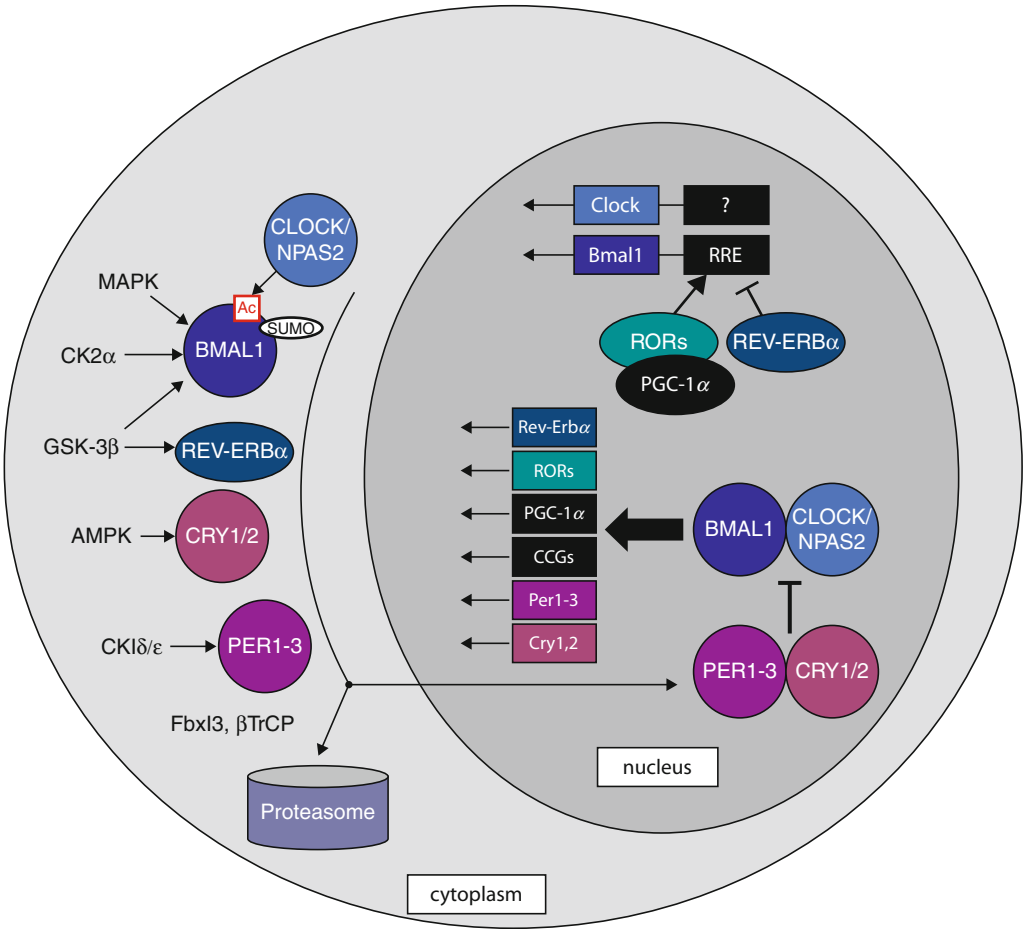

Figure 364.4

Schematic of the molecular clock transcriptional-transalational feedback loop. The "positive limb" is initiated by binding of BMAL1:CLOCK/NPAS2 heterodimers in the nucleus that activate the transcription of clock-controlled genes (CCGs). Upon translation in the cytoplasm, several of these CCGs, including the PERs and CRYs re-enter the nucleus, and inhibit the activity of the BMAL1:CLOCK complex, closing the feedback loop. Note that clock proteins undergo extensive post-translational modification that contribute importantly to their dynamics

of thermoregulatory response, resulting in effective poikilothermy and a drifting of Tb toward environmental temperature.

Slow-wave sleep is associated with secretion of growth hormone independent of circadian time. Sleep onset (and possibly slow-wave sleep) is associated with inhibition of thyroid-stimulating hormone and of the adrenocorticotropic hormone–cortisol axis, an effect that is superimposed on the prominent circadian rhythms in the two systems.

The pineal hormone melatonin is under direct modulation by the circadian pacemaker via a complex neuroanatomical pathway starting with the retinohypothalamic tract and traversing the SCN and cervical sympathetic chain. Melatonin is predominantly secreted at night independently of sleep and thus may represent a biological signature of circadian time. Exogenous melatonin increases sleepiness and sleep duration when administered in adults attempting to sleep during daylight hours (when endogenous melatonin is low). Melatonin has been used for sleep-onset and sleep maintenance insomnia in children, however neither effectiveness nor safety of long-term use have been established.

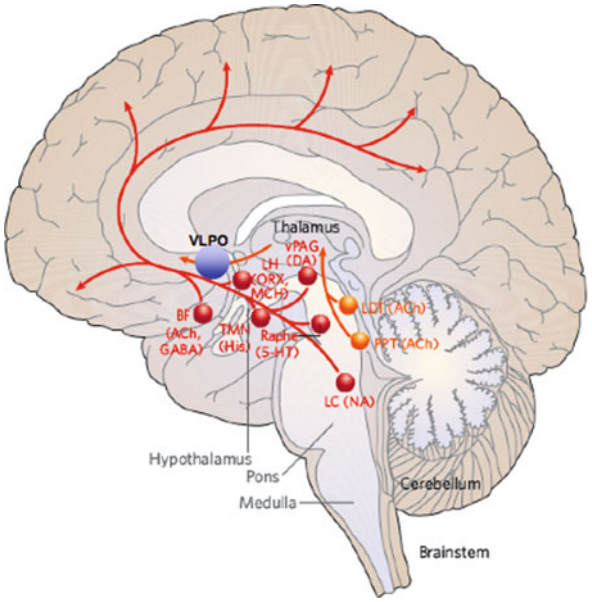

Figure 364.5
Neuroanatomy of sleep and wakefulness. TMN **tuberomamillary nucleus,** ***LC*** **locus coeruleus,** ***PPT*** **parapontine tegmentum,** ***LDT*** **lateral dorsal tegmentum,** ***vPAG*** **ventral periaqueductal gray,** ***BF*** **basal forebrain,** ***VLPO*** **ventral lateral preoptic area,** ***Ach*** **acetylcholine,** ***DA*** **dopamine (Modified after Saper, C et al** ***Nature*** **2005)**

Evaluation of Sleep Disorders in Children

Studies have shown that despite recognizing the importance of sleep, most pediatricians do not feel comfortable identifying and treating sleep disorders.

Assessment of sleep disorders should include:

Sleep history – difficulty going to bed, initiating or maintaining sleep, excessive daytime sleepiness and nocturnal awakenings, unusual behaviors at night, snoring and difficulty breathing, schedules on weekdays and weekends, and napping. Validated questionnaires such as the "BEARS" algorithm, Pediatric Daytime Sleepiness Score (PDSS), and the Pediatric Sleep Questionnaire (PSQ) can be useful for assessment of age-specific subjective sleep parameters.

Medical and psychiatric history – asthma, allergies, gastroesophageal reflux disease (GERD), chronic lung disease, sickle cell disease, epilepsy, headaches, cerebral palsy, developmental delay, ADHD, autism, depression, bipolar disorder, and anxiety.

Family history – sleep-disordered breathing, narcolepsy, sleep-related movement disorders.

Developmental screen and assessment of school functioning and behavioral assessment.

Physical examination, especially:

Growth parameters: height, weight, BMI

ENT exam: looking for deviated septum, adenotonsillar hypertrophy, adenoid facies, or oropharyngeal crowding.

Neurologic exam: especially in children with excessive sleepiness and seizures.

Polysomnography (PSG)

A PSG is a continuous recording of EEG, EKG, EOG (electro-oculogram), respiratory effort using chest and abdominal belts, airflow, gas exchange and end tidal CO2, electromyogram, snore microphone, and pH probe (Fig. 364.6).

A PSG is warranted to investigate causes of excessive daytime sleepiness such as sleep-disordered breathing, sleep fragmentation due to frequent nocturnal arousals from PLMS, bruxism, GERD, the etiology of episodic nocturnal phenomena (e.g., parasomnias versus nocturnal seizures), or as a screening tool prior to a test for excessive daytime sleepiness such as the multiple sleep latency test (MSLT).

Sleep logs. Sleep logs give an estimate of the number, duration, and timing of daily episodes of nocturnal sleep, daytime naps, and wake periods.

Actigraphy. Actigraphy has been widely recognized as a low-cost, home-based tool for screening of sleep disorders, especially circadian rhythm disorders or behavioral insomnias. Actigraphy data is limited by the confounding of influences of immobility during wakefulness or, conversely, sleep-related movements.

Multiple Sleep Latency Test (MSLT)

The MSLT is a validated objective measure of the ability or tendency to fall asleep. It is indicated as part of the evaluation of patients with suspected narcolepsy and idiopathic hypersomnia. This test involves five 20-min opportunities to nap during the day with each nap being separated by 2 h. The sleep onset for each nap is determined as sleep latency. A sleep latency between 5 and 10 min indicates mild/moderate daytime sleepiness, whereas <5 min indicates severe daytime sleepiness). Onset of REM sleep within 15 min of sleep onset is determined as SOREMP (sleep onset REM period) (Fig. 364.7).

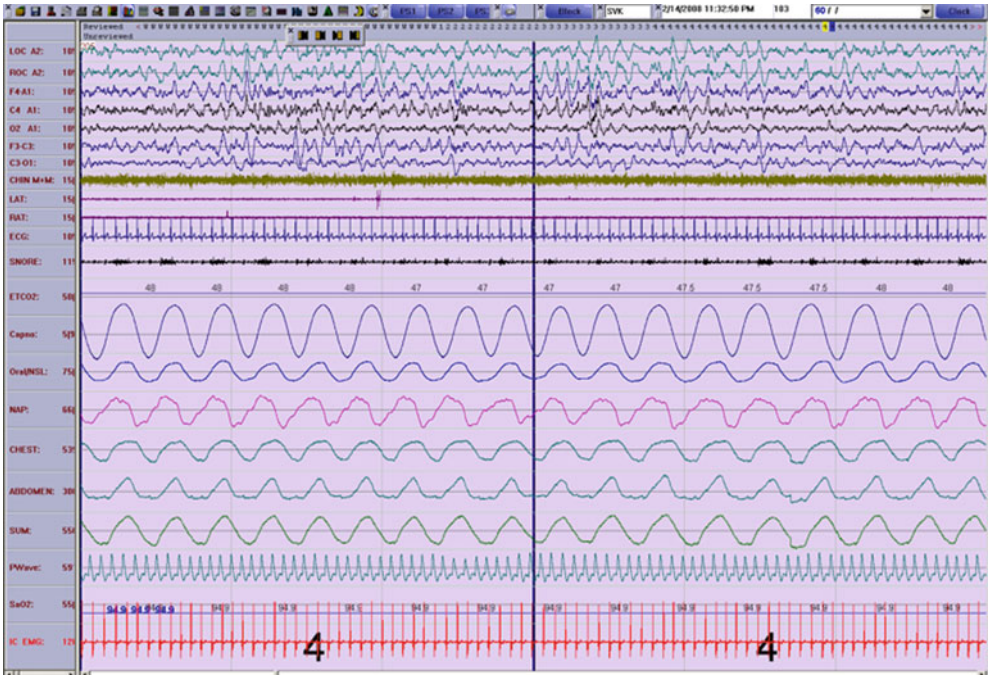

Figure 364.6

Normal polysomnography. From *top* to *bottom*: *LOC*/*ROC* left and right oculography; EEG (next 5 lines). Green = chin EMG. *LAT* and *RAT* left and right anterior tibialis EMG, respectively. ECG, snore microphone, $EtCO_2$, capnography; *NAP* nasal air pressure; chest and abdomen movement and sum of two; oxygen saturation, *IC EMG* intercostals EMG

Disorders of Sleep Onset and Maintenance in Children

Insomnia

Insomnia is defined by repeated difficulty with sleep initiation, duration, consolidation, or quality despite adequate time and opportunity for sleep that results in some form of daytime impairment (defined as at least one of the following: fatigue, attention or concentration impairment, poor school performance, vocational dysfunction, mood disturbance or irritability, daytime sleepiness, decreased motivation or initiative, proneness for errors, tension, headaches, or gastrointestinal symptoms in response to sleep loss, or concerns or worry about sleep). Insomnia can be difficult to assess in young children because signs and symptoms are expressed by caregivers with limited accuracy and reliability. Population-wide studies suggest that there is a high prevalence of children getting inadequate sleep. Parental or child self-reported problems with sleep initiation or maintenance in school-age children varies from 30% to 41%. Finally, insomnia can have a profound effect on family dynamics and, conversely, familial distress can be a risk factor for development of insomnia, even into adulthood.

The Primary Insomnias

Infants and toddlers. The most common cause of sleeplessness in the youngest children – with estimated prevalence of 10–30% – is behavioral insomnia of childhood (BIC). BIC can been subdivided into two: (1) sleep-onset association type characterized by a child's dependency on stimulation or objects for return to sleep (e.g., parental touch, coddling, co-sleeping, or pacifier) and (2) learned-onset type typically characterized by stalling at bedtime secondary to inadequate limit setting.

Preschool-aged children (3–5 years). Bedtime resistance and sleep onset insomnia are common in preschool children as an expanding communicative palette results in further limit-testing behavior. Differential diagnosis for insomnia includes anxiety disorder, post-traumatic stress disorder (PTSD), child abuse, and use or acute disuse of medications that interfere with REM sleep such as clonidine or selective serotonin reuptake inhibitors (SSRIs).

Problems with sleep hygiene are a common cause of insomnia in this age group frequently secondary to duration of time in bed that exceeds the child's sleep requirement. This frequent phenomenon results in varying constellations of sleep fragmentation with nocturnal

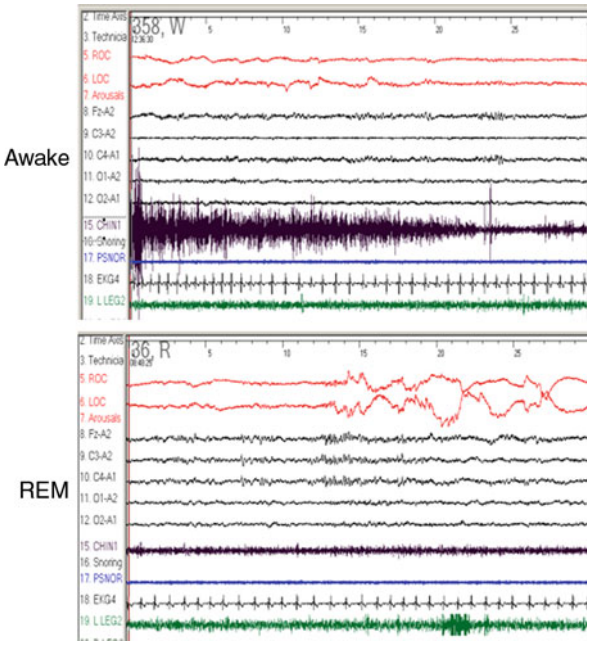

Figure 364.7
MSLT montage comparing appearance of wake to REM sleep

arousals, sleep onset insomnia, and an exacerbation of behavioral difficulties associated with sleep.

School-age children (6–11 years). Inadequate sleep and poor sleep hygiene are common in school-age children as the increased social, educational, and parental demands are made of them. Bedtime resistance, shortened sleep duration, and sleep-onset delay are common in this age group.

Adolescents (12–18 years). Hormonal changes that accompany adolescence have been hypothesized to result in the prominent changes in adolescent sleep patterns that include reduced daytime alertness, delayed sleep phase syndrome (DSPS) with delayed bedtimes, and reduced sleep timing (see below). A combination of increased autonomy and the psychosocial, familial, and educational demands of adolescent life also promote poor sleep hygiene.

Psychophysiological insomnia. Characterized by a heightened level of arousal in bed, psychophysiological insomnia often manifests as excessive anxiety about sleep, heightened inability to relax in bed, or an ability to sleep better away from home can also present in adolescents.

Idiopathic insomnia. The term idiopathic insomnia refers to a relatively rare uncommon condition characterized by lifelong insomnia without identifiable cause, with usual onset in childhood or adolescence, and strong family history. In children, it must be distinguished from behavioral insomnia and should always remain a diagnosis of exclusion. Patients with idiopathic insomnia can be distinguished from normal short sleepers because the latter are not distressed by relatively reduced total sleep time.

Secondary or Comorbid Insomnia

Medical and Psychiatric Conditions. Several medical conditions may impair sleep onset or maintenance including pain, colic, otitis media, asthma, allergies, gastroesophageal reflux, sickle cell disease, fibromyalgia, and cancer. It can be particularly difficult to distinguish sleep dysfunction as a contributing cause as opposed to a symptom of an underlying psychiatric disorder. Anxiety disorders, major depression, and post-traumatic stress disorder should always be considered in the differential diagnosis of insomnia. In older children and adolescents, use of alcohol and other recreational drugs should be explored as possible causes for insomnia.

Neurological Conditions. Children with neurological conditions are at particular risk of insomnia. Attention-deficit disorder (ADD) with or without hyperactivity has been repeatedly identified as either the cause or a symptom of sleep onset and/or sleep maintenance insomnia. Low ferritin levels (less than 50 ng/mL) have been associated with both ADD and sleep-related movement disorders (see below). Sleep and epilepsy have a mutual relationship with sleep quality strongly affecting seizure control. Many anti-convulsants alter sleep macroarchitecture and can also contribute to both sleep initiation and maintenance difficulties. For unknown reasons, insomnia is common in children with autistic spectrum disorders (ASD). Insomnia is common in children with cerebral palsy (CP) and those with severe visual impairment are especially affected. Sleep maintenance is extremely disrupted in Angelman syndrome and Rett syndrome; however, little is known about the underlying pathophysiology. Finally, children with the rare Smith–Magenis syndrome demonstrate circadian cycle inversion and may suffer from significant insomnia.

Circadian Rhythm Sleep Disorders (CSRD)

Circadian oscillations are the manifestation of an endogenously working clock that has, in each individual, a genetically specified period. Yet, the circadian system is extraordinarily plastic and responds to environmental cues – so-called zeitgebers (or "time-givers") including light, food, and social interactions – that serve to synchronize the clock with geophysical and sociobiological time.

CSRDs result from a misalignment of the endogenous clock with the socially mandated schedule and can result from: (1) environmentally imposed behavior or cues such as shift work, jet lag, or a dearth of normal light/dark cues; (2) decreased sensitivity to synchronizing cues such as light (e.g., with blindness); and (3) genetic variability in the biological clock itself that renders a relatively short or long period or inappropriate responsiveness to *zeitgebers*.

Delayed Sleep Phase Syndrome (DSPS). DSPS is the most common CSRD in the pediatric population, especially adolescents (prevalence ~7%), and is characterized by a delay in the phase of circadian clock mechanism relative to local time. DSPS presents with sleep-onset insomnia, daytime sleepiness, and sleep deprivation until the restrictions on the mandated schedule are relieved (e.g., during the weekend) and the circadian phase is "expressed." When patients with DSPS are permitted to sleep without restriction, sleep is normal, differentiating it from psychophysiological insomnia. Delays in melatonin secretion, changes in core body temperature, and sleep/wake cycle have been demonstrated in DSPS patients. Treatment has focused on resetting the circadian clock (chronotherapy) by advancing sleep times and/or light therapy in which subjects are exposed to bright light at the same time every morning after the normal physiological temperature nadir. Pharmacologically, exogenous melatonin administered prior to desired sleep time has been shown to have efficacious hypnotic and phase-shifting effects.

Advanced Sleep Phase Syndrome (ASPS). ASPS refers to a condition in which an individual falls asleep and wakes early relative to local time. A tendency toward relative phase advancement occurs with normal aging. True ASPS is uncommon however, and may have a strong genetic basis. Mutations in two regulators of the "negative limb" of the circadian feedback loop – *Per2* and *CK-1ε* – have been identified in familial cohorts (◉ *Fig. 364.2*).

Blindness. Because blind individuals do not benefit from the entraining influences of light on the endogenous circadian clock, they may exhibit a "free-running" rhythm in which the circadian phase cycles independently of local time often resulting in severe insomnia. Melatonin has proven valuable as an exogenous entraining signal in these patients. A free-running circadian rhythm is extremely rare in sighted individuals.

Jet Lag Disorder and Shift Work Disorder. Children are not frequently exposed to jet lag or regular shift work. Both can result in chronic sleep disruption secondary to misalignment of internal clock with local time.

Hypersomnias in Childhood

Narcolepsy

Narcolepsy is a disabling disorder of sleep characterized by excessive daytime sleepiness for at least 3 months duration in the absence of another primary sleep disorder and/or episodes of emotionally triggered cataplexy. The presence of cataplexy (i.e., a paroxysmal, bilateral decrease of muscle tone) with excessive daytime sleepiness is sufficient to make a diagnosis. Narcolepsy has other features that vary in prevalence including hypnagogic (occurring with falling sleep) or hypnopompic (occurring with waking) hallucinations, sleep paralysis, and an urge to sleep that is often uncontrollable.

Narcolepsy has an estimated prevalence in the United States of 0.8 per 100,000; however, the prevalence is higher in Japan and lower in Europe. It is more common in women and has a bimodal age of diagnosis: the first peak occurs at about 15 years and the second, smaller peak, at about 36 years. Narcolepsy with cataplexy can be familial. Interestingly, about 85–95% of patients with narcolepsy with cataplexy carry the HLA DQ1B*0602 haplotype, suggesting a genetic predisposition to the disease (importantly however, 99% of individuals with this haplotype do not have narcolepsy).

Elegant genetic studies in narcoleptic dogs in conjunction with molecular studies in mouse models have identified the orexin/hypocretin system as the culprit signaling defect in narcolepsy. The orexins are a family of neuropeptides produced exclusively in the lateral nucleus of the hypothalamus. These orexinergic neurons make extensive projections both caudally into the brainstem arousal system and rostrally into the basal forebrain (◉ *Fig. 364.5*). In *postmortem* brains from patients with narcolepsy with cataplexy, an absence of orexin-expressing neurons has been noted. It has been hypothesized that orexins stabilize the transitions between REM and NREM sleep. Thus, loss of orexinergic signaling results in sleep-state instability with frequent and abrupt wake/REM transitions, sleep fragmentation, and the other associated symptoms of the disease. The underlying mechanisms of cataplexy remain controversial. Orexin levels in the cerebrospinal fluid (CSF) of patients with narcolepsy with cataplexy are severely reduced or undetectable. Importantly, individuals with narcolepsy *without* cataplexy have normal CSF orexin levels.

The diagnosis of narcolepsy is made on clinical grounds. Supporting tests of sleepiness such as the MSLT are recommended. A mean sleep latency of less

than 8 min and presence of two or more sleep-onset REM periods on an MSLT is supportive of a diagnosis of narcolepsy. These values are not validated for children. Diagnosis can be difficult in the pediatric population, especially in young children. Misdiagnoses include laziness, attention-deficit, epilepsy, opposition-defiant disorder, depression, tics, and even psychosis.

Consolidation of nocturnal sleep and control of cataplexy are the treatment goals of narcolepsy therapy. Optimization of sleep hygiene is a required first step. Scheduled daytime naps can be remarkably helpful. Sleep-stabilizing medication such as sodium oxybate is increasingly used. Stimulants such as modafinil or amphetamine derivatives (e.g., methylphenidate or dextroamphetamine) can effectively offset daytime sleepiness and limit unwanted diurnal sleep bouts. Sodium oxybate (or g-hydroxybutyrate), a GABA-B receptor agonist, is approved for treatment of cataplexy and is also beneficial in sleep consolidation, daytime fatigue, and possibly hypnagogic hallucinations. Sodium oxybate is not approved for children; however, it has been used off-label. Cataplexy can be controlled with selective serotonin/noradrenaline reuptake transporters and their derivatives (e.g., venlafaxine) or with second-generation tricyclic antidepressants (e.g., clomipramine or desipramine).

Other causes of cataplexy. Niemann–Pick disease C, Prader–Willi Syndrome, and myotonic dystrophy can present with cataplexy and should be differentiated from idiopathic narcolepsy with cataplexy.

Other Hypersomnias

Idiopathic hypersomnia. Idiopathic hypersomnia is an incompletely defined disorder reserved for daytime sleepiness in the absence of cataplexy or identifiable cause; it is always a diagnosis of exclusion.

Kleine–Levin syndrome. This rare disorder is characterized by relapsing–remitting episodes of hypersomnia, cognitive disturbances, and behavioral disturbances usually of primal functions including hyperphagia and hypersexuality. Between episodes, sleep and wake behavior are normal. Hypersomnia episodes may last for a few days to several weeks. The cause of this syndrome remains obscure. Symptomatic cases of Kleine–Levin syndrome associated with structural brain lesions have been reported, but most cases are idiopathic. The syndrome is often linked to an antecedent respiratory illness of presumed viral origin.

Pediatric Parasomnias

Definitions

Parasomnias are defined as undesirable physical events or experiences that occur during entry into sleep, during sleep, or during arousals from sleep. They are classified as (1) disorders of arousals from non-rapid eye movement (NREM) sleep, (2) parasomnias associated with rapid eye movement (REM) sleep, and (3) other parasomnias.

Disorders of Arousal from NREM Sleep

Most disorders of arousals occur during slow wave sleep (SWS) during incomplete transitions into wakefulness, and are characterized by automatic behavior, altered perception of the environment, and variable degree of amnesia for the event. They tend to occur in the first third of the night when SWS is more prominent. The EEG during the episodes demonstrates an admixture of theta, delta, and alpha frequencies. They are felt to be due to a faulty switch that prevents normal sleep cycle progression. They are brought out by sleep deprivation, medications, noisy or stimulating environments, stress, fever, and sleep fragmentation due to obstructive sleep apnea (OSA) or periodic limb movements of sleep (PLMS). Several studies suggest a genetic predisposition to some of the arousal parasomnias.

Evaluation should include a complete description of the event, time of night when they happen, frequency of episodes, recollection of the event by the child, and presence during daytime naps. Information regarding whether the movements are rhythmic and stereotypical, associated with eye deviation, and focal tonic clonic activity may support an epileptic origin to the events. Examination should focus on looking for evidence of upper airway obstruction such as adeno-tonsillar hypertrophy, midfacial hypoplasia, and retrognathia. In appropriate cases, a video-EEG may be indicated to rule out seizures. Overnight polysomnography is indicated when there is concern for an intrinsic sleep disorder like OSA or PLMS, rather than to document the parasomnia per se.

Management usually includes reassurance, securing the environment, voidance of known precipitants such as sleep deprivation, caffeinated drinks, and avoiding any attempts of restraining or awakening the child during the episode which may actually be counterproductive. Medications should be reserved for protracted cases with no associated sleep disorders, frequent

events or those associated with a threat for injury. Low-dose clonazepam or tricyclic antidepressants for a short duration have been used with good success in such cases.

Sleep walking (somnambulism): Occurs in up to 17% of children, highest at 12–13 years of age, and with equal frequencies amongst males and females. It is further classified as calm or agitated subtype, with the former more common in children. The major concern during these benign behaviors is risk for injury.

Confusional arousals: Occur mainly in infants and toddlers, in up to 17.3% of the population. A typical event begins with moaning, evolving to confusion, and agitated behavior lasting 5–15 min. Attempts to wake up the child fully are unsuccessful.

Sleep Terrors: Occurs in 1–6% of children with peak frequency between 4 and 8 years of age. The child may sit up suddenly and scream with a blood-curdling battle cry. There is an expression of intense fear on the face and is accompanied with autonomic activation including mydriasis, tachycardia, and diaphoresis. Some children may report indistinct recollections of threat such as monsters, spiders, and snakes from which they have to defend themselves. In most cases, however, there is no recollection of the event. The event may last from a few minutes up to 20 min. Most cases go into a natural remission by adolescence.

Nocturnal seizures: Parasomnias must be differentiated from nocturnal seizures. Frontal lobe seizures are especially important since they occur predominantly in sleep, sometimes many times per night, and are characterized by stereotypical movements, thrashing of entire body, vocalizations, and dystonic posturing lasting 20 s to a few minutes with minimal postictal drowsiness or confusion. Paroxysmal nocturnal dystonia, which is now considered to be a frontal lobe seizure, is characterized by an arousal from NREM sleep, accompanied with dystonic posturing, bizarre movements of the extremities, and vocalization, with minimal EEG correlation due to a deep-seated focus of seizure onset in the mesial frontal region.

REM Parasomnias

Nightmares. These are characterized by vivid dreams in the second half of the night with intense feelings of terror or dread that typically awaken the child from sleep. The child can be easily aroused, with good recollection of the event. They are frequently seen between the ages of 3 and 6 years. Prevalence ranges from 30% to 90% for occasional and 5–30% for frequent episodes. In children, psychiatric disorders are seen more often in those experiencing nightmares than those without nightmares. They may also be a marker for a history of sexual abuse in children and adolescents.

REM sleep behavior disorder (RBD). This disorder is characterized by enacting of unpleasant and combative dreams with complex movements that can be vigorous and violent due to lack of REM sleep atonia. The disorder occurs more often in the sixth or seventh decade in males, and may precede onset of Parkinson's disease, or progressive supra-nuclear palsy. The disorder is uncommon in children, but may be seen in association with use of selective serotonin reuptake inhibitors like fluoxetine, or accompanying narcolepsy, and Tourette's syndrome. RBD responds very well to clonazepam given at bedtime.

Recurrent isolated sleep paralysis. This is characterized by a generalized inability to speak, or to move the trunk, head, and limbs that occur during the transitional period between sleep and wakefulness. The episodes are brief and transient, but may be accompanied with vivid hallucinations which make them very distressing. Usually seen with narcolepsy, they may be seen as an isolated form in otherwise healthy individuals, with a strong family history in some cases.

Sleep-related hallucinations. These are characterized as vivid dreams, or perceptions not based in reality, that occur at sleep onset (hypnagogic hallucinations) or on awakening (hypnopompic hallucinations) that occur in otherwise healthy individuals, but are frequent seen as part of the symptoms of narcolepsy. They may be visual, tactile, auditory, or kinetic in nature. They probably represent brief intrusion of REM sleep into NREM sleep or wakefulness.

Sleep-related enuresis. Nocturnal enuresis (bedwetting) refers to involuntary passage of urine while asleep. It occurs in almost 15–25% of children at 5 years of age, more often in boys, and in almost 1–3% of adolescents. It may be classified as primary (when present from birth) or secondary (with periods of at least 6 months of dryness prior to recurrence of enuresis) and nocturnal or diurnal. Three major pathological factors have been considered as possible etiologies: Group 1, volume dependent with polyuria; Group 2, detrussor dependent, with involuntary detrussor contractions, and small urinary bladder; Group 3, with decreased arousability. There are strong associations of enuresis with genetic and familial factors, and high prevalence of secondary enuresis in children with OSA. Treatment involves removal of inciting factors, reassurance, behavioral programs, and use of nasal desmopressin, or oral tricyclics like imipramine.

Exploding head syndrome. It is a harmless but potentially terrifying situation usually occurring while a patient is falling asleep, and is characterized by a terrifying loud

noise, accompanied by myoclonic jerks, or the perception of a flash of light. Events are very brief. There is no headache or pain accompanying these episodes; and they can begin in childhood. No treatment is needed.

Sleep-related eating disorder. Usually seen accompanying sleep walking and daytime eating disorder, it is characterized by out-of-control eating binges, predominantly of carbohydrate-containing diets, 2–3 h after sleep onset, with no recall of the event subsequently. They can be seen to begin in childhood, but are more often seen in teenage years and adulthood. These behaviors have recently been described in association with use of hypnotics like zolpidem.

Catathrenia. Also called nocturnal groaning, this can occur in REM or NREM sleep during expiration in clusters of 2 min to an hour, ending with a snort, and accompanied with changes in heart rate. The onset may begin during childhood or adolescence. The exact etiology is unknown, and no specific therapy has been found to be effective.

Sleep starts. Also called hypnic jerks, these are sudden whole body jerks experienced by individuals during sleep–wake transition. Variations include sensory; auditory, including exploding tinnitus; and visual sensations, which may occur without the motor jerks. No treatment other than reassurance is necessary for them.

Sleep-sex disorders. Inappropriate sexual behavior occurring during sleep without conscious awareness has been reported in adults, with onset around adolescence in some cases.

Sleep-talking. Is very common in the general population, and can occur in REM or NREM sleep with a strong familial and genetic propensity.

Hypnic headaches. This is characterized by diffuse headache occurring 4–6 h after sleep onset at a consistent time, lasting 30–60 min, seen in older adults accompanied by nausea but no other autonomic features.

Rhythmic Movement Disorders of Sleep

Restless Legs Syndrome (RLS) and Periodic Limb Movements of Sleep (PLMS)

RLS is a common sensorimotor disorder of unclear cause characterized by (1) an urge to move the limbs often in association with an unpleasant sensation, (2) the urge to move is worse at night or occurs only at night, (3) the urge to move is present while at rest, and (4) the urge to move or unpleasant sensation is relieved by movement. Diagnosis can be extremely challenging in children. Periodic limb movements of sleep (PLMS), a related disorder, is diagnosed almost exclusively by 0.5–5 Hz limb movements seen during polysomnography and thus, most patients with PLMS are unaware of the presence of the movements (*Fig. 364.8*). When PLMS is associated with sleep disturbance and daytime sleepiness, it is referred to as periodic limb movement disorder (PLMD). RLS and PLMS, like other disorders that potentially alter sleep quality and duration can have demonstrable impact on cognitive function, mood, neurological status, and quality of life. Primary RLS is idiopathic whereas secondary RLS has been associated with iron deficiency, pregnancy, end-stage renal disease, neuropathy, and certain medications.

Epidemiology. The prevalence in the pediatric population has been estimated at about 2% in 8–17 year olds in the United States and United Kingdom. Thus, RLS affects an estimated 984,000 of the school-age pediatric population in the United States. The prevalence of PLMS in children is unknown. While RLS and PLMS can exist independently of one another in the same individual, many patients with RLS also have PLMS.

Diagnosis. For children over the age of 12, adult definitions of RLS apply. Because of the difficulty of expressing sensory symptoms in younger children, modifications to the adult diagnostic criteria have been adopted (*Table 364.2*).

Etiology and Associations. In children with confirmed RLS, a history of RLS in a biological parent can be found in more than 70%, suggesting that genetic factors may play a prominent causative role. Polymorphisms in at least four independent loci have been identified that confer increased risk of PLMS and/or RLS. Whether these polymorphisms will provide insight into the etiology and neuropathology of RLS is unclear. Both RLS and PLMS are associated with attention-deficit hyperactivity disorder (ADHD) and interestingly, all three disorders have been associated with iron deficiency, suggesting that iron metabolism may represent a common pathophysiological pathway. The prevalence of ADHD or ADHD symptoms in patients with RLS symptoms is 18–26% whereas the converse prevalence of RLS (or RLS symptoms) in patients with ADHD is 10.5–44%, again supportive of mechanistic overlap between these disorders.

Treatment. The primary treatment of RLS and PLMS are the dopaminergic agonists ropinirole and pramipexole; however, neither has been approved for use in children. Serum ferritin below 50 ng/mL has been associated with increased severity of RLS; furthermore, supplemental iron administration has demonstrated benefit in RLS.

Head banging. Also called *jactatio capitis nocturna*, it is now classified as a rhythmic movement disorder of sleep

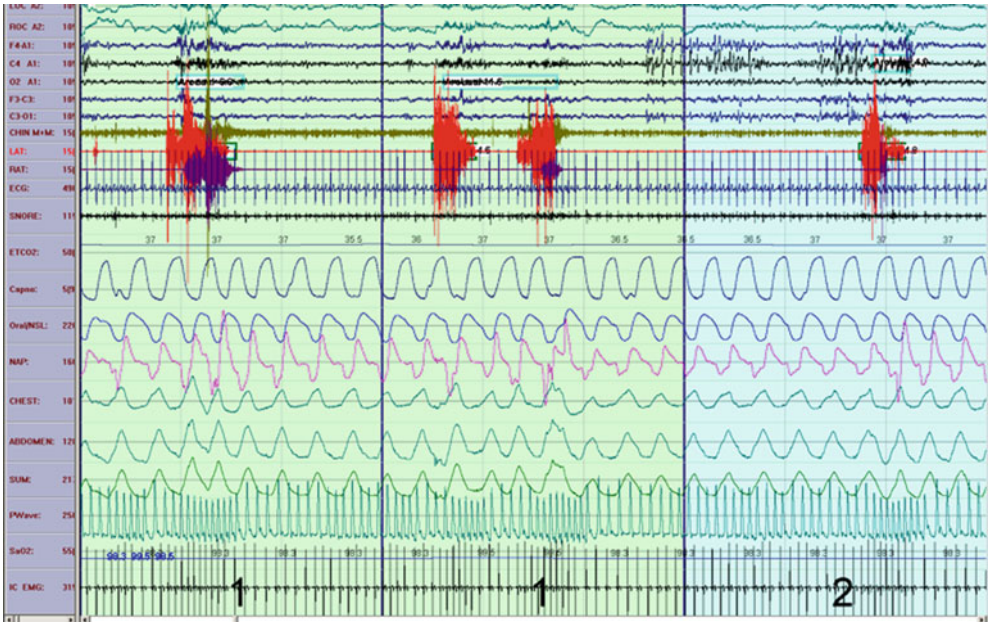

Figure 364.8
***Polysomnographic characteristics of periodic limb movements of sleep*. Note high amplitude paroxysmal activity of both legs lasting 1–2 s per movement**

Table 364.2
Criteria for making the diagnosis of definite RLS in children

1. The child meets all four essential adult criteria for RLS (the urge to move the legs, is worse during rest, relived by movement and worse during the evening and at night)
2. The child relates a description in his or her own words that is consistent with leg discomfort (the child may use terms such as "oowies," "tickle," "spiders," "boo-boos," "want to run," and "a lot of energy in my legs" to describe the symptoms. Age-appropriate descriptors are encouraged)
Or
1. The child meets all four essential adult criteria for RLS
2. Two of the three following supportive criteria are present
(a) Sleep disturbance for age
(b) A biologic parent or sibling has definite RLS
(c) The child has a polysomnographically documented periodic limb movement index of 5 or more per hour of sleep

and is characterized by rhythmic movements of head and body at sleep onset in infants and toddlers. It is seen more often in children with developmental disability and autism, but may be seen in normal children. No specific treatment other than reassurance is indicated.

Bruxism. The prevalence of bruxism (teeth grinding) is 14–17% in childhood, decreasing over the lifespan. Sleep-related bruxism without clear cause is termed primary, whereas secondary sleep-related bruxism may be associated with the use of psychoactive medications, recreational drugs or a variety of medical disorders. It can lead to abnormal wear of teeth, jaw muscle pain, or temporal headache. Dental examination and oral appliance may be indicated. The cause of bruxism is unknown; however, it may represent a motor manifestation of sleep-disordered breathing.

Sleep-Disordered Breathing: Obstructive Sleep Apnea

Obstructive sleep apnea syndrome (OSAS) was first reported in children over 30 years ago; however, it remains underdiagnosed despite strong evidence of increasing incidence. OSAS is a form of sleep-disordered breathing (SDB) that comprises one end of a spectrum of sleep-associated changes in upper airway resistance that in its most severe form constitutes recurrent hypoxia and subsequent arousals from sleep. OSAS is diagnosed on polysomnography by the presence of obstructive apneas (absence of airflow for at least two breaths) or hypopneas

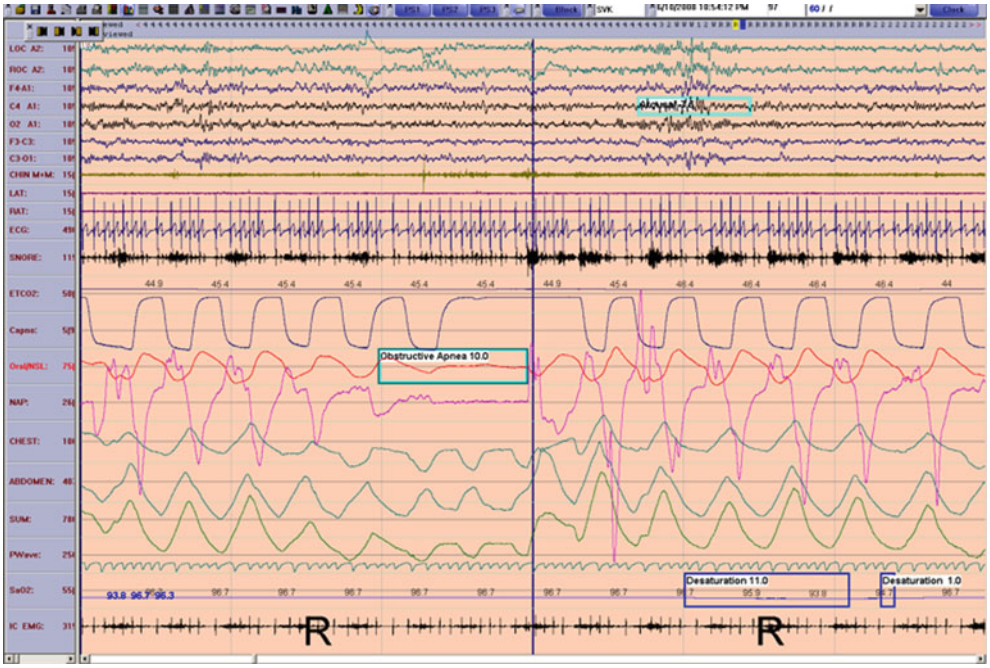

Figure 364.9
Polysomnographic characteristics of obstructive sleep apnea. Note diminution and then absence of oral thermistor (oral) and nasal air pressure (NAP) followed by an EEG arousal, brisk recovery breath, and delay of desaturation

(a greater than 30% reduction in baseline nasal airflow with an associated decrease in oxyhemoglobin saturation of at least 3%) and in children, an apnea-hypopnea index (AHI = (number of apneas + number of hypopneas)/total sleep time) of greater than one per hour (Fig. 364.9). Recurrent respiratory effort–related arousals (RERAs; defined as a decrease in airflow without associated desaturation) occurring in the absence of frank hypopnea, apnea, or gas exchange abnormalities is referred to as upper airway resistance syndrome (UARS). UARS has been hypothesized to result from a decreased arousal threshold in relation to respiratory fluctuations during sleep.

Epidemiology. OSAS affects 2–3% of middle school children and as many as 13% of children aged 3–6 years. Importantly, the prevalence may be two- to fourfold higher in vulnerable populations: children with adenotonsillar hypertrophy, craniofacial anomalies, African-American race, preterm birth, and relatively low household income may have increased odds of having OSAS. In children, OSAS has been associated with adverse cardiovascular and metabolic outcomes: higher blood pressure, left ventricular hypertrophy, higher C-reactive protein, and increased insulin resistance. Whether these associations translate into increased risk of disease in adulthood remains unknown.

Symptoms. Symptoms of OSAS include snoring, mouth breathing, daytime sleepiness, frequent nocturnal arousals, and cognitive-behavior problems, especially attention-deficit, mood impairment, and poor school performance.

Pathophysiology. The pathophysiology of pediatric OSA includes neurophysiological, anatomical, and mechanical factors that conspire to increase upper airway resistance during sleep. Studies have demonstrated a correlation between the degree of airway narrowing and apnea-hypopnea index (AHI). Anatomic causes of upper airway narrowing such as adenotonsillar hypertrophy are the most common cause of pediatric OSA. Increased airway collapsibility during inspiration has been described in children with OSA suggesting either increased airway compliance or abnormal neuromuscular compensatory changes in pressure oscillation during sleep-associated breathing.

Obesity. Body mass index is among the strongest predictors of both presence and severity of OSAS in adults. Several studies have demonstrated that incremental increases in AHI correlate with increases in body mass index (BMI). Childhood overweight (>95% of BMI for age) and obesity are rising at an alarming rate with prevalence tripling over the past two decades. The Cleveland Family Study demonstrated a 4.6-fold increase in OSA in

overweight children compared to normal weight children. This odds ratio may increase even further when adolescents age 13–16 years are considered as a separate cohort. The mechanisms by which obesity increases OSAS risk are likely multiple and may include impairment of airway and lung mechanics or velopalatal insufficiency and do not, in contrast to adults, appear to be related to parapharyngeal fat deposition.

Association with metabolic syndrome. Adolescents with obesity and SDB are 6.5 times as likely to have metabolic syndrome (a constellation of insulin resistance, dyslipidemia, hypertension, and obesity) when compared to those without SDB and controlled for age, sex, preterm status, and race.

Treatment. The initial therapy for OSA in both obese and non-obese children is surgical tonsillectomy and adenoidectomy (T&A). The success rate of T&A is about 85%; however, efficacy is markedly reduced in obese children suggesting that obesity itself independently contributes to sleep-related airway resistance. For patients in whom T&A do not resolve symptoms, continuous positive airway pressure (CPAP) delivered via a mask interface is extremely effective in stenting the airway. CPAP initiation can be difficult in certain children, especially those with neurodevelopmental disorders. Other therapies include oral appliances that advance the mandible, rapid maxillary expansion, and reconstructive surgeries such as maxillary mandibular advancement and uvulo-palato-pharyngioplasty.

Central sleep apnea. Central sleep apnea (CSA) is defined as the absence of airflow accompanied by a lack of effort to breath. CSA likely results from abnormal neurological control of breathing. CSA after the postnatal period should prompt investigation of central nervous system (CNS) causes including congenital causes (i.e., central alveolar hypoventilation syndrome), infection, structural lesions (e.g., Arnold–Chiari malformation, midline tumors, holoprosencephaly), or peripheral disorders such as myasthenia gravis or motor neuron disease (e.g., spinal muscular atrophy).

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365 Coma

David J. Michelson · Stephen Ashwal

Case History

A woman left her house at 1:45 pm to go shopping, leaving her 11-month-old son in the care of her two teenaged children. An hour later her 16-year-old son called her in a panic, crying that his "little brother is dead." Paramedics were called and arrived within 4 min to find the little boy pulseless and apneic. The boy's 15-year-old sister explained that she had found him with his head in a bucket she had been using to mop the floors. The paramedics started chest compressions and mask ventilation with 100% oxygen. They transported the boy to a nearby emergency room, where he was intubated and given three successive intravenous doses of epinephrine. A spontaneous pulse was first recovered after 35 min of resuscitation. His temperature was 90°F (32°C), his pupils were fixed and dilated, and he had no corneal or gag reflex or facial grimace to pain. His first arterial blood gas showed a pH of 6.72 and a base deficit of 31 mEq/L, and he was given multiple boluses of normal saline and bicarbonate. He had episodes of body stiffening that were concerning for seizures and was given an intravenous loading dose of phenobarbital and transferred to a tertiary care center for further management. His initial head CT showed mild cerebral edema (*Fig. 365.1*). He was weaned off of mechanical ventilation and from all sedating medications, but he continued to lie in bed with his eyes closed, unresponsive to voice, with only flexion of the right arm with noxious compression of the sternum. His pupils were minimally reactive to light, and he had brisk oculocephalic reflexes, but his eyes were disconjugate at rest, and he demonstrated no visual tracking. Magnetic resonance imaging of the brain done on the fifth day of hospitalization showed brightness on diffusion and T-2 weighted images bilaterally in the thalami, basal ganglia, and subcortical white matter (*Figs. 365.2–365.4*). Magnetic resonance spectroscopy showed N-acetyl aspartate to creatine ratios more than four standard deviations below the mean for age in cortical and subcortical gray matter and a small amount of lactate in the occipital gray matter (*Figs. 365.5* and *365.6*). At the parents' request, the boy had a gastrostomy tube placed, and he was discharged 2 months later to their care in a condition best described as a coma due to a severe global hypoxic-ischemic brain injury.

Definition/Classification

Coma is a disease state of persistent unconsciousness that derives from the ancient Greek word for deep sleep. Patients may *awaken* from coma into normal consciousness or into other pathological states of altered or depressed consciousness, but this awakening does not occur in response to external stimuli of any kind. In coma, dysfunction of the brain prevents the generation of arousal and awareness, the two necessary components of full consciousness. The severe metabolic and structural injuries capable of causing coma carry a high risk of death and severe long-term neurological disability.

A patient who is fully conscious demonstrates both arousal or wakefulness and awareness of both their internal states, such as hunger, thirst, and pain, and their external world, such as it comes to them through visual, auditory, tactile, olfactory, or gustatory stimulation. Patients who are said to be *falling into* a coma show gradually decreasing levels of awareness, attention, and arousal, such that increasingly intense stimulation is required for them to show any response as they become lethargic, stuporous, and obtunded, and finally, comatose.

Most patients are only comatose for a short time, typically a period of several days to weeks, before either dying from their medical problems or beginning to show signs of improvement. When improvement occurs in arousal alone, with patients regaining spontaneous eye-opening and sleep–wake cycles but lacking clear signs of awareness of their internal or external state, purposeful action, or communicative ability, the condition is described as a *vegetative state*. If awareness partially recovers but is insufficient for consistent communication, a patient may be described as being in a *minimally conscious state*. Some patients recover from coma dramatically, passing quickly from lower to higher levels of function. Other patients remain in a prolonged or *permanent* vegetative or minimally conscious state.

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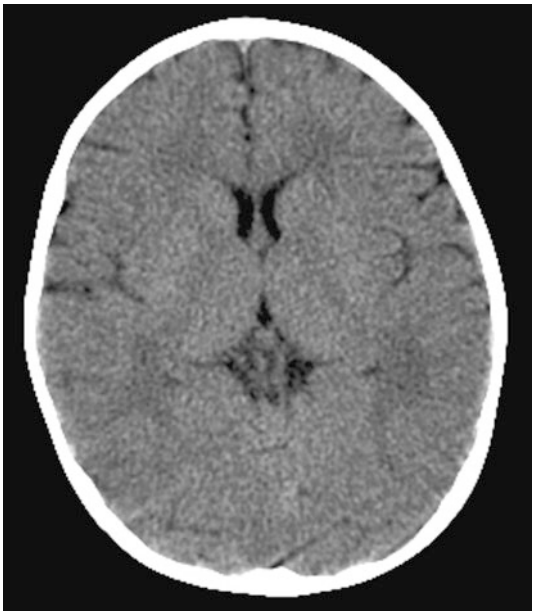


Figure 365.1
Eight hours after an 11-month-old boy suffered cardiopulmonary arrest, computed tomography showed loss of the distinction between the cortical gray and subcortical white matter with relative hypodensity of the supratentorial structures, suggesting bihemispheric cerebral edema

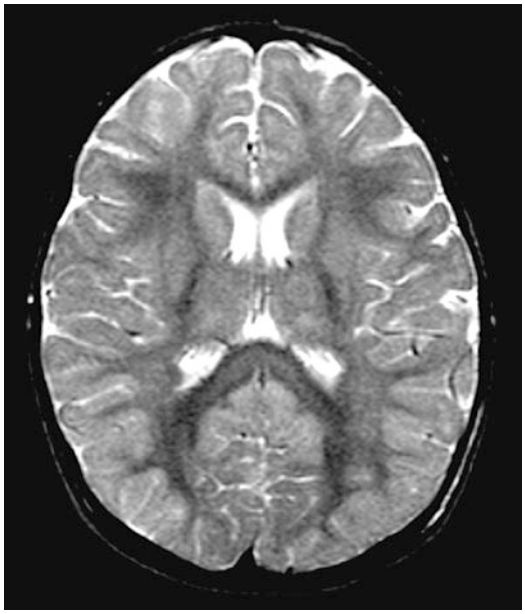


Figure 365.2
Five days after an 11-month-old boy suffered cardiopulmonary arrest, magnetic resonance imaging showed brightness on T2 weighted (Fig. 365.2) and diffusion weighted (Fig. 365.2) axial sequences and darkness on the apparent diffusion coefficient map (Fig. 365.3) within the bilateral subcortical white matter, corpus callosum, basal ganglia, and thalami, consistent with diffuse hypoxic-ischemic injury

Other disorders of consciousness include *delirium*, in which arousal may be heightened or depressed but in which attention and awareness fluctuate rapidly, and *akinetic-mutism*, in which arousal may be normal, but patients demonstrate minimal signs of attention and awareness only intermittently. The *locked-in syndrome* is often discussed with disorders of consciousness because it can mimic coma in many ways. Patients in a locked-in state are fully awake and aware but have motor impairments that make it difficult or impossible for them to demonstrate this on examination. Patients with psychiatric illnesses such as depression and schizophrenia may present with *catatonia* or *pseudocoma*, demonstrating dramatically reduced voluntary behavior and responsiveness, although they maintain normal consciousness and lack any structural or metabolic disturbance of brain function.

Brain death is also frequently discussed in association with coma. It was initially described by French physicians as a *state beyond coma* in which all signs of consciousness and all brainstem reflexes, including the respiratory drive, are irrevocably destroyed by injury. In most countries, this has come to be accepted as an alternative to cardiorespiratory arrest for defining the end of life. The major distinctions between the disorders of consciousness are outlined in *Table 365.1* and the differences between the vegetative and minimally conscious states are outlined in *Table 365.2*.

Etiology

Arousal is initiated and sustained by a complex neuronal network that widely distributes multiple sensory and circadian inputs to the cerebral cortex. Awareness and full consciousness likely arise from the integrated processing of this input in the polymodal association areas of the cortex. Coma can occur with relatively small structural injuries to the brainstem, more widespread cortical or subcortical injuries to both cerebral hemispheres, or diffuse metabolic disturbances that cause generalized impairment of neuronal function.

There are four main anatomical structures involved in the generation of arousal: the brainstem, thalamus, basal forebrain, and hypothalamus. Within the brainstem, the

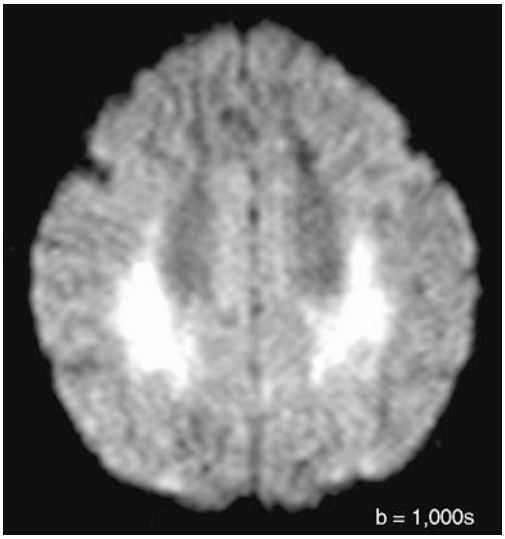
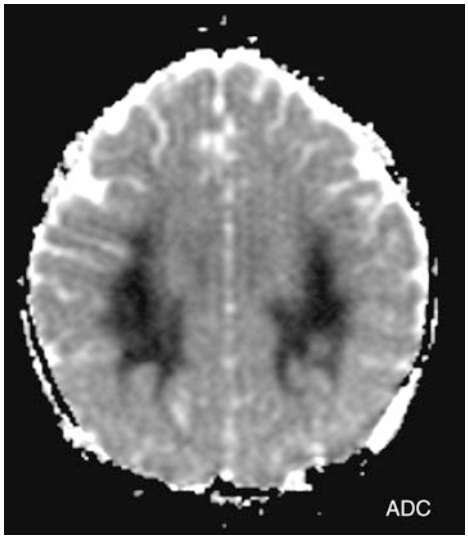


Figure 365.3
Five days after an 11-month-old boy suffered cardiopulmonary arrest, magnetic resonance imaging showed brightness on T2 weighted (Fig. 365.2) and diffusion weighted (Fig. 365.2) axial sequences and darkness on the apparent diffusion coefficient map (Fig. 365.3) within the bilateral subcortical white matter, corpus callosum, basal ganglia, and thalami, consistent with diffuse hypoxic-ischemic injury



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ascending activating system (AAS) composed of excitatory glutamatergic neurons within the upper pontine and lower midbrain tectum relays a variety of stimuli along two pathways, the first to the thalamus and the second to the basal forebrain. Other structures and neurotransmitters from the brainstem, the pedunculopontine tegmental and laterodorsal nuclei (acetylcholine), locus ceruleus (noradrenaline), midline raphe nuclei (serotonin), and substantia nigra pars compacta (dopamine) modify arousal through both cortical and subcortical (thalamus, basal forebrain, and striatum) connections.

The thalamus participates in the generation of arousal through circuits which relay specific sensory inputs to the cortex and through nonspecific output from midline, medial, and intralaminar nuclei. The basal forebrain arousal system consists of the nucleus basalis of Maynert, the substantia innominata, the diagonal band of Broca, the magnocellular preoptic nucleus, the medium septum, and the globus pallidus. These structures receive input from the brainstem and hypothalamus and assist in the maintenance of the waking state via cholinergic excitation of the thalamus and cortex.

The hypothalamus contains histaminergic nuclei, predominantly in the tuberomammilary and posterior regions, which influence the activity of basal forebrain and thalamocortical neurons. The perifornicеal and lateral areas of the hypothalamus contain neurons that secrete orexins (hypocretins), which not only influence nearby histaminergic, noradrenergic, and serotonergic neurons but also have widespread arousal-promoting connections throughout the cerebral cortex.

The functional correlates of altered consciousness have been examined through advanced imaging studies of cerebral metabolism in conditions of physiologic (sleep), pharmacologic (anesthesia), and pathologic unconsciousness. The most consistent change across etiologies is the deactivation of the polymodal association cortices, including the bilateral lateral frontal, medial frontal, parietotemporal, posterior parietal, precuneal, and posterior cingulate areas. The posterior cingulate in particular shows early and dramatically decreased metabolism in unconsciousness, even beyond that seen in the thalamus, and it has the highest basal metabolism in normal conscious wakefulness.

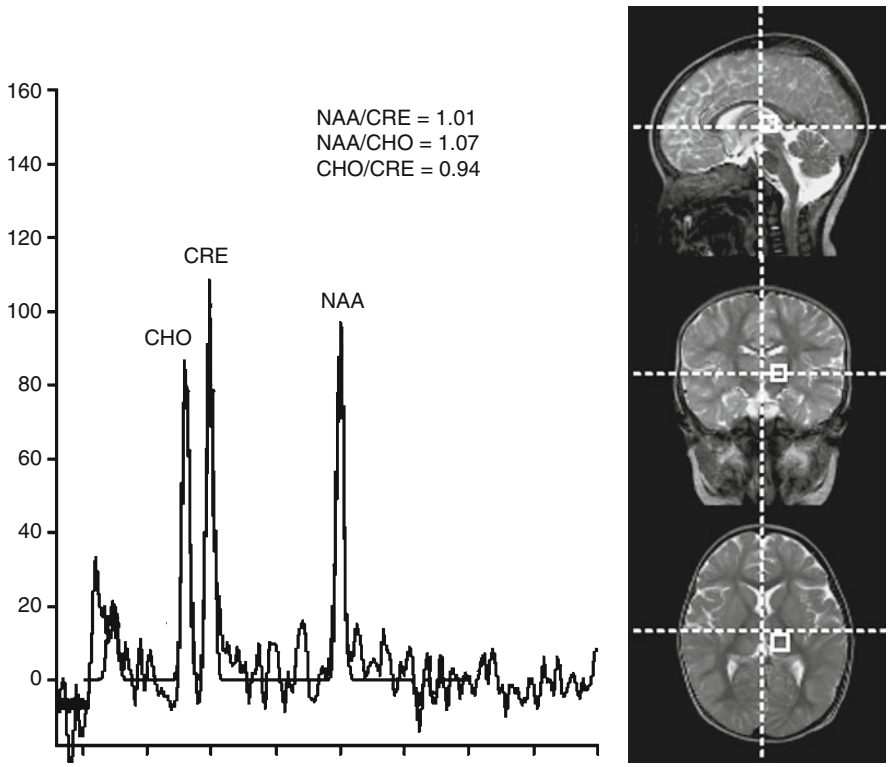

Figure 365.5

Five days after an 11-month-old boy suffered cardiopulmonary arrest, magnetic resonance spectroscopy showed NAA/Cr ratios more than four standard deviations below the mean in the occipital gray matter (*Fig. 365.5*) and left thalamus (*Fig. 365.6*). A small lactate peak was also discernible in the occipital cortex, consistent with the injury being due to ischemia

In most cases of coma, such as those resulting from severe traumatic brain injury, global hypoxic ischemic injury, or the progression of a previously known disease state, the etiology is clear from the initial history and physical examination. An unexplained coma is a true medical emergency and such patients require immediate testing for treatable causes. A listing of broad categories for the etiology of coma, along with subcategories and specific examples, is given in *Table 365.3*.

Epidemiology

In the United States, coma has a yearly incidence of approximately 60 per 100,000 children, and cases are fairly evenly divided between traumatic and non-traumatic causes of brain injury. A prospective, population-based study of non-traumatic coma in the United States from 2001 found that infection was responsible for 38% of pediatric cases, with *Neiserria meningitidis* being the most commonly identified organism. Toxic ingestions, both accidental and non-accidental, were responsible for 10% of all cases and for 35% of cases among adolescents. Seizures, congenital heart disease, brain malformations, accidental drowning, diabetes, and inborn errors of metabolism were among the other common etiologies of non-traumatic coma in children. A smaller but more recent study from India also found infection to be the most common cause of pediatric non-traumatic coma. Sixty percent of cases were attributed to infections and *Mycobacterium tuberculosis* was the most commonly identified organism.

In their now landmark study from 1984 of 500 adults with coma of initially unknown cause, Plum and Posner found that 65% had diffuse metabolic causes, usually from poisonings and intoxications. They also found that 20% had supratentorial mass lesions, including 77 hemorrhages and 9 infarctions, and that 13% had infratentorial lesions, which were mainly brainstem infarctions. Eight of their patients had psychiatric pseudocoma.

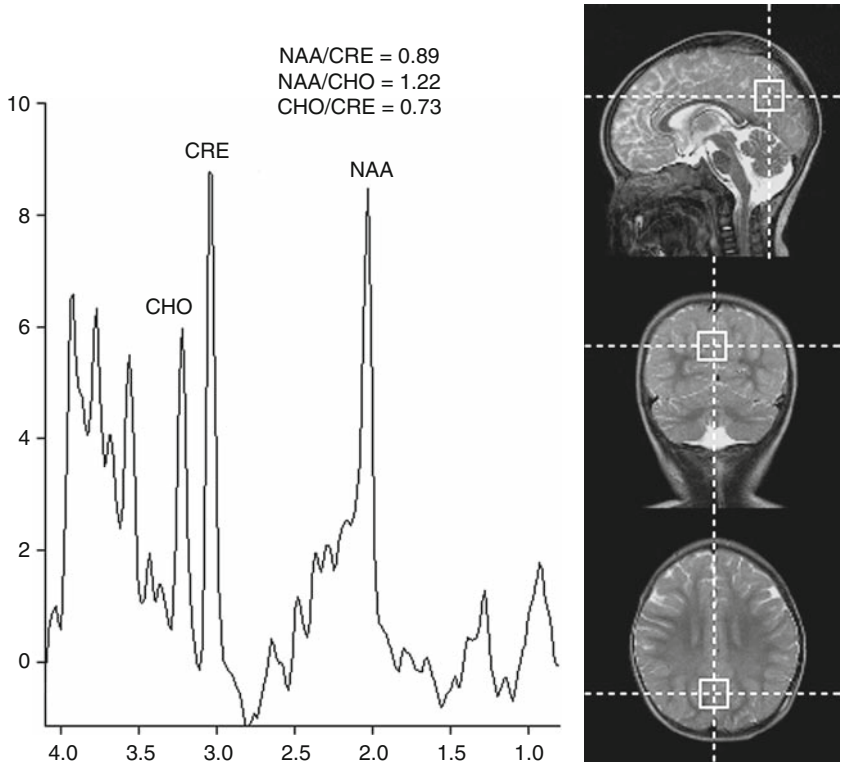

Figure 365.6

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Table 365.1

Disorders of consciousness. The disorders of consciousness discussed in the text are differentiated from normal by the degree to which arousal, awareness, and motor function are impaired

Condition	Arousal	Awareness	Motor function
Normal consciousness	Normal	Normal	Normal
Locked-in syndrome	Normal	Normal	Low to absent
Akinetic-mutism	Normal	Low	Intermittent
Delirium	High or low	Low	High or low
Lethargy	Mildly low	Mildly low	Mildly low
Stupor	Moderately low	Moderately low	Moderately low
Obtundation	Severely low	Severely low	Severely low
Coma	Absent	Absent	Low
Vegetative state	Variable	Absent	Low
Minimal consciousness	Variable	Low	Low
Brain death	Absent	Absent	Absent

Table 365.2

Vegetative and minimally conscious states. The diagnostic criteria for these disorders of consciousness have been put forward by the American Academy of Neurology

Vegetative state	Minimally conscious state
No evidence of self- or environmental awareness, with demonstration of all of the following: • No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tactile, or noxious stimuli • No evidence of language comprehension or expression • Intermittent wakefulness occurring with sleep–wake cycles • Sufficiently preserved autonomic function to survive with supportive care	Limited but reproducible evidence of self- or environmental awareness, demonstrated by one of the following: • Purposeful movements or affect expressions in response to relevant environmental stimuli that are not purely reflexive • Simple command following, gestural or verbal yes/no responses (regardless of accuracy), or intelligible verbalization

Table 365.3

Etiologies for coma. Broadly defined etiologic categories for coma, along with subcategories and specific examples

Category	Subcategory	Examples
Non-structural	External toxins	Carbon monoxide, cyanide, ethylene glycol, lead, methanol, mushrooms, thallium
	Medications	Alcohol, amphetamines, anticholinergics, antipsychotics, barbituates, bromides, lithium, monoamine oxidase inhibitors, opioids, paraldehyde, phencyclidine, salicylates, sedative hypnotics
	Organ failure	Hyper- or hypocalcemia, cortisolism, glycemia, natremia, tension, thermia, or thyroidism; hyperammonemia, hypercapnea, hypoxia, ketoacidosis, porphyria, uremia, Wernicke encephalopathy
	Infections	Cerebral malaria, encephalitis, meningitis, post-infectious encephalitis, sepsis, syphilis, typhoid fever
	Other	Postictal state
Structural – symmetrical	Supratentorial	Bilateral anterior cerebral or carotid artery occlusion, hydrocephalus, thalamic hemorrhages, traumatic brain injury
	Infratentorial	Basilar artery occlusion, midline brainstem tumor, pontine hemorrhage
Structural – asymmetrical	Supratentorial	Acute disseminated encephalomyelitis, adrenoleukodystrophy, cerebral abscess, cerebral vasculitis, chemotherapy-related leukoencephalopathy, Creutzfeldt–Jakob disease, disseminated intravascular coagulation, fat embolization, hemispheric mass (tumor, bleed, and abscess) with herniation, intracerebral bleeds, massive or bilateral infarctions, progressive multifocal leukoencephalopathy, multiple sclerosis, nonbacterial thrombotic (marantic) endocarditis, pituitary apoplexy, subacute bacterial endocarditis, thrombophlebitis, thrombotic thrombocytopenic purpura
	Infratentorial	Brainstem hemorrhage, brainstem infarction

Clinical Evaluation

The initial assessment and management of a comatose patient should address the adequacy of basic life support functions, ensuring that the patient has a patent airway and adequate respiration, oxygenation, and circulation.

Patients with an altered level of consciousness can aspirate oral secretions and thus may require

prophylactic intubation and ventilation even when the underlying cause of their coma has not otherwise compromised their respiratory function. Patients with a traumatic or unknown cause of coma should be assumed to have a spinal cord injury until proven otherwise and treated with appropriate spinal precautions. Initial measurement of blood sugar as well as repeated measurements of the vital signs, including temperature, arterial blood gas determination (hypoxia, hypercarbia), blood pressure, heart rate, and respiratory rate, aid in the diagnosis and avoidance of correctable causes of further injury. Some patients will require urgent medical or surgical interventions before they are stable enough for a detailed neurodiagnostic evaluation.

All patients should be given high concentrations of supplemental oxygen until continuous oxygen saturation monitoring is possible. In patients with known diabetes, coma of unknown etiology, or measured hypoglycemia (less than 60 mg/dL), treatment with supplemental glucose is warranted. A 0.5 g/kg intravenous bolus of dextrose should be given using a 10% solution in neonates, a 25% solution in children under 30 kg, and a 50% solution in larger children. Unlike adult patients, who may have unrecognized chronic malnutrition, children do not require intravenous thiamine prior to receiving intravenous dextrose to prevent Wernicke encephalopathy. The benefits of treating coma due to hypoglycemia outweigh any theoretical drawback of giving supplemental glucose to patients with anoxic or ischemic brain injury. Diabetics with hypoglycemia should also be given a 0.1 mg/kg (maximum 1 mg) intravenous dose of glucagon.

Intravenous naloxone hydrochloride should be given to patients with coma of unknown etiology at a dose of 0.1 mg/kg (maximum 2 mg) to reverse possible accidental or intentional opioid toxicity. Most children are at little risk for the severe withdrawal effects, which can be precipitated by naloxone use in patients with established opioid dependence.

A detailed and systematic general physical examination, done once the patient has been stabilized, can help determine the underlying cause of coma. The sections that follow review some of the more important considerations.

Vital Signs

Hypotension will cause loss of consciousness when the mean arterial blood pressure drops below levels for which cerebral autoregulation can maintain adequate cerebral blood flow. Hypotension may result from shock, poisoning, or damage to the medullary pressor center. Hypotension due to hypovolemia, whether from dehydration or hemorrhage, is associated with peripheral vasoconstriction and cool extremities. Hypotension due to septic shock and Addisonian crisis is associated with peripheral vasodilation and warm extremities.

Severe hypertension will overwhelm the autoregulatory capacity of cerebral blood vessels and lead to vasogenic edema and hemorrhagic infarction. Hypertension may be seen with renal disease, poisoning, or as an adaptive response to any cause of increased intracranial pressure (ICP). The Kocher–Cushing reflex response to increased ICP, frequently referred to as *Cushing's triad*, consists of hypertension, bradycardia, and irregular respirations and is caused by compression or ischemia of the medullary pressor center.

Bradycardia can also be seen with myocardial injury and with poisonings, such as with beta-blockers or cholinergic agonists. Tachycardia may result from hypotension, hyperthyroid storm, fever, anemia, hypoxia, and poisoning with stimulants and anticholinergics.

Respiratory depression can be seen with poisonings and with carbon dioxide retention from impaired pulmonary gas exchange. Tachypnea can be seen with hypoxia, fever, and various causes of metabolic acidosis, including sepsis, diabetic ketoacidosis, renal failure, hepatic failure, and poisonings with such substances as methanol, ethylene glycol, paraldehyde, and salicylates. Damage to the basal forebrain, thalami, or hypothalamus may result in *Cheyne-Stokes respirations*, with slowly alternating hypoventilation and hyperventilation. The emergence of such a respiratory pattern in a comatose patient may be an early sign of central herniation.

Other abnormal respiratory patterns can be seen with brainstem injuries and can be seen sequentially during central herniation. Damage to the low midbrain ventral to the aqueduct of Sylvius or of the upper pons ventral to the fourth ventricle can cause *central neurogenic hyperventilation*. Hyperventilation in comatose patients is far more commonly caused by compensation for metabolic acidosis or hypoxia. Metabolic acidosis, such as with diabetic ketoacidosis, can cause *Kussmaul breathing*, with deep, regular respirations. Lesions of the dorsolateral tegmentum of the middle and caudal pons medulla may cause *apneustic breathing*, in which the patient breathes inward quickly, pausing at full inspiration. *Cluster breathing* shows great variability in the pauses between breaths and can be seen with lower pontine tegmental lesions. Progressively irregular respiratory rate and rhythm may be referred to as *ataxic or agonal breathing*, seen with damage to the reticular formation of the dorsomedial medulla, at times immediately prior to the onset of complete apnea.

Fever may occur as a result of subarachnoid hemorrhage, intraparenchymal hemorrhage, or hypothalamic injury. Fever can also result from heatstroke, thyroid storm, and from poisonings such as with anticholinergic toxicity, neuroleptic malignant syndrome, or serotonin syndrome. Shivering without sweating is suggestive of fever of neurologic or toxic etiology. However, fever is usually a sign of infection and, in a comatose patient, it should prompt consideration of a diagnosis of meningitis or encephalitis, whether or not meningismus is present. Fever may be absent when infection occurs in young infants or in the setting of renal failure, hypothyroidism, or immunocompromise. Empirical use of broad spectrum intravenous antibiotics at meningitic doses is preferable to waiting for the results of cerebrospinal fluid (CSF) testing by lumbar puncture. In patients with altered consciousness or any focal neurological disturbance, use of computed tomography (CT) of the brain is favored, if available, to look a supratentorial mass lesion that might lead to the lumbar puncture precipitating downward transtentorial herniation and brainstem compression.

Hypothermia is usually due to cold exposure but can also be caused by sepsis, hypothyroid coma, hypopituitarism, Wernicke encephalopathy, lesions of the posterior hypothalamus, and poisonings such as with barbiturate overdose. Hypothermia is more likely to be due to a neurological cause in patients who are sweating but not shivering. Several well-described toxidromes are summarized in *Table 365.4*.

Head, Eyes, Ears, Nose, Throat, and Neck

The head and neck examination may reveal occult signs of trauma, such as scalp laceration, scalp edema or hematoma, or depressed skull fracture. Anterior basal skull fracture may cause bruising around the orbits (*raccoon eyes*) and temporal bone fracture may cause bruising over the mastoid portion of the bone (*Battle's sign*) but these findings may first appear several days after injury. Signs of meningismus, including nuchal rigidity, may be masked by coma but generally indicate meningeal irritation, which can occur with meningitis, inflammation of surrounding structures (e.g., retropharyngeal abscess), carcinomatosis, subarachnoid hemorrhage, or transtentorial herniation. Patients with hypothyroidism or hyperthyroidism may have a generally enlarged, asymmetrical, or nodular thyroid gland.

Edema of the conjunctiva or eyelids suggests fluid overload, as occurs in congestive heart failure, or reduced osmotic pressure, as occurs with hypoalbuminemia or nephrotic syndrome. Sunken orbits would suggest severe (>10%) dehydration. Conjunctival petechiae can be seen with thrombophilia as well as with fat embolism, as may occur after long bone fracture from trauma or surgery. The sclerae may become icteric with hyperbilirubinemia and liver disease. The lenses may show band keratopathy with hypercalcemia or cataracts with hypocalcemia. Brown Kayser–Fleischer rings at the margin of the iris are seen with copper deposition in patients with Wilson's disease.

The funduscopic examination may show the chronic effects of long-standing medical conditions, such as hypertension or diabetes, or reveal acute changes such as papilledema due to increased ICP, retinal hemorrhages from trauma, retinal edema from methyl alcohol poisoning, or grayish retinal deposits from lead poisoning.

The otoscopic exam may reveal a middle ear infection or evidence of a fracture through the temporal bone with evidence of hemotympanum or CSF otorrhea. Clear or serosanguinous drainage from the ear canal or nose can be tested for glucose or, more specifically, beta trace protein (prostaglandin B synthase) or beta-2-transferrin, to identify CSF leakage.

The patient's breath may suggest alcohol intoxication, diabetic ketoacidosis, or acetone, phenol, or salicylate ingestion (fruity acetone odor); uremia (ammonia odor); hepatic encephalopathy (musty odor or *fetor hepaticus*); arsenic, phosphorus, organophosphate, or thallium poisoning (garlic odor); cyanide poisoning (bitter almond odor); or oral, pharyngeal, or sinus infection (foul odor). Examination of the oral cavity may find lacerations of the tongue to suggest convulsions or blue-black gingival staining to suggest bismuth, mercury, or lead poisoning.

Skin

A comprehensive head-to-toe and back-to-front inspection of the skin, hair, and nails may show signs of dehydration, drug exposure, trauma, or infection. The skin may be hot and dry in the setting of heatstroke or anticholinergic poisoning or hot and sweaty as part of the sympathetic response to hypotension or hypoglycemia. The relevance of various skin findings to the etiology of coma is reviewed in *Table 365.5*.

Other General Examination

Cardiac auscultation can reveal arrhythmias and murmurs associated with structural heart disease, cardiomyopathy,

Table 365.4

Toxidromes with coma. The characteristic changes associated with various categories of poisonings

Toxidrome	Pupils	Cardiovascular --- Respiratory	Temperature --- Skin	Other	Examples
Anticholinergics	Dilated	Tachycardia, hypertension --- Tachypnea	Hyperthermia --- Dry and flushed	Dry mucous membranes, quiet bowel sounds, urinary retention, myoclonus and seizures	Antihistamines, tricyclic antidepressants, cyclobenzaprine, orphenadrine, antiparkinson agents, antispasmodics, phenothiazines, atropine, scopolamine, belladonna alkaloids (Jimson Weed)
Sympatho-mimetics	Dilated	Tachycardia, hypertension, widened pulse pressure --- Tachypnea, Hyperpnea	Normal --- Diaphoresis	Tremors, hyperreflexia, seizures	Cocaine, amphetamines, ephedrine, pseudoephedrine, phenylpropanolamine, theophylline, caffeine
Hallucinogens	Dilated	Tachycardia, hypertension --- Tachypnea	Hyperthermia --- Normal		PCP, LSD, mescaline, psilocybin, MDMA, MDEA
Opioids	Small	Bradycardia, hypotension --- Bradypnea, pulmonary edema	Hypothermia --- Needle marks		Opioids (heroin, morphine, methadone, oxycodone, hydromorphone), diphenoxylate
Sedative-hypnotics	Small	Bradycardia, hypotension --- Bradypnea, hypopnea	Hypothermia --- Normal	Hyporeflexia	Benzodiazepines, barbiturates, carisoprodol, meprobamate, glutethimide, alcohols, zolpidem
Cholinergics	Small	Bradycardia, hypertension or hypotension --- Tachypnea or bradypnea	Normal --- Diaphoresis	Salivation, urinary and fecal incontinence, diarrhea, emesis, lacrimation, GI cramps, bronchoconstriction, fasciculations, seizures	Organophosphate and carbamate insecticides, nerve agents, nicotine, pilocarpine, physostigmine, bethanecol, urecholine
Serotonin syndrome	Dilated	Tachycardia, hypertension --- Tachypnea	Hyperthermia --- Diaphoresis and flushing	Tremor, myoclonus, hyperreflexia, trismus, rigidity, diarrhea	MAOIs, SSRIs, meperidine, dextro-methorphan, TCAs, L-tryptophan
Tricyclics	Dilated	Tachycardia, hypertension then hypotension, arrhythmias and cardiac conduction disturbances --- Hypopnea	Hyperthermia --- Normal	Seizures, myoclonus, choreoathetosis	Amitriptyline, nortriptyline, imipramine, clomipramine, desipramine, doxepin

Table 365.5

Skin changes in coma. Various skin findings which may be seen in association with unexplained coma and examples of the underlying causes

Skin change	Underlying cause
Antecubital needle marks	Opioid abuse
Pale skin	Anemia or hemorrhage
Sallow, puffy appearance	Hypopituitarism
Hypermelanosis	Porphyria, Addison's disease, chronic nutritional deficiency, disseminated malignant melanoma, chemotherapy
Generalized cyanosis	Hypoxemia, carbon dioxide poisoning
Grayish-blue cyanosis	Methemoglobin (aniline or nitrobenzene) intoxication
Localized cyanosis	Arterial emboli, vasculitis
Cherry-red skin	Carbon monoxide poisoning
Icterus	Hepatic dysfunction, hemolytic anemia
Petechiae	Disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, drugs
Ecchymosis	Trauma, corticosteroid use, abnormal coagulation from liver disease or anticoagulants
Telangiectasia	Chronic alcoholism, vascular malformations of the brain
Vesicular rash	Herpes simplex, varicella, Behcet's disease, drugs
Petechial-purpuric rash	Meningococcemia, gonococcemia, staphylococcemia, *pseudomonas* infection, subacute bacterial endocarditis, allergic vasculitis, purpura fulminans, Rocky Mountain spotted fever, typhus, fat emboli
Macular-papular rash	Typhus, *Candida* infection, *Cryptococcus* infection, toxoplasmosis, subacute bacterial endocarditis, staphylococcal toxic shock, typhoid, leptospirosis, *Pseudomonas* sepsis, immunological disorders, systemic lupus erythematosus, dermatomyositis, serum sickness
Ecthyma gangrenosum	*Pseudomonas* sepsis
Splinter hemorrhages, Osler's nodes, gangrene of digits	Subacute bacterial endocarditis, anemia, leukemia, sepsis

and valvular disease associated with endocarditis. Peritoneal lavage may be required to exclude hemorrhagic abdominal injury in a comatose patient with known or suspected trauma. Bowel sounds are hypoactive in many acute abdominal conditions and with anticholinergic poisoning. Hyperactive bowel sounds are seen with acetylcholinesterase inhibitor toxicity.

Hepatomegaly is seen with right heart failure, lysosomal and glycogen storage disorders, and hepatic tumors. A nodular or hard liver edge can be seen with hepatic tumors and with cirrhosis. Splenomegaly can be seen with portal hypertension, hematological malignancies, infections, and collagen vascular diseases. Ascites can be seen in association with liver disease, right heart failure, and ovarian cancer.

Breast, testicular, and rectal examination may reveal primary tumors. Stool testing for occult gastrointestinal bleeding may indicate a bowel carcinoma. Gastrointestinal bleeding can precipitate hyperammonemic encephalopathy in patients with cirrhotic liver failure. Generalized lymphadenopathy can be seen with hematologic malignancy, infections, immunodeficiency states, collagen vascular diseases, hyperthyroidism, Addison disease, and drug reactions. Localized adenopathy suggests a nearby malignancy or infection.

Level of Consciousness

The state of consciousness should be described in detail to avoid ambiguity. The patient should be tested with cues of increasing intensity, with stimulation progressing from verbal to visual to noxious, and the maximal response should be recorded. Voluntary eyelid and vertical eye

movements are sometimes preserved in locked-in syndromes due to anterior brainstem injuries and should be tested for in all patients with apparent coma.

The Glasgow Coma Scale (GCS) records the best eye opening, motor, and verbal response of the patient and is in widespread use in emergency rooms and intensive care units around the world. The verbal response scale has been modified for preverbal children in the Pediatric Coma Scale (PCS) (*Table 365.6*). The GCS and PCS correlate with long-term morbidity and mortality but have low predictive value as single measures of the severity of injury. One significant drawback of these scales is that patients who are intubated or who have suffered severe facial trauma will necessarily score lower in the eye opening and verbal subscales. Another is that neither of the scales directly records brainstem reflexes, such as the pupillary light reflex, that are strongly predictive of the outcome.

Pupillary Reflexes

Normal pupillary dilation in dim light depends on intact sympathetic efferents which arise in the hypothalamus, synapse in the thoracic level of the spinal cord, synapse again in the superior cervical sympathetic ganglion, and then travel along with the internal carotid arteries to the ciliary ganglia and the pupillodilator muscles of the iris. Constriction of the pupils in response to light depends on the afferents from the optic nerves reaching their projections to the parasympathetic Edinger–Westphal nuclei of the midbrain tectum and on the efferent nerves arising there and traveling along the surface of the oculomotor nerves to the ciliary ganglia and the pupillosphincter muscles of the iris.

Thalamic lesions, pontine lesions, and toxic-metabolic causes of coma that impair sympathetic inputs to the pupils leave them small, even pinpoint, but reactive. The reaction to light may be so slight as to require magnification, such as through an otoscope, to observe. Lesions along the sympathetic pathway can also cause *Horner syndrome*, a triad of ipsilateral miosis, mild ptosis due to denervation of the superior and inferior tarsal muscles of the eyelids, and anhydrosis of the face, neck, and arm. Midbrain lesions that interrupt both sympathetic and parasympathetic pathways result in fixed and irregular midposition pupils which may be unequal. An injury to the midbrain or to the third nerve that only affects parasympathetic function causes the ipsilateral pupil to be large and unresponsive to light. A sluggishly reactive pupil may be due to partial compression of the oculomotor nerve and occurs early during uncal herniation, prior to pupillary dilation and oculomotor palsy. Pupillary abnormalities can be of a fixed nature due to prior ocular or neurological injury or may be transient due to seizures

Table 365.6
Coma scales. The components and scores for the Glasgow Coma Scale and Pediatric Coma Scale are outlined

Sign	GCS	PCS	Score
Eye opening	Spontaneous	Spontaneous	4
	To command	To sound	3
	To pain	To pain	2
	None	None	1
Verbal response	Oriented	Age-appropriate vocalization, smile, or orientation to sound	5
	Confused, disoriented	Irritable, consolable, uncooperative, aware of the environment	4
	Inappropriate words	Irritable, inconsistently consolable	3
	Incomprehensible sounds	Inconsolable, unaware of the environment, restless, agitated	2
	None	None	1
Motor response	Obeys commands	Obeys commands, spontaneous movements	6
	Localizes pain	Localizes pain	5
	Withdraws	Withdraws	4
	Abnormal flexion to pain	Abnormal flexion to pain	3
	Abnormal extension to pain	Abnormal extension to pain	2
	None	None	1
Best total score			15

or ophthalmic or systemic medications with effects on the autonomic nervous system.

Ocular Movements

Normal conjugate ocular motility, whether spontaneous or reflexive, requires intact function of the brainstem from the vestibular nuclei at the pontomedullary junction to the oculomotor nuclei in the midbrain. Its presence helps to reduce suspicion for a brainstem injury as a primary cause of coma. The resting position of the eyes when the patient is maximally stimulated may show a discrepancy in eye position, representing weakness of one of the extraocular muscles. Oculomotor or third nerve palsy from a midbrain lesion or from compression of the nerve results in severe ptosis and downward and lateral deviation of the eye. Abducens or sixth nerve palsy results in inward deviation of the eye and can result from an injury to the nucleus in the pons or to compression of the nerve anywhere along its extensive course, which can be due to increased ICP. Trochlear or fourth nerve palsies are inapparent in comatose patients. Conjugate eye deviations at rest are usually due to lesions that disrupt the input to the lateral gaze centers adjacent to the abducens nuclei (parapontine reticular formations) from the contralateral frontal eye fields in the premotor cortex. Downward deviation of the eyes is seen not only in midbrain injury, particularly compression of the midbrain tectum but also in hepatic failure and some other metabolic causes of coma. Downward and inward deviation of the eyes, such that patients appear to be looking at their nose, can occur with thalamic or subthalamic lesions. Conjugate upward deviation of the eyes is not a particularly helpful sign for the localization of lesions causing coma.

Nystagmus can be a sign of an irritative or epileptogenic cause of coma, which can occur in isolation or with other subtle motor signs of seizure activity such as twitching movements of the eye, eyelid, face, jaw, or tongue. Vertical *ocular bobbing*, whether upward or downward, generally indicates diffuse and severe brain injury. When the bobbing involves rapid downward jerking and a slow return to midposition, in association with lateral gaze paralysis, it is typically due to an acute pontine injury. *Ocular flutter*, with conjugate horizontal saccades, is reflective of dysfunction of the cerebellum.

Reflexive ocular movements can be elicited by sudden, rapid head turning (oculocephalic reflex), or by cold water irrigation of the ear canals (vestibuloocular reflex). The oculocephalic reflex clearly cannot be tested in patients with a known or possible cervical spine injury. When the oculocephalic reflex is preserved, the eyes move conjugately in a direction opposite to the direction the head turns, as would be required to maintain gaze fixation. This is sometimes referred to as the *doll's eye* reflex or phenomenon being positive, but due to ambiguity regarding these terms the ocular response should simply be described. Caloric testing is done with the patient supine, with the head raised 30° from horizontal to maximally stimulate convection currents in the endolymph of the lateral semicircular canal. The ear canal is visualized to ensure that it is unobstructed, and that the tympanic membrane is intact, and 10 mL of ice-cold water is slowly instilled. When the vestibuloocular reflex is intact, the eyes will show conjugate deviation toward the cold ear canal. Corrective nystagmus away from the slow deviation and back to a point of visual fixation is seen only in conscious subjects. Irrigation of the ear canals with warm water causes slow conjugate eye deviation away from the warmed canal in the comatose patient and additional nystagmus back toward the point of visual fixation in the conscious patient. The mnemonic COWS (cold opposite, warm same) refers to the fast phase of the nystagmus seen in conscious patients. Simultaneous bilateral cold water irrigation would result in slow downward eye deviation and simultaneous bilateral warm water irrigation would cause slow upward eye deviation. Oculocephalic and caloric testing can be abnormal due to diffuse brainstem lesions, individual cranial nerve palsies, restrictive eye disease, including severe globe and eyelid edema, or vestibular dysfunction due to ototoxic, sedative, paralytic, or anticholinergic medications.

Motor Exam

The purposeful and reflexive movements of the limbs are helpful localizing signs in the examination of the comatose patient. Flaccid hemiparesis with conjugate gaze toward the paralysis indicates a pontine lesion affecting the contralateral pyramidal tract and the ispilateral abducens nucleus. Flaccid hemiparesis with conjugate gaze away from the paralysis can occur with a supratentorial lesion disrupting the contralateral pyramidal tract and corticobulbar tract to the parapontine reticular formation. Generalized flaccidity can be seen early with any cause of coma, including diffuse supratentorial injuries, brainstem injuries, or metabolic encephalopathies. Hypertonicity of the limb muscles due to injury to the motor system, whether unilateral or generalized, usually takes time to develop.

Decorticate posturing is flexion at the elbow and wrist, adduction of the shoulder, and extension of knee and

ankle. Its presence indicates disruption of corticospinal tracts above the rubrospinal pathway from the midbrain (upper limb flexion) and the vestibulospinal pathway from the pontomedullary junction (upper and lower limb extension). *Decerebrate posturing* is extension at the elbow and wrist, adduction and internal rotation of the shoulder, and extension of the knee and ankle. Bilateral decerebrate posturing is usually due to bilateral midbrain or pontine lesions that disrupt the corticospinal and rubrospinal tracts, leaving the vestibulospinal pathways unopposed. Bilateral decerebrate posturing is a far more ominous sign than decorticate posturing or unilateral posturing of either kind, which can be seen with transient injuries anywhere along the motor system.

Posturing may sometimes be mistaken for tonic or clonic seizure activity but it needs to be recognized because it may indicate progressive brainstem compression due to an expanding posterior fossa mass lesion or to transtentorial herniation. Convulsive movements due to seizures may be overt but also can be quite subtle, particularly in established refractory status epilepticus. Myoclonus that is non-rhythmic and not generalized can occur with many metabolic causes of coma, including global hypoxic-ischemic encephalopathy or hepatic encephalopathy. Myoclonus that is rhythmic and generalized can occur with anoxic injury and is predictive of a dismal outcome when caused by myoclonic status epilepticus. Rhythmic myoclonus due to a brainstem injury and tonic posturing due to hypocalcemia can also mimic epileptic convulsions.

Limb movements in response to local pain should be tested and recorded, although many such responses are mediated by spinal reflexes that can easily be mistaken for purposeful withdrawal and are generally unhelpful for defining the cause or severity of coma. Withdrawal of an arm from a painful stimulus that includes abduction at the shoulder is reliably non-reflexive and indicates some preservation of the spinothalamic and corticospinal tracts. Purely reflexive withdrawal of the arm can be as complex as to include adduction of the shoulder, flexion of the elbow, and pronation of the arm. The complex but purely reflexive withdrawal of the leg known as the *triple flexion response* includes flexion of the hip, flexion of the knee, and dorsiflexion of the ankle. The extensor plantar reflex of the foot or *Babinski sign* is nonlocalizing and can be seen in coma from any cause.

Brain Herniation

The Monroe–Kellie hypothesis states that because the volume of the skull is fixed, when there is an increase in the volume of any one of the intracranial contents (brain, blood, CSF), there must be a compensatory decrease in the volume of the others. This will hold true for an infant with unfused sutures if the changes in volume and pressure are too great or rapid for suture widening to accommodate. In the setting of an expanding intracranial mass lesion such as a subdural hematoma, for example, there will initially be a compensatory decrease in CSF volume due to the compression of lateral ventricles and arachnoid cisterns, and a decrease in cerebral blood volume due to the compression of cerebral veins and sinuses. When the hematoma is small, these compressible spaces allow increases in volume to have little effect on the ICP and the system is described as compliant. When these spaces are maximally compressed, however, the system loses its compliance. Further and relatively small increases in hematoma volume will cause more dramatic increases in ICP and dangerous displacements of arterial blood and brain tissue.

Caudal displacements of brain tissue include *uncal herniation* of the medial temporal lobe beneath the tentorium and *central herniation* of the diencephalon through the tentorium and of the brainstem through the foramen magnum. Comatose patients with known or suspected increased ICP must be watched carefully for signs of these forms of life-threatening herniation. In most, in the setting of an expanding lateral mass lesion, there is a lateral shift of the diencephalon away from the mass and compression of the third nerves against the tentorium. Typically, this involves the third nerve ipsilateral to the mass lesion, but the contralateral third nerve can be affected first, or both nerves can be affected simultaneously. Early compression leads to dysfunction of the more superficially located parasympathetic fibers to the eye and to a dilated and nonreactive pupil. Further compression of the third nerve leads to ptosis and a fixed lateral and downward gaze. With further lateral displacement of the diencephalon and midbrain, there is a compression of the cerebral peduncles of the midbrain against the tentorium, causing signs of pyramidal tract dysfunction such as hemiplegia or decorticate posturing. This may occur on either side but usually occurs first in the contralateral cerebral peduncle, causing the *Kernohan's notch phenomenon*, with pyramidal dysfunction in the limbs ipsilateral to the mass lesion. Loss of the sympathetic input to the eye from the diencephalon will cause a previously dilated pupil to become midposition but remain nonreactive. Severe lateral displacement will finally lead to actual herniation of the most medial portion of the temporal lobe (uncus) through the tentorium and to caudal displacement of the brainstem through the foramen magnum or central herniation.

Central herniation can also occur directly with the downward displacement of the diencephalon, such as might be caused by bilateral mass lesions, including obstructive hydrocephalus. The signs of central herniation may evolve in a rostrocaudal fashion, with loss of midbrain function being followed by loss of pontine and then medullary function. Early signs of midbrain dysfunction include deepening coma, loss of sympathetic inputs to the eyes that leave them small but reactive to light, loss of reflexive vertical gaze, and bilateral corticospinal tract dysfunction with weakness or posturing. Lower midbrain injury can cause further loss of parasympathetic inputs to the eyes that leave them midpositioned and nonreactive to light, more complete loss of eye movements mediated by the third nerve nuclei, and loss of the rubrospinal tract that causes posturing to become decerebrate. Central neurogenic hyperventilation is sometimes, but infrequently, seen with midbrain compression. Diencephalic and midbrain injuries in an unventilated patient are more likely to present with a Cheyne-Stokes pattern of respiration.

Involvement of the pons and midbrain will lead to a loss of virtually all cranial nerve reflexes, flaccid paralysis with loss of all posturing, and increasingly dysfunctional respiratory patterns described as apneustic, ataxic, and, finally, agonal. Central herniation does not always progress in a slow or stepwise fashion, and medullary signs of severe autonomic dysfunction may be present early. Herniation may progress precipitously soon after the first signs of increased ICP are noted and the structural injuries associated with the brainstem signs outlined above may be irreversible. Close monitoring and early intervention are needed to manage increases in ICP. The measures available for decreasing ICP are outlined in *Table 365.7*.

Table 365.7
Interventions to decrease ICP

Decrease cerebral blood volume
30° head elevation in neutral position
Hyperventilation to a pCO_2 of 25–30 mmHg
Anesthetic agents (barbiturates, propofol) to reduce $CMRO_2$
Paralytic agents to reduce resistance to ventilation
Analgesic agents to reduce agitation
Prevention of hyperthermia with aggressive cooling measures
Decrease extracellular fluid and CSF volume
Osmotic diuretics (mannitol, 3% saline)
Loop diuretics (furosemide)
Corticosteroids (dexamethasone)
Carbonic anhydrase inhibitors (acetazolamide)
Intraventricular drainage of CSF
Decrease/ameliorate intracranial brain tissue volume
Decompressive lesionectomy
Decompressive resection of adjacent brain tissue
Decompressive craniectomy and dural expansion

History

Ideally, a clinical history will be obtained concurrently by the physician or other team members while the patient is being transported, stabilized, and put through initial examinations and laboratory tests. Attempts should be made to contact those who may know about the patient's past medical history or who may have witnessed the events leading up to the patient's loss of consciousness. A family member or bystander may have witnessed trauma or seizures. Others caring for the child may be aware of a past history of disease predisposing to loss of consciousness or be aware of the presence and time course of any prodromal symptoms. Complaints from the child suggestive of increased ICP or meningeal irritation, such as headache, nausea, vomiting, photophobia, or nuchal rigidity, would suggest subarachnoid hemorrhage, meningitis, or hydrocephalus. Symptoms such as dyspnea or chest pain would suggest a respiratory, cardiac, or neuromuscular disorder. Symptoms of cranial nerve dysfunction such as diplopia, dysphagia, dysarthria, and dizziness would suggest direct brainstem injury or compression from a posterior fossa mass.

If the loss of consciousness remains unexplained, the child's environment should be evaluated for the presence of illicit drugs or prescription medications that may have been accidentally or intentionally ingested. Children failing to emerge from anesthesia after surgery should be investigated for such surgical complications as fat embolism, adrenal insufficiency, hypothyroid coma, and opioid overdose.

Pseudocoma

There are several findings on examination of the eyes inconsistent with unconsciousness that are helpful in identifying patients who are either purposefully feigning coma or appear unarousable as a manifestation of psychiatric illness. A history of prior psychiatric illness or of precipitation of the apparent coma by a stressful event should be taken into account but do not exclude medical causes of coma. In true coma, passive eyelid opening will

not induce movement of the eyes and the eyelids will close slowly and gradually when released. In pseudocoma, patients will often actively resist eye opening, either forcefully, attempting to keep their eyes tightly shut, or subtly, inducing a Bell's phenomenon of upward eye rolling during eyelid opening. When released, the eyelids will close quickly or hesitantly. Nystagmus with the vestibuloocular reflex test is not seen in true coma. The severe vertigo and nausea induced by cold caloric testing may *awaken* a patient with pseudocoma.

Diagnostic Testing

Laboratory Testing

The testing that should be done for all patients with unexplained coma should begin with a bedside test of blood glucose, followed by formal laboratory testing of serum glucose as well as a complete blood cell count (CBC), a chemistry panel that measures serum electrolytes (Na, K, Cl, HCO3, Ca, Mg, Phos) and renal function (BUN, Cr) and liver function tests (ALT, AST, Alk Phos, Tbili, Albumin, Ammonia, PT, PTT). Tests for accidental and intentional toxic ingestions should include a screening urine test for common drugs of abuse and serum tests for alcohol, salicylates, acetaminophen, and tricyclic antidepressants. These tests will identify around 80% of all toxic overdoses. Additional testing can be ordered through urine thin layer chromatography or specific serum tests when there is a suspicion that a patient had access to other potentially toxic compounds.

An arterial blood gas will help in the identification and differentiation of metabolic and respiratory disturbances associated with altered consciousness (Table 365.8).

Inborn errors of metabolism may be hinted at by abnormalities in the screening laboratory tests such as hypoglycemia, metabolic acidosis, or hyperammonemia but will require more detailed testing for identification. Small amounts of plasma, serum, and urine should be collected, frozen, and saved for later analysis when a child presents with a possible inborn error of metabolism, as testing after the child has been stabilized may be less diagnostic. Secondary analysis can include measures of urine ketones, amino acids, and organic acids, plasma lactate and pyruvate, plasma amino acids, and serum acylcarnitine profiles.

Other tests can be ordered depending on clinical suspicion or when the cause of coma remains obscure after other assessments are done. These tests include blood cultures, urine cultures, and lumbar puncture for CSF culture regarding possible infection and thyroid function and cortisol studies regarding possible endocrine disorders. Neuroimaging should be performed prior to lumbar puncture to look for any evidence that the procedure could precipitate herniation, such as midline shift, a posterior fossa mass, or loss of any of the cisternal spaces (suprachiasmatic, basilar, superior cerebellar, quadrigeminal plate). Lumbar puncture should also be deferred in the presence of an uncorrected coagulopathy. The serum cortisol level should be elevated in the stressful setting of coma and a low to normal value should prompt further laboratory testing for adrenal insufficiency. Patients who have suffered generalized trauma or who

Table 365.8
Arterial blood gas and respiratory rate evaluation. Interpretation of the respiratory rate and arterial blood gas results

Respiratory rate	Metabolic pattern	ABG results	Causes
Increased	Metabolic acidosis	pH < 7.35 $PaCO_2$ < 30 mmHg HCO_3 < 17 mmol/L	Uremia, diabetic ketoacidosis,lactic acidosis, poisoning with salicylates, methanol, and ethylene glycol
Increased	Respiratory alkalosis	pH > 7.45 $PaCO_2$ < 30 mmHg HCO_3 > 17 mmol/L	Hepatic failure, acute sepsis, acute salicylate poisoning, cardiopulmonary disease with hypoxemia, psychogenic hyperventilation
Decreased	Respiratory acidosis	pH < 7.35 (acutely) $PaCO_2$ > 90 mmHg HCO_3 > 17 mmol/L	Respiratory failure due to CNS disease, neuromuscular disease, or cardiopulmonary disease
Decreased	Metabolic alkalosis	pH > 7.45 $PaCO_2$ > 45 mmHg HCO_3 > 30 mmol/L	Vomiting, alkali ingestion

remain immobile for a prolonged period of time should be monitored for elevated serum creatine kinase levels indicating rhabdomyolysis.

Electrocardiography

In addition to continuous monitoring of the heart rate, comatose patients should undergo electrocardiography to identify myocardial infarction, arrhythmia, or conduction disturbance that may indicate an electrolyte abnormality or toxidrome prior to confirmation by blood tests.

Computed Tomography and Magnetic Resonance Imaging

Following stabilization, the patient with unexplained coma should undergo neuroimaging. A CT scan of the brain without contrast can be obtained rapidly in most medical centers and visualizes most abnormalities that would require immediate intervention, including intracranial hemorrhage, hydrocephalus, cerebral edema, and impending herniation. MRI is superior to CT in identifying acute stroke, diffuse axonal injury, and lesions of the posterior fossa but its use is limited by the longer image acquisition times, need for patient immobility, and patient inaccessibility within the scanner. MRI done with special sequences, including diffusion weighted imaging, diffusion tensor imaging, and proton spectroscopy can identify abnormalities in patients with unexplained coma and can contribute to the assessment of a child's prognosis for recovery, as discussed below.

Electroencephalography

An electroencephalogram (EEG) can identify seizure activity in patients suspected to be unconscious due to status epilepticus, including those who have prolonged depressed consciousness following a witnessed seizure. The presence of focal epileptiform discharges, slowing, or suppression on EEG suggests an underlying focal lesion as may occur with hemorrhage, infection, or stroke. Temporal lobe periodic lateralized epileptiform discharges (PLEDs) are frequently seen with herpes simplex encephalitis but are nonspecific. Metabolic encephalopathies associated with hepatic or renal failure are often associated with frontally predominant triphasic, high-amplitude slow waves. EEG activity that is generally slow or suppressed is a nonspecific indicator of brain dysfunction but does exclude pseudocoma; such patients will typically have EEG findings consistent with normal wakefulness.

Prognosis

The diagnostic evaluation of a patient in coma will often result in sufficient information to provide an estimate of the degree of brain injury that has occurred and of the level of recovery that can be expected. Other than patients who meet the clinical criteria for brain death, however, there are rarely situations in which the neurologist can have certainty regarding either survival or neurological prognosis. Nevertheless, giving families early estimates of the likelihood of a good recovery will help to prepare them to understand later, more definitive declarations regarding prognosis and to make decisions about the appropriateness of future resuscitative efforts.

Many academic reports of outcomes in children use qualitative terms such as good or poor without tying them to quantitative measures that would be comparable between studies. The majority of studies of brain injury in adults report overall long-term outcomes using the simple five-category Glasgow Outcome Scale (GOS), describing patients as either dead, vegetative and unresponsive, severely disabled and dependent on others, moderately disabled but able to live independently, or doing well enough to return to work or school. When the GOS is used, the upper two categories are often considered good outcomes. An eight-category version, the GOS Extended, subdivides each of the three higher categories into halves to further distinguish levels of disability. Other measures that are frequently reported in adults include the 8-item Disability Rating Scale, the 12-item Functional Independence Measure (FIM), and the 8-category Rancho Los Amigos Scale of cognitive function. Scales of global outcome developed for children include the six-category Pediatric Cerebral Performance Category Scale Score, the WeeFIM, and the KOSCHI (King's Outcome Scale for Childhood Head Injury) score.

There is a considerable difference in the general prognosis for coma that is drug induced, otherwise non-traumatic, or traumatic in origin. For drug-induced coma, a good recovery can usually be expected for patients identified early and provided with good supportive care. Brain injury is usually secondary to at least potentially avoidable metabolic or systemic derangements such as hypotension, hypoxia, or hypoglycemia. For non-traumatic coma due to hypoxic-ischemic injury and for traumatic coma, the clinical features present during the initial

resuscitation may not be highly predictive of outcome, but a number of clinical, laboratory, and radiological findings in subsequent days have been found to help predict a favorable or unfavorable outcome.

Non-traumatic Coma

The prognosis for patients in coma secondary to non-traumatic and non-drug-induced reasons is generally poor, with only 15% of patients recovering independent function. The outcome for children with coma due to hypoxic-ischemic encephalopathy, as might occur following cardiopulmonary arrest, is significantly worse than for those with potentially reversible metabolic encephalopathies, as might be seen with hepatic or renal failure. Naturally, more extensive structural brain injury is correlated with poorer outcome, as is the length of time of coma before some degree of recovery is seen. A child's age does not predict the degree of recovery in most analyses.

A practice parameter published by the AAN regarding the prognosis of comatose adults following resuscitation for cardiac arrest identified a number of clinical and laboratory findings that show evidence of being very highly predictive of a poor outcome, including (1) absent pupillary or corneal reflexes or absent or extensor motor responses to stimulation after 3 days, (2) myoclonic status epilepticus within the first day, (3) bilaterally absent cortical somatosensory evoked potentials (SSEP) in the first 3 days, and (4) a serum neuron-specific enolase level greater than 33 ng/L. There was evidence to suggest that the presence of burst-suppression, generalized suppression, or generalized epileptiform discharges on EEG was associated with a poor prognosis but was not specific enough to be used for outcome prediction.

Studies of the outcomes of resuscitation for cardiopulmonary arrest in children have shown that a number of clinical factors are associated with a poorer prognosis. Mortality and morbidity is generally higher in patients with cardiac arrest rather than respiratory arrest. In one study, 57% of 21 children with pure respiratory arrest died before leaving the hospital and 10% were severely impaired or dead a year later, while 92% of 80 children suffering cardiac arrest died prior to leaving the hospital and another 4% were in a vegetative state or had died a year later. Another study of 599 children with out-of-hospital combined cardiopulmonary arrest showed that only 8.6% survived to hospital discharge and that few of them had good neurological outcomes.

Cardiac and cardiopulmonary arrests that occur in hospital have a better rate of survival and of good neurologic outcome. One study of 880 children found that 27% survived to discharge and that the majority of survivors had good neurologic function at the time of discharge. Cardiopulmonary resuscitation that continues for more than 10–15 min or requires more than one bolus of epinephrine suggests a poor prognosis, but there have been cases with good outcomes despite 60 min of resuscitation for children with in-hospital arrest or ice-water submersion.

Few findings on the initial physical examination have been found to be as predictive of outcome from hypoxic-ischemic coma as those seen after 24 h. Poor outcomes were seen in all children with absent pupillary responses after 24 h in one study and in all children without purposeful movement or normal brainstem reflexes in another, but there have also been reports of children with better outcomes despite these findings. Along these lines, while lower GCS scores are associated with poorer outcomes, with one study finding that none of the children who had a GCS of 3 or 4 after the first 24 h had a good recovery, there are reported exceptions and predicting outcomes using a child's GCS score at the scene, or on admission is even less accurate. The effect of paralytic or sedative medications must be taken into account when assessing these physical findings.

Several studies have suggested that somatosensory evoked potential (SSEP) testing in children with severe hypoxic-ischemic brain injury is as useful as in adults with cardiac arrest for accurately predicting poor outcome when there is no cortical response. However, other studies have shown this finding to have a specificity of 92–95% and sensitivity of 61–75% for poor outcomes, making its clinical use far more problematic in children than in adults. Other electrophysiologic studies, including EEG, brainstem auditory evoked potentials, and visual evoked potentials, are all even more prone to error in predicting outcome, although severe abnormalities show a correlation with poorer outcomes. Conversely, initial or follow-up EEGs showing little to no slowing or suppression, normal reactivity to stimuli, or normal sleep rhythms in comatose survivors of hypoxic-ischemic injury have been correlated with favorable outcomes, suggesting a potential prognostic value to repeated or continuous monitoring.

Studies of the use of MRI for predicting outcomes for children in coma from hypoxic-ischemic injury have found that there is a greater sensitivity and specificity to abnormal findings 3–4 days after the injury, with one showing universally poor outcomes (vegetative state or death) for children with T2 hyperintensity within the brainstem or within both the cortex and basal ganglia. Studies of magnetic resonance spectroscopy have found

that severely depressed N-acetylaspartate levels and elevated lactate levels are also associated with poorer neurological outcomes.

Traumatic Coma

Children with traumatic coma can have a good outcome despite prolonged coma and generally do better than children with non-traumatic coma, but this makes predicting long-term prognosis even more difficult.

The most accurate predictors in early research studies were age, the GCS score on presentation and within the first week, and the presence or absence of pupillary reactivity. A recent study of 309 children compared the predictive value of the GCS score, other clinical variables including injuries to other organs, and the results of head CT scans and found that the GCS score was the best predictor of survival, with few children with an initial GCS score of 3 or 4 showing better than moderate disability. CT findings of cerebral edema and intracranial hemorrhage were also associated with poorer outcomes.

One study of children with severe traumatic brain injury showed continued clinical improvement after hospital discharge with the number of children who were independent in all areas of function increasing over an average of 2 years from 37% to 65%. Another study found that cognitive impairments in children who had survived for more than 1 year after suffering severe TBI were better predicted by the duration of coma measured as the time to follow commands, than by the initial GCS score. Other studies have shown that the duration of posttraumatic amnesia is also a better predictor than the GCS score for long-term cognitive impairment.

Additional predictors of poorer recovery include open head injuries, multiple skull fractures, deeper, more diffuse and more severe brain injury on neuroimaging, increased ICP, fever, seizures, and unstable blood pressure. For infants, a non-accidental etiology of the head trauma is often associated with signs of secondary ischemic brain injury and is predictive of greater morbidity and mortality.

Persistent Vegetative State

Children who awaken from coma into a vegetative state have some chance to regain consciousness; most who do will do so early in their recovery and will continue to have severe disability. When the vegetative state persists for more than 1 month following non-traumatic coma, or for more than 3 months after traumatic coma, improvements are very unlikely. Survival in the vegetative state is precarious and requires meticulous medical and nursing care, but recovery to a state of independence is almost unheard of for patients in such a state for more than a year and has never been reported for patients in a persistent vegetative state for 3 years. There are a significant number of patients who are initially misdiagnosed as being vegetative but later reclassified as being in a minimally conscious state following repeated and more detailed evaluations that consider the possibility of fluctuating levels of consciousness and limitations on interactions due to sensory deficits. Most of the older reports of patients making surprisingly good recoveries from the vegetative state were likely minimally conscious patients who had been misdiagnosed as vegetative. However, there have been more recent reports of the use of functional brain imaging to identify vegetative patients with preserved receptive language function who did make exceptional late recoveries.

Brain Death

The clinical requirements on physicians for declaring a child as having died from brain death are fairly consistent across most regions of the world, although, when surveyed, knowledge of these requirements and documentation of the examinations performed is often incomplete. The difficulties that physicians face in presenting a diagnosis of brain death to a child's family are universal. Although brain death has been used in clinical practice since the 1970s, families are likely to have little familiarity with the concept and to see ambiguity in the ongoing use of cardiopulmonary support systems, especially when physicians persist in referring to them as providing *life support*.

The diagnosis of brain death requires that there be an irreversible cause of injury to the brain that precludes any chance for recovery of consciousness. In a few countries, including the United Kingdom, it is sufficient for the injury to involve only the brainstem, although in most countries, including the United States, there is a requirement for *whole brain* death that involves both the brainstem and the cerebral hemispheres.

With the loss of all brainstem function, there should be no spontaneous movements, postures, or convulsions, no movements in response to stimulation other than those mediated by spinal reflexes, no brainstem reflexes including pupillary, corneal, oculocephalic, vestibuloocular, or gag reflexes, and no spontaneous respiration despite elevation of the partial pressure of CO_2 from at or below 40

mmHg to above 60 mmHg on arterial blood gas testing, or a 20 mmHg elevation from an initial level above 40 mmHg. For a purely clinical diagnosis to be accurate, the examination cannot be confounded by factors that interfere with the examination, such as facial trauma, or that might induce unresponsiveness, such as significant hypothermia, hypotension, metabolic disturbance, or significantly elevated serum levels of sedating or paralyzing medications. When the clinical examination is limited in any way, confirmation can be obtained using a radionucleotide scan that shows absent cerebral blood flow. Confirmatory testing with EEG to show electrocerebral silence has been recommended for children under 1 year of age but this test is prone to being influenced by metabolic derangements and is less helpful in the setting of confounding circumstances.

Following brain death, patients frequently develop cardiac and cardiovascular instability despite intensive supportive care. Continuous intravenous infusion of vasopressin has been found helpful in preventing the severe diuresis and hypotension resulting from the loss of pituitary function. Patients whose organs are not being maintained for donation can be withdrawn from artificial support, with intravenous drips, ventilators, and all monitors turned off to allow families a period of time with their child before the absence of a heartbeat is confirmed by a physician through auscultation and palpation and the absence of cardiac activity is documented by an electrocardiogram. In rare instances when there have been reasons to continue supportive care indefinitely, organ failure usually occurs in less than a week, although there are bodies that have been maintained following brain death for months or years.

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366 Acute, Subacute, and Chronic Progressive Encephalopathies

Generoso Gutierrez-Gascón

Introduction

Definitions and Exclusions

For purposes of this chapter, "encephalopathy" will mean *a disorder in which there is an altered mental state, which, depending on the type and severity, can include loss of cognitive function, personality changes, inability to concentrate, confusion, delirium, stupor, or coma.* It does not refer to a single disease, but to a syndrome of global brain dysfunction, which can be caused by many different illnesses, both systemic, secondarily affecting the brain, and primary in the brain itself. The onset may be acute, subacute, chronically progressive, or static. This chapter will not discuss the static or nonprogressive encephalopathies such as the mental retardation or cerebral palsy syndromes, nor will it discuss neuropsychiatric disorders such as the autistic spectrum disorders (See Dr. Pamela High's section on ❯ Developmental and Behavioral Disorders). Furthermore, it will exclude traditional acute infectious etiologies such as viral encephalitis (e.g., Herpes Simplex encephalitis), bacterial and fungal meningitis, toxic encephalopathies from ingested heavy metals like lead, accidental poisoning, drug ingestion in suicide attempts, or inhaled toxins, such as carbon monoxide.

Encephalopathies discussed in this chapter are likely to be seen by pediatricians and primary care practitioners throughout the world, although some are seen in some parts of the world more than others. For example, HIV encephalopathy (AIDS) is not uncommon in Africa and south Asia, and subacute sclerosing panencephalitis (SSPE) in Turkey and India, but early cases of the encephalopathy associated with the H1N1 influenza pandemic, though first described in Mexico and southern California, have been seen throughout the world.

Classification

This chapter will arbitrarily discuss encephalopathies by age group (infancy and early childhood, mid-childhood, and late childhood/adolescence), with stratification by clinical course (acute, subacute, chronic progressive) (See ❯ *Tables 366.1* and ❯ *366.3*).

Etiology and Clinical Presentation

Etiologies discussed in this chapter include inborn errors of metabolism, lysosomal storage disorders, epileptic encephalopathies, infection-related such as acute toxic encephalopathy and Reye syndrome, immune-mediated, slow virus infections, and progressive encephalopathic degenerative diseases. Because there are many different etiologies, the disturbance in mental status may be accompanied by other neurological symptoms or signs, such as seizures, ataxia, weakness, movement disorders or visual loss, depending on the part of the brain affected. The mental status change, especially in the progressive encephalopathies, may also be expressed as specific higher cortical dysfunction, such as aphasia, apraxia, or agnosia, before progression to a dementia. Dementia is defined as a loss of previously acquired cognitive and/or behavioral function and is central to the neurodegenerative diseases.

Management

Adopting a mind set of searching for treatable and reversible etiologies can focus the diagnostic and treatment approach. The neuropathologic substrate, particularly in the acute toxic-metabolic encephalopathies, is usually cerebral edema. This can be indicated by CT brain findings of decreased attenuation periventricularly and in subcortical white matter or increased T2 signal intensity on brain MRI. Functional techniques such as magnetic resonance spectroscopy (MRS) and positron emission tomography (PET), single photon emission computerized tomography (SPECT) show the pathophysiology better, but are not widely available in non-tertiary care centers and in the developing world. CSF findings may show increased

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Table 366.1

Acute, subacute, and progressive encephalopathies in infancy and early childhood

Age	Acute	Subacute	Progressive
Infancy/early childhood	Hypoxic-ischemic	Biotinidase deficiency	Tay–Sachs
	Aminoacidurias Organic acidurias Urea cycle	Early myoclonic encephalopathy	Sandhoff
			GM1 gangliosidoses
		Ohtahara syndrome	NCL[a]
	Vitamin-dependent	FIRES[b]	Infantile
	Fatty acid oxidation	Leigh's disease	Late infantile
	Neurotransmitter	MELAS[c]	Juvenile
		MERRF[d]	Mucolipidoses
			MPS[e]
			Hurler
			Hunter
			San Filippo
			Leukodystrophies
			Krabbe
			Metachromatic
			Austin
			Pelizaeus-Merzbacher
			Canavan
			Alexander
			POLG-related
			Alpers-Huttenlocher
			MCHS[f]
			Aicardi–Goutieres

[a]Neuronal ceroid lipofuscinosis
[b]Febrile infection-related epilepsy syndrome
[c]Mitochondrial encephalomyelopathy, lactic acidosis, stroke-like episodes
[d]Myoclonic epilepsy with ragged red fibers
[e]Mucopolysaccharidoses
[f]Myocerebrohepatopathy

opening pressure, no pleocytosis, and normal protein. Electroencephalography (EEG) reveals diffuse slow background activity of low or high voltage, indicating depressed brain functioning. If an inborn error of metabolism is suspected, blood for amino acid determination by gas-liquid chromatography (GLC), urine for organic acid determination by gas chromatography-mass spectroscopy (GCMS), or better yet, a blood spot on filter paper to be sent to a regional or national laboratory for tandem mass spectroscopy (tandem MS) should be obtained. Also, samples for blood pH, electrolytes, lactate, pyruvate, ammonia, glucose, carnitine, liver function tests, and CSF for lactate and pyruvate should be obtained. For possible future studies, samples of the following should be stored frozen: 3 ml of CSF for future possible studies such as neurotransmitter metabolites, polymerase chain reaction (PCR) amplification for viral DNA fragments, immunoglobulins, oligoclonal bands, myelin basic protein, and measles-specific antibody titers; 5 ml of urine; and 5 ml of blood (−20°C), 1 ml in a fluoride tube and the rest in a heparinized tube. Until a specific diagnosis is made, if the initial tests suggest an organic aciduria, broad spectrum cofactor supplementation for possible treatable and reversible acute encephalopathies can be given without risk of adverse reactions. A starting combination is thiamine (300 mg plus per day), biotin (50 mg twice a day), riboflavin (100 mg/kg/day), and L-carnitine (100 mg/kg/day in three divided doses). If a mitochondrial disease of

Table 366.2
Progressive genetic encephalopathies

Age	Gray matter	White matter
Infancy/early childhood	Gangliosidoses, GM1, GM2	Leukodystrophies
	NCL,[a]infantile, late infantile	Krabbe
	Nieman-Pick	Metachromatic
	Gaucher, infantile	Canavan
	Mucolipidoses	Alexander
	Hurler, Hunter	Austin
	San Filippo	Pelizaeus–Merzbacher
	POLG[b] disorders	Leukoencephalopathies
	Alpers–Huttenlocher	Vanishing white matter
	Myocerebrohepatopathy	Megancephalic with subcortical cysts
	Aicardi–Goutieres	Neuroaxonal dystrophy, Type 1
	Pompe (glycogen storage disease Type 1)	
Late childhood/ adolescence	NCL, juvenile (Kufs)	Adrenoleukodystrophy
	Nieman Pick Type C	
	Sialidosis Type 1 (cherry-red spot-myoclonus)	
	Huntington's	
	Wilson's	
	PANK2[c], Neurodegeneration with brain iron accumulation	

[a]NCL neuronal ceroid lipofuscinosis
[b]POLG polymerase gamma gene
[c]PANK2 pantothenate kinase gene

oxidative phosphorylation is suspected, one can add vitamin K, vitamin C, and coenzyme Q. Specific therapy can then await specific diagnosis (See ❯ Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism" by Ozand and Al-Essa).

The specific etiology, pathogenesis, genetics, neuropathology, clinical manifestations, diagnostic investigations, differential diagnosis, and treatment will be discussed, when appropriate, for the individual diseases that are not otherwise discussed elsewhere in this book, such as in the section on ❯ Inborn Errors of Metabolism (Pinar Ozand), ❯ Chap. 360, "Neonatal Neurology" (William Brown and Mara Coyle), or ❯ Chap. 362, "Epilepsy" (John Gaitanis). For single gene disorders, prenatal diagnosis is possible through amniocentesis or chorionic villus sampling. If the single gene mutation in a progressive debilitating or fatal disease is already known in a family, having been identified in a previously affected child, and abortion is not an option, preimplantation genetic diagnosis (PIGD), using in vitro fertilization (IVF) techniques, can be utilized as preventive treatment, in IVF centers with technically qualified obstetricians and geneticists.

Web-Based Resources for Physicians

For readers who desire in-depth information beyond this chapter, web-based resources are the quickest way to access information at the point of service, since computers and internet access are now available almost everywhere, except in the most remote locations. For diagnostically puzzling patients whose presentations suggest some kind of chromosomal, genetic or unrecognized syndrome, www.simulconsult.com can be helpful in narrowing down differential diagnostic possibilities. For more detailed descriptions of genetic diseases with Mendelian inheritance, consult OMIM (Online Mendelian Inheritance in Man) at www.ncbi.nlm.nih.gov/omim. For succinct information on clinical presentation and management of any genetic disease, click on "Gene Reviews" in www.genetests.org. For information on availability of molecular genetic testing, on a clinical or research basis, for any of the genetic diseases discussed in this chapter, click on "Laboratory Directory" in www.genetests.org. For information on ongoing clinical trials, consult www.clinicaltrials.gov. For evidence-based

Table 366.3

Acute, subacute, progressive encephalopathies, mid-childhood and adolescence

Mid-childhood	Infection-related Acute toxic, Reye–Johnson, Influenza-associated Acute necrotiz Encephalopathy, ADEM[a], AHLE[b], Hepatic encephalop, Uremic encephalop, Hypertensive, Hypoglycemic	Cerebral malaria Trypanosomiasis, Epileptic encephal, ESESS[c], Landau-Kleffner, CSWS[d]	Adrenoleukodystrophy, Nieman-Pick Type C, Juvenile Huntington's
Adolescence	Acute Confusional Migraine, Immune-mediated: Hashimoto's, Rassmussen's, AERRPS[e], DESC[f], NORSE[g]	Nonconvulsive status epilepticus	SSPE[h]
			HIV[i]
			PMFL[j]
			Wilson's disease
			Hallervorden–Spatz
			Progressive myoclonic epileptic encephalop: Sialidosis Type 1, Unverricht-Lafora, MERRF[k]

[a]Acute demyelinating encephalomyelitis
[b]Acute hemorrhagic leukoencephalitis
[c]Electrical status epilepticus in slow-wave sleep
[d]Continuous spike waves in sleep
[e]Acute encephalitis with refractory, repetitive partial seizures
[f]Devastating epileptic encephalopathy in school-aged children
[g]New onset refractory status epilepticus
[h]Subacute sclerosing panencephalitis
[i]Human immunodeficiency virus
[j]Progressive multifocal leukoencephalopathy
[k]Myoclonic encephalopathy, ragged red fibers

information on efficacy of treatments, consult www.cochranereviews.com.

Infancy and Early Childhood

Acute Encephalopathies

Hypoxic-ischemic encephalopathy (HIE)
Inborn errors of metabolism
- Aminoacidurias
- Organic acidurias
- Urea cycle disorders
- Vitamin-dependent disorders
- Fatty acid oxidation (FAO) disorders
- Neurotransmitter-related disorders

Neonatal encephalopathy describes an obtunded newborn with abnormal pediatric Glasgow Coma Scale, often experiencing seizures and exhibiting hypotonia. In developed countries, 2–3 per 1,000 live term birth infants develop acute, moderate to severe encephalopathy. Rates are 10 times that in less developed nations (See *Table 366.1*).

Most commonly *hypoxic-ischemic encephalopathy (HIE)* is the cause. Neonatal encephalopathy and HIE are covered in the Chap. 360, "Neonatal Neurology" by William Brown and Mara Coyle Brown, and in the Neonatology section.

It is in this age group that *the inborn errors of metabolism (IEM)* are most likely to present. The devastating metabolic diseases of the newborn are discussed in the chapter by P. Ozand and M Al-Essa, on Disorders of Amino and Organic Acidurias. The aminoacidurias, such as non-ketotic hyperglycinemia, organic aciduras such as methylmalonic and propionic acidemia, fatty acid oxidation disorders and vitamin-dependent disorders, such as pyridoxine dependency present as neonatal encephalopathies in developed countries, but are much more common in populations where there are large families and a high rate of consanguineous marriages.

Moammar et al. report that in the Eastern Province of Saudi Arabia, over 25 years, IEM had a cumulative incidence of 150/100,00 live births. Small-molecule disorders were diagnosed in 134/248 patients (54%). Organic acidurias were the most common (48/248 patients; 19%), methylmalonic aciduria being the most frequently observed (13/48 patients; 27%). Lysosomal storage diseases were diagnosed in 74/248 patients (30%), of which mucopolysaccharidosis was the most frequently observed (28/74; 38%).

Fatty Acid Oxidation Disorders (FAO)

Medium-chain acyl Co-A dehydrogenase deficiency (MCAD)
Very long chain acyl Co-A dehydrogenase deficiency (VLCFA)
Multiple acyl Co-A dehydrogenase deficiency (Glutaric aciduria Type 2)

Medium-, long-, and short-chain acyl-CoA dehydrogenase deficiencies (MCAD, LCAD, SCAD) are due to defects of the β-oxidation spiral. The encephalopathic presentations are acute toxic encephalopathy with nonketotic hypoglycemia in infancy and toddlerhood provoked by fasting (primarily MCAD), the syndrome of nonketotic hypoglycemia plus very low plasma carnitine and absent dicarboxylicaciduria (carnitine transport defects), and sudden infant death (SIDS). MCAD is the most common mitochondrial β-oxidation disorder, occurring in 1/10,000 to 1/20,000. Children usually present between ages 3 and 15 months. A common presentation is vomiting, lethargy, followed by fasting and associated with a preceding viral gastrointestinal or respiratory infection. In the emergency room, it presents as an acute toxic encephalopathy or coma, with hypoketotic hypoglycemia, hyperammonemia, and abnormal liver function tests. Serum carnitine is low, urine acycarnitines are increased. The differential diagnosis includes other fatty acid oxidation disorders, exogenous toxin ingestion, and true Reye syndrome. Management utilizes10% dextrose intravenously, L-carnitine 100 mg/kg/day orally in divided doses, frequent short feeds. Prognosis: the risk of death with first episode is about 20%. If treatment is delayed, developmental retardation, behavioral problems, seizures, and failure to thrive may result. Preventive treatment: living siblings should be screened with acylcarnitine profiles and subsequent siblings should be screened in the neonatal period.

For further discussion of MCAD, as well as other FAOs – very long chain acyl-CoA dehydrogenase deficiency, multiple acyl-CoA dehydrogenase deficiency (glutaric aciduria Type 2), see chapter by Ozand and Al-Essa, Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism".

Neurotransmitter-Related Disorders

These disorders are due to a relative deficiency or excess of a neurotransmitter. Two of these disorders present as encephalopathy in the neonatal period – biopterin-dependent PKU and non-ketotic hyperglycinemia. In biopterin-dependent PKU, the etiology causing encephalopathy *is 6-PTS deficiency (6-pyruvoyltetrahydropterin synthase). In non-ketotic hyperglycinemia*, it is the excessive glycine (a CNS neurotransmitter), due to defects in various components of the mitochondrial glycine cleavage enzyme system, that causes the seizures and encephalopathy in the acute neonatal presentation. Clinical presentation and treatment are discussed in the chapter by Ozand and Al-Essa, Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism".

Other

Other rare miscellaneous acute encephalopathies to be mentioned but not discussed here are acute chemotherapy-related leukoencephalopathy, usually in leukemia patients treated with methotrexate, and bronchiolitis-associated encephalopathy in critically ill infants, seen in pediatric intensive care units.

Subacute Encephalopathies

Biotinidase deficiency
Epileptic encephalopathies
  Early myoclonic encephalopathy
  Early infantile epileptic encephalopathy (Ohtahara syndrome)
  Febrile infection-related epilepsy syndromes (FIRES)
Mitochondrial disorders (of oxidative phosphorylation)
  Subacute necrotizing encephalomyelopathy (Leigh's disease)
  Mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS)
  Myoclonic epilepsy with ragged red fibers (MERRF)

Biotinidase Deficiency

This subacute to progressive encephalopathy is mentioned because it is eminently treatable, by giving biotin, L-carnitine, and Polycitra. In areas of the world where neonatal metabolic screening is done, the encephalopathy can be prevented because of early diagnosis and treatment. The disorder is described in the chapter by Ozand and Al-Essa, Chap. 38, "Disorders of Organic Acid and Amino Acid Metabolism".

Epileptic Encephalopathies

The epileptic encephalopathies are disorders that present as seizures of various kinds that are refractory to

medication treatment and are accompanied by developmental behavioral arrest or regression. In infancy, these are the infantile spasms or West syndrome, in early childhood, the Lennox Gastaut syndrome and Severe Myoclonic Epilepsy (Dravet syndrome). These are discussed in the Chap. 362, "Epilepsy" (John Gaitanis). Two epileptic encephalopathies appear in the neonatal period – early myoclonic encephalopathy and early infantile epileptic encephalopathy with burst-suppression, or Ohtahara syndrome.

Other Selected Epileptic Encephalopathies

Early Myoclonic Encephalopathy (Neonatal Myoclonic Encephalopathy). This clinical-EEG syndrome presents in the neonatal period with partial or fragmentary erratic myoclonus, massive myoclonias, and frequent partial motor seizures. The EEG displays complex spike bursts, sharp waves, and slow waves, separated by flattening of the background and localized discharges, so-called suppression bursts. These become more apparent in sleep and may persist into late childhood, after a transient hypsarrhythmia in late infancy. The etiology is usually nonstructural/ metabolic, for example, non-ketotic hyperglycinemia. Treatment is directed at the etiology. Symptomatic suppression of seizures with antiepileptic drugs is rarely successful in this refractory epileptic encephalopathy. Prognosis is severe, with early death, or severe and profound psychomotor retardation.

Early Infantile Epileptic Encephalopathy with Burst-Suppression (Ohtahara Syndrome). Tonic spasms are the main seizures, often appearing in clusters. Suppression bursts appear in both wake and sleep. They evolve into hypsarrhythmia at 3–4 months of age and West syndrome, then eventually to diffuse slow spike waves and the Lennox–Gastaut syndrome. The etiology most commonly is structural brain lesions such as prenatal cerebral dysgenesis. Prognosis is dire, with early death or marked psychomotor retardation and seizure intractability, despite treatment with ACTH, corticosteroids, vigabatrin, or ketogenic diet.

Febrile Infection-Related Epilepsy Syndrome (FIRES), A Nonencephalitic Epileptic Encephalopathy. Previously healthy children develop prolonged or recurring seizures lasting days after fever onset, usually with respiratory or nonspecific infections. CSF shows no pleocytosis and no pathogens. EEG usually reveals diffuse slowing or multifocal discharges. Neuroimaging is normal and no inflammation is seen on brain biopsies, when done. The course is dire. A.van Baalen reported only two recovered in a series of 22 children in Germany. Two died, two had behavioral disturbances, eight continued with impaired consciousness, and eight developed medically refractory epilepsy. The pathogenesis is likely neuronal hyperexcitation rather than inflammatory cerebral damage.

Mitochondrial Disorders: Disorders of Oxidative Phosphorylation

Leigh's disease
MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes)
MERRF (myoclonic epilepsy associated with ragged red fibers)

Leigh's Disease (Subacute Necrotizing Encephalomyelopathy)

Leigh syndrome is a relatively common disease. About one-half are diagnosed before the age of 6 months. A previously healthy infant begins with brain stem signs such as poor feeding, sucking, and swallowing, and supranuclear ophthalmoplegia. A central hypoventilation syndrome is prominent early. Seizures may occur early, movement disorders late. Developmental arrest and then deterioration follows. Diagnosis is made by noting the typical course, elevated CSF lactate and pyruvate, and a typical distribution on brain MRI of paramedian T2 increased intensity lesions in brainstem, cerebellum, and basal ganglia. Magnetic resonance spectroscopy (MRS) reveals elevated lactate peaks in these lesions. The differential diagnosis includes the organic acidurias presenting as progressive encephalopathy like glutaric aciduria type 1, biotinidase deficiency, and biopterin-dependent PKU, the primary lactic acidoses, atypical peroxisomal disorder, and infantile neuraxonal dystrophy. Leigh's disease is caused by mitochondrial DNA as well as autosomal recessive, nuclear coded DNA mutations. Although several enzyme complexes of the respiratory chain, primarily in Complex IV, are involved, the most commonly reported defect is in the ATPase6 gene at mtDNA position 8993, causing defective ATP production. The pathology consists of spongy degeneration, demyelination, gliosis, necrosis, with relative sparing of neurons, and capillary proliferation. Treatment is primarily supportive and symptomatic. Metabolic treatment using mitochondrial "cocktails" have been used, with inconclusive results. These usually include biotin 50 mg/day or more, thiamine 300 mg/day or more, coenzyme Q10, vitamin K, and vitamin C. Dichloroacetate has been used to lower serum lactate levels. Patients with pyruvate dehydrogenase complex deficiency may respond to the ketogenic diet. The prognosis is grave, this being a fatal disease, although there may be periods of arrest of progression.

MELAS – Mitochondrial Encephalomyopathy, Lactic Acidosis, and Stroke

MELAS (mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes) is a multisystem disorder typically beginning usually between 2 and 10 years of age. Development is usually normal, though stature may be short. The most common initial symptoms are generalized tonic-clonic seizures, recurrent headaches, anorexia, and recurrent vomiting. Exercise intolerance or proximal limb weakness can present early. Sensorineural hearing loss is common. Stroke-like episodes of recurrent transient hemiparesis or cortical blindness may be associated with altered consciousness. Motor abilities, vision, and mentation are impaired by adolescence.

The diagnosis rests on a combination of clinical findings and molecular genetic testing. Mutations in the mitochondrial DNA (mtDNA) gene *MT-TL1* encoding $tRNA^{Leu(UUR)}$ are causative. The most common mutation, present in over 80%, is an A-to-G transition at nucleotide 3243. Mutations can usually be detected in mtDNA from leukocytes. However, because of heteroplasmy in mitochondrial disorders, the pathogenic mutation may be undetectable in leukocytes but can be detected in other tissues, such as cultured skin fibroblasts grown from skin biopsies or, most reliably, skeletal muscle obtained from muscle biopsy.

No specific treatment for MELAS exists. Sensorineural hearing loss has been treated with cochlear implantation. Seizures respond to antiepileptics. Coenzyme Q10 and L-carnitine have been beneficial in some individuals.

MELAS is transmitted by usually asymptomatic mothers. A male with a mtDNA mutation cannot transmit it to any of his offspring. A female (affected or unaffected) transmits the mutation to all of her offspring. Prenatal diagnosis for MELAS is available if a mtDNA mutation has previously been detected in the mother.

MERRF – Myoclonic Epilepsy, Ragged Red Fiber Syndrome

MERRF is a multisystem disorder characterized by myoclonus, which is often the first symptom, followed by generalized epilepsy, ataxia, weakness, and dementia. Onset is usually in childhood, occurring after normal early development. Common findings are hearing loss, short stature, optic atrophy, and cardiomyopathy with Wolff–Parkinson–White (WPW) syndrome. Less common are pigmentary retinopathy and lipomatosis.

The clinical diagnosis of MERRF is based on the clinical history and exam of myoclonus, generalized epilepsy, ataxia, and ragged red fibers (RRF) in the muscle biopsy. The mitochondrial DNA (mtDNA) gene *MT-TK* encoding $tRNA^{Lys}$ is the gene most commonly associated with MERRF. The most common mutation, present in over 80% of affected individuals with typical findings, is an A-to-G transition at nucleotide 8344 (m.8344A>G). Mutations are usually present in all tissues and can be detected in mtDNA from blood leukocytes. However, because of "heteroplasmy" in mitochondrial disorders, the pathogenic mutation may be undetectable in mtDNA from leukocytes and may only be detected in other tissues, such as cultured skin fibroblasts from skin biopsy or, most reliably, skeletal muscle obtained by muscle biopsy.

Levetiracetam, clonazepam, zonisamide, and valproic acid (VPA) have been used to treat the myoclonic epilepsy. However, VPA may cause secondary carnitine deficiency and should be avoided or if used, L-carnitine must be added. Coenzyme Q_{10} (100 mg 3 × /day) and L-carnitine (1,000 mg 3 × /day) are often used in hope of improving mitochondrial function.

Mitochondrial genetics dictates that the mother of an affected child usually has the mtDNA mutation and may or may not have symptoms. The father is not at risk for having the disease-causing mtDNA mutation. If a male has an mtDNA mutation, he cannot transmit it to his children. A female with the mutation (whether affected or unaffected) transmits the mutation to all of her offspring. Prenatal diagnosis for MERRF is possible if an mtDNA mutation from the mother has been identified.

Progressive Encephalopathies

Incidence

Progressive encephalopathy (PE) in children is a heterogeneous group of diseases mainly composed of metabolic diseases, but consists also of neurodegenerative disorders where neither metabolic nor other causes are found. In an epidemiologic study from Norway by Stromme P et al. from 1985 to 2003, 84 PE cases were registered in Oslo, with 28 different diagnoses. The age-specific incidence rates per 100,000 were 79.89 (<1 year), 8.64 (1–2 years), 1.90 (2–5 years), and 0.65 (>5 years). Furthermore, 66% (55/84) of the cases were metabolic, 32% (27/54) were neurodegenerative, and 2% (2/84) had HIV encephalopathy. In regard to presentations by age group, 71% (60/84) of the cases presented at <1 year, 24% (20/84) were late infantile presentations, and 5% (4/84) were juvenile presentations. Neonatal onset was more common in the metabolic (46%) (25/55) compared to the neurodegenerative group (7%) (2/27). Unspecified neurodegenerative disease occurred in 20% (17/84) of all cases. Overall two-thirds of the cases were metabolic, of which almost half presented in the neonatal period.

One way to conceptualize the progressive genetic encephalopathies in infancy and early childhood is to consider whether progressive degeneration at the onset occurs primarily in the gray matter or in the white matter (See *Table 366.2*, Progressive Genetic Encephalopathies).

Although the disturbance in mental status, usually heralded by developmental arrest and then deterioration, may seem similar, early accompanying neurological symptoms/signs differ. Most of the lysosomal storage diseases are primarily gray matter diseases, because symptoms are due to abnormal storage of metabolic products in neurons. Seizures present early in the course. These are best exemplified by the GM2 gangliosidoses (Tay–Sachs, Sandhoff) and the neuronal ceroid lipofuscinoses. In the white matter diseases (leukodystrophies or leukoencephalopathies), there is progressive degeneration, or hypomyelination, of myelin, and present with long tract (pyramidal) signs early in the course.

Lysosomal Storage Diseases

GM2 gangliosidoses (Tay–Sachs, Sandhoff)
GM1 ganlgiosidoses
Neuronal ceroid lipofuscinosis, Infantile Form (Santavuori), Late Infantile (Jansky–Bielslchowsky), juvenile (Batten–Spielmeyer–Vogt)
Mucolipidoses
Mucopolysaccharidoses (Hurler, Hunter, San Filippo)
Leukodystrophies
- Globoid Cell leukodystrophy (Krabbe disease)
- Metachromatic Leukodystrophy
- Multiple Sulfatase Deficiency (Austin's disease)

These disorders, all presenting in the neonatal and early childhood period, are discussed in the Chap. 39, "Lysosomal Storage Diseases", by Ozand and Al-Essa.

Other Leukodystrophies, Leukoencephalopathies

The term leukoencephalopathies is a broad one which includes any disorder which primarily affects brain white matter or myelin, and so includes disorders of hypomyelination or dysmyelination. The leukodystrophies are inherited disorders characterized by progressive degeneration of the white matter of the brain.

Ozand and Al-Essa (Chap. 39, "Lysosomal Storage Diseases" chapter) discuss the traditional leukodystrophies:
- Globoid cell leukodystophy (Krabbe's disease)
- Metachromatic leukodystrophy (MLD)
- Multiple sulfatase deficiency (Austin's disease)

Other leukodystrophies discussed here are:
- Pelizaeus–Merzbacher disease
- Canavan's disease
- Alexander's disease

Two relatively recently described leukoencephalopathies are:
- Vanishing white matter disease
- Megalencephalic leukoencephalopathy with subcortical cysts

Pelizaeus–Merzbacher Disease (PMD)

PMD is an x-linked leukodystrophy secondary to mutations in the proteolipid protein (PLP) gene, which presents in infancy or early childhood, with "wheeling" nystagmus, hypotonia, and impaired cognition. Hypotonia evolves into spasticity, the nystagmus disappears but cerebellar ataxia, choreoathetosis may appear, as well as optic atrophy. Death occurs in the second to third decade. A connatal form presenting in the first 3 months of life has a much more severe course, with laryngeal stridor, and early death. The clinical diagnosis is based on clinical signs and symptoms, diffuse T2 hyperintensity of the brain MRI, an x-linked inheritance pattern, and finding mutations of the PLP1 gene. Abnormalities of the PLP gene also cause a phenotypically different entity, spastic paraplegia type 2 (SPG 2), which presents at a later age. Treatment is symptomatic and supportive, aimed at preventing secondary complications with multidisciplinary surveillance. Although *PLP*1-related disorders are inherited in an x-linked manner, *de novo* mutations have been reported. Males with the PMD phenotype do not reproduce; males with the SPG2 phenotype may have children. All daughters of a male proband will be carriers; no sons will inherit the mutation. All sons of a female carrier are at a 50% risk of inheriting the mutation and having the disease; all daughters are at a 50% risk of being carriers. Carrier testing for at-risk relatives and prenatal testing for pregnancies at increased risk are possible in families in which the disease-causing *PLP*1 mutation has been identified.

Canavan Disease (CD)

In CD, macrocephaly begins in the first year of life, with failure to sit and marked hypotonia, which eventually evolves into spasticity. In CD, there is diffuse T2 hyperintensity of the white matter which on magnetic resonance spectroscopy shows markedly elevated NAA (n-acetylaspartic acid). Urine shows acetylaspartic aciduria. ASPA is the only gene associated with CD. Three common mutations account for

approximately 99% of the disease-causing alleles in Ashkenazi Jewish patients and approximately 50–55% of disease-causing alleles in non-Jewish patients. There is a later presenting rare juvenile form of CD. CD is inherited as an autosomal recessive. This disease is the next targeted disease for prevention by genetic screening of the population at risk, Ashkenazi Jews, following the decreasing incidence of Tay–Sachs disease because of genetic screening.

Alexander Disease (AD)

The classical presentation, the infantile form, affects 51% of patients with AD. It presents in the first 2 years of life with megalencephaly, frontal bossing, psychomotor deterioration, seizures, pyramidal signs, and hydrocephalus due to aqueductal stenosis. There is also a neonatal form, a juvenile form, onset 4–10 years, affects about 23%, and an adult form (about 24%) with wide variability of symptoms. Children with the infantile form survive from weeks to years; with the juvenile form, to the 20s and 30s. In AD, increased T2 hyperintensity predominates in the frontal lobes. Brain biopsy shows inclusion bodies (Rosenthal fibers) in astrocytes. *GFAP*, which encodes glial fibrillary acidic protein, is the only gene currently known to be associated with AD. Molecular genetic testing has eliminated the need for diagnostic brain biopsy. Treatment is symptomatic and supportive.

Vanishing White Matter Disease (Childhood Ataxia with Central Hypomyelination)

Vanishing white matter (VWM) is one of the most prevalent inherited childhood leukoencephalopathies, but this may affect people of all ages, including neonates and adults. It is a progressive disorder clinically dominated by cerebellar ataxia and in which minor stress conditions, such as fever or mild trauma, provoke major episodes of neurologic deterioration. Typical pathological findings include increasing white matter rarefaction and cystic degeneration, oligodendrocytosis with highly characteristic foamy oligodendrocytes, meager astrogliosis with dysmorphic astrocytes, and loss of oligodendrocytes by apoptosis. Vanishing white matter is caused by mutations in any of the genes encoding the five subunits of the eukaryotic translation initiation factor 2B (eIF2B), EIF2B1 through EIF2B5. eIF2B is an ubiquitously expressed protein complex that plays a crucial role in regulating the rate of protein synthesis. Vanishing white matter mutations reduce the activity of eIF2B and impair its function to couple protein synthesis to the cellular demands in basal conditions and during stress. Reduced eIF2B activity leads to sustained improper activation of the unfolded protein response, resulting in concomitant expression of proliferation, prosurvival, and proapoptotic downstream effectors. Consequently, VWM cells are constitutively predisposed and hyperreactive to stress. VWM genes are housekeeping genes, so it is surprising that the disease is primarily a leukoencephalopathy. The pathophysiology of selective glial vulnerability in VWM remains poorly understood.

Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC)

MLC is an autosomal recessive disease characterized by infantile-onset macrocephaly, often in combination with mild gross motor developmental delay and seizures, gradual onset of ataxia, spasticity, and sometimes extrapyramidal findings. Mental deterioration is late and mild. Some die in the second and third decades of life, others are alive in their forties.

Magnetic resonance imaging (MRI) shows diffusely abnormal and swollen cerebral white matter and subcortical cysts in the anterior temporal or frontoparietal areas. On follow-up, atrophy ensues. Approximately 80% of MLC patients have mutations in MLC1, the only gene associated with MLC. Sequence analysis detects mutations in approximately 60–70% of affected individuals. Two phenotypes can be distinguished among the non-MLC1 mutated MLC patients: a classical and a benign phenotype. Management utilizes antiepileptic drugs for seizures, physical therapy for motor dysfunction, and special education.

The differential diagnosis is essentially that of white matter diseases that present with a large head, namely, Canavan's disease (CD), due to aspartoacylase deficiency, and Alexander's disease. Both present in the first year of life and are inherited in an autosomal recessive fashion. Neuroimaging differentiates these from each other and from MLC.

POLG (DNA Polymerase Gamma) – Related Disorders

POLG-related disorders comprise a continuum of overlapping phenotypes that were clinically defined long before their molecular basis was known. Mitochondrial DNA is replicated by DNA polymerase gamma. Onset of the *POLG*-related disorders ranges from early childhood to late adulthood. Diagnostic criteria do not exist. Two POLG-related diseases that occur in early childhood with encephalopathy are Alpers–Huttenlocher syndrome (AHS) and childhood myocerebrohepatopathy spectrum (MCHS). Establishing the diagnosis requires identification

of two disease-causing *POLG* mutations, for each of these syndromes.

Alpers–Huttenlocher Syndrome (AHS)

AHS affects approximately one of every 51,000 and is characterized by childhood-onset progressive severe encephalopathy with intractable epilepsy and hepatic failure. As the illness progresses, neuroimaging shows gliosis initially in occipital areas and generalized brain atrophy. Molecular genetic testing consists of targeted mutation analysis and sequence analysis. The p.Ala467Thr mutation is the most common *POLG* mutation associated with AHS and is found in almost half of all affected individuals. Two other specific mutations tested are p.Trp748Ser and p.Gly848Ser. These are found in 70% of AHS patients. The rest require full-sequence analysis of both POLG alleles.

Depletion of mitochondrial DNA (mtDNA) develops in clinically affected tissues causing a mitochondrial oxidative-phosphorylation defect. The central nervous system regions affected in AHS are the same as those affected by Leigh syndrome but typically evolve in the reverse order. In AHS, the gliosis is most severe and occurs earliest in the cerebral cortex, followed by the cerebellum, basal ganglia, and brain stem.

Treatment is symptomatic and supportive. Valproic acid (Depakene®) and sodium divalproex (Depakote®) should be avoided. Because other anticonvulsants have also been implicated in accelerating liver deterioration, liver enzymes should be monitored every 2 to 4 weeks after introducing any new antiepileptic medications.

Childhood Myocerebrohepatopathy Spectrum (MCHS)

MCHS presents between the first few months of life up to about age 3 years with developmental delay or dementia, lactic acidosis, and a myopathy with failure to thrive. Other features of a mitochondrial disorder that may be present include liver failure, renal tubular acidosis, pancreatitis, cyclic vomiting, and hearing loss. Seizures are not present, at least early in the disease course.

Aicardi–Goutieres Syndrome (AGS)

AGS is an early-onset encephalopathy that results in severe mental and physical handicap. A subgroup of infants with AGS presents at birth with abnormal neurologic findings, hepatosplenomegaly, elevated liver enzymes, and thrombocytopenia, a picture similar to congenital infection. Otherwise, affected infants present at variable times after the first few days of life, frequently after a period of apparently normal development. Typically, they demonstrate the subacute onset of a severe encephalopathy characterized by extreme irritability, intermittent fevers, loss of skills, and slowing of head growth. Between 20% and 50% of affected individuals have generalized tonic-clonic or focal tonic seizures. As many as 40% have chilblain skin lesions on the fingers, toes, and ears.

The most important clinical laboratory tests are CSF examination for number of white cells and concentrations of interferon alpha and neopterin. These are most likely to be informative early in the disease and are frequently normal after the first few years of life. CSF IFN-α concentration is greater than 2 IU/mL (normal: <2 IU/mL). Lymphocytosis is defined as more than 5 lymphocytes/mm^3 CSF. Typical values range from 5 to 100 lymphocytes/mm^3. CSF concentrations of neopterin (and less so biopterin) are frequently raised in molecularly proven AGS. Levels of the neurotransmitter metabolites 5HIAA, HVA, and 5MTHF are normal.

The diagnosis can be confirmed in children with typical clinical findings, calcification of the basal ganglia and white matter on CT brain scan and leukodystrophic changes in brain MRI, and identifiable mutations in one of the four known causal mutations. Mutations in *TREX1*, *RNASEH2A*, *RNASEH2B*, and *RNASEH2C* are identified in approximately 80% of individuals.

Management includes chest physiotherapy and treatment of respiratory complications; attention to diet and feeding methods to assure adequate caloric intake and avoid aspiration; and seizure control. Infants should be monitored with repeat ophthalmologic examinations in the first few months for glaucoma. Older children should be followed for evidence of scoliosis, insulin-dependent diabetes mellitus, and hypothyroidism.

Most AGS is inherited in an autosomal recessive manner. Most individuals with AGS do not reproduce. Prenatal testing is possible for pregnancies at increased risk if the disease-causing mutation(s) in the family have been identified. Rarely, AGS can be caused by *de novo* autosomal dominant mutations in *TREX1*.

Neuronal Ceroid Lipofuscinoses (NCLs)

The neuronal ceroid-lipofuscinoses (NCLs) are the most common hereditary progressive neurodegenerative

diseases. The prevalence is about 1.5–9 per million population. The incidence ranges from 1.3 to 7 per 100,000 live births, depending on the country.

The NCLs are inherited lysosomal storage disorders presenting early with seizures, then intellectual and motor deterioration, progressive blindness, and death. They are to be differentiated from other disorders called in old terminology "the familial amaurotic idiocies," of which Tay–Sachs, Sandhoff's diseases (the GM2 gangliosidoses) are the prototype. NCLs and GM2 gangliosidoses commonly present in infancy or late infancy, with seizures and visual loss. However, the blindness in GM2 gangliosidoses is due to macular degeneration with a cherry red spot (cerebromacular degeneration) on opthalmoscopic examination, while in the NCL's, progressive blindness is due to retinitis pigmentosa (cerebroretinal degeneration).

Phenotypes have been characterized clinically by age of onset and order of appearance of the clinical features: infantile neuronal ceroid-lipofuscinosis (INCL, Santavuori), late-infantile (LINCL, Jansky–Bielschowsky), juvenile (JNCL, Batten–Spielmeyer–Vogt), adult (ANCL, Kuf's disease), and Northern epilepsy (NE, progressive epilepsy with intellectual disability). The clinical presentations of INCL, LINCL, and JNCL are discussed in the Chap. 39, "Lysosomal Storage Disorders" chapter by Ozand and Al-Essa. The differential diagnosis, genetics, diagnostic tests, and management are discussed here.

Differential Diagnosis

For INCL, Santavuori type (infantile onset):

Tay–Sachs and Sandhoff diseases, Leigh syndrome, Rett syndrome, the infantile peroxisomal disorders (infantile Rhefsum's, neonatal adrenoleukodystrophy), subacute presentations of non-ketotic hypoglycinemia, pyridoxine dependency, CSF glucose transporter deficiency (Devivo syndrome), Niemann–Pick disease types A and B. The distinguishing feature usually is lack of retinal degeneration in these disorders. The differential diagnoses are as follows:

For LINCL, Jansky–Bielschowsky type (late infantile onset):

The epileptic encephalopathies, particularly Severe Myoclonic Epilepsy of Infancy (Dravet syndrome) and Lennox-Gastaut syndrome, and other lysosomal storage disorders.

For JNCL, Batten–Spielmeyer–Vogt type (juvenile onset):

MELAS, MERRF, juvenile onset GM2 gangliosidoses.

The retinal degeneration of JNCL differs from classic retinitis pigmentosa in that in JCNL there is loss of central vision first, not peripheral, and rapidly progresses, with total blindness in 1–2 years.

Genetics

All are inherited as autosomal recessive.

For INCL, Santavuori type: Age of onset 6–24 months. Major gene involved is PPT1.
For LINCL: Classic Jansky–Bielshcowsky type: Onset 2–4 years, major gene is TPP1.
But, there are less common variants:
Finnish variant: Onset 4–7 years. Gene is CLN5.
Early juvenile variant: Onset 18 months to 8 years. Gene is CLN6.
Other variants: Onset 3–7.5 years. Genes are MFSD8, CLN8, CTSD, PPT1.
For JNCL: Batten–Spielmeyer–Vogt: Classic presentation, gene is CLN3.
Rarer variants: Genes are PPOT1, TPP1, CLN9.

Diagnosis

With a good pediatric hematopathologist, diagnosis can be made clinically by electron microscope analysis of lymphocytes in the buffy coat, achieved by centrifuging a sample of blood, which reveal curvilinear or fingerprint bodies or granular osmophilic deposits typical of NCL. Such storage material can also be seen by obtaining ganglion cells through rectal biopsy or conjunctival biopsy, although analyzable samples are technically difficult to obtain. Skin biopsies can also be sampled. White blood cells and cultured skin fibroblasts can be examined for three enzymes: PPT1 (palmitoyl-protein thioesterase 1), TPP-1 (tripeptidyl peptidase 1), and CTSD (cathepsin D). Molecular genetic testing utilizes targeted mutation analysis or sequence analysis.

Management

Treatment is symptomatic and supportive. Drugs used may be antiepileptics, anti-dystonia drugs such as trihexyphenidyl, benzodiazepines for spasticity, antidepressants, and antipsychotics. Phenytoin and carbamazepine need to be avoided because they may activate seizures and and increase rate of deterioration. Lamotrigine can exacerbate myoclonus and seizures, particularly in the late infantile form.

Mid-Childhood

Acute Encephalopathies

Infection-related encephalopathies
- Acute toxic encephalopathy
- Reye–Johnson syndrome
- Influenza-associated encephalopathy
  - Acute necrotizing encephalopathy
- ADEM
- AHLE
- Metabolic encephalopathies
  - Hepatic encephalopathy
  - Uremic encephalopathy
  - Hypertensive encephalopathy (PRES, posterior reversible encephalopathy syndrome)
  - Hypoglycemic encephalopathy

Infection-Related Encephalopathies

Acute Toxic Encephalopathy

Acute toxic encephalopathy results from bacterial toxins from a number of agents: *Bordetella pertussis*, *Shigella*, *Campylobacter jejunum*, *Salmonella*, *Bartonella henseke*. It presents with acute change in mental status, but is not due to infectious encephalitis or meningitis. The treatment is antibiotics directed at the infectious agents.

Reye–Johnson Syndrome

Reye–Johnson syndrome (See Chap. 217, "Hepatopathies and Reye Syndrome") presents 3–5 days after a viral infection, often influenza, as an acute change in mental status associated with hypoglycemia, hyperammonemia, fatty infiltration of the liver, and cerebral edema. Four clinical and EEG stages have been postulated in the past, with patients recovering if in Stage 1 or 2, equivocal in Stage 3, almost always progressing to death in Stage 4. The association of aspirin and Reye syndrome is now considered spurious, and the rise and fall in the incidence of Reye syndrome remains unexplained.

The biochemical explanation for Reye-like symptoms is a generalized disturbance in mitochondrial metabolism, eventually resulting in metabolic failure in the liver and other tissues. The etiology of "classical" Reye syndrome is unknown. Hypothetically, the syndrome may result from an unusual response to the preceding viral infection, which is determined by host genetic factors but can be modified by a variety of exogenous agents.

For the past decade or so, reported cases of Reye or Reye-like syndromes have usually had a biochemical explanation, usually the fatty acid oxidation disorders. The treatment of Reye syndrome was always supportive, with the therapeutic aim of reducing cerebral edema.

Influenza-Associated Encephalopathy

Influenza-associated encephalitis/encephalopathy is an uncommon but potentially more serious complication widely reported in Japanese populations, although cases from other East Asian countries, North America, and Europe have been described. Clinical manifestations are diverse, and typically involve febrile seizures and abnormal behaviors in mild cases, with rapid evolution through decreased consciousness to coma in severe forms. Influenza is also a known trigger for a number of rarely encountered, yet often serious, CNS diseases, including Reye–Johnson syndrome. In cases of serious disease, the prognosis is often poor, with outcomes including death or severe neurological sequelae.

Acute necrotizing Encephalopathy (ANE). First described by Mizuguchi et al., ANE occurs early after influenza A and H1N1 infection and presents with encephalopathy and seizures, no CSF pleocytosis, no elevated blood ammonia, and symmetrical multifocal brain lesions and hypoxia, intoxication, hemolytic uremic syndrome, metabolic and neurodegenerative disorders have been ruled out. Most cases occurred in children younger than 5 years of age of Asian origin. Sporadic cases have been reported in Europe and North America. Brain MRI using T2 weighted images, diffusion-weighted imaging (DWI), and apparent diffusion coefficient (ADC) maps show symmetrical lesions in the pons, thalami and geniculate bodies, with swelling. Pathology shows necrosis with petechiae in thalamus and tegmentum of the pons and myelin pallor in cerebellar and cerebral subcortical white matter.

Pathogenesis of IAE is not fully understood but may involve viral invasion of the CNS, proinflammatory cytokines, metabolic disorders, or genetic susceptibility. An autosomal dominant viral acute necrotizing encephalopathy (ANE) was recently found to have missense mutations in the gene Ran-binding 2 (RANBP2).

Acute Disseminated Encephalomyelomyelitis (ADEM)

Acute disseminated encephalomyelitis (ADEM) is a diffuse, monophasic demyelinating disease that follows either a viral infection or, rarely, a viral immunization. Symptoms typically develop a week or two after the antecedent infection and include headache, lethargy, and coma. The clinical course is rapid, and as many as 20% of those affected die; the remaining patients recover completely. ADEM

is discussed in detail, and AHLE briefly, by Tanuja Chitnis, ❯ Chap. 375, "Parainfectious and Autoimmune Disorders".

Acute Hemorrhagic Leukoencephalomyelitis (AHLE)

Acute hemorrhagic leukoencephalomyelitis of Weston Hurst is a rare fulminant disorder typically affecting young adults and children and is thought to be a hyperacute form of ADEM. AHLE often presents with abrupt onset of fever, neck stiffness, seizure, and/or focal neurologic signs several days following a viral illness or vaccination. The illness is preceded by a recent episode of upper respiratory infection, most often of unknown cause. The differential diagnosis considers a direct central nervous system infection or a toxic ingestion. Pathology shows lesions much more severe than those of ADEM and includes destruction of small blood vessels, disseminated necrosis of white and gray matter with acute hemorrhage, fibrin deposition, and abundant neutrophils. Scattered lymphocytes are seen in foci of demyelination. An autoimmune pathophysiology is likely, with immune cross-reactivity between myelin basic protein moieties and various infectious agent antigens. Although treatment is not well-established; some authors report that a combination of immunosuppressant medications and/or therapeutic plasma exchange may be of benefit. Prognosis is severe, with death in days to a week after symptom onset. Significant residuals remain in the few who survive.

Hepatic Encephalopathy (See chapter on ❯ Liver Failure). Specific neurologic features in *hepatic encephalopathy* are asterixis, and an EEG pattern of triphasic waves upon a slow background, although the latter is nonspecific and may be seen in other encephalopathies. The toxin most implicated is ammonia. The most important component of managing a child with hepatic encephalopathy is basic intensive care with regulation of fluid status, glucose, and electrolyte homeostasis. Specific management includes measures to reduce serum ammonia concentrations, and the prevention and prompt treatment of complications. Methods to reduce ammonia target various steps in its metabolism. This includes reducing its production in and absorption from the intestine and promoting its metabolism in the liver. Specific pediatric care issues, approaches to treatment of fulminant hepatic failure, the role of artificial liver support devices, and decision for liver transplantation are beyond the scope of this chapter.

Uremic Encephalopathy. In *uremic encephalopathy* (See chapter on ❯ Chronic Renal Failure), hypertension is often associated (see chapter on ❯ Hypertension in Children), and the syndrome of posterior reversible encephalopathy (PRES) is seen. Pavlakis, et al. assert that PRES is just a new name for hypertensive encephalopathy. Clinical presentation is usually with seizures, headache, visual disturbances including cortical blindness, and encephalopathy. PRES is a clinical-neuroradiological syndrome, with bilateral posterior parietal-occipital increased T2 and FLAIR signal intensities, which resolve over time. PRES has been reported with a number of different conditions in normotensive children – cancer chemotherapy, usually leukemia, systemic lupus erythematosus, measles vaccination, glomerulonephritis, vasculitis, immunosuppressive treatment, renal failure and eclampsia, but it is likely that a comorbid acute hypertensive episode has occurred. The rise in blood pressure is probably rapid, and may be brief, so that it may not have been clinically observed before the clinical/radiological picture emerges. Jones BV et al. postulate that children develop hypertensive encephalopathy at lower absolute pressures than adults owing to the relative "left shift" of their range of cerebral blood flow autoregulation. Neuroradiological perfusion techniques that were applied in their patients support vasodilatation, rather than vasoconstriction and edema, as the primary pathogenic event, with breakdown of blood-brain barrier, and extravasation of protein and fluid. Arterioles situated a short distance from the cortical surface are most affected, and sympathetic nervous activity affords protection from these effects. The posterior circulation has significantly less sympathetic innervation than the carotid circulation, which may explain why the majority of lesions in hypertensive encephalopathy are found in the vascular territory of the posterior circulation. The syndrome is reversible, if secondary complications, such as hemorrhage into the leukoencephalopathic areas, do not occur.

Hypoglycemic Encephalopathy. The multiple different causes of hypoglycemia in infants, children, and adolescents are discussed in the chapter on ❯ Hypoglycemia. Encephalopathic presentations of hypoglycemia vary in different ages. Neonates may be asymptomatic. Older children may show palpitations, perspiration, and pallor, with a feeling of weakness and hunger if hypoglycemia is rapid, which usually precede encephalopathic manifestations like disorientation, confusion, headache, inability to concentrate, somnolence, and seizures. If blood glucose levels dip to 10 mg/dL or less, coma ensues, with pupillary dilatation, bradycardia, hypotonia, and shallow breathing. The pathogenesis may involve energy depletion, accumulation of metabolites from nonglucose metabolism, and changes in levels of neurotransmitters. Pathologically, laminar necrosis of the cerebral cortex has long been described, the hippocampus being particularly sensitive.

Recent studies have also reported extensive lesions in cerebral white matter and reversible lesions in the splenium of the corpus callosum (Gallucci M), thought to be due to cytotoxic edema. The management requires prompt glucose replacement, whatever the etiology, with thiamine supplementation. In malnourished patients, niacin, to prevent pellagra, should also be given.

Subacute Encephalopathies

Two parasitic diseases are worth discussing here, since their presentations are essentially with encephalopathy.

Cerebral malaria
Trypanosomiasis (African sleeping sickness)
Epileptic encephalopathies
- Electrical status epilepticus in slow-wave sleep (ESESS)
- Landau–Kleffner syndrome
- Continuous spike waves in slow-wave sleep (CSWS)

Cerebral Malaria (See chapter on Malaria)

Cerebral malaria is a rapidly progressive encephalopathy with a 20% mortality in the pediatric population. This means 80% of children survive, but often with neurological residuals. Although rare relative to the total number of infections, cerebral malaria significantly contributes to approximately 1,000,000 deaths per year and disproportionately affects children less than 6 years of age in sub-Saharan Africa.

A cardinal feature of the pathology is the massing of red cells containing *Plasmodium falciparum* toward the end of its life cycle within the cerebral capillaries. Adhesion of these parasitised red cells to endothelium, an event which may initiate cerebral malaria, is being studied at the molecular level. Basic pathogenesis in mouse models and human studies focus on cytokines, inflammation, cytoadherence, and endothelial activation. Coagulation is variably important, but it is most likely the end point of a series of processes.

One model of pathogenesis is cytokine storm and TNF activation. Lessons from the mouse model and in vitro tissue culture have definitely demonstrated that the endothelium must be stimulated via inflammatory/activation agents before the ligands on the surface are sufficient for sequestration to occur. The correlation of retinal and cerebral pathology suggests that those pediatric patients with features of malarial retinopathy who survive must have had similar changes in the brain including ring hemorrhages. However, anti-TNF agents applied when patients are in coma have not proven effective. They probably have to be given before the TNF cascade begins.

Low levels of nitric oxide, and its precursor arginine, have been found, in cerebral malaria, suggesting that less localized nitric oxide is available to provide for vascular dilatation, which subsequently leads to endothelial activation, upregulation of proadherent molecules, and damage of alternative pathways, including activation of superoxide dismutase. This suggests the possibility of L-arginine as a treatment.

Clinical presentation is a diffuse, febrile encephalopathy, with nonfocal signs, in a *P. falciparum* endemic area (or in travelers who have recently been in such an area). The incubation period is usually 10–18 days. The fever may be intermittent, irregular, or continuous. Generalized seizures occur in 50%, nuchal rigidity rarely occurs, and bilateral pyramidal tract signs when severe, which may proceed to decorticate and decerebrate posturing. Most important is examination of the fundus. Ophthalmoscopic examination to evaluate the retinas in comatose children greatly increases the accuracy of diagnosis of cerebral malaria. It is also a measure of prognosis in patients with evidence of retinopathy with or without papilledema and is a tool for stratifying or triaging patients into treatment or further diagnostic workup. The pediatric retinal findings are peripheral whitening, orange and white vessels, hemorrhages, and papilledema.

Regarding treatment, chloroquin is used for non-*falciparum* malaria. But there is now widespread resistance in endemic areas. All cases *of falciparum* malaria must be admitted for therapy owing to the high mortality of the disease. Falciparum malaria is treated with atovaquone-proguanil (Malarone) or quinine sulfate plus doxycycline, tetracycline, or clindamycin. Cerebral malaria is treated with intravenous quinidine. Since 1991, quinidine gluconate has been the only parenterally administered antimalarial drug available in the United States. A loading dose of 6.25 mg base/kg (10 mg salt/kg) of quinidine gluconate is infused intravenously over 1–2 h, followed by a continuous infusion of 0.0125 mg base/kg/min (0.02 mg salt/kg/min). At least 24 h of quinidine infusion is recommended. Once the patient can take oral medication, and the parasite density is less than 10%, the treatment course is completed with oral quinine at a dosage of 10 mg salt/kg every 8 h. The combined treatment course of quinidine/quinine is 7 days, if the disease was acquired in Southeast Asia, and for 3 days if from South America and Africa. The availability of artemisinin combination therapy in adults across most of Africa produces more

rapid cures with no definitive drug failures at present. However, the resistance and delayed clearance patterns seen in Southeast Asia and Africa are worrying for emerging resistance. Clinical trials with artemisinin compounds have shown decreased mortality in adults with severe disease after 48 h of treatment, compared to quinine. No such studies in pediatric patients have been published and almost all mortality in children with cerebral malaria occurs within the first 48 h. Regarding prevention, the RTS,S vaccine trials ongoing in multiple African nations are showing positive results with decreases in both disease incidence and severe disease.

African Trypanosomiasis (Sleeping Sickness)

Sleeping sickness is caused by two organisms: in East Africa, *Trypanosoma brucei rhodesiense,* which causes the more severe form, and in West Africa, *Trypanosomoa brucei gambiense.* They are transmitted by tsetse flies, who feed primarily on wild animals, causing a painful, red swelling at the site of the bite. The infection then spreads through the blood circulation, causing episodes of fever, headache, sweating, and swelling of the lymph nodes. When it reaches the brain, behavioral changes such as fear and mood swings occur, followed by headache, fever, delirium, and asthenia. Patients experience drowsiness during the day, but nighttime insomnia. Symptoms may include anxiety, headache, mood changes, and an uncontrollable urge to sleep. West African trypanosomiasis is primarily a problem in rural populations, and tourists rarely become infected with *T. b. gambiense.* East African trypanosomiasis is an occupational hazard for persons such as game wardens who work in areas where infected wild animals and vectors are present, and in occasional tourists who visit game parks.

Patients without CNS involvement are treated with suramin. The protocol is available through the Centers for Disease Control (CDC). Patients who have positive lumbar punctures should be treated with melarsoprol, a trivalent arsenic compound which, however, has significant toxicity. It can cause hepatotoxicity, cardiac arrhythmias, albuminuria, vomiting, abdominal pain, peripheral neuropathy, and paraplegia. Arsenic encephalopathy occurs in as many as 10% of treated patients and is frequently fatal. The 5–10% risk of mortality from the therapy is outweighed by the risk of the disease. The mortality of CNS African trypanosomiasis is 100%. As is true for suramin, melarsoprol is only available in the United States through the CDC.

Other regimens being explored include a combination chemotherapy, eflornithine alongside nifurtimox, to decrease the time frame and overall dosing of eflornithine, in order to reduce the risk of emerging drug resistance. A nitroheterocycle, fexinidazole, whose trypanocidal activity was first shown nearly 30 years ago, has entered clinical trials. The World Health Organization has declared a campaign to eradicate human African trypanosomiasis.

Epileptic Encephalopathies

Electrical status epilepticus in slow-wave sleep (ESESS)
Landau–Kleffner syndrome (LKS)
Continuous Spike Wave in Sleep (CSWS)

ESESS is an EEG finding and is defined as epileptiform discharges occurring in 80–85% of nocturnal slow-wave sleep. The terms continuous spike wave in slow-wave sleep (CSWS) and Landau–Kleffner syndrome (LKS) describe the clinical epileptic syndromes, among others, that can be seen with ESESS.

LKS is a disorder of uncertain etiology, presenting usually in early childhood, with subacute loss of both comprehension and production of language over weeks to months, where seizures occur concurrently or after language loss begins, and a behavioral change occurs with hyperactive, impulsive, and inattentive behavior. Seizures are usually mild and easy to control, but suppression of seizures does not necessarily herald recovery of language function. The initial language loss often appears as an auditory verbal agnosia, but other childhood aphasia syndromes may occur. Although anecdotal papers have reported remarkable reversal of seizures and language loss with IV or oral steroids, IV IgG, high-dose diazepam, ketogenic diet, or multiple subpial transaction, no controlled studies have been done, and many children with LKS have long-standing language and learning disabilities lasting into adulthood. The reacquisition of oral language is aided by use of visual systems, such as signing.

Although there is an overlap between LKS and CSWS, children with CSWS present with a more global regression, have more problematic epilepsy, and have EEG foci located predominantly in frontotemporal or frontocentral regions. In contrast, children with LKS present with language, not cognitive, loss, have fewer seizures, and the EEG foci are said to be predominantly in the posterotemporal regions. Reports from Japan tout high-dose valproic acid or a combination of valproic acid and ethosuximide as causing remission of CSWS in 2/3 of their patients. Other reports from Europe report levetiracetam as being the most effective AED, causing remission in 40% of patients. Most reports agree that early age of onset and longer duration of ESESS in CSWS bode for poor prognosis.

Chronic Encephalopathies

Adrenoleukodystrophy
Niemann–Pick Type C (see Ozand and Al-Essa chapter on Lysosomal Storage Diseases)
Juvenile Huntington's disease

Adrenoleukodsystrophy (ALD)

ALD is a disorder where a defective enzyme, lignoceroyl-coenzyme A interrupts the normal β-oxidation of very long chain fatty acids (VLCFAs) in the peroxisomes, resulting in the accumulation of the C-26 and above VLCFAs, a main component of myelin. Excess VLCFAs stimulate adjacent astrocytes and macrophages, which initiate a tumor necrosis factor cytokine cascade which results in demyelination. ALD is an x-linked disorder, the gene *ABCD1* being mapped to Xq28. In neuroimaging studies, increased T2 and FLAIR intensity is primarily in bilateral occipito-parietal areas.

Although there is a neonatal form and an adult form, adrenomyeloneuropathy, which presents as a progressive spastic diplegia, the most common childhood presentation is between the ages of 4 and 8 years. Initial presentations are a decline in school work and ADHD-like symptoms, then early visual agnosia, cortical blindness, progressive dementia, upper motor neuron dysfunction, with adrenal insufficiency, which often predates neurological symptoms and may manifest over time as progressive darkening of the skin and requires ACTH stimulation tests for confirmation.

There is another phenotype, Addison's disease only, presenting with adrenal insufficiency usually by age 7–8 years, with no neurologic signs, but who, in about 10%, later in life usually develop adrenomyeloneuropathy. About 20% of female carriers develop mild neurological signs later in life, usually after age 35.

Diagnosis is made by the typical history, clinical neurological signs, the brain MRI, and elevated serum levels of VLCFAs. Molecular genetic testing of *ABCD1*, the only gene known to be associated with X-ALD, is clinically available.

Differential diagnosis includes other leukodystrophies like metachromatic and globoid cell leukodystrophies, other childhood dementing disorders such as NCL, the juvenile or Batten–Spielmeyer–Vogt presentation, and subacute sclerosing panencephalitis (SSPE).

Management includes replacement steroid therapy for the adrenal insufficiency, psychological, supportive, and educational support. Bone marrow transplantation is an option available for boys with the typical childhood form, who have brain MRI abnormalities, but with still preserved cognitive function (performance I.Q.>80) and a normal neurological examination. An investigational therapy is Lorenzo's oil, a 4:1 mixture of the triglycerides of oleic and erucic acid, prepared from olive oil and rapeseed oil, given to presymptomatic boys treated with Lorenzo's oil who had reduction of C26, and resulted in reduced risk of later brain MRI abnormalities. However, some still developed ALD. Lorenzo's oil remains an investigational therapy.

Juvenile Huntington's Disease

The prevalence of Huntington's disease is 3–7/100,000 in people of western European ancestry. It is much less in African blacks, Chinese, and Japanese. The highest prevalence in the world is probably in the Lake Maracaibo region of Venezuela. It is an autosomal dominant progressive degenerative disease that usually presents in midlife with chorea and slowly progressive dementia. It is due to an expansion of 36 or more CAG trinucleotide triple repeats in the Huntington gene HTT (See Movement Disorders chapter, by Yasser Awaad). In any triple repeat disease, there is the phenomenon of anticipation; that is, the disease expresses itself at younger and younger ages in subsequent generations. *Juvenile Huntington's Disease* is defined as presenting before the age of 20 years and occurs primarily through paternal transmission of HTT. In adolescents, it presents with rigidity rather than chorea, and with mental status changes such as attention and concentration problems, cognitive slowness, and impaired executive functioning, so it should be in the differential diagnosis of decrease in school performance. There may be depression, personality changes, intermittent explosiveness, and even psychosis. Seizures occur in up to 50% of children presenting before the age of 10 years. The pathology shows selective degeneration of neurons in the corpus striatum – the caudate and putamen. Brain MRI can show striatal atrophy 10 years before clinical symptoms appear. Treatment is supportive and symptomatic. Antiparkinsonian agents containing L-DOPA aimed at decreasing rigidity risk increasing chorea. Haloperidol, tetrabenazine, or benzodiazepines may suppress chorea. Psychiatric disorders can be treated with appropriate psychotropic medications. Genetic counseling is mandatory for at-risk, presymptomatic children under age 18 years. The consensus at present is not to gene-test these children because of the psychosocial, legal, and ethical implications of genetic testing of children and adolescents for a disease that has no definitive treatment.

Late Childhood – Adolescence

Acute Encephalopathies

Acute confusional migraine
Immune-mediated encephalopathies
- Hashimoto's encephalopathy
- Rassmussen's encephalitis

Other immune mediated epileptic encephalopathies
- Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
- Devastating epileptic encephalopathy in school-aged children (DESC)
- New onset refractory status epilepticus (NORSE)

Acute Confusional Migraine (ACM)

Gascon and Barlow first described pubertal and early adolescent children who presented to emergency rooms with the acute onset of confusion, disorientation, and short-term memory loss lasting hours. If an EEG was done during this period, it showed high-voltage diffuse delta slowing, most prominent posteriorly. After an overnight sleep, they recovered and returned to normal. In retrospect, the presence of mild headache was elicited. Some neurologists consider these episodes similar to, if not identical with, the syndrome of transient global amnesia in adults. The differential diagnosis includes nonconvulsive status epilepticus, drug ingestion, concussion, encephalitis, or acute posychosis. Brain MRIs and CSF studies are normal. A history of migraine headaches preceding the confusional episode can be obtained, or subsequently, conventional migraine with or without aura develops (See chapter on ❯ Headache by Mack and Matarese). No treatment is necessary, since the episodes resolve spontaneously after sleep (See ❯ *Table 366.3*).

Immune-Mediated Encephalopathies

Hashimoto's encephalopathy
Rassmussen's encephalitis

Hashimoto's Encephalopathy

Hashimoto's encephalopathy is of presumed autoimmune origin and is characterized by high titers of antithyroid peroxidase antibodies. It is more common in women than in men and has been reported in pediatric, adult, and elderly populations throughout the world.

The clinical presentation may be relapsing and remitting and include seizures, stroke-like episodes, cognitive decline, neuropsychiatric symptoms, and myoclonus. Thyroid function tests are normal. Diagnosis is made first, by excluding other toxic, metabolic, and infectious causes of encephalopathy, and secondly, finding elevated titers of antithryoid antibodies. Pathological findings can suggest an inflammatory process, but features of a severe vasculitis are absent. It may be that Hashimoto's encephalopathy will be subsumed into a group of nonvasculitic autoimmune inflammatory meningoencephalopathies, such as paraneoplastic limbic encephalitis, which usually occurs in women with ovarian teratomas, who have elevated NMDA receptor antibodies. Treatment with corticosteroids is almost always successful, although relapse may occur if treatment is abruptly terminated. Intravenous immune-globulin and plasma exchange may also be effective.

Rassmussen's Encephalitis

This is a rare, disabling disease of childhood, presenting first as epilepsia partialis continua, may progress to refractory focal seizures and focal status epilepticus, hemiplegia, and dementia. Neuroimaging studies show progressive hemiatrophy of the brain. Anti Glu-R3 antibodies (against the glutamate receptor subunit 3) have been reported in some, but not all, patients. The pathology shows inflammation, with cytotoxic T cell reactions against neurons. Immunotherapy using corticosteroids, IV IgG, tacrolimus, and intraventricular alpha interferon, and plasmapheresis have temporarily arrested the course of the disease, all of which supports an autoimmune pathogenesis. Eventually, however, the patients are candidates for hemispherectomy for refractory seizures.

Other Immune-Mediated Epileptic Encephalopathies

Acute encephalitis with refractory, repetitive partial seizures (AERRPS)
Devastating epileptic encephalopathy in school-aged children (DESC)
New onset refractory status epilepticus (NORSE)

What these epileptic encephalopathies with different acronyms all have in common is an acute or subacute onset of status epilepticus after a febrile illness, with no evidence of encephalitic infection, followed by

drug-resistant partial epilepsy, reported from Japan, France, the United Kingdom, and Singapore. They appear like a more acute, rapidly evolving Rassmussen's encephalitis, but not limited to a hemisyndrome. AERRPS was defined as a prolonged acute phase of more than 2 weeks, partial seizures frequently evolving into convulsive status, drug resistance, with viral encephalitis and metabolic disorders excluded. DESC was described as status epilepticus and fever at onset, later occurrence of drug-resistant epilepsy and neuropsychological deficits. Response to steroid treatment in DESC patients was unsuccessful. Specchio et al. described eight cases which overlapped with AERRPS and DESC. In two AERRPS cases, antibodies against Glu ε2 were found. In Specchio's eight cases, two had anti-GAD (glutamic acid decarboxylase), one had a CL (anti-cardiolipin) and anti-B2-GPI (anti-beta 2 glycoproteinI autoantibody), and one had ASMA (anti smooth muscle) auto-antibodies. Only one patient recovered; the rest had chronic epilepsy. Response to steroid treatment in DESC patients was unsuccessful.

Subacute Encephalopathies

Non-convulsive status epilepticus (NCSE)
- Absence status
- Psychomotor status (complex partial status epilepticus)
- Comatose patients

Nonconvulsive status epilepticus (NCSE) is defined as a state of altered mental status that can vary from confusion to obtundation to coma for at least 30 min, where an EEG records continuous or frequent electrographic seizures. It constitutes about 25% of all cases of status epilepticus, 8% in subarachnoid hemorrhage, and 8–10% in coma. In *absence status epilepticus*, the child may constantly blink the eyes or may stare blankly, and the EEG shows continuous three cycles per second spike-wave complexes. *In psychomotor status, also called complex partial status epilepticus,* in addition to an altered mental status, there may be automatisms. The EEG shows repetitive high-voltage theta waves in temporal areas. The diagnosis is verified by return to a normal state of consciousness concomitant with suppression of the EEG discharges by intravenous AEDs, usually diazepam or lorazepam. Both of these forms of NCSE present in a patient who is ambulatory, and where the differential diagnosis includes acute confusional migraine, drug ingestion, or psychosis. For primary generalized absences, if benzodiazepines do not stop the status, intravenous valproate (Depacon) is most appropriate. For psychomotor status, if benzodiazepines do not stop it, intravenous phenobarbital or phenytoin (or IM fosphenytoin) would be appropriate. General anesthesia with agents like short-acting barbiturates, propofol, or ketamine, which are options in refractory convulsive status epilepticus (CSE), are not usually necessary in NCSE.

Then there is the critically ill patient, where it occurs in 8–10% of patients in coma. There is a bimodal distribution of NCSE in critically ill patients, affecting children (age <1 year) and the elderly. It is commonly detected in an intensive care unit, after a patient has been hospitalized for overt CSE. After successful suppression of clinically observed seizures, the patient fails to wake up and this is not accounted for by medication-induced drowsiness. The estimated incidence is 15–40% after CSE. It may also occur in any patient who fails to awaken after any acute brain illness, whether an acute stroke, subarachnoid hemorrhage (incidence 8%), head injury, acute encephalitis, hypoxic-ischemic encephalopathy, or postoperatively, for example, after surgery for correction of congenital cardiac anomalies. In this setting, NCSE is diagnosed by a high index of suspicion and by continuous EEG monitoring.

The presence of NCSE is a risk for clinical deterioration and poor prognosis, independent of the original acute brain insult. Not enough studies have been done yet to determine whether early recognition and prompt suppression of electrographic seizures significantly improves outcome.

Chronic Encephalopathies

Slow virus diseases
- Subacute sclerosing panencephalitis (SSPE)
- HIV encephalopathy (See chapter on Human Immunodeficiency Virus)
- Progressive multifocal leukoencephalopathy (PMFL)

Progressive genetic encephalopathies
- Wilson's disease (see Movement Disorder chapter, Yasser Awaad)
- Juvenile Huntington's disease (See previous section in this chapter)
- Neurodegeneration with brain iron deposition (PANK2)
  - Formerly called Hallervorden–Spatz disease
- Progressive myoclonic encephalopathies
  - Unverricht
  - Lafora
  - MERRF (See previous section in this chapter)

Slow Virus Diseases

Subacute Sclerosing Panencepalitis (SSPE)
Human immunodeficiency virus (AIDS encephalopathy)
See chapter on Human Immunodeficiency Virus
Progressive multifocal leukoencephalopathy

What these all have in common is the persistence over years of a virus, in mutated form, after an initial infection, either from long known common viruses like measles, or viruses that were previously unknown but emerged in the late twentieth century, human immunodeficiency virus and papova virus. Recovery from the initial systemic infection occurs, but after a prolonged latent period, symptoms of brain dysfunction appear, and slowly progress.

Subacute Sclerosing Panencephalitis (SSPE)

SSPE is a progressive degenerative encephalopathy due to persistence in the CNS of a mutated form of the measles virus (MV). (See chapter on Measles) It is now extremely rare in the developed world, where countries have reached or exceeded 80% of the population being immunized with the measles vaccine, but still endemic in the developing world where that standard of immunization has not been reached. The viral genome consists of biased hypermutations affecting principally the matrix (M) gene. There are high CSF titers of antibodies to measles virus, with infiltrations of B and T cells into the CNS. The pathogenesis starts with measles infection at a critical stage of maturation of the CNS and immune system, usually before the age of 2 years. The infection is not contained, despite what seems like initial recovery from childhood systemic measles. There is no major histocompatibility complex in neurons. The mutations of the MV genome affect viral epitopes that are critical for recognition of infected cells. Therefore, there is a defective cytotoxic lymphocyte response and lack of viral clearance. The mutated virus lies dormant in the CNS for years until it becomes activated. What triggers the activation is not known. The pathology reveals nuclear inclusions in neurons that contain the viral antigens. Neurofibrillary tangles can be seen in neurons and oligodendrocytes. Perivascular cells are predominantly CD4+ T cells, with B cells seen more in parenchymal inflammatory infiltrates.

The typical clinical presentation usually starts with cognitive and behavioral deterioration, often mimicking the symptoms of attention deficit hyperactivity disorder, with decline in school performance, over weeks to months. Periodic myoclonus then reveals itself as sudden falls or uncontrolled periodic movements, which in the beginning may be as subtle as eye blinks or slight postural changes, but then proceed to falls. If not treated at this stage, motor and mental deterioration inexorably proceed, until a neurovegetative state or death. The stages of deterioration were first proposed by Jabbour and modified by Gascon et al. (See *Table 366.4*.)

The typical presentation discussed above can occur anywhere from mid-childhood through adolescence, and presents subacutely, followed by a chronic, progressive course.

Atypical presentations have been reported in infancy as an encephalopathy without the typical myoclonus, in childhood as an acute fulminant encephalopathy, as an ADEM presentation, and in adulthood.

The following drugs have been used in anecdotal reports: amantadine, cimetidine, corticosteroids, intravenous immunoglobulin, interferon beta, inosiplex, alpha interferon, and ribavarin. In the only published randomized, controlled treatment study, which compared oral inosiplex to combination inosiplex and intraventricular alpha interferon, carried out by the International Consortium on SSPE in Ankara, Mumbai, and Manila, there was no statistically significant difference between the two treatments. However, there was a satisfactory treatment outcome, meaning improvement or stabilization, in 34% of those treated with inosiplex alone, and 35% in those who had combined treatment. These are higher than the spontaneous remission rates of 5–10% reported in the literature. The conclusion is that neither treatment is

Table 366.4
SSPE stages

IA	Behavioral, cognitive, personality changes
IB	Myoclonic spasms – aperiodic, focal, subtle, infrequent
IIA	Myoclonic spasms – periodic, generalized, synchronous, frequent. EEG relatively normal background activity, but with PSWCs
IIB	Apraxias, agnosias, speech/language, spasticity, ataxia. Ambulatory with assistance
IIIA	Sits independently, may stand, no walking, no ADLs. Speaks less, visual difficulties. Spasms frequent, multifocal
IIIB	Bedridden, no spontaneous speech, poor comprehension, may be blind, dysphagia, chorea-ballismus-athetosis. EEG delta background; PSWCs obscured
IV	No myoclonic spasms, neurovegetative state. EEG background attenuation, no PSWCs

PSWC's periodic slow-wave complexes, ADLs activities of daily living (Modified from Gascon et al. 1993)

Table 366.5
CSF IgG synthesis index

Total intrathecal IgG synthesis (mg/day) = [(IgGCSF – IgGserum/615)–(AlbCSF-Albserum/291) × (IgGserum/Albserum)(0.43)] × 5

Concentrations in mg/dL, 615 and 291 are the average normal serum/CSF ratios for IgG and albumin, 0.43 the molecular mass ratio of albumin to IgG, and 5 the average daily production of CSF in deciliters (From Conrad AJ et al. 1994)

statistically superior to the other, but treatment is superior to no treatment. The critical laboratory value to follow for treatment response is the CSF IgG Synthesis Index, the best indication of immune response activation. (See *Table 366.5*.)

At this writing, although inosiplex has been available throughout the world, it has recently been approved by the FDA for restricted use in the USA. Clinical trials using ribavarin are being carried out in Japan and the Philippines.

Progressive Multifocal Leukoencephalopathy (PMFL)

PMFL is a rare slow virus infection of the brain caused by the JC virus, a common papova virus often acquired during childhood. The virus remains dormant unless certain circumstances, such as an immunosuppressive state, foster viral reactivation. Once reactivated, the virus may infect the brain and cause PML. It is a demyelinating disease caused by direct infection of oligodendrocytes by the JC virus.

It was first recognized through post-mortem examination in patients with severe illnesses, usually lymphomas or Hodgkins disease, who were immuno-compromised. Later, it was recognized as one of the superinfections in acquired immunodeficiency syndrome (AIDS) due to human immunodeficiency virus (HIV). With the advent of antiretroviral therapy, all the superinfections in AIDS have been decreasing in incidence. With the advent of neuroimaging, PML can be recognized in life through brain MRI. Recently, it has been recognized to occur in association with a drug used to treat multiple sclerosis, natalizumab, if there are multiple treatments.

The symptoms of PML may begin gradually, usually worsen rapidly, and vary depending on which part of the brain is infected. These may include difficulty with walking and other movements, decline in mental function, speech and visual difficulties. Rarely, headaches and seizures occur. Symptoms of PML are similar to the presenting symptoms of multiple sclerosis. A diagnosis of PML is made on the basis of results from magnetic resonance imaging of the brain, which shows T2-hyperintense, small to large, sometimes confluent lesions in the white matter, sparing the subcortical U-fibers. The diagnosis is confirmed by polymerase chain reaction (PCR) for JC virus in cerebrospinal fluid. The treatment is either cessation of immunosuppressive therapy in cancer patients or successful restoration of the immune system in HIV infection.

Pantothenate Kinase-Associated Neurodegeneration (PKAN)

Also called neurodegeneration with brain iron deposition (NBIA)
Formerly called Hallervorden–Spatz disease
(See also, Movement Disorders chapter by Yasser Awaad)

PKAN usually presents with dystonia, rigidity, and retinitis pigmentosa before age 10 years, and is due to progressive deposition of iron in astrocytes, microglia, and neurons of the globus pallidus. About one-fourth of patients present in adolescence, with slower progression, psychiatric symptoms, and intellectual decline.

The diagnosis is made by noting a progressive dystonia coupled with the "eye of the tiger" sign on brain MRI, a small region of hyperintensity surrounded by a rim of hypointensity in the globus pallidus, which, on coronal or transverse T2-weighted images, appears like a tiger's eye. Sequence analysis detects the mutations in PANK2, the only gene abnormality found in this disease.

Iron chelation therapy has not proven effective. The parkinsonian signs may respond to levodopa and bromocriptine, but not to anticholinergics. Botulinus toxin injections may help muscle rigidity or spasticity, as well as oral or intrathecal baclofen with a baclofen pump. Surgical approaches are ablative pallidotomy or deep brain stimulation.

Genetic counseling for the family is the same as for any autosomal recessive disease. Carrier testing for relatives at risk and prenatal testing for pregnancies at risk are possible if the disease-causing mutations have already been identified in an affected family member. The prognosis is dire, with death by age 20 years in about half of patients.

Progressive Myoclonic Epileptic Encephalopathies

Unverricht–Lundborg disease
Lafora disease

Unverricht–Lundborg Disease

Unverricht–Lundborg disease (EPM1) is an autosomal recessive neurodegenerative disease with onset from age

6–15 years, stimulus-sensitive myoclonus, action myoclonus, myoclonic seizures, and generalized convulsions. Some years after the onset, ataxia, incoordination, intentional tremor, and dysarthria develop. Individuals with EPM1 are initially mentally alert but show emotional lability, then mild cognitive decline over time. EPM1 results from defective function of cystatin B, a cysteine protease inhibitor, due to mutations in the *CSTB* gene. Brain MRI is normal. EEG shows generalized spike and polyspike/slow-wave discharges upon a slow background, and photic activation. The diagnosis can be confirmed by identifying disease-causing mutations in *CSTB* through targeted mutation analysis or sequence analysis. The differential diagnosis includes myoclonic epilepsy with ragged red fibers (MERRF) (See previous section on ❯ MERRF in this chapter), neuronal ceroid-lipofuscinosis (Kufs type), and Lafora disease. The drug of choice is valproic acid, to which clonazepam can be added. High-dose piracetam suppresses the myoclonus. Levetiracetam can suppress myoclonus and myoclonic seizures. Sodium channel blockers (carbamazepine, oxcarbazepine), GABAergic drugs (tiagabine, vigabatrin), and gabapentin and pregabalin may aggravate myoclonus and myoclonic seizures. Phenytoin aggravates neurologic symptoms and can accelerate cerebellar degeneration.

Lafora Disease

Lafora disease (LD) is a progressive degenerative disease which begins in adolescents between 12 and 17 years with symmetrical, multifocal, or generalized myoclonus and/or generalized tonic-clonic seizures. Emotional disturbance and confusion are common soon after seizures begin and are followed by dementia. Dysarthria and ataxia appear early; spasticity late. Death results a decade later from status epilepticus or complications of nervous system degeneration.

Diagnosis is usually based on the history, clinical course, and detection of mutations in the genes known to be associated with LD: *EPM2A* or *NHLRC1(EPM2B)*. Skin biopsy to detect pathognomonic Lafora bodies is sometimes necessary to confirm the diagnosis.

Of the antiepileptic drugs, phenytoin, and possibly lamotrigine, carbamazepine, and oxcarbazepine exacerbate seizures. Piracetam has been reported to be particularly effective, but is not available in the USA. Levetiracetam is the closest related drug. Treatment is otherwise supportive and aimed at preventing complications.

LD is inherited through autosomal recessive transmission. Carriers (heterozygotes) are asymptomatic. DNA testing for at-risk relatives and prenatal diagnosis for at-risk pregnancies are possible if the disease-causing mutations in the family are known.

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367 Ataxias

S. H. Subramony

Ataxia: Definition

Ataxia refers to a syndrome of neurological dysfunction characterized by problems with balance and poor coordination of movements. Typically, it results from pathology in the cerebellum and its connecting pathways. It leads to difficulties with gait and stance, poor dexterity of limb movements, often a dysarthric speech and changes in eye movements that can produce visual symptoms such as blurry vision or a sense of oscillation of the environment called oscillopsia. Occasionally, a similar poor coordination of limb movements and imbalance can result from lesions that affect sensory input to the central nervous system, especially proprioceptive input. This is called sensory ataxia. Patients with cerebellar ataxia present with gait and balance in the absence of any demonstrable muscle weakness. Tasks requiring fine coordination such as writing, handling tools and utensils become difficult, and in the case of lower limbs, activities like biking and skating can suffer before regular walking becomes abnormal. Speech becomes slurred and appears to have abrupt changes in pitch and volume.

Neurological examination of patients with cerebellar ataxia reveals many abnormalities. Gaze-evoked nystagmus is usually seen and primary position nystagmus can also occur. For example, downbeat nystagmus in primary position is considered to be a pathognomonic sign of a lesion at the cranio-vertebral junction. Visual pursuit is abnormal and becomes jerky because pursuit of visual objects is achieved using small saccades (saccadic pursuit). Sacccades (quick, targeted eye movements) usually have normal speed with cerebellar lesions but are not accurate; they can over- or undershoot the target with subsequent corrective saccades to cancel the error (hypermetric and hypometric saccades). The dysarthria of cerebellar disease is characterized by unnecessary changes in pitch and volume and wrong emphasis on various syllables ("scanning dysarthria"). Limb motility and posture can be disturbed in several ways. There can be an action tremor that appears when a limb is maintained in sustained posture such as when the fingers are pointed at each other with elbows up. This type of tremor becomes even more overt when the limbs are moved in a purposeful, target-oriented fashion such as touching the examiner's finger and patient's nose repeatedly (finger to nose test) or the heel is slid along the shin from the knee to the ankle (heel to shin test). The oscillation of limbs in these situations is a form of kinetic tremor. A tremor of the head and trunk can occur (titubation). Also, fast movements that require accuracy result in either over- or under-reaching the target (hypermetric or hypometric movements). This can be shown by the finger chase test in which the patient is asked to touch the examiner's finger tip again and again as the latter is moved to a new location in a rapid manner. Multi-jointed movements become decomposed; the rapid pronation and supination of the forearm over the thigh is an example (dysdiadochokinesis). With increasing cerebellar dysfunction, patients have increasing sway of the body when placed in the feet together position of stance (such maneuvers as tandem stance and one foot stance become abnormal even earlier, but may not be specific). Eventually, patients tend to have a broad-based stance in their natural position. Tandem gait (heel to toe walking) becomes abnormal early with cerebellar ataxia. Later, regular gait becomes broad based, lurching and veering in quality.

With sensory ataxia, patients can have stance and gait problems and limb incoordination, but do not have speech or eye movement difficulties. The ataxia results from sensory loss (especially position and kinesthetic sense). Patients may admit to numbness, but this is not always the case. The deep tendon reflexes are lost or diminished because of the sensory fiber dysfunction. In many of the inherited types of ataxias, both sensory and cerebellar components are present. This chapter will give an outline of the various ataxic disorders with an emphasis on the genetic forms of the disease. An approach to a patient presenting with ataxia will be presented.

Etiological Classification of Ataxias

Ataxias are broadly grouped into acquired and inherited forms. Any overt structural lesions in the cerebellum and connecting pathways can lead to ataxia. These can usually be diagnosed readily when imaging studies are obtained,

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especially MRI scans of the brain. In these cases, signs of cerebellar disease are often accompanied by signs related to damage to contiguous structures being affected by the structural lesion. Signs and symptoms may be asymmetric depending on the location of the lesion. However, there are many acquired lesions of the cerebellum in which an evident lesion of the cerebellum may be lacking. *Table 367.1* lists acquired causes of cerebellar ataxia that are common in pediatric age groups.

A more difficult diagnostic situation occurs when progressive ataxia is related to an atrophic or degenerative process in the cerebellum, brainstem, and other connecting pathways. In childhood, almost all of these are related to genetic disorders. Information on the mutations and genes involved is available in many but not all of these diseases. The majority of inherited ataxias in childhood have autosomal recessive (AR) inheritance; thus the parents (who are carriers) are asymptomatic, but siblings may be affected. With small family sizes, most of these cases present as singletons. Consanguinity may be a clue to AR inheritance. Other inherited ataxias of childhood have mitochondrial or X-linked inheritance. The analysis of the pedigree may point to the mode of such inheritance, though many of these patients are also singletons. Lastly, autosomal dominant (AD) ataxias may occasionally present in childhood, though commonly they are of adult onset. The diagnostic process in childhood is particularly difficult because many inherited diseases, not usually grouped as primarily ataxic in character, can present with ataxia (in addition to other signs) in this age group. *Table 367.2* lists the inherited diseases which are conventionally classified as an ataxia. *Table 367.3* is a list of disorders usually with childhood onset in which ataxia can be a major feature, but these are not typically classified as ataxias. Lastly, a special group of ataxic diseases have onset in the neonatal period. These are classified as congenital ataxias.

Table 367.1
Acquired ataxias seen in pediatric age groups

Entities with overt structural lesions on imaging	Entities in which an overt structural abnormality is not universally seen
Tumors in the posterior fossa	Infections
	Acute cerebellar ataxia of childhood
	Post-infectious
Cranio-vertebral junction anomalies	Toxic disorders
	Chemotherapy (5FU, Ara C)
	Anticonvulsants (DPH)
Vascular disease	Sequel to hypoxic encephalopathy
Demyelinating disease	Hypothyrodism
Infections (cerebellar abscess, Bickerstaff encephalitis)	Autoimmune
	Paraneoplastic (e.g. opsoclonus-myoclonus syndrome)

Epidemiology

Ataxias are rare disorders. Epidemiological studies generally have tried to estimate prevalence of degenerative ataxias and the usual figures range up to 9.3 per 100,000. There are interesting variations in the occurrence of genetic ataxias among various geographic and ethnic groups. Thus, Friedreich's ataxia, the most common recessive ataxia is confined to Indo-European populations. There are pockets of high prevalence of certain SCAs, likely the result of isolated population kinetics: examples include high prevalence of SCA 1 among the Iakut in Siberia, SCA 2 in the Eastern provinces of Cuba, and SCA 3 in the Portuguese Azores.

In the following sections, different types of acquired and inherited ataxias are described, including their pathogenesis, clinical features, therapy, and prognosis.

Acquired Ataxias in Childhood

A number of disorders in which imaging studies can be diagnostic can have an ataxic presentation in childhood. These include posterior fossa tumors such as cerebellar astrocytomas and pontine gliomas, congenital malformations at the cranio-vertebral junction, and bacterial infections such as a cerebellar abscess. The term brainstem or Bickerstaff encephalitis is used for an acute clinical picture that includes ataxia and oculomotor palsy with added clinical signs such as obtundation and Babinski sign that distinguish the disease from Miller-Fisher variant of Guillain–Barre Syndrome (GBS). MRI often shows signal density changes in the brainstem. Vascular lesions, including ischemic strokes and malformation, can occur in the pediatric age group, but again can be diagnosed readily be imaging. Demyelinating diseases like multiple sclerosis can present with lesions in the cerebellum and connecting pathways. Ataxia in these situations usually develops fairly rapidly, and correct diagnosis leads to appropriate intervention. Other ataxias of nongenetic origin such as those related to hypothyroidism and previous hypoxic

Table 367.2
Inherited ataxias

Autosomal recessive ataxias	Autosomal dominant ataxias	X-linked ataxias	Mitochondrial ataxias
1. Friedreich ataxia (FA)	1. Spinocerebellar ataxias types 1 through 31 (There is no SCA 9 or 24)	1. Fragile X tremor ataxia syndrome (FXTAS)	1. Neurogenic weakness, ataxia, retinitis pigmentosa (NARP)
2. Ataxia with oculomotor apraxia (AOA) type 1 and 2	2. Machado–Joseph disease (MJD also known as SCA 3)	2. Other X-linked ataxias	2. Other mtDNA diseases such as MERRF, MELAS, and KSS can have ataxia as a feature
3. Ataxia telangiectasia (AT)	3. Dentatorubral-pallidoluysian atrophy (DRPLA)		
4. Ataxia with vitamin E deficiency (AVED)	4. Episodic ataxias types 1 through 6		
5. Autosomal recessive ataxia of Charlevoix-Saguenay (ARSACS)			
6. Polymerase gamma related ataxias: mitochondrial recessive ataxia syndrome (MIRAS), sensory ataxic neuropathy, dysarthria and ophthalmoplegia (SANDO), myoclonic epilepsy myopathy sensory ataxia (MEMSA)			
7. Autosomal recessive cerebellar ataxia 1 (ARCA 1)			
8. Ataxia Telangiectasia–like disorder (ATLD)			
9. Spinocerebellar ataxia with axonal neuropathy (SCAN 1)			
10. Marinesco–Sjogren syndrome			

Table 367.3
Autosomal recessive or X-linked syndromes with ataxia and other features

1. Amino acid disorders: Hartnup disease, urea cycle diseases, triple H syndrome
2. Carbohydrate disorders: pyruvate dehydrogenase complex (PDHC) deficiency
3. Storage disorders: late-onset Tay–Sachs (LOTS); Ceroid lipofuscinosis; Neimann–Pick disease, type C
4. Aceruloplasminemia
5. Eukaryotic initiation factor 2 gene related diseases (vanishing white matter disease)
6. Congenital disorders of glycosylation (CDG's)
7. Others: proteolipid protein (PLP) mutations; cerebrotendinous xanthomatosis; Regsum diseases; Giant axonal neuropathy

encephalopathy are rare, but may have cerebellar atrophy on imaging studies. The following section deals with some special types of acquired ataxias seen in children.

Acute Cerebellar Ataxia of Childhood and Post-Infectious Ataxia

Acute cerebellar ataxia (ACA) of childhood refers to a problem of involving only the cerebellum that occurs in children, usually in the setting of a preceding viral infection. Post-infectious encephalomyelitis can have ataxia as a major feature, but usually evidence for a more diffuse affliction of the nervous system including the hemispheres and spinal cord can be found. Some authors use the term acute cerebellitis (AC) to refer to a more severe disorder with associated cerebellar edema and features of increased intracranial pressure.

Pathogenesis: The speculation has been made that ACA may be a post-infectious immune phenomenon whereas AC may be the result of a direct infection.

Clinical features and diagnosis: The antecedents can be a nonspecific viral syndrome, but varicella is a trigger in many, with a peak incidence at the age of 5–6 years. A similar syndrome following Epstein–Barr virus or vaccinations has been reported in teenage years. Children with ACA develop an acute ataxic disorder that is not associated with a more diffuse process reflected by seizures, meningismus, or obtundation. CSF may show some elevation of protein, and a modest mononuclear pleocytosis and PCR may allow identification of a specific etiology such as EBV. Edema, hydrocephalus, and herniation have been described in some and may require decompressive surgery. Some authors refer to this as acute cerebellitis (AC) in which additional features of headache, menigismus, fever, and obtundation can occur. Patients with AC usually have prominent MRI abnormalities in the form of cerebellar edema and diffuse T2 hyperintensity in the cerebellar cortex, and secondary features of compression are often seen with hydrocephalus and tonsillar herniation. In contrast, MR imaging in acute cerebellar ataxia may be normal or show spotty changes in the cerebellum and its peduncles (◉ *Fig. 367.1*).

Differential diagnosis: Other types of acute cerebellar or balance disorders such as tumors, demyelinating disease, toxic diseases, and inborn metabolic errors need to be considered in the acute situation. Acute labyrinthitis and migraine can present with associated balance problems.

Treatment: Patients with evolving features of intracranial hypertension obviously need careful monitoring and decompressive procedures such as posterior fossa decompression and ventriculostomy. These authors in their review also note that occasionally a direct infective agent can be identified by PCR and this may need an appropriate antibiotic. Steroids have been suggested to reduce swelling.

Prognosis: In the majority of children, the prognosis is excellent with full recovery over a few weeks to months. A minority may have residual neurological problems.

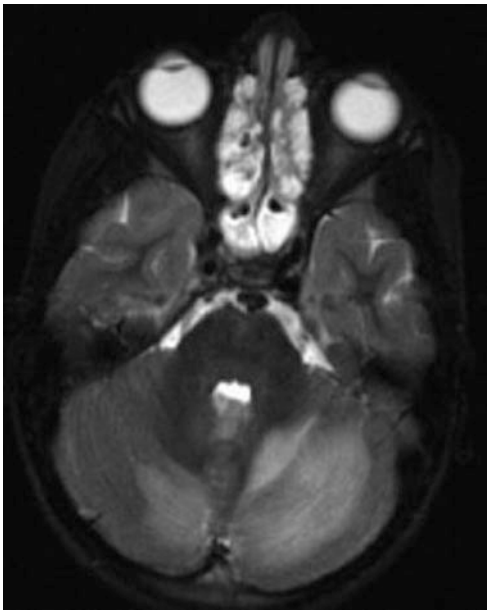

Figure 367.1
Signal density changes in cerebellar cortex in acute cerebellar ataxia of childhood (From Bruecker Y, Claus F, Demaerel P et al (2004) MRI findings in acute cerebellitis. Eur J Radiol 14:1478–1483. With permission)

Toxic Causes of Ataxia

Alcohol which is a common cause of ataxia among adults (both acute intoxication and chronic alcoholic cerebellar degeneration) is not of particular concern in young children. However, iatrogenic ataxia related to pharmacological agents is not uncommon. Antiepileptics are particularly prone to cause ataxia when their levels are supratheraputic, though there is considerable individual variation as to the level that is cerebello-toxic. History of chronic antiepileptic use, together with inappropriate dosing or introduction of another drug that may result in an interaction, is often obtained. It is well recognized that older antiepileptics such as diphenylhydantoin and carbamazepine can produce gait ataxia and other cerebellar disturbances at toxic levels. In a meta-analysis of second generation antiepileptics (gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, or zonisamide) used as adjunct therapy, all of them were found to increase the risk of imbalance with the exception of gabapentin and levetiracetam. A dose-response relation was seen with almost all of the drugs. Zacarra et al. reported that gabapentin, lamotrigine, pregabalin, topiramate, oxcarbazepine, and zonisamide were all found to produce ataxia or dizziness. Measuring drug levels may be useful to diagnose antiepileptic induced ataxia.

Some cancer chemotherapeutic agents such as 5 fluorouracil and cytosine arabinoside produce ataxia as a side effect. An acute cerebellar dysarthria has been reported with infusions of the agent irinotecan.

Opsoclonus-Myoclonus Syndrome(OMS)

This syndrome is characterized by the acute or subacute onset of imbalance and ataxia, soon followed by opsoclonus, a chaotic, irregular, and involuntary movement of the eyes ("dancing eyes").

Pathogenesis: It is likely a result of an autoimmune phenomenon triggered by an underlying neoplasm, but can be idiopathic. It has been postulated that in OMS associated with neuroblastomas, there is an immune reaction against the tumor that has cross reactivity with neuronal tissue. Antibodies against cerebellar Purkinje cell antigens have been noted in the sera of OMS patients, and some have antibodies to neurofilament and the Hu antigen.

Clinical features and diagnosis: Opsoclonic eye movements are conjugate, fast, and multidirectional and can be often precipitated by changes in fixation. This is associated with myoclonic movements and behavioral changes including usually extreme irritability, sleep disturbance, developmental regression, and sometimes loss of speech. In young children, about 50% of cases have an associated neuroblastoma, but this figure may be higher if high-resolution imaging of abdomen is obtained. In older children and adults, OMS can be associated with a direct infection such as with West Nile virus or parainfectious process or other types of malignancies such as lymphomas, lung cancer, and breast cancer. All young patients with OMS require a thorough search for neuroblastoma with high-resolution scans through the adrenals, measurement of catecholamine metabolites in urine, and metaiodobenzylguanidine (MIBG) scan.

Treatment: Apart from treatment of any neoplasm found, a number of immunomodulatory therapies such as corticosteroids and ACTH have shown benefit in many of the motor aspects of this disorder. IVIG, other immunosuppressants such as azathioprine, and plasma exchange have also been used in an anecdotal fashion. Any neuroblastoma needs to be removed. Neuroblastomas associated with OMS tend to be small and localized.

Prognosis: Opsoclonus tends to resolve even with no treatment, and the ataxic disturbance also improves, though not completely. Recovery in speech and language, as well as behavioral abnormalities, tends to be incomplete, and children often require long-term therapy for relapses. As adolescents, these children can exhibit poor school performance and behavioral difficulties such as impulse control and mood disorders. Adults with OMS tend to recover after a monophasic illness.

Cerebral Folate Deficiency

This disorder is characterized by insomnia, agitation, declining head growth, and cognitive decline. There is associated gait ataxia, speech changes, and epilepsy. Serum and RBC folate levels are normal, but CSF 5-methyl tetrahydrofolate levels are decreased. The disorder has been linked to folate receptor antibodies and defective folate transport.

Congenital Ataxias

The concept of congenital ataxia may not have an exact definition. However, these rare syndromes are characterized by onset very early in life, usually in the neonatal period, the presence of cerebellar hypoplasia rather than atrophy and often, but not always, a nonprogressive course. Cerebellar hypoplasia may be differentiated from atrophy by a small cerebellum that does not show the open pattern of folia seen with atrophy and is nonprogressive when examined serially. In a series of nonprogressive ataxia in 78 children from Sweden, no imaging abnormalities occurred in 61%. Among the rest, MRI showed varying patterns of abnormalities including focal or generalized maldevelopment, or extensive malformations consistent with Dandy–Walker syndrome, Joubert syndrome, and cerebellar hypoplasia, as well as lesions that were more consistent with acquired pathology. Some form of genetic etiology was established in close to 20%, including chromosomal abnormality, Angelman syndrome, and Joubert syndrome. Some cases had an autosomal dominant inheritance pattern (see also SCA 29). Others had what appeared to be acquired lesions, including hypoxic-ischemic pathology by imaging. Clinical picture included ataxia with delayed milestones, mental retardation in 60%, refractory and other types of visual problems in 58%, and hearing loss.

Joubert syndrome (JS) is recognized by an autosomal recessive (AR) inheritance, hypotonia, developmental delay, neonatal tachypnea or apnea, and altered eye movements. Infants have mental retardation, episodic hyperpnea or apnea, oculomotor apraxia, and later ataxia. Imaging shows a deep posterior interpeduncular fossa, prominent superior cerebellar peduncles and hypoplasia, and clefting of the superior vermis producing a molar tooth sign (*Fig. 367.2*). Chance et al. in their review describe a number of related clinical phenotypes including the following: Arima syndrome (vermal hypoplasia, retinopathy, polycystic kidneys, AR inheritance); Senior–Loken syndrome (vermal hypoplasia,

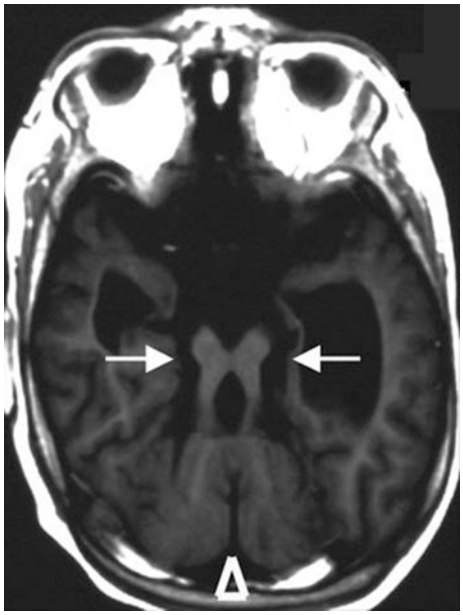

Figure 367.2
Typical molar tooth sign in patient with Joubert syndrome (From Louie CM, Gleeson JG (2005) Genetic basis of Joubert syndrome and related disorders of cerebellar development. Hum Mol Genet 14:R235–R242. With permission)

retinopathy, juvenile onset nephronophthisis, AR inheritance); vermal hypoplasia and retinopathy alone; COACH syndrome (vermal hypoplasia, coloboma, nephronophthsis, hepatic fibrosis); and vermal hypoplasia and nepheonophthisis alone. In Joubert's syndrome, there are no renal, hepatic, or other systemic features, including retinopathy.

The essential feature of many of these conditions include a characteristic set of imaging abnormalities that include a deep posterior interpeduncular fossa, prominent superior cerebellar peduncle and hypoplasia of the superior vermis that lead to a "molar tooth sign" appearance of the upper brainstem on axial images. The clinical picture in Joubert syndrome includes onset in infancy, developmental delay and hypotonia, episodic apnea and hyperpnoea, oculomotor apraxia and hypotonia. Recently, some advances have occurred in identifying genes responsible for such diseases. One variety of JS, associated with cerebral cortical abnormalities has been related to mutations in the AHI 1 gene (Abelson helper integration 1) which encodes the protein Jouberin. Another syndrome associated with nephronophthisis is related to mutations in the NPHP 1 gene, which appears to have a functional role in ciliary function.

Inherited Ataxias

Ataxias can be inherited in autosomal recessive, autosomal dominant, X-linked, and mitochondrial fashion (*Table 367.2*). Childhood ataxias are predominantly autosomal recessive; this group can be further divided in to those diseases which are traditionally classified as ataxias and a second group in which ataxia forms a variable part of a more complex phenotype ("genetic-metabolic" diseases).

Autosomal Recessive Ataxias

Friedreich's Ataxia (FA)

Epidemiology: This is the most common recessive ataxia and perhaps the most common inherited ataxia among Indo-European populations.

Genetics and pathogenesis: FA results from an unstable expansion of a repeated trinucleotide (GAA) sequence within the first intron of the *FRDA* gene on chromosome 9q13-21.1. Most of the normal alleles have fewer than 10 repeats. Long normal alleles (12–40 repeats) appear to be confined to Caucasian populations and serve as the reservoir for expansion into pathogenic mutations. Expanded alleles have 66 to over 1,000 repeats. Over 95% of the affected FA patients have the GAA expansion in both alleles (homozygous expansion). Rarely, patients with clinical findings compatible with FA have only one expanded allele; such patients harbor point mutations in the unexpanded allele. Sequencing of the unexpanded allele to document a point mutation will have to be done in this situation. Point mutations located in the carboxy terminal half of the mature frataxin appear to be associated with a typical FA phenotype. However, missense mutations in the amino terminal half of the protein such as the G130V mutation appear to result in a milder phenotype with less ataxia and greater spasticity and no dysarthria. All the patients with point mutation to date have been compound heterozygotes with one expanded allele. Homozygous point mutations will cause complete lack of frataxin, and this may be incompatible with life. This has been further supported by the fact that complete knockout of the gene in animal models is embryonically lethal.

There is an inverse correlation between the size of the GAA repeat and the age at onset. This correlation is better with the smaller of the two expanded alleles. Cardiomyopathy and diabetes also tend to occur in patients with larger expansions (>700 GAA repeats). All of the variation in age at onset and severity of disease cannot be

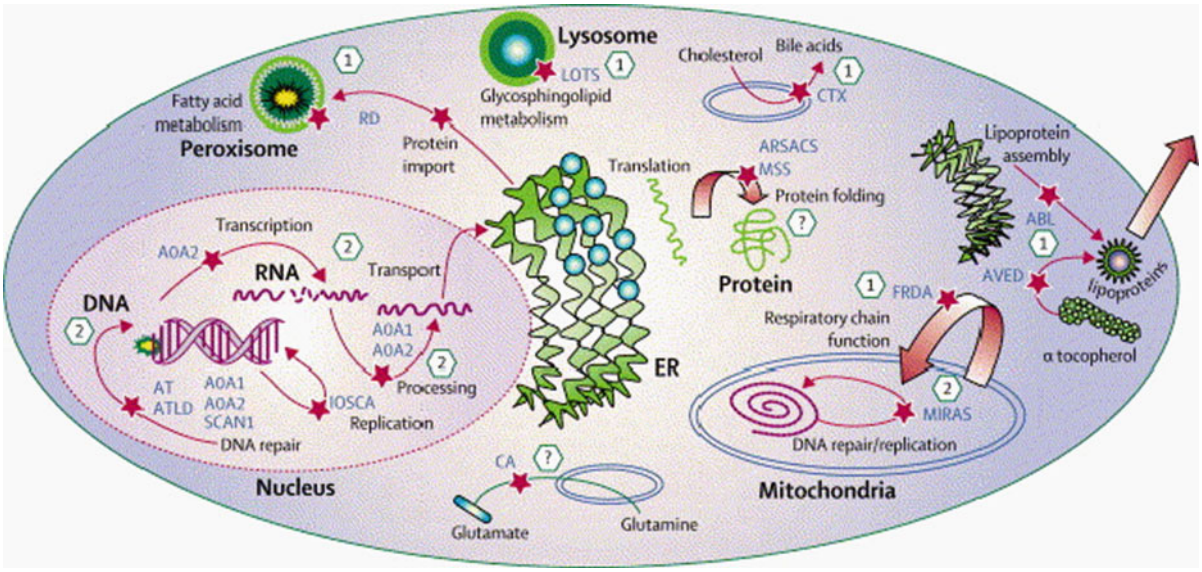

Figure 367.3

Cellular mechanisms in autosomal recessive ataxias. The pathways or sites affected by the various underlying mutations causing the different autosomal recessive ataxias are indicated by a red star. Oxidative stress and DNA repair abnormalities appear major targets in AR ataxias (Numbered 1 and 2). In FA and MIRAS, there are intrinsic mitochondrial abnormalities. In AT and AOAs, DNA repair mechanisms may be affected. ARSACS and MSS may be related to protein folding defects. Other defects depicted include peroxisomal and lysosomal defects and abnormal handling of vitamin E. *ER* endoplasmic reticulum, *FRDA* Friedreich's ataxia, *AVED* ataxia with vitamin E deficiency, *ABL* abetalipoproteinaemia, *RD* Refsum's disease, *LOTS* late-onset Tay–Sachs disease, *CTX* cerebrotendinous xanthomatosis, *MIRAS* mitochondrial recessive ataxia syndrome, *SCAN*1 spinocerebellar ataxia with axonal neuropathy, *AT* ataxia telangiectasia, *AOA*1 ataxia with oculomotor apraxia, type 1 *AOA*2 ataxia with oculomotor apraxia, type 2 *ARSACS* autosomal recessive ataxia of Charlevoix-Saguenay, *IOSCA* infantile-onset spinocerebellar ataxia, *CA* Cayman ataxia, *MSS* Marinesco–Sjögren syndrome (From Fogel BL, Perlman S (2007) Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. Lancet Neurol 6:245–257. With permission)

correlated with the GAA size alone. Other genetic and possibly environmental factors may contribute to this variation. In addition, variation in clinical picture can result from somatic mosaicism of the repeat size with different tissues having significant differences in the size of the expansions.

The mutation in the FA gene leads to a partial deficiency of the protein frataxin. The reduced transcriptional efficiency of the mutated gene has been attributed to an unusual "sticky DNA" configuration of the expanded repeat. In addition, there is evidence for chromatin condensation and remodeling which can further suppress frataxin transcription. The exact role of frataxin in normal biology is still not clear, but many studies suggest that it is a mitochondrial protein (*Fig. 367.3*).

Knockout of the frataxin homologue in yeast leads to accumulation of iron in the mitochondria, a finding of interest in view of the presence of iron in the cardiac muscle in human disease; more recent data suggest that such overt iron accumulation may be a late event. Activity of enzymes, such as aconitase and complex I, II, and III of the respiratory chain, that contain iron-sulfur clusters is reduced in cardiac muscle biopsies of patients with FA. The ISC synthesis defect results from the role of frataxin in the process and probably is the cause of iron accumulation. It has been hypothesized that the presence of excess iron as well as excess oxidative stress related to impaired respiratory chain function can induce oxidative stress via the Fenton reaction and cause progressive nuclear and mitochondrial damage. Frataxin may function both as an iron storage protein and as an iron chaperone with a role in ISC and heme synthesis.

Pathology: There is loss of dorsal root ganglion cells, resultant degeneration of the dorsal columns, degeneration of spinocerebellar and corticospinal tracts, and loss of cells in the cerebellar dentate nucleus.

Clinical features: Typical FA has onset before age 25 years with gait difficulties and clumsiness, usually

around puberty. Examination reveals ataxia which appears related to loss of proprioceptive sense in the limbs. There is loss of tendon reflexes usually in a generalized fashion or just in the lower limbs. These findings are related to the early pathology in the dorsal root ganglion cells. Additional signs indicating involvement of the cerebellum, such as dysarthria, and eye movement abnormalities, such as square wave jerks, appear soon after. Further progression causes disabling ataxia, appearance of upper motor neuron signs such as extensor plantar reflexes and weakness in lower limbs and dysphagia. Rarely, patients may present with cardiac disease or a spinal deformity and then develop neurological disease. Patients tend to lose ambulation within 15 years of onset. At this stage, patients have increasing ataxia of upper and lower limbs, profound proprioceptive loss, areflexia, weakness of lower limb muscles, flexor spasms, dysarthria, and dysphagia. Optic atrophy and hearing loss may occur in a minority of patients. Since the FA mutation was identified, it has been noted that about 15% of patients with the mutation have onset after 25 years of age (late-onset FA or LOFA), occasionally even after 50 years of age. Others continue to retain tendon reflexes (about 10%), a finding not seen in classic cases (FA with retained reflexes or FARR). Some of these patients can be spastic in their lower limbs and have pathologically brisk reflexes.

Heart disease is common with abnormal EKG's in most patients. ECHO-cardiography shows hypertrophic cardiomyopathy in many. Cardiac symptoms, such as atrial fibrillation and occasionally a dilated cardiomyopathy with heart failure, may arise. Cardiac disease is the cause of death in a significant proportion. Skeletal abnormalities such as spinal deformities and foot deformities are common and add to ambulatory and respiratory problems. The mean age of death among patients with FA has been reported to be late in the fourth decade; this however does not take into account the more recent information on late-onset cases. Diabetes occurs in about 10% and appears to be related to both beta cell dysfunction and peripheral insulin resistance.

Diagnosis: Nerve conduction studies show absence or reduction of sensory nerve potentials in a diffuse fashion. Central motor conduction studies show abnormalities that evolve over the course of the disease and may reflect the progression of the disease. MRI scans of the brain reveal no abnormalities in the cerebellum; rather the upper cervical cord shows atrophy. Signal density changes may be seen in the posterior columns by MRI, and the cerebellar dentate has been reported to show increased iron content and volume loss. Diagnosis is confirmed by targeted mutation analysis to detect the homozygous GAA expansion found in the vast majority of patients. Patients with clinical features of FA but only one expanded allele need sequencing of their unexpanded allele to establish the presence of a point mutation. All other types of recessive ataxias figure in the differential diagnosis, but FA is the most common and does not usually have cerebellar atrophy on imaging studies.

Treatment of FA: Based on evidence for excess oxidative stress and poor defense mechanisms of FA tissue to such stress, antioxidant therapy has been tried over the last 10 years. At least 11 studies using idebenone in patients with FA have been reported until 2008. It has been reasonably well tolerated in doses of 900 mg or more per day by FA patients, the main adverse effect being gastrointestinal. At doses of 5 mg/kg/day, it appeared to have beneficial effect on the cardiomyopathy of FA. In a 6 month study, idebenone given in high doses appeared to improve neurological function, as measured by the ICARS scale in ambulatory FA patients. Newer approaches, now in experimental phase, include gene replacement and the use of molecules that may enhance frataxin production even in the presence of the GAA expansion. Recent open label experience suggests some beneficial effect from erythropoietin.

In addition, there have been many attempts at symptomatic therapy of FA patients with possible neurotransmitter replacements such as cholinergic, serotoninergic, and dopaminergic drugs which have shown variable and usually less than optimal results.

The supportive care of FA patients includes adequate rehabilitation efforts aimed at mobility, using appropriate devices. Monitoring and caring for the systemic complications are also important. Such systemic problems include skeletal deformities, cardiomyopathy, and diabetes.

Ataxia with Oculomotor Apraxia Types 1 and 2 (AOA 1, AOA 2)

Oculomotor apraxia refers to a peculiar inability to initiate saccades; eye movement recordings suggest that while saccades can be produced, they have increased latency. Children typically use head thrusts to move eyes from one target to another.

Epidemiology: Ataxia with oculomotor apraxia type 1 is likely the most common AR ataxia in Japan and second only to FA in Portugal. AOA 2 is the most frequent AR ataxia next to FA in European series.

Genetics and pathogenesis: AOA 1 results from mutations in the aprataxin (*APTX)* gene. Nonsense, missense,

and splice site mutations as well as deletions have been described. Aprataxin is a nuclear protein that has an N terminal fork-head associated (FHA) domain resembling PNKP, a histidine triad (HIT) domain and a C terminal zinc finger domain. Most of the mutations affect the HIT domain. The protein may function in base excision repair, a form of single strand DNA repair mechanism. The C terminal is also known to interact with XRCC1 which plays a role in single strand break repair. It is unclear how this functional role is related to neurodegeneration in the cerebellum.

AOA 2 has been linked to mutations in the senataxin gene (*SETX)* which codes for senataxin. Many different mutations have been identified including nonsense, missense and frameshift mutations as well as deletions and duplications. The normal function of senataxin is unclear. Its C-terminal region has homology to the superfamily of helicases, so the DNA/RNA helicase function may contribute to the pathogenesis of neurological dysfunction.

Clinical features and diagnosis: AOA 1 has onset about 10 years of age, with a range from early childhood to the 20s in some cases. It causes progressive ataxia associated with MRI evidence for cerebellar atrophy. Chorea and dystonia occur in about 80% of cases. Oculomotor apraxia appears a mean of 9 years after onset and is seen in over 80% of cases. Children use head movement to fixate on eccentric targets with a head eye lag; this may result from very hypometric saccades and the need for multiple small amplitude saccades to make the movement. Mental retardation can occur in about 40% of cases. Later, patients develop a sensory motor polyneuropathy. Low albumin and high cholesterol levels occur in the majority of patients after some years. Muscle CoQ 10 levels may be decreased in some patients with AOA 1, and symptomatic improvement may occur with high-dose CoQ 10 therapy. There are no other systemic features such as telangiectasia and elevated alpha fetoprotein.

Ataxia with oculomotor apraxia type 2 is a progressive AR ataxia associated with cerebellar atrophy and an axonal polyneuropathy, which are the most prevalent features together with elevation of serum alpha fetopotein. The age at onset is around 15 years, and the disease progresses to a stage requiring significant ambulation devices in about 15 years. Oculomotor apraxia does not occur universally, being seen in about 50% cases. Ocular recordings show increased horizontal saccade latencies and hypometria. Other clinical signs noted are upper motor neuron signs in about 20%, dystonia, chorea, head tremor, and strabismus. Anheim et al. note that with a non-FA patient, the elevation of serum alpha fetoprotein to over 7 μg/l may be predictive of AOA 2. Other features that have been noted infrequently include elevation of serum CK and hypogonadotrophic hypogonadism. No other systemic features such as high risk for malignancy, telangiectasia, or radiation sensitivity are seen.

Treatment: Treatment remains purely supportive.

Ataxia with Vitamin E Deficiency (AVED)

Epidemiology: It is most common in North Africa where its prevalence approaches that of FA.

Genetics and pathogenesis: AVED results from mutations in the α tocopherol transfer protein (αTTP) gene; αTTP is involved in the hepatic handling of vitamin E facilitating the incorporation of vitamin E into very low-density lipoproteins. The mutations in the αTTP gene are variable and include missense, nonsense, frameshift, and splice site mutations; some mutations allow for residual function and thus a milder phenotype.

Clinical features and diagnosis: AVED is a childhood onset ataxia with clinical features similar to FA. The onset is usually in childhood but can be later. There is progressive ataxia and evidence for a polyneuropathy with loss of proprioception and tendon reflexes. Retinitis pigmentosa and visual loss can accompany this syndrome. Patients often have head titubation. Cardiomyopathy can occur but is less common than in FA. Vitamin E levels are very low (less than half the lower limit of normal) but are not the result of impaired absorption.

Treatment: Vitamin E supplementation allows the stabilization of the neurological features, especially when started early in the disease, but some features may show worsening despite therapy.

Abetalipoproteinemia

This disorder results from mutations in the gene *MTTP* which codes for a subunit of the microsomal triglyceride transfer protein; this results in impaired lipid absorption in the intestine including lipid soluble vitamins like vitamin E. The ataxia resembles that in AVED but is associated with evidence for malabsorption. Vitamin E and cholesterol levels are low, and apolipoprotein B is absent on lipoprotein electrophoresis. Acanthocytes are found in peripheral blood smear. Transaminases may be high and INR elevated due to vitamin K deficiency.

Cayman Ataxia

This is an autosomal recessive ataxia described from the Cayman Islands, characterized by early onset of minimally progressive ataxia and mental retardation. The gene involved is on chromosome 19p and codes for a neuron-restricted protein (Caytaxin) that contains a CRAL-TRIO motif common to proteins, including α tocopherol transfer protein, which bind small lipophilic molecules. This suggests a pathogenic similarity to AVED.

Polymerase Gamma Mutations and Ataxia

Recessive mutations in the gene encoding the alpha subunit of polymerase gamma (POLG 1), an enzyme involved in the replication of mtDNA, result in ataxia. Mitochondrial inherited recessive ataxia syndrome (MIRAS) is common in Finland and has onset from childhood to early adult life. Progressive ataxia can be associated with tremor and myoclonus. Schulte et al. recently analyzed the phenotype associated with POLG 1 mutations. Patients who had sensory ataxic neuropathy associated with dysarthria and ophthalmoplegia (SANDO) had a high (80%) prevalence of POLG 1 mutations, whereas only a quarter of patients with ataxia and neuropathy with no eye movement defects had POLG mutations. The syndrome of myoclonic epilepsy, myopathy, sensory ataxia (MEMSA) can also be associated with POLG mutations.

Infantile-Onset Spinocerebellar Ataxia (IOSCA)

This syndrome, also common in Finland, causes an infantile onset of ataxia, mental retardation, seizures, ophthalmoplegia, and neuropathy. Recessive mutations of the gene *C10orf2* which codes for Twinkle, a protein that interacts with POLG 1 in the synthesis of mtDNA have been reported in IOSCA.

Ataxia Telangiectasia

Epidemiology: The occurrence of AT has been estimated to be 1 in 20,000–100,000 live births.

Genetics and pathogenesis: The disease is caused by mutations in the ATM gene on chromosome 11. ATM codes for the ATM protein which appears to be a transducer protein involved in DNA double-strand break repair; this can explain the radiosensitivity seen in AT. ATM is a serine-threonine kinase which autophosphorylates in response to DNA double-strand break and in turn activates many substrates. AT is one of several diseases in which genes involved in DNA repair mechanisms have been implicated in cerebellar ataxia.

Clinical features and diagnosis: This disorder has its onset early in the first decade with truncal instability and impaired gait. This is followed by progressive ataxia associated with evidence for a polyneuropathy such as hypotonia and loss of reflexes. Choreiform movements are frequent. Characteristic eye movement abnormalities are seen with the need for a rapid head thrust for fixating on targets to one side with the eyes following later (eye-head lag). This is referred to as oculomotor apraxia. Telangiectasia tend to appear about 5 years of age and are most frequent on the conjunctivae (Fig. 367.4), but can also occur over the ear lobes and popiteal fossa and other locations.

There is evidence for an immune deficiency with frequent bronchopulmonary infections. The children are at risk for malignancies, especially hematologic tumors like lymphomas and leukemias; other types of cancers occur if the patient reaches adult ages. Because of better care for infections and malignancies, the life span of AT children has increased to over 25 years. Clinical diagnosis is usually apparent, but laboratory features can further support the diagnosis. The serum α fetoprotein is usually elevated (above 10 ng/ml) and immunoglobulin levels are low. Karyotyping often shows chromosomal abnormalities, especially a 7:14 translocation. Increased sensitivity of

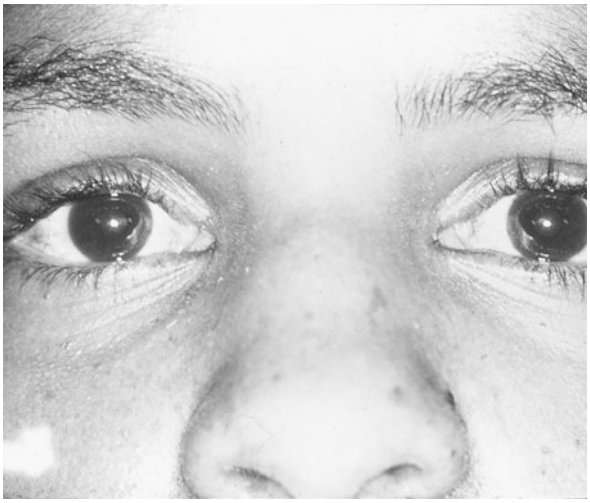

Figure 367.4
Telangiectasia of conjunctiva in ataxia telangiectasia

cultured fibroblasts to radiation can be documented by the "colony survival assay." The definitive way of establishing diagnosis is immunoblotting for the ATM protein; 90% of patients have no protein, 10% have trace amounts, and rare patients have normal ATM levels but no kinase activity ("kinase-dead") (www.geneclinics.org). Further molecular confirmation can be achieved by detecting the mutation; however, this can be difficult because of the size of the ATM gene and the lack of mutation "hot-spots." Sequence analysis of the coding regions of the ATM gene will detect 90% of the mutations but miss intronic alterations and heterozygous deletions. Also benign polymorphisms and pathogenic alterations may be difficult to distinguish. Other types of DNA-based tests include protein truncation tests (examining for premature stop codons) which can detect about 70% of the mutations and mutation scanning using DHPLC which has a sensitivity of 85%.

Treatment: Treatment remains supportive and includes appropriate rehabilitation measures. Children need to be monitored for infections and malignancies. Chronic intermittent immunoglobulin therapy is used to prevent infections, usually in those noted to have very frequent infections. Radiation therapy and investigations with high-dose X-ray exposure have to be managed with great caution and expertise as also chemotherapy because of the radiation sensitivity. Endocrinopathies such as diabetes and gonadal failure need to be looked for and treated appropriately.

Ataxia Telangiectasia–Like Disorder (ATLD)

ATLD is related to mutations in the gene coding for MRE 11, another protein involved in double-stranded DNA break repair. It has a clinical picture resembling AT, but has a milder course, no telangiectasia, and no elevation of serum α fetoprotein.

Spinocerebellar Ataxia with Neuropathy 1 (SCAN 1)

SCAN 1 is a rare disorder, reported in patients from Saudi Arabia, with onset in the second decade; ataxia is associated with sensory motor polyneuropathy, but there are no systemic features. Mutations affecting the tyrosyl-DNA-phosphodiesterase (TDP 1) gene have been identified. TDP 1 gene is involved in single strand DNA break repair.

Other DNA Repair Defects

Both xeroderma pigmentosum and Cockayne syndrome are characterized by photosensitivity. A proportion of these individuals develop neurological problems including ataxia, spasticity, cognitive decline, and seizures.

Autosomal Recessive Ataxia of Charlevoix-Saguenay (ARSACS)

ARSACS was initially identified in children with spastic ataxia among French Canadians in the Charlevoix-Saguenay province of Quebec, Canada, an inbred population with a high carrier frequency for the gene. ARSACS has since then been documented in other geographic areas such as Turkey, Japan, Spain, and Italy. Clinically, it is characterized by very early onset, prominent spasticity followed by ataxia and amyotrophy of distal muscles. Myelinated optic nerve fibers are seen in the French Canadian patients but not in others, and patients from non-Canadian regions have had a more variable phenotype. Mutations in the SACS gene, encoding a protein-labeled SACSIN, are related to ARSACS. The C terminal region of this protein has a DnaJ motif that can interact with Hsp70, and the N terminus has homology to HSp90. Thus, SACSIN may have a chaperone function involved in protein folding.

Marinesco–Sjogren Syndrome

This rare early-onset syndrome is characterized by ataxia, mental retardation, cataracts, and evidence for a myopathy. Peripheral neuropathy, epilepsy, and hypogonadism may be all seen in this disease. Mutations in the gene *SIL 1* have been described; the *SIL 1* product appears to have interactions with one of the Hsp70 chaperone proteins.

Autosomal Recessive Cerebellar Ataxia Type 1 (ARCA 1)

This term has been used to describe an autosomal recessive ataxia in a population isolate of French Canadians from Quebec. The disorder begins in young adult life (17–46 years) and causes progressive ataxia, dysarthria, and mild eye movement problems. Reflexes were normal or slightly brisk, and there was cerebellar atrophy on imaging studies. Molecular studies have revealed that

this is related to mutations in the *SYNE 1* gene. It is thought that *SYNE 1* is a member of the spectrin family of cytoskeletal proteins that may be involved in anchoring actin to the plasma membrane and appears enriched in Purkinje cells.

Autosomal Recessive Cerebellar Ataxia Type 2 (ARCA 2)

This term has been used to denote cerebellar ataxia associated with CoQ 10 deficiency. CoQ 10 is a lipid soluble component of cell membranes and is involved in transport of electrons between complex I and II of the electron transport chain to complex III. Ataxia associated with deficiency of muscle CoQ 10 is heterogeneous. This combination can be seen in some patients with AOA 1 as well as in some with defined abnormalities in CoQ 10 metabolism. Ataxia is associated with pyramidal signs and mild cognitive decline. Some patients may have hypogonadism. CoQ 10 deficiency can be associated with other phenotypes such as an infantile multisystem disease, encephalomyopathy with ragged red fibers, and Leigh's syndrome. Some gene mutations have been identified in the infantile cases. The syndrome may respond to CoQ 10 replacement therapy.

Other Poorly Defined Recessive Ataxias

Among 102 patients with recessive ataxias reported by Anheim et al., extensive molecular studies led to a genetic diagnosis in only 57. The cases that could not be molecularly classified had a slightly later onset (>20 years), and milder course. Cerebellar atrophy is seen in 68% of these individuals and polyneuropathy in about 50%. A small proportion of these individuals had oculomotor apraxia and elevated alpha fetoprotein and serum CK. A number of clinically defined syndromes may be seen in this group, including ataxia with hypogonadism, deafness, and myoclonus.

Autosomal Recessive or X-Linked "Genetic-Metabolic" Diseases with Ataxia as a Feature

A number of disorders of childhood or young adult onset are not classified as an ataxia, yet often have ataxia as a feature. In many, other CNS and systemic features occur, cognitive decline or mental retardation is common, and imaging studies may be distinctive. These tend to separate them from the classical ataxias (◉ *Table 367.3*).

Cerebrotendinous Xanthomatosis

This disease is caused by mutations in the CYP 27 gene encoding 27-hydroxylase that cleaves a side chain off cholesterol and this leads to reduced bile acid synthesis and increased formation of intermediates such as cholestanol and 27-C bile alcohols. There is increased serum and tissue levels of cholestanol and tissue deposits of sterols. The clinical picture includes chronic diarrhea beginning in the first decade and a neurological syndrome that combines spastic ataxia and cognitive decline. Xanthomas can be seen by 15 years of age, usually over Achilles tendon, tibial tuberosities, or fingers (◉ *Fig. 367.5*). Juvenile cataracts are also a feature. Later in the course, osteoporosis, easy fractures, and coronary disease occur. Diagnosis can be established by clinical features and elevated serum cholestanol levels as well as by mutation analysis of CYP 27. Therapy with chenodeoxycholic acid and statins may arrest disease progression.

Urea Cycle Defects

The late-onset varieties of these can present in childhood with episodes of encephalopathy, nausea, and vomiting

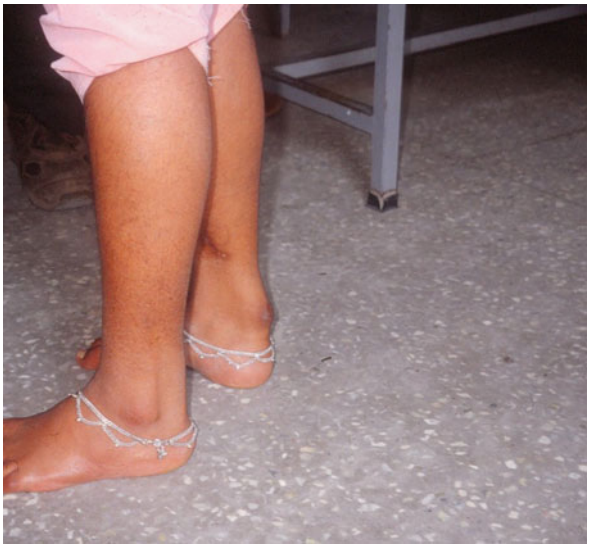

Figure 367.5
Achilles tendon xanthoma in cerebrotendinous xanthomatosis

associated with ataxia. One variety (arginase deficiency) can present with spatic paraplegia. Brain MRI may be normal or show edema during episodes. Serum ammonia is elevated to over 80 μmol.

Hartnup Disease

This disease is caused by mutations in the neutral amino acid transporter gene (SLCGA 19) and results in neutral aminoaciduria. Clinical picture includes growth delay, skin rash, diarrhea, ataxia, and psychosis. Tryptophan metabolism abnormality leading to a deficiency of serotonin has been proposed as a mechanism for the clinical picture. Diagnosis is established using plasma and urine amino acid levels.

Pyruvate Dehydrogenase Complex Deficiency

This can be X-linked or autosomal recessive depending on the component of the PDHC complex that is abnormal. The disease presents with episodic dysfunction including ataxia and encephalopathy; later, there are persistent deficits associated with cognitive decline and neuropathy. Optic atrophy is common and MRI may show putaminal necrosis in the brain. Serum and CSF lactate and pyruvate are increased with decreased lactate to pyruvate ration. Diagnosis is established by estimating PDHC activity in cultured skin fibroblasts. Therapy with high-dose vitamin B1 and ketogenic diet may help.

Late-Onset Tay–Sachs Disease (GM1 Gangliosidosis)

Though Tay–Sachs disease is typically infantile in onset, a late-onset form (age at onset 8–36 years) has been described. The clinical picture is characterized by ataxia, neurogenic weakness with atrophy and fasciculations due to anterior horn cell loss, psychosis and cognitive decline. Mutations in the hexosaminidase gene can be established and leuokocyte hexosamonidase A and total hexosaminidase levels are reduced.

Aceruloplasminemia

This disease results from mutations in the ceruloplasmin gene. Ceruloplasmin transports copper and also has ferroxidase activity that allows it to mobilize tissue iron. Both homozygous and heterozygous mutations can cause disease. The former causes ataxia, cognitive decline, chorea, Parkinosinian features, and retinal degeneration. MRI of the brain shows T2 hypointensity in the cerebral and cerebellar cortex, basal ganglia, and the dentate nucleus. Heterozygous mutations cause ataxia, tremor, and chorea with no T2 hypointensity on MRI. Serum and urine copper is low, ferrtitin high, and ceruloplasmin absent. Therapy with chelation may improve the clinical picture.

Vanishing White Matter Disease

This disorder has been linked to mutations in five eukaryotic initiating factor 2B genes (EIF 2B 1–5). Patients present with ataxia and upper motor neuron signs between 2 and 5 years of age. Episodes of rapid progression after stress have been reported. MRI is characterized by cavitating bilateral leukoencephalopathy. An adult variant of this disease has also been seen with a mean age at onset of 31 years and spasticity, ataxia, cognitive decline, and seizures. Imaging studies show cerebral atrophy, cystic breakdown of white matter, and increased T2 signal in cerebellum and corpus callosum.

Refsum Disease

A deficiency of phytanyl CoA hydroxylase results in increased phytanic acid in tissue peroxisomes. The clinical picture is characterized by a polyneuropathy associated with ataxia, hearing loss, and ichthyotic skin changes. Plasma phytanic acid is high, and a low phytanic acid diet may slow disease progression.

Giant Axonal Neuropathy

This autosomal recessive disease is characterized by onset between 2 and 7 years of age. Neurologically, there is severe ataxia, mental retardation, and sensory motor polyneuropathy with weakness and atrophy of muscles. Hair appears kinky and red. Variant phenotypes include a spastic syndrome with mild ataxia and no kinky red hair. MRI shows diffuse white matter changes in the hemispheres and cerebellum. Nerve biopsy shows distended axons with microfilament accumulation by electron microscopy. Mutations in the gene gigaxonin that is involved in microtubular stability are responsible for this condition.

Congenital Disorders of Glycosylation Syndromes (CDG Syndromes)

These are disorders characterized by defective synthesis of N-linked oligosaccharides. There are 21 enzymes in this pathway that are known to be defective in the CDG syndromes. The disorders have a wide phenotypic spectrum with developmental delay, cerebellar hypoplasia, liver disease, and abnormal fat tissue as possible manifestations. During early childhood, patients have hypotonia, ataxia, and delayed language. Peculiar slow rolling eye movements have been described. Other features that can occur include seizures, stroke-like episodes, elevated liver enzymes, coagulopathy, and joint contractures. Systemic features include hepatomegaly, proteinuria, orange peel appearance of skin, hypogonadism, and large ears. Diagnosis can be suspected by an abnormal serum transferring glycoforms detected by isoelectric focusing.

Neuronal Ceroid Lipofuscinoses

These are autosomal recessive lysosomal storage diseases of infancy and childhood which have been classified into many types. Some varieties of this such as the late infantile type, the adult onset type, and the Gypsy-Indian type are associated with ataxia, but other features such as cognitive decline, seizures, and visual loss usually dominate the clinical picture. Measuring palmitoyl priten thiesterase 1 (PPT 1) and tripeptidyl peptidae 1 (TPP1) may be useful indicators of NCL. Electron microscopy of conjunctival or skin biopsies and of the buffy coat may reveal characteristic lysosomal storage material in the form of curvilinear, fingerprint, or granular osmiophilic bodies. Genetic mutations in the genes CLN 1 through CLN 8 have been identified but diagnosis can be difficult.

Niemann–Pick Disease Type C

This is a rare autosomal recessive disease with a wide range of age at onset (perinatal period to over 15 years) and phenotypic variability related to mutations in the genes NPC 1 and 2. A wide variety of motor phenomena are seen with ataxia, dystonia, and dysarthia being very common. Cognitive decline, hearing loss, myoclonus, and seizures are seen commonly at different age groups, and vertical supranuclear gaze palsy appears to be a frequent phenomenon. Cataplexy and hearing loss also have been described. Hepatosplenomegaly is common but may need ultrasound to detect in older patients. Elevation of plasma chitotriosidase may be a diagnostic clue but not specific. Examination of tissue (bone marrow, skin, liver biopsy, lymph nodes) can reveal characteristic foam cells or sea blue histiocytes. Cultured fibroblasts can be subjected to the filipin test to detect typical perinuclear cholesterol filled vesicles. Mutation analysis of the two responsible genes (NPC 1 and 2 associated with 96 and 4% cases respectively) may establish the diagnosis, but novel polymorphisms can be difficult to distinguish from pathogenic mutations.

PLP-1 Related Disease

Classic Pelizaeus–Merzbacher disease is characterized by onset <5 years, nystagmus, hypotonia, spastic ataxia, dystonia, and decreased cognition. A milder variant causes spastic ataxia, mild cognitive decline, and neuropathy. MRI shows diffuse leukoencephalopathy. Diagnosis is established by PLP1 mutation analysis, FISH for duplication or chromosomal microarray.

Adrenomyeloneuropathy

Though this X-linked disorder typically presents as adrenoleukodystrophy in young boys with progressive cerebral and motor problems, milder phenotypes have been described in both males and females. Occasional patients may present with a spinocerebellar ataxia presentation, and imaging abnormalities in the brain may be scant. Screening for this disease by measuring very long chain fatty acids should be done in patients with ataxia in whom other causes have been excluded.

Miscellaneous Disorders

The following disorders can all be associated with ataxia in addition to other more diffuse CNS symptomatology: late-onset maple syrup urine disease, methylmalonic academia, propionic academia, isovaleric academia, arginase deficiency, and Lafora disease.

Mitochondrial Diseases with Ataxia

The term mitochondrial disease refers to a clinical disorder that is thought to have its origin in a primary defect of a respiratory chain component, whether the component is coded by a nuclear or mitochondrial gene. The phenotype

of mitochondrial diseases may include both neurological and systemic features and be quite variable. Many classic phenotypic syndromes related to mtDNA mutations such as Kearns–Sayre syndrome (KSS), myoclonic epilepsy with ragged red fibers (MERRF), mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS), neurogenic weakness with ataxia and retinitis pigmentosa (NARP) can all have ataxia as one of the features. While many of the more-recently-recognized nuclear mutations causing respiratory chain defects lead to complex neurological diseases, ataxia may be a feature of nuclear mutations resulting in multiple mtDNA deletions.

Autosomal Dominant Ataxias

Autosomal dominant (AD) ataxias with a progressive course are labeled spinocerebellar ataxia (SCA) followed by a number indicating the particular chromosomal locus or gene mutation that is responsible. At this time, SCA 1 through SCA 31 have been recognized, with the following caveats: SCA 9 was reserved for a family which appears not to have been followed up, and at the moment its status is unclear; SCA 15 and 16 have been recently found to be related to the same gene mutation; SCA 19 and 22 may be allelic diseases, but this has not been settled; SCA 24 was identified in a family which likely has a recessive mode of inheritance, and this is now called Spinocerebellar ataxia with saccadic intrusions (SCASI). The preferred name for SCA 3 is Machado–Joseph disease (MJD). Dentato-rubral pallido-luysian atrophy (DRPLA) is grouped with the ataxias, but has no SCA designation.

In addition, there are autosomal dominant ataxias in which symptoms are episodic; these are labeled as episodic ataxia syndromes (EA) with the numbers (EA 1 through 6) denoting distinct chromosomal loci. There is more experience worldwide with SCA 1, 2, 3 (MJD), 6, 7 and EA 2 than the other AD ataxias, and thus their clinical picture is better defined for the most part. With the other SCAs, clinical experience is restricted to single families or small number of families, and the phenotypic spectrum may change as more experience is accumulated.

Genetics and pathogenesis: Many of the initial gene mutations identified in the SCAs were unstable expansion of CAG triplets within coding sequences of different genes (◉ *Table 367.4*).

The CAG repeat codes for a string of glutamines and, therefore, these ataxias are also called polyglutamine ataxias. Other repeat expansions discovered to cause ataxia occurred in noncoding regions and include a CAG expansion in the promoter sequence for SCA 12, a CTG expansion in the 3'UTR for SCA 8, and an intronic ATTCT repeat expansion for SCA 10 and finally a TGGAA pentanucleotide insertion for SCA 31. More recently, identified gene mutations in the SCAs have been other types of gene alterations, including

Table 367.4
Autosomal dominant ataxias related to expanded nucleotide repeat motifs

Disease	Gene, repeat, and locus	Normal repeat numbers	Mutable normal alleles	Reduced penetrance alleles	Pathogenic alleles
SCA 1	ATXN 1, CAG, 6p23	6–44	36–38		39–91[a]
SCA 2	ATXN2,CAG,12q	<31	None		32–>200
SCA 3 (MJD)	ATXN 3, CAG, 14q	<44		45–51	52–86
SCA 6	CACNA1A, CAG,19p	<18		19[b]	20–33
SCA 7	ATXN 7, CAG, 3p	<19	28–33	34–36	37–400
SCA 8	ATXN8OS, CTG-CAG, 13q	15–50 combined $(CTA{\cdot}TAG)_n(CTG{\cdot}CAG)_n$			71–1,300[c]
SCA 10	ATXN 10, ATTCT, 22q	10–29		280–850	800–4,500
SCA 12	PP2R2B, CAG, 5q	4–32		40–62	51–78
SCA 17	TBP, CAG, 6q	25–42		43–48	49–66
DRPLA	ATN, CAG, 12p	6–35	May exist		48–93

[a]Note the overlap between upper end of normal and lower end of pathogenic range. Normal and pathogenic alleles of the same size can be distinguished by the presence of CAT interruptions in the former. The interruptions can be detected using Sfa NI restriction site testing
[b]19 repeat allele has been seen in asymptomatic elderly persons, in a person with atypical symptoms, in a homozygous individual with typical symptoms and has been shown to expand into a pathogenic range in the offspring of an individual with no symptoms
[c]Alleles of the same size can be seen in asymptomatic individuals

missense and nonsense mutations, insertions, deletions, and chromosomal duplications (Table 367.5).

Lastly, in many SCAs chromosomal loci are known, but the mutations are yet to be identified. The EA mutations identified so far have involved missense and nonsense mutations in ion channel or transporter proteins (Table 367.6).

The pathogenesis of the polyglutamine ataxias has been related mainly to a toxic gain of function by the product of the mutant allele. The protein product of the mutant allele has a longer glutamine tract and undergoes misfolding and aggregate formation, and this is believed to trigger many pathogenic cascades (Fig. 367.6). Examples of such altered cellular pathways include transcriptional dysregulationn of other genes because of the presence of misfolded protein in the nucleus, colocalization of chaperone proteins with the aggregates, disruption of preoteasome pathways and mitochondrial dysfunction and apoptosis. The role of posttranslational modification of the mutant protein such as phosphorylation and the need for nuclear transport and cleavage of the protein for pathogenicity are also being investigated as possible therapeutic targets. Shutting off the mutated gene using siRNA has succeeded in reducing pathology in many model systems. Other types of therapeutic options may include targeting some of the secondary cascades triggered by the mutations.

In the case of the more-recently-discovered non-polyglutamine ataxias, a diverse series of pathogenic mechanisms may play a role. In SCA 8 and SCA 10, repeat expansions in noncoding regions of the gene may be pathogenic due to an RNA-based mechanism with the long transcript being toxic to a number of cellular mechanisms. In other diseases such as SCA 5, SCA 13, SCA 14, and SCA 27, such processes as cytoskeletal integrity, channel function, and signaling pathways may be altered.

In the episodic ataxia syndromes, mutations involve proteins that function as channels or transporters, and they appear to be examples of neuronal channelopathies. Mutant channels may express a variety of aberrant properties and produce haploinsufficiency or a dominant negative effect, leading to abnormal channel physiology.

Clinical features: In general, the SCAs have onset in young to middle adult life and are not high on the diagnostic list in pediatric age groups, though reported range of age at onset is very wide for many of the SCAs. In many of the better known SCAs which result from unstable nucleotide repeat expansions, anticipation in age at onset is prominent and onset in childhood and even neonatal period has been described. Typically, in these diseases, age at onset is inversely correlated with expansion size so that, with larger expansions, onset can be in teen or early childhood years. There are also more-recently-described SCAs unrelated to nucleotide repeat expansions with onset in early years, but with a very slow progression.

The clinical picture of the SCAs is usually dominated by cerebellar ataxia. In some, ataxia is the loan clinical finding. In others, ataxia is associated with evidence for pathology in many other neural systems including the upper motor neurons, basal ganglia, brain stem neurons, anterior horn cells, cortical neurons,and peripheral nerves. Thus, patients with these SCAs have an array of clinical signs in addition to ataxia such as brisk tendon reflexes, spasticity, Babinski signs, akinesia, rigidity, tremor of different types, oculomotor deficits of many

Table 367.5
Autosomal dominant ataxias with defined mutations unrelated to nucleotide expansions

Disease	Gene	Locus	Mutation
SCA 5	SPTBN 2	11p	Deletions, point mutation
SCA 11	TTBK 2	15q	Insertion/deletion
SCA 13	KCNC 3	19q	Point mutations
SCA 14	PRKCG	19q	Deletions, point mutations
SCA 15/16	ITPR 1	3p	Deletions, point mutations
SCA 20	Unknown	11q	Duplication
SCA 27	FGF 14	13q	Point mutations
SCA 28	AFG3L2	18p	Point mutations

AFG3L2 ATPase family gene 3-like 2 gene, *FGF* 14 fibroblast growth factor 14 gene, *ITPR 1* inosine triphosphate receptor 1 gene, *PRKCG* protein kinase C gamma gene, *KCNC 3* voltage gated potassium channel/member 3 gene, *STBPN 2* beta-III spectrin gene, *TTBK 2* tubulin tau kinase 2 gene. In SCA 20, the region duplicated has multiple genes

Table 367.6

Episodic ataxia syndromes (Modified from Manto M, Marmolino D (2009) Cerebellar ataxias. Curr Opin Neurol 22:419–429)

Disease	Phenotype	Onset	Mutation
EA 1	Very brief episodes of ataxia; interictal skeletal myokymia	Early childhood	*KCNA1*
EA 2	Ataxic episodes lasting hours; interictal nystagmus	Childhood to young adult	*CACNA1A*
EA 3	Episodic vertigo and tinnitus		Linked to 1q
EA 4	Episodic vertigo; interictal nystagmus	Late onset	
EA 6	Associated with hemiplegic migraine		
EA 7	Attacks of vertigo, weakness, slurred speech	<20 years	Linked to 19q

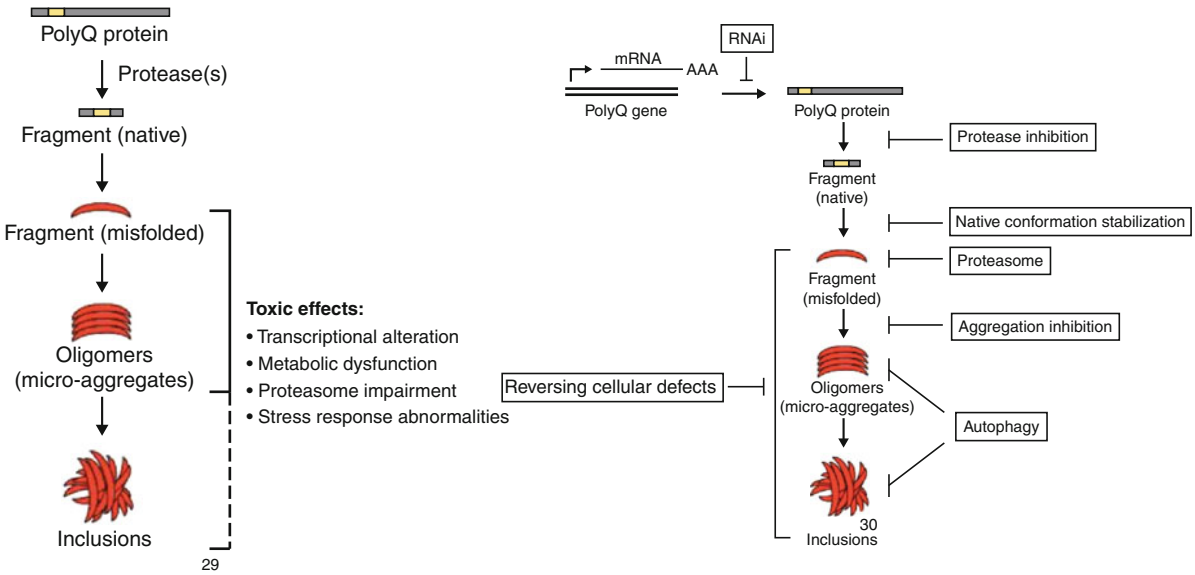

Figure 367.6

Pathogenesis of spinocerebellar ataxias related to CAG repeat expansions. The polyglutamine protein product of the mutated allele tends to misfold and form oligomers and aggregates, sometime after cleavage by proteases. Such misfolded protein can be pathogenic due to a variety of reasons, including interference with transcriptional machinery in general, and with the proteasome, chaperone, and autophagy systems. Numerous secondary events may cascade from these effects including changes in mitochondrial function, apoptosis, and abnormal calcium homeostasis. On the right, some of the potential interventions that may be useful are illustrated, including the use of siRNA to inhibit the mutant gene and therapies that may influence aggregation, autophagy, and proteasome (From Shao and Diamond 2007. With permission)

types, dysarthria, dysphagia, tongue and facial atrophy with fasciculations, muscle atrophy, cramps, muscle fasciculations, sensory loss and areflexia in varying combinations. Seizures, cognitive decline, and retinopathy with visual loss occur in some SCAs.

While the genotypic diagnosis of a particular type of SCA from clinical signs alone is very difficult, certain clinical features may be seen more typically in some SCAs. The course of the SCAs is progressive, with loss of ambulation 15–20 years after onset and death resulting from severe motor disability and resultant complications. Both the array of clinical findings and the course of the disease can be influenced by the repeat expansion size. The diagnosis of an SCA can be made by the documentation of a progressive degenerative ataxic disease with an autosomal dominant inheritance pattern. Further confirmation can be achieved by obtaining mutation analysis for the various SCA genes. In the subsequent section, the SCAs are described in brief with emphasis on those that may have a pediatric presentation.

Spinocerebellar Ataxia 1

The mean age at onset is in the fourth decade, but there is a wide range of age at onset, and childhood onset is possible. In typical cases, clinical picture is characterized by progressive ataxia, dysarthria, upper motor neuron signs, and a mild sensory polyneuropathy. Cognitive decline may occur, especially with younger age at onset. The disease is related to a CAG repeat expansion in the ataxin 1 gene on chromosome 6p.

Spinocerebellar Ataxia 2

Typically, SCA 2 has onset in the fourth decade and is characterized by progressive cerebellar signs associated with slow saccades and polyneuropathy often leading to areflexia. SCA 2 results from a CAG expansion in the ataxin 2 gene on chromosome 12q. Yis et al., Abdel-Aleem and Zaki, Moretti et al., Babovic-Vukasnovic et al. have described a number of pediatric onset cases. In addition to the typical features of ataxia, slow saccades, and loss of reflexes, the childhood cases exhibit cognitive decline and extrapyramidal features. Cases with neonatal onset have hypotonia, developmental delay, ocular problems, and dysphagia. Diagnosis of a dominant condition may be missed because the affected parent (usually the father) may be asymptomatic at the time the children get symptoms. Careful family history and drawing at least a three-generation family pedigree is important. Neonatal cases may have "hyperexpansions" of the CAG tract in the ataxin 2 gene, and these may not be detected by the usual PCR method of mutation detection. When suspicion exists, a "normal" result from such a PCR test should be followed by a Southern blot to detect hyperexpansions.

Spinocerebellar Ataxia 3 or Machado–Joseph Disease

Age at onset can vary from 5 to 75 years, but onset in childhood is rare. There is an inverse correlation between the number of repeats and age at onset, so that pediatric onset typically occurs with repeat sizes over 75 in the mutant allele. This type of early-onset disease is characterized more by extrapyramidal features, including bradykinesia, rigidity, and dystonia, together with spasticity. Ataxia may not be prominent. This has been called the type I MJD phenotype as opposed to type II, which has onset in young adult life and is characterized by ataxia and upper motor neuron findings. Type III disease is characterized by ataxia and neuropathy leading to loss of tendon reflexes. Rare patients with homozygous expansion in the ataxin 3 gene can have a severe phenotype and onset below 10 years of age, but heterozygous expansion also has led to a very early onset. Carvalho et al. reported one homozygous patient who had motor regression and dysphagia starting at age 4, followed by dystonia and spasticity with only minor ataxia.

Spinocerebellar Ataxia 4

SCA 4 has been localized to chromosome 16q and causes a combination of sensory motor neuropathy and ataxia. A "pure" cerebellar ataxia with dominant inheritance, reported from Japan, has an overlapping chromosomal locus and segregates with a single nucleotide substitution in the puratrophin gene within this region; but it is not certain whether this is allelic to SCA 4.

Spinocerebellar Ataxia 5

This dominant adult onset ataxia causes slowly progressive ataxia and has been linked to a mutation in the β spectrin gene (*SPTBN 2)*.

Spinocerebellar Ataxia 6

SCA 6 is characterized by a progressive, pure cerebellar syndrome with onset in the fifth decade and a slow course. It is related to a CAG expansion in the α subunit of the neuronal calcium channel gene (*CACNA1)*.

Spinocerebellar Ataxia 7

SCA 7 is caused by a CAG expansion in the ataxin 7 gene on chromosome 3p. It has wide range of age of onset and the considerable instability of the CAG expansion, especially on paternal transmission, often causes major anticipation in age of onset, with childhood and infantile onset. Adult onset cases are characterized by ataxia and other cerebellar signs, spasticity, and other upper motor neuron signs and a variable occurrence of visual loss related to a cone-rod dystrophy in the retina. Childhood onset has been described both in molecularly confirmed families and in the pre-molecular era. Onset below age was seen with repeat expansion sizes of over 67, and early-onset cases often have visual loss preceding the ataxia,

a situation different from adult onset cases. Early-onset patients also have an accelerated course often leading to death within 5 years of onset and a clinical picture with many features other than ataxia, such as cognitive decline, muscle weakness and atrophy, myoclonus and epilepsy. Infantile onset can be associated with developmental delay, dysphagia, hypotonia, poor visual tracking, and evidence for cardiomyopathy. Similar to that in SCA 2, the "hyperexpansions" associated with such infantile onset can be missed by routine PCR testing and need Southern blotting.

Spinocerebellar Ataxia 8

The CTG expansion in ataxin 8 gene associated with SCA 8 has been seen in both sporadic cases and in some families with dominant ataxia. SCA 8 patients have ataxia, some upper motor neuron signs, and mild sensory loss. The direct role of the expansion in the causation of ataxia is still debated since the same expansion occurs with some frequency in non-ataxic individuals; both an RNA-based mechanism and a "polyglutamine" mechanism based in bidirectional transcription of the gene have been proposed.

Spinocerebellar Ataxia 10

This disease which causes a combination of ataxia and epilepsy is related to a pentanucleotide (ATTCT) expansion in the 5'untranslated region of the ataxin 10 gene and appears confined to people of central and South American ancestry.

Spinocerebellar Ataxia 11

SCA 11 has been described in a limited number of families and causes ataxia, upper motor neuron signs and abnormal eye movements. Mutations have been described in the tubulin tau kinase gene (TTBK2).

Spinocerebellar Ataxia 12

SCA 12 causes a variable combination of ataxia, tremor, basal ganglia signs, and dementia. The causative mutation is a CAG expansion in the promoter sequence of the gene PPP2R2B gene.

Spinocerebellar Ataxia 13

The limited experience with SCA 13 indicated both childhood and adult onset of very slowly progressive ataxia, sometime associated with mild mental retardation. Mutations in a potassium channel gene (KCNC3) are responsible.

Spinocerebellar Ataxia 14

This disorder results from mutations in the protein kinase C γ gene and causes a variable phenotype including childhood onset, though most patients have onset in adult life. The clinical picture has varied from one of pure cerebellar ataxia to one that has additional features including axial myoclonus, choreic movements, diplopia and gaze palsy, and facial myokymia. Rigidity, dystonia, proprioceptive loss, and slow saccades also have been noted from time to time.

Spinocerebellar Ataxia 15 and 16

SCA 15 and 16 were originally reported from Australia and Japan, respectively, but more recent findings suggest that the same gene mutation underlies these entities. The disease causes pure cerebellar ataxia, but the Japanese cases had postural tremor as well. Deletions involving two contiguous genes (SUMF1 and ITPR1) were found in the Australian kindred, but in the Japanese patients, only the ITPR1 gene was deleted, suggesting that this is the critical gene.

Spinocerebellar Ataxia 17

SCA 17 is caused by a CAG expansion in the TATA-binding protein (TBP) gene. It is a polyglutamine disorder. It has a wide range of age at onset, including childhood, and has a very variable phenotype including ataxia, extrapyramidal signs, psychiatric features, epilepsy, and dementia.

Spinocerebellar Ataxia 18

Brkanac et al. described a chromosome 7q22–q32-linked autosomal dominant condition characterized by both ataxia and a sensory motor neuropathy in a five generation American family of Irish ancestry.

Spinocerebellar Ataxia 19

Schelhaas et al. reported a family of Dutch origin with a mild ataxia, myoclonus, irregular postural tremor, and cognitive impairment. Among 11 family members with clinical data, many also had decreased proprioception and tendon reflexes. The disorder in this family was mapped to chromosome 1p21–q21 by Verbeek et al.

Spinocerebellar Ataxia 20

SCA 20 was described in an Australian family with a wide range of age at onset, prominent dysarthria and dysphonia, and the presence of calcification in the cerebellar dentate. The disease is localized to chromosome 11 and appears related to the duplication of a 260 Kb segment on chromosome 11q. Its pathogenesis remains unclear.

Spinocerebellar Ataxia 21

In a family with autosomal dominant ataxia with onset in childhood and young adult life, a new gene locus was established at chromosome 7p. In addition to ataxia, the patients had tremor, rigidity, and cognitive impairment.

Spinocerebellar Ataxia 22

Chung et al. (2003) reported a Chinese family with dominant ataxia, hyporeflexia, onset between 10 and 46 years of age and MRI showing isolated cerebellar atrophy and established a locus at chromosome 1p, overlapping that reported in SCA 19.

Spinocerebellar Ataxia 23

In a single family with adult onset dominant ataxia, the locus was mapped to chromosome 20p.

Spinocerebellar Ataxia 25

In a single family from France, Stevanin et al. noted childhood onset of a dominant ataxia with variable progression and an associated peripheral neuropathy. Linkage studies localized the disorder to chromosome 2p.

Spinocerebellar Ataxia 26

Yu et al. have a described a single family of Norwegian descent with relatively pure cerebellar ataxia with little in the way of extracerebllar signs. Age at onset was from 33 to 60 years. MRI showed cerebellar atrophy, but brainstem was spared. Genetic mapping has localized this disease to chromosome 19p13.3 adjacent to the SCA 6 locus.

Spinocerebellar Ataxia 27

This disease, related to mutations in the fibroblast growth factor 14 gene, has onset in childhood with tremulousness and then progressive ataxia which is slowly progressive. Orofacial dyskinesias, cognitive decline, and aggressive outbursts were noted in some patients.

Spinocerebellar Ataxia 28

There is limited experience with this disease in two families of Italian origin. The phenotype is characterized by juvenile onset (range 12–36), slow progression of ataxia, nystagmus, and later in the disease course, ophthalmoparesis with ptosis and slow saccades. Point mutations have been discovered in the SCA 28 gene in these two families, located on chromosome 18p.

Spinocerebellar Ataxia 29

In an Australian family with congenital, nonprogressive ataxia and "cerebellar hypoplasia" on imaging studies, Dudding et al. identified a locus on chromosome 3p.

Spinocerebellar Ataxia 30

An Australian family with dominantly inherited ataxia of late onset was mapped to chromosome 4q.

Dentato-Rubral-Pallido-Luysian Atrophy (DRPLA)

This disease with a very complex phenotype is usually classified among the ataxias. It is most prevalent in Japan, but molecularly proven DRPLA has been reported from Europe and the USA. The original African-American

family in which the typical neuropathology was described many years ago is now known to carry the same mutation as the Japanese cases. DRPLA has a variable age of onset from infancy to old age and anticipation is common. With onset below 20 years of age, the clinical picture is one of seizures, myoclonus, ataxia, and intellectual decline. With older onset, the disease is characterized by ataxia, chorea, dementia, and psychiatric features. Thus, the differential diagnosis varies with age and includes the progressive myoclonic epilepsy syndromes in children and adolescents, and Huntington's disease in older persons. Diagnosis can be established by documenting an expanded CAG repeat in the atrophin 1 gene.

Episodic Ataxias

The episodic ataxias are characterized by brief, reversible attacks of ataxia of variable duration often associated with other neurological features. However, in some of them, a more persistent neurological deficit may develop or may be present from the very onset, blurring the distinction from the SCAs. Conversely, some of the SCAs (such as SCA 6) may have features reminiscent of episodic attacks. Many of the EA syndromes have pediatric onset.

Onset of EA 1 is in early childhood with very brief episodes of ataxia lasting seconds to minutes associated with a coarse tremor and dysarthria. Between attacks of ataxia, patients have skeletal muscle myokymia that may be detected clinically or only by electrophysiological studies. Children with EA 1 may have other features such as partial epilepsy, transient postural abnormalities, and tight heel cords. Some patients may have only peripheral myokymia with no ataxia, and some may have persistent cerebellar findings and cerebellar atrophy on scans. Mutations in the potassium channel gene, *KCNA 1,* have been identified in EA 1.

EA 2 also has a childhood onset in the majority of patients. Episodes of ataxia last many hours and are associated with other symptoms such as headache, nausea, vomiting, diplopia, and dysarthria. Interictally, many EA 2 patients have mild cerebellar deficits including nystagmus (often downbeating) and difficulty with tandem gait. EA 2 patients may have a progressive ataxia later in life. Unusual features have been described, including children with features of benign paroxysmal vertigo and cognitive decline associated with attention deficit disorder. In addition, the EA 2 mutations may be associated with seizures, coma, and cerebral edema after mild head trauma. EA 2 is allelic to two other diseases, familial hemiplegic migraine (FHM) and SCA 6. All of them are related to mutations in the α subunit of the neuronal calcium channel gene, *CACNA1A*; EA 2 and FHM are related to point mutations in the gene and SCA 6 to a CAG expansion.

Other EAs have been defined by the presence of familial episodic ataxia or vertigo and exclusion of the EA 1 and EA 2 mutations. EA 3 is characterized by brief episodes of ataxia and vertigo, associated with tinnitus. It has been localized to chromosome 1q42. EA 4 has been reported to produce late-onset episodic vertigo and ataxia (vestibulocerebellar ataxia) lasting many hours; linkage to EA 1 and EA 2 loci has been excluded, but no other genetic information is available. EA 5 has clinical features similar to EA 2; mutation in the β4 subunit of the calcium channel gene, *CACNB4,* has been reported in one family. Finally, EA 6 was reported in a single child with episodes of ataxia, hemiplegia, and seizures with a mutation in an astrocytic glutamate transporter gene (*SLC1A3)*. The mutation was shown to have lead to loss of function of the protein with a dominant negative effect on the wild type product by functional studies.

Treatment: EA syndromes respond to many drugs with reduction in the number of episodes. Whether these drugs prevent long-term, progressive deficits is not clear. EA 1 responds to carbamazepine, valproate, and sometimes to acetazolamide. Acetazolamide often leads to dramatic improvement in EA 2; other drugs that may ameliorate attacks include flunarazine and 4-aminopyridine.

For the SCAs, there is no proven therapy at this time. Supportive and rehabilitative care need to be organized as for many other disabling neurological illnesses. As in all genetic diseases, appropriate referral for genetic counseling is indicated.

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368 Approach to Diagnosis and Treatment of a Child with Motor Unit Diseases

Mustafa A. M. Salih

Definition/Classification

The anatomical route of the lower motor neuron, which composes the motor unit, has four subunits. These subunits consist of a motor neuron in the brainstem or ventral horn of the spinal cord and its axon, which together with other axons form the peripheral nerve; the neuromuscular junction; and the group of muscle fibers innervated by a single motor neuron. Disorders affecting these motor subunits can be further subdivided into hereditary syndromes and acquired diseases, and into acute and chronic disorders.

Epidemiology

Diseases of the motor unit affect all races and are common in children. A world survey of the commoner neuromuscular diseases estimated an overall prevalence of 286 per million populations. Nevertheless, the prevalence of some disorders in particular countries, such as congenital muscular dystrophy in Finland and Japan, spinal muscular atrophy and severe childhood autosomal recessive muscular dystrophy (SCARMD, limb-girdle muscular dystrophy [LGMD]) in Middle East and North African populations, reflects inbreeding in these communities, which increases the relative incidence of recessive disorders.

Diagnostic Approach

The recent advances in molecular biology has dramatically changed the diagnostic approach to neuromuscular disorders (NMDs), paved the way for accurate genetic counseling and for potential treatment by gene or cell therapy. Yet, a careful history and physical examination remain the cornerstones that guide the molecular and other investigative tools available to the clinician.

Symptoms

In childhood, common presenting symptoms of NMDs include floppiness or hypotonia, delayed motor milestones, abnormal gait, tendency to fall, as well as muscle weakness, cramps, or stiffness. It is also important to ascertain in the history whether certain activities that the child had difficulty with remained static or deteriorated. These activities include running, climbing stairs, and getting up from the floor. Questions pertaining to increase in muscle weakness as the day progresses, fatigue on effort and improvement on rest (suggesting myasthenia), and increased disability with inactivity and improvement with activity (suggesting myotonia) are also important. History of recurrent episodes of muscle weakness points toward periodic paralysis (in channel disorders), myasthenia gravis, dermatomyositis or polymyositis, and rhabdomyolysis or relapsing polyneuropathy. The occurrence of muscle cramps with exertion and their relief by rest may be the manifestation of some of the slowly progressive forms of muscular dystrophy (MD) such as Becker MD. They also occur in metabolic disorders of muscle (glycogenosis types V and VII and lipid metabolic disorders due to carnitine palmitoyl transferase deficiency, as well as other syndromes associated with myoglobinuria). Any observed muscle enlargement (hypertrophy) or wasting should also be ascertained. Difficulty with chewing or swallowing and associated respiratory deficit or disturbed sleep (indicating sleep apnea) are also vital components of enquiry.

Detailed family history of a similar condition is essential in each case and a pedigree chart will point toward an X-linked disease when the male relatives on the maternal

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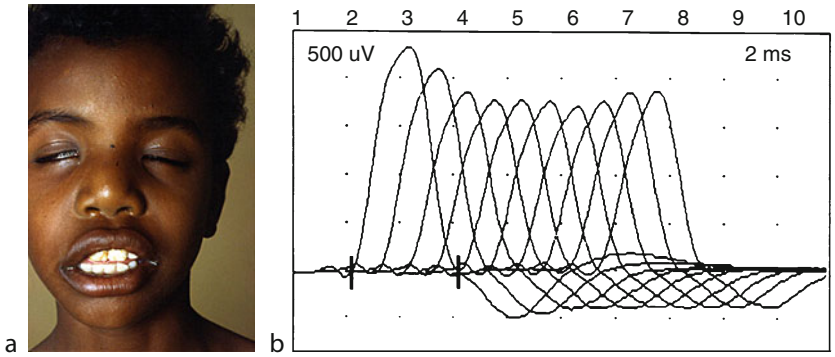

Figure 368.1
(a) Bilateral lower motor neuron facial weakness in a 12-year-old boy with fascioscapulohumeral muscular dystrophy. The patient cannot bury the eyelashes when asked to close his eyes tightly. The mouth is open with trickling saliva. (b) Repetitive electrical stimulation of a motor nerve showing myasthenic decremental response. There is a fall-off in the size of muscle action potential of greater than 10% between the first and fifth response

side are affected. Consanguineous parents having earlier normal generations and affected siblings of both sex may be carriers of autosomal recessive conditions.

Signs

A considerable proportion of the physical examination can be done while the child is still clothed sitting in one of parent's lap. Using an examination couch and undressing a child for formal assessment invites uncooperativeness and irritability. Uncomfortable procedures, like inspecting the tongue (for fibrillations) and palatal movement of a young child should be deferred to the end. An infant can be given an object of interest to handle, like small cubes or one of the parent's keys. This activity will assess the baby's ocular motility and the pincer grasp. It will also assess coordination and ability to raise the arms against gravity. Facial expression should be noted, especially the presence of an open, drooping, or triangular mouth. Ability to raise the eyebrows on looking up speaks against lower motor neuron facial weakness. The older child can be asked to shut the eyes tightly. In the presence of facial weakness, he or she will not be able to bury the eyelashes completely (see *Fig. 368.1a*). The lower face can be assessed by asking the child to pout, blow (or whistle), smile, show the teeth, and puff out the cheeks.

Examination of the upper and lower limbs should take note of muscle bulk, tone and power, whether weakness is proximal or distal, symmetric (involving both sides of the body) or asymmetric. The Medical Research Council (MRC) scale for evaluation of muscle (*Table 368.1*) is a useful and practical guide for comparing muscle groups (proximal vs. distal) initially and during follow-up examinations.

Table 368.1
Medical research council grading scale for evaluation of muscle power

Grade	Muscle response
0	No contraction
1	Flicker of contraction
2	Active movement, with gravity eliminated
3	Active movement against gravity
4	Active movement against gravity and resistance
5	Normal power

Deep tendon reflexes are generally lost in neuropathies and in motor neuron diseases (including spinal muscular atrophy) and are diminished, but preserved, in myopathies and dystrophies. In Duchenne MD, the ankle jerks are often retained and may even be brisk until late in the disease.

Joint abnormalities should also be assessed. These can manifest as laxity of ligaments or limitation of joint movement as a result of permanent shortening (contractures). They usually take the form of flexion contractures of the hips, knees, and other joints in the non-ambulant child. In inherited peripheral neuropathies, pes cavus is the usual

joint abnormality to be seen when the child is still walking. With loss of ambulation, scoliosis usually develops in various neuromuscular disorders, but can be prevented by adequate seating and other supportive measures.

Assessment of gait can start from the time an ambulant child comes into the consulting room. Toe-walking can be a transitory phenomenon in normal children but is a common feature in various neuromuscular disorders, spastic diplegic type of cerebral palsy, and hereditary spastic paraplegias. Walking on heels and heel-to-toe walking along a straight line are also useful in assessment. Ability to sit up from the supine position, get up from the floor, or from a chair are important details to elicit for examining the degree of hip girdle muscle weakness.

Following assessment of a child, it should be easy to determine whether the history and physical signs are indicative of a specific neuromuscular disorder or one outside the neuromuscular system.

Investigations

Three modalities of investigations are still used for diagnosing neuromuscular disorders. These are serum enzymes, electrophysiological procedures, and muscle and sural nerve biopsies. With the advent of molecular genetic markers, DNA analysis has become a routine definitive diagnostic test in several neuromuscular disorders, surpassing electromyography (EMG) and muscle biopsy.

Serum Enzymes

Creatine kinase (CK), which is released by damaged or degenerating muscle fibers is separated into three isoenzymes: MM for skeletal muscle, MB for cardiac muscle, and BB for brain. Serum CK determination is a very useful screening test for a suspected neuromuscular disease. (See Chap. 374, "Hereditary and Acquired Myopathies")

Electrophysiological Investigations

Nerve Conduction Studies

Motor and sensory nerve conduction can be measured by a relatively simple technique using surface electrodes. The conduction velocity is dependent on the diameter and the degree of myelination of the axon. At birth, conduction is about half of the adult value and reaches the mature value by 3–5 years of age. In peripheral neuropathies, the pathology may be primarily in the axon (axonal neuropathy) or, if in the supporting Schwan cell, it leads to segmental demyelination (demyelinating neuropathy). The nerve conduction velocity (NCV) is markedly decreased in demyelinating neuropathies. In axonal neuropathy, the NCV may be normal or slightly decreased, whereas the compound muscle action potential (CMAP) will be significantly low. Determining whether the neuropathy is demyelinating or axonal is of great help in guiding the DNA tests for the various forms of Charcot–Marie–Tooth disease (CMT, hereditary motor and sensory neuropathy [HMSN]).

In dominantly inherited demyelinating CMT, it is also important to assess the NCV in both parents and siblings, to detect subclinical cases. Post-infectious polyneuritis (Guillaine–Barre syndrome and diphtheritic polyneuropathy) may manifest as a demyelinating neuropathy. Measurement of the sensory conduction velocity and sensory action potential are useful diagnostic tools in mixed and complex neuropathies, such as CMT and Friedreich's ataxia, and in hereditary sensory and autonomic neuropathies.

Repetitive electrical stimulation of a motor nerve supplying a muscle aids diagnosis of congenital myasthenic syndromes and myasthenia gravis. Fatiguability of the muscle can be demonstrated by the falloff in the size of the muscle action potential (myasthenic decremental response) (*Fig. 368.1b*).

Electromyography (EMG)

This technique is capable of showing whether a particular muscle is normal or abnormal and whether the abnormality is myopathic or neuropathic. However, it is less useful in children than in adults because it requires insertion of a needle into the belly of a muscle, and because the amount of received information is directly proportional to the degree of cooperation. It has been largely replaced by more specific diagnostic tools, namely DNA analysis (such as in Duchenne MD and spinal muscular atrophy [SMA]) and muscle biopsy. Nevertheless, EMG is the diagnostic modality of choice in muscle diseases manifesting with myotonia, including myotonia congenita, myotonic dystrophy, and Schwartz–Jampell syndrome. It shows the pathognomonic spontaneous myotonic bursts of activity with gradual decrement. A typical sound of the "dive bomber" or "departing motor cycle" sound will be heard on acoustic amplification. It is usually present in dominantly inherited congenital myotonic dystrophy, but appears later

after the age of 2–3 years. The minimally affected mother of a suspected baby will usually show these pathognomonic bursts.

Muscle Biopsy

If a specific diagnosis of hereditary disease is not provided by molecular genetic testing in blood, which is currently available in many centers, a muscle biopsy is essential for establishing a definitive diagnosis in any patient with a suspected neuromuscular disorder. When interpreted by an experienced pathologist, it distinguishes between neurogenic, myopathic, and dystrophic processes. It can also indicate the type of myopathy and specify the deficient protein or enzyme.

An open biopsy, done under local anesthesia is preferable to needle biopsy, since it allows obtaining adequate tissue for additional biochemical studies, such as respiratory chain enzymes for investigating mitochondrial diseases. The vastus lateralis (quadriceps femoris) is the muscle usually sampled. Conventional paraffin sections of the biopsied specimen are not adequate, since that technique does not allow the diagnosis of many congenital and metabolic myopthies. Histochemical studies of frozen sections are, hence, obligatory. Immunohistochemistry is now essential, because it demonstrates the expression of dystrophin protein in Duchenne MD and Becker MD, as well as a number of other dystrophin-associated proteins. Deficiency of the latter causes a variety of autosomal recessive dystrophies. A portion of the biopsy specimen should be fixed in gluteraldehyde for potential electron microscopy, for diagnosis of several congenital myopathies and mitochondrial myopathy.

Sural Nerve Biopsy

The sural nerve is the most commonly biopsied nerve in neuropathies. Electron microscopy of a sural nerve sample can accurately differentiate between axonal and demyelinating neuropathies, as well as assess the types of fibers in hereditary sensory and autonomic neuropathies. Teased fiber preparations are useful in showing segmental demyelination, but are not done routinely since they are labor intensive.

Imaging of the Motor Unit

Differential involvement of muscle occurs in several neuromuscular disorders and this can be assessed by either ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI). Ultrasound, performed by an experienced operator, is a rapid and practical method to apply before sampling a muscle for biopsy. However, in advanced dystrophies a muscle biopsy might need MRI guidance. The latter technique is also useful in inflammatory myopathies of infectious (bacterial and parasitic), as well as immune (dermatomyositis) origin. Imaging of the spinal cord, nerve root, and plexus is best achieved using MRI.

Respiratory and Cardiac Investigations

Respiratory function tests should be done for children with diseases of the motor unit initially and on regular follow-up. In certain conditions with fluctuating weakness, like congenital myasthenic syndromes and myasthenia gravis, sleep studies need also to be arranged to explore the possibility of the occurrence of sleep apnea and hypoventilation. Electrocardiography (ECG) is also important in the clinical evaluation of muscular dystrophies and in inflammatory and metabolic myopathies to explore an associated subclinical conduction defect or cardiomyopathy. Regular follow-up with a pediatric cardiologist (on yearly or biennial basis) and serial assessment by electrocardiography are required in muscular dystrophies and certain congenital and metabolic myopathies.

Floppy Infant Syndrome

The complex of floppiness/hypotonia is a common neurologic symptom in infancy; and the floppy infant syndrome refers to an infant with generalized hypotonia presenting at birth or in early life. The diagnostic work up is often challenging, if a systematic evaluation of infants with hypotonia is not followed. Hypotonia usually manifests as unusual postures, such as lying in frog-leg position when supine (*Fig. 368.2a*). Hypotonia becomes more apparent by positioning the infant in certain ways. On ventral suspension, a floppy infant will lose the ability to maintain the head in line with body. The limbs will be dangling (*Fig. 368.2b*). On pulling to the sitting position by traction on hands, prominent head lag occurs (*Fig. 368.2c*). After the neonatal period, floppy infants usually present with delay in motor milestones.

A Practical Approach to Diagnosis

It has been a standard practice to decide first, whether the hypotonia is a manifestation of a motor unit disease or if it

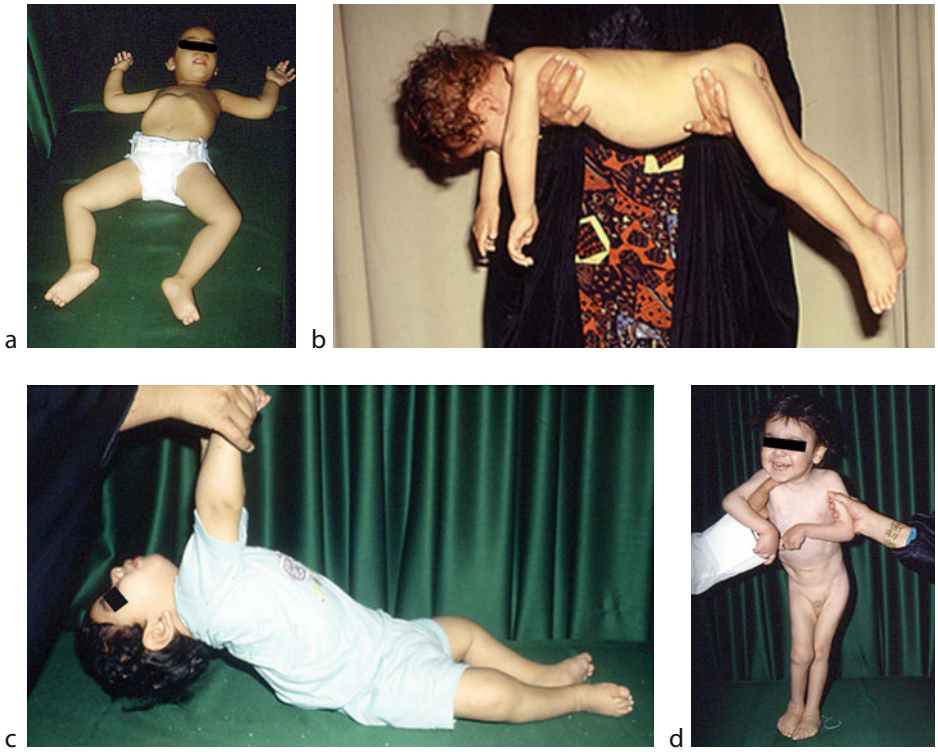

Figure 368.2
(a) A floppy infant with frog-like position when supine. (b) On ventral suspension, the limbs are dangling. (c) Prominent head lag on pulling to the sitting position. (d) Central nervous system (CNS) disorder causing floppy infant syndrome. When assessing the ability to support weight, there is scissoring of legs, flexion of elbows and clenching of the hands

is due to a disorder of the central nervous system (CNS), or another system in the body. Significant degree of weakness is usually associated with motor unit diseases. On the other hand, hypotonia without weakness includes disorders of CNS, and metabolic, nutritional, and endocrine disorders. Assessing weakness can be achieved even in very young infants by observing the spontaneous movements of the face and limbs, response to stroking the soles, and the ability to sustain passively elevated arms or legs. Other features that point to hypotonia being caused by disorders of CNS include the easily elicited (or brisk) deep tendon jerks, whereas in a disease of the lower motor unit, reflexes are typically diminished or absent. With increasing age, hypotonia is gradually replaced by hypertonia in disorders of CNS and there is persistence of neonatal reflexes such as the grasp, Moro, and tonic-neck reflex. When assessing the ability to support weight of such older infants, the legs will be kept crossed (scissoring) and there is plantar flexion of the feet. The elbows are usually flexed, hands are clenched, and the thumb is kept across the palm (fisting position) (*Fig. 368.2d*).

Disorders of the CNS (Cortical, Subcortical, and Cerebellar)

Congenital or acquired disorders of the CNS account for the majority of the causes of floppy infant syndrome (*Table 368.2*).

Clinical Manifestations

History: Pregnancy, Birth, and Perinatal

Important features to ascertain when considering hypotonia due to disorders of CNS include age of the mother at time of birth. Advanced age increases the chance of chromosomal disorders. Other features include history of fever, infections or teratogens especially during early pregnancy, polyhydramnios or oligohydramnios, recurrent abortions or stillbirth, and if any abnormalities were detected on screening ultrasound.

Table 368.2
Disorders of the central nervous system (CNS) manifesting as floppy infant syndrome

Static encephalopathy
Cerebral dysgenesis/dysplasia: Lissencephaly, holoprosencephaly, Joubert syndrome, pontocerebellar hypoplasia
Perinatal hypoxic/ischemic insult, kernicterus and intracranial hemorrhage
Congenital infections: TORCH
Genetic syndromes and chromosomal abnormalities: Down syndrome (Trisomy 18, Prader-Willi syndrome, Cri-du-chat [5p-] syndrome).
Metabolic disorders:
Disorders of carbohydrate metabolism: galactosemia, hereditary fructose intolerance
Disorders of amino acid metabolism: Phenylketonuria, tyrosinosis type 1, sulphite oxidase deficiency, nonketotic hyperglycinemia, argininosuccinic aciduria
Organic acidemias: Maple syrup urine disease (MSUD), methylmalonic academia, glutaric aciduria, propionic academia, malonic aciduria, multiple carboxylase deficiencies (defects in utilization of biotin).
Mitochondrial disorders: Respiratory chain and Kreb cycle disorders, Leigh's syndrome, pyruavete carboxylase deficiency, pyruvate dehydrogenase complex deficiency.
Lysosomal storage disease: Mucopolysaccharidosis, lipidosis (Gauher type 2, Nieman-pick type A, Tay-Sachs disease), mucolipidosis (sialidosis type II, I-cell disease).
Perioxosomal disorders: Zellweger syndrome, rhizomelic chondrodysplasia punctata.

The duration of pregnancy and the birthweight are also vital. Preterm delivery increases the risk of perinatal hypoxic-ischemic insult and intraventricular hemorrhage. The mode of delivery, whether assisted by ventose or through a cesarean section following difficult birth and the Apgar score 5 min after birth is important. If this is not available, asking whether the baby breathed spontaneously and cried immediately after birth gives a reasonable idea, provided the mother has not been under the effect of anesthesia for cesarean section. Difficulties in sucking and swallowing during the first 24 h after birth may reflect the severity of the hypoxic-ischemic insult. Whether the baby needed to be shifted to the neonatal intensive care unit (NICU), required mechanical ventilation or had seizures, and the duration of stay in the NICU are also salient points.

History of delayed motor, speech, or cognitive development following the neonatal period points toward genetic disorders or cerebral dysgenesis. Loss of previously acquired milestones usually heralds neurodegenerative and metabolic disorders. Seizure disorders may be associated with cerebral dysgenesis or chromosomal disorders.

Signs

Obtunded appearance of the baby may reflect consequences of neonatal insult or brain dysgenesis, and the presence of encephalopathy out of the context of birth history points toward an underlying metabolic disorder. Dysmorphic features give important clues to identifying genetic disorders. Skin examination may reveal neurocutaneous signs. Anthropometry (weight, height, and head circumference) should be routine. Obesity and short stature are features of Prader–Willi syndrome, whereas microcephaly is common in chromosome abnormalities, brain dysgenesis (e.g., microcephaly and lissencephaly syndromes), and TORCH (Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, Herpes simplex virus) infections (except for congenital toxoplasmosis, which can present with hydrocephalus).

Ophthalmologic examination may reveal important diagnostic signs. Oculomotor apraxia is a feature of Joubert syndrome, ataxia telangiectasia, and ataxia-oculomotor apraxia syndromes. A cherry red spot indicates an underlying lipidosis. Retinitis pigmentosa may indicate other storage diseases, such as neuronal ceroid lipofuscinosis. Ptosis and ophthalmoplegia (or ophthalmoparesis) are found in congenital myasthenia, congenital myasthenic syndromes, and some mitochondrial disorders.

Examination of the chest, cardiovascular system, and abdomen may reveal an underlying multisystem involvement. In particular, the presence of hepatosplenomegaly may be associated with TORCH infections, glycogen storage disease, and lipidosis (e.g., Nieman–Pick disease types A and C) (*Fig. 368.3a*).

Spinal Cord Lesions

These lesions can follow damage to the spinal cord during delivery, the presence of a congenital tumor, or dysraphic states (tethered cord and myelomeningocele). Traumatic lesions involve either the lower cervical and upper thoracic cord with breach delivery, or the upper cervical region with cephalic presentation. Mid-forceps

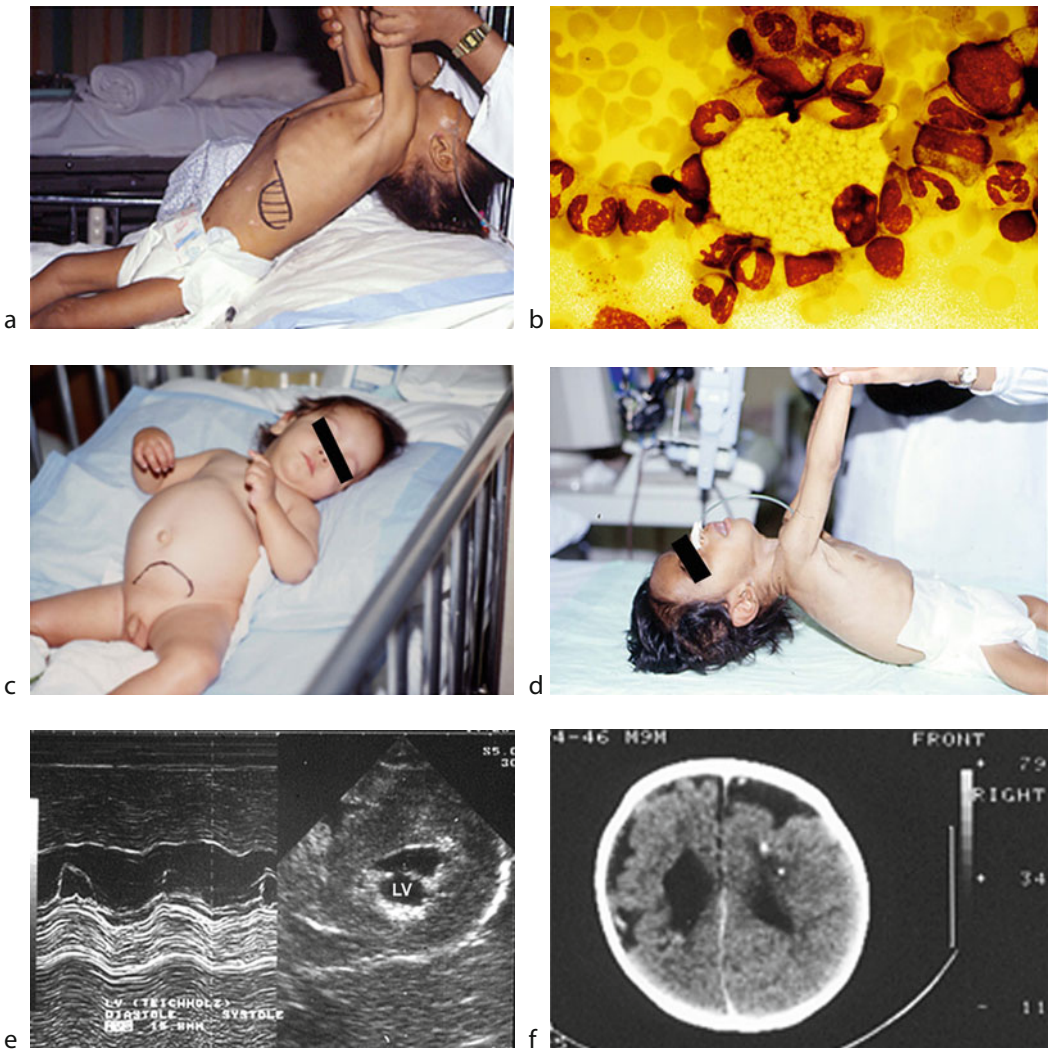

Figure 368.3

(a) Floppy infant syndrome due to Niemann-Pick disease. The enlarged liver and spleen are marked. (b) Bone marrow showed the characteristic foam cell (arrow). (c) Bladder distension associated with hypotonia due to spinal cord injury. (d) An infant with Pompe disease (glycogenosis type II). (e) Echocardiography showed hypertrophic cardiomyopathy and small left ventricle (LV). (f) Cranial computed tomography (CT) scan showing periventricular calcification and brain malformation in congenital cytomegalovirus infection (Figs. 3d and e are courtesy of Dr. Elsayed Ali)

extractions with excessive longitudinal traction or rotation are known risk factors.

The clinical picture is characterized by hypotonia, which may persist or evolve into spasticity, associated with paraplegia or tetraplegia, respiratory insufficiency or paradoxical breathing in some cases, bladder distension, impaired bowel control, pyramidal tract signs, and sensory level (*Fig. 368.3c*). The lower roots of the brachial plexus may be affected and manifest with paralysis of the intrinsic hand muscles. Congenital spinal cord tumors present with similar localizing signs.

Diseases of the Motor Unit

Disorders of the motor unit account for 18–47% of the causes of the floppy infant syndrome. In these conditions, the infant has a significant degree of weakness in

Table 368.3
Diseases of the motor unit associated with the floppy infant syndrome

Anterior horn cell
Acquired: Poliomyelitis, other viral syndromes (e.g., Coxsackie A)
Hereditary: Spinal muscular atrophy (SMA) type 1 (Werdnig–Hoffman disease and SMA type 2).
Peripheral nerve
Acquired: Guillaine-Barre syndrome
Hereditary: Congenital hypomyelination neuropathy
Neuromuscular junction
Transient neonatal myasthenia, congenital myasthenic syndrome
Botulism
Muscle
Congenital myopathies: Myotubular myopathy, nemaline myopathy, congenital fiber type disproportion, central core disease, multiminicore disease, Salih myopathy
Metabolic myopathies: Glycogenosis types II (Pompe disease) and III.
Mitochondrial myopathies, lipid storage myopathies, periodic paralysis
Congenital myotonic dystrophy, neonatal Schwartz-Jampel syndrome
Congenital muscular dystrophies

association with hypotonia. The anatomic localization of these disorders is detailed in *Table 368.3*.

Clinical Manifestations

History: Pregnancy, Birth, and Perinatal

It is always pertinent to ask whether the mother has been diagnosed to have a neuromuscular disease such as myotonic dystrophy or myasthenia gravis. History of polyhydramnios is a common feature in congenital myotonic dystrophy. Diminished fetal movements may be noticed by the mother in congenital myotonic dystrophy and spinal muscular atrophy (SMA) type 1 (Werdnig–Hoffman disease). On ultrasound screening, brain abnormalities are detectable in Walker–Warburg phenotype of congenital muscular dystrophy (CMD). Arthrogryposis multiplex can also be noted. Breech presentation is common in neuromuscular births. Poor respiratory effort and difficulties in sucking and swallowing may also be a feature, as in congenital myotonic dystrophy, myotubular myopathy, nemaline myopathy, neonatal myasthenia, congenital myasthenic syndrome, and the Walker–Warburg type of CMD.

Signs

Assessment for associated features should also be done, such as the presence of hepatomegaly, respiratory, and/or cardiac signs in glycogenoses types II (Pompe disease) and III, lipid storage myopathies, and mitochondrial myopathies.

The distribution and degree of weakness may help to distinguish between the various causes of hypotonia of neuromuscular origin. Loss of antigravity movement of the limbs points toward proximal muscle weakness, whereas distal weakness is indicative of a peripheral nerve disorder. In SMA type 1, the intercostal muscles are severely affected and breathing is diaphragmatic. Tongue fasciculation is a helpful sign. Ocular muscle involvement, in the form of ophthalmoplegia and/or ptosis is a feature of disorders of neuromuscular junction (transient neonatal myasthenia, congenital myasthenic syndrome, and botulism), mitochondrial myopathy, some congenital myopathies (e.g., myotubular myopathy), and myotonic dystrophy. Asymmetric ptosis is found in some cases of Salih myopathy. Facial muscle involvement is common in CMD, myotonic dystrophy, and congenital myopathies, but it is not present in SMA. Pursed-mouth appearance during crying is a feature of neonatal Schwartz–Jampel syndrome. Asymmetric association of the sixth and/or seventh cranial nerves is seen in acquired causes of floppy infant syndrome, namely poliomyelitis and diphtheritic polyneuropathy. Facial nerve involvement is symmetric in Guillaine–Barre syndrome. Deep tendon jerks are usually diminished in neuromuscular disorders but absent in SMA.

Contractures and arthrogryposis are common in congenital myotonic dystrophy and CMD. Nevertheless, Ullrich type of CMD is characterized by a peculiar combination of proximal contractures and distal laxity with congenital hip dislocation. Neonatal Schwartz–Jampel syndrome features pectus excavatum, camptodactyly, bowed lower limbs, and talipes.

Systemic Disorders

Apart from disorders of CNS and diseases of the motor unit, certain systemic disorders can present as floppy infant syndrome, as detailed in *Table 368.4*.

Table 368.4
Systemic disorders that may manifest floppy infant syndrome

Endocrine disorders
Hypothyroidism, hyperparathyroidism
Nutritional disorders
Primary: Severe childhood undernutrition (protein-energy malnutrition), rickets
Secondary: Malabsorption syndromes (celiac disease and cystic fibrosis), AIDS, cardiac disease, renal disease, pulmonary disease (tuberculosis)
Electrolyte disorders: Renal tubular acidosis, marble bone-marble brain disease (type III osteopetrosis)
Connective tissue disorders: Congenital laxity of ligaments, osteogenesis imperfecta, Ehlers–Danlos syndrome, Marfan syndrome, arachnodactyly.

Investigations

These investigations should be guided by the clinical presentation, symptoms, and the elicited physical signs. During the neonatal period, especially when there are features of encephalopathy or recurrent vomiting, investigations for inborn errors of metabolism should receive priority. Most inborn errors of metabolism, when presenting in the neonatal period, are lethal if specific treatment is not initiated immediately.

Measurement of serum concentrations of ammonia, bicarbonate, and pH should be done first. Many inborn errors of metabolism cause a metabolic acidosis due to excessive production of ketoacids, lactic acid, and/or other organic anions. Elevation of blood ammonia is usually caused by urea cycle defects. Such infants have normal serum pH and bicarbonate values. Determination of anion gap ($[Na^+] - [Cl] - [HCO_3]$) is the next pertinent step. High anion gap associated with serum ammonia is found in organic acidemias, whereas normal anion gap and normal serum ammonia are found in aminoacidopathies and galactosemia. Lactic acidosis unrelated to an enzymatic defect occurs in hypoxemia. When lactic acidosis results from an enzymatic defect in gluconeogenesis or pyruvate dehydrogenase complex, both lactate and pyruvate are increased and the ratio is normal. In hypoxemia and in mitochondrial diseases due to defects in the respiratory chain, the serum pyruvate concentration may remain normal with an increased lactate:pyruvate ratio. Elevation of lactic dehydrogenase (LDH), serum glutamate-oxaloacetate transaminase (SGOT), and serum glutamate-pyruvate transaminase (SGPT) indicates hepatic involvement in galactosemia, urea cycle defects, aminoacidurias, and organic acidurias. Other blood tests that should be done routinely include complete blood count (for neutropenia and thrombocytopenia seen in organic acidurias), glucose, urea, electrolytes (Na, K, and Cl), creatinine, blood gases, and thyroid function tests.

Biochemical neonatal screening is now available in many countries using tandem mass spectrometry (MS/MS); the diseases being screened emphasize differences in their incidence and prevalence among different populations. In addition to the tandem mass spectrometry, blood spots obtained from a newborn on Guthrie card can also be used to screen for hypothyroidism, biotinidase deficiency, congenital adrenal hyperplasia, and galactosemia, using high throughput fluorometric assays. In suspected cases of nonketotic hyperglycinemia, the diagnosis is highly significative by the demonstration of elevated plasma and cerebrospinal (CSF) glycine levels, with a high glycine CSF/plasma ratio, and confirmed by glycine cleavage enzyme assay on liver biopsy. In organic acidurias, findings in tandem mass spectrometry can be further confirmed by gas chromatography/mass spectrometry analysis of the urine organic acid profile.

In countries where a comprehensive neonatal screening program is not available, simple urine screening tests can be used. These tests include the ferric chloride test (phenylketonuria [PKU], tyrosinosis), the dinitrophenylhydrazine test (PKU, Maple syrup urine disease), the sodium cyanide-nitroprusside test (homocystinuria), Benedict's reagent or Clinitest tablets test (galactosemia), ketones (organic acidurias), and cetyltrimethylammonium bromide (mucopolysaccharidoses). These tests can be used as a basis for initiation of therapy when the clinical manifestations suggest the diagnosis. Nevertheless, they should never be considered definitive.

Special investigations when suspecting a disease of the motor unit include creatine kinase.

In Duchenne and Becker MDs, the level is grossly elevated (up to 50 times the normal limit) in the early stages, whereas in SCARMD and congenital muscular dystrophy, it is 5–10 times normal. Other forms of dystrophy such as Emery–Dreifuss MD may have a more modest elevation. In congenital myopathies with structural muscle abnormalities, it is likely to be normal or only slightly elevated. The levels are usually normal in neurogenic diseases, like the spinal muscular atrophies. Mild degrees of elevation are also seen in some carriers of Duchenne MD and in subclinical malignant hyperthermia.

CK is moderately elevated in congenital muscular dystrophy (CMD) but can range from normal to marked

elevation, depending on the underlying degree of muscle degeneration. It is also likely to be normal or only slightly elevated in several congenital myopathies with structural abnormality, such as central core disease or nemaline myopathy. In Salih myopathy, serum CK is mildly elevated in the first 4 years of life (four times the upper normal limit) and increases slightly more by 10 years (5.5 times the upper normal limit). In SMA types 1 and 2 and other neurogenic syndromes serum CK is usually normal. The transminases (alanine aminotransferase, ALT and aspartate aminotransferase, AST) are also elevated in muscular dystrophy. Finding an associated elevation of CK will spare an unnecessary liver biopsy.

Chest X-ray is helpful in congenital myotonic dystrophy and may show diaphragmatic elevation due to hypoplasia of the diaphragm. It may also show thin ribs, which points to the antenatal origin of the condition. Cardiomegaly in Pompe's disease (type II glycogenosis) can also show on chest X-ray, as well as the radiologic features of rickets and osteopetrosis in the ribs and spine, respectively. Vertebral anomalies can also be seen in mucopolysaccharidosis, although bone survey is more suited for that.

Electrocardiography (ECG) is very useful in SMA since it shows the characteristic tremor (minipolymyoclonus) of the baseline, particularly in the limb leads, probably reflecting the fasciculation of skeletal muscle. In type II glycogenosis (Pompe's disease), ECG reveals features of hypertrophic cardiomyopathy, which is better assessed by echocardiography (*Fig. 368.3d, e*).

Bone marrow aspiration and biopsy helps to show the characteristic cells in type 2 Gaucher disease and the Nieman–Pick disease (NPD) types A and C (*Fig. 368.3b*).

Neuroimaging

Cystic encephalomalacia, intraventricular hemorrhage, porencephaly, and hydranencepahly can be detected by cranial ultrasound. Cranial computed tomography (CT) is helpful in detecting any neonatal intracranial hemorrhage or brain edema secondary to hypoxic-ischemic encephalopathy (HIE), some of the inborn errors of metabolism (e.g., glutaric aciduria type 1), and the presence of lissencephaly. It is also more sensitive than MRI in identifying intracranial calcification, which is seen with congenital TORCH infections, isolated sulphite oxidase deficiency, and marble brain disease with renal tubular acidosis (*Fig. 368.3f*).

Later in infancy, it will show the periventricular leukomalacia and bilateral thalamic calcification of HIE and also of isolated sulphite oxidase deficiency. It may also show the basal ganglia cavitations that characterize biotin-responsive basal ganglia disease.

On the other hand, magnetic resonance imaging (MRI) is superior to CT in showing the features of HIE but it is difficult to use in the perinatal period. Nevertheless, MRI is the most sensitive modality to characterize the brain malformations associated with some forms of congenital muscular dystrophy (CMD). It also delineates the characteristic white matter alterations found in merosin-negative CMD, and basal ganglia and brainstem lesions in Leigh's disease.

Neurophysiology

Nerve conduction velocity (NCV) is a relatively simple technique requiring only surface electrodes, which can identify cases of peripheral neuropathy and characterize whether they are primarily axonal or demyelinating. On the other hand, electromyography (EMG), which requires needle insertion, is more invasive and frightening for babies. It does not detect myotonia in congenital myotonic dystrophy. However, myotonia can be confirmed in the asymptomatic mother on EMG. In a young child with a febrile illness and weakness, EMG is contraindicated in countries where oral poliovirus (OPV) vaccine is used. Intramuscular injection is a known risk factor for the development of vaccine-associated paralytic poliomyelitis. This also applies to places where vaccination coverage is still inadequate. It has long been noted that intramuscular injections administered during the incubation period of wild-type poliovirus causes what is known as "provocation" poliomyelitis. The author has seen a young child with extensive paralysis following an EMG, done at the start of weakness, within a few days after receiving OPV.

Decremental response following repetitive nerve stimulation (RNS) is diagnostic of congenital myasthenic syndrome (CMS) and can be positive when edrophonium test is negative. This test can be life saving in COLQ-mutant CMS where most patients are severely disabled from an early age with respiratory difficulties and no effect, or even worsening, after administration of acetyl choline esterase (AChE) inhibitors.

Muscle Biopsy

The muscle biopsy provides the definitive diagnosis in congenital myopathies and dystrophies, with the exception of congenital myotonic dystrophy when it may lead to

misdiagnosis of other pathologies. In congenital myopathies, the specific structural defect can be revealed by histochemistry of muscle. Accumulation of glycogen is seen in type II glycogenosis (Pompe's disease) and accumulation of lipid in lipid storage myopathy. The characteristic ragged-red fibers may be seen in mitochondrial myopathy associated with absence of COX staining (complex IV of the mitochondrial respiratory chain). Electron microscopy, although time consuming and not widely available, has high diagnostic yield in the congenital myopathies. Dystrophic features are seen in muscular dystrophies, and immunohistochemistry can delineate the missing glycoprotein such as in merosin-deficient CMD.

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369 Cranial Nerve Disorders

Mustafa A. M. Salih

Congenital Cranial Dysinnervation Disorders

Congenital cranial dysinnervation disorders (CCDDs) are a group of neuromuscular diseases characterized by motor unit abnormalities involving ocular motility, eyelid, and/or facial muscles. These disorders result from developmental errors of cranial nerve (CN) innervations. The group includes Duane syndrome, congenital fibrosis of the extraocular muscles (CFEOM), congenital ptosis, horizontal gaze palsy with progressive scoliosis (HGPPS), Bosley–Salih–Alorainy syndrome (BSAS), congenital facial palsy (CFP), and Moebius syndrome.

Duane Syndrome

Duane syndrome is characterized by congenital limitation of horizontal eye globe movement and some globe retraction on attempted adduction of the eye. It constitutes the most common of the CCDs with prevalence of 1:10000 (1–4% of strabismus cases), and 10% of cases are familial. The condition results from reduction or absence of the abducent nerve (CN VI) motor neurons associated with aberrant innervations of the lateral rectus by the oculomotor nerve (CN III). In type 1 Duane syndrome (which constitutes about 80% of cases), abduction is affected with normal or minimally defective adduction, associated with narrowing of the palpebral fissure of the adducting eye. Both abduction and adduction are limited in type 3 Duane syndrome, whereas in type 2 Duane syndrome, adduction is limited.

Congenital Fibrosis of the Extraocular Muscles (CFEOM)

Various forms of CFEOM result from primary dysinnervation of oculomotor (CN III) and/or trochlear (CN IV) innervated extraocular muscles. Individuals with CFEOM1 have congenital nonprogressive bilateral external ophthalmoplegia, and congenital bilateral ptosis; inability to raise either eye above the horizontal midline and an infraducted primary position of each eye. The condition is inherited as autosomal dominant and, in most families, results from heterozygous mutations in *KIF21A* gene. Rare probands of CFEOM1 harbor mutations in the *FEOM3* gene.

Individuals with CFEOM2 are born with bilateral ptosis, with their eyes primarily fixed in an exotropic position and severely limited horizontal and vertical eye movements. The condition results from primary developmental defect of both oculomotor (CN III) and trochlear (CN IV) nuclei, and the only normally functioning extraocular muscle is the abducens (CN VI) innervated lateral rectus that pulls each eye outward. The condition is inherited as autosomal recessive and results from *PHOX2A* gene mutations. In CFEOM3, at least one affected family member does not meet CFEOM1 criteria. The condition results from a variable defect of the oculomotor (CN III) nucleus development. Inheritance is autosomal dominant with incomplete penetrance. Mutations of the *KIF21A* gene were detected in a minority of families with CFEOM3. Recently, and in 17 unrelated families and 12 unrelated individuals, CFEOM3 was found to be caused by heterozygous mutations in the *TUBB3* gene. These lead to a common defect in axonal guidance during development, which can result in additional neurologic involvements other than those manifesting in the ocular muscles.

Horizontal Gaze Palsy with Progressive Scoliosis (HGPPS)

Individuals affected with HGPPS are born with absent horizontal gaze movements and develop severe progressive scoliosis, starting in infancy or childhood (*Fig. 369.1a*). Horizontal gaze palsy, which is nonprogressive, results from hypoplasia of the abucens (CN VI) nucleus with interneuron dysinnervation (medial longitudinal fasciculus and pontine paramedian reticular formation). Unlike other CCDDs, the abducens (CN VI) nerve is present bilaterally and the extraocular muscles are normal. Inheritance is autosomal recessive and the

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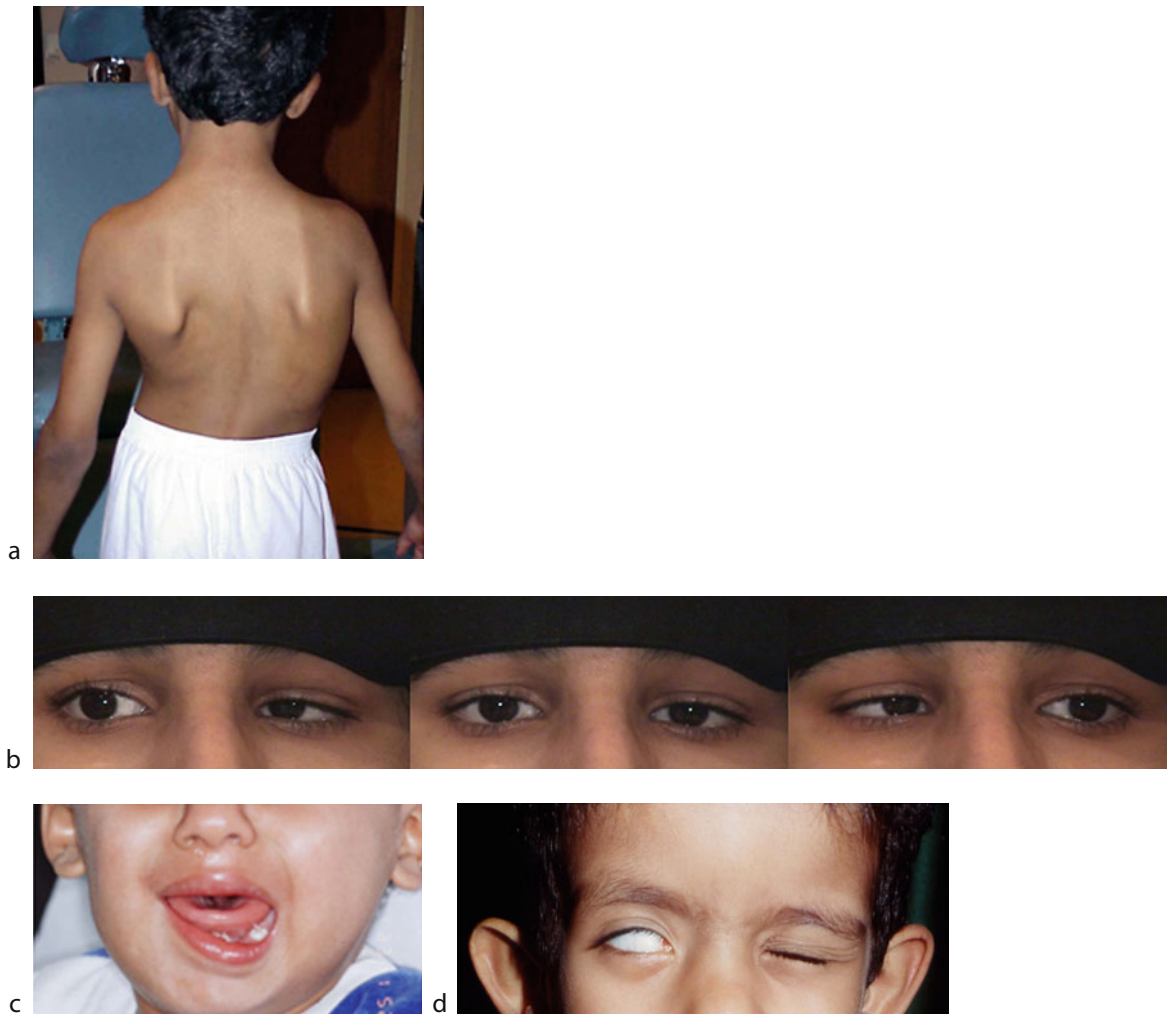

Figure 369.1

(a) Early scoliosis in a patient with horizontal gaze palsy with progressive scoliosis (HGPPS). (b) Bilateral Duane syndrome in an adolescent with Bosley-Salih-Alorainy syndrome (BSAS). There is limitation of horizontal eye globe movement with reduced abduction of both eyes associated with narrowing of the palpebral fissure of the adducting eye (Courtesy of Prof. Thomas M. Bosley). (c) Isolated weakness of the depressor angulae muscle. The right corner of the mouth fails to be lowered on crying. (d) Attempted closure of the eyes showing upward rolling of the right eye (Bell phenomenon) in a patient with right facial (VII cranial nerve) palsy

condition has been reported in consanguineous pedigrees of several different ethnicities. It results from homozygous or compound hererozygous mutations in *ROBO3*. The *ROBO3* gene encodes a transmembrane receptor required for hindbrain axon midline crossing. Electrophysiologic studies and tractography, using magnetic resonance imaging (MRI) diffusion tensor imaging, showed that affected individuals have ipsilateral corticospinal and dorsal column-medial lemniscus tract innervations.

Bosley–Salih–Alorainy (BSAS) and Athabascan Brainstem Dysgenesis Syndromes

Children with BSAS have bilateral Duane syndrome (*Fig. 369.1b*), associated in a subset of them with congenital sensorineural deafness secondary to bilateral absence of the cochlea, semicircular canals and vestibule, malformations of the internal carotid arteries and cardiac

outflow tract, mental retardation and autism in some patients. The phenotype of BSAS overlaps with that of Athabascan brain dysgenesis syndrome (ABDS), which includes, in addition, central hypoventilation, facial weakness, and vocal cord paralysis. Both syndromes result from mutations in *HOXA1*, a homeobox gene essential to the development of head and neck structures, including hindbrain, ear, and occipital and hyoid bones. Homozygous mutations of *HOXA1* have been identified in BSAS consanguineous pedigrees in the Middle East (Saudi Arabia and Turkey) and as a sporadic trait in Native American (Athabascan) children from the American Southwest. In *Hoxa1*-knockout mice, the abducens nerve (CN VI) is absent, and it is likely that abducens (CN VI) development and consequent innervations of the lateral rectus muscle is aberrant in BSAS and ABDS patients.

Congenital Facial Palsy

Congenital nontraumatic facial weakness can occur in isolation or in association with abnormal ocular motility. Isolated congenital facial nerve (CN VII) weakness is thought to result from facial nuclei and/or nerve maldevelopment. The condition is unilateral or bilateral, often asymmetrical, and is inherited as autosomal dominant with variable penetrance. It can rarely be associated with congenital deafness.

Moebius Syndrome

Moebius syndrome is defined as facial weakness combined with an ocular abduction deficit. It is a rare sporadic disorder with an estimated prevalence of one case per 50,000 newborns in the USA and four cases per 189,000 newborns in the Netherlands. Necropsy studies in Moebuis patients have shown defects ranging from hypoplasia to agenesis of the respective cranial nuclei. Nevertheless, it has not been established yet whether nerve, brain stem, or muscle aplasia is the primary event leading to this phenotype. CNs IX (glossopharyngeal) and X (vagus) may be affected. The hypoglossal nerves (CN XII) are involved in a minority of cases, whereas the oculomotor (CN III) and trochlear (CN IV) can be involved on rare occasions.

Clinical Manifestations

The condition presents at birth with facial diplegia, incomplete eye closure during sleep, difficulty in sucking and drooling. Examination reveals masklike immobile facial appearance associated with various gaze palsies in about 80% of patients. Involvement of the hypoglossal (XII) nerve (in approximately 25% of cases) leads to atrophy and inability to protrude the tongue. Musculoskeletal abnormalities may be present in about a third of patients. These include talipes equinovarus, congenital amputations, arthrogryposis, syndactly, brachydactyly, and, occasionally (15% of patients), hypoplasia or absence of the pectoralis muscle and breast associated with ipsilateral hand malformation (also called Poland anomaly). Features of autism are known to be associated with some cases of Moebius syndrome.

Diagnosis and Differential Diagnosis

Most cases are recognized during infancy, but the diagnosis soon after birth may be difficult because of the rarity of the condition. Moebius syndrome can be confused with facial palsy secondary to birth trauma (especially with the use of forceps in breach deliveries), congenital myotonic dystrophy, congenital myopathies, or congenital muscular dystrophy.

On electromyography (EMG), no features of active denervation will be seen in the facial muscles, which are hypoplastic or aplastic. Conversely, in birth trauma, denervation potentials will be recorded 2–3 weeks (or more) after the facial nuclei or nerves are injured.

Cranial computed tomography (CT) may demonstrate bilateral calcifications in the region of the abducens (CN VI) nuclei. Bilateral calcifications of the basal ganglia have also been reported. MRI may show hypoplasia of the brain stem and exclude other associated cerebral malformations.

Treatment

This is generally supportive and symptomatic, depending on the severity of the patient's deficits. Attention should be given to check the development of corneal abrasion/ulceration, aspiration pneumonia, dysphagia, and poor nutrition. Physical and occupational therapies are useful for managing associated musculoskeletal problems. Speech therapy is also helpful, as well as psychiatric management when there is an associated autism. Symptomatic and cosmetic surgical care may be required such as tracheostomy, for supporting airway; gastrostomy, for feeding; and correction of foot deformities. Surgery for strabismus is usually delayed because the condition frequently improves

with age, and plastic surgery may be required to counteract facial nerve paralysis.

Prognosis

Death may occur shortly after birth in 28% of patients, mainly due to bulbar or respiratory problems. Otherwise, Moebuis syndrome is a static neurologic defect with no mortality in its mild form.

Perinatal Factors and Other Causes of Congenital Facial Palsy (CFP)

Due to the relatively superficial course of the extracranial facial nerve (CN VII), it can be damaged during birth. This can follow instrumentation in assisted delivery, and intrapartum compression where the fetal head is compressed against the maternal bony prominences such as the ischeal spines, the pubic rami, and sacral prominence. Apart from Moebius syndrome and Poland sequence, other syndromes have CFP as part of their symptoms. These include Goldenhar syndrome, which is characterized by unilateral facial hypoplasia (occasionally associated with facial palsy), epibulbar dermoid, preauricular skin tags, and cervical vertebral defects. Cardiofacial syndrome can be confused with CFP. However, in this condition, there is isolated weakness of the depressor anguli oris and quadratus labii inferioris muscles, and the lower corner of the mouth on the involved side fails to move downward on crying (*Fig. 369.1c*). On the same side, the lower lip may be slightly everted. In a minority of patients, the condition was found to be associated with congenital heart disease.

Acquired Facial Paralysis

Bell's Palsy

Definition/Classification

Bell's palsy is one of the most common neurologic disorders affecting the CNs and is characterized by abrupt unilateral peripheral facial paresis or paralysis with no detectable cause.

Epidemiology

The annual incidence of Bell's palsy is about 25 cases per 100,000 persons in the USA, similar to the rest of the world except for Japan, which has the highest incidence. The incidence of Bell's palsy is 2.7 per 100,000 in the first decade of life and 10.1 per 100,000 in the second decade. The palsy can occur bilaterally at a rate of less than 1%, and about 1.4% of patients have a family history of the disorder.

Etiology and Pathophysiology

Bell's palsy is thought to be caused by inflammation and swelling of the facial (VII) nerve resulting in its compression as it passes through the bony canal (a portion of the temporal bone commonly referred to as the facial canal). Nevertheless, the precise pathophysiology is still unclear, although it is assumed that herpes simplex virus (HSV) is the etiologic agent, being reactivated after remaining latent in the geniculate ganglion and causing, thereafter, local damage to the myelin of the facial nerve. The efferent component of the facial nerve stimulates the muscles of facial expression, with a small branch to the stapedius muscle in the middle ear. The afferent and smaller portion contains taste fibers to the anterior two-thirds of the tongue, some pain fibers and secretomotor fibers to the lacrimal and salivary glands.

Clinical Manifestations: Symptoms and Signs

Symptoms

The condition may manifest with posterior auricular pain, which precedes the paresis by 2–3 days in a quarter of patients. In the majority, it presents with acute onset of unilateral upper and lower facial paralysis over a period of 48 h. This might be associated with decreased tearing, taste disturbances, and hyperacusis due to paralysis of the stapedius muscle.

Signs

On the affected side, weakness and/or paralysis due to involvement of the facial (VII) nerve affects the entire upper and lower part of the face. When the child is asked to raise the eyebrows or look upward, without moving the head, the forehead with the palsy will remain flat. When asked to smile, the face lateralizes to the side opposite to the palsy. On attempted eye closure, Bell phenomenon is observed: the eye on the affected side rolls upward and outward (*Fig. 369.1d*). This phenomenon is a normal

response to eye closure. Although the disease can affect both sides, bilateral facial palsy should prompt workup for other causes besides Bell's palsy.

Diagnosis

Immediate imaging is not necessary if the history and physical examination lead to a diagnosis of Bell's palsy. Enhancement of the facial nerve, at or near the geniculate ganglion, may be detected on MRI. When the paralysis progresses over weeks, it is no longer Bell's palsy, and MRI brain is mandatory to exclude tumors compressing or involving CN VII, such as schwannoma, meningioma, hemangioma, pontine glioma, and rhabdomyosarcomas.

Differential Diagnosis

Otitis media and mastoiditis should always be considered as antibiotics and/or surgery may be requested. X-rays or CT of the temporal bone are indicated if the history and examination are suggestive. Hypertension is rarely associated with Bell's palsy and should systematically be looked for. Herpes zoster of the geniculate ganglion (Ramsay Hunt syndrome) is an uncommon cause of facial palsy in children. Other viruses that may cause facial weakness include mumps, chicken pox, and Epstein-Barr viruses.

Bacterial causes of facial palsy include Lyme disease (neuroborreliosis), in which it may be an early sign, brucellosis and diphtheria. Facial palsy may be associated with *Mycoplasma pneumoniae* infections, sometimes in the absence of respiratory symptoms. Traumatic paralysis of the facial nerve is revealed by history, and CT scan of the temporal bone may be required. Other causes include Guillain–Barré syndrome (bilateral facial palsy), sarcoidosis, and tumors of the brain stem or meninges.

Investigations

Laboratory studies should include serological tests for Lyme disease (IgG and IgM titres) and brucellosis (ELISA) in endemic areas. Serum titres for *Mycoplasma pneumoniae* (IgM) and for HSV may be obtained. Nerve conduction studies and EMG are useful in severe Bell's palsy. They are most informative when performed 3–10 days after the onset of paralysis. Comparison to the contralateral (unaffected) side has prognostic implications and helps to determine the extent of nerve injury.

Treatment

Impaired eye closure and abnormal tear flow require tear substitutes, lubricants, and eye protection with eye glasses or patches. Significant improvement in outcome was shown in two recent randomized controlled trials, when prednisolone was started within 72 h of symptom onset. The recommended pediatric dose is 1 mg/kg/day up to 60 mg/day for 7–10 days. Despite evidence to support HSV as a major cause of Bell's palsy, a recent trial showed no added benefit with the addition of acyclovir to prednisolone.

Prognosis

The majority of patients (85%) with Bell's palsy will achieve complete recovery, 10% have some persistent facial muscle asymmetry, and 5% have severe cosmotic sequelae. Patients showing complete paralysis during the acute phase are at a higher risk for severe sequelae. Bell's palsy recurs in 10–15% of patients, and recurrences are usually associated with a family history of recurrent Bell's palsy.

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370 Anterior Horn Cell Diseases

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Definition/Classification

Disorders of the anterior horn cell (AHC) can either be acquired or inherited. Acquired diseases are mainly of viral origin and most of these run an acute course. They include poliomyelitis and similar diseases due to enteroviruses other than poliovirus. Following the global control of poliomyelitis by widespread immunization, inherited degenerative diseases currently account for most cases of AHC disease.

Paralytic Poliomyelitis

The polioviruses belong to the Piccornaviridae family, in the genus *Entrovirus,* and include three antigenically distinct serotypes (types 1, 2, and 3). They spread by the fecal–oral route and humans are the only known reservoir. Polioviruses are known to be resistant and can retain infectivity for several days at room temperature.

Epidemiology

Paralytic poliomyelitis occurs in about 1/1,000 infections among infants to about 1/100 infections among adolescents. Prior to universal vaccination, epidemics of paralytic poliomyelitis occurred in developed countries primarily in adolescents, whereas in developing countries with poor sanitation, infections occurred early in life resulting in infantile paralysis. When the Expanded Program on Immunization (EPI) was established by the World Health Organization (WHO) in 1974, oral poliovirus (OPV) vaccine was introduced for developing countries to use exclusively. In the pre-EPI era, 600,000–800,000 cases of polio occurred annually, the vast majority in developing countries. Following the WHO program for global eradication of poliomyelitis (from 1988), paralytic poliomyelitis started to disappear. Nevertheless, due to occasional revertants (by nucleotide substitution) of these vaccine strains, a neuro-virulent phenotype leads to vaccine-associated paralytic poliomyelitis (VAPP). The annual incidence of VAPP was determined by the WHO to be 0.4–3.0/million vaccinated children with intercountry variations. The incidence of VAPP in India was estimated to be seven/million birth cohorts, one of the highest in the world. Cases of poliovirus following a circulating vaccine-derived poliovirus were documented in Egypt, the Dominican Republic and Haiti, Madagascar, the Philippines, and Romania.

Pathogenesis and Pathology

Polioviruses infect cells by adsorbing to poliovirus receptor and gain host entry via the gastrointestinal tract. Wild type poliovirus and neurovirulent revertant vaccine strains probably access the central nervous system (CNS) through the peripheral nerves. Infection by polioviruses is inapparent in 90–95% of cases or is associated with a mild nonspecific febrile illness in about 5% of patients (abortive) poliomyelitis. About 1% of patients infected with wild-type poliovirus develop lymphocytic meningitis (nonparalytic poliomyelitis), whereas paralytic poliomyelitis develops in about 0.1%. The pathological lesions primarily involve the motor neuron cells in the spinal cord (AHC) and the medulla oblongata (the cranial nerve nuclei). Involvement of the reticular formation compromises the vital centers controlling respiration and circulation. Hyperasthesia and myalgia, which are typical of acute poliomyelitis, are caused by the involvement of the intermediate and dorsal horn and dorsal root ganglia in the spinal cord. Other affected areas are the cerebellar vermis and, to a lesser extent, the thalamus and layers III and V of the motor cortex.

Clinical Manifestations

The clinical manifestations usually appear after an incubation period of 8–12 days (range 3–35 days). The initial symptoms comprise fever, malaise, and headache. There may also be sore throat, abdominal or muscle pain, and irregular vomiting. After an apparent recovery for 2–5 days, the previous symptoms recur associated with

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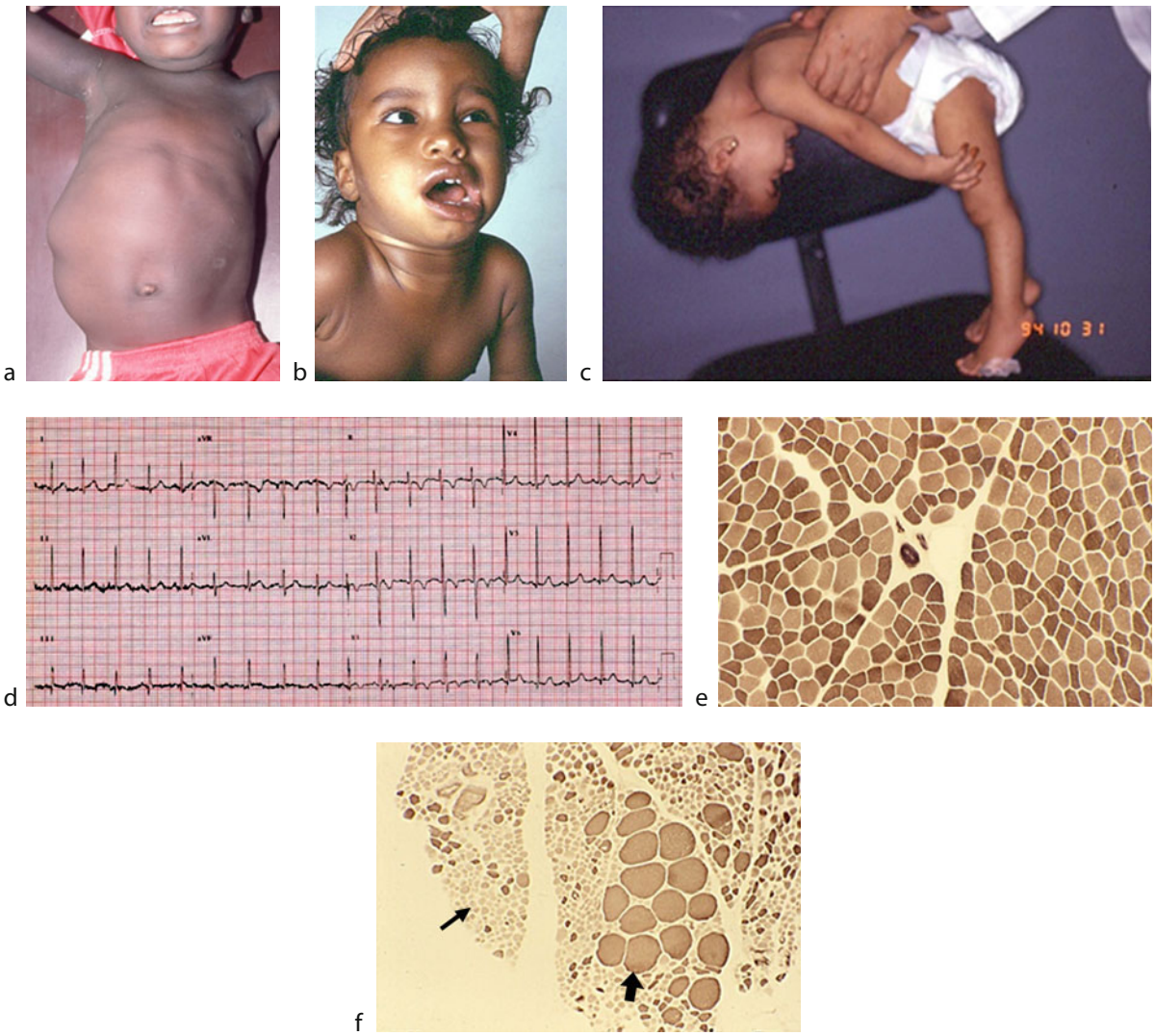
fever, muscle pain, and sensory and motor phenomena (hyperesthesia, paraesthesia, spasms, and fasciculations). Paralysis appears within 2 days and is characterized by asymmetrical flaccid paralysis involving the legs, arms, and/or trunk with absent tendon reflexes. The proximal areas of the limbs tend to be involved to a greater extent than the distal areas. Sensation is intact and the presence of sensory disturbances suggests an alternative diagnosis. Urinary retention is present at onset in 20–30% of cases. In developing countries, history of intramuscular injections precedes paralytic poliomyelitis in 50–60% of patients (also termed provocation paralysis). Asymmetric involvement of the abdominal muscles results in bulging of the affected side (phantom hernia) (◉ *Fig. 370.1a*). Progression of the paralytic manifestation stops once the temperature returns to normal.



◘ Figure 370.1
(a) Asymmetric involvement of the abdominal muscles resulting in bulging of the right side (phantom hernia) following poliomyelitis. (b) Right lower motor facial nerve palsy in bulbar poliomyelitis. (c) Floppy infant syndrome due to spinal muscular atrophy (SMA) type 1. (d) Electrocardiography (ECG) showing baseline tremors in SMA type III. These are most prominent in leads II and III. (e) The checkerboard pattern in a normal muscle biopsy as compared to (f) which shows group atrophy (thin arrow) and compensatory hypertrophy (thick arrow) of muscle fibres

The bulbar form (bulbar poliomyelitis) is rarely isolated and the cervical cord is involved in at least 90% of cases. All cranially innervated muscles may be affected (*Fig. 370.1b*). Involvement of vital centers in the medulla manifests as irregularities in rate, depth, and rhythm of respiration. It may also manifest as cardiovascular system alterations, including blood pressure changes, cardiac arrhythmias, and rapid changes in body temperature. A rare form of poliomyelitis is polioencephalitis in which higher centers of the brain are severely involved. Spastic paralysis with increased reflexes may be involved. Peripheral or bulbar paralysis may coexist with the condition or ensue during its course.

Diagnosis

Poliomyelitis should be suspected in any unimmunized or partially immunized child with paralytic disease. Paralytic disease occurring 7–14 days after receiving OPV is a major clue to the development of VAPP. In countries where wild-type poliovirus has been eradicated, VAPP can occur later if the OPV has been given to the child or contact.

Cerebrospinal fluid (CSF) examination shows a pleocytosis of 20–300 cells/mm^3. Initially, these cells are predominantly polymorphonuclear cells, followed after 5–7 days by a lymphatic pleocytosis. The cell count falls to near-normal values by the second week. Initially the CSF protein is normal or only slightly elevated but usually rises to 50–100 g/L by the second week. In polio encephalitis, the CSF may show minor changes or remain normal.

Poliovirus may be isolated from the stools of 80–90% of acutely ill patients and from <20% within 3–4 weeks after onset of paralysis. According to the WHO recommendations, two stool specimens should be collected 24–48 h apart, as soon as the diagnosis of poliomyelitis is suspected. Poliovirus isolates should be sent to either the Centre for Disease Control and Prevention in the USA or to one of the WHO-certified poliomyelitis laboratories, located in several regions of the world, where DNA sequence analysis can be performed. This investigation is performed to differentiate between wild poliovirus and neurovirulent revertant OPV strains.

Differential Diagnosis

Even in countries where the disease has been eradicated, the possibility of poliomyelitis should be considered in any case of acute flaccid paralysis. The diagnoses most often confused with polio are Guillaine–Barre syndrome, transverse myelitis, West Nile virus, and other enteroviruses. Guillaine–Barre syndrome differs in the mode of onset, the symmetrical distribution of weakness, and CSF characteristics (few cells but elevated protein level). Transverse myelitis is characterized by acute symmetric paralysis of the lower limbs associated with sensory level and bladder dysfunction. The CSF is usually normal. A syndrome closely resembling poliomyelitis (Hopkins syndrome) has been reported following acute attacks of asthma or status asthmaticus.

Injury of the spinal column, sometimes associated with periostitis or osteomyelitis, may present with a polio-like paralytic syndrome. Other rare causes include snakebite, spider bite, scorpion sting, tick bite, and schistomiasis involving the spinal cord. Chemical poisons that cause paralytic syndromes include arsenic, triorthocresyl phosphate, and organophosphorus insecticides.

Treatment

The management of paralytic poliomyelitis is supportive and there is no specific antiviral therapy. The objectives are to limit progression of the disease, prevent ensuing skeletal deformities, and provide psychological support for the child and family. Intramuscular injections, including insertion of an electromyography (EMG) needle, and surgical procedures are contraindicated since they precipitate provocation paralysis. This can happen particularly in the first week of illness.

The management of bulbar poliomyelitis consists of maintaining the airway, avoiding the risk of aspiration, observing for respiratory insufficiency, and circulatory disturbances. Tracheostomy and mechanical ventilation might be needed when there is vocal cord paralysis or constriction of the hypopharynx.

Prognosis

The mortality in spinal poliomyelitis, with or without less severe bulbar involvement, is about 5–10%. In severe bulbar poliomyelitis, the mortality rate may reach up to 60%. Following the paralytic phase of the illness, which takes 2–3 days, there is a period of stabilization followed by gradual return of muscle function. Recovery of affected muscles takes up to 6 months. Muscles still paralyzed thereafter, remain so indefinitely. Following an interval of 20–40 years, a progressive

motor neuron disease (postpolio syndrome) may affect 30–40% of those who survived paralytic poliomyelitis in childhood.

Prevention

Vaccination is the only effective method that can prevent poliomyelitis. The live-attenuated OPV vaccine is more economic, easy to administer, and limits the replication of the wild poliovirus and its transmission by fecal spread. Nevertheless, it may undergo reversion to neurovirulence and cause VAPP. The more expensive to operate injectable inactivated poliovaccine (IPV) is equally immunizing and does not cause VAPP. In countries where the risk of VAPP is higher than the risk for transmission of poliomyelitis, IPV is being used routinely. Adoption of a policy of initial vaccination by the parenteral route (using IPV) followed by OPV has been shown to greatly reduce the risk of VAPP.

Spinal Muscular Atrophy

Definition/Classification

Spinal muscular atrophy (SMA) is an autosomal recessive inherited motor unit disease characterized by progressive muscle weakness resulting from degeneration and loss of the anterior horn cells in the spinal cord and the brain stem nuclei. The single gene responsible for SMA was mapped to chromosome 5q11.2–13.3 and identified as the survival motor neuron (SMN) gene. Classification of SMA, based on clinical criteria, was found to be useful for prognosis and management, although the phenotype of the disease-causing mutations of the SMN gene spans a continuum with no sharp distinction between the subtypes. These criteria include age of onset and maximum function attained. Spinal muscular atrophy type 1 (SMA I, Werdnig–Hoffman disease) is characterized by onset before 6 months of age, failure to achieve sitting without support and death by 2 years of age. Onset of SMA II (previously named chronic SMA) is between 6 months and 12 months, the patient ultimately attains independent sitting when placed and may live into adolescence or even longer. The onset of SMA III (juvenile SMA or Kugelberg–Welander disease) is after 12 months (usually after 18 months) and all patients walk independently at some stage of their life that extends into the sixth decade. Spinal muscular atrophy type IV is a disease of adults.

Epidemiology

In a world survey, the prevalence of SMA was estimated to be 12/million populations. The estimated prevalence among Norwegian children was $1.7/10^6$. Considerably higher prevalences of 133 and $172/10^6$ populations were found in Saudi Arabia and Tunisia, respectively, reflecting the high rate of consanguinity in these communities. Significantly higher carrier frequency of 5% was reported from Saudi Arabia, i.e., one carrier in each 20 persons compared to one in 50–80 in the USA and Europe.

Pathogenesis

The two genes associated with SMA are *SMN1* and *SMN2*. The *SMN1* gene is believed to be the primary disease-causing gene. Homozygous absence of exons 7 and 8 of *SMN1* is found in 95–98% of individuals with SMA. About 2–5% of patients are compound heterozygotes for absence of exons 7 and 8 of the *SMN1* and a point mutation in *SMN1*. On the other hand, there is a dose relationship between *SMN2* copies; most patients with the milder form (SMA II) have three *SMN2* copies, whereas most patients with the mildest form (SMA III) have three or four *SMN2* copies.

Pathology

Postmortem findings in SMA included decreased number of motor neurons and gliosis in the anterior horns of the spinal cord and motor cranial nerve nuclei V and VII–XII. This is reflected in the changes observed in muscle biopsy with features of acute and chronic denervation.

Clinical Manifestations

Onset of SMA I is from birth to 6 months. Sucking or swallowing problems may be noticed in the first few months of life, along with paradoxical or abdominal breathing. With inhalation, the chest caves in as the diaphragm contracts. There is poor muscle tone associated with muscle

weakness manifesting as the "floppy infant syndrome" (Fig. 370.1c). There is lack of motor development and the child never achieves ability to sit unsupported. Nevertheless, there is normal cerebral function and the baby has an alert appearance. Facial weakness is minimal or absent and fasciculations of the tongue are seen in most, but not all, affected children. Postural tremor of the fingers (minipolymyoclonus), due to fasciculations of intrinsic hand muscles, is seen occasionally. The distribution of muscle weakness is proximal and symmetrical, involving the upper and lower limbs. Contractures are mild, often at the knees and rarely at the elbows. Tendon reflexes are absent and there is no sensory loss. Survival is for about 2 years, although it can be extended with improved respiratory and nutrition care.

The usual onset of SMA II is after 6 months of age, but can be earlier. These patients achieve the ability to sit independently when placed in a sitting position, but will not be able to walk. They have decreased muscle tone, associated with symmetrical proximal muscle weakness and wasting, and may also present as "floppy infant syndrome." A postural tremor of the fingers is seen almost invariably and is a helpful diagnostic feature. Tendon reflexes are absent in 70% of affected children. Patients are cognitively normal with average intellectual skills during the formative years and above average by adolescence.

Onset of SMA III is after the age of 12 months (usually 18 months) and the patient will achieve the ability to walk. Weakness usually manifests between 2 years and 5 years with frequent falls or difficulty in walking up and down stairs. Symmetric proximal limb weakness and wasting ensues slowly with legs more severely affected than the arms. Examination shows a positive Gowers maneuver and absent knee jerks, with preservation of the ankle jerks and upper limb reflexes. Gait is waddling and calf hypertrophy may be present in some patients leading to an erroneous diagnosis of muscular dystrophy. Coarse tremor of the hands is shown by many patients. The disease progresses very slowly but the development of pes cavus is frequent.

Clinical Variants of SMA

A prenatal form of SMA with arthrogryposis associated with a deletion of *SMN* gene has been described. This form presents with weakness at birth with the face being minimally affected. Segmental SMA, with asymmetrical weakness and atrophy involving the distribution of several contiguous spinal roots, is a rare variant. Facial weakness and severe peripheral neuropathies have also been associated with a deletion of the SMA gene.

Diagnosis

Currently, the diagnosis of SMA is based on molecular genetic testing. Neurophysiological tests and muscle biopsy are done when the molecular genetic testing of the *SMN1* gene is normal.

The motor and sensory nerve conduction velocities are normal. Electromyography (EMG) reveals features of denervation and diminished motor action potential amplitude. Spontaneous motor unit activity is a unique feature of SMA and is most commonly seen in SMA I, occasionally in SMA II, but not in SMA III. Positive sharp waves and fibrillations are present in all individuals with SMA. This is reflected in the electrocardiogram (ECG), which shows tremor of ECG baseline even in SMA III (Fig. 370.1d). Muscle biopsy shows signs of denervation in the form of group atrophy in type l and type ll muscle fibers as opposed to the normal checkerboard pattern (Fig. 370.1e and f). Lipid deposits and glycogen are not seen, excluding lipid and glycogen storage disorders.

Differential Diagnosis

Arthrogryposis multiplex congenita (AMC) may be due to causes other than *SMN* mutations. For types I and II SMA, the differential diagnosis includes other causes of the floppy infant syndrome. A diagnosis of muscular dystrophy may be entertained in cases of SMA III with raised CK concentration. Congenital and metabolic myopathies may also present similarly.

Treatment

A recent consensus document has addressed the diagnosis and treatment of patients with SMA. This document included issues of respiratory and nutritional care in patients with SMA I, II, and III. Children with SMA I (Werdnig–Hoffman disease) can survive beyond 2 years of age on tracheostomy and noninvasive respiratory support. However, such an intervention raises ethical questions. Intermittent positive-pressure breathing was found to be effective in children with SMA, as well as other

neuromuscular disorders, and leads to lung volume expansions and clearance of airway secretions. Nighttime use of continuous positive airway pressure prevents daytime fatigue caused by sleep apnea in SMA III patients.

About 50% of SMA patients develop scoliosis before age 10 years. Although orthosis allows the patient to be upright rather than bedridden, it does not prevent the development of scoliosis. Spinal surgery is required especially in those non-ambulatory patients who develop curvatures greater than 50°. Hip dislocation is common in SMA, but does not require surgical correction if it was asymptomatic. Clinic surveillance should be at least every 6 months and weaker children need more frequent visits. Clinical evaluations should include respiratory function, nutritional state, and orthopedic status.

While assessing respiratory function, note should be taken whether there is normal or abdominal breathing patterns. Children over the age of 4 years can accurately use the hand-held spirometer to measure the forced vital capacity (FVC). When FVC is above 40%, decompensation during respiratory infection is less likely. If abdominal breathing is noted and/or the FVC is less than 30%, options for management should be discussed with the family including "do not resuscitate" status.

During periods of intercurrent illness or fasting, children with SMA develop a poorly understood complication consisting of severe metabolic acidosis associated with dicarboxylic aciduria. Judicial administration of intravenous fluids prevents this condition.

Through the use of special education and electric wheelchairs, children with SMA type II can be integrated into normal schools. Parents and families with various types of SMA require active social and psychological support.

Specific medical treatment of SMA still does not exist. Nevertheless, several medications/chemicals that increase the activity of *SMN2* gene are under investigation. These include histone deacetylase (HDAC) inhibitors (aclarubicin), valproic acid, phenylbutyrate (a drug used in the treatment of urea cycle disorders), indoprofen (a nonsteroidal anti-inflammatory drug) and gabapentin. Clinical trials of Rilutek (Riluzole) in infants with SMA and hydroxyurea (a medication that enhances expression of human fetal hemoglobin gene and SMN protein levels) are underway.

Prognosis

Life expectancy reflects the type of SMA, although this has changed over the past few years with better respiratory and nutritional care. Recurrent pneumonia, scoliosis, and hip dislocation punctuate the progress of the disease.

Prevention

The optimal option for prevention is through family planning. In regions with high carrier rate, as in the Middle East, premarital screening is being introduced into the system. When faced with a married couple who are carriers of the disease, discussion of availability of prenatal testing should be made before pregnancy.

Prenatal testing is available for high-risk pregnancies. This can be achieved by analysis of fetal DNA obtained either through chorionic villous sampling (at 10–12 weeks of gestation) or through amniocentesis, usually at about 15–18 weeks of gestation. Samples will be analyzed for the known *SMN1* gene mutation or for the previously identified linked markers. Preimplantation genetic diagnosis (PIGD), available in centers with in vitro fertilization capability, can be done for parents in future pregnancies, when disease-causing mutations have been identified in an affected child.

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371 Plexopathies and Radiculopathies

Mustafa A. M. Salih

Several disorders of the brachial plexus and the lumbosacral plexus occur during childhood. These can either be traumatic or inflammatory disorders.

Brachial Plexus Palsy

Definition/Classification

The brachial plexus is composed of a group of nerves arising from the nerve roots of cervical segments 5 through thoracic segment (C5–T1). Injury to the upper plexus (C5 and C6 roots) leads to the Erb–Duchenne type of plexus paralysis. Involvement of the lower brachial plexus cervical 7, 8, and thoracic root 1 result in Klumpke paralysis.

Etiology

Brachial plexus injuries usually occur following shoulder dystocia in large-for-gestational-age newborns (macrosomic infants). This can result from forceful lateral deviation of the head from the shoulder during delivery due to impaction of fetal shoulders within maternal pelvis. Injury of the lower plexus results from traction on the trunk with breech delivery, or from traction on the adducted forearm during vertex delivery. Brachial plexus unassociated with shoulder dystocia or difficult delivery has been reported suggesting an intrauterine origin such as deformation from uterine constraint in cases of bicornuate uterus.

Pathogenesis and Pathology

Brachial plexus palsy has rarely been detected in babies delivered by cesarean section indicating that long-standing in utero stretching of the brachial plexus could lead to the development of palsy. In utero stretching could be due to constriction bands, uterine constraints from oligohydramnios or bicornuate uterus, intrauterine maladaptation or congenital aplasia of the roots of the brachial plexus. The most common and mildest form of brachial plexus injury is neuropraxia, which is due to edema following pressure on the nerve roots. Axonotmesis is more severe and is due to disruption of the axon of the nerve with an intact myelin sheath. Total disruption of the postganglionic nerve constitutes neurotmesis, whereas avulsion designates complete disruption of the ganglia from the spinal cord at both the anterior and posterior roots.

Clinical Manifestations

Paralysis is recognized from the first days of life in the majority of babies. In upper (Erb–Duchenne) palsy, the affected arm hangs limply adducted and internally rotated, with extended elbow, pronated forearm, and variably flexed wrist (*Fig. 371.1a*). The Moro reflex is absent on the affected side (asymmetric Moro reflex), as well as the biceps and brachioradialis reflexes. Associated significant C7 involvement manifests as weakness of the triceps and extensors of forearm and digits. In lower brachial plexus (Klumpke) palsy (*Fig. 371.1b*), intrinsic hand muscles are paralyzed, the grasp is absent and a Horner syndrome is frequently present. Horner syndrome manifests as meiosis, ptosis, and facial anhydrosis, and is caused by injury of the sympathetic fibers of the first thoracic root. The phrenic nerve, arising from C3, C4, and C5, can be involved in brachial plexus palsy resulting in ipsilateral diaphragmatic paralysis and produces symptoms of respiratory distress.

Diagnosis and Differential Diagnosis

Due to the unique physical findings of brachial plexus palsy, the diagnosis is readily apparent. Nevertheless, other possibilities that need to be considered are cerebral injury, cervical spine injury, fracture, dislocation or epiphyseal separation of the humerus, and fracture of the clavicle. Another brachial plexopathy that needs to be considered is brachial neuritis (neuralgic amyotrophy, Parsonage–Turner syndrome). Although pediatric cases are much rarer than in adults, this disease may occur from infancy.

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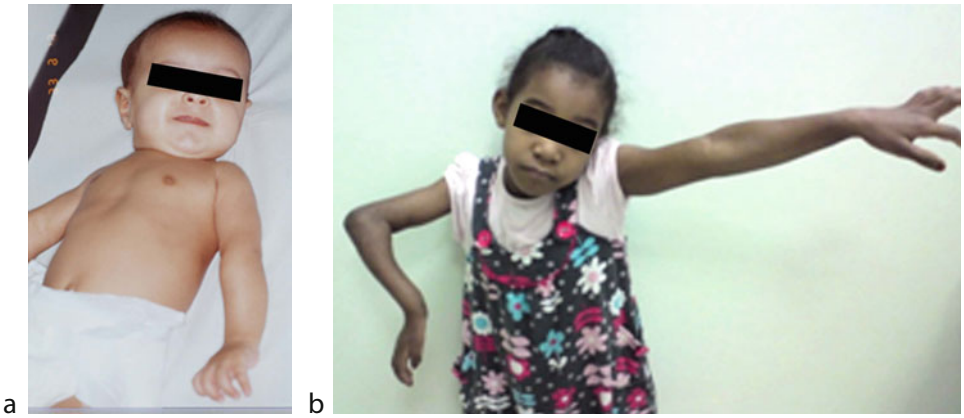

Fig. 371.1
(a) Erb-Duchenne palsy. The left arm is internally rotated, and the forearm is extended and pronated. (b) Lower brachial plexus (Klumpke) palsy of the right upper limb. The elbow is flexed and the hand is paralyzed and atrophic

Diagnostic work-up for brachial plexus palsy is best achieved by magnetic resonance imaging (MRI) of the spinal cord and roots. It has the advantage of avoiding the ionizing radiation of the computed tomography (CT). It also helps to detect the integrity of the brachial plexus, including root avulsion, and the presence of a pseudomeningocele. Electromyography (EMG) can be used to support the diagnosis of root lesions and is capable of detecting signs of denervation and reinnervation in recovery. Associated phrenic nerve injury leading to diaphragmatic involvement is assessed by plain radiography and real-time ultrasonography at the bedside.

Treatment

During the first 1 or 2 weeks, management consists of partial immobilization and appropriate positioning of the affected limb to prevent the development of contractures. Physiotherapy can be initiated after the first 10–14 days to allow delivery pain to subside. Immobilization should be intermittent, between feedings and while the infant is asleep, by abducting the arm to 90°, with external rotation at the shoulder, full supination of the forearm, slight extension at the wrist, and maintaining the palm turned toward the face. Splinting the wrist in the neutral position and placing a pad in the fist, is to be used in lower arm or hand paralysis. Range of motion exercises constitutes the required physical therapy to prevent ligament tightening and the discomfort following contractures. Monthly evaluations for range of motion, return of function, and development of contractures are required. Recovery of brachial plexus palsy occurs in about 70–80% of affected babies, with the remaining patients having residual deficits. Flaccid paralysis of the extremity, Horner syndrome, and diaphragmatic paralysis herald a poor outcome. Patients who do not show signs of recovery for 3–6 months require surgical intervention. Nevertheless, surgical intervention, which includes neurolysis, nerve grafting, and neurotization, requires the availability of microsurgical technique and intraoperative neurophysiologic recordings, and surgeons familiar with the techniques. For older children who did not improve, muscle release around the shoulder joint and tendon transfers may be required.

Prevention

Prompt recognition of shoulder dystocia and avoidance of excessive downward traction on the fetal head by the attending caregiver is the most important preventive step. Since this task requires skills and teamwork, conducting team training in shoulder dystocia as part of risk reduction strategy for improving perinatal outcome has been recommended.

Other Traumatic Plexopathies

After the neonatal period, brachial plexus injury affects principally adolescents, mainly due to motor vehicle (especially motorcycle) and sports accidents, and has guarded prognosis. Conversely, lumbosacral plexus injuries are rare, have been reported in neonates and children, and have favorable outcomes.

Inflammatory Plexopathies

Neuralgic Amyotrophy (Parsonage–Turner Syndrome, Brachial Plexus Neuritis)

Definition/Classification

Neuralgic amyotrophy is a syndrome characterized by episodes of neuropathic pain and rapid multifocal weakness and atrophy (amyotrophy) in the upper limbs. The syndrome has both an idiopathic and hereditary form with similar clinical symptoms but generally more episodes and an earlier age of onset in the hereditary form.

Etiology

An immune-mediated process is thought to underline the attacks, which may be triggered by viral or bacterial illnesses (influenza, Coxsackie-virus, parovirus B-19, Epstein-Barr virus, Q fever, human immunodeficiency virus (HIV) disease, mycoplasma pneumonia, bacterial pneumonia, typhoid, syphilis, and brucellosis). It can also follow immunizations such as tetanus toxoid, diphtheria, recombinant hepatitis B vaccination, swine flu, and immune sera. It may also be triggered by periods of physical or emotional stress. Hereditary neuralgic amyotrophy (HNA) is inherited as autosomal dominant. The proportion of HNA attributed to the mutations in the only known causative gene (*SEPT9*) is about 85%. Idiopathic neuralgic amyotrophy (INA) has a reported incidence of 2–3/100,000/year. The prevalence of hereditary neuralgic amyotrophy (HNA) is unknown and about 200 families are reported worldwide. Both disorders are likely to have higher prevalence because of underdiagnosis.

Pathogenesis and Pathology

Triggering factors are thought to render the brachial plexus more susceptible to an autoimmune damage. The limited nerve biopsies performed in this condition revealed focal decreases in myelinated fibers within individual nerves in the majority, and multiple perineural mononuclear infiltrates in three of four upper extremity nerve biopsies.

Clinical Manifestations

The disorder usually starts with intense pain localized to the shoulder or involving the whole upper limb. Weakness either develops simultaneously with the pain or follows it by days to few weeks. The mean age of onset of INA is about 40 years (range 10–80 years) with 3% of patients suffering the first attack in childhood (<16 years). The mean age of onset of HNA is significantly earlier at 28 years (range 3–56 years) with 23% having their first attack during childhood. Paralysis affects the upper part of the brachial plexus in the majority of patients (about 70%), the whole plexus in 14%, and involves predominantly the lower plexus in 3–8%. The mean time to onset of amyotrophy ranges between 8 days and 14 days after the initial pain. Sensory symptoms and signs are common during the attack affecting more than two third of patients in the form of large proximal hypoesthetic areas. Diaphragmatic paralysis (unilateral or bilateral) is present in about 7% of patients and may predominate in the clinical picture. Hereditary neuralgic amyotrophy affects a younger age group and is characterized by recurrent, often bilateral attacks. Dysmorphic features in the form of hypertelorism, long nasal bridge, and facial asymmetry can be present.

Diagnosis and Differential Diagnosis

Neuralgic amyotrophy needs to be differentiated from diseases that lead to pain or atrophic paralysis around the shoulder girdle and arm. Poliomyelitis can be distinguished by the absence of constitutional symptoms, cutaneous sensory symptoms and a normal CSF. Cervical disk disease and cervical root compression can be demonstrated by EMG and MRI or CT scan.

Routine laboratory studies are usually within the reference range. Complete blood count (CBC) and erythrocyte sedimentation rate (ESR) are helpful nonspecific indicators of systemic diseases presenting as neuralgic amyotrophy, such as systemic lupus erythematosis and lymphoma. Raised ESR may also point toward neurobrucellosis, sarcoidosis, and other granulomatous infiltrations of the brachial plexus. Human immunodeficiency virus (HIV) serology should be done in regions with high prevalence of childhood AIDS.

Imaging of the brachial plexus, using MRI, may reveal enlarged nerves with increased signal intensity on T2-weighted images. It may also help to rule out carcinomatous or granulomatous infiltration.

Electrodiagnostic tests (nerve conduction studies and EMG) are important for diagnostic and prognostic information. It is also important to rule out other conditions such as radiculopathy, neuropathy, and amyotrophic lateral sclerosis. Approximately 50% of unilateral clinical involvement demonstrates bilateral EMG abnormalities.

Features of denervation in affected muscles can be revealed by EMG 2–3 weeks after onset of disease.

Treatment

In the acute stage of the disease, pain management is the primary goal of therapy. Analgesics, using a nonsteroidal anti-inflammatory drug and opiates (if necessary) are required in the initial period. Immunosuppressive therapy, using steroids, do not alter the outcome of the disease. Intravenous immunoglobulin was reported to result in significant improvement in pain and to accelerate recovery of function. This should be followed by physical therapy in the form of passive and active range of motion exercises to avoid a frozen shoulder. Occupational therapy in the form of assistive devices and orthotics may be required when residual disabilities are established. A randomized placebo-controlled trial of oral prednisone is being conducted in the Netherlands.

Prognosis

Brachial neuritis has an overall good prognosis regarding functional recovery. About 80% of patients recover functionally within 2 years and 90% within 3 years. Patients with upper brachial plexus lesions improve earlier and bilateral disease has a less favorable outcome compared to unilateral disease. The recurrence rate of the idiopathic form is between 5% and 26%, and in the inherited form is approximately 75%.

Prevention

In hereditary neuralgic amyotrophy (HNA), at risk individuals younger than age 18 years are typically not offered genetic testing during childhood. This is because no preventive or ameliorating treatment is available for the disease. Since HNA does not affect intellectual or life span, prenatal testing for the condition is not required. However, preimplantation genetic diagnosis (PIGD) may be available for families in which the disease-causing mutation has been identified, although this technique is usually reserved for life-threatening hereditary diseases.

Lumbosacral Plexopathy

This is similar to neuralgic amyotrophy and constitutes its counterpart in the lower limb. The condition is rare but occasional cases are on record in adolescents and even in toddlers. It presents with pain located in a femoral or sciatic distribution, refusal to walk, or limping. The condition usually follows an intercurrent infection but has also been reported in association with schistosomiasis. Recovery is generally faster than neuralgic amyotrophy although mild residual weakness may persist.

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372 Peripheral Nerve Disorders

Mustafa A. M. Salih

Traumatic Mononeuropathy

The sciatic nerve can be injured as a result of injections into the nerve or its vicinity. This can follow intramuscular injections into the buttocks, or following injection of drugs into the umbilical artery leading to thrombosis of the inferior gluteal artery. Other causes include stretch injury following closed reduction of hip dislocation and rarely as a result of breech delivery. The resultant paralysis commonly affects the peroneal nerve but may affect the whole territory of the sciatic nerve. The condition frequently presents with foot drop and amyotrophy of the corresponding leg.

Radial nerve injury or paralysis may result from subcutaneous fat necrosis of the upper arm in the neonatal period or following constraint of the forearm for intravenous infusion. Injury of the median nerve may follow arterial stick at the wrist and attempted catheterization of the radial or humeral artery. Femoral nerve injury may follow attempted puncture of the femoral vein or, rarely, trauma to the nerve along the psoas muscle during herniorrhaphy or appendectomy. Peroneal nerve injury may follow casting and orthopedic appliance to the region.

Entrapment Neuropathy

Carpal tunnel syndrome is rare in childhood and usually presents with motor symptoms and wasting of the thenar muscles, rather than pain and paresthesia, which is more marked in adults. During childhood, it may be associated with mucopolysaccharidosis and hyporthyroidism.

Familial Pressure Neuropathy (Hereditary Neuropathy with Liability to Pressure Palsies)

This is a rare dominantly inherited condition due to a deletion at chromosome 17p11.2 locus that encodes peripheral myelin protein P22 (PMP22). Symptoms usually start after the first decade, but may be earlier. A single nerve trunk is usually involved, the most common being the popliteal nerve as a result of prolonged squatting or sitting cross-legged. The cubital nerve may also be involved secondary to pressure on the elbow and patients may develop a carpal tunnel syndrome of early onset. The diagnosis is made when the amount of trauma is out of proportion to the degree of paralysis and when there is a similar family history. Nerve conduction studies confirm the diagnosis by revealing delay in conduction velocities outside the affected territory. Recovery, which takes days to weeks, is usually complete.

Neuropathy of Infectious Diseases

Diphtheritic Neuropathy

Diphtheritic neuropathy is the most common severe complication of *Corynebacterium diphtheriae* infection. Following the introduction of childhood immunization, the disease became a rarity in the US and Western Europe. Nevertheless, the disease is endemic in countries of the Caribbean and Latin America. In the late 1970s, 1980s, and 1990s, outbreaks were reported in both industrialized (Germany, Sweden) and developing countries (Ecuador, China, Nepal, Sudan, Thailand). A large epidemic occurred from 1990 to 1995 throughout the States of the former Soviet Union. Outbreaks also occurred in Ecuador, Algeria, and Central Asia. Historically, diphtheria infected children less than 12 years and declined following childhood immunization with diphtheritic toxoid. Recently, due to incomplete immunization, or lack of it, the disease shifted to the adult population.

Pathogenesis and Pathology

C. diphtheria produces a 62-kd polypeptide exotoxin, which leads to demyelinating neuropathy because it

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inhibits the synthesis of myelin proteolipid and other basic proteins. The exotoxin also causes local tissue necrosis and cardiomyopathy.

Clinical Manifestations

Diphtheria neuropathy follows respiratory or cutaneous diphtheritic infection. Respiratory diphtheria usually involves the tonsils, pharynx, and larynx with a characteristic membranous exudate. The latency in development of diphtheritic polyneuropathy ranges between 5 and 70 (mean = 37) days. Bulbar disturbance appears first with nasal speech, nasal regurgitation, diplopia, and dysphoria. Palatal palsy is the commonest, affecting 72% of patients and is the first to appear at a mean of 22 (range 5–41) days after onset of diphtheria. Generalized peripheral neuropathy usually appears between the 5th and 6th week and may be associated with, or shortly followed by, pharyngeal paralysis, abducens (CN VI) palsy, and weakness of neck muscles (*Fig. 372.1a*). Bilateral facial nerve (CN VII) palsy manifest between the 6th and 10th week (mean = 54 days). Patients have sensory disturbances of all modalities in the distal extremities, tendon reflexes are absent or depressed, and plantar responses are flexor. Autonomic instability is common in diphtheritic polyneuropathy and may be difficult to differentiate from myocarditis. Paralysis of the diaphragm and respiratory muscles may occur and require mechanical ventilation. Clinical recovery of the neurological complications of diphtheria follow the same pattern except for pharyngeal paralysis and peripheral weakness, which take longer to resolve (6–7 weeks), and facial weakness, which resolves more rapidly (about 4 weeks).

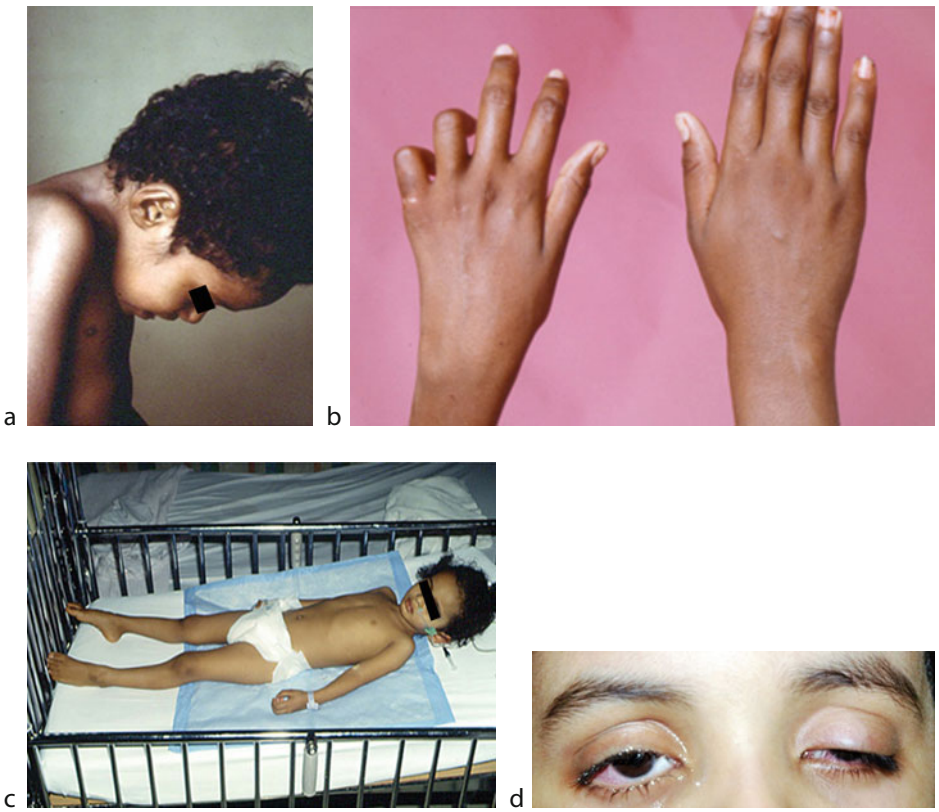

Figure 372.1
(a) Weakness of neck extensors in a patient with diphtheritic polyneuropathy. (b) Left hand clawing following ulnar nerve mononeuritis in an adolescent with leprosy. Note the atrophy of the small muscles of the left hand and the hypothenar muscles. (c) Guillain-Barre syndrome (GBS). Nasogastric tube feeding was needed due to swallowing difficulties, and there is bilateral foot drop. (d) Bilateral ptosis of eyelids in Miller Fischer variant of GBS. The patient also had ophthalmoplegia

Diagnosis

Nose and throat swabs should be obtained from suspected cases and their close contacts, and cultured to isolate *C. diphtheriae*, determine the biotype (gravis, mitis, or intermedius), and whether the isolate produces toxin (toxigenicity test). Cultures are usually negative if the patient had received antibiotics before reporting to hospital. Nonviable *C. diphtheriae* organism can be detected by polymerase chain reaction (PCR) test from specimens taken after antibiotic therapy has been initiated. It can also confirm infection with toxigenic strains. Toxigenicity tests are not available in many laboratories and isolates need to be sent to a reference laboratory.

Neurophysiology studies show prolongation of distal motor latency, slowing of conduction velocity, and delayed F-wave latency. Because pathological changes appear later in the peripheral nerve segment than in the ganglia and root, the nerve conduction abnormalities might be mild even when the limb weakness is severe. Brainstem auditory evoked potentials (BAEP) may reveal auditory (VIII) nerve impairment, and autonomic tests may show impaired R-R variation on valsava testing.

Treatment

Diphtheritic polyneuropathy has no specific treatment. Attention should be paid to the airway and impending respiratory failure, which needs mechanical ventilation. Autonomic disturbances and circulatory collapse require prompt management.

Prognosis

The overall mortality of diphtheria is about 20% and is mainly due to mechanical airway obstruction or cardiac involvement. Mortality increases with severity of local disease and delay of administration of antitoxin. Gravis strain of *C. diphtheriae* accounts for the most severe and virulent disease. Other prognostic factors include the age and immunization status of the patient.

Prevention

The disease is preventable through routine childhood immunization programs and booster doses of diphtheria vaccine.

Leprosy

Leprosy is a systemic chronic granulomatous disease caused by infection with *Mycobacterium leprae*, and has a marked predilection for nerves and skin. The worldwide incidence of the disease is 2 cases per 10,000 populations and the disease is endemic in Africa and Asia, particularly in the Indian subcontinent. In northern Brazil, 10% of cases develop in children younger than 15 years.

Intimate person to person contact and vertical transmission have been considered the most likely routes of transmission. Hosts with high resistance to the organism develop paucibacillary (tuberculoid) leprosy, and those with low resistance develop multibacillary (lepromatous) leprosy. Borderline leprosy is characterized by the presence of single or multiple skin lesions with a raised central area.

The incubation period is long, averaging 5 years. The disease presents with hypopigmented lesions mostly observed in the cool areas of the body (earlobes, nose, dorsal surface of the hands, and feet). In multibacillary (lepromatous) leprosy, pure sensory polyneuritis develops in a glove and stocking distribution, with loss of touch, pain, and temperature sensation. Deep sensitivity is preserved. Pure mononeuritis is rare and enlargement of the peripheral nerves (such as the posterior auricular and ulnar nerves) may be present (*Fig. 372.1b*). Nerve biopsy is useful for diagnosis and detection of persistent infection. To prevent antimicrobial resistance, treatment uses multidrug therapy including rifampin, dapsone, clofazimine, ofloxacin, minocycline, and clarithromycin. A single dose of bacilli Calmette-Guerin (BCG) vaccine was reported to be 50% protective in preventing leprosy.

Lyme Neuroborreliosis

Lyme disease is a multisystem infectious disease caused by a spirochete, *Borrelia burgdorferi* and affects, most commonly, the skin, nervous system, joints, and heart. It is transmitted from animals (deer) to man by the *Ixodes* tick. The disease is endemic in the US, with incidence averaging 9.1 cases per 100,000 persons. It is also prevalent throughout temperate Europe and Asia, and the estimated incidence was as high as 206 cases per 100,000 populations in Slovenia. Although few studies demonstrated multifocal perivascular inflammation in nerves, the pathophysiology of peripheral nerve and brain involvement remain to be clarified.

Clinical Manifestations

The first stage of the disease is characterized by an erythematous, macular, usually painless rash (erythema migrans), located in the area of the tick bite (the target sign). This is seen in 90% of infected patients and is associated with minor constitutional symptoms. The second stage of disseminated infection can involve the nervous system in approximately 15% of patients. This consists of part or all of the triad of lymphocytic meningitis, cranial neuropathy, and painful radiculitis. The facial nerve (CN VII) is the most commonly involved and may manifest as bilateral facial palsy. Other cranial nerves can be involved. The painful radiculitis may present as brachial plexopathy or lumbosacral plexopathy. A plexopathy resembling Guillain-Barre syndrome may also be seen. The third stage of persistent infection may be observed in untreated infection from one to several years. Its clinical features include chronic arthritis, chronic encephalomyelitis or a mild peripheral neuropathy, and focal mononeuropathy multiplex or polyradiculopathy.

Diagnosis and Differential Diagnosis

The diagnosis of Lyme disease rests on history of exposure in an endemic area, a clinical picture compatible with early Lyme disease (erythema migrans, constitutional flu-like symptoms) and laboratory demonstration of *Borrelia* infection. In suspected cases of neuroborreliosis, lumbar puncture is essential to evaluate the presence of specific antibodies to *B. burgdorferi*. Analysis of cerebrospinal fluid (CSF) will show significant pleocytosis, helping to differentiate the disease from Guillain-Barre syndrome, particularly when there is associated facial diplegia. In patients presenting with peripheral neuropathy, neurophysiologic studies are often consistent with axonal degeneration. Approximately 15–20% of patients with neurologic manifestations of Lyme disease show MRI abnormalities, usually in the form of punctuate lesions of the periventricular white matter.

Treatment

Treatment of neurologic Lyme disease is effectively accomplished with a 2-week course of parenteral penicillin, ceftriaxone or cefotaxime, or oral doxycycline. Approximately 90–95% of patients will be cured when receiving appropriate antimicrobial therapy early. A minority of patients, who had early treatment, develop late sequelae, but this rarely occurs in children.

Prevention

This is achieved by avoiding *Ixodes* tick bites through avoidance of infested areas, wearing appropriate clothing and using tick repellent with lower concentrations to avoid potential neurotoxicity in children.

Neurobrucellosis

On rare occasions, the nervous system is involved in systemic brucellosis. The clinical presentation of neurobrucellosis is diverse and reported neurological presentations in childhood range from acute to chronic forms. The former includes meningitis and meningoencephalitis, whereas the latter includes behavioral disturbance, brain abscess, stroke, myelitis, cerebellar ataxia (with or without cranial nerve involvement), radiculopathy, and peripheral neuropathy. Neurobrucellosis can present as Guillain-Barre syndrome, and bacteriological and serological tests should be part of the work-up for Guillain-Barre syndrome in endemic areas for brucellosis.

Toxic Neuropathies

Many toxins can induce polyneuropathy in children (*Table 372.1*). Antimicrobial drugs that may cause neuropathy include nitrofurantoin, mainly in children with renal insufficiency. Isoniazid interferes with the metabolism of pyridoxine, which should be supplemented in patients treated with tuberculosis. Phenytoin neuropathy

Table 372.1
Exogenous toxins that cause polyneuropathy

Agent group	Name
Antimicrobial	Nitrofurantoin, isoniazid, ethambutol, ethionamide, metronidazole, amphotericin
Chemotherapy	Vincristine, cisplatin, chlorambucil, adenine arabinoside, cytosine arabinoside
Miscellaneous drugs	Phenytoin, lithium, thalidomide, amitriptyline, amiodarone, pyridoxine abuse
Metals	Lead, mercury, thallium, arsenic
Organic chemicals	Organophosphates, N-hexane, triorthocresyl phosphate, carbon monoxide, cyanate, hydroxyquinolines
Biological toxins	Tick bites, serum sickness, immunizations, cassava plant ingestion

is usually subclinical and most drug induced neuropathies are reversible following discontinuation of the causative drug. Lead poisoning rarely presents with peripheral neuropathy in children. Toxicity with other metals and organophosphates is associated with accidental ingestion of insecticides, usually in rural communities. Neuropathy from N-hexane results from glue sniffing, an addictive habit among adolescents. Cassava consumption causes tropical neuropathy because of its high cyanide content, whereas tick paralysis is seen in the US and Australia.

Guillain-Barre Syndrome

Definition/Classification

Guillain-Barre syndrome (GBS), or acute inflammatory demyelinating polyradiculoneuropathy (AIDP), is an inflammatory disease of the peripheral nervous system characterized by progressive motor weakness and areflexia. It can be divided into several forms based on the involved nerve fibers (motor, sensory and motor, cranial), and the predominant mode of fiber injury (demyelinating versus axonal). Autonomic and brainstem involvements are also common.

Epidemiology

Following virtual global eradication of poliomyelitis, GBS is the most common cause of acute paralysis in children. The overall incidence ranges from 0.6 to 2.4 cases per 100,000 population per year, whereas the incidence in individuals younger than 18 years ranges from 0.5 to 1.5 per 100,000. The disease has no racial predilection and males seem to be more susceptible to develop GBS, with a male to female ratio of 1.26:1. Seasonal predilections were observed in some countries with *Campylobacter*-related GBS (China, northern India, Bangladesh, northwestern Iran, Egypt, Mexico) occurring in the summer, and upper respiratory tract illness-related GBS occurring in winter. In children, the average age of onset ranges from 4 to 8 years, but can involve younger children.

Pathology and Pathophysiology

The mechanism of the disease is thought to involve an abnormal T-cell response triggered by a preceding infection. About two-thirds of cases of GBS follow an infection, usually viral (including cytomegalovirus, Epstein-Barr virus, HIV, hepatitis B or C, and smallpox-vaccinia), but sometimes mycoplasmal or bacterial (*Campylobacter jejuni*). An immune-mediated injury to the peripheral nerve occurs including cytotoxic T cell-mediated lyses and membrane damage from cytokines and free radicals. This is thought to be due to the molecular mimicry of the triggering pathogens, which resemble antigens on peripheral nerves including myelin P-2, ganglioside GQ1b, GM1, and GT1a. High titers of IgG anti-GM1, GM1b, or GD1a antibodies are more common in the acute motor axonal neuropathy (AMAN) than in the demyelinating forms of GBS. Acute motor axonal neuropathy is associated with infection by *C. jejuni*, the polysaccharide of which has a GM1 ganglioside-like structure. Other antecedent events associated with GBS include vaccination and surgery.

Clinical Manifestations

Symptoms

Onset of symptoms occurs within 2–4 weeks of illness or immunization. The preceding illness involves upper respiratory tract infection, fever, and muscle pains. History of vomiting is found in the demyelinating form of GBS and diarrhea is more likely to precede AMAN. The chief complaints include weakness and/or ataxia, associated with pain (in about half of affected children), dysesthesia, and urinary retention (in 10–15% of cases).

Signs

Weakness typically starts in the legs and ascends to the upper extremities, involving both sides of the body and evolving over a period of several days (Fig. 372.1c). Evolution is complete after 2 weeks in half of the cases, after 3 weeks in over 80%, and after 4 weeks in over 90%. Weakness can be mild or severe leading to total paralysis and death from respiratory failure. Signs of autonomic dysfunction are common and include sinus tachycardia (in >50% of severe cases), bradycardia, orthostatic hypotension, and fluctuating hypertension and hypotension. Later in the disease course, objective sensory loss can be demonstrated in 75% of cases. Deep tendon jerks are usually absent or markedly diminished.

Other Variants of Guillain-Barre Syndrome

A small group of patients develop primary axonal degeneration associated with severe fulminant paralysis, sensory

loss, and incomplete recovery. This variant is now termed *acute motor and sensory axonal neuropathy* (AMSAN). Conversely, the other variant of GBS (*acute motor axonal neuropathy* [AMAN]), usually follows antecedent *C. jejuni* infection and has a more rapid progression than the demyelinating form of GBS. Some patients with AMAN recover rapidly. The *Miller Fischer* variant of GBS is characterized by ophthalmoplegia, ataxia, areflexia, and relatively little weakness (Fig. 372.1d). Some patients present with *polyneuritis cranialis* variant characterized by facial and ocular motor nerves involvement but infrequent limb weakness. The *pharyngeal-cervical-brachial* form of GBS is characterized by acute oropharyngeal, neck, and shoulder weakness, with sparring of the limb muscles. Another form is termed *acute sensory neuropathy of childhood* that presents as acute sensory loss but no weakness, although nerve conduction studies show features of demyelination. *Acute dysautonomia* variant, with no concomitant motor or sensory deficit, is rare. In this form of GBS, dysautonomia involves both the sympathetic and parasympathetic systems and may manifest with orthostatic hypotension, hypertension, sinus tachycardia, sweating abnormalities, and pupillary dysfunction.

Diagnosis

Support for the clinical diagnosis of GBS is provided by cerebrospinal (CSF) examination, neurophysiologic studies, and occasionally MRI findings. The CSF is acellular in all but 10% of patients; most of these have fewer than 10 cells/mm^3 and mild pleocytosis (10–50 cells/mm^3) may occasionally be seen. The finding of more than 50 cells/mm^3 on CSF examination suggests an alternative diagnosis. The CSF protein level rises about 1 week after the onset of symptoms, is usually elevated by 10 days, and reaches a peak in 3–4 weeks.

Nerve conduction studies (NCS) are frequently normal early. The most sensitive parameter of NCS is the F-wave. Within the first week of symptom onset, absent, impersistent, dispersed, or prolonged F response is seen in 88% of cases. This is compared to the finding, during this period, of increased distal latencies in 75%, conduction block in 58%, and reduced motor and sensory nerves conduction velocity in 50%. Electrodiagnostic criteria of the axonal forms of GBS are severe reduction in compound muscle action potential (CMAP) amplitudes, and minimal features of demyelination, with or without abnormalities in sensory nerves. F-wave latencies and blink response latencies are usually abnormal in Miller Fisher syndrome, but slowing of conduction velocities in the limbs may be absent. Electromyography (EMG) is contraindicated in GBS since the child may be harboring poliomyelitis, and EMG will lead to provocation paralysis.

Lumbosacral MRI may show, about 2 weeks after presentation of symptoms, enhancement of the cauda equina nerve roots with gadolinium in 95% of typical cases. The sensitivity of this study is 83% in acute GBS.

Serological Tests

High titers of IgG anti-GM1, GM1b, GD1a, and GalNac-GD1a was reported in 64% of children who develop the acute motor axonal neuropathy form of GBS, and was associated with more prolonged recovery and residual symptoms. Conversely, anti-GQ1b was found to be associated with Miller Fisher syndrome and anti-GT1a with pharyngeal-cervical-brachial variant of GBS.

Differential Diagnosis

Acute anterior horn infections by poliovirus, Coxsackie virus, and West Nile virus can produce an acute motor syndrome, but in contradistinction to GBS, CSF usually shows pleocytosis. Acute motor paralysis, associated with hyporeflexia or areflexia, can also be seen at the onset of transverse myelitis and acute spinal cord compression. The finding of a sensory level, associated with early involvements of the bowel or bladder, is supportive of these two diagnoses. In particular, acute spinal cord compression should not be missed to prevent the occurrence of a permanent cord infarct. Myasthenic crises and botulism may be considered when ophthalmoplegia is present in GBS. A history of fatiguabilily and fluctuating ocular symptoms favors the diagnosis of myasthenia, in which repetitive nerve stimulation on NCS shows decrement response. The presence of dilated unreactive pupil and severe constipation are indicative of botulism. Other causes of acute neuropathies include organophosphate poisoning, lead and heavy metals poisoning, and chemotherapy with vincristine. In endemic areas, tick paralysis can cause an ascending paralysis that dramatically improves after removal of ticks.

Treatment

Supportive therapy should be instituted immediately. Blood pressure, heart rate, temperature, respiratory capacity, blood gasses (when necessary), and urine output should

be maintained. Children with oropharyngeal weakness with inability to protect their airway, vital capacity below 15 mL/kg body weight, or arterial pressure of oxygen below 70 mmHg should be considered for elective endotracheal intubation. These children and others with autonomic instability should be monitored in the intensive care unit. Orthostatic hypotension and urinary retention need judicious management. Measures to prevent infection (e.g., pneumonia and urinary tract infection), deep venous thrombosis, decubitus ulcers, and contractures should be instituted. After the acute phase, activity with physical and/or occupational therapy should be encouraged.

In children, immunomodulation using intravenous immunoglobulins (IVIG) is the treatment of choice. It reduces the severity of the disease and the duration of symptoms, although the long-term outcome may not be affected. It has several advantages over plasmapheresis, which is equally effective. Plasmapheresis is limited to children weighing more than 10–15 kg, requires a central line vascular access (which indicates intensive care unit management), and has several potential serious complications. These include bleeding due to depletion of clotting factors, autonomic instability, and hypercalcemia. Also, plasmapheresis would only remove free-circulating antibodies whereas IVIG can displace antibodies bound to motor nerves and possibly prevent complement activation. This may particularly be effective in cases of acute motor axonal neuropathy associated with positive autoantibodies.

The recommended dose of IVIG, which is administered by peripheral intravenous route, is 0.4 g/kg given daily for 5 days. This can lead to improvements within 2–3 days after start of therapy. When there are signs of rapid deterioration, IVIG can either be given as a single dose of 2 g/kg, or over 2 days using a single dose of 1 g/kg each day. Adverse reactions and effects to IVIG can occur in about 10% of patients and they are usually minor. These include fever, chills, wheezing and urticaria, headache, and 10% increased risk of aseptic meningitis.

Prognosis

Children with GBS have more favorable outcome compared to adults. The mortality rate is estimated to be less than 5% and usually follows respiratory failure, cardiac arrhythmias, and dysautonomia. The mortality rate is higher in areas with insufficient medical facilities. Approximately 90–95% of patients have full recovery within 3–12 months, 5–10% significant permanent disability and 5% have recurrence of GBS. Affected children with cranial nerve involvement, quadriplegia, and need for ventillatory support usually have significant delay in motor recovery. Patients with acute motor axonal neuropathy have longer recovery time compared to those who have the demyelinating variant of GBS. About 12% of patients may have recurrence 2–3 weeks after IVIG. When that happens, the differential must include *chronic inflammatory demyelinating polyneuritis (CIDP)*, which has a relapsing-remitting course in childhood, and unlike GBS, responds to steroids.

Hereditary Neuropathies

Charcot-Marie-Tooth Disease

Definition/Classification

Charcot-Marie-Tooth (CMT) disease or hereditary motor and sensory neuropathy was first recognized independently by Charcot and Marie in France and by Tooth in England.

Based on neurophysiologic and neuropathologic studies, two major types of CMT have been distinguished. The demyelinating form (CMT1) shows moderately to severely decreased nerve conduction velocity (NCV) of the median nerve (<38 m/s), whereas the axonal type (CMT2) exhibits normal or mildly reduced MCV (>38 m/s). Both CM1 and CMT2 are clinically indistinguishable and are usually inherited (in Europe and North America) as autosomal dominant disorders. A third form is autosomal dominant intermediate CMT, which is characterized by NCV overlapping those observed in CMT1 and CMT2, ranging between 25 and 50 m/s. The clinical, neurophysiological, and neuropathological phenotype of the X-linked forms of CMT is also intermediate between CMT1 and CMT2. The group of progressive motor and sensory axonal or demyelinating neuropathies with autosomal recessive inheritance is known as CMT4. Complex forms of CMT, in which the peripheral neuropathy is associated with other symptoms (ataxia, mental retardation, optic atrophy, pigmentary retinal degeneration) have also been recognized, and their pattern of inheritance and genes involved are being discovered. The autosomal dominantly inherited hereditary neuropathy with liability to pressure palsies (HNPP) is also included in the CMT group, and is clinically characterized by recurrent episodes of peripheral nerve palsies due to mechanical trauma.

Etiology

The disease is an inherited degenerative disorder of the peripheral nervous system with the primary pathological

process affecting the axons of motor or sensory cells or both, or other myelin sheath and associated Schwann cells.

Epidemiology

Estimates of the frequency of CMT vary widely, yet the disease is one of the most common heritable neurologic disorders. A world survey estimated a prevalence of 10 cases per 100,000. The prevalence was reported to be 36 per 100,000 in Norway and 20 cases per 100,000 population in Finland. The incidence in Japan was estimated to be 10.8 per 100,000 population. The demyelinating autosomal dominant form (CMT1) accounts for about 50% of cases, the axonal autosomal dominant (CMT2) for 20–40%, whereas the X-linked inherited form constitutes 10–20% of cases. In contrast, in communities with a high percentage of consanguineous marriages (such as in North Africa and the Middle East), autosomal recessive CMT is likely to account for 30–50% of all CMT cases. In childhood, CMT constitutes approximately 40% of chronic neuropathies.

Pathogenesis

Charcot-Marie-Tooth (CMT) disease is inherited as autosomal dominant, X-linked or autosomal recessive. The inheritance pattern and molecular genetics constitutes the basis of classification of the various types of CMT. Nevertheless, mutations in a single gene are occasionally associated with both autosomal dominant and autosomal recessive inheritance, and/or both axonal, or demyelinating neuropathy. Tables ◉ *372.2–372.4* detail, respectively, the currently known molecular genetics of dominant, X-linked, and autosomal recessive forms of CMT. Demyelinating CMT is caused by diseases of the Schwann cell and the myelin, and the lesions are either diffuse or segmental (i.e., limited to the internode, which is formed by the part of the nerve depending on one Schwann cell). Diffuse demyelination leads to slowing of NCV, whereas segmental demyelination manifests as conduction block in some fibers and temporal dispersion as recorded on nerve conduction studies (NCS). Axonal CMT is characterized primarily by involvement of the axon and manifests with normal or only slightly slowed NCV.

The term *Dejerine–Sottas syndrome (DSS or CMT3)* was described as a hypertrophic polyneuropathy with onset in infancy or early childhood. It was first assumed to be inherited as autosomal recessive. Nevertheless, during the molecular biology era, patients with DSS were found to be heterozygous for point mutations in genes associated with CMT1 including *PMP22* (CMT1A), *MPZ* (CMT1B), and *EGR* (CMT1D). The entity designated as *congenital hypomyelination neuropathy (CHN)* is usually considered as a form of DSS, and can present as floppy infant syndrome. It is also associated with point mutations in *PMP22*, *MPZ*, and *EGR*. *Hereditary neuropathy with liability to pressure palsies* (HNPP) is a dominantly inherited disease characterized by acute onset of recurrent, painless, focal motor, and sensory neuropathy in a single nerve due to deletion or point mutations of *PMP22* gene.

Pathology

The pathology of CMT has mainly been studied by muscle or nerve biopsy. The rare postmortem examinations in CMT1 showed degeneration of the posterior columns, some loss of the anterior hom cells, and degeneration of the anterior and posterior spinal roots. Sural nerve biopsy shows reduced number of myelinated fibers, mainly those of large caliber with preservation of unmyelinated fibers. On electron microscopy, the classical onion bulbs are seen. These are thought to result from repeated demyelination and remyelination of Schwann cell wrappings around individual axons. In CMT2, the disease process is presumed to occur in the axon or cytoplasm of the anterior hom cell, and anterior hor cell loss has been found in two autopsies. Large-caliber fibers are reduced in number and the internodes are shortened and of irregular length. Three of the autosomal recessive forms of CMT (CMT4B1, CMT4B2, and CMT4H) are characterized by the presence, on sural nerve biopsy, of irregular redundant loops of focally folded myelin sheaths (◉ *Fig. 372.2a*). Onion bulbs are seen in CMT4A, CMT4C, CMT4D, CMT4F, and CMT4H. The onion bulbs in CMT4A are characteristically composed of basal laminae (◉ *Fig. 372.2b*).

Clinical Manifestations

Symptoms and Signs

The age of onset of CMT1 ranges from infancy (resulting in delayed walking) to the fourth or later decades but patients usually become symptomatic between age 5 and 25 years. The cardinal symptoms in children are difficulty in running or walking, or foot deformity. Gait disturbance includes clumsy walking, frequent falls, and high steppage gait. Foot deformity is characterized by pes cavus, often

Table 372.2
Genes and proteins involved in autosomal dominant demyelinating. (CMT1) and axonal (CMT2) forms of CMT

Type of CMT	Chromosomal locus of the gene	Gene symbol	Protein product
CMT1: Dominant; Demyelinating			
CMT1A	17p11	*PMP22*	Peripheral myelin protein 22
CMT1B	1q22	*MPZ*	Myelin P0 protein
CMT1C	16p13	*LITAF*	Lipopolysaccharide-induced tumor necrosis factor-alpha factor
CMT1D	10q21	*EGR2*	Early growth response protein 2
CMT2: Dominant; Axonal			
CMT2A1	1p36	*KIF1B*	Kinesin-like protein KIF1B
CMT2A2	1p36	*MFN2*	Mitofusin-2
CMT2B	3q13	*RAB7A*	Ras-related protein Rab-7a
CMT2B1	1q21	*LMNA*	Lamin A/C
CMT2B2	19q13.3	Unknown	Unknown
CMT2C	12q23–q24	*TRPV4*	Transient receptor potential cation channel subfamily V member 4
CMT2D	7p15	*GARS*	Glycyl-tRNA synthase
CMT2E*	8p21	*NEFL*	Neurofilament light polypeptide
CMT2F	7q11	*HSPB1*	Heat-shock protein beta-1
CMT2G	12q12–q13.3	Unknown	Unknown
CMT2L	12q24	*HSPB8*	Heat-shock protein beta-8

*Some individuals with mutations in NEFL, which typically cause CMT2E, have features of demyelination manifesting as slow nerve conduction velocities. This entity is referred to as CMT1F

Table 372.3
Genes and proteins involved in X-linked forms of CMT

Type of CMT	Chromosomal locus of the gene	Gene symbol	Protein product
CMTX1	Xq13	*GJB1*	Gap junction beta-1 protein (connexin 32)
CMTX2	Xp22.2	Unknown	Unknown
CMTX3	Xq26	Unknown	Unknown
CMTX4 (Cowchock syndrome)	Xq24–q26.1	Unknown	Unknown
CMTX5	Xq21.3–q24	*PRPS1*	Ribose-phosphate pyrophosphokinase 1

associated with hammer toes, but pes planus and valgus deviation of the feet may be present in some children. Symptoms are usually insidious and most patients are seen only after several years.

Difficulty in heel-walking is an early manifestation of the disease. Clinical examination reveals symmetrical peroneal muscle atrophy, later involving the calf muscles and eventually the lower third of the thigh, leading to stork leg appearance (*Fig. 372.2c*). Atrophy of the small muscles of the hands (including the thenar and hypothenar muscles) is usually late. When advanced, this leads to claw hands (*Fig. 372.2d*).

Loss of deep tendon reflexes (especially the ankle jerks) is a frequent early manifestation, and can be used to assess at risk children who have affected relatives. Sensory abnormalities are mild, and usually manifest after the age of 5 years. They are limited to subtle deficits in deep sensation, while pain and touch sensation are not impaired. Nerve enlargement is frequent whereas scoliosis, lordosis, and calf muscle hypertrophy may occur.

Table 372.4
Genes and proteins involved in autosomal recessive forms of CMT

Type of CMT	Chromosomal locus of the gene	Gene symbol	Protein product
CMT4A	8q13	*GDAP1*	Ganglioside-induced differentiation-associated protein 1
CMT4B1	11q22	*MTMR2*	Myotubularin-related protein 2
CMT4B2	11p15	*SBF2*	Myotubularin-related protein 13
CMT4C	5q32	*SH3TC2 (KIAA1985)*	SH3 domain and tetratricopeptide repeats containing protein 2
CMT4D (Lom)	8q24	*NDRG1*	Protein NDRG1
CMT4E	10q21	*EGR2*	Early growth response protein 2
CMT4F	19q13	*PRX*	Periaxin
CMT4H	12p11.2	*FGD4*	FYVE, RhoGEF, and PH domain-containing protein 4
CMT4J	6q21	*FIG4*	Polyphosphoinositide phosphatase

The full clinical picture of CMT1 may not occur until the second decade of life, progression is slow over many years, and arrests are common and often prolonged.

The age of onset of hereditary neuropathy with liability to pressure palsies (HNPP) ranges from the first to the eighth decade of life (typically the third or fourth decade), but can present at birth. The recurrent acute mononeuropathy is often related to minor nerve compression, usually after resting on a limb in an awkward position, such as squatting or sitting cross-legged. Affected nerves at sites of anatomic vulnerability to compression include the peroneal nerve at the fibular neck, the ulnar nerve at the cubital tunnel, the radial nerve at the spiral groove of the humerus, and the median nerve at the carpal tunnel. The brachial plexus may also be involved. Examination between episodes of focal weakness may be normal or mildly abnormal.

The clinical features of CMT2 are similar to those of CMT1 but onset is usually later, during the second or third decade, and the course of the disease is slower. Phenotypic variation is common between and within affected families. Areflexia, pes cavus and hammer toes may be less common than in CMT1, but nerve hypertrophy is absent.

In males, symptoms of CMTX1 usually begin in childhood or adolescence. Females are often asymptomatic but may have late onset of mild symptoms because of predominant inactivation of the X chromosomes that bears the normal allele of the gene. Atrophy, particularly of intrinsic hand muscles, paresthesia, and sensory loss, may be more common in this form of CMT than other subtypes.

The onset of the autosomal recessive type of CMT (CMT4) is significantly earlier than either CMT1 or CMT2. In its severe form, it overlaps with Dejerine–Sottas syndrome and can present at birth with congenital hypotonia.

CMT4A was first identified in families in Tunisia. It starts in early infancy with delayed motor development, and distal muscle weakness and atrophy of feet that progress to involve the proximal muscles by the end of the first decade. Atrophy of the hand muscles may occur later and loss of ambulation is often by the age of 30 years. Scoliosis and skeletal deformities may occur. The disease is associated with *GDAP1* mutations, which cause both demyelinating and axonal phenotypes. The axonal form is linked to vocal cord and diaphragmatic paralysis with onset in midlife.

CMT4B1 was first described in an Italian family. Mutations in the causative gene (the first identified autosomal recessive CMT gene) were found in families of Italian and Saudi Arabian ancestory. Onset is usually before the age of 4 years with progressive distal and proximal weakness of the lower limbs. Pes cavus foot deformity is common, and facial, bulbar, and diaphragmatic weaknesses are known associations. Adults frequently require wheelchairs by age 20 years and death may occur as early as the end of the second decade, or in the fourth to fifth decade.

A summary of the salient clinical features of the subtypes of CMT4 is depicted in (*Table 372.5*).

Investigations

Electrodiagnostic Studies

When carefully done, electrodiagnostic studies (including nerve conduction study [NCS] and electromyography [EMG]) are almost always abnormal in cases of CMT.

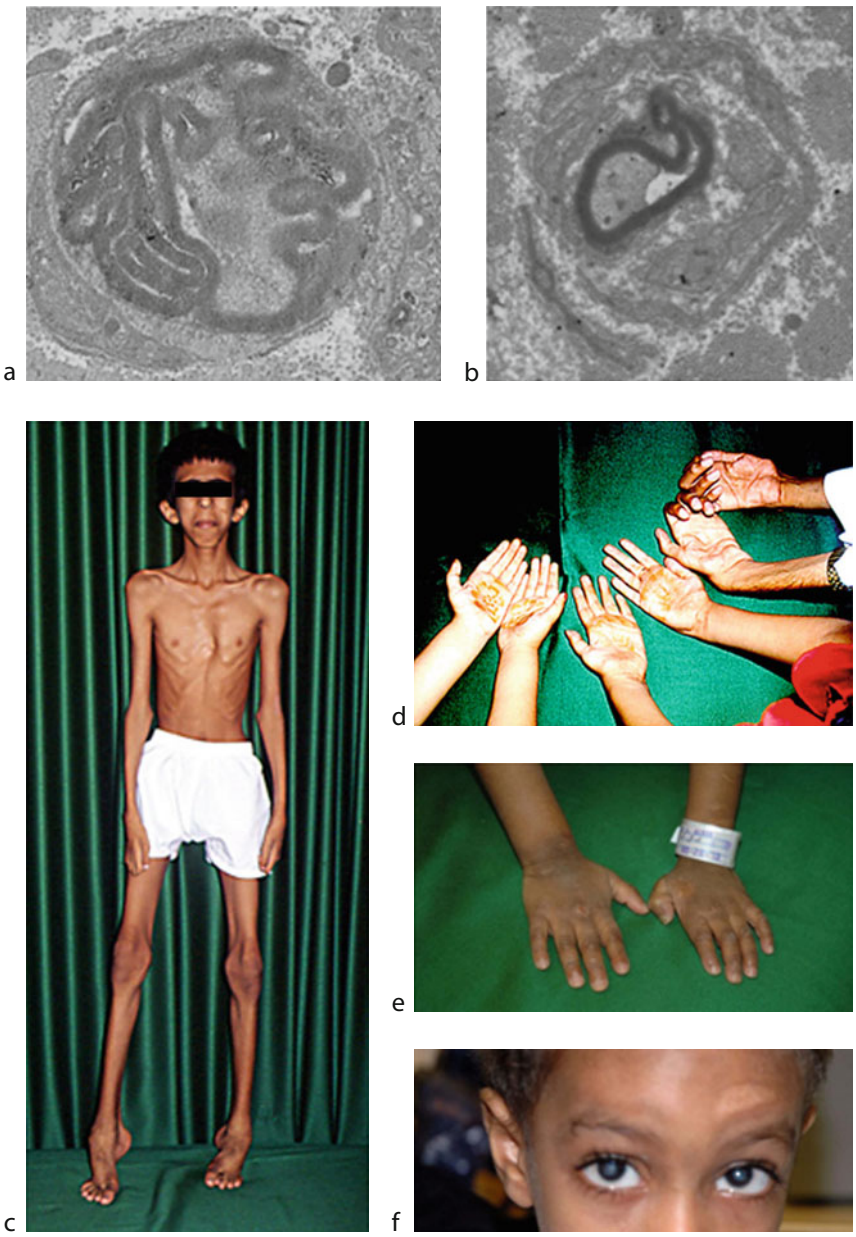

Figure 372.2
(a & b) Electron microscopic examinations of sural nerve biopsies showing (a) redundant loops of focally folded myelin sheaths, and (b) onion bulb formation. (c) Symmetrical distal muscle atrophy in Charcot-Marie-Tooth (CMT) disease. Note the stork leg appearance. (d) Progressive atrophy of the small muscles of the hands in two children and an adult from a family with CMT4B1. Note the development of claw hands in the elder patient to the right. (e) Healed traumatic hand injuries in a child with hereditary sensory and autonomic neuropathy. Note the resorption of the left thumb. (f) The patient had neuropathic keratitis leading to bilateral corneal opacities. Note the traumatic scar over the left eye-brow

Median motor nerve conduction velocity (NCV) is below 38 m/s in CMT1 and above in CMT2. Nerve conduction slowing is diffuse and uniform in CMT1 compared to acquired neuropathies where conduction block and temporal dispersion are common. F-wave responses are usually prolonged and EMG shows evidence of denervation. In CMT2, median NCV is typically above 38 m/s, and is associated with reduced compound muscle action

Table 372.5
Main clinical features of CMT4

Disease	Age at onset	Main clinical features
CMT4A	<3 years	Distal and proximal limb weakness, vocal cord, and diaphragmatic paralysis
CMT4B1	<4 years	Distal and proximal limb weakness. Facial, bulbar, and diaphragmatic weakness
CMT4B2	First decade	Distal and sometimes proximal limb weakness. Early-onset glaucoma
CMT4C	First or second decade	Distal and sometimes proximal limb weakness. Progressive, often severe, and early scoliosis
CMT4D	First decade	Distal and proximal limb weakness, sensorineural hearing loss, and tongue atrophy
CMT4E	Birth	Congenital hypotonia. Dejerine–Sottas syndrome-like presentation
CMT4F	First decade	Distal and sometimes proximal limb weakness
CMT4H	1–2 years	Distal limbs, weakness more in lower than upper limbs. Severe scoliosis
CMT4J	First decade	Severe childhood-onset demyelinating neuropathy

amplitude (CMAP) and reduced sensory nerve action potential (SNAP). Sural nerve sensory responses can be absent and EMG shows signs of chronic denervation. Nevertheless, the distinction between demyelinating and axonal CMT may not always be clear. In children, NCS shows normal results at birth, except for congenital hypomyelination neuropathy and Dejerine–Sottas syndrome. Abnormalities manifest at 2–4 years, as the peripheral nervous system matures, even in asymptomatic patients. The parents should always have NCS to ascertain asymptomatic neuropathy in either of them. In autosomal recessive forms (CMT4), both parents have normal findings on NCS.

Nerve conduction studies in hereditary neuropathy with liability to pressure palsies (HNPP) reveal bilaterally delayed median distal motor latency (DML), slowed median sensory nerve conduction velocities at the wrist, and slowing of peroneal nerve motor conduction velocity or DML.

Sural nerve biopsy is not routinely performed in children, but is occasionally helpful in establishing the diagnosis by showing relatively characteristic lesions in CMT1. It was found to be extremely helpful in autosomal recessive forms of CMT. Identification of myelin outfolding on sural nerve biopsy in two Saudi Arabian families lead to the recognition, and a later discovery in a joint research involving Italian families, of the gene for CMT4B1, which was the first identified gene for the recessive forms of CMT. The axonal form of CMT4A due to GDAP1 mutations is characterized by the presence of onion bulbs composed of basal laminae.

Imaging Studies

Enlarged nerves, both at the level of the spinal roots and also in the limbs, can be shown by magnetic resonance imaging (MRI), as well as subclinical central nervous abnormalities in several subtypes of CMT. Significant involvement of peroneal nerve-innervated muscles was seen in CMT1A patients, in contrast to fatty infiltration involving superficial posterior compartment in CMT2A cases.

Differential Diagnosis

Mental retardation, seizures, dementia, and blindness are not features of CMT and their presence should suggest another diagnosis. Acquired, especially treatable, causes of peripheral neuropathy should also be excluded such as vitamins B_1, B_6, B_{12}, folate, or E deficiencies. Vitamin E deficiency may be due to abetalipoproteinemia and biliary insufficiency that prevents normal emulsion of fat in the bowel lumen resulting in poor absorption associated with steatorrhea. Other diseases leading to fat malabsorption, such as cystic fibrosis and celiac disease, chronic liver disease (especially ductal hypoplasia) can lead to vitamin E deficiency. Other causes of acquired peripheral neuropathy include lead poisoning and heavy metal intoxication, leprosy, neurosyphilis, and immune-mediated neuropathies such as chronic inflammatory demyelinating polyneuropathy (CIDP).

Giant axonal neuropathy is a chronic polyneuropathy of childhood accompanied by characteristically kinky hair, curly eyelashes, and unique posture of legs. Sural nerve biopsy shows typical findings on electron microscopy, with the axons being distended by tightly woven neurofilaments. It is inherited as autosomal recessive and is caused by mutations encoding a protein named gigaxonin.

Hereditary neuropathies may constitute part of more complex neurological diseases involving the central nervous system (CNS). The autosomal recessively inherited

Friedreich's ataxia may present with sensory loss, depressed tendon reflexes, high-arched feet, and hammer toe. Some of the other degenerative disorders are either treatable or deserve accurate diagnosis to anticipate associated complications outside the CNS. These are briefly mentioned in (Table 372.6).

Treatment

Treatment of CMT is symptomatic and therapy should focus on the management and prevention of the development of the physical disability related to CMT. Affected children are better evaluated by a multidisciplinary team

Table 372.6
Complex hereditary neurological diseases associated with neuropathies

Disorder	Brief clinical features	Suggestive diagnostic investigations
Mitochondrial disorders		
NARP	Neuropathy, ataxia, retinitis, pigmentosa	Muscle biopsy for biochemical, morphological, and mitochondrial DNA abnormalities
MNGIE	Mitochondrial neurogastrointestinal encephalomyopathy	Muscle biopsy for biochemical, morphological, and mitochondrial DNA abnormalities
Peroxisomal disorders		
Refsum disease	Ataxia, areflexia, atypical retinitis pigmentosa, deafness, ichthyosis, disorders of cardiac function	Very-long-chain fatty acids and phytanic acid
Juvenile adrenoleukodystrophy	Dementia, personality disorder, sensory ataxia, areflexia	Very-long-chain fatty acids
Leukodystrophies		
Krabbe	Floppiness, loss of milestones, seizures, ocular movement abnormalities	Galactocerebrosidase
Metachromatic	Progressive spastic diplegia, optic atrophy	Arylsulphatase A assay
Sialidosis type 1	Action and intension myoclonus, retinal cherry red spot, no dysmorphism, normal intelligence	Sialidase (α-neuraminidase) assay
Pelizaeus–Merzbacher disease	Rotary nystagmus, hypotonia, dystonia, pyramidal and cerebellar signs, optic atrophy	Intense signal from white matter on T2-weighted MRI sequence and absence of myelin signal on T1-weighted MRI sequence
DNA Processing(damage/repair) disorders		
Xeroderma pigmentosum	Photosensitivity, poikiloderma, skin cancer, hearing loss, cognitive impairment, microcephaly, neurodegeneration	BAEP
Cockayne syndrome	Photosensitivity, growth retardation, hearing loss, cognitive impairment, progeria, microcephaly, neurodegeneraion	Cerebellar atrophy on MRI
Ataxia telangiectasia	Ataxia, oculomotor apraxia, recurrent sinubronchial infections, immune defects, neurodegeneration, choreoathetosis, malignancy	Elevated levels of AFP and CEA, immunoglobulins profile (dysgammaglobulinemia)
Ataxia telangiectasia-like disease	Ataxia, oculomotor aprxia, neurodegeneration. Choreoathelosis	Normal levels of AFP, cerebellar atrophy on MRI
Spinocerebellar ataxia with neuropathy type 1 (SCAN1)	Ataxia, epilepsy (some cases)	Cerebellar atrophy on MRI
Ataxia and oculomotor apraxia type 2 (AOA2)	Ataxia, oculomotor apraxia, neurodegeneration	Normal levels of AFP, cerebellar atrophy on MRI

Abbreviations: AFP: alpha-fetoprotein; CEA: carcinoembryonic antigen; MRI: magnetic resonance imaging

that includes pediatric neurologists, orthopedic surgeons, and physical and occupational therapists. Orthotics and ankle-foot orthosis (AFO) frequently enable patients to continue performing their daily activities while preventing falls that might result in injuries. Special shoes, including those with good ankle support can delay the need for ankle braces. Orthopedic surgery to correct severe pes cavus deformity and scoliosis might be needed at a certain stage. Exercise is encouraged within the child's capacity, daily heel cord stretching exercises are helpful in preventing Achilles tendon stretching, and obesity should be avoided because it makes walking more difficult. Medical conditions, situations, and interventions which can lead to systemic or focal neuropathies should be avoided or early managed. These include diseases such as diabetes mellitus and hypothyroidism, prolonged immobilization of limbs during surgery, vitamin deficiencies, carpal tunnel syndrome, and neurotoxic drugs. Symptoms of sleep apnea, vocal cord, and bulbar paralysis should be detected early and managed promptly.

Maladjustment and depression, especially in teenagers, should also be detected and managed. The importance of investing in education should be emphasized since CMT does not usually affect intellect, life span, or independent living.

Treatment with steroids (prednisone) or intravenous immunoglobulin has been reported to improve a few individuals with CMT1 who develop sudden worsening of their peripheral neuropathy. Other therapies under investigation include the effects of neurotrophin-3 on CMT1A patients. Ascorbic acid reduced PMP22 over expression and ameliorated the phenotype in a transgenic CMT1A mouse model, whereas a progesterone antagonist improved neuropathy in a transgenic rat model of CMT1A. A clinical trial is underway to address the possible role of high doses of ascorbic acid in CMT1A patients.

Prognosis

With the exception of CMT4, Dejerine–Sottas syndrome (DSS) and congenital hypomyelination neuropathy (CHN), life expectancy is normal in most patients with CMT. Nevertheless, the degree of disability varies according to the CMT subtype, and between and within families. Patients with CMT4A and CMT4B1 often require wheelchairs by the end of the second or third decade; and those with CMT4B1 may die by the third to fifth decade. Individuals with DSS are often disabled in early childhood and CHN may lead to early death. Approximately 10% of patients with HNPP have incomplete recovery from the acute nerve palsies, and cases of respiratory failure have been reported.

Prevention

Since CMT does not usually affect intellect, independent living, or life span, most affected parents choose to have children. Prenatal diagnosis for pregnancies at increased risk for some types of CMT4 is possible by chorionic villous sampling (at 10–12 weeks of gestation) and by amniocentesis (by about 15–18 weeks). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified.

Hereditary Sensory and Autonomic Neuropathy

Definition/Classification/Etiology

Hereditary sensory and autonomic neuropathy (HSAN) forms part of the inherited peripheral neuropathies where sensory dysfunction prevails and autonomic nervous system is involved to a varying degree. They are clinically and genetically heterogeneous with controversy over terminology. Based on clinical presentations, the distinct populations of affected nerve fibers, associated genes, and inheritance pattern, five types of HSAN have been defined (*Table 372.7*). With the exception of HSAN type I, which is transmitted as autosomal dominant, the other types are transmitted as autosomal recessive traits.

Epidemiology

Type I variant of HSAN is the most frequent and has been described in Portuguese, Belgian, Australian, and English families. HSAN III (Riley–Day syndrome) is most prevalent among individuals of Eastern European Jewish extraction, with incidence of 1 per 3,600 live births. HSAN IV, also known as congenital insensitivity to pain and anhidrosis (CIPA), has been described in most ethnic groups but seems to have high prevalence in Bedouin Arabs living in Israel. Types II and V are rare autosomal recessively inherited forms of HSAN.

Table 372.7
Genes and loci associated with various types of hereditary sensory and autonomic neuropathy (HSAN)

HMSN type	Inheritance	Locus	Gene
HSAN I	Autosomal dominant	9q22.2	*SPTLC1*
HSAN II	Autosomal recessive	12p13.3	*HSN2*
HSAN III (Riley–Day syndrome, familial dysautonomia)	Autosomal recessive	9q31	*IKBKAP*
HSAN IV (Congenital insensitivity to pain and antidrosis [CIPA])	Autosomal recessive	1q21–22	*NTRK1*
HSAN V	Autosomal recessive	1p13.1	*NGFB*

Pathogenesis/Pathology

Mutations in the genes associated with HSAN are thought to lead to malfunction in vesicular transport along the axons. In humans, sensory axons can extend for one or more meters and most proteins must be transported along the axon to reach their destination at the cell bodies of nociceptive neurons. A founder mutation (C133N mutation) estimated to have originated 900–1,600 years ago, was found in British families with the dominantly inherited HSAN1. Pathological examination of this type showed degeneration of the dorsal root ganglia and the spinal dorsal roots supplying the lower limbs. Histopathological findings in HSAN III include loss of neurons in the posterior root, dorsolateral tract (Lissauer tract), and intermediolateral gray columns. The Lissauer tract and dorsal spinal roots are also affected in HSAN IV.

Clinical Manifestations: Symptoms, Signs

Symptoms of HSAN1 appear in late childhood or adolescence with a progressive loss of sensation in the lower extremities leading to acromutilations following episodes of cellulitis and trophic ulcerations of the feet. Spontaneous stabbing (lancinating) pain may occur. Initially, there is predominant loss of pain and temperature sensation with preservation of tactile sensation. Later, all sensory modalities are lost and the distal upper limbs may become involved. Variable distal motor weakness and wasting is also a feature of the disease.

The onset of HSAN II is either congenital or during first to second decades. There is universal absence of pain sensation resulting in burns and mutilations of the lips, tongue, and fingertips. There are also painless fractures, especially of the metatarsals, a delayed development and lack of fungiform papillae on the tongue. Bladder sensation may be impaired leading to its distension, and hearing loss affects 30% of patients.

The clinical manifestations of HSAN III are mainly due to autonomic disturbances. Sucking difficulties, a poor cry, vomiting, and hypotonia are present from birth. Affected children also have pain and temperature sensory loss, alacrima (loss of overflow tears), excessive sweating, and unstable temperature and blood pressure. On examination, they have absence of fungiform papillae on the tongue, and diminished or absent deep tendon reflexes. Death, which occurs in infancy or childhood, is usually caused by bouts of apnea and pneumonia. Intelligence remains normal but the occurrence of kyphoscoliosis, esophageal dilation, and impaired gastric motility are frequent.

The onset of HSAN IV is congenital with markedly decreased or absent sweating leading to episodic unexplained fever and hyperpyrexia, often related to environmental temperature. Insensitivity to pain is universal and promotes repeated traumatic and thermal injuries, and severe mutilations of the hands and feet (*Fig. 372.2e*). Tongue-biting and osteomyelitis, especially of the lower extremities are frequent. Despite normal lacrimation, affected children are prone to neuropathic keratitis, associated with absent corneal sensation and very poor corneal healing, and resulting in corneal ulceration and opacities (*Fig. 372.2f*). Affected children usually have mild mental retardation, frequently associated with hyperactivity and emotional liability. Examination reveals sequelae of anhidrosis in the form of calloused appearance of the skin, lichenification of the palms, areas of hypotrichinosis on the scalp, and dystrophic nail changes. Muscle power and deep tendon reflexes are usually preserved.

The phenotype of HSAN V is similar to that of HSAN IV with the exception of the presence of less severe anhidrosis and lack of mental retardation in patients with HSAN V. Affected patients have severe loss of deep pain perception, which prevents them from recognizing pain from bone fractures and joint injuries resulting in destroyed joints in childhood.

Diagnosis

The congenital or early-onset forms of HSAN can be suspected when an infant shows insensitivity or indifference to

pain inflicted by the first intramuscular routine immunization injection. Attention should also be drawn to the condition when there are bouts of recurrent unexplained fever.

Investigations

Neurophysiologic Tests

Neurophysiologic tests that can be used to assess the various types of HSAN include nerve conduction studies (NCS) and electromyography (EMG). Sympathetic skin responses (SSR), utilizing the routine EMG equipment, can also be used to identify indirect evidence of sweat production via measurement of changes in skin conductance on the palm/sole in response to an electrical stimulus. Another helpful test is quantitative sensory testing (QST), which permits comparison of sensory thresholds by using vibration and temperature perception to assess both large- and small-fiber modalities. However, QST needs cooperation of the patient, which is usually lacking in young children.

Because the involved fibers in HSAN are small myelinated and unmyelinated fibers, motor nerve conduction velocity (NCV) and EMG are usually normal. Nevertheless, sensory NCV is low or absent in all forms except in HSAN V, and EMG may show features of chronic axonal neuropathy in HSAN I. Sympathetic skin responses (SSR) were reported to be absent in HSAN IV and temperature threshold is increased in HSAN V.

The histamine test is also a valuable diagnostic tool. This is done by injecting 0.1 ml of histamine (in a concentration of 0.275 mg histamine phosphale/ml) intradermally using a fine needle tuberculin syringe. In normal individuals, there is a bright red histamine flare (due to capillary vasodilation) within 5 min. Dyautonomic reaction demonstrates only a narrow areola surrounding the wheel. This lack of axon flare is universal and consistent in patients with HSAN II, III, and IV.

Histologic Findings

Sural nerve biopsy can indicate the diagnosis in HSAN by revealing the selective loss of particular fiber types. In HSAN I, there is reduction in the number of small myelinated and unmyelinated fibers, associated with loss of large myelinated fibers. HSAN II is characterized by severe reduction in the number of myelinated axons but unmyelinated fibers are usually normal or slightly diminished. Loss of unmyelinated and myelinated fibers in peripheral nerves, associated with decreased number of large myelinated fibers, characterizes HSAN III. Histopathological findings are striking in HSAN IV by the visual absence of unmyelinated nerve fibers in the peripheral nerves. In HSAN V, there is selective decrease in small myelinated fibers and mild reduction in unmyelinated fibers. Skin biopsy is useful in HSAN IV (congenital insensitivity to pain with anhidrosis) and shows lack of nerve fibers in the epidermis and only a few hypotrophic and uninnervated sweat glands in the dermis.

Treatment

Management of HSAN is symptomatic and preventative. Ulcero-mutilating complications are the most serious and should follow the guidelines given for diabetic foot care. Removal of pressure to ulcers, eradication of infection, and specific protective footwear are of paramount importance to avoid further complications like amputations. Careful daily inspection for unrecognized injury is important. Significant feeding problems, especially when associated with gastroesophageal reflux are managed with gastrostomy and fundoplication. The risk of aspiration pneumonia should be minimized in HSAN III by attention to posture and by meticulous precautions during feeding. Blood pressure liability (postural hypotension and hypertension) should be managed promptly. Alacrema and corneal analgesia, which predispose to corneal ulcerations, require frequent administration of topical lubricants. Control of hyperthermia in HSAN IV is important using acetaminophen and/or ibuprofen or direct cooling in a bath. Smoothing of the teeth or extraction, to prevent self-mutation of the tongue and lips, might be needed in some children. Chlorpromazine has been found to be effective in controlling bouts of rages, hyperactivity, and irritability, as well as behavior modification. Families of affected children need considerable psychological support.

Prognosis

HSAN I is a slowly progressive disease and does not influence life expectancy. Prognosis for the other congenital types is improving with time and increasing numbers of patients are reaching adulthood. This followed improved diagnosis and appropriate interventions and treatments. Understanding the pathomechanism underlying HSAN by knowing specific gene actions will have an impact on definitive therapeutic interventions.

Prevention

Prenatal diagnosis can be done in families where the diseases causing mutation is known. Nevertheless, termination of pregnancy is challenged with ethical justification, especially in HSAN I. Preimplantation genetic diagnosis is also another reproductive option following identification of the disease-causing mutation in the specific family.

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373 Neuromuscular Transmission Disorders

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Congenital Myasthenic Syndromes

Definition/Classification/Etiology

Congenital myasthenic syndromes (CMSs) are a heterogeneous group of inherited disorders caused by genetic defects that affect transmission of information to muscles at the neuromuscular junction (NMJ). Based on the site and molecular mechanism of the underlying defect of neuromuscular transmission, they are classified into presynaptic, synaptic (basal lamina-associated), and postsynaptic CMS.

Epidemiology

Postsynaptic CMS are the most frequent accounting for approximately 80% of all genetically diagnosed cases. Synaptic CMS account for about 15% whereas presynaptic CMS are rare (approximately 5%). Patients with CMS are observed less frequently than those with autoimmune myasthenia gravis, but they are often misdiagnosed or remain undiagnosed for several years. Since the majority of CMS are inherited as autosomal recessive, some forms were noted to be endemic in communities of the Middle East where consanguineous marriages are relatively frequent. As of the year 2009, sodium channel entity of CMS has been reported in a single patient, whereas another form caused by a defect in muscle-specific receptor tyrosine kinase (MuSK) has been described in only two families (from France and Sudan).

Pathogenics/Pathology

In humans, the NMJ consists of a presynaptic and a postsynaptic domain separated by the synaptic cleft. A single nerve impulse triggers the release of acetylcholine (ACh) quanta within the presynaptic side into the synaptic space leading to activation of the acetylcholine receptors (AChRs) located on the postsynaptic side resulting in an endplate potential (EPP). This local depolarization of EPP is converted by voltage-gated sodium channels into a propagated action potential that activates muscle contraction. In each form of CMS, the safety margin of neuromuscular transmission is compromised by one or more mechanisms. This safely margin is a function of the difference between the postsynaptic depolarization caused by the EPP and the depolarization required to activate the voltage-gated sodium channels.

Rapsyn (receptor-associated protein at synapse) is a protein synthesized by muscle which, under the influence of agrin and MuSK, concentrates AChRs on the terminal expansion of the postsynaptic junction folds. Dok-7 (downstream of kinase 7 protein) activates MuSK and is therefore critical in endplate development and AChRs aggregation.

The AChR is a transmembrane glycoprotein ligand-gated receptor that has five subunits and is anchored to the muscle membrane and cystoskeleton by rapsyn. The adult isoform of AChR is composed of two alpha (α) subunits, and one beta (β), one delta (δ), and one epsilon (ε) subunit. In humans, the gamma (γ) subunit appears at about the ninth developmental week but is subsequently replaced by the adult epsilon (ε) subunit and is no longer present at fetal end plates after 31 weeks of gestation. Pathogenic mutations residing in different subunits of the AChR may cause *slow-channel syndrome* due to prolongation of the opening events of the AChR. This in turn prolongs the duration of the synaptic potentials and elicits a second compound muscle action potential (CMAP). The prolonged synaptic response also causes cationic overloading of the postsynaptic region resulting in degeneration and loss of the AChR from the folds. The majority of slow-channel syndrome mutations are autosomal dominant, although recessive mutations have also been described. Due to the variable penetrance and expression of the autosomal dominant mutations, they may give the appearance of a sporadic or recessive disorder. On the other hand, pathogenic mutations residing in different subunits of the ACR may cause *fast-channel syndrome* by decreasing the rate at which the channel opens or increasing the rate at which it closes. A third group of mutations

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lead to primary endplate AChR deficiency characterized by patchy and attenuated AChRs at the junctional folds.

Presynaptic defects causing CMS affect the number of molecules per synaptic vesicle, the size of a single vesicle, or the reorganization of the ACh. Choline acetyl transferase (encoded by *CHAT* gene) is the rate-limiting enzyme in the resynthesis of ACh from acetyl-coenzyme A and choline within the nerve terminal. In the synaptic space, acetylcholinesterase (AChE) hydrolyzes ACh back into choline and acetyl-coenzyme A. AChE is composed of globular catalytic subunits, which are attached to the basal lamina of the postsynaptic membrane by ColQ protein. The absence of the AChE prolongs the lifetime of ACh in the synaptic space, which increases the duration of the endplate current so that it outlasts the refractory period of the muscle fiber and excites a second CMAP. The prolonged endplate currents lead to overloading of the synaptic space with cations, resulting in endplate myopathy and loss of AChRs.

Currently, mutations in ten genes have been identified to cause CMS (Table 373.1). They are classified according to their target at the NMJ as presynaptic, synaptic (basal lamina-associated) and postsynaptic.

Clinical Manifestations: Symptoms, Signs

CMS may present in utero with history of reduced fetal movements. Some patients harboring mutations in the AChR delta subunit, or rapsyn, are born with arthrogryposis multiplex. Escobar syndrome is a prenatal myasthenic syndrome caused by recessive mutations in the fetal gamma subunit of AChR. Affected babies have characteristic facies with mild ptosis and small mouth with downturned corners. They have several musculoskeletal abnormalities including arthrogryposis multiplex, small muscle bulk, and multiple pterygia (webbing of the neck, axilla, elbows, fingers, and/or popliteal fossa), camptodactyly, and rocker bottom feet with prominent heels. Since the fetal gamma AChR subunit is replaced by the adult epsilon subunit and is no longer present at fetal endplates after 31 weeks of gestation, myasthenic symptoms are absent after birth in babies with Escobar syndrome.

During the neonatal period, babies affected with CMS may present with respiratory insufficiency, episodes of apnea, stridor due to palsy of the vocal cords, or choking spells. They are hypotonic with a feeble cry and feeding difficulties due to poor sucking. They have symmetric ptosis and their symptoms are worsened by crying. Motor milestones are usually delayed. In childhood, they may manifest with fatigable ptosis, ophthalmoparesis, dysphagia, chewing and feeding difficulties, and flaccid dysarthria. Symptoms increase by the end of the day and worsen during hot days in countries with high ambient temperature. In such a country, symptoms of these children were noticed to improve following a cold shower or afternoon nap.

Clinical examination reveals fatigable ptosis and extraocular muscle weakness (ophthalmoparesis). There is also bilateral facial weakness with tenting of lips. Dysmorphic features may be present in the form of high-arched palate and prognathism. The muscle bulk is

Table 373.1
Genes known to cause, if mutated, congenital myasthenic syndrome (CMS)

Defect causing CMS	Gene symbol	Name/function
Presynaptic defect Choline acetyltransferase deficiency	*CHAT*	Choline acetyltransferase gene
Synaptic defect (basal lamina) Endplate acetylcholinesterase (AChE) deficiency	*COLQ*	Encodes the triple-stranded collagenic tail (ColQ) of the synaptic cholinesterase
Post synaptic defect Acetylcholine receptor (AChR) mutations	*CHRNA1, CHRNB1 CHRND, CHRNE*	Genes encoding the different subunits of the AChR
Rapsyn mutations	*RAPSN*	Encodes rapsyn protein
Muscle-specific kinase (MuSK) mutations	*MuSK*	Encodes MuSK
Dok-7 mutations	*DOK7*	Encodes MuSK-interacting cytoplasmic protein Dok-7
Sodium channel mutations	*SNA4A*	Encodes sodium channel SCN4A

reduced (muscle hypotrophy) and they may have scoliosis or lordosis (which increases on standing) manifesting later in life. Characteristically, the weakness in slow-channel CMS involves muscles of the neck and distal regions of the upper limbs (especially intrinsic hand muscles and digit extensors) more prominently than other regions. Patients with endplate AChE deficiency may have, as well, slowed pupillary responses to light and prominent respiratory crises.

Family history may reveal affected siblings in autosomal recessive disorders or generational transmission in the autosomal dominantly inherited slow-channel CMS. There may also be history of spontaneous abortions or sudden infant death syndrome.

Diagnosis

The diagnosis of CMS can be confirmed by three main types of investigations:

1. The edrophonium chloride (Tensilon) test is the principal test used to confirm the diagnosis of myasthenia. Edrophonium is an AChE inhibitor with very short action. Because serious respiratory or cardiac complications may rarely occur, resuscitation equipment and a nurse should be present before starting the test. Also an intravenous (IV) line should be established prior to the test. Subcutaneous atropine before edrophonium chloride injection neutralizes the muscarinic cholinergic effects of the drug, which include increased oral and bronchial secretions, bradycardia, abdominal cramps, and red, watery, painful eyes. The dose varies with age, ranging between 1 mg in infants and 8 mg in older children. A test dose of 1 or 2 mg is given first. This is because some patients may have severe muscarinic side effects to even a small dose of edrophonium. The rest of the dose can be given IV over 30–60 s periods if there is no response. Taking serial photographs of the child before and 1 min after injection, or video, allows objective documentation of any change. Intramuscular neostigmine (0.04 mg/kg, up to 1.5 mg total in an older child) may also be used. The effect is slower, starting after 10–15 min and reaching a maximum at 30 min (*Fig. 373.1a, b*). In CMS patients, the edrophonium or neostigmine test is usually positive except in endplate AChE deficiency (*COLQ*-mutant CMS), and in some cases of *slow-channel syndrome*, *DOK7*- and *MuSK*-mutant CMS.

In CMS, serological tests for circulating antibodies directed against AChR, MuSK are negative and help to rule out the autoimmune myasthenia gravis. Tests to exclude botulism may also be required in some infants.

Neurophysiologic Tests

While performing nerve conduction studies (NCSs), repetitive stimulation of nerves at 2–3 Hz will induce a decrement of greater than 10% of the fifth compared to the first-evoked CMAP in multiple muscles, especially those with significant weakness (see Fig. 368.1b of Chap. 368, "Approach to Diagnosis and Treatment of a Child with Motor Unit Diseases"). Single nerve stimulation of rested muscles typically shows repetitive (or double) CMAP in cases of slow-channel syndrome and in endplate AChE deficiency. Needle electromyography (EMG) helps to differentiate congenital myasthenia from myopathies and other neurologic disorders. If repetitive nerve stimulation (RNS) studies fail to show decremental response, then single fiber EMG study is needed. This demonstrates increased "jitter" in contraction of pairs of fibers. As a diagnostic tool, single fiber EMG is more sensitive than NCS, but is difficult to perform in children and is not available in many hospitals.

Differential Diagnosis

CMS appearing during the neonatal period or infancy should be differentiated from other causes of the floppy infant syndrome, as has been detailed in the subchapter on Floppy Infant Syndrome. Extraocular muscle involvement in CMS may also simulate the manifestations of brainstem anomalies, Moebius syndrome, and congenital fibrosis of the extraocular muscles (cranial dysinnervation syndromes). Transient neonatal myasthenia gravis, in infants born to myasthenic mothers, and infantile botulism should always be entertained since they are treatable.

When manifesting in later childhood, AChR or MuSK-seropositive and seronegative autoimmune myasthenia gravis should be considered first. Other important diseases to consider include mitochondrial myopathy and fascioscapulohumeral muscular dystrophy. Slow-channel CMS may simulate radial nerve palsy or peripheral neuropathy.

Treatment

In CMS, there is either decreased or increased synaptic response to ACh. Anti-AChE drugs, which increase the number of AChRs activated by each quantum of ACh, are used in the forms of CMS where there is reduced synaptic

response. Another useful drug is 3,4-diaminopyridine (3,4-DAP), which increases the number of quanta released by nerve impulse. When there is increased synaptic response, as in slow-channel CMS, blockers of the AChR channels: quinidine and fluoxetine are used instead. Acetycholinesterase (AChE) inhibitors (pyridostigmine and neostigmine) are contraindicated in endplate AChE deficiency since they can result in serious complications leading even to fatal outcome. Their long-term use is also harmful in Dok-7 myasthenia and in slow-channel syndrome.

The two commonly used anti-AChE medications are pyridostigmine bromide (Mestinon) and neostigmine bromide (Pyridostigmine). Pyridostigmine acts within 45 min and its effects last from 3 to 6 h. It is less likely to cause muscarinic side effects (diaphoresis, nausea, vomiting, abdominal cramps, bradycardia, and myosis), and may be more effective in controlling bulbar weakness than neostigmine bromide (Pyridostigmine).

Pyridostigmine bromide (Mestinon) is available in 60 mg tablets and as syrup containing 12 mg/ml. The pediatric oral dose ranges between 1.0 and 7.0 mg/kg/day given in divided doses every 4–6 h.

When given orally, neostigmine bromide (Pyridostigmine) acts within 30 min and its effects last for 3–4 h. It is available in 15 mg tablets, and one tablet is equivalent to 60 mg tablet of pyridostigmine bromide (Mestinon). The recommended dose in infants and children is 2 mg/kg/day in divided doses (taken every 3–4 h). Muscarinic side effects can be alleviated by concurrent administration of atropine or glycopyrrolate. Neostigmine methylsulfate is available for intramuscular or intravenous injections. The recommended parenteral dose is 0.01–0.04 mg/kg every 3–4 h.

The adrenergic agents ephedrine and albuterol show positive effects in different forms of CMS such as AChE deficiency and Dok-7 deficiency. In patients seen and followed by the author, ephedrine positively transformed the life of two patients with *COLQ*-mutant CMS, but had severe side effects in a patient with MuSK mutation, who developed respiratory failure during an episode of pneumonia.

In children, the dose of ephedrine is 3 mg/kg/day in three divided doses. It is usually started as 1 mg/kg/day and is increased with caution. Side effects include nervousness, insomnia, palpitation, and hypertension. The dose of albuterol is 2 mg given three to four times daily in children aged 6–12 years and 0.1 mg/kg three times daily in children aged 2–6 years.

Both quinidine sulfate and fluoxetine are long-lived, open-channel blockers of the AChR. They are used only in the slow-channel CMS and are contraindicated in all other types of CMS. The dose of quinidine sulfate is 15–60 mg/kg/day in children, given in four to six divided doses. Side effects include gastrointestinal symptoms (diarrhea), hypersensitivity symptoms, cardiac conduction defects, including aggravation of a prolonged QT interval, and inhibition of cytochrome P450IIDA, which impairs several metabolic pathways. In contrast to quinidine sulfate, fluoxetine is eliminated more slowly, but the dose in children has not been established yet.

Prevention

Drugs known to cause NMJ block should be avoided by CMS patients. These are detailed in *Table 373.2*. Prenatal diagnosis for pregnancies at increased risk for CMS is possible by chorionic villus sampling (at 10–12 weeks of gestation) and by amniocentesis (by about 15–18 weeks). Preimplantation genetic diagnosis may be available for families in which the disease-causing mutations have been identified.

Table 373.2
Medications that may adversely affect neuromuscular transmission

Groups/drug effect	Drugs (other uses)
Antibiotics	
Aminoglycosides	Gentamicin, kanamycin, streptomycin, neomycin, tobramycin
Macrolides	Erythromycin, azithromycin, telithromycin
Fluoroquinolones	Ciprofloxacin, levofloxacin, norfloxacin
Antiarrhythmics	Quinine (also used for treating malaria), quinidine, procainamide, lidocaine, trimetaphan, beta-adrenergic blockers
Miscellaneous	
Drugs with ion channel effects	Chloroquine (used for treating malaria), phenytoin (anticonvulsant), magnesium salts

Myasthenia Gravis

Definition/Classification

Myasthenia gravis is an acquired autoimmune disorder characterized clinically by weakness and increased fatigability on muscular exercise. On the basis of the distribution and severity of weakness, a grading system was recently adopted by the Myasthenia Gravis Foundation of America to help in patient management and for use in therapeutic research trials. Class I is when the disease is ocular, Classes II, III, and IV when it is mild generalized, moderate generalized, or severe generalized, respectively. These three classes are designated IIa, IIIa, or IVa,respectively, when the weakness predominantly involves the limb and/or axial muscles. Subclasses IIb, IIIb, and IVb refer to weakness predominantly affecting oropharyngeal and/or respiratory muscles and when there is a need to use a feeding tube. Class V is defined by the need for intubation, with or without mechanical ventilation, except when used during routine postoperative management.

Etiology

Myasthenia gravis is idiopathic in most patients and is considered to be the prototype of autoimmune antireceptor antibody disorders. The disease is caused by autoantibodies directed against epitopes on or around the AChR in the muscle membrane.

Epidemiology

Because of improved survival and the availability of more effective therapies, estimates for prevalence rates have progressively increased over the years. The most recent prevalence estimate is 1 per 10,000, and approximately 10% of all cases of myasthenia gravis occur during childhood. The disease has a bimodal distribution, between 15 and 30 years old or between 60 and 75 years old.

Pathogenesis and Pathology

Myasthenia gravis results from disruption of the normal neuromuscular transmission by the binding of autoantibodies to proteins involved in signaling at the NMJ. These antibodies are directed against the AChR in 80–85% of cases. The loss of functional AChRs is caused by one of three mechanisms. Rarely, these antibodies attach to ACh binding sites leading to blockade of the AChR. More frequently, there is complement-mediated lysis of the muscle end plate, triggered by the autoantibody response, leading to distortion and simplification of the postsynaptic muscle membrane. A third mechanism is through accelerated internalization and degeneration of the AChRs as a result of cross-linkage of AChR by immunoglobulin G (IgG)

Between 40% and 70% of patients who are seronegative for anti-AChR antibodies have detectable antibodies directed against the MuSK. MuSK plays a critical role in postsynaptic differentiation and clustering of AChRs, resulting in reduced numbers of functional AChRs at the NMJ.

The role of the thymus gland in myasthenia gravis is incompletely understood. Nevertheless, most patients with myasthenia gravis have thymic abnormalities. Thymic tumor is found in 10–15%, and 70% of those without tumor demonstrate lymphoid follicular hyperplasia, especially younger patients and HLA-DR3 positive females. Patients with anti-MuSK myasthenia gravis are less likely to have thymic hyperplasia and rarely have thymoma. Muscle histology may show denervation atrophy in cases of longstanding disease, as well as focal collections of small lymphocytes (lymphorrhages) around necrotic fibers.

Clinical Manifestations

The onset of symptoms is always after 1 year of age and young adolescent females predominate. Initially, the symptoms involve the ocular muscles in up to 85% of patients with myasthenia gravis. This manifests as unilateral asymmetric ptosis, intermittent diplopia, or both. Drooping of the eyelid varies during the course of the day, often worsening after exercise, reading, or exposure to direct sunlight. In 20–40% of patients, weakness remains limited to the extraocular muscles. The majority of others develop the *generalized form* with extension of the weakness to proximal limbs and bulbar muscles. Involvement of the lower limbs is less common and may cause diagnostic difficulties. Early in the course of myasthenia gravis, 20% of patients may have prominent oropharyngeal symptoms, including dysarthria, dysphagia, and difficulty chewing. This percentage is higher in anti-MuSK-positive myasthenia gravis where it may be present with minimal associated ocular symptoms. Dysarthria becomes worse with prolonged talking, and weakness of palatal muscles may result in nasal quality of the voice. Dysphagia may be limited to difficulty with solid foods in mild cases, and nasal regurgitation of liquids and aspiration indicate severe disease. The majority of patients with

respiratory muscle weakness have associated ocular and bulbar involvement. Orthopnea is an early symptom of diaphragmatic weakness, and shallow rapid breathing is indicative of respiratory muscle weakness. In rare cases, weakness may not be focal, that is, affecting distal limb muscles or neck extensors. Affected children feel normal on awakening and by the evening, they may have difficulty chewing and choke on food.

Signs

Characteristic signs of myasthenia gravis include ptosis, ophthalmoparesis, bulbar weakness, and fatigable limb muscle weakness. The eyelid elevators are involved to different degrees, and the pattern of extraocular muscle weakness is typically asymmetric, with the medial rectal muscle being most severely affected followed by the superior and lateral rectus muscles. Pupillary responses are normal. Sustained upward gaze for 30–60 s enhances ptosis and elicits medial rectus weakness. Ptosis may improve following local cooling of the lid. Involvement of the facial muscles is characterized by loss of facial expression and elevation of the eyebrows by contracting the frontalis muscle in an attempt to compensate for ptosis. When asking the patient to smile, weakness of the orbicularis oris produces the characteristic myasthenic snarl. Patients also have difficulty in pursing the lips and weakness of the buccinators leads to difficulty in puffing their cheeks.

Patients with bulbar symptoms may develop nasal speech, and labial and lingual dysarthria when asked to count up to 50. Those with dysphagia should be examined for palatal weakness. Difficulty in chewing is associated with weakness of jaw closure due to masseter and temporalis muscle weakness. This is tested by attempting to separate the clamped jaws by applying downward pressure on the chin for a period of 30 s. Even with relatively severe weakness of the masseter muscles, weakness of jaw opening due to pterygoid muscle weakness is rarely seen in myasthenic gravis.

A patient with weak respiratory muscles may look anxious and have tachypnea associated with shallow breathing. Inspiratory muscle strength can be assessed by asking the patient to inspire forcefully and loudly through the nose (inspiratory sniff). Expiratory muscle function can be assessed by asking the patient to cough or clear his throat. If the diaphragm is weak, the abdominal contents will be pushed upward and there will be no outward protrusion of the abdomen against the examiner's hand. Patients with weak respiratory muscles often have an associated weakness of neck flexion or extension.

Weakness may be limited to the neck flexors when the disease is mild, typically with weaker neck flexion than extension. Isolated neck extensor weakness may be the presenting sign in MuSK-antibody positive myasthenia gravis. In the upper limbs, finger and wrist extensors are most likely to be affected, whereas the foot dorsiflexors and hip flexors are most frequently involved in the lower limbs. Fatigable muscle weakness may be demonstrated by asking the patient to sustain abduction of the arms for 2 min. This results in either the patient becoming unable to hold the arms up, or weakness becomes apparent with subsequent manual testing. The lower limbs can be similarly tested by sustained elevation of leg for 90 s while lying supine. Repeated arising from a low chair (up to 20 times), without using the arms, is capable of testing hip extensor muscle fatigue.

Diagnosis

Autoimmune myasthenia gravis is confirmed by pharmacologic, electrophysiologic, and immunologic tests.

Bedside testing using edrophonium chloride (Tensilon) has a sensitivity of 60–95% in patients with significant ptosis or ophthalmoparesis (*Fig. 373.1c, d*). Nevertheless, the results are subjective and require a carefully performed and judiciously interpreted examination. The protocol for the test is similar to that described previously for congenital myasthenic syndrome. Application of an ice pack locally to a ptotic eyelid may improve ptosis. This adjunctive diagnostic test has a sensitivity of 89% and is particularly helpful if the edrophonium test is contraindicated or not available.

Neurophysiologic tests consist of RNS of a selected peripheral nerve (typically at a frequency of 2–5 Hz) while recording the compound motor action potential (CMAP) produced by the resulting recurrent contractions of selected muscle innervated by that nerve. Characteristically in myasthenia gravis, a decremental response of at least 10% occurs, similar to that observed in CMS (see Fig. 368.1b of Chap. 368, "Approach to Diagnosis and Treatment of a Child with Motor Unit Diseases"). RNS is more likely to be abnormal in clinically weak muscles. The diagnostic sensitivity of RNS ranges between 53% and 100% in generalized form, and 10–17% in ocular myasthenia gravis.

Single fiber EMG is performed when RNS is normal, despite high suspicion of NMJ disorder, as has been previously detailed in the investigations for congenital myasthenic syndromes. It has a sensitivity of 95% or greater in generalized and 90% or greater in ocular myasthenia gravis, when appropriate muscles are tested.

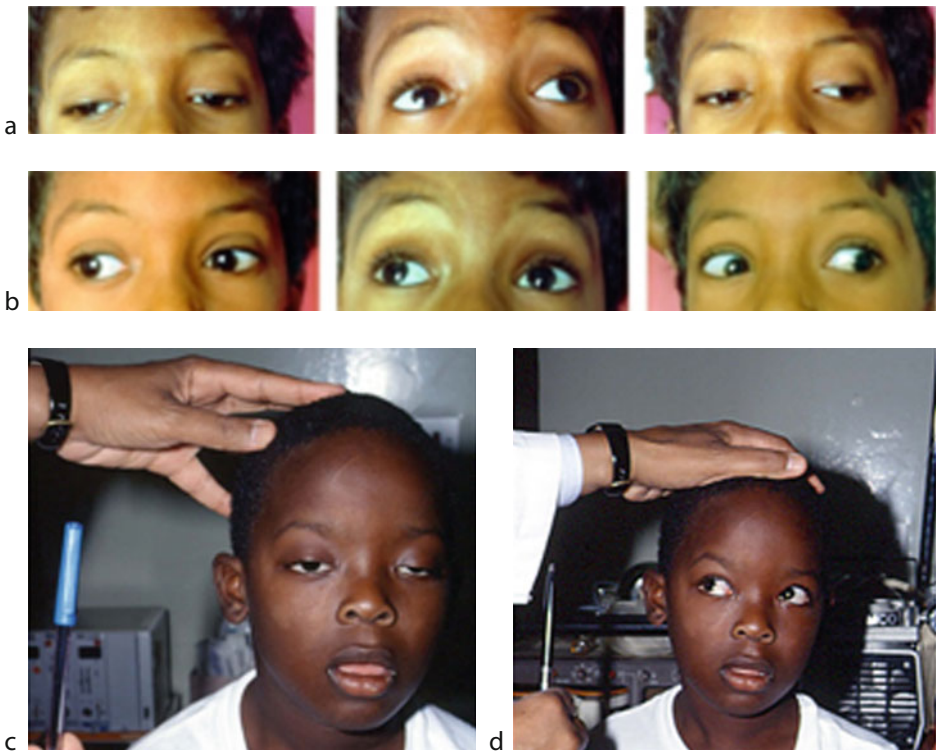

Figure 373.1
Neostigmine test in a child with congenital myasthenic syndrome. (a) There is bilateral ptosis and partial ophthalmoparesis on attempted looking to the right, upwards and to the left. (b) Dissapearance of ptosis and remarkable improvement in ocular motility following neostigmine administration. (c) Bilateral ptosis and ophthalmoparesis in myasthenia gravis. The patient was asked to look at the pen to his right side. Note also the remarkable facial weakness and open mouth. (d) Positive edrophonium chloride (Tensilon) test. Part of the rescuscitation equipment appears behind the patient

Nevertheless, the specificity of this technique is limited since abnormal results can be obtained in a variety of neuromuscular diseases.

Immunologic tests include assay of antibodies that react with AChR proteins. The AChR-binding antibody assay is the most widely used diagnostic test for myasthenia gravis. Anti-AChR-antibodies are detected in 80–85% of patients with generalized myasthenia gravis but only in 55% with purely ocular symptoms. Serum concentration of AChR-binding antibodies cannot reliably predict the severity of disease in individual patients, but tends to decline in successfully treated patients.

Approximately 40% of patients with anti-AChR-antibody negative (seronegative) generalized myasthenia gravis have anti-MuSK antibodies. They may represent a distinct group of autoimmune myasthenia gravis with some characteristics, as a group, that differentiates them from AChR-positive patients.

Since myasthenia gravis often coexists with autoimmune disorders, particularly thyroid disease, testing of thyroid function and antibodies should be arranged. Other autoimmune serologic tests should be considered if clinically indicated.

Differential Diagnosis

The differential diagnosis of myasthenia gravis includes other neuromuscular disorders in which fatigability can sometimes be marked. Seronegative myasthenia gravis may be difficult to differentiate from CMS. Nevertheless, the onset of CMS is in infancy or early childhood and on NCSs, repetitive CMAP can be detected in certain forms (see above). Botulism is characterized by ptosis and ophthalmoplegia, but there is a rapid descending pattern of disease progression associated with pupillary and

autonomic involvement. NCSs reveal low-amplitude CMAP. Mitochondrial disorders are characterized by more gradual onset with no fluctuation of symptoms. There is often no diplopia despite severe ophthalmoplegia. RNS does not show decremental response, as in myasthenia gravis, but single fiber EMG may be mildly abnormal. Structural lesions of the midbrain such as tumors may present with fatigable ptosis and ophthalmoplegia, but careful neurological examination reveals additional defects. MRI brain demonstrates the brainstem lesion.

Treatment

The aims of treatment are to improve neuromuscular transmission, through the use of AChE inhibitors, and to prevent continuing immunological interference with synthesis, maintenance, and catabolism of AChRs by immunomodulating therapy, plasma exchange (plasmapheresis), or thymectomy.

The AChE inhibitor pyridostigmine may be initiated at a dose of 0.5–1.0 mg/kg every 4–6 h with a maximum dose of 7 mg/kg/day. The short-acting AChE inhibitor neostigmine (Pyridostigmine) should be used only if pyridostigmine is unavailable. Details of the use of these medications and their side effects have been mentioned earlier.

Corticosteroids were the first immune-directed therapy for myasthenia gravis and they are the most commonly used therapy today. Their dramatic efficacy since their use in the early 1970s resulted in widespread adoption before placebo-controlled studies could be initiated. Nevertheless, most experts consider corticosteroids a mainstay of therapy for myasthenia gravis. They are indicated when generalized or ocular symptoms of myasthenia gravis are not adequately controlled by AChE inhibitors alone. Long-term treatment with corticosteroids may induce complete remission or cause marked to moderate improvement in most patients.

No single regimen is internationally accepted for corticosteroid treatment of myasthenia gravis. Some use high doses initially to achieve quicker response; others start with low dose and increase gradually. In the high-dose regimen (used in many centers including the author's), prednisone is given in a dose of 1–2 mg/kg/day over several (usually 2–3) months until a positive response is obtained. The patients are then switched to an alternate-day regimen until a good response is sustained, followed by progressive tapering. Transient exacerbation of myasthenic symptoms is not rare at the beginning of high-dose steroid therapy. It has been reported to occur in approximately one-third to one-half of patients, with the severity of weakness requiring intubation in about 9%. Hence, it is advisable that the patients be hospitalized for 5–7 days during initiation of the high-dose daily prednisone, especially when there is significant oropharyngeal or respiratory symptoms. Following admission, the patients also receive intravenous immunoglobulin (IVIG) as a short-term immune-directed therapy, known to prevent steroid-induced exacerbation. In ocular or mild generalized myasthenia gravis, a lower initial dose of prednisone (30–40 mg/day) may be as effective in producing marked improvement or remission. Other centers prefer to use gradually intermittent doses of prednisone on an alternate-day therapy regime until an effect is obtained, then maintaining the effective dose for 3 months before tapering. High-dose pulses of methylprednisolone have been used successfully in children with refractory disease.

The second most commonly used immunosuppresive medication in myasthenia is azathioprine (Imuran), either in conjunction with steroids or in isolation. Patients receiving azathioprine had fewer relapses and a higher incidence of remission. They could also be maintained on a lower prednisolone dose, but these beneficial effects were not seen for 18 months. Hepatotoxicity and leukopenia are important adverse effects but are reversible if the dose of azathioprine is adjusted or discontinued. Cyclosporine has been used mainly as a steroid-sparing agent in patients in whom azathioprine is either ineffective or not tolerated. The most significant side effects are hypertension and nephrotoxicity. The risk of certain malignancies (melanoma, lymphoma) may be increased with long-term use.

Plasma exchange (plasmapheresis) is another modality of short-term immune-directed therapy that is used during myasthenic crises or in patients who have experienced sudden worsening of myasthenia gravis. It is also used in combination with high-dose daily prednisone to prevent steroid-induced exacerbation. A third indication is prior to surgery, especially thymectomy, to achieve rapid postoperative recovery and to shorten the period of assisted ventilation. Plasma exchange reduces the levels of circulating antibodies, and produces improvement within days but this usually begins to wear off after 3–4 weeks. Its availability is restricted to major medical centers and the frequent need for large-bore venous catheter makes it difficult to perform in young children. It can also reduce coagulation factors, particularly with repeated daily treatments, leading to bleeding tendencies.

IVIG was found in randomized controlled trials to have comparable efficacy in treatment response compared to plasma exchange. Its indications are similar to those of

plasma exchange, namely, to induce rapid improvement in patients with severe disease or crises, prior to surgery (thymectomy) for the reduction of perioperative morbidity, and as chronic therapy in selected refractory cases. It is also used during initiation of a high-dose daily prednisone regimen of therapy to prevent steroid-induced exacerbation. Weakness usually improves within 7–10 days and lasts for 4–8 weeks. The dose of IVIG is 2 g/kg in the initial course, divided over 2–5 days depending on patient age, ability to tolerate the volume load and renal function. Maintenance doses for selected refractory patients range from 0.5 to 1 g/kg usually on a monthly basis. The side effects of IVIG have been detailed in the subchapter ◉ Guillain–Barre Syndrome.

Thymectomy has been proposed as first-time therapy in most patients with generalized myasthenia gravis, and is definitely indicated in the presence of thymoma, which is observed in approximately 10–20% of adult patients (mean age of 50 years). The mechanism through which thymectomy works in nonthymomatous myasthenia gravis remains controversial. Nevertheless, it frequently results in significant and lasting improvement in children, although long-term immunosuppressive therapy remains necessary in many cases. In juvenile onset myasthenia gravis (onset 12–18 years), the remission rate increased significantly: up to 60% of those who had thymectomy compared to 29% in a group of nonoperated patients. In a collaborative study involving patients followed by the author, 30 children with myasthenia gravis (aged 4–16 years) had thymectomy. These had mild, moderate, or severe generalized weakness. Complete remission was noted in 43% and improvement in about 47%. Remission rate was 33% at 3 years and about 47% at 5 years of follow-up. Although controversy exists regarding the preferred surgical approach, transcervical–transternal "maximal" thymectomy is adopted in many centers to assure complete resection of all thymic and ectopic thymic tissues. In the above-mentioned study, the presence of ectopic thymic tissue was a significantly poor prognostic factor for outcome of surgery. Thymectomy may be the treatment of choice for children because of the possible side effects of prolonged treatment with AChE inhibitors or immunosuppressants. Even in the absence of complete remission, most patients benefit from thymectomy by way of improvement of their symptoms or reduction of their medications, especially steroids. Thymectomy has been performed with reported favorable results even in patients less than 5 years, including some followed by the author. Currently, there is an ongoing international, prospective, single-blinded, randomized trial of thymectomy (controlling for medical therapy) in nonthymomatous myasthenia gravis.

In ocular myasthenia gravis, AChE inhibitors may control symptoms adequately in some patients, but the benefit is often partial and not maintained and prednisone is often quite effective. Thymectomy is not considered in purely ocular myasthenia gravis.

Myasthenia gravis with anti-MuSK antibodies often manifest with prominent axial, bulbar, and respiratory muscle weakness, and up to 70% of patients were reported to have poor response to AChE inhibitors. In small series, a dramatic response to azathioprine and IVIG has been reported. Effective therapies (other than plasma exchange) included prednisone, cyclosporine, mycophenolate mofetil, and rituximab. Thymectomy is questionable in patients with anti-MuSK antibodies because their thymic tissue lacks the hyperplastic changes seen in patients with anti-AChR-antibodies.

Prognosis

Recent advances in intensive care and immunotherapy have contributed to significantly favorable outcome for myasthenia gravis in most patients. Untreated myasthenia gravis carries a mortality rate of 25–31% and with recent treatment the mortality rate has declined to about 4%. The natural course of juvenile myasthenia gravis is variable and is generally slowly progressive with marked fluctuations. The disease may remain limited to the extraocular muscles in 20–40%. Myasthenic crises, occurring spontaneously or following febrile illnesses, may require assisted ventilation and are potentially fatal. Spontaneous remissions were reported in 30% of children with myasthenia gravis after a 15 year follow-up. Nevertheless, remission rate was significantly lower in patients with extremity weakness.

Prevention

Numerous medications have been reported to worsen preexisting myasthenia gravis and induce myasthenia in previously asymptomatic patients. Drugs that are absolutely contraindicated include curare and related drugs, D-penicillamine, interferon alpha, and botulinum toxin. Caution should also be taken when using certain drugs that may exacerbate weakness in some patients with myasthenia gravis. These include beta-blockers, calcium channel blockers, iodinated contrast agents, lithium, and statin drugs. Other contraindicated drugs known to affect neuromuscular transmission have been detailed in ◉ *Table 373.2*.

Fetal and Transient Neonatal Myasthenia Gravis

In myasthenic mothers, a variety of AChR and other antibodies are transferred to the fetal circulation through the placenta, beginning at 20 weeks of gestation, and are present in the amniotic fluid. The sequelae of these maternal pathogenic autoantibodies may manifest in utero, producing reduced fetal movements, polyhydramnios, arthrogryposis, and stillbirth. Approximately 10–20% of infants born to myasthenic mothers are affected by transient neonatal myasthenia gravis, which may occur in both anti-AChR-positive and anti-AChR-negative mothers.

The onset of symptoms is usually delayed to a few hours after birth and may be up to 3 days. Affected babies show the classical features of the floppy infant syndrome with hypotonia and weakness. They have poor crying, feeding difficulties due to poor sucking and/or swallowing, and facial diplegia. Ptosis is present in only a minority of cases. Some infants may have respiratory distress requiring mechanical ventilation.

The diagnosis is easy, if the mother is known to have myasthenia gravis, and may be difficult if the mother had latent disease, as has been observed in some cases. Confirmation is by intramuscular or subcutaneous injection of neostigmine. NCSs can also be done to look for decremental response. Nevertheless, it is painful and technically difficult to perform at this age.

Treatment is supportive including nasogastric tube feeding and ventilatory support, if needed. Exchange transfusion may be indicated in severe cases with respiratory distress and/or profound hypotonia. Pyridostigmine (0.5–1.0 mg/kg) administered in divided doses 30 min prior to feeding may be useful. Alternatively, neostigmine in a dose of 0.1 mg prior to feeding (adjusting the dose according to need) is often sufficient to permit adequate nutrition. Affected neonates need to be monitored for respiratory failure for 1–2 weeks after birth. Marked hypotonia and weakness may persist beyond the first 3 or 4 weeks in some atypical cases.

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374 Hereditary and Acquired Myopathies

Mustafa A. M. Salih

Congenital Myopathies

Definition/Classification

The congenital myopathies (CM) are a heterogeneous group of inherited neuromuscular disorders characterized by distinctive and specific morphologic abnormalities in skeletal muscle on light and/or electron microscopy as the main pathological feature. Their onset is typically at birth or in the first years of life with delayed milestones. Within each subgroup, there is wide variation in clinical severity, including onset in childhood or in adulthood. Based on genetic and morphological features, they are divided into 4 main groups and 11 subgroups (*Table 374.1*).

Epidemiology

The exact incidence of CM is unknown because many cases are either not recognized or muscle biopsy is not performed. The incidence of all CM is estimated to be about 0.06/1,000 or one-tenth of all cases of neuromuscular disorders. Studies from western Sweden and Ireland suggest a prevalence of 3.5–5.0/100,000 in the pediatric population.

Pathogenesis

Mutations in genes that encode for muscle proteins have been identified in the various forms of CM (*Table 374.1*). The specific morphological features of muscle biopsy samples may have resulted from loss or dysfunction of these proteins. Some CM are genetically heterogeneous, others exhibit phenotypic homogeneity. Mutations in at least six genes cause nemaline myopathy. Several others cause core pathology and congenital fiber type disproportion. But, mutations in β-tropomyosin can cause nemaline myopathy and cap disease; and mutations in selenoprotein N1 can manifest as multiminicore disease and congenital fiber type disproportion, as well as dystrophic pathology.

Pathology

In CM, muscle pathology is the mainstay of diagnosis, provides insight into pathogenic mechanisms of each subtype, and also guides molecular testing.

Muscle enzyme histochemistry reveals rods, which are the pathological hallmark of nemaline rod myopathy. These are only visible on modified Gomori trichrome (GT) stain as dark purple/red structures (*Fig. 374.1a*).

They are usually subsarcolemmal but may be intranuclear. Electron microscopy shows that the rods (which are derived from the Z-line) are often in continuity with it. Hyaline bodies, which characterize myosin storage myopathy, are subsarcolemmal areas, which are devoid of sarcomeres. They stain pink on hematoxylin and eosin (H&E) and pale green on modified GT staining. Reducing body myopathy is characterized by the presence of round or polymorphic inclusions that stain pink with H&E and purple with modified GT. Central core disease (CCD) is characterized by the presence of clear central areas devoid of oxidative enzyme activity and remarkable type 1 fiber predominance (*Fig. 374.1b*). Electron microscopy shows that the cores are devoid of normal muscle fibrils and of mitochondria and reveals disorganization of myofilaments. On the other hand, multiminicore disease is characterized by the presence of multiple areas of sarcomeric disorganization associated with diminished oxidative activity (*Fig. 374.1c*). They differ in their morphology from central core by the presence of multiple small lesions within one muscle fiber and by never extending the length of the muscle fiber. Other features may include type 1 fiber predominance and increased internal nuclei.

Salih myopathy is characterized by the presence of minicore-like lesions, abundant centrally located nuclei, and remarkable type 1 fiber predominance in muscle biopsies obtained in early childhood (*Fig. 374.1d*). Dystrophic lesions of variable severity are seen in muscle specimens taken in the second decade.

Most fibers in myotubular myopathies are small and round, resembling fetal myotubes, which normally have central nuclei. These central nuclei are large, and there is also predominance of type 1 fibers. Small type 1 muscle fibers (at least 12% smaller in diameter than type 2 fibers)

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Table 374.1
Genetic and morphological classification of congenital myopathies

	Gene	Inheritance	Protein
Myopathies with protein accumulation			
Nemaline myopathy	*ACTA1*	AD or AR	Skeletal ∝-actin
	NEB	AR	Nebulin
	TPM3	AD	∝-tropomyosin
	TPM2	AD	β-tropomyosin
	TNNT1	AR	Troponin T
	CFL2	AD	Cofilin – 2
Myosin storage myopathy (hyaline body myopathy)	*MYHZ*	AD	Slow/β-cardiac myosin heavy chain
Cap disease	*TPM2*	AD	β-tropomyosin
Reducing body myopathy	*FHL1*	XLD/R	Four and a half lim domain-1 protein
Myopathies with cores			
Central core disease	*RYR1*	AD or AR	Ryanodine receptor
Core-rod myopathy	*RYR1*	AD	Ryanodine receptor
Multiminicore disease	*SEPN1*	AR	Selenoprotein N1
	RYR1	AD, AR	Ryanodine receptor
Salih myoapthy (congenital myopathy and fatal cardiomyopathy)	*TTN*	AR	Titin
Myopathies with central nuclei			
Myotubular myopathy	*MTM1*	XLR	Myotubularin
Centronuclear myopathy	*DNM2*	AD	Dynamin 2
	B1N1	AR	Amphiphysin
	RYR1	AD	Ryanodine receptor
Myopathies with fiber-size variation			
Congenital fiber type disproportion	*ACTA1*	AD	Skeletal ∝-actin
	SEPN1	AR	Selenoprotein N1
	TPM3	AD	∝-tropomyosin

AD autosomal dominant, *AR* autosomal recessive, *R* recessive, *XLD* X-linked dominant, *XLR* X-linked recessive

characterize congenital fiber type disproportion. Type 1 fiber predominance and reduced or absent type 2B fibers are common features.

Clinical Manifestations

Nemaline myopathy is classified on the basis of age at onset and severity, and distribution of muscle weakness. The mild or typical congenital form of nemaline myopathy is probably the most common. Onset is within the first year with hypotonia, feeding difficulty, and generalized limb weakness. Patients usually have elongated, myopathic, expressions face, tent-shaped mouth, high-arched palate, and retrognathia due to abnormal muscle stresses on the developing mandible (*Fig. 374.1e*). Progression of the disease is either very slow or static, and patients can lead an independent life if stabilized. The severe congenital form (and probably most uncommon) can start in utero, leading to fetal akinesia sequence and polyhydramnios.

Affected babies may die in utero or are born with severe respiratory failure, no antigravity limb movement, and generalized arthrogryposis. Bulbar weakness causes poor feeding and recurrent aspiration, and early mortality is common. The intermediate congenital form presents in early childhood with weakness and delayed milestones followed by contractures. The childhood-onset form manifests with distal leg weakness in the late first or early second decade, with later involvement of the proximal muscles. The adult-onset form presents between 20 and 50 years of age.

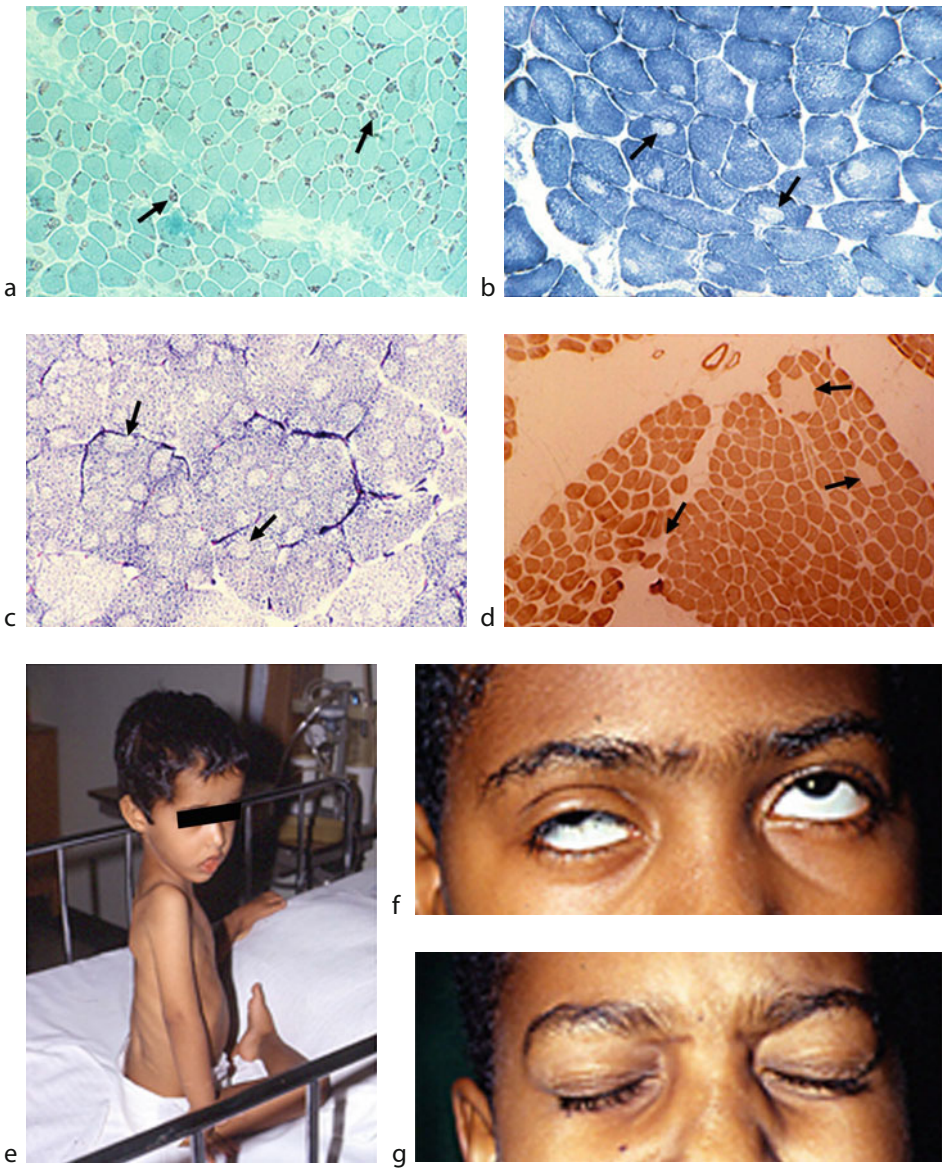

Figure 374.1

Muscle biopsy specimens in congenital myopathies showing (a) nemaline rods (arrows) typical of nemaline myopathy, (b) central cores characteristic of central core disease (arrows), (c) minicores (arrows) in multiminicore disease and (d) type I fibre predominance (dark brown fibres) over type II fibres (pale fibres, arrows) in Salih myopathy. (e) Nemaline myopathy. Note the micrognathia, elongated face, thin slender muscles and hypotonic posture of the lower limbs. (f) Asymmetric ptosis in a patient with Salih myopathy, and (g) bilateral facial weakness of his elder brother revealed by inability to bury the eyelashes on attempted tight closure of the eyes

Older children with nemaline myopathy are usually slender. All skeletal muscles, including the diaphragm, can be affected. Nevertheless, the proximal limb muscles are most severely affected and manifest as a wadding gait in ambulant patients. In congenital nemaline myopathy, respiratory involvement is virtually universal. It is also frequent in patients with onset later in life. Chest deformity may be observed at birth or develop later with age. Cor pulmonale, secondary to the associated respiratory complications, is the most common cardiac complication

of nemaline myopathy. Hypertrophic and dilated cardiomyopathy may also occur. The development of distal and large-joint contractures is common with increasing age, although joint hypermobility may be seen in hypotonic infants and children. Scoliosis is also common with advancing age, and the rigid spine syndrome is occasionally seen. Cognition and central nervous system functions are usually normal in nemaline myopathy. However, the autosomal recessive variant due to mutation in the gene for troponin T, described only in the Old Order Amish, is characterized by jaw and limb tremors starting in the first few months of life and resolving over a few months.

The onset of *myosin storage myopathy* (*hyaline body myopathy*) is in infancy or childhood with variable penetrance. Some patients may even be asymptomatic in the fifth decade of life. The distribution of muscle weakness can be proximal, distal and proximal, or scapuloperoneal, with very slow or minimal progression in the majority of cases. Cardiac arrhythmias may be present in some cases.

The childhood-onset phenotype of the X-linked recessive or dominant *reducing body myopathy* presents in boys with weakness before age 10 years. Ambulation was lost in a boy (who had FHL1 mutation) as a teenager, and another had cardiomyopathy and was ventilator dependent in the second decade. Onset was before the age of 4 years in two girls who presented with severe weakness with rapid progression and death, following respiratory failure, before 10 years of age.

Cap disease, due to mutation in the gene for β-tropomyosin, has congenital or childhood onset with hypotonia associated with facial and slowly progressive proximal muscle weakness. Patients have long narrow face, develop scoliosis, and may die of the disease in teenaged years due to respiratory failure.

Central core disease, due to autosomal recessively inherited mutation in the ryanodine receptor, is typically associated with history of decreased fetal movement or breech presentation. Onset is at birth or in early childhood with hypotonia, nonprogressive limb weakness, and facial weakness. Affected children most commonly present with orthopedic abnormalities including congenital hip dislocation, kyposcoliosis, and foot deformities. Ligamentous laxity may be pronounced in older children. Patients usually have slim habitus due to a general decrease in muscle bulk. Deep tendon reflexes may be normal, decreased, or absent on rare occasions.

Other presentations in autosomal recessive (and autosomal dominant) central core disease include onset in infancy with generalized weakness, external ophthalmoplegia, and bulbar and respiratory weakness. Children with recessive central core disease may present with fetal akinesia, arthrogryposis, and respiratory failure in the neonatal period requiring ventilatory support. The disease may start in adolescence as a slowly progressive limb-girdle syndrome or remain asymptomatic. Such asymptomatic individuals may present with high creatine kinase (CK) level or malignant hyperthermia. Susceptibility to malignant hyperthermia is found in about 25% of patients with central core disease, and extreme care should be taken when surgery is contemplated for such patients and for patients who are relatives of known cases. Slight improvement in functional abilities and muscle strength with age is common. Cardiomyopathy is not a feature of central core disease although conduction defects have been reported in some patients.

More recent studies found that the histopathological spectrum of central core is much wider. An autosomal dominant congenital myopathy with core and rods (*core-rod myopathy*) was found to be caused by mutation in the same gene (RYR1), which is associated with typical central core disease and encodes the skeletal muscle ryanodine receptor.

Multiminicore disease is a clinically heterogenous disorder, and four major phenotypes are now recognized. The classic and most common phenotype is often due to a mutation in the gene for selenoprotein N1. It presents in the neonatal period or first year of life and is characterized by hypotonia, and proximal and axial muscle weakness, which is either nonprogressive or only minimally progressive. A history of reduced fetal movements can be elicited in about a third of cases, and antenatal polyhydramnios may be noted. Congenital abnormalities such as cleft palate, dislocated hips, and arthrogryposis are seen in some patients. There is usually absent head control in infancy because of the characteristic weakness in head flexors associated with delayed motor development. Affected children are often slim due to decreased muscle bulk, and failure-to-thrive is common in children with significant weakness. Intelligence is normal. Facial and bulbar weakness is common, but extraocular muscles are spared.

There is mild-to-moderate weakness of the proximal limb muscles and affected children often show Gowers sign when rising from the floor. Distal muscles are either normal or mildly affected. The limb weakness may be static, slowly progressive, or may appear to improve with age. Nevertheless, weakness of the axial muscles is progressive and often leads to torticollis, chest deformities, rigid spine, and scoliosis. Most patients are ambulatory in adulthood, even in the presence of significant respiratory compromise resulting from axial muscle weakness. Minor, generally nonproblematic, joint contractures may develop in the elbows, knees, and hips. Cardiac involvement is

usually in the form of cor pulmonale secondary to respiratory insufficiency, which may affect about two-thirds of patients in late adolescence or early adulthood.

A second form of multiminicore disease, similar to the classic phenotype and characterized by external ophthalmoplegia, accounts for fewer than 10% of cases and is most often due to a mutation in the gene for the ryanodine receptor.

A third phenotype is characterized by predominant hip girdle weakness with relative sparing of respiratory and bulbar muscles similar to central core disease. It is also due to a mutation in the ryanodine receptor. Other features include joint laxity, hip dislocation, and arthrogryposis.

A fourth and rare phenotype presents in the neonatal period with arthrogryposis multiplex congenita, as a consequence of fetal hypokinesia. Other features include high-arched palate, low-set ears, short neck, clinodactyly, proximal muscle weakness, and respiratory insufficiency. Scoliosis or kyphosis is severe.

Salih myopathy (*Congenital myopathy* and *fatal cardiomyopathy*) is a recently identified congenital myopathy, in patients from Sudan and others of Moroccan ancestry, due to autosomal recessive mutation in the gene encoding for titin (*TTN*). Titin is the largest protein known and spans half of the sarcomere in muscle. The disease manifests as neonatal hypotonia in some patients, and delayed motor development in all of them. Autonomous walking is attained at ages ranging between 20 months and 4 years. Patients later develop symmetric, generalized muscle weakness predominantly affecting proximal limb muscles. Other features include high-arched palate, mild facial muscle weakness, asymmetric ptosis, distal joint laxity, and relative calf muscle hypertrophy (◉ *Fig. 374.1f* and *g*). Progressive dilated cardiomyopathy, with rhythm disturbances, develops between ages 5 and 13 years. Death occurs in all patients before 20 years of age, but the majority survive into their teenage years.

The onset of the X-linked *myotubular myopathy* is prenatal with decreased fetal movements, polyhydramnios, and premature birth. The affected male newborns present with severe weakness and hypotonia, feeding difficulty, and respiratory distress. Many fail to establish spontaneous respiration and lack antigravity movements. Bilateral ptosis, facial weakness, and ophthalmoplegia are common. Tendon reflexes are mostly absent. Other features of the disease include elongated birth length, low birth weight and large head, long face, micrognathia, slender long digits, cryptorchidism, pectus carinatum, and knee and hip contractures. The disease usually follows a fatal course with approximately one-third of patients dying in the first year of life. About 75% of those surviving beyond the first year require ventilatory support, have nonprogressive weakness, and can live into adulthood.

Female carriers are mostly asymptomatic; but may have mild facial and limb weakness evolving into gait difficulty and kyphoscoliosis. Weakness in infancy, feeding difficulties, and skeletal deformities are seen in carriers with skewed X-inactivation.

Most patients with the autosomal dominantly inherited *centronuclear myopathy* due to mutations in dynamin 2 (*DNM2*) have mild phenotype with onset in adolescence or adulthood. Clinical features of the disease include ptosis, facial weakness, axial and distal more than proximal weakness, and contracture deformities. A severe phenotype of centronuclear myopathy due to dynamin 2 mutations has recently been described. Onset is at birth with hypotonia and feeding difficulty. Other features include ptosis, ophthalmoplegia, high-arched palate, joint hyperlaxity, and contractures. Milestones are delayed, although ambulation is usually attained, and weakness is distal more than proximal.

The first causative gene for autosomal recessive *centronuclear myopathy* has recently been identified as amphiphysin 2 (*bridging integrator; BIN1*). The disease may manifest with reduced fetal movements and oligohydramnios, and usually presents at birth. Clinical features include ptosis, ophthalmoplegia, facial weakness, hypotonia, proximal weakness, contractures and dilated cardiomyopathy. Onset of the disease was delayed to 8 years of age in one patient. The course is slowly progressive, and more than half survive childhood.

Centronuclear myopathy caused by dominant mutation in the ryanodine receptor (*RYR1*) gene has been reported in one case in 2007. The clinical features included generalized weakness, extraocular involvement, and moderate bulbar and respiratory impairment similar to the multiminicore disease due to recessive mutations in the *RYR1* gene.

The clinical features of *congenital fiber type disproportion* vary according to the underlying mutated gene. Onset is usually before 1 year of age with mutations in the gene encoding ∝-tropomyosin (*TPM3*), but may be delayed to young adulthood. The disease manifests with hypotonia and delayed motor development, but ambulation is achieved later. Other clinical features include thin body habitus, ptosis, and facial, axial, proximal limb and ankle dorsiflexor muscle weakness, and scapular winging. Respiratory insufficiency develops in most patients, and about half of them need nocturnal noninvasive ventilation between ages 3 and 55 years.

The presentation of the phenotype caused by autosomal recessive mutations in the gene for selenoprotein

N1 is during the first year of life with hypotonia and poor head control. Other features of the disease include neck and axial muscle weakness, scoliosis, which may require spinal fusion surgery, osteoporosis and fractures, wheelchair dependency in adulthood, and respiratory insufficiency requiring nocturnal ventilation in the third decade of life.

The phenotype due to mutations in the gene for skeletal muscle α-actin (*ACTA1*) presents at birth with severe weakness, respiratory insufficiency often requiring invasive ventilation, and feeding difficulties. There is also weakness of the facial, proximal and truncal muscles. Death is usually before 4 years of age following progressive respiratory failure.

Diagnosis

The diagnosis of congenital myopathy depends on the typical histopathological findings on muscle biopsy in combination with suggestive clinical features (see section "Pathology" above).

Pathological examination of muscle should be done in experienced hands, and ultrastructural examination is often necessary since several pathologic features are based on the electron microscopic appearance of muscle. Selective muscle involvement on magnetic resonance imaging (MRI) may complement clinical assessment and guide genetic testing in cases with equivocal features.

In all of the congenital myopathies, serum creatine kinase (CK) is either normal or mildly elevated. Moderately elevated CK is seen in some cases of central core disease (CCD) and in others who are asymptomatic carriers of the ryanodine receptor mutation in CCD.

Nerve conduction studies are normal, and electromyography (EMG) either reveals normal results or shows the typical low amplitude, short-duration motor unit potentials that are seen in myopathies. Fibrillations and positive sharp waves (which characterize anterior horn cell disease like spinal muscular atrophy) are rare.

Electrocardiography (ECG) is important since cardiac disease may be prominent in nemaline myopathy or, sometimes, in other congenital myopathies. Dilated cardiomyopathy is a cardinal feature of Salih myopathy. In cases with abnormal ECG and in Salih myopathy, serial echocardiographic evaluations should be arranged.

Differential Diagnosis

The differential diagnosis varies depending on the age of onset and the symptoms of the patient at the time of diagnosis. In children presenting at birth or within the first 2 years of life, the differential diagnosis includes diseases manifesting as floppy infant syndrome (see section on "Floppy Infant Syndrome"). When infantile hypotonia is associated with ptosis, extraocular muscle and/or facial weakness, infantile myotonic dystrophy, congenital myasthenic syndrome, and mitochondrial cytopathies become important categories to exclude. For patients presenting for diagnosis at a later age, muscular dystrophy, metabolic myopathy, myotonic dystrophy, and type III spinal muscular atrophy take a higher position in the list of differential diagnoses.

Since clinical overlap of symptoms and signs is common in patients with congenital myopathies, the definitive diagnosis is usually reached only by means of muscle biopsy with histochemistry and electron microscopy. Histological changes suggestive of one form of congenital myopathy can be found in a different entity of congenital myopathy or another disease. Rods, which characterize nemaline myopathies, can be seen in many other diseases including inflammatory myopathies, muscular dystrophies, and mitochondrial myopathies. Multiminicores may also be present as a nonspecific feature in mitochondrial diseases, central nervous (CNS) disorders, and denervation. Muscle fibers with central nuclei can be seen in regenerating muscle fibers, in denervation, and in any chronic myopathy. Fiber type disproportion occurs as a secondary phenomenon in a wide range of skeletal and neuromuscular disorders.

Treatment

No specific treatment is currently available for any of the congenital myopathies. In the severe forms, which manifest at birth, survival depends on the degree of respiratory intervention, and the decision regarding the duration of respiratory support that should be made on an individual basis rather than on diagnosis alone. In congenital myopathies, respiratory failure can occur at any age but may be independent of the degree of limb weakness. Close monitoring of the respiratory function is needed with baseline pulmonary function tests (PFTs) that are repeated in at least yearly intervals. Early treatment of respiratory infections, manually assisted cough, and chest physiotherapy should be adopted. Noninvasive ventilation and tracheostomy combined with ventilation may be required during the course of the disease.

Maximal functional ability and ambulation should be maintained by preventing the development of contractures through exercises, bracing, passive stretching, and

surgical release procedures. The management of scoliosis requires either bracing or surgical correction.

Special caution should be taken to avoid the development of malignant hyperthermia following the use of muscle relaxants as succinylcholine and volatile anesthetics in patients with congenital myopathies. Malignant hyperthermia is known to occur in patients with central core disease and has been reported in patients with minicore disease and centronuclear myopathy. Hence, anesthetics should be given with caution and formal testing for a predisposition to malignant hyperthermia should be considered prior to elective anesthesia, especially in children with central core disease. Restricting calories by a diet tailored to caloric needs of the child is needed for children with restricted mobility.

An open-label pilot trail of salbutamol (a beta-2 against) therapy in children with central core and minicore disease reported a small but significant improvement in strength measured by myometry and Medical Research Council Scores, and in the vital capacity relative to baseline.

Prognosis

The prognosis generally depends on the form of CM, the mode of inheritance, and the underlying gene defect. Severe disease often results in death in the neonatal period. A disease with moderate severity can result in lifelong disability, whereas cases who are milder from the outset may achieve reasonable quality of life with minor disability. Mortality from CM is usually related to pulmonary insufficiency, which may be of insidious onset. It is more common or more severe in X-linked and autosomal myotubular/centronuclear myopathy, nemaline myopathy, multiminicore disease, and reducing body myopathy.

Prevention

Definitive prenatal and preimplantation genetic diagnoses are possible if the disease-causing mutation is known. Genetic counseling is particularly important in families with central core disease to help avoiding malignant hyperthermia in asymptomatic relatives.

Muscular Dystrophies

Definition/Classification

Muscular dystrophies (MDs) are a heterogeneous group of genetically determined, progressive primary myopathies. The term *dystrophy* means abnormal growth, and is derived from the Greek *trophe* meaning "nourishment." By adopting this definition, nonhereditary myopathies such as dermatomyositis are excluded. The definition also excludes nonprogressive myopathies such as the congenital myopathies, and diseases where muscle atrophy is secondary to neurogenic disorders such as spinal muscular atrophy.

Before the era of molecular genetics, MDs were classified clinically according to the pattern of inheritance, age at onset, rate of disease progress, and the distribution of selective muscle weakness and wasting (i.e., proximal versus distal). Although this clinical classification is still useful, delineation of the pathogenesis of MDs through molecular biology had its impact in the nomenclature and grouping of the various types. It became evident that some categories of dystrophies, such as limb-girdle muscular dystrophy, constitute syndromes, which include several distinct myopathies.

Epidemiology

In a world survey of inherited neuromuscular diseases by Emery, the overall prevalence of muscular dystrophy (MD) was estimated to be 286 per million population. However, there is a wide regional variation in the estimated prevalence of each of the major types of MD.

Pathogenesis

Cloning of the Duchenne MD gene and identification of its protein product (dystrophin) paved the way for delineating the pathogenesis of MDs. Dystrophin is a component of the membrane skeleton of muscle cells. Its absence in the inner face of the plasma membrane leads to membrane instability and ultimately results in myofiber destruction. Identification of dystrophin has led to the discovery of a large complex of sarcolemmal glycoproteins that are associated with dystrophin. In skeletal muscle, this dystrophin-glycoprotein complex (DGC) spans the sarcolemma to provide a linkage between the subsarcolemmal cytoskeleton and the extracellular matrix. This transmembrane complex has several functions, including structural support and signaling across the membrane.

Apart from Duchenne MD and Becker MD, disruption of this DGC causes most of the congenital MDs, and several of the limb-girdle MDs. This is due to the mismatch between muscle breakdown and repair, which is reflected in the markedly elevated creatine kinase (CK) values during the period of maximal muscle breakdown.

Pathology

The common pathological features shared by all muscular dystrophies include necrosis of fibers with signs of regeneration, and a mixture of atrophic and hypertrophic fibers. These fibers are randomly distributed without grouping of abnormally small fibers (as seen in spinal muscular atrophy), or selective involvement of a specific histochemical fiber type (as seen in congenital fiber type disproportion). Hypercontracted and hyalinized fibers may also been seen together with mononuclear inflammatory cell infiltrates as a reaction to muscle fiber necrosis. There is also marked proliferation of collagen and fat between the remaining muscle fibers, especially in late stages of the disease (*Fig. 374.2*). This proliferation of connective tissue and fat is largely responsible for the pseudohypertrophy, which characterizes the major types of MD.

Duchenne and Becker Muscular Dystrophies (MDs)

Definition/Classification/Etiology

Duchenne and Becker MDs are common inherited disorders of muscle affecting all races and ethnic groups. Both are transmitted as X-linked traits, are caused by mutations of the dystrophin gene, and are therefore named *dystrophinopathies*. Fundamentally, both types of MD are the same, but clinically Becker MD follows a milder and more protracted course.

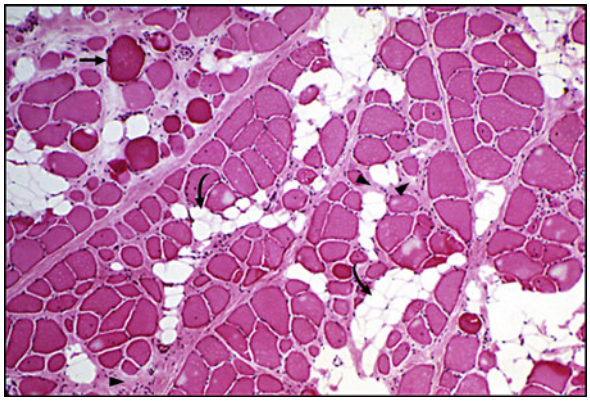

Figure 374.2
Pathological features of muscular dystrophy in haematoxylin-eosin (H&E) stained histological section of muscle. Note necrosis of fibres, irregular caliber of fibres, intramuscular fibrosis (arrowheads) and fat proliferation (curved arrows), and hypercontracted and hyalinized fibres (arrow)

Epidemiology

Duchenne MD is the most common hereditary neuromuscular disease with an incidence of 1 in 3,500 male births, and estimated overall prevalence of 32 to 63 cases per million population. The estimated prevalence of Becker MD is 24 cases per million.

Pathogenesis

The dystrophinopathies are inherited as X-linked recessive. However, one-third of these cases are due to spontaneous mutations. These de novo mutations may have occurred in the maternal ova at the time of the affected child's (proband) conception and is therefore present in every cell of the proband's body. Alternatively, the mutation may have occurred after conception and is thus present in some but not all cells of the proband's body (somatic mosaicism).

The gene causing dystrophinopathies is at the Xp21 locus and is one of the largest genes, occupying almost 2% of the X chromosome and nearly 0.05% of the entire genome. The gene product dystrophin is a 427-kd cytoskeletal protein, which consists of two opposed globular heads with a flexible rod-shaped center (*Fig. 374.3*). One of the globular heads, carboxyl-terminus (or C-terminus) attaches to the sarcolemma via β-dystroglycan, whereas the other head amino-terminus (or N-terminus) attaches to the actin myofilaments. A cysteine-rich domain is also related to the carbonyl-terminus of α-actinin.

β-dystroglycan anchors DGC to the basal lamina via α-dystroglycan and laminin-α2 (merosin). Dystrophin is also expressed in the heart, brain, and smooth muscles.

About 65% of patients with dystrophinopathies have deletions, and only 7% exhibit duplication of the dystrophin gene. Deletions or duplications that do not disturb the reading frame still permit translation of coding sequence further downstream on the gene. These "in frame" changes, particularly when located within the amino-terminal or central regions, produce a semifunctional dystrophin expressed clinically as Becker MD. In contrast, mutations that disrupt the reading frame, including premature stop codons, result in severely truncated, unstable dystrophin manifesting as classic Duchenne MD. The functional loss of dystrophin results in secondary loss of the DGC components, sarcolemma breakdown, oxidative cellular injury,

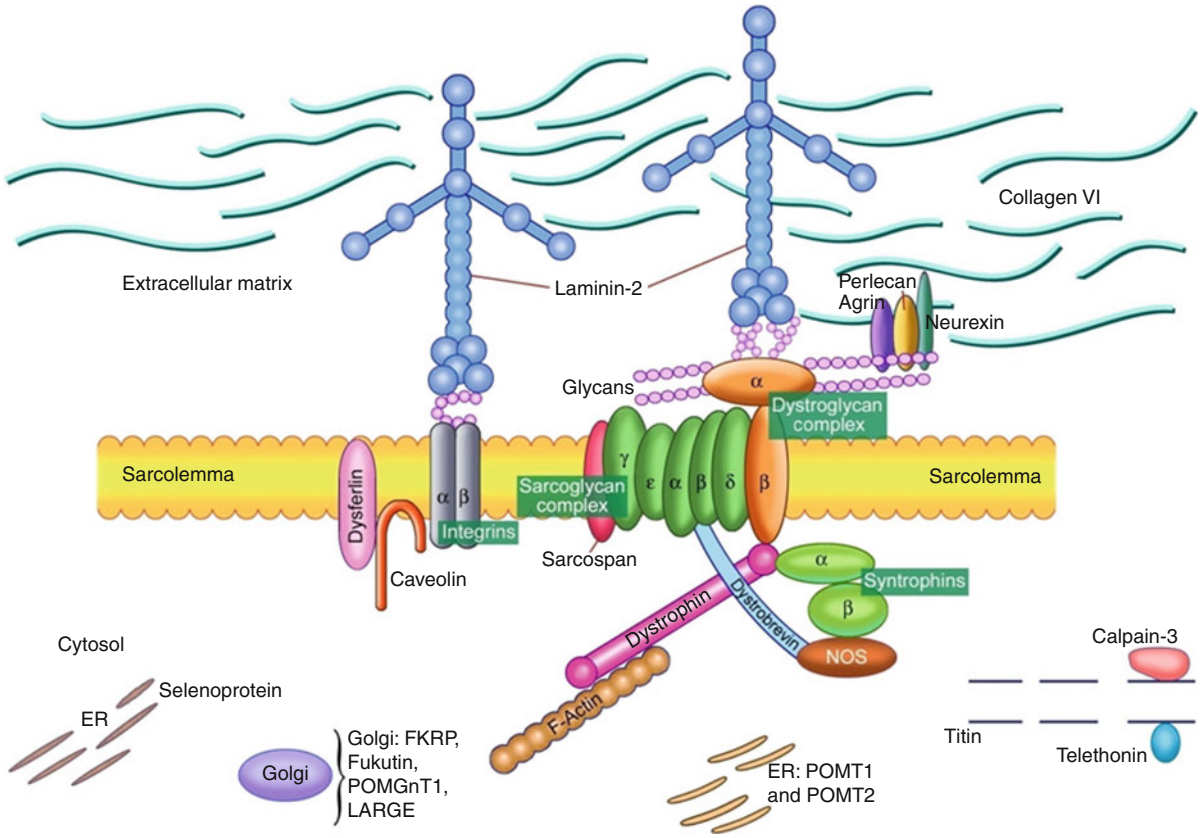

Figure 374.3
Schematic presentation of the main proteins involved in muscular dystrophies, their localization and interactions. Abbreviations: ER, endoplasmic reticulum

and phospholipase activation following calcium ion influx. This leads to muscle fiber necrosis.

Clinical Manifestations

The onset of Duchenne MD is in early childhood, but the first manifestations are often overlooked. Walking may be delayed past 15 months, and waddling gait, manifesting in children aged 2–6 years, is often the first symptom. Difficulties with climbing stairs, arising from floor secondary to hip girdle muscle weakness, are also early symptoms of the disease. A modified Gowers sign is often evident by age 3 years and is fully expressed, with the patient climbing up the legs, in 5–6 years (*Fig. 374.4a*). Muscle weakness and atrophy are symmetrical and contrast with the hypertrophy of the calf muscles, and less frequently the tongue, the vastus lateralis, the deltoids, and the forearm muscles. Patients with classic Duchenne MD become wheelchair dependent before the age of 13 years. Nevertheless, some are confined to a wheelchair by 7 years. Immobilization in bed and surgical operation may be associated with rapid progress of the disease. Weakness later involves the neck flexors, shoulders, and arms, with relative preservation of the function of distal muscles. The deep tendon reflexes progressively decrease, but the ankle jerk is preserved unless ankle contractures are severe. Following loss of ambulation, scoliosis often develops and may be rapidly progressive leading to further respiratory compromise.

Cardiomyopathy, manifesting as persistent tachycardia and cardiac failure, is seen in 50–80% of patients, and its severity does not correlate with the degree of weakness found in skeletal muscle. The incidence of cardiomyopathy increases steadily in the teenage years with one-third of individuals being affected by age 14 years, and all individuals after age 18 years.

Intellectual impairment is a remarkable feature of many cases of Duchenne MD, although only 20–30% fall in the subnormal range with IQ <70. Recently, a specific cognitive profile of boys with Duchenne MD has emerged,

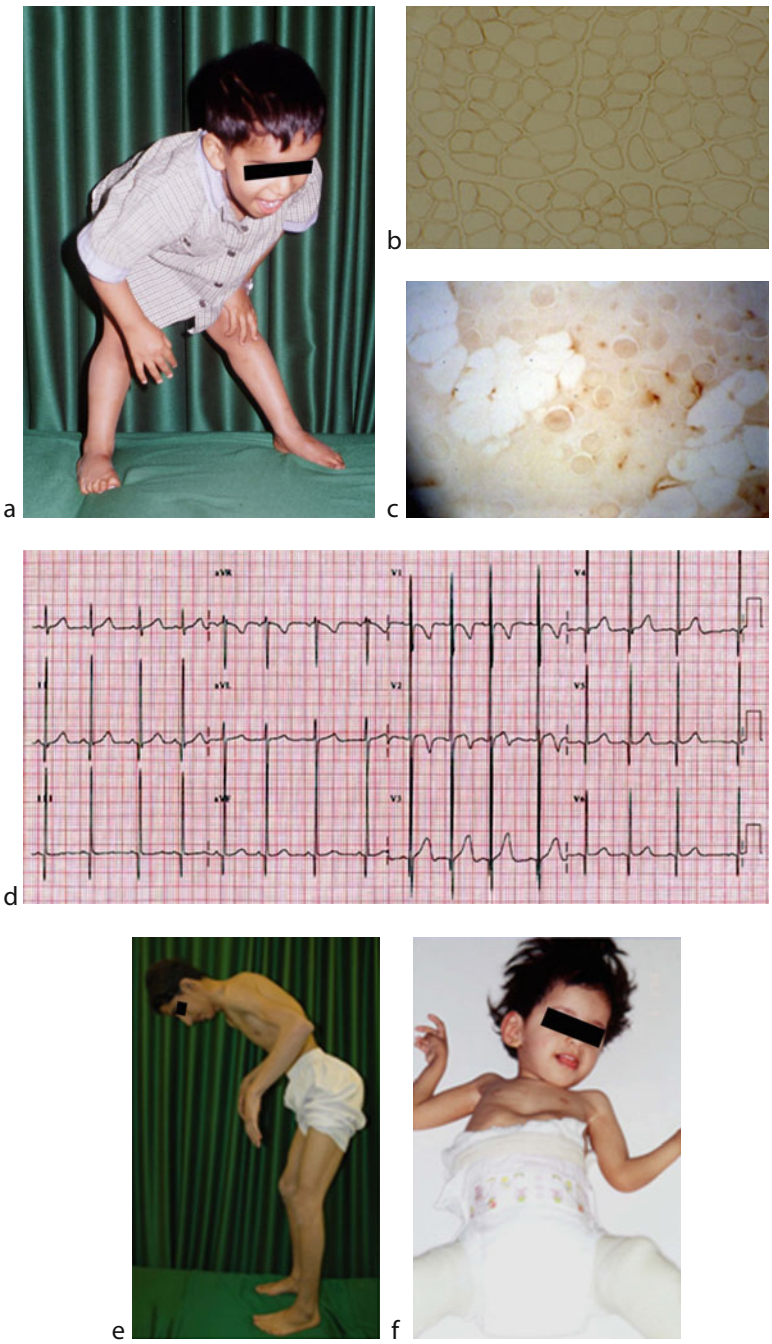

Figure 374.4

(a) A 3 ½ - year - old boy with Duchenne muscular dystrophy (DMD) showing modified Gowers sign. (b) Normal dystrophin staining demonstrated by immunohistochemical reactivity in the muscle biopsy. The sarcolemmal membrane in every fibre is strongly stained. (c) In Duchenne dystrophy the myofibres express no detectable dystrophin. (d) Electrocardiography (ECG) in DMD shows deep Q waves and tall right precordial (leads VI and V2) R waves. (e) An adolescent with Emery-Dreifuss muscular dystrophy due to mutation in *FHL1* gene. Note the limitation of neck flexion, contracture of elbow flexors, and wasting of the biceps, triceps and peroneal muscles. (f) Ullrich congenital muscular dystrophy with bilateral congenital dislocation of the hip joints. Note the hypotonic posture and chest deformity

demonstrating deficits in working memory and executive function. Nevertheless, the majority of children with Duchenne MD can function in a regular classroom, with remedial help.

Death usually occurs at 18–20 years, commonly caused by respiratory complications and cardiomyopathy.

Becker MD is characterized by later-onset skeletal muscle weakness with preservation of ambulation until late adolescence or early adult life. Calf pseudohypertrophy is a feature of the disease, and heart failure from dilated cardiomyopathy is a common cause of morbidity and the most common cause of death. Death often occurs in the mid to late 20s, and the mean age of death is in the mid-40s.

Occasionally, females have clinical features of Duchenne MD as a result of X-chromosome rearrangements involving the Duchenne MD locus. Females with Turner syndrome (i.e., complete or partial absence of an X chromosome) who carry a disease-causing *DMD* gene mutation present with Duchenne MD phenotype. Also, more than 90% of female carriers with skewed X-chromosome inactivation (defined as ≥75% of nuclei harboring the mutant *DMD* gene on the active X chromosome) develop moderate-to-severe muscular dystrophy.

Diagnosis

Serum creatine kinase (CK) is always increased in patients with Duchenne and Becker MDs, even in presymptomatic stages, including at birth. It is often raised to levels that are 50–200 times the reference range (i.e., as high as 35,000 IU/L [normal <160 IU/L]). Other lysosomal enzymes present in muscle such as aldolase and aspartate aminotransferase (AST), as well as the liver specific alanine aminotransferase (ALT) are also elevated. The associated presence of high CK should rule out considering a liver biopsy.

If the clinical features and serum CK are consistent with the diagnosis, blood polymerase chain reaction (PCR) for the dystrophin gene mutation is the primary test to be done. Currently, most laboratories use multiplex PCR to detect deletions, which account for appropriately 65% of mutations in individuals with Duchenne MD and 85% of those with Becker MD. This method has a 98% detection rate for deletions. Duplications, which account for 6–10% of mutations, can be detected by several quantitative techniques.

In patients without detectable mutations of the dystrophin gene, diagnosis requires muscle biopsy for dystrophin protein quantification. The ideal muscle to biopsy is one that is easily accessible and exhibits moderate weakness (i.e., has 80% strength). The most common muscles sampled are the vastus lateralis (quadriceps femoris) and the gastrocnemius. Histochemical examination of frozen muscle biopsy shows florid features (see section "Pathology" above). Immunohistochemical staining of frozen sections using antibodies directed against the rod domain and the carboxyl and amino terminals of dystrophin shows no detectable sarcolemmal staining in boys with Duchenne MD (*Fig. 374.4b* and *c*). Patients with Becker MD show deficient but not totally absent dystrophin expression, with more fragmented and patchy staining of sarcolemmal regions. Immunoblot analysis of muscle biopsy homogenate is also used by some laboratories to quantify the dystrophin molecule. Patients with Duchenne MD have greatly decreased or absent amounts of dystrophin, whereas patients with Becker MD exhibit moderately reduced amounts of dystrophin but with an altered molecular size.

Electrocardiography (ECG) provides a simple mean for aiding in the diagnosis since it may demonstrate deep Q waves and elevated right precordial R waves early in the course of the disease (*Fig. 374.4d*). It may also uncover sinus arrhythmias later on. Echocardiography is also important for revealing subclinical cardiomyopathy.

Electromyography (EMG) is not diagnostic and is difficult to conduct in young frightened children. When performed, it shows myopathic features in the form of short-duration, polyphasic motor unit action potentials with normal to reduced amplitudes.

Radiographs to screen for scoliosis are important, particularly in patients with Duchenne MD after they become wheelchair dependent. Serial chest X-rays are also required when dyspnoea develops in a patient. Baseline pulmonary function testing is recommended in patients with Duchenne MD before confinement to a wheelchair (usually at the age of 9–10 years).

Differential Diagnosis

Severe childhood autosomal recessive muscular dystrophy (SCARMD) is a subgroup of limb-girdle muscular dystrophy (LGMD), which closely resembles Duchenne MD but occurs in both sexes. This phenotype of dystrophy is more prevalent in communities with high consanguinity rate (see "SCARMD" below). From the authors previous experiences, several boys with SCARMD are referred and managed as having Duchenne MD. In children with SCARMD, creatine kinase (CK) is usually lower than in cases of Duchenne MD, and muscle biopsy reveals normal

dystrophin staining. Becker MD may also be mistaken for other forms of LGMD with either autosomal recessive or autosomal dominant inheritance.

Treatment

Since there is currently no medical cure for Duchenne or Becker MD, attention is focused to improve the quality of life of affected children, anticipate, and treat the complications and prolong lifespan.

Supportive care requires coordinated and multidisciplinary team approach. Maximizing functional status and delaying wheelchair dependence may be achieved by daily joint-stretching exercises, night splints, and braces such as ankle-foot orthosis and knee-ankle foot orthosis. Ambulation may be prolonged by as long as 2 years with judicious use of tendon release surgeries. Excessive exercise or training should be avoided, since it can cause further damage to the muscle cells, and gentle sports or activity (such as swimming and tricycle/bicycles) may be encouraged.

As recommended by The American Academy of Pediatrics, complete cardiac evaluation is required for optimal care at least every 2 years. For patients with Duchenne MD, this should begin in early childhood. At approximately 10 years, or at the onset of cardiac signs and symptoms, evaluation should be annual. Complete cardiac evaluation is recommended about age 10 years, or at the onset of signs or symptoms, for Becker MD patients. This should continue at least every 2 years.

Before confinement to a wheelchair (usually at about 9–10 years), baseline pulmonary function testing should be performed for children with Duchenne MD. Twice yearly evaluation by a pediatric pulmonologist is required after the age of 12 years, confinement to a wheelchair or reduction in vital capacity below 80% predicted. As the disease continues to progress, sleep studies followed by noninvasive ventilator support may be required. The two major minimally invasive and easy to use options in this regard are the bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). Annual administration of pneumococcal vaccine and influenza vaccine is recommended.

At the stage of wheelchair dependency, adaptive devices to maximize upper extremity mobility and cushioning to prevent pressure sores, and customizing the chair for the patients needs will be required. Monitoring for orthopedic complications, especially scoliosis, is important at this stage. Spinal instrumentation or fusion may become necessary with worsening of spinal curvature.

Dietary modifications can prevent excessive weight gain and exposure to sunshine, and a balanced diet rich in vitamin D and calcium improves bone density and reduces risk of fractures. Social and psychological supports are crucial for improving psychosocial dynamic of families with an affected child.

Corticosteroids are the only medication, which have demonstrated some success in modifying the course of Duchenne MD. They prolong ambulation by 2–3 years, maintain strength and function, delay the development of scoliosis, and demonstrate favorable effects on cardiac function. Their mechanism of action is thought to be through reduction of tissue inflammation, stimulation of myoblasts, improvement of calcium homeostasis and suppression of cytotoxic cells. Nevertheless, corticosteroids have significant side effects, which include excessive weight gain, cushingoid appearance, short stature, decrease in linear growth, hypertension, diabetes, cataracts, and behavioral changes. There is also an increased frequency of vertebral and long bone fractures with prolonged corticosteroid use. Recommendations by the American Academy of Neurology and the Child Neurology Society advise starting prednisone (0.75 mg/kg/day) in boys with Duchenne MD who are older than age 5 years. This dose should be maintained if side effects are not severe, and should be decreased to 0.5 mg/kg/day if excessive weight gain occurs (>20% over estimated normal weight for height over 12 month period). In case excessive weight gain still continues, the dose should be further decreased to 0.3 mg/kg/day after 3–4 months.

To reduce the incidence of steroid-associated side effects, other regimens were adopted by several centers, including alternate day dosing, lower dose daily regimes (e.g., 10 days on/10 days off); high dose on weekends.

Deflazacort is a synthetic derivative of prednisolone used in Europe but not currently available in the USA. It has a more favorable side effect profile compared to prednisone, including less excess weight gain and less slowing of growth, but has a higher risk of asymptomatic cataracts. It can be used to treat Duchenne MD in a dose of 0.9 mg/kg/day. Currently, an international trial is evaluating the efficacy of deflazacort 0.9 mg/kg/day versus prednisone 0.75 mg/kg/day versus prednisone 0.75 mg/kg/day used as 10 days on, followed by 10 days off.

To date, clinical trials have not shown favorable results with the use of myoblast transplantation or stem cell transplantation into patients with Duchenne MD. Nevertheless, recent promising preclinical and clinical trial results of antisense oligonucleotides (AOs) could provide a therapeutic option for the majority of children with Duchenne MD. Oligonucleotides are small synthetic

RNA molecules that can bind to specific sequences within the dystrophin pre-mRNA. They are capable of reestablishing an open reading frame of the dystrophin gene, resulting in a functional dystrophin mRNA, which is translated into functional dystrophin protein. This technique could possibly benefit 70–80% of Duchenne MD patients. Clinical trials are currently underway to evaluate its efficacy, safety, and tolerability.

Prognosis

Apart from Duchenne and Becker MDs, the clinical spectrum of dystrophinopathies ranges from a severe neonatal MD to asymptomatic children with persistent elevation of CK levels (>1,000 IU/L). In general, patients with Becker MD have much greater phenotypic variability compared to those with Duchenne MD. They may become wheelchair bound as early as age 20 years or as late as age 70 years.

Prevention

A crucial step in prevention of Duchenne and Becker MDs is carrier detection to guide the genetic counseling of affected families, which remains the sole intervention for preventing the disease. About two-thirds of asymptomatic female carriers of Duchenne and Becker MDs have elevated serum CK values, usually in the magnitude of hundred or a few thousand. Nevertheless, it should be remembered that some ethnic and racial groups (e.g., African Americans) have normally elevated CK levels without the presence of any pathology. Muscle biopsy of suspected female carriers may detect an additional 10% in whom serum CK is not elevated by showing mosaic pattern for dystrophin immunofluorescence. However, many female carriers of Duchenne or Becker MDs show no abnormality in dystrophin immunostaining. Molecular genetic testing is increasingly being used in suspected female carriers to identify heterozygosity for a deletion, duplication or point mutation. Female carriers should have cardiac surveillance since they may develop cardiomyopathy without muscle weakness. Prenatal testing is possible for pregnancies of women who are carriers if the Duchenne MD mutation has been identified in a family member or if linkage has been established. Testing is done either by chorionic villus sampling (at about 10–12 weeks of gestation) or by amniocentesis, which is usually performed at approximately 15–18 weeks of gestation. Preimplantation genetic diagnosis (PGD) is also available for families in which the disease-causing mutation has been identified.

Emery–Dreifuss Muscular Dystrophy

Definition/Classification

Emery–Dreifuss muscular dystrophy (EDMD) is a rare hereditary disorder characterized by joint contractures that begin in early childhood, slowly progressive muscular dystrophy with humeroperoneal preponderance and cardiac involvement.

Epidemiology

Accurate data on the frequency of EDMD is lacking although the disease has been described in various ethnic groups. The combined prevalence of X-linked (due to emerin mutations) and autosomal EDMD has been estimated to be about 1–2 cases per 100,000 people.

Pathogenesis

Emery–Dreifuss muscular dystrophy (EDMD) is a genetically heterogeneous disorder. The disease can be transmitted in a recessive X-linked manner as a result of mutations in *EDM* gene, encoding the emerin protein, or in an autosomal dominant or recessive mutations in *LMNA*, encoding the lamin A and C proteins. The precise functions of emerin and lamins A and C are still unknown, but both are components of the nuclear envelope and interact with each other. Sequence variants in *SYNE1* and *SYNE2* genes were recently identified in patients with EDMD-like phenotype. These two genes encode, respectively, nesprin 1 and 2 proteins that bind both emerin and lamins A and C, and form a network in muscle linking the nucleoskeleton to the inner and outer nuclear membranes. It is postulated that disruption of the inner nuclear membrane and the nuclear lamina, due to mutations in these genes, causes disorganization of nuclear chromatin and gene expression or leads to structural and signaling defects in mechanically stressed tissues of the heart and skeletal muscles. Most recently, several families, including one followed by the author, had EDMD caused by mutations in *FHL1* gene. Reduced *FHL1* expression may have an impact on myogenin expression, myoblast fusion, maintenance of cellular structural integrity, and on the regulation of cell signaling.

Pathology

Routine histochemical studies of muscle biopsies show unspecific myopathic picture characterized by variation in fiber size, significant increase in internal nuclei, mild increase in endomyseal connective tissue, associated occasionally with necrotic and regenerating fibers. Type 1 fibers are predominant and often relatively atrophic in EDMD caused by emerin mutations and in lamin A/C-associated disease. Immunohistochemical staining shows absence of normal staining of the inner nuclear membrane by antiemerin antibody in the X-linked EDMD caused by mutations in emerin gene. This lost staining can be observed in buccal cells, peripheral leukocytes, and skin fibroblasts. In female carriers of this X-linked phenotype of EDMD, immunostaining of muscle nuclei is lost in ranging proportions.

Clinical Manifestations

Age of onset, severity, and progression of muscle and cardiac involvement demonstrate both inter- and intrafamilial variability. The features of the disease tend to develop independently from one another so that the diagnosis can be difficult in young patients. Generally, joint contractures appear during the first 2 decades, and are followed by muscle weakness and wasting. Early contractures involve the elbow flexors, Achilles tendons (heel cords), and neck extensors resulting in limitation of neck flexion, followed by spinal rigidity (*Fig. 374.4e*).

Weakness and wasting are slowly progressive and follow scapulohumeroperoneal distribution. There is symmetric weakness of the biceps, triceps, and peroneal muscles associated with scapular winging. The wasting of the biceps is often quite striking, affecting the proximal more than the distal portion. Ocular and facial muscles are spared. In the lower limbs, the thigh muscles are usually preserved or occasionally hypertrophied. Cases of EDMD with mutations in FHL1 gene have additional features characterized by facial weakness in some cases and dysphonia due to vocal cord paralysis.

Cardiac involvement usually starts after onset of weakness and manifests in the second or third decade as atrial fibrillation, flutter and standstill, supraventricular and ventricular arrhythmias, and atrioventricular conduction defect. Late findings may include dilated cardiomyopathy. Conversely, some patients with FHL1 mutation have hypertrophic cardiomyopathy. About 10–20% of female carriers have cardiac conduction defects, weakness, or both, and are prone to die suddenly.

Diagnosis

The diagnosis of EDMD is based on the phenotype of the disease and other ancillary investigations.

Serum creatine kinase (CK) is either normal or moderately raised (2–20 times the upper normal limit). Elevated CK is seen at the early rather than the late stage of the disease. Neurophysiological investigations reveal normal nerve conduction studies, and electromyography (EMG) usually shows myopathic features. Neurogenic features have been reported in the X-linked phenotype associated with emerin deficiency and in the autosomal dominant EDMD. Characteristic findings in the calf muscles on MRI have also been reported in the latter form. Muscle histopathology and immunohistochemistry are helpful diagnostic tools (see section "Pathology" above). Molecular diagnosis detects mutations in *EMD* (emerin) and *LMNA genes* in about 35% of EDMD patients.

Differential Diagnosis

The phenotype of EDMD is relatively easy to recognize and differentiate from other forms of childhood-onset muscular dystrophies (MDs) or myopathies. Nevertheless, myopathies and MDs presenting as the rigid spine syndrome may closely mimic EDMD. This syndrome is characterized by marked limitation in flexion of spine, including cervical spine, and is associated with limited extension of the elbows and ankles. It was found to be caused by a mutation in the selenoprotein N gene (*SEPN1*) and can present as a congenital myopathy or rigid spine muscular dystrophy 1 (see section "Congenital Muscular Dystrophy").

Treatment

The general care and nonspecific treatment of children with EDMD are similar to that detailed for Duchenne/Becker MD (see above). Cardiac complications of the disease require specific treatments including antiarrhythmic drugs, cardiac pacemaker, implantable cardioverter defibrillator (ICD), and therapy for heart failure. Heart transplantation may be performed in patients who do not have severe skeletal muscle and respiratory involvement. Heterozygous carriers of the X-linked EDMD phenotype (due to either *EMD* [emerin] or *FHL1* gene mutations) may manifest cardiac disease and require similar management.

Prognosis

Patients with EDMD often die in mid adulthood from progressive pulmonary or cardiac failure. Sudden cardiac death, which is a frequent cause of early mortality, can be prevented with early cardiac pacing.

Prevention

Similar to Duchenne and Becker MDs, prenatal testing is possible for pregnancies at increased risk for EDMD if the disease-causing mutation of an affected family member is known. Preimplantation genetic diagnosis may also be available for families in which the disease-causing mutations have been identified.

Congenital Muscular Dystrophy

Definition/Classification

The category of congenital muscular dystrophy (CMD) embraces a number of genetically and clinically heterogeneous disorders characterized by congenital hypotonia, delayed motor development, progressive muscle weakness of early onset, and dystrophic features on muscle biopsy. Following the rapid increase of separate variants of CMD in the molecular era, a classification of CMD based on the primary biochemical defect has been proposed. As of 2009, identified genetic defects in CMD involve:

1. Proteins of the extracellular matrix or peripheral membrane. These include collagen VI which causes Ullrich CMD, laminin-α2 chain (or merosin), which results in merosin-deficient CMD (MDC1A); and integrin-α7 causing CMD with integrin deficiency (◉ *Fig. 374.3*).
2. Putative or demonstrated glycosyltransferases, which affect the glycosylation of α-dystroglycan. These include protein O-mannosyltransferase 1 and 2 (POMT1 and POMT2, respectively), O-mannose beta-1, 2-N-acetylglucosaminyltransferase (POMGnT1), fukutin, fukutin-related protein (FKRP); and LARGE. These diseases are collectively referred to as α-dystroglycanopathies.
3. Selenoprotein N gene (*SEPN1*), which encodes an endoplasmic reticulum protein of unknown function and causes, when mutated, rigid spine muscular dystrophy1.
4. Lamins A and C, which were recently found to be associated with clinicopathological features overlapping with congenital muscular dystrophy.

Epidemiology

The estimated prevalence of CMD is 4.7 cases per 100,000 children in Italy while in Sweden the incidence is estimated at 6.3 cases per 100,000 births. However, the frequencies of the different subtypes of CMD show regional and ethnic variations. Merosin-deficient CMD (MDC1A) accounts for 30–40% of all forms in the European continent and in Brazil. Ullrich CMD is the second most common subtype in Europe, Australasia (12%), and Japan (9.4%). In Japan, it comes after Fukuyama CMD, which has a rate of approximately 50%. Congenital muscular dystrophies (CMDs) due to defects in O-glycosylation of α-dystroglycan are estimated to account for 25–50% of all cases.

Pathogenesis

Ullrich CMD is an autosomal recessive (or more rarely dominant) disorder caused by mutations in one of three collagen type VI genes (*COL6A1*, *COL6A2*, *COL6A3*). Collagen VI, which is manufactured primarily in interstitial fibroblasts, has cell adhesion properties and binds to numerous extracellular matrix proteins, including perlecan and other collagens (◉ *Fig. 374.3*). Anchoring the basement membrane to the underlying connective tissue is thought to be the major role of collagen VI.

Laminins are glycoproteins that form the backbone of the basement membrane. Laminin-α2 (merosin) is a heterotrimer (α2 – β1 – γ1), which binds to a member of molecules including α-dystroglycan and integrin-α7 (◉ *Fig. 374.3*). Loss of laminin-α2 (merosin) results in mechanical instability of muscle associated with a secondary loss of α-dystroglycan and integrin-α7. The α2 subunit of laminin (merosin) is also expressed in the basal lamina of Schwan cell-axon unit, and a peripheral demyelinating neuropathy is a feature of merosin-deficient CMD.

Integrin-α7 deficiency is inherited as autosomal recessive and is caused by mutations in the gene encoding for this protein. Integrin-α7 comprises transmembrane adhesion molecules composed of one α and one β chain, and plays a role in the formation of myotendinous and neuromuscular junctions. It forms a transmembrane link between laminin-α2 (merosin) and the muscle membrane that is independent of the dystrophin-glycoprotein complex (◉ *Fig. 374.3*).

Rigid spine muscular dystrophy1 is an autosomal recessive disease due to a mutation in the selenoprotein N gene (*SEPN1*). Selenoprotein N is an endoplasmic

reticulum protein of unknown function, which is involved in oxidation/reduction reaction (Fig. 374.3).

Six genes are involved in O-glycosylation of α-dystroglycan. These are *POMT1*, *POMT2*, *POMGnT1*, *FCMD*, encoding fukutin, *FKRP*, and *LARGE*. Mutations in any of these six genes will result in abnormal glycosylation and therefore abnormal function of α-dystroglycan. Through its binding with the transmembrane β-dystroglycan, α-dystroglycan is thought to act as a link between the basal lamina and the cytoskeleton, and is crucial in the formation and maintenance of the basement membrane. The binding of α-dystroglycan to the extracellular matrix proteins laminin-α2 (merosin), agrin, perlecan, and neurexin is glycosylation dependent.

Pathology

Various degrees of dystrophic features (muscle fiber necrosis and regeneration with endomyseal and perimyseal regeneration) occur in merosin-deficient CMD and in α-dystroglycanopathies. In complete merosin (laminin-α2) deficiency, infiltrates of mononuclear cells may be seen in biopsy samples obtained in infancy. Mild myopathic features, with little or no necrosis, are often seen in partial laminin-α2 (merosin) deficiency. Regarding α-dystroglycanopathies, muscle tissue may look normal shortly after birth in babies with muscle-eye-brain disease or fukutin-related proteinopathy due to FKRP gene mutations.

Muscle histology varies from mildly myopathic to dystrophic in Ullrich CMD, and in integrin-α7 deficiency, mild variations in fiber size are noted. Rigid spine muscular dystrophy1 due to deficiency of selenoprotein N manifests with myopathic features associated with type1 fiber predominance or atrophy. Muscle fiber necrosis is rare, and minicores may be present.

Clinical Manifestations

Ullrich congenital muscular dystrophy presents in the neonatal period with hypotonia, torticollis, kyphosis of the spine and hip dislocation (Fig. 374.4f). There are also proximal joint contractures combined with distal joint hyperlaxity and protruding calcaneus. Contractures eventually affect the previously lax ankles, wrists, and fingers excluding the interphalangeal joints, which tend to remain lax. Evolution of motor weakness is variable; most patients never walk but others walk and lose ambulation, mostly due to contractures, after 2–10 years. The skin shows follicular hyperkeratosis, keratosis palmaris, and keloids. Intelligence is normal, but ventilatory insufficiency invariably develops in the first or second decade. Ullrich CMD is allelic to and shares similar features with Bethlem myopathy, an autosomal dominant condition, also due to mutation in the gene for collagen VI.

Merosin-deficient CMD (*MDC1A or Classic CMD*) presents at birth or in the first months of life with hypotonia, weakness, feeding difficulty, and respiratory insufficiency usually not requiring assisted ventilation. Most infants eventually sit unsupported, usually by the age of 3 years, but standing or walking with support is rare. Weakness is minimally progressive or static, but functional abilities regress with increase in flexion deformities at the hips, knees, ankles, and elbows, followed by rigidity and scoliosis of the spine. Intelligence is usually normal although mild mental retardation or perceptual-motor difficulties may be observed in few cases. Even with normal intelligence, periventricular white matter changes are constantly seen on magnetic resonance imaging (MRI). About 30% of patients develop seizures, a subclinical demyelinating motor and sensory neuropathy is present in many, and neuronal migration defects have been found in few patients. In severe cases, death may occur after 10–30 years due to respiratory failure.

Mild allelic variants of partial deficiency of laminin-α2 (merosin) have frequently been described. Despite their hypotonia and weakness early in life, these patients may reach the ability to walk unsupported, in contrast to patients with complete laminin-α2 (merosin) deficiency who never achieve this ability. They also demonstrate cerebral white matter changes on MRI and peripheral demyelinating neuropathy.

Integrin-α7 deficiency causing CMD is a rare disorder and has been described in only two children. They presented with hypotonia and delayed milestones. One patient had mental retardation with brain MRI changes, and another had contractures and respiratory failure.

Congenital Muscular Dystrophies Caused by Defects in the Glycosylation of α-Dystroglycan (α-Dystroglycanopathies)

These are autosomal recessive disorders, which are clinically and genetically heterogeneous, caused by deficiency of one of the glycosyltransferases leading to a hypoglycosylation of α-dystroglycan. Mutations in at least six genes *POMT1*, *POMT2*, *POMGnT1*, *FCMD*, *FKRP*, and *LARGE* are known to result in α-dystroglycanopathy. Clinically, they either manifest with pure

muscular involvement or variable degrees of central nervous system and/or ophthalmic involvement.

Fukuyama Congenital Muscular Dystrophy

This autosomal recessive disorder was first described in 1960 by Fukuyama and associates. It represents one of the most common autosomal recessive disorders in the Japanese population and is caused by a founder mutation of the fukutin gene (*FCMD*). In the general population, this founder mutation is observed with a frequency of 1 in 88 individuals and is rare outside the Japanese population.

Onset of the disease is often in utero with decreased fetal movements, but severe arthrogryposis is rare. Hypotonia, weak sucking, and poor head control are noticed early in life. Most patients can stand or walk a few steps at the age of 2–8 years. Those with severe disease may be able to sit only with support. Progressive weakness ensues and is associated with respiratory failure in the mid-to-late teens. Enlargement of tongue, quadriceps, and calf muscles is common. Profound mental retardation is associated with severe weakness, although most patients manage to speak short sentences. Seizures occur in about 50% of patients, usually before age 3 years. Similar to the other α-dystroglycanopathies, MRI shows the characteristic cobblestone (type II) lissencephaly, with abnormalities ranging from cobblestone polymicrogyria and/or pachygyria to complete agyria due to neuronal migration abnormalities. Cerebellar cysts and dysplasia of the pyramidal tracts are common, and there is usually transient delay of myelination. Ocular involvement is seen in about 50% of cases. This ranges from abnormal eye movements, poor visual pursuit and strabismus to microphthalmia, severe myopia, hyperopia, cataracts, and retinal detachment.

Mutation in the fukutin gene was reported in a limb-girdle phenotype of muscular dystrophy (LGMD2M) with normal intelligence and brain MRI (see section ❯ "Limb-Girdle Muscular Dystrophy").

Muscle-Eye-Brain (MEB) Disease

First reported from Finland in 1997, this autosomal recessive disorder is characterized by CMD, structural eye abnormalities, and cortical malformations. Mutations in *POMT1*, *POMT2*, *POMGnT1*, *fukutin*, and *FKRP* can cause this syndrome. The condition was initially considered to be exclusive to the Finnish population, but following advances in molecular biology, it was found to have a worldwide distribution and broader clinical spectrum.

The congenital eye abnormalities are variable but are more severe than those of Fukuyama CMD. They include severe myopia, glaucoma, cataracts, hyperplastic primary vitreous, optic nerve hypoplasia, retinal hypoplasia, and retinal detachments. Similar to Fukuyama CMD, MEB shows clinical variability with regard to muscular or mental involvement. Severely affected patients manifest profound motor and cognitive delay or even autistic features, while some patients with milder disease are able to walk and develop speech. Patients with severe disease never achieve sitting and may die during the first years of life. Intra-familial variability of the clinical features has been reported. Seizures are common and central nervous system abnormalities are constant findings, including moderate-to-severe mental retardation.

Brain MRI changes are similar to those seen in Fukuyama CMD but are more variable. Severe changes include cobblestone (type II) lissencephaly with pachygyria and/or polymicrogyria/agyria. Mild changes include flattening of the pons, vermal hypoplasia, and cerebellar cysts. Evidence of dysmyelination may be seen on MRI, and severe ventricular dilatation may result in obstructive hydrocephalus requiring shunt placement.

Walker–Warburg Syndrome

Mutations in all six glycosyltransferases (*POMT1*, *POMT2*, *POMGnT1*, *fukutin*, *FKRP*, and *LARGE*) can result in this most severe of the α-dystroglycanopathies. The condition is inherited as autosomal recessive CMD in combination with eye malformation and cobblestone (Type II) lissencephaly, not compatible with survival beyond 2–3 years of age. Affected children do not achieve any motor or mental milestones; and encephaloceles and severe hydrocephalus are often detected prenatally.

The congenital ocular anomalies are both anterior and posterior eye malformations and frequently lead to blindness. They include microphthalmia, buphthalmos, megalocornea corneal opacity, coloboma and other iris malformations, congenital or infantile glaucoma, cataract, hypoplastic optic nerve, and retinal detachments (❯ *Fig. 374.5a*).

Brain malformations include complete type II lissencephaly (cobblestone lissencephaly), with absence of sulcation and an irregular gray-white matter junction, marked ventriculomegaly, and severe dysplasia of posterior fossa structure, including cerebellar and brainstem hypoplasia (❯ *Fig. 374.5b* and *c*). Meningocele or encephalocele, usually of the posterior fossa, is present in

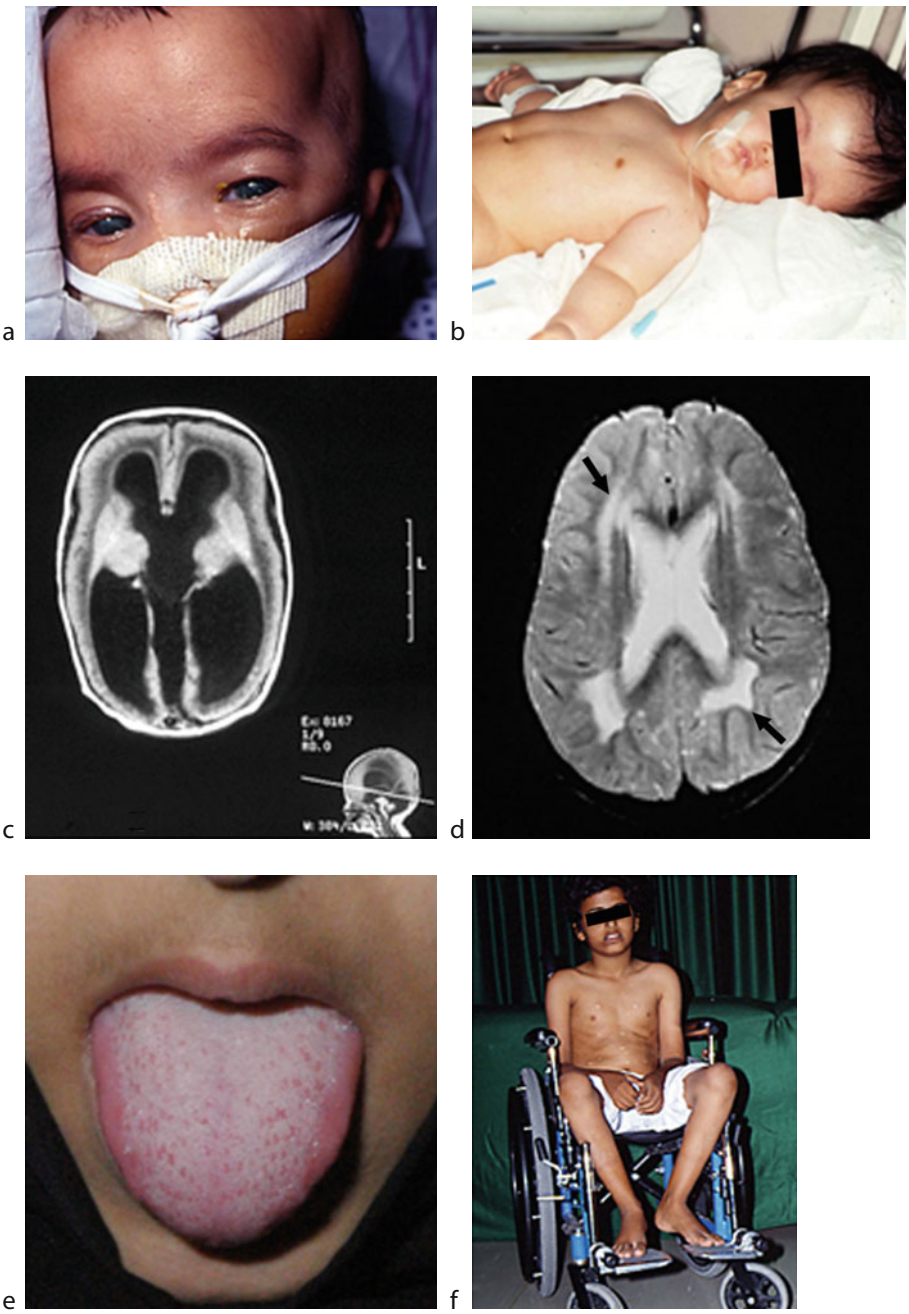

Figure 374.5

(a) Ocular malformations in Walker-Warburg syndrome (WWS). Note the megalocornea and corneal opacities associated with glaucoma. (b) Hydrocephalus in WWS. Note the hypotonic posture of the upper limbs. (c) Magnetic resonance imaging (MRI) in WWS. There is cobblestone lissencephaly with absence of sulcation, an irregular grey-white matter junction, and marked ventriculomegaly. The small saggital image on the right hand corner shows a large posterior fossa and severe dysplasia of posterior fossa structures. (d) Brain MRI in merosin-deficient congenital muscular dystrophy showing periventricular white matter changes (arrows). (e) Enlargement of the tongue in severe childhood autosomal recessive muscular dystrophy (SCARMD). (f) A 13-year-old male who had SCARMD mistaken for Duchenne muscular dystrophy. Muscle biopsy showed normal dystrophin and absent adhalin (α-sarcoglycan)

25% of patients. Obstructive hydrocephalus and microcephaly are common.

Congenital Muscular Dystrophy Type 1C (MDC1C)

This was reported in 2001 as a form of CMD with secondary laminin-α2 (merosin) deficiency and abnormal glycosylation of α-dystroglycan due to fukutin- related protein gene (*FKRP*) mutations. The features of this phenotype included weakness and hypotonia from birth or the first few months of life and a marked delay of motor milestones. Sitting and taking a few steps can be achieved by some patients in the first decade. Nevertheless, progressive weakness leads to respiratory insufficiency and death or ventilatory dependence in the first or second decade. There is pseudohypertrophy of the calf and thigh muscles followed by tongue enlargement. Intelligence is normal, and there are no radiological features of CNS involvement in MRI. However, a wide spectrum of phenotypes were found to be associated with *FKRP* mutations, from in utero or lethal Walker–Warburg syndrome, or muscle-eye-brain disease to a limb-girdle phenotype of muscular dystrophy (LGMD2I, see section "Limb-Girdle Muscular Dystrophy").

LARGE Congenital Muscular Dystrophy

This was described in a 17-year-old female adolescent who had compound heterozygous mutation in the *LARGE* gene. She presented with weakness and hypotonia at age 5 months, and had severe mental retardation. Neuroimaging revealed defects of brain migration and white matter abnormality. An abnormal electroretinogram suggested eye abnormalities.

A phenotype similar to Walker–Warburg syndrome was reported in two siblings who were seen by the author, and had a homozygous intragenic deletion in the *LARGE* gene. They presented at birth with severe hypotonia and respiratory difficulty, both had eye abnormalities and died within 6 months. Creatine kinase was markedly elevated, and cranial computed tomography showed severe hydrocephalus and features of structural brain disease.

Rigid Spine Muscular Dystrophy

This is an autosomal recessive condition, which presents with axial hypotonia and weakness in the first year of life, and motor difficulties secondary to mild-to-moderate proximal muscle weakness. The majority of patients eventually walk, but a few never gain independent walking. Ambulation is usually maintained into adulthood. Facial and palatal weakness (manifesting as nasal speech), and scapular winging are common. The overall muscle bulk may be reduced. The most characteristic pattern is spinal rigidity and scoliosis, which may develop between 3 and 12 years of age. Contractures are usually mild and affect the ankles. Respiratory insufficiency is common and progressive, and ventilatory assistance may be needed as early as the first decade of life to treat nocturnal hypoventilation. There is usually no cardiac involvement, and intelligence and MRI are normal.

Diagnosis

The diagnostic workup for CMD relies mainly on biochemical, imaging, and muscle biopsy studies.

Remarkable elevation of creatine kinase (2–150 times normal) is seen in most patients with CMD due to laminin-α2 (merosin) mutations or abnormal glycosylation of α-dystroglycan. Normal or mildly elevated levels (≤5 times normal) is seen in patients with Ullrich CMD, integrin-α7 deficiency, and rigid spine muscular dystrophy1 (due to deficiency of selenoprotein N).

Brain MRI is normal in patients with Ullrich CMD, integrin-α7 mutations, and in rigid spine muscular dystrophy1. The changes on MRI seen in CMD due to laminin-α2 (merosin), with periventricular white matter changes (increased T2 signal) being the most common abnormality, may be mistaken for a leukodystrophy (*Fig. 374.5d*). These white matter changes appear as hypodensity on cranial computed tomography (CT) scan.

Nerve conduction studies are normal except in patients with laminin-α2 (merosin) deficiency where features of demyelinating motor and sensory neuropathy can be revealed. Electromyography shows myopathic features and is usually not a helpful diagnostic procedure in children with CMD. However, myotonic discharges can be detected in older children who present with myotonic muscular dystrophy simulating CMD.

Brain auditory evoked responses (BAER) may reveal features of sensorineural hearing loss in patients with laminin-α2 (merosin)-deficient CMD and in an unclassified variant of CMD (seen by the Author) associated with cobblestone (type II) lissencephaly without eye malformations (OMIM 601170).

Muscle Biopsy

Muscle biopsy is essential in suspected cases of CMD for diagnostic confirmation and for the exclusion of other causes of weakness. The histopathological features of the various forms have been detailed previously in the "Pathology" section. Immunohistochemical studies also need to be done since they are of help in differentiating the various subtypes of CMD. In Ullrich CMD, collagen type VI staining around surface of muscle fiber is usually reduced or absent. However, staining may occur in connective tissue. Integrin-α7 deficiency CMD is characterized by decreased staining for integrin-α7, but this can also be seen in CMD with laminin-α2 (merosin) deficiency.

All of the α-dystroglycanopathies are characterized by decreased staining for α-dystroglycan, which is localized to the muscle cell surface. There is also decreased molecular weight of α-dystroglycan on western blot studies.

Patients with the classical MDC1A phenotype show complete loss of staining for laminin-α2 (merosin) on immunohistochemical staining. This is observed in both muscle and skin, since normal skin also expresses laminin-α2 in the basement membrane at the junction of the dermis and epidermis. Partial staining is seen on the allelic variants characterized by partial merosin (laminin-α2) deficiency, and in any CMD associated with α-dystroglycanopathy. Laminin-α2 (merosin) antibodies should be used against both the 300- and 80-kd subunits of the protein. Muscle biopsies in cases of CMD with partial laminin-α2 (merosin) deficiency may demonstrate an absence of laminin-α2 with one antibody but not the other.

Differential Diagnosis

This includes diseases, which present as the floppy infant syndrome. However, clinical evaluation of a child with suspected CMD, followed by immunohistochemistry and immunostaining of a muscle biopsy, can usually indicate specific genetic testing. Nevertheless, one rare entity can cause confusion and is important to recognize despite its rarity. It is the autosomal recessively inherited systemic hyalinosis, characterized by hyaline deposits in the papillary dermis and other tissues. The condition typically presents at birth or infancy with severe pain with movement, progressive joint contractures, and often with severe motor disability. Nonsteroidal anti-inflammatory drugs are cardinal in the management of such babies, and physiotherapy for joint contractures should be within the patient's tolerance for pain. Another important disease to differentiate is Marinesco–Sjögren syndrome. This is characterized by cerebellar ataxia with cerebellar atrophy, congenital or early-onset cataract, mild-to-severe mental retardation, hypotonia, and muscle weakness. Muscle biopsy shows myopathic features, leading to the condition being mistaken for one of the forms of CMD with mental retardation.

Treatment

Nonspecific treatment for CMD is similar to that detailed for Duchenne MD. A multidisciplinary approach is vital for children with CMD due to the various associated anomalies. Management of nonmuscle-related issues requires ophthalmic care, assessment for gastric tube feeding, management of seizures, and handling of profound mental retardation. Patients with fukutin-related proteinopathy commonly have cardiac complications, which are also occasionally seen in patients with laminin-α2 (merosin) deficiency. In such cases, treatment of dilated cardiomyopathy with ACE inhibitors and beta-blockers may be necessary.

Prognosis

The prognosis of CMD depends on the particular subtype. Children with Walker–Warburg syndrome rarely survive beyond 3 years of age. Occasionally, patients with laminin-α2 (merosin) deficiency and some patients with mutations in *FKRP* (fukutin-related proteinopathy) have a relatively normal life span.

Prevention

In laminin-α2 (merosin)-deficient CMD (MDC1A), prenatal diagnosis is possible by laminin-α2 (merosin) staining, since laminin-α2 is expressed in 9-week trophoblasts, allowing detection of the protein in chorionic villus. However, protein detection may not be reliable in families with partial laminin-α2 deficiency. Collagen VI immunostaining of the trophoblast can also be used for prenatal diagnosis of Ullrich CMD. A combination of linkage or direct mutation detection is possible for prenatal diagnosis in these two conditions (MDC1A and Ullrich CMD), and other types of CMD, when the disease-causing mutation is known. Preimplantation genetic diagnosis may also be available for families in which the diseases-causing mutation has been identified in an affected family member.

Limb-Girdle Muscular Dystrophy

Definition/Classification

Limb-girdle muscular dystrophy (LGMD) is a descriptive term with a wide range of phenotypic variability. Historically, the LGMD has been reserved for childhood-or-adult-onset muscular dystrophies (MDs) that are distinct from the X-linked forms. It is characterized by weakness involving the shoulder or pelvic-girdle muscles, expression in either male or female sex and autosomal recessive, or less frequently, autosomal dominant inheritance.

With the advent of molecular genetics, LGMD classification was changed during a consortium meeting, under the auspices of the European Neuromuscular Centre, in 1995. The suggested classification was based on identified genetic loci for LGMD. The dominant LGMD loci were designated LGMD1A, B, C, etc. and the recessive forms as LGMD2A, B, etc. in the order of their identification. Nevertheless, the classification of LGMD is still an ongoing process.

Epidemiology

The overall prevalence of all forms of LGMD has been estimated to range from one in 14,500 to one in 123,000. Different populations often have different frequencies of the various forms of LGMD.

Pathogenesis

Identification of dystrophin has led to the discovery of a large oligomeric complex of sarcolemmal glycoproteins that are associated with dystrophin. These dystrophin-associated glycoproteins span the sarcolemma to provide linkage between the sarcolemmal cytoskeleton and the extracellular matrix (*Fig. 374.3*). They were first identified by their molecular weight in kilodaltons (kd). The 156-kd dystrophin-associated glycoprotein (156 DAG, α-dystroglycan) is located extracellularly and provides a binding site for laminin-α2 (merosin:muscle-specific isoform of laminin). α-dystroglycan (156 DAG) is linked to β-dystroglycan (43 DAG), which is a transmembrane protein that binds intracellularly with dystrophin and extracellularly with α-dystroglycan. β-dystroglycan also interacts with the sarcoglycan complex, which is formed of adhalin (α-sarcoglycan, 50 DAG ["adhalin" is derived from the Arabic word "adhal," which means "muscle"]), β-sarcoglycan, γ-sarcoglycan, and δ-sarcoglycan. Adhalin (α-sarcoglycan) can also be replaced by ε-sarcoglycan, forming a minor complex in skeletal muscle, but the major sarcoglycan in smooth muscle, where α-sarcoglycan is not expressed. Deficiency of one or more these dystrophin-associated glycoproteins disrupts the linkage between sarcolemmal cytoskeleton and extracellular matrix, thus rendering muscle cells susceptible to necrosis.

Other molecular components (*Fig. 374.3*) that are known to be associated with LGMD include calpain-3, which is expressed exclusively in muscle and is likely anchored by titin, and telethonin protein (titin-cap protein), which is present in the Z disk that binds to titin and several other Z-disk proteins. Titin is the largest protein found in humans, spans the entire sarcomere from the M line to the Z disk, and plays a mechanical role in muscle contraction. Myotilin is a sarcomeric protein that binds to α-actinin and is associated with the Z-line, whereas lamin A/C is an intermediate filament in inner nuclear membrane and nucleoplasm of almost all cells. Dysferlin protein is a large membrane protein, which is thought to be involved in the docking and fusion of intracellular vesicles to sarcolemma during injury-induced membrane repair, whereas calveolin-3 is a protein involved in membrane trafficking in the myofiber.

Binding of α-dystroglycan to extracellular matrix proteins laminin-α2 (merosin), neurexin, agrin, and perlecan is glycosylation dependent (*Fig. 374.3*). In mammals, a unique carbohydrate structure containing O-linked mannose has been found on α-dystroglycan. Defects in O-glycosylation of α-dystroglycan lead to its disruption, and several genes encode for proteins, which are involved in the glycosylation of α-dystroglycan. Abnormalities of these glycosyltransferases usually result in several phenotypes of congenital muscular dystrophy but were also found recently to manifest as LGMD in some cases. Putative or demonstrated glycosyltransferases, which affect the glycosylation of α-dystroglycan include protein O-mannosyltransferases1 and 2 (POMT1 and POMT2). They also include O-mannose beta 1, 2-N-acetylglucosaminyltransferase (POMGnT1), fukutin, fukutin-related protein (FKRP), and LARGE.

The molecular genetics of the 14 autosomal recessive and 3 autosomal dominant forms of LGMD with currently known genes is detailed in *Table 374.2*.

Pathology

On muscle histology, pathological features of the LGMDs are generally similar to those seen in Duchenne and Becker

Table 374.2
Molecular genetics of the limb-girdle muscular dystrophies (LGMDs) with currently known genes

	Locus	Gene symbol	Protein product
Autosomal recessive LGMDs			
LGMD2A	15q15.1–q212.1	*CAPN3*	Calpain – 3
LGMD2B	2p13.3–p13.1	*DYSF*	Dysferlin
LGMD2C	13q12	*SGCG*	γ-sarcoglycan
LGMD2D	17q12–q21.3	*SGCA*	Adhalin (α-sarcoglycan)
LGMD2E	4q12	*SGCB*	β-sarcoglycan
LGMD2F	5q33	*SGCD*	δ-sarcoglycan
LGMD2G	17q12	*TCAP*	Telethonin
LGMD2H	9q31–q34.1	*TRIM32*	Tripartite motif protein 32
LGMD2I	19q13.3	*FKRP*	Fukutin-related protein
LGMD2J	2q24.3	*TTN*	Titin
LGMD2K	9q34.1	*POMT1*	Protein O-mannosyltransferase 1
LGMD2L	9q31	*FKTN*	Fukutin
LGMD2M	1p34–p33	*POMGnT1*	Protein O-linked-mannose beta-1,2-N-acetylglucosaminyltransferase 1
LGMD2N	14q24.3	*POMT2*	Protein O-mannosyltransferase 2
Autosomal dominant LGMDs			
LGMD1A	5q31	*TTID*	Myotilin
LGMD1B	1q21.2	*LMNA*	Lamin A/C
LGMD1C	3p25	*CAV3*	Caveolin-3

MD. However, the various forms of LGMD are characterized by variable degrees of fiber degeneration and regeneration, central nuclei, fiber-size variation, and endomyseal fibrosis. In addition, significant inflammatory changes are sometimes observed in LGMD2B (dysferlinopathy) and the presence of myopathic changes with rimmed vacuoles characterizes LGMD2G (telethoninopathy). Dystrophic features are often associated with inflammatory infiltrates in LGMD2L, LGMD2M and LGMD2N; and with type 1 fiber predominance in LGMD2I (*Table 374.2*).

Clinical Manifestations

Severe childhood autosomal recessive muscular dystrophy (SCARMD) was recognized as a precise nosological entity in 1983 following studies from Sudan and Tunisia on a Duchenne-like phenotype of muscular dystrophy, which affects both sexes equally (autosomal recessive).

Except for LGMD1B (dysferlinopathy), mutations in all autosomal recessive LGMD genes can present as SCARMD phenotype. The phenotype of SCARMD is seen in mutations of the genes encoding for the sarcoglycans, which account for about 20–25% of the LGMDs. Adhalin (α-sarcoglycan) deficiency accounts for 40% of the sarcoglycanopathies, followed by LGMD2C (γ-sarcoglycan) and LGMD2E (β-sarcoglycan), each accounting for about 23%. LGMD2F (δ-sarcoglycan) is rare outside Brazil where it constitutes 14% of cases. Sarcoglycanopathies (LGMD2C, 2D, 2E, and 2F) usually present as SCARMD, although unusual Becker-like phenotypes have been described.

Typically, SCARMD is characterized by onset before the age of 5 years (mean 8-5 years) in both sexes. Weakness progresses steadily until the child is unable to walk at about 10–15 years of age. Both sexes may become completely dependent by 16 years and die by 20 years or during the third decade. Selective muscle weakness in the upper and lower limbs has the same pattern as that seen in classical Duchenne MD. The facial muscles are mildly involved, as the disease progresses. Hypertrophy of the calf and other muscles is common, and the tongue may become enlarged (*Fig. 374.5e*). Intelligence is normal, a feature which differentiates SCARMD from Duchenne MD.

LGMD2A (*Calpainopathy*) is a common form of LGMD and accounts for about 30% of cases. The average age of onset is between 8 and 15 years, and the course of

the disease resembles that of Becker MD. Calf muscles are atrophic, and there is no facial or cardiac involvement.

LGMD2A (*Dysferlinopathy*) starts in late adolescence (onset between 17 and 23 years). The distribution of muscle weakness is distal and/or pelvic-femoral with no scapular winging. Rarely, there is transient hypertrophy of the calf muscles.

LGMD2G (*telothinoninopathy*) and *LGMD2H* (*TRIM32-related dystrophy*) tend to have a mild phenotype, with limb-girdle weakness. However, there is phenotypic variability between and within families in telethoninopathy, and patients eventually develop distal weakness. Mild cardiac involvement occurs in about 50% of patients.

The phenotype of LGMD2I (*fukutin-related proteinopathy*) can vary from severe congenital muscular dystrophy to mild, late-onset LGMD. Patients can present with typical SCARMD phenotype similar to that seen in sarcoglycanopathies (LGMD2C-2F).

The onset of *LGMD2J* (*titinopathy*) is at 5–25 years with proximal weakness. The disease follows Becker MD course with no facial muscle or cardiac involvement. It is noteworthy that mutations in the *titin* gene cause the autosomal recessive Salih myopathy and the dominant distal (tibial) muscular dystrophy described in Finnish patients (see section on "Congenital Myopathies" above).

Four phenotypes of LGMD are associated with defective glycosylation of α-dystroglycan due to mutation in genes also known to cause congenital muscular dystrophy (*Table 374.2*). *LGMD2K* (*due to POMT1 gene mutation*) is characterized by onset between 1 and 6 years, mental retardation, severe proximal weakness with slow progression, hypertrophy of the calves and thighs, and development of contractures in some patients. *LGMD2L* (*due to fukutin gene mutation*) presents with hypotonia before 1 year, proximal muscle weakness affecting the lower more than the upper limbs, and normal intelligence. Affected children have worsening of their weakness after intercurrent illness, which improves with steroids.

One affected female was reported with *LGMD2M* (*due to mutation in POMGnT1 gene*). Onset was at 12 years with proximal more than distal muscle weakness, calf hypertrophy, severe myopia, and normal intelligence. Ambulation was lost at 19 years. The phenotype of *LGMD2N* (*due to POMT2 mutation*) is characterized by slowness in running and getting up, scapular winging, mild lordosis, calf hypertrophy, and mental retardation. One of the described female patients was asymptomatic at 5 years.

The autosomal dominant *LGMD1A* (*myotilinopathy*) is a disease of adulthood, whereas *LGMD1B* (*laminopathy*) can start from childhood (<10 years) to the mid-30s. LGMD1B is due to mutations in the gene encoding for lamin A/C and can present as Emery–Dreifuss or congenital muscular dystrophy phenotypes, or as axonal Charcot-Marie-Tooth disease. The disease manifests with proximal lower limb weakness and mild contractures of elbows. Cardiac disease develops between 25 and 45 years and is in the form of arrhythmias and dilated cardiomyopathy.

The onset of *LGMD1C* (*calveolinoapthy*) ranges from the first decade to late adulthood. Childhood-onset disease is characterized by mild-to-moderate proximal weakness, exercise-induced cramps, and calf muscle hypertrophy. Cardiac involvement is also common.

Diagnosis

Serum creatine kinase (CK) is always increased in autosomal recessive LGMD. Levels are elevated by 10–150 times normal in sarcoglycanopathies (LGMD2C-2F) and in dysferlinopathy (LGMD2B). Elevations of CK are 3–80 times normal in other autosomal recessive LGMDs. Autosomal dominant LGMDs result in CK levels between normal and 15 times normal, but high results (ranging between 4 and 25 times normal) can be seen in LGMD1C (calveolinopathy).

Magnetic resonance imaging shows hyperintense signal changes on T1-weighted image in more severely affected muscles. Patients with LGMD2D (adhalinopathy, α-sarcoglycanopathy) and those with Becker MD show more severe MRI changes in the anterior thigh compartment than in the posterior thigh. In LGMD2I (fukutin-related proteinopathy), the most severe changes are in the posterior and adductor thigh muscles, with less severe changes in gluteal and calf muscles. Patients with LGMD2A (calpainopathy) have more severe and selective involvement of the medial gastrocnemius and soleus muscles associated with severe involvement of the posterior and adductor thigh muscles.

Nerve conduction studies are normal in LGMDs. Electromyography (EMG) shows myopathic features but is usually not a helpful diagnostic tool in children. Neurogenic features on EMG, in the form of fibrillations and positive sharp waves, should raise the suspicion for an inflammatory myopathy, such as polymyositis.

Electrocardiography (ECG) provides a simple means for aiding in the diagnosis, especially in young boys with LGMD. In sarcoglycanopathies, it may show ST-segment and T-wave changes involving leads II, III, and AVF, suggesting basal myocardial involvement with the dystrophic process, but none of the tall right precordial R waves in the lateral and left leads which are characteristic of

Duchenne MD. It will also detect cardiac involvement, which is common in the other recessive LGMD2G (telethoninopathy) and LGMD2I (fukutin-related proteinopathy). Cardiac involvement is also common (50–65%) in the autosomal dominant LGMD1A (myotilinopathy) and LGMD1B (laminopathy).

Muscle biopsy is an important diagnostic tool in LGMD. Histochemical examination of frozen muscle biopsy shows typical dystrophic features in most cases (see "Pathology" in Duchenne and Becker Muscular Dystrophies (MDs)). Severe dystrophic features are often seen in the sarcoglycanopathies (LGMD2C-2F) and in LGMD2I (fukutin-related proteinopathy). In LGMD2A, (calpainopathy) the muscle biopsy may show perimyseal and perivascular T-cell infiltrates similar to the histological findings in polymyositis.

Immunohistochemical staining is essential to help in guiding the molecular pathological investigations. Dystrophin should be tested first by using antibodies to N-terminus, rod, and C-terminus. Nevertheless, it should be remembered that minor reduction in dystrophin staining can be seen in sarcoglycanopathies, and minor reduction in sarcoglycan staining may occur in dystrophinopathies. Hence, both dystrophin and sarcoglycan immunostaining must be performed in the same sample. Normal dystrophin immunostaining and complete deficiency of the sarcoglycans suggest mutations in one of the sarcogycan genes as being causative. All sarcogycans are usually absent in β- and δ-sarcoglycanopathies. In adhalinopathy (α-sarcoglycanopathy), α-sarcoglycan (adhalin) is most reduced and there is selective preservation of γ-sarcoglycan, while in γ-sarcoglycanopathy, α-sarcoglycan is most reduced with variable preservation of other sarcoglycans. Nevertheless, no immunostaining pattern is specific enough to identify which of the four sarcoglycan genes may be involved. Muscle biopsy shows decreased staining for α-dystroglycan in the five phenotypes of LGMD associated with defective glycosylation of α-dystroglycan (*Table 374.2*: LGMD2I, LGMD2K, LGMD2L, LGMD2M, LGM2N). There is also decreased molecular weight of α-dystroglycan on Western blot studies. Laminin-α2 (merosin) staining may also be deficient.

Protein analysis of LGMD2A (calpainopathy) needs to be interpreted with caution since sensitivity and specificity for both immunostaining and Western blot analysis are reduced. Deficiency of calpain-3 on immunostaining is seen in LGMD2A (calpainopathy) as well as in many types of LGMD as a secondary effect. In LGMD2B (dysferlinopathy), immunohistochemistry of muscles reveals absence of dysferlin, but partial deficiency has been observed in some cases.

Differential Diagnosis

Careful clinical assessment and raised serum CK help to limit the differential diagnosis of LGMDs. However, SCARMD phenotype, especially in males, is usually mistaken for Duchenne MD (*Fig. 374.5f*). Becker MD may also be mistaken for the milder forms of LGMDs. Type III spinal muscular atrophy (Kugelberg–Welander disease) and subacute or chronic polymyositis may on occasions need to be considered as differential diagnoses. Metabolic myopathies, such as glycogenosis, can give a clinical picture that resembles LGMD.

Treatment

No specific treatment is available for any of the LGMDs. As detailed previously for Duchenne and Becker MDs, a team approach is needed to provide supportive care, prevent and correct skeletal abnormalities, manage cardiopulmonary complications, and maximize functional ability. In LGMD1B (laminopathy), cardiac arrythmias can be a major cause of morbidity and mortality due to sudden cardiac death, and placement of a pacemaker may be life-saving.

Clinical trials of steroids in LGMDs have not been reported yet. However, a beneficial effect of steroids on LGMD2D (adhalinopathy, α-sarcoglycanopathy) and LGMD2I (fukutin-related proteinopathy) has been reported.

Experimental gene transfer has been tried in sarcoglycanopathies and in calpainopathy using non-viral and viral vectors (adenovirus and adeno-associated virus). More recently, human clinical trials have begun in human sarcoglycan deficiencies. The possibility of restoring muscle function by cell therapy, using stem cells or early precursor cells capable of regenerating damaged tissue, has been studied in sarcoglycanopathies and in dysferlinopathies.

Prognosis

The development of cardiomyopathy, cardiac arrhythmia, pulmonary insufficiency, joint contractures, and scoliosis are the major operating factors regarding mortality. These are dictated by the specific genetic mutation, as outlined previously (see section "Clinical Manifestations" above).

Prevention

Genetic counseling helps affected families regarding future pregnancies. Prenatal diagnosis for pregnancies at

increased risk is possible for some types of LGMD through chorionic villus sampling (at about 10–12 weeks of gestation) or amniocentesis (at about 15–18 weeks' gestation). Prior knowledge of the disease-causing alleles in an affected family member is required before performing this test. Preimplantation genetic diagnosis is available for families in which the disease-causing mutation has been identified.

Facioscapulohumeral Muscular Dystrophy

Definition

Facioscapulohumeral muscular dystrophy (FSHD) is characterized by progressive weakness and wasting with a facioscapulohumeral distribution due to an autosomal dominantly inherited muscular dystrophy.

Epidemiology

The estimated prevalence of FSHD is between 4 and 10 per 100,000 population, and the disease is the third most common muscular dystrophy. A molecular genetics-based epidemiological study in central Italy found a prevalence of 4.6 per 100,000.

Pathogenesis

Facioscapulohumeral muscular dystrophy (FSHD) is inherited as autosomal dominant. In 70–90% of affected individuals, the disease-causing deletion is inherited from a parent and 10–30% has the disease as a result of de novo deletion. Approximately half of the de novo FSHD cases result from mosaicism, and mosaic males are more susceptible to FSHD than mosaic females.

About 95% of individuals with FSHD have a contraction mutation of the repeat sequence of the D4Z4 locus in the subtelomeric region of chromosome 4q35. However, as of 2009, no causative FSHD-specific transcription has been identified from the D4Z4 locus or the 4q35 region. In unaffected individuals, both D4Z4 alleles have 11–100 repeat units, whereas in affected individuals, one D4Z4 allele is contracted to between 1 and 10 repeat units, and the other D4Z4 allele is normal (11–100 repeat units). Recently, specific sequence variations within the 4q35 region were found to be associated with FSHD. Haplotypes (i.e., different combinations of single nucleotide polymorphisms [SNPs] at one locus that are inherited together) telomeric to the D4Z4 locus, designated 4A and 4B, contribute to the pathogenicity of a contracted D4Z4 mutant allele. Whereas contractions of the D4Z4 allele on the haplotype designated 4A161 cause FSHD, other contractions on the haplotype designated 4A166 and 4B are nonpathogenic.

Clinical Manifestations

The usual presentation of FSHD is between the first and third decades. However, the age of onset is variable and rare infantile cases have been described. More than 90% of affected individuals show clinical features by age 20 years. Disease manifestation is higher in males; asymptomatic cases are more common in females. Severe infantile FSHD present with weakness at birth, whereas some individuals remain asymptomatic throughout their lives.

Shoulder weakness is the most common initial finding and is the presenting symptom in more than 82% of patients. Weak scapular fixation results in scapular winging and its upward movement when attempting to flex or abduct the arms (*Fig. 374.6a*). Some individuals have facial weakness before the onset of shoulder weakness. Facial affection presents with inability to purse the lips, bury the eyelashes when attempting to close the eyelids tightly, or turn up the corners of the mouth when smiling, resulting in a transverse smile. Extraocular and pharyngeal muscles are spared.

The biceps and triceps muscles are selectively involved, while the deltoids remain minimally affected until late in the disease. The contrast between the atrophic upper arm and the spared forearm muscles gives the appearance of "Popeye arms." Abdominal muscle weakness results in exaggerated lumbar lordosis and protuberance of the abdomen. Lower abdominal muscles are weaker than upper abdominal muscles, resulting in upward displacement of the umbilicus upon flexion of the neck in supine position (Beevor sign).

The legs are variably involved, but tibialis anterior muscle weakness is characteristic and posterior muscles of the leg are spared, resulting in foot drop. Tendon jerks are often diminished, whereas sensation is preserved.

Slow and continuous progression of the disease is usual, although a fluctuating course with periods of disease inactivity followed by periods of rapid deterioration is described by many patients. About 20% of affected individuals become wheelchair-bound.

Reported extraocular manifestations in patients with FSHD include high-tone sensorineural hearing loss in about 60%, atrial arrhythmias in 50%, and restrictive

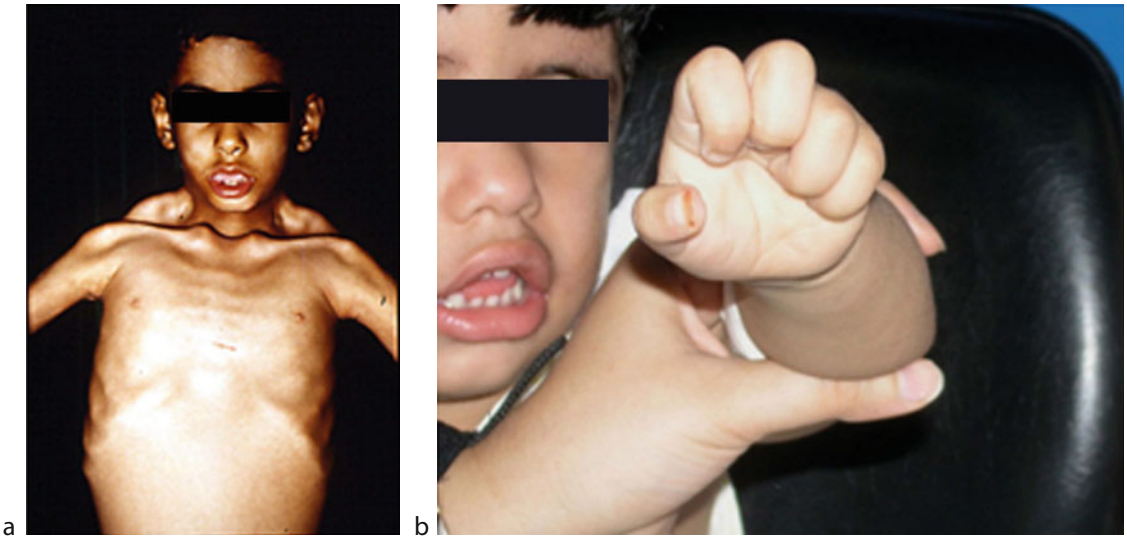

Figure 374.6
(a) Upward lifting of scapula in fascioscapulohumeral muscular dystrophy when abducting the arms. Note the facial weakness, open mouth and atrophic upper arm muscles. (Courtesy of the late Dr. Awad H. Mahdi). (b) Grip test in myotonic dystrophy (dystrophia myotonica). After contraction of the fist, the patient is unable to relax the muscles of the hand. Note the myopathic face and open mouth

respiratory disease in 1%. Ocular manifestations include retinal telangiectasia and micro aneurysms, seen in 40–60%, usually without affecting vision, and Coats syndrome (retinal vasculopathy with telangiectasia, exudation, and retinal detachment). Mental retardation and epilepsy have been reported in early-onset FSHD, often with associated deafness and retinopathy.

Clinical variants of FSHD in individuals with a contraction mutation of the D4Z4 locus in the subtelomeric region of chromosome 4q35 include scapulohumeral dystrophy with facial sparing, and FSHD with chronic progressive external opthalmoplegia (reported in one kindred).

Diagnosis

Serum Creatine Kinase (CK) is normal or mildly raised (three to five times the upper limit of normal), and CK level over 1,500 IU/L suggests an alternative diagnosis. Electromyography usually shows mild myopathic changes.

Muscle biopsy is indicated in suspected cases of FSHD, in whom molecular genetic testing was not confirmed. Nonspecific chronic myopathic changes are the most common pathological features, and mononuclear inflammatory reaction is present in up to 40% of muscle biopsies. The intensity of the inflammatory reactions may, on rare occasions, suggest an inflammatory myopathy. Molecular genetic testing is the preferred method to confirm the diagnosis.

Differential Diagnosis

Certain neuromuscular disorders may simulate FSHD but can be differentiated by their specific clinical features and distinct muscle histopathology. These include congenital myopathies, polymyositis, and mitochondrial myopathies. Scapuloperoneal muscular dystrophy syndromes and myotonic dystrophy (types 1 and 2) with mild facial weakness may be challenging to differentiate from FSHD. Definitive exclusion of these two conditions can be done by molecular genetic testing.

Treatment

Currently, no definitive therapy is available for FSHD. General care should include the use of lubricants to prevent exposure keratitis in individuals who sleep with their eyes partially open. Aerobic training may improve exercise performance. Assessment and surveillance of sensorineural hearing loss, and evaluation for the need for assistive

devices are important components of management. Ankle/foot orthosis can improve mobility. Surgical fixation of the scapula to the chest wall (scapulopexy) often improves range of motion of the arms. Surveillance of retinal telangiectasia is crucial, and retinal photocoagulation may prevent serious consequences of Coats syndrome.

Prognosis

The size of the DNA deletion affects disease severity and prognosis. Individuals with a large contraction of the D4Z4 locus tend to have earlier-onset disease and more rapid progression than those with smaller contractions of the D4Z4 locus. On average, de novo mutations are associated with larger contraction mutations of D4Z4. Nevertheless, life expectancy is normal in most patients with FSHD.

Prevention

Prenatal testing is available for pregnancies at 50% risk of FSHD by analysis of DNA extracted from chorionic villus sampling at approximately 10–12 weeks of gestation or from fetal cells obtained by amniocentesis (at approximately 15–18 weeks' gestation). Since FSHD does not usually affect the life span, prenatal diagnosis for the purpose of pregnancy termination should be discussed with the concerned family within its ethical perspective.

Myotonic Dystrophy

Definition/Classification

Myotonic dystrophy (dystrophia myotonica, DM) comprises a group of dominantly inherited, multisystem diseases that share the common features of myotonia, weakness, and early onset cataracts. Classic DM (first described by Steinert and called Steinert's disease or myotonic dystrophy type 1 [DM1]) was identified to be associated with the presence of an abnormal expansion of CTG trinucleotide repeat on chromosome 19q13.3 (the DM1 locus). A similar but distinct and less common disorder was found to be caused by alterations in a different gene on chromosome 3q21, and was designated as myotonic dystrophy type 2 (DM2).

Epidemiology

Myotonic dystrophy has an estimated prevalence ranging between 5 and 20 per 100,000. Higher prevalence has been reported from certain regions around the world including Sanquenay-Lac St. Jean region of Quebec, Canada (162 per 100,000), Istria region of Croatia, Basque region of Spain and Norbotten in North Sweden. In a population survey in the eastern province of Saudi Arabia, the prevalence of myotonic dystrophy was recorded to be 88 per million population. Myotonic dystrophy type 1 (DM1) has been rarely reported in sub-Saharan Africa, Australia, Southern China, Thailand, and the Pacific Islands. The proportions of myotonic dystrophy caused by DM1 and DM2 are unknown. A higher prevalence of DM2 was observed in Germany and Poland in individuals of German or Polish descent.

Pathogenesis

Myotonic dystrophy type 1 (DM1) is caused by expansion of a CTG trinucleotide repeat in the dystrophia myotonica protein kinase (*DMPK*) gene on chromosome 19q13.3. The disease is inherited as autosomal dominant, and in most cases, the mother is the affected parent because the gene is less stable in the maternal DNA of the ovum than in the paternal contribution in the sperm. Normal individuals have 5–30 CTG trinucleotide repeats in leukocyte DNA, whereas patients with DM1 have a wide range of CTG repeat sizes, with more severely affected individual having repeat sizes in the thousands.

One of the characteristics features of DM1 is the phenomenon of anticipation, which is defined as the earlier onset of more severe clinical manifestations in offspring of affected individuals. This is due to the progressive increase in the size of the CTG repeats in successive generations in the eggs of the female and the sperm of the males who carry the DM1 mutation. The CTG repeat enlargement occurs to a greater degree in the eggs than in the sperm of affected individuals, and explains the almost exclusive restriction of cases of congenital MD1 to offspring of mothers with DM1.

The molecular pathomechanism leading to the manifestations of DM1 is likely to result from a toxic effect of the abnormally expanded RNA that accumulates in the target tissues. These include the insulin receptor and the muscle-specific chloride channels and lead to insulin resistance and myotonia, respectively. Other sequela of expanded RNA is inhibition of myoblast differentiation, leading to muscle maturational arrest, impairment of muscle regeneration, and an aberrant alternative splicing of a number of genes in the cortical neurons leading to mental retardation.

Myotonic dystrophy type 2 (DM2), which is a disease of adult life, results from an unstable four nucleotide

repeat expansion, CCTG, in intron 1 of the zinc finger protein 9 (*CNBP*) gene on chromosome 3q21.

Pathology

The muscle biopsy in congenital myotonic dystrophy (DM1) shows true maturational arrest with myoblasts, myotubes, mature myofibers, and histochemically undifferentiated myofibers within the same fascicles. There is persistent fetal expression of vimentin and desmin intermediate filaments. Occasionally in congenital DM1, muscle fiber – type disproportion is observed, and manifests as uniform smallness and more than 80% predominance of type 1 fibers.

Clinical Manifestations

Onset of the congenital form of myotonic dystrophy (DM1) is prenatal. Polyhydramnios is present in about half of the cases because of inadequate fetal swallowing of amniotic fluid. Breech and premature deliveries are frequent. Congenital contractures manifest at birth and range from simple equinovarus deformities to arthrogryposis multiplex congenita involving the lower limbs more than the upper limbs. Hypotonia, weakness, and facial diplegia are the most striking features. Pharyngeal weakness and dysphagia are common and usually necessitate gavage feeding and eventually gastrostomy. Respiratory insufficiency due to diaphragmatic and intercostal muscles weakness occurs in about half of the patients. A hemidiaphragm may be nonfunctional. Apnea is common, and neonatal or early infancy death is frequent. Other commonly seen features include undescended testis of male infants, poor peristalsis due to smooth muscle involvement leading to abnormal distension, and cholelithiasis or cholestasis due to poor muscle function of the gall bladder. Endocrine abnormalities may include insulin resistance, and involvement of the thyroid and adrenal medulla. The resulting abnormal regulation of blood sugar requires special vigilance for the development of hypoglycemia. Congenital cataracts are frequent and electrocardiographic (ECG) abnormalities are found in a minority, usually in the form of conduction defects rather than cardiomyopathy. Affected babies do not develop seizures unless secondary to intrapartum asphyxia. Almost all of the less severely affected patients who survive the neonatal period develop mental impairment.

The clinical presentation of myotonic dystrophy type 1 (DM1) is variable, and varieties may occur in the same kindred. Myotonia is demonstrated by percussion of the thenar muscle or tongue, the thumb remaining opposed, the tongue being dimpled for several second, after percussion of its side using a triangular hammer. Ocular myotonia is elicited by having the patient shut the eyes tightly for seconds, and then ask to suddenly open them. The orbicularis oculi remains closed before slowly opening. Grip myotonia is elicited by shaking hands or having the patient squeeze the examiner's fingers, and then asking to suddenly let go. After contraction of the fist, the patient is unable to relax the muscle of the hand (*Fig. 374.6b*).

There is selective distribution of muscle weakness and atrophy, which begins in the face and involves the masseters and temporal muscles, giving the phenotype of long thin face and hollowed temporal fossae. There is also facial diplegia with tent-shaped upper lip, open mouth, and mild ptosis. Involvement of the limbs includes wasting of the brachioradialis and the muscles of the anterior compartment of the leg. When atrophy is visible before 20 years of age, it is likely to be progressive, and severe distal weakness becomes established by middle adult life. Smooth muscle involvement leads to decreased gastric motility and chronic constipation. Cataracts are usually not seen before 8–10 years of age and may occur in isolation in asymptomatic DM1.

Patients with DM1 who present in the second and third decades usually develop progressive dysarthria, gastric regurgitation, difficulty swallowing, insulin resistance, hypogonadism, deficient release of growth hormone, and cognitive and neurophysiological alterations. They also usually develop sleep apnoea, hypersomnia, decreased forced vital capacity, conduction cardiac disturbances, and other subclinical cardiac involvement manifesting as decreased myocardial Doppler velocities. Lifespan may be shortened due to respiratory failure, cardiac conduction disturbances, or pneumonitis.

Diagnosis

The diagnosis of the classical form of DM1 is usually easy. EMG shows the myotonic discharges confirming the diagnosis. However, neonatal DM1 closely simulates congenital myopathies, congenital myasthenia, and congenital muscular dystrophies. Examination of the mothers for myotonia is the best clue, and EMG is likely to show myotonic discharges. EMG of the neonate is not helpful since myotonia is not yet developed. Muscle biopsy is

indicated only when examination of the mother and the genetic marker of the disease are equivocal.

Required imaging studies for neonatal DM1 include chest and abdominal X-rays, which frequently demonstrate thin ribs and help determine the status of diaphragmatic and gastrointestinal functions. To further define diaphragmatic hemiparesis, ultrasound or fluoroscopy may be needed. Electrocardiography is important in all cases of myotonic dystrophy. A slit-lamp examination for congenital cataracts is necessary since direct ophthalmoscopy is not adequate.

Serum creatine kinase (CK) is not diagnostic and is usually normal. Endocrine studies for blood sugar, thyroid function, serum cholesterol and insulin should be arranged.

The gold standard for establishing the diagnosis of DM1 is to determine the presence of abnormal expansions of CTG repeats in 19q13.3 myotonic dystrophy type1 gene.

Treatment

Neonatal myotonic dystrophy requires prompt and multidisciplinary management regarding the respiratory and feeding requirements. Arthrogryposis requires early physiotherapy and might need surgical correction. Attention to gastrointestinal motility and cardiac function is important.

The basic approach of DM1 in later childhood is also symptomatic and required surveillance for cardiac, respiratory, and ophthalmic complications. Myotonia in DM1 is typically mild to moderate and rarely requires treatment. Anecdotal reports describe individuals who have responded to mexiletine, imipramine, or carbamazepine.

Prognosis

Infants with DM1 who have respiratory insufficiency and dysphagia have poor prognosis and most of them die early. Survivors usually have learning disabilities later in life or mental retardation. The life-threatening complications in DM1 are primarily respiratory (respiratory failure) and cardiac (heart block or other serious conduction disturbances).

Prevention

Prenatal diagnosis is available from either chorionic villus samples or amniocentesis. The analysis of DNA from these samples shows accuracy in CTG repeat size that predicts the severity of neonatal disease. Both prenatal diagnosis and preimplantation genetic diagnosis require prior confirmation of the diagnosis of DM1 by molecular genetic testing in an affected family member.

Schwartz-Jampel Syndrome

Schwartz-Jampel syndrome (SJS) is a term applied for two different autosomal recessive disorders namely, SJS type I and SJS type II. Type I SJS is a rare myotonic syndrome, which is relatively more prevalent in communities of the Middle East with high consanguinity rate. It is characterized by mask-like facies, narrow palpebral fissures (blepharophimosis), microstomia, generalized myotonia, muscular hypertrophy, osteochondro-dysplasia, and growth retardation. Type I SJS is divided into two subtypes IA and IB, which are similar. The classical type IA SJS is apparent in childhood and is less severe, whereas type IB is apparent immediately at birth and is more severe clinically.

Both types IA and IB are caused by mutations of the same gene, the *HSPG2* gene that codes for perlecan, a heparin sulfate proteoglycan, which is the major proteoglycan of the basement membranes (*Fig. 374.3*). The exact role of perlecan in the causation of myotonia in SJS is still unknown.

The diagnosis of SJS is made by the clinical features, which resemble those seen in myotonic disorders. Electromyography (EMG) typically shows the continuous and spontaneous electrical activity (dive bomber or "departing motor cycle") activity, similar to that observed in myotonic dystrophy. However, the electrical activity often lacks the waxing and waning quality seen in the latter condition. X-ray can reveal the skeletal deformities, minor elevations of serum creatine kinase and aldolase may be detected, whereas muscle biopsy is consistent with myopathy.

Morbidity in type I SJS is mainly related to the muscle stiffness, the problems with blepharospasm, and skeletal abnormalities. The disease is associated with increased risk for the development of malignant hyperthermia.

Treatment modalities include medication with anticonvulsants (e.g., phenytoin and carbamazepine) and antiarrhythmics (e.g., mexiletine), which are useful in myotonic disorders. In children, carbamazepine is a safer option.

Significant cosmetic and functional improvement of blepharospasm was reported following judicious use of BOTOX (botulinum toxin) injections. If not working,

surgical intervention may maintain a sufficiently wide-open eye. The risk of the development of malignant hyperpyrexia should always be kept in mind.

Inflammatory Myopathies

See chapter Dermatomyositis and Polymyositis "Pediatric Rheumatology section."

Ion Channel Disorders

Chloride Channel Disease: Myotonia Congenita

Myotonia congenital is a genetic disorder caused by mutations in chloride channel gene (*CLCN1*) on chromosome 7q. The disorder is transmitted as either autosomal dominant or recessive trait, and is often sporadic.

The autosomal dominant form (Thomsen disease) is often present from birth or infancy. It is characterized by painless muscle stiffness after rest and difficulty to initiate movement, which disappears following activity. The stiffness increases by exposure to cold, and many patients have generalized muscle hypertrophy as a consequence of continuous muscle contraction.

The recessive form (Becker disease) is more severe and is characterized by stiffness associated with weakness. Onset is between 3 and 12 years of age, and the disease is often progressive to age 30 years. Muscle hypertrophy may coexist with distal atrophy.

The diagnosis of myotonia congenita is established by demonstrating myotonia clinically and neurophysiologically by electromyography (EMG). Absence of type 2B fibers is found on muscle biopsy, which is rarely indicated. The condition may be associated with malignant hyperthermia, and treatment in the more severe cases may be with carbamazepine in the usual anticonvulsant dosage.

Periodic Paralyses

Definition/Classification

These are heterogeneous group of nondystrophic muscle diseases, characterized by episodes of flaccid muscle weakness, which occur at irregular intervals. Periodic paralyses can be divided into primary or secondary disorders. The primary periodic paralyses (PP) are hereditary disorders resulting from defective ion channels, which might be associated with myotonia. Most PP are associated with alteration in serum potassium level.

Epidemiology

The prevalence of hypokalemic periodic paralysis is estimated to be 1 case per 100,000 population. The frequencies of other types of periodic paralyses (PP) are not known.

Pathophysiology

Sodium channel diseases are due to various mutations in the sodium channel gene (*SCN4A*) on chromosome 17q. These include hyperkalemic PP (or HyperPP), hypokalemic PP (HypoPP2), paramyotonia congenita, and potassium-aggravated myotonia.

Calcium channel disease manifests as hypokalemic PP (HypoPP1). On the other hand, *potassium channel diseases* include Andersen–Tawil syndrome, and hyperkalemic PP or hypokalemic PP.

The physiologic basis of flaccid weakness in all of these channel disorders is inexcitability of the muscle membrane (i.e., the sarcolemma). Alteration of potassium metabolism is a result and not a principal defect in primary PP.

Clinical Manifestations

Hyperkalemic Period Paralyses

The age of onset of this group of disorders is before 10 years of age and may even occur in infancy. Attacks are often triggered by moderate exercise and last for few minutes to less than 2 h (mostly <1 h). Weakness starts in the thigh and claves, spreads to arms and neck, and myotonia is often associated with the weakness. Electrical myotonia may be detected in 50–75%, but clinically apparent myotonia is seen in $<20\%$ of patients. In children, a myotonic lid lag (lagging of upper eyelid on downward gaze) may be the earliest symptom. Triggering factors for the attacks include exposure to cold, low carbohydrate intake (fasting), and rest following exercise. Other triggering factors include infections, trauma, and emotional stress. Paresthesias and muscle pains may be reported by some patients.

Hypokalemic Periodic Paralysis

Onset is usually between 5 and 16 years, but mild cases may present as late as the third decade. The intensity and extent of weakness are very variable and range from slight transient weakness of an isolated muscle group to severe generalized weakness. Severe attacks commonly begin in the morning and are often precipitated by meals rich in carbohydrate or by exercise following rest. Exposure to cold may also be a trigger. Other reported precipitating factors include Chinese food, lack of sleep and fatigue, fever and upper respiratory tract infections, and change in the barometric pressure or humidity. Weakness affects proximal limb muscles in some patients, and is generalized in others, facial muscles are rarely affected, whereas extraocular and respiratory muscles are not involved. Because of intracellular accumulation of water in muscles, urinary output is decreased. Hypertrophy of the calves has been observed in some patients. The age of onset is earlier in the calcium channel disease HypoPP1 (10 years) compared with the sodium channel disease HypoPP2 (16 years). The duration of symptoms is longer in HypoPP1 (20 h) compared to that seen in patients with HypoPP2 (1 h). About 70% of patients with HypoPP1 develop fixed proximal weakness, but this does not occur in HypoPP2.

Potassium-Aggravated Myotonia

This rare autosomal dominantly inherited disorder resembles Thomsen disease (the dominant form of myotonia congenita). The myotonia is aggravated by potassium intake and cold exposure, and muscle weakness is not a significant feature. It has been divided into three categories, namely, myotonia fluctuans, myotonia permanens, and acetazolamide-responsive myotonia congenita (MC). Stiffness and muscle pain due to myotonia are episodic in myotonia fluctuans and acetazolamide-responsive MC, but are continuous in myotonia permanens.

Paramyotonia Congenita

This is a dominantly inherited sodium channel disease characterized by myotonia, which is present from infancy and involves especially the eyelids, facial muscles, hand muscles, and sometimes the pharyngeal muscles. Myotonia worsens with activity (paradoxical myotonia), cold temperatures, and potassium loading, but in some patients, lowering of the serum potassium may precipitate the attacks. Many patients also experience episodes of weakness, which usually last for a few minutes, but may last for days. Patients may also develop muscular atrophy. Pathologically, the condition has been associated with absence of type 2B fibers.

Andersen–Tawil Syndrome

This is a potassium channel disorder, which is characterized by the triad of dysmorphic features, periodic paralysis, and cardiac arrhythmias. The periodic paralysis, which is not associated with myotonia, may be spontaneous but usually follows physical activity, and lasts for a few hours to several days. The dysmorphic features include hypertelorism, micrognathia, low-set ears, and clinodactyly of the fifth finger. Patients also have short stature and scoliosis. The most common cardiac manifestations are prolonged QT interval and ventricular arrhythmias.

Secondary Periodic Paralyses

Secondary hypokalemic periodic paralyses are mainly caused by urinary or gastrointestinal losses of potassium. Urinary potassium wasting occurs in hyperaldosteronism, Bartter syndrome, Conn syndrome, Licorice intoxication, renal tubular acidosis, amphotericin B therapy, and thiazide treatment. Gastrointestinal potassium wasting occurs with severe diarrhea and vomiting, and draining intestinal fistulae. Hypokalemic periodic paralysis is often associated with hyperthyroidism in Oriental patients, but this occurs rarely in Western countries.

Secondary hyperkalemic periodic paralysis may result from potassium load, therapy with potassium-sparing diuretics, chronic renal failure, ileostomy with tight stoma, Addison disease, and hyporeninemic hypoaldosteronism.

Diagnosis

The diagnosis of hypokalemic periodic paralysis can be suspected from the characteristics of the paralysis and family history. Although serum potassium may be as low as 1.5 mmol/L, it is often only slightly lowered. A random urine potassium-creatinine ratio of less than 1.5 indicates poor intake, gastrointestinal loss, and potassium shift into the cells. Serum creatine kinase (CK) is raised during the attacks. Electrocardiographic (ECG) changes include bradycardia, prolonged PR and QT intervals, and flattening of T waves.

The diagnosis of hyperkalemic periodic paralysis (PP) may be confirmed by demonstration of ECG changes, such as peaked T waves, and the finding of elevated potassium concentration (to as high as 5–6 mmol/L). Serum sodium level may fall as potassium level rises, and increase in CK level may also occur at the end of an attack.

Electrophysiologic studies reveal declining of the compound muscle action potential (CMAP) amplitude during the paralytic attack more often in hypokalemic PP. In hyperkalemic PP, repetitive nerve stimulation may show progressive decrement in CMAP (accentuated by cooling) without tendency to recover as in myasthenia gravis. The presence of myotonia on electromyography (EMG) excludes the diagnosis of hypokalemic PP. Myotonia is often associated with the weakness in hyperkalemic PP, and no abnormality is detectable between attacks.

Differential Diagnosis

The differential diagnosis of periodic paralyses (PP) includes peripheral neuropathy of acute onset, such as Guillain-Barre syndrome and porphyria. The presence of sensory level and sphincter involvement help to differentiate myelopathy (due to transverse myelitis, cord abscess, trauma or ischemia) from periodic paralyses. The finding of ptosis and extraocular muscle involvement helps exclude myasthenia gravis and Lambert–Eaton syndrome (which is rare in children).

Treatment and Prevention

Treatment of acute attacks of hypokalemic PP, in patients with normal renal function, is by oral potassium chloride administration in a dose of 5–10 g, which may be repeated. Intravenous potassium is reserved for cardiac arrhythmia, accessory respiratory muscle paralysis, or airway compromise due to ictal dysphagia. Both acetazolamide and dichlorphenamide can be used as prophylaxis against the attacks. Potassium-sparing diuretics (triamterene and spironolactone) are used as second-line drugs in those who do not respond to carbonic anhydrase inhibitors.

In hyperkalemic periodic paralyses, the attacks are usually mild and rarely require treatment. Weakness responds well to high-carbohydrate foods and also to beta-adrenergic stimulants, such as salbutamol (contraindicated in patients with cardiac arrhythmias). Treatment of severe attacks includes administration of glucose and insulin, with continuous ECG monitoring. Prevention is by avoidance of cold and by administration of thiazide diuretics and carbonic anhydrase inhibitors.

Treatment of paramyotonia congenita is aimed at reducing myotonia since weakness is uncommon. Mexiletine has been shown to be helpful in this respect. On the other hand, treatment with mexiletine or a thiazide diuretic may reduce the severity of myotonia in potassium-associated myotonia.

Combined therapy of amiodarone and acetazolamide may result in long-lasting improvement in Andersen–Tawil syndrome. Other reported effective treatments included potassium-sparing diuretics, potassium supplementation, and beta-adrenergic blockers. Cardiac defibrillator has rarely been implanted.

Hypokalemic periodic paralysis (PP) with calcium channel mutations may be associated with malignant hyperthermia susceptibility. Patients with PP undergoing surgery require to be monitored for this complication.

Metabolic Myopathies

Definition/Classification

Metabolic myopathies are a heterogeneous group of muscle disorders caused by inherited enzymatic defects, which result in skeletal muscle dysfunction. They are classified into abnormalities of glycogen, lipids, purine, or mitochondrial biochemistry. Metabolic myopathies due to abnormalities of glycogen are referred to as glycogen storage diseases (or glycogenosis). They are named by Roman numerals that correlate to the time of their discovery, according to their defective enzyme function, or by an eponym. For example, Pompe disease, due to acid maltase deficiency, is glycogenosis type II. McArdle disease, due to muscle phosphorylase deficiency, is termed glycogenosis type V.

Etiology

Metabolic myopathies are caused by inability of muscle fibers to maintain adequate energy and adenosine triphosphate (ATP) concentrations.

Epidemiology

Due to difficulties in diagnosis and application of diagnostic techniques to large populations, the exact incidence and prevalence of metabolic myopathies are uncertain. Pompe disease (glycogenosis type II, acid maltase deficiency) is seen in about 1 in 40,000 population, whereas McArdle disease

(glycogenosis type V, muscle phosphorylase deficiency) affects approximately 1 of 100,000 people.

Compiling recent epidemiologic studies, the incidence of mitochondrial diseases is at least 1 in 5,000 live births. However, the gene frequency of the various types varies between different populations.

Pathogenesis

The energy demands of exercising muscle require a sustained supply of adenosine triphosphate (ATP), which is obtained through glycogen and lipid metabolism, and from phosphocreatine stores and mitochondria. Glycogen is the main form of stored carbohydrate in the muscle, and is degraded to glucose to provide the needed energy for muscle during exercise. Disturbances in either the synthesis or the degradation of glycogen result in glycogenosis (or glycogen storage disease). The genetics and enzyme deficiencies of the common glycogenoses, which present as metabolic myopathies are detailed in *Table 374.3*.

Mitochondria, which convert fuel from food into ATP, have two membranes that define four compartments. These consist of the outer membrane, the inner membrane, the intermediate space between the inner and outer membranes, and the mitochondrial matrix consisting of the region defined by the inner membrane.

During sustained exercise or fasting, long-chain fatty acids constitute the major source of energy. Their passage through the mitochondrial membrane for beta-oxidation requires binding with carnitine, which is mainly synthesized in the liver and is actively transported into the muscle. This binding to carnitine by acylcarnitine transferases, such as carnitine palmitoyltransferase I (CPT I), occurs in the outer mitochondrial membrane. Through the action of acylcarnitine translocase, the resulting new compound passes through the inner mitochondrial membrane. Carnitine palmitoyltransferase II (CPT II) splits this transferred compound to free fatty acids and carnitine, within the mitochondrial matrix where the beta-oxidation of the long-chain fatty acids is then carried out. Myopathic carnitine deficiency is attributed to impairment in the active transportation of carnitine from the plasma into muscle cells. On the other hand, impaired hepatic biosynthesis and/or excessive renal excretion of carnitine leads to systemic carnitine deficiency. Two carnitine palmitoyltransferase (CPT) enzymes are essential in the transport of long-chain fatty acids from the cytosol to the mitochondria. These are CPT I and CPT II. The more common deficiency of CP II is inherited as autosomal recessive, and the gene is located on chromosome 1p32.

During anaerobic exercise, ATP is replenished through the reaction of myoadenylate deaminase enzyme, which catalyzes transformation of adenosine monophosphate (AMP) to inosine monophosphate (IMP) and ammonia.

Apart from enzymes for the beta-oxidation of fatty acids, other enzymes within the mitochondrial matrix include enzymes for the Krebs cycle (tricarboxylic acid cycle), the pyruvate dehydrogenase complex, and the peptidases plus chaperonins necessary for mitochondrial protein import and oxidative phosphorylation enzyme assembly. Pyruvate carboxylase is a biotin-dependent mitochondrial enzyme, which catalyzes the conversion of pyruvate, the glycolytic end-product, to oxaloacetate (an important component of the Krebs cycle). It is inherited as autosomal recessive, and the gene has been localized to chromosome 11q13. On the other hand, pyruvate dehydrogenase is a multienzyme complex, which controls the entry of pyruvate into mitochondria for oxidative metabolism.

Mitochondria are involved in various pathways of metabolism, including the generation of cellular energy through the respiratory chain, disposal of potentially toxic ammonia, removal and production of reactive oxygen species, and programmed cell death (apoptosis). The most

Table 374.3
Genetics and enzyme deficiencies of the common muscle glycogenoses

Type (eponym)	Inheritance (gene location)	Deficient enzyme
Glycogenosis type II (Pompe disease)	Autosomal recessive (17q23)	Acid maltase
Glycogenosis type V (McArdle disease)	Autosomal recessive (11q13)	Muscle phosphorylase
Glycogenosis type VII (Tarui disease)	Autosomal recessive (12q13.3)	Phosphofructokinase
Glycogenosis IX	X-linked recessive (Xq13)	Phosphoglycerate kinase
Glycogenosis X	Autosomal recessive (7p12–pl3)	Phosphoglycerate mutase
Glycogenosis XI	Autosomal recessive (11p15.4) (Isoenzyme LDH-M on chromosome 11; LDH-H on chromosome 12)	Lactate dehydrogenase (LDH)

critical mitochondrial function is oxidative phosphorylation (OXPHOS), which results in the synthesis of ATP from adenosine diphosphate (ADP) and inorganic phosphate. This entails transformation of energy derived from metabolism of nutrients to the synthesis of ATP in the presence of oxygen. The respiratory chain, or OXPHOS, is the terminal step for energy production after metabolic substrates have undergone glycolysis and fatty acid oxidation, and then entered the Krebs cycle (tricarboxylic acid cycle), which produces residual metabolites ($NADH_2$, $FADH_2$). The system of OXPHOS includes five large multienzyme complexes, designated complexes I through IV and ATP synthase (Complex V). These enzyme complexes are composed of many different proteins encoded by either nuclear or mitochondrial genes.

The mitochondrion is the only organelle other than the nucleus, which contains DNA. The mitochondrial DNA (mtDNA) codes for 13 polypeptide subunits of the OXPHOS enzymes with the remaining 70 subunits encoded by the nuclear DNA. Apart from the 13 genes coding for the protein subunits of the respiratory chain complex, human mtDNA encodes 22 transfer RNA (tRNA) genes, and 2 ribosomal RNA (rRNA) genes.

The term "mitochondrial diseases" usually refers to primary disorders of mitochondrial metabolism affecting oxidative phosphorylation (OXPHOS). These diseases can be caused by mutations of nuclear or mtDNA. Nuclear DNA mutations are transmitted by autosomal recessive, autosomal dominant, X-linked, or rarely isodisomy mechanisms. Mitochondrial DNA (mtDNA) defects are transmitted by maternal inheritance. At birth, each human cell contains thousands of copies of mtDNA, which are usually all identical (homoplasmy). Individuals with mtDNA mutations may harbor a mixture of mutant and wild-type mtDNA within each cell (heteroplasmy). The proportion of mutant mtDNA must exceed a critical threshold level before a cell expresses a biochemical abnormality of the respiratory chain (the threshold effect).

Nuclear DNA mutations decrease mitochondrial coenzyme Q10 (CoQ10) levels, which leads to OXPHOS impairment. On the other hand, CoQ10 impairs the flow of electrons from complexes I and II to complex III resulting in reduced ATP synthesis.

Pathology

In the infantile form of acid maltase deficiency (Pompe disease, glycogenosis type II), there is massive accumulation of glycogen in liver, heart, and skeletal muscles. In juvenile acid maltase deficiency, glycogen excess in muscle is relatively less marked, and is little or absent in liver and heart. On muscle biopsy, glycogen storage is demonstrated with a classical vacuolar appearance. The vacuoles contain PAS-positive material and stain intensely for acid phosphatase (one of the lysosomal enzymes) (*Fig. 374.7a*). On electron microscopy, glycogen is shown to be mainly contained within single membrane-limited lysosomal sacs.

In lipid metabolic disorders, muscle histochemistry shows an increase in the number of lipid droplets, mainly in type I muscle fibers, with minimal or no increase of mitochondria on electron microscopy.

Histochemistry of muscle biopsy in mitochondrial diseases may show proliferation of subsarcolemmal and intermyofibrillar mitochondria with myofibril degeneration,

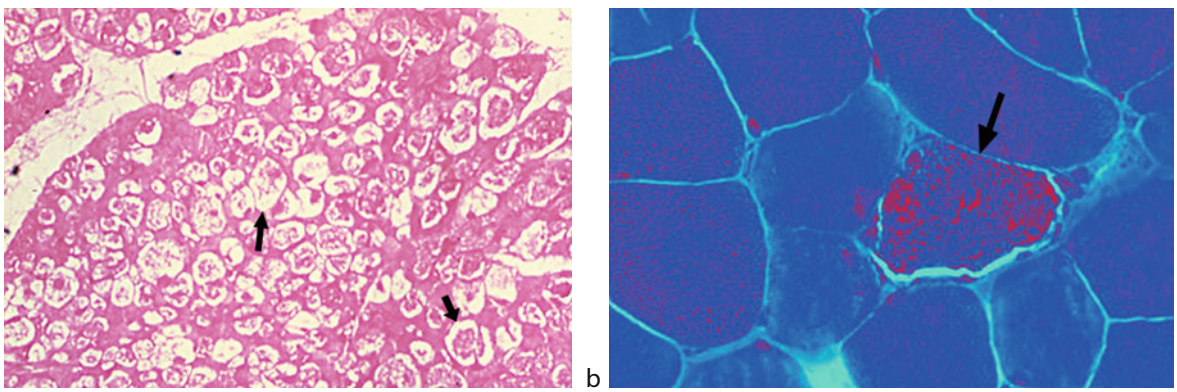

Figure 374.7

(a) Classical vacuolar appearance of muscle (arrows) in a case of glycogenosis type II (Pompe disease). (b) Ragged-red fibre (arrow) in a 13-year-old boy with Kearns-Sayre syndrome. Note the deposits of the red material representing mitochondria mainly in the subsarcolemma of the muscle fibre

giving the characteristic ragged-red fibers detected by Gomori-Trichrome staining (*Fig. 374.7b*). The percentage of ragged-red fibers may range from 2% to 70% of the total fibers, and they also have mild accumulations of glycogen and neutral lipid.

Staining with succinate dehydrogenase (SDH) also shows mitochondrial proliferation (ragged-blue fibers), whereas staining for cytochrome c oxidase (COX) usually shows that ragged-red fibers are Cox-negative. The number of COX-negative fibers is frequently larger than the number of ragged-red fibers. However, in patients with the syndrome of mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), ragged-red fibers are usually COX-positive. Blood vessels characteristically show an increased succinate dehydrogenase reaction. Nevertheless, in many individuals, the muscle histology is normal or shows nonspecific changes but does not usually display dystrophic features in the form of increased connective tissue or significant muscle fiber necrosis.

Clinical Manifestations

Glycogen Storage Diseases (Glycogenoses)

The classic infantile acid maltase deficiency presents before 12 months and is fatal by 2 years of age. The condition presents as "floppy infant syndrome" with hypotonia and weak bulky muscles. There is also macroglossia, cardiomegaly and congestive heart failure, and hepatomegaly. Death is usually caused by cardiorespiratory failure. Another form of the disease is the nonclassic infantile acid maltase deficiency, which is similar, but milder than the classic type.

The onset of juvenile acid maltase deficiency ranges from 2 to 18 years. It presents with delayed motor milestones and weakness, which is usually greater in the proximal than in distal muscles. Rarely, the tongue and liver are enlarged, and enlargement of calf muscles may occur. There is usually no cardiac involvement but respiratory muscles are selectively involved and lead to death from respiratory failure, usually in the second decade of life. Some patients may live longer than 20 years, and the condition has been reported to be associated with basilar aneurysm, which may lead to subarachnoid hemorrhage.

McArdle disease (glycogenosis type V, myophosphorylase deficiency) is a pure myopathy, which usually presents in childhood or early adolescence. The disease is characterized by exercise intolerance and cramps, but the patients are able to continue with their activities after 10 minutes of exercise (i.e., second-wind phenomenon). Rhabdomyolysis and myoglobinuria occur in 50%, and in older patients, mild muscle weakness is common.

Exercise intolerance and myoglobinuria also characterize glycogenoses types VII, IX, X, and XI (*Table 374.3*). Patients with types VII, X, and XI glycogenoses have normal muscle strength whereas those with glycogenoses IX develop slowly progressive weakness. Other clinical features include the presence of mild hemolytic anemia in glycogenosis VII, and seizure and mental retardation in one form of glycogenosis type IX.

Disorders of Lipid Metabolism

Primary muscle carnitine deficiency manifests during childhood or early adult life. It is characterized by proximal limb weakness, exertional myalgia, or rarely, myoglobinuria. Systemic carnitine deficiency can produce muscle symptoms or episodes of hepatic and cerebral dysfunction precipitated by fasting or sustained exercise, often simulating Reye syndrome. Cardiomyopathy and congestive heart failure, which are common, may be the direct cause of death.

Carnitine palmitoyl transferase (*CPT*) deficiencies are mostly associated with intermittent manifestations following fasting conditions or prolonged effort. The onset of disease is usually in late childhood or adolescence with myalgia and fatiguability. Severe cramps are not observed, whereas myoglobinuria is common. The severity of the disease is variable, partial deficiencies may be observed, and respiratory muscles may be involved. Permanent weakness is rarely observed, and fatal rhabdomyolysis may occur. Deficiencies of CPT I or CPT II may cause a rare but severe fatal disease in the neonatal period or early infancy. CPT I deficiency has been identified in a few patients who presented with episodes of severe hypoglycemia without ketonemia triggered by fasting or intercurrent illness. CPT II may manifest in infancy with hypoketotic hypoglycemia, lethargy, seizure, hepatomegaly and hepatic failure, and coma.

Abnormality of purine metabolism secondary to *myoadenylate deaminase* deficiency is a familial trait. Deficiency of myoadenylate deaminase has been found in muscle samples of patients with infantile hypotonia, with progressive myopathies of childhood onset, and in asymptomatic individuals.

Mitochondrial Diseases

Mitochondrial diseases might present at any age, usually involve multiple organ systems and often present with

prominent neurologic and myopathic features. The ubiquitous presence of mitochondria in all cells is likely to be responsible for the various organ dysfunctions. Also, the proportion of abnormal mitochondria can vary widely from one tissue to another, thus accounting for different presentations of the same defect. As a generalization, nuclear DNA abnormalities present in childhood and mtDNA abnormalities (either primary or secondary to a nuclear DNA abnormality) presented in late childhood or adult life.

Although there is often considerable clinical variability, many patients manifest a cluster of clinical features that fall into a discrete clinical syndrome. The primary and additional features of these syndromes are summarized in *Table 374.4*.

Diagnosis

The definitive diagnosis of all types of glycogenosis depends on the demonstration of glycogen storage by muscle biopsy (see section "Pathology" above) and the reduction or absence of the corresponding enzyme in muscle.

Table 374.4
Mitochondrial diseases: clinical syndromes

Syndrome	Clinical features
Chronic progressive external ophthalmoplegia (CPEO)	Onset in adolescence or adult life
	Bilateral ptosis, progressive external ophthalmoplegia (PEO), mild proximal myopathy
Kearn-Sayre syndrome	Infantile, childhood or adolescent onset
	Primary features include PEO, pigmentary retinopathy, and one of either raised cerebrospinal fluid (CSF) protein (>1 g/L), heartblock, or cerebellar ataxia. Other features include myopathy, bilateral deafness, dysphagia, hypoparathyroidism, diabetes mellitus, and dementia
Leigh disease (Subacute necrotizing encephalopathy)	Infantile onset of subacute relapsing encephalopathy, associated with cerebellar and brainstem signs
	Basal ganglia lucencies on cranial computed tomography (CT) scan
	Bilateral hyperintense signals on T2-weighted magnetic resonance images (MRI) in the basal ganglia, thalamus, brainstem, or cerebellum
Infantile myopathy and lactic acidosis (fatal and nonfatal forms)	Present in the first year with hypotonia, and feeding and respiratory difficulties
	Cardiomyopathy and/or the de Toni-Debri-Fanconi syndrome is associated with the fatal form of the disease
Pearson syndrome	Childhood sideroblastic anemia, pancytopenia, and exocrine pancreatic failure. Additional features include renal tubular defects
Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS)	Stroke-like episodes, seizures, cerebellar ataxia, recurrent migraines, hearing loss, diabetes mellitus, pigmentary retinopathy, short stature, cognitive impairment, and cardiomyopathy (initially hypertrophic; later dilated)
	Ragged-red fibers on muscle histochemistry and/or lactic acidosis
Neurogenic weakness with ataxia and retinitis pigmentosa (NARP)	Onset in late-childhood or adulthood of peripheral neuropathy, ataxia, and pigmentary retinopathy
	Findings include features of sensorimotor neuropathy, abnormal electroretinogram, and basal ganglia lucencies
Myoclonic epilepsy with ragged-red fibers (MERRF)	Progressive myoclonic epilepsy, mitochondrial myopathy with ragged-red fibers, ataxia, hearing loss, optic atrophy, peripheral neuropathy, spasticity, multiple lipomata, and slowly progressive dementia
Leber hereditary optic neuropathy (LHON)	Onset is usually in adolescence or early childhood, but may be quite variable even in the same kinship. Males are more affected than females (ratio of about 4:1)
	Characterized by subacute painless bilateral visual failure
	Associated neurological features may include ataxia, dystonia, paraplegia, and cardiac pre-excitation syndromes

Creatine kinase (CK) is elevated in 95% of patients with acid maltase deficiency (Pompe disease, glycogenosis type II), being highest in the infantile form (usually ten times the upper normal limit). The liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are raised in most patients but may be normal in the adult form. Electrocardiography (ECG) and echocardiographic abnormalities are most common in the infantile form, and giant QRS complexes and very short PR interval are suggestive features. Marked thickening of the interventricular septum and posterior left ventricular wall is seen on echocardiography, associated with trabecular hypertrophy and left ventricular outflow obstruction (see Fig. 368.1e of Chap. 368, "Approach to Diagnosis and Treatment of a Child with Motor Unit Diseases"). Selective atrophy and fatty changes of the hamstrings and paraspinal muscles are useful diagnostic findings when using CT or preferably MRI. Biochemical analysis of enzyme activity can be performed on dried blood spots (DBS), muscle tissue, lymphocytes, or skin fibroblasts. If the enzyme was found to be reduced on DBS, confirmatory assay in cultured skin fibroblasts is required.

The diagnosis of McArdle disease is confirmed by the ischemic exercise test and by muscle biopsy. Increase in serum venous lactate, which is normally greater than 2 mmol/L, fails to develop and cramps may occur during the ischemic exercise test. About 90% of patients have increased levels of CK, and elevated potassium level during exercise may be seen in some. Definitive diagnosis requires the biochemical demonstration of decreased myophosphorylase activity in muscle.

Plasma, liver, and muscle carnitine levels are reduced in systemic carnitine deficiency. In myopathic carnitine deficiency, carnitine level is reduced in muscle, but is normal or slightly decreased in plasma and liver. Plasma carnitine level may be increased in CPT I deficiency, but is usually normal in CPT II. Definitive diagnosis of CPT deficiency requires the biochemical demonstration of marked decrease or complete absence of enzyme activity in the muscle, or by identification of the genetic defect.

Mitochondrial disorders should be considered in the differential diagnosis of any progressive multisystem disorder. Clinical tests, which are used to support the diagnosis of mitochondrial disease include measurement of serum lactate and pyruvate. Fasting blood lactate concentration above 3.0 mmol/L, cerebrospinal fluid (CSF) lactate concentration above 1.5 mmol/L, or increased lactate/pyruvate ration (normal less than 20) in blood or CSF supports a diagnosis of mitochondrial disease.

Normal plasma or CSF lactate concentration does not exclude the presence of mitochondrial disease. Elevated fasting glucose may indicate diabetes mellitus.

Cardiac involvement in the form of cardiomyopathy or atrioventricular conduction defects can be investigated by electrocardiography and echocardiography.

Electroencephalography (EEG) may reveal generalized slow wave activity in patients with encephalopathy, and focal or generalized spike and wave discharges in those with seizures. In patients with limb weakness, nerve conduction studies may be normal, or show axonal sensorimotor polyneuropathy. Electromyography (EMG) is usually normal but may show myopathic features. An abnormal electroretinogram is seen in mitochondrial diseases associated with retinal degeneration.

Neuroimaging is helpful in mitochondrial diseases. Both cranial CT and MRI can depict suggestive features, as detailed in *Table 374.4*. Cerebellar atrophy is a prominent feature in pediatric cases of mitochondrial diseases. Brain MRI may also reveal generalized leukoencephalopathy, and brain magnetic resonance spectroscopy (MRS) may reveal elevated lactate peaks.

Specific tests require a muscle biopsy, which is analyzed for histochemical evidence of mitochondrial disease (see section "Pathology" above). Studies on respiratory chain complex are carried out on skeletal muscle or skin fibroblasts, but require a laboratory with special expertise.

An important cause of mitochondrial diseases, which is amenable to treatment is due to coenzyme Q10 deficiency. Phenotypes associated with CoQ10 deficiency include isolated myopathy, Leigh syndrome, severe infantile multisystemic disease with nephrosis and cardiomyopathy; cerebellar ataxia with cerebellar atrophy syndromes (including patients with aprataxin gene mutations); and recurrent myoglobinuria, mental retardation, ataxia, seizures, and ragged-red fiber myopathy. Muscle coenzyme Q10 (CoQ10) quantitation on serum or cultured fibroblasts is essential to diagnose its deficiency.

Quantitative mtDNA analysis is important for diagnosing mtDNA depletion diseases, and direct sequencing of nuclear genes or mtDNA is available in specialized laboratories.

Differential Diagnosis

Infantile acid maltase deficiency presents as "floppy infant syndrome," but has associated cardiac features, which will guide the diagnosis. The juvenile form of acid maltase deficiency, and myopathies due to glycogenoses and lipid storage disorders, may simulate Becker muscular

dystrophy, limb-girdle muscular dystrophy, or polymyositis. Exercise-induced muscle cramps and myoglobinuria are important differentiating clinical features.

Mitochondrial syndromes with ptosis and external ophthalmoplegia may be confused with congenital myasthenic syndromes or myasthenia gravis. However, in mitochondrial disorders, the ocular manifestations are fixed and do not worsen as the day progresses. Mitochondrial diseases associated with white matter abnormalities might also mimic leukodystrophies. Other causes of lactic acidosis should also be kept in mind since elevated blood and CSF lactate can be seen following a seizure or ischemic stroke.

Treatment

A multidisciplinary team including a neurologist, genetic counselor, cardiologist, pulmonologist, metabolic disease specialist, and physical therapist is required for the management of acid maltase deficiency (Pompe disease, glycogenosis type II). A high protein diet (25–30% protein) combined with physical training was found to help in decreasing glycogen deposition. Enzyme replacement therapy with intravenous recombinant acid alpha-glucosidase (rhGAA, Myozyme) is effective in the infantile form of acid maltase deficiency by prolonging survival, and improving motor development and cardiac function. Myozyme is administered as 20 mg/kg infusion biweekly. Side effects include anaphylactic reactions and fever.

A diet high in complex carbohydrates (65%) and low in fat (20%), low-dose creatine (60 g/kg/day), and regular aerobic dynamic exercise at low or moderate intensities were found to be effective and useful in McArdle disease.

Management of carnitine palmitoyltransferase deficiency consists mainly of avoidance of fasting and prolonged exercise. A high-carbohydrate low-fat diet and frequent small meals may reduce the frequency of attacks.

Management of mitochondrial diseases should also be multidisciplinary because many of the phenotypes display multiorgan involvement. In an attempt to increase mitochondrial ATP and decrease free radical production in OXPHOS diseases, several metabolic therapies are used. Those with the best data supporting a therapeutic benefit include coenzyme Q10 (CoQ10), creatine monohydrate, folinic acid, and L-arginine.

Clinical and metabolic improvement with low-dose CoQ10 (30–300 mg/day) administration was reported in a number of OXPHOS diseases. Patients with CoQ10 deficiencies can show significant responses to CoQ10 treatment. High-dose therapies are preferred because of difficulties in achieving appropriate tissue levels of CoQ10. The recommended dose in children is 4.3 mg/kg/day in 2 divided oral doses. Creatine monohydrate, given at dosages of 0.1–0.2 mg/kg/day and divided into two or three dosages, was reported to improve cycle ergometry in children with mitochondrial disease.

Secondary cerebral folate deficiency can be associated with certain groups of mitochondrial diseases, and it manifests as leukoencephalopathy and seizures. Dramatic improvement of these symptoms was reported following treatment with folinic acid or 5-methyltetrahydrofolate.

Patients with MELAS may be prone to stroke due to reduced nitric oxide levels in cerebral vasculature. Supplementation with oral L-arginine in a dose of 0.5 g/kg/day may increase the nitric oxide levels and reduce the risk of stroke. Patients with complex I and/or complex II deficiency may benefit from oral administration of riboflavin.

Additional treatment considerations for patients with mitochondrial diseases include management of diabetes mellitus, cardiac pacing, ptosis correction, intraocular lens replacement for cataracts, cochlear implants for hearing loss, and liver or cardiac transplantation when other organs are likely to be spared.

The role of exercise therapy in mitochondrial myopathies is currently being evaluated since aerobic training not only protected patients against deconditioning but also improved their exercise capacity.

Prevention

In acid maltase deficiency (Pompe disease, glycogenosis type II), prenatal diagnosis is possible on trophoblasts or amniotic cells.

Decompensation in patients with mitochondrial diseases may be prevented by avoiding exposure to agents known to induce mitochondrial dysfunction. These include antiretroviral drugs (e.g., zidovudine); haloperidol, chlorpromazine, and thioridazine (which lead to complex I inhibition); cylclosporin (complex V inhibition); nonsteroidal anti-inflammatory drugs like aspirin and diclofenac (OXPHOS uncoupling); and chloramphenicol and aminoglycosides (impaired mitochondrial protein synthesis). Of paramount importance is to avoid the use of valproate for managing epileptic seizures, which is the first recognized symptom in about 53% of patients with mitochondrial encephalomyopathies. Valproate is known to induce reactive oxygen species generation, impair fatty acid oxidation, worsen disease

activity in patients with MELAS, and induce liver failure in patients with mitochondrial diseases.

Prenatal testing is possible in families with mitochondrial disease due to nuclear DNA mutation. For mtDNA disorders, interpretation of prenatal genetic testing is difficult because of mtDNA heteroplasmy. The percentage of mutant mtDNA in a chorionic villus sample may not reflect that found in other fetal tissues. Preimplantation genetic diagnosis (PIGD) may be available for families in which the disease-causing mutation has been identified in an affected family member.

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Online Resources

clinicaltials.gov

genetests.org

treat-nmd.eu

375 Parainfectious and Autoimmune Disorders

Tanuja Chitnis

General Approach

In this section, we have focused on immune-mediated demyelinating diseases, including ADEM, multiple sclerosis, and neuromyelitis optica. In each section, we have provided a brief overview, epidemiology, pathophysiology, clinical presentation, and definitions, as well as diagnostic evaluation, differential diagnosis, treatment, and outcomes (◉ *Fig. 375.1*).

Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis (ADEM) is defined as a monophasic demyelinating disease associated with vaccination or a systemic viral infection, which may affect both adults and children.

Epidemiology

ADEM can occur at any age, but it is generally more prevalent in children than in adults. The mean age of presentation reported in recently published pediatric cohorts was 5–8 years. Rare cases in older adults have been reported.

A recent study conducted in San Diego County, USA, found the mean incidence of ADEM as 0.4/100,000/year among persons less than 20 years of age living in that region. ADEM was more common in the winter and spring months. Five percent of these patients had received a vaccination within 1 month prior to the ADEM event, and 93% reported signs of infection in the preceding 21 days. A similar study conducted in Germany found the incidence of reported pediatric ADEM patients, defined using the International Pediatric MS Study Group criteria, to be 0.07/100,000 persons under the age of 16 years. There was a threefold increased incidence in patients under the age of 10 years, compared to those 10–15 years old. In contrast, the mean incidence of multiple sclerosis (MS) in persons under the age of 16 years in this study was 0.3/100,000. Some regional cases of ADEM are linked to specific vaccines, including the Semple rabies vaccine, small pox vaccine, and older forms of the measles vaccine. In both the San Diego and German studies, there was no gender predominance in ADEM cases. However, a male predominance has been described in other pediatric ADEM cohorts, with reported F:M ratios of 0.4, 0.6, and 0.8. These results contrast to the 2:1 female preponderance frequently described for postpubertal onset MS.

Pathophysiology

Postinfectious forms of ADEM typically begin within 2–21 days after an infectious event; however, longer intervals have also been described. Viral infections commonly associated with ADEM include influenza virus, enterovirus, measles, mumps, rubella, varicella-zoster, Epstein-Barr virus, cytomegalovirus, herpes simplex virus, hepatitis A, and coxsackievirus. Bacterial triggers include *Mycoplasma pneumoniae*, *Borrelia burgdorferi*, *Leptospira*, and beta-hemolytic *Streptococcus*. Acute hemorrhagic leukoencephalomyelitis (AHLE) typically follows influenza or upper respiratory infection.

The only epidemiologically and pathologically proven association between ADEM and vaccinations is with the Semple form of the antirabies vaccine. Patients with serum antibodies to myelin basic protein had a higher incidence of neurological complications. Other immunizations that have been temporally related to ADEM include hepatitis B, pertussis, diphtheria, measles, mumps, rubella, pneumococcus, varicella, influenza, Japanese encephalitis, and polio. Vaccines produced in neural tissue culture including the Semple form of the rabies and Japanese B encephalitis vaccines carry a higher risk of developing ADEM, which may be related to contamination with host animal myelin antigens. It is important to note that vaccines with historically high rates of complications are no longer in use and have been replaced by modern formulations based on recombinant proteins.

Pathologically, ADEM is characterized by perivenular infiltrates of T cells and macrophages, associated with

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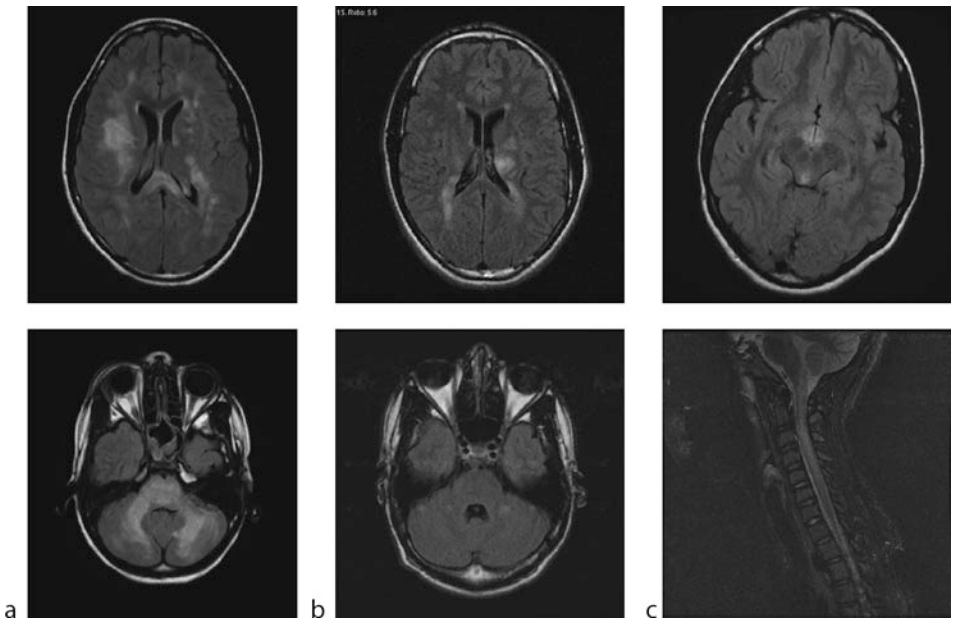

Figure 375.1

(a) Brain FLAIR image of a 13-year-old boy with ADEM. Lesions are located in the subcortical white matter and diffusely in the pons and middle cerebellar peduncles. (b) Brain FLAIR image of a 13-year-old boy with multiple sclerosis. Lesions are located in the periventricular white mater and focal lesions in the middle cerebellar peduncles. (c) Brain FLAIR image of a 14-year-old girl with neuromyelitis optica, and T2-weighted image of the spinal cord from the same patient. Lesions are located in the peri-third and peri-fourth ventricular areas. There is a longitudinally extensive lesion from the brainstem to C7

sleeves of perivenular demyelination. ADEM shares common pathological features with MS; however there are no systematic studies comparing the histopathology of these two diseases. The CNS white matter contains perivascular inflammatory infiltrates, as well as demyelination. Although ADEM is typically described as demyelination with relative preservation of axons, axonal damage confined to the perivenular area has been described. The CSF is characterized by elevated protein and white blood cells. Oligoclonal bands may occur in up to 30% of ADEM patients, and may be transient.

Acute hemorrhagic and acute necrotizing hemorrhagic leukoencephalitis (AHEM, AHL, ANHLE) of Weston Hurst shares some inflammatory histological features with ADEM; however, demyelination is often more widespread throughout the CNS and is frequently associated with a pronounced neutrophilic infiltrate. ANHLE is also characterized by destruction of small blood vessels associated with acute and multiple small hemorrhages and fibrin deposition superimposed on demyelination.

The most likely mechanism by which ADEM occurs is molecular mimicry. Experimental evidence has shown that T cells isolated from patients with ADEM are ten times more likely to react with MBP than controls, likening this disease to EAE in animal models. Because of the monophasic nature of the illness, it appears that the immunological response occurs acutely, but in contrast to MS, further amplification of inflammation within the CNS is suppressed.

Clinical Presentation

The initial symptoms and signs of ADEM usually begin within 2 days to 4 weeks after a viral infection or vaccination, and include a rapid onset of encephalopathy associated with a combination of multifocal neurological deficits, leading to hospitalization within a week. A prodromal phase with fever, malaise, headache, nausea, and vomiting may be observed shortly before the development of meningeal signs and drowsiness. The clinical course is rapidly progressive developing maximum deficits within 2–5 days.

ADEM can also present as a subtle disease, with nonspecific irritability, headache, or somnolence lasting more than 1 day. In some cases, there is rapid progression

of symptoms and signs to coma and decerebrate rigidity. Respiratory failure secondary to brainstem involvement or severe impaired consciousness occurs in 11–16% of cases.

A wide variety of neurological symptoms in children have been described at clinical presentation, according to the distribution of demyelinating lesions. Unilateral or bilateral pyramidal signs (60–95%), acute hemiplegia (76%), ataxia (18–65%), cranial nerve involvement (22–45%), visual loss due to optic neuritis (7–23%), seizures (13–35%), spinal cord involvement (24%), impairment of speech [slow, slurred, or aphasia] (5–21%), and hemiparesthesias (2–3%). Mental status is invariably involved, ranging from lethargy to coma. Seizures are mainly seen in children younger than 5 years of age, usually as prolonged focal motor seizures.

Peripheral nervous system (PNS) involvement in ADEM patients has been reported in children, while PNS involvement is observed in 16/36 (44%) adult patients.

A unique ADEM phenotype has been reported in association with group A-beta hemolytic streptococcal infection. The syndrome affected children under the age of 6, with prominent behavioral disturbances, dystonic movements, and basal ganglia abnormalities on MRI. The condition usually followed an acute pharyngitis infection and was associated with elevated antibasal ganglia antibodies.

Rarely, children may present with recurrent or multiphasic ADEM, which are defined below. These cases may be difficult to distinguish from pediatric multiple sclerosis.

ADEM Definitions

To avoid misdiagnosis and develop a uniform classification, the International Pediatric MS Study Group (Study Group) has proposed that the following three terms be applied to variations of ADEM.

1. *ADEM*: A first clinical event with a polysymptomatic encephalopathy, with acute or subacute onset, showing focal or multifocal hyperintense lesions predominantly affecting the CNS white matter; no evidence of previous destructive white matter changes should be present; and no history of a previous clinical episode with features of a demyelinating event. If a relapse takes place within 4 weeks of tapering steroid treatment or within the first 3 months from the initial event, this early relapse is considered temporally related to the same acute monophasic condition and would replace the terms "steroid-dependent ADEM" or "pseudorelapsing ADEM."
2. *Recurrent ADEM*: New demyelinating event fulfilling diagnostic criteria for ADEM, occurring at least 3 months after the initial ADEM event and at least 4 weeks after completing steroid therapy, showing the same clinical presentation and affecting the same areas on MRI as the initial ADEM episode.
3. *Multiphasic ADEM*: Refers to one or more ADEM relapses, including encephalopathy and multifocal deficits, but involving new areas of the CNS on MRI and neurologic exam. Relapses take place at least 3 months after initial ADEM attack and at least 4 weeks after completing steroid therapy.

Diagnostic Evaluation

Basic diagnostic evaluation for ADEM includes neurological examination, MRI of the brain and spine, serum and CSF testing for infections in suspicious cases, and standard CSF evaluation including cell count, bacterial and fungal cultures, and oligoclonal bands and IgG Index testing. Fundoscopic examination, visual evoke potentials, and orbital MRI should be considered in cases where optic neuritis is a concern. MRI usually demonstrates multifocal white matter lesions involving the cerebrum, brainstem, cerebellum, and spinal cord, which may or may not enhance with gadolinium. Brain lesions generally involve the subcortical and cortical white matter, and may involve cortical and deep gray matter nuclei. Several MRI patterns have been described, and include the presence of: (1) small focal punctate lesions, (2) bithalamic lesions, (3) diffuse large white matter lesions, and (4) hemorrhagic, demyelinating lesions, consistent with AHLE. Lesions generally resolve over time; however, the clinical picture may precede MRI improvement. CSF is characterized by normal pressure, moderately elevated cell count (5–100/μL), moderately elevated protein (40–100 mg/dL), and normal glucose. The presence of red blood cells may indicate a diagnosis of hemorrhagic leukoencephalitis. CSF evaluation should include testing for infections, including viral encephalitides if suspected. Oligoclonal bands may be present and have been described in up to 29% of ADEM patients, and are generally transient.

Differential Diagnosis

The association of an acute encephalopathy and disseminated demyelination of the CNS in a child represents a diagnostic challenge. A large number of inflammatory

and noninflammatory disorders may have a similar clinical and radiological presentation and should be considered in the diagnostic evaluation.

Due to the acute therapeutic implications, the exclusion of acute CNS infections should be the first and most important diagnostic step to be considered in every child with a febrile illness and neurological signs, by lumbar puncture and further microbiological laboratory tests. Serology for suspected organisms, CSF viral, fungal, and bacterial cultures, as well as CSF viral polymerase chain reaction assay for HSV, CMV, EBV, enterovirus, VZV, and West Nile should be performed. Mycoplasma serology may reveal an underlying infection. Neuroimaging may play a particularly helpful role in the differential diagnosis. A standard MRI scan of the brain and spinal cord, with and without gadolinium enhancement will be useful to define the regional distribution of demyelination and MRI lesion appearance.

Treatment

Acute episodes of ADEM should be treated with intravenous corticosteroids. The usual dose is 1 g/day of methylprednisolone for 5 days in adults and 20–30 mg/kg/day for 5 days for children up to 40 kg. Treatment with corticosteroids requires careful monitoring of blood pressure, urine glucose, serum potassium, and administration of gastric protection. Refractory cases have been treated with 5 exchanges or plasmapheresis or IVIG up to 2 g/kg distributed over 2–5 days. Cases that are suspicious for MS should be followed with annual or biannual MRI studies.

Supportive care in the acute stage is critical and early antiviral treatment with acyclovir (30 mg/kg/day) is highly recommended acutely, particularly when viral encephalitis, particularly herpes simplex encephalitis, is a consideration. Antibiotic prophylaxis for suspected bacterial meningitis may also be instituted in cases where this is a consideration.

Use of high-dose intravenous immunoglobulin (IVIG) for acute ADEM treatment has been reported in several case studies. The usual total dose of IVIG is 2 g/kg, administered over 2–5 days. IVIG may be useful in cases refractory to intravenous steroid treatment, and our policy is to start treatment 2–3 days following a 5-day steroid course. IVIG may also be useful in cases of steroid-dependent demyelination, when new or fluctuating signs and symptoms occur as corticosteroids are tapered.

The use of plasmapheresis in ADEM has been reported in a small number of severe cases, who were generally unresponsive to corticosteroid or IVIG treatment. 3–5 exchanges are generally employed, which is felt to be sufficient to reduce antibody and inflammatory factors. Moderate to severe anemia, symptomatic hypotension, hypocalcemia, and heparin-associated thrombocytopenia have been described related to TPE.

Acute hemorrhagic leukoencephalitis is often considered the most acute and severe form of ADEM, with high rate of mortality within hours to days after the onset of neurologic symptoms if untreated. Survival in pediatric patients has been reported in a small number of children receiving combined high-dose IV corticosteroid therapy, IVIG, TPE, and decompressive craniotomies. In cases of progressive deterioration due to increased uncontrolled intracranial pressure, aggressive strategies such as surgical decompression should be considered to prevent secondary injury to the brain and brainstem.

Outcomes

There is limited data regarding the natural history of ADEM. In the available case studies, there is considerable diversity with respect to antecedent infections, clinical presentation, and neuroimaging findings, further complicating outcomes analysis. Case series from Japan, India, and Russia suggest that the natural history of untreated ADEM in most children is one of gradual improvement over several weeks, with 50–70% of patients experiencing full recovery. Studies from other centers in largely treated patients demonstrate similar outcomes with 8–30% experiencing residual focal neurological deficits, and 4–30% having residual behavioral or cognitive problems. Behavioral problems were most prominent in the young-onset ADEM group with poorer visuospatial/visuomotor function, even in those with fully resolved MRIs. In most cases, the MRI appearance improves significantly; however, the continued presence of residual MRI lesions may correlate with chronic deficits.

Recovery may depend in part on antecedent infections based on serology. In a cohort of patients with detailed serology, antecedent infections included rubella (33%), varicella (29%), and unknown (22%). Seventy percent of the ADEM cases without a defined infection had a good outcome, versus 54% and 43% reported for post-varicella and post-rubella ADEM, respectively. Specific recovery times were described as approximately 3 weeks for post-rubella ADEM and up to 12 weeks for multiphasic ADEM, with intermediate but more variable recovery time in the post-varicella and unknown ADEM groups. Taken together, these reports suggest that approximately two-thirds of patients make a complete recovery.

Children who have experienced an episode of ADEM are at higher risk of developing recurrent or chronic demyelination than the general population. Some children may develop recurrent or multiphasic ADEM. While others may go on to develop MS. The distinction between recurrent or multiphasic ADEM in some instances is unclear, and our policy has been to consider chronic immunosuppressive therapy in children with more than two clinical episodes.

At present, there are no clear prognostic factors that determine whether a child who has experienced an acute demyelinating event will develop MS. Clinical studies have been hampered in part by the lack of consistent definitions used across publications, and the small numbers of subjects at any one site. In available studies, the risk of developing MS after ADEM has been reported as 0% in a study from Argentina, 9.5% in a study from San Diego, 18–29% in studies from France. Varying criteria used to define ADEM and pediatric MS, which may have contributed to the wide range of incidence among these publications.

The KIDMUS study group from France examined pediatric patients with an acute demyelinating syndrome, including clinically isolated syndromes and ADEM events, and showed that overall, 57% developed a second attack, 86% of patients with initial optic neuritis developed MS, while 50% of those with an initial brainstem syndrome developed MS. The majority of children converted to MS within a 2-year period. Overall, positive predictive factors for the development of MS were: age at onset 10 years or older or optic nerve lesion. A lower risk of developing MS was found in patients with mental status change at presentation, suggesting that the presence of encephalopathy may be a negative predictive factor. Of patients with an initial diagnosis of ADEM, 29% developed MS. In a subsequent publication by this group, when the diagnosis of ADEM was redefined by the KIDSEP study to include "change in mental status" as a qualifying criterion, 18% of children were found to develop MS, as defined by the development of a second event after a mean follow-up of 5.4 years.

Multiple Sclerosis

Epidemiology

Multiple sclerosis (MS) affects approximately 400,000 persons in the United States, with an onset predominantly in early adulthood. It is increasingly recognized that MS can present in childhood or adolescence. The youngest onset of MS in the medical literature is 2 years of age; however the majority of children are diagnosed in their early teens. Studies have estimated the prevalence of pediatric onset MS, to range from 2.7% to 10.5% of total MS populations. We have recently found that 3.06% of our adult MS population of 4,399 patients with an electronic MS history record experienced a first attack under the age of 18 years, suggesting that these patients may represent a pediatric-onset population. Recent studies have suggested that there are significant differences in ethnic and racial characteristics of children with MS as compared to an adult MS population. In our study of adults MS patients from one Center, we found a higher proportion of non-Caucasian patients in the pediatric-onset group (11.7%) when compared to an adult-onset group (6.18%; $p = 0.014$), supporting this finding. Moreover, of patients from our pediatric MS Center, 33.3% were non-Caucasian, compared to 5.5% in the comparative adult MS cohort.

Pathophysiology

There is limited data regarding the underlying immunopathophysiology of pediatric MS. There are no systematic studies comparing the immunopathophysiology of pediatric MS to adult MS, which would shed light on the similarities and differences between these two age groups. A recent study of a large cohort of children with CNS inflammatory demyelination, type I diabetes (T1D) and CNS injury demonstrated that children with CNS inflammatory demyelination, CNS injury, and T1D exhibited heightened peripheral T-cell responses to a wide array of self-antigens. Children with autoimmune diseases and CNS injury also exhibited abnormal T-cell responses against multiple cow-milk proteins. A smaller study evaluating T-cell responses to myelin basic protein (MBP) and myelin oligodendrocyte glycoprotein (MOG) epitopes in adult and pediatric MS found similar responses predominantly to MBP 83–102, 139–153, 146–162, and MOG- 1–26, 38–60, and 63–87, in both groups to the same set of peptides. Interestingly, responses to fetal-MBP were minimal, and similar in both groups. Using a tetramer approach, up to 20% of children with ADEM, but none with pediatric MS demonstrated elevations of anti-MOG antibodies.

Cerebrospinal fluid (CSF) studies have demonstrated that children younger than 11 years exhibit a distinct cellular profile in comparison to their adolescent counterparts. Younger children with their first MS event were more likely to lack OCB or elevated IgG index, and had a higher percentage of neutrophils in their CSF suggesting an activation of the innate immune response as opposed to an activation of the adaptive response in older patients.

The absence of neutrophils in the CSF was associated with an earlier second event.

Studies examining markers of axonal damage in the CSF found minimal changes in the majority of children with MS; however, a subgroup with prominent clinical symptoms at the time of CSF examination exhibited elevated levels of tau protein.

Clinical Presentation

Children with MS overwhelmingly experience a relapsing-remitting course at onset. Primary progressive MS is extremely rare. We have recently shown that children with MS experience two to three times as many relapses than adults with MS. The International Pediatric MS Study Group recently proposed new clinical criteria for pediatric MS and related demyelinating disorders; however, definitive MRI criteria for these conditions are still lacking.

Common presenting symptoms of MS in children include sensory deficits (26%), optic neuritis (21.6%), cranial nerve or brainstem symptoms (12.9%), and gait disorders (8.6%). Pediatric patients typically have a polysymptomatic presentation, although monosymptomatic presentations are not uncommon. Other features that are more common in children compared to adults with MS are encephalopathy and seizures, likely representing the overlap of acute disseminated encephalomyelitis (ADEM) and MS that is almost exclusive to children (see ADEM discussion below). In addition to physical disability, children with MS are particularly vulnerable to cognitive dysfunction. A recent cross-sectional study found that 59% of pediatric MS patients demonstrated deficits in at least one major area, and 35% were impaired in two areas. Areas that were predominantly affected were complex attention, recall, language, naming, and visual-spatial functions. Forty-nine percent reported fatigue as a major symptom. In a subset of patients who underwent psychiatric evaluation, almost half were diagnosed with depression or an anxiety disorder. These findings underline the need for routine neuropsychological testing and psychiatric evaluation as a part of the management of childhood MS. Interaction with the school system is critical in order to insure that a tailored educational program is implemented for each child.

MRI lesions in children with MS are generally located in the periventricular and subcortical white matter. It is unknown whether cortical lesions are present, and some preadolescent children with MS may present with atypical MRI patterns. Recent studies have shown that at the time of their MS defining attack, children meet adult MS McDonald MRI criteria only 67% of the time, suggesting a low lesion burden than adults at the time of diagnosis; however, a formal comparison to adults has not been performed. Few studies have formally compared the extent and distribution of lesions in children with MS compared to adults with MS. One study of 58 children with CIS and adults with RRMS found that children with CIS had fewer lesions infratentorially overall; however, in a subset of patients with brain lesions, children had higher volumes of infratentorial lesions. Another study of 4 pediatric-onset patients found a higher frequency of large confluent T2 lesions and fewer black holes in comparison to adult-onset MS. We have recently shown that children with MS demonstrate anisotropic abnormalities on diffusion tensor imaging in major white matter tracts including the corpus callosum, longitudinal association fibers, and the corticospinal tracts.

Pediatric MS Definition

The International Pediatric MS Study group proposed that for a diagnosis of pediatric MS the McDonald criteria for MS may be applied to patients under the age of 10 years, including dissemination in time by MRI. Neurological events should be separated by at least 3 months, and occur while off steroids for at least 1 month to prevent confusion with steroid-dependent relapses. The MRI must show three of the following four features: (1) nine or more white matter lesions or one gadolinium enhancing lesion, (2) three or more periventricular lesions, (3) one juxtacortical lesion, and (4) an infratentorial lesion. The combination of an abnormal CSF and two lesions on the MRI, of which one must be in the brain, can also meet dissemination in space criteria; the CSF must show either oligoclonal bands or an elevated IgG index. These definitions stipulated that an event of ADEM cannot contribute to an MS diagnosis; however, several studies have since suggested that ADEM may be the presenting feature of MS in younger children.

Diagnostic Evaluation

Evaluation of a child with suspected multiple sclerosis includes neurological examination, MRI of the brain and spine, fundoscopic examination and visual evoked potentials and potentially MRI of the orbits. CSF examination may be performed, especially in younger children, or in those with progressive or atypical presentations. Serology to rule out other mimics of multiple sclerosis should include ANA, ESR, CRP, ACE level and chest x-ray, folate,

B12 levels, and TSH. Testing for other disorders should be considered on a case-by-case basis.

Differential Diagnosis

The differential diagnosis of pediatric multiple sclerosis includes tumor, infections, vascular disorders, metabolic disorders, mitochondrial disorders, nutritional disorders, and other autoimmune disorders (Table 375.1). Patients presenting with white matter lesions should be subclassified into those with static versus progressive disorders. Patients with longstanding static white matter lesions should be closely evaluated for perinatal hypoxic ischemic injury. Determining whether the presentation is episodic or progressive is critical, since in most cases MS in children is an episodic disorder. Progressive presentations should be fully evaluated for other structural, vascular, or metabolic defects. Evaluation should include a dermatological exam to look for stigmata of neurofibromatosis, tuberous sclerosis, Lyme disease, SLE, Fabry's disease, and Behcet's

Table 375.1
Differential diagnosis of pediatric MS

Demyelinating
–Optic neuritis
–Transverse myelitis
–Devic's disease (neuromyelitis optica)
–ADEM
–AHEM
–Recurrent ADEM
–Multiphasic ADEM (MDEM)
Tumor
–Lymphoma
–Astrocytoma
–Metastasis
Immunologic
–SLE
–Anti-phospholipid syndrome
–Rheumatoid arthritis
–Post-streptococcal syndrome
–Behcet's disease
–Sarcoidosis
–Sjogren syndrome
–Wegener's granulomatosis
–Lymphomatoid granulomatosis
–Langerhan cell histiocytosis
–Hemophagocytic lymphohistiocytosis
–Hashimoto's thyroiditis
Infection
–Lyme disease
–HIV
–HSV
–HTLV-1
–PML
–Neurosyphilis
–Cat scratch disease (*B. henselae*)
–Whipple's disease
Vascular disorders
–Stroke
–AVM
–Sickle cell disease
–Moya moya
–CADASIL
–Complicated migraine
–Isolated angiitis of the CNS
–Susac's syndrome
Nutritional
–B12 deficiency
–Folate deficiency
o(Methylenetetrahydrofolate reductase deficiency)
Metabolic
–Fabry's disease
–Biotinidase deficiency
–3-Methylglutaric acid deficiency
–Neuronal ceroid lipofuscinosis
Leukodystrophy
–Adrenoleukodystrophy or adrenomyeloneuropathy
–Metachromatic leukodystrophy
–Alexander's disease
–Krabbe disease
–Pelizaeus–Merzbacher disease
–Vanishing white matter disease
Mitochondrial Disease
–MELAS
–LHON
–Leigh's disease
Degenerative
–Hereditary spastic paraparesis
–Friedrich's ataxia
–Spinocerebellar atrophy

disease. Disorders that should be considered in cases of optic neuritis include sarcoidosis, Leber's hereditary optic neuropathy (LHON), vitamin B12 deficiency, and adrenoleukodystrophy (ALD). The differential of immune-mediated transverse myelitis includes HTLV-1, ischemia, and vitamin B12 deficiency. Devic's disease (NMO) should be considered, particularly in cases associated with optic neuritis (see section below). Complicated migraine, antiphospholipid syndrome, CADASIL, and arteriovenous malformation (AVM) should be considered in cases where headache is a prominent feature. Basal ganglia lesions may suggest Leigh's disease, Wilson's disease, post-streptococcal syndromes, histiocytosis, and Moyamoya syndrome. Friedrich's ataxia and the inherited spinocerebellar ataxias should be considered in cases with predominant cerebellar deficits. In the presence of white matter lesions with a peripheral neuropathy, adrenomyeloneuropathy (AMN), Krabbe's disease, metachromatic leukodystrophy (MLD), and mitochondrial disorders should be considered.

Treatment

Acute relapse–related care for pediatric MS typically involves intravenous corticosteroids. Typical dosing is methylprednisolone 20–30 mg/kg to a maximum of 1 g daily for 3–7 days. Intravenous immune globulin (IVIG) at a dose of 0.4 g/kg/day for 5 days or plasma exchange (five to seven exchanges) are employed in refractory cases.

Beta-interferons (Avonex, Betaseron and Rebif) and glatiramer acetate (Copaxone) have been used as prophylactic therapy with reasonable success in children. Available studies have shown that both treatments are relatively safe, and the side effect profile is similar to that observed in adults. Typical side effects of the beta-interferons include post-injection flu-like symptoms and myalgias, headaches, depression, increased liver function tests, and, rarely, suppression of white blood cell counts. Side effects of glatiramer acetate include injection-site reactions, lymphadenopathy, and, rarely, immediate post-injection anxiety syndromes. Although placebo-controlled double-blind studies have not been performed in children, the majority of studies have demonstrated a reduction in relapse rate following the initiation of first-line treatments. However, some children continue to experience breakthrough disease. The definition of treatment failure is not uniform across clinicians and centers; however, evidence of ongoing relapses, MRI activity, and disability accrual may suggest switching first-line treatment or escalating to second-line therapy.

There are few studies describing the use of second-line treatments in children with MS. We conducted a retrospective study of 17 children, aged 9–18 years, treated with cyclophosphamide at either pulse or induction therapy. In the majority of cases, the relapse frequency and EDSS improved 1 year following cyclophosphamide therapy. There are several reports of natalizumab (Tysabri) treatment in adolescents with MS. Although natalizumab was effective in controlling relapse rates in these very active cases, the risks of PML and other serious side effects in children requires further assessment.

Outcomes

Several studies have demonstrated that initial disease progression is slower as measured by the EDSS scale, in patients with pediatric-onset MS (POMS) compared with geographic-region-matched patients with adult-onset MS (AOMS). Cognitive dysfunction can present early in the course of pediatric multiple sclerosis. One study of 37 children with MS found that 60% experience cognitive difficulties in one major domain and 35% have difficulties in 2 domains. The areas that were most commonly affected were complex attention, naming, delayed recall, and visual memory. In contrast, verbal fluency and immediate recall were relatively intact. Another study of 61 children found that 31% of patients exhibited significant impairment in three assessed domains of cognitive functioning and 53% failed at least two tests.

Neuromyelitis Optica

Neuromyelitis optica (NMO) or Devic's disease is a subtype of MS characterized by clinical episodes of optic neuritis and transverse myelitis, and the demonstration of contiguous lesions in the spinal cord.

Epidemiology

NMO occurs rarely in children. The current literature is limited to small series or case reports of NMO in children. The largest series from the Mayo clinic described a cohort of 88 children who were found to be seropositive for the NMO IgG antibody. Of those with available clinical information, 42 patients (73%) were non-Caucasian and 20 (34%) had African ethnicity. Median age at symptom onset was 12 years (range 4–18); 88% were girls. In another series of children with demyelinating disease,

seven to nine of those with a relapsing NMO phenotype were seropositive for the NMO antibody. In contrast, no children with relapsing-remitting MS were NMO IgG seropositive. Additional autoantibodies were detected in 57 of 75 patients (76%) and 16 of 38 (42%) had a coexisting autoimmune disorder recorded (systemic lupus erythematosus, Sjogren syndrome, juvenile rheumatoid arthritis, Graves disease).

Pathophysiology

NMO has a distinct lesion distribution compared to multiple sclerosis or ADEM, although there may be some overlap between the syndromes. NMO is characterized by optic neuritis and longitudinally extensive transverse myelitis (LETM). Lesions typical of MS are characteristically absent on brain MRI; however lesions may be present in aquaporin-4-rich areas, including the periaqueductal gray area. Pathologically, NMO is characterized by demyelination with extensive macrophage infiltration associated with large numbers of perivascular granulocytes and eosinophils and rare CD3(+) and CD8(+) T cells, as well as a pronounced perivascular deposition of immunoglobulins (mainly IgM) and complement C9neo antigen in active lesions. A serum antibody to aquaporin-4, a water channel present predominantly on the astroyctic foot processes of the blood–brain barrier (BBB), is observed in approximately 76% of those presenting with an NMO phenotype and appears to be a sensitive and specific marker of the disease. In vitro, it has been shown that NMO-IgG binds to astrocytes and alters aquaporin-4-polarized expression and increases permeability of a human BBB endothelium/astrocyte barrier. In vitro models demonstrated astrocyte killing by NMO-Ab-dependent cellular cytotoxicity and complement-dependent granulocyte attraction through the BBB model.

Clinical Presentation

NMO can present with either optic neuritis or transverse myelitis. The clinical symptoms of optic neuritis include blurred vision, pain on eye movement, and loss of color vision. Typically children may complain of eye pain and frequent eye rubbing occurs. Transverse myelitis may present with lower extremity and upper extremity weakness or numbness. Gait may be affected, and bowel or bladder retention or incontinence is common. Pain in the lower extremities and a band-like sensation around the torso may be present. Lesions in the brainstem or area postrema may result in nausea, vomiting, or hiccups. In children, an encephalopathic syndrome has been described, which may in some cases overlap with the clinical presentation of ADEM. In the Mayo clinic series, 45% of children had episodic cerebral symptoms (encephalopathy, ophthalmoparesis, ataxia, seizures, intractable vomiting, or hiccups).

Diagnostic Definition

The International Pediatric MS study group proposed the following diagnostic definition for pediatric NMO, adapted from the 2006 NMO adult criteria:

1. The presence of optic neuritis and myelitis
2. Spinal cord lesion extending over 3 or more vertebral segments or NMO antibody positive
3. Brain MRI relatively normal; exceptions with lesions in aquaporin-4-rich areas (hypothalamus, peri III, IV ventricles, corpus callosum)

Diagnostic Evaluation

Diagnostic evaluation of suspected NMO includes serum NMO IgG, testing for other autoimmune disorders including SLE (ANA, ESR), Sjogren's syndrome, rheumatoid arthritis, and autoimmune thyroid disease. In some cases, NMO IgG in the CSF may be positive in the absence of serum antibody. Standard CSF testing demonstrates elevations in WBC (5–600) with approximately equal lymphocyte and neutrophil proportions. Protein may be elevated. Oligoclonal band testing is generally negative. MRI of the brain can demonstrate lesions in the subcortical white matter, periaqueductal gray, and the hypothalamus. Spinal cord MRI typically demonstrates longitudinally extensive lesions. Optic neuritis may be diagnosed clinically but is supported with fundoscopic examination, visual evoked potential testing, and orbital MRI.

Differential Diagnosis

The differential diagnosis of NMO largely includes MS and ADEM. LHON and B12 deficiency may be considered in cases of chronic optic neuritis. ALD, HTLV-1, and ischemia should be considered for transverse myelitis presentations.

Treatment

There is no FDA-approved treatment for NMO. Intravenous steroids are typically used for acute relapses, and are administered at a dose of 20–30 mg/kg (up to 1 g/day) for a 3–5 day period. Plasmapheresis may be used as first- or second-line treatment for acute attacks, and five exchanges are administered every other day or as tolerated. NMO titers may be reduced following plasmapheresis, suggesting that the antibody is linked to relapses. IVIG (up to 2 g/kg divided into two to five doses) has been used as third-line therapy by some investigators. Prophylatic therapies used for NMO in adults include Rituximab (anti-CD20 antibody), azathioprine, mycophenolate mofetil, and mitoxantrone. The same treatments have been used in children with NMO, and one group has outlined their approach as initial immunosuppression with azathioprine or mycophenolate mofetil, while refractory cases are treated with Rituximab.

Outcomes

In adults with NMO disability can accrue after relapses; however, disease progression that occurs in MS is typically absent. It is unknown whether this applies to children. In one study of children with NMO, after resolution of the acute attacks, visual impairment persisted in 26 patients (54%) and 21 patients (44%) had residual weakness. Cognitive dysfunction in children with NMO has not been systematically studied.

Conclusion

This past decade has seen significant advances in pediatric immune–mediated demyelinating diseases. However, several outstanding questions remain, including the identification of optimal treatment and greater insight into the causes of these diseases in children. National and multinational studies are underway to address these questions and should lead to promising insights in the next 5 years.

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376 Cerebrovascular Disorders in Children

Warren Lo · Geoffrey Heyer · Steve E. Roach

Clinicians have become increasingly aware of cerebrovascular disorders in children, and the widespread application of noninvasive diagnostic studies in recent years has made diagnosis more straightforward. The general term *stroke* is used to include either ischemic brain infarction or hemorrhage into the brain parenchyma. Intracranial hemorrhage includes subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), or hemorrhage into the subdural or epidural space. By convention, an ischemic neurological deficit that resolves within 24 h is referred to as a *transient ischemic attack* (TIA). However, many of these patients have radiologic or pathologic evidence of cerebral infarction despite the rapid resolution of their symptoms.

This chapter will describe the etiology, clinical manifestations, diagnosis, and treatment of non-traumatic cerebral hemorrhage, acute ischemic infarction, and cerebral venous sinus thrombosis.

Etiology of Stroke

The occurrence of multiple strokes generally predicts a poor long-term outcome, and the identification and treatment of stroke risk factors is essential if additional strokes are to be prevented. Often, the risk factors themselves contribute to the patient's long-term outcome. Numerous risk factors for childhood stroke have been identified (*Tables 376.1* and *376.2*). Although there is considerable overlap, the conditions that promote ischemic stroke are relatively distinct from those leading to hemorrhage. If a complete assessment is done, one or more risk factors can be identified in about three quarters of the children with ischemic infarction. A likely cause can be pinpointed in most children with hemorrhagic stroke.

Causes of Hemorrhage

Congenital vascular anomalies such as arteriovenous malformations, cerebral aneurysms, and cavernous malformations are collectively the most common risk factor for nontraumatic brain hemorrhage in children. *Table 376.1* summarizes the risk factors identified from several case series. When case series were pooled, just over half of the hemorrhagic strokes were found to have occurred in children with an intracranial vascular anomaly. Other children have thrombocytopenia or coagulation defects. Hemorrhage into a brain tumor is a surprisingly common cause of hemorrhagic stroke. Typically, these children have a highly malignant tumor and present with acute signs and symptoms that are identical to those of a hemorrhagic stroke in the absence of a tumor. In contrast to adults, systemic hypertension is not a common cause of brain hemorrhage in children.

Causes of Infarction

There are too many risk factors for ischemic stroke in children to discuss them individually, but many of the common and unusual risk factors are listed in *Table 376.2*. One or more risk factors can be identified in about three fourths of the children with ischemic stroke, provided that a thorough diagnostic evaluation is performed. The most common risk factors for acute ischemic stroke in children are various forms of congenital heart disease and sickle cell disease.

Congenital or acquired heart disease accounts for about 20% of the children with ischemic stroke in most series. Complex cardiac anomalies carry the greatest stroke risk, but stroke has been documented with most cardiac lesions. Most children with stroke due to a cardiac lesion were known to have had heart disease prior to the stroke, although occasionally an obvious cardiac lesion is discovered after a stroke occurs. A right-to-left cardiac shunt may allow a venous (paradoxical) embolus to bypass the pulmonary circulation and reach the brain.

About a fourth of the individuals with sickle cell disease develop symptomatic ischemic brain infarctions, and half or more of the patients develop clinically silent ischemic lesions that are readily apparent on magnetic

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Table 376.1
Risk Factors for intraparenchymal hemorrhage in children (Modified from Biller (1994))

AVM/AVF
Cavernous malformation
Aneurysm
Brain tumor (primary or metastatic)
Hematologic/Coagulopathy
Afibrinogenemia
Disseminated intravascular coagulation
Leukemia
Sickle cell disease
Thrombocytopenia
Bone marrow transplantation
Hemophilia (Factor VIII or factor IX deficiency)
Factor VII (proconvertin) deficiency
Factor XIII (fibrin stabilizing factor) deficiency
Liver failure
Liver transplantation
Warfarin therapy
Vitamin K deficiency
Anticoagulant/thrombolytic/antiplatelet agents
Hemorrhagic infarction
Venous sinus thrombosis
Intracranial dissection
Moyamoya disease or syndrome
Miscellaneous
HIV infection
Systemic lupus erythematosus
Herpes simplex encephalitis
Angiophilic fungal organisms
Drug related (amphetamines, cocaine, etc)
Vasculitis of the cerebral arteries
Systemic hypertension

AVM = arteriovenous malformation; AVF = arteriovenous fistula
PCP = Phencyclidine.

Table 376.2
Risk factors for ischemic stroke in children (Modified with permission from Roach and Riela (1995))

Congenital Heart Disease	**Hematologic Disorders/ Coagulopathy**
Ventricular septal defect	Hemoglobinopathy
Atrial septal defect	Thrombotic thrombocytopenic purpura
Aortic stenosis	Thrombocytosis
Mitral stenosis	Polycythemia
Coarctation	Disseminated intravascular coagulation (DIC)
Cardiac rhabdomyoma	Leukemia or other neoplasm
Complex congenital heart defects	Oral contraceptives
Acquired Heart Disease	Pregnancy/postpartum period
Rheumatic heart disease	Antithrombin III deficiency
Prosthetic heart valve	Factor V Leiden mutation
Libman-Sacks endocarditis	Hyperhomocysteinemia
Infectious endocarditis	Protein S deficiency
Cardiomyopathy	Protein C deficiency
Myocarditis	Prothrombin mutation
Atrial myxoma	Lupus anticoagulant
Arrhythmia	Anticardiolipin antibodies
Systemic Vascular Disease	**Structural Anomalies**
Systemic hypertension	Arterial fibromuscular dysplasia
Volume depletion or systemic hypotension	Arterial agenesis or hypoplasia
Hypernatremia	Sturge-Weber syndrome
Diabetes	Intracranial arterial aneurysm
Vasculitis	**Trauma**
Meningitis	Fat or air embolism
Systemic infection	Foreign body embolism
Herpes simplex encephalitis	Carotid ligation (e.g., with ECMO)
Systemic lupus erythematosus	Abrupt cervical rotation
Polyarteritis nodosa	Traumatic arterial dissection
Granulomatous angiitis	Blunt cervical arterial trauma
Takayasu's arteritis	Arteriography
Rheumatoid arthritis	Carotid cavernous fistula
Dermatomyositis	Coagulation defect with minor trauma
Inflammatory bowel disease	Amniotic fluid/placental embolism
Drug abuse (cocaine, amphetamines)	**Vasospastic Disorders**
Hemolytic-uremic syndrome	Migraine
Vasculopathies	Ergot poisoning
Ehlers-Danlos type 4	Vasospasm & subarachnoid bleed
Moyamoya syndrome	
Fabry disease	
Malignant atrophic papulosis	
Pseudoxanthoma elasticum	
NADH-CoQ reductase deficiency	
Transient vasculopathy	
Williams syndrome	

resonance imaging (MRI). Vascular lesions sometimes occur in individuals with other hemoglobinopathies or in those who are heterozygous for sickle hemoglobin, although much less often than with homozygous sickle hemoglobin. Children between birth and 5 years of age have the highest risk of ischemic stroke, but stroke can occur at any age. About two thirds of the sickle cell disease

patients who survive an initial stroke go on to have additional strokes.

Arterial dissection is probably under diagnosed in children with stroke. Traumatic dissection occurs more often in adolescents and in males. However, spontaneous arterial dissection and stroke is well recognized, and the injury preceding dissection is not always severe. Fibromuscular dysplasia and other arterial abnormalities increase the risk of arterial dissection. Except for the absence of trauma, the clinical manifestations of spontaneous and traumatic arterial dissection are identical. Neurologic deficit can begin immediately after the dissection or be delayed for several hours or days.

Carotid artery occlusion after peritonsillar injury is well documented. The internal carotid artery courses behind the pharyngeal tissue and can be injured during surgery or when the child falls with an ice cream stick, toothbrush, or pencil in the mouth. The intraoral injury may not seem severe, but intimal injury leads to arterial dissection with ischemic infarction distally.

Causes of Sinovenous Thrombosis

Thrombosis of a cortical vein or dural sinus often occurs in an individual with a hypercoagulable state (*Table 376.3*). The likelihood of a venous thrombosis is greater in individuals with adjacent infections such as chronic otitis, sinusitis or orbital cellulitis. Other risk factors include hemoglobinopathy, congestive heart failure, polycythemia, and dehydration. Many individuals with sinovenous thrombosis have multiple risk factors.

Table 376.3
Risk factors for cerebral venous sinus thrombosis in children

Hematologic Disorders
Autoimmune hemolytic anemia
Paroxysmal nocturnal hemoglobinuria
Polycythemia
Thrombocytosis
Leukemia
Iron deficiency anemia
Sickle cell disease
Thalassemia
Hyperviscosity
Thrombotic thrombocytopenic purpura
Coagulation Disorders
Antithrombin deficiency
Protein C deficiency
Protein S deficiency
Homocystinuria
Activated protein C resistance with or without factor V Leiden mutation
Prothrombin gene mutation G20210A
Fibrinogen disorders
Plasminogen activator inhibitor disorders
Anticardiolipin antibodies and lupus anticoagulant
Hypercoagulable state with malignancy
Pregnancy or postpartum period
Infections
Bacterial meningitis
Mastoiditis
Ear infections
Tonsillitis
Sinusitis
Systemic Conditions
Dehydration
Congestive heart failure
Hypoxia
Post-strangulation
Diabetes mellitus
Inflammatory bowel disease
Nephrotic syndrome
Systemic lupus erythematosus
Thyrotoxicosis
Behçet's disease
Trauma
Closed head injury
Hydrocephalus or shunting
Post-lumbar puncture
Post-catheterization
Jugular and subclavian vein catheterization
Medications
L-asparaginase
Oral contraceptives
Corticosteroids
Erythropoietin

Epidemiology

Schoenberg and colleagues analyzed the number of children with stroke in Olmsted County, Minnesota, from 1965 through 1974. They identified three children with hemorrhagic stroke and one with an ischemic stroke in an at risk population of 15,834 over ten years, for an estimated annual incidence rate of 2.52/100,000 children/year for children through 14 years of age (1.89/100,000/year for hemorrhagic stroke and 0.63/100,000/year for ischemic stroke). Similarly, Broderick and colleagues found an estimated 2.7 pediatric stroke cases/100,000/year. A more recent report found a stroke risk of 13.0/100,000 children/year. Several reports suggest that stroke occurs more often in boys than in girls, even after adjusting for the increased likelihood of trauma in boys.

Data from the US National Hospital Discharge Survey from 1980 through 1998 indicate a stroke rate during the first month of life of 26.4/100,000 (hemorrhagic stroke occurred in 6.7/100,000 and ischemic stroke occurred in 17.8/100,000). Based on these numbers, stroke in neonates occur in approximately 1 per 3,000 to 4,000 live births per year.

Early incidence calculations almost certainly underestimate the risk of ischemic stroke in children, and full ascertainment continues to be problematic. The early reports antedate the widespread use of MRI. These studies typically exclude neonates, who have the highest stroke rate among children, as well as children with preceding trauma, perhaps eliminating patients with stroke due to arterial dissection. Most estimates of childhood stroke incidence analyze medical record discharge diagnoses, but these records are often incomplete and incorrect. One recent analysis, for example, found 2.4 ischemic strokes per 100,000 patient-years, a figure that is three to four times the incidence in other papers. Yet only about a fifth of these children were identified via ischemic stroke diagnosis codes in the medical records; the other cases were identified by analysis of radiographic reports and selected other diagnosis codes.

The incidence of stroke in children is somewhat of a mobile target. Surgical correction of congenital heart lesions tends to be done earlier now, reducing the time spent at highest risk for stroke. Aggressive transfusion therapy for high risk individuals with sickle cell disease has lowered the risk of ischemic stroke in these individuals. Vaccines for varicella and the common meningitis-causing organisms have all but eliminated the risk of stroke due to these infections. In contrast, the occurrence of stroke in children is now more widely known by physicians, and thus the identification of stoke in these patients has probably become more common.

The reported frequency of hemorrhagic and ischemic stroke in children varies. After the first month of life, hemorrhagic stroke accounts for 37–54% of all childhood strokes, a substantially higher proportion of hemorrhagic stroke than occurs in adults. One large population-based study found that hemorrhagic stroke accounted for 54% of non-traumatic strokes occurring after the neonatal period. Another small population-based cohort registered five children with hemorrhagic stroke and three children with ischemic stroke. Analysis of a national US administrative database indicated that hemorrhagic stroke constitutes 39% of all children with a stroke diagnosis. Together these studies suggest that hemorrhagic stroke accounts for almost half of the cases of childhood stroke.

Clinical Manifestations

The signs and symptoms of cerebrovascular disorders in older children generally resemble those of adults, but younger children tend to have more subtle and variable findings. The clinical manifestations are largely determined by the size and location of the lesion and whether the stroke is ischemic or hemorrhagic. The nature of any underlying risk factors also plays a significant role in the clinical presentation of some children.

Intracranial Hemorrhage

Classically, individuals with an ICH complain of sudden, severe headache followed by vomiting and progressive deterioration of consciousness. Seizures occur in up to a third of the children with brain hemorrhage. Children with smaller hemorrhages often have less dramatic manifestations, which are clinically indistinguishable from those of ischemic infarction. Younger children may have surprisingly few signs and symptoms even with a larger lesion, especially when the lesion does not involve the motor pathways or brainstem. The array of the focal neurological deficits due to a brain hemorrhage depends on the location of the bleeding and whether cerebral herniation has occurred.

Severe SAH is heralded by sudden, severe headache, vomiting, meningismus, and alteration of consciousness. Less severe subarachnoid bleeding may produce a less distinctive presentation, limited to unexplained

irritability, vomiting, photophobia or seizures. Location of the headache does not dependably predict the origin of the bleeding, but more severe hemorrhage is more likely to generate more impairment of consciousness. Focal or generalized seizures occur in up to a quarter of the children with SAH. Signs of increased intracranial pressure are typical, and papilledema may be found within a few hours, although it is difficult to document in an uncooperative child with photophobia.

Acute Ischemic Stroke

Acute ischemic stroke in children results from occlusion of one or more of the brain's arteries either by an embolism or by intraluminal thrombosis. Regardless of the stroke's pathophysiology, the clinical manifestations depend primarily on the size and location of the occluded artery. Most cerebral emboli in children result from cardiac lesions, while the artery to artery emboli that are common in adults with stroke due to carotid artery atherosclerosis are rare in children.

The arteries most frequently occluded by an embolus are the supraclinoid internal carotid arteries and the middle cerebral arteries, so the most common resulting clinical signs are hemiparesis, hemisensory loss, and aphasia. However, emboli to other arteries produce an array of signs or symptoms. Classically, an embolus causes sudden-onset symptoms with an almost immediate maximum deficit followed, in some individuals, by an equally dramatic resolution of the deficit as the embolism breaks apart and allows reperfusion of the tissue. However, this pattern occurs infrequently, especially in very young children, who are more likely to present with a deficit of unknown duration.

Arguably the most frequent location of acute ischemic infarction in children is the basal ganglia and thalamus. As with adults, children with small infarctions in this area develop deficits such as pure motor hemiparesis, monoparesis, or hemianesthesia. These lesions in children seldom result from chronic hypertension. Instead, basal ganglia infarctions in children often result from occlusion of the small end arteries of the region secondary to occlusion of the adjacent internal carotid artery or the middle cerebral artery. Ischemic infarction within the vertebrobasilar circulation typically presents with ataxia, depressed consciousness, or cranial nerve dysfunction.

Cerebral infarction in neonates constitutes a special subset of acute ischemic stroke in pediatrics. Affected babies most often present with focal motor seizures on the first or second day of life, although a few are identified later because of developmental delay or epileptic seizures. The majority of cerebral infarctions in neonates occur in the left cerebral hemisphere, suggesting that these lesions arise via embolism that is facilitated by the unique features of the fetal circulation. Radiographic findings suggest that some of these babies develop an infarction prior to delivery.

Transient Ischemic Attacks (TIAs)

Transient ischemic deficits are rare in children, although some of the transient deficits seen with moyamoya syndrome may arise from an artery to artery embolism. In children, TIAs sometimes result from small emboli or local hemodynamic factors, which temporarily prevent adequate perfusion. Small infarctions can sometimes be demonstrated radiographically or pathologically, even in patients whose clinical dysfunction resolved completely within a few hours.

Sinovenous Occlusion

Thrombosis of a cortical vein or dural sinus can be overlooked because the clinical findings are often less obvious than with arterial occlusion and because a sinovenous occlusion is not always apparent with routine computed tomography (CT) and MRI procedures. Focal or generalized seizures commonly occur after a cortical vein thrombosis. Dural sinus thrombosis often results in increased intracranial pressure, and visual loss may occur in individuals with severe or prolonged pressure elevations. As with acute ischemic infarction, focal neurologic dysfunction is common with sinovenous occlusion although such deficits are sometimes confused with a postictal deficit in individuals with focal seizures.

Diagnostic Evaluation

Risk Factor Evaluation

Space limitations do not allow a complete discussion of each of the many risk factors for stroke in children. Often, a likely explanation for the stroke is obvious, as in patients known to have sickle cell disease or congenital heart disease. Even in these individuals, however, there may be secondary

risk factors that contribute to the risk of recurrent stroke. Even after a thorough assessment, no obvious risk factors are identified in about a quarter of the children with ischemic stroke. However, a likely cause is identified much more often in children with intraparenchymal hemorrhage.

The initial evaluation should include simple noninvasive tests with low cost and high yield. A complete blood count may identify polycythemia, hemoglobinopathy, infections, or isoimmune thrombocytopenic purpura. Hemoglobin electrophoresis should be done on patients at risk for hemoglobinopathy if they have not been tested already. A sedimentation rate, prothrombin time (PT), and partial prothrombin time (PTT) are usually done. Tests to identify coagulation disorders are reasonable even when one or more risk factors are already known to exist. Many children have more than one risk factor, and it is often more practical and cheaper to do several studies at the same time, adding or deleting specific studies to fit the clinical situation.

Cardiac lesions are the leading cause of ischemic stroke in children, although most of the time the diagnosis is known even before the stroke occurs. Nevertheless, it is reasonable to obtain a consultation from a pediatric cardiologist, with an electrocardiogram, and a chest x-ray. Ambulatory cardiac rhythm monitoring and echocardiography are sometimes helpful, but their yield is low if the cardiac examination and earlier cardiac studies are normal. The significance of a patent foramen ovale, if any, is still being investigated.

Any child with an unexplained acute focal neurological deficit who does not have significant mass effect should undergo a lumbar puncture. Nonvascular disorders such as herpes simplex encephalitis can mimic vascular lesions, and the diagnosis may be evident only by lumbar puncture. Cerebrospinal fluid analysis is mandatory in a stroke patient with unexplained fever or signs of central nervous system infection. Chronic meningitis or early tuberculous meningitis can present with stroke; bacterial meningitis often causes stroke although not typically as the presenting sign. Syphilis serology should be done in at risk adolescents with an unexplained ischemic stroke; some reports also link human immunodeficiency virus to cerebrovascular dysfunction. Mild SAH, unapparent on CT, can be demonstrated via lumbar puncture, although a lumbar puncture is usually unnecessary when the subarachnoid bleeding is obvious radiographically.

Radiographic Evaluation

A stroke can usually be depicted by radiologic studies such as MRI and CT. These studies also enable the clinician to eliminate nonvascular conditions from consideration. Magnetic resonance angiography (MRA), CT angiography (CTA), and catheter angiography often allow one to identify the specific vessel that is responsible for the stroke and to pinpoint the cause of the vascular dysfunction.

Cranial CT or MRI should be done early in the evaluation. Cranial CT is often done first because it can be performed quickly and is widely available after hours. CT effectively demonstrates ICH and SAH (*Fig. 376.1*). Either scan will often confirm a cerebrovascular lesion and help to eliminate other diagnoses. Smaller ischemic infarctions are more reliably seen with MRI, and recent infarctions are often evident with diffusion weighted MRI before they are apparent with CT (*Fig. 376.2*). However, CT and MRI often provide complementary information.

MRA and magnetic resonance venography (MRV) provide a non-invasive way to image the intracranial vessels (*Fig. 376.3*). These studies are ideal for patients at extra risk for catheter angiography or those whose diagnosis is suspected but not definite. However, MRA is less reliable than catheter angiography especially when evaluating the smaller arteries, and one must also consider the risk to the patient should a diagnosis be missed. In experienced hands, the reliability of CT angiography approaches that of catheter angiography, and it is becoming the modality of choice for imaging the intracranial arteries.

In neonates, cranial ultrasonography can be done without sedation at the bedside without transporting a critically ill baby to an outside imaging suite. The presence of an infarction, hemorrhage, or even a vascular malformation may often be visualized on ultrasound and the age of the lesion estimated. However, ultrasonography is less precise and less reliable than either CT or MRI, and it is easy to miss lesions in the anterior or posterior regions of the hemispheres. Transcranial Doppler is also useful in certain situations.

Catheter angiography remains the most accurate imaging technique for visualizing smaller intracranial arteries and demonstrating subtle changes in larger vessels. In skilled hands, catheter angiography carries a low risk, but it is an invasive test so some complications are inevitable. For this reason, CTA or MRA are often substituted for catheter angiography despite its superior reliability.

Catheter angiography is especially important for individuals with hemorrhagic stroke because of their high frequency of congenital intracranial vascular lesions (*Fig. 376.4*) and the risk of re-bleeding from these treatable lesions.

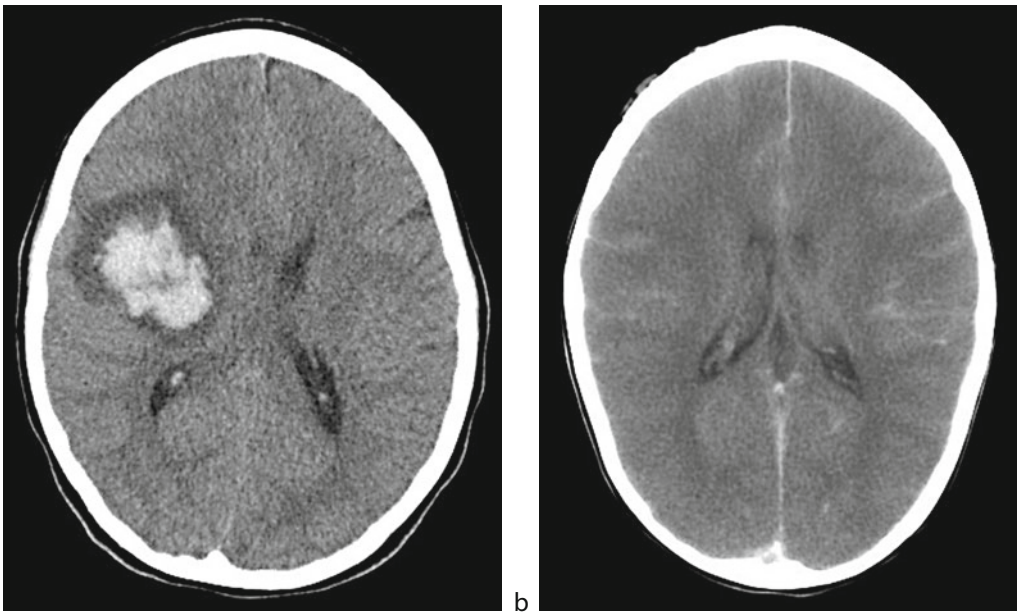

Figure 376.1
(a) Axial CT shows an intracerebral hemorrhage in the right frontal and parietal lobes with compression of the adjacent lateral ventricle. (b) Cranial CT scan shows blood filling the subarachnoid space and cerebral sulci. Diffuse cerebral edema is also evident

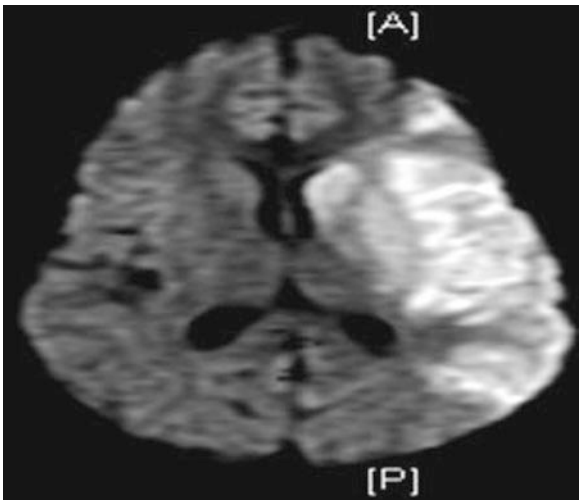

Figure 376.2
Magnetic resonance brain scan. Diffusion-weighted MRI reveals cerebral infarction in the left middle cerebral artery territory

Delayed Diagnosis of Childhood Stroke

Several studies confirm that delays in diagnosis occur at multiple stages in children with stroke. Although there is sometimes a delay in seeking medical attention, the majority of the delays occur after the child reaches medical care. Delayed diagnosis is a particular problem for ischemic stroke occurring after the neonatal period. Stroke is relatively rare in children, and acute focal deficits are relatively common with nonvascular disorders as well as with stroke. Nevertheless, failure of clinicians to appreciate that stroke occurs in children is probably responsible for many of the delays. The key to rapid, accurate diagnosis is a high index of suspicion for a diagnosis of stroke in children with acute neurological deficits. The astute clinician will suspect a stroke if a child's acute neurological deficits can be explained by ischemia or hemorrhage involving a vascular distribution of the central nervous system.

Differential Diagnosis

Any nonvascular lesion that produces acute neurological dysfunction can mimic stroke, and some vascular disorders cause gradual or intermittent loss of function. One retrospective chart review from a tertiary care children's hospital in the USA found that of 79% of 143 consecutive consultations for suspected stroke had a stroke diagnosis, but 30 children (21%) eventually were shown to have another condition that mimicked stroke, such as complicated

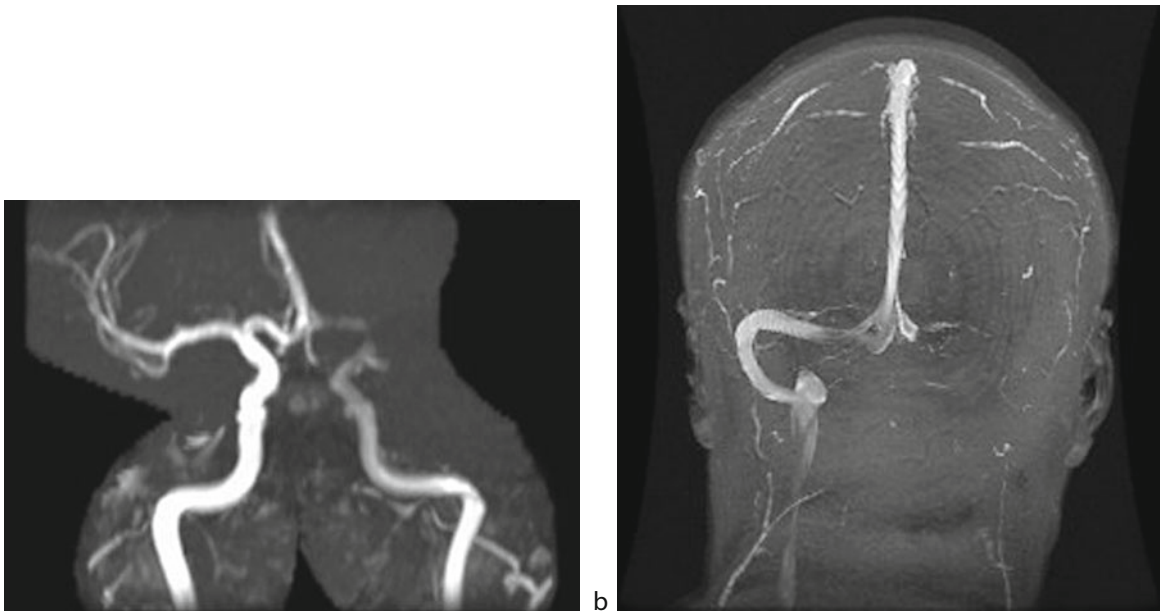

Figure 376.3
(a) Magnetic resonance angiogram shows occlusion of the left internal carotid and left middle cerebral arteries. Photograph courtesy of Dr. Khaled Zamel. (b) Magnetic resonance venogram demonstrates an occluded left transverse sinus

migraine, epilepsy, or psychogenic disorders. Moreover, cerebrovascular lesions can develop concurrently with disorders such as meningitis, abscess, and encephalitis. The diagnostic evaluation should be complete enough to eliminate nonvascular conditions and, once a cerebrovascular lesion has been identified, find its cause.

Focal intracranial infections must be considered because they sometimes cause acute neurological deficits that resemble those of stroke. Particularly important are herpes simplex encephalitis, intracerebral abscess, and tuberculoma. Cerebral infarction is a common complication in children with arteritis due to bacterial meningitis, although not usually as a presenting sign. Stroke can be the means of presentation in chronic or subacute meningitis, as in the early stages of tuberculous meningitis or even viral meningitis. Even an apparently straightforward cerebral abscess can be confusing because a common cause of abscess is a septic cardiac embolus.

A neoplasm can produce acute symptoms that mimic a vascular lesion via several mechanisms. Hemorrhage into a tumor or tumor infarction with acute edema can cause headache, focal deficits, and depressed consciousness, findings very similar to those of an ICH in the absence of a tumor. Localized compression or invasion of intracranial vascular structures can produce thrombosis and infarction,

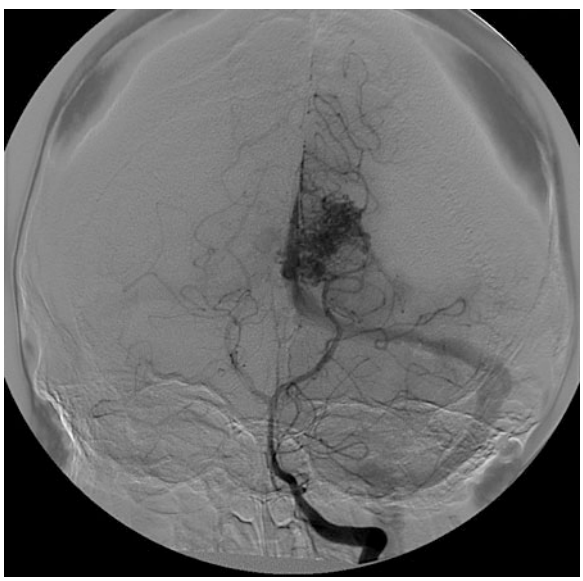

Figure 376.4
Catheter cerebral angiogram via the left vertebral artery confirms an arteriovenous malformation. Note the tangle of abnormal arteries and the early filling of the transverse sinus

so it is possible for the same individual to have both tumor and stroke. Brain herniation is another mechanism for acute deterioration due to tumor. Acute obstruction of the ventricular system by an intraventricular tumor produces sudden headache and deterioration of consciousness similar to the pattern seen with ICH or SAH.

Transient hemiplegia or other focal deficits sometimes follow protracted seizures. If the seizure is witnessed and prolonged, there is seldom any confusion about the nature of a post-ictal deficit. Prolonged focal seizures are more likely to leave a focal post-ictal deficit, but the dysfunction typically begins to improve within an hour or two after the seizure stops and has completely resolved within 24 h. Failure of a post-ictal deficit to resolve within this time frame suggests that a seizure is not the sole cause of the persisting dysfunction. Vascular occlusion or hemorrhage, for example, may cause both focal deficits and seizures, often leading to the mistaken diagnosis of a post-ictal deficit.

Treatment

General Treatment Measures

The supportive measures used in children with cerebrovascular dysfunction are the same for intracranial hemorrhage, acute ischemic stroke, and sinovenous thrombosis. The patient should be carefully monitored by an experienced staff, and clinical deterioration warrants transfer to an intensive care unit for more intensive monitoring and possible intervention. The unit should be able to monitor brain functions including intracranial pressure (ICP), and if available, cerebral blood flow and cerebral blood oxygenation. Children with a stroke are at risk for depressed consciousness, aspiration, and hypoventilation. Supportive care must insure airway protection and adequate oxygenation. While there is no current evidence that hypothermia improves outcome, fever increases cerebral metabolism; so, fever should be treated.

Elevated blood pressure should be managed with care in order not to compromise cerebral perfusion pressure. Severe elevation of blood pressure may promote re-bleeding from an aneurysm, but there is little evidence that lowering of the blood pressure reduces clot expansion with an ICH. An elevated blood pressure may reflect an effort to preserve cerebral perfusion pressure via cerebral autoregulation, and overly aggressive treatment may induce cerebral hypoperfusion. While it is clinically appropriate to treat severe hypertension, there are no data that support the lowering of blood pressure to a specific range.

Both convulsive and non-convulsive seizures increase the cerebral metabolic rate. Convulsive seizures can also increase the risk for re-bleeding from an aneurysm or arteriovenous malformation (AVM), so seizures should usually be treated and seizure prophylaxis may be considered especially in individuals with SAH.

If there is no clinical evidence for increased ICP, the patient can be observed carefully. There are multiple means to treat increased ICP, all of which have limitations. Intubation and hyperventilation to a pCO_2 of 30–35 mm Hg can reduce ICP, but the ICP effect is often temporary and excessive hyperventilation can reduce cerebral blood flow. Treatment with intravenous mannitol and hypertonic saline can reduce ICP, but these measures can complicate fluid and electrolyte management, and there is limited evidence that hyperosmolar treatment improves outcome. Ventriculostomy and cerebrospinal fluid (CSF) drainage should be performed if there is acute hydrocephalus. Intravenous sedation, neuromuscular blockade, and barbiturate coma can reduce the ICP, but can promote a range of problems including systemic hypotension, atelectasis, and pneumonia.

Therapy of Intracranial Hemorrhage

Rational therapy of hemorrhagic stroke is hampered by a paucity of randomized controlled trials from which to develop evidence-based guidelines, and such studies are nonexistent in children. The recent American Heart Association recommendations for the diagnosis and treatment of pediatric stroke reflect the sparse data but provide consensus guidelines for the treatment of hemorrhagic stroke in children. In addition to specific measures to alleviate the effects of the hemorrhage, conditions that led to the hemorrhage should be corrected whenever possible.

The management of ICH related to anticoagulation warrants special mention. Patients treated with warfarin who develop intracranial hemorrhage can be treated with intravenous vitamin K, fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa to increase levels of coagulation factors and to decrease the risk of acute recurring bleeding. Patients treated with unfractionated heparin can be treated with protamine sulfate; however, it only reverses the effect of low-molecular weight heparin by 70%. All of these measures pose some risk of thromboembolic complications.

There is little data to suggest that craniotomy improves the outcome of most patients with a supratentorial ICH. Limited data suggest some benefit for the evacuation of superficial lobar clots in patients with mild neurological deficits (GCS > = 9). Patients should undergo ICP monitoring in an intensive care unit and further clinical deterioration should be monitored with CT scans. Ventriculostomy and external drainage are helpful when hydrocephalus develops or when intraventricular hemorrhage is present. Cerebellar hemorrhage that is large (>3 cm in adults), and causes brainstem compression or hydrocephalus should be evacuated early. If a cerebellar hemorrhage is small and there is no brainstem compression, then the hemorrhage can be managed medically.

Given the frequency of congenital vascular lesions in children with brain hemorrhage and the risk of re-bleeding with these lesions, surgical obliteration or endovascular occlusion of AVMs is indicated. Partial occlusion of an AVM may make the lesion more amenable to later surgical correction. Radiotherapy may be useful for deep-seated cavernous malformations or small arteriovenous malformations. Death or poor outcome due to re-bleeding is a particular concern in patients with an aneurysm, so early intervention to occlude an aneurysm should be pursued when the patient is sufficiently stable. Calcium-channel blocking agents, such as nimodipine, may benefit vasospasm due to SAH. While there are no well-controlled studies that blood pressure control reduces re-bleeding, sustained severe hypertension should be treated without compromising cerebral perfusion to reduce the risk of re-bleeding.

Therapy of Acute Ischemic Stroke

A complete discussion of the therapeutic options for children with acute ischemic stroke is beyond the scope of this chapter, but recently published evidence-based consensus guidelines provide additional detail. Much of the therapeutic effort is aimed at secondary prevention and modification of risk factors. Early correction of congenital cardiac lesions, for example, reduces the risk of ischemic stroke. Similarly, treatment of cerebral arteritis and stroke-related metabolic conditions should diminish the risk of stroke.

Anticoagulation with warfarin or low molecular weight heparin is recommended for children thought to have a high risk of recurrent cardiogenic embolism, patients with a severe hypercoagulable state, and individuals with a cervical arterial dissection. Anticoagulation is continued for 3–6 months in patients with dissections, and until the risk diminishes in patients with cardiac disease. Anticoagulation is not recommended for an intracranial dissection because of the tendency of these individuals to develop an SAH. Detailed instructions for initiating and maintaining anticoagulation in children have been published.

Aspirin is often prescribed in children in an effort to prevent recurrent stroke following TIA or stroke. Long-term aspirin at the recommended doses (1–5 mg/kg/day) seems to be safe in children, but data about its effectiveness and optimal dosing are limited. Randomized controlled trials do not exist, and the results of cohort trials have been mixed, which is hardly surprising given the small numbers of patients studied and the variable nature of the risk factors. Despite this paucity of data, aspirin is recommended for secondary stroke prevention in children who do not require anticoagulation. Other antiplatelet agents are sometimes utilized, but information about their safety and efficacy in children is largely nonexistent.

Several case reports document the successful use of tissue plasminogen activator (tPA) in children, but additional studies are needed to confirm the safety and efficacy of thrombolytic therapy in children. While it may be reasonable to use tPA in selected older children, the appropriate dose, timing, and exclusion criteria for children have not been established.

Periodic blood transfusions limit the production of sickle hemoglobin and dramatically reduce the likelihood of stroke due to sickle cell disease, although toxicity from iron overload requires the concomitant use of a chelating agent. Chronic transfusions have long been started after the initial stroke because of the very high risk of subsequent infarctions. A controlled clinical trial showed that periodic transfusions also strikingly reduce the likelihood of an initial stroke even in high risk individuals. The current recommendation is to begin transfusions after an ischemic stroke due to sickle cell disease and in individuals with a very high stroke risk based on abnormal transcranial Doppler findings. Hydroxyurea is not as well studied but may be of use in some patients.

Therapy of Sinovenous Thrombosis

Supportive treatment of cerebral venous sinus thrombosis (CSVT) includes hydration, control of seizures, control of increased intracranial pressure, and the administration of appropriate antimicrobials to children with an adjacent infection. Very ill children require admission to an intensive care unit, and those at high risk for clinical or subclinical seizures may benefit from continuous

electroencephalographic monitoring. Discontinuation of estrogen-containing medications may reduce the risk of recurrent CVST.

Adults with cerebral venous sinus thrombosis evidently benefit from anticoagulation, even when there is an associated brain hemorrhage. The evidence for a similar improvement in children, however, is less robust. Several case reports and small case series of children suggest that anticoagulation is well tolerated. A prospective study of anticoagulants in 30 children with CVST documented 3 deaths among 8 untreated children, but no deaths among the 22 anticoagulated children. Thus, older children with or without parenchymal hemorrhage should probably be anticoagulated. Although there is little objective data to guide the duration of treatment, the most common approach is to treat patients with warfarin or low molecular weight heparin for 3–6 months. Anticoagulation is not usually recommended for neonates except for those with a severe prothrombotic disorder, progressive clinical deterioration, or radiologic evidence of clot propagation. Thrombolysis has been used successfully in a few children, but is not routinely used.

Prognosis

Arterial Ischemic Stroke

The acute mortality of arterial ischemic stroke in children is comparable to that in adults. Recent estimates of mortality following ischemic stroke in children range from 3% to 5.3%. The likelihood of ischemic stroke recurrence in children depends on the type of risk factors that are present, ranging in published series from 7% to 19%. The risk factor associated with the highest percent of recurrences was a primary abnormality of the cervical or cerebral vessels (vasculopathy). In a prospective cohort of 212 neonates and children in a British tertiary care center, 14% had a recurrent stroke, 2% died of a recurring stroke, and 20 of 103 clinically asymptomatic children had another infarction detected by neuroimaging. Low birth weight and the presence of moyamoya vasculopathy were independent predictors for recurrence in the entire group .

The eventual cognitive function following a perinatal middle cerebral artery ischemic infarction ranges from normal to severe impairment. There is no precise relationship between the size or side of the infarct with cognitive function; individuals with triplegia or quadriplegia tend to have severe cognitive impairment. The presence of seizures also increases the likelihood of cognitive impairment. Similarly, the use of seizure medication and dependence upon others for activities of daily living predicted lower levels of functioning after stroke in older children. Stroke occurring very young in life or in the teenage years is associated with a worse outcome. In one case series of 21 children, mean IQ fell within the normal range, but the patients had deficits in specific areas such as digit span, arithmetic, divided attention, and alertness. Attention deficit-hyperactivity disorder symptoms were more frequent than in the general population.

Hemorrhagic Stroke

Few studies examine the outcome after hemorrhagic stroke in detail. The existing studies are retrospective and differ in their definition of outcome and the type of outcome measures used. Nevertheless, several broad conclusions are supported by the collective reports. About 35% of children had a good outcome with little or no impairment. Approximately 30% of the patients died from the acute hemorrhage, recurrent hemorrhage, or their underlying disorder. The remaining patients were left with impairments ranging from mild to severe.

In two case series, the outcomes were examined in more detail. One study performed neuropsychological examinations of 31 survivors. No cognitive deficits were found in 15, mild or diminished cognitive function were found in 8, and 7 had moderate to severe global cognitive deficits. Another study of 26 patients found that half of the survivors had cognitive deficits and 38% had motor deficits.

Cerebral Venous Sinus Thrombosis

In one report, follow-up data were available in 143 of 160 consecutive children with cerebral venous sinus thrombosis. There were 12 deaths (8%), half of which resulted from the venous thrombosis. Seventy seven of these children (54%) were neurologically normal and 54 (38%) had some type of residual neurological deficit. Over half of these children were treated with anticoagulants; nevertheless, these numbers illustrate the serious nature of venous sinus thrombosis in children.

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377 Head Injury in Children

Daniel S. Tsze · Thomas H. Chun

Definition/Classification

A head injury can be broadly defined as an acute traumatic insult to the head by an external force. While any part of the head can be injured in this way, the focus of this chapter is injuries to the scalp, skull, brain parenchyma, and their associated anatomic structures. Acute head injuries thus covers a wide spectrum of severity, ranging from benign contusions to intracranial hemorrhage, which may result in increased intracranial pressure, brainstem herniation, and death. The term traumatic brain injury (TBI) has also been used to encompass the alteration in brain function resulting from a blunt or penetrating force to the head, manifesting as confusion, altered level of consciousness, seizure, coma, or focal sensory or motor neurologic deficit.

Head injuries can be classified in many different ways. Isolated injuries to the scalp, skull, and brain can and do occur. However, injuries to more than one structure are commonly encountered. As such, a system of classifying injuries solely on the basis of anatomic location lacks clinical utility. Similarly, classifying injuries on the basis of mechanism (e.g. "blunt vs. penetrating") fails to define head injuries in a clinically meaningful way, as each type of mechanism does not exclusively result in either an open or closed head injury. Therefore, one should not assume that a given mechanism of injury is consistently synonymous with a particular type of injury incurred. Distinguishing open from closed head injuries is another system that is commonly used. Open head injuries occur when blunt or penetrating trauma transgress the scalp and skull, exposing the brain to the external environment. By definition, all open head injuries require emergent neurosurgical consultation. With closed head injuries, on the other hand, the traumatic sequelae or the condition of the intracranial contents may not be readily apparent. Care of these patients will depend on their clinical condition and may also depend on the results of diagnostic imaging.

In summary, no single classification system captures all the relevant clinical information of head injuries. The most clinically useful method of categorizing head injuries incorporates elements of all these systems, and includes an assessment of clinical neurologic status (e.g. Glasgow Coma Scale).

Etiology & Epidemiology

Traumatic brain injuries are a global phenomenon that affects over ten million people annually. Despite the ubiquitous nature of head injuries, there are differences in incidence and etiology between countries, due to a multitude of factors.

The global rate of TBI has been reported to be as high as 193 per 100,000. Developing areas of the world have higher rates of TBI, led by Sub-Saharan Africa, Latin America and the Caribbean, and India, with rates of 359, 258, and 250 per 100,000, respectively. These numbers, however, may still underestimate the true incidence for a number of reasons. Access to health care in these countries may be challenging, resulting in milder TBI going unreported and more severe events ending in death prior to reaching a hospital. In such instances, TBIs may not be accurately recorded in the country's health statistics. Most data is also derived from urban hospital-based studies, meaning that injuries that present to primary care services or in rural areas are also neglected. Countries with lower rates of TBI include China and countries of the Middle Eastern Crescent, with reported rates of 115 and 123 per 100,000. However, these statistics may also be subject to the same limitations described earlier. Countries with established market economies (e.g. France, USA) have reported rates of 144 per 100,000.

Traumatic brain injuries cause tremendous mortality and morbidity. In high income countries such as the United States, an estimated 1.4 million TBI hospitalizations and ED visits occur each year, with 50,000 deaths amongst these events. An estimated 80,000 to 90,000 people experience permanent disability as a result of their injury. Children are heavily affected as well, as TBI is the most frequent cause of disability and death in the US. The burden of TBI is also significant in low and middle income countries. India, for example, has an estimated two million people who are injured and 200,000 who die from TBI. Specific regions have reported as many as 30% of their TBI cases to be children less than 15 years old, which account for 75% of all pediatric trauma hospitalizations and 80% of pediatric trauma deaths.

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When examining the causes of TBI worldwide, etiologies vary from country to country. Road traffic injuries (RTI) are the most common cause globally. In developing countries, RTIs account for as much as 60% of TBIs. The World Health Organization (WHO) estimates that by the year 2020, RTI will be the third leading cause of premature death amongst all age categories. The next most common mechanism of TBI is falls, which account for approximately 20–30% of TBIs. Of these fall-related TBIs, 50% of these injuries are reported in India. Ten percent of TBIs result from violence, which is more common than falls in countries like Sub-Saharan Africa, Latin America and the Caribbean. In Sub-Saharan Africa, violence and war account for 33% and 53%, respectively, of TBIs. Finally, an additional 10% of TBIs worldwide occur from a combination of work place and sports-related injuries.

In developed countries, etiology is strongly associated with socioeconomic status. In more affluent communities, TBIs are dominated by RTIs, falls, and recreational activities, with less than 10% related to violence. Areas characterized by dense population, poverty, high rates of unemployment, crime, and substance abuse report rates of TBI due to violence as high as 34%. Adolescents and young adults, males and ethnic minorities are also at increased risk of TBI due to violence and RTI.

TBI is particularly relevant to pediatric populations because the incidence of TBI is tri-modal, with peaks in early childhood, late adolescence/early adulthood, and in the elderly. Falls dominate among children as the most common cause of TBI in high income and low income countries alike, whereas RTI and violence account for the majority in adolescents and young adults. Unfortunately, the majority of these injuries occur in the poorest countries. The WHO estimates that over 98% of childhood injuries occur in these countries, with injury rates as much as five times higher than their industrialized counterparts.

Pathogenesis

When a child experiences head trauma, significant intracranial injuries (ICI) may result. Intracranial injuries are divided into primary and secondary brain injuries. Primary injuries are the mechanical damage directly caused by the traumatic event. These include penetrating foreign bodies, the brain impacting the skull interior, or shearing forces that tear white matter tracts or bridging blood vessels.

Secondary brain injury refers to the metabolic events that follow the initial insult, and damage neurons which were previously unharmed. These events include hypoxia, hypoperfusion, ischemia, and metabolic derangements. The most deleterious secondary event is brain ischemia resulting from inadequate cerebral blood flow. This can occur from vasospasm of cerebral vasculature, especially associated with subarachnoid hemorrhages, excessive extracranial bleeding causing systemic hypovolemia, or thrombosis leading to tissue infarction. Brain ischemia can be further aggravated by hyperthermia, which increases cerebral metabolism. Hyperglycemia can also hasten cerebral injury in the injured brain, as can inflammatory mediators released in response to brain injury.

An important sequelae of primary brain injury is increased intracranial pressure (ICP). The intracranial space is a fixed volume occupied by the brain, cerebrospinal and interstitial fluid, and blood. Hemorrhages, large cerebral contusions, or diffuse brain swelling can cause any of these components to increase in volume. A decrease in either one or both of the other intracranial spaces must occur to avoid increases in ICP. The main compensatory mechanism is displacement of CSF into the spinal canal, but once the limits of compensation have been reached, any subsequent increases in volume in the intracranial spaces will result in rapid increases in ICP. Increased ICP may cause compression of CSF outflow tracts resulting in ventricular dilatation and hydrocephalus, or compression of ventricular spaces due to increases in brain or blood volume. Increased ICP may also impede cerebral blood flow and perfusion, leading to ischemic damage.

The most dramatic consequence of increased ICP are cerebral herniation syndromes (Fig. 377.1), in which part of the brain is forced through an inappropriate passage or space due to increased ICP. Each syndrome is defined by the anatomic location of the herniation. The most well known syndrome is tentorial herniation, in which the uncus of the temporal lobe is forced through the space between the cerebral peduncle and the tentorium. This results in compression of the oculumotor nerve and an ipsilateral dilated nonreactive pupil; hemiparesis or decerebrate posturing from compression of the cerebral peduncle; and bradycardia, hypertension, and irregular respirations (Cushing's Triad) due to brainstem compression. Bilateral signs may occur if there are bilateral lesions or diffuse swelling. If this progression is not treated, respiratory arrest and death may ensue.

Clinical Manifestations: Symptoms, Signs

An important part of clinically assessing a child who has suffered a head injury is to determine their level of

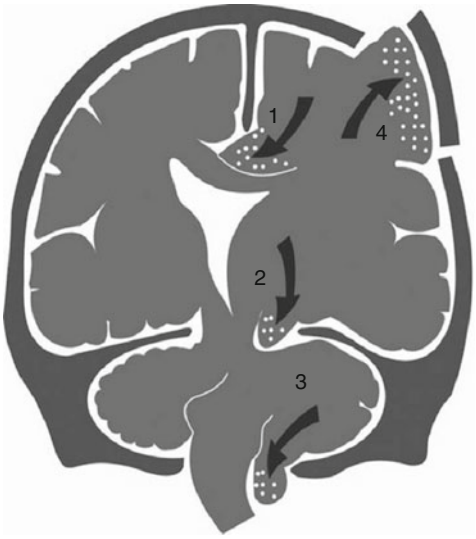


Figure 377.1
Cerebral herniation syndromes (1) Cingulate (subfalcine); (2) Uncal (transtentorial); (3) Tonsillar; (4) Transcalvarial (Dempsey and Hwang, 2010)

consciousness. The Glasgow Coma Scale (GCS) is an internationally recognized neurological scale for rating the severity of a head injury and objectively monitoring neurologic status during the acute management of head injuries. The GCS is modified for use in very young children (e.g. less than 2 years old) who may not be able to communicate and obey commands like adults (*Table 377.1*). The resulting scores, however, are still interpreted in the same manner: the lower the score, the more severe the injury. Scores of 3 to 8 indicate a severe brain injury; 9 to 12 are moderate injuries; and 13 and greater are minor injuries.

Skull fractures can be hidden beneath hair and difficult to appreciate by palpation unless severely depressed. Skull fractures may be associated with overlying soft tissue swelling or hematoma. Basilar skull fractures should be suspected if there is hemotympanum, CSF otorrhea or rhinorrhea, periorbital ecchymosis ("raccoon eyes", as shown in *Fig. 377.2*), or postauricular ecchymosis (Battle's sign, as shown in *Fig. 377.3*).

All ICIs can present with similar signs and symptoms, including headache, vomiting, irritability, focal

Table 377.1
Glasgow Coma Scale and Pediatric Glasgow Coma Scale

Score	Adult	Pediatric
Eye Opening Response		
4	Spontaneous	Spontaneous
3	Open to verbal command, speech, or shout	Open to verbal command, speech or shout
2	Opens to pain	Opens to pain
1	None	None
Verbal Response		
5	Oriented and converses	Coos or babbles (normal activity)
4	Confused, but able to answer questions	Irritable and continually cries
3	Inappropriate responses, words are discernable	Cries to pain
2	Incomprehensible speech or sounds	Moans to pain
1	None	None
Motor Response		
6	Obeys commands for movement	Spontaneous or purposeful movement
5	Purposeful movement to painful stimuli	Withdraws from touch
4	Withdraws from pain	Withdraws from pain
3	Decorticate posture, abnormal flexion	Decorticate response, abnormal flexion to pain
2	Decerebrate posture, extensor response	Decerebrate response, extension to pain
1	None	None

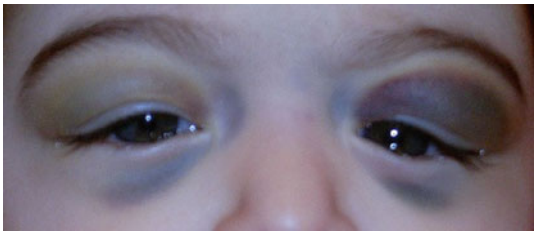


Figure 377.2
Raccoon eyes (Gumus, 2007)

neurologic symptoms, and altered level of consciousness. Seizures may occur, but are less common. Injuries resulting in cerebral herniation may present with unilateral, bilateral, or autonomic changes as described in the pathogenesis section. Posterior fossa involvement may present with cerebellar findings such as ataxia or nystagmus.

Certain features may be useful in differentiating ICI's. The classic presentation of an epidural hematoma is an initial loss of consciousness, followed by a "lucid interval" of up to several hours, and finally a deterioration in neurologic status as the expanding hematoma exerts

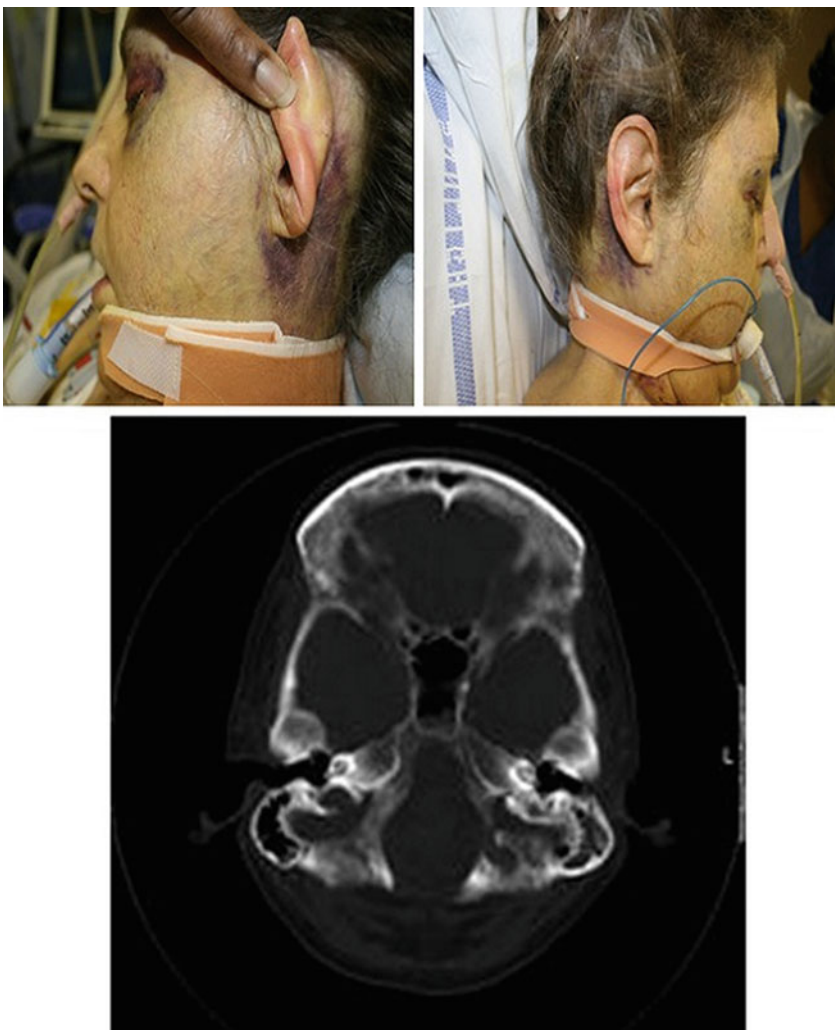


Figure 377.3
Above: Battle's sign. Below: CT scan of basilar skull fracture (from Ackland et al.) © Humana Press, 2008

a mass effect on the brain. A subarachnoid hemorrhage (SAH) may cause meningeal irritation and may thus mimic the signs and symptoms of meningitis, e.g. nuchal rigidity and photophobia. Patients with diffuse axonal injury (DAI) and cerebral contusions can present with a wide range of symptoms, from headache to loss of consciousness. Most patients with diffuse brain swelling will be comatose and continue to deteriorate with time. Signs of cerebral herniation as described previously should alert the clinician and prompt immediate intervention.

The clinical signs and symptoms of a concussion are quite varied. Loss of consciousness may or not be present. Symptoms may be somatic (e.g. headache), cognitive (e.g. feeling disoriented or clouded, slowed reaction times), or emotional (e.g. lability, irritability). Physical signs include loss of consciousness, amnesia, or sleep disturbances (e.g. drowsiness). Some people describe the experience of having a concussion as being momentarily stunned or dazed.

Seizures after a head injury may occur at three distinct points in time relative to the head injury. "Immediate" (sometimes also called "impact") seizures occur within seconds of the traumatic event. These seizures are probably the result of traumatic depolarization of the cerebral cortex. They are usually brief, self limited, generalized seizures, with a rapid return to near or full baseline neurologic functioning. While most impact seizures occur in the absence of significant ICI, one should maintain a high suspicion for such pathology if other concerning signs or symptoms are present. "Early" seizures occur within a week of the head injury, with most occurring within the first 24 h. There is usually an underlying ICI associated with early post-traumatic seizures. The occurrence of such a seizure should thus prompt an evaluation for an ICI. "Late" seizures occur more than 1 week after the head injury. Late seizures are usually due an ICI, one which is already apparent by the time that the seizure occurs. Many of these patients will have subsequent seizures, either during the course of the current injury or later in life after the acute event has resolved.

Diagnosis, Investigations

The most definitive means of determining whether an ICI is present is to perform a computed tomography (CT) scan of the head. Extra-axial collections such as epidurals (*Fig. 377.4*) and subdural hematomas (*Fig. 377.5*) will appear as biconvex ("lens-shaped") and crescentic hyperdensities, respectively. Axial findings will also be apparent. Cerebral contusions will manifest as hypodense areas of edema (*Fig. 377.6*); intraparenchymal hemorrhages (*Fig. 377.7*) and diffuse axonal injuries will appear as small hemorrhagic lesions of white matter, the

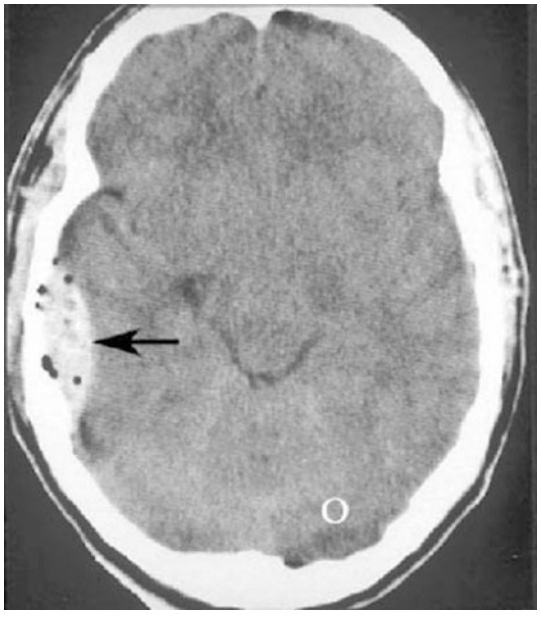


Figure 377.4
Epidural hematoma (from Newton and Mrak © Humana Press, 2008)

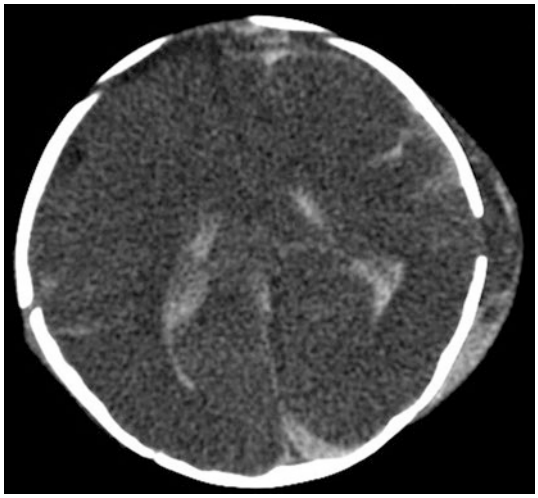


Figure 377.5
Subdural Hemorrhage. Acute subdural hemorrhage due to non-accidental trauma in a 10 week old (Images courtesy of Kathleen McCarten, MD)

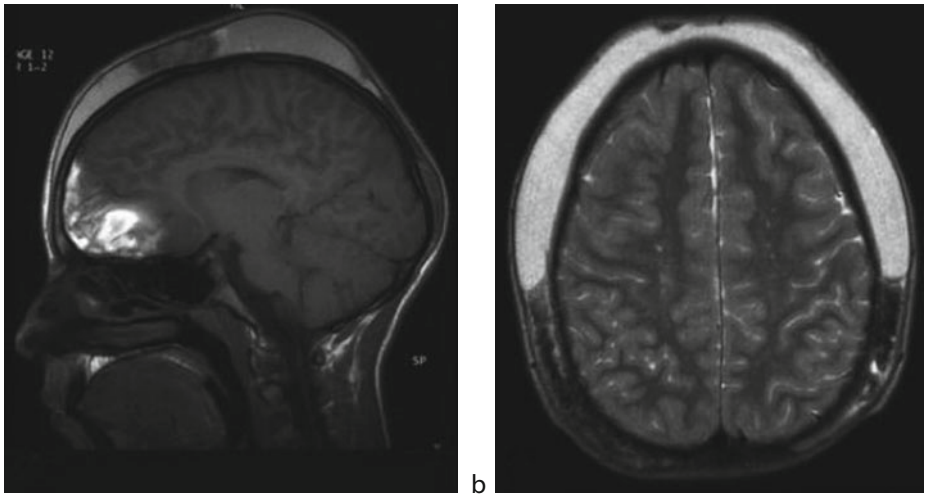


Figure 377.6
Cerebral Contusion (from Parizel et al. 2005)

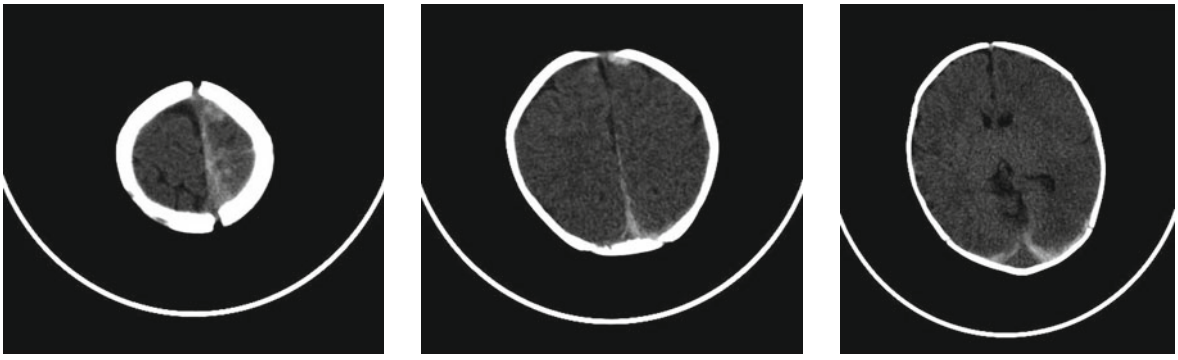


Figure 377.7
Intraparenchymal Hemorrhage. Basal ganglia intraparenchymal hemorrhage due to a road traffic injury in a 7 year old (Image courtesy of Kathleen McCarten, MD)

latter typically found at the gray-white junction of the cerebral hemispheres; and subarachnoid hemorrhages appear as a collection of hyperdense fluid in the brain sulci, fissures, and cisterns (*Fig. 377.8*). Computed tomography is also very helpful in identifying any midline shift, or change in ventricular size indicating mass effect or obstruction of ventricular drainage.

Computed tomography can also identify skull fractures (*Fig. 377.9*), but may miss horizontal fractures that are parallel to the CT image cuts. Skull radiographs may be considered for identifying skull fractures, and have the benefit of exposing a child to less than 5% of the radiation required for a head CT scan. However, skull radiographs provide no information about the presence of ICIs. It is critical to recognize that the absence of a skull fracture does not rule out the possibility of an ICI. Skull radiographs are also limited by the fact that their interpretation is significantly dependent on the skill, experience, and expertise of the person reading the x-ray. Therefore the sensitivity of skull radiographs for detecting skull fractures will vary from institution to institution. A skull radiograph may be considered as a screening tool if CT scan is not readily available, or resources for sedation for younger, non-compliant children are unavailable. The presence of a skull fracture should prompt further evaluation for ICI.

Although CT scans can reliably identify intracranial injuries, they are not indicated, nor should not be obtained, for every pediatric patient who presents with a head injury. No single sign or symptom is a good predictor of an ICI, and imaging a child based on the presence of only one of these factors may result in a large number of unnecessary tests. The radiation exposure of a CT scan, particularly in children, may increase the risk of subsequent brain malignancies. There are also the risks associated with sedation in children who are unable to remain still for the CT scan. It is therefore incumbent upon clinicians to be able to identify patients who are at high or low risk for ICI. High risk patients warrant prompt imaging, while low risk patients can be initially managed more conservatively.

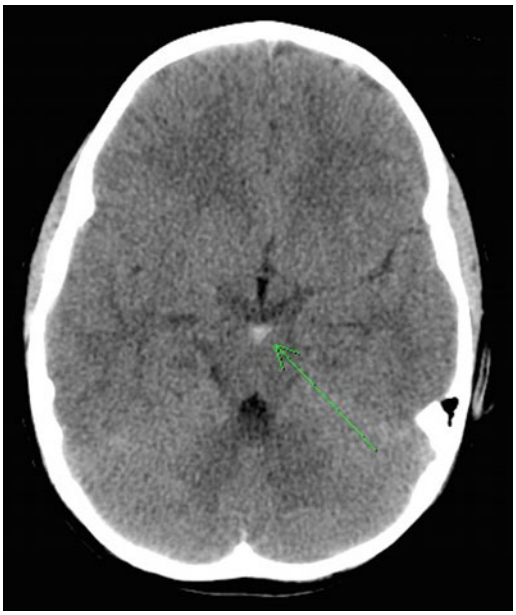


Figure 377.8
Subarachnoid Hemorrhage. Diffuse, acute subarachnoid hemorrhage, with an intraventricular bleed and left parietal skull fracture, due to non-accidental trauma in a 6 week old (Image courtesy of Kathleen McCarten, MD)

Guidelines published by the American Academy of Pediatrics (AAP) suggest that high risk signs and symptoms of ICI include depressed mental status, focal neurologic deficit, signs of depressed or basilar skull fracture, seizure, irritability, acute skull fracture, bulging fontanelle, significant scalp hematoma in children under 2 years, vomiting five or more times or for more than 6 h, and loss of consciousness for 1 min or longer. Children less than 2 years of age also warrant closer attention given that they may present with more subtle findings and are more likely than their older counterparts to have an ICI and be asymptomatic.

Recent literature has suggested that if a patient fulfills certain criteria, they can be considered low risk, have imaging deferred, and be managed conservatively (*Fig. 377.10*). Although the absence of these symptoms makes a significant ICI unlikely, the presence of one of these findings does not necessarily mean that imaging is required. The only findings that immediately prompt CT imaging are a GCS of less than 14, other signs of altered mental status, a palpable skull fracture, or signs of basilar skull fracture. The risk of a clinically important ICI in the presence of any of these findings are 4.3–4.4%. If any of the other signs or symptoms are present, or there are any concerning historical features (e.g. occipital, parietal or temporal scalp hematoma; severe mechanism of injury;

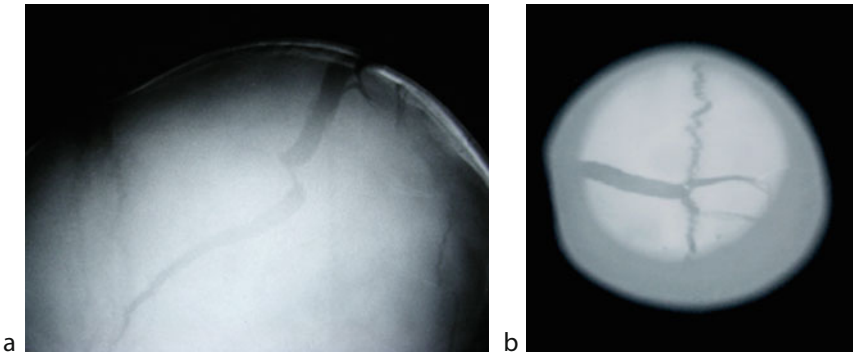
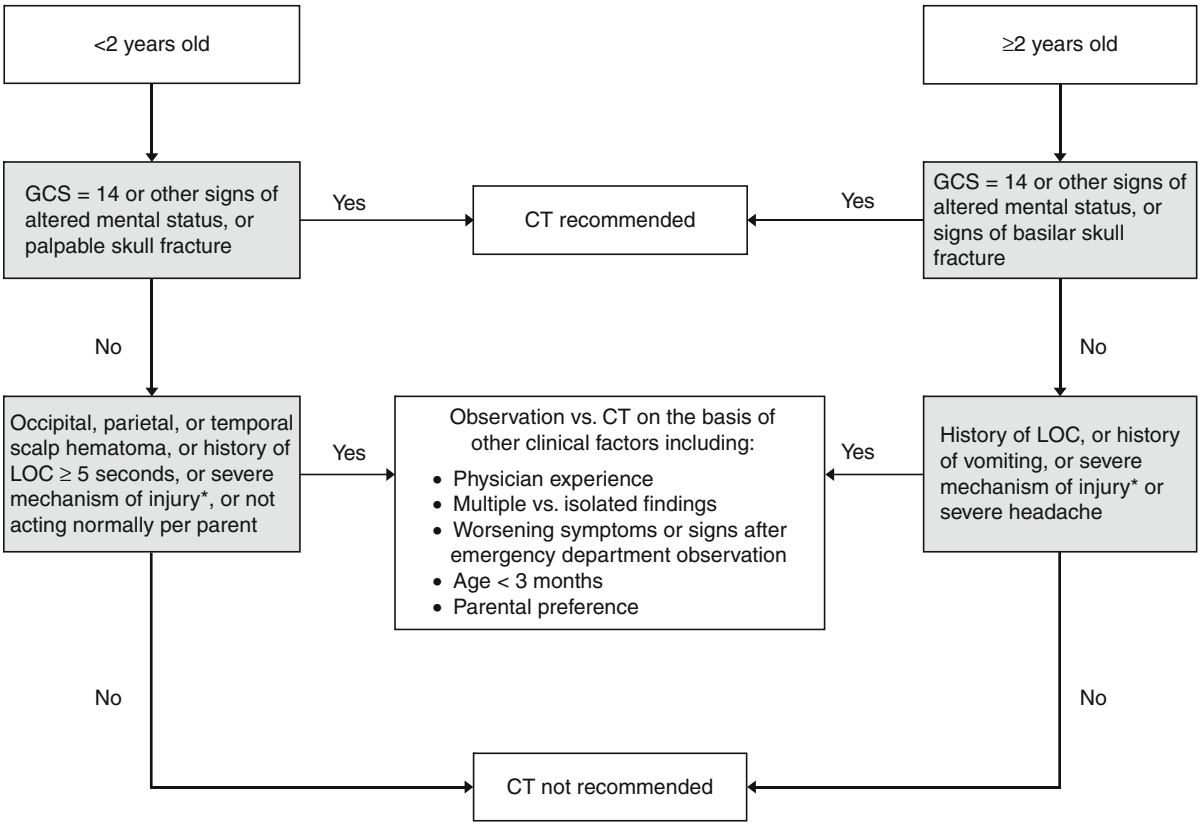


Figure 377.9
Skull Fracture. Plain radiographic and computed tomographic images of a large parietal skull fracture due to a fall in a 4 month old (Images courtesy of Kathleen McCarten, MD)



*Severe mechanism of injury: motor vehicle crash with patient ejection, death of another passenger, or rollover; pedestrian or bicyclist without helmet struck by a motorized vehicle; falls of more than 0.9 m (3 feet) if < 2 years old, or more than1.5 m (5 feet) if ≥ 2 years old; or head struck by a high-impact object.

Figure 377.10
Suggested CT algorithm for children with GCS scores of 14–15 after head trauma (Adapted from Kuppermann N et al. 2009)

severe headache; history of vomiting), the decision to observe or image should be based on clinical factors such as physician experience, multiple vs. isolated findings, worsening of symptoms during period of observation, age < 3 months, and parental preference.

Magnetic resonance imaging (MRI) is another option for neuroimaging a child with a head injury. While MRI has the benefits of not exposing the patient to ionizing radiation and more detailed image quality, there are several disadvantages to MRI. Although there is some evidence that MRI is as accurate as CT for the detection of hyperacute hemorrhage (i.e. < 6 h), MRI tends to be less accessible than CT, is more time consuming and will likely require prolonged sedation for uncooperative children. This is especially problematic for patients who require urgent neurosurgical intervention. When such injuries are suspected, immediate head CT is the imaging modality of choice.

In infants with open fontanelles, head ultrasound may identify large intracranial hemorrhages, dilated ventricles, or midline shift. However, this modality is limited by its dependence on user proficiency as well as its inability to visualize the entire intracranial vault. Additionally, ultrasound does not reliably detect acute cerebral hemorrhage. Therefore, ultrasound should not be considered a reliable means of excluding intracranial injury.

A concussion is a clinical diagnosis which should be considered in patients who have experienced a closed head injury, do not have an apparent ICI, but have signs and symptomatology consistent with concussion, as described in the signs and symptoms section. Conventional neuroimaging with CT scans and standard MRI do not reveal any structural abnormalities in concussed patients. Detailed neuropsychological testing is not necessary in the acute phase of diagnosing a concussion, but may be

useful for eliciting more subtle sequelae of the event at a later time.

Differential Diagnosis

Head trauma can cause a variety of different injuries. The scalp can be lacerated or contused, and may present differently depending on the layer of the scalp affected (Fig. 377.11). Scalp hematomas can form anywhere from hours to days after the injury, and may last anywhere from days to weeks. A subgaleal hematoma occurs when blood accumulates below the galea and above the periosteum. It is usually fluctuant and boggy, and may cross suture lines. A cephalohematoma is a collection of blood below the periosteum and above the skull. Cephalohematomas will not cross suture lines, and tend to be more tense and firm. Due to the high degree of vascularity of the scalp, lacerations may bleed profusely. As a result, scalp lacerations and hematomas may be associated with a large degree of blood loss sufficient to result in tachycardia or hypotension, especially in infants.

Scalp hematomas in infants and young children are also significant because they are associated with an increased risk of underlying skull fractures and ICI. A high level of suspicion is warranted during a child's first year of life, as the skull is thinner during this time. The parietal bones are most commonly fractured, followed by the temporal and occipital bones, and finally the frontal bone. A linear fracture is the most commonly occurring fracture. Basilar skull fractures, most often involve the petrous portion of the temporal bone, but can also involve the occipital, sphenoid and/or ethmoid bone. They are relatively uncommon, but may involve damage to blood vessels and nerves when the foramen magnum is involved, as well as the cranial nerves to which the basilar skull is in close proximity. Depressed skull fractures require evaluation for an associated ICI, and may need neurosurgical intervention to repair the fracture.

Intracranial injuries may occur after a head injury and can be life threatening. Epidural hematomas are as common in children as in adults. They frequently occur in association with a skull fracture and meningeal artery or vein bleeding. Subdural hematomas, on the other hand, are more common in adults than children. The mechanism is usually acceleration-deceleration, resulting in tearing of the bridging veins. Acute interhemispheric subdural hematomas may occur in infants who have suffered a shaking injury, or a young child with an impact injury from abuse. Subarachnoid hemorrhages occur after blunt trauma to the head, or after experiencing shear forces that tear the small vessels of the pia mater.

In addition to intracranial blood collections, children may incur cerebral contusions, which are bruises of the cerebral cortex. An intraparenchymal hematoma may occur as a complication of the contusion, potentially causing impaired blood flow or even mass effect. Severe acceleration-deceleration or angular rotational forces may cause diffuse axonal injury (DAI), which are shear injuries of the axons and associated vasculature causing diffuse primary injury to the white matter tracts of the brain. Diffuse brain swelling may also occur. It is often due to multiple factors, including cytotoxic and/or vasogenic edema. These factors are the result of either a primary brain injury, or are a manifestation of hypoxia and hypoperfusion due to secondary brain injuries.

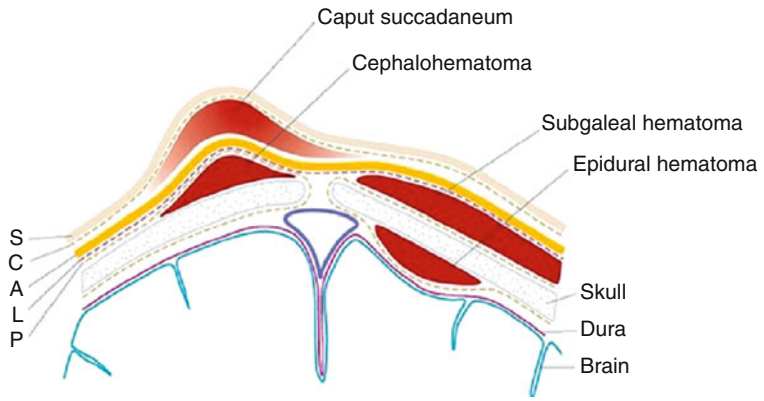


Figure 377.11
Layers of the scalp (Kim and Taragin, 2009)

When no intracranial pathology is readily identified, symptomatic patients may have a concussion, which is often described as any alteration in mental status. Patients with a concussion may or may not experience a loss of consciousness. Symptoms of concussion include confusion, headache, dizziness, nausea, vomiting, and amnesia. Although a CT scan may not reveal any injury, an MRI may reveal abnormalities in cerebrovascular autoregulation, subtle evidence of brain contusion, or diffuse axonal injury. Abnormalities on neuropsychological testing are frequently found with concussions. If the aforementioned symptoms of confusion, headache, dizziness, nausea, vomiting, amnesia, or neuropsychological deficits persist for weeks or months after the acute event, post-concussion syndrome should be considered, as discussed in more detail in the prognosis section.

Another significant complication post-concussion is "second impact syndrome". This is a rare event in which a patient who has experienced a recent concussion suffers a subsequent minor head injury, leading to uncontrolled cerebral edema and either death or severe morbidity. The exact mechanism is not completely understood, but it has been suggested that the second impact exacerbates a state of abnormal cerebrovascular autoregulation and cerebral metabolism caused by the first impact, thus causing the potentially fatal cerebral swelling.

Treatment

Initial management of patients who have experienced a head injury should always begin with assessment and management of airway, breathing and circulation. Cervical spine precautions should be maintained if there are any complaints of cervical spine pain, any neurologic symptoms or deficits, as well as in the context of severe mechanisms of injury, such as fall from heights or significant motor vehicle accidents. A preliminary assessment of neurologic status should also be completed to ensure that there are no signs of impending cerebral herniation. If such signs are present, treatment for increased ICP and neurosurgical consultation and intervention should be immediately instituted.

Treatment of impending cerebral herniation includes endotracheal intubation; optimizing oxygenation and ventilation; and obtaining intravenous access and administering isotonic crystalloid solutions to normalize and maintain mean arterial pressure, and ultimately cerebral perfusion pressure.

Elevating the head of the bed to 30° and maintaining the head and neck in a midline position facilitates downward drainage of cerebral spinal fluid and improves venous drainage from the head. Mild hypocarbia due to moderate hyperventilation results in reflex vasoconstriction of the cerebral arteries, thereby decreasing intracranial blood volume and lowering ICP. Continuous end-tidal CO_2 monitoring is necessary to avoid the extremes of ventilation, both of which may be harmful. Overventilation results in excessive vasoconstriction, impeding cerebral blood flow and decreasing cerebral perfusion pressure. Hypoventilation results in vasodilation and increases ICP. A patient's PCO_2 should be maintained between 30 and 35 mmHg. Sedation and/or paralysis should be considered to minimize patient agitation and prevent choking on an endotracheal tube, both of which increases intrathoracic pressure, obstructs venous drainage from the brain, and aggravates ICP.

Intravenous mannitol decreases intravascular volume and reduces ICP by increasing serum osmolarity. The increased serum osmolarity draws fluid into the intravascular space, which then expands the circulating volume, decreases blood viscosity, and improves cerebral blood flow. Additionally, water is drawn out of neurons and the interstitial space, thereby decreasing the volume occupied by the brain and interstitial fluid and reducing ICP. Mannitol is best administered as a bolus because a prolonged continuous infusion of mannitol would have the opposite effect. When given as an infusion, mannitol molecules would cross into the cerebral interstitial space and cause water retention in the brain, thereby increasing cerebral edema and increasing ICP. A mannitol bolus rapidly exerts its effect, decreasing ICP within minutes. It is important to balance the therapeutic effects of mannitol with its potential for adverse effects. Mannitol's diuretic effects can cause hypovolemia, ultimately resulting in decreased cerebral blood flow. It is therefore best to reserve mannitol for impending cerebral herniation. An alternative to mannitol for decreasing ICP is hypertonic saline. It also increases serum osmolarity and produces the same effects, but does not have a diuretic effect and may be helpful when circulatory status is tenuous.

Seizures should be aggressively treated because they can exacerbate intracranial pressure and cerebral metabolic demands, both of which increase cerebral blood flow and, ultimately, intracranial pressure. Choice of antiepileptic medication should be based on the patient's respiratory and hemodynamic status. Benzodiazepines may be used to treat acute seizure activity. Phenytoin or fosphenytoin are frequently used for seizure prophylaxis in patients with intracranial hemorrhages.

Neurosurgical consultation and intervention will ultimately be required in patients with increased ICP. This may include the placement of an intracranial drain or

pressure monitor so that ICP can be closely monitored and CSF removed as necessary. A burr hole may be performed to relieve impending herniation, but may be of low yield since most causes of increased ICP in children are due to diffuse brain swelling, rather than a focal space-occupying hemorrhage causing mass effect. A burr hole is also a procedure that should only be performed by clinicians with the appropriate expertise, and after all medical options have been exhausted. Another potential means of relieving increased ICP in infants may be to tap the ventricles through an open fontanelle or suture. This procedure should also only be performed by clinicians with the appropriate expertise, and when all other medical options have failed. Tapping the ventricles will, by necessity, cause damage to the brain parenchyma, and runs the risk of causing other life threatening complications.

Fortunately, most patients who experience minor closed head injuries do not require anything more than supportive measures and symptomatic treatment. If a patient has a laceration, ample irrigation and wound closure is often adequate. Hematomas do not require any intervention beyond assuring that the patient is hemodynamically stable. Additionally, patients and parents should be educated about the possibility that the hematomas may continue to expand over the next few days, and may persist for even up to a few weeks. Patients less than 2 years of age with isolated skull fractures should have follow up arranged so that they can be re-evaluated for the development of a growing skull fracture or a leptomeningeal cyst (*Fig. 377.12*).

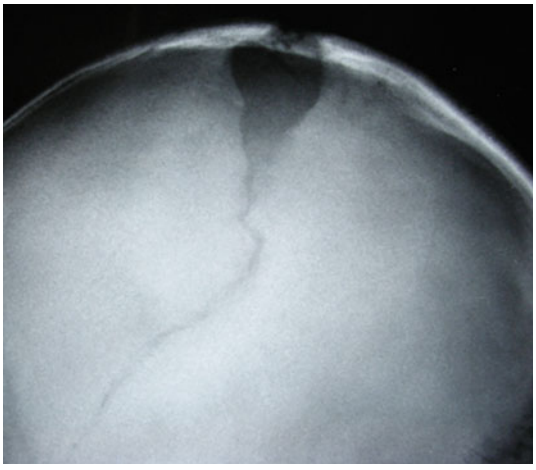


Figure 377.12
Leptomeningeal Cyst. Large "growing skull fracture," 2 months after the initial fracture seen in *Fig. 377.9* (Image courtesy of Kathleen McCarten, MD)

Most patients with concussions can be safely managed on an out-patient basis. Observation and/or hospitalization may be considered for patients with severe headache, dizziness, nausea, or vomiting. If a concussion is managed as out-patient, it is imperative to instruct the patient and parents on the signs of ICI that should prompt immediate medical re-evaluation, as well as recommendations on how and when to return to activity and play. Patients who return to activity too soon after an initial insult put themselves at risk for both second impact syndrome, and potential aggravation and persistence of concussion symptoms.

Patients should not return to activity until their symptoms have resolved. The most widely used guidelines for when patients may resume normal activity is a consensus statement by the International Symposia on Concussion in Sport. The guiding principle is that of "physical and cognitive rest until symptoms resolve and then a graded program of exertion prior to medical clearance and return to play". There is a stepwise escalation of activity during which a patient must be asymptomatic before progressing to a higher level of exertion (*Table 377.2*). Each step should take at least 24 h, which means that the entire process may take as little as 1 week. If a patient experiences post-concussive symptoms at any point, they must drop back to the previous level of exertion and may attempt to progress again after another 24 h period. Although there are specific circumstances in which adult athletes may return to play on the same day of injury, same-day return to play is not recommended for the adolescent or pediatric athlete. A more conservative approach is recommended for this population because children may have different physiological responses and require longer recovery periods compared to adults. There are also concerns that children and adolescents may exhibit a delay in onset of concussive symptoms or neuropsychological deficits that may not be evident at the time of injury that would have indicated that same-day return to play was inappropriate. Comprehensive neuropsychological testing may be useful in this context to assist decision-making regarding the appropriate time for concussed athletes to safely return to play.

Prognosis

Prognosis varies greatly depending on the underlying pathology. Isolated scalp hematomas are often benign, but may appear to grow bigger over time as clotted blood begins to liquefy and the hematoma becomes boggy. Parents should be counseled to expect this development approximately 5–7 days after the injury.

Table 377.2
Graduated Return to Play Protocol

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
1. No activity	Complete physical and cognitive rest	Recovery
2. Light aerobic exercise	Walking, swimming or stationary cycling keeping intensity <70% MPHR; no resistance training	Increase HR
3. Sport-specific exercise	Skating drills in ice hockey, running drills in soccer; no head impact activities	Add movement
4. Non-contact training drills	Progression to more complex training drills, e.g. passing drills in football and ice hockey; may start progressive resistance training	Exercise, coordination, and cognitive load
5. Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and asses functional skills by coaching staff
6. Return to play	Normal game play	

Complications arising from skull fractures depend on which part of the skull is damaged. Basilar skull fractures carry the risk of intracranial infection due to potential involvement of mastoid air cells or paranasal sinuses. Temporal bone fractures may also result in facial nerve injury or damage to inner ear structures, such as the ossicles or labyrinth, leading to hearing problems. A rare but significant injury that may result are intimal tears of the carotid artery which could lead to intracranial aneurysms or stroke. Prognosis is best for patients with basilar skull fractures who have a normal neurologic exam, no identified intracranial abnormality, and no evidence of CSF leak. The presence of any of those factors require more aggressive management to identify and prevent the discussed complications.

A complication of isolated skull fractures unique to children less than 2 years of age are growing fractures, which are caused by leptomeningeal cysts. The two terms are often used interchangeably, as the former cannot occur without the development of the latter. Leptomeningeal cysts develop when there is a dural tear associated with the skull fracture, allowing the arachnoid tissue and subarachnoid CSF to herniate out through the dural defect. The resulting cyst prevents the bone from properly reapproximating and healing, thereby exacerbating the defect, causing erosion of the fracture site, and thus resulting in the "growing fracture". The intracranial contents herniate out because of the pressure caused by the rapid rate of brain growth and expansion unique to this age group, which exceeds the rate at which the fracture heals. Growing skull fractures involving the basilar skull may present as exophthalmos due to cranial nerve impingement. They may present weeks or months after the time of injury, and may present as a boggy or pulsatile soft tissue mass, or palpable bony defect. Since growing fractures require neurosurgical repair, children less than 2 years of age with an isolated skull fracture should have follow up arranged, where they can be re-evaluated for this complication.

Prognosis of patients with intracranial injuries is highly variable. In general, prognosis correlates with the patient's neurologic status on presentation, severity of the lesion, and the presence or absence of other lesions. Patients with secondary systemic insults also have worse prognosis, as factors such as hypotension and hypoxia may exacerbate secondary brain injury. Patients with intraparenchymal hematomas often have poor outcome, compared to patients with small petechial hemorrhages, who may recover with little sequelae. Patients with DAI and diffuse brain swelling tend to do poorly, although children often have better outcomes than adults in both cases. In DAI, mortality rates range from 10% to 15%, with persistent neurologic dysfunction in 30% to 40% of survivors. Patients with SAH have been shown to have mortality rates as high as 24%, and 24% of survivors have poor neurologic outcomes.

Patients with epidural hematomas tend to do comparatively better than patients with SAHs. Mortality rates for epidural hematomas range from 0% to 10%, with up to 15% of survivors with poor neurologic outcomes. Although the general rule of presenting neurologic status correlating with outcome applies to these patients, many patients who present with coma or nonreactive pupils have a moderate or good neurologic outcome after surgical intervention.

Patients with subdural hematomas, on the other hand, do not fare as well. Mortality rates are as high as 10% to 20%, and persistent neurologic sequelae are common amongst survivors. However, like patients with epidural hematomas, those with subdural hematomas who initially

present very poorly may still recover and have moderate or good functional outcomes. A small percentage of patients who are managed conservatively and do not undergo an operation to drain their subdural hematoma may go on to develop chronic subdural hematoma that may be associated with seizures or developmental delay.

Although concussions may occur in the absence of clearly visible pathology, they can cause longstanding sequelae. Post-concussion syndrome may develop, consisting of a constellation of symptoms in the areas of cognitive, somatic, and/or affective and emotional complaints. Cognitive complaints would include decreased memory, attention, and concentration; somatic complaints include headache, fatigue, and dizziness; and affective and emotional complaints include depression, irritability, and anxiety. They can last any where from weeks to even months after the initial injury. Although patients with a lower GCS on presentation have been reported to have more symptoms at 6 weeks after injury, there is discussion regarding whether social and personal factors post-injury may also contribute to the persistence of symptoms.

Prevention

It is difficult to prevent or ameliorate the potentially devastating sequelae of head injuries. Therefore, primary prevention of head injuries is paramount and the best method of decreasing the costs and burdens of head injuries. Pediatricians can play an important role in preventing head injuries in children on multiple levels. Interactions with families provide opportunities to strongly encourage the use of helmets for common outdoor activities, including bicycling, skiing, and snowboarding. Physicians can also facilitate prevention at the community level by advocating for the implementation of playground safety standards, as well as modifications to unsafe pedestrian physical environments. And finally, physicians can support legislature that would enforce these protective measures and help to ameliorate the burden of disease brought upon by head injuries.

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378 Headache and Head Pain

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Headache is a common childhood complaint. Headaches can be divided into the primary headache disorders, such as migraine, and the secondary headache disorders, which are due to an underlying disorder.

Primary Headache Disorders in Children

Migraine

Migraines are severe, often bilateral, throbbing headaches frequently located in the temples or frontal head regions. Migraine occurs in 2–5% of preschool children, 10% of school-aged children, and 20–30% of teenage girls. Approximately 20% of migraine patients experience their first attack when younger than 5 years of age.

Symptoms of migraine vary with the age of the child. In preschool children, migraine often consists of episodes involving an ill, pale appearance, abdominal pain, vomiting, and the need to sleep. Pain may be expressed by irritability, crying, rocking, or seeking a dark room in which to sleep. Five- to 10-year-old patients with migraine tend to experience bilateral frontal, temporal, or retro-orbital headache with associated nausea, abdominal cramping, vomiting, photophobia, phonophobia, and a need to sleep. Parents may describe these children as pale with dark circles under the eyes. Older children tend to present with a unilateral, temporal headache and the location and intensity of pain often change within or between attacks.

Migraine can occur with or without aura. Only 10–20% of children with migraine experience an aura, often for the first time after the age of 8 years. The aura usually precedes the headache by less than 30 min and lasts for 5–20 min. The aura may present without headache. Children often are unaware or unable to describe their aura. The visual aura is the most common form in children, consisting of blurred vision, fortification spectra (zigzag lines), scotomata (field defects), scintillations, black dots, kaleidoscopic patterns of various colors, micropsia, macropsia (distortion of size), and metamorphopsia ("Alice in Wonderland" syndrome). Visual auras often are reported as moving or changing shapes; other auras include attention loss, confusion, amnesia, agitation, aphasia, ataxia, dizziness, vertigo, paresthesia, or hemiparesis. Aura symptoms vary widely within and between attacks.

The headaches can last 60 min to 48 h, but usually last less than 4 h. Some young patients report short headaches lasting 10–20 min. The severity of childhood headache often is milder than adult migraines. The headache phase can be associated with cold extremities, nausea, anorexia, vomiting, diarrhea or constipation, dizziness, chills, excessive sweating, ataxia, numbness, photophobia, phonophobia, memory loss, or confusion. Often the patient cannot concentrate or function effectively during or immediately after episodes. Relief typically is associated with sleep. After the headache phase, the patient may feel either elated and energized or more typically exhausted and lethargic. This stage of migraine may last from hours to days.

Migraine is associated with a variety of comorbid conditions. Psychiatric symptoms such as depression, panic attacks, anxiety disorders, or phobia may be present. Epilepsy and migraine often occur within the same individual, although most patients with migraines do not have seizures. Migraineurs are more prone to motion sickness than patients without migraine. Intermittent vertigo is found frequently in patients with migraine. There is a higher cardiovascular reactivity to postural changes in patients with migraine and this may result in dizziness. Migraines are also associated with sleep disturbances and ice cream headache in some patients.

Types of Migraine

Status migrainosus is a severe form of migraine in which the headache attack is continuous for longer than 72 h. Patients usually have a preexisting migraine history. In those who vomit, rehydration is often the necessary first step. One often effective treatment can be intravenous (IV) fluids, and antiemetic, and dihydroergotamine (DHE).

Familial hemiplegic migraine is an autosomal-dominant form of migraine with aura. Patients have a prolonged hemiplegia that can be accompanied by numbness, aphasia, and confusion. The hemiplegia may

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precede, accompany, or follow the headache, and symptoms may last for hours to days. The headache usually is contralateral to the hemiparesis. Some familial hemiplegic migraine is associated with cerebellar ataxia. Other types of severe familial hemiplegic migraine may present with coma, fever, and meningismus. Some forms of familial hemiplegic migraine respond to acetazolamide or calcium channel blockers. Structural lesions, vasculitis, cerebral hemorrhage, brain tumor, mitochondrial myopathy, encephalopathy, alternating hemiplegia, and lactic acidosis need to be considered in the differential diagnosis.

Basilar-type migraine is a subtype of migraine with aura, and is observed mostly in adolescent and young adult females. Headache pain may be located in the occipital area. Basilar-type migraine is characterized by disturbances in function believed originating from the brain stem, occipital cortex, and cerebellum. The occipital headache must have at least two of the following aura symptoms: dysarthria, vertigo, tinnitus, hyperacusia, diplopia, bi-field visual symptoms, ataxia, and decreased level of consciousness or bilateral paresthesias. A history of typical migraine exists in many families. Some patients experience basilar migraine attacks intermingled with typical migraine attacks.

Benign paroxysmal vertigo of childhood is a condition characterized by brief episodes of vertigo, disequilibrium, and nausea, usually found in children aged 2–6 years. The patient may have nystagmus within but not between the attacks. The child does not have hearing loss, tinnitus, or loss of consciousness. Symptoms usually last only a few minutes. These children often develop a more common form of migraine as they mature. Brain magnetic resonance imaging (MRI) can be obtained to exclude posterior fossa abnormalities, especially if abnormalities in the neurologic exam are found between episodes.

Acute confusional migraine is characterized by transient episodes of amnesia, acute confusion, agitation, lethargy, and dysphasia. This form of migraine is often precipitated by minor head trauma. The child may have a receptive or expressive aphasia, and the confusional state may either precede or follow the headache. Some children also experience recurrent episodes of confusion. The patient usually recovers within hours. The child may not have a history of headache but usually develops typical migraine attacks when older. It is important to exclude intoxications, encephalitis, structural lesions, and seizures (*Table 378.1*).

Migraine-associated *cyclic vomiting syndrome* is characterized by recurrent periods of intense vomiting separated by symptom-free intervals. Many patients with cyclic vomiting have regular or cyclic patterns of illness. Symptoms usually have a rapid onset at night or in the early morning and last 6–48 h. Associated symptoms include abdominal pain, nausea, retching, anorexia, pallor, lethargy, photophobia, phonophobia, and headache. The headache may not appear until the child is older. Migraine-associated cyclic vomiting syndrome usually begins when the patient is a toddler and resolves in adolescence or early adulthood; it rarely begins in adulthood. More females than males are affected by cyclic vomiting. Usually a family history of migraines in the parents or siblings is present. These children often experience severe fluid and electrolyte disturbances that require intravenous fluid therapy. Migraine-associated cyclic vomiting

Table 378.1
Suggested acute treatment options for pediatric migraine

Medication	Typical dose	Side effects
Ibuprofen	10 mg/kg/dose	Stomach irritation
Paracetamol (acetominophen)	10–15 mg/kg/dose	Liver toxicity with overdose
Naproxen sodium	5 mg/kg/dose	Stomach irritation
Sumatriptan (other triptans also available)	Children over the age of 10 years and 50 kg typically tolerate 25–100 mg oral, or 20 mg nasal: Children between the age of 6–10 years should first start with the 5 mg nasal spray form	Paresthesias, chest tightness, worsening headache

Drug dose available form:
Acetaminophen 10–15 mg/kg per dose tabs 80 mg, 160 mg, 325 mg; syrup 160 mg/tsp
Ibuprofen 10 mg/kg per dose tabs 200 mg, 400 mg, 600 mg, 800 mg; chewable tablets 50 mg, 100 mg; syrup 100 mg/tsp
Naproxen sodium 5 mg/kg per dose tab 220 mg (OTC); Tab 250 mg, 375 mg, 500 mg
5-HT Agonists (Triptans):
Sumatriptan tabs 25 mg, 50 mg, 100 mg; subcutaneous injection 6 mg; nasal spray 5 mg, 20 mg
Zolmitriptan 2.5 mg, 5 mg; disintegrating tabs 2.5 mg

syndrome is a diagnosis of exclusion. Other causes of cyclic vomiting include gastrointestinal disorders (malrotation), neoplasms, urinary tract disorders, metabolic, endocrine, and mitochondrial disorders.

In *abdominal migraine*, the patient may suffer from recurrent bouts of generalized abdominal pain with nausea and vomiting, but often with no headache present. The episodes are often relieved by sleep and later the child awakens feeling better. Abdominal migraine may alternate with typical migraine and can lead to typical migraine as the child matures. These children respond to migraine prophylactic medication.

Paroxysmal torticollis of infancy is an uncommon disorder characterized by repeated episodes of head tilting associated with nausea, vomiting, and headache. Attacks usually occur in infants and may last from minutes to days. Posterior fossa abnormalities should be considered in the differential diagnosis. Recent data has linked these symptoms to mutations in the CACNA1A gene in some patients.

Acephalgic migraine of childhood (migraine sine hemicrania) is characterized by a migraine aura without headache, usually visual auras, and a female predominance. A family history of migraine is frequent.

Evaluation and Diagnosis of Migraine

No specific diagnostic tests for migraine exist and the diagnosis is made through the history, physical exam, and clinical judgment. The child with migraine should have a normal general physical examination and a normal detailed neurologic examination. Only a small percentage of headache patients require further laboratory and radiologic studies. An imaging study should be considered in patients with a history of seizures, recent head trauma, significant change in the headache, or evidence of focal neurologic deficits or papilledema upon physical examination. No absolute rules exist in the evaluation of the headache patient; the need for a neuroimaging study ultimately is based on clinical judgment. Electroencephalography (EEG) is not useful in the routine evaluation of headache patients. It should be considered in patients with an atypical migraine aura, episodic loss of consciousness, or symptoms suggestive of a seizure disorder. Lumbar puncture is indicated if meningitis, encephalitis, subarachnoid hemorrhage, or high–low pressure syndromes are considered. Patients in whom elevated intracranial pressure is suggested or with focal neurologic deficits should undergo a neuroimaging study prior to a lumbar puncture.

Treatment and Prognosis

The treatment of migraine headaches should emphasize identification of environmental trigger factors, pain control at the time of the headache, and preventative medication. The treatment of children with mild, infrequent attacks consists primarily of rest, trigger avoidance, and analgesics. The patient and parents benefit from a simple explanation of the headache pain and reassurance that it is not caused by a brain tumor or other life-threatening condition. A regular bedtime, regular meal schedules, and avoidance of overloading the child's schedule with activities are important. Helping the child recognize migraine triggers is helpful but often difficult. It is important that the patient has realistic expectations; identifying and avoiding triggers reduces the frequency of migraine headache but does not eliminate headaches.

Psychological triggers include stress, anxiety, worry, depression, and bereavement. Emphasizing to the patient and family that migraine is not an imagined or psychological illness is important. Stress is not the sole cause of the headaches, although it makes migraines more difficult to manage. Physiological triggers include fever or illness, missing a meal, fatigue, and sleep deprivation. Environmental triggers of migraine include fluorescent light, bright light, flickering light, fatigue, barometric pressure changes, high altitude, strong odors, computer screens, or rapid temperature changes. Some patients report that complex visual patterns like stripes, checks, or zigzag lines may trigger migraines. Physical exertion can trigger childhood migraine. Some migraineurs report that they are more likely to get a headache after participating in sports or being extremely active. Minor head trauma (e.g., being hit in the head with a ball, falling on one's head) also may result in a migraine attack. Travel or motion may cause migraine, particularly in young children.

At the time of the headache, advise the child to lie down in a cool, dark, quiet room and fall asleep. Sleep is the most potent antimigraine treatment. Some patients find that ice or pressure on the affected area of pain can alleviate pain temporarily. Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective if taken at an appropriate dosage during the aura or early headache phase. Gastric stasis occurs in migraine patients and causes delay in absorption of oral medications. Occasionally, carbonated beverages may improve absorption. Nonpharmacologic treatment modalities such as self-relaxation, biofeedback, and self-hypnosis may be reasonable alternatives to pharmacologic treatment in managing childhood migraine, particularly in adolescents.

Prophylactic or preventative medications are taken on a daily basis to reduce the frequency or severity of headaches and associated symptoms. A good response to prophylactic medications is often considered a 50% reduction in the frequency or severity of attacks. Consider the use of prophylactic drugs for children with frequent (>2 per week), prolonged, and disabling migraine attacks that do not adequately respond to other treatments. Often, several weeks are necessary before therapeutic gains are observed with prophylactic medications. Possible preventative medications include amitriptyline, propranolol, gabapentin, valproate, topiramate, flunarizine, verapamil, and riboflavin.

Migraines may change in frequency as children move into adulthood. In one of the few longitudinal studies of childhood migraine patients, children with migraine were followed for 40 years. The average onset of the migraines occurred at 6 years. During puberty or young adulthood, 62% of the children were migraine free for at least 2 years, ~33% of these children regained regular attacks after an average of 6 migraine-free years, and a surprising 60% of the original 73 children still had migraines after 30 years, while 22% of the subjects never had a migraine-free year. Of those patients who became parents, 52% have at least one child in their present or previous families who developed recurrent migrainous headache.

Chronic Daily Headache

Chronic daily headache is a disorder where the diagnosis is based on the presence of headache for greater than or equal to 15 headache days in 1 month, over a period of three consecutive months, with no underlying organic pathology. The headaches last for more than 4 hours per day. This headache disorder tends to affect teenagers and adults, but can occur in preteens. It can occur in up to 4% of young women and up to 2% of young men, with similar prevalence rates seen in studies from Asia, Europe, and the United States.

Silberstein and others have defined four different categories of chronic daily headache based upon symptoms. These include transformed or chronic migraine, chronic tension type headache, new daily persistent headache, and hemicrania continua. Many teenage patients with chronic daily headache have a past history of episodic migraine. The transformation to a chronic migraine may occur over a period of weeks to months, or it may occur abruptly over a matter of hours. Approximately a quarter of teenagers with chronic daily headache will have no significant past headache history and an infection such as mononucleosis or a minor head injury may incite a new daily persistent headache. A smaller number of patients will have a history of tension type headaches prior to their chronic daily headache.

Most commonly, the youngster with chronic daily headache will complain of at least two types of headaches. Prominent are severe intermittent headaches that are migraine-like. They tend to be pan-cephalic or frontal in location. The severe headaches will be described as throbbing, severe, crushing, knife like, or hatchet like. They are often associated with nausea during the most severe times, and the patient will frequently have photophobia, phonophobia, and osmophobia. For this more severe headache pain, sleep will sometimes help, but they will still have persistent headache when they awaken. The frequency of these severe headaches will vary with the individual. The severe episodes typically occur multiple times a week.

In addition to these severe intermittent headaches, the patient with chronic daily headache will often complain of a continuous headache that is present 24 h a day, 7 days a week. This continuous headache may wax and wane in severity, often being worse either in the morning or at the end of the school day. The characteristics of the all-the-time headache pain are similar to the episodes of severe headaches, only much less intense. Some patients may also describe this all-the-time headache as having features of a tension type headache, with the pain being band-like or crushing rather than throbbing.

Headache is not the only symptom in chronic daily headache; it is really a multi-symptom complex. Sleep is disrupted in at least two thirds of the patients who have chronic daily headache. Typically, the headache syndrome will not resolve until the sleep is improved.

Many chronic daily headache patients also complain of dizziness which is associated with feeling weak, unsteady, and with blurry or loss of vision. This is often positional, and may involve syncope or near syncope several minutes after standing. There is typically no vertigo, except during severe headache episodes. The dizziness is particularly prominent in the morning. A difference in blood pressure or pulse rate between sitting and standing may be noted and the patient often experiences mild symptoms of this dizziness if stood up for several minutes in the office. One may see either a significant tachycardia with standing (postural orthostatic tachycardia syndrome) and/or a decrease in the systolic blood pressure with standing.

Mood problems and anxiety also frequently coexist with chronic daily headache. The mood problems may precede or follow the onset of the headache. Both the symptoms of headache and mood need to be addressed.

If there are significant problems with mood and anxiety, it is difficult to control the headaches until these symptoms are improved. Other frequent comorbid symptoms include nonspecific abdominal pain, back pain, neck pain, and diffuse muscle and joint pain and often no additional organic etiology is found to explain these additional pain symptoms. There are important environmental factors that play a role in these headaches. There is an interesting seasonal variability in the degree of chronic daily headache symptoms. Most patients will do better in the summertime and frequently have a worsening of their headaches at the start of the school year, and school absence can be a significant problem.

Evaluation

Neuroimaging studies will be normal in the overwhelming majority of chronic daily headache patients. Occasionally in these patients, white matter abnormalities, arachnoid cysts, or pineal cysts will be seen that are generally believed to be of no clinical significance to the chronic daily headache. If a patient has had a significant history of head or neck trauma, particularly at the onset of the chronic daily headache, then an MR angiogram (MRA) of the neck should also be considered to rule out a possible carotid dissection. When pseudotumor cerebri is a strong consideration, then a magnetic resonance venography (MRV) should also be considered since sinus thrombosis can cause elevated intracranial pressure. Serum studies to consider include evaluation of the thyroid, sedimentation rate, and ANA. Many patients will transition from a headache-free period or episodic migraines to chronic migraines during an infection so consideration should be given to serology for Epstein-Barr virus, West Nile virus, and other viral or bacterial infections.

Treatment and Prognosis

Chronic daily headache is difficult to control and it typically takes weeks to months to effect a change in headache control. The cornerstones of therapy are education, preventative medications, and attention to environmental trigger factors. It is difficult for many families to comprehend that the head pain can persist for such a long time, that there are no abnormalities showing up on diagnostic testing, and that the medications they are prescribed are not immediately effective. It is thus useful to spend adequate time with the patient and family discussing the role of medications, when not to use pain relievers, the role of non-medication approaches (such as biofeedback or physical therapy), and what the family should expect in the short and long term. After 1 month of an effective therapy, a reasonable expectation would be to have less frequent severe headache episodes, and a decrease in the intensity of the all-the-time, 24/7 headache. It is rare to see complete resolution of the headaches after a short period of time. Once a trend toward improvement is seen, the dose of medication is adjusted for optimal control of the headaches, and the patient is continued on the preventative for at least 6 months of good (but rarely complete) symptom control. It is not unusual to make frequent adjustments in management initially, and it may take months before matching up the right preventative medication or the right therapeutic approach with the individual patient.

Preventative medications are traditionally used in episodic migraines to reduce the frequency of the migraine headaches. However, in chronic daily headache, a reasonable therapeutic goal would be to make the severe intermittent headaches less frequent, and to make the all-the-time headache less intense. The most published experience of preventatives in chronic migraine or chronic daily headache is the use of medicines that work on the serotonergic system or the anticonvulsants. Unfortunately, there have been few prospective randomized controlled studies in children to give us guidance as to what is the most effective or safe medication to use in chronic daily headache (*Table 378.2*).

Studies in adults and children have shown that tricyclic antidepressants, such as amitriptyline, are helpful in chronic daily headache. Consideration needs to be given to follow electrocardiogram (EKG) changes, as this drug may prolong the QT interval. Weight gain is a significant concern in teenage patients with these medicines, and it affects some children more than others. Amitriptyline can also be helpful for sleep onset. Other tricyclics, such as nortriptyline or protriptyline, may cause less sedation.

Other serotonergic agents such as the selective serotonin reuptake inhibitors (SSRIs) have also shown to be effective in some adults with chronic headache. The SSRIs seem to be less effective than the tricyclics for pain control, although they are more helpful in children for their positive effects on mood. In select patients, the use of an SSRI can be very useful.

Studies in headache patients have shown anticonvulsants are also useful. Valproate, topiramate, and gabapentin have been used. Choice of rational pharmacotherapy to treat the patient's other problems is ideal. Antidepressants can address underlying mood disorders as well as sleep problems. Beta-blockers can make depression worse; however, they may be helpful for patients with

Table 378.2
Migraine and chronic daily headache: suggested preventive agents

Medication	Typical target dose	Side effects/monitoring
Amitriptyline	0.5–3 mg/kg/day; patients metabolize at different rates; need for 25–150 mg/day	EKG and drug levels at higher doses; weight gain
Topiramate	1–2 mg/kg/day; 50–200 mg/day	Decreased appetite; difficulty thinking and word finding, kidney stones, decreased sweating
Propranolol	1–2 mg/kg/day; 60–120 mg/day	Occasional exercise intolerance; irritability; nightmares; asthma
Verapamil	1–6 mg/kg/day; 80–480 mg/day	Constipation; dizziness; need to follow PR and QT intervals on EKG
Gabapentin	10–40 mg/kg/day; 300–3,600 mg/day	Tiredness; swelling
Valproate	10–30 mg/kg/day; 250–1,000 mg/day	Weight gain; teratogenic; rare liver and pancreatic problems

a postural orthostatic tachycardia syndrome. Calcium channel blockers are useful for patients who also have hypertension, but cause constipation and orthostatic hypotension. If the patient needs to lose weight, topiramate is a good choice, although this may result in mental clouding. The use of botulinum toxin shows promise as well.

Hemicrania continua is a rare headache syndrome, occurring in approximately 1% of chronic daily headache patients. It is a persistent unilateral headache pain. The pain may be characterized by a stabbing sensation, and may be associated with autonomic changes. It is important to recognize this entity since these patients may respond to daily doses of indomethacin to ameliorate this condition.

Pain control at the time of the headache is a very difficult problem for patients. Analgesics that are typically effective for episodic migraine headaches are not very effective for chronic migraine or chronic daily headaches. Most patients report that pain relievers are not effective for the all-the-time, 24/7 headache. It is reasonable to discourage patients from trying to use analgesics to treat the all-the-time headache, since this may result in analgesic overuse and a potential analgesic rebound headache. Combating rebound from those substances is part of the treatment. Medications implicated in this overuse syndrome include most OTC analgesics and decongestants, opioids, butalbital, isometheptene, benzodiazepines, ergotamine, and triptans.

In contrast, for the more severe intermittent headache episodes with migrainous qualities, analgesics should be considered. Approaches can include the use of migraine pain relievers such as triptans, indomethacin or other nonsteroidal anti-inflammatory agents. Compounds that contain caffeine, barbiturates, opiates, or that have a high potential for rebound should be limited or avoided. Patients typically find that when the preventative medication starts working, the pain analgesics will become more effective. Additional treatment strategies include dihydroergotamine, IV valproate, or steroids. Non-pharmacological approaches to the headaches are also very important. Because of the chronic nature of the pain, some patients will benefit with a consultation with a psychologist to at least be introduced to the techniques of relaxation therapy and biofeedback. Many of the patients have been ill for months to years and have become physically "deconditioned." Starting a reconditioning exercise program is very important. Patients should be encouraged to start slowly. For the most severely affected patients, begin with 10 min of aerobic exercise a day and then increase the time by 10% a week. There is limited data looking at the outcome of chronic daily headache in children. The average duration in childhood is unknown, but it is not unusual to see children who have chronic daily headaches persisting for months to years.

Tension Type Headache

Migraine and tension type headache are the most common types of headache in children and adolescents. The actual prevalence of tension type headache in children is uncertain because it varies with the defining criteria, but studies have reported anywhere from 0.9% to 73% of affected children. Age of onset has been reported in studies as between 5 and 12 years. The headaches tend to occur more frequently in females during adolescence and genetics plays less of a role in this disorder than in migraine. The pathophysiology is incompletely understood but may involve trigeminal activation. The headaches are characterized by a variable intensity, bilateral, dull, pressure pain with occasional associated phonophobia that lasts

minutes to days. There are three subtypes defined by the International Headache Society classification. Episodic tension type headache may be infrequent (less than 1 day per month) or frequent (1–14 days per month) and chronic tension type headache occurs 15 or more days per month. Diagnosis is based on the clinical history and a normal neurologic exam, including vital signs and funduscopic exam. The differential diagnosis is broad and includes a variety of organic disorders such as infection, malformation, bleed, and systemic disorders. The value of neuroimaging in the presence of a typical history and normal neurologic exam is low, but is recommended if there is vomiting, a history of trauma, seizure or an abnormality on exam. Tension type headache or medication overuse headache may progress into chronic daily headache. Treatment of episodic tension type headache involves reassurance, stress reduction, psychological and cognitive behavioral therapies, and appropriate use of an acute analgesic medication, such as a nonsteroidal anti-inflammatory drug. Treatment of chronic tension type headache may involve the above in addition to a prophylactic medication such as an antidepressant.

Trigeminal Autonomic Cephalgias

Trigeminal autonomic cephalgias refer to a group of headaches that are characterized by repetitive, brief episodes of severe unilateral pain associated with ipsilateral autonomic features including rhinorrhea, nasal congestion, lacrimation, and conjunctival injection. They include cluster headache, paroxysmal hemicrania, and SUNCT syndrome (short-lasting unilateral neuralgiform headache with conjunctival injection and tearing). They each differ in the duration, frequency, and rhythmicity of attacks. All are more common in adults and have rarely been reported in children.

Cluster Headache

Cluster headache is the most common trigeminal autonomic cephalgia. The prevalence in adults is less than 1% and has a male predominance. The prevalence in childhood and adolescence has been estimated to be 0.1%. Studies have noted childhood onset at ages between 5 and 19 years. The pathophysiology is not completely understood but theories involve hypothalamic activation and neurogenic inflammation. Symptoms include several bouts per day, generally with circadian rhythmicity, lasting weeks of severe unilateral orbital, supraorbital, or temporal head pain lasting 15 min to 3 h with associated unilateral autonomic features and associated restlessness. Children may experience thrashing about or emotional outbursts secondary to the severe pain. There are episodic (most common) and chronic forms and a familial predisposition. Diagnosis is made clinically but a head computed tomography or magnetic resonance imaging should be performed to exclude an underlying brain lesion. The differential diagnosis includes other trigeminal autonomic cephalgias and an underlying brain lesion. Treatment involves preventative medications such as verapamil and acute treatment such as oxygen, triptans or steroids. The patient should be cautioned against triggers, such as smoke and alcohol.

Paroxysmal Hemicrania and SUNCT Syndrome

Paroxysmal hemicrania is rare in children. Attacks are shorter (minutes), more frequent, and less severe than in cluster headaches. These headaches are exceptionally responsive to treatment with indomethacin. SUNCT syndrome is also rare in children. Attacks are very short in duration (seconds to minutes), triggered by touching the face or chewing, have limited associated autonomic features, and occur up to hundreds of times per day.

Ice Pick Headaches

Ice pick headaches are a benign primary headache disorder characterized by sudden ice pick–like pains. These pains may last for seconds to minutes, typically occur at different parts of the child's head, and are often seen in patients prone to migraines. They are fairly infrequent and most often do not require treatment. There are case reports of these headaches responding to indomethicin.

Secondary Causes of Headache in Children

Cerebral Venous Sinus Thrombosis

Cerebral venous sinus thrombosis is a serious disorder that frequently presents with headache. Diagnosis and treatment may be delayed secondary to its varied clinical presentation unless it is considered and investigated as a potential etiology. The annual incidence in a multicenter

Canadian registry of children 18 years of age and younger was 0.67/100,000. In children, there is no female predominance as is seen in young adults. Risk factors and presenting symptoms are related to age. Neonates are most commonly affected and risk factors include hypoxic encephalopathy or other perinatal complications, infection, and dehydration. In children, risk factors include acute or chronic systemic illnesses, anemia, infection (especially of the head and neck), prothrombotic states, and dehydration.

The clinical presentation in neonates includes seizures and diffuse neurologic signs. In children it may include headache, changes in mental status, papilledema, emesis, and focal neurologic signs. Headache is the most frequent symptom. The headache onset is generally acute to subacute and the intensity moderate to severe. The pain is typically continuous and localized, exacerbated by recumbency and Valsalva maneuvers and unrelieved by analgesics. Neuroimaging should be performed and include head magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) because head computed tomography (CT) may be normal in about 30% of patients. This will demonstrate an absence of blood flow in the cerebral veins. Treatment involves antithrombotic therapy utilizing intravenous heparin followed by warfarin for several months. In cases of extensive thrombosis, thrombolytic therapy and mechanical thrombectomy may be considered. Outcomes vary from resolution with normal neurologic function in about half to neurologic sequelae (motor, cognitive, speech) and death.

Pseudotumor Cerebri (Idiopathic Intracranial Hypertension)

Idiopathic intracranial hypertension is a syndrome of increased intracranial pressure with normal neuroimaging studies, normal CSF composition, and elevated CSF pressure. In adults, it is frequently associated with obese females of childbearing age. In children, however, it is less frequently associated with obesity and female gender. Symptoms include those of elevated intracranial pressure, headache, nausea, vomiting, and visual disturbances. Headache is the most common presenting symptom and may be daily, pulsatile, and exacerbated by supine positioning. Infants with headache may present more subtly with only changes in sleep and behavior. Neurological exam may demonstrate cranial nerve palsies, especially abducens palsy and papilledema. Papilledema is considered a characteristic finding; however, it may not be seen in infants because of their unfused sutures, and is an inconsistent finding in children and adolescents. Associated factors to inquire about in the history include the use of acne medications, antibiotics, and oral contraceptives.

Diagnosis is one of exclusion and is based upon the 1985 Modified Dandy Criteria: an awake and alert patient, signs/symptoms of increased ICP, absence of localizing findings on neurologic exam except for abducens nerve palsy, normal CSF findings except for increased pressure (>250 mm water), absence of ventricular system anomaly on imaging studies, and lack of other cause identified. Neuroimaging should be performed to evaluate for mass lesions causing obstructive hydrocephalus or dural venous sinus thrombosis. A lumbar puncture should be performed after a mass lesion has been ruled out by imaging to evaluate for increased intracranial pressure. Treatment in children may involve acetazolamide, corticosteroids, serial lumbar punctures, lumboperitoneal shunting or optic nerve sheath fenestration. Patients should be referred to an ophthalmologist for an exam including visual field testing and continued visual monitoring as visual loss is a complication. Outcome is generally favorable.

Chiari Malformations

Headaches may be a presenting symptom of a Chiari I malformation. There are four types of Chiari malformations but because the other malformations are generally evident at birth, a type I malformation is the most likely to be discovered in childhood. Type I Chiari malformation refers to the downward displacement of the cerebellar tonsils through the foramen magnum. It may be associated with obstructive hydrocephalus and syringomyelia. The incidence is unknown because many patients are asymptomatic and remain undiagnosed. Headache is a common presenting symptom and may be exacerbated by Valsalva maneuver or physical exertion. The head pain may be located in various areas and may occur multiple times daily and last seconds to minutes. Presenting complaints may also include neck pain, sensory, motor, or gait impairments, or oropharyngeal dysfunction. Neurologic exam findings may include scoliosis, abnormal deep tendon reflexes, and cranial nerve deficits. Diagnostic testing should include magnetic resonance imaging of the brain, including the posterior fossa, craniovertebral junction, and upper cervical levels. Surgical treatment for children presenting with headache is generally controversial but may include suboccipital craniectomy and cervical laminectomy.

Trauma

Epidural Hematoma

Trauma is a common cause of injury and loss of consciousness in children and may be associated with a potentially life-threatening epidural hematoma. In an epidural hematoma, there is hemorrhage, commonly from the middle meningeal artery, and accumulation of blood between the dura mater and the skull. This blood initially strips the dura away from the skull, causing pain and eventually exerts mass effect on the brain which can lead to herniation and death. Thus it is important to quickly recognize the symptoms and efficiently manage children with epidural hematoma who may present with headache.

Risk factors include falls, motor vehicle accidents, direct head injuries, and skull fractures. Patients may experience an asymptomatic, lucid interval following the initial injury, and then develop headache with associated nausea, vomiting, and altered mental status. Late and ominous findings indicating compression of the brain stem include focal neurologic findings, pupillary changes, bradycardia, hypertension, and respiratory depression. Clinical presentation varies with age. In newborns, epidural hematomas may complicate delivery and may present with seizures, hypotonia and pallor. Older children may present with headache, nausea, and vomiting several hours following a head injury associated with loss of consciousness. Diagnosis is via head CT which demonstrates a convex, hyperdense mass that generally does not cross suture lines. Treatment depends on the physical exam and head CT findings. Surgical management involves hematoma evacuation and nonsurgical management involves serial imaging and observation. Outcome can be favorable with prompt diagnosis and surgical management.

Subdural Hematoma

Subdural hematomas result from venous tearing and hemorrhage into the potential space located between the dura and arachnoid. Risk factors include falls, motor vehicle accidents, and trauma. Infants are predisposed to subdural hematomas because they have relatively larger heads, subdural spaces, and weaker neck muscles compared with older patients. Other predisposing factors include a history significant for a bleeding disorder, an arachnoid cyst, or shunted hydrocephalus. Onset of symptoms may be delayed days to weeks due to the relatively lower-pressure venous system. Infants may present with a bulging fontanelle and irritability. Young children may present with seizures, increasing head circumference, hypotonia, and focal neurologic signs. Non-accidental trauma should be considered in the differential diagnosis of a young child with a subdural. Associated factors may include retinal hemorrhages, bruises, fractures, or a previous history of abuse. Older children may present with altered mental status, headache, and vomiting. Late findings indicating compression of the brain stem include focal neurologic findings, pupillary changes, bradycardia, hypertension, and respiratory depression.

Diagnosis of subdural hematoma is by head computed tomography (CT) which demonstrates a concave, hyperdense mass which crosses suture lines. Additional studies to consider in a child with a subdural hematoma include a blood count, coagulation studies, funduscopic exam and skeletal survey. Treatment depends on the physical exam and head CT findings and outcome varies. Surgical management involves hematoma evacuation or shunt placement and nonsurgical management may involve serial imaging, observation, and intracranial pressure monitoring.

Meningitis

Meningitis refers to inflammation of the tissues surrounding the brain and spinal cord. Etiology includes bacteria, viruses, fungi, and parasites.

Bacterial Meningitis

Bacterial meningitis is life threatening and the most common causative agents depend on patient factors such as age, immunization status, and presence of underlying predisposing factors. Risk factors include living in an endemic area, immunocompromise, lack of immunization against Haemophilus influenza type b or *Streptococcus pneumoniae*, recent infection (especially upper respiratory, ear, or sinus), head trauma, ventricular shunts, or cochlear implants.

The most common etiologic organism varies with age and location. In neonates, group B streptococci, Listeria monocytogenes, and gram negative enteric bacilli (*Escherichia coli,* Klebsiella, *Enterobacter*, *Salmonella*) are common agents. Worldwide, *S. pneumoniae*, *N. meningitides*, and *H. influenza* type b are common causes of bacterial meningitis in young children and *S. pneumoniae* and *N. meningitides* are common in older children. Clinical features and exam findings may include headache, fever, neck stiffness, photophobia, altered mental status, nausea,

vomiting, irritability, seizures, cranial nerve palsies, petechiae, and purpura.

Evaluation should include CSF cell count, differential, glucose, protein, culture and serum blood count, differential, glucose, culture and possibly neuroimaging. Imaging should be performed prior to lumbar puncture if there is concern for increased intracranial pressure that may result in herniation during the lumbar puncture. Disease progression may be fulminant so empiric antibiotic therapy may need to precede lumbar puncture and imaging; however, a blood culture should be obtained initially.

CSF findings include pleocytosis with neutrophil predominance, elevated protein, decreased glucose, and a positive gram stain. A positive CSF culture is diagnostic as is a positive blood culture in the setting of CSF pleocytosis. Complications include shock, increased intracranial pressure, seizures, and subdural effusions and abscesses. Treatment should be initiated empirically while awaiting culture results and then altered if necessary when a specific organism is identified. Recommendations for empirical therapy of bacterial meningitis by the Infectious Disease Society of America include vancomycin plus a third-generation cephalosporin for children older than 1 month. Adjunctive dexamethasone use to decrease the inflammatory response is recommended in infants and children with *H. influenzae* type b meningitis and should be given prior to the initiation of antimicrobials and continued for 2–4 days. Outcomes vary but persistent neurologic sequelae are not uncommon following bacterial meningitis.

Viral Meningitis

Viral meningitis is more common than bacterial meningitis in children. It is also known as aseptic meningitis and refers to an inflammation of the meninges without evidence of bacteria in the CSF. Various infectious agents such as enterovirus, herpesvirus, arbovirus, influenza, and rabies may be responsible but non-polio enteroviruses are the most common cause of viral encephalitis in the United States. Worldwide, there is a diverse range of pathogens that may cause viral encephalitis. Arboviruses have a global distribution but are found primarily in tropical regions. West Nile virus is an arbovirus that is found in North America. Pediatric West Nile Virus may present with a febrile illness and may include meningitis, encephalitis, and a poliomyelitis-like illness.

Clinical presentation may include fever, headache, nausea, vomiting, photophobia, and change in mental status. Young children may present with fever, irritability, rash or seizures. Common etiologies include group B coxsackieviruses and echoviruses. Evaluation should include lumbar puncture and CSF analysis to rule out a bacterial etiology. Pleocytosis is seen and may be neutrophilic initially and then become more lymphocytic. Treatment is supportive and prognosis is generally favorable.

Brain Tumors

Headache may be the presenting symptom of a brain tumor in children. Brain tumors are the most common solid organ cancer and second to leukemia as the most common overall cancer in children. Presenting signs and symptoms vary with the age of the child and with the location of the tumor but frequently include headache (especially nocturnal or early morning), nausea, vomiting, unsteadiness, seizures, behavior changes, papilledema, and focal neurological deficits. The majority of childhood brain tumors are located infratentorially. Location of the tumor determines clinical presentation. For example, brainstem gliomas may present with cranial neuropathies due to their compression of exiting cranial nerves. Cerebellar astrocytomas and medulloblastomas may present with ataxia due to their location in the cerebellum as well as symptoms of increased intracranial pressure because of fourth ventricular compression. Ependymomas tend to arise from the floor of the fourth ventricle, which is near the vomiting center, and may present with nausea, vomiting, or obstructive hydrocephalus. Supratentorial midline tumors such as craniopharyngiomas and gliomas may present with visual deficits, eye movement abnormalities, neuroendocrine dysfunction, and behavioral and appetite changes due to their location near the optic chiasm and pituitary gland.

Headache is a common complaint in children and deciding which children to image can be challenging. Recent studies have investigated clinical predictors of underlying brain tumor in children presenting with headache and found that a headache that causes nocturnal awakening or is present upon awakening as well as a negative family history of migraine were predictors of underlying brain tumor. Additional predictors include headache duration of less than 6 months, vomiting, seizures, confusion, and an abnormal neurological exam. Diagnosis is via neuroimaging with and without the use of contrast. Magnetic resonance imaging is generally preferred over computed tomography because the posterior fossa is better visualized. Treatment depends on the histological diagnosis, tumor location, and age of the child but

may involve surgery, chemotherapy, radiation, and other modalities such as anticonvulsant medications or bone marrow or stem cell reconstitution. Prognosis varies with tumor type.

Vascular Malformations

Cerebral vascular malformations include venous angiomas, arteriovenous malformations, capillary telangiectasias, and cavernous malformations. Venous angiomas are the most common and are usually benign. Clinical presentation may include headache as well as dizziness, incoordination, seizures, motor or sensory deficits. Diagnosis is via magnetic resonance imaging and treatment is conservative. Capillary telangiectasias are usually asymptomatic and may be found incidentally on neuroimaging studies.

Cavernous malformations and arteriovenous malformations are more likely to cause neurologic symptoms. Cavernous malformations may be sporadic or familial. Clinical presentation may include headache, hemorrhage, seizure, or focal neurologic sign. Diagnosis is via magnetic resonance imaging and treatment depends on symptoms and location but may involve surgical resection, or stereotactic radiosurgery.

Arteriovenous malformations involve a loss of the normal vascular organization. They consist of abnormal collections of dilated arteries and veins in the brain parenchyma. The most common presenting sign is hemorrhage but additional presentations include headache, seizures, and neurologic deficits. Hemorrhagic strokes are relatively common in children and may be due to an underlying arteriovenous malformation. Diagnosis is via neuroimaging, including computed tomographic angiography which provides vascular detail or magnetic resonance imaging/angiography which provide visualization of surrounding structures. Angiography is the gold standard however, because it allows for visualization of the lesion and is useful in the assessment of hemorrhage risk. Treatment depends on many factors and may include surgical resection, radiosurgery, or embolization.

Brain Abscess

Brain abscesses are generally uncommon in children but may develop in children with predisposing factors. Studies have identified congenital heart disease, otitis media, sinus or intracranial infections, intracranial hardware, skull fractures, intracranial surgery and immunosuppression (organ transplantation, chemotherapy, HIV) as predisposing factors for brain abscess development. Pathogenesis involves the invasion of microorganisms (bacteria, fungi, parasites) into the brain parenchyma and can result from direct extension, hematogenous spread, or penetrating trauma. Infants being treated for meningitis may present with a bulging fontanelle and increased head circumference. Older children may present with more obvious signs including vomiting, fever, headache, photophobia, mental status changes, seizure, and focal neurologic signs such as hemiparesis or visual field deficits. Early diagnosis and treatment leads to improved outcome. A brain abscess should be considered in a child with a history of congenital heart disease, immunosuppression, recent neurosurgical procedure or ear or sinus infection presenting with new onset headache, seizure, or focal neurologic sign. Neuroimaging with contrast should be performed and will demonstrate an enhancing rim around an area of decreased attenuation. Treatment generally involves monitoring with frequent brain imaging, several weeks of antibiotics and possible surgical intervention. Outcome may include hydrocephalus, seizures, developmental delay, neurologic deficits, or death.

Hydrocephalus

Hydrocephalus is due to the accumulation of cerebrospinal fluid (CSF) secondary to an imbalance in its production and reabsorption. This may result from increased CSF production, decreased absorption or obstruction to flow, which is the most common cause. This increased pressure results in dilatation of the ventricular system, affects its lining and the surrounding white matter. Congenital hydrocephalus may be a result of intrauterine infection, toxin exposure, or central nervous system (CNS) tumor or malformation. Acquired hydrocephalus may be the result of CNS infection, hemorrhage, or tumor, causing ventricular obstruction. Signs and symptoms include an increase in head circumference, headache (especially morning), nausea, vomiting and changes in vital signs, level of consciousness, and papilledema. Acute hydrocephalus presents more obviously than chronic hydrocephalus, as the system has time to adjust to the changes. Diagnosis can be made by neuroimaging including cranial ultrasound in infants or head computed tomography or magnetic resonance imaging. Treatment depends on the underlying cause but may involve CSF drainage and shunt placement. Complications of shunts include mechanical malfunction and infection. Headache is a frequent complaint in patients with shunts and should raise the suspicion for shunt malfunction or infection. Prognosis depends on

cause, time to treatment, and complications but may include seizures and developmental delay. Prognosis in untreated hydrocephalus is poor and may include death.

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Michelle A. Miller

Overview

Pediatric rehabilitation involves those measures taken to decrease the functional impact of a disease process or trauma on that child and the family. It includes the family unit at its core and integrates the child's developmental levels into its expectations. The chapters in this section have discussed the wide variety of neurological findings in children, how to establish the diagnosis when possible, prognosis, and treatment approaches. This chapter will outline the common impairments associated with neurological disease and trauma and how they might be addressed.

Disability

The World Health Organization has defined disability as being "an umbrella term covering impairment, activity limitations, and participation restrictions." Impairment is that area of body function or structure which has a deficit. This would include weakness, a visual field cut, or aphasia, for example. Activity limitations refer to difficulty with performing a specific task because of the impairment. With the examples above, this could include walking, reading, or talking, respectively. Finally, participation restrictions put this in the context of society and how the child is affected within typical life situations. Therefore, the child who has difficulty walking may not be able to walk to school any longer and the child with a visual field cut and/or aphasia may not be able to order food at a restaurant because he is unable to read the menu or voice his choices. Disability may be temporary as in the case of a child with Guillain–Barre syndrome, who has a full recovery or chronic such as for the child with cerebral palsy (CP). Regardless of whether the child is born with a disability or acquires it later in life, the child and the family are forever changed.

Historical Perspective

Children with disabilities have not always been treated kindly in history. In Ancient Greece, Aristotle proposed "death for the deformed child." Later, Jesus, Buddha, Confucius, and Mohamed all extolled concern for all humankind whether disabled or not. In the Middle Ages, disabled children were tolerated as long as they could work. However, the Roman Catholic Church then began to switch its stand from "children of innocence" to "products of the devil." The time of the Inquisition saw many deaths as they were viewed as people without souls or witches. These beliefs continued into the 1600s when, for example, a Massachusetts General Court in 1641 pronounced that "the birth of a defective or abnormal child was always suspect, reflecting either God's wrath or the work of the devil." In the 1800s, individuals with disabilities were often indentured servants or held in jail. Perspectives began to change when philanthropists such as DuPont, Frick, Watson, Carnegie, and others supported the formation of custodial care institutions in 1923 to shelter and care for those individuals who were felt to be unable to manage in the general society. Attitudes continued to switch with the advent of the polio epidemics. The onset of modern-day rehabilitation was further sparked by the returning, injured veterans of World War II and the Vietnam War. Many countries have now adapted policies of inclusion and advocated for the removal of architectural and philosophical barriers to those with disabilities. Pediatricians should be aware of those resources in their community to support and enhance the lives of disabled children.

The Rehabilitation Evaluation

The medical diagnosis relies on a thorough history and physical examination with appropriate testing as indicated. Treatment is focused on curing or alleviating the medical problem. The rehabilitation evaluation documents the functional consequences of that medical diagnosis. All of the child's impairments are considered and placed in the context of how they are able to perform age appropriate tasks such as talking, feeding, dressing, toileting, walking, and playing.

If the disease or trauma cannot be cured through medical or surgical intervention, then therapy is instituted to minimize the impairment. For example, glasses are

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provided for a child with a visual acuity deficit, or a weak muscle can be strengthened. In some cases, the impairment is permanent and cannot be minimized. The physician must then evaluate those skills that are intact and use them to adapt to the environment.

Case Example

A 4-year-old boy has been diagnosed with spinal muscular atrophy (SMA) type II. He is inquisitive and social, but limited in his interactions by his inability to get his body from point A to point B. Working with a therapist and a durable medical equipment specialist, he learned how to operate a power wheelchair. After obtaining the power wheelchair, he was able navigate around his preschool class, talk with friends, and explore the environment. His intact capabilities included his normal cognition, inquisitiveness, and social skills. By increasing his mobility, he was able to take advantage of new learning opportunities through increased interactions with his peers and his classroom.

Rehabilitation of the Brain

The brain has a prolonged developmental course with synaptic proliferation, pruning, and myelination proceeding into the 2nd and 3rd decades of life. With this understanding, it is hypothesized that the brain has a certain degree of plasticity to recover from injury and regain function. The brain may be injured as the result of trauma or illness. It may not form correctly during gestation. The lesions may be static as in cerebral palsy or traumatic brain injury (TBI) or may be progressive as with the leukodsytrophies (see Chap. 366, "Acute, Subacute and Progressive Encephalopathies" by G. Gascon).

The leading cause of mortality in children in developed countries is traumatic brain injury (TBI). For those who survive, there may be a high associated morbidity. Luckily, the majority of TBI is mild and often classified as concussion. These injuries are the ones most likely to present to the pediatrician's office. A careful neurologic examination is warranted to evaluate for any focal deficits. Most commonly the child presents with complaints of headaches, body pain, mood/behavioral changes, fatigue, and difficulties in school. Treatment tends to be symptomatic with the addition of medication to help with sleep if warranted. A period of cognitive rest is recommended until the headaches and fatigue have improved. This may mean temporary absence from school, a decrease in reading workload, and postponing any school testing. At home, television watching and computer use may need to be curtailed. Typically, children can return to school and sedentary activities within a week. When the child is involved in sports, they should not resume play until symptoms have resolved and neuropsychological testing as may be available by ImPACT or CogSport have returned to baseline. Alternative testing may include paper and pencil tests such as trail making, digit symbol substitution, and the Stroop word color tests (*Fig. 379.1*).

General conditioning and noncontact sports–related skills should be practiced first. Children should not progress to contact skills or actual play until they can perform all skills without symptoms. Guidelines for return to play have been well described in the Consensus Statement on Concussion in Sport 3rd International Conference on Concussion in Sport Held in Zurich, November 2008. Studies have shown that higher-level balance skills even with a mild brain injury may be impaired for up to 3 months following the injury (see Chap. 377, "Head Injury in Children" by Daniel Tsze and Tom Chun for further detail).

A rare, but deadly complication after concussion, second impact syndrome, may occur in some children and

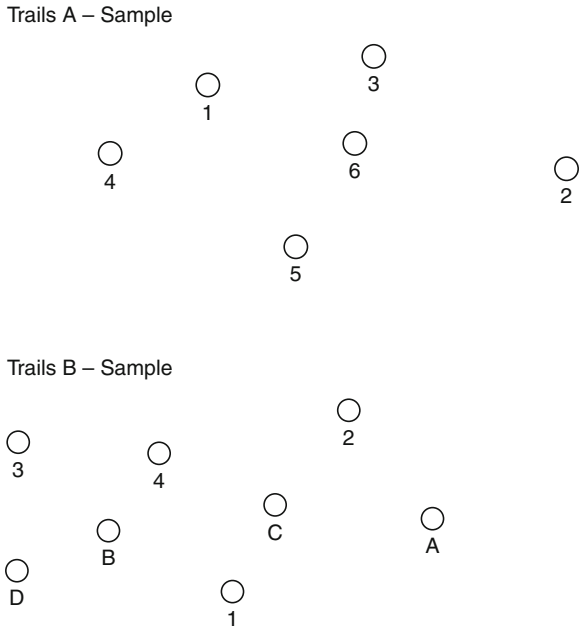

Figure 379.1
Examples of trail-making tests A and B. Individuals must connect the circles sequentially by number for trails A and by alternating the number and alphabet for trails B. Time for completion of the test is standardized

adolescents. In a child who has not fully recovered from a concussion, a second seemingly minor head trauma may result in severe brain swelling. On CT, diffuse brain swelling is noted that may lead to brain herniation and death.

For children who sustain a moderate to severe TBI, the rehabilitation plan is more complex and intense. Impairments may include eye muscle weakness, vision loss, facial weakness, hearing loss, dysphagia, sensory loss, weakness, balance difficulties, behavioral changes, and cognitive changes especially involving attention, memory, and organization. If the severe TBI was the result of a motor vehicle collision, there may be associated bony or peripheral nerve injuries adding to the impairment (see Chap. 377, "Head Injury in Children" by Daniel Tsze and Tom Chun for further details). Rehabilitation starts with preventing secondary injury. As complications following the injury increase, the prognosis for functional recovery declines. In the acute setting, the goals include maintaining limb range of motion, managing spasticity, managing pain, preventing skin pressure injury, managing agitation, and improving awareness of self and the environment. The stages of recovery from a brain injury are nicely described by the Ranchos Los Amigos Scale (*Table 379.1*). Education of the family and the child, as possible, with respect to the injury and typical course of recovery are of paramount importance.

Therapies typically involve physical therapy, occupational therapy, speech therapy, psychology, and rehab nursing at a minimum. Children and families receive significant benefit when therapeutic recreation, a school teacher, a nutritionist, and a massage therapist are included. These therapies will focus on strengthening muscles that are weak, improving or maintaining range of motion, evaluating and strengthening oral musculature and control to help with swallowing, improving balance, and working on functional skills. These could include sitting, transferring from sit to stand, walking, toileting skills, eating, dressing, bathing, talking, hand writing, and social interaction.

Bracing to decrease spasticity, maintain range of motion, support a weak limb, or correct a deformity may be needed. For example, a child with spastic hemiplegia following a TBI may benefit from an ankle foot orthosis (AFO) to help clear his foot and control his knee while walking (*Fig. 379.2*).

Medications such as Botulinum toxin, baclofen, diazepam, and dantrolene sodium may be employed to help with spasticity not responding to physical measures. However, their benefit must be weighed against the possible side effects including increased somnolence, decreased

Table 379.1
Rancho Los Amigos cognitive scale

Level	Description	Detail
I	No response to tactile, auditory, or visual stimulus	
II	Generalized reflex response to pain	Decorticate or decerebrate posture, physiologic changes or vocalization with often the same response regardless of the stimulus.
III	Localized response	Blinks to light, turns toward/away from sound, responds to physical discomfort, and has inconsistent response to commands.
IV	Confused/agitated	Alert, very active, aggressive, or bizarre behaviors, performs motor activities but behavior is nonpurposeful, extremely short attention span, generalized agitation.
V	Confused/non-agitated	Gross attention to environment, highly distractible, requires continual redirection, difficulty learning new tasks, agitated by too much stimulation or specific irritant. May engage in social conversation but with inappropriate verbalizations.
VI	Confused/appropriate	Inconsistent orientation to time and place, retention span/recent memory impaired, begins to recall past, consistently follows simple directions, and has goal-directed behavior with assistance.
VII	Automatic/appropriate	Performs daily routine in highly familiar environment in a non-confused but automatic robot-like manner. Skills noticeably deteriorate in unfamiliar environment. Lacks realistic planning for own future.
VIII	Purposeful/appropriate	

Source: Malkmus D, Booth D, Kodimer C (1980) Rehabilitation of the head injured adult: comprehensive cognitive management. Rancho Los Amigos Hospital, Inc.

Figure 379.2
This young man has a KAFO (knee ankle foot orthosis) on the left and an AFO on the right which allows him to stand and walk without assistance

seizure threshold, and increased muscle weakness. Assistive devices such as a walker, cane, crutches, or a wheelchair can enhance mobility. Often, the physical impairments have a good recovery with return of ambulatory abilities and self-care skills at or near baseline. However, cognitive impairments may have a much greater functional impact. Speech therapists can work on memory and organizational skills. Medications can be used to help with secondary attention deficits. However, a full battery of neuropsychological testing gives the best input to a child's areas of strengths and weaknesses. This information should be shared with the schools to facilitate school reentry and develop plans for education. In the United States, Individualized Education Plans (IEPs) are developed based on the results of a multifactored evaluation (MFE) which assesses physical and cognitive function within the school. They may include therapy services in the school to promote attainment of school-related activities such as computer access or opening containers in the lunchroom. Typical modifications recommended for the TBI population with significant impairments include a copy of the teacher's notes, a smaller classroom setting, dismissal from class early to allow safe navigation of the hallways, an extra set of books to be kept at home, an aide to keep a child on task or find his way through the school, reduction in homework load to assess mastery of the topic as opposed to busy work, multiple-choice testing instead of essay questions, a quiet setting with extra time for testing as well as accessible transportation to and from school. If a child's needs are not as complex, a 504 plan for in-classroom or school accommodations would allow a child access to use an elevator, for example, while healing from a fractured leg. It provides accommodations to a child in the regular classroom setting as opposed to a special education setting.

As the child progresses from the acute stage of recovery to subacute and chronic stages, a pediatrician should watch for signs of depression. Often, the full impact of the injury does not strike the child until months after discharge from the hospital. As they become more aware of their deficits and limitations, the child may become depressed or angry. Ongoing counseling can be beneficial either at the school or in a private setting. Children may also present to their pediatrician with an apparent worsening of their physical or cognitive skills. This is not uncommon with typical viral illnesses, although the pediatrician should ask about any further head trauma, seizure activity, or signs of hydrocephalus.

Other causes of brain injury such as stroke or brain tumor often present with more focal areas of deficit related to the area of the brain involved. (Please refer to Chap. 376, "Cerebrovascular Disorders in Children" by Steve Roach for further discussion.) The rehabilitation approach is similar with a close evaluation of the impairment and the resulting functional impact of that impairment. For a child with severe aphasia, an assistive communication device may be warranted. Additional education may need to be provided to the child and family if there is likelihood for additional strokes or recurrence of the brain tumor in the future. If the tumor is malignant, then acute goals may need to be tempered with future prognosis. A child who regains walking ability may still need a wheelchair due to fatigue from chemotherapy or progression of the disease.

An earlier presentation of brain injury is represented in the cerebral palsy population. The etiologies of cerebral palsy (CP) are varied, but by definition the insult to the brain must be nonprogressive, occur in the developing fetal or infant brain, and result in motor and postural impairments. (Please refer to the chapters on Chap. 359, "Congenital Brain Malformations and Hydrocephalus" by John Gaitanis and Chap. 360, "Neonatal Neurological Disorders" by William Brown and Mara Coyle Brown for further discussion.) CP is

the most common motor disability of childhood. Its classification is based on the anatomic distribution of weakness and the movement disorder. Children may be hemiplegic, diplegic, triplegic, or quadriplegic. Triplegia has also been described as hemiplegia on diplegia in that both lower limbs are involved as well as an upper limb. Movement patterns include spastic, dystonic, athetoid, choreiform, ataxic, hypotonic, and mixed forms. Purely hypotonic cerebral palsy is rare. Infants typically present hypotonic at birth and later develop spasticity, choreoathetosis, or ataxia as their neurologic system matures.

Early diagnosis of CP allows for early therapeutic intervention and assessment for associated disorders such as visual deficits, hearing impairment, seizure disorder, speech delay, swallowing and motility disorders, hip subluxation/dislocation, scoliosis, and cognitive impairments. Hearing impairment in CP is relatively rare except in children with congenital TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes) infections or a history or kernicterus. Visual deficits are varied and may include more severe impairments such as cortical blindness or retinopathy of prematurity (ROP) to the less severe such as amblyopia or strabismus. Early treatment with laser therapy for ROP to eye patching or glasses for amblyopia or strabismus, for example, can have a profound impact on future function. Infants with swallowing or oral motor dysfunction may need feeding tubes to allow for adequate nutrition and to decrease the risk of aspiration and pneumonia. Early, progressive hip subluxation may require surgical intervention such as a hip adductor tenotomy to prevent dislocation of the femoral heads (*Fig. 379.3*).

In addition to assessment and treatment of the associated disorders to help prevent or decrease further functional impairment, rehabilitation includes therapies such as physical therapy, occupational therapy, and speech therapy. These therapies may address management of spasticity, strengthening, range of motion, and developmental milestones. Constraint-induced therapy may be employed to force use of the weak upper limb. The nonaffected upper limb is immobilized so that the child is forced to use the weaker limb. Studies are ongoing to determine which children may respond best to this type of therapy. Other therapies which have been reported beneficial include aquatic therapy, hippotherapy, and acupuncture. Bracing may help to correct and/or support joint position altered by spasticity and weakness. Medications to decrease spasticity may also be indicated to improve function or decrease pain. Adaptive equipment such as walkers, crutches, and wheelchairs help with mobility. Other types of equipment such as bath chairs and lifts help to alleviate caregiver burden and improve safety especially as a more severely impaired child grows. Adaptive equipment may also include augmentative or assistive communication devices, utensils with built-up handles or straps for self-feeding, and dressing aids (*Fig. 379.4*). Technology has progressed so that children may access environmental control units to turn on lights, computers, or televisions.

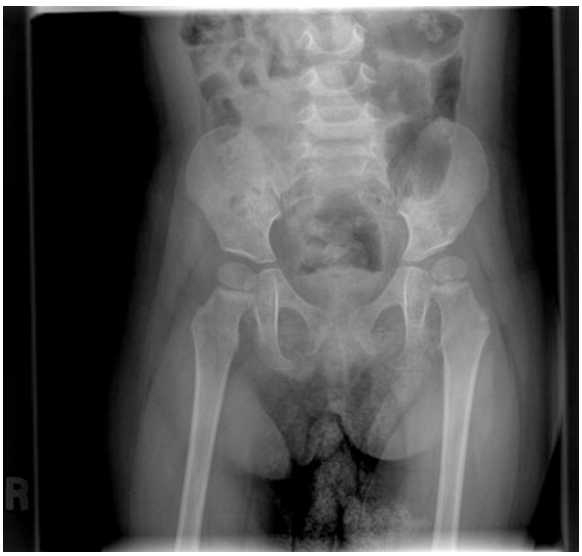

Figure 379.3
Note the bilateral coxa valga, shallow acetabuli, and hip subluxation which are common in the nonambulatory child with CP

Figure 379.4
With the use of a mouth stick with a pen attached, this young man who is quadriplegic is able to write his name

As the child with CP ages, other medical concerns may arise. A child with hemiplegia may develop a significant leg length discrepancy that not only affects gait, but also may cause a scoliosis if left untreated. Children who are nonambulatory often develop a progressive scoliosis. In addition, they are at high risk for osteoporosis and resultant fractures. Children may have early onset of puberty and referral to an endocrinologist is warranted. As adults, these children often complain of cervical pain, back pain, hip pain, and hand parasthesias. Competitive employment of adults with cerebral palsy in a European population–based study was only 29% compared to 82% of the control group. Proposed reasons for the difference included cognitive impairment, difficulties with accessibility, attitudes toward individuals with CP, poor social skills, and employment policies.

Rehabilitation of the Spinal Cord

There are many processes which can affect spinal cord function acutely including traumatic spinal cord injury, transverse myelitis, infarct, tumor, and epidural hematoma. These all present with some degree of loss of sensation and motor function and if untreated, may progress. History and physical examination and an MRI will differentiate most of these cases.

Even with appropriate treatment, residual impairment is likely. These impairments include decreased or absent sensation, paralysis, neurogenic bladder, and neurogenic bowel. Acute medical complications include hypercalcemia, renal calculi, urinary tract infection, constipation, ileus, autonomic dysreflexia, pressure ulcers, spasticity, pneumonia in children with cervical or high thoracic injury, and difficulties with temperature regulation. Autonomic dysreflexia (AD) may occur in a child with an injury at the T6 level or higher. When there is a noxious stimulus below the level of injury, there is an increase in sympathetic activity leading to hypertension due to vasoconstriction below the level of injury. The central nervous system responds with increased vagal tone and resultant bradycardia. If untreated, this can be fatal with extreme hypertension. Symptoms include a pounding headache, flushing, and sweating above the level of injury, and "goose" flesh. When symptoms arise, have the child sit up immediately and then search for the cause. Symptoms will resolve with removal of the noxious stimuli. The most common causes are an over distended bladder and constipation. Other causes include tight-fitting clothing, fracture below the level of injury, and appendicitis, for example. If the cause cannot be determined quickly, nitropaste is effective in bringing blood pressure down and can be removed quickly to prevent hypotension when the noxious stimulus is removed. Parents and children at risk should be taught the signs and symptoms of AD and how to respond. Deep venous thrombosis (DVT) and pulmonary embolism (PE) are not as common in children who are prepubertal, but may occur not only in the legs, but also around deep lines. Symptoms may include calf swelling or tenderness, tachycardia, chest pain, or irritability. Usual presentation is within the first few weeks following the spinal cord injury. Doppler ultrasound will confirm the diagnosis of DVT and spiral CT or VQ scan will confirm the diagnosis of PE. Low-molecular-weight heparin or warfarin treatment of the PE and/or DVT should continue for 3–6 months. Factor anti-Xa levels and INR should be followed to measure therapeutic dosing for low-molecular-weight heparin and warfarin, respectively. Complications include bleeding and heparin-induced thrombocytopenia.

Subacute and long-term medical complications include latex allergy, pressure ulcers, heterotopic ossification, scoliosis, syrinx, and osteoporosis. The incidence of latex allergy has been reported to be 6–18% in children after spinal cord injury. Heterotopic ossification (*Fig. 379.5*) occurs most commonly around the hips

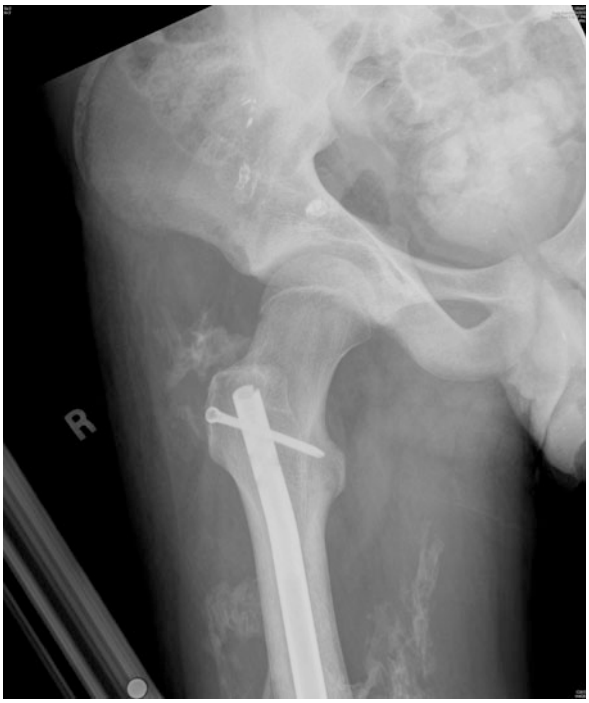

Figure 379.5
Heterotopic ossification noted near the left ASIS

and shoulders and should be aggressively treated with nonsteroidal anti-inflammatory drugs such as indocin and range of motion. Scoliosis occurs in the growing child whose primary means of mobility is in a wheelchair. Bracing may help to slow the progression of the curve, but it will not cure it. A referral to orthopedic surgery is recommended for appropriate timing of spinal fusion if needed.

Rehabilitation focuses on recognizing and treating the medical complications, education of the family and child regarding the injury and resultant effects, and addressing the impairments. Sensory loss may reverse with time. However, in the meantime, children are taught to visually inspect skin for injury daily and to test water temperature, for example, to prevent a burn of insensate areas. There may be associated neuropathic pain which may respond to medications such as gabapentin, pregabalin, or amitryptiline. Pressure relief should be performed every 15 min while awake and every 2 h when asleep by weight shifting or turning to prevent pressure ulcers in those without any sensation. Areas at highest risk in infants are the occiput and sacrum. In older children, the sacrum, ischii, lateral epicondyles, and malleoli are high risk areas.

Weakness can be treated with exercise, electric stimulation, and bracing to improve function. Ventilatory support, biPAP, or CPAP may be needed by children with injuries at the C5 level and higher. The level of injury will determine the eventual functional capabilities of the child. Neurological classification of the injury in the United States is determined by the American Spinal Injury Association guide (◉ *Fig. 379.6*). In general, children at a C7 level and below can be independent with mobility and basic self-care skills at the wheelchair level. Children with a functional level of L3 and below should be able to ambulate with assistive devices. Newer technology has included robotic exoskeletons to assist with walking, but these are not currently available to children due to the size and weight.

Spasticity often interferes with function and may cause pain and decreased range of motion. However, it may also provide stability as in the case of a paraplegic who uses that spasticity to stand. Therefore, treatment of spasticity must take into account function. Initial treatment includes stretching, bracing, and modalities such as superficial heat. When these do not adequately control the spasticity, medications may be beneficial. For focal spasticity, botulinum toxin injections may be helpful. If the spasticity is more widespread, options include baclofen, diazepam, dantrolene, tizanidine, and clonidine. The side effects and efficacy must be evaluated for each medication prior to initiation.

Initially following the injury, bladder and bowel function stops. The bladder is flaccid, and incontinence is usually due to overflow. Overdistention of the bladder is common and can cause a secondary injury to the bladder wall. With aggressive fluid resuscitation, a Foley catheter is the best management of the bladder. As fluids become more balanced, children should be switched to an intermittent catheterization program. Children can be taught to self-cath by age 5. The goals of the bladder program include preventing kidney injury, preventing urinary tract infections, and continence. As the child recovers from the initial insult, the bladder may become spastic. In this case, children will void small amounts frequently. A urinary tract infection should be ruled out as this will cause a similar voiding pattern. Baseline studies should include a renal ultrasound and a voiding cystourethrogram (VCUG). Urodynamic studies may be performed at a later date when bladder function has stabilized. Oxybutynin is an effective treatment for a spastic bladder. In children with recurrent urinary tract infections, prophylactic antibiotics may be indicated. The leading cause of death in individuals with a spinal cord injury prior to the introduction of bladder catheterization was renal failure.

Bowel function is similarly disrupted. Initially, an ileus is common and the anal sphincter may be flaccid. As spinal reflexes return, anal sphincter tone returns, but gastric motility continues to be very slow. Medications are used to assist with peristalsis and elimination from the rectal vault at a specific time to allow for continence. Medications to assist with peristalsis include stimulants such as senna, bisacodyl, milk of magnesia, and hyperosmolar agents such as polyethylene glycol (Miralax). Rectal agents include bisacodyl suppositories, therevac mini enemas, enemas, and/or rectal stimulation. The program must fit in with the child's lifestyle and knowing their premorbid elimination pattern may be helpful. Generally, the goal is to have a bowel movement daily following the rectal program.

The impact of a spinal cord injury on a child and family is life altering. A psychologist can be very helpful in helping a child and the family deal with the feelings and adjustment to a potentially new way of life. Depression in the weeks to months following the injury is very common.

Myelomeningocele presents with many of the same issues as spinal cord injury although the pattern of weakness and sensory loss may be patchy. In addition, children often have a Chiari malformation and associated hydrocephalus (◉ *Fig. 379.7*).

Therefore, children may have cognitive impairments in addition to the sensory, motor, and bladder/bowel

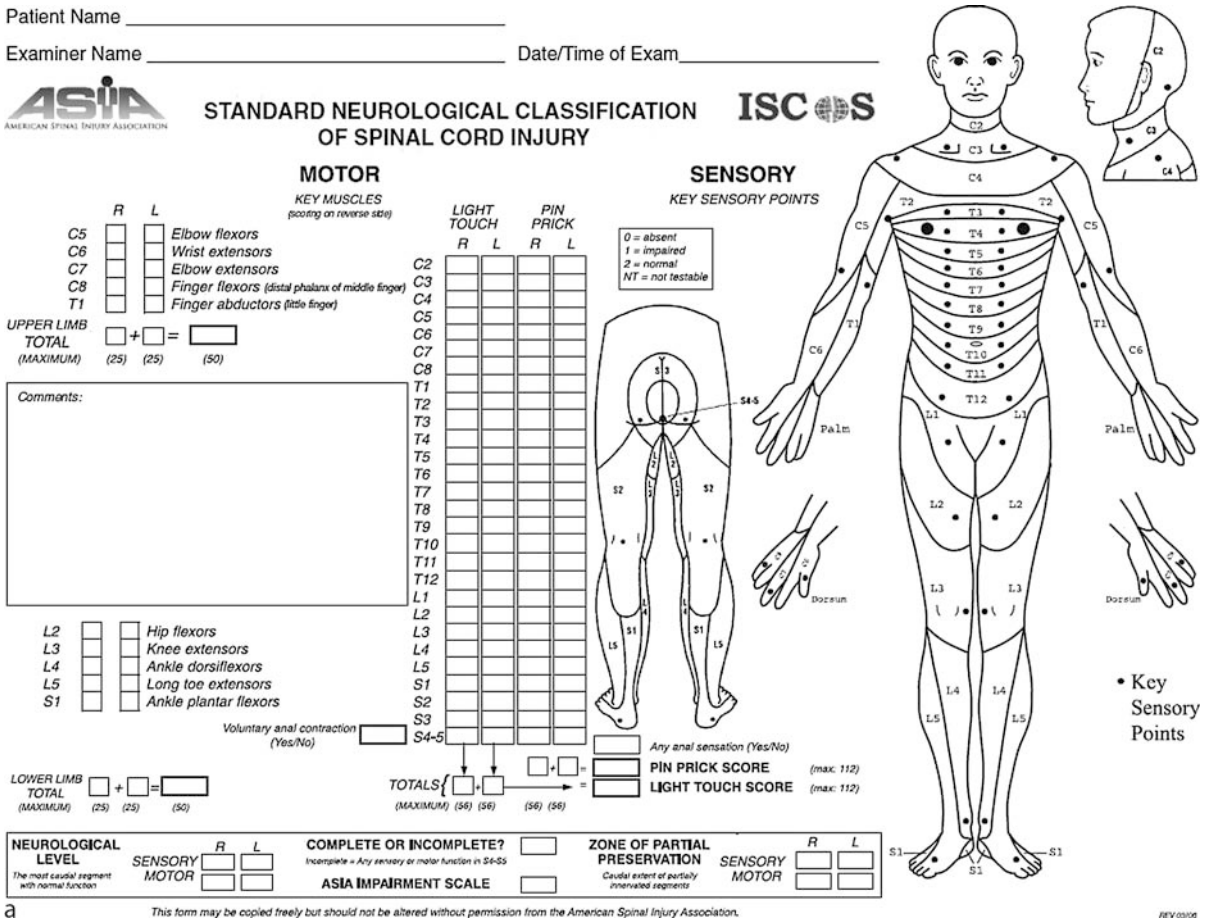

Figure 379.6
(Continued)

Muscle grading

0 Total paralysis

1 Palpable or visible contraction

2 Active movement, full range of motion, gravity eliminated

3 Active movement, full range of motion, against gravity

4 Active movement, full range of motion, against gravity and provides some resistance

5 Active movement, full range of motion, against gravity and provides normal resistance

5* Muscle able to exert, in examiner's judgement, sufficient resistance to be considered normal if identifiable inhibiting factors were nor present

NT not testable. Patient unable to reliably exert effort or muscle unavailable for testing due to factors such as immobilization, pain on effort or contracture.

Asia impairment scale

☐ A = Complete: No motor or sensory function is preserved in the sacral segments S4-S5.

☐ B = Incomplete: Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.

☐ C = Incomplete: Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.

☐ D = Incomplete: Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.

☐ E = Normal: Motor and sensory function are normal.

Clinical syndromes (Optional)

☐ Central cord
☐ Brown-sequard
☐ Anterior cord
☐ Conus medullaris
☐ Cauda equina

Steps in classification

The following order is recommended in determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
2. Determine motor levels for right and left sides.
   Note: In regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level.
3. Determine the single neurological level.
   This is the lowest segment where motor and sensory function is normal on both sides, and is the most cephalad of the sensory and motor levels determined in steps 1 and 2.
4. Determine whether the injury is Complete or Incomplete (sacral sparing).
   If voluntary anal contraction = No AND all S4-5 sensory scores = 0
   And any anal sensation = No, then injury is COMPLETE.
   Otherwise injury is incomplete.
5. Determine ASIA Impairment Scale (AIS) Grade:

Is injury Complete?
NO ↓ — If YES, AIS = A Record ZPP (For ZPP record lowest dermatome or myotome on each side with some (non-zero score) preservation)

Is injury motor incomplete?
YES ↓ — If No, AIS = B (Yes = voluntary anal contraction OR motor function more than three levels below the motor level on a given side.)

Are at least half of the key muscles below the (single) neurological level graded 3 or better?

NO ↓ AIS = C

YES ↓ AIS = D

If sensation and motor function is normal in all segments, AIS = E
Note: AIS E is used in follow up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact: the ASIA Impairment Scale does not apply.

b

Figure 379.6
Neurological classification of spinal cord injury

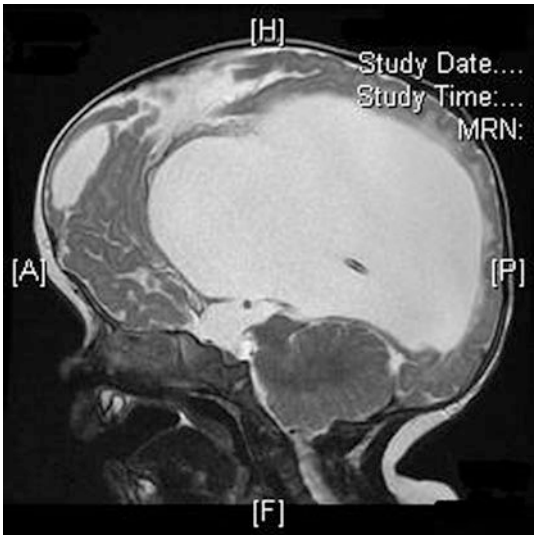

Figure 379.7
Note the Chiari II malformation with the cerebellar tonsils herniating through the foramen magnum and the severe hydrocephalus

dysfunction. Medical complications may include shunt failure and tethered cord in addition to those listed above for spinal cord injury. The incidence of latex allergy in this population has been reported to be as high as 72%. Obesity is also prevalent in children with myelomeningocele. Dietary guidelines include a diet low in fat and carbohydrates and high in protein and fiber. Caloric intake should be decreased by 10–20% of typical recommendations for children.

Rehabilitation of Peripheral Nervous System

Disorders of the peripheral nervous system may be due to trauma such as a brachial plexus injury, autoimmune response such as Guillain–Barre Syndrome (GBS), or due to hereditary diseases such as Charcot–Marie Tooth (CMT) disease. In addition, there are a number of neuropathies that may be caused by medications or developmental disorders such as hypomyelination. These conditions may have a favorable prognosis such as brachial plexus injury or GBS or be slowly progressive such as CMT (Please see Chap. 375, "Parainfectious and Autoimmune Disorders" by Tanuja Chitnis).

Birth brachial plexus injury results typically from shoulder dystocia during delivery. The infant often has an increased birth weight and becomes stuck under the pelvic brim. There may be an associated clavicle fracture. The infant often does not move the upper limb initially. Immobilization of the shoulder by pinning the sleeve of the infant's shirt to the shirt is recommended to allow the clavicle to heal and to prevent further injury to the arm. Gentle range of motion to the shoulder, elbow, and wrist should begin at 2 weeks of age. Most commonly the upper trunks of the plexus are involved (Erb's palsy, C5–C6 nerve roots); less commonly the lower trunks (Klumpke's palsy, C8–T1 nerve roots). In severe injuries, the complete plexus is involved. An EMG at 6–8 weeks of age can delineate the areas of injury and any reinnervation that may have occurred. If a nerve root avulsion or neurotmesis (complete disruption of the nerve and myelin sheath) is revealed by MRI of the cervical spine and cord, referral to neurosurgery at 4–6 months of age is recommended for a primary repair. For all other cases which demonstrate evidence of recovery, therapy includes range of motion, activities to facilitate use of the affected limb and possibly electrical stimulation if tolerated. As the child develops, there may be imbalances in muscle strength leading to joint contractures at the shoulder or elbow. These may respond to stretching, serial casting, or surgery. Bracing may be helpful with maintaining range of motion at the elbow.

Guillain–Barre syndrome presents with ascending sensory loss and weakness in the limbs. It may be demyelinating or axonal. The axonal variant tends to have a poorer prognosis for recovery. Rehabilitation includes strengthening weak muscles, treating neuropathic pain, and teaching adaptive techniques for self-care skills and mobility until strength improves. Endurance is the last area to recover and often rest breaks are required upon return to school and home activities.

The progressive neuropathies often require bracing to support weak muscles to allow for continued functioning. Daily stretching and range of motion exercises will help to preserve joint mobility. Adaptive techniques and equipment help with energy conservation. Continued reevaluation of functional capabilities is required to adjust bracing and equipment as needed. Therapeutic exercise should be within tolerance and never to the point of fatigue.

Rehabilitation of Conversion Reaction

Some children may present to their pediatrician or the hospital with symptoms such as weakness, difficulty walking, pseudoseizures, sensory abnormalities, or pain that

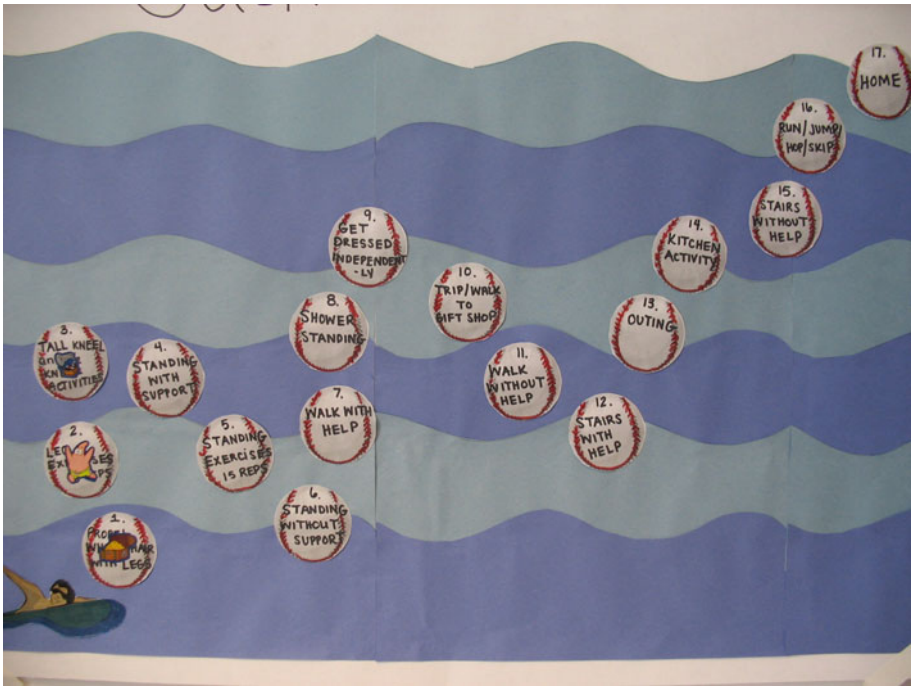

Figure 379.8
Example of a goal mountain for a child who has difficulty walking

upon further evaluation do not have an organic basis. The diagnosis of conversion reaction is given when other plausible etiologies have been ruled out. Conversion reaction is classified as one of the somatoform disorders. It is felt to be the body's subconscious response to a stressor or stressors. Children may or may not be aware of the stressor and classically do not demonstrate concern for their impairment – "la belle indifference." These children are often very intelligent, high achievers, and set very high expectations for themselves. Females tend to be at higher risk for this disorder than males. Early diagnosis and treatment is key to a favorable prognosis.

In many cases, the pediatrician may be able to simply give reassurance that the symptoms will resolve quickly and parents should downplay or ignore the symptoms. It is very beneficial to explain the diagnosis to parents so that they do not inadvertently reinforce the symptoms. However, giving the diagnosis to the child is often counterproductive as children feel that others think they are making up the symptoms or are crazy. A referral for counseling is helpful in teaching children coping techniques for stress.

When this approach is not enough, there are two different treatment approaches: psychiatric intervention and physical rehabilitation. If the conversion reaction has a physical manifestation such as a gait abnormality, for example, a structured rehabilitation program may be beneficial. However, parents must have accepted the diagnosis and agreed to the program for the best results. Treatment is aimed at a systematic reacquisition of skills to meet the expected functional outcome; walking normally, for example. The program is kept very structured and children receive positive reinforcement only when they have achieved the individual goals set for them on their goal mountain (*Fig. 379.8*).

Symptoms are largely ignored and children may not progress up the goal mountain until the goal is performed correctly on two consecutive therapies. In addition to the physical therapy, children receive daily counseling with a psychologist to evaluate stressors and teach coping techniques. Parents also participate in counseling for education regarding the disorder and how to address any regression once children return home. Oftentimes, children require ongoing counseling after discharge from the rehabilitation program. Good prognostic indicators include early diagnosis and good family support. Poor prognostic factors include longer duration of symptoms, history of sexual abuse, and family denial of diagnosis.

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Endocrine Disorders

Khalid Hussain

380 Introduction to Endocrine Disorders

Khalid Hussain

Background to Hormone Physiology

The endocrine system uses the internal secretion of hormones to convey messages to target cells via cognate receptors. Hormones are defined as chemical messengers that are released into the blood stream that then act on distant target tissues. Hormones can also bind to receptors on cells that are expressed close to the site of release. When hormones act on neighboring non-hormone-producing cells, the action is called "paracrine." The synthesis of hormones occurs in specialized cells designed for that specific purpose. Hormones must be able to travel in the blood stream and diffuse in effective concentrations into tissues.

Many protein hormones such as growth hormone, prolactin, insulin, and glucagon are produced in dedicated cells by standard protein synthetic mechanisms common to all cells. These secretory cells usually contain specialized secretory granules designed to store large amounts of hormone and to release the hormone in response to specific signals. For example in the case of steroid hormones, the precursor is cholesterol which is modified by various chemical reactions to form glucocorticoids, androgens, and estrogens, and their biologically active derivatives.

Hormones are synthesized in response to biochemical signals generated by various modulating systems. Many of these systems are specific to the effects of the hormone product. For example, parathyroid hormone synthesis is regulated by the concentration of ionized calcium, whereas gonadal, adrenal, and thyroid hormone synthesis is regulated by the signals from the hypothalamic-pituitary axis. Specialized cells in the hypothalamus and pituitary monitor the circulating hormone concentrations and secrete trophic hormones that activate specific pathways for hormone synthesis and release. Typical examples are luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid-stimulating hormone (TSH), and adrenocorticotropic hormone (ACTH). In the case of the thyroid gland, hypothalamic TSH-releasing hormone (TRH) stimulates TSH secretion from the anterior pituitary. TSH then initiates TH synthesis and release from the thyroid gland. TRH and TH inputs regulate the hypothalamic-pituitary-thyroid axis (see *Fig. 380.1*).

Hormones may be fully active when released into the circulation or may require activation in specific cells to produce their biological effects. These activation steps are often highly regulated. For example, the T4 released from the thyroid cell is a prohormone that must undergo a specific deiodination to form active 3,5,3 triiodothyroxine (T3). This deiodination reaction can occur in target tissues such as the central nervous tissue.

Hormones produce their effects by interacting with cell surface receptors. Others (such as steroid and thyroid hormones) must enter the cell to bind to cytosolic or nuclear receptors. Receptor proteins may be localized in the cell membrane, cytoplasm, or nucleus. Membrane-associated receptors usually consist of extracellular sequences that recognize and bind ligand, transmembrane anchoring hydrophobic sequences, and intracellular

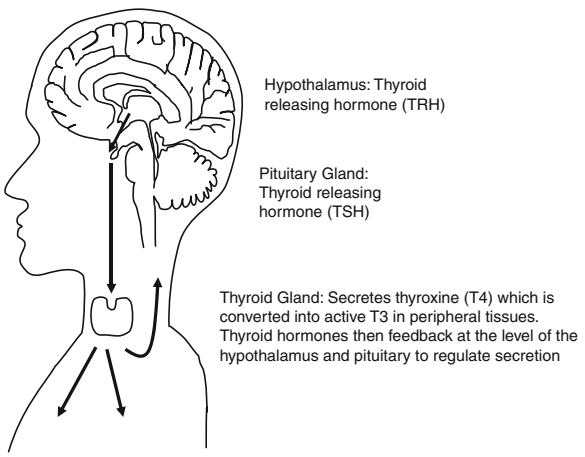

Figure 380.1
Summary of thyroid hormone secretion: Thyroid hormone (TH) plays an important role in development, growth, and cellular metabolism. TH production is controlled by a complex mechanism of positive and negative regulation. Hypothalamic TSH-releasing hormone (TRH) stimulates TSH secretion from the anterior pituitary. TSH then initiates TH synthesis and release from the thyroid gland. Serum concentrations of T_4 and its biologically active form T_3 are maintained in a narrow range by the ability of thyroid hormone (TH) to limit its own production by negative feedback at the hypothalamic TSH-releasing hormone (TRH) neuron and pituitary thyrotroph

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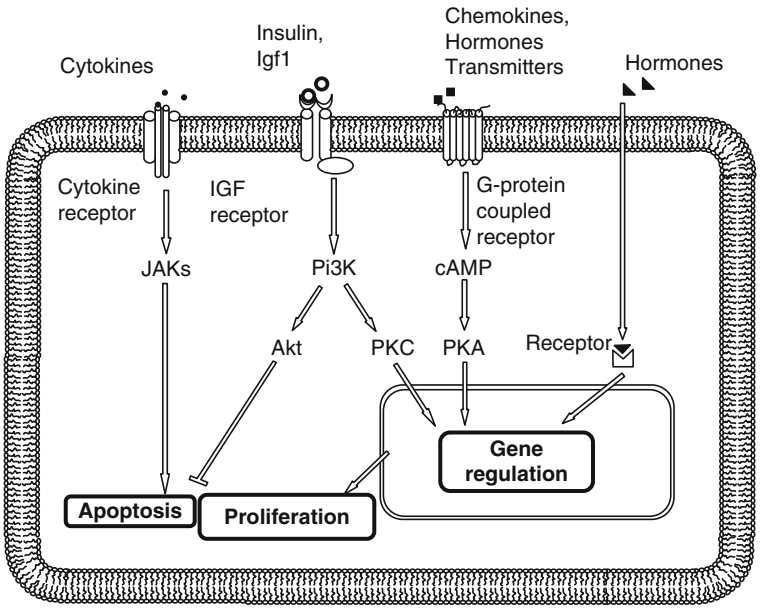

Figure 380.2

An outline of cell signaling pathways; cytokines, hormones, and transmitters interact with corresponding receptors and the signal is transduced through various pathways. Some hormones, for example, estrogen enter the cell through the membrane and interact with a receptor. Janus kinase (JAK) is a family of intracellular non-receptor tyrosine kinases that transduce cytokine-mediated signals via the JAK-STAT pathway. Phosphoinositide 3-kinases (PI 3-kinases or PI3Ks) are a family of related intracellular signal transducer enzymes capable of phosphorylating the 3 position hydroxyl group of the inositol ring of phosphatidylinositol. AKT protein family, whose members are also called protein kinases B (PKB), plays an important role in mammalian cellular signaling. Cyclic adenosine monophosphate (cAMP, cyclic AMP, or 3′-5′-cyclic adenosine monophosphate) is a second messenger important in many biological processes

sequences which initiate intracellular signaling. Intracellular signaling is mediated by soluble second messengers (such as cyclic AMP) or by activation of intracellular signaling molecules (such as signal transducers and activators of transcription protein (STAT) proteins). Receptor-dependent activation of heterotrimeric G-protein comprising ά, β, and γ subunits may either induce or suppress effector enzymes or ion channels. Several growth factors or hormone receptors (insulin) behave as intrinsic tyrosine kinases or activate intracellular protein tyrosine kinases. *Figure 380.2* shows an outline of the various receptors involved in hormonal signaling.

Introduction to Endocrine Disorders

A large number of childhood endocrine disorders may present to the pediatrician. Thus it is important for the pediatrician to have an understanding of the common endocrine problems so that a prompt diagnosis can be made or the patient can be appropriately referred. Conditions such as short stature and diabetes mellitus are some of the most common endocrine problems observed in the childhood period.

Common causes of short stature presenting to the pediatrician include familial short stature and idiopathic short stature. On the other hand, diabetes mellitus is one of the most common chronic pediatric diseases. Type 1 diabetes mellitus is the leading form of diabetes in young white people, especially those of northern European ancestry. Type 2 diabetes mellitus is now on the increase in the pediatric population on a worldwide scale.

The endocrine section of this book contains chapters on growth, puberty, disorders of sexual development (DSD), adrenal, thyroid, and pituitary and calcium disorders. There are separate chapters on diabetes mellitus section and hypoglycemia. Each chapter is clinically orientated to provide the practicing clinician with a thorough knowledge of the clinical problem. There are clear guidelines on investigation and patient management. In addition, each chapter provides a state-of-the-art overview of the recent research advances in the relevant field.

381 Disorders of Calcium Homeostasis

Ravi Chetan · Assunta Albanese

Physiology of Bone and Calcium Metabolism

The metabolism of calcium and bone are closely linked. Ninety-nine percent of the total body calcium is present in the skeleton; the remaining 1% is labile between bone, extracellular and intracellular fluid. The total serum calcium concentrations range from 2.2 to 2.6 mmol/L. At a physiologic pH (7.4) 40% of total calcium is bound to albumin, 10% exists as complexes with bicarbonate/phosphate/citrate, and 50% is free ionized calcium. The normal range for ionized calcium in blood plasma is 1–1.25 mmol/L. Ionized calcium has the primary regulatory role, it is in turn the regulated component. The homeostasis of calcium (Ca^{2+}) is intimately linked to that of magnesium (Mg^{2+}) and phosphorus. Dietary intake, fecal and urinary excretion, and bone turnover need to be balanced. Phosphorus is more widely distributed with 85% in bones as hydroxyapatite and 15% as a component of phospholipids, phosphoproteins, and nucleic acids. In blood, phosphorus exists in two ionic forms HPO_4^{2-} and $H_2PO_4^{-}$, together called inorganic phosphorus (P_i), and normal plasma or serum phosphorus concentration changes during life with the highest levels been found in neonates. Homeostasis of phosphorus is done mainly by the kidneys.

The plasma levels of calcium and phosphorus are subject to regulation by the interaction of three hormones – parathormone (PTH), vitamin D (as 1,25-dihydroxyvitamin D), and calcitonin (CT) – acting on three organs, bone, intestines, and kidneys. The influences of other hormones, notably sex steroids, growth hormone, and thyroxine and several novel gene products involved in this homeostasis are becoming clear.

Pathophysiology: Disorders of calcium and bone metabolism are common and best understood by examining changes in: parathyroid hormone, 1,25-dihydroxyvitamin D, urinary excretion of calcium and phosphorus, and bone turnover.

Parathyroid Hormone (*PTH*) is an 84-amino-acid peptide secreted by parathyroid glands (usually 2 pairs) located at the back of the thyroid gland in the neck. PTH acting on bone and the kidney influences several changes that increase plasma levels of circulating calcium. Calcium in turn has a negative feedback role on parathyroid glands to suppress parathyroid hormone secretion; so there is a reciprocal relationship between circulating levels of PTH and calcium. Extracellular ionized Ca^{2+} acts on calcium sensing receptor (CaSR) on the surface of parathyroid cells to detects and respond to very small changes in the Ca^{2+}concentration. The same sensor also regulates the responses of thyroid C-cells, which secrete CT in direct relationship to extracellular Ca^{2+}, and on the distal renal tubules where calcium excretion is regulated, and in several other tissues

The effects of PTH are mediated by a specific receptor called PTH receptor. A protein that is similar to PTH, known as parathyroid hormone-related peptide (PTHrP), is secreted and acts locally (paracrine/intracrine) within the bone. PTHrP is also secreted by many tumors (thus causing hypercalcemia). PTHrP acts on the same receptor as PTH. The receptor is thus known as the PTH/PTHrP receptor. Both CaSR and PTH/PTHrP receptor belong to the family of G-protein receptors that act via adenylate cyclase systems. The main effects of PTH are stimulating renal reabsorption of calcium, inhibiting renal reabsorption of phosphate, stimulating bone resorption, and inhibiting bone formation and mineralization. PTH also stimulates synthesis of Calcitriol. The net effect is an increase in serum Ca^{2+} and decrease in serum phosphorus.

Vitamin D is a secosterol present in humans in two forms: vitamin D3 or cholecalciferol (endogenously synthesized or ingested from animal sources) and vitamin D2 or ergocalciferol (ingested from plant sources). Their relative distribution ratio is 2:1. Cholecalciferol is synthesized in skin from the cholesterol metabolite 7-dehydrocholesterol under the influence of ultraviolet radiation. Vitamin D2 (ergocalciferol) is produced by ultraviolet irradiation of the plant sterol – ergosterol. Both forms of vitamin D are further activated by similar sequential hydroxylation at carbon position 25 (in the liver) and 1 (in the kidneys) give the Vit D-hormone – 1,25-dihydroxyvitamin D (Calcitriol). Hydroxylation also

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renders water solubility. Hepatic hydroxylation is dependent entirely on the amount of native vitamin D (D2 & D3) available; hence, laboratory measurements of 25-hydroxyvitamin D are good indicators of body vitamin D status. C-1 hydroxylation of 25-hydroxyvitamin D in the kidneys is self regulated by levels of 1,25-dihydroxyvitamin D and by PTH (and therefore indirectly by plasma Ca^{2+} levels). C-1 hydroxylation of 25-hydroxyvitamin D also occurs in lymphocytes, macrophages and monocytes; this is unregulated and potentially can lead to toxic levels of 1,25-dihydroxyvitamin D in certain situations resulting in hypercalcemia. The role of 1,25-dihydroxyvitamin D in Calcium regulation is fourfold. (A) It increases active absorption of Ca^{2+} from intestine. Fifteen to twenty percent of dietary calcium is usually absorbed; this is increased during periods of accelerated skeletal growth, pregnancy, and lactation. 1,25-dihydroxyvitamin D increases the permeability of brush border for uptake of Ca^{2+} from the luminal surface by increasing the Calcium-binding Proteins (CaBP) which facilitate Ca^{2+} transfer across the basolateral surface if the luminal epithelial cells and enhancing Mg^{2+} absorption (Magnesium is important for PTH secretion and action). Vitamin D acts synergistically with PTH on bone to increase bone resorption and restore normal Ca^{2+} levels. This is done by inducing macrophages to change into osteoclasts. It increases bone mineralization, possibly by both enhancing osteoblasts activity and increasing extracellular supply of calcium and phosphate in the osteoid matrix. It has no direct action on the kidney but, as mentioned above, it auto-regulates 1-α hydroxylase activity and hence its own synthesis. It should be noted that when vitamin D levels are low there will be a compensatory increase in PTH levels and thus severe (symptomatic) hypocalcemia is most unlikely.

Calcitonin is secreted by the parafollicular C-cells of thyroid in response to hypercalcemia. Its actions largely oppose the effects of PTH to decrease plasma Ca by impairing osteoclast formation and osteolytic activity and increased urinary excretion of calcium. It is of questionable importance in physiological regulation of calcium in post-natal life, but may have a role to play in fetal bone mineralization. It is a useful marker in Multiple Endocrine Neoplasia-2 and is used therapeutically to reduce plasma Ca^{2+} when there is hypercalcemia.

Urinary excretion of Phosphorus: Phosphorus homeostasis is mainly achieved by the kidneys. 90% of dietary phosphorus is freely filtered across the glomerulus. Of this, 90% is reabsorbed in the proximal tubule and 10% in the distal tubule. HPO_4^{2-} mostly undergoes active reabsorption while $H_2PO_4^-$ is passively reabsorbed. When the glomerular filtration rate is normal the amount of phosphate reabsorbed in the proximal tubules determines the serum phosphate concentration. PTH is the primary phosphaturic hormone; it dramatically inhibits reabsorption of Pi from proximal renal tubules. PTH simultaneously enhances active Ca^{2+} reabsorption from ascending limb of loop of Henle and distal convoluted tubule. Serum Pi levels and vitamin D also influence the homeostasis of phosphorus.

Three novel genes viz. phosphate-regulating endopeptidase (PHEX) gene at locus Xp22.2-p22.1, Fibroblast-Growth-Factor-23 (FGF-23) gene at locus 12p13.3, and the klotho gene (KL) on locus 13q12 play important roles in the regulation of Pi homeostasis. The PHEX gene encodes an endopeptidase, predominantly expressed in bone and teeth, but not in kidney. FGF-23 codes for a peptide that is a substrate of this endopeptidase. Cleaved FGF-23 fragments promote renal reabsorption of Pi. Klotho generates the FGF-23 receptor and is essential for endogenous FGF-23 function.

Active reabsorption of the filtered load of Pi across renal tubules is via Sodium-phosphate co-transporters (NaPi). Three sodium–phosphorus cotransporters are expressed in proximal tubule cells. NaPi-I and NaPi-II are located in the apical membrane, whereas NaPi-III is expressed in the basolateral membrane. In proximal tubule cells (and in enterocytes), the activity of NaPi-II limits transepithelial phosphate transport.

Determining the renal reabsorption of phosphate: The proportion of filtered phosphate which is not reabsorbed is represented by the ratio of the phosphate clearance to the glomerular filtration rate, and an approximate value for the latter can be obtained from the endogenous-creatinine clearance. The phosphate/creatinine clearance ratio (C_p/C_{cr}) is calculated as: (urine phosphate $\times$ plasma creatinine) $\div$ (plasma phosphate $\times$ urine creatinine). The tubular reabsorption of phosphate (TRP) is then calculated:-TRP = $(1 - C_p/C_{cr}) \times 100$. Normal levels: $C_p/C_{cr} = 0.02 - 0.22$. TRP = 78–98%.

Alternatively using the nomogram of Walton and Bijvoet renal phosphate threshold (TRP) normalized for the glomerular filtration rate (TRP = TMP/GFR) can be calculated. The normal range is 2.5–4.2 mg/100 ml.

The TMP (maximal reabsorption rate for Pi) is variable and is regulated by diet and the calcitropic hormones. TMP is reduced by high dietary phosphorus intake. PTH and CT both increase Pi excretion while 1,25-dihydroxyvitamin D decreases excretion. A low TRP in the hypophosphatemic patient indicates an appropriate renal response to hypophosphatemia, and usually implicates gastrointestinal loss or intracellular shift. A high TRP

in hypophosphatemia is indicative of increased renal excretion (secondary to a PTH-mediated mechanism, Fanconi syndrome, X-linked or autosomal dominant hypophosphatemic rickets, or oncogenic rickets/osteomalacia).

Urinary excretion of Calcium: Calcium (>90%) is reabsorbed passively by the proximal tubule and Loop of Henle. This can be inhibited by frusemide. Less than 10% of filtered load is actively reabsorbed in the distal tubule which is hormonally regulated; inhibited by CT, stimulated by PTH while vitamin D has small stimulatory effect). Klotho stimulates calcium reabsorption in the distal convoluted tubule by deglycosylating and stabilizing the epithelial calcium channel TRPV5 on the surface of cellular membrane. Distal tubular reabsorption of Ca^{2+} is stimulated by thiazides.

Bone turnover: Bone tissue is in constant state of flux with the extracellular fluid. Bone formation and resorption are part of a continuous remodeling process taking place on the bone surface of microscopic units called osteons. Annually 25% of trabecular and 3% of cortical bone undergoes turnover. Three types of cell produce and maintain bone. Osteoblasts (bone-forming cells) work at bone surfaces and secrete osteoid (unmineralized collagen). They modulate the crystallization of hydroxyapatite and influence the activity of osteoclasts. Osteoclasts (bone-resorbing cells) are responsible for the resorption of bone. They are necessary for the repair of bone surfaces and the remodeling of bone. Osteocytes are mature osteoblasts which have become embedded within the mineralized regions of bone. They are involved in the sensing and translation of information about the internal bone environment.

Markers of bone formation: Osteocalcin is a noncollagenous protein (gamma-carboxyglutamate) found in bone and dentin, secreted by osteoblasts and thought to play a role in mineralization and calcium ion homeostasis. Osteocalcin may also function as a negative regulator of bone formation, although its exact role is unknown. Osteocalcin is used as a preliminary biomarker of the effectiveness of a given drug on bone formation. P1NP (N-propeptide of type I collagen) is a marker of newly formed collagen. Alkaline phosphatase (ALPL) comprises a group of enzymes that catalyze the hydrolysis of phosphate esters in an alkaline environment, generating organic radical and inorganic phosphate. In mammals, there are four alkaline phosphatase isoenzymes: placental, placental-like (germ cell), intestinal, and tissue-non-specific (liver/bone/kidney). All four isoenzymes are anchored to the outer surface of the plasma membrane by a covalently attached glycosylphosphatidylinositol (GPI) anchor. Human alkaline phosphatases have four metal binding sites: two for zinc, one for magnesium, and one for calcium ion. The tissue-non-specific isoenzyme (ALPL) plays a role in skeletal mineralization. Defective ALPL leads to Hypophosphatasia. Conversely in other cause of defective mineralization ALPL levels are elevated. ALPL is also elevated during periods of rapid bone growth, e.g., infancy and puberty.

Markers of bone resorption: Biochemical markers of bone resorption are substances formed during modification of bone collagen (collagen type I) and released into the blood when osteoclasts degrade bone matrix. Breakdown products of collagen include deoxypyridinoline and pyridinoline and their associated cross-link telopeptides at C- and N- terminals (NTX and CTX). Antibody assays against these proteins therefore provide information about osteoclast activity and collagen breakdown. Despite some derived from collagen breakdown in other tissues as well the collagen cross-link deoxypyridinoline appears to be the marker with least contribution from non-osseous tissues. C-telopeptide-related octapeptide is another assay that identifies an aminoacid sequence of collagen type I involved in the formation of intermolecular cross-links.

Hypocalcemia

Definition

Hypocalcemia is total serum calcium of less than 2.1 mmol/L in children, less than 2 mmol/L in term neonates, and less than 1.75 mmol/L in preterm neonates

In the fetus plasma Ca^{2+} is maintained up to 0.5 mmol/l higher than in the mother. There is active transport of Ca^{2+} across the placenta. Fetal bones have high rate of Ca^{2+} accretion, the highest rates are seen in the late third trimester. Preterm birth thus significantly reduces this. At birth, Ca^{2+} levels drop physiologically for 24–48 h with a nadir around 2.0 mmol/l. Plasma Ca^{2+} levels are then maintained by a physiological temporary suspension of bone uptake.

Etiology

Causes of hypocalcemia can be considered in two groups.

Neonatal Hypocalcemia: Early neonatal hypocalcemia (within 48–72 h of birth) and late neonatal hypocalcemia (usually 3–7 days after birth; can occur as late as 6 weeks of age). A higher risk of early neonatal hypocalcemia is seen in low birth weight babies – 30% of

infants <1,500 g have hypocalcemia, preterm infants born <32 weeks gestation, infants of diabetic mothers, and infants affected by with birth asphyxia. The mechanisms of early onset hypocalcemia are not entirely understood and might be due to delay response to the rise in PTH following "physiological" postnatal hypocalcemia. It often corrects itself spontaneously but calcium supplementation can be needed. In infants of diabetic mothers, maternal magnesium depletion might lead to fetal hypomagnesemia that induces functional hypoparathyroidism and hypocalcemia in the infant. Late neonatal hypocalcemia may be due to (a) exogenous high phosphate load: Hypocalcemia is caused by feeding with phosphate-rich milk, e.g., whole cow's milk has 7 times the phosphate load of breast milk (956 v 140 mg/L), (b) magnesium deficiency, (c) transient hypoparathyroidism of newborn, (d) hypoparathyroidism due to other causes, (e) maternal hyperparathyroidism, (f) maternal vitamin D deficiency, and (g) in association with gentamicin use, especially with once-every-24-hour dosing schedule.

Maternal vitamin D deficiency and hypoparathyroidism can present at any time after birth.

Childhood Hypocalcemia is best considered in three groups. (1) Parathyroid disorders and Hypocalcemia due to reduced PTH secretion or impaired PTH action. (2) Vitamin D disorders: vitamin D deficiency, impaired vitamin D metabolism, or impaired Renal Function. (3) Abnormally active Calcium Sensing Receptor, i.e., Familial Hypercalciuric Hypocalcemia.

Clinical Approach to Hypocalcemia

Hypocalcemia is often asymptomatic and comes to notice by a low serum/plasma calcium level on a blood test done for some other reason. When symptoms occur they include: tetany, stridor, paraesthesia (especially in hands and feet), and focal or generalized seizures. Trousseau's sign (carpal spasm on inflating the sphygmomanometer cuff) and Chvostek's sign (facial and eyelid twitching induced by a sharp tap on the facial nerve) may be elicited. The ECG may show a prolonged QTc interval. Chronic hypocalcemia may manifest with cataracts/calcification of the lens, papilloedema, enamel hypoplasia, and calcification in basal ganglia/frontal lobe seen on CT scan. In infants with hypocalcemia secondary to vitamin D deficiency cardiomyopathy may also occur. Some syndromes associated with hypocalcemia have characteristic dysmorphic features, e.g., Williams syndrome.

Initial investigations include: plasma calcium, phosphate and magnesium, alkaline phosphatase, albumin, creatinine, serum PTH level, and plasma level of 25-OH vitamin D. [Calculate corrected Calcium using the formula: *corrected calcium (mmol/L) = uncorrected calcium (mmol/L) + 0.02 × (40-albumin)*]. Serum should be stored for later measurement of 1,25-dihydroxyvitamin D if indicated. Urine for calcium, phosphate, creatinine. X-ray of wrist + hand (or knee + chest in infants and toddlers) for suspected rickets or skeletal survey for other suspected bone abnormalities.

The above plasma and urine investigations might need to be performed in the child's parents.

From these initial investigations it is useful to categorize the cause of hypocalcemia according to PTH results: (a) If undetectable or low PTH: *Hypoparathyroidism, hypomagnesemia* are most likely causes. (b) Normal PTH: *Abnormal CaSR*. (c) High PTH: *Vitamin D deficiency/impaired metabolism, pseudohypoparathyroidism, osteopetrosis, renal failure*.

Treatment of Hypocalcemia

Severe/Symptomatic Hypocalcemia is treated using IV Calcium. Dose is 0.11 mmol/kg of Ca^{2+} given slowly over 5–10 min. This dose can be repeated if symptoms do not abate. Alternatively use a continuous infusion of Ca^{2+} 0.5–1.0 mmol/kg in 24 h. This can be added to the maintenance fluid. (Maximum dose is 8.8 mmol/24 h.) Switch to oral calcium supplements as soon as possible. Parenteral preparations available include: 10% solution of Calcium gluconate contains 0.22 mmol Ca^{2+}/ml). The maximum volume per dose is 20 ml of 10% Calcium gluconate. 10% Calcium chloride injection is also available containing 680 micromol of Ca^{2+}/ml.

Asymptomatic/mild hypocalcemia is treated by the oral route. Oral calcium dose is 0.25 mmol/kg 4 times-a-day for neonates and children up to 5 years age; from 5 to 12 years age, 0.2 mmol/kg 4 times-a-day; and for those >12 years, 10 mmol 4 times-a-day.

The dose is adjusted depending on response. Common preparations include Calcium Sandoz® syrup – a mixture of calcium salts providing 2.7 mmol of Ca^{2+}/5 ml. and Sandocal® effervescent tablets provide 400 mg or 1,000 mg (equivalent to 10 mmol of Ca^{2+} or 25 mmol of Ca^{2+}, respectively).

Magnesium can be used if response to calcium alone is poor or if hypomagnesemia is present. Twenty percent magnesium sulfate contains 0.8 mmol/ml of Mg^{2+}, while 50% magnesium sulfate contains 2 mmol/ml of Mg^{2+}). The dose of Mg^{2+} is 0.4 mmol/kg for neonates, 0.2 mmol/kg for ages 1 month–12 years, and 4 mmol for children

age >12 years. Magnesium sulfate can be given as deep IM injection or as IV infusion over at least 10 min after diluting it to a 10% solution with 5% or 10% Dextrose or 0.45% or 0.9% sodium chloride solution.

Vitamin D *and not one of its analogues* is used to treat hypocalcemia due to vitamin D deficiency. Vitamin D analogues are used to treat hypoparathyroidism and pseudohypoparathyroidism.

Practice points: (1) Vitamin D deficiency is the commonest cause of hypocalcemia in childhood, outside of the neonatal period. (2) Vitamin D deficiency must first be eliminated or corrected before the other causes of hypocalcemia can be diagnosed. (3) Hypocalcemia can result from vitamin D deficiency without rickets and without raised phosphates and PTH values. (4) Adequate blood and urine samples should be collected and stored before commencing treatment.

Hypocalcemia with Low PTH Level = Hypoparathyroidism

Definition

Hypoparathyroidism is a rare condition caused by a group of heterogeneous conditions in which hypocalcemia and hyperphosphatemia occur as a result of deficient parathyroid hormone (PTH) secretion or the absence of parathyroid glands. Primary hypoparathyroidism can be congenital or acquired. In neonatal period hypoparathyroidism can be transient.

Etiology

Transient Neonatal Hypoparathyroidism: PTH secretion is normally suppressed in the fetus because of high placental transfer of calcium, particularly in the third trimester. At birth cord clamping abruptly stops calcium transfer; serum calcium concentrations decrease rapidly and PTH secretion is triggered. Prolonged delay in parathyroid response causes a transient hypoparathyroidism. Preterm infants are at increased risk, and up to 50% of very low birth weight infants may have hypocalcemia. Infants of diabetic mothers may be born prematurely, and also have hypomagnesemia resulting from maternal magnesuria accompanying glucosuria. Low serum magnesium impairs PTH release and action. Maternal hyperparathyroidism causes more prolonged suppression of PTH secretion in the neonate.

Clinical Symptoms and Signs

Hypocalcemia with its clinical manifestations are the presenting features; in addition specific craniofacial features and assessment of cardiac and renal systems are necessary to exclude a syndromic cause. Similarly, autoimmune hypoparathyroidism can occur as an isolated endocrine condition or with other glandular deficiencies in APS1, requiring evaluation of other endocrine dysfunction. Long term effects of hypoparathyroidism may involve teeth (poor enamel), nails, hair, and skin, and there may be calcium deposits or kidney stones. Anxiety and depression may be present as low calcium and/or low PTH levels are linked to emotions. There may also be problems with memory and general fogginess. Fatigue and muscle weakness is common.

Isolated Inherited Hypoparathyroidism: These conditions are inherited as autosomal dominant (AD), recessive (AR), or X-linked modes. Several genes are involved. Human PTH gene is located at 11p15. Several inherited mutations lead to isolated defects in synthesis and secretion of PTH. In X-linked recessive hypoparathyroidism, the mutant gene (Xq26–27) is most likely involved in parathyroid gland development. Autosomal recessive loss of function of GCM2 (glial cells missing-2) and GCMB (glial cells missing-B) gene impairs normal parathyroid gland embryology and is responsible for isolated hypoparathyroidism. Gain-of-function mutations in the calcium-sensing receptor (CASR) gene (3q13.3–q21) cause autosomal dominant hypocalcemia. The serum PTH levels are normal; this is discussed in the next section.

The investigation of hypoparathyroidism is as discussed for hypocalcemia.

Treatment of Hypoparathyroidism

The goal of treatment in hypoparathyroidism is threefold: to raise the serum calcium to alleviate acute symptoms and this is then maintained at the lower limit of normal range (2.00–2.12 mmol); to prevent the complications of chronic hypocalcemia; and to prevent the key complication of vitamin D intoxication (hypercalcemia and hypercalciuria) with its adverse effects on the renal and central nervous system.

Calcium is administered both for acute treatment and maintenance as detailed in the treatment of hypocalcemia.

Vitamin D is preferably given as calcitriol (0.25–0.5 μg/day) or as alphacalcidol (dose 15–50 ng/kg/day). Calcitriol is preferred because of its potency and rapid onset and offset of action. Alphacalcidol is rapidly

converted to 1,25-dihydroxyvitamin D in vivo and has the same potency and rapidity of action. Cholecalciferol and ergocalciferol are both more cumulative and therefore potentially more toxic.

Monitoring is done by measurements of serum and urine calcium. 24 h urine calcium excretion is high when treatment is started, even before normocalcemia is achieved, and nephrocalcinosis is a risk. Ultrasound monitoring is necessary. If despite adequate calcium supplements and calcitriol the serum calcium levels are not normalized, thiazides are used in symptomatic patients to reduce urinary calcium excretion.

The elevated serum phosphate levels usually need no active treatment; with the correction of serum calcium there is a decline in phosphate. Phosphate-binding agents such as aluminum hydroxide are occasionally helpful in reducing hyperphosphatemia in initial stages of therapy. Human recombinant PTH has become available but is currently not licensed for the treatment of hypoparathyroidism. Hypoparathyroidism is one of the few endocrinopathies for which hormone-replacement therapy is not readily available. For an excellent review of the current status of replacement therapy see reference.

Hypomagnesemia

Definition

Serum levels of magnesium are in the range of 0.65–1.0 mmol/L. Lower levels constitute hypomagnesemia. Magnesium is a ligand for CaSR. Hypomagnesemia both blunts the release of PTH and also its action. Therefore hypocalcemia secondary to hypomagnesemia can only be corrected once magnesium levels are normalized.

Etiology

The main congenital causes of hypomagnesemia are inherited intestinal absorption defect or a renal tubular reabsorption defect. Acquired causes include any malabsorption, malnutrition, and renal tubular damage (e.g., Cisplatinum).

Familial Primary Hypomagnesemia due to selective defect of Mg^{2+} absorption in small intestines presents with generalized hypocalcemic-hypomagnesemic seizures by 3–8 weeks age. It does not respond to calcium but does to magnesium. Prompt diagnosis and treatment with magnesium prevents permanent neurological impairment. Urinary magnesium/creatinine ratio after an IM dose of Magnesium sulfate (normal = 1.5 mmol/mmol) helps to distinguish whether the defect is a renal tubular leak or a selective defect in intestinal absorption of Mg^{2+}.

Hypomagnesemia is also a cardinal finding in Gitelman Syndrome in association with hypocalciuria and hypokalemic alkalosis.

Treatment

Acute/symptomatic deficiency is treated using IV or deep IM Magnesium sulfate as discussed in the section on treatment of hypocalcemia. Long term supplementation of Magnesium is with oral Magnesium-L-Aspartate. Magnaspartate® powder 6.5 g/sachet provides 10 mmol of Mg^{2+}. It can be dissolved in water. The starting dose in children 1 month–2 years is 0.2 mmol/kg 3 times daily. Half a sachet (5 mmol) dissolved in 100 ml of water daily in children aged 2–10 years and 1 full sachet (10 mmol) daily in 200 ml water is used in children >10 years. Doses are adjusted as required.

Familial Hypercalciuric Hypocalcemia = Hypocalcemia with Normal PTH

The combination of hypercalciuria with hypocalcemia and normal PTH is reflective of an abnormality of Calcium-Sensing Receptor (CaSR).Activating mutations of the CaSR are usually inherited autosomal dominant or sporadic. There is an inappropriately suppressed PTH; in other words a lowered set-point for PTH secretion, i.e., a small fall in plasma calcium, is unable to stimulate the CaSR to signal PTH release. This heterozygous gain of function mutation of CaSR is also called Familial Hypercalciuric Hypocalcemia.

Clinical Features

Presentations range from asymptomatic to severe. Most common symptoms are polyuria and polydipsia even at normal plasma calcium levels due to increased renal calcium excretion. The urine calcium/creatinine ratio is >0.3 mmol/mmol.

Bartter syndrome is a genetically heterogeneous disorder characterized by deficient renal reabsorption of sodium and chloride, and hypokalemic metabolic alkalosis with hyperreninemia and hyperaldosteronemia. Hypocalcemic patients with deficient parathyroid hormone secretion, characteristics of Bartter

syndrome, and activating mutations of the CASR gene have been described.

Treatment

Most patients have mild asymptomatic hypocalcemia and require no treatment. Severe, symptomatic hypocalcemia necessitates cautious use of calcium and vitamin D as treatment may exacerbate baseline hypercalciuria resulting in nephrocalcinosis and renal insufficiency. Several patients have been treated successfully with PTH therapy, averting hypercalciuria and renal failure. More data are needed before its use can be recommended in practice.

Drugs that antagonize the extracellular calcium-sensing receptor (i.e., calcilytic agents), in trials stimulate endogenous PTH, are a promising alternative for disorders with intact but hypofunctioning parathyroid glands.

Hypocalcemia with High PTH suggests vitamin D deficiency/impaired metabolism (discussed later) or pseudohypoparathyroidism (PHP).

Pseudohypoparathyroidism (PHP)

There are several types Ia, Ib, Ic, II, and also pseudopseudohypoparathyroidism (PPHP). The prototype variant Type Ia is eponymous as Albright's Hereditary Osteodystrophy.

Definition

These patients have clinical and biochemical features consistent with hypoparathyroidism but with raised PTH levels and do not respond to exogenous parathyroid hormone (lack of urinary cAMP and phophaturic response to PTH infusion).

Biological resistance to PTH is present and causes hypocalcemia due to impaired mobilization of calcium from bone and reduced intestinal absorption of calcium. Plasma levels of Phosphate are high.

PHP is twice as common in females as males. The commonest genetic mutation is in the GNAS1 gene (Chr20q3.2). Inheritance is autosomal dominant. The resistance to PTH is caused by a defect in G-protein, a ubiquitous protein required for functional cyclic AMP production. Plasma membrane–bound hormone receptors communicate with the catalytic unit of adenylate cyclase through the interaction of a pair of guanine nucleotide binding regulatory proteins (G-proteins). There are many G-proteins, some of which are stimulatory (Gs) or inhibitory (Gi). Patients with PHP type Ia have a 50% reduction in G-stimulatory protein alpha (GSα) in all tissues due to a variety of mutations in the GSα gene.

Clinical Features

As expected patients with PHP Ia display partial resistance to several other hormones and may present with short stature, hypothyroidism, hypogonadism, mental retardation, subcutaneous calcifications, ovulatory, gustatory, and auditory dysfunction. Characteristic dysmorphology includes large head, round facies, obesity, short stature, short neck, and short 4th metacarpals and metatarsals. They tend to grow below the 9th percentile but have blunted pubertal growth spurt. Symptoms and signs of hypocalcemia such as muscle spasms, tetany, etc., can be present. This constellation of developmental and somatic defects is referred to as Albright's Hereditary Osteodystrophy (AHO). Not all features are seen in every patient as there is enormous phenotypic variability. Characteristic hand changes evolve gradually and may not be apparent before the age of 4 years. Shortening of the fourth (and fifth) metacarpals causes short digits, recognized as dimpling over the knuckles of a clenched fist (Archibald sign). Shortening of the distal phalanx of the thumb is identified by the increased ratio of the width of the nail to its length (so-called murderer's thumb or potter's thumb).

In PHP type Ib hormone resistance is confined to only PTH receptors. The biochemical picture is identical to PHP type Ia; however, there are none of the phenotypic features. Mild TSH resistance may be found. Some patients have features of hyperparathyroidism bone disease suggesting that bones respond to PTH. It may be inherited dominantly from an affected mother but sporadic cases are usual.

PHP Ic is rare and involves multiple hormone resistance and phenotypic features of AHO but normal Gsα activity. The defect may be in other components of the receptor-adenylate cyclase system or in mutations in exon 13 affecting only the Gsa–receptor interaction.

PHP type II is a clinically heterogeneous syndrome with no clear genetic basis. The molecular defect is unknown. There is resistance to PTH action but phenotypic features of AHO are absent. The pathophysiology is poorly understood. There may be normal cyclic AMP response but an absent phosphaturic response to PTH. Hypocalcemia, decreased bone mobilization response to

PTH, and decreased serum 1,25-dihydroxyvitamin D are the prominent features of PTH resistance.

Pseudopseudohypoparathyroidism (PPHP) is genetically similar to PHP type Ia. The GNAS-1 gene on Chr20q3.2 displays imprinting. If the maternal abnormal gene is functional it results in PHP Ia, while paternal transmission leads to PPHP. The imprinting is also tissue specific. Only the maternal gene is expressed in the kidneys; thus renal resistance to PTH is only seen in PHP Ia and never in PPHP. PPHP patients express the AHO phenotype but have normal serum calcium levels and have no other evidence of hormone resistance. Some patients may have other affected family members who also have hormone resistance and are diagnosed as PHP Ia.

Investigations

Serum calcium is low. Serum phosphate levels are elevated. Elevated serum concentration of PTH in a hypocalcemic patient suggests either a form of PHP or secondary hyperparathyroidism. An assessment of skeletal and renal responsiveness to PTH is done by measurement of changes in serum calcium, phosphorus, cAMP, and calcitriol concentrations and in urinary cAMP and phosphorus excretion after administration of the biosynthetic N-terminal fragment of PTH. Evaluation of other endocrine functions: thyroid function tests gonadotropins, testosterone or estrogen levels, and growth hormone and insulin-like growth factor-1 axis. X-ray hand may show shortening of the bones (the distal phalanx of the thumb and the third through fifth metacarpals) and small areas of soft tissue calcifications/ossifications. CT scanning may reveal calcification of the basal ganglia. Analysis of the *GNAS1* gene helps identify the specific genetic defect in patients with PHP type 1a while methylation studies help to identify PPHP.

Treatment

Severe symptomatic hypocalcemia is initially treated with intravenous calcium. Oral calcium with calcitriol (0.25–0.5 μg/day) or Alphacalcidol dose (15–50 ng/kg/day) is the mainstay of treatment. The goals of therapy are to maintain serum total and ionized calcium levels within the reference range to avoid hypercalciuria and normalize PTH levels. This is important because elevated PTH levels in patients with PHP could cause increased bone remodeling and can lead to hyperparathyroid bone disease.

Hypocalcemia of Renal Failure

The hypocalcemia of renal failure is mainly due to hyperphosphatemia. Impaired synthesis of 1,25-dihydroxyvitamin D plays a less important role. Hyperphosphatemia alters calcium and phosphate ion solubility products, and calcium deposition in soft tissue may occur. Hyperphosphatemia inhibits lα-hydroxylase activity in the kidney. 1,25-dihydroxyvitamin D deficiency impairs intestinal absorption of calcium. This also results in increased PTH secretion. Secondary hyperparathyroidism from long-term hyperphosphatemia is usually associated with renal insufficiency. Ectopic calcification in tissues may occur, including blood vessels, skin, periarticular tissues, and cornea (band keratopathy).

Other causes of hyperphosphatemia include: use of phosphate-containing enemas or overzealous use of oral phosphate; vitamin D administration; transcellular shift of phosphorus from cells into the extracellular fluid compartment is seen in tissue destruction or increased metabolism, e.g., in acute leukemia, lymphomas; and following chemotherapy for large bulky tumors lead to a rapid release of cellular phosphorus causing a "tumor-lysis-syndrome." Rhabdomyolysis and severe intravascular hemolysis may lead to a similar syndrome.

Hypocalcemia and tetany may occur if serum phosphorus rises rapidly.

Treatment should be directed toward the hyperphosphatemia in order to correct the hypocalcemia.

Medications causing hypocalcemia include oral, rectal, or parental phosphate preparations; drugs that inhibit bone resorption – mithramycin (plicamycin), bisphosphonates; and calcitonin. Hypocalcemia due to bisphosphonates can be prolonged. Anticonvulsants – phenytoin or Phenobarbital – also cause hypocalcemia. Hypocalcemia occurs in patients undergoing exchange transfusions and plasmapheresis with citrated blood. Radiographic contrast dyes that contain the calcium chelator; ethylenediaminetetra-acetic acid (EDTA); Gadolinium administered for MRI imaging; and chemotherapeutic agents, e.g., combined use of 5-fluorouracil and leucovorin, lead to hypocalcemia. Cisplatinum induced hypocalcemia is secondary to hypomagnesemia.

Rickets and Osteomalacia

Definition

Since the primary action of vitamin D is the uptake of calcium from the intestine and its subsequent deposition

as bone mineralization the main effect of vitamin D deficiency is failure of bone mineralization.

Rickets is the failure of mineralization of growing osteoid tissue. Osteomalacia is the general term for failure of bone mineralization; "rickets" is used in growing children, while osteomalacia is used in adults when bones have stopped growing.

Defective bone matrix mineralization can be caused by either calcium or phosphate deficiency and so we have Calcipenic (hypocalcemic) rickets and Phosphopenic (hypophosphatemic) rickets. Rickets can also be due to primary defects in local bone processes (e.g., hypophosphatasia)

Calcium deficiency is rarely primary nutritional deficiency in the UK (but not so in developing countries). Calcium deficiency secondary to disorders of vitamin D metabolism is more common. Phosphorous deficiency (e.g., due to increased renal phosphate clearance as in X-linked Hypophosphatemia) is uncommon.

Etiology

Causes of calcipenic rickets (i.e., rickets caused by a deficiency of vitamin D or defect in its metabolism or action): Deficiency of vitamin D is most common worldwide and accounts for up to 95% cases. The deficiency may be due to deficient intake vitamin D in diet or lack of effective exposure to sunlight (reduced synthesis of vitamin D by skin) or deficient absorption, e.g., celiac disease, pancreatic insufficiency, short gut syndrome, etc.

Impaired metabolism of vitamin D is the next most important cause and includes (a) impaired C-25 hydroxylation in liver disease and (b) impaired C-1 hydroxylation in kidneys due to renal failure or Type 1 Vitamin D Resistant Rickets (XLD inherited deficiency of 1α hydroxylase enzyme; also called vitamin D dependent rickets).

Target organ resistance to 1,25-dihydroxyvitamin D results in Type 2 Vitamin D Resistant Rickets.

Enhanced metabolic breakdown of vitamin D by P450 hepatic microsomal enzyme induction (anticonvulsants) can also cause rickets.

Epidemiology

Incidence of symptomatic vitamin D deficiency in children <5 years age in the UK is 7.5 per 100,000 children per year. There are notable ethnic differences within the UK. Black African or African-Caribbean children have an incidence of 95, South-Asian 38, and white ethnic origin 0.4 per 100,000.

Clinical Features

Clinical Features include bone deformity, bone pain, pathological fractures, frontal bossing, craniotabes (posterior flattening of the skull), bow legs (genu varum), knock knees (genu valgum), widening of wrists, bowing of arms, "Rachitic rosary" (beading of costochondral junctions of ribs), Harrison's sulcus' (an indentation in the lower chest wall), weakness (proximal myopathy), hypotonia, and protuberant abdomen.

Delayed walking and dentition, poor appetite, and growth failure are nonspecific features. As previously mentioned signs of hypocalcemia are rare.

Radiological Features

Thin bones with wide irregular cupped and poorly mineralized metaphyses are best seen at the growing ends of long bones, e.g., in X-rays of wrist and knee. Apparent widening of the joint space is a result of absence of epiphyseal calcification. Bone deformity and sometimes greenstick fractures are seen. Chest radiographs show the costochondral thickening. Osteopenia is a feature of calcipaenic rickets but not seen on x-rays in phosphopenic rickets. Looser's zones are lines of pathological fractures.

Vitamin D Deficiency: Stages and Clinical Signs

1. Stages of vitamin D deficiency
   Stage I
   25-OH-D level decreases, resulting in hypocalcemia and normal phosphate levels; 1,25-dihydroxyvitamin-D may increase or remain unchanged
   Stage II
   25-OH-D level continues to decrease; PTH acts to maintain calcium through demineralization of bone; the plasma calcium normalizes with hypophosphatemia; slight increase in the skeletal alkaline phosphatase
   Stage III
   Severe 25-OH-D deficiency with hypocalcemia, hypophosphatemia, and increased alkaline phosphatase; bones have overt signs of demineralization
2. Clinical signs of vitamin D deficiency
   - Dietary calcium absorption from the gut decreases from 30–40% to 10–15% when there is vitamin D deficiency
   - Low concentrations of 25-OH-D trigger the release of PTH Rickets/Osteomalacia and osteopenia seen
   - Abnormal immune function with greater susceptibility to acute infections and other long-latency disease states (see below)

3. Potential latent disease processes associated with vitamin D deficiency
   - Dysfunction of the innate immune system is noted with vitamin D deficiency Immuno-modulatory actions may include
     - Potent stimulator of innate immune system acting through Toll-like receptors on monocytes and macrophages
     - Decrease threshold for long-latency diseases such as cancers (including leukemia and colon, prostate, and breast cancers), psoriasis, diabetes mellitus, and autoimmune diseases (e.g., multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosis)

Investigations: Plasma calcium, phosphate and magnesium, alkaline phosphatase, albumin, creatinine, serum PTH level, and plasma level of 25-OH vitamin D. Serum should be stored for 1,25-Di-OH vitamin D. Urine investigations: calcium, phosphate, and creatinine. X-ray of wrist + hand (or knee + chest in infants and toddlers).

The 3 main groups of Rickets can be biochemically distinguished.

Treatment of Nutritional Deficiency Rickets

Treatment for rickets is vitamin D administered over several months or in a single dose. Both calcitriol and alphacalcidol bypass the natural physiologic controls and are potentially toxic.

Gradual method: Ergocalciferol liquid (1 ml contains 3,000 units) is used in small children. Dose: children <6 months give 1 ml daily; in children 6 months–12 years give 2 ml daily. Ergocalciferol tablets of 250 μg (10,000 units) and 1.25 mg (950,000 units) are also available. Vitamin D treatment is given daily for 6–8 weeks (sometimes longer) until healing is well established and the alkaline phosphatase concentration is approaching the reference range. Adherence to daily treatment over weeks is essential. Single-day treatment (also called Stoss therapy) vitamin D in a total dose of 15,000 mcg (600,000 U) is administered in a single day in 4 or 6 divided oral doses. An intramuscular injection (Cholecalciferol or ergocalciferol 7.5 mg equivalent to 300,000 units) can be given as a single dose of 600,000 units. Vitamin D given as this large dose is well tolerated and stored in the body to be gradually released over many weeks. The single-day therapy avoids problems with compliance. It is helpful in differentiating nutritional rickets from XL-Hypophosphatemic rickets. In nutritional vitamin D deficiency rickets, the phosphorous level rises in 96 h and radiographic healing is visible in 6–7 days. Neither happens with XLD Hypophosphatemic rickets.

Maintenance supplement after the rickets is healed as 400 units daily vitamin D is needed. In patients with chronic intestinal malabsorption or liver disease higher therapeutic doses up to 40,000 units daily may be needed. If severe deformities have occurred, orthopedic correction may be required after healing. Most of the deformities correct with growth.

Other types of calcipaenic rickets:

Vitamin D–Resistant Rickets Type I (VDRR 1)

Also known as Vitamin D–dependent rickets (type I) and as vitamin D pseudodeficiency (PDDR) this disorder results from an inherited deficiency of 1α-hydroxylase that converts 25(OH) cholecalciferol to 1,25-dihydroxycholecalciferol (1,25-dihydroxyvitamin D) in the kidney. Inheritance is autosomal recessive; the gene locus is 12q13.3. Clinical findings are similar to those seen in nutritional rickets. Serum levels of 1,25-dihydroxyvitamin D are low. These patients develop rickets despite receiving vitamin D at the recommended preventive doses. Treatment: oral calcitriol (0.5–1.5 mcg/day). These patients may also respond to high doses of vitamin D (5,000–10,000 U/day).

Vitamin D–Resistant Rickets Type II (VDRR 2)

Also known as receptor defect rickets and as type II vitamin D–dependent rickets and Hereditary 1,25-dihydroxyvitamin D–resistant rickets (HVDRR) this results from an autosomal recessive inherited abnormality in the calcitriol receptor, causing an end-organ resistance to the vitamin. HVDRR can be lethal in the perinatal period. The clinical features appear in early infancy and consist of all the musculoskeletal symptoms and signs of nutritional rickets with very severe hypocalcemia and usually normal phosphate levels. Alopecia is an associated feature, although a variant without alopecia has been reported. Serum levels of 1,25-dihydroxyvitamin D are typically elevated. Several mutant forms of receptor defect rickets are known, with a wide range of phenotypic severity and response to treatment. Calcitriol is the treatment. Some patients are totally resistant to therapy. Patients without alopecia appear to respond better to treatment with calcitriol. Some patients benefit from intravenous calcium (400–1,400 mg/m^2/day) followed by

oral therapy with high doses of calcium (with risks of nephrocalcinosis, hypercalciuria, nephrolithiasis, and cardiac arrhythmias). Patients with mutations in the ligand-binding domain (LBD) region of the receptor are more likely to respond to high-dose vitamin D treatment than patients with mutations in the DNA-binding domain (DBD) region of the receptor.

Hypophosphatemic Rickets

Primary (Inherited) forms include X-linked (dominant) Hypophosphatemia (XLH), Autosomal Dominant Hypophosphatemic Rickets (ADHR), Autosomal Recessive Hypophosphatemic Rickets (ARHR), Hereditary hypophosphatemia with hypercalciuria (HHRH), McCune-Albright syndrome, and Fanconi syndromes.

Secondary hypophosphatemic rickets are due to oncogenic and drug-induced nephrotoxicity (e.g., ifosfamide toxicity). Some mesenchymal tumors release FGF-23 which causes phosphaturia and cause hypophosphatemic osteomalacia.

Inherited Hypophosphatemic Rickets

X-linked hypophosphatemia (XLH) is an X-linked dominant disorder characterized by growth retardation, rickets/osteomalacia, hypophosphatemia, and renal defects in phosphate reabsorption and vitamin D metabolism (defective 1α hydroxylation). XLH is caused by mutations in the phosphate-regulating endopeptidase gene (PHEX, locus Xp22.2-p22.1). The mutated PHEX gene allows accumulation of the peptide encoded by FGF-23 causing unregulated renal phosphate leak. Defective osteoblast function contributes to the pathology. XLH presents in toddlers with bowed legs, bent femurs, waddling gait, and short stature. Family history is important. Recurrent dental abscesses are frequent. Asymptomatic neonates may have low phosphate levels. Normal ranges of serum phosphate vary with age: newborns, 1.61–2.52 mmol/L; 1 month–1 year, 1.23–2.0 mmol/L; 1–10 years, 1.16–1.81 mmol/L; and after 10 years and in adults, 1.0–1.65 mmol/L.

Other inherited forms of hypophosphatemic rickets include:

Autosomal recessive form (ARHR) – mutations in the dentin matrix acidic phosphoprotein (DMP1) gene (locus 4q21), a nuclear protein that regulates the expression of osteoblast-specific genes.

Autosomal dominant form (ADHR) – mutation occurs in the gene encoding a member of the fibroblast growth factor family, FGF23 (locus 12p13). Mutations at the furin cleavage site prevent the processing of a fibroblast-growth-factor peptide (encoded by the gene FGF-23), into fragments, leading to the accumulation of a "stable" circulating form of the peptide which inhibits renal Pi reabsorption.

X-linked recessive form – mutation in the CLCN5 gene (locus Xp11.22, which encodes a voltage-gated chloride channel) that leads to defective apical endocytosis of PTH and 25-hydroxyvitamin D, resulting in hyperphosphaturia and hypocalciuria.

Hereditary Hypophosphatemic Rickets with Hypercalciuria (HHRH) is caused by mutation in the sodium-phosphate co-transporter gene SLC34A3 at locus 9q34.

A variety of hypophosphatemic rickets with hyperparathyroidism is caused by a translocation at locus 13q13.1 that results in an increase in plasma alpha-klotho and FGF-23 levels.

In Tumour-Induced Osteomalacia (TIO) a similar mechanism exists wherein ectopic overproduction of FGF-23 overwhelms its processing and degradation by PHEX, leading to the accumulation of FGF-23 products in the circulation that inhibit renal Pi reabsorption.

Investigations: X-rays in hypophosphatemic rickets show changes of rickets like wide splayed metaphyses but not the osteopenic changes like cupping and fraying. Diagnosis is made by laboratory investigations: low serum phosphate, moderately elevated alkaline phosphatase, normal serum PTH, 25 OH vitamin D, and 1,25-dihydroxyvitamin D. Normal urine calcium excretion and a low% TRP and TmP/GFR are the keys to diagnosis.

Treatment

The primary objectives of treatment are to prevent bone deformity and orthopedic surgery, normalize growth and activity, and avoid complications. Short stature can be improved if treatment is started early by ~2 years. Phosphate replacement: 70–100 mg/kg/day needs to be given 4–5 divided doses because each dose will be excreted in about 4–5 h. Preparations available in the UK include Phosphate Sandoz 500 mg tablet and Joules solution 28 mg/ml. (K Phos Neutral 250 mg capsules are available in the USA.) Alfacalcidol (1α cholecalciferol):10–50 ng/kg/day (maximum 1 μg/day). One Alpha Drops contain 2 μg/ml (1 drop is equivalent to 100 ng). One Alpha capsules is 250 ng strength. Injection (2 μg/ml) is also available. Alternatively Calcitriol (1,25-dihydroxyvitamin D) can be used in a dose of

15 ng/kg/day (maximum 250 ng/day). Each capsule contains 250 ng of the medication.

The balance between the phosphate and Alphacalcidol needs meticulous monitoring. Serum phosphate is a poor index; alkaline phosphate is not sensitive enough. Monitoring is by growth and clinical assessments with serum PTH and calcium levels and urine calcium/creatinine ratio. Serum PTH should be normally monitored at least every 6 months. Elevated serum PTH with normal serum calcium indicates the need to increase alphacalcidol dose and/or to reduce phosphate supplementation. Hypercalciuria and/or elevated serum calcium with normal serum PTH suggests reduction in alphacalcidol dose. If both serum calcium and serum PTH indices were to be elevated, it suggests tertiary hyperparathyroidism, and if confirmed (repeat serum chemistry), parathyroidectomy may be necessary. Ultrasound of kidneys is done 2 yearly. About half the patients will develop some nephrocalcinosis but most will have normal renal functions.

Renal Rickets

Fanconi syndrome is a disorder of proximal renal tubular transport characterized by phosphate, amino acids, glucose, bicarbonate, and uric acid wasting. Tubular phosphate reabsorption via the sodium-phosphate cotransporter is impaired. Additionally there is defective endocytotic reabsorption of vitamin D – vitamin D–binding protein complex. Acid–base regulation is affected. These three factors are responsible for the pathogenesis of bone mineralization defects.[25] The disorder may be inherited or acquired.

Lowe disease (Oculocerebrorenal syndrome) *OCRL1* gene (locus Xq26.1) and Dent disease – Dent disease type 1 *CLCN5* gene (locus Xp11.22) and Dent disease type 2 *OCRL1* gene (locus Xq26.1) – all cause X-linked hypercalciuria, hypophosphatemia, nephrolithiasis, and rickets.

Cystinosis, a lysosomal storage disorder of cystine transport protein, cystinosin (mutations of CTNS gene locus 17p13), and tyrosinemia (fumaryl acetoacetase/fumaryl acetoacetate hydrolase deficiency, FAH gene locus 15q23–q25) are other inherited conditions included in this group of conditions with renal phosphate wasting along with aminoaciduria and glucosuria.

Distal renal tubular acidosis, through phosphate wasting, may also cause rickets.

Renal osteodystrophy. In end-stage renal disease, renal 1-hydroxylase is diminished or lost, and excretion of phosphate is defective. This leads to low levels of 1,25-dihydroxyvitamin D, hypocalcemia, and failure of osteoid calcification. This is the only type of rickets with a high serum phosphate level. It can be adynamic (a reduction in osteoblastic activity) or hyperdynamic (increased bone turnover). See also ❯ "Hypocalcemia of Renal failure."

Acquired Fanconi syndrome results from various toxins, including heavy metals (mercury, lead) and drugs (cisplatinum, ifosfamide).

The clinical picture varies with age and cause and includes severe hypophosphatemic rickets, failure to thrive, and metabolic acidosis. Treatment is by managing the underlying cause (when possible) and vitamin D therapy (or calcitriol).

McCune Albright Syndrome (MAS)

McCune Albright syndrome (MAS) is defined as the association of 2 out of following 3 features: polyostotic fibrous dysplasia (PFD), precocious puberty, and café au lait spots. Other endocrinopathies coexist. MAS is due to a postzygotic activating mutation of the GS alpha gene in the affected tissues. Hypophosphatemic rickets is a potential complication that may worsen the bone disease associated with PFD. The hypophosphatemia is usually mild and secondary to excessive urinary phosphate leak induced by fibroblast growth factor 23 (FGF-23), so PTH levels remain normal. Severe hypophosphatemia is rare in MAS and, if untreated, results in severe clinical rickets and short stature. Treatment is vitamin D and phosphorus supplements. Patients with must be monitored closely for hypercalcemia and secondary hyperparathyroidism.

Hypercalcemia

Definition

Serum calcium level > 2.62 mmol/l (normal 2.12–2.62 mmol/l) OR ionized calcium Ca^{2+} level > 1.31 mmol/l (normal 1.16–1.31 mmol/l).

Clinical Manifestations of Hypercalcemia

Asymptomatic hypercalcemia: verify that the blood result is not a laboratory error. The most common reasons for falsely elevated serum calcium levels are hemoconcentration and elevated serum albumin levels. Acidosis increases the level of ionized calcium (but not total calcium) by changing plasma protein binding. A high intake of phosphate may also falsely elevate the serum calcium level.

Symptoms and signs vary depending on whether the hypercalcemia is of acute onset and severe (>3 mmol/l) or whether it is chronic and relatively mild. Patients generally tolerate higher serum calcium levels if the elevation is gradual; most patients are symptomatic at levels about 3.5 mmol/l. In either case the major manifestations affect gastrointestinal, renal, cardiac and central nervous and musculoskeletal systems.

Investigations

Serum/Plasma Calcium, Phosphate, Parathyroid hormone, Parathyroid hormone related peptide (PTHrP), 25 hydroxyvitamin D and 1,25-dihydroxyvitamin D. Urine for Calcium/Creatinine ratio and to assess renal tubular function (bicarbonate, pH, amino acids).

In the neonate, in addition to calcium, determine serum protein, phosphate, and PTH levels as well as the levels of maternal calcium and maternal PTH. Serum calcium levels from father, siblings, and other family members may also be helpful, e.g., in NSHPT both parents may have mild and asymptomatic familial hypocalciuric hypercalcemia (FHH). In a baby with hypercalcemia, the serum PTH level should be <10 pg/mL. A definitive diagnosis of hyperparathyroidism is confirmed by a PTH level >50 pg/mL.

Interpreting blood biochemistry: When PTH is high or inappropriately normal, consider hyperparathyroidism, familial hypocalciuric hypercalcemia, secondary hyperparathyroidism, and, rarely, malignancy. High PTH levels usually indicate primary hyperparathyroidism if the urine calcium/creatinine ratio is high while low urine calcium/creatinine ratio indicates FHH, which can be confirmed with DNA sequence analysis for *CASR* gene. When PTH is suppressed, the possible causes are malignancy, granulomatous disease, iatrogenic causes, adrenal insufficiency, thyrotoxicosis, and vitamin D intoxication. Low PTH levels usually indicate hypervitaminosis D if 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels are high and indicate malignancy if they are low. If malignancy is suspected, evaluate accordingly and also check for high PTHrP level.

Etiology and Pathophysiological Mechanisms of Hypercalcemia

Neonatal Hypercalcemia

Transient neonatal hypercalcemia secondary to transient hyperparathyroidism is induced by a hypocalcemic feto-maternal environment. Mothers with hypoparathyroidism, pseudohypoparathyroidism, or vitamin D deficiency transfer low amounts of calcium to their fetuses. Fetal hypocalcemia induces a secondary hyperparathyroidism in the fetus that persists for several weeks after birth leading to hypercalcemia. It is often mild and asymptomatic, usually with serum calcium levels around 2.8 mmol/l picked up during blood investigations for other reasons. If asymptomatic it does not need further investigation or treatment. It is useful to check maternal parathyroid calcium and vitamin D status.

Neonatal Severe Primary Hyperparathyroidism (NSHPT) seen with homozygous inheritance of CaSR mutation (or in compound heterozygotes with little functional CaSR), presents within a week of birth and is characterized by severe life-threatening hypercalcemia, hypermagnesemia, increased circulating PTH concentrations, massive hyperplasia of the parathyroid glands, and relative hypocalciuria. Skeletal abnormalities including demineralization, craniotabes, widening of the metaphyses, osteitis fibrosa, and fractures may occur. Serum PTH levels are very high. Though the course of NSHPT can be self-limited, aggressive medical management is first indicated in all patients of NSHPT and prompt surgical intervention including total parathyroidectomy with immediate or delayed parathyroid autotransplantation should be performed. Postoperatively these infants develop "Hungry Bone Syndrome" needing large replacements of calcium for which a central access is desirable. PTH levels return to normal 2–4 days after surgical treatment.

Absorptive Hypercalcemia

Absorptive Hypercalcemia – inappropriately high absorption of dietary calcium from the gut is seen in Williams syndrome, Idiopathic Infantile Hypercalcemia (IIH), subcutaneous fat necrosis (of the newborn), vitamin D toxicity, and granulomatous disease. In Williams syndrome (a sporadic multisystem disorder with "elfin facies," supravalvular aortic stenosis, and hypercalcemia usually due to a microdeletion of chromosome 7q11.23, which represents a continuous gene deletion that includes the elastin gene (ELN)) hyperabsorption of calcium begins a few months after birth and spontaneously resolves between the ages of 2–4 years. A similar pattern is seen in Idiopathic Infantile Hypercalcemia but without other features of Williams syndrome. The mechanism is not understood but infants and toddlers have symptomatic hypercalcemia and most also have elevated levels of serum

1,25-dihydroxyvitamin D. Treatment is usually needed. Investigations in absorptive hypercalcemia show: elevated serum calcium, 1,25-dihydroxyvitamin D, and urine ca/creatinine ratio (valid only after the age of 1 year). Serum Phosphate is normal or mildly raised. 25 hydroxyvitamin D is normal while serum Parathormone is low.

Subcutaneous fat necrosis: Symptomatic hypercalcemia occurs at 3–6 weeks age, usually in a term infant with perinatal hypoxia who develops violaceous nodules on the back, buttocks, and thighs with thrombocytopenia. Hypercalcemic symptoms are subtle, vomiting and failure to thrive may be confused as resulting from perinatal hypoxia. Hypercalciuria and nephrocalcinosis occur. Hypercalcemia is due to excessive conversion of 25 hydroxyvitamin D to 1,25-dihydroxyvitamin D by the macrophages.

Granulomatous disease: Extra-renal production of 1,25-dihydroxyvitamin D occurs in various cell (tumor cells, macrophages, granulomatous cells). This alone or in conjuction with lymphoid cytokines is responsible for the hypercalcemia.

Vitamin D toxicity: due to overdoses of vitamin D (or analogues), e.g., during Stoss therapy or regular supplementation. Levels of 25 hydroxyvitamin D and 1,25-dihydroxyvitamin D are both elevated.

Childhood Hypercalcemia

Hypercalcemia due to increased bone resorption occurs in (1) prolonged immobilization, (2) hyperparathyroidism, (3) familial hypocalciuric hypercalcemia, and (4) endocrine disorders associated with increased bone resorption but without excess PTH production such as Hyperthyroidism, Hypoadrenalism, and Jansen's Metaphyseal Chondrodysplasia.

Hypercalcemia associated with childhood malignancies such as non-Hodgkin or Hodgkin lymphoma, Ewing sarcoma, Neuroblastoma, Langerhans cell histiocytosis, Rhabdomyosarcoma with metastases and ovarian small cell carcinoma in adolescents *and* Renal tumors with rhabdoid histology in infants.

The pathophysiologies responsible for oncological hypercalcemia are three. (1) Due to osteolytic secondaries causing bone destruction. (2) Due to elevated Parathyroid hormone related peptide (PTHrP): 50–90% of patients with solid tumors (squamous cell carcinomas of various tissues especially lung, renal cell carcinoma, bladder and ovarian carcinoma, pheochromocytoma and pancreatic islet-cell tumors) and hypercalcemia and 20–60% of patients with hematologic malignancies (non-Hodgkin's lymphoma, chronic myeloid and lymphoblastic leukemia, adult T cell leukemia/lymphoma (ATL), and multiple myeloma) have elevated circulating PTHrP. (3) Due to substances other than PTHrP. Tumor cells produce several bone resorbing substances besides PTHrP: proteases which facilitate tumor cell progression through unmineralized matrix, cytokines, eicosanoids, and growth factors (e.g., EGF) which can act on osteoblasts to increase production of cytokines such as Macrophage-Colony Stimulating Factor and RANKL and to decrease production of osteoprotegerin (OPG). Receptor activator of NF-κB ligand (RANKL) binds to its receptor RANK in osteoclastic cells, and increases production and activation of multinucleated osteoclasts which can resorb mineralized bone. Osteoprotegerin (OPG) also known as osteoclastogenesis inhibitory factor (OCIF) blocks RANK-L and inhibits the production of osteoclasts.

Parathyroid hormone related peptide (PTHrP): In 1941 Albright, observed that hypophosphatemia should not accompany hypercalcemia if the tumor was simply causing osteolysis. He suggested that the tumor might be secreting a substance which hypercalcemic and phosphaturic, which lead to the concept of "ectopic" PTH production. However neither PTH nor PTH-mRNA be detected in these patients. Bioassays subsequently identified PTH-like bioactivity in both blood and tumor extracts which lead to identifying a novel protein called PTHrP (1988 by Broadus et al.). PTH(1–34) and PTHrP(1–34) act similarly at the PTH receptor type 1 (PTH-R1) to raise blood calcium, phosphorus, reduce renal calcium clearance, and inhibit tubular reabsorption of phosphate. PTHrP has important physiological roles in fetal life for active transplacental transport of calcium. PTHrP also acts as an endocrine, autocrine/paracrine, and intracrine hormone that regulates epithelial-mesenchymal interactions during the formation of the mammary glands and during lactation regulates the mobilization and transfer of calcium to the milk. PTHrP is critical in the intraosseous phase of tooth eruption where it acts as a signaling molecule to stimulate local bone resorption. Without PTHrP, the bony crypt surrounding the tooth follicle will not resorb, and therefore the tooth will not erupt. It regulates endochondral bone development by maintaining the endochondral growth plate at a constant width.

Endocrine disorders causing Hypercalcemia can do so with or without elevated PTH levels. Those that do so without elevated PTH include: (1) Hyperthyroidism, increased triiodothyronine directly increases bone turnover and resorption. The liberated calcium suppresses PTH release so that 1,25-dihydroxyvitamin D levels are reduced and renal calcium reabsorption is diminished.

Therapy of the hyperthyroidism reverses the hypercalcemia. (2) Hypoadrenalism causes hypercalcemia by an unclear mechanism. Elevated ionized Ca^{2+} suppresses PTH and 1,25-dihydroxyvitamin D. Treatment of hypoadrenalism with replacement glucocorticoids and restoration of intravascular volume corrects the hypercalcemia. (3) Jansen's Metaphyseal Chondrodysplasia (JMC) is a very rare disorder that results from ligand-independent activation of the PTH-R1 due to activating mutations. Levels of PTH and PTHrP are low. The mutation leads to auto-activation of the PTH-R1 signaling. Short limbed dwarfism with disorganized metaphyses and normal epiphyseal plates with hypercalcemia, hypophosphatemia and elevated urinary calcium, phosphorus, and cyclic AMP are seen. There is no known treatment although bisphosphonates have been tried. Endocrine conditions with elevated PTH are hyperparathyroidism of various types.

Hyperparathyroidism

Etiology

Primary hyperparathyroidism is due to enlargement of one or more of the parathyroid glands (adenoma). It is rare in children; the typical patient being an elderly female. In primary sporadic hyperparathyroidism PTH is generally overproduced by a single parathyroid adenoma. There is net increase in plasma calcium and decrease in plasma phosphate. Urine calcium/creatinine ratio is high. 25 hydroxyvitamin D level is normal. Bone loss manifested by discrete lesions including subperiosteal bone resorption of the distal phalanges, osteitis fibrosa cystica characterized by bone cysts and "brown tumors" (i.e., collections of osteoclasts intermixed with poorly mineralized woven bone), and pathological fractures. Severe skeletal manifestations reflect uncontrolled disease and are seen in <2% adults with parathyroid adenoma. Nephrocalcinosis/nephrolithiasis occurs in 20% patients.

Primary Familial Hyperparathyroidism occurs in four situations.

Multiple Endocrine Neoplasia, Type I (MEN1) Syndrome: Autosomal dominant, with tumors of the parathyroid glands (80–100%), anterior pituitary (usually prolactinomas), and pancreatic islets. The mutation affects MENI gene (locus 11q13) which encodes the nuclear protein, menin.

Multiple Endocrine Neoplasia Type II (MEN2) Syndrome: MEN2A is characterized by medullary thyroid carcinoma (MTC, calcitonin-secreting) bilateral pheochromocytomas and hyperparathyroidism which result from activating mutations in the receptor tyrosine kinase (RET) proto-oncogene (locus 10q11.2).[27] MTC and pheochromocytomas have high malignant potential and common. Hyperparathyroidism is milder and less frequent (5–20%). The treatment of parathyroidism in MEN is surgical.

Hyperparathyroidism – Jaw Tumor Syndrome: an autosomal dominant disorder characterized by early onset of single or multiple cystic parathyroid adenomas and fibro-osseous jaw tumors which lack osteoclasts and therefore differ from "brown tumors." Mutations occur in tumor suppressor gene, HRPT2 (locus 1q25–q31), which encodes the protein parafibromin. Renal lesions like benign cysts, hamartomas and Wilms tumor are associated.[28] Due to a high malignant potential surgical removal is indicated.

Familial Hypocalciuric Hypercalcemia (FHH): is due to an autosomal dominant inactivating mutation in the Calcium sensing receptor (CaSR) gene (locus 3q13.3–q21). In heterozygotes the kidney CaSR has diminished ability to detect plasma calcium leading to enhanced renal tubular reabsorption of calcium and magnesium i.e. hypercalcemia and hypermagnesemia. Parathyroid gland CaSR also inadequately senses plasma calcium so mild hyperplasia occurs and "normal" levels of PTH are secreted despite the hypercalcemia which is mild to moderate. In patients with co-existing vitamin D deficiency FHH may be masked. Parathyroidectomy should not be done; the renal defect is not correctable.

Secondary Hyperparathyroidism is when persistent hypocalcemic states, e.g., renal failure induces a parathyroid hyperplasia with secondarily elevated PTH.

Tertiary Hyperparathyroidism – occasionally secondarily elevated PTH levels persist even after removal of the primary cause, e.g., renal transplant. This then causes hypercalcemia and may need parathyroidectomy.

Investigations

Blood: Calcium, PTH and 1,25-dihydroxyvitamin D – elevated. Phosphate low. Urine: high Calcium/creatinine ratio. Localization of parathyroid adenoma(s)/ectopic location can be done by Ultrasonography of neck and Tc99-labeled Sestamibi scan.

Management of Hypercalcemia

Acute Hypercalcemia

Hydration is the initial step using isotonic saline (3 L/m^2). Hydration helps decrease the calcium level through

dilution and increase renal calcium clearance. Calciuresis with Loop diuretics (e.g., frusemide) can be used with hydration to increased calcium excretion and lower serum calcium levels within 24–48 h. Thiazides are contraindicated because they increase tubular reabsorption of calcium. Regular (6–8 hourly) monitoring of serum calcium, phosphate, urea, creatinine, and sodium, magnesium, potassium during diuresis is essential. Bisphosphonates inhibit bone resorption. Pamidronate (Aredia) (dose 1–1.5 mg/kg, maximal adult dose 90 mg) lowers serum calcium levels over a period of days to months. Repeat dosing is based on a further rise in serum calcium levels and should not be done more than once a month. Fever, musculoskeletal discomfort, and vomiting are common side effects as is hypocalcemia. Glucocorticoids are useful in hypercalcemia caused by vitamin D toxicity, certain malignancies (e.g., multiple myeloma, lymphoma), sarcoidosis, and other granulomatous diseases. They are ineffective in patients with solid tumors or primary hyperparathyroidism. Hydrocortisone (2.5 mg/kg IV qds) or prednisolone (2 mg/kg, maximum 40 mg/day) reduce non-renal alpha-1-hydroxylase activity and 1,25-dihydroxyvitamin D–induced calcium absorption from the gut. Dialysis is needed in patients with kidney failure. Calcitonin: subcutaneous or intramuscular (2–6 mcg/kg every 6 h) works within hours to decrease skeletal reabsorption of calcium and inhibits renal reabsorption. Effects are limited to initial 2–3 days because of tachyphylaxis. Serum calcium reduces by only 0.5 mmol/L. Adverse effects include nausea, cramping, abdominal pain, and flushing. It use is now largely supplanted by bisphosphonates. Cinecalcet hydrochloride (Sensipar) is a calcimimetic that resets the configuration of the CaSR making it more sensitive to serum calcium. Primarily indicated for chronic renal disease and secondary hyperparathyroidism its efficacy has been substantiated in adults but there are no large pediatric studies. It may prove valuable in children with FHH.

Management of Absorptive Hypercalcemia: Stop all vitamin D supplements and restrict dietary calcium intake to <1/4th of the recommended intake for that age. A special low calcium and low vitamin D formula milk may be used to feed infants with Williams syndrome and IHH (e.g., Locasol® which contains no vitamin D and calcium <7 mg/100 ml). Standard infant feeds contain 50–90 mg of calcium/100 ml. Avoid hard water and use clothing and sunscreen crèmes to reduce exposure to sunlight. Glucocorticoids may be used for short periods.

Monitoring blood biochemistry and clinical status is important as the conditions are self resolving over 2–4 years. This includes (1) aim to normalize the serum calcium levels and (2) keep urine calcium/creatinine ratio <75 (mmol/mmol). Monitor BP and avoid iatrogenic rickets due to overzealous restriction of calcium in diet. Dentist input is important as enamel hypoplasia can occur as well as annual ultrasonography to monitor nephrocalcinosis.

Serum PTH remains suppressed during the hypercalcemic phase of illness. When PTH begins to rise again, it may mark the end of this phase of the illness (in Williams syndrome and IHH) and a slow and cautious withdrawal of restrictions with vigilant monitoring of clinical and biochemical parameters.

Surgery: Parathyroidectomy is indicated in hyperparathyroidism due to adenoma(s). Preoperative investigations include imaging to localize the tumor, parathyroid arteriography, and intraoperative selective venous sampling. Early referral to an experienced parathyroid surgeon is necessary.

Osteoporosis in Children

Definition

Osteoporosis literally means "porous bones"; these bones are fragile and can easily fracture. NIH consensus (2001) definition: Osteoporosis is a condition characterized by reductions in bone strength, leading to an increased risk of fractures. World Health Organization (WHO) classification defines osteoporosis as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture, which typically involves the wrist, spine, or hip. Limitations to WHO definition: (1) This definition is based on bone densitometry, in Caucasian adults, on epidemiological data. It is unsuitable for use in children. (2) The relationship between bone density and fracture risk in children is currently unknown. It is therefore not possible to define thresholds below which fracture risk increases. (3) Bone density measurements in children are affected by body size. Current methods of bone densitometry are based on area and not volume; thus, a child who is short for age will have smaller bones and so the areal bone density measured will be less than that for the mean for that age, leading to an inappropriate diagnosis of osteoporosis.

International Society for Clinical Densitometry statement on Fracture Prediction and Definition of Osteoporosis (2007): Fracture prediction should primarily identify children at risk of clinically significant fractures, such as

fracture of long bones in the lower extremities, vertebral compression fractures, or two or more long-bone fractures of the upper extremities.

The diagnosis of osteoporosis in children and adolescents should *not* be made on the basis of densitometric criteria alone.

The diagnosis of osteoporosis requires the presence of both a clinically significant fracture history and low bone mineral content or bone mineral density.

A clinically significant fracture history is one or more of the following: (a) long-bone fracture of the lower extremities, (b) vertebral compression fracture, and (c) two or more long-bone fractures of the upper extremities

Low bone mineral content or bone mineral density is defined as a BMC or areal BMD Z-score that is less than or equal to −2.0, adjusted for age, gender, and body size, as appropriate.

Etiology

Primary Osteoporosis

Primary Osteoporosis – due to an intrinsic bone abnormality (usually inherited) is subdivided in three groups: (1) Osteogenesis imperfecta (OI): 1 in 10,000 to 100,000 births. Osteogenesis imperfecta (OI) is a disorder of congenital bone fragility caused by mutations in the genes that encode type I procollagen (i.e., COL1A1 and COL1A2). Subtypes of OI: Type I – mild forms, Type II – extremely severe, Type III – severe, Type IV – undefined. (2) Idiopathic juvenile osteoporosis (IJO) occurs in children from the ages of seven to the early teens. It is extremely rare, affecting less than 100 children in the UK. Allelic polymorphisms in low-density lipoprotein receptor–related protein-5 (LRP5) gene (locus 11q12–13) have association with osteoporosis.(3) Osteoporosis pseudoglioma syndrome: very rare genetic syndrome due to heterozygous loss of function of gene encoding low-density lipoprotein receptor–related protein-5 (LRP5) (locus 11q13.4).

Secondary Osteoporosis

Secondary osteoporosis – occurs due to the following factors acting singly or in combination. (1) Conditions with elevated inflammatory cytokines like juvenile idiopathic arthritis (JIA), Crohn's disease, and systemic lupus erythematosis. (2) Conditions with reduced mobility such as cerebral palsy, spinal cord defects or injury, head injury, spinal muscular dystrophy, and other neurodisability states. (3) Long-term, high-dose oral corticosteroids inhibit osteoprotegerin and stimulate osteoclast activity. (4) Delayed puberty or pubertal arrest due to a primary endocrine disorder or secondary to effects of chemotherapy, radiotherapy, or iron overload causes poor bone development. (5) Low body weight as in anorexia nervosa or undernutrition are associated with poor bone development. In many secondary osteoporotic conditions several of the above factors coexist, e.g., in JIA there may be a combination of inflammatory cytokines, glucocorticoids, immobilization, undernutrition, and delayed puberty.

Clinical Presentation of Osteoporosis

Recurrent long bone fractures due to low impact injuries. Mild forms of OI and osteoporosis secondary to immobilization present this way. Distal femur and proximal tibia are the commonest sites. Some may be flagged up as possible non-accidental injury. Vertebral compression fractures may be asymptomatic and get diagnosed by a spinal x-ray or cause back pain, spinal deformity, and potential loss of height. JIO, OI, and osteoporosis secondary to poor nutrition, prolonged immobilization, or post chemotherapy manifest as vertebral compression fractures. A high index of suspicion in children with disorders which predispose may lead to investigation for secondary osteoporosis. A family history is often a pointer, but occasionally the diagnosis of OI in a child leads to the identification of other affected family members.

Prevention of Osteoporosis

Calcium and or vitamin D deficiency should be treated appropriately, but their routine supplementation is not recommended. One study showed that calcium carbonate supplementation of adolescent boys increased skeletal growth, resulting in greater stature and bone mineral acquisition, but whether this reflects a change in the tempo of growth or an effect on skeletal size that persists into adulthood is unclear. There is no good evidence to support their use to prevent secondary osteoporosis, especially corticosteroid induced. Hypogonadism treated with the appropriate hormone replacement therapy improves bone density. Growth hormone has been shown to increase bone thickness in JIO but there is no good evidence to recommend its use to prevent osteoporosis. Increased physical activity improves BMD but this may be challenging in children with neuromuscular disabilities. A small double-blind, placebo-controlled clinical trial of intravenous pamidronate administered for 3 consecutive days repeated at 3-month intervals for 1 year to treat

osteopaenia in nonambulatory children with cerebral palsy found it to be safe and efficacious. Current data are inadequate to support the use of bisphosphonates in children to treat reductions in bone mass/density alone. More research is needed to define appropriate indications for bisphosphonate therapy and the optimal agent, dose, and duration of use in pediatric patients.

Treatment

Bisphosphonates are analogues of pyrophosphates. First generation bisphosphonates (Etidronate and Clodronate) form ATP analogues and inhibit ATP-dependent enzymes. They get incorporated into hydroxyapatite and shorten the life span of osteoclasts reducing bone resorption. Second generation bisphosphonates (Pamidronate, Alendronate, Zoledronate) are nitro-bisphosphonates that inhibit the enzyme farnesyl diphosphate synthase and protein prenyltion. They decrease serum calcium in 2–4 days with a peak effect at 4–7 days. Bisphosphonates particularly etidronate and pamidronate have been used in children with hypercalcemia due to a variety of causes including immobilization, leukemia, hyperparathyroidism, and subcutaneous fat necrosis in children. Bisphosphonate use in children in other diseases associated with pathological effects on the skeleton, that is, osteopathy; and in conditions associated with soft tissue calcification, that is, calcinosis have been shown to be beneficial. However data regarding lowest effective dose and frequency as well as long term safety (some bisphosphonates stay in the bones for several years) in children is yet to be established.

Bisphosphonates are currently the treatment modality with most evidence of benefit, however this evidence falls short of recommending their use in routine clinical care. Pamidronate has been the most studied bisphosphonate in secondary osteoporosis. Benefits include increased bone density, reduction in fracture frequency and relieving pain associated with vertebral compression fractures. The latest Cochrane review of the results of the controlled studies justifies use of bisphosphonates in the context of pediatric clinical trials. The favorable short-term profile of bisphosphonates and preliminary positive effects on BMD and pain reduction may justify their use on compassionate grounds in severe cases where there is clinical evidence for bone fragility that significantly impacts patient quality of life. Bisphosphonates in OI for at least 2 years have shown that there is increase in cortical and trabecular bone width and trabecular number in long bones. Similar benefits to lumbar spine bone density and reduction in fracture risk are also noted.

The management of osteoporosis remains multidisciplinary with inputs from radiologists, surgeons, physiotherapists and occupational therapists, and community pediatrician coordinating with a pediatrician with expertise in bone diseases.

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382 Disorders of Puberty

Nicola A. Bridges

Introduction

Puberty occurs in most animal species, and it is the means by which immature animals are protected from having to reproduce until they reach sufficient size, or the environment is appropriate. Human puberty is under the control of neuropeptides that suppress development until an appropriate time, which is determined by size and nutrition. Normal puberty occurs over a wide age range, but the pattern of development in males and females is very predictable.

Normal Puberty

Historical evidence of various kinds (e.g., records of military recruits and choirboys) confirms that the age at which puberty occurs has decreased through the centuries. The trend for younger age of pubertal onset over time is probably related to improved health with fewer infectious diseases and better nutritional status during childhood. The age of development has continued to decrease in developed countries during the twentieth century, but there is some evidence that this trend has started to slow. There is also evidence that the age of onset of puberty in girls has changed more than the age of menarche. A study looking at girls and boys attending office pediatricians in the USA suggested that African American girls appeared to mature earlier than white American girls. There also appears to be a genetic influence over pubertal timing, with correlation between time of menarche in twins, and in mothers and daughters.

The hypothalamo-pituitary gonadal axis is active antenatally with a flare of activity in the immediate neonatal period (sometimes called "minipuberty"). There is a fall in activity during the first few years of life, although even in mid-childhood there is some activity with occasional gonadotropin pulses. The secretion of the gonadotropins, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) is stimulated by gonadotropin-releasing hormone (GnRH) produced in the hypothalamus (see *Fig. 382.1*). GnRH is secreted by neurons within the hypothalamus and passes into the blood vessels of the hypothalamo-pituitary portal system. GnRH is secreted in pulses and as a result the secretion of LH and FSH is pulsatile. There is a gradual increase in the number and amplitude of LH and FSH pulses in the years before puberty. Kisspeptin, a neurotransmitter which is made within the hypothalamus, appears to be an important factor in the change in activity in the years before the onset of puberty. Kisspeptin (encoded by the gene KiSS-1) was originally described as a factor in controlling metastasis but subsequently found to be involved in the onset of puberty. The receptor for kisspeptin (called GPR54) is located on the surface of GnRH secreting neurons and stimulates GnRH secretion. Activation of the kisspeptin receptor has been demonstrated to initiate pubertal development in animal models. Kisspeptin appears to be an important factor controlling the timing of the onset of puberty. Expression of kisspeptin and GPR54 is influenced by leptin, which may be one of the routes by which nutrition has an influence over pubertal onset.

Gonadotropin secretion stimulates gonadal growth, and an increase in sex steroid secretion. Pulsatile LH and FSH are secreted mainly at night in prepuberty and early puberty. Single blood samples for gonadotropins and sex steroids taken during the day in early puberty may show low (prepubertal) levels. In puberty, LH concentrations are higher than FSH, and this distinguishes pubertal development from some other forms of sexual precocity such as premature thelarche, and thelarche variant (see below) where FSH levels are greater than LH. As changes in gonadotropin secretion progress, sex steroid concentration eventually becomes high enough for secondary sexual characteristics to develop – this is counted as the start of puberty although endocrine changes precede this by several years. With progress through puberty, both the amplitude of gonadotropin pulses and the time over which they occur increase, with gonadotropin pulses occurring over the whole 24 h by late puberty. Sex steroid feedback controls gonadotropin secretion. Sex steroids act on receptors in the hypothalamus and pituitary, and reduce the amplitude and frequency of gonadotropin pulses. In gonadal failure, there is no sex steroid feedback, and

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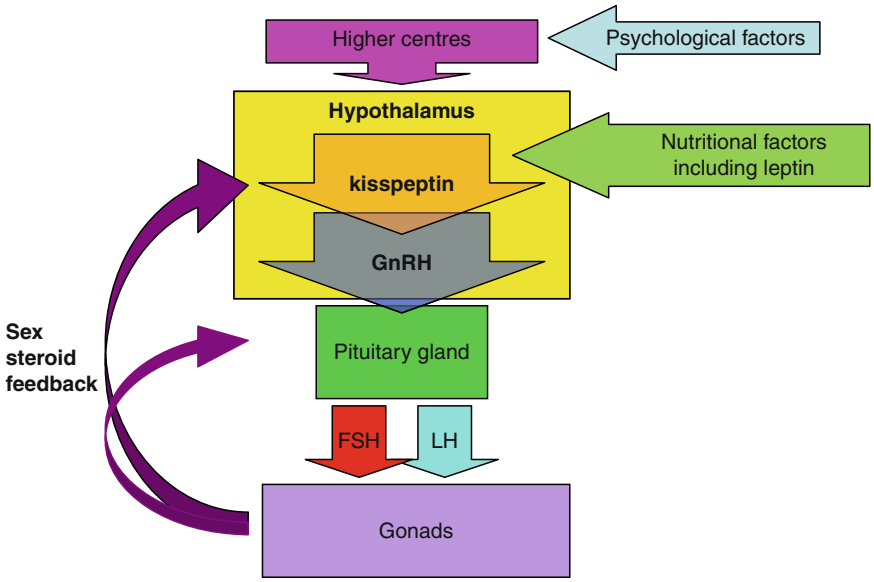

Figure 382.1

LH and FSH levels become elevated with rapid pulse frequency (hypergonadotropic hypogonadism).

In females, the first sign of puberty is usually breast development and in males, testicular enlargement with an increase to 4 ml testicular volume defined as the start of puberty. In normal male puberty, testicular development is accompanied by pubic hair growth and genital development, and in female puberty, breast and pubic hair development progress together, with menarche occurring at Tanner breast stage 4 or 5. In girls, there is progression in the appearances at pelvic ultrasound. The ovaries show a gradual increase in follicular activity in the years before puberty and then increase in size as puberty progresses. The uterus is cylindrical in shape prepubertally. Changes in the shape of the uterus commence with the onset of breast development; there is an increase in length and width and the uterus becomes pear shaped. The endometrium becomes thicker, with at least 5 mm of endometrium usually needed for menstruation to occur. The pattern of development in males and females is preserved whatever age the development occurs. The same pattern of progress is seen in children with central precocious puberty, and if progress does not follow this pattern the diagnosis is not likely to be centrally mediated precocious puberty. If, for example, menarche occurs very early in puberty or male genital development without testicular enlargement, this is abnormal even if it is happening at the normal age for puberty.

The Pubertal Growth Spurt

Sex steroids stimulate skeletal growth independently but also stimulate increased growth hormone (GH) secretion from the pituitary. Individuals with no GH secretion have a pubertal growth spurt, although it is reduced. The pubertal growth spurt in girls commences at the start of puberty (breast stage 2–3) and in boys not until testicular volume of 10–12 ml is reached. As pubertal growth occurs, there is skeletal maturation and the bone age advances. At the peak height velocity, bone age can advance by up to 2.6 bone age years per chronological year. At the end of puberty epiphyseal fusion occurs, with those in the peripheral skeleton fusing first, so that bone age in the hand will be mature before growth has stopped. The last part of growth in height is in the spine, with the last epiphyses to fuse in the pelvis. In girls growth slows after menarche, with 4–5 cm left at this point, and in boys growth slows when they reach full maturity (15–25 ml testicular volume). A single case report of a man with an inactivating estrogen receptor mutation has demonstrated that bone age maturation and epiphyseal fusion is estrogen mediated, even in males. This individual was found to be still growing in adult life with a prepubertal bone age despite being fully mature in puberty. He also had severe osteoporosis, demonstrating the role of estrogen in the acquisition of mature bone density, even in males. Bone density increases during puberty and maximum

levels are reached a few years after the completion of growth. Since it decreases with age after this, one of the aims of pubertal induction is to achieve optimum bone density because of concerns that reduced bone density at the end of puberty may contribute to later fracture risk. The increment in height gained during puberty is greater in those who start earlier, compensating for the age of onset of puberty. Individuals with slightly early puberty do not lose out in terms of height and those with pubertal delay do not gain adult height because of their delay.

Abnormalities of Puberty

Concerns about puberty are a very common reason for referral to pediatric services. Many abnormalities of puberty go unreported or unnoticed, and referral patterns vary, so the true prevalence of pubertal disorders is not known. Most abnormalities of puberty are related to timing – secondary sexual characteristics too early, or puberty too early or too late. In addition, pubertal boys may present because of gynecomastia, or girls because of delay in menarche or the development of hirsutism.

Delay of Puberty and Pubertal Failure

Definition/Classification

Most individuals with pubertal delay are healthy individuals who are at the extreme of the normal range and will go on to develop without problems (see *Table 382.1*). Many boys referred with pubertal delay come with concerns about height; a boy who has been among the shorter ones during childhood will start to feel increasingly left behind if he is late in puberty and his peers have had their pubertal growth spurt. Investigations are aimed at identifying those for whom pubertal delay is the presenting feature of an underlying medical condition, and the small number who have a permanent defect interfering with pubertal development.

Table 382.1
Causes of pubertal delay or pubertal failure

Pubertal delay
Idiopathic-constitutional delay in growth and puberty
Nutritional including anorexia nervosa
Chronic disease
Inflammatory bowel disease and other gastrointestinal disorders
Sickle cell disease
Cystic fibrosis
Associated with genetic syndromes
Noonan syndrome
Prader–Willi syndrome
Pseudohypoparathyroidism
Pubertal failure or arrested puberty
Gonadal disorders – *hypergonadotropic hypogonadism*
Turner syndrome
Klinefelter syndrome
Gonadal failure related to chemotherapy
Testicular failure related to orchitis
Undescended testes
Biosynthetic disorders of sex steroids
Autoimmune gonadal failure
Hypothalamo-pituitary disorders – *hypogonadotropic hypogonadism*
Developmental defects (septo optic dysplasia, multiple pituitary hormone deficiency)
gonadotropin or GnRH deficiency (including Kallman syndrome)
Tumors, for example, craniopharyngioma, germinoma, glioma, pituitary adenomas including prolactinoma
Langerhans cell histiocytosis
After CNS trauma
Iron overload related to transfusion
After CNS infection

Etiology

Pubertal delay is more common in individuals with a range of chronic diseases (such as inflammatory bowel disease, cystic fibrosis, poorly controlled asthma, or sickle cell disease). A number of genetic conditions (such as Noonan syndrome, Prader–Willi syndrome, and pseudohypoparathyroidism) are associated with pubertal delay. Anorexia nervosa can present with pubertal delay or with arrest of pubertal development, and pubertal delay has been reported in female athletes in intensive training. Boys presenting with pubertal delay frequently report delay in their father or brothers, suggesting an inherited tendency.

Epidemiology

The majority of those referred for pubertal delay are boys; the problem appears to be more common in boys and for social reasons boys may be more likely to seek medical input. The commonest cause of gonadal failure in girls is Turner syndrome, which has an estimated prevalence of 50 per 100,000 female births.

Pathogenesis

Pubertal failure, either not starting to develop in puberty at all or failing to complete pubertal development, can be related abnormalities of the pituitary or hypothalamus, or gonadal factors. Developmental defects of the pituitary, which result in multiple pituitary hormone deficiencies can include gonadotropin deficiency. Usually, other pituitary hormone deficiencies will have presented earlier in childhood, for example, ACTH or GH deficiency. These defects may be associated with structural abnormalities of the pituitary, and for a proportion of these there are demonstrated genetic causes (see Chap. 385, "Disorders of the Posterior Pituitary").

Causes of hypogonadotropic hypogonadism without other pituitary hormone defects include mutations in the GnRH gene, the genes for LH, and in the receptor for Kisspeptin. However, the majority of individuals with hypogonadotropic hypogonadism have no genetic defect demonstrated. In Kallman syndrome, failure of the migration of GnRH neurons along the olfactory nerves in embryonic life causes hypogonadotropic hypogonadism, and abnormal development of the olfactory nerves results in absent sense of smell or a limited sense of smell. Several different mutations have been demonstrated to cause Kallman syndrome. The commonest is a mutation in the X-linked gene KAL1, with autosomal forms of Kallman syndrome caused by mutations in the fibroblast growth factor receptor 1 (FGFR1), prokineticin-2 gene (PROK2), the G protein–coupled prokineticin receptor-2 gene (PROKR2), chromodomain helicase DNA-binding protein 7 (CHD7), and the fibroblast growth factor 8 gene (FGF8). Some individuals with clear clinical features of Kallman syndrome do not have any of these mutations. X-linked Kallman syndrome can be associated with unilateral renal agenesis and mirror hand movements (bimanual synkinesia). Kallman syndrome was previously thought to always cause permanent hypogonadotropic hypogonadism, but it has been found that surprisingly a proportion of individuals with clear clinical features of Kallman syndrome go on to have partial or full pubertal development, which can occur well into adult life.

Damage to the hypothalamo-pituitary axis because of trauma, infection, radiotherapy, or surgery can cause pubertal failure, and is likely to result in loss of other pituitary hormone secretion as well as LH and FSH. Iron overload related to regular transfusion for hemoglobinopathies without adequate chelation (or with poor adherence to chelation) can result in pituitary hormone deficiencies. Gonadotropin defects are usually the first to develop in this situation, so failure to develop in puberty can occur without signs of other pituitary hormone deficiencies.

In boys, anorchia, undescended testes, orchitis, or torsion of the testes can result in gonadal failure. Gonadal failure can occur in both sexes secondary to chemotherapy, radiotherapy, or autoimmune disease. Autoimmune gonadal failure that presents prepubertally or in puberty may be associated with one of multiple autoimmune endocrinopathy syndromes; other autoimmune disorders and autoantibodies are usually present. The commonest cause of ovarian failure is Turner syndrome. Ovarian failure unrelated to Turner syndrome frequently has no demonstrable cause.

Approximately 50% of individuals with Turner syndrome have 45 XO karyotype, and the rest other karyotypes including isochromosome Xq, and mosaic karyotypes (e.g., 45 XO/46XX mosaicism). Over 80% of girls with Turner syndrome have retained their maternal X chromosome. A small proportion (7–12%) will have Y chromosome elements within their karyotype. This group has a significant risk of developing gonadoblastoma, which can be prevented by gonadectomy. Accelerated loss of ovarian follicles in Turner syndrome results in ovarian failure, which often occurs before puberty. Up to 20% of girls with Turner syndrome make some progress in puberty; in the majority, development will not be completed but some will have menarche, and pregnancies have been reported in Turner syndrome. Girls with the classical physical features of Turner syndrome, or a well recognized association like coarctation of the aorta, are the most likely to be diagnosed in early childhood. Many are not diagnosed until they present with pubertal delay, amenorrhea, or early menopause. Typically, those with late diagnosis have less obvious physical features and the diagnosis should be considered in any girl with pubertal delay and short stature.

Pathology

In pubertal failure related to abnormalities of the hypothalamus or pituitary both gonadotropin and sex steroid levels are low (hypogonadotropic hypogonadism).

In pubertal failure secondary to failure of sex steroid production, gonadotropin levels are elevated because of failure of feedback to the pituitary and hypothalamus from sex steroids (hypergonadotropic hypogonadism).

Clinical Manifestations

Significant factors in the medical history include any long-term medical condition, even if it is now resolved, and

anything that suggests an undetected underlying condition, for example, diarrhea, chronic abdominal pain, or headaches. Height and weight should be plotted and pubertal stages noted. The degree of pubertal delay should be allowed for when assessing growth. An individual with pubertal delay will continue to grow at a prepubertal rate until they start their growth spurt and will fall in centile position, because growth standards compare them to children with normally timed puberty. Examination should look for wasting or any other feature of a chronic disease. Healthy individuals with mild delay of puberty and a typical growth pattern may not need investigations. Further investigations in pubertal delay are indicated if pubertal delay is associated with short stature; there is a history suggesting an underlying chronic disease, or a risk factor for gonadal failure such as previous chemotherapy or undescended testes. Investigations should be considered if the individual is a long way out of the normal range (e.g., over 16 years), although there is no evidence to support any age limit for investigation.

Diagnosis

Investigations include markers of chronic disease and malabsorption (including celiac antibodies) and thyroid function tests. Single blood samples for LH and FSH are only likely to be helpful in the exclusion of gonadal failure, when they will be elevated. Low levels of LH, FSH, and sex steroids on a single sample cannot distinguish between a central defect causing hypogonadotropic hypogonadism and pubertal delay. Because of the diurnal variation in these hormones, the levels can be very low during the day in individuals who have already started to develop in puberty. A GnRH stimulation test can give more information on hypothalamo-pituitary gonadal function, but may not indicate future progress. A completely absent gonadotropin response to GnRH suggests a central defect but this can change with time. A stimulated LH and FSH in the prepubertal range fits with pubertal delay, but does not give an indication of when or if progress will happen. In gonadal failure, there is an exaggerated gonadotropin response to GnRH stimulation.

If there are concerns about height, an X-ray for bone age should be performed. Bone age remains prepubertal (12–13 years) until development starts, whatever the chronological age. Because the increment in growth achieved at puberty gets smaller with age, individuals who present very late prepubertal and with a prepubertal bone age may actually have very little growth to come. Pelvic ultrasound in prepubertal girls can confirm normal anatomy and may demonstrate ovarian activity with follicular development. Some follicles are seen throughout childhood and their appearance does not necessarily indicate that puberty will start soon. Uterine changes (increase in size with change to a pear shape and endometrial thickening) do not occur until breast development has started. MRI of the hypothalamo-pituitary area should be performed in any individuals where there is any suspicion of a central lesion, if the investigations suggest hypogonadotropic hypogonadism, there is an elevated prolactin level or puberty appears to have started and then stopped. MRI should be considered if there are no signs of puberty in someone well over the normal pubertal age range. In Kallman syndrome, the abnormal olfactory nerves may be visualized at MRI.

Treatment

General Care (Nonspecific Treatment)

Any individual with a central defect or gonadal failure, where it is known that spontaneous puberty is unlikely to occur spontaneously, will need treatment to induce pubertal development and should be given information about their need for long-term therapy and likely prospects for fertility. Most individuals with pubertal delay do not need any treatment and can be reassured that they are likely to have a problem of timing, which will resolve itself. For individuals with mild pubertal delay and no obvious risk factors, the chances of an underlying defect are very small, but monitoring for a period of time will confirm that they have a normal growth pattern and that they go on to develop with time.

Specific Treatment

Any child who is not going to develop spontaneously in puberty should be given treatment to induce pubertal development at an age in keeping with their peers. Studies in Turner syndrome have demonstrated no advantage in delaying pubertal induction beyond the normal age, and there is no evidence that delaying pubertal induction in other causes of pubertal failure increases adult height. These individuals will need treatment to give normal pubertal growth and development and then in most cases must continue with sex steroids as adults to maintain development and bone density (see *Table 382.2*). Endocrine status can change, particularly for those who appear to have a central defect and all individuals should be reassessed at the end of growth and development.

If investigation suggests pubertal delay but the individual is significantly delayed, they may benefit

Table 382.2
Treatment to induce pubertal development

Male
Sustanon 50 mg im every 4 weeks for 6 months then Sustanon 100 mg im every 4 weeks for 6 months then Sustanon 100 mg im every 3 weeks for 6 months then Sustanon 100 mg im every 2 weeks, increasing this dose if necessary to get adult serum testosterone levels Adult maintenance: continue with Sustanon, 3 monthly im depot testosterone, or testosterone patches or gel
Female
Ethinyloestradiol 2 μg or 2.5 μg oral daily for 6 months then Ethinyloestradiol 5 μg oral daily for 6 months then Ethinyloestradiol 10 μg oral daily for 6 months then Ethinyloestradiol 15 μg oral daily for 6 months then Ethinyloestradiol 20 μg oral daily for 6 months Adding in progestogen as norethisterone 5 mg/day or levonorgestrel 30 μg/day for 7 days out of every 28 days when dose of ethinyloestradiol is 10–15 μg or the first vaginal bleed occurs Adult maintenance: continue with ethinylestradiol as above, low-dose oral contraceptive pill, or HRT preparations (oral or patch)

psychologically from treatment to induce puberty. Doses of sex steroids the same as those given to induce puberty (*Table 382.2*) should be given, and treatment stopped when spontaneous puberty occurs (usually after 3–6 months).

Testosterone as Sustanon is the most widely used formulation to induce male puberty. This is suspended in peanut oil and an alternative should be used in allergic individuals. Oral testosterone undecanoate and testosterone patches have been used to induce puberty but evidence supporting this is quite limited. In girls, oral ethinyloestradiol is the most commonly used preparation, although other oral and topical estrogen formulations have been used. Ethinyloestradiol is started at a low dose and gradually increased (*Table 382.2*). Cyclical progesterone should be given when the ethinylestradiol dose is 10–15 μg or as soon as a vaginal bleed occurs. Ethinyloestradiol given on its own will result in a thickened endometrium with erratic bleeding. Treatment to induce puberty should be monitored by measuring height and weight and reassessing pubertal stages at 3–4-month intervals. The need for long-term treatment should be reassessed at the end of puberty.

Prognosis

Pubertal delay can cause significant psychological upset. In the longer term, final height and bone density are normal in pubertal delay. Individuals with permanent defects will require long-term sex steroid replacement. For women with Turner syndrome, there is evidence of long-term psychological benefit from pubertal induction at an appropriate time. As well as optimizing final height, estrogen therapy in Turner syndrome is aimed at inducing normal uterine growth and bone density. Studies in adult women with Turner syndrome suggest that they may not attain normal adult uterine dimensions, and this may impact on the success of fertility treatment by ovum donation. Adult women with Turner syndrome also have an increased risk of low bone density and increased fracture risk.

Premature Development of Secondary Sexual Characteristics: Sexual Precocity or Premature Sexual Development

Definition/Classification

The conventional definition of sexual precocity is the appearance of any secondary sexual characteristic before 8 years in a girl and before 9 in a boy (see *Table 382.3*). Following studies in the USA confirming earlier development in normal children, it was suggested by the American Paediatric Association that puberty before 6 years in African American girls and before 7 in girls and boys of other ethnic groups should be regarded as precocious. This new definition has not been universally adopted.

Etiology

The majority of children presenting to medical attention with secondary sexual characteristics too early are not actually progressing in true puberty, and have premature thelarche, premature adrenarche, or variations of these conditions. A small proportion of those with sexual precocity are developing in true puberty and have the endocrine and physical changes seen in normal puberty occurring at an abnormally early age (central precocious puberty). Sex steroid–secreting or gonadotropin-secreting

Table 382.3
Sexual precocity

Premature thelarche Thelarche variant and slowly progressing precocious puberty Premature adrenarche or exaggerated adrenarche Premature menarche
Central precocious puberty
Idiopathic central precocious puberty – no underlying defect Congenital or acquired CNS disorders: Hydrocephalus Neurofibromatosis CNS neoplasms, for example, hypothalamic hamartoma, optic nerve glioma After CNS infection, trauma, or irradiation Secondary to previous elevated circulating sex steroids, for example, congenital adrenal hyperplasia or peripheral precocity
Peripheral precocious puberty
Autonomous gonadal function: McCune–Albright syndrome Testotoxicosis Familial testotoxicosis Congenital adrenal hyperplasia Sex steroid–secreting or gonadotropin (HCG)-secreting tumors Autonomous ovarian follicular cyst Hypothyroidism Exogenous steroids

tumors, or autonomous sex steroid production (peripheral precocious puberty) are rarer causes of sexual precocity.

Epidemiology

Many cases of sexual precocity clearly do not present to medical attention, and the prevalence of different forms of sexual precocity reported in case series varies considerably, probably because of differences in referral patterns.

Premature Thelarche

Definition/Classification

Premature thelarche is isolated breast development without progress in puberty. Typically, it occurs in girls under 1 year, and may be one sided and fluctuate with time. Development stops as the child gets older (2–3 years) although a small amount of breast tissue may persist. Older girls can present with breast development which may be accompanied by some pubic hair growth; they may either not progress at all or make very slow progress into puberty. This pattern of development is either described as thelarche variant or slowly progressive central precocious puberty.

Pathogenesis

Endocrine studies in premature thelarche show gonadotropin pulsatility which differs from that seen in puberty, with FSH levels higher than LH.

Clinical Manifestations

If the history and examination for a girl presenting with breast development is typical of premature thelarche, further investigations may not be needed. However, breast development may be the first feature in someone who will go on to develop central precocious puberty, so a period of follow-up of growth and development is necessary to confirm a diagnosis of premature thelarche.

Exaggerated or Premature Adrenarche, Also Called Premature Pubarche

Definition/Classification

The premature development of pubic hair without progress in puberty is called premature adrenarche, exaggerated adrenarche, or premature pubarche. Presentation is typically between 5 and 9 years; hair growth gradually progresses and is often accompanied by the development of axillary hair and an "adult" body odor.

Epidemiology

There appears to be an ethnic variation in rates of presentation. Girls are in the majority of those referred; there may be a sex difference but also the problem may go unnoticed in boys.

Pathogenesis

The development is associated with adrenarche, which is the maturation of adrenal sex steroid production which

occurs in late childhood in normal children. The term "exaggerated adrenarche" is sometimes also used because the development is often occurring at the normal age for adrenarche, and so is not actually premature. There is an increased risk of developing premature adrenarche if a child was of low birth weight.

Clinical Manifestations

Most children with premature adrenarche have no underlying endocrine defect. Investigations should be performed to exclude an underlying adrenal problem such as late onset congenital adrenal hyperplasia or an androgen-secreting tumor.

Pubic hair development occasionally presents in infants. It is thought that this is a different clinical entity from premature adrenarche although the cause is not known. Reported series have demonstrated no underlying endocrine pathology, although investigations should be done to exclude adrenal defects, as in older children.

Central Precocious Puberty

Definition/Classification

In central precocious puberty, all the physical and endocrine changes of true puberty occur too early, including the pubertal growth spurt.

Etiology

The majority of children with central precocious puberty are girls, and in most (over 80%) there is no obvious underlying cause. Approximately 15% of those with central precocious puberty are boys, and most of these have an underlying pathology.

Pathogenesis

Central precocious puberty can be caused by a variety of CNS lesions including tumors, which may not all be directly (see *Table 382.3*) related to the hypothalamo-pituitary area. Hypothalamic hamartoma (see *Fig. 382.2*) results in an abnormal pattern of gonadotropin secretion with an exaggerated LH response to GnRH testing. The tumor can also result in developmental delay, and an unusual form of epilepsy called gelastic

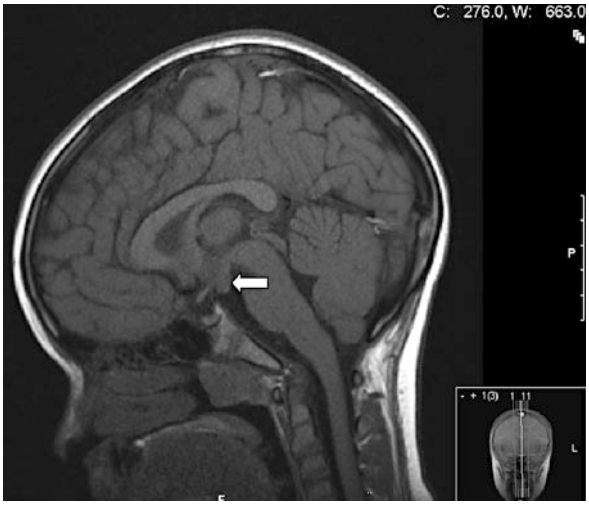

Figure 382.2

epilepsy (where the seizure is said to resemble laughter). Most hypothalamic hamartomas associated with central precocious puberty are small and not associated with neurological defects. Hypothalamic hamartomas are benign and usually do not increase in size after diagnosis. The MRI appearances are characteristic but repeat scan is of value in confirming the diagnosis for a lesion where biopsy is almost always not possible.

Raised intracranial pressure in the neonatal period related to hydrocephalus causes a decrease in the age of pubertal development and increased incidence of precocious puberty. This occurs even if intracranial pressure has been maintained at a normal level after the neonatal period by a ventricular shunt. The elevated intracranial pressure, even for a short period appears to permanently "reset" the hypothalamic clock. A similar effect can occur if there is a period of raised sex steroid concentration in childhood. There is an increased risk of central precocious puberty in congenital adrenal hyperplasia if there has been a period of time where the androgen levels have not been adequately controlled because the diagnosis has not been made or adherence to treatment is poor. The risk remains even if treatment brings the androgen levels down to normal. For the same reason, central precocious puberty can occur in children who have originally presented with peripheral precocious puberty or after treatment of a sex steroid–secreting tumor. The prevalence of central precocious puberty is increased in girls adopted in early childhood from developing countries. The reason for this is not known. There is speculation that it is related to rapid catch-up growth with change in environment.

Central precocious puberty has also been described because of activating mutations in the receptor for kisspeptin, GPR54.

Clinical Manifestations

A significant proportion of children with sexual precocity present with a clinical picture which does not fit exactly into one of the diagnostic labels described above. Children presenting with apparent premature adrenarche can subsequently start to progress in true puberty. The pace of development of girls with thelarche variant or central precocious puberty can vary considerably. If investigations exclude underlying pathology, following the child for a while to monitor the pace of development can be useful in this situation.

Premature Menarche

Definition/Classification

Premature menarche is the occurrence of periods without any other signs of puberty.

Etiology

The endocrine cause of this phenomenon is not known, although abnormal gonadotropin secretion has been reported.

Clinical Manifestations

Long-term follow-up suggests that this is a benign condition. Since there is no test to confirm premature menarche, the diagnosis requires exclusion of other causes of recurrent vaginal bleeding such as foreign body, tumors, and trauma.

Peripheral Precocious Puberty: Autonomous Sex Steroid Production

Definition/Classification

In testotoxicosis and McCune–Albright syndrome, gonadotropin receptors are activated without either gonadotropin production or gonadotropin binding to the receptors. Sex steroids are produced autonomously by the gonads.

Pathogenesis

Sex steroid secretion in the gonads is normally stimulated by LH and FSH binding to specific membrane-bound receptors. Sex steroid concentrations are normally controlled by LH and FSH secretion, and LH and FSH concentrations regulated by feedback by sex steroids on the pituitary and hypothalamus. Testotoxicosis is caused by mutations of the LH receptor, which result in continuing activation of the receptor without LH binding. The problem is inherited in an autosomal-dominant fashion, but is only manifested in males because both LH and FSH action are required for estrogen secretion in females. In McCune–Albright syndrome, the defect is not in the LH receptor but in the second messenger related to the receptor, a G protein which is shared between a number of different hormone receptors (including TSH, ACTH, PTH, and GHRH). McCune–Albright syndrome occurs in males and females. Other hormone excess syndromes can occur because the defect has the same effect on the other receptors which share this G protein, for example, thyrotoxicosis, Cushing syndrome, and acromegaly. There are associated areas of skin hyperpigmentation with a characteristic jagged edge and bone abnormalities (polyostotic fibrous dysplasia of bone). McCune–Albright syndrome is not inherited and occurrence of the mutation as a germ cell mutation is probably not compatible with fetal survival. The defect is a somatic cell line mutation occurring during early fetal development, and individuals with McCune–Albright syndrome carry both affected and unaffected cell lines. For this reason, the syndrome is very variable and depends on which cell types carry the mutation. Polyostotic fibrous dysplasia of bone can occur without other clinical features of McCune–Albright syndrome. A proportion of girls with functioning ovarian cysts probably have a very localized form of McCune–Albright syndrome.

Clinical Manifestations

Sex steroid concentrations are not regulated by gonadotropin feedback at the hypothalamus and pituitary, and so concentrations can be much higher than normal.

Feedback by sex steroids suppresses gonadotropin secretion, and LH and FSH concentrations are very low.

The pattern of physical development can be variable and will not necessarily follow the same pattern as in centrally mediated puberty.

Congenital Adrenal Hyperplasia

Pathogenesis

In the commoner types of congenital adrenal hyperplasia, 21 hydroxylase deficiency and 11 beta hydroxylase deficiency, failure to suppress ACTH secretion results in elevated adrenal androgen levels. This occurs if the disorder is either not diagnosed or diagnosed but undertreated.

Clinical Manifestations

The elevated adrenal androgens result in rapid growth with bone age advance, pubic hair development, and hirsutism. As discussed above, individuals with congenital adrenal hyperplasia are at risk of developing central precocious puberty if they have a period with elevated androgens, either before diagnosis or related to poor compliance with medication.

Sex Steroid–Secreting or Gonadotropin-Secreting Tumors

Pathogenesis

Tumors that secrete either sex steroids or HCG are rare causes of sexual precocity. Sex steroid–secreting tumors most commonly originate in the gonads or adrenal glands, and most secrete androgens, although estrogen-secreting tumors occur. Adrenal tumors that cause Cushing syndrome usually secrete androgens, and virilization can be present as well as typical features of Cushing syndrome. Very few gonadotropin-secreting adenomas of the pituitary gland been described, but gonadotropin secretion (as HCG) has been described from tumors including hepatoblastomas, teratomas, and germ cell tumors.

Clinical Manifestations

The typical features of sex steroid–secreting or gonadotropin-secreting tumors are high sex steroid concentrations with suppressed LH and FSH concentrations, and very rapid development.

Autonomous Ovarian Follicular Cyst

Pathogenesis

Individual estrogen-secreting cysts within the ovary can present with vaginal bleeding with little or no breast development, or with a history of rapid onset of breast development or breast tenderness.

Clinical Manifestations

Pelvic ultrasound shows a single, large simple cyst within one ovary and endometrial thickening within a small uterus. Estrogen concentrations can be higher than those seen in normal puberty, and FSH and LH are suppressed. Typically, the cyst disappears after a few weeks and estrogen levels fall to prepubertal levels, and most girls do not have any recurrence.

Hypothyroidism

Pathogenesis

Hypothyroid individuals with very high TSH values also have elevated FSH concentrations because of an overlap in the stimulation pathway within the hypothalamus and pituitary.

Clinical Manifestations

Severe hypothyroidism can result in enlarged testes in prepubertal boys, and signs of pubertal development, including breast development and vaginal bleeding in girls. The development usually regresses with treatment of the hypothyroidism.

Exogenous Steroids

Pathogenesis

Most reports of sexual precocity related to exogenous sex steroids are related to contact with creams used by adults. One of the disadvantages of topical testosterone creams is that there is a risk of transfer if it is not allowed to dry completely, and virilization has been reported in children because of transfer from their fathers. The role of contact

with environmental factors in the timing of puberty is unclear. Phytoestrogens like soya have no proven role in provoking early puberty. Ingestion of soya products in children does not seem to be linked to precocious puberty, and the age of pubertal development is not reduced in countries where large quantities of soya products are eaten.

Diagnosis of Premature Development of Secondary Sexual Characteristics

The majority of children who present with sexual precocity have a self-limiting problem with no long-term sequelae. There is a balance between trying to limit excessive investigations in children who have a totally benign condition and the requirement not to miss significant pathology. Initial investigations should be guided by an assessment of the most likely source of the sex steroids, with the results of biochemical investigations likely to guide any imaging investigations.

Biochemistry

As in pubertal delay, individual tests of LH and FSH may be unhelpful because of the pulsatile and diurnal pattern of secretion. Sex steroid secretion also has a diurnal rhythm; so a low concentration of estradiol or testosterone during the day does not rule out precocious puberty. In central precocious puberty, a pubertal pattern of secretion is seen after GnRH stimulation. Typically, the stimulated LH is very high in hypothalamic hamartoma. In peripheral precocious puberty (McCune–Albright syndrome or testotoxicosis), or development related to sex steroid–secreting tumors, the gonadotropin response to GnRH will be suppressed and sex steroid concentrations very high. Pubertal concentrations of sex steroids are not seen in premature thelarche or premature adrenarche. In premature adrenarche, plasma levels of adrenal androgens (17-β hydroxyprogesterone, androstenedione, and testosterone) should be measured as a screening test for congenital adrenal hyperplasia or other adrenal pathology, either baseline or after stimulation by ACTH. Urine steroid profile should be performed if there is any suspicion of congenital adrenal hyperplasia or androgen-secreting tumor.

Imaging

Sex steroid concentrations in the pubertal range will advance bone age, and in central precocious puberty the bone age advances into the pubertal range. Bone age is not significantly advanced in premature thelarche. In premature adrenarche, a degree of bone age advance is common, but not into the pubertal range. In girls, ultrasound can help to confirm a diagnosis of precocious puberty. Uterine and ovarian development keeps pace with puberty, and so in central precocious puberty ultrasound appearances are pubertal. In premature thelarche, the ultrasound appearances remain prepubertal whatever the breast stage. In central precocious puberty, MRI of the head should be performed, if there is not an already documented lesion. A minority (10–15%) of girls with central precocious puberty have a CNS lesion, and many present with this already documented, but almost all boys with central precocious puberty will have an underlying CNS defect. If a boy with central precocious puberty does not have a CNS lesion detected, a repeat scan at an interval should be considered.

Treatment

General Care (Nonspecific Treatment)

Premature adrenarche and premature thelarche can cause considerable distress to families, but unfortunately there is no effective treatment to regress the development. Parents can be reassured that trimming pubic hair is safe and this can help if the child is embarrassed by it.

Specific Treatment

Gonadotropin-releasing hormone analogues (GnRHa) will arrest development in central precocious puberty, although they are ineffective in other forms of sexual precocity. Endogenous GnRH is secreted in a pulsatile pattern by the hypothalamus and stimulates the secretion of LH and FSH. Early studies of exogenous GnRH showed that if it is administered in a non-pulsatile pattern at a high dose, the receptors are downregulated and gonadotropin secretion is suppressed. This effect is utilized in GnRHa designed to suppress gonadotropin secretion, usually given as long-acting depot preparations (lasting 1 or 3 months). There is often an advance in pubertal stage at the start of treatment, because gonadotropin levels are stimulated before they suppress. Oral cyproterone acetate can be given for the first 4–6 weeks to control this advance. If any endometrium at all has formed, there is likely to be a vaginal bleed 4–6 weeks into treatment, and parents should be warned about this. Side effects of GnRHa are very rare; the most common are problems at the site of injection, such as irritation or scarring. GnRHa are effective in halting pubertal progress; secondary sexual characteristics are likely to regress but rarely disappear completely. After stopping treatment, gonadotropin

pulsatility takes 3–4 months to return to normal and puberty then restarts. Most girls start their periods within a year of stopping treatment. Long-term follow-up after stopping treatment has demonstrated normal fertility and bone mineral density in adult life. GnRHa are the first-line treatment for centrally mediated precocious puberty. Cyproterone acetate and medroxyprogesterone were used before the availability of GnRHa but although they have the advantage of oral administration, they are much less effective in halting puberty and have more side effects.

GnRHa treatment should be considered because of the social and psychological problems associated with central precocious puberty, and to reduce the impact on adult height. Data on the impact of GnRHa on adult height are variable. Published studies have often used individuals who have declined treatment as controls or compared adult height with height prediction at the start of treatment. Adult height predictions based on bone age have limited accuracy in untreated precocious puberty with large discrepancies between height prediction and height achieved. Treatment with GnRHa usually arrests or slows bone age advance, and because growth continues while bone age advance is arrested, the calculated height prediction inevitably increases during treatment. The true final height reached after treatment is stopped is usually less than the prediction at the end of treatment. Studies with GnRHa in central precocious puberty suggest that there is an improved adult height with treatment, but wide variations between studies mean that it is difficult to quantify this. It is not possible to give an individual child a realistic estimate of the likely height benefit from treatment. Children with a less-advanced bone age at the start of treatment have a better height outcome. For very young children with central precocious puberty, the need to treat is usually completely clear for social and psychological reasons. For children at the older end of the spectrum for precocious puberty, adult height is not likely to be significantly improved, and the disadvantages of treatment (regular injections and hospital monitoring) may well outweigh the potential advantages of stopping periods. Studies using GnRHa in children with early but not precocious puberty, or a normally timed puberty and short stature, have not demonstrated any benefit to adult height.

In peripheral precocious puberty, GnRHa are ineffective and the choice of medication is less clear. Cyproterone, which suppresses gonadotropin secretion and acts as an antiandrogen, has been widely used in this indication. More recently, aromatase inhibitors and tamoxifen have been studied as potential treatment. Suppression of pubertal development is much more difficult in this group of patients and there is no evidence that it increases adult height.

Prognosis

Short- and Long-Term Effects of Sexual Precocity

Premature thelarche and premature adrenarche do not usually affect age at true puberty. Premature thelarche has no long-term sequelae. Follow-up studies in girls with premature adrenarche have suggested that this group may be at increased risk of developing polycystic ovarian syndrome and metabolic syndrome although not all investigators have confirmed this finding.

Central precocious puberty can result in short stature, although the adult height reported in series of untreated individuals with central precocious puberty varies considerably. As discussed above, the magnitude of the pubertal growth spurt is greater in younger children, compensating for variations in the age of onset of puberty. This compensation is lost for the youngest children, who have not completed enough growth in childhood before the onset of puberty. For girls at the upper end of the age range defined for precocious puberty, there is minimal impact on adult height.

In precocious puberty, behavioral difficulties are frequently reported, and children with precocious puberty frequently require psychological input during childhood. However, these problems usually resolve and studies looking at adults whose puberty was precocious find they do not differ significantly from the rest of the population. In the longer term, fertility is normal for most girls with central precocious puberty. Early menarche does not appear to be related to early menopause. If central precocious puberty is secondary to hypothalamic hamartoma, there may be menstrual irregularity in adult life related to continuing abnormal patterns of GnRH secretion. The underlying defect also remains after pubertal growth and development has completed for those with peripheral precocious puberty such as McCune–Albright syndrome, and can result in menstrual irregularity.

Problems in Normally Timed Puberty

Gynecomastia

Definition/Classification

Approximately 50% of normal boys have a small amount of breast development during puberty. Development is often one sided and many boys complain of breast tenderness.

Pathogenesis

The cause of the development in normal boys is thought to be increased circulating free estrogen compared to androgen during pubertal development. The appearances can be made much worse by obesity. Gynecomastia usually regresses as puberty ends, although this may take several years to occur.

Any conditions resulting in an excess of estrogen or estrogen action can cause gynecomastia, including Klinefelter syndrome, estrogen-secreting tumors, ovotestis, enzyme defects such as aromatase deficiency, and exogenous estrogen-like substances (including lavender and tea tree oil).

Clinical Manifestations

A pathological cause is much more likely to be present in gynecomastia presenting in prepubertal boys, and these individuals should all be investigated. If a boy is in mid-puberty, with mild gynecomastia and no other features of endocrine disorder, they are extremely unlikely to have any pathological cause.

Diagnosis

The majority of publications about gynecomastia describe individual rare causes and there are no data to guide whether it is worth investigating boys with no risk factors for pathology. LH, FSH, testosterone assay, and karyotype (to look for Klinefelter syndrome) will exclude most likely pathological causes.

Treatment

General Care (Nonspecific Treatment)

Most boys are content with being reassured that the development is harmless and will wait for it to disappear.

Specific Treatment

Studies of medical treatments for gynecomastia have examined blocking estrogen action with tamoxifen, inhibiting estrogen production with aromatase inhibitors (e.g., anastrozole), or giving extra androgen as danazol. There have been no controlled trials, and no agent has been very effective. In addition, there is the concern that treatment would inevitably interfere with the normal hormonal changes of puberty. Surgical removal or liposuction can give good cosmetic results and should be offered if there is significant psychological distress.

Polycystic Ovarian Syndrome

Definition/Classification

Polycystic ovarian syndrome is a common cause of menstrual disorders, infertility, and hirsutism in adult women. Because it is associated with insulin resistance and changes in lipid profile, PCOS in adult women is a risk factor for type 2 diabetes and cardiovascular disease. A consensus meeting 2003 proposed that the diagnosis should be made on the basis of any two out of the following features: oligo or anovulation; hyperandrogenism, clinical or biochemical; and polycystic ovaries on ultrasound. The characteristic biochemical findings are elevated androgens (or free androgen index) with elevated LH compared to FSH. The typical ultrasound features include 12 or more follicles of 2–8 mm diameter and ovarian volume over 10 cm^3.

Pathogenesis

There are genetic factors in PCOS, and the biochemical and ultrasound features often develop during puberty. Premature adrenarche has been identified as a risk factor. Polycystic appearances at ultrasound are found in approximately 20% of all women, but only 5–10% have any other features of polycystic ovarian syndrome.

Polycystic features can be seen in prepubertal ovaries, and PCOS can present in pubertal and post pubertal girls, causing hirsutism, acne, greasy skin, delayed onset of menarche, and irregular periods or amenorrhea. If there is significant virilization (severe hirsutism or acne, clitoromegaly), other causes of elevated androgens such as late onset congenital adrenal hyperplasia or adrenal tumor must be excluded. Insulin resistance is part of the spectrum of PCOS, and measurement of fasting glucose and insulin levels or an oral glucose tolerance test should be considered in girls who are obese, have acanthosis nigricans, or a strong family history of type 2 diabetes.

Treatment

General Care (Nonspecific Treatment)

Weight loss has been demonstrated to be effective in improving the biochemical and clinical features of PCOS, and weight gain makes them worse. Adolescent girls with PCOS should be advised to try not to gain excessive weight and to lose weight if already obese.

Specific Treatment

The most frequently used medical therapies for PCOS are the antiandrogen, cyproterone acetate (often given as part of an estrogen containing oral contraceptive pill, Dianette), and metformin, an insulin-sensitizing agent. Both are effective in suppressing androgen production and giving regular periods. Metformin can help weight loss, but side effects can include nausea, gastrointestinal symptoms, and hypoglycemia. Other antiandrogen medications have been used such as spironolactone, but there is less evidence as to effectiveness. Treatment does not resolve the underlying problem, which may recur when the medication is stopped and so it is only worth offering treatment if the symptoms at the time warrant it. Changes in acne or hair growth on treatment may take 3–4 months to start, and patients should be warned about this. Hirsutism and acne can have a very significant impact on an adolescent girl's self-esteem and social skills. Treatment can make a huge difference in appropriate cases. The opinions of parents and their daughter may differ considerably as to how significant they think the problem is. Severe acne can occur in girls without PCOS, and there are a number of effective topical and oral treatments available. Cyproterone or metformin are only likely to be effective in treating acne if investigations confirm elevated androgens.

Hirsutism

Etiology

Adolescent girls who present complaining of hirsutism often have increased hair growth due to a combination of hormonal (such as PCOS) and genetic factors.

Pathogenesis

The increased hair growth related to increased androgens in PCOS is typically on the face (upper lip, cheeks, and chin), and often associated with acne, greasy hair, and other features of PCOS such as irregular periods. Increased hair on the trunk and limbs is less likely to be related to hormonal status and has a strong genetic element.

Treatment

Antiandrogen treatment will only improve hormonally mediated hair growth. Other treatment options may be more satisfactory, such as bleaching and waxing. Electrolysis or laser treatment can be helpful for severe cases and can be used in combination with medical treatments. Both treatments can only treat small areas at a time, can be expensive, and also carry the risk of hyperpigmented scarring after the treatment. A topical treatment containing eflornithine (an ornithine decarboxylase inhibitor) is effective in reducing hair growth of nonhormonal cause. The cream must be applied evenly over the affected area twice daily and is only effective as long as it is being applied, so in practice is best for relatively small areas such as the face.

Puberty in Children with Learning Disabilities

Central precocious puberty can be caused by a variety of CNS lesions, and so children with cerebral palsy and severe learning disabilities are overrepresented in this group. If a girl is likely to be unaware of their pubertal development, they may not get any benefit from treatment for central precocious puberty, and adult height may be irrelevant in children who cannot walk. If a child is not mobile, increasing weight at puberty may mean that their family has more difficulty caring for them. Parents and carers are often concerned about how girls with learning disabilities will manage periods, even if these happen at a completely normal time. For parents, pubertal development in a child with severe learning disabilities brings up complex psychological and practical concerns about how the child will manage as an adult. For girls, treatment to give regular periods or to improve heavy periods can help with managing the situation. Therapy to stop periods completely carries the risk of osteoporosis if estrogen is suppressed, and if started, it can be very difficult to stop in a child who is never going to be mature enough to deal with puberty. There are wide variations in the approach to this problem. Pubertal delay or arrest may go unnoticed for much longer in children with learning disabilities. There is frequently a concern for children with developmental delay or behavior problems (particularly boys) that treatment to induce puberty will result in more difficult behavior. There are few data to support this concern, and even for children with very severe learning disabilities, induction of puberty can bring benefits in terms of increased psychological maturity as well as normal bone density.

The Psychology of Puberty

Late Puberty

Late pubertal development can be associated with psychological distress. Treatment to induce puberty can be

helpful although there are few studies confirming a psychological benefit of treatment. For girls with Turner syndrome, induction of puberty at a similar time to their peers carries psychological benefits. There is no evidence that treatment to induce puberty with sex steroids increases behavior problems in normal children.

Early and Precocious Puberty

A study following 466 girls born in the same Swedish town in 1955 (interviewing them at 13, 15, 27, and 43 years of age) examined the effect of early menarche (before 11 years) and late menarche (after 13 years). The early maturing group was more likely to be overweight as adults than the late maturing group. At age 15–16 years, the early maturing groups were more likely to exhibit delinquent behavior, more likely to use alcohol or drugs, and had more advanced sexual experiences. Early maturing girls were less likely to have university degrees. However, assessment later on as adults aged 43 found no adverse effects of early maturation on quality of life. Other studies have confirmed an association between early maturation and conduct disorder.

The psychological impact of early development is often a great concern for the families of children with precocious puberty. Children with precocious puberty may have behavior changes related to their hormonal levels but in addition there is the impact of the response of those around them to their early development, and the social difficulties associated with appearing much older than their true age. Studies confirm satisfaction with treatment, but it is much less clear whether psychological difficulties are resolved by treatment. Investigation and treatment of precocious puberty will inevitably focus the attention of families onto their child's pubertal development in a way that would not happen with a normally timed puberty, and occasionally this manifests as distress when the treatment is stopped and normally timed puberty occurs.

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383 Disorders of Sexual Development

Jamal Raza · Garry L. Warne

Definitions and Terminology

Disorders of sex development (DSD) are defined as *congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.* The initial determination of sex by genes directing the bipotential gonad to become an ovary or a testis is called *sex determination.* The subsequent development of the genital appearance resulting from the function of that gonad is called *sex differentiation.*

Some useful and at times confusing terminologies used over the years need to be clarified for a better understanding of the subject. *Chromosomal sex* is referred to as the sex based on the number of sex chromosomes. *Gonadal sex is* the sex according to the gonadal differentiation. *Phenotypic sex* is the sex based on the external anatomy of the genitalia. *Gender identity* is the individual's perception about his/her own gender. In some individuals, gender identity is different from the phenotypic sex. *Intersex* is a term no longer in use; it has now been replaced by the term DSD. *Ambiguous genitalia* refers to the appearance of external genitalia that are not easily classified as male or female.

Epidemiology

The reported incidence across the world is about 1:4,500 to 1:5,000 live births. This group of disorders affects approximately 85,000 children per year in the European community. Geographically, the incidence is variable. Egypt, for example, has reported a high incidence, 1:3,000.

Gonadal Differentiation

The Bipotential Gonad

In the embryo, the gonads develop in two phases. Initially, the gonad is described as "indifferent" or "bipotential." At this stage, the histological appearance of a gonad destined to become a testis is identical to the one destined to become an ovary. In the second phase, the bipotential gonad is directed into the pathway of differentiation into either a testis or an ovary.

The central portion of the intermediate mesoderm, or mesonephros, is the precursor of the urogenital ridge. Subsequently, part of the urogenital ridge becomes the genital ridge and it here that the bipotential gonad forms. The portion of the ridge lying caudal to the central portion is the pronephros; it gives rise to the adrenal cortex. The portion distal to it is the metanephros, from which the kidney develops. In addition to mesoderm, the genital ridge is also comprised of cells from coelomic epithelium which are destined to become supporting cells (either Sertoli cells in the testis or granulosa cells in the ovary). Steroid-secreting cells, which have an uncertain origin, are also present in the early gonad. They later develop into Leydig cells if the gonad is to be a testis or theca cells in cases of ovarian development.

As early as the second week of gestation, the germ cells from the primary ectoderm migrate, first into the yolk sac and then dorsally into the body wall by the sixth week. The germ cells will eventually develop into the mature gametes, i.e., spermatozoa and oocytes. The germ cell clusters come to rest on either side of the midline.

The primordial germ cells also express a number of transcription factors such as, POU5F1 (also known as octamer binding transcription factor (OCT)3/4 [OMIM No. 164177]), placental/germ alkaline phosphatase (PLAP), testis-specific protein Y encoded (TSPY), and VASA but lose expression for these markers following entry into the genital ridge. Pathologists are able to distinguish undifferentiated from differentiated germ cells by staining for these gene products, because undifferentiated germ cells express them, whereas differentiated ones do not, and the persistence of undifferentiated germ cells in a postpubertal testis is evidence that the germ cells are displaying primitive characteristics that should have disappeared, correlating with high risk of germinoma.

Differentiation of the Gonad into a Testis or an Ovary

The switch that initiates the pathway of differentiation of bipotential gonad into a testis is the expression of SRY, the *s*ex-determining *r*egion on the *Y* chromosome. This first

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occurs in cells referred to as pre-Sertoli cells, which then, under the influence of another gene, SOX9, transform into Sertoli cells.

The Sertoli cells then aggregate to form *seminiferous cords*, which increase in density and extend into the medulla of the developing testis. There they subdivide to form a network, the rete testis. Within the seminiferous cords, the Sertoli cells surrounding the germ cells are in turn surrounded by a layer of peritubular myoid cells which migrate from the mesonephros. These cells resemble smooth muscle and have contractile capability, so it is thought that they may be the means by which sperm are propelled along the seminiferous tubules of the mature testis.

Initially, the seminiferous cords communicate with the surface epithelium of the testis but lose this communication following the development of a thick fibrous capsule, the *tunica albuginea*. The seminiferous cords are solid, with no lumen, until the onset of spermatogenesis at puberty. Androgen receptor expression in Sertoli cells is very low until 5 months' gestation and increases after that; it has been suggested that spermatogenesis, being androgen-dependent, does not occur until androgen receptor expression has reached a critical level.

The testes descend to the abdominal wall by a retroperitoneal route, reaching the internal inguinal ring by 17 weeks. A long cord of gelatinous connective tissue, called the *gubernaculum* (or "rudder"), connects each testis to the bottom of the developing scrotum. There are two phases of testicular descent: the transabdominal phase and the trans-inguinal phase. The trans-inguinal phase in the rat is regulated by calcitonin gene-related peptide (CGRP), which is released from sensory endings of the genitofemoral nerve in an androgen-dependent manner and which is able to stimulate contractions in the gubernaculum.

Unlike the trans-inguinal phase, the transabdominal phase is androgen-independent. In patients with complete androgen insensitivity syndrome, whose androgen receptor gene is not expressed in any tissue of the body, the testes are usually found at the inguinal ring or in the inguinal canal, having completed transabdominal descent.

Hormone Secretion by the Fetal Testis

Müllerian inhibitory substance (MIS, also known as Anti-Müllerian hormone or AMH (gene locus 19p13.3-p13.2)) is a glycoprotein with two identical subunits that is secreted by Sertoli cells in the early phase of testicular differentiation under the influence of SOX9. MIS gene expression is regulated by SF1, GATA factors, WT1, DAX1, and FSH. MIS has the function of suppressing the development of the Müllerian ducts, which would otherwise develop into the uterus and Fallopian tubes (see ❯ Genes Involved in Sex Determination in this chapter).

Sertoli cells also secrete a second glycoprotein, Inhibin B, by a process requiring the presence of germ cells. Inhibin B has nonidentical subunits, α and β, and it is thought that the α-subunit is made by the Sertoli cells while the β-subunit is contributed by germ cells. Inhibin is an important regulator of FSH, which controls the increase in the germ cells.

Leydig cells lie in the interstitium outside the testis cords, often close to blood vessels and secrete testosterone from as early as 7 weeks. Each testis contains approximately 24×10^6 Leydig cells by the 15th week, but their numbers then decline to about 9×10^6 per testis by the time of birth.

It is now thought that *fetal* Leydig cells, which are derived from the mesonephros and which disappear within 3–6 months after birth, are a distinct population from *immature* Leydig cells, which differentiate after birth, become operative in the first year of life and persist throughout childhood, *adult* Leydig cells, which differentiate after birth from mesenchymal cells of the interstitium and become active at puberty. Unlike adult Leydig cells which can respond only to LH, fetal Leydig cells are sensitive to both luteinizing hormone and adrenocorticotropic hormone (ACTH), fetal and adult Leydig cells predominantly secrete testosterone, but immature Leydig cells are distinguished by mainly secreting androstane-3α, 17β-diol.

The differentiation and proliferation of fetal Leydig cells is regulated by two paracrine factors of Sertoli cell origin: Desert hedgehog (DHH; gene locus in the human 12q13.1) and fibroblast growth factor-9 (FGF-9). Experimental evidence suggests that exposure of the fetal testis to the antiandrogen flutamide can interfere with Desert hedgehog signaling and impair differentiation of fetal Leydig cells, thus causing abnormal testis development and sex differentiation (❯ *Figs. 383.1* and ❯ *383.2*).

Leydig cells (before and after birth) also secrete a protein hormone, insulin-like 3 (INSL3; gene locus 19p13.2), which acts on the gubernaculum during testicular descent through a cellular receptor known as leucine-rich repeat-containing G protein-coupled receptor 8 (LGR8; also known as GREAT). INSL3 is a member of the insulin-like hormone superfamily which comprises insulin, relaxin, IGF-1, and IGF-2. Maternally inherited mutations in INL3-GREAT were shown in an Italian study to account for 9.2% of boys with bilateral cryptorchidism.

After 10 weeks' gestation, the gonad separates from the developing adrenal and kidney. This process is inhibited by expression of the gene, *WNT4*. Rests of adrenocortical cells are commonly found along the line of testicular descent and

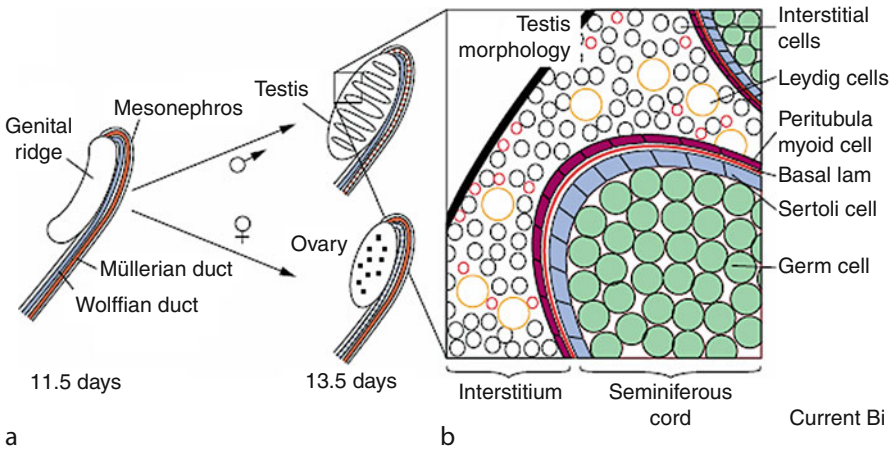

Figure 383.1
Differentiation of the internal genitalia into testicular tissue

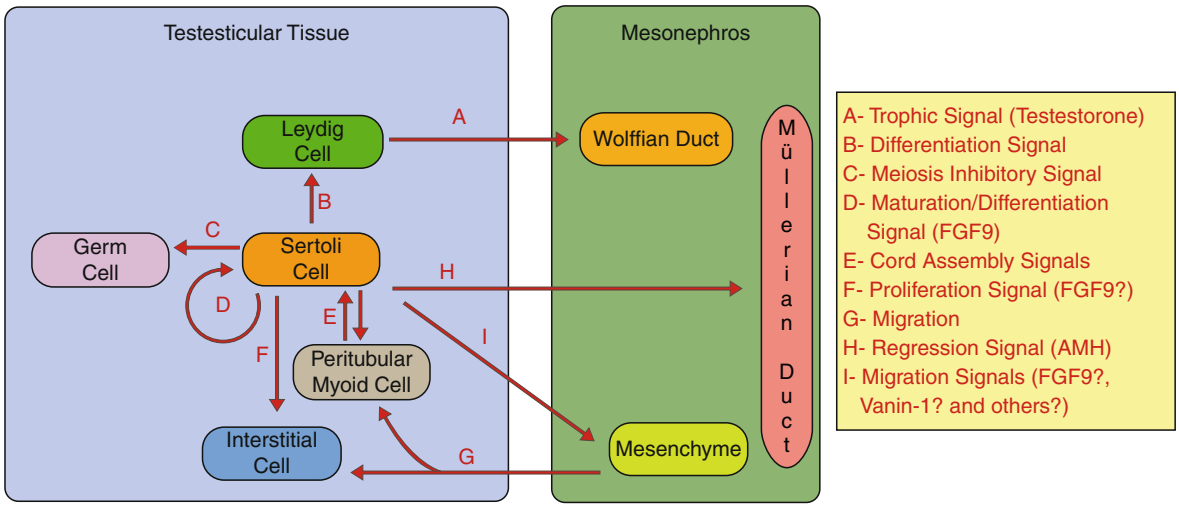

Figure 383.2
Differentiation of testicular tissue and role of migration factors

within the testis itself (surgeons are familiar with them and refer to them as "golden granules"). Under prolonged ACTH stimulation, these adrenal rests may undergo hyperplasia, particularly in men with poorly controlled congenital adrenal hyperplasia, in whom one testis (or both) may enlarge so markedly that a malignant tumor may be mistakenly diagnosed.

Development of the Human Ovary

The fetal ovary in the female develops later than the testis in the male. In the male, SRY triggers rapid testicular development, but there is no comparable factor stimulating rapid ovarian development. In the mouse, female-specific genes are beginning to show expression at the same time as *SRY* in the testis, but morphological changes are not obvious until weeks later. The cells of the sex cords surrounding germ cells develop as follicles, and oocytes are seen in the 11th–12th week. The number of primordial follicles in both ovaries (six to seven million) peaks at 20 weeks and is then reduced, by apoptosis, to only two million by term. The germ cells within the follicles all commence meiosis to create gametes by the fifth month of gestation, after which the gametes become dormant until puberty. Retinoic acid,

via stimulation of *Stra8* expression is thought to initiate meiosis. Until recently, it was believed that the number of female gametes was fixed at birth, but bone marrow has been found to contain germ line stem cells, and it is therefore possible, although as yet unconfirmed, that fresh oocytes for the ovary could be derived from this source. The fetal ovary makes no MIS until late gestation and very little estrogen. The human ovary secretes both Inhibin A and Inhibin B, but the testis secretes only Inhibin B, making Inhibin A a specific marker of the ovary after birth. In the mouse, Inhibin A is expressed in the ovaries from an early stage and increases with gestational age, but in the human, the lack of any difference between umbilical arterial and venous blood levels of Inhibin A suggests that most Inhibin A comes from the placental membranes rather than from the fetal organs.

Genes Involved in Sex Determination

Genes Expressed During Differentiation of the Genital Ridge: WT1, SF1

The following genes are expressed when the bipotential genital ridge is differentiating from the intermediate mesoderm: *WT1, SF1, SOX9, DMRT1, DHH, ATRX, TSPYL1, Gata4/Fog2, Fgf9/Fgfr2, Pod1, Pdgfr-α, Vanin-1, Tescalcin, Testatin, Dax1, Sox3, Sox8, RSPO1, WNT4,* and *DAX1.*

WT1, the Wilms' tumor suppressor gene (located at 11p13), is expressed in the less differentiated cells undergoing the transition from mesenchyme to epithelium which are both the primitive kidney and the genital ridge. A transcription factor, *WT1* has ten exons and four zinc fingers and binds to an ERG1 consensus binding sequence. At least four splice variants are known to occur. One variant results in Frasier syndrome, similar to Denys–Drash syndrome without the Wilms' tumor. The splice variants are divided into those which have the KTS tripeptide, WT1(+)KTS, and those which do not, WT1(−)KTS. In vitro experiments show that the testis determining factor, *SRY,* is strongly activated by WT1(−)KTS but not by WT1(+)KTS isoforms. The MIS gene is strongly repressed in vitro by the WT1(−)KTS isoforms, as is the androgen receptor (AR) gene promoter. At present, the relevance of these findings to what happens in vivo in unknown. The Denys–Drash syndrome, in which renal abnormalities (either Wilms' tumor or a progressive form of glomerulosclerosis, or both) and gonadal abnormalities (streak gonad with high neoplastic potential) coexist, is caused by germline mutations in WT1.

Steroidogenic factor-1 (SF-1; also called the adrenal 4-binding protein and NR5A1), is a nuclear hormone receptor, that in the rat, regulates the expression of the cytochrome P450 enzymes. It is expressed in the urogenital ridge prior to the differentiation of the gonad and is then expressed in the developing testis, but not in the developing ovary. Homozygous male and female *SF-1* knockout mice develop neither adrenal glands nor gonads. In addition, they show impaired gonadotrophic function and agenesis of the ventromedial hypothalamic nucleus. SF-1 also regulates the adrenocorticotropin receptor, the steroid acute regulatory protein (StAR), and in the pituitary, the α-subunit of the glycoproteins. Recent evidence indicates that certain oxysterols (particularly 25-hydroxycholesterol) show specific binding to SF-1 and stimulate SF-1-dependent transcription. There is evidence that WT-1 and SF-1 exert a synergistic effect on expression of the MIS gene. Mutations in SF1 have been identified in 46,XY patients with the combination of hypogonadism and adrenal insufficiency but also in 46,XY patients with gonadal dysfunction and normal adrenal function. Mutations in this gene are also found in patients with 46,XX ovarian dysgenesis and 46,XX primary ovarian insufficiency, suggesting that it plays an important part in the development of the ovary.

Genes Expressed in Male Sex Determination: SRY, SOX 9, DAX1, DMRT1, and Testatin

SRY: The Testis Determining Gene

SRY, the *s*ex-determining *r*egion of the *Y* chromosome, was cloned as the result of gene-mapping studies of Y chromosome deletions in XY females with gonadal dysgenesis and of Y-to-X translocations in XX. Mutations in *SRY* account for only 15% of cases of 46,XY complete gonadal dysgenesis, but 90% of cases of 46,XX individuals who have testes can be explained through the abnormal presence of SRY through translocation. This gene is crucial in switching the indifferent gonad into the pathway of testicular development and if *Sry is* transfected into the genome of a female mouse embryo, the gonads that differentiate are testes, not ovaries (but spermatogenesis is absent).

Another gene that is expressed in the genital ridge at an early stage is *SOX-9*. The *SOX* genes are defined by possession of the same HMG b*ox* as *SRY* and were detected by a genome-wide search for genes containing this sequence. In the developing embryo, *SOX-9* is expressed in the genital ridge and in the skeleton. Mutations in *SOX-9*

result in *campomelic dysplasia*, a severe birth defect causing bowing of the long bones (SOX9 directly regulates the type-II collagen gene) and sex reversal due to gonadal dysgenesis in 75% of XY individuals. In the mouse, high levels of *Sox9* mRNA are found in male (XY) but not female (XX) genital ridges and are localized to Sertoli cells within the sex cords of the developing testis.

DAX-1, DMRT-1, and Testatin

Duplications of DAX-1 are found in patients with X-linked 46XY DSD due to gonadal dysgenesis. DAX-1 is a member of the nuclear receptor superfamily which is expressed in steroidogenic tissues as well as in Sertoli cells, pituitary gonadotrophs, and in the ventromedial hypothalamus. Loss-of-function mutations of *DAX-1* were already known to cause adrenal hypoplasia congenita (AHC). The physiological role of DAX-1 is considered to be inhibitory to testis development through an anti-*SRY* effect. In Y-1 adrenocortical cells, DAX-1 has been shown to inhibit steroidogenesis at multiple levels, including the rate-limiting step controlled by StAR (the steroid acute regulatory protein).

The distal portion of 9p is a region implicated in human 46,XY DSD. A gene called *DMRT1* maps to that chromosomal region and is expressed only in testis. Its role in the regulation of testis differentiation has yet to be fully elucidated.

Testatin was detected using the signal peptide differential display screening technique, and it is a member of a gene family that encodes cystatins (cysteine protease inhibitors). Expression of testatin is confined, in the mouse, to fetal gonads, where it is expressed in pre-Sertoli cells during testis cord formation. These cells are believed to be the source of the testis determining factor, Sry, and testatin is expressed immediately following peak *Sry* expression. This suggests that testatin may have a role in tissue reorganization during early testis development. Testatin is also expressed in adult testis.

Genes Expressed in Female Sex Determination: RSPO1, WNT4, and β-Catenin

Two genes, Wnt4 and RSPO1, are currently considered to be candidates for ovary-determining genes. Wnt4, possibly assisted by RSPO1, opposes the action of two genes considered to promote testis development, SOX9 and FGF9. Wnt-signaling is involved in endocrine regulation and in the pathogenesis of some endocrine disorders and these actions, which are associated with expression of a transcriptional coactivator, β-catenin.

R-spondin 1 (RSPO1) has been cited as the female counterpart of the *SRY* gene. During gonadal development, both males and females have a low expression of *SOX9*, which in males is upregulated under the influence of SRY and leads to further testis development. In females, SOX9 is turned off, leading to the development of ovaries. This turning off seems to be under the influence of RSPO1. Mutations in the human RSPO1 gene give rise to an autosomal recessive syndrome of 46,XX testicular DSD. Other features of the reported phenotype include palmoplantar hyperkeratosis and increased risk of squamous cell carcinoma. Affected individuals lack Müllerian structures and have masculinized external genitalia, indicating that both fetal Sertoli cells and Leydig cells functions had been affected. Overexpression of SOX9 in females is also responsible for the masculinization seen in some cases of 46XX males.

Sexual Differentiation

The External Genitalia

The external genitalia of male and female fetuses are indistinguishable until 8–9 weeks (Fig. 383.3). Initially, the allantois, the large intestine, the postanal gut, and the Wolffian (mesonephric) ducts open into a common cloaca. At 6 weeks, the cloaca is subdivided into separate openings for the gut and the urogenital sinus. Bilateral cloacal tubercles coalesce at the anterior end of the cloaca to form the genital tubercle. This phallic structure at 9 weeks is a prominent structure resembling a penis in both sexes but it can develop into either a penis or a clitoris. The inner and outer genital folds form the lateral flanks of the urogenital sinus.

Leydig cells are first seen in the fetal testis at around 7 weeks and the effects of testosterone on the external genitalia are seen between 9 and 12 weeks. At 12–16 weeks, fetal serum testosterone reaches a peak approaching the adult male level.

Differentiation of the fetal genitalia is androgen-dependent. Furthermore, it requires dihydrotestosterone, an androgen 10–20 times more potent than testosterone because of its greater affinity for the androgen receptor. The genital tissues are rich in 5α-reductase-2, an enzyme which converts testosterone to 5α-dihydrotestosterone (DHT). Under the influence of DHT, the genital tubercle shows differential growth to become the penis and the inner genital folds fuse from posterior to anterior to enclose the penile urethra and *corpus spongiosum* (or spongy urethra). This is lined by endoderm derived from the urogenital sinus;

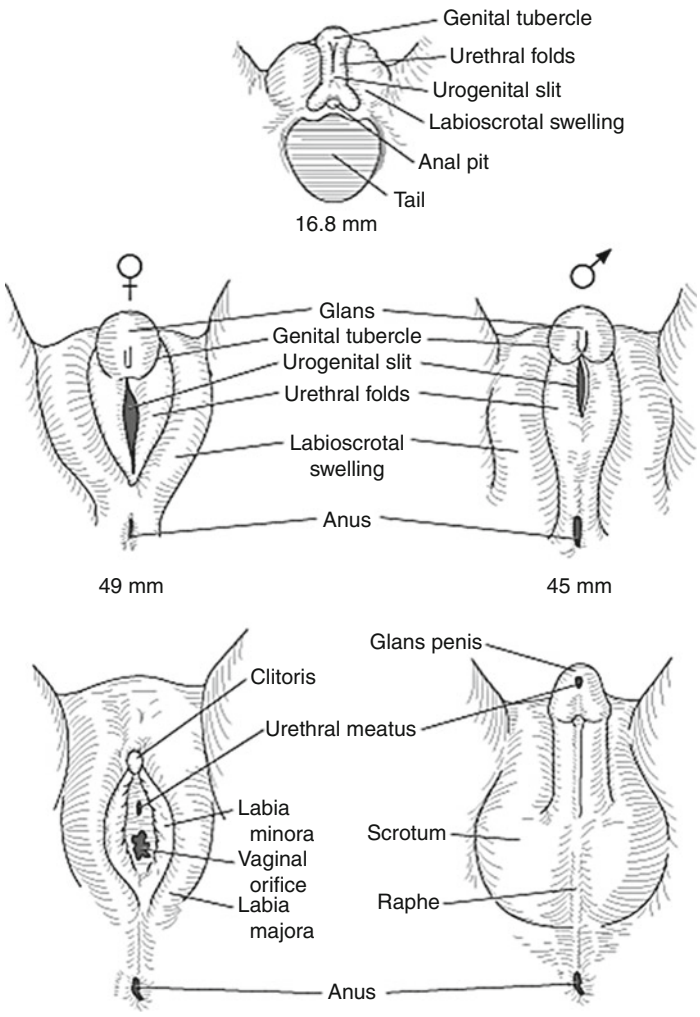

Figure 383.3
Differentiation of the external genitalia

it subsequently connects with an ingrowth of epithelium originating from the tip of the penis. At around the 12th week, the epithelium near the tip of the penis starts to invaginate in a circular fashion to create the prepuce or foreskin. This invagination divides to create two layers of epithelium which are initially adherent but later separate, allowing the foreskin to retract. (It is common for the foreskin to remain nonretractile for some years after a boy's birth.) The outer genital folds fuse to form the scrotum. This process is typically completed by 12–14 weeks and after that, the main changes are in the length of the penis.

In the female, the genital tubercle becomes the clitoris, the inner genital folds form the labia minora, and the outer genital folds, the labia majora. These changes occur in the absence of testosterone. In 46,XY individuals with complete androgen insensitivity, which is due to an inactivating mutation of the androgen receptor gene, the external genitalia are completely female, despite the presence of very high circulating testosterone levels. Feminization of the urogenital sinus commences after follicles have begun to grow in the ovaries, so a role for ovarian steroids in this process has been postulated. If the clitoris of a 46,XX female is exposed to high levels of androgen during fetal life, such as in a child with a genetic deficiency in the adrenal enzyme, 21-hydroxylase, it is possible for the urethra to be fully enclosed and reach the tip of the

phallus, just as it does in normal males. A lesser degree of androgenization will result in persistence of the urogenital sinus, so the baby is born with a single orifice on the perineum, instead of separate ones for urethra and vagina. With greater degree of virilization, the urogenital sinus is longer. Surgeons planning feminizing genitoplasty surgery on a child born with ambiguous genitalia due to a condition like congenital adrenal hyperplasia always need to make a careful assessment of the length of the urogenital sinus because the mobilization of a high junction between urethra and vagina requires great surgical skill and is potentially more damaging to the tissues than mobilization over a shorter distance.

The Genital Ducts

In the indifferent phase of embryonic development, two pairs of internal ducts – the Wolffian and Müllerian ducts – develop from the mesonephros during the seventh week (Fig. 383.4). The development of both is initially thought to be independent of the gonad. In both sexes, the *Wolffian* ducts grow caudally, penetrate the cloacal wall on the sides of a swelling called the Wolffian tubercle, and are then canalized. The ureters bud off the Wolffian ducts just behind the Wolffian tubercle on each side and connect with the metanephros (the precursor of the definitive kidney). The *Müllerian* ducts originate as a longitudinal invagination of

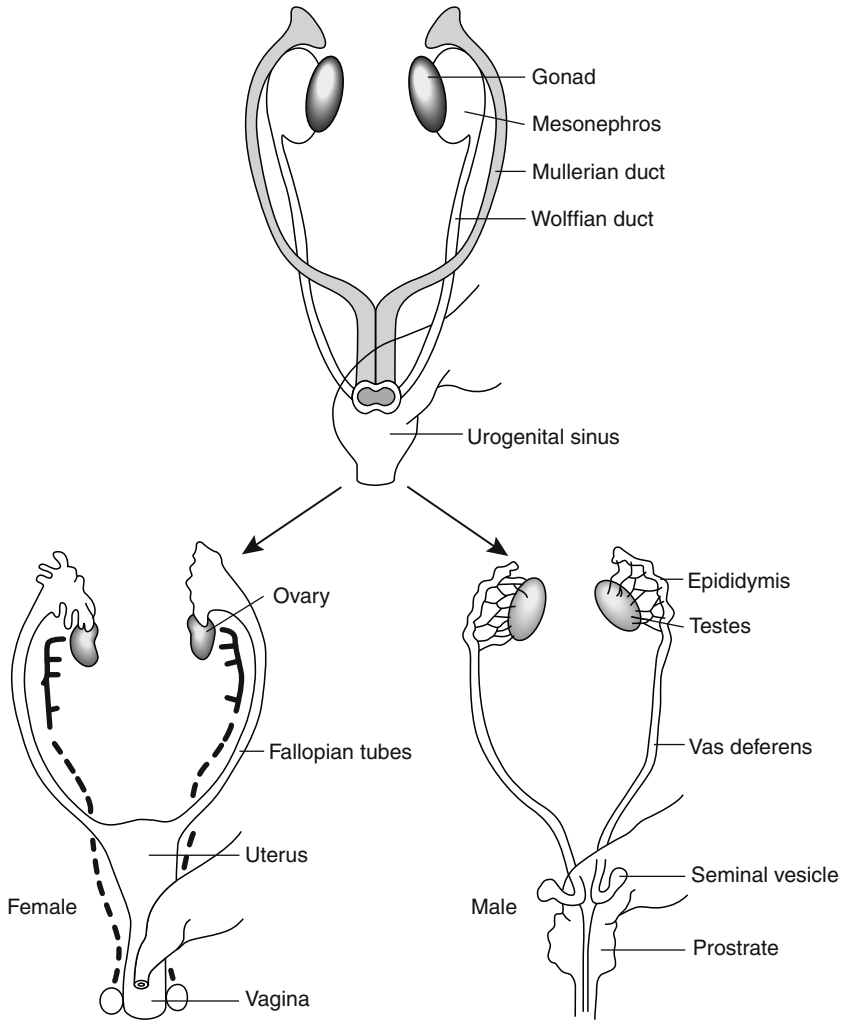

Figure 383.4
Differentiation of the genital ducts

the coelomic epithelium which grows caudally as a solid projection, lateral to, and in close apposition to, the Wolffian ducts. The Wolffian ducts precede and guide the Müllerian ducts to the urogenital sinus. At the pelvic brim, the Müllerian ducts swing medially, cross in front of the Wolffian ducts, then meet and continue migrating side by side to the urogenital sinus. They then fuse at 10–13 weeks to form the uterovaginal primordium. The uterus and vagina are recognizable by 16 weeks, but the vagina does not attain a lumen until 20 weeks. The hymen is imperforate until 20 weeks, when it breaks down. After the Müllerian ducts have been guided to their destination, the Wolffian ducts atrophy, but are represented postnatally by Gartner's ducts which open onto the vestibule. Paraovarian cysts, which are found incidentally during laparoscopy in some women, may also be of Wolffian duct origin. They are almost always benign but can be malignant.

Initially the internal ducts develop independently of the gonad, but the presence or absence of a functional testis determines the outcome once gonadal hormone secretion commences. Development of each Wolffian duct is stimulated by testosterone secreted by the Leydig cells contained in the testis of the same side. There is some direct evidence to support the hypothesis that testosterone diffuses down the Wolffian duct during sexual differentiation, the Wolffian duct enlarges and differentiates (by the third fetal month) into the vas deferens, the seminal vesicle and the epididymis. This is a direct action of testosterone that does not require the prior conversion of T to DHT. In the external genital tissues, DHT is the active androgen. The action of both T and DHT on the reproductive tract during sexual differentiation requires the presence of the androgen receptor (AR) and also involves several growth factors, particularly IGF-1 and epidermal growth factor (EGF). The cystic fibrosis transmembrane regulator gene (*CFTR*) is involved in maintaining the integrity of the vas deferens, and there are mild mutations in *CFTR* that only affect Wolffian duct differentiation without causing cystic fibrosis. The prostate gland and the bladder are both derived from the urogenital sinus. The commitment of undifferentiated stem cells to the prostate cell lineage is regulated by tumor protein p63. Formation of the lobes of the prostate and budding of the ducts is regulated by SOX9, retinoic acid, BMP (mesenchyme), and the BMP antagonist NOGGIN (postnatal ductal development). The prostatic utricle is commonly thought of as a Müllerian remnant, but this is incorrect. It, too, is derived from the urogenital sinus.

The *Müllerian, or paramesonephric, duct* develops independent of the coelomic mesoderm above the mesonephros. The part above the mesonephros gives rise to the infundibulum and fimbria of the fallopian tube; the part that runs alongside the mesonephros contributes to the ampulla and possibly the isthmus. It is argued by some writers that, in the region of the mesonephros, the Müllerian duct fuses with the Wolffian duct, and the ampulla and isthmus are Wolffian derivatives. Initiation of Müllerian duct morphogenesis from mesenchyme in both sexes requires expression of *WNT4,* a gene which is also required for ovarian differentiation the Müllerian duct can only proceed in the *absence* of any effect from MIS. The type-II MIS receptor has homology to the TGF-β/activin receptor family. In the absence of MIS, the Müllerian ducts grow and differentiate to form the two fallopian tubes and, through a distal midline fusion between the two Müllerian ducts and also involving the Wolffian duct, the uterus, and the upper vagina. This process is completed in the third fetal month. The fused portion of the Müllerian ducts connects to the expanded lower end of the urinary tract to form the *urogenital sinus.* The greater part of the vagina is derived from the urogenital sinus and only the upper portion is of Müllerian duct origin. Being of urogenital sinus origin, it is subject to the inhibitory effects of testosterone and does not develop when testosterone is actively promoting masculine development.

A point of practical significance is that an infant with a disorder of sex development who has a vagina will not have a prostate gland as well. A vagina cannot develop when there has been a marked response to testosterone, and a prostate gland cannot develop without it.

The fetal ovary does not produce MIS until late in gestation when it is secreted by the granulosa cells. MIS continues to be produced by the postnatal ovary, but by this time, the fallopian tubes, uterus, and vagina have become completely unresponsive to its effects.

In the mouse, the *Wnt7a* gene is expressed perinatally in the luminal epithelium of the uterus. Homozygous *Wnt7a-/-* knockout transgenic mice have abnormalities in the vagina (shallow fornices, vaginal concretions and epithelial inclusions in the vaginal stroma, stratified epithelium with reduced stroma and glands) and malformed oviducts. In addition, Wolffian duct remnants persist in the female reproductive tract of these animals as parovarian cysts.

Clinical Presentation of DSD

There is a range of clinical presentations for DSD:

- The infant with ambiguous genitalia
- The 46,XY female who is found to have inguinal testes (e.g., CAIS, 17α-hydroxylase deficiency)
- 46,XY Females who progressively virilize during childhood (e.g., 17β-HSD)

- 46,XY Females who develop breasts but no menses (e.g., CAIS)
- 46,XY Females with absent pubertal development (e.g., complete GD)
- Girls with absent uterus and vagina (vaginal agenesis)
- Males with hypospadias ± undescended testes
- Adolescent male with recurrent hematuria (CAH)
- Male with micropenis and adolescent gynecomastia (e.g., PAIS)
- Male with a uterus (persistent Müllerian duct syndrome)
- 46,XX male with impaired sexual development
- Male discovered to have chromosomal aneuploidy (45,X/46,XY mosaicism; 47,XXY, etc.)
- Adult male or female with an intra-abdominal gonadal tumor of germ cell origin

Classification of DSD

The present classification of the disorder places them in three major categories:

1. 46,XY DSD
   (a) Disorders of testicular development
      (i) 46,XY complete gonadal dysgenesis
      (ii) 46,XY partial gonadal dysgenesis
      (iii) 46,XY Ovotesticular DSD (formerly referred to as True hermaphroditism)
   (b) Disorders of androgen synthesis or action
      (i) Androgen biosynthetic defect
      (ii) Defect in androgen action
      (iii) LH receptor defect
      (iv) Deficiency of Müllerian inhibitory substance (MIS) or its receptor
   (c) General category
      (i) Hypospadias
      (ii) Cloacal exstrophy
      (iii) Bladder exstrophy
2. 46,XX DSD
   (a) Disorder of gonadal development (formerly called 46,XX male syndrome)
      (i) 46,XX testicular DSD (SRY translocation on X chromosome-90%)
      (ii) R-spondin1 genetic mutation
      (iii) SOX9 duplication or overexpression
      (iv) Ovotesticular DSD
   (b) Androgen excess
      (i) Fetal adrenal
         - 21α-hydroxylase deficiency
         - 11β-hydroxylase deficiency
         - 3β-hydroxysteroid dehydrogenase
      (ii) Fetoplacental
         - Aromatase deficiency
         - POR deficiency
      (iii) Maternal
         - Drugs
         - Tumors
3. Sex chromosome aneuploidy DSD
   (a) Klinefelter syndrome
   (b) Turner syndrome and its variant
   (c) Mixed gonadal dysgenesis
   (d) Ovotesticular DSD

46,XY DSD

46,XY Complete Gonadal Dysgenesis

Also known as Swyer syndrome, it represents failure of testicular differentiation at an early embryonic stage, resulting in gonadal dysgenesis. The gonads may be streaks, meaning that they contain no germ cells, or hypoplastic/dysgenetic testes. In about 15% of cases, a mutation in *SRY* is found.

Affected patients will have a female phenotype, and mostly present around puberty with reduced pubic hair, delayed breast development and primary amenorrhea. They possess normal female external genitalia with impalpable gonads. They have normal stature and lack any dysmorphic features. Raised gonadotrophins (FSH, LH) and a low basal and stimulated testosterone are found, and ultrasound is unable to pick up gonads, but usually a small uterus is found. Sex of rearing is unequivocally female and is not an issue. Gonadectomy should be carried out when the diagnosis is first established, due to the high risk of malignancy in these patients. Hormone replacement with estrogen and progesterone is required for the development of female phenotype. In the presence of uterus, pregnancy is a possibility with donor egg fertilization, but certain religious groups, e.g., Roman Catholics, orthodox Jews, and Muslims, have ethical objections to egg donation.

46,XY Partial Gonadal Dysgenesis (PGD)

In a 46,XY child without mosaicism, when there is incomplete differentiation and development of the testes and some degree of masculinization of the genitalia, the condition is labeled as Partial Gonadal Dysgenesis (previously also referred to as male pseudohermaphroditism). This may result from a heterogeneous group of chromosomal,

gonadal, and phenotypic abnormalities. Wolffian duct development depends on the amount of androgens made earlier during gestation, while regression or otherwise of the Müllerian duct depends on whether damage has occurred before the seventh week, when MIS was produced. Externally, some degree of ambiguity is mostly present; however, a male phenotype is also a possibility. Usually a smaller penile size with some chordee and a variable degree of hypospadias is found. Asymmetry of gonads, due to one gonad being palpable and the other being undescended, often gives a clinical clue to the diagnosis. The sex of rearing depends on the severity of ambiguity among other factors, but the preference is for male sex of rearing. Intra-abdominal gonads need to be removed due to high risk of malignancy if they cannot be bought down, while an inguinal gonad should be brought down and monitored periodically for any changes. Hormone replacement, if required, should commence around puberty time.

Ovotesticular DSD (OT-DSD) (OMIM #235600)

Histological presence of both ovarian and testicular tissue in one or both gonads is imperative for the diagnosis of OT-DSD. A definite requirement for an ovarian element would be at least one follicle, i.e., a large ovum surrounded by a layer of flattened cells, or better, with more cells. For testicular tissue, the requirement would be a seminiferous tubule, i.e., a tubular structure lined by at least Sertoli-like cells, and better with germ cells, although the presence of germ cells is not an absolute requirement. There may be a combination of one gonad being an ovary and the other being a testis, while both ovarian and testicular tissue may be present in the same gonad (ovotestis) on one or both sides. Ovotestis was found in about 45% in one large series. The frequency of this disorder is variable, with geographical pockets of high frequency. It is particularly prevalent in the Bantu-speaking black community in South Africa. In one cohort of 228 DSD patients, OT-DSD was diagnosed in 5.7% patients, and similar incidence has been reported elsewhere. No etiology for the disorder has been found, although about 10% of 46,XX cases have the *SRY* gene and a case report in a syndromic OT-DSD has suggested a mutation of the RSPO-1 gene. Familial cases have also been reported and both autosomal recessive and sex-limited autosomal mechanisms have been suggested.

A variable karyotype thus can be found in OT-DSD, including 46,XY, 46,XX, and a variety of mixed chimeric patterns such as 46,XX/46,XY. The commonest one is 46, XX, representing 97% of cases in Africa, 72% in North America, and over 50% in Europe. 46,XY was reported in about 7% in both series, while the chimeric pattern constitutes 41% in European series, as opposed to 21% in North America. In experimental mice, crossbreeding between similar but slightly different breeds gives rise to litters of 46,XY pups, some of which have gonadal dysgenesis while other littermates have ovotesticular DSD. This occurrence is explained by a timing mismatch between the two mouse species in the switching on of *sry*.

There are also various configurations for internal genitalia. Most classically, there is a Wolffian system on one side and a Müllerian duct system on the other. However, a combination of these may also coexist.

The external genitalia also vary in the degree of ambiguity. Usually, at least one gonad is palpable in the inguinoscrotal region. This is more often seen on the right and is often associated with an inguinal hernia. Fertility is usually not seen; however, there have been 21 reported cases of pregnancies in OT-DSD. Investigations of these individuals may include chromosomal analysis (minimum of 50 cells to be counted, to detect mosaicism), FISH for SRY (when the karyotype is 46,XX), imaging to locate the gonad (pelvic ultrasound, MRI), an hCG stimulation test to assess the testicular function, and a serum Inhibin A level to identify ovarian tissue.

The management plan for a person with OT-DSD will be an individualized one, taking into account the chromosomal type, the internal and external anatomy, the presence of functional ovarian or testicular tissue, the sex in which the person has already been raised, the availability of medical and surgical expertise, and other social and cultural factors.

Disorder in Androgen Synthesis or Action

This is further divided into:

1. Defects in testosterone biosynthesis (*Fig. 383.5*)
2. Defect in the synthesis of dihydrotestosterone (DHT), 5α-reductase-2 deficiency
3. Leydig cell hypoplasia
4. End organ resistance: Complete Androgen insensitivity syndrome (CAIS) and partial androgen insensitivity syndrome (PAIS)

Testosterone Biosynthetic Defects

A number of enzymes are involved in testosterone biosynthesis. A single enzyme deficiency may be enough to block hormone synthesis.

1. Steroidogenic acute regulatory protein (StAR protein) (OMIM 600617)
2. 3 β-HSD type-II deficiency (OMIM 201810)
3. CYP17 (17α-hydroxylase/17,20 lyase defect) (OMIM 202110)
4. CYP17 (17,20 lyase defect) (OMIM 202110)
5. P450 oxidoreductase deficiency (OMIM 201750)
6. 17 β-HSD type-III deficiency (OMIM 605573)

Congenital Lipoid Adrenal Hyperplasia

Lipoid adrenal hyperplasia is caused by a mutation in the gene regulating the steroidogenic acute regulatory protein, StAR, which is the transporter protein responsible for transferring cholesterol across the mitochondrial membrane of steroidogenic cells in the adrenal cortex and the gonad. Once inside the mitochondrion, cholesterol becomes the substrate for all of the steroidogenic enzymes. Absence of StAR results in the toxic accumulation of lipid material in the cytoplasm of adrenocortical cells and Leydig cells.

Mutation in the gene results not only in severe undervirilization but also in severe salt wasting, leading to hyponatremia, hypovolemia, hyperkalemia, acidosis, and often death during infancy, if treatment with corticosteroids is delayed. Lipoid CAH is relatively common in the Japanese, Korean, and Arab populations.

Irrespective of the chromosomal sex, nearly all reported cases have a female phenotype. The Leydig cells in 46,XY patients are also affected, leading to inadequate testosterone secretion. Most would die in infancy due to mineralocorticoid deficiency if not correctly diagnosed, but with early and appropriate glucocorticoid and mineralocorticoid treatment, patients should survive and do well.

While most 46,XY children with lipoid adrenal hyperplasia have a female phenotype, phenotypic male children with normal phenotype presenting primarily with glucocorticoid deficiency have been reported.

Interestingly, most 46,XX individuals with the mutation reach menarche and go through puberty but as well as being infertile, they experience a premature menopause and are prone enlargement of the ovaries, which become lipid-laden and cystic and which are prone to torsion. Pregnancy following IVF has been reported in this condition.

The primary defect is genetic loss of steroidogenesis that is dependent on StAR protein. There is a subsequent loss of steroidogenesis that is independent of StAR, due to cellular damage from accumulated cholesterol esters.

The adrenals are grossly enlarged with a yellowish appearance. Histology shows the classic appearance of fat laden adrenal gland.

3 β-Hydroxysteroid Dehydrogenase Type-2 Deficiency (OMIM 201810)

The two 3 β-Hydroxysteroid Dehydrogenases (3βHSD) are the enzymes responsible for the conversion of Δ^5 to Δ^4 steroids. 3βHSD type 1 is expressed in skin, breast and placenta whereas type 2 is expressed in adrenals and gonad and it is this enzyme, when deficient, that causes DSD. The type 2 gene is located at 1p13.1 and the condition is autosomal recessive.

The adrenal involvement results in salt wasting; deaths have been reported despite the steroid replacement. Some reports have also shown cases without salt loss. The diminished androgen synthesis and gonadal involvement in a male would result in variable degree of lack of virilization, ranging from a female phenotype to hypospadias. In a genetic female fetus, the accumulation of adrenal androgen (DHEA) causes overgrowth of the clitoris and partial fusion of the labioscrotal folds.

Typically, a raised level of 17-hydroxypregnenolone for the patient's age and sex is expected. Serum 17-hydroxyprogesterone may also be increased, leading to an incorrect diagnosis of 21-hydroxylase deficiency. This may result from the peripheral conversion of 17-hydroxypregnenolone by the type 1 enzyme which is present there. A raised DHEA sulfate is also found in these patients.

Hormone replacement with glucocorticoid and, as necessary, mineralocorticoid is essential. Appropriate replacement of sex hormone should be carried out around the time of puberty.

CYP17 (17α-Hydroxylase/17,20 Lyase Defect) (OMIM 202110) and CYP17 (17,20 Lyase Defect)

A member of the cytochrome p450 family of enzymes, this very rare condition is transmitted as autosomal recessive. The genetic defect is located at 10q24.3. These two conditions can coexist, or the latter can sometimes occur as a separate disorder. The deficiency of 17α-hydroxylase results in inadequate conversion of pregnenolone and progesterone to 17-hydroxypregnenolone and 17-hydroxyprogesterone respectively. The lack of cortisol leading to excess ACTH, however, results in the overproduction of deoxycortisone which causes hypokalemic hypertension.

The degree of undervirilization seen in 46,XY patients varies according to the severity of the enzyme defect, and the persistence of Müllerian structures has been reported. Analysis of urine steroids by GC-MS shows a characteristic profile. Circulating levels of DOC, 18-OH DOC, corticosterone, and ACTH are elevated, while the levels of aldosterone and PRA are reduced. Serum testosterone does not rise in response to hCG. Treatment constitutes of replacement of glucocorticoids, and this also corrects the hypertension.

P_{450} Oxidoreductase POR Deficiency (OMIM 201750)

An autosomal recessive condition with a defect in POR gene, this disorder presents with a wide range of clinical presentations. POR is a flavoprotein which plays a central role in the electron transfer in P_{450} enzymes. Although the POR reduction plays a crucial role in the 17,20 lyase reaction, there are 57 microsomal P_{450} enzymes, many of those are influenced by this defect, hence the clinical spectrum is wide. The cortisol deficiency may range from insignificant to life threatening.

Men may suffer from variable undervirilization and present with ambiguous genitalia. Females may have vaginal atresia, fused labia, large clitoris, primary amenorrhea, and large cystic ovaries.

The most severe form results in Antley–Bixler syndrome, which has a variable combination of craniofacial defects (craniosynostosis, brachycephaly, depressed nasal bridge, broad nose, cleft palate), skeletal anomalies (radiohumeral synostosis, bowing of legs, campodactyly, neonatal fractures), and urogenital anomalies (ambiguous genitalia, horse shoe kidney, ectopic kidney, hypoplastic ureters).

The diagnosis can be made by analyzing urine with GC-MS (which shows a unique steroid metabolism suggestive of impaired activity of both 17-hydroxylase and 21-hydroxylase) and confirmed with genetic analysis.

Steroid 5α-Reductase Type-2 Deficiency (OMIM 611715)

5α-Reductase-2 deficiency has been reported in many countries, especially the Dominican Republic, Turkey, India, and Papua New Guinea, but it is relatively rare in Caucasians.

This defect in androgen synthesis results in inadequate conversion of testosterone to dihydrotestosterone. As DHT is mainly involved with external appearance of genitalia, its deficiency would result in significant undervirilization. There may be a small phallus with chordee and penoscrotal hypospadias, a bifid scrotum, and a urogenital sinus.

As testosterone production is normal, the Wolffian duct develops and differentiates into the epididymis, seminal vesicle, and vas deferens, while Müllerian regression also takes place. Gonadal descent is impaired to a variable extent, and testes are found in the inguinal canal or labioscrotal folds.

A significant feature of the condition is virilization occurring at puberty, with the phallus becoming enlarged, labioscrotal folds becoming pigmented and rugose, testes enlarging and then descending into the labioscrotal folds. The hallmark investigation to diagnose the condition is the measurement of testosterone and dihydrotestosterone following hCG stimulation. In 5α-reductase-2 deficiency, the T:DHT ratio is very high (>36, as opposed to normal 8–16). The block results in high unstimulated and stimulated testosterone levels, while the DHT level remains low.

Leydig Cell Hypoplasia/Aplasia (OMIM 152790)

First described in 1976, the condition has been divided into aplasia or hypoplasia. The complete absence of Leydig cells would result in presentation similar to that of Swyer syndrome (complete gonadal dysgenesis). The cause is a defect in LH signal transduction due a mutation in the LH receptor gene.

The presentation is often a complete female phenotype with intra-abdominal gonads, rudimentary Wolffian and absent Müllerian structures. They fail to attain puberty and pubic hair does not develop. Failure of testosterone to rise with hCG stimulation is the diagnostic clue which is confirmed on histological absence of Leydig cells on testicular biopsy and an LH receptor gene defect on mutational analysis. A partial form of this disorder with lesser severity also exists.

Androgen Insensitivity or Androgen Resistance (OMIM 300068)

The effects of androgen in mediating the differentiation and development of the normal male phenotype are exerted by a single protein called androgen receptor. Defects regarding androgen resistance were noticed as early as in 1953 by John Morris; however, the receptor gene (locus Xq11-12) was not cloned until 1989. Since then, more than 400 mutations have been reported. The clinical phenotypes are variable and are divided into three types:

1. Complete androgen insensitivity
2. Partial androgen insensitivity
3. Mild androgen insensitivity

Complete Androgen Insensitivity

These may present with female genitalia with absence of Wolffian structures such as the vas deferens, epididymis, and seminal vesicles. Müllerian structures are usually absent, although a number of recent reports have found some Müllerian structures such as a Fallopian tube. At puberty, breast development may occur (due to high testosterone conversion to estradiol), but pubic and axillary hair remains absent. Failure to menstruate may be the first sign or presentation to a gynecologist, or sometimes when they operated for a suspected "inguinal hernia." The length of the vagina is usually about two third that of non-CAIS women, but sometimes it is extremely short and penetrative intercourse may be impossible without some procedure to lengthen it. Lengthening the vagina can sometimes be achieved by nonsurgical means. Localized pressure, as in repeated attempts at intercourse, can substantially lengthen a short vagina over time. Women with CAIS tend to be taller than average women. Because they have a 46,XY karyotype, they may have other X-linked conditions, such as red-green color blindness.

Partial Androgen Insensitivity

Patients with PAIS present with a variety of phenotypes. Depending on the severity of the androgen insensitivity in the tissues and even within a family, there may be substantial phenotypic variation between affected family members. More severe forms present with variable degree of ambiguity and cryptorchidism, while the less severe ones present with just clitoral enlargement, some pubic hair, and labial fusion. Wolffian structures may be partially to fully developed, but Müllerian structures are usually completely absent. Affected individuals can expect to develop gynaecomastia when they reach puberty. This differentiates PAIS from similar conditions such as 5α-reductase-2 deficiency and 17β-hydroxysteroid dehydrogenase deficiency, in which gynaecomastia is not expected.

Mild Androgen Insensitivity (MAIS)

This condition usually presents with a coronal hypospadias or a midline raphe in the scrotum. Later in puberty, they develop gynaecomastia, a high-pitched voice, sparse sexual hair, and impaired spermatogenesis and fertility.

Investigations

High testosterone and LH are found in the first 3 months and then at puberty, indicating androgen resistance. hCG stimulation reveals a high basal and higher stimulated levels of both testosterone and DHT, indicating a problem at the receptor level. High serum estrone is also found (conversion of high testosterone). MIS and Inhibin B are also present in normal amount as Sertoli cell functions remain unaffected.

Management of these children depends on the severity, age, and type of presentation. For instance, a girl diagnosed for the first time during puberty and found to have CAIS should be brought up as a girl and have the testes removed after puberty has been completed, whereas a child whose appearance is more like an undervirilized boy would generally be reared as a male with orchidopexy and hypospadias repair.

Timing of Gonadectomy and the Risk of Malignancy

Testes carrying androgen receptor gene mutations are at an increased risk of germ cell malignancies, the risk being highest in partial AIS with an intra-abdominal testis. The risk in women with complete AIS is lower. Intra-abdominal testes that cannot be brought down should be removed. Inguinal testes may be left in situ until after puberty as the risk before this time appears to be extremely low. Retention of testes in a child raised female allows spontaneous breast development to occur at puberty, but may also be associated with virilization in a child with partial AIS, and this may be unwanted. The testes in women with CAIS are the same size as in men but are in a superficial inguinal position where they may be very painful when compressed by clothing or during sporting activities. This is another reason why some women choose to have them removed (*Table 383.1*).

Persistent Müllerian Duct Syndrome (PMDS)

Mutations in the MIS gene located on the chromosome 19p 13.3 account for about half of all cases of this rare syndrome and in the other half, mutations in the MIS receptor gene are found. Clinically, it presents as

Table 383.1

Risk of type-II germinal cell tumors (GCTs) in the various categories of disorders of sex development (DSD) patients, classified into high-, intermediate-, low-, and no-risk groups

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (n)	Patients (n)
High	GD[a] (+Y)[b] intra-abdominal	15–35	Gonadectomy[c]	12	>350
	PAIS non-scrotal	50	Gonadectomy[c]	2	24
	Frasier	60	Gonadectomy[c]	1	15
	Denys–Drash (+Y)	40	Gonadectomy[c]	1	5
Intermediate	Turner (+Y)	12	Gonadectomy[c]	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)[c]	Unknown	Biopsy[d] and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy[d] and irradiation?	0	0
Low	CAIS	2	Biopsy and Gonadectomy	2	55
	Ovotestis DSD	3	Testis tissue removal?	3	426
	Turner (−Y)	1	None	11	557
No (?)	5α-reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

CAIS complete androgen insensitivity syndrome, 17β-*HSD* 17β-hydroxysteroid dehydrogenase deficiency, *PAIS* partial androgen insensitivity syndrome.
[a]Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).
[b]GBY region positive, including the TSPY gene.
[c]At time of diagnosis.
[d]At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.

a phenotypic male usually along with bilateral cryptorchidism and an inguinal hernia. Leydig cell functions are usually well preserved, but azoospermia is common usually due to malformation of the *vas deferens* or agenesis of the epididymis. At operation, the surgeon finds a Fallopian tube in the hernial sac. The testes are normal, apart from perhaps being unable to secrete MIS. The anatomy is important; the vas runs down the lateral wall of the uterus, so removing the uterus removes whatever small chance of fertility there might have been.

Hypospadias and DSD

The dividing line between hypospadias and DSD is not a clear one. Hypospadias is extremely common, affecting 1:125 boys in the USA, so it would appear unreasonable to look for evidence of an underlying DSD in every case. It is usually sporadic, and some cases are found with underlying defects of the urogenital system. A careful study of a series of 32 boys presenting consecutively with hypospadias failed to detect any significant endocrine defects. Fukami et al. described a mutation in an X-linked gene, Cxorf6, in three boys with penoscrotal hypospadias and micropenis.

Currently, investigations on the following types of hypospadias patients are recommended: those with severe perineo-scrotal hypospadias; those with an undescended testis; those with micropenis; those with dysmorphic features and/or short stature suggesting a chromosomal or genetic syndrome; and those with a positive family history of hypospadias. A chromosome analysis, pelvic ultrasound, serum FSH and LH, and serum testosterone, DHT, and androstenedione would all be useful in such cases.

46,XX Testicular DSD

Some degree of masculinization is sometimes found in children with a 46,XX karyotype. This condition is clinically comparable to Klinefelter syndrome. It represents some degree of testicular determination in the gonad. It may present with ambiguous genitalia at birth or may sometimes present later in with hypergonadotrophic hypogonadism, delayed puberty, or at times with complete masculinization and infertility.

This may result from the following conditions:

1. SRY mutation: Translocation of a small segment of Y chromosome is by the commonest cause of this condition accounts for about 80% of these cases.
2. SOX9 duplication: SOX9 has been proposed as a downstream gene responsible for the actions of

SRY; thus an overexpression has recently been found to be a significant cause of this condition.

3. Ovotesticular DSD: Ovotesticular DSD would definitely result in some testicular tissue formation hence the ambiguity.
4. Another gene linked with this condition is DAX 1. Although, classically responsible for hypogonadotrophic hypogonadism, sometimes it is also one of the genes regulating the expression of SRY, thus a mutation may result in maleness in individuals with 46,XX without the SRY mutation.
5. Other candidate genes and possible mechanisms have been proposed in individuals negative for SRY and the above genes. Some familial cases have been reported, and monozygotic twins have been reported with one having ovotesticular DSD and the other 46,XX testicular DSD without any cause, suggesting a similar mechanism.

Management

Correction of genital ambiguity depends on the sex of rearing assigned after taking into consideration the exact diagnosis, the genital appearance, the presence and location of gonads, and the future possibilities.

Another major factor which is to be considered is the high risk of dysgerminoma in gonads with testicular tissue, especially if they are located intra-abdominally.

Management

46,XY DSD

Appropriate Diagnosis

The first step in the proper management of these children is to make an appropriate diagnosis as far as possible. This is often difficult as the specialized tests, especially for the genetic markers, are not available in most places. However, a near accurate diagnosis should be made with the help of available investigations.

Factors Influencing the Decision on the Sex of Rearing

Time of Presentation

There is general agreement that every child with ambiguous genitalia should be assigned as either a male or a female and named appropriately. In the past, it was thought that the decision about sex of rearing had to be made as a matter of great urgency for psychosocial reasons. Decisions were made by doctors without much discussion with parents, or vice versa, and without waiting for the results of all the investigations. While parents may find waiting difficult, it is better to assign the appropriate gender after a complete diagnostic workup and a detailed discussion with the parents. If parents bring the child having already decided the sex for themselves, they greatly limit the options regarding the medical management.

When the Sex Has Already Been Assigned

If a sex has already been assigned by the family before a physician has been consulted, especially if some time has already elapsed, the family will be very defensive about their decision. They will want to avoid the change of sex, having to give a difficult explanation to the rest of the family and friends. Also, they would fear such information to generate a lifelong stigma, isolating the parents and the child. This factor greatly compounds the difficulty of medical management.

Underlying Diagnosis

This may influence the outcome, for example, in someone with severe partial androgen resistance, and the response to endogenous testosterone or even to testosterone supplements at the time of puberty is likely to be relatively poor. On the other hand, patients with 5α-reductase-2 deficiency and 17β–hydroxysteroid dehydrogenase deficiency are likely to show much better virilization and the descent of the testes at the time of puberty.

Appearance of External Genitalia

The severity of undervirilization with a more female type of genitalia also influences the decision of sex of rearing and the final outcome. Gonads may or may not be palpable. Once a decision has been made to rear the child as male, every attempt should be made to bring the testes down into the scrotum. If intra-abdominal testes cannot be brought down, they should be removed because of the risk of cancer.

Expertise Available Regarding Surgical Correction of the Problem

Pediatric urologic surgical expertise is a highly specialized area especially in regard to patients with ambiguous genitalia. The number of available cases is also limited and a wide spectrum of malformations exists. This is a major practical problem, especially in some of the more poorly resourced countries. Lack of specialized surgeons and/or their level of comfort with which they can handle these

cases vary a great deal across the world. This then becomes a limiting factor in provision of care to these children. Even in the resource constrained environment, it is best to identify and develop specific persons in the field so that they can acquire some kind of expertise and comfort level in dealing with these complex cases.

Long-Term Issues Regarding Sexuality

Penile size and urethral orifice: As is clearly acknowledged, there is severe limitation in the way penile reconstruction can be carried out even in the most developed countries when phallic size is small. Even the hypospadias repair in severe cases may require fairly exhaustive, staged surgeries that are not always followed by the ideal results. This may carry very serious psychological issues as the boy approaches puberty.

Erection and sexual intercourse: Boys who have had surgery to correct ambiguous genitalia face very significant problems as they approach puberty. They will need skilled counseling about their capacity to marry and enjoy intimate physical relationships. Long-term outcome studies provide some encouragement. Some boys experience a major psychological impact. Their thinking is sometimes much distorted, and this problem may be much bigger than the actual physical handicap. The consultation between the parents and the physician, endocrinologist, and surgeon should take into account all findings from the initial assessment and evaluation. It is reasonable to provide the family a realistic understanding of what is going to be possible, as far as the evidence can tell us. Only after all of this can a decision about the male sex of rearing be made.

Fertility: It is often not possible in these disorders, but a clear understanding must occur on parts of parents and the child himself once he is at the age where he is able to understand.

Social Issues

In many cultures around the world, the social acceptance of an unmarried male is more than an unmarried woman. Also men in some cultures have greater opportunities to be independent financially and socially than women, regardless of marital status.

Psychological Issues Around DSD

Psychological well-being is an important part of the quality of life. This is also of utmost importance in situations like DSD, where it is not just the physical state that matters, but also the state of mind.

A recent meta-analysis reviewed previously published literature on the psychological impact and well-being of individuals with DSD. There is a great degree of variation in the outcome and the number of people suffering from psychological disorders later in their life. There have been diverse results from different studies, some showing no impact and others reporting that 40–60% were affected.

Cultural Issues and Limitations in Management

Education and Health Economics

In resource-poor developing countries with poor literacy rates, high economic burden, and poor access to health care and resources, high dependence on alternative medicine makes the diagnosis and management of these hugely complex disorders extremely difficult. With the poor health resources, the priority is with other issues like malnutrition, infectious disease, and accidents which accounts for the bulk of mortality and morbidity. Logistic difficulties in access to health care make the situation worse. Doctors and other health workers in these far-flung areas have very little in terms of continuous medical education, making their knowledge far from adequate to deal with these conditions. Reliance on expensive and relatively advance testing like chromosome analysis even for the sake of classification also becomes a constraint in populations where these tests are not available or affordable.

Traditional Values and Beliefs

Strong cultural and traditional beliefs have a strong impact, and they significantly influence the way these disorders may be managed. Patients with disorders such as DSD which are not easy to explain scientifically often fall prey to people with beliefs in myths and misconceptions. This is further compounded by taboos and unwillingness of the communities to discuss and share the information with other even medical professionals and resorting to faith healers and shrines and purveyors of magic.

Male Preference

In developing countries, high infant mortality leads to a great insecurity in the families about the survival of their children which paradoxically increase the family size. This leads to an increase in financial burden on the

already poor families; hence the greater need for males as bread winner is perceived. In countries and cultures with land holding, often boys are destined to inherit more than the girls, and look after the affairs of cultivation, etc. Thus, a son is seen as insurance for the parents, someone to look after their need in old age. Hence, the insistence on male sex of rearing often results in poor management of these disorders. In Pakistan, there are families with CAH taking their babies away when they were told about the female gender of the child, refusing point blank to raise the baby as a female and insisting that something should be done to convert this into a boy.

Summary

To summarize the management of children with 46 XY DSD, an underlying diagnosis, its impact, and factors discussed above should be considered and shared with the family. Only then a decision is made about the proposed sex of rearing for the child. Once that decision has been made, subsequent management will vary according to the sex of rearing. In cases of female, a reconstructive surgery and gonadectomy is required. This would later be followed with female hormone replacement at puberty. In sex assigned males, all effort should be made to preserve and bring the gonads down, with removal of any gonad that cannot be brought down to a location where it can easily be palpated. In addition, a reconstructive surgery (hypospadias repair) is often required. Hormone replacement at the time of puberty would depend on whether or not gonads are able to produce some androgens.

Congenital Adrenal Hyperplasia (CAH)

Certain types of congenital adrenal hyperplasia in females fall under the category of DSD. The virilizing types of CAH (classical 21-hydroxylase deficiency, 11β-hydroxylase deficiency, 3β-hydroxysteroid dehydrogenase deficiency [3β-HSD]) are, together, the most common cause of genital ambiguity. In addition, two forms of CAH (17α-hydroxylase deficiency and 3β-HSD) are capable of causing undervirilization leading to ambiguity in genetic males.

The most common cause of CAH is 21-hydroxylase deficiency, which leads to inadequate glucocorticoid and mineralocorticoid synthesis. The higher ACTH as a feedback to insufficient cortisol production then results in an excess of precursors upstream of the block, some of which are channeled into enhanced androgen synthesis. The high androgen induces masculine changes: lengthening of the urogenital sinus internally, enlargement of the clitoris and fusion between the genital folds, causing ambiguity in a 46XX infant. The virilization at times may be severe enough for the child to be assigned a wrong sex at birth.

Adrenal Steroidogenesis

Steroidogenesis pathway (◉ *Fig. 383.5*).

Clinical Features of CAH

21 Hydroxylase Deficiency

This is by far the most common defect accounting for 90–95% cases of CAH. This is further divided into three different clinical phenotypes. The term "classical" indicates an enzyme deficiency severe enough to cause genital changes at birth in the sex most likely to be affected (female in the case of the virilizing forms, male in the forms causing undervirilization). The salient features of three subtypes are presented in (◉ *Table 383.2*).

1. Classical salt-losing form
2. Classical non-salt-losing form (sometimes referred to as "simple virilizing CAH")
3. Nonclassical form (formerly called "late onset" CAH)

Salt-Losing CAH

About 75% of patients with CAH fall into category, which is the most severe form of CAH. 21-Hydroxylase enzyme activity in these patients is almost zero. The resulting mineralocorticoid deficiency then causes excessive loss of sodium in the urine and retention of potassium, leading to hyponatremic dehydration (serum sodium can fall below 100 mmol/l) and moderate to severe hyperkalemia (levels above 11 mmol/l may be seen), which can cause cardiac arrest. The baby starts to vomit, worsening dehydration, becomes listless and anorexic with persistent vomiting of every feed, blood pressure falls, and blood glucose may become very low (because cortisol is a glucocorticoid). This severe illness, called an *adrenal crisis*, typically presents toward the end of the first week of life but may be delayed for weeks or even months. Females are born with genital ambiguity and *should* be diagnosed promptly because of this and not go into adrenal crisis, but this is not always

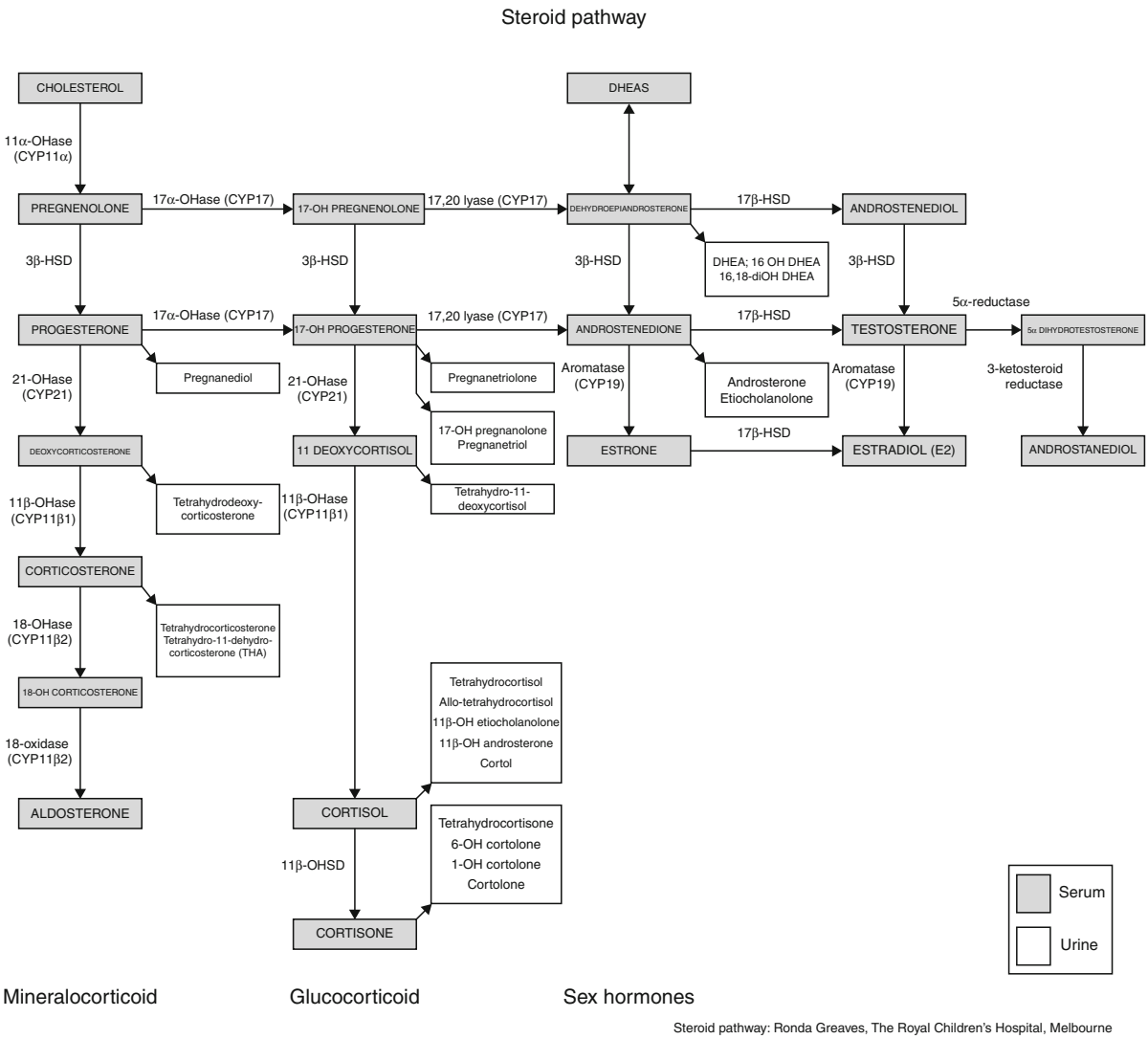

Figure 383.5
Steroidogenic pathway

the case. In males, there is no obvious genital change, and the onset of adrenal crisis, with persistent vomiting, is the first indication that there is something wrong.

Genetic Defect

21-Hydroxylase deficiency has an average gene frequency of 1:50, making CAH a relatively common autosomal recessive disorder. The gene for this disorder lies on chromosome 6 within the HLA locus. Two homologous genes exist. CYP21 is the active form and CYP21P is the inactive pseudogene. Most mutations result from the transfer of sequence between the pseudogene and the active gene, a phenomenon called *gene conversion,* but deletions, point mutations and many other types of mutation have been described.

Non-salt-Losing Form

This is the less severe variety of the disease, in that adrenal crisis is unlikely, because around 1–2% of enzyme activity is retained. Although some degree of salt wasting does occur in

Table 383.2
Characteristics of different types of congenital adrenal hyperplasia in 21-hydroxylase deficiency

	Salt wasting	Simple virilizer	Nonclassical
Frequency	1: 20,000	1:60,000	1:1,000
Enzyme activity	0%	1–2%	10–75%
Common genetic defect	236 Ile → Asp	172 Ile → Asp	281 Val → Leu
	237 Val→ Glu	356 Arg → Trp	30 Pro → Leu
	239 Met → Lys		
	8 bp deletion		
	Aberrant splicing		
Age of presentation	Newborn to 2 months	0–4 years	Child to adult, usually Puberty
Genital ambiguity	Present at birth	From birth to later	None
Somatic growth	Poor, −2 to −3 SDS below mean	Low, −1 to −2 SDS	Normal
Na	↓	N	N
K	↑	N	N
17 OH Progesterone	Markedly elevated	Moderately elevated	Normal basal level, High level in response to ACTH stimulation
Renin	↑	Normal or ↑	N

these children (as indicated by high levels of plasma rennin activity), it does not reach symptomatic levels, except perhaps in the neonatal period when renal tubular reabsorption of sodium is relatively inefficient in all infants. There will be, however, a variable degree of genital ambiguity in a 46 XX patient. If this passes unnoticed, the girl may experience progressive virilization over months or even years; the clitoris can become extremely large, linear growth and bone age advancement may be accelerated, gender behavior will be masculine, and if the condition goes on untreated for long enough, gender identity may be affected, making a girl think she is a boy. This happens commonly in resource-poor countries, and it leads to major problems for affected individuals.

Nonclassical Variety

Although not strictly falling under the purview of DSD, this variety is mentioned here for the sake of completeness of different forms. Cortisol deficiency and hence the ambiguity of genitalia is not found. However, the androgen excess manifests itself either later in childhood, in puberty or in adult life. The female patient may present with severe acne, hirsutism, male type of baldness, oligo/amenorrhea, and/or infertility.

Medical Management of 21-Hydroxylase Deficiency CAH

Glucocorticoid Replacement

The primary steroid that should be used during childhood is hydrocortisone, preferably in three divided doses, as other forms may have an adverse impact on growth. Later, when the bone age matures either prednisolone or dexamethasone may be used as replacement drug.

Dosage has been a matter of concern and controversy over the years, as it is difficult to find the right dose that will suppress the corticotrophin axis and thereby prevent the androgen excess, without incurring adverse effects of over-treatment. The currently favored dose is 12–15 mg/m^2 in two or three divided doses. The higher dose is given in the morning to mimic the circadian rhythm of steroid secretion.

Mineralocorticoid Replacement

It was previously thought that mineralocorticoid replacement was only needed by patients with salt wasting CAH, but it is now clear that it should be used even in the non-salt wasting form as it allows lower doses of

glucocorticoids to be used and this is beneficial for linear growth. Fludrocortisone is administered in a dose of 150 μg/m^2/day once daily and monitored using a plasma renin activity assay. Where a PRA assay is not available, a dose of 100–200 μg can be used, irrespective of body weight and regular arterial blood pressure monitoring would reduce the risk of overdosage. Infants are relatively resistant to the renal effects of fludrocortisone. As the child grows older, the dose actually goes down.

Children affected with salt wasting CAH should be given sodium chloride 2 mmol/kg/day along with their milk. As they grow older, they themselves develop a craving and liking for the salty food.

Stress dosing is needed to prevent adrenal crisis. As the glucocorticoids are used as replacement, this should mimic the natural responses of their hormones in the moments of stress. The usual advice is to double the dose of hydrocortisone for a short time (2–3 days) during intercurrent illnesses, especially those associated with fever or severe pain. In the surgical situation, intravenous steroids are usually required (◉ *Table 383.3*).

Table 383.3
Corticosteroid doses required during surgery in children with congenital adrenal hyperplasia

Minor surgery			
	3–10 kg	10–20 kg	>20 kg
Hydrocortisone			
Either before "nil by mouth"	25 mg PO	50 mg PO	100 mg PO
OR at induction of anesthesia	25 mg IV	50 mg IV	100 mg IV
Postoperative	Same dose six hourly until oral fluids		
Major Surgery			
	3–10 kg	10–20 kg	>20 kg
At Induction	25 mg IV	50 mg IV	100 mg IV
During surgery	1 mg/h IV infusion	2 mg/h IV infusion	3 mg/h IV infusion
After surgery	Continue IV same dose until tolerating oral fluids	Then oral dose doubled for 24 h	Then normal oral dose
Fludrocortisone	Restart as soon as tolerating oral fluids		
Intravenous fluids			
	<10 kg	10–30 kg	>30 kg
Amount of fluids	100 ml/kg	80 ml/kg	60 ml/kg
Type of fluids	5% Dextrose 0.45% Saline		

Surgical Management

Bilateral Adrenalectomy

A number of papers have discussed the option of removing both adrenal glands in patients, particularly females, who's CAH proves especially difficult to manage. The argument in favor is that abolition of adrenal androgen production eliminates androgen-related problems. Since it is no longer necessary to use suppressive doses of glucocorticoids, replacement doses can be lowered. The contrary arguments are that there is a risk of mortality and morbidity associated with surgery and anesthesia and that the irreversibility of adrenalectomy eliminates the option of further medical intervention. The authors believe that bilateral adrenalectomy does have a place, but it should be reserved for the difficult cases when all other avenues have been tried.

Genital Reconstruction

Until the mid-1960s, the treatment for an enlarged clitoris was total removal. Thankfully, this practice has now been abandoned in most places. Clitoral reduction, which can be done using a variety of different surgical techniques, is now preferred. Patient advocacy groups have seriously challenged the need for clitoral reduction, arguing that an enlarged clitoris can function perfectly well as a sexual organ when it is intact, but may not retain full sensitivity following surgery. Parents generally want to have the surgery done because they would prefer not to be reminded of the ambiguity. Patients who have not had surgery do experience discrimination; they would need emotional support during childhood and adolescence if they were asked to grow up with their original anatomy, and their families might also need support. Vaginoplasty is necessary at some stage to correct fusion of the genital folds in female patients. Those who have a uterus will menstruate and the blood needs to be able to escape. Without vaginoplasty, sexual intercourse will be impossible. The timing of the procedure varies from place to place depending upon the expertise available and the comfort level of the surgeon to carry out the procedure. However, it generally ranges from 2–4 months to 2 years on an average. Sometimes the introitus requires dilatation or minor surgery during adolescence.

Sex Chromosome Aneuploidy DSD

Klinefelter Syndrome

Although genital ambiguity is not usually a feature of Klinefelter syndrome (47,XXY or mosaic), it does occasionally occur and can be associated with gender dysphoria.

Turner Syndrome and Its Variants

Turner syndrome (monosomy X) affects one girl in every 2,500 births. Although classically the karyotype is 45,X, many patients have mosaic karyotypes such as 45,X/46,XX. The clinical features of Turner syndrome vary considerably. Some girls are severely affected, with webbing of the neck (a feature remaining after a cystic hygroma has resolved), coarctation of the aorta, gonadal dysgenesis, linear growth retardation, renal anomalies, and many other possibilities. Others, however, have a normal appearance but have growth impairment and gonadal dysgenesis. A full description of Turner syndrome and its management is beyond the scope of this chapter.

Some girls with the Turner syndrome phenotype have ambiguous genitalia, and most are found to have either 45,X/46,XY mosaicism or 45,X (+mar), meaning that a chromosomal fragment, called a marker, is present in all cells. Markers are often derived from the Y chromosome, and their presence may indicate that the girl has an increased gonadoblastoma or dysgerminoma. For this reason, when a marker is identified, it is necessary to investigate further and determine the chromosome of origin of the marker, using both X and Y probes. If Y-chromosome material is found, the streak gonads must be removed.

45,X/46,XY Partial Gonadal Dysgenesis

Of all fetuses conceived who have this karyotype, only 5% are born with ambiguous genitalia. The other 95% have a normal male phenotype, although 27% of these will have abnormal gonadal histology. The term "mixed gonadal dysgenesis" was used to refer to a patient with a streak gonad on one side and a better differentiated, but still dysgenetic, testis on the other. The term "partial gonadal dysgenesis" is now the preferred term. The condition carries a high risk of gonadal malignancy, and to manage the risk, all intra-abdominal streaks must be removed at diagnosis, as must any intra-abdominal testis that cannot be brought down. If the patient is raised female, both testes would be removed. If the patient is raised male and a scrotal testis is retained, lifelong surveillance for the development of cancer is mandatory. A biopsy after the onset of puberty is advised. The biopsy material should be sent for immunohistochemical staining with OCT 3/4 and Placental/germ alkaline phosphatase (AP) as these are markers of carcinoma in situ when positive during adolescence.

Approach to a Child with DSD

History

- Family history of ambiguous genitalia, any DSD in the family
- History of unexplained early deaths in siblings or still births
- Maternal history of drugs (especially anabolic steroids, etc.), alternative medicine like hakim, ayurvedic medicine (often contain steroids)
- Maternal illnesses like tumors, etc.
- Pregnancy: any history of virilization during pregnancy

Examination

- Any dysmorphic features, especially cleft lip, palate, limb deformity
- Complete systemic examination to look for any other system involvement especially congenital heart disease etc.

Genitailia

- Excessive pigmentation
- Phallic size: measure the stretched length from pubic tubercle to the tip of penis, age appropriate centile charts are available with standard deviation to plot the penile size
- One should also observe the presence or absence of chordae
- Urethral opening and location, any other perineal opening
- Scrotal development
- Presence and location of gonads, feeling of gonads, presence of epididymis
- Assess the degree of virilization: This is graded by either Prader stage or external masculinization score

Investigations

The first investigation is to perform the chromosomal analysis in order to classify and categorize these children

properly. However, cytogenetic testing may not be readily available in some parts of the world. Also, even if done during the first day, it can take weeks before the results come back. Thus the possibility of a salt-losing variety of DSD must immediately be covered.

1. Chromosomal analysis
2. Pelvic ultrasound: for uterus, gonads, and internal genitalia
3. Serum electrolytes to look for the possibility of hyponatremia and hyperkalemia

Further investigation may differ depending on the chromosomal type.

46 XY DSD

1. Basal or stimulated testosterone level
2. FSH/LH
3. Urine steroid profile
4. Genitogram
5. Genetic testing when required
6. Androgen receptor assay in cultured fibroblast
7. Gonadal biopsy (if required)

46 XX DSD

1. Serum 17 OH Progesterone
2. Serum 17 OH Pregnenolone
3. Serum 11 Deoxycortisol
4. Plasma renin activity
5. Serum aldosterone
6. Serum ACTH
7. Serum testosterone/androstenedione
8. Urine steroid profile
9. Genetic analysis
10. Gonadal biopsy (if required)
11. Androgen receptor mutation analysis
12. Genetic screening for gene responsible for gonadal differentiation if the above investigations fail to clinch an appropriate diagnosis

A Vignette from Pakistan

An 8 year old walked into my clinic, hailing from a remote area, after having travelled nearly a thousand miles for the consultation. She covered herself with a head scarf which covered part of her face as well, and kept sitting in clinic with her head down, avoiding to look towards me and barely speaking. She was delivered at home, no virilization was appreciated at that time, mother noticed that she started developing pubic hairs enough for her to remove by the time she was 2. A surgeon was consulted for her associated clitromegaly and down came the knife. She had her clitoral resection and then left without any treatment. When she saw me at 8, she had a clear moustache and a beard with a deep masculine voice. She was later found out to have a 46XX DSD, CAH of non salt wasting type.

This to me was the classic example of things going wrong around the management of DSD in a developing country in this day and age. Wrongly diagnosed, wrongly managed both surgically as well as medically and lack of further monitoring or follow ups, she ended in disaster, for a relatively easy to manage disorder.

Issues Regarding DSD Management in the Developing Countries

1. Medical awareness about the condition may be poor even among the health workers. The subject is not covered enough in the medical curriculum, or in the lower diploma of pediatrics, and therefore the physicians are not clear in their understanding about the subject or confident in the ways they handle them.
2. Poor accessibility to health care. In remote areas, traveling and cost both greatly limit accessibility.
3. Lack of referral system: retards the process of referral to a specialized center.
4. Poverty: limits the referral, and following medical advice.
5. Poor literacy.
6. Social taboos: already mentioned add to the misery.
7. Lack of investigation facilities: endocrine investigations being very sensitive and generally expensive are not available for a large portion of population.
8. Lack of availability of medicines: Hydrocortisone and fludrocortisone, despite being life-saving medications, are not registered in many countries. Pharmaceutical mergers and sell outs, general recession, and the products not being hugely profitable have added to the difficulty in availability, and this worsens the misery of patients.
9. Lack of expertise: Pediatric endocrinologists and trained surgeons skilled to do the job and an understanding of the subject is a rare commodity among the developing countries.

Future Directions

Dramatic changes are expected to come in the area of genetic diagnosis. As gene chip (microarray) technology develops, it will be possible to rapidly and accurately screen a patient's entire genome for mutations. Such

screening will not only simultaneously examine all of the genes currently known to cause DSD, but will also detect mutation "hot spots" in other genes which, until now, have not been implicated in DSD. In countries able to afford such technology, most patients will receive an accurate diagnosis. Will it be possible to predict gender identity any more accurately than it is done now? At present, there is very limited understanding of the factors that determine gender identity in any individual, whether affected by a DSD or not. It is possible, however, that there are centers in the brain which are permanently altered, structurally, functionally, or both, when exposed to critical levels of androgen at critical times and that these changes control gender identity. It may become possible, using a combination of functional brain imaging and genetic (or epigenetic) screening, to identify where such changes take place and what the nature of them is. This would make it possible to design hormonal and surgical treatment programs that would avoid the disastrous complication of gender identity disorder.

The broader society is starting to take an interest in the ethics and human rights aspects of medical management of DSD and this is a good thing. Medical management of DSD has been influenced far too much by the imagined need to make life-altering decisions of extraordinary importance on behalf of infants with DSD because of the "social emergency." The sense of emergency would evaporate if the broader community was well educated about DSD and more accepting of it as a variation, albeit one with serious medical implications. Parents would then be able to take more time in deciding about the sex of their baby and in weighing up the options regarding treatment. The influence of culture and belief on attitudes and decision making is a subject worthy of much more detailed analysis. Many long-term outcome studies have already been done, but they have often been very superficial and have failed to examine the issues most important to the sufferers themselves. Future studies will take into account the more exact genetic diagnosis, the broader perspectives of the community in which the patients have grown up, and outcomes in control groups. Broader and deeper comparisons of outcomes between societies with very different attitudes toward gender and sexuality will be extremely helpful.

Many resource-poor countries are currently unable to meet even the most basic needs of their citizens who have chronic medical conditions, and mortality rates are high. Survivors with DSD suffer terribly. A huge effort on the part of governments, pharmaceutical companies, and aid organizations is needed to ensure *access for all* to essential medications, such as hydrocortisone and fludrocortisone for children with CAH. Laboratory scientists can help by developing cheaper and more robust assays for steroids such as DHT, 17-hydroxyprogesterone, and androstenedione, suitable for widespread use in developing countries. Mental health service planners should continue to advocate improved access to mental health services in the world's poorest countries.

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384 Disorders of the Adrenal Gland

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Adrenal Disorders

Disorders of the adrenal glands specifically the adrenal cortex are being recognized with increasing frequency in pediatric age group. The anatomical presence of the gland was detected in mid sixteenth century but the importance of its function was not realized upto mid-nineteenth century, till Addison's description of adrenal insufficiency. The terms *glucocorticoids* and *mineralocorticoids* were proposed by Selye in 1930s. Reichstein and Kendall shared the Nobel prize in Medicine in 1950 for detailing the structure and isolating various adrenal steroids which helped chemical synthesis of these hormones, led to better understanding of the relationship of adrenal steroids to their precursor products and their physiologic role. Based on this, both Wilkins et al. and Bartter et al. tried to treat CAH with cortisone for the first time in 1950. In past 5 decades very significant advances have been made in isolating some of the steroidogenic enzymes, understanding the pathways of steroid hormone biosynthesis, identification of the genes encoding these steroidogenic enzymes and characterizing the enzymatic errors responsible for the various inherited adrenal and gonadal disorders. Synthesis of many new potent analogs of the naturally occurring steroid hormones have augmented clinical research, and promoted their physiologic and pharmacologic uses in a variety of adrenal as well as nonadrenal systemic disorders.

Adrenal Embryology

The steroidogenic cells of the adrenal cortex and gonads have a common origin in the gonadal ridge appearing by 5–6 weeks followed by migration of adrenal cells retroperitoneally and caudal migration of the gonadal cells. The encapsulated adrenal gland with adrenal cortex of mesodermal origin and adrenal medulla consisting of chromaffin cells derived from neuroectoderm is clearly visible by 8th week of gestation close to the upper poles of the relatively small kidneys. By 9–10 weeks the cells of the fetal zone are capable of steroidogenesis.

The fetal adrenal glands at birth weigh nearly 8–9 g approximately twice the size of the adult adrenals, and function actively during fetal life with cortisol biosynthesis occurring by first trimester. The fetal adrenal cortex has two principal zones, an outer "definitive" zone responsible for the production of both mineralocorticoids and glucocorticoids and a much larger "fetal zone" generating androgenic precursors for the placental synthesis of estriol. After birth the large fetal zone involutes and disappears by 1 year of age. Full differentiation of the two outer zones is attained by 3 years of age. The zona reticularis is not fully developed until puberty.

Presence of specific nuclear transcription factors is essential for the development and steroidogenic function of adrenal glands. One such factor is DAX-1 (dose sensitive sex reversal-adrenal hypoplasia congenital X chromosome related) where loss of function mutation causes primary adrenal deficiency manifesting soon after birth and later failure of pubertal development. Mutations of DAX1 gene encoded on Xp21, cause congenital adrenal hypoplasia and hypogonadotropic hypogonadism. Mutation in transcription factor SF-1 (steroidogenic Transcription Factor −1) encoded on chromosome 9q33 causes complete adrenal aplasia with gonadal agenesis. Besides these two adrenal specific transcription factors, and genes, IGF1 and II, other factors like fibroblast and epidermal growth factors - activin and inhibin, influence adrenal development, Underdeveloped ventral medial hypothalamus also influence adrenal development.

Adrenal Histology and Physiology

The three histologically identified zones of the adrenal cortex are the zona glomerulosa next to the capsule synthesizing aldosterone, the fasciculata synthesizing glucocorticoids in the middle and the inner most, zona reticularis synthesizing adrenal androgens. The adrenal medulla is involved with synthesis of catecholamines. The three cortical zones constitute 15%, 75% and 10% of the adrenal cortex of the older child and adults. The histologic characteristics of the three zones of the adrenal cortex also differ, as regards cellular size and their arrangement, the cytoplasmic : nuclear ratio and intracellular lipid inclusions. The zona fasciculata is characterized

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by larger cell size, higher C:N ratio, higher lipid content in comparison with the other two zones. The cells are arranged in radial cords. In the inner most zona reticularis, cells are arranged in irregular anastomosing cords. Despite histologic demarcation of the three zones there is some degree of functional as well as histological overlap as shown by immunocytochemical data overlap. The zonal borders are somewhat arbitrary.

Zona glomerutosa is characteristically defined by the expression of aldosterone synthase (P450c 11As) and the absence of 17α-hydroxylase and 17,20-lyase expression (P450c17). The glomerulosa cells specific enzyme is P450c11As and has abundant angiotensin II and ACTH receptors, the later playing a permissive role for mineralocorticoid synthesis. P450c17 deficiency is associated with modest degree of glucocorticoid deficiency as corticosterone produced in excess has some degree (nearly half as potent) of glucocorticoid action. This excess of corticosterone converted to deoxycorticosterone (DOC) leads to mineralocorticoid hypertension, and salt retention along with low aldosterone levels. The zona fasciculata is the principal site associated with cortisol production and is characterized by the presence of P450c11B and P450c17 but absence of P450c11As, and relative lack of angiotensin II receptors. P450c21 deficiency is the most common defect of the zona fasciculata. The gene for P450c21 is expressed in all three zones of the adrenal cortex and can explain why its mutations can destroy all 21-hydroxylase activity leading to absence of mineralocorticoid and glucocorticoid biosynthesis. Absence or low levels of cortisol stimulate excess ACTH secretion diverting pregnenolone to the adrenal androgen pathway with androgen overproduction leading to prenatal virilization of female fetuses. Missense mutations that spare some amount of 21-hydroxylase activity manifests as non-salt wasting "simple virilizing" condition. Low levels of enzymatic activity in these patients with minimal cortisol production helps in producing near normal amounts of aldosterone.

Adrenocortical Steroidogenesis

The main pathways of adrenal steroidogenesis includes only few steroids though many have been isolated from adrenocortical tissue. The pathways of steroid biosynthesis is shown in ❯ *Fig. 384.1*.

Cholesterol uptake, storage, transport: Initial steps in adrenal steroidogenesis consist of cholesterol uptake, storage and transport of cholesterol which is the precursor and the initial substrate for all adrenocortical steroid hormones. Nearly 80% of its supply is provided by plasma low-density lipoproteins (LDLs) derived from dietary cholesterol though denovo synthesis by adrenals from acetate is possible. The cortical cells take up LDL cholesterol esters by specific cell surface receptors by endocytosis to be stored or converted to free cholesterol. The transfer (importation) of cholesterol across the mitochondrial outer and inner membrane is the initial rate limiting step in adrenal steroidogenesis. Storage of cholesterol in lipid droplets is controlled by cholesterol esterase and synthetase. ACTH stimulates esterase and inhibits synthetase.

StAR protein is synthesized by steroidogenic cells in response to trophic hormone stimulation. Steroidogenic acute regulatory protein or StAR plays an important role as a factor necessary for the rapid flux of cholesterol (from outer to inner mitochondrial membrane). It promotes acute synthesis of aldosterone following angiotensin II stimulation, of cortisol after ACTH stimulation, and of gonadal sex steroids after LH stimulation. Mutation of StAR is noted in lipoid CAH. It has a very short half life and is the main short term regulator of steroid hormone biosynthesis. Although StAR plays central role in the synthesis of steroid hormones, some steroidogenesis can occur independently.

Steroidogenic Enzymes

The generic term *cytochrome P450* (so named for pigment 450) is used for a large family members of steroidogenic oxidative enzymes consisting of about 500 aminoacids with a molecular mass of about 50 kDa with a central hememoiety. Majority of these enzymes metabolizing numerous exogenous and endogenous toxins, drugs, environmental pollutants, xenobiotics are in the endoplasmic reticulum of the liver. There are five distinctive P450 enzymes located in adrenal mitochondria, which are necessary for adrenal steroidogenesis. These are shown in ❯ *Fig. 384.1*. Two isoenzymes (P450c11B and P450c11As) of P450c11, catalyze 11β-hydroxylase, 18-hydroxylase and 18-methyloxidase activities. 17α-hydroxylase and 17,20-lyase activities are catalyzed by P450c17 located in the endoplasmic reticulum and P450c21 catalyzes the 21-hydroxylation of both mineralocorticoids and glucocorticoids. The association of cytochrome P450 with 21-hydroxylation was first demonstrated in 1965. P450aro in the endoplasmic reticulum in the gonads and few other tissues, catalyzes aromatization of androgens to estrogens.

P450scc: The *cholesterol side-chain cleavage enzyme* P450scc formerly known as 20,22-desmolase, with a molecular mass of 50 kDa, is encoded by a single gene on chromosome 15. All steroid hormone biosynthesis is

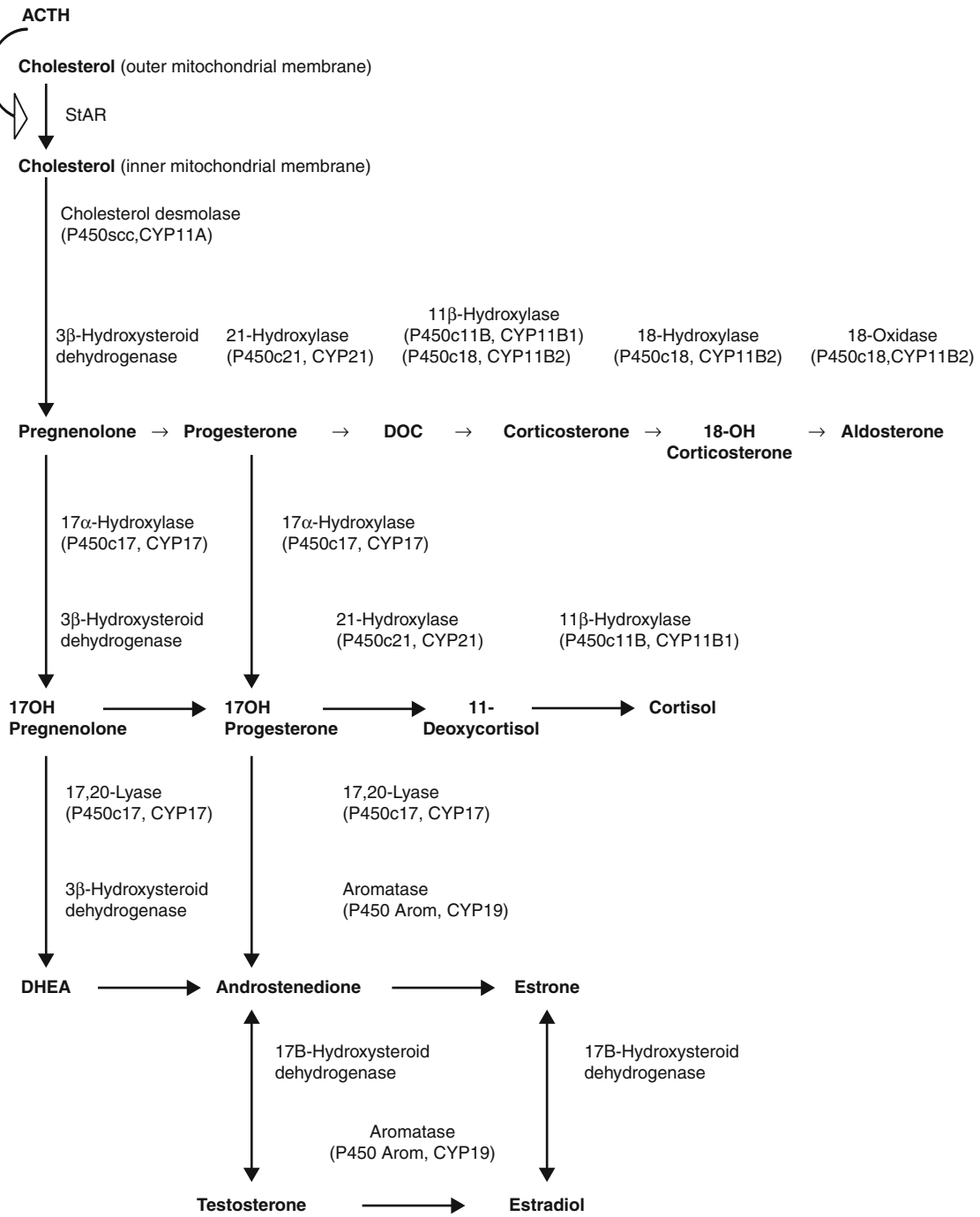

Figure 384.1

Pathways of steroid hormone biosynthesis for adrenal synthesis of mineralocorticoids (aldosterone), glucocorticoids (cortisol), and androgens (DHEA, androstenedione) arranged vertically with corresponding enzymatic activity for bioconversion as indicated. Names for the activities mediated by specific cytochromes P450 are indicated in parentheses. Dashed arrows indicate reactions which are extraadrenal primarily in gonads. P450c18mediates 11B-hydroxylase activity in the zona fasciculat to convert 11-deoxycorticosterone (DOC) to corticosterone and 11-deoxycortisol to cortisol. P450c18 mediates 11B-hydroxylase, 18-hydroxylase, and 18-oxidase activities in the zona glomerulosa for the conversion of DOC to aldosterone

initiated through the action of this one enzyme. Mitochondrial conversion of cholesterol to pregnenolone is the first rate – limiting and hormonally regulated step in the synthesis of all steroid hormones. It mediates 20α and 22α hydroxylation and scission of cholesterol side chain to yield pregnenolone at the mitochondrial inner membrane (Fig. 384.1). Pregnenolone then diffuses out of mitochondria into the endoplasmic reticulum for further processing into adrenal zone dependent adrenocortical hormones. Experimental evidence shows that deletion of the gene for P450scc, the initial step in steroidogenesis (Fig. 384.1) is incompatible with life. Rapid or acute release of cortisol into the circulation is controlled by cholesterol access to the rate limiting P450scc enzyme while as long term regulation of steroidogenesis by ACTH occurs at the level of gene transcription. Two accessory proteins, adrenodoxin reductase and adrenodoxin help in three successive oxidative reactions to cleave the C20, 22 carbon bond.

Hydroxysteroid dehydrogenases: This group of enzymes, play a critical role in both, the adrenals and the gonads. The different isoenzymes, include the 3α and 3β-hydroxysteroid dehydrogenases the two 11β-hydroxysteroid dehydrogenases, and a series of 17β-hydroxysteroid dehydrogenases.

3β-Hydroxysteroid dehydrogenase/Δ5 – Δ4 Isomerase: There are two isoenzymes of 3β HSD, encoded by separate genes. Type II enzyme catalyzing 3βHSD activity in the adrenals and gonads and Type 1 in placenta, breast and extraglandular tissues. Pregnenolone produced from cholesterol may undergo 17α-hydroxylation by P450c17 to yield 17-hydroxypregnenolone or can be converted to progesterone by 3β-hydroxysteroid dehydrogenase considered the first biologically important steroid in the pathway. A single enzyme 3-βHSD converts Δ5 to Δ4 steroids (Fig. 384.1): pregnenolone to progesterone, 17α-hydroxypregnenolone to 17α-hydroxyprogesterone (17-OHP), dehydroepiandrosterone (DHEA) to androstenedione (AD) and androstenediol to testosterone.

P450c17: This is a single enzyme with activity of two enzymes, causing 17α-hydroxylation of pregnenolone to 17-OH pregnenolone and of progesterone to 17-OHP progesterone (Fig. 384.1). The 17,20lyase activity of P450c17 converts 17-OH pregnenolone to DHEA but very little 17-OHP is converted to androstenedione (AD). The absence of this enzyme P450c17 prevents synthesis of both adrenal and gonadal steroids. The single gene for P450c17 has been cloned which localizes to chromosome 10q24.3. This deficiency is rare. To date 26 mutations have been identified.

P450c21: P-450c21 activity is localized to adrenal glands however 21 hydroxylase activity is described in extraglandular tissues in the fetus and adults. Hence, in patients with absent adrenal 21-hydroxylase appreciable concentration of 21-hydroxylated steroids may be detected in the plasma. The 21-hydroxylation of progesterone to Deoxycorticosterone (DOC) and of 17-OHP to 11-deoxycortisol is catalyzed by the enzyme (P450c21) 21α hydroxylase (Fig. 384.1). This 21-hydroxylating step is of great clinical interest as more than 90% of all cases with congenital adrenal hyperplasia (CAH) have this abnormality. This inherited genetic disease is associated with salt wasting with high mortality in early infancy if unrecognized especially in male infants. Complex problems of management are related to deficiency of glucocorticoids and mineralocorticoids (aldosterone) and diversion of precursors with formation of excess of androgenic compounds leading to virilization. There are two separate 21-hydroxylating enzymes differentially expressed in the adrenal cortical zones synthesizing aldosterone or cortisol. P450c21 characterization suggests that there is only one 21-hydroxylase encoded by a single functional gene on chromosome 6p21. This gene lies in the middle of the major HLA locus and is closely linked to specific human leucocyte antigen types.

P450c11β and P450c11AS: These two closely related enzymes encoded by tandemly duplicated genes on chromosome 8q21-22, are important for catalyzing the final steps in the synthesis of glucocorticoids and mineralocorticoids. The more abundant and classic 11β hydroxylase (P450c11β) converts 11-deoxycortisol to cortisol and 11-deoxycorticosterone to corticosterone. P450c11β involved in synthesis of cortisol is encoded by a gene CYP11β1 primarily induced by ACTH. Thus patients with disorders in P450c11β have classic 11β-hydroxylase deficiency but can still produce aldosterone, whereas patients with disorders in P450c11AS have the ability to produce cortisol but have a rare form of aldosterone deficiency (corticosterone methyloxidase deficiency). P450c11AS is found only in the zona glomerulosa where it has 11β-hydroxylase, 18-hydroxylase and 18-methyloxidase (aldosterone synthase) activities finally needed to convert DOC to aldosterone.

17B-hydroxysteroid dehydrogenase: There are several 17-βHSDs with some of these with very little 17βHSD activity. The actions of enzymes 17βHSD-III and I occur principally in the testes and ovaries while 17βHSD-II is confined to placenta, liver, and other tissues. Type I is also known as estrogenic 17βHSD and expressed in ovarian granulosa cells, where it produces estriol. 17βHSD-III is the androgenic form expressed only in testes, and associated with male pseudohermaphroditism often termed as 17-ketosteroid reductase deficiency. 17βHSD-III converts dehydroepiandrosterone (DHEA) to androstenediol, and

androstenedione (AD) to testosterone, whereas 17βHSD-I converts estrone to estradiol.

Aromatase: P450aro; A microsomal aromatase produces estrogens by aromatization of androgens. It is also expressed in extraglandular tissues especially adipose tissue which converts adrenal androgens to estrogens. At the epiphyses of the growing bones it can convert testosterone to estradiol thus accelerating epiphyseal maturation.

Steroid sulfatransferase and sulfatase play a role in hydrolyzing steroid sulfatase. In the fetal adrenal and placenta, diminished or absent sulfatase deficiency reduces the pool of free DHEA available for placental conversion to estrogen, with resulting low concentration of estriol, in maternal blood and urine. It also converts peripheral DHEA sulfate (DHEAS) to active DHEA.

11β-Hydroxysteroid Dehydrogenase converts cortisol to cortisone which is metabollicaly inactive. The interconversion of cortisol and cortisone is mediated by two isoenzymes of 11β-hydroxysteroid dehydrogenase (11βHSD), each one with oxidase and reductase activity.

The Type I (11βHSD-I) enzyme is expressed on glucocorticoids responsive tissues such as liver, testis, lung and proximal convulted tubule. 11βHSD-II catalyzes oxidation of cortisol to cortisone and prevents cortisol from overwhelming renal mineralocorticoid receptors, placenta and fetal tissues, hence it plays an important role in fetal life.

Fetal Adrenal Steroidogenesis

The Fetoplacental Unit

Fetal adrenocortical steroidogenesis begins around 6 weeks of gestation and differs from that in the postnatal gland. Major cholesterol source for steroid synthesis in the fetal adrenal gland is provided by fetal liver. The relatively low 3βHSD-II activity and high 17,20-lyase activity in the large fetal zone of the adrenal, accounts for the huge amount of DHEA and DHEAS production for conversion to estrogens by the placenta. The high sulfotransferase activity also favors conversion of DHEA to DHEAS. The DHEAS undergoes 16α-hydroxylation to 16α-OH DHEAS in the fetal liver. The placenta with its high steroid sulfatase activity uses DHEA and DHEAS as substrates for estrone and estradiol, and 16α-OH DHEAS as a substrate for estriol. Thus placental estrone and estradiol are derived equally from fetal and maternal precursors; estriol is exclusively of fetal origin. The significant amount of cortisol produced by fetal adrenals is converted to cortisone by the enzyme 11-β hydroxysteroid dehydrogenase. Towards term, adrenal cortisol secretion increases and the conversion to cortisone decreases. Aldosterone production is low in midgestation but increases near term.

Fetuses with genetic disorders of adrenal steroidogenesis can produce sufficient adrenal androgens so as to cause virilization in a female fetus. The process of masculinization of the genitalia being completed by 12th week of gestation. Prenatal treatment with oral dexamethasone given to the mother at 6–10 weeks of gestation can significantly reduce fetal androgen production and thus minimize virilization of female fetuses.

Regulation of Steroidogenesis

The Hypothalamic-Pituitary-Adrenal Axis

Cortisol Secretion

Cortisol the major secretory product of the adrenal cortex is regulated by the interaction of the hypothalamus, pituitary, adrenal glands and other neural stimuli. Hypothalamic corticotrophin-releasing factor (CRF) a 41-aminoacid peptide, synthesized by neurons of the paraventricular nucleus is the most important stimulator of anterior pituitary ACTH secretion. The same hypothalamic neurons also produce the decapeptide arginine vasopressin (AVP) also known as ADH. AVP augments CRH action. Both are secreted in the hypophyseal portal circulation in a pulsatile manner leading to pulsatile release (ultradian rhythm) of ACTH in varying amplitude through 24 h with pulses of ACTH and cortisol occurring every 30–120 min. The normal diurnal rhythm of ACTH and cortisol begins to be established by 1 year of age and often is well established by 3 years of age with ACTH peaking around the time of waking (4–6 AM) and cortisol by 8 AM. The levels are low in late afternoon and evening being lowest 1–2 h after sleep at night. The intrinsic rhythmicity of synthesis and secretion of CRF by the hypothalamus probably constitutes the basis of this diurnal rhythm as the hypothalamic content of CRF is lowest at 4 AM but this may be influenced by other factors like light/dark and feeding cycles Physical stress of severe infection, trauma, major surgery can increase the secretion of ACTH and cortisol.

Pituitary ACTH a 39-aminoacid peptide, is derived from a larger molecule, a 241-aminoacid protein known as pro-opiomelanocortin (POMC) (*Fig. 384.2*). Ectopic ACTH, in ACTH producing tumors in adults is derived from POMC precursor secreted from extrapituitary sites. This precursor peptide is also the source of (β-LPH), β lipoprotein, ACTH. β-LPH on cleavage can yield several

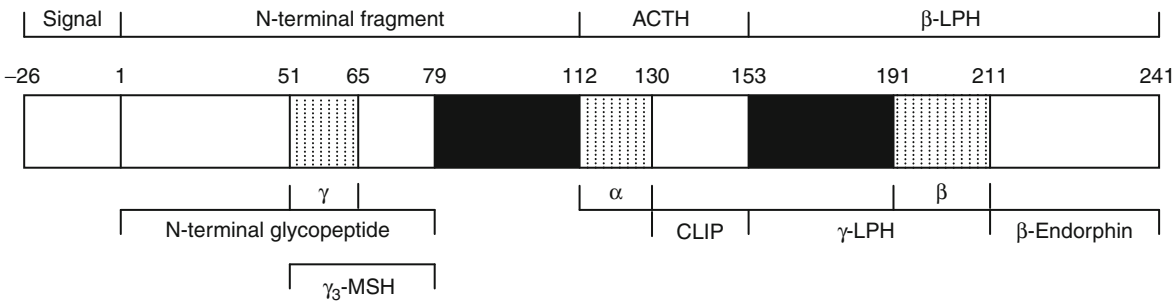

Figure 384.2

Structure of human pre-pro-opiomelanocortin (POMC). The "constant" regions α, β and γ MSH are indicated by dotted areas; the "variable" regions are represented by solid areas. The aminoacid numbers refer to the N-terminal aminoacid of each cleavage site. CLIP, Corticotrophin like intermediate lobe peptide (The numbers do not correspond exactly as in the text)

biologically active peptides, α and β melanocyte stimulating hormone, corticotrophin-like intermediate lobe peptide, (CLIP), γLPH, β and γ endorophin, and enkephalin. Cortisol has a negative feedback effect on the synthesis and secretion of ACTH, CRH and AVP. ACTH inhibits its own secretion by a feedback effect on the hypothalamus. Cortisol and other glucocorticoids cause feedback inhibition of both CRF and ACTH, and probably influence adrenal faciculata cells also. The secretion of ACTH is the result of interaction of the hypothalamus, pituitary and adrenal glands and is also affected by other neural stimuli.

ACTH acting through a G protein-coupled receptor, activates adenylate cyclase and increases levels of cyclic AMP which has short term effect varying from minutes to hours, on cholesterol transport into mitochondria by increasing expression of StAR protein. This constitutes "acute" effect or acute response of steroidogenesis to ACTH. The adrenals contain only modest amounts of steroid hormones; hence release of preformed cortisol does not contribute significantly to the acute response to ACTH. For acute responses to occur, large supply of cholesterol to mitochondrial P450scc is required. The long term or "chronic" effects of ACTH are to increase the uptake of LDL-cholesterol is expressed by stimulating the transcription of the genes encoding the enzymes for cortisol synthesis. The stimulating effect is at each step in the pathway not only at the rate-limiting step, P450scc. Part of this increased activity is achieved through the activity of protein kinase A.

Aldosterone Secretion

The rennin-antiotensin system and potassium levels are major regulators of aldosterone synthesis with ACTH having a short term effect. The rate of aldosterone synthesis is 100–1,000-fold less than that of cortisol synthesis. Renin the proteolytic enzyme secreted by the juxtaglomerular apparatus of the kidney in response to decreased intravascular volume cleaves angiotensinogen (renin substrate) produced by the liver to yield the inactive decapeptide angiotensin I. The converting enzyme in lungs and other tissues rapidly cleaves angiotensin I to its active form angiotensin II with further cleavage of II to angiotensin III. The Angiotensin II and III are potent stimulators of aldosterone the former being more potent, causing arteriolar vasoconstriction by direct action within a few seconds and aldosterone secretion within a few minutes. Increased plasma potassium also has a powerful and direct action on aldosterone synthesis and release. Aldosterone has the most powerful mineralocorticoid activity, causing renal sodium retention and potassium loss, resulting in increased intravascular volume and blood pressure. Angiotensin II functions through receptors that stimulate production of phoshatidylinositol, mobilize intracellular and extracellular calcium 2+, and activate protein kinase. This stimulates transcription of the P450scc gene independently. Phosphorylation of transcriptional regulating factors by CaM kinases, increases transcription of the aldosterone synthase (CYP1B2) enzyme required for aldosterone synthesis. Potassium ion increases uptake of Calcium 2+ with consequent hydrolysis of phosphoinositides to increase phosphatidylinositol. Thus angiotensin II and potassium work at different levels of the same intracellular second messenger pathway but the mode action of ACTH differs.

Adrenal Androgens

The regulatory mechanisms for the synthesis of dehydroepiandrosterone (DHEA) and androstenedione (AD) are

not fully understood. ACTH is the primary stimulus for adrenal androgen production. Additional factors such as a relative decrease in expression of 3β-hydroxysteroid dehydrogenase in the zona reticularis (which also continues to mature histologically till nearly 15 years of age) and increases in 17,20-lyase activity or increased cytochrome b5 expression have been implicated. DHEA and AD can peripherally be converted to testosterone however, they have little capacity to bind to and activate androgen receptors, and hence are like androgen precursors. Fetal and neonatal adrenals secrete DHEA and DHEAS in abundance but their concentration fall rapidly as the fetal adrenal zone involutes after birth. The levels remain low till onset of adrenarche (independent of puberty) around 6 years of age which precedes the onset of puberty by about 2 years. There is progressive increase in androgen secretion between the ages of 6–20 years. The trigger for adrenarche remains unknown. DHEA and DHEAS reach maximal values in young adulthood and decline till "adrenopause" in the elderly. ACTH probably plays a permissive role in adrenarche. Premature and exaggerated adrenarche has been found in association with insulin resistance and in girls with premature exaggerated adrenarche. Both these groups have higher risk for PCOs. Infants born small for gestational age may have increased risk for this syndrome.

Actions of Adrenal Cortical Hormones

Mineralocorticoids

Aldosterone is the most important mineralocorticoid and also 11-deoxycorticosterone (DOC) which is less potent. Corticosterone and cortisol have mineralocorticoid effect only when in excess. They maintain intravascular volume by promoting sodium retention and elimination of potassium and hydrogen ions in the distal convoluted tubule of the kidneys and exert some effect on the gut, salivary and sweat glands as well. In the medullary collecting duct with their permissive action they allow vasopressin to increase osmotic water flux. Mineralocorticoid receptors are found in the heart and vascular endothelium also. The mechanism of their action is unclear but is presumably due to gene expression mediated by the mineralocorticoid receptors. In response to aldosterone, levels of subunits of both the Na^+, K^+ – ATPase and the ENac (epithelial sodium channel) increase. Aldosterone also increases the expression of the sgk kinase thereby increasing the number of open sodium channels. The mineralocorticoid receptor has affinity for cortisol also. Therefore pharmacologic or genetic inhibition of the enzyme allows cortisol to occupy renal mineralocorticoid receptors and cause sodium retention and hypertension. Mineralocorticoid deficiency leads to hypotension, hyponatremia, hyperkalemia and weight loss while excess leads to hypertension, hypokalemia, sodium retention and metabolic alkalosis.

Glucocorticosteroids

Cortisol is the predominant glucocorticoid secreted by the adrenal cortex. Cortisol is essential for survival and homeostasis and has a significant impact on carbohydrate, protein, and fat metabolism. Glucocorticoids also regulate immune, circulating and renal function, and also influence growth development, bone metabolism and central nervous system activity. During stress their levels increase tenfold which enhances survival through actions on cardiac contractility and output, increase sensitivity to the pressor effects of catecholamines and other pressor hormones, as well as work capacity of the skeletal muscles and help mobilization of energy for stress.

Carbohydrat metabolism: Stimulation of gluconeogenesis by the liver is the most well known metabolic effect of the glucocorticoids. Cortisol increases the activity of enzymes needed to convert amino acids to glucose in the liver, mobilizes amino acids from extrahepatic tissues predominantly from muscle, thus increases the availability of substrates for gluconeogenesis. It increases cellular resistance to insulin in the adipocytes, muscle cells and fibroblasts, but also along with insulin enhances glycogen deposition and production in liver by stimulating glycogen synthetase and decreasing glycogen breakdown. Hence excess of cortisol can cause hyperglycemia and deficiency can cause hypoglycemia. It also decreases the rate of glucose utilization elsewhere in the body. The cumulative effect of these actions is a rise in serum glucose.

Protein metabolism: Except in the liver, cortisol reduces protein stores via decreased protein synthesis and increased protein catabolism. The actions are antianabolic. Decreased transport of amino acids into extrahepatic cells decreases the intracellular concentration with a consequent reduction in protein synthesis. Proteins already present within the cells are catabolized and amino acids are released into the circulation, leading to a rise in plasma amino acid concentration. It leads to depletion of protein stores elsewhere in the body increases plasma proteins with a concomitant increase in hepatic protein.

Fat metabolism: It promotes mobilization of fatty acids from adipose tissue, at least in part via diminished

transport of glucose into fat cells. The resultant paucity of glucose in fat cells leads to a decrease in α-glycerophosphate, which is derived from glucose and is essential for deposition and maintenance of triglycerides in these cells; in the absence of α-glycerophosphate, cells release fatty acids. This increase of plasma free fatty acids allows for increased utilization of free tatty acids for energy. Oxidation of free fatty acids in cells is also promoted by cortisol. In times of starvation or other physiological stress, this combination of increase mobilization of fats and increased oxidation of fatty acids helps to shift the metabolism of the cells from utilization of glucose to utilization of fatty acids for energy. This is important for long-term conservation of body glucose and glucose stores.

Effects of stress: Cortisol is essential for survival during times of physiological stress. There is a rapid and marked increase in ACTH secretion from the pituitary, followed by increased secretion of cortisol from the adrenal cortex. Stressors like fever, serious infection, trauma, and surgery cause an acute glucocorticoid surge.

Growth: Through its direct inhibitory effect on epiphyses, excess inhibits linear growth and skeletal maturation. This may be mediated by decrease in the levels of growth hormone and IGF-1 and increase in IGFBP-1, the binding protein and decrease in free IGF-1. Physiologic amounts are also necessary to promote normal growth and development and in the fetus and neonate, for development and differentiation of various tissues, the hepatic and gastrointestinal systems and surfactant in fetal lung. Hence it is administered to mother at risk, for premature delivery.

Cardiovascular effects: Glucocorticoids have a positive inotropic influence on the heart and promote normal cardiovascular function. It exerts permissive effects on catecholamines, angiotensin II, and arginine vasopressin (AVP), whose vaso-constricting effects maintain adequate cardiac function and vascular tone. Cortisol deficiency causes, decreased cardiac contractility and peripheral vascular tone which may cause potentially fatal systemic hypotension and cardiovascular collapse. States of cortisol excess, in contrast, are associated with hypertension.

Anti-inflammatory and immunologic effects: Glucocorticoids have anti-inflammatory effects and play a role in immune regulation. They interfere with early stages of inflammation and help resolve established inflammation. Through stabilization of lysosomal membranes, cortisol hinders the rupture of intracellular lysosomes and reduces release of proteolytic enzymes from damaged cells, decreases capillary membrane permeability, prevents leakage of plasma. However, migration of leukocytes into inflamed areas and phagocytosis of damaged cells are decreased. It inhibits synthesis of glycolipids, prostaglandin precursors, histamine, cytokines, and bradykinin and blocks their actions, thus diminishes the inflammatory process. By suppressing the immune system circulating T lymphocytes and also antibodies are decreased. These properties of glucocorticoids are utilized in the management of diseases such as rheumatoid arthritis, glomerulonephritis and to prevent rejection of transplanted organs. High levels of glucocorticoids decrease inflammatory and cellular immune responses and increase susceptibility to certain bacteria., viral, fungal and parasitic infections.

Hematological effects: Cortisol increases red blood cell synthesis and decreases circulating eosinophils and lymphocytes. Excess cortisol secretion leads to polycythemia, eosinopenia, and lymphocytopenia.

Excess cortisol causes significant atrophy of lymphoid tissue, decreases output of T cells and antibodies and reduces immunity against foreign invaders of the body hence organisms that would otherwise be easily destroyed by an intact immune system may cause overwhelming, even lethal, infections.

Effects on skin, bone and calcium: Inhibition of fibroblasts leads to bruising and poor wound healing, cutaneous atrophy, as seen with Cushing syndrome. They decrease serum calcium by decreasing intestinal absorption and renal reabsorption of calcium and phosphorus hence they are used as emergency therapy for hypercalcemia. Long term use affects osteoblasts leading to osteoporosis and decrease in osteoclastic activity leads to low bone turnover and an overall negative balance. Tendency to lower serum calcium and phosphorus levels cause secondary hyperparathyroidism with decreased bone accretion and net loss of bone mineral.

Central nervous system: The ready penetration of blood–brain barrier helps decrease CNS edema and use of corticosteroids in reducing increased intracranial pressure. Appetite is stimulated, memory concentration may be affected and emotional ability may be increased with a feeling of eruption. Both excess and deficiency states may cause depression. Excess has occasionally led to psychosis.

Androgens

The actions of adrenal androgens are mainly exerted through their conversion to active androgens or estrogens such as testosterone, dihydrotestosterone, estrone, and estradiol. Androgens are important for normal development of the male genitalia in utero. Newborns have markedly elevated levels of androgens, specifically

androstenedione, dehydroepiandrosterone (DHEA), and testosterone. Androgen levels fall within the first few weeks of life and for the most part remain low throughout prepubertal years. DHEA, begins to rise in mid-childhood approximately around 6 years of age. In some children with increased end-organ sensitivity, this rise in DHEA may manifest with benign premature adrenarche. The chief adrenal androgens DHEA and DHEAS, reach a peak in early adulthood and then decline. Beneficial systemic effects of DHEA administration have been speculated in some of the deficiency states or at an older age. Development of pubic and axillary hair during normal puberty is attributed to adrenal androgens. In adult men, less than 2% of the biologically important androgens are derived from adrenal production, whereas in women approximately 50% of androgens are of adrenal origin.

Androstenedione is the most potent adrenal androgen. It is converted to testosterone and estradiol primarily in the gonads. In the target tissue, testosterone is converted to dihydrotestosterone (DHT). Both these hormones bind to androgen receptors and facilitate major actions of androgens promoting gonadotropin regulation, spermatogenesis, sexual differentiation and maturation. They also play an important role in the pathophysiology of congenital adrenal hyperplasia, premature adrenarche, adrenal tumors, and Cushing syndrome. Diminished secretion can manifest as sparse pubic and axillary hair as in adolescents with Addison disease.

Adrenal Medulla

The physiologically active catecholamines of the adrenal medulla are dopamine, norepinephrine, and epinephrine. Catecholamine synthesis also occurs in sympathetic nerve endings, in chromaffin tissue and the brain outside the adrenal medulla. Metabolites of catecholamines are excreted in the urine, principally as 3-methoxy-4-hydroxymandelic acid (VMA), metanephrine, and normetanephrine. Urinary metanephrines and catecholamines are measured to detect pheochromocytomas of the adrenal medulla and sympathetic nervous system.

In the adrenal gland, the proportions of epinephrine and norepinephrine vary with age. In early fetal stages, thereis practically no epinephrine; at birth, norepinehprine is predominant. In adults, norepinephrine constitutes only 10–30% of the pressor amines in the medulla.

The effects of catcholamines are mediated through a series of G protein-coupled adrenergic receptors. Both epinephrine and norepinephrine raise the mean arterial blood pressure, but only epinephrine increases cardiac output. By increasing peripheral vascular resistance, norepinephrine increases systolic and diastolic blood pressures with only a slight reduction in the pulse rate. Epinephrine increases the pulse rate, decreases the peripheral vascular resistance and decreases the diastolic pressure. The calorigenic effect of norepinephrine and hyperglycemic effect are much less pronounced than are those of epinephrine.

Hypoadrenocorticism

Adrenal insufficiency can be due to congenital or acquired lesions of the adrenal cortex (primary) or involvement of the hypothalamus or anterior pituitary gland (secondary). Primary adrenal cortical insufficiency can be acute usually transient, or more often chronic, persistent, and insidious in onset. Congenital or inherited forms of primary deficiency can be due to adrenal cortical dysgenesis, inherited inborn errors of steriodogenesis due to an acquired destructive process within the adrenal glands, commonly an autoimmune adrenalitis or chronic infections. The term Addison disease indicates both an autoimmune or idiopathic cause. In secondary adrenal insufficiency, deficient corticotrophin (ACTH) secretion leads to hypofunction of the adrenal cortex, the onset being acute or insidious, based on the underlying cause.

Acute Primary Adrenal Insufficiency

Acute adrenal crisis in childhood is more frequently encountered in children with undiagnosed chronic adrenal insufficiency, when it tends to be precipitated by stress of major illness, trauma, or surgery. Very few conditions cause acute adrenal failure in infancy and childhood as listed in *Table 384.1* and briefly.

In large infants born after difficult labor or breech delivery, acute primary adrenal insufficiency can occur due to massive adrenal hemorrhage, it is uncommon with a probable incidence of 3 per 100,000 live births. Occasionally it occurs in fetal life when it may be detected as an incidental suprarenal mass on antenatal sonography. Presenting signs include an abdominal mass, shock, pallor and collapse. Unexplained jaundice or scrotal hematoma may occur. Exsanguination and death can occur. Massive adrenal hemorrhage may occur in children with meningococcemia and meningitis, (Waterhouse-Friderichsen syndrome) and can lead to shock, collapse and a comatose state. Other septicemic states may also cause a similar picture. Immaturity of the H-P axis, partial

Table 384.1
Causes of primary adrenal insufficiency

Genetic disorders	Autoimmune adrenalitis
Inborn errors of steroidogenesis	Isolated/idiopathic
Congenital adrenal hyperplasias	Autoimmune polyendocrinopathy syndrome
Lipoid (star protein mutation)	APS-Type 1 (AIRE)
21-Hydroxylase deficiency	APS-Type 2
11β-Hydroxylase deficiency	Infections/infiltration
3β-HSD type 2 deficiency	Tuberculous adrenalitis
17α-Hydroxylase deficiency	Fungal
Adrenal hypoplasia congenita	Viral – AIDS, cytomegalo
X-linked (DAX 1 gene mutation)	Hemorrhage/infarction
Xp-21 (contiguous gene syndrome)	Trauma – neonatal, postnatal
SF-1 linked (XY sex reversal)	Waterhouse–Friderichsen syndrome
ACTH insensitivity syndromes	Anticoagulants
Familial glucocorticoids deficiency	Drugs
Type 1, and type 2	Ketoconazole, aminoglutethamide, mitotane
Triple A syndrome (Allgrove's)	Medroxyprogesterone, rifampicin, dilantin
Adrenoleukodystrophy/ adrenomyeloneuropathy	
Metabolic and syndromic adrenal insufficiency	
Disorders of cholesterol synthesis/metabolism	
Wolman disease	
Smith–Lemli–Opitz	
Antley–Bixler	
Kearns–Sayre	
IMAGe	

adrenal insensitivity to ACTH, diminution of steroidogenic activity may all contribute to inappropriately low cortisol levels in neonates with RDS, sepsis or shock. Very low cortisol levels in presence of stress are indicative. Cortisol supplementation may be advisable. Child abuse and treatment with anticoagulants are other causes. Fluid and electrolyte replacement, ample doses of glucocorticoids and supplementation with mineralocorticoids can be life saving. Therapy of precipitating illness is necessary. Majority of these conditions are transient usually with complete recovery.

Chronic Primary Adrenal Insufficiency

Developmental aberrations of adrenal glands and inherited genetic conditions though congenital, may not always manifest in infancy. They cause variable degree of adrenocortical insufficiency. Acquired conditions like autoimmune adrenalitis are encountered during childhood and adolescence but are more common in adults. Various etiologic factors leading to primary and secondary form of adrenal cortical deficiency are listed in *Table 384.1* and briefly discussed.

Clinical Manifestations

Majority of clinical manifestations of chronic adrenal insufficiency are common to all these conditions with some variations based on the underlying cause and involvement of the respective zone/zones of the adrenal cortex. Symptoms vary with severity of deficiency. These patients may complain of weakness, fatigue, apathy anorexia, poor weight gain, weight loss, dehydration, vomiting, diarrhea, darkening of skin. Hypotension, hyperpigmentation (*Fig. 384.3*), hypoglycemia, rarely hyperthermia may be noted. All these manifestations are more indicative of glucocorticoids deficiency. Signs of mineralocorticoid deficiency like (hyponatremia, hyperkalemia, acidosis, and hypochloremia may not be evident during early stages. Hypotension, tachycardia, low voltage on ECG, small heart on chest radiograph, all may be indicative of significant mineralocorticoid deficiency. Low concentration of plasma cortisol stimulates hypersecretion of ACTH and other POM peptides including the various forms of MSH which brings about hyperpigmentation of skin and mucosa. This is more prominent in skin exposed to sun and on flexor surface of knees, elbows, and knuckles.

When diagnosis of primary adrenal insufficiency is suspected clinical pointers to detect the underlying causes need to be looked for, and family history of consanguinity and sibling affection should be elicited. Male infants and newborns with this disorder are often suspected as having CAH which is much more

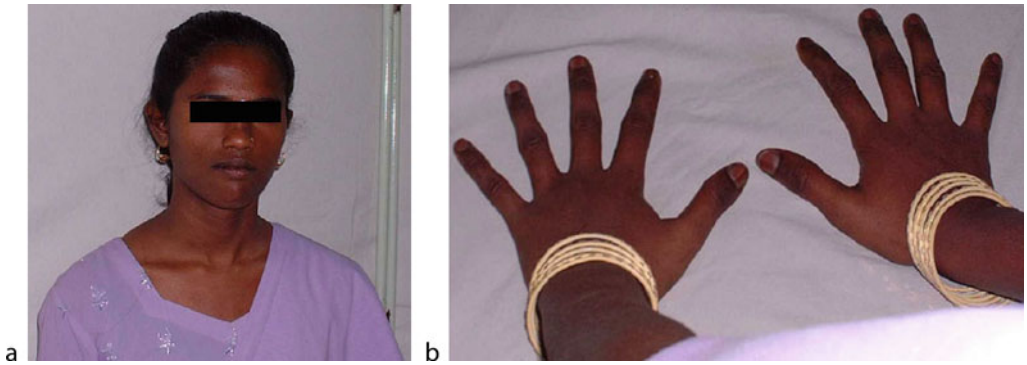

Figure 384.3
(a, b) Thirteen-year-old girl with chronic adrenal insufficiency due to glucocorticoid resistance syndrome. The figure shows a thirteen-year-old girl with gradually progressive darkening of the skin for the past 7–8 years, minimal weakness and fatigability for the past 2 years and slight delay in onset of puberty. Her hands and nails showed well marked pigmentation with pigmentation of the lips and generalized darkening of the skin. For her age, her height was within normal range. Investigations revealed low levels of cortisol, ACTH in the supra-normal range and no abnormality of the aldosterone axis, with CT adrenals showing adrenal hypoplasia. There was no past history of infective illnesses. No alacryma or achalasia. She was presumed to have isolated glucocorticoid resistance

frequently encountered. In some of these sick newborns the mild to moderately elevated 17-OHP may confuse the diagnosis. The flow chart for arriving at the underlying cause of primary adrenal insufficiency is shown in *Fig. 384.4*.

Genetic Disorders

These are inherited disorders manifesting usually at an early age due to a variety of molecular genetic abnormalities (*Table 384.1*). These disorders causing adrenal insufficiency include inborn errors of steroidogenesis leading to various forms of congenital adrenal hyperplasia, metabolic disorders like adrenoleukodystrophy (schilder disease), primary xanthomatosis (Wolman disease), cholesterol ester storage disease, hereditary unresponsiveness to ACTH, and adrenal hypoplasia congenita.

Inborn Errors of Steroidogenesis

Congenital hyperplasia due to inborn defects of steroidogenesis constitute the most common cause of adrenocortical insufficiency in infancy and childhood are discussed later. Salt wasting forms with associated deficiency of aldosterone synthesis predominate.

Adrenal Hypoplasia Congenita

Congenital adrenal hypoplasia has been associated with inactivating mutations of DAX1 and SF1 genes.

DAX-1 deficiency: This disorder has an x-linked recessive transmission and is caused by mutation of the DAX1 (NROB1) gene, a member of the nuclear hormone receptor family, located on Xp21. More than 50 mutations (nonsense, missense, frameshift) are described in patients with adrenal hypoplasia due to loss of DAX1 activity. It affects primarily boys. Usually they present with acute adrenal insufficiency in the neonatal period but onset of symptoms may be insidious and delayed until mild or later childhood or even adolescent age. Severity of presentation may vary in siblings. Histologic examination of the hypoplastic adrenal cortex reveals disorganization and cytomegaly. Puberty may not occur or its progression may be arrested due to hypogonadotropic hypogonadism. Both AHC and hypogonadotropic hypogonadism are caused by the same mutated DAX1 gene. Cryptorchidism, often noted in these boys, is probably an early manifestation of hypogonadotropic hypogonadism. In female carriers adrenal function is not compromised but delayed puberty or hypogonadotropism may occur. DAX1 may also appear as a part of contiguous gene deletion syndrome (glycerol kinase deficiency, Duchenne & Becker muscular dystrophy, chronic granulomatous disease.

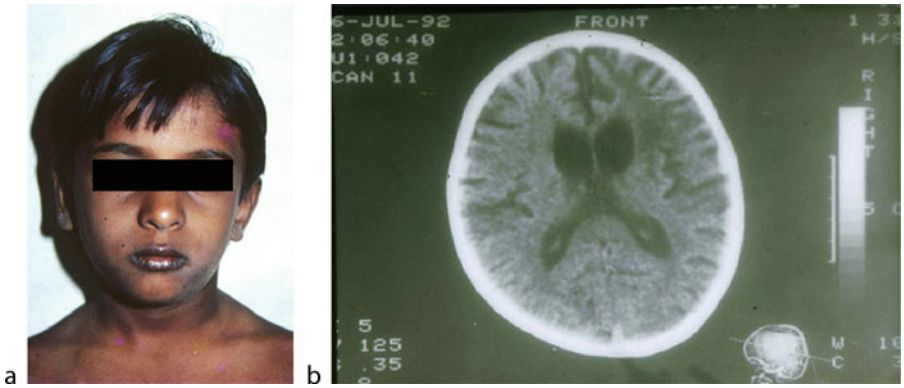

Figure 384.4
(a, b) Patient with chronic adrenal insufficiency confirmed to have adrenoleukodystrophy. A seven-year-old boy presented with gradual onset of weakness, tiredness, loss of weight, progressive darkening of skin, for 6 months. Patient was prepubertal, growth parameters equivalent to Indian average of 6-year-old boys. Generalized pigmentation of the skin, gums, tongue, lips, nails, nipples as visible in the picture. Doing well in school. Neurodevelopment normal till now. Serum cortisol was very low with ACTH in supranormal range. Health improved with corticosteroid (hydrocortisome) replacement. By 9 years of age showed scholastic backwardness, gradually progressive dementia, behavior disorder and visual difficulties. At this stage very long chain fatty acids (VLCFA) showed characteristic high levels. Lorenzo's oil introduced in therapy – progressive deterioration and death occurred by age of 13 years. Brain imaging showed cerebral demyelination. This patient had adrenoleukodystrophy presenting with cortisol deficiency as initial manifestation with CNS involvement at a later stage

SF-1 deficiency: The transcription factor SF-1 is required for adrenal and gonadal development. Very rare patients with a heterozygous mutation in SF-1 (NR5A1) may have adrenal insufficiency. Males have impaired development of the testes and may appear as females, similar to patients with lipoid adrenal hyperplasia. Some mutations of SF-1 lead to male to female sex reversal, adrenal and gonadal agenesis with GnRH deficiency and feminine differentiation of mullerian duct-derivative structures in XY fetus.

ACTH Insensitivity Syndromes

Familial Glucocorticoid Deficiency

This is an autosomal recessive disorder due to insensitivity to ACTH. Homozygous or compound heterozygous loss of function (missense or nonsense) mutations in MC2R gene have been identified in affected individuals. A number of mutations in the gene for the ACTH receptor have been described in approximately 40% of these patients. The disorder affects both sexes equally and is inherited in an autosomal recessive manner. Familial glucocorticoid resistance may be heterogenous as patients with similar findings but normal MC2R have been identified (MC2R, Type 2). A postreceptor error(s) in signal transduction is postulated. It may manifest in early infancy or early childhood. This form of chronic adrenal insufficiency is characterized by isolated deficiency of glucocorticoids markedly elevated levels of ACTH, and normal aldosterone production. Serum electrolytes and plasma renin activity are normal. Patients present with hypoglycemia, seizures, and increased pigmentation (*Fig. 384.3*) during the 1st decade of life. Linear growth is often increased due to unexplained mechanisms. Hypoandrogenemia marked by decreased pubic hair growth in females, becomes evident in puberty. There is marked adrenocortical atrophy with relative sparing of the zona glomerulosa.

Triple A (Allgrove) Syndrome

Another syndrome due to ACTH resistance causing adrenocortical insufficiency occurs in association with achalasia of the gastric cardia and alacrima. It is also known as Allgrove or ALADIN Syndrome. The adrenal zona fasciculata is absent with intact zona glomerulosa and normal aldosterone levels, hence symptoms are related to deficiency of glucocorticoids. These patients often have a progressive neurologic disorder that includes autonomic dysfunction (pupillary reflex aberrations, postural hypotension), mental retardation, deafness, and motor

neuropathy. This syndrome is also inherited in an autosomal recessive fashion, and the AAAS gene has been mapped to chromosome 12q13. The encoded protein, ALADIN belongs to a family of proteins expressed in the CNS and gastrointestinal system.

Glucocorticoid Resistance

A rare syndrome of glucocortioid resistance characterized by hypercortisolemia and hypercortisoluria without clinical signs of cortisol excess or deficiency is described. ACTH induced hyperandrogenism as well as mineralocorticoid induced hypertention and hypokalemic alkalosis can occur.

Metabolic and Syndromic Adrenal Insufficiency

This group of disorders have underlying characteristic metabolic abnormality due to specific enzyme deficiencies involved in cholesterol synthesis ultimately leading to adrenal insufficiency. Some of these disorders have associated dysmorphic features and constitute characteristic syndromes. Majority of these disorders are uncommon.

Disorders of Cholesterol Synthesis/ Metabolism

Adrenocortical hypofunction occurs in patients with disorders of cholesterol synthesis or metabolism, including abetalipoproteinemia with deficient lipoprotein B-containing lipoproteins, and familial hypercholesterolemia, with decreased or impaired LDL receptors. *Wolman disease* is a rare autosomal recessive disorder caused by mutations in the gene encoding human lysosomal acid lipase. Cholesteryl esters accumulate in lysosomes in most organ systems, leading to organ failure. During very early infancy hepatosplenomegaly, steatorrhea, abdominal distention, and failure to thrive occurs. Adrenal insufficiency and bilateral adrenal calcification are present, and death usually occurs in the first year of life. The genetic defects in patients with Wolman disease have been elucidated and the gene for lysosomal acid lipase has been mapped to chromosome 10q23.2-23.3.

Adrenal insufficiency has been reported in patients with *Smith-Lemli-Opitz syndrome* (SLOS), an autosomal recessive disorder presenting with facial anomalies, microcephaly, limb anomalies, and developmental delay due to mutations in the gene coding for sterol Δ7-reductase, mapped to 11q12-q13. Resulting impairment in the final step in cholesterol synthesis causes marked elevation of 7-dehydrocholesterol, abnormally low cholesterol, and adrenal insufficiency. Pyrooxidoreductase deficiency leads to *Antley-Bixler Syndrome*. In *Kearns-Sayre syndrome*, deletion of mitochondrial DNA is associated with myopathy, deafness, hypoparathyroidism, and adrenal insufficiency. IMAGe syndrome is associated with IUGR, metaphysieal dysplasia, adrenal insufficiency and genital anomalies.

Corticosteroid-binding globulin (CBG) deficiency and decreased cortisol-binding affinity: These disorders result in low levels of plasma cortisol but normal urinary free cortisol and normal plasma ACTH levels. A high prevalence of hypotension and fatigue has been reported in some adults with abnormalities of CBG.

Adrenoleukodystrophy (ALD)

ALD is an x-linked recessive disorder with a frequency of 1 in 20,000 male live births. It is a disorder of fatty acid transport with intracellular accumulation of very long chain fatty acids (VLCFAs more than 24 carbon or C26-hexacosanoate) as esters of cholesterol in the adrenal cortex and CNS white matter. It is associated with adrenocortical deficiency and demyelination in the central nervous system due to impaired β-oxidation in the peroxisomes (Fig. 384.4). The X-linked adrenal leukodystrophy (X-ALD) is caused by mutations in the ABCD1 gene located on Xq28, which encodes a transmembrane transporter involved in the importation of very long chain fatty acids into peroxisomes. More than 400 mutations have been described in patients with X-ALD; mutations do not correlate with phenotypes. X-ALD families may have a unique mutation with clinical phenotypes varying within families, due to modifier genes or other unknown factors. There is no correlation between the degree of neurologic impairment and severity of adrenal insufficiency.

Adrenal insufficiency often precedes progressive neurologic symptoms of spastic paraparesis severe dementia and deterioration of vision, hearing, speech, and gait, with death occurring within a few years. A milder form of X-linked ALD is adrenomyeloneuropathy (ALM), which begins in later adolescence or early adulthood. Many patients have evidence of adrenal insufficiency at the time of neurologic presentation, but Addison disease may be present without neurologic symptoms or may precede them by many years. Prenatal diagnosis by DNA analysis and family screening by very long chain fatty acid assays and mutation analysis are available. Women who are heterozygous carriers of the X-ALD gene may develop symptoms in midlife or later. In them adrenal insufficiency is rare.

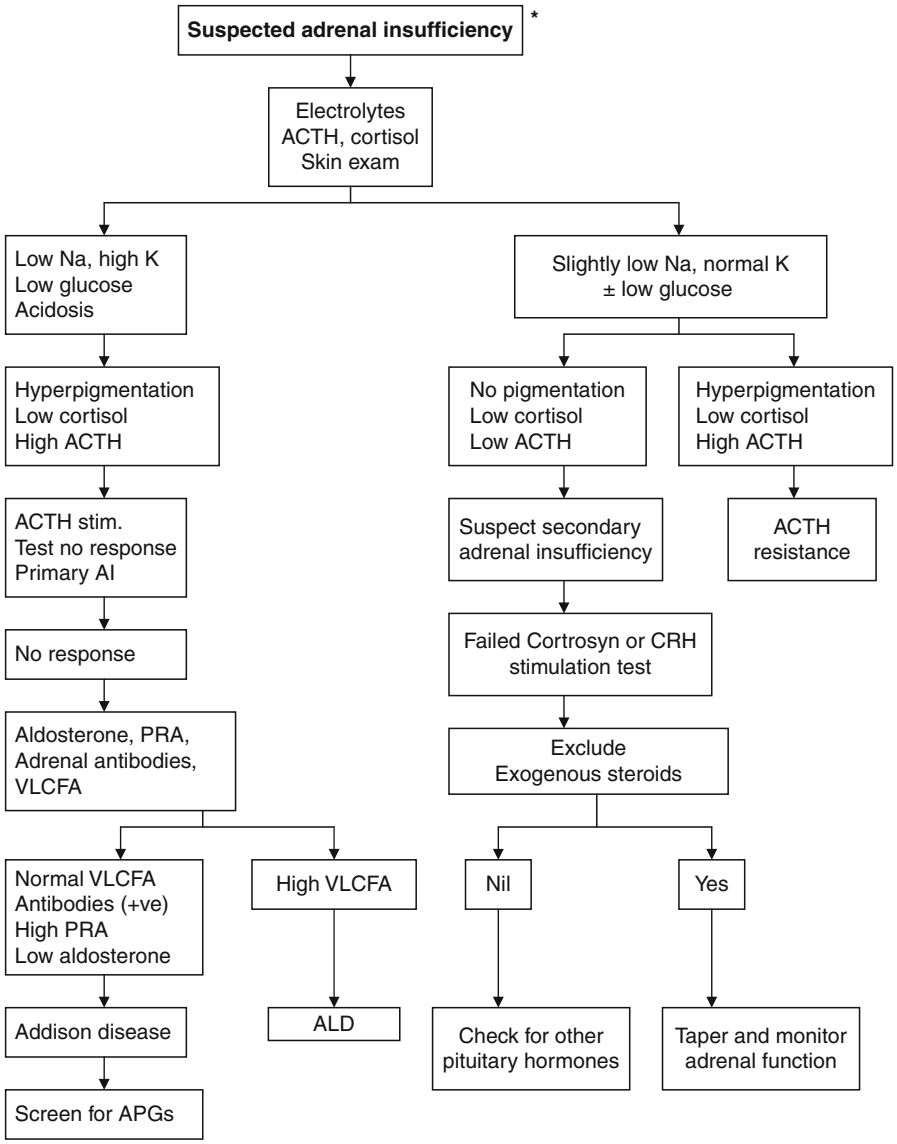

Figure 384.5
Investigative evaluation for adrenal insufficiency (AI). Precise history examination and family history help suspect AI. VLCFA – very long chain fatty acids. APG5 – autoimmune polyglandular syndrome

Neonatal ALD is a rare autosomal recessive disorder with neurologic deterioration and adrenocortical dysfunction in neonatal period or developing during infancy. Most patients have severe mental retardation and die before 5 year of age. This disorder is a subset of Zellweger (cerebro-hepato-renal) syndrome, in which peroxisomes do not develop owing to mutations in any of the several genes controlling the development of this organelle.

Autoimmune Adrenalitis

Addison Disease

The most common cause of primary adrenal insufficiency is Addison disease which is due to autoimmune destruction of the adrenal glands. The glands may become extremely atrophic, marked lymphocytic infiltration occurs but the medulla is intact. At autopsy only remnants of the glands may be seen. The incidence is approximately

1 in 20,000 and is more frequent in adults between 24 and 45 years of age with 70% of these occurring in women. It may be associated with autoimmune dysfunction of other endocrine glands as well in nearly 50% of adults.

The incidence in pediatric age group is not known. Isolated cortisol deficiency with accompanying symptoms of glucocorticoids deficiency appear first and during its clinical course, deficiency of mineralocorticoids appears. Androgen production may also be affected. Most patients have antiadrenal cytoplasmic antibodies to (CYP21) 21-hydroxylase autoantigen.

Addison disease may occur as a component of autoimmune *polyendocrine syndromes* in particular Type 1 (APS-1 or APECED) or Type II (APS-2). The components of APS-1 are mucocutaneous candidiasis with ectodermal dystrophy which is often the initial manifestation followed by hypoparathryoidism and lastly Addison disease occurring towards adolescence. Gonadal failure, alopecia, vitiligo, keratopathy, enamel hypoplasia, intestinal malabsorption, and chronic active hepatitis may be associated manifestations of autoimmune syndrome. Hypothyroidism and Type I diabetes mellitus occur in less than 10%. Adrenal failure may evolve rapidly. It is inherited as autosomal recessive condition hence screening siblings for this disorder may lead to early detection. In APS-1, autoantibodies to CYP21, CYP17 and CYP11AI enzymes are noted. There is a loss of function mutation in the affected gene in APS-1, designated as autoimmune regulator-1, (AIRE1) gene, which is a transcription factor mapped to chromosome 21q22.3. Nearly 40 different mutations are described in patients with APS-1 with 2 mutations (R257× and a 3-bp deletion) most frequent. The disease is reportedly more common among Finnish, Sardinian and Iranian Jewish people.

Addison disease may be a component of Type II autoimmune polyendocrinopathy (APS-2). Here Addison disease is associated with autoimmune thyroiditis (Schmidt syndrome) or Type I diabetes (carpenter syndrome). Some of the other manifestations may be gonadal failure, vitiligo, alopecia and chronic atrophic gastritis with or without pernicious anemia. Hypoparathyroidism and mucocutaneous candidiasis are not seen. Presence of HLA-D3 and HLA-D4 increases the risk for development of this disorder. Type 2 is associated with the same HLA markers as idiopathic autoimmune adrenalitis which could be a form of APS Type 2. It can occur at any age, less common in childhood and has higher incidence in young adults especially in middle aged females. It may occur in many generations of the same family. The overall incidence is 1.4 to 2 per 100,000 population and is transmitted as autosomal dominant trait with incomplete penetrance. Autoantibodies to the same adrenal enzymes as mentioned in APS-1 are encountered.

Secondary Adrenal Insufficiency

Dysfunction of hypothalamus and/or pituitary can cause adrenal insufficiency due to insufficient tropic hormone (CRH/ACTH) production and stimulation of the adrenal cortex (◉ *Table 384.2*). Involvement of the H-P axis can be due to idiopathic congenital developmental abnormalities (mid line lesion like septoptic dysplasia), inherited genetic (PROP1 gene) or organic forms of hypopituitarism. CNS tumors can damage the cells producing CRF and/or POMC. Cranial radiation can also affect the H-P axis. Rarely autoimmune lymphocytic hypophysitis, pituitary

Table 384.2
Etiology of secondary adrenal insufficiency

Congenital/genetic	Pituitary irradiation
Isolated ACTH deficiency	Leukemia, neoplasia
? POMC cleavage enzyme defect, POMC gene mutation	Autoimmunity, infection, infiltration
Combined pituitary hormone deficiency	Isolated or APS Syndrome
PROP-1, HESX-1, midline brain defects	Lymphocytic hypophysitis
Head trauma	Histiocytosis
Neoplasia	Tuberculosis, sarcoidosis
Pituitary tumors	Chronic glucocorticoid excess
Tumors – hypothalamic pituitary region	Exogenous more than 4 weeks
Craniopharyngioma, ependymoma, others	Endogenous – Cushing syndrome

infiltration or granuloma can cause isolated ACTH deficiency, or be associated with other tropic hormone deficiencies. Chronic suppression of tropic cells can also result from long term glucocorticoid therapy.

Idiopathic/genetic hypopituitarism is more often a disorder of hypothalamus rather than pituitary where deficient secretion of GH, gonadotropins, TSH and ACTH is related to insufficient secretion of corresponding hypothalamic hormones. ACTH deficiency is more often an associated deficiency along with deficiency of GH, gonadotropins and TSH in that order. Isolated ACTH deficiency is a rare and unusual disorder with clinical and genetic heterogeneity. It may present in infancy with hypoglycemia and seizures or later in life with failure of growth and delayed adolescence. In patients with ACTH deficiency, (either with or without deficiency of other anterior pituitary hormones) hypocortisolism may be relatively mild with no deficiency of mineralocorticoids. Adrenal reserve is compromised because of chronic understimulation of biosynthesis. Diagnosis may not be apparent unless a CRF or metyrapone test is performed to assess pituitary ACTH response and intravenous ACTH test to study adrenal reserve. Associated TSH deficiency can mask ACTH deficiency as cortisol metabolism is slowed down. An acute adrenal crisis may be precipitated if thyroxine therapy is introduced in such patients without adequate glucocorticoid cover.

CNS tumours like craniopharyngiomas can be associated with ACTH deficiency in nearly 25% of patients and the incidence may be higher with tumours such as germinomas and astrocytomas and also following surgery and radiation. Cortisol cover should be offered during therapeutic intervention and thereafter for required duration of time. Inapparent deficiency of vasopressin can also be unmasked after instituting cortisol replacement therapy for ACTH deficiency with clinical symptoms of diabetes insipidus becoming evident.

Long term therapy for steroid responsive systemic disorders can suppress the H-P-A axis by suppressing POMC gene transcription, synthesis and storage of ACTH and CRF and decrease the number of receptors for CRF in the pituitary. Considerable length of time based on the duration and dosage of glucocorticoids may elapse (6 months of more) before recovery of H-P-A axis, occurs and probably takes longer for diminished adrenal reserve to return to normal. Hence, gradual stepwise withdrawal to physiologic doses of 10 mg/m^2/day or little less is advocated. Dexamethasone used for the treatment of fetal adrenals in CAH and in preterm babies to enhance lung maturation can occasionally lead to transient hypocortisolism.

Clinical Presentation

The clinical manifestations are usually insidious in onset, gradually progressive and less severe in the secondary form. Hyperpigmentation, a characteristic feature of primary adrenal insufficiency is not seen in the secondary form of the disorder. Aldosterone secretion remains normal hence electrolytes are normal. Newborns often present with hypoglycemia. Signs related to respective hormonal deficiencies may be seen. Micropenis, neonatal jaundice, and poor growth after first year of life are suggestive of associated gonadotropin, TSH and GH deficiencies, respectively. Midface or optic nerve hypoplasia with visual impairment, wandering nystagmus or other midline defects are some of the clinical indicators of H-P axis involvement.

Management of Adrenal Insufficiency

Primary agent of choice in the management of either primary or secondary adrenocortical insufficiency is cortisol. Based on the underlying cause, long term or life long glucocortical supplementation in optimal doses will be required. Irrespective of the underlying cause, in acute adrenocortical insufficiency urgent treatment will be required. Precipitating cause should be taken care of.

In any suspected case, if the diagnosis has not been established, before administering cortisol a blood sample should be drawn for cortisol, ACTH, electrolytes, glucose, aldosterone and plasma renin activity. Depending on patient's condition an ACTH stimulation test to study cortisol response may be undertaken. Adrenal androgens and precursors like 17-hydroxy progesterone may be estimated as required. Urgent infusion with 5% glucose with normal saline (0.9%) will help correct hypoglycemia, hyponatremia and hypovalemia. Severe hyperkalemia may need treatment with intravenous calcium and/or bicarb, IV glucose and insulin or intrarectal Potassium binding resin (Kayexalate). Water soluble form of hydrocortisone needs to be given intravenously. Six hourly doses of cortisol 100 mg/m^2, or 10, 25, 50 and 100 mg for infants, toddlers, older children and adolescents respectively should be administered for first 24 h. During the ensuing 24 h doses may be reduced based on condition of the patient. High dose of hydrocortisone will also have mineralocorticoid effect. Mineralocorticoid support is given as oral fludrocortisone (Florinef) 0.05 upto 0.2 mg daily if required.

Most patients require chronic replacement therapy for cortisol and aldosterone deficiencies. Hydrocortisone is given orally 10–15 mg/m^2/24 h daily in three divided

doses. Equivalent doses (20–25% of hydrocortisone dose) of prednisone or prednisolone divided into two doses can be administered. ACTH levels may be used to monitor adequacy of glucocorticoid replacement in primary adrenal insufficiency while in CAH levels of precursor hormones can be used. A larger amount, 40–50% of the dose can be given in the morning based on individual feeling of well being or based on the morning ACTH levels if found to be in the supranormal range. The dosage of cortisol is maintained at the lower end of the therapeutic range to prevent inhibition of endogenous or GH stimulated linear growth and excess weight gain. Measurements of cortisol and ACTH help in establishing the correct dosage of cortisol.

Dose of hydrocortisone is increased 2–3 fold during acute stress of illness, or surgery. Higher doses as in treatment of acute adrenal insufficiency are required during major surgical procedures. Measurement of plasma renin activity, blood pressure, and electrolytes help in monitoring adequancy of mineralocorticoid replacement. Fludrocortisone (0.05–0.2 mg per day) is given in two divided doses and Sodium chloride to maintain eunatremia, Hypervolemia and hypertension, need to be avoided. Clinical monitoring for growth parameters like height and weight is essential. Osteoporosis can occur due to chronic glucocorticoid overdosages. DHEA replacement in older age group and adults need more study.

Underlying cause of adrenal insufficiency may need careful attention e.g., Loranzo's oil (glyceroltrioleate and glycerol trierucate) for adrenoleukodystroophy, or bone marrow transplantation or lovastatin for metabolically mediated deficiencies.

Congenital Adrenal Hyperplasia

This group of disorders with insufficient cortisol production often associated with genital ambiguity constitute one of the most common inborn errors of metabolism of the adrenal cortex, almost worldwide. The inheritance is autosomal recessive. Steroid Hormone Synthesis of all three classes of adrenal cortical hormones – mineralocorticoids, glucocorticoids, and sex steroids, has been discussed earlier. Deficiency of any one of the enzymes along the pathway (*Fig. 384.1*) disrupts adrenal cortical function and is associated with a characteristic pattern of deficiency, of one or more of the hormones with a concomitant many fold excess of precursors and/or other products along the biosynthetic pathway. *Table 384.3* refers to a brief summary of various types of CAH encountered in clinical practice. Almost 90–95% of CAH cases are caused by 21-hydroxylase deficiency (CAH-21OHD) which in its classic salt wasting form (about 75% of 21OHD) can be potentially life threatening. Inability of the adrenal cortex to synthesize adequate amount of cortisol leads to trophic hormone stimulation with increase in CRH and ACTH causing the adrenal hyperplastia. In 21-OH and 11β-hydroxylase (11β-OH) deficiencies and to a lesser extent in 3β-hydroxysteroid dehydrogenase deficiency (3β-OHD), this leads to formation of excess sex steroid precursors which are processed extraadrenally to active androgens (testosterone and dihydrotestosterone) and some to estrogens (estrone and estadiaol) (*Fig. 384.1*). In these disorders intrauterine virilization occurs in females or postnatally early virilization in males in 21-OHD and 11β-OHD. In males, with deficiency of the enzymes 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase or cholesterol desmolase, inadequate androgen production leads to undervirilized genitals. Interruption of aldosterone formation interferes with sodium balance as with lipoid adrenal hyperplasia, aldosterone synthase deficiency and most cases of 21-OHD and 3β-HSD deficiencies.

21-Hydroxylase Deficiency

Mutations in the gene encoding adrenal P450c21 is most common.

Epidemiology: In most populations the incidence of classical 21-hydroxylase deficiency is 1 in 15,000–20,000 births. Approximately 70–75% of affected infants have the salt-losing form, whereas upto 30% have the simple virilizing form. Alaskan YupikEskimos have a high incidence of (1:280); so also, in natives of French island of Reunion (1:2,100), Brazil (1:7,500), and the Philippines (!:7,000). CAH is less common in African Americans compared with white children (!:42,000 vs 1:15,500) in USA. Nonclassical disease has a prevalence of about 1 in 1,000 in the general population but occurs more frequently, 1–3% in specific ethnic groups such as Ashkenazi Jews, Hispanics, and Yugoslovians.

Genetics: There are two steroid 21-hydroxylase genes – CYP21P (CYP21A1P, CYP21A) and CYP21 (CYP21A2, CYP21B) in the HLA major histocompatibility complex on chromosome 6p21.3 between the HLA-B and HLA-DR loci. CYP21 is the active gene; CYP21P is 98% identical in DNA sequence to CYP21 but is a pseudogene due to nine different mutations. More than 90% of mutations causing 21-hydroxylase deficiency are recombinations between CYP21 and CYP21P and approximately 20% are deletions. The deleterious mutations in CYP21P affect enzymatic

Table 384.3

A summary of clinical and laboratory findings in congenital adrenal hyperplasia

Enzyme deficiency	Presentation	Laboratory findings	Therapeutic measures
Lipoid congenital adrenal hyperplasia (StAR)	Salt-wasting crisis	Low/absent levels of all steroid hormones	Glucocorticoid and mineralocorticoid replacement
	Male pseudohermaphroditism	Decreased/absent response to ACTH	Estrogen replacement at age ≥12 years
			Gonadectomy of male pseudohermaphrodite and salt supplementation
		Decreased/absent response to hCG in male pseudohermaphroditism	Glucocorticoid and mineralocorticoid replacement
		↑ in ACTH and PRA	Salt supplementation
			Surgical correction of genitalia
			Sex hormone replacement as necessary
3β-HSD	Salt-wasting crisis	↑ Δ5 steroids before and after ACTH	Glucocorticoid and mineralocorticoid replacement
	Male and female pseudohermaphroditism		Salt supplementation
		↑ Δ5/Δ4 serum steroids	Surgical repair of female pseudohermaphroditism
		Suppression of elevated adrenal steroids after glucocorticoids administration	
P450c21	Classic form: Salt-wasting crisis	↑ ACTH and PRA	Glucocorticoid administration
			Surgical repair of female pseudohermaphroditism
	Female pseudohermaphroditism	↑ 17OHP before and after ACTH	
	Pre- and postnatal virilization	↑ Serum androgens and urine 17KS	
	Nonclassic form: Premature adrenarche,	Suppression of elevated adrenal steroids after glucocorticoids therapy	
	Menstrual irregularity,		
	Hirsuitism, acne,	↑ ACTH and PRA	
	infertility		
P450c11β	Female pseudohermaphroditism	↑ 11-Deoxycortisol and DOC before and after ACTH	Mineralocorticoid replacement salt supplementation
	Postnatal virilization in males and females	↑ Serum androgens and urine 17 KS	
		Suppression of elevated steroids after glucocorticoids administration	
		↑ ACTH and ↓ PRA	
		Hypokalemia	

Table 384.3 (Continued)

Enzyme deficiency	Presentation	Laboratory findings	Therapeutic measures
P450c17	Failure to thrive	Hyponatremia, hyperkalemia	Glucocorticoid administration
	Weakness	↑ Corticosterone	Surgical correction of genitalia and sex steroid replacement in male pseudohermaphroditism consonant with sex of rearing
	Salt loss	↓ Aldosterone and ↑ PRA	
			Estrogen replacement in female at ≥12 years
	Male pseudohermaphroditism	↑ DOC, 18-OHDOC, corticosterone	Testosterone replacement if reared as male (rare)
	Sexual infantilism		
	Hypertension	Low 17α-hydroxylated steroids and poor response to ACTH	
		Poor response to hCG in male pseudohermaphroditism	
		Suppression of elevated adrenal steroids after glucocorticoids administration	
		↑ ACTH and ↓ PRA	
		Hypokalemia	

ACTH adrenocorticotropic hormone (corticotrophin), *DOC* deoxycorticosterone, *hCG* human chorionic gonadotropin, *PRA* plasma renin activity, 17*OHP* 17-hydroxyprogesterone, 17*KS* 17-ketosteroids, 18-*OHDOC* 18-hydroxydeoxycroticosterone

activity when transferred to CYP21. Mutations can prevent synthesis of a functional protein or missense mutations result in amino acid substitutions with enzymes having 1–50% of normal activity. There is good correlation between disease severity and the mutations carried by an affected individual. Salt-wasting is associated with mutations on both alleles that destroy enzymatic activity completely. In compound heterozygotes, severity of the disease expression is mainly determined by the activity of the less severely affected of the 2 alleles.

Pathogenesis: This P450 enzyme (CYP21, P450c21) hydroxylates progesterone and 17-hydroxyprogesterone (17-OHP) to yield 11-deoxycorticosterone (DOC) and 11-deoxycortisol, respectively. Both cortisol and aldosterone are deficient as both require 21-hydroxylation for their synthesis. Less severely affected patients are able to synthesize adequate amounts of aldosterone but have elevated levels of androgens of adrenal origin and have simple virilizing disease. "Salt-wasting" form of this disorder is the most common form of CAH encountered in clinical practice. These two forms together constitute CAH with classical 21-hydroxylase deficiency. The salt wasting form involves nearly 75% of classical 21-OHD. Accumulation of precursor steroids occurs proximal to the enzymatic block. In 21-hydroxylase deficiency, these precursors include 17-hydroxyprogesterone and progesterone. These precursors are diverted into the androgenic pathway (*Fig. 384.1*) with the formation of excess androgenic compounds and extraadrenal conversion to testosterone. In the affected female fetus abnormal genital development begins by 8–10 week of gestation. The accumulated 17-hydroxyprogesterone shunted into the pathway for androgen biosynthesis, leads to high levels of androstenedione and ultimately to testosterone. In the male fetus this additional testosterone has little demonstrable phenotypic effect but it leads to masculinization in the female fetus. The degree of virilization ranges from mild clitoromegaly with or without partial to complete labioscrotal fusion or in extreme instances urethra traversing the enlarged clitoris. The vagina and urethra open into the common urogenital sinus (refer *Fig. 384.6*). The enlarged clitoris resembles a penis as the urethra opens below it (*Fig. 384.7*). Some affected females may be mistakenly presumed to be males with hypospadias and cryptorchidism and raised as males (*Fig. 384.7*). The internal genital organs are normal with normal ovaries (*Fig. 384.7*). Progesterone and perhaps other metabolites act as antagonists of the mineralocorticoid receptor and thus may exacerbate the effects of

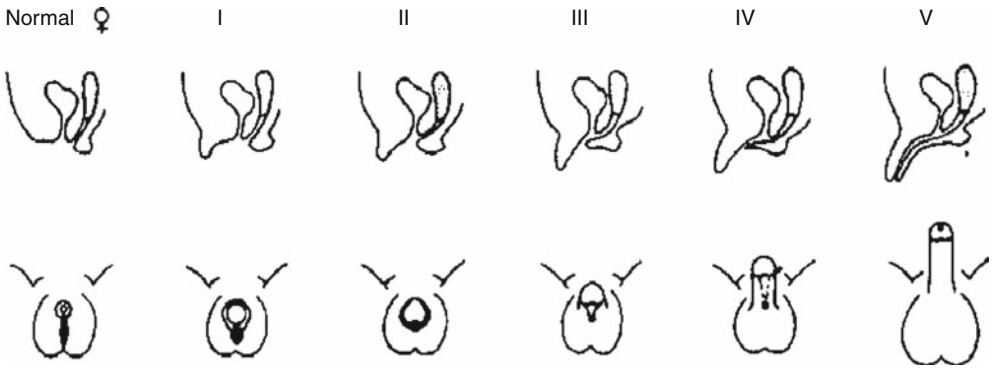

Figure 384.6
Staging system of Prader showing various stages of virlization of external genitalia. Spectrum from normal female to normal male. (*top*) – sagittal section, (*bottom*) – perineal view. This can occur either by the virlization of a normal female, as in congenital adrenal hyperplasia, or from an error in testosterone synthesis in the male

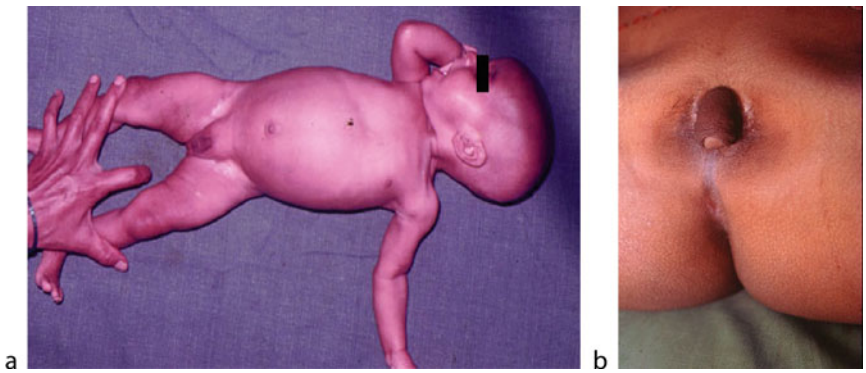

Figure 384.7
(a, b) Salt wasting CAH (21 hydroxylase deficiency) in a three-month-old girl presenting with ambiguous genetalia. This infant presented for repeated episodes of dehydration, failure to thrive and hospitalization. Examination showed genital ambiguity with slight pigmentation and a clitoral length of almost 2.5 cms, with a single opening, no palpable gonads and a single urogenital opening. 17-OHP level was very high, with low sodium and high potassium. USG confirmed presence of mullerian structures. Karyotype was 46 XX. Clinical and investigative evaluation confirmed salt wasting 21 hydroxylase deficiency. Patient showed remarkable improvement with hydrocortisone and fludrocortisone replacement

aldosterone deficiency in untreated patients. The signs and symptoms are similar to those described earlier under primary adrenal insufficiency and include progressive weight loss, anorexia, vomiting, dehydration, weakness, hypotension, hypoglycemia, hyponatremia, hyperkalemia and pigmentation. Transplacental transfer of maternal corticosteroids prevents symptoms from occurring during first 2 weeks after birth. Without treatment, shock, cardiac arrhythmias, and death may occur within days or weeks. Patients with nonclassical disease have relatively mildly elevated levels of androgens and may have signs of androgen excess developing after birth.

Prenatal Clinical Findings

The severity of virilization is usually greatest in female infants with the salt-losing form of 21-hydroxylase deficiency. Male infants appear normal at birth. Diagnosis is often delayed till signs of adrenal insufficiency develop. Many boys with this disorder may succumb before this disease is recognized. Institution of neonatal screening for this disorder has prevented many such deaths. Family history of early neonatal and infant deaths in male children or a previous female sibling with ambiguous genitalia should alert the attending physician. Genital

pigmentation in a male infant with failure to thrive and episodes of dehydration should also alert the physician.

Simple virilizing form of 21-OHD CAH can often go unrecognized in boys till signs of androgen excess appear in late infancy or early or mid childhood (◉ *Fig. 384.8*). Little attention is paid to rapid somatic growth which is often not considered abnormal. Inadequately treated children of both sexes develop signs of androgen excess. In these children signs of adrenal insufficiency with salt wasting may appear during periods of stress. Accelerated skeletal maturation leads to premature closure of the epiphyses (early cessation) results in stunted stature in adulthood. Pubic and axillary hair appear early; and acne and a deep voice may develop. The penis, scrotum, and prostate may enlarge (in affected boys); however, the testes are usually prepubertal in size and appear relatively small in contrast to the enlarged penis. Occasionally in some cases, testicular adrenal rest tumors occur. In girls the clitoris may enlarge further, breast development and menstruation may not occur unless the excessive production of androgens is suppressed by adequate treatment.

In nonclassical 21-OHD, milder signs of androgen excess may occur. In this attenuated form, cortisol and aldosterone levels are normal and affected females have normal genitals at birth. Many females and males are completely asymptomatic. Children of both sexes present with precocious pubarche and early development of pubic and axillary hair. Hirsuitism, acne, menstrual disorders, and infertility may develop later in life.

There is ongoing debate on prenatal exposure of the brain to high levels of androgens which may influence subsequent sexually dimorphic behavior in these females with preference for toys and games boys like to play. At an older age women may have decreased interest in maternal

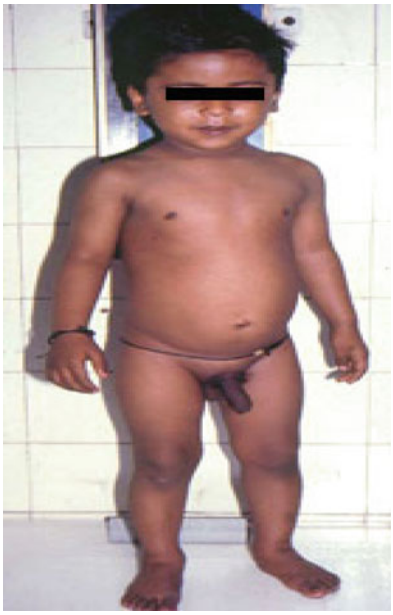

Figure 384.8
A 2½-year-old boy presenting with sexual precocity due to non-salt wasting CAH caused by 21 hydroxylase deficiency. Presentation for gradually progressive sexual precocity, darkening of the skin and rapid growth over past 1 year. No episodes of salt wasting or dehydration, similar history in cousin brother. Height age – 5 years, testicular volume 2 mL, pubic hair growth Tanner 3, penile size (increased), Bone age – 5 years (Greulich and Pyle), Height Age – 4.5 years, 17-OHP markedly elevated, adrenal androgens and elevated testosterone. The patient was confirmed to have CAH due to non-salt wasting 21 hydroxylase deficiency

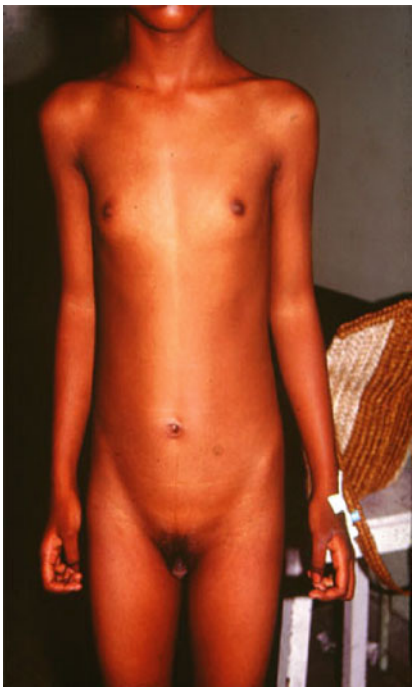

Figure 384.9
A fourteen-year-old patient referred for absence of gonads and gynaecomastia. Genital ambiguity was noted at birth but the patient was brought up as a boy (her younger sibling brought at the same time was confirmed to have non-salt wasting 21 hydroxylase deficiency). Investigations confirmed the same diagnosis in this patient. Parents and the patient were explained the underlying diagnosis. They wished to continue to raise the patient as a male, sex change to female gender was refused

roles with an increased frequency of homosexuality. However, most seem to function heterosexually with no gender identity confusion. Rearing and other postnatal psychosocial environmental factors may influence individual attitudes.

Laboratory Diagnosis

In patients with salt-losing disease cortisol and aldosterone deficiency lead to hyponatremia, hyperkalemia, metabolic acidosis, and often hypoglycemia, developing usually by 2 weeks after birth. 17-hydroxyprogesterone (17-OHP) levels are markedly elevated (>2,000 ng/dL after 24 h of age). As circulating level tends to be high during the first 2–3 days of life even normally, hence it is better to estimate it 48 h after birth. In sick or premature newborns it is often high therefore careful interpretation is necessary. Serum cortisol is usually low in salt-losing 21-OHD and often normal in patients with simple virilizing 21-OHD, but may be inappropriately low in relation to the ACTH and 17-hydroxyprogesterone levels. In addition to 17-OHP, levels of androstenedione and testosterone are elevated in affected females; testosterone levels are not helpful in affected males as testosterone levels tend to be higher during infancy. Urinary metabolites, 17-ketosteroids and pregnanetriol are elevated but are now rarely used in clinical practice. Elevated ACTH levels have limited diagnostic utility over 17-OHP. Plasma levels of renin are elevated, and serum aldosterone is inappropriately low, however, normally renin levels are high in the first few days of life. In some cases 17-OHP estimation at 0′, 30′ or 60′ min after an intravenous bolus of 0.125–0.25 mg of cosyntropin (ACTH 1–24) helps to establish the diagnosis. Nomograms help distinguish normals from patients with nonclassical and classical 21-OHD. Heterozygous carriers of this autosomal recessive disorder tend to have higher ACTH-stimulated 17-OHP levels than unaffected individuals, but significant overlap is seen in these two categories.

Differential Diagnosis

Thorough physical examination to define the anatomy of the genitals, locate the urethral meatus, palpate the scrotum or labia and the inguinal regions for testes (palpable gonads almost always indicate the presence of testicular tissue and suggests that the infant is a genetic male). Presence of other anatomic abnormalities should be excluded. Ultrasonography helps in demonstrating the presence or absence of uterus and location of gonads. A rapid karyotype (such as fluorescence in situ hybridization of interphase nuclei for X and Y chromosomes) can quickly determine the genetic sex of the infant. These studies help in determining the sex of rearing, counseling the parents and deciding future course of action. Most surgeons prefer to outline the urogenital sinus with an injection of contrast medium to formulate a plan for surgical management during infancy. ❯ *Figure 384.10* shows a flow diagram of approach to diagnosis of a newborn with CAH.

Management

Glucocorticoid replacement: This form of therapy introduced in 1950 takes care of cortisol deficiency and also suppresses excessive production of androgens by the adrenal cortex thus minimizing excessive growth, skeletal maturation and virilization. However, management of this disorder still remains difficult. Secretory rate of cortisol is around 12.5 ± 3 mg/m^2 per day but is probably substantially lower. Newborns and newly diagnosed patients often require substantially higher doses to suppress the CRH-ACTH-adrenal axis. Glucoccorticoid equivalence as compared to hydrocortisone is mentioned in ❯ *Table 384.4*. The requirement of glucocorticoids is often higher (15–20 mg/m^2/24 h of hydrocortisone daily administered orally in three divided doses) than with other causes of adrenal insufficiency. Double or triple the doses are indicated during periods of stress, such as infection or surgery. This therapy has to be continued lifelong but may not be necessary in patients with nonclassical disease unless signs of androgen excess are present. Therapy must be individualized. Growth monitoring is helpful as crossing to higher height percentiles may suggest undertreatment, whereas loss of height percentiles and excess weight gain often indicate overtreatment. Growth and skeletal maturation as well as pubertal development should be monitored periodically. Hormone levels, particularly 17-hydroxyprogesterone and androstenedione, should be measured early in the morning (beyond infancy cortisol circardian rhythm gets established) before taking the morning medications, or at a consistent time after medication dosing. Desirable 17-OHP levels are maintained in the high-normal range or little higher; low normal levels are often achieved only with excessive glucocorticoid doses.

Pubertal development and menarche occurs at the appropriate age in girls with early institution of treatment in whom good control has been achieved but can be delayed in girls with suboptimal control.

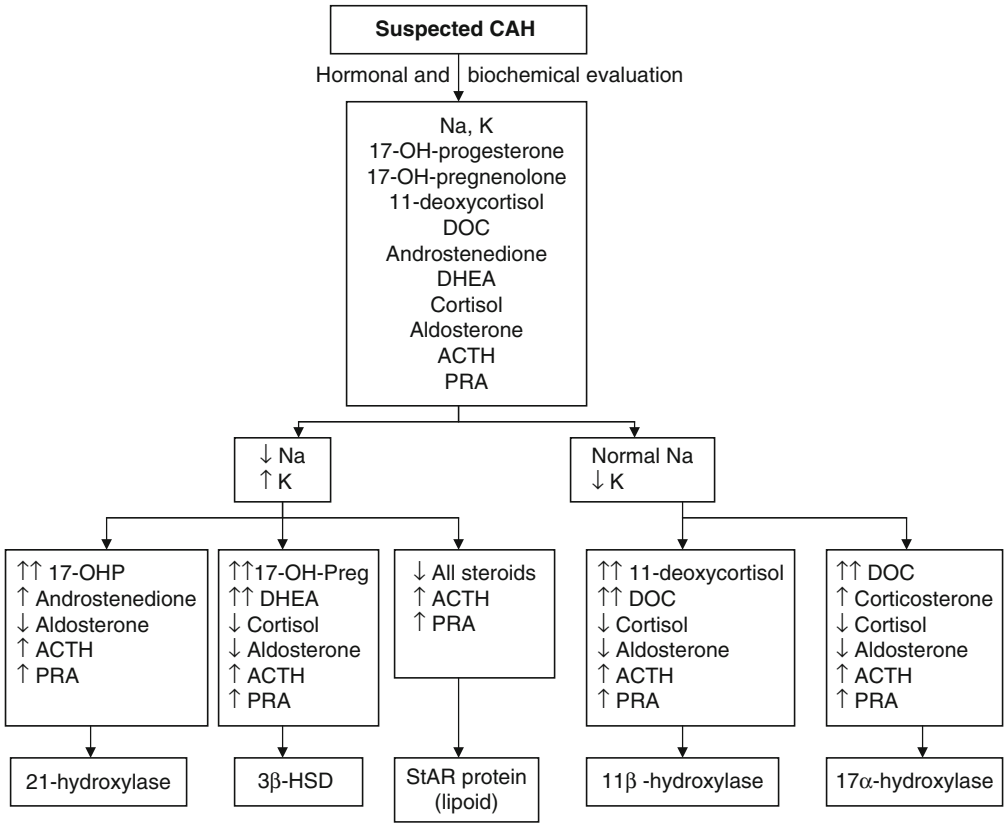

Figure 384.10

Approach to the Infant with Suspected Congenital Adrenal Hyperplasia. In genetic females (46XY) ambiguous genitalia (46,XX) is caused by 21-hydroxylase deficiency,11β-hydroxylase deficiency, and 3β-hydroxysteroid dehydrogenase deficiency. Ambiguous genitalia in genetic males (46, XY) is due to 3β-hydroxysteroid dehydrogenase deficiency and 17α-hydroxylase deficiency. Genetic males with lipoid congenital adrenal hyperplasia have a female phenotype

Children with simple virilizing disease, particularly males, are frequently not diagnosed until 3–7 year of age by which time skeletal maturation may have advanced by 5 year or more. If the bone age is 12 year or more, spontaneous gonadotropin-dependent puberty may supervene when treatment with glucocorticoids is instituted as suppression of adrenal androgen production brings about release of pituitary gonadotropins if appropriate hypothalamic maturation has occurred. Superimposed true precocious puberty may be treated with a gonadotropin hormone-releasing hormone analog such as leuprolide.

In males with inadequate corticosteroid therapy adrenal rest testicular tumors may develop, which usually regress with increased steroid dosage. Testicular MRI, ultrasonography, and color flow doppler may be helpful. Testis-sparing surgery for steroid-unresponsive tumors may be required.

Mineralocorticoid Replacement

Patients with salt-wasting disease (aldosterone deficiency) require mineralocorticoid replacement with fludrocortisone. Requirements of mineralocorticoids is higher in infancy in the first few months of life, usually 0.1–0.3 mg daily in two divided doses. Sodium supplementation (sodium chloride, 1–3 g) is often required. About 20 mg of hydrocortisone has a mineralocorticoid effect of 0.1 mg of 9α-fluorocortisol. Older infants and children are usually maintained with 0.05–0.1 mg daily of fludrocortisone. In some patients, simple virilizing disease may be easier to control with a low dose of fludrocortisone in addition to hydrocortisone even though these patients may have normal aldosterone levels. Presence of tachycardia and hypertension indicate overteatment. Serum electrolytes should be regularly monitored. Plasma renin activity helps determine adequacy of therapy. It should be maintained in or near the normal range but not suppressed.

To improve outcome additional approaches such as the use of an antiandrogen which inhibits aromatase (blocks conversion of androgens to estrogen), growth hormone with or without LHRH agonists, have been used. Adrenalectomy may be required for poorly controlled patients.

Family Education, Psychosocial Support and Genetic Counseling

As with all chronic diseases and intersex problems, family and patient (at a later age) education is extremely important. Early sex assignment is important. This is often a noncontroversial issue in this disorder. Parents and family members must understand that the disorder can be life threatening. Full implications of the diagnosis, life long optimal treatment, importance of periodic monitoring, stress management with adequate genetic counseling are all important aspects of management of these children. Chance of recurrence of this disorder is 25% with every pregnancy. Availability of antenatal diagnosis and prenatal treatment in specialized centers is explained. As they grow, full understanding of their condition must be explained to the patients. There are individuals and groups who are proponents of the patient's rights to decide about surgical procedures and suggest differing these to a later age. However, for CAH with 21-OH deficiency there is less controversy.

Surgical Management of Ambiguous Genitals

Moderate clitoromegaly often becomes less noticeable as the patient grows. In virilized females reduction clitotoplasty with partial excision of the corporal bodies and preservation of the neurovascular bundle may be undertaken between 3 and 6 months of age after discussion with parents. Vaginoplasty and correction of the urogenital sinus are usually performed at the same time which may need revision in adolescence. Confused psychosexual identity is not common in majority of cases where diagnosis and treatment is early.

In adolescent and adult females with poorly controlled 21-hydroxylase deficiency (hirsuitism, obesity, amenorrhea) bilateral laparoscopic adrenalectomy (with hormone replacement) may be superior to standard medical hormone replacement therapy.

Prenatal Diagnosis and Treatment

Prenatal diagnosis and therapy for 21-OHD in the female fetus to minimize the urogenital structural morbidity has been pursued for over past 2 decades but remains controversial. Fetal adrenal steroidogenesis begins early in gestation hence measurement of elevated 17-OHP in amniotic fluid during the second trimester has been used for antenatal diagnosis. Both, 17-OHP and $\Delta 4$ androstenedione are elevated in amniotic fluid in case of fetuses with severe salt wasting CAH. When parents are known heterozygotes, or if earlier child is affected, then HLA typing or DNA analysis of fetal amniocytes is used, if same HLA type as previous affected child is noted then fetus is affected; if one parent's HLA type is shared with index case then the fetus is heterozygous carrier and presence of both hapotypes differing from index case suggests unaffected fetus. Analysis of DNA obtained by chorionic villus sampling by 6–8 weeks to determine the sex and the genotype is very helpful in prenatal diagnosis in families with an affected child. Usually the CYP21 gene is analyzed for frequently occurring mutations, but closely linked, highly polymorphic microsatellite markers may be used if an affected child (i.e., the proband) is available for genetic comparison.

Early accurate diagnosis is essential prior to initiating prenatal treatment. In a female fetus with CAH if fetal adrenal steroidogenesis can be suppressed early (as soon as pregnancy is diagnosed) by 6–8 weeks by maternal administration of dexamethasone, virilization can be suppressed or eliminated. It is given in 2–3 divided doses of 20 ug/kg of maternal body weight (prior to pregnancy). Male fetus does not require prenatal treatment. No short term deleterious effects are observed in children exposed to this therapy. Hypertension in later life and neurotoxicity are noted in experiments on rats. Hence antenatal treatment is still considered experimental and recommended at few specialized centers. Maternal side effects of prenatal treatment have included edema, excessive weight gain, hypertension, glucose intolerance, cushingoid facial features, and severe striae.

Newborn Screening for 21-OHD

As 21-hydroxylase deficiency is the most common cause of CAH in the newborn (95% of all cases with CAH) and often remains undiagnosed in affected males who succumb to the disease early in life, screening has effectively prevented adrenal crisis in affected males. Many American states and other countries have instituted neonatal screening for the classical form of this disorder which are linked with existing neonatal screening programs. These programs analyze 17-hydroxyprogesterone (17-OHP) levels in dried blood obtained on filter paper cards by heel-stick, prick. Potentially affected infants are recalled for additional testing (electrolytes and repeat 17-OHP approximately by 2 weeks

of age by which time these infants may not yet be severely sick. To reliably detect all affected infants, the cut off 17-OHP levels for recalls are set very low resulting in a very high frequency of false-positive results. Effort is underway to set up universal standards. The predictive value is low, in premature infants. The nonclassical form of the disease is not reliably detected but that has little clinical significance. Genotyping for CYP21 might improve specificity but is not routinely available.

CAH due to 11B-Hydroxylase Deficiency

Etiology

Mutation in the CYP11B1 gene located on chromosome 8q24 causes deficiency of 11β-hydroxylase. As stated earlier CYP11B1 gene located on chromosome 8q24. CYP11B1 mediates 11-hydroxylation of 11-deoxycortisol to cortisol (*Fig. 384.1*). As 11-deoxycortisol is not converted to cortisol, levels of corticotrophin are high. In consequence, precursors – particularly 11-deoxycortisol and deoxycorticosterone – accumulate and are shunted into androgen biosynthesis (in the same manner as occurs in 21-hydroxylase deficiency). Patients are able to synthesize aldosterone normally as the adjacent CYP11B2 gene encoding aldosterone synthase is unaffected in this disorder.

Epidemiology

This disorder accounts for ~5% of cases of CAH; with a probable incidence of 1/250,000 to 1/100,000. More than 30 different mutations in CYP11B1 have been identified. It is more frequently seen in Israeli Jews of North African origin (1 in 15,000 – 17,000 live births); in this ethnic group almost all alleles carry an Arg448 to His (R448H) mutations. Affected patients present in a classical, severe form. Nonclassical milder form is rare.

Clinical Manifestations

It is unusual for these patients to manifest signs of adrenal insufficiency such as hypoglycemia or hypotension, hyponatremia, and hyperkalemia as aldosterone synthetic capacity is normal with some corticosterone being synthesized from progesterone by the intact aldosterone synthase enzyme although cortisol is not synthesized efficiently. Hypertension a consequence of elevated levels of deoxycorticosterone manifests in approximately two thirds of patients although this can take several years to develop. Interestingly, with institution of treatment with hydrocortisone, infants may transiently develop signs of mineralocorticoid deficiency. This is presumably due to sudden suppression of deoxycorticosterone secretion in a patient with atrophy of the zona glomerulosa caused by chronic suppression of renin activity. All signs and symptoms of androgen excess found in 21-hydroxylase deficiency also occur in 11-hydroxylase deficiency.

Laboratory Findings

Plasma levels of 11-deoxycortisol and deoxycorticosterone are elevated and because of deoxycorticosterone and metabolites, plasma renin activity is suppressed. Consequently, aldosterone levels are low even though the ability to synthesize aldosterone is intact. Hypokalemic alkalosis occasionally occurs.

Treatment

Hydrocortisone in doses similar to those used for 21-hydroxylase deficiency are used. Mineralocorticoid replacement is sometimes transiently required in infancy but is rarely necessary otherwise. Hypertension often resolves with glucocorticoid treatment but may require additional therapy if it is of long standing. Calcium channel blockers may be beneficial under these circumstances.

CAH due to 3β-Hydroxysteroid Dehydrogenase Deficiency

Etiology

This enzyme is required for conversion of Δ5 to Δ4 steroids (*Fig. 384.1*). Deficiency of this enzyme results in decreased synthesis of cortisol, aldosterone, and androstenedione but increased secretion of DHEA. The 3B-HSD enzyme expressed in the adrenal cortex and gonad is encoded by the HSD3β2 gene located on chromosome 1p13.1. 3β-HSD occurs in fewer than 2% of patients with CAH. Over 30 mutations in the HSD3B2 gene have been described in patients with 3β-HSD deficiency.

Clinical Manifestations

As cortisol and aldosterone are not synthesized in patients with the classical form of the disease, infants are prone to

salt-wasting crises. Lack of synthesis of androstenedione and testosterone leads to incomplete virilization in boys. Varying degrees of hypospadias may occur, with or without bifid scrotum or cryptorchidism. Postnatally, continued excessive DHEA secretion can cause precocious adrenarche. During adolescence and adulthood, hirsuitism, irregular menses, and polycystic ovarian disease can occur in females. Males manifest variable degrees of hypogonadism, although appropriate male secondary sexual development may occur. Girls are mildly virilized, with slight to moderate clitoral enlargement due to weak androgenic action of DHEA. High Δ5 to Δ4 steroid ratio in testicular effluent suggests persistent defect of 3β-HSD.

Laboratory Findings

Marked elevation of the Δ5 steroids (such as pregnenolone, 17-hydroxypregnenolone and DHEA) preceding the enzymatic block is indicative of this disorder. Elevated levels of 17-OHP may be noted because of the extra-adrenal 3B-HSD activity in peripheral tissues; these patients may be mistaken for patients with 21-hydroxylase deficiency. However, the ratio of 17-hydroxypregnenolone to 17-hydroxyprogesterone is markedly elevated in 3B-HSD deficiency, unlike the decreased ratio in 21-hydroxylase deficiency. Plasma renin activity is elevated in the salt-wasting form.

Differential Diagnosis

It has been suggested that children with premature adrenarche, or women with signs of androgen excess, with mild to moderate elevations in DHEA levels may have "nonclassical 3β-HSD deficiency." However, mutations in the HSD3β2 gene are often not found in such patients. Nonclassical form of this deficiency must actually be quite rare. The activity of 3β-HSD in the adrenal zona fasciculata and reticularis, relative to CYP17 (17-hydroxylase/17,20-lyase) activity, normally decreases during adrenarche to facilitate DHEA synthesis, and so modest elevations in DHEA in pre-teenage children or women usually represent a normal variant.

Treatment

Patients require glucocorticoids and mineralocorticoid replacement with hydrocortisone and fludrocortisone, respectively, as in 21-hydroxylase deficiency. Incompletely virilized genetic males in whom a male sex of rearing is contemplated may benefit from several injections of a depot form of testosterone early in infancy to increase the size of the phallus. They may also require testosterone replacement at puberty.

Lesions in Isozymes of P450c11

Corticosterone Methyloxidase Deficiencies

These deficiencies are uncommon. There are two distinct forms of 11-hydroxylase, P450c11β mediates the 11β-hydroxylation of 11-deoxycortisol to cortisol and that of DOC to corticosterone in the zonae fasciculata and reticularis. P450c11AS, or aldosterone synthase, is found only in the zona glomerulosa and mediates 11β-hydroxylation, 18-hydroxylation, and 18-oxidation; thus, it is the sole enzyme required to convert DOC to aldosterone.

P450c11AS, the isozyme of P450c11β is 93% identical in its amino acid sequence, is expressed exclusively in the zona glomerulosa, where it catalyzes 11β-hydroxylase, 18-hydroxylase, and 18-methyloxidase activities. Disorders of P450c11AS cause the so-called corticosterone methyloxidase (CMO) deficiencies, wherein aldosterone biosynthesis is impaired, while the zona fasciculata and reticularis continue to produce corticosterone and DOC. The absence of aldosterone biosynthesis will generally result in a salt-wasting crisis in infancy. These infants typically present with hyponatremia, hyperkalemia, and metabolic acidosis, but the salt-wasting syndrome is less severe than with 21-OHD or lipoid CAH because of the persistent secretion of DOC. Spontaneous recovery may occur with age, due to increasing sensitivity to mineralocorticoid action with advancing age. Hence, PRA is markedly elevated in affected children, it is usually normal in affected adults.

CMO type I deficiency is the result of loss of 450c11AS activity so that no 18-hydroxylase or 18-methyloxidase activity is present. CMO type II deficiency results from amino acid replacement mutations in P450c11AS that selectively delete the 18-methyloxidase activity while preserving the 18-hydroxylase activity. The distinction between CMO types I and II is not always clear.

Adrenocortical Hyper Function

Pediatric Cushing syndrome (CS) is an uncommon disorder and poses challenge in diagnosis and management. It

Table 384.4
Classification of Cushing syndrome

ACTH dependent CS	ACTH independent CS
Cushing disease (ACTH secreting pituitary adenoma)	Exogenous glucocorticoid administration
Ectopic ACTH syndrome	Adrenocortical tumors (adenoma/carcinoma)
Iatrogenic (treatment with ACTH)	Primary adrenocortical hyperplasia
	Primary pigmented nodular adrenocortical disease (PPNAD)
	Macronodular adrenal hyperplasia (AIMAH)
	McCune–Albright syndrome (MAS)

is the result of high circulating levels of glucocorticoids, either produced endogenously or administered exogenously. There is usually a delay in suspecting the diagnosis which leads to high morbidity and mortality. This disorder is best understood as ACTH dependent and ACTH independent CS. (*Table 384.4*).

Etiology

Commonest cause of hypercortisolism in children is exogenous glucocorticoid administration. Glucocorticoids are used for multiple disorders and resultant clinical picture rarely poses diagnostic dilemma. It is associated with side effects of long term glucocorticoids use namely retardation of linear growth, hyperglycemia, hypertension and osteoporosis, which needs to be addressed as a management issue.

ACTH Dependent CS

Cushing Disease (ACTH Secreting Pituitary Adenoma)

The commonest cause of endogenous Cushing syndrome in children >7 year of age is Cushing disease i.e., ACTH secreting pituitary adenomas. These adenomas are usually micro adenomas (<1 cm in diameter) and frequently show positive immunostaining for ACTH and its precursor, pro-opiomelanocortin (POMC).

Ectopic ACTH Syndrome

Ectopic ACTH secretion, accounting for 15% of CS in adults, is a rarity in children. Bronchial and thymic carcinoids and neuroendocrine tumours of pancreas predominate as etiological factors. There are case reports of association of CS with islet cell carcinoma of the pancreas, neuroblastoma, ganglioneuroblastoma, hemangiopericytoma, and Wilms tumor. Clinical manifestation of hypercortisolism may be masked by that of the underlying disorder. However in cases of bronchial carcinoids clinical picture may mimic that of CD.

ACTH Independent CS

In infants and younger children, endogenous hypercortisolism is most often caused by a functioning adrenocortical tumor, usually a carcinoma, McCune-Albright syndrome or PPNAD.

Adrenocortical Tumors

Adrenocortical Carcinoma (ACC) as a cause of CS occurs in younger individuals unlike adrenocortical adenomas in older patients. ACC is a rare malignancy with heterogeneous presentation and generally poor prognosis. Exceptionally high incidence of ACC is known to occur in southern Brazil (4.2 per million vs. 0.3 per million) related to p53 tumor suppressor gene mutation. ACC is further described under section on adrenal carcinoma.

PPNAD

PPNAD is a rare but important cause of pediatric CS. It is associated with Carney Complex, with autosomal dominant inheritance, though sporadic mutation can occur. It typically occurs in adolescence or early adulthood. The adrenal lesion shows multiple, small, pigmented, adrenocortical nodules surrounded by cortical atrophy. Diagnosis of this disorder may be difficult as it can be cyclical in nature. Apart from management of CS, patient requires

lifelong monitoring to detect associated serious lesions of Carney complex like cardiac myxoma, pituitary and testicular tumours. Germ line mutations of regulatory sub unit of R1A of protein kinase A (PRKAR1A) are present in 45% of patients and gene for the same is mapped to chromosome 17q 22–24.

McCune-Albright Syndrome

McCune-Albright syndrome as a cause of CS presents early in infancy. It is due to activating mutation of GNAS1 gene. Adrenal involvement results in constitutive steroidogenesis in adrenal nodules. Associated involvement with activating mutations may occur in gonads, thyroid, pituitary and bones. Clinical picture is determined by underlying organ involvement.

Clinical Findings

There is a large spectrum of manifestations from subclinical to overt syndrome depending on duration and intensity of excess steroid production. Distinct catabolic manifestation of hypercortisolism like fatigue, purplish striae, easy bruisabilty, proximal muscle wasting, weakness, osteoporosis and pathological fractures, are late manifestations in childhood cushing as compared to adults. Also the centripetal distribution of fat is not that marked in children. Childhood Cushing almost invariably has generalized obesity and growth retardation. The obvious dissociation between height and weight on the growth chart may be the first indication and is also specific sign of glucocorticoid excess state. Weight gain is accompanied by mooning of face and plethora. *Figure 384.11* shows classical appearance of a child with CS.

Varied degree of androgenisation in form of hirsutism, acne, and isosexual precocity, can be present. Delayed puberty, oligomenorrhoea, polycystic ovaries are other manifestations of gonadotropin axis involvement. Minerocorticoid excess due to spillover effect of excess glucocorticoid may manifest as hypokalemia, and hypertension. Cushing syndrome should be borne in mind as differential when evaluating for hypertension in a child. Other renal manifestations include microalbuminuria, glycosuria, hypercalciuria and renal calculi.

ACTH dependent cushing has generalized hyperpigmentation, more marked over the pressure areas. This may confused with acanthosis nigricans which is a marker of insulin resistance and can coexist. Glucose intolerance and insulin resistance is common in CS.

The common psychological symptoms range from emotional lability, agitated depression, panic attacks, and mild paranoia to mania. Obsessive compulsive behavior is specifically associated with childhood hypercortisolism. Learning, cognition and memory may be impaired in the diseased child. Loss of diurnal rhythm of cortisol may lead to insomnia.

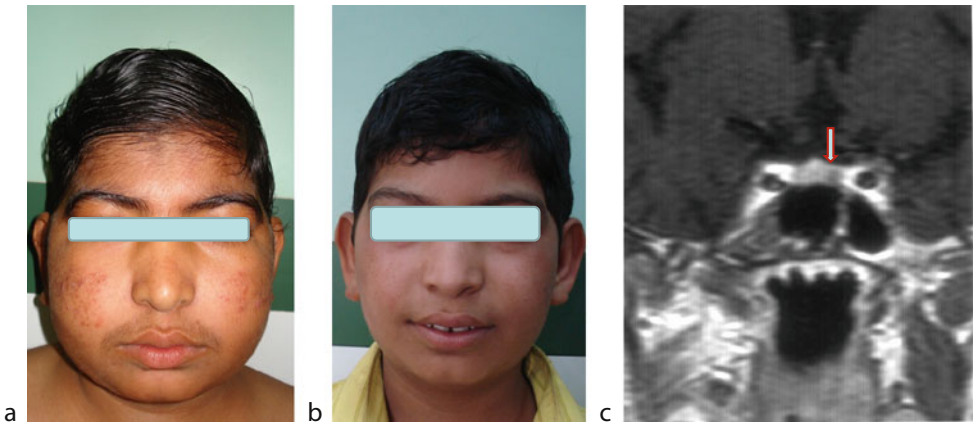

Figure 384.11
(a, b, c) Classical fascial appearance of a patient with Cushing syndrome. Thirteen-year-old boy presented with facial swelling, weight gain, abdominal striae, hyperpigmentation and growth failure. ACTH driven endogenous hypercortisolism was proven with midnight serum cortisol: 14.78 μg/dL and plasma ACTH of 112.6 pg/mL. Dynamic contrast MRI showed a pituitary microadenoma, which was excised by transsphenoidal route. There was marked reduction in cushingoid features at 3 months post surgery with basal cortisol of 2.3 μg/dL, suggestive of cure

The spectrum of clinical manifestations, at any given level of hypercortisolism varies. Progressive features and appearance of new signs increase the probability of syndrome. Duration of symptoms in all patients' ranges from 2 months to few years as diagnoses is often not suspected. Though there is clear female preponderance in adult Cushing, in children such preponderance may not exist.

Diagnosis of Cushing Syndrome

Investigations in a suspected case of hypercortisolism are done in 2 phases. Tests to establish endogenous hypercortisolism are followed by tests to localize source of endogenous hypercortisolism.

Test for Establishing Endogenous Hypercortisolism

It is very important to rule out exogenous glucocorticoid intake, before beginning any test to establish hypercortisolism. History of chronic steroid intake and suppressed basal cortisol is suggestive of suppressed hypothalmo pituitary adrenal axis secondary to exogenous steroid intake. Initial tests to prove endogenous hypercortisolism are 24 h Urinary free cortisol(UFC), late night salivary or serum cortisol, and over night or standard 2 days low dose dexamethasone suppression tests (LDDS).

In this setting goal, is to choose tests with high sensitivity. Conditions associated with hypercortisolism in absence of CS like morbid obesity, physical or mental stress, depression, and CBG excess states can give false positive results on initial screening tests. Another basic principle applied in interpreting the test is that increasing the diagnostic cut-off point, increases its specificity at the cost of reduced sensitivity.

UFC

Twenty-four hour urinary cortisol excretion is an integrated measure of the serum free cortisol concentration. Sensitivity of this test is close to 90% when upper limit of normal is used as diagnostic criteria. It needs to be ensured the collection is complete and state of high fluid intake is avoided. False negative results can occur in mild Cushing disease. One can be confident of the diagnosis in patients in whom measures of integrated cortisol production are unequivocally increased (threefold above the upper limit of normal for the assay). The cut off value for normal UFC excretion is suggested to be <72 μg (198.7 nmol)/m^2/day.

Cortisol Circadian Rhythm

Late night salivary cortisol: The most validated assays used are ELISA and LCMS. Using these two methods normal subjects will have salivary cortisol (midnight) less than 1.4 ng/mL. Various studies have reported its sensitivity as 92–100% and specificity as 93–100%. Obtaining two separate samples increases the diagnostic yield of the test. Confounding factors like oral gels with steroids, brushing of teeth, smoking at least 2 h prior etc. must be meticulously avoided. If salivary cortisol estimation is used as the test, it is important to choose a laboratory that provides a validated response range, because cortisol measurements of the same sample using different assay techniques may yield different results.

Midnight serum cortisol: Sleeping mid night sleeping cortisol >1.8 μg/dL has high sensitivity (100%). Specificity however is poor as shown in recent larges series at 20%. In patient with high clinical index of suspicion but with normal UFC and LDDS, a midnight cortisol >1.8 μg% increases the probability of Cushing syndrome. While obtaining sleeping sample it is essential to draw blood within 5 min of awakening, preferably through an indwelling catheter. Awake midnight serum cortisol cut off value used is >7.5 μg/dL for diagnosis of Cushing syndrome.

Dexamethasone Suppression Tests

Overnight 1 mg dexamethasone suppression test (ODS) consists of administration of 1.0 mg of dexamethasone at 11 PM, and measurement of serum cortisol at 8 AM the next morning. There is lack of data to interpret the performance of this test in childhood. However in adult population, at cut of 1.8 μg/dL, it gives sensitivity of 95% and specificity of 80%. Based on its greater specificity, Low dose 48 h dexamethasone suppression test is preferred, but is more cumbersome than the overnight test. In pediatric patients with weight >40 kgs, the dose of dexamethasone is 0.5 mg 6 h for 48 h. Patients with weight <40 kgs, need 30 μg/kg/day in four divided doses. Serum cortisol is measured at baseline and 6 h after the last dose of dexamethasone. *Figure 384.12* describes approach to a suspected case of CS.

In patients with high pretest probability and initial negative screening tests, further assessment preferably by an experienced person is a must. In other patients with normal test results, unless clinical signs and symptoms progress, further testing is not needed. If one of the tests is positive, further assessment for confirmation and localization are warranted.

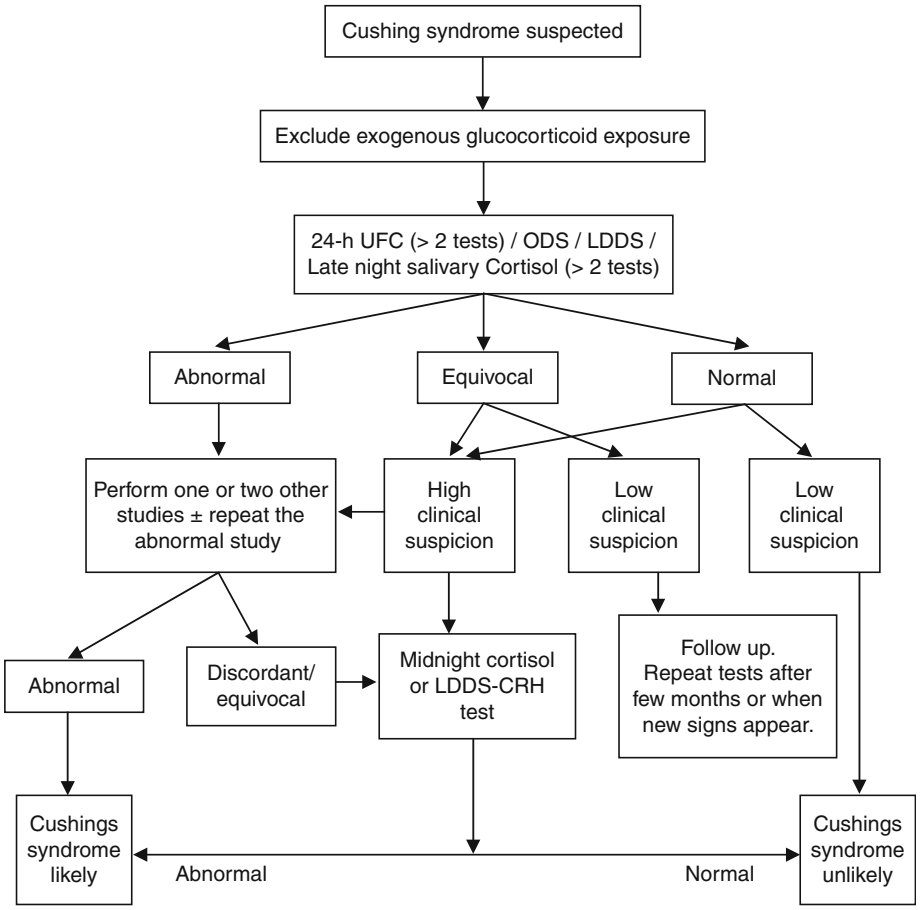

Figure 384.12

Algorithm for Investigating Patients Suspected Of Having Cushing syndrome. Interpretation of all the tests must be combined with the clinical picture. Experience is necessary to adopt the correct test and interpret the results

Localization of the Cause of Cushing Syndrome

Basal ACTH

Having confirmed the presence of Cushing syndrome, ACTH-dependent or ACTH-independent disease needs to be established. This can be done by measuring basal plasma ACTH. ACTH using immunometric assay is a useful parameter for diagnosis of adrenal Cushing syndrome, in a manner similar to suppressed TSH in Graves disease. Suppressed basal ACTH (<5 μg) is highly suggestive of ACTH independent nature of the disease. ACTH levels >15 pg/mL suggest ACTH dependent disease. Levels between 5 and 15 pg/mL are inconclusive and may need to be repeated.

Adrenal Imaging

A low plasma ACTH concentration <5 pg/mL (1.1 pmol/L) is an evidence of ACTH-independent disease and needs adrenal imaging. Most adrenal tumors are visible on MRI scan. In PPNAD, adrenals are normal in size, mostly with distinct small (<6 mm) nodules which may not be visible on the scan. Another peculiar characteristic of PPNAD is the paradoxical rise in cortisol value after dexamethasone suppression test which was classically described by Liddle. Patients with McCune-Albright syndrome may have normal adrenal glands or an adenoma. Presence of associated findings like skin pigmentation, fibrous dysplasia, hyper functioning states of thyroid/pituitary/gonads help to achieve diagnosis.

Pituitary Imaging

Plasma ACTH value >15 pg/mL (4.4 pmol/L) indicate that cortisol secretion is ACTH-dependent. Vast majority of them are likely to have corticotroph secreting adenoma. Dynamic contrast MR pituitary is the next test to be performed. The reported sensitivity of contrast MRI with spoiled gradient sequences is up to 64%. In patients with microadenoma >6 mm, the diagnosis of pituitary corticotroph adenoma can be confirmed and patients can be subjected to surgery.

Bilateral Inferior Petrosal Sinus Sampling

Failure to localize a pituitary adenoma in patients with ACTH dependent CS will necessitate invasive test like inferior petrosal sinus sampling. CRH stimulated bilateral simultaneous inferior petrosal sinus sampling is the only test which fares better than the pretest probability of lesion being in pituitary (98% vs. 85–90%). A central-to-peripheral plasma ACTH gradient of ≥2.0 before CRH administration, or ≥3.0 after CRH, is diagnostic of a pituitary source of ACTH. False negative results could be due to poor catheter placement or anomalous or asymmetric venous drainage. Lateralization of tumor is possible in up to 70% as reported in various studies. *Figure 384.13* describes an approach to localization in a proven case of endogenous hypercortisolism.

Management of Cushing Syndrome

Transsphenoidal surgery (TSS) is the preferred mode of treatment for Cushing disease. Prior to the Surgery, blood

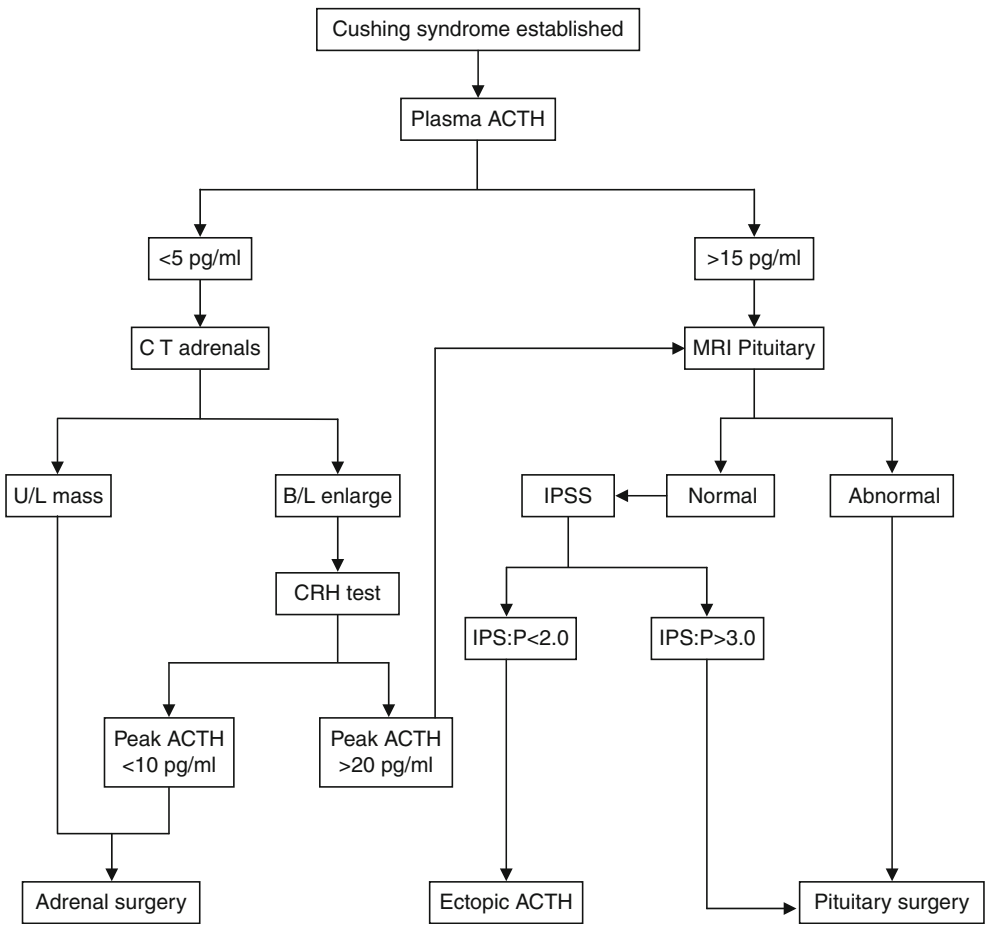

Figure 384.13

Flow chart showing approach to a patient with proven endogenous hypercortisolism. The flow chart is applied only after the state of endogenous hypercortisolism is proven. Unit with experience in IPSS may be necessary to undertake accurate localization. Correct localization is the key to success in management of patients with Cushing syndrome

pressure, plasma glucose and potassium should be stabilized and chest physiotherapy instituted to ensure early recovery in post operative period. Inhibitors of adrenal steroidogenesis (metyrapone, ketoconazole, aminoglutethimide) have been used in severe cases preoperatively to normalize circulating cortisol levels and reduce perioperative morbidity and mortality. TSS in the experienced hand results in cure rate of 80–90% with risk of mortality being, <1%. Post operative serum cortisol values of <2 μg/dL defines cure. Delayed cure up to 6–12 weeks after TSS is documented; hence additional therapeutic measures should be adopted only after documenting persistent hypercortisolism. Recurrences are treated with re-operation, pituitary irradiation, or bilateral adrenalectomy. If surgery is unsuccessful, radiotherapy is effective second line management, with majority of childhood cases achieving remission within a year. Long term risks of radiation are cognitive impairment, panhypopituitarism, increased prevalence of cerebrovascular accidents, and rarely development of secondary tumors. Adrenalectomy may lead to increased ACTH secretion by an unresected pituitary adenoma, evidenced mainly by marked hyper pigmentation; this condition is termed Nelson syndrome. Lower age at the time of adrenalectomy is an important predictive factor for the development of Nelson syndrome; hence caution needs to be observed before offering bilateral adrenalectomy as treatment option in childhood CD. Centrally acting agents like D2 receptor agonist, cabergoline and new somatostatin analog, SOM230 (paseriotide) have shown promising outcomes in recent studies. Bilateral adrenalectomy is also done in cases where ectopic ACTH secreting tumour is non localizable. Benign cortical adenomas are treated with unilateral adrenalectomy. In primary adenal hyperplasia (PPNAD, McCune-Albright syndrome or MAH) the treatment option is bilateral adrenalectomy with lifelong steroid replacement.

Even after cure is achieved, patients with CS need long term follow up, considering the fact that risk of recurrence is high and is related to length of follow up. Linear growth retardation remains a concern and it stems from continuing growth hormone deficiency with or without combined gonadotropin deficiency resulting from TSS and radiotherapy. Institution of GH therapy is warranted in patients who fail to catch up and are proven to have GH deficiency state. In addition obesity with increased risk of metabolic syndrome necessitate appropriate ongoing monitoring. Osteoporosis though uncommon in childhood CS, needs to be evaluated and treated if necessary.

Primary Aldosteronism

Primary aldosteronism (PA) comprises of group of disorders where aldosterone formation is inappropriately high, and relatively independent of the renin-angiotensin system (RAS) (see *Table 384.5*). This condition needs to be recognized as it has higher cardiovascular morbidity and mortality than the same degree of essential hypertension. Hypertension needs distinct treatment and could be even cured in many.

Table 384.5
Classification of mineralocorticoid excess states

Primary aldosteronism	Deoxycorticosterone excess
Aldosterone-producing adenoma	Congenital adrenal hyperplasia
Bilateral idiopathic hyperaldosteronism	11 β-Hydroxylase deficiency
Unilateral adrenal hyperplasia	17 α-Hydroxylase deficiency
Bilateral macronodular adrenal hyperplasia	Tumor
Familial hyperaldosteronism type I and type II	Glucocorticoid resistance syndrome
Aldosterone-producing adrenocortical carcinomas	Apparent mineralocorticoid excess (AME) state
Ectopic aldosterone-secreting tumors (e.g., neoplasms of the ovary, kidney)	Genetic
	Type 1 AME
	Type 2 AME
	Acquired
	Licorice ingestion
	Cushing syndrome

Epidemiology

The prevalence data of this rare disorder in children is not known. In adults it was earlier reported to occur in <1% of patients with mild to moderate hypertension. Hypokalemia was considered to be *sine qua non* for diagnosis. However PA is found to be causative factor in up to 10% of hypertensive adults in cross sectional and prospective studies.

Clinical Manifestations

It may be asymptomatic, as revealed on evaluation of incidentally detected high blood pressure or adrenal mass lesion. Hypertension and hypokalemia are the two major clinical findings, but normokalemic hypertension constitutes the most common presentation of the disease, with hypokalemia probably present in only the more severe cases.

Aldosterone excess leads to sodium retention, mild volume expansion, and hypertension. A steady state is reestablished due to pressure natriuresis and lack of edema is characteristic of this entity. Urinary potassium loss leads to metabolic alkalosis and hypokalemia which may be asymptomatic or manifests as polyuria, muscle weakness, intermittent paralysis and failure to thrive. Excessive secretion of aldosterone is associated with an increased risk of cardiovascular disease and morbidity, including left ventricular hypertrophy, myocardial infarction and stroke.

Laboratory Investigations

Case detection of PA is recommended in patients with moderate, severe, or resistant hypertension, hypertension with spontaneous or diuretic-induced hypokalemia, adrenal incidentaloma, or a family history of early-onset hypertension or cerebrovascular accident at a young age (<40 year). Family screening for hypertension and further evaluation is warranted in diagnosed case of primary aldosteronism.

Hypokalemia, metabolic alkalosis, mildly elevated sodium may be found. Serum calcium concentration is usually normal. Ratio of plasma aldosterone to plasma rennin activity (PAC/PRA) is the initial screening test. Drugs that affect RAS should be avoided for several weeks prior to testing. These include aldosterone antagonists, diuretics, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, clonidine and nonsteroidal anti-inflammatory agents. If required α-adrenergic blockers or calcium channel blockers can be used. Patient should be ambulatory for 2 h and made to sit for 15 min prior to blood collection. PAC/PRA (ng/dL per ng/mL/h) of >30 and PAC >15 ng/dL are highly suggestive of the diagnosis. Further to confirm the aldosterone secretion is inappropriately high either of the following tests need to be performed; oral sodium loading, saline infusion, fludrocortisone suppression, or captopril challenge test.

Imaging

CT scan may pick up single discriminatory lesion; however it has limitation in differentiating aldosterone producing adenoma (APA) from hyperplasia and lateralizing the disease. CT scan is particularly useful in ruling out adrenal carcinoma, that may be responsible for mineralocorticoid excess state, which is usually more than 4 cm in size. Occasionally they may be smaller where CT characteristics of malignancy help to identify them. In patients where surgical treatment is desired by the family the distinction between unilateral and bilateral disease is achieved by adrenal venous sampling.

Figure 384.14 shows an approach to suspected patient of PA.

Differential Diagnosis

Primary aldosteronism should be distinguished from familial forms of PA; Familial Hyperaldosteronism (FH) type I, [glucocorticoid-remediable hyperaldosteronism (GRA)], which is specifically treated with glucocorticoids and FH type II. An autosomal dominant pattern of inheritance should raise suspicion for the familial forms of PA. GRA is usually associated with bilateral adrenal hyperplasia accounting for <1% of cases of primary aldosteronism. The mutation in patients with GRA is fusion of the promoter region of the gene for CYP11B1 and the coding sequences of CYP11B2, resulting in ACTH-dependent activation of the aldosterone synthase effect on cortisol, corticosterone, and cortisol precursors. Unlike FH-I, FH-II, does not suppress with dexamethasone, and GRA mutation testing is negative. The molecular basis for FH-II is unclear, although several linkage analyses have shown an association with chromosomal region 7p22.

Glucocorticoid-remediable hyperaldosteronism is diagnosed by specific genetic testing rather than measurements of urinary levels of 18-hydroxycortisol, 18-oxocortisol or

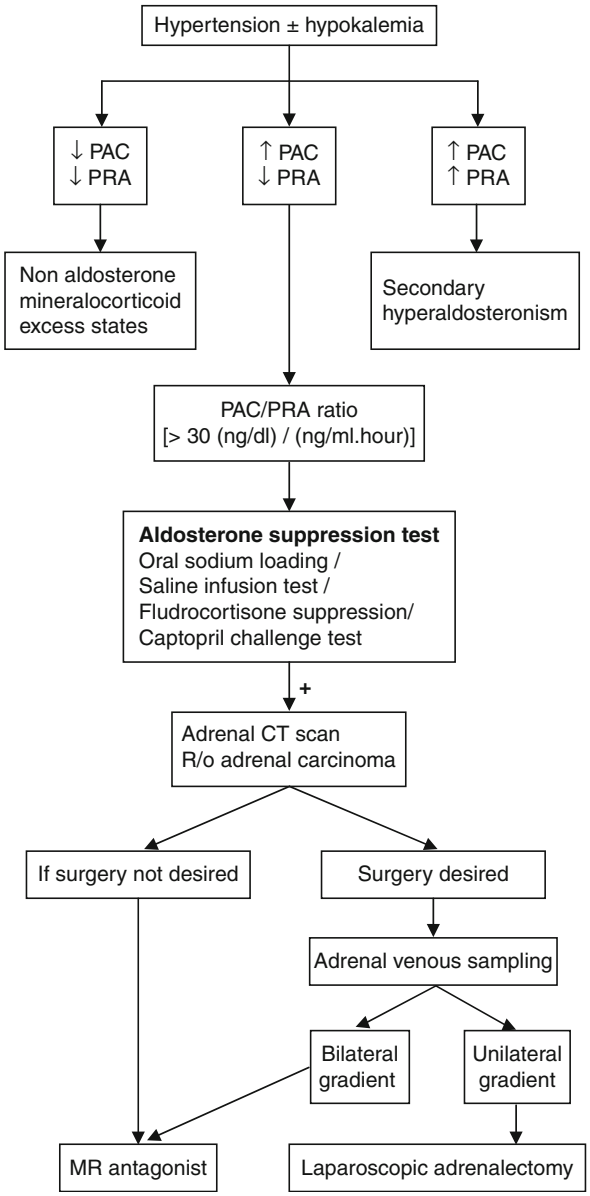

Figure 384.14
Approach to a child with hypertension and/or hypokalemia suspected to have mineralocorticoid excess state

performance of dexamethasone suppression test which may be misleading. Genetic testing to rule out GRA is indicated in patients with confirmed PA and family history of PA, strokes at young age, or onset of HT below 20 years of age. More generally, primary aldosteronism should be distinguished from other forms of hypertension by means of the testing previously discussed.

Treatment

Treatment aims beyond normalization of the serum potassium, blood pressure, and is targeted towards reversal of the effects of hyperaldosteronism on the heart.

For unilateral aldosterone hyper secretion (e.g., adrenal adenoma or unilateral adrenal hyperplasia), laparoscopic adrenalectomy is the treatment of choice. Patients with bilateral adrenal hyperplasia or confirmed unilateral adrenal aldosterone hyper secretion, not desiring surgery, mineralocorticoid receptor antagonist are first line drug treatment as they additionally act on the mineralocorticoid receptors on the heart. Spironolactone is the preferred drug, and can be replaced by eplerenone if side effects particularly anti androgenic effects are limiting factor.

Adrenocortical Carcinoma

Epidemiology

Adrenocortical carcinomas (ACC) are rare malignancy; with overall incidence of 1–2/million population per year and 0.3/million children/year. Children in Southern Brazil have the highest reported annual incidence of ACC (3.4–4.2/million). Girls are more often affected than boys. The age distribution is bimodal with a first peak before the age of five and a second higher peak in the 4th and 5th decade.

Molecular Basis of ACC

Although most cases of ACC appear to be sporadic with mutation in p53 tumor suppressor gene, some have been described as a component of several hereditary cancer syndromes: Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, and Multiple Endocrine Neoplasia type 1. Two hit theory with evolution of adrenal adenoma to carcinoma is unclear at present. Mutation at 11p15 locus with IGF-II acting via IGF-I receptor leading to adrenal cancer cell proliferation has been shown in vitro.

Clinical Manifestations

In children ACCs are usually hormone-secreting (90%). They may present with virilization alone (50–80%), or a mixed Cushing and virilization syndrome (20–40%),

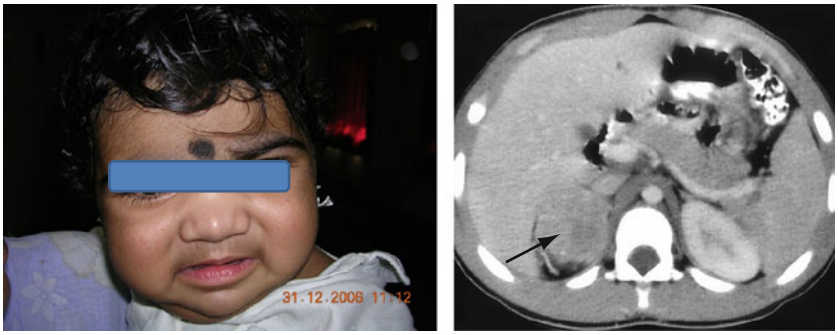

Figure 384.15
Clinical picture of a child with adreno cortical carcinoma and CT scan showing right adrenal mass. This 3 years 4 months old child presented with rapid weight gain and onset of pubic hair development. Examination revealed facial mooning, plethora, and acne with mild hirsuitism observed on the upper lip. She had pubic hair (stage 3) and clitoromegaly. CT scan showed a large lesion on right side suggestive of right adrenal carcinoma

while isolated glucocorticoid excess (Cushing syndrome) is much less common (<5%). Rapidly progressing Cushing syndrome (CS) with or without virilization is a frequent presentation. Androgen secretion in girls can present as virilization with acne, clitoromegaly, growth spurt and premature adrenarche. *Figure 384.15* shows typical facial appearance and CT scan of young child with ACC. In boys virilization presents with acne, muscle development, premature development of pubic, axillary and facial hair. Hypertension (HT) with marked hypokalemia is present in aldosterone secreting ACC. However HT with hypokalemia more often occurs due to cortisol excess state with apparent mineralocorticoid excess state leading to overwhelming of 11 β-hydroxysteroid dehydrogenase type 2 activity. Occasionally patient can present with fever, vomiting, anorexia, weight loss as presentation with very few symptoms/signs of hormone excess state. Feminizing adrenocortical tumors presenting as gynecomastia in males or premature thelarche in girls are reported due to high levels of aromatase activity found in these tumors.

Laboratory Findings and Imaging

Hormonal work up to prove hypercortisolism, increase in sex steroids or its precursors and mineralocorticoid excess state are required. Urinary 17-ketosteroids and serum dehydroepiandrosterone (DHEA), DHEA sulfate, androstenedione and testosterone are usually elevated. Additionally 17 β estradiol (boys), tests for hypercortisolism and hyperaldosteronism are required. Hormonal secretory pattern may point to malignant potential of the tumour. High concentration of DHEAS, estradiol in boys and sex steroid precursors are suggestive of malignant potential and would help to select laprotomy against minimal access surgery. Biochemical exclusion of pheochromocytoma is advisable because imaging modalities cannot reliably differentiate between ACC and pheochromocytoma. ACC are usually more than 4 cm in diameter when discovered. CT scan with delayed contrast wash out studies and MRI with chemical shift technique are equally effective in distinguishing malignant from benign lesions. PET scanning with fluorodeoxyglucose is of value for identifying unilateral adrenal tumors with a higher index of suspicion for malignancy.

Treatment

Initial treatment in patients with potentially resectable disease, is complete surgical resection of the tumour. Even after complete resection of the tumour cure may not be achieved, presumably because occult micrometastases are present at the time of initial presentation. Mitotane is an adrenocorticolytic drug that has been used for primary therapy, in the adjuvant setting, and for the treatment of disease recurrence, either alone, or in combination with other cytotoxic agents (etoposide, doxorubicin and cisplatin). Long term prognosis is dismal, but the disease is less aggressive in children as compared to adults. Prognosis depends upon the size, resectibility, and residual and distant metastasis.

ACC has variable clinical presentation and biological behavior. Progress in better understanding of molecular basis of ACC will allow prediction of response to various

therapeutic agents as well as development of newer modalities of treatment.

Adrenal Incidentaloma

An adrenal incidentaloma is a mass lesion >1 cm in diameter, serendipitously discovered by radiologic examination carried out for indications other than evaluation of adrenal disorder. Reported frequency in adults varies from 4–6% as shown in autopsy and imaging data. The differential diagnosis includes adrenal cyst, haematoma, myelolipoma, adrenal adenoma, adrenocortical carcinoma, pheochromocytoma and metastasis from extra adrenal sources. Commonest cause is benign adrenal adenoma. Diagnostic approach consists of defining hormonal secretory status of the tumor and delineation of its imaging characteristics. Imaging phenotype of the mass may help determine whether the tumor is benign or malignant. Adrenocortical carcinomas are significantly associated with mass size, with 90% being more than 4 cm in diameter when discovered. In the report from the National Italian Study Group, a 4-cm cutoff had a 93% sensitivity of detecting adrenocortical carcinoma; even though specificity was limited (76% of masses larger than 4 cm in diameter were benign). All patients with adrenal incidentalomas should be evaluated for the possibility of subclinical hormonal hyperfunction and cancer. A thorough history and physical examination are important in the initial assessment. Endocrine assessment should be performed to document glucocorticoid, mineralocorticoid, androgen or catecholamine excess state. A homogeneous adrenal mass <4 cm in diameter, with a smooth border, and an attenuation value <10 HU on unenhanced CT, and rapid contrast medium washout (e.g., >50% at 10 min) is very likely to be a benign cortical adenoma. The imaging characteristics that suggest adrenal carcinoma or metastases include: irregular shape, inhomogeneous density, high unenhanced CT attenuation values (>20 HU), delayed contrast medium washout (e.g., <50% at 10 min), diameter >4 cm, and tumor calcification. Fine needle aspiration may be useful to rule out inflammatory or metastatic lesion. Excess catecholamine secretory state must be ruled out before undertaking FNAC as hypertensive crisis is reported in unsuspected cases of pheochromocytoma. Hormonally active tumors, tumors with characteristics of malignancy and lesions > 4 cm in size are recommended to be excised surgically. Smaller lesions which are hormonally inactive are recommended to be followed up at periodic interval for any emerging characteristics like increase in size or manifestations of hormonal secretion where appropriate investigations may be carried out followed by suitable therapeutic intervention.

Pheochromocytoma

Pheochromocytoma is a tumor that arises from the catecholamine producing chromaffin cells in the adrenal medulla. It is defined as an intra-adrenal paraganglioma by World Health Organization in 2004. Closely related tumors that arise from extra-adrenal sympathetic and parasympathetic ganglia are classified as extra-adrenal paragangliomas. Intra-adrenal and extra-adrenal sympathetic paragangliomas commonly secrete catecholamine, whereas parasympathetic paragangliomas are usually nonfunctional. Sympathetic paragangliomas are most commonly found in the abdomen (para-aortic and peri-adrenal), pelvis and rarely in thorax, whereas parasympathetic paragangliomas are most commonly found in head and neck.

With advances in molecular genetics, germ line mutations have been identified in up to 59% and 70% of apparently sporadic pheochromocytomas presenting before 18 and 10 years of age respectively. Pheochromocytomas in children are malignant in 1/4th, bilateral in 1/3rd, familial in 1/5th and extra-adrenal in 1/5th of cases.

Pheochromocytomas account for approximately 1% of hypertensive cases in children. Although pheochromocytoma is rare, it is the most common pediatric endocrine tumor. Estimated incidence of benign pheochromocytoma in children is 0.11 per million children, whereas it is 0.02 per million children for malignant pheochromocytomas.

Etiology

None of the etiologic factors that are implicated in the development of pheochromocytoma are known, except the genetic ones. However, the exact mechanisms leading to the initiation of pheochromocytoma development in patients with genetic mutations are still not fully elucidated. Most genetic mutations associated with pheochromocytoma are inherited as autosomal dominant traits. VHL gene, located on chromosome 3p25-26 is the most commonly mutated gene in children presenting with a pheochromocytoma. Other commonly mutated genes include the RET proto-oncogene located on chromosome 10q11.2 predisposing to multiple endocrine neoplasia type 2 (MEN2) or the NF1 gene located on 17q11.2

predisposing to neurofibromatosis 1 and genes coding the subunits B and D of succinate dehydrogenase (SDHD and SDHB) located on chromosome 11q23 and 1p35-36.1, predisposing to hereditary paraganglioma syndromes 1 and 2 respectively. Pheochromocytomas are very rarely associated with succinate dehydrogenase C (SDHC) mutations, tuberous sclerosis, Sturge-Weber syndrome and ataxia telangiectasia. SDHB mutation is associated with increased risk of malignancy where as extra-adrenal location is common in SDHD, SDHB and VHL mutations.

Histopathology

Histopathological pattern is quite variable. Tumors are composed of polygonal to spindle shaped chromaffin cells or chief cells, clustered with sustentacular cells into small nest or alveoli (Zellballen). Immunohistochemical staining for chromogranin A and synaptophysin may be used to confirm the diagnosis of pheochromocytoma. None of the histological features can differentiate malignant tumors from the benign ones. However, a combination of factors including presence of necrosis, mitotic index, tumor cellularity and growth pattern may be used to predict the likelihood of malignant nature. Presence of metastasis is the only definitive evidence of malignancy. Histopathlogy may also vary with the associated syndromic disease, which may help to direct the genetic screening. Intra-adrenal and extra-adrenal paragangliomas can have identical histological appearances; hence, extra adrenal tumors in the periadrenal location need histopathologic differentiation from intra-adrenal tumors due to their association with higher rates of malignancy.

Clinical Presentation

The average age at presentation of pheochromocytoma in children is 11 years (6–14 years). The clinical manifestations of pheochromocytomas are mainly due to excessive catecholamine secretion, although local tumor related complaints may be the presenting features in few cases. Presentation of childhood pheochromocytoma is highly variable, from incidentally detected adrenal masses to hypertensive crises. Common symptoms are palpitations, headache, excessive sweating, pallor, nausea and vomiting. Less frequent symptoms include weight loss, polyuria, visual disturbances, constipation, flushing and fever. Paroxysms may be triggered by direct stimulation of the tumor (e.g., bladder pheochromocytoma), physical activity and certain drugs. Hypertensive encephalopathy or acute left ventricular failure leading to pulmonary edema may occur in severe cases. Circulatory shock may be the presenting manifestation in rare cases, especially in case of epinephrine producing tumors. Hypertension is the most consistent sign and unlike adults it is more often sustained than paroxysmal. Orthostatic hypotension may be a characteristic feature. Fundus examination may reveal changes of hypertensive retinopathy including papilledema in severe cases.

Diagnosis

Biochemical diagnosis should be the first step in the evaluation of patients with suspected pheochromocytoma. Measurement of catecholamines or their metabolites like metanephrines in plasma or 24-h urine and vanillylmandelic acid (VMA) in 24-h urine are the commonly used tests for biochemical diagnosis. Metanephrines are produced continuously and independently of intracellular catecholamine release. Therefore, quantification of plasma free metanephrine and normetanephrine or 24-h urinary fractionated metanephrines serve as the most accurate biochemical tests for pheochromocytoma in all age groups including children and are characterized by a sensitivity of 100% and a specificity of 94–95% in pediatric age group. Catecholamines levels are usually measured by radioimmunoassay or high performance liquid chromatography. The rate of urinary excretion of catecholamines and metanephrines in young children especially can be less than a third of those in adults and requires age-appropriate reference intervals. Blood samples should essentially be obtained in supine position and care should be taken to avoid drugs like tricyclic antidepressants, beta blockers, calcium channel blockers and acetaminophen and dietary factors like caffeine and vanilla containing fruits and foods that can alter the estimation of catecholamines and their metabolites.

Localization can be achieved either with computerized tomography or magnetic resonance imaging, both of which have very high sensitivity (90–100%) but low specificity. *Figures 384.16* and *384.17* show imaging findings in patients with unilateral and bilateral Pheochromocytoma respectively. MRI may be preferred over CT because radiation exposure associated with the latter. MIBG is very specific (98–100%) but has low sensitivity (78%) and can be used to confirm the catecholamine secreting nature of the tumor. It also helps to localize extra adrenal tumors. Functional [18 F] fluoro-2-deoxyglucose or

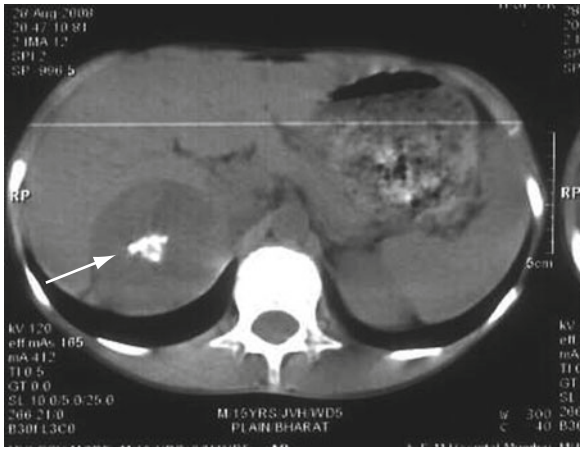

Figure 384.16
CT Scan showing right sided pheochromocytoma. 15-years-old boy presented with pain in abdomen. CT scan was ordered which showed right sided adrenal mass lesion with calcification. Blood pressure was noted at this stage to be 150/105. 24 h urinary VMA was elevated at 26.8 mg/day. Laparoscopic adrenalectomy was performed and patient made uneventful recovery. Post op blood pressure normalized

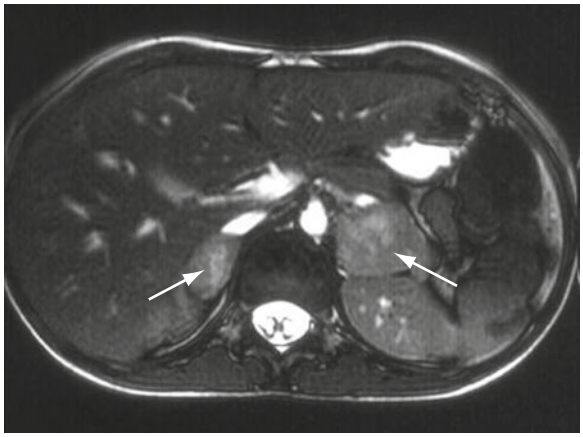

Figure 384.17
MRI scan showing bilateral pheochromocytoma. 12-years-old boy presented with hypertensive encephalopathy. His younger sister was diagnosed to have left sided pheochromocytoma at the age of 8 years. MRI of the patient showed bilateral adrenal masses (*Right*:1.9 × 1.5 × 2.7 cm and *Left*: 3.8 × 3.2 × 2.7 cm). 24 h urinary VMA was 50.1 mg. After adequate alpha and beta blockade, he underwent laparoscopic bilateral cortical sparing adrenalectomy. Patient became normotensive after surgery

[18 F] fluorodopamine positron emission tomography are new modalities for diagnosis of pheochromocytomas especially in those tumors that are difficult to localize.

Differential Diagnosis

Pheochromocytoma has to be differentiated from other causes of young hypertension including renal or renovascular causes, congenital adrenal hyperplasia, coarctation of aorta, Cushing syndrome, primary hyperaldosteronism and essential hypertension. However, neuroblastoma is the most difficult to differentiate since it simulates pheochromocytoma both in terms of biochemical diagnosis and localization. Catecholamine secretion may be excess in both but hypertension is rare with neuroblastoma. Dopamine and homovanillic acid are more elevated in neuroblastoma while other catecholamines are predominantly elevated in pheochromocytoma.

Genetic Screening

Children and their families should be evaluated and detailed assessment including a three-generation family history, clinical examination for neurofibromatosis 1 and genetic counseling should be done before molecular analysis for genetic mutations. In situation where mutation analysis is not readily available, further investigation of the index case and first-degree relatives may be required to direct further screening. Since the genetic testing is not currently cost-effective for every gene in every patient, consideration of tumor location, presence of multiple tumors or metastases, and type of catecholamine produced could be useful in deciding which genes to test.

Follow-up After Molecular Confirmation

Patients or family members with germ line mutations in RET, VHL, SDHB and SDHD genes, should undergo annual screening with blood pressure recording, adrenal ultrasound and plasma free metanephrines (after 5 years of age). Children with VHL mutation need additional screening with annual ophthalmologic review and renal ultrasound after 5 years of age. Triennial MRI of abdomen (after 5 years of age) and triennial MRI of brain and spinal cord (after 10 years of age) are recommended. Additional screening with 6 monthly serum calcitonin, annual calcium and parathyroid hormone is recommended for children with RET mutations. Prophylactic thyroidectomy is

recommended during infancy in MEN-2B and between 2 and 5 years in MEN-2A. In patients with SDHB mutation triennial MRI abdomen and thorax (after 7 years of age) and triennial MRI neck (after 20 years of age) are recommended. Biennial abdominal MRI and 5 yearly thoracic MRI after 7 years of age and biennial MRI neck after 20 years of age are recommended for children with SDHD mutation.

Treatment

Surgery is the definitive treatment but is associated with significant intra-operative risk. It can be minimized by adequate preoperative α blockade which can be achieved with phenoxybenzamine, doxazosin or prazosin. Phenoxybenzamine, a noncompetitive α-blocker may be preferred over competitive blockers such as doxazosin or prazosin. Recommended dose of phenoxybenzamine is 0.5–1 mg/kg twice daily, adjusted according to response. A β-adrenoceptor blocker is added to oppose the reflex tachycardia often associated with a blockade. Adequate α-blockade should be ensured by use of α-blockers for a minimum of 10–14 days before starting beta blockers to avoid worsening of hypertension due to unopposed vasoconstriction. Selective beta blockers like metoprolol and atenolol (1–2 mg/kg PO qd) may be preferred over nonselective blockers like propranolol (1 mg/kg PO qd). Calcium-channel blockers could be useful when α-blockade alone is not sufficient to control blood pressure. Liberal salt and water intake should be encouraged during α-blockade to facilitate volume expansion. Preoperative volume expansion by saline infusion is recommended to reduce postoperative hypotension but due care should be taken to prevent pulmonary edema which is more common in children. Invasive monitoring of BP should be started before or immediately after induction of anesthesia. Acute episodes of hypertension during surgery can be controlled with sodium nitroprusside infusion. Hypotension may occur in immediate postoperative period after resection of the tumor and infusions of dobutamine and/or norepinephrine may be required to maintain normotension for a variable period after surgery. Currently laparoscopic adrenalectomy is the preferred mode of surgery and cortical-sparing adrenalectomies must be considered in children with or at risk of bilateral disease. Tumor embolization, systemic therapy with 131MIBG, or chemotherapy (mostly a combination of cyclophosphamide, vincristine, and dacarbazine) can provide short-lived tumor regression and symptom relief in malignant pheochromocytomas.

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385 Disorders of the Posterior Pituitary

Mohamad Maghnie · Andrea Secco · Natascia Di Iorgi

Definition/Classification

Diabetes insipidus is a disease in which large volumes of dilute urine (polyuria) are excreted due to vasopressin (AVP) deficiency (central diabetes insipidus), vasopressin resistance (nephrogenic diabetes insipidus), or excessive water intake (primary polydipsia). Polyuria is characterized by urine volume in excess of 2 L/m^2/24 h or approximately 150 ml/kg/24 h at birth, 100–110 ml/kg/24 h until 2 years, and 40–50 ml/kg/24 h in the older child and adult.

Etiology

In many patients, central diabetes insipidus (CDI) is caused by the destruction or degeneration of neurons originating in the supraoptic and paraventricular nuclei of the hypothalamus. The known causes of these lesions include local inflammatory or autoimmune diseases, vascular diseases, Langerhans cell histiocytosis (LCH), sarcoidosis, germinoma or craniopharyngioma, trauma resulting from surgery or an accident, metastases, and midline cerebral and cranial malformations. In rare cases, genetic defects in AVP synthesis, inherited as autosomal dominant, autosomal recessive, or X-linked recessive traits are the underlying cause. X-linked (Xq28) nephrogenic diabetes insipidus (NDI) is secondary to *AVPR2* mutations, which results in a loss of function or dysregulation of the renal AVP receptor-2 (V_2 receptor). Abnormalities of *AQP2* (aquaporin 2) the water channel gene, located on chromosome 12 at 12q13 explain familial autosomal recessive and dominant forms of nephrogenic diabetes insipidus (*Table 385.1*).

Epidemiology

Diabetes insipidus is a rare disease with a non-univocal reported prevalence of 1:25,000. Less than 10% of diabetes insipidus can be attributed to hereditary forms. In particular, X-linked nephrogenic diabetes insipidus (OMIM 304800) represents 90% of cases of congenital NDI and occurs with a frequency of 4–8 per 1 million male live births; autosomal NDI (OMIM 125800) accounts for approximately 10% of the remaining cases. No gender difference was reported for the other forms.

While the prevalence of Wolfram diseases has been reported as 1–9/1,000,000 (www.orpha.net), the precise frequency of autosomal dominant central diabetes insipidus is currently unknown.

Pathogenesis and Pathology

Anatomy

The posterior pituitary consists of magnocellular neurons that produce the peptide hormones, vasopressin and/or oxytocin. The cell bodies of magnocellular neurons are located in the paraventricular nuclei (PVN) and in the supraoptic nuclei (SON) in the hypothalamus, and axons project to the neurohypophysis, where the hormones are secreted into the blood stream. These axons store quantities of vasopressin large enough to sustain basal release for 30–50 days or to allow maximum antidiuresis for 5–10 days.

While the blood supply for the anterior pituitary is via the hypothalamic-pituitary portal system from the suprahypophyseal arteries, the vascularization of the posterior pituitary is direct from the inferior hypophyseal arteries, which are branches of the posterior communicating and internal carotid arteries. The drainage is into the cavernous sinus and internal jugular vein (*Fig. 385.1*). The adult neurohypophysis weighs on average 120 mg, with weight increasing slightly with age.

Posterior Pituitary Organogenesis

During embryogenesis, neuroepithelial cells of the lining of the third ventricle migrate to the walls of the third ventricle where they mature into paraventricular nuclei (PVN). Some cells continue to migrate laterally to and above the optic chiasm to form the supraoptic nuclei (SON). Their unmyelinated axons traverse the basal hypothalamus, form the neural stalk, and terminate at the floor of the third

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Table 385.1
Etiologies of diabetes insipidus

Central diabetes insipidus	Familial
	• Autosomal dominant/recessive (OMIM 125700), AVP mutation (OMIM 192340)
	• X-linked (OMIM 304900)
	• Congenital hypopituitarism with central diabetes insipidus (OMIM 241540)
	• Wolfram (DIDMOAD) syndrome (OMIM 222300), wolframin (WFS1) mutation (OMIM 606201)
	• Unknown genes (?)
	Acquired
	• Idiopathic
	• Intracranial tumors – germinoma, craniopharyngioma, glioma
	• Autoimmune: lymphocytic hypophysitis/ lymphocytic infundibulo-neurohypophysitis/lymphocytic infundibulo-hypophysitis
	• Autoimmune (antibodies against vasopressin-producing cells, T-cells damage)
	• Granulomatosis (tuberculosis[a], sarcoidosis[a], Langerhans cell histiocytosis, [a]Wegener)
	• Infections/post-viral (varicella; congenital CMV and toxoplasmosis; encephalitis, meningitis)
	• Traumatic brain injury
	• Vascular impairment/Hypoxic-ischemic
	• Metastases[a]
	Cerebral malformations
	• Midline brain developmental defects (septo-optic dysplasia, holoprosencephaly, etc.)
	• Associated with ectopic posterior pituitary, anterior pituitary hypoplasia, and congenital hypopituitarism
Nephrogenic diabetes insipidus	Familial
	• X-linked (OMIM 304800), AVPR2 mutation (OMIM 300538) (90%)
	• Autosomal recessive/dominant (OMIM 125800), AQP2 mutation (OMIM 107777) (10%)
	• Nephrogenic diabetes insipidus with mental retardation and intracerebral calcification (OMIM 221995)
	Acquired
	• Hypokalemia, hypercalciuria, alkalosis
	• Polycystic renal disease, others
	• Pyelonephritis, postobstructive
Primary polydipsia	• Psychogenic
	• Dipsogenic

[a]Rare in children

ventricle and in the median eminence. It should be noted that the SON ultimately contain *only* oxytocin and vasopressin-containing neurons, whereas the PVN have distinct cell populations, such as those containing corticotrophin-releasing hormone, TSH-releasing hormone (TRH), and synthesizing somatostatin. Others contain neurotransmitters destined to control the autonomic nervous system.

The early differentiation of these cell lineages has recently become much more comprehensible through the elucidation of the role of transcription factors in hypothalamic development. The SIm1, ARNt2, OTP and BRN2 genes appear to be involved in the cascade of transcription factors implicated in the development of the neuroendocrine hypothalamus leading to the completion of posterior pituitary development by the end of the first trimester, when vasopressin and oxytocin can be detected in neurohypophyseal tissue.

The posterior pituitary gland is formed by the evagination of neural tissue from the floor of the third ventricle. It consists of the distal axons of the hypothalamic magnocellular neurons that shape the neurohypophysis. After its downward migration, it is encapsulated together with the ascending ectodermal cells of Rathke's pouch, which form the anterior pituitary. In a recent study, a *Hes1*-null pituitary gland was revealed to be reduced in size but was otherwise morphologically normal compared with the control. Indeed, in *Hes1-Hes5* double-mutant mice, the evagination of the infundibulum was affected and the neurohypophysis was lost compared to both the wild type and *Hes1*-null mice, suggesting that both *Hes* genes are essential for the formation of the neurohypophysis. A number of transcription factors have been implicated in the development of the hypothalamo-neurophypophyseal system (HNS) and null mutations for these factors caused severe defects in proliferation, migration, and survival during early embryogenesis. Recently, large numbers of genes were identified in a study as being expressed in rat HNS

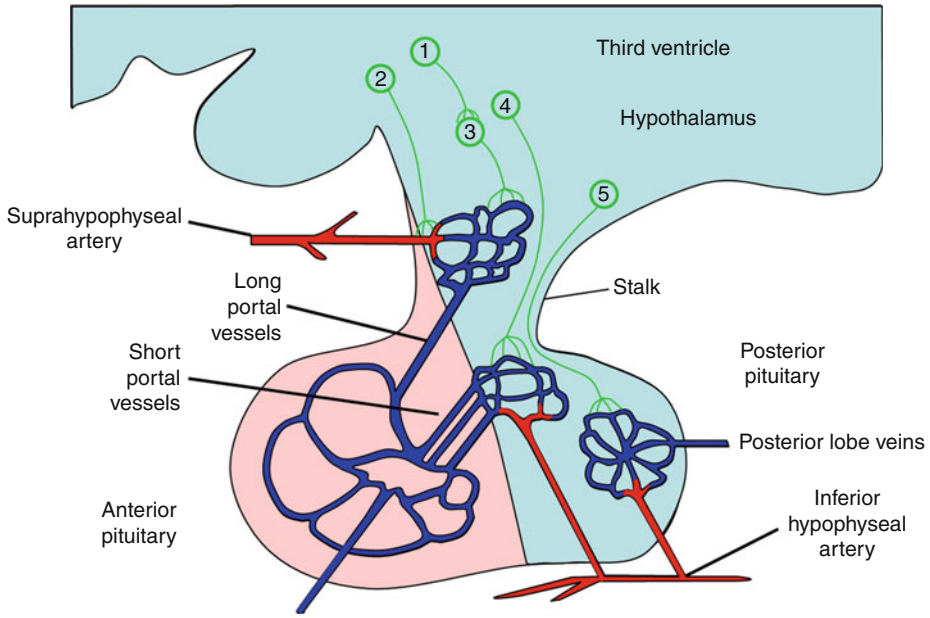


Figure 385.1

Anatomy and vascularization of the posterior pituitary. 1,2,3,4,5 represents the paraventricular and supra-optic nuclei from where vasopressin and oxytocin migrate along the axons projecting to the neurohypophysis where the hormones are secreted into the blood stream

neuronal tissues after dehydration. The pattern of HNS transcripts with marked differences in gene expression indicates that these genes are candidate regulators and effectors of HNS activity and remodeling.

Vasopressin Biosynthesis

The AVP-neurophysin II gene (*AVP-NPII*) is located distally at the short arm of chromosome 20 (20p13). It covers 2.5 kb and comprises three exons. Exon 1 encodes the signal peptide of 19 amino acid residues, the nonapeptide AVP, and the N-terminal region of NPII (9 amino acid residues); exon 2 encodes the central highly conserved region of the NPII peptide (67 amino acid residues); and exon 3 encodes the C-terminal region of NPII (17 amino acid residues) and a 39 amino acid glycopeptide known as copeptin (*Fig. 385.2*).

The *AVP-NPII* gene product, the AVP preprohormone is co-translationally targeted to the endoplasmic reticulum (ER), where the signal is cleaved off by signal peptidase and the copeptide is core glycosylated. Vasopressin and NPII associate after cleavage and then form the tetramer, which increases the binding affinity of vasopressin for NPII. After formation of seven disulphide bonds within NPII and one within AVP and after glycosylation of the copeptide, the proprecursor is packaged into neurosecretory granules and then cleaved into the product peptides during axonal transport to the posterior pituitary. Neurophysin serves to stabilize the hormone during its transport and storage, while recent data suggest the important role of copeptin in the correct structural formation of the AVP precursor as a prerequisite for its efficient proteolytic maturation. Vasopressin and its protein carrier NPII are released from the posterior pituitary by calcium-dependent exocytosis when the axon is depolarized by osmoreceptor or baroreceptor stimuli.

Physiology of Water Homeostasis

The maintenance of water balance in healthy humans is achieved principally by three interrelated determinants: thirst, vasopressin, and kidney function.

Recently, apelin – a bioactive peptide – has been isolated from bovine stomach extracts (like ghrelin, another stomach-hypothalamus association). It is expressed in the supraoptic and the paraventricular nuclei and exerts its action on specific receptors situated on the vasopressinergic neurons. Apelin acts as a potent diuretic neuropeptide which

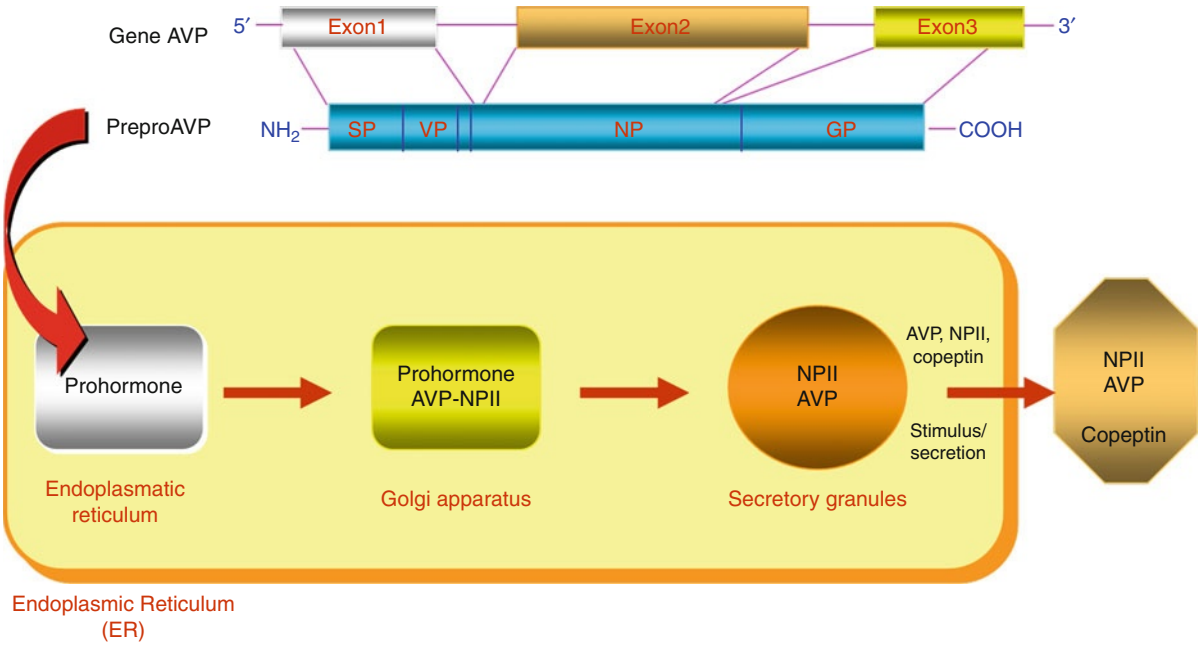


Figure 385.2
Schematic structure of the AVP gene and AVP synthesis and release. Abbreviations: *SP* signal peptide, *VP* vasopressin, *AVP* arginine-vasopressin, *NP* neurophysin, *GP* glycopeptide

counteracts vasopressin actions through inhibition of AVP neuron activity and AVP release. The coexistence of apelin and AVP in magnocellular neurons, and their opposite biological effects and regulation, are likely to play a key role in maintaining body fluids.

As early as the middle of the nineteenth century, the question was asked: how does water get through the lipid bilayer of the cell membrane? The answer used to be "*. . .membranes have pores*." It was not until 1988 that Peter Agre isolated a membrane protein that he realized must be the long-sought-after water channel. He called it aquaporin. This discovery opened the door to a whole series of biochemical, physiological, and genetic studies of water channels in bacteria, plants, and mammals. Today, researchers can follow a water molecule in detail on its way through the cell membrane and understand why only water and not other small molecules or ions can pass through the membrane. In 2000, Agre reported the first high-resolution images of the three-dimensional structure of aquaporin. Now, it is possible to construct a detailed map of water channel functions. Currently, ten mammalian aquaporins (AQP0-AQP10) have been identified.

Vasopressin acts on its major target organ, the kidney, where it increases urine osmolality (*Fig. 385.3*). The hormone binds to the V2-receptors in the basolateral membrane of the renal collecting tubular and activates the Gs – adenyl cyclase system, increasing intracellular levels of cyclic 3′,5′-adenosine monophosphate (cAMP). The latter activates protein kinase A, which in turn phosphorylates preformed acquaporin-2 (AQP2) water channels localized in intracellular vesicles. Phosphorylation promotes trafficking to the apical membrane, followed by exocytic insertion of AQP2 vesicles into the cell membrane. The insertion of AQP2 renders the collecting-duct water permeable, allowing free movement of water from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient, thus concentrating the urine. The synthesis of AQP2 channels, as well as their movement, is regulated by AVP stimulation, while acquaporin-3 and acquaporin-4, responsible for the subsequent passage of water from within the cell into the renal interstitium, are constitutively present in the basolateral membrane.

Regulation of Vasopressin Secretion

Vasopressin release is under the control of osmoreceptors (osmotic), baroreceptors (hemodynamic), and other regulatory mechanisms (*Table 385.2*). The maintenance of

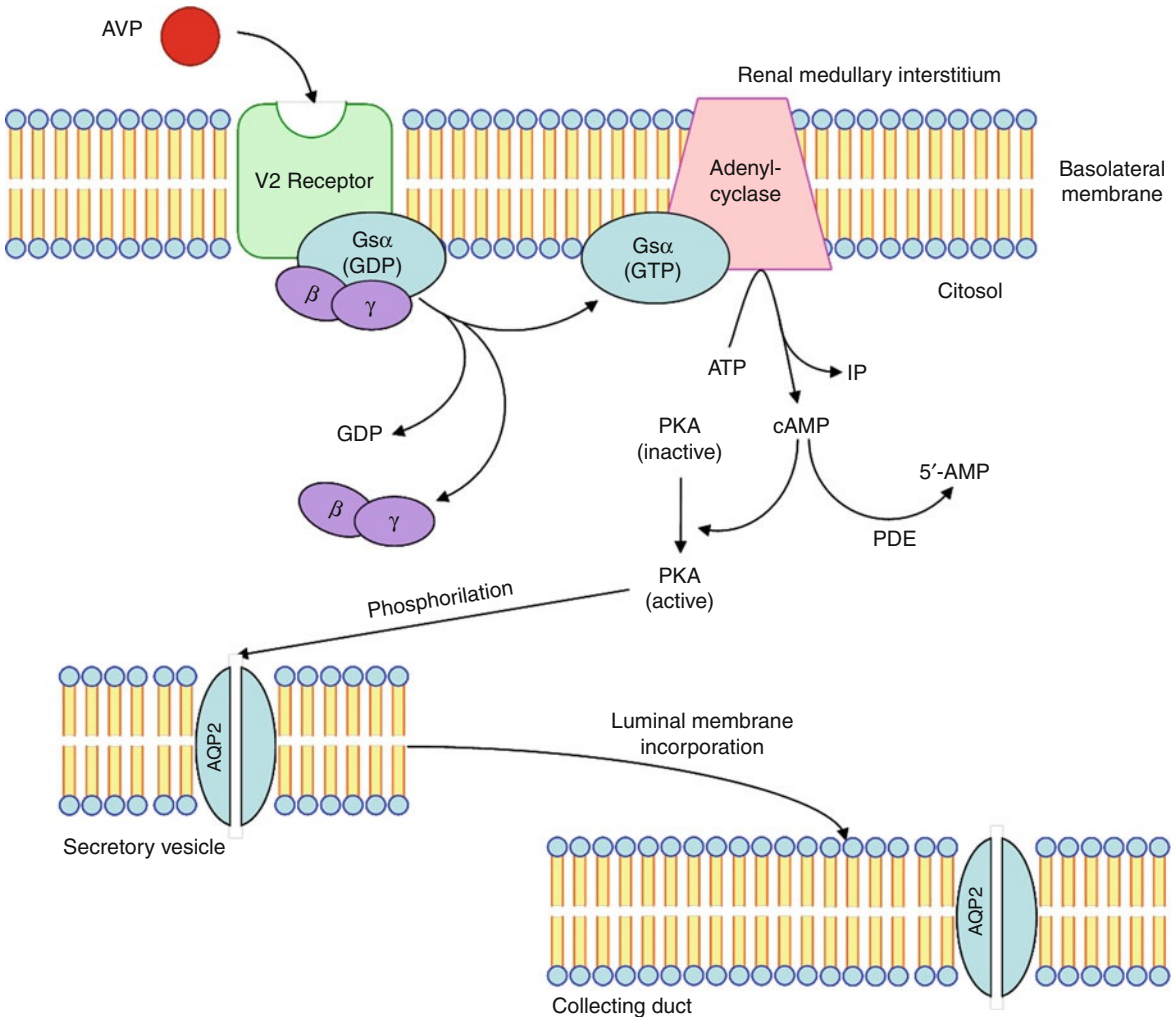


Figure 385.3

V_2 vasopressin receptor signaling cascade. In principal cells of the renal collecting duct, AVP binding to V_2 receptor (V_2R) on the basolateral membrane stimulates adenyl cyclase through the activated $G_s\alpha$-subunit, which leads to an increased formation of the second messenger cAMP. The cAMP-dependent protein kinase phosphorylates aquaporin 2 (AQP2). AQP2 phosphorylation leads to both activation of AQP2 and translocation of AQP-containing vesicles to the luminal surface of the cell. The translocation and vesicle fusion processes lead to the insertion of AQP2 into the apical membrane and thus enhances its water permeability Abbreviations: *AVP* arginine-vasopressin, *ATP* adenosine triphosphate, *cAMP* cyclic adenosine monophosphate, *IP* inorganic phosphate, *5′-AMP* 5′-adenosine monophosphate, *PDE* phosphodiesterase, *PKA* protein kinase A, *AQP2* aquaporine 2, *GTP* guanosine triphosphate, *GDP* guanosine diphosphate

water balance starts with the sensing of plasma osmolality, predominantly represented by the plasma sodium concentration. This sensing mechanism is controlled by specialized neural osmoreceptors in the anterolateral hypothalamus responsible for AVP production and secretion. The osmoreceptors are quiescent below a plasma threshold osmolality of about 280 mOsm/kg H_2O. When plasma osmolality rises above this threshold value, osmoreceptor cells are progressively stimulated to cause AVP release.

Small changes in plasma osmolality regulate AVP release from the posterior pituitary. When water is lost and plasma osmolality increases by as little as 1%, an increased secretion of AVP stimulates water retention by

Table 385.2
Regulation of vasopressin secretion

Mechanism	Receptor	Causes
Osmotic	• Hypothalamic osmoreceptors	• Plasma osmolality
		• Hyperglycemia
		• Hypertonic/ hypotonic solution infusion
		• Water balance change
Hemodynamic	• High pressure arterial baroreceptor (carotid sinus, aortic arch)	• Blood volume/ hypovolemia/ hemorrhage
	• Low pressure volume receptors (atria and pulmonary venous system)	• Blood pressure
		• Vasovagal reaction
		• Congestive heart failure
		• Cirrhosis
		• Nephrosis
		• Pregnancy
Emetic	• Area postrema of the medulla "chemoreceptor trigger zone"	• Nausea
Other		• Drugs (morphine, vincristine, cyclophosphamide, nicotine, carbamazepine, glucocorticoids, ethanol, etc.)
		• Temperature
		• Stress

the kidneys. There is a sensitive, linear relationship between increased osmolality and increased AVP secretion; there is, similarly, a linear relationship between increased plasma AVP and increased urine osmolality. Osmolality is tightly regulated around each individual's normal value which falls between 280 and 295 mOsm/kg H_2O in the general population. Maximum antidiuresis is attained with plasma AVP concentrations of about 2–5 pmol/l.

In circumstances where individuals lose large amounts of body water, plasma osmolality may rise above 300 mOsm/kg H_2O, but increased AVP secretion of more than 5 pmol/l cannot concentrate urine any further (1,000–1,200 mOsm/kg H_2O). Urine volume does not change markedly over wide variations of urine osmolality until urine osmolality approaches maximum dilution and plasma AVP is completely suppressed. There is then a remarkable exponential increase in urine volume to approximately 18 l/day in adults. The glomerular filtrate is largely reabsorbed in the descending loops of Henley in the kidneys and only approximately 18 l of dilute fluid enter the collecting duct.

Pathogenesis

Increasing polyuria occurs when more than 80% of the AVP-secreting neurons are damaged. Extensive destruction can be caused by a variety of pathologic processes including genetic causes. Autopsy studies after traumatic section of the pituitary stalk have revealed a loss of the large neurosecretory cells in the hypothalamic nuclei. This occurs within 4–6 weeks, with higher damage for lesions that occur at the level of the infundibulum or above it. Autopsy studies of patients with a familial form of diabetes insipidus show a selective loss of magnocellular neurons in the paraventricular nuclei associated with moderate gliosis and relative preservation of small neurosecretory cells, suggesting that the disorder is due to degeneration of these hypothalamic neurons.

Genetic Forms of Central Diabetes Insipidus

At present, more than 50 different mutations resulting in a defective prohormone and a deficiency of vasopressin have been identified in familial neurohypophyseal DI; all except a few show an autosomal dominant pattern of inheritance. One unique homozygous missense mutation in the region encoding the AVP domain shows an autosomal recessive pattern of inheritance which does not seem to affect intracellular trafficking, but rather the final processing of the prohormone into neurophysin II and AVP hormone. Despite some clinical similarities with the dominant form, the symptoms appear to be secondary to the reduced biological activity of the mutant vasopressin peptide. This hypothesis is supported by the high circulating level of mutant hormone, the absence of normal AVP hormone in the homozygous state, and the absence of clinical or subclinical abnormalities in heterozygous carriers.

Indeed, no mutations in the coding region, the intronic region, or the 1.5-kb upstream region from the initial transcription site of the AVP-NPII gene were found in

a Chinese family showing an autosomal dominant inheritance pattern of overt central diabetes insipidus. Linkage analysis indicated that the corresponding gene(s) responsible for the autosomal dominant form in this family was located in a 7-cm interval defined by two short tandem repeat markers on chromosome 20. This suggests the presence of locus heterogeneity of autosomal dominant central diabetes insipidus and implies a genetic diversity in the cause of CDI.

The autosomal dominant inheritance of this disease can occur through many mechanisms including dominant negative activity by interactions of mutant and wild type (WT) precursor, accumulation of mutant precursor in the ER leading to stress protein response and autophagy, and cellular toxicity by pathways that are still not completely defined. The study of the trafficking and processing of the mutant vasopressin prohormone in vitro has demonstrated that the mutation abolishes ER exit and processing of the vasopressin prohormone, resulting in an aberrant endoplasmic morphology and possible cell dysfunction and death. The presence of cytosolic autophagy suggests non-apoptotic cell death; however, programmed cell death cannot be excluded.

Mutations involving the signal peptide decrease its ability to initiate the proper processing of the prepro-AVP-NPII; mutant precursors also impair intracellular trafficking of the WT precursor by forming heterodimers, thus reducing the bioavailability of active AVP by means of a "nontoxic mechanism," i.e., a dominant negative effect.

Recently, the demonstration of two pathways of degradation (via the ER lumen and directly from the cytosol), involving both the WT and the mutant prohormone, suggests that the cytotoxic effect may result from processes that are quantitatively but not fundamentally different from those occurring in cells expressing the WT protein.

Acquired Forms of Central Diabetes Insipidus

Idiopathic CDI

Although 20–50% of cases CDI are considered idiopathic, the identification of antibodies against vasopressin-secreting cells on the one hand, and recent advances in imaging techniques on the other, have shed new light on pathophysiological aspects of CDI, making the idiopathic form a much less common condition.

Various clinical observations suggest an important role for autoimmunity in the pathogenesis of CDI. Indeed, autoimmune polyendocrinopathy and CDI associated with an MRI picture of thickened pituitary stalk suggest that patients with CDI and thickened pituitary stalk may share a common etiology. Indeed, circulating vasopressin-cell autoantibodies (AVPc-Abs) were found in 75% of children and young adults with idiopathic CDI, suggesting that hypothalamic-neurohypophyseal autoimmune involvement is more common in children and young adults with idiopathic CDI than has generally been thought; the higher frequency of AVPc-Abs in pediatric patients, compared to the one third found in adult patients with identical disease duration, underlines the fact that an autoimmune cause in idiopathic CDI is quite frequent. In addition, AVPc-Abs were found in approximately 77% of subjects with combined posterior and anterior pituitary dysfunction, a finding that goes well beyond the reported association of anterior pituitary hormone defects in as many as 23% of subjects with isolated vasopressin deficiency. This indicates that anterior pituitary (AP) involvement in the course of idiopathic CDI is highly suggestive of an autoimmune neurohypophyseal basis and fits well with the bioptic demonstration of the lymphocytic infiltration of the pituitary stalk. In about one fourth of patients with idiopathic CDI, there is a temporal relationship between a viral infection (trigger) and the onset of CDI. This hypothesis is strengthened by the fact that the pituitary gland is susceptible to CD8 T-cell-mediated autoimmunity, triggered by a cell-specific model autoantigen, as well as to the development of autoimmune hypophysitis by immunizing female SJL/J mice with mouse pituitary extracts. The identification of AVPc-Abs in subjects who could have either idiopathic CDI or LCH or germinoma, however, indicates that this finding cannot be considered a completely reliable marker of autoimmune CDI. Thus, to ensure a definitive etiological diagnosis, close clinical and MRI follow-up are needed since AVPc-Abs may mask germinoma or LCH.

The underlying process of pituitary stalk thickening in "idiopathic" CDI is not completely understood. Recent reports of a thickened pituitary stalk in association with autoimmune or inflammatory disease, termed "lymphocytic hypophysitis," "necrotizing infundibulo-hypophysitis," or "lymphocytic infundibulo-neurohypophysitis" focus on adults with histological features of lymphocyte and plasma cell infiltration, fibrosis, and necrosis. Hence, lymphocytic hypophysitis is a rare chronic inflammatory process that variably affects the pituitary gland. It is noteworthy that clear-cut criteria for the diagnosis of lymphocytic hypophysitis in children and adolescents are still lacking and that CDI is manifest in only about 20–25% of cases.

The term "lymphocytic infundibulo-hypophysitis" has been coined to distinguish children and adolescents with CDI, anterior pituitary hormone deficiency,

reduction of AP size, and transient or persistent pituitary stalk (PS) thickening from adult patients with similar posterior pituitary (PP) and PS findings at MRI, but normal AP size and function according to recent diagnostic criteria, and GHD defined in adult patients as GH response after pharmacological stimulation tests higher than 10 μg/l. In adult cases such as those described, the term "lymphocytic infundibulo-neurohypophysitis" is more appropriate.

Vascular CDI

CDI may be caused by vascular brain damage, but the pathophysiology of such a mechanism has never been precisely understood. In a group of patients with idiopathic CDI and normal anterior pituitary function, standard MRI showed normal PS and AP gland size. Indeed, dynamic MRI studies after contrast medium injection demonstrated the absence of posterior pituitary lobe enhancement whereas normal enhancement of the AP was present. The lack of contrast enhancement of the posterior lobe suggests that a selective vascular injury to the inferior hypophyseal arteries could be causally linked to CDI. The mechanism affecting posterior pituitary blood supply remains largely undefined, but the possibility that a congenital lack/poor development of the posterior pituitary vascular system (without any evidence of macroscopic morphological abnormality of the pituitary gland at MRI or secondary changes of vascular supply due to a local inflammatory process) (vasculitis?) cannot be ruled out.

Langerhans Cell Histiocytosis (LCH)

Central diabetes insipidus is the most frequent CNS manifestation of LCH, occurring in 10–50% of all patients. A retrospective multicenter analysis of LCH patients shows that the risk of developing CDI, after diagnosis and specific therapy, was 16% at 5 years and 20% at 15 years, respectively, and strongly correlates with the presence of a multisystem disease followed by lesions in the craniofacial area. Some patients with CDI and endocrinopathies seem to be at risk for neurodegenerative CNS disease. Growth hormone deficiency (GHD) is the most frequent additional deficit accounting for 42% of cases with CDI and LCH. The 10-year cumulative incidence of GHD in the French nationwide LCH survey was approximately 54% among patients with CDI. The identification of circulating AVPc-Abs in LCH patients and their tendency toward spontaneous clearance suggest that these autoantibodies might be an LCH-related immune epiphenomenon.

Pituitary stalk thickening (PST) can be found in approximately 50–70% of patients with LCH at presentation or at follow-up and may even be present before CDI onset. With PST, anterior pituitary size has been found to be normal, reduced or, rarely, enlarged. The search for extracranial lesions (dermatological and bone survey; chest x-ray; ear, nose, and throat examination) suggestive of LCH in patients with PST is recommended and could reduce the need for intracranial biopsies.

Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown etiology; the involvement of the central nervous system occurs in approximately 5–15% of patients and precedes additional symptoms in 25–30% of cases. Autopsy studies have demonstrated that sarcoid granulomas have a predilection for the hypothalamus and less commonly involve the PS or the pituitary gland. Thus, patients with neuroendocrine sarcoidosis commonly have hypothalamic dysfunction and often exhibit hypothalamic disturbances and AP hormone deficiency. Endocrinopathy is relatively rare, polyuria-polydipsia being the most common symptom, reported in 25–33% of adult patients affected by neurosarcoidosis. In pediatric patients, hypophyseal dysfunction was documented in 21% of cases, 66% of whom shows CDI. Children with neurosarcoid behave differently than adults and are more likely to have seizures and less likely to have cranial nerve palsies; eye diseases such as uveitis may occur in younger children.

Brain MRI studies showed heterogeneous features, including periventricular white matter foci, leptomeningeal enhancement, hydrocephalus and enlargement of the PS; the latter entity has been described in four of the five patients reported by Bullmann et al. To our knowledge, only a few pediatric cases of CDI secondary to neurosarcoidosis have been described.

Tumors

Germinomas: Intracranial germ tumors comprise 7.8% of primary pediatric brain tumors. MRI findings suggest that suprasellar and neurohypophyseal germinomas primarily arise from the posterior pituitary to the infundibulum. Partial or complete stalk thickening is detectable in 78–100% of cases at presentation and may be the only finding at presentation in small germinomas; its presence increases the risk of malignancy to about 15–17%, while the risk decreases to 3% in patients with a normally sized stalk.

Serial contrast-enhanced brain MRI in patients affected by CDI with PST (every 3–6 months for the first 2 years) may reduce the amount of time for diagnosis of germinoma by 1 year. However, a thickened stalk has been reported up to 5 years after the onset of CDI and preceded

by lymphocytic tissue infiltration as a host reaction to the presence of a germinoma that could mask diagnosis. Exceptionally, germinoma can mimic multisystemic LCH, with vertebral compression, recurrent ear infections, thickened PS, enlarged pineal gland, serum and negative cerebrospinal fluid for germ cell tumor markers, as demonstrated in a 9-year-old female.

The role of hCG and other tumor markers in the early diagnosis of germinoma is not very well understood. A negative finding for hCG in cerebrospinal fluid does not exclude a diagnosis of germinoma. The presence of circulating AVPc-Abs in these patients prior to treatment could also mask the diagnosis of germinoma and calls for further confirmation. Pituitary stalk biopsy is mandatory in the presence of a progressive thickening of the lesion up to more than 6.5–7 mm and/or anterior pituitary enlargement. Growth arrest and multiple pituitary hormone deficiency are common and early findings in pituitary germinomas (almost 100% of cases at follow-up), but hormone deficiency is not predictive of their presence.

Craniopharyngioma and post-surgical CDI: Craniopharyngioma is a benign tumor arising from squamous cell nests in the primitive Rathke's pouch. It constitutes approximately 6–9% of all intracranial tumors in children and is the most frequent suprasellar neoplasm in the pediatric population, i.e., 54% of cases. Classical presentation includes visual impairment due to chiasmal compression and bilateral optic atrophy; systemic symptoms related to raised intracranial pressure account for 60–75% of cases at presentation. In diverse large pediatric series, signs and symptoms of AP dysfunction were detected in about 20–70% of cases. Central diabetes insipidus and multiple pituitary hormone deficiency are common complications of childhood craniopharyngioma. The frequency of pre-surgery CDI varies from 16% to 55%, while post-surgical and permanent CDI accounts for up to 80% of cases; transient CDI is reported in 13% of affected cases.

Impairment of hypothalamic-posterior pituitary function after complete section of the PS is a common, predictable outcome characterized by the classic triphasic response of urine volume. The initial phase of CDI (1–4 days) is followed by a second phase of oliguria which may reflect degeneration and death of neurosecretory neurons, with release of stored AVP into the circulation (4–7 days), and by a third and final phase of permanent CDI. The diagnosis of CDI after surgery is often made within a few hours, although abnormalities of AVP secretion and fluid balance often begin during the intra-operative period. The trans-sphenoidal approach is now widely used for intrapituitary and some suprasellar tumors, and is associated with a lower incidence of post-operative CDI. CDI after trans-frontal approach has been reported in association with high plasma vasopressin (AVP)-immunoreactivity, but the plasma showed no antidiuretic bioactivity; moreover, antidiuretic response to standard AVP was greatly attenuated, suggesting the presence of a circulating vasopressin antagonist affecting the renal action of endogenous and exogenous AVP.

Metastasis: Metastasis to the posterior pituitary is a well-known event in systemic cancer due to the direct arterious vascularization of the posterior pituitary lobe. The incidence of pituitary metastases varies from 0.14% to 28.1% of all brain metastases and is higher in adult autopsy series. Pituitary metastases most frequently originate from lung carcinoma, breast cancer, gastrointestinal carcinomas, and leukemia/lymphoma with symptoms seen particularly in terminal stages. About 20% of these metastases to the pituitary-hypothalamic axis are diagnosed clinically and CDI is the main presenting symptom. A review of the literature showed that CDI has been reported in association with leukemia in 39 of 5,778 children (0.6%), 4 of whom were under 10 years of age.

In cases of metastasis, a destructive and inhomogeneously enhancing intrasellar and suprasellar lesion and involvement of adjacent structures can be observed at MRI; the pituitary stalk can be involved and appears entirely or partially thickened. Progressive thickening of the PS has been the presenting symptom in various pediatric cases of primary lymphoma of the central nervous system or of myeloid leukemia. CDI and multiple AP hormone deficiencies can precede by one or more years the diagnosis of malignancy.

Other Entities

CDI has been reported in Wegener granulomatosis, a disease characterized by necrotizing vasculitis and granulomatous inflammation of the upper and lower respiratory tract, together with glomerulonephritis; MRI showed an isointense suprasellar mass and enlargement of the infundibulum. Two months after corticosteroid treatment, MRI showed nearly complete resolution of pituitary lesions and dramatic clinical improvement.

Transient CDI associated to CNS tuberculosis is a well-known entity. Tuberculosis of the CNS is the most serious complication in children, accounting for about 3–4% of untreated tuberculosis infections in developed countries. It usually arises from a "metastatic" caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. A few pediatric reports refer to tuberculous meningitis followed by acute onset of CDI, variably

associated with seizure and/or communicating hydrocephalus; in these cases, MRI showed pituitary stalk thickening.

Acute post-traumatic CDI has been reported in 22 of 85 patients who suffered a moderate to severe traumatic brain injury (TBI); 5 of these patients had persistent abnormal water deprivation test at a median time of 17 months from TBI and expression of permanent partial CDI; the remaining patients had complete recovery of PP function. In the study, permanent CDI correlated with lower Glasgow coma scale but not with age, gender, basal skull fracture, or operative mass evacuation.

Post-traumatic DI may result from inflammatory edema around the hypothalamus or the posterior pituitary, with resolution as the swelling resolves. It can also result from direct damage to the paraventricular and supraoptic hypothalamic neurons, to the pituitary stalk, or to axon terminals in the posterior pituitary.

Clinical Manifestations: Symptoms, Signs

Clinical examination may provide important clues to possible underlying diagnoses. The age at which symptoms develop, together with the pattern of fluid intake, may influence subsequent investigation of diabetes insipidus (*Fig. 385.4*). Leading symptoms are represented with persistent poliuria and polydipsia, and young children may have severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive, and growth retardation. Nocturia in children often presents as enuresis. Severe dehydration of early onset in males is highly suggestive of nephrogenic diabetes insipidus; some mental retardation has been reported, probably caused by repeated and unrecognized dehydration before the diagnosis has been established.

In a large cohort of patients with CDI of different etiologies, 40% of the patients had symptoms other than polyuria and polydipsia at presentation; while headache was not discriminatory, visual defect was associated with intracranial tumor. Growth retardation was not significantly more common in patients with CNS tumors, in contrast with previous reports indicating that such delays strongly suggest an intracranial tumor as the cause of central diabetes insipidus.

In autosomal dominant CDI, the clinical disease onset typically ranges from the first to sixth year of age, but various cases of early or delayed onset are also reported.

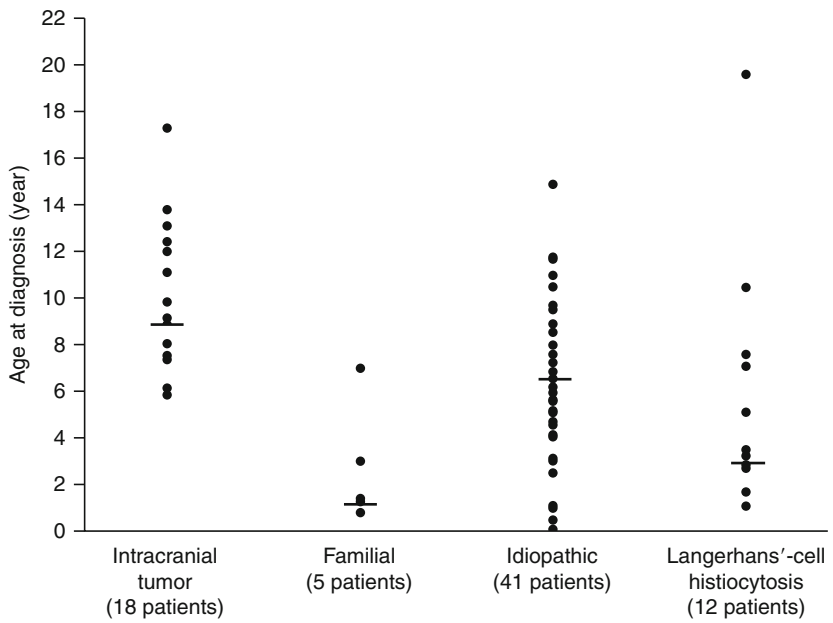


Figure 385.4

Age at diagnosis according to the cause of central diabetes insipidus. The patients who did not have an intracranial tumor were significantly younger at diagnosis than those who did ($P < 0.001$ for all comparisons). The horizontal lines indicate the medians (Reproduced with permission from The Publishing Division of the Massachusetts Medical Society – Publishers of The New England Journal of Medicine)

Usually symptoms worsen with age in patients with early onset of mild polyuria and polydipsia, especially before 10 years of age, but it is also possible that complete CDI is expressed from the neonatal period. The wide variability in the age of onset and the severity of the AVP deficiency among patients with the same mutation may be attributed to individual differences among such patients, such as the rate of production of the mutant precursor, the intensity of neurohypophyseal stimulation, individual susceptibility to the toxic effect of the mutant precursor, the capacity to degrade mutant precursors, and variations in secretory reserve capacity or the development of the gland itself. Further studies on the contribution of any of the mechanisms involved in cell dysfunction and/or impaired AVP secretion, together with MRI follow-up, would help to better understand the disease. The majority of the mutations currently described affect NPII moiety; only a few mutations have been identified within the signal peptide sequence. No substantial temporal relationship between the type of mutation, the time of disease onset, and the degree of severity was found among patients affected by the same missense mutation.

In Wolfram syndrome (WS), diabetes mellitus has been reported to be the usual first symptom to present at a median age of 6 years, followed by onset of optic atrophy at a median age of 11 years. The phenotype–genotype correlations in a series of nine WS families show an average age at onset of diabetes mellitus of 8.4 years in agreement with other studies. The development of polyuria and/or enuresis can indicate diabetes insipidus, and the time of onset varies considerably and does not generally appear until the second or third decade; CDI may initially be partial. The frequency of CDI varies between reports ranging from 48% to 78%.

A wide spectrum of abnormalities affect the endocrine glands and the central nervous system and include anosmia, ataxia, seizures, nystagmus, gaze palsies, dysarthria, dysphagia, psychiatric abnormalities, cognitive deficits, hypo- or areflexia and neurogenic bladder, central sleep apnea, neurogenic upper airway collapse, myoclonus, Parinaud's syndrome, hypothyroidism, hypogonadism, and ACTH deficiency. Treatment with DDAVP can be very successful.

Diagnosis

Measurement of Osmolality

Osmolality measured in vitro by means of freezing point depression usually correlates well with the ton that is the effective osmotic pressure. However, while tonicity and osmolality of sodium and other electrolytes are identical, urea and glucose show large differences between the osmotic pressure ascertained by freezing point depression and the effective osmolality in vivo. The accuracy of the measurement of plasma osmolality by routine hospital laboratories and by freezing point depression is usually not high enough to fulfill the quality criteria required (coefficient of variation of 1% or less at 290 mOsm/kg H_2O), especially when osmolality is determined in serum or frozen plasma.

As a matter of fact, extracellular and plasma osmolality can be reasonably considered to represent sodium salts. Thus, plasma osmolality can be estimated quite well by 2 × plasma sodium concentration. However, the contributions of two other solutes, glucose and urea, should be included to more closely approximate plasma osmolality: Posm = 2 $[Na^+]$ + [blood glucose] + [urea].

The molecular weight of glucose is 180, and that of the two nitrogens in urea is 28. The plasma contents of both are usually expressed as mg/dl (instead of mg/l), so molecular weights must be divided by 10. Thus, glucose can be estimated by the plasma glucose content (in mg/dl)/18 and urea can be estimated by the blood urea nitrogen (BUN, in mg/dl)/2.8. Finally, a good estimation of plasma osmolality, usually accurate to within 1–3% (i.e., within 9 mOsm/kg H_2O) of what is determined directly by osmometry, can be obtained with the formula:

$$P = 2[Na^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8} \qquad (1)$$

Diagnosis of Diabetes Insipidus

For accurate diagnosis, it is essential that 24-h urine volume is completed and polyuria confirmed. A range of baseline investigations including plasma electrolytes, random plasma osmolality and urine osmolality, as well as an assessment of kidney function, may assist in a correct diagnosis. In the absence of an immediate diagnosis, the child's fluid intake and output should be studied in greater detail. The ability of the central nervous system to produce and of the kidney to respond to vasopressin should be established by means of a formal water deprivation test and DDAVP trial.

A 7-h (or less) deprivation test is usually sufficient for diagnosis, except in cases of primary polydipsia, where a longer dehydration period is sometimes required. The test must be discontinued if weight loss exceeds 5% of starting weight and/or plasma Na^+ is found higher than

143 mEq/l and/or plasma osmolality higher than 295 mOsm/kg H_2O and/or urine osmolality increases to normal (Table 385.3, Fig. 385.5).

Diagnosis of CDI is based on the demonstration of plasma hyper-osmolality (>300 mOsm/l) associated with urine hypo-osmolality (<300 mOsm/l or urine/plasma osmolality ratio <1) and polyuria (urinary volume > 4–5 ml/kg/h for two consecutive hours post-surgery). Adrenocorticotropin deficiency may mask signs of partial CDI, and polyuria may become manifest after corticosteroid replacement therapy.

The administration of desmopressin will help to make a differential diagnosis between central and nephrogenic diabetes insipidus. Recently, copeptin and aquaporin-2 have also been used in the differential diagnosis of central versus nephrogenic diabetes insipidus. Aquaporin is both synthesized in the kidney and excreted in urine in response to vasopressin. Patients with CDI show no increase in aquaporin-2 with dehydration, but their excretion increases in response to desmopressin, suggesting that aquaporin-2 expression persists in patients with CDI. Thus, the main value of aquaporin-2 in the differential diagnosis of diabetes insipidus would be to specify a diagnosis of nephrogenic diabetes insipidus when there is no increase in aquaporin excretion following desmopressin administration.

Once the diagnosis of CDI has been established, other investigations are mandatory, including tumor markers, skeletal survey (in LCH, the skull is involved in as many as 85% of cases), and especially brain neuroimaging (Fig. 385.6). On an MRI, the posterior pituitary can be seen as a hyperintense signal on sagittal T1-weighted imaging under basal conditions. A lack of posterior pituitary hyperintensity (although not specific) is a hallmark of hypothalamic-posterior pituitary disorders and may represent the early stage of occult local tumors. In autosomal dominant CDI, the identification of posterior pituitary hyperintensity does not necessarily indicate that the functional integrity of the hypothalamic-neurohypophyseal axis is preserved. When present, the signal disappears on a regular basis at follow-up.

Thickening of the pituitary stalk or infundibulum, defined as exceeding 3 mm, although not specific, is observed in approximately one third of children with CDI. Pituitary stalk size at presentation is variable and can change over time. In two large pediatric series of idiopathic CDI patients, pituitary stalk thickening was found in approximately 50–60% of subjects. Spontaneous evolution of thick pituitary stalk was similar in both reports from unchanged (30%), to reduction (30–50%) or further enlargement (10–20%) of stalk size. Among patients with idiopathic CDI and thick pituitary stalk, 90–94% developed anterior pituitary hormone deficits with isolated GHD accounting for 60% of cases. Multiple pituitary hormone deficits were present in 30–50% of patients with widened pituitary stalk while only 10% of the 19 patients with normal pituitary stalk had an additional hormonal deficit.

Clinical, radiological and endocrine studies are necessary during follow-up. In particular, MRI follow-up is recommended for all patients with widened pituitary stalk (every 3–6 months); enlargement of the pituitary stalk lesion (>6.5 mm) or of the AP gland (AP size is age-dependent) or third ventricle involvement are all indications for pituitary stalk biopsy (Table 385.4, Fig. 385.7). Dynamic MRI may help to identify cases of CDI and normal PS size associated with abnormal blood supply to the posterior pituitary.

Table 385.3
Interpretation of water deprivation test and DDAVP test

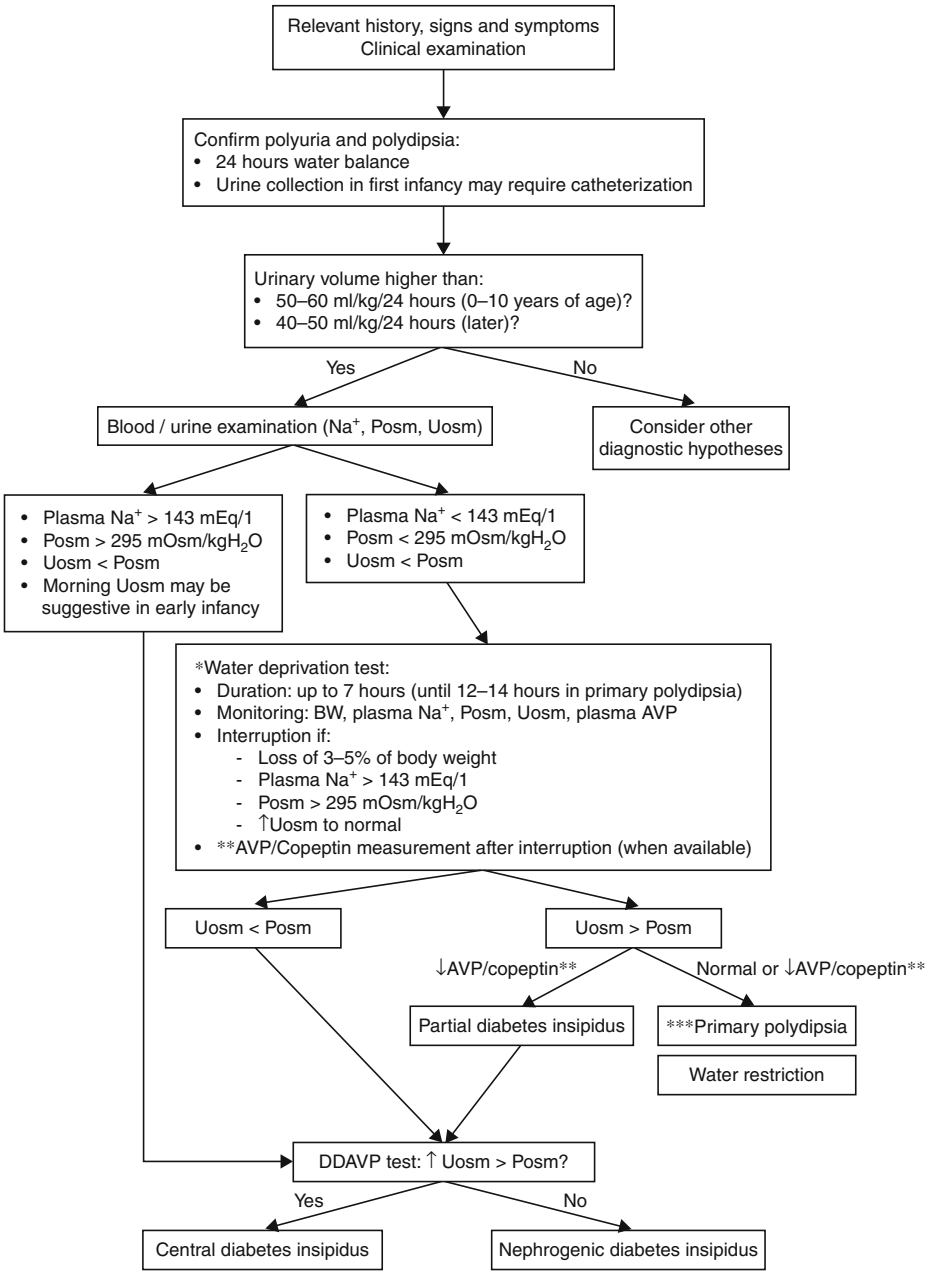
Urine osmolality (mOsm/kg)		
After fluid deprivation	After DDAVP	Diagnosis
<300	>750	CDI
<300	< 300	NDI
>750	–	PP
300–750	<750	? Partial CDI
		? Partial NDI
		? PP

CDI central diabetes insipidus, *NDI* nephrogenic diabetes insipidus, *PP* primary polydipsia

Differential Diagnosis

Nephrogenic Diabetes Insipidus

Nephrogenic diabetes insipidus may reflect an intrinsic renal defect or it may be an acquired disorder that is secondary to metabolic disease, including hypercalcemia and hypokalemia, that impairs the action of vasopressin on the distal nephron. There are now a few recognized forms of hereditary NDI: X-linked NDI, which is due to abnormalities of the gene for the vasopressin V2-receptor *(AVPR2)* in the kidney with resistance of renal tubules to the action of vasopressin, and autosomal recessive or autosomal dominant NDI, due to abnormalities of the acquaporin-2 (*AQP2*) water channel. Molecular studies have identified a number of genetic mutations or deletions



Legend:

Diagnostic flow chart of polyuria-polydipsia. NB: Normal ratio: Uosm/Posm>1.5).
BW, Body Weight; Posm, Plasma Osmolality; Uosm, Urine Osmolality.
*Laboratory **confirmatory mainly in partial diabetes insipidus.
***Primary polidipsia has different pattern of Na and Posm which did not reach the reported cut-off

Figure 385.5
Diagnostic flowchart for polyuria – polydipsia

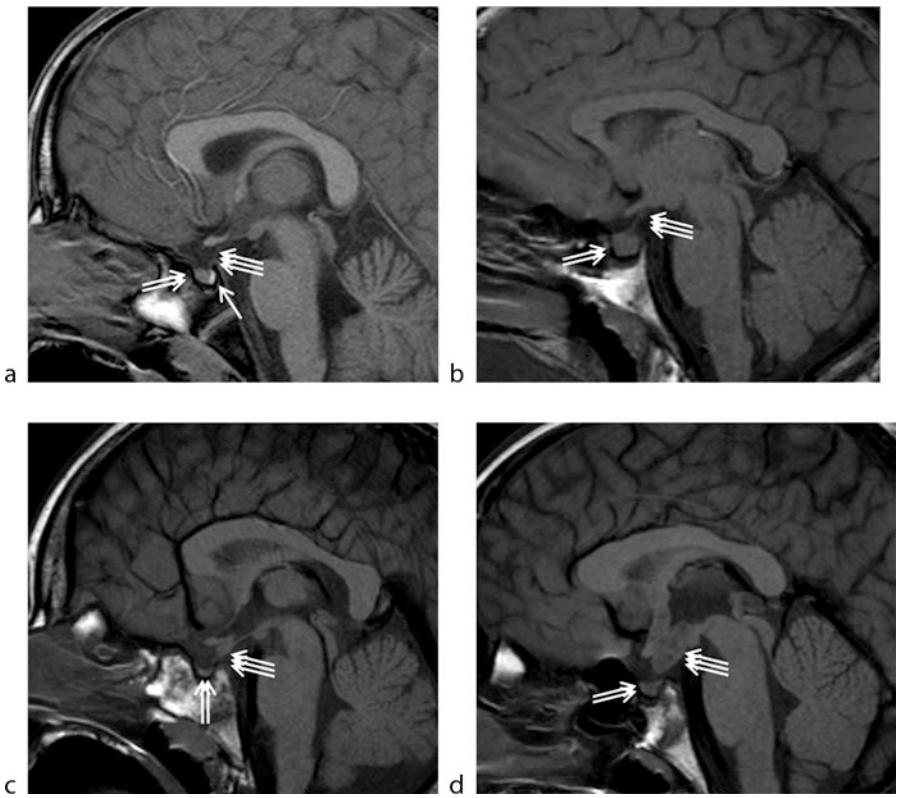


Figure 385.6
Sagittal T1-weighted MRI scans of: (a) normal subject showing normal posterior pituitary hyperintensity (*single arrow*), normal anterior pituitary (*double arrow*), and normal pituitary stalk size (*triple arrow*); (b) subject with idiopathic central diabetes insipidus showing absent posterior pituitary hyperintensity, normal anterior pituitary for age and sex (*double arrow*), and normal pituitary stalk size (*triple arrow*); (c) subject with idiopathic central diabetes insipidus showing absent posterior pituitary hyperintensity, small anterior pituitary (*double arrow*), and enlarged pituitary stalk (*triple arrow*); (d) subject with central diabetes insipidus and germinoma, showing absent posterior pituitary hyperintensity, normal anterior pituitary (*double arrow*), and huge mass encompassing pituitary stalk and hypothalamus (*triple arrow*)

Table 385.4
Biopsy criteria of thick pituitary stalk

Author	Years	PST and CSF-hCG	PST	PST	Additional findings
Mootha	1997	+	Increase		
Leger	1999	+	Increase	7 mm	
Maghnie	2000/2007	+/−	Increase	>6.5 mm	Increase AP
					Pineal calcifications
					Third ventricle involvement
Al-Agha	2001	+	Increase		
Alter	2002	+	Increase		

CSF-hCG, cerebrospinal fluid–human chorionic gonadotropin, *PST* pituitary stalk thickening, *AP* anterior pituitary

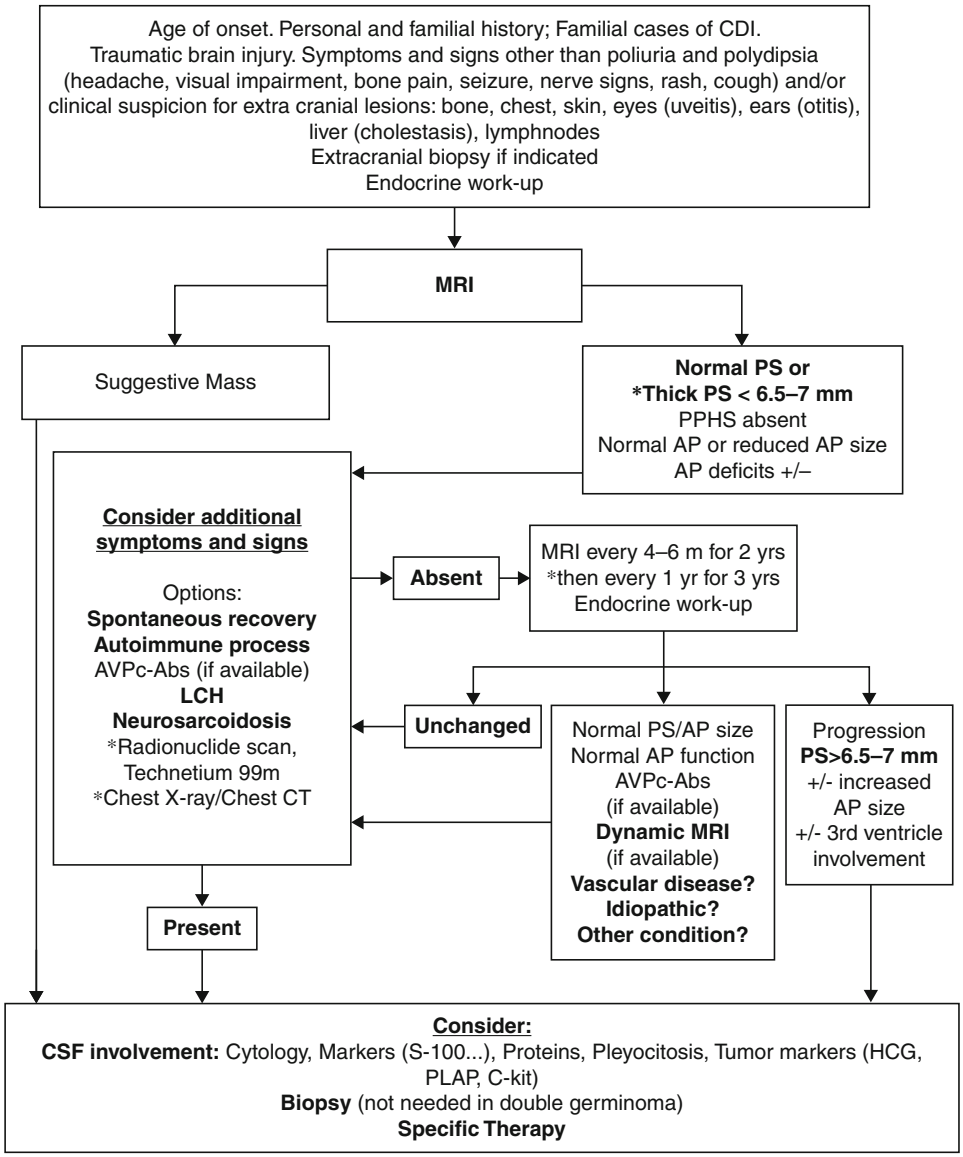


Figure 385.7
Diagnostic flowchart for central diabetes insipidus

of the gene that encodes for the vasopressin V2-receptor located on Xq28. The V2-receptor is a seven-domain transmembrane protein, and genetic abnormalities have been located in the transmembrane domain as well as in the external and internal segments of the receptor. At present, more than 180 different mutations in *AVPR2* have been described. These mutations all cause congenital nephrogenic diabetes insipidus and, consistently, are inactivating mutations, resulting in receptor malfunction at different levels, such as reduced receptor expression at the cell surface or disturbances in hormone binding and G protein coupling. The autosomal recessive form accounts for 10% of patients with familial NDI.

Primary Polydipsia

Primary polydipsia is characterized by excessive water drinking that suppresses vasopressin secretion. The ingested water causes an increase in body fluids and

a modest dilution of serum osmolality. The causes of primary polydipsia include psychogenic and dipsogenic primary polydipsia, whereas frank psychiatric compulsive drinking is an uncommon cause in children. The polyuria and polydipsia are temporary and reversible and strictly correlated to the improvement of the underlying cause. Patients usually remain normonatremic despite large fluid intake, although plasma sodium and osmolality may be low-normal or slightly reduced (*Table 385.3*).

Central Diabetes Insipidus and Thirst Abnormalities

Adipsic disorders are characterized by inappropriate lack of thirst, with consequent failure to drink to correct hyperosmolality. The incidence of postoperative CDI and thirst abnormalities have recently been reported to be about one third of patients with craniopharyngiomas. Adipsic CDI is characterized by abnormally low thirst scores and no thirst response to marked plasma hypertonicity during hypertonic saline infusion.

Patients with craniopharyngioma who develop an adipsic syndrome and postoperative CDI fail to increase serum AVP in response to drug-induced hypotension; moreover, they do not express thirst sensation after either a fall in blood pressure or hypertonic saline infusion, indicating that both osmotic and non-osmotic pathways are involved. A failure to secrete AVP in response to hypotension or hypovolemia may increase the risk of dehydratation and life-threatening hypernatremia. In adipsic patients, a fixed daily fluid intake appropriate for a weight at which the patient is known to be eunatremic and euvolemic should be established. Desmopressin is then administered at a dose and frequency capable of establishing an appropriate urine output and neutral fluid balance, allowing for insensible losses; regular weighing and checking of serum sodium levels are mandatory.

The Syndrome of Inappropriate Antidiuretic Hormone Secretion

Causes of hyponatremia in children include the syndrome of appropriate antidiuretic hormone secretion (SAADH) and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Although often less discussed and considered than SIADH, SAADH is by far the most common cause of hyponatremia in the pediatric population. Cerebral salt wasting syndrome (CSWS) as a cause of hyponatremia may exist, but is often diagnosed and reported without substantiation. It has been suggested that brain injury results in the direct secretion of natriuretic factors that result in renal salt losses, volume concentration, and AVP secretion, though available evidence shows that the heart is the major source of most circulating natriuretic peptides. The clinical status, assessment of extracellular fluid space volume status, measurement of urinary electrolytes, and responses to infusion of saline solutions can distinguish these conditions. Classical SIADH has basically been defined as an exclusion diagnosis when other causes for hyponatremia can be excluded: (1) in the absence of hypovolemia, (2) no evidence of diseases accompanied by edema, (3) non-endocrine dysfunction, including adrenal insufficiency and hypothyroidism, (4) no renal failure, and (5) no administration of drugs that can influence water homeostasis.

A novel disorder of water balance, with a SIADH-like clinical picture, which has been termed "nephrogenic syndrome of inappropriate antidiuresis" has been reported. Feldman and coauthors describe two unrelated male infants with euvolemic hyponatremia and serum hypo-osmolality, along with inappropriately elevated urine osmolality and urine sodium concentrations. At first glance, the disorder in these boys resembles the syndrome of inappropriate antidiuretic hormone secretion, a relatively common disorder characterized by insufficient suppression of AVP secretion in relation to the degree of hypo-osmolality, which leads to inappropriate urine concentration. Since serum AVP levels were undetectably low in both boys, Feldman et al. ruled out SIADH and hypothesized that a hyperactive V2 receptor could be the underlying cause of the disorder. Sequencing of *AVPR2* in the two patients revealed a hemizygous point mutation in each. In an in vitro functional assay, both mutations were shown to lead to the production of a constitutively active V2 receptor. The consequence was AVP-independent and, therefore, inappropriate, activation of V2 receptor–mediated renal urine concentration. Remarkably, and for reasons that remain unexplained, neither patient showed any clinical or biochemical sign of constitutive activation of extrarenal V2 receptors, which are known to mediate increases in circulating coagulation and fibrinolytic factors and a decrease in diastolic blood pressure after AVP stimulation.

Treatment

Treatment of CDI

The drug of choice for the treatment of diabetes insipidus is desmopressin (DDAVP), a synthetic analog of the endogenous hormone arginine vasopressin, but with a

2,000–3,000-fold lower vasopressor effect. Desmopressin may be administered orally, intranasally, or parenterally. Given intranasally or orally, maximum plasma concentrations are reached in 40–55 min. The drug's half-life is 3.5 h. Generally, urine output will decrease 1 or 2 h after administration, and the duration of action will range from 6 to 18 h. There is broad individual variation in the dosage required to control diuresis. Daily dosages for oral preparations vary from 100 to 1,200 μg in three divided doses, for the intranasal preparation approximately 2–40 μg, and for the parenteral, 0.1–1 μg. A low dose should be used initially and increased as necessary. Oral desmopressin has been shown to be particularly helpful in childhood. Its positive characteristics include better absorption, fewer complications and, due to the easy route of administration, good compliance among children and adolescents. Symptomatic dilutional hyponatremia is the only potential hazard if desmopressin is administered in excess over a prolonged time period. Symptoms of hyponatremia include headache, nausea, vomiting, and seizure. Untreated, these symptoms can lead to coma and death. However, asymptomatic hyponatremia can also occur. Particular attention is required in cases of multidrug therapy because of the risk of extrapontine myelinolysis.

Rare side effects with intranasal delivery of DDAVP include eye irritation, headache, dizziness, rhinitis or epistaxis, cough, flushing, nausea, vomiting, abdominal pain, chest pain, palpitations, and tachycardia. Evidence to date indicates that the use of DDAVP during pregnancy is safe and is not related to adverse effects on the mother or fetus/child.

In the presence of adipsia or hypodipsia, diabetes insipidus presents a difficult challenge and initially is best managed by adjusting the DDAVP dosage and fluid intake in a hospital setting. Daily weight can be used as an index of fluid balance, but regular monitoring of electrolytes will be required as well.

In early infancy, intranasal preparations can be administered by either rhinal tube (dose range 1–10 μg) or by a metered dose spray (5–10 μg). When infants are treated with DDAVP, dilute preparations of the rhinal tube solutions are often used. Because DDAVP stability is reduced by dilution, these preparations should not be used for more than 1 week.

Treatment of Nephrogenic Diabetes Insipidus

To date, no specific treatment that is aimed at restoring the function of the mutant V2 receptor is available to treat patients with X-linked NDI. Volume contraction and thiazide diuretics, amiloride, and indomethacin act only indirectly by decreasing the amount of tubular fluid presented to the distal tubule. Successful treatment has been reported with a combination of amiloride (20 mg/1.73 mq2 per day or 0.3 mg/kg per day orally three times a day) and/or hydrochlorotiazide (1–3 mg/kg/day two to three times per day orally) and/or indomethacin (1–3 mg/kg/day two to three times per day orally).

Treatment of SIADH

The key to effective management of hyponatremia is establishing the type and its cause, so that the cause can be removed, if possible, and management will be appropriate. It is paramount to clarify whether the hyponatremia has developed quickly (over a few days) and is acute, or whether it has developed over days to weeks and is chronic. The speed at which the serum sodium concentration is corrected should be closely linked to the suspected time over which the hyponatremia has developed. If the patient has only mild hyponatremia symptoms (headache, lethargy, dizziness), or is asymptomatic, and the hyponatremia is not severe, with sodium level >125 mmol/l, a conservative approach is recommended. Discontinuation of all possible offending drugs is important. In SIADH or the edema-producing states, a trial of water restriction to less than 1–1.25 l/day (depending on the degree of hyponatremia and the age of the patient) can be attempted; the serum sodium level should be measured at regular intervals to measure improvement. If the serum sodium level continues to fall, the patient may require an intravenous trial of normal saline to clarify the diagnosis: if the patient has ECF volume contraction as in CSWS (which may not be clinically apparent), a trial of saline will always improve serum sodium levels, whereas in cases of SIADH, the hyponatremia will worsen. The trial should be done with caution, following the "rules" for sodium correction by using 3–5% saline infusion at 0.1 ml/kg of body weight/min (up to 1–2 ml/kg of body weight/h) (*Table 385.5*).

Rapid correction can result in osmotic demyelination syndrome, with resultant severe brain injury and, potentially, death. Oral urea for the treatment of chronic syndrome of inappropriate antidiuresis in children has been reported to be successful; 30% oral urea solution at a starting dose of 0.1 g/kg/day divided into four doses and increased gradually to 2 g/kg/day.

Table 385.5
"Rules" for sodium correction

• In general, correct serum sodium concentration at an hourly rate of no more than 0.5 mmol/l
• If symptoms are severe, more rapid correction is necessary in the first 2–3 h, since the patient is at risk of cerebral edema
• Choose an intravenous solution according to the symptoms. Isotonic saline should, as a rule, raise serum sodium concentration by 1–2 mmol/l of infused saline. Reserve hypertonic saline (5 mmol/10 ml) for patients with severe symptoms
• Three to five percent hypertonic saline 0.1 ml/kg body weight/min (up to 1–2 ml/kg body weight/h) for 2 h; this solution should correct serum sodium concentration by about 10 mmol/l over the first day
• In extracellular fluid (ECF) volume contraction, isotonic saline should be the first choice for therapy, as it will expand the ECF volume, which will lead to decreased AVP release and help correct serum sodium concentration

Future Developments

Chaperones in NDI

The indirect forms of treatment of NDI are most effective in patients who have mild to moderate forms of X-linked NDI and bear incomplete loss-of-function mutations. These patients with mild to moderate disease are rare as most patients are completely unresponsive to AVP or DDAVP. The proposed pharmacologic chaperone-based therapy could represent a potential general treatment of severe forms of NDI.

Hyponatremia and Vasopressin Antagonists in Clinical Development

Currently, there are four nonpeptide agents in various stages of clinical trials. Conivaptan is a combined V1aR and V2R antagonist, whereas the others are selective V2R antagonists. In December 2005, conivaptan was approved by the FDA for the treatment of euvolemic hyponatremia, and in February 2007 this indication was extended by the FDA to include hypervolemic hyponatremia. All agents of this class are inhibitors of the cytochrome P450 3A4 (CYP3A4) system, but conivaptan appears to be the most potent in this regard. Although the drug is orally active, to minimize the possibility of drug interactions, the FDA has restricted its distribution to a parenteral form for short-term (4-day) in-hospital use only. The remaining V2R antagonists appear to have more limited CYP3A4 interactions and are currently being developed for long-term oral use.

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386 Growth Disorders

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Definition/Classification

Short stature is defined as height that is 2.5 SD or greater below the mean for age. However, suboptimal growth that may be present without absolute short stature should also warrant attention. Suboptimal growth is defined as height velocity less than the 3rd percentile for age. It is important to keep in mind that the most commonly available growth charts may not be applicable to all ethnic groups since they have been derived from primarily white populations.

The differential diagnosis for short stature and abnormal growth is extensive and includes both endocrine and non-endocrine causes. Growth disorders can be broadly categorized into three groups: (1) primary growth abnormalities in which there are intrinsic defects of the growth plate; (2) secondary growth abnormalities in which growth failure is due to chronic disease or endocrine disorders; and (3) genetic short stature. Examples of primary growth abnormalities include intrauterine growth retardation and chromosomal abnormalities. Examples of secondary growth abnormalities include malnutrition, hypothyroidism, and growth hormone deficiency. Given the broad range of causes of short stature, one must consider the pathogenesis/pathology in terms of the specific etiology of short stature. However, regardless of the etiology of short stature, it is important to understand normal growth and the factors that regulate normal growth. The next section will review normal growth. Later clinical manifestation and pathogenesis/pathology will be discussed in the differential diagnoses as they pertain to specific etiologies of short stature.

Etiology

Normal Growth

One of the most important roles of physicians taking care of children is the careful assessment of their growth. Though many factors contribute to growth, children normally grow in a fairly predictable manner. Growth rates vary at different stages in life. Prenatal growth averages 1.2–1.5 cm/week. During the first 2 years of life, growth velocity averages 15 cm/year and slows during mid-childhood to 6 cm/year. The pubertal growth spurt begins earlier in girls than in boys. Total pubertal growth is about 17% of adult height in boys and about 15% in girls. In general, girls grow an additional 5 cm after menarche. Though the timing of the pubertal growth spurt varies in normal children, the final height is not normally affected by the time of onset of the pubertal growth spurt. Growth is complete when chondrocyte proliferation in the growth plate slows and epiphyses fuse, forming the adult skeleton.

Endocrine Regulation of Growth

The pituitary gland is extremely important in understanding the regulation of growth. The pituitary gland is formed from two distinct sources – The adenohypophysis (anterior, intermediate, and infundibular pituitary) is derived from Rathke's pouch and the neurohypophysis (posterior pituitary) is derived from the neural ectoderm of the floor of the forebrain. The adenohypophysis is normally 80% of the pituitary, of which the anterior pituitary is the largest part and contains the most hormone producing cells. Growth hormone (GH)–producing cells can be detected in the adenohypophysis by 9 weeks gestation.

The pituitary is normally found in the sella turcica so that the volume of the sella turcica is a good indicator of pituitary size. The pituitary is also in close proximity to the optic chiasm so that any child with optic chiasm hypoplasia, congenital blindness, or nystagmus should be evaluated for hypothalamic/pituitary dysfunction. This anatomic proximity also explains why pituitary tumors may initially present with visual complaints or decreased peripheral vision.

Growth Hormone

Human GH is a single chain, 191 amino acid, 22-kDa protein. The pulsatile secretion of GH secretion is regulated by the interaction between two hypothalamic peptides, growth hormone–releasing hormone (GHRH),

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and somatostatin (somatotropin release-inhibiting factor [SRIF]). GHRH regulates GH production mainly at the transcription level. The GHRH receptor is a member of the G-protein-coupled receptors. Abnormalities in the connection between the hypothalamus and the anterior pituitary that prevent GHRH binding to somatotropes are thought to be the most important causes of clinical GH deficiency in children. Somatostatin is believed to be involved in the timing and amplitude of pulsatile GH secretion. Other factors that stimulate GH secretion are: fasting, deep sleep, hypoglycemia, stress, sex steroids, and ghrelin. Factors known to suppress GH secretion are: obesity, glucocorticoids, hyperglycemia, hypothyroidism, and insulin-like growth factor 1 (IGF-1). IGF-1 regulates the synthesis and secretion of GH through feedback regulation.

The pulsatile secretion of GH is characterized by intermittent bursts in serum GH levels separated by periods of low serum GH levels. During these periods of decreased GH secretion, GH levels are normally low, making random serum sampling of GH useless. GH levels peak during deep sleep. The biologic effect of pulsatile GH secretion on growth is not completely understood; however, studies show that larger swings in GH output in an irregular sequence is associated with better growth.

Prenatally, fetal GH can be detected in the serum by the end of the first trimester with peak levels in midgestation. During the neonatal period, GH levels drop and continue to drop through childhood and early puberty. During adolescence, GH secretion peaks again, resulting in high serum IGF-1 levels associated with puberty. GH and IGF levels start to decline from late adolescence into adulthood.

GH exerts its biologic actions both through IGF-dependent and IGF-independent mechanisms. Though GH may have some effect on skeletal growth independent of IGF activity, most of its effect is likely through its ability to stimulate the IGF axis. In addition to its effects on growth, GH has important metabolic effects. In muscle, it increases lean tissue mass by increasing amino acid transport and nitrogen retention. In adipocytes, it causes insulin resistance by decreasing glucose transport and increasing lipolysis.

Growth Hormone Receptor and Binding Protein

The human GH-receptor (GHR) gene is located on chromosome 5p13.1-p12. Upon binding to its receptor, GH stimulates phosphorylation of Janus kinase 2 (JAK2), a tyrosine kinase protein associated with the receptor. Activation of JAK2 leads to phosphorylation of intracellular tyrosines of the GHR, which provide docking sites for important intermediary proteins such as signal transducers and activators of transcription (STATs). In particular, STAT5b plays a crucial intermediary role in GH regulation of *IGF-1* gene transcription and growth.

Growth hormone binding protein (GHBP) is the extracellular domain of the GH receptor and modulates GH binding to its receptor. It is thought that GHBP increases the half-life of GH by impairing its glomerular filtration. GH-receptor levels and activity are directly related to GHBP levels such that GH insensitivity is associated with low levels of GHBP. Various physiologic factors affect levels of GHBP. Low levels are associated with malnutrition, chronic diseases such as diabetes mellitus, hypothyroidism, liver disease, and various inherited abnormalities of the GH receptor; whereas high levels are associated with obesity, refeeding, early pregnancy, and estrogen treatment. GHBP levels are low in infancy, rise through childhood, and stabilize during puberty and adult life.

Insulin-Like Growth Factors

Insulin-like growth factors (somatomedins) are a family of peptides that mediate many of GH actions. IGFs are characterized by having their serum concentrations dependent on GH, having insulin-like activity in extraskeletal tissues, promoting the incorporation of sulfate into cartilage, and stimulating DNA synthesis and cell multiplication. Two types of IGFs are IGF-1 and IGF-2. Both are structurally similar to insulin giving them the ability to bind to the insulin receptor. However, structural differences between the IGFs and insulin prevent insulin from binding with high affinity to the IGF-binding proteins.

GH is apparently the primary regulator of IGF-1 gene transcription via STAT5b. Regulation of IGF-2 gene expression is less clear. IGF-2 gene expression is high in fetal life, but declines postnatally. The IGF system is important for both intrauterine and postnatal growth.

Currently, the most practical method to accurately assess IGF levels with minimal IGFBP interference is done with either ELISA or IRMA. It is important for individual laboratories to develop their own population-specific reference ranges and to take into account ethnic, nutritional, and environmental variations that may impact "normal" IGF-1 values.

IGF-1 levels are relatively low during fetal life. Serum levels rise during childhood and reach adult levels at the

onset of puberty. During adolescence, levels correlate more closely with Tanner stage or bone age than with chronological age. IGF-1 levels peak to about two to three times adult levels during puberty. Levels gradually decline after adolescence to adult levels.

IGF-1 levels are more GH-dependent than IGF-2 levels. However, IGF-1 levels are also affected by age, pubertal status, and nutritional status. In normal children less than 5 years of age, IGF-1 levels are low. There is also overlap between normal values and values in GH-deficient children. IGF-2 levels are less age-dependent, but are less GH-dependent than IGF-1.

Numerous studies have been done to examine the relationship between GH status and IGF-1 levels. Rosenfeld and colleagues found that in 68 GH-deficient children, 197 children with normal stature, and 44 normal children with short stature, 18% of the GH-deficient children had normal IGF-1 levels for age and 32% of normal short children had low IGF-1 levels for age. Fifty-two percent of the GH-deficient children and 35% of normal short children had low IGF-2 levels. However, they found that when IGF-1 and IGF-2 assays were combined, only 4% of GH-deficient children had normal levels of both IGFs and only 0.5% of normal children and 11% of normal short children had low serum levels of both IGFs. The inconsistent correlation between GH status and IGF-1 levels demonstrated in this study may partially be explained by the arbitrary definition of GH-deficiency based on GH stimulation tests and variations in GH assays.

IGF-Binding Protein

IGF-binding proteins (IGFBPs) are a family of proteins that complex with IGFs and extend their serum half-lives, transport them to target cells, and modulate their interaction with surface membrane receptors. Six different human IGFBPs (IGFBP-1 to 6) have been described.

In general, IGFBPs appear to inhibit IGF action by competing with IGF receptors for binding IGF peptides. However, in some situations, IGFBPs may also promote IGF action by helping to deliver IGF to target receptors.

The majority of IGF peptides are carried in a ternary complex made up of one IGF molecule, one IGFBP-3 molecule, and one acid-labile subunit (ALS) molecule. It is the large size of this ternary complex that extends the half-life of IGF from 10 min for IGF alone, to 1–2 h for IGF-IGFBP-3 binary complex, to 12–15 h for the ternary complex. Both IGFBP-3 and ALS levels are GH-dependent. Due to this GH regulation of the IGF axis, patients with GH deficiency or insensitivity have little IGF in the ternary complex with most being in the binary complex with IGFBP-3 or bound by other IGFBPs.

Levels of IGFBP-3 may be most valuable clinically given its GH dependence. In fact, IGFBP-3 measurements may be superior to IGF-1 measurements in the evaluation of GH deficiency since IGF-1 levels are low in childhood and often overlap in normal and GH-deficient children; whereas IGFBP-3 levels reflect both IGF-1 and IGF-2 levels, and are therefore less age-dependent.

Diagnosis

Assessment of Growth

Anthropometric

Deviation in normal growth is often an early sign of an underlying disease, either endocrine or non-endocrine. It is therefore important to review the proper techniques in accurately measuring growth and using growth charts.

Children less than 2 years of age should have their supine length measured. The infant's legs should be fully extended and its head in the Frankfurt plane. Older children who are able to stand should have their height measured using a wall-mounted "Harpenden" stadiometer with a rigid headboard. The child should be fully erect with the head in the Frankfurt plane and the back of the head, thoracic spine, buttocks, and heels touching the vertical axis of the stadiometer. Since diurnal variation in standing height has been observed, serial measurements should ideally be done at the same time of day.

Additionally, it is ideal to have the same individual perform serial measurements of length or height. The average of triplicate measurements should be recorded, with no more than 0.3 cm variation among the values. A minimum of 3–6 months, with 6–12 months being ideal, between measurements is necessary for accurate determination of growth velocity.

When assessing abnormal growth, it is also important to assess disproportionate growth by measuring and comparing the following to published age standards: head circumference, lower body segment (distance from the superior pubic symphysis to the floor), upper body segment (sitting height), and arm span.

After careful assessment of height, the child's height should be evaluated in the context of normal standards, which are typically cross-sectional. The most recent growth charts using cross-sectional data were published in 2000 by the National Center for Health Statistics (NCHS) (www.cdc.gov/growthcharts). These charts allow assessment of

a child's height and growth relative to the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles of normal American children. However, these charts have two major limitations. First, the growth rates of children below the 5th or above the 95th percentiles are not provided. Second, cross-sectional data are more valuable during infancy and childhood than in adolescence when growth rates can vary due to variations in the onset and progression of puberty. A Dutch web-based growth analyzer is also available at www.growthanalyser.org. Tanner and colleagues have developed longitudinal growth charts that account for timing of puberty. Height velocity standards have also been developed using cross-sectional and longitudinal data. Additionally, disease-related growth charts are available for conditions associated with growth failure such as Turner syndrome, achondroplasia, and Down's syndrome.

Since children normally grow in a remarkably predictable manner between the age of 2 years and the onset of puberty, any "crossing" of height percentiles or abnormal height velocities during this time period merit further evaluation.

Radiologic

Genetic factors and hormones such as growth hormone (GH), thyroxine, and gonadal steroids, particularly estrogen, are involved in controlling the appearance and maturation of ossification centers in normal children. The "bone or skeletal age" can be used to estimate the growth potential in tubular bones by evaluating the progression of ossification in the epiphyses compared to normal age-related standards. The bone age is commonly obtained using a radiograph of the left hand and wrist and compared to the published male and female standards of Greulich and Pyle. It is important to keep in mind that the determination of bone age requires experience in order to minimize variability between observers. Additionally, normal skeletal maturation rates depend not only on gender, but also on ethnicity; the standards of Greulich and Pyle were developed between 1931 and 1942 in normal American white children, and are still widely used worldwide. Finally, given the standards were determined using normal children, extrapolation to children with endocrine abnormalities or skeletal dysplasias may be limited.

Height Prediction. A child's adult height can be predicted based on the degree of skeletal maturation observed on the bone age. The more delayed the bone age relative to the chronological age, the more time there is before epiphyses fusion and growth cessation. The more advanced the bone age, the more accurate the predicated adult height since the patient is closer to the final height. The most commonly used height prediction method was developed by Bayley and Pinneau, and utilizes the bone age, height, and a semiquantitative allowance for chronologic age.

Midparental Target Height and Parent-Adjusted Growth Curves

It is helpful to assess the child's growth relative to that of the parents and siblings given the importance of genetic factors in the determination of a child's growth and height potential. Additionally, the child's predicted adult height can be compared to the midparental target height. When there is a discrepancy between these comparisons, one should consider the possibility of a pathologic process. The midparental target height is equal to the mean of the parental heights with the addition of 6.5 cm for boys and subtraction of 6.5 cm in girls. Two standard deviations for the calculated height is ±10 cm.

Biochemical

Upon initial assessment, the following serum values should generally be obtained: complete blood count, chemistry profile, liver function tests, thyroid function tests, sedimentation rate, IGF-1, IGFBP-3, and celiac screening panel. A karyotype should be done on all short, slow-growing females to rule out Turner's syndrome.

Figure 386.1 provides an algorithm for evaluating growth failure.

Diagnosing IGF Deficiency/GH Deficiency

Documentation of serial heights and height velocity provides the foundation for the diagnosis of GH/IGF deficiency. Evaluation of pituitary GH production is difficult given the pulsatile secretion of GH. Additionally, spontaneous GH secretion varies with gender, age, pubertal stage, and nutritional status. GH levels are usually undetectable with conventional assays in between normal pulses of GH secretion, making random GH measurements virtually useless, except in cases of GHI and GH excess. Therefore, GH stimulation tests have been used to measure GH reserve. GH stimulation testing is notoriously difficult to perform and its results often inconsistent. Additionally sex steroid priming in prepubertal children is not physiologic. While some have interpreted these difficulties in measuring GH as a reason to stop performing GH

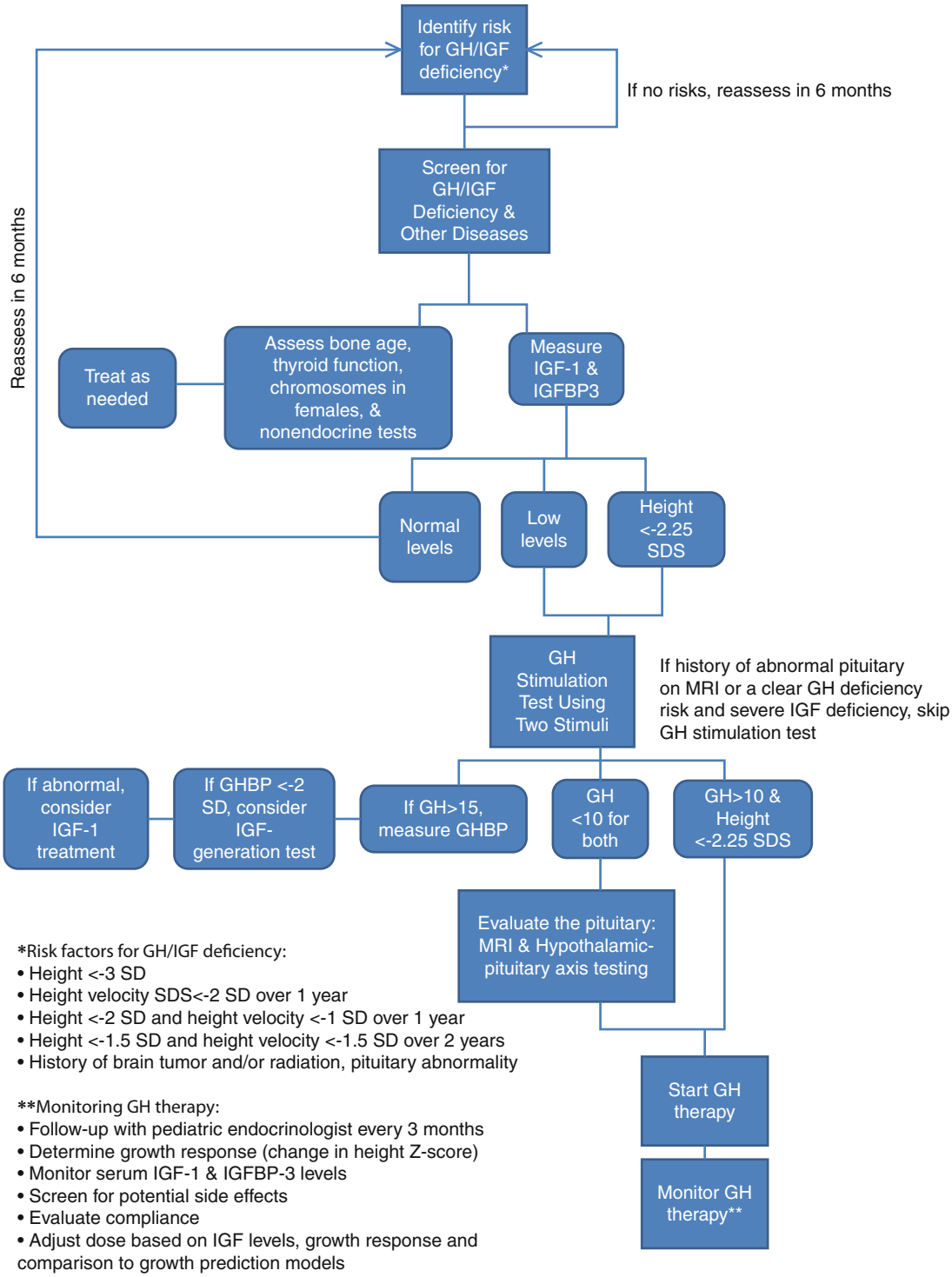

Figure 386.1
Algorithm for evaluating growth failure

Table 386.1
Growth hormone stimulation tests[a]

Stimulus	Dosage	Samples (min)	Comments/side effects
Levodopa (PO)	<15 kg: 125 mg	0, 60, 90	Nausea, emesis, headache
	15–30 kg: 250 mg		
	>30 kg: 500 mg		
Clonidine (PO)	0.15 mg/m^2	0. 30, 60, 90	Fatigue, postural hypotension
Arginine HCl (IV)	0.5 g/kg (max 30 g)	0, 15, 30, 45, 60	Late hypoglycemia
	10% arginine HCl in 0.9% NaCl over 30 min		
Insulin (IV)	0.05–0.1 IU/kg	0, 15, 30, 45, 60, 75, 90, 120	Hypoglycemia, requires supervision[b]
Glucagon (IM)	0.03 mg/kg (max 1 mg)	0, 30, 60, 90, 120, 150, 180	Nausea, late hypoglycemia

[a]Tests should be performed after an overnight fast. Patients should be euthyroid at time of testing
[b]Insulin-induced hypoglycemia is a potential risk of this procedure, which is designed to lower the blood glucose by at least 50%. D50W solution and glucagon should be available. Not recommended in newborn or small children

stimulation testing, it is still strongly recommended. It is critical to differentiate GH deficiency from idiopathic short stature (ISS) and secondary IGF deficiency from primary IGF deficiency. GH stimulation testing is still a cornerstone in the evaluation of short stature though GH measurements must be complemented with IGF-1 and IGFBP-3 measurements.

Physiologic stimuli of GH include fasting, sleep, and exercise. Pharmacologic stimuli include levodopa, clonidine, glucagon, propranolol, arginine, and insulin. *Table 386.1* includes information on pharmacologic GH stimulation testing. Stimuli that are easily administered, have low toxicity and risk, and of low specificity are used for screening and include exercise, fasting, levodopa, and clonidine. Stimuli that are used for definitive testing include arginine, insulin, and glucagon. Many centers will use fasting and a screening stimulus followed by fasting and a definitive stimulus. A child is generally considered to have GHD if there is failure to respond, defined as a peak GH level less than 10 ng/mL, to two separate stimuli.

Differential Diagnosis

Endocrine (Secondary) Causes of Short Stature

GH/IGF-1 Deficiency

Given the integral role of IGF-1 in both prenatal and postnatal growth and the complexity of the GH-IGF-1 axis, the category of GH/IGF-1 deficiency encompasses a wide range of disorders that ultimately result in IGF-1 deficiency (IGFD). IGFD is divided into two main categories – primary and secondary IGFD. Primary IGFD includes disorders characterized by decreased IGF-1 production along with normal or elevated GH secretion, such as in states of GH insensitivity. Secondary IGFD includes disorders in which defects of the hypothalamus or pituitary cause decreased GH and subsequent IGF-1 production. Examples include tumors, infection, trauma, radiation, inflammation to the hypothalamus and/or pituitary, and molecular defects in pituitary development.

Clinical Features of GH/IGF Deficiency

The clinical features of GH/IGFD are dependent on the onset of IGF-1 deficiency. Though IGF-1 is critical to both prenatal and postnatal growth, its production in utero is mostly GH-independent, whereas its production postnatally is largely GH-dependent. Therefore, patients with secondary IGFD or with primary IGFD due to defect of GH action usually have near-normal birth size with growth failure becoming more obvious at several months of age. In contrast, patients with primary IGFD due to defects of the IGF-1 gene resulting in IGF-1 deficiency early in gestation have significant fetal growth retardation. Neonates can present with hypoglycemia, prolonged jaundice with direct hyperbilirubinemia due to cholestasis, microphallus, cryptorchidism, and scrotal hypoplasia. In severe GH/IGFD, growth failure can be evident in the first month of life with lengths 3–4 SD below the mean by 6–12 months. Bone age may be delayed relative to the chronological age, but similar to the height age. However, bone age and chronological age could be matched in acquired GHD, such as with a CNS tumor. Other clinical features include: "infantile" fat distribution, increased

weight/height ratios, poor musculature causing gross motor developmental delay, delayed fontanel closure with normal growth of the skull leading to an appearance of hydrocephalus, facial bone growth retardation causing an underdeveloped nasal bridge and frontal bossing, infantile voice due to hypoplasia of the larynx, sparse and thin hair growth, slow nail growth, small penis, and often delayed puberty. *Table 386.2* lists key history and physical exam findings that may indicate GHD.

Causes of GH/IGF-1 Deficiency

Hypothalamic. Some of the hypothalamic factors that regulate GH synthesis and secretion are GHRH and GH-releasing peptides such as ghrelin and somatostatin. Some cases of IGF deficiency may be explained by mutations in the genes encoding these and other hypothalamic proteins.

A common cause of hypopituitarism is hypothalamic dysfunction from congenital malformations of the brain or hypothalamus. However, somatotropes still differentiate and proliferate despite the absence of hypothalamic regulation, resulting in reduced serum levels of GH and IGF-1 starting in the intrauterine period. GH deficiency is increased in cases of simple clefts of the lip and/or palate alone.

Septo-optic dysplasia (SOD) is a rare syndrome consisting of hypoplasia or absence of the optic chiasm and/or optic nerves, agenesis or hypoplasia of the septum pellucidum and/or corpus collosum, and hypothalamic insufficiency. Pituitary hormone deficiencies can range from isolated GH deficiency or in combination with TSH, ACTH, and/or gonadotropins deficiencies. Structural abnormalities of the pituitary stalk and ectopic posterior pituitary can be identified on MRI in some cases. Familial forms of SOD are associated with mutations of HESX1, which is expressed in early pituitary and forebrain development.

In "idiopathic" hypopituitarism or GHD, the hormone deficiencies are thought to be secondary to abnormalities of synthesis or secretion of hypothalamic hypophysiotropic factors. Idiopathic GHD has also been shown to be associated with abnormal pituitary structure on MRI, with more severe GHD associated with more significant structural abnormalities.

Brain tumors, especially midline tumors, such as optic nerve gliomas, germinomas, meningiomas, and ependymomas, are a major cause of hypothalamic insufficiency. Metastases from extracranial carcinomas, local extension of craniopharyngeal carcinomas, and Hodgkin's disease of the nasopharynx can also cause hypothalamic insufficiency.

Radiation of the brain can cause both hypothalamic and pituitary dysfunction. Damage to the hypothalamus occurs more often as it is more radiosensitive than the pituitary. The degree of dysfunction is relative to the dose of radiation administered with low doses associated more with isolated GHD and higher doses with multiple hormone deficiencies. The length of time after radiation also contributes to the number of deficiencies, which can develop over time. Chemotherapy can also impair adult height due to GH insensitivity, though to a lesser degree than radiation. GH stimulation testing may be normal in such cases due to radiation therapy; however, spontaneous GH secretion may be blunted due to a decrease in pulse amplitude. Radiation can also cause decreased spinal growth potential, and early puberty with premature epiphyseal closure. The use of exogenous GH therapy in children with GHD and growth failure has not been associated with increased relapse of the primary neoplasm, though the response to therapy is variable.

Psychosocial dwarfism is an extreme form of growth failure resulting from a poor home environment and parenting. Fortunately, catch-up growth is possible once the child is removed from the dysfunctional environment.

Table 386.2
The Growth Hormone Research Society 2000 Criteria that may indicate growth hormone deficiency

• Neonatal hypoglycemia, prolonged jaundice, micropenis, or traumatic delivery
• Cranial irradiation
• Head trauma or central nervous system infection
• Consanguinity and/or and affected family member
• Craniofacial midline abnormalities
• Severe short stature – height more than 3 SD below the mean
• Height more than 1.5 SD below the midparental target height
• Height more than 2 SD below the mean and a height velocity over 1 year more than 1 SD below the mean for chronological age, or a decrease in height SD more than 0.5 over 1 year in children over 2 years of age
• In the absence of short stature, a height velocity more than 2 SD below the mean over 1 year or more than 1.5 SD sustained over 2 years; this may occur in GHD, presenting in infancy, or in organic-acquired GHD
• Signs indicative of an intracranial lesion
• Signs of multiple pituitary hormone deficiency
• Neonatal symptoms and signs of growth hormone deficiency

Additionally, abnormal GH secretion during GH stimulation testing associated with psychosocial dwarfism normalizes after removal from the dysfunctional environment. The diagnosis of psychosocial dwarfism is confirmed by normalization of GH secretion and subsequent catch-up growth. The neuroendocrinological mechanism of psychosocial dwarfism is not clear. Although GH secretion is low, exogenous GH therapy is typically not effective until removal from the dysfunctional environment.

Other hypothalamic causes of GHD include myelomeningocele, shunted hydrocephalus, head trauma, inflammation of the brain/hypothalamus due to infections and sarcoidosis, and neurofibromatosis.

Pituitary GH Deficiency. There are a number of abnormalities that specifically affect pituitary somatotrope development and function. Multiple genetic causes of GHD have been described affecting GH production, secretion, and bioactivity. GHD can also result from multiple pituitary hormone deficiency (MPHD) due to mutations of specific genes such as PROP1, POU1F1, SOX3, LHX3, and LHX4.

Primary tumors of the pituitary such as craniopharyngiomas can cause GHD. Growth failure exists at presentation in most children with craniopharyngiomas. The most common associated pituitary hormone deficiencies are GH and gonadotropins, though TSH, ACTH, and/or diabetes insipidus can also occur. Other pituitary tumors that can cause GHD include pituitary adenomas, though rare in childhood and adolescents. The incidence of hypopituitarism is higher with macroadenomas compared to microadenomas.

Langerhans cell histiocytosis is a disorder that is classically associated with diabetes insipidus, though studies have shown 50–75% of patients to have growth failure and GHD at presentation.

GH-Receptor Abnormalities. Primary GH insensitivity (GHI) was initially reported by Laron and colleagues. Approximately 250 worldwide cases have been identified, mostly from the Mediterranean region or Ecuador. Patients with GHI do not respond to exogenous GH with increases in serum IGF-1 and IGFBP-3 levels, growth, and metabolic changes. To date, more than 60 mutations of the GHR gene causing GHI have been reported. Most of the mutations are in the extracellular (GH-binding) domain of the GHR, which impairs GH from binding to its receptor leading to decreased circulating GHBP. Other GHR receptor mutations include those affecting the transmembrane or intracellular domains of the GHR. Levels of GHBP can be elevated in such individuals as the mutant receptor protein becomes detached from the cell receptor surface. As with congenital GHD, the range of clinical phenotypes of GHI due to GHR abnormalities is wide. Some features associated with growth failure due to GHR abnormalities include elevated serum GH levels in children (though may be normal in adults), decreased serum GHBP levels (though may be elevated as mentioned above), and profoundly decreased serum IGF-1, IGF-2, and IGFBP-3 levels.

GHR Signaling Defects. Seven cases of severe growth failure with markedly low serum levels of IGF-1, IGFBP-3, and ALS despite normal levels of GHBP and normal GHR gene sequence have been found to have GHR signaling defects due to mutations of the STAT5b gene. STAT5b is involved in a critical step in the pathway of STAT activation of IGF-1 gene transcription. It is also involved in the signaling pathway for multiple cytokines, which may be related to the immune dysfunction and recurrent pulmonary infections noted in the above cases.

ALS Mutations. Twenty cases with markedly reduced serum levels of IGF-1 and IGFBP-3 have been found to have mutations of the ALS gene. However, their growth relative to patients with mutations of GHR or STAT5b was only modestly affected, with some cases attaining normal adult height.

IGF-1 Gene Deletions. One case of a partial deletion of the IGF-1 gene resulting in a truncated IGF-1 molecule has been identified. IGF-1 levels were low, but IGFBP-3 and GHBP levels were normal. This individual had severe prenatal and postnatal growth failure, sensoneural deafness, mental retardation, and microcephaly, suggesting a role for prenatal IGF-1 in CNS development. Additionally GH overproduction was thought to cause the hyperinsulinism and insulin resistance noted in this patient. The patient was unresponsive to GH therapy, but responded well to IGF-1 therapy.

One case of an inactivating mutation of the IGF-1 gene has also been reported. The patient had similar phenotypical features as the individual with the IGF-1 gene deletion, but IGF-1 levels were markedly elevated.

Other causes of primary IGF-1 deficiency include genetic insensitivity to IGF action, primary defects in IGF transport, and clearance and primary defects in IGF-1 receptor production or responsivity.

Hypothyroidism

Thyroxine is essential for linear growth during the first year of life making early detection of congenital hypothyroidism with newborn screening critical. With proper replacement therapy, patients with congenital hypothyroidism can have normal growth and bone

mineral density, as well as normal pubertal growth and final adult height. In acquired hypothyroidism, growth failure is often the most prominent manifestation, though it can take years to become clinically evident. Children tend to be overweight for their height as linear growth is more affected. Bone age can be very delayed and body proportion is immature with an increased upper to lower body segment ratio. Hypothyroidism is associated with both delayed and precocious puberty, though the former is more common. In acquired hypothyroidism, replacement therapy causes rapid catch-up growth; however, full growth potential may not be attained because skeletal maturation during the first 18 months of treatment is rapid. Deficits in adult stature correlate with the duration of hypothyroidism before starting replacement therapy. Initiating replacement therapy near puberty may compromise catch-up growth even more so that lower replacement doses or pharmacologic delay of puberty may be considered.

Cushing's Syndrome

Both excessive endogenous and exogenous glucocorticoids can cause growth failure by impairing normal bone metabolism through inhibition of osteoblastic activity and enhanced bone resorption. GH secretion and IGF and IGFBP levels are typically normal. The effects of glucocorticoids on the epiphyses may persist even after correction of chronic excessive glucocorticoid exposure so that patients may fail to reach target heights. The degree of catch-up growth is directly related to the duration and level of glucocorticoid excess. Growth arrest may be the presenting sign of Cushing's syndrome in children; however, this may be masked in cases of adrenal tumors that secrete both excess glucocorticoids and androgens.

Pseudohypoparathyroidism

Growth failure is a common feature of pseudohypoparathyroidism along with characteristic dysmorphic features – short metacarpals, truncal obesity, subcutaneous calcifications, round facies, mental retardation, and hypocalcemia and hyperphosphatemia due to end-organ resistance to parathyroid hormone.

Rickets

Prior to the supplementation of vitamin D in breastfed and formula-fed babies, hypovitaminosis D was a major cause of short stature. Vitamin D is important for normal growth as evidenced by the association of the vitamin D receptor gene polymorphism with birth length, growth rate, adult stature, and bone mineral density.

In hypophosphatemic rickets, treatment with oral phosphate replacement and calcitriol improves rickets, but may not correct growth failure; however, earlier initiation of treatment in infancy may result in greater childhood and adult heights. GH therapy has been shown to improve skeletal growth and bone mineral density in some trials.

Idiopathic Short Stature

Idiopathic short stature is a very broad category in which the cause of short stature is unknown/idiopathic and encompasses groups of patients with constitutional delay of growth and maturation (CDGM) and genetic/familial short stature. The cause of such delay in growth and puberty is not well established. ISS is a condition in which an individual's height is more than 2 SD below the mean height for a given age, sex, and population group without systemic, nutritional, chromosomal, or endocrine abnormalities. Individuals with ISS have normal birth weights. Many children classified as having idiopathic short stature may have heights less than the 3rd percentile, slowed linear growth velocity, delayed bone age, and impaired or attenuated pubertal growth spurt. They typically have normal GH secretion, though GH stimulation test results may be blunted, especially in cases of delayed puberty. GH-dependent peptides can be lower based on chronological, but not necessarily, bone age. Children with ISS are often considered variants of normal growth and will naturally grow to final adult heights that are acceptable based on midparental target heights. However, some of these children are as short as those with GHD. Linear growth in children with ISS is often enhanced by treatment with GH.

ISS should be subdivided into those children with a familial history of short stature, whose heights fall within the expected range for parental target height, and those who are short relative to their parents. Children with no family history of short stature tend to have lower adult height compared to target height. ISS should also be subdivided into those with and without delayed bone age as an indicator for the possibility of delayed growth and puberty.

The following screening tests should be performed in the evaluation of ISS: complete blood count, ESR,

liver function tests, chemistry panel, TSH and free T4, IGF-1 levels, celiac screening panel, karyotype for all girls and for boys with genital anomalies, and a bone age X-ray. In order to make the diagnosis of ISS, growth hormone deficiency must be excluded based on clinical and biochemical evaluations. Children with history and physical exams consistent with GHD, low growth velocities, or low IGF-1 levels should be evaluated with growth hormone stimulation testing. However, most experts agree that children with normal growth velocities, no bone age delays, and IGF-1 levels above the mean for age do not require growth hormone stimulation testing. Hypothalamic-pituitary MRI is not indicated if a diagnosis of ISS is made.

Constitutional Delay of Growth and Maturation

Children with constitutional delay of growth and maturation are considered normal variants with respect to rate of maturation. They have short stature, relatively normal growth velocities during childhood, delayed puberty and growth spurt, and achieve normal adult height. Deviation from the normal growth curve occurs early in life around the 5th percentile by the age of 2 years, and may decrease more through the mid-childhood years without impacting final adult height. Final height is often at the lower end of the midparental target height range and is typically less than the predicted height based on bone age, though it is difficult to predict. Delayed growth may adversely affect bone mineralization and lead to the development of osteopenia.

Lower levels of gonadal steroids during delayed puberty may be associated with decreased GH secretion along with a transient partial GH deficiency. Given the lower levels of gonadal steroids, these children have delayed bone ages, normal or slightly low IGF-1 levels, normal IGFBP-3 levels for skeletal age, and normal GH stimulation tests if pretreated with gonadal steroids. Any child that does not fit these parameters should be evaluated for an underlying pathology causing short stature. Predicted adult heights should be normal (greater than 163 cm in males and 150 cm in females) in children with pure CDGM given sufficiently delayed bone ages. Children with both CDGM and familial short stature may have both delayed pubertal growth spurt and short final height.

Table 386.3 lists criteria for presumptive diagnosis of constitutional delay of growth and maturation.

Table 386.3
Clinical criteria that may indicate constitutional delay of growth and maturation

• Delayed puberty: – Males – failure to achieve Tanner G2 by age 13.8 years or P2 by 15.6 years – Females – failure to achieve Tanner B2 by age 13.3 years
• Delayed bone age (more than 1 year delayed)
• Family history of delayed puberty and growth
• No history of systemic illness and/or medications
• Normal nutrition
• Normal physical examination without evidence of skeletal dysplasias
• Normal laboratory findings: thyroid function tests, renal function tests, complete blood cell count, erythrocyte sedimentation rate, electrolytes
• Height between −2.5 and −1.5 SDS
• Height velocity >−1 SDS
• Normal predicted adult height: – Males > 165 cm (65 in.) – Females > 152 cm (60 in.)

Familial Short Stature

Given the polygenic nature of growth, it is important to evaluate a child's growth pattern in the context of familial growth and stature. Thus, a child whose growth rate is inconsistent with that of the family should be further evaluated. Additionally, many disorders, such as mutations of the GH-receptor gene, GH gene deletions, mutations of the PROP-1 or POUF-1 genes, and numerous other endocrine and non-endocrine diseases, causing growth retardation are inherited. Therefore, identifying a short child in the context of a short family requires an evaluation for the possibility of an underlying cause of short stature within the family.

Familial short stature (FSS) represents a constellation of clinical findings that is considered a normal variant. Height is at or below the 5th percentile, but the growth velocity is normal. FSS differs from constitutional delay of growth and maturation in that onset and progression of puberty is normal, resulting in a bone age that is commensurate with the chronological age. Both parents are short, often below the 10th percentile, and with histories of having normal puberty. Final height is short in FSS, but normal for the family. Though the GH-IGF system is normal in FSS, treatment with GH during childhood may improve growth velocity and final height.

Primary Growth Disorders

In primary growth disorders, the abnormalities seem to be intrinsic to the growth plate.

Small for Gestational Age

Babies born small for gestational age (SGA) have weights and lengths more than 2 SD below the mean for their gestational age (2.3 percentile). There are three subtypes of SGA: SGA with low birth weight, SGA with low birth length, and SGA with low birth weight and length. The classification is important for prognosis and response to GH therapy. It has been estimated that 2.3–10% of all infants are born SGA. Though most infants born SGA attain appropriate catch-up growth within the first 2 years of life, about 15% do not and continue to have poor growth throughout childhood. Premature infants born SGA may take longer to catch up. In addition to poor growth and short stature, individuals born SGA are at risk for metabolic disorders. Infants born SGA who have short parents tend to have catch-up growth to the lower familial range based on their parents' heights.

Though the endocrine mechanisms contributing to catch-up growth is not clear, it has been suggested that the mechanisms reside within the growth plate and are based on a delay in normal growth plate senescence. The stature of individuals born SGA seem to be highly dependent on the growth response of infants in the first months of life as most catch-up growth occurs during this time. It has been suggested that SGA neonates are GH insensitive as they have high levels of GH, but low levels of IGF-I. However, the GH-IGF axis normalizes in early postnatal life and most children born SGA have a normal response to GH stimulation testing and have normal levels of IGF-I and IGFBP-3. Children born SGA who do not achieve catch-up growth often require higher doses of GH therapy due to GH resistance. Additionally, children born SGA who do not demonstrate catch-up growth have much higher fasting levels of plasma cortisol than those that achieve catch-up growth. Cortisol may limit IGFBP-3 proteolysis in the perinatal period, leading to decreased availability of circulating IGFs and early growth retardation.

Down's Syndrome

The most common chromosomal disorder associated with growth retardation is probably trisomy 21/Down's syndrome, which affects approximately 1 in 600 live births. Average birth weights are about 500 g below normal and average birth lengths about 2–3 cm shorter than normal. Postnatal growth retardation continues and is usually associated with delayed skeletal maturation and delayed pubertal growth spurt, leading to adult heights of 135–170 cm in males and 127–158 cm in females. There is no known reason for growth retardation in Down's syndrome. One possible explanation is a generalized biochemical abnormality of the epiphyseal growth plate. Though some children with Down's syndrome have been found to have low serum levels of GH and IGF-1 and exogenous GH has been found to increase growth velocity, such treatment should be reserved for study protocols given the risk of leukemia in individuals with Down's syndrome. Thyroid function tests should be evaluated as Hashimoto's thyroiditis is common in Down's.

Turner's Syndrome

Short stature is the most common feature in girls with Turner's syndrome (gonadal dysgenesis), occurring in 95–100% of girls with 45X karyotype. The following abnormal growth features are associated with Turner's syndrome: (1) mild intrauterine growth retardation with average birth weights of 2,800 g and average birth lengths of 48.3 cm, (2) slow growth during early infancy falling to −3 SD by 3 years of age, (3) decline in height velocity from 3 years until about 14 years of age, and (4) prolonged adolescent growth phase with a partial return toward normal height and delayed epiphyseal fusion. Genetic and ethnic factors play an important role in final adult height in girls with Turner's syndrome, with the average adult height in the United States and Europe ranging from 142 to 146.8 cm.

The etiology of growth retardation in Turner's syndrome is unclear. Girls with Turner syndrome are haploinsufficient for the SHOX gene (short stature homeobox-containing gene) located on the short arm of the X chromosome. Two thirds of the height deficit in Turner's syndrome may be due to this defect. It may also account for the skeletal dysplasias, such as Madelung's deformity, often seen in girls with Turner's syndrome. Most girls with Turner's syndrome have normal GH and IGF levels during childhood. The lower levels seen in adolescence may be secondary to low levels of gonadal steroids. Despite the normal levels of GH and IGF, GH therapy is effective in increasing short-term growth and adult height in girls with Turner's syndrome. Turner's syndrome should be considered in any girl presenting with

unexplained growth retardation, especially if she is short relative to her family, but growing between the 5th and 10th percentiles during childhood.

Noonan's Syndrome

Noonan's syndrome affects males and females and is inherited in an autosomal dominant fashion, though 50% of cases are sporadic. Individuals with Noonan's syndrome have normal sex chromosomes. Common physical characteristics include webbing of the neck, malformed ears, a low posterior hairline, cubitus valgus, ptosis, microphallus and cryptorchidism in boys, and cardiac anomalies. Patients may have delayed or incomplete puberty. Mental retardation is present in about 25–50% of patients. Birth weight is usually normal, but mean growth in length and weight throughout most of childhood is below the 3rd percentile in about 50% of Noonan syndrome patients. In contrast to Turner syndrome patients, many Noonan syndrome patients are not short. Though endogenous GH secretion may be slightly reduced, it is not the cause of short stature in Noonan's syndrome. Instead, a gain of function mutation in these individuals may decrease GH-induced IGF production.

Prader–Willi Syndrome

Prader–Willi Syndrome (PWS) occurs in 1 of 10,000–25,000 live births and is due to a functional deletion of the paternal allele within chromosome 15q11–13. Clinical findings include profound neonatal hypotonia, cryptorchidism, microphallus, and hypogonadotropic hypogonadism. Growth failure may be present at birth, but becomes more pronounced postnatally with mean adult heights more than −2 SD below the mean and midparental target height. Hyperphagia and obesity become more obvious with increasing age. Short stature is probably due to GH deficiency secondary to an unidentified hypothalamic defect. The physical characteristics typical of GHD patients, such as small hands and feet, increased fat mass, and low muscle mass and bone mineral density, are similar to those found in patients with PWS. Patients with PWS demonstrate low GH responses after GH stimulation testing and also have low GH-dependent peptides, as opposed to patients with exogenous obesity who have normal levels of GH-dependent peptides despite low GH production. PWS is therefore an IGF-deficient condition due to a deficiency in GH production. Ghrelin levels are low. PWS is now a Food and Drug Administration (FDA)-approved indication for GH treatment, which results in improved growth velocity and final height potential, increased muscle mass, and decreased fat mass. PWS patients receiving GH treatment must be monitored for insulin resistance, diabetes mellitus, and sleep apnea. PWS patients who are very obese and have tonsillar hypertrophy should be treated with extreme caution, if at all.

Russel–Silver Syndrome

The common features of Russel–Silver syndrome (RSS) include IUGR, postnatal growth failure, congenital hemihypertrophy, and small triangular facies. Other less specific findings include clinodactyly, precocious puberty, delayed closure of the fontanels, and delayed bone age. Final adult heights are typically −4 SD below the mean. GH secretion is similar to other short children born IUGR. RSS is likely due to a heterogeneous group of disorders and so far no genetic or biochemical basis has been identified.

18q Deletion

The prevalence of deletion of the long arm of chromosome 18 is approximately 1 in 40,000 live births and has been found to be associated with short stature. Children with 18q deletion have also been found to have low IGF-1 and IGFBPs levels and reduced GH responses to GH stimulation testing. Children with 18q deletion treated with GH have been shown to not only have net height increases +2 SD compared to untreated children, but also improvement in cognitive measures.

Osteochondrodysplasias

Osteochondrodysplasias include a heterogeneous group of disorders that are characterized by abnormalities intrinsic to cartilage and/or bone. At least 100 osteochondrodysplasias have been identified. Short stature is usually disproportionate.

The frequency of achondroplasia is 1:26,000, making it the most common type of osteochondrodysplasia. Its transmission is autosomal dominant, though 80–90% of cases are de novo mutations. Infants with homozygous mutations have small thoraces and typically die in infancy due to respiratory failure. Though short stature may not be obvious until after the first 2 years of life, growth

retardation begins in infancy, leading to mean adult heights of 130 cm in males and 120 cm in females. Growth curves for achondroplasia should be used to follow these patients. GH secretion is normal.

Hypochondroplasia is also an autosomal dominant disorder caused by a mutation in the FGFR3 gene. Short stature in hypochondroplasia is milder than in achondroplasia. Growth retardation may not occur until after the first 2 years of life, but progressive deviation from normal growth after this age leads to adult heights between 120 and 150 cm. Disproportionate growth may not be evident until adulthood often making the diagnosis difficult in childhood. These children can be erroneously considered to have ISS.

Other Secondary Causes of Short Stature

Malnutrition

The most common cause of growth failure worldwide is inadequate caloric and/or protein intake. Marasmus is due to inadequate caloric and protein intake and presents with minimal subcutaneous fat and marked muscle wasting. Kwashiorkor is due to inadequate protein intake. Multiple vitamin and mineral deficiencies are evident in both conditions, and the two conditions often overlap. During the neonatal period, failure to gain weight precedes failure of linear growth by a short period of time, whereas at older ages it may be several years. The GH-IGF system is affected by both acute and chronic malnutrition. Though impaired growth may be associated with low, normal, or elevated GH levels, serum IGF-1 levels are low so that malnutrition may be considered a form of GH insensitivity. GHBP and IGFBP levels are also low. GH insensitivity may be an adaptive response to spare protein from the lipolytic and anti-insulin actions of GH.

Prior to epiphyseal fusion, anorexia nervosa and bulimia can be associated with impaired growth and decreased adult height. Bone mineralization during adolescence is impaired leading to osteopenia in adulthood. Malnutrition can also cause delayed puberty/menarche. The GH-IGF profiles are similar to those seen in other cases of malnutrition mentioned above, and levels return to normal once refeeding is established.

Malabsorption

Growth failure may be the presenting sign of malabsorption and/or chronic inflammatory bowel diseases such as Crohn's disease and celiac disease, which impair absorption of calories and proteins. IGF-1 levels are often reduced due to malnutrition. Malabsorption must be documented by various measures of gut function and fecal analyses in order to differentiate between malnutrition, GHD, and other causes of IGF-1 deficiency.

In Crohn's disease, growth retardation is likely multifactorial resulting from malnutrition, chronic inflammation, trace mineral deficiencies, and treatment with glucocorticoids. The degree of growth failure correlates with disease severity and IGF-1 levels are low. Screening can be done with an elevated erythrocyte sedimentation rate, anemia, and low serum albumin; however, diagnosis is based on colonic biopsy and imaging studies. GH therapy should be considered given poor growth and reduced final height occurs in 30% of patients and about 20% of patients have adult heights more than 8 cm below midparental target heights.

Celiac disease is an autoimmune disorder that often presents with impaired linear growth due to damage of intestinal mucosa by dietary gluten. Celiac disease is associated with Turner's syndrome, Down's syndrome, type 1 diabetes mellitus, and William's syndrome. Patients with celiac disease may have delayed onset and progression of puberty and delayed menarche. Screening for celiac disease is done by measurement of IgA tissue transglutaminase antibody though false negative results can occur in patients with IgA deficiency. Diagnostic testing is confirmed by small intestinal biopsy to demonstrate characteristic mucosal flattening. Changes in clinical status are reflected in changes in serologic profiles. The mainstay of treatment is gluten withdrawal, which typically results in rapid catch-up growth, decreased clinical symptoms during the first 6–12 months of treatment, normalization of IGF-1 and IGFBP-3 levels, and normal final adult height.

Diabetes Mellitus

Most children with insulin-dependent diabetes mellitus (IDDM) grow normally during prepuberty, though growth velocity may decrease during puberty. However, those with longstanding poor glycemic control can experience growth failure. One rare, but extreme condition is the Mauriac syndrome which is characterized by poor glycemic control, severe growth failure, and hepatosplenomegaly due to increased glycogen deposition. Mechanisms for growth impairment in IDDM include chronic intermittent acidosis, hypothyroidism, malnutrition, increased glucocorticoid production, and decreased

sensitivity to GH or IGF. In addition to acquired GH insensitivity, GHBP levels are decreased, supporting the concept of impaired GH-receptor number or function and IGFBP-1 levels are increased due to hypoinsulinism, which may inhibit IGF action.

Renal Disease

Growth can be impaired in any form of renal impairment. Some of the causes of poor growth include decreased caloric intake, osteopenia due to inadequate formation of 1,25-dihydroxycholecalciferol, metabolic acidosis, loss of electrolytes needed for normal growth, protein wasting, chronic anemia, and impaired GH and IGF production and action. Levels of GH vary from normal to elevated depending on the degree of renal failure. The half-life of GH is prolonged up to twofold in children with end-stage renal disease on dialysis and preterminal chronic renal failure. Serum IGF-1 and IGF-2 levels are usually normal, but increases in IGFBPs may interfere with their actions. However, serum IGF-1 and IGFBP-3 levels are low in nephrotic syndrome due to urinary loss of IGF-IGFBP complexes. Treatment with chronic glucocorticoid therapy also interferes with growth by decreasing GH release and interfering with IGF-1 action at growth plates. Chronic renal disease with elevated GH and low IGF-1 levels is considered a state of relative resistance to GH and also IGF-1 in some cases. Growth does not necessarily normalize after successful renal transplant. Final adult height after transplantation is associated with height at the time of transplantation, cumulative doses of steroids, and duration of reduced GFR. Therefore it is important to improve growth velocity and absolute height prior to transplantation. GH treatment is FDA approved in chronic renal diseases and may act by increasing the molar ratio of IGF peptides to IGFBPs and thus overcome the inhibitory actions of IGFBPs.

Liver Disease

Short stature in children with chronic liver disease is due to a combination of malnutrition, malabsorption, and an abnormal GH-IGF system consistent with an acquired GH insensitivity syndrome that persists even with adequate caloric intake. There is a close correlation between GH-dependent peptides and liver function. Improvement in growth is variable after liver transplantation, and is often limited due to treatment with glucocorticoids. Additionally, growth is directly correlated with the degree of growth impairment prior to transplantation. Treatment with exogenous GH has been shown to improve growth in some patients.

Hematologic Disorders

Growth failure can be seen in chronic anemias. Often growth failure is more evident during the adolescent years as puberty and menarche and the subsequent adolescent growth spurt can be delayed. Final adult height may be normal. The mechanism for growth failure in chronic anemias is probably based less on the GH-IGF system and more on impaired oxygen delivery to tissues, increased hematopoiesis, increased cardiovascular workload, and impaired nutrition. However, in disorders requiring chronic transfusions, such as thalassemia, growth failure may also be due to impaired IGF-1 synthesis, hypothyroidism, gonadal failure, and hypogonadotropic hypogonadism, especially in male patients.

Cardiovascular Disease

Growth failure can occur in children with congenital heart disease with cyanosis or chronic congestive heart failure. The most common cause of growth failure in these children is inadequate caloric intake. Additionally chronic congestive heart failure is associated with malabsorption and a greater basal metabolic rate due to increased cardiac and respiratory work.

Pulmonary Disease

Growth impairment can occur in children with asthma depending on the severity of pulmonary disease. Poor linear growth is not necessarily associated with abnormalities of the GH-IGF system, but rather is associated with impaired nutrition, increased energy requirements, chronic stress, and increased endogenous glucocorticoid production. Growth is further impaired in those patients receiving glucocorticoid therapy, especially in the form of prednisone or dexamethasone. The use of alternate-day or inhaled glucocorticoids may decrease the adverse effect on growth.

Early growth failure is also seen in patients with bronchopulmonary dysplasia, and is due to treatment with dexamethasone, chronic pulmonary infections, poor nutrition, long-term hypoxemia, and reactive airway disease. In patients with cystic fibrosis, growth failure is

due to chronic pulmonary infections and exocrine and endocrine pancreatic insufficiency. The degree of growth failure is more closely related to the severity of pulmonary disease than to pancreatic dysfunction. There may also be evidence of acquired GH insensitivity.

Chronic Inflammation/Infection

Growth failure is a common feature of chronic inflammatory diseases. One possible mechanism may be an IL-6-mediated decrease in IGF-1 production. Growth failure is also a feature of childhood acquired immunodeficiency syndrome (AIDS). In developing countries, growth impairment is seen with chronic infections with parasites such as schistosomiasis, hookworm, and roundworm.

Treatment and Prognosis

Growth Hormone Deficiency

Subcutaneous recombinant growth hormone (GH) is used to treat children with growth hormone deficiency. The recommended starting dose is 0.18–0.35 mg/kg/week divided into seven daily doses. The mean American dose is 0.3 mg/kg/week. Response to exogenous GH varies depending on frequency of administration, dosage, age, and weight. Typically a child with GHD goes from a pretreatment growth rate of 3–4 cm/year to 10–12 cm/year in year 1 of therapy and to 7–9 cm/year in years 2 and 3. GH efficacy wanes over time. The current cost of GH therapy in the United States for a 20-kg child at a dose of 0.3 mg/kg/week is from $12,000 to $15,000 per year.

Long-term studies have shown that factors that correlate with enhanced adult height were baseline height, younger age at onset of treatment, longer treatment duration especially during prepubertal years, and a greater growth velocity during the first year of treatment.

Endogenous GH normally increases two- to fourfold during the pubertal growth spurt along with a dramatic increase in IGF-1. Increased pubertal GH doses result in increased near-final height without a more rapid acceleration of skeletal maturation. Combination therapy with a GnRH agonist or aromatase inhibitor to delay puberty may be used when normal or precocious puberty limits the response to GH.

According to a recent consensus guideline, patients with definite GHD due to organic causes can be transitioned to adult protocols directly. However, in idiopathic GHD, GH therapy should be discontinued, and patients should be retested according to adult protocols to determine the need for continued therapy using adult GHD dosing.

IGF-1 Deficiency

Various studies evaluating the use of exogenous IGF-1 therapy in the treatment of growth hormone insensitivity have shown promising results in increasing growth velocities though not as successful as GH. However, the total number of children treated in such studies is still only several hundred, and few have been treated long term. Therefore, little is known about long-term side effects of IGF-1 and ideal dosing and frequency of administration. Studies suggest that the waning effect of IGF-1 may be more than that of GH. Additionally, IGFPB-3 levels do not increase with the administration of IGF-1. Phase II studies are now under way combing IGF-1 and GH in the treatment of ISS. Early results suggest a possible synergism between the two drugs. Side effects in studies include hypoglycemia, headache, convulsions, urolithiasis, and papilledema.

Idiopathic Short Stature

There are several parameters to consider while initiating growth hormone treatment of ISS. Height criteria vary based on geographical and clinical parameters. In the United States and seven other countries, regulatory authorities have approved GH treatment for children shorter than −2.25 SDS (1.2 percentile). Children whose heights are below −2.0 SDS and who are more than 2.0 SD below their MPTH and/or have a predicted height below −2.0 SDS should also be considered for treatment. Age should also be considered with the optimal age for initiating treatment between 5 years to early puberty. Currently there are no biochemical criteria for initiating GH treatment in ISS. Psychological factors such as whether a child himself or herself is concerned about being short should also be considered.

There are several alternatives to GH treatment for ISS. In males with CDGP and mild to moderate short stature, anabolic steroids such as oxandrolone and low dose testosterone may cause short-term acceleration of linear growth without much impact on final adult height. In ISS children who do not respond to GH treatment, IGF-1 treatment is an option, though data regarding efficacy and safety in this population is lacking. The use of GnRH analogues as monotherapy is generally not

recommended. However, combination therapy of GnRH analogues and GH may have potential benefits if height prediction is below −2 SDS at the time of pubertal onset in either sex and if the GnRH analogue is used for at least 3 years. Aromatase inhibitors have been found to increase predicted adult height in males with ISS, but adult height data are not available. The long-term efficacy and safety of aromatase inhibitors has not been well established. Aromatase inhibitors are not treatment options for females with ISS. Psychological counseling should be considered either instead of or as an adjunct to hormone treatment.

In children with ISS who are treated with GH for an average of 4–7 years, the mean increase in adult height is 3.5–7.5 cm compared to initial predicted adult height, though responses are highly variable and dose dependent. Various factors are thought to affect growth response though many are unknown. The first year response is negatively affected by age at start of treatment. It is positively affected by GH dose, weight at start of treatment, and difference from target height. Adult height outcome is negatively affected by age at start of treatment, and positively affected by midparental target height, height at start of treatment, bone age delay, and the first year response to GH. Two-year studies suggest that short-term height gain correlates with rise in IGF-1 levels.

The upper GH dose limit used in ISS is approximately 0.49 mg/kg/day, though the long-term safety of doses greater than 0.35 mg/kg/day in children with ISS is not certain. The duration of GH treatment in ISS can be based on two outcomes. One is to stop treatment when near adult height is achieved (height velocity <2 cm/year and/or bone age >16 years in boys and >14 years in girls). The other is to stop treatment when height is in the "normal" adult range (above −2 SD).

Constitutional Delay

Most children with constitutional delay of growth and maturation can be closely observed once evaluation to rule out other causes of delayed growth and puberty is performed. The bone age can be used to explain the potential for normal growth to patients and parents. However, for patients who are psychologically disabled by the social stigmata of short stature and delayed puberty, use of short-term gonadal steroids can be considered. Androgen treatment targets two aspects of constitutional delay. The first is short stature, especially in boys ages 10–14; the second is delayed puberty after age 14. Oral oxandrolone (0.1 mg/kg/day) has been used extensively to treat the younger age group with studies showing increased linear growth velocity without negatively impacting predicted or actual final height. Intramuscular testosterone enanthate (50–200 mg every 3–4 weeks for four to six injections) has been used successfully in older boys for delayed puberty. Criteria for treatment include minimal age of 14 years, height below the 3rd percentile, prepubertal or early Tanner stage G2 with an early morning serum testosterone less than 3.5 nmol/L (<1 ng/mL), and a poor self-image despite reassurance alone. Early secondary sex characteristics are usually visible by the fourth injection with an average of 10 cm growth in the ensuing year. Testosterone enhances growth velocity through a direct effect as well as by increasing GH. Short courses of testosterone do not cause rapid skeletal maturation, compromise adult height, or suppress pubertal maturation. It is important to emphasize to the patient that he is normal and that therapy allows puberty to progress earlier than it would on its own and that final adult height will not necessarily increase. Other forms of testosterone such as the gel and patch, which are approved for treating adult hypogonadism, can also be used though dosing has not been well established in children. The use of aromatase inhibitors in combination with testosterone therapy can also be considered.

Short-term estrogen therapy for girls with constitutional delay can be used; however, the doses required for enhanced growth velocity and sexual maturation poses a higher risk of bone age advancement.

Current Food and Drug Administration Indications for GH Treatment

The United States FDA has approved GH for use in the following pediatric conditions: growth hormone deficiency, Turner syndrome, chronic renal insufficiency, small for gestational age or intrauterine growth retardation, Prader–Willi syndrome, idiopathic short stature, SHOX gene haploinsufficiency, and Noonan syndrome.

Monitoring GH Treatment

Children receiving GH should be monitored every 3–6 months for height, weight, pubertal development, and adverse effects. A successful first year response to therapy includes an improvement in height SD score of at least 0.3–0.5, an increase in height velocity great than 3 cm/year, or a height velocity SD score of great than 1. Annual bone age assessments can be obtained to reassess height prediction and to consider potential intervention to modify

pubertal progression. Biochemical assessment of efficacy, safety, and compliance can be made with serial IGF-1 measurements during GH therapy, though the significance of abnormally elevated levels remains unknown. IGF-1 levels can help guide GH dose adjustments. Thyroid function tests should be monitored annually.

The maximal recommended doses for GHD are 0.25–0.35 mg/kg/week before puberty and 0.7 mg/kg/week during puberty. Doses may be higher in indications such as Turner's syndrome, SGA, and ISS. If after 2 years of treatment, the growth rate is inadequate despite maximal recommended dosing, GH therapy should be discontinued and alternative treatments considered.

GH Side Effects

Though the safety profile of GH has been encouraging over the past 20 years, there are numerous potential complications that require continued assessment. GH manufacturers have played a large part in this assessment through extensive databases. The most common side effects include edema, joint pain, and bruising at the injection site. Rare complications include recurrence of central nervous system tumors, pseudotumor cerebri, slipped capital femoral epiphysis, and type 2 diabetes mellitus. Other potential side effects include prepubertal gynecomastia, pancreatitis, growth of nevi, behavioral changes, scoliosis and kyphosis, worsening of neurofibromatosis, tonsillar and adenoidal hypertrophy, and sleep apnea. The management of such side effects may include a dose decrease or temporary interruption of treatment.

Studies suggest that GH therapy is not associated with future development of neoplasms in the absence of other risk factors; however, long-terms studies are still needed. The Drug and Therapeutics Committees of Lawson Wilkins Pediatric Endocrine Society and European Society of Pediatric Endocrinology have recommended the monitoring of IGF-1 and IGFBP-3 and dose adjustments accordingly in order to avoid IGF-1 levels at the upper end of normal.

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387 Diabetes Mellitus

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Introduction

Diabetes mellitus is a syndrome characterized by disturbed metabolism of carbohydrate, fat, and protein with persistent fasting or postprandial hyperglycemia resulting from defects in insulin secretion or insulin action. Diabetes mellitus occurs when the glucose disposition index, the product of insulin secretion and insulin sensitivity (*Fig. 387.1*), is inadequate to prevent hyperglycemia and its clinical consequences of polyuria, polydipsia, and weight loss.

Diabetes mellitus may be the result of absolute insulin deficiency or absolute insulin resistance or, more commonly, a combination of milder defects in insulin secretion and action. The chronic metabolic derangements affect small and large blood vessels causing long-term complications that result in retinopathy, nephropathy, neuropathy, ischemic heart disease, and cerebral and peripheral vascular disease.

Definition and Diagnosis of Diabetes in Children

Diabetes mellitus is diagnosed in one of four ways: (1) classic symptoms plus a plasma glucose (PG) $\geq$ 11.1 mmol/L (200 mg/dL), (2) fasting (for at least 8 h) PG $\geq$ 7.0 mmol/L (126 mg/dL), (3) 2 h post load PG $\geq$ 11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test (OGTT), or hemoglobin A1c $\geq$ 6.5%. *Table 387.1* shows the biochemical criteria for diabetes mellitus and lesser degrees of impaired glucose tolerance. In the absence of acute metabolic decompensation with unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The OGTT is not recommended for routine clinical use. When indicated, it should be performed after at least 3 days of adequate carbohydrate consumption ($\geq$150 g/1.73 m^2) using 1.75 g/kg anhydrous glucose dissolved in water for individuals $\leq$43 kg and 75 g for weight >43 kg.

When the renal threshold of ~180 mg/dL is exceeded, osmotic diuresis from glucose lost in urine causes polyuria, dehydration leads to polydipsia, loss of calories causes weight loss and sometimes polyphagia; blurred vision results from lens swelling caused by the osmotic effects of hyperglycemia. Chronic hyperglycemia in infants and toddlers of both genders and in girls commonly leads to perineal candidiasis. The diagnosis of type 1 diabetes mellitus (T1D) is usually obvious because most children present with classic symptoms for several days to a few weeks accompanied by marked hyperglycemia or with diabetic ketoacidosis (DKA) (see below).

The quoted definitions are based on venous PG levels. Portable glucose meters are useful for screening purposes in clinics and physicians' offices, but the diagnosis of diabetes mellitus must be confirmed by measurement of venous PG on an analytic instrument in a clinical chemistry laboratory. Blood samples should be processed and promptly delivered to the laboratory to prevent glucose utilization by erythrocytes, which would spuriously lower PG concentration (*Table 387.1*).

Classification

Diabetes mellitus is a heterogeneous group of disorders that lead to abnormal glucose tolerance. *Table 387.2* shows an etiologic classification of diabetes mellitus in children modified from the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" published by the American Diabetes Association. Among the insulin-dependent forms, severe insulinopenia resulting from autoimmune destruction of ß-cells, referred to as type 1a diabetes, accounts for most cases of childhood diabetes mellitus. Genetic defects in insulin secretion cause the monogenic forms of diabetes (formerly referred to as maturity onset diabetes of youth [MODY]) and neonatal diabetes mellitus, and contribute to the spectrum of type 2 diabetes (T2D) (*Table 387.2*).

Severe insulin-dependent diabetes, clinically indistinguishable from the autoimmune form, may have no evidence of autoimmunity and can result from mitochondrial or other gene defects that interfere with the generation of intraislet energy required for insulin

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secretion or, rarely, from pancreatic agenesis. The more severe monogenic forms of diabetes may also require insulin. Clinically similar forms of diabetes may occur secondary to cystic fibrosis, from exposure to drugs such as cyclosporine and tacrolimus, with the hemolytic uremic syndrome, or after pancreatectomy for congenital hyperinsulinism.

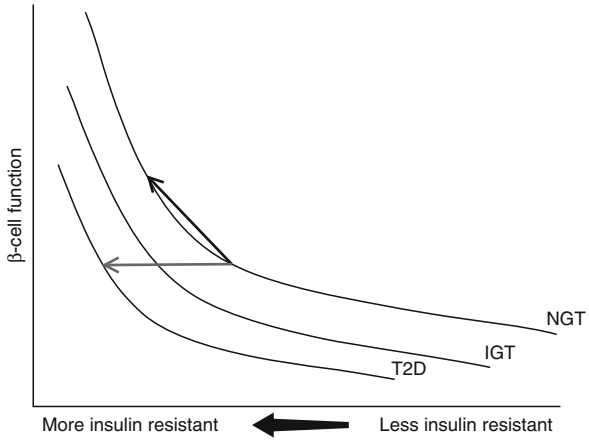

Figure 387.1

The hyperbolic relationship of insulin resistance and ß-cell function. In a subject with normal ß-cell reserve, an increase in insulin resistance results in increased insulin release and normal glucose tolerance (*black arrow*). In an individual in whom the capacity to increase insulin release is compromised, increased insulin resistance with no ß-cell compensation results in progression from normal glucose tolerance to impaired glucose tolerance to diabetes (*gray arrow*). The product of insulin sensitivity (the reciprocal of insulin resistance) and acute insulin response (a measurement ß-cell function) has been called "disposition index." This index remains constant in an individual with normal ß-cell compensation in response to changes in insulin resistance. IGT, impaired glucose tolerance; NGT, normal glucose tolerance; T2D, type 2 diabetes

Type 1 Diabetes Mellitus

Etiology, Genetics, and Family Risk of Type 1a Diabetes

Type 1a diabetes mellitus (T1aD) occurs in genetically susceptible individuals as a consequence of chronic T-cell-mediated destruction of insulin-secreting ß-cells of the islets of Langerhans. Markers of immune-mediated destruction of ß-cells include circulating autoantibodies to cytoplasmic and cell surface components of islet cells, including antibodies to insulin (IAA), glutamic acid decarboxylase (GAD_{65}), the tyrosine phosphatases IA-2 and IA-2ß, and the zinc transporter ZnT8 (Slc 30A8). At least one autoantibody is present in 85–98% of newly diagnosed children. Insulitis characterized by lymphocytic infiltration of the islets of Langerhans was observed in children who died soon after the onset of type 1 diabetes (T1D). There is strong linkage to the major histocompatibility complex (MHC) locus. Variation in the MHC locus accounts for about half of the genetic risk for T1aD. Increased susceptibility to T1aD is conferred by certain MHC alleles such as HLA-DR4-DQ8, and HLA-DR3-DQ2, whereas decreased susceptibility is conferred by several MHC alleles including HLA-DR2-DQ6. Numerous non-MHC genetic loci weakly contribute to the risk of T1aDM.

Approximately 90% of new cases of T1aDM occur in persons *without* an affected first-degree relative. It is estimated that a sibling sharing both HLA D haplotypes with an index case has a risk for T1D of 12–20%; for a sibling sharing only one haplotype, the risk is 5–7%; and with no haplotypes in common, the risk is 1–2%. HLA typing is not recommended for routine practice. For purposes of genetic counseling, in whites the overall risk of occurrence in siblings is approximately 6% if the proband was younger than 10 years of age and 3% if older at the time of diagnosis. The risk to the child of a parent with T1aD is 1.3–4% or 6–9%, respectively, depending on whether the mother or the father has diabetes. The cumulative incidence of T1aD is 65% in monozygotic twins who were

Table 387.1

Biochemical criteria for diabetes mellitus and lesser degrees of impaired glucose regulation

Test	Normal	Impaired fasting glucose (IFG)	Impaired glucose tolerance (IGT)	Diabetes mellitus
FPG mmol/L (mg/dL)	<5.6 (<100)	5.6–6.9 (100–125)		≥7.0 (126)
2 h PG mmol/L (mg/dL)	<7.8 (<140)		7.8–11.0 (140–199)	≥11.1 (200)
Casual PG mmol/L (mg/dL)	<11.1 (200)			≥11.1 (200)
Hemoglobin A1c %	4–6			≥6.5

Table 387.2
Etiologic classification of diabetes mellitus

1. *Type 1 Diabetes (ß-cell destruction usually leading to absolute insulin deficiency)*
A. Immune mediated
B. Idiopathic
II. *Type 2 Diabetes (variable combinations of insulin resistance and insulin deficiency)*
A. Typical
B. Atypical
III. *Genetic defects of ß-cell function*
A. MODY syndromes
1. MODY 1 chromosome 20, HNF-4α
2. MODY 2 chromosome 7, glucokinase
3. MODY 3 chromosome 12, HNF-1α, TCF-1
4. MODY 4 chromosome 13, IPF-1
5. MODY 5 chromosome 17, HNF-1ß, TCF-2
6. MODY 6 chromosome 2q32, neuroD1
7. MODY X-several candidate genes identified in the 5%–10% of patients with clinical characteristics of MODY who do not have the gene defects of 1–6
B. Mitochondrial DNA mutations (includes one form of Wolfram syndrome; Pearson syndrome; Kearns-Sayre, diabetes mellitus, deafness)
C. Wolfram syndrome – DIDMOAD (diabetes insipidus, diabetes mellitus, optic atrophy, deafness); WFS-Wolframin – chromosome 4p
1. Wolfram locus 2–chromosome 4q22–24
2. Wolfram mitochondrial
D. Thiamine responsive
IV. *Drug or chemical induced*
A. Anti-rejection–cyclosporine
B. Glucocorticoids (with impaired insulin secretion; e.g., cystic fibrosis)
C. L-Asparaginase
D. ß-Adrenergic blockers
E. Vacor (rodenticide)
F. Phenytoin (dilantin)
G. α-Interferon
I. Diazoxide
H. Nicotinic acid
V. *Diseases of exocrine pancreas*
A. Cystic fibrosis
B. Trauma – pancreatectomy
C. Pancreatic – ionizing radiation

Table 387.2 (Continued)

VI. *Infections*
A. Congenital rubella
B. Cytomegalovirus
C. Hemolytic-uremic syndrome
VII. *Variants of type 2 diabetes*
A. Genetic defects of insulin action
1. Rabson–Mendenhall syndrome
2. Leprechaunism
3. Lipoatrophic diabetes syndromes
4. Type A insulin resistance – acanthosis
B. Acquired defects of insulin action
1. Endocrine tumors – rare in childhood
A. Pheochromocytoma
B. Cushing syndrome
2. Anti-insulin receptor antibodies
VIII. *Genetic syndromes with diabetes and insulin resistance/ insulin deficiency*
A. Prader–Willi syndrome, chromosome 15
B. Down syndrome, chromosome 21
C. Turner syndrome
D. Klinefelter syndrome
E. Other syndromes
1. Bardet-Biedel
2. Alstrom
3. Werner
IX. *Gestational diabetes*
X. *Neonatal diabetes*
A. Transient – chromosome 6q24, KCNJ11, ABCC8
B. Permanent – agenesis of pancreas, homozygous glucokinase deficiency, KCNJ11, ABCC8

initially discordant for diabetes, whereas the incidence in dizygotic twins is similar to that of siblings. Over 40 genes have now been identified as contributing to T1DM, the majority of which relate to immune regulation.

Factors other than inheritance must be involved in the pathogenesis of T1aD, because not all monozygotic twins become concordant, DR3 or DR4 occurs in approximately 50% of the general population and other DQ markers occur in approximately 20% of white non-diabetics in the United States, yet the risk for T1aD in these individuals is one-tenth that of the HLA-identical sibling of an index case with T1aD. Also, approximately 10% of patients with T1aD have neither HLA-DR3 nor -DR4. These data suggest that environmental triggers or

post-zygotic processes such as the selection of certain autoreactive T-cell clones that bear receptors recognizing "self" must be involved.

The environmental factors that contribute to the pathogenesis of the disease are unknown and, as yet, there are no proven environmental interventions that reduce the risk of T1aD. Overweight in a child at risk may hasten the onset of clinical presentation. Possible environmental trigger factors currently under investigation include viral infections, dietary factors, hygiene, and toxins.

Chronic progressive destruction of the ß-cells of the pancreas eventually leads to severe insulinopenia and dependence on exogenous insulin to prevent ketosis and preserve life. Basal plasma insulin concentrations may be normal in newly diagnosed patients; however, insulin production in response to a variety of secretagogues is blunted and progressively decreases over months to years usually disappearing completely by 5 years from the date of diagnosis. The rate of ß-cell destruction is variable, being rapid in some individuals, especially in infants and young children, and slower in adolescents and adults, some of whom may retain the ability to secrete insulin for years.

Type 1 diabetes with no known etiology, referred to as type 1b diabetes, accounts for a minority of cases in which there is neither an HLA-association nor evidence of ß-cell autoimmunity.

Epidemiology

Diabetes mellitus is one of the most common chronic diseases of childhood. The incidence of T1D varies enormously among geographic regions, with age-standardized rates as high as 64.2/100,000 per year in Finland in 2005 and as low as 0.1/100,000 per year in areas of China and Venezuela. The incidence in children $\leq$14 years of age is similar in the United Kingdom and the United States, 15–26 and 15–18 per 100,000 per year, respectively. Secular increases in the incidence of pediatric T1D during the mid-late twentieth century have been documented in North America and Western Europe at rates higher than can be explained by genetic shifts. The incidence of childhood diabetes is rising worldwide at a rate of approximately 2.8% per year, with increases documented in six continents. There has also been an alarming trend toward a younger age of onset and diabetes is no longer uncommon in toddlers and preschool aged children in whom the onset is frequently more abrupt than in older children.

T1aD predominantly affects Europoid Caucasians, is less frequent in African Americans, and is much less common in Asians and Native North Americans. Males and females are almost equally affected. There is no apparent correlation with socioeconomic status. Peaks of presentation occur in two age groups: at 5–7 years, corresponding to a time of increased exposure to infectious agents with the beginning of school, and during puberty, which is characterized by physiologic insulin resistance.

Seasonal variations, most apparent in the adolescent years, and long-term cyclical variations have been observed in the incidence of T1D. New cases are more common in the autumn and winter. There is no consistent pattern linking long-term cyclicity with the incidence of viral or other infections.

Type 2 Diabetes Mellitus

T2D is a heterogeneous disorder characterized by deficiency of insulin as well as resistance to its actions in various tissues. It has long been known that obese individuals with diabetes secrete less insulin than equally obese individuals or those with comparable degrees of insulin resistance but without diabetes. Thus, the degree of insulin deficiency is relative. In absolute terms, the amounts of insulin secreted in response to any stimulus in patients with T2D may be greater than that of lean healthy individuals without diabetes. Implicit is the concept that there must be genetic defects in insulin secretion and this would be consistent with the strong familial aggregation of T2D and its greater prevalence among certain populations such as the Native American Indian, African American, Hispanic, Pacific Islanders, and Southeast Asian populations. Recent studies have identified more than 20 genes responsible for deficient insulin secretion among patients with T2D. Generally, these defects are sufficiently mild to permit glucose tolerance to be normal when the patient is young, lean, and insulin sensitive (Fig. 387.1). However, when the patient develops resistance to insulin, as occurs during puberty (because of increased GH secretion) or with obesity, or in both as with the obese adolescent, and has limited ability to compensate for insulin resistance by increasing insulin secretion, then diabetes develops (Fig. 387.1). Although numerous genes that contribute to obesity have now been uncovered, the modern epidemic of obesity is a reflection of our changing lifestyle and not our gene pool, which could not possibly have changed in the past 50 years. The "epidemic of obesity" has unmasked the prevalence of defects in insulin secretion and brought with it an "epidemic" of T2D. The prevalence of T2D is increasing and in some geographic areas accounts for up to 30–50% of all new childhood cases of diabetes. The "metabolic syndrome" characterized by dyslipidemia, hypertension, acanthosis nigricans,

features of polycystic ovary syndrome, and increased levels of inflammatory markers such as soluble C-reactive protein also is strongly linked with obesity and insulin resistance.

Atypical Diabetes Mellitus

Atypical forms of diabetes mellitus referred to as Flatbush diabetes, idiopathic type 1 diabetes, ketosis-prone diabetes, and type 1.5 diabetes have been described in various populations. There is no consensus definition, but the hallmark characteristic is a propensity to hyperglycemia with ketosis or ketoacidosis without key features of T1aD such as evidence of autoimmunity or sustained insulin dependence. These forms of diabetes have been described primarily in individuals of African or Asian ancestry and there is often a strong family history; however, the genetic defects remain to be determined in the majority of cases. Treatment of atypical diabetes is based on the clinical characteristics particular to each case. Characteristics that are helpful in distinguishing among the more common forms of diabetes in children and adolescents are shown in ❯ *Table 387.3*.

Genetic Defects of Insulin Secretion

Maturity Onset Diabetes of the Young (MODY)

MODY was originally described as a form of non-insulin-dependent or "maturity-onset"-type diabetes with onset before age 25 and inherited in an autosomal dominant pattern. MODY, which may account for 1–5% of all cases of diabetes in industrialized countries, is now known to be a heterogeneous group of disorders caused by a variety of monogenic mutations (❯ *Table 387.2*). Mild to moderate hyperglycemia resulting from varying degrees of insulin deficiency, with minimal or no defect in insulin action, typically begins during puberty or as a young adult. Other features common to each MODY type include a family history of diabetes in successive generations, absent pancreatic autoantibodies, no propensity to ketosis, and no predisposition to obesity beyond that of the general population (❯ *Table 387.3*). Confirmation of the diagnosis and identification of the specific type of MODY requires molecular genetic testing.

Table 387.3
Characteristics of prevalent forms of primary diabetes mellitus in children and adolescents

	Type 1a	Type 2	MODY	Atypical DM[a]
Prevalence	Common	Increasing	≤5% in Caucasians	≥10% in African American
Age at onset	Throughout childhood	Pubertal	Pubertal	Pubertal
Onset	Acute severe	Insidious to severe	Gradual	Acute severe
Ketosis at onset	Common	~1/3	Rare	Common
Affected relative	5–10%	60–90%	90%	>75%
Female:male	1:1	1:1–1.7:1	1:1	Variable
Inheritance	Polygenic	Polygenic	Autosomal dominant	Autosomal dominant
HLA-DR3/4	Association	No association	No association	No association
Ethnicity	All, Caucasian highest risk	All	Caucasian	African-American/Asian
Insulin secretion	Decreased/absent	Variable	Decreased	Variably decreased
Insulin sensitivity	Normal when controlled	Decreased	Normal	Normal
Insulin dependence	Permanent	Variable	Variable	Episodic
Obesity	No[b]	>90%	Uncommon	Varies with population
Acanthosis nigricans	No	Common	No[b]	No[b]
Pancreatic Autoabs	Yes[c]	No	No	No

[a]Atypical diabetes mellitus (ADM), also referred to as Flatbush diabetes, type 1.5 diabetes, ketosis-prone diabetes, and idiopathic type 1 diabetes mellitus In North America, type 2 diabetes predominates in African-American, Mexican-American, Native American, Canadian First Nation children and adolescents and is also more common in Asian and South Asian than in Caucasians
[b]Mirrors rate in general population
[c]Autoantibodies to insulin (IAA), islet cell cytoplasm (ICA), glutamic acid decarboxylase (GAD), or tyrosine phosphatase (insulinoma associated) antibody (IA-2 and IA-2ß) at diagnosis in 85–98%

The specific MODY variant predicts the therapeutic response; certain MODY variants respond to sulfonylureas. Exercise and medical nutrition therapy (MNT) to maintain normal weight and insulin sensitivity should be emphasized. Pharmacologic treatment, when necessary, is tailored to the patient's specific MODY type and level of hyperglycemia. Regardless of mode of therapy, patients require careful monitoring to insure good glycemic control.

Mitochondrial Diabetes

Diabetes may be the presenting manifestation of syndromes caused by mutations in mitochondrial DNA. *Maternally inherited diabetes and deafness syndrome* (MIDD, MIM#520000) may present in childhood or adulthood. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition. This and other mutations in related tRNA mitochondrial genes can be associated with multiple other features including myopathy, encephalopathy, lactic acidosis, and myoclonic epilepsy. *Kearns–Sayre syndrome* (MIM #530000) is also caused by various mitochondrial gene mutations. It is characterized by ophthalmoplegia, retinal pigment degeneration, cardiomyopathy, and may include several hormone deficiencies including diabetes in approximately 13% of cases. Initially, diabetes can be treated with diet and sulfonylureas but may require insulin. Patients with impaired mitochondrial function are inherently prone to develop lactic acidosis; therefore, metformin should not be used.

Neonatal Diabetes Mellitus

A monogenic defect can be determined in the majority of cases of diabetes with onset within the first 6 months of life and, occasionally, when the onset is between 6 and 12 months of life. Many of the monogenic etiologies are associated with various congenital defects, conditions, or syndromes. Approximately half the cases are transient, resolving within months; however, in a substantial proportion mild non-insulin-dependent diabetes recurs in adolescence or early adulthood. Imprinting defects in chromosome region 6q24 are the most common cause of transient neonatal diabetes. Activating mutations in the Kir6.2 inwardly rectifying ATP-sensitive potassium channel (KCNJ11) or the sulfonylurea receptor (ABCC8) genes as well as autosomal dominant or recessive mutations in the insulin gene itself account for a majority of the remaining cases; they are associated with later onset and less microsomia than 6q24 defects and often can be successfully treated with sulfonylureas. Sulfonylurea treatment may also improve some of the peripheral nerve abnormalities that can accompany neonatal diabetes mellitus caused by KCNJ11 mutations, but sulfonylureas cannot be used in the insulin gene mutations causing neonatal DM.

Insulin is initially used to control hyperglycemia in neonatal diabetes and catch-up growth is usually rapid. A trial of therapy with a high dose (0.5–1.0 mg/kg/day) of glibenclamide (glyburide) should be attempted in patients with mutations of KCNJ11 or ABCC8.

Secondary Causes of Diabetes

Cystic Fibrosis–Related Diabetes (CFRD)

The life expectancy of patients with cystic fibrosis has increased dramatically over the past few decades and CRFD has become more common (*Table 387.2*). Insulinopenia is caused by pancreatic destruction and amyloid deposition in the islets; first-phase insulin release is particularly affected. Insulin resistance is prominent during exacerbations of pulmonary disease and whenever glucocorticoids are used, causing deterioration in glucose tolerance. DKA is rare. CFRD can present in the first decade, but usually is seen in the second and third decades. The development of CFRD is associated with progressive clinical deterioration and increased mortality. Screening for glucose intolerance should begin at the age of 14 years and hyperglycemia should be treated aggressively. Insulin is the only recommended treatment for CFRD. It prevents protein catabolism, promotes weight gain, and improves pulmonary function. The ideal treatment is a flexible basal-bolus regimen using a long-acting insulin and rapid-acting insulin with meals (see "Insulin Therapy" below). Diet should not be restricted in CFRD. Patients should be taught how to count carbohydrates and to use rapid-acting insulin with meals. Destruction of the pancreatic alpha cells results in glucagon deficiency and chronic use of glucocorticoids can cause adrenocortical insufficiency. Patients with CFRD are at increased risk for severe hypoglycemia owing to malabsorption and impaired counterregulatory responses.

Presentation of Type 1 Diabetes Mellitus

Most children with newly diagnosed T1D present with classic symptoms (polyuria, polydipsia, weight loss) for a few days to several weeks. Other presentations include

recent onset of enuresis in a previously toilet-trained child, failure to gain weight appropriately in a growing child, vulvovaginal candidiasis, candidal balanitis in uncircumcised boys, recurrent pyogenic skin infections, irritability, and deteriorating school performance. Some children have an insidious onset characterized by lethargy, weakness, and weight loss. Diabetes should be suspected in a child with unexplained weight loss and confirmed or ruled out by measurement of the postprandial PG concentration and/or hemoglobin A1c concentration. In the child with polyuria, the urine should be tested for glucose.

The frequency of DKA at diabetes onset varies widely by geographic location, ranging from 15% to 67% in Europe and North America and is even more common in developing countries. There is an inverse correlation between the frequency of DKA and the background incidence of T1D in different populations. DKA at initial presentation is more frequent in infants, toddlers, and preschool-age children (in whom the history of polyuria and polydipsia may be not be elicited), in children who do not have a first degree relative with T1D, and in children whose families are of a lower socioeconomic status. The early manifestations of DKA may be relatively mild consisting of nausea, vomiting, polyuria, and dehydration. In more prolonged and severe cases, Kussmaul respiration, which may be confused with bronchiolitis or asthma, is present and there is an odor of acetone on the breath. Abdominal pain may be present and mimic an acute abdominal emergency such as appendicitis or pancreatitis. The abdominal manifestations usually disappear after several hours of fluid and insulin treatment. Cerebral obtundation and, ultimately, coma are related to the severity of acidosis and hyperosmolality. Laboratory findings include glucosuria, ketonuria, hyerglycemia, hyperketonemia, and metabolic acidosis. Leukocytosis and nonspecific hyperamylasemia are common; serum lipase levels are usually not elevated. Management of DKA is discussed below.

The progression of T1D tends to follow a characteristic course including an abrupt onset of classical symptoms that rapidly disappear after starting insulin replacement therapy. This is often followed by a temporary remission ("honeymoon phase") with partial recovery of endogenous insulin secretion, demonstrable by plasma C-peptide levels and characterized by stable near-to-normal blood glucose levels and decreasing insulin requirements. Severe DKA and young age at presentation reduce the likelihood of a remission phase. Recurrence or persistence of the autoimmune attack leads to further ß-cell destruction and progressive decline in insulin production until, eventually, it ceases completely.

Presentation of Type 2 Diabetes Mellitus

At onset, the characteristics of pediatric type 2 diabetes (T2D) include frequent family history of T2D, female preponderance, average age in mid-puberty, acanthosis nigricans, and obesity (*Table 387.3*). The presentation can range from insidious to severe and DKA is not uncommon, which contrasts with adult onset T2D in which ketoacidosis is rare. Many youth with T2D present with classic symptoms, including weight loss. Diagnosis in asymptomatic individuals is also common, either as a consequence of the incidental finding of glucosuria or hyperglycemia or as a result of screening individuals at risk. It is likely that many individuals with youth onset T2D experience a prolonged period of mild hyperglycemia with minimal or no symptoms.

Distinguishing Between Type 1 and Type 2 Diabetes in Children

The phenotype of T1D used to be that of a thin child with a classic history. The current high prevalence of overweight and obesity in children and adolescents and an increasing incidence of T2D in youth have presented clinicians with a diagnostic challenge when evaluating a child or adolescent with new-onset diabetes mellitus. As many as 25% of newly diagnosed T1D patients are obese. Because there may be considerable overlap in presentation, distinguishing between T1D and T2D may be difficult (*Table 387.3*). Insulin requirements typically decrease after several weeks of treatment of T2D, which may resemble the remission or "honeymoon" period of T1D. Measuring pancreatic autoantibodies and markers of insulin secretion (fasting C-peptide levels) at the time of diagnosis helps to distinguish between T1 and T2D in obese patients. A fasting plasma C-peptide level >0.85 ng/mL suggests T2D; however, initially, C-peptide may be temporarily low in T2D owing to glucotoxicity and lipotoxicity, and rechecking the level after several weeks or even months of therapy will sometimes demonstrate hyperinsulinemia indicating insulin resistance and help to confirm a diagnosis of T2D. The fasting insulin-like growth factor binding protein-1 (IGFBP-1) level, whose secretion is acutely inhibited by insulin, is a marker of insulinization, and may be another useful biochemical parameter. An IGFBP-1 concentration ≤3.6 ng/mL is

highly suggestive of T2D. The subgroup of children with clinical features of T2D and autoantibody positivity has been referred to as latent autoimmune diabetes in youth (LADY). A binary classification is not always possible at the time of diagnosis; there are patients who have clinical and biochemical features of both insulin deficiency and insulin resistance (*Fig. 387.1*). Regardless of the type of diabetes, the choice of initial therapy must be based on a clinical assessment of the metabolic state. Subsequent therapy is modified, if necessary, guided by the individual patient's response to treatment.

Differential Diagnosis

Other Causes of Glucosuria

Diabetes mellitus occasionally is diagnosed in an asymptomatic individual because glucosuria is discovered incidentally. The diagnosis must always be confirmed by at least two independent measurements of PG concentration. Glucosuria can occur *without* hyperglycemia as a result of renal tubular dysfunction, e.g., Fanconi–Bickel syndrome (GLUT2 deficiency), or Fanconi syndrome from causes such as heavy-metal intoxication; an isolated reduction of the renal tubular threshold for glucose reabsorption (benign renal glucosuria) is diagnosed by performing an OGTT with simultaneous measurements of PG and urine glucose concentrations. Glucosuria will be evident, whereas PG concentrations are in the normal range. Hepatic glycogen synthase deficiency (glycogen storage disease type 0) is a rare cause of intermittent postprandial hyperglycemia and glucosuria in children. Intermittent postprandial hyperglycemia (frequently followed by hypoglycemia) is common after bolus feeds in patients who have a gastrostomy and Nissen fundoplication.

Transient Hyperglycemia

The incidence of transient hyperglycemia is approximately 1 per 8,000 pediatric office visits and 1 per 200 emergency department or hospital visits and is common in patients with asthma treated with sympathomimetics and glucocorticoids. A minority of children with transient hyperglycemia will develop diabetes mellitus. When transient hyperglycemia is detected in a child with a minor illness, the risk of developing diabetes is much higher than if a severe illness is present. The presence of pancreatic autoantibodies strongly predicts progression to diabetes.

Management of Diabetes Mellitus

Initial Management of Newly Diagnosed Type 1 Diabetes Mellitus

The goals of initial management depend on the clinical presentation and are: to restore fluid and electrolyte balance, to stabilize the metabolic state with insulin, and to provide basic diabetes education and self-care training for the child (if age and developmentally appropriate) and other caregivers. The diagnosis of diabetes in a child is a crisis for the family. Shocked, grieving, and overwhelmed parents typically require at least 2–3 days to learn basic "survival" skills while they cope with the emotional upheaval that typically follows the diagnosis of diabetes in a child. Even without severe metabolic decompensation, children with newly diagnosed T1D usually are admitted to hospital for metabolic stabilization, diabetes education, and self-management training. Outpatient or home-based management is preferred at some centers that have the appropriate resources.

Psychosocial Issues

Parents should receive sympathetic support and not be overwhelmed by unrealistic expectations from the diabetes treatment team. A medical social worker should perform an initial psychosocial assessment of all newly diagnosed patients to identify families at high risk who need additional services. Thereafter, the mental health specialist should be consulted when emotional, social, environmental, or financial concerns are suspected or identified that interfere with the ability to maintain acceptable diabetes control.

The treatment of pediatric diabetes is complicated by multiple factors inherent to childhood. Because childhood is characterized by cognitive and emotional immaturity, the involvement of responsible adults is essential for optimal treatment of pediatric diabetes. Treatment-related conflicts are not uncommon, arising in part due to natural discord in goals between caretakers and the child. Each phase of childhood has intrinsic characteristics that complicate treatment, e.g., the unpredictable eating of toddlers and the spontaneous intense physical play of school age children that can hinge on unpredictable factors such as the weather. Adolescence is characterized by multiple

physiologic and psychosocial factors that make maintenance of glycemic control more difficult. Diabetes treatment goals and regimens should be tailored to each child and family based on factors such as age, family resources, cognitive faculties, the schedule and activities of the child and family, and their goals and desires.

Mental health should be given equivalence to screening for other diabetes-related complications. Routine screening for behavioral disturbance should begin in children at the time of diabetes diagnosis, with further assessment of parental mental health and family functioning for those children identified as being "at risk." Interventions can then be targeted based on the specific needs of individual children and families.

Outpatient Diabetes Care

The Diabetes Team

Because the care of children with T1D is complex and time consuming, children should be managed by a multidisciplinary diabetes team that provides diabetes education and care in collaboration with the child's primary care physician. The team consists of a pediatric endocrinologist or pediatrician with training in diabetes, a pediatric diabetes nurse educator, a dietitian, and a mental health professional, either a clinical psychologist or social worker. A physician or nurse should always be available by telephone to respond to metabolic crises that require immediate intervention and to provide guidance and support to patients.

Initial Diabetes Education

Parents and children with newly diagnosed diabetes are typically overwhelmed and cannot assimilate a large amount of abstract information. Therefore, the education program should be staged: initial educational goals should be limited to essential "survival" skills so that the child can be safely cared for at home and as soon as possible return to his or her daily routine. At this stage, diabetes education and self-management training should include: understanding what causes diabetes, how it is treated, how to administer insulin, basic meal planning, self-monitoring of blood glucose and ketones, recognition and treatment of hypoglycemia, and how and when to contact the diabetes team. When the child is medically stable and parents and other care providers have mastered "survival" skills, the child is discharged from the hospital or ambulatory treatment center.

Continuing Diabetes Education and Long-Term Supervision of Diabetes Care

In the first few weeks after diagnosis, frequent telephone contact provides emotional support, helps parents to interpret the results of blood glucose monitoring and, if necessary, insulin doses are adjusted. Within a few weeks of diagnosis, many children enter a partial remission, evidenced by normal or near-to-normal blood glucose levels on a low dose ($\leq$0.5 units/kg/day) of insulin. Most patients and parents are less anxious, have mastered basic diabetes management skills, and are now ready to learn the intricate details of intensive diabetes management. The diabetes team should provide patients and parents with the more advanced knowledge and skills needed to maintain optimal glycemic control while coping with the normal challenges of a child's life. In addition to teaching facts and practical skills, the education program should promote desirable health beliefs and attitudes in the young person with a chronic incurable disease. For some children, this is best accomplished in a nontraditional educational setting such as a summer camp for children with diabetes. Parents, grandparents, older siblings, school nurse, and other important people in the child's life are encouraged to participate in the diabetes education program so they can share the burden of care and help the child to participate fully in school and extracurricular activities.

In the first month after diagnosis, the patient is seen frequently to review the diabetes education and consolidate the practical skills acquired in the first few days and to extend the scope of diabetes self-care training. Thereafter, follow-up visits should occur at least every 3 months and, as cognitive development progresses the child should become more involved in diabetes management and assume increasing age-appropriate responsibility for daily self-care.

Goals of Therapy

The Diabetes Control and Complications Trial (DCCT) and the long-term follow-up observations of the DCCT cohort (Epidemiology of Diabetes Interventions and Complications, EDIC), the Stockholm Diabetes Intervention Study, and the UK Prospective Diabetes Study (UKPDS) in adults with T2D all unequivocally demonstrated the importance of lowering glycated hemoglobin (HbA1c) values to reduce the risk of development and progression of retinopathy, nephropathy, neuropathy, and macrovascular disease. Treatment that reduces average HbA1c to ~7% (about 1% above the upper limit of normal) is associated with fewer long-term micro- and

macrovascular complications. Moreover, a sustained period of improved glycemic control also is associated with a decreased rate of development of diabetic complications (see chronic complication of type 1 diabetes below).

The aim of diabetes management is to achieve recommended glycemic targets known to reduce the risk of long-term complications. There is no consensus on appropriate targets for children of different ages. Management of young children with diabetes, especially those younger than 5 years, must balance opposing risks of hypoglycemia and future complications. The relative contribution of the prepubertal years to the development of microvascular complications is uncertain. Recent evidence indicates that longer prepubertal duration of diabetes increases the risk of retinopathy and, possibly, microalbuminuria in adolescence and young adulthood albeit at a slower rate than the postpubertal years.

Biochemical treatment goals for children and adolescents recently published by the International Society for Pediatric and Adolescent Diabetes (ISPAD) are: ideal HbA1c <6.5%, optimal <7.5%, suboptimal 7.5–9.0%, and action is required when the value exceeds 9.0%. The ISPAD guidelines are accompanied by the statement: "... each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia as well as frequent mild to moderate hypoglycemia."

The risk for microalbuminuria increases steeply with HbA1c >8%. Based on these considerations, an HbA1c of ≤8.0% is a reasonable general goal for children with diabetes; however, biochemical goals should be individualized taking into account both medical and psychosocial considerations. Less stringent treatment goals are appropriate for preschool age, children with developmental handicaps, psychosocial challenges, or lack of family support, children who have experienced severe hypoglycemia, and those with hypoglycemia unawareness.

Insulin Therapy

Plasma insulin levels in nondiabetic individuals are characterized by basal levels on which are superimposed meal-related spikes in insulin concentrations. The ideal insulin regimen should attempt to mimic physiologic insulin patterns by employing a basal-bolus approach to insulin replacement. Insulin pump therapy and multiple daily insulin injections most closely mimic insulin secretion (*Fig. 387.2*). Truly physiologic replacement of insulin, however, remains an elusive goal because insulin is injected or infused subcutaneously rather than directly into the portal vein, rates of absorption are variable, and doses are determined empirically, lacking the precision of endogenously secreted insulin. Also, other islet hormones such as glucagon and amylin are not present when a patient receives exogenous insulin.

Practical considerations, including socioeconomic circumstances, age, supervision of care, ability and willingness to self-administer insulin several times each day, and

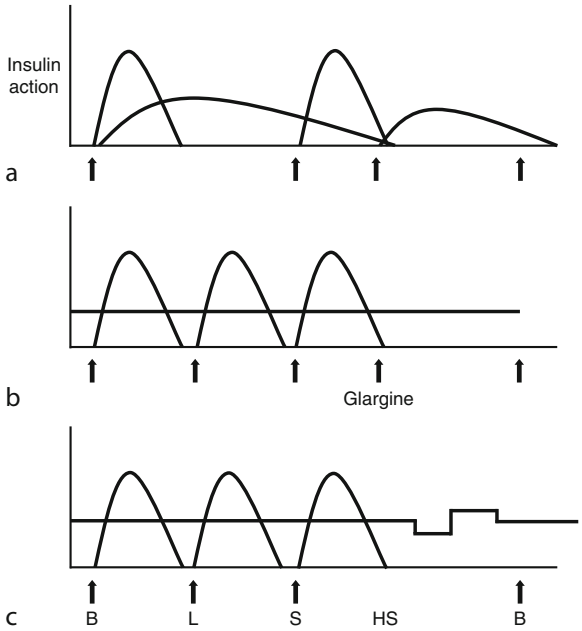

Figure 387.2
Commonly used insulin regimens. (a) Schematic representation of idealized insulin action provided by a regimen consisting of a mixture of rapid-acting insulin analog (lispro, aspart, or glulisine) with intermediate-acting insulin (NPH, isophane) before breakfast, rapid-acting insulin before supper, and a smaller dose of NPH at bedtime. (b) Schematic representation of idealized insulin action provided by an insulin regimen consisting of four daily injections: rapid-acting insulin before each meal (B, L, S) and a separate injection of insulin glargine or detemir, either at bedtime (as shown here) or at dinner or breakfast. (c) Schematic representation of idealized insulin effect provided by continuous subcutaneous insulin infusion via an insulin pump delivering rapid-acting insulin. In this figure, alternative basal rates are illustrated; insulin delivery is shown to decrease from midnight to 3 a.m. and to increase before breakfast to combat the dawn phenomenon. B, breakfast; L, lunch; S, supper; HS, bedtime. Arrows indicate times of insulin injection or boluses before meals

difficulty maintaining long-term adherence, make physiologic replacement of insulin challenging. No single insulin regimen can be used for all children with T1D. The diabetes team has to design an insulin regimen that best meets the needs of the individual patient and is acceptable to the patient and/or family member(s) responsible for administering insulin to the child or supervising its administration. Whenever possible, subcutaneous (SC) insulin treatment in the newly diagnosed child should start with at least three injections per day (*Fig. 387.2*, panel A) or a basal-bolus regimen (*Fig. 387.2*, panel B). All insulin regimens have the same general goal: to provide basal insulin throughout the day and night and additional insulin for meals and snacks.

In addition to severity of metabolic decompensation, the child's age, weight, and pubertal status guide selection of the initial insulin dose. When diabetes has been diagnosed early, before significant metabolic decompensation, 0.25–0.5 unit/kg/day usually is an adequate starting dose. When metabolic decompensation is more severe (e.g., ketosis without acidosis or dehydration) the initial dose typically is at least 0.5 unit/kg/day. After recovery from DKA (an insulin-resistant state), prepubertal children usually require at least 0.75 unit/kg/day, whereas adolescents require at least 1 unit/kg/day. In the first few days of insulin therapy, while the focus of care is on diabetes education and emotional support, it is reasonable to aim for premeal blood glucose levels in the range 4.5–10 mmol/L (80–180 mg/dL) and to supplement at 3–4 h intervals, if necessary, with 0.05–0.1 unit/kg of rapid- or short-acting insulin SC.

Three major categories of insulin preparations are available, classified according to their time course of action (*Table 387.4*). Various insulin replacement regimens consisting of a mixture of short- or rapid-acting insulin and an intermediate- or long-acting insulin are used in children and adolescents, typically given two to

Table 387.4
Insulin preparations classified according to their pharmacodynamic profiles

	Onset of action (h)	Peak action (h)	Effective duration of action (h)
Rapid-acting			
Insulin lispro[a]	0.25–0.5	0.5–2.5	≤5
Insulin aspart[a]	<0.25	1–3	3–5
Insulin glulisine	<0.25	1–1.5	3–5
Short-acting			
Regular (soluble)	0.5–1	2–3	5–8
Intermediate-acting			
NPH (isophane)	1–2	4–10	10–16
Long-acting			
Insulin glargine[a]	2–4	Relatively peakless	20–24
Insulin detemir[a]	0.8–2	Relatively peakless	12–24[b]
Premixed combinations			
50% NPH, 50% regular	0.5–1	dual	10–16
50% NPL, 50% lispro	<0.25	dual	10–16
70% NPH, 30% regular	0.5–1	dual	10–16
70% PA, 30% aspart[a]	<0.25	dual	15–18
75% NPL, 25% lispro[a]	<0.25	dual	10–16

[a]Insulin analog developed by modifying the amino acid sequence and/or chemical adducts of the human insulin molecule
[b]Dose dependent; 12 h for 0.2 U/kg; 20–24 h for ≥ 0.4 U/kg
Pharmacodynamic effects of lispro insulin and insulin aspart appear to be equivalent
PA, protamine-crystallized insulin aspart suspension; NPL, neutral protamine lispro suspension. Both PA + soluble aspart and NPL + lispro are stable premixed combinations of intermediate- and rapid-acting insulins
The human insulins and insulin analogs are available in vials, prefilled disposable pen injectors, and cartridges for non-disposable pen injectors
These data are for human insulins and are approximations from studies in adult test subjects. Time action profiles are estimates only. The kinetics of NPH insulin may be more rapid in children
The times of onset, peak, and effective duration of action vary within and between patients and are affected by numerous factors, including size of dose, site and depth of injection, dilution, exercise, temperature, regional blood flow, and local tissue reactions

four (or more) times daily. Clear superiority of any one regimen in children and adolescents in terms of metabolic outcomes has not been demonstrated.

NPH-Based Conventional Treatment Regimens

For many years the "split-mixed" regimen, which typically consisted of two daily doses of Neutral Protamine Hagedorn (NPH, isophane) and short-acting (regular) insulin (*Table 387.4*) mixed together in the same syringe, was a standard approach to insulin replacement. A practical advantage of this regimen is that the child does not receive an injection before lunch. More recently, the regular insulin component usually is replaced by a rapid-acting insulin analog. The total daily dose typically is divided so that about two-thirds is given before breakfast and one-third is given in the evening. With a three-dose regimen, short- or rapid-acting insulin is given before supper and the second dose of NPH insulin is given at bedtime rather than before the evening meal (*Fig. 387.2*, panel A). The initial ratio of rapid- to intermediate-acting insulin at both times is approximately 1:2. Individual components of the regimen are subsequently adjusted based on results of blood glucose monitoring. The optimal ratio of rapid- or short-acting to intermediate-acting insulin for each patient is determined empirically guided by the results of frequent blood glucose measurements. At least five daily measurements are initially required to determine the effects of each component of the insulin regimen. The blood glucose concentration is measured before each meal, before the bedtime snack, and once between midnight and 4 a.m. Parents are taught to identify patterns of hyperglycemia or hypoglycemia that indicate the need for a dose adjustment. Adjustments are made to individual components of the insulin regimen, usually in 5–10% increments or decrements, in response to patterns of consistently elevated (above the target range for several consecutive days) or unexplained low blood glucose levels, respectively. This is referred to as pattern adjustment. The insulin dose is adjusted until satisfactory blood glucose control is achieved with >50% of blood glucose values in the child's target range.

Within several days to a few weeks, many children enter a period of partial remission ("honeymoon") during which normal or nearly normal glycemic control is relatively easily achieved with a low dose of insulin. The doses of rapid-acting insulin may be reduced or discontinued due to low prelunch and bedtime values. As further destruction of ß-cells occurs, the insulin dose increases ("intensification phase") eventually reaching a full replacement dose. The average daily insulin dose in normal weight prepubertal children with long-standing diabetes is approximately 0.8 unit/kg/day and in adolescents about 1–1.5 unit/kg/day. Beyond the remission period, it is usually not possible to achieve near-normal glycemia with two injections per day without causing hypoglycemia during the overnight period. A major limitation of a two-dose "split-mixed" regimen is that the peak effect of the predinner intermediate-acting insulin occurs at the time of lowest insulin requirement (midnight to 4 a.m.), increasing the risk of nocturnal hypoglycemia. Thereafter, insulin action declines from 4 to 8 a.m., when the basal insulin requirement normally increases. Consequently, the tendency for blood glucose levels to rise before breakfast (dawn phenomenon) may be aggravated by waning insulin effect before breakfast and/or by counterregulatory hormones secreted in response to a fall in blood glucose levels during sleep.

A three-dose insulin regimen with mixed short- or rapid- and intermediate-acting insulin before breakfast, short- or rapid-acting insulin before dinner, and NPH insulin at bedtime (*Fig. 387.2*, panel A) may reduce these problems. An alternative regimen substitutes glargine or detemir, injected at dinnertime, for the bedtime dose of NPH. Intensive insulin regimens that employ intermediate-acting insulin demand consistency in the daily meal schedule, amounts of food consumed at each meal, and the timing of insulin injections.

Basal-Bolus Regimens and Continuous Subcutaneous Insulin Infusion

A basal-bolus insulin regimen or continuous subcutaneous insulin infusion (CSII) using an insulin pump can more closely simulate normal diurnal insulin profiles and permit flexibility with respect to timing and content of meals. A peakless long-acting insulin, glargine or detemir (*Table 387.4*), is used to provide basal insulin (typically 40–60% of the total daily dose) and is used together with short- or rapid-acting insulin injected before each meal (*Fig. 387.2*, panel B). Insulin glargine is injected once daily (in the morning, evening, or at bedtime), has a 20–24 h duration of action and little peak activity. Insulin detemir is an alternative long-acting, peakless basal insulin with effects similar to those of glargine during the first 12 h after administration. Thereafter, its effect wanes; accordingly, it usually has to be administered twice daily in patients with severe insulin deficiency. Doses of rapid-acting insulin are selected based on preprandial

glucose values, anticipated carbohydrate intake, and physical activity after the meal.

There has been a marked increase in the number of children and adolescents using CSII (pump) therapy. Pumps are battery powered, about the size of a beeper, and contain a reservoir (a modified syringe) to hold insulin, and deliver insulin via an infusion set consisting of fine plastic tubing with a tiny cannula at the end, which is inserted into the subcutaneous tissue. The infusion set is replaced every 2–3 days. Small amounts of rapid-acting insulin (down to 0.025–0.05 unit/h) are infused at a basal rate and bolus doses are given before each meal or snack. The basal rate can be programmed to change over the course of the day to meet an anticipated increase or decrease in need (*Fig. 387.2*, panel C). This feature can be advantageous in combating the dawn phenomenon or preventing hypoglycemia during or after exercise.

Increased lifestyle flexibility, reduced blood glucose variability, improved glycemic control and a reduced frequency of severe hypoglycemia are all documented advantages of CSII. Success requires a high degree of motivation to achieve normal or near-normal blood glucose levels, frequent blood glucose monitoring, record keeping, accurate carbohydrate counting, and frequent contact with the diabetes team. Only short- or rapid-acting insulin is used with CSII; therefore, any interruption in the delivery of insulin rapidly leads to metabolic decompensation. To reduce this risk, meticulous care must be devoted to the infusion system and blood glucose levels must be measured frequently.

Medical Nutrition Therapy (MNT)

Nutrition recommendations and interventions for diabetes are described in a detailed position statement from the American Diabetes Association and are supplemented by commentary and evidence-based nutrition practice guidelines from the American Dietetic Association. Evidence-based recommendations are available for adults with T2D, but not yet for children and adolescents. The guidelines are targeted at three levels. First, primary prevention to prevent T2D; MNT is used in conjunction with public health interventions in obese individuals and those with pre-diabetes. Secondary prevention is used for metabolic control of diabetes. Tertiary intervention aims to delay and manage complications of diabetes. Primary prevention is addressed below as part of lifestyle interventions for obesity with or without T2D.

Here we focus on the principles of MNT for metabolic control of diabetes. Key points emphasize caloric needs; proportions of carbohydrate, protein, and fat; the use of sucrose-, fructose-, and calorie-dense fruit juices and soft drinks; the use of carbohydrate counting and/or exchange lists to facilitate insulin dose adjustments; the composition of the fat components of MNT; recommended fiber intake; and formulation of a meal plan.

Calories

Two convenient formulas often are used to determine total calories. Some recommend using the formula 100 kcal/kg/day for the first 10 kg of body weight; 1,000 kcal plus 50 kcal/kg/day for weight between 10.1 and 20 kg; 1,500 kcal plus 20 kcal/kg/day up to 75 kg of *ideal* body weight. An alternative approach is 4 kcal/kg/h in year 1 of life; 2 kcal/kg/h from 1 to 6 years of life; 1 kcal/kg/h thereafter. In practice, these guidelines are virtually identical since 4 kcal/kg/h is equal to 96 kcal/kg/day, in line with the recommended 100 kcal/kg/day in the first year of life when an infant attains a weight of approximately 10 kg. To lose weight, a 20% reduction in daily calories for ideal body weight is recommended. During the pubertal growth spurt, calorie needs are generally at least 20% greater. In addition, the total caloric intake is influenced by the degree of physical activity; less for sedentary lifestyles and significantly more for those who are active, particularly in adolescents who participate in structured sports.

Proportions of Macronutrients

Of the total caloric needs, approximately 50% should derive from carbohydrate (1 g = 4 kcal). The American Diabetes Association guidelines emphasize that the composition of the diet should include carbohydrates from a variety of sources: fruits, vegetables, whole grains, legumes, and low-fat milk. Carbohydrate intake should be monitored by either carbohydrate counting or use of exchanges. Some people use experience-based estimation. All methods are valuable in achieving good glycemic control. Sucrose-containing foods can be substituted for other carbohydrates providing that they are covered with the appropriate amount of insulin and care is taken to avoid excess energy intake. Likewise, consumption of moderate amounts of fructose is beneficial rather than harmful; however, care should be taken to avoid high-fructose-, high-calorie-containing soft drinks and fruit juices. Patients should be encouraged to consume a variety of fiber-containing foods; the recommendation is for 14 g of fiber per 1,000 kcal consumed per day. Non-nutritive

sweeteners are safe when consumed within the daily intake levels recommended by the Food and Drug Administration.

Protein

Protein should constitute 15–20% of daily energy intake (1 g = 4 kcal). Protein intake >20% of calories is not practical and not recommended; moreover, the long-term effect on diabetes complications is unknown. The recommended daily allowance of protein is approximately 0.8 g of good-quality protein per kilogram body weight per day. This amounts to approximately 10% of daily calories and may be doubled in growing children to achieve 15–20% of total daily energy intake. Examples of good-quality proteins are meat, poultry, fish, eggs, milk, cheese, and soy. Cereals, grains, nuts, and vegetables are not considered to be sources of good-quality protein.

Dietary Fat and Cholesterol

Fat should constitute 30–35% of daily calories. Saturated fat should be limited to <7% of total daily calories and intake of *trans* fat should be minimal. Cholesterol should be limited to <200 mg/day. Finally, two or more servings of fish (but not commercially fried fish filets) provide n-3 polyunsaturated fatty acids and are recommended. The optimal mix of macronutrients, micronutrients, and antioxidants is addressed in the ADA position statement.

The distribution of total daily caloric intake is formulated to provide 20–30% at breakfast, 20% at lunch, and 30% at dinner, leaving 20–30%, which can be distributed as a mid-morning, mid-afternoon, and bedtime snack. Consultation with and counseling by a certified dietician trained in the management of diabetes is invaluable. Planning meals according to lifestyle is crucial. For example, adolescents frequently omit breakfast, whereas vigorous structured exercise will require more calories to match expenditure. The bedtime snack is important to reduce the risk of nocturnal hypoglycemia; a mid-morning snack often is omitted if hypoglycemia does not occur at that time.

Adherence to a structured meal plan and particularly to its carbohydrate content by using carbohydrate counting or exchange lists is critical for the optimal management of diabetes and to inform decisions to adjust daily insulin doses for either T1 or T2D. Sample meal plans are published by the United States Department of Agriculture: www.health.gov/dietaryguidelines.

Exercise

Children with diabetes should be encouraged to participate in sports and include regular physical exercise in their lives because this normalizes the child's life, enhances self-esteem, improves physical fitness, helps to control weight, and may improve glycemic control. Regular exercise increases insulin sensitivity, cardiovascular fitness, and lean body mass, improves blood lipid profiles, and lowers blood pressure.

Although physical exercise is complicated for the child with T1D, especially by the need to prevent hypoglycemia, with proper guidance and planning, exercise can be a safe and enjoyable experience. Blood glucose responses to prolonged moderate-intensity exercise are repeatable when pre-exercise meal, exercise, and insulin regimens are kept constant. Exercise acutely lowers the blood glucose concentration by increasing utilization of glucose to a variable degree that depends on the intensity and duration of physical activity and the concurrent level of insulin in the blood. In T1D, acute strenuous anaerobic exercise increases levels of epinephrine and glucagon and may cause transient hyperglycemia for 30–60 min.

Hypoglycemia can usually be prevented by anticipatory reduction in the pre-exercise insulin dose or a temporary interruption or reduction of basal insulin infusion (with CSII) and supplemental snacks before, during, and after physical activity, depending on its duration and intensity. Nearly all forms of activity lasting more than 30 min require some adjustment to food and/or insulin. Continuous moderate-intensity exercise tends to cause a lesser decline in blood glucose levels than intermittent high-intensity exercise of short duration. The optimal strategy depends on timing of the exercise relative to the child's meal plan and the insulin regimen. Factors to be considered when selecting the content and size of the snack are the current blood glucose level, the action of insulin most active during and after the period of anticipated exercise, the interval since the last meal, and the duration and intensity of physical activity. The appropriate amount is learned by trial and error; a useful guide is to provide up to 1 g of carbohydrate per kilogram of body mass per hour of strenuous exercise. Prolonged and strenuous exercise in the afternoon or evening should be followed by a 10–30% reduction in the presupper or bedtime dose of intermediate- or long-acting insulin or

an equivalent reduction in overnight basal insulin delivery in patients using CSII. To reduce the risk of nocturnal or early-morning hypoglycemia caused by the lag effect of exercise, the bedtime snack should be larger than usual and contain carbohydrate, protein, and fat. Parents should be encouraged to monitor the blood glucose concentration in the middle of the night until they are experienced modifying the evening dose of insulin after exercise.

Blood glucose monitoring is essential for the active child with diabetes because it allows identification of trends in glycemic responses. Records should include blood glucose levels, timing, duration, and intensity of exercise as well as the strategies used to maintain glucose concentrations in the target range.

If possible, the insulin injection preceding exercise should be given in a site least likely to be affected by exercise (usually the abdomen). Because physical training increases tissue sensitivity to insulin, children who participate in organized sports are advised to reduce the dose of the insulin preparation most active during the period of sustained physical activity. The dose reduction is best determined by measuring blood glucose levels before and after exercise, but is generally reduced by 10–30% or more of the usual dose.

In the child with poorly controlled diabetes, vigorous exercise can aggravate hyperglycemia and ketoacid production; accordingly, a child with uncontrolled diabetes and ketonuria should not exercise until satisfactory biochemical control has been restored.

Management of Type 2 Diabetes Mellitus

The management of T2D in children and adolescents is targeted at its two major interacting causes – insulin resistance and insulin deficiency. To reduce insulin resistance and enhance insulin sensitivity, lifestyle interventions aimed at weight loss and physical fitness coupled with an oral insulin sensitizer, principally metformin, are used. Also important, if applicable, is the reduction or elimination of drugs that antagonize insulin action such as glucocorticoids and certain atypical antipsychotic medications. To correct insulin deficiency, exogenous insulin injections or secretagogues of endogenous insulin are used. The decision to initiate insulin injections is determined by the severity of metabolic decompensation at the time of presentation. For patients with T2D presenting with DKA or non-ketotic hypersosmolar coma (NKH), fasting glucose >200 mg/dL or HbA1c $\geq 8.5\%$, exogenous insulin is recommended as the primary therapy in order to rapidly correct hyperglycemia and, possibly, allow for recovery of endogenous insulin secretion. Insulin secretion may be depressed as a consequence of the deleterious effects of glucotoxicity and lipotoxicity, which refers to the negative effects of chronic hyperglycemia and elevated FFA levels on insulin secretion.

Lifestyle Interventions

Lifestyle interventions are obligatory in obese or overweight patients. The goals of lifestyle intervention are to achieve and maintain a 5–10% reduction in body weight through a healthy, low-calorie, low-fat diet. The general principles are those recommended for adults in whom such an intervention, coupled with exercise to increase calorie expenditure, have been highly effective in preventing progression from impaired glucose tolerance to T2D. Practice guidelines for the treatment and prevention of pediatric obesity have recently been published. In children and adolescents, total recommended calories and dietary composition must be developmentally appropriate, nutritionally balanced, and include recommended fiber intake, minerals, and vitamins. The participation of a trained dietician with experience in managing nondiabetic children with obesity and non-obese children with diabetes is invaluable. Published recommendations are from consensus and expert committees, but evidence-based recommendations await the results of the TODAY (Treatment Options for Diabetes in Adolescents and Youth) study currently in progress.

Closely linked to nutritional modifications are guidelines for increased physical activity to increase energy expenditure. Here, evidence-based guidelines for school-age youth are available. These recommend *daily* moderate to vigorous physical activity for a total of 60 min or more. The physical activity need not be completed in a single session, may involve a variety of activities, and should be developmentally appropriate and "enjoyable." Incorporating these activities as part of the daily school curriculum or through other structured programs is under investigation.

Insulin Therapy

As described above, insulin therapy is used in the more severe presentations of T2D. Before starting exogenous insulin, we recommend testing patients with clinically suspected T2D for the presence of pancreatic autoantibodies (ICA, GAD65, IA-2, IAA). A positive result

suggests the coexistence of autoimmunity, which implies that the patient has both T1D and T2D. This has prognostic value as patients with autoantibodies may have ongoing autoimmune destruction of ß-cells that may preclude them from being weaned off insulin and they predict that the patient will require insulin in the future. After correcting DKA or NKH, we recommend a basal-bolus regimen using a long-acting insulin (glargine or detemir) at bedtime plus a rapid-acting insulin before meals. The total daily dose (TDD) must be empirically determined, being of the order of 0.5–1.0 unit/kg, of which approximately 50% is basal and the remaining 50% bolus insulin divided among the three main meals according to the patient's blood glucose responses. This requires extensive education of the patient and family in all aspects of diabetes mellitus management (as described above for T1D), including blood glucose testing, types, use and mixing of insulins, recognition of hypoglycemia and its treatment, as well as principles of MNT. This is best accomplished as an inpatient. We recommend insulin treatment for 3 months to allow recovery of endogenous insulin secretion (reversal of glucotoxicity and lipotoxicity) before attempting to wean the patient off insulin. In some patients with T2D, a single injection of a long-acting insulin is sufficient to achieve acceptable glycemic control. In patients with poor compliance a premixed insulin preparation (e.g., 70% NPH/30% rapid-acting insulin; *Table 387.4*) is given twice daily, before breakfast and dinner, and may suffice to maintain reasonable metabolic control. Some physicians recommend measuring fasting C-peptide levels to gauge residual insulin secretory capacity before weaning patients off exogenous insulin.

If the patient now has, or originally presented with, mild to moderate hyperglycemia, defined as a fasting PG 126–199 mg/dL (7–11 mmol/L) and/or a hemoglobin A1c of <8.5%, the lifestyle modification program in combination with metformin is a safe and effective regimen in pediatric patients. Metformin is a biguanide that acts as an insulin sensitizer by decreasing hepatic glucose production and increasing insulin-mediated glucose uptake in peripheral tissues, principally muscle. Metformin is approved for use in pediatric patients with T2D. The starting dose is 850 mg once daily or 500 mg twice daily with increments of 500 mg every 2–4 weeks to a maximum of 2 g/day. The limiting factor is its gastrointestinal side effects such as nausea, vomiting, and abdominal discomfort, which generally subside if the patient perseveres in taking the medication. Lactic acidosis is rare in children with normal renal function. Renal and liver function tests should be performed before starting metformin; contraindications to its use include renal impairment, markedly abnormal liver enzymes, and cardiopulmonary insufficiency. Metformin should be discontinued before undergoing a radiographic procedure involving use of contrast agents that are known to predispose to lactic acidosis. If glucose control is not satisfactory after 3–6 months of lifestyle modification and metformin, consideration should be given to using insulin secretagogues or exogenous insulin.

Insulin Secretagogues

Insulin secretagogues such as the sulfonylureas (glyburide, glipizide and glimepiride) and the meglitinides such as repaglinide increase insulin secretion in response to eating. Their side effects include hypoglycemia, increased appetite, and weight gain, which is undesirable in T2D. These agents are not commonly used in children. Thiazolidinediones are not approved for use in children, although rosiglitazone is under investigation in children with T2D. Other agents are rarely used.

Experimental Therapies for Type 2 Diabetes in Children

These approaches are not presently standard therapy in children but are used extensively in adults with T2D. Surgically induced weight loss by means of gastric banding or bypass procedures in adults has been successful in reversing T2D. A small cohort of adolescents who underwent gastric bypass for morbid obesity experienced remission of T2D and a significant improvement in fasting PG and insulin concentrations, hemoglobin A1c and insulin sensitivity. In addition, markers of cardiovascular risk such as blood pressure and serum lipid levels improved. Although it is not generally recommended, in selected cases gastric bypass may be an option for morbidly obese adolescents with T2D.

In adults, analogs of glucagon-like peptide I (GLP-1) and drugs that prevent its inactivation, dipeptidyl peptidase-IV inhibitors (gliptins), have found increasing acceptance. GLP-1 increases insulin secretion, reduces glucagon secretion, and delays gastric emptying without increasing hypoglycemia. Exenatide, an agent that binds to the GLP-I receptor, and gliptins are widely used by adults with T2D. The long-term actions and safety of these drugs are unknown and their use in childhood has been extremely limited.

Pramlintide, a synthetic amylin analog, also has been used in adults with both T1D and T2D. It decreases

glucagon secretion and delays gastric emptying thereby facilitating weight loss without causing hypoglycemia. Its major drawback is that it must be given by injection with each meal. As more experience is gained, these drugs are likely to become part of the armamentarium used to treat adolescents with T2D.

Biochemical Outcomes in Type 2 Diabetes Mellitus

Glucose and HbA_1c

Ideal treatment outcomes for T2D in adolescents are fasting PG of 80–125 mg/dL (4.4–6.9 mmol/L) and 2 h postprandial values of <140 mg/dL (7.8 mmol/L). Two hour postprandial PG values up to 160 mg/dL (8.9 mmol/L) would maintain an HbA_1c of 7% or less, which is the recommendation of the ADA. Some investigators recommend that an HbA_1c of <6.5% should be the goal to avoid micro- and macrovascular complications.

Lipids

Dyslipidemia is common in T2D and targets for its management in children and adolescents with T2D have been promulgated by the ADA. Somewhat different targets have been recommended by the American Heart Association (AHA). Target goals for lipids are: total cholesterol <170 mg/dL, low-density lipoprotein (LDL) <130 mg/dL, triglycerides (TG) <150 mg/dL, and high-density lipoprotein (HDL) > 40 mg/dL.

If lifestyle modifications alone do not reduce hyperlipidemia to normal levels after 6 months, then HMG-CoA reductase inhibitors (e.g., atorvastatin, lovastatin, pravastatin) are recommended. Statins are especially recommended for boys older than 10 years and for postmenarcheal girls with hyperlipidemia and a family history of familial hypercholesterolemia and coronary artery disease or early myocardial infarction in first-degree relatives.

Monitoring Diabetes Control

Self-monitoring of Blood Glucose (SMBG)

SMBG is the cornerstone of modern diabetes care. Glucose meters are accurate to within 5–10% of laboratory measurements. Patients/parents must be taught how to use the data to assess the efficacy of therapy and to adjust the components of their treatment regimen to achieve individual blood glucose goals. Most glucose meters have an electronic memory; however, it is valuable for patients/parents to keep written records of their results and to analyze the data for patterns and trends and to make adjustments when necessary. Patients with T1D should routinely measure blood glucose levels at least four times daily: before each meal and at bedtime. To minimize the risk of nocturnal hypoglycemia, blood glucose should be measured between midnight and 4 a.m. once each week or every other week and whenever the evening dose of insulin is adjusted. If HbA1c targets are not being met, patients should be encouraged to measure glucose levels more frequently, including 90–120 min after meals. Frequency of glucose monitoring is a predictor of glycemic control in children with T1D. Children who are able to independently perform SMBG must be properly supervised because it is not unusual for children to fabricate data with disastrous consequences.

Continuous Glucose Monitoring (CGM)

The technology of continuous glucose monitoring (CGM) has evolved rapidly over the past several years. Current CGM devices measure glucose in the interstitial fluid by means of a short, thin glucose oxidase–based electrochemical probe inserted into the subcutaneous tissue, which can be used for 3–7 days. The accuracy of CGM devices has improved, but is not yet considered sufficient to substitute for SMBG by glucose meters, and treatment decisions are based on glucose results from a meter. Furthermore, each newly placed CGM probe must be calibrated during a period of stable glycemia over several hours by performing simultaneous capillary blood glucose measurements. Importantly, there is a lag of several minutes between actual PG and interstitial glucose concentrations; thus, current CGM devices cannot substitute for SMBG.

Real-time CGM (RT-CGM) devices report the estimated PG values in real time every 1–5 min via a user interface. Several such RT-CGM devices are commercially available and approved for use in the United States and Europe. Information from RT-CGM allows the user to detect the early phases of a hyperglycemic or hypoglycemic episode, thereby enabling corrective action to be taken after confirmatory SMBG. A short-term (6 month) controlled trial RT-CGM has demonstrated significantly improved HbA1c concentrations in intensively treated T1D in adults and more modest benefits in children. The long-range goal is to develop a closed-loop system whereby the CGM

regulates the rates of insulin infusion anticipating both the rise and fall of PG and appropriately adjusting the rates of insulin delivery to prevent hypo- and hyperglycemia.

Urine Ketone Testing

Urine should routinely be tested for ketones during acute illness or stress, when blood glucose levels are persistently elevated (e.g., two consecutive values >300 mg/dL [16.7 mmol/L]), or when the patient feels unwell, especially with abdominal pain, nausea or vomiting. False-negative readings may occur when the strips have been exposed to air (improperly stored) or when urine is highly acidic (e.g., after consumption of large doses of ascorbic acid). Urine ketone tests using nitroprusside-containing reagents can give false-positive results in patients who take valproic acid or any sulfhydryl-containing drug, including captopril.

Blood Ketone Testing

Meters that measure blood ß-hydroxybutyric acid (ßOHB) levels are available for home use; however, strips are expensive. Quantification of blood ßOHB, the predominant ketone body, is preferred over urine ketone testing for diagnosing and monitoring metabolic decompensation during intercurrent illness, with pump failure, and in DKA. Blood BOHB determination is helpful in managing patients via the telephone and avoiding emergency room visits and offers the advantage of accurately assessing improvement after starting treatment.

Glycated Hemoglobin, Hemoglobin A1c (HbA1c)

HbA1c is a minor fraction of adult hemoglobin, which is formed slowly and nonenzymatically from hemoglobin and glucose. Because erythrocytes are freely permeable to glucose, HbA1c is formed throughout the lifespan of the erythrocyte; its rate of formation is directly proportional to the ambient glucose concentration. The concentration of HbA1c, therefore, provides a "glycemic history" of the previous approximately 120 days, the average lifespan of erythrocytes. Although HbA1c reflects glycemia over the preceding 6–12 weeks, it is weighted toward the most recent 4 weeks. HbA1c measurement is a fundamental component of the management of patients with diabetes and is used to monitor long-term glycemic control and as a measure of the risk for the development of diabetes complications.

More than 30 different methods are used to measure hemoglobin A1c, which has led to different nondiabetic reference ranges because different glycated hemoglobin fractions are measured. The International Federation of Clinical Chemistry has developed a new reference method that precisely measures the concentration of glycated hemoglobin (betaN1-deoxyfructosyl-hemoglobin), and a recent study has accurately determined the relationship between mean blood glucose over many weeks and the glycated hemoglobin concentration: Average Glucose (mg/dL) = 28.7 × A1c − 46.7. It is anticipated that the new assay will be reported as "estimated average blood glucose" or "A1c-derived average glucose," and the units will be mmol/L or mg/dL.

HbA1c should be measured approximately every 3 months to determine whether a patient's metabolic control has reached or has been maintained within a target range. Average glucose levels are underestimated by HbA1c in conditions that shorten the average circulating red blood cell lifespan, such as hemolysis, sickle cell disease, transfusion, and iron deficiency anemia. When accurate HbA1c measurement is not possible, as in the above conditions, alternative measures of chronic glycemia such as fructosamine or glycated serum albumin should be used. These measure the glycation of serum proteins rather than hemoglobin, and reflect glycemia over the preceding 2–4 weeks.

Acute Complications of Diabetes

Diabetic Ketoacidosis (DKA)

DKA is a potentially life-threatening medical emergency that reflects metabolic decompensation in a patient with diabetes mellitus. The biochemical criteria for the diagnosis of DKA include hyperglycemia (blood glucose >11 mmol/L) (~200 mg/dL) with acidosis (venous blood pH <7.3 and/or serum bicarbonate ≤ 15 mmol/L), ketonemia with total serum ketones (ß-hydroxybutyrate and acetoacetate) >3 mmol/L, and ketonuria. The risk of DKA in patients with established type 1 diabetes is 1–10% per patient per year, and is increased in children with poor metabolic control or previous episodes of DKA; peripubertal and adolescent girls; children with psychiatric disorders, including those with eating disorders; and those with difficult family circumstances, including lower socioeconomic status and lack of health insurance. In the era of insulin pump therapy, interruption of insulin delivery is an

important cause of DKA. Children seldom have DKA when insulin administration is closely supervised or performed by a responsible adult.

Pathophysiology

DKA is the result of absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counterregulatory hormones, catecholamines, glucagon, cortisol, and growth hormone. Absolute insulin deficiency occurs in previously undiagnosed type 1 diabetes and when patients on treatment deliberately or inadvertently do not take insulin. Relative insulin deficiency occurs when the concentrations of counterregulatory hormones increase with stress (e.g., sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting). Low serum levels of insulin and high concentrations of the counterregulatory hormones lead to an accelerated catabolic state whose effects are: increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis (*Fig. 387.3*). Hyperglycemia and hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, which often is aggravated by vomiting. Ketoacidosis is aggravated by lactic acidosis from poor tissue perfusion and/or sepsis.

DKA is characterized by severe depletion of water and electrolytes. Despite dehydration, patients continue to have considerable urine output unless they are extremely

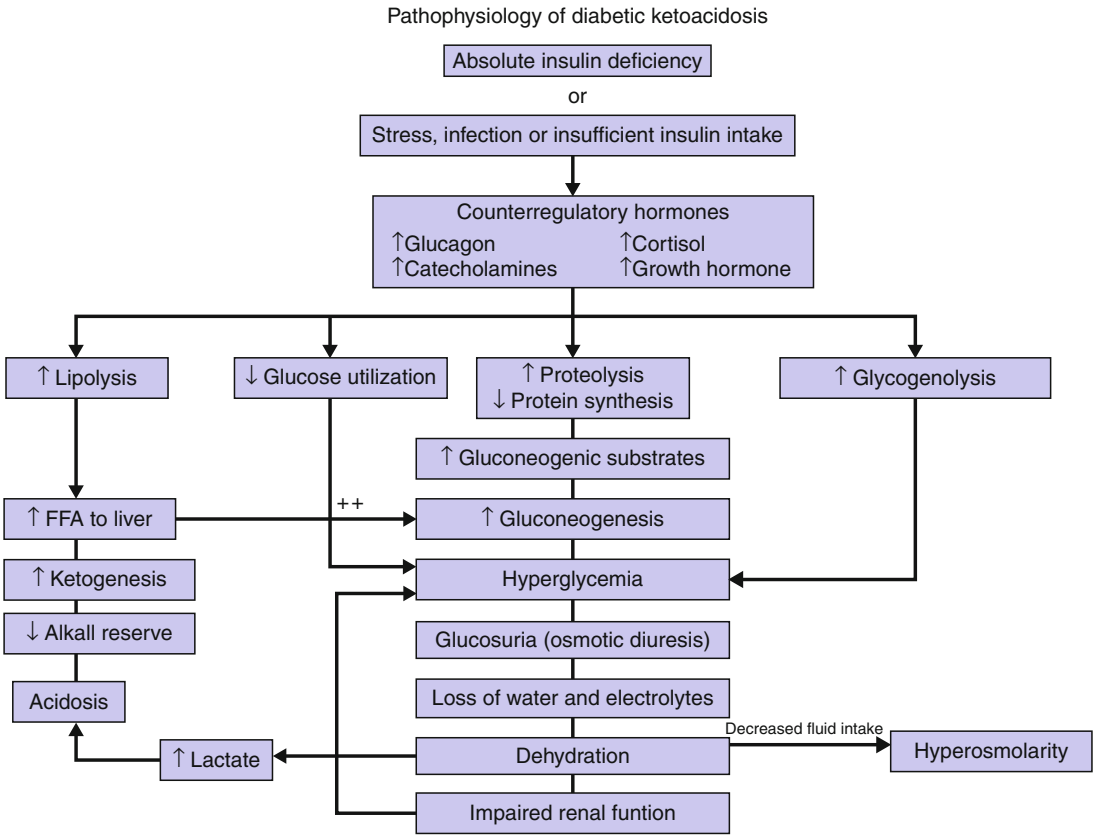

Figure 387.3

The pathophysiology of diabetic ketoacidosis is illustrated as a function of absolute insulin deficiency or insufficient insulin administration in the presence of stress, which leads to increased levels of the counterregulatory hormones. These changes increase glucose production via glycogenolysis and gluconeogenesis resulting in hyperglycemia, osmotic diuresis, and dehydration. Simultaneously, increased lipolysis leads to ketone body production and acidosis, which is augmented by lactic acidosis from dehydration

volume depleted. The magnitude of specific deficits in an individual patient at the time of presentation varies depending upon the duration of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, as well as the content of food and fluids consumed before presentation.

DKA should be distinguished from hyperosmolar nonketotic coma (HNK), a metabolic state characterized by severe hyperglycemia (blood glucose $\geq$ 600 mg/dL), absence of or only mild ketosis, nonketotic acidosis, severe dehydration, depressed sensorium or frank coma, and various neurologic signs that may include grand mal seizures, hyperthermia, hemiparesis, and positive Babinski signs. Although infrequent in children, HNK occurs in children with neurologic damage and in obese youth presenting with T2D.

Treatment of HNK is similar to that of DKA (described below), and is directed, initially, at repletion of the volume deficit with isotonic saline until the condition is stable, and then gradual correction of the hyperosmolar state over ~48 h. Insulin may be infused as for DKA, or at 0.05 unit/kg/h, half the amount typically used for DKA.

Management of DKA

The immediate aims of therapy are expansion of intravascular volume; correction of deficits in fluid, electrolyte, and acid–base status; initiation of insulin therapy to correct intermediary metabolism; and the exclusion of a treatable precipitating event such as infection. Treatment should commence as soon as the diagnosis is confirmed.

Initial Evaluation

- Perform a clinical evaluation to establish the diagnosis and determine its cause (especially any evidence of infection). Weigh the patient and measure height or length. Determine body surface area. Assess the patient's degree of dehydration.
- Determine the blood glucose concentration with a glucose meter and the blood or urine ketone concentration.
- Obtain a blood sample for laboratory measurement of glucose, electrolytes, and total carbon dioxide (TCO2), blood urea nitrogen, creatinine, serum osmolality, venous (or arterial in critically ill patient) pH, pCO2, hemoglobin, hematocrit, total and differential white blood cell count, and calcium, phosphorus, and magnesium concentrations.
- Perform a urinalysis and obtain appropriate specimens for culture (blood, urine, throat).
- Perform an electrocardiogram for baseline evaluation of potassium status.

Supportive Measures

- Secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration in the unconscious or severely obtunded patient.
- Antibiotics should be given to febrile patients after obtaining appropriate cultures of body fluids.
- Oxygen should be given to patients with severe circulatory impairment or shock.
- If the child is unconscious or unable to void on demand (e.g., infants and very ill young children), the bladder should be catheterized.
- A flowchart is essential to record the patient's clinical and laboratory data, including vital signs (heart rate, respiratory rate, blood pressure, level of consciousness [Glasgow coma scale]), details of fluid and electrolyte therapy, amount of administered insulin, and urine output. A key to successful management of diabetic ketoacidosis is meticulous monitoring of the patient's clinical and biochemical response to treatment so that timely adjustments in therapy can be made when indicated by the patient's clinical or laboratory data. Frequent reexamination of laboratory parameters is required to prevent serious electrolyte imbalance and administration of either insufficient or excessive fluid.
- A heparin-locked intravenous catheter should be placed for convenient and painless repetitive blood sampling.
- A cardiac monitor should be used for continuous electrocardiographic monitoring.

Fluid and Electrolyte Therapy

All patients with DKA are dehydrated and suffer total body depletion of sodium, potassium, chloride, and phosphate, of the order of 5–13, 3–6, 3–9, and 0.5–2.5 mmol/kg, respectively. The high effective osmolality of the extracellular fluid (ECF) compartment results in a shift of water from the intracellular fluid compartment (ICF) to the ECF and decreases the serum sodium concentration ~1.6 mmol/L per 5.6 mmol/L (100 mg/dL) of blood glucose above normal. The serum sodium concentration, therefore, may give a misleading

estimate of the degree of sodium deficit. The effective osmolality at the time of presentation is frequently in the range 300–350 mOsm/L. Increased serum urea nitrogen and hematocrit are useful markers of severe ECF contraction. At the time of presentation, patients have a contracted ECF, and clinical estimates of the deficit in patients with severe DKA are usually in the range of 7–10%. In mild to moderately severe DKA, fluid deficits are more modest, in the range 30–50 mL/kg. Shock with hemodynamic compromise is uncommon in childhood.

The onset of dehydration is associated with a reduced glomerular filtration rate (GFR), which results in decreased glucose and ketone clearance. Intravenous fluid administration expands the intravascular volume and increases glomerular filtration, which increases renal excretion of glucose and ketones, and results in a prompt decrease in blood glucose concentration. The goals of fluid and electrolyte replacement therapy in DKA are: restoration of circulating volume, replacement of sodium and water deficits, and restoration of GFR with enhanced clearance of glucose and ketones from the blood, and avoidance of cerebral edema. Although there is no compelling evidence showing the superiority of any fluid regimen over another, there are data that suggest that rapid fluid replacement with hypotonic fluid in the first several hours of treatment is associated with an increased risk of cerebral edema and slower fluid deficit correction with isotonic or near-isotonic solutions results in earlier reversal of acidosis. Large amounts of 0.9% saline have also been associated with the development of hyperchloremic metabolic acidosis.

Initial intravenous fluid administration and, when necessary, volume expansion, should begin immediately with 0.9% saline. The volume and rate of administration depends on the patient's circulatory status. When volume expansion is clinically indicated, 10–20 mL/kg is given over 1–2 h and may be repeated if necessary. Continue to use 0.9% saline for at least 4–6 h. Thereafter, use a solution with a tonicity $\geq$0.45% saline with added potassium. The rate of intravenous fluid administration should be calculated to rehydrate the patient at an even rate over 48 h. The daily volume of fluid should usually not exceed 1.5–2 times the usual daily requirement based on age, weight, or body surface area (*Table 387.5*). Urinary losses should not be added to the calculation of replacement fluids. The development of hyponatremia or failure to observe a progressive rise in serum sodium concentration with a concomitant decrease of blood glucose concentration during treatment is a risk factor for cerebral edema. Monitor the effective serum osmolality and allow it to decrease gradually. If the effective osmolality starts low or does not increase appropriately as the plasma glucose concentration falls, increase the infused sodium concentration.

When the blood glucose concentration reaches ~17 mmol/L (300 mg/dL), 5% dextrose is added to the infusion fluid; the concentration is adjusted to avoid hypoglycemia. Because hyperglycemia corrects more quickly than ketoacidemia, it may be necessary to use $\geq$10% dextrose while continuing with insulin infusion to correct ketoacidosis. Administration of intravenous fluids and insulin should be continued until acidosis is corrected (venous pH $\geq$7.30 and anion gap is near to normal) and the patient can tolerate fluids and food. Inadequate fluid administration should be evident from examination of the cumulative fluid balance and persistent tachycardia in the absence of a fever.

Table 387.5

Replacement procedure for a child (30 kg, 1 m^2) with diabetic ketoacidosis estimated to be 10% dehydrated. Normal saline 10 mL/kg is given over 1 h for initial volume expansion; thereafter, the child is rehydrated over 48 h at an even rate at two times the maintenance rate of fluid requirement

Approximate duration and rate	Fluid composition and volume	Sodium mEq	Potassium mEq	Chloridem Eq	Phosphate mmol
Hour 1 (300 mL/h)	300 mL 0.9% NaCl (normal saline)	46	–	46	–
Hour 2–4 (125 mL/h) Start regular insulin at 0.1 unit/kg/h	375 mL (normal saline) + 20 mEq K acetate/L + 20 mEq K phosphate/L	58	15	58	5.1
Hours 5–48 (125 mL/h) Continue regular insulin 0.1 unit/kg/h until pH $\geq$ 7.3 or $HCO_3 \geq$ 18 mEq/L	5,500 mL (1/2 normal saline + dextrose) +20 mEq K acetate/L + 20 mEq K phosphate/L	424	220	424	75
Total in 48 h	6,175 mL fluid	528	235	528	80

Potassium phosphate 4.4 mEq potassium and 3 mmol phosphate (1 mEq potassium and 0.68 mmol phosphate)

Insulin

Whereas hydration per se decreases the plasma glucose concentration, insulin is essential to restore blood glucose to normal and suppress lipolysis and ketogenesis, and to reverse ketoacidosis. Low-dose intravenous insulin administration is the standard of care. At a dose of 0.1 unit/kg/h, intravenous regular (soluble) insulin suppresses glucose production, significantly increases peripheral glucose uptake, and inhibits lipolysis and ketogenesis. The dose of insulin should typically remain at 0.1 unit/kg/h until resolution of ketoacidosis. In insulin-sensitive patients (especially young children and patients with mild to moderate DKA), the dose may be reduced to 0.05 unit/kg/h; however, even if the blood glucose concentration is near to normal, intravenous insulin must not be discontinued until ketoacidosis has resolved. Continuous intravenous insulin should be administered via an infusion pump. Regular insulin is diluted in normal saline (50 units regular insulin in 50 mL saline) and is given at a rate of 0.1 unit/kg/h. The insulin infusion should commence *after* initial volume expansion (1–2 h after starting fluid therapy). An intravenous priming dose is unnecessary and may increase the risk of cerebral edema.

Rare patients with severe insulin resistance do not satisfactorily respond to low-dose insulin infusion and require two or three times the usual dose. It is essential to monitor the blood glucose, venous (or arterial) pH, and anion gap response to insulin therapy. Also, one should consider other possible explanations for failure to respond to insulin (sepsis or an error in insulin preparation). When intravenous insulin is not possible, the intramuscular or subcutaneous route of administration may be used and hourly or 2-hourly rapid-acting insulin (lispro or aspart) may be preferable to regular insulin in these circumstances. Poor tissue perfusion in a severely dehydrated patient impairs SC absorption of insulin and, initially, insulin should be given intramuscularly.

When ketoacidosis has resolved and the change to SC insulin is planned, the first SC injection should be given at an appropriate interval before stopping the infusion to allow sufficient time for the injected insulin to begin to be absorbed.

Potassium

Acidosis causes intracellular potassium to enter the extracellular compartment from which it is lost in urine and vomitus. Upon presentation, serum potassium concentrations may be normal, increased or, infrequently, decreased. Hypokalemia at presentation is related to prolonged duration of disease and persistent vomiting, whereas hyperkalemia primarily results from impaired renal function. Total body potassium deficits are of the order of 3–6 mmol/kg. Insulin promotes uptake of glucose and potassium by cells, and correction of acidosis promotes the return of potassium to the intracellular compartment. The serum potassium concentration may decrease abruptly, predisposing to cardiac arrhythmias. In the unusual patient who presents with hypokalemia, potassium replacement should be started immediately and insulin administration should be deferred. Otherwise, it should be started *after* initial volume expansion and concurrent with insulin administration. If the patient presents with hyperkalemia, potassium administration should be delayed until urine output has been documented and the potassium concentration has decreased to the upper limit of the normal range. The amount of potassium administered should be sufficient to maintain serum potassium levels in the normal range. The usual starting potassium concentration is 40 mmol/L and the maximum rate of intravenous potassium administration is 0.5 mmol/kg/h. Potassium administration should continue throughout the period of intravenous fluid therapy. Careful monitoring of the serum level and provision of adequate potassium is essential to prevent hypokalemia. The plasma potassium concentration should be rechecked every hour if the plasma concentration is outside the normal range. Potassium may be given as the chloride, acetate, or phosphate salt. Use of potassium acetate and potassium phosphate reduces the total amount of chloride administered and partially corrects the phosphate deficit.

Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis. After starting therapy, plasma phosphate levels rapidly decrease as a result of urinary excretion and because insulin causes phosphate to reenter cells. Low serum phosphate levels have been associated with a variety of metabolic disturbances; however, the effects of hypophosphatemia on 2,3-diphosphoglycerate concentrations and on tissue oxygenation are especially relevant to DKA management. Although phosphate depletion persists for several days after resolution of DKA, prospective studies have not shown any significant clinical benefit from phosphate replacement. Nevertheless, serum phosphate should be monitored and severe hypophosphatemia treated with

potassium phosphate while serum calcium is carefully monitored to avoid phosphate-induced hypocalcemia.

Acidosis and Bicarbonate

Even severe acidosis is reversible by fluid and insulin replacement. Insulin stops synthesis of ketoacids and promotes ketone utilization. The metabolism of ketones results in the regeneration of bicarbonate and correction of acidemia. Treatment of hypovolemia improves tissue perfusion and restores renal function, thus increasing the excretion of organic acids and reverses any lactic acidosis.

In DKA, the anion gap is increased primarily because of a marked increase in the concentrations of the major ketone bodies, ß-OHB and acetoacetate (AcAc). Acetone is formed by spontaneous decarboxylation of AcAc. AcAc and acetone, but not ß-OHB, are measured by the commonly used clinical reagent strip or tablet methods based on the sodium nitroprusside reaction. At initial presentation with DKA, the concentration of ß-OHB is four- to tenfold higher than that of AcAc. With insulin therapy and correction of the acidosis, ß-OHB is reoxidized to AcAc, which is eventually metabolized. Blood ketone meters only measure ß-OHB.

Controlled trials of sodium bicarbonate in children and adults have not shown clinical benefit or any important difference in the rate of rise in the plasma bicarbonate concentration. There are physiologic reasons not to use bicarbonate. Its use may cause paradoxical CNS acidosis. Bicarbonate combines with H^+ and then dissociates to CO2 and H2O. The HCO3− diffuses poorly across the blood–brain barrier, whereas CO2 freely diffuses into the cerebrospinal fluid. Hence, the use of bicarbonate may worsen acidosis within the central nervous system while serum acidosis improves. Rapid correction of acidosis causes hypokalemia, may aggravate sodium load, and contributes to serum hypertonicity. It may, also, impair tissue oxygenation by increasing the affinity of hemoglobin for oxygen (i.e., shift the hemoglobin–oxygen dissociation curve to the left). Alkali therapy may increase hepatic ketone production and thus slow the rate of recovery from ketosis. The use of bicarbonate in children with DKA is associated with an increased risk for cerebral edema.

There may be selected patients, however, who may benefit from cautious alkali therapy, including patients with severe acidemia (arterial pH <6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia. Administration of bicarbonate is indicated when acidosis is severe (arterial pH $\leq$ 6.9), and when hypotension, shock, or an arrhythmia is present: 1 to 2 mmol/kg sodium bicarbonate is infused over 2 h and the plasma bicarbonate level is rechecked. Bicarbonate should not be given as a bolus because this may precipitate an acute cardiac arrhythmia.

Clinical and Biochemical Monitoring

Initially, plasma glucose should be measured hourly. Thereafter, plasma glucose, serum electrolytes (and corrected sodium), pH, pCO2, TCO2, anion gap, calcium, and phosphorus should be measured every 2 h for the first 8 h, and then every 4 h until they are normal. The data must be carefully recorded on a flow sheet.

Investigating the Cause of Ketoacidosis

The management of DKA is incomplete until its cause has been identified and treated. An intercurrent infection is not usually the cause when the patient/family is properly educated in diabetes management, is receiving regular follow-up care, and has telephone access to a diabetes team. In established patients, omission of insulin is the most common cause. In patients who use an insulin pump, failure to take extra insulin with a pen or syringe when unrecognized failure of insulin delivery occurs (hyperglycemia with hyperketonemia or ketonuria) is a common cause of DKA. There is often an important psychosocial reason for insulin omission: an attempt to lose weight in an adolescent girl with an eating disorder, a means of escaping an intolerable or abusive home situation, clinical depression or other reason for the inability of the patient to manage his or her own diabetes unassisted. A psychiatric social worker or clinical psychologist should be consulted to help to identify the psychosocial reason(s) underlying the development of DKA.

Morbidity and Mortality from DKA in Children

DKA is the leading cause of acute morbidity and mortality in children with T1D. Reported mortality rates are in the range of 0.15–0.31%. In areas with sparse medical facilities the risk of dying from DKA is greater, and children may die before receiving treatment. Cerebral edema accounts for 57–87% of all deaths from DKA. The incidence of cerebral edema is approximately 0.5–1% and mortality rates are 21–25%. Significant morbidity occurs in

10–26% of survivors. Other causes of DKA-related morbidity and mortality include hypokalemia, hyperkalemia, hypoglycemia, sepsis, and other CNS complications such as thrombosis.

Cerebral edema typically occurs 4–12 h after commencement of treatment, but can occur before treatment has begun or at any time during treatment. Symptoms and signs are variable and include onset of headache, change in neurological status (restlessness, irritability, drowsiness, deterioration in level of consciousness), inappropriate slowing of the heart rate, and an increase in blood pressure. Cerebral edema is more common in children with severe DKA, new onset T1D, younger age, and longer duration of symptoms. The cause of cerebral edema remains poorly understood.

Treatment of Cerebral Edema

Treatment should be initiated as soon as the condition is suspected, and maintaining a high index of suspicion is the best safeguard for early intervention. Give intravenous mannitol (0.5–1 g/kg) and repeat if there is no response in 30 min. Hypertonic saline (3%), 5–10 mL/kg over 30 min, has been used as an alternative to mannitol and is recommended if there is no response to mannitol. Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO_2 <22 mmHg [2.9 kPa]) has been associated with poor outcome and is not recommended. *After* treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (10% of cases), especially thrombosis or hemorrhage, which may benefit from specific therapy.

Side Effects of Treatment

Weight Gain

Intensively treated subjects in the DCCT had a considerably increased risk of becoming overweight and weight gain was greatest in individuals with higher baseline HbA1c levels. Weight gain is attributable to reduced glucosuria, to a reduction in daily energy expenditure, frequent symptomatic hypoglycemia necessitating consumption of carbohydrate to restore normoglycemia and, possibly, lack of amylin to regulate appetite.

Children and adolescents who adopt basal-bolus insulin therapy may be tempted to eat more liberally and increase their calorie consumption as they are no longer obliged to follow a regimented meal plan. Anticipatory counseling should candidly address this issue. The highly motivated patient can take advantage of the flexibility of a basal-bolus regimen to carefully balance insulin replacement with calorie intake to avoid obesity or even lose weight.

Local Effects of Insulin

Lipohypertrophy refers to the accumulation of excess adipose tissue at the sites of SC insulin injection. It is the most common cutaneous side effect of insulin administration, occurring in 25–50% of individuals with T1D. Rotation of injection sites usually prevents lipohypertrophy. Apart from its undesirable cosmetic appearance, lipohypertrophy causes erratic absorption of insulin.

Lipoatrophy and insulin allergy are much less common with use of human insulin preparations. Insulin allergy may result in local or systemic effects, with acute (redness, itching, burning, hives) or chronic reactions. Since the exclusive use of synthetic human insulins, severe reactions such as generalized urticaria and anaphylaxis are rare. Some patients are allergic to the diluent or excipients used in insulin preparations. In rare instances, insulin desensitization may be necessary and should be done in a supervised setting after preliminary skin testing.

Cellulitis or abscess may occur at the injection site, but is rare when patients use sterile disposable syringes and needles and employ basic principles of hygiene. Insulin pump therapy is associated with increased rates of cellulitis, abscess, and local scarring at the sites of subcutaneous cannula insertion. It is essential to replace the infusion set every 2–3 days and immediately remove a cannula if the site becomes red or painful.

Hypoglycemia

Hypoglycemia is the most common acute complication of the treatment of diabetes mellitus in children and adolescents and is the principal barrier to the pursuit and maintenance of near-normal glycemic control. Patients, parents, and the diabetes team have to continuously balance the risks of hypoglycemia against those of long-term hyperglycemia. Concern about nocturnal hypoglycemia causes more anxiety for some parents than any other aspect of diabetes, including the fear of long-term complications.

Biochemical hypoglycemia (with or without symptoms) is defined by the American Diabetes Association

as any PG $\leq$70 mg/dL (3.9 mmol/L), the level at which counterregulatory hormone responses engage and at which awareness of symptoms normally occurs in nondiabetic adults. In healthy 8–16-year-olds and in children and adolescents with T1D who have poor glycemic control, such responses may be triggered at higher PG levels. In nondiabetic children, the initial response to falling PG levels is suppression of insulin secretion and an abrupt increase in the circulating concentrations of glucagon and epinephrine, which acutely counteract the effects of insulin. Cortisol and growth hormone levels also rise; however, these hormones are less important in acutely counteracting the effects of insulin because their effects on glucose metabolism are delayed. Exogenously supplied insulin levels do not decrease and the glucagon response to hypoglycemia is lost early in the course of the disease. Consequently, patients with T1D depend on sympathoadrenal responses to prevent or correct hypoglycemia. Repeated mild hypoglycemia itself reduces epinephrine responses and symptomatic awareness of subsequent episodes of hypoglycemia. The repeated episodes of mild hypoglycemia that frequently occur in intensively treated patients blunt catecholamine responses to and symptom awareness of subsequent hypoglycemia. This phenomenon, referred to as hypoglycemia-associated autonomic failure (HAAF), significantly increases the risk of hypoglycemia. Catecholamine responses to hypoglycemia are impaired during sleep, another important reason most severe hypoglycemia episodes occur during the night.

Patients with T1D are susceptible to hypoglycemia because of errors related to insulin dosage, erratic eating behaviors, decreased food intake, unplanned exercise, and other factors. Long after strenuous exercise has ended, there is a sustained increase in insulin action on muscle and liver and blunting of the counterregulatory response to hypoglycemia. Exercise in the afternoon, therefore, increases the risk of hypoglycemia during the night. Collectively, these factors account for 50–85% of episodes of hypoglycemia in children and adolescents. After years of living with diabetes, some patients and/or their parents conduct their routine diabetes self-care practices without carefully considering the intricate interplay among insulin, food, and exercise.

Symptoms and Signs of Hypoglycemia

Symptoms and signs of hypoglycemia are caused by neuronal deprivation of glucose and are either autonomic (sweating, trembling, pallor, palpitations, tachycardia, apprehension) or neuroglycopenic (hunger, confusion, drowsiness, unusual behavior, speech difficulty, incoordination, seizures, and coma). Mood and behavioral changes are often the primary manifestation of hypoglycemia in young children. This has important implications for parent education on hypoglycemia.

Hypoglycemia is classified in terms of its severity as mild, moderate, or severe. Most episodes are mild. Cognitive impairment usually does not accompany mild hypoglycemia and older children are able to treat themselves. Mild symptoms abate within 15 min of treatment with rapidly absorbed carbohydrate. Moderate hypoglycemia has both neuroglycopenic as well as adrenergic symptoms, causes more protracted symptoms and may require a second treatment with oral carbohydrate. Young children typically require assistance with treatment because they are often confused and have impaired judgment; also, weakness and poor coordination may make self-treatment difficult. Severe hypoglycemia is characterized by unresponsiveness, unconsciousness, or convulsions and requires emergency treatment with parenteral glucagon or intravenous glucose.

Improved methods of replacing insulin (CSII and multiple dose regimens with insulin analogs) combined with education specifically informing subjects about hypoglycemia, behavioral educational approaches such as blood glucose awareness training, and intermittent CGM, may enable patients to achieve improved glycemic control with less risk of severe hypoglycemia than was previously possible. Insulin pump therapy is associated with fewer hypoglycemic events despite improved glycemic control. Rapid-acting insulin analogs decrease the frequency of hypoglycemia, and when compared to NPH combined with regular insulin, insulin glargine together with premeal insulin lispro decreases the incidence of nocturnal hypoglycemia in adolescents.

Treatment of Hypoglycemia

Except in preschool-age children, most episodes of symptomatic hypoglycemia are self-treated with rapidly absorbed carbohydrate, e.g., glucose tablets, glucose gel, fruit juice, soft drinks, candy, crackers, or milk. Glucose tablets raise blood glucose levels more rapidly than orange juice or milk, and the dosage is easily calibrated and is the treatment of choice for children old enough to chew and safely swallow large tablets. The recommended dose is 5–15 g of oral fast-acting carbohydrate or 0.3 g glucose per kilogram body weight. Blood glucose should be remeasured 15 min after treatment, and treatment should

be repeated if the blood glucose level does not exceed 3.9–4.4 mmol/L (70–80 mg/dL). The glycemic response to oral glucose usually lasts less than 2 h. Therefore, after treatment with oral glucose, unless a scheduled meal or snack is due within an hour, the patient should be given either a snack or a meal containing carbohydrate and protein.

Severe reactions (unresponsiveness, unconsciousness, or convulsions) require emergency treatment with parenteral glucagon (IM or SC). The usual recommended dose is 0.5 mg if less than 5 years and 1 mg if older than 5 years. Glucagon raises blood glucose levels within 5–15 min and usually relieves symptoms of hypoglycemia. The increase in blood glucose concentration after glucagon administration is sustained for at least 30 min. Because the glycemic response is transient after bolus administration of glucose, intravenous glucose infusion should be continued until the patient is able to swallow safely. Parents and school nurses need to be instructed on when and how to perform an injection of glucagon.

If severe hypoglycemia was prolonged and the patient had a seizure (hypoglycemic encephalopathy), complete recovery of mental and neurologic function may take many hours despite restoration of blood glucose levels to normal. Permanent hemiparesis or other neurologic sequelae are rare; however, the post-ictal period may be complicated by headache, lethargy, nausea, vomiting, and muscle ache.

Driving a Motor Vehicle

Driving is impaired at PG concentrations $\leq$3.3 mmol/L (60 mg/dL). The adolescent with diabetes who is learning to drive should be counseled to always measure his blood glucose level before driving and not to drive unless it is $>$4 mmol/L (70 mg/dL). The glove compartment should be stocked with a source of rapidly absorbed carbohydrate and nonperishable snacks. When symptoms of hypoglycemia are perceived, the diabetic driver should stop the car as soon as it is safe to do so.

Dead in Bed Syndrome

Sudden unexplained deaths during sleep are a rare occurrence in adolescents and young adults with T1D. Lethal cardiac arrhythmias triggered by hypoglycemia may be responsible for some cases; severe hypoglycemia related to recreational drug abuse may account for others.

Other Autoimmune Diseases Commonly Associated with Type 1a Diabetes

Autoimmune diseases affecting thyroid, upper small intestine, and adrenal are more common in patients with T1aD. Antithyroid autoantibodies can be detected in up to 20% of children and adolescents with T1aD, but only a minority of patients with thyroid autoimmunity develop hypothyroidism, whose earliest manifestation is an elevated TSH level. Annual measurement of TSH is recommended for patients with T1aD. Likewise, celiac disease occurs in up to 5–7% of patients with T1aD; weight loss or failure to gain weight, erratic blood glucose control, and unexpected hypoglycemic episodes should alert the clinician to perform a tissue transglutaminase determination, along with measurement of serum IgA, to screen for celiac disease. Definitive diagnosis requires endoscopy and a duodenal biopsy before initiating treatment with a gluten-free diet. Adrenal failure is the least common associated autoimmune disease and may be heralded by increasing frequency of unexplained hypoglycemia, reduction in insulin requirement, weight loss, asthenia, and pigmentation of skin and buccal mucosa. The combination of T1aD and either thyroid or adrenal autoimmunity or both is known as Schmidt syndrome.

Chronic Complications of Diabetes Mellitus

Management of diabetes mellitus in children requires eternal vigilance by the patient and family in monitoring blood glucose, delivery of insulin by manual or automated devices, and integration of food intake, with or without exercise, in an overall plan to achieve near-normal glycemia while avoiding hypoglycemia and DKA. Microvascular complications include retinopathy, nephropathy, and neuropathy that greatly contribute to increased morbidity and increased mortality of patients with diabetes. Macrovascular complications, primarily cardiovascular disease (CVD), are due to atherosclerotic obstruction of large blood vessels with their resultant cerebral, cardiac, and lower limb ischemia and infarction. These complications contribute markedly to the reduction in life expectancy among patients with both T1D and T2D. Estimates from the United States indicate that children diagnosed with diabetes mellitus at the age of 10 years will lose approximately 19 years of life expectancy when compared to nondiabetic controls. In Norway, the overall standardized mortality ratio (SMR) was fourfold higher in both

men and women with diabetes mellitus and the SMR was 20-fold higher for ischemic heart disease in those over 30 years of age. Acute metabolic complications such as DKA and hypoglycemia, dead in bed syndrome and violent deaths, were the most likely causes of death in those <30 years of age.

The DCCT conclusively demonstrated that glycemic control reduces the rate of microvascular complications; these beneficial effects persisted during follow-up of the original cohort in the EDIC study. Intensive treatment also reduced macrovascular disease in this cohort followed for up to 17 years. Compared with the conventional treatment group, those who received intensive treatment reduced their risk of retinopathy, neuropathy, or nephropathy by 50–60%, benefits which persisted for several years even when metabolic control as judged by HbA_1c had reverted to the level of the conventional treatment group. Thus, in the 17 year follow-up period of the EDIC study, the formerly intensive treatment group had 50–85% less retinopathy, nephropathy, and neuropathy and had less macrovascular disease. Also, improved metabolic control over the past 25 years has had a significant impact, reducing the rates of proliferative retinopathy and renal complications in a nationwide cohort. An impact on macrovascular disease and mortality is less apparent.

In addition to metabolic control, other factors significantly contribute to the risk of developing microvascular complications. A positive family history of microvascular complications increases risk for retinopathy and nephropathy reflecting that genetic factors contribute to risk. Puberty and duration of diabetes post puberty contribute to the risk; younger prepubertal children are somewhat protected. Poorly controlled diabetes causes an inflammatory stress response with deleterious effects on vascular endothelium. Hypertension, dyslipidemia, higher BMI, sedentary lifestyle, and smoking all contribute to increased risk of micro- and macrovascular complications. Cessation of smoking is of paramount importance and risk factors must be appropriately treated.

To identify and manage these vascular complications early so as to delay or prevent their progression, ISPAD has published screening guidelines. Screening for retinopathy and microalbuminuria should start at age 11 years in children who have had T1D for 2 years and from age 9 years in those who have had T1D for 5 years. Annual retinopathy screening examinations performed by a trained observer by means of dilated pupil ophthalmoscopy generally suffice. The presence of background retinopathy, defined as microaneurysms and dot-blot hemorrhages, requires at least biannual monitoring and more detailed evaluation to determine the extent of involvement by fundus photography, and/or fluorescein angiography. Depending on the extent of involvement, consideration may be given to using retinal laser therapy to reduce the likelihood of visual loss.

Annual screening for microalbuminuria is done by several methods described in the ISPAD guidelines. Because menstruation and exercise may confound results, screening should not be performed in a female who has recently menstruated or after vigorous exercise. Normal values for albumin excretion rate (AER) are <21 mcg/min corresponding to <30 mg/24 h. AER in the range 30–300 mg/24 h constitutes microalbuminuria; if present in two consecutive samples, the patient should be carefully monitored with repeated AER measurements at 6 monthly intervals to determine if microalbuminuria has regressed or is progressing. In the early stages, albuminuria may be transient, may appear in adolescence, and may regress thereafter without being progressive. Persistent or progressive microalbuminuria or albuminuria >300 mg/24 h (macroalbumuria) require expert care by a diabetologist and nephrologist working in tandem.

Fasting lipid screening should be performed in children with diabetes mellitus after the age of 12 or as early as 2 years of age if there is a family history of hyperlipidemia and/or early onset CVD in first-degree relatives. Persistent hypercholesterolemia above the 95th percentile for age, despite attempts to correct it by dietary means and optimizing metabolic control, requires referral for specialist care and consideration of the use of a statin.

Nonvascular Complications of Diabetes Mellitus

Infections

Patients with diabetes mellitus are generally not more prone to infectious disease when metabolic control is adequate, e.g., $HbA_1c \leq 8\%$. Two exceptions are mucocutaneous candidiasis and rhinocerebral mucormycosis. Candidiasis occurs primarily in the vulovaginal area and under the prepuce because candida thrives in high glucose concentrations. Rhinocerebral mucormycosis, a rare but life-threatening fungal infection, is more frequent in patients with diabetes especially during DKA. Presentation is with facial or ocular pain, nasal stuffiness, proptosis, chemosis, and necrosis of the nasal mucosa. Alertness to this occurrence and early intervention by surgical debridement and antifungal agents are the keys to a successful outcome.

Eating Disorders

Eating disorders are reported in 5–10% of women with T1D, a much higher prevalence than in control female populations, and may be a means to control weight gain. Omission of insulin is another method adolescent females with diabetes commonly use to control their weight. These disorders are associated with poor metabolic control and an early onset and high incidence of microvascular complications.

Connective Tissue and Joint Diseases

The glycation of various connective tissues such as joints, skin, and periarticular areas leads to stiffness and deformity, limited joint mobility, and stiff hand syndrome, features seen in poorly controlled diabetes mellitus. With improved metabolic control over the past 25 years, these connective tissue abnormalities are now seldom seen.

Psychiatric Disorders

Depression, suicidal ideation, and psychosis occur in patients with diabetes. It is not clear, however, if they do so at an increased rate as compared with the general population. These disorders may contribute to the increased mortality during the first 10 years of diabetes, as reported in a survey from Sweden where social and mental dysfunction and careless use of alcohol or drugs contributed to the increased mortality. By contrast, in a well-developed health care system, no clear excess death rate was caused by suicide or traffic accidents among young diabetic subjects in whom the chief causes of early death were DKA and hypoglycemia.

Concluding Remarks

Diabetes mellitus is a manifestation of failing insulin secretion compounded by resistance to its actions in various tissues. The remarkable increase in our understanding of the various forms of diabetes, the development of new insulin formulations and increasingly sophisticated devices to deliver them, and improved methods to monitor patients have made it possible to achieve better metabolic control and has markedly improved the prognosis for children with diabetes. The quickening pace of discovery suggests that many unanswered questions will be solved for the benefit of children affected by this complex disease.

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388 Thyroid Disorders

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Introduction

Thyroid hormones play a critical role in prenatal and postnatal brain development, growth, and metabolism. These effects on growth, development, and metabolism are achieved by regulating protein synthesis, cell growth, and affecting metabolic pathways. Thyroid disorders are common in pediatric practice. Congenital hypothyroidism is the most common disorder of the thyroid gland in the childhood period and is a preventable cause of mental retardation. A goiter is also a common clinical presentation in the childhood period, and worldwide, the most common cause for goiter is iodine deficiency. Graves' disease and Hashimoto's thyroiditis make up the autoimmune thyroid diseases and important causes of hyperthyroidism and hypothyroidism, respectively. Transient hypothyroxinemia is the most common thyroid dysfunction in preterm infants and is defined by temporary low levels of T4, T3, and normal or low TSH. This chapter provides a clinical overview of the common thyroid disorders.

Thyroid Anatomy and Embryology

The thyroid gland is located in the neck and consists of two lobes (left and right) which are connected by the isthmus. It lies against and around the larynx and trachea, reaching posteriorly the esophagus and carotid sheath. Microscopically, the thyroid is composed of spherical follicles, each composed of a single layer of follicular cells surrounding a lumen filled with colloid (mostly thyroglobulin). Embryologically, the thyroid gland develops from the fusion of a medial outpouching from the floor of the primitive pharynx (which will give rise to the precursor of the thyroxine (T4)-producing follicular cells) and bilateral evaginations of the fourth pharyngeal pouch (which will form the parafollicular or calcitonin (C)-secreting cells).

A number of key transcription factors (such as *NKX2.1*, *FOXE1*, *and PAX8*) are involved in regulating the development and growth of the thyroid gland. As the developing thyroid gland moves caudally, the pharyngeal portion of the gland contracts to form a narrow stalk (thyroglossal duct). A thyroglossal cyst can develop anywhere along a thyroglossal duct, and it is usually located as a midline neck lump (in the region of the hyoid bone) that is typically painless, smooth, and cystic.

In humans, the development of the thyroid gland is complete by 10–12 weeks of gestation. At this gestational age, follicle precursors can be seen, iodine binding can be identified, and thyroglobulin detected in follicular spaces. T4 and triiodothyronine (T3) are measurable in fetal serum by 11–12 weeks of gestational age. As gestational age advances, there is a progressive increase in T4 and T3 as well as serum thyroxine-binding globulin (TBG). Whereas the TBG and total T4 levels rise throughout gestation, the concentrations of free T4, and TSH rise until 31–34 weeks, declining thereafter to term. The progressive increase of the free T4 concentration allows maturation of the hypothalamic-pituitary-thyroid axis.

The Hypothalamic-Pituitary-Thyroid Axis

Thyroid gland function is dependent on the proper development and maturation of the hypothalamus and pituitary gland. Levels of thyroid hormones in serum are tightly regulated by the hypothalamic-pituitary-thyroid axis. Hypothalamic thyrotropin-releasing hormone (TRH) is secreted mainly from the paraventricular nucleus in the hypothalamus and reaches the median eminence through axonal transport. TRH is then carried via the hypothalamic portal vein to thyrotrophs, which produce thyroid-stimulating hormone (TSH), where it binds to TRH receptors and stimulates the genes that express the TSH β subunits. Apart from these thyrotropic effects, TRH also regulates the conjugation of the TSH α and β chains and glycosylation of the TSH molecule to control its biological activity.

Mature TSH is secreted from the pituitary gland and reaches the thyroid gland, where it stimulates thyroid hormone production and release. TRH and TSH start being secreted from the fetal hypothalamus and pituitary respectively at 18–20 weeks of gestation. Fetal production of T_4 reaches a clinically significant level at 18–20 weeks whereas fetal T_3 remains low (less than 15 ng/dL) until

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30 weeks of gestation, and increases to 50 ng/dL at term. The negative feedback control of thyroid hormone synthesis and secretion is established at about 20 weeks of gestation.

Physiology of Thyroid Hormones

The thyroid gland uses tyrosine and iodine to manufacture T4 and T3. The iodine comes from the diet as iodide and gets converted in the gut to iodide which is then rapidly absorbed. Iodide is taken into the thyroid follicular cells by an active transport system (against a concentration gradient) and then oxidized to iodine by thyroid peroxidase.

The incorporation of iodine into thyroglobulin for the production of thyroid hormone (organification) occurs when iodine is attached to tyrosine molecules located on thyroglobulin, forming monoiodotyrosine (MIT) and diiodotyrosine (DIT). The coupling of two molecules of DIT forms tetraiodothyronine (T4). The coupling of one molecule of MIT and one molecule of DIT forms T3.

Both T4 and T3 are composed of a phenyl ring attached via an ether linkage to a tyrosine molecule. Both have two iodine atoms on their tyrosine (inner) ring. They differ in that T4 has two iodine atoms on its phenyl (outer) ring, whereas T3 has only one. The compound formed if an iodine atom is removed from the inner ring of T4 is 3, 3′, 5′-triiodothyronine (reverse T3, rT3), which has no biological activity. Thyroglobulin, with T4 and T3 attached, is stored in the follicular lumen. TSH activates the enzymes needed to cleave T4 and T3 from thyroglobulin. In most situations, T4 is the primary hormone produced by and released from the thyroid gland. *Figure 388.1* outlines the physiology of thyroid hormones.

Approximately 20–30% of T3 is released by the thyroid gland, the remainder being produced by monodeiodination (removal of the iodine from carbon atom number five) of T4 in peripheral tissues. T3 is the primary mediator of the biologic effects of thyroid hormone and does so by interacting with a specific nuclear receptor. T3 has a half-life of 2.5 days whereas T4 has a half-life of 6 days.

Serum concentrations of T4 and T3 are maintained by a negative feedback loop involving T3-inhibition of hypothalamic thyrotropin-releasing hormone (TRH) and pituitary thyroid-stimulating hormone (TSH) secretion. TSH stimulates the secretion of T4 and T3 by stimulating multiple steps involved in the production of thyroid hormone biosynthesis. Thyroid hormone receptors bind to enhancer elements in the promoters of target genes, and can regulate both positive and negative transcription. Cellular actions of thyroid hormone may be initiated within the cell nucleus, at the plasma membrane, and in the cytoplasm.

Fetal and Neonatal Thyroid Function

The fetal hypothalamic-pituitary-thyroid axis develops independently of the maternal axis, but it is dependent on the maternal-placental system for adequate supply of iodide substrate. This iodide is supplied by direct transfer

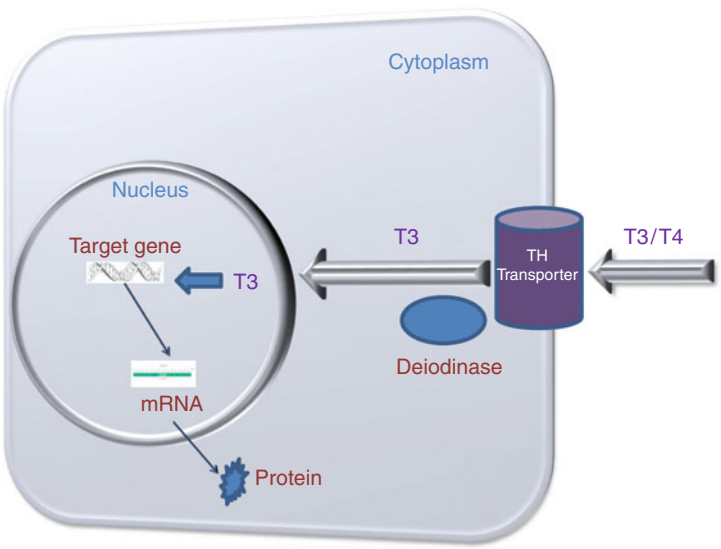

Figure 388.1
Thyroid hormone action

Table 388.1
Causes of hypothyroidism

Congenital hypothyroidism	
Primary	Secondary
1. *Thyroid dysgenesis* Thyroid agenesis Hypoplastic gland Ectopic gland 2. *Synthetic defects (Dyshormonogenesis)* Iodide transport defect Organification defect (Pendred syndrome) Thyroglobulin defect Peroxidase deficiency Deiodinase deficiency 3. *Iodine deficiency (Endemic goiter)* 4. *Transient Neonatal hypothyroidism* Perinatal stress (e.g., sepsis, birth asphyxia) Transplacental transfer of maternal antibodies Maternal drugs e.g., carbimazole, amiodarone 5. *Miscellaneous* Down's syndrome	1. TRH deficiency 2. TRH resistance (TRH receptor mutations) 3. TSH deficiency (mutations in β chain, panhypopituitarism, Pit-1 mutations) 4. TSH resistance ($G_s\alpha$ mutation, TSH receptor mutation)
Acquired hypothyroidism	
Primary	Secondary
1. *Autoimmune* Hashimoto's thyroiditis Polyglandular autoimmune syndromes 2. *Irradiation* Craniospinal irradiation Radioiodine therapy 3. *Surgery (Thyroidectomy)* 4. *Drugs* Lithium Amiodarone Propylthiouracil 5. *Goitrogens*	Intracranial tumors (Craniopharyngioma) Cranial Irradiation Neurosurgery Infection Granulomas Traumatic brain injury Empty sella syndrome

of maternal plasma iodide and by placental deiodination of T4. In addition, although placental transport of iodothyronines is limited, significant maternal-fetal transfer of T4 occurs, accounting for approximately 30% of the average 10 μg/dL serum-T4 concentration in fetal-cord blood at term. Current information suggests that this maternal contribution to the fetal-T4 levels is important for normal fetal maturation, particularly of the central nervous system. In fetuses with hypothyroidism, maternal T4 provides (possibly by alterations in iodothyronine metabolism) sufficient T3 to prevent irreversible brain damage in most cases. Combined maternal-fetal hypothyroxinemia can lead to irreversible fetal central nervous system damage. At the time of birth, cord blood T4 and free T4 are higher than the respective maternal T4 levels. There is a surge of TSH about 90 min after birth possibly related to the exposure to the extrauterine environment. However by day 3, normal T4 levels are reached.

Hypothyroidism

Introduction

The most common cause of hypothyroidism in children is congenital hypothyroidism. Transient hypothyroxinemia

is the most common thyroid dysfunction observed in preterm infants. Hashimoto's thyroiditis accounts for most of the acquired juvenile hypothyroidism cases and is a common cause of nontoxic goiter. Secondary hypothyroidism occurs when the hypothalamus produces insufficient TRH or the pituitary produces insufficient TSH. *Table 388.1* summarizes the causes of hypothyroidism.

Congenital Hypothyroidism

Congenital hypothyroidism (CH) is the most common endocrine disorder observed in newborn infants. The incidence figures vary between 1 in 2,500 and 1 in 3,500. The typical biochemical finding is an elevated TSH level with low T4 levels except in patients with abnormalities in the hypothalamic-pituitary axis. The causes of CH can be classified into two major subgroups. Approximately 85% of the cases are due to disturbances in the gland's organogenesis, which result in a thyroid gland that is absent (thyroid agenesis or athyreosis), hypoplastic (thyroid hypoplasia), or located in an unusual position (ectopic thyroid). All these entities are grouped under the term "thyroid dysgenesis" (TD). The remaining 15% of cases are due to abnormalities in the enzymatic pathways involved in thyroid hormone synthesis (dyshormonogenesis).

Most cases of TD are sporadic where the underlying cause is not known and there is a clear female preponderance. In some rare cases, defects in several transcription factors have been identified. For example, mutations in the transcription factor *NKX*2.1 are associated with CH and neonatal respiratory distress, ataxia, and developmental delay. Similarly, mutations in *FOXE*1 (*TTF*2) have been found in siblings with CH and combination of thyroid agenesis, cleft palate, spiky hair, and choanal atresia. Finally, mutations in *PAX*8 have been reported in some patients with sporadic thyroid dysgenesis.

A number of enzymatic defects lead to CH. These inborn errors of thyroid hormonogenesis are commonly associated with an autosomal recessive form of inheritance, consistent with a single gene abnormality. These include defects in the genes for the TSH receptor (*TSHR*), the sodium–iodide symporter (*NIS*), thyroid peroxidase (*TPO*), dual oxidase (DUOX) 2, thyroglobulin (*Tg*), and iodotyrosine deiodinase (*DEHAL1*). Pendred syndrome is now known to be caused by mutations in the pendrin gene (*PDS*, now called *SLC26A*4), which encodes a sulfate transporter of iodide on the apical surface of the thyroid follicular cell as well as the cochlea. Mutations in this gene have also been found to be an important genetic cause of isolated sensorineural deafness. All of the inborn errors of thyroid hormonogenesis except decreased TSH responsiveness are associated with a normally placed ("eutopic") thyroid gland that may be increased in size at birth.

Screening for Congenital Hypothyroidism

The introduction of neonatal screening programs for congenital hypothyroidism in the 1970s is now regarded as a highly cost-effective strategy to detect the commonest congenital metabolic disorder seen in the newborn. There is no doubt that early diagnosis and treatment of the condition has led to the disappearance of mental retardation, which was the most dramatic long-term sequel of congenital hypothyroidism. Screening for CH involves measurement of T4 and/or TSH from a blood sample collected on filter paper on day 1–4 of life. In parts of the USA and Holland, T4 is measured initially and then TSH is checked on the same blood spot in those specimens in which the T4 concentration is low. Using T4 as a screening method, primary hypothyroidism, secondary or tertiary hypothyroidism, babies with a low serum T4 level but delayed rise in the TSH concentration, TBG deficiency, and hyperthyroxinemia can be identified. However, this method can miss subclinical hypothyroidism.

In many parts of Europe, the screening approach involves measuring TSH as a first step. The T4 concentration is measured in the initial blood spot in all babies in whom the screening TSH is high. Using a TSH screening approach, overt and subclinical hypothyroidism will be identified, but secondary or tertiary hypothyroidism, a delayed TSH rise, TBG deficiency, and hyperthyroxinemia can be missed.

Clinical Presentation of CH

Screening for congenital hypothyroidism was introduced in the early 1970s and now is routine in most of the industrialized world. Neonatal thyroid screening is highly successful in the early diagnosis and the improvement of developmental prognosis in the hypothyroid neonate. Careful management of detected infants is essential, and it is important to remember that some infants (possibly up to 10% of the total) may escape detection in screening programs. A high index of suspicion is therefore necessary to assure early clinical detection and treatment of these infants. As cases can be missed, so it is important to be aware of the early symptoms and signs of hypothyroidism.

Infants born with congenital hypothyroidism may show no symptoms, or may display mild effects that often go unrecognized as a problem. The typical symptoms include hypothermia, constipation, jaundice, poor feeding, hoarse cry, lethargy, somnolence, macroglossia, and hypoactivity.

On examination, there may be presence of umbilical hernia, edema of genitals and extremities, cardiomegaly, bradycardia, goiter, and asymptomatic pericardial effusion. Both anterior and posterior fontanelles tend to be wide-open with coarse facies as well as hypertelorism, depressed nasal bridge, puffiness of eyes, open mouth, and a short neck. The skin may appear yellow due to carotenemia and the hairline reaches far down on forehead. The infant's voice will be hoarse and child might have hypotonia. As the child grows, infantile proportions are maintained and child may have disproportionate short stature. *Table 388.2* summarizes the symptoms and signs of hypothyroidism.

Those infants identified to have abnormal thyroid function tests on the screening program must have repeated laboratory serum measurements of T4/TSH as soon as possible (preferably within 24 h). The diagnosis of neonatal hypothyroidism is confirmed by the demonstration of a decreased concentration of T4 (<6.5 μg/dL; 3.7 nmol/L) and an elevated TSH level (>20 mU/L after 1 day of life) in serum.

The next stage of investigation will involve arranging a radionuclide scan. Technetium^{99m} (^{99m}Tc) Pertechnetate and Iodine^{123} are both used and both have advantages and disadvantages. ^{99m}Tc is more easily available and is cheaper. Iodine^{123}, if available, is usually preferred because of the greater sensitivity and because Iodine^{123}, unlike pertechnetate, is organified. These radionuclide scans provide information about the location, size, and trapping ability of the thyroid gland; ectopic thyroid glands, frequently sublingual, may be located anywhere along the pathway of thyroid descent from the foramen cecum to the anterior mediastinum. Thyroid scintigraphy may provide insights into clinical and genetic correlates in CH.

The use of ultrasound in CH has become an increasingly popular alternative to thyroid scintigraphy to provide information about the size and location of the thyroid gland. Ultrasound appears to be somewhat less sensitive than a radionuclide scan in detecting ectopic thyroid tissue and does not provide information about function.

Table 388.2
Clinical manifestations of hypothyroidism

Neonate	
Symptoms	*Signs*
Poor feeding	Lethargy
Prolonged neonatal jaundice	Jaundice
Weak and hoarse cry	Macroglossia
Sleepiness	Coarse facies
Constipation	Goiter
Failure to thrive	Mottled skin
	Umbilical hernia
	Distended abdomen
	Hypothermia
	Edema of the extremities
Children and adolescents	
Symptoms	*Signs*
Poor growth	Goiter
Excessive weight gain	Short stature
Constipation	Widely patent fontanelle
Cold intolerance	Myxedematous facies
Menstrual irregularity	Obesity
Poor school performance	Dry skin
	Pallor
Delayed puberty (rarely precocious puberty)	Delayed dentition
	Delayed relaxation phase of deep tendon reflexes
Mental retardation	Pseudohypertrophy of muscles

Treatment of CH

The importance of thyroid hormone to brain growth and development is demonstrated by comparing treated and untreated children with congenital hypothyroidism. Thyroid hormone is necessary for normal brain growth and myelination and for normal neuronal connections. The most critical period for the effect of thyroid hormone on brain development is the first few months of life.

The overall goals of treatment are to assure normal growth and by restoring the serum T4 concentration rapidly to the normal range followed by continued clinical and biochemical euthyroidism. Therefore, once the diagnosis of CH is confirmed, treatment with L-thyroxine should be commenced as soon as possible. Parents will need to be counseled with regard to the diagnosis and the importance of compliance. The prognosis will be good in most babies if therapy is started early and is adequate. Oral T4 is the treatment of choice. Although T3 is the more biologically active hormone, the majority of brain T3 is derived from local deiodination of T4; thus, it is not necessary to use T3. The aim of replacement therapy is to normalize the serum T4 level as quickly as possible and an initial dosage of 10–15 μg/kg is generally recommended. Initial T4 dose and faster time to normalization of thyroid function are important for optimal neurodevelopmental

outcome. In severe CH, it is important to choose an initial dose at the higher end of the recommended range to achieve these goals. Hence, some studies have suggested using an even higher initial dose (12–17 μg/kg).

Thyroid hormone tablets should be crushed and administered with juice or formula, but care should be taken that all of the medicine has been swallowed. Thyroid hormone should not be given with substances that interfere with its absorption, such as iron, soy, or fiber. Recently an oral thyroid hormone solution has become available (Evotrox). Evotrox Oral Solution contains the active ingredient levothyroxine sodium and is indicated for hypothyroidism (congenital or acquired) and also for diffuse, nontoxic goiter or Hashimoto's thyroiditis and thyroid carcinoma.

Transient Hypothyroxinemia in Premature Infants

Transient hypothyroxinemia is the most common thyroid dysfunction in preterm infants and is defined by temporary low levels of T4, T3, and normal or low TSH. Low T4 levels in preterm infants are associated with persistent neurodevelopmental deficits in cognitive and motor function. The etiology of transient hypothyroxinemia is complex. There are significant contributions from the withdrawal of maternal-placental thyroxine transfer, hypothalamic-pituitary-thyroid immaturity, developmental constraints on the synthesis, and peripheral metabolism of iodothyronines and iodine deficiency. Observational studies have shown an association between transient hypothyroxinemia and abnormal neurodevelopmental outcome, suggesting that thyroid hormone therapy might prevent this morbidity. However, several large Cochrane reviews do not support the routine use of thyroid hormones in preterm infants to reduce neonatal mortality, improve neurodevelopmental outcome, or to reduce the severity of respiratory distress syndrome.

Primary Hypothyroidism in Infants and Adolescents

Autoimmune thyroid diseases are characterized by the presence of antibodies directed toward different components of the thyroid gland. Graves' disease and Hashimoto's thyroiditis make up the autoimmune thyroid diseases. Autoimmune thyroid diseases arise due to complex interactions between environmental and genetic factors. Three gene regions consistently associated with autoimmune diseases include the Human Leucocyte Antigen (HLA) region, CTLA4, and PTPN22, which represent general autoimmune risk loci and encode molecules vital for correct immune system function.

Hashimoto's thyroiditis accounts for most of the acquired juvenile hypothyroidism cases and is a common cause of nontoxic goiter. Thyroglobulin or microsomal antibodies are present in serum of virtually all individuals. Asymptomatic goiter is the most common presentation though subclinical hypothyroidism and growth failure are frequently seen. Thyroid function is variable depending on the degree of thyroid destruction.

Children typically present with a goiter and possibly growth failure. In the early stages of the disease, patients may be hyperthyroid but will eventually develop hypothyroidism. Once hypothyroid, they may have symptoms of cold intolerance, constipation, dry skin, poor memory, and bradycardia. Hypothyroid children have delayed puberty, but in severe long-standing hypothyroidism, sexual precocity can also occur, and in some cases, galactorrhea has been reported. In boys, testicular enlargement may be found with normal gonadotropin levels. The extremely elevated TSH in the serum can cross-react with the follicle-stimulating hormone (FSH) receptor, leading to the syndrome of "pseudopuberty" in hypothyroid patients. Serum prolactin levels are also elevated due to the elevated TRH which stimulates prolactin as well as TSH release.

If the hypothyroidism is severe and long standing, immature facies with an underdeveloped nasal bridge and immature body proportions (increased upper-lower body ratio) may be noted. Dental and skeletal maturation are delayed, the latter often significantly.

Radiologically, in children with long-standing severe hypothyroidism, there may be enlargement of the sella turcica due to hyperplasia of the thyrotrophs. Hypothyroid children have an increased incidence of slipped femoral capital epiphyses. The combination of severe hypothyroidism and muscular hypertrophy is known as Kocher–Debre–Semelaigne syndrome, giving the child a "Herculian" appearance.

Laboratory Investigations

Serum T4 and TSH should be measured in patients suspected of primary hypothyroidism. An elevated serum TSH with low or undetectable serum T4 will support the diagnosis. TRH testing has been used in the past to distinguish a hypothalamic versus pituitary origin of the hypothyroidism; in hypothalamic hypothyroidism, there tends to be a delayed peak in TSH secretion (60–90

min versus the normal maximal response at 15–30 min), whereas in hypopituitarism, there usually is little or no TSH response. However, this test is not reliable in the pediatric population.

Treatment

Replacement therapy with thyroxine should be commenced as soon as possible. In those children with long-standing primary hypothyroidism, the lowest dose possible of thyroxine should be commenced and gradually titrated if no side effects develop. If normalization occurs too rapidly, then there may be side effects (deterioration in school performance, short attention span, hyperactivity, insomnia, and behavior difficulties). Pseudotumor cerebri is a rare side effect of replacement therapy.

Secondary Hypothyroidism

Secondary hypothyroidism occurs when the hypothalamus produces insufficient TRH or the pituitary produces insufficient TSH. Sometimes, deficient TSH secretion due to deficient TRH secretion is termed tertiary hypothyroidism. Patients with secondary hypothyroidism typically will present with multiple other pituitary hormone deficiencies. The causes of secondary hypothyroidism include traumatic brain injury, subarachnoid hemorrhage, hypothalamic-pituitary tumors, Sheehan syndrome, and mutations in genes involved in regulating the development (such as TRHR, POU1F1, PROP1, HESX1, SOX3, LHX3, LHX4, and TSHB) of the hypothalamic-pituitary region.

Hyperthyroidism

Introduction

Hyperthyroidism can occur in the neonatal period and is usually due to an autoimmune basis (associated with maternal Graves' disease) or rarely due to mutations in the stimulatory G protein. Graves' disease is an important cause of hyperthyroidism and is caused by TSH receptor antibodies that mimic the action of TSH with stimulation of adenyl cyclase, thyroid hormonogenesis, and growth.

Neonatal Hyperthyroidism

Neonatal hyperthyroidism occurs in two forms. An autoimmune form (transient) is associated with maternal Graves' disease, resulting from transplacental passage of maternal thyroid-stimulating antibodies. A non-autoimmune form occurs due to mutations in the stimulatory G protein (McCune–Albright syndrome) or the thyrotropin receptor (TSHR), causing constitutive activation of intracellular signaling cascades. About 1–2% of infants born to mothers with Graves' disease or Hashimoto's thyroiditis develop neonatal hyperthyroidism.

Fetal hyperthyroidism may be associated with intrauterine growth retardation, nonimmune fetal hydrops, craniosynostosis, and intrauterine death. Features of this condition in the neonate include hyperkinesis, diarrhea, poor weight gain, vomiting, ophthalmopathy, cardiac failure and arrhythmias, systemic and pulmonary hypertension, hepatosplenomegaly, jaundice, hyperviscosity syndrome, thrombocytopenia, and craniosynostosis.

The diagnosis of hyperthyroidism is confirmed by the demonstration of an increased concentration of circulating T4 (and free T4, and T3, if possible) accompanied by a suppressed TSH level in neonatal or fetal blood. Demonstration in the baby or mother of a high titer of TSH receptor antibodies will confirm the etiology of the hyperthyroidism.

The time course of neonatal hyperthyroidism depends on etiology; remission by 20 weeks is most common in neonatal Graves' disease.

Treatment of hyperthyroidism in neonates may require the use of antithyroid drugs, beta-adrenergic receptor blocking agents, iodine, or iodinated contrast agents, and at times, with glucocorticoids and digoxin. Nonremitting causes of neonatal hyperthyroidism may even require ablative treatments such as thyroidectomy.

Graves' Disease

Graves' disease is another type of autoimmune thyroid disease with female to male ratio being 6–8:1. Graves' disease is caused by TSH receptor antibodies that mimic the action of TSH with stimulation of adenyl cyclase and thyroid hormonogenesis and growth. Although it can occur at any age, it is most common in adolescence. Prepubertal children tend to have more severe disease, to require longer medical therapy, and to achieve a lower rate of remission as compared with pubertal children. This appears to be particularly true in children who present at <5 years of age. Patients with Graves' disease have an increased risk of developing other autoimmune diseases such as diabetes mellitus, Addison's disease, vitiligo, systemic lupus erythematosus, rheumatoid arthritis, myasthenia gravis, periodic paralysis, idiopathic

thrombocytopenia purpura, and pernicious anemia. There is an increased risk of Graves' disease in children with Down syndrome (trisomy 21).

Clinical Presentation of Graves' Disease

Patients with Graves' present with some degree of thyroid enlargement, and most have symptoms and signs of excessive thyroid activity (tremors, inability to fall asleep, weight loss despite an increased appetite, proximal muscle weakness, heat intolerance and tachycardia). There may also be a shortened attention span, and emotional lability may lead to behavioral and school difficulties. Some patients complain of polyuria and of nocturia, the result of an increased glomerular filtration rate. Acceleration in linear growth may occur, often accompanied by advancement in skeletal maturation (bone age).

Physical examination reveals a diffusely enlarged, soft or "fleshy" thyroid gland, smooth skin and fine hair texture, excessive activity, and a fine tremor of the tongue and fingers. A thyroid bruit may be audible. In contrast, the finding of a thyroid nodule suggests the possibility of a toxic adenoma. The hands are often warm and moist, and on cardiovascular examination, a tachycardia, a wide pulse pressure, and a hyperactive precordium may be found. Café au lait spots, particularly in association with precocious puberty, on the other hand, suggests a possible diagnosis of McCune–Albright syndrome while if a goiter is absent, thyrotoxicosis factitia should be considered. The ophthalmopathy characteristic of Graves' disease in adults is considerably less common in children, although a stare and mild proptosis are observed frequently.

Thyroid storm, also referred to as thyrotoxic crisis, is an acute, life-threatening, hypermetabolic state induced by excessive release of thyroid hormones in individuals with thyrotoxicosis (Graves' disease). Thyroid storm may lead to life-threatening heart, liver, or kidney failure. Thyroid storm begins suddenly and may be caused by a stressful event. Thyroid storm may be the initial presentation of thyrotoxicosis in undiagnosed children, particularly in neonates. The clinical presentation includes fever, tachycardia, hypertension, and neurological and gastrointestinal abnormalities. Hypertension may be followed by congestive heart failure that is associated with hypotension and shock. Because thyroid storm is almost invariably fatal if left untreated, rapid diagnosis and aggressive treatment are critical.

The clinical diagnosis of hyperthyroidism is confirmed by the finding of increased concentrations of circulating thyroid hormones (T4 and T3). In hyperthyroidism, the circulating T3 concentration frequently is elevated out of proportion to the T4 because, like TSH, TSH receptor antibodies stimulate increased T4-to-T3 conversion. The diagnosis is confirmed by the demonstration of TSH receptor antibodies in serum.

Therapy

There are three possible forms of therapy (medical therapy, radioactive iodine, or surgery). The three therapeutic options should be individualized and discussed with the patient and his/her family. Each approach has its advantages and disadvantages with respect to efficacy, both short- and long-term complications, the time required to control the hyperthyroidism, and the requirement for compliance.

Medical Therapy

The thiouracil compounds propylthiouracil, methimazole, and carbimazole exert their antithyroid effect by inhibiting the organification of iodine and the coupling of iodotyrosine residues on the thyroglobulin molecule to T3 and T4.

Radioactive Iodine

Definitive therapy with either medical (radioactive iodine) or surgical thyroid ablation is usually reserved for patients who have failed drug therapy, developed a toxic drug reaction, or are noncompliant. In recent years, however, radioactive iodine is being favored increasingly, even as the initial approach to therapy. The advantages are the relative ease of administration, the reduced need for medical follow-up, and the lack of demonstrable long-term adverse effects. Radioactive iodine therapy should be used with caution in children <10 years of age and particularly in those <5 years of age because of the increased susceptibility of the thyroid gland in the young to the proliferative effects of ionizing radiation.

Surgery, the third therapeutic modality, is performed less frequently now than in the past. An advantage of this form of therapy is the rapid resolution of the hyperthyroidism. Near-total thyroidectomy is the procedure of choice in order to minimize the risk of recurrence. Surgery usually is reserved for patients who have failed medical management, who have a markedly enlarged thyroid, who refuse radioactive iodine therapy, and for the rare patient with significant ophthalmopathy in whom radioactive iodine therapy is contraindicated. The most common potential complication is transient hypocalcemia which occurs in approximately 10% of patients. Other, less

common potential complications are keloid formation (2.8%), recurrent laryngeal nerve paralysis (2%), and hypoparathyroidism (2%).

The Approach to a Child with Goiter

Introduction

The term "goiter" simply refers to the abnormal enlargement of the thyroid gland. Goiter may extend into the retrosternal space, with or without substantial anterior enlargement. Because of the anatomic relationship of the thyroid gland to the trachea, larynx, superior and inferior laryngeal nerves, and esophagus, abnormal growth may cause a variety of compressive syndromes. The presence of goiter does not necessarily mean that the thyroid gland is malfunctioning. Goiter can be associated with hyperthyroidism, hypothyroidism, or euthyroidism.

Individuals with multinodular goiters have one or more nodules within the gland which cause thyroid enlargement. This is often detected as a nodular feeling gland on physical exam. Patients can present with a single large nodule with smaller nodules in the gland, or may show as multiple nodules when first detected. Multinodular goiter and solitary thyroid nodule are rare in the pediatric age group: Both conditions can reveal a malignant lesion. In this case, a total thyroidectomy should be performed. Long-term outcome is excellent with an exception for medullary carcinoma which can be part of a multiple endocrine neoplasia (MEN type 2 A).

Causes of Goiter

Worldwide, the most common cause for goiter is iodine deficiency. In countries that use iodized salt, Hashimoto's thyroiditis is the most common cause and Graves' disease can also cause goiter. The different etiologic mechanisms that can cause a goiter are shown in *Table 388.3*.

Examination of the goiter is best performed with the patient upright, sitting, or standing. Inspection from the side may better outline the thyroid profile, as shown below. Asking the patient to take a sip of water facilitates inspection. The thyroid gland should move upon swallowing. A retrosternal goiter may not be evident on physical examination. Palpation of the goiter is performed either facing the patient or from behind the patient, with the neck relaxed and not hyperextended.

A firm rubbery thyroid gland suggests Hashimoto thyroiditis, and a hard thyroid gland suggests malignancy or Riedel struma. Multiple nodules may suggest a multinodular goiter or Hashimoto thyroiditis. A solitary hard nodule suggests malignancy, whereas a solitary firm nodule may be a thyroid cyst. Auscultation of a soft bruit over the inferior thyroidal artery may be appreciated in a toxic goiter. Palpation of a toxic goiter may reveal a thrill in the profoundly hyperthyroid patient.

Table 388.3
Causes of goiter

Iodine deficiency
Puberty
Autoimmune thyroiditis – Hashimoto's, postpartum thyroiditis, Graves' disease
Excess iodine
Goitrogens (including drugs such as lithium and amiodarone)
Stimulation of TSH receptors by TSH from pituitary tumors, pituitary thyroid hormone resistance, gonadotropins, and/or thyroid-stimulating immunoglobulins
Inborn errors of metabolism causing defects in biosynthesis of thyroid hormones
Exposure to radiation
Thyroid hormone resistance
Subacute thyroiditis (de Quervain thyroiditis)
Silent thyroiditis
Riedel thyroiditis
Granulomatous disease

A toxic goiter is associated with hyperthyroidism (diffuse toxic goiter as in Graves' disease, toxic multinodular goiter, and toxic adenoma (Plummer disease)). A nontoxic goiter is associated with hypothyroidism or euthyroidism. It may be diffuse or multinodular, but a diffuse goiter often evolves into a nodular goiter. Examination of the thyroid may not reveal small or posterior nodules. Examples of nontoxic goiters include chronic lymphocytic thyroiditis (Hashimoto's disease), goiter identified in early Graves' disease, endemic goiter, sporadic goiter, congenital goiter, and physiologic goiter that occurs during puberty. Autonomously functioning nodules may present with inability to palpate the contralateral lobe. Unilobar agenesis may also present like a single thyroid nodule with hyperplasia of the remaining lobe.

Thyroid Nodules

Thyroid nodules are common in clinical practice. They may be solitary within a "normal" thyroid gland or

dominant within a multinodular goiter. The incidence of thyroid nodules has been on the rise in recent decades, mainly due to the wider use of neck imaging. Therefore, the incidental finding of a thyroid nodule in an asymptomatic patient is not rare. The differential diagnosis of a thyroid nodule is crucial, as malignancy necessitates surgery, while strict patient follow-up is necessary in the case of benignity. Fine-Needle Aspiration biopsy is considered to be the "gold standard" in the selection of patients for surgery. Ultrasonography (US) can be used to determine changes in the size of nodules during follow-up or to detect recurrent lesions in patients suspected for thyroid malignancy, although there are no specific US findings that suggest malignancy. Surgery is mandatory in cytologically malignant nodules or in cases suspicious for malignancy. The definite diagnosis and consequent therapy is based on the histological findings after surgery.

Cancer of the Thyroid Gland

Thyroid malignancy is rare in children. More than 50% of isolated thyroid nodules are cysts or benign adenomas. The most common types of thyroid cancer are papillary and follicular carcinomas. Anaplastic carcinoma, medullary thyroid carcinoma, lymphoma, and metastatic tumors include the rare forms. Genetic factors and irradiation are the major risk factors. Girls are affected twice more than the boys. The clinical manifestations include painless rapidly enlarging thyroid nodule, hoarseness of voice, dysphagia, and lymphadenopathy. The lungs are the most common site of metastases outside the neck, while the other sites include mediastinum, long bones, skull, and axilla. Nearly all patients are clinically euthyroid. Ultrasound is useful in identifying the cystic lesions, which are nearly always benign. Radioisotope scan is indicated for non-cystic lesions to identify cold, warm, or hot nodules.

Fine-needle aspiration biopsy is the most definitive diagnostic test. Surgery includes removal of the affected lobe followed by total thyroidectomy if frozen sections confirm malignancy. Radioactive iodine treatment is used for patients with metastatic disease. Postoperatively, adequate thyroxine therapy is essential to suppress TSH to avoid tumor regrowth. Regular follow-up including periodic measurements of thyroglobulin and ultrasound is useful to detect tumor recurrence. The prognosis in the papillary and follicular carcinomas is very good, while aggressive treatment is necessary for anaplastic carcinoma in view of poor prognosis.

Medullary thyroid carcinoma arises from the parafollicular C cells of the thyroid. It can be isolated or part of multiple endocrine neoplasia syndrome (MEN syndrome). In children with a family history of MEN 2A or 2B syndrome, complete thyroidectomy before the age of 5 years is now recommended if the genetic studies confirm that the child is affected. Calcition is used for the follow-up of patients with medullary thyroid carcinoma.

Rare Thyroid Disorders

Thyroid Hormone Resistance Syndrome

Some patients have resistance to the action of thyroid hormone, which is variable among the tissues. They present with goiter and elevated levels of T3 and T4 and may be misdiagnosed as Grave's disease. However, unlike Grave's disease, TSH levels are inappropriately normal or elevated. Most patients are clinically euthyroid, although subtle clinical features of hypothyroidism may be present. The condition is most often inherited in an autosomal dominant fashion due to mutations in the gene encoding the β thyroid hormone receptor. No treatment is necessary unless growth retardation is present. Rarely, the resistance to thyroid hormone may be selective and affect the pituitary gland while the other tissues remain sensitive. Such patients present with goiter and features of hyperthyroidism and elevated T3 and T4 levels. Treatment includes T3 (aimed at suppressing TSH) and propanalol.

Disorders of Thyroid-Binding Globulin

The major carrier proteins for circulating thyroid hormones are TBG, thyroid-binding prealbumin (TBPA), and albumin. The role of these carrier proteins seems to be a buffer to maintain relatively normal hormone concentrations. Unbound, or free, T4 accounts for only about 0.03% of circulating T4 and is the portion that is metabolically active. TBG levels are influenced by liver disease as well as sex steroids (estrogen and progesterone increase whereas androgens decrease TBG level). Conditions leading to hypothyroidism can cause TBG levels to increase whereas hyperthyroidism leads to a decrease in TBG levels. Infants born with low levels of TBG, as in congenital TBG deficiency, have low total T4 levels but are physiologically normal. Familial congenital TBG deficiency can occur as an X-linked recessive or autosomal recessive condition.

Euthyroid Sick Syndrome

Euthyroid sick syndrome is the abnormal findings of thyroid function tests in the setting of a nonthyroidal illness, without preexisting hypothalamic-pituitary and thyroid gland dysfunction. The most prominent alterations observed in this syndrome are low serum T3 and elevated reverse rT3. TSH and T4 are affected in variable degrees based on the severity and duration of the nonthyroidal illness. As the severity of the illness increases, both serum T3 and T4 levels drop and gradually normalize as the patient recovers.

Subacute Thyroiditis

This is a self-limiting disorder where the pathogenesis is not completely understood. In some cases, there is a history of a viral infection which might be the cause of the inflammation. Patients present with an enlarged painful and tender thyroid gland that tends to come on quite rapidly. Biochemically, there is evidence of hyperthyroidism in some patients which is transient. This occurs due to disruption of the thyroid follicles giving rise to the elevated serum T4 and T3 concentrations. Rarely, there may be transient hypothyroidism.

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389 Hypoglycemia

Chela James · Khalid Hussain

Introduction

Hypoglycemia is one of the most common biochemical abnormalities observed in the neonatal, infancy, and childhood periods. Despite the commonality, there is still confusion about the definition and management of hypoglycemia. Hypoglycemia can be due to many causes in the neonatal, infancy, and childhood period. For example, hyperinsulinemic hypoglycemia is the most severe form of hypoglycemia in the neonatal period whereas "ketotic" hypoglycemia presents in the childhood only during an intercurrent illness. Thus, having an understanding of normal glucose physiology will not only help the clinician to understand the biochemical basis of hypoglycemia but will also allow the clinician to organize appropriate investigations and institute the correct management. The early recognition and prompt management of hypoglycemia is the cornerstone in preventing brain injury. The aim of this chapter is to provide a brief background to normal glucose physiology, review the mechanisms that help to maintain normoglycemia, and then from a clinical perspective, to focus on the clinical approach to a patient with hypoglycemia and finally to review the different causes of hypoglycemia in the childhood period.

Definition

The definition of hypoglycemia remains one of the most contentious and confusing areas (especially in the newborn) in glucose physiology. This is because there is poor correlation between plasma glucose concentrations, the onset of clinical symptoms, and the long-term neurological sequelae. It is difficult to define a blood glucose level that will require intervention (especially in neonates) since there is uncertainty over the level and duration of hypoglycemia that can cause neurological damage.

Several different approaches have been used to define hypoglycemia (an approach based on clinical manifestations, the epidemiologic approach based on measured range of glucose values, an approach based on acute changes in metabolic and endocrine responses and on neurologic function, and an approach based on long-term neurologic outcome) but none of these approaches is satisfactory. The approach based on neurophysiological responses to falling blood glucose concentrations has led to the proposal that hypoglycemia should be defined as a concentration less than 2.6 mmol/L as measured with a laboratory research method. However, around 20% of entirely normal full-term infants will demonstrate blood glucose concentrations less than this in the first 48 h after delivery. These infants will show a concurrent hyperketonemia and the assumption (which still needs to be proved) is that the babies will not demonstrate neural dysfunction at this time because of the protective effect of the availability of alternative fuels.

Recently, it has been recommended that operational thresholds are used when assessing an interventional response in a patient with hypoglycemia. An operational threshold is defined as the concentration of plasma or whole blood glucose at which clinicians should consider intervention, based on the evidence currently available in the literature. Significant hypoglycemia is not and can never be defined by a single number that can be applied universally to every individual patient. Rather, it is characterized by a value(s) that is unique to each individual and varies with both their state of physiologic maturity and the influence of pathology. It can be defined as the concentration of glucose in the blood or plasma at which the individual demonstrates a unique response to the abnormal milieu caused by the inadequate delivery of glucose to a target organ (for example, the brain).

Thus, it is not possible to define a blood glucose level that requires intervention in every newborn infant because there is uncertainty over the level and duration of hypoglycemia that cause damage, and little is known of the vulnerability, or lack of it, of the brain of infants at different gestational ages for such damage. It is therefore clear that hypoglycemia is a continuum and the blood glucose concentration should be interpreted in the context of the clinical presentation, counter-regulatory hormonal responses and in relation to the intermediate metabolites.

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Normal Glucose Physiology

Metabolic and Endocrine Changes at the Time of Birth

At birth, the healthy term newborn must adapt to an independent existence. The transplacental supply of nutrients including glucose is interrupted and the newborn must now initiate metabolic and endocrine responses to maintain adequate circulating blood glucose concentrations. For extrauterine adaptation there must be adequate glycogen stores, intact and functional glycogenolytic, gluconeogenic and lipogenic mechanisms and appropriate counter-regulatory hormonal responses.

A normal infant at term shows an immediate postnatal fall in blood glucose concentrations during the first 2–4 h from values close to maternal levels to around 2.5 mmol/L. The trigger for the metabolic and endocrine adaptation with reference to glucose control is unclear but surges in catecholamines and glucagon secretion are thought to be important. The raised plasma insulin to glucagon ratio is reversed at birth allowing glucagon to activate adenylate cyclase and increase the activity of cAMP-dependent protein kinase, PKA. This in turn activates phosphorylase kinase, which facilitates glucose release.

The catecholamine surge activates lipolysis and lipid oxidation resulting in increases in the levels of glycerol and free fatty acids. Free fatty acids are then used to generate ketone bodies, which are used as an alternative source of fuel. Healthy term breast-fed babies have significantly lower blood glucose concentrations than those who were bottle-fed, but their ketone body concentrations were elevated in response to breast feeding. Major changes occur in the function of several physiological systems after birth, which enables the neonate to adapt to postnatal nutrition. Successful enteral feeding in healthy term newborns triggers the secretion of gut peptides and plays a key role in triggering a cascade of developmental changes in gut structure and function, and in the relation of pancreatic endocrine secretion to intermediary metabolism. Hence full-term infants are functionally and metabolically programmed to make the transition from their intrauterine-dependent environment to their extrauterine existence without the need for metabolic monitoring or interference with the natural breast-feeding process. This complex metabolic and endocrine adaptation process is incomplete and compromised when the infant is born prematurely or following intrauterine growth retardation.

The Endocrine and Metabolic Changes During Feeding and Fasting

A normal (fasting blood glucose levels 3.5–5.5 mmol/L) circulating blood glucose concentration is vital for brain function. Any defect that leads to hypoglycemia will cause hypoglycemic brain injury. Glucose homeostasis is regulated systemically by hormones such as insulin and glucagon, and at the cellular level by energy status. A complex network of transcription factors, coactivators, and corepressors coordinates changes in blood glucose levels. Despite periods of feeding and fasting, in normal individuals plasma glucose remains in a narrow range. This tight control of glucose concentration is determined by a balance between glucose absorption from the intestine, production by the liver, and uptake in muscle and fat. The liver can produce glucose by breaking down glycogen (glycogenolysis) and by *de novo* synthesis of glucose from non-carbohydrate precursors such as lactate, pyruvate, glycerol, and alanine (gluconeogenesis). Glycogenolysis occurs more rapidly, beginning within 2–3 h after a meal in humans, but gluconeogenesis assumes a much greater importance with prolonged fasting. In liver, glycogen is mainly stored as a glucose reservoir for other tissues. As a consequence, the level of hepatic glycogen changes considerably (between 1 and 100 mg) with the feeding condition. The estimated contribution of hepatic glycogenolysis to the total glucose production during the first day of starvation varies from 40 to 80%, depending on the experimental design and methodology.

In liver, the glycogen-metabolizing enzymes have properties that enable the liver to act as a sensor of blood glucose and to store or mobilize glycogen according to the peripheral needs. The prime effector of hepatic glycogen deposition is glucose, which blocks glycogenolysis and promotes glycogen synthesis in various ways. Other glycogenic stimuli for the liver are insulin, glucocorticoids, parasympathetic (vagus) nerve impulses, and gluconeogenic precursors such as fructose and amino acids. Hepatic gluconeogenesis plays a key role in the maintenance of glucose homeostasis. In addition to the key hormones such as insulin, glucagon, and glucocorticoids, the rate of hepatic gluconeogenesis is also controlled by nutrients, but how the nutrient response is controlled is unclear. The rate of gluconeogenesis is controlled principally by the activities of certain unidirectional enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), fructose-1,6-bisphosphatase, and glucose-6-phosphatase (G6Pase). The genes encoding these proteins are powerfully controlled at the transcriptional level by key

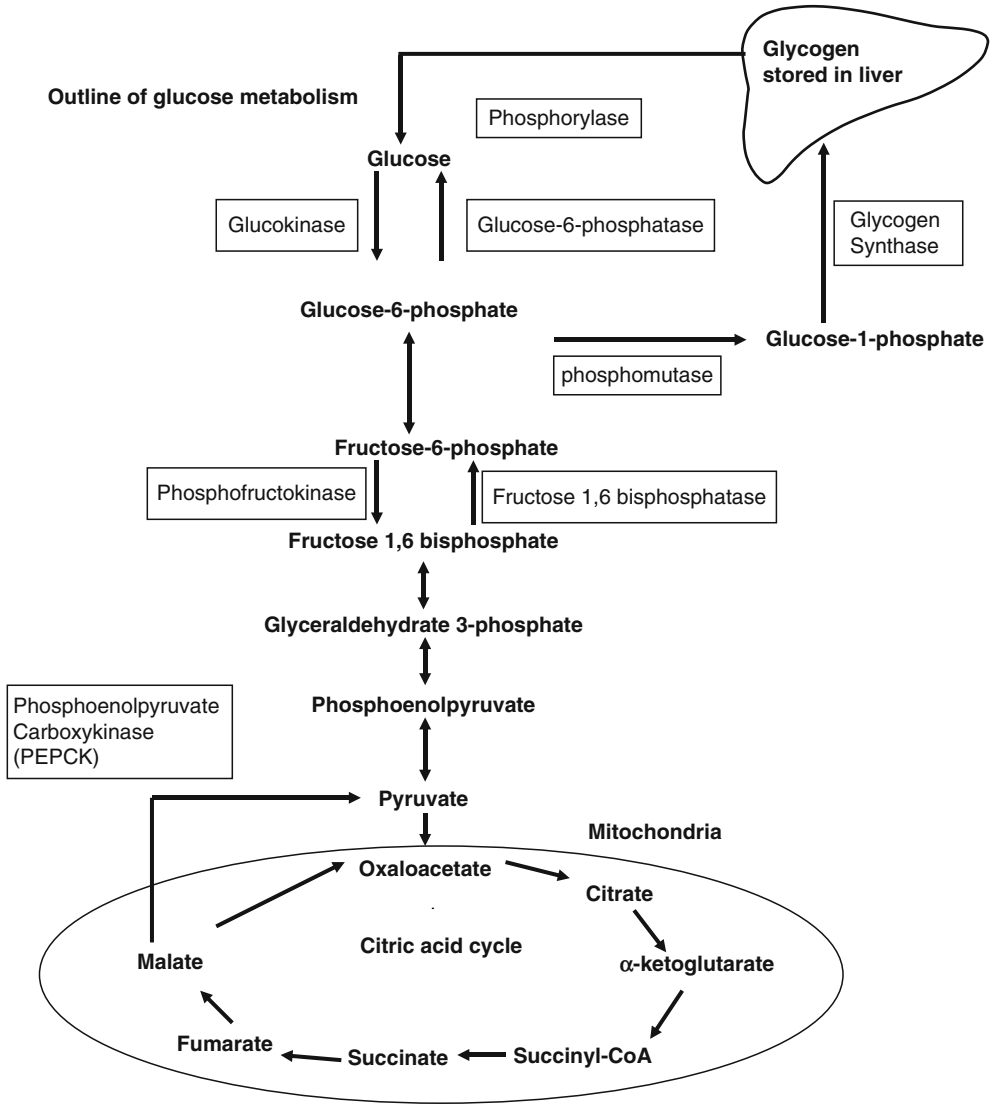

Figure 389.1
Outline of the processes of glycolysis and gluconeogenesis

hormones, particularly insulin, glucagon, and glucocorticoids. In the fasted state, insulin levels drop while glucagon secretion goes up resulting in increased glycogenolysis and gluconeogenesis. In the fed state, insulin suppresses glycogenolysis and hepatic glucose production.

The molecular mechanisms that regulate gluconeogenesis are complex and still not completely understood in humans. Pancreatic glucagon normally triggers the activation of catabolic programs in the liver in part via the cAMP-response element binding protein (CREB). CREB in turn stimulates hepatic gluconeogenesis as well as fatty acid oxidation by inducing expression of the nuclear hormone receptor coactivator PGC-1α (peroxisome proliferation-activated receptor-g coativator-1). The ability of CREB to regulate gluconeogenesis is largely dependent on the transcription factor PGC-1 α. CREB has been identified as a critical transcriptional checkpoint for the induction of hepatic gluconeogenesis in response to cAMP.

Prolonged fasting is characterized by low insulin concentrations and high glucagon, glucocorticoids, and

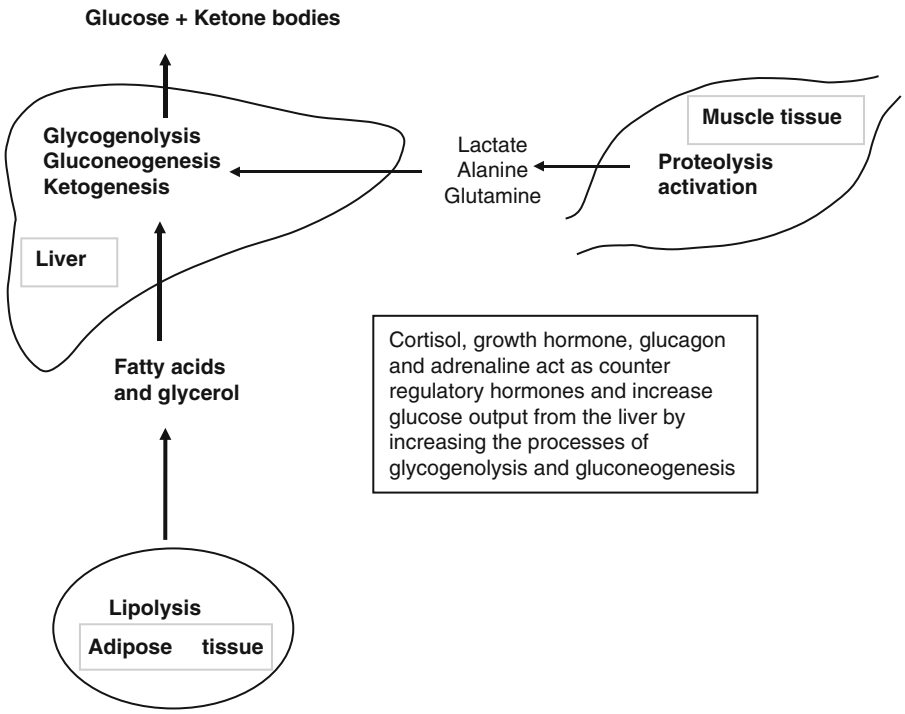

Figure 389.2
Summary of the role of counter-regulatory hormones in glucose physiology

adrenaline (noradrenaline) concentrations in plasma. This hormonal profile promotes the hydrolysis of triacylglycerols in adipose tissue, thereby increasing the concentration of free fatty acids in plasma. The fatty acids are taken up by the liver, where they are either re-esterified to triacylglycerol and secreted as very-low-density lipoprotein (VLDL) or oxidized in the mitochondria via β-oxidation. During late stages of fasting, free fatty acids become the predominant substrate for energy production. The majority of fatty acids are only partially oxidized to acetyl-coenzyme A (acetyl-CoA), which then condenses with itself to form ketone bodies, an important fuel for the brain. The energy released in the process of β-oxidation is used by the liver to carry out gluconeogenesis from substrates such as glycerol, lactate, and amino acids. Thus, efficient hepatic fatty acid oxidation is obligatory to the metabolic response to fasting. *Figure 389.1* outlines the processes of glycolysis and gluconeogenesis.

Counter-regulatory Hormonal Responses

During the post-absorptive phase (4–6 h interval following the ingestion of a meal), plasma glucose concentrations are maintained by interactions between insulin and the various counter-regulatory hormones including glucagon, cortisol, growth hormone, adrenaline, and noradrenaline. Glucagon allows the controlled release of stored glycogen from the liver and insulin restrains the effects of glucagon by preventing accelerated lipolysis and proteolysis. The counter-regulatory hormones including cortisol and growth hormone play permissive roles in setting the sensitivity of the peripheral tissues to glucagon and insulin.

Growth hormone and cortisol play an essential role in the regulation of a normal blood glucose concentration. Both of these hormones counteract the actions of insulin on glucose metabolism. Both hormones reduce the peripheral utilization of glucose as well as increasing the rates of gluconeogenesis. Cortisol as with growth hormone decreases insulin-induced peripheral utilization of glucose, increases hepatic glucose production, and stimulates protein breakdown. This has the effect of providing amino acids for gluconeogenesis.

Cortisol secretion from the adrenal gland is regulated by adrenocorticotropic hormone (ACTH). This is cleaved from a larger precursor protein (pro-opiomelanocortin, POMC). The release of ACTH from the anterior pituitary

is regulated by corticotropin-releasing hormone (CRH), from the hypothalamus. Growth hormone is produced and secreted by specialized cells in the anterior pituitary called the somatotrophs. Both cortisol and GH have numerous effects on glucose metabolism. *Figure 389.2* summarizes the role of counter-regulatory hormones in glucose physiology.

The Diagnostic Approach to a Patient with Hypoglycemia

The careful clinical history, description of symptoms, physical examination, and a systematic step-by-step approach are the cornerstones of diagnosis. Given the complexity of the metabolic and endocrine adaptations that occur at birth, hypoglycemia occurs more commonly during the first days after birth than at any other time of life. Furthermore, it is a transient phenomenon in the majority of the cases. The symptoms of hypoglycemia may be very nonspecific (*Table 389.1*); hence any symptomatic child must have a blood glucose level measured and documented.

In the neonatal period, the clinical history should include details of pregnancy and delivery, birth weight, gestational age of the infant, noting in particular any evidence for fetal distress, birth asphyxia, and smallness for dates. The relationship of a hypoglycemic episode to the most recent meal can be important diagnostically. Hypoglycemia occurring after a short fast (2–3 h) may be suggestive of glycogen storage disease. Hypoglycemia occurring after a long fast (12–14 h) may suggest a disorder of gluconeogenesis. Postprandial hypoglycemia may indicate galactosemia, hereditary fructose intolerance, or the dumping syndrome. A family history of sudden infant deaths may be a clue to an unrecognized, inherited metabolic disorder. Any provocation factors such as an upper respiratory tract infection or an episode of gastroenteritis leading to hypoglycemia should be documented.

From the history and physical examination, certain at-risk groups of infants (*Table 389.2*) can be identified on the basis of obvious conditions that are usually associated with transient hypoglycemia and need monitoring.

The recognition and diagnosis of hypoglycemia in the neonatal period depends on routine monitoring of blood glucose levels at frequent intervals after birth in asymptomatic infants at risk, and in any infant who demonstrates any symptom which might be suggestive of hypoglycemia. Again in this group, it is important to monitor blood glucose in relation to the time of feeds. Thus, a blood glucose concentration that increases after a feed is probably less worrying than one which is

Table 389.1
Summary of the symptoms of hypoglycemia

The symptoms of hypoglycemia may be very nonspecific
Symptoms of hypoglycemia
The blood glucose concentration must be measured in any patient with any symptom
Any nonspecific symptom may indicate hypoglycemia
Feeding poorly
Irritability
Lethargy
Stupor
Apnea, cyanotic spells
Hypothermia
Hypotonia, limpness
Tremor
Seizures
Coma

Table 389.2
Risk factors for hypoglycemia

Risk factors for hypoglycemia
Prematurity
Intrauterine growth retardation
Maternal diabetes mellitus (insulin dependent and gestational)
Perinatal asphyxia
Erythroblastosis fetalis
Beckwith–Wiedemann syndrome
Macrosomia
Any "sick" infant
Polycythemia
Hypothermia
Congenital heart disease
Infections such as malaria
Maternal administration of some drugs such as sulphonylureas/beta-blockers

persistently low. If low concentrations are obtained during routine bedside monitoring in asymptomatic high-risk infants or at the time of symptoms in symptomatic infants, it is necessary to confirm the result in the laboratory, but intervention does not need to wait for the result in infants who are severely symptomatic and in whom reagent strip test results suggest hypoglycemia. Resolution of symptoms after glucose confirms that they were due to hypoglycemia.

Other important points from the history and examination include the presence or absence of maternal diabetes or rhesus incompatibility. Increased birth weight and macrosomia should raise the possibility of neonatal hyperinsulinism. Distinctive physical signs such as transverse ear lobe creases, exomphalos, and macroglossia should raise the possibility of the Beckwith–Wiedemann Syndrome (BWS), while the presence of micropenis and undescended testes might indicate the presence of hypopituitarism. Midline defects, including cleft palate, could also indicate congenital hypopituitarism while the existence of ambiguous genitalia could indicate congenital adrenal hyperplasia.

Hepatomegaly should always be looked for and is associated with abnormal glycogen metabolism, defects in gluconeogenesis, and galactosemia. Moderate hepatomegaly due to glycogen accumulation may, however, also develop in infants with hyperinsulinism who are receiving very high infusion rates of glucose to maintain normoglycemia. In the childhood period, particular attention should be paid to the rate of growth, micropenis, undescended testes, skin pigmentation, blood pressure, and weight loss.

After the clinical history has been taken and the examination completed, a diagnostic cascade of appropriate tests is necessary. These may be guided in the context of the most common causes of hypoglycemia as listed *Table 389.4*.

Blood Sample at Time of Hypoglycemia

By far the most important investigation is the obtaining of a blood sample at the time of hypoglycemia. The blood glucose must be considered in the context of the whole fuel economy and in the light of concurrent hormone concentrations. Essential diagnostic information can be obtained by measuring the metabolites and hormones listed in *Table 389.3*, in the blood sample drawn at the time of hypoglycemia. The next urine sample, which is passed, should also be deep frozen for subsequent assay for abnormal constituents.

Table 389.3
Routine baseline investigations in patients with suspected hypoglycemia

Blood	Urine
Glucose	Ketones
Insulin	Reducing substances
Cortisol	
Lactate	Organic acids
Growth hormone	
Non-esterified fatty acids	
3β-hydroxybutyrate	
Carnitine (free and total)	
Blood spot acylcarnitine	
Ammonia	

The Diagnostic Fast

In many conditions, hypoglycemia occurs only in relation to periods of low caloric intake or starvation. Starvation tests are potentially very dangerous, and they must be conducted only under strictly controlled conditions by staff experienced in their administration, with a secure intravenous infusion available for immediate correction of hypoglycemia. The hazards are greatest in defects in fatty acid oxidation, since the induced hyper-fatty acidemia carries a risk of inducing a cardiac arrhythmia. Sequential measurements of intermediary metabolites and glucose are taken throughout the fast, with the crucial blood sample being drawn when hypoglycemia occurs. The urine sample passed then or after restoration of normoglycemia should be deep frozen for measurement of organic acids and other abnormal metabolites.

Other measurements from this specimen obtained at the time of hypoglycemia can also help in diagnosis. Thus, cortisol deficiency will be revealed by showing a low cortisol concentration. Further tests to define the integrity of the hypothalamo–pituitary–adrenal axis are mandatory if a low cortisol level is found at the time of hypoglycemia since cortisol deficiency may be lethal if not corrected by appropriate substitution therapy. Low growth hormone levels at the time of fasting hypoglycemia do not rule out or indicate deficiency. If this deficiency is suspected from abnormal growth, then a validated test such a glucagon provocation test should be performed.

The documentation of abnormal urinary organic acids is particularly helpful when hypoglycemia is due to methylmalonic acidemia, maple syrup urine disease

(MSUD), or mitochondrial beta-oxidation defects. In the latter, clues to the deficient enzymes are provided by the chain length of the dicarboxylic acids in the urine and the presence of hydroxyl groups or unsaturated bonds. The presence of urinary glycine conjugates may also be diagnostic of fatty acid oxidation defects.

Overview of the Different Causes of Hypoglycemia in Childhood

Hypoglycemia in childhood can be due to many causes. These can be broadly summarized into those due to hormonal abnormalities such as hyperinsulinism, cortisol or growth hormone deficiency, defects of hepatic glycogen release/storage, defects in gluconeogenesis, defects in carnitine metabolism, defects in fatty acid oxidation, postprandial, metabolic, and unknown causes such as idiopathic ketotic hypoglycemia. These are summarized in *Table 389.4*.

Hypoglycemia due to Hormonal Abnormalities

Hyperinsulinism of Infancy (HI)

Hyperinsulinism of infancy (HI) is the commonest cause of recurrent and severe hypoglycemia in the neonatal and infancy period. It is characterized by the excessive and inappropriate secretion of insulin in relation to the prevailing blood glucose concentration. HI can be either persistent or transient. In adolescents or older children presenting with HI, insulinoma must be considered as a possibility. Insulinomas may be a part of multiple endocrine neoplasia (MEN1) and hence a family history may provide a diagnostic clue in the familial cases.

Transient Hyperinsulinism

The transient form of HI is associated with maternal diabetes mellitus, intrauterine growth retardation, perinatal asphyxia, erythroblastosis fetalis, the Beckwith–Wiedemann syndrome, after the maternal administration of some drugs such as sulphonylureas, and after intravenous maternal glucose infusions during labor. The mechanism/s causing transient HI in these conditions is not clear. In these cases, the HI tends to resolve spontaneously. However, in some infants with intrauterine growth retardation, the HI may be protracted and require treatment with diazoxide. Iatrogenic hyperinsulinism due to a malpositioned umbilical artery catheter was reported in two infants. Repositioning of the catheter to avoid direct infusion into the arterial blood supply to the pancreas resulted in prompt cessation of hyperinsulinemic hypoglycemia. However, transient HI is seen most commonly in the infant born to a poorly controlled diabetic mother.

Most infants of diabetic mothers (IDM) have transient asymptomatic hypoglycemia before a spontaneous increase in blood glucose levels occurs after the age of 1–4 h. Others have a more prolonged period of severe symptomatic hypoglycemia and a minority develop late hypoglycemia after an initial benign course. However, all regain normal blood glucose control within the first few days after birth.

IDMs have hyperinsulinism at birth due to increased placental transfer of glucose and other nutrients submitting increased insulin secretion. The pancreas shows hyperplasia and hypertrophy in the islets of Langerhans, without any evidence of so-called nesidioblastosis. Some infants fail to develop the normal increase in plasma glucagon at 2–4 h of age although others have demonstrated a substantial counter-regulatory hormone response, which may curtail the period of hypoglycemia.

In relation to management, peripheral blood glucose values should be monitored 3–4 h before feeds for 6–12 h after birth. Transient hypoglycemia may be prevented by giving enteral feeds with milk within 1–2 h after delivery. Sick infants unable to tolerate enteral feeding or those who remain hypoglycemic despite full enteral feeds should receive an intravenous infusion of glucose at a rate of 4–6 mgs/kg/min in the first instance to prevent the development of hypoglycemia. Slow withdrawal of glucose support should then be instituted.

HI may also be associated with syndromes. Beckwith–Wiedemann syndrome (BWS) is a congenital overgrowth syndrome which is clinically and genetically heterogeneous. Phenotypically BWS is associated with pre- and postnatal overgrowth, organomegaly, hemi-hypertrophy, omphalocele, ear lobe anomalies, and renal tract abnormalities with predisposition to embryonic tumors. Genetically BWS is a multigenic disorder caused by dysregulation of imprinted growth regulatory genes within the 11p15 region. At this location, genetic imprinting with loss of maternally expressed tumor and/or growth suppressor genes (p57KIP2 and H19) or duplications and uniparental disomy of paternally expressed growth promoter genes (IGFII) have been implicated in the pathogenesis of BSW (21). About 20% of patients with BWS have paternal uniparental disomy for 11p15.

Table 389.4
Summary of the causes of hypoglycemia

Hyperinsulinemic hypoglycemia
Transient: Infant of diabetic mother/perinatal asphyxia/ Rhesus disease/intrauterine growth retardation/ Beckwith–Weidemann syndrome
Congenital: *ABCC8/KCNJ11/GCK/GDH/HADH/HNF4A/ SLC16A1*
Insulinomas
Hormonal deficiency
ACTH/cortisol/growth hormone/glucagon/adrenaline
Hormone resistance
Laron syndrome
Defects in hepatic glycogen release/storage
Glycogen storage diseases: glucose-6-phosphatase, amylo 1–6 glucosidase deficiency, liver phosphorylase deficiency. GSD type 0.
Defects in gluconeogenesis
Fructose-1, 6-bisphosphatase deficiency, (PEPCK) deficiency
Pyruvate carboxylase deficiency
Carnitine metabolism
Carnitine deficiency (primary and secondary)
Carnitine palmitoyl transferase deficiency (CPT 1 and 2)
Fatty acid oxidation
Medium-chain acyl-CoA dehydrogenase (MCAD) deficiency
Very-long-chain acyl-CoA dehydrogenase (VLCAD) deficiency
Short-chain Acyl-CoA dehydrogenase (SCAD) deficiency
Long-/Short-chain-L-3-hydroxy-acyl CoA (L/SCHAD) deficiency
Defects in ketone body synthesis/utilization
HMG CoA synthase deficiency/HMG CoA lyase deficiency
Succinyl-CoA: 3-oxoacid CoA-transferase (SCOT) deficiency
Metabolic conditions (common ones)
Organic acidemias (propionic/methylmalonic)
Maple syrup urine disease, galactosemia, fructosemia, tyrosinemia
Hereditary fructose intolerance
Glutaric aciduria type 2
Mitochondrial respiratory chain complex deficiencies
Congenital disorders of glycosylation (CGD)
Drug induced
Sulphonylurea/insulin/beta-blocker/salicylates/alcohol
Miscellaneous causes (mechanism/s not clear)
Idiopathic ketotic hypoglycemia (diagnosis of exclusion)
Infections (sepsis, malaria), congenital heart disease

The incidence of hyperinsulinemic hypoglycemia in children with BWS is about 50%. This hypoglycemia can be transient or prolonged which in the majority of infants will be asymptomatic and resolve within the first 3 days of life but about 5% of children will have persistent hyperinsulinemic hypoglycemia beyond the neonatal period requiring either continuous feeding or a partial pancreatectomy. The milder forms respond to treatment with diazoxide and somatostatin analogues. There are only few detailed histological studies of the resected pancreas in patients with BWS and all suggest that the histology may be similar to the diffuse form of hyperinsulinism of infancy. The underlying mechanism/s leading to persistent hyperinsulinemic hypoglycemia in this syndrome is/ are unclear. It is not clear why the HI of this syndrome is usually a transient phenomenon.

Congenital Hyperinsulinism of Infancy (CHI)

Of all of the conditions causing persistent hypoglycemia in infancy and childhood, that caused by organic hyperinsulinism is by far the most difficult to manage clinically. It is associated with a very high incidence of neurological handicap. Up to 20% of infants with this condition may have persistent neurological handicaps. The organic hyperinsulinism causes hypoglycemia primarily as a result of increased utilization of glucose together with a decreased rate of endogenous glucose production. These effects are entirely due to inappropriate secretion of insulin. CHI is the most common cause of severe persistent hypoglycemia in neonates and infants during their first year of life. It has previously masqueraded under a variety of different descriptive names including "idiopathic hypoglycemia of infancy", leucine sensitive hypoglycemia, neonatal insulinoma, microadenomatosis, focal hyperplasia, nesidioblastosis, and persistent hyperinsulinemic hypoglycemia of infancy (PHHI).

Both sporadic and familial variants of congenital hyperinsulinism of infancy are recognized, with sporadic forms being relatively uncommon (incidence 1 per 40,000 live births), and familial forms being common in communities with high rates of consanguinity; in these communities the incidence may be as high as 1 in 2,500 live births.

Clinical Presentation

The condition presents primarily in the newborn period and during the first 2–6 months after birth in term and preterm neonates. Many neonates have a characteristic appearance resembling strikingly that of an infant of

a diabetic mother. It may also be present in infants and even in the childhood period.

Diagnosis

The characteristic metabolic and endocrine profile in a blood sample drawn at the time of hypoglycemia is one of hyperinsulinemic, hypoketotic, hypo-fatty acidemic hypoglycemia with inappropriately raised insulin and accompanied by high concentrations of C-peptide levels. High intravenous infusion rates of glucose may be required to maintain a blood glucose concentration above 3.5 mmol/L. Because of the anabolic effects of insulin, the hypoglycemia occurs despite a liver engorged with glycogen that can be mobilized by administration of glucagon. It is important to emphasize that the level of insulin in the blood may not necessarily be particularly high. However, what is an appropriate insulin concentration for normoglycemia becomes inappropriate in the presence of hypoglycemia. The demonstration of any measurable insulin in a hypoglycemic sample is strong evidence for a failure of basal insulin control.

Management

The immediate imperative is to give sufficient glucose to maintain blood glucose concentrations above 3.5 mmol/L. Infusion rates in excess of 4–6 mg/kg/min may be necessary, rarely; infusion rates $>$ 20 mg/kg/min may be needed. Having stabilized the blood glucose concentration, it is then imperative to determine whether or not the patient will respond to the conventional medical therapy of a combination of diazoxide together with a diuretic. It is important to give both drugs concurrently to overcome the tendency of diazoxide to cause fluid retention and to capitalize on the fact that both drugs have a synergistic effect in increasing blood glucose concentration. A convenient starting dose of diazoxide is 5–10 mg/kg/day in three 8 hourly aliquots, increasing to a maximum of 20 mg/kg/day. The administration of glucagon by continuous infusion (starting dose 1.0ugm/kg/h) concurrently with a continuous infusion of the somatostatin analogue Octreotide (initial dose 10ugm/kg/day) may confer substantial benefit.

Pathophysiology of CHI

The pancreatic ß-cell adenosine triphosphate-sensitive potassium channels (K_{ATP} channels) play a pivotal role in glucose-stimulated insulin secretion. These channels are hetero-octameric complexes comprising of four inwardly rectifying potassium channel (Kir6.2) subunits and four of the sulphonylurea receptor 1 (SUR1) subunits. The channels couple glucose metabolism to membrane electrical activity and insulin release in pancreatic ß-cells. Glucose metabolism leads to an increase in the intracellular ratio of ATP/ADP within the ß-cell causing closure of the channels; this results in cell membrane depolarization, Ca^{2+} influx via voltage-gated calcium channels and insulin exocytosis.

The SUR1 and Kir6.2 proteins are encoded by the *ABCC8* and *KCNJ11* genes, respectively. Therefore, it is not surprising that the most common known cause of congenital hyperinsulinism (CHI) is loss of function mutations in these two genes. These mutations either impair the ability of MgADP to stimulate channel activity, or affect the expression of the K_{ATP} channels at the surface membrane. This results in continuous depolarization of the ß-cell membrane and dysregulated insulin secretion. The majority of K_{ATP} channel mutations have been known to act recessively. However, recent reports of autosomal dominantly inherited mutations in patients with CHI.

Heterozygous activating mutations have been reported in the glucokinase gene (*GCK)* in patients with CHI. Glucokinase is the rate-limiting enzyme for glucose metabolism in the ß-cell and hence is pivotal in regulating glucose-induced insulin secretion. Activating mutations cause an increased affinity of glucokinase for glucose with increased rates of glycolysis at low blood glucose concentrations. This increases insulin secretion independent of blood glucose concentration.

Heterozygous mutations in the *GLUD1* gene, which encodes the enzyme glutamate dehydrogenase (GDH), have been identified in patients with hyperinsulinism and hyperammonemia (HI/HA Syndrome) with plasma ammonium levels being persistently raised to 3–8 times the upper limit of normal. HI/HA syndrome typically causes protein-sensitive hypoglycemia, in addition to the fasting hypoglycemia. The mechanism by which *GLUD1* mutations cause hyperammonemia remains to be determined.

Recently, three further rare genetic etiologies have been described in patients with CHI. Recessively inherited mutations in the *HADH* gene that encodes the enzyme hydroxyacyl-Coenzyme A dehydrogenase (HADH) (previously known as short-chain L-3-hydroxyacyl-CoA dehydrogenase (SCHAD)) have been described in a few patients with CHI. HADH catalyzes the penultimate step in fatty acid ß-oxidation in the mitochondria. Patients typically present with raised plasma hydroxybutyrylcarnitine and urinary 3-hydroxyglutarate levels. The precise mechanism of dysregulated insulin secretion in patients with a HADH deficiency is not understood.

More recently, heterozygous loss-of-function mutations in the hepatocyte nuclear factor 4A (*HNF4A*) gene, resulting in transient or persistent CHI, and heterozygous

gain-of-function mutations in the *SLC16A1* gene, which encodes the monocarboxylate transporter (MCT-1) causing physical exercise-induced hyperinsulinism (EIHI), have been reported.

The Therapeutic Dilemma

The pediatrician is faced with an important challenge when managing a child who proves to be unresponsive to conventional therapy with diazoxide. There are two options, either contemplate the long-term combined continuous subcutaneous infusion of glucagon and somatostatin or consider surgical resection of the pancreas.

Partial pancreatectomy is not without risk and is not a procedure to be undertaken lightly. The operation most commonly performed at present is a 95% pancreatectomy in the first instance. Some children remain hypoglycemic despite this then a further attempt can be made to control the procedure by diazoxide therapy. In a minority of cases, a total pancreatectomy may be necessary to control the severe hyperinsulinism.

Two main histological subtypes have been described in patients with CHI. Focal pancreatic lesions appear as small regions of islet adenomatosis measuring 2–10 mm, which are characterized by ß-cells with enlarged nuclei surrounded by normal tissue. In contrast, diffuse pancreatic disease affects all the ß-cells within the islets of Langerhans. The histological form of CHI can be a guide as to the mode of inheritance. Diffuse disease can be familial or sporadic and can result from recessively inherited or dominantly acting mutations in the genes previously described while focal disease is always sporadic.

Focal disease results from paternal uniparental disomy (UPD) encompassing chromosome11p15.5-11p15.1 within a single pancreatic ß-cell, which unmasks a paternally inherited K_{ATP} channel mutation at 11p15.1. Paternal UPD at 11p15.5 causes altered expression of a number of imprinted genes, including the maternally expressed tumor-suppressor genes *H19* and *CDKN1C*, and the paternally expressed growth factor *IGF2*, which is likely to lead to clonal expansion of the single cell and dysregulated insulin secretion from the resulting focal lesion.

Patients with a paternal mutation in *ABCC8* and *KCNJ11* (or those with no mutations in these genes) potentially have a focal disease and thus will require further imaging studies with ^{18F}DOPA-PET scan for precise preoperative localization of the focal lesion. Patients with genetically confirmed diffuse disease do not require further imaging studies. However it is important to be aware that mutational analysis may not be definitive in some cases. The principle of ^{18F}DOPA-PET scan is based on the fact that pancreatic islets take up L-3, 4- dihydroxyphenylalanine (L-DOPA), and convert it to dopamine by DOPA decarboxylase, present in the islet cells. The uptake of the positron emitting tracer ^{18F}DOPA-PET is increased in ß-cells with a high rate of insulin synthesis and secretion compared to unaffected areas allowing visualization of the focal lesion. The sensitivity for detecting focal lesions varies between 88 and 94% with a specificity of 100%. Patient with diffuse disease will require a near total pancreactectomy or long-term therapy with octreotide in combination with high calorie and volume feeds.

Postprandial Hyperinsulinemic Hypoglycemia (PPHH)

PPHH refers to the development of hypoglycemia within a few hours of meal ingestion. It is associated with inappropriate insulin secretion in response to the meal. The most common cause is due to the "dumping" syndrome in infants who have undergone gastro-esophageal surgery. PPHH occurs in the insulin autoimmune syndrome, which is characterized by the presence of insulin-binding autoantibodies in subjects that have not been previously exposed to exogenous insulin (38). Most other causes of PPHH have been reported in adults.

Hypoglycemia due to Hormone Deficiency

Glucagon and adrenaline are the two hormones that are important in the immediate restoration of the blood glucose concentration, whereas cortisol and growth hormone are thought to have permissive roles in restoring normoglycemia.

Deficiency of any one of these hormones can cause hypoglycemia. Glucagon and adrenaline deficiency is extremely rare and so far no true human genetically proven defect in glucagon and adrenaline deficiency have been described.

Growth hormone and cortisol have numerous effects on glucose metabolism including increasing the rates of gluconeogenesis and glycolysis and antagonizing the effects of insulin. In adults, the glycemic thresholds for the activation of glucose counter-regulatory hormones such as growth hormone and cortisol lies within or just below the physiological blood glucose concentration and slightly higher than the threshold for symptoms. This implies that growth hormone and cortisol start to rise in response to blood glucose concentrations within the normoglycemic range and it is thought that these increases are inversely proportional to the nadir in blood glucose.

Serum growth hormone and cortisol respond differently to spontaneous hypoglycemia and that induced by the insulin tolerance test. This is not related to the pulsatile nature of growth hormone secretion but may be related to the rate of fall of the blood glucose concentration. Hence, a low serum growth hormone value at the time of spontaneous hypoglycemia may not necessarily indicate growth hormone deficiency.

The etiology of the hypoglycemia due to cortisol and growth hormone deficiency is due to a combination of factors including reduced gluconeogenic substrate availability (decreased mobilization of fats and proteins) and increased glucose utilization due to increased insulin sensitivity of tissues in the absence of these two hormones.

Congenital hypopituitarism may present with life-threatening hypoglycemia, abnormal serum sodium concentrations, shock, microphallus in males, and, only later, growth failure. Causes of congenital hypopituitarism include septo-optic dysplasia, other midline syndromes, and mutations of transcription factors involved in pituitary gland development. Children with acquired hypopituitarism typically present with growth failure and may have other complaints depending on the etiology and the extent of missing pituitary hormones. Acquired hypopituitarism may result from tumors (most commonly craniopharyngioma), radiation, infection, hydrocephalus, vascular anomalies, and trauma. The incidence of hypoglycemia due to panhypopituitarism can be as high as 20%, and hypoglycemia associated with hypopituitarism may be a cause of sudden death in the childhood period. Appropriate replacement therapy with hydrocortisone and growth hormone can alleviate the hypoglycemia. ACTH deficiency will also cause hypoglycemia and may be isolated or part of multiple pituitary hormone deficiency.

Laron syndrome is an autosomal recessive disorder caused by defects of growth hormone receptor (GHR) gene. It is characterized by severe postnatal growth retardation and characteristic facial features as well as high circulating levels of growth hormone (GH) and low levels of insulin-like growth factor I (IGF-I) and insulin-like growth factor binding protein-3 (IGFBP-3). Children with Laron syndrome can present with episodes of hypoglycemia.

Hypoglycemia due to Defects in Hepatic Glycogen Release/Storage

Glucose is stored as glycogen mainly in the liver but also in the muscle and in the kidneys. Defects in the storage or release of hepatic glycogen can also cause hypoglycemia. Glucose-6-phosphatase deficiency (glycogen storage disease type I, Von Gierke's disease) is the commonest of the glycogen storage diseases causing hypoglycemia. The deficiency of this enzyme results in the inability to release free glucose from glucose-6-phosphate, with resultant hepatomegaly due to stored glycogen. These children present with recurrent hypoglycemia associated with lactic acidosis, hyperuricemia, and hyperlipidemia. The aim of treatment is to prevent hypoglycemia. Continuous nasogastric tube feeding and cornstarch form the mainstay of therapy.

The two other glycogen storage diseases causing hypoglycemia are due to deficiencies of the enzymes amylo-1,6-glucosidase (glycogen storage disease type III) and liver phosphorylase (glycogen storage disease VI). The clinical and biochemical features of GSDIII subjects are quite heterogeneous. The clinical manifestations of GSDIII are represented by hepatomegaly, hypoglycemia, hyperlipidemia, short stature and, in a number of subjects, cardiomyopathy and myopathy. Glycogen-storage disease type VI (GSDVI) represents a heterogeneous group of hepatic glycogenoses with mild clinical manifestations and benign course. Patients typically exhibit prominent hepatomegaly, growth retardation, and variable but mild episodes of fasting hypoglycemia and hyperketosis during childhood. Hyperlacticacidemia and hyperuricemia characteristically are absent. In addition, patients may demonstrate elevated serum transaminases, hyperlipidemia, hypotonia, and muscle weakness.

The enzyme hepatic glycogen synthase plays an important role in the storage of glycogen in the liver. Hepatic glycogen synthase deficiency is a rare cause of hypoglycemia in childhood. The characteristic features include fasting hypoglycemia, with hyperketonemia but with normal lactate. After a meal, the plasma lactate will increase as glucose is channeled along the glycolytic pathway with hyperglycemia. Mutations in the liver glycogen synthase gene (*GYS2*) localized on chromosome 12p12.2 have been described in some patients.

Hypoglycemia due to Defects in Gluconeogenesis

Gluconeogenesis, or the formation of glucose from mainly lactate/pyruvate, glycerol, glutamine, and alanine, plays an essential role in the maintenance of normoglycemia during fasting. Inborn deficiencies are known in each of the four enzymes of the glycolytic–gluconeogenic pathway that ensure a unidirectional flux from pyruvate to glucose: pyruvate carboxylase, phosphoenolpyruvate

carboxykinase (PEPCK), fructose-1,6-bisphosphatase, and glucose-6-phosphatase. Gluconeogenesis can essentially be viewed as a reversal of glycolysis but with few important differences. Patients with defects in gluconeogenesis present with fasting hypoglycemia and lactic acidosis. Pyruvate carboxylase deficiency may lead to a more widespread clinical presentation with lactic acidosis, severe mental and developmental retardation, and proximal renal tubular acidosis.

Hypoglycemia due to Disorders of Carnitine Metabolism and Defects of Fatty Acid Oxidation

Serious clinical consequences may occur if fatty-acid oxidation (FAO) is impaired, including hypoglycemic seizures, muscle damage, cardiomyopathy, metabolic acidosis, and liver dysfunction. Fatty acids are taken up by hepatocytes and muscle, where they are subsequently activated to their coenzyme A (CoA) esters. FAO disorders are individually rare, but they are collectively common because of the number of different enzymes affected. They are typically inherited in an autosomal recessive pattern. When defects occur in fatty-acid degradation, excess acylcarnitine intermediates accumulate in the tissues, including heart, liver, and skeletal muscle, which can lead to organ dysfunction. The diversion of acyl-CoA intermediates into beta-oxidation results in accumulation of toxic dicarboxylic acids. Acylcarnitines that spill into the blood provide a marker for diagnosis, including early detection on newborn screening. The diagnosis of some FAO disorders may require more invasive specimens to be tested because substrate profiles alone can be normal or only mildly abnormal. Cultured skin fibroblasts are useful for testing enzyme activity or metabolism of labeled fatty-acid substrates.

Primary carnitine deficiency is an autosomal recessive disorder of fatty acid oxidation that can present at different ages with hypoketotic hypoglycemia and cardiomyopathy and/or skeletal myopathy. This disease is suspected based on reduced levels of carnitine in plasma and confirmed by measurement of carnitine transport in the patient's fibroblasts. Carnitine transport is markedly reduced (usually $<5\%$ of normal) in fibroblasts from patients with primary carnitine deficiency.

The "hepatic" CPT1 isoform is expressed in liver, kidney, and fibroblasts and at low levels in the heart, while the other isoform (muscle) occurs in skeletal muscle and is the predominant form in heart. Patients with hepatic isoform of CPT 1 deficiency present with hypoketotic hypoglycemia, hepatomegaly with raised transaminases, renal tubular acidosis, transient hyperlipidemia and, paradoxically, myopathy with elevated creatinine kinase or cardiac involvement and seizures and coma in the neonatal period. The typical biochemical finding in the urine is dicarboxylic acids of chain lengths C6–C10.

CPT2 deficiency has several clinical presentations. The infantile-type CPT2 deficiency presents as severe attacks of hypoketotic hypoglycemia, occasionally associated with cardiac damage commonly responsible for sudden death before 1 year of age. In addition to these symptoms, features of brain and kidney dysorganogenesis are frequently seen in the neonatal-onset CPT2 deficiency, almost always lethal during the first month of life. Treatment is based upon avoidance of fasting and/or exercise, a low-fat diet enriched with medium-chain triglycerides and carnitine.

The commonest disorder of fatty acid β-oxidation is medium-chain acyl-CoA dehydrogenase (MCAD). This is an autosomal recessive condition characterized by intolerance to prolonged fasting, recurrent episodes of hypoglycemic coma with medium-chain dicarboxylicaciduria, impaired ketogenesis, and low plasma and tissue carnitine levels. MCAD deficiency usually presents between infancy and 2 years of age, although onset of symptoms can occur as early as the first days of life to as late as 6 years. Children are typically asymptomatic except during times of fasting and metabolic stress, usually associated with a viral illness. They present with fasting non-ketotic hypoglycemia associated with vomiting, lethargy, apnea, coma, encephalopathy, and sudden death. If undiagnosed, 20–25% of affected patients will die during the first episode. Routine laboratory studies during an acute illness may show hypoketotic hypoglycemia, metabolic acidosis, lactic acidosis, hyperammonemia, increased blood urea nitrogen and transaminases, and elevated uric acid. Serum and urine-free carnitine levels may be normal or low. Elevated suberylglycine and hexanoylglycine (dicarboxylic acid esters of glycine) are typically found in urine. Enzyme deficiency can be shown in fibroblasts. Screening of the *ACADM* gene often identifies a common A985G mutation that accounts for 85% of mutations. Some of the children detected with newborn screening have a genotype that may not be associated with clinical manifestations. The disorder may be severe, and even fatal, in young patients. Other defects of β-oxidation (long-chain acyl-CoA dehydrogenase) may present with hypoketotic hypoglycemia associated with neurological (hypotonia) and cardiovascular complications (cardiomyopathy). The pattern of

dicarboxylicaciduria accumulation is characteristic for each enzymatic defect of the β-oxidation spiral.

As is true for the defects in carbohydrate metabolism leading to hypoglycemia, treatment of the fatty acid oxidation defects involves avoidance of fasting and provision of adequate glucose. Restriction of dietary fat intake and supplemental L-carnitine therapy are recommended.

Hypoglycemia due to Defects in Ketone Body Synthesis/Utilization

Ketone bodies are an alternative form of fuel to glucose especially for the brain. Each ketone body is synthesized from the combination of Acetyl-CoA and Acetoacetyl-CoA to from hydroxymethylglutaryl-CoA (HMG-CoA), which is then split by HMG-CoA lyase to yield acetoacetate. Acetoacetate is then converted to β-hydroxybutyrate. Defects in either the synthesis or the utilization of ketone bodies may lead to hypoglycemia. Hereditary deficiency of mitochondrial HMG-CoA synthase can cause episodes of severe hypoketotic hypoglycemia. Typical biochemical findings include hypoketosis, elevated free fatty acids, normal acylcarnitines, and specific urinary organic acids during acute episodes. A rare cause of hypoglycemia due to the inability to utilize ketone bodies is deficiency of succinyl-CoA: 3-oxoacid CoA-transferase (SCOT). This is characterized by intermittent ketoacidotic crises and persistent ketosis.

Idiopathic Ketotic Hypoglycemia

Idiopathic ketotic hypoglycemia usually presents between the ages of 18 months and 5 years and remits spontaneously by the ages of 9–10 years. The typical history is of a child who may miss a meal and develop hypoglycemia usually following an upper respiratory tract infection. The hypoglycemic episodes seem to be unpredictable, only developing sometimes. Biochemically, the hypoglycemia is associated with raised ketone bodies and free fatty acids with suppressed insulin levels. Ketotic hypoglycemia is characterized by low levels of plasma alanine but the precise mechanism responsible for the hypoglycemia is not understood.

Idiopathic ketotic hypoglycemia is a poorly defined term and may include groups of conditions in which there is no clear cause of the hypoglycemia. Conditions such as hepatic glycogen synthase deficiency and acetoacetyl CoA thiolase deficiency have been reported as presenting with ketotic hypoglycemia. Ketotic hypoglycemia is a diagnosis of exclusion.

Miscellaneous Causes of Hypoglycemia

Metabolic

Hypoglycemia can also occur due to a number of metabolic conditions including galactosemia, fructosemia, tyrosinemia, organic acidemias, maple syrup urine disease, glutaric aciduria type II, and in mitochondrial respiratory chain defects. Hereditary fructose intolerance, caused by catalytic deficiency of aldolase B (Fructose 1,6-phosphate aldolase), is a recessively inherited condition in which affected homozygotes develop hypoglycemic and severe abdominal symptoms after taking foods containing fructose and cognate sugars. Continued ingestion of noxious sugars leads to hepatic and renal injury and growth retardation.

Factitious

Hypoglycemia can also be induced pharmacologically, either intentionally as a diagnostic tool, accidentally as a complication of the treatment of diabetes mellitus, or as a consequence of poisoning either with insulin itself or with drugs such as sulphonylureas, which stimulate insulin release. Whenever severe hypoglycemia occurs with documented hyperinsulinism, the possibility of Munchausen syndrome by proxy should be considered. The possibility of malicious administration of insulin or an oral sulphonylurea should always be suspected in cases of sudden onset of hypoglycemia in a previously healthy child. In the case of insulin administration, the clue in the biochemistry will be a raised insulin level with normal C-peptide.

Summary

Hypoglycemia is one of the most common biochemical abnormalities observed in the childhood period. Any symptomatic child must have his/her blood glucose level measured and documented. Hypoglycemia (especially hyperinsulinemic hypoglycemia) is a major cause of brain injury, hence the urgent need to identify and manage patients appropriately. A thorough medical history followed by a careful clinical examination in combination

with routine biochemical testing should help to elucidate the underlying cause of the hypoglycemia.

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Adolescent Medicine

Leslie R. Walker

390 Normal Adolescent Development

Laura Kastner · Elizabeth McCauley

Adolescence represents one of the healthiest periods in the life span with respect to physical illness but is marked by a dramatic increase in problems related to the control of emotions and behavior such as accidents, mental health concerns, and substance use. During this period, adolescents are experiencing the most rapid growth phase outside of infancy, ushering in biopsychosocial changes which intensify teens' own emotional experiences of themselves and those of the adults interacting with them. Structural remodeling takes place in the prefrontal cortex starting in early adolescence. The prefrontal cortex helps make possible the executive functioning skills of planning, reasoning, impulse control, and weighing risks and rewards. Until brain maturation is complete in the early twenties, cognition and decision-making are compromised. Put simply, behavior is often governed more by the emotional region of the brain than the cognitive region especially in high arousal situations.

A 15-year-old adolescent boy named John is accompanied by his mother who complains of his decline in grades at school (from A's and B's, to several C's), sullen attitude, completing chores only with reluctance, withdrawal whenever possible to his room and general emotional reactivity. She read on a web site that these characteristics could be symptoms of depression or substance abuse. She would like to know if these problems exist or if there is a physical reason for his marked behavioral and emotional changes in the last year.

Adolescent health-care practitioners are frequently asked whether there is a clinical diagnosis, or "is it just adolescence?" Epidemiological studies indicate that only about 20% of adolescents have clinical disorders, but most teens do experience increased moodiness, conflicts with parents, and risk-taking behaviors during this period of life. To fully assess the psychosocial *and* health status of teenage patients, their behaviors must be evaluated within the developmental context of their family, school, community, and culture.

Physical Development

Pubertal Development

The physical changes associated with puberty are of central concern to most teens, but the equally important neurodevelopmental changes occurring in adolescence are also triggered by pubertal hormones. Neuroscientists now suggest that the pubertal hormones stimulate the brain systems that regulate arousal and appetite which leads to changes in the intensity of emotions and motivations. This in turn contributes to alterations in the sleep–wake cycle and increases in romantic interests, risk-taking or novelty-seeking behavior, and moodiness observed in many adolescents.

Last year John seemed happy hanging out at home and even spending time with his younger sister playing video games. In middle school, he was a bit smaller than some of the other boys in his class and not very interested in what he wore or how he looked. Over the summer, his mother noticed that his voice began to change and he had more acne, then he grew about 3 in. "overnight." Now he is talking about getting "piercings," likes to stay up late at night, and is always texting to keep up with what his friends are doing.

Understanding the meaning and implications of puberty for an individual adolescent requires consideration of both timing and tempo of pubertal development as well as the youth's gender and cultural/ethnic context. Youths, whose development is "out of synch" from the majority of their peers are at increased risk for behavioral and emotional problems. However, the youths' perceptions that they are developing earlier or later than their peers, may be more important than the actual timing of pubertal changes. Also, youth may be more vulnerable if visible markers, such as breast development, are seen as early or late than if less visible indicators, such as menses, are early or delayed. Early maturing girls, with obvious physical changes, are the most at risk group. A number of well-designed studies have documented increased risk for

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conduct problems, early drinking, and depression among these girls. For boys, early pubertal development was long considered to have positive effects on self-confidence and social status but more recent research suggests that both early and late maturation confer increased risk for depression and anxiety in boys as well as girls. Coupled with timing, the pace of the developmental process can also shape how well the young person adjusts to pubertal changes. Experiencing rapid physical changes particularly during early adolescence can be very disruptive especially since physical coordination may not keep pace with an accelerated growth rate. So the tall, lanky eighth or ninth grader who gets asked about basketball all the time may be very self-conscious about his/her lack of coordination and avoid even trying out for the team.

Early pubertal development is thought to increase risk because it presents the adolescent with a set of challenges that his/her friends are not yet facing. Evidence suggests that early developing girls seek out peers who are like them physically and in turn find themselves in demanding social and emotional situations without the necessary coping skills. Pubertal development does not hasten all aspects of development, so the early maturing teen does not have the benefit of advanced cognitive, social, or problem-solving skills. Early development is most problematic when friendships with more deviant peers develop in the context of lax parental supervision. Parents can be encouraged to take an active role in helping their child navigate these challenges by working to establish and promote healthy activities, by continuing involvement with positive peers, and by keeping actively involved in their youth's life. Parents sometimes think of supervision as only rulemaking or reminding their children to do chores or homework but it can come in the form of being willing to drive to the movies, having kids "hang out" at their house, or making the effort to attend their adolescent's school and sports activities.

Alterations in Sleep

Changes in sleep are another marker associated with the physical brain development of adolescence. A physiological shift or phase delay occurs with adolescents shifting naturally to later bedtimes. Changes in sleep architecture also occur such that adolescents engage in less deep, slow wave sleep. Homework, social and work demands also take time away from sleep. A recent survey found that 45% of adolescents report not getting enough sleep on school nights and many endorse feeling irritable and sleepy during the day. Insufficient sleep negatively impacts mood and ability to perform in school. Adolescents' night owl patterns frequently upset parents and interfere with getting up for school. Simple adjustments in acceptable bedtimes may be all that is needed, but significant reversals in sleep–wake cycles can occur if youth get "online" or communicates with peers late into the night. Many young people try to make up for the lost sleep by sleeping in on the weekends. Some compensatory sleep may be helpful but it can also perpetuate a pattern of late nights followed by struggles to get up for school. Practitioners need to educate parents and teens about these normative shifts in sleep patterns while stressing the importance of getting adequate sleep and simple strategies for getting to sleep at night such as turning off computers and cell phones, trying to stick to a regular bedtime schedule and routine, and developing relaxation strategies to avoid lying in bed worrying.

Vulnerability to Drugs

Experimentation with alcohol and drugs is one important component of the risk-taking behavior that characterizes adolescent development and is triggered in part by the physical changes in the adolescent's brain. The Monitoring the Future Study, 2008 reports widespread use (e.g., 42% of 12th graders report use of alcohol in the last 30 days) even though these figures support a gradual decline in substance use since peaks in the 1990s. While some experimentation has been associated with more positive psychosocial outcomes than total abstinence, use of drugs in adolescence can be particularly risky. Initiation of drug use during adolescence is associated with an "accelerated dependency course" with, in relation to alcohol and marijuana use, shorter time between first use and dependence. Adolescents drink less frequently than adults, but when they drink, they are more likely to drink to excess or "binge." As substance use becomes more significant, negative consequences are more common, such as falling grades, fighting or doing something that the teen later regrets. Alcohol use, specifically, appears to play an important role in lowering the threshold for self-harm.

There is also evidence to suggest that adolescents have an insensitivity to some of the negative effects of alcohol (feeling or acting intoxicated) that might contribute to increased intake. They are also more likely to become more sensitive to experiencing a reduction in social inhibition, which may reinforce alcohol use. It is common for adolescents to report that they drink because it helps them feel "less shy" and more able to "think of things to say" in social situations. Gonadal hormone increases and rapid

rate of growth might also contribute by altering drug metabolism and excretion rates. It has been hypothesized that the increased dopamine inhibitory input to the prefrontal cortex noted in early adolescence may lead to changes in "excitatory drive" or experience of reward. This in turn may lead some adolescents to seek out more novelty, which could increase risk of drug use, vulnerability to abuse, and other risk-taking behaviors.

Psychosocial Development

Cognitive Development

The cognitive changes that adolescents undergo are dramatic as they become increasingly capable of high-level thinking, which can approximate an adult's reasoning abilities by the age 15 or 16. They begin to think in terms of cause and effect, make elaborate plans for the future, and evaluate alternative outcomes for various actions. As impressive as their thinking capacity may be in some circumstances, like on a trigonometry test or in a conversation about the health impact of smoking, adolescent cognition truly depends on the situation. Students with "A's" in health class who understand statistical risk (and want to avoid) the potential consequences of unprotected sex, drinking and driving, or smoking may engage in any one of these behaviors without knowing quite how to explain themselves later when pondering their regrets.

Although John's mother acknowledged that he mostly obeyed home rules of curfew and staying in touch, he recently lied in order to go to a rock concert on a school night, claiming that he was going to "study group" for a school project that did not exist. He reported that he felt guilty about lying but was resentful that his parents were strict about social restrictions on school nights.

When adults come face to face with what is considered irrational adolescent behavior, they often ask, "What were you thinking?" Or they chide about poor "choices." Clinicians are often tempted to offer health education, even when their adolescent patients may already have sufficient information about management of their sexual health, chronic illness, or substance use. What they are lacking is rational decision-making, motivational clarity, and lucid thinking while under the influence of their strong emotions in social contexts. Not only are adolescents put off by lecturing, but an exclusive reliance on information obscures the complexity of all the neurological, social, and emotional factors in play when a teen is on a lark with friends.

With the expanded ability of adolescents to reason and analyze, they enjoy the process of arguments (especially with parents) and testing out their theories, new ideas, and wild speculations. Life experience and interpersonal relating with both the peer and adult world help alleviate the teen's egocentric and off-base thinking over time, but it is easy to become ensnared in an adversarial encounter with an adolescent who may claim, "AIDS is not the big deal it was in the 1980s" or "school is stupid and does not matter." While exploration of these topics may be important, the adult who can stay respectful, Socratic, and calm will do far better maintaining rapport with the teen than the one who merely criticizes, counters, and corrects.

Cognition lays the foundation for moral reasoning, analyzing the consequences of possible actions, and evaluating values, laws, and ethical codes. Adolescents enjoy reveling in their newfound autonomy, both in thinking and action, but the adult world of parents, teachers, mentors, and others remind them of the importance of responsibilities, competencies, and the ethic of care for others that truly create a civil society.

Emotional Development

Emotional development in the adolescent usually includes self regulation, coping with feelings, coordinating cognition and emotion, and building a sense of identity. Emotional regulation refers to the ability to identify, process, and express feelings appropriately. Moodiness, emotional reactivity, and impulsivity have long been the rocky turf of burgeoning adolescence, but now research has documented a neurophysiological basis for these behaviors with imaging techniques that reflect limbic brain activity. With the immaturity of the prefrontal cortex, the incomplete myelination process, and the proclivity for neurons to fire in the limbic area during arousal, adolescents possess vulnerability for temper outbursts. Indeed, hot emotions like fear, anxiety, and anger register in the amygdala, which is part of lower cortical limbic area of the brain, and cool logic and higher intellectual functions are associated with neuronal activity in the neocortex, which is still under active reorganization during the adolescent years.

Another complaint from John's mother in the initial interview is that John seems be "blowing his top" all the time, whether he is being asked to take out the garbage or reminded of his regular baby-sitting obligation to a neighbor. He snipes at his sister regularly during dinner no matter how kind she is to him. John goes along with the mandated "electronic-free" study hall imposed by his parents to help him bring up his grades, but the focus of his life seems to be music and his friends. Although he still attends church with

the family, John acknowledges that his favorite activity is downloading music, adjusting his playlist, and writing music reviews for his Facebook homepage. He admits to "losing it" when his mother nags and criticizes him for his computer "addiction." He loves to write music reviews – his friends rave about them!

The cognitive control network in the adolescent brain is disrupted by the activation of social and emotional parts of the brain. As described by Steinberg (2008), the adolescent is like a driver who has a big engine, poor driving skills, no map, faulty brakes, and high octane gas in the tank. The development of emotional regulation capabilities is a work in progress for the average adolescent. Poor emotion regulation is a key component of the increase in both risk-taking and mental health problems observed in adolescence. Parents can influence their adolescents' emotional regulation by using warm, firm intervention strategies, selective reinforcement, modeling, and active parental monitoring. Guidance for both parents and pediatric specialists addresses the specific importance of emotional regulation in adolescents and in the families.

Identity Development

Identity is a fuzzy concept but it refers to the establishment of a coherent sense of self in the context of relationships, values, and goals. The "who am I?" question involves notions of one's current self as well as the future and possible self – i.e., who I might become and who I want to become. Identity can include personal characteristics (e.g., short, math geek), roles (e.g., mama's boy, best Hebrew scholar), goals (e.g., ballerina, construction manager), and personal beliefs and philosophies (e.g., Christian fundamentalist, progressive democrat, open source software enthusiast). Although identity development is traditionally cast as the central task of adolescence, it is now considered to continue actively into early adulthood, if not the rest of life to some degree.

Although anxiety is associated with the "who am I?" questioning process and the adolescents who are firmly adherent to parental beliefs can seem quite stable from a behavioral perspective, identity exploration seems to reflect a certain security in investigating the unknown. Since parent support and monitoring are associated with higher identity achievement, practitioners can reassure parents that there is a "method to the madness." With the positive involvement of parents, adolescents as a group develop desirable strengths and qualities as a result of the exploration process, as long as they stay safe within their experimentation.

Social Development

Although adolescents generally shift their focus from their family to their friends as the center of their social world, parent attachment is vital. Research demonstrates the important role of parents in virtually all areas of adolescent health. With parents as the secure base, adolescents can afford to take them for granted while they try out interesting and novel social experiences. Peers serve as a new reference group for trying out innovations, adopting customs of the new tribe, and experimenting with new exciting behaviors, which may include novel ways of dressing, talking, walking, dancing, and relating.

Peer acceptance is important for long-term adjustment, while popularity is not. Although sometimes parents are concerned about the number of friendships their children develop, more important is whether they have friends at all. Social isolation among peer-rejected children and adolescents has been associated with negative outcomes like academic difficulty, delinquency, and psychosocial maladjustment, whereas peer acceptance and the development of social relationships have been linked to positive outcomes.

Younger adolescents yearn for acceptance and the predominant focus is "being cool." It is not until there is some consolidation of the new self by the end of middle adolescence (14–16 years) that the adolescent can feel confident to shed some of the need for conformity. The term "peer pressure" implies overt and extrinsic influence, which can certainly occur amongst adolescents, but it is dwarfed by the intrinsic drive that adolescents have to belong to the new teen culture. The value on individuality, mutuality, and intimacy in friendships develops between middle and later adolescence.

Beyond age, research has demonstrated that there are differences in adolescent social development based on gender, race, class, culture, and temperament. For instance, the social context of development for African-American adolescents is different from mainstream white teens when they experience economic stress, high-risk neighborhoods, and crowded schools. Introverted adolescents will have fewer friends. Novelty-seeking boys will seek out the same so that they can be exhilarated in the presence of their friends. Girls will enjoy spending their time with friends talking, whereas boys will seek out more action-oriented activities. Compared to mainstream whites, family loyalty and respect for elders are more highly valued by Asian-American adolescents and Latinos.

Sexuality Development

Sexual Behavior

Pubertal maturation, and the developmental changes in arousal, motivation, and emotion that come with it, stimulates romantic and sexual interest. Biological development is far more important than chronological age in determining sexual interests. There is also a link between puberty and both sensation seeking and a sensitivity to social status, all of which helps to explain why pubescent adolescents can become preoccupied with fantasy, jealousy, sexual yearning, and outlets for their sexual curiosity.

One of their recent conflicts was when John's mother found pornography on his computer. His father gave him a stern but sympathetic warning and there seemed to be no further violations. In the computer raid, John's mother found huge amounts of "instant messenger" contacts with a particular girl. Subsequently she noted that John's decline in his grades did accompany what his mother called the "the major crush."

Romantic patterns and dating have changed markedly among adolescents in the last generation with Internet use, "cyberdating," and group socializing, and savvy kids know how to throw their parents off their tails by referring to partners as "just friends." Often younger adolescents will refer to "going out" with a particular person, when they have not even shared a single direct conversation. "Hooking up" is a similar term which is vague, in that it can refer to anything from kissing to sexual intercourse. Does "having sex" refer to just sexual intercourse or does it include oral sex? Practitioners are advised to inquire directly to make sure they understand their patients' meanings of terms.

Adolescent relationships usually last for a few months, and as the time in the relationship increases, sexual involvement is more likely to occur. Approximately, 47% of high school students in 2005 reported having had sexual intercourse at least once, ranging from one third of 9th graders and increasing to a majority of 12th graders. Rates are higher among males than females at every age. Racial differences occur, with rates of 12th-grade sexual activity among African-Americans at 68%, Hispanic students at 51%, and white students at 43%.

Despite public impressions about problems associated with teens and sexuality, rates of adolescent sexual activity, pregnancy, and childbirth have actually decreased over the last decade. Still, the United States has the highest rate of adolescent pregnancy in the Western industrialized world, even though the adolescent sexual activity rate is similar to that of Canada and Europe.

Research has shown that adolescents with the most connected relationships with their parents have the most responsible sexual behaviors, including delaying intercourse, having fewer partners, and practicing safer sex. Most health experts agree that teens need and deserve comprehensive sexuality education, which includes information about abstinence, refusal, and negotiation skills and up-to-date information about birth control and sexually transmitted infections.

Sexual Identity

As adolescents explore their sexuality, they may think about or experiment with people of the same sex. Same sex attractions do not necessarily mean that the adolescent is homosexual – they may or may not be. Sexuality can be fraught with anxiety for anyone but particularly so for young people who may be trying to consolidate a minority sexual identity in a society that discriminates against homosexuals. Homosexuality was eliminated from psychiatric diagnostic manuals decades ago, but that has not eliminated the risk factors associated with being a gay, lesbian, or bisexual youth.

Sexuality, Psychosocial Development, and Media Influences

The effect of electronic media on the psychosocial development of the average adolescent is unknown, but studies have linked exposure to many negative outcomes in adolescent health. Violent media exposure has been associated with aggression, hostility, and poor school performance as well as violent behavior in adulthood. Viewing sexually explicit online media has been correlated with casual attitudes about sex. Television advertizing exposure has been associated with parent–child conflict and materialism. The enormous amount of time that adolescents spend interacting with social networking sites, instant messenger, music downloading, gaming, blogging, and various entertainment has been well documented.

While electronic media plays a role in the lives of virtually all adolescents, the tricky question for practitioners is when this role may be destructive. Given the importance of time allotted to physical fitness, sleep, education, direct interaction in social relationships, talent development, family, religion or spirituality, and even spending time in the natural world, one way to evaluate the way media affects the individual adolescent is calculating how much it robs time from other important avenues of healthful child development.

Table 390.1
Stages of normal adolescent development

	Early (10–13 years)	Middle (14–16 years)	(17–19 years)
Physical	Beginning of physical changes in the brain, shifting of sleep/wake cycle and rapid physical development: Girls: breast buds, pubic hair, start of growth spurt, menarche for many Boys: 1–2 years after girls, testicular and penile growth, pubic hair	Ongoing brain maturation and sexual development with most girls moving into Tanner stages VI and V and boys experiencing continuing development of testicles, penis, body and facial hair, and beginning of linear growth spurt	Brain maturation continues into young adulthood with maturation of frontal lobes which facilitates regulatory competence. Most youth reach Tanner Stage V
Cognitive	Gradual shift to hypothetical ("what if") and abstract thinking from concrete operations of childhood; self-centeredness is characterized by egocentricism, self-consciousness, and self-absorption	Cognitive comparisons between real and ideal in parents, friends and selves, mature analytic thinking in "cold logic" contexts (e.g., lab, classroom, and other low-arousal situations) but frequent lapses in "hot" or emotional circumstances	Maturing of accurate perspective taking and self-reflection, increased consideration of future life goals, improved executive functioning skills (planning, reasoning, judgment, and impulse control)
Emotional	Increased moodiness, irrational behavior, emotional reactivity and impulsivity related to puberty and changes in the prefrontal cortex	Increased arousal and novelty seeking, low motivation for what is perceived as boring; increased conflict with parents, emotional dysregulation hyper-aroused amygdala	Growing ability to recognize and manage emotions, demonstrate empathy, resolve conflicts constructively, and work cooperatively with others
Social	Increased desire to be with friends, push for greater independence, less contentment in being exclusively with family, increased identification with peer culture, value on independence and individualism highly influenced by culture and ethnic background	Identity formation and values exploration, strong preference for the company of friends but still connected to parents for support, desire for approval and long-term attachment, peer conformity driven by strong desire for peer acceptance	Integration of values internalized from parents, experience, and generational influences; friendship choices less related to similar interests and more to valued individual characteristics and qualities; intimacy increasingly sought

Summary

With the information reported by John and his mother thus far, there is a lack of clinical evidence for ruling a problem in or out. All of the behaviors of concern to his mother could be considered within normal developmental limits for a teen of his age (see *Table 390.1*). In fact, the initial interview revealed "protective factors" suggestive of resilience and positive development. These include John's compliance (albeit reluctant) with parental expectations regarding curfew, his baby-sitting job, chores, imposed study hall time at home, and church attendance, as well as other family factors associated with adaptive teen development like authoritative parenting, organized family life (e.g., the family dinner), and successful mediation of previous conflicts.

Although further interviewing and a physical exam are needed in order to address the family's questions, it is remarkable how much preliminary developmental data has already been collected. The practitioner's challenge is to ask questions skillfully so that the teenager feels comfortable, respected, and validated for whatever concerns he may present as the evaluation proceeds. The practitioner who is aware of normal adolescent developmental issues will demonstrate a genuine appreciation in John's array of interests, ranging from independence and sexuality to music and friendships as well as his behavioral competencies.

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391 Adolescent Nutrition and Weight Control

Alicia Dixon Docter · Cora Collette Breuner

Factors Influencing Nutritional Needs

The onset of puberty and emergence into adolescence presents unique nutritional challenges due to dramatic changes in physical, cognitive, and emotional development. There is increased demand for nutrients due to pronounced change in body composition, linear growth and increases in muscle mass, subcutaneous fat, and bone density. Layered on to this is substantial individual variability for each adolescent dependent on their genetic, environmental, and psychosocial milieu. Reliance on peers, greater independence in food choice, and widely variant increases in physical activity add complexity to helping adolescents meet their nutritional needs. School, community, and societal influences are appropriate to acknowledge when working with this population.

Normal Eating and Adolescent Nutrition

An adolescent's relationship with food has been developing since infancy. In an ideal situation, the teen will gradually emancipate and begin to meet their own nutritional needs during the latter half of adolescence, usually between 18 and 25 years of age.

Common eating patterns emerge include: grazing, skipping breakfast, fast food consumption, drinking excessive sugar-sweetened beverages, restrictive eating to control weight, and non-traditional eating patterns, often to establish identity. One-third of teens use a multivitamin/mineral supplement. Seventy-five percent use caffeine daily in the form of carbonated beverages, energy drinks, and coffee drinks. Fast food intake has increased over time. In a review of project EAT (population-based, longitudinal study in Minnesota), almost a quarter of adolescents ate fast food $\geq$3 times/week, which increases to one third in young adult males. At follow-up in early young adulthood, this eating behavior increased among males (33%, $p < .001$), yet there was no further increase among females (23%; $p = .16$). Baseline snack frequency was positively associated with frequency of fast food intake at follow-up among both genders. Baseline peer support for healthy eating among males and concern about health and self-efficacy for healthy eating among females were inversely related to follow-up fast food intake. Among females, baseline perceptions of time and taste barriers to healthy eating, lunch frequency, television viewing, and unhealthy food availability at home were also positively associated with fast food intake. A small but significant positive association was seen between fast food consumption and overweight status. Within-person comparisons showed that energy intakes were higher on a fast food day than on a non-fast food day. Conclusion: Fast food consumption was associated with a diet high in energy and energy density and low in essential micronutrient density. Frequent fast food consumption may contribute to weight gain.

By late adolescence, a teen should be expected to eat at least three meals a day and a snack after school. Breakfast is an important fulcrum and has been associated with less overeating later in the day and in some cases, with a lower BMI. In one review, it was found that 10–30% of those living in the United States and Europe skipped breakfast. Importantly, children who reported eating breakfast had better nutritional profiles and were less likely to be overweight than their peers who did not eat breakfast. Does eating breakfast improve cognitive function, memory, school performance, and even attendance? In this review there is some evidence that this is true, although more research is necessary. In another paper looking at a school feeding program in Jamaica, children ages 12–13 had improved performance in arithmetic and attendance, but no weight gain.

A teen should be encouraged to manage daily activities and snacking in order to make family meals a priority. Regular family meals have been associated with positive regard for family. Teens should be encouraged to find their own ways with food away from home: what to eat, how

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much to eat, how to get what he needs. Finally, before teens leave home, meal planning, food preparation, and shopping should be reviewed and practiced.

Nutrition Needs Due to Growth

Clinicians should consider Sexual Maturity Rating (SMR) or Tanner staging when making nutritional recommendations as chronological age is a poor indicator of physiological maturity.

Weight gain should be expected through adolescence due to increases primarily in bone, lean body mass, and adipose tissue. For females, the average increase in height is estimated at 8.24 in. (20.5 cm). During the peak of the growth spurt, females gain roughly 3.5 in. (8–9 cm) per year. Adolescent males experience increases in height of 4–12 in. (10–30 cm) during puberty, with an average of 2.8–4.8 in. (7–12 cm) attained each year. Pubertal weight gain accounts for approximately 50% of an individual's ideal adult body weight. More than 90% of adult bone mass accrues by 18 years of age.

During childhood boys and girls have relatively equal proportions of lean body as skeletal mass and body fat. By the end of puberty, however, men have 1.5 times more lean body mass and skeletal mass than women who have double the fat mass.

While girls experience a slightly less intense growth spurt in height, less marked increase in skeletal muscle, and a more continuous increase in fat mass than boys, this should be normalized so that the girl feels positive about her growth experience. Average weight gain for females are equal to 38.5 lb(17.5 kg). While weight gain slows around menarche, females may gain as much as 14–20 lb(6.36 kg–9.09 kg). during the latter half of adolescence. Adolescent males may gain an average of 20 lb(9.09 kg). per year during the pubertal growth surge. Overall, males gain an average of 52.2 lb. (114.8 kg).

Nutrient Needs in Adolescence

The Dietary Reference Intake (DRI) is the most up-to-date data; however, it is based on chronological age. A clinician needs to consider growth and sexual maturation status. That said, DRIs are general guidelines and are set to meet 97–98% needs (see *Table 391.4*). In Europe, investigators from various countries are working together to standardize diet and nutrition methods for nutrition surveys to overcome uncertainties over the nutritional quality of the diets of European children and adolescents.

Table 391.1
Percentage of body fat during puberty

Stage of puberty	% Body fat
Female	
1	15.7
2	18.9
3	21.6
4	26.7
Male	
1	14.3
2	11.2
* Percentage of body fat remains unchanged in stages 3, 4, and 5 in males	

From Malina R, Bouchard C, Bar-Or O (2004) Growth, maturation, and physical activity, 2nd edn. Human Kinetics, Champaign

In the Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study, an assessment of food intake in 13–16-year-old European adolescents showed that mean energy intake in boys range from 1,532 to 2,868 kcal per day and from 1,450 to 2,818 kcal per day in girls. Overall, there was a tendency to report a lower energy intake with increasing BMI.

In the 2003 Children's Lifestyle and School-Performance Study, a survey of Canadian fifth graders of height and weight were also asked to respond to the question "I like the way I look." Response choices included "never or almost never," "sometimes," and "often or almost always." Interestingly, 7.3% of girls and 7.8% of boys had "bad body satisfaction."

Researchers also found that rural girls or those with poorly educated parents were likely not to like their bodies. Austin et al. found that links between body satisfaction, weight-related behaviors, and weight gain require that overweight prevention in children can be enhanced through better knowledge of factors underlying body dissatisfaction. Mechanisms should also be studied in families with low parental education and in rural communities.

Nutritional Concerns in Adolescence

Risks associated with undernutrition include delayed puberty, amenorrhea, decreased bone mineralization, iron deficiency, and dehydration.

Situations that include an inadequate intake of nutrients, including energy (calories) in which teens may need some additional guidance, include:

- The adolescent athlete
- Alternative dietary preferences
- Eating disorders
- Obesity and overweight

Nutrition needs related to pregnancy, drug and alcohol use, and chronic illnesses are found elsewhere in this textbook.

The Adolescent Athlete

In the teen athlete, energy needs are very high due to growth and development needs as well as sport energy needs. Specific nutrient recommendations vary based on age, developmental stage and should be tailored by assessment of a nutrition professional with expertise in adolescents and sports. The over-arching approach is to help the teen athlete achieve an adequate baseline intake and tailor eating around individual preferences and tolerance at practice and events. Regular menstrual periods indicate the patient is meeting energy requirements.

Meal or snack skipping due to sport, studies, and busy lifestyle may prevent meeting energy needs. Adolescent athletes need a baseline of three full meals and two to three snacks per day. A meal should include four to five items representing a variety of food groups including grains, protein, fruits, vegetables, fats and oils, and dairy as appropriate. Desserts and snack foods may be considered as a way to ensure that the athlete is consuming adequate caloric daily requirements. Meals should include high quality proteins supported by adequate carbohydrate and fat. Teen athletes should be reminded that energy bars are not acceptable meal replacements in that they do not provide calories equivalent to that in a balanced meal.

During exercise, primary goals are to replace fluid losses and provide carbohydrates (approximately 30–60 g/h) for maintenance of blood glucose levels. Athletes need to immediately replenish energy used (within 30 min and then again every 2 h for up to 4–6 h after exercise) after practice or competition by having small snacks high in carbohydrate (1.0–1.5 g/kg body weight) or a combination of carbohydrate and protein.

Athletes should have unlimited access to fluids *during* exercise to improve hydration and temperature regulation. Athletes must be urged to rehydrate themselves because the thirst mechanism imprecisely guides water needs. After exercise, the athlete should drink adequate fluids to replace sweat losses during exercise, approximately 450–675 mL (16–24 oz) for every 0.5 kg (1 lb.) of body weight lost during exercise.

Athletes should be counseled regarding the appropriate use of ergogenic aids. Such products should only be used after careful evaluation for safety, efficacy, potency, and legality.

An Adolescent with Alternative Dietary Preferences

Teens with alternative dietary preferences require clear, practical nutrition education about functions of foods in order to understand that eliminate of food, requires up for the deficit in calories or a nutrient by substituting in an alternative that supplies those nutrients. For example, vegetarians cannot eliminate protein and expect to meet their needs – they need to utilize foods that will provide high biological value proteins. Additionally, teens need to understand the concept of getting enough energy (calories) to support growth as well as lifestyle. As with all teens, they will need education about food selections and how the body uses food to avoid dichotomous thoughts that may interfere with what they require. With guidance in meal planning, vegetarian diets can be appropriate and healthful choices for adolescents.

Nutrition Assessment

A physical nutrition assessment should include: plotting weight, height, and BMI (kg/m^2) on gender-appropriate CDC growth charts (2–20 years). This data should be compared with weight and height history to determine change in weight and growth velocity. An optimal healthy weight range, often referred to as ideal body weight (IBW), is estimated based upon available growth history and is generally between the 25th and 75th percentile of BMI-for-age. A weight goal is typically 90–110% of IBW. A weight at $\leq$85–90% IBW may increase risk of delayed puberty or amenorrhea. Arm muscle and fat stores measured by the Registered Dietitian can be a helpful assessment and educational tool.

A dietary assessment should include a diet history from infancy to present, preferred and disliked foods, dietary restrictions/food allergies, and any supplements. It should also include a review of a typical day: schedule, activities, foods and beverages consumed with approximate amounts. Family composition, food availability,

location of meals and snacks, rules around food, involvement in school feeding programs, and involvement in extracurricular activities need to be evaluated.

If a medical provider does not have the time to conduct a thorough review yet suspects eating issues, a referral should be made to a nutrition professional who has training with adolescents and is comfortable collaborating with a team. The designation, R. D. (Registered Dietitian), ensures that the professional has rigorous clinical training.

Eating Disorders

Introduction

Eating disorders, including anorexia and bulimia nervosa, originate in late childhood and early adolescence. Prevalence rates for anorexia range from 0.5% to 1.0% in females and 0.1% in males. Bulimia nervosa is not as common in those under 18 years of age; bulimic behaviors occur in 1–3% of females and less than 0.2% of males.

Depression and anxiety are particularly common comorbidities for anorexia nervosa and bulimia nervosa. It has been reported that 50–70% of patients with anorexia and bulimia also have depressive, obsessive-compulsive, or anxiety disorders.

Despite a relatively broad base of knowledge about this disorder, the treatment of eating disorders in children and adolescence is limited to few controlled studies. It is unclear whether all aspects of the illness must be addressed simultaneously or in sequence if treatment is to be successful, or whether by solely addressing the eating habits other concerns will also be effectively managed.

An interdisciplinary team including pediatrics or general medicine, nutrition, and mental health provides the most comprehensive treatment approach when all providers are in regular contact with one another and share a similar philosophy in the understanding and treatment of the disorder.

- Questions to ask: What is your maximum and minimum weight? What is your desired weight?
- Do you eat with your family?
- Are there any "off limit" foods?
- Any friends/family members with abnormal eating behavior?
- How much do you exercise? How do you feel if you cannot exercise?
- Do you ever eat more than what feels comfortable to you? Then what do you do?
- How is your sleep?
- Are you taking any supplements to lose weight? Improve your sleep?

Nutrition Approach to Eating Disorders

In both inpatient and outpatient settings, the clinician needs to identify what teens and families are doing in terms of eating. Then, through education and support, the teen should be encouraged to make small changes to allow for a balanced meal pattern that will support gradual weight restoration (.5–1 lb. (1.1–2.2 kg)) per week. Education regarding the role of nutrients, the need for adequate nutrients and energy, and effects of semi-starvation can be helpful. It is important to work with a collaborative multidisciplinary team that is familiar not only with eating disorders but also with adolescents. Refeeding to stabilize a teen medically in an inpatient setting, may be more aggressive but should still be gradual over a 3–7 day period.

Psychological Approach to Eating Disorders

There are many different types of psychotherapeutic interventions including cognitive behavioral therapy, narrative therapy, body image therapy, and motivational interviewing. The challenge of using any of these options is that in patients with anorexia nervosa they often lack motivation for weight gain and this must be addressed

Table 391.2
Criteria for hospitalization in the adolescent eating disorder patient

• Sinus bradycardia, rate less than 40 beats per minute
• Other arrhythmia, including prolonged corrected QT interval
• Hypothermia (temperature $<97.5^{\circ}$F)
• Orthostatic hypotension by pulse or by blood pressure
• Precipitous weight loss in a short time period
• Severe electrolyte imbalances (potassium <3.0, phosphorus <2.0)
• Unable to eat or drink, acute food refusal
• Intractable vomiting
• Marked depression, with suicidal ideation and intent
• Failure to progress in outpatient treatment, especially when risk of growth delay is present

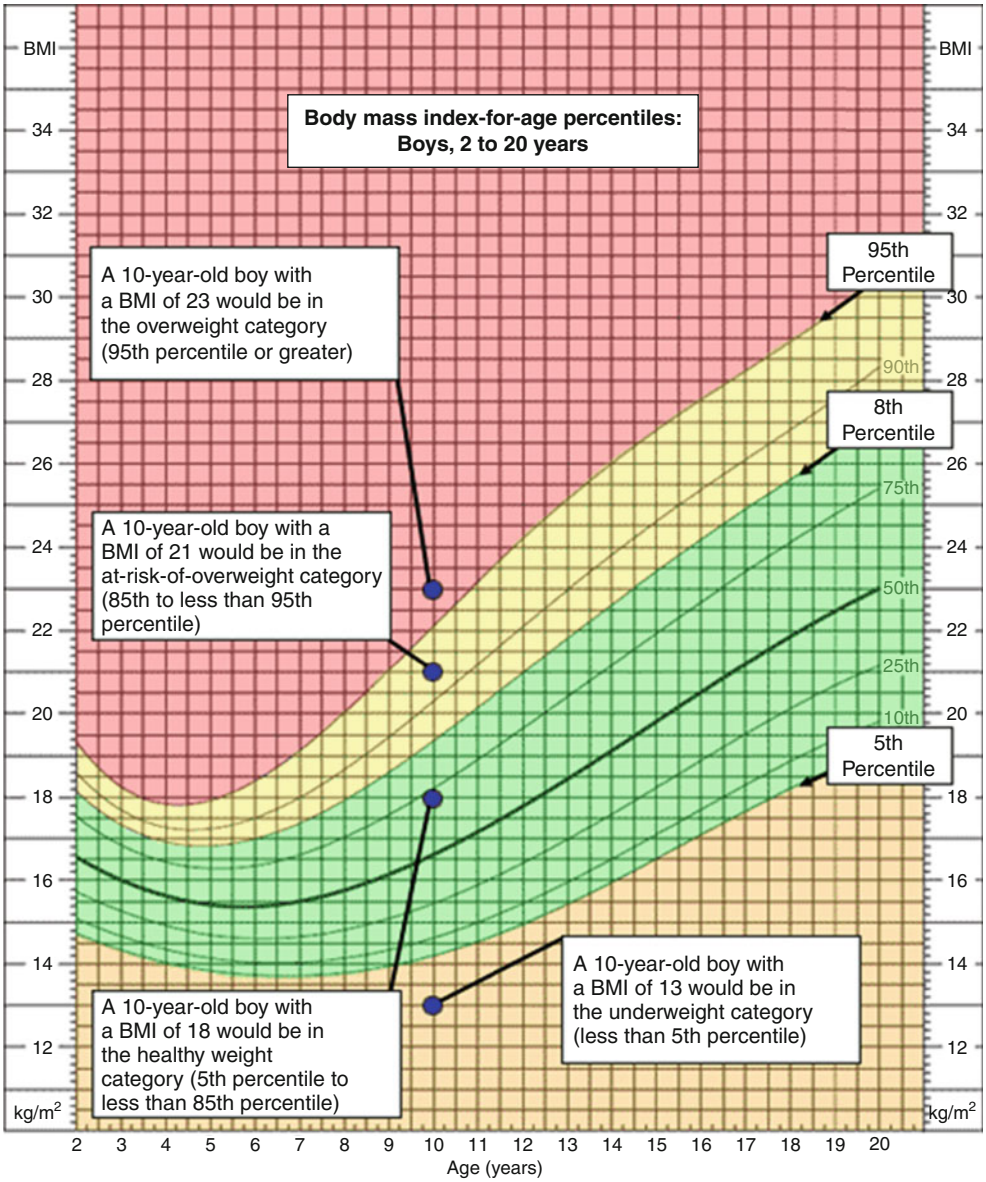

Figure 391.1

What is BMI? Body Mass Index (BMI) is calculated from a child's weight and height. BMI is a reliable indicator of body fat for most children and teens. Your child's pediatrician should assess BMI at each well visit beginning at age 2. For children and adolescents, BMI is age- and sex-specific and is often referred to as BMI-for-age. After BMI is calculated for children and teens, the BMI is plotted on the CDC BMI-for-age growth charts (for girls or boys) to obtain a percentile ranking

first in the initial phase of treatment in order to cultivate and sustain motivation for change. In family-based therapy (FBT), parents are directly involved in the patient's treatment and recovery process. Patients with an eating disorder are often in denial about the seriousness of their disease and generally incapable of making good choices regarding their health and eating habits. In one randomized control trial of 80 patients and their families, participants with less severe eating disorder psychopathology (Eating Disorder Examination global score), receiving FBT, were more likely to meet criteria for partial remission at follow-up.

Medical Approach to Eating Disorders

The medical management of the adolescent with an eating disorder requires knowledge of the physical presentations and quick attention to the medical complications that may occur. Some of the physical symptoms and findings include dry skin, cold intolerance, acrocyanosis, constipation, bloating, lanugo hair, scalp hair loss, delayed gastric emptying, weakness, fatigue, delayed puberty, primary or secondary amenorrhea, breast atrophy, atrophic vaginitis, and pitting edema of extremities. Cognitive changes have been found in some anorexic patients. Mouth sores, pharyngeal trauma, dental caries, heartburn, chest pain, muscle cramps, weakness, bloody diarrhea (in laxative abusers), bleeding or easy bruising, irregular periods or amenorrhea, fainting and swollen parotid glands are noted in those with bulimia nervosa. Recognizing these signs and symptoms as the mortality for those with eating disorders is the highest among psychiatric conditions in adolescents.

Myocardial abnormalities include sinus bradycardia, sinus arrhythmia, low blood pressure, or myocardial abnormalities. In anorexia nervosa, a pulse differential of greater than 30 beats/min, with underlying bradycardia, suggests excess vagal tone counterbalanced by excess sympathetic tone. Prolonged QT interval, fatal ventricular dysrhythmias, and abnormal contractility have been noted in both adults and adolescents. Reversal does occur with restoration of weight.

Electrolyte abnormalities include hypophosphatemia, hypokalemia, noted predominantly in bulimic patients, and hypomagnesaemia and should be treated with oral supplements until they normalize.

It is known that peak bone mass is gained during puberty and also that hypoestrogenemic osteopenia may be seen in as many as 50% of adolescents with eating disorders. The impact that this may have on the developing bone mass in a young woman can have significant deleterious effects in the adult. The treatment of an abnormal DEXA scan in the patient with an eating disorder has been controversial. It is known that weight-recovered patients had improved BMD (bone mineral density). Estrogen replacement has not been shown to be an effective treatment for decreased bone mineral densities in adolescents except in those with exceedingly low weight.

The absence of menses in the adolescent with an eating disorder is commonly observed and may be due to a decrease in leptin levels and thyroid dysfunction.

Hospitalization is imperative when a patient is severely medically impaired but does it improve long-term outcome of those with eating disorders? Only one randomized controlled trial has compared the benefits of admission with no treatment or outpatient psychological therapies. A further study has questioned the medium to long-term benefits of admission for adolescent anorexia nervosa. Unfortunately, there is still no clear data supporting the theory admission of adolescents with an eating disorder is associated with improved medium- to long-term outcome (*Table 391.2*).

Obesity and Overweight

Obesity is an excess percentage of body weight due to fat that puts people at risk for many health problems. In children older than 2 years of age, obesity is assessed by a measure called the Body Mass Index (BMI) (*Fig. 391.1*). Evidence increasingly identifies higher levels of physical inactivity (watching television and computer screen time), lower levels of moderate physical activity (active play), and excessive consumption of sugar-sweetened beverages as critical contributors to the ever higher rates of childhood obesity. In infancy, breast feeding appears to provide some protection against later obesity.

Table 391.3
Problems associated with obesity

• Glucose intolerance and insulin resistance
• Type 2 Diabetes
• High blood pressure
• High cholesterol
• Hepatic steatosis (fatty liver disease (FLD))
• Cholelithiasis (gallstones)
• Sleep apnea
• Asthma
• Skin conditions
• Menstrual abnormalities
• Impaired balance
• Orthopedic problems
• Low self-esteem
• Negative body image
• Depression
• Stigma
• Teasing and bullying
• Negative stereotyping
• Discrimination
• Social marginalization

Adapted from National Alliance for Nutrition and Activity Obesity Fact Sheet, 2009

Children and adolescents with a BMI over the 85% but less than the 95th percentile are considered overweight and those with a BMI greater than the 95th percentile are considered obese.

Overweight or obese children and adolescents are at risk for many health problems. Some of the negative health outcomes that may be more obvious to children and their parents are asthma, sleep apnea, skin infections, and complaints of joint pain (*Table 391.3*). All of these are significant health problems and need attention by a doctor; however, in addition to these there are other serious health risks associated with obesity that may be less obvious to the child or parent, such as high blood pressure (hypertension) and Type 2 Diabetes. These conditions can have serious long-term health effects and may require ongoing medical treatment and management. The bottom line is obesity can cause immediate health problems as well as a number of very serious chronic health conditions.

Research indicates that obese children have lower self-esteem and self-confidence than their thinner peers. Low self-esteem and self-confidence have been linked to poor academic performance, fewer friends, and depression. For all of these reasons it is important to try and prevent childhood obesity and identify overweight and obese children quickly so they can begin treatment and attain and maintain a healthy weight. Over the past 2 decades, the prevalence of children who are obese has doubled, while the number of adolescents who are obese has tripled. According to the National Health and Nutrition Examination Survey (NHANES), 31.9% of children and adolescents were overweight (BMI at or above the 85th percentile) and 16.3% were obese (BMI at or above the 95th percentile).

Although overweight has increased for all children and adolescents over time, NHANES data indicate disparities among racial/ethnic groups. Non-Hispanic black girls and Mexican American girls are more likely to have high BMI-for-age than non-Hispanic white girls. Among boys, Mexican Americans are more likely to have high BMI-for-age than non-Hispanic white boys.

As for treatment of obesity, it has been suggested that a much disciplining team provide care. Additionally, at least 25 hours of contact over 6 months has been found to improved BMI.

Table 391.4
Important nutrients for the adolescent

Nutrient	Function	Approach/food Source
Energy	Growth and development; normal menstruation that supports healthy bone accrual; adequate energy intake allows adolescent to meet nutrient needs	Female: 9–13 years: 2,071 kcal/day; female 14–18 years: 2,368 kcal/day
		Male: 9–13 years: 2,279 kcal/day; male: 14–18 years: 3,152 kcal/day
Protein	Growth and development	20% of total energy, which is generally achieved with eating normal meals and snacks at estimated goal energy level; needs may be higher with athletes
Carbohydrates	Energy	50–65% of energy needs, depending on activity
Fat	Cell structure; energy; satisfaction	25–30% of energy needs
Iron	Iron is required for adequate developmental, growth, and healthy red blood cells	• Bioavailability of iron sources (meats, egg yolk, breads, and cereals) and vitamin C intake (tomatoes, peppers, oranges, melons)
		• Supplement if medically necessary
Calcium	Bone health	Adequate; if amenorrhea – 1,500 mg/day (five servings high calcium foods per day)
Vitamin D	Assists with calcium metabolism: immune function	Sunlight; food sources: fortified milk, fish, liver, egg yolk. Provider to determine deficiency and supplement
Folic acid	Cell health and prevent of birth defects (neural tube defects)	Explore intake and food choices (e.g., fresh oranges and/or fortified cereals)
Zinc	Normal growth and reproductive health; skin health	Meat, cheese, legumes, whole grains

Source: Created by Alicia Dixon Docter (2009). Adapted from Institute of Medicine, Foods Nutrition Board, Natural According of Sciences, 2001

Approaches to Communication with Adolescents in Nutrition Intervention

- It is essential to develop a rapport using Motivational Interviewing (MI) tools such as *open-ended questions*, *reflective listening* and *affirmations*, and *working with resistance*.
- Adolescents are typically well educated with respect to "healthy" food choices or calories, but often have a distorted sense of regular eating frequency, meal and snack patterns, and appetite/satiety awareness.
- Expect experimentation with unhealthy eating behaviors. Help patient identify the pros and cons of less healthy choices.
- Connect education to life goals or to something the patient cares about such as continued height increase, appearance, and muscle mass development.
- Ask patient to identify 1–2 goals he/she is willing to work on over a specified period of time to improve health.
- Avoid making choices or giving ultimatums to teens. Instead, recognize what the teen is doing well and provide education and recommendations to consider when making his/her own wise choices.
- Respect patient's wishes for independence and privacy from parents. Ask teens if there are acceptable ways that parents can help meet goals.

Conclusion

Nutritional care during adolescence is challenging requiring patience, flexibility, and sensitivity to the adolescent wherever they are socially, emotionally, and physically. Food and adequate diet are not panaceas that solve juvenile delinquency and learning problems, improve athletic performance, and allow youth to attain new and exciting cognitive achievements. It is fun. It is hard. It is worth it (*Table 391.4*).

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392 Adolescent Gynecology: Approach to the Female Adolescent

Taraneh Shafii · Gale R. Burstein

Adolescent Gynecology: Approach to the Female Adolescent

Broaching the topic of sexuality can be challenging for some healthcare providers and adolescent alike. However, it is an opportunity for healthcare providers to guide young women in understanding their bodies, controlling their reproductive future, and developing healthy sexual relationships.

Healthcare Providers' Personal Views of Adolescent Sexuality

Teenagers having sex can be an emotionally charged subject and may conflict with clinicians' personal beliefs. Regardless of individual ideology, to ensure the health and well-being of their patients, providers must offer adolescents comprehensive and scientifically based reproductive healthcare or else refer them to colleagues who are able and willing to do so.

Starting the Sex Conversation: Do You Talk About Sex with a 13-Year Old the Same Way as with a 17-Year Old?

Adolescents' ability to reason lies somewhere between the continuum of concrete operations of childhood and formal operations of adulthood, so before initiating an interview with an adolescent, it is helpful for providers to be aware of adolescent psychosocial development (psychsoc dev). For example, when asked if she is sexually active, the concrete adolescent may think that the provider is asking if she is "active" during sex instead of whether she has *ever* had sex.

The early adolescents (11–13 years) are unable to think abstractly or develop a plan for the future, which limits their ability to seek hormonal contraception or condoms prior to sex and limits their ability to think of the potential consequences of unprotected sex such as sexually transmitted infections (STIs) and unintended pregnancy. Middle adolescents (14–16 years) develop capabilities for abstract thinking and conceptualization, yet their ability to carry out such behavior may be limited. They may revert back to concrete thinking during times of stress such as triggered by peer pressure or alcohol and drug use. Late adolescents (17–21 years) are able to plan for and effectively use contraception and condoms; however, as the use of hormonal contraception increases in these older adolescents, condom use decreases, thereby providing an opportunity for STI transmission.

How Do You Know If Your Patient Is Having Sex?

In the United States, 62% of high school 12th-grade students have had vaginal intercourse and more than one third of all high school students have had sex in the past 3 months with 14% having had four or more lifetime partners.

The average age of first sex in the United States is 16.5 years. Unfortunately, many adolescents do not seek healthcare until well after first intercourse. Providers must always consider that their patients may already be engaging in oral, anal, or vaginal intercourse and are, therefore, at risk of STIs and pregnancy and should be screened through sexual history and laboratory testing.

How Young Is Too Young to Ask About Sex?

As 6% of US youth report first vaginal intercourse before 13 years of age, it is important to ask even early adolescents (11–13 years) about sexual behavior.

What About Cultural and Religious Differences?

Healthcare providers must be in tune with the varying cultural and religious beliefs of their patient population

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and demonstrate cultural sensitivity to different practices. For example, youth may be resistant to discussing the topic of sex regardless of their level of sexual experience because sexual activity prior to marriage is shunned by many cultures and religions. Therefore, framing information about sexuality in the context of helping their peers and friends who may be or become sexually active is a nonthreatening and effective method to provide sexual education to all patients.

How Do I Get My Patients to Tell Me What They Are Actually Doing?

Building rapport is the most important skill a provider needs in taking care of adolescents to create an environment where the patient feels safe disclosing confidential sexual behaviors and health concerns. Adolescents are surprisingly candid about sensitive topics when they feel safe, respected, and are promised confidentiality.

Tell Her What You Are Going To Do Today

Since genital exams are a source of great anxiety and embarrassment for youth, if a genital exam will take place, the provider should inform the adolescent patient. If a pelvic exam will be performed, a full explanation is imperative, especially if this is the patient's first exam. Allowing the adolescent to remain dressed during the interview and covered as much as possible during the exam contributes to feelings of safety and a sense of being in control of their bodies and their environment. Showing the adolescent the speculum, and even letting her handle it, usually helps in diminishing rather than escalating the anxiety. Diagrams or plastic genitalia models and mirrors during the exam are useful to educate youth as most young females are unaware of their anatomy and unfamiliar with proper terms. Many young women have never seen their own anatomy.

Ensure Confidentiality from Your Office and the Bill that Is Sent Home

All young people (age minimum varies per state) in the United States may legally give consent for their own sexual healthcare, so confidentiality may be offered to young women with the exception of the three caveats of harm: "What we talk about today is confidential from your family unless I am worried that you are thinking about hurting yourself; hurting someone else; or if someone is hurting you."

Health insurance presents another confidentiality challenge. However, insurance regulations mandate commercial health plans to provide subscribers explanation of benefits listing services received. To avoid disclosure through billing, providers can use as ICD-9 codes *symptoms* (e.g., dysmenorrhea, irregular menses) and general *clinical findings* (i.e., vaginal discharge, pyuria, or urinary complaints) rather than specific STI diagnoses such as trichomonas or chlamydia.

What Kind of Sex and with Whom?

What Kind of Sex?

As adolescents present in varying stages of cognitive development and sexual knowledge and sexual experience, providers need to ask very specific questions to make an accurate assessment of sexual health and risks. "Have you had sex with guys, girls or both? Have you ever had oral sex? Anal sex? Vaginal sex?" If in doubt of a youth's understanding of the definitions of oral, anal, or vaginal sex, the provider should pose the questions to ensure they are discussing the same behavior. "Tell me what 'having sex' means to you." The provider then has the opportunity to provide the definitions, for example, "I want to make sure we are talking about the same thing: so oral sex means your partner puts his/her mouth on your vagina/penis; some people call it 'going down on each other,' have you ever done that?"

With Whom?

Adolescents are in the process of understanding and accepting their sexuality, and survey data suggests that anywhere from 3% to 10% of US adults report being lesbian or gay. Sensitivity and awareness of sexual minorities is important when interviewing and obtaining a sexual history from an adolescent. For example, a provider is interviewing a 15 year-old female about her sexual behavior and asks, "So do you have a boyfriend?" If that young woman is struggling with her sexuality, the provider may have alienated her, when instead, he/she could have offered a safe venue for discussion of sexual feelings. An *alternative* example of initiating a conversation about sex: "You are at the age when you start figuring out if you are interested in or attracted to guys, girls or

both . . . have you thought about that yet? Have you ever had sex with a guy, girl or both?" By acknowledging different sexual orientations, providers are sending the message that same-sex attractions are within the range of human sexuality. For the heterosexual youth, providers are modeling a position of acceptance and tolerance for sexual minorities.

Could the 15-Year Old with Abdominal Pain Really Be Worried that She Is Pregnant? (If You Ask They Will Tell You; If You Don't They Won't)

The *Hidden Agenda* is the phenomenon of adolescents seeking care for a sensitive health issue (e.g., pregnancy symptoms) and assuming that their provider will know what is wrong with them without actually verbalizing the problem. For example, an adolescent female presents with complaints of a belly ache; the provider works up the abdominal pain but does not screen for sexual behaviors and treats the patient for presumed gastritis. The patient leaves the office reassured that she is not pregnant since she believes that the provider is omniscient and would have told her if she were pregnant. An adolescent will not always volunteer her true health concerns but is surprisingly candid when asked directly. Providers must ask the questions to which they want answers and should not rely on adolescents to bring them up themselves.

The Physical Exam

Foremost, the provider should always make the adolescent feel like she is in control. Providers should let the adolescent know what part of the exam is going to be performed next and that the physical examination will stop at any time if she is uncomfortable. Providers should explain that they are doing the exam to best take care of their patients' health and want to make sure that they are indeed healthy. As many options as possible can be offered during the exam to empower the patient and make her feel as safe and comfortable as possible. For example, the adolescent can be asked if she would be more comfortable completely undressing and changing into a gown before the exam or would prefer to undress only the part of the body being examined to remain partially dressed throughout the exam. Younger adolescents may prefer the latter option since they may feel insecure about their bodies. Also, females who require only an external genital exam can be permitted to continue wearing their underwear. For the genital exam, the provider can shift the underwear to one side allowing full visibility of the genitalia.

With new urine-based STI testing and revised Pap testing guidelines (recommending first Pap smear at age 21 years) many asymptomatic adolescent females do not require a pelvic exam. However, females presenting with genital symptoms and/or requiring their first Pap smear do need a pelvic exam performed.

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393 Adolescent Gynecology: Birth Control

Yolanda Evans

Contraception

Adolescent pregnancy is a worldwide problem with rates that vary by nation. For example, the following are pregnancy rates for 15–19 year olds per 1,000 females: Japan, 4.6; Australia, 18.4; the UK, 30.8; and the USA, 52.1. Overall, rates have been declining since the 1990s, in part due to availability of contraception. Among sexually active high school students in the USA, an estimated 46% of pregnancies occurred from failure to use contraception. Counseling teens on appropriate contraceptive options is an important step in preventing adolescent pregnancy, and should involve assessing risk and contraindications to various methods with an emphasis placed on determining the option that will be most effectively adhered to.

Barrier Methods

Barrier methods of contraception include the male condom, female condom, diaphragm, and cervical cap. They may be used in conjunction with spermicides. The male latex condom is by far the most widely used. It is readily accessible, portable in packaging, and somewhat easy to use. It is also the only method, aside from abstinence, that has been proven effective in preventing the spread of sexually transmitted infections and the human immunodeficiency virus. Diaphragms and cervical caps have never been the most popular barrier methods and must be fitted by a clinician. The female condom is difficult to use and users often complain that it comes out of place. As there is not sufficient awareness or proper training in the use of the female condom, it is not used consistently by adolescent women. Use of all barrier methods must be anticipated and planned; during adolescence, having forethought about actions, especially during sexual encounters is a difficult developmental task.

Combined Oral Contraceptive Pills

The combined oral contraceptive pill (OCP) is the most commonly used method of contraception among adolescents. It is a well accepted and safe method of contraception for teens. All combined pills in the USA contain ethinyl estradiol and a progestin. The mechanism of action is inhibition of ovulation, but there are also effects on cervical mucus and the endometrium that contribute to efficacy. There are a wide range of estrogen doses and various types of progestins available, making the choice of the best pill somewhat of a challenge. Many practitioners chose pill preferences based on comfort and familiarity with a particular formulation. The major disadvantage of the pill is that it must be taken daily and around the same time to have maximum benefit. All combined OCPs have similar side effect profiles and benefits. The benefits include predictable, regular periods that are often associated with lighter menstrual flow and less menstrual cramping. Most also help with acne. The newer progestin, drospirenone, has antimineralcorticoid properties and has been approved to help with symptoms of premenstrual dysphoric disorder (PMDD). Common side effects of OCPs include headache, breakthrough bleeding, breast tenderness, and nausea or bloating. These typically all improve with continued use. Hypertension can also result, so blood pressure should be monitored. Contraindications are based mainly on the estrogen ingredient. They include a history of thromboembolic event or known thrombogenic mutations, migraine headache with aura (significant increased risk of stroke), and liver failure. Patients receiving contraception containing estrogen should be counseled on signs of deep vein thrombosis, including severe acute onset of chest pain, abdominal pain, and lower extremity pain without a history of trauma.

Combined OCP packing typically consists of 21 days of hormone containing pills and 7 days of placebo or spacer pills. During the 7 days of placebo, a menstrual

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period is expected. Continuous, or extended cycling consisting of taking 84 hormone containing pills, then seven spacer pills is often used and has been shown to have similar efficacy and compliance. If patients desire shorter menstrual periods or have estrogen withdrawal headache, regimens consisting of taking 24 hormone containing pills with four spacer pills can also be used.

Other Combined Hormonal Methods

Other common combined estrogen and progestin containing methods include the transdermal patch and the intravaginal ring. Both methods have the same mechanism of action, contraindications, and side effect profiles as combined OCPs.

The transdermal patch is applied for 1 week for 3 consecutive weeks, followed by a patch-free week during which withdrawal bleeding occurs. It should not be applied to the breasts. Unlike oral contraceptive pills and the ring, it is not recommended for continuous use. Compared to 30 μg estrogen containing OCPs, the patch is associated with a 60% increased estrogen exposure over the course of a month. This may translate to increased side effects, but there is not clear evidence that it increases venous thromboemboli. In women >90 kg, there have been greater incidences of unplanned pregnancy, even with consistent use of the patch when compared to combined oral contraceptive pills, so the patch is not recommended for morbidly obese patients.

The intravaginal ring is flexible and easy to insert. It is used for 3 weeks, and then removed for 1 week of withdrawal bleeding. The majority of women find it easy to use and partners typically do not feel the ring during intercourse. To place the device, patients should be instructed to hold it between the thumb and forefinger, than place it into the vagina as far as possible. If it is uncomfortable, the device may not have been placed far enough. Providers may offer to place the ring in the office for the first insertion. The intravaginal ring does not need to be fitted. It rests around the cervix and is held in place by the pelvic muscles. To remove the device, patients should use the forefinger to hook around the ring and gently remove it. Placement and removal is similar to use of tampons that do not have applicators. Placement and removal of the ring from the vagina may not be acceptable to some adolescents; however, adherence is made easier because it is only changed once per month. Adverse events include foreign body sensation (it may not be placed far enough into the vagina), expulsion, and sensation of the device by the sexual partner. The ring can be used for continuous use in a similar regimen as combined OCPs, usually with four menstrual cycles per year.

Progestin-Only Methods

Progestin-only methods are often options that are used if there is a contraindication to estrogen. The mechanism of action is thinning of the endometrial lining and thickening of cervical mucus. The higher dose used in the intramuscular injection also inhibits ovulation.

The progestin-only pill can have similar efficacy as the combined OCP, but it has a shorter half-life and must be taken daily and at the same time (within 3 hours). Irregular bleeding can occur during the first few months of use. The need for very regular timing of this pill makes it a less optimal choice for teens.

Depot medroxyprogesterone is an intramuscular injection administered every 12 weeks. Non-daily use is a benefit, so compliance is facilitated, but receiving an injection can be a deterrent. Bleeding can be irregular, especially with initiation, but often is lighter than the usual menstrual flow. It is associated with a high rate of amenorrhea (30–50% after 1 year of use) and is often used to control menses. Adverse effects include significant weight gain, decreased bone mineral density (BMD), and a delayed return to fertility. Weight gain is caused because the high dose of progestin stimulates appetite. Patients should be counseled on this side effect and appropriate diet and exercise. The decrease in BMD is related to ongoing use. The rate of loss is progressive for the first 18–24 months, than seems to plateau and levels of BMD are regained after the injections are stopped. Pregnancy rates at 1 year after stopping injections are the same as control populations, but there can be a delay in ovulation of up to 10 months.

The subdermal implant containing etonogestrel is a single rod that is placed along the biceps muscle. It provides contraception for 3 years, but can be associated with unpredictable irregular bleeding for the duration of time it is in place. which may be unacceptable to some patients. It does not cause significant weight gain or decreased BMD.

Emergency Contraception

Emergency contraception is a nonabortifacient hormonal medication that can be used up to 5 days after unprotected

intercourse. It is most effective if used within 72 hour. The most efficient method consists of levonorgestrel 1.5 mg that can be divided into two doses taken 12 hour apart or all at once. Emergency contraception is available in most industrialized countries and widely available throughout Asia and Africa. US. federal law has recently been changed so that people 17 years of age or older can purchase emergency contraception from a pharmacy without a prescription; however, providers can prescribe it to any sexually active individual. Teens should be counseled on the availability of emergency contraception, when discussing reproductive options.

Intrauterine Devices

Intrauterine devices (IUDs) have the distinct advantage of being completely reversible, highly effective, and have no need for regular administration. Adolescent patients should be counseled on their use as an option for contraception.

The levonorgestrel-releasing intrauterine system provides contraception for up to 5 years. Overall, it is as effective as tubal ligation in preventing pregnancy, but is reversible and not associated with a significant delay in fertility. It is safe to place in nulliparous patients, those with a contraindication to estrogen, and is not associated with increased rates of pelvic inflammatory disease. Due to the local release of progestin, many women have lighter menstrual periods and some have amenorrhea. Hormonal side effects include headache, acne, or breast tenderness. All IUDs should be placed by an experienced clinician due to the risk of uterine puncture and infection during placement. Expulsion can occur, but is rare.

The copper IUD offers a nonhormonal long-term option. It primarily acts as a spermicide (copper ions inhibit sperm motility and activation). It is effective for 10 years. Women may have heavier menses with more cramping, but hemoglobin levels are maintained and many do not notice significant changes in their menses.

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394 Adolescent Gynecology: Menstrual Irregularities

Ann Giesel

Case: C.N., a 17-year old with primary amenorrhea with pubertal development beginning at age 11 years. Breasts are small, Tanner stage 4; genital exam shows pubic hair Tanner stage 5 with clitoromegaly. Laboratory evaluation shows negative pregnancy test, 17-hydroxy-progesterone is elevated at baseline and after cortrosyn-stimulation testing, and testosterone is elevated. Patient is diagnosed with late-onset congenital adrenal hyperplasia and referred to an endocrinologist for treatment recommendations.

Normal Menstruation

Irregular or heavy menstrual bleeding is a common complaint for adolescents. Knowledge of the normal range of flow is helpful in determining the cause of the menstrual irregularities. The mean interval of the menstrual cycle in adolescents is 28 days, ±7 days, with an average duration of 3–7 days. Median blood loss is 30–40 mL/month, with an upper limit of 60–80 mL. It is difficult to determine the amount of blood loss by teens' report and obtaining a hematocrit is important in assessing the amount of blood loss. *Oligomenorrhea* is infrequent periods, with intervals greater than 45 days. *Menorrhagia* is prolonged (greater than 7 days) or excessive uterine bleeding (greater than 80 mL) with a regular interval. *Metrorrhagia* is irregular menses with frequent intervals, and variable amount. *Amenorrhea* is absence of menses. *Menometrorrhagia* is prolonged uterine bleeding, with irregular intervals. *Polymenorrhea* is uterine bleeding at regular intervals of less than 21 days. *Dysfunctional uterine bleeding* is abnormal uterine bleeding unrelated to an anatomic cause.

Amenorrhea

Primary amenorrhea is defined as the absence of menarche by 14 years of age without secondary sexual characteristics, or the absence of menarche by 16 years of age in the presence of secondary sexual characteristics. *Secondary amenorrhea* is absence of menses for 3 months or more after having achieved menarche. There is some overlap between the etiology of primary and secondary amenorrhea. Primary amenorrhea with no pubertal development and uterus and vagina present may be due to genetic causes such as Turner syndrome (45 XO) or pure gonadal dysgenesis (46, XX), or isolated pituitary gonadotropin deficiency, hypothalamic failure with inadequate GnRH, constitutional delay of puberty, or premature ovarian failure, which may also be secondary to oophoritis (viral or autoimmune), or post therapy for cancer. Primary amenorrhea with breast development, but no uterus present may be due to androgen insensitivity syndrome (AIS) or Mullerian agenesis. Forty percent of those with Mullerian agenesis have associated renal anomalies. Rarely, a young woman with no breast development and no uterus may have an enzyme deficiency, or agonadism. When pubertal development is present with normal uterus and vagina, the cause may be pregnancy, hypothalamic, pituitary, ovarian, imperforate hymen, transverse vaginal septum, or vaginal agenesis. See *Table 394.1*.

Secondary amenorrhea may be caused by pregnancy, stress, exercise, weight loss or gain, eating disorders, systemic illness, drugs, partial gonadal dysgenesis or hormonal causes, such as polycystic ovarian syndrome, ovarian failure, prolactinoma, thyroid disease, adrenal or ovarian tumor.

In the evaluation of amenorrhea, it is important to take a careful history, including sexual history, history of illness, stressors, dietary history, exercise, drugs, and family history. Physical exam should include height, weight, blood pressure, Tanner staging, evaluation of signs of hyperandrogen including hirsutism, acne, clitoromegaly, and acanthosis nigricans. Consider pelvic exam or pelvic ultrasound, possibly rectal bimanual exam. The laboratory evaluation for secondary amenorrhea should include a pregnancy test, thyroid-stimulating hormone, free thyroxine, prolactin, luteinizing hormone, and follicle-stimulating hormone. Consider complete blood count, sedimentation rate, urinalysis, and androgens, including free and total testosterone, DHEAS, 17 hydroxy-progesterone as dictated by the history and physical examination. Karyotype, central nervous system imaging, and further evaluation for possible chronic illness may be done as indicated. The workup may proceed in a stepwise fashion, after initially ruling out pregnancy and

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Table 394.1
Etiology of primary amenorrhea

	No pubertal development	Some or normal pubertal development
Absent uterus and vagina	Enzyme deficiency agonadism	Androgen insensitivity syndrome (AIS) or Mullerian agenesis
Present uterus and vagina	Turner syndrome (45 XO), pure gonadal dysgenesis (46, XX) Isolated pituitary gonadotropin deficiency hypothalamic failure with inadequate GnRH constitutional delay of puberty premature ovarian failure	Pregnancy, low weight, weight loss, anorexia, hypothalamic, stress, pituitary, ovarian, CNS tumor, imperforate hymen, transverse vaginal septum, or vaginal agenesis

reproductive tract obstruction, which may be a gynecologic emergency.

Treatment depends on the underlying cause of the amenorrhea. In low estrogen states, it is important to support bone mass with estrogen replacement, however, in girls with amenorrhea caused by anorexia nervosa, estrogen replacement has not clearly been shown to affect bone density. Calcium intake of 1,300 mg/day is recommended. If the young woman is well estrogenized, monthly periods may be induced with daily progesterone for 12–14 days every 1–3 months to prevent endometrial hyperplasia.

Oligomenorrhea

Often adolescents are concerned about irregular and infrequent menses, occurring every few months. It is normal to have irregular menses in the first 2 years after menarche. The later the menarche, the longer it may take to achieve regular menses. Hypothalamic amenorrhea associated with change in weight or exercise is common, as is polycystic ovarian syndrome (PCOS) or other androgen excess syndrome. PCOS may present with menstrual irregularity more than 2 years after menarche, acne, hirsutism, or obesity. Other signs of virilism are clitoromegaly, deepening of the voice, increased muscle mass, widening of the upper torso, and loss of breast tissue. The anovulation and noncyclic production of estrogen and progesterone leads to amenorrhea or oligomenorrhea. Treatment is aimed at the underlying cause and, in the case of PCOS, treatment with combination oral contraceptive pills to decrease the risk for endometrial cancer. For those young women with hypothalamic hypogonadism, support of bone density acquisition is important, via improved nutrition or estrogen replacement.

Dysfunctional Uterine Bleeding

Dysfunctional uterine bleeding is defined as abnormal endometrial bleeding in the absence of structural pelvic pathology and usually is associated with anovulation, often due to immaturity of the hypothalamic–pituitary–ovarian axis. It is a diagnosis of exclusion and the differential diagnosis is extensive, including pregnancy and complications, trauma, coagulation disorders, benign and malignant neoplasms, genital tract infections, endocrinopathies, exogenous medications, and chronic systemic disease. Coagulation disorders include thrombocytopenia, von Willlebrand's disease, leukemia, or factor deficiencies.

Endocrinopathies include polycystic ovarian syndrome, hyperprolactinemia, hypothyroidism, or hyperthyroidism.

In obtaining the history for evaluation of the patient with heavy and/or frequent bleeding, it is important to note the timing of menarche, the menstrual pattern, the presence or absence of cramping and to take a careful sexual history. Inquire about nosebleeds, easy bruisability, or excessive bleeding with previous surgical procedures. Physical exam should include height, weight, vital signs, Tanner staging, thyroid gland examination, and evaluation of signs of hyperandrogen including hirsutism, acne, clitoromegaly, and acanthosis nigricans. Consider pelvic exam or pelvic ultrasound, possibly rectal bimanual exam. The laboratory evaluation should include a pregnancy test, complete blood count with platelet count, testing for Chlamydia and gonorrhea, thyroid function tests, prolactin, and coagulation studies. Consider luteinizing hormone, follicle-stimulating hormone, and androgens as indicated by history and exam. Type and cross if severe bleeding or significant anemia is present.

For treatment of mild dysfunctional bleeding, which may present with irregular bleeding and a hemoglobin greater than 12 g/dL, reassurance is indicated. Nonsteroidal anti-inflammatory drugs (NSAIDS) will decrease blood loss and help with symptoms of dysmenorrhea as well. Advise patient to keep a menstrual calendar, supplement with iron as necessary, and reevaluate periodically. Hormonal therapy may be considered.

For treatment of moderate dysfunctional bleeding, which presents with irregular, prolonged, and heavy bleeding with a hemoglobin of 10–12 g/dL, cyclic progestins

that stabilize the endometrium, or combination oral contraceptive pills, are indicated in addition to the above treatment for mild bleeding.

For treatment of severe dysfunctional uterine bleeding, with irregular, prolonged, and heavy bleeding, with a hemoglobin less than 10 g/dL, if the patient is not actively bleeding, combination oral contraceptive pills, iron supplementation, and close monitoring is indicated. If the patient is actively bleeding, hospitalize with preparation to transfuse if necessary. It is important to evaluate for a possible coagulation defect when the hemoglobin has dropped to this degree. Consider instituting hormonal therapy with conjugated estrogens intravenously along with progestins, or combination oral contraceptive pills given by mouth every 6 h, and then taper. Bleeding should stop within 24 h and if not, consider the need for surgical treatment with dilatation and curettage.

Continue oral contraceptive pills for at least 6–12 months, and reevaluate to see if continued treatment is desired for ongoing menstrual control or for contraception.

Dysmenorrhea

Dysmenorrhea occurs at some time in two-thirds of menstruating girls. Ten percent are incapacitated, and it is the leading cause of short-term school absenteeism in teens. Primary dysmenorrhea occurs 6–12 months after menarche, and the duration of pain is usually 48–72 h. Release of prostaglandins has been associated with the symptoms of dysmenorrhea including pelvic cramping, nausea or vomiting, fatigue, nervousness, dizziness, diarrhea, back pain, and headache. Secondary dysmenorrhea may be caused by endometriosis, pelvic inflammatory disease, adenomyosis, or uterine polyps or myomas. Recommended treatment of primary dysmenorrhea is with prostaglandin synthetase inhibitors (nonsteroidal anti-inflammatory drugs), or with oral contraceptive pills. Treatment of secondary dysmenorrhea is directed at the underlying cause.

Premenstrual Syndrome/Premenstrual Dysphoric Disorder

Premenstrual syndrome (PMS) is a recurrent luteal phase condition characterized by physical, psychological, and behavioral changes of sufficient severity to result in deterioration of interpersonal relationships and normal activity. Premenstrual dysphoric disorder (PMDD) is considered a severe form of PMS. Symptoms of PMS have been reported to affect as many as 90% of women of reproductive age sometime during their lives. Nearly 20% of women experience PMS; approximately 10% are affected severely with PMDD.

Healthy diet and exercise are recommended as they help to reduce stress as well.

Nonsteroidal anti-inflammatory drugs (NSAIDS) are useful for managing the general aches, pains, and dysmenorrhea associated with PMS.

Combination oral contraceptive agents also may help in the treatment of PMS, decreasing both mood and somatic symptoms.

Selective serotonin reuptake inhibitors (SSRIs) are the first-line drugs for severe emotional symptoms.

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395 Adolescent Gynecology: Sexually Transmitted Infections

Taraneh Shafii · Gale R. Burstein

Adolescents and young adults have the highest sexually transmitted infection (STI) rates, with half of the almost 19 million STI cases in the USA diagnosed annually occurring in 15–24-year-olds. Among females, the highest reported gonorrhea and chlamydia rates are among 15–19-year-olds followed by 20–24-year-olds. Recent comparative international statistics are difficult to access. However, an extensive review of 17 developed countries using 1994–1996 data for 15–19-year-olds reported that Belgium, Sweden, and Switzerland had the lowest rates of gonorrhea with the Russian Federation and the USA having the highest. The lowest rates of chlamydia were found in Belgium, France, and Switzerland as compared to the highest rates in the USA and Denmark. Chlamydia rates for the Russian Federation were unavailable. Common to almost all countries was that adolescents accounted for 20–33% of all cases reported. These data do not account for differences between countries in reports and screening programs.

HIV/AIDS is now the seventh leading cause of US mortality in persons <25 years and accounts for 13% of all cases diagnosed annually; however, these numbers do not compare to the significant burden of HIV in Sub-Saharan Africa. Data from national adolescent surveys of Burkina Faso, Ghana, Malawi, and Uganda found that in 2006, 40% of new HIV infections were in 15–24-year-olds.

Adolescents are at High Risk for Acquiring STIs

Factors that increase adolescents' STI risk can be categorized as (1) biological susceptibility; (2) psychosocial development; (3) health-care utilization and compliance; and (4) confidentiality, ethical and legal issues. These four factors contribute to adolescent health risk and influence high-risk behavior in the setting of evolving sexuality and sexual behavior as youth progress through puberty.

Biological Factors

Due to developing physiologic characteristics, adolescent females are more vulnerable to STIs than adult females. The immature and incompletely estrogenized cervix is characterized by persistence of columnar epithelium extending to the ectocervix, referred to as cervical ectopy (*Fig. 395.1*). Columnar epithelium is more susceptible to invasion by pathogens, such as *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, than squamous epithelium, which covers the vagina and the mature adult female cervix. Adolescent females tend to have thinner cervical mucus than adult females, thereby presenting a weaker barrier to pathogens infecting the cervix and upper reproductive tract.

Lower estrogen levels present in early adolescence results in thinner genital tissue. In addition, insufficient sexual arousal results in inadequate vaginal lubrication prior to penetration. This combination places adolescent females at increased risk for trauma and/or irritation to the female genital tissue creating potential portals of entry for pathogens.

Serial Monogamy

An interesting societal trend contributing to adolescent sexual risk is the adolescent relationship pattern, described as *serial monogamy*. Adolescents have relatively short-duration relationships (e.g., 2 weeks or 2 months) with an individual partner, and change partners more frequently. So while adolescents may be monogamous in each relationship, which they may interpret as a lower risk, as they accrue an increased number of partners over time, they accrue significant STI-exposure risk. To assess true STI-exposure risk and obtain a more valid assessment of sexual risk behaviors, providers should inquire about the number of partners in the past 3, 6, and 12 months.

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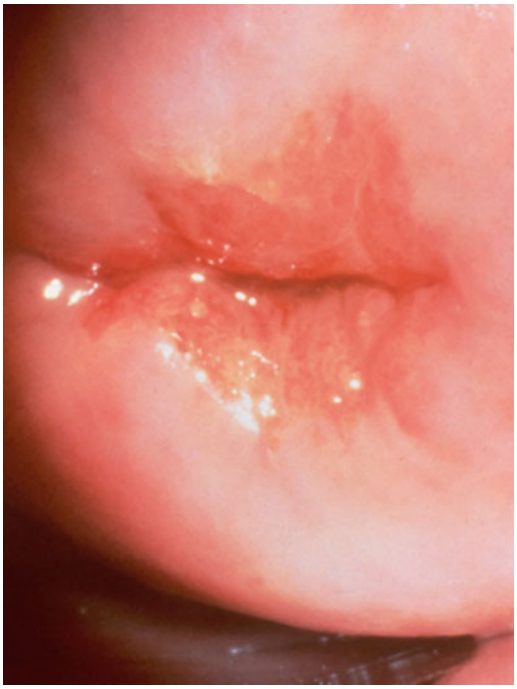

Figure 395.1
Cervical ectopy (Source: Seattle STD/HIV Prevention Training Center at the University of Washington/Claire E. Stevens)

Trend for Earlier Puberty, Earlier Sexual Debut, and Delayed Marriage

In the USA, the median age of menarche is approximately 12.4 years (12.1 years in Black females); the median age of first sexual intercourse is 16.5 years and; the average age of marriage is the late 20s (an increase in approximately 5–8 years from the 1950s). Therefore, the average number of years when females are hormonally primed for sexual activity and not married has increased significantly over the past 50 years resulting in the potential for a higher number of lifetime sexual partners and increased likelihood for STI contact.

The Adolescent Female with Vaginal Discharge

Vaginosis, vaginitis, and cervicitis may present as a complaint of vaginal discharge changes. Infectious etiologies of vaginitis include *Candida albicans* (not considered an STI) and *Trichomonas vaginalis*. Bacterial vaginosis is predominantly caused by *Gardnerella vaginalis*. *Chlamydia trachomatis*, *Neisseria gonorrhea*, and *Mycoplasma genitalia* cause cervicitis presenting as vaginal discharge. If cervicitis remains untreated, it can progress to pelvic inflammatory disease (PID) and the possibility of future tubal infertility and ectopic pregnancy. PID is a clinical diagnosis, and in the absence of other diagnoses, can be confirmed by uterine, cervical, or adnexal tenderness with immediate treatment recommended.

Laboratory Tests to Evaluate Vaginal Discharge

CDC recommends using a nucleic acid amplification test (NAAT) for diagnosing genital chlamydia and gonorrhea infections. NAATs are the most sensitive chlamydia tests available. In addition to testing endocervical and urethral specimens, NAATs allow for noninvasive STI testing via the urine and self-collected vaginal swabs. Although not FDA approved, many clinical labs perform NAATs on rectal and oropharyngeal specimens. Microscopy of vaginal discharge identifies bacterial vaginosis, Candidiasis, and Trichomoniasis. More sensitive vaginitis tests include the OSOM Trichomonas Rapid Test and OSOM BV BLUE Test (Genzyme Diagnostics, Cambridge, Massachusetts), point of care tests providing results in approximately 10 min and the Affirm™ VP III (Becton Dickenson, San Jose, California), a nucleic acid probe test that evaluates for *T. vaginalis*, *G. vaginalis*, and *C. albicans*, providing results in 45 min. Culture is the most sensitive commercially available trichomonas test. There are currently no commercially available *M. genitalia* tests.

Adolescent Female with Genital Lesions

Infectious genital lesions in adolescents are most commonly caused by human papillomavirus (HPV) and herpes simplex virus (HSV). One in four to five Americans has genital herpes. In a study of American female college students, HPV infection incidence was 37% within 1 year of first intercourse. By adulthood, it is estimated that 80% of women will have been infected with HPV. An international prevalence study of over 15,000 women with normal cervical cytology from 11 countries reported the age-standardized prevalence for HPV ranged from a low of less than 2% in Vietnam to a high of more than 25% in Nigeria. Although syphilis rates are not as high in adolescents as in older age groups, any adolescent presenting with a genital lesion should be tested. Other common

etiologies of genital lesions include folliculitis from pubic hair removal, scabies (*Sarcoptes scabiei*), and molluscum contagiosum.

Laboratory Tests to Evaluate Genital Lesions

There is no commercially available genital wart screening test. Revised Pap testing guidelines recommend performing the first Pap test at age 21 years, regardless of age at coitarche (Cervical cytology screening (2009)). Herpes culture of genital lesions remains the standard HSV test. HSV DNA polymerase chain reaction (PCR) assays are more sensitive than culture and are increasingly used in many settings. Since herpes viral shedding is intermittent, providers cannot assume that a negative HSV culture or PCR tests confirm absence of HSV. The utility of herpes serology screening in young people has yet to be determined.

Screening Guidelines

Current adolescent primary care guidelines recommend yearly chlamydia screening of ALL sexually active females and gonorrhea screening adolescent females at risk. Syphilis screening should be based on local epidemiology. Currently, CDC recommends HIV screening for all Americans 13–64 years at least once and more often as indicated by sexual risk behaviors. Since reinfection is common, all adolescents testing positive for chlamydia or gonorrhea, and all females testing positive for trichomonas should return in 3 months for a test of reinfection.

Treatment

In all 50 states, adolescents may consent for their own, confidential sexual health care. However, states vary in minimum age to consent for STIs-related health care. Providers should check their state law for age-specific guidelines. CDC-recommended adolescent STI management does not vary from that of adults, except with the caveat of ensuring completed treatment and can be found in detail at www.cdc.gov/std/treatment. Since adolescents are notorious for poor compliance, single dose, directly observed therapy is recommended if available.

Uncomplicated chlamydia infection is treated with a single dose of Azithromycin 1 g. In light of gonorrhea resistance to fluoroquinolones and decreasing susceptibility to some cephalosporins, WHO and 2010 CDC guidelines recommend dual therapy with either a single dose of Ceftriaxone 250 mg IM if possible, or an oral cephalosporin of Cefixime 400 mg orally PLUS azithromycin 1 gram orally or doxycycline 100 mg twice daily for 7 days. Dual therapy for gonoccocal infections is recommended at all anatomic sites due to concerns about the possible emergence of cephalosporin resistance gonorrhea. PID may be treated as an outpatient with Ceftriaxone 250 mg IM in a single dose or another parenteral third-generation cephalosporin plus Doxycycline 100 mg orally twice a day for 14 days with or without Metronidazole 500 mg orally twice a day for 14 days in an adolescent who is nontoxic appearing, not vomiting, and reliable to return for follow-up care in 48 h and after completion of therapy.

Adolescents with laboratory-confirmed HSV infection may be offered suppressive therapy with Acyclovir 400 mg orally twice daily or Valacyclovir 500 mg or 1 gram daily. Daily suppressive therapy has been shown to decrease the number of outbreaks, severity, and duration of lesions in the index patient and also decreases their asymptomatic viral shedding, thus, decreasing the likelihood of infecting their sexual partner.

Management of Sex Partners

Providers should verify that all STI-positive patients' sex partners within the last 60 days have been tested and treated (or last partner if it has been longer than 60 days since last sex). One strategy to increase partner treatment and decrease reinfection rates of chlamydia, gonorrhea or trichomonas is expedited partner therapy (EPT): treating a partner of an STI-infected individual without requiring a prior clinical examination. EPT is usually practiced by patient-delivered partner therapy (PDPT). With PDPT, the provider gives the index patient medications or a prescription for medications to deliver to their partner(s). The medication is usually accompanied by a brochure describing the infection, the medication, and the need to see a clinician for a complete STI evaluation. As of November 2010, EPT is legally permissible in 27 states and 1 city for providers caring for heterosexual individuals infected with gonorrhea or chlamydia. For more information on EPT, including legal status, go to www.cdc.gov/std/ept.

Prevention of STIs

Abstinence from sexual contact is the only reliable means of avoiding infection with an STI. In lieu of abstinence, condoms remain the *best* protector against STI acquisition from an infected partner. In addition, male circumcision

has proven to be a significant prevention method against the transmission of HIV/STIs. Other preventive measures for adolescents include limiting their number of sexual partners and getting themselves and their partners tested before they initiate sexual contact and with each partner change.

List of Web Sites for Providers

The California STD/HIV Prevention Training Center: www.stdhivtraining.org/educ/training_module/tools.html

Centers for Disease Control and Prevention: www.cdc.gov/std/treatment

The Center for Young Women's Health (CYWH): http://www.youngwomenshealth.org/

The Guttmacher Institute: http://www.guttmacher.org/

Kaiser Family Foundation web site at: http://www.kff.org/

List of Web Sites for Adolescent Patients

The Center for Young Women's Health (CYWH): http://www.youngwomenshealth.org/

Planned Parenthood Teens: http://www.teenwire.com/

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396 Approach to the Adolescent Male and Reproductive Health Disorders

David J. Breland

Male health has become an emerging area of interest in an effort to improve the health status and quality of health care for men. Adolescent male health is particularly relevant, since many antecedents of adult illness originate in adolescence, such as alcohol and tobacco use. Many policies and programs have chiefly addressed young women's reproductive health needs and largely overlooked male health needs. Currently, it is recognized that adolescent male health is a vital element for all adolescent care. Data looking at health care utilization by adolescent males have found that, overall, the percentage of total healthcare visits by males were significantly less than that of females. In addition, there are age differences in the use of health care services. Older adolescent (16–20 years) males, as compared to young adolescent males, (11–15 years) show decreasing trends in hospital-based outpatient visits and increasing trends in emergency department visits. Adolescent female use of health care services is promoted by reproductive issues such as menarche, contraceptive needs, sexually transmitted infections (STIs), and pregnancy management. These health services are not readily available to adolescent and young adult males. There are fewer opportunities for preventive health messages for male adolescents. Boys often hold a more traditional "masculine" attitude that put them at increased risk for engaging in high risk behaviors such as having unprotected sex and illicit substance use. Nevertheless, male adolescents are often concerned about the same health issues as their female counterparts and are more likely to engage in health-compromising behaviors (i.e., substance abuse) and suffer serious health consequences (i.e., suicide completion). The clinician has to connect with them in a safe and unthreatening manner that will promote open and honest conversations about their fears and doubts.

As a clinician, it is important to realize that most male patients may not be upfront with any concerns they may have about their health. Boys will often have questions/concerns about growth/development and, therefore, it is an essential topic to raise. The health provider can introduce this topic by asking if he has any concerns regarding his athletic performance, strength, or endurance. These questions could lead the discussion of any feelings he may have about his changing body. Examples of such questions include, "Do you have any questions or worries about your height or physical appearance?" or "Are there any concerns about the development of your genitalia?" In addition, it is important to know that some male patients prefer a female provider to do the genital exam. Chaperones of the opposite sex of the health care professional should be utilized if the provider or the patient feels uncomfortable. Another important point is to normalize the genital exam and be comfortable performing this exam. One suggestion is to inform the young man before he changes for his physical exam that you will perform a head to toe examination that includes screening for genital abnormalities such as hernias and cancer. In addition, the provider should explain these conditions and why they are important to discover.

Pubertal Gynecomastia

Definition

Breast development in the pubertal adolescent male.

Etiology

It is thought to be the result of an imbalance of estrogen stimulatory effects relative to androgen inhibitory effects at the breast tissue level.

Epidemiology

Pubertal gyneconastia is thought to affect up to 60–70% of adolescent boys, beginning in middle adolescence. It can be unilateral or bilateral. Twenty five percent of cases may persist for $\geq$2 years and is called persistent pubertal gynecomastia.

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Pathogenesis

It is characterized by ductal proliferation and formation of vascular connective tissue.

Clinical Manifestations

Predominantly, it is mild proliferation (less than 3–4 cm) of breast tissue under the areola. Many boys can find breast development embarrassing and wonder if something is wrong with them. Onset of gynecomastia correlates with pubertal development (*Table 396.1*). This condition will spontaneously resolve in 1–2 years without intervention.

Diagnosis

Neither laboratory nor radiologic studies are recommended unless the patient is prepubertal, undervirilized, has an eccentric mass or rapid progression of mass, or a testicular mass or persistence beyond the 12–18 month observation period. Initial laboratory tests are outlined in *Fig. 396.1*. Ultrasound is usually not indicated.

Differential Diagnosis

Pseudogynecomastia is seen in obese boys secondary to increased adipose tissue. The differential diagnosis also includes: lipomas, hemangiomas, neurofibromas, lymphangiomas, dermoid cyst, and breast carcinoma. Rarely, gynecomastia can be related to underlying conditions such as testicular cancer, Klinefelter's syndrome, chronic disease, medication (antipsychotic), or drug use (anabolic steroids or heavy marijuana use).

Treatment

Often, no treatment other than psychosocial support is needed. Antiestrogens, nonaromatizable androgens (including dihydrotestosterone), and first generation aromatase inhibitors have been used to treat gynecomastia with variable success. If it persists beyond 1 year, then chronic fibrous changes may occur. In persistent cases where there is a significant psychosocial problem, surgical reduction of the breast tissue is done. Options include open excision, conventional liposuction, or a combination of both. Caution is advised if performed before the completion of pubertal development to avoid the risk of recurrence.

Table 396.1
Genital stage at onset of Gynecomastia (Adapted from Neinsteins et al. 2008)

Genital stage 1–20%
Genital stage 2–50%
Genital stage 3–20%
Genital stage 4–10%

Genital Development/Circumcision

Adolescent males are often concerned about whether their penis size or shape is normal. They often have an unfounded perception of normal or even desirable penis size. Mean flaccid length of the penis is 8.2–9.7 cm (range 5.0–15.5 cm). The mean erect length is 15.1 cm (range 11.4–19.0 cm). No predictable relationship exists between the size of the flaccid penis and erect length. It is important to emphasize that men come in all shapes and sizes, and there is a relative unimportance of penis size for sexual function and pleasure. The young man should be warned against using any chemicals or mechanical devices that claim to change penis size. In addition to concerns regarding size, there may be questions/concerns regarding circumcision and its protection against HIV and other STIs. Circumcision has been found to provide partial protection for men against acquiring HIV infection through heterosexual sex. Countries in sub-Saharan Africa have developed prevention strategies involving male circumcision. Benefits have been found in developing countries, but whether the same benefits exist in develop countries is controversial. One study in the United States showed reduced prevalence in HIV risk in circumcised men. It is important for the clinician to know the risk and benefits of circumcision, in order to give comprehensive reproductive health care to the adolescent male.

Pearly Pink Papules

Definition

Pearly pink papules are a misnomer in that they are often pearly but can be flesh colored.

Clinical Manifestations

They are small papules, 1–3 mm that are found along the corona of the penis.

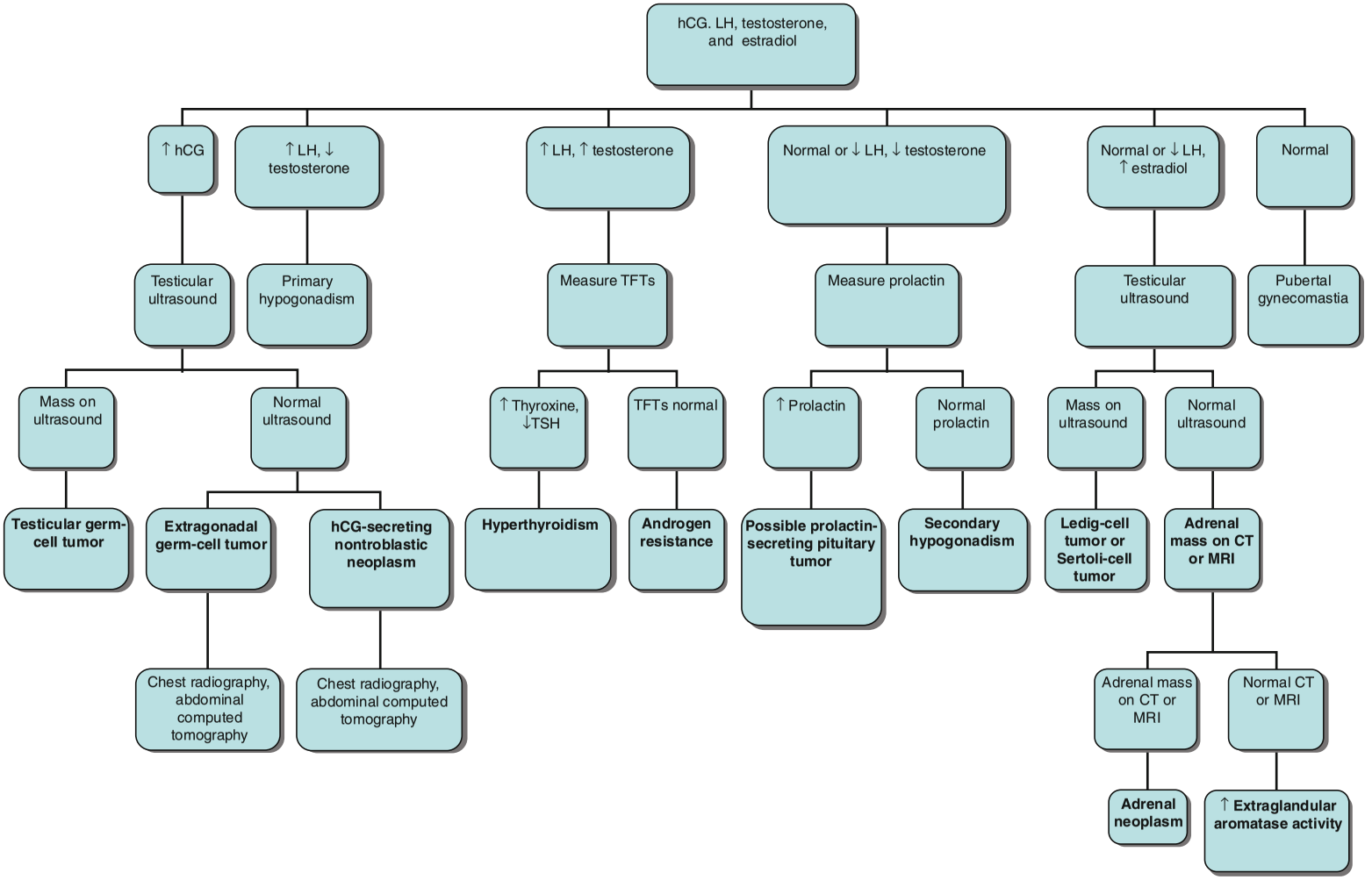

Figure 396.1

Serum hormone interpretation and recommendation for further evaluation of an adolescent male with gynecomastia. Diagnoses are presented in bold face type. CT, computer tomography; hCG, human chorionic gonadotropin; LH, luteinizing hormone; TFTs, thyroid function test; TSH, thyroid stimulating hormone (Adapted from Braunstein 2007)

Epidemiology

They are found in 15–20% of adolescents.

Treatment

They require no treatment, just reassurance.

Phimosis and Paraphimosis

Definition

Phimosis is the constriction of the prepuce orifice so as to prevent the foreskin from being withdrawn to reveal the glans penis.

Etiology

Commonly occurs when the foreskin experiences small amounts of inflammation such as normal erections, or from poor hygiene.

Treatment

Treatment can be conservative, such as Vitamin E creams and topical steroids to soften the phimotic ring. Significant phimotic rings will need definitive treatment, such as ring excision or conventional circumcision.

Definition

Paraphimosis occurs when the foreskin is tight but retractile and is pulled back but cannot be repositioned over the glans penis.

Etiology

Often paraphimosis is iatrogenic in the setting of a Foley catheter placed in an uncircumcised male patient.

Clinical Manifestations

Patients present with a tender, swollen penis with a large ventral penile skin bulge.

Treatment

This is an emergency and needs prompt attention. Urgent reduction is warranted, and usually a subsequent circumcision.

Prognosis

If untreated, edema causes constriction of the lymphatic and venous flow, leading to distal penile ischemia.

Testicular Torsion

Etiology

An exact etiology of testicular torsion is not known, but there is an anatomical abnormality that has been described that can predispose a patient to torsion of the testis.

Epidemiology

Incidence peaks at 15–16 years of age and 2/3 of cases occur between 12 and 18 years.

Pathogenesis

The abnormality that is implicated is called the "bell clapper" deformity. In this deformity, the tunica vaginalis is completely surrounding the testicle, including the posterior aspect of the testis. As a result, the testicle hangs within the scrotum by its vascular pedicle, which is analogous to a pendulum of a bell.

Clinical Manifestations

Clinicians must have a high index of suspicion for this condition, secondary to a short window of opportunity to salvage the testicle. Torsion commonly presents with an abrupt onset of scrotal pain. Associated nausea, vomiting, fever, and abdominal pain are also present. Often on physical exam, the scrotum is swollen, tender, and erythematous. The cremasteric reflex is almost always absent.

Diagnosis

The diagnosis can be made by physical examination and/or with the use of Doppler ultrasound. Doppler

ultrasound has a sensitivity of 89–100% and a specificity of 77–100%. Unfortunately, time is not on the side of the clinician. Viability of the testes declines to 0% after 24 h.

Differential Diagnosis

The differential diagnosis includes appendage torsion, epididymitis, trauma, and orchitis.

Treatment

Torsion of the testicles (*Fig. 396.2*) represents a surgical emergency. Therefore, treatment should involve prompt surgical exploration and ultimately detorsion of the testis. There is a high incidence of retorsion of the testis and also torsion of the contralateral testis. The testis along with the contralateral testis is fixed to the scrotum (scrotal orchiopexy).

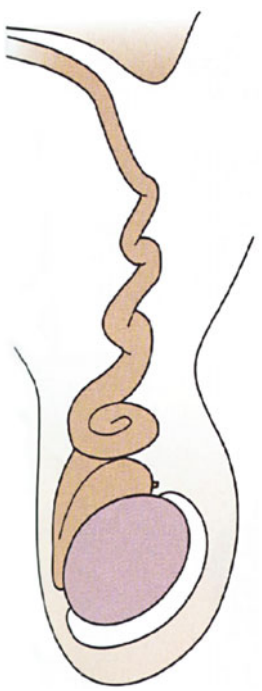

Figure 396.2
Testicular Torsion (From Zitelli and Davis 2007)

Torsion of Testicular or Epididymal Appendage

Epidemiology

Typically boys aged 7–12 years old.

Pathogenesis

The testis and the epididymis have remnants of the Wolffian and Müllerian duct system called appendages.

Clinical Manifestations

Boys present with pain, nausea, and vomiting. On palpation of the testis, there is tenderness over the superior or inferior pole of the testis with or without a palpable mass. Usually the cremasteric reflex is present. The characteristic "blue dot" sign, when present, will represent the infarcted appendage.

Diagnosis

Commonly made clinically. If torsion of the testis cannot be differentiated, then color flow Doppler examination is warranted.

Differential Diagnosis

Testicular torsion and trauma.

Treatment

Supportive treatment is indicated and includes analgesics, anti-inflammatory agents and elevation of the scrotum. If the pain persists for longer than 5 days, a consultation from a pediatric urologist is recommended.

Hernia and Hydrocele

Etiology

Two common congenital abnormalities in the inguinal canal include hernia and hydrocele.

Pathogenesis

When fluid tracks down the inguinal canal into the tunica vaginalis, it forms a communicating hydrocele. They may also occur secondary to other primary processes such as trauma, infection, testicular torsion, or neoplasm. Within the hernia sac, small intestine, omentum, bladder, or genital contents may be found.

Clinical Manifestations

Both hernias and hydroceles will present as scrotal swelling.

Diagnosis

Hydroceles are often found as an incidental finding on exam and often represent a benign mass in the scrotum. On exam, hernias are more firm and will not transilluminate, whereas hydroceles will transilluminate showing the presence of fluid. Hydroceles will often feel supple and fluid filled.

Treatment

Hernias may become incarcerated (twisting of a loop of bowl cutting off blood supply), and may need surgical repair. Hydroceles are often benign and are corrected electively, but a search for a primary cause should be performed.

Orchitis

Definitions

Orchitis or inflammation of the testis occurs in predominantly the pubertal males.

Etiology

There are multiple infectious causes of orchitis including mumps virus, coxsackievirus, echovirus, adenovirus, varicella, and tuberculosis, among other bacteria. Mumps virus is the most common cause of orchitis and usually follows parotitis by 4–8 days, but can present up to 6 weeks. If a bacterium is implicated, then it is often a consequence of a contiguous spread from an epididymitis.

Clinical Manifestations

Often associated with constitutional symptoms such as fever, nausea, lower abdominal pain, and can be both insidious and abrupt in onset.

Diagnosis

Exam may reveal unilateral or bilateral involvement and present with tenderness of the testis with edema and erythema of the adjacent skin.

Treatment

Bacterial orchitis is treated with an antibiotic in addition to supportive care. Viral orchitis is only treated symptomatically with rest and analgesics.

Prognosis

A rare but possible complication of orchitis is infertility.

Testicular Neoplasms

Epidemiology

Testicular neoplasms (TN) occur in prepubertal boys to postpubertal men. They represent 1–2% of neoplasms in men and boys. There has been increasing incidence worldwide, particularly in industrialized countries, but TN incidence varies in different geographical areas. It is highest in Scandinavia/Switzerland, intermediate in the USA, Australia and the UK, and lowest in Asia and Africa.

Etiology

Increased risk with a history of cryptorchidism.

Epidemiology/Pathology

Histologic types commonly found in adolescence are the germ cell tumors (seminoma, embryonal carcinoma, teratoma, and choriocarcinoma) and account for 95% of cases. Tumors that are of stromal origin are Leydig and Sertoli tumor cells, and can occur at any age.

Clinical Manifestations

TN present as painless scrotal masses that are of gradual onset. Pain is not a common feature, but if present may represent a hemorrhaged or necrotic tumor.

Diagnosis

On physical exam, there is usually a firm, irregular mass that will not transilluminate. They can also present as soft masses and represent cystic or necrotic areas of the neoplasm. The contralateral testis should be examined for comparison and to determine the presence of neoplasm. Once detected, a complete physical exam should be done looking for the following: gynecomastia, lymphatic or venous stasis in the genitalia or leg, prostatitis, epididymitis, and cervical or supraclavicular lymph nodes. Tumor markers can be useful tests for certain histologic types and should be obtained before orchiectomy. Human chorionic gonadotropin (hCG) is elevated in choriocarcinoma, nonseminomatous mixed germ-cell tumors, and seminoma with syncytiotrophoblasts. The α-fetoprotein (AFP) is elevated in nonseminomatous germ cell tumors, particularly yolk sac tumors and embryonal carcinoma. Note that 92% of pure seminomas produce no tumor markers. Imaging is done using either ultrasound or MRI and staging requires a chest and abdominal CT.

Differential Diagnosis

This includes orchitis, spermatocele, inguinal hernia, benign testicular cyst, and benign hydrocele. Any testicular mass is malignant until proven otherwise.

Treatment

Treatment is determined by staging and histology. It includes orchiectomy, retroperitoneal lymph node dissection, radiation, and chemotherapy.

Prognosis

The overall survival rate is greater than 95% of patients in Stage I or II.

Varicoceles/Spermatoceles

Definition

Varicoceles (*Fig. 396.3*) are defined as dilation of the pampiniform venous plexus within the scrotum.

Etiology

Is largely unknown yet there are several theories to its etiology. One theory is the presence of incompetent valves within the veins along the spermatic cord. Causing a back-up of blood and results in engorged veins. Another theory includes the "nutcracker effect." The left renal vein is compressed between the aorta and superior mesenteric artery resulting in an increase pressure that is transmitted to the left testicular vein. This theory is supported by the fact that varicoceles are present on the left side in 85–90% of cases.

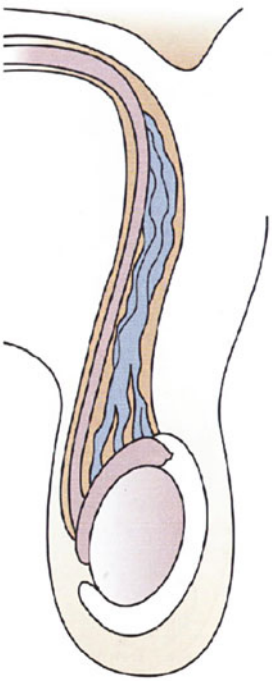

Figure 396.3
Varicocele (From Zitelli and Davis 2007)

Epidemiology

It is common in the 10–20 year age-group and has a prevalence of 15%. Most are clinically evident (85%) on the left side and 15% are bilateral. When a varicocele is found on the right, it is often associated with tumors and should be investigated.

Clinical Manifestations

Most varicoceles are asymptomatic in adolescents but can present with a dull ache after long periods of standing.

Treatment

Repair is offered to adolescents who show testicular growth arrest, abnormal semen analysis in those who have high grade varicoceles, bilateral varicoceles, and any symptomatic varicoceles.

Prognosis

There is controversy surrounding the clinical relevance of varicoceles and is related to the risk of infertility. There seems to be a time-dependent testicular growth arrest and abnormal semen analysis in adolescents.

Etiology

Spermatoceles (◉ *Fig. 396.4*) are found commonly on examination and represent an accumulation of sperm within the head of the epididymis.

Clinical Manifestations

They are soft cysts that are smooth and found on the superior pole of the testicle.

Diagnosis

A spermatocele will transilluminate on exam.

Treatment

Spermatoceles do not need treatment unless symptomatic.

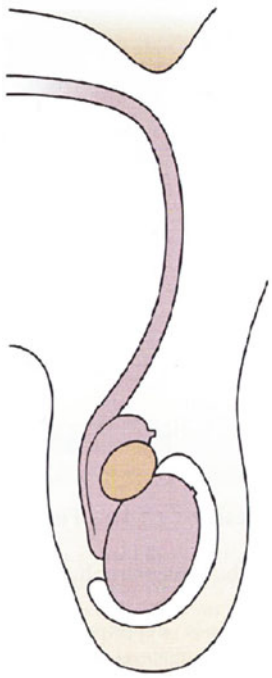

Figure 396.4
Spermatocele (From Zitelli and Davis 2007)

Epididymitis

Etiology

Epididymitis (◉ *Fig. 396.5*) is an inflammatory process of the epididymis that is commonly secondary to STIs (sexually transmitted infections) in adolescence.

Epidemiology

It is uncommon in prepubertal males and non-sexually active males without a history of genitourinary tract abnormalities.

Pathogenesis

Thought to be secondary to retrograde extension of *Chlamydia trachomatis* from the vas deferens. *Neisseria gonorrhoeae* is the second most common organism.

Clinical Manifestations

Commonly present with gradual onset of scrotal pain and swelling in addition to nausea, fever, abdominal or flank

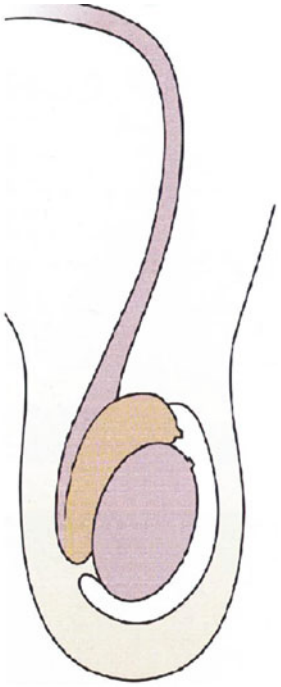

Figure 396.5
Epididymitis (From Zitelli and Davis 2007)

pain and urethral discharge. The scrotum is usually edematous and erythematous. The epididymis is often tender to palpation.

Diagnosis

A maneuver that can help distinguish epidiymitis from testicular torsion is the Prehn sign. The Prehn sign occurs when there is improvement in pain with scrotal elevation.

Treatment

The treatment includes the use of antibiotics directed at the most common etiologies (*Table 396.2*) and treatment should also be given to his sexual partners. If he fails to improve over 72 h, he must be evaluated for the possibility of an abscess.

Prognosis

Bilateral involvement has an increased risk of sterility.

Table 396.2
Treatment recommendations for epididymitis (Center for Disease Control and Prevention http://www.cdc.gov/std/Treatment/2006/updated-regimens.htm)

Ceftriaxone 250 mg IM in a single dose PLUS Doxycycline 100 mg orally twice a day for 10 days
For acute epididymitis most likely caused by enteric organisms or with negative gonococcal culture or nucleic acid amplification test
Ofloxacin 300 mg orally twice a day for 10 days OR Levofloxacin 500 mg orally once daily for 10 days

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397 Behavioral and Mental Health Issues

Henry Berman

Behavioral concerns, including such problems as depression, anxiety, and attention-deficit/hyperactivity disorder, are among the most frequent problems seen in an ambulatory practice. Most physicians feel not enough time was spent in their training to make them comfortable with diagnosing and treating these problems, but a shortage (or, in some communities, a complete absence) of child psychiatrists plus the stigma that many teens and parents attribute to "needing to see a psychiatrist" lead to the need for many primary care physicians to be able to provide effective care for these adolescents.

Is This Normal?

Often, the first step for the physician is to determine whether the problem presented by the adolescent or the parent is normal adolescent development. Conflicts over curfews, privacy, rebellion, parental expectations, and peer relationships are to be expected. Problems with sibling relationships are common, if unpleasant for parents. The switch to middle school often brings problems, either in academic performance or in peer relationships.

Parental concerns over "time-wasting" activities, including playing video games, talking and texting on cell phones, and the use of online social networks, may be more common than in the past. And there are always ongoing concerns about ignoring household responsibilities, not keeping their rooms clean, and spending "too much" time in their room. Finally, and more importantly, parental concerns about drug experimentation and sexual activity are often in the fore. This chapter is not about such normal adolescent development, but rather about how to distinguish such concerns from those disorders that need a clinical intervention.

Depression and Risk of Suicide

Ten percent or more of teens seen in primary care may be depressed at a given time, with many more than that depressed over their teen years. The teen may present with deteriorating school performance, irritability, out-of-control behavior (e.g., truancy, running away from home, and theft), the use of drugs or alcohol, excessive self-criticism, expressions of hopelessness, or withdrawal from daily activities. A useful approach to screen for depression is to use the Patient Health Questionnaire 2 (PHQ-2). It consists of the following two questions:

In the past 2 weeks, have you been bothered by:

1. Little interest or pleasure in doing things?
2. Feeling down, depressed, or hopeless?

If the answer to either is "yes," a full PHQ-9 needs to be administered. The first step is to quantify the above questions by asking whether these feelings occurred for "several days," "more than half the days," or "nearly every day," scored as 1, 2, or 3 points. The remaining questions, scored as 0 (for "not at all") or 1, 2, or 3 as above are given in *Table 397.1*.

Scoring: One of the answers to first two questions must be a "2" or more, plus answers to 5 or more of the questions in all must be a "2" or more to make a diagnosis of significant depression. In addition, functional impairment must be "somewhat difficult" or higher. A total score of 5–9 represents minimal symptoms of depression; 10–14 is consistent with mild major depression, treated with watchful waiting, therapy, or medication; 15–19 is consistent with major depression, treated with therapy or medication, and 20 or higher is considered severe major depression, treated with both therapy and medication.

Since it can take some time to arrange for a referral for therapy and for therapy to be useful, many physicians choose to start medication for moderately severe depression, using a selective serotonin reuptake inhibitor (SSRI). Fluoxetine has the strongest evidence base for effectiveness in children and adolescents; other SSRI's that have been evaluated as effective in children and adolescents are sertraline, citalopram, paroxetine, and escitalopram. In all cases, the patient should be seen as often as weekly for the first 4 weeks of treatment, and frequently during the first 3 months. After 4–6 weeks, if the improvement in the PHQ-9 form is less than 5 points, the dose of medication should be increased. In addition to medication, counseling for patient and family as well as education about depression are important elements of treatment.

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Table 397.1
The PHQ-9 form for diagnosing depression

During the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all 0	Several days 1	More than half the days 2	Nearly every day 3
1. Little interest in doing things				
2. Feeling down, depressed, or hopeless?				
3. Trouble falling or staying asleep or sleeping too much				
4. Feeling tired or having little energy				
5. Poor appetite or overeating				
6. Feeling bad about yourself – or that are a failure or have let yourself or your family down				
7. Trouble concentrating on things, such as reading the newspaper or watching television				
8. Moving or speaking so slowly that other people could have noticed. Or the opposite – being so fidgety or restless that you have been moving around a lot more than usual				
9. Thoughts you would be better off dead, or of hurting yourself in some way				
Totals				
10. If you checked off *any* problems, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?			Not difficult at all_____ Somewhat difficult____ Very difficult____ Extremely difficult_____	

A positive response of any kind to question 9 needs to be explored to assure current safety

Risks of treatment: There is evidence of an increased risk of thoughts of suicidality in adolescents treated with an SSRI (i.e., suicide ideation, preparatory acts, or suicide attempts, usually in the first few weeks of treatment). The United States Preventive Services Task Force states "conservative estimates from analyses show that treatment with antidepressants leads to a 1 percent or 2 percent absolute increase in the risk of suicidality. No suicide deaths are associated with these studies."

Another risk of antidepressant use is the risk of conversion from a unipolar depression to a *bipolar depression*. Symptoms of a bipolar disorder include, in addition to those of depression, *manic symptoms*. This includes severe changes in mood, either extremely irritable, prone to destructive outbursts, or overly silly and elated; grandiosity; increased energy; decreased need for sleep, with very little or no sleep for days without tiring; increased talking, changing topics frequently, cannot be interrupted; distractibility, with attention moving constantly from one thing to the next; hypersexuality in thoughts, feelings, behavior, or use of language; increased goal-directed activity or physical agitation; engaging in spending sprees; and excessive involvement in risky behaviors or activities.

Patients presenting with bipolar symptoms should not be started on an antidepressant, and should, if possible, be referred to a child psychiatrist for evaluation and treatment. Patients on an antidepressant who develop manic symptoms should have their SSRI discontinued, and be referred for further treatment.

Risk of suicide: Suicide is the third most common cause of death in adolescents, after unintentional accidents and homicide. A history of previous suicide attempts is the most important risk factor for subsequent suicide attempts. Approximately one-third of teens who die by suicide have made a previous attempt. Other common indicators of risk include depressive symptoms, severe anxiety, hopelessness, withdrawal, recklessness, suicidal ideation, having a family history of suicidal behavior, substance abuse, having a friend with a history of suicidal behavior, and the recent death by suicide by a family member or a close friend. Also, LGBTQ youth are at higher risk. Although many adolescents who die by suicide come from difficult family

circumstances, others grow up in supportive families. Many show problems in school or at home; others are excellent students, with many friends. The best summary statement may be "suicides are rare and unpredictable."

However, clinicians need to be alert to the possibility that teens presenting with any of the above risk factors may be contemplating suicide. A routine, confidential discussion of any previous history of self-harm, suicidal ideation, or present thoughts of self-harm may lead to a teen revealing that he or she has active thoughts of suicide. In that situation, emergency steps must be taken. In most cases, that would mean a visit to an emergency department of the nearest hospital that has mental health staff in the ED or on call. If no such hospital is convenient, the clinician needs to discuss with the family how to keep the teen safe until an evaluation by a mental health specialist can be done. Reducing access to lethal means, such as firearms, prescription medications, and alcohol (24% of those who die by suicide show alcohol intoxication) is very useful. A commitment on the part of the family to have an adult close to the teen at all times until an experienced professional can do a full evaluation can be lifesaving. Although adolescent girls are at higher risk for attempting suicide, adolescent boys are at six times the risk of completing suicide, given their propensity to use such lethal means as firearms and hanging.

Anxiety Disorders

Although all the anxiety disorders combined are more common than depression, they seem to be overlooked more commonly than depression (*Tables 397.2* and *397.3*).

Treatment: All of the anxiety disorders are best treated with cognitive behavioral therapy; more severe cases do better with medication in addition. For moderate or severe disorders, an SSRI is generally indicated, with

Table 397.2
Signs and symptoms of adolescent anxiety disorders (After Foa et al. 2005)

Anxiety disorder	Key diagnostic feature	Other criteria	Other
Social anxiety	Extreme fear in social situations that involve unfamiliar people	Must show the capacity for age-appropriate social relationships	Typically develops in late childhood or early adolescence
Generalized anxiety disorder (GAD)	Excessive worry on most days for 6 months	Apprehension when anticipating a feared event; often accompanied by somatic symptoms	Often occurs in association with other anxiety disorders, and with depression
Panic disorder	Sudden unexpected fear or anxiety along with somatic symptoms like palpitations or shortness of breath	Must be recurrent, and include concern about additional attacks or changes in behavior	Rare before puberty; may progress to agoraphobia
Separation anxiety	Related to being separated from home or a particular individual	Can include worry about harm to a specific individual	Typically develops in early childhood, may remit in adolescence
Specific phobia	Marked and excessive fear of a specific object or situation	Apprehension when anticipating an upcoming feared event	Generally lower level of impairment than other anxiety disorders
Post-traumatic stress disorder (PTSD)	Following a frightening exposure to trauma, development of recurrent experience of the event, with attempts to avoid stimuli associated with it	Can include flashbacks, nightmares, or images. Increased arousal can involve insomnia or irritability	Associated with many comorbid disorders, including major depression, other anxiety disorders, and behavioral disorders
Obsessive–compulsive disorder (OCD)	Recurrent, persistent, intrusive, anxiety-provoking thoughts (obsessions), or repetitive acts (compulsions) that the person feels driven to perform	The thoughts or acts are recognized as unreasonable, and consume at least 1 h per day	Stereotypical thoughts or acts, often involving counting or checking routines, or hand washing

Diagnosis. A brief screening tests can be useful in encouraging the clinician to consider an anxiety diagnosis. *The SCARED-5* (Screening Children for Anxiety-Related Emotional Disorders) has been validated in children and adolescents

Table 397.3
The SCARED-5 for screening for anxiety disorders

During the past 3 months, how true is each statement	Not true or hardly ever true	Somewhat true or sometimes true	Very often or often true
I get frightened for no reason at all	0	1	2
I am afraid to be alone in the house	0	1	2
People tell me I worry too much	0	1	2
I am scared to go to school	0	1	2
I am shy	0	1	2

A total score of $\geq$3 makes the diagnosis of anxiety likely

sertraline often a good choice. Specific phobias are generally treated with a desensitization approach, while OCD responds well to exposure and response prevention (ERP). For the latter, it is especially important for the patient to be treated by a therapist with specific expertise in using the ERP approach.

School Problems

Significant learning disorders should have been picked up long before adolescence; however, some bright teens may have a focused disorder that has been masked until the coursework gets more complex. There are a number of behavioral problems that can cause a teen with an acceptable, or even an excellent school record in elementary school to show deterioration in middle school or high school. Besides depression or anxiety, discussed above, substance abuse, family conflict, chronic illness, or ADHD are common causes of deteriorating school performance in middle school or early high school.

ADHD: This disorder is the behavioral problem that once diagnosed, is most easily treated by primary care physicians. Approximately 5–8% of adolescents, with a male to female ratio of 3:1, have this problem. Generally, the hyperactive type or the combined type is diagnosed at an earlier age. But children with inattentive ADHD do not cause problems for teachers, and many of them with above-average intelligence make their way through elementary school with good grades and no identified problems (Table 397.4).

Problems occur when the children, now adolescents, are promoted to a school in which they must change classes, no longer have a single teacher who recognizes what approach facilitates learning in a given child, and face more complex school subjects that require more focus. Their poor grades are often accompanied by behavior problems, including irritability at home and getting into trouble at school. Once a diagnosis such as depression, anxiety, or oppositional defiant disorder (ODD) has been eliminated, the next step should generally be to interview the parent, with the teen present, for the presence of inattentive ADHD. The following questions should be asked, with possible responses being "never or rarely," "sometimes," "often," or "very often."

Describe your child's behavior over the past 6 months. Then combine the "often" and "very often" answers; if they total at least 6 of 9 (some believe that for adolescents 5 of 9 is adequate), you can make a diagnosis of possible inattentive ADHD. To confirm the diagnosis, the behaviors must occur in at least two settings – generally in this age group that would mean home and school. Forms such as the Vanderbilt (which is also helpful in diagnosing ODD) should be completed by each teacher who has regular contact with the teen. If several teachers see the same problems the parent does, a diagnostic of inattentive ADHD can be made.

Treatment: The primary treatment for ADHD is a stimulant drug, preferably long acting. The recommended drugs are methylphenidate OROS, or mixed amphetamine salts, extended release. There are many other alternatives, including the non-stimulant atomoxetine, or the combination of a long-acting medication with an after school boost of a short-acting medication in the same family of drugs, to extend the effects of the medication long enough for homework to be completed. Studies show that medication plus parent education and behavior management is more effective than either treatment alone.

School refusal (also called school phobia): Frequent absences can sometimes be explained by any of the diagnoses discussed above, substance abuse, or other problems. Referral for psychological testing may be appropriate if there is no apparent behavioral cause of the problem, or poor performance is related to a specific

Table 397.4
Screening for ADHD without hyperactivity

	Never or rarely	Sometimes	Often	Very often
1. Fails to give close attention to details or makes careless mistakes in school work, work, or other activities				
2. Has difficulty sustaining attention to tasks or leisure activities				
3. Does not seem to listen when spoken to directly				
4. Does not follow through on instructions and fails to finish school work or chores				
5. Has difficulty organizing tasks and activities				
6. Avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort (such as school work or homework)				
7. Loses things necessary for tasks or activities (e.g., school assignments, pencils, books, or tools). (Note: ask about losing *completed* homework)				
8. Is easily distracted by extraneous stimuli				
9. Is forgetful in daily activities				

subject. However, some teens present with a puzzling history of missing many days of school with no clear diagnosis. At times, they present with fatigue and/or difficulty sleeping; it may be helpful to rule out chronic fatigue syndrome and/or a sleep disorder. In about one-third of these cases, no specific diagnosis can be made. The most common diagnosis that can be made is separation anxiety disorder, with all the anxiety disorders combined representing two-third of those who do end up with a diagnosis. Treatment with an SSRI can be helpful.

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398 Substance Abuse

Michael J. Mason · Leslie R. Walker

Etiology

The initiation and establishment of adolescent substance use occurs as a result of many factors. In the past, attention was paid to environmental and physiologic factors, but increasing information is being uncovered about the genetic/biologic factors that play an important role.

There are different stages of adolescent substance use:

Experimentation – Using a substance for the first time and has a physical response to the substance; Of note, this response does not have to be a pleasant one, just one that elicits a new physical or mental response.

An example: Johannes takes his friends amphetamine to a party to see what will happen.

Misuse – Returning to a substance for a desired response; Johannes thought he was having a great time on the amphetamine and never got tired dancing. He decides at the next party he will take some again.

Abuse – Repeatedly using a substance or substances in order to get a desired effect even to his own detriment and in the face of severe consequences; Johannes has increased his amphetamine use to the point he had a near-death episode, where his friends had to drop him off at the hospital for care. He still uses amphetamines every chance he can get.

Drug Addiction and Dependency – Using substances now just to be "normal" no longer gets the desired effect; continued escalation of consequences but psychologically and or physically unable to stop; Johannes has been incarcerated for stealing to support his substance use and he has needed to use other drugs to augment his amphetamine drug of choice. He is no longer enrolled in school.

Epidemiology

Substance use disorders effect adolescents worldwide. Depending on the country, substance use patterns may differ. With over 72% of US high school youth reporting using alcohol and 47% reporting trying illicit drugs, the USA has the highest use of legal and illicit substances when compared to 17 other countries. Alcohol use is not uniform, with New Zealand, Americas, Europe, and Japan reporting much higher use than the Middle East, Africa, and China. An emerging problem worldwide is the misuse and abuse of prescription drugs. The abuse of these drugs has surpassed all illicit drugs combined except for cannabis. Internationally, 17% of adolescents are current tobacco smokers. In the USA, there has been a decrease in adolescent tobacco use over the last decade from 36.4% to 20%.

Marijuana and Alcohol remain the most commonly abused substances in this age group and they are responsible for the majority of adolescent drug dependence and treatment. Other substances that are abused but much less commonly during adolescence, are hallucinogens, cocaine, methamphetamine, anabolic steroids. Many of these other substances are used within the context of polysubstance abuse. While it is important that a provider stay current on the trends of specific substances adolescents are using in their community, what is more important is identification that an adolescent is abusing or dependant on any illicit or legal substance that is used for purposes other than what is prescribed. Any of these youth are at risk for poor health outcomes, school and job failure, poor family and interpersonal relationships, trauma, delinquency, and exploitation.

Substance abuse affects youth regardless of socioeconomic or ethnic or gender group status. All youth are potentially at risk for substance use and abuse, only screening those deemed to be high risk for this behavior will miss many who may be amenable to intervention and prevention.

Pathogenesis

Adolescent substance occurs through many pathways involving the environment, genetics and individual personality and resilience. While it would be hard to pinpoint a single direct pathway for a specific adolescent's initiation into substance use, there has been some exciting work that has begun looking at genetics and brain development in substance use and abuse.

The adolescent brain is still making new connections and pruning those it does not need, the areas that are most active during adolescence and young adulthood are those areas that govern emotions and executive functioning, these areas are also thought to be the most vulnerable to

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alcohol effects. Looking at genetic risk factors is beginning to show some important correlations as well, such as the relationship between nicotine receptors in the brain and Attention Deficit Disorders. Making it genetically more likely someone with ADHD would begin to use nicotine and have a harder time quitting when desired. Familial genetic predisposition is also apparent when statistics show that substance abuse and dependence run in families. It is nine times more likely for males and three times more likely for females to develop alcoholism when there is a positive family history of alcoholism.

It is commonly believed that substance use and ADHD are associated when a dual diagnosis of conduct disorder is present, but there is little evidence to suggest that substance use is associated with ADHD alone. While the relationship between ADHD and substance-use disorders may not be exclusive, it is likely that the severity of both ADHD and SUD will increase when the symptoms are combined. For instance, Biederman and colleagues found support for the theory of a causal pathway from ADHD to cigarette smoking to substance use, with ADHD youth who smoke significantly more likely to use substances compared to non-smoking controls. Manuza and Klein found that children with ADHD were four times as likely to develop an SUD by adulthood than those who had not been given an ADHD diagnosis (16% vs 4% of control subjects).

Child and adolescent substance abuse is inextricably linked to comorbid psychiatric conditions including ADHD, conduct disorder, depression, anxiety, a variety of stress disorders, oppositional defiant disorder, and reactive attachment disorder. The Substance Abuse and Mental Health Services Administration (SAMHSA) has further demonstrated the linkage and interactivity between emotional and behavioral problems and substance involvement. Adolescents who demonstrated behavioral and emotional problems were seven times more likely to be dependent on substances than those who presented with fewer symptoms. Finally, for those teens entering substance abuse treatment, 75% will have one or more psychiatric conditions, with 50% having three or more.

Clinical Manifestations: Symptoms and Signs

Symptoms and signs of substance abuse in adolescents include:

Physical	Personality	Home	School
Odors of marijuana, alcohol, solvents on clothes, in house or car	Sudden changes in mood, depression	Legal problems	Change in school performance
Decreased personal hygiene	Memory loss	Increased financial problems, i.e., selling of personal or family possessions	Truancy, dropout
Slurred speech or intoxication, lethargy	Increased belligerence and arguing	Increased family arguments	Change in interactions with teachers and students
Unsteady gait	Lack of motivation or interest	Less interested in family activities	Bringing alcohol or other substances to school grounds
Red eyes	Excessive energy, unusually talkative	Drugs or drug paraphernalia, matches, lighter in laundry, backpack, or bedroom, etc.	Increased disciplinary action
persistent coughing	Secretiveness	Runaway behavior, breaking curfew	Disengagement in school goals
Increased or slowed heart rate	Sudden paranoia, distrustfulness	Excessive sleepiness, decreased ability to get up in the morning	Sleeping in class
Sudden weight loss or weight gain	Hallucinations: auditory, visual	New group of friends and activities	Decreased interest in extracurricular school activities and sports participation
Increased or decreased blood pressure	Extreme opinions, language and dress	Prescription drugs missing from household	Stealing from school

Diagnosis

The substance use disorders can be divided into two categories: (1) substance abuse and (2) substance dependence. Substance abuse is more likely in individuals who have only recently started using a substance and is characterized by a maladaptive pattern of substance use observable by recurrent and significant adverse consequences due to repeated use of substances.

Criteria for Substance Abuse

1. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:
   (a) Recurrent substance use resulting in failure to fulfil major role obligations at work, school, or home (e.g., repeated absences, suspensions, or expulsions form school; neglect of children or household)
   (b) Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)
   (c) Recurrent substance-related legal problems (e.g., arrests for substance-related disorderly conduct)
   (d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)
2. The symptoms have never met the criteria for substance dependence for this class of substance.

Substance dependence is characterized by a cluster of cognitive, behavioral, and physiological symptoms, indicating that the individual continues use of the substance despite recurrent and significant substance-related problems. Dependence is evidenced by a pattern of repeated substance use that can result in tolerance and withdrawal. Although not listed as a criterion, craving a substance (strong subjective drive to use the substance) is likely to be evident in most individuals with substance dependence.

Criteria for Substance Dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. Tolerance, as defined by either of the following:
   (a) A need for markedly increased amounts of the substance to achieve intoxication or desired effect
   (b) Markedly diminished effect with continued use of the same amount of the substance
2. Withdrawal, as manifested by either of the following:
   (a) The characteristic withdrawal syndrome for the substance
   (b) Substance is taken to relieve or avoid withdrawal symptoms
3. The substance is often taken in larger amounts or over a longer period than was intended.
4. There is a persistent desire or unsuccessful efforts to cut down or control substance use.
5. A great deal of time is spent in activities necessary to obtain the substance (e.g., visiting multiple doctors or driving long distances), use the substance (e.g., chain-smoking), or recover from its effects.
6. Important social, occupational, or recreational activities are given up or reduced because of substance use.
7. The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

Differential Diagnosis

Substance use disorders are differentiated from:

- Nonpathological substance use (e.g., "social" drinking)
- Use of medications for appropriate medical purposes

Repeated episodes of substance intoxication are almost always prominent features of substance abuse or dependence; however, one or more episodes of intoxication alone are not sufficient for a diagnosis of substance abuse or dependence. It is the presence of impaired psychosocial functioning that differentiates nonpathologic from pathologic use. Research has now established that substance abusing and dependent adolescents presenting with co-occurring psychiatric disorders are the norm, not the exception, with the majority of untreated adolescents likely to have a comorbid psychiatric disorder. These issues are clearly linked as adolescents with a substance use disorder are at a sixfold greater risk for co-occurring

disorders than those without a substance use disorder, with 78–90% of adolescents in substance abuse treatment programs endorsing internalizing or externalizing problem and 42–61% endorsing for both. The most common form of psychopathology observed in substance-dependent adolescents includes conduct disorder, ADHD, major depressive disorder, anxiety disorder, and posttraumatic syndrome disorder.

Treatment

General Care

In 2005, 1.5 million youths (6.1% youths aged 12–17) were classified as needing alcohol treatment in the past year and about 1,11,000 youths (7.2% of those needing alcohol treatment) received treatment for alcohol in the past year. About 1.4 million youths (5.4%) were classified as needing illicit drug use treatment in the past year and 1,24,000 (9.1% of those needing illicit drug treatment) received treatment for an illicit drug in the past year. As may be expected, most youths aged 12–17 who were in need of substance use treatment in the past year and did not receive treatment were not likely to perceive a need for substance use treatment. However, the good news is that within the last 10 years, the literature on adolescent substance abuse treatment has grown substantially in the quantity and in the quality of clinical studies. There is now a robust body of evidence to support evidence-based treatments that have demonstrated efficaciousness in addressing adolescent substance abuse.

Research has demonstrated that a quality treatment enables adolescents to offset addiction's powerful disruptive effects on their brain and behavior and to regain control of their lives. The specific type of treatment is dependent upon severity of symptoms and can be offered in formats such as typical outpatient settings, day treatment programs (partial hospitalization), and inpatient programs. Based upon the level of care needed and accompanying medical and safety concerns, the appropriate setting can be determined by a comprehensive evaluation of the adolescent and family. The types of effective treatment vary by their focus, style, and length. In general, no one treatment has emerged as superior to all others and no one treatment approach appears to be similarly efficacious for all adolescents. Recent research has demonstrated that the evidence-based treatments briefly reviewed below, have on average, produced large effects on substance-related outcomes across demographic differences.

Specific Treatment

Family Therapy Approaches

Brief Strategic Family Therapy is predicated on the assumption that the adolescent substance abuse is a product of maladaptive family interactions. Treatment focuses on enhancing family engagement, identifying maladaptive interaction patterns, and restructuring new, adaptive patterns.

Functional Family Therapy is an integrative ecological approach that combines a family systems perspective on family functioning with behavioral techniques. The focus is on enhancing treatment engagement and increasing family's motivation to change along with improving family communication and problem solving.

Multisystemic Therapy addresses the factors associated with serious antisocial behavior in children and adolescents who abuse alcohol and other drugs. By participating in intensive treatment in natural environments (homes, schools, and neighborhood settings), most youths and families complete a full course of treatment.

Multidimensional Family Therapy (MDFT) is a comprehensive and multisystemic family-based outpatient or partial hospitalization program for substance-abusing adolescents, adolescents with co-occurring substance use and mental disorders.

Individual Approaches

Cognitive behavioral therapy (CBT) is a behavioral model that assumes that cognition precedes emotions, which activate moods and behaviors. CBT identifies distorted thinking patterns and couples this with communication, problem-solving, and coping skills. CBT focuses on the acquisition of problem-solving, affect-regulation, and social skills.

Motivational Interviewing (MI)/Enhancement Therapy seeks to enhance readiness for change by helping clients explore and resolve ambivalence toward behavioral problems. MI is typically conducted in brief formats, one to five sessions, with some single session interventions being 20 min.

The Adolescent Community Reinforcement Approach to alcohol and substance use treatment is a behavioral intervention that seeks to replace environmental contingencies that have supported alcohol or drug use with prosocial activities and behaviors that support recovery.

Future Development

Drug-abusing adolescents have unique treatment needs. Research has shown that treatments designed for and tested in adult populations often need to be modified to be effective in adolescents. Due to the rapid changes occurring in adolescents' neurocognitive and psychosocial development, attending to the unique biopsychosocial needs of the adolescent is critical. The adolescent brain undergoes a critical process of development and refinement, during which a developmental shift occurs where actions go from more impulsive to more reasoned and reflective. For example, the areas of the brain associated with decision-making, judgment, and impulse control undergo a period of rapid development during adolescence, underscoring the unique developmental issues associated with adolescent substance abuse treatment. The future of adolescent substance abuse treatment will incorporate current neurocognitive developmental science with established evidenced-based treatment protocols to refine treatments that can be more individually tailored.

Prognosis

For some adolescents, experimentation with alcohol and other drugs of abuse can lead to substance abuse and for others, dependency. The progression and complexity of these disorders are now better understood making treatment more successful. If substance abuse has become chronic, relapses are probable, even after long periods of abstinence. Relapse occurs at similar rates to other chronic illnesses such as diabetes, hypertension, and asthma. Therefore, repeated treatment episodes are not uncommon for individuals seeking sustained abstinence and productive lives. Making ongoing lifestyle changes to support healthier living is critical for the long-term success of any individual dealing with an addiction. Often, this is most successfully accomplished with the support of others, just as individuals with diabetes need to make significant changes in their lifestyles and support systems.

In general, adolescents who get into and remain in effective treatment stop using alcohol and drugs, decrease their criminal activity, and improve their educational, social, and psychological functioning. Given that adolescents are particularly sensitive to social influences with peer groups and families, treatments that facilitate positive parental involvement integrate other systems in which the adolescent participates (such as school and athletics) and recognize the importance of prosocial peer relationships as among the most effective. Adolescents who have access to comprehensive assessment, treatment, case management, and family-support services that are developmentally, culturally, and gender-appropriate, are most likely to be successful in their treatment.

Prevention

The field of prevention science has produced a very solid knowledge base regarding the epidemiology, etiology, developmental timing, expression, and prevention of substance use and associated psychiatric and behavioral disorders. Prevention research is predicated upon a risk and protective model that identifies factors or processes that increase (risk factor) or decrease (protective factor) the likelihood of substance use. The most frequently identified protective processes against adolescent substance use are parental engagement and family functioning, self-regulation social competence, and school bonding and academic performance. The most effective evidence-based preventive programs are designed to focus on these protective processes and target interactions between the adolescent and these significant domains (family members, students, family–school interactions).

The U.S. National Registry of Effective Prevention Programs has recently developed a searchable database that contains detailed descriptions and evaluations of interventions for the prevention and treatment substance use and mental health disorders (see site at http://www.nrepp.samhsa.gov/index.asp).

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399 Community Violence

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Introduction

There are many violence types in our community, including, but not limited to, suicide, bullying, sexual assault/rape, assaultive behaviors, gang, dating, school, media, and firearm violence. Many types of violence are interrelated and may occur simultaneously. Although homicide has declined over the last decade, recent violence in some of the nation's urban and rural areas and across socioeconomic classes reminds us that much work remains to be done by clinicians and others. Understanding community violence and its manifestations is an important step toward reducing its impact on young people's psychological and physical well-being.

Definition

The World Health Organization (WHO) and the Centers for Disease Control and Prevention define violence as: the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation. Community violence has been used to define violence that occurs in and around neighborhoods, schools, and the streets of communities. It typically excludes violence committed in the home such as child abuse or neglect. Community violence exposure has focused on experiences through direct and indirect victimization such as witnessing.

Epidemiology/Prevalence

The national prevalence of witnessed community violence in the USA is estimated at 38%. Internationally, this prevalence approaches or exceeds 90% in some war-torn regions; thus, community violence is a relevant global public health concern. In this chapter, the authors have limited the types of community violence exposure to interpersonal, bullying, intimate partner or dating, and firearm violence.

Interpersonal Violence. According to the Monitoring the Future Study of high school seniors, the violence index (hit an instructor or supervisor, got into serious fight at school or work, taken part in a fight where group of friends are against another group, hurt someone badly enough to need bandages or doctor, used knife or gun to get something from someone) has been at a high level for almost 20 years. Approximately 30% of high school seniors, age 13–18 years, reported having committed one of these violent acts in the past year. This estimate of 30% is only slightly higher than the available estimates of the violence index for youth in other countries. This estimate ranges from 16% to 26% in several European countries – England/Wales, the Netherlands, Spain, and Italy.

When examining homicide rates, most countries with rates higher than 10/100,000 are nonindustrialized or experiencing rapid social and economic transformation. The exception is the USA with an 11/100,000 homicide rate. Countries with low youth homicide rates tend to be in Western Europe – for example, France (0.6/100,000), Germany (0.8/100,000), and the UK (0.9/100,000) – or in Asia, such as Japan (0.4/100,000). Several countries such as Hong Kong, New Zealand, and Denmark had fewer than 20 youth homicides a year compared to 16 persons between the ages of 10 and 24 murdered daily in the USA. In addition to homicide, more than 780,000 United States youth aged 10–24 are treated in emergency departments annually for violence-related injuries.

Bullying. Bullying can be defined as a form of aggression, which involves one or more students verbally, physically, and/or psychologically harassing another student repeatedly. Prevalence estimates for bullying vary widely due to the lack of an agreed-upon definition and consistent measures. Some researchers focus solely on physical bullying, while others include nonphysical behaviors such as name calling. Despite these challenges, studies have produced useful estimates of bullying. One such study of middle school students found that 80% reported that bullying was a problem in their school, and 30% of students in grades 6–10 report moderate or frequent involvement in bullying, as a victim (11%), perpetrator (13%), or both (6%).

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However, bullying is not limited to the USA. One study, of students in 11 European countries, found that approximately 20% of students were bullying victims; the highest prevalence of 30% was in the UK. Interestingly, a separate study comparing rates of peer victimization in the USA and the UK found no significant differences. Finally, another study found that among the USA, Israel, Ireland, Portugal, and Sweden, students in the USA reported the second highest frequencies of bullying and other school violence (after Israel).

Dating or Intimate Partner Violence. Annually, 1 in 11 adolescents report being a victim of physical dating abuse. However, other prevalence estimates of psychological abuse range from 14% to 82%. Between 11% and 41% of adolescents report using some form of physical violence against their dating partners. Between 4% and 14% of adolescents report using forms of violence against dating partners that are likely to result in serious physical injury such as hitting a partner with an object, beating up a partner, and using a knife or gun against a partner. Approximately 3–10% of adolescents report perpetrating sexual violence against a date.

The prevalence of intimate partner violence in the UK is highest amongst women aged 16–24 years. A New Zealand study found that the rates of partner violence among women seeking emergency healthcare to be high at 20%. In the cohort of women aged 16–24 years, this statistic increased to 25%. Similarly, in the outpatient setting, 23% of women screened positive for dating or intimate partner violence.

Firearm Violence. Firearms are the major weapon used in the leading causes of death among adolescents and young adults – suicides and homicides. Homicides and suicides are the second and third leading causes of death, respectively among 15–24-year-olds in the USA. In 2006, firearms were used in 84% of homicides and 47% of suicides. Exposure to unsafely stored firearms is a major risk factor for childhood and adolescent injury. Parents of adolescents are actually more likely than other parents to keep household firearms stored unsafely.

Youth firearm death rates are not uniform in the industrialized world – the USA has the highest rate. Total firearm deaths among youth are approximately 12 times higher in the USA than in all of the other countries combined; homicide rates are approximately 5 times higher; and youth suicide rates are approximately twice as high. Five countries, three of which are in Asia, report none or few firearm deaths among children under 15 years old.

Armed conflict is a major cause of adolescent community violence worldwide. In armed conflict, there are also health consequences from the displacement of populations, breakdown of health and social services, and heightened risk of disease transmission.

The prevalence of community violence among youth continues to be a global public health concern that requires early detection and effective intervention. The following section highlights some of the most salient risk factors for violence perpetration and victimization. Early recognition of these factors can play an important role in addressing subsequent negative effects of exposure.

Risk and Protective Factors

Several factors are associated with a higher probability that an individual will engage in violent behavior. Such risk factors may differ depending on the age of the individual and onset of violence, circumstances, and social context. Protective factors that appear to decrease the probability of violence or buffer the individual against the potentially harmful effects of risk factors have also been identified.

The ecological perspective posits that many risk behaviors, and protective factors are influenced by factors that operate at different but interrelated dimensions starting with the individual as the central unit of interest out to the influence of the society. The domains include individual, family, peer group, school, and community. *Table 399.1* includes a list of risk factors associated with the violent behavior during different developmental periods and a list of protective factors for each ecological domain. As with any major public health concern, the underlying predictors of community violence exposure are multifactorial.

Although persons of color in the USA are disproportionately affected by community violence, race/ethnicity is not thought to be a risk factor but instead is considered a risk marker, because it is often highly correlated with known risk factors such as poverty, low socioeconomic status, neighborhood characteristics, and discrimination.

Impact

Youth exposed to community violence may be more likely to engage in fighting and aggressive behavior as a result of an arousal created by frustration. Children and adolescents who live with the constant threat of violence may also become desensitized to the threat and consequences of violence. These individuals may attempt to gain a sense of control over their lives through repeated encounters with life-threatening situations. Additionally, evidence

Table 399.1
Summary of risk and protective factors for violence, by domain

Domain	Risk factor Early onset (6–11 years)	Risk factor Late onset (12–14 years)	Protective factor
Individual	General offenses	General offenses	Intolerant attitude toward deviance
	Substance use	Substance use	High IQ
	Being male	Being male	Being female
	Aggression (males only)	Aggression (males only)	Positive social orientation
	Psychological condition (hyperactivity)	Psychological condition (restlessness, difficulty concentrating, risk taking)	Perceived sanctions for transgressions
	Antisocial behavior, attitudes	Antisocial behavior, attitudes	
	Medical, physical		
	Low IQ	Low IQ	
		Crimes against persons	
		Physical violence	
Family	Low socioeconomic status		Family connectedness
	Antisocial parents		Parental monitoring
	Poor parent–child relations		
	Broken home		
	Abusive parents		
School	Poor attitude, performance	Poor attitude, performance	Commitment to school
		Academic failure	Recognition for involvement in conventional activities
	Weak social ties	Weak social ties	Friends who engage in conventional behavior
	Antisocial peers	Antisocial, delinquent peers	
		Gang membership	
Community		Neighborhood crime, drugs	
		Neighborhood disorganization	

has consistently shown that witnessing gruesome acts of brutality as a bystander or a victim during the critical developing years has far-reaching negative consequences on adolescents' behavior and emotional and physical well-being. The psychological and physical impact of exposure is described below.

Psychological Impact. The psychological impact ranges from the traditional sequelae of depression, anxiety, and posttraumatic stress disorder (*Table 399.2*) to the more recently studied effect on identity development. Specifically, the exposed adolescent may struggle with coping in appropriate ways, defining a positive self-perception,

Table 399.2
Psychological impact of community violence

• Depression
• Anxiety
• Posttraumatic stress disorder
• Negative self-perception or identity
• Substance abuse
• Misplaced aggression
• Suicidal ideation

negotiating a moral compass, and attaining the altruism desired for his or her future. Exposure to significant community violence before or during adolescence can lead to the establishment of pathologic character traits.

Misplaced aggression is one of the most commonly cited coping mechanisms employed by the youth exposed to violence. In some environments, this aggression is simply a product of believing that hostility is the only means to achieving basic survival. In other settings, the aggression turns inward and manifests as suicidal tendencies. For example, at risk youth may solve the feeling of helplessness by owning suicidal ideation; thus the adolescent can manage the fear of death by controlling when and how it will happen.

A large multi-country study using WHO data found that women involved in intimate partner violence (including 15-year-old adolescents) were significantly more likely to report suicidal thoughts and attempts. The effects of physical intimate partner or dating violence are not restricted to females. Evidence suggests that both male and female victims have increased risk of depressive symptoms and developing a chronic mental illness. Finally, psychological effects may be a direct result of physical harm. A classic example involves females in abusive relationships, who sustain multiple untreated and unreported losses of consciousness. In these circumstances, eventual reports of memory loss and difficulty with daily activities or chronic headaches may actually represent inadequately diagnosed sequelae of neurologic damage from battering.

Worldwide, among child soldiers, the predominance of male exposure to violence is extremely high as well as the violent victimization experienced by many young girls and women. Some common psychological effects of war-related abduction, sexual assault, and child soldiering among adolescents in countries engaged in war are PTSD and depression.

Physical and Health-Related Impact. While the mental effects are well defined, the physical manifestations can be vague and variable in nature. These physical manifestations may also result in frequent visits to the physician, particularly through emergency visits. Postulated physiologic changes resulting from witnessed violence range from altered cortisol levels to worsening asthma morbidity. The reasoning for this depends in part on the hypothesis that chronic stress weakens the immune system.

Victims of dating violence are not only at increased risk for injury; they are also more likely to engage in binge drinking, drug use – including cocaine, unhealthy weight control, suicidality, physical fights, and sexual behaviors that can lead to unintended pregnancy, sexually transmitted diseases, and HIV infections. Rates of drug, alcohol, and tobacco use have been demonstrated to be more than twice as high in girls who report physical or sexual dating abuse than in girls who report no abuse.

To further complicate the matter, the clinical presentation can be quite unpredictable. Often, victims of dating violence do not present with noticeable trauma but rather with vague symptomatology. When injuries are present in battered young women, they are more likely to involve the face, head, neck, thorax, breast, and abdomen compared to women injured by other mechanisms.The sequelae of intimate partner violence and other violence types range from chronic pain to central nervous system effects to physical symptoms and disease (see *Table 399.3*). These consequences can be seen in both men and women who also have increased risk of: becoming a perpetrator, poor health, injury, and developing a chronic disease. Physical fitness of adolescents may also be affected. Adolescents in violent communities may avoid group recreational play.

School-Related Impact. Community violence can also impact school performance. For example, bullying victimization is associated with school absenteeism and feeling

Table 399.3
Physical and health-related manifestations

• Altered cortisol levels
• Worsening asthma
• Weakened immune system
• Injuries
• Chronic pain especially headache
• Syncope
• Seizures
• Chronic irritable bowel syndrome
• Decreased appetite
• Eating disorder
• Hypertension
• Abdominal pain
• Chest pain
• Back pain
• Gynecological symptoms (STIs, UTIs, dsypareunia, pregnancy)
• Loss of consciousness
• Memory loss
• Poor general health
• Poor physical fitness

unsafe at or on the way to school. Feeling unsafe at school and the resultant anxiety can lead to distraction and inability to focus and concentrate on school work.

Screening

Investigating exposure to community violence should be a standard part of health screening for all adolescents presenting at emergency departments and inpatient and outpatient settings. This screening should include questions about the school environment, neighborhood, and relationships. Many of the sequelae of violence exposure have a proven treatment record in the adolescent population, including depression, PTSD, and anxiety disorders. Thus, proper screening and identification of at-risk adolescents could lead to improvements in their health outcomes.

Screening Tools. Commonly used evidence-based screens for adolescent depression include the Beck Depression Inventory-Primary Care Version and PHQ-A (Patient Health Questionnaire for Adolescents). One tool appears to directly address the issue of community violence: the Screen for Adolescent Violence Exposure created by Hastings and Kelly. Also, the commonly used GAPS (Guidelines for Adolescent Prevention Services) questionnaire contains questions regarding violence exposure that help clinicians identify community violence to allow them to initiate a discussion such as: Do you or anyone you live with have a gun, rifle, or other firearm? Have you ever seen a violent act take place at home, school, or in your neighborhood? FISTS is a pneumonic that reminds clinicians to screen for violence risks and includes history of Fights, Injuries, Sexual violence, Threats, and Self-defense strategies. For example, have you ever been involved in a fight? Have you ever been hit, slapped, or physically hurt on purpose by your partner? Have you ever been injured in a physical fight or with a weapon? Have you ever been forced to have sexual intercourse or do something sexual when you did not want to? Have you ever been bullied or bullied others? Have you ever been threatened with a weapon? Have you ever carried or used a weapon?

Tools in international settings include the War Trauma Experience Checklist (WTECL-15) and the Adolescent Complex Emergency Exposure Scale. The UK reported the HITS (Hurts, Insults, Threatens, and Screams) scale to be the best of short screening tools used in their healthcare arena.

Timely use of screening provides the opportunity for intervention, prevention, and improvement in physical and mental health outcomes. The ideal screening tool is not only employed before permanent harm but must also be practical to implement.

What Clinicians Can Do?

Youth exposed to community violence are the patients of a broad range of clinical providers including pediatricians, family practitioners, internists, obstetrician gynecologists, emergency department (ED) physicians, physical therapists, nurse practitioners, and physician assistants. Each of these providers has the opportunity to advocate for violence prevention. For example, ED physicians can play an important role in the prevention of retaliatory violent acts amongst injured youth. For the purposes of this textbook, the chapter focuses on the unique role of the pediatrician.

Pediatricians not only have access to adolescents exposed to community violence but also have the opportunity to intervene during the early formative years. In fact, the American Academy of Pediatrics (AAP) offers relevant anticipatory guidance that begins at the age of 2 days through 21 years. In its publication entitled *Connected Kids: Safe, Strong, Secure*, the AAP specifically seeks to enable the primary health-care provider to use intentional violence and injury prevention strategies in daily practice. The adolescent portion of these recommendations is summarized in *Table 399.4*.

In 2009, an AAP policy statement updated the pediatrician's role in youth violence prevention with four areas of emphasis to focus preventive efforts:

1. *Clinical Practice*
   (a) Understand the *Connected Kids* protocol.
   (b) Have parent and youth education materials available.
   (c) Employ timely treatment and/or referral once violence-related problems are indentified.
   (d) Maintain current database of community-based counseling and treatment resources.
2. *Advocacy for*
   (a) Community-based behavioral health services
   (b) No firearm exposure amongst youth
   (c) Awareness of bullying
   (d) Multimedia responsibility to minimize violent images, messages, or themes
   (e) Role of health professionals as "public health messengers"
   (f) Electronic health records with content related to youth violence prevention

Table 399.4

Primary care guide to violence prevention strategies for adolescence (Training Resource, adapted from Sege et al. 2005)

Visit	Introduce	Reinforce	Brochures
Early	• Family time together	• Reducing access to firearms • Establishing routines and setting limits	Talking with your teen: tips for parents
11–14 years	• Peer relationships • Support system • Staying safe • Mental health • Conflict resolution • Healthy dating • Gaining independence • Plans for future	• Alcohol and drug abuse prevention • School performance	Staying cool when things heat up Expect respect: healthy relationships Teen dating violence: tips for parents
Middle	• Plans for future	• Alcohol and drug abuse prevention	Teen suicide and guns
15–17 years	• Firearms and suicide prevention, including reducing access to firearms • Depression prevention • Resiliency	• Peer relationships • Healthy dating • Gaining independence	Next stop- adulthood, tips for parents
Late	• Transition to independence	Peer relationships	Help stop teenage suicide
18–21 years	• Negotiating a new environment (Post-High School)	• Plans for future • Depression prevention	Connecting with your community

3. *Education*
   (a) Attend relevant CME or professional development programs.
   (b) Learn about resources in your community.
   (c) Get involved with providers in training, for example, elective work at medical school.
4. *Research*
   (a) Participate in practice-based research focusing on youth violence prevention.
   (b) Contribute data to existing surveillance systems.
   (c) Advocate for your local injury surveillance system to be municipally supported and legislatively mandated.

Summary

Exposure to community violence must be viewed as a preventable health problem. Pediatricians and Adolescent Medicine Specialists are an integral component of successful youth violence prevention. Although these providers are well trained in identifying the physical victimization, it is critically important that they become more astute at identifying the risk factors, psychological signs, and vague physical symptoms associated with direct and indirect victimization. The use and integration of valid and reliable screening tools during regular primary care visits could be beneficial in indentifying and intervening to reduce the short- and long-term effects of community violence exposure.

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400 Delivery of Adolescent Health Care

Anisha Abraham · Kirsten Hawkins

Adolescence, the transition between childhood and adulthood, is defined by the World Health Organization as the time period between ages 10 and 18 and by the American Academy of Pediatrics as ages 11–21. Taking care of adolescents requires a different approach than caring for children or adults. The goals of an adolescent medicine provider are to oversee a teen's health care, provide support and counseling for the many issues that may arise during puberty, and enable an adolescent to segue successfully to adulthood. Visits should reinforce good health practices, while discouraging high-risk behaviors such as unprotected sexual activity or substance use. A comprehensive history is the most important aspect of the preventive service evaluation. Taking a thorough adolescent history can be time consuming and occasionally challenging but provides essential information for health maintenance and risk prevention.

Communication

The initial encounter with an adolescent sets the tone for future visits. Moreover, the ability to engage youth in health promotion is tied to a provider, forming an effective relationship. The following are the recommendations regarding communicating with adolescent patients. Attempt to greet the adolescent first before the parent and make the teen patient the primary historian. To increase a teen's willingness to communicate and feel comfortable, consider opening the discussion by asking the teen a nonmedical question. For example, ask about the book the adolescent is carrying, the outfit the teen is wearing, plans for upcoming holidays, etc. During the actual interview, sit at eye level with the patient and be attentive. Try to use understandable language and open-ended questions such as asking "what do like to do for fun?" Attempt to remain nonjudgmental and refrain from assessing behaviors in relation to one's own experiences. Also, avoid lecturing without regard to a teen's willingness to hear a message. Communication should be culturally sensitive with respect to different customs, traditions, and religions. Providers should try to listen to their adolescent patient, trust their intuition, and be open to "hidden agendas" that the adolescent patient may be reluctant to disclose.

A strength-based approach, highlighting the positives, creates a trusting relationship and helps teens develop their own solutions to problems. At the completion of the interview and examination, allow the teen to ask final questions. Prioritize problems by level of risk. While low-risk situations can be managed by dispensing health information and specific suggestions, high-risk situations may require return visit or more in-depth interventions. Attempt to focus counseling on key areas of need and involve the adolescent in developing the plan. Work with patients to incorporate cultural issues and preferences into the individualized care plan. Finally, inform the teen how to best obtain medical information and schedule follow-up appointments. Consider using electronic communication to facilitate the communication.

Clinical Approach to the Adolescent

Questionnaires and screening forms can help collect information prior to the actual interview. In fact, many patients may find it easier to disclose personal information through written or computer-based questionnaires. The American Medical Association has developed the Guidelines for Adolescent Preventive Services (GAPS) which are available for adolescents and parents and can be a useful screening tool.

The components of the adolescent history include the past medical history, family history, psychosocial history, and review of systems. The *past medical history* is best obtained from both the teen and parent/guardian and should include medications (including vitamins and over-the-counter/alternative medicines), allergies, developmental history, childhood illnesses, hospitalizations, surgeries, mental health history, and immunizations. The *family history* should be obtained primarily from the parent/guardian with the teen present and should include

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significant medical and mental health issues among family members such as hypercholesterolemia, hypertension, diabetes, and depression.

The *psychosocial history* can be taken mainly from the adolescent. Providers often use a standard screening format to ensure that they cover key issues. One such example is *SSHADESS*, an updated version of the widely used HEADSS concept. SSHADESS begins with general questions and progresses to ones which are more sensitive in nature and includes *S*trengths, *S*chool, *H*ome, *A*ctivities *D*iet/*D*rugs, *E*motions, *S*exuality, and *S*afety.

The institutional or office policy regarding confidentiality should be clearly reviewed with the teen and parent at the onset of an appointment. Information regarding confidentiality and legal issues is reviewed later in this chapter.

In conducting the SSHADESS psychosocial interview, begin by letting the teenager state their *strengths* or interests. If the teen has difficulty answering, then ask "What do you do best? What makes you proud? What would your friends say about you?" The strength-based questions focus on resiliency and can be useful in reinforcing a teen's ability to make healthy decisions and minimize high-risk ones.

After discussing strengths, progress to questions regarding school and employment. Poor attendance and grades have been shown to be risk factors for early sexual activity, teen pregnancy, and alcohol use. Employment can have both positive and negative effects on teens depending on factors such as hours worked and the reason for employment. Questions regarding *school* can include: What grade or level are you in? What are your educational and life goals? How many days have you missed in the past year and what was the reason? Have you ever had any educational setbacks? Adolescents are often employed either part-time or fulltime. Questions regarding *employment* include: Do you work after school? What type of work do you do? How many hours a week? Do you have any home chores or responsibilities?

Determining a teen's concept of their *home* and family is important. Questions regarding home include: Who lives in the home with you? How are your relationships with siblings, parents, and relatives? What are the rules like at home? Ever been homeless, in a shelter or foster care?

Worldwide, adolescents are increasingly using several forms of media each day. For a variety of reasons, teens often report inadequate sleep and sleep-related problems. Youth participation in extra-curricular activities such as after-school sports has been shown to be protective against violence and juvenile crime. Questions regarding *activities* include how many hours do you sleep every night? What do you do for fun? Are you involved in sports, religious activities, youth groups, music, and arts? How many hours per day do you watch TV? Use the Internet or computer? Play video games?

Body image disorders such as binge eating disorder and anorexia/bulimia often evolve during adolescence. Providers should screen for dietary practices and self-image. Questions regarding *diet* include: What do you think your ideal weight should be? What do you like about your body? How many meals do you eat per day? If there are concerns regarding low weight or weight restriction – do you exercise excessively, vomit, use diuretics or laxatives? If the concern is being overweight: What do you drink with meals and between meals? Do you skip meals? Do you exercise?

At this point in the interview, the provider should remind the parents about the importance of talking to an adolescent alone and review the policies regarding confidentiality. If the parents leave the room, the provider should reiterate confidentiality policies with the teen and progress to questions regarding drugs, emotions, sexuality, and safety. If the patient (generally a younger adolescent) prefers to have the parent present, a limited SSHADESS may be performed.

Most adolescents experiment with drugs at some point in their development whether limited to alcohol, caffeine, and cigarettes or extended to marijuana, cocaine, or other drugs. Adolescents who use *drugs* to manage stress are of particular concern as this can interfere with coping skills, responsible decision-making, and lead to lifelong addiction. Do you spend time with smoke, drink, or use drugs? How frequently and how much? Do you smoke or chew tobacco? Do you use anabolic steroids? Do you drink alcohol such as beer, wine, hard liquor? Do you use any illicit drugs such as marijuana or cocaine? Have you abused prescription drugs?

It is important to screen all teenagers for depression, not just those who may look depressed. Worldwide, suicide is the third leading cause of death in 15–34-year-olds. A sense of hopelessness, low self-esteem, and high self-blame are associated with the adolescent suicide. Questions regarding *emotion* include: What is your usual mood – happy, sad, both? What do you do to cope with or relieve stress? Have you ever received counseling and/or therapy? Have you ever tried cutting? Have you thought or tried to kill yourself? It is important to note that the screening for sensitive topics such as suicide does not increase the likelihood that a teen will actually become suicidal or engage in other high-risk behaviors.

As adolescents develop, many will have questions regarding their bodies, sex, pregnancy, and sexually transmitted infections, and the majority will begin sexual

experimentation. Less than half of US primary physicians routinely discuss sex, condoms, sexually transmitted diseases, contraception, and sexual orientation with their adolescent patients. However, discussing sex with adolescent patients in a clinic or office setting provides opportunities for personalized information, for confidential screening of risk status, and for health promotion and counseling. Questions regarding *sexuality* include: Are you attracted to males, females, or both? Have you ever had a sexual relationship with anyone? Have you been forced to have sex against your will? Do you use protection or contraception? What was the age of first intercourse? Sexual history should also include history of vaginal, oral, anal sex, number of lifetime sexual partners, and history of pregnancies and sexually transmitted infections.

Safety questions include screening for violence risks and should include history of fights, injuries, sexual violence, threats, and self-defense strategies. For example, have you ever been involved in a fight? Have you ever been bullied or bullied others? Have you ever used a weapon or witnessed violence? If the teen is driving, questions should also include do you drive after using alcohol or substances? Do you drive while talking on your cell phone or texting? Do you use a seat belt? Discussion should also include risks of Internet predators.

Teens are generally physically healthy but their needs vary by their developmental and physical circumstances. The *Review of Systems* should include vision, hearing, dental as well as specific questions regarding each organ system from ears, nose, and throat to musculoskeletal. The *Physical examination* allows the provider to determine the growth and pubertal development and detect abnormalities. Teens should be fully clothed for the interview portion of the visit. Before the start of the actual exam, the provider should leave the room and allow the teen to change into a gown with a screen or closed door to ensure privacy.

The height, weight, body mass index should all be obtained and plotted for age-specific norms. Blood pressure and pulse should also be obtained. Visual acuity often changes during adolescence, and teens should have vision tests during early, middle, and late adolescence. Hearing screening should be done at the baseline and repeated if there are any concerns. A dental visit should be encouraged at least once a year. In addition to the components of a routine physical, the adolescent-specific exam should include a complete assessment of sexual maturity rating, screening for scoliosis and overuse injuries (particularly prior to sports participation) and acne.

Developmentally delayed teens and young adolescents may want to have a parent with them during the exam. Chaperone policies should be well established. For example, providers may use a chaperone during the breast and genital exam of patients. *Lab tests* should be kept to a minimum. Screening for anemia, diabetes, and hypercholesterolemia should be considered based on risk factors such as poor nutrition, family history, and obesity. Screening for sexually transmitted infections should also be considered. Specific recommendations regarding adolescent screening tests and the physical exam can be found at Bright Futures: http://brightfutures.aap.org/web/

Legal Issues/Confidentiality

Adolescents can give independent consent for some health services if their capacities for understanding have sufficiently evolved. The International Convention on the Rights of the Child, almost universally ratified, limits parental powers, and duties, by adolescent's "evolving capacities" for self-determination. The Convention on the Rights of the Child (CRC) marks the age of 18 as the age of adulthood. Anyone below the age of 18 is a child unless the law applicable to the child, majority is attained earlier." Individual countries may establish an earlier age than 18 for adulthood. In 1986, the landmark British case of *Gillick v West Norfolk and Wisebech Area Health Authority* established the "mature minor principle," where an adolescent under the age of 18 years is capable of giving informed consent when she or he "achieves a sufficient understanding and intelligence to enable him or her to understand fully what is proposed."

The majority of legal systems recognize "mature minors" as enjoying adult rights of medical consent. Mature minors enjoy confidentiality and the right to treatment according to their wishes rather than their best interests. Minors incapable of self-determination may grant or deny assent to treatment for which guardians provide consent. Emancipated minors' self-determination may also be recognized, for instance, on marriage or default of adults' guardianship. Many adolescents are capable of giving consent for health problems that can occur in adolescence such as pregnancy, sexually transmitted infection (including HIV infection), mental disorders, and substance misuse.

Unfortunately, the majority of teens do not think that they have an access to confidential care. In a study of teens in the Caribbean, more than a third of respondents felt that they could not obtain confidential care from a physician. In a study of US girls aged 12–17 years, nearly 60% reported that if their parents were notified, they would stop using all or some sexual health services and

delay testing and treatment for sexually transmitted infections. Access to confidential care in most parts of the world is not well studied.

While courts have established the mature minor principle, they have not outlined what factors indicate sufficient maturity. Psychological research into adolescent decision-making has found that adolescents as least as young as 14 years are capable of making informed decisions. However, such capacities vary by the intelligence and social experiences of the individual. Health-care providers must be able to identify when a teenager can and cannot be deemed a mature minor. Parents of adolescents with intellectual deficiencies or with conditions affecting their cognitive abilities (such as brain wasting in severe anorexia or suicidality in a patient with severe depression) will often need to be involved in decision-making. Guidelines recommend that health-care providers maintain confidentiality with adolescents unless the adolescent consents to disclosure or disclosure is necessary to protect their well-being. Some states and countries have mandatory notification laws for adolescents in need of protection against neglect or abuse. Additional exceptions may arise when there is a serious or imminent threat to the life or health of an individual (e.g., suicide) or another person (e.g., transmission of serious infection or homicide). It is generally best to discuss the disclosure with the adolescent first.

Some clinicians themselves may not realize the decision-making capacity of their adolescent patients and may not be familiar with local laws and customs. Therefore, clinicians who work with teens must be familiar with local statutes and customs and advocate for enforcement of delegated responsibilities.

The emphasis that has been placed on the adolescent's growing need for privacy in these preliminary attempts at self-determination should not be seen as a denial of the role of parents in the lives of young people. The health-care team providing services to the adolescent needs to achieve a balance between supporting this important developmental task and encouraging the youth to involve parents or guardians or other trusted adults for the wisdom and experience they could contribute to the youth's decision-making. Young people who fear parental reaction to the decisions they are making about their sexuality may resist parental involvement. The reasons for resistance need to be carefully explored with the young person to facilitate self-examination. One study of unmarried pregnant teenagers found that a third of youth who did not want to inform their parents of the pregnancy had experienced family violence and feared it would reoccur if the pregnancy was shared with their parents.

Adolescents who have been granted the ability to consent may then decide whether their confidences can be shared with others such as their parents, teachers, and employers. Unfortunately, compromises of confidentiality may arise when adolescents are dependent on their parents or adults for payment of medical services. Involuntary disclosure can occur through billing or insurance records. Most countries and states do not have safeguards in place for prevention of such disclosure. However, some states in the United States and provinces in Australia have managed to provide confidential care through unique programs. In New York State, for example, the Family Planning Benefit Program provides publicly funded limited coverage for family planning services. Teens are eligible for services despite parental income or insurance status. Insurance bills are not sent to the patient so that adolescents can receive services and providers can seek payment without worrying about breaching confidentiality.

Summary

Although some teens suffer from chronic illnesses, the majority of teens are physically healthy and their interactions with the medical community are limited. The adolescent interview is a unique opportunity to reinforce good health practices, while discouraging high-risk behaviors. Prime consideration should be given to confidentiality, communication, and cultural sensitivity. The SSHADES is an example of a strength-based screening format for obtaining the psychosocial history, which focuses on the positive. During the course of the interview, teens should be empowered to develop their own solutions to problems and to take responsibility for their own health care.

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401 Special Adolescent Concerns: Complementary and Alternative Medicine in Adolescents

Cora Collette Breuner

Complementary and alternative medicine (CAM) treatments are increasingly utilized in pediatric and adolescent medicine. Approximately 12% of teens in the general population use some form of CAM therapy. These therapies are more commonly used in children and adolescents with chronic illness.

Herbal Therapies

Herbal therapies and supplements are used for the prevention and treatment of upper respiratory tract infections, sleep issues, headaches, and depression/anxiety. The following is a brief description of a most frequently used herbal therapies and supplements.

Echinacea

Echinacea is widely popular as a natural immune booster and has been traditionally used to prevent and treat colds and other infections. In a Cochrane review, *Echinacea* preparations were found to be better than placebo for the treatment of upper respiratory symptoms. In the 2–11-year age group, Echinacea was not reported to decrease severity of upper respiratory infections.

Adverse effects may include skin rash in those allergic to ragweed, gastrointestinal (GI) upset, and diarrhea.

Chamomile

Chamomile has been used for GI discomfort, infantile colic, and mild anxiety. Chamomile contains chamazulene: an anti-inflammatory agent, apigenin: contains benzodiazepine properties, and bisapolol: an anti spasmodic.

Chamomile is regarded as safe although cases of contact topic allergic reactions have been reported.

Ginseng

Ginseng has been purported to enhance both mental and physical strength. In a meta-review, ginseng was noted to improve physical performance in young, active volunteers during cycle ergometer exercises.

Adverse effects may include nervousness, insomnia, bleeding, and GI disturbance. Importantly, ginseng may interact with oral anticoagulants, antiplatelet agents, corticosteroids, and hypoglycemic agents.

St. John's Wort

St. John's wort is currently used for depression and anxiety. Hypericin and hyperforin, two of at least ten active ingredients in St. John's wort, inhibit the reuptake of serotonin, norepinephrine, and dopamine. In mild depression, St. John's wort was superior to placebo.

Adverse effects include gastrointestinal (GI) symptoms, dizziness, phototoxicity, and serotonin syndrome when used with selective serotonin reuptake inhibitors (SSRIs). St. John's wort has been shown to induce the cytochrome P-450 metabolic pathway and therefore may interfere with metabolism of cyclosporine, oral anticoagulants, oral contraceptives, and certain antiretroviral agents.

Valerian

Valerian has been employed as a sedative agent, which may be due to its binding of gamma-aminobutyric acid (GABA) receptors. Efficacy of valerian as a sedative or anxiolytic has not been determined.

Adverse effects include headache, excitability, irritability, and cardiac disturbances. Valerian should not be taken when consuming sedatives and/or alcohol.

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Melatonin

Melatonin is a neurohormone used in the treatment of delayed sleep syndromes. In one study in teens, participants had quicker sleep onset, longer sleep duration, and a decrease in school problems. In adults with primary sleep disorders, a meta-review showed a reduction in sleep latency. Melatonin is considered relatively safe when used for a period of days or a few weeks. The safety of long-term use is not known.

Feverfew

Feverfew is well known for its use the prevention of migraine headaches. 2 randomized trials have shown benefit of feverfew for the prevention of migraines.

Adverse effects include occasional mouth ulcerations, contact dermatitis, dizziness, diarrhea, and bleeding due to its inhibition of platelet aggregation.

Safety Issues

Adverse events associated herbal therapies should be reported as soon as possible to FDA MedWatch program (800)332–1088 or www.fda.gov/Safety/MedWatch/default.htm.

Acupuncture

Acupuncture originated as an ancient Chinese therapeutic treatment and is based on the theory that energy (*Qi*,Chi) flows along channels known as meridians, connected by acupuncture points. Disruption of the meridians may lead to disease; realignment of flow by acupuncture is felt to restore health. Acupuncture may be beneficial in patients who have dental pain, postoperative nausea and vomiting, or chemotherapy nausea and vomiting. Other opportunities for promoting use of acupuncture in the adolescent include migraine headaches, dysmenorrhea, and substance abuse.

Complications include pneumothorax, septic sacroilitis, epidural, and temporomandibular abscess.

Massage

Massage is commonly utilized in the pediatric and adolescent population and is thought to release muscle tension, remove toxic metabolites, and facilitate oxygen transport to cells and tissues. In the pediatric population, massage has been shown to be beneficial in preterm infants, ADHD, and juvenile rheumatoid arthritis. It may also decrease anxiety in those with eating disorders and improve postpartum depression. Massage can improve lung function in those with cystic fibrosis and asthma. In a Cochrane review on massage for adults with low back pain, massage was considered beneficial.

Adverse effects include temporary pain or discomfort, bruising, swelling, or sensitivity or allergy to massage oils.

Chiropractic

Chiropractors (DC) treat many conditions including low back pain, cervical pain, headache, otitis media, dysmenorrhea, and carpal tunnel syndrome. Chiropractic is based on the theory that most diseases can be traced to malpositioned bones in the spinal column called "subluxations" that lead to the entrapment of spinal nerves. Physical adjustment of the spine restores proper alignment of the spine by relieving nerve entrapments.

In an adult study comparing chiropractic spinal manipulation, sham manipulation, and a back education program, improvement was greater in the manipulation group than in other groups. In separate studies, the results were not as encouraging. Additional controlled studies are needed to evaluate the long-term cost-effectiveness of chiropractic in children.

Complications include strokes, myelopathies, and radiculopathies after cervical manipulation.

Homeopathic Medicine

Homeopathy aims to stimulate the body's own healing responses through the ingestion of extremely small doses of substances that when larger doses are taken, may produce characteristic symptoms of illness in healthy people. In a meta-analysis of 32 trials in adults, individualized homeopathy was significantly more effective than placebo in treating symptomatic seasonal allergies. However, when the analysis was restricted to the methodologically sound trials, no significant effect was seen. Complications are rare and include aggravation of symptoms.

Mind–Body Therapies/Yoga

Meditative interventions have been used to decrease symptoms associated with treatment of cancer, disordered sleep, diabetes, affective disorders, irritable bowel

syndrome, and eating disorders. More research is needed to support these therapeutic approachs to healing.

Spirituality/Reiki/Prayer

Pediatric patients and their families may bring their spirituality and faith into the office in regard to their children's health. In a thoughtful review by Barnes et al. (2000), providers are given suggestions on how to incorporate some approaches to spirituality in their practice. Also education and further research, opportunities are discussed.

Table 401.1

Talking with your patients about CAM (Breuner 2002 Complementary medicine in pediatrics: a review of acupuncture, homeopathy, massage, and chiropractic therapies. Curr Probl Pediatr Adolesc Health Care 32(10):353–384)

Be open-minded. Most patients are reluctant to share information about their use of CAM therapies because they are concerned their physicians will disapprove. By remaining open-minded, you can learn a lot about your patients' use of unconventional therapies. These strategies will help foster open communication
Ask the question. I recommend asking every patient about his or her use of alternative therapies during routine history taking. One approach is simply to inquire, "Are you doing anything else for this condition?" It is an open-ended question that gives the patient the opportunity to tell you about his or her use of other health care providers or therapies. Another approach is to ask, "Are you taking any over-the-counter remedies such as vitamins or herbs?"
Avoid using the words "alternative therapy," at least initially. This will help you to avoid appearing judgmental or biased.
Do not dismiss any therapy as a placebo. If a patient tells you about a therapy that you are unaware of, make a note of it in the patient's record and schedule a follow-up visit after you have learned more – when you will be in a better position to negotiate the patient's care. If you determine that the therapy might be harmful, you will have to ask the patient to stop using it. If it is not harmful and the patient feels better using it, you may want to consider incorporating the therapy into your care plan
Discuss providers as well as therapies. Another way to help your patients negotiate the maze of alternative therapies is by stressing that they see appropriately trained and licensed providers and knowing whom to refer to in your area. Encourage your patients to ask alternative providers about their background and training and the treatment modalities they use. By doing so, your patients will be better equipped to make educated decisions about their health care
Discuss CAM therapies with your patients at every visit. Charting the details of their use will remind you to raise the issue. It may also help alert you to potential complications before they occur

Conclusion

Health-care providers should ask about CAM use in order to help pediatric and adolescent patients navigate their own health. Improved communication can be addressed by following the recommendations in *Table 401.1*.

Web Sites

American Academy of Pediatrics Holistic Medicine. http://www.aap.org/sections/chim/default.cfm

National Center for Complementary and Alternative Medicine. http://www.nccam.nih.gov

HerbMed Database. http://www.herbmed.org

Natural Medicines Comprehensive Database. http://www.naturaldatabase.com

The Stress Reduction Clinic at the University of Massachusetts. http://www.umassmed.edu/cfm/clinical. cfm

http://www.americanyogaassociation.org/

American Association of Oriental Medicine. http://www.aaom.org

American Academy of Medical Acupuncture. http://www.medicalacupuncture.org

American Chiropractic Association. http://www.amerchiro.org

International Chiropractors Association. http://www.chiropractic.org

National Center for Homeopathy. http://www.homeopathic.org

American Massage Therapy Association. http://www.amtamassage.org

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402 Special Adolescent Concerns: Military Service

C. Anita Robinson · Jeffrey W. Hutchinson · William P. Adelman

The opinions expressed herein are those of the authors and do not represent the official policy or position of the US Army, US Navy, US Air Force, US Department of Defense, or the US Government

Military Culture and the Adolescent

Across the globe, sovereign countries rely disproportionately upon their adolescents and young adults to make up their military population. Professional militaries have a service focus, an expert knowledge, a professional ethos, and a unique culture. Military culture is the common set of norms within the military that helps with organization and provides the individual with a sense of continuity and community. Military culture exerts great influence upon individual military members, with vast and sometimes conflicting data, supporting dual roles of military culture as protective against certain negative health outcomes (e.g., obesity), while contributing to others (e.g., tobacco use). Health-care providers of military adolescents must appreciate the influence of military culture upon adolescent development and health in order to provide optimal care to this population.

The form of military service influences the significance of service for the individual. For example, in countries with a compulsory military or national service (e.g., Austria, Israel, Norway), failure to perform military service due to health or other reasons places the adolescent outside of his or her peer norm and may have negative developmental consequences. In contrast, in large countries where military service is voluntary (e.g., the USA), the adolescent who chooses a military career may be part of a small minority and so may have difficulty finding a provider, outside of the military health-care system, who is culturally sensitive to his needs. The role of the military and its inherent culture influences health care among this adolescent population.

The adolescent health provider is likely to interact with two different adolescent populations associated with the military – dependent children of active duty or retired military personnel and the adolescent active duty member. Understanding the unique cultural milieu in which these adolescents live, work, and receive health care will assist the practitioner with directed, sensitive, and optimal health care. The purpose of this chapter is to review common military-specific adolescent health issues and offer an approach to adolescents associated with the military. While the topics addressed are applicable internationally, most examples provided are of the US military based upon the expertise of the authors.

Dependent Youth

A 13-year-old Colombian female, whose father is a member of the Colombian Armed Forces assigned to the Colombian embassy in Washington, DC, presents with a history of right-sided headache and jaw pain that began intermittently 6 months prior to relocation that progressed to constant pain since the move. There was no history of trauma, dental issues, previous headache, or family history of headache. This was the first move for the family. Despite having her parents and sister with her, she still missed her neighborhood, school friends, and family in Colombia. A careful psychosocial history revealed her anxiety since the relocation. She was diagnosed with temporomandibular joint disorder and anxiety. She was referred to oral surgery and counseling.

The Approach to the Dependent Adolescent

In general, dependent adolescents have similar medical illnesses as their civilian counterparts. Cultural differences not withstanding the provider's approach to the military dependent adolescent should be the same worldwide. The provider should approach each patient in a developmentally appropriate manner and interview the

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parent and teen together as well as the teen separately. In the USA, the rate of risk-taking behaviors is slightly less for the dependent youth of active duty military as compared with the youth not associated with the military community.

Unique Issues Affecting the Dependent Adolescent: Relocation and Deployment

The possibility and reality of relocation, frequent moves, and deployment of a parent to a combat zone presents unique cultural influences upon a dependent youth of active duty military. A military youth self-identifies as culturally separate from his/her peers in this context. Undergoing these stressors serves to build resilience in some youths and causes worsening health outcomes in others. An increase in somatic complaints and mental health issues can surface before, during, and after a relocation or deployment. Conditions such as school problems, learning disabilities, attention-deficient hyperactivity disorder, hypertension, eating disorders, anger, fear, anxiety, depression, substance use, and child abuse may be influenced by the military lifestyle.

The emotional adjustment for these life events has been described within the context of four discreet stages: *pre-deployment* (soldiers are notified of impending deployment and some are sent away from their families temporarily to train for the mission), *deployment* (soldiers are sent away indefinitely), *sustainment* (roles within the family unit change as new routines emerge), and *redeployment* (preparation to return home and readjustment for the returning soldier and the family). Reactive symptoms to deployment have been described in all four stages, and a youth may present at any stage with new somatic complaints, mental health concerns, or exacerbation of a chronic illness. The external environment heightens the internal stress of a youth during these times. Thus, the provider has to expand the psychosocial interview from school, home, and friends to include the role of community. For some adolescents, usually those with strong home and community supports, stressors of deployment and relocation builds resiliency, as adolescents adapt to new challenges. For other adolescents, such as those with difficulty at home prior to deployment, or who lack community support, stressors exacerbate baseline problems. When there are instances of problematic adjustments, the provider should review the questions in *Table 402.1* and gather detailed information regarding previous stressors with new situations, past and current school problems, mental health disorders, chronic illness, and undiagnosed family issues. A provider who is not familiar with the military culture must strive to understand the unique cultural milieu facing the dependent youth whose parents are associated with military service.

Table 402.1
Militaryspecific psychosocial screening questions

Family member adolescents	Active duty adolescents
How often have you moved? When was your last move? Who do you go to for support? Has anyone in your family deployed? How has your life changed during deployment? How has deployment impacted your roles and responsibilities at home, at school, with work, with free time? Have you noticed any changes in your family members before, during, or after deployment? Are there any deployments planned for the future? What have you learned from the last deployment that will help you with the next deployment?	Tell me about your experience in the military How long are you planning to serve in the military? Have you had any military experiences that affect your life now? Do you use anything to give yourself an advantage or to make your body or mind feel better or stronger? Why? Do you drink alcohol more than you want to? Do you use alcohol or drugs to feel better emotionally? (Substance use screening tool can be used here) Do you have anyone you can talk to? Do you feel like a valued member of your unit? Do you own a weapon?

Adolescents in Active Military Service

A 19-year-old female medic returned 6 months ago from Afghanistan after a 12-month tour with her unit. She comes to the office seeking contraceptive counseling. Her unit is tasked to deploy again in 6 months. She is in good health but upon psychosocial review of systems, she reports insomnia and binge drinking. During her prior deployment, she cared for critically injured military personnel and noncombatants and has not spoken with anyone at home because none of her other friends are in the military. She was diagnosed later with Post Traumatic Stress Disorder and referred for counseling. She returned to the clinic a month later with some improvement, though not in counseling.

The Approach to the Adolescent in the Military

Military leaders describe military culture as disciplined, loyal, hardworking, and honest, with members who value self-sacrifice, courage, and physical rigor. When these cultural influences combine with the developmental stage of late adolescence, there is potential for medical conditions to be minimized or hidden from the provider, especially if the condition is feared to influence military advancement or reputation within a unit. The military labor force, in direct contrast to the civilian labor force, is adolescent centric, with the largest group of those in the military under 25 years old. Some branches of service (e.g., US Marines) employ adolescents for almost half of their forces. Providers who care for those in the military should appreciate that many adolescents perceive invulnerability, while frontal lobe critical thinking is still in development.

In countries like the USA, with a comprehensive universal military health-care system, civilian providers are still likely to care for service members in areas of large military populations because Reservist, National Guardsmen, and a small number of adolescents, who have been medically retired because of disabilities, typically live away from major military facilities. The majority of service members seen are well, which allows health-care providers to focus on injury prevention and fitness in addition to treating acute and chronic illnesses. However, all aspects of medical care must be considered, including the impact of service. Like civilian adolescents, military members require psychosocial screening such as the home, education/employment, activities, drugs, sex/sexuality, suicide (HEADSS) and additional questions that are military specific. See *Table 402.1*.

Most service members are not directly involved in fighting, yet may experience emotional or physical trauma when deployed or while training. Assessment of preventable behavior and resilience can guide providers in appropriate anticipatory guidance. Suicide, depression, disordered eating, and substance use including tobacco are typically discussed with patients when there is a related chief complaint; however, the frequency of conditions and at-risk behaviors amongst active duty personnel suggests that these issues require more frequent discussions. An informal behavioral screening may identify highly visible issues such as suicidal thoughts as well as common issues such as stress and coping mechanisms. Providers can incorporate behavioral questions into visits, creating the opportunity to identify these significant behavioral issues.

Screening adolescents before military service is as important as providing comprehensive health care to the adolescents engaged in military service. In countries with mandatory service, physicians need to screen for conditions that may have a negative impact on their service or health while serving. In countries with voluntary service, screening determines if the applicant is fit to serve before training begins. Adolescents in both situations may benefit from withholding information. Those in a mandatory service circumstance can achieve a more desirable position by withholding information, and conditions like uncontrolled attention deficit hyperactivity disorder (ADHD), asthma, or depression may disqualify adolescents who desire to serve in a voluntary capacity. Providers should be aware of what service entails and approach the interview with the question of how this adolescent will cope with the stresses of being in the military. In the military, readiness to perform missions is a priority and central to the culture. The medical community is an essential element in maintaining a healthy force able to complete objectives. Health-care providers who care for military personnel and their families will do well to include educated questions about military service in their assessment of adolescents.

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403 Special Adolescent Concerns: Transition to Adult Care

Anisha Abraham · Kirsten Hawkins

Transition is defined as the process of transferring care from a pediatric to an adult health-care practice or reorienting within a family medicine or internal medicine pediatrics practice, so that an adolescent assumes responsibility and management for his or her own health decisions. Transition is based on the teen's needs, taking into account individual strengths and interests as well as developmental status and age. Health-care providers are of unique importance in this process because of their contact with teen patients and the close relationships that often develop. A well-timed transition from child-oriented to adult-oriented health care, overseen by the provider, allows young people to optimize their ability to assume adult roles and functioning.

In the last several decades, survival rates associated with chronic illnesses have improved dramatically, so that a high number of children with chronic illnesses and/or disability now survive to adulthood. In the United States, for example, more than 90% of children with chronic illness survive beyond their 20th birthday. Most young people with special health-care needs are able to find their way into and negotiate through adult systems of care. However, some adolescents and young adults with severe medical conditions and disabilities experience difficulty transitioning from child to adult health care.

There are numerous potential barriers to achieving successful health-care transitions. For example, the patients, families, and health-care providers may be very reluctant to sever an established relationship and allow the transition to occur. Adolescents in transition may have difficulty obtaining adequate insurance and health-care coverage. There may be a lack of institutional support and inadequate time to address important transition issues. Finally, there may be difficulties obtaining a suitable health-care provider.

The goals of transition are to provide continuous, comprehensive, and compassionate health care. The following are the recommendations regarding transition:

1. **Start early:** The transition should be organized well ahead of time. Create a written individualized health-care transition plan by age 14 with input from the teen and family. The transition plan should be introduced as a normal part of growing up to lessen the likelihood that the teen and family feel they are being pushed out of the practice. The plan should include what services need to be provided, who will provide them, and how they will be paid for. The plan should be reviewed and updated annually and whenever transfer occurs. Ideally, the process should occur slow enough to allow the teen time to adjust and take responsibility for care.
2. **Provide a portable medical record:** Prepare and maintain an up-to-date medical summary that is portable and accessible. This information is the key to successful health-care transition and provides the common link for collaboration among health-care professionals.
3. **Identify knowledge and skills:** Self-evaluation should be an important part of the plan. Ensure that the patient and family (particularly those that are reluctant to transition) are involved in the process and understand the process of receiving adult-centered care.
4. **Create a health-care transition plan:** This applies to all adolescents but is of particular importance for patients with special health-care needs. Outline educational goals, steps to independent living, and emergency plans. Identify an adult health-care professional who is sensitive to the needs of young people and can assume responsibility for current health care, care coordination, and future health-care planning. Schedule an appointment with an adult practice prior to the patient transferring, leaving for secondary education or independent living. This ensures that if the teen encounters problems with the adult provider or practice, a backup is still in place.
5. **Review health insurance:** Depending on the country and health-care system, coverage for young adults may be vastly different than for children and adolescents. Ensure that the teen has access to an affordable and ongoing health care.

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6. **Ensure consistent guidelines:** Apply the same guidelines for primary and preventive care for all adolescents and young adults. Recognize that young people with special health-care needs may require more resources and services than do other young people to optimize their health.

Transition involves a reorientation of clinical services to parallel the teen's increasing maturity and emerging adulthood. The purpose of transition is to maximize lifelong functioning and potential through the provision of developmentally appropriate health care that continues as the individual moves from adolescence to adulthood. There are a number of web-based resources available for providers, families, and teens such as the Health Care Transitions tool kit available at http://hctransitions.ichp.edu/. If done properly, transition of care can have a lasting impact on a teen's well-being.

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Pediatric Orthopedics

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404 About Children Bones

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Lower-Extremity Alignment in Children – What Is Normal?

Lower-extremity alignment is a common cause for concern among pediatricians and families. The most common concern is rotational malalignment, which manifests as "intoeing" or less commonly "outtoeing." Often, parents will associate this with tripping commonly seen at this age as the child is beginning to walk, and a history of parental treatment with "special shoes" is common. There are three main causes of an internally rotated gait: metatarsus adductus, internal tibial torsion, and excessive femoral anteversion. These are all, to some extent, a result of "packaging" and in most cases will self correct with growth.

Metatarsus Adductus is characterized by a curved lateral border of the foot. It should be assessed for rigidity. Mild deformities that are passively correctable often require no treatment. Prior to walking age, parents may affect the resolution by stretching the foot to a corrected position several times a day. When the child begins walking, supportive leather shoes will maintain the medial border in a corrected position and the baby will experience corrective forces with each step. Multiple studies have shown prescription shoes to add no benefit to the resolution of flexible metatarsus adductus. In difficult, less flexible cases, short or long leg casting may be indicated. If shoe wear is not a problem, some amount of metatarsus adductus is acceptable at the conclusion of treatment.

Internal Tibial Torsion is physiologically normal in the 2–4 year-old child. It is more common in boys than girls. In early fetal development, the lower extremities are internally rotated and undergo "unwinding" throughout gestation and in the first several years of postnatal development. Depending on the degree to which the tibiae correct prior to weight bearing, the feet may be internally rotated during the first years of life. It is easy to quantitate tibial torsion by examining the child prone. With the knee flexed to 90°, the thigh–foot angle is estimated from above. While the growth plates at the proximal and distal tibia are responsible for longitudinal growth of that bone, there is some limited capacity for the same growth plates to correct the rotational deformity. Parents can expect to see torsional improvements in the tibia and the resultant intoeing gait pattern, up to age 4. Parents are cautioned that children may prefer to sit on the floor directly on top of their feet, but this creates an internal force on the tibia that the growth plate may be unable to overcome. The normal range for the adult foot is between 10° external and 5° internal. After the age of 4, if persistent tibial torsion exceeds this limit and the child has difficulty with gait due entirely to pathologic rotation of the tibia, surgical osteotomy and realignment can be performed, although it is rarely necessary.

Increased Femoral Anteversion results from a greater-than-average amount of internal femoral rotation. This results in an intoeing gait where the patellae can be seen to be internally rotated as well as the feet. These children often prefer to sit in a "W" position. Femoral Anteversion is best assessed prone. With the knees at 90°, it is easy to quantitate hip internal rotation and external rotation. This range should ideally be evenly split between the two. If there is significantly more internal range than external, excessive femoral anteversion is likely (see ❯ *Fig. 404.1a* and *b*). To estimate this version, the greater trochanter can be palpated as the hip is rotated. The position in which the trochanter is felt to be most prominent estimates anteversion. Excessive anteversion can be expected to grow out by age 8. If anteversion persists beyond that age and activities are difficult due to tripping, the femurs can be surgically realigned, although this is rarely required.

Outtoeing is a less common concern and is often due to an external rotation contracture of infancy. As the child begins to walk, this will usually resolve without treatment. After eliminating hip or neuromuscular etiologies for this gait, parental reassurance will suffice as treatment.

Frontal-plane deformities include genu varum (bow-legs) and genu valgum (knock-knees). As children first begin to bear weight, their centers of gravity must remain very low and their base of support must be very wide to provide the greatest stability for this new skill. The combination of subtly bent femora and tibiae with a broad, bent-knee posture gives the appearance of bowed legs. Internal tibial torsion, which is physiologic at this age, compounds this perception. The physician is advised to examine the child supine. Care should be taken to position the knee caps directly forward and then cover the feet. Often the apparent bow legs will then disappear.

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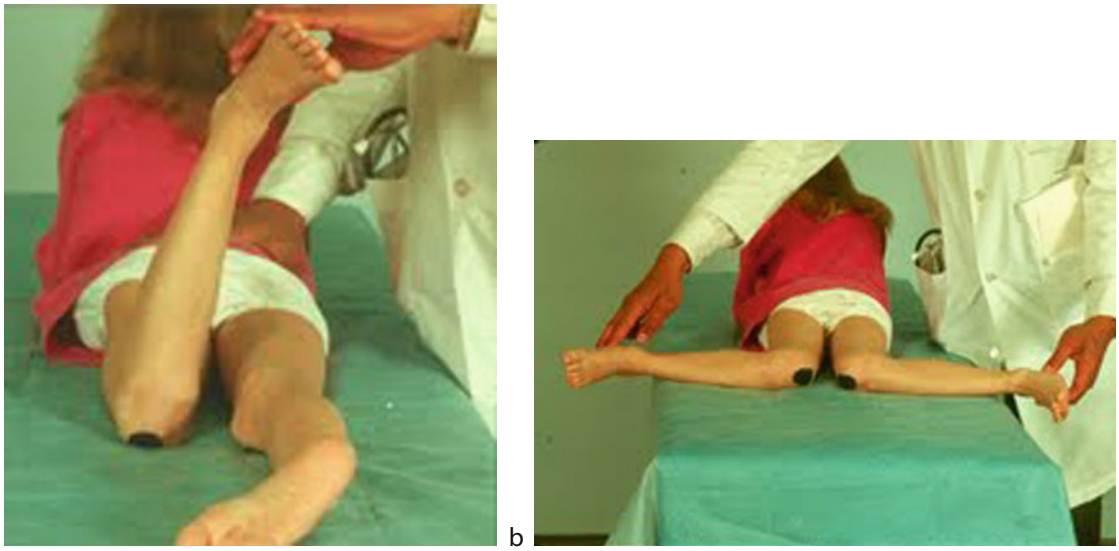

Figure 404.1

Some amount of bowing is expected prior to age 18–24 months, after which the lower-extremity growth plates tend to overcorrect this deformity such that children from age 3–5 tend to appear knock-kneed. The adult normal range is approximately 7° of valgus at the knees and will be attained by 7 years. In general, children may have bowing of the lower extremities as a physiologically normal phenomenon until about age 2. Persistent bowing should raise concern for Blount's disease or a metabolic syndrome such as rickets. Children with Blount's disease suffer from a poorly functioning medial growth plate that leads to progressive deformity. Bracing is often required in these cases, as severe deformity refractory to nonoperative treatment may develop. In general, heightened concern is appropriate in children with very short stature, dysmorphic features, family history of dwarfism, obesity, generalized osteopenia with wide physes, or extreme deformity. In the case of asymmetric genu valgum, obtain a fracture history for the involved extremity as proximal tibial metaphyseal fractures are known to grow into valgus for about 18 months after the injury and then tend to self correct.

Limb-length discrepancies less than 2 cm are common in the adult population. Discrepancies which are expected to be less than 2 cm at skeletal maturity are most often asymptomatic or can be treated adequately with an in shoe lift on the short side. Once a child has been identified as having a limb length discrepancy, it is important to attempt to determine the source of the discrepancy as well as the leg that is the pathologic leg (the long or the short). Depending on the etiology, a variety of patterns of progression can be anticipated. From serial examinations, the expected limb length discrepancy at skeletal maturity can be estimated accurately. The clinical examination includes assessment of pelvic obliquity done standing behind the patient with the patient's knees straight, ankles together, and examiner's fingers on the iliac crests. A gross estimate of discrepancy can be documented. If a discrepancy is noted, blocks are placed under the short leg to level the standing pelvis, which gives a more accurate estimate. With the patient supine, the examiner can measure the distance from the ASIS to the medial malleolus side to side. A Galeazzi test is performed by flexing the hips to 90° with the knees bent, which demonstrates a femoral inequality and then placing the heels on the exam table with the knees remaining bent to estimate the tibial contribution. Treatment options vary by estimated discrepancy at skeletal maturity.

Anticipated LLD at skeletal maturity	Preferred intervention
<2 cm	Shoe lift only if symptomatic
2–5 cm	Timed epiphysiodesis
5–15 cm	Lengthening +/− contralateral epiphysiodesis
>15 cm	Amputation

There are a variety of surgical techniques for epiphysiodesis. In general, approximately 9 mm of length can be gained from the distal femoral physis and 6 mm of length from the proximal tibia each year until the conclusion of growth. The surgery is aimed at ablating one or more growth plates in the long leg at a time calculated to correct the discrepancy at the conclusion of growth. Alternatively, if there is inadequate growth remaining or the discrepancy is too large to address with epiphysiodesis without compromising proportion, limb lengthening can be undertaken. Often the lengthening is limited by the soft tissue structures, including nerves, vessels, and tendons. Additionally, surgical lengthening is fraught with complications including pin tract infections, premature consolidation, fracture through regenerate, failure to obtain desired length, as well as lengthy encumbrance and unsightly scars. In the unfortunate rare patient who has a LLD at skeletal maturity anticipated to be greater than 15 cm, the most comfortable, predictable surgical option is definitive amputation.

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405 Limping Child

John R. Fowler · James T. Guille

Musculoskeletal complaints are a common reason for presentation to the primary care physician, emergency department, and orthopedic surgeon. The limping child presents a diagnostic challenge with many nonspecific findings and the potential for significant morbidity if the diagnosis of a serious condition is missed. Efficient and cost-effective diagnosis and treatment of the underlying condition requires a systematic approach.

Definition/Classification

Limping is defined as the pathologic alteration of the smooth, rhythmic, and regular gait pattern. The evaluation of gait in a child is complicated by the observation that children do not achieve a mature gait until the age of 3 and an adult gait until the age of 7. Further confusion results from the observation that toddlers walk with a wide-based gait, increased flexion of the hips and knees, and spend an increased amount of time in double stance phase to maintain balance. To understand abnormal gait, the normal gait cycle must be defined.

Abnormal gait can be classified as either painful (antalgic) or painless (non-antalgic). Antalgic gait is a reflex response to prevent pain in an extremity and results in decreased stance phase on the injured side and decreased stride length on the contralateral extremity, allowing less time to be spent in stance phase on the injured extremity.

Etiology

Pain, weakness (neuromuscular problem), and structural/mechanical factors are the primary causes of a limp. Obtaining a thorough history and performing a careful examination can often identify the origin of the pain, and the differential diagnosis can be narrowed. Broadly, the etiology of limp can be broken into six major categories: trauma, infection, malignancy, inflammatory, congenital, and neurologic. The main concern in the child with a limp is not to determine an exact etiology, but rather to avoid missing serious pathology and expeditiously to begin appropriate management of the underlying condition. Oudjhane found that 20% of children less than 5 years old with an acute limp of unknown etiology had unsuspected fractures.

Clinical Manifestations

The specific etiology of the limp leads to different clinical manifestations. Infection or inflammatory conditions may manifest as systemic illness. Patients with septic arthritis will have fever, swelling, eyrthema, and decreased range of motion of the affected joint. Complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) will be elevated. Patients with inflammatory arthritis may have signs similar to septic arthritis, may have fever and elevated WBC, and elevated rheumatoid factor (RF) and anti-nuclear antibody (ANA). Diskitis may present with back pain and decreased spinal range of motion, although this sign is present in only 50% of cases. Diskitis in adolescents may manifest as buttock and leg pain as a result of nerve root irritation. Patients with underlying malignancy may have night pain and constitutional symptoms. Children less than 3 years old often present acutely with limp or a refusal to bear weight on the lower extremities. Overuse syndromes often manifest as pain with activities.

Diagnosis

Diagnosis begins with a focused history and physical examination that direct appropriate laboratory and radiographic studies. The history should focus on defining the character of the limp. An important distinction in evaluating a limp is the presence of pain. The absence of pain suggests a neuromuscular, metabolic, or congenital/developmental abnormality. A failure to achieve appropriate developmental milestones warrants a neuromuscular and/or metabolic workup. When pain is present, determining the duration and frequency is essential. Acute onset of pain over a few days is more indicative of trauma or infection, while a gradual worsening over weeks is more consistent with inflammatory disorders or mechanical

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symptoms. Malignancy may have either an acute or insidious onset of symptoms. Constant, unremitting pain is especially concerning, suggesting an intramedullary process such as tumor or infection. The temporal character of the pain is another important aspect. Morning pain may suggest an inflammatory disorder whereas pain after activity is more consistent with an overuse injury such as a stress fracture. Night pain is often attributed to "growing pains," but malignancy must also be considered. Conditions such as slipped capital femoral epiphysis and diskitis can result in referred pain to the leg. The anterior branch of obturator nerve passes close to the hip joint, and if irritated, can cause medial knee pain. A careful history should investigate for subtle trauma, mechanism of injury, and attempt to localize the problem to a specific area. Adolescents may need to be questioned separately from their parents to obtain a proper sexual history and assess risk for gonococcal arthritis. Pain that prevents children from participating in activities or play is worrisome.

After a careful history has been obtained, a focused physical examination is undertaken. The best opportunity to observe a true limp is by observing when the child does not know he or she is being watched, such as when the child is walking to the exam room with the parent. Most authors recommend adopting a systematic approach to analyzing gait, noting how the foot strikes the floor, any abnormal limb rotation, asymmetry of stance phase, and limited dorsiflexion of the ankle. Once in the exam room, the patient should be examined in the standing position. The spine should be examined, noting any signs of scoliosis, trunk shift, pelvic obliquity, and shoulder asymmetry. The skin should be examined for evidence of café au lait spots, hairy patches, and sacral dimples.

After the standing examination, the child should be placed on the table and examined. The lower extremities should be inspected for asymmetry, deformity, rash, swelling, and puncture wounds. The soles of the feet should be examined for the presence of foreign bodies. Note the resting position of the limbs (a child with septic arthritis of the hip will hold the hip flexed and externally rotated). Leg length should be measured from the ASIS (anterior superior iliac spine) to the medial malleolus. Inspect for muscle hypertrophy and/or muscle atrophy. An attempt should be made to identify a point of maximal tenderness and to localize the area of pathology. Take each joint through its full range of motion; note any pain, contracture, or muscle spasticity. Specifically examine the metaphyseal region of each long bone, as this is a common location of pathology. Test the patellofemoral joint for signs of apprehension and pain. Test the sacroiliac joint by direct percussion posteriorly and by stressing the joint with the FABER (flexion-abduction-external rotation of the hip) position. A child that will crawl, but not walk, localizes the pathology to an area below the knee.

Radiographic evaluation of the child with a limp begins with orthogonal plain radiographs of the affected limb, adding oblique views as needed. Plain radiographs may identify fractures, osseous lesions, and/or joint space widening consistent with effusion. MRI with and without contrast may be the most useful imaging study in the evaluation of pediatric patients suspected of musculoskeletal infection or malignancy. Bone scintigraphy has a role in the assessment of children who do not have obvious localizing signs of infection. The triple phase technetium 99 m bone scan has been demonstrated to be superior to other standard screening tests for infection. The triple phase bone scan, however, has a low sensitivity for septic arthritis, especially when there is adjacent osteomyelitis. Acute leukemia may also result in a cold scan. If the region of pain is easily identified, an MRI of the specific region is preferable for diagnosing infection. Ultrasound is used to detect an effusion in the patient suspected of having a septic joint, with a sensitivity of greater than 95%, although it is unable to differentiate between sterile effusion and sepsis.

Laboratory testing is indicated when a child presents with an acute, nontraumatic limp and signs and symptoms of fever, malaise, night pain, or localized complaints. Initial testing should include a complete blood count with differential, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), anti-nuclear antibody (ANA), and rheumatoid factor (RF). Lyme titers should be obtained in any patient with acute arthritis who lives in an endemic area or has recently traveled to one. If septic arthritis is suspected, blood cultures should also be obtained, although they are positive in only 40–50% of cases. ESR becomes elevated within the first 24–48 h and returns to normal over 3 weeks whereas CRP rises within 6 h and returns to normal within 6–10 days of treatment.

Differential Diagnosis

The differential diagnosis for the child with a limp is extensive (see *Table 405.1*). The differential can be divided into six main categories: trauma, infection, inflammatory, neurologic, neoplasm, and developmental. The differential ranges from benign diagnoses such as transient synovitis to serious disorders such as malignancy and septic arthritis. The vast differential diagnosis can be narrowed by separating the conditions by the ages at which they most commonly occur (*Table 405.2*). The most likely diagnoses in patients less than 4 years old

Table 405.1
Differential diagnosis by category

Trauma	Infection	Inflammatory	Neurologic	Neoplasm	Developmental
Fracture	Septic joint	Juvenile rheumatoid arthritis	Cerebral palsy	Osteosarcoma	Legg–Calve–Perthes
Osteochondritis dissecans	Osteomyelitis	Lyme disease	Meningitis	Acute leukemia	Clubfoot
Stress fracture	Foreign body	Transient synovitis	Muscular dystrophy	Osteoblastoma	Congenitally short femur
Slipped capital femoral epiphysis	Diskitis	Sever's apophysitis	Myelomeningocele	Osteoid osteoma	Accessory tarsal navicular
Chondromalacia patellae	Appendicitis	Acute rheumatic fever		Ewing Sarcoma	Osgood–Schlatter
Sickle Cell Osteonecrosis	Psoas abscess	Reactive arthritis		Neuroblastoma	Sinding-Larsen–Johansson
Child abuse	Cellulitis	Systemic lupus erythematosus		Spinal cord tumor	Tarsal coalition
Sprain/strain					Developmental dysplasia of hip
					Leg length discrepancy
					Discoid lateral meniscus

include septic arthritis, diskitis, osteomyelitis, transient synovitis, developmental dysplasia of the hip, coxa vara, cerebral palsy, leukemia, and trauma from child abuse. The differential from ages 4–10 expands to include a variety of diagnoses. Infectious etiologies such as septic arthritis, osteomyelitis, and diskitis are still prevalent. Legg–Calve–Perthes disease is a common painless hip disorder responsible for limping in this age group.

The most common diagnoses in patients older than 10 years include fracture, slipped capital femoral epiphysis, transient synovitis, tumor, and osteomyelitis. Overuse syndromes such as Osgood–Schlatter syndrome, Sinding-Larsen–Johansson (SLJ) syndrome, and stress fractures are also common in adolescents. It is important to recognize that although these are the most common diagnoses in each age group, one should never exclude a diagnosis based solely on age.

Infection

A major objective of the treating physician is to differentiate between infectious and noninfectious causes of limp. Septic arthritis presents with rapid onset of joint pain, progresses to a febrile systemic illness, and leads to the child's refusal to use the extremity. The joint is tender and swollen and laboratory values will demonstrate obvious signs of infection. Transient synovitis also presents as acute onset of joint pain, limp, and restricted joint range of motion, but patients usually do not have fever or signs of systemic illness and it usually follows a recent respiratory illness. Transient synovitis is the most common cause of idiopathic limp in children and generally has a good outcome. Osteomyelitis, sometimes adjacent to a septic joint, is another infectious etiology that must be considered in the child with limp.

Bacteria most commonly gain access to joints by the hematogenous route and are deposited in the rich vascular network in the sub-synovial layer. The bacteria may then cross through permeable blood vessels into the joint space. In the acute inflammatory phase of septic arthritis, polymorphonuclear cells rapidly enter the joint, followed by the formation of a tense effusion. The increased capsular pressure caused by the effusion results in pain and decreased range of motion. Articular cartilage destruction occurs via degradation by proteolytic enzymes and activation of interleukin-1 to release acid proteases from chondrocytes and synoviocytes.

Table 405.2
Differential diagnosis by age

<4	4–10	>10 years
Toddler's fracture	Fracture	Stress fracture
Osteomyelitis	Osteomyelitis	Osteomyelitis
Septic arthritis	Septic arthritis	Septic arthritis
Diskitis	Diskitis	Diskitis
JRA	Legg–Calve–Perthes	Slipped capital femoral epiphysis
Lyme disease	Transient synovitis	Osgood–Schlatter
Discoid lateral meniscus	Discoid lateral meniscus	Sinding–Larsen–Johansson
Foreign body in the foot	Sever's apophysitis	Osteochondritis dissecans
Benign or malignant tumor	Accessory tarsal navicular	Chondromalacia patellae
	Foreign body	Lyme
	JRA	Gonococcal arthritis
	Lyme	Accessory tarsal navicular
	Tumor	Tarsal coalition
		Tumor

Patients with suspected septic arthritis should undergo routine laboratory testing, including a CBC, ESR, CRP, Lyme titer, RF, and ANA. An ESR >50 mm/h and CRP >2 mg/dL is indicative of acute inflammation and/or infection. In transient synovitis, the WBC is usually less than 15,000 cells/mL. Alternatively, juvenile rheumatoid arthritis (JRA) may present with moderate to severe anemia and leukocytosis. Lyme arthritis often mimics a septic joint, although a large effusion with seemingly little pain is the hallmark.

Plain radiographs may demonstrate a joint effusion, which can be confirmed by ultrasound. If the physician has a high index of suspicion for septic arthritis, joint fluid should be obtained by aspiration under sterile technique. Aspiration of a suspected septic hip is performed under sedation and with ultrasound guidance. A cell count with a WBC >80,000 cells/mL with >75% PMN is highly suggestive of joint sepsis.

Diskitis is a bacterial infection of the disc space and adjacent vertebral endplates. The most common cause of diskitis is hematogenous spread of infection through the nutrient arteries, usually with preceding or concomitant infections such as otitis media, urinary tract infections, and respiratory infections. The patient will usually have tenderness to palpation over the vertebral levels in question. Paraspinal muscle spasm, decreased range of motion, and hamstring tightness are common. Most patients will not have localizing neurologic findings. A good test for diskitis is to ask the child to pick an object up from the floor. If the child has diskitis, he or she will refuse to pick up the object or will bend only at the hips while holding the back straight.

Trauma

Occult fracture is another common cause of limp in children. Initial orthogonal radiographs may not identify a fracture. Oblique views are sometimes needed and often the fracture line is not visible until several weeks later when periosteal reaction is noted with fracture healing. The classic toddler's fracture, described by Dunbar, is a spiral fracture of the tibia without concurrent fibular fracture.

Slipped capital femoral epiphysis (SCFE) is a common hip disorder characterized by posteroinferior displacement of the capital femoral epiphysis on the metaphysis of the proximal femur. These patients are usually overweight, with at least half of patients in the 95th percentile for weight. Overuse syndromes such as stress fracture, Osgood–Schlatter disease, Sinding-Larsen–Johansson (SLJ) syndrome, and Sever's disease are common in adolescents and result from repetitive microtrauma. There is usually point tenderness over the affected area and compensatory muscle weakness. Confirmatory radiographic testing for stress fracture may include bone scan and MRI.

Neuromuscular

The muscular dystrophies are hereditary disorders of progressive weakness and muscle wasting that presents most commonly in males from age 2 to 5. Laboratory workup reveals elevated creatine phosphokinase (CPK) levels. Electromyography demonstrates myopathic features. The pathogenesis of muscular dystrophy is the deficiency of dystrophin protein in skeletal muscle. The child may have a history of delayed ambulation and now presents due to stumbling, falling, and difficulty climbing stairs. Patients demonstrate Gower's sign and often have calf pseudohypertrophy. Cerebral palsy is a nonprogressive, static encephalopathy resulting in abnormal motor control. Cerebral palsy may present as a limp with spasticity in the heel cord, resulting in equinus gait. A thorough history and physical examination should rule out progressive disorders of the nervous system such as muscular

dystrophy, spinal cord tumors, and metabolic syndromes before assigning a diagnosis of cerebral palsy.

Inflammatory

Juvenile rheumatoid arthritis (inflammatory arthritis of childhood) is characterized by synovitis of the peripheral joints, resulting in morning stiffness, limited range of motion, joint effusion, and often a limp. The patient may have systemic signs such as rash, fever, and swollen lymph nodes. Pauciarticular inflammatory arthritis is a specific form of the disease that mainly affects joints in the lower extremity, often with only a single joint initially involved. The acutely limping child may, therefore, represent the initial presentation of the disease. On physical examination, the joint demonstrates mild swelling, warmth, and restriction of range of motion that presents gradually. The subtalar joint, knee, and ankle are the most common locations. The male to female ratio is 1:4. The diagnosis is confirmed with laboratory tests, including CBC, ESR, ANA, and RF. Laboratory testing often reveals an elevated WBC, platelet count, ESR, and CBC. ANA is elevated in 40–80% of patients.

Neoplasm/Tumor

Acute leukemia is the most common neoplasm in children under the age of 16, with a peak incidence between 2 and 5 years old. Children with advanced disease typically present with pancytopenia, pallor, fatigue, easy bleeding, and bruising. Laboratory evaluation may reveal subtle abnormalities, but diagnosis ultimately requires a bone marrow biopsy. Osteosarcoma and related tumors predominantly arise in children and adolescents. The most common locations include the distal femur and proximal tibia, often resulting in limp as a presenting sign. Patients may have a localized mass with tenderness and overlying skin changes. Diagnostic workup should begin with plain radiographs and advance to MRI of the involved area with CT of the thorax for staging purposes. Spinal cord tumors usually present with a gait disturbance, sometimes described as a limp by the parents. Plain radiographs may demonstrate widening of the pedicles or neuroforamen and diagnosis is confirmed with MRI.

Congenital

Legg–Calve–Perthes disease is a common cause of usually painless limp in children ages 3–10 years. It is characterized by necrosis of the femoral head, followed by resorption, collapse, and repair. Although ischemia is thought to contribute to the disorder, experimental data has failed to show a direct correlation. Clotting factors, increased blood viscosity, and endocrine abnormalities have all been implicated as potential causes. Discoid meniscus is a common congential knee pathology known to result in limp.

Treatment

General Care

The most important aspect in the evaluation of the limping child is the efficient identification of conditions requiring immediate specialty consultation and/or intervention. These conditions include, but are not limited to: septic arthritis, osteomyelitis, slipped capital femoral epiphysis, developmental dysplasia of the hip, and tumor.

Specific Care

Discussion of the specific treatment of each condition in the vast differential for the child with a limp is beyond the scope of this chapter. Several conditions, however, do warrant further discussion. Septic arthritis requires urgent decompression, irrigation, and debridement to prevent further damage to the joint and articular cartilage. Acute infection causes synovial edema and increased synovial fluid production. Bacterial hyaluronidase decreases the viscosity and function of synovial fluid. Accumulating fluid and purulence rapidly increases the intra-articular pressure and can permanently injure vessels and articular cartilage.

Intravenous antibiotics should be initiated immediately in the toxic patients, but held until cultures are obtained in the stable patient. *Staphylococcus aureus*, Group A *Streptococcus*, and *Streptococcus pneumoniae* are the most common organisms overall, but each age groups has its own specific organisms. For children less than 3 years old, *Haemophilus influenzae* is common, but is decreasing due to vaccination. *Neisseria gonorrhea* and Group B *Streptococcus* must be considered in neonates. Sexually active adolescents are susceptible to *Neisseria gonorrhea* septic arthritis, while sickle cell patients are more likely to be infected by *Salmonella*. In cases of septic arthritis, empiric therapy is initiated with nafcillin, clindamycin, and gentamycin in the infant less than 3 months old and with ampicillin-sulbactam and clindamycin in the child

between 3 months and 4 years old. Methicillin-resistant *Staphylococcus aureus* (MRSA) has recently emerged as a community-acquired pathogen. Vancomycin should be added to the empiric regimen in any patient with a history of MRSA infection or with risk factors for MRSA colonization. Diskitis is treated with intravenous antibiotics for a duration of 4–8 weeks, followed by oral antibiotics for an additional 3–6 months. Bracing has not been shown to improve the clinical course, but may be indicated to decrease pain and minimize deformity.

Transient (toxic) synovitis is treated with symptomatic relief, rest, and anti-inflammatory medications. The symptoms often resolve in 1–2 weeks. Routine aspiration of effusions is not recommended. Children with oligoarticular juvenile rheumatoid arthritis often respond well to nonsteroidal anti-inflammatory medications. Patients with polyarticular disease require an additional anti-inflammatory, including methotrexate, infliximab, or etanercept. All patients require a referral to a rheumatologist for further evaluation and possible workup for pericarditis, myocarditis, and iridocyclitis as indicated.

Future Developments

Improved clinical decision models and more sensitive and specific diagnostic testing will improve the ability of physicians to more efficiently make the diagnosis and initiate treatment. These will not, however, replace a careful history and physical examination as the prime method for diagnosis.

Prognosis

The prognosis of the limping child depends greatly on the underlying etiology of the limp. The prognosis of selected disorders will be discussed. Patients with a diagnosis of transient synovitis often demonstrate a full recovery with no long-term sequelae, with a reoccurrence rate reported to be 4–17%. Patients with diskitis often experience full recovery with antibiotics alone, although a small minority require biopsy and surgical intervention. Patients with septic arthritis who receive expeditious decompression and irrigation often fully recover and experience a full recovery. Delayed diagnosis and treatment can lead to permanent joint destruction and early onset of degenerative arthritis. Risk factors for poor outcome in septic arthritis include: age less than 6 months, delay in treatment greater than 4 days, associated osteomyelitis, and infection with *Staphylococcus aureus.*

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406 Orthopedic Management of Systemic Conditions

J. Channing Tassone

Cerebral palsy (CP), or static encephalopathy, is a central nervous system condition characterized by a disordered communication between the brain and muscles. The etiology is variable. Some cases have a specific prenatal or perinatal incident or a later hypoxic event that are believed causes for the condition. Other cases have no known etiology. The most involved infants first have feeding issues and hypotonia, which progresses to hypertonia with development. The diagnosis in the minimally affected cases may be unclear. Early signs are: (1) Early handedness – very young children showing hand dominance. (2) Velocity dependent tone – palpable muscle resistance during rapid joint range of motion. (3) Pathologic reflexes – presence (i.e., clonus) or maintenance (i.e., Babinski). (4) Posturing of an upper extremity with rapid gait or running. (5) Unilateral toe walking. The two basic types of cerebral palsy are spastic (difficulty controlling volitional movement) and dystonic (increased or constant nonvolitional motion). The subtypes of spastic CP are hemiplegia – one side affected more than the other, diplegia – legs affected more than arms, quad or tetraplegic – total body involvement.

The spine is often affected in CP. The level of involvement of the patient plays a role in how affected the spine is. Ambulatory hemiplegic and diplegic patients have fewer spine issues than wheelchair bound patients. Regular monitoring of the spine in more involved patients is important to diagnose scoliosis. The natural history of scoliosis in these patients is "relentless progression." This progression will also continue after skeletal maturity, in distinct contrast to idiopathic scoliosis. Treatment is controversial but includes wheelchair modification, bracing, growing devices, and fusion. Bracing yields questionable results and will not stop the progression of the curve. At best, bracing may slow the progression of the curve and improve seated posture. Bracing has also been criticized for decreasing patients' trunk strength and control. Surgical indications and outcomes are also controversial. Some believe that the risk of surgery is not warranted given the inconclusive outcomes benefits. Untreated scoliosis will eventually cause seating issues, pulmonary and cardiac compromise. The decision to perform surgery needs to be patient and family specific, taking into consideration a patient's pelvic obliquity and seating issues, their trunk position, and how it affects their ability to interact with their environment and communicate, and their medical comorbidities. Fusion surgery can be successful in achieving the goals of correction of curve, prevention of progression, and correction of pelvic obliquity. It is still debated whether or not this creates true quality of life improvements and eases long-term care. Various studies have come down on both sides of this question further making the decision as to whether or not perform surgery surgeon and center specific. Advances in technology have allowed for an increased number of posterior-only fusions, limiting the need for anterior/posterior combined surgery, which decreases the overall surgical morbidity.

The hip is also commonly affected in CP. The amount of pathology is related to the patients' global involvement with quadriplegic patients having more hip issues. With growth, tight adductor and flexor muscles can cause the hip to subluxate and eventually dislocate. A primary goal is to keep the hip from dislocating by preventing or treating contractures of the muscles. Physical therapy plays a role in achieving this during growth. Botulinum toxin (botox) can be used in conjunction to increase the range of motion and keep contractures from forming. Once contractures are present, then surgical lengthening of the muscles (often the adductors and hip flexors) can help to minimize or correct subluxation and prevent dislocation. Over time, bony changes occur, which lead to a loss of the normal angle of the femoral neck and an enlarged acetabulum with a more vertical orientation. These changes can become significant enough to warrant surgical intervention to prevent dislocation. The surgery involves the previously described muscle lengthening, along with a reorientation of the proximal femur and reshaping the acetabulum to a smaller size and horizontal orientation. CP patients may present with dislocated hips that are not painful. Surgery in this case is more controversial. While some believe that surgery is unnecessary as the condition may remain painless, others believe that

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reducing the hip prevents deterioration of the joint, which improves sitting balance and reduces the risk of the hip pain. Once a dislocated hip becomes painful, then reduction alone will not relieve pain and the patient will require additional procedures. In the ambulatory diplegic patient, tight adductors can also lead to a scissoring gait, which can also be addressed with the previously described modalities.

The most common deformity about the knee in CP is a flexion contracture, which may be progressive with growth. Tight hamstrings often lead to flexion contractures. This may be part of a larger constellation described as a crouch gate. Crouch gate is the result of a combination of hamstring contractures, hip flexor contractures, and ankle equinus secondary to a heel cord contractures. It is imperative that all three levels of deformity are appreciated and addressed. The treatment ranges from physical therapy and stretching, to botox for more significant tightness without contracture, and finally to surgical lengthening when the musculotendinous units are contracted to the point where they are unable to be stretched.

The foot and ankle in CP are a final lower extremity component of deformity that need be addressed. Equinus contracture secondary to tight gastro-soleus complex is often found as an isolated deformity. This is treated with stretching, botox, or surgery. Preventing this deformity or its recurrence can also be achieved with orthotics. An ankle foot orthosis (AFO) is utilized to keep the ankle in a neutral position. The foot can have several major deformities: equinovarus (foot down and in) or its opposite, calcaneovalgus (foot up and out). A tight heel cord and mid-foot collapse may lead to an equinovalgus foot. These deformities are primarily treated with orthotics. If the foot is too rigid to achieve a neutral position with bracing, then surgery is warranted. Tendon lengthening or transfer to alter the deforming forces or bony realignment may be necessary.

Spina Bifida

Myelodysplasia or Spina Bifida is caused by a failure of neural tube closure at varying levels of the spine. This is commonly associated with other conditions like hydrocephalus, Arnold–Chiari malformation, and other CNS lesions. The spinal cord level of involvement and the involvement of potential comorbidities determine a child's prognosis and treatment. The orthopedic treatment of these children revolves around the spinal deformity and the lower extremity deformities. Globally, the goal of treatment is to maximize function.

The lower extremity may have deformity at the hip, knee, ankle, and foot. There can be contrasting deformities (flexion or extension contractures, equinus, or calcaneus). If stretching does not allow the limb to achieve a position that enables bracing and an appropriate level of mobility, then surgery must be considered. The treatment of paralytic hip dislocation is more controversial. Studies have shown that except in the very high functioning patient with distal spina bifida, there is not a functional improvement from reducing the hip. In addition, the goal of maintaining flexibility may be hindered by surgical reconstruction.

The knee can be affected by either congenital or developmental flexion or extension deformities. Depending on the level of function and the amount of the deformity, either stretching or surgery may be necessary to appropriately position the knee. The foot and ankle can also be affected by a myriad of conditions ranging from clubfoot, congenital vertical talus, calcaneovalgus to equinus, varus, or valgus. Initially, stretching is a reasonable treatment plan, especially in the very young. Almost inevitably, surgical intervention should be undertaken early enough to attempt to place the foot and ankle in a neutral position for brace wear and ambulation.

Spinal deformities typically manifest as kyphosis or kyphoscoliosis. This is secondary to the inherent bony abnormalities involved in spina bifida or secondary to neurologic impairment. The spine must be monitored closely in this patient population as progression of the deformity is common. Progression can lead to sitting and balance issues or skin integrity issues. Bracing is an ineffective treatment for kyphosis or scoliosis in these patients and surgery may be necessary.

This population is particularly susceptible to pathologic fractures secondary to the combination of osteopenia and decreased protective sensation. Due to the lack of pain that spina bifida patients experience, it is important to always consider infection while evaluating for a fracture or musculoskeletal injury. Fractures are far more common than infection, and should be easily seen on a plain radiograph. Fractures heal well, but should be immobilized for as short a time as possible. The immobilization is necessary to avoid malunion, but prolonged immobilization may worsen contractures and have an adverse functional implication.

Neurofibromatosis

Neurofibromatosis (NF) is an autosomal dominant condition caused by a chromosomal abnormality leading to

the abnormal growth of cells originating from the neural crest. There are two types of NF. The most common is Type 1, or peripheral NF, which presents with café au lait spots, axillary and inguinal freckling, and a variety of other peripheral neurofibromas. Type 2, or central NF, presents with acoustic neuromas and little orthopedic concerns. NF should also be in the differential for patients being worked up for hemi-hypertrophy.

Most patients with NF need no orthopedic care, but those who do, have two primary associated orthopedic conditions: scoliosis and congenital pseudoarthrosis of the tibia. Scoliosis in NF is of two distinct varieties: dystrophic- and idiopathic-like. Idiopathic-like scoliosis in NF patients is treated in the same way as idiopathic scoliosis (see scoliosis section for treatment). These patients must be monitored to ensure the scoliosis does not become dystrophic. Dystrophic scoliotic curves are typically short, sharp curves. They are usually thoracic and may progress rapidly, carrying with them a higher neurologic risk. They must be monitored more closely than idiopathic curves. Bracing tends to be ineffective, so surgical fusion is often indicated to halt progression.

Congenital pseudoarthrosis of the tibia (CPT) is the other skeletal condition associated with NF-1. This is characterized by an anterolateral bow of the tibia and the leg. This is in contrast to the benign condition of posteromedial bowing of the leg associated with the calcaneovalgus positional foot deformity of birth that spontaneously resolves. CPT is characterized by structural and biologic abnormalities of the tibia, which increases the risk of fracture and causes poor fracture healing. The treatment ranges from bracing to prevent fracture to complex surgery to amputation if surgery fails.

Osteogenesis Imperfecta

Osteogenesis Imperfecta is an autosomal dominant condition caused by a mutation of type-1 collagen genes Col1A1 and 1A2 (on chromosomes 7 and 17). The classic classification described by Sillence subdivides OI into 4 types. More recently, Shapiro's modification of Looser's classification has better prognostic value.

The orthopedic treatment of OI primarily revolves around the treatment of fractures. A common dilemma that must first be delineated is the distinction between non accidental trauma (NAT) and OI. Young children presenting with stories of fractures from minimal trauma or suspicious circumstances must be evaluated for NAT before considering a diagnosis of OI. Diagnosing OI early in these children allows for appropriate interventions. Minor fractures are treated with reduction and casting. Fractures requiring surgical intervention are better served by intramedullary fixation with rods in contrast to plate and screw fixation. Limb deformity from recurrent fractures can also be addressed with this type of treatment. Curved bones can be cut and then straightened with a rod. Telescoping rods are utilized and remain in place growing with a patient providing continuing protection to the bone. Fortunately, children with OI have good fracture healing potential. Medications like pamidronate have also helped reduce the number of fractures. Children with OI have increased risk for scoliosis. Heightened awareness and appropriate monitoring for scoliosis is necessary in all patients with OI, and scoliosis treatment recommendations are similar to idiopathic scoliosis.

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407 The Spine

Craig P. Eberson

Scoliosis

Scoliosis is classified as a lateral curvature of the spine greater than 10°, as measured by the Cobb method. A line is drawn parallel to the top endplate of the upper vertebra in the curve, and a second line drawn parallel to the lower endplate of the most caudal vertebra in the curve. The angle formed between two lines drawn perpendicularly to the first two lines is the Cobb angle (*Fig. 407.1*). Rotation of the spine in the axial plane results in the rib "hump" seen on exam. By definition, idiopathic scoliosis has no known cause, although recent evidence indicates a genetic inheritance. Other forms of scoliosis must be excluded via a thorough history and physical examination (*Table 407.1*).

Scoliosis can be classified by etiology and patient age in order to better guide evaluation and treatment. The three main categories of scoliosis are *idiopathic*, *congenital*, and *neuromuscular*. Idiopathic scoliosis can be subdivided by age into infantile (younger than 3 years of age), juvenile (age 3–10), and adolescent (older than 10). Congenital scoliosis implies an abnormal formation of the vertebral bodies, which leads to deformity, and is diagnosed at any age. Fused vertebrae, hemivertebrae (*Fig. 407.2*), or a combination of the two may cause curvatures of varying severity in the frontal, sagital, or axial planes and often are accompanied by abnormalities of the spinal cord (dysraphism), kidney, and heart, due to the temporal relationships of the organ systems with respect to intrauterine development. These other systemic abnormalities should be sought (MRI, renal ultrasound, cardiac evaluation) and prompt orthopedic referral made, as these deformities are often rapidly progressive, with many requiring surgery at a young age. Neuromuscular scoliosis is seen in patients with previously diagnosed conditions (i.e., myelomenigocele, neurofibromatosis, cerebral palsy, muscular dystrophy) as well as in "normal" patients whose scoliosis is the presenting symptom of an underlying disorder (i.e., syringomyelia, tethered spinal cord, Friedrich's ataxia). A thorough physical examination will reveal the presence of these disorders. Finally, other miscellaneous causes exist, such as connective tissue disease related (i.e., Marfan's syndrome), tumor related (i.e., osteoblastoma), and other syndromic causes of scoliosis. Of primary concern to the practicing pediatrician is adolescent idiopathic scoliosis, although the ability to rule out other causes is paramount. The remainder of the discussion will therefore focus on idiopathic scoliosis.

Patients with idiopathic scoliosis may present in one of several ways. Often a rib prominence is noted on a school screening examination or during a routine physical examination. The majority of cases of scoliosis are initially asymptomatic, although patients and their families may notice a waist asymmetry, a rib hump, or a difference in breast size resulting from the rotation of the curve. Infants are often diagnosed after a family member notices a spinal asymmetry while bathing. As with all conditions, a detailed history and physical examination will confirm the diagnosis of idiopathic scoliosis.

The history should focus on the presence of neurologic symptoms, pain, headaches, numbness, or weakness. Roughly 25% of patients with idiopathic scoliosis will complain of some pain, so its presence is not necessarily worrisome. Physical examination requires a systematic evaluation of the spine, as well as the skin and nervous system. The Adams forward bending test is performed by having the examiner sit behind the patient, who then bends forward at the waist with the arms hanging free. A prominence of the ribs or paraspinal muscles should alert the examiner to a curve. A scoliometer can be used to quantify the amount of rotation. Prior to bending, the patient's waist, scapulae, and shoulders should be examined for symmetry. The iliac crests should be palpated to look for evidence of pelvic obliquity from a limb length discrepancy. Skin exam can rule out systemic disorders (Marfan's syndrome, Ehlers Danlos syndrome, neurofibromatosis) or signs of spinal dysraphism (hairy patch or midline hemangioma), while neurologic examination seeks evidence of tethered spinal cord, or other underlying neurologic dysfunction. Reflexes should be checked (including the abdominal reflex), in addition to motor and sensory testing.

The diagnosis of scoliosis is confirmed by radiographs, ideally standing full-length x-rays of the entire spine. Most experts agree that a scoliometer reading greater than 7° should prompt radiographic evaluation. For patients with

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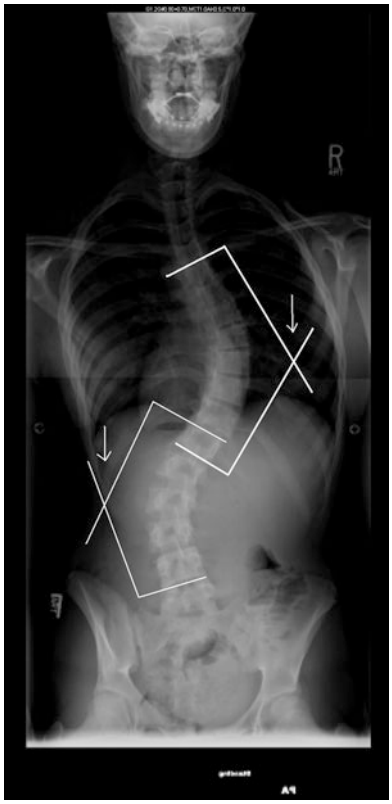

Figure 407.1
A patient with idiopathic scoliosis. The cobb angle is indicated by *arrows*, representing an intersection of the lines drawn perpendicularly to the endplates of the end vertebrae of the curves

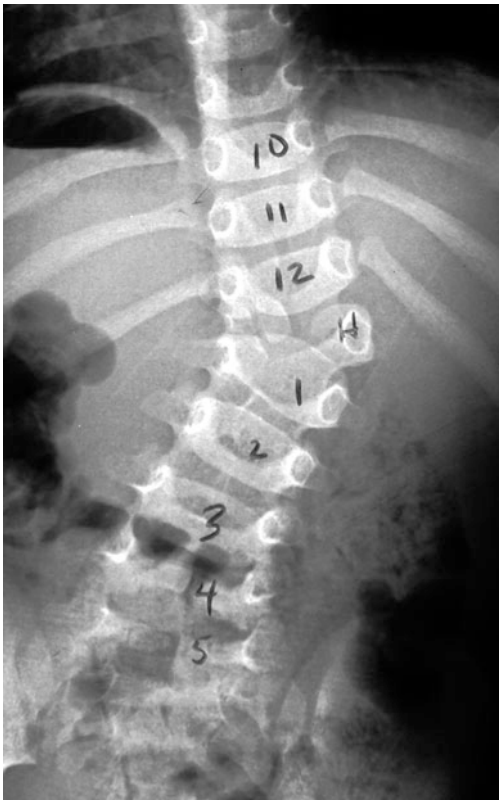

Figure 407.2
Congenital scoliosis. A hemivertebra is located between T12 and L1, causing a curvature to form. In this patient, worsening occurred with groth and the hemivertebra was excised

Table 407.1
Etiology of scoliosis

Idiopathic
Neuromuscular
Cerebral palsy
Myelodysplasia
Friedrich's ataxia
Connective tissue disease
Marfan's syndrome
Ehlers Danlos syndrome
Central nervous system
Chiari malformation
Syringomyelia
Other
Neurofibromatosis
Tumor

a suspicion of neurologic dysfunction (young age, abnormal neurologic exam, left-facing thoracic curve, severe associated kyphosis, unexplained pain), magnetic resonance imaging (MRI) should be considered. Usually, this will be ordered by the specialist.

Treatment of scoliosis depends upon two factors: the age of the patient and the size of the curve. Skeletal maturity can be assessed in several ways; spinal growth usually ceases 2 years after the onset on menarche in girls. The Risser sign, which is determined by the percentage of the iliac apophysis which is ossified on the scoliosis radiograph, can be useful as well; girls spinal growth continues until Risser stage IV (100% ossification but not closure of the growth plate), boys can progress until Risser V (growth plate closed – "adult" pelvis). Patients with curves less than 25° usually do not require treatment, but must be followed through skeletal maturity. Radiographs taken every 6 months during rapid growth are helpful to identify curve progression. In general, curves greater than 20°

should be referred to a specialist for observation. For patients with at least 1 year of growth remaining with curves greater than 25–30°, bracing is often prescribed. The type of brace and wear schedule vary (Boston-full time, Providence and Charleston-nighttime only), but the concept is the same: to prevent curve progression in an at-risk patient. Curve correction is not usually seen, underscoring the necessity of early diagnosis to allow early brace initiation. DNA testing is currently available to help determine risk of progression and guide bracing recommendations. Bracing is continued until skeletal maturity, or until curve progression requires surgery. Operative intervention is usually undertaken for curves greater than 40–50°, due to the risk of progression after skeletal maturity and potential cardiopulmonary compromise.

Scoliosis in children less than 10 years old can be characterized as early onset scoliosis (EOS). Vigilance in looking for these curves is important, as the large amount of growth remaining portends a poor prognosis if untreated. Often bracing alone is insufficient to control the curve. Casting or "growing instrumentation" are two additional options for progressive curves. The latter technique involves inserting rods into the spine without a fusion, which are then lengthened at regular intervals until sufficient growth has been attained. Alveolar branching is complete by age 8, but more recent evidence suggests that fusion performed at that age significantly impairs pulmonary development, and the definitive procedure is usually delayed as long as possible. A recent technique, vertebral stapling, holds promise as a means of controlling or even correcting curves in these young patients.

Kyphosis

Kyphosis is defined as a curvature in the sagittal plane greater than normal (20–40°). Two types of kyphosis are seen: flexible and rigid. Flexible kyphosis is seen in patients with "poor posture"; they are able to actively correct their deformity if asked. Often, examination reveals tight hamstring muscles and poor flexibility in general. Physical therapy to increase flexibility and strengthen the spinal extensors is helpful, and specialist referral is usually unnecessary. Scheuermann's kyphosis is rigid and often painful, with radiographic changes consisting of increased sagittal angulation, wedging of three consecutive vertebral bodies, and vertebral endplate irregularities known as Schmorl's nodules. While physical therapy can be helpful for decreasing symptoms, the rare patient with a large progressive curve (greater than 75°), or who has pain recalcitrant to nonsurgical measures, often undergoes surgery to correct the deformity. Posterior osteotomy and pedicle screw fixation usually eliminates the need for an anterior procedure, which had been the standard of care in the past. Smaller curves in growing children may respond to bracing as is the case for scoliosis, although this is not universally accepted. Kyphosis in the presence of a significant scoliosis is not typical, and investigation for underlying neurologic abnormality should be undertaken.

Torticollis

Torticollis, or wry neck is a common entity in childhood. The differential diagnosis includes congenital muscular torticollis, ocular abnormalities, gastrointestinal reflux, posterior fossa brain tumors, rotary subluxation of C1–C2, and congenital spinal deformity. Definitive diagnosis is contingent upon a thorough history and physical examination.

Congenital muscular torticollis is the most common type. Often, this results from intrauterine positioning and can be associated with other "packaging" problems, such as metatarsus adductus or hip dysplasia. Because of this, imaging of the hips is recommended in children with torticollis. Alternately, traction during delivery may result in injury to the sternocleidomastoid (SCM) muscle. Hemorrhage and fibrosis may lead to a mass, or pseudotumor, which is palpable in the muscle. Treatment of torticollis consists primarily of physical therapy. Ocassionally, bracing with a collar may be helpful in older children. Neglected cases may require surgery; left untreated facial asymmetry will persist into adulthood. Early presenting cases may also be due to visual disturbance, so ophthalmologic consultation may be helpful. In addition, patients with gastrointestinal reflux may exhibit intermittent spasmodic posturing due to esophageal irritation (Sandifer syndrome). Cases presenting long after birth may be due to posterior fossa tumors, so MRI is warranted.

Acute torticollis in childhood may lead to atlantoaxial rotary subluxation. The inability to return the rotated head to the midline should raise suspicion for this condition. It can be seen after minor trauma, or occasionally after an upper respiratory infection due to the relationship of the retropharyngeal lymphatics to the C1–C2 joints. If symptoms exist for a short duration (less than 1–2 weeks), muscle relaxants and a soft collar may allow reduction and can be discontinued when full motion is achieved. Symptoms of longer duration may require halter or halo traction for reduction. Failure to achieve or maintain reduction, or symptom duration longer than 3 months, usually will require atlantoaxial fusion.

Spondylolysis/Spondylolisthesis

A common cause of low back pain in adolescents is spondylolysis/spondylolisthesis. In spondylolysis, a fracture exists in the pars intraarticularis region of the vertebra, usually L5. It may be acute from high-energy trauma, or more chronic, such as the case with stress fractures. Highly repetitive hyperextension activities (gymnastics, crew) are thought to play a role in the pathogenesis of the stress fracture, which may be uni- or bilateral. The initial workup should include anteroposterior and lateral radiographs of the lumbar spine, as well as oblique radiographs. In cases where plain films are normal, several options exist. MRI may show edema in the adjacent pedicle, pointing to the diagnosis, and is helpful in identifying stress reactions, i.e., a pre-fracture. Computed tomography is helpful for identifying fracture lines not seen on plain radiographs. Traditionally, SPECT scanning has been suggested to determine if the lesion is "hot," i.e., possessing adequate blood flow for healing. Treatment varies from activity modification to bracing or even surgery for cases failing to respond to conservative measures.

Spondylolisthesis (*Fig. 407.3*) implies a slippage forward of one vertebrae in relationship to the subjacent one. The cause may be a defect in the pars intraarticularis (isthmic), a dysplastic L5-S1 facet (dysplastic), or as a result of severe trauma (traumatic). Listheses are graded according to the percentage of slippage. Painless slips less than 50% (grade 2) are usually observed. Slips greater than 50% (grades 3–5) in skeletally immature patients are likely to continue slipping and are often treated with spinal fusion. Lower grade slips with symptoms uncontrolled by nonoperative measures also may benefit from surgery. Because in dysplastic spondylolisthesis the posterior elements of the vertebra are intact and slide forward with the vertebral body, there is a higher incidence of neurologic compromise from root compression in these patients. Signs and symptoms of neural dysfunction should be sought (numbness, tingling, bowel or bladder dysfunction).

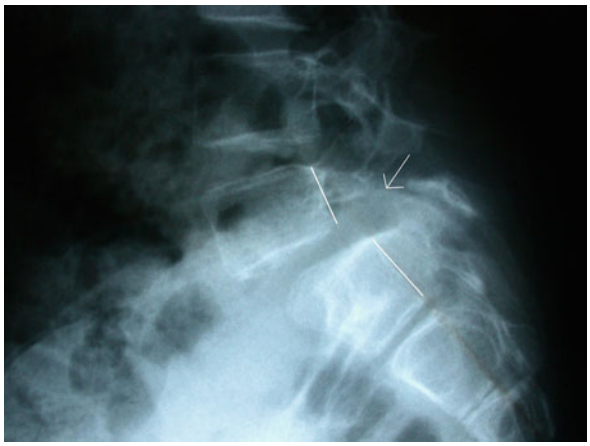

Figure 407.3
Spondylolisthesis. The L5 vertebral body has slipped anteriorly in relation to S1. The *arrow* points to a defect in the pars intraarticularis region of L5

Back Pain

Back pain in children and adolescence is a common complaint. Distinguishing minor ailments from significant pathology requires a thorough knowledge of potential etiologies. A stepwise approach is paramount.

The initial evaluation begins with the history. The location of the pain (localized versus diffuse) is important, as is any history of injury (minor injury versus major fall/accident). Radicular symptoms suggestive of a neurogenic etiology should be sought. Constitutional symptoms suggest leukemia, infection, or other multisystem disorder. Physical examination should include spinal range of motion in flexion/extension, tenderness to palpation, hamstring tightness, as well as a thorough neurologic exam, including straight leg raise.

It is helpful to consider potential causes of back pain when assessing the results of the history and physical examination. Trauma (compression fracture) often results in decreased range of motion and a history of a significant injury mechanism. Tumors (osteoid osteoma, osteosarcoma, leukemia, etc.) and infections often have an insidious onset, lead to severe pain, often at night, as well as fatigue and other systemic symptoms. While acute infections (disciitis, osteomyelitis) typically present with fever, chronic infections may not.

In general, patients with significant back pain should have plain radiographs. Those with suspicious histories should have appropriate bloodwork (complete blood count, erythrocyte sedimentation rate, c-reactive protein). If symptoms are mild, a short course of nonsteroidal anti-inflammatory medication, rest, and activity modification are appropriate. Physical therapy is appropriate for patients with tight hamstrings or generalized deconditioning. For patients who do not respond to simple measures, further imaging is helpful. Magnetic resonance imaging is helpful for ruling out infection, tumor, disk disease, occult fracture, or spinal cord pathology. Computed tomography can be helpful to evaluate for

spondylolysis. SPECT scanning can also be helpful in evaluating for occult pars fracture or stress reaction. Further evaluation is best done by a specialist.

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408 Pediatric Upper Extremity

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Brachial Plexus Injuries

The incidence of obstetrical brachial plexus injuries is reported in 0.4–2.5 per 1,000 births. Maternal risk fractures include maternal obesity and gestational diabetes with large birth weight. Women who have had a child with a brachial plexopathy have an increased risk with subsequent pregnancies. Shoulder dystocia may be related to an upper plexus injury because of traction on the shoulder inferiorly during delivery, causing a stretching of the upper plexus. A clavicle fracture in this situation is advantageous because it allows the shoulder to be compressed during delivery instead of getting stuck and stretching the plexus. Children delivered by caesarian section may also be at risk of a lower trunk injury if they are delivered head last. If the arms are over the child's head and traction is applied pulling the arms away from the body, there may be stretching of the upper trunk.

Most obstetrical brachial plexus injuries are upper or upper and middle trunk involvement. These injuries include muscles innervated by the fifth, sixth, and seventh cervical root. Limited shoulder motion is the biggest functional deficit of these children long term.

Referral within the first month to a surgeon or neurologist is appropriate. Approximately 90% resolve in the first 2 months. These children have almost normal shoulder function. If the children do not recover biceps function by 5–6 months, surgical intervention may be required. Those that show enough recovery to not require surgery may need prolonged physical therapy to ensure good shoulder motion.

Polydactyly and Syndactyly

Polydactyly is the duplication of parts. It can involve any part of the upper limb but most commonly the fingers. Preaxial polydactyly, or duplicate thumb, is most common in white or Asian children. Correction usually requires surgery at 6–24 months of age. Post axial polydactyly, an extra small finger, is most common in African-American children and there often is a strong family history. These can be tied off in the nursery if the skin bridge is small enough without significant bone involvement.

Syndactyly is the most frequent congenital limb deformity occurring in 1:2,000 births. It may be sporadic, inherited, or syndromic such as Apert's, Mobius, or Pierre-Robin syndrome. The syndactyly may be to the fingertip (complete) or just webbing (incomplete). There may be bone involvement (complex) or normal boney anatomy (simple). With the exception of a minimal web contracture, surgery is usually performed. If there is a significant length discrepancy between the digits with tethering, surgery may be performed as early as 6 months. Otherwise, surgery is typically performed at about 24 months of age. All of these children require a skin graft, typically from the groin. The advantage of waiting until about 2 years of age is that there is less web creep, or redevelopment of the webbing, the most common complication of the procedure.

Clinodactyly and Camptodactyly

These two diagnosis, angular deformities of the fingers, fall into the classification of failure of differentiation. Clinodactyly is a deformity of the finger affecting the middle phalynx of the small finger causing the tip to be deviated radially. There is a rare functional issue and no treatment is usually required. If there is a significant overlap of the fourth and fifth finger in flexion, an osteotomy of the small finger middle phalynx may be required in adolescence but is extremely rare. There is a strong family history of this deformity and there are no concerns for associated anomalies.

Camptodactyly means crooked finger. The deformity is a flexed position at the proximal interphalangeal joint. This deformity is typically diagnosed during the accelerated growth of adolescence. Full extension is the only functional deficit. Serial casting or splinting is appropriate treatment. Surgical treatment is rarely indicated for two reasons. Conservative treatment is usually very successful and the exact reason for the deformity is not clearly identified. Abnormal skin, flexor tendons,

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intrinsic muscles, or even a boney deformity. Because of the unknown etiology, surgical treatment has limited indications.

Pediatric Trigger Thumb

Pediatric trigger thumb, or "congenital trigger thumb," is triggering or catching of the thumb as in adults. It is a fixed flexion deformity of the thumb interphalangeal joint due to limited excursion of the flexor pollicis longus tendon at the A1 pulley. The parent's usually notice that the thumb does not fully extend with the interphalangeal joint held in flexion. Passive extension may produce pain or cannot be achieved. The differential diagnosis includes congenital clasped thumb, absent or aberrant extensor tendons, arthrogryposis, or spasticity. A nodule, termed a "Notta's nodule," is usually palpable over the volar portion of the thumb metacarpophalangeal joint in trigger thumb, which is not typically present in other diagnoses. This nodule moves as the tendon moves (*Fig. 408.1*).

The condition has been described to occur in newborns, often based on parental history or recollection, hence the original description as congenital trigger thumb (G). Other studies have suggested that the trigger thumb develops postnatal; thus, Slakey and Hennrikus recommend using the term "acquired thumb flexion contracture." Moon et al. examined 7,700 newborns prospectively and found no congenital cases. The origin remains unknown. The age at which symptoms first appear vary from birth to 4½ years.

Overall, pediatric trigger thumb is a rare condition, but still ten times more common than pediatric trigger finger. The incidence is reported to occur in 1–3.3% of children.

Unlike trigger thumbs in adults, pediatric cases are rarely seen to trigger or catch. More commonly, the condition is not noticed until there is a thumb interphalangeal flexion deformity. In contrast to adults, the pathology in the pediatric patient is more frequently found to reside within the tendon itself with thickening and synovial proliferation, resulting in a Notta node, as originally described in 1850.

Some have postulated that the condition may arise secondary to the common clasped thumb fisted posture of neonates. Patel believed this adducted thumb position caused tendon kinking at the A1 pulley with a resultant inflammatory reaction, which results in the thickened nodule. However, Buchman et al. performed electron-microscopic evaluation of tendon nodules and A1 pulleys in 11 trigger thumbs and showed that there were large amounts of mature collagen surrounding spindle-shaped fibroblasts in the tendon, with normal appearing A1 pulleys. They concluded that an infectious, inflammatory, or degenerative process is an unlikely etiology.

Reports differ regarding the optimum treatment. Some studies have shown spontaneous resolution whereas Ger et al. observed no cases of spontaneous resolution. Dinham and Meggitt observed a spontaneous recovery rate of 30% for congenital cases and 12% for patients presenting between 6 and 30 months of age. Other studies have shown 63% of cases resolving spontaneously.

Dinham and Meggitt's original algorithm for treating pediatric trigger thumbs recommended observation for deformities present at birth for 12 months and 6 months for cases noticed between the ages of 6 and 30 months. They suggested operative treatment before the age of 4 years to prevent residual flexion deformities; however, subsequent studies have shown no untoward events with operative treatment in the older child.

Observation, passive range of motion or stretching, and splinting have been reported to result in satisfactory trigger thumb improvement or resolution in 50–90% of patients in some series. However, these conservative treatment results are not always reproducible.

Most would recommend operative release of the A1 pulley overlying the flexor pollicis longus tendon in cases with painful triggering, severe compensatory hyperextension of the metacarpophalangeal joint, or in those cases

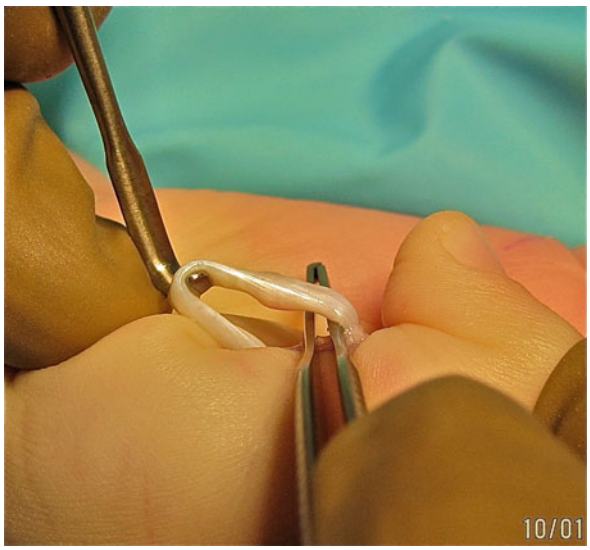

Figure 408.1
Thickening or "Notta's nodule" in the thumb flexor tendon

that have failed nonoperative measures. Historically surgeons excised the intratendinous nodule; however, current practice consists of pulley release alone for trigger thumbs. Recently, van Loveren et al. showed that release of the A1 pulley alone was sufficient to relieve the triggering in only 19% of their cases, suggesting either a separate annular pulley between A1 and A2, or a longer than normal annular pulley that extends into to proximal phalanx, which must also be divided.

Pediatric Trauma

As developing children begin to explore the environment around them, the hands they use to gather information are at risk for injury. The health care providers that encounter these injuries are faced with circumstances that are unique to the pediatric population. What may appear initially as a trivial injury may have significant consequences for the function of the hand. Children have an impressive ability to heal compared to the adult counterpart, but with this accelerated healing potential comes a narrowed opportunity to treat or alter treatment. In fact, within 5–7 days, the potential to treat injuries by closed means may be lost. Fractures can heal within 2–3 weeks, leaving treatment by open means impossible. Unless injuries are timely recognized and treated, one is left with the most common complication, malunion. Treating pediatric hand injuries requires consideration of the age at presentation, digits involved, presence of a growth plate injury, and fracture configuration.

Pediatric hand fracture occur more commonly in children younger than 2 years of age and those greater than 12. The female-to-male ratio is equal in toddlers and children, with increasing incidence in males during adolescent years. Border digits, the thumb and small finger, are more commonly involved. The mechanism for the majority of toddlers is a crush injury of the distal phalanges with associated nail bed injuries. Children and adolescents injure the hand more commonly during sports with a combination of twisting, bending, torquing, and axial loading of the digits.

Knowledge of anatomy can help in understanding fracture patterns. The growth plate of every phalanx is at its base, contrary to the metacarpals that have the physis in the metacarpal head. The exception is the thumb metacarpal where the growth plate is proximal. Salter and Harris classified growth plate fractures into five categories, determined by the fracture pattern around the growth plate. Non-epiphyseal, condylar fractures can be categorized as unicondylar, bicondylar (T or Y), or transcondylar. Shaft fractures can be described as transverse, short oblique, or spiral.

The developing child has an amazing ability to remodel fractures. Remodeling can occur if 2 years of growth remain; however, its potential decreases as the child reaches skeletal maturity. The further the fracture is from the growth plate, the less potential for correction of deformity over time.

The majority of pediatric hand injuries can be treated my closed means. Thick periosteum helps prevent significant displacement and often provides a thick tether to help hold fractures once reduced. Operative treatment is required in 10–20% of cases and is reserved for those that failed closed treatment.

The small finger metacarpal is the most commonly injured with the so-called "boxer's fracture" that occurs at the neck of the metacarpal because of an axial load from punching. Fractures that are further away from the physis, adolescents that are near the end of growth, coronal and rotational deformities are treated more like injuries in adults. Accepted sagital plane (flexion-extension) angulation is less than 15° in the neck and less than 10° in the shaft for index and middle finger metacarpals. The increased mobility of the fourth and fifth ray allows the small and ring finger to tolerate greater degrees of malreduction. Acceptable reduction in the small and ring finger is considered to be less than 30°–40° in the neck and 20° in the shaft. The Jahss maneuver is used for metacarpal neck fractures. A palmar force is placed on the proximal metacarpal fragment and PIP and MCP are bent at 90° and a counter force is created directed from the flexed PIP, axially and dorsally. Due to the mobility of the CMC joint, as much as 30° of angulation may be tolerated in the sagital plane of the thumb. No rotational deformity can be tolerated regardless of the digit involved.

In the proximal and middle phalanx, up to 10°–20° of angulation can be acceptable in the sagital plane, taking into consideration the impact on the flexor and extensor lever mechanisms. Coronal (medial-lateral) and rotational deformities are less forgiving and any malreduction leading to a clinically significant deformity should be treated with operative fixation and early range of motion after 2–3 weeks of immobilization.

Distal phalanx tuft fractures are the most common in toddlers due to crush injuries. Associated nail bed injuries are common and are considered an open fracture. Subungual hematoma greater than 50% requires removal of the nail, irrigation and debridement, and repair of the nail bed with 6–0 absorbable suture. Recently, the use of dermabond has been published as an alternative to suture fixation of the nail bed with good results.

Articular fractures, regardless if they are of the phalanx or metacarpal, usually require near anatomic reduction. Articular gap or step off of 1–2 mm and angulation of greater than 5° is generally considered an indication for surgical treatment. Phalangeal condylar fractures are intra-articular fractures that require near anatomic reduction and can be particularly unstable. Those that are displaced and shortened can lead to joint instability and arthritis. Dedicated lateral radiographs of the joint are necessary and double density sign of the condyles may indicate offset of a displaced fractured condyle. Subcondylar or transcondylar fractures of the phalangeal neck can also be unstable and typically have dorsal translation and extension angulation.

The "Seymour Fracture" is an example of a Salter Harris I or II injury of the distal phalanx with avulsion of the proximal edge of the nail from the eponychial fold (*Fig. 408.2*). This is an open fracture. Removal of the nail allows copious irrigation and reduction of the abnormally overlying nail plate underneath the eponychial fold. One example of a Salter Harris II fracture is the so-called extra-octave fracture of the small finger. Reduction can be achieved by using a pencil placed in the fourth webspace to apply counterpressure to the proximal fragment while

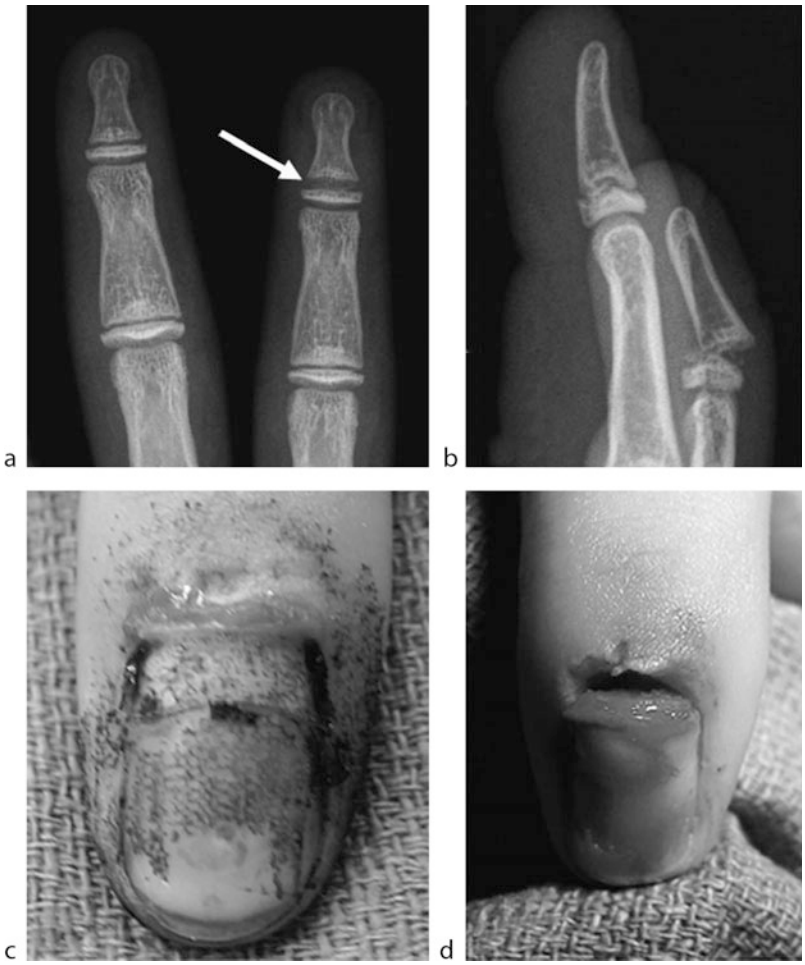

Figure 408.2

Seymour fractureThese (a) AP and (b) lateral radiographs show a typical Seymour fracture. Note the widening of the physis on the anteroposterior view and the flexion deformity and dorsal physeal widening on the lateral view. (c) The clinical appearance of the same fracture shows exposure of the proximal end of the nail plate from underneath the eponychial fold. Note the lack of skin laceration, which can lull the physician into believing the injury is closed. (d) After removal of the nail plate, the open physis is seen easily though the nail bed laceration

the metaphysis and shaft are brought radialward. Another reduction maneuver for proximal phalanx fractures is to bringing the small proximal piece into flexion. This places tension on the collateral ligaments that are attached to the proximal fragment and stabilizes it, allowing one to manipulate the distal fragment until reduction is achieved.

Carpal Fractures

Knowledge of the appearance of carpal bone ossification centers is important in evaluating pediatric hand trauma. The capitate is the first bone to appear at 6 months and the pisiform is the last to ossify at 6–8 years of age. The scaphoid appears at approximately 4 years of age and is the most frequently injured bone in children. As with adult fractures, any suspicion of a scaphoid fracture with tenderness at the snuffbox or distal pole of the scaphoid requires immobilization and repeat evaluation. The majority of these injuries can be treated in a thumb spica cast for 6–8 weeks.

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409 Hip Pathology

Mark C. Lee

Transient Synovitis of the Hip (Toxic Synovitis)

Case: A 6-year-old boy presents with 2 days of low grade temperature with refusal to bear weight on the right leg. Exam demonstrates mild irritability and limitation of motion of the right hip. Labs reveal WBC of 10,000 cells/μL and ESR of 20 mm/h. X-rays of the right hip are negative but ultrasound shows a small hip effusion. The patient is given NSAIDs and symptoms improved markedly over 2 days, with complete resolution 10 days after presentation.

Transient synovitis is an idiopathic, self-limiting inflammatory condition of the pediatric hip that occurs in younger children. The etiology is unclear, but occasionally follows an upper respiratory infection. Incidence is estimated at 0.2% per year for children aged 1–13 years, with peak onset between 4 and 10 years of age. Boys are affected 2–3 times more frequently than girls.

Typically, a young child presents with a low grade fever and acute onset of limp or refusal to bear weight. The child is usually in mild distress with moderate limitations in hip range of motion.

The differential diagnosis for such a presentation is broad and includes septic arthritis, Lyme arthritis, deep pelvic or psoas abscess, femoral osteomyelitis, and fracture. Early Legg–Calvé–Perthes disease and juvenile rheumatoid arthritis (JRA) may also present in this fashion and should necessarily be excluded.

Of the utmost importance, the clinician must distinguish transient synovitis from a septic arthritis of the hip. Patients with septic arthritis are usually less comfortable and have greater restrictions in range of motion, but the presentation may vary. The following four criteria are used as a guideline for operative decision-making: fever $>38.6°C$, inability to bear weight, ESR >40 mm/h, WBC $>12{,}000$ cells/μL. If three or four of these criteria exist, then septic arthritis is likely and hip aspiration in the OR with the possibility of further operative drainage is performed. If septic arthritis is thought unlikely, then symptomatic management with an around-the-clock course of NSAIDs for several days is all that is required.

The prognosis for transient synovitis is excellent. Patients typically improve rapidly over the course of 2 days, with full resolution of symptoms by 7–14 days. No significant long-term clinical sequelae have been identified. This is in contradistinction to a neglected septic arthritis of the hip, where the long-term outcomes range from debilitating early onset osteoarthritis of the hip to fulminant sepsis with the possibility of death.

Developmental Dysplasia of the Hip

Case: A 6-week-old infant presents with a right hip "click" on exam. Physical examination demonstrates a positive Ortolani sign. Ultrasound of the bilateral hips shows mild right acetabular dysplasia with the femoral head in a subluxated position. The patient is placed in a flexion harness for 6 weeks with weekly physical examinations as well as monthly ultrasound examinations to confirm the congruence and the development of the hip. At 1 year of age, the hip is stable with a normal appearance to the acetabulum. However, follow-up continues to ensure appropriate hip development to skeletal maturity.

Developmental dysplasia of the hip (DDH) is a spectrum of disorders of hip development in which the femoral head and acetabular couple is disrupted, resulting in a mutual disturbance in development. Manifestations of the disorder are seen at all ages, but will most commonly be identified in the infant. Infantile DDH manifests as hip instability that is usually associated with poor development of the acetabulum. The infantile hip may be dislocatable, partly dislocatable (subluxatable), or reducible from a dislocated resting position.

The etiology is multifactorial and is influenced by hormonal and genetic elements. Numerous theories exist as to the exact cause of neonatal hip dysplasia. However, none have been definitively proven. The incidence varies with location and ethnicity, with a high incidence noted in a district of Manitoba, Canada as well as in the Navajo Native American children. The overall incidence varies from 1.7 per 1,000 live births to 188.5 per 1,000 live births. Known risk factors for DDH include female gender, first

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born status, family history of DDH, breech presentation, oligohydramnios, metatarsus adductus, and torticollis.

The clinical presentation depends on the age of the patient. The neonate will present with either a dislocatable hip (positive Barlow's sign or ability to dislocate the hip from a located position with hip flexion and posterior pressure on the knee) or a reducible hip (positive Ortolani's sign or ability to reduce the hip with gradual abduction of the hip and anterior pressure on the greater trochanter). The signs may be difficult to elicit in an uncooperative child and may change over the course of a week as the initial infantile ligamentous laxity from maternal hormones improves. As the child enters infancy, asymmetry in hip abduction becomes a more reliable finding in a unilateral hip dysplasia. When the hips are flexed to 90°, the height of the knee from the exam table may be less in the dysplastic hip (positive Galeazzi sign).

The differential diagnosis is broad and includes neonatal septic arthritis, teratologic dislocation with underlying neuromuscular disorder, fracture, or congenital femoral deficiency.

The initial treatment for DDH is Pavlik harness (flexion harness) application. The hip is closely monitored in the harness with serial ultrasound examination for improvement in the femoro-acetabular relationship. If no improvement is noted at 3–4 weeks, the harness is discontinued and surgical reduction, through closed or open means, is attempted after 6 months of life. Even if Pavlik harness treatment is initially successful, long-term follow-up is required to ensure that no residual hip deformity develops.

The short- to mid-term prognosis depends on the specific clinical instability. Up to 60% of Ortolani positive hips and >90% of Barlow positive hips will respond to Pavlik Harness treatment. Long-term outcomes are uncertain as it is unclear which patients will progress to adolescent or adult dysplasia despite acceptable short-term radiographs. Therefore, long-term clinical and radiographic follow-up is required to ensure that the patient does not develop residual hip deformity.

Preventative measures include screening of the neonate by physical examination. Universal screening of neonates with ultrasonography is a matter of controversy. Currently, ultrasound screening is recommended for female infants carried in a breech position or with a positive family history.

Legg–Calvé–Perthes Disease

Case: A 6-year-old boy without significant past medical history or antecedent trauma presents with a limp and mild right hip pain. Examination reveals mild limitation in range of motion, especially in abduction and internal rotation. X-ray of the pelvis demonstrates unilateral fragmentation of the femoral head sparing most of the lateral pillar. (*Fig. 409.1*) Labs demonstrate no evidence of infection. The patient is managed symptomatically and, by age 9, notes no hip pain and no residual limp. X-rays at that point show mild deformity in the femoral head and acetabulum.

Legg–Calvé–Perthes Disease is an idiopathic avascular necrosis of the femoral head. The most clinically useful grading is that of Herring, who divides the femoral head involvement into A, B, and C groups depending upon the involvement of the lateral column of bone along the femoral epiphysis, with the C group having <50% of intact lateral column structure.

The exact etiology continues to escape careful scrutiny, although a multifactorial cause is favored. It is postulated that there is an intrinsic propensity in affected individuals to abnormal clotting of small vessels through an abnormality in the clotting cascade. The worldwide incidence is approximately 1 in 1,200. The disorder is most prevalent in the 4–12 age group, but can be seen from 18 months of age to skeletal maturity. Boys are more frequently affected

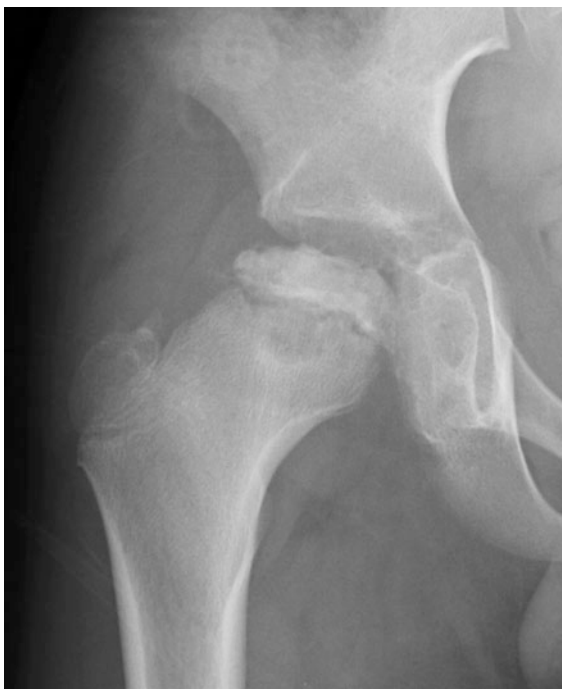

Figure 409.1
Hip pathology – Perthes

than girls in a 4:1 ratio and bilaterality occurs in 10–12% of patients.

Patients typically present with complaints of a limp or hip or knee pain that is usually aggravated by physical activity and worse later in the day. The child is typically smaller in stature, thin, and reportedly hyperactive. The initial examination will reveal various degrees of loss in range of motion and guarding with a gait asymmetry manifested by an antalgic/Trendelenburg pattern.

The differential diagnosis for this clinical and radiographic presentation is broad. Avascular necrosis from specific etiologies (sickle cell disease, thalassema, steroid medication), epiphyseal dyplasias (multiple epiphyseal dysplasia), and syndromes (trichorhinophalangeal syndrome, osteochondromatosis) must be excluded.

No standard treatment protocol exists. Symptomatic treatment is practiced by most but surgical treatment remains controversial with disagreement between large centers. Surgical treatment focuses on containing the irregular femoral head in the acetabulum to maintain sphericity. The recommendations for surgical treatment are dictated by the age of onset and the relative involvement of the femoral head, as described by the lateral pillar system. Generally, the older the patient and the more involved the femoral head, the less efficacious is surgical treatment.

Prognosis depends on the radiographic involvement of the femoral head and the age of the patient. Patients <6 years of age generally fare well while patients >9 years of age generally fare poorly, although older patients with minimal head involvement can have excellent hip function. Long-term function of the hip is directly correlated to the degree of residual femoral head and acetabular deformity at skeletal maturity.

Slipped Capital Femoral Epiphysis

Case: A 12-year-old boy presents with groin and knee pain for 3 months and is still able to bear weight. Radiographs reveal posterior displacement of the femoral epiphysis with respect to the femoral neck and chronic, bony remodeling of the femoral neck. The patient is placed in a wheelchair and taken for in situ screw fixation that evening. At 2-week-follow-up, pain is significantly improved despite residual femoral deformity on radiographs.

Slipped capital femoral epiphysis (SCFE) is the posterior displacement of the femoral epiphysis relative to the femoral neck through the level of the proximal femoral physis. The condition may be classified temporally as acute (symptoms ≤ 3 weeks), chronic (symptoms >3 weeks), or acute-on-chronic (worsening symptoms for ≤ 3 weeks in the setting of chronic symptoms). The most clinically useful classification involves the ability to bear weight on the affected extremity. Patients unable to bear weight are termed "unstable" and those able to bear weight are termed "stable." Unstable slips have a high risk of subsequent femoral head avascular necrosis despite timely surgical intervention.

No clear etiology has been identified for SCFE. Hormonal predisposition is thought to play a factor as most slips occur in obese males with hypogonadal features during the adolescent growth spurt and slips occur in patients with known endocrine abnormalities. SCFE is a disease of adolescence and will uncommonly occur, in the absence of an endocrinopathy, in patients less than the age of 10 or greater than the age of 16. Incidence varies according to race, sex, and geographic region, with a range of 1–7 per 100,000 worldwide. Polynesian children have the highest prevalence of slips while Indo-Mediterranean children the lowest. Blacks have an approximately twofold greater prevalence than whites. Bilateral involvement occurs with a frequency of 20–25%, with symptoms in the contralateral hip appearing within 18 months of the initial presentation.

The patient presents with either acute or chronic complaints of hip or knee pain with an associated limp. An adolescent complaining of knee pain, particularly if overweight, has a SCFE until proven otherwise. If the slip is unstable, the ability of the patient to bear weight is compromised. For chronic SCFE, the hip will demonstrate little to no internal rotation and obligate external rotation with hip flexion. For unstable slips, any hip motion will cause the patient discomfort. An AP and frog lateral view of the pelvis typically reveals the deformity (*Fig. 409.2*).

Anteroposterior (AP) (a) and frog leg lateral (b) views of the hips demonstrating a left hip slipped capital femoral epiphysis. The blue line on the AP (Klein's line) drawn along the femoral neck demonstrates the relative varus of the femoral epiphysis. A similar line drawn on the lateral demonstrates the relative posterior displacement of the left femoral epiphysis compared to the normal right hip.

The differential diagnosis for this condition is limited. Unstable slips must be distinguished from a femoral neck fracture. Stable slips should be distinguished from late deformity resulting from Perthes disease or hip dysplasia as well as congenital conditions such as congenital coxa vara.

Surgical stabilization is required in all cases of slipped capital femoral epiphysis to prevent rapidly or slowly progressive deformity. Immediate non-weight bearing of

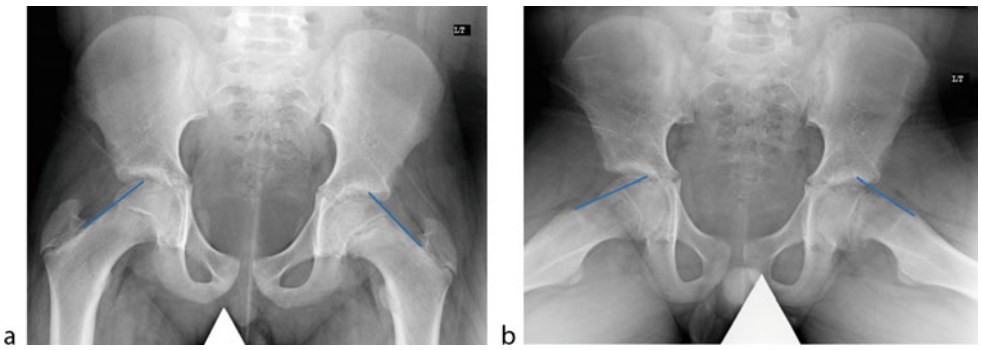

Figure 409.2
Hip pathology – slipped capital femoral epiphysis

the affected extremity is instituted and in situ screw fixation is performed. Open reduction with stabilization is sometimes recommended for acute unstable SCFE in the hopes of salvaging the tenuous blood supply.

Hip function and the risk of late degenerative hip arthritis is directly correlated to the residual deformity of the femoral head once healing has taken place. If avascular necrosis has occurred, the prognosis for good long-term hip function is poor. Of even greater import than appropriate surgical stabilization is early recognition of the SCFE diagnosis, so that the short-term and long-term consequences of the disease may be minimized or prevented.

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410 Foot Pathology

Jonathan R. Schiller

Human walking begins as early as 10 months old and is subject to changes in the normal development of the foot. The foot comprises three divisions: the hind foot (calcaneus, talus, proximal cuboid, and proximal navicular), midfoot (distal cuboid and navicular, cuneiforms), and forefoot (metatarsals, phalanges). Soft tissue attachments of muscles, ligaments, tendons, and plantar fascia are responsible for maintenance of the longitudinal arch and normal joint biomechanics in all three divisions. Ossification begins in utero, starting with the talus, calcaneus, and metatarsals and finishing with the navicular at 3 years of age or later. Arrested development may delay ossification and alter intra-articular relationships, producing the relatively common presentation of foot deformities in children seen in 5% of newborns.

Polydactyly and Syndactyly

Polydactyly and syndactyly are common foot deformities in the pediatric population. Polydactyly is a duplication of one or multiple digits in the foot (*Fig. 410.1*). It may be bilateral up to 50% of the time, although not always symmetric. Observed in 1 in 1,000 live births, it is more frequent in blacks, up to 4 in 1,000 births. Syndactyly is observed in 20% of patients and one-third have polydactyly of the hand. Thirty percent of patients have a positive family history, and an autosomal dominance with incomplete penetrance has been described. The Hox genes have been cited as a possible cause, leading to apical ectodermal ridge disruptions in Bmp4. Polydactyly may be associated with syndromes such as Ellis van Creveld, Trisomy 13, tibial hemimelia, and Down syndrome.

Duplication may be on the great toe side (pre-axial) or the small toe side (post-axial), and may vary from a well-formed digit to a rudimentary "nubbin." Bone involvement may be a distal phalanx to a complete independent or connected duplication of the metatarsal. The majority of cases (80%) are post-axial, with duplication of the phalanx, metatarsal, or a wide metatarsal head.

Treatment is aimed to provide improved foot appearance and comfortable shoe wear. Suture ligation of duplicated digits is employed when only connected by soft tissue; radiographs are mandatory to determine osseous anatomy. Residual bone or cartilage will lead to future deformity and possible surgery. Surgery is recommended after 1 year of age to reduce anesthetic risk, as well as allow the child to begin walking. The most lateral or medial toe is removed with simple excision, whereas central digit duplication requires intermetatarsal ligament and capsular repair.

Syndactyly is congenital webbing of the toes (*Fig. 410.2*), most often involving the proximal portion of the toe (incomplete); however, it can involve the entire toe (complete) including the nail. Most frequently it is seen between the second and third toe, followed by the fourth and fifth toe. It may be seen with polydactyly and involve synostosis of the metatarsals as well. Isolated syndactyly is a cosmetic deformity and presents no functional problems. Parental counseling often alleviates concerns of cosmesis and functional limitation. When separated, a skin graft is usually required for closure. Except in cases of complex deformity, no surgery is usually the best option.

Metatarsus Adductus

Metatarsus adductus, metatarsus varus, and skewfoot are foot deformities characterized by forefoot adduction. Metatarsus adductus involves medial deviation of the forefoot and a neutral or slightly valgus calcaneus. Metatarsus varus, although similar, is characterized by forefoot supination in addition to medial deviation. Skewfoot is a rigid deformity characterized by forefoot adduction, cavus, equinus, and varus. Presentation varies from mild, moderate, to severe, determined by the ability to actively (mild) or passively (moderate) correct the foot, or without correction (rigid). Forefoot adduction is seen in 1 of every 1,000 live births, increasing to 1 in 20 for subsequent children. Considered to be secondary to intrauterine positioning, the increased incidence with subsequent children has raised doubt as to potential in utero packaging problems. To date, no genetic cause has been demonstrated.

Clinically, the forefoot is medially deviated on the hindfoot, most notable when examining from the plantar surface and following the lateral border. Assessment of

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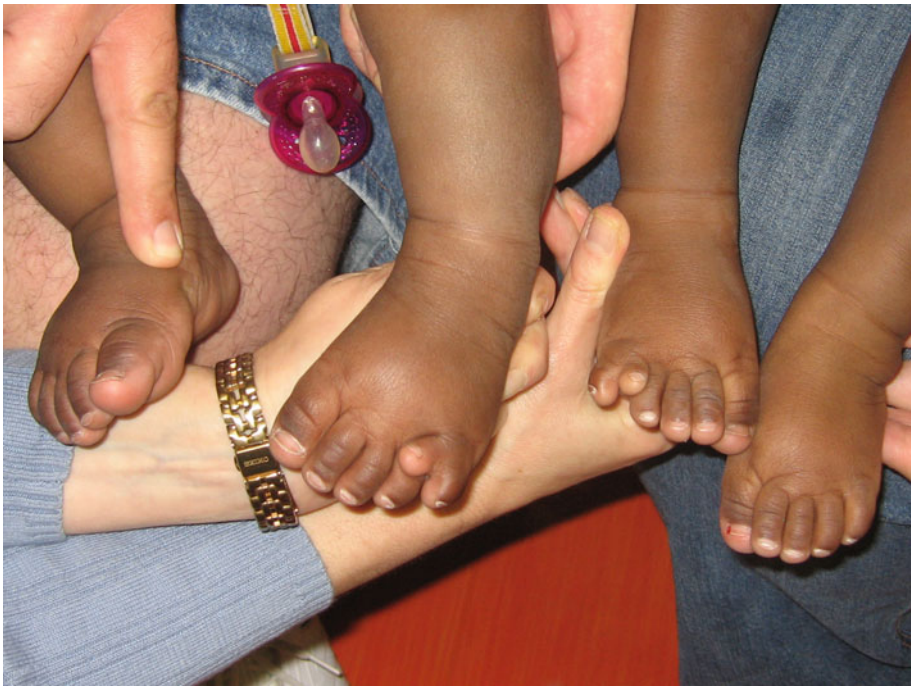

Figure 410.1

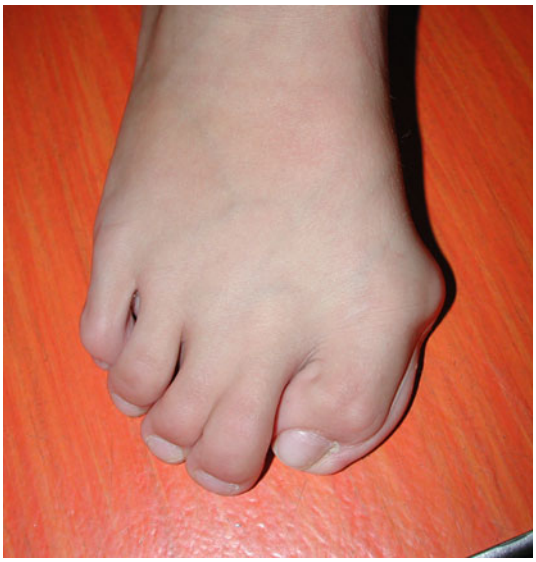

Figure 410.2

forefoot motion is essential to determine flexibility. Flexible deformities actively correct to neutral when the lateral border of the foot is stroked and passively correct beyond neutral. Partly flexible deformities only correct to neutral, while rigid deformities do not correct to neutral. Frequently accompanying metatarsus adductus, internal tibial torsion is the most frequent parent complaint, though this is unrelated to the foot deformity and should be dealt with separately. Radiographs are not necessary as this is a clinical diagnosis.

Flexible feet, demonstrated by active correction require no treatment. Parents are taught home stretching and stimulation exercises to improve active correction, however, the deformity will resolve spontaneously in nearly 90–95% of patients. Debate exists whether to treat passively correctable feet. Serial casting is initiated in children less than 6 months of age to passively correct the foot. Casting is followed by reverse or straight last shoes to maintain correction and avoid recurrence. Rigid feet should begin with serial casting between 4 and 6 months of age followed by stretching, with gradual correction over a period of months. Surgery is rarely necessary, although older children with chronic deformity, pain, and difficulty in shoe wear may require intervention.

Talipes Equinovarus

Talipes equinovarus, or clubfoot, occurs in 1 to 2 in 1,000 births. Comprised of cavus, metatarsus adductus, hindfoot

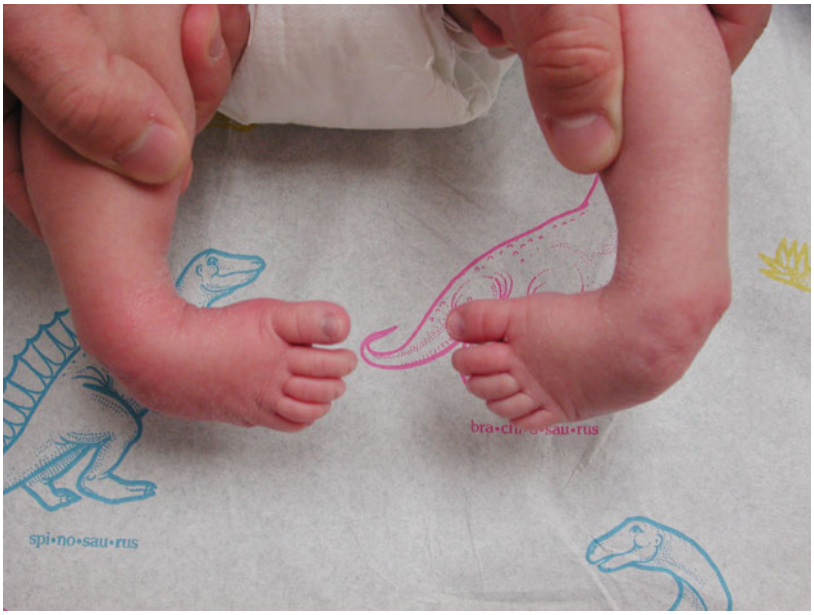

Figure 410.3

varus, and equinus (*CAVE*), clubfoot is more common in males (M:F, 2.5:1) and may be bilateral 50% of the time. Usually recognized during the newborn exam (*Fig. 410.3*), clubfoot varies from a benign, flexible deformity to a severe, rigid foot. The etiology of clubfoot is multifactorial as numerous causes including intrauterine factors (positional compression, oligohydramnios), vascular abnormalities (hypoplasia or absence of the anterior tibial artery), abnormal muscle insertion and development (increase in the type I: type II muscle fiber ratio, muscle fibrosis, anomalous muscles), and environmental factors (amniocentesis, cigarette exposure) have been implicated. Genetic factors play a role in clubfoot development. A positive family history is present in 25% of children with clubfeet and both siblings are affected in 32.5% of monozygotic twins. More severe forms of clubfoot are seen in diseases involving the nervous system, most notably myelomeningocele and arthrogryposis, as well as rare disorders such as spinal muscular atrophy, sacral agenesis, Trisomy 18, and Larsen's Syndrome.

A complete physical examination is critical to discover associated conditions. Typically, patients present with a smaller calf and foot on the affected side, most notable in unilateral involvement. This is a permanent difference and will not change with intervention. Dimpling of the skin, due to loss of subcutaneous fat, and contractures suggest arthrogryposis. Hindfoot equinus and varus results from the calcaneus "locked" position under the talus and a tight heel cord. This results in talar deformity, evidenced by a foreshortened talar head, medial angulation of the neck, and tilting of the body. The forefoot is adducted as the navicular is situated medially relative to the talus. The Dimeglio classification system was developed to score to the physical findings of the foot (hindfoot varus, calcaneopedal rotation, equinus, forefoot adduction, medial and posterior skin crease, cavus, and muscle tone) and correlates with severity. Radiographic examination is usually not required and is limited secondary to difficulty positioning the foot, lack of ossification, rotational distortion, and inability to bear weight. Older children amenable to radiographs demonstrate on anteroposterior (AP) radiographs, a talocalcaneal angle (Kite's Angle) of less than 20° (normal 25–45°) and medial displacement of the cuboid ossification center, while the lateral talocalcaneal angle is less than 35° (normal 35–50°).

Nonoperative methods are the gold standard when initiating treatment for clubfoot. Two distinct modalities exist to treat deformity in the infant patient, the French physiotherapy method composed of stretching, manipulation, and taping, and the Ponseti method, which involves serial casting. Physiotherapy focuses on stretching the soft tissues through longitudinal traction, attempting to reduce the talonavicular joint. Taping and continuous passive motion maintains stretch and correction of the foot, with successful results 90–95% of the time.

The Ponseti method involves serial long leg plaster casting, changed weekly to gradually correct the deformity. Percutaneous Achilles tenotomy is required over 70% of the time. Ponseti casting yields over 90% success, although there can be up to 50% recurrence, despite casting up to 2 months. Some form of bracing is usually used for 2 or 3 years after casting to prevent recurrence. Results with bracing, casting, and percutaneous heel cord lengthening have increased success to greater than 95%. Nonoperative treatment is not without complications. Pressure sores are common, as are iatrogenic deformities such as a flat-top talus (excessive dorsiflexion compresses talus between tibia and calcaneus), rocker-bottom foot (forced dorsiflexion of forefoot attempting to correct equinus prior to forefoot adduction and heel varus), and a bean-shaped foot (correction of adduction is attempted before varus).

When nonoperative treatment fails, soft tissue releases are often attempted first to correct the deformity, especially in the skeletally immature child. Surgery may be performed anytime after 6 months, although, waiting until the child is a year old permits easier surgical anatomy and allows the child to be closer to walking age. Operative complications increase with the severity of deformity. Almost 10% of patients require revision surgery. This is often predicated on patient complaints of pain, cosmesis, or difficulty in shoe wear. Resistant deformities may require osteotomies of the calcaneus, cuboid, and cuneiforms in the near or skeletally mature foot. Triple arthrodesis, limited talonavicular arthrodesis, and Ilizarov external fixation are used for salvage reconstruction.

Sever's Disease

Calcaneal apophysitis is a common cause of foot pain in young immature athletes. The age of onset is 8–13 years old, coinciding with ossification and subsequent fusion of the apophysis to the calcaneus. Sixty percent of patients have bilateral involvement. The condition is more common in males, and can be as high as 4 to 1. The etiology of Sever's is unknown, although repetitive traction injuries at the Achilles tendon or plantar fascia insertion is thought to lead to disruption of endochondral bone formation as the apophysis attempts to heal, leading to inflammation and pain.

History and physical examination reveals complaints of pain after athletic activity, located on the plantar or plantar-medial aspect of the foot, especially with prolonged activity. Similar to plantar fasciitis, pain or stiffness upon awakening is also common. Symptoms are common at the start of the season or a new sport. Cessation of sports leads to immediate comfort. Squeezing the heel reveals tenderness of the plantar or medial aspect of the calcaneal apophysis. The Achilles tendon is almost always tight. The differential diagnosis includes stress fracture, infection, inflammatory arthropathy, and calcaneal tumor (unicameral bone cyst, osteoid osteoma). Radiographs are typically not necessary; however, weight-bearing radiographs are obtained to exclude other pathology, especially with a history of night or unilateral pain. Increased density and fragmentation of the calcaneal apophysis may be present, although the former is a normal radiographic finding in children.

Treatment involves activity modification, and Achilles tendon stretching. Some patients benefit from gel heel cups to decrease impact trauma to the plantar portion of the apophysis. Rarely is casting or discontinuation of athletic activity necessary except for extreme cases, although some patients may need to limit their participation during acute exacerbations. Immobilization with a cast or walking boot results in complete resolution in patients refractory to activity modification and physical therapy.

Kohler's Disease

Kohler's disease is an uncommon, self-limiting, avascular necrosis of the navicular. Affecting children between the ages of 2 and 9, this idiopathic condition is usually unilateral and more common in boys. The repetitive compressive forces on the navicular during weight bearing may lead to avascular necrosis, secondary to delayed ossification, and vulnerable peripheral blood supply.

Patients primarily complain of midfoot pain, often exhibiting a limp, and weight bearing on the lateral border of the foot to relieve pressure along the longitudinal arch. Navicular tenderness and swelling may be present, and contraction of the posterior tibialis tendon exacerbates pain. Radiographs of the navicular demonstrate sclerosis, flattening, and a loss of the normal trabecular pattern evidenced by a uniform increase in density, fragmentation, or collapse.

The mainstay of treatment is conservative, consisting of arch supports, medial heel wedge, and activity modification in symptomatic patients. Severe, persistent pain may be treated in a short leg walking cast for 4–8 weeks, followed by orthotics. Immobilization has decreased the duration of symptoms and morbidity and is universally effective in relieving symptoms. The prognosis is excellent as the navicular regains its normal architecture before the foot completes growth, thus patients can be expected to have a normal foot in adulthood. Operative treatment is rarely necessary.

Flatfoot

Flatfoot, or pes planus, is one of the most common conditions seen in pediatric orthopedic practice, present in 1 in 1,000 live births and nearly 25% of the adult population. It has been described as, "usual in neonates and infants, common in children, and within the normal range in adults." Characterized by loss of the medial arch and increased weight bearing on the medial border of the foot, children and adolescents are often brought in by parents, potentially under the perception the deformity will be associated with pain in adulthood. Differentiating the benign, flexible from the painful, rigid form is essential to determine the need for treatment.

Nearly all neonates and infants have the appearance of a flatfoot, owing to excessive fat and lack of development of the arch, which normally begins by age 5. The infant with a calcaneovalgus foot will have a flexible flatfoot that easily dorsiflexes against the tibia, and a heel in valgus. The anatomy is normal, however it is important to ensure the patient does not have a vertical talus or posteromedial bowing of the tibia. Gentle stretching into plantar flexion and inversion can be performed, and most deformities will resolve by 6 months. Patients with posteromedial bowing of the tibia will have a limb-length discrepancy, most likely not requiring treatment.

The older child and adolescent may not have an arch when weight bearing, however the flexible flatfoot arch reconstitutes when the child stands on their tiptoes. Heel cord tightness may be responsible for the deformity and make the hypermobile flatfeet symptomatic. Inspection of the shoes may demonstrate a lack of lateral heel wear, further indicating a tight heel cord. Gait should always be evaluated for suggestion of a neuromuscular cause (cerebral palsy, poliomyelitis, peripheral neuropathy, Duchenne's muscular dystrophy). Failure of the arch to reconstitute upon toe raising signals a rigid deformity, as seen with congenital vertical talus (rocker-bottom deformity more common), tarsal coalition, and skewfoot. Often, these conditions are typified by limited subtalar motion, pain, and difficulty with activity.

Diagnostic radiographs are rarely indicated for a flexible flatfoot. If radiographs are obtained, they should be weight bearing. The most important reason to obtain radiographs is to establish other diagnoses causing the deformity and not to relieve parental concerns when a flexible flatfoot is evident.

The majority of patients are asymptomatic, thus treatment is rarely indicated other than parental reassurance. Heelcord tightness can be stretched manually or with serial casting. Though many children rebuff inserts, orthotics are often tried despite evidence that the long-term outcome remains unchanged. The most inexpensive orthotics should be tried first since custom inserts can be costly and often are not covered by insurance. Surgical treatment has been described for pain and persistent deformity, although this is rarely required. Subtalar or triple arthrodesis has been effective in relieving symptoms, albeit at the expense of subtalar and hindfoot motion. Calcanealcuboid and medial cuneiform osteotomies, as well as lateral column lengthening, have yielded good results while preserving joint motion.

Accessory Navicular

The accessory navicular is an ossicle on the medial side of the midfoot, proximal to the navicular and in continuity with the tibialis posterior tendon. Commonly, 20% of normal feet have an accessory navicular, lending to the thought it is a normal anatomic and radiographic variant. Considered idiopathic, accessory navicular is frequently observed in multiple family members and an autosomal dominant inheritance pattern with incomplete penetrance has been described. Patients are typically active adolescents with a flexible flat foot, often presenting with a painful prominence and swelling on the medial arch of foot at the region of the navicular. The prominence may be associated with erythema, callus formation, tenderness, and a fluid-filled bursa. Inversion against resistance may elicit pain at the prominence and along the tibialis posterior tendon and is considered diagnostic. Shoe wear may become increasingly difficult, often aggravated by tight shoes. The differential diagnosis for medial midfoot pain should include: Kohler's disease, tibialis posterior tendon rupture, enthesiopathy of the tibialis anterior tendon, and navicular stress fracture.

Three types of accessory navicular have been classified. Type 1 has an ossicle within the tibialis posterior tendon, anatomically separate from the navicular; type 2, a cartilaginous bridge between ossicle and navicular; and type 3, where the accessory ossicle fuses to the navicular. Weight-bearing AP and lateral foot radiographs and an external oblique view demonstrate the accessory ossicle, aiding in classification and guiding treatment (*Fig. 410.4*). Computed tomography (CT) scans are used to differentiate the accessory ossicle from the navicular, although are not routinely needed. Bone scan and magnetic resonance imaging (MRI) may be helpful when the etiology of medial foot pain is unclear.

Treatment for asymptomatic accessory navicular is not required. A painful prominence or difficulty with shoe

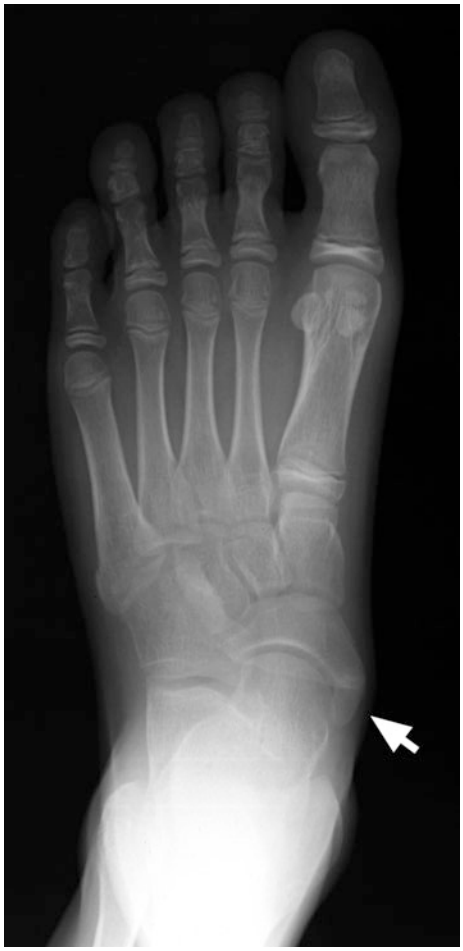

Figure 410.4

wear should be treated initially with a doughnut-shaped piece of mole skin and comfortable wide-based shoes. Longitudinal arch supports may relieve pressure over the medial arch and resist pronation of the foot. Cast immobilization for 6–8 weeks may be warranted for severe pain. Although less than 1% requires surgery, failure of conservative measures leads to operative intervention to relieve the persistently symptomatic accessory navicular. Traditionally, excision of the accessory ossicle and transfer of the tibialis posterior tendon plantarly have been successful in relieving pain. A painful scar may result if placed directly over the symptomatic prominence, and care must be taken to keep the tibialis posterior tendon intact. Good results with pain relief and fatigue are expected in patients having undergone excision; however correction of the flatfoot may require a bony procedure such as lateral column lengthening to restore the medial arch. Percutaneous drilling of the accessory navicular bone has shown to be efficacious in young athletes, though most continue to advocate simple excision for a symptomatic accessory navicular.

Tarsal Coalition

Tarsal coalition is an abnormal connection in the hindfoot, a result of failure of segmentation of mesenchymal tissue with subsequent failure of formation of normal joints. Previously called the peroneal spastic flatfoot, the peroneals are neither a cause nor result in a coalition. Coalitions may be fibrous, cartilaginous, or osseous, and they are observed in 1–3% of the population. The etiology is unknown although a family history is observed and autosomal dominance with variable penetrance has been reported. Calcaneonavicular coalition occurs in 60%, while bilateral talocalcaneal coalitions occur in 50% of cases. Coalitions are associated with symphalangism, fibular hemimelia, proximal femoral focal deficiency, phocomelia, Apert syndrome, and Nievergelt–Pearlman Syndrome.

Symptoms typically develop during adolescence and skeletal maturity, appearing after a traumatic event or with increased activity, though many patients are asymptomatic. Ossification of a bony coalition may decrease subtalar motion, resulting in symptoms. Often there is a history of sprains, and walking over uneven ground exacerbates symptoms primarily through stressing the subtalar joint. Pain may be located in the sinus tarsi or along the peroneal tendons. Decreased subtalar motion is present as evidenced by decreased passive inversion and eversion, less evident with calcaneonavicular than talocalcaneal coalitions. The foot is often everted and pain is present with resisted inversion. Patients are unable to stand on lateral border of their foot and no inversion of the heel is evident when attempting to stand on the toes. Tarsal coalition is differentiated from a flexible flatfoot by examining hindfoot range of motion.

Radiographs should include weight-bearing AP and lateral foot films. For coalitions difficult to visualize on plain films, computed tomography (CT) is performed. A coronal CT scan is the preferred method of diagnosis for talocalcaneal coalition and a longitudinal CT scan is preferable to identify a calcaneonavicular coalition, and should include both feet since 50% will be bilateral.

Initially, conservative treatment is required for any patient. Patients with incidental findings do not require treatment, but should be followed. Patients with minor

pain may try orthotics. Short-leg walking casts are attempted for severe symptoms, often followed with a University of California Berkley Laboratory (UCBL) insert. Surgery is indicated for persistent pain and failure of conservative treatment. A calcaneonavicular coalition is treated with resection and interposition of extensor digitorum brevis or fat. This portends good results in 80% of patients. Younger patients fare better due to increased potential for return of joint mobility, with the best results observed in patients with a cartilaginous coalition less than 16 years old at the time of surgery. Anecdotal results of subtalar arthrodesis are good or excellent in nearly 80% of patients, though published reports have yet to support these results. Surgery of talocalcaneal coalitions are not as predictable as with calcaneonavicular coalitions. Subtalar joint motion needs to be assessed after resection as the goal of surgical treatment is to provide increased subtalar motion. Unresectable coalitions, commonly involving greater than 50% of the subtalar joint usually require triple arthrodesis. If coalition resection fails to relieve symptoms or degenerative changes are seen at presentation, a triple arthrodesis is the salvage procedure.

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411 Pediatric Sports Medicine

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Pediatric Hip Disorders

Apophyseal Avulsion Injuries

Skeletally immature patients frequently suffer avulsion injuries about the pelvis due to weakness of the open apophysis. Avulsion fractures commonly occur at the anterior superior iliac spine (ASIS), the anterior inferior iliac spine (AIIS), and the ischial tuberosity as a result of sudden contraction of the sartorius, rectus femoris, and hamstring muscles, respectively. Patients often describe feeling a pop at the time of injury (e.g., kicking a ball) and frequently present with localized pain and swelling. Radiographic examination is important to determine the size and displacement of the avulsed fragment. These injuries are usually managed conservatively, including rest, ice, protected weight bearing with crutches, and gradual stretching and return to activity once symptoms resolve. Although most of these injuries can be treated non-operatively, large fragments displaced more than 2–3 cm may require surgical intervention.

Snapping Hip Syndrome

This syndrome has both external and internal etiologies. The *external form* is more common and involves snapping of the iliotibial (IT) band over the greater trochanter with hip flexion and extension. The snapping is further accentuated with knee extension and hip adduction, which serves to tighten the IT band. With the development of pain, conservative treatment is pursued, including rest, IT band stretching, and nonsteroidal anti-inflammatory medications. The *internal form* of this condition stems from the catching of the iliopsoas tendon on the pelvic brim (iliopectineal eminence) or the femoral head. This occurs with hip extension and may be associated with chronic bursitis. A similar treatment protocol is employed as for external snapping.

Iliotibial (IT) Band Syndrome

This condition commonly occurs in runners and dancers and is due to friction between the iliotibial band and the lateral femoral condyle. While some patients complain of knee pain, patients more often have tenderness localized to the greater trochanter due to rubbing of the iliotibial band. The ober test is used to evaluate for contracture of the IT band. During this test, the patient lies on the normal hip, while flexing the affected hip and knee. Abduction and extension of the hip from this position centers the IT band on the greater trochanter. Adduction will be limited in the case of IT band contracture. Patients often improve with conservative measures, including rest, iliotibial band stretching, and nonsteroidal anti-inflammatory medications.

Pediatric Knee Disorders

Osgood-Schlatter Disease

Osgood-Schlatter Disease (OSD) is a common knee problem in children between the ages of 10 and 15 years. The condition often occurs in sports such as soccer, basketball, gymnastics, and volleyball and is thought to result from repetitive microtrauma or a traction apophysitis of the tibial tuberosity. Athletes usually report intermittent anterior knee pain and swelling, made worse with activity. The low-grade ache is usually localized to the area of the tibial tubercle. Thirty to forty percent of adolescents with OSD report bilateral symptoms. Examination reveals tenderness and swelling over the tibial tubercle, while the remainder of the knee exam is usually normal. Radiographs are not generally indicated; however, they may reveal prominence or fragmentation of the tubercle or even a discrete ossicle. MRI or advanced imaging is rarely necessary.

Management consists largely of conservative measures including use of nonsteroidal anti-inflammatory drugs, rest from activity, and stretching of the thigh

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musculature. Patients may benefit from physical therapy at the time of diagnosis. If ambulation is difficult, crutch ambulation may be used with a knee immobilizer before the athlete initiates a stretching and strengthening program. If a patient experiences severe symptoms, a cylinder cast may be used with crutch ambulation for 2–4 weeks. OSD typically resolves within 6–18 months, coinciding with growth plate closure. Symptoms may recur with resumption of sports activities and can require a repeat cycle of rest from activity, stretching, and strengthening. The condition is usually self-limited, ceasing with the completion of growth and the fusion and maturation of the tibial tubercle. Following skeletal maturity, those patients with residual symptoms and loose fragments within the patellar tendon may require surgical excision.

Sinding–Larsen–Johansson Syndrome

Sinding–Larsen–Johansson Syndrome is thought to be due to an overuse injury at the junction of the developing patella and patellar tendon. It occurs most commonly in boys aged 9–13 years and is often associated with sports involving running or jumping, stair climbing, or repetitive kneeling. This condition is similar to jumper's knee (patellar tendinosis), which occurs in skeletally mature athletes. Jumper's knee involves a partial tear of the deep layers of the proximal patellar tendon and tends to be difficult to treat. Patients with Sinding–Larsen–Johansson Syndrome will often complain of anterior knee pain, worsened with activity. Physical examination reveals tenderness at the distal pole of the patella and insertion of the patellar tendon. As in Osgood-Schlatter disease (OSD), these athletes frequently have tight, relatively weak quadriceps. Radiographs often show fragmentation with ossicle formation, elongation of the distal pole of the patella, or small calcifications in the proximal patellar tendon. Fragmentation may also represent a patellar sleeve fracture, which is usually acute and associated with a specific traumatic event. Patients with patellar sleeve fractures require referral to a pediatric orthopaedist for surgical repair. MRI or other forms of advanced imaging are not necessary. Management is similar to OSD, focusing mainly on pain control, rest from activity, cross-training, and stretching and strengthening of the quadriceps. This condition is usually self-limited; however, severe symptoms may necessitate immobilization to promote healing prior to initiating muscular rehabilitation.

Patellofemoral Syndrome

Patellofemoral pain is extremely common in adolescent female athletes and may stem from conditions such as patellofemoral dysplasia or patellofemoral instability. This condition is often associated with activities that increase load across the patellofemoral joint, including squatting, running, stair climbing, and kneeling. The etiology of patellofemoral disorders is usually multifactorial. Several structures including the anterior synovium, infrapatellar fat pad, subchondral bone, and medial or lateral retinaculae are among those considered most likely to be the origin of patellofemoral pain. The development of this condition has also been associated with abnormal lateral tracking of the patella within the trochlea, creating areas of increased stress on the patellofemoral joint. Changes in forces across the patella may be related to rapid growth during adolescence, the strong lateral pull of the vastus lateralis and iliotibial band, or quadriceps tightness, all of which can lead to the onset of anterior knee pain and instability.

Athletes with patellofemoral syndrome usually describe a vague, aching pain on the anterior aspect of the knee, which is worse with sports activity or prolonged sitting with the knee flexed. There are rarely any associated mechanical symptoms of locking and catching. Patients often complain of pain with patellar compression during quadriceps contraction and pain with resisted extension. It is important to evaluate the alignment of the quadriceps, patella, and tibial tubercle both passively and actively, as malalignment problems are common, treatable causes of anterior knee pin. A line drawn through the center of the patellar tendon from the patella to the tibial tuberosity defines the patellar tendon vector; whereas a line from the anterior superior iliac spine to the patella defines the quadriceps vector. The angle formed by the junction of these two vectors is known as the quadriceps or Q angle. Several factors can influence the Q angle, including the patient's height, the degree of knee valgus, and the width of the pelvis. A Q angle of greater than 20° causes lateral patellar tracking and subsequent stress on the trochlear groove and the lateral aspect of the patella, often leading to anterior knee pain. In the office, these patients should undergo a thorough examination of the lower extremity evaluating specifically for femoral internal rotation, genu valgum (knock-knees), tibial external rotation, and pes planus (flat foot), since each of these conditions can lead to an increased Q angle (*Fig. 411.1*).

The mainstay of treatment for patellofemoral syndrome is nonoperative and requires avoidance of exacerbating activities. Ice and nonsteroidal anti-inflammatory

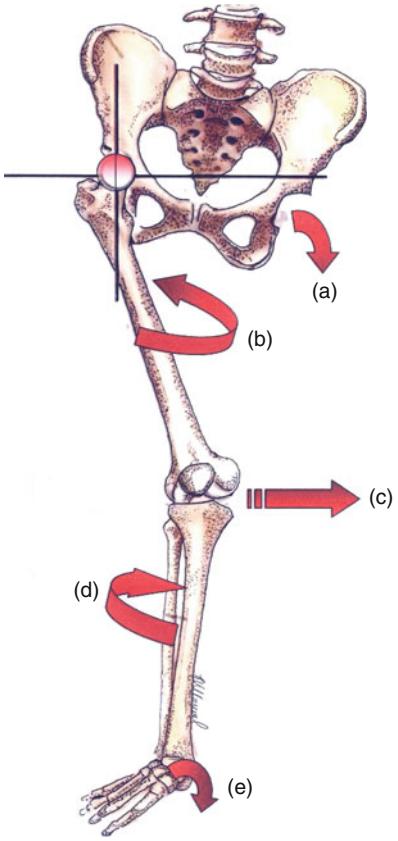

Figure 411.1
Schematic representation of potential causes of limb malalignment and malrotation, all of which can lead to increased Q angle: (a) hip adduction, (b) femoral internal rotation, (c) genu valgum, (d) external tibial rotation, (e) pes planus (flat foot)

drugs can be used to control pain. Physical therapy is frequently utilized to restore patellar alignment through quadriceps muscle strengthening exercises, stretching, patellar taping or bracing, biofeedback, and use of corrective foot orthoses. A neoprene knee sleeve or patellar stabilizing knee brace worn during athletic activity may be helpful. Surgical intervention is rarely warranted, usually reserved for those with a defined lesion that's amenable to surgical repair.

Patellar Dislocation

Patellar dislocation is a common acute knee injury in children and adolescents, with a peak incidence at age 15 years. There are several predisposing factors including a positive family history, patellofemoral dysplasia, and female gender. Acute patellar dislocation occurs more often in female athletes and is thought to be due to a higher incidence of lower extremity valgus and rotatory malalignment in women. Athletes will typically describe the injury as a "knee dislocation." The mechanism usually involves a flexion, twisting injury with the foot planted. Often, the patella will spontaneously reduce. When it remains dislocated, athletes will complain of extreme pain and an inability to extend the knee. The laterally displaced patella can usually be reduced with knee extension. Following reduction, physical exam often reveals significant swelling and tenderness along the medial aspect of the knee along the torn retinaculum. MRI is not required on initial presentation, although it can be useful to rule out cartilaginous fracture fragments. Radiographs of the knee, including Merchant or sunrise view, should be obtained to confirm reduction and to assess for osteochondral fractures. These injuries commonly occur on the medial side of the patella after lateral dislocation. Patellar dislocation can also lead to tearing of the medial patellofemoral ligament (MPFL), which is the primary restraint to lateral displacement of the patella.

Treatment following reduction should include a brief period of knee immobilization. A patellar stabilizing brace or taping can be substituted for the immobilizer after a period of 1–2 weeks. The athlete should begin a dedicated rehabilitation protocol immediately, including quadriceps strengthening, stretching, and coordination exercises. Gradual resumption of aerobic activities can follow with avoidance of activities involving twisting and cutting until full strength and motion have been attained.

Surgical repair is often recommended for recurrent dislocations, injuries with large associated osteochondral fractures or, rarely, in the high-demand athlete after a first-time dislocation. Patients with atraumatic patellar dislocations often have underlying ligamentous laxity or patellofemoral malalignment. Nonsurgical treatment is usually recommended in this group of patients, although surgery is required in extreme cases.

Baker's Cyst

The term "Baker's cyst" is commonly used to describe cysts occurring on the posteromedial aspect of the knee between the medial head of the gastrocnemius and the semimembranosus tendons. In adults, popliteal cysts have a high association with intra-articular lesions including rheumatoid arthritis, osteoarthritis, meniscal tears, and conditions that cause synovitis. In children, this is rarely

true, as most arise spontaneously. Baker's cysts commonly present as a mass in the posteromedial aspect of the knee. In children, these masses are usually asymptomatic and are brought to the attention of the pediatrician when the parent is concerned about the swelling or bulge in the popliteal fossa. Popliteal cysts can rupture suddenly, producing significant pain behind the knee and swelling extending down the calf region. Radiographs are frequently normal, but may occasionally reveal some soft tissue swelling. Ultrasonography is a common, noninvasive technique for evaluating popliteal cysts, and is helpful to rule out non-cystic masses. In children, popliteal cysts are often benign and self-limited, requiring no specific intervention.

Osteochondritis Dissecans of the Knee

Osteochondritis dissecans (OCD) can cause anterior knee pain in children and adolescents. OCD primarily affects subchondral bone, with secondary effects on articular cartilage. The etiology of this condition is unclear, but several hypotheses have been proposed including inflammation, genetics, ischemia, ossification, and repetitive trauma. The most commonly proposed etiology of OCD is repetitive microtrauma, which may stimulate a stress reaction, ultimately progressing to a stress fracture of the subchondral bone. Persistent loading may prevent the subchondral bone from healing, leading to fragment necrosis, dissection, separation, and nonunion. The "classic" location of knee OCD lesions is the posterolateral aspect of the medial femoral condyle (70–80% of cases), but it may also occur in the femoral trochlea (<1%), the patella (5–10%), and the lateral femoral condyle (15–20%). This condition most often presents in patients between ages 10 and 15 years, with a 2:1 male to female ratio. In 15–30% of cases, bilateral lesions are discovered, emphasizing the need to evaluate both knees in patients presenting with OCD.

There are two distinct forms of osteochondritis dissecans, juvenile (open physes) and adult. In the skeletally immature patient, there may be a disturbance in normal epiphyseal development, leading to formation of small areas of subchondral bone that separate from the main ossification center of the epiphyseal plate. Minimal trauma may then lead to osteonecrosis in this area. The adult form may result from a direct traumatic event or perhaps it represents a delayed presentation of a previously asymptomatic juvenile OCD that failed to heal. Fifty percent of patients with juvenile OCD demonstrate healing within 6–18 months of nonsurgical treatment; whereas, patients with adult OCD more often require surgical intervention to promote healing.

Patients usually present with vague anterior knee pain, occasionally associated with intermittent swelling. Adolescents with stable osteochondritis dissecans may ambulate with an antalgic gait; however, there is usually no effusion, crepitus, or pain through normal range of motion. Unstable lesions are often associated with persistent swelling and symptoms of catching, locking, or giving way. The Wilson test, which attempts to reproduce the knee pain by internally rotating the tibia during knee extension from 90° to 30° and subsequently relieving the pain with external rotation of the tibia, is often positive.

Standard weight-bearing anteroposterior and lateral radiographs of both knees should be obtained to assess growth plate status and to characterize the lesion. Since the "classic" location of osteochondritis dessicans can be difficult to visualize on the AP radiograph, tunnel views or flexed knee views can often provide valuable information. If patellar OCD is possible, skyline views should be obtained. Magnetic Resonance Imaging (MRI) has become a valuable tool in the diagnostic evaluation of OCD, providing an estimation of the size of the lesion as well as the status of cartilage and subchondral bone. Several additional findings including presence of loose bodies, extent of bony edema, and a high signal zone beneath the fragment are also important pieces of information revealed on MRI. The presence of an area of high signal intensity behind the osteochondral fragment is most indicative of an unstable lesion; whereas stable lesions are defined by the absence of any signs of dissection.

Skeletal age at the time of symptom onset is the most important factor in determining prognosis and guiding the overall treatment plan. Patients with open physes and stable lesions will likely recover with nonsurgical management, the goal of which is to promote lesion healing and to prevent fragment displacement. This treatment protocol consists primarily of activity modification, limited weight bearing (e.g., crutches or braces) for approximately 6 weeks, and non-steroidal anti-inflammatory medication (e.g., acetaminophen) for pain control. Immobilization in a cast should last no longer than 4–6 weeks and is reserved for noncompliant patients. Athletes are prohibited from participating in sports until they are pain free and physical examination as well as radiographs show evidence of healing. Surgical intervention is often required in unstable lesions or in stable lesions that have failed a period of nonsurgical management. Techniques such as in situ drilling, fixation, fragment removal, and chondral resurfacing are among the surgical procedures utilized.

Discoid Lateral Meniscus

Discoid meniscus, which refers to the presence of meniscal tissue across the entire tibial plateau, rather in a semicircular shape, occurs predominantly on the lateral side of the knee. Bilateral discoid menisci occur in approximately 20% of patients. Watanabe described a classification system for the discoid lateral meniscus. Type I menisci are complete, extending across the entire lateral tibial plateau. Type II menisci are incomplete, with the central portion of the meniscus stretching farther across the tibial plateau than normal. Type III menisci are referred to as the Wrisberg-ligament type, and lack attachment of the posterior horn of the meniscus to the tibia, resulting in instability.

Symptomatic discoid lateral meniscus occurs predominantly in children ages 10–15 years. Some athletes with this condition present with swelling, catching, popping, and tenderness over the lateral joint line. Symptoms are often related to the type of discoid meniscus, stability of the meniscus, and the presence or absence of a meniscal tear. Snapping knee syndrome is considered pathognomonic of a discoid meniscus and is often associated with the Wrisberg-ligament type. In these cases, the meniscofemoral ligament of Wrisberg provides the only stabilization to the lateral meniscus, which leads to increased mobility and shifting of the posterior horn of the meniscus into the femoral notch as the knee extends. Athletes often experience intermittent locking of the knee, as well as a palpable clunk as the knee moves through a full range of motion.

Plain radiographs of the knee are often normal, but may reveal a squared-off lateral femoral condyle, a widened lateral joint space, and cupping of the lateral aspect of the tibial plateau. Currently, MRI is the most accurate means of diagnosing a discoid meniscus. No treatment is indicated for asymptomatic discoid lateral menisci. For patients with stable, complete or incomplete discoid menisci, the first line of treatment is arthroscopy with partial meniscectomy or saucerization. Meniscal repair may also be indicated in the presence of a meniscal tear or instability. Traditionally, unstable discoid menisci were treated with complete meniscectomy; however, total meniscectomy in children has been shown to produce poor long-term results. Protected weight bearing and progressive rehabilitation is important to ensure complete recovery following surgical intervention.

ACL Injuries

Increased participation in high-demand sports by adolescent athletes has led to an increased frequency of ACL injuries in this patient population. Diagnosis has improved considerably with the heightened awareness of the injury and improved diagnostic tests. ACL tears in skeletally immature athletes occur secondary to both contact and noncontact mechanisms. Athletes often describe a "pop" with immediate inability to bear weight and swelling that resolves over several days. Patients may complain of diffuse pain; however, pain localized to the joint line or collateral ligaments may also be present in cases of associated bone bruise, meniscal or collateral ligament injuries. An effusion is often present as well as an inability to fully extend the knee. The anterior drawer and Lachman tests are usually positive, but can be difficult to elicit in an uncomfortable patient with muscle guarding.

On initial evaluation, plain radiographs are warranted to rule out physeal injury, osteochondral injury, fracture, or dislocation. MRI may be indicated to evaluate for ligamentous (*Fig. 411.2*), meniscal, and osteochondral injuries, especially in cases where physical examination is limited secondary to pain and swelling.

Nonsurgical management of ACL tears involves activity modification and a period of dedicated rehabilitation to restore knee range of motion. Several recent studies have indicated a failure of conservative treatment in this patient population, citing the risk for persistent pain and swelling, chronic instability, meniscal tears, chondral injury, and early-onset arthritis. For this reason, many surgeons support ACL reconstruction in skeletally immature patients.

Current recommendations for surgical reconstruction of ACL tears in skeletally immature athletes are based on

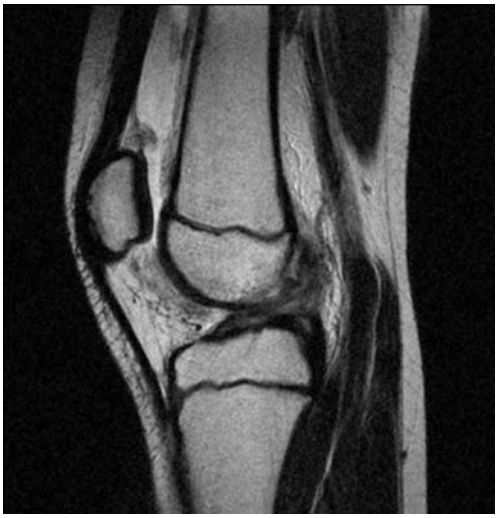

Figure 411.2
T2-weighted sagittal MRI image showing a proximal complete ACL tear in an 11-year-old male

skeletal age. Nonanatomic extraphyseal reconstruction is recommended in young children with substantial remaining growth; whereas partial transphyseal reconstruction is advocated in adolescents with decreased growth potential. Anatomic transphyseal reconstruction is recommended in adolescents nearing skeletal maturity.

Tibial Spine Avulsion Fractures

Tibial spine avulsion fractures result from a similar mechanism as with intrasubstance ACL tears and athletes may present with the same symptoms. Examination of the knee may reveal inability to fully extend secondary to both pain and displacement of the tibial spine into the femoral notch (*Fig. 411.3*). Displaced fractures require surgical repair. There is often residual laxity of the ACL following either nonoperative or operative fixation, secondary to stretching of the ACL at the time of injury.

Upper Extremity Injuries

Panner's Disease

Panner's disease, an osteochondrosis of the elbow capitellum, often presents in boys aged 5–12 without a history of repetitive throwing. This condition usually involves the dominant extremity and presents with symptoms of pain and stiffness in the elbow, aggravated by activity. This condition is not necessarily related to mechanical stress; however, adolescents may describe mild trauma or overuse. Examination reveals a small effusion and pain directly over the capitellum. Standard anteroposterior and lateral radiographs of the elbow may show fissuring or fragmentation of the capitellum. Panner's disease is often self-limited. Treatment includes cessation of activities that stress the radiocapitellar joint (i.e., throwing), immobilization, and anti-inflammatory medication. On resolution of Panner's disease, radiographs will reveal symmetrical ossification of the capitellum. Symptoms may persist for several months; however, adolescents usually have excellent long-term results.

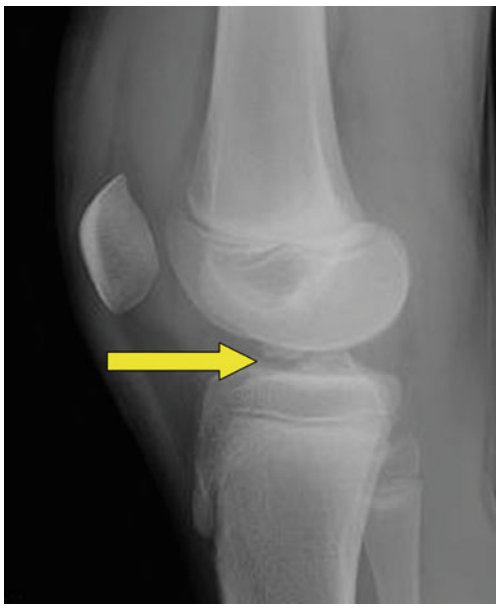

Figure 411.3
Lateral x-ray of the knee demonstrating a tibial spine avulsion fracture (*arrow*) in a 14-year-old male

Little Leaguer's Elbow

Little leaguer's elbow refers to a variety of conditions in adolescent throwing athletes, including osteochondritis dissecans (OCD) of the capitellum or radial head, olecranon apophysitis, and fragmentation or growth alteration of the medial epicondyle. The combination of a strong triceps contraction during the early acceleration phase of throwing and the movement of the olecranon into the humeral fossa during follow-through may lead to posterior elbow pain in throwing athletes (*Fig. 411.4*). Olecranon apophysitis, loose bodies, and avulsion fractures may occur as a result. OCD of the capitellum tends to occur in repetitive throwing sports, such as football or baseball. Frequent valgus stress, causing compression on the lateral aspect of the elbow, and pull on the flexor muscles in the forearm can lead to inadequate vascular supply of the subchondral bone and the development of OCD. Adolescents presenting with osteochondritis of the capitellum often complain of pain and an inability to fully extend the elbow. A report of catching or locking may indicate the presence of loose bodies within the joint. Examination may reveal a small effusion, tenderness directly over the capitellum, and crepitus with forearm rotation.

Radiographic evaluation includes anteroposterior and lateral radiographs of the affected elbow, as well as radiographs of the contralateral elbow for comparison. Findings on plain radiographs include irregular ossification of the capitellum, a fragmented border, subchondral lucencies, and loose bodies. In little leaguer's elbow, OCD typically affects the anterior aspect of the capitellum. MRI may be used in certain cases to completely define the lesion.

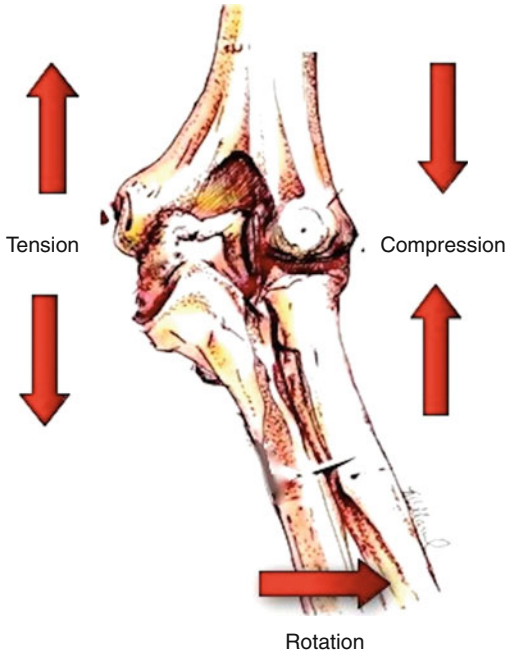

Figure 411.4
Schematic representation of the impact of valgus compression force on the elbow. The presence of valgus force pushes the olecranon against the medial aspect of the olecranon fossa, which may lead to osteophyte formation, chondral injury, and potentially the generation of loose bodies

For adolescents with a stable or mildly symptomatic lesion, conservative treatment is often appropriate, consisting of rest and immobilization. The athlete should refrain from all throwing activities until symptoms have resolved completely. Patients who continue to experience pain despite nonoperative treatment or those with displaced osteochondral lesions, loose bodies that cause catching or locking, or fractures of the articular cartilage will often require surgical intervention. Arthroscopy of the elbow is often performed to evaluate the articular surface and to remove any loose bodies. Subchondral drilling or fixation of the osteochondral fragment may also be performed at the same time. Rehabilitation following surgery includes strengthening and range of motion exercises.

Little Leaguer's Shoulder

Little leaguer's shoulder, also known as proximal humeral epiphysitis, occurs in male pitchers between the ages of 11 and 13. Although the exact etiology is unknown, it is thought to be related to repetitive overhead throwing and poor throwing mechanics. Patients complain of lateral shoulder pain with throwing. Examination may reveal tenderness and swelling over the lateral aspect of the shoulder as well as weakness with abduction and external rotation. Radiographs of the affected shoulder reveal widening of the proximal humeral physis. Treatment consists of activity modification and education on proper throwing techniques. Physical therapy is an important component of the rehabilitation and includes stretching and strengthening of the rotator cuff, periscapular muscles, and the shoulder capsule. Adolescent athletes can gradually return to play as symptoms resolve.

Shoulder Dislocation

Most shoulder dislocations in adolescent athletes are anterior and are due to trauma to the affected upper extremity. At the time of impact, the shoulder is usually in an abducted, externally rotated position. Prominence of the lateral acromion following shoulder dislocation may cause the shoulder to appear "squared off." The athlete often experiences severe pain and an inability to move the arm. In the absence of a physician or trainer with experience in shoulder reduction, the athlete's arm should be supported in a position of comfort for transport to an emergency room. Standard radiographs of the shoulder indicate the position of the humeral head as well as the presence of any fractures.

Management of a traumatic first-time dislocation in adolescents is controversial, although nonoperative treatment is the most commonly employed. Nonoperative treatment consists of immobilization in a sling for 1–2 weeks followed by 2–4 months of range of motion and strengthening exercises. Recurrence rates have been reported to be as high as 90% in patients younger than age 20, with rates dropping considerably for each subsequent decade. Rotator cuff tears occur very rarely in children or adolescents with shoulder dislocations. Patients experiencing recurrent instability or pain should undergo surgical repair consisting of either arthroscopic or open capsulolabral repair. Early specialty referral is important to discuss treatment options.

Although posterior dislocations are much less common, they can occur in collision sports (e.g., football, hockey) or following seizures. The mechanism of injury is a posteriorly directed force on a forward flexed upper extremity. Following dislocation, the arm is held in an internally rotated, adducted position. As with anterior

dislocations, reduction should not be attempted on the playing field in the absence of an experienced physician or athletic trainer. Nonoperative management is similar to that seen with anterior dislocations. Posterior shoulder dislocation can cause posterior labral tears, which may require surgical treatment.

Multidirectional instability is atraumatic and occurs primarily in adolescent female athletes (e.g., swimming, gymnastics). Patients report multiple episodes of painless subluxation with spontaneous reduction. Examination reveals increased shoulder translation in more than one direction as well as generalized ligamentous laxity. Radiographs are usually normal. Treatment consists largely of physical therapy, with a focus on strengthening the rotator cuff and periscapular muscles. A less commonly seen variation is the voluntary dislocator. These patients can control their dislocations and frequently are attention-seeking.

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412 Trauma

Peter G. Fitzgibbons · Craig P. Eberson

Growth Plate Fractures

Growth plate fractures involve physeal region at the end of the bone which is responsible for longitudinal development. Fractures involving the physis are common and occur due to the structural weakness of the cartilaginous growth plate relative to the adjacent bone. Like all fractures in the pediatric population, the capacity for successful healing is great, but the possibility of growth disturbance necessitates careful immediate and follow-up treatment. In addition, the proximity of growth plates to the end of the bone means that disruption of the joint surface can occur, and this requires careful reduction in order to prevent subsequent cartilage degeneration.

The physis consists of several layers of cartilaginous tissue that progress from a *resting zone* farthest from the center of the bone (diaphysis) to a *zone of provisional calcification* from which new bone arises. The physis thus allows for longitudinal growth by moving away from the diaphysis. A secondary center of ossification at the tip of the bone (epiphysis) gives the physis its characteristic radiolucent line appearance.

The Salter–Harris classification system is used to characterize physeal fractures (*Fig. 412.1*). Type I fractures occur through the plane of the physis, are typically not visible on x-ray, and heal predictably without growth disturbance or joint incongruity. Type II fractures begin through the physis and then exit through the flare at the end of the bone (metaphysis), leaving a fragment of bone that can generally be reduced back into place with manipulation. Type III fractures begin similarly through the physis but exit through the epiphysis, while Type IV fractures extend from the metaphysis to the epiphysis, crossing the physis. Type V injuries involve a crushing of the physis.

One large study of physeal fractures among American children found that the male-to-female incidence of fractures was 2 to 1 with the highest incidence among 11–12-year-old girls and 14-year-old boys.

Clinically, growth plate fractures present with pain, swelling, and deformity following a traumatic event. While at times the diagnosis is clear, sometimes the degree of deformity is not significant and adequate radiographs of the bone in question as well as joints above and below should be obtained to diagnose and characterize the fracture. For Type I and II fractures, x-ray imaging is usually sufficient, but Type III and IV fractures may require CT scanning to evaluate the degree of displacement and step-off of the articular surface. While Type I and II fractures can often be treated with cast immobilization (with or without manipulation), Type III and IV fractures may require operative reduction and fixation in order to maintain as close to an anatomic joint surface as possible.

Predicting growth plate injury is difficult but the likelihood increases with higher Salter–Harris classes. Physeal fractures require consistent follow-up in order to identify and monitor growth disturbance that can lead to angular deformity and/or limb length discrepancy. The degree of deformity is a function of the severity and location of injury as well as the years of growth remaining. Close monitoring will allow for interventions such as physeal bar resection or epiphyseodesis (induced growth plate closure) that can mitigate the functional impairment. Patients and their families should be counseled at the time of injury regarding the possibility of growth complications and necessity of vigilant follow-up.

Long Bone Fractures

Fractures of the shaft of the bone (diaphysis) in children are often amenable to closed manipulation and casting. Unlike adult bone, in which the surrounding periosteum is a thin soft tissue layer, pediatric periosteum is thick and robust, providing significant benefit in two key areas of fracture healing. First, it provides the underlying bone with a generous blood supply that brings the growth factors and signaling mechanisms necessary for the production of callus, or immature primary bone. Second, when a properly molded cast puts tension on the periosteum, it provides structural support to the fractured bone. High-energy injuries that significantly disrupt the periosteum, particularly in older children, may not have such advantages and therefore can require fixation to maintain an acceptable position until healing occurs.

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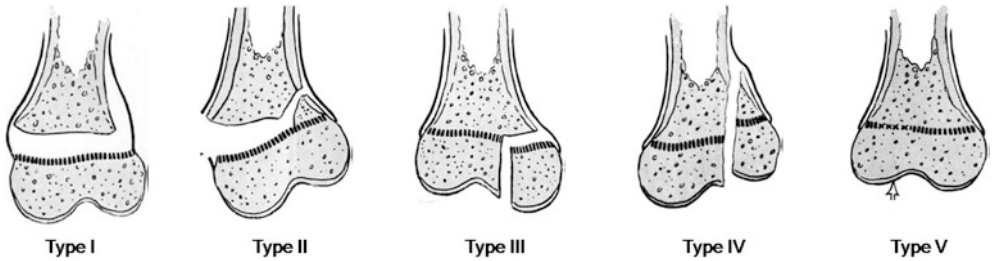

Figure 412.1
Salter-Harris classification system of physeal fractures

Table 412.1
Association with non-accidental trauma of various fractures

High specificity	Moderate specificity	Low specificity
Metaphyseal lesions	Multiple fractures	Clavicular fracture
Posterior rib fracture	Fracture of different ages	Long bone shaft fracture
Scapular fracture	Epiphyseal separation	Linear skull fracture
Spinous process fracture	Vertebral body fracture	
Sternal fracture	Digital fracture	
	Complex skull fracture	

The only absolute indication for surgery for a diaphyseal fracture is an open fracture, which requires adequate debridement and irrigation of the bone ends and often fixation as well. Otherwise, the need for surgery is determined by the ability to obtain and maintain a satisfactory reduction without an operation in terms of angulation, shortening, and rotation at the fracture site. Tolerance for deformity is a function the specific fracture site and the age of the child, with younger children more forgiving of deformity due to their ability to remodel bone with growth.

Options for fixation of long bone fractures include plate and screw constructs as well as flexible intramedullary rods that are inserted into the canal of the bone through small incisions away from the fracture site. Often, hardware is removed from pediatric patients following fracture healing although the necessity of this practice is controversial.

Non-accidental Trauma

Child abuse is an unfortunate reality in pediatrics, and orthopedic injuries are a common manifestation. The incidence of child abuse is difficult to establish and varies widely due to regional and reporting differences. The incidence of severe child abuse in one study from Wales (with fracture as an inclusive criterion) was 54/100,000 for children <1 year old, 9.2/100,000 for children 1–4 years old, and 0.47/100,000 for children 5–13 years old, while an Indian study of street children found that 36.6% of children reported severe or very severe abuse. In both studies, as in others, younger children experienced a higher incidence of child abuse.

In addition to a careful history surrounding the circumstances of an injury, certain findings should warrant extra vigilance in suspecting and reporting the potential for child abuse (*Table 412.1*). A retrospective study from Hong Kong found that of 29 patients with fractures from non-accidental trauma, 52% were under the age of 3, 38% had fractures of different ages, and 31% had inappropriate/contradictory histories. Many abused children will initially present with a fracture. There is a significant risk of further abuse, often resulting in further injury or even death. Lower extremity long bone fractures in children who are not yet walking, spiral fractures of the extremities, or unexplained injuries warrant referral to the appropriate child protective services.

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Pediatric Otolaryngology

Mohamed O. Abuzeid

413 Nasal Obstruction and Rhinorrhea

Mohamed O. Abuzeid

Introduction

Understanding nasal physiology and function is mandatory for the management of nasal obstruction and rhinorrhea. The nose plays a major role in the function of the respiratory system, including the warming, filtration, clarification, and humidification of inspired air. The nose is the sole area of olfaction and is also important in the resonance of the voice. When these functions are interrupted by disease, symptoms such as obstruction, rhinorrhea, anosmia, epistaxis, hyponasality, and cosmetic deformities result.

Several normal physiologic conditions of the nose are associated with obstruction and rhinorrhea without local or systemic diseases. They are seen more in older children and include paradoxic nasal obstruction, nasopulmonary reflex, puberty, menses, psychosomatic factors, and environmental causes. The etiology of nasal obstruction and discharge in disease includes congenital, inflammatory, traumatic (including foreign bodies), allergic, metabolic, neoplastic, and idiopathic causes. Other causes can occur in the nasopharynx.

Congenital Causes

Congenital disorders are caused by exogenous teratogenic elements or inherited genes. Two such disorders, total nasal agenesis (anasia) and proboscis lateralis, are very rare.

Choanal Atresia

This is the obstruction of the posterior nasal aperture. It is the most common congenital cause of nasal obstruction, with an incidence of one in 8,000 live births. A familial tendency has been noted. Choanal atresia may be unilateral or bilateral (*Fig. 413.1*), and complete or incomplete. The stenosis is bony rather than membranous in about 90% of cases. Unilateral atresia, usually recognized in later life, is twice as common as bilateral atresia.

As many as 50–70% of cases are associated with other anomalies as part of the CHARGE syndrome, which comprises

*C*oloboma of the iris and retina
*H*eart disease
*A*tresia choanae
*R*etarded development of the central nervous system
*G*enital hypoplasia
*E*ar anomalies with deafness

The diagnosis of CHARGE syndrome is made when four of the six categories are present. Other anomalies not included in the CHARGE categories are motor anomalies, seen in 26% of cases, and a single anomaly in 16%. Newborns are obligatory nasal breathers; therefore, cases with bilateral choanal atresia present with respiratory distress. Unilateral cases present with unilateral nasal obstruction and rhinorrhea.

The diagnosis of choanal atresia is suspected when a size five or six French feeding catheter fails to pass into the nasopharynx. Confirmation is obtained with a computerized tomography (CT) scan, which has superseded choanograms as the diagnostic imaging modality of choice.

Immediate therapy is mandatory. This involves placement of an oral airway such as a McGovern nipple and the institution of gavage feeding, followed by surgical intervention. Various surgical approaches, each with its own advocates, have been described. These include transantral and transnasal approaches using perforators and drills and, more recently, microscopic and endoscopic techniques. The transpalatal approach is the most common procedure used, despite the theoretical drawbacks of its adverse effect on maxillary development and the rare occurrence of oronasal fistulas.

Whatever method of approach is used, stenting the newly created passage is necessary. Stenting methods include placement of Silastic nasotracheal tubes fixed in different ways. The duration ranges from 4 week to 4 months. Endoscopic examination with frequent clearance and dilation has increased the success rate of patency and prevention of restenosing.

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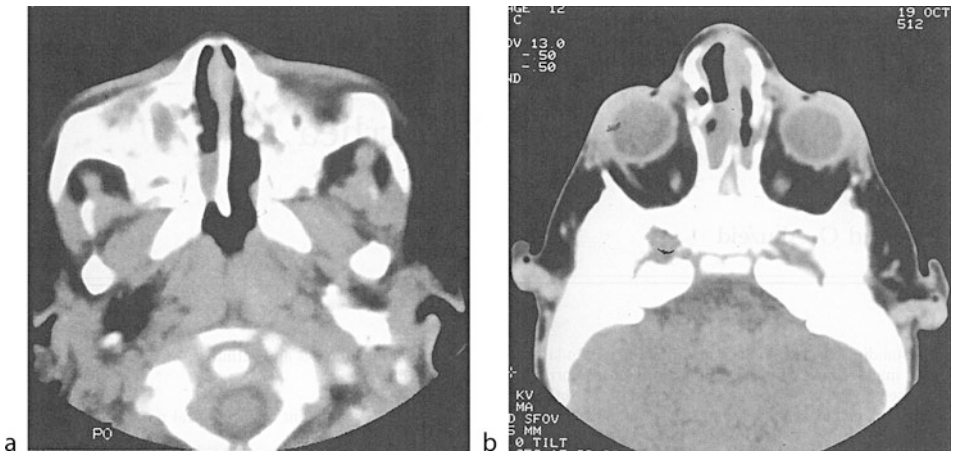

Figure 413.1
Axial computerized tomography scan of the choanal area showing (a) unilateral choanal atresia with fluid level in the left atretic side, and (b) bilateral bony choanal atresia with complete isolation of the nasal cavity from the nasopharynx

Congenital Nasal Deformity and Obstruction

Congenital nasal deformity and obstruction can occur as part of the various mandibulofacial dystocias, such as Crouzon disease and Treacher Collins syndrome. These are the result of intrauterine disturbance during the development of the first and second branchial arches. The obstruction occurs due to hypoplasia of the palate, maxilla, and molars. Nasoseptal deformities are seen in cleft palate deformities, causing alteration of endonasal structures.

Congenital Cysts

Congenital cysts, such as dermoid, nasoalveolar, nasolacrimal duct, dentigerous, and mucous cysts of the floor of the nose, can cause a degree of nasal obstruction. Nasal obstruction in the neonatal period can occur secondary to congenital cerebral herniation into the nose in the form of meningocele, meningoencephalocele, or encephalocele. These may lead to spontaneous cerebrospinal fluid (CSF) leakage.

Teratomas

Teratomas are congenital masses that contain ectoderm, mesoderm, and endoderm. These may include cartilage, bone, muscle, thyroid, and glial tissue. Radiologic evaluation is important before surgical removal is attempted.

Tornwaldt Cyst

Tornwaldt cyst is a diverticulum-like structure that lies in the midline of the posterior wall of the nasopharynx. It is seen in less than 3% of the population, and its origin may be related to the formation of a potential space between the pharyngeal epithelium and notochord remnants. The symptoms of nasal obstruction and headaches occur during periods of nasal inflammation. Lateral neck X-rays will show a distinct circumscribed soft tissue in the nasopharynx. Surgical excision or marsupialization is necessary for cure.

Traumatic Causes

Traumatic events are common causes of nasal obstruction in children, involving a blunt or penetrating trauma to the nose. It is important to diagnose and treat these deformities to prevent future complications, including nasal obstruction, possible malformation during facial and dental growth, and nasopulmonary pathophysiology.

Mucosal injury and mucostasis may lead to bacterial invasion, causing mucopurulent discharge with mucociliary damage and atrophic mucosa leading to rhinorrhea and nasal obstruction. This sequence, together with increased turbulence of the nasal air flow and stasis in the nose, results in the accumulation of allergens and other matter, causing more vasomotor, allergic, and inflammatory reactions.

Nasal obstruction can occur at any age due to traumatic events, but it may be asymptomatic in young infants

and neonates unless it is severe enough to cause respiratory distress in obligatory nasal breathers.

Perinatal Trauma

Nasal trauma may occur at birth during vaginal delivery with or without the use of forceps. Some septal deformity may be evident on careful examination in as many as 70% of newborns secondary to intrauterine or delivery trauma. In the acute traumatic period, intermittent bleeding, swelling, and nasal obstruction suggest the development of a septal hematoma. This is more common in children due to their thicker and more elastic mucoperichondrium, and is caused by the disruption of septal vessels. Throbbing pain and an elevated temperature indicate a septal abscess, which may lead to septal perforation if left untreated, due to the interruption of cartilaginous blood supply, leading to airway turbulence disturbance, obstruction, and rhinorrhea.

Foreign Bodies

Children younger than 3 years frequently stuff their noses with foreign bodies, causing intensive vasomotor reaction, rhinorrhea, and obstruction. If the object is left undetected for a period of time, purulent, offensive unilateral nasal discharge and obstruction are the main symptoms. Suctioning with the use of topical decongestants will make the diagnosis easier. If the removal of foreign bodies is not possible in an office setting, it must be done under general anesthesia. In all of these children, the other nostril and ears should be properly checked for further foreign bodies.

During the removal of a foreign body without a leading edge (e.g., a bead), the use of forceps will usually push it deeper into the nasal cavity rather than facilitate removal. The best method is to use a blunt hook, which can be slid along one of the nasal walls until the tip is beyond the foreign object, then turned 90° to pull the object out. Depending upon the type of the foreign body and the length of time, granulation tissue and concretions form around it, producing a rhinolith.

Differentiation of Cerebrospinal Fluid Leak

Special attention should be paid to differentiating between a CSF leak and rhinorrhea after trauma. A CSF leak usually occurs after skull base trauma and may be accompanied by CSF otorrhea presenting as rhinorrhea as it leaks along the Eustachian tube. Spontaneous CSF leak is not common. It indicates the presence of a variety of intracranial lesions (e.g., intrasellar tumors), and can be present in young infants secondary to congenital bone dehiscence.

The presence of CSF leakage is suggested by the history and nature of the nasal discharge. A unilateral clear, salty fluid after head injury is highly suggestive of this pathology, especially if it increases with change of position of the head, Valsalva maneuver, and internal jugular compression. The fluid can be tested rapidly using glucose oxidase-impregnated test sticks, bearing in mind that lacrimal or nasal secretions can give false-positive results. Biochemical analysis of the fluid for protein, glucose, and electrolytes will confirm the diagnosis. CT scans provide superior anatomic demonstration of the site of the bone dehiscence at the base of the skull. The treatment may be spontaneous healing, endoscopic repair, external exploration and repair, or neurosurgical approach and repair.

Inflammatory Nasal Disease

An inflammatory response of the nasal mucosa to infection, allergy, and chemical or toxic agents is the most common cause of nasal obstruction and discharge. The nasal response to this is a vasomotor reaction of the mucosa to bring specific antibodies, immunoglobulins, and lysozymes to the region as a defense action. The result of this response is an increase in surface area, congestion, and secretions, leading to obstruction and rhinorrhea.

An inflammatory response results in vasodilation and exudation of protein-rich fluid with migration of polymor-phonuclear leukocytes and monocytes into the nasal mucosal tissue. Recurrent episodes of infection result in abnormal motility and transport system of the cilia, with ultrastructural abnormalities; an increase in goblet cells and submucosal cells; and alteration of the periciliary fluid due to increased tissue leakage and increased mucous and purulent secretions due to microabscesses. These changes may take up to several weeks to heal after resolution of the inflammatory process. Chronic inflammation may be the end result.

Infectious Causes

Acute viral rhinitis or rhinopharyngitis (the common cold) is the most common cause of nasal obstruction and rhinorrhea in children. It is a self-limiting disease caused by a number of different viruses, including rhinovirus; adenovirus, which includes influenza and parainfluenza; respiratory syncytial virus; and Coxsackievirus A and B.

Chlamydia infection in newborns and infants can occur during birth, leading to conjunctivitis and pneumonia. A culture swab should be taken from children with nasal obstruction and rhinorrhea when *Chlamydia trachomatis* is suspected. Spirochetal infection is very rare nowadays, with the reduction of syphilitic cases caused by *Treponema pallidum*, either congenital or acquired. Other treponemal diseases, such as bejel, yaws, and pinta, are rare causes of nasal symptoms.

Fungal infection is more common than previously thought. Nasal and paranasal fungal infection should be suspected in debilitated, immunodeficient, or immunosuppressed children. Such infections occur more frequently with the use of chemotherapy or immunosuppressive drugs, as in organ transplantation. Mucormycosis and aspergillosis are the most common fungal infections. The diagnosis should be confirmed by biopsy and culture, as well as by microscopic examination. Early diagnosis and treatment are essential to prevent the serious complications of such infections.

Allergic Causes

Allergic rhinitis is another common cause of nasal obstruction and rhinorrhea in pediatric patients. It is due to the sensitized mast cells releasing mediators such as histamine, leukotrienes, thromboxanes, and prostaglandin. This response triggers the acute phase of allergic reaction, producing vasodilation, increased capillary permeability, and intense vasomotor reactions.

Nasal and Sinus Polyps

Nasal and sinus polyps are very rare in children and, if present, are the result of chronic inflammation of the mucous membrane of the nose and paranasal sinuses, manifested by hypersecretion and hyperplasias. This leads to polyp formation, representing a focal exaggeration of hyperplastic rhinosinusitis involving stromal binding of the intracellular fluids. Nasal polyps occur in allergies such as aspirin intolerance, intrinsic asthma, Young syndrome, cystic fibrosis, Kartagener syndrome, and ciliary dyskinesis syndrome.

Cystic Fibrosis

Cystic fibrosis (CF) is a generalized exocrinopathy that leads to pulmonary and pancreatic insufficiency. It is the most lethal genetic disorder in the white population. The CF gene has been localized to the q31 region of chromosome 7 and is responsible for the transportation of chloride in a transmembrane regulator. The sweat test is generally accepted as the most simple and reliable laboratory procedure for the diagnosis of CF. Sodium values in excess of 60 mEq/L are regarded as abnormal. A repeat test may be needed for highly suspicious cases with lower values.

Radiologic investigations include CT scan, which usually shows opacity with pansinusitis. A characteristic picture is an expanded maxillary sinus medially with accumulation of mucosequestral secretions, mostly in advanced cases. Medical treatment for nasal symptoms in CF includes the use of intranasal beclomethasone dipropionate.

Approximately 10–20% of CF cases will eventually require some form of surgical intervention for their sinus disease. The recurrence rate after nasal polypectomy alone is high, approaching 70% of cases. Combining nasal polypectomy with a sinus procedure such as Caldwell Luc, external ethmoidectomy, or endoscopic sinus surgery significantly reduces the recurrence rate. All of these measures result in symptomatic relief of nasal symptoms but do not eradicate sinus disease.

The most exciting area in CF research is gene therapy. The administration of CF transmembrane conductance regulator (CFTR) cDNA, using an adenovirus vector, offers promising results in correcting the CF genetic lesion and reversing the pathophysiologic abnormality of the nasal epithelium. It is anticipated that, with time, management of CF may be essentially medical except for management of disease-related complications, which will remain primarily a surgical matter.

Hypertrophy of Nasopharyngeal Adenoid Tissue

The most common cause of nasal obstruction in children is hypertrophy of the nasopharyngeal adenoid tissue. This part of the Waldeyer ring in the upper aerodigestive tract plays a key role in the development of the immune process. Adenoids are minimal at birth but rapidly increase in size, usually at 1–2 years of age, receding at puberty. They are continually exposed to nasal and paranasal secretions passing through the posterior choana to the nasopharynx, carrying antigens such as bacteria, viruses, and allergens. These lead to hypertrophy of the tissue as adenoids form their own complement of antibodies in response to these antigens. Such a reaction may occur with or without hypertrophy of the tonsils, and could lead to increased

nasal airway obstruction, resulting in alveolar hypoventilation. This results in a further pulmonary vasoconstriction with increased pulmonary vascular resistance and cor pulmonale.

Environmental Factors

Environmental factors are becoming increasingly important, especially in large, crowded, industrial cities. Inhaled substances act as chemical irritants, reacting with nasal mucosa and initiating a vasomotor response resulting in obstruction and rhinorrhea. Urban pollutants include carbon monoxide, ozone, nitrogen, aldehydes, ketones, chlorine, ammonia, sulfur dioxide, and hydrocarbons. The main sources of these chemicals are industrial waste, motor vehicle exhaust, and tobacco smoke.

Rhinitis Medicamentosa

Rhinitis medicamentosa is an iatrogenic cause of nasal obstruction in children. The causative over-the-counter medications include sympathomimetic agents and different topical decongestants that are applied locally. A nasal toxic reaction occurs due to the rebound phenomenon as the medications are used for longer periods than indicated in spite of enclosed labels and instructions. Examination of these patients usually demonstrates an edematous, erythematous, and thickened nasal mucosa. Therapy depends upon elimination of all vasoconstrictive nose drops and sprays, with an explanation of the problem to the patient and parents. Many patients could benefit from the institution of systemic antihistamines and a short course of topical or oral steroids. In patients with irreversible mucosal changes, turbinate surgery may be needed.

Neoplastic Diseases

Neoplasms of the nasal cavity are rare in children. These neoplasms may be ectodermal, mesodermal, neurogenic, or odontogenic in origin. Nasal obstruction and rhinorrhea with epistaxis are the most common presenting symptoms of nasal tumors, but are often overlooked because of their common occurrence in normal children. These symptoms occur early in nasal cavity tumors but are delayed in tumors of the nasopharyngeal and paranasal sinuses until the nasal cavity is affected. Primary congenital neoplasms such as angiomas, angiofibromas, hemangiopericytomas, and teratomas may present with these symptoms. Hamartomas, craniopharyngiomas, and chondromas are other recognized neoplasms, but they are quite rare in pediatric otolaryngology.

Juvenile nasopharyngeal angiofibromas are of special interest. These occur predominantly in males aged 7–17 years, with an average age of onset of 14 years. The symptoms are progressive obstruction and epistaxis of the involved side. CT scans with contrast and magnetic resonance imaging are essential for diagnosis. These modalities have eliminated the need for resorting to biopsy of the lesion, which could result in severe hemorrhage. The treatment of angiofibroma is primarily surgical, except when the cavernous sinus, pituitary gland, or optic chiasm is involved.

The incidence of nasopharyngeal carcinoma in childhood varies greatly according to geographic and racial factors. It represents less than 1% of childhood malignancy but constitutes 20–50% of pediatric malignancies of the nasopharynx (*Fig. 413.2*). The primary treatment is a full course of radiation therapy. The impact of chemotherapy on long-term survival remains uncertain.

Olfactory neuroblastoma is another rare tumor in pediatric patients. It presents with obstruction and epistaxis due to tissue destruction.

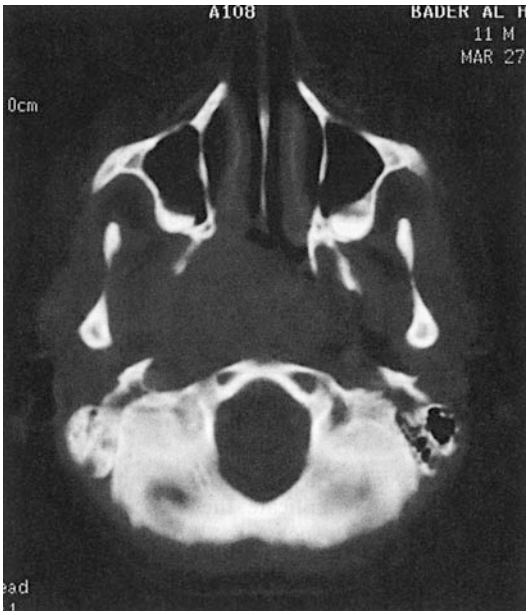

Figure 413.2
Axial computerized tomography scan of the nasopharynx showing a nasopharyngeal carcinoma in an 8-year-old child presenting with nasal obstruction

Miscellaneous Causes of Nasal Obstruction and Rhinorrhea

Rare causes of nasal obstruction include Wegener granulomatosis, systemic lupus erythematosus, scleroderma, rheumatoid arthritis, and psoriatic arthritis. Atrophic rhinitis (ozena, rhinitis fetida, or rhinitis crustosi) is a chronic progressive atrophy of the nasal mucosa leading to disturbance of normal streamlined airflow. It is characterized by a foul, smelly, green, crusted, and impacted nasal cavity. Nutritional deficiencies of vitamins and iron are blamed for this condition. Diagnosis is usually confirmed by isolation of *Klebsiella ozaenae* from the nasal cavity.

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414 Pediatric Epistaxis

Mohamed O. Abuzeid

Bleeding from the nose (epistaxis) is a common pediatric problem. It can be slight but exaggerated by the patient and/or the parents, but it can also be severe and life threatening. It is usually a frightening experience for the patient and occasionally frustrating to the treating physician. In the majority of cases the bleeding is from the anterior part of the nose, mainly the septum, turbinates, and anterior two thirds of the inferior meatus. In most cases the bleeding stops spontaneously. Posterior epistaxis is usually from the nasopharynx, at the posterior edge of the septum.

Surgical Anatomy

The most common site of nosebleeds from the anterior septum is at the Kiesselbach plexus in Little's area. This area has an extremely rich blood supply, consisting of

1. The septal branch of the superior labial artery, a branch of the facial artery from the external carotid artery
2. Septal branches of the anterior ethmoid artery, a branch of the internal carotid artery
3. Septal branches of the sphenopalatine artery, the terminal branches of the internal maxillary artery
4. The anterior septal branch of the greater palatine artery

The next most common site is the anterior part of the inferior turbinate. The blood supply is also rich in this area, and consists of

1. Branches of the anterior ethmoid artery
2. Lateral nasal branches of the sphenopalatine artery
3. Nasal branches of the greater palatine artery
4. Nasal branches of the anterior inferior dental artery, a branch of the infraorbital artery

Posterior epistaxis is rare, occurring most often in juvenile nasopharyngeal angiofibroma, usually in teenage boys. The bleeding comes from the vascular distribution of the sphenopalatine artery (i.e., the nasopalatine, inferior, and middle turbinate arteries).

Regardless of the nerve supply of the nose, topical anesthesia is sufficient for freezing the bleeding area of the nose.

Etiology of Epistaxis in Children

Epistaxis in children can have many different causes (*Table 414.1*). The most common causes of nosebleeds in the pediatric population are idiopathic. The epistaxis occurs mainly during the night and, on waking up, the pillows and bed sheets are found to be soaked in blood. Nose picking is another common cause, which is usually denied by the patient and parents.

Upper respiratory tract infection may be acute or chronic, bacterial or viral with allergic rhinitis. Infection causes congestion of the nasal mucosa, which become more friable and irritable, leading to ulceration, erosion, and bleeding. Foreign body placement is a common problem in children, presenting with epistaxis and a purulent, foul-smelling discharge. This is usually unilateral.

Septal perforation from nose picking and repeated cauterization leads to nosebleeds. Environmental causes include dry air, which leads to ulceration and cracks to the anterior nasal mucosa, as in dry desert areas with low humidity. Forced-air heating with low humidity in winter leads to a similar effect.

Although neoplasm is a cause of nosebleeds, it is still quite rare, yet there are several cases of nasopharyngeal carcinoma in children and young adults in the Arabian peninsula. The most common cause of posterior epistaxis in young people is juvenile angiofibroma of the nasopharynx. This affects usually adolescent boys; therefore, any male patient in his teens who presents with posterior epistaxis should be suspected of having juvenile angiofibroma until proved otherwise. A computerized tomography scan with contrast is diagnostic (*Fig. 414.1*), and biopsy should be avoided. Embryonal rhabdomyosarcoma of the sinonasal tract can occur in children presenting with nasal bleeds as a symptom.

Vascular anomalies causing epistaxis include Osler-Weber-Rendu disease (hereditary hemorrhagic

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Table 414.1
Etiology of epistaxis in children

Idiopathic
Inflammatory
Upper respiratory tract infection
Acute/chronic rhinitis with allergies
Acute/chronic sinusitis
Foreign bodies leading to granulation formation and infection
Trauma
Nose picking (most common)
Nasal fracture (as in sports)
Facial injuries
Nasogastric and nasotracheal intubation
Chemical and caustic agents
Environmental
Dry and low humidity
Central air-conditioning, weather hot or cold with low humidity
Septal deviation and perforation
Neoplasms
Juvenile nasopharyngeal angiofibroma
Hemangioma
Carcinoma (nasopharyngeal)
Papilloma
Sarcoma (embryonal rhabdomyosarcoma)
Vascular anomalies
Arteriovenous malformation
Rendu-Osler-Weber syndrome (hereditary hemorrhagic telangiectasia)
Hematologic
Platelet abnormalities
Primary (idiopathic thrombocytopenic purpura)
Acquired (aspirin, leukemia)
Coagulopathies
Primary (von Willebrand disease, hemophilia)
Acquired (warfarin, liver diseases)
Drug-related thrombocytopenic purpura

telangiectasia), which is an autosomal dominant familial disease with a frequency of 1–2 per 100,000 population. More than 90% of patients will eventually present with recurring epistaxis, with a mean age of onset of 12 years and a mean number of epistaxis episodes of

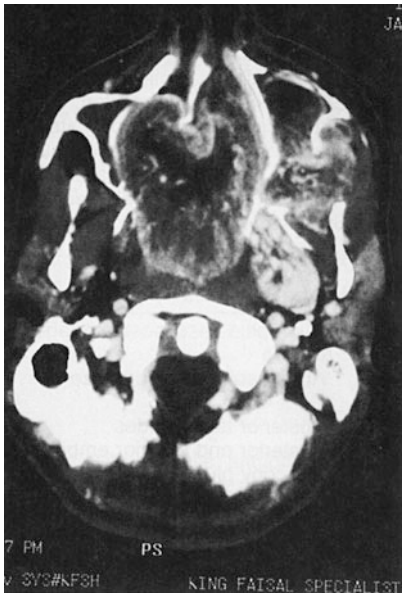

Figure 414.1
Axial computerized tomography scan of the nasopharynx showing enhanced juvenile angiofibroma (the patient presented with severe epistaxis)

18 per month. Arteriovenous malformations are other causes of nosebleeds in children.

Nosebleeds can result from primary or acquired coagulopathies. The diagnosis in such cases is obvious from the case history and family history of hemophilia or von Willebrand disease, which is a combination of factor VIII defect and platelet abnormality. A history of unusual bleeding, bruises, recent use of platelets, use of inhibiting agents such as aspirin, or use of anticoagulants may be associated with nosebleeds. Rosenthal disease (factor XI deficiency) and Christmas disease (factor IX deficiency) are rare causes of nosebleeds.

Management

When a patient is first seen with heavy bleeding, a careful history is taken from the child or the parents, bearing in mind the previously noted etiology of nosebleeds. Physical examination is performed first by asking the patient to blow his or her nose to clear the blood clots if possible; if not, a suction device is used carefully to clear the nose. Then a suitable vasoconstrictor spray is used, or, cottonoids or ribbon gauze soaked in a vasoconstrictor combined with a local anesthetic (e.g., 4% lidocaine with epinephrine 1:100,000).

Table 414.2
Management of pediatric epistaxis

Anterior epistaxis	
Humidification: saline lavage to the nose, face, and cheeks	
Reflex vasoconstriction: ice to the nose, face, and cheeks	
External nasal compression: with the head down and breathing through the nose	
Cotton soaked in a vasoconstrictor agent	
Treatment of the underlying cause, if found	
Anterior nasal packing: gauze strips, Gelfoam, Avitene, Merocele, surgical, etc.	
Nasal cautery: chemical, electrocautery, argon or YAG laser	
Systemic evaluation of coagulopathy	
Posterior epistaxis	
Known diagnosis	**Unknown diagnosis**
Suction plus vasoconstrictor agents	Suction plus vasoconstrictor agents
Pressure	Endoscopic evaluation
Absorbable packing gauze	Computerized tomography and/or magnetic resonance imaging
Posterior tamponades	Arteriography plus selective embolization
Posterior and anterior embolization	Packing, embolization, or arterial evaluation
Endoscopy plus direct cautery: electric or chemical ligation	Systemic disorders
Correction of systemic causes such as coagulopathies	
Operative methods for anterior and/or posterior epistaxis	
Direct cautery	
Ligation of supplying arteries	
Septoplasty for deviated septum	
Closure of septal perforation	
Resection of neoplasm (e.g., angiofibroma)	

The management of pediatric epistaxis can be divided into that of anterior and posterior epistaxis (*Table 414.2*).

Anterior Epistaxis

The anterior nasal cavity is inspected using a xenon head light or a rigid 2.7-mm diameter telescope, first at 0° and then at 30°. These are usually tolerated well by most children. The inspection is first concentrated on the anterior septum, as most of the bleeding comes from Little's area. Active bleeding points can be identified and treated first with pressure using a cotton-tipped applicator or cotton ball or simply pressing the nasal ala against the septum for a few minutes. Silver nitrate sticks or electrocautery can be used to cauterize the point. The cautery should be applied to the exact site of bleeding, not to the whole nasal mucosa. Cautery should not be applied bilaterally at the same time; otherwise necrosis and septal perforation can result. The application of antibiotic cream or a similar petroleum-based ointment is effective in preventing further bleeding.

Recurrent Bleeding

In recurrent bleeding, the history may indicate an underlying cause such as allergic rhinitis. Suitable treatment, such as immunotherapy or drug therapy, can then be applied. In dry areas, suitable humidification of the nasal mucosa is effective in preventing further bleeding; for example, normal saline spray or drops, a humidifier, and application of ointment to maintain the humidity of the nasal cavity can be used. These measures also have mechanical actions, preventing sticky mucus and crust formation and washing out pollens, dust, and molds.

If sinusitis is diagnosed as the underlying cause, suitable measures, such as antibiotics, are indicated.

Hematologic investigations should be carried out, including blood count, platelet count, prothrombin and partial thromboplastin times, and bleeding times for primary or acquired blood disorders such as von Willebrand disease.

Anterior Nasal Pack

In rare cases when these measures fail to stop the bleeding, an anterior nasal pack is considered. Ribbon gauze soaked in suitable ointment can be used, but this has the drawbacks of discomfort, pressure, laceration, and nasal blockage with headaches. Several absorbable materials are available, such as oxidized cellulose (Oxycel), gelatin sponge (Gelfoam), and microfibrillar collagen hemostat (Avitene). There have been reports of toxic shock due to nasal packing, so nasal packs should contain antibiotic cream, with antibiotic administration and early removal of nonabsorbable packs, if use of this type of pack is unavoidable. This is more important and should be carefully considered in immunocompromised patients. Bilateral nasal packs can cause blockage of sinus ostia, nasal blockage with accumulation of secretions, sleep apnea, hypoxia, and possible death.

The gauze packing should be used precisely in a layer manner, starting at the floor to prevent it from hanging down to the oropharynx and hypopharynx and causing irritation, vomiting, laryngeal spasm, and suffocation. In some cases it is wise to remove the pack gradually over several hours to prevent further bleeding. If bleeding occurs after removal, pressure over the soft parts of the nose and application of ice packs over the nose will induce regional vasoconstriction. Usually these measures are enough to control the bleeding. This is also true after nasal surgery.

In severely deviated septum, the spur causes the overlying mucosa to be weak and friable. If simple measures do not control the bleeding, then septoplasty can be performed to stop further bleeding.

Posterior Epistaxis

Good vasoconstriction is needed to examine the posterior part of the nose and nasopharynx to find the bleeding point. The area supplied by the sphenopalatine artery and its branches is inspected. In modern practice, rigid or flexible fiberoptic nasopharyngoscopes are indispensable instruments for the diagnosis and management of endonasal conditions. If posterior epistaxis is expected, a rigid or flexible endoscope or a microscope is used in a cooperative child to inspect the posterior part of the nose and nasopharynx. A bleeding point can be identified at the maxillary ostium in the middle meatus or high in the vault. These are from branches of sphenopalatine or ascending pharyngeal vessels. If the patient is not cooperative, then examination and appropriate management can be applied under general anesthesia. Bleeding sites, foreign bodies, tumors, vascular anomalies, sinusitis, and nasal polyps can be diagnosed in a matter of minutes under reassurance or local or general anesthesia.

Similar treatment measures as in anterior bleeding can be applied in many cases. The visualized bleeding point can be cauterized. Posterior packing using ribbon gauze impregnated in antibiotic ointment is the traditional method. Nowadays, catheter balloons are applied to improve comfort and efficiency in managing nosebleeds in both adults and children. Similar devices include the Foley catheter, Fox balloon, Merocele Pope posterior nasal tampon, and Gottscholk nasostat and epistat. The patient is usually managed in the hospital because of risks of sleep apnea, suffocation, and further bleeding. Bed rest is available, and the patient can be sedated with replacement of intravenous fluids and/or blood, if needed, and further investigations may be carried out.

Arterial embolization is considered in cases of severe epistaxis refractory to other therapeutics, provided that an expert radiologist is available to avoid the risk of embolization of the internal carotid artery, with its devastating results (Fig. 414.2). By applying this technique, one avoids open surgery, with its obvious disadvantages.

Arterial ligation is rarely needed in children. In cases of posterior and superior nasal bleeding, ligation of the anterior and posterior ethmoidal arteries is needed. If the bleeding is from the posterior part of the nose, ligation of the terminal branches of the internal maxillary artery is required. The need for ligation of the external carotid artery is even rarer in the pediatric group. It is mandatory to identify at least two branches before the ligation as the internal carotid has no branches in the neck. These open procedures need to be done under general anesthesia and carry certain risks, such as denervation of the teeth, infraorbital nerve hyperesthesia or paresthesia, ophthalmoplegia, sinus complications, and inadvertent vidian nerve neurectomy.

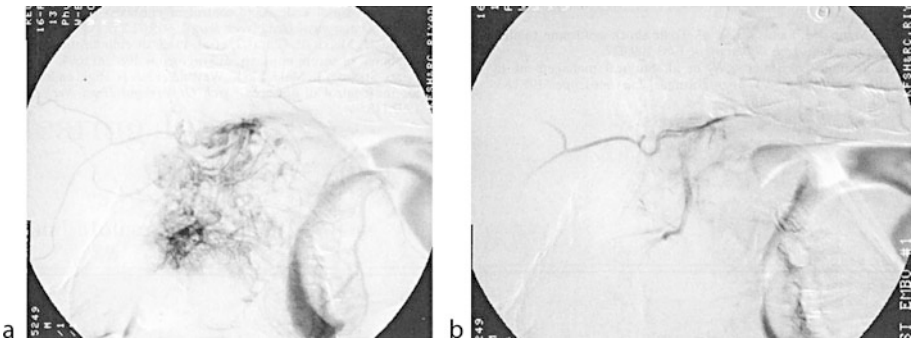

Figure 414.2
Angiogram of the nasopharynx (a) with blush in a child with juvenile angiofibroma of the nasopharynx prior to embolization, and (b) disappearance of the blush following arterial embolization

If the bleeding does not stop after arterial ligation of the internal maxillary artery, several options are available:

1. Return to the nasopharyngeal tamponade sequence
2. Ligation of the contralateral internal carotid artery
3. Ligation of the anterior ethmoid artery
4. Ligation of the external carotid artery

Conclusion

Most occurrences of epistaxis are controlled using simple measures. Step-by-step management is needed, starting with simple, uncomplicated methods. Severe and recurrent epistaxis warrant further investigation to exclude coagulopathies, tumors, and other recognized rare conditions. The physician should be aware of the complications of nose-bleeds as well as of the treatment.

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Pediatric Ophthalmology

Selwa A.F. Al-Hazzaa

415 Ophthalmologic Disorders

Selwa A. F. Al-Hazzaa

Visual development is a highly complex maturation process. Healthy infants are born with the potential, but not the ability, to see. The eyes must be anatomically normal, and the media must be optically clear. The infant must have visual input for good vision to develop, and, if binocular function is to develop, the eyes must be aligned. Normal vision develops as a result of genetic coding and experience in a normal visual environment.

The infant eye is not simply a small adult eye. The pediatric eye is a growing eye, which differentiates it in many ways from the adult eye. At birth, the normal visual responses are to light or bright objects. At 6 weeks of age a normal infant is able to maintain eye contact, and, by 6 months small objects, toys, and fingers within several feet are seen. The infant's world of visual interest gradually expands, and, by $2\frac{1}{2}$ years, some children recognize Allen pictures equivalent in size to 20/20 Snellen letters.

The developing immune system predisposes children to reactions to inflammation and diseases that are distinctly different from those of adults. The central nervous system is in its formative period. It is particularly vulnerable to growth abnormalities and developmental interruptions.

No child is too young to have an assessment of vision. Children may pose a difficult visual assessment problem. In children less than $3\frac{1}{2}$ years, acuity may be evaluated by the CSM method: *C* refers to the normally reflected light from the center of the cornea, *S* to the steadiness of fixation to the examiner's light, and *M* to the ability of the strabismic patient to maintain alignment. Signs of poor visual development include nystagmus, wandering eye movements, lack of response to familiar faces and objects, staring at bright lights, and forceful rubbing of the eyes (oculodigital massage). Nystagmus secondary to decreased sensory input usually occurs at 2–3 months of life and not at birth. The most common causes of decreased vision in the pediatric age group are albinism, optic nerve atrophy and hypoplasia, cortical visual impairment, anterior segment anomalies, and retinal abnormalities.

Amblyopia

Amblyopia is a defect of central vision that cannot be attributed directly to the effect of any structural abnormalities of the eye or the posterior visual pathways in the visual cortex or in the lateral geniculate bodies. It is caused by abnormal visual experience early in life, usually resulting from ocular misalignment, uncorrected bilateral high refractive errors, difference in refractive error, or disorders that degrade the quality of images transmitted to the brain from the eye. Amblyopia is responsible for more reduced vision of childhood onset than all other causes combined. Nearly all amblyopia is reversible or preventable with appropriate treatment. The role of the pediatric ophthalmologist in identifying children with amblyopia or at risk for developing it at a young age (when the prognosis for successful treatment is best) is important and cannot be overemphasized. Voluntary vision screening programs are important in the detection of amblyopia. Treatment of amblyopia involves eliminating any physical abnormality of the eye, correcting the refractive error by optical prescription, or forcing the use of the poorer eye by occlusion therapy.

Cortical Visual Impairment

Cortical visual impairment (cortical blindness) may be congenital or acquired. Both prenatal and perinatal etiologies, such as intrauterine infection, cerebral dysgenesis, asphyxia, intracranial hemorrhage, hydrocephalus, infection, trauma, child abuse, shunt malfunction, meningitis, encephalitis, and asphyxia, may be found. Examination reveals normal ocular structure, normal pupillary responses, and searching eye movements. The electroretinogram is normal, while the visually evoked response may be abnormal. Neuroimaging may reveal changes in the occipital cortex. Cortical visual impairment can be transient or permanent and can be an isolated finding; it is more commonly associated with multiple neurologic handicaps.

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Nystagmus

Nystagmus consists of rhythmic oscillation or tremors of the eyes that occur independently of normal ocular movements. Nystagmus in pediatric patients is divided into congenital and acquired types. A complete ophthalmologic examination and electrophysiologic testing are sometimes required for the evaluation of a patient with congenital nystagmus. The most common causes of congenital nystagmus are albinism and optic nerve pathology. *Congenital motor nystagmus* is a term applied to nystagmus of unknown etiology. The nystagmus may be either pendular, jerk, or both. No treatment has been found that is always successful. Surgical treatment has been advocated for nystagmus associated with abnormal head posture. Acquired nystagmus, at any age, requires thorough evaluation, including neuroimaging.

Strabismus

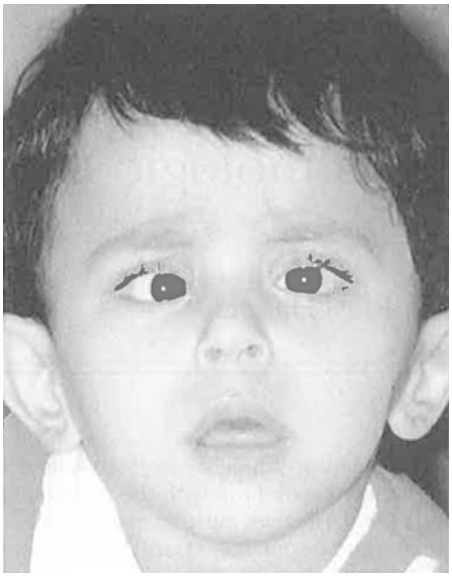
The term *strabismus* is derived from the Greek word *strabismos* (to squint or to look obliquely) and implies ocular misalignment. Defects of ocular motility constitute a large proportion of ophthalmic problems. A vast majority of children admitted to the ophthalmic service have strabismus that requires surgery for functional or cosmetic reason. Strabismus can be the first sign of retinoblastoma, and cataract must be excluded as a cause. The diagnosis and quantification of strabismus is the major focus of the pediatric ophthalmologic examination. No classification is perfect or all-inclusive. Strabismus may be classified on the basis of direction of the deviation: if the visual axes converge, there is esodeviation; if they diverge, there is exodeviation.

Esodeviations

Esodeviations are the most common form of misalignment and represent over 50% of ocular deviations in the pediatric population. They are caused by accommodative (most frequent), innervational, mechanical, refractive, and genetic factors.

Congenital Esotropia

Infants with congenital esotropia develop a large angle of esotropia at several months of age. Because it is not present at birth, some ophthalmologists prefer to name this condition infantile (early-onset) esotropia (◘ *Fig. 415.1*). The cause is unknown, and the abnormality is usually isolated. There is often a family history of strabismus, but well-defined genetic patterns are unusual. It occurs in otherwise normal infants, but it is quite common (up to 30%) in infants with developmental delay.



◘ **Figure 415.1**
A child with early-onset esotropia and large-angle esodeviation of the right eye

The angle of deviation is usually large. About one half of these infants see equally well with each eye. These infants alternate fixation from one eye to the other. In the other half of such infants, one eye sees better than the other. Amblyopia is present in the nonpreferred eye when there is constant in turning. The amblyopia must be treated by patching until the vision is equal, as determined by the infant spontaneously fixating with either eye.

The refractive errors in these infants, as determined by cycloplegic refraction, are the normal refractive errors of this age. Repeat refractions are essential. The treatment for this condition is surgery. However, surgery should be undertaken only after correction of significant refractive errors and treatment of amblyopia. Most agree that surgery should be performed early, before 2 years of age, to stimulate the infant to gain some binocular function and fusion. Most surgery is performed any time after the child is 6 months of age; this produces a better sensory and motor outcome when compared to surgery after 24 months. The success rate for surgery in the short term is quite high. Within the first years of life, some of these

children develop an abnormal head position: a face turn or a head tilt to either side. For most of these children, no cause can be found for the abnormal head position.

Pseudoesotropia

Pseudoesotropia, the illusion of esotropia, is a common reason infants are referred to ophthalmologists. Normal infants have a flat nasal bridge with prominent medial epicanthal folds and small interpupillary distance. As the infant looks straight ahead, it may appear that either or both eyes are turned inward. This illusion is aggravated in side gaze. As the child grows, the distance between the eyes increases and the nasal bridge grows forward, effectively pulling each medial canthus toward the midline. The pseudoesotropia then disappears. This underlies the old wives' tale that esotropia in infancy goes away spontaneously.

Accommodative Esotropia

Accommodative esotropia, the most common type, is produced by or caused by accommodation. Many of these cases occur as a result of uncorrected hypermetropia. The average age of onset is 2.5 years, and the condition develops between 6 months and 6 years of age. Treatment is by full hyperopic refractive correction as determined by cycloplegic refraction, visual rehabilitation if necessary, and surgical therapy. Initially therapy with spectacles may reduce the deviation, but, if esotropia persists, the clinician must decide whether it is sufficient to require surgery. The long-term use of miotic agents has largely been abandoned. Amblyopia must be fully treated prior to surgery.

Exodeviations

Most exodeviations develop in the first 4 years of life. Many children develop an exotropia that typically begins intermittently. The age of onset of exotropia varies but is often from infancy to 4 years. The cause is unknown. Amblyopia is uncommon, but photophobia is common. Exotropia may be induced by daydreaming, fatigue, illness, visual distraction, and distance viewing. Refraction of patients with exotropia reveals myopia. Exotropias are commonly associated with craniofacial anomalies and may be associated with neurologic impairment. Treatment is to maximize vision by treating amblyopia or anismetropia, by orthoptic exercises or surgery.

Infections and Allergic Ocular Disease

Prenatal and Perinatal Infections of the Eye

Maternally transmitted congenital infections can cause ocular damage in several ways: (a) through direct action of the infecting agent, which damages tissue; (b) through a teratogenic effect resulting in malformations; or (c) through a delayed reactivation of the agent after birth, with inflammation that damages developed tissue. The predominant organisms can be remembered by the acronym TORCHS: *to*xoplasmosis, *r*ubella, *c*ytomegalic inclusion disease (CID), *h*erpes simplex, and *s*yphilis.

Toxoplasmosis

In neonates, the disease occurs in a continuous clinical spectrum ranging from no signs or findings to severe necrotizing chorioretinitis that can usually be diagnosed from the typical fundus appearance. The animal reservoir is in the cat. Toxoplasmosis is found in about 80% of severely affected individuals with congenital infections of the eye. It is bilateral and frequently involves the macula, causing visual loss. *Toxoplasma gondii* is most often a congenital infection with lifelong ocular toxicity. Satellite foci are highly characteristic of toxoplasmosis. Scattered foci of calcification within the brain may be present in congenital cases and will be visible on computerized tomography (CT) scan. Hydrocephalus, mental retardation, and epilepsy can occur. Many authorities recommend treatment with sulfonamides and pyrimethamine or clindamycin to destroy the organism, together with steroids to suppress the inflammatory response. In newborns, the differential diagnosis of toxoplasmosis should include CID, herpetic infection, retinoblastoma, Coats disease, candidiasis, acquired immunodeficiency syndrome, and Aicardi syndrome.

Rubella

Rubella ("German measles") is caused by the rubella virus and is distributed worldwide. Rubella is typically a childhood disease. About 10–15% of women in the childbearing years are susceptible to rubella. The earlier in pregnancy the infection is contracted, the greater the risk to the fetus. Seropositive infants born to mothers infected between the first and eighth weeks of pregnancy

have about an 82% chance of developing severe defects. The most common cause of congenital cataracts is maternal rubella occurring during the first trimester of pregnancy. Other ocular manifestations consist of unilateral or bilateral microphthalmos, corneal opacification, chronic uveitis, congenital glaucoma, iris hypoplasia, and retinal degeneration. A diffuse salt-and-pepper retinopathy is often seen in rubella that does not significantly affect vision. The differential diagnosis includes syphilis, measles, varicella, and influenza. This syndrome has become rare with the advent of live attenuated virus vaccine.

Cytomegalic Inclusion Disease

CID is caused by cytomegalovirus (CMV), a virus of the herpes family. About 0.2% of all newborns are infected with CMV. The ophthalmic manifestations of CMV are highly variable and nonspecific. Strabismus, nystagmus, microphthalmos, cataracts, uveitis, optic disc anomalies, optic nerve atrophy, and anophthalmus are often seen. Retinochoroiditis occurs in 15–29% of severely affected neonates. Periventricular calcifications may occasionally be found on CT scans of the brain. CMV infection is usually subclinical in healthy children. Ganciclovir and foscarnet are currently the treatment of choice. Reactivation is treated with modest success with both drugs at the same time.

Herpes Simplex Virus

All members of the herpesvirus family have similar characteristics and infect a wide range of animals, including humans. There are two types of herpes simplex virus, herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). HSV-1 frequently affects the eye. The source of perinatal herpes simplex infection is usually maternal. Infection from the cervix is most common. Most neonatal HSV infections are acquired at the time of delivery, accounting for 50% of cases following vaginal delivery. The most common features of neonatal HSV infection are vesicular skin lesions, ulcerative mouth sores, and keratoconjunctivitis. HSV produces ocular symptoms in approximately 13% of infants with neonatal herpes; these include conjunctivitis, keratitis, cataracts, and retinochoroiditis. Eye involvement alone without other clinical manifestations may occur. The long-term prognosis for any infant with symptomatic HSV is poor due to serious neurologic sequelae.

Syphilis

Syphilis caused by *Treponema pallidum* is a reportable disease. Fetal infection occurs following maternal spirochetemia. If the mother contracts primary or secondary disease, one half of her offspring will be infected. Clinical signs develop during the first few months of life. Interstitial keratitis is seen secondary to untreated congenital syphilis in children who develop keratitis in the first decade of life. It presents as a rapidly progressive corneal edema followed by abnormal vascularization, giving the cornea a salmon pink color. Congenitally acquired infection can lead to neonatal death or premature labor. Salt-and-pepper retinopathy, glaucoma, and uveitis occur in some infants. Parenteral penicillin is given for 10–14 days to treat congenital syphilis.

Ophthalmia Neonatorum

Ophthalmia neonatorum, or neonatal conjunctivitis, is characterized by redness, discharge, and swelling of the conjunctiva in the newborn. It is uncommon in developed countries. Causes of ophthalmia neonatorum are *Neisseria gonorrhoeae*, trachoma inclusion conjunctivitis (TRIC), *Chlamydia*, chemical toxicity, and, rarely, HSV. Gonococcal and chlamydial infections are usually contracted from the maternal genital tract during delivery. Approximately 5–10% of maternal cervices harbor these infections.

Although gonorrheal conjunctivitis of the newborn is a vision-threatening conjunctival infection, it is rarely seen in the ophthalmologist's office. Its incubation period is so short that it is usually recognized in the newborn nursery and is diagnosed and treated by the pediatrician. It is characterized by marked purulent discharge and swollen lids, and is usually seen within the first several days of life. Appropriate smears and cultures should be taken. Systemic treatment is essential, and third-generation cephalosporins are mainstays of treatment. The patient should be isolated. Local treatment consists of irrigating or wiping away the purulent material.

Much more often seen is TRIC or chlamydial conjunctivitis in the newborn. The disease manifests at 1–2 weeks of age with marked swelling of the lids, copious mucoid discharge, and redness of the bulbar conjunctiva. The diagnosis can be confirmed by one of the commercially available rapid tests for *Chlamydia* infections. The treatment is 2 weeks of oral erythromycin (50 mg/kg/day in four divided doses), which greatly reduces the likelihood of pneumonitis and otitis media that may follow topical treatment only. The mother, father, and any sexual

partners should be treated. Fluorescent antibody staining and DNA probes of the patient's ocular surface and the cervix of the mother for *Chlamydia* have become important diagnostic tests.

Chemical conjunctivitis quickly follows topical silver nitrate instillation, and tends to be a mild conjunctivitis with watery discharge. Herpetic eye disease in the newborn can present as a blepharoconjunctivitis with herpetic vesicles of the lid margin. Diffuse chorioretinitis and encephalitis can result. This disease is associated with systemic illness. The overall mortality from neonatal HSV is 60%. Newborns may also develop a nonspecific conjunctivitis, usually from infection with *Haemophilus, Staphylococcus*, or *Streptococcus* organisms. Gonorrhea should be excluded by the appropriate smear and culture. Topical treatment is individualized based on the suspected organism and the results of the stain and culture.

Cellulitis

Cellulitis is divided into preseptal and orbital. *Preseptal cellulitis* is a common infection in children. It is an inflammatory process anterior to the orbital septum. Infections may be secondary to trauma, minor skin abrasions, insect bites, or spread from contagious structures. It can be associated with upper respiratory tract infections. Lid edema is common. Proptosis is not a feature, and the globe remains normal. Full ocular motility and absence of pain on eye movement distinguish preseptal from orbital cellulitis. *Staphylococcus aureus* and *Streptococcus pneumoniae* are the most common causes of preseptal cellulitis. Pediatric consultation is important in the management of *Haemophilus influenzae* cellulitis because a secondary meningitis can occur. Children less than 5 years of age are often admitted to the hospital. If there is no visible local source of infection, a CT scan is required to evaluate the paranasal sinuses. If positive, otolaryngologic consultation is required. Preseptal cellulitis is treated with systemic broad-spectrum antibiotics. Incision and drainage of the preseptal space may be required in severe cases with abscess loculation. There are usually no complications following mild preseptal cellulitis.

Orbital cellulitis is an infection of the orbit that involves the tissues posterior to the orbital septum. In children, it is a potentially fatal emergency that requires pediatric consultation, hospitalization, and intravenous antibiotics. It occurs in association with sinusitis in 90% of cases but can follow penetrating injury of the orbit. Signs include lethargy, fever, leukocytosis, headache, rhinorrhea, purulent nasal discharge, orbital pain, increasing proptosis, lid edema, and limitation of ocular motility. The etiologic agents responsible for orbital cellulitis vary with age. *Staphylococcus aureus, Escherichia coli*, and gram-negative bacilli are common in the neonate. *Haemophilus influenzae* and *S. pneumoniae* are common in children between 6 months and 5 years of age. *Staphylococcus aureus, Streptococcus pyogenes*, and *S. pneumoniae* are common in older children. Gram-negative organisms are common in immunosuppressed patients.

Paranasal sinusitis is the most common cause of bacterial orbital cellulitis. In children under 10 years of age, this is usually ethmoiditis. CT of the paranasal sinuses and orbit can determine and define the presence and extent of abscesses. Blood cultures should be obtained. Treatment includes emergent drainage of the sinuses and of any orbital abscess (Fig. 415.2). Parenteral third-generation cephalosporins, along with nafcillin, are given. Complications include cavernous sinus thrombosis or intracranial extension in the form of subdural or brain abscesses or meningitis, which may result in death.

Vernal Disease

Bilateral inflammation of the conjunctiva occurs on a seasonal basis during spring and summer. This is

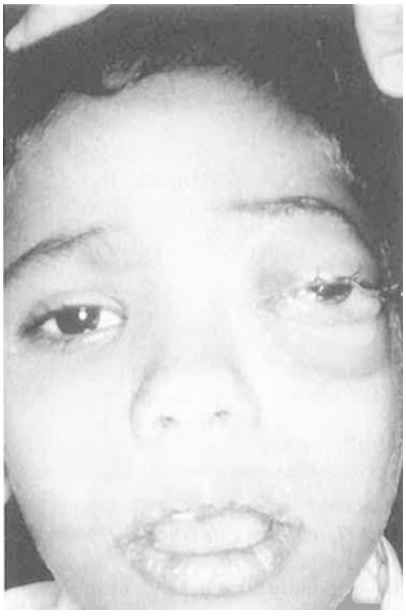


Figure 415.2
Acute orbital cellulitis with a swollen and tender upper left lid and chemosis of the conjunctiva

a common but self-limiting disease. It occurs more commonly in boys between the ages of 6 and 20 years. It is thought to be due to an allergic diathesis. The most prominent features are photophobia and severe itching. The discharge is characteristically thick, filamentous, and gray and contains a large number of eosinophils. Vernal conjunctivitis is easily differentiated from other causes of conjunctivitis. The prognosis for recovery is excellent, although prolonged. Cold compresses and oral antihistamines may be helpful. Topical cromolyn sodium is the long-term treatment and reduces the need for steroids. Use of topical steroids should be limited to acute severe cases under an ophthalmologist's supervision. Long-term use of steroids may lead to complications such as glaucoma and cataract.

Congenital Ptosis

Conditions that cause ptosis (lid droop) can be divided into congenital and acquired. Healthy children may be born with one or both upper eyelids abnormally low. The most common cause of congenital ptosis is an isolated dystrophy of one or both levator muscles (*Fig. 415.3*). Some patients are born with a nondystrophic type of ptosis. Myasthenic syndromes must be excluded. If one or both ptotic lids cover the upper portion of the pupils, the infant or child must maintain a chin-up position to look at something straight ahead. If the lid margin occludes the pupillary axis, an urgent effort should be made to lift the eyelid to expose the visual axis in order to prevent amblyopia and stimulate normal visual development. In the majority of cases, surgery can often be deferred until the child is old enough for a more accurate assessment of his or her condition. This usually occurs around the preschool age (4–5 years old). In all cases of ptosis, refraction is mandatory as molding of the cornea by the lid may occur, causing anisometropia and secondary amblyopia. These patients must be followed by a pediatric ophthalmologist. Evaluation of ptosis includes a thorough history, a complete examination, and documentary photos.

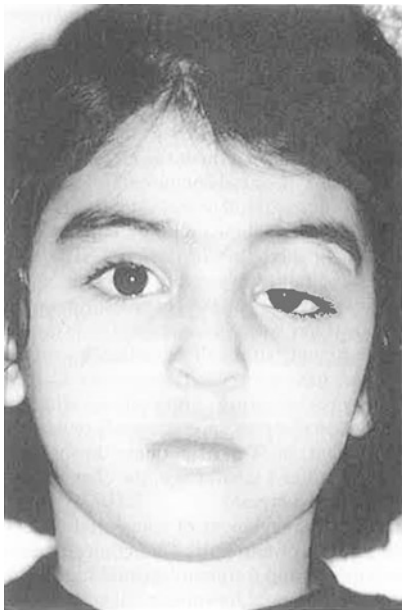


Figure 415.3
A child with unilateral congenital dystrophic ptosis of the left eye in which the lid margin occludes the pupillary axis

Lacrimal Drainage System

Dacryocystocele

Congenital dacryocystocele is a rare condition in which cyst-like swelling of the lacrimal sac occurs as a result of obstruction of the lacrimal drainage system. Dacryocystocele presents at birth as a bluish swelling below and nasal to the medial canthus about 1 cm in diameter. Its appearance is quite distinctive. Digital massage coupled with topical antibiotic administration may lead to resolution of the condition without complications. If the condition does not resolve, infection and inflammation may develop (dacryocystitis), requiring systemic antibiotic therapy. Persistence of symptoms necessitates probing of the nasolacrimal canal (see "Nasolacrimal Duct Obstruction" below).

Nasolacrimal Duct Obstruction

Clinically evident obstruction of the lacrimal system is usually due to a thin mucosal membrane (Hasner valve) at the lower end of the nasolacrimal duct (NLD). Symptoms of NLD obstruction include epiphora and sticky mucoidal or mucopurulent discharge of the eye. NLD obstruction occurs in 5% of full-term newborns. Symptoms manifest by 1 month of age in 80–90% of cases. Bilateral involvement, though asymmetric, is common. There is no effect on visual development, although secondarily acute bacterial infections may have serious consequences. Culture of the discharge may reveal various strains of bacteria. Congenital NLD obstruction

resolves, spontaneously or with conservative management, in 90% of patients during the first 12 months of life. After 1 year of age, the chance of a spontaneous resolution decreases.

Conservative management of congenital NLD obstruction includes topical antibiotic (the choice is not critical) drops or ointment and frequent lacrimal sac massage. This management often provides substantial and complete relief of symptoms. When symptoms persist, surgical probing of the lacrimal system is indicated. The success rate of initial probing for congenital NLD obstruction exceeds 90% in infants up to 12 months old. Patients who fail one or two initial probings should have silicone tube insertion in the nasolacrimal duct for at least 9 months.

Diseases of the Cornea

Neonatal Corneal Opacities

Sclerocornea

Sclerocornea is a congenital condition in which the cornea is opaque and resembles the sclera. The central cornea is clearer than the periphery. It often occurs in association with other abnormalities of the eye.

Tears, Breaks, or Ruptures of the Descemet Membrane

Such injuries may be caused by a difficult delivery leading to a unilateral central opacity. They are sometimes associated with transient stromal edema, which invariably subsides. Severe amblyopia may result.

Mucopolysaccharidosis and Mucolipidosis

Mucopolysaccharidosis (MPS) is caused by abnormal carbohydrate metabolism. Mucolipidosis is a lysosomal disorder. Corneal clouding and haziness may be present in early life in MPS IS and mucolipidosis. The diagnosis is established by electron microscopic examination of a conjunctival biopsy. All of the mucopolysaccharides except MPS III (Sanfilippo syndrome) may have depositions in the cornea leading to some degree of corneal cloudiness. Mucolipidosis causes a cherry-red spot (*Fig. 415.4*).

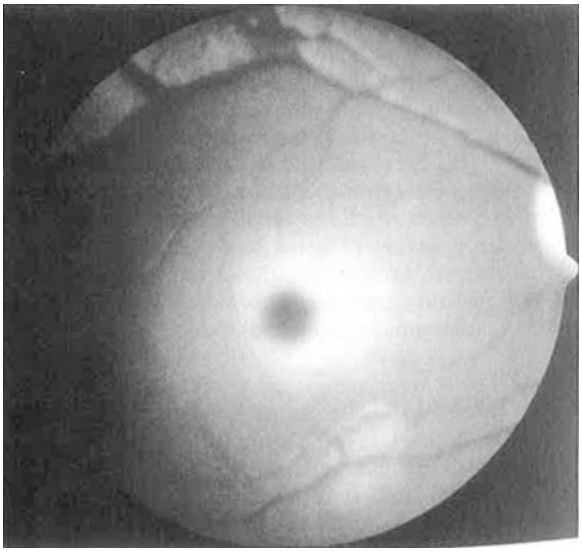


Figure 415.4
A fundus photo showing a characteristic cherry-red spot in mucolipidosis

Peters Anomaly

This anomaly causes a corneal opacity that can range from a faint stromal opacity to a dense, opaque central leukocoria that may be vascularized. In many cases, the stromal opacity decreases with time.

Dermoids

A corneal dermoid is a hamartoma that sometimes contains hair follicles, sebaceous glands, and sweat glands. They appear as raised, circumscribed, pale yellowish growths, and are usually present at birth. Limbal dermoids are often seen with Goldenhar syndrome.

Congenital Hereditary Endothelial Dystrophy

Congenital hereditary endothelial dystrophy is an unusual autosomal recessive condition that is noticed at birth. Both corneas are uniformly and diffusely hazy and edematous. The cornea is thicker than normal, with a normal diameter. The intraocular pressure is normal. These three findings differentiate this condition from congenital glaucoma. The condition remains unchanged, and vision is usually good.

Congenital Infantile Glaucoma

Glaucoma in an infant can make the cornea hazy, cloudy, opaque, or enlarged (see "Congenital or Infantile Glaucoma" below)

Systemic Diseases with Corneal Manifestations in Childhood

Mucopolysaccharidosis and congenital syphilis (see above) both have corneal manifestations in childhood. Other systemic diseases with such manifestations include cystinosis and Wilson disease.

Cystinosis

This is a metabolic disease characterized by elevated cystine within the cell. Cystinosis occurs in three forms, all of which have the characteristic corneal crystals (*Fig. 415.5*). The infantile form is associated with failure to thrive, renal failure, rickets, decreased pigmentation, and early death. The adolescent form has only the renal complications. The crystals in the cornea are mainly in the anterior stroma. Iridescent crystals, elongated and needle shaped, are distributed throughout the conjunctiva and the cornea (*Fig. 415.5*). The ocular findings are pathognomonic.

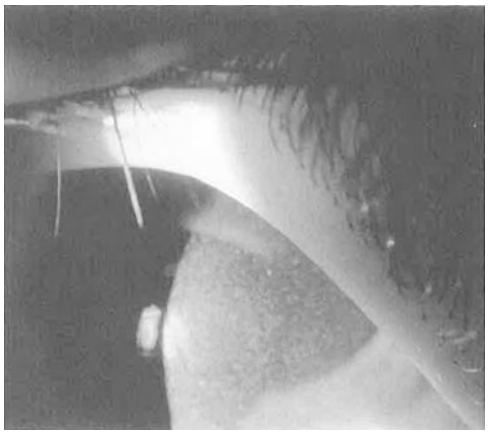


Figure 415.5
Slit-lamp photography showing elongated crystals in the cornea secondary to cystinosis

Hepatolenticular Degeneration (Wilson Disease)

Hepatolenticular degeneration is an autosomal recessive disorder of copper metabolism that affects the basal ganglia of the central nervous system, the liver, and the kidneys. Copper deposits in the periphery of the cornea in a copper-colored ring fashion referred to as a Kayser-Fleischer ring (*Fig. 415.6*). The stain is usually most marked near the upper and lower limbus of the cornea. This arc of deposition spreads, eventually encircling the entire cornea. This corneal finding is usually pathognomonic of Wilson disease. The ring resolves with treatment.

Iris Anomalies

Many pediatric patients present with congenital anomalies of the iris. Some of the most common anomalies are discussed below.

Aniridia

The condition is congenital, panocular, always bilateral, and often familial, transmitted in an autosomal dominant fashion with complete penetrance but variable. Expressively, two-thirds of all aniridic patients have affected parents. The iris is hypoplastic, often hidden behind the sclera on direct view, and visible only by gonioscopy. The sporadic form of aniridia is associated with Wilms tumor of the kidney in one-third of cases. The risk is increased

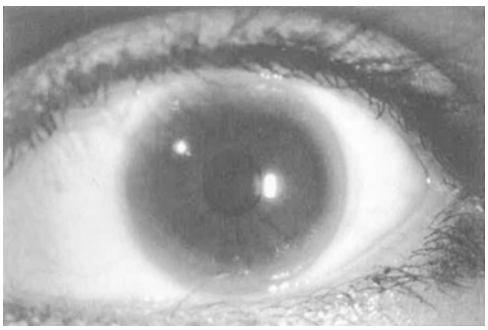


Figure 415.6
A copper-colored ring referred to as a Kayser–Fleischer ring encircles the cornea in Wilson disease

further if the patient has genitourinary anomalies or mental retardation (ARG triad). All patients with sporadic aniridia should have periodic ultrasound examinations of the kidneys to detect such tumors early; 80% of cases are diagnosed before the age of 5.

Typically, there is hypoplasia of the fovea and optic nerve resulting in nystagmus and decreased vision. In a sense, aniridia is a progressive disease. Photophobia and cataracts that are visually significant may develop, and the lens may partially dislocate. A major problem is the development of glaucoma, which is difficult to treat.

Coloboma of the Iris

A coloboma of the iris is considered typical if it occurs in the inferonasal quadrant. It is an external sign of a defect in the closure of the fetal fissure in the fifth week of gestation. The pupil is shaped like a lightbulb, keyhole, or inverted teardrop (*Fig. 415.7*). It may be unilateral or bilateral, sporadic or autosomal dominant. It may be an isolated ocular defect or associated with cardiac, hearing, anal, choanal, central nervous system, and probably other defects. If it is an isolated iris defect, it is compatible with normal or near-normal vision. It may involve the ciliary body, choroid, retina, and optic nerve. Nystagmus is usually present. Typically, an eye with a coloboma is smaller than normal, a condition called colobomatous microphthalmos. Many chromosomal abnormalities are associated with iris coloboma, as are many well-recognized syndromes.

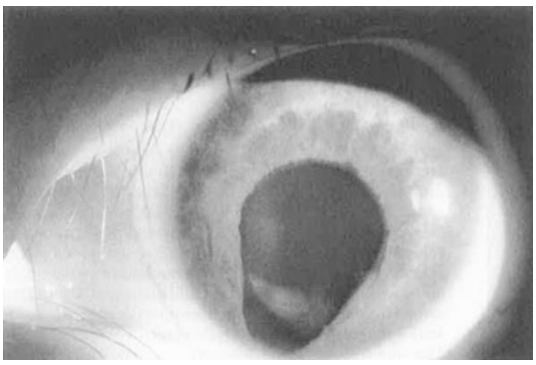


Figure 415.7
A lightbulb-shaped pupil showing a coloboma of the iris in the inferonasal quadrant

Lisch Nodules

Lisch nodules are common hamartomas associated with neurofibromatosis type 1. They are raised and tan in color. The prevalence and number increase with age.

Juvenile Xanthogranuloma

Juvenile xanthogranuloma is primarily a cutaneous disorder with a predilection for the head and face. Vascular iris lesions may occur as discrete yellowish nodules or as diffuse infiltration causing heterochromia. Spontaneous hyphema can occur.

Congenital or Infantile Glaucoma

The incidence of congenital glaucoma is about 1 in 12,500 births. It is not inherited as a simple mendelian trait but appears to be multifactorial. It is usually considered to be the result of maldevelopment of the angle. Infant and adult eyes react differently to raised intraocular pressure: the sclera of the younger eye is able to stretch more, and high intraocular pressures can produce ocular enlargement known as buphthalmos (ox eye) prior to 2 years of

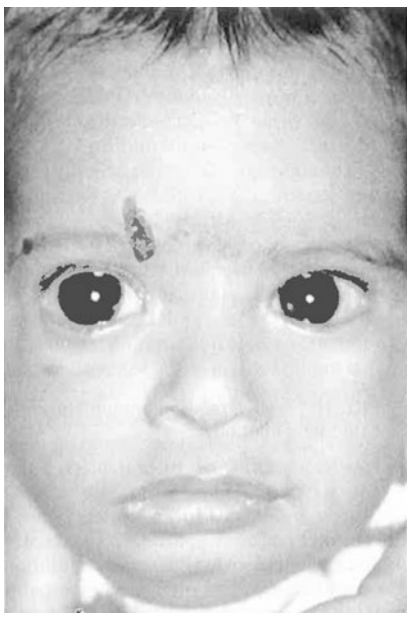


Figure 415.8
Congenital glaucoma of the right eye in an 8-month-old infant showing corneal enlargement and corneal opacity typical of buphthalmos

age (Fig. 415.8). Intraocular pressure is elevated in congenital glaucoma. The measurement of intraocular pressures in infants is difficult. Corneal changes are the earliest findings in congenital glaucoma. Any apparent difference in the diameter of the cornea should be considered to be congenital glaucoma until proven otherwise. The hallmarks of buphthalmos are corneal edema and corneal enlargement. Photophobia and reflex tearing are common symptoms. Vision is severely affected due to corneal edema, amblyopia, or optic nerve damage.

Congenital or infantile glaucoma can be divided into primary uncomplicated congenital glaucoma or secondary complicated glaucoma, which can be associated with several systemic syndromes and various ocular conditions. Systemic associations include Sturge-Weber syndrome, neurofibromatosis, oculocerebroneural syndrome, oculodentodigital syndrome, Rubenstein syndrome, and rubella. In general, surgery is the appropriate management for the childhood glaucomas. The prognosis is usually poor in the secondary type, but good results have been documented in the primary type.

Pediatric Lens Disorders

Cataracts

Certain types of lens opacities are common in pediatric ophthalmology and unique to infants and children, and are due to a variety of etiologies. Congenital cataracts are one of the leading causes of blindness in children. In bilateral cataracts, one-third are inherited, one-third are associated with other syndromes, and one-third are idiopathic.

The cause of poor vision in children with cataracts is irreversible amblyopia. They should be treated in the first months of life for optimal visual potential. Screening protocols are a must for all infants in the nursery stage and can be accomplished by evaluating the red reflexes by ophthalmoscopy. The gestational age of cataract formation determines the location of the lens opacity. Leukocoria is a common sign with complete cataracts (Fig. 415.9). Nystagmus usually develops due to poor visual development, especially with unilateral cataracts.

Hereditary cataracts are usually present at birth; others develop with time. They can be autosomal dominant, recessive, or X-linked. They can be associated with a variety of metabolic disorders, syndromes, and chromosomal disorders, such as trisomy 13, 18, and 21. A family history of cataracts and ocular anomalies can help in the diagnosis. Families with inherited cataract should receive genetic counseling. Surgical intervention (lensectomy) is essential and should be planned accordingly. Visually significant congenital cataracts should be removed urgently within 6–8 weeks of life. Aphakic optical correction, contact lenses, intraocular lens implantation, and keratorefractive surgery have all been utilized in the treatment of pediatric aphakia. The prognosis for children with congenital or infantile cataracts has improved markedly with early diagnosis and proper therapeutic technique.

Lens Dislocation (Ectopia Lentis)

Dislocated lenses (Fig. 415.10) cause decreased vision due to large errors of refraction. Diplopia and/or photophobia may be present. The condition is bilateral when

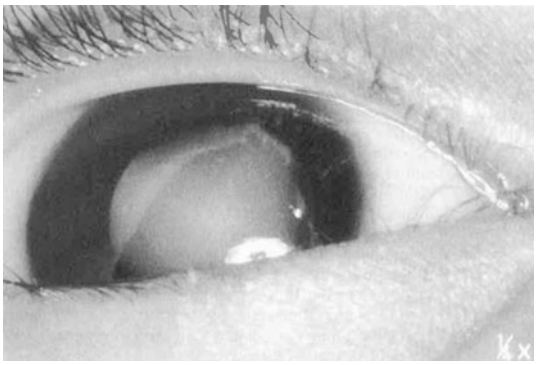


Figure 415.9
Congenital cataract in a 2-month-old revealing no red reflex and leukocoria

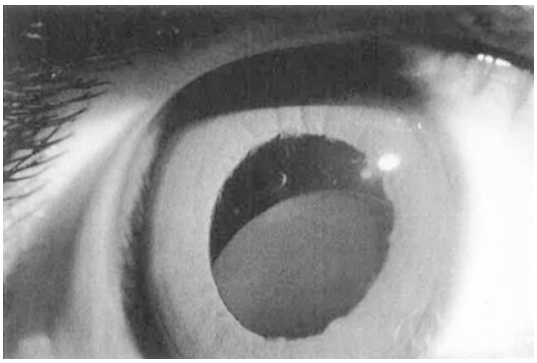


Figure 415.10
A slit-lamp photograph showing a dislocated lens inferiorly

inherited. There is usually a family history of decreased vision. Movement of the iris (iridodonesis) is common. Common ocular conditions associated with dislocated lenses include simple ectopia lentis, ocular trauma, aniridia, and ectopia lentis and pupillae. The associated systemic disorders include Marfan syndrome, homocystinuria, Weill-Marchesani syndrome, hyperlysinemia, sulfate oxidase deficiency, syphilis, and Ehlers-Danlos syndrome. A thorough history, physical, and ocular examinations are indicated.

Anterior Uveitis

Juvenile rheumatoid arthritis (JRA) is the most common cause of anterior uveitis in children. It is characterized by a chronic nonsuppurative synovial inflammation that includes low-grade fever, malaise, hepatosplenomegaly, lymphadenopathy, and anemia. Onset may be at any age but is rare before the second year of life. Several of the JRA subgroups have a genetic predisposition. Chronic iridocyclitis that is present in one or both eyes is most frequently associated with the pauciarticular forms of JRA. Individuals with JRA who are seronegative for the rheumatoid factor and positive for the antinuclear antibody are at increased risk for developing anterior uveitis.

Anterior uveitis, which can occur in a white eye, is detected with a slit lamp and can be seen at any time during the disease. Ocular inflammation often remains for years, frequently with long-term sequelae such as glaucoma and cataract formation. Suppression of the inflammatory process is the cornerstone of systemic treatment. Ophthalmic care of patients with JRA includes periodic examinations. The management is difficult in many cases. Topical steroids, cycloplegics, dilating agents, subconjunctival steroid injections, and systemic steroids have all been used. The parents should have a clear understanding regarding progress and prognosis. When the disease is chronic, vocational planning is indicated because the condition may lead to eventual blindness.

Leukocoria

The term *leukocoria* means white pupil. The differential diagnosis is important and includes retinoblastoma (until proven otherwise), retinopathy of prematurity (ROP), persistent hyperplastic primary vitreous (PHPV), retinal coloboma, Coats disease, posterior cataracts, uveitis, toxocoriasis, congenital retinal folds, vitreous hemorrhage, retinal dysplasia, and other tumors.

Retinoblastoma

Retinoblastoma is the most frequent intraocular malignancy of childhood. The disease is caused by a mutation in the long arm of chromosome 13. To initiate tumor growth, both chromosomes must contain a mutation. Single tumors occur in two-thirds of retinoblastoma patients (somatic form), and these mutations are limited to the retina. Multiple tumors occur in one-third of cases (germinal form) and are thereby reproduced in every cell of the body. A positive family history is present in 5–10% of retinoblastoma patients.

Retinoblastoma is diagnosed in the first year of life in the familial bilateral cases and between 1 and 3 years of age in the sporadic unilateral cases. The most common initial sign is leukocoria (white pupil), followed by strabismus. Retinoblastoma is usually diagnosed on clinical grounds by an experienced observer. This can be confirmed by demonstration of typical intraocular calcification with CT. All family members should be examined.

The preferred therapy for this tumor has undergone extensive changes. Enucleation is no longer the sole and immediate treatment. Treatment of large retinoblastomas, failure of conservative treatment, or extensive vitreous disease requires enucleation in the majority of cases. It is important to operate without unnecessary delays. Conservative management to salvage at lease one eye includes external beam radiation (for larger and posteriorly located tumors), brachytherapy (intermediate tumors), cryotherapy (small, anteriorly located tumors), photocoagulation (small posteriorly located tumors), and, more recently, thermal-enhanced chemotherapy. Chemotherapy remains investigational. The decision regarding the treatment of retinoblastoma is complex and is best approached by a team of experienced specialists.

Retinoblastoma patients with germinal mutation and unilateral involvement are at risk for developing additional ocular and nonocular tumors. Primary intracranial tumors originating in the pineal gland with retinoblastoma-like histopathology are described as "trilateral retinoblastoma." Sarcoma in the orbit and throughout the body occurs up to 30 years after retinoblastoma treatment. Primary extraocular tumors associated with retinoblastoma have a very poor prognosis for survival.

Retinopathy of Prematurity

ROP is an abnormal vasoproliferation in the retina of premature infants (see Chap. 304, "Proximal Renal Tubular Disorders"). Prematurity may trigger the onset

of ROP, causing abnormal neovascularization. With progression, fibroglial proliferation occurs that can lead to retinal traction or detachment. ROP is common in infants with birth weights of less than 1,500 g. As gestational age and birth weight decrease, the risk of ROP increases.

Supplemental oxygen has been implicated as a cause of ROP, although factors other than hyperoxia play a role in ROP. Gestational age and birth weight are inversely correlated to the development of ROP. The amount of time of oxygen therapy correlates well but the limit of oxygenation does not. Certain diseases are commonly seen in association with ROP, including respiratory distress syndrome, patent ductus arteriosus, apnea, bradycardia, intracranial hemorrhage, sepsis, anemia, and jaundice. An international classification of ROP has been developed that describes the disease in detail.

The initial fundus examinations of infants weighing less than 1,500 g is at 4–6 weeks after birth. The Cryotherapy for Retinopathy of Prematurity Cooperative Group study has shown that cryotherapy decreases visual loss by 46%. Laser photocoagulation is a newer treatment modality and considered by leading authorities as superior to cryotherapy. Vitamin E has been proposed as a treatment to reduce ROP, although no confirming data have been established. ROP regresses in most cases. Grave sequelae of advanced disease include retinal detachment, retinal folds, dragging of macula, amblyopia due to high myopia, microphthalmos, cataract, glaucoma, and phthisis bulbi. Enucleation is sometimes necessary.

Persistent Hyperplastic Primary Vitreous

PHPV is the most common cause of a unilateral cataract in a newborn or infant. An eye with PHPV is usually smaller than the normal eye. In mild PHPV, the only abnormality may be a persistent hyaloid artery, with or without a small opacity on the posterior surface of the lens. In a more advanced stage, an opacity is detected in the posterior portion of the lens cortex. The more advanced stage is characterized by a total cataract and a flat anterior chamber.

This condition is usually unilateral. It is not inherited, and it is not associated with any systemic condition or disease. In the extremely unusual event that PHPV is bilateral, Norrie disease should be considered in the differential diagnosis.

PHPV in the moderate or advanced stage is treated surgically by removing the lens and the retrolental membrane. The visual outcome can be poor because of the amblyopia characteristic of a unilateral cataract and the foveal hypoplasia that typically accompanies PHPV, although some reports have reported a good visual outcome.

Many eyes with PHPV can be saved by early surgical intervention followed by aggressive contact lens wear combined with eye patching.

Shaken-Baby Syndrome

Shaken-baby syndrome was first identified in the early 1970s. It became widely recognized as one of the most important forms of child abuse. These infants are victims of violent shaking by a parent and are always under 3 years of age. The characteristic clinical findings support the diagnosis of shaken-baby syndrome even in the absence of a history.

The most common ocular manifestation of shaking injury in most cases is retinal hemorrhage that is concentrated around the macula or involves nearly the whole retina. Vitreous hemorrhage may also develop. The vitreous becomes almost completely opacified by dispersed hemorrhage within a few days of injury, and this opacification may persist for many months or even years. The retinal hemorrhage in shaken-baby syndrome resolves over a week to several months. The mechanism of ocular injury in the shaken-baby syndrome is controversial. Some believe that intraocular hemorrhage results from increased pressure in the retinal veins secondary to increased intracranial pressure or increased intrathoracic pressure. Others have postulated that the shaking trauma itself causes retinal tissue damage and secondary hemorrhage. Retinal hemorrhage due to birth trauma is common in newborns but seldom persists beyond 1 month of age. Complete or near-complete recovery of vision is common in shaken-baby syndrome.

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Pediatric Surgery

Thomas F. Tracy

416 Surgical Conditions Presenting During Fetal Development

Rajan K. Thakkar · Francois I. Luks

As prenatal imaging techniques have evolved, so has the ability to diagnose and treat surgical conditions in the developing fetus. The prevalence of major birth defects is around 3% of live births, while the incidence of minor birth defects is at least three times as common. Surgically correctible births defects are seen in less than 1% of live births. Many surgical diseases arising in utero cause anatomic abnormalities that interfere with normal organ development. This makes in utero therapeutic strategies tempting and is one reason why fetal intervention continues to be an area of intense research. In utero imaging, in combination with molecular analysis, amniocentesis, chorionic villus sampling, fetal tissue biopsy, and other modalities, not only provides ever more precise diagnosis, but often prognostic information as well. This gives us the ability to counsel parents about therapeutic options and realistic outlook. While prenatal intervention may be entertained in certain cases, the vast majority of surgical conditions diagnosed in utero are best treated after birth.

Definition and Classification

A surgical condition can be diagnosed prenatally in three ways: First, the diagnosis can be suggested through genetic or biochemical testing. A classic example is open neural tube defect (spina bifida). Prenatal screening includes an elevated maternal serum alpha-fetoprotein (MSAFP) level. This suggests leakage of fetal proteins through an integumental breach (a neural tube defect, but also an abdominal wall defect such as gastroschisis). Second, the surgical condition itself may be visible on prenatal imaging. A typical example might be a large thoracic mass, an abdominal cyst, or a sacrococcygeal teratoma. Third, the mechanical effects of a surgical problem may become apparent. These secondary manifestations are relatively limited in number, and can give a clue as to the etiology and location of the primary defect. The most common of these signs is amniotic fluid volume. After the first trimester, amniotic fluid is mostly produced through fetal voiding. The fetus swallows the fluid, which is then absorbed through the small bowel and ultimately filtered and excreted through the kidneys, thus completing the cycle. Any interruption along this pathway can lead to abnormal amniotic fluid volume. Thus, interruption of the gastrointestinal tract proximal to the jejunum (such as duodenal atresia or complete esophageal atresia) will be associated with decreased intestinal fluid absorption and polyhydramnios. Polyhydramnios may also be due to kinking of the esophagus or gastroesophageal junction: This is often seen with congenital diaphragmatic hernia, when the intrathoracic stomach compresses the esophagus. Conversely, bilateral or distal obstruction of the urinary flow will cause oligohydramnios.

Surgical conditions can be classified as thoracic, abdominal, and parietal. They can be anatomic defects or proliferative lesions, both benign and malignant.

Thoracic Anomalies

Tracheoesophageal Fistula (TEF)/Esophageal Atresia (EA)

Esophageal atresia (EA) is a birth defect in which a portion of the primitive foregut is interrupted. The condition is most commonly associated with tracheoesophageal fistula (TEF), an abnormal connection between the trachea and esophagus. The trachea develops around the fourth week of gestation and disruption of the esophagus, with or without fistulization of the trachea, is believed to occur around this time. It is a defect of lateral septation of the foregut due to defective cellular signaling. Because of these improper cellular interactions, TEF/EA is often associated with other congenital anomalies. Grouping of these disorders makes up the VACTERL association (Vertebral, Anorectal, Cardiac, Tracheo-Esophageal, Renal, and Limb). The classification is based on the anatomic relationship between the esophagus and the trachea. The incidence is approximately 1 in 3,500 live births with a slight male predominance.

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The presentation of TEF/EA depends on the type. If there is no esophageal atresia (type E), which occurs in 5% of cases, the diagnosis is often made long after birth. In cases with EA, the fetus cannot swallow amniotic fluid, which may lead to polyhydramnios, as is often seen in type A (isolated atresia). The combination of excess amniotic fluid, a visibly distended upper esophagus, and absence of gastric and intestinal fluid on prenatal ultrasound is highly suggestive of type A esophageal atresia. Type B, the least common variant, has an associated proximal TEF – the proximal esophageal pouch may therefore be decompressed and not visible, but polyhydramnios and non-visualized stomach are typical. The differential diagnosis in utero includes other causes of polyhydramnios, such as intestinal atresia, some neurological disorders with impaired fetal swallowing, and other, rare disorders of the oropharynx. Examples are laryngotracheoesophageal clefts, esophageal strictures, and tubular esophageal duplications. Most commonly, however, an associated distal tracheoesophageal fistula allows fluid to bypass the atresia and make its way into the distal esophagus. The most common form is a blind-ending proximal esophageal pouch and a fistula between the distal trachea and the distal esophagus (type C). Because amniotic fluid volume is typically normal and fluid is seen in the stomach and intestines, prenatal diagnosis is usually not possible.

Whether it was suspected prenatally or not, final diagnosis is made after birth. Excessive salivation and the inability to pass a nasogastric tube into the stomach is the main feature in the diagnosis of EA. A chest radiograph is obtained to demonstrate the nasogastric tube coiled in the proximal esophagus, but a contrast study (instillation of 1 mL of barium will coat the upper pouch) is rarely necessary.

The immediate care of a newborn with TEF/EA should be decompression of the proximal EA with a nasogastric tube to prevent aspiration and further respiratory compromise. Most newborns with TEF undergo an attempt at definitive repair within the first few days of life. A preoperative workup with a thorough physical exam is critical to detect other associated anomalies, particularly the VACTERL association. A preoperative echocardiogram can help detect cardiac anomalies, which are seen in 20% of patients. More recently, minimally invasive thoracoscopic repair of TEF and EA has been described, but it is not yet known whether its long-term results match those of traditional repair.

Survival of isolated TEF/EA is 90–95%, but this rate may be lower if there are associated anomalies (cardiac defects and chromosomal abnormalities in particular). Surgical complications include anastomotic strictures and anastomotic leak. These patients may go on to develop disorders of esophageal motility, gastroesophageal reflux, tracheomalacia, and reactive airway disease.

Laryngeal atresia and tracheal atresia are very rare foregut anomalies that lead to lung fluid trapping, causing dramatic distension of the lungs. On prenatal imaging, the lungs will appear very large and fluid filled, and the diaphragms flattened or inverted (concave). In some cases, the increased intrathoracic pressure may even lead to mediastinal compression and hydrops. If the anomaly is diagnosed prenatally and the atresia is high, emergency tracheostomy at the time of an Ex-Utero, Intrapartum (EXIT) procedure may be lifesaving. While rare, this anomaly (which some have dubbed Congenital High Airway Obstruction, or CHAOS) is the experiment of nature that formed the basis for fetal tracheal occlusion as a treatment for severe pulmonary hypoplasia (see under "Congenital Diaphragmatic Hernia").

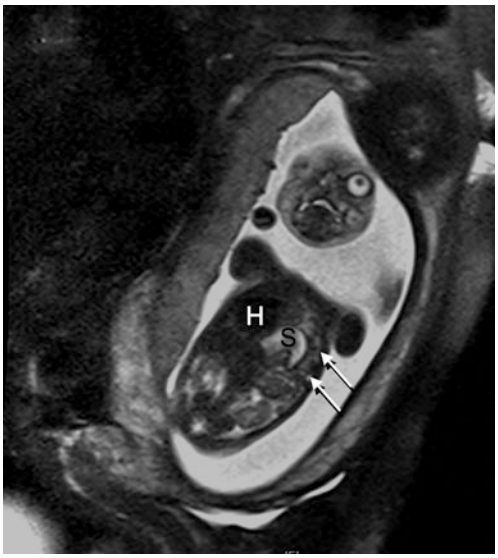
Congenital Diaphragmatic Hernia

In congenital diaphragmatic hernia (CDH), a defect in the diaphragm allows migration of abdominal contents into the thoracic cavity. The incidence of CDH is 1 in 2,000 to 3,000 live births. The most common and most frequently significant form is a posterolateral defect (Bochdalek). Herniation through a persistent foramen of Morgagni (an anterior, retrosternal defect in the diaphragm) is less common, and often diagnosed later in childhood. Posterolateral CDH is left sided in 80% and right sided in 20%. Bilateral CDH is extremely rare. The prognosis of CDH was long considered dismal, and severe forms are still often lethal. However, progress in neonatal management and respiratory care has significantly impacted the prognosis of CDH. Data from the CDH Registry show that isolated CDH (not associated with chromosomal or cardiac anomalies) now has an overall survival rate of greater than 70%. The pathogenesis of CDH is believed to occur from a failure of closure of the pleuroperitoneal folds during the fourth to tenth week of gestation. This time frame overlaps with a period of critical fetal lung development, from the 3rd to 16th week of gestation, suggesting a direct correlation between the severity of the diaphragmatic defect and the morbidity of this disease. Compression of the lungs by the abdominal contents causes pulmonary hypoplasia and interferes with the development of the pulmonary vasculature. This may ultimately lead to severe, refractory pulmonary hypertension after birth – the most common cause of death in CDH. Although early lung development and branching

morphogenesis may be seriously impaired by an intrathoracic mass effect, late lung maturation, at the end of the second trimester, is equally critical in ensuring normal postnatal pulmonary and pulmonary vascular function. The idea that mid-gestation reduction of the hernia or stimulation of accelerated lung growth (by fetal tracheal occlusion) may still reverse the effects of pulmonary hypoplasia lies at the basis of fetal surgery to treat severe CDH.

Diaphragmatic hernia can be diagnosed prenatally by ultrasound, which demonstrates abdominal viscera in the chest. In left-sided CDH, a fluid-filled stomach may be present in the same axial plane as the heart. In right-sided CDH, one may see a homogenous liver above the diaphragm. Because of the relatively solid appearance of fetal lung, it is not always easy to distinguish it from liver by ultrasound. Polyhydramnios may be present if there is compression of the esophagus or kinking of the gastroesophageal junction. However, hydrops (from compression of the mediastinum and impaired venous return) is rarely seen.

Magnetic resonance imaging (MRI) can be a useful diagnostic adjunct to confirm the diagnosis of CDH, to evaluate for other congenital anomalies, and to assess lung volume (◉ *Fig. 416.1*). The presence of abnormal structures in the fetal thorax can be a sign of CDH – or of other space-occupying thoracic masses. Differential diagnosis includes congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration (BPS), bronchogenic cysts, and, rarely, lymphangiomas, enteric cysts, and teratomas.



◘ Figure 416.1
Fetal MRI of a left-sided congenital diaphragmatic hernia. Coronal view of the fetus (T2-weighed image) showing small bowel loops (*arrows*) and stomach (S) in the left thoracic cavity, displacing the heart (H) into the right chest

Infants born with CDH most commonly present in severe respiratory distress. A chest radiograph typically demonstrates abnormal gas patterns in the left hemithorax, curling of the nasogastric tube in an intrathoracic stomach (left CDH), or presence of liver in the right hemithorax (right CDH). The mediastinum is deviated toward the contralateral side. Although the primary insult in CDH is pulmonary hypoplasia, it is rare for lung tissue to be so diminutive as to be incompatible with life. Rather, early hypoxia, hypercapnia, and acidosis all contribute to reflex vasoconstriction of the pulmonary arterial system and pulmonary hypertension (persistent fetal circulation), leading to refractory hypoxemia because of severe ventilation/perfusion (V/Q) mismatch. Right-sided heart failure may further complicate the infant's critical pulmonary condition. In severe cases, extracorporeal membrane oxygenation (ECMO) offers the only hope of temporary pulmonary rest and recovery from the cardiopulmonary insult.

Operative correction of the defect is never an emergency. Delayed repair allows stabilization of the infant during the transitional phase from fetal to adult circulation. Once surgical repair is indicated, it is typically performed through an abdominal incision, more rarely through the chest. During the procedure, the viscera are reduced into the abdomen and the diaphragm is closed primarily in most cases. If there is insufficient native diaphragmatic tissue, a synthetic graft is used.

No single prenatal factor to date can accurately predict survival in patients with CDH. There have been attempts at judging the degree of pulmonary hypoplasia and other perinatal factors, but they have had little success. However, the combination of several parameters, including early gestational age at diagnosis, polyhydramnios, mediastinal shift, a small lung-thorax transverse area ratio, left ventricle/right ventricle index, left heart hypoplasia, and the presence of stomach or liver in the chest, suggests a worse prognosis. The only parameter that comes close to predicting survival based on estimated fetal lung size is the lung-to-head ratio (LHR). It considers the surface area of the contralateral lung in a four-chamber view of the heart as a surrogate for three-dimensional lung size (volume), and is divided by the head circumference to normalize for gestational age. Normal LHR is greater than 2.5–3.5; an LHR greater than 1.4 is generally considered to indicate good prognosis, and an LHR between 1.0 and 1.4 considered an intermediate risk. Fetuses with an LHR

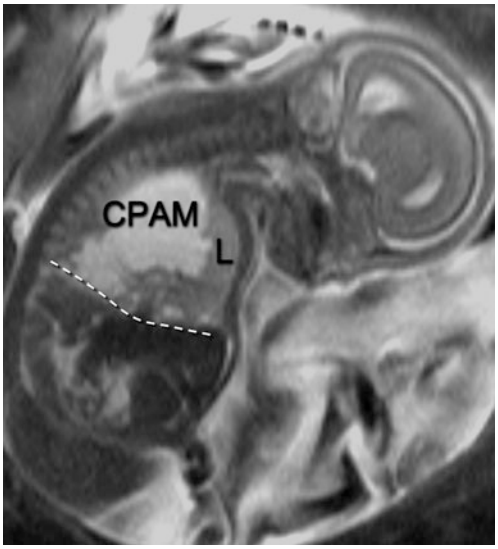
below 1.0 (most accurately measured at 26 weeks gestation) have the worse prognosis, with postnatal survival rates of 10–30% or less. Infants with CDH who survive the initial respiratory insult and management face many complications, including gastroesophageal reflux, foregut dysmotility, developmental delay, feeding difficulties, pulmonary hypertension, reactive airway disease, and chronic lung disease.

Bronchopulmonary Malformations

Congenital pulmonary airway malformations (CPAM) are a diverse group of rare developmental anomalies of the respiratory tract. The incidence of congenital lung cysts ranges from 1 in 8,300 to 35,000 live births. CPAMs, the more current term for what used to be called congenital cystic adenomatoid malformations (CCAM), are histologically divided into five types. The spectrum, from type 0 to type IV, is believed by some to mimic the normal bronchopulmonary anatomy from proximal airway to distal alveoli. A more practical classification considers their gross appearance: macrocystic (a few large cysts), microcystic or mostly solid. CPAMs usually have microscopic bronchial communications (pores of Conn) and arterial and venous branches that derive from the normal pulmonary circulation.

Bronchopulmonary sequestration (BPS) is another type of congenital pulmonary lesion. Intralobar sequestrations are found within the lung parenchyma, and resemble CPAMs. Extralobar sequestrations, by contrast, are invested with their own visceral pleura, are distinctly separate from the lung, and typically have an arterial feeder off the systemic blood supply. As these lesions typically occur in the lower thoracic cavity, the feeding artery comes off the descending aorta, often from its infradiaphragmatic portion. While sequestrations have a more homogeneous histology that resembles normal lung parenchyma, up to 50% of these also harbor CPAM elements.

The clinical manifestation can vary from a fatal condition in the fetus to a mild lesion in a child leading to recurrent pulmonary infections. Many CPAMs and sequestrations are diagnosed on routine prenatal ultrasound. Fetal MRI may be used to further define the lesion. The differential diagnosis includes bronchogenic cysts, congenital lobar emphysema, and congenital diaphragmatic hernia. The prognosis is largely based on the type of malformation and the extent of disease. Large lesions may cause severe mediastinal shift and even fetal hydrops, or lead to lung compression and pulmonary hypoplasia (◉ *Fig. 416.2*). In these situations, *in utero* intervention



◘ Figure 416.2
Large right-sided CPAM, compressing normal lung (L) and right hemidiaphragm, which is concave (*dotted line*). Sagittal view on fetal MRI

may be the only option: Large cysts can be decompressed with a needle or by cyst-amniotic shunt. If they are microcystic or solid in appearance, drainage is not an option and open fetal surgery with fetal thoracotomy and resection is warranted. Fortunately, more than 70% of CPAMs regress over the course of fetal development and never require fetal intervention. Most peak at 20–24 weeks gestation; if hydrops has not developed, observation is in order, and gradual decrease in size is typically observed by early third trimester. By then, late lung development can occur unimpaired, and most infants have no symptoms at birth.

Bronchogenic cysts are almost always unilocular, rarely become large enough to cause mediastinal shift, and have a very benign course. While they can be detected prenatally, many are found on a routine chest radiograph or unrelated chest CT scan later in childhood, and even in adulthood.

Postnatal management of congenital lung lesions is the subject of some debate. Due to their direct communication with the bronchial tree, some of these lesions can lead to air trapping, recurrent pneumonia, and abscess formation (◉ *Fig. 416.3*). In these cases, drainage may be warranted, followed by resection. Asymptomatic patients should be followed, and elective resection at 1–2 years of age is recommended by many. The risk of infection is

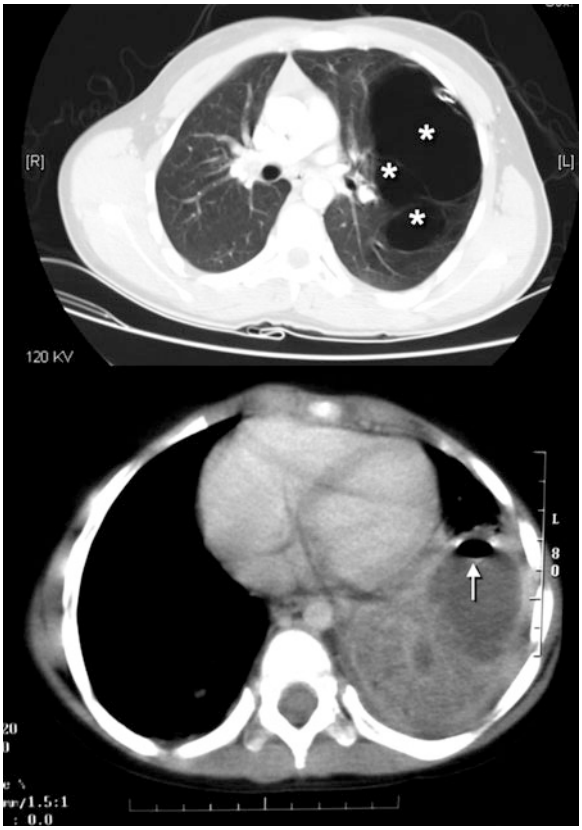


Figure 416.3
CT scan in children with CPAM. Top: several large air-filled cysts within the left lung (*asterisks*), suggesting communication with the tracheobronchial tree. Bottom: different patient with known CPAM of the left lower lobe, presenting with recurrent infections of the lesion (*arrow*: air-fluid level in an abscess)

most often cited as indication, but there appears to be a risk of malignancy as well, albeit very small. The controversy stems from the real malignant potential: Some lesions that were previously reported as malignant transformation in a CCAM were most likely pulmonary blastomas, a malignant tumor of early childhood that is radiologically and histologically similar to CPAM. Extralobar pulmonary sequestrations do not communicate with the tracheobronchial tree and are therefore not at risk of infection. However, 50% of these lesions contain some elements of CCAM – whether that increases the risk of malignancy later in childhood is a matter of debate. Today, elective resection of most of these lesions can be performed using minimally invasive techniques.

Abdominal Anomalies

Intestinal Obstruction

There are many causes of gastrointestinal obstruction in the developing fetus. While the exact nature of the obstruction may be difficult to diagnose in utero, certain patterns and association can help narrow the differential diagnosis. This rarely impacts on clinical decision making, but greatly helps counsel future parents regarding the need for postnatal intervention and long-term outcome. Obstructions can occur anywhere along the gastrointestinal tract, from the foregut to the hindgut, and may be due to atresia (intrinsic obstruction) or extrinsic compression (such as Ladd's bands or an annular pancreas).

Duodenal obstructions can be intrinsic or extrinsic. Duodenal atresia has an incidence of 1 in 30,000 live births and is thought to arise from incomplete vacuolization or recanalization around weeks 8–10 of gestation. This is in contrast to most other forms of intestinal atresias, which are believed to occur as a result of a vascular accident (see below). Recanalization of the duodenum, around the sixth week of gestation, occurs while the dorsal and ventral buds of the pancreas develop and ultimately fuse; this explains why duodenal atresia is often associated with an annular pancreas. Prenatal diagnosis of duodenal obstruction is relatively straightforward, even if its exact cause is not. Obstruction of the second part of the duodenum will cause distension of the proximal duodenum which, together with the stomach, creates a "double bubble" in the upper abdomen of the fetus. Because the obstruction is proximal, swallowed amniotic fluid cannot be absorbed and polyhydramnios is common. This, in turn, increases the risk of preterm delivery. While the majority of duodenal obstructions are isolated, up to 30% of duodenal atresias are associated with trisomy 21. Amniocentesis is therefore offered if the parents want to know whether there is a chromosomal anomaly.

At birth, the clinical features of duodenal obstruction, be it from an atresia or an annular pancreas, are bilious emesis without significant abdominal distension. This is due to the fact that most duodenal atresias occur just distal to the ampulla and the small and large intestine are collapsed. Characteristic imaging findings include gas distension of the stomach and proximal duodenum – the double bubble. If no distal gas is seen, the occlusion is complete – typically, an atresia. Annular pancreas more commonly causes a partial obstruction, and some scattered gas can be seen in distal bowel loops. A partial obstruction is also seen with a perforated duodenal web or extrinsic

compression by Ladd's bands in case of intestinal malrotation. With a classic double bubble and an otherwise gasless abdomen, no further studies are usually necessary, and surgical exploration should be performed. In cases of incomplete duodenal obstruction, the diagnosis may be more difficult as infants may be able to tolerate some feeds. If a partial obstruction is suspected, the patient should undergo an upper gastrointestinal contrast study to delineate the cause. Duodenal atresia itself is not a surgical emergency, but midgut volvulus is – and any suspicion of this requires a fast and efficient workup. Surgical repair can be done by open surgery or minimally invasive laparoscopic techniques. Long-term prognosis in patients with duodenal atresia is excellent and survival should exceed 90%. Mortality is generally due to associated anomalies.

Atresias and other forms of obstruction can occur along the entire intestinal tract, but small bowel atresia is much more common than colonic atresia. Unlike duodenal atresia, intestinal atresia is thought to result from vascular disruption during fetal life. This may be secondary to vascular occlusion, constriction, or even external compression of mesenteric vessels, leading to sterile necrosis of the affected intestinal segment – which in turn is followed by scarless resorption of the dead tissue and proximal and distal blind ends. The more proximal the intestinal atresia, the more likely it is associated with polyhydramnios. More distal obstructions are associated with multiple dilated loops of bowel, hyperechoic bowel, and ascites. The differential diagnosis of intestinal atresia includes malrotation, intestinal duplication, Hirschsprung's disease, and meconium ileus. Meconium ileus, in particular, must be ruled out as it is almost always associated with cystic fibrosis. Moreover, intestinal loops that are distended with thick, tenacious meconium may undergo volvulus, causing vascular occlusion and secondary intestinal atresia. In utero perforation of an intestinal loop secondary to volvulus may cause leakage of meconium into the peritoneal cavity. Although sterile, the meconium produces an intense inflammatory reaction (meconium peritonitis) characterized by ascites and, later, stippled calcifications of the peritoneum. It can also lead to a walled-off collection of meconium-stained fluid termed meconium pseudocyst.

Most cases of intestinal atresia are confirmed shortly after birth, when then infant presents with abdominal distension and vomiting. Passage of meconium in the first 24–48 h does not rule out an intestinal atresia, as the obstruction may be proximal. The diagnosis is typically suspected on the basis of history and physical examination, and confirmed by radiographic studies. The appearance of multiple loops of distended bowel and air-fluid levels suggests a distal obstruction, whereas few loops are seen in a proximal obstruction. A contrast enema can be done to evaluate and confirm the presence of an unused "microcolon" and to look for other, more distal segments of intestinal atresia (*Fig. 416.4*). As with all forms of obstruction, immediate treatment aims at hydration, correction of electrolyte derangements, and gastrointestinal decompression with a nasogastric tube. Operative repair is generally accomplished once the infant is hemodynamically stable and other associated anomalies are ruled out. A primary anastomosis is typically performed if the size discrepancy between proximal and distal ends is moderate. If the proximal pouch is much larger than the distal, collapsed bowel, a temporary stoma may be necessary.

If meconium ileus is suspected as the source of the obstruction, workup and treatment of the infant may have to be altered. An abdominal radiograph at birth will show numerous dilated loops of bowel, but because the thick meconium does not layer out, air-fluid levels will be absent. Instead, a "soap bubble" appearance is seen as a result of gas trapped in the viscous meconium. Patients with meconium ileus may present with severe dehydration, and intravenous resuscitation is crucial. If the infant is stable and in the absence of meconium

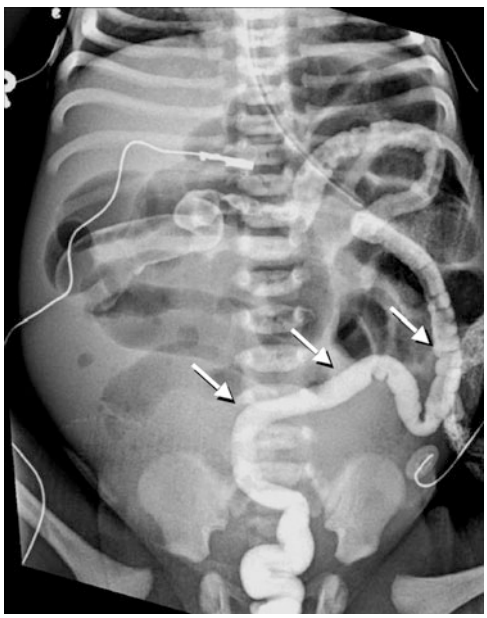


Figure 416.4
Intestinal obstruction in the neonate, secondary to meconium ileus. Note dilated gas-filled small bowel loops and a small, unused "microcolon" (*arrows*) on a contrast enema study

peritonitis, nonoperative treatment may be attempted. Retrograde rectal irrigation with hyperosmolar water-soluble contrast material may loosen the inspissated meconium. The need for adequate hydration cannot be overstated, as these agents have significant hygroscopic properties. If attempts at nonoperative management are unsuccessful, surgical intervention is required. The prognosis of meconium ileus is good, but the long-term outlook is determined by the underlying cystic fibrosis. Of note, the presence of meconium ileus does not represent a worse prognosis for cystic fibrosis – and may allow diagnosis and preventive measures even before any respiratory problems arise.

Hepatobiliary Anomalies

Choledochal cysts are congenital anomalies of the biliary tract characterized by either single or multiple cystic dilatations of the extrahepatic or intrahepatic bile ducts. The incidence of this disease ranges from 1:100,000 live births in Western countries to as high as 1:1,000 in Japan, with an overall female predominance. Most cases are diagnosed postnatally, sometimes in late childhood and even adulthood. However, with the evolution of ever-better fetal ultrasonography and magnetic resonance imaging, more cases are diagnosed *in utero*.

There are many theories to explain the pathogenesis of choledochal cysts. The most popular theory is that of an abnormal arrangement of the pancreaticobiliary ductal system in which the pancreatic duct enters the common bile duct at an abnormal angle. This allows reflux of pancreatic enzymes resulting in damage to the ductal wall and cystic dilation. Alternative theories implicate the common portion of the pancreatic and biliary ducts, which may be longer than normal and predispose to bile duct damage by pancreatic secretions, or a congenital defect in the proliferation of the bile duct epithelium. The most common clinical presentation is jaundice in the neonatal period or beyond, with or without a palpable abdominal mass. *In utero* detection of a cystic mass in the right upper quadrant may lead to the suspicion of a choledochal cyst. Fetal MRI may further delineate the hepatobiliary anatomy and confirm the diagnosis. This early detection can allow prompt diagnosis postnatally and lead to early referral to a tertiary care center. A cyst at the confluence of the right and left hepatic ducts may also be a sign of biliary atresia, which has a more guarded prognosis and requires expeditious workup after birth.

Postnatal ultrasonography of a suspected choledochal cyst may demonstrate dilated extrahepatic (and often intrahepatic) biliary ducts. The diagnosis may be confirmed by computed tomography with intravenous and oral contrast or, more commonly today, by magnetic resonance choledochopancreatography (MRCP). A technetium-99 m diisopropyliminodiacetic acid (DISIDA) scintigraphy can be performed to assess bile drainage. The differential diagnosis includes biliary atresia, hepatic cysts, and gallbladder duplication. Drainage of the cyst is no longer considered standard of care as patients may go on to develop cholangitis and biliary cirrhosis. Surgical resection of the cyst with enteric drainage via a Roux-en-Y hepaticojejunostomy is the most effective treatment. The prognosis of this disease largely depends upon the presence of cirrhosis or portal hypertension prior to surgical resection.

Genitourinary Anomalies

Obstructive Nephropathy

Fetal hydronephrosis is one of the most common findings on prenatal ultrasound. However, it is usually mild and its prognosis is excellent. Prenatal detection allows early postnatal diagnosis and management. In most cases, the condition is self-limited, but close follow-up by a pediatric urologist is necessary to protect against recurrent infections and deterioration. In some cases, the hydronephrosis is severe and surgical intervention is required in infancy or beyond.

In case of bilateral ureteral or renal disease, fetal renal function may be impaired. Since amniotic fluid is mostly fetal urine, bilateral urinary tract obstruction or anuria leads to oligo- or anhydramnios which, as outlined above, results in extreme pulmonary hypoplasia incompatible with postnatal life. The exact cause of the urinary obstruction is less important than its effect. Hydronephrosis and hydroureters in the presence of normal amniotic fluid volume is best monitored and left alone until after delivery. On the other hand, oligohydramnios and evidence of urinary obstruction can be treated *in utero* by vesico-amniotic shunting, typically under ultrasound guidance. Bilateral urinary tract obstruction occurs mostly in males, and is almost always due to posterior urethral valves.

While vesico-amniotic shunting theoretically bypasses the obstruction and relieves pressure on the urinary system, renal outcome is often compromised, and many of these infants go on to develop renal failure. However, restoration of amniotic volume can be lifesaving as it prevents the progression to pulmonary hypoplasia. The most difficult therapeutic decision is patient selection: If renal

failure is too advanced, urine production may no longer be sufficient to restore amniotic fluid volume. Several tests of fetal renal function exist, including ultrasound appearance of the kidneys and fetal urinary electrolyte and beta-2-microglobuline determination – but no test can predict renal function with sufficient accuracy.

Ovarian Cysts

The female fetus is sensitive to maternal hormonal stimulation, and small cysts of the fetal ovaries are not uncommon. With the dramatic improvements in fetal imaging, fetal ovarian cysts are diagnosed increasingly often. The differential diagnosis includes any other abdominal cyst, including choledochal cyst, intestinal duplication, mesenteric cyst and lymphatic malformation, and neurenteric cyst and liver cyst. However, the presence of a cyst in the pelvis in a female fetus is almost always ovarian in origin.

As long as it remains relatively small, observation is in order, and parents can be reassured that the cyst will regress after birth, once maternal hormones no longer stimulate the infant's ovaries. However, larger cysts are at risk of torsion and adnexal ischemia (*Fig. 416.5*). A cyst diameter of 4–5 cm has been used as predictor of torsion, but smaller cysts have been known to twist, while many larger ones have not. Fetal intervention, in the form of ultrasound-guided cyst aspiration, had been proposed in the past. Now, however, most specialists agree that the theoretical risk of torsion of one of two ovaries is not worth the risk of fetal complications, infection, or even pregnancy loss. Large cysts are best monitored closely, however, and ultrasound-guided aspiration after birth is recommended.

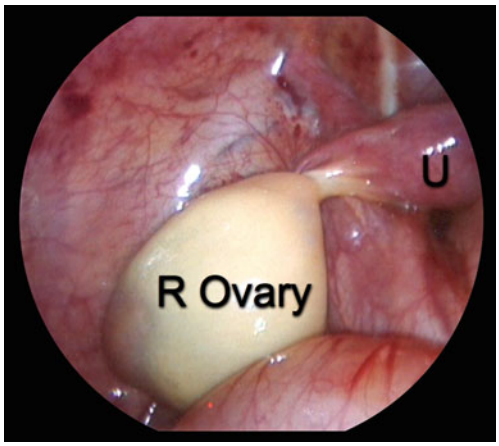


Figure 416.5
Torsion and necrosis of the right ovary and salpinx in a newborn (laparoscopic view). Prenatal torsion of a large ovarian cyst was suspected by ultrasound. U: uterus

Parietal Anomalies

Abdominal Wall Defects

Abdominal wall defects (AWD) are commonly diagnosed by prenatal imaging. The two most common types of AWD are gastroschisis and omphalocele. Other rare types include ectopia cordis (isolated, or as part of a pentalogy of Cantrell) and cloacal exstrophy.

Gastroschisis is a defect of the anterior abdominal wall, which allows evisceration of the intestines. The defect is typically small and is almost always located to the right of an intact umbilical cord. The incidence of gastroschisis is 1 in 3,000 live births. Males and females are affected equally, and most are born to young mothers. Gastroschisis is not typically associated with other congenital anomalies, except intestinal atresia, which occurs in 5–10%. Because atresia in this setting is likely the result of mesenteric vascular compromise through a small abdominal wall defect, it is more a complication of gastroschisis than an associated anomaly. In extreme cases, the vascular strangulation occurs at the root of the mesentery, leading to necrosis of the entire midgut (jejunum to mid-colon) and devastating short-bowel syndrome. The pathogenesis of gastroschisis is not clearly understood. Some have implicated early disappearance of a right umbilical vein (in the young embryo, umbilical veins are paired), or weakness of the umbilical cord at the site of the vitelline vessels. The pathogenesis is distinct from that of omphalocele, which is an abnormal herniation into the umbilical cord. Most cases of gastroschisis are diagnosed *in utero*. Ultrasonography demonstrates a cluster of bowel loops protruding into the amniotic cavity, lateral to a normal umbilical cord insertion. Early diagnosis allows referral to a tertiary care medical center for delivery. While altering the place of delivery ensures a smooth transition to postnatal care, altering timing (preterm) or mode of delivery (Cesarean section) has not proven beneficial. Some have even advocated aggressive fetal treatment by exchange amnioinfusions, in the belief that "caustic" amniotic fluid causes the typical damage to the intestinal wall and mesentery. However, the correlation between exposure to amniotic fluid and intestinal "peel" has never been confirmed, and prenatal intervention introduces a risk to the pregnancy that is difficult to justify.

At the time of delivery, these infants require neonatal intensive care monitoring. They have high sensible loss because of the exposed viscera, which also places them at high risk of hypothermia. The most expeditious and safe maneuver is to place the infant up to the chest into a sterile bowel bag. At the bedside, a silicone rubber (Silastic®) "silo" can be placed around the visceral contents and sealed intra-abdominally around the defect with a watertight spring-loaded elastic ring. The abdominal cavity adapts to the gradual reduction of the viscera (by gravity and gentle manual compression); once near-reduction of the visceral contents has been achieved (typically at 1 week of life), a delayed primary repair is performed in the operating room. Parenteral nutrition is crucial as these infants typically have an ileus, which may last for weeks. Rarely, the defect and the herniation are small enough so that primary repair can be achieved at birth. However, the wide availability of preformed spring-loaded silos, which do not require abdominal wall dissection or suturing, has made delayed repair the preferred approach in most cases. The survival rate for patients born with gastroschisis is greater than 90% for those who have adequate resuscitation, nutrition, and surgical intervention. Morbidity is largely due to sepsis (including necrotizing enterocolitis), short-bowel syndrome if multiple atresias are present, and TPN-related complications. An extreme form of abdominal wall defects is associated with extreme spine deformity and sometime grotesque truncal, facial, or limb anomalies. This limb-body-wall-complex or amniotic band syndrome (ABC) is due to early gestation amniotic disruption and is not compatible with life.

Omphalocele is also the result of an abdominal wall defect, but herniated viscera are typically covered by an umbilical membrane. The defect may be larger than that of gastroschisis, and the umbilical cord inserts into the sac. The incidence of omphalocele is 1 in 5,000 live births. In contrast with gastroschisis, infants with omphalocele are more likely to have other congenital anomalies. These include Pentalogy of Cantrell (omphalocele, diaphragmatic defect, sternal cleft, pericardial defect, and cardiac anomalies), cloacal exstrophy (also termed OEIS, for omphalocele-exstrophy-imperforate anus-spinal defects), and chromosomal disorders, including trisomies 13 and 18. The diagnosis of omphalocele is typically made on prenatal ultrasound, which demonstrates a mass anterior to the abdominal cavity at the site of cord insertion (*Fig. 416.6*). The abdominal cavity itself may appear scaphoid, and the relative paucity of abdominal contents accounts for a small abdominal circumference by ultrasound measurement. The presence of an omphalocele on prenatal ultrasound should raise the suspicion of other associated anomalies.

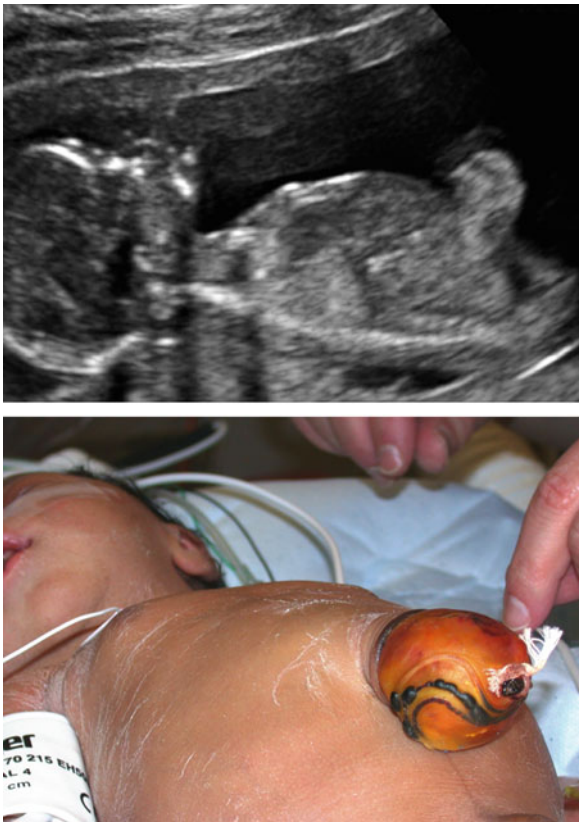


Figure 416.6
Small omphalocele. *Top*: prenatal ultrasound showing a small abdominal wall defect. *Bottom*: same infant at birth; note thrombosed umbilical arteries on the surface of the omphalocele sac

The clinical presentation and management varies with the size of the omphalocele. Omphaloceles that contain a large portion of the liver, in addition to hollow viscera, are termed "giant" omphaloceles and are more difficult to manage than those with a smaller defect. Herniation of the liver creates a tortuous and angulated inferior vena cava in which attempts at acute reduction can impair venous return and compromise the infant's cardiovascular function. These patients will require a more gradual reduction and possibly a staged abdominal wall closure. Morbidity varies based on the size of the defect and the presence or absence of liver within the sac. Mortality is most often related to associated congenital anomalies.

Open Neural Tube Defects (Spina Bifida)

The incidence of primary neural tube defects is around 1 in a 1,000 live births, but varies with ethnicity. There is

a higher prevalence in Americans than in Asians, and those of Irish descent have reported rates as high as 1 in 100 live births. The most common primary neural tube defect is a myelomeningocele (MMC), which is a lesion that contains both meningeal and neural components. It results from the failure of the neural tube to fully close during the fourth week of gestation. This leads to exposure of the neural plate along the midline of the back. Widespread prenatal screening with maternal serum markers (maternal serum alpha-fetoprotein, MSAFP) and ultrasonography have greatly increased prenatal detection, while vitamin B12 supplementation of a pregnant woman's diet has greatly reduced its incidence. Screening studies (MSAFP) and ultrasonography are typically followed by amniocentesis for karyotyping and to measure AFP and acetylcholinesterase levels. Fetal MRI offers higher resolution images of the defect. The majority of patients with myelomeningocele have a defect along the lumbar area and present with a cystic mass containing the neural placode, arachnoid, dura, nerves, and cerebrospinal fluid. The level of the lesion dictates the level of the corresponding motor dysfunction, which can range from mild gait problems to paralysis and stool and urine incontinence. Associated anomalies almost always include bifrontal indentation of the skull ("lemon" sign), changes in the cerebellar anatomy ("banana" sign), and some degree of hindbrain herniation (Chiari II malformation). While myelomeningocele is not a lethal condition, some of its complications (hydrocephalus and acute hindbrain herniation) can be devastating in infancy and early childhood. Prenatal diagnosis allows referral to a tertiary care facility with neurosurgical support, and discussions regarding timing and mode of delivery.

At birth, infants with an open neural tube defect need to be assessed for the level of the lesion, and care should be taken to keep the defect sterile. Treatment is aimed at early closure of the defect, typically within the first 72 h of life. The prognosis of patients born with spina bifida is highly variable and depends on the level of the lesion, along with the presence or absence of any other severe central nervous system anomalies. In 2011, the results of the 8-year randomized controlled "Management of Myelomeningocele Study" (MOMS trial) were published. It was revealed that *in utero* repair of the defect delayed the need for ventriculoperitoneal shunting and improved motor function at 30 months. However, infants who had undergone prenatal surgery were born more prematurely than controls, and maternal morbidity was not insignificant.

Fetal Tumors

Fetal tumors are very rare – and most are benign. They can cause serious harm to the fetus and the neonate, however, depending on their location and their size. The most common tumors are teratomas, neuroblastomas, and lymphatic/vascular malformations.

Teratomas

By definition, teratomas contain derivatives of all three primitive cell layers (endoderm, mesoderm, and ectoderm). They typically occur in the migration path of totipotential cells along the primitive streak – but they can also migrate cephalad of the umbilical cord, giving rise to thoracic and cervical tumors. Two major types have perinatal significance: sacrococcygeal teratomas and cervical tumors.

Sacrococcygeal teratomas arise from the primitive node of Hensen, and can be predominantly intrapelvic or external. The intrapelvic tumors may be diagnosed as a cystic mass and obstruct the urinary system, giving rise to bilateral hydronephrosis. Rarely, they may cause intestinal obstruction as well, as evidenced by dilated intestinal loops on prenatal ultrasound. Sacrococcygeal teratomas with a large external component can cause significant shunting of blood away from the fetus, leading to cardiac failure and hydrops. Often, placentomegaly is present, and the mother is at a higher risk of preeclampsia – a phenomenon dubbed "mirror syndrome," as both mother and fetus exhibit signs of cardiovascular failure. As long as hydrops is not present, no intervention is necessary and the course of pregnancy is typically benign. If the tumor is very large, Cesarean section may be indicated to avoid rupture and bleeding from the middle sacral artery (a branch of the aorta). Despite the sometimes disfiguring effect of the tumor on the perineal structures, complete surgical resection is almost always feasible and patients do well postoperatively. Gross continence problems are rare, but constipation is not uncommon. Up to 10% of sacrococcygeal teratomas contain malignant elements. This incidence increases with age, and recurrence must be avoided by complete excision of all external and internal tumor components, as well as the coccyx.

If the fetus shows signs of impending hydrops (typically, before 25 weeks gestation), or there is evidence of preeclampsia, urgent intervention is indicated. Open fetal surgery and resection of the tumor may be the only option, other than termination – but is a very invasive

undertaking, best performed in specialized centers. Attempts at endoscopic or ultrasound-guided occlusion of the tumor's feeding vessels have been described, but results have been disappointing.

The second most common location for fetal teratomas is the neck. Cervical teratomas, while mostly benign, can become very large and produce significant compression and displacement of neck structures. The biggest threat comes at the time of delivery – if the tumor is large enough to obstruct the airways, it is unlikely that the infant can be intubated in a timely fashion (◉ *Fig. 416.7*). In these cases, a planned, modified Cesarean section allows the team to secure an airway even before the umbilical cord is clamped. This approach, initially termed Operation On Placental Support (which makes for an unfortunate acronym), is now better known as EX-utero/InTrapartum, or EXIT procedure. It requires a lot of preparation and coordination between the obstetrical and neonatal teams to allow sometimes prolonged procedures while the uterus remains relaxed, the placenta functional, and the fetus partially exteriorized. EXIT procedures are also recommended for other forms of upper airway obstruction, including large lymphatic or vascular malformations, extreme hypognathism, and fetal tracheal occlusion to treat congenital diaphragmatic hernia (see above).

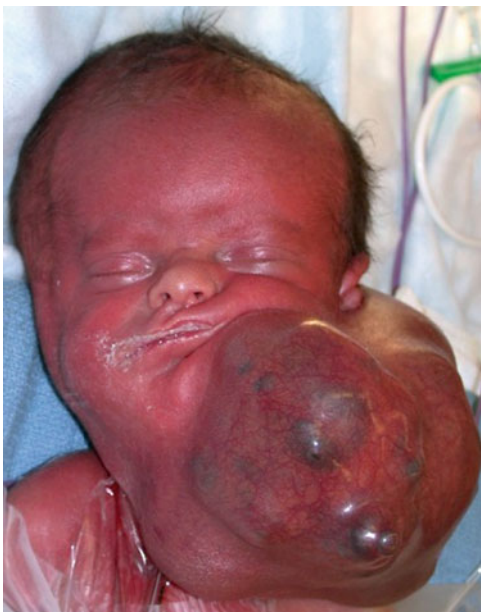


Figure 416.7
Large cervical teratoma distorting the normal head and neck anatomy. If diagnosed in utero, an EXIT procedure may be indicated to assure airway control before the umbilical cord is clamped

Neuroblastoma

Neuroblastoma is the most common of the very rare malignant tumors of the fetus. These are tumors of neural crest origin and may arise anywhere along the sympathetic chain, the most common site being the adrenal gland. The incidence of these tumors is about 1 in 10,000 live births, with a slightly higher rate in males. When detected prenatally, these are seen as adrenal masses, most often during the third trimester. The differential diagnosis includes adrenal hemorrhage and developmental anomalies such as intestinal duplications and subdiaphragmatic pulmonary sequestrations. Based on autopsy series, up to 1% of fetuses have foci of neuroblastoma within the adrenal glands; however, they usually undergo apoptosis during the third trimester and regress spontaneously. Although malignant, congenital neuroblastoma most often has a course that is even more favorable than infant neuroblastoma. The presence of an adrenal mass on fetal ultrasound warrants close follow-up throughout the pregnancy and once the infant is born.

Vascular and Lymphatic Malformations

Vascular and lymphatic malformations may be seen on prenatal ultrasound as complex cystic lesions. These vascular anomalies are some of the most common birth defects seen worldwide. During embryonic development, the vascular structures develop in close relation to the lymphatic system, and errors in development of these structures account for vascular and lymphatic malformations. Lymphatic malformations (also referred to as lymphangiomas or cystic hygromas) are most commonly located in the upper part of the body, with a predilection for head and neck. When they occur in the abdominal cavity, the differential diagnosis includes mesenteric cysts, enteric duplication cysts, choledochal cysts, teratomas, neuroblastomas, and urachal cysts. These lesions are classified according to the predominant vessel involved and mixed lesions are labeled with each involved channel. In extreme cases, large malformations can lead to fetal hydrops. These lesions do require close follow-up and further evaluation after birth.

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417 Chest and Abdominal Wall Anomalies

Kenneth S. Azarow

Chest Wall Anomalies

Definition

Thoracic body wall anomalies have been grossly characterized into depressions: pectus excavatum, protrusions: pectus carinatum, and mixed deformities resulting in either protrusion or depression with rotation. Fusion deformities are those resulting in sternal cleft; the most severe form resulting in Cantrell's pentalogy: cleft sternum, ventral diaphragmatic hernia, omphalocele, and ecotpia cordis with the pericardial defect being at the apex, and intracardiac defects. Rib deformities can also be associated with soft tissue defects as in Poland's syndrome characterized by the absence of costal cartilages or portions thereof form the second to fourth ribs, hypoplasia and absence of the nipple and breast, minimal subcutaneous fat, absence of axillary hair, absence of the pectoralis minor muscle, and absence of the costosternal portion of the pectoralis major muscle.

Etiology

Although the etiology of these disorders was once debated in the literature, it is now generally agreed that pectus excavatum and carinatum deformities are a result of dysmorphic growth of costal cartilage, resulting in an abnormal position/rotation of the sternum. As a result, these defects may or may not be recognizable at birth and are often accentuated during growth spurts. Sternal cleft is an embryologic phenomenon caused by failure of lateral mesodermal plates to fuse during the first weeks in utero. This deformity is recognizable at birth, and usually presents in isolation and is not typically part of any syndrome.

Epidemiology

The prevalence of pectus excavatum is approximately 1/400 live births. There is no known genetic link, but 40% of patients with pectus excavatum (PE) report that a family member has a chest wall deformity. It is more common in males, with a male-to-female ratio of approximately 5:1. Most series report that excavatum is more common than carinatum at rates 6–10:1. A true incidence of sternal cleft cannot be accurately estimated as the condition is considered rare. Most series report only a handful of cases. Based upon the volume of reports and the extensive nature of the experiences published, the incidence of chest wall deformities appears to be higher in South America although specific epidemiologic data is lacking. One study estimates the incidence of pectus deformities as high as 2% in the city of Manaus, Brazil.

There is no known chromosomal abnormality associated with pectus excavatum, but it has been reported in conjunction with Marfan's syndrome, Ehlers–Danlos syndrome, osteogenesis imperfecta, syndactylism, club foot, and Klippel–Feil Syndrome. Of interest, over one fourth of these patients have scoliosis.

Pathology and Clinical Manifestations: Symptoms, Signs

Pectus deformities result in a significant cosmetic deformity with consequential psychological effects that affect social development. From a physiologic perspective, there is ongoing controversy on the relative impact of the restrictive components of the deformity. In pectus excavatum, the anterior-posterior diameter of the chest is diminished and the heart is often displaced to the left. Subjectively, patients complain of dyspnea with exertion, diminished exercise capacity, chest pain, palpitations, frequent upper respiratory infections, and wheezing. A disproportional number of patients are diagnosed with exercise-induced asthma based solely on subjective descriptions of possible symptoms. Pulmonary function testing usually reveals a mild restrictive pattern, with total lung capacity (TLC), forced vital capacity (FVC), and vital capacity (VC) in the low-normal range. The severity of the pectus deformity correlates roughly with the reduction in VC and TLC. The ratio of forced expiratory volume in 1s (FEV1) to FVC is normal, indicating absence of obstructive disease. Abnormalities on the electrocardiogram have

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been described, namely, right bundle block and right axis deviation. There is a known association between PE and mitral valve prolapse.

For the patients who complain of exercise intolerance, the results of exercise testing have been inconclusive. Some investigators found that upon exercise testing on a treadmill, there were no objective differences in cardiorespiratory function or aerobic capacity between patients with excavatum and control subjects. In fact, subjective exercise intolerance may be the result of physical deconditioning. Thus, others have controlled for level of conditioning and found the maximum oxygen uptake (VO2max) to be 75% of predicted, suggesting mild impairment. One theory suggests the right atrium and ventricle are compressed by the sternum when upright, causing decreased filling and subsequent inability to increase stroke volume and oxygen delivery during exercise. In fact, compression and reduced filling have been documented in several studies. In addition, others have demonstrated that the oxygen uptake (VO2) plateau in the supine position was higher than in the sitting position, and supine exercise stroke volume was higher than sitting exercise stroke volume. Therefore, it is likely that some patients with severe pectus excavatum have a real exercise limitation that is cardiac in origin. Contradictions in the literature are probably related to differences in conditioning based on psychosomatic limitations induced by the strong aversion to exposure and participation, differences in the severity of disease, and difficulty obtaining true exercise capacity independent of patient effort. Whether or not the situation is improved by surgery is discussed later in this chapter.

Although most patients with sternal cleft are asymptomatic, cardiopulmonary effects of cleft sternum may result from altered respiratory dynamics, as there is paradoxical motion of the anterior chest. Some have reported cyanosis, dyspnea, and recurrent pneumonia. However, the main impact of sternal cleft is the potential for mediastinal/cardiac trauma since the protective function of the "breast bone is absent."

Diagnosis

Excavatum and mixed deformities: Morphologic description has been helpful to classify the deformity. Terms such as cup or saucer refer to localized versus diffuse depression. Short versus long length of the depression can assist in determining extent of surgery or number of corrective bars to be utilized in the repair. Symmetry and torsion refer to the rotation of the sternum, while slope and position of maximal depth can imply the potential underlying malposition of the heart. Unique patterns such as "steer horn depression" have also been coined to describe these defects.

Carinatum and mixed deformities: One of several patterns may be noticed and are classified as follows: Type I or chondrogladiolar deformities are also known as keel chest and involve protrusion of the gladiolus and inferior cartilages. Type II or chondromanubrial deformities are much less common and are also called pouter pigeon breast. This type is described as prominence of the manubrium and protrusion of the superior costal cartilages. Type III or lateral pectus carinatum is asymmetric deformity characterized by unilateral protrusion or rotation of the sternum.

There are three types of sternal cleft that may be noted on examination. *Superior cleft sternum* is most common. It is an incomplete defect involving the upper sternum or manubrium. The inferior aspect of the sternum is fused, creating a "U" or "V" type of deformity. In the "V" deformity, there is often only a narrow bridge at the xiphoid process, and this is sometimes referred to as a *subtotal sternal cleft*. Patients with this abnormality may also have a midline raphe or band-like scar that extends to the umbilicus. *Complete cleft sternum*, also called bifid sternum or sternal fissure, is the rarest type, and the sternal bars are completely separate. There may also be diastasis of the rectus muscles. *Inferior cleft sternum* is also an incomplete defect: The upper sternum is fused, but there is a gap inferiorly. This type may be associated with other abnormalities of midline fusion.

Evaluation

One should obtain a history of the duration and progression of the sternal depression, family history, any other medical conditions, and a thorough review of systems, especially focused on cardiac and pulmonary symptoms/disease. Diagnosis is easily made on physical examination, with a prominent depression deformity of the sternum. One should also carefully note the presence or absence of scoliosis or a heart murmur. It is essential not to undertake a course of treatment until such associated conditions such as Marfan's are ruled out.

The deformity may be further characterized by a computed tomography (CT) of the chest. The most commonly used index is also known by some as the "Haller index," which is derived from a CT image through the deepest part of the pectus deformity. The transverse diameter of the chest is divided by the anterior-posterior diameter at this level. In Haller's original report, patients who had

operative correction of PE had an index greater than 3.25. Preoperative chest x-ray is mandatory, and the use of CT scan is dependent on individual practice. It rarely affects management and some argue that it exposes children to unnecessary radiation. However, some view it as a critical tool in preoperative decision making and planning as well as postoperative follow-up.

Further workup may include pulmonary function tests (resting spirometry), exercise testing, and echocardiography. Some order these tests as a matter of routine, while others selectively obtain them if the patient complains of significant respiratory symptoms or if a heart murmur is detected on physical examination.

Specific Treatment

For 50 years after Ravitch's paper in 1949, his technique was considered the standard for both excavatum and carinatum repair. The procedure is usually done through a transverse inframammary incision (vertical incisions in the midline have also been used). Skin flaps are raised, followed by subpectoralis flaps to expose the deformed cartilages. The deformed cartilage is resected in the subperichondrial plane, using care to leave some cartilage laterally near the growth plate and the entire perichondrium in place. This must be done bilaterally and symmetrically, even if only one side appears deformed. The retrosternal space is mobilized bluntly. A wedge-shaped transverse osteotomy is made on the anterior sternum at the superior aspect of the depression and carried down to the posterior table, which is then fractured. Some advocate the use of a retrosternal bar, first made popular by Rehbein and Adkins, while others oppose this technique. This splint or strut must eventually be removed (usually after 6 months) and has been known to dislodge and migrate. The sternal osteotomy is then closed with heavy nonabsorbable suture; to correct carinatum defects a wedge of cartilage or bone in the osteotomy to obtain a better contour. Subcutaneous or pleural drains (if the pleura are entered) are placed. The pectoralis muscles are closed in the midline and approximated to the rectus abdominus muscle inferiorly.

In 1998, Nuss and colleagues reported a new technique, the minimally invasive repair of pectus excavatum. By placing a convex steel bar under the sternum through small bilateral thoracic incisions, he was able to mold the chest wall over a 1–3-year period akin to braces molding a patient's bite. The placement was directed at the deepest point of deformity from mid-axillary to mid-axillary line. Initially, the bar was placed blindly through a substernal tunnel, but after one report of myocardial injury, many now perform the procedure using video thoracoscopy or with a third, subxiphoid, incision to manually guide the bar. Lateral stabilizers are now used to fix the bar and prevent displacement. More than one bar is used for severe deformities in older patients where cartilaginous ossification may have begun. Bar removal is performed after 2 years as an outpatient procedure.

The primary repair for sternal cleft varies somewhat based on the type of cleft. Vertical midline incision is made and the skin and sternal bands dissected away from the pericardium and pleura. In complete cleft sternum, the bands may usually be brought together as one closes a midline sternotomy. Superior cleft sternum requires separation of the inferior bridge, often excising a wedge of cartilage, thus converting the defect to a complete one, and then approximating the two bands. Division of the sternoclavicular joints may also facilitate primary repair. The pectoralis muscles are then united and closed in the midline.

Patients who have delayed referrals require more complex repairs. Young patients have pliable cartilage and may be manipulated so that sliding lateral chondrotomies followed by approximation of the sternal bands are possible. If the costal cartilages are not pliable enough, then it is not possible to approximate the sternum by mobilizing and advancing ribs; this can be circumvented by several other techniques that have been described. Gaps between the sternal bands can be filled with autologous chondral or rib graft. In cases where the pectoralis muscle does not come together in the midline, a sheet of Marlex mesh, pectoralis muscle flap, or acrylic plaque has been used.

The surgical approach to chest wall deformities has recently come full circle with the popularity of external bracing for the repair of pectus carinatum. First reported out of Brazil in 1992, the use of an external brace, in lieu of the Ravitch procedure described above, has gained popularity around the world. Using the brace to slowly remold the chest wall requires a schedule starting at 23 h/day for at least 3 months and then tapering down to 12 h a day over the next 1–2 years. If the patient complies with this schedule, a success rate of 80% is reported. However, approximately 20% of patients refuse to wear the brace outright and another 20% can be expected to be noncompliant.

Prognosis

Functional outcome after pectus repair has been the source of controversy and debate for years. As discussed above, patients have mild restrictive lung disease and diminished exercise tolerance, probably due to sternal

compression of the right atrium and ventricle. Anecdotally, some patients subjectively feel that their dyspnea, exercise tolerance, and chest pain improve after operation. However, it is not clear whether this is a psychological or a physical phenomenon. Several papers have compared cardiopulmonary parameters pre- and postoperatively. Most have found that pulmonary function tests worsen after open repair, with a decrease in TLC, residual volume (RV), functional residual capacity (FRC), and FEV1. This is likely due to a limitation of thoracic cage expansion and decreased chest wall compliance after operation. Others have reported that pulmonary function did not worsen in their patients post-op, perhaps because they did a less extensive operation. While pulmonary function does not improve with open pectus repair, several investigators have found that exercise tolerance, VO2max, and SV do increase after operation. However, this conclusion is not universally accepted. Most evidence seems to indicate that patients show physiological (as opposed to symptomatical) improvement after open pectus repair, not because of improvement in lung function but due to an increase in stroke volume during exercise. The cardiopulmonary effects of the Nuss procedure have now been reported and controversy still remains. Nuss' group reported that pulmonary function tests significantly improved in 72% with the bar in place and remained so after bar removal. Sigalet showed a sustained improvement in aerobic activity after bar removal. Aronson et al. found exactly the opposite: Pulmonary function was neither improved nor harmed by the procedure.

The conclusion that can be drawn at this time is that pectus excavatum patients have an aerobic limitation that can be measured. This limitation can be improved with surgical correction of the defect by objective measurements of pulmonary function and aerobic activity in a monitored setting. An unknown percentage of patients will achieve symptomatic relief and increase their exercise tolerance. However, whether the measured increase in pulmonary function or stroke volume during exercise relates to a true symptomatic relief that can be reliably predicted remains a controversy today.

Future Development

Despite its moniker of "minimally invasive," the post-procedure pain associated with Nuss bar placement for pectus excavatum can be significant. Given the success of external bracing in the treatment of pectus carinatum, the future of chest wall remolding for depression deformities may possibly be with an external approach that can reduce pain. Such a concept was introduced by Harrison in the form of magnetic energy to reposition of remold the chest. While in its infancy, this concept quite possibly represents the future direction of structural reshaping of the thoracic wall.

Abdominal Wall Anomalies

Definition/Classification

An umbilical hernia consists of protruding viscera through the umbilicus which is covered by normal skin. An omphalocele on the other hand is an opening bound by the umbilical ring with protruding contents covered by a double layer of cord material without any normal skin. The inner layer consists of peritoneum and the outer of amnion. In between these layers is the characteristic embryonic connective tissue ("Wharton's Jelly"). The cord and its vessels insert onto the membranous sac as opposed to the abdominal wall. The size of the defect subdivides omphalocele into hernia of the cord (<2 cm), omphalocele (2–5 cm), and giant omphalocele (>5 cm). Gastroschisis was classically thought to be a defect to the right of the umbilicus and not contiguous with the umbilical ring; however, now, that concept is being challenged through several embryologic and fetal observations. What is not challenged is the concept that the cord and its vessels insert onto the abdominal wall and the defect is usually within the right side of the umbilical ring. Typically, no hernia sac is present and the bowel is open to the air. Prune belly refers to muscular absence (either complete or partial) resulting in an inability to maintain a normal abdominal contour.

Etiology

Typically, omphalocele is thought to occur due to a genetic predisposition that makes the fetus arrest umbilical development secondary to some event that happens prior to the tenth week of life. This prevents the abdominal contents from returning to the abdomen and in doing so prevents the lateral body wall folds from closing. This theory also explains why omphalocele is associated (>75% of the time) with many other defects that result from developmental arrest during the first trimester.

The etiology of gastroschisis remains an enigma. Originally thought to be due to a ruptured omphalocele, over the years, it was realized that this was a separate entity. It is generally considered to be an isolated defect with an incidence of associated genetic anomaly of approximately 2%. Theories such as a defect in the dorsal myotomes

preventing complete rectus sheath formation to ischemic injury with the right umbilical artery or umbilical vein being implicated have been popular. Toxins and environmental influences have become popular as the incidence has increased among younger mothers without access to prenatal care. Finally, we have come full circle with the umbilical ring being implicated again. It has been observed that if left alone once the bowel is reduced, the umbilicus returns to its normal size over time and the abdominal wall defect will spontaneously close mimicking the umbilical ring closure during development.

Theories surrounding prune belly range from a secondary defect due to increased abdominal wall pressure from urinary tract anomalies to a first trimester event that prevents the lateral somatic mesoderm from invading the ventral body wall. In any event, there are no familial tendencies and most attention is focused on the development of the urinary system which is always anomalous.

Epidemiology

Historically, the teaching was that omphalocele was 3 times more common than gastroschisis with an incidence of approximately 1:3,000 live births for omphalocele. Worldwide this incidence for omphalocele remains stable. Gastroschisis on the other hand has increased in epidemic proportions in the USA and around the world. By 2000, the incidence was reported as 1:2,000, surpassing that of omphalocele. Furthermore, the incidence is continuing to rise: Over the past 20 years, it has increased at least by threefold. The true incidence is still changing and at present is unknown. Theories such as the increasing rates of teenage pregnancy, geographic epidemic tendencies, and increased use of recreational drugs during pregnancy remain inconclusive. What is clear is that the incidence of gastroschisis is higher with maternal age under 20 and increases with environmental exposures. Smoking and other vasoactive substances (cocaine and pseudoephedrine) have been classically implicated. In the state of Washington, when women resided within 25 km of known surface water impregnated with atrazine (a common agricultural chemical), there was an increased prevalence of gastroschisis with an odds ratio of 1.6.

Pathogenesis

Gastroschisis usually presents as an isolated defect. Any associated anomalies are usually gastrointestinal in nature and directly related to the abdominal wall defect. IUGR is a common association however. Approximately 10–15% of these infants will have an associated bowel atresia that is caused by an ischemic event secondary to a tenuous blood supply coursing through the abdominal wall defect. Complete bowel loss is also seen in the instance of umbilical ring closure around the defect, thus cutting off all mesenteric flow to the protruding GI tract. The incidence of an associated anomaly outside of the GI tract is under 2% with gastroschisis.

Omphalocele on the other hand has a strong genetic association. Approximately 75% have associated anomalies. In 30% of cases, a trisomy will be present. Trisomies 13, 14, 15, 18, and 21 are all reported to have omphalocele associated with them. Ten percent of cases are associated with Beckwith–Wiedemann syndrome (macroglossia, organomegaly, hypoglycemia, and an increased risk of developing childhood tumors). The most commonly associated anomaly is an intracardiac defect.

Pathology

The primary pathologic process in gastroschisis is gastrointestinal dysfunction. Decreased absorptive capability and decreased motility is the hallmark of the disease. The predominant theory explaining this dysfunction is an abnormally high level of inflammatory cytokines in the amniotic fluid that comes into direct contact with the bowel. Some feel the length of time the bowel is in contact with the amniotic fluid determines the severity of the GI dysfunction, while others dispute this claim. As a result there is an ongoing debate about the timing of delivery in this disease. Once delivered, the bowel loses fluid at an extraordinary rate since it is exposed to the air. This represents a surgical emergency, and either primary closure or silo covering of the bowel needs to be done as soon as possible.

In omphalocele, there may be no GI dysfunction despite the enormity of the defect. Patient can be fed immediately, and the most significant GI concern is that of reflux. All abdominal defects to include congenital diaphragmatic hernia have variable expressions of foregut dysmotility. Attention should be paid to the associated anomalies with omphalocele leaving the defect repair to a more elective situation. IUGR is less common in omphalocele and is probably due to associated anomalies.

Diagnosis

Prenatal diagnosis has become standard in the United States. Serum maternal Alpha fetal protein levels are almost ten times the normal in gastroschisis and are five times the normal in omphalocele. An elevated AFP usually

triggers a prenatal ultrasound. Position of the cord alongside the bowel (gastroschisis) or coming of the end of a sac separated from the bowel (omphalocele) distinguishes between the two diagnoses; however, this differentiation is not always clear.

After delivery, the diagnosis is obvious with the cord coming of the end of the omphalocele sac or in gastroschisis an intact cord with a defect to its right.

Treatment

As mentioned, the timing and method of delivery have triggered an emotional debate among perinatologists, pediatric surgeons, and neonatologists. Excluding maternal factors, there is evidence to support recommendations ranging from full-term (>36 weeks) vaginal delivery to timed elective c-section as soon as lung maturity is determined by amniocentesis. Most evidence supports the concept that neither early delivery nor elective c-section confers any outcome advantage.

General Care: For an omphalocele, review of a complete history and physical examination to identify all associated anomalies along with genetic counseling is warranted. The omphalocele is then sized with hernias of the cord being repaired electively in the first week of life. Omphalocele of 4–8 cm may be repaired electively based upon other anomalies, and giant omphaloceles should be delayed by up to 1–2 years prior to potentially staged repair. There have been recent reports of rapid closure (2–8 months) with techniques utilizing intra-abdominal l tissue expanders to achieve adequate abdominal compartmental domain. Resection of the sac or rupture of the sac creates a surgical emergency where repair of the sac, primary closure, or prosthetic covering will be required. The sac should be protected by a number of methods during the period of delay.

Upon delivery, gastroschisis patients need to have the bowel covered and kept warm assuring inspection to determine that there is no torsion of the delicate vascular pedicle. A material that is transparent is best so that the bowel can be continuously assessed. The use of a bowel bag has become popular in many centers. The infant is placed in the bag entirely up to the level of the axilla. The bowel should be oriented off to the right to prevent kinking of the mesenteric blood supply. Expeditious primary repair or silo placement needs to be performed to avoid excessive hypothermia and fluid loss. Most infants will require isotonic fluid at least two times their calculated maintenance.

In addition, the placement of a PICC line or central line in the first 48 h will be critical as these children will be completely dependent upon TPN until bowel function develops. Whether or not the infant should have a planned staged repair vs. an attempt at primary repair has been a great source of debate. Arguments supporting attempted primary repair include shorter time to regain intestinal function and shorter hospitalizations. Arguments supporting routine silo placement and staged repair include decreased incidence of abdominal compartment syndrome and improved renal and splanchnic blood flow during a period of extreme fluid shifts.

Specific Treatment

Omphalocele closure is usually very straightforward in the case of a hernia of the cord. A standard umbilical hernia repair can take placed with adequate skin coverage. Giant omphalocele is also straightforward in the newborn period. An inflammatory topical agent (most commonly silvadene) is applied several times daily until a pseudo skin develops. Having the infant constantly on its back while sleeping will allow gravity to slowly reintroduce the bowel and abdominal organs back into the peritoneal cavity. One determination that an attempted repair is indicated the decision process becomes more complicated. This situation is identical to the primary repair of a standard omphalocele. Once the sac is resected, a bridge has been crossed that cannot be regained, thus many elect to attempt closure over top of the sac. Thus, if the repair does not hold the bowel, it is still covered. However, once there is no longer a covering sac, several options have been described from primary skin coverage to component separation of the lateral musculature, to prosthetic mesh placement (now more popular than ever due to the development of biologic mesh materials), and tissue expanders. Most recently, negative pressure dressings have been incorporated into the management of difficult abdominal wall closures with excellent results.

Operative decision making in gastroschisis can be life altering for these infants. Mesenteric blood supply must be maintained at all costs. If the bowel is reinserted into the abdomen, care must be taken to maintain perfusion. Measures of peak pulmonary pressure, intra-abdominal pressure, and splanchnic perfusion pressure have all been used. However, surgical judgment still is the critical factor in this decision. In cases of closed gastroschisis, the fascia will have to be opened prior to any primary closure attempt or silo placement. If the bowel cannot be safely replaced into the abdomen, a prosthetic material (classically siliconized Teflon) is placed to cover the bowel and to continuously reassess. Approximately 15 years ago, preformed, spring

loaded silos became available. They have now been extensively studied and are considered standard when secondary closure is undertaken.

It is important to mention the surgical treatment of prune belly. That is simply because the urologic consequences of this anomaly take precedence. The surgical management is undertaken electively or in combination with a urologic procedure: Typically Fowler-Stephens staged orchiopexies, ureteral reimplantations, bladder augmentations, etc. The functionality of abdominal reconstruction has never been proven; however, it is considered to be a cosmetic benefit to abdominoplasty.

Future Development

Sutureless gastroschisis repair is now being popularized. Primary or secondary closures are being done by simply covering the defect with remaining umbilical cord and sterile dressing. Over time the umbilical ring closes down. Approximately two third of the patients will have their umbilical hernias resolved and the remaining will require delayed repair.

Prognosis

Prognosis for both omphalocele and prune belly is specifically related to the anomalies they are associated with. The exception to this is a giant omphalocele that ruptures. The survival in gastroschisis has gone from below 30% 50 years ago to now over 90%. The seminal advancement that has made this possible is the development of TPN. A lifelong risk for adhesive obstruction exists and has been estimated to be as high as 18%. In the 5–10% of nonsurvivors, there are usually sequelae of multiple atresias or extensive bowel necrosis at birth resulting in short gut and sepsis. Gastroschisis is a major etiology contributing to the pediatric short gut population and the intestinal transplant population. However, for children who undergo intestinal transplantation, there is a worse prognosis for those with gastroschisis as their underlying diagnosis than for other etiologies.

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418 Congenital Intestinal Obstruction

Deepika Nehra · Allan M. Goldstein

Introduction

Vomiting, abdominal distension, and failure to pass meconium in the newborn period all suggest the possibility of intestinal obstruction. The cause of the obstruction can be mechanical or functional (❯ *Table 418.1*); but regardless of the final diagnosis, prompt assessment is essential in order to avoid treatment delays that can have catastrophic consequences for the infant. The initial management of neonatal bowel obstruction includes resuscitation with intravenous fluids and broad-spectrum antibiotics. Nasogastric suction is important in order to decompress the stomach, which can improve diaphragmatic excursion and ventilation while reducing the risk of pulmonary aspiration. Once resuscitation is underway, a detailed history and physical examination are essential. Based on the differential diagnosis thus generated, targeted imaging studies will usually lead to an accurate diagnosis. Occasionally, a plain radiograph may be the only study necessary prior to operative exploration in a critically ill child. Because of the time-sensitive nature of some causes of bowel obstruction, early consultation with a pediatric surgeon is important.

The history should begin with the findings on prenatal ultrasound. The presence of dilated echogenic loops of bowel is suggestive of fetal intestinal obstruction. Polyhydramnios also occurs in bowel obstruction, especially in more proximal obstructions, like esophageal, duodenal, and jejunoileal atresia. Meconium peritonitis, diagnosed when intraperitoneal calcifications are identified on fetal ultrasound, indicates prenatal intestinal perforation and can be seen in association with intestinal atresias, volvulus, and meconium ileus. Nonintestinal anomalies seen on prenatal ultrasound are also important as they may direct the physician toward specific syndromes or associations. A maternal history, including a history of diabetes or drug use, is helpful, as is a thorough family history for cystic fibrosis, Hirschsprung's disease, and any intestinal anomalies.

The presence of prematurity is important as these infants often have delayed passage of meconium. Other important aspects of the newborn history include the ability to tolerate feedings at any point postnatally. If feeds were initially tolerated, a proximal atresia is unlikely. The presence of emesis, and whether it is bilious or not, may be the most important question, since bilious emesis in a newborn must be assumed to be caused by midgut volvulus until proven otherwise. The timing of onset of emesis is also important, as proximal obstructions cause emesis earlier than more distal obstructions. The timing of passage of the first meconium stool is critical. Delayed passage beyond 24–48 h suggests a distal, often colonic, process, such as Hirschsprung's disease. If meconium passes but looks like white mucus rather than bile-stained, then an intestinal atresia should be suspected. If meconium is seen coming from the urethra or from the perineum, then the infant likely has an anorectal malformation with a rectourethral or rectoperineal fistula, respectively.

Physical examination should be thorough in order to identify associated anomalies or syndromic features. The abdominal examination is paramount. Is the abdomen distended, flat, or scaphoid? In general, more distal obstructions cause more prominent distension. Is there tenderness or even peritonitis? The presence of bilious emesis in a newborn with abdominal distension and peritonitis is ominous, raising concern for midgut volvulus with compromised bowel. The presence of an incarcerated inguinal hernia could explain bowel obstruction. Anal examination is critical in order to determine whether there is an anal opening that is in the normal position, patent, and normal in caliber.

A plain abdominal radiograph is a very useful first test, and in some instances, such as in duodenal atresia, may be sufficient alone to make the diagnosis. Depending on the suspected level of obstruction based on the clinical history, physical examination, and initial abdominal radiograph, an upper gastrointestinal series or contrast enema usually follows. In the majority of cases of neonatal bowel obstruction, these studies will suffice to direct medical and surgical therapy. Additional imaging will be guided by the specific diagnoses being considered.

Abdelaziz Y. Elzouki (ed.), *Textbook of Clinical Pediatrics*, DOI 10.1007/978-3-642-02202-9_418,

Table 418.1
Causes of neonatal intestinal obstruction

Mechanical causes	Functional causes
Malrotation with midgut volvulus	Prematurity
Duodenal atresia	Sepsis
Annular pancreas	Maternal narcotic use
Jejunoileal atresia	Magnesium use
Colonic atresia	Congenital hypothyroidism
Meconium ileus	Small left colon syndrome
Anorectal malformation	Meconium plug syndrome
Presacral mass	Hirschsprung's disease

Duodenal Atresia and Stenosis

Duodenal atresia (DA) and stenosis is a cause of intestinal obstruction in neonates that occurs with a reported incidence of 1:5,000 to 1:10,000 births. DA is thought to occur as a result of failure of vacuolization of the duodenum following its solid cord stage during weeks 8–10 of gestation. Although DA is an isolated finding in 30–50% of cases, it can be associated with cardiac (38%), renal (14%), esophageal (6%), anorectal (5%), and vertebral malformations (6%). Other anomalies of the midgut, including annular pancreas, anterior portal vein, choledochal cyst, biliary atresia, malrotation, and jejunoileal and colonic atresia, can also occur in children with DA. Approximately 20–25% of infants with DA have Down syndrome and up to 38% have associated cardiac anomalies.

DA is classified into three types of defects. Type I defects are the most common and consist of a mucosal diaphragmatic membrane that occludes the duodenal lumen. In some cases, this membrane may resemble a "windsock," in which the site of origin of the web may be a few centimeters proximal to the perceived site of obstruction. This web frequently involves the opening of the bile duct at the ampulla of Vater, an important consideration for the surgeon. Additionally, this luminal membrane or web may have an opening of variable size resulting in a congenital intrinsic stenosis. Large openings may provide a large enough conduit to delay symptoms until later in life. Type II defects consist of a short fibrous cord connecting two ends of atretic duodenum. Type III defects, which are the least common, have a complete separation of the two ends of atretic duodenum and an associated mesenteric defect.

DA is often diagnosed antenatally by the presence of the characteristic "double-bubble sign" on prenatal US in which the stomach and duodenal bulb are seen as two bubbles. Other ultrasound findings suggestive of DA include polyhydramnios, noted in 50% of patients with DA, a dilated loop of bowel, hyerpechoic bowel, and ascites. Generally, proximal atresias such as DA are more likely to be detected on prenatal ultrasound than more distal atresias. If DA is diagnosed prenatally, a detailed evaluation for other associated anomalies should be performed, as well as an amniocentesis for chromosomal analysis. Several studies have demonstrated that prenatal diagnosis improves outcomes by allowing earlier recognition of the defect, which leads to prompt surgical intervention and fewer metabolic complications.

Neonates with DA are often born premature (46%) and almost all are small for gestational age (90%). In approximately 80% of cases of DA, the obstruction occurs distal to the ampulla of Vater, typically resulting in bilious emesis and feeding intolerance within the first few hours of life. Although generalized abdominal distention is not commonly seen due to the proximal location of the obstruction, a fullness in the upper abdomen may be appreciated. Affected infants may pass meconium after birth if the distal intestinal tract is normal.

The classic abdominal radiographic finding in a neonate with DA is the "double-bubble sign" in which an air-filled stomach and duodenal bulb are seen as two bubbles separated by the pylorus (*Fig. 418.1*). If no air is present in the intestine distal to the duodenal bulb, then the diagnosis of DA is secured and no further diagnostic studies are necessary. The presence of air distal to the duodenum may indicate an incomplete obstruction due to duodenal stenosis or a fenestrated web. However, of major concern is the possibility intestinal malrotation with midgut volvulus, which would require emergent surgical intervention. Therefore, the presence of air distal to a "double-bubble" mandates a prompt upper gastrointestinal series to exclude malrotation. All newborns with duodenal atresia need specific diagnostic tests to evaluate for associated anomalies. An echocardiogram should be performed to look for congenital heart disease (patent ductus arteriosus, atrio-ventricular canal defect, atrial or ventricular septal defect, tetrology of Fallot), a chest radiograph to assess for vertebral anomalies, and a renal ultrasound to rule-out renal anomalies (renal agenesis or dysplasia, ectopic kidneys, duplicated or incomplete collecting system). A rectal biopsy should be considered if there is any suspicion of Hirschsprung's disease, which is of particular concern in the neonate with both DA and Down syndrome.

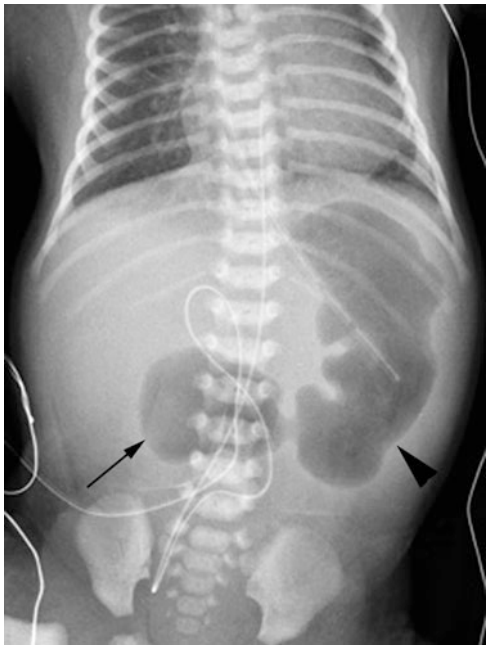

Figure 418.1
Abdominal radiograph showing the classic "double-bubble sign" of duodenal atresia. Note the dilated gas-filled stomach (*arrowhead*) and proximal duodenum (*arrow*) with an otherwise gasless abdomen consistent with a complete obstruction

DA requires operative correction. Preoperative management includes intravenous hydration, correction of electrolyte imbalances, and placement of a nasogastric tube to decompress the stomach and decrease the risk of aspiration. DA is not a surgical emergency and the infant should not undergo operative repair until hemodynamic and fluid and electrolyte status are stable. Additionally, in the case of a very premature infant, consideration must be given to delaying operative intervention, while continuing nasogastric decompression and parenteral nutrition, to allow the child to gain weight to reduce the risk of operative intervention. The ideal timing of surgery in such instances is determined on a case by case basis. Additionally, preoperative consultation with a cardiologist and cardiac surgeon should be considered in any infant with DA and a concomitant cardiac defect to determine the need for and optimal timing of operative correction of the cardiac defect and any preoperative steps necessary prior to correction of the DA.

DA is approached through a transverse right upper quadrant incision. The surgical treatment for Type II and III defects involves a bypass of the obstructed segment of duodenum with a side-to-side or proximal transverse to distal longitudinal (diamond-shaped) duodenoduodenostomy. In cases where the proximal duodenum is markedly dilated, a tapering duodenoplasty may be necessary to reduce the duodenal caliber, which may improve postoperative duodenal emptying. A Type I defect can be corrected with a transduodenal web excision or a duodenoduodenostomy. The ampulla is often closely associated with the web and must be carefully identified and preserved. Identification of the ampulla can be facilitated by gentle compression of the gallbladder, which releases bile in the region of the ampulla. During the procedure, it is imperative to examine the distal bowel for other intestinal atresias, as these are associated with DA. This can be accomplished by passing a catheter into the distal bowel and insufflating air or saline to distend the small intestine.

Neonates generally do well following surgical correction of DA with an operative mortality of <5% and reported 15-year survival of 86%. The majority of the early and late deaths in infants with DA occur secondary to severe associated cardiac defects. Commonly reported late complications include adhesive bowel obstruction, megaduodenum with abnormal motility often requiring tapering duodenoplasty, and gastroesophageal reflux that is often unresponsive to medical management and may require antireflux surgery.

Jejunoileal Atresia

The small intestine is the most common site of intestinal atresia in neonates, and the incidence is higher in the ileum than in the jejunum. The reported incidence of jejunoileal (JI) atresias ranges from 1:1,500 to 1:5,000 births. JI atresia is an acquired lesion thought to result from a vascular accident resulting in ischemic necrosis of a segment of fetal intestine. This vascular accident may be secondary to intestinal volvulus, intussusception, internal herniation, or strangulation of bowel in a tight abdominal wall defect. The necrotic segment of intestine resorbs, resulting in a blind proximal and distal end often with a gap in the associated mesentery. Interestingly, maternal smoking and use of vasoconstrictive medications in the first trimester of pregnancy, in addition to inherited thrombophilias, increase the risk of small intestinal atresia. Although most cases of JI atresia are sporadic in nature, some familial cases of Type IIIB and Type IV atresias have been reported, suggesting a genetic component.

JI atresias are classified into four types based on their anatomic characteristics (*Fig. 418.2*). In Type I atresias,

the lumen is obstructed by an intact membrane composed of mucosa and submucosa while the outer muscularis and serosa are intact. This results in no obvious external discontinuity of the bowel, but an obstructed lumen (Fig. 418.3a). Type II atresias involve a gap in bowel continuity with the proximal and distal ends connected by a short fibrous band. Type III atresias are subdivided into Types IIIA and IIIB. Type IIIA atresias consist of a gap in intestinal continuity with no tissue connecting the two blind ends and a mesenteric defect between them (Fig. 418.3b). Type IIIB atresias are characterized by a proximal small bowel atresia and the absence of a large segment of bowel that is normally supplied by the distal superior mesenteric artery, resulting in a large gap in the small bowel mesentery. The small bowel distal to the atresia is foreshortened and coiled, leading to the designation "apple peel" or "Christmas tree" deformity. Type IV atresias refer to the presence of multiple Type II or IIIA atresias, giving the bowel the appearance of a "string of sausages" (Fig. 418.3c).

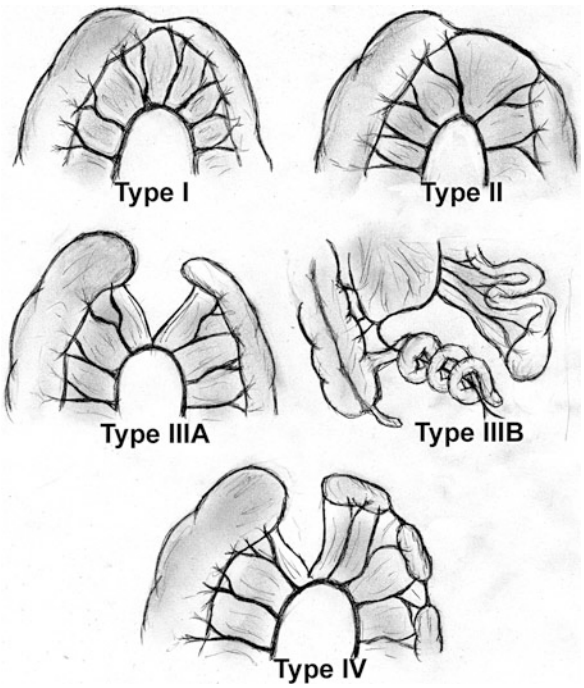

Figure 418.2
Classification of intestinal atresia

Fewer than one-third of all JI atresias are diagnosed prenatally. Maternal polyhydramnios is a common finding with intestinal atresia. Other prenatal findings include ascites, dilated loops of bowel, and increased bowel echogenicity. Generally, proximal jejunal lesions are more likely to be detected antenatally as they result in more severe dilation of the proximal bowel due to continued fetal swallowing of amniotic fluid without the potential for intestinal absorption. Neonates with JI atresia have a high incidence of prematurity (44%) and being small for gestational age (25–50%).

Neonates with JI atresias typically develop obstructive symptoms, including abdominal distention and bilious emesis, within the first 48 h of life. These infants usually do not pass meconium. Infants with JI atresias can have associated gastrointestinal anomalies including abnormalities of intestinal rotation and fixation (13%), gastroschisis (16%), duodenal atresia (4%), and colonic atresia (2%). Associated extra-abdominal anomalies are rare but include cardiac defects (8%), skeletal anomalies (2%), and renal abnormalities (4%). JI atresias may also occur

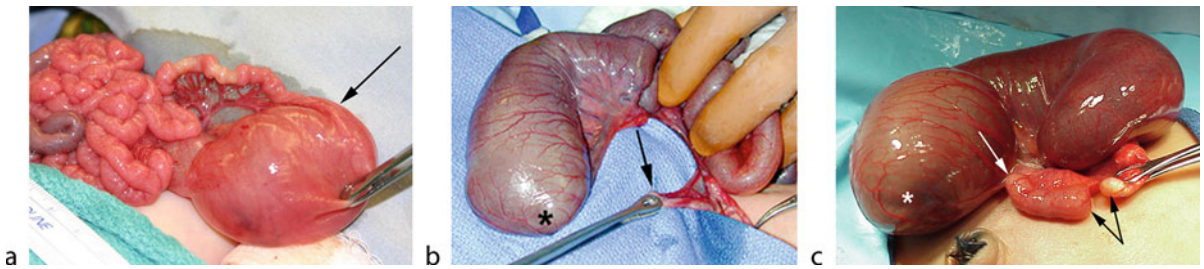

Figure 418.3
Jejunoileal atresias. (a) Type I atresia. Note the lack of external discontinuity of the bowel and the notable size discrepancy between the proximal dilated and distal decompressed bowel (transition point marked with an *arrow*). (b) Type IIIA atresia with a very dilated proximal end of the bowel (*asterisk*) compared to the distal end (*arrow*) and a mesenteric defect between the two blind ends. (c) Type IV atresia with a very dilated proximal end of intestine (*asterisk*) and multiple blind-ending segments (*arrows*) giving the bowel an appearance resembling a "string of sausages"

in association with meconium ileus, which is almost always due to cystic fibrosis (CF). The inspissated meconium associated with CF may cause intestinal dilation and can lead to a localized volvulus which results in ischemic necrosis of a segment of bowel, thus forming an atresia. Among neonates with JI atresia, 12% are found to have cystic fibrosis.

Plain abdominal radiographs in the setting of JI atresias are notable for dilated loops of bowel (*Fig. 418.4*). The number of dilated bowel loops is indicative of the level of obstruction. The presence of intraperitoneal calcifications is indicative of meconium peritonitis, suggesting an intrauterine intestinal perforation. Although a contrast study is not necessary to make the diagnosis of a proximal atresia, a contrast enema is useful to rule out an associated colonic atresia. For patients with a suspected distal atresia, a contrast enema can help define the level of obstruction and identify the location of the cecum to rule out abnormalities of intestinal rotation and fixation. The contrast enema in a newborn with JI atresia often reveals a microcolon, resulting from lack of use of the distal bowel. Neonates with JI atresia in association with meconium ileus or meconium peritonitis should undergo mutation analysis for CF. In the absence of signs or symptoms of a cardiac anomaly, routine echocardiography is not necessary for patients with JI atresias due to the low incidence of associated congenital heart disease.

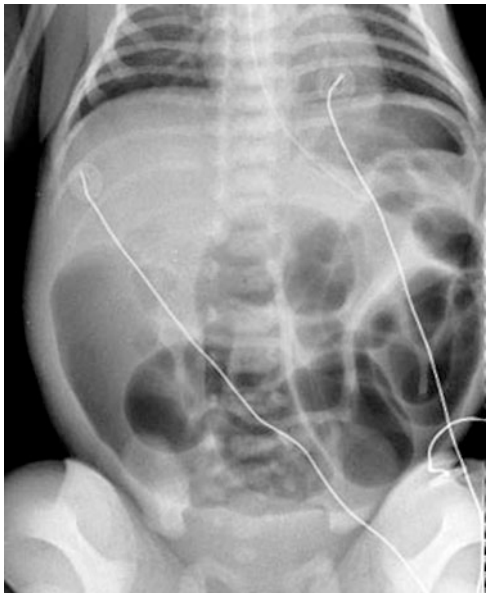

Figure 418.4
Abdominal radiograph in JI atresia. The x-ray shows multiple dilated loops of bowel consistent with an intestinal obstruction. The number of dilated loops can provide an indication of the level of obstruction

JI atresias require operative correction. Preoperative management, as with any intestinal obstruction, includes hydration, correction of electrolyte abnormalities, and nasogastric decompression. Complicating factors, such as prematurity or congenital heart disease, should be recognized and included in preoperative planning. The surgical approach and technique vary depending on the level and type of atresia present. However, several principles are constant, including judicious use of resection to preserve maximum bowel length, restoration of intestinal continuity, and careful inspection of the entire bowel to rule out associated atresias. Primary anastomosis can be challenging due to the marked size discrepancy between the proximal and distal segments. In patients with an isolated atresia and a short segment of dilated proximal intestine, resection of the excessively dilated segment with a primary end-to-oblique anastomosis can be performed. In cases with a long segment of very dilated proximal bowel, antimesenteric tapering enteroplasty or imbrication of the proximal bowel should be considered in order to reduce the caliber of the proximal bowel while preserving intestinal length. Tapering enteroplasty or imbrication is required in less than one-third of JI atresias. In some cases, a Type I atresia or web can be treated by simple web excision or stricturoplasty. The evaluation for associated distal atresias can be facilitated by flushing the intestine distal to the site of obstruction with saline. Intestinal atresia in the setting of gastroschisis can be a challenging problem. Identification of the atretic segment is particularly difficult in the setting of thickened and inflamed bowel, and healing of the intestinal anastomosis can be tenuous under these conditions. For these reasons, for JI atresias in the setting of gastroschisis, consideration should be given to reduction of the viscera into the abdominal cavity followed by definitive repair of the JI atresia after the acute inflammation has subsided.

The reported operative mortality associated with repair of a JI atresia is 0.8% and the long-term survival is 86–92%. Postoperative complications include adhesive bowel obstruction, prolonged ileus, anastomotic leak, and short bowel syndrome, which is most common in Type IIIB and Type IV atresias. The long-term survival of children with JI atresias has increased markedly over the last 40 years most notably due to the ability to provide these infants with long-term parenteral nutrition, which can be necessary for weeks to months following surgical repair. Currently, the late mortality is most commonly related to complications of short bowel syndrome including liver disease and sepsis.

Intestinal Malrotation and Midgut Volvulus

The incidence of rotational abnormalities of the midgut is difficult to determine, but autopsy studies indicate an incidence as high as 1% of the population. In contrast, symptomatic malrotation is estimated to occur in 1:6,000 births. Intestinal malrotation results from a failure in the normal embryologic sequence of bowel rotation and fixation. In a landmark article in 1923, Norman M. Dott first described intestinal malrotation by applying embryological observations to his clinical experiences treating five patients. Intestinal rotational disorders can encompass an array of anatomical abnormalities including nonrotation, reversed rotation, and varying degrees of incomplete rotation. The classic appearance of intestinal malrotation is depicted in *Fig. 418.5a*.

Two anatomic features of malrotation are responsible for the clinical symptoms that occur. First, the malrotation often positions the duodeno-jejunal junction very close to the ileocecal valve. Since these represent the proximal and distal ends of the small intestinal mesentery, respectively, their abnormal proximity creates a narrow mesenteric base that allows the root of the mesentery to twist, resulting in midgut volvulus. Second, duodenal obstruction can result from Ladd's bands, which are abnormal attachments that typically develop between the ascending colon and the right abdominal sidewall, crossing over and constricting the duodenum. Neonates with intestinal malrotation typically present with bilious emesis. The abdominal examination is often initially benign. However, a benign exam should not lead to complacency. Midgut volvulus can rapidly lead to intestinal ischemia and the infant can develop abdominal distention, tenderness, hematemesis, hematochezia, hypotension, and shock. These findings are ominous in the setting of bilious emesis as they are highly suggestive of intestinal ischemia. Although bilious emesis in a newborn can be due to other surgical or nonsurgical causes, it is imperative that intestinal malrotation with midgut volvulus be ruled out before other diagnoses are considered due to the potentially devastating complications of intestinal ischemia associated with delaying this diagnosis.

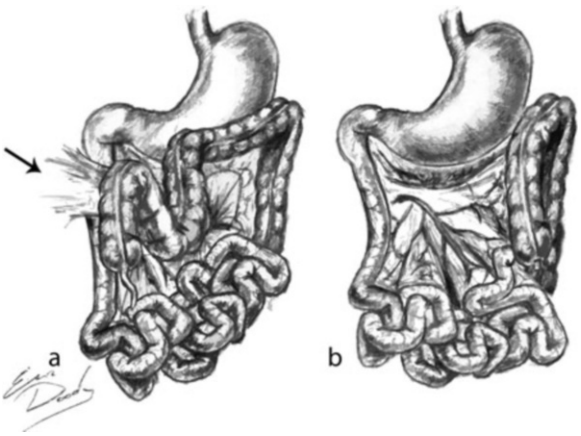

Figure 418.5
Intestinal malrotation. (a) The duodenum courses down the right side of the abdomen and the ligament of Treitz fails to cross the midline to the left side. Ladd's bands (*arrow*) are seen extending from the right colon, across the duodenum, to the right lateral abdominal wall. (b) After Ladd's procedure for malrotation, the small bowel is predominantly on the right side, with the colon on the left. Ladd's bands have been divided, the base of the mesentery broadened by lysing adhesions, and the appendix removed (Reprinted from Nehra D, Goldstein AM (2011) Intestinal malrotation: varied clinical presentation from infancy through adulthood. Surgery 149(3):386–393, Copyright 2011, with permission from Elsevier)

Approximately 30–60% of neonates with intestinal malrotation have an associated congenital anomaly, the majority of which are related to the gastrointestinal tract. Rotational defects are known to be present in all patients with congenital diaphragmatic hernia, gastroschisis, and omphalocele although volvulus is less common in these conditions. As many as 50% of children with duodenal atresia and 10–20% of children with jejunoileal atresia may have associated intestinal malrotation. Other associated anomalies involving the cardiac, respiratory, genitourinary, and central nervous systems have been reported but are much less common. It is important to note that although intestinal malrotation is classically thought to be a disease of neonates and infants, malrotation can present at any age and with a variety of acute and chronic symptoms. A recent report on intestinal malrotation found that fewer than 50% of all patients with malrotation are diagnosed prior to 1 year of age.

If there is clinical suspicion of intestinal malrotation with midgut volvulus in a newborn with peritonitis, hemodynamic instability, or any clinical deterioration, valuable time should not be wasted on radiographic imaging and the focus should be placed on aggressive resuscitation and prompt surgical exploration. In a stable child, upper gastrointestinal series is the gold standard to evaluate for malrotation. The ligament of Treitz, which is located at the duodeno-jejunal junction, should normally be located to the left of midline and roughly at the level of the pylorus. An abnormal position of the ligament of

Treitz indicates malrotation. The presence of a "corkscrew" appearance to the duodenum and proximal jejunum is consistent with volvulus. Duodenal obstruction, often with a "bird beak" appearance, is also concerning for volvulus (*Fig. 418.6*). Plain radiographs are not usually helpful in the diagnosis of malrotation and volvulus, but may demonstrate a gasless abdomen, intestinal dilatation, or may be completely normal. Findings that are suggestive of malrotation on plain radiographs include a nasogastric or orogastric tube that extends into an abnormally positioned duodenum or a "double-bubble sign," signifying duodenal obstruction, with the presence of distal gas. Ultrasonographic findings suggestive of malrotation include abnormal position of the superior mesenteric vein either anterior or to the left of the superior mesenteric artery, the "whirlpool sign" of volvulus (caused by twisting of the mesentery and vessels around the narrow mesenteric base), or a dilated duodenum indicating obstruction from Ladd's bands or volvulus. Additionally, an abnormally placed cecum on barium enema may indicate a rotational abnormality, but this study is of limited benefit as an abnormally placed cecum is not pathognomonic of malrotation and a normally placed cecum does not rule out malrotation since the cecum is in a normal location in 20% of individuals with malrotation.

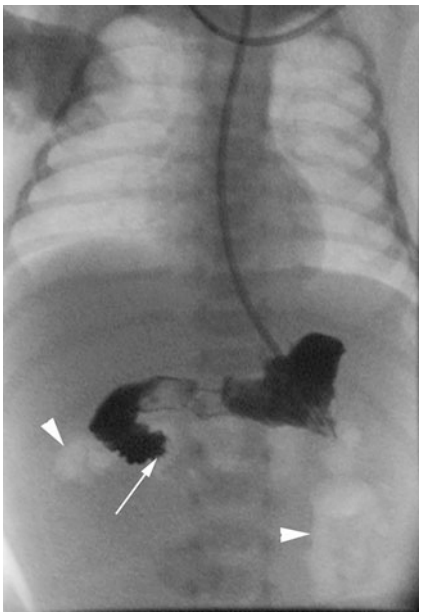

Figure 418.6
Upper gastrointestinal series (UGI) demonstrates an abrupt cutoff at the level of the duodenum (*arrow*) with visible distal gas (*arrowheads*). This constellation of findings is concerning for malrotation with midgut volvulus

Intestinal malrotation with or without volvulus is treated surgically. Malrotation with midgut volvulus is a surgical emergency. In contrast, asymptomatic malrotation, which may be discovered incidentally on an imaging study performed for other reasons, can be approached in a less urgent fashion. Midgut volvulus is present in up to 50% of patients operated on for malrotation and is more common in neonates with malrotation than it is in older children and adults. In 1936, William Ladd wrote the classic article on the treatment of intestinal malrotation describing the corrective procedure that now bears his name. The Ladd's procedure involves counterclockwise detorsion of the midgut, division of bands crossing from the cecum to the lateral peritoneal gutter, and widening of the mesenteric base with placement of the colon in the left side of the abdomen and the small bowel in the right. The appendix is removed to prevent future diagnostic confusion due to its abnormal location. *Figure 418.5b* depicts the anatomy after a Ladd's procedure for intestinal malrotation. If the viability of a portion of the bowel is questionable following detorsion of the midgut, warm sponges and observation for a period of time may allow reperfusion of the intestine and improvement in its appearance. If segments of bowel with questionable viability remain, the abdomen can be closed and the intestine re-evaluated at a second operation performed 24–36 h after the initial procedure. Complete necrosis of the midgut in cases of severe or prolonged volvulus is catastrophic.

Complications following the Ladd's procedure are uncommon in the absence of compromised bowel. Patients with volvulus may require extensive bowel resection resulting in short bowel syndrome. These complications are preventable by prompt recognition and operative intervention for symptomatic malrotation. The mortality rate after surgical intervention for malrotation is 3–9% and is higher in the setting of volvulus, intestinal necrosis, prematurity, and other associated anomalies. It is important to recognize that a history of a Ladd's procedure does not rule out the possibility of future volvulus. Recurrent volvulus is estimated to occur in 2–7% of children following a Ladd's procedure.

Colonic Atresias

Atresias of the colon are rare, with an incidence of approximately 1:20,000, accounting for about 5–10% of all intestinal atresias. Colonic atresias are classified using the same

classification system used for small intestinal atresias (Fig. 418.2). Type III defects are the most common and usually occur proximal to the splenic flexure. Type I atresias are the second most common type encountered in the colon (Fig. 418.7).

The clinical presentation of a colonic atresia is consistent with that of a high-grade distal intestinal obstruction and is characterized by severe abdominal distension, bilious emesis, minimal or no passage of meconium, and feeding intolerance. Neonates with colonic atresia are often premature (29%).

Plain abdominal radiography will show very dilated loops of bowel, often with air-fluid levels and absence of air in the rectum. Pneumoperitoneum can occur. In the absence of intestinal perforation, a contrast enema is obtained. In the setting of colonic atresia, contrast will fill a distal microcolon and stop at the level of the atresia. Proximally dilated air-filled bowel will be seen.

Colonic atresias are associated with several anomalies, including gastroschisis, skeletal abnormalities, congenital heart disease, and jejunoileal atresias. The coexistence of colonic and jejunoileal atresias supports the importance of preoperative contrast enemas in all neonates with atresias of the jejunum or ileum in order to avoid missing a colonic obstruction following operative repair of the small intestinal atresia. The association of colonic atresia with Hirschsprung's disease has been reported, but is rare. At the time of surgery, the resected atretic segment should be sent to pathology with the specific request to evaluate the distal end for the presence of ganglion cells.

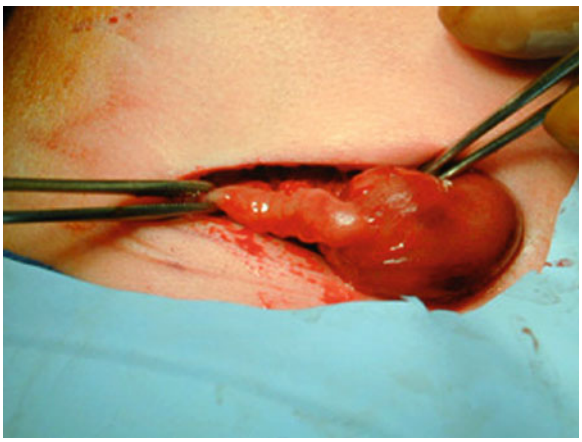

Figure 418.7
Type I colonic atresia. The sigmoid colon proximal to the atresia is dilated, while the distal segment distal to the atresia is narrow

Surgical treatment of colonic atresia involves resection of the atretic segment along with any excessively dilated proximal bowel. The length of resection is minimized and effort is made to preserve the ileocecal valve when possible. Primary anastomosis can be performed safely regardless of the level of the atresia. However, some authors have reported high rates of anastomotic leak and recommend initial diverting colostomy. This is a safe alternative and should be considered in more complex cases, such as those associated with gastroschisis, Hirschsprung's disease, or in critically ill newborns.

Hirschsprung's Disease

Hirschsprung's disease (HD), or congenital megacolon, is characterized by the absence of ganglion cells (aganglionosis) extending from the distal end of the rectum proximally for a variable distance. Named for the Danish pediatrician, Harald Hirschsprung, who first described the disease in 1886, HD disease occurs in 1:5,000 live-births, with a male to female ratio of 4:1. In 80% of cases, the aganglionosis is limited to the rectosigmoid colon, and this is referred to as "short-segment" disease. The remaining cases have "long-segment" disease, in which the aganglionic segment extends proximal to the sigmoid colon. Total colonic aganglionosis occurs in about 5% of cases, and total intestinal aganglionosis is quite rare, occurring in <1% of all cases.

The enteric nervous system (ENS) is made up of a complex network of neurons and glial cells that are located in the wall of the gastrointestinal tract and comprise the largest component of the autonomic nervous system. The ENS regulates critical functions of the gut, including intestinal motility as well as absorption and secretion across the mucosa. The ENS is organized into two concentric rings of ganglia situated on either side of the circular smooth muscle layer, with the submucosal plexus located on the inner side of this layer and the myenteric plexus located between the circular and longitudinal muscle layers. When the ENS is absent, as it is in the aganglionic bowel of HD, normal motility cannot occur and a functional bowel obstruction develops. The cellular and molecular etiology of intestinal aganglionosis is an area of intense scientific interest. The cells that comprise the ENS arise from the neural crest along the dorsal aspect of the embryonic neural tube. Those neural crest-derived cells that will form the ENS originate in the vagal region of the neural tube, from where they migrate to the foregut and then proceed in a proximal-to-distal direction along the entire length of the gastrointestinal tract. This process occurs during weeks 4–7 of human gestation.

In rodents and avians, a smaller contribution of cells arises from the distal (sacral) region of the neural tube and contributes cells to the colorectal ENS. Whether the sacral neural crest contributes cells to the human ENS is unknown. Formation of a mature and functional ENS requires that the neural crest-derived cells undergo extensive cellular proliferation to generate a sufficient number of cells to colonize the entire bowel. These cells must also be capable of migrating distally and of differentiating into neurons and glial cells. The cells must cluster to form ganglia and pattern into two concentric plexuses. Hirschsprung's disease, in which there is aganglionosis of the distal colorectum, has several potential etiologies, each of which has experimental support. These possibilities include (1) inadequate proliferation of neural crest-derived cells to complete colonization of the distalmost bowel, (2) premature differentiation of ENS precursor cells into a neuronal phenotype, thereby preventing their continued proliferation and migration along the gut, and (3) death of enteric neurons either along their normal migratory path or after they have colonized the colon.

Several genes are essential for normal ENS development. The most important gene in the etiology of HD is Ret, a receptor tyrosine kinase expressed on the surface of enteric neural crest cells. Its ligand, glial-derived neurotrophic factor (Gdnf), is expressed by the intestinal mesenchyme. Gdnf-Ret signaling regulates proliferation, migration, differentiation, and survival of enteric neural crest cells. Null mutations of Gdnf or Ret in mice lead to total intestinal aganglionosis. Nearly all patients with HD have a mutation in the Ret gene, either in the coding sequence or in a noncoding regulatory region. Other important genes in the pathogenesis of HD include endothelin-3, endothelin receptor B, and Sox 10.

While most cases of HD are isolated and sporadic, familial cases can occur. However, the pattern of inheritance in these cases is not Mendelian. One of the interesting hallmarks of this complex genetic disorder is that the recurrence risk within a family depends on gender and the length of aganglionosis. For example, the risk for HD is 1% for a female sibling of an affected male with short-segment disease, while it is 33% for a male sibling of a female patient with long-segment disease. Syndromic cases comprise a minority of Hirschsprung's patients. About 2–8% of patients with HD have Down's syndrome. Shah–Waardenburg's syndrome represents the association of HD, sensorineural deafness, and pigmentation abnormalities. Haddad syndrome refers to the coexpression of Ondine's curse and HD. Mowat–Wilson syndrome is the association of HD, mental retardation, microcephaly, and dysmorphic facial features.

HD presents in the newborn period in 90% of cases. The disease is suspected when a neonate fails to pass meconium within the first 48 h of life and is often associated with abdominal distension and vomiting. In healthy newborns, 94–99% pass meconium within 24 h of life, and 100% pass meconium by 48 h, so a failure to pass meconium by 48 h of life should prompt further investigation. In patients presenting outside the newborn period, typical symptoms include longstanding constipation, abdominal distension, and failure to thrive. Up to 12% of patients will present with vomiting, distension, loose stools, and fever. This constellation of symptoms should raise concern for Hirschsprung's-associated enterocolitis, the most serious source of morbidity in HD. The presence of diarrhea in these patients should not distract the clinician from including HD in the differential.

Several conditions need to be considered in the differential diagnosis of a child being evaluated for HD. Examination of the anus is important in order to rule out anal stenosis or an anoperineal fistula, both of which can cause significant constipation. In neonates, other causes of distal bowel obstruction should be considered. *Meconium ileus* can present similarly to HD. Imaging can distinguish the two, showing a ground-glass appearance in the right lower quadrant on plain abdominal radiography (◉ *Fig. 418.8*)

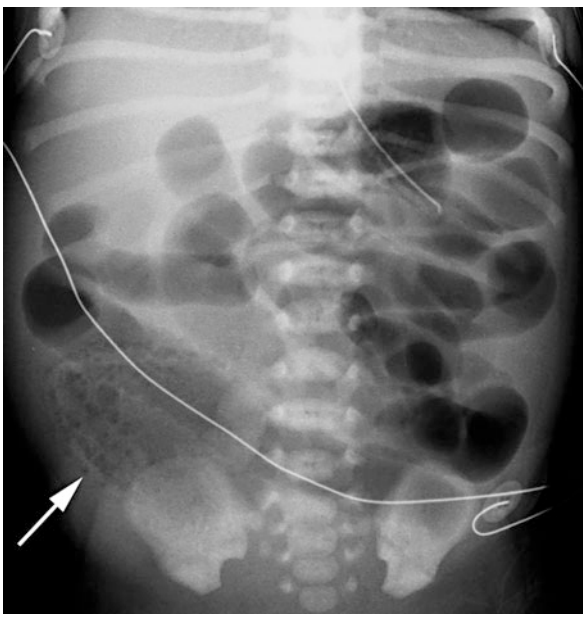

Figure 418.8
Abdominal radiograph showing distended loops of bowel and a ground glass appearance in the right lower quadrant (*arrow*) secondary to inspissated stool mixed with air, a classic finding in meconium ileus

and a microcolon on contrast enema in meconium ileus. *Small left colon syndrome* is a condition that is associated with maternal diabetes in about 50% of cases. It is due to transient dysmotility in the left colon and is hypothesized to be caused by release of glucagon in the neonate in response to hypoglycemia. It has a clinical presentation similar to HD, including distension, vomiting, and failure to pass meconium. The contrast enema often will show a narrow descending and sigmoid colon with the transition at the splenic flexure. Unlike in HD, the rectum is often normal in caliber in small left colon syndrome (Fig. 418.9). *Meconium plug syndrome*, which has an incidence between 1:500 and 1:1,000, also presents as a distal intestinal obstruction. Contrast enema will show many filling defects in the colon, consistent with retained plugs of meconium (Fig. 418.10). The cause appears to be transient colonic dysmotility and/or abnormal meconium. In all three conditions – meconium ileus, small left colon syndrome, and meconium plug syndrome – contrast enema is both diagnostic and therapeutic. Surgery for these conditions is rarely necessary and is indicated only in cases of intestinal perforation or cases refractory to radiologic resolution. Rectal biopsy should be performed in children with small left colon syndrome and meconium plug syndrome to rule out coexisting HD.

A plain abdominal radiograph may demonstrate findings suggestive of HD, including multiple dilated loops of bowel consistent with a distal bowel obstruction and the absence of gas in the rectum (Fig. 418.11a). When the diagnosis of HD is suspected, a contrast enema should be obtained. The proximal (ganglionated) colon will be distended, while the distal (aganglionic) colon will be contracted. Between dilated and contracted colon there is classically a funnel-shaped transition zone (Fig. 418.11b). These features may not be present in the neonate, where proximal dilatation has not yet developed, or in cases of total colonic aganglionosis. Finding retained contrast in the colon 24 h after the contrast enema is highly suggestive of HD.

Rectal biopsy is required to make a definitive diagnosis of HD. Suction biopsy can be performed at the bedside and is successful in the majority of young children. If the sample is not diagnostic, or in older children, full-thickness biopsy can be performed under anesthesia. The most important and diagnostic histologic feature of HD is the absence of ganglion cells. Additional features often seen include the presence of hypertrophic nerve fibers,

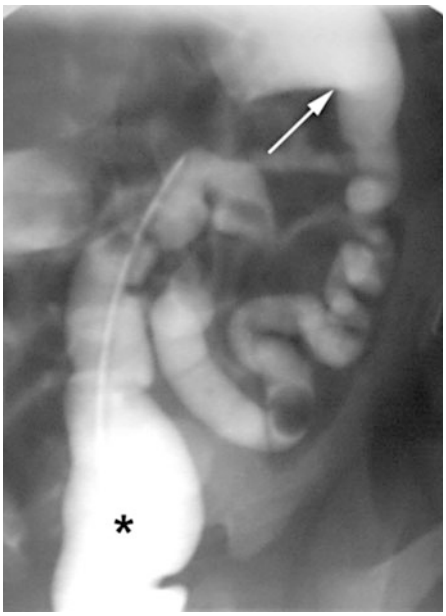

Figure 418.9
Contrast enema in small left colon syndrome shows a contrast-filled rectum (*asterisk*) and narrow descending and sigmoid colon with a transition visible at the splenic flexure (*arrow*)

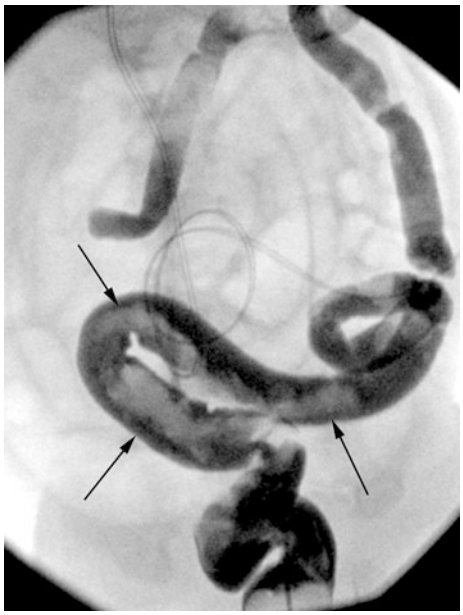

Figure 418.10
A contrast enema from a child with meconium plug syndrome demonstrating multiple filling defects (*arrows*) in the colon consistent with retained plugs of meconium

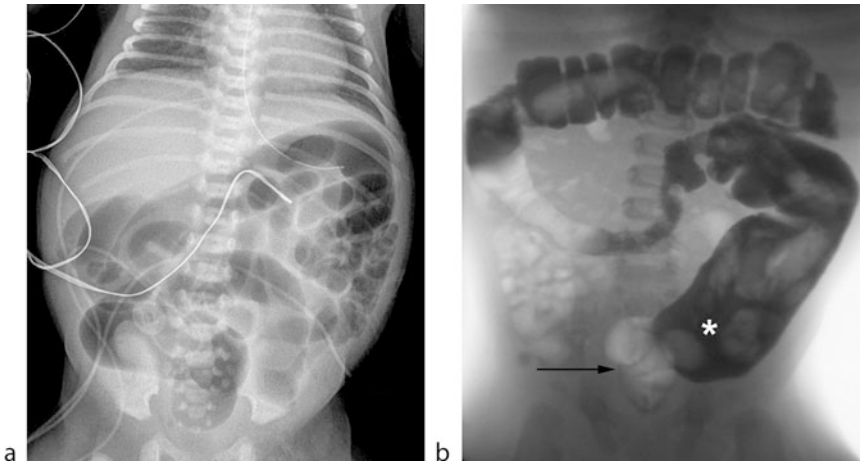

Figure 418.11

Hirschsprung's disease. (a) Abdominal radiograph with multiple loops of dilated bowel and the absence of gas in the rectum, suggestive of a distal bowel obstruction, such as Hirschsprung's disease. (b) Contrast enema of a patient with Hirschsprung's disease demonstrates a dilated proximal segment of colon (*asterisk*) with a classic funnel-shaped transition zone (*arrow*)

increased acetylcholinesterase staining of thickened submucosal nerves, and decreased calretinin staining.

Anorectal manometry can be used to support the diagnosis of HD. Normally, distension of a balloon in the rectum leads to reflex relaxation of the internal anal sphincter. This recto-anal inhibitory reflex (RAIR) is absent in HD. Anorectal manometry may be particularly helpful in cases of ultrashort segment disease, also referred to as anal sphincter achalasia. In these cases, rectal biopsy, which is performed at least 2 cm above the dentate line, may demonstrate ganglion cells. However, these children, who often suffer from chronic, refractory constipation, will have an absent RAIR. Treatment for this condition includes injection of botulinum toxin into the internal anal sphincter or sphincter myotomy.

Once the diagnosis of HD is made in a neonate, surgery is planned. The surgical approach depends on the level of aganglionosis. In all cases, the operation generally begins with multiple seromuscular biopsies, either laparosopic or through a small laparotomy. Frozen section evaluation identifies the level at which ganglion cells are present. If the patient has short-segment disease, then a one-stage transanal pull-through procedure can be performed. In long-segment disease, a diverting colostomy or ileostomy at the level of normal ganglion cells is made and the patient is brought back at a later date for an elective pull-through. In all cases, the definitive procedure involves resection of the distal aganglionic bowel and anastomosis of proximal, normally innervated bowel to the distal rectum or anus. The three most commonly used operations are Soave, Duhamel, and Swenson procedures, all of which yield similar results. The choice of procedure is based on surgeon preference.

Postoperative complications include anastomotic leaks, strictures, abscess formation, and intestinal obstruction, as can be seen following any intestinal surgery. Specific to HD is the possible development of Hirschsprung's-associated enterocolitis (HAEC). HAEC can occur either before or after definitive pull-through surgery. The typical presentation includes abdominal distension, loose stools that are often explosive and foul-smelling, fever, and vomiting. Lethargy and bloody stools can also occur. However, HAEC is highly variable and can present with only mild diarrhea and distension or with septic shock. HAEC remains the leading cause of morbidity and mortality in HD. Mild cases are treated with oral metronidazole and anal dilations. Severe HAEC requires hospitalization, bowel rest, rectal irrigations, and broad-spectrum antibiotics. Another complication specific to HD is the development of obstructive symptoms, which occurs in at least 10% of patients. These patients present with chronic constipation or recurrent episodes of enterocolitis. Possible causes for obstructive symptoms include (1) mechanical obstruction, (2) persistent or acquired aganglionosis, (3) intestinal motility disorders, (4) internal sphincter achalasia, or (5) behavioral disorders. Diagnosing the cause allows targeted therapy, although in some cases no etiology is identified.

Anorectal Malformations

Anorectal malformations (ARMs) represent a spectrum of anomalies characterized by an ectopic, stenotic, or absent opening of the anorectal canal. Considered the most common gastrointestinal anomaly at birth, the worldwide incidence of ARM is reported to range between 1:1,500 and 1:5,000 births. In a large Canadian study, the incidence was 1 in 2,524 live-births, with a similar incidence of 1 in 2,295 in Poland and 1 in 2,500 in the USA. Available data support a slight male predominance at 1.55 males for each female affected.

The embryologic cause of ARMs remains unclear, largely due to a poor understanding of normal anorectal development. Classic teaching held that the cloaca is divided into a ventral urogenital sinus and a dorsal anorectal canal by descent of the urorectal septum and its fusion with the cloacal membrane. ARMs were believed to be due to abnormal partitioning of the cloaca. However, several studies on human embryos have found no evidence that the urorectal septum fuses with the cloacal membrane. Instead, as the septum gets close to the cloacal membrane, the membrane undergoes apoptosis and ruptures, leaving a dorsal anal opening and a ventral urogenital sinus, with the end of the urorectal septum forming the perineum. ARMs are now thought to be due to abnormal development of the dorsal cloacal membrane, which normally gives rise to the anal orifice. A short or absent dorsal membrane leads to a deficient dorsal cloaca. As a consequence, the anal orifice is shifted anteriorly, causing it to enter the urogenital tract in severe cases or the perineum in milder cases. Targeted mutations of the Sonic hedgehog or Wnt signaling pathways lead to ARMs in mice, suggesting critical roles for these pathways in cloacal morphogenesis.

Classification of the various forms of ARMs traditionally separates them into high, intermediate, and low anomalies, as in the commonly used Wingspread classification. Based on the embryologic origin of these defects, the abnormal communication of the distal anorectum with the urinary or genital tract is best perceived as an ectopic anal orifice. The location of that orifice is critically important in determining treatment and prognosis. Therefore, a clinically relevant classification system describes the anomaly entirely based on the location of the anorectal fistula (*Table 418.2*).

Table 418.2
Classification of anorectal malformations

Males	Females
Rectoperineal fistula	Rectoperineal fistula
Rectourethral fistula	Rectovestibular fistula
Rectobladder neck fistula	Rectovaginal fistula
Imperforate anus without fistula	Cloaca
Rectal atresia	Imperforate anus without fistula
	Rectal atresia

In males, the anorectal fistula can open into the perineum, the urethra, or the bladder. The lowest fistulas are rectoperineal and these have a variety of presentations. They can present as (1) an anal orifice, often stenotic, anterior to the normal anal position (*Fig. 418.12a–b*) or (2) a subepithelial tract with the fistula opening along the midline raphe. A "bucket-handle" deformity can be seen in a male with a rectoperineal fistula (*Fig. 418.12c*). Rectoperineal fistulas are associated with a well-developed buttocks and gluteal cleft, normal sacrum, good muscle development of the anal sphincter, and a low incidence of associated anomalies. The most common ARM in males is the rectourethral fistula, which can open into the bulbar (distal) or prostatic (proximal) urethra. Rectourethral fistulas account for about 50% of cases in boys. The highest fistula in males is the rectovesical fistula, which enters at the bladder neck and occurs in only 10% of cases. The higher fistulas are associated with flatter buttocks (*Fig. 418.12d*), poor midline cleft development, abnormal sacrum, poor sphincter muscle development, and an increased risk of associated defects. While the vast majority of ARMs have an anorectal fistula, about 2% of patients with ARMs, including boys and girls, present with imperforate anus without a fistula. These cases are usually associated with Down's syndrome. Even rarer, occurring in only 1% of cases, is rectal atresia. In these cases, the anus appears grossly normal. However, upon attempting to pass a thermometer or catheter into the anal canal, one finds that it ends blindly at about 1–2 cm and does not communicate with the rectum immediately above it.

In females, the lowest fistula, as in males, is the rectoperineal fistula (*Fig. 418.12e*). Often referred to as an "ectopic" or "anterior" anus, these anomalies should be considered ARMs with a rectoperineal fistula. The most commonly encountered ARM in females is the rectovestibular fistula, in which the anorectal orifice is located at the posterior end of the vaginal vestibule. Diagnosis is made by clinical examination with careful inspection of the introitus in a newborn female with an imperforate anus. Fistulas to the vagina are rare. The highest and most complex ARM in females is the

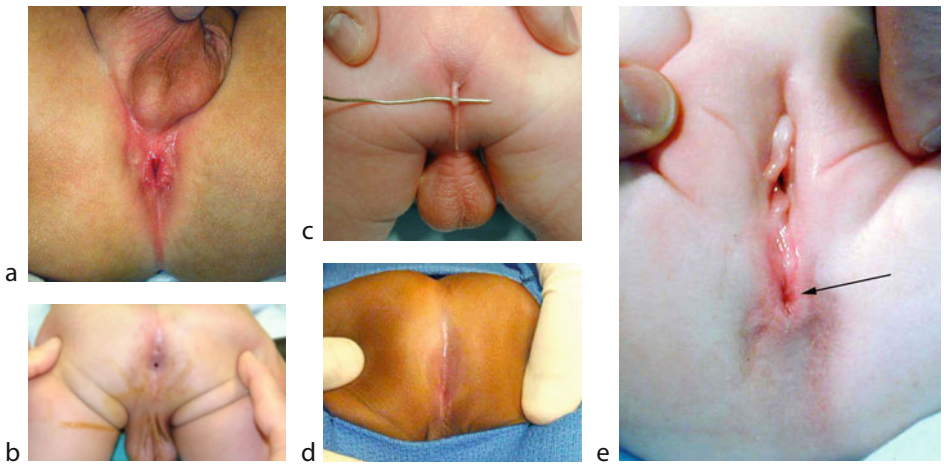

Figure 418.12

Anorectal malformations. (a) Abnormally positioned anal orifice located anterior to the normal anal position. (b) A rectoperineal fistula presenting as a stenotic anal orifice anterior to the normal anal position. (c) A "bucket-handle" deformity in a male with rectoperineal fistula. (d) Absence of the anal orifice in association with a flat buttocks and poor gluteal cleft development are consistent with a high fistula, in this case a rectourethral fistula in a male. (e) Rectoperineal fistula in a female with the anal orifice anterior to the normal anatomic position, leaving a very short perineum

persistent cloaca, in which the rectum, vagina, and urinary tract all fuse and exit as a single channel. The incidence of this rare anomaly is about 1:50,000 births. The anatomy of the pelvic organs in these patients is highly variable and very complicated. Careful physical examination is critical to distinguish this from the rectovestibular fistula, as only a single common orifice will be seen in the cloaca.

ARMs are associated with other congenital anomalies in approximately two-thirds of children. The higher the fistula, the greater the likelihood that the child has an associated anomaly. The anomalies most commonly encountered are listed by organ system in *Table 418.3*. The incidence of these associated anomalies varies widely in the literature, likely due to the vigilance with which each anomaly is sought and also to the relative numbers of high versus low ARMs in a given series. Nevertheless, the incidence of a given anomaly is not critical. What is important is to be familiar with the potential coexistence of specific anomalies in order to guide a thorough physical examination and targeted imaging of the newborn to prevent missed or delayed diagnoses. Preoperative imaging should include plain abdominal radiography to evaluate the lumbosacral spine, abdominal ultrasound to rule-out hydronephrosis or other renal pathology, and echocardiography to assess for congenital heart disease. Voiding cystourethrography and spinal ultrasound should also be performed to rule out vesicoureteral reflux and tethered cord, respectively. Pelvic ultrasound is important in girls with cloacal defects, as these are highly associated with genitourinary anomalies, including hydrocolpos and hemivaginas. The possibility of syndromic disorders should also be considered, as ARMs are known to occur in the setting of several syndromes. For example, Currarino's triad consists of an ARM (usually anal stenosis) with a sacral defect and a presacral mass. ARM is also a feature of Pallister–Hall syndrome, which is due to a mutation in Gli3, a gene downstream of Sonic hedgehog. The VACTERL association includes *V*ertebral defects, *A*RMs, *C*ardiac defects, *T*racheo*E*sophageal anomalies, and *R*enal and radial *L*imb defects. Diagnosis of an ARM should therefore prompt a search for any of these other anomalies. Down's syndrome is known to be associated with ARM, occurring in 2–5%. A karyotype should be obtained in children with ARMs to evaluate for any chromosomal abnormality.

As already mentioned, initial evaluation of a newborn with imperforate anus includes careful perineal examination, thorough physical examination, and appropriate imaging. No decision should be made regarding the presence or location of the anorectal fistula until 24 h of life. This allows time for meconium to appear at the perineum in cases of rectoperineal fistula, or in the urine in cases of rectourethral or rectovesical fistula. If a stenotic perineal fistula is present, then an anoplasty can be performed within the first few days of life. If there is a perineal fistula and the anal opening is not stenotic, allowing passage of

Table 418.3
Anomalies associated with anorectal malformations

Anomaly	% Incidence
Urinary tract	15–31
Renal agenesis	
Hydronephrosis	
Multicystic dysplastic kidney	
Vesicoureteral reflux	
Reproductive tract	8–16
Ambiguous genitalia	
Cryptorchidism	
Bifid scrotum	
Hypospadias	
Skeletal	28–43
Vertebral anomalies	
Spina bifida	
Abnormal rib number	
Polydactyly	
Club foot	
Cardiovascular	17–27
Ventricular septal defect (VSD)	
Atrial septal defect (ASD)	
Tetralogy of Fallot	
Pulmonary stenosis	
Gastrointestinal	17–18
Esophageal atresia	
Duodenal atresia	
Abdominal wall defects	
Craniofacial	34
Cleft palate	
CNS	12
Tethered cord	
Meningomyelocele	

meconium, then the neonate can be discharged with anal dilations and the procedure performed at around 1 month of age. If no evidence of a perineal fistula exists, then the safest course of action is to proceed with a colostomy at 24–48 h of life. Some authors advocate in these cases a prone cross-table lateral radiograph with the pelvis elevated in order to determine the distance from the rectum to the anal skin. Cases in which that distance is less than 1 cm may be amenable to repair without a colostomy. However, this technique can be imprecise and may lead to misinterpretation of the level of the fistula, especially when done in less experienced centers. A divided colostomy with mucous fistula is the safest approach in equivocal cases. This allows later performance of a distal colostogram, which is done by injecting contrast into the mucous fistula in order to identify accurately where the rectum empties. Precisely defining this anatomy preoperatively reduces the risk of injury, especially to the urinary tract, during the definitive repair, which is usually performed at several months of age. A vestibular fistula can be managed either by primary repair or after a diverting colostomy. Either approach is reasonable, but needs to be based on the experience of the operating surgeon. Definitive repair of ARMs is performed using a posterior sagittal approach through the midline of the gluteal cleft with the patient in the prone position. Laparoscopy or laparotomy is added as needed, particularly in cases of high fistulas. The initial management of cloacas is complex, often requiring decompression not only of the colon, but also of the urinary tract and vagina. Definitive repair requires significant experience and therefore appropriate surgical expertise is essential in the proper management of these very complex cases.

Functional intestinal disorders are the most common complication of ARMs and their repair. Constipation is very common, especially among patients with low fistulas, such as perineal or vestibular fistulas. The cause of the constipation is unknown, but may be due to chronic rectal dilatation, abnormal rectal motility, or increased rectal compliance. Constipation typically presents at around the age of toilet training and can often be managed with laxatives. Fecal soiling is a common and challenging problem following repair of ARMs and is reported in about two-thirds of patients. The higher the anomaly, the more likely incontinence will occur. The incontinence is often associated with poor neuromuscular development of the continence mechanism. Surgical injury to those structures during repair or encopresis due to overflow in patients with severe constipation are other reasons for soiling in these children. Patients with fecal incontinence can be managed with laxatives and enemas to clean out the colon daily and thereby minimize the incidence of soiling. Refractory cases may respond well to an appendicostomy or cecostomy for administration of antegrade colonic enemas (ACE). Severe and unrelenting cases benefit from a diverting ileostomy or colostomy. ARMs are also associated with significant psychosocial morbidity, a high rate of behavioral problems, and an increased risk for suicidal ideation. These risks should be assessed proactively in order to provide support for these young patients early in their course.

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419 Acquired Abdominal Conditions

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Pyloric Stenosis

Introduction

The first complete description of hypertrophic pyloric stenosis was presented more than a century ago by Harald Hirschsprung, who is also credited with the first patient series of esophageal atresia, the treatment of intussusceptions by hydrostatic enema reduction, and the description of and congenital megacolon (Hirschsprung's disease). The disease course is well known and its surgical treatment, as devised by Fredet and Ramstedt in the early 1900s, is straightforward. The etiology of pyloric stenosis, however, remains unknown.

Hypertrophic pyloric stenosis is one of the most common surgical conditions in infancy, occurring in 1 in 250 children. It is usually not present at birth, but develops in the first few weeks of life. There appears to be a slight familial incidence without a clear pattern of inheritance. Sporadic cases are much more common than familial ones. There is a strong male preponderance; first-born infants tend to be more often affected. If pyloric stenosis occurs in a girl, her children are at a significantly increased risk of contracting stenosis also. Pyloric stenosis is more common in full-term infants. When preterm infants are affected, they are typically several weeks older than their term counterparts.

Clinical Presentation

Pyloric stenosis appears to be a progressive process of pyloric muscular hypertrophy, often preceded by a period of intermittent pyloric spasm. The infant first vomits formula but not water or Pedialyte, which can be interpreted as intolerance to a particular type of formula. Not uncommonly, formula changes will have been tried before pyloric stenosis is suspected. Nevertheless, there appears to be an increased awareness among pediatricians and primary care physicians so that pyloric stenosis is often suspected earlier in the disease course.

The hallmark of pyloric stenosis is projectile, nonbilious vomiting. The absence of bile helps rule out more distal causes of intestinal obstruction, such as midgut volvulus or Hirschsprung's disease. The appearance of coffee ground vomiting suggests associated gastritis and is often associated with a delay in diagnosis. The child with pyloric stenosis appears otherwise well and extremely hungry, and does not present with associated signs such as diarrhea or abdominal tenderness. Mild jaundice is not uncommon and is believed to be secondary to glucuronyl transferase deficiency.

If allowed to progress untreated, the infant will become dehydrated and lethargic. In severe cases, there may be signs of malnutrition, constipation, oliguria, and profound alkalosis. The latter is a pathognomonic, sign of pyloric obstruction. As the child vomits chloride- and hydrogen-rich gastric contents, hypochloremic alkalosis sets in. Hypokalemia is a result of intracellular shift of potassium ions (in exchange for hydrogen ions) and renal loss as the body attempts to conserve sodium. As potassium is depleted, sodium is exchanged for hydrogen ions in the proximal tubules, giving rise to paradoxical aciduria. The latter hastens systemic alkalosis and, ultimately, cardiovascular collapse.

Today, the full syndrome is very seldom seen. However, most large pediatric surgical centers treat at least one or two patients each year with profound electrolyte imbalance due to longstanding pyloric stenosis.

Clinical Examination

It is often said that pyloric stenosis can be diagnosed clinically in the vast majority of cases. However, palpation of the hypertrophic pylorus, referred to as the "olive" or "tumor," is sometimes difficult and it requires patience. It is important to have the infant in a parent's lap and in a quiet environment, calmed with either a pacifier or a few sips of clear fluid (5% dextrose in water or Pedialyte). If the stomach is full, one-time nasogastric aspiration facilitates the examination. Prior to aspiration, strong gastric peristaltic waves can be visible in the left upper quadrant. The examiner gently palpates the abdomen from the right to the left upper quadrants in a crosswise and up and down fashion. It is useful to first recognize the contour

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of structures most likely to be confused with an enlarged pylorus: the right kidney, the spine, and the right and left rectus muscles. The pylorus is then gently teased from under the liver edge and rolled between the examining fingers and the infant's spine.

If pyloric stenosis is suspected, very few laboratory tests need to be obtained. A simple urinalysis may confirm mild or moderate dehydration and, less commonly, aciduria. The most important test, however, is a serum electrolyte panel. Hypokalemia, hypochloremia, alkalosis, and dehydration can all be confirmed and quantified to guide to fluid and electrolyte replacement before surgical correction is entertained. Blood should be drawn carefully (no heel stick) to avoid hemolysis and an erroneously elevated serum potassium value. In general, no other laboratory tests are needed unless other diagnoses are entertained. Imaging studies are theoretically superfluous if a clinical diagnosis was made. In reality, contrast radiographs or an ultrasound will often have been obtained before the child is referred to a surgeon. In cases where the clinical diagnosis is uncertain, these tests are very helpful. Until the late 1980s, an upper gastrointestinal series was the radiographic examination of choice. Typical radiographic signs are the "mushroom" impression of the antrum and protruding pyloric mucosa, the "track" sign caused by an elongated pyloric channel with straight, parallel mucosal folds, and the "number 3" or "umbrella" sign formed by contrast in the first portion of the duodenum. A contrast radiograph helps to rule out gastroesophageal reflux, which is the most common differential diagnosis.

Ultrasonographic examination of the pylorus has become the most accepted imaging test, supplanting the upper GI. The ultrasound signs of hypertrophic pyloric stenosis are well established. The pyloric channel should be less than 16 mm in length, the total thickness of the pylorus should be less than 14 mm, and the muscular thickness should be less than 4 mm. With pyloric stenosis, any or all of the above values are increased. In addition, an experienced ultrasonographer will be able to see propulsive peristaltic waves of the antrum, pyloric spasm and, if present, gastroesophageal reflux secondary to the obstruction.

Management

Surgical correction of pyloric stenosis is the only sensible form of treatment. The operation for pyloric stenosis is not considered an emergency. Rather, the infant should be well hydrated and the electrolyte anomalies should be completely corrected. In severe cases, this may take 1–2 days, although today, less than 10% of all infants with pyloric stenosis present with any electrolyte abnormality resulting in a delay of surgical intervention. A nasogastric tube is not routinely used unless the child continues to vomit after feedings have been withheld. Intravenous hydration should take into account the source of fluid and electrolyte losses: 0.45 N saline or, in severe cases, 0.9 N saline solution should be used, supplemented with potassium chloride (10–30 mEq/L) after urine output has been documented. If electrolyte anomalies are present, they should be corrected gradually.

At the time of operation, any infant with pyloric obstruction is considered to have a full stomach. Studies have demonstrated that the risk of aspiration on induction is not reduced by nasogastric suctioning, even if performed immediately before anesthesia. Therefore, rapid sequence or awake intubation, with cricoid pressure, is the preferred methods of induction.

The technique of pyloromyotomy has not changed since its initial description. However, many approaches and incisions have been tried. Today, the vertical midline and Robertson incisions (a right upper quadrant muscle-splitting incision, in an attempt to prevent dehiscence in severely malnourished infants) are rarely used. A laparoscopic approach has been well described and is now widely embraced by pediatric surgeons, offering cosmetic and functional advantages to the open technique. For those surgeons who prefer the palpable control over visual superiority, the umbilical approach has become popular. It is a cosmetically gratifying, but anatomically awkward incision, and delivering the pylorus is more difficult.

A nasogastric tube is not necessary and is dangerous postoperatively. Feeding are usually resumed within 6 h and advanced gradually from 15 to 30 mL of an electrolyte solution (Pedialyte) to full formula or breast milk. This will typically take five to six feedings, each 3 h part. Many different feeding regimens exist, and differences may not be relevant. A few principles should be observed: some vomiting is still expected postoperatively, either from gastric spasms if the child has been ill for a prolonged period of time or, more commonly, because of coexisting gastroesophageal reflux. If this happens, feedings can be held, but should be resumed 3 h later. As feedings are advanced, it is important to introduce formula or breast milk (full- or half-strength) early on, before increasing the volume. Clear fluids alone are not enough to keep the pylorus open, and recurrent pyloric stenosis may occur if curds are not allowed to stimulate the pyloric channel. The infant is discharged home once a full feeding schedule is attained, usually within 24 of 36 h.

Complications and Outcome

Major complications are very rare unless the infant was severely malnourished preoperatively. Wound infection may occur and appears to be slightly more common than with comparable, clean operations (e.g., inguinal herniorrhaphy). The incidence of wound complications may be as high as 4–5%, according to some series. Skin or fascial dehiscence may occur as well with those that perform an open technique. Treatment is conservative unless fascial dehiscence or evisceration is present. Antibiotic prophylaxis has been advocated by some, but has not been shown to alter the risk of infectious complications.

Recurrent pyloric stenosis is well described and requires a repeat pyloromyotomy. However, it is a very unusual event today, and most instances of postoperative vomiting are due to reflux. Unrecognized mucosal perforation (usually on the duodenal side) and peritonitis are serious complications that can be avoided by meticulous technique and vigilance. The success rate of pyloromyotomy for infantile pyloric stenosis should approach 100%, and late recurrence does not occur.

Intussusception

Introduction

Intussusception is the most common abdominal emergency seen in the early childhood years (3 months to 6 years), exceeding appendicitis in this age group. Under the age of 3 years, 80–90% of patients experience idiopathic ileocolic intussusception for which, in the absence of peritonitis, nonsurgical management is the mainstay of therapy.

The mechanism of intussusception is clearly understood and occurs when one segment of intestine (intussusceptum) is circumferentially invaginated and propelled into an adjacent distal segment (intussuscepiens). This results in luminal obstruction with progressive venous, lymphatic, and eventually arterial compromise. The most widely held theory is that the submucosal lymphoid aggregates (Peyer's patches) enlarge in response to antigenic stimulation from newly introduced food substances or viral infections as suggested by seasonal variation coincident with viral gastroenteritis and respiratory infections. Additional evidence for this mechanism follows the observations of a spike in the number of intussusceptions after a series of former Rotavirus vaccinations. Stimulated Peyer's patches project into the lumen of the intestine, presenting a transient and pseudopolypoid lead point. Alternative theories include the differential size and motility of adjacent segments of intestine. This theory may be most relevant to postoperative intussusception, which usually involves the proximal jejunum and is devoid of Peyer's patches.

The progress in the management of intussusception has covered centuries. Successful operative management was first reported in the mid-nineteenth century when infants and children continued to have a high rate of mortality related to sepsis and dehydration. In 1878, Harold Hirschsprung, in another of his seminal contributions to the care of infants and children, first proposed hydrostatic reduction. The survival rates of 50% with hydrostatic reduction were superior to those achieved with operative reduction. In the United States, William Ladd of Boston was a proponent for the use of the contrast enema for diagnosis in 1913, but only in 1948 was it accepted for therapeutic intervention. Air reduction techniques were first reported from China, where there is an inordinate incidence of intussusceptions. This technique was slowly introduced to the United States in the 1990s. Sonographic evaluation of the abdomen is a less invasive tool for the diagnosis of intussusception. Doppler imaging with ultrasound provides the advantage of being able to assess intestinal blood flow using and thus identifying those patients that would not benefit from attempts at hydrostatic reduction.

Clinical Presentation

Boys and girls, and various ethnic and racial groups appear to be equally affected. The typical history is that of a child, 6 months to 2 years of age (two thirds occur before age 1 year), with the abrupt onset of abdominal pain causing the child to double over and draw their legs to the abdomen. This episode resolves with the child either returning to sleep or resuming normal activity, only to be interrupted again by a wave of colicky abdominal pain. Occasionally, the pain is accompanied by emesis and passage of a normal stool. The child frequently is diaphoretic and pale during these episodes and with time becomes progressively more apathetic and lethargic. As the bowel obstruction persists, emesis progresses to bilious emesis and the child may pass a bloody, mucus stool (currant jelly stool). Depending on the duration of symptoms, the physical signs may vary. By the time a surgeon is typically asked to see the patient, the child may be quite lethargic and apathetic from dehydration. Between episodes of pain, it is possible to palpate the abdomen and identify the essentially pathognomonic features of an empty RLQ

(sign of Dance) accompanied by a sausage-like mass in the RUQ. Gross or occult blood is often detected at this stage. During acute episodes of colic, no reliable abdominal exam can be elicited and may lead to the false conclusion of an acute abdomen, prompting potentially unnecessary laparotomy. Consideration of this diagnosis and patience with the examination are thus necessary.

Management

In the patient with a high index of suspicion for intussusception, intravenous access should be promptly established and fluids administered in the form of isotonic fluid to correct any deficit. This assessment relies on the adequacy of peripheral perfusion, the presence of lethargy, electrolyte derangements, or metabolic acidosis. The use of antibiotics (i.e., ampicillin and gentamicin), although routine in the past, has now been reserved for those patients requiring operative intervention.

Radiographic studies useful in establishing the diagnosis of intussusception include supine and left lateral views of the abdomen, which may delineate a paucity of gas in the RLQ with a density in the RUQ. In advanced cases, a small bowel obstruction will be apparent. The abdominal film can, however, be completely unremarkable and this should not exclude the diagnosis in a patient with a strong clinical history.

If expert sonographic evaluation is available, it is often used for diagnosis. The intussusception appears as a target shaped lesion. When confirmed by sonogram or suspected by radiograph or exam, the next intervention is the contrast or pneumatic enema. This intervention is performed only after ascertaining that there are no peritoneal signs or other severe compromise from bowel obstruction. Although not essential, some radiologists request that the child be sedated to facilitate the reduction. General anesthesia is not warranted. The method of choice for hydrostatic or pneumatic reduction varies with institutions and includes barium, iso-osmolar water-soluble agents, and air reduction. A catheter inserted into the rectum must be secured to assure an airtight seal. Most radiologists use a catheter with a bulb tip and tape the buttocks together. Guidelines for the height of the contrast column or pressure generated by air insufflation are followed to minimize the risk of perforation. When present, in ileocolic intussusception the intussusceptum can be seen outlined as it moves retrograde toward the ileocecal valve. It is critical to visualize the complete reduction of the intussusception demonstrated by free reflux of contrast or air into the distal small intestine. Multiple attempts at reduction may be required before complete reduction is achieved. Hydrostatic reduction should involve the most experienced personnel before a decision is made that it has failed to achieve a complete reduction. Once the intussusception is reduced, the child often immediately acts as if he/she feels better and typically falls into a sound sleep. A fever may follow directly after a reduction as well. Patients are admitted for continued hydration and are observed for any recurrence of the intussusception, which has been found in 5–8% of patients within 24 h of reduction. If asymptomatic the following morning the child is offered liquids and a diet is advanced to diet for age prior to discharge. Recurrent symptoms are treated with repeat hydrostatic reduction, again ensuring that a complete reduction is achieved. Older children with recurrences at greater intervals must be suspected to have a pathologic lead point.

Surgical intervention becomes necessary when a patient presents with unequivocal peritonitis that usually follows a history of abdominal pain in excess of 48 h. Other indices of severe ischemia or gangrene include sonographic findings documenting an absence of mural blood flow or inability to reduce the intussusception with optimal technique. In the latter circumstance, it is acceptable in some institutions with the appropriate personnel to proceed with one final attempt at hydrostatic reduction in the operating room under general anesthesia. Inability to reduce the intussusception may also indicate a pathologic lead point such as with a Meckel's diverticulum or lymphoma of the small bowel.

Special Considerations in Pediatric Intussusception

Only 2–8% of children under age 2 with intussusception will have a pathologic lead point. This most commonly consists of a Meckel's diverticulum. The prevalence of pathologic lead points may be as high as 57% after age 4 years, but markedly less than found in adults (97%). These atypical causes often lead to ileal–ileal rather than ileocolic intussusceptions which are not as easily diagnosed or amenable to hydrostatic reduction. Ultrasound plays a major role in these diagnoses. Other lead points may be provided by hamartomas associated with Peutz Jegher's syndrome or mural lesions such as heterotopic pancreatic nodules, enteric cysts, adenoma, acute lymphoblastic leukemia, neurofibroma, or hemangioma. Conditions resulting in mucosal and submucosal hemorrhage such as in Henoch–Schonlein purpura, disseminated intravascular coagulation, hemophilia, and even trauma

have been associated with intussusception. Although cystic fibrosis may present with intestinal pseudo-obstruction in the later childhood years, one must consider the possibility of intussusception, which in these cases is most often associated with an enlarged, congested appendix.

Idiopathic intussusception occasionally occurs after unrelated upper abdominal or even thoracic procedures. The main feature of an early postoperative bowel obstruction from an intussusception is a high nasogastric tube output despite a decompressed appearing distal intestine by plain radiograph. The diagnosis is established by either ultrasound or upper intestinal series.

The primary complications related to intussusception result from a delayed diagnosis. The consequent dehydration acidosis and potential sepsis account for a fatality rate of about 1%. The most serious complications related to the hydrostatic reduction are intestinal perforations either in the rectum related to the catheter or more proximally related to intraluminal distension against a fixed obstruction. The rates of perforation are reported to be 0.18% with hydrostatic reduction in contrast to between 1% and 2% with pneumatic reduction with successful hydrostatic reduction parents must be warned of the potential for recurrence, which is suspected on the basis of recurrent abdominal pain and is again treated with hydrostatic reduction.

The vast majority of children that experience idiopathic intussusception are managed with hydrostatic or pneumatic reduction. Successful reduction by barium enema is approximately 85% within 12 h of onset of symptoms and decreases to 70% after 24 h, with an overall success rate of 80%. This rate of success despite prolonged symptoms supports an attempt at hydrostatic or pneumatic reduction, in the absence of peritoneal signs or definite evidence of a small bowel obstruction. The rate of successful reduction was found to be improved with repeated attempts at either barium enema or air reduction after a rest period of variable duration (30 min to several hours) only if there was some retrograde movement of the intussusception with consecutive attempts. Of those patients requiring surgery, approximately 60–80% can be managed without requiring resection.

Meckel's Diverticulum

Introduction

Meckel's diverticulum derives its name from Johann Friedrich Meckel, professor of anatomy at Halle, whose 1809 account of the origin of this diverticular structure was so clear that his name has been eponymously attached to it ever since. Meckel's diverticulum is a vestigial structure, which results from failure of the omphalomesenteric (vitelline) duct to involute. The yolk sac is connected by the omphalomesenteric duct to the primitive gut. This duct attenuates, involutes, and separates from the intestine between the fifth and seventh weeks of gestation. Failure of the yolk sac to involute results in a persistent omphalomesenteric duct remnant whose anatomy is determined by the stage at which the arrest occurs. In a small proportion of diverticula, an omphalomesenteric duct remnant extends from the apex of the diverticulum to the undersurface of the umbilicus. This may be a patent mucosal lined fistula, cystic mass, or fibrous band. Most often there is no connection between the diverticulum and the undersurface of the umbilicus.

A Meckel's diverticulum is a true diverticulum arising from the antimesenteric border of the ileum. As such it contains all layers of the intestinal wall. The mucosa of the diverticulum can contain heterotopic gastric or pancreatic mucosa. Grossly, the diverticulum is usually several centimeters long, although occasional cases of giant Meckel's diverticulum have been described. The diverticulum may have either a broad or a narrow base. The blood supply of the Meckel's diverticulum is usually the same as that of the ileum. Occasionally, the blood supply can arise from the abdominal wall. Meckel's diverticulum is usually located within 100 cm of the ileocecal valve. The Meckel's diverticulum is the most common congenital anomaly of the GI tract. Meckel's diverticulum occurs in between 1.3% and 2.2% of the population based on autopsy studies. The ratio of males to females in asymptomatic patients is nearly equal while the incidence in symptomatic patients is three to one. They are associated with several other congenital and acquired disorders. The incidence of Meckel's diverticulum is increased sixfold in patients with esophageal atresia and fivefold in patients with imperforate anus. Some studies point to an increase in Meckel's diverticulum in patients with cardiac or neurologic abnormalities. Exomphalos also increases the likelihood of having a Meckel's diverticulum. Interestingly, Crohn's disease is associated with a higher incidence of Meckel's diverticulum with a threefold increase noted in patients who required surgery for Crohn's disease.

Clinical Presentation

Most Meckel's diverticula are clinically silent and only 40% become symptomatic presenting in a variety of ways depending on the pathophysiology involved.

Complications of Meckel's diverticulum include obstruction, inflammation, or bleeding. The original descriptions of Meckel's diverticulum assumed a complication rate of 25%, however; a review of a baseline population of over one million people over a 15-year period determined the chance of a Meckel's diverticulum being a cause of disease to be 6% over one's lifetime. Symptomatic lesions are age dependent accounting for 85% of the cases in children less than 1 month of age and 77% between 1 month and 2 years of age. In contrast, symptomatic lesions were found in only 15% of cases of children over 4 years of age. More than 50% of patients with symptoms referable to Meckel's diverticulum will be identified before 2 years of life.

Hemorrhagic causes of pathophysiology in Meckel's diverticulum arise from heterotopic gastric mucosa which results in peptic ulceration of adjacent mucosa causing lower gastrointestinal bleeding. Inflammatory consequences may result from perforation secondary to either peptic ulceration or penetration by a foreign body, which cause Meckel's diverticulitis. Obstruction as a result of the diverticulum can follow events that include: intussusception in which the Meckel's diverticulum acts as a lead point, volvulus around a persistent omphalomesenteric remnant, internal herniation through a mesodermal band (vitelline artery remnant), incarceration of a Littre's hernia, external compression by a omphalomesenteric cyst, or segmental intestinal fibrosis from peptic stricture. Congenital abnormalities leading to pathophysiology include umbilical fistula secondary to patent omphalomesenteric duct or paraumbilical cysts or cords caused by omphalomesenteric duct remnants.

Bleeding is the most common clinical presentation of Meckel's diverticulum. Bleeding accounts for between 25% and 56% of patients who present with symptomatic lesions. Usually the patient presents with painless gastrointestinal bleeding before 5 years of age. The lower gastrointestinal bleeding can produce either melena or hematochezia. The bleeding varies considerably in quantity and character but is usually episodic and often causes anemia requiring transfusion. Occult bleeding with anemia is an infrequent presentation of Meckel's diverticulum.

Management

When bleeding is the presenting symptom for a Meckel's diverticulum gastric mucosa is nearly always present. Scintigraphy can be used to detect gastric mucosa based on the uptake and excretion of pertechnetate isotope by gastric mucosa. Normally the stomach and urinary bladder demonstrate a dense uptake of the radionucleotide while the duodenal loop and proximal jejunum demonstrate accumulation. A positive study shows an abnormal accumulation of radionucleotide usually in the right lower quadrant. The sensitivity of this study is 85%, the specificity is 95%, and the accuracy is 90%. Pentagastrin, histamine blockers, and glucagon can be used to increase the accuracy of scanning.

Because the bleeding from a Meckel's diverticulum tends to be episodic and frequently stops spontaneously, elective surgery can usually be deferred until the diagnosis is confirmed and the patient is stabilized. Blood transfusion and rehydration are usually necessary. Emergent exploratory surgery is usually not required. Appropriate treatment is resection of all heterotopic gastric mucosa through either diverticulectomy or segmental ileal resection. Areas of bleeding or ulceration should be sought and resected or oversewn. Incidental appendectomy is usually also performed. The bleeding should not recur after surgery, if it does a retained portion of gastric mucosa should be ruled out. Overall results for diverticulectomy or segmental ileal resection are excellent.

Obstruction: Clinical Presentation

Meckel's diverticulum may cause intestinal obstruction through many mechanisms. Intussusception and volvulus are the most frequent causes of obstruction secondary to Meckel's diverticulum. In a combined series of over 1,000 patients, intussusception accounted for 46% of the obstructions and volvulus 24%. Typically intestinal obstructions present with crampy abdominal pain and vomiting that can become bilious. If an obstruction persists and progresses from a partial to a complete blockage, the intestine will become ischemic and can eventually become gangrenous and perforate. At this point peritoneal signs will develop and the pain will become constant. Associated symptoms can include fever, dehydration, lethargy, diarrhea, or hematochezia. The diagnosis of intestinal obstruction is a clinical diagnosis. Plain abdominal radiographs including a flat and upright or a decubitus view are also essential to making the correct diagnosis. Meckel's diverticulum is rarely diagnosed preoperatively as the cause of the bowel obstruction. If intussusception is suspected the diagnosis can be confirmed using ultrasound or the patient can proceed directly to fluoroscopy where a barium enema or air contrast enema is performed for diagnosis and to reduce the intussusception. If a Meckel's diverticulum is the lead point of the

intussusception the chance of reducing the intussusception nonoperatively is unlikely.

Inflammation: Clinical Presentation

Meckel's diverticulitis is a common cause of a complication of a Meckel's diverticulum but it is unusual in children. Typically, patients present with vague abdominal pain which localizes to the right lower quadrant. Associated symptoms include anorexia, nausea, vomiting, and fever. Meckel's diverticulitis is usually misdiagnosed as acute suppurative appendicitis and should be suspected in all operations for suspected appendicitis in which the appendix is normal. The diagnosis is therefore usually made during laparotomy. The indications for surgery are the same as those of appendicitis and are typically based on clinical findings. If considered within the diagnostic workup for appendicitis, computed tomography and ultrasound can be valuable adjuncts to making the diagnosis.

Fistula: Clinical Presentation

A fistula connecting the ileum to the umbilicus is the result of a persistent omphalomesenteric duct usually present only during the newborn period. A patent duct should be suspected in all infants with umbilical polyps or granulation tissue especially if there is an associated sinus tract. A history of discharge of ileal contents or passage of flatus through the fistula is pathognomonic for a patent omphalomesenteric duct. In the case of a complete omphalomesenteric duct, there can be varying degrees of mucosal prolapse based on the diameter of the fistula. When the fistula is short and broad, the ileum may intussuscept onto the surface of the umbilicus producing a double horned segment of bowel, inside out, with the lumen evident on each horn. When the fistula is incomplete there is either an associated cyst which typically presents after the newborn period due to secondary infection or a cord which may act as the source of intestinal obstruction. The diagnosis of a fistula can be confirmed by performing a sinogram to demonstrate the communication between the umbilicus and ileum in the case of a complete fistula. Ultrasound is another useful tool for diagnosing incomplete, cystic omphalomesenteric duct remnants.

Resection by open or laparoscopic methods is the treatment for all symptomatic cases. This is accomplished with or without small bowel resection and the outcome for all children is universally good.

Appendicitis

For most pediatricians and pediatric surgeons, appendicitis continues to be one of the major emergency evaluations performed either in office or hospital settings. The history and nuances of the evolution of the workup of right lower quadrant pain has occupied numerous texts and articles. Our fascination with the deviations in the course of appendicitis and its outcome has formed the basis of many pediatric and surgical investigations. Just as the diagnostic evaluation of appendicitis has marched forward to utilize imaging techniques of ultrasound, CT, and most recently MRI, so to have positive technical innovations progressed from open appendectomy to the almost universal laparoscopic appendectomy. Although no etiologies have been determined for appendicitis, it still remains open to investigation with evidence of increasing western obesity coinciding with an increasing incidence of appendicitis. These observations point to diet as a main contributory factor.

Clinical Presentation

It is well known that acute appendicitis can mimic any intra-abdominal process; however, the majority of cases of appendicitis appears straightforward and is easily determined by a careful history and physical examination. Most children between the ages of 6 and 18 years old experience epigastric and periumbilical pain followed by nausea, some vomiting, and anorexia. Subsequently, there is localization of the pain to the right lower quadrant. Physical signs indicate right lower quadrant abdominal rigidity and over the course of time there is rebound tenderness indicating peritoneal irritation.

The real diagnostic dilemmas come in the absence of a classic history of appendicitis or a delay in treatment. For those patients with a history of recurrent episodes of abdominal pain or a recent viral or streptococcal illness, the apparent cause of acute appendicitis may not be clear. Many patients lack anorexia as a symptom and similarly many may have diarrhea as a result of peritoneal irritation. It is essential that pediatricians and pediatric surgeons should not abandon the diagnosis of appendicitis or jump to the diagnosis of gastroenteritis as these may be late signs of advanced peritoneal irritation or a pelvic abscess. The anatomic position and the appendix may lead to different symptoms especially irritative urinary symptoms of frequency and urgency which may accompany findings of pelvic appendicitis. Findings on urinalysis of blood or white cells may prompt one to consider

infection or calculus in association with the abdominal pain. Retrocecal acute appendicitis may have no anterior abdominal findings; however, it would present with flank pain as the chief complaint. Finally, abnormalities in the bowel rotation may lead to peritoneal findings in the upper abdominal quadrants.

Fever and anorexia may or may not be present as symptoms and a high fever may indicate advanced appendicitis and perforation. The history obtained from each child allows the physician to generate a differential diagnosis. It is important to note the age, sex, and previous medical history are all important for primary consideration for appendicitis. The physical findings with right lower quadrant tenderness or other signs of peritoneal irritation will lead to the next steps in the diagnostic workup. In older children, it is important to perform rectal and occasionally pelvic examinations to determine whether any other pelvic pathology as the cause of pain and inflammation. Pelvic inflammatory disease must be considered in the differential diagnosis.

Once the diagnosis suspected acute appendicitis and majority of cases should be confirmed by appropriate laboratory studies to include a complete blood count with differential and urinalysis.

Over the past decade, there has been significant controversy over the best examination that will determine appendicitis with uniform high sensitivity and specificity. In centers with outstanding ultrasonagraphy, the sensitivity and specificity can be greater than 85%. CT scanning with contrast has a similar high sensitivity and specificity; however, it comes with the concerns for significant radiation exposure. It is beyond the scope of this chapter to discuss the merits of each as most centers will have a clear understanding of the protocols and clinical pathways that have led to the highest rates of accurate diagnosis to achieve treatment with the lowest rates of complications.

The treatment for acute appendicitis still remains as appendectomy. Whether it is performed through a right lower quadrant incision or performed laparoscopically, patients are usually prepared for surgery with fluid resuscitation and perioperative antibiotics. There are many institutional variations on the types and duration of antibiotic coverage; however, for acute appendicitis a single dose of preoperative antibiotics has been found to be the most effective at reducing wound infection. For those patients who present with advanced appendicitis or are found to have intra-abdominal abscess by imaging, antibiotics are started to reduce the incidence of associated sepsis.

Minimally invasive drainage of intra-abdominal abscess by catheter techniques has reduced significant morbidity from laparotomy in cases where enterotomies and hemorrhage may be significant complications. Many patients with limited symptoms presenting with an abdominal mass in the right lower quadrant have been treated with courses of antibiotics alone followed by interval appendectomy. If the mass fails to respond after between 2 and 5 days of conservative management, an abscess is almost always certainly present and should be drained either by either percutaneous means or by an open operative intervention.

Infants and children under 5 years old have notoriously variable presentations and frequently present with perforation. They often are suspected of having advanced gastroenteritis which further complicates their course and leads to a delay in diagnosis. These patients clearly are most in need of advanced pediatric surgical and often critical care expertise. First and foremost they should be aggressively resuscitated and undergo expert evaluation. Often surgical suspicion and judgment lead to an exploratory laparotomy as the only diagnostic and therapeutic option.

Pediatricians often face complications from appendicitis following appendectomy for acute suppurative, gangrenous, or perforated appendicitis with or without abscess formation. The most common complication is a wound infection. This may occur in the right lower quadrant McBurney incisions in approximately 30% of patients with perforated appendicitis. Alternatively, surgeons may have chosen to leave these wounds open. In the face of a local wound infection, the skin should be opened and dressings utilized to clear any subcutaneous abscess. Wound healing by secondary intention usually follows over 2 weeks.

More rarely, wound infections can occur at the sites of trocar placement for laparoscopic appendectomy. The treatment is the same. Following appendectomy patients may present with diarrhea due to long courses of antibiotic use for intra-abdominal abscess. The most serious complication comes from Clostridium difficile-associated diarrhea. Stool cultures are essential and treatment must be rapid.

A more complicated postoperative presentation may occur in patients with recurrent intra-abdominal abscess. On these occasions, these patients may present with intermittent high fever, nausea and vomiting, diarrhea, and even bowel obstruction due to ileus or mechanical factors. Upper abdominal abscesses may present with shoulder pain or pleural effusions and lower abdominal abscesses may present with diarrhea or urinary symptoms. In these cases, imaging by CT scan is essential to rule out abscess and to define bowel obstruction. Percutaneous abscess

drainage is necessary for most cases. Occasionally, an intra-abdominal phlegmon is determined and a secondary course of antibiotics will be sufficient.

Long-term complications include small bowel obstruction secondary to adhesions along with theoretic implications for fertility due to pelvic inflammation. In all cases of appendicitis, it is essential that there be a continuum of care beginning with the patient's pediatrician that extends to pediatric emergency physicians, pediatric surgery, and back again to the patient's general pediatrician. This allows for the best outcome for these patients and their families.

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420 Thoracic Surgical Procedures

Erica R. Gross · Robert A. Cowles

Thoracic surgery in children is indicated for the treatment of both congenital and acquired diseases. Congenital disorders include pulmonary and gastrointestinal (GI) malformations. The most common congenital pulmonary abnormalities result from anomalous development of the lung parenchyma or distal airways, resulting in congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration (BPS), congenital lobar emphysema (CLE), or bronchogenic cysts (BC). The esophagus is the gastrointestinal organ located in the thorax, and esophageal atresia (EA) is the most common congenital malformation of this organ requiring surgical intervention. Parapneumonic effusion, with or without empyema, is the most commonly acquired thoracic disease that warrants surgical consultation. This chapter will review these most common thoracic surgical conditions affecting infants and children, focusing on presentation, evaluation, and surgical therapy.

Esophageal Atresia

Definition/Classification

Esophageal atresia (EA) is a congenital defect of esophageal development, resulting in a blind-ending upper esophageal pouch and a lower esophageal remnant. There are four anatomic forms of esophageal atresia, three of which are associated with an anomalous communication between the esophagus and the trachea, known as a tracheoesophageal fistula (TEF) (*Fig. 420.1*, types B–D). The fistula may connect the proximal or distal esophagus, or both remnants, to the trachea. EA with a distal TEF is the most common anomaly accounting for approximately 85% of cases. A fifth anatomic variant exists in which only a TEF exists without EA (*Fig. 420.1*, type E).

Etiology/Epidemiology

The trachea and esophagus derive from the foregut during the fourth week of embryogenesis. At this time, the foregut divides into a ventral respiratory tract and a dorsal gastrointestinal (GI) tract, consisting of the esophagus proximally. This separation is not complete in patients with EA, which occurs in approximately 1 in 3,500 live births. Environmental or genetic factors have been speculated to play a role in the pathogenesis of EA, but no definitive etiology has been identified.

No single gene has been found responsible for the development of EA, and the inheritance pattern is multifactorial. The increased risk of having a second child with EA is only 1%. Associated anomalies occur in 50% of patients with EA. Only 6–10% of patients with EA, however, have a defined genetic syndrome. The following genetic syndromes associated with EA have been identified: anophthalmia-esophageal-genital syndrome (SOX2), CHARGE syndrome (CHD7), Feingold syndrome (MYCN), Pallister-Hall syndrome (GLN13), and VACTERL (FANCB).

Clinical Manifestations

Increased utilization of screening ultrasound (U/S) during pregnancy has allowed for identification of EA prenatally in the fetus. Since ultrasonographic findings are not specific for EA, however, it is not uncommon for EA to be diagnosed after birth. Neonates with EA are classically described as having copious oral secretions and respiratory distress, often with initial feeding attempts. Inability to successfully pass an orogastric tube is a common clinical finding. Physical examination may reveal associated anomalies, such as vertebral or limb abnormalities, but in isolated cases of EA with or without TEF, the rest of the physical will be normal.

Diagnosis

Prenatal diagnosis of EA is possible and is based on the findings of polyhydramnios, a small stomach, and decreased fetal weight on fetal U/S or magnetic resonance imaging (MRI). Sometimes, a fluid-filled upper esophageal pouch can be seen, suggesting the diagnosis.

Postnatally, EA is commonly diagnosed clinically by the failure to pass an orogastric tube at birth in a child with

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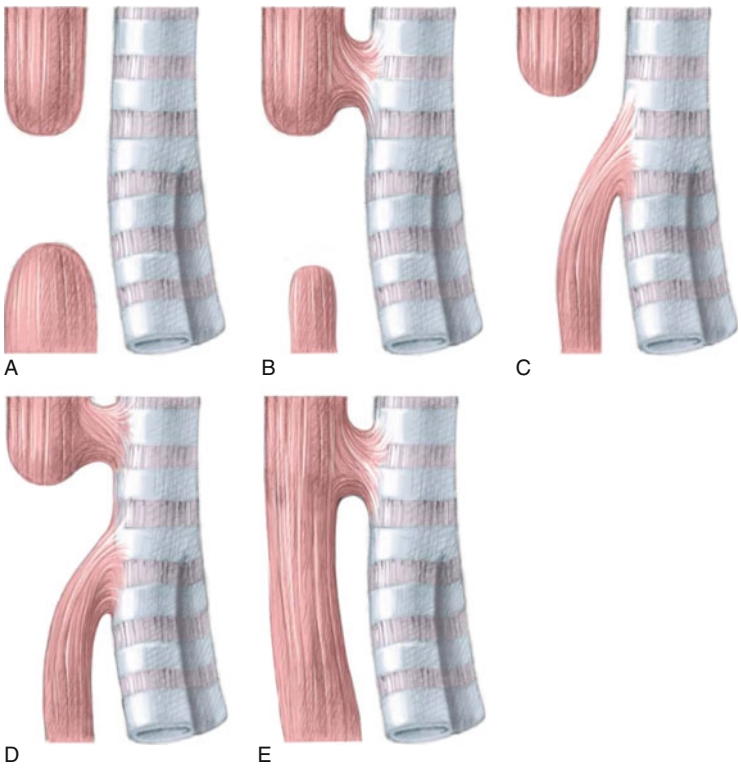

Figure 420.1
Illustrations of Esophageal Atresia and/or Tracheoesophageal Fistula: (A) Pure esophageal atresia. (B) Esophageal atresia with proximal tracheoesophageal fistula. (C) Esophageal atresia with distal tracheoesophageal fistula. (D) Esophageal atresia with both proximal and distal tracheoesophageal fistulae. (E) Tracheoesophageal fistula without esophageal atresia

excessive drooling or after vomiting the initial feed. Chest radiography (CXR) shows coiling of the tube in the upper esophagus. If a TEF connecting the airway to the lower esophageal remnant is present, a normal bowel gas pattern will also be seen. When no connection is present as is seen in pure esophageal atresia, the CXR will show a gasless abdomen (type A). Bronchoscopy can identify the specific location of an upper TEF. A careful esophagogram with contrast administered via the nasoesophageal tube under fluoroscopy can be used to confirm the diagnosis in unclear cases and to evaluate the presence of upper esophageal fistulas.

It is important to assess all patients with EA for the presence of associated anomalies. Epidemiologic studies indicate that 60% of patients with EA have congenital anomalies that may or may not be part of a defined association, such as VACTERL or VATER. Limb and anorectal abnormalities can be appreciated on physical exam, while vertebral, renal, and cardiac malformations require additional imaging. Spinal radiography, renal ultrasound, and echocardiogram are recommended. An echocardiogram also aides in surgical planning by determining the side of the aortic arch.

Differential Diagnosis

It is important to keep in mind that any obstruction of the esophagus in utero will cause polyhydramnios. Therefore, other esophageal, gastric, and duodenal pathology should be considered. Another condition that can mimic EA is iatrogenic perforation of the esophagus at the level of the pharynx. Bloody output from the esophageal tube should alert the surgeon and the neonatologist to this possibility.

Treatment

Initial management of EA focuses on control of oral secretions to minimize aspiration pneumonitis. The infant

should not be fed by mouth, a Replogle tube should be placed and maintained on low continuous wall suction, and the head of bed should be elevated to minimize reflux.

Surgical management consists of separation of the airway and GI tract, esophageal reconstruction, and access for enteral feeding. A distal TEF allows reflux of gastric acid into the respiratory tract, and semi-urgent surgery is necessary to divide this fistula and prevent respiratory complications. Closure of a distal TEF also allows the neonate to be ventilated safely, without distention of the GI tract. A TEF of the upper pouch may be managed acutely with a Replogle, and urgent surgery may be planned for fistula closure. Timing and approach to esophageal reconstruction depends on the size of the gap between the two esophageal pouches and the presence or absence of a TEF. Ideally, primary anastomosis of the proximal and distal esophageal remnants would be performed at the time of fistula division. Primary repair of the esophagus may be delayed in low birth weight infants or neonates with significant cardiac or respiratory comorbidities. Pure esophageal atresia suggests that a long gap exists between the two portions of the esophagus. Therefore, in these cases a gastrostomy tube is placed for enteral feeding while the infant is permitted to grow. Surgery for EA is accomplished via a right thoracotomy unless the TEF is in the cervical region or when the aortic arch is right-sided.

Prognosis

Historically, Waterston et al. determined that prognosis was very closely related to birth weight, as an index of prematurity, associated anomalies and pneumonia. At the time of Waterston's report, overall survival was only 50%, while patients that did not have any of the aforementioned risk factors had a survival of 95%. Today, overall survival approaches 90% and Waterston's criteria have been re-evaluated. Birth weight under 1,500 g and the presence of major congenital cardiac disease have been reported as the remaining significant risk factors contributing to mortality of patients with EA. Advances in neonatal intensive care and surgical and anesthetic techniques have improved the prognosis of infants with EA, but these patients still have significant short- and long-term morbidity.

Anastomotic leak is the most concerning perioperative complication, occurring in 13–20% of cases. Significant leaks can lead to sepsis and may require surgical reintervention. Minor leaks, which are more common, typically present on imaging as extravasation of contrast during post-op esophagogram prior to feeding. When this occurs, management is usually conservative, consisting of prolonged drainage of the retropleural space and postponement of enteral feeding. The majority of these minor leaks close without further intervention.

With improved overall survival, long-term morbidity after EA repair is a major concern. Poor feeding, esophageal stricture, and gastroesophageal reflux (GER) are postoperative sequelae that require active management. Poor feeding is usually secondary to impaired esophageal motility, but stricture must be ruled out. Stricture is a common, early complication and occurrence has been reported as high as 80%. Symptomatic patients with evidence of stricture on imaging studies should undergo dilation. Dilation may be required in approximately 70% of these patients. Stricture may be a complication of the original surgery (anastomosis under tension and/or poor vascularization of anastomosis) or as a result of ongoing GER. Stricture has been reported in >50% of patients with GER versus >20% without GER. Patients with pure esophageal atresia are at the highest risk for stricture.

GER occurs early, and lifelong management is essential in EA patients. Engrum et al. reported 40% of infants had GER after EA repair. Many patients have GER despite not having symptoms and therefore require empiric acid suppression therapy. Extended endoscopic surveillance of patients after repair of EA has shown that 15% of patients have evidence of esophageal metaplasia only 10 years after surgery. Some of these patients had no evidence of reflux on investigation with pH probes. EA is a risk factor for metaplasia and all patients regardless of symptomatology or evidence of GER should have endoscopic surveillance for mucosal changes. Six cases of esophageal cancer have been reported in patients with repaired EA, ranging from 22 to 46 years of age at presentation, with both squamous and adeno-carcinomas having been documented.

Recurrence of TEF is a possible short- or long-term complication. This can occur in the early postoperative period, but may not be recognized or become symptomatic for months, typically presenting as recurrent pulmonary infections. Incidence has been reported as 5–10%, and patients present between 2 and 18 months after EA repair.

Prevention

There is no known prevention.

Congenital Lung Malformations

Screening prenatal U/S has increased in accuracy and this has led to earlier identification of congenital lung

malformations that may otherwise have been asymptomatic after birth. While they can be seen prenatally, these lesions are best differentiated postnatally and fall into several different categories. Congenital pulmonary airway malformations (CPAM), bronchopulmonary sequestration (BPS) or hybrid lesions are most common, and congenital lobar emphysema (CLE) or bronchogenic cysts (BC) occur less frequently. All four lesions require surgical management, but may present differently.

Definition/Classification/Etiology/Epidemiology

Congenital Pulmonary Airway Malformation (CPAM). Previously referred to as congenital cystic adenomatoid malformation (CCAM), CPAM is characterized by an overgrowth of terminal bronchioles, forming various sized cysts. CPAM probably results from a cessation of bronchomaturation and concomitant overgrowth of mesenchymal elements during the fifth to sixth week of gestation. CPAMs are intrapulmonary masses. They are hypovascular and show signs of hyperproliferation. Histologically, cartilage is absent and smooth muscle and elastic tissue are increased in cyst walls. These lesions do not participate in gas exchange, although often there is a small bronchial communication allowing for infection and overinflation of the cyst. CPAMs can rapidly proliferate causing mediastinal shift and hydrops in utero or respiratory distress secondary to restrictive ventilation after birth. U/S studies have shown evidence of regression in antenatal lesions; however, postnatal CT scans are highly sensitive in identifying these lesions. Stocker et al. designed a classification system based on pathological features and cyst size, describing three types of CPAMs. Adzick et al. simplified this classification based on gross anatomy and ultrasound findings.

Bronchopulmonary Sequestration (BPS). BPS is a mass of nonfunctional lung tissue that receives blood supply from an anomalous systemic artery and lacks bronchial connections. The arterial supply can arise from the supradiaphragmatic or infradiaphragmatic aorta. Either the pulmonary or the systemic veins are responsible for venous drainage. Incidence in the general population is estimated at 0.15–1.7%. There are two types of pulmonary sequestration, intralobar (IPS) and extralobar (EPS). Intralobar sequestrations are more common, incorporated and surrounded by normal lung tissue, and commonly located in the lower lobes, left more common than right. Blood supply to an IPS originates from the descending aorta and is typically found within the inferior pulmonary ligament. EPS is isolated from normal lung by a separate visceral pleura. EPS can be found in the thorax or in the abdomen, in a subdiaphragmatic position. These lesions predominate in males and are more commonly identified in the left hemi-thorax. Approximately 4% of cases of EPS are associated with congenital diaphragmatic hernia (CDH), eventration, or tracheoesophageal fistula. Some lesions demonstrate pathology of both CPAM and BPS and are characterized as a hybrid lesion. This shared pathology suggests a shared embryologic origin.

Congenital Lobar Empysema (CLE). CLE results from an abnormality of cartilage formation within the bronchial tree. The flexible cartilage allows for air trapping and overdistention of alveoli, simultaneously compressing adjacent lung tissue and further decreasing surface area available for oxygenation and ventilation. These lesions can become so distended that they cause mediastinal shift. The etiology of CLE is unknown, and the incidence is 1 in 20,000–30,000. CLE is usually unilateral and most often affects the left upper lobe. Upper lobe disease is generally more symptomatic than middle or lower lobe disease.

Bronchogenic Cyst (BC). BCs can be located in the lung parenchyma or more commonly in the mediastinum near the carina. They result from the anomalous budding of the tracheobronchial tree and are part of the spectrum of foregut duplication cysts. They are lined with ciliated epithelium and contain mucoid material. These cysts can communicate with the bronchial airway and are at high risk for infection. If they occur in the mediastinum, they can present with dysphagia rather than respiratory distress.

Clinical Manifestations

Presentation of pulmonary malformations depends less on the specific diagnosis and more on the size of the lesion or the rate of its growth. CLE, CPAM, and IPS are the most likely lesions to become symptomatic in the antenatal or neonatal period. BCs are usually asymptomatic, but may cause recurrent pulmonary infection in childhood. EPS is the least likely lesion to be symptomatic because of the lack of communication with the airway, and typically presents as an incidental finding.

Antenatal. The majority of these lesions are identified on screening prenatal U/S as early as 18–20 weeks gestation. According to a recent meta-analysis, 79% of pulmonary malformations are diagnosed by antenatal screening U/S. Typically, these lesions are asymptomatic in utero and can show regression in the third trimester. A large thoracic mass in utero can lead to mediastinal shift, lung hypoplasia, polyhydramnios, and cardiovascular

compromise resulting in hydrops and even fetal demise. One prospective study showed a 30% rate of hydrops in a cohort of 120 fetuses prenatally diagnosed with CPAM. A similar rate of hydrops was seen in a cohort of 39 cases of extralobar sequestration.

Postnatal. Patients can present in the neonatal period, with respiratory distress, tachypnea, wheezing, grunting, and/or cyanosis secondary to a space occupying lesion and/or mediastinal shift. In a meta-analysis, 17% of live births diagnosed antenatally with CPAM became symptomatic, requiring surgery, in the neonatal period. The majority of patients with CLE present in the first 6 months of life.

Childhood. In childhood, symptomatic patients present with chronic cough, recurrent upper respiratory or pulmonary abscess.

Diagnosis

Antenatal. Prenatal U/S and MRI are sensitive, but not specific in differentiating between congenital pulmonary anomalies. Macrocystic CPAMs are composed of single or multiple cysts $\geq$5.0 mm in diameter on prenatal U/S, whereas microcystic lesions are solid, echogenic masses on sonography. Serial prenatal U/S can show regression of CPAM lesions. BC appears as unilocular well-defined echodense, fluid-filled, homogeneous mass on prenatal ultrasonography. Color-flow Doppler may identify a systemic arterial supply to these lesions. If no arterial artery supply is identified, a microcystic CPAM and BPS are difficult to differentiate on U/S. Intralobar and extralobar sequestrations cannot be differentiated on prenatal ultrasound.

Postnatal. If a mass has been identified antenatally, and the neonate is asymptomatic at birth, a CXR should be the initial imaging study. Normal chest radiography (CXR) does not exclude congenital lung pathology. Computed tomography is 100% sensitive and necessary to evaluate the size and nature of the lesion and should be performed in the first 3 months of life for operative planning.

If the child is symptomatic, immediate CXR will rule out pneumothorax or show mediastinal shift. If the neonate is stable after medical management, a CT can be performed to aide surgical resection. If a child presents with recurrent upper respiratory infection and there is concern for underlying congenital lung pathology, a CT should be performed despite a negative CXR.

In CLE, CXR shows a hyperinflated lobe, often with mediastinal shift. This finding can be misinterpreted as a pneumothorax and mistreated with tube thoracostomy. If this occurs, CT scan is more sensitive than CXR to confirm the diagnosis of CLE. Extralobar pulmonary sequestions are echodense and have a systemic arterial blood supply arising from the aorta. This "feeding vessel" can be seen on CT and less often seen on fetal ultrasound. Significant discrepancy exists between diagnosis of cystic lung lesions made by imaging and histopathological diagnosis.

Differential Diagnosis

The differential diagnosis for a fetal thoracic mass can include CPAM, BPS, CLE, BC, or congenital diaphragmatic hernia (CDH). Prenatal MRI can aide with differentiation, but results will not change in utero management. With a delayed diagnosis of CPAM or BPS in the second and third decades, malignant transformation needs to be ruled out.

Treatment

Surgical excision is the mainstay of treatment for all four entities. Timing of surgery depends on presentation and comorbidities of the child.

Symptomatic. When identified in utero with morbid complications, such as hydrops or polyhydraminos, fetal intervention should be considered. Thoracoamniotic shunting, laser ablation, and fetal lobectomy (intrauterine surgery) are available at a few, highly specialized centers.

For patients that present in the neonatal period in respiratory distress, after medical stabilization, lobectomy is indicated. The surgeon should be present at induction of anesthesia to perform an emergent thoracotomy if needed to relieve intrathoracic pressure, which can cause vascular collapse if sustained. This is especially true for CLE.

Complete surgical resection with lobectomy is also recommended in patients that present outside of the neonatal period with chronic cough and/or recurrent pulmonary infection.

Asymptomatic. For infants that are diagnosed antenatally, and remain asymptomatic through the first month of life, thoracoscopic lobectomy of the affected lobe is recommended to prevent infection and possible malignant degeneration. The average time of onset of symptoms is 7–10 months. Elective lobectomy is typically performed between 3 and 6 months of age to reduce postoperative ventilation days, maximize intrathoracic space to utilize laparoscopic equipment, and decrease the likelihood of infection.

Surgical Approach. Lobectomy, rather than segmentectomy of the affected lobe is recommended because recurrence of infection in incompletely resected lesions (segmentectomy) has been reported. Thoracoscopic lobectomy is an attractive alternative to thoracotomy, which may result in fewer ventilator days and shorter hospitalizations. Thoracoscopy, however, may not be tolerated by all patients, especially in an emergent setting. Extralobar BPS and BC can be treated with segmental resection alone; however, intralobar BPS, CLE, and CPAMs require lobectomy to prevent postoperative complication such as prolonged air leak or recurrence of infection, which requires reoperation.

Prognosis

Overall prognosis depends primarily on the size of the lesion, rather than the type. Presentation with hydrops during pregnancy is an indicator of poor outcome. In fetuses with prenatal diagnosis of CPAM, Adzick et al. reported 100% mortality after expectant management of hydropic fetuses (n = 25). All nonhydropic fetuses (n = 76), that were expectantly managed, survived to discharge, with or without (13%) surgical management. Eight of 13 (62%) hydropic fetuses that underwent intrauterine lobectomy, survived to follow-up of 1–7 years.

Complete resection results in cure. Asymptomatic antenatal diagnosis is very favorable. In a meta-analysis, of all antenatally diagnosed CPAM, 4% died in utero and only 1% of live-born infants died in the neonatal period prior to surgery. The same study reported a 7.5% perioperative mortality rate and a 28% morbidity rate after resection in symptomatic neonates. Elective neonatal cases had a lower rate of perioperative complication (9%) and 0% mortality. After the neonatal period, complications were reported in 17% of patients that were symptomatic prior to surgery, with a mortality rate of 3%. The complication rate in elective surgery was 5%, with one reported mortality (0.3%). Residual disease was reported in 15% of patients after segmentectomy, while no recurrence was reported after lobectomy.

Approximately, 30 cases have been reported with malignant degeneration of CPAMs and BCs. Pathology has been identified as bronchoalveolar carcinoma, embryonal rhabdomyosarcoma, and mucinous adenocarcinoma. The age at diagnosis of malignant degeneration has been reported as 20–40 years old; however, embryonal rhabdosarcoma arising in a CPAM has been documented as early as 22 months old. Few pulmonary function tests have been performed and reported in these patients, however, new alveoli and acini are forming until approximately 5 years of age, followed by enlargement of existing alveoli.

Prevention

There is no known prevention. However, because of documented cases of malignant degeneration of these lesions, resection is strongly recommended, even when asymptomatic.

Parapneumonic Effusions and Empyema

Definition/Classification/Etiology

Pneumonia is an infection of the lung parenchyma. If not quickly or effectively treated with antibiotics, a transudative (parapneumonic) effusion can develop. When a parapneumonic effusion becomes consolidated, purulent and fibrinous, it is classified as an empyema. This evolution has been separated into three stages. The initial stage, or exudative stage, is characterized by increased permeability secondary to inflammation resulting in a collection of fluid in the pleural space. When sampled, the fluid is thin, is typically serous, contains neutrophils, has a normal pH and glucose, and is often sterile. The fibrinopurulent stage occurs after translocation of bacteria into the pleural space, increasing the inflammatory reaction, neutrophil activation, and fibrin deposition. Glucose and pH levels decrease and protein and LDH levels increase. Finally, in the organizing stage a pleural peel develops secondary to fibroblast proliferation, and restrictive lung disease develops.

Epidemiology

Complicated parapneumonic effusions are increasing in incidence in the United States and Europe. In the United States, the incidence is approximately 10 per 10,000 cases of pneumonia or 1 in every 150 children that are hospitalized with pneumonia.

Pathogenesis

The pleural inflammatory response activates the coagulation cascade, favoring increased procoagulant activity and depressing fibrinolysis. This new balance favors fibrin deposition. Fibrin strands act as a framework for

fibroblasts to deposit basement membrane proteins, creating loculations and the pleural "peel" that are seen on imaging studies and at surgery.

Pathology

Patient age or immune state typically defines the bacteriology of the infection. The most common organisms in the pediatric population are *Streptococcus pneumonia* and *Staphalococcus aureus*. Group A strep can be seen as a complication of an infectious skin disorder, such as varicella or impetigo. *Haemophilus influenzae* is seen in patients who have not been adequately vaccinated. Methicillin-resistant *Staph aureus* is growing in incidence in the older pediatric and adolescent age groups.

Clinical Manifestations

In general, patients with parapneumonic effusions present with the same clinical manifestations of bacterial pneumonia, such as fever, cough, pleuritic chest pain, and dyspnea. These symptoms may be suppressed in the immunocompromised population. Patients with empyema may have worsening respiratory distress secondary to lung restriction. The course of empyema is different between children and adults. Children commonly develop empyema after community acquired pneumonia, whereas adults more commonly have risk factors, such as diabetes, neurologic impairment, or underlying respiratory disease that put them at higher risk for developing empyema after pneumonia.

Diagnosis

Radiographic evaluation and fluid analysis are the mainstay for diagnosis of parapneumonic effusion. CXR is the first step in assessment, including an upright view and a lateral decubitus to evaluate for mobility of the pleural fluid. Ultrasound is helpful in evaluating loculations. CT scan aids in identification of consolidated lung or fibrinous tissue, as well as necrotic lung parenchyma. Fluid should be sampled for culture, cell count, glucose, pH, and LDH.

Differential Diagnosis

Differential diagnoses of parapneumonic effusions include: pleural effusion, hemothorax, congestive heart failure, pulmonary infarction, pulmonary sequestration, or nephritic syndrome.

Treatment

Treatment of parapneumonic effusions depends on the stage. If imaging and fluid analysis indicates a transudative stage, simple thoracostomy tube insertion for drainage of the fluid and expansion of the lung is recommended. Deep breathing exercises and pain control are also important management strategies to decrease atelectasis and consolidation. The tube can be removed when the lung reexpands and drainage stops. Antibiotic treatment should continue as indicated for pneumonia, usually 10–14 days. If fevers continue, drainage does not decrease, or if the patient remains hypoxic, the thorax should be reimaged to evaluate for loculations, missed collections, or necrotizing pneumonia. Cross-sectional imaging, such as CT scan with intravenous contrast, is often the best test.

If imaging suggests a more complicated stage, treatment may range from tube insertion and fibrinolysis to thoracotomy. Patients with loculated effusions require debridement, which can be achieved with fibrinolysis or mechanically with surgery. After the advent of thoracoscopy, the mainstay of surgical management is now video-assisted thoracoscopic surgery (VATS) rather than formal thoracotomy. Fibrinolysis or VATS has been shown to result in earlier and more complete resolution of empyema than tube drainage alone.

Two randomized controlled trials have been performed, comparing fibrinolysis to VATS for treatment of emypema in children. Both studies found no difference in days of hospitalization after intervention, days of oxygen therapy, days until afebrile, or analgesic requirements between patients that received tube thoracostomy and fibrinolysis (urokinase or tPA) or VATS. Both groups also showed a 16% failure rate. St. Peter et al. did report higher costs in the VATS treatment group.

Fibrinolysis should be continued until drainage is 1 cc/kg/12 h period and symptoms (fever, oxygen requirement) have resolved. Fibrinolytic treatment should not be continued based on radiologic images alone. Patients may still have evidence of disease in the pleural space for up to 6 months after symptoms resolve. Also, Stefanutti et al. found that the efficacy of intrapleural fibrinolysis was not influenced by the duration of symptoms or hospital stay before the initiation of treatment. Therefore, all patients with loculated parapneumonic effusions can undergo a trial of fibrinolytic treatment (without contraindications, like drug

allergy or other coagulopathy) prior to evaluation for surgical intervention.

Prognosis

Tube thoracostomy drainage is an effective therapy in greater than 50% of patients. Pulmonary function testing in children (≥6 years old) 6 weeks after resolution of symptoms (treated with antibiotics alone or closed thoracostomy tube) showed no evidence of restrictive lung disease. However, 50% of those examined had evidence of mild obstructive airway disease.

Prevention

The best prevention is early diagnosis of pneumonia and prompt treatment with antibiotics with surveillance for development of a simple parapneumonic effusion. Early diagnosis and treatment with tube thoracostomy and directed antibiotic therapy is essential for preventing evolution of a parapneumonic effusion into empyema.

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421 Head and Neck

Christopher S. Muratore

Overview of Pediatric Head and Neck Masses

Head and neck masses are a common clinical concern in infants, children, and adolescents. The differential diagnosis for a head or neck mass across these age groups is broad and includes congenital, inflammatory, and neoplastic lesions (Table 421.1). An orderly and thorough examination of the head and neck with an appropriate directed workup will facilitate the diagnosis. The most common entities occur repeatedly within the various age groups and can be differentiated with a clear understanding of embryology and anatomy of the region, and an understanding of the natural history of a specific lesion.

Congenital lesions most commonly found in the pediatric population include the thyroglossal duct cyst and the branchial cleft and arch anomalies. Hemangiomas, lymphatic malformations, dermoid cysts, bronchogenic cysts, teratomas, and thymic cysts are other common congenital lesions. The *inflammatory masses* are secondary to local or systemic infections. The most common etiology for cervical adenopathy in children is reactive lymphadenopathy following a viral or bacterial illness. Persistent unilateral adenopathy over several months observation is concerning and can include acquired etiologies such as mycobacterium tuberculosis, the atypical mycobacterium spectrums such as mycobacterium avium intracellulare, and mycobacterium scrofulaceum, granulomatous processes, or cat scratch disease.

The midline lesions most commonly are represented by thyroglossal duct sinus and cyst conditions and dermoid cyst are usually easily distinguished from the more lateral lesions represented by branchial cleft sinus and arch anomalies. Acute bilateral or diffuse cervical adenopathy is often the result of a recent viral infection and is usually a self-limited process. Acute unilateral adenopathy, particularly in infants and young children, may be associated with pyogenic sources such as Staphylococcus aureus or group B Streptococcal infections. Persistent adenopathy raises more concerns but is usually still secondary to an infectious etiology. Enlarged lymph nodes within the posterior triangle or supraclavicular space, nodes that are painless, firm, and not mobile, or a single dominant node that persists for more than 8–10 weeks should all heighten concern for malignancy. *Malignant lesions* such as non-Hodgkin's and Hodgkin's lymphoma, neuroblastoma, salivary, parathyroid, and thyroid gland carcinoma need to be differentiated from benign lesions. In the pediatric population, 80–90% of all head and neck masses represent benign conditions. Hemangioma is one of the most common benign tumors of infancy and childhood and is found in the head and neck region approximately 60% of the time. Cystic lymphatic malformations (cystic hygromas, lymphangiomas) are benign vascular lesions that arise from an embryological disturbance in lymphatic development most commonly found in the head and neck region. They can be detected antenatally on a prenatal ultrasound or may be noted at birth; most present before the age of 2 years.

Finally, the ex utero intrapartum treatment (EXIT) procedure, initially developed for reversal of fetal tracheal occlusion in fetuses with severe congenital diaphragmatic hernia, has evolved and can be employed by a multidisciplinary team to treat peripartum airway obstruction. The indications for the EXIT procedure have expanded to include management of giant fetal neck masses, lung or mediastinal tumors, and congenital high airway obstruction. It is important, therefore, for surgeons to appreciate the relevant embryology, anatomy, and natural history of head and neck lesions and to be familiar with their appropriate evaluation and management.

Evaluation: History and Physical Examination

A detailed history and physical examination is the usual starting point. Historical information including the patient's age, onset and duration of symptoms, as well as any systemic signs of disease such as fever, night sweats, fatigue, or weight loss should be taken into consideration. Although some congenital neck lesions, particularly cysts, may not present until later in childhood after the accumulation of secretions or becoming secondarily infected, many congenital lesions present at birth or are noted shortly thereafter.

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Table 421.1
Differential diagnosis of pediatric head and neck masses

Congenital masses	Inflammatory masses	Neoplastic disease
Thyroglossal duct cyst	Reactive lymphadenopathy	Benign
Brancial cleft cyst/sinus	Bacterial	Lipoma
Vascular anomalies	Viral	Fibroma
Hemangioma	Granulomatous	Neurofibroma
Lymphatic	Mycobacterium tuberculosis	Thyroid nodule
Capillary	Atypical mycobacterium	Malignant
Venous	Toxoplasmosis	Hodgkin' lymphoma
Arterial	Histoplasmosis	Non-Hodgkin's
Mixed	Sarcoid	Rhabdomyosarcoma
Dermoid cyst	Cat scratch disease	Neuroblastoma
Bronchogenic cyst		Thyroid carcinoma
Teratoma		Metastasis

Modified from Dickson PV, Davidoff AM (2006) Malignant neoplasms of the head and neck. Semin Pediatr Surg 15(2):92–98. Reprinted with permission

Features from the history and examination should help to elicit and narrow the etiology. Specific questions to ask include whether the adenopathy is an acute or chronic process; whether the adenopathy was associated with a recent upper respiratory illness or following contact with an individual with a recent illness; whether the neck masses were associated with a systemic infection; if there had been any known animal bites or scratches; and whether there had been any recent changes in the character of the lesion. The physical examination should be directed at a systematic evaluation of each cervical lymph node region. The size, laterality, tenderness, overlying skin changes, and mobility should be noted. Finally, an examination of the chest, abdomen, groin, genitalia, and extremities must not be forgotten. A firm painless mass with fixation to underlying structures or overlying skin is always concerning for malignancy. Although most pediatric cervical adenopathy is of benign etiology, rapidly enlarging, nontender, or long-standing, persistent adenopathy particularly within the supraclavicular space or posterior cervical triangle are concerning for malignant disease.

The experienced clinician will seldom require laboratory evaluation for the classic midline or lateral congenital lesions associated with branchial arch anomalies; however, the workup for persistent adenopathy is more extensive and should include a complete blood count with differential, a chest X-ray, PPD skin test, and serological studies to investigate Epstein-Barr virus, cytomegalovirus, HIV, toxoplasmosis, or to establish a background of Bartonella. Radiographic studies are usually unnecessary for evaluation of these lesions. However, persistent adenopathy suspicious for malignant disease warrants a chest X-ray. A plain chest X-ray might detect pulmonary or mediastinal lesions as a source for cervical or supraclavicular adenopathy. Ultrasonography has advantages, particularly in the pediatric population, because it does not involve ionizing radiation and is readily available. It can easily distinguish solid from cystic masses. It is helpful in evaluating the thyroid and parotid lesion and may be useful in diagnosing confusing congenital lesions. Ultrasound is also helpful in evaluating and characterizing the long-standing solitary lymph node (*Figs. 421.1* and *421.2*).

Congenital Cystic Lesions

Thyroglossal Duct Cyst

Thyroglossal duct cysts are the most common congenital midline cervical anomalies in children. The thyroid gland originates in early gestation from a diverticulum between the anterior and posterior muscle complex of the tongue. This region represents the proximal remnant of the foramen cecum. As the embryo elongates and the thyroid gland descends, it does so in the vicinity of the eventual location of the hyoid bone. As this occurs, the median thyroid anlage elongates with the descending gland forming the thyroglossal duct. The thyroglossal duct generally obliterates by the fifth week of gestation leaving behind a proximal remnant as the foramen cecum. A thyroglossal duct sinus persists when the thyroglossal duct fails to obliterate before the formation of the hyoid bone.

Based on this embryological descent, a thyroglossal duct cyst and sinus tract remnant can occur anywhere from the base of the tongue to the lower midline neck. The most frequent presentation is a midline painless cystic mass in the region of the hyoid bone. Most thyroglossal duct cysts present during the first 5 years of life. Clinically, the uncomplicated cyst typically moves cranially with swallowing and protrusion of the tongue because of its close relationship with the hyoid bone and the foramen cecum. Dermoid cysts, the most likely item in the

differential diagnosis, typically do not move with this maneuver. Infection is a complication seen in thyroglossal cysts because of the close anatomic association with the oral cavity. Many patients will present with a concurrent or recent history of an upper respiratory tract infection. The infected thyroglossal duct cyst usually resembles other abscesses, with intense erythema and fluctuance (*Fig. 421.3*). The most common pathogens are Haemophilus influenza, Staphylococcus aureus, and Staphylococcus epidermidis. It is unusual for a thyroglossal duct cyst to present as a communicating sinus tract to the skin, since the thyroglossal duct does not communicate with the ectoderm during the development. However, up to 25% of these lesions may present as a draining sinus tract in the midline, thought to represent a spontaneous rupture.

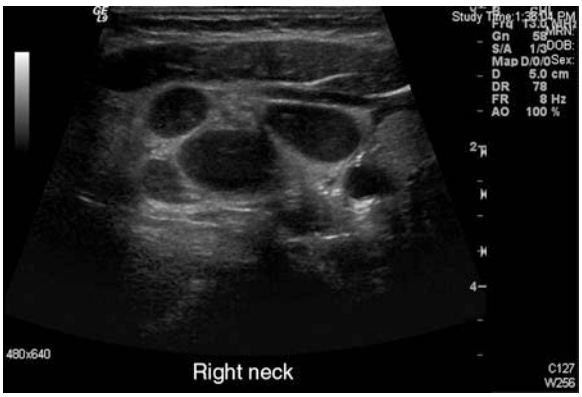

Figure 421.1
Ultrasonography of a large, bulky mass at the base of the neck. Differential diagnosis included lymphoma, cystic lymphatic malformation, or combined vascular malformation. Ultrasound demonstrated cystic structures surrounded by stroma

Thyroglossal duct remnants can contain functional thyroid tissue and may have a solid component since they are lined by ductal epithelium. A patient who presents with symptoms of hypothyroidism should be worked up for the possibility of median ectopic thyroid. In approximately 1% of patients with a thyroglossal duct cyst, the only functional thyroid tissue is located within the cystic mass. These patients are frequently hypothyroid with elevated thyroid stimulating hormone (TSH) levels. The incidence of thyroid carcinoma in a thyroglossal duct cyst remnant is reported to be less than 1%. However, since the majority of thyroglossal duct cysts are removed in childhood, the absolute risk is unknown. With the exception of medullary carcinoma of thyroid, all types of thyroid malignancy have been reported, with the majority being papillary. Approximately 90% of cases of presumed thyroglossal duct carcinoma have presented in adulthood.

The diagnosis of thyroglossal duct cyst is usually straightforward and almost never requires an extensive evaluation. The literature does, however, contain controversial claims regarding the need for preoperative thyroid scanning to identify those patients that have a median

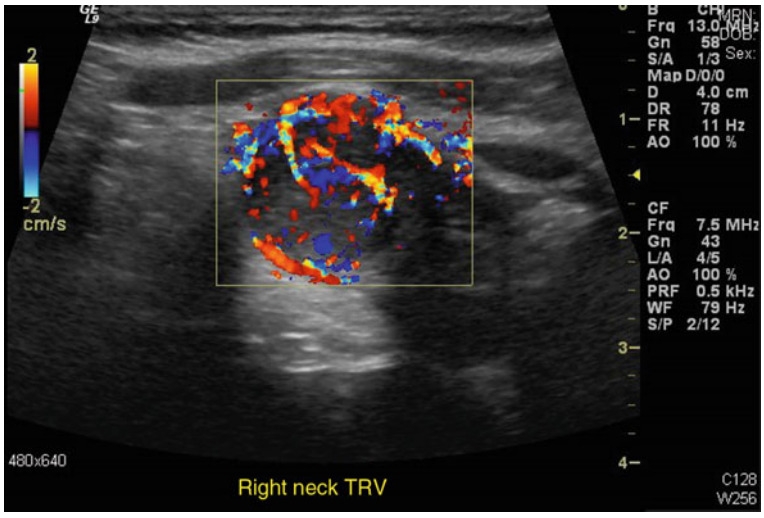

Figure 421.2
Duplex Doppler ultrasound evaluation of the same lesion reveals the vascular pattern characteristic of an infiltrative pattern involving a lymph node raising the suspicion for lymphoma

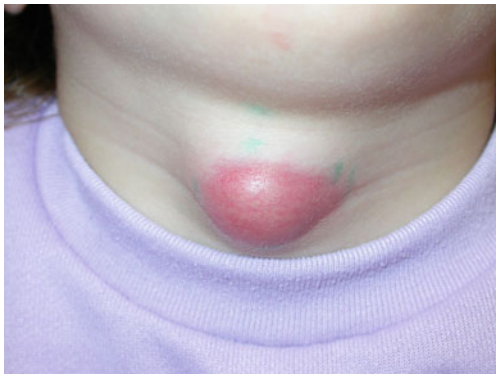

Figure 421.3
Five-year-old girl with infected thyroglossal duct cyst initially treated with a first-generation cephalosporin for 10 days without improvement. Surgical evaluation diagnosed a fluctuant abscess which subsequently spontaneously drained

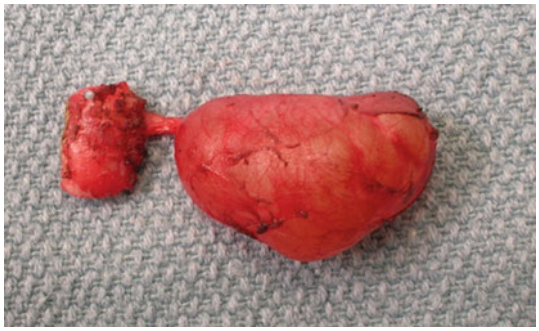

Figure 421.4
Thyroglossal duct specimen demonstrating the intact cyst, the fistulous tract, and the attached mid portion of the hyoid bone. Excision performed in the manner described by Sistrunk

ectopic thyroid. Others argue that the cost of routine scanning is excessive given the overall incidence of 1–2%, and exposes many patients to unnecessary radiation. A safe approach is to perform a thorough history looking for signs and symptoms consistent with hypothyroidism. If hypothyroidism is suggested then TSH screening and preoperative ultrasound of the midline neck should provide the necessary information to select patients for preoperative thyroid scanning.

Surgical Management

In the uncomplicated thyroglossal duct cyst, an elective procedure described by Sistrunk is the operation of choice. The patient is positioned supine, with the head of the table slightly elevated and the neck extended, and a transverse incision is used. Careful dissection is performed to identify the distal tract. Dissection around the cyst proceeds cranially toward the hyoid bone, which is facilitated by elevating the cyst out of the wound. Once the hyoid bone is reached, its central portion associated with the tract is resected. En bloc resection of the proximal tract is important to ensure complete removal of the lesion. The anesthesiologist or another surgeon may, if necessary, insert a finger into the mouth and press against the base of the tongue to ensure proximal dissection is complete. The tract is suture ligated at the most proximal end and the block is removed (*Fig. 421.4*).

Occasionally patients will present with an infected thyroglossal duct cyst unresponsive to initial antibiotic therapy. Intense erythema and fluctuance suggest an abscess, and formal incision and drainage may be necessary to control the infection. There is some concern that drainage procedures can "seed" the surrounding tissues, predisposing to recurrence. Occasionally the thyroglossal duct cyst or abscess will spontaneously erupt. A Sistrunk procedure is performed once the infection has cleared (after incision and drainage or spontaneous drainage). A clinically palpable mass usually remains. It is important to excise an ellipse of skin including the area of the drainage in order to prevent recurrence. The infection usually makes the otherwise elegant Sistrunk procedure more challenging secondary to the inflamed surrounding tissues. Although the presence of a preoperative or concurrent infection has historically been associated with increased recurrence rates, a recent review of 100 patients from a major pediatric hospital found no association between preoperative infection and increased recurrence rates.

Branchial Cleft Cyst and Sinus

Branchial cleft anomalies are the second most common congenital head and neck lesion found in children, after thyroglossal duct cysts. These anomalies are composed of a heterogeneous group of congenital malformations that arise from incomplete obliteration of the pharyngeal clefts and pouches during embryogenesis. Most branchial cleft anomalies involve the first and second cleft and pouch complexes. Normally the first branchial arch forms the mandible and a portion of the maxillary process of the upper jaw. This arch is also involved in development of portions of the inner ear, whereas the cleft and pouch

become part of the external auditory canal and mastoid ear cells. The second arch contributes to the hyoid bone and the adjacent area of the neck. This pouch becomes the palatine tonsil and supratonsillar fossa. Understanding this developmental process clarifies the clinical presentation of branchial anomalies. First branchial cleft and pouch anomalies enter the external auditory canal and occasionally the middle ear, while second arch anomalies enter the supratonsillar fossa. Third and fourth sinuses and fistula may appear similarly to the second cleft sinus externally. However, as a rule it is the internal opening of the sinus that is crucial in defining the cleft or pouch origin and the exceedingly rare third and fourth derivatives enter the pharynx through the pyriform sinus.

Presentation and Diagnosis

First cleft remnants typically present as a cyst sinus or fistula somewhere between the external auditory canal and the submandibular area. These lesions have an intimate relationship with the parotid gland and the branches of the facial nerve. Second branchial cleft anomalies account for the vast majority of all branchial cleft disorders and usually present as a fistula or cyst found in the lower anterior lateral region of the neck. Fistulas are usually diagnosed in infancy in childhood and typically have intermittent and chronic drainage from the opening along the anterior border of the sternocleidomastoid muscle. Cysts are more often diagnosed in adults as a nontender mass in the neck. The second branchial arch anomalies can be intimately associated with the glossopharyngeal and hypoglossal nerves, and enter the pharynx at the level of tonsillar fossa. Third and fourth arch anomalies are uncommon. Branchial cleft cysts are lined by squamous epithelium but can contain respiratory epithelium as well.

Surgical Management

The definitive treatment for all branchial cleft remnants is complete surgical excision. If incompletely resected, there is a high incidence of recurrence. Second branchial arch remnants are usually approached through a cosmetic transverse surgical incision. This cyst is meticulously dissected from the superficial tissue at fascia and dissected proximally keeping the fistulous tract intact. It is possible to cannulate the tract with a small probe to aide in its dissection. Some surgeons prefer to inject the tract with a small amount of methylene blue. It is occasionally necessary to use a step-ladder incision to gain better visualization of the upper portion of the tract as the dissection moves superiorly. Once the proximal opening near the pharynx has been identified, the tract is ligated and divided.

Preauricular Cysts

Preauricular cysts do not represent true cysts or sinuses of the neck but need to be distinguished from first branchial cleft cysts. Unlike branchial cleft cysts, preauricular cysts are common, often bilateral, tend to be inherited and are rarely complicated by infection. Furthermore, they neither are involved with the facial nerve nor do they enter the external auditory canal. They are thought to arise from abnormal formation of the external ear from the developing hillocks and are successfully excised by removing all the ductal epithelium through an inverted "L-shaped" incision.

Inflammatory and Infectious Adenopathy

Clinically palpable cervical lymphadenopathy occurs with a reported prevalence of 28–55% in otherwise normal infants and children. Acute bilateral cervical lymphadenopathy is most commonly caused by viral respiratory tract infections or streptococcal pharyngitis, whereas unilateral cervical lymphadenitis is usually caused by streptococcal or staphylococcal infection in 40–80% of cases. Acute suppurative lymphadenitis is typically caused by bacterial infections from penicillin-resistant Staphylococcal, group A Streptococcal infections, or both. Infants commonly have Staphylococcal lymphadenitis; anaerobic bacteria, group B streptococcal, and haemophilus influenza type B are less frequent. Local signs of inflammation, suppuration, erythema, fever, and malaise should preclude a search for primary infection around the oropharynx, head, and neck. Initial empiric treatment includes 5–10 days of an oral beta lactamase-resistant antibiotic directed at the most likely organism. Failure to note improvement indicates the need for further diagnostic testing, including the use of serology, ultrasonography, fine needle aspiration with or without sedation, with a gram stain evaluation of the collected material, and aerobic and anaerobic cultures. Bacterial infections, usually Staphylococcal aureus or Streptococcal pyogenes cause 40–80% of acute unilateral cervical lymphadenopathy in the 1–4 years old age group. Group B strep may cause unilateral facial or submandibular swelling, erythema, tenderness, and fever associated with poor feeding and irritability in the infant. Anaerobic bacteria can occur in the older child with dental caries or periodontal disease. Community acquired methicillin-resistant staphylococcus

aureus (MRSA) has become more prevalent as the etiology for pediatric suppurative adenitis. If MRSA is identified then clindamycin or Bactrim should be started. Bactrim is effective for simple skin and soft tissue infections but is generally ineffective against group A and B Streptococcal infections. Clindamycin is highly effective treatment for pediatric MRSA, covers group A and B Streptococci and clindamycin-resistant strains of MRSA remain uncommon. Since the spectrum of antibiotic resistance and the most common types of MRSA infections vary from one location to another, it is imperative to have a working knowledge of the local prevalence of clindamycin resistance to combat MRSA effectively.

Many cases of bilateral cervical adenitis are caused by upper respiratory tract infections of viral etiology including rhinovirus, parainfluenza virus, respiratory syncytial virus, cytomegalovirus and Epstein-Barr virus. Less frequent etiologies include mumps, measles, rubella, herpes simplex, and human herpes simplex 6 (roseola) and coxsackie viruses. Virally induced adenopathy rarely suppurates and generally resolves spontaneously.

Surgeons generally do not see children at the time of initial presentation for isolated cervical adenopathy. Most physicians would administer therapy for 10 days, and cover for 5 days beyond the resolution of acute signs and symptoms. In most cases, symptomatic improvement should be noted after 2–3 days of therapy, although complete resolution may require several weeks. Failure to improve usually brings a patient to a pediatric surgeon. The question of surgical intervention becomes more controversial with respect to persistent lymphadenopathy of greater than 2 weeks duration on antibiotic therapy, or unilateral adenopathy in the supraclavicular or posterior triangle. Fluctuance develops in 25% of patients with acute bacterial adenitis, and may be managed by additional antibiotics and or multiple needle aspirations. However, adequate drainage may not be obtained, particularly in the young and uncooperative child. These patients are best managed with a formal operative incision and drainage under general anesthesia. This allows for proper drainage of all associated loculations and cavities not amenable to single needle aspiration attempts. The abscess cavity is usually packed with gauze to facilitate continued drainage and to prevent early premature closure. The gauze pack is removed over a period of several days, either as an inpatient completing an intravenous antibiotic course or as an outpatient. Surgical intervention is indicated for atypical mycobacterial adenitis, suppurative inflammatory or fistulous lymphadenopathy.

Atypical mycobacterial infections usually present in a subacute pattern, with relatively nontender, indurated, and suppurative nodes. PPD positivity is variable, and pulmonary involvement is absent. Although complete resection is the definitive therapy, macrolide antibiotics (such as clarithromycin) may have some utility. In one recent series, 30/45 (67%) of children treated with cervicofacial atypical mycobacterial infections resolved with antibiotic therapy. A trial of medical therapy may be worthwhile in these children.

Fungal Disease

Histoplasma capsulatum, Blastomyces dermatitidis, and Coccidioides immitis are soil saprophytes endemic to certain geographic regions of the United States that cause fungal infections in humans. Most patients present with pulmonary or mediastinal involvement, with cervical lymphadenopathy secondary to the primary infection. Fungal disease must therefore be considered in the diagnosis in the child or adolescent with a mediastinal mass and cervical adenopathy, particularly in an endemic area or in an immunocompromised patient. Serological or skin testing is usually diagnostic and most infections resolve spontaneously.

Neoplastic Adenopathy

By far the most common head and neck malignancy in children is lymphoma. However, cervical rhabdomyosarcoma, neuroblastoma, and teratoma account for many pediatric neck lesions. Half of malignant neoplasms in the head and neck region are made up of lymphomas: 60% are non-Hodgkin's lymphoma, and Hodgkin's lymphoma makes up the remaining 40%. Commonly, the origin of lymphoma is from the lymph node. However, lymphomas of the head and neck may also arise from extra nodal sites and often are associated with extensive lesions within the mediastinum. Neck lesions associated with mediastinal findings might represent nonmalignant disease such as fungal or systemic inflammatory conditions and must be distinguished from neoplastic lesions (*Figs. 421.5* and *421.6*).

Hodgkin's Disease

Hodgkin's disease has a bimodal age distribution, with adolescents accounting for 15% of cases. Hodgkin's disease is rare in children under 10 years of age, and is responsible for approximately 5% of all pediatric malignancies. The etiology is likely multifactorial, with a known

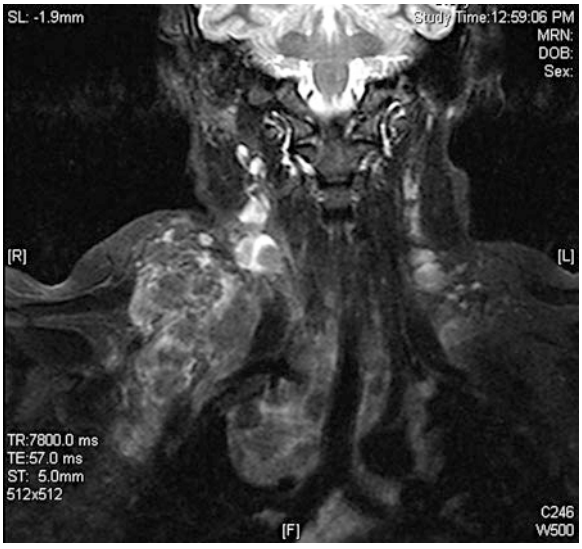

Figure 421.5
MRI evaluation of extensive Hodgkin's lymphoma presenting as a complex neck mass. Note the nodular appearance and surrounding fibrosis characteristic of nodular sclerosing Hodgkin's disease involving the mediastinum surrounding the airway and great vessels

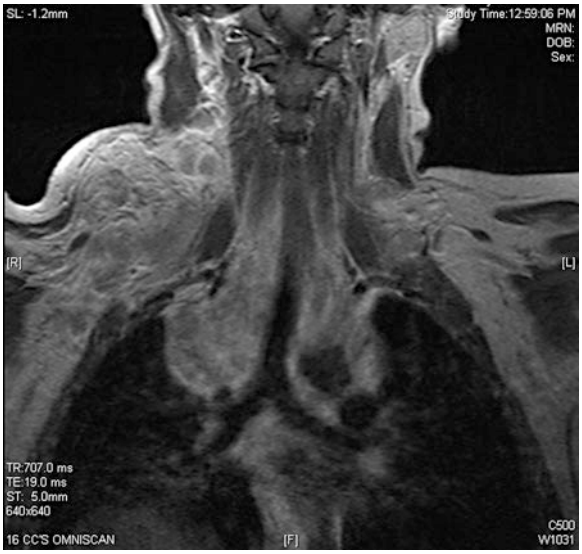

Figure 421.6
MRI evaluation of extensive Hodgkin's lymphoma presenting as a complex neck mass. Note the nodular appearance and surrounding fibrosis characteristic of nodular sclerosing Hodgkin's disease involving the mediastinum surrounding the airway and great vessels

association to Epstein-Barr viral (EBV) exposure. The precise role of EBV in the pathogenesis and biology in Hodgkin's lymphoma is not entirely clear. However, clinical studies indicate EBV infection precedes expansion of the tumor cell population. Hodgkin's lymphoma is characterized by a small number of clonal tumor cells surrounded by a pleomorphic inflammatory cell population that constitutes the bulk of the tumor tissue. Only a small percentage of the cells (usually less than 10%) are represented by the malignant monoclonal expansion. It is therefore imperative that Hodgkin's lymphoma be differentiated from the subtypes of non-Hodgkin's lymphoma that present with similar morphologic characteristics, and from other benign reactive lymphoid hyperplasias. The WHO classifications recognize two major classes of Hodgkin's lymphoma: classic Hodgkin's lymphoma has four subtypes: nodular sclerosing, mixed cellularity, lymphocyte rich, and lymphocyte depleted. Nodular lymphocytic predominate Hodgkin's lymphoma (NLPHL) contains only rare Reed–Sternberg cells (in contrast to the classic Hodgkin's lymphoma). "Popcorn cells" are seen histologically. NLPHL is seen in 10–15% of all Hodgkin's lymphoma patients, is more common among males under 10 years of age, presenting often as localized disease in an otherwise asymptomatic patient.

Clinical Management

Patients usually present with painless persistent supraclavicular or cervical lymphadenopathy. The affected lymph nodes are firmer than inflammatory lymph nodes and are usually characterized as firm, rubbery, and nontender. Importantly, more than two thirds of patients with cervical Hodgkin's lymphoma will have mediastinal involvement at the time of presentation. When a mediastinal mass is confirmed by plain radiographs it is advisable to evaluate the mediastinum more completely with a CT scan. In this setting, it is best to start with the assumption that airway compression exists in planning the approach to cervical Hodgkin's lymphoma.

All patients with Hodgkin's disease require a biopsy of the involved lymph node to establish the diagnosis and confirm and histological subtype. Needle aspirations and frozen sections are inadequate: permanent hematoxylin/eosin sections must always be obtained and tissue procured for more detailed studies including immunohistochemistry and cytogenetics. Excisional lymph node biopsy or incisional biopsy of an enlarged or matted group of lymph nodes is essential to make an accurate diagnosis. The contemporary therapy uses a risk-adapted approach that considers disease-related factors such as the

presence of constitutional symptoms, stage, number of involved nodal regions, and the presence of tumor bulk.

Non-Hodgkin's Lymphoma

Non-Hodgkin's lymphomas in children and adolescents are a diverse group of neoplasms with 10% of these tumors arising in the head and neck region. The etiology of non-Hodgkin's lymphoma (NHL) is unknown. There is a marked male predominance in all age groups, particularly in children younger than 15 years of age. Compared to Hodgkin's disease (which is mostly of nodal origin), NHL often arises as a mass in extra nodal tissues. NHLs are classically divided into Burkett's and non-Burkett's lymphomas, lymphoblastic lymphomas, diffuse large B cell lymphomas, and anaplastic large cell lymphomas. The pathogenesis of NHL appears to relate to a malignant transformation of a single B or T-cell of origin along its path of terminal differentiation.

Clinical Management

A contrast enhanced CT scan or MRI of the head and neck is helpful to define the tumor in relation to other anatomic structures. Complete metastatic scanning is an important part of the staging process, because NHLs are often diffuse at diagnosis and the treatment involves multi-agent chemotherapy based on stage. It is important to remember that childhood lymphoma is a systemic disease: The operative procedure should not delay institution of chemotherapy. Initial surgical management should include an incisional biopsy, followed by intense multi-agent chemotherapy once the diagnosis is confirmed, except in the cases of small and easily resectable isolated lesions. Cervical primary tumors should undergo initial diagnostic biopsies with procurement of enough tissue to determine the histological subtype.

Mediastinal Masses Associated with Neck Masses

Because non-Hodgkin's and Hodgkin's lymphoma are often associated with lesions in the mediastinum, it is imperative for the pediatric surgeon to determine from the history and physical examination whether the possibility of airway compromise exists, particularly when contemplating a biopsy and the potential need for general anesthesia. Respiratory collapse under general anesthesia is a recognized complication associated with anterior mediastinal masses. Identification of patients at risk has been a major challenge because the presence of specific respiratory symptoms has not been shown to correlate with the severity of airway compression. Preoperative measures for identifying patients at risk for respiratory collapse upon induction of general anesthesia have centered on measurement of the tracheal cross-sectional area by CT scans, in combination with pulmonary function tests. Shamberger et al.'s prospective study of the risk assessment in 31 children with mediastinal masses, using the combination of cross-sectional area of the trachea and peak expiratory flow rate, demonstrated that all patients with values greater than 50% for both predicted peak expiratory flow rate and tracheal area underwent administration of general anesthesia without respiratory complications. Conversely, all children with peak expiratory flow rate and tracheal areas that were less than 50% of predicted received local anesthetic for their biopsy without sequelae.

All patients with cervical adenopathy and a significant mediastinal mass discovered by plain films should therefore be evaluated by a CT scan of the chest to determine the cross-sectional area of the trachea, the burden of mediastinal disease, and also the possibility of pleural effusion. The peak expiratory flow rate has been determined to be the best predictor for evaluating the magnitude of an extra thoracic obstruction.

Cervical Neuroblastoma

Cervical neuroblastoma may occur as a primary tumor but is more commonly a site of metastatic disease from and abdominal or thoracic primary tumor. Primary cervical disease may occur as a mass in the lateral neck or retropharyngeal space. Metastatic disease may cause proptosis, periorbital swelling, ecchymoses, acute cerebellar ataxia characterized by opsoclonus-myoclonus and chaotic nystagmus. Primary cervical neuroblastoma has a favorable outcome. Localized lesions or low stage disease has an excellent prognosis with complete surgical resection. Radiation therapy and or chemotherapy and secondary surgeries are strategies to eradicate residual disease.

Cervical Teratomas

Teratomas are tumors with elements derived from all three germ-cell lineages in various degrees of differentiation. Teratomas arise in a variety of locations throughout the body. Most are sacrococcygeal, with cervical teratomas

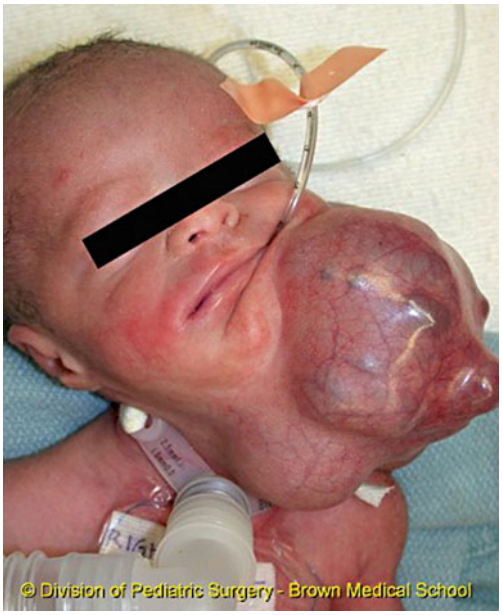

Figure 421.7
Antenatal diagnosis of a threatened airway by a cervical teratoma mandated the EXIT procedure. Neonatal tracheostomy was performed on placental support after bronchoscopy failed to secure the airway

representing less than 10%. Most cervical teratomas in infants and children are benign lesions. The diagnosis is usually obvious at birth but due to the widespread use of prenatal ultrasound, there has been an increase in the diagnosis of fetal neck masses, particularly airway threatening lesions. The vast majority of cases of fetal airway obstruction are due to cervical teratomas or lymphatic malformations. Fetal MRI provides better detail about the size and position of the mass and its anatomic relationship to the airway. A compromised airway secondary to cervical teratoma is an indication for the EXIT (ex utero intrapartum treatment) procedure (*Fig. 421.7*).

Vascular Anomalies

Introduction

Vascular anomalies are best classified as vascular tumors or vascular malformations. The biological classification based on cellular kinetics and clinical behavior distinguishes vascular tumors as lesions that arise by endothelial hyperplasia. In contrast, vascular malformations are congenital lesions derived from capillaries, veins, lymphatic vessels, arteries, or a combination of these. They are lesions that arise by dysmorphogenesis but exhibit normal endothelial turnover.

Vascular Tumors of the Head and Neck: Hemangioma

Hemangioma is one of the most common tumors of infancy and childhood and is found in the head and neck region approximately 60% of the time. Most cutaneous hemangiomas appear approximately 2–4 weeks after birth. Hemangiomas of infancy follow a predetermined course of proliferation followed by involution. The proliferative phase is characterized by rapid growth in the first 6–8 months of infancy. There is a variable period of quiescence followed by the involution phase. Maximum involution occurs in approximately 50% of children by age 5 years, and 90% of children by age 9 years. Based on the anatomic depth, hemangiomas are characterized as superficial, deep, or combined. Superficial lesions tend to be soft, red, raised, and occasionally telangiectatic. Deep lesions may show a spectrum of appearances and consistency ranging from soft and subtle to raised and more firm with a bluish color. Combined lesions appear as red dermal tumors with epidermal and dermal components along with subcutaneous masses.

A variation of hemangioma is the congenital hemangioma; unlike the hemangiomas of infancy, these lesions are fully developed at birth and do not undergo additional postnatal proliferative growth. These congenital hemangiomas fall into two distinct subgroups: rapidly involuting congenital hemangiomas (RICHs) and non-involuting congenital hemangiomas (NICHs). Both are high flow lesions that can be misdiagnosed as arterial-venous malformations. The RICHs rapidly regress over the first year of life, while NICH does not.

Sixty-five percent of patients with hemangiomas have cervicofacial involvement and hemangiomas account for 60% of all pediatric salivary gland neoplasms. Of the salivary gland hemangiomas, 80% arise in the parotid glands (*Fig. 421.8*), 18% arise in the submandibular glands, and 2% arise in the minor salivary glands. Lesions that cover a beard distribution including the chin, jaw line, and preauricular areas may have associated airway involvement. Infants with hemangiomas in the beard distribution area should be inspected for glottic and subglottic hemangiomas, the two most common locations in the airway. Treatment should be initiated if airway involvement is confirmed. Localized lesions are managed

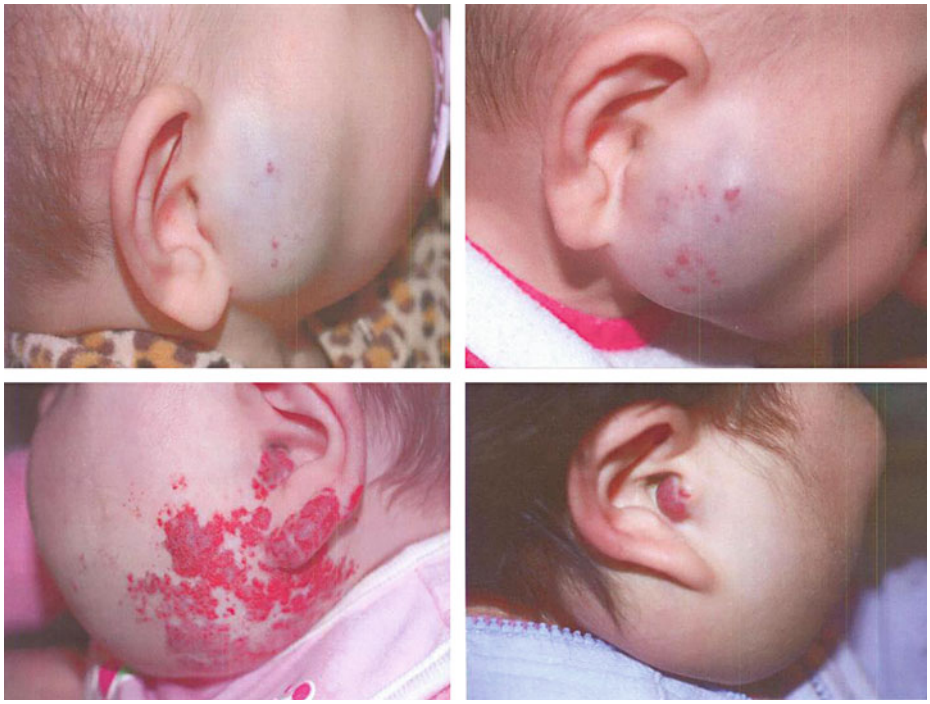

Figure 421.8
Infantile parotid hemangioma. Photographs depict bulky parotid glandular involvement, superficial cutaneous stigmata, and encroachment on external auditory meatus. Treatment options included ±prednisone and hearing exams

with laser therapy, intralesional steroids, or surgical resection. These lesions can proliferate for up to 12–16 months and require systemic treatment if the airway is compromised; tracheostomy should be reserved for patients who fail medical therapy.

Treatment

Since many hemangiomas spontaneously involute, with little or no functional disability or cosmetic defect, reassurance and observation is usually all that is required. It is important to periodically see these patients so the lesions can be monitored for signs of ulceration, growth, and complications that may indicate additional therapy. The decision to intervene with a cervical facial hemangioma is based on the size and location of the lesion, presence of complications such as ulceration or bleeding, age of the patient, and the phase of growth at the time of the evaluation. Larger lesions that interfere with the function of vital structures (such as the eye or eyelid, mouth, or nares), are likely to require some form of treatment. Additional therapies include corticosteroids (either systemically or via intralesional injection), propranolol, laser therapy, and surgical excision. Intralesional cortical steroid injection should be considered for small localized cutaneous hemangiomas located on the nasal tip, cheek, or eyelid. Triamcinolone (25 mg per ml) is injected slowly at low pressure with a 3 ml syringe and a 25-gauge needle. A dosage of 3–5 mg/kg per injection is administered every 6–8 weeks for three to five injections. Oral corticosteroids historically have been the first-line treatment for problematic, endangering, or life-threatening hemangiomas. Prednisone or prednisolone is administered at 2–4 mg/kg/day for 2 weeks. The use of systemic corticosteroids accelerates the involutional phase. Propranolol, a nonselective beta-blocker, is emerging as a first-line therapy for complicated lesions. Clinical results are superior to agents previously used and propranolol appears to have an excellent risk-to-benefit ratio. Various clinical protocols exist however; it is generally dosed at 2–3 mg/kg/day, divided three times per day. Some incorporate cardiac clearance, ECG, echocardiography or Holter monitoring, however, most frequently, vital signs and glucose measurements are used especially with initiation of therapy. The mechanism of action of propranolol for hemangioma remains unclear. Hypotheses include decreased expression of angiogenic factors such as basic fibroblastic

growth factor (bFGF) and vascular endothelial growth factor (VEGF). Interferon alpha 2A or 2B should be considered as a second-line drug for endangering or life-threatening hemangiomas. Laser treatment for cervicofacial hemangioma remains controversial. Surgical excision is usually reserved for cervicofacial hemangiomas that present a threat to vital structures associated with complications such as ulceration, hemorrhage, or infection unresponsive to pharmacological therapy. Surgical excision may be indicated for the residual scar after complete involution, or when the emotional burden to the child or family is significant and potential for cosmetic deformity is quite low. The timing of surgery remains controversial, particularly in regard to the growth phase of the lesion and the age of the patient. Although lenticular excision has traditionally been commonplace, a useful approach with circular hemangioma is the technique of circular excision followed by a purse string closure. This technique has been widely used with excellent results.

Vascular Malformations

The classifications of these anomalies is based on the clinical and histological appearance of the abnormal channels as resembling either capillaries, lymphatics, veins, arteries, or combinations thereof. Cystic lymphatic malformations (formerly referred to as cystic hygromas, lymphangiomas) are benign vascular lesions that arise from an embryological disturbance in lymphatic development. They are most commonly found in the head and neck region. They can be detected antenatally on a prenatal ultrasound or may be noted at birth; most present before the age of 2 years. Lymphatic malformations can be characterized as microcystic, macrocytic, or combined. The prenatal diagnosis of anterior or posterior cervical lymphatic malformations may have significant clinical implications with potential neonatal airway obstruction. Prenatal consultation is usually obtained and observation over the remainder of pregnancy occurs with follow-up level II ultrasounds and fetal MRI scans to judge the size and development of the lymphatic malformation and potential for airway obstruction. The EXIT procedure is a technique that occasionally needs to be employed by a multidisciplinary team in order to deliver the child and obtain control of the airway in a timely fashion (Fig. 421.9).

Postnatally, most cervicofacial lymphatic malformations are easily diagnosed by physical examination. All patients should have a chest X-ray to identify cervical extension into the mediastinum, which is common. Ultrasound is helpful to determine the macrocystic

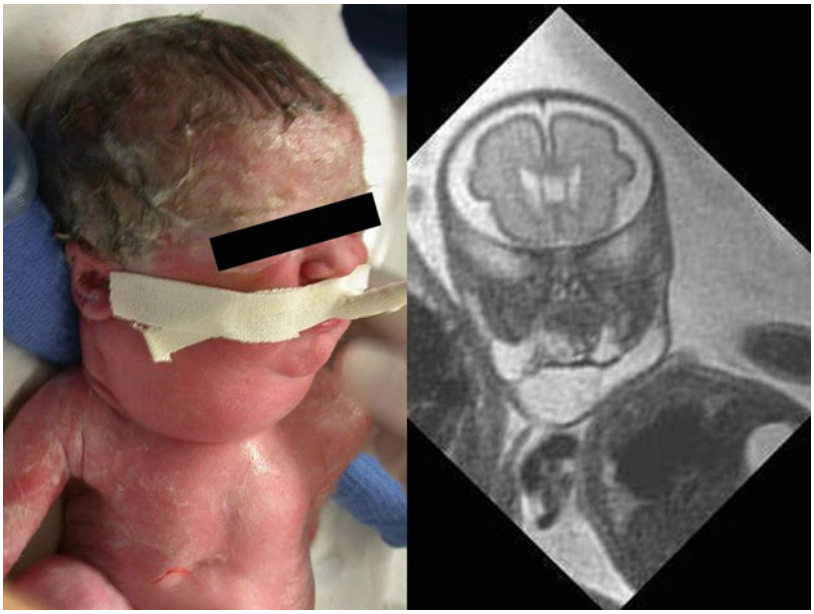

Figure 421.9
Cervical macrocystic lymphatic malformation. Airway was secured with bronchoscopy and intubation via EXIT procedure as the fetal MRI demonstrated cervical macrocysts and potential airway catastrophe

and microcystic features. However, it is less valuable in showing deep extension into the structures of the neck and mediastinum. CT and or MRI are superior modes to demonstrate the anatomical relationships.

Treatment depends on the clinical presentation, size, and complications of the lymphatic malformation. Small lesions may be amenable to complete surgical excision with excellent results, whereas other macrocytic lesions might be better served with intralesional sclerotherapy. The microcystic or combined macro- and microcystic lymphatic malformations, particularly ones that traverse different tissue planes of both the neck and mediastinum require a careful and deliberate approach, usually in a staged fashion. Cervical cystic lymphatic malformations may become infected. General enlargement or swelling of the lymphatic malformation may be associated with cellulitis, and can occur following an upper respiratory tract infection. Asymptomatic patients may develop respiratory distress secondary to the concurrent infection. Expectant management of the patient's airway is prudent in these cases, with administration of intravenous antibiotics. Another cause of rapid enlargement is hemorrhage into cyst. Other complications include lymphatic leakage, and chylothorax. Since surgical excision is a large undertaking for complex and combined micro- and macrocytic lesions of the head and neck, sclerotherapy has frequently become an alternative initial approach, particularly for patients with macrocystic disease. A number of sclerosing agents have been used (Bleomycin, OK-432, fibrin glue, and others). However, ethanol is most commonly utilized in this country because of its efficacy and availability. The lymph is aspirated under ultrasound guidance and ethanol is injected into the cyst. The procedure is usually done under general anesthesia. Fever, erythema, tenderness, and leakage are not uncommonly noted. As mentioned previously, swelling in the malformation is a dangerous side effect following sclerotherapy, potentially causing airway compromise when the lesion involves the cervicofacial and mediastinal locations. Good results (partial or complete regression) are obtained slightly more than 50% of patients in the literature, dependent on the nature of the lesion, patient selection, and other variables.

Summary

Head and neck lesions are some of the most common entities encountered in the pediatric population and can be distinguished as congenital, inflammatory, or neoplastic. The majority of these lesions are benign conditions that are readily diagnosed and have a predictable natural history. The role of the pediatric surgeon is to facilitate the diagnosis and provide definitive care for these lesions.

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422 Vascular and Lymphatic malformations

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Hemangiomas are the most common soft tissue lesion encountered in infancy. The pediatric practitioner must recognize and distinguish them from other soft tissue lesions and lymphatic or vascular malformations, in order to correctly predict the natural course of these lesions, which are often of great concern to parents. The ability to provide up-to-date and accurate information on diagnosis and potential treatment is critical. Much of the nomenclature of the past has contributed to the ongoing confusion in diagnosis and consequent poor correlation with predictions for growth and resolution. This fundamentally changed with the classification system proposed by Drs. Mullikan and Glowacki in 1982, which was based on pathologic characteristics, rather than macroscopic descriptive features. With revisions, this was ultimately the basis for the staging system adopted by the International Society for the Study of Vascular anomalies in the 1990s. This system is based on the observation that there are two classes of vascular anomalies – (1) those that exhibit increased endothelial activity which correspond to periods of proliferation and (2) those lesions that exhibit normal endothelial activity. The former group corresponds to the behavior expected of a neoplasm, and thus these lesions correctly carry the terminal "oma" (as in hemangioma). The second set of lesions, the vascular malformations, is best described as a constellation of lymphatic and vascular anomalies, which are the consequence of embryonic errors in vasculogenesis. They have no proliferative features, but as with other congenital anomalies, may expand and change with time. *Table 422.1* depicts the major lesions in each of these categories.

Vascular lesions are differentiated by a number of features, including the timing of their appearance (at birth, in first few months of life vs adolescence), physical characteristics (color, texture, size location, involvement of subcutaneous or deeper tissues, presence of pulse, thrill or bruit), and the association with other disorders. When clinical findings are insufficient, adjunctive studies, which can include handheld Doppler flow examinations, ultrasound with flow assessment, MRI, and angiography will generally establish the diagnosis. Although biopsy is rarely necessary, pathologic analysis will describe the endothelial characteristics and further analysis can evaluate gene and protein expressions, which often is characteristic to specific lesions and syndromes.

Unfortunately, while some consistency has been developed in establishing the clinical diagnosis, based on the development of multidisciplinary clinics in which dermatologists, surgeons (plastic and pediatric), and interventional radiologists simultaneously see the patient and come to a consensus diagnosis, pathologic terminology has not adjusted, leading to potential confusion unless the microscopic findings are clearly described. Since treatments can range from simple observation to interventions both in radiology and surgery, a clear understanding of the nature of the lesion needs to be appreciated before making treatment recommendations.

General Characteristics of Hemangioma Lesions

Infantile Hemangioma

This common lesion is often mistaken for other complex vascular malformations. It is estimated that 4–5% of Caucasian children are diagnosed with infantile hemangioma (IH) and that it is more frequent in premature (<1,200 g) infants and particularly in females (up to 5×). Typically, a single site is involved (80%) and 60% involve the head and neck (H and N). The trunk and extremities are involved in 25% and 15% respectively. They are typically small lesions that become protuberant from the surrounding skin, although much larger lesions involving a dermatomal region, referred to as segmental hemangiomas, can also be encountered. The initial appearance of these lesions depends on how superficial their origin is, with those involving the superficial tissues often being bright red, while deeper lesions having a bluish hue through the overlying skin. While most IH become clinically apparent after the second week of life, this can be further delayed when the lesion arises from deeper tissues.

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Table 422.1
Categories of vascular lesions based on endothelial activity

Hemangiomas	Vascular malformations
Increased endothelial activity	Normal endothelial turnover
Juvenile/infantile hemangioma (IH)	*High flow lesions*
	Arteriovenous malformation (AVM)
Rapidly involuting congenital hemangioma (RICH)	*Low flow lesions*
	Venous Malformation (VM)
Non-involuting congenital hemangioma (NICH)	Lymphatic malformation (LM) (aka cystic hygroma, lymphedema)
Kaposiform hemangioendothelioma (KHE)/tufted angioma	Capillary malformation (CM) (aka portwine stain, stork bite)
Capillary hemangioma (pyogenic granuloma)	Combined lymphatic – venous malformation (CLVM)

The hallmark of the IH is that it grows faster than the child for a period of time (typically the first 9 month) and reaches 80% of size by 3–4 months of age, then plateaus and flattens and starts to fade after age 12 months, ultimately resolving by 5 years of age. With involution, the color fades and the mass effect recedes, often leaving some lax skin and fibro-fatty tissue at the site of the original lesion.

Evaluation with ultrasound demonstrates a homogenous lesion, which is generally well circumscribed and has high flow characteristics on Doppler interrogation, indicating a significant arterial inflow. These features are also evident on magnetic resonance imaging, which shows a generally uniform, well-circumscribed lesion with high signal intensity on T2. The pathologic features depend on the phase of the hemangioma, but proliferation of endothelial cells is the hallmark finding. The cellular regulation of these proliferative lesions is associated with Glut-1, which is an erythrocyte type glucose transporter protein. Testing for glut-1 is commercially available to pathology laboratories and allows for definitive diagnosis of IH. While biopsy is rarely necessary, there are instances when concern for soft tissue tumor, such as infantile fibrosarcoma, leads to pathologic evaluation.

Congenital Hemangioma (CH)

This lesion is present at birth, has a ruddy-red violaceous coarse surface with central pallor and pale halo surrounding it base, and generally measures up to 5 cm in diameter. In contrast to the infantile lesion, it does not show postnatal growth and it is more likely to occur on the extremities. The gender incidence is equal. There are two types of CH that are distinguished by their behavior: the rapidly involuting and the non-involuting congenital hemangioma (RICH and NICH). RICH commences involution after birth and 50% will have completed regression by 7 months of age, while the remainder will resolve within 14 months. These are highly vascular lesions, and with increased size and flow, they can be associated with heart failure. In the process of involution, there can be superficial ulceration and necrosis, which places the infant at risk for significant hemorrhage. NICH does not involute and rarely ulcerates. In contrast to the infantile form, neither RICH nor NICH stains with glut-1, helping discriminate them from IH. *Table 422.2* illustrates some of the radiographic features associated with this lesion.

Kaposiform Hemangioendothelioma (KHE)

In contrast to the first two forms of hemangioma, this lesion is considered a vascular neoplasm that is locally aggressive, but does not metastasize. Fifty percent of KHE are present at birth. There is an equal gender distribution, and these solitary lesions can occur at any site (cutaneous and visceral) and will often achieve sizes of >5 cm. The clinical feature, which often sets this lesion apart, is the association with pain. While there may be some regression starting at age 2 years, this is often incomplete. Importantly, this lesion is associated with the *Kasabach–Merritt phenomenon* in 50% of patients. This is a diffuse consumptive coagulopathy associated with thrombocytopenia, which is associated with enlargement of the underlying KHE or tufted angioma, a related lesion. Pathology reveals sheets or nodules of endothelial cells lining capillaries. Treatment response to vincristine has been reported, but unlike IH, these do not respond to steroids (see "Treatment Strategies for Vascular Anomalies"). Acceleration of growth has been noted with heparin.

Table 422.2
Radiographic features of hemangiomas and vascular malformations

Lesion	General/clinical findings	U/S characteristics	MRI/MRA characteristics
Infantile hemangioma	Well-circumscribed mass	Very homogenous parenchymal component, lobulated when proliferating. Variable echogenicity	(+) parenchymal component. Iso-intense to muscle on T1 weighted images (T1)/ hyper-intense on T2 weighted images (T2)
		High flow lesion, generous vascularity with low resistance arterial waveforms	High flow vessels manifest as flow voids on T2
			Contrast enhances intensely and diffusely in proliferative stages, becomes less homogenous with involution
RICH/NICH	Difficult to separate from IH on basis of radiology	Greater number of discernable vessels, intravascular thrombi, calcifications, aneurysms	Indistinguishable from IH on MRI
			MRI and angiography may help distinguish these from infantile fibrosarcoma
KHE	Painful cutaneous lesions	High flow vascular lesion with soft tissue edema	Ill-defined soft tissue mass, contrast intense, but heterogeneous. Prominent fat stranding. Flow voids correspond to high flow vessels
			Usually infiltrative, crosses tissue planes, and may exhibit osseous destruction
Lymphatic	Macrocystic	Uni- or multilocular cysts (>1 cm) with thin septations, which may have vascular channels	Cysts hypo-intense on T1, hyper-intense on T2
		No color flow within cysts	Fluid-fluid levels in cysts, no flow voids, no phleboliths
			Contrast enhancement only of septae
	Microcystic	Ill-defined hyper-echoic mass which may appear to be solid	Solid, minimal enhancement with contrast, difficult to distinguish from soft tissue mass.
Venous malformation	Cavitary type	Spongy mass w/venous channels containing stagnant blood which is evacuated with compression	Multi-locular, lobulated septated masses that infiltrate into adjacent structures especially muscle. Anomalous venous drainage system. Phleboliths correspond to signal voids
	Ectasia/dysplastic	Multiple irregular varicose veins. Color flow seen in both cysts and septae	Delayed post contrast images with central enhancement, phleboliths
AVM	Vascular lesion without parenchymal component	Poorly defined hypervascular lesion w/o soft tissue mass	No soft tissue mass but edema and abnormal enhancement in surrounding tissues, overlying skin thickening, underlying osteolytic changes
		Tortuous feeding arteries with increased diastolic flow. Draining veins large with pulsatile high velocity flow	Contrast fills feeding branches with early enhancement of draining veins. Feeding and draining vessels visible connected by dilated central channels = AV shunts

Capillary Hemangioma (Pyogenic Granuloma)

The capillary hemangioma is a lesion which is clinically similar to infantile hemangioma except that it presents later in childhood. These are rapidly growing, shiny red protuberances emerging from the skin on head and neck, trunk and extremities and can also involve mucosal surfaces. They are often described as starting as a "mosquito-bite" lesion and expanding into a lesion 5–10 mm in

diameter. They rarely present in infancy, with the mean age at presentation being approximately 6 years, but extending well into adulthood. These lesions are extremely friable and will bleed vigorously with minimal trauma, but quickly respond to the application of gentle pressure. Superficial cautery (i.e., silver nitrate) is often inadequate, and excision is advised for complete eradication.

Specific Considerations for Hemangiomas Based on Site, Multifocality, and Associated Syndromes

Hemangiomas can occur as focal lesions (small or segmental), multifocal lesions, and diffuse lesions. While the above sections have focused on the cutaneous presentation of hemangiomas, these can also occur within other tissues and regions of the body. Among the more concerning are hemangiomas involving the aerodigestive tract and specifically subglottic lesions. One of the hallmarks for possible airway involvement is a large segmental hemangioma of the face, which is often associated with one or more of the following congenital anomalies: posterior fossa brain malformation, cardiac anomalies, coarctation of the aorta, eye abnormalities, and sternal clefts. This constellation of associated findings is known as the *PHACES syndrome* or complex. This is a sporadic disorder affecting female infants most often.

Subglottic hemangiomas may also present as symptomatic lesions with biphasic stridor, retractions, and recurrent croup symptoms. Although one of the more rare causes of airway compromise, they should be suspected in the presence of cutaneous hemangiomas. Plain airway films may suggest the presence of a mass, and this may need to be augmented with CT or MRI evaluation; however, endoscopic evaluation will be the best diagnostic modality. Whereas even in the recent past, these were primarily treated with endoscopic laser therapy, they have now been shown to be responsive to beta-blocker therapy (i.e., propranolol), which may obviate neonatal airway interventions.

Hemangiomas may also involve the digestive tract and most frequently the liver, although multifocal involvement of the small intestine has been reported as presenting with intestinal bleeding and with perforation. Other forms of presentation can include obstruction and intussusception, which become less frequent as these lesions spontaneously involute. Hepatic involvement has been reported sporadically, but tends to be impressive. With the variability in presentation, there has been much ambiguity as to the optimal method for intervention, especially when the treatment recommendations are as extensive as consideration of hepatic transplantation.

An attempt to categorize these lesions and establish an international registry for future reference has been proposed. In this schema, focal lesions are generally diagnosed by screening studies pre- or postnatally. They tend to resemble the RICH lesions in that they are larger, glut-1-negative, and may spontaneously regress over time. Multifocal lesions, also referred to as hemangiomatosis, are frequently identified when screening liver ultrasound is obtained due to the presence of three or more cutaneous hemangiomas. These lesions behave like their infantile hemangioma counterparts in that they are glut-1-positive and resolve. The most significant hepatic lesions present as diffuse involvement of the liver resulting in cardiac failure, fulminant hepatic failure, or abdominal compartment syndrome. Severe hypothyroidism due to overproduction of type III iodothyronine deiodinase has been reported and can also contribute to cardiac failure and lead to mental retardation. These lesions do not respond favorably to either pharmacologic management or embolic therapies and may be the only instance in which liver transplantation may become a lifesaving intervention for hemangioma. These behave akin to the kaposiform hemangioendothelioma in that they may be associated with platelet consumption as part of the Kasabach–Merritt phenomenon. This condition must be differentiated from epithelioid hemangioendothelioma, which is a malignant condition with metastatic potential.

General Characteristics of Vascular and Lymphatic Malformations

AV Malformations

The arteriovenous malformations (AVM's) are the consequence of errors in embryonic development, resulting in the absence of developed capillary bed. Direct communications between the arterial and venous circulation persist with complete transduction of arterial pressures on the thin-walled venous structures. This is thought to be the result of failure of apoptosis of the primitive arteriovenous shunts. This is probably of most consequence in the cerebral circulation where AVMs are believed to occur in up to 1% of the population and may cause fatal hemorrhage especially during the adolescent years and young adulthood. There is 20-fold higher incidence of intracranial vs extracranial AVM's, which is believed to be related to the milieu of the developing brain.

The extracranial sites for these lesions are not confined to the superficial tissues of the head and neck; they may also arise on the limbs and trunk and involve the deeper structures. Because they initially tend to be flat lesions, they may not be as easily apparent as the hemangiomas, especially during infancy. These may start as innocuous, ill-defined, homogenous pink areas, which progress over time and become more complex and most apparent in later childhood. Hormones may contribute to expansion during adolescence. This natural history is utilized in the Schobinger staging system which considers the progressive potential for ulceration, bleeding, and CHF. With decreased oxygen delivery through shunting, the higher pressures lead to hemorrhage through venous structures or rupture of arterial aneurysms. Generally, these lesions progress over time and recur after treatment. The choice and timing of interventions should receive considerable thought, and parents should be cognizant that these are not lesions to be "cured."

While hemangiomas and AV malformations share Doppler characteristics of high flow, they are radiographically dissimilar. Most distinguishing is the fact that AVM's do not have significant parenchymal mass and MRI, which is the study of choice, will show the nidus and vascular channels. The use of angiography is limited to diagnostic dilemmas and mostly for the purpose of intervention. (See *Table 422.2*)

Venous Malformations

These anomalies also arise from an error in vascular morphogenesis which results in venous structures that are relatively deficient in smooth musculature or have abnormal smooth musculature. Although present at birth, they may not become apparent until later childhood. The natural history is that of slow progressive enlargement as these veins dilate. Blood flow stagnates, and thrombosis occurs. There is the potential for pulmonary emboli and chronic pulmonary hypertension on the basis of recurrent small emboli. These anomalies can occur in skin, mucous membranes, and internal organs including the intestine. In the skin and subcutaneous tissues, these present as isolated soft, blue lesions that are generally >5 cm. When in dependent positions, engorgement occurs and drainage results with elevation. Superficial color changes are also noted with compression.

Five to ten percent of patients with venous malformations will have multiple lesions and a family history. *Glomu-venous lesions* (previously, glomangiomas) are cutaneous bluish purple lesions that are extremely sensitive to touch. These lesions can be focal or widespread and often are in multiple locations. They tend to be flat and cannot be compressed. This characteristic and the painful response to touch make them ineligible for compression therapy, and resection is often advocated. Pathology reveals the glomus cells which are likely improperly differentiated vascular smooth muscle cells.

Another specific variant of venous malformations is the *blue rubber bleb nevus* syndrome: rare variant with involvement of skin, soft tissue, and GI tract – associated with recurrent GI bleeds. These are usually not massive life-threatening events, but result in chronic anemia with the need for iron supplementation or chronic transfusion. The optimal mode for management is not evident, and given the multifocal nature, operative resections may not be feasible.

Lymphatic Malformations

These common lesions were previously referred to as lymphangiomas or cystic hygromas. Their origin is an error in embryonic development of the lymphatic system, resulting in budding off of sprouting lymphatics from lymphatic sacs or the development of lymphatic channels in abnormal locations. Lymphatic malformations comprise 6% of benign lesions of infancy and childhood, and 75% are cervicofacial. They are clinically apparent by 2 years of life in 80–90% of patients with only 50–60% apparent at birth. The resultant anomalies are classified based on the size of the lymphatic cysts: micro (<1 cm), macro (>1 cm), and mixed. The macroscopic variants (previously known as cystic hygromas) are most commonly encountered in the head and neck, axilla, chest, and perineum. Although there is some tendency toward regression (in up to 16% cases), they often necessitate interventions. The advances in sclerotherapy have benefited these lesions greatly, since surgical resection was always compromised by their infiltrative nature. Involvement of vital neurovascular structures required leaving residual LM and was frequently associated with development of seromas or prolonged lymphatic drainage from the surgical wound. Infection, while at times a complication of surgical therapy, was also often therapeutic in establishing a milieu of inflammation and fibrosis which supported resolution of the lymphatic leak. The use of various sclerosants, including a streptococcal wall derivative developed in Japan (OK432), had variable results. Absolute alcohol and 5% ethanolamine oleate have become the favored agents, but the potential for side effects remains, particularly with concern for necrosis

of the overlying skin and adjacent nerves, hemoglobinuria, and cardiovascular events.

Mixed lesions (CLVM) are often encountered recognizing that the origin of the lymphatic system is closely related to that of the venous system. For this constellation of slow flow lesions, sclerotherapy and surgical therapy are the primary modes of treatment. Timing and sequence are determined based on symptoms, and location and size of the lesion.

Capillary Stains and Malformations

The most common region of discoloration seen immediately at the time of birth is the capillary stain. It affects 40% of infants. They are not associated with pathologic entities and probable result from dysregulation of the autonomic nervous system, resulting in vasodilation of the capillaries in the papillary dermis. They are most often seen on the glabella, nose, eyelid, nape of neck (stork bite mark) and generally lighten with time.

Capillary Malformations

True capillary malformations are congenital lesions, which rather than fading will persist with time and often become more complex with the development of telangiectasias and vascular ectasias. They have been referred to as portwine stain and nevus flammeus and are a deeper red color than the transient pink capillary stains. The can occur over any portion of the body, but when they occur in a dermatomal distribution particularly in the face, they must be considered in the context of associated syndromes (discussed in the following separate section on vascular anomalies and associated syndromes)

Associated Syndromes, Musculoskeletal Disorders, and Tumors

While most vascular malformations occur in isolation and are not associated with hereditary/genetic syndromes, there are some important conditions to consider when a congenital vascular malformation is evident.

While capillary stains are the most common and often transient, the occurrence of a butterfly pattern over the sacrum can be an indicator for an underlying spinal disorder and screening ultrasound/MRI may be recommended. Other considerations related to skeletal problems include the potential effect of the vascular lesion on limb growth. While some lesions exist within the bone and result in expansion of the bone itself, other lesions have an effect by virtue of the increased blood flow to the extremity and result in musculoskeletal overgrowth with consequent limb length discrepancies. When assessing infants born with enlarged extremities, considerations should include the hemihypertrophy syndromes, the presence of an extremity soft tissue lesion which can be a lymphovascular malformation or potentially a soft tissue tumor. This differential diagnosis must be considered and appropriate radiographic imaging and/or biopsy instituted to assure a correct diagnosis.

One of the most confounding diagnostic dilemmas in early infancy is the *infantile fibrosarcoma*, which enlarges during the first few weeks of life and by virtue of the associated telangiectatic skin changes, and even deeper vascular changes appear to be a benign infantile hemangioma or potentially a congenital hemangioma (RICH or NICH). Physical characteristics which may be useful in distinguishing the lesions include the consistency of the lesion. While both have significant parenchymal components, the hemangioma should have greater compressibility. Ultrasound for both will delineate a highly vascularized lesion which may have high flow components. In contrast to the infantile hemangioma, the tumor will have less of a consistent internal structure on MRI and MRA. In particular, the MRA may show larger feeding vessels and neovascularization to suggest the need for biopsy.

Sturge Weber syndrome consists of a facial capillary malformation in the distribution of the facial nerve (V1), an ipsilateral leptomeningeal vascular malformation, and choroidal malformation of the eye. Clinical features include seizures, hemiparesis, migraines, and developmental delay (50%).

Macrocephaly – CM denotes a sporadic association, for which no genetic basis has been identified, of a blotchy, poorly demarcated facial capillary malformation with macrocephaly, hypotonia, and developmental delay

Cutis marmorata telangiectasia congenita (*CMTC*) presents on the extremities as a region of discoloration that may resemble the reticular pattern seen with poor perfusion in infants. It, however, does not respond to local warming measures. Even when not associated with extremity hyper- or hypoplasia at birth, it is necessary to follow these patients long term, as there may be associated leg length discrepancies that develop. Overall this has a better prognosis that when associated with the venous and lymphatic components seen in *Klippel–Trenaunay Syndrome* (*KTS*). It has no known genetic basis.

Syndromes Associated with Combinations of Vascular Anomalies and Overgrowth

Capillary malformation – arteriovenous malformation syndrome is the consequence of an autosomal dominant mutation of the RASA1 gene, which is an inhibitor in the Ras – Map kinase pathway. Clinically, these present as small multifocal CM's with underlying AVM's when evaluated with Doppler probe. They may be components of the Parkes Weber syndrome.

Although *Klippel–Trenaunay Syndrome* was traditionally described as a CM (port wine stain) with visible venous varicosities particularly over the lateral aspect of the leg and bony and soft tissue overgrowth, the actual vascular anomaly is best described as a CLVM. These patients develop progressive venous stasis and lymphedema with resultant thrombosis and ulceration.

Parkes Weber syndrome is clinically very similar to KTS in that there is significant skeletal hypertrophy of the affected limb. The capillary malformation is accompanied by multiple AV fistulas which alter the constellation of problems presented to the patient.

PTEN-associated vascular anomaly affects a subset of patients with PTEN gene mutations. They have altered function of a tumor suppressor gene and are at risk for PTEN hamartoma tumor syndrome (Cowden's syndrome) which is an autosomal dominant condition. In addition to surveillance for endocrine and GI malignancies, these patients may have arteriovenous malformations particularly involving the musculature in 50% with resultant overgrowth of bone and soft tissue.

Treatment Strategies for Vascular Anomalies

The options for treatment vary with the type of lesion (hemangioma vs vascular malformation), location (skin/soft tissue vs cranial, orbital or airway) and involvement of deeper tissues (superficial CM vs intramuscular AVM).

Since hemangiomas are proliferative lesions, pharmacologic options are available which would be expected to play a lesser, or no, role in the vascular anomalies. The decision to intervene on an infantile hemangioma or congenital hemangioma is generally driven by its location and inherent complications. Lesions that threaten eyesight and or airway (life) as well as large segmental hemangiomas have been the traditional candidates for treatment. Parental reassurance is the primary treatment for the isolated hemangioma that can be predicted to involute without adverse consequences. As the therapies offered become safer, there may be less reluctance to provide an intervention for nontraditional indications.

Corticosteroid therapy has remained the first-line therapy at initial doses of 2–4 mg/kg/day, extended over a period of 9 months to cover the period of proliferation. While effective in >80% of cases, the associated side effects (behavioral disturbances including sleeplessness, cushingoid features, growth delay, and hypertension) often limit tolerance. Intralesional injections separated by 6–8 weeks are instituted to avoid the systemic effects, but do not eliminate them. Topical therapy using steroid creams and another immune-modulating agent imiquinod has very limited effectiveness.

When corticosteroid therapy was ineffective or not tolerated, the next line agent was *interferon alpha*, which was initially developed as an antiviral agent but was recognized to have potent antiangiogenic properties. Although it had clinical efficacy, unfortunately, the incidence of neurologic complications, which included irreversible spastic diplegia, limited the use of this agent. *Vincristine* became a second-line agent when its effect on KHE was appreciated and the use as a mitotic inhibitor during the proliferative phase of hemangiomas was supported clinically. Both agents have since been replaced with *beta-adrenergic antagonists* such as propranolol which serendipitously was noted to have a dramatic regression effect on a steroid recalcitrant hemangioma in a child who required a beta-blocker for a cardiomyopathy. Although standardized protocols have not been developed, there are a multitude of reports of its efficacy. The potential side effects include hypoglycemia, bradycardia, and hypotension, but this agent has been well tolerated to date.

Nonpharmacologic Interventions

Therapies in this category are employed for both hemangiomas and vascular malformations. It is imperative that the indications are delineated clearly to parents and caretakers and that an understanding exists that these are intended to either: (1) resolve a cosmetic issue, (2) address a eyesight or life-threatening lesion, (3) address superficial ulceration and necrosis associated with aneurysmal dilation of either arteries or veins in complex malformations (*Table 422.3*).

Beyond their proliferative phase, when pharmacologic therapy is optimal, or when this is inadequate, hemangiomas may require interventions using laser therapy, angiographic interventions, or surgical excision. Laser therapies are based on thermal-induced coagulation initiated by the absorption of a specific wavelength of light by a target, such as oxyhemoglobin, which results in elevation

Table 422.3

Physical findings and their clinical context

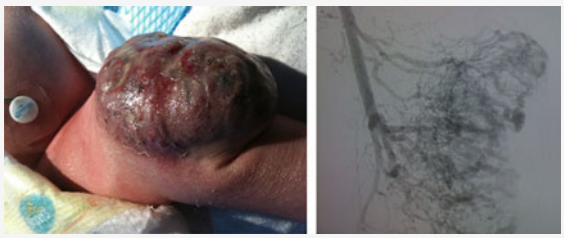
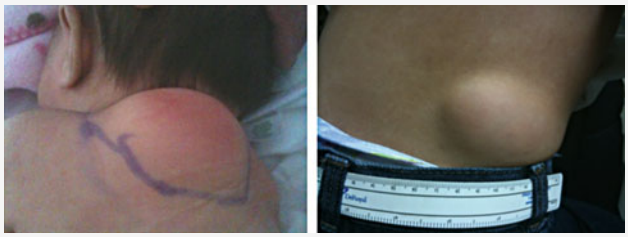
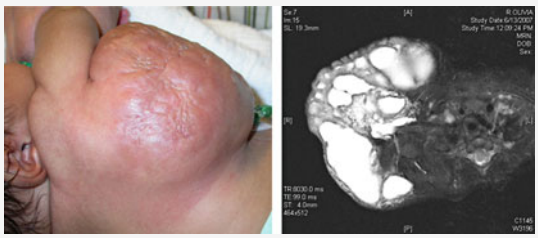
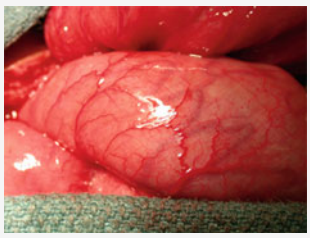
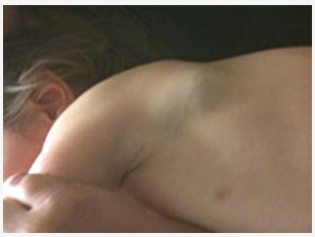
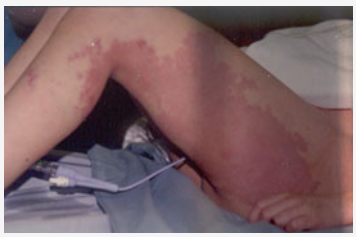
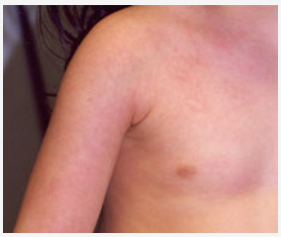
Lesion	Physical findings	Clinical context
Infantile hemangioma (IH)		(a) Four-month-old infant with expanding vascular lesion with irregular surface c/w hemangioma in proliferative phase (b) Infant with multiple cutaneous hemangiomas
RICH/NICH		(a) Two month old with highly vascular lesion on thigh and knee present from birth with superficial ulceration and consequent hemorrhage (b) Arteriogram pre-embolization (Photograph courtesy of C. Muratore, MD)
Lymphatic (LM)		(a) Lymphatic malformation that suddenly became apparent in 3 month old as consequence of infection. No soft tissue mass was appreciated prior to infection (b) Two year old with microcystic LM
		(a) Subaxillary lymphatic malformation diagnosed prenatally (b) Note macro- and microcystic components on MRI (Photographs courtesy of C. Muratore, MD)
Venous malformation (VM)		Ten-year-old male who presented at age 4 years with recurrent GI bleeding, ultimately determined to arise from venous malformation in distal ileum. Note prominent veins in submucosa

Table 422.3 (Continued)

Lesion	Physical findings	Clinical context
Combined lesion (CLVM)		Combined venous and lymphatic malformation in posterior axillary fold. Note bluish hue
Capillary malformation (CM)		Preadolescent female with capillary malformation involving lower extremity and perineum
Arteriovenous malformation (AVM)		Six-year-old girl with limb hypertrophy and heat radiating from right chest and arm as consequence of high flow vascular malformation c/w AVM

of local tissue temperature. Effectiveness is primarily limited by the depth of energy penetration, and therefore, this modality is most frequently used for superficial dermal lesions. There are many forms of laser therapy, and a discussion of specifics is beyond the scope of this text. Airway lesions have traditionally been treated with the carbon dioxide laser.

Ultrasound-guided and angiographic techniques are principally used for the vascular and lymphatic malformations. The principle of these therapies is either to occlude inflow to a lesion reducing its size, cause necrosis, or reduce the shunting that led to congestive heart failure. Angiographic interventions are limited by the complications associated with access to the arterial system. While appropriate size catheters and embolic devices have been developed, particularly for cerebrovascular interventions, access via the small caliber femoral vessels has been associated with thrombosis and limb length discrepancies on the basis of arterial insufficiency. These risks have to be balanced with the indications for considering an intervention. In extensive AVMs, the occlusion of one source of inflow is often accompanied by an increased flow via other channels. Furthermore, the actual induction of hypoxemia as a consequence of embolic therapy is a potent stimulator of vascular neogenesis.

To offset the risks of femoral access, direct puncture into lesional vessels can be another effective technique. Agents instilled for thrombosis include dehydrated alcohol which acts as a sclerosant. This injection of vessels is often guided by ultrasound. These interventions require sedation and/or general anesthesia with considerations for good pain management in the postprocedure phase. Sclerosis can be used as an independent intervention or as a preliminary step to facilitate resection.

Surgical resection has generally been limited to the residual skin and soft tissue anomalies after regression of a hemangioma. Intervention in a well-vascularized lesion for resection is naturally associated with the potential for significant bleeding. Adjuncts such as use of an extremity tourniquet, hemostatic topical agents, and even systemic

therapies such as Novo7 have allowed for higher risk surgical interventions to be performed with acceptable morbidity and mortality.

Summary

Vascular lesions in the infant and child should be categorized into hemangiomas or vascular malformations based on their clinical and radiographic features. With an understanding of the natural history of the lesions, appropriate discussions can be held regarding the indications for and timing of interventions. The multidisciplinary approach to the patient with a vascular lesion will allow for a multimodality treatment approach.

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Drug Dosing in Pediatrics

Kristine A. Parbuoni

423 Drug Dosages: Pediatric Pharmacokinetics and Pharmacodynamics

Donna Huynh · Kristine A. Parbuoni

In order for drugs to exert their therapeutic and toxic effects, they need to reach their site of action. Pharmacokinetics describes the process by which drugs are absorbed, distributed, metabolized, and eliminated by the body. With the exception of the intravenous route of administration, drugs need to be absorbed into the systemic circulation in order to reach their site of action. Once absorbed into the systemic circulation, drugs are distributed to the various tissues. To eliminate the drug from the body, drugs may undergo a series of enzymatic reactions which can lead to an active form of the drug, a toxic metabolite, or a molecule that can be more easily excreted by the kidneys. Some drugs can be eliminated by the kidneys without undergoing any metabolism by the body. Important pharmacokinetic differences exist between children and adults which can have significant implications on drug dosing in pediatric patients.

Oral Drug Absorption

Drug absorption using the enteral route can be affected by gastric pH, gastric emptying time, and enzymes and efflux transporters that are found in the gastrointestinal tract. Neonates and infants have a higher gastric pH in comparison to adults due to a reduction in acid production and secretion by the stomach. The higher gastric pH leads to the decreased absorption of drugs that are weak acids, such as phenobarbital, and therefore higher oral doses are required in comparison to adults. In contrast, there is an increased absorption of basic or acid-labile drugs such as penicillin G in neonates compared to adults. The gastric pH reaches adult values by 2 years of age. Gastric emptying time is also delayed in neonates and infants due to decreased peristalsis and motility in the gastrointestinal tract. The delayed gastric emptying time prolongs the time it takes to reach peak concentration in neonates and young infants when compared to adults. In addition to gastric emptying time, the lack of mature efflux transporters and enzymes in the gastrointestinal tract of neonates and young infants can also reduce the absorption of specific medications such as gabapentin.

Other Routes of Administrations

There is decreased muscle mass and erratic blood flow to the muscles in neonates compared to adults. This may result in slower and reduced absorption of some drugs using the intramuscular route in neonates in comparison to adults. Intramuscular injections should be avoided if possible in neonates due to pain and questionable absorption. If given to neonates and infants, intramuscular injections should be given to the anterolateral aspect of thigh.

Neonates and infants have increased absorption of topical medications compared to older children and adults. Percutaneous drug absorption occurs more readily in neonates and infants due to larger body surface area to body mass ratio, thinner stratum corneum, and increased hydration and perfusion to skin. Neonates and infants are at an increased risk for toxicities from drugs applied to the skin, and certain topical medications such as povidone-iodine should be avoided in neonates.

Drug Distribution

In neonates and infants, there is a greater total body water and less fat content when compared to adults. The volume of distribution for hydrophilic drugs is increased and for lipophilic drugs is decreased in neonates and infants. In order to reach the same therapeutic drug levels as in adults, a larger dose needs to be given to neonates and infants for hydrophilic drugs such as gentamicin.

Protein binding can also affect drug distribution since only unbound drug is active and is able to exert its therapeutic effect. Neonates and infants have decreased concentrations of albumin and α_1-acid glycoprotein which are

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the primary proteins that bind drugs. In addition, they have a high concentration of fetal albumin which has a decreased binding affinity for drugs compared to albumin. This means that there is an increased fraction of unbound drugs in neonates and infants for highly protein bound drugs such as phenytoin. There are also higher concentrations of endogenous substances such as bilirubin that can compete with drugs for binding sites. It is important to avoid drugs that can displace bilirubin from albumin binding sites which can lead to kernicterus. Ceftriaxone and sulfonamides should be avoided in infants less than 2 months of age.

Drug Metabolism

Drugs are metabolized in the body via two different categories of reactions. Phase I reactions are responsible for oxidation and reduction type reactions. Phase II reactions are responsible for conjugation reactions such as sulfation and glucuronidation. The isoenzymes of the CYP450 system mature at different rates and are responsible for the majority of the Phase I reactions in the body. For example, CYP1A2 is responsible for the metabolism of caffeine and is only at 50% adult capacity by 0.9 years of age. The sulfation pathway is fully developed at birth which makes infants and young infants more tolerant to acute ingestion of acetaminophen. The glucuronidation pathway is only at 10% adult capacity at birth but reaches adult values by 2 years of age. As a result of this, chloramphenicol should be avoided in neonates and infants due to increased risk of grey baby syndrome.

Drug Elimination

The elimination of drugs by the kidney is dependent on renal blood flow, glomerular filtration rate, and tubular secretion. Renal blood flow is decreased in neonates and young infants in comparison to adults with only 5% of cardiac output at birth in comparison to 15% of cardiac output in adults. Both glomerular filtration and tubular secretion are decreased at birth and reaches adult values by 1 year of age. Therefore, for drugs that are eliminated by the kidneys, they have a slower clearance and a longer half-life. This means that drugs are often dosed less frequently in neonates and infants in comparison to adults. To estimate creatinine clearance in neonates and children, the Schwartz equation should be used.

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424 Drug Dosages: Administration of Medications

Jill A. Morgan · Kristine A. Parbuoni

Patients should be educated about their medications. For recommended pharmacologic treatments, providers should explain the dosing frequency, common adverse events that should be expected, and what to do if they occur or the condition worsens. The patient and caregiver should also be counseled on how to administer the medication.

Children can generally swallow pills around 7 years of age. Therefore, most oral medications for children are in the liquid form. Administration errors with liquid medications are frequent with 50–60% of parents incorrectly measuring the dose of a medication. In 1975, the American Academy of Pediatrics (AAP) published a statement on the inaccuracies of administering liquid medications to children. It is well known that household teaspoons measure anywhere from 2.5 to 7.8 mL; therefore, the AAP has recommended using oral syringes to measure liquid medication doses.

Yin and colleagues described errors related to medication dosing cups including confusing the teaspoon measure with the tablespoon measure and assuming the whole dosing cup was the prescribed dose. Medication cups were associated with a statistically significant increased number of errors compared to oral syringes. Researchers also noted the lack of eye level dose verification with plastic dosing cups.

In another study, McMahon (1997) demonstrated that parents are able to correctly measure liquid doses if given a demonstration, verbal instructions, and a marked, oral syringe with a line. For parents given verbal instructions, 37% measured a correct dose. When given verbal instructions and a marked syringe, 83% were able to measure the correct dose. For parents who received verbal instructions, a demonstration, and a marked syringe, 100% measured the correct dose.

Sobhani looked at the ability of adults to measure 5 mL using an oral syringe and the provided dose cup from the manufacturer. In a survey completed at the beginning of the study, participants were asked about measuring devices they had previously used. The survey revealed that 68% of participants had used droppers, 67% of participants had used dose cups, and only 49% of participants had used oral syringes previously at home. In this study, 66.7% measured a dose correctly using the oral syringe versus 14.6% with the dose cup. It is interesting to note that more people thought the dose cup was easier to manipulate than the oral syringe (87% vs. 63%). Also, about 30% of participants were not able to correctly measure a dose using the oral syringe.

Each prescription should be dispensed with an oral syringe that is marked for that medication. Color-coded syringes can help to decrease confusion if there is more than one medication or child at home on medications. Parents and caregivers must be taught how to measure the dose in an oral syringe with verbal instructions and a demonstration. The pharmacist should also consider recommending the use of bottle adaptors to make the manipulations of the oral syringe easier for parents and to decrease medication loss.

For oral medications, infants and toddlers may need to be restrained before giving a dose. Have the parents hold the child in their lap. Cradle the child's head in the crook of their arm. Reach the same arm around the child and hold their free arm. The child's other arm should be pressed against the parent's body. Place the child's legs between the parent's legs. Administer the liquid in 1 mL increments to the inside of the cheek. Gently blowing on an infant's face will elicit the swallowing reflex. Older children can sit or stand for the administration of oral medications.

For ophthalmic medications, tell the patient or caregiver to wash their hands and remove contact lenses before applying eye drops. Most ophthalmic agents contain the preservative benzalkonium chloride, which is known to permeate contact lenses; therefore, remove contact lenses prior to instilling the ophthalmic preparation and wait 10–15 min before placing the contact back in the eye. Check the expiration date, clarity, and color of the ophthalmic solution to ensure there is no change from the original formulation. Discard the product if it has expired, changed color, or is cloudy. Instruct the patient to tilt their head back, look up and pull down the eyelid to make

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a pouch, instill a drop into the pouch, then close the eyes while applying light pressure with a finger to the lacrimal sac for 1–2 min after instillation. This prevents the medication from draining away from the eye. For young children that may resist the instillation of the ophthalmic preparation, there are a couple of useful techniques that will help to ensure safe administration of the medication. Have the child lay down on a couch or bed. If two caregivers are available have one caregiver hold the child in place by stabilizing the head while the second caregiver pulls down the eyelid to make a pouch and instills the ophthalmic drop. If only one caregiver is available do the following: if the child is an infant, swaddle the baby to stabilize or while the child is lying down with their arms folded in their lap, use one arm to stabilize the child's body. The hand on the arm that is used to stabilize the body is used to form a pouch in the lower eyelid. With the other arm, hold the forehead still and use the hand on this arm to instill the ophthalmic preparation. The purpose of using the hand on the arm holding the forehead for instillation is that the ophthalmic bottle will move with the child and should not cause injury to the eye with undesired movement(s) of the child. In order to avoid contamination of the eye dropper, do not touch the top of the dropper bottle to the eyes, fingers, or any other surface.

For rectal medications, have the parent wash their hands and possibly put on gloves. An infant can lie across an adult's lap on their belly or on a bed on their belly. An older child should lie on their left side with the right leg bent toward the chest. Remove the suppository from the wrapper and put some petrolatum on the end of it. With one hand, separate the child's buttocks and gently insert the suppository into the anal opening. With the pinky finger, gently push the suppository into the rectum until there is no resistance (about ½ in. in infants <6 months of age and 1 in. in older children). Hold the child's buttocks together until the urge to go to the bathroom is gone. Have the child remain in the prone position for 20 min.

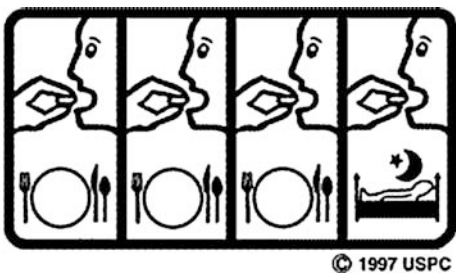
For otic medications, have the parents warm the medication in their hands to prevent nausea and dizziness. The child can lie down or sit up and tilt their head to the side. If the child is <3 years, straighten the ear canal by pulling the ear lobe down and back. If the child is ≥3 years, straighten the ear canal by holding the upper part of the ear and pulling up and back. Instill the drops into the ear canal on the side, not directly in the canal and do not touch the dropper to the ear. Have the child continue to lie on their side or tilt their head for 5 min.

When administering medication to children, parents and caregivers should be able to explain what they are going to do to the pharmacist or medical practitioner. Medication administration should follow a routine. Parents and caregivers should not refer to medications as candy. It is important to praise their child for good behavior and cooperation during medication administration.

Education

Pharmacists and providers should counsel parents and children on their medications. Counseling needs to be directed to the child even if the child might not understand all of the information shared. The education materials should be tailored to the developmental stage of the child. Materials for young children should not contain medical jargon and should explain terms using a child's language. They should consist of mainly pictures. Young children will only remember 2–3 messages per session. Older children and adolescents can have more complex information in their education materials. The material should contain pictures and text.

A variety of methods are available to help improve understanding of medical information. Pictograms have been shown to improve medication knowledge in patients with 7 years of schooling and English as a second language. The HELPix project developed medication instruction sheets that are patient-specific with plain language and pictograms for medication preparation, route, frequency, storage, and duration. This program was developed to help patients with low literacy. Yin (2008) and colleagues evaluated this program and found that the pictogram-based medication information sheets used in conjunction with a counseling program decreased medication errors and increased adherence in children treated at an urban ED. Samples of medication information sheets can be located at the HELPix website: http://helpix.med.nyu.edu/the-helpix-intervention/overview-helpix. Another patient-friendly site for patient education handouts is www.safemedication.com. Also, pictograms can be downloaded for free from www.usp.org. Below is a sample pictogram from USP:



Take 4 times a day, with meals and at bedtime (http://www.usp.org/audiences/consumers/pictograms/)

Schillinger (2003) introduced the concept of assessing knowledge taught in counseling sessions by having the patients repeat back what information was shared. This process may be very helpful in gauging the parent's and child's understanding of the information delivered in the counseling session.

The following information should be conveyed in each counseling session: the indication for use, directions on how to administer (including taking with or without food) and how often, patient-specific drug interactions, special storage instructions, and side effect information. Explain common adverse reactions as well as rare serious adverse reactions. It is important for parents to know how to handle an adverse event and when to involve the physician. Also, for prescription products, it is important to highlight to parents and caregivers that if any adverse drug event occurs they can call the toll-free phone number listed on the product labeling. Lastly, explain when the medication should take effect or when a child should see improvement and what to do if this does not happen.

Counseling sessions should also reinforce the importance of adherence. Encourage and give children charts to track adherence. A child can color or place stickers on the chart after administration of a dose. For complicated tapers or patients on chronic medications, calendars can be developed that can be marked off as doses are administered. Pharmacists should recommend that parents keep the charts near the medications (e.g., on the refrigerator door).

Adherence can be linked to the palatability of the medication. This can be increased using products that flavor medications. Also, a child can numb their taste buds with a popsicle or a piece of ice before taking a medication. The metallic aftertaste from some medications such as metronidazole and clarithromycin can be reduced with orange juice or chocolate. After the administration of a poor tasting medication, encourage the child to eat some peanut butter (check for allergies first), drink a carbonated beverage, or have chocolate sauce to remove the taste from the tongue. In general, bitter medications can be masked with chocolate flavors, citrus can be used for sour medications, and salty can be masked with peanut butter, cinnamon, or butterscotch.

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425 Drug Dosages

Donna Huynh · Jill A. Morgan · Kristine A. Parbuoni

Table 425.1
PALS resuscitation medications

Medication	Indication	Dose	Comments
Adenosine	Supraventricular tachycardia	0.1 mg/kg (max dose: 6 mg)	Rapid IV/IO bolus
		Repeat dose: 0.2 mg/kg (max dose: 12 mg)	May repeat after 2 min
Amiodarone (Cordarone®, Pacerone®)	Ventricular tachycardia	5 mg/kg IV/IO (max dose: 300 mg)	Push if no pulse
	Ventricular arrhythmia	May repeat up to max total daily dose: 15 mg/kg (2.2 g/day)	Administer over 20 min if pulse present
			Monitor for hypotension
			Use caution with other QT prolonging agents
Atropine	Bradycardia	IV/IO: 0.02 mg/kg	Repeat once if needed
	Primary AV block	ETT: 0.04–0.06 mg/kg	
		Minimum dose: 0.1 mg	
		Maximum dose: 0.5 mg (child), 1 mg (adolescent)	
Calcium chloride (10%)	Hypocalcemia	20 mg/kg IV/IO (0.2 ml/kg)	Slow push
	Hyperkalemia		Repeat as needed
	Hypermagnesemia		
	Calcium channel blocker overdose		
Dextrose (glucose)	Hypoglycemia	0.5–1 g/kg IV/IO	D10W: 5–10 ml/kg
			D25W: 2–4 ml/kg
			D50W: 1–2 ml/kg
Epinephrine	Bradycardia	0.01 mg/kg IV/IO (0.1 ml/kg, 1:10,000)	May repeat every 3–5 min
	Asystole	Maximum dose: 1 mg	
	Pulseless arrest	0.1 mg/kg ETT (0.1 ml/kg 1:1,000)	
		Maximum dose: 2.5 mg	
Insulin	Hyperkalemia	0.1 units/kg IV/IO with 0.5 g/kg dextrose	
Lidocaine (Xylocaine®)	VF	1 mg/kg IV/IO	
	Pulseless VT	2–3 mg/kg ETT	
Magnesium sulfate	Torsades de Pointes	25–50 mg/kg IV/IO	Push if no pulse
	Hypomagnesemia	Maximum dose: 2 g	Administer over 10–20 min if pulse present

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Table 425.1 (Continued)

Medication	Indication	Dose	Comments
Naloxone (Narcan®)	Opioid overdose	Total reversal: 0.1 mg/kg IV/IO/IM/SQ	May repeat as needed
		Maximum dose: 2 mg	
		Respiratory depression with therapeutic opioid use: 1–15 mcg/kg IV/IO/IM/SQ	
Sodium bicarbonate	Metabolic acidosis	1 mEq/kg IV/IO	Administer slowly
	Hyperkalemia		Dilute 1:1 with sterile water for patients <10 kg
	Tricyclic antidepressant overdose		

Table 425.2
Respiratory medications

Medication	Indication	Dose	Comments
Beta-agonists			
Albuterol (ProAir®HFA, Proventil®HFA, Ventolin®HFA)	Asthma quick relief of bronchospasm	Acute attack: 2.5–5 mg via nebulizer every 20 min then every 1–4 h as needed	Tolerance can develop.
			Use >2/week indicates poor control of asthma
		Can increase to 10–15 mg/h	Use spacer with MDI. Shake MDI well before use
			Wait 1 min between inhalations
		MDI: Four to eight puffs every 20 min then every 1–4 h as needed	May cause hyperactivity, insomnia, coughing, hoarseness, tachycardia, palpitations, chest pain, and hypokalemia (with continuous use)
		Non-acute attack: 2.5 mg via nebulizer every 4–6 h as needed	Remove canister and wash plastic inhaler once a week and air dry to prevent clogging of medication
		MDI: One to two puffs every 4–6 h as needed	Inhaler requires priming
Terbutaline	Asthma quick relief of bronchospasm	Loading dose: 2–10 mcg/kg IV followed by 0.1–10 mcg/kg/min continuous infusion	Titrate drip up 0.1 mcg/kg/min every 30 min
			Can administer undiluted (1 mg/ml)
			May cause hyperactivity, insomnia, coughing, hoarseness, tachycardia, palpitations, chest pain, hyperglycemia, and hypokalemia, QT prolongation, CPK isoenzyme elevation

Table 425.2 (Continued)

Medication	Indication	Dose	Comments
Corticosteroids			
Budesonide (Pulmicort Respules®, Pulmicort Flexhaler™, Rhinocort® Aqua®)	Asthma controller	Oral inhalations: ≤4 years:	Not first line therapy for asthma attack
	Seasonal and perennial rhinitis	Low dose: 0.25–0.5 mg	Increase dose every 2 weeks until achieve control
		Medium dose: >0.5 to 1 mg	Nebulization: Administer nebulized doses once or twice a day. Shake before use. Administer with a compressed air jet nebulizer. Avoid exposure to eyes
		High dose: >1 mg	
		5–11 years:	For the flexhaler: Divide dosing twice daily. Remove cap. Hold inhaler with mouthpiece up to load dose. Turn bottom to right and back until clicks. Do not shake or prime. Put mouthpiece between lips and inhale fast and deep. Do not exhale or blow into inhaler. Replace inhaler when dose counter reads "0." Contains lactose. Avoid in allergic patients
		Low dose: 0.5 mg neb or 180–400 mcg/day (90 mcg 2–4 inhalations/day)	
		Medium dose: 1 mg neb or 400–800 mcg/day (180 mcg 2–4 inhalations/day)	
			Wait 1 min between inhalations
		High dose: 2 mg neb or >800 mcg/day (180 mcg >4 inhalations/day)	Rinse mouth and spit or brush teeth after each administration to decrease risk of thrush
		≥12 years	May cause HPA suppression and growth suppression
		Low dose: 180–600 mcg/day (90 mcg 2–6 inhalations/day)	For nasal spray: Shake well. Blow nose before use. Insert applicator into nostril, keep bottle upright, and close off the other nostril; breathe in through nose; press pump to release dose. Avoid spraying into eyes. May cause nose bleeds, nasal burning or irritation, and nasal ulcers
		Medium dose: 600–1,200 mcg/day (180 mcg 3–6 inhalations/day)	
		High dose: >1,200 mcg/day (180 mcg >6 inhalations/day)	Max effect for nasal use seen in 2 weeks, for oral use seen in 2–6 weeks
		Nasal: ≥6 years: 1–2 sprays each nostril once a day	Bioavailability 11%

Table 425.2 (Continued)

Medication	Indication	Dose	Comments
Fluticasone (Flovent®, Flonase®)	Asthma controller	Oral inhalations	Not first line therapy for asthma attack
	Seasonal and perennial rhinitis	Low dose: 88–176 mcg (44 mcg 2–4 puffs/day)	Increase dose every 2 weeks until achieve control
		Medium dose: 177–352 mcg (110 mcg 2–3 puffs/day)	Administer inhaler twice daily
			Use spacer with MDI. Shake MDI well before use
		High dose: >352 mcg (220 mcg ≥2 puffs/day)	Wait 1 min between inhalations
			Rinse mouth and spit or brush teeth after each administration to decrease risk of thrush
		Nasal: ≥4 years: 1–2 sprays in each nostril once a day	May cause HPA suppression and growth suppression
			For nasal spray: Shake well. Blow nose before use. Insert applicator into nostril, keep bottle upright, and close off the other nostril; breathe in through nose; press pump to release dose. Avoid spraying into eyes. May cause nose bleeds, nasal burning or irritation, and nasal ulcers
			Inhalers and nasal sprays require priming
			Max effect seen in 2 weeks
			Bioavailability 1%
Mometasone (Asmanex® Twisthaler®, Nasonex®)	Asthma controller	4–11 years: 110 mcg one inhalation every evening	Not first line therapy for asthma attack
			Increase dose every 2 weeks until control is achieved
		≥12 years:	For the twisthaler: Remove twisthaler from foil pouch and write date on cap. Discard inhaler 45 days later. Hold inhaler with mouthpiece up and colored base on bottom. Hold base and turn cap in counterclockwise fashion to remove and load dose. Do not shake or prime. Put mouthpiece between lips and inhale fast and deep. Do not cover ventilation holes. Do not exhale or blow into inhaler. Replace cap and turn clockwise until hear click. Wait 1 min between inhalations
		Low dose: 200 mcg one inhalation every evening	
		Medium dose: 400 mcg (200 mcg two inhalations every evening)	
		High dose: >400 mcg (200 mcg >2 inhalations)	
			Rinse mouth and spit or brush teeth after each administration to decrease risk of thrush
			May cause HPA suppression and growth suppression
			Contains lactose. Avoid in allergic patients
			Do not wash inhaler. Wipe with dry cloth if needed
			Max effect seen in 2 weeks
			Bioavailability <1%

Table 425.2 (Continued)

Medication	Indication	Dose	Comments
Antihistamines and Others			
Cetirizine (Zyrtec®)	Allergic Rhinitis	6 months–5 years: 2.5 mg once a day, can increase to 5 mg/day	May cause drowsiness and photosensitivity reactions.
	Urticaria	≥6 years: 5–10 mg once a day	Caution in children <2 years
Diphenhydramine (Benadryl®)	Treatment of allergy symptoms	5 mg/kg/day divided every 6 h (Max dose = 300 mg/day)	May cause drowsiness, dizziness, hypotension, wheezing, dry mouth, constipation, and urinary retention. May cause paradoxical excitation, hallucinations in children
	Mild sedation	Adolescents: 25–50 mg every 4–6 h	
	Relief of pain and itching from insect bites		Avoid in asthmatics (due to thickening of mucous in lungs and wheezing)
	Treatment of dystonic reactions		Do not apply topical preparations to large portion of body or open skin due to risk of psychosis and seizures
	Prevents motion sickness		Caution use in closed-angle glaucoma, peptic ulcer disease, and hyperthyroidism
Loratadine (Claritin®)	Allergic Rhinitis	2–5 years: 5 mg once a day	May cause drowsiness, dry mouth, discolor urine, and photosensitivity reactions
	Urticaria	≥6 years: 10 mg once a day	Food increases bioavailability by 40%.
			Check for drug interactions that may impair Loratadine's hepatic metabolism
Caffeine citrate (Cafcit®)	Apnea of prematurity	Loading dose: 10–20 mg/kg as caffeine citrate (5–10 mg/kg as caffeine base)	If received theophylline in last 3 days, decrease loading dose by half
		Maintenance dose: 5 mg/kg/day as caffeine citrate (2.5 mg/kg/day as caffeine base)	Start maintenance dose 24 h after loading dose
			Monitor heart rate, caffeine levels once a week, and number of apnea episodes
			Therapeutic level: 8–20 mcg/ml
			Each 1 mg/kg dose will increase level by 1 mcg/ml
			May cause cardiac arrhythmias, agitation, hyperactivity, muscle tremors, and hyper- or hypoglycemia
			Can administer IV form orally
			Avoid use of caffeine sodium benzoate to prevent gasping syndrome in neonates
Ipratropium Bromide (Atrovent®)	Status asthmaticus to prevent hospital admission	0.5 mg via nebulizer every 20 min then every 6 h for 24 h	Not first line therapy for asthma attack
			May cause dry mouth
		MDI: Four to eight puffs every 20 min then every 6 h for 24 h	Avoid spraying aerosol in eyes due to risk of blurred vision
			Caution some generic inhalers contain soy and should be avoided in peanut and soybean allergic patients
			No evidence to use routinely in asthma patients

Table 425.2 (Continued)

Medication	Indication	Dose	Comments
Montelukast (Singulair®)	Asthma controller	6 months–5 years: 4 mg once a day	Not first line therapy for asthma attack
	Seasonal and perennial rhinitis	6–14 years: 5 mg once a day	Administer at bedtime
	Prevent exercise bronchospasm	>14 years: 10 mg once a day	Administer 2 h before exercise as needed to prevent bronchospasm
			Administer granules within 15 min of opening package by placing directly into mouth or can mix in applesauce, mashed carrots, rice, or ice cream. Do not dissolve granules into liquid
			May cause headaches, insomnia, nightmares, agitation, aggression, depression (rare)

Table 425.3
Opioid analgesics

Drug	Onset (min)	Duration (h)	Equianalgesic dose (mg/kg/dose)	Route	Comments
Codeine	30–60	4–6	0.5–1	PO	Not for children <6 months old
					Converted in liver to morphine. 10% of US population cannot convert codeine to morphine therefore will not experience analgesia
Fentanyl	1–2	0.5–1	0.001	IV	Chest wall rigidity can occur with rapid infusion; treat with naloxone or neuromuscular blockers
Hydrocodone	10–20	3–6	0.1	PO	Formulated with acetaminophen; consider acetaminophen dose limits
Hydromorphone (Dilaudid®)	5–10	3–4	0.015	IV	Less pruritis than morphine
	30–60	4–5	0.03–0.08	PO	
Meperidine (Demerol®)	5–10	2–3	0.75–1	IV	Not recommended for routine use due to potential for accumulation of a neurotoxic metabolite; interacts with MAO inhibitors; use low dose (0.1–0.25 mg/kg) for shivering
	15–60	2–4	1.5–2	PO	
Methadone	10–20	Acute: 4–6	0.1	IV	Consider a pain/palliative care specialist consult. Prolonged elimination half-life that increases with repeat doses and drug accumulation. Wide variations in response to methadone. May prolong QT interval
	30–60	Chronic: >8	0.1	PO	
Morphine (MS Contin®, Oramorph® SR)	5–10	3–4	0.1	IV	Can cause significant histamine release
	15–60	3–5	0.3	PO–IR	
	90–120	8–12	0.3	PO–SR	
Oxycodone IR (Roxicodone®, Oxycontin®)	15–30	3–4	0.1–0.2	PO	Controlled-release tablets should be swallowed whole; Caution in severe renal impairment
	60	12	0.1–0.2	PO–CR	

Table 425.4
Non-opioid analgesic medications

Drug	Dose	Route	Comments
Acetaminophen (Tylenol®)	10–15 mg/kg every 4–6 h Max: 90 mg/kg/day or 4,000 mg/day	PO, PR	Acetaminophen does not have antirheumatic or systemic anti-inflammatory effects; may cause severe hepatotoxicity with overdose
Aspirin	Analgesic, antipyretic, antiinflammatory 10–15 mg/kg every 4–8 h Max: 100 mg/kg/day or 4,000 mg/day Antiplatelet effects: 5 mg/kg/day once daily	PO, PR	Do not use aspirin in children and teenagers who have or who are recovering from chickenpox or flu symptoms (due to the association with Reye's syndrome)
Choline Magnesium Trisalicylate	10–15 mg/kg every 6–8 h Max: 4,500 mg/day	PO	No antiplatelet effect; Do not use in children and teenagers who have or who are recovering from chickenpox or flu symptoms (due to the association with Reye's syndrome)
Ibuprofen (Motrin®, Advil®)	5–10 mg/kg every 6 h Max: 40 mg/kg/day or 3,200 mg/day	PO	To reduce the risk of adverse cardiovascular and GI effects, use the lowest effective dose for the shortest period of time
Ketorlac (Toradol®)	0.5 mg/kg every 6–8 h Max: 30 mg/dose	IV IM	Use caution in renal impairment; do not exceed 48–72 h in children <2 years of age; do not exceed 5 days of therapy in patients 2–16 years of age
Naproxen (Naprosyn®)	5–7 mg/kg every 8–12 h Max: 20 mg/kg/day or 1,000 mg/day	PO	To reduce the risk of adverse cardiovascular and GI effects, use the lowest effective dose for the shortest period of time

Table 425.5
Sedation agents

Drug	Onset (min)	Duration (h)	Dose	Route	Comments
Chloral hydrate	10–20	4–8	Procedural sedation: 25–75 mg/kg/dose 30–60 min prior to procedure; may repeat in 30 min to total max of 120 mg/kg or 1,000 mg infants, 2,000 mg children	PO	Avoid use in renal impairment
Diazepam (Valium®)	1–3	0.25–1	0.1 mg/kg	IV	Poor choice for procedural sedation; ideal for prolonged sedation or muscle relaxation; painful IV injection
	7–15	2–3	0.2–0.3 mg/kg	PR	
	30–60	2–3	0.2–0.3 mg/kg	PO	
Lorazepam (Ativan®)	1–5	3–4	0.03–0.1 mg/kg	IV	Ideal for prolonged anxiolysis
	10–20	3–6	0.05 mg/kg	IM	
	30–60	3–6	0.05–0.1 mg/kg	PO	
Midazolam (Versed®)	1–3	1–2	0.05–0.1 mg/kg	IV	Rapid onset; use IV form for intranasal and rectal
	5–10	1–2	0.1–0.2 mg/kg	IM	
	5–10	1–2	0.2–0.3 mg/kg	INH	
	10–30	1–2	0.3–1 mg/kg	PO/PR	

Table 425.5 (Continued)

Drug	Onset (min)	Duration (h)	Dose	Route	Comments
Ketamine (Ketalar®)	0.5–2	0.25–2	0.25–0.5 mg/kg	IV	Induces general anesthesia; dissociative agent, may cause hallucinations; increases heart rate and blood pressure; causes bronchodilation and increased secretions
	10–15	0.5–4	1.5–3 mg/kg	IM	
Pentobarbital (Nembutal®)	1–10	1–4	0.5–1 mg/kg	IV	Associated with slow wake up and agitation
	5–15	2–4	2–6 mg/kg	IM	
	15–60	2–4	2–6 mg/kg	PO	
			Max: 100 mg		

Table 425.6
Medications used for attention-deficit hyperactivity disorder

Medication	Type of agent	Initial dosing	Formulations and duration of action	Comments
Dextroamphetamine and Amphetamine (Adderall®, Adderall XR®)	Stimulant	IR: 2.5–5 mg 1–2 times/day. Max: 40 mg/day	Immediate release tablet (IR): 4–6 h	Use with caution in patients with pre-existing cardiac abnormalities. Monitor for weight loss, insomnia, hypertension, tachycardia, and increased irritability
		ER: 10 mg daily. Max: 30 mg/day	Extended release capsule (ER): 12 h	
Methylphenidate (Concerta®, Daytrana™, Metadate CD®, Metadate® ER, Methylin®, Methylin® ER, Ritalin®, Ritalin LA®, Ritalin-SR®)	Stimulant	IR: 0.3 mg/kg/dose twice daily. Max: 2 mg/kg/day or 60 mg/day	Immediate release (IR) tablet: 2–4 h	Use with caution in patients with pre-existing cardiac abnormalities. Monitor for weight loss, insomnia, hypertension, and tachycardia
		Osmotic: 18 mg daily. Max: 2 mg/kg/day or 72 mg/day	Sustained/extended release tablet and capsules: 6–8 h	
			Osmotic released oral delivery tablet: 12 h	
			Transdermal patch: 9–12 h	
Atomoxetine (Strattera®)	Non-stimulant	0.5 mg/kg/day. Max: 1.4 mg/kg/day or 100 mg/day	Capsule: 6–8 h	Monitor for increased irritability, suicidal thinking, or changes in behaviors. Requires dosage adjustments in patients with hepatic insufficiency. Extensively metabolized by CYP 2D6 system therefore dosage adjustment required in patients who are poor metabolizers
Clonidine (Catapres®)	Non-stimulant	0.05 mg divided 3–4 times/day. Max: 0.3–0.4 mg/day	Tablets: 6–10 h	Rebound hypertension may occur with abrupt withdrawal of medication. Taper gradually over greater than 1 week
			Transdermal patch: 24 h	

Table 425.7

Properties of antiepileptic medications

Drug name	Indications	Dosing	Comments	Target drug levels
Levetiracetam (Keppra®)	Generalized and partial seizures	Initial: 10 mg/kg/dose twice daily; Max: 30 mg/kg/dose twice daily	Avoid abrupt withdrawal of medication due to increase risk of seizures. Requires dose adjustments in patients with renal insufficiency. IV to PO conversion is one-to-one	Therapeutic range has not been established
Oxcarbazepine (Trileptal®)	Partial seizures	Initial: 8–10 mg/kg/day divided 2 times/day; Max: 900 mg–2,100 mg/day (based on weight)	Monitor for hyponatremia and severe dermatological adverse drug reactions. Requires dose adjustments in patients with renal insufficiency	Therapeutic trough levels for epilepsy (Carbamazepine): 4–12 mcg/ml
Phenobarbital	Generalized and partial seizures	Status epilepticus	Potent inducer of the CYP450 system leading to drug–drug interactions. Requires dose adjustments in patients with renal and hepatic insufficiency	Therapeutic trough levels for epilepsy: 15–40 mcg/ml
		Loading dose: 15–20 mg/kg/dose (Max: 40 mg/kg/dose or 1,000 mg/dose)		
		Anticonvulsant		
		Maintenance dose		
		Neonates: 3–4 mg/kg/day daily		
		Infants: 5–6 mg/kg/day divided 1–2 times/day		
		Children:		
		1–5 years: 6–8 mg/kg/day divided 1–2 times/day		
		5–12 years: 4–6 mg/kg/day divided 1–2 times/day		
		>12 years and adults: 1–3 mg/kg/day divided 1–2 times/day		
Phenytoin (Dilantin®, Phenytek®)	Generalized and partial seizures	Status epilepticus: I.V	Potent inducer of the CYP450 system leading to drug–drug interactions. Requires dose adjustments in patients with renal and hepatic insufficiency	Therapeutic trough levels for epilepsy: Total: 10–20 mcg/ml
		Loading dose		
		All ages: 15–20 mg/kg/dose		
		Maintenance dose		Free: 1–2 mcg/ml
		Neonates: Initial: 5 mg/kg/day in two divided doses; usual: 5–8 mg/kg/day in two divided doses		
		Infants and Children: Initial: 5 mg/kg/day in two to three divided doses; usual doses		
		0.5–3 years: 8–10 mg/kg/day		
		4–6 years: 7.5–9 mg/kg/day		
		7–9 years: 7–8 mg/kg/day		
		10–16 years: 6–7 mg/kg/day		
Topiramate (Topamax®)	Generalized and partial seizures	Initial: 1–3 mg/kg/day (max: 25 mg) daily. Maintenance: 5–9 mg/kg/day given in two divided doses (max: 1,600 mg/day)	Requires dose adjustments in patients with renal and hepatic insufficiency. Use caution in patients with sulfa hypersensitivity	Therapeutic levels: 2–20 mg/dl

Table 425.7 (Continued)

Drug name	Indications	Dosing	Comments	Target drug levels
Valproic Acid Derivatives (Depacon®, Depakene®, Depakote®, Stavzor®)	Generalized and partial seizures	Initial: 10–15 mg/kg/day in one to three divided doses; maintenance: 30–60 mg/kg/day in two to three divided doses	Brands are not bioequivalent. Avoid use in children <2 years old due to increased risk of hepatotoxicity.	Therapeutic trough levels for epilepsy: 50–100 mcg/ml
Zonisamide (Zonegran®)	Generalized and partial seizures	Initial: 2–4 mg/kg/day given in two divided doses/day; maintenance dose: 4–8 mg/kg/day divided twice a day; max: 12 mg/kg/day or 400 mg/day	Requires dose adjustments in patients with renal and hepatic insufficiency. Avoid use in patients with sulfonamide hypersensitivity	Proposed therapeutic trough range: 10–30 mcg/ml

Table 425.8
Immunosuppressant medications

Drug name	Dosing	Comments	Supportive care measures
Cyclophosphamide	Systemic lupus erythematosus: I.V.: 500–750 mg/m^2 every month; max: 1 g/m^2	Requires dose adjustments in patients with renal insufficiency. Monitor for hemorrhagic cystitis, nephrotoxicity, SIADH, and pulmonary fibrosis	Use mesna and hydration to prevent hemorrhagic cystitis
	Juvenile rheumatoid arthritis: I.V.: 10 mg/kg every 2 weeks		
	Nephrotic syndrome: Oral: 2–3 mg/kg/day every day		
Cyclosporine (Gengraf®, Neoral®, Sandimmune®)	Transplantations	Requires dose adjustments in patients with hepatic insufficiency. Brands are not bioequivalent. Therapeutic trough levels varies with type of organ transplant and type of assay	
	Renal: 9 mg/kg/day (range: 6–12 mg/kg/day) divided every 12 h		
	Liver: 8 mg/kg/day (range: 4–12 mg/kg/day) divided every 12 h		
	Heart: 7 mg/kg/day (range: 4–10 mg/kg/day) divided every 12 h		
	Focal segmental glomerulosclerosis: Oral: Initial: 3 mg/kg/day divided every 12 h		
	Autoimmune diseases: Oral: 1–3 mg/kg/day		
Methotrexate (Rheumatrex®, Trexall™)	Juvenile rheumatoid arthritis: Oral, I.M., SubQ: Initial: 10 mg/m^2 once weekly	Requires dose adjustments in patients with renal insufficiency. Monitor for hepatotoxicity, nephrotoxicity, and neurotoxicity	High dose treatment will require leucovorin rescue. Add sodium bicarbonate to intravenous fluids to help clear methotrexate

Table 425.8 (Continued)

Drug name	Dosing	Comments	Supportive care measures
Tacrolimus (Prograf®)	Children:	Requires dose adjustments in patients with hepatic insufficiency. Many drug–drug interactions. Therapeutic trough levels varies with type of organ transplant and type of assay	
	Oral:		
	Liver transplant: Initial: 0.15–0.2 mg/kg/day divided every 12 h		
	Heart transplant: Initial: 0.1–0.3 mg/kg/day divided every 12 h		
	Kidney transplant: Initial: 0.2–0.3 mg/kg/day divided every 12 h		
	I.V.:		
	Liver transplant: 0.03–0.05 mg/kg/day as a continuous infusion		
	Heart transplant: 0.01–0.03 mg/kg/day as a continuous infusion		
	Kidney transplant: 0.06 mg/kg/day as a continuous infusion		

Table 425.9
Properties of corticosteroids

Drug name	Formulations	Relative mineralocorticoid/glucocorticoid potency	Conversions
Dexamethasone (Decadron®)	IV, PO	0/25–30	0.75 mg of dexamethasone is equivalent to 5 mg of prednisone
Hydrocortisone (Solu-cortef®)	IV, PO	1/1	20 mg of hydrocortisone is equivalent to 5 mg of prednisone
Methylprednisolone (Solu-medrol®)	IV, PO	0/5	4 mg of methylprednisolone is equivalent to 5 mg of prednisone
Prednisolone (Orapred®, Pediapred®, Prelone®)	PO	0.8/4	1 mg of prednisolone is equivalent to 1 mg of prednisone
Prednisone	PO	0.8/4	1 mg of prednisolone is equivalent to 1 mg of prednisone

Table 425.10
Antibiotic medications

Medication	Indication	Dose	Comments
Penicillins			
Amoxicillin	Acute otitis media (AOM)	Oral:	May cause rash, anaphylaxis, GI upset, diarrhea, anemia, thrombocytopenia, acute interstitial nephritis with large doses of PCN and nafcillin, hepatotoxicity, and phlebitis with nafcillin therapy; and seizures with decreased renal function or increased levels
	Sinusitis	Neonates: 20–30 mg/kg/day divided every 12 h	
	Skin and skin structure infections		
	Urinary tract infections	Infants >3 months and children <40 kg: 25–45 mg/kg/day divided every 8–12 h	
	Community acquired pneumonia (CAP)	AOM: 80–90 mg/kg/day divided every 12 h	
	Lyme disease	CAP: 80–100 mg/kg/day divided every 6–8 h	Take on empty stomach except amoxicillin and amoxicillin/clavulanate
	Endocarditis prophylaxis	Endocarditis prophylaxis: 50 mg/kg 1 h prior to procedure, max 2 g	Adjust doses in renal dysfunction except nafcillin
	H. pylori eradication		
	Postexposure inhalation anthrax prophylaxis	Postexposure inhalation anthrax prophylaxis	
		<40 kg: 45 mg/kg/day divided every 8 h	
		>40 kg: 500 mg every 8 h	
Amoxicillin/ Clavulanic Acid (Augmentin®)	Acute otitis media (AOM)	Oral	
	Sinusitis	Neonates: 30 mg of amoxicillin/kg/day divided every 12 h	
	Skin and skin structure infections	Infants and children <40 kg: 25–45 mg of amoxicillin/kg/day divided every 12 h	
	Urinary tract infections		
	Community acquired pneumonia (CAP)	AOM: 80–90 mg of amoxicillin/kg/day divided every 12 h	
		CAP: 80–100 mg of amoxicillin/kg/day divided every 8 h	
		Children >40 kg: 500 mg every 12 h	
		More severe infection: 500 mg every 8 h	
		Sinusitis and CAP: 2,000 mg every 12 h	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Ampicillin	Neonatal sepsis and meningitis	Children PO: 50–100 mg/kg/day divided every 6 h	
	Endocarditis prophylaxis	IV, IM	
	Susceptible bacterial infections caused by streptococci, pneumococci, enterococci, nonpenicillinase-producing staphylococci, *Listeria*, meningococci	Neonates: 100 mg/kg/dose every 6–12 h depending on postnatal age and birth weight	
		Children: 100–200 mg/kg/day divided every 6 h	
	Some strains of *H. influenzae*, *P. mirabilis*, *Salmonella*, *Shigella*, *E. coli*, *Enterobacter*, and *Klebsiella*	Meningitis: 200–400 mg/kg/day divided every 6 h	
		Endocarditis prophylaxis: 50 mg/kg 30 min before procedure, max 2 g	
Ampicillin/ Sulbactam (Unasyn®)	Skin and skin structure infections	IV, IM	
	Aspiration pneumonia	Infants: 100–150 mg/kg/day of ampicillin divided every 6 h	
	Abdominal infections	Meningitis: 200–300 mg/kg/day of ampicillin divided every 6 h	
	Pelvic inflammatory disease (PID)		
		Children: 100–200 mg/kg/day of ampicillin divided every 6 h	
		Meningitis: 200–400 mg/kg/day of ampicillin divided every 6 h	
		Max 8 g of ampicillin/day	
Nafcillin	Osteomyelitis	Mild: 100 mg/kg/day divided every 6 h IV	
	CNS infections	Severe: 100–200 mg/kg/day divided every 4–6 h IV, max 12 g/day	
	Endocarditis		
	Sepsis	Endocarditis: 200 mg/kg/day divided every 4–6 h IV for 6 weeks or longer (if prosthetic valve add gentamicin and rifampin for first 2 weeks)	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Penicillin G (Parenteral/ Aqueous) (Pfizerpen®)	Sepsis	IV, IM	Aminoglycosides can inactivate penicillins. Do not mix and separate administration by 30–60 min
	Meningitis	Neonates: 50,000 units/kg/dose every 6–12 h depending on postnatal age and birth weight	
	Pericarditis		
	Endocarditis	Group B Strep meningitis: 250,000–450,000 units/kg/day divided every 6–8 h	
	Pneumonia		
		Infants and children: 100,000–250,000 units/kg/day divided every 4–6 h	
		Severe infections: 250,000–400,000 units/kg/day divided every 4–6 h	
		Max 24 million units/day	
Penicillin V Potassium	Skin and skin structure infections	Children <12 years: 25–50 mg/kg/day PO divided every 6–8 h, max 3 g/day	
	Urinary tract infections		
	Upper respiratory tract infections	≥12 years: 125–500 mg PO every 6–8 h	
	Prophylaxis for rheumatic fever and pneumococcal infections		
Piperacillin/ Tazobactam (Zosyn®)	Sepsis, empiric	IV	
	Skin and skin structure infections	Infants <6 months: 150–300 mg/kg of piperacillin/day divided every 6–8 h	
	Abdominal infections	Children >6 months: 240–400 mg/kg of piperacillin/day divided every 6–8 h (use higher doses divided every 6 h for severe or pseudomonas infections), max 16 g of piperacillin/day	
	Appendicitis		
	Peritonitis		
	PID	Abdominal infections, appendicitis, peritonitis	
	Post-partum endometriosis	Infants <9 months: 240 mg/kg of piperacillin/day divided every 8 h	
	Lower respiratory tract infections		
	Urinary tract infections	Infants and children >9 months and <40 kg: 300 mg/kg of piperacillin/day divided every 8 h	
		Children >40 kg: 3 g of piperacillin (3.375 g of Zosyn) every 6 h	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Carbapenems			
Meropenem (Merrem®)	Multi-drug resistant infections	IV	Meropenum can decrease valproic acid levels
	Meningitis	Children ≥3 months:	
	Neutropenic fever	Skin infections: 10 mg/kg/dose every 8 h up to 500 mg per dose	
	Sepsis, empiric		
	Skin and skin structure infections	Abdominal infections and neutropenic fever: 20 mg/kg/dose every 8 h up to 1,000 mg per dose	
	Abdominal infections		
	Lower respiratory tract infections	Meningitis and CF: 40 mg/kg/dose every 8 h up to 2,000 mg per dose	
	CF exacerbations		
	Urinary tract infections		
Cephalosporins			
Cefazolin (Ancef®)	IV first generation cephalosporin	IV, IM	May cause rash, anaphylaxis, GI upset, diarrhea, pseudo-membranous colitis, headaches, dizziness, neutropenia, anemia, eosinophilia, aplastic anemia, thrombocytopenia, and reversible interstitial nephritis. In children <3 years see increase in BUN without increase in creatinine
	Skin and skin structure infections	Neonates: 20 mg/kg every 8–12 h depending on postnatal age and birth weight	
	Lower respiratory tract infections		
	Urinary tract infections	Infants and Children: 25–100 mg/kg/day divided every 6–8 h, max 6 g/day (use 100 mg/kg/day for severe infections)	
	Biliary tract infections		
	Bone and joint infections		
	Genital infections		
	Septicemia		
Cefdinir (Omnicef®)	Oral third generation cephalosporin	PO	Cefdinir may discolor stools and needs to be separated from antacids
	AOM	≥6 months	
	Pharyngitis/tonsillitis	AOM and sinusitis: 14 mg/kg/day divided every 12 h for 5–10 days or 14 mg/kg/day once daily for 10 days, max 600 mg/day	
	Sinusitis		
	Skin and skin structure infections		There is a 10–15% chance of cross reactivity with hypersensitivity reactions from penicillins
	CAP	Skin: 14 mg/kg/day divided every 12 h for 10 days, max 600 mg/day	
	Acute bronchitis		Adjust doses in renal dysfunction except ceftriaxone
	CF exacerbations		

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Cefepime (Maxipime®)	IV fourth generation cephalosporin	IV, IM	
	Neutropenic fever	Neonates: 30 mg/kg/dose every 12 h	
	Skin and skin structure infections	Children 2 months–16 years: 50 mg/kg/dose IV every 8 h, max 2 g/dose	
	Abdominal infections (with metronidazole)		
	Pneumonia	>16 years: 1–2 g every 12 h (may need dosing every 8 h for pseudomonal infections)	
	Urinary tract infections		
	Pyelonephritis		
Cefixime (Suprax®)	Oral second generation cephalosporin	PO	
	Respiratory tract infections	Infants and children: 16 mg/kg/day divided every 12 h × 1 day, then 8 mg/kg/day once daily, max 400 mg/dose	
	Urinary tract infections	Prophylaxis after sexual attack: 8 mg/kg/dose once daily plus azithromycin, max 400 mg/dose	
	Uncomplicated gonorrhea	Adolescents and adults: Uncomplicated gonorrhea: 400 mg PO × 1 dose plus azithromycin or doxycycline	
Cefotaxime (Claforan®)	IV third generation cephalosporin	IV, IM:	
	Skin and skin structure infections	Neonates: 50 mg/kg/dose every 8–12 h depending on postnatal age and birth weight	
	Lower respiratory tract infections		
	Intra-abdominal infections	Infants and children:	
		<50 kg: 100–200 mg/kg/day divided every 6–8 h	
	Genitourinary tract infections	Meningitis: 200–300 mg/kg/day divided every 6 h	
	Bone and joint infections	>50 kg: Moderate infection: 1–2 g every 6–8 h	
	Meningitis	Severe: 2 g every 4 h, max 12 g/day	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Ceftriaxone (Rocephin®)	IV third generation cephalosporin	IV, IM	Ceftriaxone can cause gallbladder sludge. Avoid use in neonates since ceftriaxone will displace bilirubin from albumin and increase risk of kernicterus. Also, do not administer ceftriaxone with calcium containing fluids. Precipitates have occurred in the lungs and kidneys of neonatal patients
	Skin and skin structure infections	Neonates: Gonococcal prophylaxis: 25–50 mg/kg × 1 dose, max 125 mg	
	Lower respiratory tract infections	Infants and children: 50–75 mg/kg/day divided every 12–24 h	
	Intra-abdominal infections	Meningitis: 100 mg/kg/day divided every 12 h, max 4 g/day	
	Urinary tract infections		
	Bone and joint infections	AOM: 50 mg/kg/dose × 1 dose, max 1 g	
	Meningitis	May repeat once daily × 3 doses for persistent AOM	
	Sepsis	Uncomplicated Gonococcal infection:	
	AOM	Children ≤45 kg: 125 mg IM × 1 dose	
	Gonococcal or chancroid infections	Children >45 kg: 250 mg IM × 1 dose	
		Chancroid: 50 mg/kg IM × 1 dose, max 250 mg	
Cefoxitin (Mefoxin®)	IV second generation cephalosporin	IV, IM	
	Respiratory tract infections	Neonates: 90–100 mg/kg/day divided every 8 h	
	Skin and skin structure infections	Infants ≥3 months and children: 80–100 mg/kg/day divided every 6–8 h	
	Bone and joint infections		
	Urinary tract infections	Severe infections: 100–160 mg/kg/day divided every 4–6 h, max 12 g/day	
	Gynecologic infections		
	Septicemia	Perioperative prophylaxis: 30–40 mg/kg 30–60 min prior to surgery and repeated every 6 h for no more than 24 h following surgery	
	Surgical prophylaxis		
	Intra-abdominal infections		

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Cephalexin (Keflex®)	Oral first generation cephalosporin	PO	Cholestatic jaundice with cephalexin
	Skin and skin structure infections	Children: 25–100 mg/kg/day divided every 6 h, max 4 g/day	
	Respiratory tract infections		
	Genitourinary tract infections	Pharyngitis: 25–50 mg/kg/day divided every 12 h	
	Bone infections		
Macrolides			
Azithromycin (Zithromax®)	AOM	PO	May cause rash, anaphylaxis, GI upset, epigastric pain, diarrhea, chest pain, heart palpitations, jaundice, and photosensitivity reactions. The erythromycin stearate can cause cholestatic hepatits. The IV formulations can cause phlebitis, more common with erythromycin
	Sinusitis	Infants <6 months: Pertussis: 10 mg/kg/dose once daily × 5 days	
	Skin and skin structure infections		
	Urinary tract infections	Children >6 months: 10 mg/kg (max 500 mg) on day 1, then 5 mg/kg (max 250 mg) days 2–5	
	CAP		
	Upper and lower respiratory tract infections	CAP and Sinusitis alternate dosing: 10 mg/kg daily × 3 days, max 500 mg/dose	
	PID	AOM: 30 mg/kg × 1 dose, max 1,500 mg OR 10 mg/kg daily × 3 days, max 500 mg/dose	Stevens-Johnson syndrome and toxic epidermal necrolysis has been seen with azithromycin
	Chancroid and Chlamydia	OR 10 mg/kg (max 500 mg) on day 1, then 5 mg/kg (max 250 mg) days 2–5	
	Pertussis	Pharyngitis: 12 mg/kg/day (max 500 mg) once daily × 5 days	
	CF (to decrease inflammation in chronic pseudomonal infections)		
		Chanroid and Chlamydia: 20 mg/kg × 1 dose, max 1 g	
		CF: 25–40 kg: 250 mg on Monday, Wednesday, and Friday	
		≥40 kg: 500 mg on Monday, Wednesday, and Friday	
		IV	
		Children 6 months–16 years: 10 mg/kg once daily	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Erythomycin (Erythrocin®, E.E.S. ®, EryPed®)	Skin infection	Neonates: 25–40 mg/kg/day IV divided every 6 h for Ureaplasma	Erythromycin can cause hypertrophic pyloric stenosis in infants. Generally avoid in infants <1 month
	Upper and lower respiratory tract infections	PO	Erythromycin and clindamyin are antagonistic
	Chancroid and Chlamydia	Infants and children: Base and ethylsuccinate: 30–50 mg/kg/day divided every 6–8 h, max 2 g/day for base and 3.2 g/day for ethylsuccinate	Erythromycin has many drug interactions. Caution use with theophylline, digoxin, carbamazepine, and warfarin
	Pertussis		
	Lyme disease	Chlamydia: 50 mg/kg/day divided every 6 h × 14 days, max 2 g/day	
	Increase motility		
	Ureaplasma in neonates	Pertussis: 40–50 mg/kg/day divided every 6 h × 14 days, max 2 g/day	
		Motility	
		Infants: 3–10 mg/kg/dose every 6–8 h	
		Children: 10–20 mg/kg/day divided every 6–8 h (with meals and at bedtime)	
		IV	
		Lactobionate: 15–50 mg/kg/day divided every 6 h, max 4 g/day	
Miscellaneous			
Ciprofloxacin (Cipro®)	Fluoroquinolone	Children:	Has caused arthropathy of cartilage in weight bearing joints of animals, green discoloration of teeth in newborns, Achilles tendonitis, and rupture. Monitor for CNS stimulation, dizziness, increased ICP, toxic psychosis, tendon pain or swelling, and photosensitivity reactions. Check for drug interactions with ciprofloxacin. Modify dose in renal dysfunction. Administer extended release tablets 2 h after a meal. Do not administer oral suspension into a feeding tube (will adhere to the tube). Separate ciprofloxacin from dairy products, antacids, mineral supplements, iron, zinc, calcium by at least 2 h before and after the dose
	Respiratory or UTI infection with pseudomonas	PO: 20–30 mg/kg/day divided every 12 h, max 1,500 mg/day	
	Skin infections	IV: 20–30 mg/kg/day divided every 12 h, max 800 mg/day	
	Bone and joint infections	Complicated UTI or pyelonephritis:	
	Complicated UTI or pyleonephritis	PO: 20–40 mg/kg/day divided every 12 h, max 1,500 mg/day	
	Infectious diarrhea		
	Cystic fibrosis pulmonary exacerbations	IV: 18–30 mg/kg/day divided every 8 h, max 1,200 mg/day	
	Otitis externa	CF	
	Osteomyelitis	PO: 40 mg/kg/day divided every 12 h, max 2,000 mg/day	
	Gram negative bacterial infections	IV: 30 mg/kg/day divided every 8 h, max 1,200 mg/day	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Clindamycin (Cleocin®)	Respiratory infections	Neonates: 5 mg/kg/dose IV every 6–12 h depending on postnatal age and birth weight	Shake solution well before each dose. Take capsules with water to prevent esophageal irritation. Decrease dose in severe renal or hepatic dysfunction. Monitor for severe diarrhea or pseudomembranous colitis
	Skin infections		
	Pelvic inflammatory disease	Infants and children	
	Sepsis	PO: 10–30 mg/kg/day divided every 6–8 h, max 1.8 g/day	
	Intra-abdominal infections	IV: 25–40 mg/kg/day divided every 6–8 h max 4.8 g/day	
	Endocarditis prophylaxis in penicillin allergic patient	Bacterial endocarditis prophylaxis for dental procedures in penicillin allergic patients: 20 mg/kg IV/PO 1 h before procedure	
	Babesiosis		
	Acne	Babesiosis: 20–40 mg/kg/day PO divided every 8 h for 7 days plus quinine	
Doxycycline (Adoxa®, Doryx®, Vibramycin®)	Rickettsia	Children <8 years	Take capsule and tablets with plenty of water to prevent esophageal ulceration. Separate doxycycline from dairy products, antacids, iron by at least 1 h before and 2 h after the dose. Can give with food to decrease stomach upset. Can see some staining of the teeth in children <8 years; may discolor fingernails. Monitor for photosensitivity reactions, GI pain, and IV extravasations
	Ehrlichiosis	Ehrlichiosis: 2 mg/kg PO/IV every 12 h, max 200 mg/day	
	Chlamydia	Tickborne rickettsial disease: 2.2 mg/kg PO/IV every 12 h, max 200 mg/day	
	Mycoplasma		
	Listeria	Children ≥8 years: 2–4 mg/kg/day PO/IV divided every 12 h, max 200 mg/day	
	Clostridium		
	Anthrax		
	Ureaplasma urealyticum		
	Lyme disease		
	Acne		
Linezolid (Zyvox®)	Pneumonia	PO, IV	Avoid pseudoephedrine, SSRIs, and high tyramine foods due to risk of serotonin syndrome. Monitor for vision changes, diarrhea, and vomiting. If on therapy >14 days, monitor for thrombocytopenia. Suspension contains phenylalanine
	Skin infections	Neonates, infants and children:	
	Bacteremia with vancomycin-resistant *Enterococcus faecium* (VREF)	Complicated skin infections, pneumonia, VREF	
		10 mg/kg/dose every 8 h, max 600 mg/dose for children less than 12 years old	
		Uncomplicated skin and skin structure infections	
		Children <5 years: 10 mg/kg every 8 h	
		Children 5–11 years: 10 mg/kg every 12 h	

Table 425.10 (Continued)

Medication	Indication	Dose	Comments
Metronidazole (Flagyl®)	Anaerobic antibacterial agent	Neonates: PO, IV: 7.5 mg/kg every 12–48 h depending on postnatal age and birth weight	Avoid alcohol for 48 h after last dose. Monitor for GI upset, diarrhea, black furry tongue, and red-brown urine. Caution use in patients with seizures and aseptic meningitis. Can decrease metallic taste with acidic liquids
	Trichomoniasis		
	Amebiasis	Anaerobic infections, AAPC:	
	Giardiasis	Infants and children: PO, IV: 30 mg/kg/day divided every 6 h, max dose 4 g/day	
	Antibiotic-associated pseudomembranous colitis (AAPC)	Amebiasis: 35–50 mg/kg/day PO divided every 8 h	
	Skin and skin structure infections	*Helicobacter pylori* infections (in combination with amoxicillin and bismuth subsalicylate): 15–20 mg/kg/day PO divided every 12 h	
	Bone and joint infections		
	CNS infections		
	Intra-abdominal infections		
	Gynecological infections		
Sulfamethoxazole/Trimethoprim (Bactrim™, Septra®, Sulfatrim®)	UTI	Mild infections: 6–12 mg/kg/day of trimethoprim PO/IV divided every 12 h	Do not use in children <2 months of age due to risk of kernicterus. Avoid use in sulfa allergic patients
	Chronic bronchitis		
	Shigella	Severe infections/PCP treatment: 15–20 mg/kg/day of trimethoprim PO/IV divided every 6 h	Adjust dose for renal impairment. Rare cases of Stevens-Johnsons Syndrome reported. Discontinue medication if rash appears
	Nocardia		
	Pneumocystis jiroveci pneumonitis (PCP)		
		PCP prophylaxis: 150 mg trimethoprim/m^2/day PO divided every 12 h 3 days/week on consecutive or alternate days	Administer oral formulations with plenty of fluids
		UTI prophylaxis: 2 mg/kg/day of trimethoprim PO given once daily	
Vancomycin (Vancocin®)	MRSA	IV	Administer IV over 60 min. If rash or redness appears on face or neck, slow infusion to 90–120 min
	Coagulase negative *Staphylococcus*	Neonates: 10–15 mg/kg/dose every 8–24 h depending on postnatal age and birth weight	
	Endocarditis		
	Meningitis	Infants and children: 10–15 mg/kg/dose every 6 h	Monitor for hearing loss and renal dysfunction. Monitor serum troughs around third to fourth dose. Goal trough is 10–20 mcg/ml
	Osteomylitis	Serious infections (meningitis, MRSA): 15–20 mg/kg/dose every 6–8 h	
	Line infections		
	VP shunt infections	PO (Antibiotic-associated pseudomembranous colitis, AAPC)	
	Graft infections		
	Prosthetic valve infections	Children: 10 mg/kg/dose every 6 h, max 2 g/day (metronidazole is initial drug of choice)	

Table 425.11
Antifungal medications

Medication	Indication	Dose	Comments
Amphotericin B	Severe infections or meningitis caused by *Candida*, *Histoplasma*, *Cryptococcus neoformans*, *Aspergillus*, *Mucor*, *Blastomyces*, *Torulopsis glabrata*	IV	Administer over 4 to 6 h. Rapid infusions cause hypotension, hypokalemia, and arrhythmias
		Initial dose: 0.25–1 mg/kg/day once daily	
		Severe infections: 1 mg/kg/day once daily	Monitor for anaphylaxis with first dose. Infusion related reactions include chills, rigors, and fever. This can be prevented with administration of acetaminophen and diphenhydramine. Meperidine can be used if rigors occur. Other adverse reactions include renal failure, hypokalemia, hypomagnesemia, hyperglycemia, phlebitis, increase in LFTs
			Sodium loading before each dose can help to prevent renal failure. Administer 10–20 ml/kg of NSS or 0.45% NSS before the dose
Amphotericin B Liposome (AmBisome®), Amphotericin B Lipid Complex (Abelcet®)	Febrile, neutropenic patients	AmBisome, IV	Administer over 1 to 2 h
	Severe infections or meningitis caused by *Candida*, *Histoplasma*, *Cryptococcus neoformans*, *Aspergillus*, *Mucor*, *Blastomyces*, refractory to conventional amphotericin	Empiric therapy: 3 mg/kg/day once daily	
		Systemic fungal infections: 3–5 mg/kg/day once daily, up to 10 mg/kg/day in documented *Aspergillus* infections	Monitor for anaphylaxis with first dose. Infusion related reactions include chills, rigors, and fever. This can be prevented with administration of acetaminophen and diphenhydramine. Meperidine can be used if rigors occur. Other adverse reactions include renal failure (incidence less common than with conventional amphotericin), hypokalemia, hypomagnesemia, hyperglycemia, phlebitis, increase in LFTs
		Cryptococcal meningitis: 6 mg/kg/day once daily	
	Fungal infections in patients with renal impairment	Abelcet, IV	
		2.5–5 mg/kg/day once daily	
Caspofungin Acetate (Cancidas®)	Febrile, neutropenic patients	IV	Administer over 1–2 h
	Severe infections caused by *Candida*, or *Aspergillus*	Preterm neonates to infants <3 months: 25 mg/m^2/dose once daily	Use caution in patients with hepatic dysfunction
		3 months–17 years: 70 mg/m^2/dose on day 1, then 50 mg/m^2/dose once daily	Monitor for anaphylaxis, phlebitis, vomiting, diarrhea, abdominal pain, cough, edema in extremities, and chest pain
		Can increase dose to 70 mg/m^2/dose if no clinical response, max dose 70 mg	
		Patients receiving enzyme inducers should receive 70 mg/m^2/dose once daily	

Table 425.11 (Continued)

Medication	Indication	Dose	Comments
Fluconazole (Diflucan®)	Susceptible *Candida* infections	Neonates >2 weeks, infants, and children: 6–12 mg/kg/day IV/PO once daily	Better activity against *C. albicans*
			Shake oral suspension well before each dose. Suspension is stable for 14 days at room temperature
	Prophylaxis in bone marrow transplant patients		Monitor for bleeding, bruising, skin rash, nausea, vomiting, headache, yellowing of skin, or eyes and anaphylaxis with first dose
			Check for drug interactions with other therapies
Voriconazole (VFEND®)	Treatment of invasive *Candida*, or *Aspergillus*	IV	Administer oral medication on empty stomach
	Treatment of serious fungal infections caused by *Scedosporium apiospermum* or *Fusarium*	Children >2 years to Adults: 6 mg/kg every 12 h × 2 doses, then 4 mg/kg every 12 h	Monitor for vision changes (blurry), photophobia, rash, increased LFTs, hepatitis, cholestasis, acute renal failure, hypokalemia, photosensitivity, cardiac arrhythmias, and QT prolongation
		Invasive aspergillosis: 5–7 mg/kg/dose every 12 h	
		PO	
		<40 kg: 100 mg every 12 h; if response inadequate, may increase to 150 mg every 12 h	Check for drug interactions with other therapies
		>40 kg: 200 mg every 12 h; if response inadequate, may increase to 300 mg every 12 h	IV formulation should not be used in patients with renal dysfunction (CrCl <50 ml/min)
Griseofulvin (Grifulvin V®, Gris-PEG®)	Tinea on skin or hair	>2 years: 20–25 mg/kg/day once daily PO for 6–8 weeks	Shake oral suspension well before each dose. Administer with fatty meal to increase absorption
			Monitor for photosensitivity reactions, nausea, vomiting, diarrhea, and increases in LFTs (generally not seen in first 6–8 weeks of therapy)
Nystatin	Oral *Candida*	Neonates: 50,000 units to each side of mouth four times daily	Shake oral suspension well before each dose
		Infants and Children: 100,000 units to each side of mouth four times daily	Monitor for local irritation, diarrhea, vomiting. Rare cases of Stevens-Johnsons Syndrome reported

Table 425.12
Antiviral medications

Medication	Indication	Dose	Comments
Acyclovir (Zovirax®)	Initial and prophylactic treatment of herpes simplex virus (HSV1) and (HSV2) infections	HSV encephalitis:	Shake suspension well before each dose
		Neonates – 12 years: 20 mg/kg/dose IV every 8 h	Administer IV slowly over 1 h to avoid crystalluria
	HSV encephalitis	Children >12 years–Adults: 10–15 mg/kg/dose IV every 8 h	Adjust dose in renal dysfunction
	Herpes zoster (shingles) infection	HSV infection, first infection: Children: 40–80 mg/kg/day PO divided three to four times daily, max 1,000 mg/day	With IV monitor for phlebitis, renal dysfunction, bone marrow suppression, increases in LFTs, and hyperbilirubinemia
	Varicella–zoster (VZV) infection	Recurrent HSV infection: Children: 40–80 mg/kg/day PO divided three times daily, max 1,000 mg/day	
		Herpes zoster (shingles) in immunocompetent patient	
		PO: ≥12 years: 800 mg five times a day	
		IV: Infants <1 year: 10 mg/kg/dose every 8 h	
		Children ≥1 year: 10 mg/kg/dose or 500 mg/m^2/dose every 8 h	
		Herpes zoster (shingles) in immunocompromised patient	
		Infants to adults (all ages): 10 mg/kg/dose IV every 8 h	
		Varicella zoster in immunocompetent patient	
		PO: Children ≥2 years and ≤40 kg: 20 mg/kg/dose four times daily, max 3,200 mg/day	
		Children ≥40 kg to Adults: 800 mg four times daily	
		IV: Children ≥2 years: 10 mg/kg/dose or 500 mg/m^2/dose every 8 h	
		Varicella zoster in immunocompromised patient	
		Infants <1 year: 10 mg/kg/dose IV every 8 h	
		Children 1–12 years: 10–20 mg/kg/dose or 500 mg/m^2/dose IV every 8 h	
		Children >12 years–adult: 10–15 mg/kg/dose IV every 8 h	

Table 425.12 (Continued)

Medication	Indication	Dose	Comments
Ganciclovir (Cytovene®)	Treatment or prophylaxis of CMV	IV	Administer oral medication with food. Do not open or crush oral capsules. Administer IV slowly over 1 h. Handle as cytotoxic medication
		Congenital CMV infection: Neonates and Infants: 12 mg/kg/day divided every 12 h	
			Adjust dose in renal dysfunction
		Prophylaxis of CMV: 10 mg/kg/day divided every 12 h for 1–2 weeks, then 5 mg/kg/day once daily or 30 mg/kg/dose PO every 8 h, max 1,000 mg/dose for maintenance	Monitor for phlebitis, renal dysfunction, nausea, vomiting, pancreatitis, vision changes, neutropenia, thrombocytopenia, and increases in LFTs
Lamivudine (Epivir®)	Treatment of HIV infection	PO	Adjust dose in renal dysfunction.
	Prophylaxis of HIV exposure	HIV infection	Use with extreme caution in pediatric patients with a history of pancreatitis
	Treatment of chronic hepatitis B infections	Neonates <30 days: 2 mg/kg/dose twice daily	
		Infants 1 month of age to adults: 4 mg/kg/dose every 12 h, max 150 mg every 12 h	Monitor for pancreatitis, lactic acidosis, hepatomegaly, persistent severe abdominal pain, nausea, vomiting, numbness, or tingling. Avoid alcohol
		Chronic hepatitis B infection	
		Children 2–17 years: 3 mg/kg/dose once daily, max 100 mg/day	
		HIV postexposure prophylaxis: Children ≥16 years to adults: 150 mg twice daily or 300 mg once daily (in combination with zidovudine, tenofovir, stavudine, or didanosine, with or without a protease inhibitor)	
Oseltamiviz (Tamiflu®)	Treatment of influenza A or B infection	PO	Treatment should be initiated within 48 h of symptoms
		Treatment: Children ≥1 year to adults	
			Adjust dose in renal dysfunction
	Prophylaxis of influenza A or B infection	≤15 kg: 30 mg twice daily for 5 days	Monitor for hallucinations, confusion, unusual behavior, and self-injury
		>15 kg to 23 kg: 45 mg/dose twice daily for 5 days	
		>23 kg to 40 kg: 60 mg/dose twice daily for 5 days	Other adverse reactions include diarrhea, abdominal pain, vomiting, and anaphylaxis
		>40 kg: 75 mg/dose twice daily for 5 days	
		Prophylaxis: Children ≥1 year to adults:	
		≤15 kg: 30 mg once daily	
		>15 kg to ≤23 kg: 45 mg once daily	
		>23 kg to ≤40 kg: 60 mg once daily	
		>40 kg: 75 mg once daily	

Table 425.12 (Continued)

Medication	Indication	Dose	Comments
Palivizumab (Synagis®)	Prevention of serious lower respiratory infections due to respiratory syncytial virus (RSV) in infants and children at high risk for RSV disease	Infants <24 months of age: 15 mg/kg IM once a month during RSV season	Monitor for rare anaphylaxis
		The American Academy of Pediatrics recommends RSV prophylaxis with palivizumab during RSV season for:	
		Infants <3 months of age who were born between 32 and $34^{6}/_{7}$ weeks gestational age and have one of the following: Daycare attendance; ≥1 sibling who is <5 years of age living in the same household	
		Infants <6 months of age who were born between 29 and $31^{6}/_{7}$ weeks gestational age	
		Infants <12 months of age who were born ≤28 weeks gestational age	
		Infants <12 months of age with congenital airway abnormality or neuromuscular disorder that decreases the ability to manage airway secretions	
		Infants and children <24 months of age with chronic lung disease (CLD) necessitating medical therapy within 6 months of age prior to the beginning of RSV season	
		Infants and children <24 months with congenital heart disease and one of the following: Receiving medication to treat congestive heart failure; Moderate to severe pulmonary hypertension; Cyanotic heart disease	
Valacyclovir (Valtrex®)	Varicella zoster (chickenpox) infection	PO	Adjust dose in renal dysfunction
	HSV and VZV prophylaxis in immunocompromised children	Varicella zoster: 2 years–18 years: 20 mg/kg/dose three times daily, max 1,000 mg/dose	Monitor for thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, headache, nausea, vomiting, vision changes, behavioral changes, bleeding or bruising, neutropenia, thrombocytopenia, and increases in LFTs
	Herpes labialis	HSV or VZV prophylaxis: 15–30 mg/kg/dose three times daily, max 2,000 mg/dose	
		Herpes labialis: Children >12 years: 2 g every 12 h for 1 day	
Valganciclovir (Valcyte®)	Treatment or prophylaxis of CMV	PO	Do not substitute these capsules for ganciclovir. They are not equivalent
		Congenital CMV infection: >7 days to 3 months: 16 mg/kg/dose every 12 h	Administer oral medication with food. Do not open or crush oral capsules. Handle as cytotoxic medication
		Prophylaxis of CMV: 4 months to 16 years	

Table 425.12 (Continued)

Medication	Indication	Dose	Comments
		7 × BSA × creatinine clearance = dose once daily, max 900 mg/day	Monitor for renal dysfunction, nausea, vomiting, pancreatitis, vision changes, hallucinations, peripheral neuropathy, psychosis, seizures, dehydration, hyperglycemia, hypocalcemia, hypomagnesemia, hypophosphatemia, neutropenia, thrombocytopenia, and increases in LFTs
Zidovudine (Retrovir®)	Treatment of HIV infection	Prophylaxis of perinatal HIV transmission	May be administered without regard to meals. Administer IV over 1 h. Hazardous agent; use appropriate precautions for handling and disposing
	Prophylaxis to reduce perinatal transmission	Neonates <35 weeks gestational age (GA) at birth	
		IV: 1.5 mg/kg/dose every 12 h	Check for drug interactions with other therapies
	Prophylaxis of HIV exposure	PO: 2 mg/kg/dose every 12 h	Monitor for muscle weakness, shortness of breath, headache, insomnia, signs of infection, unusual bleeding, rash, lactic acidosis, hepatotoxicity, anemia, and bone marrow suppression
		Increase to every 8 h dosing	
		GA at birth <30 weeks: Increase above dose to every 8 h at 4 weeks of age	
		GA at birth ≥30 weeks: Increase above dose to every 8 h at 2 weeks of age	
		Neonates >35 weeks gestational age at birth	
		IV: 1.5 mg/kg/dose every 6 h	
		PO: 2 mg/kg/dose every 6 h	
		Treat for first 6 weeks of life. Use IV route only until oral route can be given	
		HIV infection	
		Dosing based on body surface area	
		Infants ≥4 weeks old to <18 years	
		240 mg/m^2/dose every 12 h, max 300 mg every 12 h or 160 mg/m^2/dose every 8 h, max 200 mg every 8 h	
		Dosing based on weight	
		4 to <9 kg: 12 mg/kg/dose twice daily or 8 mg/kg/dose 3 times/day	
		≥9 to <30 kg: 9 mg/kg/dose twice daily or 6 mg/kg/dose 3 times/day	
		≥30 kg: 300 mg twice daily or 200 mg 3 times/day	
		HIV postexposure prophylaxis: Children ≥12 years to Adults: 300 mg twice daily or 200 mg 3 times/day (in combination with lamivudine or emtricitabine, with or without a protease inhibitor)	
		Begin therapy within 2 h of exposure if possible	

Table 425.13
Hematologic medications

Drug	Indications	Dosing	Comment	Monitoring and administration instructions
Deferasirox (Exjade®)	Treatment of chronic iron overload due to blood transfusions	Initial: 20 mg/kg daily Maintenance: 20–30 mg/kg/day; Max: 40 mg/kg/day	Monitor for renal and hepatic impairments and gastric bleeds	Disperse tablets in water, orange juice, or apple juice
Enoxaparin (Lovenox®)	Prophylaxis and treatment of thromboembolic disorders	Infants <2 months Prophylaxis: 0.75 mg/kg/dose every 12 h	Requires dose adjustments in patients with renal insufficiency	Therapeutic antifactor Xa levels for treatment: 0.5–1 units/ml
		Treatment: 1.5 mg/kg/dose every 12 h	Higher doses may be needed in neonates and infants	Therapeutic antifactor Xa levels for prophylaxis: 0.2–0.45 units/ml
		Infants ≥2 months and Children ≤18 years Prophylaxis: 0.5 mg/kg/dose every 12 h Treatment: 1 mg/kg/dose every 12 h		
Epoetin Alfa (Epogen®, Procrit®)	Treatment of anemia associated with chronic diseases	Anemia of prematurity: Neonates: 25–100 units/kg/dose 3 times/week or 100 units/kg/dose 5 times/week or 200 units/kg/dose every other day for ten doses Anemia in cancer patients Children 6 months to 18 years: 25–300 units/kg 3–7 times/week	Patients need to have adequate iron stores	Goal is hemoglobin between 10–12 g/dl
Ferrous Sulfate (Fer-In-Sol®)	Prevention and treatment of iron deficiency anemia	Severe iron deficiency anemia: 4–6 mg elemental iron/kg/day in 3 divided doses Mild to moderate iron deficiency anemia: 3 mg elemental iron/kg/day in one to two divided doses Prophylaxis: 1–2 mg elemental iron/kg/day iron/day	Oral is the preferred route of administration. Should be dosed in mg of elemental iron	May interfere with the absorption of tetracyclines and fluoroquinolones. Do not take with milk or antacids
Filgrastim (Neupogen®)	Reduction of the duration of neutropenia	Neonates: 5–10 mcg/kg/day Children and adults: 5–10 mcg/kg/day	May be given subcutaneous or intravenous	Monitor absolute neutrophil counts to determine duration of therapy
Heparin	Prophylaxis and treatment of thromboembolic disorders	Neonates and Infants <1 year: I.V. infusion: Initial loading dose: 75 units/kg given over 10 min; then initial maintenance dose: 28 units/kg/h; adjust dose to maintain antifactor Xa level of 0.35–0.7 units/ml Children >1 year I.V. infusion: Initial loading dose: 75 units/kg given over 10 min, then initial maintenance dose: 20 units/kg/h; adjust dose to maintain antifactor Xa level of 0.35–0.7 units/ml	High alert medication. Many different concentrations exist	Goal is antifactor Xa level of 0.35–0.7 units/ml or PTT 1.5–2.5 times control value

Table 425.13 (Continued)

Drug	Indications	Dosing	Comment	Monitoring and administration instructions
Phytonadione	Prevention and treatment of hypoprothrombinemia caused by vitamin K deficiency	Hemorrhagic disease of the newborn: Neonates: SubQ, I.M. Prophylaxis: 0.5–1 mg within 1 h of birth Treatment: 1–2 mg/day	Oral route preferred due to increased risk of hypersensitivity reaction with IV administration	Maximum IV rate is 1 mg/min
Rasburicase (Elitek™)	Management of hyperuricemia in patients at risk for tumor lysis syndrome	0.2 mg/kg/dose once daily, duration based on uric acid levels	Avoid use in patient with G6PD deficiency	Can interact with uric acid measurements in the laboratory
Warfarin (Coumadin®)	Prophylaxis and treatment of thromboembolic disorders	Initial loading dose on day 1: 0.1–0.2 mg/kg (max dose: 10 mg) Usual maintenance range: 0.05–0.34 mg/kg/day	Maintain consistent Vitamin K intake. Many drug–drug interactions	Goal INR is two to three for deep vein thrombosis

Table 425.14
Gastrointestinal medications

Drug	Drug class	Indication	Dosing	Comments and special administration instructions
Lansoprazole (Prevacid®)	Proton-pump inhibitor	Gastroesophageal reflux disease, Zollinger-Ellison syndrome, and ulcers associated with *Helicobacter pylori*	Oral Infants ≥3 months: 1–2 mg/kg/day or 7.5 mg twice daily or 15 mg once daily Children 1–11 years ≤30 kg: 15 mg daily >30 kg: 30 mg daily Max: 30 mg twice daily	Administer dose 30 min before meals
Pantoprazole (Protonix®)	Proton-pump inhibitor	Gastroesophageal reflux disease, Zollinger-Ellison syndrome, ulcers associated with *Helicobacter pylori*	Children: Oral/IV: 0.5–1 mg/kg/day Max: 40 mg twice daily	Administer dose 30 min before meals
Ranitidine (Zantac®)	Histamine 2 receptor antagonist	Ulcers, gastroesophageal reflux disease (GERD)	Premature and Term Infants <2 weeks Oral: 2 mg/kg/day divided every 12 h I.V.: 1.5–2 mg/kg/day divided every 12 h Children ≥1 month to 16 years Oral: 4–8 mg/kg/day divided twice daily; max: 300 mg/day I.V.: 2–4 mg/kg/day divided every 6–8 h; maximum: 200 mg/day	Requires dose adjustments in patients with renal insufficiency. Administer with meals and at bedtime

Table 425.14 (Continued)

Drug	Drug class	Indication	Dosing	Comments and special administration instructions
Sucralfate (Carafate®)		Gastrointestinal ulcers; prevention of stress ulcers	Oral: 40–80 mg/kg/day divided every 6 h; Max: 1 g/dose	Avoid use in patients with renal insufficiency due to potential accumulation of aluminum. May interfere with the absorption of other medications. Recommend administering other medications 2 h before or after sucralfate administration
Metoclopramide (Reglan®)	Dopamine antagonist	Gastroesophageal reflux and prevention of nausea and vomiting	Oral/IV: 0.4–0.8 mg/kg/day in four divided doses	Requires dose adjustments in patients with renal insufficiency. Monitor for extrapyramidal symptoms. IV to PO conversion is one-to-one
Ondansetron (Zofran®)	5-HT3 receptor antagonist	Prevention of nausea and vomiting associated with chemotherapy or radiotherapy	Oral	Requires dose adjustments in patients with hepatic insufficiency
			<0.3 m^2: 1 mg 3 times/day	
			0.3–0.6 m^2: 2 mg 3 times/day	
			0.6–1 m^2: 3 mg 3 times/day	
			>1 m^2: 4 mg 3 times/day	
			or	
			Children 4–11 years: 4 mg 3 times/day	
			Children >11 years and Adults: 8 mg 3 times/day or 24 mg once daily	
			IV: 0.15 mg/kg 30 min prior to chemotherapy	
Ursodiol (Actigall®)		Prevention and treatment of gallstone. Primary biliary cirrhosis and treatment of cholestasis	10–15 mg/kg/day (Max: 30 mg/kg/day in two to three divided doses)	Monitor for hepatotoxicity
Pancrelipase (Creon®, Pancreaze™, Pancrelipase™, Zenpep™)	Pancreatic enzymes	Treatment of exocrince pancreatic insufficiency	≤ 1 year: Lipase 2,000–4,000 units per 120 ml of formula, breast milk, or per breast-feeding	Brands are not bioequivalent. Do not chew or crush capsules
			>1 to <4 years: Initial dose: Lipase 1,000 units/kg/meal. Dosage range: Lipase 1,000–2,500 units/kg/meal. Max: Lipase 10,000 units/kg/day or lipase 4,000 units/g of fat/day	
			≥ 4 years: Lipase 500 units/kg/meal. Dosage range: Lipase 500–2,500 units/kg/meal. Max: Lipase 10,000 units/kg/day or lipase 4,000 units/g of fat/day	
Polyethylene Glycol 3350 (Miralax®)	Osmotic laxative	Treatment of constipation	Children >6 months: 0.5–1.5 g/kg daily (Max: 100 g/day)	Mix 17 g in 120–240 ml of water, juice, or other beverages

Table 425.15

Properties of insulin preparations

Type of insulin	Insulin	Onset of action	Time to reach peak (h)	Duration of action (h)	Total daily insulin dose
Long-acting	Detemir (Levemir®)	1–2 h	6–8	10–20	0.5–1 units/kg/day
	Glargine (Lantus®)	1–1.5 h	No peak	20–24	
	NPH (Humulin N®, Novolin N®)	1–2 h	4–12	18–20	
Short-acting	Regular (Humulin R®, Novolin R®)	30–60 min	2–5	5–8	
Rapid-acting	Aspart (Novolog®)	5–15 min	0.5–2	3–5	
	Glulisine (Apidra®)	20 min	0.75–1	5	
	Lispro (Humalog®)	5–1	0.5–2	3–5	

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